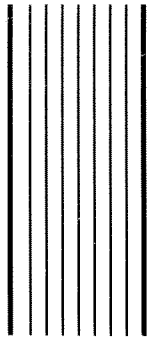

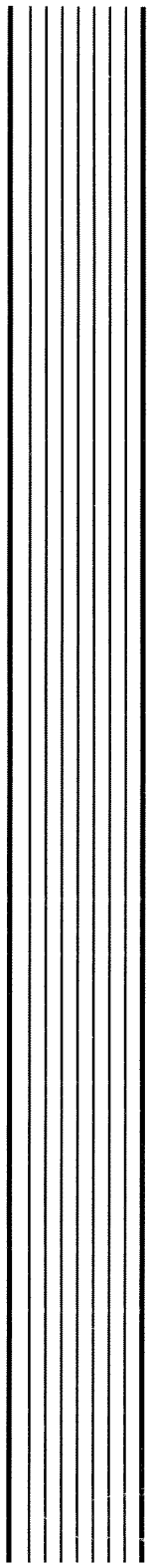

DIET, BLOOD CHOLESTEROL AND CORONARY HEART DISEASE: A CRITICAL REVIEW OF THE LITERATURE.

VOLUME 2

RUSSELL L. SMITH, Ph.D

IN CONSULTATION WITH

EDWARD R. PINCKNEY, M.D.

VECTOR ENTERPRISES

NOVEMBER 1991

DIET, BLOOD CHOLESTEROL AND CORONARY HEART DISEASE: A CRITICAL REVIEW OF THE LITERATURE
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CHOLESTEROLISM

HOLESTEROLISM

OLESTEROLISM

LESTEROLISM

MESTEROLISM

McSTEROLISM

McCTEROLISM

McCAEROLISM

McCARROLISM

McCARTOLISM

McCARTHLISM

McCARTHYISM

POSITIONS

"Americans should reduce their blood cholesterol levels to below 200mg. They may die sooner than usual but they will at least reduce their chances of dying of coronary heart disease."

(NHLBI/AHA)[a]

"I will prescribe regimen for the good of my patients according to my ability and my judgment and never do harm to anyone."

(From the Hippocratic Oath)

"If our military strategy and competence in the Gulf War were the same as our CHD epidemiological research strategy and competence, Operation Desert Storm would have been Operation Desert Dew."

(Russell L. Smith)

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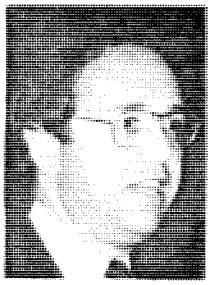
a Logical derivation from statements made by members of the National Heart, Lung and Blood Institute and the American Heart Assoication (e.g., see Kannel[1448] and Kannel et al.[1083])

ROGUES'

Basil Rifkind

Ancel Keys

William Castelli



James Cleeman

Scott Grundy

Jeremiah Stamler

Herbert Naito

William Roberts

William Connor

Bernadine Healy

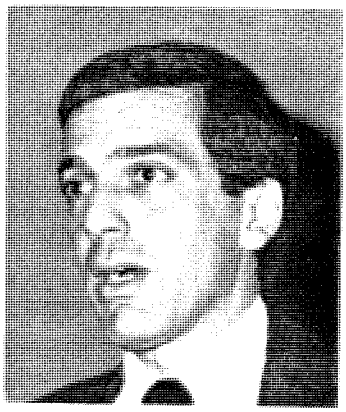
David Blankenhorn

Claude Lenfant

GALLERY

Ancel Keys
The man who started it all 40+ years ago recently said, "I've come to think that cholesterol is not as important as we used to think it was."
William Connor
Long-time American Heart Association (AHA) member, claims he tries to prove that dietary cholesterol doesn't raise blood cholesterol but designs confounded experiments to make it appear that dietary cholesterol has "profound effects."
Claude Lenfant
Current National Heart, Lung and Blood Institute (NHLBI) director and responsible for the greatest scam in medical history.
Bernadine Healy
Caught in an embarassing conflict-of-interest situation, she was subsequently rewarded with the AHA presidency and then the directorship of the National Institutes of Health.
Basil Rifkind
Director of the Lipid Research Clinics trial, he introduced the much publicized but grossly erroneous concept that reducing blood cholesterol 1% reduces CHD event rate 2%.
William Castelli
Framingham study director and unquestionably the record holder of self-contradictions and mislesding statements.
Jeremiah Stamler
Long-time AHA member and possibly the most prolific writer of unscientific nonsense in the history of mankind.
William Roberts
NHLBI staff member and editor of American Journal of Cardiology, does not believe that man should kill animals for food but apparently believes that it is O.K. to kill them for medical research.
Scott Grundy
Long-time AHA member who is second only to Stamler in producing unscientific nonsense and one of the leaders in re-writing history.
Herbert Naito
National cholesterol Education Program (NCEP) Laboratory Standardization Panel Chairman, encourages national screenings of cholesterol levels even though he knows most cholesterol tests are grossly inaccurate.
James Cleeman
NCEP coordinator advises the press not to listen to anything but NHLBI/AHA dogma.
David Blankenhorn
Wrote prolifically on the inaccuracies inherent in using angiograms as measures of determing development of atherosclerosis and then uses angiograms for just such a purpose.

ROGUES'



John LaRosa

W. Virgil Brown

Robert Levy

Frederick Stare

DeWitt Goodman

Myron Weisfeldt

Phil Sokolof

Daniel Steinberg

Glen Griffin

Antonio Gotto

Irvine Page

William Kannel

GALLERY

Robert Levy
Former NHLBI director who helped NHLBI become a puppet of AHA in the 1970s.
William Kannel
Former Framingham study director and second only to Castelli in uttering self-contradictory and misleading statements.
Antonio Gotto
Former AHA president, considered high-polyunsaturated fat diets "prudent" until evidence accumulated indicating serious harm and then redefined "prudent" as low polyunsaturated fat.
John LaRosa
Long-time member of AHA believes dietary cholesterol is more atherogenic than blood cholesterol.
DeWitt Goodman
NCEP Panel Chairman and vice-chairman of the committee that published the largest biased review of the relevant literature in modern times, i.e., "Diet and Health."
Frederick Stare
The most prolific syndicated columnist/book writer who promoted the AHA's dogma for about 20 years and then began preaching the opposite point of view, making money doing both.
Myron Weisfeldt
Former AHA president who believed it was his duty to admonish Michael DeBakey for being seen in the company of those who disagree with the AHA's dogma and who admitted privately that he has no expertise on the diet-CHD issue.
Irvine Page
Former AHA president, believed diet was important to developing CHD, was not important, was important, was not important...
W. Virgil Brown
Current AHA president.
Glen Griffin
Editor of Post-Graduate Medicine, had a bypass operation with a cholesterol level under 150 mg and said, "You can be sure I'm going to be eating very little saturated fat."
Daniel Steinberg
Long-time AHA member and Chairman of 1984 cholesterol consensus conference, believes "There is no doubt that those having a high HDL are strongly protected...against atherosclerosis" "but I don't think we have any data showing us that a high HDL will protect an artery against atherosclerosis."
Phil Sokolof
Brainwashed by NHLBI and AHA, this millionaire spent a great deal of his own money promoting the diet-CHD dogma in the media.

ACKNOWLEDGEMENTS

I again want to thank Dr. Edward R. Pinckney for his continuous, unselfish support during the three years of preparing this volume. I also appreciate the many compliments I received from many researchers and physicians who read Volume 1. I was particularly pleased and honored to receive phone calls and letters from such outstanding individuals as Drs. Edward Ahrens, George Mann, Michael DeBakey, Michael Oliver, Eliot Corday, Raymond Reiser and Robert Olson. I was also fortunate to form on-going productive relationships with some researchers and physicians. For example, biochemist Dr. Mary Enig taught me much about fatty acids and the effects of hydrogenation, and pathologist Dr. William Stehbens taught me the differences between human atherosclerosis and the atherosclerosis-like disease induced by cholesterol feeding in some animals and by very high levels of blood cholesterol in humans.

Finally, I want to thank two of the nicest and most capable people around, without whom this volume could not have been completed, namely Gloria Senior and Mary Sanders.

PREFACE

It was emphasized in Volume 1 of this review that the National Heart, Lung and Blood Institute (NHLBI) and the American Heart Association (AHA) control nearly all medical research on heart disease, have long been committed to the diet-blood cholesterol-coronary heart disease (CHD) relationship, and have published numerous statements beseeching researchers nationwide to stop debating the issue and accept the NHLBI/AHA dogma. As noted in the present volume, NHLBI has even defined a good scientist as one who demonstrates no "skepticism" of its dogma. This unholy combination of power, narrow-mindedness demagoguery ans self-righteousness has resulted in the most stupendous waste of time, money and manpower in the history of medicine. Why was it happening?

It is painfully evident that the primary epidemiologists promoting the diet-cholesterol-CHD relationship have little or no academic training in the scientific method and scientific reasoning. They are physicians who apparetnly believed that all there is to being a scientist is to "do science." Such a state-of-affairs would not be disasterous if trained scientists were teamed with the physicians and made sure that the studies and documentation were properly conducted and prepared, respectively. Unfortunately, that has rarely been the case, as evidenced by the writings of the epidemiologists. However, imcompetency does not comprise the major reason why the diet-cholesterol-CHD relationship is being promoted in the face of insurmountable unsupportive evidence, although it is certainly a contributing factor.

The massive literature on the diet-cholesterol-CHD relationship has resulted in a great accumulation of data. Often data are presented properly but analyses, interpretations and conclusions are quite improper. Often data are presented in ways that conceal their true characteristics and importance. And often specific and important data are simply omitted, allowing completely distorted conclusions to be drawn. In fact, there is no doubt that a great deal of data is routinely presented or omitted in ways which deceive, rather than enlighten readers. Further, many epidemiologists introduce biases in their writings as though it were a perfectly acceptable means of expressing scientific findings. In sum, the relevant literature is permeated with fraudulent material that is designed to convert negative evidence into positive evidence with respect to the lipid hypothesis. That fraud is relatively easy to detect, although the process is extremely time-consuming because the literature is enormous and reports describing a single study are often numerous and distributed far and wide. The present volume's primary purpose was to uncover that fraud en masse. While that goal was achieved, the question, "why was it happening," was less satisfactorily answered.

Volume 1 and 2 comprise the largest, the most comprehensive and the most critical review of the diet-cholesterol-CHD literature ever performed. Would that the process of exposing the fraud and its promoters be accomplished in many fewer pages. Unfortunately, it cannot. If only a few studies, such as the Framingham and Seven Countries studies were shown to be fraudulent, readers would likely conclude that one should not condemn a barrel of apples because of a few rotten ones. It was necessary, therefore, to show that some degree of fraud is evident in nearly all of the studies used by NHLBI and AHA to promote the lipid hypothesis. But despite the size of this review, much more fraud could have been documented because it is never ending. However, one eventually reaches a point after which further documentation becomes merely another unnecessary "nail in the coffin."

NHLBI and AHA handpicked their own staff and supporters to put together a mass of review reports that the medical and lay communities were led to believe were independently generated. The more prominent of these reviews were the 1984 Consensus Conference report, the 1988 Food and Nutrition Board report, and the 1989

Surgeon General's report. There were a great many "experts" involved in their preparation and there obviously were great expenditures of time and taxpayers' money. In contrast, the present review (Volumes 1 and 2) was prepared by one individual over a five year period at a cost to the taxpayer of zero dollars. Yet, all of the reviews of NHLBI and AHA do not account for more than one-tenth of the material in the present review and none are one-tenth as objective.

These volumes do not constitute and should not be construed as suggesting a condemnation of medical research in general. The fraud described was perpetrated by members of NHLBI, AHA and the many researchers who were willing to accept these agencies' dogma in return for continuous research funding. This writer is sympathetic with some of the latter who apparently concluded that they had little practical choice. However, those who commit scientific fraud must be prepared to accept criticism. As President Harry Truman once said, "If you can't stand the heat, stay out of the kitchen." A rogues' gallery of many of the most prominent and influential promoters of the fraud was shown earlier on pages iv to vii. A great deal of that fraud is presented in detail in this volume.

Volume 1 aroused anger from some quarters, as expected, and it received considerable praise from other quarters. The present volume will greatly polarize those feelings but that cannot be helped. The lipid hypothesis promoters have little regard for scientific honesty and they will defend their position at all costs by denying the validity and legitimacy of their opposition and refusing to debate. They are dedicated to preserving their egos and the gigantic financial empire created by the National Cholesterol Education Program. This writer, on the other hand, is dedicated to the people whose money supports the entire medical research community. Americans deserve to know how and why their taxes have been wasted. And clinical physicians deserve to know how and why they have been manipulated.

Russell L. Smith, Ph.D.

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1. INTRODUCTION

"Epidemiologic data on diet is a risky analysis because it seems that people who eat the most cholesterol and the most fat have the lowest blood cholesterol levels. People who eat the most calories seem to weigh less than those who eat the least. This is just the opposite of what one might expect."

(William Castelli, 1987[1179])

"There is overwhelming data that...you will live a little longer by following a better diet."

(William Castelli, 1989[3377])

"In my opinion, to this day, there is no study that shows a survival benefit from cholesterol reduction in asymptomatic men or women."

(William Castelli, 1990[3337])

"There is no justification for suggesting the public be exposed to more articles on the lack of scientific proof about blood cholesterol levels."

(Gordon Bendersky, 1987[2224])

Volume 1 of this review focused on an overview of the entire diet-blood cholesterol-coronary heart disease (CHD) issue. For example, it summarized the results of hundreds of prospective studies, between and within population studies, clinical trials and dietary experiments. The abstract for that volume follows:

"The National Heart, Lung and Blood Institute (NHLBI) and the American Heart Association (AHA) are involved in a massive campaign to convince all Americans that diet is a major cause of high blood cholesterol level and CHD. This report is a comprehensive and critical review of nearly 1700 medical research articles and reports, including food consumption trend studies, prospective investigations, the major between and within population studies, dietary cholesterol and fat experiments and clinical trials. In addition, literature relating CHD with alcohol, exercise, aspirin and fish oils is also critically reviewed. Also, a detailed discussion of the effects of cholesterol-lowering and cholesterol-lowering agents is presented.

"It is concluded that diet is, at best, only negligibly related to CHD, particularly for the vast majority of persons. Moreover, all the major epidemiological studies reveal an extremely weak relationship between blood cholesterol and CHD, often showing an increase in annual CHD rate of less than 1% across most or all of the blood cholesterol range. This fact alone indicates that diet cannot possibly have more than a very minor influence on CHD.

"A major reason why diet and blood cholesterol appear to be important determinants of CHD is because data are often presented in unorthodox ways, weak data are often interpreted as 'powerful,' and numerous reviews of the literature are invariably incomplete and strongly biased. In fact, the majority of relevant literature is either ignored or erroneously cited as supporting the diet-blood cholesterol-CHD relationship. While NHLBI and AHA frequently state that the evidence 'overwhelmingly' supports the relationship, clearly the reverse is true. It does not seem possible that objective scientists without vested interests could interpret the literature as supportive."

LOGIC VS THE NHLBI/AHA ALLIANCE

During the preparation of Volume 1 this writer was continuously shocked by the low quality of epidemiologic research literature. It was initially thought that this condition was due entirely to the relatively poor academic training in the scientific method enjoyed by many physicians-turned-epidemiologists. However, by the time Volume 1 was completed, it became clear that another and more insidious factor was involved. There is an unmistakable, massive amount of fraudulent material that seems to be orchestrated to compensate for the abundance of evidence that does not support the alliance's lipid hypothesis. And therein constituted the primary reason for preparing the present volume.

The political and financial power of the NHLBI and AHA team, often referred to in this volume as the "alliance," is enormous and without equal. And because the alliance has substantial credibility in the eyes of the public and most practicing physicians, it has become a juggernaut, able to use its power and prestige to suppress a great body of unsupportive evidence and even defy the most fundamental tool of scientists, logic. The defiance of logic is perhaps science's worst enemy because there can be no progress in its absence. For example, as will be seen in Chapters 4 and 6, large prospective studies show no differences in CHD death rates between vegetarians and nonvegetarians, and they show no relation between CHD rates and intakes of fat, saturated fat or cholesterol. Further, autopsy studies show no differences in severity of atherosclerosis between vegetarians and nonvegetarians. That is the bottom line.

The vegetarians studies represent the natural experiments of the effects of diets on atherosclerosis development and, therefore, the ultimate proof that neither diet nor blood cholesterol level is a cause of atherosclerosis. The reader should think about this for a few moments. What is the point to all of the massive research that has been conducted for many decades when we already know from vegetarian studies that changing one's diet and reducing one's blood cholesterol level does not alter CHD rates in the real world? These are superordinate data that cannot logically be set aside in favor of subordinate data such as those derived from clinical trials. In fact, blinded and randomized clinical trials rarely show benefits of cholesterol-lowering and when they do (e.g., the Lipid Research Clinics and Helsinki II drug trials), the "benefits" are trivial, i.e., 0.23% and 0.28% reductions, respectively, in CHD event rates per year. Even these small benefits may have been the result of improper procedures such as violations of the blind diagnosis procedure (see Chapter 7). When the reader completes this volume, he/she will find so many examples of systematic fraud that he/she may find it difficult to believe anything the alliance prints.

To further set the stage for this volume, consider the two most important concepts of the alliance. Total blood cholesterol is said to be "powerfully" correlated with CHD and low density lipoprotein (LDL) is said to be the atherogenic component of total cholesterol. Yet, in 40 years of several hundred Framingham reports, this writer has found neither an actual correlation coefficient published for either total or LDL cholesterol nor a figure showing the CHD mortality and/or morbidity rate as a function of LDL level.[a] The reader should ponder these facts for a few moments--no correlation coefficients and no LDL-CHD rate figures in 40 years to support the purported "powerful" relationships. Why? Did the Framingham investigators forget to publish those data? Hardly! Did they consider those data unimportant? Hardly! The

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[a] Referring to the open literature, i.e., medical journals.

only reason for the blatant omission of such important supportive data over a 40 year period is that they were and continue to be embarrassing to the lipid hypothesis.[a]

Examination of published Framingham data (e.g., Figures 3-25 and 3-26 in Chapter 3) indicate that the correlation between CHD and total or LDL cholesterol is probably under 0.3. The objective and statistically sophisticated scientist would consider these correlations as unrepresentative of cause and effect relationships and would analyze the associated data base to find reasons why the observed correlations occurred at all. Although Framingham investigators never directly suggest that the correlations are very low, they indirectly strongly imply such a state-of-affairs by defining atherosclerosis as a multifactorial disease and spending decades seeking new correlations with new factors. Castelli[2598] recently announced that the Framingham study had thus far discovered 200 factors correlating with CHD. The reader should ponder <u>that</u> fact for a few moments.

In addition to the facts that dietary cholesterol has negligible effects on blood cholesterol in most people and that saturated fats have trivial to modest effects, Castelli[1179] emphasized, "people who eat the most cholesterol and the most fat have the lowest blood cholesterol levels." Therefore, the correlation between diet and blood cholesterol level cannot be greater than 0.5. If we assume a correlation of 0.5 and a likely correlations of 0.3 between blood cholesterol and CHD, then diet cannot at maximum explain more than (0.5^2 X 0.3^2 = 0.225 or) 2.3% of the variance due to CHD. This relationships is totally negligible and it is consistent with results from vegetarian studies.

Consistent with the fact that Framingham investigators have withheld the mathematical and graphic relationships between LDL and CHD event rate is the fact that they have also dismissed the ratio of LDL to HDL cholesterol in favor of total to HDL cholesterol. If indeed LDL is "bad" and HDL is "good" and both are related to CHD in a graded fashion, then the theoretically most important ratio should be LDL to HDL. But that ratio is not used, indicating again the weakness of the presumed relationship between LDL and CHD.

In sum, total cholesterol correlates weakly (< 0.3) with CHD events rates and it is composed of LDL (which apparently correlates even more weakly), VLDL and IDL (which apparently do not correlate at all) and HDL (which correlates negatively), and yet it is total cholesterol that is used to relate lipids with CHD events. If anyone can make theoretical or even logical sense out of this, the present writer would be happy to listen.

Finally, it must be emphasized that the alliance claimed in 1971[705] and again in 1991[3361] that a diet clinical trial was and continues to be "unfeasible" because it would require more than 100,000 individuals for 7 to 10 years just to show a <u>statistically</u> significant effect of diet on CHD rates (Chapter 7). The reader should ponder <u>that</u> fact for a few moments. If so many individuals must be followed for so many years just to show a very small, statistical effect of diet, then by definition, diet cannot possibly have practical effects on CHD rates. There is no other conclusion to be drawn from the alliance's rationale for rejecting the conduction of a diet trial.

Given just the facts presented in this subsection, anyone with good inductive reasoning must conclude that the relationship between diet, blood cholesterol and CHD

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[a] Moreover, in other contexts the alliance admits that LDL <u>per se</u> cannot even enter the arterial wall (Chapter 8).

is weak to nonexistent and that, therefore, the National Cholesterol Education Program (NCEP) has no justification whatsoever. Unfortunately, despite the logic, attitudes developed over many years of virtual brainwashing by the powerful and prestigious alliance are too strongly rooted in the psyches of large numbers of people to be altered by mere logic. The foregoing facts were probably heretofore unknown to most people and may have shocked many readers. Nevertheless, it is likely that most will still set them aside in favor of the redundant subordinate data that have been presented them over so many years. This volume, therefore, critically reviews that subordinate data and shows that they do not logically yield the conclusions drawn by the alliance. In effect, superordinate and subordinate data are consistent in revealing no practical relationships between diet, blood cholesterol and CHD.

In attempting to find a colorful analogy that illustrates the magnitude of the fraud inherent in the epidemiologic literature, what came to mind was a long parade of horses walking continuously around an oval track, excreting a never ending array of droppings. The droppings must be continuously gathered and set aside in order to see the track. To a large extent, this review involved the formidable task of separating the alliance's enormous number of droppings from the scientific facts. There is no doubt that the lipid hypothesis will one day be thoroughly rejected because mortality and morbidity statistics will so overwhelmingly deny the utility of cholesterol lowering by either diet or drugs. In the meantime, however, like the great and costly catastrophe that followed the initiation of prohibition, the NCEP is now unleashing yet another huge costly catastrophe.

The leading edge of the NCEP catastrophe is the elderly population. From 1977 to 1987 Framingham investigators Kannel and Castelli have stated repeatedly that there is no relationship between total blood cholesterol and CHD, particularly among men even after 30 years of follow-up. They have also acknowledged that many other studies revealed the same findings.[a] While Castelli has since (1989) reversed his stance on this issue, i.e., "Serum cholesterol has emerged as a primary risk factor in patients older than 65 years"[2292] and "The data now suggests...that the older you get, the greater the impact of cholesterol,"[2660,b] he used the same 30-year follow-up data as his source and presented no data showing a significant relation between total cholesterol and CHD among the elderly, especially for the alliance's key target population, males. Despite the massive negative evidence, leading alliance members such as Rifkind,[2660] Lenfant,[2837] Goodman,[2837] Kwiterovich[2270] and Castelli[2660] encourage physicians to give cholesterol tests to the elderly and treat them with drugs. Indeed, 59% of those currently taking cholesterol-lowering drugs are over 60 years of age.[2726] In effect, the population that can least afford the costs of tests and drugs and that least needs such tests and drugs is the very population that is bearing the burden of such costs. This is perhaps the most inhumane characteristic of the alliance and its NCEP and it is rather powerful evidence of their real motives--to generate huge incomes for the medical and pharmaceutical industries. (See Chapter 9 for a more detailed discussion of this subject.)

The critical nature of this review will not win friends or influence the people who are committed to the alliance's program. The fraud is so blatant and so pervasive that it was considered necessary to take some liberties with the usual staid rhetoric of a scientific review and inject stronger language to emphasize the problem. Those who

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[a] 453,523,787,1046,1083,1091,1366,1531

[b] 3166,3167,3168,3169,3243,3244,3245 Castelli[2660] referred to the idea that cholesterol is no longer important among the elderly as "the old myth." If it were a myth, Castelli was most certainly its prime promoter.

are the targets of this language will disregard the validity of the criticisms and focus exclusively on defending their egos. Bad work, whether performed by incompetence or fraud, will be defended without regard to the merits of criticisms. Anger will prevail over the need to pursue scientific discourse.

Lest the reader think "strong" language should be out of place in a scientific document, he/she should be reminded that scientific fraud is far more out of place. Furthermore, the language employed in this document will be found by readers to be moderate compared to the writings of many alliance members. For example, one author reviewing another's work made the following accusations in the same article: He made "repeated distortions," "misrepresentations" and "blithe remarks"; he "ignores data," makes "fantastic pronouncements" and is "obsessive"; he "selects and omits facts," and "commits gross errors"; he is "either ignorant or "deliberately falsifies"; he has "fixations"; "writes triumphantly," "grossly fabricates," "imagines things," "produces inventions," "pompously states" and "completely ignores data"; and demonstrates "tissues of untruths." The person who uttered those descriptors was none other than Ancel Keys,[1311] the principal founder of the diet-CHD concept.

THE DEVIL'S ADVOCATE AND RUSSELL L. SMITH[a]

The Advocate

"Dr. Smith makes things easy by placing himself on top of that ivory tower called purity and perfection. He demands the same accuracy and rigidity of intervention studies or epidemiological investigations that one would expect of chemical experiments carried out in a laboratory, as if humans could be characterized with the same precision as molecules. Unfortunately, or perhaps fortunately, humans cannot be so characterized. Studies on human populations will always be clouded by the many, many factors that influence the outcome and each other in complex ways. Therefore, one cannot and should not always expect very strong correlations between any relationship observed. There are some of us, indeed the overwhelming majority, who see death and illness from coronary heart disease all around us, who want to do something about it, and who will not despair at the sight of obstacles or the low likelihood of the perfect, decisive and uncriticizable experiment. We see many indicators appearing over and over again, all pointing in the same direction. Animal and saturated fat raises blood cholesterol and elevated cholesterol is linked to higher CHD mortality and morbidity. Perhaps the results of intervention studies are not terribly impressive individually. Perhaps each has one or more flaws. But, in spite of it all, when we put them all together we see an unmistakable pattern: reduce blood cholesterol by 1% and you reduce CHD events by 2 to 3%."

The Rebuttal

The issue is not perfection or the conduction of perfect experiments or epidemiologic studies. The issue is fraud. Criteria established for significance in clinical studies are changed after examining the data. Subjects from experimental and control groups are omitted on questionable grounds after a study is completed. Conclusions are drawn that do not logically follow from the data presented. Between countries studies comparing food intakes and CHD death rates make untenable assumptions that all countries have the same capability of gathering such statistics with equal accuracy. Literature reviews routinely and purposely misinterpret previous

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[a] The content of this section, much of it word for word, was offered to this writer by Olov Holmqvist[3387] of Sweden in anticipation of those who may criticize the nature rather than the substance of this review.

findings. Large numbers of studies presenting evidence counter to the lipid hypothesis are meticulously ignored. If results do not fit preconceived hypotheses, excuses are given that 'technical difficulties' prevented the expected outcome. If results do fit preconceived hypotheses, they are called 'conclusive.' This writer has conducted many experiments with humans and is well aware of the impossibility of performing the perfect study. Again, the issue is not perfection. The issue is fraud and it is perfectly exemplified in the statement that a 1% reduction in blood cholesterol results in a 2 to 3% reduction in CHD. That 'formula' is completely fraudulent and was purposely designed to mislead everyone."

REDUNDANCIES

This volume contains two types of redundancies. First, Volume 1 presented an historical overview of the beginnings of the diet-CHD concept and some major recent events. This volume greatly expands that overview and adds considerably more detail. Second, there are a number of instances in which a given statement or quote is presented in two or even three chapters. This redundancy was considered necessary or appropriate because the statement or quote was relevant in different contexts.

CHAPTER 1

Chapter 1 is unusually large for an introductory chapter. Hopefully, the reader will find it particularly valuable before proceeding to Chapter 2. Some interesting events that occurred after the publication of Volume 1 of this review (July 1988) are described. Relevant information not generally known to physicians and the public is presented. Some philosophical discourse regarding the benefits of conquering atherosclerosis is given. And most of all, the many processes and techniques used by the alliance to distort and even re-write the history of atherosclerosis research are discussed in some detail.

Chapter 1 is concluded with extensive profiles of Ancel Keys and Irvine Page, two major promoters of the diet-CHD hypothesis, and brief profiles of past AHA president Myron Weisfeldt and Postgraduate Medicine Editor Glen Griffin. (Profiles of 11 additional major diet-CHD promoters are presented in Chapter 10.)

1988 TO 1991

Volume 1 of this review was purchased by a wide variety of individuals, organizations and institutions in 11 countries, including nearly 60 universities and colleges. Among the purchasers were Agnes Heinz of the American Council on Science and Health (ACSH) and writer-reporter Thomas Moore. Heinz was in the process of preparing a consumer pamphlet designed to give greater balance to the diet-CHD controversy than had heretofore existed. The pamphlet was to be made available in September 1989.

Moore purchased his copy of Volume 1 in June 1989, three months before his Atlantic Monthly article, the Cholesterol Myth, and his book, Heart Failure, were published. He subsequently requested "picking" this writer's brain and literature files in order to gain "ammunition" with which to use in confronting the alliance in his upcoming medical interviews/debates. This writer agreed to Moore's request on one condition, namely that Moore would give proper credit to this writer and pioneers such as Edward Ahrens, George Mann and Michael Oliver who eloquently led the opposition to the "lipid hypothesis" for many, many years before Moore or Smith offered their Johnny-come-lately contributions. Moore agreed to that condition and telephone calls ensued thereafter.

Moore's article and book appeared in September 1989.[a] While this writer was unable to interest a single newspaper, television or magazine reporter in Volume 1 of this review and while apparently no newspaper, television or magazine reporter reviewed George Mann's excellent article, The Great Diet-Heart Scam,[2502] published in the May-June 1989 issue of 21st Century, Moore's article and book received enormous publicity throughout the lay and medical media. This writer found no evidence among all the newspaper and magazine articles that Moore had kept his promise. He appeared to have played the role of the Lone Ranger, accepting all the credit for exposing the "Cholesterol Myth" and, unfortunately for him, subsequently receiving much of the criticism from both the alliance and its many media supporters.

In late September 1989 the ACSH held a conference in New York and announced the availability of its pamphlet, The Facts and Myths about Coronary Heart Disease: a Consumer Guide.[2501] The president of ACSH, Elizabeth Whelan, and a panel of well-known physicians, including Michael DeBakey, Robert Olson and Eliot Corday, indicated that blood cholesterol level was, at best, a weak risk factor for CHD and that, therefore, major changes in diet are unjustified.[2503]

The media publicity given to Moore's and ACSH's publications was moderate to strongly negative. The following are examples of responses to Moore's publications.

Howard Hiatt[2496] of Harvard University stated in his New York Times article that Moore's book was "a failed undertaking" because it was "so intent on pointing at weaknesses."[b] The coordinator of the National Cholesterol Education Program (NCEP), James Cleeman, told the USA Today and the Los Angeles Times that Moore's publications contained "important errors, omissions and distortions."[2491,2494] Abrams[2494] reported that "Cleeman said he has tried to persuade journalists who have called his office about "The Cholesterol Myth" not to cover the topic. Two networks dropped planned segments based on the article after getting the federal perspective, he claimed." So much for the First Amendment as Cleeman views it.

The Los Angeles Times' Monroe stated that Daniel Steinberg "accused Moore of selectively using studies and statistics to prove his point."[2493] A USA Today news item quoted NHLBI as saying that "the article omits some major studies, misinterprets others, and raises issues already settled."[2489] The Medical Tribune cited LaRosa as saying that Moore was "not responsible."[2487] The Medical Tribune's Trager cited Castelli as stating that Moore "has several great distortions of fact. He obviously doesn't have a scientific background. For example, he can't tell the difference between cholesterol and its component parts.[c] Moore starts off with what he wants to prove, and then he twists the data to make it fit."[2485] Elsewhere[3337] LaRosa and

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[a] Although Moore holds neither an M.D. nor a Ph.D., his book was published by Random House which in 1988 had rejected this writer's book, The Cholesterol Conspiracy, on the grounds that this writer was not a physician. Apparently, then, Random House attributes greater scientific expertise to news reporters than to scientists with Ph.D.s.

[b] Of course, Hiatt was "so intent on pointing out weaknesses" of Moore's book that he failed to appreciate its strengths. The truth is that reviews that do not point out scientific weaknesses are little more than scientifically worthless.

[c] It is doubtful that Castelli is familiar with the component parts of cholesterol. Undoubtedly, Castelli was referring to lipoproteins but these are carriers of cholesterol, not components of cholesterol.

Castelli were quoted as saying that Moore's work "was pseudoscience" and "a silly thing," respectively. LaRosa indicated that "It was a careful but unfortunately inaccurate interpretation of some of the literature" and Castelli responded, "[Moore] obviously does not know anything about science."

In their fervor to discredit Moore, Castelli and LaRosa contradicted each other. Castelli[3337] said, "There is overwhelming data that...you will live a little longer by following a better diet." And LaRosa[2533] exclaimed quite emphatically, "has there been any reputable study that unequivocally shows that by changing your diet that you'll live longer? Unequivocally, NO!" In one year Castelli's "overwhelming data" appeared to have disappeared. In 1990 he said, "In my opinion, to this day, there is no study that shows a survival benefit from cholesterol reduction in asymptomatic men or women."[3337] So much for the "expert" critics of Moore.

Alfred Bollet,[2906] editor of Internal Medicine, said, "How can the author and the magazine's editors be so totally unaware of the changes that have been occurring in the incidence of IHD, thanks in large part to the very measures being derided? The public needs facts, and journalists must be free to say whatever they think, but freedom carries responsibilities as well..." Unbelievable words from those whose writings are models of irresponsibility.

Newsweeks' Cowley said that "The evidence linking diet, blood cholesterol and heart disease is actually broader and more powerful than Moore implies."[2490] (But, of course, Cowley was a bit influenced by the AHA's Daniel Steinberg.) And a New York Times editorial concluded that "It's probably safer to bet with the experts."[2492]

A newspaper food editor, Charles Britten interviewed Moore and, in his column, he urged Moore to have a cholesterol test. "And if it is as high as 250, I suggest he do something about it."[2488] Sound medical advice from a newspaper food editor?

The U.S. News and World Report's Findley and Silberner[2484] cited and supported a joint statement by the NHLBI/AHA alliance (discussed below). They said, "The debate is not about whether cholesterol promotes heart disease. It does. It is not about whether very high levels of blood cholesterol--in the upper 200s and above--pose such a serious risk that treatment is warranted. They do. And it is not about whether you should ever eat another steak or fried egg again. In moderation, neither will kill you. The cholesterol argument focuses on numbers and their real-life implication. Clearly, more people who are identified as being at risk need to nurture dietary discipline." Newspapers, including the Wall Street Journal, also cited the joint statement and some of its contents without rebuttals from those with opposing views.[2486,2487]

Bonnie Liebman[2498] of the Center for Science in the Public Interest said that Moore "whines" and is "wrong" and that "There is compelling evidence that a cholesterol-lowering diet can drastically reduce your risk of heart disease." Of course, Liebman cited only alliance members as her sources of information, i.e., Castelli, Connor, Sacks, Rifkind, Goor, Blackburn and Shekelle.

Although the criticisms of Moore's book were generally unfounded, none were quite as absurd as that of Glen Griffin,[3425] editor of Postgraduate Medicine. He compared those who doubt the importance of diet and blood cholesterol to CHD with those who still believe the world is flat. He said, "Mr. Moore is joined by a few doctors [apparently referring to Michael DeBakey, Robert Olson, Eliot Corday, et al.] who have their head in the sand when it comes to understanding that eating less cholesterol and saturated fat can decrease the risk of having a heart attack. The evidence is solid, as the many diet trials have shown--except the one Mr. Moore criticized, which was

the MRFIT." Since every knowledgeable person knows that all blinded and randomized trials which used cholesterol-lowering diets as the sole "treatment" have failed to reduce CHD events, it is obvious that Griffin has had considerable personal experience with the ostrich technique.

The January issue of Atlantic Monthly contained a number of letters-to-the-editor from alliance members who criticized Moore's article. The following are examples of their criticisms and this writer's comments (Moore's replies,[3378] although good, are not presented here):

NHLBI director Lenfant[3380] said, "It is astonishing to suggest that diet is not significant in determining the level of blood cholesterol or the risk of heart disease. The evidence for those relationships has been very recently and exhaustively reviewed by a committee of the National Research Council, almost all of whose members were unconnected with the NHLBI." Note first that he said, "almost all" of the members were unconnected with NHLBI. Of the 18 members, four were long-time prominent promoters of the diet-CHD hypothesis, i.e., DeWitt Goodman, Henry Blackburn, Henry McGill, Jr. and Richard Shekelle. The others were unquestionably handpicked to promote the same hypothesis. As is noted in Chapter 10 the committee reviewed only five of the more than 50 dietary experiments on cholesterol and all were irrelevant because they involved liquid diets. Moreover, there never has been a unifactor clinical trial acceptable to NHLBI that showed benefits of dietary changes on CHD.

Lenfant also said that "Measurement of blood cholesterol levels can be done accurately, as more than a decade's experience in the lipid-research clinics shows." But accuracy in the lipid-research clinics is not accuracy in independent labs and doctors' offices where most people are tested. They are known to be highly inaccurate.

Steinberg's[3381] letter said, "the results of some fourteen studies in which cholesterol levels were lowered by diet treatment or by drug treatment have shown that a 10% drop in cholesterol level will probably reduce heart-attack rate by 20%. That would mean preventing about 100,000 of the 500,000 fatal heart attacks that occur in the U.S. every year." This may well be the most incompetent and/or the most misleading statement ever published by someone purporting to be a scientist. No fourteen or any number of studies have ever shown a 20%, 15%, 10% or even 5% reduction in heart attack rate per 10% reduction in cholesterol. To fully comprehend Steinberg's complete distortion of the facts, consider the following table.[a] Assume that the treated group achieved a 10% reduction in cholesterol level.

	Number	CHD Events	CHD Rate	Rate Reduction	Risk Reduction
Control group	2,000	180	0.090%	--	--
Treatment group	2,000	144	0.072%	0.018%	20%

Note first that the principal endpoint in clinical trials is the combination of fatal and nonfatal heart attacks, of which the great majority of events are always nonfatal. Second, the difference in event rates between the two groups is a mere 0.018%. But using the alliance's "risk" concept which ignores the total number of persons in the

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[a] These data are very close to that observed in NHLBI's LRC trial published in 1984 and discussed in Volume 1 and Chapter 7 of this volume.

study and looks only at the difference in events, the "risk" reduction is a whopping 20%. Thus, the risk reduction is 1,111 times greater than the actual rate reduction. How can you distort anything more than this? Steinberg did. He then fraudulently applied the risk reduction, computed mostly from nonfatal heart attacks, to the 500,000 fatal heart attacks occurring annually in the U.S. This was a double distortion.

As Steinberg and all alliance members also know, no clinical trial has ever shown a significant reduction in fatal heart attacks as a result of cholesterol reduction, and of the few acceptable trials that showed benefits for nonfatal attacks, the benefits were quite trivial. It is difficult to conceive of two sentences that contain more distortion of facts and pure fabrication than that inherent in Steinberg's two sentences.

John LaRosa's[3382] letter stated, "Moore implies that the greed of pharmaceutical companies and physicians has played some major role and, in fact, have formed the basis for the financing of the 'coalition' [NCEP] and the exclusion of dissenters. He fails to mention, however, the strong opposition to many of the cholesterol-heart disease study results which came in years past from elements of the food industry." First, what has opposition from the food industry have to do with the greed of pharmaceutical companies and physicians? Second, by introducing an irrelevancy and failing to deny the validity of Moore's implication, LaRosa indirectly, effectively admitted that the greed of pharmaceutical companies and [some] physicians were driving the NCEP.

Henry Blackburn[3383] said, "At the Second International Conference on Preventive Cardiology, Richard Peto, one of the world's leading epidemiologists, concluded, based on data from MRFIT and other long-term dietary intervention trials that a 10% reduction in serum cholesterol is associated with a 20% decrease in coronary artery disease." If Peto is one of the world's leading epidemiologists, then it is no wonder that the state-of-the-art is in such disarray. Although Blackburn did not use the term "rate," it is implied in his statement. Again, no trial, particularly a diet trial, has shown anywhere near a reduction of 2% in CHD rate per 1% reduction in blood cholesterol. Peto, according to Science,[2907] is a mathematician/statistician who is the most prominent promoter of meta-analysis (see Chapter 2) who fails to understand that the flaws in individual clinical trials will not be eliminated by combining them into one data set, and who fails to understand how misleading the relative risk concept is in discussing benefits of cholesterol-lowering. Blackburn and his alliance colleagues also cannot or will not understand the deception.

David Dodson[3384] indicated that "NIH studies showed that cholesterol levels can easily be lowered 25% and studies of vegetarians at Harvard and elsewhere have shown cholesterol levels averaging less than 150. Those vegetarians follow the macrobiotic diet, similar to the traditional Japanese diet. These exceptionally low cholesterol levels are similar to cholesterol levels of the Japanese." The question is, where has Dodson been in the last 20 years? As shown in Chapter 4, of the many studies of adult conventional vegetarians, the mean cholesterol levels hovers around 180 to 190 mg. Dodson implies that the cholesterol levels of the American people can easily be lowered by putting them all on the microbiotic diet. Common sense should reveal that at least 95% of Americans will not become moderate vegetarians, let alone vegans. Moreover, the macrobiotic diet is not similar to the traditional Japanese diet; the latter contains meat, eggs, etc. but that is irrelevant. Finally, surveys in Japan show that mean blood cholesterol levels are about 200 mg, not 150 mg.

Ellis Neufeld[3385] stated that "The table of data deduced from the Mr. FIT report suggests that a person is three times as likely to die from heart disease if his cholesterol is greater than 245 mg." Not only is this an incomplete thought, the implication of this thought is most certainly not a deduction from the MRFIT data.

Three times as likely to die from heart disease if his cholesterol is greater than 245 mg than if it is what? 240 mg? 200 mg? 132 mg? Stamler et al.'s[263] 6-year data from the MRFIT screened cohort show a relative risk of 2.88 at cholesterol levels of 245-263 mg, compared to a relative risk of 1.0 at ≤ 167 mg but the rate difference was 0.59%. Thus, the data indicate that a persons' chances of dying of CHD increases 0.59%, not 188% (same as a relative risk of 2.88).

There were additional fraudulent letters-to-the-editor but the above examples provide ample evidence of the alliance's inept attempts to discredit Moore's article.

As stated in the Preface of Volume 1, "It is foolish for any scientist to give the impression that his work is error-free." In reviewing literally thousands of documents, "common sense demands that at least some errors must have been committed."[a] Thus, it would be expected that Moore's book would also contain errors. And indeed it does--many small errors and some major errors. But it cannot begin to challenge the quantity and magnitude of errors routinely committed by alliance members.

It is of interest to note that although both NHLBI and NCI purchased multiple copes of Volume 1 in early 1989, it has been ignored by NHLBI, as predicted on Page 1-7 of Volume 1, because it is unknown to the public and, therefore, poses no threat to NHLBI's dogma--yet.

Let us now review the alliance's formal response to the publications of Moore and ACSH.

THE NHLBI/AHA STATEMENT TO THE MEDIA

On November 14, 1989 the AHA and NHLBI issued a joint statement at the AHA meeting and held a press conference thereafter. The statement was entitled, "The Cholesterol Facts."[2500] A mass produced version of the statement was somewhat different[3349] and a very brief review of the statement by the Medical Tribune introduced material that was not in either of the two versions.[3350] For example, in response to critical assertions by Moore and the ACSH the statement was said by the Tribune to say that "These assertions...are false, based on omissions of facts, misreading and distortion, and apparent ignorance." These criticisms, probably uttered after the official statement was read, characterize the alliance perfectly, as this volume will show.

The AHA/NHLBI statement presented the presumed "most frequently asked questions about cholesterol" and then gave the same biased, irrelevant, incomplete, naive and outrightly boring answers that have been published hundreds of times by the same group of alliance members. It was clearly designed for the public at large because its content could not possibly impress knowledgeable critics. The questions are presented below, followed by a summary and critique of their answers.

Is High Blood Cholesterol a Risk Factor for Heart Disease? Will Lowering Blood Cholesterol Help Prevent Coronary Heart Disease?

The oral statement said, "the answer to these questions is a resounding and emphatic 'YES'." The printed statement was less emphatic, i.e., "strong scientific data provide positive answers to both of these questions." They indicated that epidemiologic, clinical, genetic and laboratory animal studies provided supportive

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[a] And two errors of some importance committed in Volume 1 are discussed and corrected in the present volume.

evidence. Two sentences were devoted to animal studies, which is about all the subject is worth. As shown in Chapter 2 in Volume 1 and Chapter 2 in the present volume, an atherosclerosis-like disease is not induced by diet in animal models similar to humans and the atherosclerosis-like disease induced in other animal models is not true atherosclerosis at all. Rather than being supportive of their position the animal studies, in fact, strongly indicate that true atherosclerosis is not induced by diet.

The epidemiologic evidence was said to include "comparison among various populations and prospective studies of individuals within populations." Chapter 4 in the first and present volumes amply demonstrate that the between population surveys were either totally confounded and naive or subject to enormous error (e.g., the Seven Countries study). Furthermore, the vast majority of within population studies obtained no support for the diet-blood cholesterol-CHD relationship and the few that did offer support, presented extremely weak evidence based on tenuous baseline data and untenable assumptions about the stability of baseline data over many years.

The AHA/NHLBI statement maintained that "clinical trials have shown that lowering serum cholesterol levels by diet or drugs decreases the subsequent incidence of coronary heart disease." In addition to the fact that no diet clinical trial acceptable to either the alliance or its critics has demonstrated a decrease in incidence of coronary heart disease, the statement omitted the fact that the vast majority of clinical trials failed to demonstrate benefits of lowering blood cholesterol, as shown in Chapters 6 and 7 in Volume 1 and the present volume.

None of the above AHA/NHLBI "answers" were accompanied by references. It was said that "The very large body of evidence on these questions has been reviewed comprehensively in the recent report on diet and health from the National Research Council-National Academy of Sciences" (see Chapter 9 for a critique of this "comprehensive" report, generated by NHLBI/AHA members). However, four relevant studies and one irrelevant study were briefly offered as evidence, namely the Framingham Heart study, the MRFIT, LRC and Helsinki II trials and the research by Brown and Goldstein on LDL receptors.

The statement presented a curve "adapted from a 1971 Framingham study" report by Kannel et al.[1376] The curve showed a sharp increase in CHD incidence per year as blood cholesterol rose from 100 mg to 300 mg. This curve was not presented in the Kannel et al. article and it could not be generated from the data presented in that article. The curve is totally unrepresentative of the Framingham data typically presented by alliance members which show almost no increase in CHD incidence up to 295 mg. Thus, AHA/NHLBI presented false information in their statement, citing an old Framingham report and ignoring recent data in the process.[a]

In discussing the MRFIT study the alliance ignored its failure to show that reduction of three risk factors reduced CHD incidence and focused on the prospective aspect of the 360,000 plus men screened for that trial. And while the fabricated curve presented for the Framingham study used a vertical scale of CHD incidence per 1,000 per year, the sharply increasing curve presented for the MRFIT data used a scale which involved a six-year period, thus exaggerating the trend six-fold.

Just as AHA/NHLBI cited a reference that provided no data which could generate the Framingham curve, they also cited an incorrect reference for the MRFIT curve, namely, the 1982 MRFIT Research Group article which described the failure of the

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[a] Other alliance members such as Gotto and Grundy, also published this erroneous curve (see Chapter 10).

clinical trial to show benefits of cholesterol, blood pressure and smoking reductions on CHD incidence.[851] The correct reference was the 1986 Martin et al. article.[525] Even so, AHA/NHLBI performed a somewhat sloppy job in reproducing the original figure and, in addition, further exaggerated the upward trend in CHD incidence by that sloppiness and by expanding the vertical CHD incidence scale and contracting the horizontal blood cholesterol scale.

The citation of Brown and Goldstein's work on LDL receptors had no direct relevance to the questions posed above.

AHA/NHLBI cited the LRC and Helsinki II trials as demonstrating that cholesterol lowering resulted in 19% and 34%, respectively, fewer CHD "events" when, in fact, the actual rate differences between the groups were only 1.7% and 1.4%, respectively. And, as usual, the alliance failed to note in its statement the fact that overall death rates were exactly the same within the treated and control groups in both trials. Moreover, the alliance again presented the incorrect and grossly misleading statement that the two trials showed that a 1% reduction in blood cholesterol results in a 2% to 4% reduction in CHD "events."

Will You Live Longer If You Modify Your Cholesterol Level?

In responding to the criticisms that neither the LRC nor the Helsinki II trials increased life expectancy, AHA/NHLBI stated that "these two major clinical trials were not designed to demonstrate a reduction in total mortality. They were designed only to show a reduction in the incidence of total coronary disease." As noted elsewhere in these volumes, such a statement is, of course, pure rationalization. The NHLBI director during the on-going LRC trial, Robert Levy, stated on more than one occasion before the LRC results were published that trial outcomes based on "soft" (nonfatal CHD events) endpoints are "criticizable,"[288,300] so why would his trial be designed only to show a reduction in the incidence of soft endpoints? Moreover, AHA/NHLBI member Jeremiah Stamler stated unequivocally that "...all causes of mortality is the acid test."[1600] While Stamler was referring to the fact that a true decrease in CHD mortality should be reflected in a concomitant decrease in all causes of mortality, the principle also applies to clinical trials. In both the LRC and Helsinki II trials there were more (albeit, not significantly so) CHD deaths in the control groups. Apparently, these differences were necessary to achieve significance between groups when the endpoint was the combination of fatal and nonfatal MIs. Yet, these differences were not reflected in the all-cause mortality rates.

The AHA/NHLBI statement went on to say that "a reduction in total mortality was seen, however, in three recent clinical studies," i.e., the Coronary Drug Project (CDP), the Oslo diet and anti-smoking trial and the Stockholm study. The CDP itself revealed no significant effects of cholesterol lowering in five experimental groups on CHD or all-cause mortalities. A follow-up of one group which was administered nicotinic acid showed a significant decrease in all-cause mortality 9 years after the trial terminated. However, the alliance failed to indicate 9-year outcomes of the remaining four groups whose cholesterol levels were also reduced, particularly the group administered one of the most frequently used drugs in the world, clofibrate. Such selective reporting of results reflects the on-going bias of the alliance.

With respect to the Oslo diet and anti-smoking trial, it was reported in a follow-up 3.5 years after the trial was terminated that the treated group experienced significantly fewer total deaths. Since this trial included the reduction/elimination of smoking, as well as cholesterol-lowering, it was thus confounded and it cannot logically be deduced that the outcome was the result of cholesterol-lowering.

The follow-up of the Stockholm trial, first published in 1980,[840] was published in 1988 by Carlson and Rosenhamer.[2263] In view of the fact that it was an unblinded study, its results are highly suspect and cannot be taken seriously.

In concluding their response to the above question, AHA/NHLBI stated, "Finally, it should be noted that the 30-year follow-up of the Framingham Heart study showed that those with higher cholesterol levels died at an earlier age and those with the lowest cholesterol levels lived the longest." Not only did the alliance fail to cite a reference for this statement, the 30-year study to which they referred (Anderson et al.[1273]) yielded more inconsistent than supportive data. For example, while the statement was true for men aged 31 through 39 years, it was either not true or conflicting for age groups 40 to 47, 48 to 55 and 56 to 65. In addition, the results were unsupportive or inconsistent for three of the four age groups for women and partially inconsistent and generally unimpressive for a fourth. Interestingly, they omitted this assertion in their printed version of the statement.

Does Cholesterol Management Matter If You Already Have Coronary Heart Disease?

Because the CDP was a secondary trial, AHA/NHLBI used its 9-year follow-up study as evidence that cholesterol-lowering is beneficial to persons with CHD. Since the study has already been critiqued above, it will not be addressed here. Additionally, AHA/NHLBI referred to animal models as evidence that blood cholesterol-lowering reduces atherosclerotic plaque and such results will also not be addressed here because, as previously noted, inappropriate animal models were used and the "plaque" was not the plaque found in the human disease.

The AHA/NHLBI statement cited three clinical trials which purported to show "retardation or regression of atherosclerotic plaque in humans, i.e., the NHLBI Type II Coronary Intervention study, the Leiden Intervention trial and the Cholesterol Lowering Atherosclerosis study (CLAS). As emphasized in Chapter 6 of Volume 1, the NHLBI Type II study failed to find significant effects of cholesterol-lowering and the Leiden trial was without a control group. Neither study should be offered as scientific evidence for anything. The CLAS trial, authored by Blankenhorn et al.,[760] was critiqued in detail in Chapter 7 of Volume 1 and is further discussed in Chapter 7 of this volume. It was unimpressive at best and totally without merit at worst. The fact that it was funded by the Upjohn Company, makers of one of the two drugs (colestipol) used in the study, makes the results of the study suspect on conflict-of-interest grounds.

The reader should be reminded that (1) all alliance members have stated innumerable times that there is no threshold below which atherosclerosis does not progress and (2) vegetarian studies show little or no evidence that vegetarians have lower incidence of CHD than nonvegetarians. It is illogical, therefore, to suggest that the relatively little cholesterol-lowering that occurred in the CLAS study would cause retardation or regression in plaque. Moreover, all such angiographic studies use measurements based on subjective judgments which are notoriously error-prone.

Does Diet Make a Difference?

In responding to critics which stated that "a definitive trial of blood cholesterol reduction by diet and its effect on heart disease has never been conducted," AHA/NHLBI replied that "In 1968, the Arteriosclerosis Task Force of the National Heart Institute decided against such a trial because of a number of potential problems, including the difficulty of maintaining a blind study with an extremely large group of participants over a long-term period, the probable mobility of the participants, and the difficulty of recruiting a control group to ingest a cholesterol-raising diet for many years. The cost, which was expected to be huge, was another determining factor."

But in point of fact, as discussed in detail in Chapter 7 of this volume, some of these "problems" were fabricated and the remainder were equally applicable to a drug trial. In effect, the "problems" were artificially generated to justify the rejection of a diet trial in which the alliance had no faith in the first place. For example, one of the reasons for rejection by the NHLBI Task Force, not indicated in the 1989 statement, was that a diet trial "might well fail to obtain the desired definitive scientific answer from this huge undertaking."[705] Finally, the alliance cited the 1968 National Diet-Heart study final report as its reference when the Task Force report was actually published in 1971.[705]

As alternative data, the AHA/NHLBI statement cited the Seven Countries study, the Japan-Honolulu-San Francisco study, the Zutphen study, the Honolulu Heart Program, the Ireland-Boston study, the Western-Electric study and the United Nations Food and Agriculture Organization study. While the alliance claimed that these studies produced "impressive" results, Chapter 4 in Volume 1 and the present volume demonstrate that these studies were replete with design problems and extraordinarily biased analyses. These problems and biases are too extensive to even summarize briefly here. However, it should be noted that "Studies by the United Nations' Food and Agriculture Organization and the World Health Organization" were, in fact, the between population studies conducted mostly by alliance members (Chapter 4 in Volume 1) using data from the UNFAO and WHO. (AHA/NHLBI cited Stamler and Shekelle[1565] as providing an "extensive" review of these studies; in fact, they reviewed only one, a study by Stamler.[1313]) This attempt to attribute supportive diet-CHD research findings to the UNFAO and WHO is nothing less than purposeful deception.

It is noteworthy to mention one major contradiction. Both the oral and printed statements maintained that "Studies demonstrate unequivocally that high intakes of dietary cholesterol will significantly raise serum cholesterol levels in the majority of people." Yet, one year later (1991) NHLBI director Lenfant said, "some people are strongly affected by dietary cholesterol, but the majority is not."[3267]

Should Your Age Or Gender Change Your Approach To Cholesterol Control?

In response to criticisms that clinical trials with women have not been conducted, AHA/NHLBI held that there are "extensive data from epidemiologic studies that link elevated cholesterol levels in women to increased heart disease risk" and that experimental studies show that "diet has the same effects on blood cholesterol in women as in men." This reply is partially false and partially deceptive. The only American prospective study of any consequence which includes women is the Framingham study and in 1987 Anderson, Castelli and Levy reported a nonsignificant relationship between blood cholesterol level and CHD with 30 years of Framingham data.[1273] Moreover, reviews by Bush et al.[1679,1783] and Dittrich et al.[1649] revealed no relationship between LDL levels and risk of CHD in women up to age 65.[1783] (See Chapter 9 in Volume 1 and the present volume.)

The AHA/NHLBI statement cited a review by Bush et al. as supporting the need for women to lower their blood cholesterol levels. Yet these authors concluded that "The few studies that have examined the association of total cholesterol with CHD occurrence and mortality in women have consistently shown that...clearly elevated risk for CHD in women is evident only at relatively high values of total cholesterol (i.e., > 260 mg).[1618,a] Elsewhere, Bush stated that LDL level is not related to CHD in women until after age 65.[1679]

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[a] Note also that increased "risk" is an exaggeration of "rate."

The 1989 oral statement cited a 1989 article by Castelli et al. as "the most recent analysis of the Framingham data...indicating that total cholesterol is a coronary risk factor for elderly individuals. But in the updated printed statement, that article was omitted and instead a 1978 article by Kannel and Gordon was cited as showing that a "high LDL is associated with an increased risk of CHD at all ages through age 82." As will be seen in Chapter 9, Framingham investigators repeatedly indicated no relationship between total cholesterol and CHD among the elderly throughout the 1970s and most of the 1980s.

One year after the AHA/NHLBI oral statement, one of the most prominent AHA spokespersons, Scott Grundy, noted that older persons and women have yet to be evaluated in clinical trials and asked whether they should be treated "even if a primary prevention trial should prove that reduction of serum cholesterol levels will decrease CHD risk in older men and [all] women."[3083] Because older people have competing illnesses, they "have little to gain from their therapeutic reduction of cholesterol levels. Older people may be more susceptible to side effects of lipid-lowering drugs than younger individuals, and for many older people, drug therapy would result in a serious financial burden." As indicated in Chapter 6 a clinical trial with older persons and women is in its initial phases. However, the matter is academic because older people and women are now prime targets of cholesterol-lowering and they constitute the majority of people on cholesterol-lowering drugs."[2726]

Are Cholesterol Interventions Cost-Effective?

AHA/NHLBI stated that low-fat, low-cholesterol diets "are often less expensive than foods high in fat and cholesterol." Such a statement is absurdly misleading. Almost all foods "high in" or "low in" specific substances cost more than regular foods. Many of the foods that are being produced by manufacturers as "heart saving" foods will cost more than regular foods. There is little doubt that the total cost to Americans will be many billions of dollars per year. AHA/NHLBI also cited critics as indicating that the cost of cholesterol-lowering drugs, blood cholesterol tests, physician costs, etc., will be "enormous." Such an adjective is unquestionably an accurate descriptor. However, AHA/NHLBI, argued that "the critics disregard the fact that society has to compare the cost of cholesterol control with the cost of medical care for heart disease events such as heart attacks or strokes. This provides a more accurate measure of the true cost of intervention."

The AHA/NHLBI argument is totally without merit for two reasons. First, it assumes that the costly intervention program will have a major impact on the even more costly medical treatment program. Virtually all research indicates that it will have, at best, a minor impact. Second, while there is a weak association between blood cholesterol and CHD, the evidence solidly points to no relationship between blood cholesterol and stroke or peripheral artery disease. In sum, the intervention program will be almost entirely additive to current treatment costs.

One of the most frequently used words by the AHA/NHLBI alliance is "overwhelming." Thus, they concluded that "this American Heart Association statement has reviewed the overwhelming evidence of the direct role of cholesterol in the development of atherosclerosis and coronary heart disease." No statement could be further from the truth. The statement, like all other publications by the AHA, reviewed highly selected studies, representing less than 1% of the relevant literature. Moreover, the AHA did not even review these studies with objectivity.

In short, the AHA/NHLBI statement could not possibly quiet the critics of the cholesterol intervention program because it suffers from the same failings which provoked the emergence of critics in the first place. In reality, however, the statement was obviously not designed to satisfy critics but rather to satisfy media

writers and broadcasters. The success of the NCEP will be measured not by its ability to reduce the incidence of heart disease but by its ability to convince the media to convince the public to accept a $60 billion additional medical burden per year.

One faithful purveyor of the alliance's dogma is New York Times writer Jane Brody. She published a two-part article which criticized Moore's book and praised the AHA/NHLBI statement.[2504,3243] In the process she made many errors of fact and reasoning. For example, in Part 1 she said that "In China, heart disease is rare and the life expectancy exceeds 70. The diet there is primarily based on vegetable foods." It is not only doubtful that the average life expectancy in China exceeds 70, the question may be asked, so what? Since life expectancy exceeds 74 in the U.S., her line of reasoning should conclude that the high meat and fat diet in the U.S. is to be preferred.

Brody also claimed in Part 1 that "only a few countries have higher rates of heart disease than ours." In point of fact, most of the advanced "Western" countries have higher rates, e.g., England, Wales, Ireland, Scotland, New Zealand, Norway, Denmark, Australia, Sweden, Hungary, Finland and Czechoslovakia. As amply discussed in Chapter 3 of Volume 1, it is anybody's guess as to what the rates <u>really</u> are in the poorer nations whose medical systems are relatively primitive and whose death certifications are often made by nonmedical personnel.

In her attack on Moore's book, Brody countered with information from "experts," "specialists" and "studies," all of which were members of (or derived from) the alliance, the only source she considers legitimate.

In Part 2 of her article Brody stated that "even with all the attention now being paid to the health effects of various fats and oils, Americans seem more confused than ever about what to eat to preserve their heart and blood vessels. Of course this is true because writers such as Brody constantly give their readers conflicting recommendations over time. She excuses these inconsistencies by stressing that "science is constantly evolving and new information may eventually challenge some advice given today" and by recommending that "The best you can do to protect your health is to base your choices on what is now known, and make modifications later if they become scientifically warranted." On the contrary, in view of the fact that alliance members have recommended wildly different diets over the last 30 years, it would be best not to take any of the recommendations seriously until they remain stable and prove beneficial over a period of years. Americans will constantly be confused because the Jane Brody's will constantly confuse them (see Chapter 9 for specific examples of Brodys columns).

NHLBI'S RESPONSE TO "THE CHOLESTEROL CONSPIRACY"

Several months before the present volume was printed this writer had a summary lay version (book) of Volumes 1 and 2 published entitled, "The Cholesterol Conspiracy."[3250] In his distribution of review copies the publisher mailed a copy to the new Secretary of DHHS, Louis Sullivan. Sullivan apparently did not read the book but sent it on to NHLBI Director, Claude Lenfant, for his response. This was a remarkable but common example of political tomfoolery; Sullivan appointed Lenfant to review the merits of a book that was highly critical of Lenfant and his institute. Lenfant's[3251] response to the publisher was the following letter:

March 28, 1991

Dear Dr. Green:

"Your letter to Secretary Sullivan enclosing your book on cholesterol has been referred to me for response.

The linkage between diet, blood cholesterol levels, and coronary heart disease has been examined in numerous expert reports, both in the United States and in other countries. Since 1973, more than 40 groups of scientists and health policymakers from other nations have recommended changes in population eating patterns with the purpose of reducing blood cholesterol. These recommendations have been summarized by Truswell (Truswell AS, The development of dietary guidelines, Food Technology in Australia 35:498-502, 1983) and in the report of the National Research Council, "Diet and Health: Implications for Reducing Chronic Disease Risk." The European Atherosclerosis Society has recommended a combined population and patient-based strategy for lowering blood cholesterol levels to reduce coronary heart disease risk in European nations, as has been recommended in this country. If there is a "conspiracy" at work here, it includes the vast majority of scientists in the United States and abroad who are knowledgeable about cholesterol.

The scientific evidence supporting the link between diet, blood cholesterol, and coronary heart disease is well summarized in the enclosed special report. We think the evidence is conclusive and mandates action to protect and improve the health of the public. The educational programs of the Institute directed to high blood cholesterol, high blood pressure, and smoking, which are firmly based on the scientific evidence, represent the kind of action needed to reduce illness and death from coronary heart disease. The presentation of the evidence about cholesterol in your book, on the other hand, is regrettably biased by selective quotations and ad hominem arguments.

I hope this information is helpful."

Sincerely yours,
Claude Lenfant, M.D.
Director

Lenfant dismissed the book in the same simple manner that the alliance dismisses all documents that are critical of their dogma, i.e., the book "is regrettably biased by selective quotations and ad hominem arguments." He used the same boring dismissal of Moore's Atlantic Monthly article, i.e., "Regrettably, his article contains so many errors and omissions that it may mislead the American public into becoming complacent about high blood cholesterol."[3380] Somehow, one fails to perceive that Lenfant is truly sorrowful.

This writer responded by submitting the following letter to Lenfant, not in the hopes of influencing him, which would, of course, be totally impossible, but rather to provide a pair of letters representing opposite sides of the issue to others.[3252]

April 9, 1991

Dear Dr. Lenfant:

"Your response to my book, The Cholesterol Conspiracy, was entirely predictable. You and your predecessors, Drs. Cooper and Levy, have ramrodded the diet-heart disease dogma down the throats of physicians and the public for many years, knowing full well that the evidence is extremely weak and that innumerable researchers strongly disagree with you. You have literally bought the allegiance of a great many medical

researchers who have long ago realized that if they don't explicitly support NHLBI, they will not be recipients of grants from that institution. You can publicly deny this fact but we all know that it is the absolute truth. Yes, you are right that if there is a conspiracy at work here, it includes the vast majority of scientists in the U.S. It does indeed include the vast majority because only a minority is willing to maintain its scientific ethics at the expense of losing research funds from the vast storehouse of money called NIH.

"Your dogma cannot indefinitely weather the storm of counter-evidence that is growing worldwide. The Japanese diet has grown richer in saturated fat and cholesterol over the last 30 years and yet their CHD mortality rates have steadily decreased during that period. No associations between food consumption and CHD mortality trends over the decades have been found also in Israel, Poland, Italy, Spain, Finland, Norway, Belgium, Sweden, Australia, New Zealand, Greece, Yugoslavia, England, or Switzerland. Everybody knows also that the French consume more fat, saturated fat and dietary cholesterol than do Americans, have higher blood cholesterol levels and smoke equally as much as Americans, yet have the second lowest CHD mortality rates among industrialized countries. And, of course, it is well known that animal fat consumption in the U.S. never increased during this century, as NHLBI would like people to believe, but has decreased steadily as vegetable fats progressively replaced them before, during and after the so-called CHD mortality epidemic among males. (Even Ancel Keys recognized this fact in 1953 when the CHD epidemic was well underway.) But even if that were not true, white women never experienced an epidemic so how can anyone logically claim that the "rich" American diet is bad for women?

"All of the above, of course, must be well known to you. You also must know that virtually every major prospective study has shown that blood cholesterol levels cannot predict with any significant degree of accuracy whether an individual will die of CHD. You also must know that virtually every major prospective study in the U.S. and abroad has shown that higher total mortality and/or higher cancer death rates occur at cholesterol levels below 180 mg than at more average levels. You also must know that the largest studies comparing vegetarians with nonvegetarians show essentially no differences in CHD mortality rates.

"Your sentence which begins, we think the evidence is conclusive..., contains three implications. First, the 'we' consists of a long series of conferences and reports which were all designed to appear that different agencies/groups had independently come to the same conclusion that a 'rich diet' causes CHD when, in fact, they were all controlled by NHLBI and the American Heart Association. Second, the word 'think' is reflective of the real lack of proof that diet is related to CHD. You are disrupting the entire American economy by costing the American people tens of billions of dollars for cholesterol tests, special costly foods, cholesterol-lowering drugs and additional drugs to get rid of the side effects of cholesterol-lowering drugs because you think the evidence is 'conclusive'--a word, incidentally, you have used rather prolifically to describe paltry evidence. And third, it will be proven one day that not only will the National Cholesterol Education Program be shown to have no influence on CHD morbidity or mortality in the U.S., there may ensue considerable harm to the American people via (1) excessively low blood cholesterol levels which have been advocated by you and many others (e.g., 150 mg), (2) the high consumption of polyunsaturated fats which were advocated by NHLBI and AHA for many years and still practiced by many Americans who have not been told that such diets may promote cancer, depress the immune system, etc. and (3) the progressively increased consumption of trans isomers which is occurring because NHLBI and AHA encourages industry to replace tropical oils and other saturated fats in foods with ever increasing amounts of hydrogenated oils.

"Your educational programs directed to high blood cholesterol, high blood pressure, and smoking are not firmly based on the scientific evidence as you say. I have a copy of

a letter from a recent president of the American Heart Association who admits that both the blood pressure and blood cholesterol guidelines are completely arbitrary and without evidence of their likely effectiveness. And as much as I detest being around smokers, the CHD and lung cancer mortality statistics do not in any way show the effects of the great changes in smoking habits that have taken place in this century.

"I will pit the evidence about cholesterol in my Cholesterol Conspiracy and larger scientific volumes (currently in 11 countries and nearly 60 universities) against your knowledge any time, any day. In fact, I will gladly pit my knowledge on the diet-blood cholesterol-CHD issue against the entire NHLBI staff. I have no doubts that you may all be fine physicians but I have yet to see any evidence that any of you have the academic background and/or working knowledge to be called scientist.

"I have used extensive quotes in my writings to avoid the potential criticism that I might have misinterpreted the statements of others. In am dumbfounded that you view quotes as a means of bias. They are, in fact, a proof of bias, as shown by two quotes of yours in the same year--1987. When Dr. DeBakey announced in 1987 that he found no relationship between blood cholesterol level and degree of restenosis in 15,000 bypass patients, you told a reporter that I don't think that surgery patients are a good model for understanding atherosclerosis.

"But when the Blankenhorn et al. study was published in 1987 (funded by NHLBI and a drug company), which used a relative handful of bypass patients, you said for the first time, we are presented with evidence regarding regression of lesions in humans.

"That, Dr. Lenfant, is true bias, with a capital B.

"Lancet editors not so long ago referred to the lipid-diet pushers as lipid evangelists. Werko in Sweden calls them lipid missionaries. I call you for what you really are--conspirators. Just as the ancient Egyptians were promised a glorious afterlife for a life of hard labor building the pyramids, you are promising the American people no CHD if they change their diets and/or take cholesterol-lowering drugs at a cost of countless billions of dollars. It is not happening and it will not happen. You had no more to do with the CHD mortality decline, which began in 1964, than had medicine to do with the decline in all the great infectious diseases. In fact, the CHD mortality decline began in 1953 in California--before risk factors were discovered and long before any program was initiated to reduce saturated fat and cigarette consumption and the prevalence of hypertension. And there is growing evidence that reported CHD morbidity is increasing. One day NHLBI is going to find it difficult trying to explain why so much money and time were wasted chasing windmills--while some of the more brilliant physician/researchers in the world have exhausted themselves trying to open your eyes. But you will probably be safely employed by a major pharmaceutical company when the cat is finally out of the bag.

"If genuine unbiased Congressional hearings were held today regarding the validity of the diet-blood cholesterol-CHD relationship, the American people would see your position for what it is, dogma rather than scientific evidence.

"Incidentally, copies of your letter and the present letter have been sent to a variety of individuals."

Sincerely,
Russell L. Smith, Ph.D.

Copies of the above letters were sent to Secretary Sullivan (as well as many other individuals). In addition, the following brief note was included:

Dear Secretary Sullivan:

"One does not consult a murderer about the merits of his own conviction. Similarly, one should not ask the director of NHLBI to evaluate the merits of a book that accuses NHLBI of grossly deceiving the American people. I would have hoped that you or someone in your office would have evaluated my book, "The Cholesterol Conspiracy," which reflects the attitudes of many physician/researchers in this country and abroad, rather than to pass it on to Dr. Lenfant.

"Hopefully, you will at least read the enclosed letters from Dr. Lenfant and myself."

Sincerely,
Russell L. Smith, Ph.D.

Sullivan apparently did not read the letters, however, which were again sent to Lenfant for reply. Lenfant said,

Dear Dr. Smith:

"Your recent letter to Secretary Sullivan has been referred to me for response.

"As I said in my response to Mr. Green, recommendations for changes in eating patterns to reduce blood cholesterol levels have come from a wide range of scientific bodies in the United States and abroad. Far from there being a conspiracy at work, the best scientific minds have independently examined the evidence and have concluded that dietary change is needed to protect the public health.

"I am enclosing a special report, published in the May 1990 issue of Circulation. It summarizes the scientific evidence concerning the relationship between diet, blood cholesterol, and coronary heart disease. I hope you find it interesting."

Sincerely yours,
Claude Lenfant, M.D.
Director

Lenfant's letter, of course, was strictly mechanical and unresponsive. The "special report" to which he referred, was reviewed in the previous section.

Shortly after receiving Lenfant's letter this writer received the following letter postmarked in Maryland but without a return address (a portion has been blanked to protect an individual):

"Your book is brilliant and reflects good thought. Many of the Department of Health and Human Services staff agree with you and in fact there are some National Institutes of Health staff who believe you are correct.

"Here are some tips for you. Don't attack personalities. Just stick to the science. Name calling detracts from the scientific debate and you will win the debate on cholesterol if you stick to the science.

"War (and debating) is more difficult if they are fought on many fronts. Stick to one argument and avoid challenging the science regarding smoking or hypertension. The latter two have a much stronger science base and cholesterol has been trying to hide behind these two for some time. Don't get sucked in.

"Don't advocate the use of one type of oil such as the tropical oil. It will appear as if you are being paid by that group or the Malaysians.

"Get all of your facts straight. Finland has had one of the highest coronary heart disease death rates and can't be included with countries such as France.[a]

"Avoid the macho image of "I'll debate you any time any where" talk. It is unscientific and makes you appear like a barbarian.

"Get the personalities straight and find out who is really behind the push to have cholesterol a household word. There are misguided staff in the Department and at NIH. But misguided by whom? Find a nutritionist at the University of BLANK Medical center in BLANK. He will know.

"Your letters to Sullivan are effective and keep writing them. They sensitize many people who then begin to ask questions. Find sympathetic people in Congress and have them ask questions and even hold hearings. (People from dairy meat or egg producing states). This will bring more attention to the issue. Above all else stay calm--You are winning."

SONgbird

Accepting SONgbird's advice another letter was sent to Secretary Sullivan on May 13, 1991.

Dear Dr. Sullivan:

"Dr. Albert Einstein wrote to President Roosevelt, making him aware of the potential military application of on-going nuclear fission research. I am no Einstein but twice now I have attempted to make you aware of the great tragedy that is falling on the American people because of the misguided decisions of NHLBI. And twice you have turned over my book (The Cholesterol Conspiracy) and my letter to the very agency that is perpetrating the tragedy.

"I will continue to pursue this matter until you, someone on your staff or someone in Congress agrees to "hear our case." I would be receptive initially to the idea of giving a detailed and systematic 8-hour presentation to one or more relevant and open-minded individuals who would then convey to you their thoughts as to whether the matter should be pursued at higher levels. Such individuals could be selected from staff available in California. The worst that could come of this would be the loss of a relatively few dollars and manhours. The most that could be derived would be the ultimate savings of hundreds of billions of Medicare and consumer dollars and perhaps the health of millions. I urge you to consider this minimal risk, maximal payoff concept, rather than passing this letter once again to Dr. Lenfant "for response" which, of course, is no response at all.

"Incidentally, Dr. Lenfant's last "response" included a 13-page article entitled, "The Cholesterol Facts," a document which is almost completely devoid of facts and which I have already critiqued in detail in my 905 page review document.

"Let me describe the "big picture." In the 1960s almost all researchers and agencies, including the American Heart Association, indicated that definitive cholesterol-lowering trial by diet was necessary to prove that changes in the diet would reduce the incidence of coronary heart disease (CHD). No scientifically acceptable diet trial to date had provided evidence that diet changes could be beneficial. Then in 1969 the Veterans diet trial was published, demonstrating that special low-saturated fat, low-

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[a] But Finland's CHD mortality rate has nevertheless been decreasing without predicted dietary changes (see Chapter 4).

cholesterol diet over many years did not significantly reduce CHD events. In the following year the Framingham Heart study published a report showing virtually no relationship whatsoever between what Framingham subjects ate and their subsequent incidence of CHD. In 1971, therefore, the then NHLBI director, Dr. Theodore Cooper, rejected the large diet trial proposal and replaced it with a drug trial (which later showed impractical benefits of cholesterol-lowering, i.e., a drug group yielded 1.7% fewer CHD "events" than a control group over a 7.4-year period).

"The cost of a definitive diet trial was estimated to range from $70 to $300 million, depending on size. Dr. Cooper presumably rejected the proposal because of cost but I am convinced that rejection was based on a long line of unsuccessful clinical diet trials and a lack of faith that yet another trial would yield different results. Now, however, NHLBI is engaged in a nationwide experiment in which every man, woman and child are "subjects." The total cost to consumers, directly and indirectly, will probably exceed a trillion dollars if it is not stopped in the near future. Dr. Lenfant promises that the experiment will lead to reduced incidence of CHD and lower costs to government but it will, in fact, add to the current outrageously growing costs. CHD mortality has been decreasing since 1964 but morbidity has been increasing and morbidity, not mortality, represents the real cost of a disease to government. A major reason why CHD mortality has been decreasing is undoubtedly because deaths due to cancer have been increasing. If an atherosclerotic person dies of cancer, he will, of course, not become a CHD mortality statistic.

"Dr. Sullivan, I fully recognize that you have a very busy schedule but I can promise you that the little time you devote to my plea will result in a substantial reward for HHS and the American people. I have spent more than 17,000 hours critically analyzing the diet-cholesterol-CHD literature and have a wealth of knowledge to share. I hope that you will pay attention to a songbird among a horde of randomly chirping feathered creatures. I do!"

Sincerely,
Russell L. Smith, Ph.D.

No response of any kind to this letter was received at the time of this writing. Lincoln was badly mistaken; the government is not "of the people, by the people and for the people." The people cannot even communicate with government.

NHLBI'S STATEMENT TO THE MEDICAL COMMUNITY

In 1980 the Food and Nutrition Board (FNB) of the National Academy of Sciences published a report that indicated that most Americans need not be concerned about their blood cholesterol levels or what they eat.[709] Four years later, NHLBI held a cholesterol consensus conference. The conference panel, hand-picked by NHLBI, was said to have reviewed "all the available data" and concluded that the causal relation between blood cholesterol level and CHD and the benefits of cholesterol-lowering had been scientifically proven.[1845] To give physicians and the public the impression that the matter was now thoroughly settled, NHLBI hand-picked a staff of supporters to produce a report for the Surgeon General's Office[2433] in 1988 and hand-picked another staff to produce a new FNB report in 1989.[1976] Vice-chairman of the new FNB, DeWitt Goodman, indicated that "what's special about this report is not that it's all new but that it's immensely, thoroughly documented."[1977] Now that the matter was scientifically and conclusively resolved and "immensely and thoroughly documented," what more need be said? Lots!

In addition to the joint AHA/NHLBI statement published in 1989[2500] and 1990,[3349] discussed earlier in this chapter and said to contain the cholesterol facts, NHLBI published a 79 page article in 1991, 41 pages of which were devoted to "scientific

evidence for [cholesterol-lowering] recommendations affecting the public.[3361] Some 629 references were cited in a review that by then had become boring and redundant--highly selective of the literature reviewed and unable or unwilling to see the scientific flaws in many of the studies it reviewed to support the diet-cholesterol-CHD relation. The review, prepared by the same NHLBI/AHA supporters who have long committed themselves to the relation (e.g., Carleton, Goodman, Grundy, Cleeman and Rifkind), is almost entirely fraudulent regarding major studies and issues. Some examples of blatant fraud are given below and, as indicated, references are made to other chapters of this document which provide more detailed presentations of the fraud.

While the consensus report claimed that the causal relation between blood cholesterol and CHD had been proven, the 1991 statement was less than absolutely certain. It said, "Although the precise causes of atherosclerosis have not been identified fully [meaning, not all. See "Glossary of mumbo jumbo" later in this chapter], clinical, epidemiological, animal, and biochemical evidence demonstrate that many major factors contribute to the process."

The report indicated that "the linkage of CHD to national eating patterns has been established. There is widespread international consensus." Chapters 3 and 4 demonstrate unequivocally that CHD mortality trends are not at all correlated positively with total fat, saturated fat, animal fat or cholesterol intake trends in the U.S. or most European countries and Japan.

LDL cholesterol has long been incriminated by NHLBI as the atherogenic lipoprotein. The report stated that "Substantial epidemiologic evidence has accumulated over the past 40 years indicating that blood levels of...LDL cholesterol are highly correlated with severity of coronary atherosclerosis and rates of CHD." The report cited the Framingham study and, in particular, 1977 and 1981 reports by Gordon et al.[453,581] Neither of these reports presented <u>any</u> correlations, let alone high correlations, between LDL and CHD. These reports published logistic regression coefficients which are poor indicators of the relation between lipids and CHD and, even so, revealed weak and nonsignificant slopes for ages up to 69 years. As discussed at length in Chapter 3, despite its presumed preeminence, graphic presentations of the LDL-CHD relation are conspicuously absent in the Framingham literature, as are correlations. It may surprise readers to know that this writer found only one report that yielded a graphic relation and that involved the plot of relative risk, not rate, against LDL ranging from 150 mg to 650 mg.[2292] Relative risk was still under 1.0 at LDL levels of 400 mg, indicating that LDL has virtually no relationship whatsoever with CHD for more than 99% of the population. That report was published in 1989. It effectively indicates that LDL's "atherogenic" influence occurs only at very high levels, in less than 1% of the population.[a] This most unimpressive influence is undoubtedly the one and only reason why the "all-important" LDL has been relegated to nongraphic roles.

The NHLBI report said, "The role of dietary factors in Norway during World War II when deaths from CHD fell dramatically as the Nazi occupiers diverted dietary fat to munitions production." This immediate reduction in CHD mortality is in contrast to other examples given by NHLBI wherein the reduction in blood cholesterol is not followed by a mortality decline for many years. For example, 10 pages later in the NHLBI report the authors argued that a reduction in mortality in the Coronary Drug Project required 15 years to observe; blood cholesterol-lowering had no significant effects on mortality during the five years of the trial. As will be seen in Chapter 3

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[a] As discussed in Chapter 2, such high levels of cholesterol produce a "lipid storage disease," not true atherosclerosis.

and 4, NHLBI has commonly used lags from zero to 25 years in different contexts to explain the "causal" relation between cholesterol-lowering and CHD.

According to NHLBI, "The strongest epidemiologic support that diets high in saturated fatty acids contribute significantly to increased CHD risk comes from the Seven Countries study. The chemical analysis of duplicate diets collected over four seasons of the year, showed substantial variation in the amount and type of fat among the populations sampled." Chapter 4 shows that dietary data collection in this study varied inconsistently from country to country and that chemical analysis of foods eaten by the American cohort were not performed. That cohort's diet was assessed by a highly inaccurate questionnaire technique for the period of a single day.

The report cited a 1985 article by Keys et al.[82] as showing that "In the 15-year follow-up of the Seven Countries study, intakes of saturated fatty acids were found to be correlated with total mortality rates as well as with CHD rates." The term "saturated fatty acid" appeared only once in the Keys et al. report and it was not associated with either total mortality or CHD rates. The report, in fact, was exclusively concerned with the relationship between blood cholesterol level and cancer.

The NHLBI report indicated that "The epidemiologic data relating dietary cholesterol to human CHD have been reviewed in detail by Stamler and Shekelle."[1565] On the contrary, Stamler and Shekelle devoted merely 4 pages to the subject and cited 10 studies involving humans. Three of these studies, i.e., the LRC Clinical trial, the International Atherosclerosis Project and the Seven Countries study, did not correlate dietary cholesterol intake with CHD and were therefore irrelevant. Of the remaining 7 studies, two were between populations studies by Stamler that were highly confounded (see Volume 1). Four additional studies, i.e., the Ireland-Boston study, the Western-Electric study (by Stamler), the Honolulu Heart study and the Zutphen study, were completely flawed and a fifth study on Seventh Day Adventists did not show a significant relation between dietary cholesterol and CHD. Thus, Stamler and Shekelle's "detailed review" amounted to only seven relevant studies, three of which were his own and all of which presented absolutely unconvincing evidence (see Chapter 4).

The NHLBI report stated that "In the 1950s and 1960s there was an intense interest in the putative cholesterol-lowering action of linoleic acid, and some investigators of that era advocated high intakes (i.e., 10-20% of total calories). The authors went on to say that 10% should be maximum because "high intakes of linoleic acid may increase risk for gallstones and animal data indicate that high PUFA intake may promote development of tumors and suppress the immune system." The authors neglected to cite the investigators recommending high intakes of linoleic acid. As shown later in this chapter, and in Chapters 2 and 10, the primary promoters were the AHA in the late 1950s, 1960s and 1970s and the NHLBI itself in the 1970s.

The report held that high intakes of monounsaturated fatty acids in the Mediterranean region are associated with low CHD rates and that "This finding thus justifies encouraging higher intakes of oleic acid in the diet, that is, 14-16% of calories, as a substitute for saturated fatty acids." But much earlier in the report the authors had indicated that the average American intake was already 14-16%. Therefore, increasing monounsaturates from 14-16% to 14-16% is closely akin to spinning one's wheels.

The report observed that "metabolic studies indicate that high-carbohydrate diets [i.e., those advocated by NHLBI and AHA] can raise triglyceride levels and lower HDL cholesterol levels, but these changes apparently do not translate into increased risk for CHD." The reader should note the word, "apparently." As shown in Chapter 10, many studies have found carbohydrates to lower HDL disproportionately with total cholesterol, yielding a larger total cholesterol to HDL ratio, an outcome considered unfavorable by the alliance. It is the alliance's unspoken dilemma.

The report incriminated the American diet as a major cause of the CHD mortality increase in the 1940s and 1950s for both men and women. Yet, the authors admitted that "The trend in the CHD death rate was...flat among middle-age women and downward among younger women." Indeed, the increase among white women occurred only beyond 74 years of age, hardly constituting an epidemic and it is exceedingly likely that these elderly women did not consume more of the NHLBI's "deadly duo," saturated fat and cholesterol, than did younger persons. Examination of Table 3-5 in Chapter 3 reveals that males and females over 70 years not only consumed slightly less saturated fat than younger persons in two government surveys, they also consumed less cholesterol. Therefore, the diet-CHD argument for women is wholly without substance.

The report said that "the ideal study of cholesterol lowering would be a clinical trial of diet" but indicated that it was not feasible, primarily because it supposedly would require too many subjects and cost too many dollars. It was said that "It should be noted that these considerations equally apply now, just as they did in 1971 [when the diet trial was rejected by NHLBI], and that it is most unlikely that such a trial will ever be performed." Yet, one page later the NHLBI report authors praised the Oslo diet trial,[849] having less than 5% of the subjects and costing only a fraction of that presumably required for the proposed American diet trial, and indicated that it was a "well-designed major study" that yielded a reduction of CHD rate by "almost 50%." Thus, it would appear that unrich Norway can conduct a "well-designed major study" that rich America finds completely unfeasible.

The Report cited the NHLBI Type II Coronary Intervention study and the Leiden trial (Volume 1) as supporting the lipid hypothesis, even though the former yielded nonsignificant results and the latter included no control group.

A final example of the fraudulent nature of the 1991 report relates to the low-cholesterol, high mortality relation. As shown in Chapter 8, nearly all major prospective studies in the world have demonstrated that either higher cancer and/or higher all-cause mortality occurs in subjects with low cholesterol levels, i.e., below 180-200 mg, than with moderate levels. Most of these studies have also ruled out latent cancer at entry as the basis for this relationship. The NHLBI statement, however, reviewed only a small number of those studies and arrived at the following biased conclusion: "Overall, the evidence available indicates that dietary change to lower blood cholesterol is highly unlikely to increase the risk of colon cancer." Note also that NHLBI omitted the "all-cause" category.

GLOSSARY OF MUMBO-JUMBO

There is an old proverb that says, "You shouldn't believe everything you read." Indeed, that proverb should be the first principle to be followed by the reader of the diet-blood cholesterol-CHD literature. In particular, one needs to learn a whole new set of definitions for common descriptive words and terms. For example, in a 1988 article Kannel et al.[3106] indicated that "The efficacy of antihypertensive drug therapy has not been well demonstrated in some clinical trials, but the benefits for CHD mortality have not been conclusively demonstrated." Clinical trials have consistently demonstrated that antihypertensive drug therapy either increases cardiac mortality or has no effects (Chapter 9). Thus, Kannel et al.'s statement,

> "the benefits for CHD mortality have not been conclusively demonstrated"

really means,

> "the benefits for CHD mortality have not been demonstrated at all and, in fact, there are negative benefits."

The secret of decoding the alliance's mumbo-jumbo lies in the recognition of one overpowering point, i.e., the alliance's obsession with the risk factor concept compels it to use language that always best preserves the risk factor-CHD relationship. Therefore, if a reduction in a risk factor results in an increase in mortality, that relation can be correctly (albeit deceptively) described as follows: the reduction in Risk Factor A (1) did not cause a decrease in mortality, or (2) did not demonstrate conclusive benefits. If appropriate data are presented, the reader can examine them and determine the true relation, but if incomplete or no data are given (including meaningless risk ratios, regression coefficients, etc.) one can be reasonably certain that the author's descriptive remarks are designed to hide a weak relationship or an undesirable finding.

The following are some of the more commonly used alliance terms and the associated terms that this writer found to be far more accurate descriptors of the data under investigation.

Alliance Term	Real Meaning
Powerful relation	Weak
Striking	Modest and probably nonsignificant
Marked	Modest and probably nonsignificant
Modest	Trivial
Less consistent	No relationship at all or opposite to that expected
Less clear	No relationship at all or opposite to that expected
Inconsistent	Strong relationship in the opposite direction
Not fully understood	Not understood at all
Does not fully explain	Explains nothing
Has not strongly linked	No link at all
Sharp upturn	Slight upturn or an arc in a continuous curve
Overwhelming evidence	Some evidence
Conclusive evidence	Suggestive to tenuous
May	or may not
Infer	Guess without benefit of logic
Unequivocal	Equivocal
Did not decline	Increased
Did no harm	Had no benefits
Not completely confident	No confidence at all
Not strictly comparable	Not comparable at all
No definite improvement	No improvement at all or worsened
Holds after adjustment for other variables	But not significantly so

Having studied the above "codes" one should now be able to better understand the alliance's writings. As a test, consider the following statement from the 1981 NHLBI Working Group report:[3067] "As to the role of a diet high in cholesterol and saturated fat as a risk factor, the relationship is well-established for population groups, and less consistently so for individuals within populations." Looking up the term "less consistently" above, we find that it means "no relation at all or opposite to that expected." That is the proper descriptor for the fact that within populations studies consistently show no relationship between diet and either blood cholesterol or CHD. The Working Group simply did not want to admit that fact.

The foregoing discussion is not in the least intended to be humorous, although it may seem so. The use by the alliance of inappropriate and misleading terms to describe outcomes is so commonplace, it is difficult to read a single article that does not contain at least one of such terms. Clearly, the frequent use of these terms reflects the frequent weaknesses of the alliance's risk factor data.

THE ALLIANCE'S BASIC PREMISES

The alliance's position on the diet-CHD issue is based on two major proclamations that are factually untrue and undoubtedly known to be untrue by the alliance. The first is the notion that a great CHD mortality epidemic occurred during the first 63 years of this century. Chapter 3 presents, to this writer's knowledge, the most detailed and comprehensive analysis of CHD mortality statistics ever published. It is doubtful that any objective individual will believe in an epidemic after evaluating that analysis.

A second proclamation is that the reported CHD mortality epidemic was principally caused by increased consumption of animal fats and cholesterol. Chapter 3 also presents the most detailed and comprehensive analysis of food consumption trends this writer has encountered and it is also doubtful that any objective individual will believe that animal fat and cholesterol increased in the American diet after reviewing that analysis. Strangely, the alliance often claims that the so-called epidemic was caused by increasing consumption of animal fats and simultaneously presents data showing that the consumption of such fats actually decreased before, during and after the "epidemic," thereby refuting the claims. The 1981 NHLBI Working Group[3068] presented such a contradiction, discussed in detail later in this chapter.

Given that the reader comes to the conclusion that one or both of the above proclamations are false, Chapters 4 through 10 are not really essential to disproving the diet-CHD hypothesis. For example, if a CHD epidemic did not occur, food consumption trends would be irrelevant. Similarly, if animal fat and cholesterol consumption did not increase, they obviously could not comprise the cause of the reported CHD epidemic. Of course, if the epidemic and lipid trends both did not occur, the diet-CHD hypothesis would again be totally without support. Finally, if the lipid consumption trends were actually opposite to that proclaimed, and virtually every study has found this to be the case, the diet-CHD hypothesis becomes totally absurd.

To fully appreciate the above argument, let us consider the explanatory power of deductive and inductive logic.

Premise 1: John is a boy
Premise 2: All boys are males (1)
Conclusion: John is a male

We know a priori that both premises are true. The conclusion, which is the only deduction that can be drawn from the premises, must also be true because (1) the premises are true and (2) deductions are inherently correct conclusions from two or more premises.

Now consider two premises in which one or both are untrue:

Premise 1: Fibronite is a meteorite
Premise 2: All meteorites are pink (2)
Conclusion: Fibronite is pink

The conclusion is also the only deduction that can be drawn from the premises. It is a correct conclusion, given that the premises are correct. Since the premises are not correct, the conclusion must also be incorrect.

Deductions are indisputable conclusions, given that the premises from which they are drawn are correct. Inductions are not. For example,

Premise 1:	John is dead	
Premise 2:	John is in the swimming pool	(3)
Conclusion:	John died of drowning	

The specified conclusion is not a deduction because there is no information in the premises which indicates how John died, although the information is suggestive. Thus, the conclusion is an induction and only one of many equally plausible conclusions. John may have been poisoned, shot, strangled, etc. and then thrown into the pool. John may simply have suffered a fatal heart attack while swimming.

Consider now the alliance's two proclamations:

Premise 1:	A CHD epidemic occurred from 1900 to 1963	
Premise 2:	Animal fat and cholesterol consumption increased from 1900 to 1963	(4)
Conclusion:	The increased animal fat and cholesterol consumption caused the CHD epidemic	

It should be obvious that logic model (4) is similar to logic model (3). The best that can be said is that the conclusion drawn is one of possibly hundreds of equally plausible conclusions. Of course, if additional premises are accumulated, such as results from prospective studies, clinical trials, etc., then the above conclusion may loom as the most plausible induction. This is precisely the position taken by the alliance. For example, the alliance maintains that animal experiments show that cholesterol feeding induces atherosclerosis, that increasing saturated fat and cholesterol in the human diet increases blood cholesterol, that clinical trials of cholesterol-lowering reduces CHD "events," etc. If all of these premises were true or at least statistical tendencies, then the conclusion drawn from logic model (4), as well as the more general conclusion that saturated fat/cholesterol causes CHD, would be rather powerful inductions. However, the two basic premises of logic model (4) are not correct, so let us note the impact on the conclusion of correcting only Premise 2.

Premise 1:	A CHD epidemic occurred from 1900 to 1963	
Premise 2:	Animal fat and cholesterol consumption decreased from 1900 to 1963	(5)
Conclusion:	The decreased animal fat and cholesterol consumption caused the CHD epidemic	

Obviously this logical conclusion is opposite to the alliance's proclamations and given the truth of the two premises, all experimental and clinical data become statistically suspect, i.e., unrepresentative samples of the populations which generated the two principal premises.

Regardless of Premise 1, all scientific evidence, not merely the majority, indicates unequivocally that animal fat consumption never increased during the so-called CHD epidemic and actually decreased somewhat. The evidence also indicates that dietary cholesterol remained constant and vegetable fats increased substantially. These trends cannot be reconciled with subordinate data from animal studies, experiments, prospective studies or clinical trials.

With respect to Premise 1, recorded statistics do suggest a CHD epidemic among men, although Chapter 3 amply demonstrates that the epidemic was apparent rather than real. However, recorded statistics do not show a significant rise in CHD mortality among white women during the so-called "epidemic" among men. Since white women constitute nearly half the U.S. population and consume the same diets as men, it is illogical and unconscionable to ignore this exceedingly important contradiction or dismiss it as some peculiar unexplainable anomaly.

Premises 1 and 2 of model (4) are not statements of fact. All the evidence from careful analyses of mortality statistics and food consumption trends indicates, if anything, a negative correlation with animal fat and a positive correlation with vegetable fat, precisely the opposite to that espoused by the alliance.

The ready acceptance by the alliance of the reported increasing CHD mortality rate among men as an "epidemic" from 1930 or 1940 to 1963 and the parallel presumed increasing consumption of fat deserves additional attention in this introductory chapter. In 1953 Keys[279] indicated that the broad category of heart diseases included angina pectoris, coronary heart disease, myocardial infarction, chronic myocarditis and myocardial degeneration and that "In hospital and vital statistics it is rarely possible to differentiate these clearly so it is convenient to group them." One year later (1954) Irvine Page[3289] said, "The answer to the problem of the clinical recognition of latent atherosclerosis is simple; we have no way. Coronary atherogenesis can proceed undetected to an extreme degree. It is a harsh thing to say, but it needs saying; there is no reliable way to make a diagnosis of cerebral or coronary atherosclerosis." Since most people died outside of hospitals and without care by physicians, and since diagnosis of coronary atherosclerosis was effectively not possible without autopsies, of which there were few, it follows, therefore, that the so-called CHD epidemic occurring before 1954 must have been due to death certification "fashions" of the period. There is absolutely no other reasonable explanation.

The above conclusion was drawn by Starr[3295] in an editorial in Circulation in 1957. He said, "It is my strong impression that arteriosclerotic heart disease is being written on the death certificates of most elderly persons whose primary cause of death is either unknown or unclear to the attending physician and that doctors often diagnose heart disease in elderly people not for positive reasons,...but for negative reasons; they do not know what else to call it. The fact that the relative frequency with which death is attributed to arteriosclerotic heart disease varies in different parts of the nation is difficult to explain and the finding excites my suspicion that the data are being contaminated in the fashion I have suggested; diagnostic fashions change with time as well as with place. For these reasons the reported increase in the number of deaths from arteriosclerotic heart disease seems to me difficult to interpret with confidence." The reader should note that AHA's Circulation published this point of view before the AHA had committed itself to the diet-CHD relationship.

Medicine is far more sophisticated today but the problem of death certification still remains formidable for similar reasons, i.e., most deaths still occur outside of hospitals and physicians completing certifications typically have little or no knowledge of the deceased. For example, Jenkins,[3407] Elder,[3408] and Harris[3409] emphasized in 1991 that vital statistics are grossly inaccurate, particularly with respect to certification of death as CHD. The rate of postmortem examinations decreases with age in the U.S., with a low of 5% among those 85 and older.[3408] Less than half of all clinical diagnoses in those over 75 years are confirmed at postmortem examination. Harris[3409] also pointed out that the exact cause of death is often not determined even with postmortem examinations because some disorders such as cardiac arrhythimas "may be impossible to establish." The pathologist, however, is forced to give a cause of death to satisfy certification requirements and establish whether or not a person died of natural causes. Thus, the pathologist often gives his "best guess." The result

of all this is that CHD mortality statistics over the last 50 years probably do not resemble very closely the actual death rates. Most of the errors apparently occur for those over 65 years and, as will be seen in Chapter 3, this is the age group within which the so-called CHD epidemic struck. A colorful but dramatic example of the inaccuracies inherent in vital statistics was described by Egerton[3249] in 1991. He wrote, "Mr. Plowman was 89 years old. He'd been in a nursing home for several years, gradually deteriorating. Eventually, organic brain syndrome made him virtually uncommunicative. One morning a nurse found Mr. Plowman dead. Called to his bedside, I dispatched the body to the funeral home. A few days later I received a death certificate to fill out. As cause of death, I listed 'heart failure.' I could have put respiratory arrest or cardiac arrest. Mr. Plowman could possibly have had a massive CVA in the night, or perhaps a pulmonary embolism. We didn't do an autopsy, since his demise seemed to be the natural end to a prolonged aging process. So, even though it was only a guess, Mr. Plowman officially died of 'heart failure.'"

Egerton described two other cases in which the diagnoses of cause of death were either guesses or "convenient diagnoses." He then went on to ask, "What do these patients have in common? Each became a statistic. And each statistic in turn will be compiled into a study or report. These will be used to tell us how people die, or why they get admitted to the hospital, or what's the most common reason little boys see the doctor. All over the land, such statistics are being compiled, and from them conclusions are drawn, recommendations made, 'health' products promoted, pills sold, and people 'educated.' It's the statistics that are eventually skimmed from governmental records that most concern me. We're told heart disease is the biggest killer in this country. Could this be because I, and thousands of doctors like me, write 'cardiac failure' on a death certificate for people like Mr. Plowman? What if we wrote 'body failure' instead? Then, might not 'body disease' become a leading contender for top killer?" Surely every physician in the u.S. who completes death certificates must know that death rate trends may be more related to what is fashionable at the time than to the actual causes of death.

The almost whimsical way in which deaths are certified can be seen in newspapers on a daily basis. Consider, for example, the following excerpts from notices during a few days in June 1990: "he was 67 years old and his death was attributed to an apparent heart attack by a spokesperson for the family";[3353] "The medical examiner's office said the apparent cause of death was a heart attack";[3354] "George D. _____, who had a long career in academic publishing and who recently retired as president of _____ Publications died May 19, presumably of a heart attack";[3355] and "His family attributed his death to heart failure."[3356] In effect, Egerton had described not the atypical death certification process but rather the most common process. Most of the mortality statistics are based on guesses and many of the guesses are, in turn, based on fashions, biases and whatever is expedient at the time. How many deaths due to illegal drugs are certified as "heart attacks," for example, simply because family members do not wish "drug overdose" to be the "official" cause of death?

Keys[1993] was the cover story for a 1961 issue of Time Magazine in which he said, "Americans eat too much [animal] fat. With meat, milk, butter and ice cream, the calorie-heavy U.S. diet is 40% fat, and most of that is saturated fat--the insidious kind that increases blood cholesterol, damages arteries and leads to coronary disease." Keys based his statement on United States Department of Agriculture food availability data which clearly showed that animal fat availability had decreased during the first 60 years of this century, not increased. The data did show that total fat availability had been increasing to 1961 but later data showed that it also increased to 1980, 16 years after the CHD mortality decline began. The fact that Keys and others could not know at that time that the CHD mortality had peaked in 1961 and that available fat would continue to increase for many years, while mortality would decrease, is understandable but irrelevant. They were proven wrong with respect to animal and

total fat but they nevertheless cling to the animal fat-CHD hypothesis today because it is the very essence of their program to change the American diet.

101 REASONS WHY DIET AND BLOOD CHOLESTEROL LEVEL ARE NOT THE CAUSE OF CHD

The previous section demonstrated that the entire diet-blood cholesterol-CHD hypothesis is based on two untruths, i.e., (1) a great CHD epidemic occurred in this century and (2) it was caused by increasing consumption of animal fats and cholesterol. From the standpoint of logic, no further evidence need be presented. However, as emphasized in the first section of this chapter, logic alone cannot counter the resistance of those who have been thoroughly "programmed" by the alliance for many years. Therefore, we present below 101 reasons why diet and blood cholesterol level are not the cause of CHD. The list is by no means exhaustive; it is primarily intended to provide the reader with a feeling for the magnitude and varieties of the insurmountable evidence (discussed in detail elsewhere in this volume).

1. The earliest arterial lesions are seen in infants in all societies, long before "rich" diets of industrialized countries are consumed.

2. The early arterial plaques contain no more cholesterol than does surrounding tissue.

3. Severe atherosclerosis develops very quickly, in some cases within a few months, in the coronary arteries of patients who receive heart transplants. Neither diet nor blood cholesterol level could possibly be the cause of such rapid development.

4. Sudden deaths, always classified as CHD in prospective studies and clinical trials, are not related to blood cholesterol levels.

5. Although the same concentration of cholesterol flows through all arteries of the body, atherosclerosis forms at very specific locations and the extent of the disease in the four arterial beds varies among individuals.

6. High levels of LDL are said to be atherogenic but it is established that LDL per se cannot penetrate the arterial wall.

7. As noted by Castelli, about half of the deaths that are from myocardial infarctions (MI) are associated with atherosclerosis. It follows, therefore, that MIs occur equally often whether or not there is significant atherosclerosis.

8. MIs frequently precede, rather than follow, coronary thrombosis, suggesting that such MIs are not associated with atherosclerosis and thus blood cholesterol level and diet.

9. Angiograms taken before and after MIs indicate that the majority of MIs occur in the least occluded arteries.

10. Blood cholesterol levels of men and women increase with age even though fatty acids and cholesterol compositions of diets remain constant.

11. Blood cholesterol levels increase very little in men during adulthood but a great deal among women and yet CHD occurs 10 to 15 years earlier in men.

12. Blood cholesterol levels of vegetarians increase with age even though they maintain a vegetarian diet.

13. The CHD mortality rate of vegetarians is the same as that of nonvegetarians.

14. Studies show no differences in CHD mortality rates among vegetarians consuming different amounts of animal fats and cholesterol.

15. Autopsy studies show no difference in severity of atherosclerosis between vegetarians and nonvegetarians.

16. Most autopsy studies show no differences in severity of atherosclerosis among individuals having different blood cholesterol levels.

17. Autopsy studies have shown no correlation between diet and severity of atherosclerosis.

18. Autopsy studies have shown no differences in severity of atherosclerosis for all ages between Japanese and Americans, even though the reported CHD mortality rate in the U.S. is five-six times greater than in Japan.

19. The reported increase in consumption of saturated fat that was associated with the so-called CHD epidemic was of vegetable origin, not animal fat.

20. Vegetable fat consumption increased before, during and after the so-called CHD epidemic among men.

21. Animal fat consumption decreased before, during and after the so-called CHD epidemic among men.

22. CHD mortality decreased slightly among women during the so-called epidemic among men, even though women consumed the same diet as men.

23. Reported total fat increased and saturated fat remained constant <u>after</u> the CHD mortality rate began its decline.

24. Stamler, Levy and others maintain that blood cholesterol levels have been decreasing since 1948 and yet they also maintain that fat consumption and CHD mortality rates increased greatly after 1948.

25. No scientifically acceptable clinical trial has demonstrated that reducing blood cholesterol by drugs or diets reduces all-cause mortality rates.

26. No scientifically acceptable clinical trial has demonstrated that altering the diet reduces CHD morbidity or mortality rates.

27. No scientifically acceptable trial has demonstrated that the benefits of cholesterol-lowering are cost-effective.

28. The Framingham Diet study found no correlations between CHD events and the consumption of fat, saturated fat and dietary cholesterol.

29. The Framingham Diet study found no correlations between blood cholesterol levels and the consumption of fat, saturated fat and dietary cholesterol.

30-52. Ditto with 23 other within population studies (Volume 1) conducted in the U.S., India, Israel, Puerto Rico, Japan, Hawaii and England.

53. The relationship between blood cholesterol level and CHD is effectively nonexistent over the ages of 50.

54. The relationship between blood cholesterol level and CHD among men under 60 is extremely weak and overly influenced by a small percentage of individuals with apparent familial hypercholesterolemia who are affected by a lipid storage disease, as well as common atherosclerosis.

55. The relationship between blood cholesterol level and CHD among women is weak to nonexistent.

56. Blood cholesterol level cannot predict better than chance who will and will not die of CHD.

57. The alliance claims that blood cholesterol levels have been declining since 1948 and yet CHD morbidity has increased during that period, according to Framingham data.

58. A true CHD mortality epidemic would drive the all-heart diseases mortality upward. The reported CHD mortality epidemic, however, was accompanied by a strong downward trend in all-heart diseases mortality.

59. A CHD mortality epidemic was reported for men but not for women. This remarkable difference should have resulted in nonparallel trends in the all-cause mortalities of the sexes but, in fact, the trends were almost perfectly parallel.

60. The so-called CHD epidemic increased 100% in one year (1948 to 1949) but this increase was an obvious artifact of a change in the International Classification of Diseases that went into use in 1949.

61. Castelli and others claim that HDL is the most important of all risk factors. Yet, the diet recommended by the alliance, including Castelli, is to increase carbohydrates, while reducing fat, a diet that decreases HDL.

62. The alliance claims that there is no threshold of blood cholesterol below which atherosclerosis does not develop, yet claims illogically that reducing blood cholesterol can cause atherosclerosis to regress.

63-73. Of the 26 countries in the WHO MONICA project, CHD mortality rates and blood cholesterol levels were published for 21. Eleven countries had higher blood cholesterol levels than did Americans but equal or lower CHD mortality rates.

74. Dietary factors do not correlate with the CHD mortality rates occurring in different geographic regions in China.

75. Total cholesterol and LDL cholesterol levels are not correlated with CHD mortality in China.

76. Natives of Crete, Greece have cholesterol levels equal to Americans but have much lower CHD mortality rates.

77. Indians in Britain have higher CHD mortality rtes than Europeans but have lower blood cholesterol levels.

78. The French consume more fat and cholesterol than do Americans, have higher blood cholesterol levels, smoke just as much and yet have far lower CHD mortality rates.

79. Danes consumed more fat and cholesterol than Americans but had much lower CHD mortality rates.

80. CHD mortality rate in Scotland is decreasing even though blood cholesterol levels have remained constant.

81. During the last decades the dietary fat consumption trends have not correlated postively with CHD mortality trends in the U.S.

82-96. Ditto with Japan, Australia, Belgium, England, Finland, Greece, Israel, Italy, New Zealand, Norway, Poland, Spain, Sweden, Switzerland, and Yugoslavia.

97. The all-cause mortality rate in the large MRFIT screened cohort follow-up was found to increase at blood cholesterol levels below 180 mg.

98. As detailed in Chapter 7, NHLBI members concluded that as many as 115,000 to 400,000 persons would be required in a diet trial lasting 7 to 15 years in order to show a significant effect of diet on CHD rates. Clearly, such numbers and time frames indicate that diet cannot possibly have much effect on CHD.

99. The alliance maintains that LDL is the atherogenic component of cholesterol and yet Framingham investigators have never shown a correlation coefficient or a graphic relationshiop between LDL and CHD rate in 40 years of several hundred reports.

100-101+ As described in Chapter 8, many other prospective studies, including Framingham, have revealed higher all-cause and/or cancer mortality rates at blood cholesterol levels below 180-200 mg.

THE FOUNTAIN OF FEEBLENESS

As recently noted by Olshansky et al.,[2960] the total elimination of deaths due to CHD would increase life expectancy at age 50 only 3.6 years for males and 3.1 years for females. (This is in constrast to an early statement by Katz, Stamler and Pick[3201] who asserted that "Once atherosclerosis is conquered, a tremendous dent in morbidity and mortality rates will follow and the average life span will be greatly lengthened.") Moreover, the "...issue of critical importance is whether...declines in mortality would lead to an increased active life expectancy or an expanded period of frailty and dependency. Unless active life expectancy is improved from present levels, the combination of population aging, a larger than predicted elderly population, and possible shifts in the distribution of frailty conditions among the oldest-old, would have an enormous adverse impact on government-funded programs such as Social Security and Medicare." A few years of added life will result in a top heavy distribution of elderly people having a host of debilitating and painful ailments such as arthritis, Alzheimer's disease, osteoporosis, etc. It is also more than apparent that most of those who escape death from CHD will soon demonstrate clinical symptoms of other cardiovascular diseases or cancer. Worst of all, as will be discussed in some detail later in this volume, CHD morbidity is increasing in the U.S., despite the declining CHD mortality rate. Thus, the current emphasis on prolonging life will do little more than greatly increase the amount of suffering and the cost of health care.[2960,3148]

The emphasis should be placed on preserving and improving the quality of life.[3035] Such an emphasis would include the deceleration of the aging process and the conquering of the painful and debilitating aspects of nonfatal and fatal diseases. For centuries man has sought the fountain of youth. That noble goal has been set aside by NIH in favor of pursuing the fountain of feebleness. Unfortunately for the American people, recognition of what they have wrought will be perceived only very slowly by the alliance and Congress.

THE MYSTERIOUS NEGATIVE CORRELATION BETWEEN CHD MORTALITY RATE AND NUMBER OF CARDIOLOGISTS

In 1968 former AHA president Irvine Page[3080] said, "One of the great weaknesses of getting older is the belief in your own point of view and in the stupidity of others. This is the gap between the tired older generation and the tiresome younger one. To be specific, I am not happy about the effectiveness of our research endeavor in atherogenesis. As a result, I suspect the usual turn of events is occurring; the plumber surgeons are cutting in because we know neither how to prevent nor how to cure atherosclerosis."

The alliance, of course, disagrees vehemently with this attitude and points glowingly to the long-term downward trend in CHD mortality which initiated shortly before Page made his rather pessimistic statement. But as can be seen in Figure 1-1, the greater the reduction in the cardiovascular death rate, the greater the growth in the number of cardiologists.[a] If, as the alliance claims, the cardiovascular death rate has declined some 40% from 1965 to 1985 because of the control of risk factors, why has the number of cardiologists increased an incredible 547% during that same period?[1677,2798,3203] The answer, of course, is that the rates of stroke and CHD have been increasing, not decreasing, regardless of the recorded death rates. While evidence for this phenomenon is presented elsewhere in this volume, it is merely a verification of the obvious. The supply of cardiologists has increased to meet the growing demand. It is not because health care has become available to relatively more people. It has not. Cardiovascular diseases are increasing because, as Page indicated, "we [still] know neither how to prevent nor cure atherosclerosis."

HALF TRUTHS PERPETUATED

In 1971 the president of the Infectious Diseases Society of America, Edward Kass, gave the opening address to the society's members at their annual meeting. He unpretentiously and honestly admitted that the conquering of most of the killer infectious diseases of the past was clearly not due to medical research or medical care and that arguments to the contrary are based on half-truths. He emphasized that although this is a known fact, it is apparently not well known enough.

To illustrate the whole truth, Kass presented figures showing the decline in mortality rates of five infectious diseases in Britain from 1860 to 1955 (reproduced in Figure 1-2).[b] Identical trends occurred in the U.S. and other countries; British data were used because they were "reliable" and extended well into the 19th century. As can be seen, the mortality rates of these and other diseases greatly decreased through the 19th and 20th centuries and were nearly nonexistent by the time vaccines and antibiotics were discovered (represented by arrows).

Kass emphasized that "currently fashionable is the view that nutritional improvements account for the decline in mortality from common infections and that nutritional inadequacy is a major factor in explaining the present predilection of the poor for certain communicable disorders. In fact, there is little useful evidence to support this view. Experimentally, the nutritional deficiencies that are needed to substantially affect resistance to infection are generally extreme, and in the case of certain viral disorders, such deficiencies may often increase resistance. Clinically, there is not much evidence of manifest malnutrition in economically underprivileged populations in this or other industrialized countries, if the available indices of

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[a] Both CHD and stroke demonstrate similar downward trends from 1965 to 1985.

[b] Moriyama and Gover[3088] showed the decreasing mortality trends of several infectious diseases in the U.S. from 1900 to 1940.

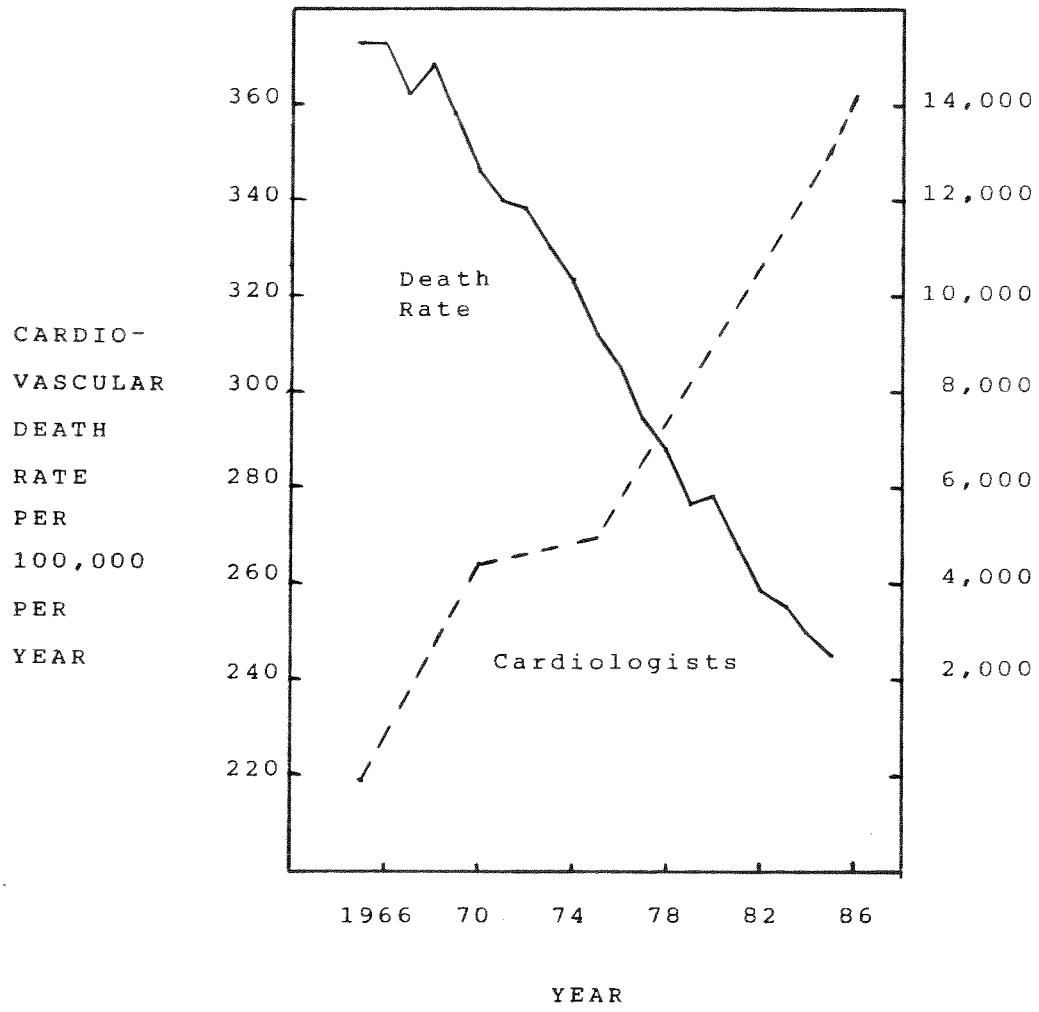

Figure 1-1. Age-adjusted cardiovascular death rate and number of cardiologists by year (adapted from Leupker and Higgins, 1988[2798] and O'Rourke, 1987[1677])

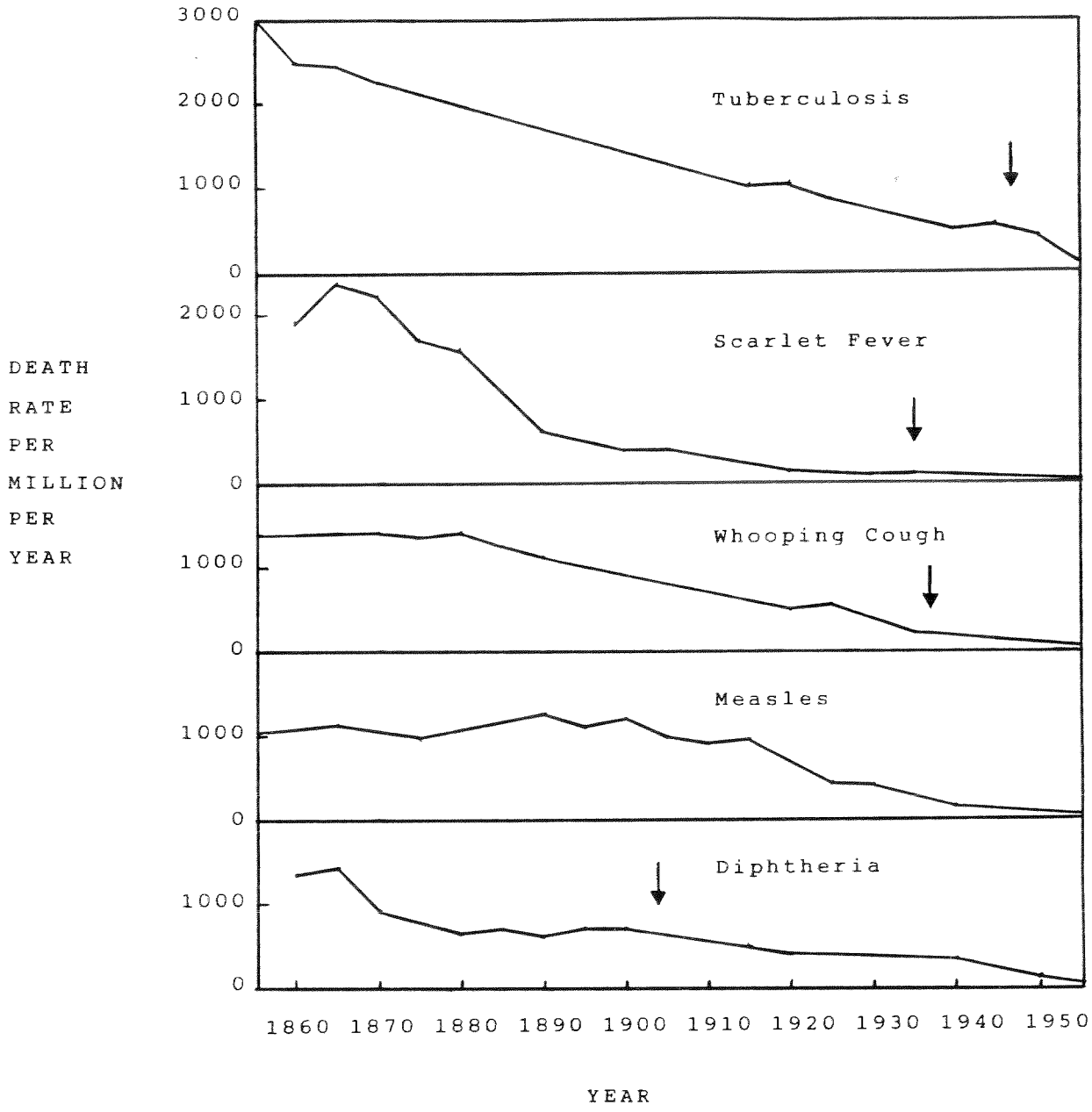

Figure 1-2. Mean annual death rate from five infectious diseases in children under 15 years of age, England and Wales (adapted from Kass, 1971[2933])

malnutrition are used..."[a]

While no one knows for certain what caused the major infectious diseases to decline, Kass indicated that it was probably due, in large part, to decreases in "crowding," particularly in bedrooms where such diseases spread easily.

The moral of Kass' discussion is that it is absurd and dishonest to claim that medicine has conquered a disease when, in fact, the incidence of the disease had substantially declined long before the medical system had the capability to intervene and the rate of decline had not changed much if at all after the medical intervention was initiated. But this moral has been virtually ignored by the NHLBI/AHA alliance for it has repeatedly claimed victory over cardiovascular diseases even though the mortalities due to these diseases had been declining long before so-called risk factors were established or manipulated. Chapters 3 and 9 discuss this issue in considerable detail and demonstrate that the declining cardiovascular disease mortalities were relatively unperturbed by medical and "life-style" interventions.

In her testimony before the 1976 Senate Select Committee on Nutrition and Human Needs, Beverly Winikoff[2934] presented two of Kass' five figures and reiterated Kass' observation that medicine had essentially nothing to do with the conquest of most of the deadly infectious diseases. However, she completely distorted the remainder of Kass' observations. For example, while Kass presented a rather powerful argument that the decline in infectious diseases was not likely to have been due to nutrition, Winikoff took the opposite position. She said, "Among other things, there is good evidence that the dramatic drop in mortality rates of industrializing Europe during the last century was due more to improvements in nutrition, to the availability of good diets, than to advances in science, to breakthroughs in preventive and curative medicine or to availability of hospitals and health care." Not only did she not present any evidence, let alone "good evidence," of the importance of nutrition, her statement was rather meaningless, i.e., since medicine had nothing to do with the mortality declines, it is not impressive to say that nutrition was more important than medical intervention. Winikoff implied that heart disease, cancer, stroke and diabetes were also due, in part, to nutritional problems.[b]

Many physicians attribute the increase in life expectancy to advances in medicine without indicating how it was accomplished. For example, Scheider and Reed[3035] said, "We [implying medicine] have made impressive gains in extending life expectancy at birth." On the other hand, Framingham's Thomas Dawber stated that "It is unlikely...that medical care per se actually contributed to life expectancy."[3001] Clearly, if medicine <u>had</u> played an important role, researchers would not disagree so vehemently.

Jeremiah Stamler[574] also employed half truths in an early (1962) article. He said, "For an adequate understanding of the problem of cardiovascular diseases in the U.S. today, it is valuable to review the evolution of the health picture during the last 50 to 100 years. This has been a period of remarkable <u>advance</u>, probably unparalleled in

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[a] Kass also noted that the substantial increase in life expectancy occurring from the 19th through the 20th century was "due almost completely to decreased infant mortality."

[b] Winikoff also reiterated Kass' statement (without citing him) that the great increase in life expectancy was due to the reduction of infant mortality. However, while he said that life expectancy in adulthood "has been extended very little," Winikoff changed this to "virtually no gain at all."

any previous era of human history. Progress has been particularly great in lengthening the expectation of life at birth. This phenomenal advance in life expectancy is attributable first of all to the conquest of infectious diseases, particularly acute infectious diseases in young children, which previously took a heavy toll." This statement strongly implies (particularly the underlined words) that medical intervention conquered the infectious diseases.

Stamler continued, "Appreciable decreases in mortality among middle-aged and older people also have occurred during recent decades, largely as a result of advances in the control of infectious diseases, particularly pneumonia and tuberculosis.[a] He referred to two figures and two tables as supporting evidence. However, there were no tables in his article and neither of the two figures showed pneumonia mortality trends. Moreover, one of his figures showed tuberculosis mortality to decline steadily since 1900, many decades before appropriate drugs were developed. Pneumonia mortality was also strongly in decline since 1900 as well.[1949] Since Stamler so profoundly misassociated medicine with the decline of infectious disease mortality, one should be a little more than suspicious regarding his subsequent statement that "The overwhelming evidence indicates that the [atherosclerotic] disease is multifactorial in causation, with diet as a key essential etiologic factor..."

Stamler and his colleagues[694] noted in a very early article (1956) that research on the atherosclerotic disease should be conducted "in the best traditions of scientific objectivity, perseverance and enthusiasm..." As can be seen throughout this volume and Volume 1, Stamler has had no short supply of perseverance and enthusiasm but he has rarely demonstrated scientific objectivity, the far more important characteristic of scientists.

As shown in Chapter 3 alliance members have presented an incredible array of half truths regarding the so-called CHD epidemic and its subsequent decline. To illustrate one such half truth, consider the following statements. In 1984 former NHLBI director Robert Levy said, "In 1930, disorders of the heart and cardiovascular system overtook infectious diseases as the leading cause of death in the U.S."[698] And in the foreword of the proceedings of a 1986 NHLBI conference, Higgins and Luepker indicated that "At the beginning of the twentieth century, heart disease was the fourth leading cause of death in the U.S. after pneumonia, tuberculosis and diarrhea. It become the leading cause of death in 1910..."[2802]

Both of the above statements strongly imply that CHD mortality rose substantially from 1900 to 1930, overtaking all other diseases. In actuality, however, the heart disease death rate assumed the number one position by default, i.e., the infectious disease mortality rates had been decreasing on their own for decades and finally dropped below heart disease by 1910. Figure 1-3 shows these trends quite clearly.

The alliance has maintained time and again that Americans underwent a great CHD mortality epidemic during this century which was caused by unfavorable changes in "lifestyles," particularly diets. The alliance has also argued redundantly that favorable changes in lifestyles resulted in the subsequent decline in CHD mortality, observed to occur in the mid-1960s. Chapters 3 and 9 demonstrate in great detail that the scientific evidence unequivocally runs counter to the alliance's arguments. Here we wish to point out four rather insurmountable obstacles over which the alliance's argument cannot transcend.

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[a] In later articles (1973, 1979) Stamler acknowledged that the tuberculosis mortality decline occurred without benefit of medicine.[573,2635]

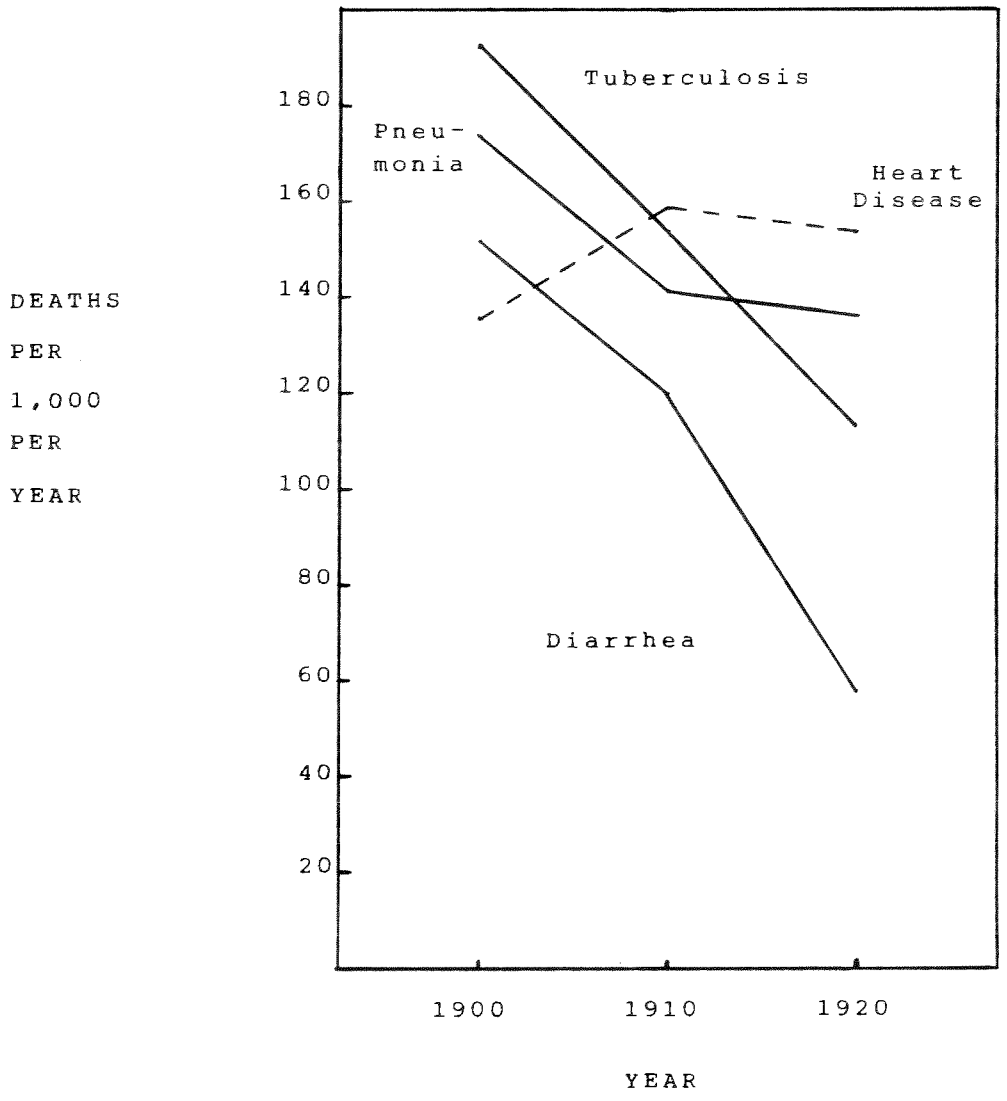

Figure 1-3. Mortality trends for heart disease and three infectious diseases (adapted from Grove and Hetzel, 1968[1949])

Figure 1-4 presents CHD mortality trends for white males and females from 1940 to 1978. It should be emphasized that these curves were computed from NHLBI tables published in 1981[3068] and 1988.[2798] As will be discussed in Chapter 3, CHD cannot be adequately traced earlier than 1949, because of radical changes in the International Classification of Diseases (ICD). Nevertheless, NHLBI[3068] attempted in 1981 to trace the disease to 1940 and, as can be seen, produced rates that were very substantially higher than the subsequent rates published by the alliance in 1988.[2798] However, this discrepancy is not of relevance here. What is relevant is the fact that both sets of data clearly show absolutely no CHD epidemic for white women. The 1981 NHLBI Working Group report all but ignored the differences between the sexes and described Figure 1-4 data as showing "the steady rise, particularly for men, both white and black, that began in 1940 or even before...for persons age 35 to 74, the age group being victimized by the epidemic of premature CHD." This statement clearly implies that there was a steady rise in CHD rate among white women, although less steep than that of men, when, in fact, there was no rise among white women at all. Because men and women were undergoing the same so-called lifestyle trends, including diet and smoking patterns, it is nonsense to attribute nearly opposite CHD trends to the same lifestyle trends. To this writer's knowledge, the alliance has never indicated to the public that American white women did not undergo a CHD epidemic but it certainly has implied and continues to imply the opposite state-of-affairs. This constitutes a half truth of monumental proportions.

Figure 1-4 shows that CHD mortality essentially stabilized by 1963 for white men and then exhibited a rather abrupt and steep decline after 1966.[a] White females also exhibited a decline after 1966, although not nearly as steep as that for men. As will be seen in Chapter 9, the alliance generally has not gone so far as to attribute all of these declines to lifestyle changes, e.g., "changes in lifestyle and lifestyle-related risk factors have made a key contribution to the decline in CHD mortality." However, it strongly implies that the lion's share was due to such changes, despite two conflicting sets of data. First, since the "unfavorable" lifestyle trends had no affect on white females, it is illogical to claim that "favorable" changes caused the CHD mortality decline among white females. And second, the CHD mortality stabilization and subsequent decline among white males occurred long before the public was made aware of "risk factors." In fact, the CHD decline occurred in California in 1954 and stabilized and declined in New York and Utah, respectively, during the 1950s, before risk factors were being "discovered" by the Framingham investigators.

Like the infectious diseases trends, the alliance has taken at least partial credit for the CHD mortality decline. As will be seen in Chapter 9, that behavior has represented another monumental half-truth. There is no evidence that anything the alliance has done has influenced the decline. To compensate for this discrepancy the alliance has suggested that it be set aside, along with skepticism, and accept the dogma. For example, the 1981 NHLBI Working Group[3068] concluded that "excessive skepticism" is harmful and quoted Charles Darwin as the source for that rather foolish remark, i.e., "I am not very skeptical, a frame of mind which I believe to be injurious to the progress of science. A good deal of skepticism in a scientific man is advisable to avoid much loss of time, but I have met with not a few men, who, I feel sure, have often thus been deterred from experiment or observations which would have proved directly or indirectly serviceable."[b] By focusing nearly all their attention on

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[a] But as will be seen in Chapter 9 and elsewhere, the actual decline began in 1964.

[b] In 1982 Stamler[3002] quoted the same statement and referred to it as "a seminal thought of Charles Darwin."

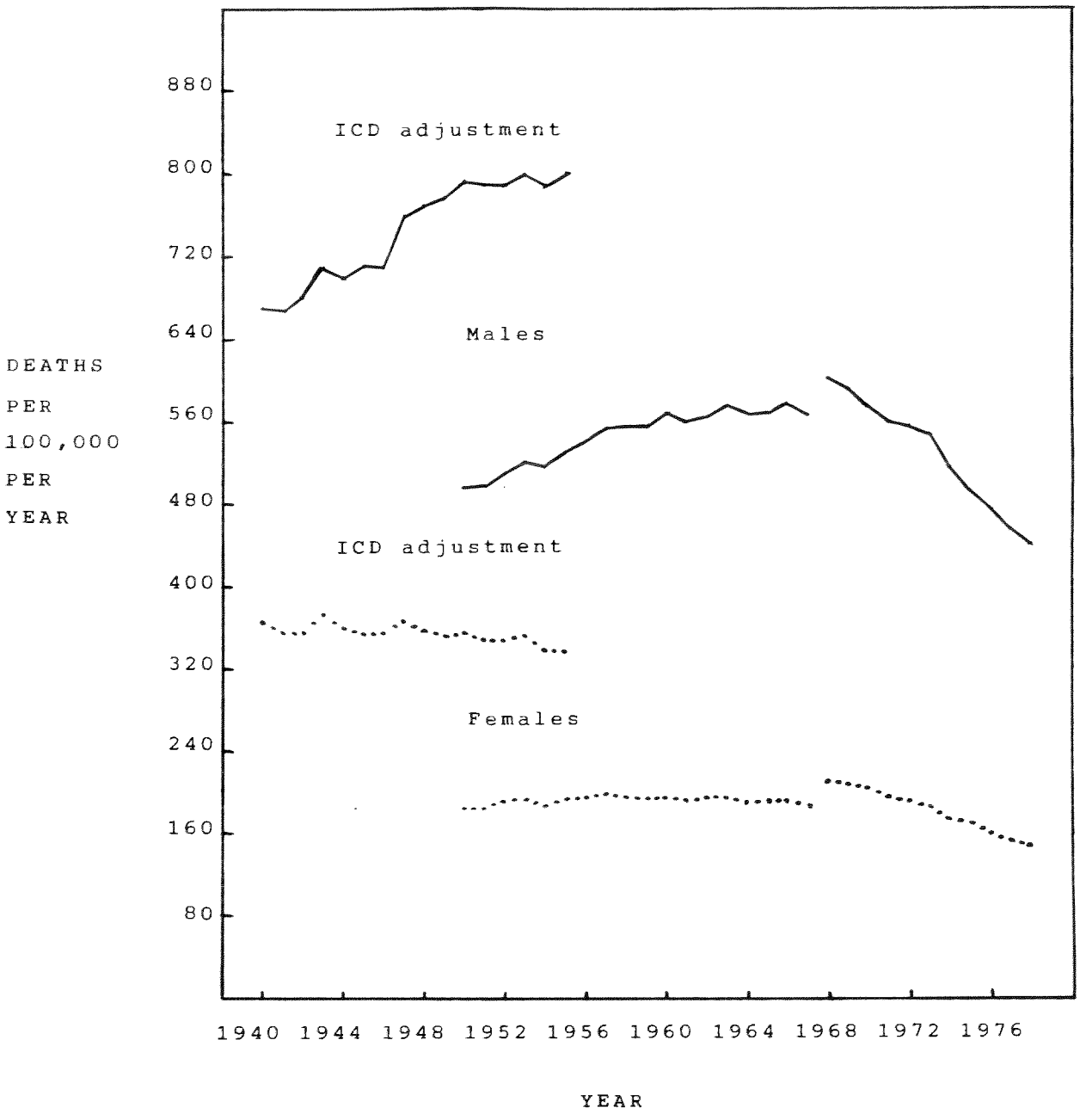

Figure 1-4. Age-adjusted CHD deaths by white males and females and year, ages 35-74 (adapted from Luepker and Higgins[2798] and NHLBI Working Group[3068])

lipids and other risk factors, the NHLBI and AHA have deterred hundreds and perhaps thousands of researchers from pursuing other more fruitful research endeavors. The alliance's attitude is similar to that of Saturday Night Live's Hans and Franz, namely, "Hear me now and believe me later."

It has long been known that the clinical symptoms of CHD among females occur 10 to 20 years later than they do in males. This discrepancy has generally been attributed to the hypothesized protection of estrogens. For example, Stamler[1125] stated in 1963 that "During the years 1949 to 1952, extensive evidence--clinico-pathologic, animal experimental, and epidemiologic--was accumulated relating estrogens to cholesterol-lipid-lipoprotein metabolism, and suggesting a possible protective effect of these hormones against clinical atherosclerotic CHD. It was recognized that middle-aged women with intact ovaries are remarkably resistant to clinical coronary disease and have significantly lower prevalence rates of severe atherosclerosis morphologically in coronary arteries--phenomena that gradually disappear in the years following oophorectomy or normal menopause."

Many years later (1986) Lerner and Kannel[3107] also maintained that women suffered a unique increase in CHD mortality during middle-age but were less sure than was Stamler with respect to causation. They said, "The reasons for the upturn in the female CHD mortality rate around the ages of 45 to 55 years have not been firmly established."

But when we call upon vital statistics, we do not see any evidence that CHD mortality rates among females after menopause depart from the trends underway before menopause.

Figure 1-5 shows the annual CHD mortality rates for males and females as a function of 10-year age groups. The data were taken from 1984 but the same trends can be seen for any year.[2798] The most obvious characteristic of these trends, ignoring their displacement for the moment, is that they are effectively identical for both sexes. If the availability or lack of estrogen had a unique effect on the female death rate, the female trend would reveal a noticeable departure from that of the male, but it does not. Like the male trend, the female trend demonstrates a perfect accelerating curve, with no unique deviation of that curve between the ages 45 to 64. Finally, the percentage difference between the sexes is initially very high but steadily decreases after age 35, not abruptly after the menopause years.

A fourth obstacle to the alliance's argument relates to the hypothesized effects of estrogens, i.e., they are said to provide a more favorable lipid profile after menopause than when estrogen therapy is not administered. But this assertion was clearly shown to be not the case by Framingham investigators.[2597] Estrogen users were found to have higher LDL levels and lower HDL levels after age 49 than did nonusers. Obviously, these trends are considered highly unfavorable by the alliance and do not support the hypothesized effects of estrogens.

In sum, the huge differences in CHD mortality between the sexes, both in rates and trends, are inexplicable in terms of diet or estrogen concentrations.

The absurdity of half truths is exceedingly visible when comparisons are made between mortality rates of CHD and cancer. The NHLBI and the National Cancer Institute both claim that fat, particularly saturated fat, is a major cause of atherosclerosis and cancer. The NHLBI also claims that the CHD mortality decrease since 1963 has been the result, in part, of Americans reducing their consumption of fat and saturated fat. But if fat and saturated fat were causes of CHD and cancer and if their consumption has decreased since before 1963, why are cancer deaths increasing as rapidly as CHD deaths are decreasing (Figure 1-6). Although much of

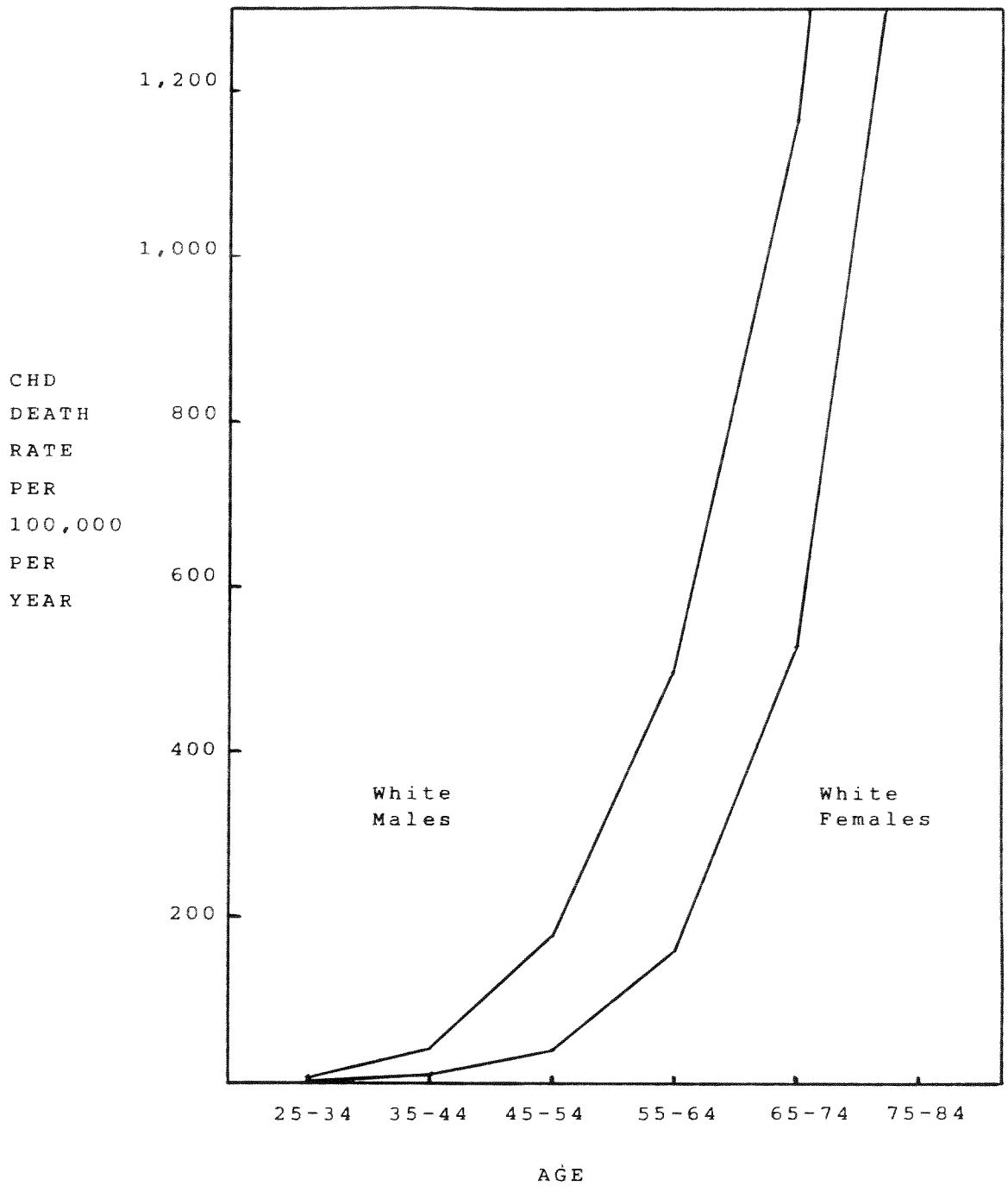

Figure 1-5. Age-adjusted CHD mortality rates for males and females by 10-year age groups-1984 (adapted from Higgins and Luepker, 1988[2798])

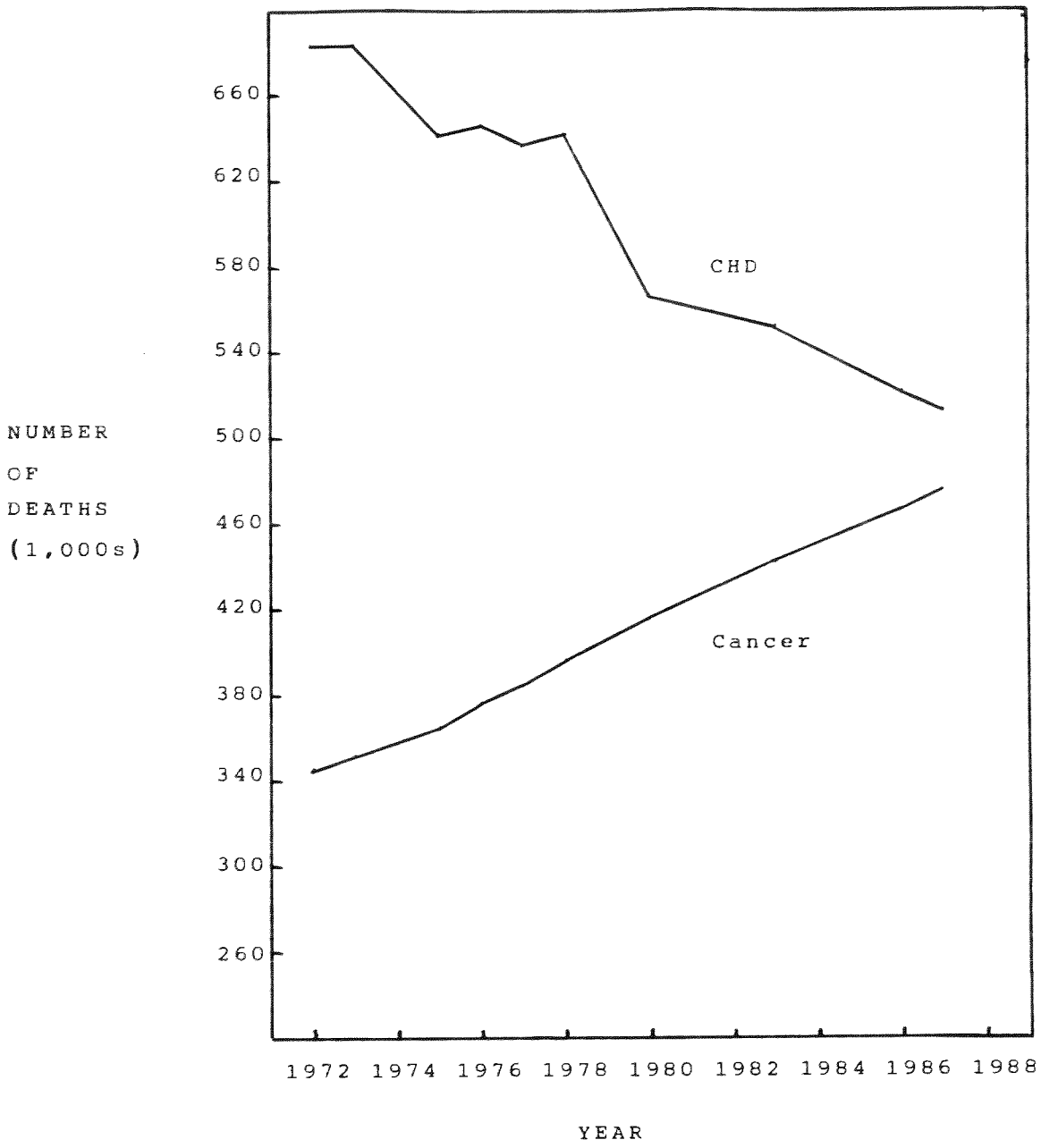

Figure 1-6 Numbers of CHD and cancer deaths from 1972 to 1987 (adapted from Statistical Abstracts1895,1896)

the increasing cancer mortality is due to lung cancer, other cancer trends are not consistent with the CHD trends as well. According to Sutherland et al.[3240] cancer overtook heart disease in 1986 as the leading cause of death among persons 35 to 64 years of age.

Consider the testimony of Gio Gori,[2936] deputy director of the National Cancer Institute, before the 1976 Senate Select Committee on Nutrition and Human Needs. He said, "Nutrition is coming of age. Only a few years ago it would have raised some eyebrows to have said that nutrition itself may be responsible for cancer or cardiovascular diseases. The evidence we have today makes this statement not only a possibility but a certainty. By and large, stomach cancer is a disease of the poor which correlates with a low dietary intake of Vitamin A and protein, and a high intake of carbohydrates."[a] But stomach cancer in the U.S. was decreasing decades before the CHD "epidemic" peaked and has continued to decrease decades afterwards.[2835] It does not correlate at all with dietary changes which the alliance claims occurred before and after the CHD "epidemic."

Gori and Ernst Wynder[2937] both maintained that low stomach and high colon and breast cancer mortality rates are typical of the "high fat" diets of the U.S. and other westernized countries. Since we have established that stomach cancer does not correlate with dietary changes purported to have taken place over the last 60 years, let us examine the breast and colon cancer trends. According to the American Cancer Society[2835] and the WHO Statistics Annual,[2835] there has been virtually no change in breast cancer mortality rates in the U.S. from 1930 to the present. Moreover, colon cancer mortality has been decreasing in women since about 1945 and has remained essentially constant among men since 1940. Therefore, the colon and breast cancer trends do not correlate, as indicated by Gori and Wynder, and they are obviously inconsistent with dietary intake trends.

Gori noted that the Japanese diet had traditionally been a low fat, high carbohydrate diet but was gradually becoming westernized since 1945. Since the U.S. diet is supposed to be moving in the opposite direction, we should expect to see opposite mortality trends, for example, in stomach and breast cancer. But, in fact, the trends in both countries have been identical. Moreover, lung cancer mortality has been much higher in the U.S. than in Japan since 1950, despite the fact that the Japanese have the highest percentages of cigarette smokers in the world.

In effect, nothing that Gori stated was consistent with mortality and dietary trends occurring in the U.S. or Japan, although some of his comments could be construed to be half truths.

Both NHLBI and the cancer agencies incriminate the same food nutrients as the causes of CHD and many forms of cancer. CHD and most of the relevant cancer mortality trends are moving in the opposite directions. The cancer groups claim it is because we are eating too many of the incriminated nutrients. NHLBI/AHA claim that we are reducing our intake of such nutrients. It is astonishing that they cannot see the fallacies of their contradictory dogma.

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[a] Ernst Wynder, president of the American Health Foundation, testified at the same hearings that the high incidence of stomach cancer "may be related partially to a low intake of Vitamin C." He made no mention of Vitamin A.

CONTRADICTIONS

Alliance members contradict themselves and each other with incredible frequency and often do not seem to recognize it. Many of the contradictions occur in different contexts but many also occur in the same context. Some appear to occur because alliance members are insufficiently educated as scientists and apparently cannot detect their own contradictions, even though the latter may be rather profound. Other contradictions appear to be the result of either ignorance of the facts (thus yielding different "stories" each time they are told) or a purposeful desire to influence others in different contexts. Examples of each follow. Many more are presented in Chapter 10.

The Total Fat Folly

Alliance members, especially Ancel Keys, have maintained for more than 30 years that total fat reduction results in lower blood cholesterol levels. For example, Ullman and (William) Connor[3341] recently said, "It must be emphasized that to decrease serum cholesterol levels and the risk of CHD, both total and saturated fat intake must be decreased" and Babayan and Blackburn[3343] held that "The real issue, and the key to educating the public, is the need for limitation of excessive caloric intake and the restriction of fat intake to not more than 30%." Yet, the same alliance members have used and/or promoted the Keys and Hegsted equations (Chapter 5) which predict blood cholesterol changes as a function of variations in saturated and polyunsaturated fats and dietary cholesterol. The equations assume total fat irrelevant. Alliance members seem not to recognize that the equation contradicts the notion that total fat reduction decreases cholesterol. (See later section in this chapter for a more detailed discussion of this topic.)

Numerators and Denominators

In his effort to discount the proposition that exercise increases the probability of sudden death, Castelli[3324] questioned the denominators used by some authors in creating rates of sudden death. He said, "Before we can draw any conclusions about how dangerous it is to run, we need to find a denominator. I often refer to classic epidemiologic studies as cohort or 'denominator' studies because they start with a large group (or cohort) of people who are alive and well and then follow them for a period of time."[a] Castelli, of course, considered the large group the denominator so that, for example, 8 (numerator) sudden deaths among a large group of 5,000 people would represent a very small rate of 8/5,000 or 0.16%. He continued, "The primary message here is that the final decision on whether something is good or bad for you or your patients cannot be made solely from the numerator of a study. When presented with the results of a numerator study, always ask, 'What's the denominator?'"

Like most alliance members, Castelli predominantly uses "risk ratios" to decide "whether something is good or bad for you." Risk ratios, of course, are derived from numerators only and ignore denominators. He is also one of the most prolific promoters of the "2% reduction in risk for every 1% reduction in blood cholesterol" concept,[1302,3337] although it is calculated without benefit of cohort numbers as denominators. For example, he stated that "The best of all these [trial] studies is the Lipid Research Clinics-Coronary Primary Prevention Trial. For a 9% fall in cholesterol, it got a 19% fall in CHD."[1302] The 19% was calculated as the

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[a] This writer has not found the word, "denominator" in any other article authored by Castelli.

percentage difference between 187 CHD events in the control and 155 events in the treated group. Following his advice, we can ask, "What's the denominator?" Had Castelli used cohort denominators, the difference between the control and treated groups would have been 1.7%, rather than 19%.

There is no doubt that Castelli recognizes his own contradictions; he simply uses opposite arguments in different contexts to propagate the alliance's dogma.

Surgery Patients as Experimental Subjects

When Michael DeBakey announced in 1987 that he and his colleagues found no relationship between blood cholesterol level and degree of restenosis in 15,000 bypass patients, NHLBI's Claude Lenfant said, "I don't think that surgery patients are a good model for understanding atherosclerosis."[677] But when the NHLBI-sponsored Blankenhorn et al. study was announced at a press conference later in the same year, suggesting that cholesterol-lowering decreased progression and increased regression in bypass patients, Lenfant used the opposite argument, i.e., "For the first time, we are presented with evidence regarding regression of lesions in humans."[859] When Lenfant criticized the use of surgery patients with respect to DeBakey's study, he undoubtedly was aware that he would soon attend a press conference praising the use of surgery patients.

High Carbohydrate Diets, HDL and LDL

Virtually all alliance members, including Castelli, encourage the reduction of blood LDL levels and recommend the consumption of high-carbohydrate, low-saturated fat diets. All alliance members also believe that low HDL is an important risk factor for CHD. Castelli maintains that HDL is the most important risk factor.[3337] Yet, it is well-known that the higher the percentage of carbohydrates in the diet, the lower the HDL level, and the lower the percentage of saturated fats in the diet, the lower the HDL level.

"Skirting the issue" can be seen in a recent article by Neil Stone.[3347] In listing the factors that reduce HDL levels he included polyunsaturated fats but omitted carbohydrates. In describing NCEP's Step 1 and Step 2 diets he indicated that recommended total fat is 30% of calories and that recommended saturated and polyunsaturated fats are 10% and 10%, respectively. He made a point of noting that polyunsaturated but not monounsaturated fats reduce HDL. Not only did he fail to describe the relationship between carbohydrates and HDL, this writer did not find the word "carbohydrate" in his discussion. Thus, Stone avoided a contradiction by omitting all references to carbohydrates.

Criteria for Treatment

Castelli[1302] said, "You only need to remember two numbers: 4.5 and 150. We want the ratio of total cholesterol/HDL cholesterol to be under 4.5 unless the person's total cholesterol is 150 or lower, in which case we don't care what his HDL cholesterol is." However, in responding to a statement that when total cholesterol is lowered, HDL is often lowered disproportionately, yielding a higher total cholesterol/HDL ratio, Rifkind[3223] held that "we think that the focus should be on reducing LDL, and that a consequent decrease in HDL is tolerable."

W. Virgil Brown[3223] either skirted the issue or had no idea what was going on. He was asked, "Suppose a patient had the following lipid profile: total cholesterol 279 mg, LDL 173 mg and HDL 78 mg. After some intervention, either diet modification or probucol therapy, these values decreased to 230, 150 and 58 mg, respectively. Would

you consider that this patient had benefited from treatment?" [Please note that Brown's "answer" was completely irrelevant.] Brown replied, "It's difficult to say, since no study has addressed that issue. We don't as yet know the long-term effects of treatment with probucol. Although it might help in theory, there are certainly cases in which this drug has had adverse effects on the lipid profile. For such a patient, I would look carefully at changes in lifestyle, since we cannot assume that the patient is not at risk just because the HDL level is high. Family history should also be considered. Certainly dietary therapy and hygienic measures such as weight loss and exercise should be initiated. In my opinion, drug therapy would not be indicated." Of course, none of this reply is responsive to the question.

The question asked Brown would be answered quite differently by Rifkind and Castelli. Rifkind would say that the patient has benefited from treatment because both total cholesterol and LDL decreased. Castelli would say that the treatment worsened the patient's condition because the total cholesterol/HDL ratio increased from 3.6 to 4.0.

Double Contradictions

The alliance also produces double or compounded contradictions. For example, many alliance members have expressed the following three assertions on many occasions: (1) the cholesterol levels of Americans are above a threshold and that is why dietary differences among Americans are not correlated with blood cholesterol levels and why CHD events occur almost as frequently below the mean cholesterol levels as above it; (2) the blood cholesterol-CHD relationship is continuous, graded and without a threshold; and (3) reducing blood cholesterol causes regression of atherosclerotic lesions. The first assertion is logically incompatible with the second and the second is logically incompatible with the third. As will be seen in Chapter 7, angiographic studies have reported regression with cholesterol reduction even though the final cholesterol levels were well above the U.S. average. Thus, the first assertion also conflicts with the third.

The first assertion is also absurd. The American population demonstrates a very wide range of cholesterol levels. If the population were over a threshold, then virtually everyone would die of CHD.

Contradicting Arguments

The Framingham investigators present opposite arguments with respect to the same subject or data. For example, Castelli, Kannel and their colleagues[453] stated in 1977 that "The common procedure of calculating ratios of HDL to total or LDL cholesterol should probably be avoided since a person may have the same ratio at a low level of HDL and LDL cholesterol or at high levels, and it is difficult to believe that these have the same medical and physiologic significance. Beyond that, it appears to be less satisfactory as a risk criterion than linear combination." But a few years later Kannel[1091] presented the opposite argument, i.e., "Both the LDL and HDL effects are independent of each other. There is no particular benefit to making linear combinations of LDL and HDL." Of course, the 1980s saw Castelli emphasizing the total to HDL cholesterol above all other lipid "risk factors."

AN ALLIANCE PASTIME: REWRITING HISTORY

The 1981 NHLBI Working Group Report[3068] presented an excellent example of how 18 "scientists" in unison can claim a causal relationship between animal fat consumption trends and CHD mortality trends and then present data which contradicts that claim. The authors stated that "The dietary pattern associated with atherosclerotic disease is...a diet with a high proportion of calories from fat-rich

animal products (meats, eggs, dairy products) and from separated (visible) fats, a sizable proportion of which is of animal origin (at least until recently in the U.S.)." They then presented a figure (Figure 1-7) which showed that animal fat consumption had steadily decreased and vegetable fat consumption had greatly increased long before, during, and after the CHD epidemic.

The Working Group authors continued, "over the decades, a remarkable change has occurred in the use of the visible fats" [see Figure 1-8]. Since 1950, use of lard...has gone down 80% per capita [but note that it had been decreasing since 1909]; and butter, 55 percent [but note that it had been decreasing since 1909], both reflecting continuation and acceleration of a decades-long downward trend [the admission that these trends occurred long before the CHD epidemic but the authors had nothing to say about the epidemic in their discussion]. Margarine has come into increasing use, with a doubling of its per capita consumption since 1950 alone [but had greatly increased steadily since 1909]... Use of vegetable shortening has also increased by 73% since 1950...[and]...there has been a marked increased in use of vegetable oils...[but note that all of these vegetable fats steadily increased throughout the century]." Although beef fat increased slightly (and mostly after the CHD epidemic asymptoted), this trend was trivial compared to the combined trends of other fats.

The Working Group's focus on 1950 as a base period for describing subsequent trends was clearly an attempt to suggest that such trends (with a 17 year latency period) could account for the CHD decline which seriously began in 1967. But not only are latency periods theoretically untenable for relationships said to be dose-related (i.e., blood cholesterol and CHD), the authors purposely ignored the obvious embarrassment of attempting to explain how a CHD epidemic could occur after 1940 when the dietary trends since 1909 were opposite to those described as being atherosclerosis promoting. The Working Group could not possibly have been so naive as to have not seen the obvious contradiction. It is also incomprehensible how the contradiction could have escaped the reader. The matter is academic, however, because NHLBI's money and power have permitted the agency to disregard embarrassing evidence and simply re-write history.

As will be seen in Chapters 2 and 3, other prominent alliance members such as Ancel Keys and Irvine Page readily acknowledged that the increasing CHD mortality rate during the 1940s and 1950s was accompanied by the increasing consumption of vegetable fats, not animal fats. When the differential effects of animal and vegetable fats became well-known in the late 1950s, Keys and others began re-writing history by maintaining that the CHD mortality rate was accompanied by increasing consumption of animal fats.

The Senate Select Committee on Nutrition and Human Needs adopted the AHA dietary recommendations in its 1977 booklet, "Dietary Goals of the U.S." In the introductory statement Senator George McGovern said, "...our diets have changed radically within the last 50 years [1927-1977], with great and often very harmful effects on our health. These dietary changes represent as great a threat to public health as smoking. Too much fat, too much sugar or salt, can be and are linked directly [he must have meant "indirectly"] to heart disease..."[1055] The booklet presented a figure showing that available fat had increased since 1910 but no trend data were given for animal and vegetable fat consumption. The heads of the Select Committee must have been buried in the alliance's propaganda because the CHD mortality rate had been declining for 14 years and animal fat consumption had been declining since the turn of the century.

McGovern indicated that "Last year every man, woman and child in the U.S. consumed 125 pounds of fat..." that statement was not only an absurd exaggeration of reality, it was also contradictory to CHD mortality trends. That amount of fat represents 155 grams per day. The average adult male did not consume anywhere near

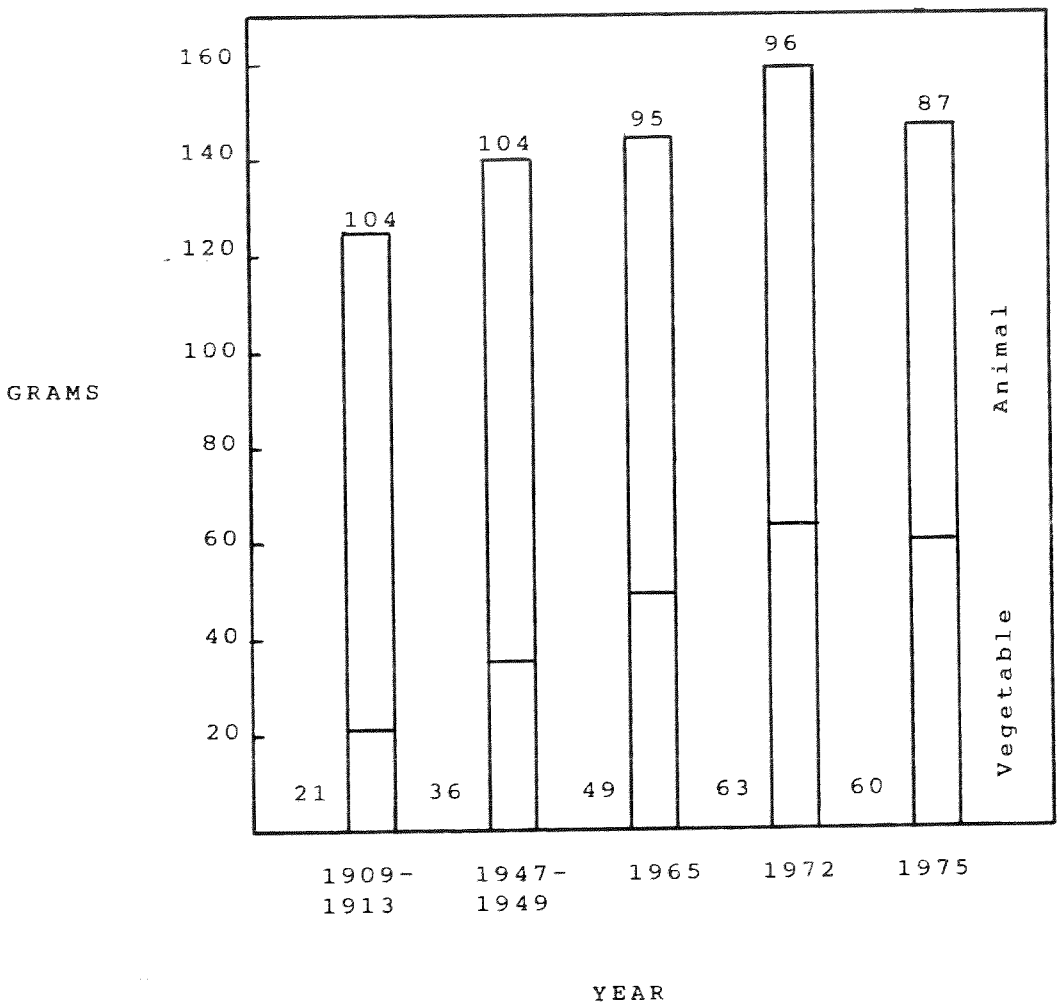

Figure 1-7. Sources of nutrient fat in the U.S. diet (adapted from 1981 NHLBI Working Group[3068])

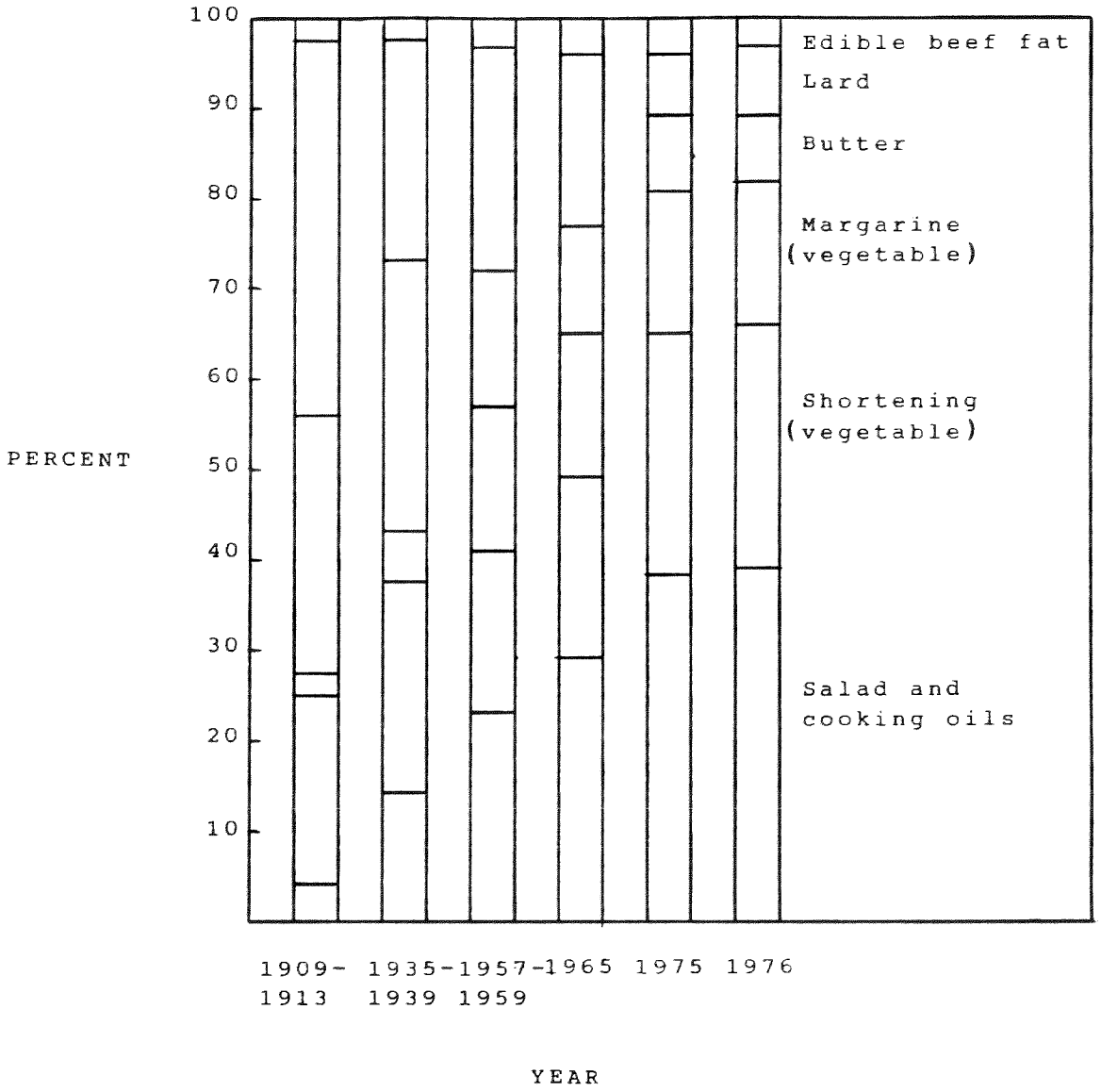

Figure 1-8. Nutrient fat from fats and oils (adapted from 1981 NHLBI Working Group[3068])

that amount (e.g., 50% of 2,800 calorie diet) and females and children consumed far less than adult males. Moreover, if there was a rising intake of fat, whether animal, saturated or what have you, why had the CHD mortality rate been declining for fourteen years? Of course, there was no logic to this argument but it was consistent with the alliance's mode of reasoning.

As discussed in detail in Chapter 2 and 10, the AHA's dietary recommendations to the public have changed substantially over the last 30 years, although such changes are vigorously denied by AHA members. This writer's staff made repeated requests of the AHA in Dallas for copies of the various recommendations during the preparation of this volume.[a] One call to Mary Winston elicited the following questions: "Why do you want them?"; and "How do you intend to use them?" Winston also indicated that we could not use the recommendations without AHA's permission. Imagine that! The AHA makes dietary recommendations to the public via the media, literature and pamphlets and then states that the public has to gain the AHA's permission to use them.

Why is the AHA so resistive to disclosing its past recommendations? Simply because it would be embarrassing to its members.

ATHEROSCLEROSIS AND HEMORRHOIDS

The term "Coronary Heart Disease" (CHD) has been badly abused in the literature by the alliance. In 1952 Patterson[278] emphasized that CHD "is not a pathological entity" but rather "a clinical term for a number of symptom complexes which result from myocardial ischemia." In 1957 Keys[276] stated that "It must be recognized that atherosclerosis is by no means synonymous with CHD...[276] In 1961 Kannel et al.[2093] reported that the majority of sudden deaths occurring in the Framingham study were not associated with atherosclerosis. In 1981 Oliver[1378] observed that "IHD is often still regarded as a homogeneous clinical entity: death, sudden death, MI and even angina are indiscriminately lumped together as 'all coronary events.'" And in 1989 Stehbens[3124] referred to CHD as "an imprecise clinical syndrome of many causes."

Castelli[1179] reported that "About half of the deaths that are from heart attack or stroke are brought about by atherosclerosis..." While this writer doubts that atherosclerosis "brings about" that percentage, let us assume the statement to be correct. The corollary is that half of all fatal heart attacks are <u>not</u> brought about by atherosclerosis. Since there is virtually no evidence or theory relating blood cholesterol with nonatherosclerotic heart attacks, the combining of <u>all</u> fatal and nonfatal heart attacks as an endpoint in prospective studies and clinical trials makes as much sense as combining atherosclerotic heart attacks with the incidence of hemorrhoids. And yet, that is precisely what the alliance has done for decades. Relevant and irrelevant heart attacks are used in statistical analyses as the effects of cholesterol lowering, as are "sudden deaths" which have been found repeatedly in the Framingham study to have no relationship whatsoever with blood cholesterol levels.

Prospective studies and clinical trials have historically been based on a great deal of irrelevant data. When it is also realized that these investigations have also been confounded by the involvement of many physicians completing death certificates, a condition known to yield considerable errors, the magnitude of irrelevant or incorrect data in studies and trials is so great, it is actually humorous. However, the humor

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[a] Since copies had already been obtained elsewhere, these requests were made in order to evaluate the openness of the AHA.

gives way to the absurd because alliance members such as Castelli and Kannel know that their well-publicized data are highly confounded and yet they pretend otherwise.

HEADS I WIN, TAILS I DON'T LOSE

Volume 1 of this review indicated that all but one clinical trial completed before 1981 had failed to demonstrate that cholesterol-lowering reduced all-cause or CHD mortality.[a] Moreover, no blinded or randomized trial demonstrated a convincing reduction of CHD events. During the 1970s the MRFIT and the LRC trials were launched instead of a large diet trial which nearly everyone, including the AHA, had recommended. The MRFIT and LRC trials were proposed in the 1971 Task Force report.[705] In 1978 NHLBI director Robert Levy created the NHLBI Working Group "to assess the impact of the Task Force report" and its recommendations. The Working Group report[3067,3068] was published in 1981 and the 18 authors (including Jeremiah Stamler) indicated that the MRFIT and LRC trials would be completed in 1982 and 1983, respectively.

In view of the fact that the rather massive number of clinical trials to date, particularly diet trials, had provided little or no evidence in support of the lipid hypothesis or lifestyle changes in general, it was not surprising, therefore, that the Working Group exhibited little optimism regarding the "success" of the MRFIT and LRC clinical trials. In fact, there is no doubt that the Working Group alerted the medical and political communities to the possibility of negative findings and, in the process, substantially downplayed the importance of such findings. Their rationale for positive and negative findings follow. The reader should note that their rationale followed the adage, "heads I win, tails you lose," which completely characterized the alliance's historical attitude of never admitting to being wrong.

The Working Group indicated that if the MRFIT findings are positive, "it will have great practical significance as a direct demonstration of the ability to influence the cause of the [atherosclerotic] disease, even when the individuals are at very high risk and the intervention efforts are undertaken as far down the road as the decades of middle age. Such results will also constitute evidence to support the conclusion that lifestyles and risk factors are important in producing the disease."

"But if the MRFIT's findings are negative, it will not represent a decisive test of the role of lifestyles in general and diet in particular, in the etiology of the disease, since it is entirely possible that such a result would be a consequence of 'too little and too late.'

"A similar analysis[b] can readily be made with respect to studies currently in progress here and abroad in the area of drug intervention to control risk factors... It is possible that these [including the LRC], too, may experience a negative or inconclusive outcome because of the problem of 'too little and too late.'

"Clearly, then, the situation again is one in which a positive outcome will be very useful practically in clarifying the benefit-to-risk ratio of drug treatment and thereby clarifying therapeutic approaches, and in further encouraging vigorous implementation of preventive approaches. Such a result would also have theoretical meaning in regard

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[a] The one exception was the Dorr et al.[843] trial, funded and conducted by the Upjohn Company which "evaluated" its own drug, colestipol. Their results have never been even remotely duplicated.

[b] More appropriate than "analysis" is "excuse."

to issues of causation. It would be further confirmation of conclusions already abundantly justified by the wealth of data from other studies of many kinds. A negative outcome will not be critically meaningful, either, in regard to the etiologic factors at work."

Heads I win, tails I don't lose.

ON THE MERRY, MERRY USE OF MAY

The frequency with which the word "may" and its synonyms are used in the scientific literature on diet, blood cholesterol and CHD is absolutely astounding. It is used almost exclusively in a strictly speculative sense, although readers are likely to erroneously view it as reflecting a high probability event. This translation is frequently performed by media writers and even other physicians. One gets the distinct impression that journal articles would be 50% of their current size were it not for "may," a word that allows researchers to explain thousands of processes and outcomes without scientific evidence. To illustrate, consider the following statements:

"A vegetarian diet may be associated with a reduced risk of ischemic heart disease" (Fisher et al., 1986[2428]); and

"Dietary treatment of atherosclerosis may 'heal' the endothelium and reduce the susceptibility to vasospasm" (Lopez and Heistad, 1988[2286]).

If the reader winces while reading the following double speculation, double negative sentence by Hegsted, it is perfectly understandable:

"The atherosclerotic lesion may not be completely irreversible but is probably nearly so in man" (Hegsted, 1978[2692]).

Consider now examples of undoubtedly thousands of statements regarding the formation of atherosclerotic plaque:

"LDLs are the low density lipoproteins that contain the greatest amounts of cholesterol and may be responsible for depositing cholesterol in the artery walls" (NIH, 1987[2288]);

"It is possible that cholesterol-enriched particles may be taken up by circulating monocytes and deposited on our arterial walls" (LaRosa, 1989[2396]);

"Small lipoproteins, LDL and certain of the smaller VLDL and remnants may enter through defects and tears in the arterial walls of arteries" (Karan, 1989[2285]); and

"Our premise is that the length of time chylomicron remains on the vessel wall may influence the amount of cholesterol deposits" (Staprans, 1989[2258]).

In his 1988 article entitled, "Mechanism of the interaction of hypertension and hypercholesterolemia in atherogenesis: the effects of antihypertensive agents," Victor Dzau used 9 "mays" in his abstract composed of 13 sentences and 27 "mays" in two pages of written text.[2081] And in his 1989 article entitled, "Recent concepts on the pathogenesis of atherosclerosis," M. Davia Haust, a former president of the Canadian Atherosclerosis Society, described the "injury and repair concept in six sentences using five "mays."[2175]

Let us now see how media writers transform "mays" into certainty, using the topic of HDL. In medical journals the preferred means of describing HDL's role in atherosclerosis is as follows:

"HDL takes on additional cholesterol from various tissues (probably including the cells of vascular intima) and this undergoes esterfication. HDL particles may deliver this cholesterol directly to the liver" (Jones and Gotto, 1989[2281]);

"HDLs...are believed to take cholesterol away from the cells in artery walls and transport it back to the liver" (NIH, 1987[2288]);

"Although it is known that HDL...arises in the liver and intestine, its role in lipid transport is unclear. HDL...may remove cholesterol from the tissues" (Levy, 1986[1427]); and

There is "a general concept that HDL facilitates the removal of cholesterol from cell membranes and either directly or indirectly targets that cholesterol for uptake and degradation by the liver" (Ginsberg, 1988[2203]).[a]

Media writers transformed the above speculative statements into certain facts, e.g.,

"HDL's job in the bloodstream is to scavenge potentially dangerous cholesterol out of the body" (Waldholz, Wall Street Journal, 1988[2283]),

"High density lipoproteins (HDL) help eliminate cholesterol from the body" (Seabrook, San Francisco Chronicl e, 1987[2209]),

"The high-density lipoproteins carry cholesterol away from the blood vessels" (Kolata, New York Times, 1987, 1988[2212,2234]),

HDL "cleanses the blood vessels of fatty deposits and flushes cholesterol out of the body" (Brody, New York Times, 1987, 1988[2211,2233]),

"HDL cholesterol is responsible for transporting cholesterol...(to)...the liver where its cholesterol is incorporated into bile acids and excreted" (Tipton, Los Angeles Times, 1988[2237]).[b]

Even physicians have indicated certainty in their writings in nonscientific publications, e.g.,

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[a] Manninen of Finland recently expressed greater certainty about HDL's role.[2214] However, it will be recalled that Finnish investigators have tended to accept questionable data as fact, particularly data from unblinded and/or nonrandomized clinical trials.

[b] A few writers have, however, maintained the uncertainty expressed in journals.[1619,2202,2205,2236]

"The helpful component, high-density lipoprotein (HDL) cholesterol, picks up excess cholesterol and brings it to the liver where it is disposed of" (Wohl, 1988[2206]),

"HDLs are considered good because they pick up cholesterol deposits all over the body and bring them back to the liver for excretion" (Miller, 1989[2239]), and

"Exercise stimulates the production of a protein called HDL, which removes fat from your blood..."(Castelli, 1990[2598]).

And uncertainty was eliminated in a description presented in a recent issue of Critical Care Nurse,

"HDL removes cholesterol from arterial walls and tissues" (Cohen, 1989[2240]).

Yet, HDL's actual role is "largely a mystery" (Lacko[2477]). NHLBI's Gordon and Rifkind emphasized in 1989 that "It has been hypothesized that HDL is involved in the 'reverse transport' of cholesterol from peripheral tissues to the liver. The relevance of these reverse-transport pathways to the rate of deposition (or removal of cholesterol in atherosclerotic plaques) has yet to be established. It is difficult to determine whether low levels of HDL cholesterol have a direct etiologic role in atherogenesis or serve only as a marker of a more fundamental disorder."[2459]

The entire history of the AHA's position on diet and CHD has been dependent on the use of the word "may." It was stated in its first recommendations to the public in 1961 that "A reduction in blood cholesterol by dietary means, which also emphasizes weight control, may lessen the development or extension of atherosclerosis..."[517] In presenting the rationale for the AHA's recommendations in 1982, Grundy et al. reported that "since no harm can be visualized, and because it may lessen the risk of CHD, a change to such a [Prudent] diet would seem prudent."[499] In 1985 the AHA indicated that "The blood cholesterol tends to rise with age, and the recommended diet may help to prevent this rise. Diets low in saturated fats and cholesterol may defer to prevent coronary heart disease."[980] In apparently the latest AHA statement the AHA said, "since reductions in blood cholesterol and blood pressure have been shown to describe the incidence of cardiovascular disease in previously healthy adults, added emphasis is placed on dietary modifications that may minimize these risk factors."[2632] Thus, the actual certainty with which the AHA attributes protection against CHD to dietary changes has not transcended "may" in a period of 30 years.

In November 1989 the FDA proposed that it would join the alliance in the use of "may."[2520,2594] The proposal would allow the following claims to be made on food labels: fiber may reduce the risk of colon cancer and heart disease; low fat may reduce the risk of cancer and heart disease; low salt may reduce the risk of high blood pressure, etc. The following year, the NCEP's Carleton[2653] said that the NCEP recommends that every American lower his cholesterol level because it "is likely to be beneficial." And in 1991 the American Health Foundation's Barone[3074] maintained that "lowering dietary fat to the 20% level may convey not only benefits regarding cancer and heart disease risk but may, according to other investigators, improve the immune system."

Finally, consider the massive subjectivity and uncertainty in a single sentence by Blankenhorn, i.e., "I think there is a majority opinion which now feels that lowering cholesterol, if its elevated, is a good idea."[2534]

This writer may win the California lottery this year but it is doubtful that anyone would bet on it. It is likewise foolish to wager that more than a fraction of the enormous speculative statements in the literature will ever be proven correct.

The prolific use of "may" and its synonyms in the literature is but one example of the "looseness" exhibited by so many diet-CHD researchers. The entire National Cholesterol Education Program is based on a series of compounded "mays." For example, there may have been a CHD epidemic during this century. The epidemic may have been caused by high blood cholesterol levels. And the high cholesterol levels may have been caused by high fat, saturated fat and cholesterol diets. Ergo, we are changing the American diet because it may reduce blood cholesterol levels which may reduce the prevalence of CHD which may reduce the CHD epidemic which probably did not occur in the first place, as shown in Volume 1 and amplified in Chapter 3 of this volume. No matter. The NCEP's Richard Carleton told the press in early 1990 with something less than strong conviction that dietary changes are "likely to be beneficial."[2653]

ACCENTUATE THE POSITIVE, ELIMINATE THE NEGATIVE

Kretch and Crutchfield[2497] observed that people routinely use opposite explanations for phenomena in different contexts and think nothing of it. For example, most people believe the adage, "Repeat a lie frequently enough and people will believe it." But in another context the same people will believe the opposite adage, "The truth will always prevail." Some additional pairs of (opposite) adages follow:

"Clothes make the man."
"You can't make a silk purse out of a sow's ear."

"You can't teach an old dog new tricks."
"Never too old to learn."

"Out of sight, out of mind."
"Absence makes the heart grow fonder."

"East is East and West is West and never the twain shall meet."
"Brothers under the skin."

The authors indicated that "These 'explanations,' if they have any value at all, are merely convenient summary statements to describe what has happened in a given case. If the next time the same reaction does not occur, then the alternative and opposite 'explanation' is used."

The reader intimately knowledgeable of the diet-cholesterol-CHD literature knows that alliance members routinely change their criteria for "proof" or "cause." When it is noted that Japan has a very high prevalence of hypertension and smoking and yet the lowest CHD mortality rate in the industrialized world, the alliance says, "Ah, but they have low cholesterol levels." When we note that Indians in England have lower cholesterol levels, lower smoking rates and eat less saturated fat than Englishmen but have higher CHD mortality rates, the alliance says, "Ah, but they have "syndrome X." When it is noted that the French consume more animal fat and cholesterol than do Americans, have higher blood pressures and smoke equally as much, and yet have one of the lowest CHD mortality rates in the world, the alliance says, "Ah, but they are

an anomaly." And when it is noted that many Americans die of CHD who have none of the major risk factors, the alliance says, "Ah, but CHD is a multifactorial disease." Since Castelli[2598] said that Framingham has discovered "as many as 200 risk factors" the alliance has a virtual inexhaustible supply to "explain" all apparent anomalies which, as will be seen throughout this volume, are numerous. What multifactorial effectively means is that when cholesterol and/or blood pressure and/or smoking correlates with CHD, the alliance says, "Ah, we told you so," and when they do not, the alliance says, "so what, the disease is multifactorial." Ipsofacto, like the Pope on matters of faith, the alliance is never wrong on matters of cause and effect.

When Keys[279] thought that all fats were alike in the early 1950s his between countries study showed a near perfect correlation between total fat and CHD mortality. Many years later when it was well established that saturated fat increased blood cholesterol and polyunsaturated fat decreased the level, he found a very high correlation between saturated fat consumption and CHD mortality in his Seven Countries study[493] but no correlation with total fat.

When Shekelle, Stamler and their colleagues[487] could find no correlation between saturated fat intake and mortality in their 19-year Western Electric study, they practically ignored that finding and emphasized instead an observed weak correlation between dietary cholesterol and CHD mortality--and they had to convert intake from absolute amount to amount per 1,000 calories to produce that correlation.

When the International Atherosclerosis Project[1080] of autopsies found a correlation between total fat and severity of atherosclerosis but no relationship with animal fat (saturated fat), Stamler and others[a] published articles emphasizing the former and completely ignoring the latter.

When Kahn[2431] and Snowden et al.[2343] could not find relationships between dairy products and fat attached to meat and either total or CHD mortality rates among a large group of subjects varying in vegetarianism over a 21-year period, they both condemned animal protein as the cause of higher CHD rates. Thus, if they could not find relations with total or animal fat, animal protein would do just as well.

It is said that the American diet has become less Westernized during the last 25 years and it is known that the Japanese diet has become more Westernized during that period. The CHD mortality rates in both countries have decreased but morbidity rates have increased. To describe the effects of these food trends the alliance says, "CHD mortality is decreasing in the U.S. because our diet is becoming less Westernized" and "CHD is increasing in Japan because its diet is becoming more Westernized." The omission of a single word, "mortality," makes a subtle but immense difference in meaning and it is apparently not detected by the typical reader unfamiliar with vital statistics.

The alliance alters its logic with incredible ease. For example, in 1983 Kannel[1091] noted that studies, including Framingham, were showing higher cancer rates at low cholesterol levels. He indicated that "The findings are inconsistent and paradoxical, because they can be demonstrated only for men." But in 1987 he said that the impact of cholesterol "tends to wane with advancing age, but remains a significant predictor of CHD in elderly women."[787] Kannel should have referred to this finding as

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[a] 539,561,573,1313,1565,3002

"inconsistent and paradoxical." Moreover, because white women aged 35-74 never experienced a CHD epidemic in the U.S., Kannel should have referred to the epidemic among men as "inconsistent and paradoxical."

Burton Sobel[1867] indicated that the in-hospital mortality rate of patients with acute myocardial infarction was about 30% before coronary care units became commonplace in the early 1960s. Thereafter, the rate dropped to 15% and then 12% in the 1970s. While this trend appears strongly related to the emergence of coronary care units, it is because an important bit of information was ignored, namely, that hospital therapy protocol changed from long to short stays in the hospital. Mortality rates have dropped, in part, simply because such patients are discharged earlier than they used to be.

Scaling, Scaling, Over the Ocean Blue

As any novice statistician knows, one can change the relationship between two variables merely by altering the scale of one or both variables. It was emphasized in Volume 1 that the true relationship between two variables cannot be observed if the scales of those variables contain intervals of unequal lengths. Not only do alliance members routinely use unequal intervals, they also rarely use the same scale from one article to another, which makes it virtually impossible to compare independent study results or even the results of a single study published over time. To illustrate, consider the following examples from the Framingham study over the period 1962 to 1990. Note that the number of intervals per scale varied between reports and that the interval lengths varied within and between reports.

In 1962 NHLBI's Cornfield[3136] used a 7-interval scale which contained five different interval lengths, i.e.,

< 200,	200-209,	210-219,	220-244,	245-259,	260-284,	≥ 285
(?)	(10)	(10)	(25)	(15)	(25)	(?)

Since his was not a quintile, quartile, etc. scale, there was no apparent legitimate reasons for creating such discrepant intervals.

Also in 1962 Kagan et al.[2728] employed two different scales in the same article. They were

< 200,	200-249,	220-239,	240-259,	≥ 260
(?)	(20)	(20)	(20)	(?)

< 219,	220-259,	≥ 260
(?)	(30)	(?)

Note that the upper scale had an observable length of 60 mg, while the lower scale had one of 40 mg.

In 1964 Kannel et al.[1885] used three different scales,

Quartile 1,	Quartile 2,	Quartile 3,	Quartile 4
(?)	(?)	(?)	(?)

< 180,	180-199,	200-225
(?)	(20)	(26)

< 200,	220-259,	> 259
(?)	(40)	(?)

They did not bother to specify the cholesterol ranges for the quartile scale and they employed different intervals for their two 3-interval scales.

In 1971 Kannel[1376] used a 5-interval scale, only two intervals of which were equal, i.e.,

< 190,	190-219,	220-249,	250-294,	≥ 295
(?)	(30)	(30)	(45)	(?)

In 1983 Kannel[1091] again used a 5-interval scale but it contained different interval lengths.

126-189,	190-219,	220-249,	250-279,	280-545
(64)	(30)	(30)	(30)	(266)

In 1986 Castelli and his colleagues published two articles which had different scales. In one article an 8-interval scale was used, while in the other a 4-interval scale was chosen.

<180,	180-199,	200-219,	220-239,	240-259,	260-279,	280-299,	≥ 300
(?)	(20)	(20)	(20)	(20)	(20)	(20)	(?)

< 200,	200-229,	230-259,	≥ 260
(?)	(30)	(30)	(?)

In 1987 Anderson et al.[1273] and Kannel[787] used 4- and 5-interval scales, respectively, and Wilson et al.[1366] apparently used the midpoints of a 6-interval scale.

≤ 180,	181-220,	221-260,	≥ 260
(?)	(40)	(40)	(?)

84-204,	205-234,	235-264,	265-294,	295-1124
(121)	(30)	(30)	(30)	(829)

185,	215,	245,	275,	305,	335
		(?)			

In 1989 Castelli et al.[2292] also apparently used the midpoints of an interval scale but it was derived from a 5-interval scale, rather than a 6-interval scale as employed by Wilson et al.

< 205,	220,	250,	280,	> 294
		(?)		

In 1990 Kannel[2893] also apparently used the midpoints of an interval scale but it was derived from a 8-interval scale, rather than the 5-interval and 6-interval scales employed by Castelli et al. and Wilson et al.

175, 200, 225, 250, 275, 300, 325, 350
(?)

The above examples, taken from Framingham reports, represent only a fraction of the different scales used throughout the literature. There is no scientific excuse for using scales having less than 10 intervals and there is no scientific excuse for using scales having unequal intervals. The only reason for departing from these requirements is the need to bias results, i.e., to force data into misleading and exaggerated relationships. The reason for the existence of a proliferation of different scales is because every set of data requires a somewhat different manipulation to yield the relationships desired by the alliance. The practice is so prolific world-wide that the song, "Scaling, Scaling, Over the Ocean Blue," is most appropriate.

EPIDEMIOLOGY: THE SCIENCE OF ASSUMPTIONS

A comedian once said that "whenever you assume something, you make an ass out of u and me." He was more right than wrong. By definition, an assumption is something taken to be true without proof. It follows, therefore, that it may be, in fact, false. Yet, much of the alliance's key evidence supporting the lipid hypothesis is based, in large part, on assumptions. Moreover, both common sense and existing evidence indicate that most of the alliance's assumptions are false. For example, Volume 1 and Chapter 4 of this volume provides many reasons why the assumptions are false that CHD mortality and fat consumption statistics vary substantially, in degree of accuracy across countries. Yet, alliance members close their eyes to all these false assumptions and use between nations studies as evidence of a relation between fat consumption and CHD rates.

Probably the most absurd assumptions are those associated with prospective studies that obtain blood cholesterol measurements and dietary intake data at entry and then correlate these measures with CHD events 10, 20 and 30 years later. Three totally untenable assumptions are involved in such studies. First, it is assumed that blood cholesterol levels remain constant over those periods. But data from Framingham, the Seven Countries study and the Western-Electric study, for example, have clearly demonstrated that blood cholesterol levels change a great deal and unsystematically over relatively short periods. Therefore, endpoint data collected many years later are correlated with fleeting blood cholesterol levels that are unrepresentative of the individuals during most of the follow-up period. Framingham investigators never analyze the effects of blood cholesterol changes over time on their results, even though they have acknowledged the fact that substantial changes occur.

Second, it is also assumed that diets remain constant over the follow-up period. The Seven Countries study found large changes in diets within 10 years in its cohorts and common sense tells us that most people change diets rather significantly over time. This assumption, therefore, is clearly false.

Finally, it is assumed that investigators obtain an accurate profile of what individuals consume at entry. Most studies, such as the Western-Electric study, obtained dietary data by interview/questionnaires. Even a cursory understanding of this procedure must lead to the conclusion that it is terribly inaccurate. Consider the following response. "On Monday I had a T-bone steak. Let's see, it was probably about 10 to 12 ounces. It was graded USDA Select and had about one-quarter inch of fat around it. Of course, I didn't eat that fat, or at least not most of it." There is

simply no way an interviewer can accurately determine the intake of saturated, monounsaturated, and polyunsaturated fat, as well as cholesterol or protein from an interview, no matter how many reference books he/she has relating to the nutrient content of foods. As noted by Keys himself (Chapter 4) heavy eaters often underestimate their food consumed because they are embarrassed to tell interviewers how much they actually consume. Thus, the interview technique has so much systematic and unsystematic error, it is remarkable that it has been employed with such scientific abandon.

The NHLBI/AHA alliance frequently praises Stamler and Shekelle's Western-Electric study as showing a slight but significant relation between dietary cholesterol (but not saturated fat) at entry and CHD events 19 years later. This study was based on all three of the above untenable assumptions and unquestionably yielded random nonsense. Yet, the authors touted it as being "the most precise and convincing study to date."[1339] If that is true, then all other similar studies should be thoroughly trashed because the Western-Electric study was abominable scientifically.

Assumptions are everywhere. LDL is assumed to be the atherogenic component of cholesterol even though there is no proof. HDL is assumed to be "good" cholesterol without proof. CHD is assumed to be multifactorial even though there is no direct scientific proof showing that even one factor causes CHD. Experimentally induced "atherosclerosis" is assumed to be human atherosclerosis even though there is no proof that the former produces advanced lesions identical to those in humans and even though there is pathological evidence that the experimentally induced disease is not, in fact, the human atherosclerotic disease. If one were to dichotomize all "evidence" into that based on assumptions and that based on scientific proof, almost all of the alliance's evidence would be that based on assumptions. But the alliance is undaunted by lack of proofs. It is perfectly content with changing the American diet and placing millions of Americans on cholesterol-lowering drugs based on data it considers "persuasive," "compelling," etc. For example, Robert Levy[266,2964] said, "There exist overwhelming persuasive data..." Howard Hiatt[2496] indicated that "The epidemiologic evidence for this [lipid hypothesis] is not ironclad--such evidence can never be--yet it is persuasive..." The 1988 Surgeon General's report[2433] (written by NHLBI) referred to the supportive evidence as "compelling" and its managing editor, Nestle[2495] stated that "You are never going to get incontrovertible evidence in nutrition." Many identical statements have been published in the literature in an apparent attempt to convince doubters of the lipid hypothesis. The argument that conclusive proof of the true cause(s) of atherosclerosis will never be obtained is sheer scientific nonsense and an excuse to move ahead with a gigantic costly program in the absence of proof.

EPIDEMIOLOGY AND THE REAL WORLD

Prospective studies, experiments and clinical trials are, of course, useful and necessary scientific endeavors if conducted and analyzed objectively and properly. But in the last analysis, the ultimate validity of a medical therapy is determined by its effect on society, not on an extremely small sample of that society, e.g., a small group in a clinical trial. For example, prospective studies have shown a relationship between cigarette smoking and increased CHD death rate. Yet, as shown in detail in Chapter 9, the fact remains that the smoking trends during this century cannot be adequately related to CHD or cardiovascular mortality trends, no matter how many times one has been told otherwise.

Prospective studies have also shown a relationship between hypertension and increased CHD and stroke death rates. Yet, as shown in Chapter 9, the cerebrovascular death rate initiated its decline at least 30 years before antihypertensive drug therapy was begun. Moreover, the decline shows progressive

linear trends during each decade between changes in the International Classification of Diseases. Also, the CHD mortality trend has been unaffected by the widespread use of antihypertensive drugs.

Most prospective studies and a few clinical trials have shown relationships between blood cholesterol levels and CHD mortality rates. Yet, as shown in Chapter 4, there are many countries in the world which have lower CHD mortality rates but high blood cholesterol levels. Further, CHD mortality initiated its decline in the U.S. before blood cholesterol levels were lowered and has sustained a long term decline in Japan despite progressively increasing blood cholesterol levels. In addition, examination of vegetarian populations reveals no advantages of vegetarianism (and low blood cholesterol levels) with respect to CHD events.

The above inconsistencies between epidemiologic studies and real world data represent the proverbial tip of the iceberg. Despite all the propaganda to the contrary, dietary, cigarette consumption and antihypertensive drug trends in the U.S. cannot be shown to have affected CHD or stroke mortalities. That is the real world. It may be difficult to reject epidemiologic findings but it should be impossible to reject the real world whether or not it contradicts the epidemiologic findings. The matter was described rather well by Kannel and Thom[1174] in perhaps one of their most objective moods. They said, "There is no unequivocal explanation as to why CHD mortality had risen so high in the first place, nor it is clear why mortality for stroke, hypertension, and all cardiovascular diseases have been declining since 1940 or earlier, antedating antihypertensive therapy. In fact, no one has yet established a convincing fit of trends for any risk factor with cardiovascular mortality trends."

An inherent and inescapable part of a practicing physician's job is the routine making of clinical judgment for medical therapies. That is the nature of an applied discipline. But the need to prescribe should not blind one's ability to recognize reality. Many presumably important epidemiologic findings are not consistent with the real world. But many epidemiologists tell their readers that they are consistent and either offer no supporting data or, incredibly, present data which actually contradict themselves.

The willingness to ignore real world data in favor of data derived from prospective studies and clinical trials is a common practice among alliance members and that behavior is probably the strongest indication that they are neither true scientists nor motivated by the best interests of society.

In reviewing the massive epidemiological literature two rather stupid flaws stand out like two tall buildings in a desert. First, the alliance has known for decades that reported CHD mortality rates differ between states and regions almost as much as between the U.S. and some countries with extremely low rates. Yet, the alliance has spent billions of dollars investigating every conceivable population in the world, ostensibly to determine the characteristics underlying those populations with high CHD rates and those with low CHD rates. Can anyone justify these expenditures? Can anyone explain why the sought-after data cannot be obtained more efficiently and less expensively by comparing various states within the U.S.?

Consider the following dialog between a lawyer and former NHLBI director Theodore Cooper in 1975:

Lawyer: "Now, doctor, would you please refer to Page 90 of that particular exhibit...that shows two maps, but I refer you only to the top map, the white male map, showing the difference in, or showing the five quintiles

really on a normal distribution of deaths by the state from the top-most death rate, if you can read it there, I think is 679 to the lowest which is 359, I think, it is not quite a two-to-one ratio, but it is an appreciable difference between the lowest and the highest, there. And we can see a generalized geographic pattern, can we not, from that particular map as to the incidence of coronary heart disease in the U.S.?

Cooper: "What do you mean, 'generalized'--there is an interesting thing, again, that is not even across the whole U.S.

Lawyer: "That is true. There are wide variations state by state.

Cooper: "There are wide variations state by state and the tendency in some areas to be grouped by region.

Lawyer: Especially like into the Middle Atlantic States, the Plains States, you have them all in the lowest quintile?

Cooper: "With the interesting exception of Nevada, which is a very interesting observation, which we pointed out many times before.

Lawyer: "And, I think we all probably have some ideas on that.

Cooper: "If you want to make a really interesting observation, if you want to make an interesting observation, make a comparison, not between California and Nevada, but Utah and Nevada.

Lawyer: "But, again, have you any explanation today why people, let's say in one state of the U.S., who certainly in their lifestyle do not differ significantly, let's say, from people in New York, Nevada, well, not Nevada, New York or South Carolina, what would explain the almost two to one, not quite 359 to 679, but almost a doubling of the coronary death rate?

Cooper: "Well, again, I could not be definitive here. I am just beginning to look into these kinds of differences in states and in a multi-factorial analytical way in trying to get better data. But some of it, in my opinion, is due to the lifestyle, specifically. There is a big lifestyle difference between Utah and Nevada.

Lawyer: "Yes?

Cooper: "There is a large environmental factor in the Atlantic corridor here as opposed to the Midwestern region. So, I think again, we come up with a lot of specific factors which we know can have impact on disease expression and that is one of the important variables in this whole problem. When we measure a heart attack as a clinical expression, there are several factors which precipitate the actual clinical events and determine whether the clinical event, itself, is either fatal or nonfatal and many of these factors are determined by some specific environmental and lifestyle differences, health care delivery differences, in these various regions.

Lawyer: "Doctor, certainly there is no basis for believing that there is any significant differences in the diets of the people in Kansas and Nebraska and Colorado and that in New York or Nevada.

Cooper: "I think so. I think so. I think there are studies, say in the Southeastern U.S. where if you do certain population studies, the diet pattern is different and it may have differences. Again, I can't be definitive on this, but overall dietary patterns, I think are different.

Lawyer: "But wouldn't, just without being definitive, naturally, to refer to any particular study, but wouldn't it appear that in the corn belt and the Great Plains and in the agricultural area of the country, that the ingestion by the population of foods of animal origin might tend to be higher than they would along, let us say, along the seaboards?

Cooper: "Well,...

Lawyer: "I think that is a reasonable supposition.

Cooper: "It is a reasonable supposition."

Aside from the fact that the above dialog reflects a good deal of rambling rhetoric, some of which is irrelevant, it is quite clear that Cooper took the position that "lifestyle" differences between the states, including diets, could explain the wide CHD mortality rate differences. He also emphasized that "I am just beginning to look into these kinds of differences in states and in a multi-factorial analytical way in trying to get better data." In truth, neither Cooper nor NHLBI nor anyone else made concerted efforts to correlate lifestyle differences with mortality differences between states or, if they did, failed to publish the results of such efforts in the open literature. There is no logical reason why such studies have not been performed--unless there was the implicit understanding that the differences in CHD mortality statistics were more the result of local "fashions" than anything else. Such an understanding would make it foolish to conduct between state studies. However, such an understanding would also suggest that the differences in CHD mortality rates between countries are also due more to fashions than anything else.

The point is, reported CHD mortality rates have been substantially different from state to state and if lifestyle differences have been the cause of the mortality rate differences, then NHLBI should have conducted between states studies instead of the hundreds of between countries studies. But it has not and such an "error" was planned, not inadvertent.

The second obvious flaw in the gigantic epidemiological deluge of research studies is the almost obscene lack of research comparing vegetarians with nonvegetarians in terms of CHD mortality rates and other causes of death. In fact, vegetarian/nonvegetarian comparisons represent natural clinical trials and the perfect bases for assessing the effects of total and saturated fat consumption on mortality. If such studies consistently demonstrate healthful advantages of low or zero animal fat diets, there is no point to conducting massive numbers of between and within population studies and no point to conducting massive numbers of dietary experiments, cholesterol-lowering trials, etc. Moreover, if such studies consistently demonstrate no healthful benefits of low or zero animal fat diets, all other research becomes irrelevant as well.

In 1957 Herbert Pollack, a co-author of the excellent 1957 AHA report[512] which indicated that there was no correlation between food consumption trends and the CHD mortality "epidemic", published an editorial in the AHA's journal, Circulation. He said, "Much time has been spent in studying vegetarian versus nonvegetarian groups. No

critical results have been made available." It is now 34 years since Pollack made that statement and there are still no "critical results" available from the U.S. As noted in Chapter 4, only a few studies which evaluated mortality rates were published and these were of unique religious groups (Seventh Day Adventists) who are not comparable to other groups because of confounding variables, i.e., they do not smoke, drink alcohol or coffee or seem to undergo the same stresses in life that are associated with typical Americans. Moreover, the data presented in these studies were badly interpreted and still revealed no real relationships between animal fat consumption and CHD mortality rates.

A large and certainly the least confounded study of vegetarians was conducted recently in England, not in the U.S., and although the authors concluded that vegetarianism reduces CHD, one can easily show from their data that the differences in CHD and all-cause mortality rates over a 7 year period were miniscule (see Chapter 4). Why are not these results given heavy publicity? Why are they ignored? Why are vegetarian studies in the U.S. not conducted? The state-of-affairs is scientifically inexcusable and again reflects the need by the alliance to protect dogma rather than to seek explanations for the true cause of CHD.

There is no doubt in this writer's mind that definitive studies have been conducted comparing one state with another and comparing vegetarians with nonvegetarians. They have not been published because they do not support the lipid hypothesis. If I am wrong, then why have not such studies been done? Between-state and vegetarian studies, if not the most important in terms of theory and practice, most certainly must be considered two of the more important epidemiologic areas of research. But they have been continuously ignored or given token consideration since the early epidemiological studies began in the 1950s.

THE TRIVIALITY OF IT ALL

From its inception the lipid hypothesis research has focused almost entirely on what the alliance has so frequently termed "premature mortality" due to CHD, i.e., CHD deaths before age 65. Let us put a few facts together about this subset of the population. First, using the NHLBI data presented by Higgins and Leupker,[2798] we note that 6.8% and 2.9% of the male and female CHD deaths, respectively, occur below the age of 65. As discussed in detail in Chapter 3, up to 50% of CHD deaths have little or no relationship with atherosclerosis. For example, this was noted in 1987 by Castelli[1179] who stated that "About half of the deaths that are from heart attack or stroke are brought about by atherosclerosis." And because atherosclerosis is a long-term gradually developing disease, with the exception of familial hypercholesterolemics, severe atherosclerosis is rare below the age of 50. Therefore, less than 3.4% and 1.9% of the male and female CHD death, respectively, below the age of 65 can be attributed to atherosclerosis. When those with genetic defects are accounted for, most of which are insufficiently responsive to dietary changes, there are almost no CHD deaths left below the age of 65 that can be classified as diet-related.

It may be noted that the above discussion does not consider the fact that the relationship between blood cholesterol and CHD is a statistical one and nonpredictive at the individual level. Let us briefly examine this relationship which Kannel and others often call "powerful." Castelli[2462] recently said that "One-half of all myocardial infarctions now occur in people whose serum cholesterol is 225 mg or less." Using the same Higgins and Leupker[2798] data, we note that 99.66% of all CHD deaths occur above the age 44. Using the cholesterol data presented in the Report of the NCEP Expert Panel,[1066] we find that the weighted mean cholesterol levels for men

and women over the age of 44 are 225.5 mg and 244.1 mg, respectively, and the weighted mean for both men and women is 235.3 mg. The combination of all of these data indicate that for the group (45 years and up) that involves effectively all CHD deaths, myocardial infarctions occur with precisely equal frequency in men below their mean cholesterol (225.5 mg) level as above and they occur more frequently in women below their mean cholesterol (235.3 mg) than above.

The immediately above analysis contains some error because (1) the Castelli statement was presumably based on Framingham data, while the cholesterol and CHD mortality data were based on the NCEP's data pool and U.S. mortality statistics, respectively, and (2) the Castelli statement involved fatal and nonfatal infarctions, while the present analysis included only mortality data. However, the error cannot be substantial. For example, as noted elsewhere in this Volume, there is a high correlation between nonfatal and fatal CHD events and if the Framingham cholesterol data differ considerably from that of the NCEP data pool, one must ask why the Framingham study is not terminated. All things considered, cholesterol level (and thus diet) has little importance for the vast majority of people who die of CHD.

In sum, at least 97% of "premature" CHD deaths cannot reasonably be attributed to diet at all and diet can only be considered as a contributing or secondary factor for the remaining 3%. It is preposterous that the entire U.S. population is being encouraged to consume costly diets and drugs in order that a very small percentage of individuals might be helped. That percentage may be far less than one percent, as indicated by clinical trials, i.e., both the Lipid Research Clinics (LRC) trial published in 1984 and the Helsinki (II) trial published in 1987 yielded only fractional reductions of annual nonfatal and fatal CHD events among (apparently) familial hypercholesterolemics. In other words, the entire National Cholesterol Education Program is representative of an elephant stepping on a flea.

INCOMPETENCE, SLOPPINESS AND FABRICATION

The subject of incompetency vs bias among many epidemiological researchers was briefly discussed in Volume 1. The present volume presents an imposing array of examples of false and/or misleading information published routinely by prominent members of the NHLBI/AHA alliance. As will be seen, the issue is not merely one interpretation of data clashing with another. The alliance's statements can be and are clearly proven to be false and/or misleading. From a legal standpoint, it may not be possible to prove that alliance members purposely publish such information because, theoretically, incompetence or sloppiness could also explain such behaviors in many cases. On the other hand, as one finally recognizes that the literature is saturated with such information, one finds it impossible to believe that the frequent, consistent and systematically presented false information can be the result of incompetence or sloppiness. The latter would yield random error and the prolific false information in the literature is anything but random.

Incompetence and sloppiness are unacceptable behaviors of "scientists" and, particularly, those so often described by the media as heart "experts," and fabricating is not only unacceptable, it borders on criminal behavior because its ramifications affect the health and pocketbooks of tens of millions of Americans. Two examples follow which illustrate the types of false and misleading information typically encountered.

Every knowledgeable researcher in the diet-CHD field knows or should know that the Framingham study found no correlations whatsoever between dietary nutrients and either blood cholesterol or CHD incidence--including former AHA president Antonio Gotto. In fact, in his statement before the 1977 Senate Select Committee on Nutrition and Human Needs, Gotto stated, "In the Framingham study, it was not

possible to make a correlation between the type of food a person ate, including the content of saturated fat, polyunsaturated fat or cholesterol, and the risk of having a heart attack."[1601] Yet, Gotto told physicians in 1988 in the publication, Drug Therapy, "Epidemiologic studies, such as...Framingham...showed that populations with low consumption of saturated fat...had virtually no atherosclerosis or CHD mortality."[2527] Thus, Gotto's statement was unequivocally false.

Kannel and his co-workers[903] indicated in 1981 that there were no significant differences in fat, saturated fat and cholesterol intakes of persons with and without CHD in the Honolulu Heart Program and the Puerto Rican Heart Health study and no correlation between these nutrients and blood cholesterol levels. Yet, in 1984 Kannel, Stamler and others[1083] said, "Middle-aged male populations studied according to similar protocols in Puerto Rico, Hawaii and Framingham show concordance between mean levels of saturated fat, cholesterol intakes, and serum cholesterol." This statement is misleading because it cleverly implies that dietary lipids were found to correlate with blood cholesterol in these studies when, in fact, it is really a totally meaningless sentence, i.e., all it says is that the (zero) relationships found in each of these studies were in agreement. There can be little doubt that the sentence was purposely constructed to mislead readers.

If the above examples occurred only occasionally in the literature, one could easily dismiss them as perhaps quirks inadvertently generated by very busy individuals who have little time to proofread their own manuscripts. As previously emphasized, however, it is effectively impossible not to find at least one and usually several or many such statements in every article written by Kannel, Stamler, Gotto, Grundy and many of their NHLBI/AHA colleagues.

If a manufacturer promotes false advertising in the media, it can be sued by the Federal Trade Commission. If the manufacturer promotes false information on the labels of food products, it can be sued by the Food and Drug Administration. But if NHLBI and AHA indoctrinate the American people with false or misleading information, there is apparently no provision within the law to cause them to cease and desist or to bring them to justice. Although the alliance is undertaking one of the largest conspiracies ever perpetrated, it is immune to criminal conspiracy.

REDUNDANCY, PROPAGANDA AND CENSORSHIP

It was noted in Volume 1 that "the amount of redundancy in the CHD medical literature is almost beyond comprehension, with hundreds of articles being essentially identical in content to hundreds of other articles." This issue cannot be overstressed because it not only artificially inflates the relevant literature, it serves as a basis for disseminating repetitive propaganda.

There are at least four distinct types of redundant articles. Undoubtedly the most common type might be called "scripted redundancy." Many alliance members publish almost identical articles, citing similar references, drawing similar conclusions and repeating similar recommendations. In the process, misleading and often totally false information is communicated to practicing physicians and the media. For example, Rifkind's original statement, "for every 1% drop in blood cholesterol, there is a 2% reduction in heart attack," is completely false and yet it has been repeated by other alliance members and the media perhaps thousands of times.

The second most common type of redundancy may be called "regurgitating redundancy." Scientific journals typically require authors to sign statements promising that their submitted manuscript has not been and will not be published in other journals. But this requirement is clearly ignored by journals and authors alike because alliance members such as Kannel, Stamler, Grundy and Gotto each publish many

redundant articles. For example, W. Virgil Brown published at least three articles in 1987 and 1988 promoting the cholesterol-lowering drug fenofibrate.[1013,1543,1544,a]

A third type of redundancy can be called "copy cat redundancy." For example, NHLBI publishes guidelines on cholesterol detection and treatment and dozens of other authors subsequently publish identical guidelines in a wide array of medical journals and magazines. Virtually hundreds of articles are published that essentially repeat the same dogma emitted by NHLBI, AHA, Framingham, etc. Innumerable incomplete and biased "reviews" are published that typically include the same selected studies and draw the same conclusions. Ninety-nine percent of these articles are noninnovative. Why are they published? Why do so many journal editors accept redundant and nonoriginal material? One cannot help but gain the impression that all of these articles are designed solely to "spread the word," and to give the illusion to readers that the diet-CHD relationship has been conclusively proven. They resemble a political campaign.

A fourth type of redundancy is called "salami slicing" and it is outrightly aggravating. Rather than publish one article which describes a follow-up of a prospective study, for example, that follow-up is published in the form of four, six or perhaps 10 articles, all of which greatly overlap and each of which contains little unique data. While salami slicing is obviously a ploy to increase the number of publications on a resume, it is an incredibly poor way of disseminating and communicating scientific information.

Without a doubt, the top salamis of salami slicing are the Framingham investigators. Framingham articles that are more or less redundant with other Framingham articles are mass-produced in assembly-line fashion. On average, five to 10 articles could be more efficiently combined to form a single, complete article.

The primary purpose of scientific journals is to disseminate scientific information and extend the state-of-the-art, not to advance careers or promote medical dogma that is closer to political philosophy than to scientific discourse. While journal editors would probably deny their journals are guilty of proliferating redundancies and the alliance's medical dogma (they <u>always</u> deny doing <u>anything</u> wrong), it is clearly observable to anyone with a mentality exceeding a seedless grape.

Much of the redundancy in the literature by alliance members is a reflection of the weaknesses of their data. The alliance is constantly reminding physicians and the lay public in scripted fashion that the diet-CHD issue is resolved and that a controversy no longer exists. Consider the following statements as but a few examples from a voluminous set of similar statements (and note the word "overwhelming"):

> "There is overwhelming agreement in the medical community that an elevated cholesterol is a cause of atherosclerosis" (Castelli[1802]).
>
> "There exist overwhelming persuasive data...that clearly link higher cholesterol levels with higher CHD morbidity and mortality" (Levy[1276]).
>
> "The scientific evidence that links cholesterol and diet to heart disease is enormous and overwhelming" (Goodman[2506]).

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[a] Two of Brown's articles appeared in "supplements" of Hospital Practice and Modern Medicine, funded by Bristol-Myers.[1543,1544]

"The overwhelming body of scientific evidence supports the concept that high blood cholesterol increases risk of CHD" (NIH[2288]).

"The evidence linking elevated blood cholesterol to coronary heart disease is overwhelming (AHA/NHLBI joint statement[2500]).

If the evidence were overwhelming, why does the alliance feel compelled to issue such statements again and again and again? The answer, of course, is that the alliance has been replacing scientific evidence with "consensus." For example, consider the following scripted statements:

"The question has now changed from whether to treat hypercholesterolemia to how to treat hypercholesterolemia" (Levy[492]). "We are no longer debating whether cholesterol reduction is beneficial" (Levy[1539]).

"There are no longer any major controversies about the importance of cholesterol in heart disease" (LaRosa[2396]).

"There are no longer any controversies about cholesterol's role in atherosclerosis" (Roberts[1595]).

"There is no longer any doubt that high plasma levels of LDL are atherogenic" (Steinberg[2389]).

"Today there is no longer any doubt about the causative relationship between hypercholesterolemia and premature atherosclerosis" (Steinberg[3081]).

"The question is no longer whether to treat high cholesterol but who to treat and how" (Rifkind[243]).

Despite the fact that blood cholesterol is only weakly related to CHD in a statistical sense and that such alliance members as Kannel and Castelli have admitted in print over many years that cholesterol level cannot predict whether an individual will or will not have a heart attack, the weak relationship is most often transformed into a strong relationship merely by replacing the word "weak" with its inappropriate antonyms, i.e.,

"The serum cholesterol is a powerful risk factor for CHD in both sexes" (Kannel[787]).

"Total plasma cholesterol is a powerful predictor of death related to coronary heart disease" (W. Virgil Brown[754]). "The LDL/HDL ratio is a powerful predictor of risk" (W. Virgil Brown[1549]).

"Low HDL is an extraordinary potent predictor of risk" (Knopp[1549]).

"HDL is a more powerful risk factor than LDL, triglycerides, or total cholesterol" (Castelli[1603]).

To increase the apparent legitimacy and validity of their recommendations, alliance members frequently emphasize that many health organizations support their recommendations. For example, the 1989 joint AHA/NHLBI statement said, "Virtually every major medical or health organization has urged Americans to decrease their consumption of saturated fat, to lower their consumption of cholesterol, and to lose excess weight. These organizations include the AHA, the AMA, The Food and

Nutrition Board...[and] the Surgeon General's Office..."[2500] However, every knowledgeable person knows that all of these organizations and more (except the AMA) produced reports which were written by AHA and/or NHLBI members. (As will be seen in Chapter 2, the AMA publicly opposed the AHA recommendations for the general public for many years before succumbing to relentless pressure and the lure of huge profits.) It is not coincidental, moreover, that the specific diet recommendations made by these many organizations, ostensibly arrived at independently, are virtually identical. The odds against such an occurrence are astronomical. However, there is little doubt that the alliance succeeded in deceiving the lay public regarding the independence of the various "health" organizations.

As emphasized in Chapter 9, censorship of information counter to the diet-CHD hypothesis is everwhere. A very recent example can be seen in an English study. On March 9, 1991 Lancet[3314] announced that "The results of a study from the Medical Research Council's Epidemiology Unit in Cardiff challenge some cherished beliefs about the relation between ischaemic heart disease (IHD) and diet. They seem to show, for instance, that men who eat butter are only as much at risk of IHD as those who spread polyunsaturated margarine on their bread. ...nearly 10% of men who drank no milk had IHD events during the period of the study, compared with 6.3% of those who drank half a pint a day or less and 1.2% of those who drank more than a pint a day. These surprising findings emerged from a five-year prospective study of 2500 middle-aged men in Caerphilly and Speedwell."

Lancet continued, "In view of the substantial evidence incriminating saturated fat as a risk factor for IHD the Caerphilly findings are hard to believe, and Dr. Peter Elwood, director of the Cardiff unit, last week warned against drawing conclusions from these figures alone. What concerns the MRC, however, is that parts of the report 'do not appear to have been assessed by outside experts.' The council is therefore convening a scientific panel to referee [censor?] the work."

W.W. Yellowlees[3315] published a letter-to-the-editor of Lancet on April 27, 1991. He said, "The possibility that milk and butter--hitherto presented as dietary villians--may be protective has sent shock waves through the ranks of officialdom. The advice of a hastily convened Medical Research Council panel to the effect that we should ignore the Cardiff findings serves only to increase the confusion" [cited Pallot, P. Research on milk and heart attacks should be ignored. Daily Telegraph, March 23, 1991]. Is not the attempt of the MRC panel to discredit the findings of the Cardiff unit a good example of what Solzhemitsyn has called 'the censorship of fashion'? The fashionable teaching about dietary fats and heart disease could never have survived without widespread censorship of evidence against a theory, made popular by the evangelism of specialists and the interests of commerce. In the 1950s Norway launched a cholesterol-lowering regimen in which soya oil was used extensively. In the next 20 years the increase in the use of soy-oil products was accompanied by a steep and continuing rise in deaths from coronary thrombosis. When Dr. Jens Dedichen, a member of the Norwegian Council for Diseases of the Heart and Arteries, drew attention to the failure of the programme he was surprised at the hostile reaction of his colleagues: 'I was quite simply accused of being ignorant, worse, I was censored.' A 1988 publication from the WHO Regional Office for Europe advises a 30% reduction in saturated fat consumption and an increase in polyunsaturated fats. The monograph ignores European epidemiological data that do not support this advice, and the list of 200 references makes no mention of papers by dissidents...who have argued against the theory that coronary heart disease can be prevented by changes in fat consumption."

Censorship is so widespread in the U.S., only the most naive medical researcher cannot observe it. It exists because the alliance cannot convince the populace without it that diet is the key to CHD.

As will be discussed in Chapter 2, NHLBI conducted periodic national surveys of Americans to determine the effectiveness of the National Cholesterol Education Program (NCEP). The surveys were conducted in 1983 (to assess opinions prior to launching the NCEP), 1986 (to assess the effects of about one year of the program), and 1990.[515,3776] The percentages of Americans who believed that lowering high blood cholsterol would have a significant effect on CHD were 39%, 64% and 74% in 1983, 1986 and 1990, respectively. Two percent of the sample indicated that they were taking cholesterol-lowering drugs, double the percent of 1983. Approximately 65% of the population is 21 years old and over. Assuming a total population of about 250,000,000, the sample 2% would represent 5 million adults on such drugs--and apparently growing. Since the percentage of persons indicating that they changed their diets to reduce blood cholesterol effectivey did not increase since 1986, it would appear that the massive NCEP is having most of its impact on the sale of drugs, an outcome not unpalatable to drug companies who are, after all, major financers of the NCEP.

COUNTERING FALSEHOODS

If Albert Einstein were alive and were he to make a profound statement about the dynamic structure of the universe, the likelihood is that the unknowledgeable public would believe him--if for no other reasons--because he has an image of credibility. Having credibility often means that one does not have to prove that his statements are correct. Credibility implies honesty and expertise.

NHLBI and AHA have long had an image of credibility in the eyes of the public (and perhaps most physician practitioners). They can and do make frequent unfounded statements which are accepted without question by both the press and the public. Not only do antagonists of the NHLBI/AHA philosophy have little access to the media to express their points of view, they are also unknown to the public and have, therefore, little or no credibility. Even if one had access to the media, his lack of credibility would render him almost completely impotent.

For every unsupported sentence uttered by an individual considered credible by the public, another individual might require 50 or more sentences and unequivocal proof to successfully counter the "credible" individual. To illustrate this problem, consider the following excerpt from the Food and Nutrition Board's 1989 report, "Diet and Health": "Examples of vigorously controlled experiments include those reported by Connor et al. (1961a,b,1964). In each of these experiments, six men were placed on cholesterol-free and high-cholesterol diets that were either formula diets or carefully selected natural foods. Cholesterol was added as egg yolk. In all three experiments, substantial increases in serum total cholesterol resulted from the addition of egg yolk to the diet."[2070] Chapter 5 provides a detailed critique of the three Connor studies, including three tables, which clearly demonstrates that his results were completely confounded because of improperly controlled diets and completely irrelevant because his diets were dominated by liquid foods, known to affect blood cholesterol levels far differently than do whole foods. The point is that it required three tables and considerable verbiage to prove that the Food and Nutrition Board's four short sentences comprised a completely fraudulent statement.

The Food and Nutrition Board's report, like hundreds of other NHLBI/AHA reports, is literally saturated with false and misleading statements. The reader probably cannot even imagine how extensive this problem is within the diet-CHD literature. It is so enormous that this writer has continuously been shocked in the process of analyzing well over 4,000 reports.

One of the most prolific writers/interviewees of all is Framingham director William Castelli. He has literally saturated the literature with misleading or outrightly false information. For example, in the April 1991 issue of Prevention Magazine he said, "If you reduce all dietary fat, you automatically knock down saturated-fat intake, because about half of the fat we eat is saturated fat."[3271] This statement is totally false for two major reasons. First, the composition of fat, not the amount of fat, determines blood cholesterol levels, as Castelli most surely knows. Second, major surveys, including the government sponsored NHANES surveys,[2557] show that saturated fat constitutes about 37% of total dietary fat, not 50%, as indicated by Castelli. Equally important, about 40% of the saturated fat in the principal red meats (beef and pork) consumed in the U.S. is cmposed of stearic acid, known to have no affects on blood cholesterol.[a] Thus, the percentage of cholesterol-raising saturated fat in the diet is approximately 0.37 x 0.41 = 15%, enormously less than the 50% presented to the American people by Castelli.

The sloppiness and bias so prolifically observed in epidemiological research has long been known but infrequently discussed. For example, Marmot noted in 1976 that "controversy exists, in part, because epidemiologists do not follow consistent criteria in deciding to accept or reject a theory. It is always possible to save a theory from refutation by erection of auxiliary hypotheses to explain away the anomalies."[2347] Marmot also maintained that "the concept of multifactorial causation has saved many a good epidemiologic theory from destruction, but unless the multifactorial theory of heart disease epidemiology can predict whether or not a particular population group will have a high CHD rate, then it cannot be considered progressive."

In 1989 Feinstein reiterated and expanded Marmot's criticisms.[2245] He indicated that there are often "absent or low scientific standards in epidemiologic studies of cause-effect relationships. He observed that epidemiologists "do not seem upset by investigators making changes in control groups after the results have been analyzed, by large numbers of studies with unresolved and unreconciled contradictions, by the infrequent precautions against ascertainment bias, by statistical maneuvers that are substituted for a true dose-response curve, or by the credulous acceptance of erroneous death certificate diagnoses."

Bernadine Healy, former AHA president, introduced the concept of "immutology," defined as the study of things that should not change. She said "the very nature of science and scientific investigation is change, but the underpinnings of the scientific process should be immutable."[2213] It is submitted that alliance members operate by a reverse rule, i.e., their scientific processes change constantly in order to maintain the science (lipid hypothesis) immutable.

This volume presents many examples of false and misleading statements by diet-CHD researchers. It would be virtually impossible to even consider the task of countering each and every falsehood because the publication of articles by the alliance is prolific. However, the many examples presented should provide the reader with some feeling about the magnitude of the problem. The U.S. is currently facing a crisis of accumulating garbage. As will be seen, the diet-CHD literature is also accumulating garbage at an alarming rate.

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[a] The meats recommended by the alliance are chicken and fish which have very little stearic acid and so they yield proportionally more cholesterol-raising saturates (see Chapter 5).

One final point. Not only does the alliance attempt to influence the public by redundant consensus events, it also attempts to influence the public by attaching large bibliographies to its reports. For example, NCEP's James Cleeman said that when critics argue against the 1990 NCEP recommendations, he "will point them to the reports' bibliography, because the scientific base behind the recommendations is very rich."[2652] This writer has found that the contents of the alliance's references bear little or no relationship to their texts. In effect, they re-write history in a manner not dissimilar to George Orwell's Newspeak in "1984."

THE "EXPERTS"

It was emphasized earlier and in Volume 1 that the competency and/or objectivity of many of the researchers promoting the diet-CHD hypothesis are quite questionable, as reflected throughout their writings. It is not necessary for an epidemiologist to memorize the formulae for all or many statistical tests. One can always have books on statistics to rapidly access such formulae. What is necessary, is that epidemiologists know the theory and use of statistics and statistical tests so that appropriate interpretations and conclusions can be made from study results. Unfortunately, not only do many epidemiologists have little understanding of the theory of statistical tests, they also have little understanding of some rather simple statistics, such as correlations.

It is also necessary for epidemiologists to understand the scientific method, how to draw proper conclusions from both confounded and unconfounded data and how to use both inductive and deductive reasoning. Again, unfortunately, many epidemiologists appear to lack most or all of these attributes. For example, the word "confound" has a very specific meaning in experimental studies and statistical analyses. Confounding occurs when two or more variables operate together to produce effects and there is no logical (scientific) basis for determining the contribution, if any, of each of the variables to the effects. Practically every book on statistical mathematics defines confounding this way.[2722,2922,2923] Yet, the 1989 Food and Nutrition Board, purported to be comprised of high quality scientists, could not define this rather simple concept accurately. The Board said, "Confounding refers to associations that are real but do not indicate a causal link. A confounding factor, or confounder, must be associated with both the exposure of interest and the effect. For example, absence of teeth is associated with the consumption of large quantities of milk, but milk is certainly not a cause of the condition."2079

Thus, the Board defined confounder as a noncausative association (correlation) between two variables and completely ignored the conventional definition. In the proper definition, a confounder most certainly can and often does have a causative association between two variables. That is why it is a confounder. If an experimenter wants to determine the effects of Variable A on Variable B but allows Variable C to be an uncontrolled part of Variable A, then Variable C is a confounder. In the strictest sense, both Variable A and Variable C are confounders, depending on which of the two one is interested.

To further illustrate the level of statistical and scientific understanding of the diet-CHD promoters, consider the testimonies of the plaintiff witnesses at the FTC-NCEN trial, namely Theodore Cooper,[2688] Jeremiah Stamler,[3279] William Connor,[3278] Henry Blackburn[2691] and Frederick Stare.[2689] (The trial is discussed in Chapter 2).

Statistics and Statistical Tests

When an attorney asked Stare to define a simple correlation, unquestionably the most common statistic used by epidemiologists in population studies, he said "I am vaguely acquainted with it... A perfect correlation I think comes out to be one." When the attorney pointed to a graph showing a correlation of .51, Stare said, "Which would be almost perfect. It indicates in this particular comparison extreme accuracy." Of course, a correlation depicts the strength of an association between two variables, not "accuracy," and .51 is not strong at all, i.e., it indicates that one variable explains only ($.51^2$=) 26% of the total variance of the second variable.[a]

Stamler discussed the between populations study which correlated CHD rates with diets, and between CHD rates and incomes. "What it just shows, there is a relationship between income and coronary rate. If you put money in your pocket you get more coronaries for some reason. If the higher the income the lower the coronary rate, a perfect correlation would be one. And in between there are a variety of correlations and that is what a correlation coefficient is. It is the movement of one variable to another variable and that is what the correlation coefficient is."

Related to correlation is the concept of reliability. When an attorney asked Cooper for his definition of "reliable," he said, "That includes not only the technology of the things that you measure but the design of the equipment itself."

Also related to correlation is a regression equation. Stare indicated that "The purpose of the regression equation is to figure out from the studies where you vary more than one variable what kind of prediction can you get."

Of course, correlations are implicitly involved in the alliance's principal concerns, i.e., risk factor association with CHD, although they are rarely published. The diet-CHD promoters disagree strongly regarding cause and effect. The attorney asked, "It is a fact, isn't it, that the cause of atherogenesis is still unknown...? It is not proven that diet modification will reduce CHD?" Cooper said, "correct. It is not proven. It is not known." He went on to say that risk factors are not the cause of CHD.

When the attorney asked Stare whether an elevated blood cholesterol causes CHD, he said, "No, you can't say that it causes. You can say it is one of the risk factors which along with other things may give rise to heart disease."

Blackburn, Stamler and Connor were adamant in their position that risk factors cause CHD but differed in the relative importance of risk factors. For example, Blackburn stated that "It is my opinion that saturated fat [and cholesterol] in the diet is causally related to heart attacks." Stamler said, "I think there are abundant sets of data showing a relationship [between blood cholesterol and CHD] that is causative." (Note the word "think.") Connor stressed that dietary cholesterol was the "sine qua non for development of atherosclerosis," except that some fat was necessary for dietary absorption.

Connor defined a linear relationship thusly, "...as more cholesterol is eaten...the concentration of cholesterol in the blood is higher." Of course, such an explanation defined a monotonic relationship, not necessarily a linear one.

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[a] The correlation can be used to define "accuracy" in measurement, e.g., the validity of a test instrument.

On the setting of a statistical significance level for cholesterol-lowering clinical trials, Blackburn said, "You have to establish your confidence values, how confident you want to be in your positive result. If you find a positive results, you want to be darn sure one out of a hundred or five out of a hundred due to chance sampling variations, so you set pretty stringent limits there."

Connor was asked to define the "null hypothesis," a concept underlying all experiments and clinical trials. It merely refers to an hypothesis which asserts that no differences will be observed between a treated group and control group. Connor used an example. "In other words, you might think that eating eggs would produce heart disease, and in most of our studies we try to take the opposite point of view. We tried to prove that perhaps the current hypotheses were incorrect.[a] I think I have defined that correctly. I may be a little off."

When the attorney asked Blackburn, "Isn't it the method of science to formulate a hypothesis and then test it by trying to disprove it?" Blackburn replied, "That is reasonable," but he went on to say that he would extrapolate positive findings from the Coronary Drug Project but not negative results, which is obviously contrary to the concept of the null hypothesis.

During their testimonies, Connor, Stamler and Stare said, "I am not a biostatistician," "I am not a statistical expert" and "I am not a statistician," respectively. Cooper also said he had no special training in biostatistics. Such statements were totally unnecessary in view of their testimonies.

In 1981 former NHLBI director Robert Levy attempted to "educate" his readers regarding the statistical concept, alpha (.05,.01, .005, etc.). He said, "Alpha factors are involved in insuring that differences will be significant, that an effect will occur only once out of 20 or 100 or 1,000 times." Those who are more than a little familiar with statistics can at once tell that Levy had only a rudimentary knowledge about that which he spoke.

In sum, it is one thing to be little versed in statistical theory and analyses. But it is quite another to pretend that one <u>is</u> versed. When alliance members publish articles with statistical analyses they typically employ statisticians to provide statistical verbiage. When they exercise their knowledge independently, it is clear that their knowledge is less than satisfactory. Yet, it is this limited knowledge that plays a major role in the attempt to change the American lifestyle.

<u>Science and Scientific Reasoning</u>

What is scientific evidence? Cooper said, "Well, my definition of 'scientific evidence' would be systematically to achieve data that is done by a technologically and acceptable method." Connor defined scientific evidence in terms of his diet experiments,..."studies began with an hypothesis, methodology was outlined as to finding out if the question could be answered. Then the studies were carried out with reputable and established methods of approach and the data was then analyzed

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[a] It is doubtful that Connor <u>ever</u> tried to prove that diet was unrelated to CHD (see a critique of his biased and confounded experiments in Chapter 5).

statistically. Conclusions were then drawn." Elsewhere he said, "...the fiber theory has been subjected to scientific proof..."

Stamler's explanation was totally unintelligible. He said that scientific evidence comes from data that "...have been collected by the established methods that studies have been done and the data collected by established methods of the scientific community, both observational methods in some cases and experimental methods in other cases; controlled experimentation in man, in animals, intervening to change things and watch what happens when you change things." Scientists use "...methods of precision which are representative of the methods of science."

Blackburn said that "Randomized procedures were generally proper" in the 1972 Helsinki hospital diet clinical trial, although no randomization whatsoever occurred in that trial.

In explaining why the Framingham Diet study failed to find associations between diet and blood cholesterol levels or CHD death rates, Connor and Stare said that all subjects were consuming so much dietary cholesterol that there was an inability to discriminate between them. In reality, the cholesterol intake ranged from about 250 mg (under the AHA's recommended limit) to about 1,500 mg in men, with a mean of 704 mg. Such a range was more than ample for discriminatory purposes.

Blackburn and Cooper offered other explanations, albeit either inconsistent with other positions held or simply irrelevant. For example, Blackburn said that "The [diet] measurement tool was fuzzy and variable, admittedly.[a] The measurement of serum cholesterol has its own variability. The variation within individuals in the dietary intake was equivalent to the variation between individuals. Without going into mathematical derivations. I can assure you that under these circumstances, it is impossible to demonstrate a relationship between diet and serum lipids." Of course, the same logic can be applied to the relationship between blood cholesterol and CHD mortality rates. And, of course, the same argument should be valid for the Seven Countries study in which Blackburn and many others cite as evidence of a relationship between diet and CHD.

Cooper's explanation was devoid of any real rational thought at all. He stated, "It is my opinion that the reason that they did not show a correlation is based on the fact that this was not an intervention study." But neither was the Seven Countries study which was partially funded by NHLBI and heavily cited by NHLBI as evidence supporting the diet-CHD hypothesis. Cooper continued rather incoherently, "so that what it was was a retrospective analysis of recall of what you ate during a reasonable period of time as sort of on a dietary basis and that was sort of evaluated and what they found was the variation in diet was pretty great but within a given population pattern which would not be unusual, because you would find, or you would expect to that in a relatively homogeneous population in a fixed city, that their eating habits would not be terribly different."

The attorney introduced a study by Michael DeBakey and his colleagues in which it was found that no correlation was observed between blood cholesterol levels and extent of atherosclerotic disease in 1,700 patients.[128] Stamler said DeBakey's study was nonscientific. "It is simply a descriptive paper of the finding of serum cholesterol at entry of, possibly, in 1,700 patients who had advanced disease who had been admitted to the hospital for surgical treatment so late, and the whole question of the

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[a] But far more extensive and less "fuzzy" than was used in the Seven Countries study in which Blackburn participated (see Chapter 4).

relationship of serum cholesterol, the development of the disease is immaterial to its factors and is not capable of being assessed with their data."

Cooper and Connor completely missed the point of DeBakey's study in their criticisms. DeBakey's study indicated that 78% of CHD patients had cholesterol levels under 300 mg, Cooper and Connor maintained that 300 mg was itself abnormally high. But this argument was irrelevant because the principal finding of the study, i.e., no correlation between blood cholesterol level and degree of atherosclerosis, was evidence against the lipid hypothesis which states that the higher the cholesterol level, the more rapid the rate of atherosclerosis development. It has been noted elsewhere in this volume that cholesterol levels have decreased greatly over the last 30 years. This reduction was probably due to progressively more accurate measurement instruments, as suggested by the very high cholesterol levels observed in vegetarians over 30 years ago and progressively lower levels through the years. It is highly likely that the distribution of cholesterol levels observed by DeBakey was on the high side because of this fact.

To say the least, Stare's criticism of the DeBakey study was absurd and irrelevant, as well as grossly hypocritical. He said, "...I would not pay any attention to any dietary advice he [DeBakey] would give or his comments relative to the inference of cholesterol in the blood on the causation of heart disease. It is out of his field." When asked if he would accept DeBakey's data if they supported the lipid hypothesis, he said, "I would think so." Thus, Stare's argument was to belittle DeBakey as a scientist, thereby implying that his study was worthless scientifically.

No discussion on DeBakey's study was found in Blackburn's testimony.

A most interesting aspect of the testimony presented at the FTC-NCEN trial was Blackburn's rather lengthy argument on why a single factor trial, including a diet-CHD trial, cannot and would not be conducted again. He said, "Our leaders have decided that national priorities are such that we can't undertake this [diet] single factor trial and they proposed an alternative, a very practical public health one that you know about, related to the the end point of coronary mortality. That is, the MRFIT trial." One must wonder how well Blackburn was keeping up with the CHD research since the single factor LRC drug trial was initiated two years before his testimony and was described by Cooper in <u>his</u> testimony.

THE INNER SANCTUM

In Volume 1 it was indicated that alliance members routinely "create" evidence in the process of writing their articles. Their statements may or may not be accompanied by citations of previous research and if they do present citations, the cited research may or may not be consistent with their statements. Frequently, they cite previous articles (often their own) which contain no original source data but which, in turn, cite other previous articles. All too often, when one tracks the citations back to the originating sources, the "evidence" turns out to be either an opinion, irrelevant, negative or grossly different from that presented by the serial "reviewers." It is almost impossible to find a review by alliance members that is free of this form of distortion and an example is given below.

It was also emphasized in Volume 1 that alliance members behave more like lipid evangelists than lipid scientists because they recognize only research that appears supportive of their dogma and they present data in ways which hide weaknesses but suggest strengths. Most highly conservative religious groups tend to interact and support each other, and minimize contact with outsiders. As will be seen below, examination of the reference lists of the most avid alliance members reveals that they

cite themselves and each other to a far greater extent than they do less avid members and they only rarely cite researchers with opposing views. When they make statements such as "epidemiologists believe..." or "most researchers agree...," they are effectively referring to themselves.

In a very real sense the alliance is an inner sanctum from which proclamations emerge via masses of redundant articles designed to convince clinical physicians and the public that their dogma is the fruit of the entire medical research community's knowledge.

Tracking the Citations

William Kannel presented a "review" in Clinical Chemistry in 1988 entitled "Cholesterol and risk of coronary heart disease and mortality in men."[1448] Although this article is replete with incorrect or highly misleading statements (discussed elsewhere), one statement is addressed here to illustrate how information/opinions become transformed via the citation process. Figure 1-9 is designed to simplify this presentation.

The top box in Figure 1-9 encases Kannel's statement. He cited three reports as evidence supporting the claims that the ideal blood cholesterol range in adults is 130-190 mg, that this range is representative of long life, and that all Americans should strive to achieve a level within that range. His three citations were reports by himself,[1083] Jeremiah Stamler[2635] and Scott Grundy.[262]

Kannel's 1984 report was yet another review article with no original data and should not have been cited, therefore, as "evidence" for his 1988 statement. Moreover, his report presented two statements which indicated quite different conclusions than the one he arrived at in his 1988 article. First, he said that the best cholesterol levels with respect to CHD were 140-180 mg, not 130-190 mg, and he cited no reference for this statement. Second, he noted (indirectly) that total mortality is higher at the low cholesterol levels than at the intermediate levels and concluded that the most favorable range was between 180-200 mg. Thus, Kannel's 1988 statement completely distorted his own previous statement.

Kannels' second citation was that of Stamler but a careful examination of Stamler's article revealed no discussion whatsoever of the 130-190 mg range, or any other range or mean value.

Kannel's third citation was a 1986 "review" article by Grundy. The latter also cited the above Stamler article as the source of the "ideal" cholesterol range of 130-190 mg.

In other words, not one of Kannel's three citations included evidence for his 1988 statement and one (his own) contradicted his statement.

Having dispensed with one generation of citations, we may now address a second generation. The second half of Kannel et al.'s 1984 statement wasaccompanied by a citation of the "Conference on the Health Effects of Blood Lipids: Optimal Distributions for Populations" which was authored by Blackburn as well as Kannel and others. That report indicated a desirable cholesterol level of 190 mg, somewhat different from Kannel's later 180-200 mg range, and an ideal range for CHD of 110-210 mg, quite different from Kannel's 1984 range of 140-180 mg.

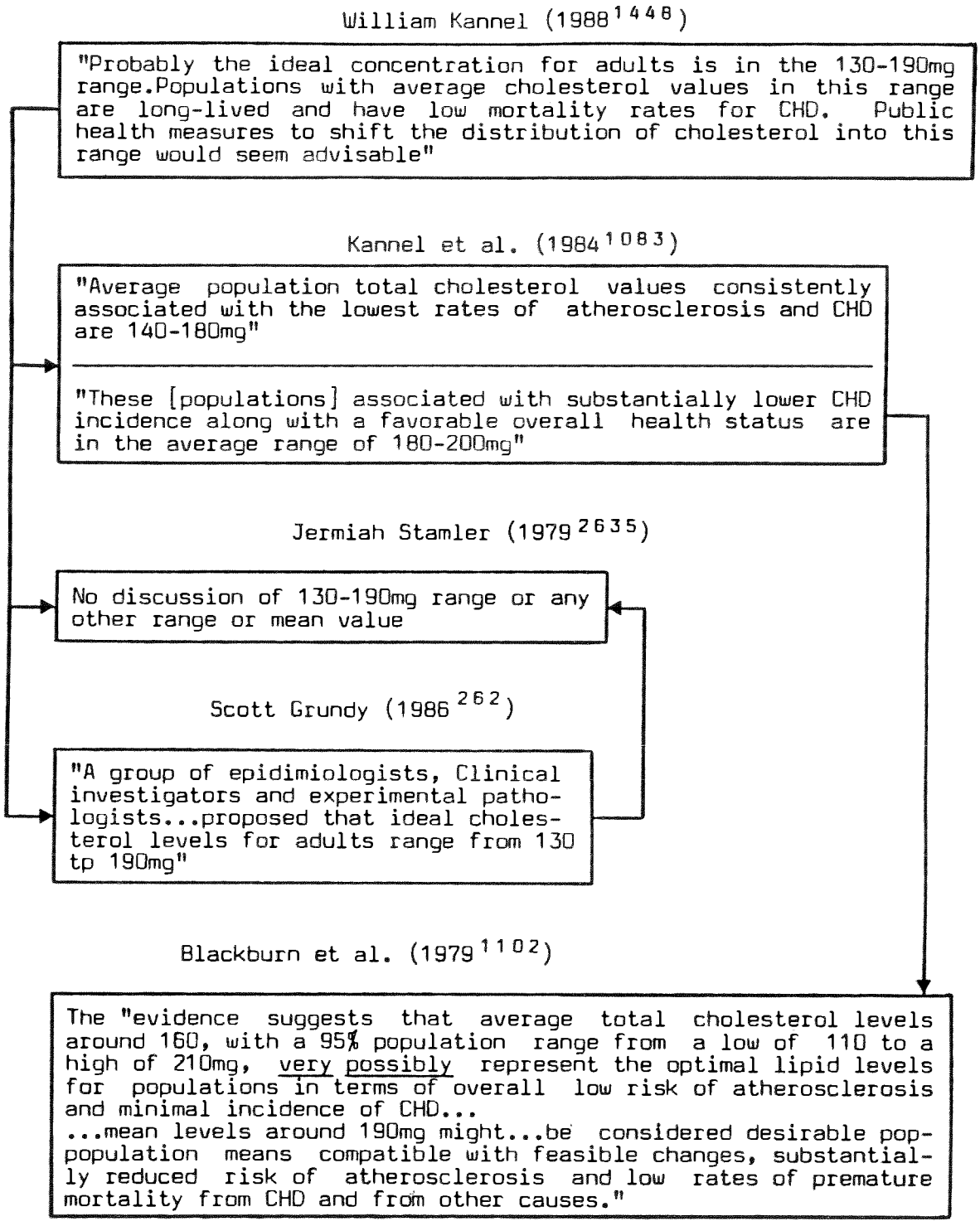

Figure 1-9. Tracking Kannel's citations

In sum, none of Kannel's 1988 citations presented original source data and two presented either different or no data at all. Very importantly, his 1988 statement omitted the most important data of all from his citations, i.e., optimal cholesterol levels for all-cause mortality. In addition, two of his cited references also botched the job of accurately citing references. The whole process was typical alliancedygook, practiced routinely by all alliance members.

All in the Family

Nine articles for which Kannel was the sole author contained a total of 118 references with names of persons.[a] Of the 118, 36% were his own previous articles and 52% were from the inner sanctum (Kannel, Castelli, Stamler, Levy, Feinleib, Grundy, Blackburn, Gordon, Steinberg and Shekelle).

Five articles for which Jeremiah Stamler was sole author included 456 references of names of persons.[b] Of the 456, 24% were his own previous articles and 40% were those from the inner sanctum (Kannel, Castelli, Levy, Feinleib, Gordon, Hegsted, Blackburn, Connor and Keys).

William Connor was sole author on three articles which contained a total of 104 references of names of persons.[350,411,560] Twenty-seven percent of those references were his own previous articles and 41% were from the inner sanctum (Keys, Stamler, Levy, Kannel, Castelli and Hegsted).

Scott Grundy authored four articles which included a total of 119 references of persons.[c] Of the 119, 36% were his own previous articles and 50% were those from the inner sanctum (Keys, Connor, Hegsted, Gordon, Castelli, Kannel, Stamler, Hegsted and Levy).

The AHA's first diet recommendation report in 1961 was written by Irvine Page, Ancel keys, Jeremiah Stamler, Frederick Stare, Edgar Allen and Francis Chamberlain.[517] It contained 21 references of personal names and 48% were those of 4 of the report's authors.

The 1988 Expert Panel report contained 47 references of names of persons.[1066] Some 32% were written by the Panel's authors and 57% were from the panel and the inner sanctum (Stamler, Castelli, Kannel, Feinleib, Hegsted and Shekelle).

The Outer Sanctum

The above section provided examples of the extent to which a relatively small group of alliance members cite themselves and each other in their articles. Lest the reader think otherwise, the remaining references of the above articles are by no means representative of the entire research community. On the contrary, most are long-time supporters of the diet-CHD hypothesis. Since they have not achieved the status of those within the inner sanctum, they may be defined as members of the outer sanctum. The inner sanctum barks and the outer sanctum wags its tail.

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[a] 519,787,823,964,1091,1174,1448,2827,2893

[b] 539,573,574,1313,2635

[c] 262,687,978,1278

The Outsiders

Rarely do alliance members cite authors who are critical of the diet-CHD hypothesis and when they do, they often defuse the authors' material by ignoring their crucial conclusions and citing a more minor issue. For example, George Mann published an article in 1977 entitled, Diet-Heart: End of an Era," in which he concluded that the diet-heart hypothesis was more "propaganda" than factually based.[129] Yet, in one of the above noted Stamler articles,[1313] Mann's article was cited as supporting the concept that extrapolating the negative results from the old CDP project to the issue of CHD prevention by diet was "entirely unsound." Mann said or implied no such thing. Rather, he merely indicated that the Project, as well as diet trials, failed to demonstrate the utility of lowering blood cholesterol by drugs or diets.

Yerushalmy and Hilleboe[551] published an article in 1957 in which they emphasized at length the fallacies of computing correlations between reported CHD death rates and reported types of food intakes across nations. One of the aforementioned Connor articles[560] included a citation of their study but ignored this all important conclusion. Instead, Connor merely said that in computing correlations between nutrients and death rates "the data of Yerushalmy and Hilleboe gave stress to calories derived from animal fat and protein."

There is little doubt that a relatively small group of alliance members consider themselves to be elite CHD researchers, despite the fact that none demonstrates the behavior of academically trained scientists. By assuming this elitism they have also assumed the power to interpret and re-write history as they see fit and thus create new "evidence" in the process. The extent to which their "reviews" have distorted the true state-of-affairs is so great there are no adjectives that can describe it adequately.

"NEW STUDYING" THE POPULATION TO DEATH

Some medical journals are submitted to the news media in advance of their publication for the obvious purpose of gaining publicity for their contents. The editor of one such journal, Arnold Relman (New England Journal of Medicine), denies this and states, "We do not promote our articles in any shape, form or manner... We're just honest brokers of information."[3394] But, of course, the mere act of submmitting one's journal to the press each week is a form of promotion. For what other possible purpose would the news media have for a journal other than giving publicity to its contents? In any event, it has become common to hear television and read newspapers every two or three weeks declare that a "new study" confirms this or that aspect of the diet-cholesterol-CHD relationship. Consider the following recent examples:

> "New research raises the possibility that diet and drugs used to reduce cholesterol levels also may help prevent two of the most deadly forms of cancer."[2765]
>
> "New cholesterol test pins down heart risk."[2769]
>
> "An aspirin every other day can cut the risk of heart attack for men over 50 and provide even greater benefits for those at highest risk of heart attack because they smoke or have diabetes, high cholesterol levels or high blood pressure, according to the final results of a landmark study published today."[2768]

"Bad news for people who've switched to decaf for their health; decaffeinated coffee raises the level of 'bad' cholesterol, which in turn may increase the risk of heart attack, new research suggests."[2766]

"Early findings from the most comprehensive large study ever undertaken of the relationship between diet and the risk of developing disease are challenging much of American dietary dogma."[2770]

"New findings from a large heart study support the belief that reductions in smoking and other health risks have contributed importantly to a sharp decline in deaths from heart disease."[2760]

"New health research strengthens the argument that men who control cholesterol levels in their blood can sharply reduce their risk of death from heart disease."[2761]

"New study strengthens suspected link between colon cancer, saturated fat."[2762]

"New light being shed on early mechanisms of coronary disease."[2763]

"Regular doses of aspirin or a common blood thinner can cut in half a person's risk of stroke from an irregular heartbeat--a striking discovery announced Wednesday."[2767]

Lest the reader think that this machine-gun-like activity is a relatively new phenomenon, consider a comment in 1964 by Wall Street Journal reporter Jerry Bishop, i.e., "Almost daily 'a leading cardiovascular researcher' reports in magazines and newspapers, some major new advance in the conquest of the number one killer."[2004] Bishop subsequently became one of the reporters providing readers with "almost daily" doses of new studies. He apparently had no choice. As recently noted by a Washington Post writer, Howard Kurtz,[3394] newspapers tend to publish stories from the journals because they are afraid someone will say, "so-and-so published this story, so why didn't we publish it?"

The news media apparently employ no scientists to critically review studies before their results are disseminated to every household. Television channels frequently employ physicians to make announcements of "new studies" but they have virtually no more capability than news reporters to evaluate these studies scientifically. As shown repeatedly in this volume, many of the studies being transmitted to the public are poorly designed and their results are even more poorly analyzed and interpreted by their authors. This is so despite statements by such persons as New England Journal of Medicine Editor, Arnold Relman, that such studies are subjected to "rigorous peer review."[3394] Relman maintains that his "journal's articles 'are blown out of proportion' and 'misinterpreted.'" This writer has found that most of the "misinterpretations" and "blowing out of proportion" occurs within the journal's articles, not by reporters. The scientifically naive news or physician reporters cannot detect these flaws and faithfully transmit them, often amplifying and sometimes distorting them in the process. The result is that Americans are constantly being bombarded by the worst kind of scientific nonsense imaginable. There is no way of telling how much damage to health is incurred by Americans from overconsumption of highly promoted products such as aspirin, fish oils, polyunsaturates, trans isomer-loaded margarines, etc., but there can be no question that damage has been done.

ANCEL KEYS: THE PONTIFF OF PANDEMIC PANDEMONIUM

Introduction

There is little doubt that the great diet-CHD crusade was initiated by Ancel Keys. The crusade began in the early 1950s and it was based almost entirely on erroneous, incomplete and/or misleading data, primarily because Keys did not hesitate to accept coincidental trends and extrapolate well beyond the current state of knowledge. One can argue that it is no crime to draw conclusions from preliminary data but it is certainly irresponsible to incite an entire population on the basis of such data.

A careful reading of Keys' published literature reveals two rather significant characteristics. First, he has often presented himself as the ultimate authority, being the first to discover nearly all important facts. He has tended to view the works of others as either "supportive" or erroneous and seldom, if ever, innovative. Second, contrary to his projected image, Keys' major pronouncements over the years have invariably been proven wrong. His entire position over time has been an evolutionary series of corrections based almost entirely on the works of others. Yet, his writings distinctly suggest otherwise.

In 1953 Keys[3296] indicated that "many factors are probably involved in the atherosclerotic development and in the clinical appearance of CHD, but there is no longer any doubt that one central item is the concentration, over time, of cholesterol and related lipoproteins in the blood serum." He cited Lyman Duff[2997] as one source for this statement. However, the statement actually makes little sense. For example, there is a "concentration" of cholesterol in the serum of all persons whether or not they develop atherosclerosis. If we assume that Keys meant that atherosclerosis is preceded by a high concentration of cholesterol, then Duff was an incorrect citation because Duff specifically maintained that high cholesterol levels were not associated with the development of ordinary human atherosclerosis (see Chapter 2). Thus, Keys initiated a long series of errors early in his career as a diet-cholesterol-CHD promoter.

It is useful to digress for a few moments in order to describe a recent "confrontation" between Keys and one of the AHA's most staunch supporters, Scott Grundy. In 1988 Bonanome and Grundy[1395] published an article that demonstrated that a diet high in stearic acid produced a much lower and somewhat lower blood cholesterol level than did diets high in palmitic and oleic acids, respectively. They concluded that "stearic acid appears to be as effective as oleic acid in lowering plasma cholesterol levels when either replaces palmitic acid in the diet." Several months later an irate letter-to-the-editor authored by Keys and Blackburn[1605] appeared in the same journal. Keys and Blackburn accused Bonanome and Grundy of claiming to have discovered the nonhypercholesterolemic effects of stearic acid and cited 1957 studies by Ahrens et al.[375] and Horlick and Craig[713] and a 1965 study by himself[1309] as having demonstrated such effects. In fact, however, Bonanome and Grundy cited Ahrens et al. and Keys et al. as having reported such effects in the first and second to last paragraphs of their article.

Keys and Blackburn also accused Bonanome and Grundy of misleading the public and opening the door for industry to exploit their results commercially. Bonanome and Grundy[1607] replied that Keys' remarks were "strange," because he "himself has recently extolled the virtues of olive oil and coronary heart disease.[282] Parenthetically, "exploitation' of our findings by the olive oil industry pales into insignificance as compared with the millions of dollars made in the putative coronary-protective effects of polyunsaturated fatty acids--a direct outgrowth of Dr. Keys' work." Indeed, Keys was unquestionably the primary instigator and promoter of the largest exploitation in the history of food processing and he was also very proud of

having caused that exploitation. As we shall see, Keys incited industry to transform healthy fats into possibly unhealthy fats, based on his own ignorance of the scientific literature and his subsequent failure to acknowledge his error when he discovered it.

Before discussing the events surrounding Keys' influential early reports, it is important to note that Bonanome and Grundy[1607] suggested that they "develop a new fat, rich in stearic acid, that can serve as a prototype for new margarines and shortenings. Not only will this fat not raise the LDL cholesterol level, but it is devoid of unnatural trans acids due to the hydrogenation of vegetable oils." We will also see that industry had produced such a fat before Keys and his followers effectively "ordered" its abandonment in favor of the current fats that are high in trans isomers. Neither Keys nor Bonanome and Grundy seemed to be cognizant of the obvious.

The First 50 Years of Hydrogenating Vegetable Oils[3303]

The hydrogenation process was discovered serendipitously in 1897. An Englishmen obtained a British patent on liquid phase hydrogenation and the process was subsequently used to hydrogenate whale oil to make soaps, candles, etc. Hydrogenation was used early in this century in the U.S. to produce shortenings and margarines from vegetable oils.[a] They were made by blending (compounding) two variations of cottonseed oil. For example, shortening was a blend of 15% fully hydrogenated oil with 85% refined oil. Unhydrogenated cottonseed oil is composed of about 25% palmitic/myristic acids, 2.4% stearic acids and about 71% oleic and linoleic acids. Since oleic and linoleic are 18-carbon chain acids, they are converted to stearic acid when fully hydrogenated. This fact was of no importance to anyone because few were concerned about atherosclerosis at that time and fat was certainly not considered to be a cause of that disease. However, it is useful to note at this point that while the shortening produced by hydrogenation had a higher content of saturated acids than was available in the refined oil, the increase was exclusively stearic acid which would be found many years later to not elevate blood cholesterol. Also, since only 15% of the shortening was hydrogenated, the shortening had a high content of polyunsaturated fatty acids.

In the 1930s both shortening and margarine were produced by partially hydrogenating most of the oil instead of fully hydrogenating part of the oil. This process change presumably was accomplished to give the products greater shelf lives, i.e., reduce randicity and maintain flavor. Partial hydrogenation involved "preferential" treatment which meant that many more polyunsaturated fatty acids received hydrogen atoms in one of their double bonds than did the double bond in monounsaturated acids. This treatment resulted in a product that increased the saturated fatty acid content very little but decreased the polyunsaturated content a great deal. Thus, the P/S ratio was decreased. In addition, partial hydrogenation resulted in the formation of trans isomers, an unnatural version of monounsaturated fatty acids. Trans isomers were solid, rather than liquid at room temperature and that is why partial hydrogenation transformed the oil into a plastic-like substance. Enig[3362] indicated that approximately one-quarter to one-third of partially hydrogenated cottonseed oil was composed of trans isomers. However, the loss of polyunsaturates and the gain in trans isomers were again of no significance to medical researchers at that time.

In the 1940s soybean oil began replacing cottonseed oil as the primary fat in margarine and later in shortenings. While cottonseed oil contained about 25% saturated fatty acids, soybean oil was composed of only 10% saturates. Moreover,

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[a] Various types of margarines had other ingredients as well.

soybean oil was much higher in polyunsaturated fatty acids (57% vs 48%), particularly linolenic acids (6.5% vs 0.0%), as shown in Chapter 5. Thus, this switch resulted in a major increase in the P/S ratio. On the other hand, because this product had a relatively short shelf life (producing an off-flavor), due to its linolenic content, industry developed a specific partial hydrogenation process that converted all of the linolenic acid and only a little of the linoleic acids. This process produced more trans fatty acids and less stearic acids than did previous partial hydrogenation techniques.[3362]

It is important to emphasize at this point that although available (see Chapter 3) saturated fat increased somewhat from 1930 to 1950, available polyunsaturated fat increased at a greater pace. Butter and lard, which were high in saturates and relatively low in polyunsaturates, were being replaced by margarines and shortenings, having much lower amounts of saturates. Furthermore, all of the newly formed saturated fatty acids produced by hydrogenation were nonhypercholesterolemic stearic acids. In addition, according to the USDA,[2557] dietary saturates did not increase after 1950, the beginning of the so-called CHD epidemic, and total calories actually decreased from 1930 to 1960. By 1943 vegetable oils (excluding tropical oils) constituted about 97% of the fats and oils used in margarines, with the remaining 3% deriving from animal fats.[3363] Although trans fatty acids would much later be determined to elevate blood cholesterol, it is to be emphasized that the increase in such acids in partially hydrogenated soybean oil over cottonseed oil was minor compared to the substantial decrease and increase in saturates and polyunsaturates, respectively. It is important to note also that the transition from cottonseed and other oils to soybean oil was due to economics, not to instruction by the medical community.

The Crusade: 1950s

Mortality Trends.

In 1953 Keys[279] admitted that the atherosclerotic disease was very difficult to diagnose in life or death and "all too seldom verified" by autopsy. In fact, he indicated that "it is rarely possible" for a physician to differentiate between any of the heart diseases. However, he maintained that the all heart disease death rate was increasing.

In 1957 Keys[276] said, "While the total mortality rate (all causes) is decreasing in life insurance statistics, the mortality rate for the total of all heart diseases is increasing, and since CHD accounts for three-fourths of all heart disease mortality [inconsistent with his 1953 statement], it seem evident that CHD has increased a great deal in the last 25 years." But as shown in Chapter 3, vital statistics show that the age-adjusted all-heart disease mortality was strongly downward throughout the 1950s, while the CHD rate was strongly upward, the opposite to that indicated by Keys. The fact that he could not know these trends at the time, because of the lag in accumulating national statistics, does not detract from the fact that Keys' logic was correct but his trend data were incorrect; thus, his conclusion was opposite to that which would have been derived using the same logic and the correct trend data.

Risk Factors. Keys effectively ruled out all currently accepted risk factors (except cholesterol) as causes or promoters of CHD. In 1956 he said, "There is some tendency for the incidence of ischemic heart disease and the serum cholesterol to be related to the level of physical activity, and it has been suggested that this may account for the low cholesterol in some populations. The latter contention, however, is easily disproved."[280] Of course, the alliance will subsequently claim that physical activity is a risk factor and that it does alter blood cholesterol.

In 1957 Keys[276] indicated that "certainly the great differences in the incidence of CHD...within the same populations and at different times are not explained by genetic factors."[a] Of course, "sex" and "family history," both genetically based, will subsequently be classified as risk factors by the alliance.

Keys also reported that "it is easy to rule out of primary consideration many factors that show no consistency with regard to the relative frequency of the disease," including alcohol and tobacco."[276] Smoking will become one of the alliance's primary risk factors and alcohol will become widely recognized as (1) a means of elevating HDL and (2) being strongly and negatively associated with CHD.

Blood pressure, one of the alliances three top risk factors, was not even a topic in Keys' articles.

Fat Consumption Trends. Using the USDA availability data (see Chapter 3), Keys[279] held in 1953 that "the proportion of fat calories in the total American food consumption has steadily increased." He used this trend as evidence supporting the fat-CHD hypothesis. The same availability data, however, show that the percentage of total calories as fat continued to increase beyond 1970, many years after the so-called CHD mortality epidemic peaked and then declined. The fact that Keys could not know these eventual trends in 1953 again does not detract from the fact that Keys' argument was subsequently proven wrong.

In the first half of the 1950s Keys considered all fats to be hypercholesterolemic. In 1953 he said, "it is clear that the biggest contributor to the fats in the American diet is fats and oils as such, excluding butter, which comprise 46.5% of the total. Meats, poultry and fish combined make a poor second at 22.1%. Any attempt to reduce the total fat intake must, then, begin with cooking fats and oils."[279] He was, of course, referring primarily to the vegetable fats and oils (margarines, shortenings and salad oils) which were increasing in the diet, while animal fats were decreasing. In 1956 the two items on the top of his list for reduction in the American diet were margarines and hydrogenated shortenings.[280] When Keys later recognized that saturated and polyunsaturated fats increase and decrease, respectively, blood cholesterol, he will immediately focus his attention almost exclusively on animal fats. But once again we must inform the reader that Keys' associations of fat per se with blood cholesterol level and CHD mortality rate were wrong; once again it was necessary for the accumulation of data or the findings of others to demonstrate his errors.

Despite the publication of several articles in the early 1950s showing that animal and vegetable fats increase and decrease blood cholesterol, Keys [80] remained unconvinced in 1956 that the type of fat was important.[b] In the same year, Bronte-Stewart et al.[343] conducted an experiment that indicated that the saturated fatty acids in both animal and vegetable fats were hypercholesterolemic. Ahrens et al.[375] and Malmros and Wigand[714] also demonstrated in 1957 that hydrogenated oils elevate

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[a] In 1973, however, Keys did attribute importance to genetics. He said, "Serum cholesterol levels often vary among men on the same diet. The differences which cannot be explained by variations in food intake are probably related to genetic factors."[2838]

[b] Kritchevsky[1797] and his colleagues were apparently the first (in 1954) to show that saturated fats increased blood cholesterol when fed with cholesterol to animals to a greater extent that unsaturated fats.

blood cholesterol level, relative to the unhydrogenated oils. Ahrens et al.[712] pointed out that those results reflected the overall loss of polyunsaturates, rather than an increase in saturates. And Horlick and Craig[713] found saturated fats to raise cholesterol, while polyunsaturates had the opposite effects in a fourth 1957 study.

Keys published a number of articles in 1957, some of which still maintained his position that all fats were comparable, although some doubt was expressed.[276,2838] Other articles in 1957 revealed his acceptance of the importance of fatty acid composition.[315,716] However, he will strangely maintain that total fat is also important, a position that is theoretically untenable and subsequently proven wrong by himself (without apparently knowing it) and others.

In 1959 Keys[715] concluded that "The alpha lipoprotein (HDL) is not altered by changes in the fat in the diet and...no dietary manipulation is known to affect the levels of the alpha fraction." Of course, this conclusion was also wrong as subsequent research showed that HDL can be elevated by saturated fat or alcohol and reduced by carbohydrates and polyunsaturated fatty acids.

Dietary Cholesterol. For many years Keys maintained that dietary cholesterol did not influence blood cholesterol. In 1953, for example, he said, "The total cholesterol concentration in the serum of man is substantially independent of the dietary cholesterol intake over the whole range of possible human diets."[279] The alliance will subsequently draw the opposite conclusion and Keys himself will accept that conclusion in 1966.[880]

Between Population Studies. When Keys believed that all fats raised blood cholesterol levels in the early 1950s he published his six countries study which showed an almost perfect correlation between amount of total fat in the diet and heart disease mortality rate.[279] But when Keys acknowledged that saturated and polyunsaturated fats have opposite effects, his Seven Countries study revealed a very low correlation between total fat and CHD but a high correlation between saturated fat and CHD.[493] Thus, once more Keys managed to find results compatible with current thinking.

Blood Cholesterol and CHD. In 1957 Keys[276] indicated that 88% of myocardial infarctions occurring in a group of men had cholesterol levels over 200 mg. In his earlier (1953) article he presented mean cholesterol levels for men aged 40, 45, 50, 55, 60, 65, 70 and 75. Although a weighted average cannot be computed from these means, a simple average was found to be 236 mg. This average is about 20 mg higher than that obtained in later studies, reflecting greater inaccuracies of measurement at that time.[a] Thus, when Keys indicated that 88% of infarctions occur above 200 mg, nearly 88% would be expected by chance because approximately 60-65% of the current male population falls above 200 mg where the mean cholesterol level is 215 mg, not the higher 236 mg. Thus, contrary to Keys' implication that most infarctions occurred at elevated cholesterol levels, most infarctions, in fact, occurred at average levels.

The Eskimo Dilemma. A typical argument used against Keys' position that all fats are hypercholesterolemic and thus atherogenic was that Eskimos have high fat diets and presumably low CHD mortality rates. Before recognizing the differential effects of saturated and polyunsaturated fats on cholesterol, Keys dispensed with the apparent Eskimo anomaly by questioning the legitimacy of "low CHD rates." he said the

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[a] Early studies also found vegetarians to have higher cholesterol levels than observed today, although there is no theoretical basis for such a difference (see Chapters 3, 4 and 5).

anomaly was "most easily answered" because "only a very few primitive Eskimos ever reach age 50" and thus "an age when they would be susceptible to CHD."[276] Much later, when the differential effects of saturated and polyunsaturated fats were firmly accepted by everyone, keys will ignore the age factor and claim that the high-fat, low CHD rate among Eskimos was consistent with the fact that the Eskimos' diets were high in polyunsaturated fats.[2838] Thus, he demonstrated once again that he can accept and reject data depending on his need to appear consistent.

The World War II Example. Several times Keys (and many others) pointed to World War II as an example of an association between fat and CHD, i.e., "It is now well known that the incidence of ischemic heart disease in some countries was remarkably reduced during World War II, only to rise to new heights a few years later. The only reasonable explanation offered is that this was a reflection of dietary changes."[280] But such a conclusion was remarkably naive because several "reasonable" explanations can be advanced. For example, millions of lives were lost that were directly attributable to the war. Soldiers and many civilians were killed and many others died of infections, malnutrition, lack of medical help and medicines, etc. All of these deaths depressed the overall CHD death rate by necessity and, of course, they all ceased at the termination of the war, permitting the degenerative diseases to once again exsert their maximum influence.

Blood Cholesterol and Age. Keys[279] assumed incorrectly that persons consume more fat as they grow older, explaining the fact that blood cholesterol increases with age. He said, "from the thirties through the fifties the serum concentration is increasingly dependent on the amount of total fat in the diet." Such an assumption was eventually proved wrong by both of the NHANES dietary surveys which showed that the percentage of total calories as fats and saturated fats remained constant from the thirties to the fifties (Chapter 3).

The Crusade: 1960s

Dietary Recommendations. Keys co-authored the AHA's first dietary recommendations to the public in 1961.[517] The principal thrust of that report was the recommendation to reduce total fat in the diet and substitute polyunsaturated fats for "substantial" amounts of saturated fats. While Keys designated vegetable margarines and shortenings, and other oils as principal culprits in the American diet in the 1950s, he and his co-authors reversed that position in the 1961 report because of the new information about saturated and polyunsaturated fats. They said, "In the usual diet eaten in the U.S., a large part of the fat is of the saturated type. Too much of this type of fat tends to increase the cholesterol in the blood. Considerable amounts of saturated fat are present in whole milk, cream, butter, cheese and meat. Most shortenings and margarines have less than half as much saturated fat, and the common vegetable oils have still less." The authors continued, "Many natural vegetable oils such as corn, cotton and soya, as well as the fat of fish, are relatively low in saturated fats and high in fats of the polyunsaturated type. When these fats are substituted for a substantial part of the saturated fats without increasing calories, blood cholesterol decreases."

Despite this recognition of the opposite effects of saturated and polyunsaturated fats, Keys and his co-workers maintained the theoretically untenable position that the reduction in fat per se also reduces blood cholesterol level. Moreover, in keeping with Keys' long-time belief that dietary cholesterol has no important influence on blood cholesterol, the AHA statement did not specifically recommend a reduction in the consumption of cholesterol, a position the AHA will later abandon.

Although margarines and shortenings appeared to be labeled "good guys" in the AHA report, they were implicated otherwise by Keys in a 1961 Time Magazine article.[1993]

He indicated that saturated fats had "become a bigger and bigger part of the American diet." Since animal fats were decreasing in the American diet, the increase in saturates was due entirely to vegetable fats and much of these saturates was nonhypercholesterolemic stearic acid. The two 1957 reports[375,713] showing little or no effects of stearic acid were ignored and Keys and his associates once again made pronouncements based on an incomplete understanding of the literature and erroneous logic related to the effects of amount and type of fats on blood cholesterol.

In the meantime, with the urging of Keys and others the industries producing margarines and shortenings increased production of products containing high levels of both polyunsaturates and trans isomers, products which the alliance will eventually condemn many years later.

The careful reader will note that Keys' leadership in the epidemiologic research on CHD began and ended in the early 1950s. He was wrong in claiming that the all heart disease mortality rate was increasing. He was wrong in assuming that total fat in the American diet was increasing simply because available fat was increasing. He was wrong in associating the increase in available total fat with the increase in CHD mortality because the former would continue to increase after 1963, while the latter would decrease after that year. He was wrong in claiming that all fats increase blood cholesterol. He was wrong in claiming that all saturated fats increase blood cholesterol. He was wrong in claiming that HDL is unaffected by diet. He was wrong in his understanding of the compositions of margarines and shortenings and their effects on blood cholesterol. He was wrong in his understanding of trans isomers. And he was wrong in urging industry to produce products with high P/S ratios because such products greatly increased trans isomers, subsequently found to increase blood cholesterol.[a] In effect, Keys was a follower of the work of others, not a leader, and continuously adjusted his pronouncements to fit the current state-of-the-art. While the adjustment of one's theoretical framework to fit current data is most certainly not inappropriate, Keys always gave the reader the impression that each adjustment was, more or less, the result of his work and represented sufficient data for application to the public and industry.

The Response of the Fats and Oils Industry. As noted previously, the hydrogenated margarines and shortenings yielded much lower saturated fats than did the products they replaced, particularly so as soybean (and safflower and sunflower) oils soon dominated the market. This fact seemed to be overlooked by Keys. Another overlooked fact was the high content of trans isomers. Sinclair acknowledged the existence of these unnatural fatty acids in 1956[3305] and Hegsted (cited by Van Itallie[353]) apparently showed that these acids increased blood cholesterol levels somewhat. Van Itallie held that "...since the possibility has not been excluded that some of the substances formed during hydrogenation may be harmful, their status should be promptly and thoroughly investigated."

On the contrary, not only were trans isomers not evaluated for their potential harm, Keys and the AHA were indirectly responsible for greatly increasing these fatty acids in the American diet. This came about with industry's response to their accusation that hydrogenated foods contained too much saturated fat and not enough polyunsaturated fat. Industry began producing soft margarines, containing less saturates and more polyunsaturates because of milder hydrogenation. However, the amount of trans isomers was high in order to give solidity to the products. Unknown to Keys and the AHA, hydrogenation processes that increased the amount of

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[a] Keys' position on risk factors other than blood cholesterol were also at variance with the subsequent beliefs of the alliance.

nonhypercholesterolemic stearic acid and decreased the amount of trans isomers would have affected blood cholesterol levels more favorably than the process promoted.

Mortality Trends. Unknown to Keys or anyone else, the CHD mortality rate peaked and initiated a decline before the new margarines and oils became widely used. Had vital statistics been available in real time, it would have been (or should have been) obvious to everyone that dietary fats could not be the cause of CHD because they were still increasing in the diet after the CHD decline began and the overall P/S ratio of the fats in the American diet were increasing during the CHD epidemic. But such statistics were not available in real time and Keys and the AHA assumed during the 1960s and early 1970s that the CHD mortality rate was still increasing and they greatly promoted a high polyunsaturated fat diet (see Chapter 2). It was not until 1974 that the decline was generally recognized by the scientific community.[2604] In effect, Americans were encouraged to reduce total and saturated fat intake and increase consumption of high polyunsaturated fat foods after the CHD mortality rate began to decline and, in the process, greatly increase the consumption of trans isomers. The 1961 dietary recommendations by the AHA and Keys were made at the time that CHD mortality had already peaked nationally and 8 years after it had started its decline in California (see Chapter 9).

Discovering Previous Discoveries. In 1965 Keys and his co-workers[1309] concluded that stearic acid was a nonhypercholesterolemic saturated fatty acid.[a] They acknowledged the 1957 work of Ahrens et al.[375] and Horlick and Craig[713] but obviously did not consider their findings on stearic acid important because "until recently we saw no reason to distinguish between stearic and palmitic acid." It is also questionable whether Keys et al. still found stearic acid important. Although on page 777 of their article they said, "stearic acid is ever present in the diet in considerable amount [note the word "considerable"], on the following page they reported that "In the usual American diets stearic acid seldom accounts for more than 3% of total calories. What were the authors trying to convey?

In their 1966 report Keys and Parlin ignored the early work of Ahrens et al., and Horlick and Craig, and cited their (above) 1965 article as "suggesting that stearic acid may have no cholesterol-increasing effect." Moreover, after many years of resisting the contention of others that dietary cholesterol was important in influencing blood cholesterol, Keys finally agreed that it has "some effects" and included it in his regression equation (Chapter 5).

Thus, Keys adjusted his theoretical framework again to account for the previous work of others.

The Crusade: 1970s. Keys and his co-workers[718] published an article in 1972 that was designed to prove that saturated fatty acids increased blood cholesterol level twice as much as polyunsaturated fatty acids decreased the level. Although their results were supportive, they also were unsupportive of Keys' long-standing belief that total fat reduction reduces blood cholesterol level. Their study demonstrated that diets having the same fatty acid composition but differing amounts of total fat yielded the same blood cholesterol levels. In their zeal to stress the relative effects of saturated and polyunsaturated fats, they completely ignored the important fact that amount of fat is irrelevant.

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[a] Others followed that confirmed the early findings.[331,877,1395]

The "finding" by Keys et al. was duplicated 14 years later by Grundy et al.,[336] a major spokesperson for the AHA. Yet, neither Keys nor Grundy nor the AHA will acknowledge the lack of importance of total fat and all will continue to stress reduction in total dietary fat.

The stress on reducing total fat by Keys is uniquely dumbfounding because the regression equation he devoted so much time developing over many years (Chapter 5) to predict change in blood cholesterol level with changes in fatty acid composition clearly assumed total fat to be irrelevant. That equation is used routinely today by alliance members who insist that the reduction of fat per se reduces blood cholesterol. Keys developed the equation before, during and after he co-authored the 1961 AHA statement that specifically indicated a relationship between total fat and blood cholesterol level.

A number of studies were cited in Volume 1 which demonstrated that blood cholesterol drops substantially when all fats are removed from the diet and such studies apparently led to the fixation by keys and others that total fat is important. Apparently no one recognized that the conventional diet has approximately three times as much saturated fat as polyunsaturated fat. Thus, when all fat is removed, blood cholesterol is reduced simply because the P/S ratio increases from about 0.3 to at least 1.0.

The acceptance of the notion that the reduction of total fat per se reduces blood cholesterol and of the regression equation which ignores total fat may be referred to as "the total fat folly," one of a long line of follies as this volume will show.

In 1974 Keys[1311] indicated that he deplored "the message that everyone is in serious danger of coronary heart disease if he does not restrict the amount of saturated fat in his diet." However, in the 1961 Time Magazine article he was quoted as saying that one of Keys' two "main messages" was that "the calorie-heavy U.S. diet is 40% fat, and most of that is saturated fat--the insidious kind that increases blood cholesterol, damages arteries, and leads to coronary disease."

In his 1974 article Keys also denied that "imprecisions actually characterized the relevant literature." Not only does Volume 1 and the present volume amply document the masses of imprecisions occurring in the diet-heart literature, one need only review this section which reveals a continuous series of imprecisions by Keys.

Keys also stated that "the margarine of 1949 to 1950 was high in saturated fat" and that this accounted for the fact that "adding vegetable fat margarine to the rice-fruit ["substantially" nonfat] diet evoked a prompt rise in serum cholesterol." Keys cited his 1950 article as the source for this information. Examination of this article failed to reveal the word "margarine." Moreover, it was said that "moderate amounts of corn oil" were added to "a diet completely free from both cholesterol and all fats." Corn oil has a high P/S ratio and can hardly be called "high in saturated fat." Finally, the majority of margarines in 1949 and 1950 were dominated by soybean oils which were extremely high in polyunsaturates.

The Keys pronouncement in the above paragraph was based on one patient with an exceedingly high blood cholesterol, i.e., about 900 mg. It is unscientific and outrightly naive to place so much emphasis on such a peculiar and singular datum.

In the 1974 article Keys appeared to have now assumed full credit for discovering that stearic acid was not hypercholesterolemic. He cited only two of his previous studies as the sources for this information.[880,3308] He went on to say that stearic acid was of little importance because "saturated fatty acids with fewer than 12 carbon atoms in the chain and those with more than 16 make up no more than 5% of the

total fat." Not only was this statement false, i.e., stearic acid makes up 12 to 14% of beef, pork and butter fat, constitutes about 30% of all saturated fat, and represents the only saturated fat produced in the hydrogenation process, Keys published an opposite statement in his earlier 1965 article, i.e., "among saturated fatty acids, only stearic acid is ever present in the diet in considerable amount."[1309] Please note the word "considerable."

Again in his 1974 article Keys criticized the following statement by Reiser: hydrogenation of the plant sterols or loss of linoleic acid can explain the loss of hypercholesterolemic activity by the hydrogenated oils, but hypercholesterolemic activity cannot be laid at the door of the saturated acids."[3307] Keys asked, "How is it possible to say that 'loss of linoleic acid can explain,' but deny that the saturated fatty acids could be involved? Here again is a situation in which both saturated and polyunsaturated fatty acids were changing in opposite directions. Without other information it is impossible to blame one rather than the other. From the results of our own multivariate analyses the prediction is that serum cholesterol would rise because of both changes in the dietary fat." This statement by Keys demonstrated without a doubt that he had very little knowledge of the hydrogenation process and, in addition, he seemed unable to transfer knowledge expressed in one part of his article to another. First, Reiser was correct; partial and selective (high production of trans isomers) hydrogenation was the predominant means of hydrogenating oils, meaning that trans isomers replaced many unsaturated fatty acids. Second, the saturated fatty acid produced by full hydrogenation of part of the oils was stearic acid. Thus, Keys' "multivariate analyses" would appear to have made the right prediction using incorrect assumptions and data, a state-of-affairs not easily explained by scientists but one in which Keys has commonly been found.

Keys' emphasis on the substitution of polyunsaturated fats for saturated fats was the primary impetus for the polyunsaturated fat craze that swept the country in the 1960s and 1970s and, to some extent, the 1980s (see Chapters 2 and 10). When it became generally recognized that high polyunsaturated diets were associated with the promotion of cancer in animals and possibly in humans (e.g., the Veterans Clinical trial published in 1968), the production of gallstones and with the depression of the immune system, Keys, the AHA and others reversed their positions and recommended less than 10% of total calories as polyunsaturates, down from as much as 20% or more. But because the public has not been officially warned about the dangers of high polyunsaturated fat diets, there are many indications that sizeable numbers of Americans are still consuming such diets.

Currently, "modern" findings now suggest that the high levels of trans isomers in hydrogenated foods increase blood cholesterol (e.g., Mensink and Katan[2859]) and that monounsaturates may be equally capable of reducing cholesterol levels as polyunsaturates when substituted for saturated fats (Mensink and Katan[2646]). When we add other relatively new facts that (1) alcohol (via HDL), (2) smoking, and (3) gorging increase blood cholesterol, while (4) carbohydrates (via HDL), and (5) nibbling decrease cholesterol, and (6) stearic fatty acid has no effects, we cannot escape from the conclusion that Keys was proven profoundly wrong time and again with amazing consistency and yet he bounced back each time with another "exact" pronouncement--which, of course, was subsequently proven wrong as well. Again, lest the reader lose sight of this important qualification, the issue is not "being proved wrong" per se but rather the irresponsible premature application to society of insufficient and erroneous information over a 35 year period and the irresponsible failure to inform the public of such erroneous information when it was detected.

The scientific community seems not to be aware of Keys' long series of erroneous conclusions. Perhaps researchers were too busy worshipping him to even conceive the possibility that he could be responsible for so many incorrect conclusions.

We cannot help but call upon a recent statement by Keys to end this discussion. After more than 50 years of inciting the medical community and public to the purported dangers of blood cholesterol, he told the New York Times in 1987, "I've come to think that cholesterol is not as important as we used to think it was. Let's reduce cholesterol by reasonable means, but let's not get too excited about it."[1192]

It is now appropriate to recall Bonanome and Grundy's boast of having created a "new fat" high in stearic acid and low in trans isomers. This fat was produced by completely hydrogenating soybean oil and then combining it with high-oleic safflower oil, yielding a fat having 43% stearic acid, slightly more than 8% palmitic/myristic acids, 39% monounsaturated acid and 9% polyunsaturated acid. The procedure was similar to that used by industry before partial hydrogenation. The only differences were the amount of oil fully hydrogenated and the substitution of high-oleic for high linoleic oils. While trans isomers are essentially nonexistent, the P/S ratio is close to 1.0 (excluding stearic acid), similar to that associated with margarines and shortenings produced before partial hydrogenation. Thus, the premature recommendations of Keys and the AHA encouraged industry to move in the wrong direction for decades.

The next section discusses another highly influential and pivotal alliance member, Irvine Page, and reveals how he vacillated with respect to the importance of diet to CHD. Subsequently, a profile is presented of medical journal editor, Glen Griffin, illustrating how blind faith in the lipid hypothesis caused him to almost completely separate himself from his common sense. Finally, the views of 1980 AHA president Thomas James are presented, showing that at least one alliance member was unwilling to set aside reality for the alliance's dogma. Chapter 10 offers additional profiles of other alliance members who contributed substantially to the dogma.

IRVINE PAGE: RIDING A PENDULUM

Many staunch supporters of the AHA's dogma eventually lost their faith. For example, Chapter 9 chronicles the evolution of Frederick Stare who promoted the dogma for many years and then criticized it for many more years. In this section we wish to chronicle the opinions of one of the most prominent CHD researchers during the AHA's national emergence, former AHA president Irvine Page.

1945

In 1945 Page[3329] acknowledged three important facts. First, he noted that atherosclerosis can develop in animals without hypercholesterolemia. Second, he observed that the lipidosis profile found in animals that metabolize cholesterol like humans is quite different from that found in animals that have great difficulty in metabolizing the substance, e.g., the rabbit. In the latter case, he indicated that the dietary cholesterol "overloading" resulted in heavy deposits in many internal organs, whereas deposits were minimal in the former animals. although Page did not suggest that the cholesterol overloading in rabbits produced a nonatherosclerotic disease as expressed earlier by Duff and later by Watanabe and Stehbens (Chapter 2), he nevertheless acknowledged the nonatherosclerotic features of experimentally induced "atherosclerosis."

The third important fact reported by Page comprised the experimental findings indicating that dietary cholesterol had little or no effects on blood cholesterol levels in humans and some animals.

1954

Page's[3289] remarks in 1954 were, in part, somewhat curious. On the one hand, he indicated dissatisfaction with the current research path, i.e., "The time seems right for a change in the tactics of research to include mechanisms other than those directly concerned with lipids." But then he seemed to accept current thinking as the explanation for the cause of atherosclerosis. Although he recognized in 1945 that atherosclerosis can develop in the absence of hypercholesterolemia, he indicated that "Most investigators now agree that it is the amount of fat rather than the cholesterol consumed which is crucial in the effect of diet on blood cholesterol; this is in marked contrast to the results of fat and cholesterol feeding in animals. Since the evidence points strongly to an association between high fat intake and increased serum lipid, the question must be answered: what sort of diet could be substituted? It is pretty well agreed that in animals the drastic reduction of fat with substitution of carbohydrate for calories ultimately leads to fatty degeneration of livers and kidneys.

It is noteworthy that most alliance members accepted animal studies as legitimate models for atherosclerosis but they rarely, if ever, cautioned against the consumption of high carbohydrate diets, as did Page, over the next 37 years.

1957

In 1957 Page headed an AHA team that reviewed the evidence associating fat with CHD.[512] In examining the food consumption and CHD mortality trends in the U.S. he concluded that "...the proposition that the character of the American diet has so changed during the past 50 years as to increase the incidence of coronary vascular disease cannot be supported." He asked, "Is there compelling evidence that, if we treat the hypercholesterolemic by dietary means, we are doing anything to lessen the chances of myocardial infarction? Perhaps the best that can be said is that there is an association that has statistical value, but that is not an obligatory association either in small groups or, and much less so, in an individual." With regard to dietary recommendations, "...the evidence at present does not convey any specific implications for drastic dietary changes, specifically in the quantity or type of fat in the diet of the general population, on the premise that such changes will definitely lessen the incidence of coronary or cerebral artery disease." Thus, despite his leaning toward dietary changes in 1954, he definitely exhibited strong resistance to such changes in 1957.

1958

By 1958 researchers were well aware of the fact that most animal fats elevated blood cholesterol levels, while most vegetable fats had the opposite effects. Page reversed his stance taken in 1954. Instead of reducing total fat in the diet he now suggested that the optimum diet could have a high fat content but with a ratio strongly favoring vegetable fats. He reasoned that "The addition of a few tablespoons of oil to a basically normal food pattern in which 42% of the calories is animal fat...will not lower the serum cholesterol level." (The total fat, let alone animal fat, did not represent 42% of total calories at that time.) Although Page indicated that it was too early to advocate nationwide, he suggested that an anti-atherogenic diet might be the reverse of the current diet, i.e., the fat being 83% vegetable, instead of 85% animal.

1959

One year after suggesting that a high fat diet predominantly composed of vegetable fat might be optimal for Americans, Page[3292] again stressed caution about dietary changes and, in fact, indicated that he personally could not tolerate a high

polyunsaturated fat diet. He said that his family had been eating such a diet for 1 1/2 years. "On a low-cholesterol, low-fat diet, I went from a hypercholesterolemic coronary type to a really very low cholesterol level for me, and then my lipids came back up after my wife and I got sick of the whole business."

Page noted that "The first dietary suggestion was the low cholesterol diet. Of all the stupid things anybody could do," he said, "this was it, because everyone knew that cholesterol is synthesized in the body." Of course, this comment was not consistent with his earlier admission that he had undertaken a low-cholesterol diet for 1 1/2 years. Also, this "stupid suggestion" will ultimately be highly promoted by his colleagues such as Stamler, as well as the AHA and NHLBI.

Page observed that "In the last few years we have told them [the public] they shouldn't eat fat, they must avoid stress, they should not lead sedentary lives and they should not smoke, drink so much alcohol or eat so much food. Let's keep our notions to ourselves for awhile until we know whether they are going to prevent atherosclerosis, or at least do good in one way or another. It is all good clean fun among us but when we begin to peddle some of our ideas to the public, the trouble begins."

1961

Two years later Page was senior author of the AHA's first official dietary recommendations.[517] In effect, he practiced not what he preached and became "chief peddler" in 1961. Although these recommendations were presumably directed toward those "at risk for CHD," they were, of course, picked up by the press and public. Obviously, if the recommendations were good for those "at risk," they certainly would be good for those not at risk as well, the press and public reasoned.

Although there was some suggestion that dietary cholesterol should be reduced, the overwhelming emphasis was on reducing total fat intake and "substituting polyunsaturated fat for a substantial part of the saturated fat in the diet." While exact amounts of total and types of fat were not indicated, there was little doubt that relatively high fat diets (35% to 40%) with high proportions of polyunsaturates were approved. Certainly, the public viewed it as such because polyunsaturated fats became a household term thereafter.

Wall Street Journal reporter Bishop asked whether such drastic dietary changes would be accepted by Americans.[1998] Page replied that such changes would indeed be accepted by Americans. Such a reply was in stark contrast with his 1959 statement which admitted his complete intolerance for the recommended diet.

Thereafter, manufacturers of vegetable oils increased their advertising indicating that their products would protect against heart disease.[3352]

1967

In 1967 Page[3351] suffered a heart attack and discussed his state-of-affairs at the AHA annual meeting. Although he had earlier indicated that he had abandoned the low-fat, low-cholesterol diet, he told the press in 1967 that he had "closely controlled his diet." Thus, it is difficult to know from his writings just what kind of diet he had actually be consuming. It is noteworthy, however, that he admitted not living up to the advice he had been giving others. He smoked cigarettes and drank alcohol. Clearly, Page was a man who did not practice what he (sometimes) preached, suggesting that he did not believe strongly in what he preached.

1968

1968 marked a year in which Page exhibited profound inconsistencies from article to article. Such inconsistencies, moreover, appeared to be highly correlated with his co-authors. For example, in two articles with Stamler, Page left no doubt that he considered diet the key to controlling atherosclerosis. He said, "Diet is a key factor in the causation of hypercholesterolemia and atherosclerosis."[3075] "Foods high in saturated fats and cholesterol must be reduced, and the intake of polyunsaturated fats should be increased."[3076] In addition to accepting this dogmatic position in general, Page also recommended the reduction in dietary cholesterol, a recommendation he once called "stupid."[a]

In a third article with co-author Brown, Page was far less dogmatic.[3079] He said, "no one thinks diet alone is the keystone to the control of coronary disease" (didn't he read his own articles with co-author Stamler?). Page, who successfully completed the National Diet-Heart Feasibility study, also beseeched the National Heart Institute to conduct a full-scale diet-heart trial as previously planned. Such a position also was suggestive of a lack of confidence in the validity of the diet-CHD relationship.

As sole author, Page[3080] published a fourth article in which he appeared quite dissatisfied with the state-of-the-art. He asserted, "I am not happy about the effectiveness of our research endeavor in atherogenesis. Surely the time has come when we who study atherogenesis, myocardial infarction, and stroke should rethink our approach. ...continued study of diet in animals would appear to have limited interest... The urgent need is for those wholly occupied with research on atherosclerosis to reduce the amount of almost trivial, repetitive investigation and increase the number of fresh, creative starts. Some believe that...[atherosclerosis]...is the invariable substitute of...[myocardial infarction]...but good evidence suggests that perhaps as many as 20% of the patients do not exhibit enough atherosclerosis to justify a cause and effect relationship."

Speaking at the 1968 AHA meeting in December, Page[2102] even more aggressively attacked the current research program. He accused the AHA of "bumbling" in its investigation of the causes of CHD and emphasized that "far too little is known about the relationship between heart disease and diet, exercise and other factors." Moreover, he indicated that researchers were engaging in "scientific gamemanship that concentrates on status seeking and the hunt for more money more than productive results."

1970

In 1970 Page appeared to have reverted back to the AHA's position that CHD is caused by high blood cholesterol which, in turn, is caused by diet. He and his colleagues said that "definite relationships exist among incidence of CHD, age, total cholesterol and total triglycerides. The relationships were strong enough to aid in discriminating CHD from normal; the most useful being age, total cholesterol and total triglycerides." Such a statement was remarkable in view of the fact that total cholesterol and total triglycerides have almost no predictive value today at the individual level and since age is nonmanipulable, what utility does it serve as a predictor?

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[a] Although the contents of the two Page and Stamler articles were highly similar to those in other articles by Stamler, suggesting that they were, in fact, written by Stamler, they must nevertheless be attributed to Page as well since he was the senior author.

1980

By 1980 Page[3387] appeared to be disgusted with the alliance's entire research program. He indicated that "the planned clinical experiments [the MRFIT and LRC] aimed at testing the hypothesis that lowering plasma cholesterol slows atherogenesis have for the most part been ill planned and financed. The great opportunity to do it properly, once offered to the U.S. Public Health Service [the proposed diet-heart clinical trial], was rejected by an 'expert' committee, whose judgment in retrospect does not appear to have been very expert." This statement was an unmitigated criticism of former NHLBI director Theodore Cooper and Cooper's 1971 Task Force, who replaced the proposed diet-heart trial with the MRFIT and LRC trials (see Chapter 7 for a detailed discussion of this topic). Page pulled no punches in referring to these individuals as something less than experts.

1984

After the results of the LRC trial were announced Page[509] continued his criticism of the alliance's programs. He said, "Despite a determined effort on the part of the LRC-CPPT to convince the public that at long last we now had the answer for the cholesterol problem, the results were disappointingly unconvincing. What we need is to abolish most committees, drown the 'decision makers,' stop the noise made by the news media, and allow the free play of the young creative research workers, who need the support of those who really want to get on with the problem. The vast diarrhea of words that already smothers the mind, can only direct the young into thought channels now turned largely arid. We are not ready to advise the public how they should live, except to insist that they not get fat or smoke, and that they include physical exercise in their regimen and do most everything else in moderation." He said that "experts" were now appearing everywhere as though they were growing "like mushrooms in a damp cellar."

One month after Page's remarks the cholesterol Consensus Conference was held, yielding more "experts" and the formal decision to "advise the public how they should live." The "vast diarrhea of words" described by Page was nothing compared to the onslaught that was initiated in 1985 under the guise of the National Cholesterol Education Program.

The Conclusion

It is clear from Page's early writings that he was struggling with the inconsistencies inherent in the research findings. His opinion regarding the diet-heart issue seemed to vary as though he were riding a pendulum. But in the end it would appear, he found the evidence disconcerting and dissatisfying and he did not hesitate to severely criticize the alliance's competence and expertise. Nevertheless, like Stare and others, it must be recognized that Page played a major role in the development and promotion of the diet-heart relationship which is today accepted by most Americans, despite the fact that the evidence against it is mountainous.

THE WEISFELDT CAPER

The arrogance of the alliance is perhaps no better illustrated than in a letter submitted to Michael DeBakey on October 4, 1989 from the then president of the AHA, Myron Weisfeldt.[3091] The letter was prompted by DeBakey's presence at the ACSH panel discussion and press conference.

October 4, 1989

Dear Dr. DeBakey:

This letter is just to express to you my personal surprise to see you associated with a group called "American Council on Science and Health, Inc." I am enclosing with this letter, hopefully for your personal review, significant portions of a recent publication by the senior people in nutrition and the president of this organization under the title of "Balanced Nutrition: Beyond the Cholesterol Scare." I hope you will have a chance to glance through this material; those areas that I and some of my colleagues at the American Heart Association have indicated are of particular note. I think at best the document and position are in many respects directly erroneous, and in others misleading or misguided.

Certainly I am sure you remember that shortly after the Surgeon General's report on smoking there were many people with scientific credentials speaking for the fact that cigarettes were not really a major health-related problem. After all there are certainly millions of people in their 30s and 40s smoking a lot of cigarettes who didn't have lung cancer at that time and didn't have atherosclerosis. There were all kinds of statements about the statistical association between cigarette-smoking and terrible disease being due to other lifestyle variables in smokers such as stress and response and exposure to other toxins and so forth. Today certainly none of us would accept those statements as being reasonable. Likewise this organization with whom you are associated places great emphasis on the cigarette-associated risk as well as the high blood pressure-associated risk. With regard to high blood pressure I would point out that in truth we still know relatively little about the importance of high blood pressure in the elderly and its treatment. I am sure you again will recall that when we adopted a blood pressure of 140/90 as a guideline for normalcy and abnormalcy, and in a sense for drug treatment, we had little or no evidence about the appropriateness of these guidelines or the appropriateness of treatment of high blood pressure in the elderly. This is a situation exactly analogous to that of cholesterol. Tom Moore's pointing out that the available studies do not consistently show a reduction in mortality but only nonfatal myocardial infarction is a poor argument. The fact that, again and again, studies show a reduction in nonfatal myocardial infarction within seven to ten years after the lowering of blood cholesterol is a very impressive result. Since most of the people who are entered in these studies were in their 40s and 50s it is not surprising that within seven to ten years (with current medical and surgical treatment) cardiovascular mortality is not very high in patients even though they develop coronary artery disease, perhaps as a consequence at least in part of high blood cholesterol. One would expect to see that an effective measure to reduce heart attacks and other manifestations of atherosclerosis would have an effect on mortality only many, many years after an effect was seen on manifestations of atherosclerosis, such as acute myocardial infarction. Beyond all this, how can one deny the clear-cut genetic links in segments of our American population between genetic abnormalities in lipoproteins and their receptors and premature ischemic heart disease? Without a broad national program, how are we going to find and appropriately manage the 40-year-old man whose father died at age 48 with ischemic heart disease, and whose brothers both have had bypass surgery, and who has a cholesterol level of 270, and is overweight and so forth, unless we go at this in a broad national consensus manner?

I wish you would personally consider my comments as well as the material that I am sending to you. I can assure you that this letter was not composed by any staff person of the American Heart Association, nor does it relate to any particular expertise that I have in lipids, risk factors or cholesterol. I have taken my responsibilities as President of the American Heart Association in a serious fashion, and in that capacity I have great concern when people of your stature in our field who (like me) have expertise tangential to the issue at hand become pawns in someone else's hands.

Most sincerely,

Myron L. Weisfeldt, M.D.
President
American Heart Association

DeBakey's[3092] reply to Weisfeldt's letter was dated October 16, 1989.

October 16, 1989

Dear Dr. Weisfeldt:

Your letter of October 4, 1989, arrived during by absence from the city; hence the delay in my response.

I was indeed astonished, and offended, by your letter, which reflected a presumptuous, supercilious, and even hubristic attitude. You state that you were "surprised to see" me "associated with a group called 'American Council on Science and Health, Inc.'" This is a presumptive, and completely erroneous, statement. I am not now, and never have been, "associated" with that organization. I was invited by that organization to participate in a panel discussion and press conference to present some of my data derived from analysis of patients who had had coronary bypass surgery. I have known Drs. Fred Stare and Robert Olson, members of the Board of Directors of that organization, for many years and have great respect for their integrity and scientific work, as I do for Dr. Whelan's. It would appear that you consider any deviation from your own views to be erroneous, and so anathema.

I found your reference to smoking and lung cancer gratuitous. You apparently do not recall, or perhaps did not even know, that, in the 1930s, with Dr. Alton Ochsner, I published a number of reports calling attention to the relationship between smoking and cancer of the lung. (Ochsner A and DeBakey ME: Primary pulmonary malignancy: Treatment by total pneumonectomy; Analysis of 79 collected cases and presentation of 7 personal cases. Surg, Gynecol & Obstet 1939;68:435-451. Ochsner A and DeBakey M: Carcinoma of the lung. Arch Surg Feb, 1941;42:209-258.) This was long before the first Surgeon General's report on smoking, at a time when we were attacked and even derided.

I found your last statement expressing "great concern when people of your stature in our field who (like me) have expertise tangential to the issue at hand become pawns in someone else's hand" to be arrogant and reflective of your own ignorance of my experience in this field of endeavor, as indicated by my publications on atherosclerosis (two among which are DeBakey ME: Patterns of atherosclerosis and rates of progression. In: Paoletti R and Gotto AM Jr (eds), Atherosclerosis Reviews, Vol 3, New York, Raven Press, 1978, pp.1-56; DeBakey ME, Lawrie GM, Glaeser DH: Patterns of atherosclerosis and their surgical significance. Ann Surg Feb 1985;201(2):115-131). I am in no position to know whether your expertise is, in your word "tangential," but my own experience in the study of atherosclerosis is direct, covering almost four decades and tens of thousands of patients. It also includes experimental studies in animals. My investigations on the clinical, anatomic, and pathologic patterns of atherosclerosis are based upon personal observations on patients with the disease. This includes actual visualization of the lesions and arteriographic studies, which in many patients involve serial observations over extended periods up to more than 30 years. My experience is thus not based solely on laboratory reports concerned with cholesterol or second- and third-hand reports comprising computerized epidemiologic studies.

I have repeatedly stated in many publications that I consider hypertension, hypercholesterolemia, cigarette smoking, and diabetes important risk factors. (I also

emphasized this position at the panel discussion of the American Council on Science and Health.) Along with Mary Lasker, I helped found, and served as Chairman of, Citizens for the Treatment of High Blood Pressure, Inc., and, as Co-chairman of that group, stimulated both the then National Heart Institute and the American Heart Association to take a more active and aggressive role in the control of hypertension. Later, this group added cholesterol education to its charge. Two books written for laymen by Dr. Goto and me emphasize control of the risk factors in heart disease.

I have never been a pawn in anyone's hands, and your accusation in this regard is not only totally unfounded and unsupportable, but disparaging, highly offensive, and contumelious.

I do not question the significance of hypercholesterolemia as a risk factor, but I do make a distinction between a risk factor and the specific cause of a disease. I consider hypercholesterolemia an important contributing factor in the development of atherosclerosis in some patients, but not the cause of the disease. In some analyses we have just completed (and have not therefore yet published) on more than 3,500 patients with severe atherosclerotic occlusive coronary artery disease requiring coronary bypass and followed up to 20 years, 27 per cent had cholesterol levels (tests performed in Dr. Gotto's laboratory) below 200 mg per dl, and another 22 per cent had levels between 200 mg per dl and 220 mg per dl. Moreover, when the patients were divided into 4 cohorts characterized by levels below 200 mg per dl and above 280 mg per dl, with the other two between these levels, Kaplan Meier survival curves over period of 20 years (with a 95% follow-up rate) showed no significant differences. Indeed, the most significant factors influencing survival over this period following operation were hypertension, diabetes, and left ventricular function.

I realize that all these patients had severe atherosclerosis at the time of operation and therefore are not comparable with those who have yet to develop the disease. The fact remains, however, that more than a fourth of the patients had perfectly normal cholesterol levels, and another fourth had levels that were considered normal prior to the decision to lower the figure to 200 mg per dl.

Although we have not yet completed the studies on the rate of progression of the disease (as you may observe from one of the enclosed reprints, we classify these rates into rapid, moderate, and slow), preliminary results show no correlation with the level of cholesterol.

Scientific integrity demands a willingness, indeed an obligation, to scrutinize, question, and assess objectively all the evidence in the search for the truth. Any scientific position that cannot withstand rigorous scrutiny and skepticism is suspect. A true scientist (or a genuine scholar) never shrinks from, or obstructs, free and full discussion of an issue, with an airing of all the available evidence, no matter how inconsistent, contradictory, or contrary to his own opinions. This includes a readiness to consider opinions and interpretations of others with whom you may disagree. In this regard, humility is essential, even for a President of the American Heart Association.

Yours sincerely,

Michael E. DeBakey, M.D.
l-ps

Apparently recognizing that he had met more than his match, and perhaps happy that DeBakey was not "associated" with ACSH, Weisfeldt[3093] apologized to DeBakey in a subsequent letter.

November 1, 1989

Dear Dr. DeBakey,

I very much regret having sent you a letter that I should have thrown in the waste basket. It was written at a moment of personal as well as professional stress that hopefully I will in the future recognize. I can make a number of excuses in this area but I don't think it is worthwhile doing that. I regret communicating to you in the fashion that I did and I apologize deeply for it. You are a magnificent leader of our field and I have, in truth, the greatest respect for you and your tremendous contributions to our field.

Sincerely,

Myron L. Weisfeldt, M.D.
Robert L.Levy Professor of Cardiology
Professor of Medicine
Director, Cardiology Division

There are many fascinating points to the above brief exchange of letters. Let us address four. First, Weisfeldt's letter reflects the evangelistic faith that AHA members have in the cholesterol-CHD relationship. Even though Weisfeldt admitted that he, the AHA president, has "expertise tangential to the issue at hand," he accepts the relationship without question and cannot tolerate another organization's point of view or a prominent medical clinical researcher's participation in a conference sponsored by such an organization. That has been the AHA's inflexible position since it published its first dietary recommendations in 1961.[517]

Second, Weisfeldt indicated that "again and again, studies show a reduction in nonfatal myocardial infarction within seven to ten years after the lowering of blood cholesterol" and that that "is a very impressive result." If Weisfeldt had more central knowledge and less tangential expertise, he would know that the studies of cholesterol-lowering which have failed to reduce fatal and nonfatal infarctions, or total mortality, far outnumber those which have shown positive results. Moreover, the two key studies showing positive results, i.e, the LRC and Helsinki trials, revealed such low reduction in MI rates that the process is simply not cost-effective.

Third, consider Weisfeldt's statement that "when we adopted a blood pressure of 140/90 as a guideline for normalcy and abnormalcy, and in sense for drug treatment, we had little or no evidence about the appropriateness of these guidelines or the appropriateness of treatment of high blood pressure in the elderly. This is a situation exactly analogous to that of cholesterol." This is a clear admission that the AHA generates and vigorously promotes guidelines that are supported by "little or no evidence," despite continuous public claims to the contrary.

And fourth, it is noteworthy to emphasize the first two sentences of DeBakey's last paragraph, i.e., "Scientific integrity demands a willingness, indeed an obligation, to scrutinize, question, and assess objectively all the evidence in the search for the truth. Any scientific position that cannot withstand rigorous scrutiny and skepticism is suspect." While DeBakey was unquestionably correct, it was seen earlier ("HALF TRUTHS PERPETUATED") that a 1981 NHLBI report cautioned that skepticism has scientific "shortcomings."

In effect, the alliance wants all researchers to support the diet-cholesterol-CHD relationship, whether or not the evidence supports it. In the same year as the above letter Weisfeldt[3127] elsewhere said, "the challenge for this association and for me in this year is to encourage new strategies in the job of forging consensus." He indicated that the AHA could be weakened without consensus and went on to say that

"I believe that forging consensus requires two things: agreeing on redefined goals and agreeing on the means to achieve them, goals and means always consistent with the best knowledge and exquisite sensitivity to our public reputation and responsibilities." It is clear that Weisfeldt was far more concerned with consensus and the AHA's reputation than with pursuing the "best knowledge" because, after all, forging a consensus is completely inconsistent with the free pursuit of knowledge.

THE GLEN GRIFFIN STORY: IGNORANCE IS BLISS

Glen Griffin is editor of Postgraduate Medicine and a co-author with William Castelli of the book, "Good fat, bad fat." He published an editorial in his own journal in 1988 which clearly demonstrated that reasoning based on knowledge and logic was not a qualification for being a journal editor.

Griffin told a story of witnessing both of his parents having bypass surgery and of then deciding to change his diet. He had not eaten liver since medical school and he "immediately began eating more fish and less meat" [less saturated fat]. He reduced his intake of eggs to two per week [less cholesterol]. He switched from butter to margarine [less saturated fat and cholesterol]. Griffin said, "I thought I was on a good preventive program to keep my coronary arteries from getting plugged... I wasn't. I thought cutting down on cholesterol was enough [note that he ignored the massive amount of saturated fat in butter and the saturated fat in meat that he had also presumably eliminated from his diet]. I was absolutely wrong."

Griffin continued, "Most people didn't think I needed to do much, since my cholesterol level always seemed okay. Later I became convinced of Bill Castelli's warning when one's total cholesterol/HDL cholesterol ratio is above 4.5. With a very low HDL, I had a ratio of about 6, even though my total cholesterol was under 150. When I became convinced that it was essential for me to cut down on saturated fat intake...Bill Castelli and I got our heads together and came up with our simplified plan of setting a simple daily limit of saturated fat..."

Then, in 1988 Griffin underwent a bypass operation. Afterwards, he said, "You can be sure I'm going to be eating very little saturated fat. I don't want to go back for a re-run of this surgery, as was necessary for both of my parents."

Question: What's wrong with this story?
Answer: Almost everything.

First, two bypass operations for <u>each</u> of his parents and one for himself should have been a clue as to the importance of heredity on coronary disease. He did not even mention the word "heredity" in his article.

Second, Griffin apparently had substantially reduced his intake of cholesterol <u>and</u> saturated fat for many years before he underwent bypass surgery but it obviously presented no benefits.

Third, his cholesterol level was "under 150 mg" which means that he had been consuming very little saturated fat or that such fat had essentially no effect on his cholesterol level.

Fourth, it is well known that the reduction of dietary saturated fat decreases HDL as well as LDL. Thus, either Griffin's total/HDL ratio remained constant with further reductions in saturated fat or it got worse (became higher) by depressing HDL still further, while apparently having no affect on LDL. In either case, he had accomplished nothing.

Fifth, Griffin's apparent "hero," William Castelli, publicly stated that "We want the ratio of total cholesterol/HDL cholesterol to be under 4.5 unless the person's total cholesterol is 150 or lower, in which case we don't care what his HDL cholesterol is."[1302] Griffin co-authored a book with Castelli without knowing this fundamental Castelli "principle."

Ignorance may be bliss to some people. However, this writer believes that medical journals would serve a far more useful purpose to the medical community if their editors exercised greater knowledge and reasoning skill. In his concluding remarks he said, "Can you imagine that in 1983 only 28% of surveyed physicians thought a high-fat diet had much to do with coronary artery disease, and that in 1986 only 40% of physicians know this important basic fact? But lots of people who should know still do not have the word." A high-fat diet has never been proven to cause coronary artery disease and it is not, therefore, a "basic fact." However, the continuous propaganda emerging from the National Cholesterol Education Program, centered initially at physicians via mailers from NHLBI and AHA, gradually increased the number of physicians accepting the alliance's dogma. Griffin appropriately put it in the religious context for which dogma is considered acceptable, i.e., lots of people "still do not have the word."

THOMAS JAMES: A GEM AMONG ROCKS

As amply shown in Volume 1 and the present volume, the long-time promotion of the diet-blood cholesterol-CHD relationship by the AHA has been based on extremely weak and indirect evidence. Almost without exception, however, the AHA has characterized that evidence as "convincing" or "persuasive." One exception was the presidential address of Thomas James[3391] in late 1980, president of the AHA in the 1979-1980 period. This address was unquestionably the most objective analysis of the diet-blood cholesterol-CHD relationship by an AHA member since the AHA made its first dietary recommendations in 1961, and that is undoubtedly the reason why it has rarely, if ever, been cited by other authors who promote the relationship. The following is a review of that address with excerpts.

"Today I want to share with you my growing concern about overpromise in coronary disease. My remarks will focus upon the matter of credibility, both of the American Heart Association and of medical science in general." James noted that intensive research had been concentrated on the diet-blood cholesterol-CHD relationship for over three decades. "Despite this remarkable concentration of scientific talent and fiscal resources, the terms 'diet-lipid hypothesis' and 'the cholesterol controversy' have become commonplace even in nonmedical publications. If something remains hypothetical and controversial over so long a time and despite intensive research, surely it is time that we take a different look at the subject.

"Those with low cholesterols as a group seem to have less coronary disease than those with high cholesterols, but this is too often extrapolated to apply directly to one individual. Epidemiologists have long recognized and publicly deplored the soft nature of the clinical data obtained from masses of people, data which they then subject to increasingly complex and sophisticated mathematical analysis [see Chapter 4 for a discussion of this topic as it relates to the Framingham study]. But no matter how marvelous such an analysis may be, there is no escaping the fact that the entire initial basis so often is less exact, less reproducible and less reliable than any of us would wish. This flaw is sometimes addressed by demands for an increase in the sample size, extensive lengthening of observation time, or the utilization of mathematical smoothing maneuvers and creation of comparable indices, as if any of these could somehow strengthen the original weakness."

"In considering our diet advice for entire populations four things merit particular attention." Thomas indicated that (1) the public should be informed regarding the

conjectural nature of the advice, (2) the medical community should describe the effects of treatment in terms of absolute reduction in CHD events rather than in the inherently misleading concept of "risk reduction," (3) the medical community should be concerned about its advice eventually becoming legislated into law without scientific proof of efficacy, and (4) the medical community should be concerned about the potential dangers of long-term changes in the diets of children. Of course, Thomas' worst fears have been realized. The NHLBI/AHA alliance now tells the public that diet is a proven cause of atherosclerosis, focuses exclusively on the fraudulent "risk" concept, tells industry to change the compositions of foods, instructs the FDA to develop labels that will effectively tell consumers what to eat, and is attempting to change the diets of all children above the age of two.

Thomas emphasized that as much as we would like to believe otherwise, "we do not yet have the means for preventing coronary disease." He also warned against the use of food substitutes without fully knowing the potential harm associated with such synthetics. The AHA already embarrassed itself with respect to recommending high intakes of polyunsaturated fatty acids (see Chapters 2 and 10) and it may one day regret its current recommendation to consume high carbohydrate diets.

Although cause of death statistics are known to be highly inaccurate, Thomas was one of a very few who questioned the validity of the declining CHD mortality. Equally important, he pointed out that the incidence of coronary disease may not be decreasing, opposite to that suggested by the mortality statistics and transmitted to the public by the alliance. Indeed, as shown elsewhere in this volume, the evidence indicates that morbidity is increasing, not decreasing. Thomas also made the important distinction between heart attacks and coronary disease, noting that they are not one and the same thing, although the public is told otherwise. While the evidence continues to mount that heart attacks are due primarily to electrical disturbances and spasms, the alliance gives the public the impression that they are exclusively due to arterial occlusion from atherosclerotic plaques or thrombi derived from the plaques.

In his concluding remarks, Thomas maintained that it was not necessary to promise Americans more than can be delivered in order to maintain their continued support. "I firmly believe that the American people can and will continue to support medical research for the conquest of coronary disease, but they will do this best and most enthusiastically when we are forthrightly honest with them, do not dissemble, do not overpromise, and restrain ourselves from shrill postures and polemic diatribes. The truth is exciting enough."

The Thomas address was astonishing in that it described rather concisely in the space of a mere 2 1/2 pages the true state-of-the-art and the pitfalls to be avoided. Unfortunately, the AHA (and NHLBI) chose not to accept reality and follow his advice. In fact, as discussed elsewhere in this volume, the alliance transformed itself from information gathering scientists to dogma disseminating evangelists. Had the advice of Thomas prevailed, medical research might well have discovered the real cause of atherosclerosis by now. At minimum, much progress toward that discovery most certainly would have been made.

The reader would do well to obtain a copy of Thomas' address and read it carefully. It is a gem among rocks.

To illustrate the impact of James' address, the AHA published a "statement for physicians" in Circulation two months earlier, authored by Kannel et al.,[3404] that maintained that the available evidence "forcefully confirm a basic concept put forward by AHA during the last 20 years: it is possible to prevent and control CHD." They went on to say, "Risk factors can be identified and modified. The rationale of intervention is based on sound logic and extensive research evidence." One month following James' address the AHA[3405] published a "Task Force" report in Circulation

in which the 1980 statement to physicians was cited as showing that CHD can e prevented by modifying risk factors. When James' address was finally published in Circulation a few months later, the AHA placed the following disclaimer at the bottom of the first page--"The contents reflect the opinions of the President and are not necessarily the position of the American Heart Association." Thus, the AHA absolved itself of any association with its own president, or intellectual reasoning in general.

A FINAL INTRODUCTORY REMARK

In 1969 this writer co-authored a critical review article with Luigi Lucaccini appearing in the Human Factors Journal.[3253] That article concluded that the common and most important finding observed by researchers of virtually hundreds of experiments investigating prolonged human attention (e.g., radar or sonar monitoring) was, in reality, an artifact of the laboratory situation and not a real-world phenomenon. Being totally opposite to conventional "wisdom," that article was ignored and never cited by the human factors community for 18 years. Then, in a special issue of the Human Factors Journal in 1987 two separate articles authored by two of the most prominent researchers on prolonged attention finally acknowledged the 1969 article and admitted its validity.[3254,3255] One author stated that "It took critics such as Smith and Lucaccini (1969) to force us to confront this issue."[3254]

Perhaps it will take another 18 years before the medical community recognizes that diet and blood cholesterol levels are not causes of CHD. That seems doubtful because there are obvious trends underway today that prove the alliance wrong and cannot be ignored or suppressed for that many years. As eloquently put by Sullivan,[2606] "If the goal is to prevent coronary heart disease, we must take off our cholesterol blinders and aggressively pursue other leads." This writer believes that the majority of researchers would agree with Sullivan but are afraid to make that attitude publicly known. The alliance is firmly committed to the diet-blood cholesterol-CHD hypothesis and dissenters risk loss of research grants. There is the possibility, however, that if a serious counter attack on the alliance's dogma is launched, the dissenters may be more willing to overtly express their opinions. This writer has spent some 17,000 hours researching and preparing this two-volume review and the lay book, "The Cholesterol Conspiracy." It is believed that these documents comprise more than sufficient ammunition for such a counter-attack. It is now up to the scientific and clinical communities to use this ammunition.

Finally, it should be more than evident that this writer has given full credit to each and every author who contributed to his documents, directly or indirectly. Unfortunately, this writer has already found evidence that material from Volume 1 and The Cholesterol Conspiracy has been used by others without due credit. A detailed discussion of one such suspected individual is presented in Chapter 9. These documents were designed to be used by others who believe that the public has the right to know the truth about the diet-cholesterol-CHD relationship. Professionalism and common courtesy would demand that credit be given in the course of that use.

2. BACKGROUND

"The Framingham study has identified several risk factors for cardiovascular disease including advancing age, hypertension, obesity, cigarette smoking, electrocardiographic left ventricular hypertrophy, elevated total and low levels of high-density lipoprotein cholesterol."

(William Kannel, William Castelli et al., Framingham, 1989[2549])

"The Framingham study has pinpointed as many as 200 factors associated with increased risk of the [CHD] disease."

(William Castelli, Framingham director, 1990[2598])

"In my view, there are not 10 atherosclerotic risk factors, there is only 1--and that is an elevated (>150 mg) serum total cholesterol and specifically an elevated serum LDL-cholesterol level."

(William Roberts, NHLBI, and editor, American Journal of Cardiology, 1989[2537])

It's quite clear that high LDL is not the major risk factor."

(Gerald Reaven, Stanford University, 1990[3131])

HISTORICAL OVERVIEW

The Beginnings

Although the main thrust of atherosclerosis research began in the early part of the present century, the disease has apparently been a common human problem for at least a few thousand years. Marc Ruffer of England provided evidence for this assertion in 1911.[2559] He autopsied many mummies dating from 1580 B.C. to 525 A.D. In general, ancient embalmers were supposed to remove all viscera, muscles, brains, etc. However, in some cases, all internal organs were left intact and in many others, parts of aortas or other arteries remained in the mummies. Ruffer concluded that "...the old Egyptians suffered as much as we do now from arterial lesions identical with those found in the present time. Moreover, when we consider that few of the arteries examined were healthy, it would appear that such lesions were as frequent three thousand years ago as they are today."

In comparing the ancient Egyptians with modern societies, Ruffer ruled out as causes of atherosclerosis tobacco, alcohol, meat, exercise and "wear and tear of human life." He said that he "cannot therefore at present give any reason why arterial disease should have been so prevalent in ancient Egypt" but considered it important "to find that it was common, and that three thousand years ago it represented the same anatomical characteristics as it does now."

Since the ancient Egyptians were primarily vegetarians and did not use tobacco, Ruffer's findings comprised exceedingly important evidence in the search for the cause(s) of atherosclerosis. It is undoubtedly for this reason that the alliance has either ignored Ruffer's findings or deflated their importance. For example, Robert Levy[1846] said, "One must suspect that the major reason why CHD was not recognized earlier (though it clearly occurred even 2000 years ago, as verified by autopsies on Egyptian mummies) is that the process of atherogenesis, the major cause of CHD, is itself silent and secret." Not only did Levy omit the information that the ancient

arteriosclerosis consists of local changes in the walls of the arteries themselves, changes which are responsible for the subsequent precipitation of lipids in the affected areas." These facts indicate that "Hypercholesterolemia of itself cannot be regarded as a cause of human atherosclerosis." Duff concluded that the two diseases [experimental and human atherosclerosis] are not identical, and that there are a number of important differences between them. "These differences are of such a nature as to suggest that the role of lipids in the development of arteriosclerosis is greatly exaggerated in experimental cholesterol arteriosclerosis as compared with arteriosclerosis in man."

McMichael[2435] also stressed that "the fat-induced lesion virtually never thromboses." Constant[1938] pointed out that the lipid deposition in induced lesions is mostly "in cells derived from blood monocytes rather than in arterial smooth-muscle cells, which are the cells mainly involved in primate atherosclerosis." Similarly, Mitchell[919] observed that "the vascular lesions produced reflect the erroneous concept of human disease which we have already discarded since such models show the intimal foam-cell/modified smooth muscle cell lesions which resemble clinically irrelevant fatty streaks rather than the multi-layer, multi-process, stenosing human lesions. Thrombosis is not found in such lipid-fed models and where occlusion has been claimed it is invariably due to foam cells blocking the lumen, rather than to the platelet-leuococyte-fibrin masses which characterize human stroke, cardiac infarction and limb gangrene." It should not be surprising that widespread deposition occurs in animals such as rabbits with induced cholesterol levels up to 20 times their normal levels.[1777]

Altschule[3304] concluded that "Most of the animal experiments are worthless. Mitchell[919] paraphrased a Churchill statement in acknowledging the sacrifice of billions of animals, i.e., "Never has so much been done so expensively to so many animals with so little result." Even 1980 AHA president, Thomas James[3392] concluded that experimental atherosclerosis "differed greatly from the usual coronary atheroma and may have little relevance to our understanding of the human lesion." Yet, research continues with every conceivable animal, including the Japanese quail.[2702]

Steinberg ignored all of the above in his lecture and went on to compare the similarities of human familial hypercholesterolemia with Watanabe LDL-receptor-deficient rabbits, tacitly accepting (as we shall see below) the untenable assumption that both produce true atherosclerosis. He repeated his dogma in a 1989 paper, i.e., this strain of rabbits develops "lesions almost indistinguishable from those of cholesterol-fed rabbits and...quite similar to human lesions."[2700] To illustrate the significance or insignificance of such terms as "quite similar," this writer would like to ask the reader a question, i.e., assuming that you have a brain tumor and just had it biopsied, would you prefer the neurosurgeon to say that it is cancerous or "quite similar" to cancer? While "quite similar" and "identical" might seem to denote subtle and insignificant differences, the differences can, in fact, be monumental. This word game has been played frequently by all alliance members. Consider the following examples. McGill[1800] referred to the rabbit disease as "human-like atherosclerotic lesions." Blankenhorn and Kramsch[1717] stated that "subhuman primates are preferred animal models for regression studies because they develop lesions that closely mimic the human disease." Rifkind[2032] noted that "Atherosclerotic lesions similar to those in humans can be induced in many different animals..." And elsewhere Steinberg[3037] himself said that "arterial lesions resembling those of human atherosclerosis can be produced in a variety of animals."

Levy and Feinleib[1401] went a little further, i.e., "the human atherosclerotic lesion develops differently from the experimentally induced atherosclerosis in animals." But perhaps most important of all, the AHA itself, via its 1957 report authored by Page

et al.[512] concluded that "atherosclerosis is similar to but not identical with that of the human type."

In Volume 1 of this review it was emphasized that the metabolism of cholesterol in most animals, including some primates,[1786] is far different from that of humans and that the induced atherosclerosis in animals presents an entirely different lipidosis profile than that observed in the human disease. This fact was described by Anitschkow et al. in 1913,[2979] has been well known for more than a half century,[1801,2092,2995,2996] and has recently been reemphasized.[210,1401,1814,1938] It has also been emphasized that "animal studies of regression have not shown regression for the more mature or complicated lesions."[3231]

The questionable relevance or the irrelevance of animal research has been underscored by many prominent researchers. Anitschkow et al.[2979] observed that "The fact that cholesterin has different effects on different animals, even closely related ones, raises the question to what degree the results described above for rabbits are valid for human pathology." Kritchevsky[2188,2924] urged "extreme caution in extrapolation of the data to humans." Connor[2436] indicated (somewhat indirectly) that "results of rabbit experiments could not be extrapolated to man." And Keys[279] said, "The attempt to extrapolate to man the findings from cholesterol experiments with rabbits and chickens can lead to absurdities."

Familial Hypercholesterolemia

Although familial hypercholesterolemia might be considered an improper topic for discussion in this chapter, it is, in fact, quite proper because it is highly related to experimental atherosclerosis. In 1987 Steinberg[1355] maintained that the work of Brown and Goldstein "firmly established the direct cause-and-effect relationship between increased levels of LDL and accelerated atherogenesis in patients with...familial hypercholesterolemia." But, of course, the work of Brown and Goldstein did no such thing. They firmly established the reason why a relatively few people have very high cholesterol levels. Steinberg's statement was again based on the assumption that familial hypercholesterolemia causes the development of true atherosclerosis, an assumption that is not supported by pathologic examinations. Watanabe[2990] himself pointed this out in 1968, i.e., "It must be emphasized that the cardiovascular lipidosis in familial hypercholesterolemic xanthomatosis is not a common atherosclerosis in adult age, but is a separate disease entity... The morphogenesis of the cardiovascular lipidosis in essential familial hypercholesterolemic xanthomatous shares a similarity with that of the aortic lesions in experimental hypercholesterolemia in the rabbit." With regard to plaque, "There were neither calcification nor ulceration."

Pathologist William Stehbens[a] has repeatedly emphasized that the induced disease, whether by familial hypercholesterolemia or by cholesterol feeding is a "lipid storage disease," wherein "the pathogenesis of the lesions differs from that of true atherosclerosis...and...the presence of extravascular lipid storage phenomena and the absence of the complications of atherosclerosis (intimal tears, ulceration, dissection, thrombosis and aneurysms) fail to corroborate the allegation that hypercholesterolemia causes atherosclerosis. The vascular changes in the familial condition are those of a lipid storage disease, the pathology of which, as with the cholesterol-fed animal, has been grossly misrepresented. The lesions and complications differ from the pathology of atherosclerosis with affected subjects succumbing most often to arterial narrowing

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[a] 1814,2069,3124,3261,3262,3263,3306

by xanthomatous infiltration of the intima. Hyperlipoproteinaemia is not a prerequisite for premature severe atherosclerosis in man or lower animals."

In addition to the fact that Steinberg refuses to acknowledge the pathological differences between common atherosclerosis and the "atherosclerosis" observed in familial hypercholesterolemics (or in animals induced by high cholesterol diets), he also demonstrates inconsistencies in reasoning on this matter. Consider, for example, the following statement in a 1990 article:[3066]

"The atherogenicity of LDL requires little discussion. Even if we had no other data, we could conclude that LDL is atherogenic simply on the basis of clinical observations on patients with familial hypercholesterolemia. ...we must conclude that their premature atherosclerosis is, directly or indirectly, related to their elevated plasma LDL levels..."

This statement clearly indicates that atherosclerosis is caused by high LDL levels. On the following page Steinberg declared,

"It is now recognized that LDL must undergo some form of modification in its structure and biological properties before it can be taken up by monocyte/macrophages at a rate sufficient to generate foam cells. A number of chemical modifications have now been shown to have this effect, but the one for which the biological evidence is strongest is oxidative modification. The evidence includes...demonstration that treatment of LDL receptor-deficient rabbits with probucol, shown by Pauthasarathy et al. to be a potent antioxidant, inhibits the progression of atherosclerotic lesions."

This latter statement clearly indicates that high LDL levels per se cannot cause or promote atherosclerosis simply because LDL must be chemically modified (e.g., oxidized). Therefore, the theoretical key process is the chemical modification of LDL. There is nothing in his statement or subsequent discussion that even remotely suggested that high levels of oxidized LDL are necessary for promoting atherosclerosis. Moreover, the notion that high LDL is a necessary condition is defied by virtually all prospective studies which show that atherosclerosis is only slightly more associated with high cholesterol levels than with low to moderate levels.

Finally, an observation by Miettinen and Gylling[3220] is of interest. They stated that "The differences in lipoprotein concentrations or even in composition of the lipoprotein particles alone (as indicated by apo B, cholesterol, and triglyceride contents) do not explain why some FH (familial hypercholesterolemic) patients develop premature arterial atheromatosis and the fatal or nonfatal clinical signs of it, while others, including some homozygotes, reach a relatively old age and may even be quite asymptomatic."

In sum, the atherosclerosis-like disease induced in animals or in human familial hypercholesterolemia is not common human atherosclerosis and it is fallacious for Steinberg and other alliance members to continuously ignore the obvious evidence and maintain that it is. Unfortunately, alliance members have become so hopelessly addicted to the lipid hypothesis that they simply do not accept or even acknowledge the existence of evidence which runs contrary to the hypothesis. Stehbens[3262] put it rather succinctly, i.e., "Upon examination of...[the]...evidence and consideration of the specific criteria for the experimenal production of atherosclerosis, any pathologist of independent mind and free from preconceived ideas would conclude that human atherosclerosis and the lesions induced by the dietary overload of cholesterol and fats are not one and the same disease. Many investigators are seemingly unaware of the extent of these differences, but to overlook them and to accept the experimental lesions as atherosclerotic rather than as a lipid storage phenomenon superimposed on

the preexisting intimal proliferation or the concomitantly developing changes of atherosclerosis is misleading and misrepresenting the facts."

Some Major Recent Events

Perhaps the first significant recent event was the reorganization of the AHA in 1948, transforming it into an organization with broad nationwide ambitions.[2003] These ambitions probably represented the beginnings of the AHA's unwavering attitude of associating diet with CHD. In the same year the National Heart Institute was established.[2700]

In 1949 the Framingham Heart study was initiated and originally funded by the U.S. Public Health Service. Investigators of this prospective survey of some 5,000 men and women in a Boston suburb have periodically examined, studied and monitored these individuals and many of their offspring to the present time. Accumulated findings from the study have been published in hundreds of reports.[1086]

Oliver referred to Ancel Keys as "the principal architect providing the foundations of the relation between dietary fat and CHD" and indicated that a 1949 article by Keys[317] was essentially the origin of the coronary risk factors.[1250] Other 1949 articles by Keys established his position that dietary cholesterol has little or no effects on blood cholesterol levels.[421,523]

In 1950 several investigators reported large reductions in blood cholesterol resulting from diets devoid of fat and cholesterol[a] and Keys re-emphasized that fat, rather than cholesterol, was the basis of controlling blood cholesterol levels.[313] He did not differentiate between saturated and unsaturated fats. Mann also considered Gofman's[404] 1950 proposal to use the various lipoproteins as an index of atherogenesis to be a major contributor to the "lipid hypothesis."[2027] In the same year an editorial in the Journal of the American Medical Association was generally critical of the growing interest in associating diet with blood cholesterol, and blood cholesterol with CHD.[2002] It pointed out that the animal studies produced dubious results, that the correlation between blood cholesterol and CHD was frequently low and that the American diet should not be tampered with without "clear-cut evidence."

Unknown to the medical world and prior to any real knowledge of the causes of cardiovascular diseases, the all cardiovascular disease mortality rate (excluding CHD) initiated a decline in 1950 that persists to the present time. But because of the usual lag in accumulating, analyzing and publishing vital statistics, the medical world would not become aware of this decline for several years.

In 1952 Kinsell et al. published the first of his several studies showing that blood cholesterol could be lowered with unsaturated fats.[363] Mann[2027] cited Groen et al. as observing the same phenomenon in the same year. And Oliver[1250] cited an investigation by Biggs and his co-workers as demonstrating that tritium-labeled dietary cholesterol entered the atherosclerotic plaque.

Apparently the first between-population study was published in 1953 by Keys.[279] He used World Health Organization data and reported a near perfect relationship

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[a] 313,316,876,947

between total fat intake and CHD mortality rate for six countries.[a] Subsequently, a series of similar studies were published over the next 22 years, incriminating total fat, saturated fat, cholesterol and a host of other food nutrients and nonfoods.

In 1953, before any correlational data were obtained from the Framingham Heart study and before "risk factor control" was any more than thoughts in the minds of some epidemiologists, the CHD mortality rate initiated strong declines in the states of California and Utah and stabilized in other states such as New York. Borhani and Hechter[2982] were apparently the first to recognize these trends in 1964 but there is little indication that NHLBI and AHA paid any attention to them.

The AHA issued its first statement on smoking and health in 1956.[3046] The statement maintained that smoking harms peripheral blood vessels and produces overt symptoms in "some persons" with coronary atherosclerosis. Intersetingly, per capita consumption of cigarettes accelerated after 1956, increasing about 20% over the next seven years.[2664] Thus, there clearly was no impact of this statement on society's smoking habits.

1957 was marked by diametrically opposite events. One of the most objective scientific reports encountered during the preparation of the present document was authored by Irvine H. Page, Frederick J. Stare, A.C. Corcoran, Herbert Pollack and Charles F. Wilkinson, Jr.[512] This report, specifically prepared for AHA, indicated serious doubt as to the occurrence of a CHD epidemic during this century and concluded that the American diet had not changed in ways consistent with the proposition that dietary cholesterol or fats could be responsible for an increase in the incidence of CHD.[b] The authors also severely criticized the medical experiments on diet which were being used by AHA and others to support recommendations for altering the American diet. They concluded that "the evidence at present does not convey any specific implications for drastic dietary changes, specifically in the quantity or type of fat in the diet of the general population, on the premise that such changes will definitely lessen the incidence of coronary or cerebral artery disease."

Also in 1957 Norman Jolliffe initiated the Anti-Coronary Club in which a group of businessmen (40-59 years) were placed on a diet he called the "Prudent Diet." Director of the Nutrition Bureau of the New York Health Department, Jolliffe was presumably an expert on weight reduction.[2016,c] No control group was established; instead, the death rate among the Prudent Dieters was to be compared with the general population of the same age group and with a "matched" group.[2026]

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[a] Fat intake figures derived from food availability or "disappearance" statistics (see Chapter 3 for a detailed discussion). Also, at the time Key's study was conducted, it was not known that saturated and unsaturated fats produced differential effects on blood cholesterol levels.

[b] One of the authors, Frederick Stare, noted independently the year before that "It should be obvious that much of what we hear these days about changes in our intake of fat--animal versus vegetable, saturate versus unsaturated--is not consistent with published facts."[2094]

[c] Before the first four years of the study were completed, Jolliffe died at age 59 of "vascular complications," the very disease his Prudent Diet was designed to eradicate.[2016]

Several studies published in 1957 demonstrated that saturated and polyunsaturated fats increased and decreased, respectively, blood cholesterol. Thus, the distinction between animal and vegetable fats was further defined.

Manufacturers of foods high in unsaturated fats initiated advertising campaigns in 1957 suggesting that their foods would reduce the chances of dying of CHD.[2000] A typical ad read, "Wheaties may actually help you live longer." As would be expected, industries producing foods high in fats were not pleased with the ads or the increasing discussions of diet and CHD.

In 1958 "a statement was disseminated to the public by the National Health Education Committee on the risk factors and their relevance to the massive coronary problem and its control."[539] This statement was authored by P.D. White, H.B. Sprague, J. Stamler, F.J. Stare, I.S. Wright, L.N. Katz, S.L. Levine and I.H. Page. It is to be noted that while the conclusions drawn in the 1957 report to the AHA were nearly opposite to those presented in the 1958 statement, two authors were associated with both, i.e., Frederick J. Stare and Irvine H. Page.

Also in 1958 results of a study were published which compared similar groups of blacks in Haiti and South Carolina.[2003] The Haitians were underweight, on average, and the South Carolinians were overweight, on average. The latter also consumed 6 to 20 times the amount of cholesterol than the former. Yet, autopsies showed that the Haitians suffered the same frequency of atherosclerosis as the South Carolinians.

The 1958 AHA president, Robert Wilkins, announced that atherosclerosis would be the AHA's prime target during the next 10 years.[2003]

By 1959 health benefits were frequently being touted by manufacturers of low saturated fat foods. Wesson, for example, recommended its cooking oil "for your heart's sake" and Mazola advertised that "science finds corn oil important to health."[2001] The AMA, however, issued another statement against such ads, i.e., "widespread, drastic revision of dietary practice seems unwarranted at this time."[2001] The FDA agreed and promulgated a law in 1959 prohibiting food manufacturers from attributing health benefits to their products <u>on labels</u>. That law follows:[39]

"(a) There is much public interest and speculation about the effect of various fatty foods on blood cholesterol and the relationship between blood cholesterol levels and diseases of the heart and arteries. The general public has come to associate the term "cholesterol" with these diseases. A number of common food fats and oils and some other forms of fatty substances are being offered to the general public as being of value in the control or reduction of blood cholesterol levels and for the prevention or treatment of diseases of the heart or arteries.

(b) The role of cholesterol in heart and artery diseases has not been established. A causal relationship between blood cholesterol levels and these diseases has not been proved. The advisability of making extensive changes in the nature of the dietary fat intake of the people of this country has not been demonstrated.

(c) It is therefore the opinion of the Food and Drug Administration that any claim, direct or implied, in the labeling of fats and oils or other fatty substances offered to the general public that they will prevent, mitigate, or cure diseases of the heart or arteries is false or misleading, and constitutes misbranding within the meaning of the Federal Food, Drug and Cosmetic Act."

While members of the alliance will later stress that they never advocated substantial increases in the consumption of polyunsaturated fats, they did, in fact, so advocate them and that is the reason why the edible oil producers promoted their products as "heart savers."

In 1960 the AHA officially sanctioned the views of Keys who regarded fat as the proven cause of high blood cholesterol and high blood cholesterol as the proven cause of CHD.[1993] Keys initiated his Seven Countries study in that year as well. In the same year Irvine Page was appointed Chairman of an Executive Committee on Diet and Heart Disease to consider the potential utility of conducting a large diet-heart trial.[3018] The Committee recommended that a small feasibility study be conducted prior to embarking on a full-scale trial.

The AHA issued its second statement on smoking and health in 1960.[3046] This statement declared that CHD mortality is greatly increased with cigarette smoking. Nevertheless, per capita consumption of cigarettes continued to climb a small amount and then stabilized at a high level over the next 8 years.[2664]

In 1961 AHA's Herbert Pollack, author of the 1957 AHA report but not the 1958 statement, emphasized that "There is no evidence that decreasing the amount of cholesterol in the blood will reduce the incidence of heart attacks."[1998] Yet, AHA published a statement which was presumably based on the 1957 review report.[517] It was referred to by Grundy et al.,[499] Jolliffe[545] and Gotto[2195] as a "revised" and "updated" version of the original report. In fact, however, the AHA statement was very brief and bore essentially no resemblance to the original report and ignored all of its major conclusions. The AHA statement recommended that Americans at risk for CHD (smokers or individuals having high blood cholesterol or hypertension) reduce their consumption of total fats and cholesterol and increase their consumption of polyunsaturated fats. Aside from its gross departure from the 1957 report, the statement was of interest for two reasons. First, cholesterol was specifically referred to as a "type of fat" which it is not. And second, the statement indicated that when polyunsaturated fats are substituted for a "substantial" amount of saturated fats, blood cholesterol decreases.[a]

The authors of the AHA statement were Irvine H. Page, Edgar V. Allen, Francis L. Chamberlain, Ancel Keys, Jeremiah Stamler and Frederick Stare. Thus, Page and Stare again remained as the lone authors from the original 1957 report and other authors were selected who agreed with AHA's philosophy. One can only conclude that Page and Stare either dramatically changed their minds from 1957 to 1958 or were simply willing to accept AHA's philosophy.

The association of Keys with the 1961 AHA statement was particularly interesting because he was quoted by Time Magazine in the same year as saying that it was "nonsense" to increase the consumption of polyunsaturated oils.[1993] Other prominent AHA members, however, were to recommend for many years the consumption of such oils by the "spoonfuls."

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[a] Because of subsequent evidence regarding the potential harm of high polyunsaturated fat diets, the AHA would later place a stringent limit on such fats.

The 1961 AHA statement effectively represented the green light for the vegetable oil industry.[2027] The promotion of unsaturated oils and fats intensified and the FDA failed to enforce its 1959 law.

Also in 1961 the AHA issued another statement on cigarette smoking, suggesting that "smoking may contribute to or accelerate the development of CHD."[3046] Despite this message, cigarette smoking continued to increase among Americans.

On August 4, 1962 the Council on Foods and Nutrition established the AMA's official position on diet and CHD.[2629] The Council's secretary, Philip White, stated that "this report is intended to serve as a guide to assist the physician who wishes to advise the regulation of dietary fat on the basis that it may be beneficial. It is not a recommendation for the general public." Although not explicitly relating them to the CHD mortality trend, the Council did note that the food consumption trend toward less animal fat and more vegetable fat had been underway before the CHD "epidemic" occurred (see Chapter 3).

The Council defined hypercholesterolemia as above 280 mg and indicated that "Increasing the ratio of polyunsaturated fat to saturated fat in the diet is the preferred method for treating the 'usual' hypercholesteremia." It offered specific diets which contained as much as 12.8% to 17.4% of total calories as polyunsaturated fats and 40% of total calories as all fats, which undoubtedly further stimulated the edible oils industry to increase their diet-heart promotional efforts. Thus, while the AHA and AMA greatly differed with regard to total fats in the diet, they both advocated "substantial" increases in polyunsaturated fats.

Finally, the Council noted that although "a direct causal relationship between diet or serum lipid concentrations and atherosclerosis has not been proved, in the light of present knowledge, it appears logical to attempt to reduce high concentrations of cholesterol and other serum lipids as an experimental therapeutic procedure." Thus, the Council effectively advocated that physicians "experiment" with patients in the absence of a causal relationship between diet and CHD.

Two months later (October 12, 1962) the AMA issued a press release which presented a different position than that of the Council on Foods and Nutrition. It said, in part, "Scientific reports linking cholesterol and heart attacks have touched off a new food fad among do-it-yourself Americans. But dieters who believe they can cut down their blood cholesterol without medical supervision are in for a rude awakening. It can't be done. It could even be dangerous to try. Neither the Food and Nutrition Board of the National Research Council nor the AMA Council on Foods and Nutrition has recognized the need for modification of dietary fat for the general public. The anti-fat, anti-cholesterol fad is not just foolish and futile, it also carries some risk."[2024]

Two and one-half months later (December 29, 1962) the AMA published an editorial by William Darby which sought to "state clearly and unequivocally the position of the AMA on this subject."[2693] In effect, the October 12 news release was issued without the review and approval of Darby's Council on Foods and Nutrition and Darby felt that "The press release contained certain dogmatic statements which could be subject to misinterpretation. They concerned the futility of individuals' attempts to modify the fat content of their own diet and the risk which these attempts entailed." An abstract of the news release of October 12 was published in JAMA and "regrettably, the writer of the abstract mistakenly credited the AMA news release to the Council on Foods and Nutrition. The Council believes that properly instituted diet therapy can significantly and safely alter the serum cholesterol and LDL concentrations of most

hypercholesteremic human subjects." The Council emphasized that diet therapy should be performed under the guidance of physicians [who, of course, have no academic background or training in nutrition] and that "there is not sufficient information available at the present time to warrant a change in the American diet aimed at preventing heart disease in the general population."

In sum, the AMA not only presented a position which differed from that of the AHA, it also differed from that of its Council on Foods and Nutrition. The oscillating nature of the AMA's position, already well established, would continue for many years to come.

A four-year report of the Anti-Coronary Club study was published in 1962 by Seymour Rinzler and his associates, following the death of Jolliffe. He reported that the Prudent Dieters suffered 5 cases of heart disease and that the number expected in the general population was 24. Thus, they concluded that this was a "clear-cut demonstration" that the Prudent Diet prevents CHD.[2026] Rinzler indicated that a control group would be added to the study, projected to continue for at least five more years.[a]

The Diet-Heart feasibility study was launched in 1962 and was directed by Irvine Page.[3018]

Unknown to anyone, CHD mortality peaked in 1963 and initiated a long-term downward trend thereafter. Thus, the trend began before any significant risk factor control activities were started and it was well underway for 10 years before it was discovered.

In early 1964 the FDA noted from a public opinion poll that most Americans associated polyunsaturated fat consumption with the prevention of CHD.[1990] Since there was not evidence to support this belief, the FDA issued a warning to food processors to cease using health claims in their advertising. In 1964 the AHA expanded its 1961 diet recommendations from those at high risk for CHD to all Americans.[499] The AHA explicitly promoted an increase in polyunsaturated fats at the expense of saturated fats. A spokesperson for a major food producer summed it up thusly, "The government says you can't promote these products and the heart people say everybody ought to use them."[1990]

The AHA's announcement apparently did not influence the AMA which indicated that the evidence did not yet warrant a major change in the American diet.[1990]

It is to be noted that the 1964 AHA statement included the qualification that there was no proof that lowering cholesterol levels by diet would reduce the risk of heart disease. AHA supporter Irvine Page disagreed with the recommendations and indicated that nationwide dietary changes should not be recommended until after diet-heart trials were held.[1990] Stamler agreed with Page.[1990]

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[a] A 5 year report subsequently revealed 8 CHD deaths among the Prudent Dieters and one in a control group.[2016] However, because there were slightly more overall CHD "events" in the control group, the Prudent Diet was said to be "successful."

The FDA initiated actions against some food producers such as National Biscuit Co. and Kraft Foods[2005,2006] but apparently did nothing to stop the promotions of the edible oil industries.

The report of the Advisory Committee to the Surgeon General on Smoking and Health was also published in 1964.[3068] Although it had no immediate impact on per capita consumption of cigarettes, it is likely that it played a role in gradually reducing the percentage of Americans who smoked.

Also in 1964 was an important article by William Kannel, describing 10-year results from the Framingham study.[1885] After noting that the cholesterol levels of those with and without CHD overlapped almost completely, Kannel concluded that "Diagnosis of heart disease on the basis of lipid levels alone is simply not feasible."[1885] He went on to say, however, that "estimation of the relative risk of developing the disease in association with various lipid levels is feasible and informative." While such a concept is valid for groups of individuals, it was not and is not valid for the individuals themselves, i.e., an individual will or will not contract CHD, independent of his cholesterol level. Hence, relative risk is meaningless to the individual and, therefore, every individual in the U.S.[a]

The AHA repeated its 1964 statement in 1965.[661] Late in that year the AMA published an official policy statement which reaffirmed its 1962 position, namely, that there was no proof that lowering blood cholesterol by diet will reduce the risk of CHD but approved dietary changes for "young men vulnerable to coronary disease" under the supervision of physicians.[2631] The Council emphasized that "...it must be recalled that definitive proof that lowering serum cholesterol, or preventing a rise in serum cholesterol, will lower the morbidity and mortality associated with CHD, is still lacking."

In 1967 investigators of the National Diet-Heart study announced that a large diet trial consisting of about 40,000 men could be conducted for $50 to $60 million.[1995] Since the commissary was already established for dispensing foods, they indicated that the trial could be initiated rapidly.[b] While many urged the government to fund the trial, including the AHA, others were against it.[1995] It was said that the 10% to 12% reduction in blood cholesterol observed in the National Diet-Heart study was not enough to produce "convincing results."[c]

In 1968 former president of the AHA and author of the original AHA statements in 1957, 1958 and 1961, Irvine Page, severely criticized the AHA, accusing it of "bumbling" in the search for the cause of CHD. He said that "far too little is known about the relationship between heart disease and diet, smoking, exercise and other factors" and that researchers were engaging in "scientific gamesmanship that

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[a] As shown in Volume 1 and elsewhere in this volume, moreover, "relative risk" is a gross exaggeration of reality.

[b] Their report published in the following year, however, gave little evidence that diet influenced the incidence of CHD.[1071] The negative outcome of this study probably represented the chief reason for ultimately cancelling the proposed diet trial.

[c] Both the MRFIT and LRC trials, eventually substituted for the diet trial, produced smaller reductions in blood cholesterol levels.

concentrates on status seeking and the hunt for more money than productive results."[2102,a]

The AHA was relentless in pursuing the diet-CHD philosophy and quantified its recommendations in 1968.[662,2101] Dietary cholesterol and total fat were limited to less than 300 mg and less than 40% of calories, respectively. The AHA specifically stated that "polyunsaturated fats should probably comprise twice the quantity of saturated fats." Thus, in a diet of 35% to 40% fat, the polyunsaturated fatty acids would comprise 15% to 20% of total calories, an amount that the AHA and others would eventually consider dangerous to health.[b] In support of the cholesterol intake recommendation the AHA cited the single (confounded) experimental study by Connor et al.[322] which employed 6 subjects, three of which were insulin dependent diabetics, i.e., "Sharp reduction in the amount of cholesterol in the diet has been found to lower the concentration of cholesterol in the serum of most people."[c]

1969 was marked by more negative findings. Cornfield and NHLI's Mitchell reviewed 10 clinical trials conducted to date and concluded that "The better the experimental design, the less the effects of diet on CHD--there is no evidence here to change the Western diet."[431,d] Dayton and Pearce also announced the results of the Veteran's diet trial in which a high polyunsaturated diet replaced the typical diet.[454,2541] They said that "The results of our own trial, even when buttressed by concordant observations in two other primary prevention studies, are not sufficient grounds for aggressive efforts to change the U.S. diet."[2541]

The finding of higher cancer rates in the polyunsaturated diet group of the Veterans study caused some concern. The AHA's medical director, Campbell Moses responded by stating that AHA's recommendations were centered on reducing fat, not on substituting polyunsaturates.[2023] But such a statement was a complete fabrication because the above noted 1968 AHA statement clearly and unequivocally recommended a large increase in the consumption of polyunsaturated fats.[2101]

Also in 1969 George Christakis recommended that businessmen all over the U.S. should organize themselves into anti-coronary clubs,[1991] despite the fact that the Anti-Coronary Club failed to prove that the Prudent Diet was beneficial.[459,467] (William Castelli will state in 1987 that "the Anti-Coronary Club Study was not good science."[1302])

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[a] The second of the two original authors of the three statements, Frederick Stare, would completely reject the AHA's diet-CHD philosophy many years later after praising the philosophy in numerous syndicated newspaper columns throughout the 1960s and early 1970s.

[b] It is interesting to note that prior to its release the 1968 statement as originally drafted omitted the word "probably."[2101]

[c] This study is described in detail in Chapter 5.

[d] In 1969 the National Heart Institute became the National Heart and Lung Institute.[2688]

Interestingly, the AHA published a monograph in 1969 admitting once again that "It is not proven that dietary modification can prevent arteriosclerotic heart disease in man."[2027] But lack of proof did not influence its belief in the diet-CHD relationship or its intention to change the American diet.

Nineteen and six years after the cardiovascular and CHD death rate declines began, respectively, Paul Dudley White addressed members at the 1969 American College of Cardiology meeting. He said, "Exercise, tobacco, rich diets: we know that these are factors (in causing CHD), but we have not yet been able to educate the public to action and change that might contribute to longer life."[1943] The medical world was still unaware that the CHD mortality rate was on the decline.

1970 was another year of major contradictions. First, a most important Framingham study was published as a technical report with limited distribution and, unlike other Framingham analyses, apparently never was submitted to a medical journal.[274] This study evaluated the relationship between diet, blood cholesterol and CHD. The authors concluded that "There is no discernible association between reported diet intake and serum cholesterol level" and that "The data strongly suggest that if there really is any association between diet intake and serum cholesterol in the Framingham study population, it is probably a weak one." No relation was found between diet and CHD incidence as well.[a]

Like all other negative evidence, the AHA was quick to reject this Framingham study. The AHA's Campbell Moses dismissed the study because, he said, there was not enough variation in the percentage of intake of calories from fat.[2010] He also said the study was not valid because the cholesterol intake among the Framingham subjects was much lower than the nationwide average. But Moses (and many other alliance members who subsequently made similar statements) was totally incorrect on both counts. There were very wide variations in total and saturated fat intakes and also in cholesterol intakes. For example, total and animal fat consumption were reported by Kannel and Gordon to vary from 18% to 53% and 32% to 97%, respectively, in men. The cholesterol consumption was reported to vary from 250 mg to 1500 mg. Additionally, the mean cholesterol intake among the Framingham subjects was higher (about 712 mg), not lower, than the nationwide average (about 515 mg). Of the hundreds of Framingham studies published in journals this was one of the few which was purposely withheld from journals, apparently to avoid wide exposure. The AHA and NHLI effectively eliminated this study from their subsequent literature "reviews."[7]

But even if the Framingham subjects consumed the exact same diets, the arguments of Moses and others would still be invalid because the wide differences in CHD observed in the study would also be unexplained by diet. This was recognized early in the Framingham study by Dawber and Kannel who said in 1958 that "If everyone were eating about the same foods and in the same amounts food intake would cease to be a variable and measurement of it would be of no value..."[2542]

Kannel and Gordon also published a technical report in 1970 which contained data on cancer that did not reach journals until many years later. In 1980 Rose and Shipley[68] noted that the reference tables in that report showed that both all-cause and non-CHD death rates were higher at low cholesterol levels than at higher levels. The

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[a] A later publication specifically noted that the number of eggs consumed by the Framingham subjects was neither related to blood cholesterol levels nor to CHD development.[163]

fact that these findings and those of the Framingham Diet study were not published in the open literature reflected the need by the alliance to selectively disseminate information in accordance with the poicy to protect the lipid hypothesis.

Also in 1970 an organization known as the Inter-Society Commission for Heart Disease Resources, created by Congress, funded by DHEW and apparently nothing more than an arm of AHA and NHLBI, published a lengthy document which recommended that all Americans consume the Prudent Diet, essentially identical to that espoused by the AHA in 1968.[701] The Commission said there was abundant evidence that a diet high in saturated fats and cholesterol would lead to a higher risk of CHD, although it admitted the evidence was not conclusive.[1975] The Commission said that limiting egg consumption would reduce risk of CHD but admitted that there was no proof of this relation.[701] Stamler, perhaps the leading advocate of reducing egg consumption, was chairman of the Commission's Atherosclerosis Study Group.[1997]

The Commission cited ten studies as supporting the Prudent Diet.[701] Of the ten, four were involved with animals and had questionable relevancy and three were clinical trials which the Commission admitted had "one or another flaws." The remaining three were population studies, all of which yielded highly confounded and uninterpretable findings. Also, the Commission cited not a single human experimental study.

Like the AHA, the Commission urged the conduction of a large diet trial and estimated the cost at $70 to $80 million.[1998] Until such a study was completed, however, the Commission recommended the AHA dietary changes, including an increase in polyunsaturated fats (recall previous remark by AHA's Campbell Moses).

Finally, the Commission attacked the FDA's stand against attributing health benefits to foods and cholesterol-lowering drugs on labels.[2011] The Commission strongly urged that certain foods and cholesterol-lowering drugs be labeled as aids to health. Although maintaining that there was still no proof that diet affects the development of CHD, the FDA apparently succumbed to the pressures of the AHA, the Commission and probably NHLBI members and announced that it would rescind its 1959 law (which it apparently never or rarely enforced on the industry for which it was designed, i.e., the edible oils industry) and allow food processors to indicate or suggest health benefits on labels.[2008] The chairman of the Inter-Society Commission, Irving Wright, hailed the FDA's decision but maintained it was only the first step.[1975]

Despite the apparent unity exhibited by the Commission and AHA, the New York Times reported that the 1970 annual AHA convention was marked by the fact that researchers could not agree on the benefits of the Prudent Diet.[39]

NHLI director Theodore Cooper handpicked a "Task Force" in 1970 with the purpose of developing a long-term plan.[1995,2688] The Task Force's report was published in 1971. The large proposed diet trial was rejected on totally illogical and inconsistent grounds (see Chapter 7). In its place the Task force recommended two other trials, one using a cholesterol-lowering drug (the Lipid Research Clinics Coronary Primary Prevention Trial, LRC) and the other using multiple means of reducing risk factors (the Multiple Risk Factor Intervention Trial, MRFIT).[705] The report quoted Cooper as saying that "evidence which is suggestive, fragmentary, even conflicting, links the American diet with the American death rate from IHD."[2691] Such a statement clearly indicated the rather weak conviction Cooper had for the diet-CHD relationship. (Former AHA president, Irvine Page, will later refer to these trials as "ill planned."[1740] He said, "The great opportunity to do it properly [a national diet-heart

trial], once offered to the U.S. Public Health Service, was rejected by an 'expert' committee, whose judgment in retrospect does not appear to have been very expert."

Senator George McGovern announced in 1971 that a Senate Committee would hold hearings on the evidence linking diet with diseases.[39,a] However, he subsequently postponed them until 1972, possibly because the dairy industry protested that the hearings' agenda appeared to be biased towards the AHA's philosophy.[39]

Noting the downward trend in egg consumption and fearing a steeper trend, the egg industry created the National Commission on Egg Nutrition in 1971, a group ostensibly charged with obtaining facts on the egg-heart disease issue and disseminating those facts to the public.[1997] It was undoubtedly established to defend the egg industry in the face of relentless attacks by the AHA, particularly by Stamler, Connor and Stare.

It was previously indicated that the FDA apparently never enforced its 1959 labeling law on the manufacturers of vegetable oils. Pinckney and Pinckney reported the following: "In 1971, the general counsel for the FDA--the man in charge of prosecuting any violations of FDA regulations (including those of mislabeled polyunsaturated products)--left the FDA to become president of the Institute of Shortenings and Edible Oils (the primary public relations group for polyunsaturates). At the same time, the man who had been the legal representative of the edible oils companies suddenly became the general counsel of the FDA--the government's lawyer now in charge of regulating and disciplining the activities of his former clients."[39,b]

The secretary of the AMA's Council on Foods and Nutrition, Philip White, apparently made the last AMA statement in opposition to the AHA's and industry's promotions of vegetable oils--at least for several years. He exclaimed that "We are all tired by now of the unending advertisements for oils and margarines that promise to clear out arteries in much the same way a drain cleaner works."[39,2016] He maintained that there still was no proof of the relation between diet and CHD.

Senator McGovern entered the presidential race in 1972 and postponed indefinitely the hearings on diet and diseases.[39] Simultaneously, the AMA reversed its position and published a joint statement with the National Academy of Sciences' Food and Nutrition Board indicating full support of the AHA's Prudent Diet.[423,2228] The statement declared, in part, "There is abundant evidence that the risk of developing CHD is positively correlated with the level of cholesterol in the plasma...[and]...there is extensive evidence that the level of cholesterol in the plasma of most people can be lowered by appropriate dietary modification." It continued, "Generally, such lowering can be achieved most practicably by partial replacement of the dietary sources of saturated fat with sources of unsaturated fat, especially those rich in polyunsaturated fatty acids, and by a reduction in the consumption of foods rich in cholesterol."

The American Health Foundation published a similar statement in 1972.[424] However, the American Academy of Pediatrics announced opposition to the Prudent Diet for children because of potential harm to brain and mental development, since

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[a] General hearings on diet and health apparently began in 1969.

[b] Pinckney and Pinckney also described similar position exchanges between the FDA and the edible oils industry before and after 1971.

the nervous system is heavily dependent on the supply of cholesterol. (The Academy repeated its opposition to the Diet in 1988 for children under 2 and emphasized the fact that breast milk contains 40% fat which "gives some clue of the importance of baby's diet."[1573]

The MRFIT study was launched by NHLI in 1972.[836] Theodore Cooper, NHLI director, presented a speech at the 1972 AHA meeting and indicated that the MRFIT and LRC trials would be "smaller" and "less expensive" than the proposed but rejected diet trial which the 1970 Task Force estimated would cost $80 to $380 million.[1996] He maintained that the two smaller trials and a third trial, which would involve the lowering of blood pressure in a group of women and young blacks (also initiated in 1972), could be done simultaneously for $112 million.[a]

Cooper's statement also strongly suggested that he did not believe that a CHD epidemic had taken place in this century, i.e., "it may be that coronary heart disease is seen by the public as a relatively new disease. For example, Dr. P.D. White is quoted in Family Circle magazine as saying: 'When I was an intern at Massachusetts General Hospital in 1941 there was no department of cardiology.' Notice Dr. White does not say that there was no heart disease, just that there was no department of cardiology. But the implication to the lay reader is that heart disease did not kill many people at that time and that it has only recently become a public health problem. In actual fact, heart disease has been the number one killer in the United States since at least 1910."[2085] The reader should recall this statement when the so-called CHD epidemic is discussed in detail in Chapter 3 of this volume and of Volume 1.

Also in 1972 Congress authorized NHLI to create and promote educational programs designed to prevent and control cardiovascular diseases.[3067] The Office of Prevention, Education and Control was established to administer these programs.

In 1973 NHLI launched its first educational program, called the National High Blood Pressure Education Program (NHBPEP).[3068] The NHBPEP continues to the present time.

The AHA issued another statement recommending the Prudent Diet in 1973 (and again in 1978, 1985, 1986 and 1988). While the AMA succumbed to the AHA in 1972, NHLBI still demonstrated caution regarding dietary changes in 1973. Corday cited an NHLBI in-preparation report which stated that "It is not yet been conclusively demonstrated in cases that modification of risk factors actually retards the process of atherosclerosis..."and that "There is circumstantial evidence that maintenance of low blood fat levels from youth will prevent or retard the progression of atherosclerosis... However, both propositions are matters of faith rather than fact."[2021]

The Lipid Research Clinics Primary Prevention Trial was initiated in 1973.[836]

Although the CHD mortality rate had initiated a decline in California in 1953 and in the entire U.S. in 1964, Jeremiah Stamler stated in 1973 that "there was no

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[a] The LRC and MRFIT trials alone ended up costing about 130% more than Cooper's estimate, i.e., $265 million, about the same amount as that estimated for the more relevant and desirable diet trial.

evidence yet of a decline."[573] He said that CHD "will result in the coming years in the greatest epidemic mankind has faced unless we are able to reverse the trend..."

The Food and Nutrition Board appeared to have second thoughts about dietary changes in 1974 in its document, "Recommended Dietary Allowances," and indicated that population studies linking diet with CHD "...are difficult to interpret."[704] In the same year the U.S. Department of Agriculture published a document stating that, "To date, studies have not shown convincingly that restriction of dietary cholesterol in the general population reduces the frequency of atherosclerosis."[126]

Also in 1974 an editorial by Weldon Walker in the Journal of the American Medical Association was published and entitled, "Coronary mortality: what is going on?"[2604] According to Thom and Kannel,[2826] "this was probably the first indication in the literature that the actuaral death rate for CHD was declining" nationally.

At the 1975 AHA meeting Ivan Franz described the failure of yet another study to demonstrate benefits of lowering blood cholesterol. Seventeen thousand persons in Minnesota State Hospitals were placed on a cholesterol-lowering diet (14% blood cholesterol decrease) over a 4.5 year period. "In the entire population--including men and women of all ages over 21--despite a satisfactory decrease in blood cholesterol, there was not the slightest hint of benefit."[201,2020]

Since its establishment in 1971 the National Commission on Egg Nutrition (NCEN) pursued an aggressive promotion of the egg. Probably its most prominent promotion was the advertisement, "There is absolutely no scientific evidence that eating eggs in any way increases the risk of heart attack." While this statement was entirely true, based on repeated statements by NHLBI and others, the AHA requested the FTC to prohibit NCEN from continuing such advertising.[2019] In 1975 administrative law judge Ernest Barnes stated erroneously that "there exists a substantial body of competent and reliable scientific evidence that eating eggs increases the risk of heart attacks or heart disease" and ordered NCEN to cease such advertising. Thus, while the FTC and FDA permitted the vegetable oil industries for many years to advertise that their products benefitted health, despite a lack of proven scientific support, they prohibited the egg industry from making scientifically accurate claims, undoubtedly because of the relentless pressure from the AHA, the organization destined to eventually control all relevant branches of the federal government. Not only had prominent American researchers repeatedly emphasized that dietary cholesterol was relatively unimportant, e.g., Keys, the Royal College of Physicians of London and the British Cardiac Society published a statement which excluded dietary cholesterol as a factor in blood cholesterol and CHD.[176,a,b] (See a later section in this chapter for a detailed discussion of the FTC-NCEN "trial".)

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[a] Very recently, the British Committee on Medical Aspects of Food recommended that "the most effective way of reducing a high serum cholesterol concentration, is to "reduce body weight."[1260] The British Committee recommended 35% and 15% of calories as total and saturated fats, respectively,[1264] approximately the percentages existing in the conventional American diet. Recommendations by the WHO Expert Committee and the European Atherosclerosis Society are identical to those of AHA.[1235,1262,1265] To date, British cardiologists tend to question the validity of the diet-CHD hypothesis.[143]

[b] A detailed review of the FTC-NCEN "trial" is presented in the next section of this chapter because it demonstrates once again the AHA's influence on government.

In 1976 NHLBI continued to resist total compliance with AHA's philosophy. An NHLBI report indicated again that no empirical evidence existed proving that reducing blood cholesterol would reduce the incidence of CHD.[705] NHLBI's Basil Rifkind said, "we don't know" and Robert Levy said that "until we prove, at least in the high-risk patients, that lowering cholesterol is beneficial or doesn't have side effects associated with it, it's hard to make these aggressive (dietary) recommendations to the entire community."[2018,a]

NHLI officially became NHLBI in 1976.

The diet-CHD issue was elevated to national prominence in 1976 and 1977 when a U.S. Senate Select Committee on Nutrition and Human Needs, chaired by Senator George McGovern, finally conducted hearings on the diet-CHD issue and published a report fully supporting the Prudent Diet.[706] Some researchers in opposition to the Prudent Diet were invited to present testimony but there is no indication that their testimonies were seriously considered. In any event, they were greatly outnumbered by diet-CHD promoters. For example, when Senator McGovern told Robert Olson that there was "overwhelming consensus" among the participants that the American diet should be altered, Olson replied, "I'm not sure you have a consensus of the health professionals in this country. You have a consensus of the witnesses you have called."[2538]

The primary report of the Senate hearings was published in 1977 and contained the exclusive dogma of NHLBI and AHA members, Levy, Gotto and Stamler.[706] In addition, it contained the entire 1972 Report of the Inter-Society Commission for Heart Disease resources and a number of other NHLBI and AHA materials, including 187 pages of "The Dietary Management of Hyperlipoproteinemia" and the "Help your Heart Eating Plan, in which numerous recommendations were made for increased consumption of polyunsaturated fats that far exceeded current recommendations. For example, Gotto urged individuals to consume 12 teaspoons of vegetable oil per day.[1601] Yet, in the same document, Levy told the Senators that "The problem, as I see it, where I sit in the NHLBI, is that we would like to demonstrate that cholesterol lowering is beneficial before we go out and do it on a massive scale. ...whether lowering cholesterol will result in a reduced incidence of heart attack...is still presumptive."[288]

It is of interest to note that the Inter-Society Commission's report included in the Senate hearings document was a revised version of the Commission's 1970 report. The revised version cited no studies supporting the Prudent Diet with respect to fat intakes and only one article in support of its recommended cholesterol intake.[411] Moreover, that article was authored by William Connor, a staff member of the Society who, in turn, cited only his few dietary cholesterol experiments, all of which produced confounded and misleading results (Chapter 5).

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[a] Interestingly, Wassersug indicated that Levy was one of three individuals (including Donald Frederickson and Robert Lees) most responsible for promoting the blood cholesterol-CHD concept. "Individually and collectively, they lectured widely and produced a seemingly endless number of articles detailing their research about the harmful effects of cholesterol."[2198]

Mark Hegsted, director of the USDA's Human Nutrition Center, announced his department's support of the Senate Committee's recommendations.[284] He urged all medical people to stop debating the diet-CHD issue and promote the Committee's goals. In so doing, he brought one more government body into the AHA fold. The Congress, the DHEW, the USDA, the FDA and, apparently the FTC, were now eager to alter the American diet rather substantially on the basis of opinions and almost exclusively negative scientific evidence.

Upon hearing the Committee's National Dietary Goals, the AMA again reversed its position and submitted a statement to the Committee which strongly opposed the Prudent diet.[180,707] The statement said that "we believe that it would be inappropriate at this time to adopt the proposed National Dietary Goals. The evidence for assuming that benefits to be derived from the adoption of such universal dietary goals as set forth in the Report is not conclusive and there is potential for harmful effects from a radical long term dietary change as would occur through adoption of the proposed national goals." The Senate Committee, however, rejected the statement.

The Senate hearings represented the first of several contrived "consensus" events designed to appear objective and comprehensive to the public and physician practitioners but were in actual fact highly biased and thoroughly uncomprehensive. They also represented the AHA's complete victory over the federal government.

In late 1977 a face-to-face meeting between the NCEN and the AHA's medical director, Campbell Moses was held.[1997] Moses admitted that the AHA's recommendation to limit egg consumption to three per week was based on "clinical opinion," rather than scientific evidence. But such an admission provided no comfort because lack of scientific evidence had never been more than an irritant to the AHA's pursuit of changing the American diet.

In 1978 the American Society for Clinical Nutrition convened a panel of medical scientists to review research/evidence on dietary fat and cholesterol.[130] The panel concluded that evidence linking diet with CHD was "unconvincing." As expected, that conclusion was rejected by the newly formed NHLBI/AHA alliance. Robert Levy also demonstrated greater willingness to be more supportive of the AHA's philosophy. He suggested that he was now aligned with researchers who were "firmly convinced that not only can diet influence cholesterol, but that it's already been proven that cholesterol lowering in man will prevent heart disease."[1994]

In 1979 AMA published a statement in which strong opposition was expressed against AHA's dietary changes for all Americans.[2627] It said, "The public is continuously distracted by announcements of hazards associated with foods, food additives, or various dietary practices. Many warnings are unfounded or premature, but the fears thus engendered adversely influence attitudes about foods. The public is also misled by extravagant claims of health benefits from the use of certain foods or nutrient supplements." The AMA reaffirmed its early 1960s position that dietary changes be restricted to those at risk for CHD and those who were obese. With regard to the latter, emphasis was placed on the reduction of total calories, not on the reduction of fats or saturated fats per se. The AMA went on to say that "The Daily Food Guide developed by Harvard University's Department of Nutriton and the U.S. Department of Argiculture is a very helpful guide to food selection. It permits people to plan adequate diets by selecting foods rather than calculating amounts of nutrients (the latter procedure being impossible in any practical sense)..." Note the word "impossible." The AMA will recommend the "impossible" four years later.

Also in 1979 Basil Rifkind reiterated previous statements, i.e., "To date, no study has actually shown that lowering cholesterol is of benefit in preventing heart attacks."[113] But Assistant Secretary of Agriculture, Carol Tucker Foreman, a former consumer advocate but clearly unknowledgeable of the subject, said that nutrition in the past 10 years had established a "virtual link" between cholesterol and saturated fats with heart disease."[120]

The present writer submitted a letter to Ms. Foreman on October 11, 1979 indicating that the evidence supporting diet, cholesterol and CHD was wholly inadequate, cautioned her as a former consumer advocate to make sure that the public receives objective information on the subject and offered her relevant literature.[950] Ms. Foreman's brief October 24, 1979 reply stated that she was acting on the best information available.[951] But a few months later (1980) the National Academy of Sciences' Food and Nutrition Board issued a statement reversing its 1972 position after reviewing the relevant research literature.[709] The Board concluded that the scientific evidence did not support dietary changes among Americans and did not rule out potential harm associated with the Prudent Diet. Although the Board's announcement concurred with that of the AMA's statement in 1977, it angered Congressman Fred Richmond who criticized the Board's reversal, criticized the medical establishment's resistance to the Prudent Diet and convened a hearing on the subject.[119,951] Subsequently, the USDA and USDHEW published "Nutrition and Your Health: Dietary Guidelines for Americans" which promoted the Prudent Diet.[710]

Of course, the AHA strongly disagreed with the Board's announcement as well.[2025] William Connor, notorious for omitting large amounts of literature in his "reviews," accused the Board thusly, "As scientists they omitted a good part of the evidence."[2025] DeWitt Goodman, chairman of AHA's Council on Arteriosclerosis, accused the Board of "expressing biases, not scientific-based conclusions."[2025] And Jeremiah Stamler said the Board conducted "bad science," ignoring "a whole chunk of scientifically based data."[2701] (Both Connor and Goodman would later become members of the Board and participate in one of the most biased reports ever prepared and practically every report published by Stamler omitted substantial amounts of data opposing the diet-CHD hypothesis.) In addition, some members of the Board were also accused of having financial ties with industry. Some or all of the accusers would also have financial ties with industry.

On the other hand, the AMA's Philip White praised the Board's report, maintaining that the diet-CHD promoters were supported more by hypotheses and suggestion than to scientific proof.[2701]

In 1981 Robert Levy again stated that "In man...there is still some doubt whether lowering cholesterol will result in a reduced incidence of heart attack."[1846]

Another major failure to support the risk factor concept was announced in 1982.[471,474] The $115 million MRFIT study failed to show benefits of simultaneously reducing blood cholesterol, hypertension, obesity and smoking. Bishop cited an unnamed MRFIT official as saying that "The MRFIT is by no means the first, nor will it be the last, large human medical experiment to fail."[1995]

Also in 1982 Grundy et al. published the rationale of the AHA's diet heart statement.[499] It consisted of essentially the same literature as in earlier years. Only a small part of the experimental diet literature was cited and most of these studies were of questionable validity, as discussed in Chapter 5.

The AMA issued another position statement in 1983.[2890] It read, "...some recent studies have shown an increased incidence of malignant neoplasma in sample populations with levels of plasma cholesterol less than 180 mg. ...it is possible that plasma cholesterol levels may correlate with different diseases at the upper and lower extremes of cholesterol distributions in western populations." Nevertheless, the AMA concluded that "...the evidence reinforces the concept that a strong relationship exists between lipid metabolism and atherogenesis. The Council...recommends that any person younger than 60 years with 'overt hypocholesterolemia,' as defined by the 90th percentile for his or her age and sex, deserves dietary treatment and, if this is not successful, drug therapy. The AMA adopted the AHA diet recommendations of 30% to 35% of calories as fat, 10% as saturated fat, and 300 mg of cholesterol. However, while the AHA recommended up to 10% of calories as polyunsaturated fat, the AMA specified "10% or more derived from fats and oils rich in polyunsaturated fatty acids." Thus, the AMA recommended what it previously said was impossible for patients to do, calculate the quantities of specific nutrients in their diets.

1984 was a banner year for the NHLBI/AHA alliance, not because of new evidence but rather because the alliance found a new and powerful ally in the media. The second of NHLBI's clinical trials was published in early 1984.[500] Although the trial findings were touted by its authors to be conclusive, they were severely criticized within the medical community. For example, former AHA president, Irvine Page, emphasized that "Despite a determined effort on the part of the LRC-CPPT to convince the public that at long last we now had the answer for the cholesterol problem, the results were disappointingly unconvincing. Nevertheless, the uncritical major media praised the trial and indicated that all doubt was now eliminated with respect to diet and CHD, even though the trial used a drug, not a diet, to lower blood cholesterol level and even though the total numbers of deaths in the treatment and control groups after 10 years were effectively identical. The media proved to be anxious to spew as much of the alliance's dogma as it could provide and it appeared unwilling to present views of others.

In late 1984 NHLBI convened a 13 member "consensus" panel (all appointed by NHLBI) and a "consensus" conference, supposedly to review research to date and prepare a consensus report outlining a program to institute its recommendations. As expected, the one-sided panel told the press that its diet change recommendations were similar to those of the AHA and the Inter-Society Commission.[2012] Indeed, since the AHA, Inter-Society Commission, American Health Foundation, NHLBI and others were all now controlled by the AHA, the Prudent Diet was the inevitable recommendation by the panel.

There was considerable disagreement among medical researchers attending the conference.[a] Edward Ahrens, one of the long-time leading researchers in the diet-CHD field, pleaded with the panel to note dissenting opinions in the panel's report but his request was denied.[264] The Panel concluded that high blood cholesterol was a cause of CHD and that the public should be educated on this matter.[253,711] Panel chairman, Daniel Steinberg, emphasized that "we think all Americans are at an unnecessarily high risk of coronary heart disease, largely because of the kind of diet we eat."[2120] (Note the word "think.") Michael Oliver, a participant at the Conference, observed that the panel "was selected to include experts who would, predictably, say that...all levels of blood cholesterol in the U.S. are too high and

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[a] 203,261,270,820

should, be lowered. And of course, this is exactly what was said."[1843] Oliver suggested that the conference might be better described as "nonsensus," rather than consensus.[a] Robert Olson concurred.[3056] And two researchers who were highly critical of the fact that the LRC study failed to demonstrate longevity, Paul Meier and Thomas Chalmers, noted that "we were as welcome as ants at a picnic."[2523]

The Consensus Conference represented the second contrived event that was designed to appear objective and comprehensive to the public and physician practitioners. As noted by Ahrens, the Conference essentially was organized to publicize pre-planned agreements.[1844] While the National Cholesterol Education Program (NCEP) was said to have been conceived at this conference,[1575] it and "consensus" were obviously conceived long before the conference took place. This was evidenced by the fact that the panel represented only NHLBI and that it totally rejected all dissenting opinions and refused to even suggest to the public that there was any controversy whatsoever. More important evidence was presented by Ronald Goor a few months after the conference. Commenting on the results of a 1983 survey of physicians and the public at large concerning their attitudes on blood cholesterol with CHD, Goor indicated that the survey was, in reality, the first step by the NHLBI and AHA in a national campaign to "educate" physicians and the public.[265] Since Goor was the coordinator of the NCEP, it is obvious that the program was initiated well over a year before it was announced to have been conceived at the "consensus" conference. And even more important evidence was documented by NHLBI director, Claude Lenfant, in a 1986 article in Circulation, namely, "In January 1984, the results of the NHLBI-sponsored CPPT were announced. Immediately after the announcement the NHLBI began to develop plans to ensure the widest possible dissemination of the CPPT results. Included in the Institute plans was a national education program modeled on the NHBPEB."[2086] This quote proves that the NCEP was conceived before the Consensus Conference and it effectively proves that the Conference was a sham. There is little doubt that the NCEP was being formulated in 1983.[b] The results of NHLBI's clinical trial were known and plans were established for their presentation to the public. Plans were apparently set also for the consensus conference. The NHLBI clearly wanted to determine the impact of the trial, the consensus conference and also the first elements of the NCEP on physician and public attitudes and so it quietly conducted its survey in 1983 for comparison against a later (1986) survey.[515] In fact, Basil Rifkind, Project Director of the clinical trial, attributed those events to changes in physicians' attitudes.[659] Claude Lenfant was chairman of the committee charged with establishing the course of the NCEP.[251]

The Consensus Conference report was published in early 1985 and was effectively redundant to numerous NHLBI/AHA reports.[1845] In addition to advising all Americans to adopt the Prudent Diet, it was stated that "Further research should be encouraged to compare the effectiveness and safety of currently recommended diets with those of alternative diets." In other words, the Panel recommended the consumption of the Prudent Diet, followed by an evaluation of its effectiveness and safety. The entire American population was effectively to become subjects in the alliance's giant experiment.

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[a] Crile observed that "It is lucky we did not have consensuses in the days when bloodletting was popular; we might still be doing it."[2076]

[b] Additional discussion of this topic is presented in Chapter 10 under a subsection entitled, "Claude Lenfant."

And now the alliance between NHLBI and AHA, with the support of the USDA, the Congress, FDA and the FTC, was fully formed, armed and financed to launch a media blitz intended to convince every man, woman and child to fear and change their diets. How successful has the blitz been? In the 1983 survey only 39% of the physicians polled believed that lowering blood cholesterol levels would have a large preventive effect on heart disease.[265] In 1986 this percentage rose to 64%.[660,1242] The percentage increase among the public was much smaller, from 64% to 72%.[657,659,1274] However, not only was the public more convinced to begin with, the stated initial goal of the NCEP was to change physicians' attitudes.[265,656] In fact, a project entitled "Physicians First," headed by the ex-director of NHLBI, Robert Levy, was established to "...target physicians as the first audience for education about cholesterol."[516] To illustrate the magnitude of this effort, one subproject involved John Hopkins and Columbia Universities which provided an "education" program for more than 40,000 physicians.[99] Obviously, NHLBI and AHA accomplished a great deal toward achieving that goal and subsequently continued their campaign to convince everyone. An NHLBI spokesperson expects the campaign to last for decades.[1005,a]

The NHLBI/AHA plan was the following. Mass screenings of Americans would occur across the country to obtain quick blood cholesterol measurements. Small, portable (and highly unreliable and inaccurate) instruments such as "finger stick" devices would be located at convenient places for quick measurements at a relatively low cost.[956] Simultaneously, physicians were being urged by NHLBI to routinely measure the cholesterol level of every patient over 17 years of age, regardless of the purpose of his/her visit.[952,953,957] The NHLBI has been sending doctors an NCEP "Physician's Kit," containing various materials on cholesterol, including a pamphlet entitled "Cholesterol Counts."[957] One package to physicians from the AHA contained so much material it weighed more than six pounds.[1233]

As noted in Cardiovascular News, the mass screening programs were expected to produce a "flood of patients seeking treatment."[609] Another article described the situation similarly, "...I believe that the cholesterol dam is about to burst..."[702] The new coordinator of NCEP, James Cleeman, was quoted as saying that 25% of all adult Americans will be told by their doctors that they have dangerously high blood cholesterol levels.[616] This was estimated to be a definite 40 million, as well as millions of additional "borderline" people.[952,1575] Perhaps the state-of-affairs was best described by the title of an editorial on the subject in a well-known medical journal, namely, "what an opportunity."[607] All of this will occur despite the fact that the measurement of cholesterol is exceedingly unreliable. All physicians, hospitals and independent laboratories obtain widely different measurements and this fact is well-known to the research community and particularly to NHLBI. (Chapter 8 in Volume 1 and this volume describe the magnitude of this measurement problem.)

A recent report by the Office of Technology Assessment, an investigatory arm of the U.S. Congress, announced that "Cholesterol screening for the elderly would probably have little effect on death rates, but would cost Medicare up to $5.4 billion."[1902] More importantly, after four years of study the U.S. Preventive Services

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[a] Louis Horlick, Chairman of the 1988 Canadian Consensus Conference on cholesterol, noted the large difference in physicians' attitudes between the 1983 and 1986 surveys and asked, "How can we explain this rapid and dramatic change in attitude?"[1732] This is analogous to asking why a man lies prone on the ground after he is hit on the head with a sledge hammer.

Task Force, an arm of the Secretary of Health, recently concluded that the evidence was inadequate to support the alliance's recommendation that all Americans should have their cholesterol levels measured.[1937]

In anticipation of the mass fear that is being generated among Americans, the food industry is producing a whole new generation of food products, including meats, that will contain lower amounts of cholesterol and saturated fat. An artificial fat developed by Procter and Gamble is currently awaiting FDA approval.[1299] The Food and Drug Administration will establish new standards of labeling the cholesterol and saturated fat content of food and will participate with NHLBI and AHA to "educate" the public.[653,a] In effect, these organizations set into motion a chain of events that will have enormous consequences, some of which will be completely unpredictable. The medical, food and pharmaceutical industries, as well as the cholesterol measurement device manufacturers, will have huge new sources of income. For example, some 100 million "preliminary" cholesterol tests at $10 to $15 each were performed in 1986 at a total consumer cost of $1 to 1.5 billion.[597,1005] These types of tests are expected to increase to a total cost of $3 billion.[1045] Since 25% of the population is expected to show "dangerously" high cholesterol levels on initial tests, they will be recommended to undergo complete cholesterol tests (see Chapter 8), estimated by NHLBI at a cost of approximately $300 each.[952] If the estimate of 40 million at risk is correct, the total annual cholesterol testing costs could exceed $12 billion. And this does not include physicians' fees.

Drug manufacturers are also reaping huge profits. Those who are being told to take cholesterol-lowering drugs for life, estimated at 2 million people, can expect annual costs to range from $1,500 to $3,000.[952] Some writers have estimated that the total sales of drugs will reach $4 billion annually.[1012] The sales of one drug alone is predicted to be more than $1 billion.[1011] However, it would seem that the actual amount will be much greater because the potential is $3,000 times 5% of the population or $36 billion.

Cholesterol test instrument manufacturers, of course, are also reaping large profits. New desk top instruments for physicians' offices sell for $800 to $10,000, while larger and more sophisticated instruments for laboratories and hospitals will cost much more.[1003] Sales to physicians, independent laboratories and hospitals is expected to top $3 billion per year.[1051]

Finally, the food industry is gaining billions of new revenues from the sales of special low cholesterol, low saturated fat foods just as they benefited from the higher priced "dietetic" line of foods. For example, NutraSweet received the first FDA approval in early 1990 of a fat substitute called simplesse.[2656,3146] Simplesse is currently being sold in an "ice cream" called Simple Pleasures.[3145,b] The fat

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[a] In 1988 FDA Commissioner Frank Young submitted a letter[2243] and a single copy of FDA Consumer[2242] which promoted the Prudent diet to U.S. physicians and offered 25 additional copies upon request.

[b] Cannot be called ice cream because it contains no cream. A container of Simple Pleasures was found by this writer to be one-quarter the size but one-half the cost of a relatively expensive ice cream (half-gallon of Dryer's). Thus, the retail cost is about 100% more than that of ice cream. It apears to contain about the same number of calories as ice cream.

substitute is composed of milk and egg proteins.[2625] As of this writing Procter and Gamble's artificial fat, olestra, has not yet been given approval. This fat is composed of 6 to 8 fatty acid molecules, instead of three, and is too complex to break down by intestinal enzymes.[1454,1455,1458] Thus, it is not absorbed in the intestinal wall. Methods are being developed to remove cholesterol from eggs, butter, beef fat, etc.[1422,1454,1752] Also, some researchers announced that removing hormones from the diets of cattle results in much lower fat content in beef,[1421] while others reported that adding hormones to the diets of hogs accomplishes the same thing for pork and ham.[1418] In the past, the higher prices for USDA "Choice" (fattier) beef has been attributed to the higher cost of fattening cattle in feedlots, rather than allowing them to feed on range grass. Now, so-called "light beef" is being produced by the "old" method of range feeding without hormones and is being retailed at more than $1 per pound more than regular beef.[1421] Also, eggs derived from chickens fed fish oils will have a somewhat lower content of cholesterol and will retail at about 40% more than regular eggs.[1419]

"Light" food sales doubled from 1979 to 1988, reaching $2.5 billion, with an expected sales of $4 billion by 1992.[2624] Literally hundreds of low-calorie foods are being introduced by food manufacturers each year.

The abuses of scientific ethics and conflicts of interest literally abound and there is little doubt that many NHLBI/AHA member's are receiving lucrative financial rewards for commercializing their own "scientific" recommendations. Both NHLBI and AHA are selling cookbooks.[1257,1668] Key supporters, such as William Connor, Ronald Goor and William Castelli, have also published cookbooks.[1256,1667] In addition, AHA advertises its herb seasonings as replacements for salt.[806]

But perhaps the most offensive behaviors of the NHLBI/AHA "scientists" are their financial arrangements with the food and drug industries. For example, as part of the NCEP, an AHA publication called "Cholesterol and your heart" was distributed by Procter and Gamble as a promotion for their Puritan Oil.[696] Materials on Puritan Oil were sent to physicians.[1370] The director of the Framingham Heart study, William Castelli, allowed his name and position to be used on such materials to give them credibility.[1053,1054] Former AHA president, Antonio Gotto, Jr., using a Baylor College of Medicine, The DeBakey Heart Center letterhead[1620,1644] and other advertising materials, essentially promoted Puritan Oil to physicians via the mail. And the AHA is outrightly promoting Mocha Mix, a non-dairy creamer.[1626]

Castelli, Gotto, Jeremiah Stamler and others are promoting the Quaker Oats Company's cereal products by allowing their names to be associated with such products.[1624]

Frederick Stare also allowed his name to be used on a pamphlet advertising Puritan Oil.[1372] In this pamphlet, Stare stated that high blood cholesterol is associated with CHD and cited two experiments and a clinical trial as evidence. Both experiments had nothing to do with CHD and the clinical trial found no effects of reducing blood cholesterol. He also cited two prospective studies as showing that saturated fat increases blood cholesterol, although both studies found no effects whatsoever.

As discussed in some detail in Chapter 9, numerous NHLBI/AHA researchers receive "consulting" fees and own stock in food and drug companies whose products they "research" and promote.

The network between government, industry and science is ominous. For example, a Procter and Gamble employee is a member of the AHA's board of directors.[692] The American Pharmaceutical Association is currently on the NCEP Coordinating Committee.[954] Drug Manufacturers are prolifically promoting their cholesterol-lowering drugs to physicians.[1386] As noted by Waldholz of the Wall Street Journal, much of the NCEP program is being financed by the food and drug industry.[1629] Also supported by industry is the media blitz which began in 1988 by the American Medical Association, spearheaded by James Sammons, Executive Vice-President of the AMA.[a] His promotions appeared in letters to physicians and in magazine advertisements and television programs.[b] He assured physicians of financial rewards by stating that "The AMA's campaign against cholesterol will bring both old and new patients to you for necessary testing, counseling and care."[1632] He also promoted a company owned by television's Arthur Ulene and Norman Lear who capitalized on the cholesterol scare with television sales of a cholesterol-lowering book.[1629,c] In an editorial in Patient Care, Edsall said, "Let us...regard this alignment of the interests of business and good health with a thankfulness almost completely free of skepticism."[2042] How incredibly naive!

The above description of the network between government, industry and certain members of the scientific community is brief and not at all representative of its true magnitude. Unfortunately, despite the tens of billions of dollars which will be borne by the American public, the average person's health will not likely be improved and the health of many, in fact, will likely be harmed, as later chapters will show.[d]

In October 1987, two years after the Consensus Conference, the first report of the NCEP campaign was announced[3100] (published in January 1988[1066]). The report, which senior author DeWitt Goodman[2034] falsely claimed incorporates "more fully the current state of knowledge about cholesterol and CHD," encouraged all physicians to measure cholesterol levels of all patients and provided guidelines for treatment of "high" levels, the latter being lower than specified previously. It also recommended that complete lipoprotein analyses be performed on those with cholesterol levels above 240 mg and on those with levels between 200 and 239 mg who have CHD or two risk factors. This was recommended despite the fact that cholesterol measurement nationwide was known by NHLBI to be inaccurate, particularly measurements of lipoproteins. Former NHLBI director Levy informed the press that "The report will for the first time take

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[a] While Sammons was putting together the AMA's "Campaign Against Cholesterol" in 1987, he was simultaneously "misappropriating" over $400,000 of AMA funds.[3095,3096] After much in-fighting in 1989, Sammons annunced that he would retire on March 31, 1991 but subsequently resigned in early 1990.[3097] Having generated much anger among the AMA members (e.g.,[3098]), it is dumbfounding why the AMA did not force him to retire upon acknowledging his misappropriations.

[b] 1630,1631,1632,1633,1657,2040,2041

[c] A Medical Tribune editorial suggested that Arthur Ulene's expertise "would seem to lie more in cable TV packaging and expostulating" than in showing how to lower blood cholesterol.[1714]

[d] The cholesterol dogma has international ramifications as well. For example, many American food manufacturers have stopped or substantially reduced imports of palm oil from Malaysia, seriously affecting that country's economy.[1682,1683,1684]

the mystery out of LDL for most doctors."[3100] Chapter 3 shows that LDL is still a mystery to the alliance!

As indicated earlier, the NHLBI/AHA alliance was most disturbed with the 1980 Food and Nutrition Board's conclusions regarding diet and CHD. The alliance avoided further disturbances by handpicking the Consensus Conference Panel in 1984. Also, the alliance selected a new Board in 1984 which, in turn, selected the Committee on Diet and Health. Further, the alliance handpicked a staff in order to prepare a redundant report under the guise of the Surgeon General's office. As noted in Internal Medicine World Report and others,[2325] both the Surgeon General's report and the Food and Nutrition Board's report,[1976] published in 1988 and 1989, respectively, "were produced by similar consensus process involving many of the same experts."[2078,a] In effect, they represented the third and fourth contrived events that were designed to appear objective and comprehensive to the public and physician practitioners.

The Committee on Diet and Health was said to have participated in a 3.5 year study which led to their 1989 document, "Diet and Health."[1976] Thomas noted that the chairman of the Committee, Arno Motulsky, "seems an odd choice to lead a blue-ribbon diet and health panel," in view of the fact that he is a medical geneticist.[1937] However, when it is recognized that agreement with NHLBI is vastly more important than relevant expertise, his choice was not at all surprising. Motulsky said that "Diet does, indeed, influence the risk of several chronic diseases. The evidence is very strong for atherosclerotic cardiovascular disease and hypertension..."[2075,2078] Of course, if it <u>were</u> "very strong," there would be no controversy and no need for the present document.

The Food and Nutrition Board appears to have used a rehearsed script in responding to the media. For example, Committee vice-chairman DeWitt Goodman, said that "What's special about this report is not that it's all new but that it's immensely, thoroughly documented.[1977] The director of the Board, Sushima Palmer, also said that "the idea of the report was not to make news but rather to subject nutrition health research to a vigorous, comprehensive review.[1933] And Committee chairman Motulsky exclaimed that "by drawing from the vast and diverse epidemiologic and laboratory data base, the Committee has attempted to ensure a comprehensive and critical review."[1976,b] But all of these statements were entirely false. The document was neither a comprehensive nor a critical review. Its recommendations were essentially carbon copies of those expressed by the AHA for many years. To exemplify its bias and lack of comprehensiveness, consider the Committee's "review of dietary cholesterol experiments. While some 60 such studies have been published, the Committee reviewed only five, three of which were authored by long-time AHA supporter William Connor and all of which produced confounded and/or nongeneralizable results (see Chapter 5). Chapter 9 provides many additional examples of strong bias and lack of comprehensiveness by the Committee.

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[a] While the 1988 Surgeon General's report was critical of the American diet, Harper pointed out that the 1979 Surgeon General's report stated that "The health of the American people has never been better."[2325] Both reports were published more than a decade after the CHD mortality decline began.

[b] Haglund noted that the Committee's repeated statements that their report was comprehensive were "at times as a defense against the complaint that their product was, frankly, predictable."[2121]

In 1988 the AHA published another statement repeating its dietary recommendations. It maintained that "For more than 25 years, the AHA has recognized the large body of scientific evidence linking dietary factors to the etiology of arteriosclerosis. During this period, additional epidemiological studies, animal experiments, and clinical research have strengthened the evidence."[2632] As evidence the AHA cited the biased and sometimes illogical reviews of AHA supporters, Grundy et al.[499] and Stamler.[1313] The statement was also replete with errors, inconsistencies or misleading implications. For example, it was said that "since low-fat foods provide more bulk per calorie, they are a logical choice in an eating pattern designed to achieve and maintain the individual's best body weight." As noted elsewhere in this volume, fats move more slowly through the gastric system than carbohydrates, reducing the hunger response. There is probably more obesity within subpopulations in the U.S. which consume high carbohydrate diets.

It was also said that "All cells in the body can make cholesterol," although nervous tissue does not, and that "there is no biochemical or physiological evidence that cholesterol is required in the diet," but also no evidence that dietary cholesterol is not required. Moreover, while urging Americans to reduce total fats to less than 30% of total calories, the statement praised the high fat diets of Mediterranean populations who presumably have very low incidences of CHD.

Perhaps its most gross and misleading error was the statement that "cholesterol intake has its greatest effect in the presence of high saturated fat intakes." Not only are the effects of cholesterol independent of the amount of fat, except for the minimal amount necessary for solution and absorption, they are also independent of the type of fat. The AHA and NHLBI frequently cite the equations of Keys and Hegsted (Chapter 5) which clearly give dietary cholesterol independence.

In sum, the sloppiness and/or incompetence reflected in the 1988 AHA statement was representative of its long-time lack of concern for scientific knowledge and reasoning.

Under continuous bombardment from the AHA and industry the FDA established a policy in 1987 not to enforce its mandate to prohibit health claims on food labels. There ensued an enormous proliferation of health claims and in 1988 the AHA announced that it would assume the FDA's and FTC's roles of regulating food labels and advertising via its HeartGuide[a] seal and media promotions.[1563,1571,1611] Perhaps in response to this announcement or simply to the appalling proliferation of false and/or misleading health claims, the FDA Commissioner Fran Young told Congress in 1989 that new labeling laws were necessary to provide consumers with necessary nutrition information and prevent misleading health claims.[2882] New White House approved FDA regulations were announced by Health Secretary Louis Sullivan in February, 1990 and simultaneously published.[2882] These regulations prohibit all health claims on labels except for a few cases. A food manufacturer may say that calcium may help prevent osteoporosis, that low fat and dietary fiber may reduce the risk of heart disease and cancer, and that low sodium may reduce the risk of hypertension.[2594] In order to use these health claims, a food company must submit scientific evidence to the FDA which satisfactorily demonstrates that their product qualifies.[2881]

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[a] Discussed in a later section of this chapter.

Secretary Sullivan also announced in March, 1990 that the FDA would propose new labeling requirements which will include facts about the fat, cholesterol and fiber contents of foods.[2620,2877,2883] Such proposed laws would presumably be created in 1990 and take effect in late 1991.[2883] By May, food labeling legislation was moving through both houses of Congress and the FDA was working on rules to enforce the legislation, as well as a complete nutrition-labeling instrument.[2885]

In 1990 the AMA, now a virtual puppet of the AHA, indicated that the consumption of tropical oils should be avoided, despite the fact that former FDA commissioner Young indicated that they represented a very small percentage of total calories consumed by Americans.[2605] As discussed in Chapter 5, the transition from tropical oils to hydrogenated vegetable oils was already well underway with most food manufacturers before the AMA statement. Interestingly, the AMA indicated no concern with the potential harmful effects of greatly increased consumption of trans isomers, the inevitable product of the hydrogenation process. The 1990 AMA statement cited a 1988 AHA dietary guidelines report[3632] as indicating that total fat intake in the U.S. is currently 37% of total calories. That was a correct citation. However, the AMA statement then cited the 1988 Expert Panel report as indicating that "many Americans consume 15% to 20% of their total energy intake as saturated fatty acids." Such a statement was misleading because it omitted the more important information in the Panel's report, i.e., the Panel said, "The average intake is 13% to 15% of total calories, but many Americans consume 15 to 20% of their calories as saturated fatty acids."[1066] It would appear that the AMA purposely selected that portion of two sentences from two reports which yielded the most exaggerated intake value.

Also in 1990 the NCEP finally adopted all of the AHA dogma by recommending the Prudent diet to all Americans above the age of two, and not simply to those with cholesterol levels above 200 mg.[2652,2653] While NHLBI director, Claude Lenfant, stated that "we feel...that the scientific evidence is so convincing that we have a responsibility to proceed with cholesterol-lowering recommendations for the general population," the chairman of the NCEP report, Richard Carleton, was vastly less certain, i.e., "For those with desirable levels of cholesterol, the evidence is that bringing down the levels will not harm them--and is likely to be beneficial." But such a statement runs counter to dozens of studies cited in Volume 1 and in Chapters 3 and 8 of this volume.

BIG BROTHERS' DIETARY RECOMMENDATIONS

Introduction

There is little doubt that the AHA has long been the driving force behind the diet-blood cholesterol-CHD concept. One by one all other groups, including NHLBI, eventually succumbed to its dogma, and each has been faithfully preaching its dogma ever since, word-for-word. Today the AHA is the undisputed leader of the largest group of medical research followers in the history of medicine. Like the Pontiff of Rome, the AHA has never been wrong on matters of faith, even if it has been wrong on matters of science. When it has committed a scientific error, it has rewritten history and altered its recommendations and the faithful have blindly accepted the new proclamations without question.

In April 1991 this writer debated a cardiologist and a nutritionist from the AHA on a talk radio program in Los Angeles. The nutritionist told listeners that the AHA has always given the American people the same dietary advice with respect to heart disease. I responded by saying, "That is absolutely false" and I indicated that for

many years the AHA effectively encouraged Americans to "load up" on polyunsaturated fats, a recommendation that it would later deny having made. This section examines the AHA's recommendations and shows how it subsequently covered its own tracks. A brief history of the American Medical Association's dietary recommendations follows. But it is first important to review some events in the 1950s.

Events Leading to Dietary Recommendations

What seems to escape most everyone, perhaps because few follow the literature carefully, is that the alliance rewrites history as new data emerges which contradicts previous arguments. Probably the first major rewrite was associated with fat consumption trends during this century. In the 1940s and early 1950s the alliance knew nothing about the differential effects on blood cholesterol of the different types of fatty acids.[a] For example, in 1953 Keys[279] believed that total fat was the factor in altering blood cholesterol levels. He described many experiments showing that high fat and low-fat diets increased and decreased cholesterol levels, respectively. He said, "The foregoing emphasizes the role of the total dietary fats in determining the serum cholesterol concentration. All the data summarized here suggest an important chain of relations between the total fat content of the diet (or the proportion of fat calories of the total metabolized), the cholesterol (and lipoprotein) concentration in the blood, the development of atherosclerosis, and the mortality from degenerative heart disease."

Keys published his 6-countries study in his 1953 article which showed a near perfect curvilinear relationship between fat calories as a percentage of total calories and heart disease death rates. This near perfect relation evoked the following: "Obviously the relation shown...[see Figure 4-1 in Volume 1]...is too regular and too marked to be explained on the grounds of possible differences between countries in the criteria for death certification."[b]

Keys continued, "The present high levels of fat in the American diet did not always prevail and this fact may not be unrelated to the indication that coronary disease is increasing in this country. From the statistics of the U.S. Department of Agriculture it is clear that the biggest contributor to the fats in the American diet is fats and oils as such, excluding butter which comprise 46.5% of the total. Meats, poultry and fish combined make a poor second at 22.1%. Any attempt to reduce the total fat intake must, then, begin with cooking fats and oils." Keys repeated this argument in another 1953 article.[3296]

Figure 2-1 shows Page 85 of the 1960 Statistical Abstract of the U.S. When Keys published his 1953 article, butter and lard had been decreasing since 1930 and 1940, respectively, while margarines, shortenings and other edible oils had been increasing for decades. In other words, animal fats had been decreasing, while vegetable fats had been increasing. Thus, when Keys stated that "Any attempt to reduce the total fat intake must, then, begin with cooking fats and oils," he was obviously referring primarily to vegetable fats. And very importantly, Keys made it absolutely clear that he believed animal and vegetable fats had identical affects on blood cholesterol, i.e.,

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[a] A few studies showing that vegetable fats reduced blood cholesterol levels were published in 1952 and thereafter but apparently were not taken seriously by Keys and others until several years later.

[b] As emphasized in Chapters 3 and 4 in this volume and Volume 1, this statement is untenable. However, the matter is irrelevant for present purposes.

"There is no indication of a difference in animal versus vegetable fat in evoking the serum response."

In 1956 Keys[280] still did not differentiate between animal and vegetable fats. To lower cholesterol he said that "A reasonable, practical conclusion from the present evidence might be to propose for American adults a sharp reduction in the total dietary fat from their current average intake in which fats account for some 40% or more of the total dietary calories."

Katz, Stamler and Pick published two articles in 1956[694,3201] and they also concluded that total fats (and cholesterol) were the cause of atherosclerosis. They said that a reduction of "total calories in the form of fat from the present 40-60% to a reasonable 25-30%" would "solve most of the problems of the present day 'rich' and unbalanced American diet."[694] They concluded, "Almost certainly, our general framework of reference, the cholesterol-lipid-lipoprotein theory, is sound."

Stare[2094] also indicated in 1956 that animal and vegetable fat consumption had been decreasing and increasing, respectively, for the last 20 years. Not only did he conclude from both USDA and survey data that a real fat increase probably had not occurred, he emphasized that "It should be obvious that much of what we hear these days (mid 1950s) about changes in our intake of fat--animal versus vegetable, saturated versus unsaturated--is not consistent with published facts."

The foregoing leaves no doubt that principal alliance members such as Keys and Stare fully recognized that the major dietary fat increase in the American diet during the first 50 years of the 20th century was of vegetable origin. Keys did not know in 1953 that animal and vegetable fats affected blood cholesterol levels in opposite directions and Stare indicated in 1956 that the fat consumption trends were not consistent with the new claims in the mid 1950s that Americans were increasing their consumption of animal fats.

In 1957 Irvine Page, Stare and co-workers[512] prepared a report for the AHA in which they "summarized and evaluated evidence for and against the concept that the fat content of the average present-day North American or North European diet is a significant factor in the genesis of cerebral, myocardial, renal, or peripheral atherosclerosis." They cited Keys' concept that variations in the proportion of fat in the diet affect blood cholesterol levels even when calories and other nutrients are held constant but indicated that the available data were confounded by other variables. They said that "There has indeed been a tendency to gloss over data that would run counter to the proposition that high-fat intake, plus hypercholesterolemia, results in atherosclerosis."

Page et al. cited the Katz, Stamler and Pick[694] (above) as stating "unequivocally that the fat content of the American diet has increased. To prove his [their] point, he [they] cited data from the Department of Agriculture going back to 1910. But these data are of food estimated to be available at the retail level and are really no true measure of the actual food consumed. The data have not been adjusted for waste in homes or wastes in institutions." They asked, "how much fat is discarded after the cooking of meats, bacon, or fat frying? Have not the cooking methods changed in this country so that more food is broiled and excess fat discarded?" As an example, they pointed to "the tremendous fat collection from kitchen waste during the war years...as...an indication of the degree of loss." Page et al. acknowledged that the proportions of animal and vegetable fats in the diet had decreased and increased, respectively, and concluded that "the propostion that the character of the American

No. 105. Nutrition—Apparent Civilian Per Capita Consumption of Major Food Commodities: 1910 to 1959

In pounds, except as noted. Data on calendar year basis except as follows: Dried fruit, pack year; fresh citrus fruits and rice, crop year beginning previous year; peanuts, crop year beginning September of year indicated; and prior to 1950, canned fruits and vegetables on a pack year. Excludes Alaska and Hawaii. Based on Bureau of the Census estimated population as of July 1. See also *Historical Statistics, Colonial Times to 1957*, series G 552-584]

COMMODITY	1910	1920	1930	1940	1950	1955	1957	1958	1959 (prel.)
Meats (carcass weight), total	146.4	136.0	129.0	142.4	144.6	162.8	159.1	162.0	158.5
Beef	70.4	59.1	48.9	54.9	63.4	82.0	84.6	80.5	81
Veal	7.2	8.0	6.4	7.4	8.0	9.4	8.8	6.7	5.8
Lamb and mutton	6.5	5.4	6.7	6.6	4.0	4.6	4.2	4.1	4.5
Pork (excluding lard)	62.8	63.5	67.0	73.5	69.2	66.8	61.5	60.7	67
Fish (edible weight), total	(1)	(1)	10.3	10.6	11.6	10.4	10.1	10.4	10.3
Fresh and frozen	(1)	(1)	5.9	5.8	6.4	6.0	5.6	5.6	(1)
Canned [2]	(1)	(1)	3.4	4.2	4.5	3.8	3.9	4.2	(1)
Cured	(1)	(1)	1.0	0.6	0.7	0.6	0.6	0.6	(1)
Poultry products:									
Eggs (number)	306	299	331	319	389	371	358	349	354
Chicken (ready-to-cook)	15.5	13.7	15.7	14.1	20.6	21.4	25.5	28.3	29.8
Turkey (ready-to-cook)	(1)	(1)	1.5	2.9	4.1	5.0	5.9	5.8	6.0
Dairy products:									
Total milk fat solids	29.7	28.9	32.1	32.5	29.4	27.3	26.4	26.2	26.0
Total nonfat milk solids	34.7	37.3	38.5	40.8	45.9	47.9	47.7	47.6	48.0
Cheese	4.3	4.0	4.7	6.0	7.7	7.9	7.8	8.2	8.3
Condensed and evaporated milk	5.8	8.6	13.6	19.3	20.1	16.2	15.4	14.8	14.1
Fluid milk and cream	315	348	337	331	349	352	350	345	348
Ice cream (product weight)	1.9	7.6	9.8	11.4	17.2	18.0	18.0	17.8	18.3
Fats and oils, total, fat content	(1)	(1)	(1)	46.4	45.9	45.9	44.4	45.9	46.5
Butter, farm and factory (actual weight)	18.3	14.9	17.6	17.0	10.7	9.0	8.5	8.4	8.3
Margarine (actual weight)	1.6	3.4	2.6	2.4	6.1	8.2	8.6	9.0	9.2
Lard	12.5	12.0	12.7	14.4	12.6	10.1	9.5	9.7	9.3
Shortening	(1)	7.6	9.8	9.0	11.0	11.5	10.4	11.3	12.0
Other edible fats and oils	(1)	(1)	(1)	7.4	8.6	10.5	10.7	10.9	11.0
Fruits:									
Fresh, total	137.9	145.4	133.6	142.1	107.4	101.6	99.3	97.9	98.9
Citrus	17.8	26.0	31.2	56.7	41.2	41.7	37.0	31.0	33.7
Apples (commercial)	[3] 59.4	[3] 63.0	[3] 42.1	29.7	23.2	20.0	19.3	22.5	22.1
Other (excluding melons)	60.7	56.4	60.3	55.7	43.0	39.9	43.0	44.4	43.1
Processed:									
Canned fruit	3.6	9.4	12.8	19.1	22.0	22.6	22.4	22.7	22.9
Canned juices (excl. frozen)	0.5	0.6	0.3	7.2	13.4	12.9	12.3	11.6	10.9
Frozen (incl. juices)	(1)	(1)	0.5	1.3	4.3	8.7	9.0	8.0	9.0
Dried	3.5	6.7	5.4	6.0	4.1	3.6	3.6	2.8	3.5
Vegetables and melons:									
Fresh (total commercial) [4]	(1)	126.8	144.9	143.4	139.5	133.8	130.3	128.0	124
Vegetables	(1)	95.0	111.9	116.9	114.6	104.6	104.6	101.1	99
Melons	(1)	31.8	33.0	26.5	24.9	29.2	25.7	26.9	25
Canned	14.6	18.9	28.2	36.4	42.1	43.5	43.9	44.8	44.5
Frozen	(1)	(1)	(1)	0.6	3.4	6.6	7.5	8.1	7.9
Potatoes	198	140	132	123	106	106	106	100	103
Sweetpotatoes	26.2	29.1	18.3	16.2	12.1	8.2	7.2	6.7	6.9
Dry edible beans	6.5	5.7	9.5	8.4	8.6	7.8	7.5	7.6	7.7
Sugar (refined)	75.4	85.5	109.6	95.7	100.8	97.5	97.0	98.1	98
Grains:									
Corn products:									
Cornmeal	51.1	35.2	28.3	21.8	11.8	8.8	8.4	8.2	8.1
Corn syrup	5.4	10.1	7.4	7.9	9.2	9.0	8.9	9.5	9.7
Cornstarch	1.0	1.6	1.5	1.3	1.9	1.8	1.4	1.4	1.5
Corn sugar	1.1	0.5	5.8	2.9	4.5	3.7	3.5	3.8	3.9
Breakfast cereals	1.3	1.5	3.0	1.9	1.5	1.7	1.7	1.7	1.7
Hominy	4.5	2.6	1.7	1.7	2.6	2.3	2.2	2.2	2.2
Oat food products	3.3	5.7	6.0	4.0	3.3	3.2	3.2	3.2	3.2
Barley food products [5]	3.5	3.1	5.4	1.1	1.4	1.1	1.1	1.1	1.1
Wheat:									
Flour [6]	214	179	171	155	135	123	119	120	119
Breakfast cereals	2.7	3.0	3.2	3.3	3.1	2.9	2.8	2.8	2.8
Rye flour	3.6	3.2	2.7	2.4	1.5	1.4	1.3	1.2	1.2
Rice, milled	8.3	6.2	5.3	5.9	5.1	5.5	5.8	5.7	5.1
Beverages:									
Coffee [7]	9.2	11.7	12.5	15.5	16.2	16.3	15.7	15.9	16.3
Tea	1.0	0.8	0.7	0.7	0.6	0.6	0.6	0.6	0.6
Cocoa beans	1.2	2.9	3.0	4.8	4.6	3.8	4.2	3.7	3.9
Peanuts (shelled)	2.5	3.0	3.2	5.0	4.5	4.1	4.5	4.5	4.5

[1] Not available.
[2] Excludes canned food products containing small quantities of fish such as clam chowder, etc.
[3] Includes apples from noncommercial areas. [4] Excludes produce from rural and urban home gardens.
[5] In terms of malt equivalent. [6] Comprises white, whole wheat, and semolina flour. [7] Green bean basis.

Source: Department of Agriculture, Agricultural Marketing Service; published quarterly in *National Food Situation*.

Figure 2-1. Page 85 from the 1960 Statistical Abstract of the United States[1891]

diet has so changed during the past 50 years as to increase the incidence of coronary vascular disease cannot be supported." Further, they said, "the evidence at present does not convey any specific implications for drastic dietary changes, specifically in the quantity or type of fat in the diet of the general population." The reader should take note at this point that the Page et al. report contained 87 references, 89% of which were published between 1943 and 1958. When AHA's first formal statement on dietary recommendations is published four years later, it will include none of these references and, in fact, no references dated before 1957.

Interestingly, Keys published two articles in 1957 and was apparently not yet convinced of the differential effects on cholesterol of animal and vegetable fats, or at least considered such early findings to be anomalies.[276,2838,a] He still believed that total fat was the key to cholesterol levels. These articles, in part, attacked the then "dilemma" that Eskimos have exceptionally high fat diets and yet demonstrate low CHD mortality rates. He said, "There is no evidence at all as to the frequency of atherosclerosis among Eskimos, let alone among the primitive Eskimos"[276] and "The fact is that nothing is really known about the incidence of CHD among Eskimos."[569] Keys also emphasized that Eskimos are not likely to have high rates of CHD because they seldom reach age 50. Years later, however, when it had long been established that polyunsaturated fats decrease blood cholesterol, Keys reversed his Eskimo argument. For example, he said "Eskimos are the only people believed to habitually consume a diet rich in polyunsaturated fats" and "The incidence of CHD is considered to be very low among Eskimos."[2838] Thus, Keys reinterpreted data to fit the current state of knowledge.

By the late 1950s both the alliance and industry were espousing the health benefits of vegetable fats, and more specifically, polyunsaturated fats. Despite his position taken in his 1957 report, Page[720] indicated in 1959 that "It is agreed that the reduction of the incidence and severity of atherosclerosis might depend, in part, on a reduction of the amount of animal fat in the national diet." He and co-author Brown suggested that an "effective" diet would have a total fat content similar to the American diet but one heavily laden with vegetable fats--as much as 83% vegetable and only 17% animal and hydrogenated fats. However, they cautioned that "There is much yet to be learned before we can recommend the present pattern as a proper modification of the American bill of fare." Stamler[376] recommended to volunteers in a Chicago program in 1960 that they consume a diet "high in polyunsaturated fatty acids...largely from vegetable and fish oils." And the makers of Mazola and Wesson oils were generating advertisements such as "science finds corn oil important to health" and "for your heart's sake," respectively.[2001]

Keys, Stare, Page and others no longer spoke of increasing vegetable fats in the American diet. Indeed, the food consumption trend data were reinterpreted to mean that animal fat had been increasing, not decreasing, in the diet, even though such interpretations were unequivocally opposite to the published facts, as Stare had stated in 1956 and as Keys had observed in 1953.

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[a] Two other articles by Keys were published in 1957 and did acknowledge the differential effects,[315,716] suggesting that the first two articles had been "in press" much longer.

The AHA Dietary Recommendations

The AHA published its first dietary recommendations to the public in 1961.[517] Although two of the authors of this statement were key authors of the 1957 report, i.e., Page and Stamler, Keys and Stamler were added and the resultant statement bore no resemblance whatsoever to the content and conclusions of the 1957 report. According to a January 1961 Time Magazine article, Keys' [modified] theory gained sanction from the AHA in December 1960.[1993,a] Indeed, the 1961 AHA statement was a complete adoption of Keys' late 1950s position and it was devoid of the 1957 insights of Page and Stare. For example, it said, "study of diets in the United States indicates that they usually contain large amounts of fat which account for approximately 40-45 percent of the calories." But, as emphasized by Page et al. in their 1957 report and by the USDA's Wells in 1959[3294] these percentages were based on food availability at retail and do not reflect the abundant waste that is associated with fat. The 1965 Statistical Abstract of the United States[1892] shows that available calories and fat in grams at retail in 1960 were 3,140 and 143 g, respectively, yielding a fat percentage of 41. The actual value after adjustment for waste would probably be about 36%, indentical to that observed in the later NHANES 1 and 2 surveys (see Chapter 3).

Although Keys, Stare and Page all noted previously that the CHD epidemic was paralleled by increasing consumption of vegetable fats, they strongly advocated the consumption of even more vegetable oils in the 1961 statement. For examples, they said, "Substitution of polyunsaturates for a substantial part of the saturated fat in the diet may also be a valuable addition to this program" and "It should be borne in mind that moderate amounts of fat, particularly those containing an appreciable quantity of the polyunsaturated type, are necessary for good health." Thus, although the reduction of total fats was moderately advocated, it was quite clear that the statement's principal focus was on recommending a high polyunsaturated, low saturated fat diet. While the AHA will much later deny this emphasis, it was nevertheless observed as such by the press, public and industry, as will be seen.

Wall Street Journal reporter Bishop quoted Page as saying that the "drastic" changes in dietary fats would be accepted by Americans.[1998] While Page undoubtedly wanted the press to believe that, it is doubtful that he did himself. Just two years earlier he had said that "On a low-cholesterol, low-fat diet, I went from a hypercholesterolemic coronary type to really very low cholesterol levels for me, and then my lipids came back up after my wife and I got sick of the whole business."[3292]

The 1961 Time Magazine's interview with Keys indicated that "polyunsaturated fats are a healthful substitute for saturated fats."[1993] Newspapers and magazines greatly amplified that message. Syndicated physician columnist Molner[2045] told his readers in 1962, "Memorize the fundamentals. Avoid the saturated fatty acids." The Wall Street Journal[2005] indicated that the AHA recommends substituting "vegetable oils and other polyunsaturated fats for animal fats." Drug stores immediately began selling bottles of artificially flavored vegetable oils high in polyunsaturated fats with the instructions to

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[a] Contrary to his 1953 statement, Keys told Time Magazine that saturated fats had "become a bigger and bigger part of the American diet."

drink it "by the spoonful to offset the effects of saturated fat in the diet."[1993,a] In 1963 an FDA survey revealed that most Americans had already accepted the notion that polyunsaturated fats were protective against heart disease."[2006]

In 1964 AHA published its second statement. This statement was not found in the medical literature and requests for a copy from the AHA in Dallas were refused by Mary Winston. A newspaper article[1990] indicated that it was similar to the 1961 statement but directed toward the general public rather than individuals "at risk."

In 1968 the AHA published its third statement and indicated desirable quantities of nutrients for consumption.[2101] Total fat was recommended to be "less than 40% of calories" and, "of this total, polyunsaturated fats should probably comprise twice the quantity of saturated fats." The statement also recommended that dietary cholesterol intake be reduced to 300 mg per day in hypercholesterolemic individuals. There was no specific reduction recommended for the general population.

The 1968 statement clearly fueled the polyunsaturated fat craze by recommending a P/S ratio of 2:1, nearly five times that existing in the American diet. The "less than 40% of total calories as fat" recommendation was effectively a recommendation to continue consuming the same amount of fat because, as noted earlier, about 36% was and is the typical amount consumed.

The early part of the 1968 statement indicated that a revision of the 1965 statement was necessary because "additional supporting data have been accumulated, particularly on the effects of diet on the occurrence rate of myocardial infarction." Such data were said to be included in five reports. Two of the five were authored by Stamler and co-workers[3287,3288] and neither presented new original data. The remaining three reports were results of three of the worst clinical trials ever conducted, two of which were nonrandomized and all of which were unblinded.[467,480,1141,b] These trials would be criticized by Cornfield and (NHLBI's) Mitchell in the following year.[488] Thus, the five cited reports were extremely poor scientific bases for the radical P/S ratio recommended in the 1968 statement.

Inherent in the 1968 statement were additional items of no little interest. For example, it said, "It should be noted that quite commonly, diets severely restricted in fats, with carbohydrate filling out the caloric requirement, may accentuate hypertriglyceridemia. Although the exact role of the triglycerides in atherogenesis is not clearly established, there is increasing evidence that hypertriglyceridemia is associated with an increased incidence of coronary disease in younger men." Perhaps more importantly, in his Lewis A. Connor Memorial Lecture in Circulation, published in 1954, Page[3289] stated that "It is pretty well agreed that in animals the drastic reduction of fat with substitution of carbohydrate for calories ultimately leads to fatty degeneration of livers and kidneys." Clearly, the AHA was being cautious regarding total fat in the 1968 statement, while being completely irresponsible with respect to polyunsaturated fats. The emphasis on polyunsaturates in the 1968 statement was reinforced by AHA's concern that an FDA regulation forbade food manufacturers "to

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[a] While Keys called this practice "nonsense" because "All this does is to increase the total fat intake and breed obesity," he and his fellow AHA members apparently could not or would not recognize that they instituted the polyunsaturated fat craze which would continue for 30 years.

[b] See Volume 1 for a detailed review.

label vegetable oil products with their actual polyunsaturated fatty acid content." The AHA was in favor of such labels and noted that following its 1961 statement "many manufacturers have made a substantial effort to increase the polyunsaturate content of vegetable oil shortenings, the lightly-hydrogenated salad and cooking oils, and especially, the tub-type margarines. Accurate labeling would make it possible to identify the brands with a high polyunsaturated fat content."

Irvine Page apparently became disenchanted with the AHA and its recommendations in 1968. He accused the AHA of "bumbling" in its search for the cause of CHD and of engaging in "scientific gamemanship that concentrate on status seeking and the hunt for more money more than productive research."[2102]

In the following year the AHA distributed a pamphlet, authored by Stare and Dwyer,[3318] that recommended diets "high in polyunsaturated fats" for all members of the family, saying that it was "best for health."

When Pearce and Dayton announced in 1971 a possible connection between high polyunsaturated fat diets and cancer, as observed in the Veterans Diet trial, the AHA's Campbell Moses falsely stated that the AHA's recommendations focused on reducing fat, not substituting high levels of polyunsaturates.[2023]

The media increased their frequency of messages to consumers regarding the benefits of high polyunsaturated fats (see Chapter 9 for a review of the frequent statements made by syndicated columnists Stare, Power, Mayer, Lamb and Brody). Suffice it here to say that some columnists promoted unlimited consumption of polyunsaturates. For example, Stare stated in 1969, "To my knowledge, I've never heard of too much polyunsaturated fat for man..."[1959] Industry responded with "a large number of items that conform to the AHA's recommendations"[2010] and the AHA continued its pressure on the FDA to permit food producers to provide polyunsaturated fat content on labels.[2008]

In 1972 the AHA published a "leaflet" entitled "The Way to a Man's Heart."[3286] It recommended that everyone consume a diet "low in saturated fat and cholesterol" and high in polyunsaturates. The recommendation for the latter was 6 to 12 teaspoons of polyunsaturates "in the form of margarine, salad dressing, and shortening." This amounts to a maximum of 56.8 g or 20% of a 2600 calorie diet for men and 24% of a 2100 calorie diet for women. By anyone's standards, such recommendations clearly encouraged high polyunsaturated fat diets. It is noteworthy, moreover, that readers were cautioned to "avoid or use sparingly peanut oil and olive oil" because "they are low in polyunsaturates and do not take the place of the recommended oils that are high in polyunsaturates. This recommendation thus indicated that the AHA did not view monounsaturates in a favorable light.

Following the FDA's approval of allowing food producers to indicate type and content of fat on labels in January, 1973[3297] that year marked the beginning of a period of major simultaneous contradictions in AHA recommendations.[a] In this fourth statement the AHA recommended a maximum fat intake of 35% of total calories instead of the presumed intake of 40 to 45% (but recall that fat intake was always under 40%).[3285] This statement advised a reduction from under 40% in 1968 to under

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[a] In an editorial in Circulation, Podell complained that the FDA did not insist that food producers indicate the saturated fat and cholesterol content on all labels.[3297]

35% in 1973. In addition, the recommended P/S ratio was reduced from 2.0 to 1.0 and the AHA recommended equal amounts of the three fatty acids. And while 300 mg of cholesterol were recommended for hypercholesterolemic individuals in the 1968 statement, that amount was now recommended for everyone. The statement indicated that the usual intake was 600-750 mg, which could not be true because the USDA total availability amount was about 530 mg (Chapter 3), meaning that actual intake after waste and spoilage was probably closer to 460 mg.

Although the 1973 statement suggested a maximum intake of polyunsaturates of about 11.7% (one-third of 35%), other AHA publications by the AHA, such as the previously noted "The Way to a Man's Heart,"[3286] recommended intakes of up to 20% and 24% for men and women, respectively. This latter publication would be promoted by the AHA throughout the 1970s.

Jean Mayer continued Stare's syndicated column and continuously encouraged the public to increase the percentage of polyunsaturates in the diet.[1978,1979]

The fifth AHA statement was published in 1978.[708] It maintained that the usual diet contained 40% of total calories as fat and recommended 30 to 35%. Both saturated and polyunsaturated fats were recommended to be no more than 10% of calories each. Thus, monounsaturates could range from 10 to 15% of calories. Intake of cholesterol remained at "under 300 mg." The statement also explicitly recommended the AHA document, "The Way to a Man's Heart," which recommended a polyunsaturated fat intake of 100% or more above that suggested in the statement.

Of interest in the 1978 statement also was the comment, current data "provide sufficient evidence to warrant taking prudent action at this time in the population at large," suggesting that such action was not recommended earlier. Of course, the AHA had been recommending such action by the public for more than a decade.

Grundy et al. presented the so-called rationale underlying the 1978 statement in 1982.[499,a] To a large extent, however, the "rationale" appeared to be an attempt to convince readers tht the AHA had never advocated high polyunsaturated fat diets. On Page 840A Grundy et al. falsely stated that "The AHA has been cautious about recomending marked increases in polyunsaturates." They went on to say that "the consequences of prolonged ingestion of large quantities of these fats are not known. To be on the safe side, the AHA has not recommended very high intakes of polyunsaturated fats for the general population." On Page 848A Grundy et al. stated misleadingly that "A common misconception is that the AHA currently recommends the intake of large quantities of polyunsaturated fats" and then falsely indicated that "the AHA has been reluctant to advocate a marked increase in polyunsaturated fats (i.e., to 15-20% of total calories) for several reasons." They then noted side effects such as cancer promotion, gallstones, cell membrane alterations, etc. and concluded that "it may be prudent for the U.S. public to avoid very large amounts of polyunsaturated fats for the present time." One page later, Grundy et al. again found it necessary to be repetitive, i.e., "the AHA does not recommend high polyunsaturated fat diets..."

Of course, by 1982 the public had already been deluged for 20 years with recommendations to consume large quantities of polyunsaturates in all forms and almost all of this long-term barrage derived directly or indirectly from the AHA.

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[a] Grundy's co-authors were Bilheimer, Blackburn, Brown, Kwiterovich, Mattson, Schonfeld, and Weidman.

Grundy et al.'s article was designed to hide the AHA's embarrassment of having made such recommendations before there was adequate scientific data to indicate that they were harmless. Such an obvious fabrication also provides an excellent example of how the alliance routinely distorts the literature to preserve its own reputation and dogma.

It is also worth noting that although the 1968 AHA statement recommended that polyunsaturates be twice the quantity of saturates, Grundy et al. falsely indicated that the statement recommended that each of the three fatty acids be qually represented in the diet.

The sixth AHA statement appeared in 1984.[3034] It was prepared by Grundy with inputs presumably by Gotto, Bierman, Connor, Ford, Frantz, Glueck, Grundy and Little. While the maximum fat intake recommended in 1978 was 35%, with equal quantities (11.7%) of saturated, monounsaturated and polyunsaturated fatty acids, the 1984 statement recommended a maximum fat intake of 30%, with equal quantities (10%) of the three fatty acids. Carbohydrates were to comprise 55% of total calories, to make up for the loss of fat and under 300 mg cholesterol remained as previously recommended.

The immediately above "diet" was referred to as Phase I. For those individuals with progressively higher blood cholesterol levels, Phase II and III diets were recommended which reduced the total fat content to 25% and 20%, respectively, and simultaneously increased carbohydrates 60% and 65%. Thus, although the AHA recommended against high carbohydrate diets in its 1968 statement, it was now advocating a diet almost completely dominated by carbohydrates. Recommended intakes of cholesterol for Phases II and III were said to be 200-250 mg and 100-150 mg, respectively.

The AHA Nutrition Committee published a seventh statement in 1985.[980,a] It's dietary recommendations were identical to those of the sixth statement in 1984. Probably the only significant aspect of this otherwise redundant article is its failure to use consistent logic. For example, in the second and third paragraphs of the article it is said that "The average cholesterol level of the population has decreased continually since the mid-1960s, probably due to changes in dietary habits and incrased exercise. This attempt to modify risk factors almost certainly has contributed to the declining death rate from heart disease in the U.S. But on the second page of the article, the authors stated that "The average American diet contains almost 40% of total calories as fat. About 16 to 18% of total calroies are saturated fats; a similar amount is monounsaturated, but only 5% to 8% are polyunsaturated." These estimates are essentially identical to those given in all previous AHA statements since 1961. The AHA's need to take credit for the declining CHD mortality rates quite clearly conflicts with its need to impress upon readers that Americans have supposedly been consuming the same atherogenic diet for 30 years.

The Nutrition Committee published an eighth statement in 1986.[1236,b] Strangely, total fat and saturated fat intakes were recommended to be "less than 30%" and "less than 10% of calories," respectively. While previous statements suggested that polyunsaturates can comprise "up to 10%" calories, the 1986 statement recommended "less than 10%," a subtle but informative difference.

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[a] Authors were Grundy, Arky, Bray, Brown, Ernst, Kwiterovich, Mattson, Weidman,Schonfeld, Strong and Weinberger.

[b] No authors were listed for this statement.

The 1986 statement indicated that "Currently, Americans are consuming an average of 15 to 20% of calories as saturated fats." It also indicated that Americans were consuming 15% and 40 to 45% of calories as protein and carbohydrates, respectively. Thus, the total fat content of the American diet, according to the authors, was 40 to 45%, the same amount specified by the AHA since 1961. Also, the polyunsaturated fat content (5 to 7%) and the saturated fat content (15 to 20%) were also essentially identical to previous statements. Recommended cholesterol intake remained at under 300 mg.

Finally, it is noteworthy that the 1986 statement recommended that polyunsaturates "contribute less than 10% of calories" because of "the relatively small amount of data on the long-term use of diets with very high polyunsaturated fat content." Clearly, far less data were available 20 years earlier when the AHA was recommending large quantities of polyunsaturates.

The ninth AHA statement, published in 1988, was effectively identical to the 1986 statement, except that there was suggestion that it would be beneficial to reduce protein intake to less than the traditionally recommended 15% and increase carbohydrates accordingly.[2632] For example, the statement indicated that "less than 70 g per day of carefully selected protein can supply sufficient amino acid in a man of average size." This amount constitutes only 10.7% of a 2600 calorie diet. Thus, the AHA gives the impression that carbohydrates should be as high as 59% (100% - 30% fat - 11% protein).

The 1988 statement indicated that "total fat in the U.S. is currently 37% of calories," "Currently, Americans consume an average 15% calories as saturated fats," and "polyunsaturated fats contribute 7-8% of total calories." While these estimates would suggest that Americans suddenly decreased their intakes of total and saturated fats from 1986 to 1988, the estimates were, in fact, close to those observed in national surveys for nearly 20 years. The AHA has merely exaggerated intakes over the years because of its use of USDA availability data which do not account for the great waste and spoilage associated with food containing fats.

The 1988 statement repeated its 1986 cautionary note about polyunsaturated fats (3 paragraphs above). More importantly, the statement indicated that "...no studies have demonstrated that increased alcohol intake will significantly reduce vascular disease in human or animal models." The authors neglected to say, however, that (1) no blinded and randomized studies have shown that dietary changes will significantly reduce vascular disease in humans, and (2) alcohol is the only nutrient that has been repeatedly shown to be associated with lower CHD rates within populations.

In 1990 a major spokesperson for the AHA, Scott Grundy, published an article that appared to prepare physicians for possibly another change in the AHA's recomendations.[3083] For example, "In recent years, the scientific community has branded saturated fatty acids as the major dietary cause of atherosclerosis.[a] This position, however, may have to be modified somewhat in the future. The recognition that all saturated fatty acids do not raise the serum cholesterol levels should add to this changing view; for example, it is now evident that stearic acid and medium-chain saturates do not increase cholesterol levels, and lauric acid may be less

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[a] Note that Grundy placed the blame on the "scientific community" rather than on the principal promoter, the AHA.

hypercholesterolemic than generally believed." Grundy cited his 1988 article as evidence for the stearic acid data (although such data were generated by others many years earlier), and he cited 1960 and 1965 studies as evidence for the medium chain and lauric acid data, respectively. Thus, such data were long known to--but ignored by--the AHA. And while the AHA incriminated fat initially as the culprit underlying hypercholesterolemia and then fat and cholesterol, Grundy concluded "That mass hypercholesterolemia" in the U.S. can be explained almost exclusively by the presence of these (palmitic, myristic, lauric and trans monounsaturate) fatty acids in the diet is doubtful."[a] Grundy also noted that high carbohydrate diets lower HDL levels but nevertheless indicated that it will likely be recommended "for many years" because low-fat diets will be recommended for many years. However, he suggested a typical diet of 35% that is high in monounsaturates (15% +) and low in saturates (<10%) and polyunsaturates (<10%) for many Americans who cannot tolerate a low-fat diet.

Now let us summarize a few trends in the AHA's recommendations. In 1961 and 1965 the AHA recommended that Americans reduce their total fat intake to below 40-45% (which they were already doing). This recommendation gradually became <40%, 35%, 30-35%, 30%, 30%, 30%, <30%, <30% and <30%. Total fats were high to begin with because AHA was concerned that low-fat dits would raise carbohydrates and thus triglycerides. As this concern diminished, the AHA recommended progressively lower total fats and progressively higher carbohydrate intakes. But by 1990 Grundy showed signs of again reducing carbohydrates because of their depression of HDL levels.

The AHA recommended the substitution of polyunsaturates for "substantial" amounts of saturates in 1961 and 1965. In 1968 the AHA recommended a P/S ratio of 2.0. And although the 1973 and 1978 "official" AHA statements indicated P/S ratios of bout 1.0, those statements promoted consumer pamphlets which recommended very high intakes of polyunsaturates, exceeding 20% of total calories. Subsequently, recommendations were for <10% of calories as polyunsaturates, although the public was still bombarded by the expression, "increase polyunsaturated fatty acids" for many years by numerous agencies including the AHA.

Finally, AHA publications from 1961 through the 1970s either recommended against the consumption of monounsaturates or recommended moderate intakes. Grundy's 1990 article suggests that monounsaturates may greatly increase in future AHA recommendations.

The above discussion clearly demonstrates that the AHA recommendations have been substantially inconsistent from 1961 to the present. Yet, the AHA and its members would have readers believe otherwise. For example, Grundy[3083] stated in 1990 that the NCEP "amplifies long-standing recommendations of the AHA." Former AHA president Myron Weisfeldt[2584] said in the same year, "It is remarkable how consistent our recommendations have been over the past 30 years."

Stamler also insisted that the AHA never recomended high polyunsaturated fat diets. In 1979 he said, "...recommendations by the AHA...have not been to eat a diet high in polyunsaturates."[2635] And in 1983 he stated, "In terms of advice to the general public, the statement in 1961...by the AHA...emphasized reduced saturated fat

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[a] In another 1990 article Grundy said, "It is no longer justifiable to identify 'saturated fatty acid' as the dietary culprit responsible for raising LDL cholesterol levels. Instead, the various culpable acids should be grouped together as cholesterol-raising fatty acids."[3175]

and cholesterol intake and moderate (not high) ingestion of polyunsaturates. Thus, there is a clear record over 20 years in regard to advice to the public."[3051]

The AHA has always operated before-the-fact, i.e., it has recommended dietary changes before there was adequate evidence that the changes were harmless. And when such evidence eventually proved harmless, it recommended other changes before it had adequate evidence regarding their consequences. In this respect, it is useful to note two remarks by Irvine Page in 1954. He said, "The first dietary suggestion was the low cholesterol diet. Of all the stupid things anybody could do, this was it, because everyone knows tht cholesterol is synthesized in the body. If cholesterol is withdrawn from the diet, the body synthesizes enough to make up the deficit."[3292] Page continued, "Let's keep our notions to ourselves for a while until we know whether they are going to prevent atherosclerosis, or at least do good in one way or another. It is all good clean fun among us, but when we begin to peddle some of our ideas to the public, the trouble begins." In 1961, however, Page spearheaded the "peddling" of AHA's ideas to the public which included the "stupid" low cholesterol diet for decades.

The AMA Dietary Recommendations

In overviewing statements by the American Medical Association (AMA) over the last 30 years, the impression can be gotten that, unlike the AHA, the AMA was, until recent years, not in favor of Americans changing their diets in an attempt to protect against CHD. This was decidedly not the case. The AMA has long promoted dietary changes but under the supervision of a physician, not by "do it yourselfers." One cannot help but gain the notion from a careful reading of AMA statements that it wanted dietary changes to come about by the expensive means of periodic consultations with physicians who, incidentally, had no education in nutrition.

The first official statement on diet and heart disease by the AMA was published in 1962.[2629,a] The Council on Foods and Nutrition indicated that the fat content of the American diet had increased from 38% to 44% during the period 1936 to 1955, according to USDA surveys. The Council stated that "These data refer to the amount of fat in the food brought into household kitchens. No allowances were made for food discarded. Discarded food would probably include relatively large amounts of fat with high losses in calories." Yet, the Council concluded that fat intake among Americans averaged about 40%. While this estimate was lower than that expressed in the first (1961) AHA dietary recommendations, i.e., 40-45%, it was still erroneously high. As noted in the discussion of AHA recommendations, USDA availability data for 1960 show that the percentage of fat in the U.S. was 41%. Thus, adjustment for losses of

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[a] While not an official position, the AMA's Council on Foods and Nutrition published an article in 1959, predating the 1961 AHA statement, which at least suggested that the AMA aproved dietary changes without official sanction.[3299] The article was entitled, "Symposium on significance of lowered cholesterol levels." The lead discussion recommended a very high fat, high polyunsaturated fat diet ("at least" 29% of a 2600 calorie diet) for "patients with manifestations or complications of atherosclerosis." The authors cautioned, however, that such recommendations for the general public would be "premature."

"relatively large amounts of fat" would reduce that intake to about 36%.[a]

The Council reported that "Increasing the ratio of polyunsaturated to saturated fat in the diet is the preferred method of treating the 'usual' hypercholesterolemia" and recommended ratios of 1.1 to 1.5, approximately 3 to 4 times that inherent in the typical American diet. The Council also offered a number of "meal plans" containing different numbers of calories. However, it was made clear that the Council's recommendations were "intended to serve as a guide to assist the physician who wishes to advise the regulation of dietary fat on the basis that it may be beneficial [note the word "may"]. It is not recommended for the general public."

The above report was published in August. Just as the 1961 AHA dietary recommendations were focused on persons "at risk for CHD" and not the general public but were nevertheless picked up and amplified by the media, the 1962 AMA report was also promoted by the media. Within two months the AMA felt compelled to issue a press release which effectively threatened Americans with potential disaster if they changed their diets without the supervision of physicians.[2064] The press release stated, in part, "the AMA Council on Foods and Nutrition has...[not]...recognized the need for modification of dietary fat for the general public. The anti-fat, anti-cholesterol fad is not just foolish and futile, however. It also carries some risk. ...dieters who believe they can cut down their blood cholesterol without medical supervision are in for a rude awakening. It can't be done."

The last sentence of the AMA's press release was, of course, completely false and it required another AMA response to correct itself. This occurred by way of an editorial by William Darby, chairman of the Council on Foods and Nutrition, in the December 1962 issue of the Journal of the American Medical Association.[2693] Darby reported that the news release was submitted by the AMA without approval by the Council and that it contained dogmatic statements regarding the "futility" and "safety" associated with changing one's diet. It was emphasized that "diets can be safely altered under the supervision of physicians." Darby said that the original Council report was aimed at physicians and that "there is not sufficient information available at the present time to warrant a change in the American diet." But such a statement is somewhat inconsistent in view of the fact that the Council's first report seemed to think there was enough information to warrant physicians to treat high blood cholesterol levels which, it admitted, were established by "setting arbitrary limits."[2629]

In 1965 the Council noted that the AHA now recommended its 1961 guidelines to all Americans. It said that it "reappraised current knowledge" and "reaffirmed its previous position that physicians should advise persons with the hyperlipidemias to undertake diet therapy." However, the Council went much further. It recommended that "physicians consider similar diet modifications to young men vulnerable to coronary disease in an attempt to prevent the rise in serum lipids which, in time, might put them into high-risk categories." Dietary therapy was recommended for men having cholesterol levels over 200 mg. Since cholesterol measurements tended to overestimate cholesterol levels in the 1960s, this recommendation effectively included most of the male population above the age of 18 to 20.

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[a] The Council also indicated that the saturated fat content of the diet was nearly 17%. As discussed in Chapter 3, this value appears to be high by about 3 percentage points.

The Council issued a joint statement with the Food and Nutrition Board in 1972.[423,2628] They said, "The evidence now available is sufficient to discourage further temporizing with this major national health problem" [word for word what was stated four years later in the 1978 AHA dietary recommendations]. They recommended measurement of cholesterol levels of all patients who undergo physical examinations and dietary treatment for all who "fall into 'risk categories.'" For those in risk categories "it is important to decrease substantially the intake of saturated fat and to lower cholesterol consumption. In practice, this entails substituting polyunsaturated vegetable oils for part of the saturated fat in the diet."

When the "Dietary Goals for the U.S." were published in 1977, sponsored by the U.S. Senate (see Chapter 2), the AMA submitted a statement to Senator George McGovern opposing the recommendation that all Americans change their diets.[180] The AMA again warned that "there is potential for harmful effects" and indicated that "the evidence supporting such goals is not conclusive." But since the AMA was already recommending diet therapy for a large number of Americans under "physician guidance," the AMA statement was again further evidence that it wanted physicians to be in charge of the lucrative business of altering diets. The letter accompanying the statement was signed by James Sammons, Executive Vice-President of the AMA.[3302] We will see that Sammons spearheaded the AMA's assault on the public in the 1980s, promising physicians increased business.

The AMA's Council on Scientific Affairs published a statement in 1979 reaffirming its previous position that dietary modifications be performed under a physician's guidance.[2627] In 1982 a book developed by the AMA was published. It was entitled, "Book of Heart Care."[3257] While it indicated that "people who do not have high cholesterol levels and are free of other coronary risk factors have no need to curtial saturated fats or cholesterol in the food they eat," it nevertheless presented guidelines which the average person undoubtedly mistook for general recommendations for all Americans. For example, it said, with regard to spreads (margarines, mayonnaise, etc.) and oils, "Look for the P/S (polyunsaturated/saturated) fat ratio, or if it is not listed, the total grams of polyunsaturated and saturated fats per tablespoon. From these figures, you can determine the ratio yourself. Any ratio of 1/1 is good, but 2/1 is better." Clearly, such advice could not but help to encourage high polyunsaturated fat diets.

The 1983 statement by the Council on Scientific Affairs finally adopted the AHA's dietary recommendations without qualifications.[2890] However, it again maintained that dietary therapy should be "individualized" and supervised by a physician, and it recommended "at least 10% of calories from oils rich in polyunsaturated fatty acids." Thus, it implied that high polyunsaturated diets would be better dietary therapy. Also, the AMA suggested a much large target population than previously, i.e., "Patients with plasma lipid levels in the range of the 50th to 90th [and above] percentile for age and sex may also benefit from diet therapy."

In 1987 James Sammons developed his "Campaign Against Cholesterol" and, with the financial support of industry, conducted a media blitz. He promised physicians in letters and advertisements that there would be financial rewards because "The AMA's campaign against cholesterol will bring both old and new patients to you for necessary testing, counseling and care."[1632]

In 1990 the Council on Scientific Affairs[2605] approved the FDA's proposal to have food producers indicate the quantities of fatty acids and cholesterol on labels if either one is declared on the label. The AMA had thus finally and formally adopted all of the AHA's dogma.

It is difficult to judge which was worse, the unrelenting evangelistic and unscientific dogma of the AHA or the greed of the AMA. It is interesting that their names differ by one letter, H versus M--which could easily represent the first letters of words that eloquently describe the groups, i.e., half-baked and money-crazed.

DECISION MAKING UNDER POLITICAL PRESSURE

Unfortunately, the AHA's and NHLBI's early decisions to promote dietary changes in the American people were unquestionably driven more by political pressure than by scientific data. This likelihood was evidenced in both direct and indirect ways. Indirect evidence can be seen in the ambiguous or contradictory statements of such prominent alliance members as former NHLBI director Robert Levy. For example, while telling the Senate Select Committee in 1977 that "...we would like to demonstrate that cholesterol lowering is beneficial before we go out and do it on a massive scale," he simultaneously recommended, apparently under the prodding of the Committee, that Americans change their diets.[288]

Although many more could be referenced, eight significant documents published between 1957 and 1983 clearly focused on direct evidence. In their report to the AHA in 1975 Page et al.[512] concluded that changes in the American diet throughout the 20th century could not have been related to the so-called CHD epidemic. They said, "This is a time when great pressure is being put on physicians to do something about the reported increased death rate from heart attacks. People want to know if they are eating themselves into premature heart disease. They are entitled to an unprejudiced answer. On the other hand, some scientists have taken uncompromising stands, based on evidence that does not stand up under critical examination." The "great pressure" described by Page must have been severely felt by him because he subsequently was senior author of the AHA's first dietary change recommendations to the public published four years later, a document that was diametrically opposite to the conclusions reached in the 1957 report.

In 1968 the director of the National Heart Institute, Donald Frederickson, appointed Edward Ahrens to chair a panel of experts to discuss the utility of conducting a large diet-heart trial. That panel consisted of 6 National Institutes of Health staff members and 10 independent researchers. They published a report in 1969 which stated, in part,

> "Various national organizations have felt compelled to issue what is regarded as prudent dietary advice about fats and cholesterol to the public. Nevertheless, it is the panel's opinion that the important points at issue remain unproven. It is not proven that dietary modification can prevent arteriosclerotic heart disease in man."[2730]

In the same year, Page[3080] said,

> "...if we don't declare our own priorities, there are those who are willing and able to do it for us. Many businessmen and legislators have become impatient with our research efforts. Atherosclerosis is just being discovered by the public, and government is reacting by demanding action..."

Also in 1968 the president of AHA, Lewis January, said,

> "This nation seems caught up in a demand for instant solutions to most of its problems. Already there is a dichotomy between the scientific community and

the government over the relationship of research to health care. This can be summed up in the words 'investigational freedom' versus 'practical results.' More and more, the large sums of federal money for medical research seem to be moving in the direction of block grants and directed research."[3202]

In 1970 Daniel Steinberg was chairman of the AHA's Council on Arteriosclerosis and a former staff member of NHLI. He stated, "There seems to be an increasing pressure by some for 'results now.' I do want to express my...concern that the 'results now' philosophy may militate against maintaining the proper mix of the two [basic and applied research programs']. We as a council are on record affirming that basic research continues to be essential as we work towards a fuller understanding of atherosclerosis. However, I don't think that many members of Congress are so convinced."[a]

In his testimony before the 1977 Senate Select Committee, Robert Olson indicated to Senator McGovern that convincing evidence that lowering blood cholesterol by diet reduces heart disease should be obtained before recommending that the American people change their diets.[2538] Senator McGovern replied, "I would only argue that Senators don't have the luxury that a research scientist does of waiting until every last shred of evidence is in. When we get the kind of overwhelming consensus that has developed before this Committee, it seems we have some obligation to share that with the American people." In response, Olson said, "I'm not sure you have consensus of the health professionals in this country. You have a consensus of the witnesses you have called."

The 1981 NHLBI Working Group report[3067] said that "In 1972 the Congress mandated that the NHLBI include programs for disease prevention and control through educational activities. An Office of Prevention, Education, and Control was created to oversee the execution of this function." This statement is notable for three reasons. It suggests that Congress commanded NHLBI to engage in these activities independent of NHLBI input. But this was highly unlikely because if NHLBI did not believe it had the knowledge to educate the public on CHD prevention, this mandate surely would not have been enacted. Second, this mandate effectively rendered the subsequent hearings (1976 and 1977) before the Senate Select Committee on Nutrition and Human Needs a facade. If one reads the Hearings documents, one has no doubt that the decision to alter the American diet was made prior to the hearings. And third, it is a contradiction in logic to undertake a public education program, while simultaneously launching the scientific program (e.g., MRFIT and LRC trials) that is designed to acquire the evidence to support the public education program. However, this form of logic is common to NHLBI's activities and should not be surprising.

Finally, Alfred Harper, a former member of the Food and Nutrition Board, stated in 1989 that "As the American population has aged, medical care costs have risen inordinately. Politicians and government officials, anxious to limit these costs, have been attracted to the idea that diet modification provides an inexpensive solution for control of chronic diseases, a sort of do-it-yourself-medicine."[2325]

Indeed, the above authors, as well as many others, emphasized a political urgency to do something, even if the effects of that something had not been adequately

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[a] Ironically, Steinberg was one of the many alliance members who eventually succumbed to the "results now" philosophy, against the wishes of many other researchers.

assessed. Although demonstrating some initial resistance, numerous alliance members soon jumped on the bandwagon because it was politically and financially expedient to do so. Those who believed jumping on the bandwagon was unconscionable subsequently found that research grants from NHLBI and AHA were difficult, if not impossible, to obtain. The bulk of the researchers, however, seemed anxious to jump aboard. In 1970 Werko[3218] indicated that the "missionaries for the diet-heart theory" became "dissatisfied and frustrated" over many studies showing negative or inconclusive findings and "have become more and more interested in advocating interference with the way people live." He cited Blackburn as saying "We cannot wait until we have scientific proof."

To illustrate the absurdity of the effects of political pressure, we are today in the midst of an immensely costly program to change the American diet which includes major transformations within the industries of food production and processing. The alliance is claiming victory over atherosclerosis. Yet, we still have no scientific evidence of the actual cause of atherosclerosis and, as will be seen elsewhere in this volume, evidence is accumulating that the frequency of the atherosclerosis diease is increasing, despite continued reduction in mortality rate. There has never been a more dramatic and costly example of "jumping to conclusions."

CREATING PROOF BY PROCLAMATION

If there is no scientific proof that life exists on other planets in other solar systems, the fact that 99% of all astronomers polled may believe that such life exists does not change one iota the state of our scientific proof. If, however, majority beliefs are accepted as proof, then such proof is obviously based on proclamation rather than scientific observation. While science does not operate by proclamation, NHLBI and AHA clearly do. In the absence of scientific proof and deluged with negative or confounded data, these organizations contrived congressional hearings, a consensus conference, a surgeon general's report and a Food and Nutrition Board report, all of which proclaimed, via the collective judgements of handpicked NHLBI/AHA members and supporters, that diet causes CHD. Such redundant events would not have been necessary, of course, had the research literature been truly supportive of the diet-CHD relationship.

The consensus events provided the initial and reinforcing "proofs" for NHLBI's NCEP, designed to convince all Americans to adopt the low-total fat, low-saturated fat and low-cholesterol Prudent diet. They now claim that their recommendations must be correct because they are supported by such diverse bodies as congress, the consensus conference, the Surgeon General's office and the Food and Nutrition Board. Of course, they neglect to inform the public that the staff of each body was handpicked and controlled by the alliance. While the scientific community is well aware of this state-of-affairs, it matters not to the alliance because the latter's primary goal is convincing a gullible press and public, not to mention, physicians as well. For example, Desmond[2380] recently stated that international rates of coronary artery disease mortality are linked to high cholesterol diets. In a letter-to-the-editor, Wolfstein[2382] indicated that Desmond's statement is not supported by the literature. Desmond[2382] subsequently cited the 1984 Consensus Conference as evidence. Thus, "consensus" was translated to mean scientific evidence to Desmond and many others.

It is worthwhile noting that in 1988 Wortman et al. reviewed 8 consensus conferences held by the National Institutes of Health between 1980 and 1982 and found them all to be guilty of selection bias, i.e., NIH selected both the questions to be addressed and the panelists to be involved in drawing conclusions. They stated that consensus conferences lacked credibility because selection biases eliminated proper discussion of controversial issues, the very purpose of such conferences. The 1984

cholesterol "consensus" conference was a perfect example of selection bias. In effect, the consensus panel concept, as applied by NIH, is precisely opposite to that which was designed into the concept initially by such individuals as Perry.[2364] "Consensus reports have replaced the traditional debate and controversy that characterize issues of science" (Blattel[1931]) but are "designed to create the illusion of purposeful activity" (Wassersug[2249]).

Table 2-1 presents the members of the 1984 Consensus Panel, the 1988 Surgeon General's report and the 1989 Food and Nutrition Board Committee. As can be seen, the staffs were saturated with long time supporters of the diet-CHD relationship and current or ex-members of NHLBI and AHA, in particular, Steinberg, Wissler, Goodman, Blackburn, Shekelle, Feinleib, and Levy.

The FTC-NCEP "Trial"

The AHA's repeated statements in the 1960s to the American public that egg consumption increases the chances of developing CHD resulted in a steady decline in egg sales and motivated the egg industry to form an organization designed to promote increased egg consumption.[2377,2379] That organization was called the National Commission on Egg Nutrition (NCEN). Among its advertisements the slogan which triggered FTC intervention was, "There is absolutely no scientific evidence whatsoever that eating eggs in any way increases the risk of heart attack."[3268] The AHA president, Richard Ross, filed a complaint with the FTC, requesting that such advertising be prohibited.[3264] On July 23, 1974 a complaint was issued against NCEN[2376] and on August 5, 1974 the FTC charged NCEN with "unfair methods of competition in commerce, and unfair or deceptive acts commerce."[2365]

The first indication that the FTC action against NCEN was a sham was the fact that the FTC's complaint was, prior to any hearings, already in the form of a conclusion. It was effectively identical to the FTC's ruling which followed subsequent hearings, namely, that NCEN "has made false and unsubstantiated claims in promoting the industry's views concerning the role of eggs in heart disease."[2376]

The FTC held hearings on the complaint against NCEN from June 12 to July 2, 1975.[2378] These hearings essentially constituted a trial in which a single FTC judge, Ernest Barnes, represented both the judge and jury. Thus, any biases generated by the influence of AHA were preserved by the avoidance of independent judges and juries. This process represented a second indication that the action against NCEN was a sham.

Testifying on behalf of the AHA and, therefore, the FTC, were several of the principal promoters of the diet-CHD hypothesis, i.e., Theodore Cooper, Jeremiah Stamler, William Connor, Frederick Stare and Henry Blackburn.[a] Testifying on behalf of NCEN were Michael DeBakey, Michael Oliver, George Mann, John Yudkin, Fred Kummerow and Kurt Oster. Some 2,389 pages of testimony were recorded, much of which was associated with comments, arguments or other irrelevant verbiage by

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[a] As noted elsewhere in this Volume, Frederick Stare would later tell the public that blood cholesterol level (and thus dietary cholesterol) is not very important to development of heart disease. Moreover, Theodore Cooper would later become chief officer of Upjohn Pharmaceutical Co., makers of cholesterol-lowering drugs.

Table 2-1

Members of the Consensus Conference Panel, the Surgeon General's report and the Food and Nutrition Board Report

1984 Consensus Conference Panel	1988 Surgeon General Report Staff	1989 Food and Nutrition Board Committee on Diet and Health[a]
Daniel Steinberg		Arno Motulsky
Sidney Blumenthal	Nutrition Policy Board	Edwin L. Bierman
Richard Carleton		DeWitt S. Goodman
Nancy Chasen		Donald B. McCormick
James Dalen	J. Michael McGinnis	Claude D. Arnard, Jr.
John T. Fitzpatrick	Faye G. Abdellah	John C. Bailar III
Stephen B. Hulley	W. Douglas Badger	Henry Blackburn
Gregory O'Keefe III	Mary M. Evert	George A. Brag
Elijah Saunders	Manning Feinleib	Kenneth K. Carroll
Robert E. Shank	Allan Forbes	Geoffrey R. Howe
Arthur A. Spector	William T. Freidwald	Lucille S. Hurley
Robert Wissler	Bernard I. Grosser	Lawrence N. Kolonel
Richard D. Remington	John Provaznik	Henry C. McGill, Jr.
	William A.Robinson	Anthony B. Miller
		Richard M. Schieken
		Richard B. Shekelle
		Louis Tobian, Jr.
		Eleanor R. Williams
	Senior Editorial Advisors	
	C. Wayne Callaway	
	Johanna T. Dwyer	
	Samuel Famon	
	Richard L. Hall	
	Robert I. Levy	
	Walter Mertz	
	Malden C. Nesheim	
	Sushma Palmer	
	Irwin H. Rosenberg	
	Theodore Van Itallie	

[a] The Food and Nutrition Board itself included William Connor as "liason."

lawyers and considerable ramblings of some of the witnesses on questionable "scientific" material. While this appendix cannot critique the entire testimonies, comments from two of the FTC's witnesses (and principal members of the alliance) are presented here to illustrate the poor level of expertise supporting the FTC.[a]

Some of the testimony presented by William Connor was all but diametrically opposite to that of Jeremiah Stamler. For example, consider the following excerpts:

Connor[3278]

Connor: "In some individuals, about five percent of our population, heredity is all-important. And the effect of diet is existent, but is not the determinant which makes the level very high."

Barnes: "You say five percent?"

Connor: "Five percent of the population. For the other 95 percent of the population, the dietary influence is paramount."

Attorney: "Five percent, of those who suffer from some sort of familial hypercholesterolemia?"

Connor: "Okay."

Stamler[3279]

Attorney: "Dr. Connor, in his testimony, and again, I am dilettante in this particular field, as you witnessed, Dr. Connor elucidated for us a particular element of the population here, and it was my impression that it was five percent, peculiarly, or a superrisk, or something like that, in this coronary event possibility."

Stamler: "We should be - let me attempt to make that explicit. You are probably referring to people with severe genetic hypercholesterolemia, 0.5 percent, or five, or five per-thousand, not five percent. They are, fortunately, much rarer than five percent..."

Not only was Connor or Stamler or both unexpert on this subject, they both disagreed profoundly on the importance of diet as a cause of CHD in the 95% to 99.5% of the population unafflicted with hypercholesterolemia.

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[a] It is of no little interest to note that as one branch of the federal government, the FTC, was busy creating constraints against the promotional efforts of NCEN, another branch (the U.S. Congress) was busy creating a law ("The Egg Research and Consumer Information Act") which would produce the quasi-governmental agency, the American Egg Board, and provide it with an annual budget of approximately $6 million to promote the sale of eggs.[2374,2375]

Connor[3278]

Attorney: "If you take the other 95%, and there was no ingestion of dietary cholesterol by those 95%, there would be not atherogenesis in that cohort, is that correct?"

Connor: "Mr. Fox, I would say that from the public health point of view, coronary heart disease would not be a major disease condition."

Attorney: "Now, that isn't the question I asked, doctor, and I would appreciate if you would answer my question. I said that, if dietary cholesterol were excluded from birth until death, in the diets of the 95%, there would be no atherogenesis detected in that 95%, is that correct?"

Connor: "That is correct."

Attorney: "In the human species, it is your statement here today that dietary cholesterol is the sine qua non of atherogenesis?"

Connor: "That statement will have to be amplified, because dietary cholesterol as a single substance is not normally ingested by human beings; it's always in the company of fat, and usually saturated fat. The two of them together, Mr. Fox, I would regard as a sine qua non for development of atherosclerosis."[a]

Attorney: "And without the two, people would not die of atherosclerotic heart disease?"

Connor: "Yes, this is correct."

Stamler[3279]

Stamler: "Here is an illustration illustrating cholesterol as a risk factor. It is the number two factor after obesity followed by elevated blood pressure followed by excessive cigarette smoking and heredity. It [CHD] is a multifactored disease, and everyone in the field doing meaningful thinking in research on it has recognized this since before I got into the field."[b]

Not only did the FTC's star witnesses contradict one another, neither judge Barnes nor the attorneys for the plaintiff and defendants appeared to recognize the contradictions. According to Stamler's statement, Connor was apparently not doing "meaningful

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[a] This statement suggests that fat is important only for the absorption of cholesterol and contrasts with a statement by Connor 14 years earlier, i.e., "the amount and type of fat in the diet are of great significance in hypercholesterolemia and atherosclerosis."[560]

[b] This is apparently not true. Stamler co-authored a paper with Katz and Pick which defined atherosclerosis as a "metabolic disease" in 1956.[694]

thinking" on CHD. There were many other discrepancies. For example, Stamler held that a cholesterol level under 250 mg was "not high," while Connor maintained that a level of "220 mg and above would be abnormal."

The testimonies of Connor and Stamler were literally replete with errors of fact, reasoning and understanding. With respect to Connor, he stated that the average blood cholesterol level in the Framingham study "is something about 230 to 240 mg," although Framingham's Kannel reported in 1971 that it was 220 mg.[1352,1376] Connor indicated that the average cholesterol consumption in the U.S. was 650 mg per day, when USDA disappearance data (themselves being recognized to be overestimates of actual consumption) indicate little more than 500 mg.[1117,1160]

When asked if dietary cholesterol can affect blood cholesterol, Connor said, "Yes, this is one of the constituents of the diet that will directly affect the level in the blood, so that if you take away the cholesterol in the blood, or take away a good deal of it, there will be a 15 to 20% decline in the serum cholesterol." Undoubtedly, Connor meant to say the removal of all or most of dietary cholesterol, in which case his estimate of a 15 to 20% decline in blood cholesterol level is an exaggeration by a factor of 3 to 4. For example, the elimination of 515 mg of cholesterol would reduce blood cholesterol about 10 mg which is a 5% decline from the average level of 220 mg (see Tables 5-1 and 5-5 in Chapter 5 of Volume 1).

Connor maintained that a number of groups, including his own, obtained the 15 to 20% reduction. When asked if these studies involved natural or formula diets, Connor said, "We have used a mixture of diets. ...obviously, formula diets should be taken to real foods as well, and this has been done and similar results have been obtained." Not only were Connor's studies not mixtures of diets insofar as fats and cholesterol were concerned (the nutrients affecting blood cholesterol), similar results are most definitely not obtained from whole foods diets, as shown in Tables 5-1 through 5-4 in Chapter 5 of Volume 1.

When asked if the results of formula diets can be extrapolated to the use of natural foods in the diet, Connor replied erroneously, "I think they can." Connor went on to say that "I think it would be impossible to have any lowering of the serum cholesterol concentration if egg consumption (7 or 8 per week) would be continued." Such a statement, of course, was not at all consistent with the well-known knowledge at the time that saturated fat reduction was and is far more important than cholesterol reduction.

Connor completely distorted the facts when he said that "The body doesn't have the metabolic capacity to handle dietary cholesterol, so that synthesis probably [note the word "probably"] continues at the same rate in most human beings and when one ingests cholesterol in the diet this is added on top of what the body ordinarily synthesizes." The combination of innumerable feeding and cholesterol absorption studies clearly demonstrated that cholesterol synthesis declines as cholesterol is consumed.

In discussing his dietary cholesterol experiments, Connor stated that "it is our feeling [note the word "feeling"] that dietary cholesterol is more important than whether the fat is relatively saturated or relatively unsaturated." Not only did Connor ignore the results of other investigators, he misinterpreted the results of his own experiments, described in detail in this volume (Chapter 5). Although his experiments were poorly designed and thoroughly confounded, Connor insisted that they "were carried out with reliable and established methods of approach."

In discussing experiments which evaluated the effects of dietary cholesterol on blood cholesterol, Stamler indicated that there were several "precise metabolic ward" studies. "These studies--there are three that are the principal ones; there are four; there is also the study by Dr. Connor in Iowa--all showed that dietary cholesterol, saturated fat, polyunsaturated fat were, by being manipulated, capable of exerting an influence on the serum cholesterol level. You could keep the polyfat, the saturated fat, the total fat constant and vary dietary cholesterol and influence serum cholesterol."[3279] Stamler actually briefly mentioned five studies and he referred to them as "exquisite." One of these "studies" was not an experiment but rather a three-part review/theoretical article.[333,719,988] The remaining four studies were those constantly cited by members of the alliance, namely, three liquid formula studies by Connor et al. and Mattson et al. and the highly deviant study by Hegsted et al. (Chapter 5, Volume 1).

Stamler emphasized that USDA food balance sheets (food disappearance data) overestimate actual consumption of foods. Although Volume 1 presented several reasons why this is so (e.g., the elimination of some fat from carcasses at the retail level and the elimination of fat by the consumer in the home), Stamler mentioned only the loss by spoilage. Even so, he ignored adjustment considerations and quoted USDA figures as indicating that Americans consume 40% and 17% of their calories as total fat and saturated fat and he also quoted the inflated cholesterol consumption estimate of 650 mg per day.

Stamler was asked how much the average person's blood cholesterol would increase if he added one egg per day to his diet. Ostensibly using an equation by Keys, Stamler concluded that the egg would raise blood cholesterol from 225 mg to 241 mg, assuming an egg to have 252 mg cholesterol and assuming the person's diet already contained 600 mg. As can be seen from Tables 5-1 and 5-5 of Volume 1, Stamler's figure was over 3 times greater than that observed by experiments with whole foods.

The testimonies of Connor and Stamler were anything but reflective of expertise in the area of diet and heart disease and both demonstrated only an elementary understanding of scientific methodology and reasoning, and what constitutes scientific evidence. Yet, they were the star witnesses of the FTC who explicitly stated that eating eggs promotes heart disease and these statements were the principal bases for the FTC's ultimate ruling against NCEN.[a]

In November of 1975 the FTC privately ruled that NCEN committed false and misleading advertising.[2368] The announcement was made public on December 11, 1975.[2370,2376] As noted by Yarbrough, Judge Barnes effectively ruled that the group representing the AHA presented the truth regarding the egg's relationship to heart disease, while the group testifying on behalf of NCEN presented something other than the truth.[2375,b] The press release included the following statements:[2368,2372,2376]

> "An administrative law judge of the Federal Trade Commission has ruled that NCEN...has made false and unsubstantiated claims in promoting the industry's views concerning the role of eggs in heart disease. Judge Ernest G. Barnes

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[a] See Chapter 1 for the "scientific expertise" of each of the FTC's star witnesses, as reflected in their testimonies.

[b] Yarbrough also correctly criticized the FTC for allowing other food producers to make medical claims on their advertisements.[2367]

issued a cease and desist order against NCEN and said 'there exists a substantial body of competent and reliable scientific evidence that eating eggs increases the risk of heart attacks or heart disease. This evidence shows, among other things, that eating eggs directly affects the serum cholesterol levels of most people; that the serum cholesterol level is directly related to the risk of CHD; and that there is a direct relationship between the level of dietary cholesterol and saturated fat in diets and the development of CHD. This evidence is systematic, consistent, strong and congruent...' Judge Barnes went on to say that '...evidence supporting the diet-heart hypothesis is not conclusive; it does not establish in fact that high cholesterol levels cause heart attacks... This lack of conclusiveness of the evidence, however, is no defense to the complaint allegations. One seldom has the final answer in medicine. The final proof or answer is very often difficult, if not impossible, to obtain.[a] The fact that the final answer on CHD is not yet established does not mean that medical science cannot base prudent judgments on the existing evidence.' Judge Barnes emphasized that there was 'no reasonable basis for the claims that there is no evidence that eating eggs, even in quantity, increases the risk of heart attacks or heart disease.'" The news release stated that "This is not a final decision of the Commission and may be appealed, staged or docketed for review."

It is quite clear, among other things, that Judge Barnes had no understanding of the word "risk," employed in his statements and obviously derived from the testimonies of Connor, Stamler and others.

In his 101 page ruling, Barnes stated that "Nutritionists have said for years that egg yolks are the leading dietary sources of cholesterol, a fatty substance that has been linked to atherosclerosis, arteriosclerosis and other circulating problems that can lead to heart disease."[2369,2690] In noting that NCEN's expert witnesses did not agree that the scientific evidence linked eggs with heart disease, Barnes concluded that "The fact that some scientists do not draw the same inference from the existing scientific evidence does not negate the fact that the evidence exists."[2365] Apparently, then, Barnes considered "evidence" per se to be the important factor, not whether it is supportive or nonsupportive of the egg-heart disease hypothesis. Barnes also cited such "reputable" organizations as the Inter-Society Commission for Heart Disease Resources, NHLI, the AMA, the AHA and the National Research Council as supporting the egg-heart disease hypothesis. The AMA, however, had argued against the diet-heart disease hypothesis for many years and would make a formal policy statement to that effect within two years after Barnes' ruling. Moreover, the 1980 National Research Council would also argue against the diet-heart disease hypothesis as well. There remained NHLI, AHA and the Inter-Society Commission, all of which were operating together, not independently.

In April 1976 NCEN appealed the 1975 ruling before the full FTC Commission.[2366,2547] But a few months later (July) the appeal was denied and NCEN was ordered to cease its advertising linking egg consumption with heart disease.[2370] (Appeals by NCEN to the U.S. Supreme Court in June 1976 and again in 1978 were also denied.[2371,2552]) The denial by the full Commission contained some statements

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[a] Barnes' statements on "proof" and "final answers in medicine" are effectively identical to those uttered by Connor in his testimony and are fundamentally erroneous. There are many "proofs" in medicine and there have been many "final answers" to many diseases and related medical problems.

which were effectively contradictory to its ruling. For example, it held that "In reaching its conclusions, the Commission emphasized that it was making no findings on the relationship between dietary cholesterol (or eggs) and heart disease."[2377] But, of course, the entire trial was based on this issue and the Commission did indeed find in favor of AHA that dietary cholesterol was a cause of heart disease. Moreover, in noting that "some scientists disagree" with regard to the diet-heart disease hypothesis, the Commission maintained that "It is certainly not the Commission's intention to determine in this proceeding whose interpretation of a difficult and incomplete body of scientific literature is superior."[2377] But, of course, that is precisely what the Commission did.

In addition to its main rulings, the FTC ordered that NCEN's future ads "must disclose in close proximity to its name that it is an organization composed of egg producers and others in the egg industry."[2377] In response to this requirement, Yarbrough legitimately asked whether the FTC would require the American Health Foundation in its ads to disclose the fact that it is supported by the makers of such foods as Wesson Oil and Mazola.[2367] To this may be added the AHA on whose Board of Directors sits a member of Procter and Gamble and many of whose members hold financial ties with food and pharmaceutical industries.

The HeartGuide "Trial"

The most recent insult to the American people was AHA's announcement in 1988 that it would depart from a long-standing policy of not endorsing foods.[1563,1571,1611] In fact, it fully intended to permit food manufacturers beginning in February 1990 to use an AHA "Stamp of approval" on products which met AHA's guidelines for cholesterol, saturated fat and sodium. The program was called "heartGuide." Before discussing its rise and fall let us present some relevant history.

In 1906 the Pure Food and Drug Act was enacted by Congress. This act made it illegal for food manufacturers to use false labels on foods. As noted earlier in this chapter, the accumulated knowledge in the early 1950s which indicated that polyunsaturated oils reduce blood cholesterol levels led food manufacturers in 1957 and thereafter to promote vegetable oils and other foods high in unsaturated fats as beneficial to health. As these promotions grew in number, the FDA finally promulgated a law in 1959 which prohibited health claims on food labels. However, in 1961 and again in 1964 the AHA recommended that the public consume "substantial" amounts of polyunsaturated fats and industry again promoted the health benefits of unsaturated foods. The FDA only infrequently enforced its 1959 law, and apparently not at all against the edible oil industry.

The Inter-Society Commission for Heart Disease Resources attacked the FDA's law prohibiting health claims on food products in 1970. And in 1977 Henry Blackburn wrote, "The existing [FDA] regulations discourage advertising based on health attributes such as 'desirable in cholesterol-lowering or weight lowering programs.' Restrictions on such claims discourage the development and marketing of attractive low-fat alternatives to the ubiquitous 'favorite' U.S. products high in saturated fats and cholesterol. This in effect serves to limit the range of choices available to the consumer and to govern his/her tastes. It has the effect of encouraging a continued and distorted American way of eating."[a] Blackburn announced that he, William

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[a] Published in the Hearings before the Select Committee on Nutrition and Human Needs.[2707]

Connor, William Kannel, Jeremiah Stamler, Jean Mayer and others had petitioned the FTC to allow advertisers to make health claims about their foods. He also praised the vegetable oil producers for making such claims in their advertisements. He said, "Such ads have surely increased public awareness of the health isues related to elevated blood cholesterol levels."[2707]

In the mid 1980s NIH (via the National Cancer Institute) endorsed the use of a statement that dietary fiber prevents cancer of the colon on Kelloggs All-bran cereal. And in 1987 the FDA officially adopted a policy of not enforcing its 1906 and 1959 laws and permitted unregulated health claims by food manufacturers.[2872] Health claims again proliferated but now more than ever.[2863] Representative Ted Weiss said that the new FDA policy "has opened the floodgates to misleading health claims."[2579] Some writers reported that about 40% of all new products introduced in the first six months of 1989 were associated with health benefits.[2872,2882] Testimonials by physicians lent credibility to such claims. For example, a photograph of Kenneth Forsyth, M.D., accompanied by the statement, "Special K fits my life-style," appeared on the back of cereal boxes.[2884] Moreover, the reader will recall earlier in this chapter that key alliance members such as Castelli, Gotto and Stamler were also promoting food products, undoubtedly for fees.

The AHA accomplished what it set out to do, namely, to eliminate government regulation of health claims on foods and to permit food manufacturers to make such claims. As soon as the FDA adopted its no enforcement policy in 1987, the AHA began development of its HeartGuide program. The AHA's communications coordinator Vicki Anderson said that HeartGuide was initiated because "there are no regulations. There's a void. If there's no longer a need for the program, then the AHA would probably back away, but realistically that's down the road."[2868] And although AHA members bombarded the FDA for many years for its prohibition of health claims on foods, the AHA's president Myron Weisfeldt indicated that the HeartGuide program was in response to no regulatory action by FDA and the fact that the proliferating health claims were confusing consumers.[2877] He said, "HeartGuide is intended as a convenient, reliable tool to help consumers counteract the confusing, often misleading claims made by some foods producers." And Mary Stiedman, vice president of AHA, stated that the HeartGuide's "Cheif goal is to reduce the confusion surrounding nutrition information. People want more help--help from a reputable health organization."[2221] In effect, the AHA created the environment which led to confusion and fraudulent advertising and then announced that it would solve the entire problem by an AHA endorsement scheme which, as will be seen, would unquestionably lead to an even greater confusing and fraudulent state-of-affairs.

The AHA initially proposed a fee of $40,000 for each food product submitted for "testing" and an additional annual "educational fee" of $5,000 to $1 million (depending on annual sales), ostensibly to fund the HeartGuide's promotion.[2222,2317] However, it announced in October, 1989 that it was reducing the annual fee from $1 million to $600,000 because there presumably has been more interest than expected from industry[2388] (or perhaps less interest?). The AHA also varied the "testing" fee from $10,000 to $40,000.[2388]

AHA spokesperson Jamy Poth emphasized that "Everything will be paid for by the participating companies and not by public contributions."[2388] But such a remark was pure nonsense. The American consumer would, of course, pay for the entire program because industry always passes on the "cost of doing business" to the consumer via increased prices.

Considerable opposition to the HeartGuide emerged in 1989 from government, industry and consumer groups.[1725,2077,2388] In October, 1989 the USDA's Lester Crawford, administrator of the USDA inspection service, submitted a letter to the AHA indicating that the agency prohibited the AHA from including fresh, processed or frozen meats or poultry in its labeling seals.[2388] He said that "attempts to label food as good or bad using inadequate nutritional criteria will undermine the public confidence in the science of nutrition."[2465] He also held that "no educational efforts will be able to counteract the confusion the [HeartGuide] seal is likely to cause."[2862] Weisfeldt accused the USDA of "bowing to the whims of special interests."[2463] He said, "it has become apparent to us that the USDA may be more sensitive to the parochial concerns of special interest groups than to the concerns of the American consumer."[2861]

Other AHA members voiced their anger as well. AHA director Dennis DeSilvey maintained that "The National Cattlemen's Association, their antilabeling coalition and the USDA may not want HeartGuide, but the American public sure does. That's why we're intent on delivering it."[2861] Jamy Poth said that "The [USDA] decision makes no sense at all[2388] and suggested legal action against the USDA.[2536] Nevertheless, the AHA indicated in November, 1989 that it would fully comply with the USDA's orders.[2860]

The FDA also voiced strong opposition to the HeartGuide Program. FDA commissioner Frank Young said, "HeartGuide is a bad idea." And FDA's Raymond Newberry said that the HeartGuide seal will give people the impression that the food is good for the heart and that foods without the seal are bad for the heart.[2860] AHA's DeSilvey confidently predicted that both USDA and FDA will "reverse their stances" after the HeartGuide program is initiated.[2860]

Many industries were opposed to the HeartGuide, as represented by The Association of Food Industries and the National Food Processors Association. For example, the president of the former, Richard Sullivan, called the HeartGuide program "an extortion racket."[2317]

Even some AHA members indicated displeasure with the HeartGuide. For example, Stephen Yarnall said, "As a past president of our county heart association and an active supporter of the AHA, I am distressed that our organization has gone ahead with this program, blind to the many powerful arguments against it. Labeling foods as 'tested and approved' and implying that they are either 'good' or 'bad' is sheer nonsense."[2876]

In 1988 two dubious consumer groups more or less supported the HeartGuide program. Sidney Wolfe, director of Public Citizen Health Research Group, indicated that the AHA should also disclose "bad brands" of foods in addition to labeling "good brands."[2223] Such a recommendation is so preposterous in its ramifications that it deserves no further discussion.

Bonnie Liebman, director of Nutrtion, Center for Science in the Public Interest (CSPI), argued that the HeartGuide's standards may be "too lenient."[2223] Because AHA refused to publish the criteria for its aproval of foods, CSPI announced in 1989 that it could not endorse the HeartGuide program. However, this concern was apparently short-lived and based on CSPI's notion that AHA's criteria "may not be stringent enough."[2317] (Interestingly, AHA's DeSilvey indicated that nondisclosure was based on the possibility that "other groups will horn in on their [AHA's] ideas and

launch a similar competing program."[2317] But why should AHA have this concern if their sole interest was to enable consumers to distinguish between healthful and unhealthful foods?)

In January, 1990 Liebman indicated "mixed feeling" about the HeartGuide program. "I'm concerned that there are certain foods, like margarines and oils, that aren't all-around terrific foods, but people will thnk they are terrific foods because they carry the seal."[2865] But in February, Liebman apparently discarded that concern when she said that "The AHA is filling the gap left by the government. There are millions of people who want a simple thumbs up or thumbs down."[2871] When the HeartGuide program was concelled in April, she said that its demise "is a shame for consumers who want simple thumbs up or thumbs down advice on whether a food is good for the heart."[2879,a] Apparently neither Liebman nor Wolfe nor the entire AHA staff could see the obvious can of worms they were attempting to open.

The beginning of the end of HeartGuide occurred in late January of 1990 with a letter from James Benson, acting commissioner of FDA, to AHA. It stated that "FDA believes that your program will increase consumer confusion and hamper any comprehensive solution to the food labeling program" and that AHA would "risk regulatory action" if it went ahead with the program.[2867,2869] Benson continued, "Your proposed program could very easily result in the endorsement of products...that quite simply do not represent the kinds of foods that ought to be promoted to achieve healthy hearts."[2872] He added, "You have been unwilling to include in your label statements that the presence of the AHA seal on the food label is made possible only by the payment of a fee."

Some 34 state attorneys general urged the FDA to prohibit all health claims on food labels[2880] and the attroneys general of seven states, including California, New York, Texas and Massachussets, submitted a letter to FDA which opposed the HeartGuide.[3274] Even newspapers criticized the HeartGuide program. An editorial in the Wall Street Journal stated that "...the role of cholesterol in heart disease is a controversial subject. But we live in messianic times, and the AHA's doctors decided to carry their anti-cholesterol crusade into the supermarkets."[2864] And an editorial in the New York Times noted that the HeartGuide seal of approval was on such items as crackers, margarines and cooking oils "which are not particularly healthful. If consumers are encouraged by the seal to eat more of these foods, even the better varieties, their diet will be worse."[3275]

In response to Benson's letter which indicated that AHA seals on margarines, cooking oils and salad dressings, all of which contain large quantities of polyunsaturates, would encourage consumers to consume unhealthful amounts, AHA's DeSilvey said, "That's absurd. The FDA is acting irrationally. Clearly, no American consumer is going to pick up a stick of margarine and eat it like a banana."[2874] But in fact, DeSilvey's remark was absurd because, as detailed in Chapter 10, AHA and NHLBI actually encouraged consumers to consume vegetable oils by the "spoonfuls" years earlier.

Weisfeldt arrogantly indicated in a letter to Benson in late January 1990 that "The association is continuing with HeartGuide. The AHA believes that the public will

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[a] Liebman[3090] promoted the "thumbs up, thumbs down," characteristic of the HeartGuide in 1988.

appreciate the help provided now by HeartGuide and participating food companies, even if done at the risk of regulatory action by the FDA."[2872,a] The AHA's Vicki Anderson noted that 102 products bearing the HeartGuide seal would appear in markets in February.[2872]

In February two companies suspended their participation in the HeartGuide program because of FDA threats, eliminating 28 of the 102 original food brands bearing the HeartGuide seal.[2870,2874] By early March a total of 64 brands pulled out of the program.[2875] Nevertheless, DeSilvey maintained that the FDA would soon endorse HeartGuide.[2874] But Raymond Newberry, deputy director of the FDA's division of regulatory guidance, indicated otherwise. He said another letter was being sent to Weisfeldt "in which many points of our previous letter will be repeated, as AHA doesn't seem to be getting the point."[2874]

In January Time Magazine reported that "HeartGuide may be around for along time."[2866] Fortunately, Time was well off the mark because in April Weisfeldt announced the cancellation of the HeartGuide program and indicated that it would be "redesigned" as a nonlabel program.[2878]

Perhaps the HeartGuide program was best bemoaned by Brown who said that "Maybe someday soon we can buy a can of beans for $6 or $8 approved by the AHA, American Cancer Society, Poison Control, American Diabetes Foundation, American Kidney Foundation and etc."[1562] Indeed, there were indications that given the success of HeartGuide, "other health groups were considering their own stamps of approval for foods."[2879] One can only imagine the massive confusion that would arise with multiple seals.

What makes the HeartGuide fiasco uniquely interesting is that it was the mirror image of the FTC-NCEN conflict discussed in the previous section. In his article appearing in the 1977 Hearings before the Select Committee on Nutrition and Human Needs, Henry Blackburn said that "This cynical [FTC-NCEN] episode, deliberately and admittedly precipitated by the Egg Council and NCEN, involved inaccurate and misleading ads prepared by expensive legal, public relations and 'expert' scientific consultation. In the end, the FTC trial resulted in the NCEN having its knuckles soundly rapped along with its advertising agency, interestingly enough, for calculated attempts to mislead. This episode is one of the more egregious examples of abuse by any commerical interest, carried out anywhere, in an unnatural defense of its economic interests." We can now say that the AHA, of which Blackburn is a part, had its knuckles soundly rapped by two government agencies for promoting a pay-for-endorsement seal which nearly everyone agrees would grossly mislead consumers. Moreover, this episode of abusive power by a wealthy and powerful private institution would have dwarfed the egg advertisements. Of course, Blackburn and his fellow AHA members would maintain that the FDA and USDA were wrong in branding the HeartGuide misleading, while holding that the FTC was right in prohibiting the egg advertisements, but that is only natural because the AHA has never admitted to being wrong on anything.

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[a] He had earlier stated that "No organization dealing with cardiovascular disease is more scientifically sound in the eyes of the scientific community or more credible in the minds of the consumer than the AHA."[2872] This was an interesting statement because it did not say that AHA <u>is</u> "sound" and "credible," but rather than it is "sound" and "credible" in the <u>eyes</u> and <u>minds</u> of the scientific community and consumers, respectively.

The Sokolof Affair: The Blind Leading the Blind

Phil Sokolof, a self-made millionaire, suffered a heart attack in 1966 at the age of 43.[3179] By his own description, he had been a nonsmoker, had low blood pressure, was slender and exercised faithfully every day. He presumably had a blood cholesterol level of 300 mg but knowing that (1) most labs in the U.S. cannot measure cholesterol accurately even today, and (2) much evidence (discussed elsewhere) exists that instruments were overestimating cholesterol levels in the 1960s, it is likely that Sokolof's actual level was considerably lower than 300 mg. Furthermore, in all the press given to Sokolof's anti-cholesterol activities, this writer observed no references to whether or not he had coronary atherosclerosis. It would appear that he had no clinical signs of atherosclerosis when he suffered an infarction and has no such signs today at age 67. As we will see in Chapters 3, 8 and elsewhere, heart attacks occur whether or not significant atherosclerosis is present. Nevertheless, someone convinced Sokolof that his heart attack was the direct result of a high blood cholesterol level.

The LRC trial results were published in January 1984. The authors, headed by Basil Rifkind, claimed that cholesterol lowering in the trial reduced heart attacks by 19%. In reality, however, it reduced heart attack rate from 8.7% in the control group to 7.0% in the treated group for a reduction of a mere 1.7% over a 7.4 year period. Since 1.7% would impress no one, Rifkind et al. computed the percentage difference between the percentages (1.7% ÷ 8.7) to come up with the erroneous 19% reduction. Not knowing this devious calculation, Sokolof (and the public) was impressed with the 19% value and apparently decided to start a national campaign.[2904]

In January 1985 Sokolof formed and funded the National Heart Savers Association (NHSA) and became involved in, funded and promoted cholesterol screening programs.[3179] In 1986 the Center for Science in the Public Interest (CSPI) called tropical oils in foods "time bombs."[1925] Riding this announcement, the soybean industry also attacked tropical oils and recommended that food manufacturers replace them with vegetable oils.[1923,1925] In the meantime, Sokolof established his "National Know Your Cholesterol Week" in April 1987.[3179] On March 29, 1988 he placed full-page ads in major newspapers entitled, "He took on a killer."[2231] The ad announced that April would be "National Know Your Cholesterol Month" and contained some erroneous information including "For every 1% you lower your cholesterol, you reduce your risk of a heart attack 2%."

Apparently influenced by the soybean industry's assault against tropical oils, Sokolof launched his own attack with a November 1, 1988 full-age ad in major newspapers.[2230] The ad read, "The Poisoning of America," and it criticized food manufacturers who used tropical oils and lard in food processing. Major food companies subsequently announced that they would cease using such fats in their foods. Another Sokolof ad appeared on March 1, 1989 which announced this fact.[2238]

Sokolof attacked McDonald's restaurants (as well as Burger King and Wendy's) in an April 4, 1990 ad entitled, "The Poisoning of America--Part III."[2999] The ad said, "McDonald's, Your Hamburgers Have Too Much Fat! And Your French Fries Are Cooked With Beef Tallow." McDonald's called the ad "reckless and misleading"[2900] and submitted a letter to newspapers maintaining that "The advertisement is recklessly and maliciously calculated to inflict the greatest possible injury on McDonald's. Any further publication of the advertisement without [corrections]...would have to be considered malicious."[2901] Sokolof's response was to place another ad in July which read, "McDonald's Your Hamburgers Still Have Too Much Fat! And Your French Fries

Still Are Cooked With Beef Tallow."[2902,a] Shortly thereafter, McDonald's indicated that it would replace beef tallow with vegetable fat for french frying potatoes and that low-fat hamburgers would be tested in its restaurants.

There seems little doubt that Phil Sokolof is a sincere person who has dedicated much of his time and money for what he considers a worthy cause and it appears that his affair with that cause is not yet over. However, in view of the fact that virtually every major prospective study in the world has shown that the total death rate and/or the cancer death rate is higher below 180 mg than at more moderate levels, the continuation of the Sokolof affair is tenuous; he indicated that his cholesterol level is now down to 150 mg.

It would be difficult to find a more dramatic example of the old adage, "The blind leading the blind."

MEDICAL RESEARCH METHODS

Associations and Risk Factors

It is most disturbing to acknowledge the fact that so many of the conclusions reached by epidemiologists during the last several decades have been based on observed associations. For example, most of the early "evidence" relating diet and exercise with CHD mortality rates was based on between-population correlations. Investigators of all prospective studies use correlations to classify blood cholesterol and a host of other variables as "risk factors," although the computed correlations themselves are rarely published.

It is also disturbing to recognize that many, if not most, of the epidemiologists who used correlations in their analyses actually had very little understanding of that statistic (see Volume 1). While they were apparently told by their statisticlaly oriented colleagues that correlations do not necessarily reflect cause-and-effect relationships, the concept of association was apparently too compelling to worry about proof of cause and effect. These epidemiologists often "did their duty" by acknowledging that correlations do not necessarily mean cause-and-effect relationships but presented lengthy discussions which suggested otherwise. An excellent example is comprised of the testimonies of Gori, Wynder and Hegsted before the 1976 Senate Select Committee on Nutrition and Human Needs. All three successfully convinced the Committee that diet was a cause of CHD and cancer even though they "did their duty" by presenting the following brief statements:

> "I want to emphasize that this is a very strong correlation, but that correlation does not mean causation.
>
> "Again, I want to emphasize we are not saying that there is a direct relationship between diet and cancer." (Gori,1976[2936])
>
> "...correlation obviously does not mean causation...

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[a] The University of California, Berkeley Wellness Letter announced its agreement with the Sokolof ads, indicating that it had little knowledge as well of the research literature on diet and heart attacks.

"Let me again stress these are correlations and do not necessarily have causative significance." (Wynder,1976[2937])

"I want to emphasize...that these associations between diet and heart disease, cancer, diabetes, etc. do not mean that the same causal factors are involved." (Hegsted,1976[2187])

If Gori, Wynder and Hegsted truly understood the concept of correlation, they would not have presented lengthy discussions of data derived from correlational analyses. Clearly, the statistically naive Committee paid no attention to the above qualifiers because, after all, the "scientists" before them strongly implied causation by virtue of the emphasis they placed on the data.

Since the term "risk factor" has long become popular among epidemiologists, it is most curious that no one seems to know who coined the term or, at least, no one seems willing to give credit to that individual. For example, in 1973 Stamler[573] defined the term and cited two of his previous articles, published in 1967 and 1972, as references, giving the reader the impression that he was the source of the term. An even earlier article by Stamler,[574] published in 1962, again included the risk factor term but failed to indicate its origin. Finally, a 1956 article by Stamler and his colleagues made no mention of risk factors.[694] They defined atherosclerosis as a "metabolic disease." Thus, somewhere between 1956 and 1962 Stamler accepted the concept that CHD was multifactorial, although he probably recognized its existence prior to that period, albeit not necessarily overtly in his writings.

Kannel suggested, in a roundabout way, that he was the originator of "risk factors." Consider the following excerpt from Primary Cardiology:[810]

"A fellow asked me where the term 'risk factors' came from."

"'Gosh', I replied, 'I haven't any idea.'"

"So this fellow pulled out an article of mine, in which in 1956 I had written about 'factors of risk' in cardiovascular disease. 'There,' he said to me, that's the first place I ever saw it.'"

"Well, I don't know about that, I told him. You'd better check back some more."

This Kannelian anecdote is peculiar for three reasons. First, being one of the original epidemiologists investigating chronic diseases, it is difficult to believe that Kannel would say, "Gosh, I haven't any idea," with regard to the origin of risk factors. Second, this writer found a 1959 article co-authored by Kannel entitled, "Some factors associated with the development of coronary heart disease,"[3048] and a 1961 article by Kannel et al. entitled, "Factors of risk in the Development of Coronary Heart Disese."[2093] Both articles represented six-year follow-ups of the Framingham study. And third, being a member of the original Framingham staff, Kannel surely must have known that the earliest Framingham publications by Dawber and his colleagues made frequent reference to "factors" contributing to "risk" of CHD. For example, Dawber, Meadors and Moore indicated in 1951 that the Framingham study was established to determine the environmental and personal factors which are associated with the subsequent development of cardiovascular diseases.[2539] And in 1957 Dawber, Moore

and Mann cited several "factors [which] appear to make independent but varying contributions to risk."[2540]

According to Dawber[3001] the first Framingham article authored by Kannel was in 1952 and it was concerned with the use of single and multiple lead electrocardiograms.[3049] His next article was in 1958.[2542] With the exception of briefly describing a planned diet-CHD study within the Framingham cohort, this article was completely redundant with a summary of the Dawber, Moore and Mann[2540] paper.

Other articles in the 1950s clearly described CHD in terms of multiple causes but did not use the term "risk factors." For example, in 1957 Mann[571] discussed a number of variables thought to be associated with CHD and in their 1957 report to the AHA, Page et al.[512] described atherosclerosis as a "multifaceted disease." They said, "Among those facets presently implicated are heredity, diet, morphologic and chemical anatomy of the blood vessel wall, arterial blood pressure, lipid content of the blood, and sex."

In his testimony before the FTC in 1975 Frederick Stare said, "I believe that the term risk factor was coined by one of the committees of the AHA, and it was a part of the AHA's continuing efforts in public education and in professional education."[2689]

While the Framingham investigators would like to take credit for coining the risk factor concept, Michael DeBakey indicated that it was used before the Framingham study began.[2551] Indeed, Hurst2821 stated that "the risk factor concept was well known and taught by Paul Dudley White and others" in the 1940s and thereafter. (Kannel did not receive his medical degree until 1949.[810]) In his 1952 textbook, J.C. Patterson[2784] devoted a section to "factors concerned in the acceleration of the arteriosclerotic process." And in 1957 Paul Dudley White[2338] repeated his earlier assertions, i.e., the "basic factors behind CHD...include the possible influence of race, the sure influence of heredity, of sex and of age, and quite likely X factors."

It is not really important, of course, who created the "risk factor" concept. However, it is important to recognize, as will be seen many times in this volume, that some Framingham investigators' self-promotions have been exceeded only by their sloppy scientific reasoning and reporting, saturated with contradictory conclusions.

The risk factor concept was originally sound but has since become badly abused and battered. Despite the many comments throughout the literature that correlations do not necessarily imply cause and effect relationships, the research community continues to offer new risk factors to a base that already numbers in the hundreds, originating from only three, i.e., (hypertension, obesity and hypercholesterolemia) proposed in the early Framingham studies.[2540,a] The following are proposed risk factors not included in Volume 1 which this writer encountered during the preparation of this volume.

Mattila et al. suggested that poor dental health may be a risk factor.[2397] Terry and Bjorntorp defined a high waist-to-hip ratio as a risk factor.[2410,2422] Bray and Bouchard called high visceral fat a risk factor.[3244] Yudkin offered sugar as a risk

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[a] Now numbering 200, according to Castelli,[2598] but many, many more if all proposed risk factors were "officially" accepted.

factor[2414] and Bloom et al. claimed that the combination of slenderness and hypertension is a risk factor.[2416]

Friedman suggested that speech hesitation is a risk factor.[2412] Although generally not accepted as such, LaRosa included triglycerides.[1574] Naito indicated that the levels of apolipoproteins are markers for CHD[2411] and Arbogast recommended that low levels of serum Toxicity Preventing Activity (TXPA) be considered a risk factor.[2413] Hamston et al. said that elevated levels of anticardiolipin antibody represent a risk factor.[2415]

A decrease in estrogen in women and an increase in men are called risk factors.[2420] Low serum testosterone is also called a risk factor in elderly men.[2418] Castelli maintained that left ventricular mass, as measured by echocardiography, is a risk factor in older persons (as opposed to ECG detected left ventricular hypertrophy).[2433] Shaper and Pocock entered body mass index into the realm of risk factors.[2421] Jacobson suggested that Indian ghee (clarified butter containing cholesterol oxides) may be a risk factor.[2419] William and Elliot confirmed earlier studies which suggested that a diagonal crease on the earlobe is a risk factor.[2417] Appels indicated that physical and mental exhaustion constitute a risk factor.[2518] Malcolm et al. indicated that being a single man is also a risk factor.[2379]

Malcolm et al.[2379] said that being a single man is a risk factor. Trevisan[2822] maintained that bald men are at greater risk than nonbald men. (Fortunately, he has a full head of hair on the top of his head and much growth on the front and bottom as well, suggesting a very powerful protection against CHD.) Finally, Palmer et al.[2823,3199] and Walker et al.[3198] concluded that being short in height is a risk factor for both men and woemn.

While it would be difficult to choose the one risk factor that appears to be the most ludicrous, latitude or geographic location must be at least within the top five. Elford et al. found an association between CHD events and North-South location in the British Regional Heart study.[2266] CHD was highest in Scotland and decreased in incidence through Southern England.[a] Fleck reported a significant correlation between 30 countries and their latitudes which implied that risk of CHD increases as distance from the equator increases.[2267] Segal also cited a WHO prospective study which indicated an increasing incidence of CHD from South-East to North-West Europe.[2277,b]

Apparently the assumption made by all latitude investigators is that CHD data across all the countries were equally accurate. The possibility and indeed the likelihood that diagnostic and death certification accuracy differences are substantial across these countries is never discussed.

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[a] However, William and Loyd reported the latitude relationship to be in the opposite direction when only Scotland was evaluated.[2269]

[b] Although an abundance of evidence exisits that essential fatty acids (EFA) are not associated with CHD (their consumption has steadily increased in the U.S. throughout this century) Sinclair still targets them as risk factors and claimed that the latitude studies reflect difference in EFA intakes rather than in geographic locarion.[2268]

Post Hoc Analyses

It was emphasized in Volume 1 that much of the literature on diet, blood cholesterol and CHD appears to be based on post hoc analyses. Investigators focus on whatever is supportive of the lipid hypothesis and ignore results which are not supportive. They also sometimes transform unsupportive data so that it becomes supportive. Before giving examples of these processes, let us first examine a hypothetical example which typifies the post hoc analyses that are commonly performed.

Table 2-2(a) shows the hypothetical results of a clinical trial. While CHD deaths were lower in the treatment group, all other types of deaths, including total deaths, were higher. Since the difference in CHD deaths was statistically significant, while the remaining differences were not, these results are typically interpreted as "conclusively" supporting the use of the treatment. The excess numbers of deaths due to stroke, cancer and "other" are typically interpreted as chance findings, even though they may exceed the excess number of CHD deaths in the control group.

While the difference between groups in CHD is interesting and suggestive, it most certainly cannot justify the use of the term "conclusive," in view of the fact that the remaining differences actually demonstrate a greater overall negative effect of the treatment.

Table 2-2(b) shows a different set of results for the same trial. Now there are no differences between groups on the three principal types of deaths but a significant difference on "other" deaths which favor the treatment. Excuses are then given as to why the difference in CHD deaths was not greater (e.g., insufficient trial duration) and great emphasis is placed on the fact that the treatment lowered overall mortality. The conclusion is reached that the treatment is effective in reducing mortality and would probably reduce CHD mortality, given a longer follow-up period.

Table 2-2(c) shows a third set of results from the trial. There are no significant differences between groups on any of the types of deaths but there is a significantly higher overall mortality in the treatment group. These results are typically interpreted as "chance" findings and, in any event, will not likely be cited in future reviews by those who are committed to the treatment.

Most clinical trials evaluating the effects of cholesterol-lowering on CHD do not support the lipid hypothesis, as demonstrated in Chapter 6 of Volume 1, and are therefore omitted in the numerous literature "reviews" by alliance members. The remaining trials which partially support and partially do not support the lipid hypothesis are analyzed and interpreted in post hoc ways to yield "conclusive" findings.

The LRC[500] and Helsinki II[1056] trials, of course, yielded results similar to that of Table 2-2(a). The results of the WHO trial were more closely related to Table 2-2(c). A recent British trial produced results closely akin to those of Table 2-2(b).[2297]

In their attempts to correlate diet with subsequent CHD deaths, Shekelle et al.[2278] and Kushi et al.[472] considered the Western Electric and Boston-Ireland studies, respectively, successful because transformed dietary cholesterol intakes correlated significantly with subsequent CHD mortality, even though the alliance's chief atherogenic dietary substance, saturated fat, did not. In the Seven Countries study,

Table 2-2

Hypothetical examples of post hoc analyses

(a)

Death mode	Number of Deaths Treatment	Control	Significance?
CHD	50	75	YES
Stroke	25	15	NO
Cancer	30	20	NO
Other	20	10	NO
TOTAL	125	120	NO

(b)

CHD	50	52	NO
Stroke	21	19	NO
Cancer	25	25	NO
Other	5	25	YES
TOTAL	101	121	YES

(c)

CHD	50	52	NO
Stroke	21	19	NO
Cancer	30	20	NO
Other	20	10	NO
TOTAL	121	101	YES

however, saturated fat was emphasized as the atherogenic agent, while dietary cholesterol was completely ignored.[a]

Whether or not alliance members will admit that they frequently indulge in post hoc analyses in order to salvage studies designed to provide evidence in support of the lipid hypothesis, it is painfully obvious that they do so indulge. Criteria for "success" change from one study to another and data are manipulated (e.g., transformed, compiled in confounded ways or even ignored) so that negative or otherwise dubious findings appear to be strongly positive.

Too many medical researchers do not understand the dangers of post hoc analyses because they simply do not understand statistics. Whenever one begins to look at all subgroupings of data, one will find statistically significant differences by chance alone, particularly if there are many differences tested. As long ago (1969) emphasized by Cornfield and (NHLBI's) Mitchell,[488] significance P values "were not really designed for the uses to which they are now put. P values are not intended to test hypotheses suggested by the data. Although all the trials considered were designed to test a general hypothesis formulated before the trial started, the P value is computed for a specific hypothesis and one necessarily suggested by the data, for a certain end point (e.g., angina pectoris), in a certain subpopulation (e.g., below age 65) and for a certain time after the initiation of treatment (e.g., five or more years). There is nothing sinful about having data suggest hypotheses. But the P value assigned to the traditional calculation to hypotheses so suggested does not have the usual interpretation of the relative frequency with which a true hypothesis would be erroneously rejected. The relative frequency is, in fact, greater and, in many circumstances, can be much greater than the nominal P value. Small P values, therefore, do not make the inferences as safe as they seem, as is indicated by the diversity of results."

In effect, if the difference between a control and a treatment group on a specific measure is significant and confirmed in subsequent experiments or trials, we may feel confident of these overall results. However, it is highly likely that post hoc analyses will reveal quite different trends among subgroups for each experiment or trial. For example, in one trial treatment may have been more effective for those over 65 than for those under 65, while in another the opposite may be the case. But in both cases, the treatment may be effective when all ages are considered. Real world examples of this issue can be seen in Stamler's and Dayton's remarks. The Minnesota Mental Hospital trial yielded no overall effects of cholesterol-lowering on CHD events.[555] Stamler[539] did not note this rather important fact but instead told his readers that the study showed significant effects for men under 40 years of age. In their report on the Veterans' Diet trial Dayton et al.[454] reported some significant findings based on post hoc (1) pooling of irrelevant data, i.e., summing cerebrovascular with coronary events, and (2) differentiating between those over and under 65 years. In an article published in the same year (1969) Dayton and Pearce[2541] explicitly criticized the reporting of post hoc significance testing. They said that "a significant effect (if one is found) should be demonstrated on the predefined primary end point, with no pooling of endpoints and with no stratification of the study population." Subsequently, Dayton[2729] told the 1977 Senate Select Committee that his trial showed that a cholesterol-lowering diet reduced CHD events in men under 65 years.

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[a] The Seven Countries, Western Electric and Boston-Ireland studies are discussed in considerable detail in Chapter 4.

The problems of post hoc analyses are by no means restricted to experiments or trials. They are evident, for example, in studies which attempt to correlate masses of independent variables with one or more dependent variables. As described elsewhere in this volume alliance members correlated all conceivable nutrients with CHD in a prospective study and found only carbohydrates to be significant. Therefore, the authors focused on the importance of carbohydrates even though fat, saturated fat and dietary cholesterol have long been accepted by the alliance to be the atherogenic nutrients.

The above discussion by Cornfield and Mitchell make it clear that NHLBI has long been aware of the problems and dangers of post hoc analysis. Yet, NHLBI has funded an enormous number of studies that perform post hoc analyses routinely. One can only conclude, therefore, that NHLBI approves of such analyses if they promote the diet-CHD notion.

Avoiding the Independent Effects of a Variable

Many studies have involved the evaluation of, for example, the effects of blood cholesterol level on death rates averaged across other variables which were included in the studies and authors have typically said that "the effects of cholesterol were significant and that this relationship held true even after controlling for variables A, B, C, etc." However, rarely have they presented the relationships after controlling for the effects of other variables, making it impossible to assess the importance of the independent effects of the primary variable of interest or that of any other variable.

Consider a hypothetical example in which the overall numbers of deaths in the low and high cholesterol groups are 250 and 300. Although this difference appears to be impressive, it could be partially, mostly or entirely due to an interaction with one or more other variables. Figure 2-2 shows one such example. The numbers of deaths are broken down into 2 X 2 X 2 table. While the total deaths in the low and high cholesterol groups are 250 and 300, respectively, it is clear from the larger table that the difference between low and high cholesterol is due solely to the "high A + high B" condition. There are no effects whatsoever of cholesterol level in the "low A" condition, whether or not B is low or high, or in the "high A + low B" condition.

If one focuses entirely on the totals within the low and high cholesterol level cells, a common practice observed in the literature, readers will obtain the misleading impression that the effects of cholesterol are essentially the same with variations in other important variables when, in fact, the effects are highly specific. If the "high A + high B" condition represents a small proportion of the population, then a conclusion drawn from the totals would be highly misleading. Some actual examples of such incomplete reporting are presented elsewhere in this volume. It is scientifically inexcusable not to present interaction effects except when they have no statistical significance. In the latter case, authors should provide results of a statistical test to assure readers that there were indeed no significant interactions. Unfortunately, authors rarely fulfill this requirement and it is suspected that this tactic is a ploy to hide undesirable results.

Some actual examples of such incomplete reporting can be found elsewhere in this volume, particularly in Chapter 10.

Meta-Analysis

Meta-analysis is a relatively new term for an old concept. If many relatively

A	Low A				High A			
B	Low B		High B		Low B		High B	
Chol.	Low chol	High chol	Low chol	High chol	Low chol	High chol	Low chol	High chol
Deaths	30	30	50	50	70	70	100	150

	Low	High
A	160	390
B	200	350
chol	250	300

Figure 2-2. Hypothetical study showing number of deaths by two levels of each of two variables, A and B, and cholesterol level.

small, clinical trials yield nonsignificant differences between treatment and control groups, the combining of all trials results in a much larger N (samle size) which is necessary for demonstrating statistically that a small difference is statistically significant. In theory, meta-analysis is a useful technique. In practice, however, it may well be another nail in the medical analysis coffin. First and foremost, as was emphasized in Volume 1, statistical significance is important because it provides a high level of probability that a diference is real but it is not a sufficient condition for assessing the importance of a difference. In an applied discipline where costs are always a major consideration, a small difference must be shown to be cost-effective, whether or not it is statistically significant.

Thomas Chalmers indicated that "Meta-analysis is the wave of the future. The days of the expert supposedly putting the state of the field [art] into a review article are numbered."[2907] Chalmers said, "The issue is the increasing recognition that scientists don't apply the rules of science when they do traditional reviews."[2909] Chalmers and others apparently believe that meta-analysis will solve the problems inherent in the subjective and biased process of reviewing the literature but, of course, it will not because the very biases that distort a literature review will certainly operate in the process of conducting meta-analyses. For example, the person who selectively omits certain studies in literature reviews because they do not conform to his hypotheses, is certainly not going to suddently include those studies in a meta-analysis. The real problem is not the goodness of technique but rther the abuse of technique. It is naive to think that meta-analysis has the capability of eliminating that abuse. It can and probably will, in fact, magnify that abuse. Equally important, the reader will be less capable of detecting abuse than in literature reviews because individual study results will likely be unobservable.

Thacker listed five major problems with literature reviews.[2908] The first was sampling bias due to reporting and publication policies. Many authors obtaining negative or neutral results may not submit their articles to journals and many journals may not accept articles with negative or neutral findings. We all know that this problem has always existed. We also know that it is equally relevant to meta-analysis.

A second problem of literature reviews noted by Thacker is the fact that many studies lack specific data necessary for comparing results of all studies. This problem is again relevant to both literature reviews and meta-analysis.

A third problem is the selective exclusion of studies by the reviewer. As noted above, this problem is certainly relevant to meta-analysis as well.

A fourth problem is comparing studies which have an "uneven quality of the primary data." Need it be emphasized that this is also a substantial problem in meta-analysis.

Thacker's fifth problem with literature reviews is the fact that reviewers often draw biased interpretations from their analysis of studies. Indeed they do but at least these biases can be detected by many readers who are at least partially familiar with the literature. Biased interpretations can be made with meta-analysis but their detection may be impossible because the biases can occur in the unobservable process of performing a meta-analysis.

There is an old computer adage--garbage in, garbage out. This adage is equally applicable to meta-analysis. If the quality of the data entered into a meta-analysis is bad, the quality of the outcome will also be bad. In Volume 1, the importance of randomization and blindedness in clinical trials was stressed. Let us examine these

concepts in relation to meta-analysis. The assumption underlying the generalizing of clinical trial results to a population is that the subjects in a trial are randomly selected from that population. Rarely has this been accomplished. In fact, clinical trials have purposely been designed to involve nonrandom samples from populations. When one combines data from these nonrandom samples from different (country) populations, one seriously violates the principle of randomization. Although the generalizing of results from such analyses is probably not appropriate, it will be done routinely because, after all, one is not going to perform a meta-analysis and then suggest that the results are not generalizable.

Mann[2907] cited Peto as indicating that only the results of randomized trials should be used in meta-analysis. As important as randomization is, in view of the biases that virtually saturate the medical literature, blindedness is an equally important criterion for inclusion of trial results in a meta-analysis. Lack of randomization can distort findings and/or make them less generizable but lack of blindedness can yield completely false results. As shown in Volume 1, the vast majority of effects observed in blood cholesterol-lowering clinical trials derived from unblinded trials. It is naive and outrightly foolish to include unblinded trial data in a meta-analysis because it is almost completely certain that such data are highly biased. Yet, that is precisely what meta-analysts will likely do because, after all, such studies are given equal weight in conventional literature reviews.[a] However, conventional reviews at least sometimes indicate which studies were and were not blinded and thus permit readers to exclude those studies from their own interpretations of the overall state-of-affairs.

A major abuse of the process of analyzing and interpreting trial and prospective study data is the emphasizing of certain findings and de-emphasizing of other findings. For example, while studies may show that the lower the cholesterol level, the lower the CHD "event" or death rate, they also often show that the total mortality increases and that other serious side effects (e.g., gallstones and gall bladder operations) result from cholesterol-lowering. The bottom line of a treatment program is overall health, not merely the resolution of a specific health problem. While conventional reviews often include at least some discussion of side effects, all-cause death rates, etc., meta-analysts are likely to exclude all but the data of prime interest, namely CHD event rates. In many (if not most) cases, the most important data will be excluded.

It is true that conventional reviews are, more often than not, atrociously biased. We emphasized that problem in Volume 1 and elsewhere in the present volume. However, meta-analysis will not in the least solve the bias problem. It will merely create the illusion of precision. In a sense, it will produce the same error to more decimal places.

Statistically speaking, the whole is more than the sum of its parts. A large clinical trial can yield more and better findings than a series of small studies whose n's are equal to N. This is because random error diminishes in importance and more variables and their interactions can be evaluated. Although small "pilot" studies are useful in determining whether a large study should be conducted, it is neither cost-effective, nor sensible for NHLBI and AHA to fund dozens and dozens of small studies when a large study can be conducted. In no way will meta-analysis somehow make a large study out of many small studies. If variables A and B are included in one trial and B and C are included in another trial, meta-analysis (or any other technique) cannot determine the individual effects of A, B and C when all are considered

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[a] For example, Holme[1899] combined 10 unblinded trials, including his own, with 9 blinded trials in his meta-analysis.

simultaneously because of notorious interactions that often occur between variables. For example, a cholesterol-lowering drug may reduce cholesterol level in hypercholesterolemics by 20% but only 5% in those having "normal" levels. Moreover, CHD mortality may be reduced in hypercholesterolemics but total mortality may be increased in hypo- or normocholesterolemics. Knowledge of these kinds of interactions are of extreme importance when generalizing results to a population. Unfortunately, the need to keep the medical research community happy by assigning thousands of individual grant projects will forever limit the number of large trials. While some give the impression that meta-analysis will somehow compensate for the lack of large trials, common and statistical sense should reveal that such most emphatically will not be the case.

Although not addressing meta-analysis per se, Cornfield and (NHI's) Mitchell[488] considered the general problem of combining trial data as long ago as 1969. They said, "If the only weakness of most previous studies were inadequate size, it could be corrected by combining results. But there are other weaknesses and there is no theorem which says that the error in the combinded results of n inadquately controlled studies decreases as the square root of n."

Garbage in, garbage out. But few people will recognize this fact, unfortunatley, and meta-analyses will be performed with repetitive abandon throughout medical research. Katerndahl and Cohen[2953] stressed that "careful meta-analytic procedure protects against most potential biases." But since biases are more often purposeful than inadvertent, few "careful" meta-analyses will likely be performed. Even when they are not purposeful, their effects will be the same. For example, Muldoon et al.[2927] conducted a meta-analysis on 6 clinical trials which met specific criteria. One of those trials was sponsored and performed by the Upjohn Pharmaceutical Company (Dorr et al.[843]) which reported, not so surprisingly, that its cholesterol-lowering drug greatly reduced both total and CHD mortality. The difference between treatment and control groups in CHD mortality for all trials was 37 and 60% of this difference was contributed by the Door et al. trial. In view of the facts that (1) no trial acceptable to either the alliance or its critics has demonstrated a significant reduction in either total or CHD mortality by cholesterol-lowering, and (2) the Dorr et al. trial was conducted by a highly vested interest company, it is dangerous and inappropriate to include it in a meta-analysis. While one may wish to give the Dorr et al. study the benefit of the doubt, it must be remembered that the ultimate recipients of errors of judgment are patients. In meta-analysis the rule of thumb should be--if there is some reason to believe that a trial is biased, the trial should be excluded. Even though the Dorr et al. study was said to be randomized and blinded, there is certainly reason to believe that the trial was quite biased.

Intention to Treat

Consider a hypothetical 5-year clinical trial composed of two groups. One group of 500 subjects were given a placebo (control group) and the second group of 500 subjects were asked to consume a cholesterol-lowering drug (treated group). Suppose that 450 subjects (90%) in the treated group refused to take the drug. Would the reader still classify these 450 subjects as treated subjects and include them in the treated group when comparing the two groups in terms of CHD event rates five years later? We would most certainly hope that not a single reader would answer in the affirmative. But while the answer is obvious, the question is not frivolous, as we shall see.

Suppose that 50% of the drug subjects refused to take the drug during the 5-year trial. Would the reader include the 250 "dropouts" in the statistical analyses? Of course not. Suppose that 5% refused the drug. Would the reader include those 25 "dropouts" in the final analyses? No, and for the same obvious reason that an

untreated subject is not a treated subject and it makes no scientific sense to compare an untreated subject with an untreated subject to determine the effects of treatment. Yet, the practice of including untreated subjects with treated subjects is commonplace. It falls under the rubric of "Intention to Treat," as though an "official" term somehow transforms a scientifically unsound procedure into scientific rspectablility.

As will be seen in Chapter 6, the recently published cholesterol-lowering trial of Buchwald et al.[3058] included 421 subjects as treated subjects even though 22 (5.2%) refused treatment at the outset. They also included another 23 subjects (5.5%) who stopped treatment during the trial. Thus, for all practical purposes, about 8% of their treated subjects were effectively untreated. More than a third (36%) of the "treated" subjects in the European Working Party on High Blood Pressure in the Elderly trial[3114] dropped out or were withdrawn from that study but were nevertheless included in the final data analyses 4.6 years later. And 30% of the subjects in the 1987 Helsinki trial[1056] dropped out of that study but not out of the data analysis.

Theoretically, the inclusion of control subjects with treated subjects would reduce the differences between groups and make it more difficult to show significant effects of treatment. Are alliance members purposely biasing their results to make it more difficult to achieve significance? If so, why did the LRC authors reduce their accepted significance level from .01 to .05 after the results were analyzed (Chapter 7)? And why do many alliance members regularly accept findings as real when they fail to reach statistical significance? Even a cursory examination of the literature reveals quite clearly that few, if any, alliance members ever attempt to prove the null hypothesis, i.e., a treatment has no specified effects. Why, then, do some investigators include dropouts and completely untreated subjects as treated subjects, while others do not?

In the dozens of clinical trials that have been conducted the differences between treated and untreated groups have been remarkably slight, even when significant differences are calculated. What this means is that the distribution of responses to treatment greatly overlap with the distribution of responses to no treatment. In effect, most untreated subjects will not exhibit CHD events during a trial and some treated subjects will exhibit such events. If dropouts or completely untreated subjects exhibit fewer CHD events than do regular control subjects, significance of "treatment" will more likely be achieved by including the untreated dropouts than by omitting them. Of course this is an unethical practice but there is abundant evidence throughout the literature that it is a common practice. As emphasized in Volume 1 and Chapter 7 of this volume, for example, there is no doubt whatsoever that unethical practices after the data were analyzed transformed the LRC trial results from nonsignificant to significant. Manipulations of groups after-the-fact are commonplace and, as noted by Feinsten,[2245] epidemiologists "do not seem upset by investigators" performing such manipulations.

Correlations

Volume 1 presented a discussion of correlations, their interpretations and abuse. Here we wish to focus exclusively on how many epidemiologists misinterpret correlations, particularly when they report many of them in a single study. Two issues are important. One is the strength of a correlation and its statistical and practical significance. The other is chance significance within groups of correlations. A 1979 autopsy study by Feinleib, Kannel and their associates[3366] may be used to illustrate these issues. This study correlated a number of antecedent risk factors with measures of atherosclerotic severity at autopsy in 127 men and women. The correlations were computed for risk factors measured 1 year, 5 years and 9 years before death. Since

there were seven risk factors, four measures of atherosclerosis and two sexes, the authors reported 168 correlations. Table 2-3 shows a sample of the 168 correlations, namely, 12 correlations between two measures of atherosclerosis and two risk factors for three risk factor measurement periods and for each sex.

The Strength and Significance of Correlations. Volume 1 indicated that when a perfect correlation exists between two variables, we can say that whenever a certain amount of Variable A occurs, we can predict the exact amount of Variable B that will occur, and vice-versa. When a less than perfect correlation exists, we can only say that whenever a certain amount of Variable A occurs, there will be a "tendency" for a certain amount of Variable B to occur. As the correlation becomes weaker, so does the tendency to predict the amount of one variable from the occurrence of the second variable. The mathematical term that describes the exact percentage of one variable from the occurrence of another is the square of the correlation. Thus, a correlation of .3 indicates that ($.3^2$ = .09 =) 9% of the variation of one variable is explainable by the occurrence of another variable. Some 91% of the variation remains unexplained. Moreover, it must always be remembered that no matter how strong a correlation is, there is absolutely nothing inherent in a correlation that suggests a cause and effect relationship. Correlations or associations occur by the millions everywhere and most are either coincidental or caused by third factors, e.g., height and foot size are highly correlated but neither affects the other; genetics determines both. The explanatory power of a squared correlation does not mean "cause." Direct, scientific evidence is necessary to establish cause and effect. However, a correlation may, in fact, be reflective of a true cause and effect relation, particularly if it is very strong.

If a correlation between blood cholesterol level and severity of atherosclerosis were .9, this would mean that cholesterol level could predict the severity of atherosclerosis in 81% of the population. If the correlation were only .3, cholesterol level would predict the severity of atherosclerosis in only 9% of the population. In the other 91% of the population, cholesterol level would have no influence whatsoever. Thus, correlations of .3 or even .4 (16%) have very little practical utility and can at best be said to be reflective of an extremely weak, possible cause and effect relationship.

Returning now to Table 2-3, it can be seen that virtually all of the correlations between atherosclerotic severity and the two variables of "age at death" and "cholesterol level" were extremely weak for men, having explanatory powers ranging from 0.01% to 13%. Modestly strong correlations can be seen between severity and age at death for women, yielding explanatory powers of 17.6% to 37.2%. However, the relation between severity and blood cholesterol remained quite weak for women as well.

Despite their weakness and very low explanatory power, a number of correlations were reported by Feinleib et al. to be statistically significant. As emphasized in Volume 1, statistical significance may (and may not) reflect a true effect but it says nothing about whether or not the effect has practical importance. For example, the cholesterol correlation suggests that one must "treat" 100 people in order to affect 5 to 13 persons. Moreover, the magnitude of the effect may be slight. As will be seen in Chapter 7, extremely costly treatment of 1900 men for 7.4 years in the Lipid Research Clinics trial resulted in the reduction of only 1.7% CHD events and no reduction in all-cause death rate. The cost per "event" saved was so high it was totally impractical to consider widespread use of the treatment. Such treatment is widespread, however, because the alliance has disregarded practical significance and focuses entirely on statistical significance.

Table 2-3

Males	Correlations Age at death	Chol.	% of Variance[a] Age at death	Chol.
1 year before death				
% luminal involvement	-.03	.27[b]	.09	7.3
% luminal insufficiency	.06	.22	.36	4.8
5 years before death				
% luminal involvement	0.1	.36[b]	.01	13.0
% luminal insufficiency	.08	.32[b]	.64	10.2
9 years before death				
% luminal involvement	.03	.32[b]	.09	10.2
% luminal insufficiency	.05	.27[b]	.25	7.3
Females				
1 year before death				
% luminal involvement	.53[b]	-.05	28.1	.25
% luminal insufficiency	.42[b]	-.05	17.6	.25
5 years before death				
% luminal involvement	.54[b]	-.06	29.2	.36
% luminal insufficiency	.47[b]	-.04	22.1	.16
9 years before death				
% luminal involvement	.61[b]	.26	37.2	6.8
% luminal insufficiency	.55[b]	.32[b]	30.3	10.2

[a] Not computed by Feinleib et al.

[b] Statistically significant.

Chance Significance. Table 2-3 shows that the correlations between atherosclerotic severity and age at death were effectively zero among men and modestly strong among women. This was a uniquely strange finding and highly unlikely to be reflective of reality because virtually all evidence indicates that atherosclerosis is highly correlated with age for both sexes (e.g., Eggen and Solberg,[3400] Rickert et al.,[3401] Okumiya et al.[3368]). But rather than even consider their findings possibly due to chance, Feinleib et al. attempted to explain them with the use of the "may" concept described in Chapter 1, i.e., "The lack of correlation between age at death and coronary artery atheromata in Framingham males might be explained by the leveling off of atherosclerosis after a certain age as shown by others." However, they cited only one study (Giertsen) and indicated that it showed a leveling off of CHD after age 40-49. Although Feinleib et al. strangely did not provide readers with the age range and mean age of those autopsied, they did present some of their data for age groups "under" and "over 65 years." Clearly, such groups should have shown a graded relation between atherosclerosis severity and age.

Feinleib et al. also said that "The strong association of diseased coronary arteries with age at death in females but not in males supports the notion that the disease progresses at different rates in men and women." They went on to contradict themselves by citing an autopsy study by Eggen and Solberg as showing that women "enjoyed less involvement with the more severe raised lesions until the 7th decade when the sexes approached equality." This explanation actually argues against Feinleib's statement, i.e., the greater growth of atherosclerosis among men until the 7th decade indicates that strong correlations should have been observed for men, while weak correlations should have been seen for women. The fact is that the correlations computed by Feinleib et al. were opposite to reality and probably reflected chance findings and/or problems in measuring the severity of atherosclerosis, likelihoods that were not addressed by the authors.

Table 2-3 also shows that the correlations between severity and cholesterol level were relatively stable for risk measurement periods of 1 to 9 years for men but were effectively zero for women until 9 years of follow-up. Feinleib et al. said, "The failure to find a strong consistent correlation between serum cholesterol and atherosclerotic involvement in women in puzzling. This may be due to the known sex differences in lipid patterns. It also substantiates the contention that the evolution of atherosclerotic heart disease may be somewhat different in men and women." But, of course, such explanations are contrary to the Framingham investigators' long-time contention that the higher the cholesterol, the more rapid the atherosclerosis development. "Sex differences in lipid patterns" and "the evolution of atherosclerotic heart disease" are simply not relevant to the issue.

To illustrate even more how alliance members use illogics to explain apparent anomalies. Feinleib et al. cited Paterson who found no correlation between cholesterol level and postmortem atherosclerosis 6 years before death. Feinleib said, "However, in contrast to the Framingham subjects, these patients were not free-living but ate approximately the same diet with a specific range of both calories and fat content." The question is--so what? Cholesterol level was the variable of importance, not diet, and Feinleib did not offer evidence or directly suggest that Paterson's subjects all had essentially the same cholesterol level.

Comments. Correlations vary from study to study, often showing opposite implications. The above comparison of Feinleib et al.'s and Paterson's findings is a case in point. Another excellent example was presented by Reed et al.[3399] in 1989. They pointed out that the Oslo [autopsy] study "found a protective effect [of HDL] in the coronary, but not the cerebral, arteries, while we found a protective effect in the cerebral, but not the coronary, arteries." Few alliance members seem to recognize

that observed correlations of about .4 or lower are very likely to be due to chance or inaccuracies in measurements. As a consequence, the literature is saturated with tables of weak correlations that contradict each other and, often, reality. Every significant correlation, no matter how weak it is, is generally taken seriously. Even nonsignificant correlations are often discussed as reflecting meaningful relationships. For example, in their table of 45 correlations, Reed et al.[3399] asterisked coefficients at both the significant .05 level and the nonsignificant .10 level suggesting that both were statistically significant. One such nonsignificant coefficient related LDL cholesterol level with percent raised lesions. The fact is that most correlations below .5 are either chance occurrences, artifacts of measurement, or of little practical utility in any event.

It is absolutely fallacious and unequivocally wrong to compute a mass of correlations and then apply statistical tests to all to determine which are and are not statistically significant. This constitutes post hoc analysis and the fact that many epidemiologists perform this analysis time and again is yet another example of their complete lack of understanding of statistical tests.

3. CORONARY HEART DISEASE, FOOD CONSUMPTION TRENDS AND BLOOD CHOLESTEROL LEVELS

"By 1940, coronary artery disease was the leading cause of death in the United States."

(Robert Levy & Manning Feinlieb, 1984[1401])

"The industrialized countries are indeed being ravaged by an epidemic of coronary disease especially among males."

(Jeremiah Stamler, 1973[573])

"It may be that coronary heart disease is seen by the public as a relatively new disease. In actual fact, heart disease has been the number one killer in the United States since at least 1910."

(NHLBI director, Theodore Cooper,1972[2085])

"Heart disease has been the number one killer of women for 81 years."

(1988 AHA president, Bernadine Healy,1989[2517])

INTRODUCTION

The biases exhibited by the alliance are no better exemplified than in discussions of the so-called 20th century CHD epidemic and decline, and their presumed causations. We will see that the ignoring of relevant data and the purposeful misinterpretation of other data have been so profound, there can be no other explanation than to conclude that alliance members engaged in a conspiracy of fraud. Let us first examine reported CHD mortality trends as, apparently, they have never been fully presented before.

Although research data and interpretations of data have so often been distorted by the alliance, it was nevertheless assumed during the preparation of Volume 1 that at least the alliance's plots of CHD mortality rates over time were probably accurate representations of the disease's trends. However, during the preparation of the present Volume, a number of independent pieces of information led to the growing suspicion that the alliance's plots might also be distortions of reality. For example, Gordon and Thom made the following statement in 1975: "From 1939 until recent years there has been a remarkable increase in reported mortality from CHD. From 1940 to 1960 the crude CHD death rate increased 49.5%."[533] Since a high crude death rate is a reflection of a population with a long life expectancy, the use of crude rates suggests that the age-adjusted rate increase was probably much lower.

CHD TRENDS OVER TIME

The use of the word "reported" implies the possibility that reported death rates may be different from actual death rates. Interestingly, a comment by Goldman and Cook regarding the CHD mortality decline probably has more relevance to the so-called epidemic than to its decline. They stated that "Although the apparent decline in ischemic heart disease mortality may represent one of the vagaries of the inaccuracies of death certificates, there is no evidence of increasing mortality from other diagnostic labels that might have been substituted for ischemic heart disease."[2353] Such a statement begs the question as to what diagnostic labels may have been replaced by ischemic heart disease during the so-called epidemic.

Of equal importance is the question--why did Gordon and Thom use "crude," rather than age-adjusted death rates. As pointed out by Tunstall-Pedoe, crude, all ages CHD death rate data are quite misleading.[2247] For example, the National Health Service in England reported that Sweden has the highest crude CHD death rate of all advanced countries.[2273] Tunstall-Pedoe explained that Sweden has a "high life expectancy and a large proportion of elderly people who die at an advanced age from CHD." When age-adjusted data are used, Sweden only ranks 12th among advanced nations.[2247] Thus, Gordon and Thom's use of crude death rates also exaggerated the U.S. data as well because of the high life expectancy in the U.S., as will be seen.

A second piece of information was discovered in an address at the 1972 AHA meeting by the then NHLI director, Theodore Cooper. He made the following statement which clearly indicated that the reported CHD mortality rates during earlier decades were not reflections of true rates: "It may be that coronary heart disease is seen by the public as a relatively new disease. Impressions given by outstanding physicians and scientists may have conveyed to the layman an idea of 'newness' in this disease. For example, Dr. P.D. White is quoted in Family Circle Magazine as saying" 'When I was an intern at Massachusetts General Hospital in 1941 there was no department of cardiology. Infectious diseases were our great problem then.' Notice Dr. White does not say that there was no heart disease, just that there was no department of cardiology. But the implication to the lay reader is that heart disease did not kill many people at that time and that it has only recently become a public health problem. In actual fact, heart disease has been the number one killer in the United States since at least 1910."[a]

It is of interest to note that in her effort to emphasize the importance of CHD in women, 1988 AHA president, Bernadine Healy, also suggested indirectly that the CHD "epidemic" was artifactual. In 1989 she said, "Heart disease has been the number one killer of women for 81 years."[2517]

The reader should recognize that the statements of Cooper and Healy, separated by 16 years, were not at all speculative or opinionated in nature but rather clear expressions of fact.

A third piece of information derived from an article by pioneer researcher, George Mann.[571] He published a very detailed analysis of the reported 20th century "epidemic in terms of changes in the International Classification of Diseases (ICD), diagnostic 'fashions' and other factors. He concluded, "the available evidence indicates that the increase in CHD revealed by vital statistics is largely artificial." Indeed, his analyses were so thorough and convincing, it is difficult to believe that any objective observer could reject them and maintain faith in the epidemic concept.

A fourth piece of information emerged from a statement by Keys in 1953, i.e., "...the broad category of heart disease, or diseases, diagnosed by the clinician as angina pectoris, coronary heart disease, myocardial infarction, chronic myocarditis and myocardial degeneration. In hospital and vital statistics it is rarely possible to differentiate these clearly so it is convenient to group them, for the present purpose, as 'degenerative heart disease.' In the past 30 years [1923-1953], which is as far as acceptable records extend, the age-specific death rate from degenerative heart disease

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[a] Yet, speaking before the Senate Select Committee four years later as an Assistant Secretary for Health, Cooper referred to CHD as "the modern epidemic."[2186]

is certainly not decreasing.[a] For males, under 70 years, in fact, it is difficult to deny that there has been a steady upward trend. This is particularly striking in view of the fact that the total age-specific death rate, from all other causes, is steadily falling."[279]

The statement by Keys is loaded with subtle clues, though apparently unintended. For example, his definition of CHD included chronic myocarditis, an infection of the myocardium, and myocardial degeneration which may derive from myocarditis, coronary artery ischemia or perhaps other causes. But in the context of atherosclerosis, myocarditis is not a relevant disease and myocardial degeneration is also not relevant if it is not caused by coronary atherosclerosis.

The emphasis on the relative inability of clinicians to distinguish between the various stated diseases in 1953 clearly illustrates the diagnostic problem and, therefore, the inaccuracies in death certification that must have occurred the first 50 to 60 years of this century. Atherosclerosis of the coronary arteries was undoubtedly a highly prevalent disease for decades but simply not recognized as such.

Other subtleties in the Keys statement include (1) the suggestion that no increase in the CHD mortality rate for females could be detected and (2) the inconsistency inherent in the concept that the CHD death rate was increasing substantially while the overall death rate was decreasing substantially. These are extremely important points which are addressed more fully later.

A fifth piece of information derived from a 1932 study by Robert Levy[3158] who would much later become a staunch promoter of the CHD epidemic concept. Levy reviewed the clinical and pathological records of a New York City hospital between 1920 and 1930. He indicated that there was a 400% increase in the frequency of reporting coronary diseases as the cause of death during that decade but pathological records showed the incidence of coronary disease had remained almost constant. Levy noted that the growing popularity of using coronary disease after 1920 was probably due to the 1912 and 1919 papers of Herrick.[b] While Levy undoubtedly detected a major flaw in the CHD epidemic hypothesis, it was not apparent in his writings in the 1970s when the CHD epidemic concept was being promoted.

It may also be added that even in 1961 Keys[1993] regarded the electrocardiograph as a poor diagnostic tool, i.e., it "doesn't hurt anybody and looks impressive in a doctor's office, but it is a poor predictor of coronary disease."

All of the above authors indicated very strongly, either directly or indirectly, that the CHD "epidemic" was an artifact, created primarily by increasing knowledge of coronary atherosclerosis, leading to major changes in ICD definitions and increasing assignment of death to CHD as a result of this knowledge and available new definitions. We believe that the considerable evidence presented below effectively proves that there was not, in fact, a CHD epidemic. However, before initiating that discussion, it is useful to first describe the alliance's steadfast position which was and is based on an almost religious belief in the occurrence of an epidemic and a general unwillingness to recognize the enormous flaws in the reported vital statistics. That

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[a] Keys will much later (1975) state "It is generally agreed that...vital statistics on CHD death rates before the 1930s are meaningless..."[540]

[b] James Herrick, founder of the AHA in 1915,[1677] was apparently the first to "link the clinical signs and symptoms of myocardial infarction with atherosclerosis and thrombosis of the coronary arteries in 1912."[1800]

position is exemplified in numerous redundant articles by Stamler. Let us consider his 1962 article.[574]

Stamler reviewed the health picture of Americans during the 20th century. "This has been a period of remarkable advance. Progress has been particularly great in lengthening the life expectancy at birth. For all persons, life expectancy at birth increased more than 20 years, from about 48 years in 1900 to about 69 years in 1959. This phenomenal advance in life expectancy is attributable first of all to the conquest of infectious diseases, particularly acute infectious diseases in young children, which previously took a heavy toll. Appreciable decreases in mortality among middle-aged and older people also have occurred during recent decades, largely as a result of advances in the control of infectious diseases, particularly pneumonia and tuberculosis. A major consequence of these developments has been a marked increase in the number of middle-aged and elderly persons in the U.S. by 1960 there were almost 17 million persons aged 65 and over--more than five times as many as in 1900. In the same period the number of middle-aged persons (45-64) increased from 10 million to 36 million. Persons 65 and over and those 45 to 64 constituted 4% and 14%, respectively, of the total population in 1900; by 1960 these percentages had increased to 9% and 20%." Now after exalting the great progress in the extension of life among middle-aged persons and among those over 65 years, Stamler continued, "However, for the increasing millions of middle-aged and elderly persons, the outlook for life expectancy today is only moderately better than it was at the turn of the century."

Stamler's exposition of this subject leaves no doubt that the population profile had moved toward a distribution burgeoned with middle-aged and elderly persons--during the period in which he and other alliance members claimed that a CHD epidemic had taken place. Since CHD is a degenerative disease, clearly a bulging older group would naturally increase the crude CHD mortality. In their 1957 report to the AHA, for example, Page et al. cited Lew as concluding that "30% of the increase in the crude death rate from CHD since 1940 is due merely to the aging of the population."[512]

Later in his 1962 article Stamler noted that "during the last 10 to 15 years knowledge of the occurrence of atherosclerotic coronary heart disease in the U.S. has increased greatly." Note that he said, "Knowledge of the occurrence of CHD," not "knowledge of CHD." No discussion whatsoever was given regarding the major change in the ICD which occurred during that period (1949) and which resulted in a huge and sudden increase in reported CHD deaths. Referring to Page et al.'s citation of Lew once again, "another 40% of the increase in the crude death rate [since 1940] can be ascribed directly to the changes in procedures and classifications adopted with the 6th revision (1949) of the International Causes of Death."[512] Moriyama and Gover[3088] illustrated the dramatic influence of an aging population on the death rate. As the percentage of the population 45 years and older increased from 18% to 27% during the period 1900 to 1940, the percentage of total deaths for that age group grew from 40% to 74%.

Stamler neglected to inform his readers that knowledge of CHD and the ability to diagnose the disease were relatively nonexistent during the first 40 years of this century and only gradually increased thereafter. Citing Page et al. once again, Lew stated that "a major part of the remaining 30% [increase in the crude death rate since 1940] represents merely the acceptance of a broader concept of coronary artery disease, better diagnosis and increasing usage of the certifying causes of death."[512]

Table 3-1 presents the major revisions of the ICD since 1900 with respect to heart diseases. As can be seen, only angina pectoris was recognized during the first 29 years of this century and, of course, that classification was a <u>symptom</u> of the underlying cause (coronary atherosclerosis) which was rarely recognized.

Table 3-1

Revisions of the International List of Causes of Death related to coronary heart disease and all heart disease (adapted from Grove and Hetzel[1949] and the National Center for Health Statistics[1950])

REVISIONS 1 & 2 (1900,1910)	
ANGINA PECTORIS	CHD
Pericarditis	
Acute endocarditis	OTHER HEART DISEASES
Organic disease of the heart	
REVISION 3 (1921)	
ANGINA PECTORIS	CHD
Pericarditis	
Endocarditis and myocarditis (acute)	OTHER HEART DISEASES
Other diseases of the heart	
REVISION 4 (1930)	
ANGINA PECTORIS DISEASES OF CORONARY ARTERIES	CHD
Pericarditis	
Acute endocarditis, specified	
Endocarditis, unspecified (under 45 years)	
Endocarditis, specified as chronic, & other valvular diseases	
Endocarditis, unspecified (45 years and over)	
Acute myocarditis	OTHER HEART DISEASES
Myocarditis, unspecified (under 45 years)	
Chronic myocarditis, myocardial degeneration	
Other diseases of myocardium	
Functional diseases of the heart	
Other and unspecified diseases of the heart	
REVISION 5 (1939)	
ANGINA PECTORIS DISEASES OF CORONARY ARTERIES	CHD
Chronic rheumatic pericarditis	
Other pericarditis	
Bacterial and other acute or subacute endocarditis	
Endocarditis (not specified as acute, chronic, or rheumatic, under 45 years)	
Diseases of the aortic valve (without mention of diseases of the mitral valve or rheumatic fever)	
Diseases of the mitral valve (whether or not specified as rheumatic)	
Diseases of other and unspecified valves and chronic endocarditis, specified as rheumatic	
Endocartis (not specified as acute, chronic, or rheumatic, 45 years and over)	
Acute myocarditis (except rheumatic)	
Myocarditis (not specified as acute, chronic, or rheumatic, under 45 years)	
Chronic myocarditis and myocardial degeneration, specified as rheumatic	

Chronic myocarditis and myocardial degeneration, not specified as rheumatic
Other myocarditis (not specified as acute, chronic, or rheumatic)
Functional diseases of the heart (without mention or organic lesion)
Other diseases of the heart, specified as rheumatic
Other diseases of the heart, not specified as rheumatic

REVISION 6 & 7 (1949, 1958)

ARTERIOSCLEROTIC HEART DISEASE, INCLUDING CORONARY DISEASE
  ARTERIOSCEROTIC HEART DISEASE
  HEART DISEASE SPECIFIED AS INVOLVING CORONARY ARTERIES CHD
  ANGINA PECTORIS WITHOUT MENTION OF CORONARY DISEASE

Rheumatic fever
Chronic rheumatic heart disease
  Diseases of mitral valve
  Diseases of aortic valve specified as rheumatic
  Diseases of pulmonary valve and toher endocarditis, specified as rheumatic
  Other diseases of heart specified as rheumatic
Chronic endocarditis not specified as rheumatic
  of mitral valve, specified as nonrheumatic
  of aortic valve, not specified as rheumatic
  of other valves, not specified as rheumatic
Other myocardial degeneration
  with arteriosclerosis
  without mention of arteriosclerosis
Other diseases of heart
  Acute mhocarditis and acute pericarditis, not specified as rheumatic
  Functional diseases of the heart
  Other and unspecified diseases of the heart
Hypertensive heart disease
  Hypertensive heart disease with arteriolar nephrosclerosis
  Other hypertensive heart disease

REVISION 8 (1968)

ISCHEMIC HEART DISEASE
  ACUTE MYOCARDIAL INFARCTION
  OTHER ACUTE AND SUBACUTE FORMS OF ISCHEMIC HEART DISEASE
  CHRONIC ISCHEMIC HEART DISEASE CHD
  ANGINA PECTORIS

Active rheumatic fever
Chronic rheumatic heart disease
Hypertensive heart disease
Hypertensive heart and renal disease
Chronic disease of endocardium
Other myocardial insufficiency
All other forms of heart disease

REVISION 9 (1979)

ISCHEMIC HEART DISEASE
  ACUTE MYOCARDIAL INFARCTION
  OTHER ACUTE AND SUBACUTE FORMS OF ISCHEMIC HEART DISEASE
  ANGINA PECTORIS CHD
  OLD MYOCARDIAL INFARCTION AND OTHER FORMS OF CHRONIC IHD

Rheumatic fever
Rheumatic heart disease
Hypertensive heart disease
Hypertensive heart and renal disease
Other diseases of endocardium
All other forms of heart disease

Figure 3-1 shows the crude death rate trends for all heart diseases, diseases associated with CHD and all other heart diseases. Note that mortality trends attributed to angina pectoris were low and increased slightly through 1930. Thereafter, the death rate ascribed to angina gradually decreased to nearly zero by 1960. The all heart disease mortality trend initiated an increase after the 3rd ICD revision in 1921. The coronary artery disease trend initiated its increase after the 4th ICD revision in 1930. Without further analysis, therefore, it would appear to the naive reader that a CHD "epidemic" did indeed begin in 1930 but literally exploded after 1948. But as we shall see, the epidemic was apparent but not real.

Reference to Figure 3-2 should be made during the following discussion. There were only four classifications of heart diseases during the first 20 years of this century. Moreover, 87% of all heart disease deaths was comprised of "organic diseases," effectively a catch-all classification representing unknown specific causes. Clearly, the state of medical knowledge about heart diseases was primitive at best during this period. There is no doubt whatsoever that many, if not most, of the deaths reported as "organic" were undetected coronary heart disease. But not only was the coronary disease essentially unknown during that period, the ICD included no such classification and, therefore, deaths could not be classified as coronary disease even if some physicians were knowledgeable of the condition.

In the 3rd ICD revision in 1921 the "organic disease" classification was dropped and replaced by an equally nonspecific classification called "other diseases of the heart." The mortality attributed to "organic diseases of the heart" in 1920 (142.2) was effectively identical to that attributed to "other diseases of the heart" in 1921 (140.2). Also, the classification of "acute myocarditis" was replaced with endocarditis and acute myocarditis but the deaths attributed to each classification were the same before and after the change.

Deaths attributed to the nonspecific classification, "other diseases of the heart," increased considerably from 140.2 to 185.9 per 100,000 from 1921 to 1929 under the 3rd ICD revision. Thus, the all heart disease upward trend seen in Figure 3-1 was based on the availability of a classification in which physicians could pigeonhole deaths which they thought might be related to the heart but were not sure and certainly did not know, by definition, the specific type of heart disease. This unspecified classification constituted 88% of all reported heart disease deaths in 1929.

As can be seen in Table 3-1 the classifications of heart diseases increased from 4 to 13 in the 4th ICD revision in 1930 and while "other diseases of the heart " represented 88% of all reported heart disease deaths in 1929, the deaths attributed to this category one year later under the new ICD revision constituted only 14% of all heart diseases. The 88% - 14% = 74% reduction of reported deaths formerly attributed to "other diseases of the heart" was immediately redistributed primarily to "specified endocarditis" (25%), which is not related to coronary heart disease, "chronic myocarditis and myocardial degeneration" (33%), the latter being related to either myocarditis or coronary atherosclerosis but clearly unknown to physicians, and "other diseases of the myocardium" (11%). Some 91% of all heart diseases in 1930 were attributed to "pericarditis," "endocarditis," "myocarditis" and "other diseases of the myocardium," and "other diseases of the heart."

The 4th ICD revision in 1930 included the classification, "diseases of coronary arteries," reflecting an international awareness of the disease for the first time. However, it was still relatively unknown, as indicated by the fact that only 3.6% of heart disease deaths was attributed to this disease during the first year the classification was available. Although it is an obvious truism, a very important point should be emphasized, i.e., regardless of the true CHD mortality rate before the 1930 ICD revision, no deaths could be attributed to this classification simply because it was not available for physicians to use. A classification <u>has</u> to be available before a

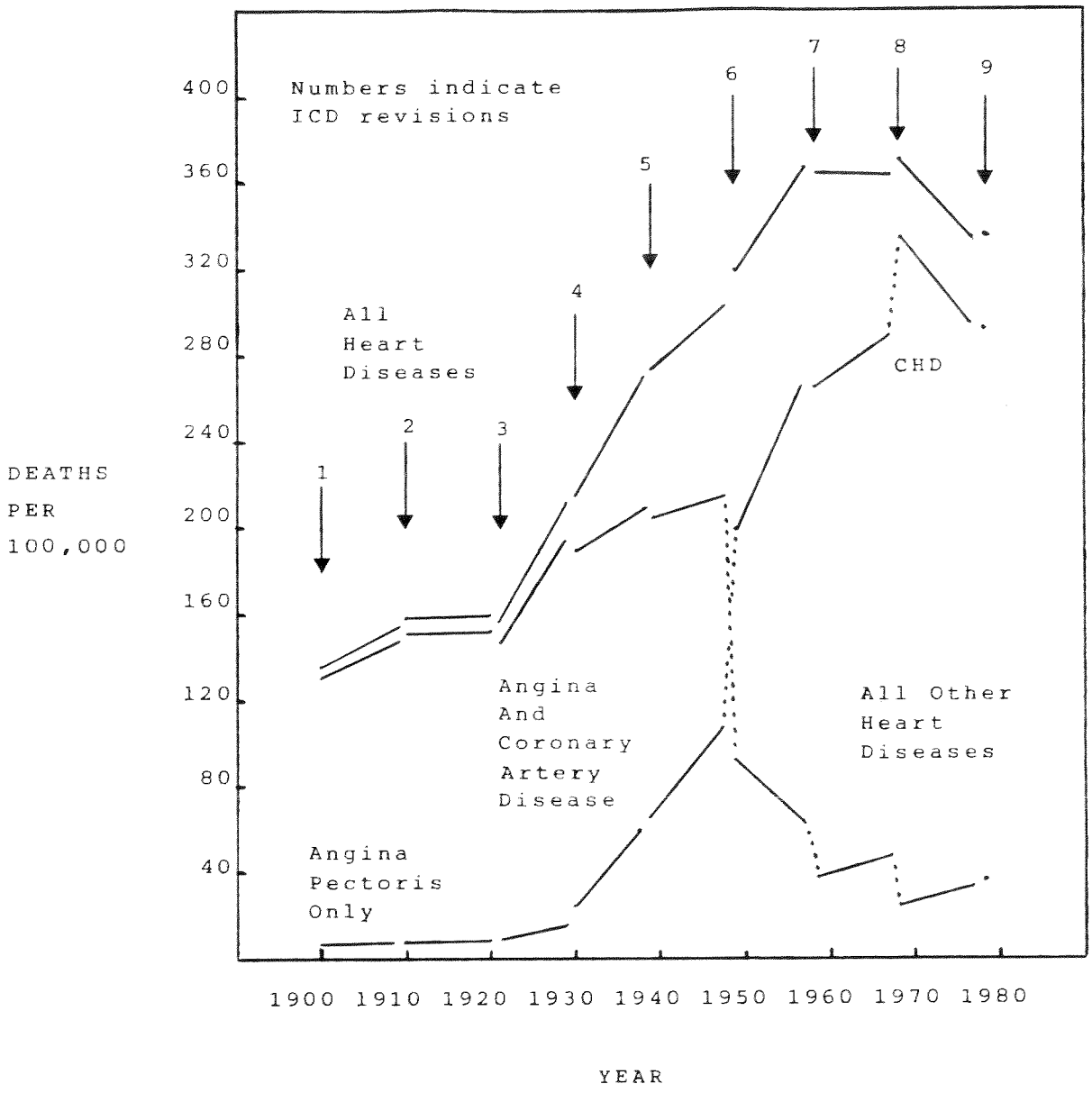

Figure 3-1. Crude death rates for all heart diseases, the classification originating as angina pectoris and ending with coronary heart diseases (adapted from Grove and Hetzel[1949] and the National Center for Health Statistics[1950])

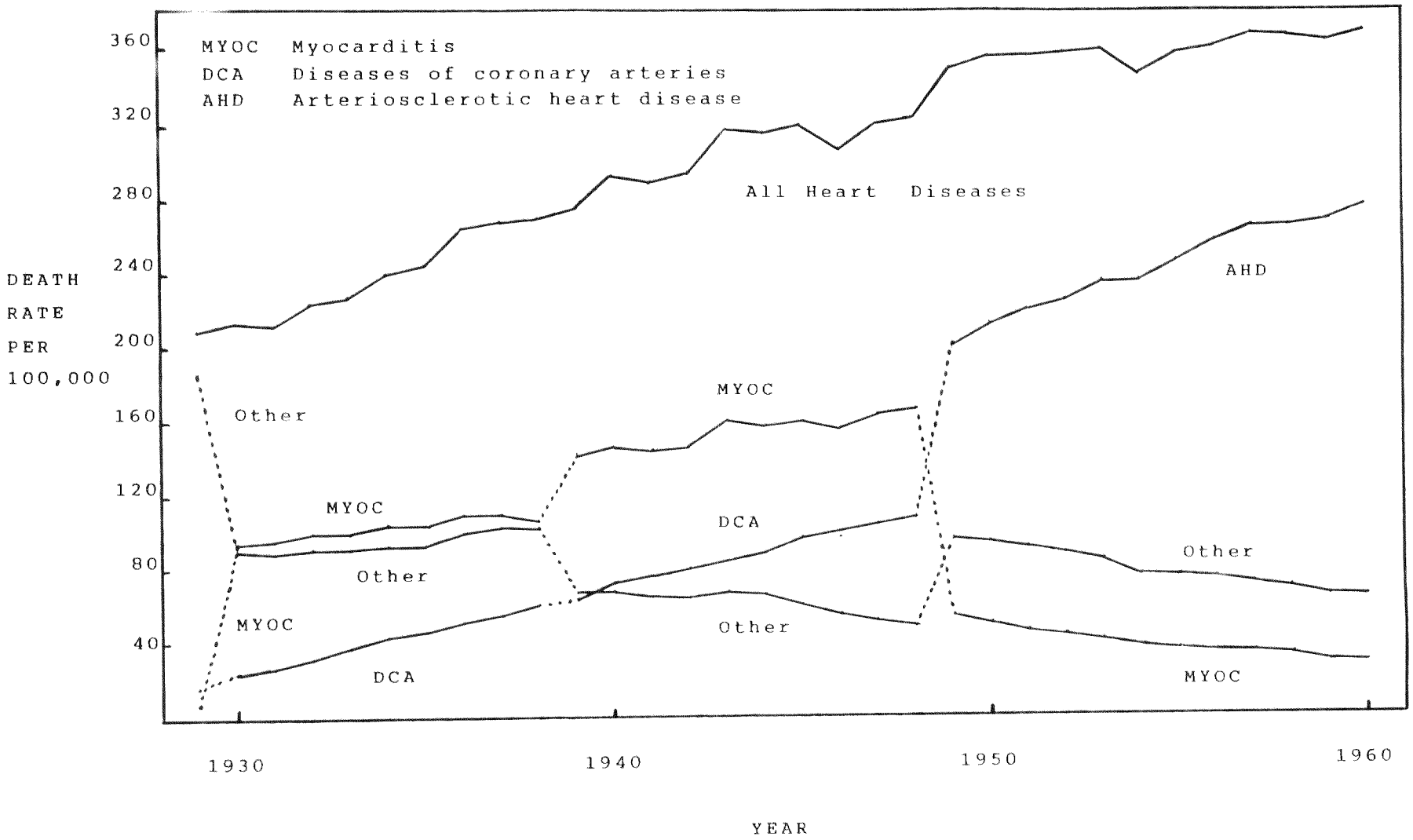

Figure 3-2. Crude all heart disease and major component death rates by year (adapted from Grove and Hetzel, 1968[1949])

disease can be reported. Furthermore, the introduction of a new classification historically represented knowledge of an old disease far more than it did the recognition of a new disease.

Figure 3-1 shows that the CHD classifications "angina" and "coronary artery disease" increased from 7.9 to 52.2 per 100,000 from 1930 to 1938. Simultaneously, deaths attributed to "myocardium diseases" and "other diseases of the heart" increased significantly, while deaths attributed to endocarditis decreased significantly. (Recall now that "other diseases of the heart" represented 88% of all heart disease deaths in 1929, dropped to 14% in 1930 and then jumped to 23% in 1938. In actuality, the absolute increase in deaths attributed to "other diseases of the heart" was 100% (Figure 3-2). The "low" 23% was due to the fact that the total deaths attributed to all heart diseases increased from 213.6 to 269.9% from 1930 to 1938.

It is quite obvious from the above that physicians increasingly used the new classifications made available to them during the 1930s. And while the absolute number of reported heart disease deaths increased from 213.6 to 269.9 per 100,000 from 1930 to 1938, this increase was unquestionably due to (1) the growing awareness and detectability of CHD, and (2) an aging population made possible by the severe depression of mortalities due to infectious diseases. With regard to the latter, the all-cause death rate continued its downward plunge during the presumed increase in heart disease mortality.[a] In 1982 Kannel said, "The long-term trend in deaths from cardiovascular disease since 1900 until recently [1963] has been upward because of an increasing proportion of older persons; control of infectious, parasitic and nutritional deficiency diseases; and an epidemic increase in fatal coronary attacks."[519] There was, of course, ample evidence to support that statement except for the "epidemic rise in fatal coronary attacks." If a population is protected from early diseases, allowed to age and then dies of heart disease, it can hardly be said that an "epidemic" is taking place. But a more important statement was made by Kannel, Stamler and others in 1984. In discussing the CHD mortality decline which occurred after 1966, they said, "The marked decline in CHD and cardiovascular mortality has been paralleled by a decline in mortality from all causes, as would be expected with an abatement of the leading determinants of death."[1083] Others have made similar arguments. For example, Beaglehole[3187] said, "Since the late 1960s there has been a consistent decrease not only in CHD mortality rates but also in mortality rates from all cardiovascular diseases as well as from all causes of death. Thus, the fall in CHD mortality rates cannot be attributed to changes in daignostic fashions, certification practices, or codings." Using the same logic, the so-called "epidemic" rise in all heart diseases, particularly CHD should have been paralleled by an increase in the all-cause death rate. Instead, the latter declined, strongly suggesting that physicians were simply changing the cause of deaths on death certificates. Considerable evidence has thus far shown this to be true. Considerably more evidence is presented below. However, a point should be emphasized before continuing.

The all-cause death rate is the most accurate of all death rate trends because its computation does not require knowledge of the specific cause of death. The all-heart disease death rate curve is much less accurate because physicians had to (and many still do) guess the cause of death in many cases. Similarly, the CHD death rate curve is the most inaccurate of all because it requires (and still does require) even more

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[a] It is sometimes said that CHD mortality represented under 10% of all deaths in 1900 and grew to 35% by the early 1960s. It is obvious, however, that regardless of the accuracy of reported data, a substantial part of that percent growth was not growth at all but merely a reflection of the substantial decline in all-cause deaths. The percentage of all deaths due to CHD would have increased significantly even if the actual CHD death rate had remained constant from 1900 to 1963.

guessing. The impact of this state-of-affairs on the interpretation of specific death rate trends was demonstrated by Woolsey and Moriyama[3148] in 1948. Figure 3-3 shows their age-adjusted data plotted in terms of successively lower subclassifications of the arterial degenerative class of diseases known as "cardiovascular-renal diseases." This class exhibited a moderate increase in rate from 1900 to 1930, after which a slight downward trend occurred. If deaths reported as senility were included in this class, and they were associated at that time with the cardiovascular-renal diseases, then the rates for the entire class demonstrated a completely constant or flat trend from 1900 to 1930.

When renal diseases are omitted, the remaining cardiovascular mortality trend shows a steady increase from 1900 to 1945. The upward climb is even steeper when stroke diseases are omitted. However, the most interesting and relevant aspect of Figure 3-3 is the fact that as "Diseases of the Coronary Arteries" (plus angina pectoris) increased 61.3 per 100,000 from 1930 to 1945, all heart diseases increased only half that amount (35.6), all heart and stroke diseases increased only one fourth that amount (16.4) and all cardiovascular-renal diseases decreased 50% of that amount (35.5).[a] These trends clearly indicate that while physicians gradually decreased their use of cardiovascular-renal diseases as causes of death after 1930, they also increased their use of "diseases of the coronary arteries" at the expense of other cardiovascualr rubrics. This phenomenon will be even more visible below when the components of all heart diseases are analyzed over time.

It is important to re-emphasize that mortalities due to all cardiovascular-renal diseases were unquestionably artificially low during the first 30 years of this century because of infectious diseases, i.e., many persons with various forms of cardiovascular diseases did not live long enough to die of such diseases because they died prematurely from an infectious disease. The increase in cardiovascular disease rates from 1900 to 1930, shown in Figure 3-3, was probably because of the decreasing mortalities due to the infectious diseases, most of which had been eliminated by 1930. Therefore, the trend after 1930 seems likely to have been a continuation of a trend that would have occurred had the infectious diseases been absent prior to 1930. Common sense indicates that this explanation must be valid. For example, CHD and cancer are currently the leading causes of death, primarily because the population has aged and these degenerative diseases predominantly affect the aged. However, were a major epidemic to strike the population, such as AIDS, the CHD and cancer mortality rates would diminish. The incidence of atherosclerosis would remain the same but the AIDS epidemic would not permit some of that incidence to reach the terminal stage.

It makes no sense whatsoever to ignore the infectious diseases mortalities and assume that the reported cardiovascular and heart disease mortalities were not depressed by the infectious diseases. Such an assumption is most certainly false.

The 13 classifications of heart diseases included in the 4th ICD revision in 1930 was expanded to 19 in 1939 but most of the deaths (77%) fell into three classifications in 1939 (Figure 3-2), i.e., "myocarditis and myocardial degeneration" (46%), "diseases of the coronary arteries" (22%) and "other diseases of the heart" (9%). However, deaths attributed to "other diseases of the heart" were definitely decreasing, reflecting newer knowledge, and would be reduced to almost insignificance by the 5th ICD revision in 1949.

From 1939 to 1948, deaths attributed to all heart diseases continued to increase (275.5 to 322.7 per 100,000, respectively). This trend was due almost entirely to increases in "myocarditis and myocardial degeneration" and "diseases of the coronary

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[a] The all-cause death rate also decreased 284 per 100,000 from 1930 to 1945.

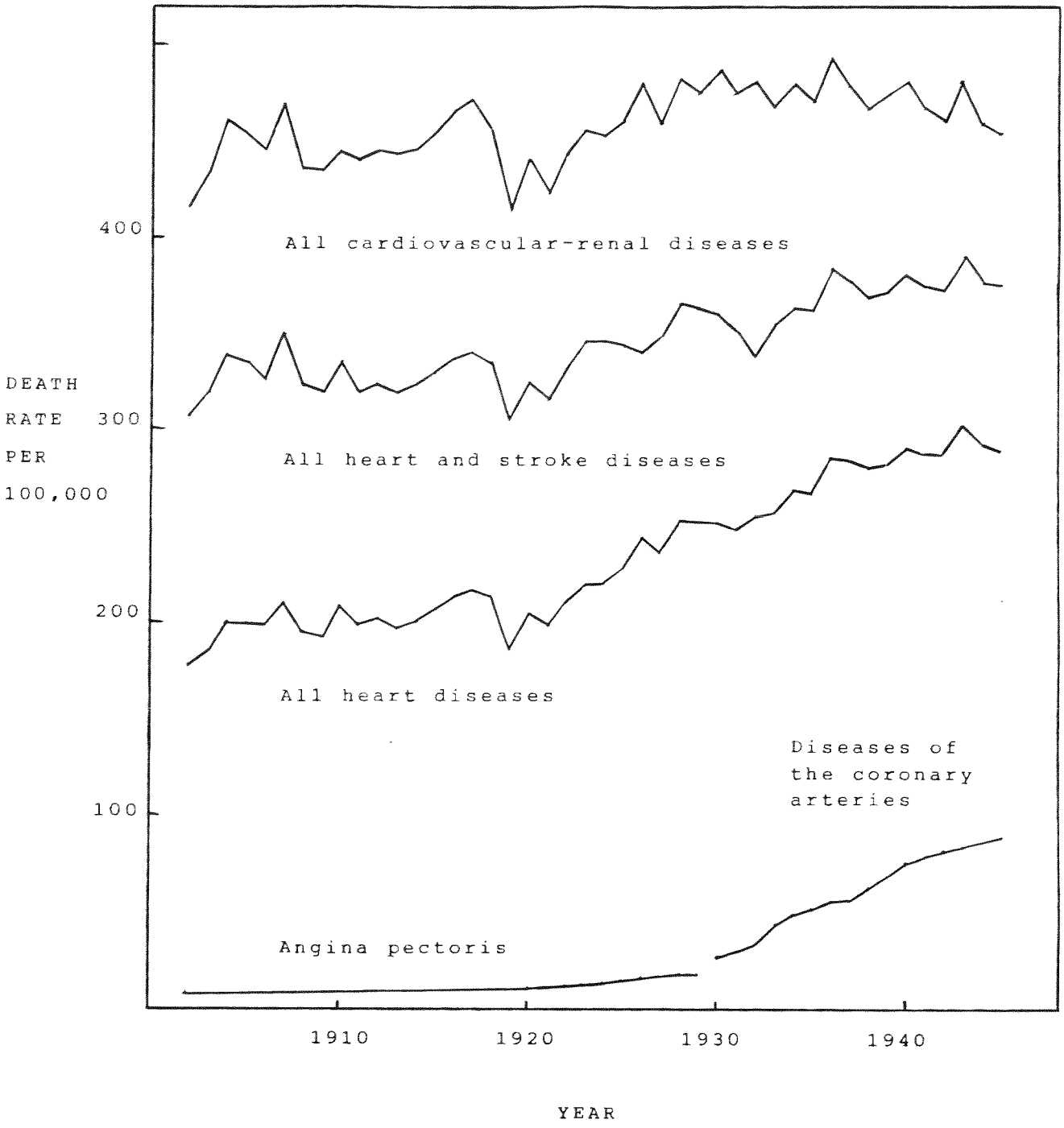

Figure 3-3. Age-adjusted cardiovascular-renal and major component death rates by year (adapted from Woolsey and Moriyama, 1948[3154])

arteries" which represented 82% of all reported heart diseases in 1948. "Other diseases of the heart" now represented only 7% of the total.

Observation of Figures 3-1 and 3-2 reveals that as the reported all heart disease death rate continued to rise from the 5th to the 6th ICD revisions, diseases other than coronary disease nearly reached an asymptote by 1938 and gained little to 1948, after which they plummeted and then progressively became a more and more insignificant set of diseases. There were, of course, no medical breakthroughs which prevented or cured all of these diseases. Most of them simply did not exist to begin with in the frequencies reported.

The 6th revision of the ICD in 1949 also contained 19 classifications of heart disease but few were identical to those of the 5th revision. The CHD classification "arteriosclerotic heart disease, including coronary disease" appeared for the first time and represented a category that can be clearly traced to the present time. As can be seen in Figures 3-1 and 3-2, the reported CHD death rate skyrocketed (and all other heart diseases plummeted) from 1948 to 1949 and all because of an ICD change. Some 57% of all heart disease deaths in 1949 was attributed to "arteriosclerotic heart disease" and that percentage grew to 75 by 1960. With one exception, the only other heart disease death rates of significance were "other myocardial degeneration." Since those diseases may have been, in fact, the result of coronary heart disease, it is probable that the true percentages of all heart diseases ascribed to arteriosclerotic heart disease were closer to 72 and 83 for 1949 and 1960, respectively. And the percentages might have been even greater were it not for the fact that an entirely new heart disease classification emerged in the 6th ICD revision, i.e., "hypertensive heart disease." Without having any prior history in the ICD, deaths attributed to "hypertensive heart disease" were 56.4 per 100,000 in 1949 or 16% of all heart diseases and then gradually decreased to 37 per 100,000 or 10% of all heart diseases. Using the alliance's reasoning, the U.S. experienced a meteoric rise of hypertensive heart diseases mortality from zero in 1948 to 56.4 one year later.

As noted earlier, the 6th ICD revision of 1949 represents the only adequate starting date for tracing CHD mortality trends over time. Since most of the reported CHD mortality since 1930 also occurred after 1949, it is useful to analyze trends after 1949 in more detail with respect to both crude and age-adjusted mortality rates.

Figure 3-4 shows the crude mortality trends for CHD and all diseases of the heart after 1948. (The total cancer death rate trend is also shown and is discussed later under the section, "Food Consumption Trends.") This figure emphasizes the apparent paradox of a substantial (45%) rise in CHD from 1949 to 1963 and only a slight rise in all-heart disease mortality. If the rise in CHD mortality were a true epidemic and not a simple exchange of death classifications, the "epidemic" most certainly would have driven the all-heart disease mortality upward. It did not, however, and that fact gives rise to the explanation that the "epidemic" was an artifact, created by ICD revisions and new knowledge of coronary artery disease.

The sharp increase and decrease in CHD mortality seen in 1968 and 1979, respectively, were due to ICD revisions. Between these dates, all death certificates which included both ischemic heart disease and hypertension were classified as ischemic heart disease. The 9th ICD revision in 1979 eliminated that classification procedure.

Figure 3-5 presents the crude death rate trends for the five major components of all heart diseases. It can be seen that "hypertensive heart disease" and "chronic endocarditis and other myocardial degeneration" sharply decreased as CHD increased. "Rheumatic fever and chronic rheumatic heart disease" also decreased modestly. The

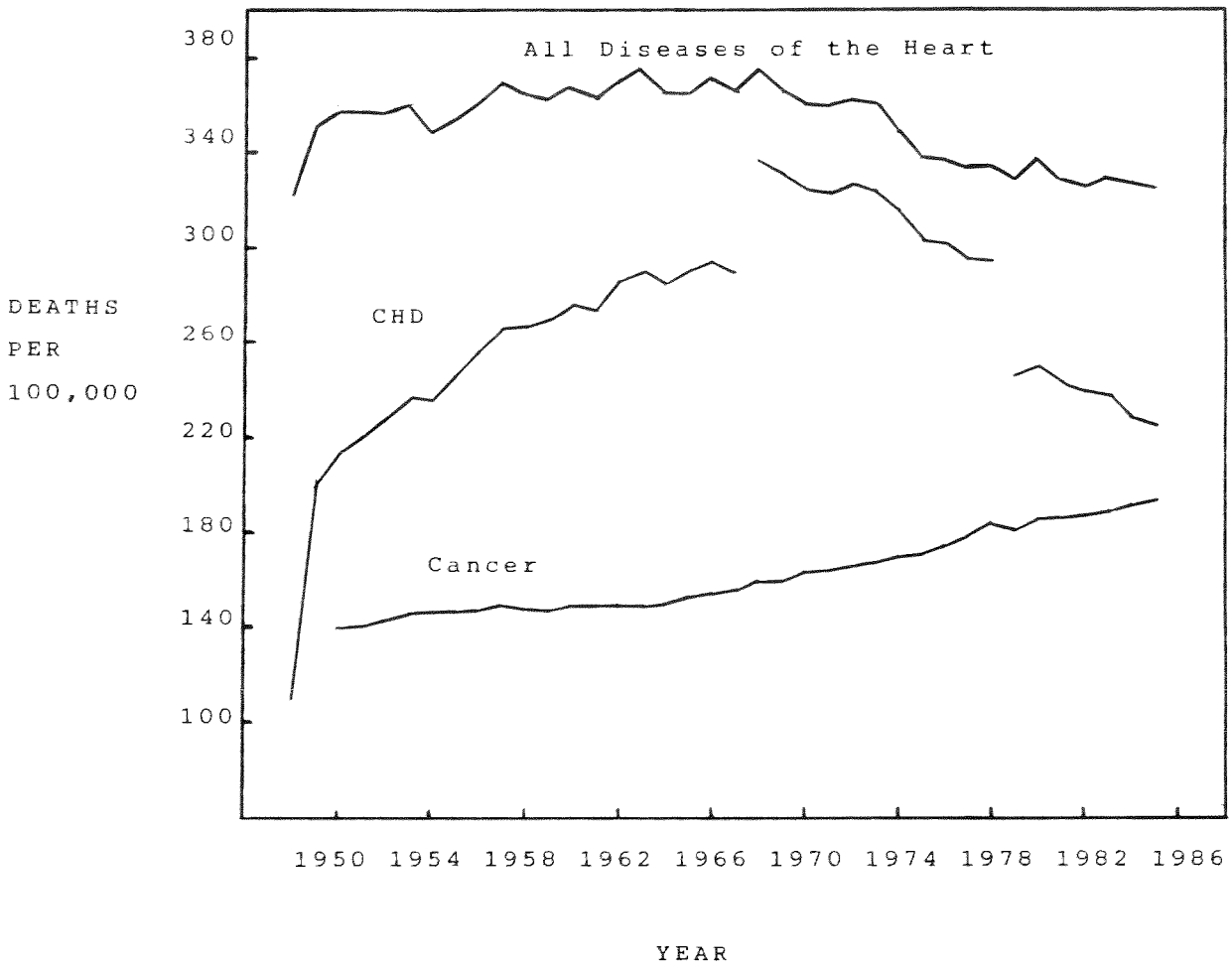

Figure 3-4. Crude death rates for all heart diseases, CHD and cancer from 1948 to 1985 (National Center for Health Statistics[1950])

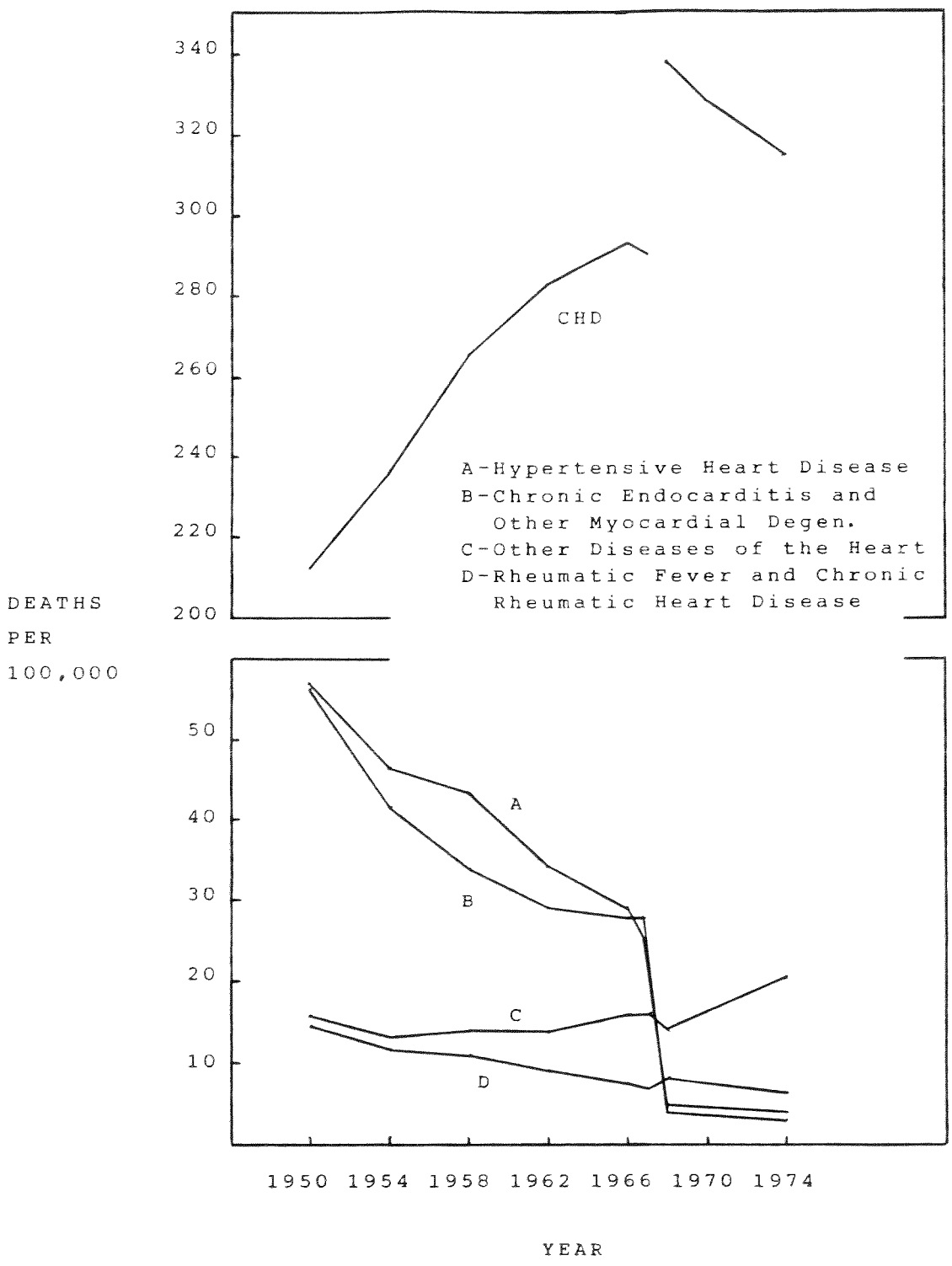

Figure 3-5. Crude death rates for 5 components of all diseases of the heart (National Center for Health Statistics[1950])

combination of these three components accounted for 89% of the CHD mortality increase. Clearly, physicians were "stealing from Peter to pay Paul."

Now let us examine the same trends in terms of more appropriate age-adjusted data (Figures 3-6 and 3-7). We now see a far greater discrepancy in trends (Figure 3-6). While the reported CHD death rate trend increased about 21%, less than half of that observed for the crude death rate,[a] the all-heart disease mortality trend was very strongly downward, rather than the constant trend exhibited in crude mortality data. This sharp downward trend underscores the apparent paradox even more dramatically. While a supposed CHD epidemic caused an increase in CHD mortality of 35 per 100,000 from 1950 to 1963, the all-heart disease mortality decreased 28 per 100,000. Figure 3-7 shows that the decrease in "hypertensive heart disease," and "chronic endocarditis and other myocardial degeneration" now more than compensated for the CHD mortality increase. In fact, mortality due to hypertensive heart disease, hypertensive disease, and chronic endocarditis and other myocardial degeneration each decreased from 1950 to 1960 in virtually every state plus the District of Columbia by 40% to 50% in both males and females.[1949] These decreases were almost entirely for men over 65 years and for women over 75 years, the same age groups for which the so-called epidemic occurred (see Sex, Race and Age below).

The foregoing figures apparently have never been published by the alliance, although they clearly comprise an obvious explanation for the so-called CHD epidemic.[b] It is inconceivable that the alliance is unaware of these data and it is scientifically and ethically inexcusable to avoid publishing them. However, it is not surprising because the omission of unsupportive and outrightly embarrassing data is a common activity by alliance members. These data <u>are</u> embarrassing to the alliance because, as noted by Hechter and Borhani[3025] and Stallones,[3027] high blood pressure is said to be a major risk factor for CHD and yet the reported CHD mortality rate increased sharply as hypertensive heart disease declined sharply. If hypertension <u>is</u> a major risk factor for CHD, then the only logical explanation for the trends shown in Figures 3-5 and 3-7 is that physicians progressively used the CHD rubric on death certificates at the expense of the hypertensive heart disease rubric.

The shifting away from components A and B to CHD undoubtedly reflects greater knowledge and diagnostic capabilities of physicians. Page et al. emphasized in 1957 that the term, "Arteriosclerotic heart disease" was introduced in the ICD in 1949 and played "a role in what is often believed to be an actual increased 'prevalence' of this disease."[512] Page et al. also noted that the use of the electrocardiogram to diagnose CHD became increasingly widespread after 1950. Prior to 1950, the electrocardiograph machine was large and unwieldy and infrequently used by physicians.[1951,c]

An important point associated with the extremely steep rise in the reported CHD mortality rate after 1948 was noted by Mann[571] in 1975. He said that "A continuing and involved problem is the assignment of death with multiple causes. Until 1949 the ICD was used in conjunction with an arbitrary Manual of Joint Causes. This, by definition, assigned the primary cause of death. The procedure was unpopular with

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[a] The reader may recall Gordon and Thom's use of the crude, rather than the age-adjusted rate, to describe the CHD "epidemic."

[b] Thom et al. plotted the all heart disease (minus rheumatic) mortality trend but did not independently plot the component mortality trends.[1952]

[c] The precordial lead electrocardiography was developed in 1944.[424]

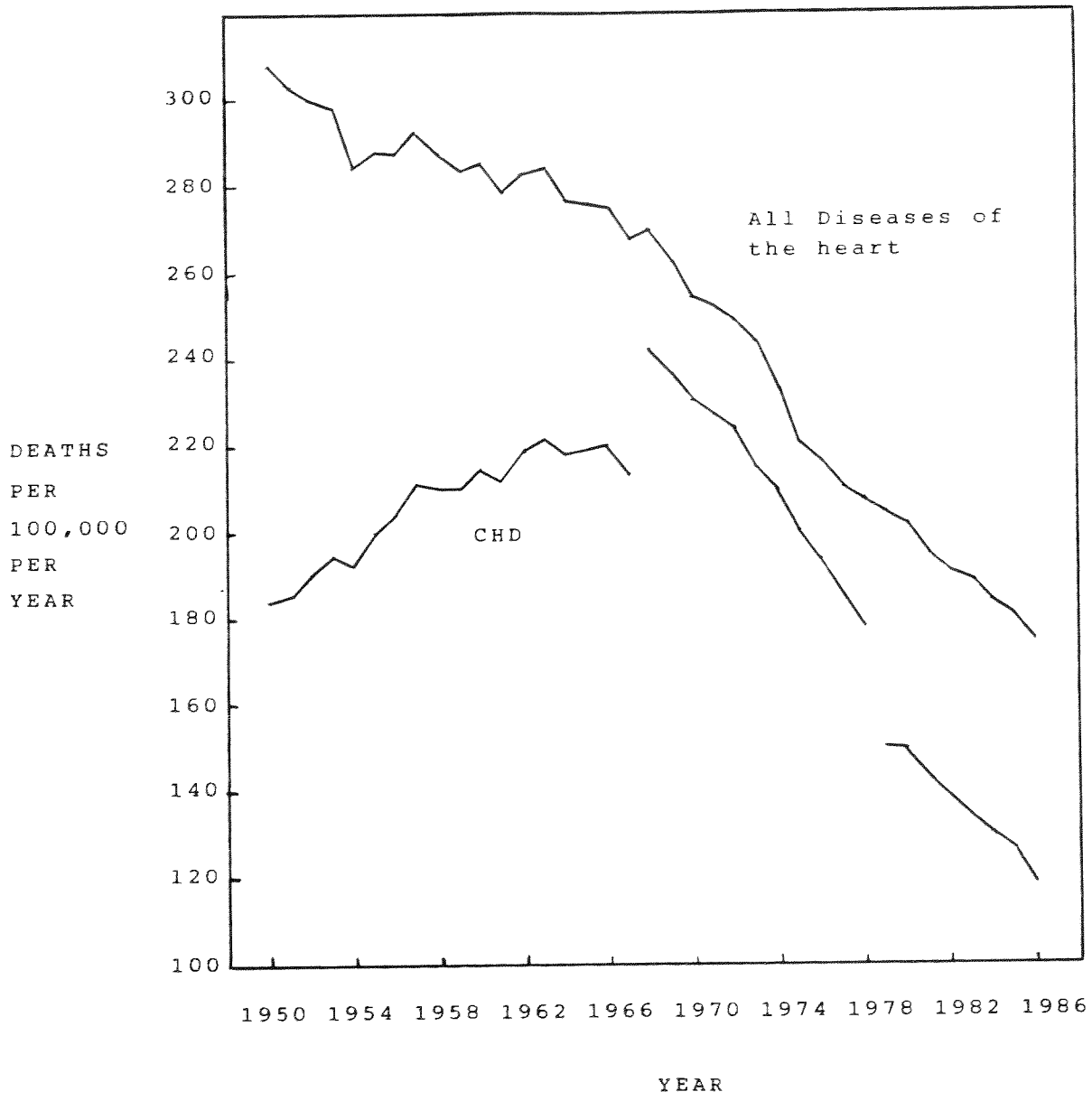

Figure 3-6. Age-adjusted death rates for all heart diseases and CHD (National Center for Health Statistics[1950])

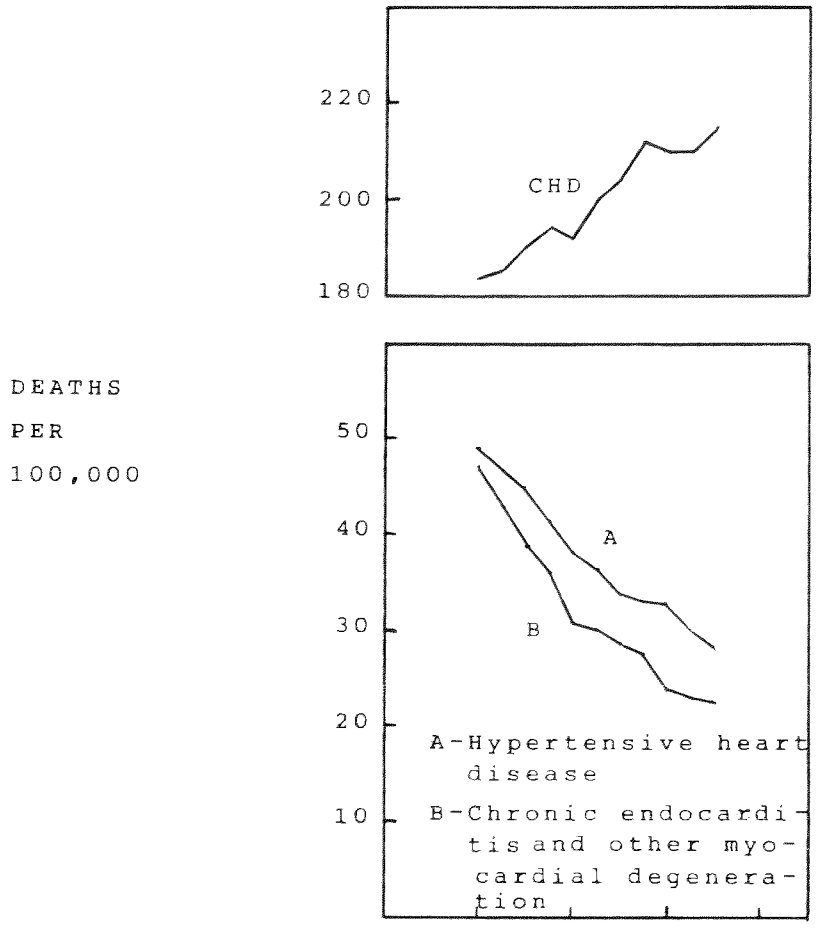

Figure 3-7. Age-adjusted death rates for 3 components of all diseases of the heart (National Center for Health Statistics[1950])

physicians and was abandoned with the sixth revision of the ICD made in 1949 and the physician has since been asked to assign the prime cause."

The AMA's Council on Long Range Planning and Development published a report in 1989 which provided significant evidence regarding the "epidemic" and knowledge of CHD, albeit without apparently recognizing the association.[2910] It will be recalled that Cooper cited P.D. White as saying that there was no department of cardiology in 1941. Indeed, the AMA's Council indicated that the American Board of Internal Medicine initiated the awarding of special qualification certificates to internists who undertook training in cardiovascular diseases. The subspecialty of cardiology in internal medicine was thus formally established. Is it any wonder, therefore, that the diagnosis of CHD improved after 1940? The Council noted that "The diagnosis of cardiovascular diseases has changed considerably during the past 20 years [1969-1989]. Prior to the introduction of high-technology tests, the diagnosis of coronary artery disease was made solely from a patient history." If one extrapolates from modern equipment and knowledge to 1940 when the cardiology specialty was begun and diagnostic equipment and knowledge were minimal, the explanation for apparently low CHD rates before 1940 should be obvious. To insist that there was a great CHD epidemic is tantamount to suggesting that the capability to diagnose CHD has been relatively constant throughout this century. Not even the most avid epidemic believers would agree with that suggestion, particularly not Ancel Keys. Recall his statment in 1953, i.e., "...the broad category of heart disease, or diseases, [is] diagnosed by the clinician as angina pectoris, coronary heart disease, myocardial infarction, chronic myocarditis and myocardial degeneration. In hospital and vital statistics it is rarely possible to differentiate these clearly so it is convenient to group them, for the present purpose, as 'degenerative heart disease.'"[279] Thus, Keys effectively admitted that up to 1953 physicians could not diagnose CHD very well and so vital statistics were in considerable error.

As observed by Lew, a biostatistician, the awakening of physicians to atherosclerosis can be seen, in part, in the vital statistics of various parts of the country.[2732] It has long been known, for example, that CHD death rates vary enormously among the states (discussed more fully in Chapter 4). Typically, the more rural or less industrialized the state, the lower the mortality rate, not unlike the profile seen among countries. Alliance members were quick to explain both observations in terms of physical activity. Such an explanation, while consistent with the risk factor concept, is merely an hypothesis and has never been adequately supported empirically.

Lew proposed that a much more reasonable explanation for the differences seen between states is that the more rural and less industrialized states have the poorest medical standards and facilities. It would be expected, therefore, that part of the "epidemic" would be due to a "time and educational lag in the recognition" of CHD by the least educated and sophisticated physicians. The effect of this lag can be seen in the vital statistics associated with 9 geographical areas of the U.S. Lew noted that the areas which reported the lowest CHD mortality rates in 1940 also showed the largest increases during the next 18 years, reflecting a knowledge "catch-up."

This lag would naturally be expected with respect to the CHD mortality decline as well. Although Levy seemed unaware of this likelihood in 1981, he noted that the initiation and rate of the decline was highly variable in the U.S., with slower rates occurring in rural areas such as the Appalachian States, "especially West Virginia and Kentucky."[1846] Thus, while alliance members have attributed lower CHD mortality rates in the rural states to less stress and greater physical activity, it would follow from such reasoning that less stress and more physical activity has caused a slower decline in the mortality rate. Of course the contradiction is absurd but the reasoning was not scientifically sound initially.

Mortality statistics for 1986 show that the crude death rates due to heart diseases was 317.5 across all 9 U.S. geographic regions.[2736] The range was 219.2 (the most rural and least dense states, i.e., Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah and Nevada) to 388.2 (the least rural and most dense states, i.e., New York, New Jersey and Pennsylvania). At the state level the range was, of course, much broader, being as low as 89.1 (Alaska) to 405.2 (Pennsylvania). There is little doubt that Lew's contention was correct; heart disease mortality is higher in states and regions which employ more medical facilities and greater medical sophistication. (Differences between the states will be addressed as well in Chapter 4.)

The alliance, of course, has steadfastly maintained that a true CHD epidemic occurred in the U.S. and has, therefore, ignored the rather dramatic reported increases and decreases of mortalities due to specific heart diseases following ICD changes. Typical of a nonexplanatory "explanation" of the CHD epidemic was that of Levy and Rifkind.[3226] In 1973 they said, "Although mortality from most causes has drastically decreased over the last 50 years, that from coronary artery diseases has not [it was not yet known that CHD mortality had been decreasing since 1963]. This 'epidemic' of deaths from coronary artery disease despite increased medical and surgical capabilities becomes understandable in the light of the growing evidence that many of these deaths (60% in the Framingham study) occur outside the hospital, and that almost 50% occur suddenly. Moreover, many of the sudden deaths occur in subjects who did not previously manifest evidence of vascular disease." How can the CHD epidemic be understood by knowing that many CHD deaths occur outside hospitals and that many are sudden in nature?

SEX, RACE AND AGE

Analyses of mortality trends with respect to sex, race and age reveal further evidence against a true CHD epidemic. Figure 3-8 presents age-adjusted CHD death rate trends by race and sex. In general, the slopes of the nonwhite and white male trends are highly similar, as are those of the nonwhite and white female trends. But while all female rates are nearly identical, the nonwhite male rate is enormously lower than for the white male rate during the epidemic and only modestly lower during the CHD decline. A second major observation that can be seen in the figure is the fact that the reported death rate increases among males was far greater than those among females.

Cooper, Stamler, Dyer and Garside[2825] maintained in 1978 that the age-adjusted death rates among those 35-74 years of age were most appropriate for analysis because there are few deaths occurring before age 35 and the rate after age 74 is so great it seriously biases the overall age-adjusted rate. Figure 3-9, therefore, presents their trends which reveal even more peculiar differences than those found in Figure 3-8. From 1940 to 1946 nonwhite males had a reported CHD mortality rate that was about 240 per 100,000 lower than that for white males. But 20 years later, the difference between nonwhite and white males had disappeared. The death rate for nonwhite females was slightly lower than that for white females from 1940 to 1946 but thereafter surpassed white females at a very accelerated rate. Moreover, the death rate for white females slowly but progressively decreased during the entire "epidemic" period.

Figure 3-8 and especially 3-9 present rates and trends that simply cannot be explained by so-called environmental or lifestyle changes. White males and females consume the same foods, as do nonwhite males and females, yet the differences in CHD rates are incredibly large. In addition, how can one explain that the rate of nonwhite males was much lower than white males, while the reverse was true for females? And how can one explain that the death rate among white females

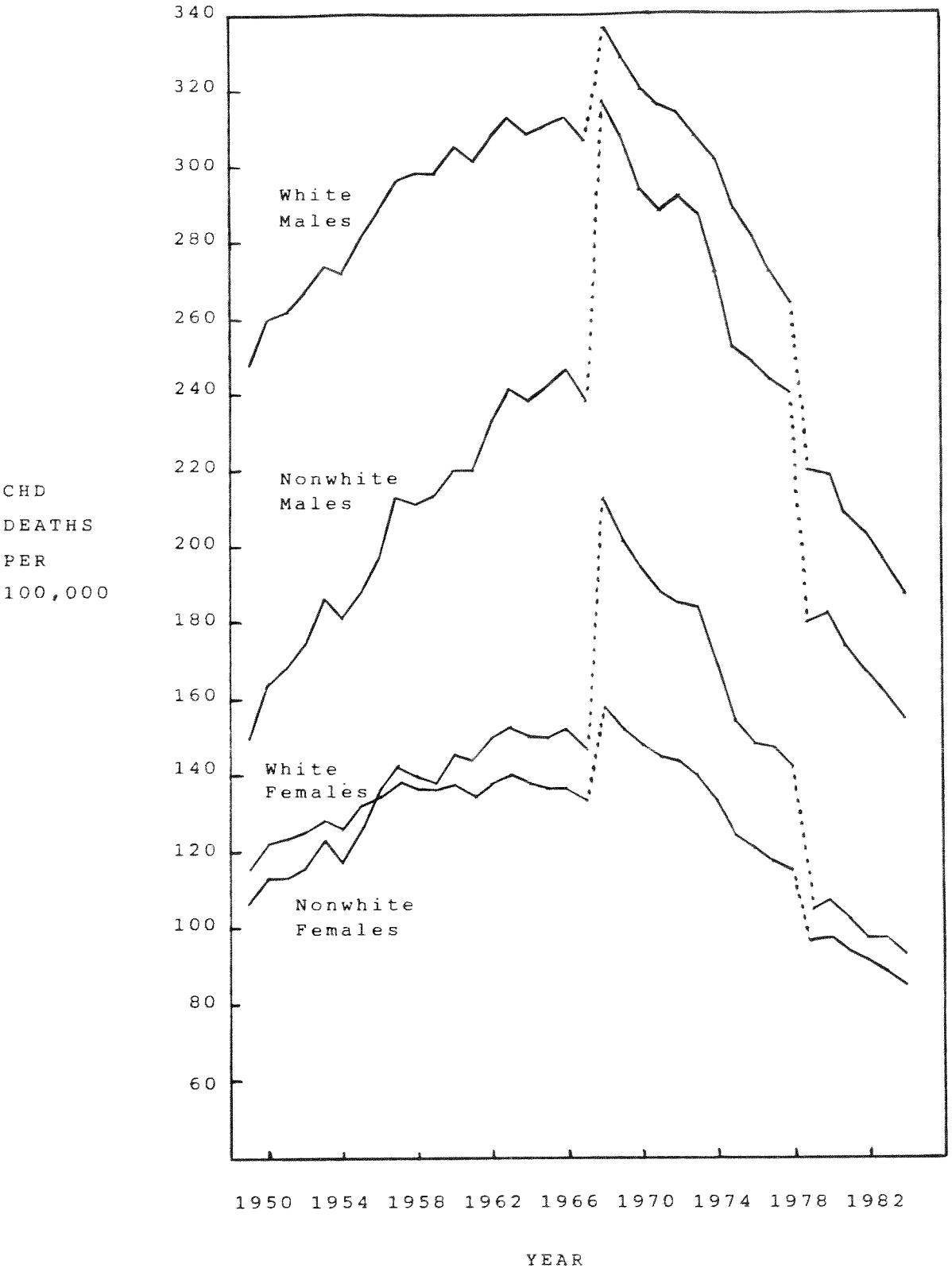

Figure 3-8. Age-adjusted CHD death rates by sex and race for all ages (adapted from Higgins Leupker, 1988[2798])

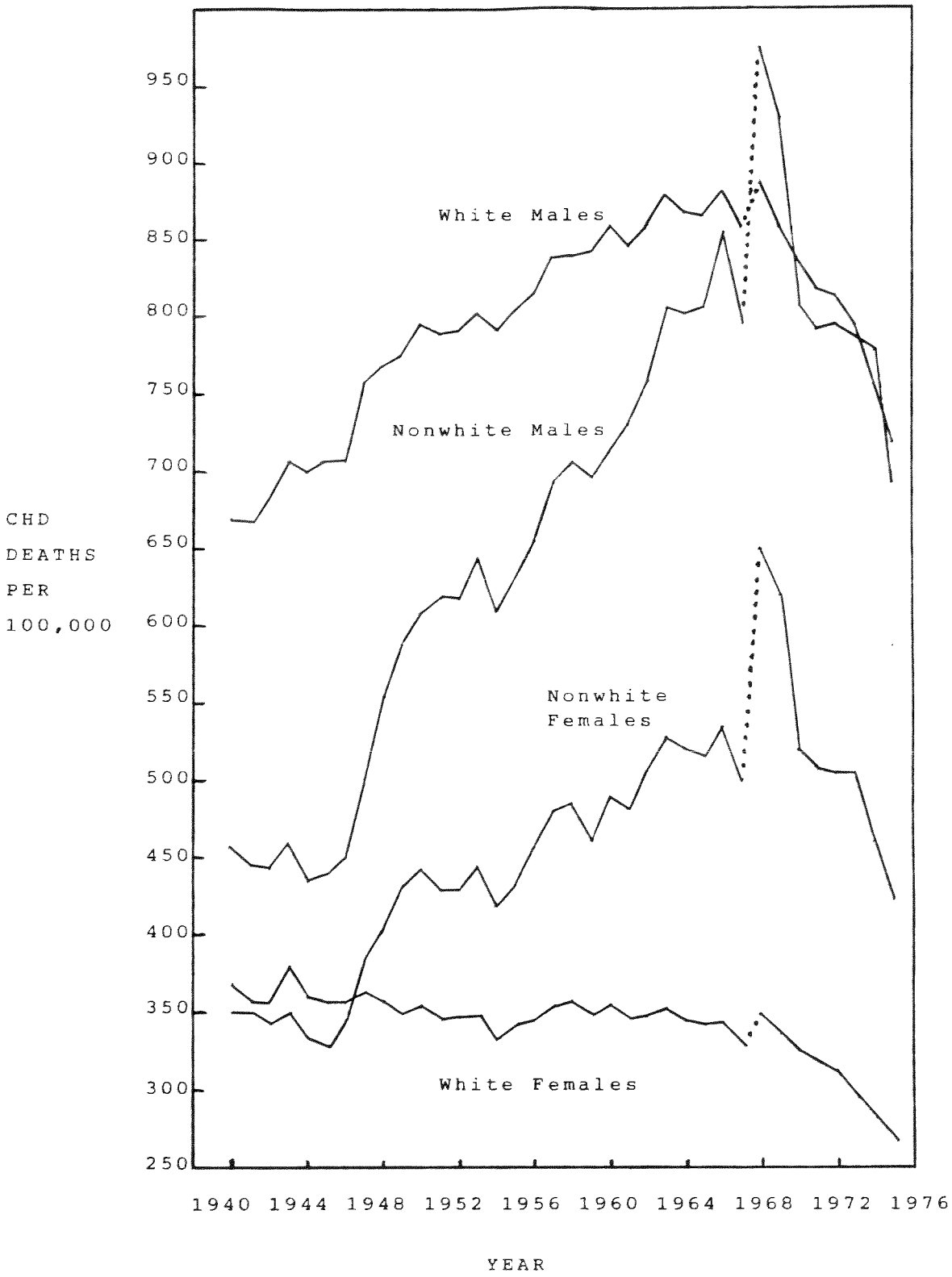

Figure 3-9. Age-adjusted CHD death rates by sex and race for ages 35-74 (adapted from Cooper et al., 1978[2825])

decreased during the epidemic, while it increased greatly among nonwhite males and females and white males?[a]

Alliance members do not attempt to explain these and other peculiarities simply because the rates and trends make no sense at all if we assume that they are a reflection of true death rates due to CHD and not artifacts arising from ICD changes, increasing awareness and knowledge of CHD, diagnostic "fashions," etc. For example, in their description of Figure 3-9, Cooper et al.'s entire discussion of the white female trend was composed of one sentence, namely, "White females in this age group maintained a highly stable rate throughout the entire period, with a range of only 42 deaths per 100,000 over 20 years."[2825] Since the alliance continuously maintains that a great CHD epidemic took place in this century, how can Cooper et al. and others give so little attention to the fact that it did not occur in white females?

In 1945, before the so-called CHD mortality epidemic, Kountz[3290] noted that a rapid rise in the middle-aged and elderly was occurring. Some 17% of the total population was over 45 years of age in 1900 and that percentage had risen to 26.5% by 1940. He warned that "...it is important that the medical profession begin to consider some of the problems that may lie ahead. We know that, unless we do something to protect this aging population, degenerative disease [underlines added] is going to cause a large group of the population to be dependent; that the hospitals for the infirm and aged must increase in number and size; and that there will be a tremendous economic, social and cultural loss.

Figures 3-10 and 3-11 show the CHD mortality trends for white males and females as a function of age groups. It can be clearly seen that the "epidemic" occurred almost entirely among men 65 years and older and among women 75 years and older. Hence, the reason why Cooper et al.'s trends showed an "epidemic" for men but no epidemic for women.

Table 3-2 shows the percent increase in CHD mortality from 1950 to the "epidemic" peak for those white males and females. The fact that there was an increase among all age groups could reflect a true epidemic or diagnostic/death certification changes or both. However, the fact that the percentage increase became progressively much larger with age indicates diagnostic bias because all life expectancy data reveal reductions in death rates at the older ages during the "epidemic." As will be seen in the next section, the mean life expectancy increased 1.8 years from 1950 to the "epidemic" peak. The percentage of persons over 65 years of age increased from 8.3% to about 9.5%, representing a relative increase of 14.5%.[1673] The mean expectation of life at age 65 increased slightly in both males and females.1895 And the total all-cause death rates decreased from 1950 to 1960 in every age group for both males and females above 45 years. It also decreased in every age group above 55 years from 1960 to 1965 except for males, who demonstrated a rate in 1960 that was somewhat greater than it was in 1950. But this latter observation has no relevance to the "epidemic" since it occurred after the "epidemic" rise. Moreover, it cannot be said that the extension of life during the middle and older ages was due to a reduction in other causes which swamped the CHD rise because all of the other major diseases had become nearly nonexistent by either 1940 or 1950 or rose during the "epidemic," e.g., cancer.

In 1958 Moriyama et al.[3155] presented additional mortality data that revealed enormous differences between the sexes and races. For all age groups the death rates

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[a] CHD rates for men and women in England were identical to those for white men and women in the U.S.[1515] There was virtually no increase in CHD mortality in women after 1950.

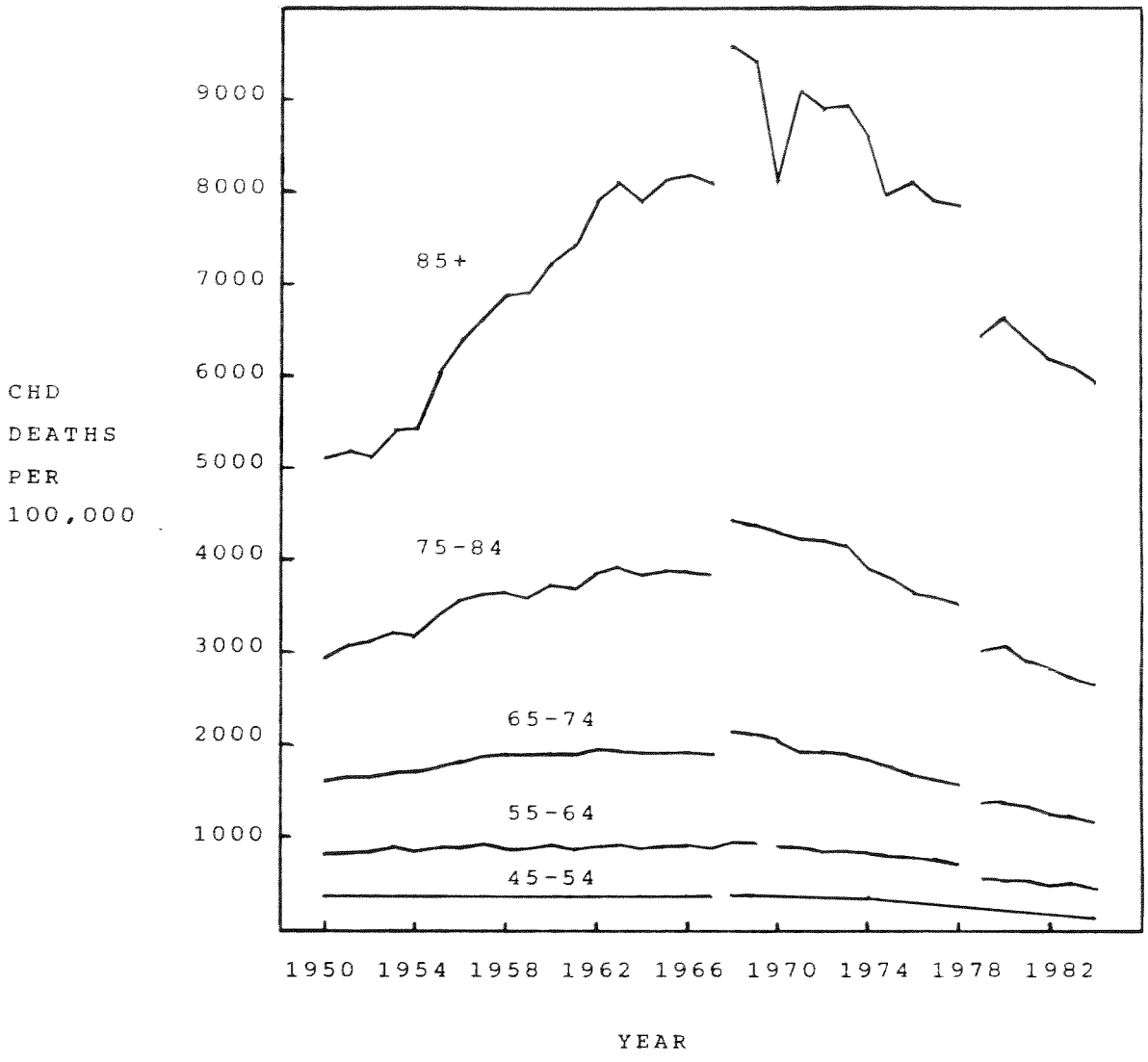

Figure 3-10. CHD death rate by age group for white males (adapted from Higgins and Leupker, 1988[2798])

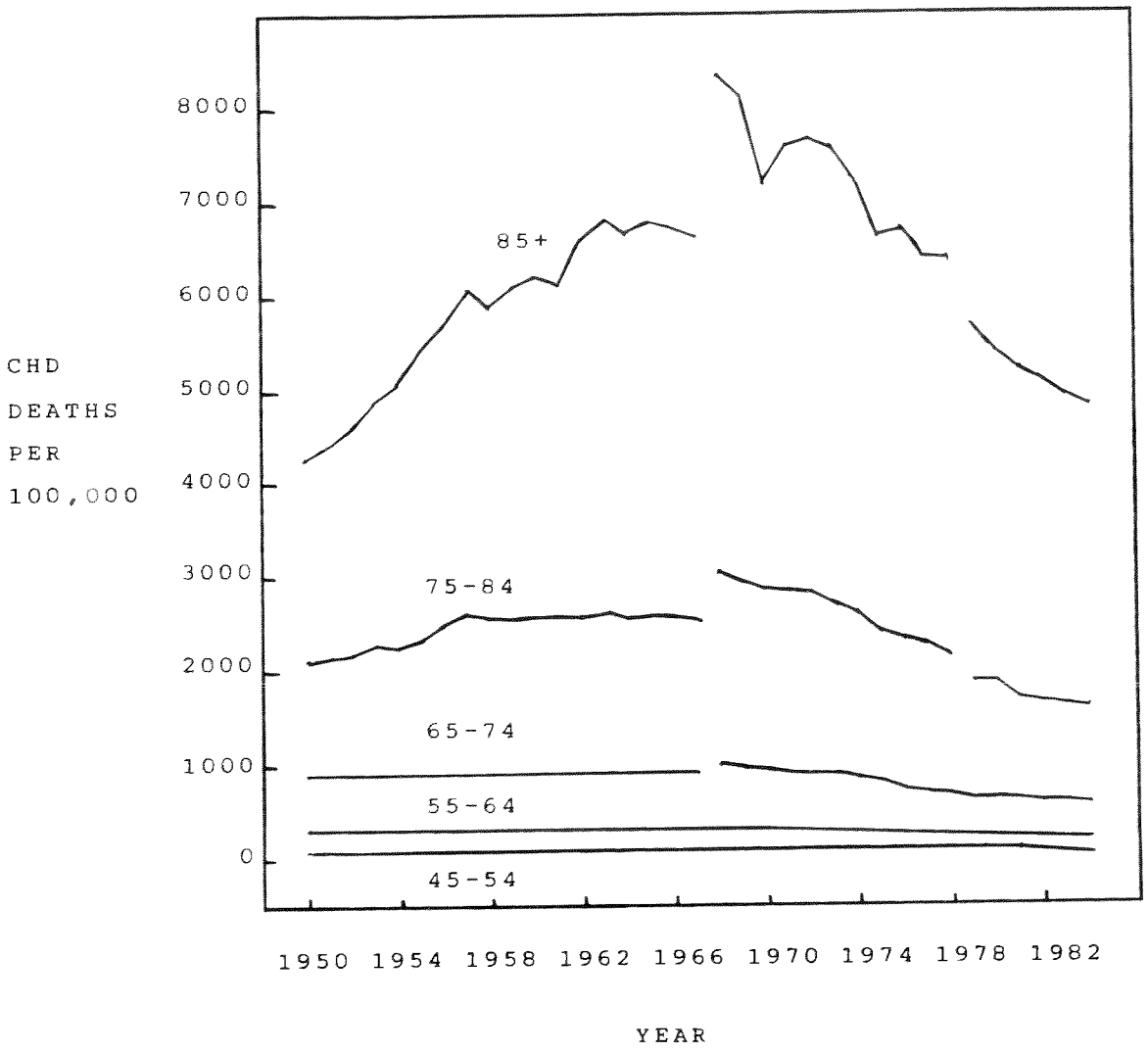

Figure 3-11. CHD death rate by age group for white females (adapted from Higgins and Leupker, 1988[2798])

Table 3-2

Percent increase in CHD mortality from 1950 to "epidemic" peak for males and females age (adapted from Higgins & Luepker et al., 1988[2798])[a]

Age	White Males	White Females
45-54	9.2	1.4
55-64	11.4	3.8
65-74	22.2	9.2
75-84	31.4	23.3
85+	59.1	58.5

[a] The "epidemic" peak varied during the 1960s for the sexes and for age groups.

due to the major cardiovascular-renal diseases were essentially identical for white males and females in 1920. They were also essentially identical for nonwhite males and females but nearly three times higher than whites. Subsequently, nonwhites and white females underwent nearly identical (parallel) and dramatic declines to 1955, while white males exhibited a strong increasing trend during that period. The difference in rates between white males and females had reached 100% by 1955.

Although papers by Moriyama typically displayed objective reasoning, his 1958 paper was saturated with unsophisticated speculations, perhaps not so surprising when it is recognized that Jeremiah Stamler was one of his co-authors. Let us see how they "explained" the peculiar trends noted above. It was said that a questionnaire was submitted to experts who then offered their explanation for the trends. However, such explanations appear to be those of vintage Stamler.

Although the downward trends for nonwhite males and females paralleled that of white females, for some peculiar reason the white females trend was classified as "most impressive." It was said that the decreased trend among white women was probably due to (1) "their resistance to coronary disease" [nonexplanatory because resistance per se does not connote a trend other than flat], (2) "a sizable decline...in death rates due to infectious diseases affecting the cardiovascular-renal system" [nonexplanatory because there was a similar decline in such death rates among males], and (3) a "decline in mortality rates due to rheumatic heart disease and the cardiovascular-renal 'complications' of diabetes" [nonexplanatory because it applies also to white males]. Moriyama et al. stated that "All these phenomena together were apparently adequate to account for the overall reduction in cardiovascular death rate exhibited by white women from 1920 to 1947." But as noted, they do not in the least explain the trend at all.

Diet was said to be the most important probable cause of the cardiovascular-renal mortality trend among white males but their conviction was less than substantial. For example, they said that "It was suggested that in recent decades men in the U.S. had increased their consumption of fats, particularly animal fats (meat, butter, eggs, etc.)." And since women consume essentially the same diet as men, they attributed the decrease in death rates among women to their higher "tolerance...for high-fat, high caloric diets and obesity." Not only is this explanation purely speculative and without scientific foundation, it is completely contrary to fact. First, as will be seen later in this chapter, animal fat consumption decreased, rather than increased, during that period. Second, atherosclerosis is said to be caused by high blood cholesterol levels. Since animal fats affect blood cholesterol levels in women equal to that in men, it is nonsense to invoke an irrelevant concept of "tolerance to fat."

Because Stamler has attributed high cardiovascular death rates in advanced countries to "rich" diets, the explanations given for the nonwhite death rate trends were also unreasonable. For example, implied in their discussion, but not discussed explicitly, was the notion that nonwhite females had no unique tolerance to high fat diets compared to nonwhite males, while white females did exhibit such a tolerance compared to white males. Such an implication is also nonsense, as was the entire discussion explaining the highly peculiar and inconsistent trends.

Further evidence against the notion of a CHD mortality epidemic can be seen in the age-adjusted all-cause death rate trends of white males and females from 1940 to 1960. Figure 3-12 shows these trends. As can be seen, the profiles are almost exactly the same, particularly during the 1950s when the so-called male epidemic occurred. If it were true that a real increase in male CHD mortality and a minor increase in white female mortality occurred during the 1950s, as indicated in Figure 3-8, that differential should have been reflected in somewhat different all-cause mortality profiles. But, in fact, they were as identical as one would expect from mortality statistics.

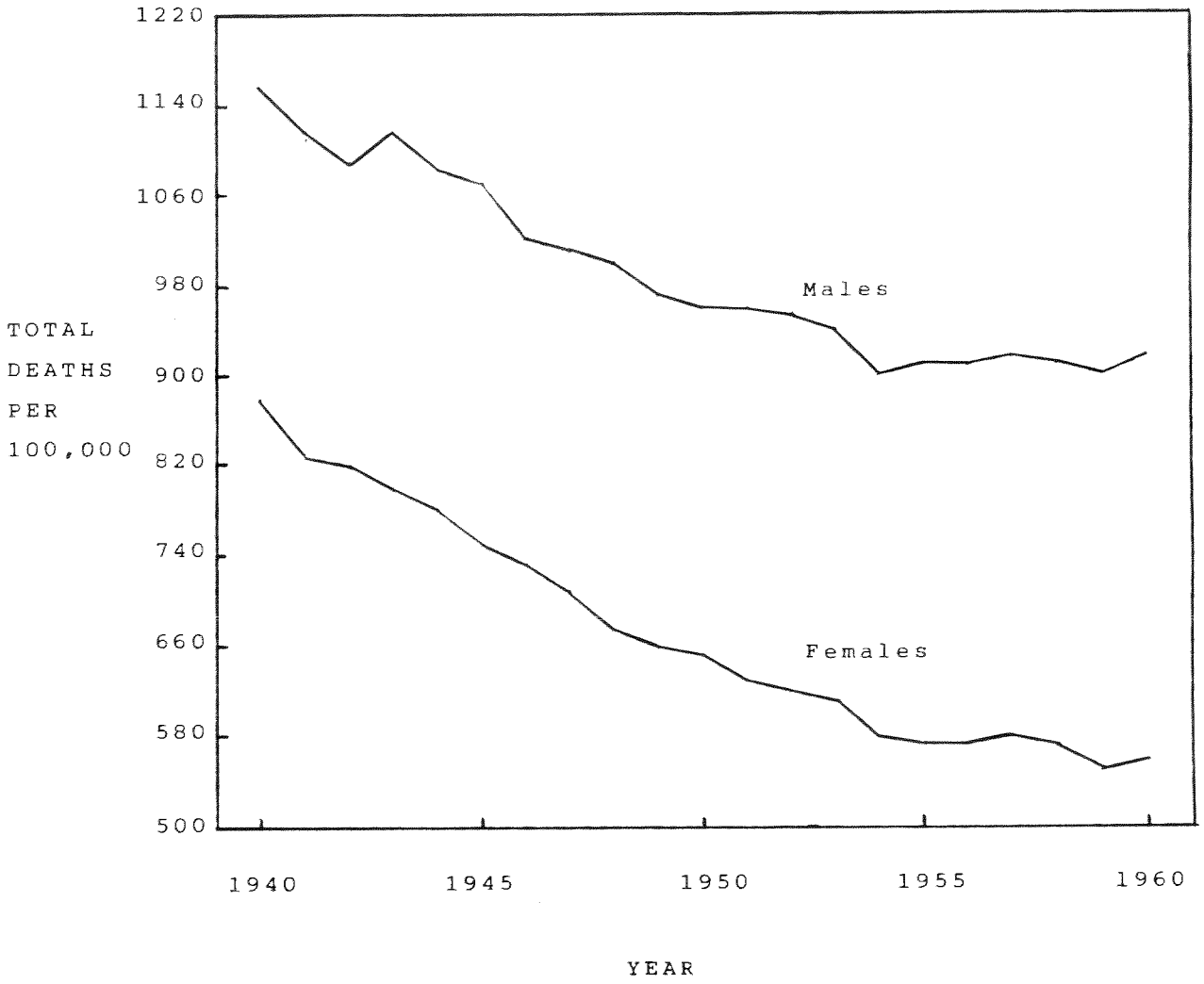

Figure 3-12. Age-adjusted all cause death rates for white males and females, 1940-1960 (adapted from Grove and Hetzel, 1968[1949])

Finally, it is useful to compare the CHD (Figure 3-10) and all-cause (Figure 3-13) death rates for white males by age groups. One can see that the all-cause death rate remained almost constant from 1935 to 1960 among men under 70 years of age. Moreover, very little change occurred between 1950 and 1960 for men of all age groups (the one deviant rate in 1955 for men age 85+ appears to be a statistical quirk). Yet, the reported mortality rates due to CHD were substantially different for the different age groups during the 1950s. This discrepancy again indicates that changes in classifications of death were occurring during that period, not actual changes in CHD mortality rates.

In effect, all of these facts, together with the discussion presented in the previous section amply demonstrate that the so-called CHD "epidemic" was an artifact of the diagnostic/death certification process and aging. No matter how you analyze the data, the "epidemic" cannot be seen as an actual increase in death rate independent of these factors.

While the alliance steadfastly maintains, in general, that the "epidemic" and current high rate of CHD, although substantially depressed compared to 27 years ago, was due, in large part, to lifestyle changes, in more subdued and objective moments they have presented other stories. For example, Thom and Maurer stated in 1988 that "The 1978 [NHLBI] Conference on the Decline in CHD Mortality pointed out that it is not known why the rise occurred..."[2799] The 1981 NHLBI Working Group[3068] indicated that "The reported incidence of these [CHD] diseases probably [note the uncertainty] reflected actual increases as well as enhanced awareness and improved methods of diagnosis." (Indeed, they acknowledged that there was not even a classification for CHD in the first four revisions of the ICD.) In 1984 Kannel and Thom stated, "Explanations of mortality trends for chronic diseases have seldom been satisfactory because of limitations in cause-of-death information on death certificates. There is no unequivocal explanation as to why CHD mortality had risen so high in the first place..."[1174] And at a 1988 NHLBI conference Higgins and Luepker said, "Neither the reasons for the rise nor the fall are well understood."[2803] They continued, "Eventually, these insights [from epidemiological studies] may lead to the recognition of causes..."

As will be seen in the section, Food Consumption Trends, changes in food consumption patterns during the epidemic were opposite to that necessary for raising blood cholesterol levels and thus CHD rates. Chapter 9 discusses in considerable detail the inconsistent relationships between the CHD increase and decrease and the remaining two major risk factors, hypertension and cigarette smoking.

It must be acknowledged that some non-alliance researchers also believe that a CHD epidemic occurred during this century. A September 1989 telephone conversation with Rei Ravenholt,[2439] for example, indicated that he was convinced that an epidemic occurred. Reference was made to his 1962 article describing the painstaking construction of coronary heart disease mortality rates in Seattle-King County, Washington, from 1910 to 1960.[2349] He and his associates reviewed and analyzed all death certificates in that community for 1881 to 1925 and every fifth year thereafter, taking into account the facts that many changes in classifications of deaths occurred during that period. The results of his study indicated a sharp increase in CHD mortality from 1925 to about 1950, after which the trend stabilized.

Although Ravenholt's study was undoubtedly an example of thoughtful and difficult work, it is nevertheless subject to all the criticisms noted above and in Volume 1. The reinterpretation of data on death certificates presupposes that all such certificates had all the information necessary to recode them according to today's definition of CHD. Such a state-of-affairs could not be the case in view of the general lack of

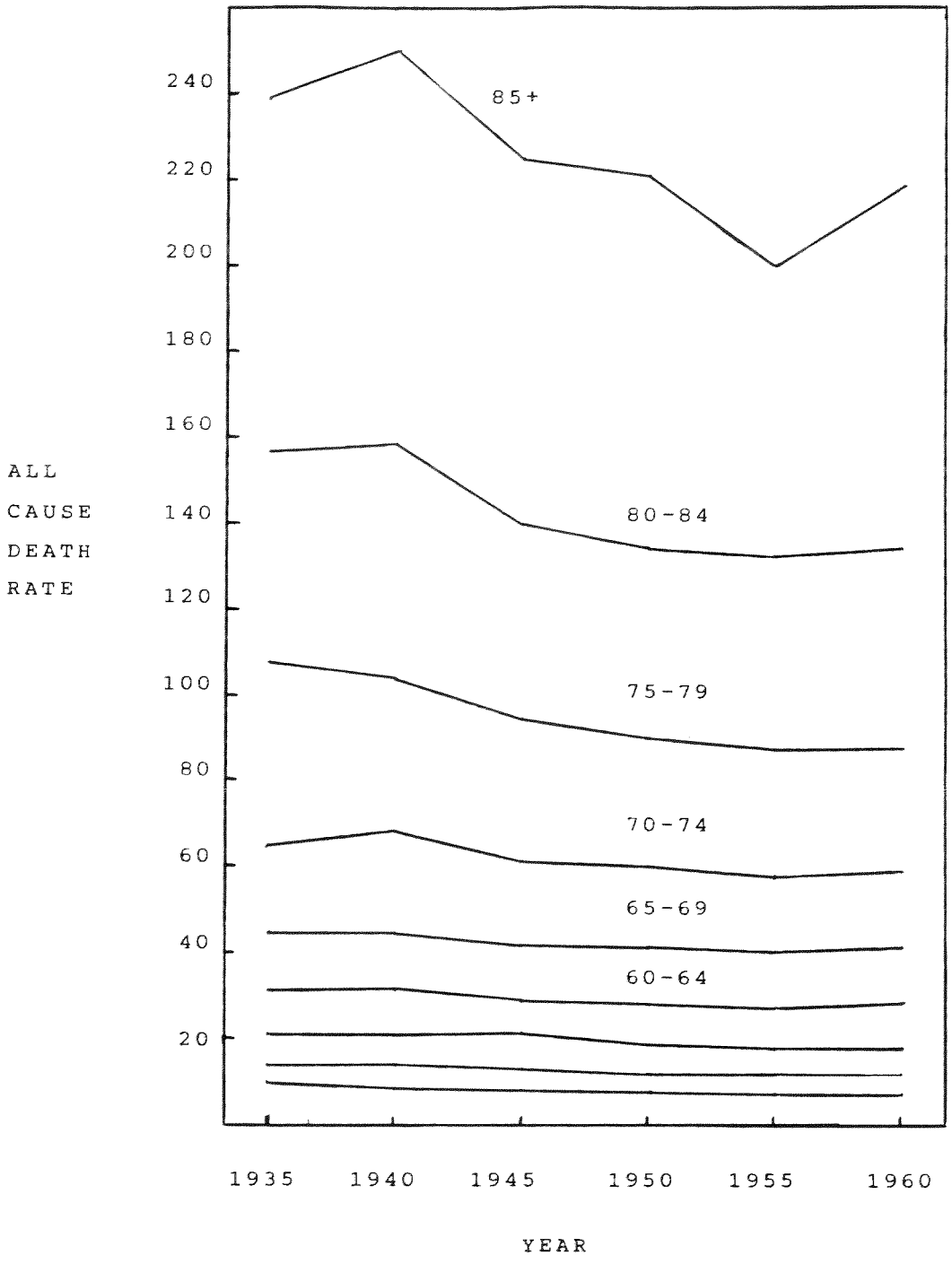

Figure 3-13. All-cause white male death rates by age groups (adapted from Grove and Hetzel, 1968[1949])

knowledge about CHD during the first half of this century, the lack of adequate diagnostic tools and the relatively low physician to population ratio.

LIFE EXPECTANCY

Life expectancy in the U.S. has continuously risen throughout this century. Figure 3-14 shows that it appeared to asymptote in 1955 but, in fact, it was still increasing, albeit slowly.[2735] The figure also shows that the percentage of persons over 65 years increased continuously throughout the century.[1673] Since almost all of the CHD "epidemic" occurred between 1930 and 1955, the steep linear increase in life expectancy during that period and the steep linear increase in the percentage of persons over 65 through 1960 are totally inconsistent with the concept of a true CHD epidemic.

Although a detailed comparison of Japanese and American life expectancy data is made in Chapter 4, it is useful to briefly discuss some factors associated with life expectancy which have been and continue to be important in the U.S. but have nothing to do with fat, saturated fat or cholesterol.

Of the 33 industrialized countries, the U.S. ranks 17th in life expectancy at 75 years and only one to several months separates the U.S. from being 12th.[2704] Although it might be naively concluded that this is an incredibly low ranking for the most powerful country on earth, it is, in fact, a remarkably high ranking in view of the many factors that operate against a high life expectancy. Several of the factors are interrelated. One of the most important is infant mortality. The U.S has nearly the highest infant mortality rate among industrialized countries, being 1,010 per 100,000 live births and twice as high as the Japanese rate of 500.[2647] A high infant mortality rate, of course, depresses the overall life expectancy at birth but it is clearly not related to "risk factors."

It is not relevant here to delve into the specific subfactors which influence infant mortality rates but it is clear that it is most prevalent among the impoverished. And therein lies the root of other factors which affect life expectancy, i.e., the derivatives of poverty. Despite its economic power, the U.S. undoubtedly has the largest percentage of poor people among all industrialized countries. Poorness entails poor medical health care and higher rates of deaths at all ages, including higher infant mortality. Poorness entails higher rates of malnutrition which also produces higher death rates, particularly during the youthful years. Poorness entails a higher rate of crime and, therefore, homicides. And poorness entails higher rates of drug involvement and deaths associated with such involvement.

To illustrate the force of poverty on early mortality, Table 3-3 shows the life expectancies of black and white males and females at various ages.[a] The wide spread between the races occurs at birth, reflecting differences in infant mortality rates. This difference gradually diminishes until it is dissolved altogether at age 75. All of the factors discussed earlier play a role in producing the differences between the races. Intuitively, it should be obvious that some of the factors (e.g., deaths due to drugs, crimes, etc.) no longer function as middle-age approaches.

The life expectancy differences between blacks and whites at birth continues to the present time.[2683] White males outlive black males an average of 7 years and white females outlive black females an average of 5.1 years.

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[a] Since there is a relatively large group of poor whites, these differences do not fully reflect the true differences between the impoverished and the nonimpoverished.

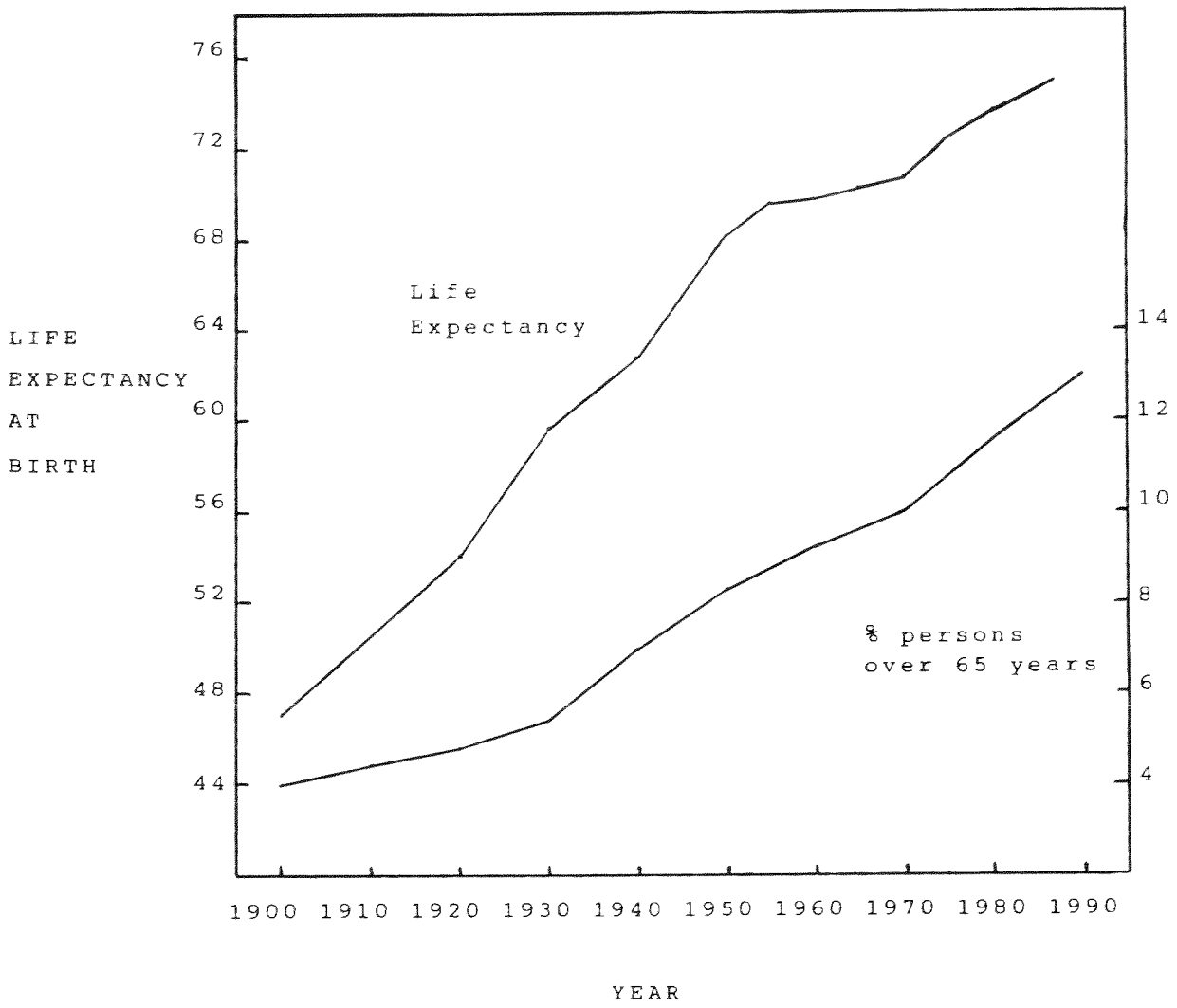

Figure 3-14. Life expectancy of Americans at birth and the percentage of persons over 65 years (adapted from National Center for Health Statistics, 1989[2735] and Anonymous, 1988[1673])

Table 3-3

Life expectancy at various ages for white and black males and females, 1983 (Statistical Abstract, 1987[1896])

Age	White Male	Black Male	White Female	Black Female	All
At birth	71.7	65.4	78.7	73.6	74.6
35	39.2	34.4	45.2	41.2	41.9
45	30.0	26.2	35.7	32.2	32.7
55	21.6	19.1	26.8	24.1	24.1
65	14.5	13.4	18.7	17.3	16.7
75	9.0	9.0	11.8	11.5	10.7

A comparison between the Japanese, which have the highest life expectancy in the world, and Americans should be made with the knowledge that all of the factors which depress the U.S. life expectancy are effectively nonexistent in Japan. If one is truly concerned about relating diet with CHD, one must extract out these factors and examine the life expectancy of middle and upperclass white Americans. The evidence will reveal that the U.S. life expectancy closely approaches or exceeds that of Japan. In fact, as will be seen in Chapter 4, the life expectancy of white women already exceeds that of Japanese women at middle-age.

FOOD CONSUMPTION TRENDS

In the previous section the recorded CHD mortality trend was seen to increase from the turn of the century until 1962-1963, decrease slightly after 1963 and then undertake a steep decline beginning in 1967. Intuitively, one would think the diet-CHD promoters would concentrate most of their efforts attempting to demonstrate that the CHD "epidemic" was associated with an increased consumption of saturated (mostly animal) fats and cholesterol and that the subsequent decline in CHD mortality was associated with a decreased consumption of such lipids. This effort would have far greater scientific impact than comparing nations for which innumerable variables cannot be controlled.

Many food-consumption trend studies were conducted by USDA staff, independent researchers and even a member of NHLI. Without exception, these studies presented data which indicated that consumption of (1) vegetable fat increased continuously throughout this century, (2) animal fat remained relatively constant until the late 1940s and then progressively decreased thereafter, and (3) saturated fat and cholesterol increased modestly until 1950 and then decreased thereafter (and please note that because total animal fats decreased, the increase in saturated fat was obviously due entirely to the saturates in vegetable fats). Because the trends during the "epidemic" were opposite to that predicted by the diet-CHD hypothesis, the literature of alliance members is almost completely devoid of references to food consumption trend studies in discussions of causations of the "epidemic." Instead, the alliance merely proclaimed that the "epidemic" was caused by Americans increasing their consumption of animal and other saturated fats and cholesterol. However, because the same food consumption trends were (obviously) consistent with the CHD mortality decline, alliance members readily cited the food consumption studies as evidence supporting the diet-CHD hypothesis. Of course, their review of those studies were limited to discussions of trends which paralleled the CHD mortality decline. For example, although vegetable fat consumption increased continuously throughout this century, alliance members implied to their readers that the trend began in unison with the CHD mortality decline. Of course this was a highly fraudulent practice but certainly consistent with the alliance's need to manipulate or interpret data to fit the diet-CHD hypothesis.

One additional point should be emphasized before analyzing food consumption trends in detail. The principal source of food consumption data, the U.S. Department of Agriculture (USDA), indicates a continuously increasing <u>availability</u> of total consumable fat throughout this century. While it is generally agreed that this trend reflects a true increase in total fat, it may or may not be the case. First, it is known that red meat availability effectively remained constant from 1910 to 1960, evidence that red meats did not contribute increasing amounts of fats.[a]

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[a] Although consumption of the higher grades of beef increased in the late 1940s, the actual increase in the associated fat <u>within</u> the lean was minimal, especially after cooking.

Second, although only a single segment of time, two major government food consumption surveys known as NHANES I and II (discussed later), conducted in the early and late 1970s, respectively, indicated virtually no change in total fat consumed. Yet, the USDA data showed a distinct increase in the fat available during that period. This fact should not be forgotten as this discussion proceeds.

Third, Americans did not enjoy as high an economic standard of living at the turn of the century as they did decades later and the food supply was not as plentiful. While it cannot be proven to be the case, it is reasonable to assume that Americans wasted less of their food than they did decades later. And since separable fat is a major food-waste, it is probable that Americans consumed more of the available fat then than they did decades later.

Regardless of the true total fat consumption trend, it is not relevant to the diet-CHD issue. It is true that the alliance has long recommended a reduction in total fat consumption but total fat per se does not increase blood cholesterol and evidence relating total fat with CHD is weak to nonexistent. In particular, alliance members often refer to the fact that dietary fat is very high and CHD rates are very low in Greece. Thus, the only trends of relevance are those related to saturated (mostly animal) fats and unsaturated (mostly vegetable) fats. As will be seen later, discussions by alliance members of specific food consumption trends, such as meat, dairy and lard products, are merely smoke screens which confuse readers and hide the overall saturated and unsaturated fat trends.

Undoubtedly a major reason why the AHA associated total fat with CHD is because of the early work of Keys whose original studies reported such associations at a time when it was not known that saturated fat increased blood cholesterol and polyunsaturated fat decreased it. Although forgotten or, more likely, ignored by the AHA and others, Keys actually incriminated vegetable fats, not animal fats as the cause of the so-called CHD epidemic. In 1953 he said, "The present high levels of fat in the American diet did not always prevail and this fact may not be unrelated to the indication that coronary disease is increasing in this country. In the past 40 years the contribution of fats to the total metabolism in the U.S. has risen 25%; in the past 20 years the rise has been almost 13%. ...it is clear that the biggest contributor to the fats in the American diet is fats and oils as such, excluding butter, which comprise 46.5% of the total. Meats, poultry and fish combined make a poor second at 22.1%. Any attempt to reduce the total fat intake must, then, begin with cooking fats and oil."[279]

Since most cooking fats and oils were derivatives of vegetable oils, this statement clearly acknowledged the fact that vegetable fats, not animal fats, had been increasing. When it was later discovered that saturated and polyunsaturated fats had different effects, Keys and his alliance colleagues then began claiming that the CHD epidemic was due to increasing consumption of animal fat. Thus, the original facts uncovered by Keys in 1953 were effectively buried by the alliance.

In a related 1953 article Keys[3296] insisted that the American diet had become increasingly fattier although acknowledging that "the actual intake of the several nutrients cannot be specified with great precision because of the uncertainties in regard to kitchen and plate waste." Indeed, as noted earlier, Keys had no evidence other than USDA availability data and we have earlier noted that the NHANES surveys showed no increasing fat intake trends, although the USDA data suggested such trends.

We now turn to the food consumption study findings. The subsequent section shows in some detail how alliance members have fraudulently distorted and misinterpreted these findings.

Food Consumption Studies

Most of the analyses of food consumption trends have been based on USDA availability or "disappearance" data, i.e., foods which leave the nation's food stores and restaurants for consumer consumption. These foods are converted to nutrients, summed for a 12 month period and then divided by the U.S. population to yield per capita consumption estimates. These estimates have been produced annually since 1909. As emphasized in Volume 1, these data are useful in examining trends but they are overestimates of actual consumption because they do not account for losses due to spoilage and waste. For example, much of the fat on retail cuts of meat is lost in the home by either the cooking process or by trimming. The outer layer of fat on red meat cuts constitutes 50 to 80% of the fat on such cuts and is typically thrown away. While there is spoilage and waste associated with other foods as well, fat waste undoubtedly represents the major reason why USDA estimates are inflated.

Virtually everyone, including alliance members, are well aware of the fact that the USDA figures are overestimates because the food consumption studies they cite clearly indicate that fact. Consider, for example, the following quotes:

The USDA data "represent food used up in an economic sense. Although not a measure of the amount of fat actually ingested, such estimates are useful for showing trends in overall patterns of consumption." (Rizek, Friend and Page, USDA staff);[2090]

"...the animal fat estimates include fat that may be trimmed and discarded in the home or restaurant." (Enig, biochemist[221]);

"The statistics published by the USDA are actually accounts of food availability, not consumption." (Van Itallie[353]); and

"Losses that occur after food is initially measured, such as in further processing, marketing or home use, are not considered in the estimates." (U.S. Dept. HHS and USDA[2557]).

Alliance members, however, seldom mention the important factors of waste and spoilage in their many articles discussing food consumption trends and give readers the impression that the USDA estimates are valid in an absolute sense. Stamler did note in his testimony at the FTC-NCEN trial (Chapter 2) that USDA data do not reflect spoilage,[2438] but such comments tended not to be included in his writings in the literature.

Other analyses of food consumption trends included USDA surveys of urban and rural households. These data suffered from the same weaknesses of the "disappearance" data. For example, the American Medical Association's Council on Foods and Nutrition pointed out that the survey data "refer to the amount of fat in the food brought into household kitchens: no allowances were made for food discarded. Discarded food would probably include large amount of fat with high losses in calories."[2629]

The USDA also conducted a Nationwide Food Consumption Survey (NFCS) 1977-78 and a Continuing Survey of Food Intakes by Individuals (CSFII), 1985-86.[2557] Finally, the National Center for Health Statistics conducted two National Health and Nutrition Examination Surveys (NHANES I and II) in the periods 1971-74 and 1976-80.[2557]

The present section will focus on the "disappearance" data and the two NHANES surveys.

Total Calories. The solid line in Figure 3-15 is a close approximation of a figure published by the U.S. Department of Health and Human Services (USDHHS) and the USDA in 1989, showing the estimated food energy intake per person per day from 1910 to 1980, based on food disappearance data.[2557] The dashed line in the figure represents more accurate data provided by USDA's Gortner.[2091] The total calorie intake averaged 3,333 with an average derivation of only 85 (2.6%) over the entire 70 years. Thus, these data suggest that there has been no change of any consequence in total energy intake in the American population from 1910 to 1980. Moreover, the two obvious trends that can be seen in Figure 3-15 suggest that energy intake decreased during the CHD growth period and increased during the CHD decline. The time period denoted as "epidemic" represents the major CHD mortality growth period.

Table 3-4 presents estimates of food energy intakes from the NHANES I and II surveys.[2557] While mean intakes for men and women across all ages and an overall mean intake were not given, it is enormously obvious that these caloric estimates are very substantially lower than those generated by the food disappearance data. In fact, the NHANES data suggest an overall mean intake for adults of about 2,000 to 2,300, some 1,000 to 1,400 calories lower than that represented by the disappearance data. These data are probably underestimates, just as the disappearance data are overestimates. It is probable that the true mean intake of Americans is somewhere in between the two, possibly around 2,600 calories. In any event, the purpose of this exercise is to demonstrate that the food disappearance data are gross overestimates of food consumption and should never be used by epidemiologists to indicate true intakes of total energy, fat or any other nutrient.

Fat and Cholesterol. Figures 3-16 and 3-17 present the fat and cholesterol disappearance data published by USDHHS/USDA. As can be seen, total fats available per capita steadily increased from about 120 grams in 1910 to about 158 grams in 1980. Since we have already established that these data are gross overestimates, we are principally concerned here with trends, not absolute amounts.

The 38 gram increase in total fat available is almost completely accounted for by increases in polyunsaturated fat (19 g) and monounsaturated fat (15 g). Thus, the saturated fat increase was a mere 4 g and, it may be noted, all of the increasing trend occurred by 1940. Saturated fat available actually decreased slightly during the major growth period of the CHD "epidemic."

These USDHHS/USDA data indicate unequivocally that the CHD "epidemic" was not correlated with the availability of saturated fat. The data also indicate no correlation with total fat or monounsaturated and polyunsaturated fats. Although the trends before 1962 would suggest such positive correlations, the fact that the CHD mortality decline occurred while fat availability was at its highest peak and still growing reduces such correlations to meaningless, coincidental associations.

Figure 3-17 shows that the availability of dietary cholesterol ranged from about 500 mg to about 585 mg per capita per day. The mean was about 534 mg and the average deviation was approximately 22 mg (4.1%). These data indicate rather trivial variations over a 70 year period. Moreover, the availability trend was decidedly downward during the major growth period of the CHD "epidemic."

Table 3-5 presents the estimated consumption values for saturated fat and cholesterol derived from the NHANES surveys. It is again clear that these values are substantially lower than the food disappearance estimates. While the food disappearance data (1970-1980) suggest a mean intake of saturated fat of about 57 grams, the NHANES data suggest a value of about 30 grams. And while the food disappearance data indicate a mean intake of cholesterol of about 520 mg, the

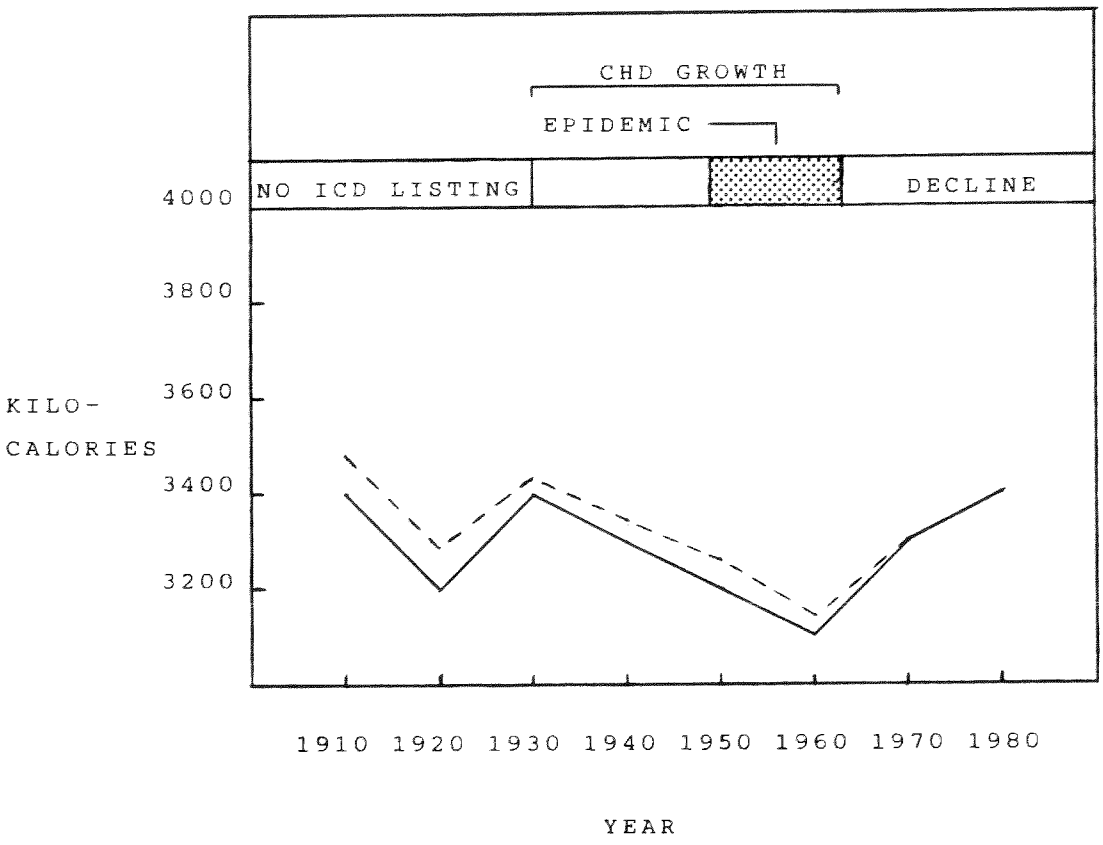

Figure 3-15. Estimated per capita food energy intake, based on food energy availability at retail (adapted from USDHHS/USDA, 1989[2557] and Gortner[2091])

Table 3-4

Estimated food energy intake
of Americans by age and sex
(adapted from USDHHS/USDA,1989[2557])

Sex and Age	NHANES I 1971-74	NHANES II 1976-80
Both Sexes		
1-2	1,350	1,287
3-5	1,676	1,569
6-11	2,045	1,960
Male		
12-15	2,625	2,490
16-19	3,010	3,048
20-29	2,850	2,899
30-39	2,668	2,554
40-49	2,428	2,421
50-59	2,157	2,203
60-69	1,976	1,961
70+	1,747	1,734
Female		
12-15	1,910	1,821
16-19	1,735	1,687
20-29	1,681	1,675
30-39	1,610	1,596
40-49	1,552	1,531
50-59	1,466	1,417
60-69	1,352	1,340
70+	1,239	1,279

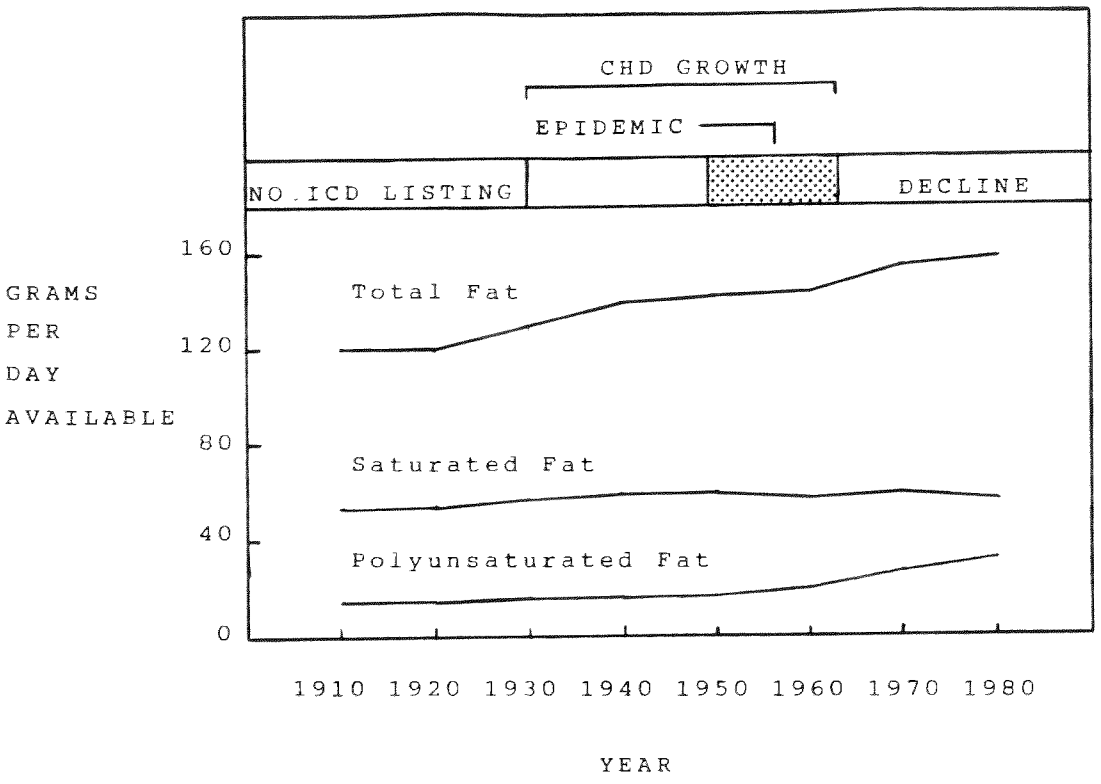

Figure 3-16. Estimated per capita total, saturated and polyunsaturated fat intakes, based on fat availability at retail (adapted from USDHHS/USDA, 1989[2557])

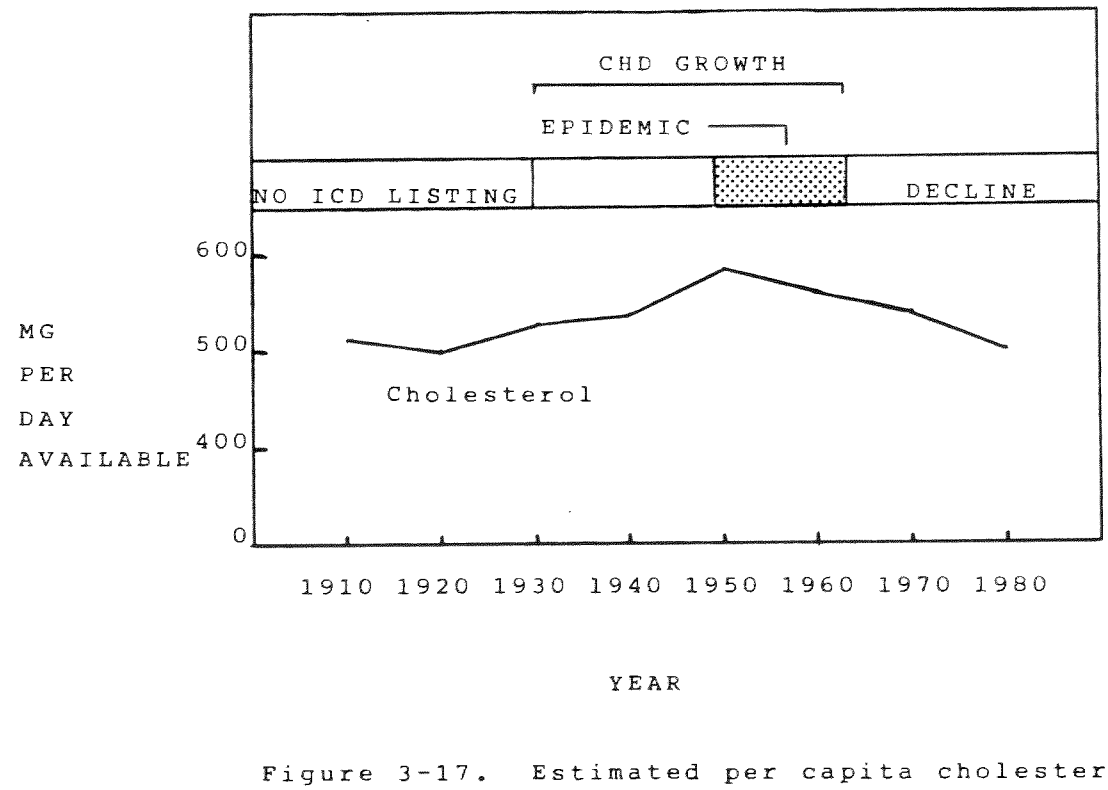

Figure 3-17. Estimated per capita cholesterol intake, based on cholesterol availability at retail (adapted from USDHHS/USDA, 1989[2557])

Table 3-5

Estimated saturated fat and cholesterol intakes of Americans by age and sex (adapted from USDHHS/USDA, 1989[2557])

Sex and Age	NHANES I		NHANES II	
	Sat. Fat(g)	Chol.(mg)	Sat. Fat(g)	Chol.(mg)
Both Sexes				
1-2	22	284	19	227
3-5	26	290	23	245
6-11	32	314	29	278
Male				
12-15	40	379	38	359
16-19	46	518	48	493
20-29	43	513	43	453
39-39	40	517	38	453
40-49	37	497	38	442
50-59	33	470	33	437
60-69	30	424	29	415
70+	26	424	25	365
Female				
12-15	30	305	27	256
16-19	26	297	25	255
20-29	25	304	24	270
30-39	24	312	23	289
40-49	23	340	23	305
50-59	22	317	20	263
60-69	19	298	18	262
70+	18	256	16	216

NHANES data suggest a value of about 366 mg. It should be particularly noted, for later recall, that the estimated consumption for adult men (16+) was 459 mg, 12% lower than the food disappearance estimate for both men and women.

Figure 3-18 shows the available total fat, saturated fat and polyunsaturated fat as percentages of total available calories. This figure can be interpreted exactly the same way as Figure 3-16. Because the CHD mortality trend declined while total fat and saturated fat availability were at their peaks and polyunsaturated fat increased steadily during both the "epidemic" and the CHD decline, these data clearly indicate no meaningful relationship between fat availability and CHD trends.

The NHANES surveys showed that the percentage of total calories consumed as saturated fat ranged from about 12.5% to about 14% for adult men and women of all age groups.[a] The mean of about 13.6% is approximately 2.4 percentage points lower than that generated by the food disappearance data for the same 1970 to 1980 period. Similarly, the NHANES surveys showed that the percentage of total calories consumed as total fats ranged from 35% to 38% for adult men and women across all age groups. The mean of 37% was 5.5 percentage points lower than that derived from the food disappearance data.

The USDHHS/USDA report, which presented both food disappearance data and NHANES survey data, did not analyze fat trends in terms of animal and vegetable sources. This is dumbfounding in view of the fact that the alliance has designated animal fat as the principal dietary cause of CHD. However, such data are directly available from USDA food consumption trend studies (Friend et al.,[1160] Rizek et al.[2090]). Figure 3-19 shows that the available animal fat per capita remained remarkably constant from 1910 through 1960, obviously correlating not at all with the CHD "epidemic." The downward trend in animal fat availability began in 1948, immediately prior to the major surge of the CHD "epidemic." Vegetable fat availability increased steadily through both the "epidemic" and the decline. Again, all of these fat trends reveal no meaningful relationships with the rise and fall of CHD mortality rate.

Figures 3-20 and 3-21 more dramatically illustrate the trends in animal and vegetable fat availability. Figure 3-20 shows the percent changes in vegetable and animal fats since 1910[1160,2090] and Figure 3-21 shows the percent of total calories as animal and vegetable fat.[1160] No matter how the data are analyzed, it is clear that vegetable fat progressively increased its role in the American diet throughout this century, while animal fat remained relatively constant until the late 1940s, after which it began a steady decline. That decline began before the major growth of the CHD "epidemic" occurred.

Tables 3-6 and 3-7 summarize some of the trend data extracted from 9 studies for the periods 1909 to 1959 and 1948 to 1959, respectively. These periods represent the overall growth period of the CHD "epidemic" and the major growth period, respectively. Call and Sanchez,[2354] Hansen and Windham,[2287] Welsh and Marston[2698] and Henderson[2734] also reviewed food consumption trend data. Although they did not provide data that fit all the cells of the tables, they did indicate identical trends. For example, Hansen and Windham stated in 1988 that "few Americans seem to be aware of the fact that they have derived a higher proportion of their fat from plant sources and less from animal sources since the turn of the century."[2287] Call and Sanchez and Welsh and Marston drew the same conclusion in 1967 and 1982,

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[a] In the much smaller Minnesota Heart study, Folsom, Blackburn and others reported the saturated fat intake to be 15%.[758]

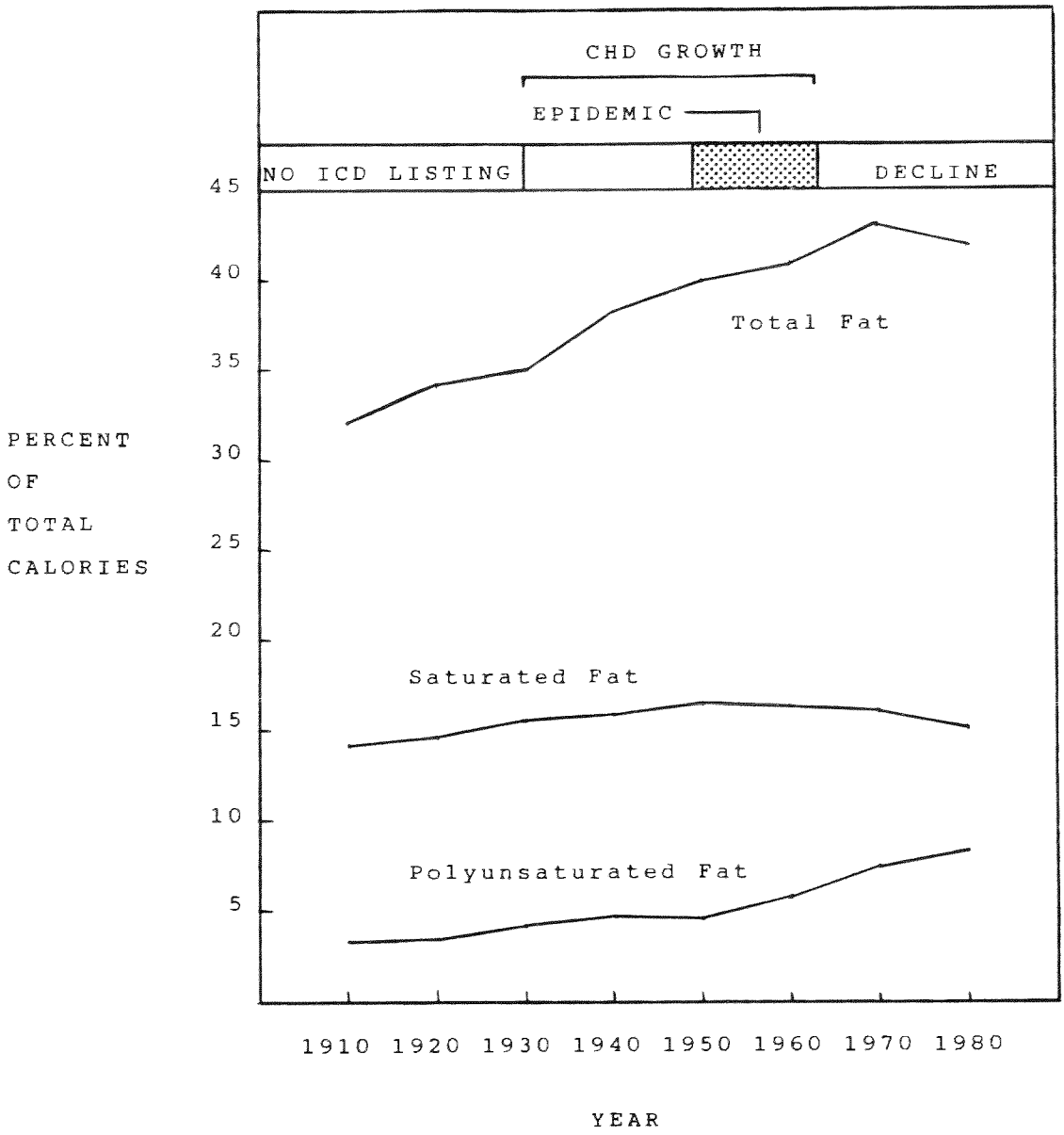

Figure 3-18. Estimated per capita total, saturated and polyunsaturated fat intake as a percentage of total calories available at retail (adapted from USDHHS/USDA, 1989[2557])

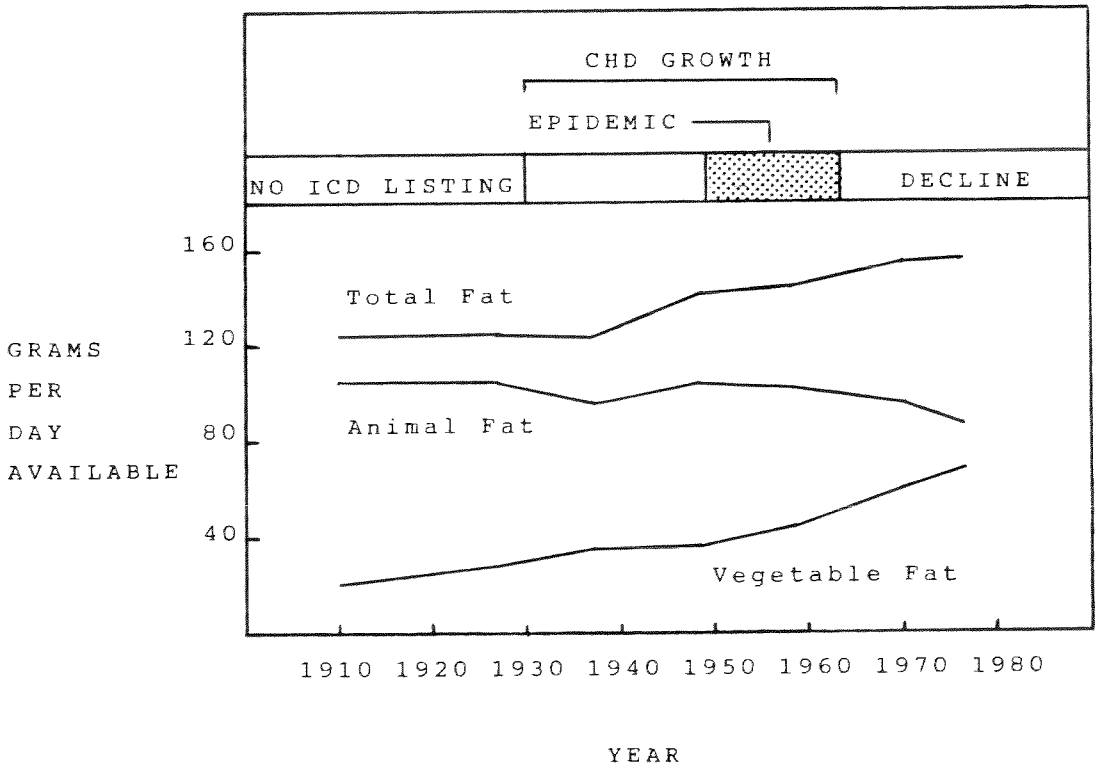

Figure 3-19. Estimated per capita total, animal and vegetable fat intakes, based on fat availability at retail (adapted from USDHHS/USDA, 1989[2557])

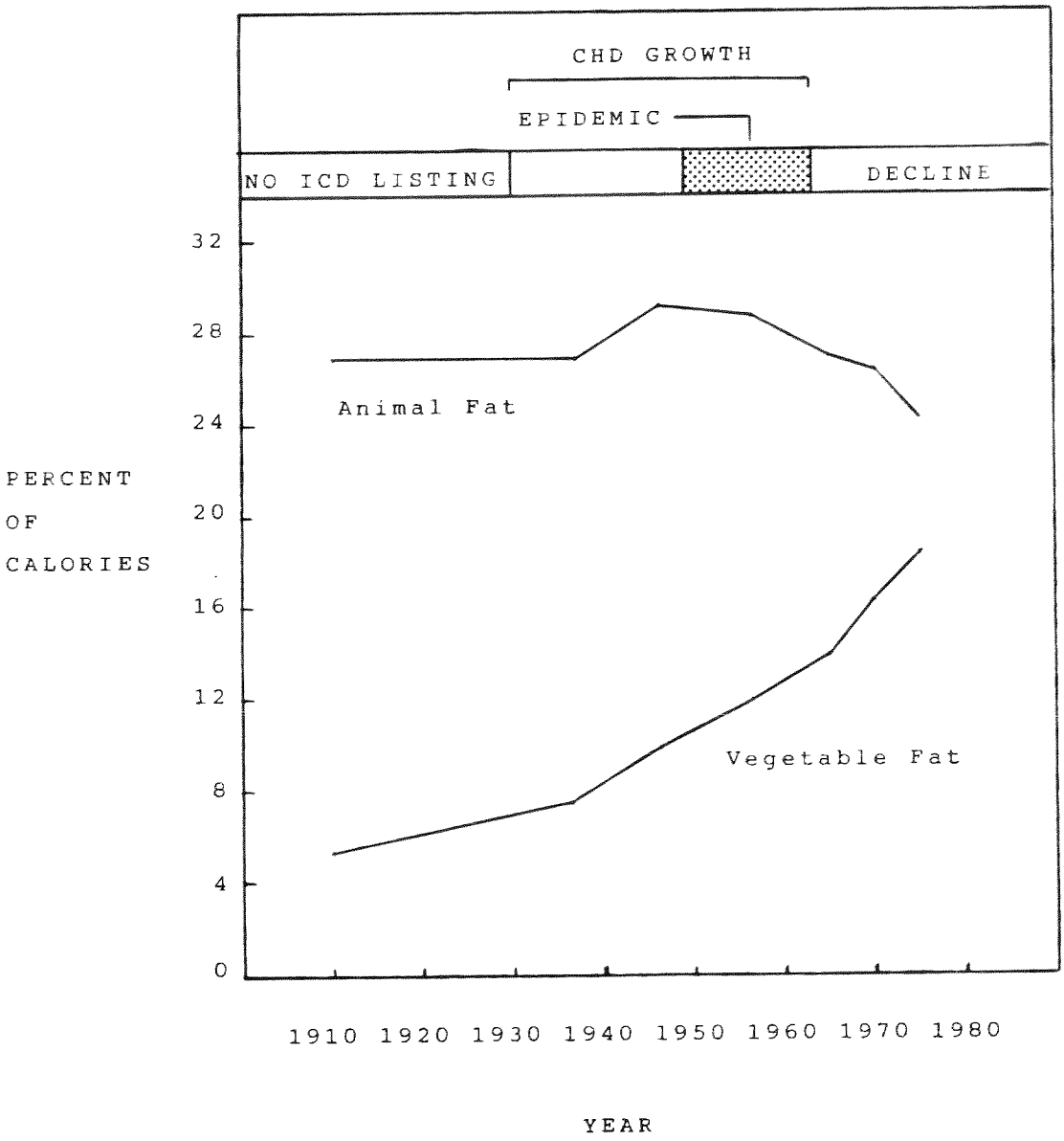

Figure 3-21. Estimated per capita animal and vegetable fat intakes as a percentage of total calories available at retail (adapted from USDHHS/USDA, 1989[2557])

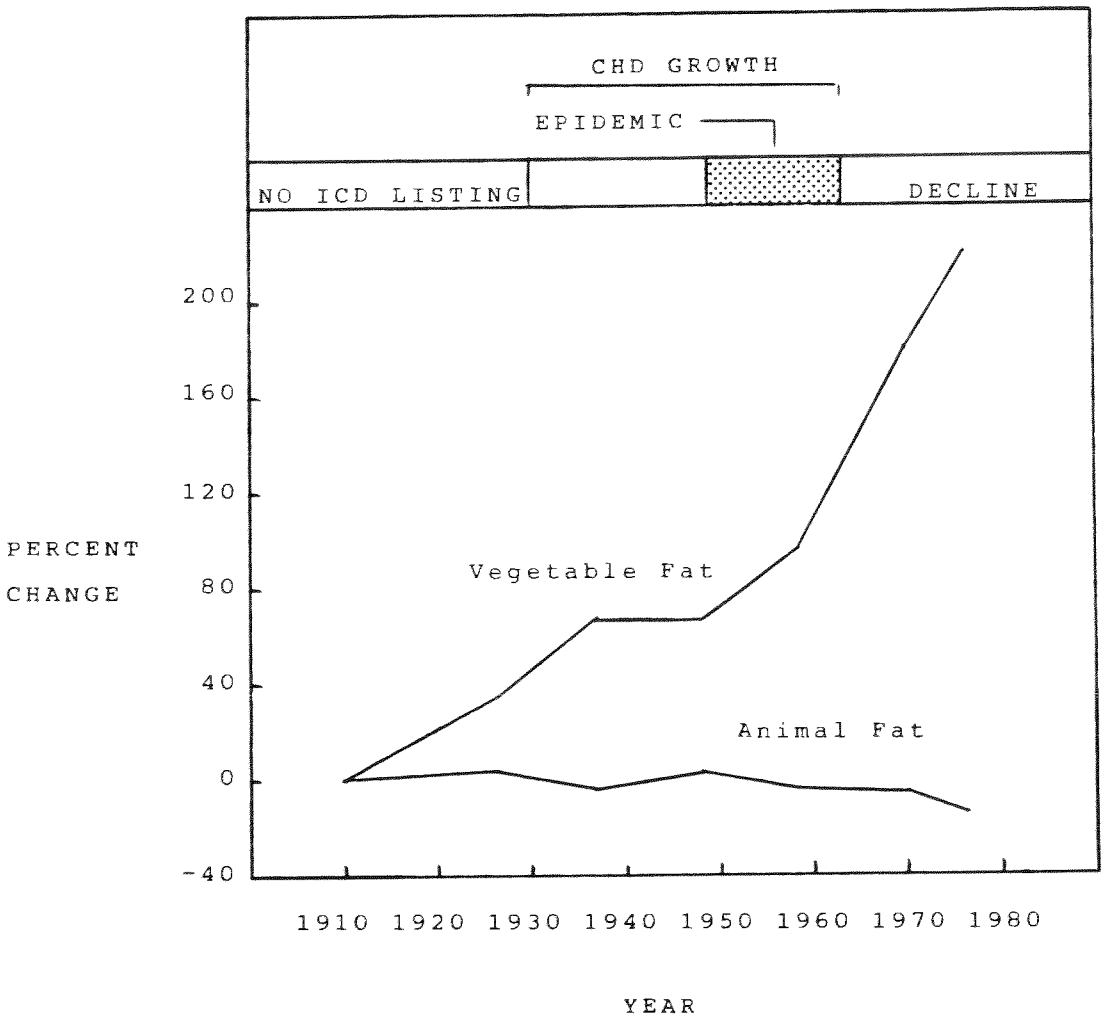

Figure 3-20. Estimated per capita vegetable and animal fat intake change since 1910, based on fat availability at retail (adapted from USDHHS/USDA, 1989[2557])

Table 3-6

Fat and cholesterol consumption trends during the period 1909 to1959

Study (Ref)	Date	% Total Fat change	% Saturated fat change	% Polyunsaturated fat change	% Animal fat change	% Vegetable fat change	% Cholesterol change
Antar (566)[1]	1964	12	7	37	ND	ND	8
Friend (549)[2]	1967	14	8.8	55	-15	72	ND
Kahn (542)[3]	1970	15	8.8	55	ND	ND	12
Rizek (2090)[2]	1974	14	8.8	55	-3	100	ND
Gortner (2091)[2]	1975	14	8.5	55	ND	ND	14
Pearson (695)[4]	1976	16	ND	ND	-7.7	133	ND
Enig (221)[5]	1978	16	12	55	-1	104	ND
Page (1117)[2]	1978	14	8[6]	UP	DOWN	UP	ND
Friend (1169)[2]	1979	14	9.2	70	-2.6	97	12
Means		14.3	8.9	54.6	-5.9	101	11.5

1 1909-1961
2 USDA study
3 NHLI study using Friend's data[549]
4 1909-1965
5 Using Rizek's data[2090]
6 Approximation
ND No data presented.

Table 3-7

Fat and cholesterol consumption trends during the period 1948 to 1959

Study (Ref)	Date	% Total Fat change	% Saturated fat change	% Polyunsaturated fat change	% Animal fat change	% Vegetable fat change	% Cholesterol change
Antar (566)[1]	1964	-0.6	-2.5	6	ND	ND	-5.7
Friend (549)[2]	1967	1.4	0.6	12	-5.3	14	ND
Kahn (542)[3]	1970	1.8	0.6	12	ND	ND	-1.3
Rizek (2090)[2]	1974	1.4	0.6	12	-3.8	17	ND
Gortner (2091)[2]	1975	2.1	0.6	12	ND	ND	0.2
Pearson (695)[4]	1976	2.8	ND	ND	-8.6	36	ND
Enig (221)	1978	1.4	0.6	12	-3.8	17	ND
Page (1117)[2]	1978	2.1	0	UP	DOWN	UP	ND
Friend (1169)[2]	1979	2.1	0.7	13	-3.8	18	-18
Means		1.6	.08	12.6	-5.1	20.2	-6.2

[1] 1950-1961
[2] USDA study
[3] NHLI study using Friend's data[549]
[4] 19048-1965
ND No data presented.

respectively. "It is clear that some major shifts have occurred in the types of fat that make up total disappearance. The increased availability of soybean oil and changing tastes and preferences of the American consumer have led to an increased disappearance of vegetable fats and oils at the expense of animal fats."[2354] Their data explicitly showed a substantial increase in polyunsaturated fats and a small reduction in saturated fats during the so-called CHD "epidemic" period of 1931 to 1965. Welsh and Marston said, "Animal fat was 83% of all fats in 1909, 75% by 1947 and 58% by 1980."[2698] Finally, Henderson emphasized that from 1909 to 1965 vegetable fat increased more than threefold while animal fat (lard, butter and edible beef fats) declined more than 50%.[2734]

Total dietary cholesterol increased about 12% from 1910 to 1950, after which it declined. The increase and decrease were driven almost exclusively by egg consumption which increased 27% from 1910 to 1950 and then decreased thereafter. The 27% increase represented about 88% of the total dietary cholesterol increase.

To better recognize the smoke screen generated by the alliance below, it is useful to describe the principal dietary changes that occurred which effectively controlled the overall animal and vegetable fat trends, as well as the saturated and unsaturated fat trends. The following data derive from the food consumption studies and annual statistical abstracts of the U.S.[a] With the exception of the depression years when availability was low, red meat availability remained constant at about 180 g per day until 1960, after which it increased. The availability of the two major animal fats, butter and lard, both remained constant until 1940, after which they decreased very substantially.[b] Simultaneously, the availability of vegetable fats (margarines and vegetable oils) increased modestly from 1910 to 1940, after which they increased very substantially. The sum total of these trends yielded decreasing and increasing availabilities of overall animal and vegetable fat trends, respectively.

The Distortion of Food Consumption Trends. Despite the massive and unequivocal evidence indicating that the rise and fall of CHD mortality were not related to animal or saturated fat consumption, like so many other aspects of the diet-CHD relationship they cannot explain, alliance members grossly distorted this evidence as well. They have done so principally by emphasizing trends during the CHD mortality decline and ignoring the trends during the "epidemic." Prior to presenting their "reviews" of food consumption studies, however, it is useful to describe some history regarding the alliance's attitude towards diet as a causation of CHD. This attitude is illustrated in the writings of Stamler who published numerous articles over a 25 year period that were highly redundant, nonempirical, opinionated and self serving, i.e., his references were often dominated by his own articles. Stamler and his associates defined atherosclerosis as a "metabolic disease" in 1956 and said that "This fundamental metabolic concept of atherogenesis rests upon an extensive foundation of knowledge. It is documented by abundant data accumulated by the three major investigative approaches to the atherosclerosis problem--the clinico-pathological, the epidemiological and the animal-experimental methods of research."[694] Note the generous use of superlatives, i.e., "extensive foundation" and "abundant data," suggesting that the single metabolic cause of atherosclerosis was conclusively established.

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[a] 1891,1992,1893,1894,1896

[b] Hubbel emphasized in 1965 that "The switch from butter to margarine occurred long before the health issue came up."[1992]

Six years later (1962) Stamler used similar superlatives to introduce a quite different causation profile: "The overwhelming evidence indicates that the disease is multifactorial in causation, with diet as a key essential etiologic factor."[574] He indicated that "extensive research, epidemiologic, clinicopathologic and experimental," supported this concept and cited five references (all his own articles) which presented "comprehensive surveys of this area." He went on to say, "diet by itself is not a sufficient cause, since premature disease does not develop in all persons habitually ingesting the implicated diet." Thus, in 6 short years Stamler altered his definition of cause from a strict metabolic disorder to a multifactorial disorder with diet being an insufficient cause. But in both articles, he had an "extensive foundation" of "abundant data" and "overwhelming evidence" to support his radically different definitions.

In 1973 Stamler stated that the "modern diet--excessive in calories in relation to energy expenditures, high in total fat, saturated fat, cholesterol, sugar and salt--leads to high prevalence rates of hyperlipidemia...in the adult population."[573] He continued, "The modern 'rich' diet also contributes significantly to current high prevalence rates of obesity, and consequently hypertensive, hyperglycemia, and hyperuricemia--and all of these are also important coronary risk factors. This diet is related to the CHD epidemic." Of course, proteins and carbohydrates also "contribute" to obesity, so the latter sentence has no scientific meaningfulness at all.

In 1978 Stamler said that "since the data from both animal and human studies...indicate that high blood pressure and cigarette smoking are minimally significant for atherogenesis in the absence of the nutritional-metabolic prerequisites, it is further reasonable and sound to designate 'rich' diet as a primary, essential, necessary cause of the current epidemic of premature atherosclerotic disease raging in the Western industrialized countries."[539] Thus, while his 1962 statement indicated that diet "is not a sufficient cause," his 1978 statement clearly suggested otherwise.

Participating at the American Health Foundation Conference in 1979 Stamler said, "Approaches to primary prevention have the greatest promise of success when based on sound scientific evidence on disease etiology and pathogenesis."[2635] As we shall see, he related diet with CHD on quite unsound and unscientific interpretations of USDA availability data.

In concluding his discussion of the diet-CHD relationship Stamler said, "'rich' diet and resultant nonoptimal serum lipid-lipoprotein levels are apparently the primary essential causes of epidemic premature atherosclerotic disease." In view of his dogmatic position, it is strange why he used the word "apparently" which adds nothing to the strength of his position and, in fact, introduces an element of doubt.

The conspiracy to defraud practicing physicians and the public at large is abundantly evident in the alliance's interpretations of food consumption trends. They are all highly similar in nature and either false or misleading. Interestingly, they differ sufficiently to reveal a highly inconsistent line of reasoning, as will be evidenced in the later discussion on "latency" or "lag" (the hypothesized period between risk factor change and change in CHD mortality rate).

It is useful to present the alliance's interpretations in historical order because the rise and fall of the CHD mortality rate influenced their selective use of the food consumption trend data.

Perhaps the major promoter of the diet-CHD relationship, at least during the "modern" examination of CHD, was Keys. In most of his writings he devoted his diet discussions to describing differences between countries in CHD mortality rates and in fat intakes when more valid comparisons would have been differences in diets before

and during the CHD "epidemic." However, he did discuss rather briefly some USDA data in a 1953 article.[279] It is to be emphasized that in 1953 nothing was known about the differential effects of saturated and unsaturated fats on blood cholesterol levels and fat per se was implicated as the CHD causation. Keys said, "The present high level of fat in the American diet did not always prevail and this fact may not be unrelated to the indication that coronary disease is increasing in this country." He continued, "From the statistics of the USDA it is clear that the biggest contributor to the fats in the American diet is fats and oils as such, excluding butter, which comprise 46.5% of the total. Meats, poultry and fish combined make a poor second at 22.1%. Any attempt to reduce the total fat intake must, then, begin with cooking fats and oils." Thus, he recommended a reduction in both animal (e.g., lard) and vegetable (oils) fats. It should be noted also that Keys referred to food supply, implying that he was aware that the fat values he quoted were overestimates of what Americans were really consuming.

This writer found only one further reference to USDA data by Keys in his many subsequent articles. Generally, he restricted his discussions to the presumed fact that the American diet was too high in fat and to recommendations to reduce that intake. For example, in 1956 he said, "A reasonable, practical conclusion from the present evidence might be to propose for American adults a sharp reduction in the total dietary fats from their current average intake in which fats account for some 40% or more of the total dietary calories. In this dietary adjustment, emphasis might be placed on reducing the consumption of margarine, hydrogenated shortenings, butterfat, and meat fats. The great nutritional values of milk and meat would be maintained, and increased, by favoring skim milk, cottage cheese, and lean meat."[280] Thus, Keys' recommendations to reduce fat again included vegetable fats as much as animal fats.

Stamler and his associates did briefly discuss USDA food availability data in 1956.[694] They stated that total dietary fat increased from 30% to 45% of total dietary calories from 1910 to 1952, respectively, and were apparently not yet aware of the need to differentiate between animal and vegetable fats. They also emphasized that milk and egg consumption had increased 36% and 35%, respectively, over that period of time. Stamler will apparently never refer to fat consumption trends on the 1910 to 1952 period in articles published after the CHD mortality decline. The reason for this omission will become obvious below.

In 1957 Keys published two articles which apparently represented his acceptance of the motion that CHD was multifactored in etiology.[276,569] He focused on the "high fat" diet in one article[276] but demonstrated recognition of the differential effects of the various fats in his statement, "With a judicial choice of fats in the diet, serum cholesterol level can be controlled without imposing extremely low-fat diets."[569]

Two additional interesting articles were published in 1957. At the request of the AHA Page and his colleagues prepared a report which, among other things, attempted to correlate food consumption trends in the U.S. with CHD mortality rates. They concluded that "The proposition that the character of the American diet has so changed during the past 50 years as to increase the incidence of coronary vascular disease cannot be supported."[512] And in his discussion of the diet-CHD relationship, Van Itallie said, "it appears that many housewives now cook meat in such a way that much of the fat is lost. Bacon fat, which used to be prized as a cooking vehicle, is now frequently discarded."[353,a] Van Itallie referred to USDA "food availability

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[a] Stephen published a remarkably similar statement 32 years later, i.e., "...much of it [fat] is simply being thrown away by the consumer. People used to value such fats as bacon grease and reuse them, but that doesn't happen so much anymore."[1751]

figures" in the context of a discussion on essential fatty acids but did not discuss the figures themselves.

In 1961 Jolliffe indicated that the American diet in 1955 contained 43.6% of total calories as fat and 18.3% as saturated fat.[545] These values were significantly higher than the maximum theoretical values expressed in the USDA availability data.

Also in 1961 the AHA published its first dietary recommendations.[517] Although the senior author of this article, Irvine Page, was the senior author of the 1957 report for the AHA which emphasized no association between the American diet and CHD mortality over time, the recommendations urged a reduction in total fat. Without referring to USDA data, they said, "Study of diets in the U.S. indicates that they usually contain large amounts of fat which account for approximately 40-45% of calories. They ignored the fact that these values were overestimates.

Also in 1970 the Inter-Society Commission gave readers the distinct impression that the long-term animal and vegetable fat consumption trends were associated with the alliance's recommendations, i.e., "As national statistics on the trends show, millions of Americans have already modified their diets, particularly their consumption of fat containing foods.[552] Furthermore, the Society cited studies (Tables 3-6 and 3-7) which showed that total fat consumption was <u>increasing</u>, not decreasing.

Using USDA food availability data, in 1970 Harold Kahn calculated the expected blood cholesterol changes to be expected from the changes in consumption of saturated and polyunsaturated fat of dietary cholesterol from 1910 to 1965.[542] He used equations generated by Keys and Hegsted (see Chapter 5). Then, he used Framingham data to estimate the changes in CHD "risk" associated with the resultant blood cholesterol changes. He concluded that "The increased risk of CHD reported to have occurred over this period is not related to dietary fat changes to a very important degree."

In 1972 Connor and Connor told their readers that the typical American diet contained 800 mg of cholesterol.[411] This value was about 260 mg higher than that theoretically possible since the USDA availability data indicated a maximum amount of about 540 mg per capita in 1970 if all available dietary cholesterol were consumed (see Figure 3-17).

Also in 1972 the American Health Foundation referred to the USDA data thusly (keeping in mind that because of lags in compiling death statistics, the CHD decline was not yet known): "Data from the USDA indicate that in the past half century, the American diet has undergone significant changes with increased consumption of meat, poultry, dairy products and simple sugars and a concomitant decreased use of cereals, potatoes and other starchy foods. The overall effect has been a gradual and significant increase in the proportion of calories derived from fat from about 30% [actually 35%] in 1930 to at least 40% in 1970. At the present time the ratio of polyunsaturated to saturated fatty acids in the average diet is about .3, indicating a preponderance of more saturated types of fat. The cholesterol intake is in excess of 600 mg per day."[424] But this statement was partially misleading and partially false. The implication inherent in the increase in fat and the P/S ratio is that animal fat consumption had been increasing. Not only was animal fat <u>decreasing</u>, they presented a figure which clearly showed this fact. And like Connor and Connor, the Foundation exaggerated the cholesterol intake of Americans. If alliance members truly adhered to known data, moreover, the Foundation and Connor and Connor might have been more consistent in their estimates of cholesterol intakes.

In 1975 Keys said that "USDA data showed a rise in per capita fat consumption during the war years and the vital statistics reported a steady increase in death

attributed to CHD."[540] As can be seen in Figure 3-16 the USDA data showed almost imperceptible rises in fat availability during World War II and the Korean War. Of equal importance were two important omissions by Keys. First, the CHD mortality decline was known in 1975 and Keys failed to note that fat availability began a significant increase at the peak of the CHD "epidemic" and continued during the CHD leveling off and subsequent decline. Second, since Keys had accepted the notion that saturated fat (mostly animal fat) was the principal cause of CHD since the late 1950s, he grossly misled readers by not mentioning the fact that animal fats never increased during the "epidemic" and actually declined somewhat (Figure 3-19).

Glueck and Connor in 1978 employed a quite different date for illustrating trends. They said that "Since 1970, there has been a decreased intake in dietary cholesterol and an increase in the P/S ratio of dietary fat."[1136,a]

Like the Inter-Society Commission in 1970, Stamler gave his readers the impression in 1977 that animal and vegetable fat consumption trends were initiated only in 1957. He said, "Literally millions of Americans in the past 20 years have begun acting against and controlling known 'risk factors'--the aspects of lifestyle that set people up for premature heart attacks..."[2633] Clearly, the trends were underway long before the Framingham study began and risk factors were known and long before Stamler became a CHD epidemiologist.

Now fully aware of the CHD mortality decline, Stamler shifted his discussion of USDA availability data in 1979 from the "epidemic" to the decline.[2635] He implied that the decline was due to a 26% decrease in egg consumption since 1950, a 39% decrease in milk fat solids since 1940 (why a different time period?) and an overall decline in dairy fat and lard and an overall increase in vegetable fats. Like Keys, he omitted the most important trend, namely that animal fat consumption remained stable during the first 50 years of this century and then gradually decreased during the major growth of the CHD epidemic and thereafter. Stamler also indicated that the total fat in the American diet was 42% and 40% of total calories in different parts of the same page in his articles. More important than being inconsistent, one cannot help but wonder why Stamler did not recognize that the CHD decline was occurring at the very height of the fat availability curve (Figure 3-17).

In another 1979 article Stamler cited the USDA study by Friend et al.[1160] (Tables 3-6 and 3-7). He repeated the specific consumption reductions of egg, whole milk, lard, butter and cream and the increase in vegetable fats since 1950. Curiously, he noted a dietary cholesterol reduction of 8% since the mid-1950s, rather than 1950 (why a different time period?). There is the implication in Stamler's two 1970 articles that it takes at least 12 to 17 years of dietary changes to affect changes in CHD mortality (see later discussion on this issue).

In 1981 Levy used yet another date to describe food consumption trends. He stated that since 1963--"the consumption of saturated fats (fats of animal origin) and oils is down by over 48% while the consumption of vegetable oils is up 74%."[1846] He maintained that dietary cholesterol used to be 600-800 mg but is now less than 500 mg per day and that the P/S ratio used to be 0.1 to 0.2 but is now closer to 0.4 to 0.5. Of course, the cholesterol intake was never 600 to 800 mg and the P/S ratio was never as low as 0.1 to 0.2. Figure 3-B indicates that the ratio has been almost constant at about 0.32 until 1960, after which it gradually increased to 0.5.

In 1984 Levy,[698] Kannel and Stamler[1083] and Kannel and Thom[1174] cited the last 20 years of USDA availability data to explain the CHD mortality decline. They

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[a] Glueck repeated this statement in 1979.[543]

reported declining consumption of eggs, butter, milk, lard and animal fats without informing their readers that these trends began long before the CHD mortality decline began. (Note also that butter, milk and lard are redundant with animal fats.) They also reported an increase in vegetable fats, a trend that initiated at the turn of the century.

Also in 1984 Gillum, Blackburn and others cited USDA staff members Welsh and Marston as saying that the decline in CHD mortality may be due, in part, to the decline in saturated fat consumption.[2696] This was an entirely false citation. Welsh and Marston did not relate food trends with heart or any other disease and did not even use the term "CHD." Moreover, their trend data clearly yielded interpretations opposite to that implied by Gillum et al.

In 1987 Fullwood, Rifkind and their colleagues observed that "There is the possibility of a change in the consumption of food with high fat content from the 1960s to 1980s."[576] They acknowledged the NHANES surveys but did not discuss food consumption trends. They also said that USDA data show increases in fat from meat, poultry and fish between the 1950s and 1980 and decreases in dairy products. They neglected to report that overall animal fat availability decreased.

In 1988 Goldman stated that cholesterol consumption peaked in 1959 and then decreased "considerably" thereafter thus partially explaining why the CHD mortality peaked a few years later and then declined. However, the USDA data show that consumption peaked more than 10 years earlier and the subsequent decrease was not at all "considerable."[2557]

A 1988 article by Slattery and Randall[1660] was profoundly replete with misleading, inconsistent and false information. They first reported that animal and vegetable fat consumption trends decreased and increased, respectively, after 1961, implying that these trends began after 1961. They plotted many trends since 1909, such as meats, cheese, dairy products, eggs and fats and oils but carefully avoided the most important trends of animal and vegetable fats. Although not explicitly stating that vegetable fats were increasing and animal fats were decreasing during the CHD "epidemic," they acknowledged this fact implicitly in their statement, "Limitations in available data frequently necessitate that a simplification of the [diet-CHD] hypothesis in epidemiological studies to state that total dietary fat is associated with CHD mortality." Not only were there not limitations in the available data on this issue, Slattery and Randall redefined the diet-CHD hypothesis to fit the data. Their reasoning was also illogical because (1) the increase in total dietary fat in the U.S. progressed during the CHD mortality decline and (2) much publicity has been given the fact that some countries such as Greece and France have very high fat diets and very low CHD mortality rates.

Slattery and Randall also reported erroneous vital statistics data. They indicated that CHD mortality increased to the "mid 1950s," when, in fact, the rate peaked in 1962-1963.

In sum, there can be no doubt that alliance members distorted the food consumption trend data in conspiratorial fashion. Speaking before Senator McGovern's Senate Select Committee in 1976, former NHLI director, Theodore Cooper, claimed that changing the American diet "would lead to a 25% reduction in incidence of CHD."[2186] And Hegsted falsely told the Committee that "The diet of the American people has become increasingly rich--rich in meat, other sources of saturated fat and cholesterol, and sugar."[2434] He went on to say, "There will be people who will contest this statement." (Indeed, virtually all the evidence contests that statement.) And carrying on the erroneous proclamations, William Roberts reported in 1989 that

"...coronary artery disease is an expensive disease. It occurs because most of us eat expensive foods."[2200]

Two final points are of considerable interest. First, as will be discussed in Chapter 9, Kannel recently presented evidence that while the CHD death rate has been decreasing, the frequency of the disease has actually increased.[1842]

Second, the cancer death rate has increased in recent years as the CHD mortality rate has decreased. The critical ages for CHD and cancer are beyond 50 years. Feinleib plotted the CHD and cancer deaths since 1968 for persons 55 to 64 years (Figure 3-22).[689] Both the alliance and the Cancer Society claim that fat and saturated fat are major causes of CHD and cancer. If one wishes to accept the alliance's untenable explanation for the CHD decrease, i.e., a reduction in animal fats and cholesterol, cigarette smoking and hypertension, then the same logic demands that decreasing animal fats and cholesterol, cigarette smoking and hypertension are causing the rise in cancer deaths. To claim that this trend explains the CHD decline but deny that it explains the cancer increase would be utterly biased nonsense.

The Latency Period Between Diet Change and CHD Change

Assuming the diet-CHD hypothesis to be true and given a significant and relevant change in the diet, one would not expect, of course, an immediate change in CHD mortality. Hence, a latency period would be required. But how long? As noted in Volume 1, scientifically acceptable clinical trials of blood cholesterol-lowering diets or drugs have not resulted in significantly lower CHD mortalities over periods up to 8 years. However, a few trials did show slightly lower CHD mortalities in an absolute sense. If these reductions were real (and the preponderance of evidence in Volume 1 and this Volume 1ndicates that they were not), one might expect a latency period of a few years.

But there is nothing about the lipid hypothesis and atherosclerosis to suggest the need for a latency period greater than perhaps a few months in the U.S. population. Atherosclerosis is a progressive disease and, therefore, bound by time, e.g., the disease progresses at a rate of X amount per unit time. The lipid hypothesis specifies a change in X per unit time for a change in blood cholesterol level (and thus diet). It follows that there should be an almost immediate change in the rate of lipid deposition into the arterial plaque. Given a population of tens of millions of Americans with various degrees of relatively advanced plaque formation, a reduction in the rate of deposition in all these individuals on Day 1 should theoretically result in a small reduction in the age-adjusted mortality rate on Day 2. While technical problems would prohibit measurement of that reduction, it most certainly should be detected in the annually collected statistics. Unless one can demonstrate empirically that a change in blood cholesterol level requires an extended latency period before a change in lipid deposition occurs, discussions of latency periods greater than a year are based on either purely speculative reasoning and/or a need to fit the data to the diet-CHD hypothesis. With these thoughts in mind, let us now consider the wildly different latency suggestions and implications in the writings of alliance members.

A one to two year latency period was implied in the writings of Keys. In 1956 he said, "It is now well known that the incidence of IHD in some countries was remarkably reduced during World War II, only to rise to new heights a few years later. The only reasonable explanation offered is that this was reflection of dietary changes."[280] The following year he was more explicit. He indicated that food rationing began in Norway in 1939, that was "seriously felt in the latter part of 1940" and that CHD mortality changes occurred in 1941. Nineteen years later he reiterated this position and indicated that there were severe food shortages, notably fats" in

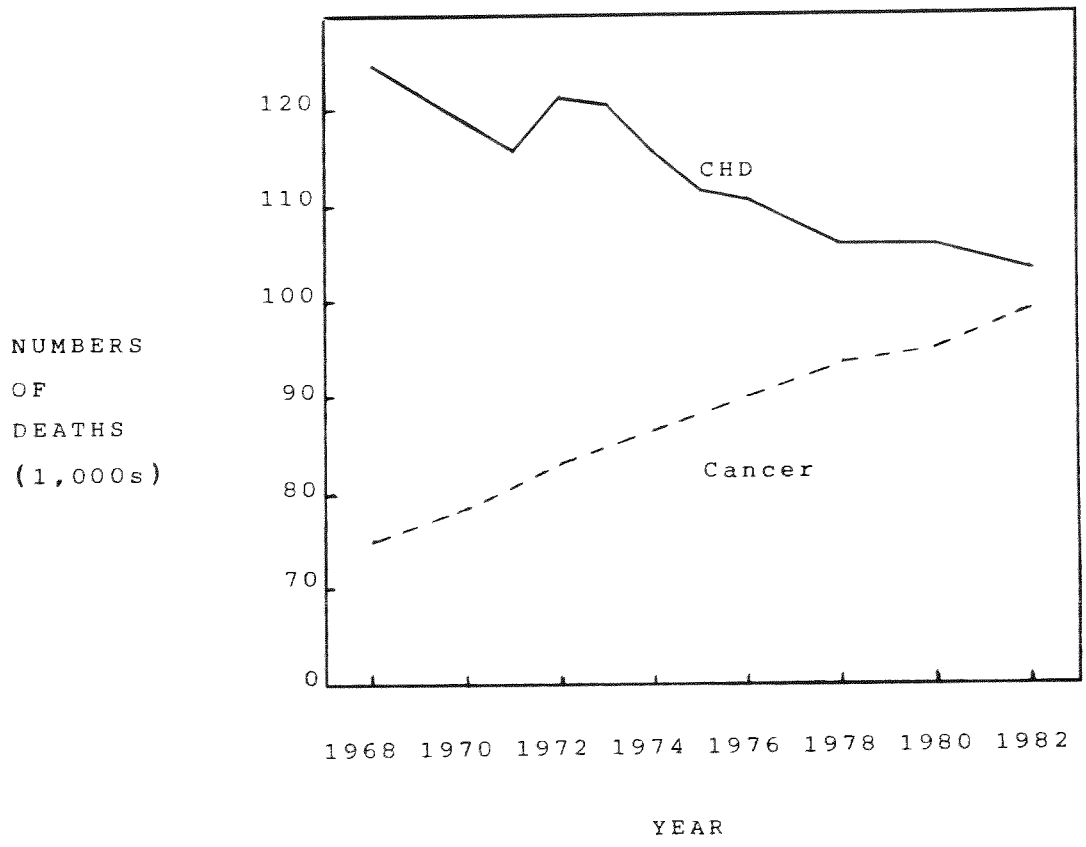

Figure 3-22. Deaths due to CHD and cancer for the age group 55-64 from 1968-1982 (adapted from Feinleib, 1984[689])

Finland and Norway during World War II and "within two years the mortality of CHD fell sharply."[540]

Stamler[539] and Glueck[543] suggested in the late 1970s essentially no latency period at all. Both maintained that the reduction in CHD mortality "immediately" after World War II began "was associated with a sharply reduced intake of total calories, total fat calories (primarily saturated) and cholesterol." Glueck indicated little or no latency period for the U.S. CHD mortality decline as well. For example, he said that the P/S ratio has decreased since 1970 and "there has been at the same time, a downward trend in CHD mortality."[543] In another article with Connor, Glueck repeated this assertion.[1136] Stamler, on the other hand, implied a 7 to 9 year latency period in one 1979 article. He said, "Overall, from the mid-1950s to the early 1970s, mean cholesterol per capita consumption declined about 8%, saturated fat intake declined about 3% and polyunsaturated fat intake increased about 49%.[1313] Since the CHD mortality decline began in 1964, his discussion suggested a 7 to 9 year latency period. But in another 1979 article he included trends since 1940, suggesting a latency period of 24 years.[2635]

In their 1984 review Kannel et al. (including Stamler) indicated that the CHD mortality decline paralleled the decline in egg and animal fat consumption and the increase in polyunsaturated fats.[1083] Their statement implied little or no latency period. W. Virgil Brown's statement suggested a similar latency period, i.e., "Americans have changed their eating habits over the past 20 years. These changes appear to explain a part of the reduction in incidence of CHD."[754]

In 1984 Keys' former student, Henry Blackburn, explicitly discussed latency periods with his colleagues. They said that the Seven Countries study suggested an "incubation period or lag time of 10 years between changes in exposure to major risk factors and changes in CHD mortality rates. However, another analysis of data from 14 countries suggested shorter lag times, on the order of...6-8 years for dietary fat changes."[2696] And in commenting on Shimamoto et al.'s findings that cholesterol levels rose 14% to 18% and animal fats rose 113% in Japan from 1963 to 1983, Blackburn and Jacobs suggested a latency of more than 20 years. They said, "We surmise, then, that neither the magnitude nor the duration of exposure to elevated atherogenic lipoproteins is as yet sufficient among the Japanese to be reflected in a major increase of coronary events. A decade or more at mean levels of 200 mg and above is probably the required population exposure."[1808] Yet, elsewhere in their article they stated that cholesterol levels were falling in the U.S. "paralleling stroke decrease." Not only did the stroke decrease precede "falling" cholesterol levels by many years, the magnitude of the reported (but dubious fall) was only 2.8% and 3.6% for men and women, far less than the Japanese increase. Thus, Blackburn and Jacobs' article was devoid of consistent and rational reasoning.

Levy implied a latency period of zero years since he associated the 1964 CHD mortality decline with changes in diet occurring after 1964.[698]

Two uniquely poor analyses of food consumption trends and latency periods were published in 1988 and 1989. The Slattery and Randall[1660] article was reviewed in the previous section and was described as being profoundly replete with misleading, inconsistent and false information. They reported that "Several dietary changes occurred and appear to have preceded the decline in CHD mortality by 10-20 years. Pertinent shifts in food consumption include a decrease in egg consumption beginning around 1950, a decrease in dairy product consumption after the late 1940s, fluctuations in fruit and vegetable consumption beginning around 1955, a decrease in whole-milk consumption and an increase in low-fat milk consumption after 1950, a change to margarine being more frequently consumed than butter occurring in mid

1950s, and an increase in poultry consumption starting in the late 1940s."[160] In addition to presenting erroneous or misleading trends, e.g., reductions in butter consumption occurred long before the mid 1950s (what unique importance is the fact that margarine surpassed butter in the mid 1950s?), they ignored the most important trend of all, i.e., the reduction in total saturated fats. In any case, they seemed willing to consider any period (10-20 years) as satisfactorily accounting for the CHD mortality decline.

The analyses of Canadian nutritionist, Alison Stephen, were equally ludicrous. She said that U.S. "food supply figures show the nationwide consumption of fats continuing to increase slightly until the 1980s, but these figures fail to take into account the amount of waste, spoilage, food diverted from human to animal consumption and other factors."[1751] While this statement is true, the implication is that the figures are exaggerations of recent trends. They are, in fact, exaggerations of intake trends throughout the century. Stephen claimed that her analysis of 170 small food intake studies since 1920 showed that the CHD mortality decline was preceded by a decline in fat intake. Stephen said that total fat rose to 40-42% of energy intake in the early 1960s and then declined in the 1960s to 36-37% by 1984. She also said that saturated fat declined from 18-20% to 12-13% from 1944 to 1984, while polyunsaturated fat rose from 2-3% to 5%. The 18-20% value for saturated fat exceeded the 16% maximum theoretical value in 1944 inherent in the USDA food availability data. But more ridiculous, Stephen apparently proposed that the reduction in saturated fat after 1944 had no influence on the great surge in the CHD epidemic beginning in 1949 and ending in 1962 but did cause the CHD decline beginning in 1967, a latency period of 23 years.

In sum, the writings of alliance members on the subject of latency, when taken as a whole, constitute a hodgepodge of incoherent reasoning. In their zeal to match food consumption trends with the CHD mortality decline, they not only were willing to accept any latency period as being satisfactory, none addressed the theoretical or technical legitimacy of such periods with respect to the physiology of the atherosclerotic process. It is an established and nondebatable fact among alliance and nonalliance researchers that atherosclerosis begins at least as early as the second decade of life and becomes symptomatic in the vast majority of people after age 50 and most people after age 60. Thus, the atherosclerotic process typically requires 40 plus years to develop the plaque needed to occlude an artery. If blood cholesterol levels truly have a major influence on the process, it is absurd to suggest that latency periods of 2 to 23 years are required to effect a change in mortality.

To illustrate the absurdities inherent in the above hypothesized latencies, consider Figures 3-23 and 3-24. In Figure 3-23 theoretical (albeit hypothetical) predictions of the lipid hypothesis are shown, i.e., the higher the blood cholesterol level, the sooner artery occlusion will be attained (solid lines). The dashed lines in the figure show the predicted effects of lowering the blood cholesterol levels on 40 year-old individuals. Because these individuals have life expectancies of 25, 35 and 45 years, obviously the latency periods for observing changes in their life expectancies would also be 25, 35 and 45 years. However, at any point in time the population consists of all ages and approximately 13% of the total now exceed 65 years of age. If we examine the effects of lowering blood cholesterol level on three 60 year olds (Figure 3-24), the latency periods are now greatly reduced to 5, 15 and 25 years.

In view of the facts that (1) the U.S. population is very large, with approximately 32 million people over the age of 65, (2) the range of blood cholesterol levels is very broad, i.e., about 120 to several hundred milligrams, and (3) the age distribution is continuous, Figures 3-23 and 3-24 clearly indicate that the latency periods of millions of individuals will be zero to five years and mortality changes should be detected in annual statistics. If not, then the lipid hypothesis is invalid. And, of course, the

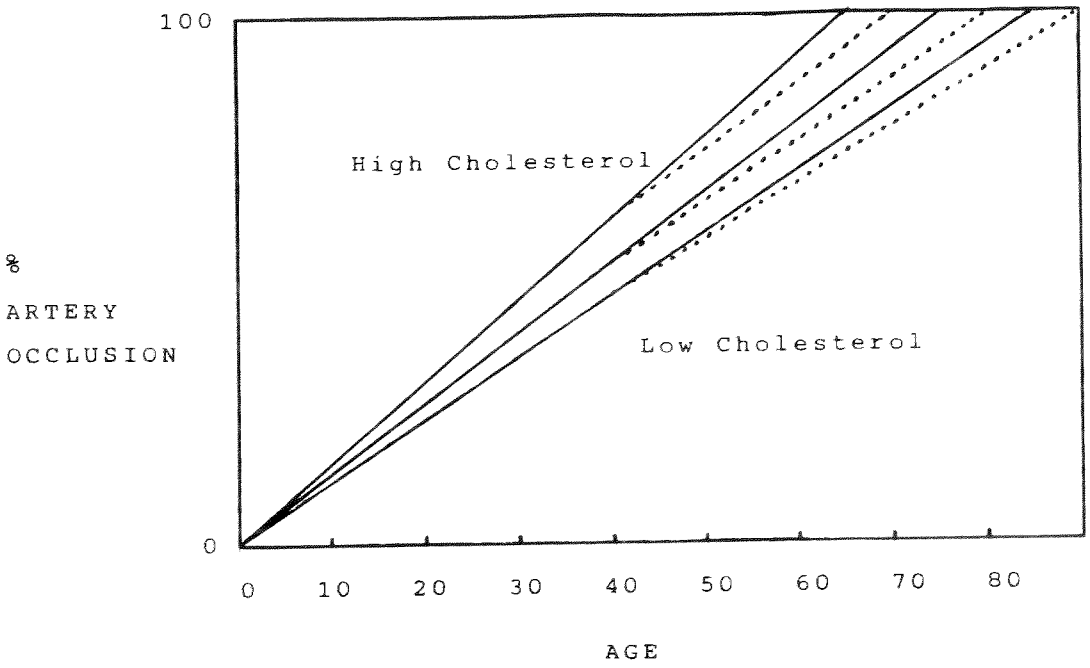

Figure 3-23. Hypothetical degree of artery occlusion by age and blood cholesterol level (solid lines) and predicted effects of lowering the level on 40 year-olds (dotted lines)

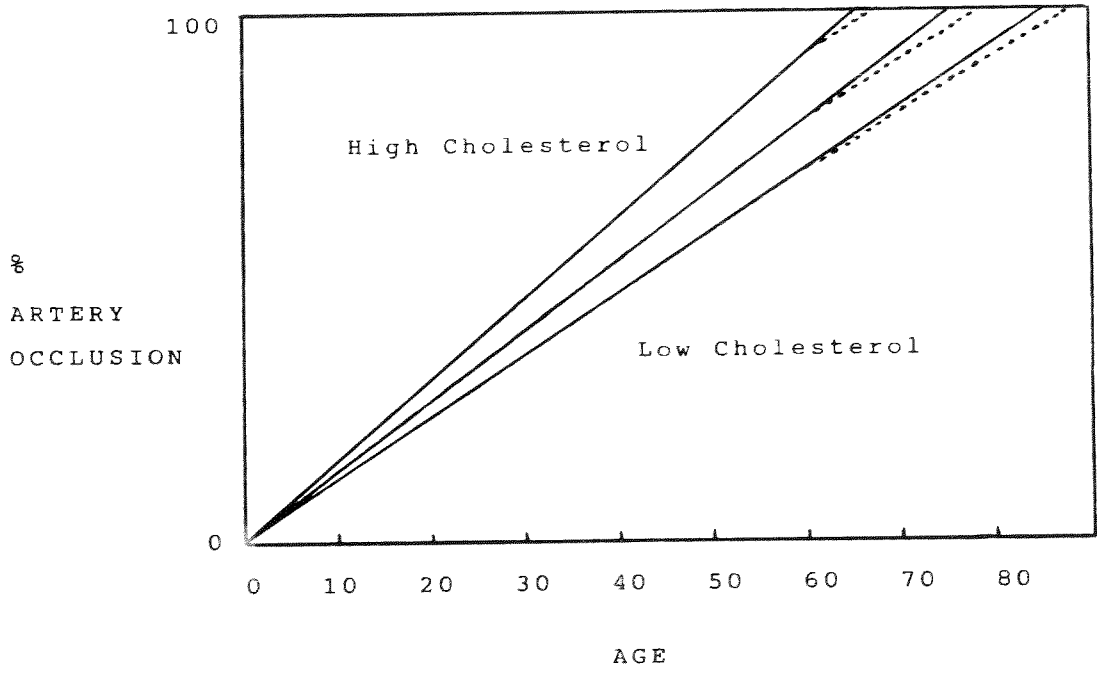

Figure 3-24. Hypothetical degree of artery occlusion by age and blood cholesterol level (solid lines) and predicted effects of lowering the level on 60 year-olds (dotted lines)

preponderance of evidence indicates that it is invalid for at least the vast majority of people. Hence discussions of latency periods reduce to fruitless exercises.

Perhaps this discussion can be capped by an observation of Stallones.[3026] In 1980 he said, "...if recent dietary changes have caused the mortality rates to fall, surely the deprivations of the [American] depression years should have left a similar mark on the curve." Obviously, death rates due to diseases of the coronary arteries/atherosclerotic heart disease increased continuously before, during and 25 years after the great depression. Stallones concluded that "Diet...does not provide a satisfactory explanation for the rise in ischemic heart disease in 1920. The death rates for ischemic heart disease did not track dietary changes in the ensuing 40 yeras, and the recent decline in mortality is not fully consonant with the changes in diet or in serum cholesterol." These facts are obvious to all but those who insist that diet is a cause of CHD.

Alliance members insist that atherosclerosis is dose-related to risk factors, particularly blood cholesterol. It is therefore wholly contradictory to speak of latency periods when diet changes cause almost immediate changes in blood cholesterol levels and thus alter the dose.

THE REAL CHOLESTEROL/CHD RELATIONSHIP AND "RISK"

The Relationship

In 1951, two years after launching the Framingham study, the then director, Thomas Dawber, and his colleagues[2949] indicated that the cause of atherosclerosis was unknown but probably multifactorial. They said, "As a working hypothesis it is assumed that these disease [including hypertensive disease] do not each have a single cause (as is the case in most infectious disease, but that they are the result of multiple causes which work slowly within the individual." In 1959 Gordon et al.[1888] maintained that the "precise etiologies" of the diseases were still unknown. Nevertheless, it is apparent from the selection of independent variables that were included in the initial examination that the Framingham investigators had a priori beliefs about likely causes.[2348] Almost all of the variables were derivatives of blood and urine analyses. Blood pressure and degree of obesity were also measured, as were other nonphysical and nonphysiological variables such as smoking habit, level of education, etc. In view of the fact that lipids, particularly cholesterol, had long been the focus of attention with respect to atherosclerosis, there is little doubt that the Framingham investigators fully intended to prove that blood cholesterol was indeed a cause of atherosclerosis. Evidence for this assertion can be seen throughout Framingham reports in that analyses were often inconsistent from one period to another and that relative risk gradually replaced absolute risk as the primary effect of varying blood cholesterol level.

In 1957 Dawber et al.[2348] published the 4-year follow-up report of the Framingham study. They said that "There is an increased risk of CHD in persons [males] with elevated cholesterol levels, but no apparent gradient below a level of 260 mg. The division at 260 mg is an arbitrary one and well above the mean level of 225.5 mg found for the entire group of Framingham men." Since the data relating CHD events with cholesterol levels were in terms of rates per 1,000 persons, the use of the term "risk" in their text could generally be considered synonymous with "rate." However, statements were made at specific points which gave no doubt that they defined risk in its relative sense, e.g., "the risk among men high in cholesterol was about six times that among men in the low group in the absence of elevation of blood pressure or relative weight." "Six times" means a 500% increase, while the actual absolute rate increase was only 6.7%. Moreover, of interest is the fact that Dawber et al. presented data for men aged 45-62 and none for women of any age. The reason for

omission of female data was the fact that only one myocardial infarction had occurred.

Kannel et al.[2093] published the 6-year follow-up in 1961. This time they reported a gradient between blood cholesterol and CHD event rates over three cholesterol intervals for both men and women. The age range was 40 to 59, different from that used in the 4-year follow-up. Rates were the primary data but relative risk was emphasized in their text.

In the 8-year follow-up (1962) Kagan et al.[2728] reported almost no gradient below 240 mg for men 30-49 years but a relatively strong gradient across five intervals for men 50-59 years (opposite to what will be revealed in later follow-ups). They also reported a positive gradient across three cholesterol intervals for women 40-49 years but a weak negative gradient from women 50-59 years. Kagan et al. concluded after 8 years that "The evidence linking serum cholesterol and coronary heart disease is, we believe, incontrovertible. At the present time it would appear that total serum cholesterol is a satisfactory index of coronary heart disease risk, at least in studies of large populations." This statement is interesting for two reasons. First, the word "satisfactory" is a far cry from the word "powerful," a word that will much later be used by Kannel to describe a long-term relationship that will be much weaker than that observed up to the 8-year follow-up. Second, the phrase, "at least in studies of large populations," was an acknowledgement of the statistical relationship between blood cholesterol and CHD in large groups, implying that blood cholesterol may not be a predictor at all of CHD events at the individual level.

In 1964 Kannel et al.[1885] reported the results of the 10-year follow-up. They did not present CHD event rates but rather morbidity ratios. While it is difficult to evaluate such ratios, it appeared that a weak to moderate gradient between blood cholesterol level and CHD events was evident across the lower three quartiles of cholesterol for men. Strangely, Kannel et al. did not define the quartiles in terms of cholesterol levels and yet for women three cholesterol intervals were used rather than quartiles. Also, the data for women were presented for the two age ranges, 30-49 and 50-59 years, while only the overall 30-59 range was used for men. A slight negative gradient was again observed for the older women, as noted in the 8-year follow-up.

By far the most important data presented in the 10-year follow-up, as well as all previous reports, can be seen in the left side of Figure 3-25, showing the overlapping distributions of cholesterol levels associated with men who exhibited CHD events and with the remaining men who exhibited no such events. Note that the upper end of the nonCHD distribution terminated at 400 mg, while the distribution for CHD subjects continued beyond 500 mg. Although Kannel et al. did not give the highest cholesterol level recorded for the CHD distribution, Kannel[788] much later reported the highest level to be 1124 mg. Let us now determine the approximate impact of these relatively few excessively high cholesterol levels on the difference between the CHD and nonCHD distributions.

As can be seen, the means of the two distributions were calculated by Kannel et al. to be 221.7 and 245 mg, a difference of 23.3 mg. Examination of the CHD distribution indicates that the percentage of subjects which had cholesterol levels between 400 mg and 1124 mg must have been about 3%. Since there were 201 persons in the group, 3% amounts to 6 persons. If we eliminate these 6 persons and assume that they all had a cholesterol level midway between 400 mg and 1124 mg, namely 762 mg, then the mean of the remaining CHD distribution would be 229.1 mg. Thus, while Kannel et al. would suggest that the mean difference between the CHD and nonCHD distributions is about 23 mg, the elimination of only 6 men (who undoubtedly had familial hypercholesterolemia due to genetic defects and not

necessarily true atherosclerosis--see Chapters 2 and 8) reduced that difference to only 7.4 mg. More importantly, however, is the obvious fact that the vast majority of subjects within either distribution had the same blood cholesterol levels.

In noting the extensive overlap of the two distributions, Kannel et al. concluded that "Diagnosis of overt heart disease on the basis of lipid level alone is simply not feasible." As observed by Kuo,[3317] if specific subgroups of subjects are eliminated, the relationship between blood cholesterol and CHD in the remaining population approaches zero. It is simply ludicrous to allow the data from such small subgroups to so profoundly influence the characteristics of the larger population. It is also fraudulent science to pretend that the overall relation between blood cholesterol and CHD is not due to specific subgroups of subjects.

The right side of Figure 3-25 shows the overlapping distributions after 16 years of follow-up. The overlap appears to be even greater than at the 10-year follow-up. Castelli and Anderson[1531] evaluated this figure thusly, "Obviously, the total cholesterol value cannot accurately predict which patients have a lipid problem [i.e., will exhibit CHD events] when the cholesterol levels are between 200 and 250 mg, or even between 150 and 250 mg." The Framingham data and the key Framingham investigators thus concurred without equivocation over the length of the Framingham study that cholesterol level cannot predict who will and will not experience a CHD event. Yet, in the 10-year follow-up Kannel went on to say that "estimation of the relative risk of developing the disease in association with various lipid levels <u>is</u> feasible and informative." We have herein an example of exceedingly poor logic which will carry forward to the present time. If diagnosis (prediction) of overt CHD on the basis of cholesterol level is not feasible, how can relative risk improve diagnostic (predictive) capability? The answer, of course, is that it cannot. But before discussing relative risk in detail, let us first examine the Framingham data more carefully. (If the reader is curious why the Framingham investigators have apparently never reported similar cholesterol distributions for women, the reason is undoubtedly that the distributions probably overlap almost completely. What other reason would there be for omitting data from half of the Framingham study population?)

Figure 3-26 shows the CHD event rate as a function of mean blood cholesterol levels per interval across five intervals in the 30-year Framingham follow-up (Kannel[787]). As can be seen, only the three middle intervals were equal in magnitude (i.e., 30 mg intervals) and the event rate across these intervals increase only slightly (2 per 1,000) for 35-64 year-olds and actually decreased slightly (1 per 1,000) for 65-94 year-olds. The substantial increase in event rate at the fifth interval was an artifact of collapsing the entire range of cholesterol levels from 295-1124 mg into one interval. If one examines the right sides of both pairs of distributions in Figure 3-25, there is no indication that CHD rates should suddenly increase significantly after 295 mg. However, beyond 400 mg, the rates are likely to be extremely high. But, as was noted earlier, the percentage of the Framingham population with such cholesterol levels and CHD rates is only about 3% and, as will be seen, less than 1% of the U.S. population.

The steeper decline in CHD event rate below the 205-234 mg interval was again an artifact of collapsing all cholesterol levels between 84-204 mg. Moreover, as the reader will note in later Chapters, the overall health of individuals with cholesterol levels below about 170 mg and particularly as low as 84 mg is more than a little questionable.

In sum, the CHD gradient in Figure 3-26 is relatively shallow for 35-64 year-olds and effectively nonexistent for 65-94 year-olds for 95% and possibly 99% of the cholesterol spectrum. This fact alone indicates that blood cholesterol cannot be an

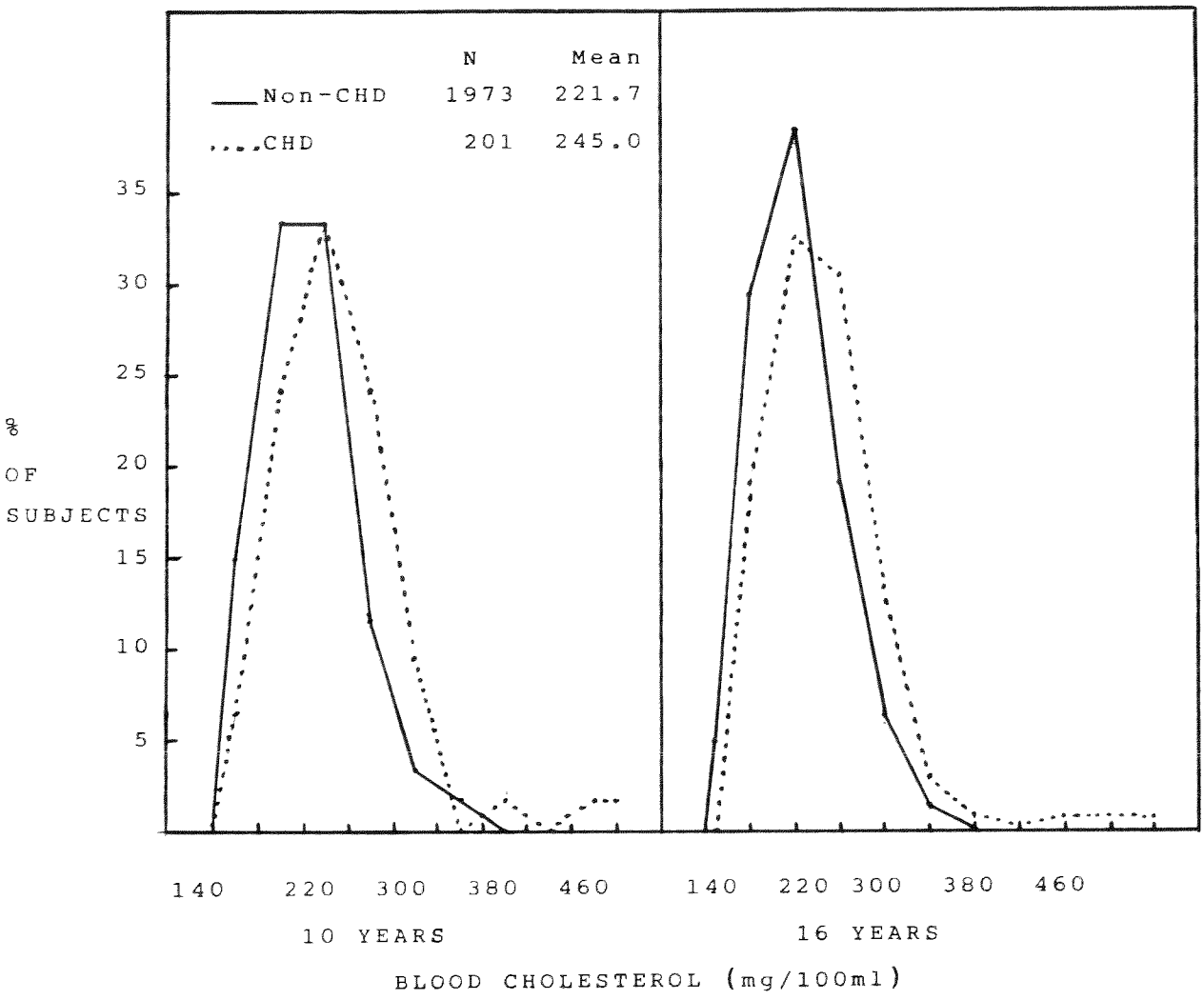

Figure 3-25. Cholesterol level distributions of CHD and non-CHD subjects in the Framingham study at 10 and 16 year follow-ups (adapted from Kannel et al., 1964[1885] and Kannel et al., 1979[1046])

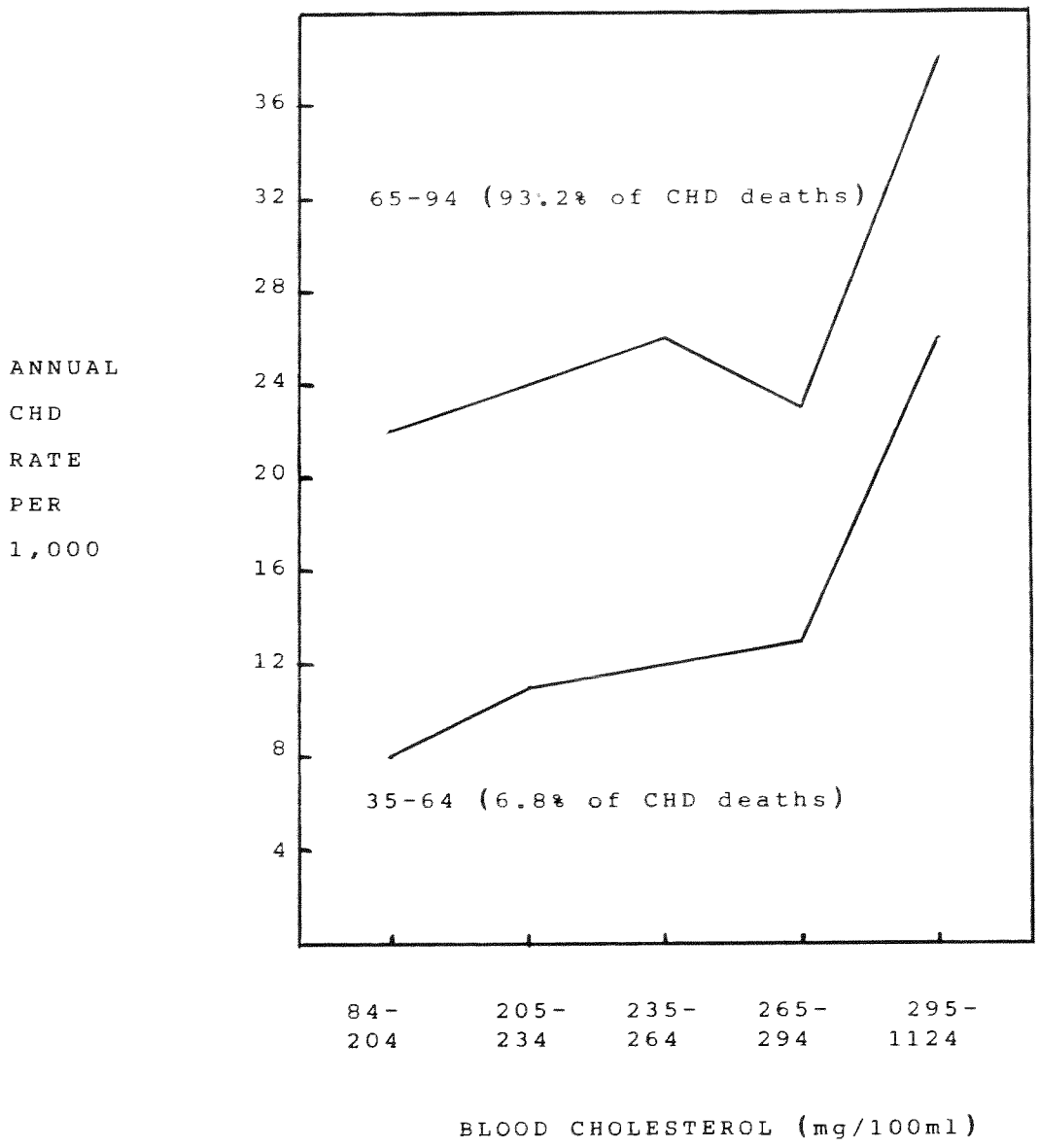

Figure 3-26. CHD rate by blood cholesterol level by age group in the 30-year Framingham follow-up (adapted from Kannel, 1987[787])

important contributor to CHD. But there is another fact which depresses the importance of cholesterol even more. As everyone knows the CHD death rate in the U.S. increases dramatically with age. In fact, the number of CHD deaths occurring among white males under the age of 65 years is only about 6.8% of the total.[2798] Thus, the curve for 35-64 year-olds in Figure 3-26 is representative of only 6.8% of all CHD deaths among white males.[a] The importance of this already small percentage diminishes upon further examination. For example, some of this percentage occurs at cholesterol levels already considered "safe" by the alliance, i.e., below 200 mg. Reference to Figure 3-25 suggests that at least 2% of the 6.8% occurs below 200 mg. Reference to the same figure suggests that about 3% of the 6.8% occurs in the upper end of the cholesterol scale, representing familial hypercholesterolemics with genetic defects (according to Kannel et al.,[2935] all of the familial hypercholesterolemics exist below the age of 50 years). There remains 1.8% distributed across the middle three intervals which, as already emphasized, show only a shallow gradient.

One final observation regarding the 35-64 year-old curve in Figure 3-26 is of no little importance. With the exception of severe familial hypercholesterolemia, which many believe with good reasons is a "lipid storage" disease and not true atherosclerosis, moderate to severe atherosclerosis is rarely encountered below the age of 50. Thus, the great bulk of the "events" underlying the 35-64 year-old curve must be attributed to myocardial infarctions and "sudden deaths" which occur despite little or no atherosclerosis. Elsewhere in this chapter considerable evidence is presented which indicates that as much as 50% or more of sudden deaths is not related to atherosclerosis. Since Framingham investigators automatically classified all sudden deaths as CHD, with the assumption that all CHD was caused by atherosclerosis, the 35-64 year-old curve in Figure 3-26 is based, in part, on irrelevant data. It is not entirely facetious to say that the vertical scale could have included, with equal relevancy, atherosclerotic events and hemorrhoids.

It has often been said that the Framingham study cohort is not closely representative of the U.S. population (see Chapter 4). In 1984 Grundy and his colleagues[3034] published an "AHA Special Report" which included tables of cholesterol measurements derived from the Lipid Research Clinics Population Studies Data Book. These data were said to be representative of the cholesterol levels of the U.S. population. The 95th percentile for white males aged 35-64 ranged from 260 mg to about 282, with an average of about 271. What this means is that the CHD event rate for the fifth interval for the 35-64 year-old curve in Figure 3-26 is representative of perhaps as little as 0.5% of the U.S. white male population.

All things considered, the 35-64 year-old curve in the Framingham study demonstrates virtually no relationship between cholesterol level and CHD (and particularly atherosclerosis) which has practical significance. It is bad science and unethical to present such data without the proper qualifications discussed here.

The 65-94 year-old curve constitutes the great bulk (93.2%) of the CHD deaths and there is effectively no relationship between blood cholesterol and CHD up to at least 294 mg (and probably higher levels if there were additional equal intervals beyond 294 mg). Moreover, according to the Lipid Research Clinics data,[3034] the 95th cholesterol percentile for white men aged 65 plus is about 280 mg. Therefore, the percentage of men within the 295-1124 mg interval must be on the order of 1 to 3% of that age

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[a] Although Figure 3-26 is based on fatal and nonfatal CHD events, while the present discussion emphasizes fatal events, Gordon and Ederer of the National Heart Institute noted long ago that the relation between cholesterol level and CHD is the same whether fatal or nonfatal or both endpoints are used.[488]

group and probably less than 1% for all white males. In any event, it is clear that cholesterol has no predictive value even at the group level, let alone the individual level, for the vast majority of men who die of CHD.

Ignoring the flatness of the relationship between cholesterol and CHD for most of the cholesterol range, ignoring the fact that only a very small percentage of men fall into the 295-1124 mg interval, ignoring the fact that only a very small percentage of men 35-64 who die of CHD fall within the 205 to 265 mg range, and blindly computing regression equations which yield "best fit" lines through the entire cholesterol range is nothing less than purposeful deception and evidence that the alliance must prove the lipid hypothesis at any cost. To compound the deception, even if all of the foregoing were not important, save for the fact that a very small percentage of men of any age have cholesterol levels above 294 mg, the Framingham data without qualification show that practical reductions of blood cholesterol by diets and/or drugs (e.g. 25 mg) would have very little impact on the CHD morbidity or mortality rate.

As indicated in Volume 1, many alliance members focused on the MRFIT screened cohort as the basic data demonstrating the relationship between blood cholesterol and CHD among men after those data were published in 1984.[263] However, the MRFIT data suffer from one of the pitfalls discussed for the Framingham data. Table 3-8 shows the CHD death rates (per 100,000 per year) and the percent of all CHD deaths as a function of age groups for the MRFIT cohort and the U.S. population. As can be seen, the MRFIT cohort consisted of 35 to 57 year-olds which represent only about 3.5% of the CHD deaths in the U.S. In other words, the MRFIT study concentrated on men in which only 3.5% of the nation's CHD deaths occur. Slightly more than one-tenth of 1% of the 356,222 man cohort died of CHD per year. That value cannot be considered a national problem and, therefore, any CHD gradient across blood cholesterol levels cannot be considered to have practical importance. And as before, most of the CHD deaths that occurred below 50 years of age were probably not due primarily to atherosclerosis anyway.

The reasoning of alliance members sometimes approaches the fantasies of the twilight zone. For example, in his 1980 book the first director of Framingham, Thomas Dawber, said, "The Framingham data provide overwhelming evidence that the level of cholesterol in the blood is a powerful factor in development of the major manifestations of coronary heart disease, MI and angina pectoris. This evidence is so convincing that it is difficult to understand how any responsible person could question the relationship."[3001] Indeed, it is difficult to understand how any responsible person could <u>not</u> question the relationship. Only a lipid evangelist can look at the overlapping distributions of Figure 3-25, ignore the above discussion and conclude that blood cholesterol is a "powerful" contributor to CHD.

<u>Relative Risk</u>

In his 10-year Framingham follow-up report Kannel et al.[1885] said that relative risk "appears to be the most sensitive method of assessing the relative importance of various lipids and other factors in the development of coronary heart disease. Since the word "sensitive," in part, refers to the ability of a measurement instrument to detect smaller difference than can an instrument with less sensitivity, Kannel et al.'s statement was totally false because relative risk is absolutely no more sensitive than <u>rate</u> from which it is derived. It should not be necessary for grown men and women, let alone "scientists," to discuss this rather silly issue but, unfortunately, it is.

Consider first the 6-year follow-up of the MRFIT screened cohort. Table 3-9 shows the death rates and associated relative risks for each blood cholesterol quintile (upper part), as reported by Stamler et al.[263] Relative risk, of course, is calculated by

Table 3-8

Death rates (per 100,000 per year) and percentage of all CHD deaths per age group in the MRFIT cohort and the U.S. white male population[263,2798]

AGE GROUP

U.S.	35-44		45-54		55-64		65-74	75-84	85+
MRFIT	35-39	40-44	45-49	50-54	55-57[a]	--	--	--	--
Rate-MRFIT	25.0	62.5	105.0	161.2	237.5				
Rate-U.S.	38.6		176.8		499.9		1169.0	2695.5	5984.3
% of all CHD deaths	0.37		1.67		4.73		11.06	25.51	56.63

a Note that this group is only one-third of the range of the U.S. group.

Table 3-9

Quintile	Cholesterol (mg)	CHD death rate	Relative Risk
1	≤ 181	3.23	1
2	182-202	4.18	1.29
3	203-220	5.60	1.73
4	221-244	7.14	2.21
5	≥ 245	11.06	3.42
Decile			
1	≤ 167	3.16	1
2	168-181	3.32	1.05
3	182-192	4.15	1.31
4	193-202	4.21	1.33
5	203-212	5.43	1.72
6	213-220	5.81	1.84
7	221-231	6.94	2.20
8	232-244	7.35	2.33
9	245-263	9.10	2.88
10	≥ 264	13.05	4.13

letting the lowest cholesterol level (here, either the first quintile or decile) equal to 1.0 and deriving the remaining relative risk values by dividing the lowest rate into the remaining rates. For example, the rate for the first quintile is divided into the rate for the fifth quintile to derive a relative risk of 3.42. This process is nothing more than a simple mathematical transformation of absolute and meaningful rate values, which have universal application, to meaningless risk values, which cannot be compared with similar values over time in the same study or with similar values between studies. No intelligent person can possibly believe that dividing the rate scale by 3.23 will yield a more "sensitive" measure of the effects of cholesterol on the development of CHD.

The only reason for using a relative risk scale is nonscientific and nonclinical, i.e., it greatly exaggerates the effects of increasing blood cholesterol. For example, while the death rate for the fifth quintile in Table 3-9 is 11.06 per thousand per six years, which is an absolute increase of only 0.73% over the rate of the first quintile, the increased "risk" at the fifth quintile becomes 242%. Using the decile scale, the absolute rate increase and the relative risk increase at the 10th decile are 0.99% and 313%, respectively.

Since relative risk is so dependent on the peculiarities of a specific study and completely unrelated to rate, comparing studies can and do lead to absurdities. For example, Figure 3-27 shows hypothetical CHD death rates as a function of cholesterol levels for three different prospective studies. Studies B and C demonstrated identical rate increases across the cholesterol spectrum but the relative risk increased to a greater extent in Study C simply because its average rate was lower, e.g., 6 ÷ 5 yields a higher "risk" (1.20) than does 21 ÷ 20 (1.05), even though the rate difference was the same for both, 1 per 1,000. Thus, two studies canproduce entirely different "risk" increases even though they produce identical rate increase.

Study A in Figure 3-27 more dramatically illustrates the impact of average rate on relative risk ratios. Here, the rate increase across the five cholesterol intervals is 20 per 1,000 while it is only 4 per 1,000 for Study C. Yet, relative risk increases to a greater extent in Study C.

The utter absurdity of risk ratios can be seen in the three most publicized clinical trials, the LRC,[500] the Helsinki II[1056] and the Physicians' Aspirin[2351] trials (Table 3-10). The percent absolute rate reduction in the LRC and Helsinki II trials were nearly the same but the percent risk reduction was twice as large in the Helsinki II trial. The percent rate reduction in the aspirin study was less than that of the LRC and Helsinki II trials and yet the percent risk reduction was much greater than calculated for those trials.

As the reader must know by now the acceptance of risk ratios by alliance members is, by definition, the rejection of the importance of the population at risk. Kannel and others would have us believe that a relative risk increase of, say 50%, is more "informative" and more "sensitive" than a rate increase of from 1 per 1,000 to 1.5 per 1,000 which yields a relative risk increase of 50% or a rate increase of 1 per 1,000,000 to 1.5 per 1,000,000 which also yields a relative risk increase of 50%. Only those desperate to believe that the lipid hypothesis is correct could accept such irrational reasoning.

Relative risk is as simple a concept as it is worthless. Yet, there is evidence that few physicians truly understand what it is and how it is calculated--even those in official positions. Consider the following quote from Marc Lalonde, Canadian Minister of National Health and Welfare: "'Risk' is a statistical term which is expressed in percentages or odds."[2189] This definition is obviously correct for rate ratios but not for risk ratios. Thus, either Lalond equates risk with rate or he uses risk synonymously with rate. In either case, it is not the risk concept employed so

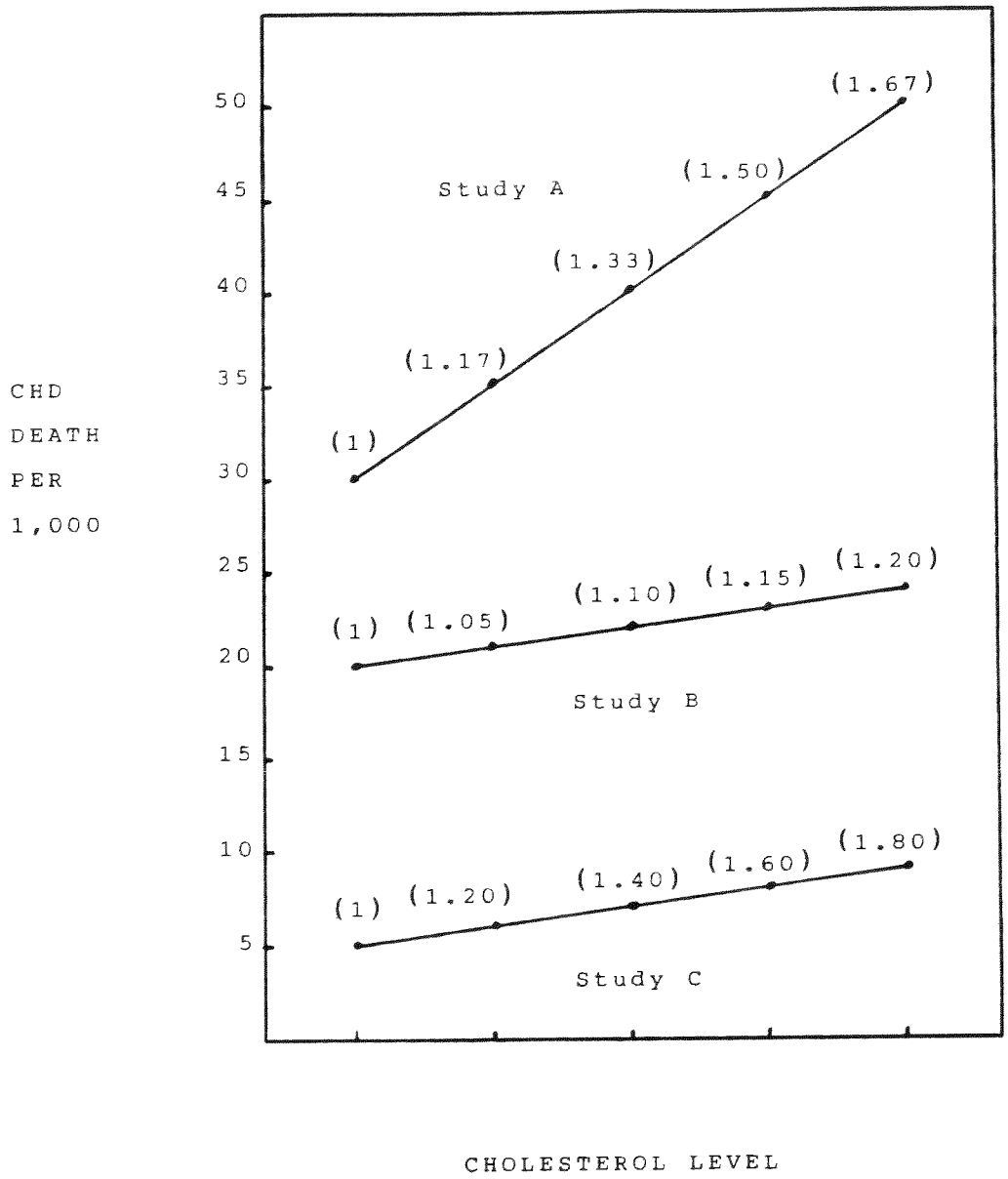

Figure 3-27. Hypothetical death rate trends and their associated relative risk ratios

Table 3-10

Percent rate and relative risk reduction in the LRC, Helsinki II and Physicians Aspirin trials

Trial	% Rate Reduction[a]	% Risk Reduction
LRC	1.16	17
Helsinki II	1.30	34
Aspirin	0.93	44

[a] Adjusted for five years for each study

prolifically by the alliance. It is rather astonishing that he would say that "it is essential that the concept of risk be understood because the application of the Health Field Concept depends on it" and then demonstrate no understanding of it himself.

This writer is, of course, not alone in criticizing the medical profession's use of the relative risk concept. In a recent editorial in the Journal of the American College of Cardiology Weisler et al.[2432] said, "It seems that the popularity of reporting the percent risk reduction lies in the simple appeal of a high percentage value. It is time to tighten our clinical trial reporting standards." England's Geoffrey Rose[3013] observed, "...the concept of relative risk has almost excluded any other approach to quantifying causal importance. It may generally be the best measure of a etiological outcome or of public health importance. ...it gives no idea of the absolute level of danger." Richard LeBlond[2505] reported, "...by emphasizing relative risks rather than absolute risk, we create an unrealistic sense of impending danger and an exaggerated senseof benefit." And Malenka and Baron[3327] said, "From a clinical perspective, the most useful measure of risk is one such as attributable risk [the diffrence between two rates] that contains information about the magnitude of potential benefit. The relative risk...fails to convey this important information."

Brett[2969] warned in 1989 that "Physicians and patients are likely to perceive a relative benefit of 20 or 30% more favorably than an absolute benefit of 1 or 2 percentage points." Indeed, a year earlier Forrow et al.[3054] asked 202 physicians to make treatment recommendations after hearing brief summaries of studies on hypertension and hypercholesterolemia. The physicians indicated greater willingness to treat patients when the summaries gave results in terms of relative risks than when absolute rates were reported." Forrow et al. concluded that relative risk discussions bias physicians' judgments and that it should be the responsibility of authors and journal editors to ensure that readers know how to interpret relative risk properly.

The Bottom Line

Relative risk is the measure of benefit being reported in the lay press, creating "an unrealistic impression of risk and benefit."[2505] Physicians are also being propagandized because "Pharmaceutical advertising highlights these relative reductions and stretches the truth to its limits."[2969] Worse, the meaningless risk ratio is being increasingly used by investigators without accompanying rate information, providing readers with no way of determining whether or not the risk ratios denote any practical importance whatsoever.[1705,1707,1720]

LeBlond[2505] emphasized that "Only a absolute-risk analysis conveys the value of the intervention in the population as a whole and neither [absolute nor relative] analysis can tell us whether an individual patient will have any benefit." As noted by Brett,[2969] the bottom line is that "No matter how the data are presented, the simple fact is that many people must be treated to benefit relatively few."

Alexander Leaf[2913] recently stated that "we are very much in need of a simple, valid, noninvasive, and inexpensive test that will identify the patients with elevated cholesterol levels in which CHD will develop." Leaf seemed oblivious to the fact that CHD occurs almost equally frequently at all cholesterol levels. As noted by Rose,[3013] "a large number of people at a small risk may give rise to more cases of disease than the small number who are at high risk." Kritchevsky[3053] observed as long ago as 1962 that "cholesterol measurements...[have failed]...to function as a reliable diagnostic tool. None of the methods available can predict the arterial condition of a given subject." David Brown[2961] emphasized that point in 1969, i.e., "no single factor has been shown to have much reliability in predicting the occurrence of IHD in the

individual subject." Rose[2913] pointed out in 1985 that early CHD was a better predictor of future fatal disease than all other risk factor measurements but "even if screening includes such tests for early disease, our experience in the Heart Disease Prevention Project still points to a very weak ability to predict the figure of any particular individual."

Despite all of the above, the alliance, as exemplified in Kannel, blindly and fraudulently concludes that "The probability of an (heart) attack is distinctly and impressively related to the antecedent level of cholesterol."[2935] As early as 1966 Kannel[3016] (and Dawber) gave readers the impression that it was easy to identify those who will contract CHD, i.e., "From observations from the Framingham study it has become clear that by using ordinary office procedures the physician can readily identify coronary-prone individuals as well as those with asymptomatic disease."

BLOOD CHOLESTEROL AND AGE

It has long been known that blood cholesterol levels increase with age in both men and women. Stamler and others have attributed this increase to a tendency for Americans to increase the "richness" of their diets as they grow older. But the evidence indicates otherwise. In both the NHANES 1 and 2 surveys, the percentage of total fat and saturated fat in the diet were found to remain constant with age, as noted earlier in this chapter. Webster and Rawson[2340] and Fraser and Swannel[2341] followed large groups of vegetarians and found their cholesterol levels to increase with age just as do nonvegetarians.[2956] Also, the Framingham data show that HDL levels remain constant with age, although LDL levels increase.[2957] Since saturated fat is known to increase both LDL and HDL levels, the Framingham data obviously do not support the "rich" diet, increasing cholesterol hypothesis.

Total cholesterol does increase with age, at least until middle-age but it is clearly not associated with diet and it is foolish to maintain that it is in the face of no supportive evidence and considerable nonsupportive evidence.

BLOOD CHOLESTEROL CHANGES OVER TIME

Chapter 3 of Volume 1 discussed the three blood cholesterol surveys conducted jointly between NCHS and NHLBI and presented a number of reasons why the reported small mean decreases in cholesterol levels over the surveys were probably due to nothing more than measurement error. Additional problems with comparing these surveys are discussed here, followed by a review of cholesterol levels from other studies at different points in time.

First, blood cholesterol was measured during the first two surveys without following a prescribed fasting schedule.[576] Authors of the third survey conducted measurements on samples of fasting and nonfasting men and women. They reported no differences between the samples of men but a 3 mg higher level for nonfasting women and concluded that "This is consistent with previous reports that recent food intake exerts little effect on total cholesterol concentration." However, the "previous reports" cited by the authors was only a manual of Lab Operations from the Lipid Research Clinics Program. The fact is that there has been essentially no adequate research which thoroughly denies differences between fasting and nonfasting samples.

Examination of Figure 3-9 in Volume 1 indicates that even a 3 mg shift in the first survey would dissolve nearly all differences between the first and second surveys for both men and women.

Gerald Cooper of the Centers for Disease Control, emphasized that "plasma or serum should be separated from the red blood cells as soon as possible and analyses

should ideally be done on fresh specimens. If a specimen needs to be kept longer than 24 hours, it should be frozen as serum at -50 to -80 C. Since the cholesterol determinations for the first survey were presumably accomplished under the supervision of Cooper, it is assumed that this freezing temperature was followed.[682] However, authors of the third survey indicated that a much warmer temperature was used, i.e., -15 C.[684] Furthermore, the blood samples underwent variable temperatures during the process of shipment and there was generally a 4 week period between sample acquisition and cholesterol measurement--about twice as long as was the case in the first survey.

The ferric-chloride cholesterol measurement method was used in the first survey. These measurements were later converted to Abell-Kendall estimates. Presumably some 134 blood samples from the survey were still available (but now how old?) and were then evaluated by the Abell-Kendall method. A regression equation was then generated in which Y = the Abell-Kendall value and X = the ferric-chloride value. The correlational plot was good but there were still significant differences. The authors noted the overall problem by saying that "whether such close correspondence is also true for the (entire) HES series cannot be stated with full confidence."

The samples of individuals for the three surveys were selected to be representative of Americans. Actual participation by these individuals was not overwhelming and the response rate decreased with each survey, i.e., 84%, 70% and 68%.

The foregoing, along with the discussion in Chapter 3, indicates a wide variety of "system" errors on every aspect of the surveys. These errors can easily explain virtually all differences between the surveys. However, there is yet another important fact that has apparently been overlooked by the alliance. In their efforts to convince the medical community that blood cholesterol levels have been diminishing since the mid 1960s, corresponding with the decline in CHD mortality, how does one explain the fact that the "downward adjusted" mean blood cholesterol levels on the first survey are considerably lower than those observed many years later? For example, the adjusted mean level for men in the first survey was 201 mg, while it was close to 220 mg in the much later and much larger MRFIT study. Such a discrepancy cannot be dismissed, just as the discrepancy between the three surveys and NHLBI's fourth survey cannot be dismissed. It is abundantly evident that there were massive errors and calibration problems which rendered all surveys noncomparable. To ignore these errors and problems is tantamount to accepting proclamation over scientific fact.

In 1979 Stamler[2635] republished a table originally published by Levy, Rifkind, Dennis and Ernst in the same year. The table, composed of a series of studies, was designed to show that blood cholesterol levels were lower in the more recent studies and higher in the older studies. Table 3-11 presents their data. In the manner in which they grouped the studies the mean cholesterol level of the early set of studies was 233 mg, while it was 217 mg in the later set. However, there are all sorts of biases and errors in the table, as we shall see.

The first problem, though minor, should be noted. The authors apparently computed the simple unweighted averages of the two groups of subjects. In view of the fact that some studies had many more men than others, the weighted means should have been computed. Interestingly, the differences between weighted and unweighted means for these particular groupings were slight, a finding that is normally highly unusual. However, it appears that they computed an incorrect mean for the earlier set of studies. The mean of those studies should have been 238 mg, whether weighted or unweighted.

A second problem with the comparison between the early and late studies is that two of the early studies, i.e., The Chicago studies (in which Stamler participated),

Table 3-11

Mean blood cholesterol levels reported in a series of prospective studies (adapted from Stamler, 1979[2635])

Study		Year	Age Range	Number of men	Blood Chol.
Albany Civil Servants	A	1953	40-59	1,712	231
Chicago Peoples Gas Co.	B	1958-59	40-59	1,264	273
Chicago Western Electric Co.	C	1957-58	40-59	1,978	247
Framingham	D	1948	40-59	1,344	227
Minneapolis-St. Paul Communities	E	1966	45-54	630	233
Northwest Railroad Workers	F	1959	40-59	2,424	231
Tecumseh Community	G	1959-60	40-59	685	231
U.S. Populations (random sample)	H	1960-62	35-64	1,634	230
	ALL	1948-66	35-64	11,671	233 wt.=238
Albany Civil Servants	I	1972	40-59	455	215
Chicago Heart Association Detection Project in Industry	J	1967-73	35-64	12,337	211
Framingham	K	1974	50-59	506	219
Minneapolis-St. Paul Communities	L	1975	53-62	628	223
Tecumseh Community	M	1967-69	40-54	595	211
U.S. Population (random sample)	N	1971-74	35-64	2,027	226
Lipid Research Clinics	O	1971-76	35-64	11,708	209
MRFIT	P	1974-75	35-57	370,599	219
	ALL	1967-76	35-64	398,855	217 wt.=218

clearly yielded mean cholesterol levels that were quite deviant from all the remaining investigations. There is simply no way that means of 273 mg and 247 mg can be considered representative of a group of adult men, being 46 mg and 20 mg higher, respectively,than that observed in the Framingham study ten years earlier. It is simply inappropriate, therefore, to include these studies in calculating the overall means. Elimination of the studies yields an overall mean of 230 mg, 8 mg down from the original 238 mg.

A third problem is associated with the "U.S. population studies." Although not explicitly indicated by Stamler, these undoubtedly were the first and second studies conducted by the National Center for Health Statistics (NCHS) in collaboration with NHLBI. The enormous problems with comparing these surveys, as well as a third NCHS survey conducted in 1976-80, beyond Stamler's date of publication, were discussed in detail in Volume 1 and the previous section of this chapter. Suffice it here to say that the first survey used an entirely different method of measuring cholesterol than was employed in the subsequent surveys and that the means of the first two surveys, shown as circles in Figure 3-28, were later adjusted downward (dots below the circles) without a proper calibration procedure. The mean of the third survey (ages 35-64) is also shown as a circle in the figure.[a] To illustrate further errors in measurement, NHLBI was also involved in the Lipid Research Clinics survey which reported the lowest mean cholesterol shown in the figure, a difference of about 17 mg in a few years period.[b]

A fourth problem is the fact that the cholesterol measurement technique in the early Framingham study (Abell method) was different from the technique used in the later Framingham study (Kendall-Abell method) which may very well have accounted for the difference observed between the two time periods.

A fifth problem was the fact that the later Framingham subjects were older, on the average, than the earlier Framingham subjects which most certainly could account for part of the apparent reduction of cholesterol level. It may be noted, in this regard that Castelli[261] reported a cholesterol drop in men aged 49 to 82 years from 220 mg in 1969-71 to 215.7 mg in 1977-79. These trends reflect the known effects of aging, not a real reduction of cholesterol, independent of age.

A sixth and very important problem was the fact that the Framingham data contain an obvious systematic bias due to a repetitive analytic procedure, i.e., at prescribed follow-up periods, subjects exhibiting CHD symptoms were eliminated from the pool in subsequent analyses. Since groups having CHD tend to have higher cholesterol levels, the progressive elimination of such groups over time will, of course, result in the progressive lowering of the Framingham population cholesterol level. Clearly this is an artificial reduction.

A seventh and very substantial problem with the comparisons presented by Levy et al. and Stamler is that when the studies are placed in the proper temporal order, the individual means reveal not a decreasing blood cholesterol level trend over time but rather a sudden drop between 1966 and 1968. Figure 3-28 shows this phenomenon rather clearly. all the studies from 1948 to 1966 show a quite constant cholesterol level, hovering about 230 mg (with the exception of the Chicago studies which can be seen to be absurdly deviant). Then there is a sudden drop of about 20 mg between

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[a] The original means of the three NCHS surveys shown in Figure 3-28 are close approximations of the true means. They were estimated from the figures of the authors' reports.

[b] The original mean of this study was even lower. It was subsequently "adjusted" upward.

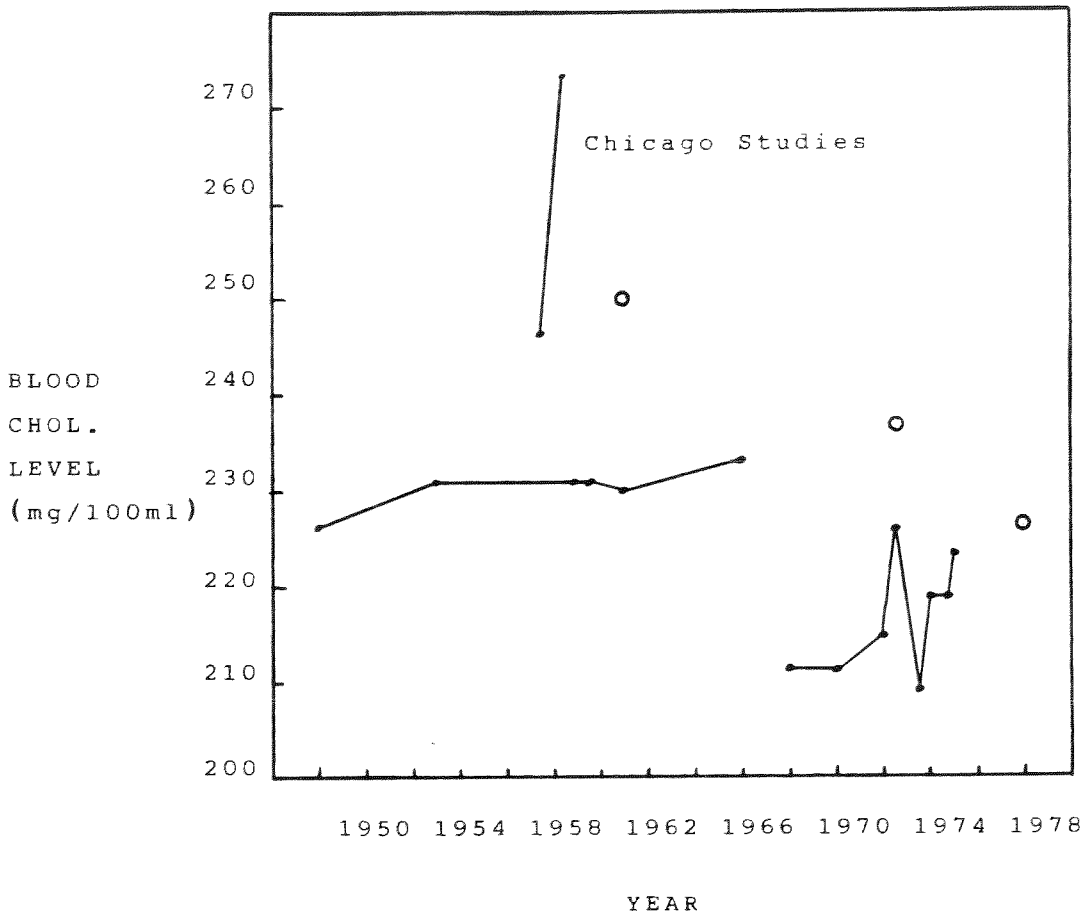

Figure 3-28. Mean blood cholesterol levels reported in a series of prospective studies by year (adapted from Stamler, 1979[2635])

1966 and 1968, followed by an upward climb to 226 mg. A drop of such a magnitude is obviously unlikely and indicates a systematic error or errors.

One such error constitutes the eighth problem with the Levy et al. and Stamler comparison. Observation of Table 3-11 will reveal that seven of the eight early studies consisted of men whose ages were 40 to 59, the range in which men have the highest cholesterol levels.[576,682,683] Only one of the eight studies used men with the lower age range of 35-64. In the later studies, on the other hand, four of the eight studies contained men with the lower age range. Therefore, the later studies were decidedly biased toward younger men. If this bias were included in the later studies, their means could easily be 5 mg to 7 mg higher than those recorded.

A second error (and ninth problem) may be more important but cannot be analyzed. It is the likelihood that the cholesterol measurement technique improved, resulting in lower cholesterol levels. Evidence is presented later which strongly supports the likelihood of this error.

All things considered, the suggestion by Levy et al. and Stamler that there was a drop from 233 mg to 217 mg between 1948 and 1976 is the erroneous product of improper temporal grouping of uncomparable studies and ignoring the obvious spurious drop in cholesterol levels between 1966 and subsequent years. These groupings appear to have been purposely designed to mislead and the enormous slop in the "system" was simply ignored. Moreover, their suggestion of such a trend is wildly inconsistent with the so-called CHD mortality epidemic, i.e., blood cholesterol was dropping since 1948 and yet reported CHD mortality greatly increased over the next 15 years.

Stamler[3288] also cited a 1952 study by Keys in which he measured blood cholesterol levels of 1492 men. The mean levels of middle-aged men (50, 55 and 60 years) were 17 to 20 mg higher than those found 10 years later in the large NHLBI sponsored national survey.[682] Not only is this trend opposite to the reported CHD mortality trend and to the fat consumption trend purported by Keys and others to have occurred, the difference between the Keys and NHLBI surveys was simply too large to be real.

There seems to be little question that blood cholesterol measurement has improved a great deal over time. This improvement has resulted in lower blood cholesterol levels than would have been obtained by old techniques. Two lines of evidence support this position. First, the early studies yielded very high blood cholesterol levels--even when vegetarians were the subjects under investigation (see Chapter 4). Since vegetarians are, by definition, unaffected by dietary trends which influence blood cholesterol levels, their levels should have been as low in the 1950s and 1960s as they are today.

Second, the early analysis of the cholesterol content of the egg revealed a concentration of 274 mg, while recent calculations indicate that the concentration is 213 mg (Chapter 5). This reduction again was likely due to more accurate measurement instruments and not to natural or man made changes in the egg.

THE RELATIONSHIP BETWEEN HDL AND CHD

It is often impossible to determine the importance of cholesterol or its components with respect to CHD because of omissions of critical data by alliance members. Tabular data or figures may appear impressive but without detailed qualifying data, these presentations are often more misleading than they are informative of the practical state-of-affairs. In particular, the Framingham investigators are notorious for selective omissions of important data, as will be illustrated in the following discussion on HDL.

Gordon et al.[453] did present important data on the relation between HDL and CHD in 1977. They measured HDL in Framingham men and women aged 49 to 82 years during the 1969-71 period and subsequently reported the CHD event rates as a function of HDL level. Figure 3-29 shows those rates per year. Ignoring for the moment the fact that part of the curves in the figure is composed of dashed lines and part is composed of solid lines, the initial impression that one obtains from the figure is that CHD event rates decrease rather substantially from the lowest to the highest HDL levels (only 4 women had HDL levels lower than 25 mg and exhibited no CHD events).

Gordon et al. also published the number of individuals at risk and the number of CHD events for each of the HDL intervals shown in Figure 3-29, which permitted a determination of the percentage of total individuals that fell within each HDL interval. Thus, for example, only 1.7% of the total population of men had HDL levels lower than 25 mg. Moreover, only 3.4% had levels above 74 mg and only 7.3% had levels above 64 mg. In other words, of the total range of rates, which was 0.0 to 44 per 1,000, 77% was generated by only 9% of the total population. For 91% of the population, the range was only 15 to 25 per 1,000 which translates to a CHD event increase of 1.0%. The importance of this 1.0% is discussed below.

The range of HDL importance is even more depressed in women. Some 95% of the female population showed a CHD event range of only 8.6 per 1,000, representing a total rate difference of 0.86%.

Given that HDL has a causative relationship with CHD, and even some alliance members have expressed uncertainty (e.g., see quote by Gordon and Rifkind in the section "In the Merry, Merry Use of May", Chapter 1), it is well known that HDL levels are not easily manipulated favorably. Exercise and alcohol may increase them a few milligrams but the high carbohydrate Prudent Diet will reduce them. With respect to drugs, gemfibrozil was shown to increase HDL levels by 4.1 mg. Now when we consider a 4 mg change in terms of the Framingham data in Figure 3-29 it is clear that its influence is quite trivial, i.e., it represents one-tenth of the HDL range, yielding a theoretical reduction in CHD even rate of 0.1%.

As emphasized in Volume 1, alliance members allow small percentages of the population to be the principal force underlying entire relationships between cholesterol and disease. The above Framingham data comprise an excellent case in point. Such relationships are certainly of theoretical value but medicine is an applied profession which depends almost entirely on practical therapies. Not only has HDL not been proven to be protection against CHD, there is no evidence that it can be increased sufficiently and, therefore, cost-effectively.

If one is not fortunate to be aware of the Gordon et al. article discussed above, he/she would likely be misled by numerous succeeding articles on HDL which omitted information related to percentages of individuals at risk in the extreme ends of the HDL distribution.

In another article published in a different journal a few months later by the same authors, Gordon et al.[523] omitted the basic data relating HDL with CHD and instead presented a regression coefficient which indicated the slope of a line which best fits the linear relationship seen in Figure 3-29.[a] But since the regression line and coefficient are inordinately influenced by the very small percentage of Framingham

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[a] In actuality, Figure 3-29 shows the mean CHD event rates for each HDL interval. Regression co-efficients are computed from all the individual points which comprise the means.

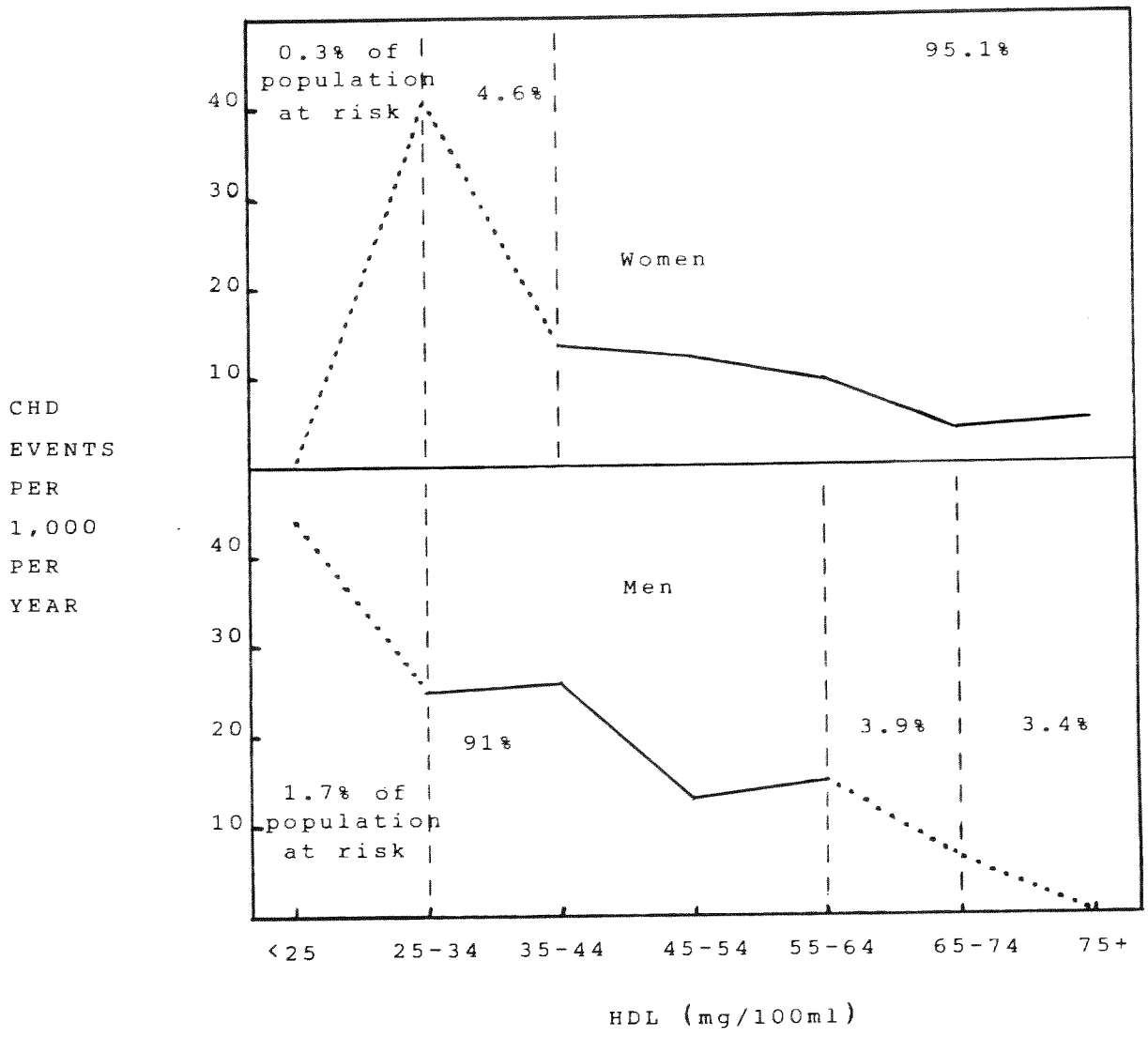

Figure 3-29. CHD event rate as a function of HDL level in men and women (adapted from Gordon et al., 1977[453])

participants, as noted earlier, they are totally misleading and have essentially no practical significance, regardless of their statistical significance. There is little doubt that the prolific reporting of regression coefficients by the alliance is nothing more than an admission to those knowledgeable of statistics that the actual relationships between lipids and CHD are weak and unimpressive. Of course, most readers probably have little knowledge of regression equations and how they can be used to generate highly misleading lines and coefficients.

The previous two articles published in 1977 were based on four years of follow-up. Gordon et al.[581] reported six-year results in 1981. They presented regression coefficients as the only data relating HDL with CHD and concluded that "higher levels of HDL cholesterol are associated with lower CHD risk, even in persons aged 49 to 82 years, the age group included in the study." Not only is this statement an incorrect assessment of the real world state-of-affairs, the expression, "even in persons aged 49 to 82 years" implies that the HDL-CHD relation was observed at younger ages. No such data were apparently reported by Framingham investigators and, in any event, they were not cited in the Gordon et al. article.

In 1983 Kannel[1091] introduced his article thusly, "This report evaluates high-density lipoprotein (HDL) from an epidemiologic standpoint and, in particular, focuses on its role as part of a lipid profile for predicting coronary disease and also as an ingredient of a cardiovascular risk profile." Although Gordon et al. reported six-year follow-up "data" in 1981,[581] Kannel apparently resorted to the original four-year data and presented it in a different form than did Gordon et al.[453] in 1977.[a] In effect, he collapsed Gordon et al.'s seven HDL interval scale into a three interval scale (Figure 3-30). The only conceivable reason for doing this appears to be an attempt to eliminate (1) the plateaus clearly visible in the seven interval scale, and (2) the zero CHD rate for women at the lowest HDL level (< 25 mg). Thus, the relatively flat slopes over most of the HDL range in the seven interval scale, are artifactually forced into much steeper slopes in the three interval scale.

Not only did Kannel purposely distort the original data, the overriding question, of course, is why he used the four year data when six and (more likely) eight year data were available to him by 1983.

In 1986 Castelli et al.[261] analyzed 8 years of follow-up data in terms of regression coefficients and presented one of the most peculiarly-derived figures this writer has encountered. Rather than present eight year follow-up data for males and females, they combined the first four years with the second four years of both male and female data and indicated that the figure represented "incidence of CHD in four years...for men and women." The total number of individuals at risk was 4,205, 70% more than the 2,470 elderly people who participated in the first four years. One would expect the number at risk to either remain at 2,470 or be doubled. The question is, what happened to the remaining 30%?

Another problem with the Castelli et al. figure is that it was composed of two independent variables, i.e., HDL and total cholesterol. Moreover, the CHD incidence scale is inconsistent in terms of the distances between numbers which makes it impossible to accurately estimate the various incidence rates for each of the HDL and total cholesterol intervals. Nevertheless, an attempt was made to estimate the incidence rates for each HDL interval, collapsed across total cholesterol intervals. Figure 3-31 shows the results of this analysis. Note first of all that these investigators used a four interval scale, one more than in Kannel's scale but having an

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[a] The CHD rate data shown for Kannel's three interval scale can be computed directly from the 1977 data published by Gordon et al.[453]

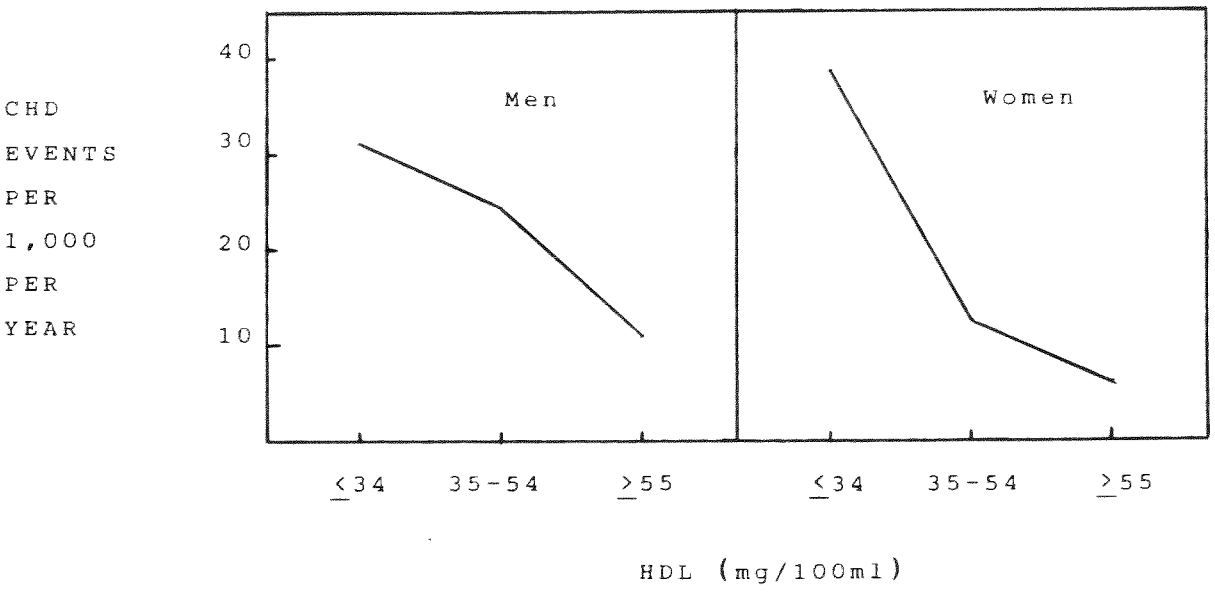

Figure 3-30. CHD event rate as a function of three HDL intervals (adapted from Kannel, 1983[1091])

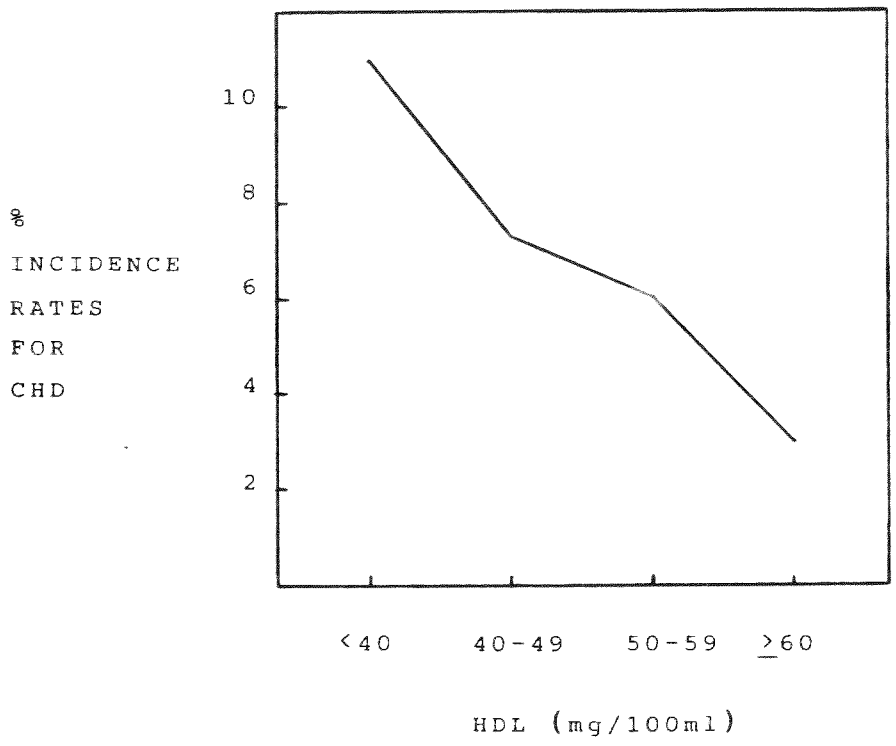

Figure 3-31. CHD rate by four HDL levels (adapted from Castelli et al., 1986[261])

identical range of about 20 mg. However, Castelli et al.'s scale was more distorted at the low HDL end of the distribution. Reference to the 1977 data (Figure 3-29) suggests that Castelli et al.'s figure is a complete distortion because the upper and lower parts of their "curve" is based heavily on small percentages of the population.

If the above criticisms were not enough, Castelli et al. indicated that 12 years of follow-up data were available for the original cohort of elderly participants. Why, then, were only eight years analyzed and why were all analyses presented in terms of "four years of surveillance"? Why also the necessity of using inconsistent HDL interval scales from article to article? It is also of no little importance to note that the correlations observed between the original HDL measurements and similar measurements 8 years later was only .68 in men and .60 in women, indicating considerable instability in the HDL-CHD relationship because 54% to 64% of the variance seen in one measurement cannot be accounted for by the other measurement. Thus, the CHD incidences were, in part, due to incorrect HDL measurements either during the first, second or both measurements. Castelli et al. concluded that "the relationship between the fasting HDL-C level and the subsequent incidence of CHD does not diminish appreciably with time." While this statement clearly implies that later follow-up data showed a diminishing effect of HDL, it cannot be seen in their data because they omitted it. In any event, it was demonstrated earlier that the first four years yielded a trivial relation between HDL and CHD events for over 90% of the population. Therefore, a diminishing effect beyond four years clearly yields an even more trivial relation.

Castelli (together with Anderson)[1531] published another article in 1986 and, rather than present 8 year or 12 year follow-up data, or the peculiar data he reported in the above 1986 paper, he presented the original four-year data of Gordon et al.'s 1977 article. Although his references included the Gordon et al. article, his text did not cite the article in relation to the HDL-CHD figure and there was no indication of the length of follow-up period in either the figure caption or text. With such old data in hand and an ignoring of much follow-up data, Castelli and Anderson stated that HDL is "a powerful predictor of coronary heart disease risk."

In 1987 Abbott et al.[3233] finally focused on 12-year follow-up results. They related HDL with fatal and nonfatal myocardial infarctions and again used a distorted scale, i.e., quartiles. Figure 3-32 shows that there was absolutely no relationship between HDL and MIs for males across 75% of the HDL distribution. And had a more continuous scale been used, that percentage might have been as much as 90% or more. It is evident that the MI rate would not have dropped off abruptly after 52 mg as shown in the figure. The quartile scale also distorted the female curve at the high and low (quartile) ends.

Comparing the four-year data (Figure 3-29) with the 12-year data (Figure 3-32) clearly shows, contrary to Castelli's above pronouncement, that the relationship between HDL and MIs diminished considerably for males, there being no relationship whatsoever for about 92% of the HDL range (see Figure 3-29).

Wilson et al.[3234] also presented 12-year data in a 1988 article but restricted the endpoint to deaths rather than to fatal and nonfatal MIs. Whereas previous articles included a 7-interval scale, a 3-interval scale, a (nonquartile) 4-interval scale and a 4-interval quartile scale, Wilson et al. used another distorted scale, 5-interval quintiles. Figure 3-33 shows that the relationship between HDL and CHD is opposite to the expected in males for the middle three quintiles. As before, the extreme quintiles distort the overall relationship and the figure clearly shows the abrupt but unreal trends before the second and after the fourth quintiles. The relationship between HDL and females appears consistent, as it did for MIs.

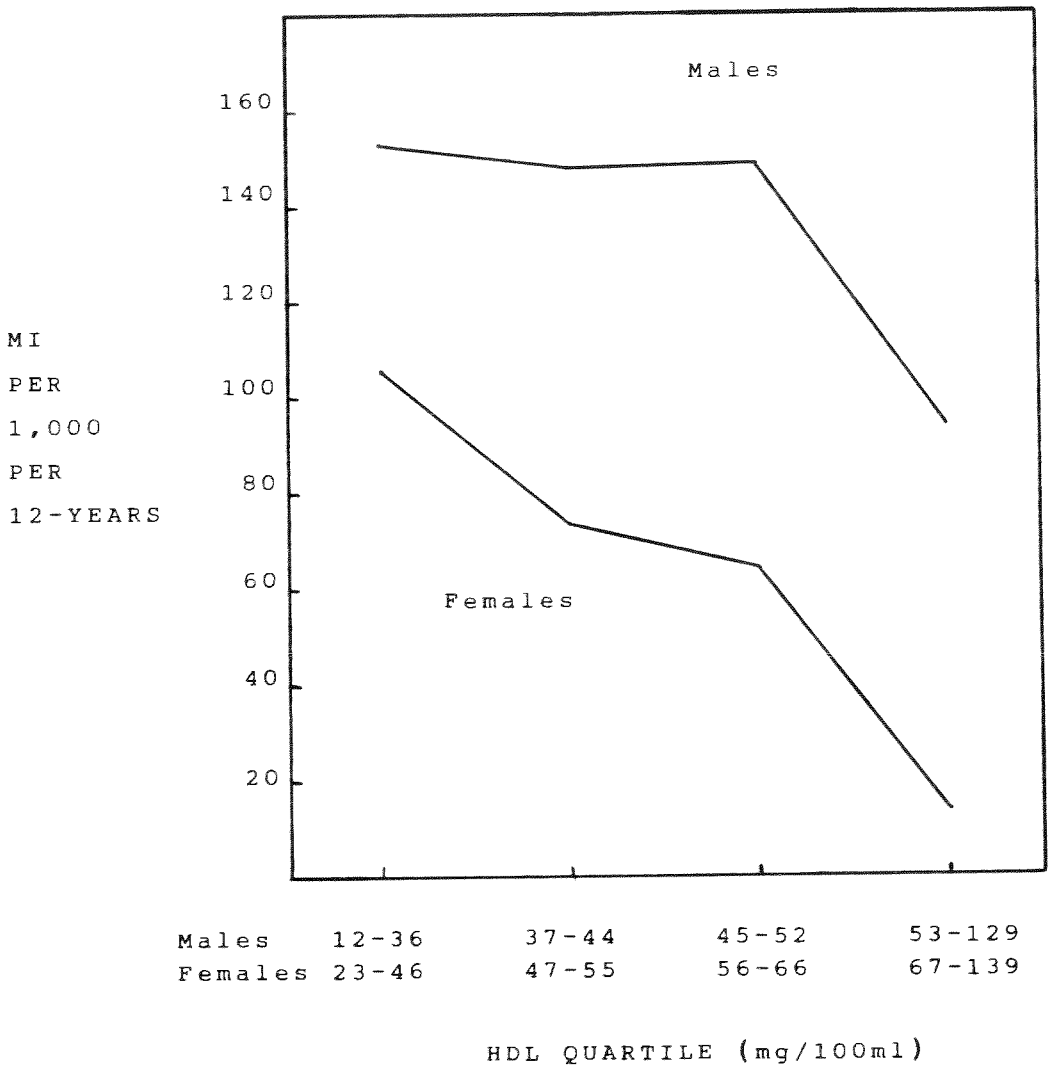

Figure 3-32. Myocardial infarctions by HDL quartile by sex (adapted from Abbott et al., 1987[3233])

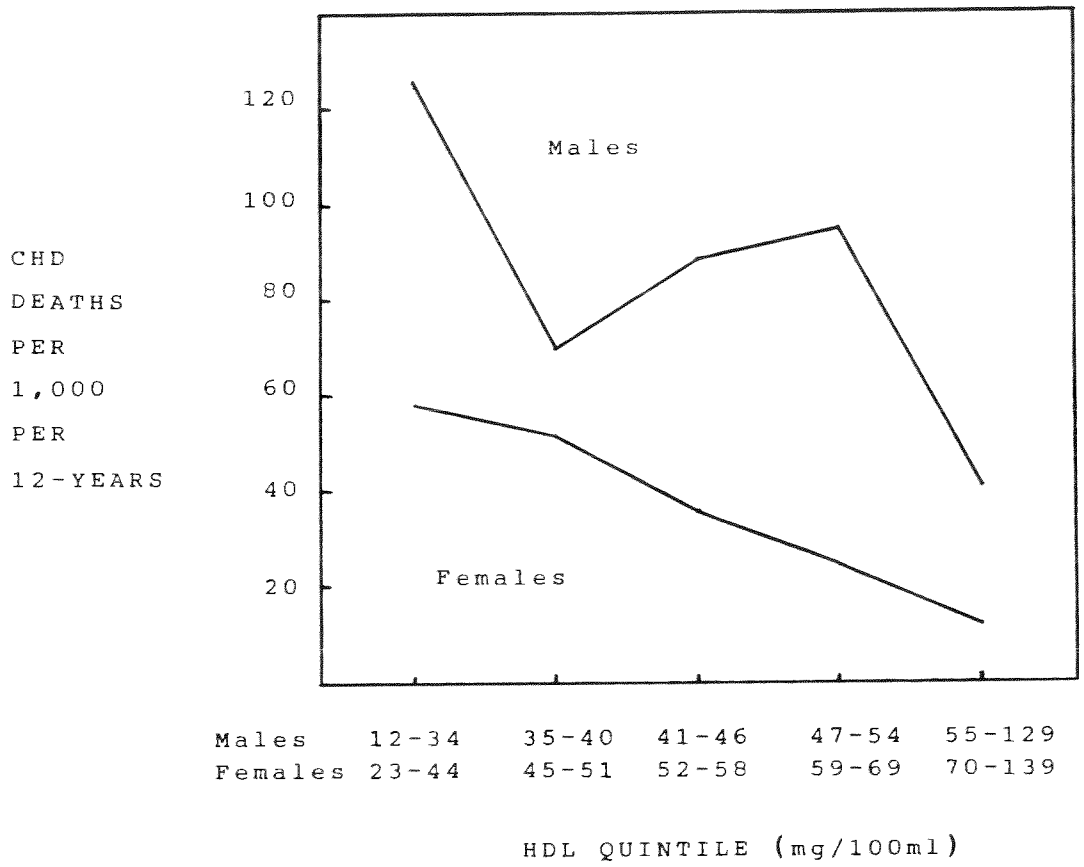

Figure 3-33. CHD deaths by HDL quintile by sex (adapted from Wilson et al., 1988[3234])

Obviously, unimpressed with the 12-year data for males, Castelli et al.[2292] again presented the original 4-year follow-up data of Gordon et al. in 1989 and concluded that "HDL cholesterol...continues to be highly predictive at all ages." In view of the fact that their data were the original data, rather than 8 or 12-year follow-ups, the word "continues" was, to say the least, highly misleading. Moreover, the data were derived from individuals over 50 years of age at entry which denies the expression, "predictive of all ages." Clearly, Castelli et al. purposely attempted to mislead readers.

In 1990 Wilson[3222] again presented the 12-year data for males but showed the relationship between HDL and CHD incidence as a function of four total cholesterol levels, i.e., 116 to 192 mg, 193 to 215 mg, 216 to 244 mg and 245 to 376 mg. He concluded that "the protective effect of HDL cholesterol with regard to the incidence of MI in men was statistically significant; as HDL cholesterol decreased and total cholesterol increased, the incidence of MI increased." In keeping with the alliance's proclivity for post hoc significance hunting, Wilson found that HDL was statistically significant only for the 116 to 192 mg range of total cholesterol, not for the remaining theee ranges. Thus, the overall effect of HDL was obviously not statistically significant, as implied by Wilson's statement. And because of the distortion inherent in scales containing few and unequal intervals, the range of total cholesterol of significance may be even more restricted, e.g., 116 to 150 mg. If so, then the range of total cholesterol showing an effect of HDL would be totally inconsequential because the percentage of males having total cholesterol levels within that range may only be 1 to 2%.

In sum, despite the importance given to HDL as a predictor of CHD by the Framingham investigators, it is a weak predictor at best and appears to have no practical importance across the vast majority of the male population.

Additional studies relating HDL with CHD have been reported. Gordon et al.[1694] presented relationships obtained from Framingham, the Lipid Research Clinics Prevalence Mortality Follow-up study (LRCF), the Lipid Research Clinics trial (LRC) and the Multiple Risk Factor Intervention trial (MRFIT). Not so surprisingly, they used the trichotomy of low, medium and high levels of HDL, rather than a more continuous scale. Hopefully, the reader will now recognize that this technique artifactually increases the slope of a relationship by allowing the extremes of a distribution to unduly influence the overall slope.

Table 3-12 presents the results of Gordon et al.'s analysis. The weighted mean death rates for the three HDL intervals across the 4 studies, were 3.2, 2.4 and 2.2. While Gordon et al. concluded that a 1 mg increment in HDL was a associated with a 2% to 3 % reduction in CHD "risk," these data clearly show that the rate reduction across the three HDL levels was only about 0.1%. Moreover, the rate difference between medium and high levels was almost zero, i.e., 0.02%. In addition, Gordon et al.'s trichotomy of 2.8, 1.3 and 0.8 was quite different from the data published in 1990 by Jacobs et al.[2645] for the LRCF study. They reported quintile rates of 2.6, 3.8, 2.4, 1.1 and 1.6. The differences between the three lowest HDL quintiles were either zero or in the unexpected direction. Further, the difference between the lowest and highest quintiles was only 1.0, less than half of the difference between the lowest and highest intervals reported by Gordon et al. Also, the CHD event rate difference between the lowest and highest quintiles for men and women were only 0.1% and 0.06%, respectively.

Pocock et al. re-evaluated the data from the British Regional Heart study (BRHS).[1720,1865] They originally found a 2.7 mg difference in HDL level between CHD cases and nonCHD cases (a common difference reported in many studies, Volume 1) and concluded that HDL was not a significant risk factor.[1074] Pocock et al.

Table 3-12

HDL level and CHD deaths per 1,000 per year in 4 studies
(From Gordon et al., 1989[1694])

Study	N	HDL Level		
		Low	Medium	High
Framingham	704	5.4	5.4	4.2
LRCF	3937	2.8	1.3	0.8
LRC	1808	3.3	2.3	2.8
MRFIT	5792	3.3	2.8	2.7
Weighted Mean		3.2	2.4	2.2

subsequently indicated that "The relative odds of a (fatal or nonfatal CHD) event occurring in the highest fifth of the...HDL cholesterol distribution compared with the lowest fifth...was...2.0."[a] At the risk of being repetitive, the avoidance of rate data in favor of risk ratios by Pocock et al. indicates that the 2.0 relative risk represents a trivial increase in actual rate. And it is probable that the CHD death rate trend was even less related to HDL level.

A 20-year follow-up of the Donolo-Tel Aviv prospective study was recently summarized in Modern Medicine.[1732] This study of 2,633 men and women, according to Livshits et al., found total cholesterol to be "relatively unimportant" as a predictor of CHD. Although they indicated that HDL was most important, no information regarding the strength of the relationship was given. Of considerable interest were peculiar statements attributed to Gotto. He was reported to say that "The Tel Aviv study demonstrates the protective value of HDL against CHD. Its findings are consistent with those of other epidemiologic studies." Yet, he went on to say, "why were the lower total cholesterol levels (< 240 mg) better independent predictors of CHD than the higher levels? I would have thought that it would have been the other way around." Indeed!

In 1990 Miller et al.[3235] evaluated HDL levels in men and women with and without CHD (as determined by angiogram) who had total cholesterol levels at or below 200 mg. They reported that there was a significantly higher prevalence of low HDL levels among those with CHD than among those without CHD. However, their data were badly confounded. For example, the CHD groups of men and women were older (7 and 4 years, respectively), had higher total blood cholesterol levels (by 8 mg and 7 mg, respectively), had a higher prevalence of cigarette smokers (by 11% and 9%, respectively), had a higher prevalence of hypertension (by 22% and 18%, respectively), and had a higher prevalence of diabetes mellitus. Because the CHD and nonCHD groups were highly uncomparable on important factors, it is not appropriate to conclude that the difference in HDL levels was the cause of CHD. The other factors also may have caused the difference in HDL levels.

One must always be reminded that the relationship between HDL and CHD, like that between total cholesterol and CHD, is always based on group data. A relatively weak relationship at the group level becomes a totally insignificant relationship at the individual level. Elsewhere in this volume the issues of group versus individual relationships and cost-effectiveness of "treating" everyone are addressed.

Despite the extremely weak associations between HDL and CHD observed over many studies, as shown here and in Volume 1, Grundy, Rifkind and Cleeman erroneously informed their readers that "Population-based studies have identified HDL as a powerful,...independent predictor of CHD in most high-risk populations."[1803] Subsequently, they made the following statements which were contradictory to the word "powerful": "Often, populations with a high prevalence of CHD have relatively high HDL concentrations... Moreover, there are populations...in which low HDL cholesterol concentrations seemingly do not convey increased risk for CHD. Finally, certain genetic causes of severely reduced HDL apparently are not accompanied by a markedly increased coronary risk." Thus, there seems to be many exceptions to their "powerful" rule. Indeed, in analyzing populations from many countries, Knuiman et al. found that the inverse association between HDL and risk of CHD is absent or even opposite to that within populations.[1824] Lewis et al. reported that HDL levels were

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[a] Miller had criticized Pocock et al. for minimizing the importance of HDL and indicated that its effect was greater than total cholesterol in the BRHS.[2279] This statement, therefore, says little about the practical importance of either total or HDL cholesterol.

almost identical in large samples of men and women from Italy, Switzerland, England and Sweden, although CHD mortality rates differed among these countries.[2167] Kestelot et al. noted that total cholesterol levels differed substantially between groups of subjects from China, Korea and Belgium but HDL levels were nearly the same for males.[2168] And Gwynne stated that "observations in at least three disciplines--epidemiology, genetics and therapeutics--have revealed exceptions to the general inverse HDL cholesterol to CHD relation...suggesting that the relation of HDL to atherogenesis is not as simple as one might have hoped."[2331]

Two interesting and relevant papers were published in 1990. In one Peter Wilson was asked, "A recent report on autopsy findings in the Honolulu Heart study indicated that the presence of coronary artery lesions was not related to HDL levels. Any comments?"[3223] Wilson replied, "I'm not sure why there would be a difference between those results and their earlier findings, perhaps there were too few autopsies to provide statistically significant results." Not only were the HDL-CHD data in the later follow-ups of the Framingham study different from those of the early follow-ups, the PDAY Research Group[3150] recently reported no relationship between HDL and extent of lesions in 390 males who died of violent causes.

Illustrative of weak and inconsistent findings are the recent comments of Gwynne and Brewer. Brewer maintained that HDL_2 is "the lipoprotein function that appears to be inversely related to atherosclerosis",[2329] while Gwynne reported that "analyses of the major HDL subfractions, HDL_2 and HDL_3, do not offer better predictive value than the measurement of the total HDL cholesterol."[2331]

It is interesting to note a comment by the original Framingham director, Thomas Dawber,[3001] i.e., "It seems strange, in view of the failure to demonstrate any benefits in predictability of CHD by the Gofman technique, that so much interst has been exhibited in determining lipoprotein types by a much cruder method. Little of practical value was gained by elaborate determination of lipoprotein types, although such studies have elucidated the manner in which cholesterol is carried in the blood stream. No advantage over simple serum cholesterol determinations has been shown insofar as predictability of CHD is concerned."

Finally, we wish to report a criticism of the current NCEP gudielines by Castelli.[3131] He maintains that 20% of all heart attacks occur in individuals with cholesterol levels under 200 mg and these individuals will be missed if 200 mg is the cutoff point. He said that "The only way you are going to find these people is to look at their HDLs, and you are going to find that their HDLs are under 40." But to this writer's knowledge, neither Castelli nor any other Framingham investigator has shown that heart attacks occur significantly more frequently in individuals with HDL levels below 40 mg than above when all have total cholesterol levels under 200 mg.

THE RELATION BETWEEN THE TOTAL: HDL RATIO AND CHD

The problem of determining the importance of the total: HDL ratio is even more difficult than that of HDL because the Framingham investigators have apparently never reported a complete distribution of ratios. They have, however, presented bits and pieces of data which allow some insight into the distribution. In addition, they have published statements regarding the total: HDL ratio that were opposite to their published data.

High density lipoprotein measurements were first taken by Framingham investigators in the 1969-71 period and it is apparent that interest in the total: HDL ratio was not generated until the 1980s. For example, in a 1977 article, Gordon, Castelli, Kannel and others said, "The common procedure of calculating ratios of HDL to total or LDL

cholesterol should probably be avoided since a person may have the same ratio at a low level of HDL and LDL or at high levels, and it is difficult to believe that these have the same medical and physiologic significance. Beyond that it appears to be less satisfactory as a risk criterion than a linear combination."[453] They will, of course, completely reverse their logic within a few years. A later article in 1977 by the same authors did not mention ratios.[523] A 1979 article by Kannel, Castelli and Gordon presented "likelihood CHD ratios for HDL: total cholesterol ratio, as they did in the early 1977 article, but no mention was made of it in their text.[1046] And while HDL was discussed at length as a risk factor in a 1981 article by Gordon, Kannel, Castelli and Dawber, there was no mention whatsoever of ratios.[581]

1983 apparently marked the year in which ratios were suddenly considered important. Kannel wrote, "...there is no particular benefit to making linear combinations of LDL and HDL compared with ratios based on likelihood ratio statistics [see the opposite argument in the immediately above paragraph]. The ratio of the 2 lipoprotein-cholesterol fractions seems to provide as efficient a discrimination of cases from noncases. Hence, the total cholesterol/HDL ratio will efficiently identify patients who are at increased risk over the usual range of total cholesterol values. A ratio of about 5 is the average or standard risk. One of about 3.5 is about half the standard risk and can be considered opitmal, whereas a ratio of 10 is double the standard risk, and a ratio of about 20 is 3 times the average risk. These are ratio numbers easy to remember."[1091] But most, if not all, of these numbers tell us nothing about the distribution of ratios and, therefore, their importance with respect to the majority of Americans. The only number that may be useful is 5.0, given that it is the average or medium of the distribution, an assumption that cannot be confirmed in Kannel's article.

Two further points should be noted regarding Kannel's introduction of ratios. First, his tabular data showing the significance of the total: HDL ratio was essentially identical to that presented in his 1977 article in which he and his colleagues considered the ratio inappropriate. Second, just as the HDL measurements were obtained only on subjects "50-70 years old," so were the total: HDL ratios. Thus, no ratios had been calculated for the population under 50 years of age.

In 1986 Castelli and Anderson[1531] presented the same tabular data showing the significance of the total: HDL ratio as was presented in the early 1977 article by Gordon et al.[453] They now described that data as demonstrating that "the ratio of total cholesterol to high-density lipoprotein cholesterol is an extremely potent predictor by itself." They later said that "we believe that the best way to predict risk is to calculate a ratio of the total cholesterol to high-density lipoprotein cholesterol, recognizing that the higher the number, the greater the risk."

Like Kannel, Castelli and Anderson fed the reader bits and pieces of the total: HDL distribution puzzle. For example, they said that the distribution of cases ranged from "approximately 3.5 and above. However, if we recommended treating everyone with a ratio of 3.5 or higher, we would be treating approximately 90% of all Americans." Obviously, if 90% of the population has ratios of 3.5 or higher, then the distribution of cases does not range from approximately 3.5 and higher; 10% were apparently below 3.5. Castelli and Anderson also said that two thirds of the men have ratios above 4.6 and, like Kannel, indicated that a ratio of 5 was the average risk. Thus far we know that 90% of men have ratios equal to or greater than 3.5, 67% have ratios equal to or greater than 4.5, and, perhaps, 50% have ratios above 5.0.

Castelli and Anderson <u>did</u> present the entire distributions of total cholesterol levels for both CHD cases and nonCHD cases. About 95% of both distributions fell within the range of 150 mg to 350 mg. This will be useful later in evaluating the

importance of total: HDL ratios, since we already know from the previous section on HDL that 91% of the male population has HDL levels between 25 mg and 64 mg.

A major problem is evident which could render the above distribution points erroneous. There is indication in the Kannel[1091] and Castelli and Anderson[1531] articles that their total: HDL ratios were derived entirely from 50 to 80 year old subjects. While these investigators generalized the ratios to the entire American population, such a generalization cannot be valid because total cholesterol levels decrease and HDL levels increase somewhat in the elderly, presenting an entirely different profile than that of the middle-aged (those trends were reported in 1987 by Kannel[787]).

Castelli et al.[261] discussed at length the presumed relationship between HDL, total cholesterol and CHD events in a 1986 article but did not mention total: HDL ratios. However, in 1987 Kannel presented data indicating that HDL was measured among all ages and that total: HDL ratios were likewise computed for all ages. Table 3-13 shows the mean ratios for various age groups and 96% of their respective ranges, based on standard deviations provided by Kannel. These ranges are likely to be off somewhat because the distributions of ratios for each age group are not likely to be perfectly normal.

Kannel also presented HDL and LDL levels of Framingham subjects as a function of age. While LDL (and thus total cholesterol) increased steadily and substantially in men from the 15-19 year groups to the 50-54 year group and then declined somewhat thereafter, HDL levels remained almost constant to age 60, after which it appears to have increased very slightly. The increasing (and subsequent decreasing) mean ratios shown in Table 3-13, therefore, reflect almost entirely the trend in total cholesterol with aging.

Kannel also presented the CHD event rate for men and women as a function of total: HDL ratio (Table 3-14).[a] While these event rate differences might appear impressive, their importance is clouded by three considerations. First, Kannel did not provide percentages of individuals at risk for each of the total: HDL ratio intervals and the above discussed articles combined do not allow us to estimate the percentages at risk for the larger ratios which, after all, are the ratios of concern. Kannel[1091] indicated in 1983 that a ratio of 5 was average risk. Since 5 is only 1.5 from the lowest ratio shown and 4.5 from the highest, it is apparent that most of the ratios used by Kannel represent a very small percentage of individuals.

Second, the data in Table 3-14 represent a 16-year follow-up of initially high risk subjects who were already 50 to 80 years old at baseline. Thus, the ratio differences were exaggerations by both length of time and by the unique population.

Third, total: HDL ratios cannot be manipulated much without drastic dietary changes or cholesterol-lowering drug usage. As emphasized in Volume 1 and Chapter 9 of the present volume, the high carbohydrate diet recommended by the alliance reduces HDL disproportionately more than it does total cholesterol. Therefore, the entire issue is perhaps more academic than significant because whether or not total: HDL ratios are predictive of CHD events, they are not likely to be manipulated to the degree needed for practical effects on CHD rates.

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[a] It is to be noted that these data, published in 1987, show significant CHD event rates in individuals having ratios less than 3.5. Yet, in 1988 Castelli stated that "in our studies, we've found no individual whose ratio was less than 3.5 has suffered a heart attack."[1567] In the same year he said elsewhere that "people with a ratio less than 3.5 appear to be at much lower risk."[1802]

Table 3-13

Mean total: HDL ratios by age and sex
(adapted from Kannel,1987[787])

	Men		Women	
Age	Mean	Range (96%)[a]	Mean	Range (96%)[a]
15 - 24	3.9	1.7 - 6.1	3.4	1.6 - 5.2
25 - 34	4.6	1.2 - 8.0	3.4	1.2 - 5.6
35 - 44	5.1	1.7 - 8.5	3.6	1.2 - 6.0
45 - 54	5.2	2.0 - 8.4	4.0	1.0 - 7.0
55 - 64	5.1	1.5 - 8.6	4.5	1.5 - 7.5
65 - 74	5.1	1.7 - 8.5	4.6	1.6 - 7.6
75 - 79	4.8	1.6 - 8.0	4.7	1.9 - 7.5

[a] These ranges comprise 96% of the distributions, based on standard deviations presented by Kannel, 1987.[787]

Table 3-14

CHD event rate by total: HDL ratio and sex
(adapted from Kannel, 1987[787])

Total: HDL Ratio	CHD Event Rate per 1,000 per 16 years	
	Men	Women
< 3.5	70	34
3.5 - 5.4	95	56
5.5 - 7.4	152	78
7.5 - 9.4	176	171
9.5+	275	281

It is unfortunate that with all the hundreds of (often redundant) articles published by the Framingham investigators, critical information needed to evaluate the importance of authors' data and conclusions are, more often than not, selectively omitted. Because this appears to be the rule, rather than the exception, it is apparent that the articles were purposely designed to mislead readers. There is simply no other explanation for the repetitive omissions of such important data by scientists.

THE RELATIONSHIP BETWEEN LDL AND CHD

To say that the alliance has defined LDL as the principal atherogenic component of blood cholesterol is very much like saying that oxygen is necessary for breathing. Although high LDL levels have not yet been proven to either initiate arterial lesions or accelerate plaque formation, the alliance nevertheless accepts the latter as fact and tends to accept the former as fact as well. Yet, in prospective studies, discussions of LDL are either absent or restricted to very minor status. While there are numerous figures and tables showing relationships between total cholesterol and CHD and between HDL and CHD, this writer has found not a single figure or table showing the relationship between the normal range of LDL values and CHD mortality or morbidity rate. The following subsections review articles from the three major U.S. prospective studies, Framingham, the large cohort screened for the MRFIT trial and the Honolulu Heart Program. Although the reader might legitimately wonder why LDL is the last lipoprotein to be discussed, in view of its presumed importance, it will soon become apparent that it is treated last (if at all) by the alliance.

Framingham

The LDL component was measured in the first and second examinations at Framingham. In a 6-year follow-up study published in 1961, Kannel et al.[2093] presented the relationship between total cholesterol and CHD but no mention was made of LDL. In a 14-year follow-up published in 1971, Kannel, Castelli and others[1376] reported a partial relationship between LDL and the CHD morbidity ratio. Not only did these investigators fail to present CHD rates, they also compared only the first quartile LDL with the fourth quartile LDL. In view of the fact that they provided readers with all four quartiles of total cholesterol, all four quartiles of phospholipids and total cholesterol and VLDL scales in relation to CHD morbidity, it is apparent that the second and third LDL quartiles, as well as an LDL scale, were omitted because they did not conform to the trends predicted by the lipid hypothesis. Otherwise, they would surely have been reported.

In 1977 Gordon, Castelli, Kannel and their co-workers[453] again omitted a quantitative relationship between LDL and CHD and instead reported regression coefficients. The coefficient for only one of three age groups was significant for both men and women but they indicated that the coefficients for all age groups combined were significant. However, they admitted that an "analysis for LDL cholesterol indicates that it is a marginal risk factor for people of these [50-90] age groups."

Gordon, Castelli and Kannel et al.[523] published a second paper in 1977. They reported somewhat larger and significant regression coefficients for the LDL-CHD relationship for men and women aged 50 to 79 years. Not only is it unclear how these coefficients for the same elderly population grew larger from May 1977 to August 1977, Gordon et al. again failed to provide readers with a figure or table showing the relationship between LDL and CHD. Nevertheless, they concluded that LDL was predictive of CHD in this age group, more or less contradictory to that stated in their earlier 1977 article.

In 1979 Kannel, Castelli and Gordon[1046] indicated that "LD lipoproteins have been shown to be a powerful predictor of risk in subjects younger than the age of 50" and

emphasized that "the LD lipoprotein cholesterol is superior to the total cholesterol as a measure of atherogenic cholesterol." They again omitted figures and tables showing the relationship between LDL and CHD and instead presented regression coefficients for men and women of various age groups. The coefficients of two of three age groups for women were not significant and one of four coefficients for men was not significant.

In 1981, Gordon, Kannel, Castelli and Dawber[581] again presented no LDL-CHD relationship data. Their regression coefficients for LDL among the elderly were nonsignificant in univariate analysis and only the male coefficient was significant in multivariate analysis. They concluded that "The positive association of LDL cholesterol with risk seems to be restricted to CHD morbidity and mortality and at these older ages is statistically significant over the full age range only for men. The finding of a negative relationship at older ages is particularly puzzling since it is well known that there is an atherosclerotic component in the genesis of stroke. However, similar findings have been reported from a study of Japanese in Japan and Hawaii which described an inverse relationship between total cholesterol level and stroke in men. There is also an inverse relation of LDL with risk of nonCHD death in either sex" at Framingham.

In 1983 Kannel[1091] said that "...it is now believed that the LDL fraction is the atherogenic component" and reported significant regression coefficients for both elderly men and women. He indicated that "there is a strong positive relationship between LDL cholesterol and the risk of coronary events" but, of course, he again presented no quantitative relationship between LDL and CHD to show this "strong" relationship. Kannel also appeared to initiate a new focus of interest in this article, away from relating total cholesterol and HDL to CHD and toward the total cholesterol: HDL ratio. He said, "Both the LDL and HDL effects are independent of each other" and "there is no particular benefit to making linear combinations of LDL and HDL compared with ratios... The ratio of the 2 lipoprotein-cholesterol fractions seems to provide as efficient a discrimination of cases from noncases. Hence, the total cholesterol/HDL ratio will efficiently identify patients who are at increased risk over the usual range of total cholesterol."

Perhaps the reader has detected two major inconsistencies in the above quotes. First, Kannel emphasized that LDL and HDL are independent of each other. Indeed, since both are components of total cholesterol, they are both correlated with total cholesterol, particularly LDL. For example, Kannel et al.[1046] reported correlations of .84 and .88 between total cholesterol and LDL for men and women, respectively in 1979. Therefore, it makes no sense at all to use the total: HDL ratio rather than the LDL: HDL ratio, since LDL is <u>the</u> presumed atherogenic component, HDL is the so-called protective component, both are independent of one another, and both are intercorrelated with total cholesterol.

Kannel's second inconsistency is the fact that he stated that the ratio of two lipoprotein-cholesterol fractions was the best predictor of CHD and then concluded that the total cholesterol: HDL ratio was his preference.

The rejection of the LDL: HDL ratio was simply a continuation of the historical rejection of LDL by Framingham investigators as a CHD predictor, no doubt because it has continuously shown a weak relationship with CHD.

Kannel also contradicted an earlier argument presented by himself and other co-workers, including Castelli. While he indicated in 1983 that "There is no particular benefit to making linear combinations of LDL and HDL compared to ratios," in 1977 they said, "The common procedure of calculating ratios of HDL to total or LDL cholesterol should probably be avoided since a person may have the same ratio at a

low level of HDL and LDL cholesterol or at high levels, and it is difficult to believe that these have the same medical and physiologic significance. Beyond that, it appears to be less satisfactory as a risk criterion than a linear combination."[453] Difficult to believe or not, they certainly ignored this argument in the 1980s.

In 1984 (Castelli[2955]) and again in 1986 (Castelli and Anderson[1531]) they finally presented a figure having an LDL scale. However, the dependent variable was CHD morbidity ratio, not CHD rate. More importantly, the LDL scale ranged from a first interval of < 300 mg to a last interval of ≥ 540 mg. Since a total cholesterol level of 300 mg already encompanses more than 95% of the entire population, this LDL scale apparently began with one interval representing perhaps 99% of the population, i.e., the LDL scale predominantly focused on only about 1% of the LDL distribution. Moreover, the morbidity ratio exceeding 100 required an LDL level of over 400 mg. Incredibly, Castelli and Anderson called LDL a "powerful and independent predictor of CHD." It was, in fact, an almost powerless predictor.

In 1986 Castelli, Kannel and others[261] published an article entitled "Incidence of CHD and lipoprotein cholesterol levels." They discussed HDL and total cholesterol at length and showed their relationships with CHD but there apparently was not a single reference to LDL. The following year Kannel[787] presented LDL levels across age groups but showed CHD relationships only with total cholesterol and with total: HDL ratios. He said, "The theoretically superior LDL/HDL ratio predicts CHD no better than the total/HDL cholesterol ratio in either sex." Knowing alliance mumbo-jumbo (Chapter 1), this statement probably means that LDL: HDL is inferior to total: HDL as a CHD predictor. Interestingly, while relegating LDL to essentially a nonfunctional predictor status, Kannel repeated an earlier statement which branded LDL as the "atherogenic" component of total cholesterol.

In another article in 1987 Kannel[964] offered the reader more inconsistent reasoning. He presented relationships between total cholesterol and CHD for men and women of all ages but again omitted an LDL relationship. He said, "The strong positive relation of the serum total cholesterol derives from its high correlation with low-density lipoprotein cholesterol." Then why did he not show the more relevant atherogenic LDL's relationship with CHD? Kannel continued, "A practical and efficient way to assess the combined influence of atherogenic LDL and protective HDL is to form a ratio. A favorable response to antilipidemic treatment...is to achieve a total to HDL cholesterol ratio of less than 5.0."

A 1989 article by Castelli et al.[2292] was similar to his 1986 report in which inconsistencies and misleading data predominated. They presented figures showing relationships between CHD and total cholesterol, between CHD and HDL, between CHD and the combination of HDL and total cholesterol and between CHD and the combination of HDL and triglycerides but, as usual, omitted that between CHD and the "atherogenic" LDL. They did show a bar graph of LDL vs CHD relative risk. Not only was this switch from CHD rate to relative risk a clue to LDL's lack of importance, the LDL scale ranged from about 150 to 650 mg. Relative risk was still under 1.0 at LDL levels of 400 mg, probably encompassing more than 99% of the population. Nevertheless, Castelli et al. referred to LDL as "a statistically powerful predictor in both men and women," although at the end of their article they used a far less impressive description, i.e., "With regard to the major component lipoproteins of cholesterol, there is a continued importance of LDL cholesterol."

Capping this short history of LDL's hide-and-seek game at Framingham was another 1989 article whose authors also included Kannel and Castelli (Levy et al.[2549]). They reported the mean total cholesterol and HDL levels, as well as total: HDL ratios, for men and women with and without CHD after follow-up. LDL was (now not so) curiously missing. They said that the Framingham study has identified several risk

factors for cardiovascular disease including advancing age, hypertension, obesity, cigarette smoking, electrocardiographic left ventricular hypertrophy, elevated total and low levels of high-density lipoprotein (HDL) cholesterol." Note that the so-called atherogenic component of cholesterol, LDL, was conspicuously absent. It must be obvious to everyone that LDL does not relate to CHD event rates with any practical significance. Such relationships are virtually never reported in 40 years of Framingham reports. And whenever LDL is related to something, it is morbidity ratio or relative risk. Relative risk is meaningless and LDL scales used with morbidity ratios are completely irrelevant for at least 98% of the population. Framingham investigators have truly pulled the wool over the eyes of the medical community.

The MRFIT Cohort

LDL was a dependent variable in the MRFIT trial[851] and was apparently measured in the 350,000 plus men screened for the trial. In view of the fact that it has long been classified as "bad" cholesterol and was a key dependent variable in the LRC trial, it would be remarkable if it were not obtained in the cohort. In any event, three major papers were published in 1986 which presented follow-up results of the cohort (Kannel et al.,[527] Martin et al.,[525] and Stamler et al.[263]) and one was published in 1989 (Iso et al.[1866]). All of these reports presented detailed relationships between total cholesterol and CHD but none even so much as mentioned the term, LDL.

The Honolulu Heart Program

The Honolulu Heart Program was the only study found that reported a quantitative relationship between LDL and CHD event rate. However, as usual, the investigators used a distorted quartile, rather than an equal interval scale. Table 3-15 presents the most pertinent data, reported in 1986 by Reed et al.[2820] If one sets the first quartile data aside for the moment, one can see that the CHD and nonCHD death rates tended to decrease as LDL increased. Moreover, because the nonfatal MI rate decreased from Quartile 2 to Quartile 3, before increasing in Quartile 4, there is the suggestion of an overall flat relationship. The inclusion of Quartile 1 is certainly suggestive of a flat relationship through the first three quartiles at least. Regardless of the first quartile data, therfore, the bulk of these data do not at all show the positive graded relationship between LDL and CHD or nonCHD events that is so often said to exist by alliance members.

The first quartile data show a low CHD death rate relative to Quartiles 2 to 4. But not only can this one quartile "trend" not override an opposite trend across three quartiles, at least part of the low CHD incidence was apparently due to the fact that the nonCHD death rate was three times as high as the CHD death rate in Quartile 1. As emphasized in Chapter 8 of this volume, the all-cause death rate has been found to be greater at low cholesterol levels than at more average levels in most prospective studies, including the Honolulu Heart Program. Thus, the depressed CHD death rate in the first quartile was clearly due more to the higher incidence of other deaths (principally stroke and cancer) than to low cholesterol per se.

Much of the range of LDL levels in the first quartile is representative of a very small percentage of the male population. Levels of 26 to 85 mg are reflective of abnormally and dangerously low total cholesterol levels. In view of the massive data that have accumulated to date (Chapter 8), virtually no reasonable epidemiologists would recommend cholesterol levels within that range.

Reed et al.[3399] reported in 1989 the results of autopsies performed on 78 of the 443 men who had died in the Honolulu Heart Program. The percent of raised lesions in the coronary arteries was correlated with LDL level. The correlation coefficient

Table 3-15

CHD and nonCHD events in the 10-year follow-up of the Honolulu Heart Program (adapted from Reed et al.,1986[2820])

LDL Quartile (mg)	CHD death rate (%)	Nonfatal MI rate (%)	NonCHD death rate (%)
26-120	1.1	2.1	3.3
121-143	2.8	3.5	3.9
144-168	2.1	2.2	2.7
169-280	2.3	5.0	2.2

was a nonsignificant .23, meaning that LDL level explained only 5.3% of the variation in atherosclerotic severity.

Of no little importance were the findings that (1) total cholesterol correlated with atherosclerotic severity more strongly (.32) than did LDL, (2) the correlation between HDL and atherosclerotic severity was near zero (-.09), and (3) the correlation between total cholesterol minus HDL and atherosclerotic severity was slightly lower (.30) than for total cholesterol alone (.32). None of these data support the concepts that LDL is atherogenic and HDL is protective.

In Sum

This section might very well have been entitled, "LDL, the atherogenic lipoprotein that never was." It is remarkable how it has been classified vigorously as the primary cause of atherosclerosis and simultaneously meticulously avoided in quantitative relationships with CHD. It is inappropriate, misleading and outrightly fraudulent to focus on total cholesterol on the tenuous grounds that it correlates highly with LDL. If LDL is indeed the atherogenic agent, it most certainly should demonstrate a linear or curvilinear relationship with CHD across its normal range and with greater strength than total cholesterol. The facts that Framingham investigators have continuously resorted to regression coefficients which are essentially worthless scientifically and clinically, and occasionally to LDL scales which encompass a range of values that have no relevancy to almost the entire population, clearly indicate that LDL is not importantly related to CHD, as observed in the two most significant U.S. prospective studies.

It would appear that the alliance is in a dilemma and knows not how to escape. Many years of dogmatic preaching on the atherogenicity of LDL are not supported by the alliance's primary data base. Rather than admit to such a state-of-affairs, the alliance has attempted to cover-up the LDL mystery in a most obvious and unsophisticated manner and maintains its allegiance to the notion that LDL is the atherogenic agent. What else can it do? It has no evidence to seriously incriminate another lipoprotein and it has committed itself fully to the proposition that diet is a primary underlying causation of excess LDL.

CHD AND OTHER DISORDERS

While non-insulin dependent diabetics are more prone to CHD development than the average person, risk factors do not explain this discrepancy according to Salonen, i.e., smoking, hypertension and hypercholesterolemia increase the chances of CHD in diabetics equally as much as they do in non-diabetics.[190] Salonen noted that "some studies believe that diabetics and
IHD may not be causally linked at all but may share a common, possibly genetic antecedent."

Levy pointed out that elevated glucose is a risk factor for CHD. However, he noted that "several drugs were used to lower blood glucose in the University Group Diabetes Program, but the patients in that study had more, not less disease."[1846]

In 1975 Stamler stated that hypothyroidism, nephrotic syndrome, primary familial hypercholesterolemia and diabetes mellitus "have nothing in common...except the one trait, that is, they all are associated with the development of severe elevation of blood cholesterol levels and...all are characterized by the development of premature inordinate severe hardening of the arteries."[2437] Since only a small percentage of those with high blood cholesterol levels develop CHD, the question is, why are not those with the above disorders automatically extracted out of the data from prospective studies in order to clearly show the relationship between blood cholesterol

level and development of CHD in otherwise normal individuals? Moreover, why are not thorough pathological profiles of the diseased arteries from individuals with the above disorders developed for comparison with the diseased arteries of those with common atherosclerosis?

CHOLESTEROL AND CHD "EVENTS"

It was emphasized in Volume 1 that all studies relating blood cholesterol with CHD have yielded relationships based, in part, on nonatherosclerotic CHD events, e.g., heart attacks not associated with atherosclerosis. This important flaw was recently noted by Kuller and Orchard who stated that "The problem of trying to equate dietary intake with atherosclerosis has been further compounded by using the heart attack or CHD mortality or morbidity as a measure of atherosclerosis. In this situation,...the disease, atherosclerosis, is not being measured adequately."[1785] In their 1988 book on nonatherosclerotic ischemic heart disease, Virmani and Foreman described many other causes of coronary artery occlusions such as spasm, embolism and thrombosis.[2276]

Alliance members typically give the impression that atherosclerosis is synonymous with myocardial infarction. For example, Levy stated in 1981 that "We now realize that almost all CHD is due to atherosclerosis."[1843] Almost the identical statement ad been made 20 years earlier in the AHA's first dietary recommendations, i.e., "A heart attack...is almost always caused by atherosclerosis."[517] Although Keys was one of the authors of the 1961 paper, he had earlier published several papers which indicated that the terms "almost all" or "almost always" were substantial exaggerations of reality. In two 1957 papers he said, "It must be recognized that atherosclerosis is by no means synonymous with CHD..."[276] and "it must be observed that atherosclerosis itself is not the only factor in the development of CHD..."[569] Indeed, in his 1956 paper Keys[280] presented an analysis of autopsies performed on 950 soldiers who died of CHD.[a] Table 3-16 (row 5) shows that 35.8% were not related to atherosclerosis at all, i.e., these were caused by thrombosis or "insufficiency" (spasm?).

Not only is 64.2% (row 6) far from being "almost all" of the cases, the data in Table 3-16 reveal that this percentage is not correct with respect to pinpointing the true underlying cause of death among the 950 soldiers. Condition 4, sclerotic and thrombotic combined, by definition, indicates that occlusion was the result of both atherosclerosis and thrombosis. This effectively means that the thrombus was essential to occlusion and, therefore, the true cause of the heart attack. It does not follow that partial occlusion per se was a primary or even secondary cause of infarction, particularly in light of Condition 2. It is noteworthy to emphasize, moreover, that these "relatively young men...were clinically healthy before the fatal attack," indicating that the state of atherosclerosis in the men was not advanced. Since some level of atherosclerosis occurs in nearly all of the male population, the fact that it occurred (in subclinical form) in the men who suffered thrombosis is hardly surprising. Thus, in ascribing the true cause of heart attacks in these men, Conditions 1, 2 and 4 should be combined to yield a percentage of 61.2 who died of thrombosis or insufficiency. The term "almost all" now becomes an absurd description of the importance of atherosclerosis to myocardial infarctions.

In 1960, Paul D. White[3298] also emphasized that "atherosclerosis and thrombus are two different problems." He stressed that "At least two-thirds of the cases of sudden death encountered by Dr. Milton Halpern, with his long experience in the Coroner's Office in New York City, showed extensive coronary atherosclerosis with no fresh thrombus. Since nearly all middle-aged persons have atherosclerosis, the absence of

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[a] Originally published a few years earlier by Yater.

Table 3-16

Causes of CHD in 950 soldiers as determined by autopsies (adapted from Keys,1956[280])

Condition	Number	%
1. Insufficiency without major thrombosis or sclerotic occlusion	119	13.6
2. Thrombotic occlusion alone	221	23.3
3. Sclerotic occlusion alone	369	38.8
4. Sclerotic and thrombotic combined	241	25.3
1 and 2	340	36.9
3 and 4	610	64.1
1, 2 and 4	581	61.2
3	369	38.8

thrombi in the majority of cases does not speak well for the atherosclerosis/blood clot/myocardial infarction theory.

Strong[2198] reported additional data on this topic from the International Atherosclerosis Project. His autopsies compare the arteries of those who were certified as dying from infarcts with those who presumably died of other causes. The specimens were from the U.S., Norway, Puerto Rico, Chili and Guatemala. Although calcified atherosclerosis was more prevalent in CHD cases than nonCHD cases, it was still highly prevalent in nonCHD cases (e.g., 92.5% vs 69% in white Americans 55 years and older). It is, of course, well known that death certification error is relatively high and Strong indicated that "variations in the criteria assigning causes of death to CHD could account for most of the discrepancies in comparing CHD and basal cases." After all, there was no proof that the CHD cases did, in fact, die of infarctions. In any event, the fact that "There is large variability in the amount of coronary atherosclerosis among CHD cases from each location-race-sex-age subgroup...suggests that there are risk factors in addition to the amount of atherosclerosis that are important in the pathogenesis of CHD."

In reviewing the literature on diet, blood cholesterol and CHD, not much data have been seen relating to this issue. Perhaps that is not surprising. If the precise relationship between atherosclerosis and myocardial infarctions were well-known and publicized, the promotion of the diet-CHD hypothesis would be seriously weakened. In any event, as was emphasized in Volume 1, the use of fatal and nonfatal infarctions and sudden death as dependent variables in clinical trials of cholesterol-lowering diets or drugs has resulted in confounded outcomes. The data presented by Keys indicate that at least one-third of all infarctions and sudden deaths are not related to atherosclerosis at all and possibly two-thirds are not substantially related. But even the lower figure would render clinical trial results meaningless. Former AHA president, Irvine Page[3080] also noted this discrepancy among patients who suffered myocardial infarctions, i.e., "good evidence suggests that perhaps as many as 20% of the patients do not exhibit enough atherosclerosis to justify a cause and effect relationship."

The Framingham study also provides examples of the inappropriate combining of endpoints. In 1961 Kannel et al. stated that "It is widely accepted that sudden death (occurring within a matter of minutes) is usually the result of coronary heart disease with or without coronary occlusion."[2093] Yet, they went on to say that of the sudden deaths that had occurred to date, only 37.5% could be attributed to pre-existing evidence of CHD. Therefore, the majority (62.5%) of the sudden deaths occurred in subjects without overt signs of atherosclerosis. A few years later (1964) Kannel plotted the morbidity ratios, with respect to sudden deaths, and concluded that "The risk of sudden death also may be greater with an 'elevated' serum cholesterol level."[1885] His plot, however, showed ratios of 96 for persons with cholesterol levels below 220, 68 for persons with levels between 220 and 259 and 183 for persons with levels of 260 or greater.[a] Thus, if Kannel interpreted the higher cholesterol interval as being associated with greater risk of sudden death, then one must interpret the intermediate cholesterol interval as being associated with a much lower than normal risk of sudden death. In any event, both the 1961 and 1964 articles indicated that atherosclerosis per se (and thus cholesterol level) had little or nothing to do with the majority of sudden deaths.

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[a] The morbidity ratio is the number of observed events divided by the number of expected events times 100. Thus, if the observed and expected events were the same, the ratio would be 100.

In 1971 Gordon and Kannel[433] defined "sudden death" as "attributed to CHD when apparently well persons were observed to suddenly and unexpectedly collapse and die within one hour (but ordinarily in a matter of minutes), and when no other cause was suggested by medical history." In effect the "diagnosis" of CHD in many deaths was based on assumption. They indicated that 120 deaths due to CHD were recorded in a 14-year follow-up of the Framingham cohort. Of these, 66 were sudden deaths, 42 were without prior CHD. Thus, 35% of all deaths attributed to CHD were not likely to be or may not have been due to atherosclerosis. In fact, all 66 sudden deaths (55% of all deaths attributed to CHD) may not have been due to atherosclerosis. Although few autopsies were performed, Gordon and Kannel indicated that "When a thrombus is found in one of the coronary arteries it is not always clear that it constitutes an explanation of the death."

In 1975 Kannel et al.[3015] compiled sudden death data accumulated over 16 years from both the Framingham and Albany studies. Some 57% of the men who suffered sudden death had no prior evidence of CHD. Moreover, the rate of sudden death decreased as blood cholesterol increased from < 220 to 259 mg and then increased beyond 260 mg. These results confirmed their 1964 findings.[1885] Despite the fact that they automatically classify all sudden deaths as CHD deaths, they said, "The proportion of sudden deaths attributed to CHD...varies widely, particularly in autopsy series."

Dawber[3001] reported in 1980 that 280 CHD deaths had been recorded by the 24-year follow-up of Framingham subjects. Of these 280, 46% were sudden deaths. Thus, nearly half the total CHD deaths were suspect insofar as atherosclerosis was concerned. This assertion was strengthened by the fact that Dawber demonstrated no real relationship between blood cholesterol level and rate of sudden death.

Apparently the latest data by Kannel et al. on sudden deaths in the Framingham study were published in 1987. These investigators again admitted that "The assignment of sudden death to coronary disease is largely by inference, in as much as few other diseases can cause death in a matter of minutes."[2289] This statement further confirms the fact that a significant percentage of Framingham mortality data attributed to CHD has been by assumption. When one considers the long-time duration, cost and impact of the Framingham study, it is inconceivable to think that reported relationships between blood cholesterol and atherosclerosis have been significantly based on assumptions, rather than valid diagnoses.

Kannel et al. reported 160 and 73 sudden deaths among men and women, respectively, over a 30 year period. Some 41% of the sudden deaths occurred in individuals with pre-existing CHD. They concluded that "since such a high proportion of sudden deaths arise from the small segment of the population with overt CHD, there is a clear need to focus preventive measures on those who have the disease." But the emphasis by Kannel et al. is entirely misleading. The dominant percentage (59%) of sudden deaths occurred in clinically healthy individuals and this fact is of enormous importance to the diet-blood cholesterol-CHD issue. It should not be sloughed aside in favor of the smaller percentage of sudden deaths which can be related to atherosclerosis.

The Kannel et al. conclusion is a reflection of the widespread abuse and misuse of statistics by alliance members. To illustrate, consider the hypothetical situation in which there are 100 sudden deaths, 50 occurring in individuals with clinical atherosclerosis and 50 occurring in individuals free of significant atherosclerosis. The most important conclusion to be drawn from this example is that the sudden deaths were equally distributed among atherosclerotic and nonatherosclerotic persons and, therefore, independent of atherosclerosis. Now, if the number of sudden deaths is significantly greater among nonatherosclerotic persons, the conclusion can be drawn

that nonatherosclerotic persons have a greater likelihood of having a sudden death than atherosclerotic persons. The conclusion cannot be drawn that the atherosclerotic persons have a higher risk of sudden death--but that is precisely the conclusion implied in Kannel et al.'s statement.

Elsewhere, Kannel, Stamler and their colleagues[1083] observed that "Of the many Americans who die of CHD each year, almost 70% of deaths occur outside the hospital. More than half are sudden and unexpected." Not only is this 70% subject to considerable diagnostic error, the term "sudden and unexpected" implies no overt manifestations of atherosclerosis.

This issue is similar to that discussed in Volume 1 concerning risk factors and CHD. It was shown that some 80% of the large cohort of men screened for the MRFIT study had one or more risk factors. It is therefore meaningless to claim that the majority of men contracting overt atherosclerosis have one or more risk factors because the majority of men have one or more risk factors to begin with. It is almost like claiming that the majority of men contracting overt atherosclerosis have one or more of the following--"inny" belly button, dark hair, height of 5'7" or greater and bad breath. Of course, the majority of men contracting anything will have one or more of these "risk" factors because they commonly exist within the entire population of men.

In 1981 Oliver observed, "There is no convincing evidence that there has been a reduction in cardiac mortality [in clinical trials] but, since approximately two-thirds of deaths due to a heart attack are sudden and the mechanisms of sudden cardiac deaths are unlikely to be associated directly with a given concentration of serum cholesterol, this is not particularly surprising."

Perhaps not recognizing the implications of his statement in 1987, Castelli[1179] said, "About half of the deaths that are from heart attack or stroke are brought about by atherosclerosis..." The corollary of this statement is: about half of the deaths that are from heart attack or stroke are not brought about by atherosclerosis.

Important studies relating to the present issue were published in 1988 and 1990 by Ambrose et al.[3003] and Little,[3153] respectively. These investigators evaluated angiograms of patients who suffered myocardial infarctions. They reported that a substantial percentage of MI patients had infarcts in arteries that were normal and that the majority of infarcts occurred in arteries that were less severely stenosed than were other arteries. These results indicate that something independent of atherosclerosis was obviously the cause of infarctions.

Another important observation was recently presented by Buja and Willerson.[3128] They pointed out that about 25% of patients with coronary spasm have no significant atherosclerosis. And since it is often emphasized that very few people escape relatively widespread atherosclerosis, it would be expected that the majority of persons with coronary spams would also have significant atherosclerosis. Buja and Willerson's results again strongly suggest that something independent of atherosclerosis must be the cause of spasms.

Buja and Willerson continued, "The frequency and significance of coronary thrombosis in various states of IHD have been the subject of controversy. Controversy over the role of coronary thrombosis in acute MI previously had been related in part to the assumption that sudden cardiac death generally represents an early stage of acute MI. Clinical studies, however, have shown that the mechanisms of sudden cardiac death in most patients is an electrical alteration, usually ventricular fibrillation, and that most patients resuscitated from sudden cardiac death do not develop diagnostic evidence of myocardial infarction."

One final note. As will be repeated in Chapter 4, Dawber[3001] cautioned that "Epidemiologic studies based on diagnostic data obtained by a number of physicians who have no common agreement on the diagnostic criteria must be accepted with reservation." Since all the deaths recorded in the Framingham study were diagnosed by different physicians and since diagnosis was hampered by the fact that the great majority of the deaths occurred outside of hospitals, one can have very little faith in the assumption that (1) all or most of the deaths recorded as CHD were, in fact, CHD deaths, (2) all or most of the deaths recorded as sudden deaths were, in fact, CHD deaths, and (3) all of most of the CHD and sudden deaths were substantially caused by atherosclerosis. The notion that atherosclerosis is the cause of sudden deaths and myocardial infarctions is based almost entirely on assumptions. The preponderance of scientific evidence indicates that atherosclerosis per se plays a minor to no role at all in these events.

An observation by Werko[3218] is of interest in reflecting the behavior of the alliance. He noted that the Intersociety Commission published preliminary data on the positive relationship between blood cholesterol and sudden death in the National Pooling Project in 1970[552] but when the relationship subsequently dissolved, the topic was omitted altogether when the Pooling Project Final Report[579] was published in 1978. Instead, "a lot of statistical sophistication is used to analyze the combined feature 'myocardial infarction, fatal and nonfatal plus sudden coronary death.'"

One may find it extraordinarily difficult to acknowledge, let alone accept, the fact that all clinical trial and prospective study data have been inflated with irrelevant "events" as endpoints. There is, nevertheless, little question that this has been the true state-of-affairs. Fatal and nonfatal heart attacks and sudden deaths have typically been the endpoints of clinical trials and prospective studies and at least half and perhaps as much as two-thirds of the "events" had nothing to do with atherosclerosis. And since there is neither scientific evidence nor sound theoretical rationale for a cause-effect relationship between cholesterol and nonatherosclerotic heart attacks, and since almost as many people die of CHD with cholesterol levels below the average as those above the average, the continued emphasis by the alliance that cholesterol is the key to heart attacks is sheer scientific madness.

THE EXPLANATORY POWER OF RISK FACTORS

In Chapter 3 it was noted that Wilson, Castelli and Kannel stated in 1987 that "with available risk factors we can account for no more than 50% of the variance in coronary incidence."[1366] They cited Epstein as the source of this 50% value.[1615] Epstein, in turn, cited a letter-to-the-editor by Blackburn et al. which presented corrected data from the Pooling Project report.[1847] To illustrate how the 50% value was presumably derived, consider first the top half of Table 3-17 which shows the corrected Pooling Project data. This part of the table presents the number of men having the specified risk factor at entry (cigarette smoking, hypercholesterolemia, hypertension), the number of CHD "events" occurring within those categories of risk factors over 10 years and the associated CHD event rates per 1,000 men at risk.

The total number of men involved was 7,328. Epstein proportionally converted the number of men within each risk category so that the total number was 1,000. Thus, the number in the first cell of the table, 1,246, became 170. The converted numbers are shown in the bottom part of Table 3-17. The number of CHD events were similarly converted. For example, the number of events for 170 men, i.e., 3.9, was proportionally computed from the rate of 23 per 1,000 (top half of the table).

While the calculations thus far make perfect sense, Epstein's remaining calculations appear more mystical than logically based. In describing the last two rows of Table

Table 3-17

Pooling Project data and "explaining" the variance of CHD due to 3 risk factors

POOLING PROJECT DATA

Risk Factor at Entry	No. of Men	No. of Events	Rate/1000[a]
None of 3	1,246	32	23
S only	2,021	120	54
C or H	1,293	82	54
S+C or S+H	1,790	195	103
S+C+H	597	95	189
Total	7,328	561	72

S = Smoking (cigarette); C = Cholesterol $\geq$ 250; H = Hypertension $\geq$ 9(

[a] Age-adjusted by 10-year age groups.

RISK FACTORS[a]

	None	S	C or H	S+(C or H)	C+H	S+C+H	TOTAL
PRESENT				554			
No. of Men	170	276	176	244	52	82	1000
Events	3.9	15.9[b]	9.5	25.1	4.8	15.5	73.8
FUTURE				250			
No. of Men	750		200		50		1000
Events	17.3		10.8		4.6		32.7

[a] Epstein's re-calculations of the Pooling Project data.

[b] Incorrect calculation. It should be 14.9

3-16, Epstein stated, "Next, it is assumed that a new generation grows up in which elevated levels of serum cholesterol and blood pressure are less common by the time it reaches middle age (25% versus 55%), shown in the lower rows. These are realistic goals, whereas the assumption of smokerless society may be beyond immediate reach. Yet, in order to calculate the degree to which these three risk factors 'explain' CHD, smoking must be excluded from the population at risk. It emerges that over half (56%) the disease in its most severe manifestations is 'explained' by the three major risk factors." Epstein arbitrarily eliminated the men at risk for categories 5, 5 + (C or H) and 5 + C + H, all categories associated with smoking. He then reduced the men at risk within the four categories involving C or H or both from 554 (55% of 1,000) to 250 (25% of 1,000) and then distributed the 250 to the two categories shown, proportional to the "present" numbers, i.e., 176 and 52. Since 1,000 - 250 is 750, the latter was shifted into the "none" category. The CHD events for the resulting three risk categories were computed based on the ratios of the "present" numbers of men to events. Summing the events yielded 32.7, a value that is 56% lower than the "present" value of 73.8. Ergo, "over half (56%) the disease in its most severe manifestations is 'explained' by the three major risk factors.

If the reader finds Epsteins' logic dumbfounding, it is entirely understandable. This writer could not make a great deal of sense out of it. It is important to note, moreover, that Epstein enclosed the word "explain" in quotes, implying that it was not used in the usual mathematical sense.

Three additional points should be addressed. First, as was discussed in Volume 1, the Pooling Project data appear to be peculiarly spurious, compared to that of other studies. Second, the data were heavily comprised of nonfatal CHD events, indicating considerable potential for diagnostic bias. And third, it is interesting that Wilson et al. cited Epstein as accounting for "no more than 50% of the variance in coronary incidence," even though Epstein reported a value of 56%.

Wolf et al. also claimed recently that the four major risk factors (including relative body weight) "account for more than 50% of the variance of coronary events."[1912] They cited no literature to support that statement.

An interesting study of risk factors was published by Kramer and his colleagues in 1983.[1766] They measured risk factors and obtained angiograms on 302 CHD patients initially and after 3 years of follow-up. One hundred and thirty-eight of the patients showed definite regression. These patients could not be predicted on the basis of their cholesterol levels, smoking habits, weight or family history (blood pressure data were inadequate to evaluate this variable). Sixty-one percent of the progression patients had cholesterol levels below 250 mg and 38% had levels above 250 mg, corresponding closely to the percentages existing in the general population.

In 1987 Stamler naively claimed that "75% of all CHD deaths [in the MRFIT screened cohort] were attributable to various combinations of these three established [hypercholesterolemia, hypertension and cigarette smoking] major risk factors."[521] As noted in Volume 1, 79.4% of this cohort had one or more of the three risk factors at entry. Thus, those who died had slightly less involvement with risk factors than did those who lived, an implication that is opposite to that suggested by Stamler.

In their evaluation of the 8,147 men who participated in the intervention group of the 5.3-year United Kingdom Heart Disease Prevention Project, Heller et al.[3007] found very little ability to predict CHD from risk factors. They reported that only 7% of men designated at high risk and without history of CHD suffered an MI, and only 22% of men designated at high risk and with a history of CHD suffered an MI. These percentages say little for the generality of "high risk."

In their review Kuller and Orchard concluded that "Increased blood pressure may be an independent risk factor for atherosclerosis of the intercranial arteries, but whether this is the same disease as atherosclerosis of the larger arteries is questionable. Increased blood pressure is probably not a strong independent risk factor for atherosclerosis of other major arteries, especially the coronary arteries." Indeed, Chapter 9 shows that study after study has failed to indicate beneficial effects on CHD incidence of lowering high blood pressure.

In point of fact, no substantive evidence is ever presented which shows that the alliance's principal risk factors explain 50%, 40% or even 20% of the variance in coronary incidence. Fifty percent of the variance would imply a correlation of .7 between risk factors and CHD incidence. The alliance rarely publishes correlations, let alone values of that magnitude. It is also irresponsible and inexcusable for authors to make unsubstantiated claims such as that recently reported by Garg and Grundy, i.e., "the risk factors for coronary heart disease are additive and perhaps multiplicative."[2327] One must wonder whether Garg and Grundy even understand the meaning of the terms "additive" and "multiplicative" because if one is sufficiently knowledgeable of the mathematical relationship between risk factors and CHD to use such terms, he should know whether the factors <u>are</u> additive <u>or</u> multiplicative. The effects of each are hugely different.

The association of numbers with risk factors without supporting evidence is also meaningless because it implies precision when speculation is more appropriate. For example, Elizabeth Whelan recently stated that "We estimate that 20% of CHD is caused by cigarette smoking... We estimate that another 20% is caused by high blood pressure...some 18%...is related to high serum cholesterol levels..."[1790] Where do these percentages drive and what of the remaining 42%?

Most risk data derive from the Framingham study. It is of interest to note Bernstein's conclusion concerning the prediction of CHD, i.e., "The Framingham study demonstrated a weak relationship between CHD and total or LDL cholesterol and an inverse correlation with HDL cholesterol. The desired combination of tests that reliably measure the probability of developing CHD or of its regression remain elusive."[2385]

An editorial in the British Medical Journal[3077] summarized the conclusions generated at a meeting of cardiologists from many countries. The editorial stated, in part, "If we take 100 men with the three major risk factors (smoking, hypertension, and raised serum cholesterol) only eight develop clinical manifestations of CHD over the next 10 years, while 92 do not; conversely, most previously fit patients who developed CHD while under observation in the Seattle 'heart-watch' programme had no conventional risk factors on entry. We must therefore realize that risk factors cannot be causal and that they have very poor predictive value."

Very recently Nixon and King[2971] observed that "most coronary patients probably do not have risk factors, yet our therapists notice a diminishing interest these days [by patients] in taking care of the important influences and a growing preoccupation with diet."

The situation has not progressed from that of 22 years ago, at which time Brown[3135] stated that "Although several so-called risk factors, including cholesterol elevation, have been identified in the development of IHD in populations, no single factor has been shown to have much reliability in predicting the occurrence of IHD in the individual subject."

THE DISTORTION OF DATA

Benfante and Reed published a 12 year follow-up of the Honolulu Heart Program in 1990.[2563] The relationship between CHD "events" and cholesterol levels for 6,860 men again presented in distorted fashion, i.e., cholesterol levels were given in quartiles. Figure 3-34 shows their data in terms of two age groups and compares them with the similar Framingham data given in Volume 1.

At the outset, it is peculiar that the initial examinations of the Honolulu men were undertaken between 1965 and 1968 and yet only a 12 year follow-up was published in 1990. One would think that a 15 to 20 year follow-up would have been possible for a 1990 publication date.

In addition to the fact that the Honolulu data show a relatively flat relationship over the majority of the cholesterol range, being quite similar to the Framingham data, they also show much lower CHD event rates than those reported in the Framingham data. Over the same cholesterol range the event rates for the Honolulu men were only 50% of those in the Framingham men for the younger age group and, at most, about 35% of those in the Framingham men for the older age group. The relationships in both cohorts are not only unimpressive for group data, they are both distorted by a cholesterol scale composed of grossly unequal intervals. The upward trend seen in the interval $\geq$ 240 mg in the Honolulu study compares with the upward trend seen in the interval $\geq$ 295 mg in the Framingham study and yet there is a 55 mg difference between the two.

The huge differences between the Honolulu and Framingham studies cannot be explained in terms of cholesterol level differences and it is not likely that they can be explained in terms of other so-called risk factors.

Because an upward trend in CHD event rate was shown in the fourth quartile for elderly men (although this is likely to be due to that relatively small percentage of the population with very high cholesterol levels; note that there was no upward trend from the 2nd and 3rd quartile), Benfante and Reed recommended that the elderly should be treated for elevated cholesterol. Goldstein[2831] pointed out that sufficient studies, including Framingham and the screened MRFIT cohort, indicate either an increasing total mortality with low cholesterol levels or no relation between overall mortality and cholesterol. Thus, no overall benefit would drive from lowering blood cholesterol in the elderly. Benfante and Reed[2831] replied that "we did not mean to suggest how elderly individuals with elevated serum cholesterol levels should be treated." Yet, they went on to recommend a reduction in saturated fat intake, reducing obesity, eliminating smoking and reducing hypertension which, of course, are all of the principal recommendations commonly made by the alliance, three of which reduce blood cholesterol levels.

In another investigation, Aronow et al. followed 192 men and 516 women whose average age at entry was 82 years.[2564,2630,2637] They considered cholesterol levels above 200 mg as hypercholesterolemic and reported a 1.6 to 1.8 times greater CHD "event" rate among men and women, respectively, with cholesterol levels above 200 mg than those having levels below 200 mg. However, these data are suspect for three reasons. First, they are wildly different from those of other more commonly accepted studies such as Framingham and the MRFIT cohort. For example, Aronow indicated that 27% and 30% of CHD events occurred in men with cholesterol levels under 200 mg and 250 mg, respectively, meaning that only 3% occurred between 200 and 250 mg. This contrasts with 50 percent in the Framingham study. Also, the 30% under 250 mg contrasts with 50% under 225 mg in the Framingham study.

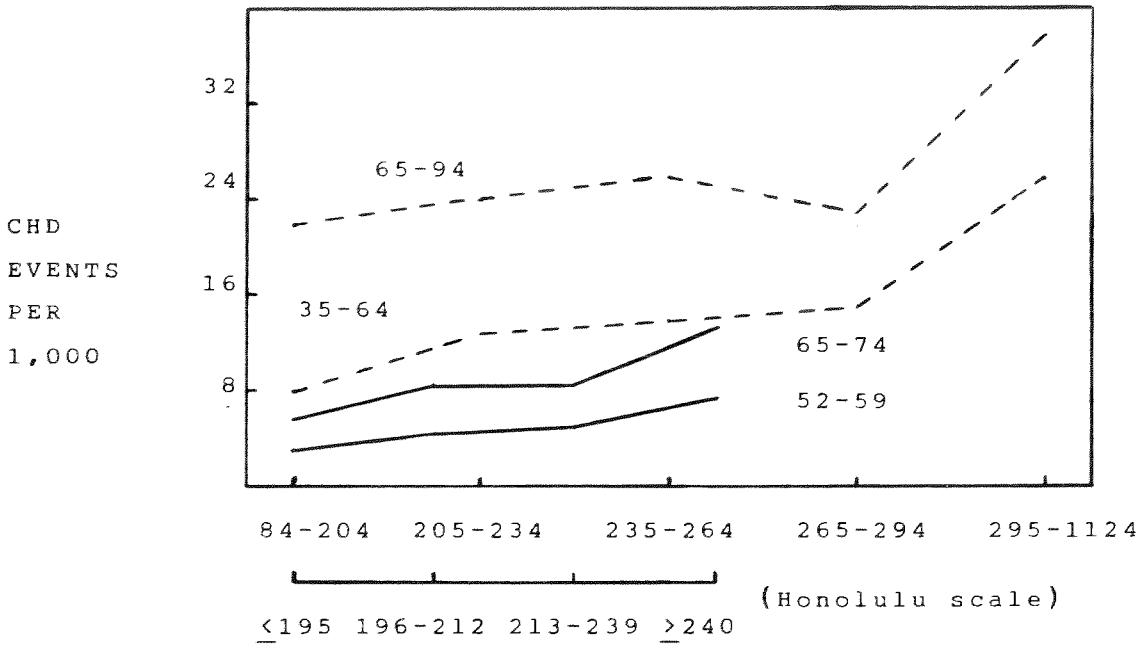

Figure 3-34. Blood Cholesterol level and CHD events by age group in the 12-year follow-up of the Honolulu Heart Program (solid curves) in comparison to the Framingham male curves (adapted from Benfante and Reed, 1990[2563] and Kannel, 1987[787])

4. EPIDEMIOLOGICAL STUDIES

"Diagnosis of overt heart disease on the basis of lipid levels alone is simply not feasible."

(William Kannel, et al., 1964[1885])

"It is now possible, using ordinary procedures and simple laboratory tests, for an industrial health unit to identify among its employees those who are prime candidates for a 'heart attack'."

(William Kannel et al., 1967[554])

"A number of studies...have found that total serum cholesterol...is a very powerful risk factor for CHD in young men."

(William Kannel et al., 1977[523])

"Serum cholesterol is not a strong risk factor for CHD. There is, to our knowledge, no such truly powerful risk factor."

(William Kannel et al., 1982[2638])

"Several personal characteristics are related to CHD risk; they include elevated blood lipids...[etc.]. None by itself is strictly determinative."

(William Kannel et al., 1984[1083])

"The serum total cholesterol is a powerful risk factor for CHD in both sexes."

(William Kannel, 1987[787])

MORTALITY AND DIET TREND

World Health Organization Data

In Volume 1 ten between population studies were reviewed in which investigators correlated CHD mortality rates from World Health Statistics Annuals with food disappearance data in Food and Agriculture documents from the United Nations. Such studies were considered wholly naive and scientifically unsound because they depended on the most untenable set of assumptions, namely that each nation has the same (1) knowledge of CHD, (2) quality and quantity of diagnostic equipment, (3) population exposure to physicians, (4) accuracy in certifying causes of deaths, (5) life expectancy, (6) prevalence of autopsies to verify causes of death, (7) diagnostic "fashions," (8) accuracy in compiling food consumption data, etc.

An earlier edition of the WHO Annual stated that "in many countries or areas...most deaths are certified by a lay attendant...[and that] the ICD [International Classification of disease] contains many diagnoses that cannot be identified by a non-medical person."[1052,a] Most physicians would unquestionably have little or no faith

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[a] Additional and more specific quotes from recent WHO documents are presented below.

in a layperson's ability to determine cause of death. Why, then, do the physician epidemiologists accept such mortality statistics without question?

Epidemiologists such as Castelli frequently point to Latin, African and Asian countries as having low CHD death rates.[1667] Not only is the accuracy of their recorded rates questionable, life expectancy in most of these countries is either the same as or lower than that of the U.S., particularly white Americans who consume what Stamler frequently refers to as a "rich" diet. Castelli would have done well fo heed his former superior's observations. Thomas Dawber[3001] said, "Epidemiologic studies based upon diagnostic criteria must be accepted with reservation. Death certificates are commonly utilized in determining the clinical diagnosis of cause of death. Unfortunately, there are no strict criteria to guide the physician [or the lay attendant] completing the death certificate, even if he were willing to follow them. Anyone familiar with the various factors that enter into the preparation of death certificates recognizes the pitfalls of total reliance on the information so provided." Thus, either Castelli, Stamler and others are not familiar with these factors or they simply ignore them.

Ignoring such statements by the WHO and Dawber, as well as the numerous problems that should be more than obvious in the between countries studies, Stamler[3002] maintained that "This is one of the areas where the data are so massive that one can speak about the relationship [between diet and CHD] as being established beyond debate."

Because of the frequent citations of WHO mortality data, and because initial data from a new project known as MONICA (multinational MONItoring of trends and determinants in CArdiovascular disease) were published in the latest (1989) WHO World Health Statistics Annual, this writer decided to examine the WHO statistics in some detail. The MONICA project apparently began in 1984 and is intended to terminate in 1993. It is designed to determine whether a relationship exists "between 10-year trends in the major cardiovascular disease risk factors of serum cholesterol, blood pressure and cigarette consumption" and whether a relationship exists "between 10-year trends in incidence rate (fatal plus non-fatal attack rates for CHD)."[2797,a] Some 39 data centers in 26 countries are collaborating in the project, which means that some countries are collecting data from several centers. The U.S., however, is represented by a single, small center, in keeping with the minimum level of effort that NHLBI devotes to gathering crucial morbidity vs mortality trend data. Presumably because it takes several years to compile statistics for a single year, the 1989 WHO annual presents only the initial MONICA data gathered in the 1984-86 period, with no morbidity trend data. However, the data are nevertheless quite amazing, at least from the standpoint of those who promote the risk factor theory, as will be seen. Since each World Health Statistics Annual presents some unique data not reported in other annuals, the following discussion employs data from the 1987, 1988 and 1989 annuals.

CHD Mortality, Geography and Language. It does not take intensive analyses to conclude that CHD mortality rates vary in quite peculiar ways among countries. If we just look at males in the U.S., Canada, Australia, New Zealand and the European countries, we find that with one exception, the English speaking countries (U.S., Canada, England and Wales, Scotland, Northern and Southern Ireland, New Zealand and Australia) had by far the highest CHD mortality rates in the 1960-64 era, averaging about 300 per 100,000 population (age-standardized to the world standard).[2825] Finland was the exception, having a rate of 335 per 100,000.

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[a] The subject of mortality vs morbidity is discussed in Chapter 9.

The CHD mortality rates of all non-English speaking European countries (Finland excepted) were at or under 220 per 100,000 in the 1960-64 period. However, they were by far the lowest in the Western and Eastern perimeter countries of Belgium, France, Portugal, Spain, Poland, Romania, Bulgaria and Greece, averaging about 92 per 100,000. The central and northern continental European countries (Netherlands, Germany, Austria, Switzerland, Luxembourg, Czechoslovakia, Hungary, Yugoslavia and Italy) had distinctly higher mortality rates, averaging about 156 per 100,000. Finally, the highest European rates were observed for the five Northern Scandinavian countries of Denmark, Iceland, Norway, Sweden and Finland, averaging approximately 232 per 100,000, but still far below the average of the English speaking countries.

The relative positions of the countries discussed did not change much over a 20-year period. The rates in Portugal, Italy and Yugoslavia dropped substantially and, although they increased somewhat in Greece, Bulgaria, Romania and Poland, virtually all the Southern, as well as the Western and Eastern European perimeter countries reported the lowest rates. Luxembourg, Austria and Switzerland, adjoining Belgium, Italy and Yugoslavia, respectively, also reported considerably lower rates. The range of rates in these countries in 1980-84 was 71 to 155, with an average of about 100 per 100,000. The four central and Northern countries of Germany, Netherlands, Czechoslovakia and Hungary exhibited the intermediate rate of about 201 per 100,000 and the five Northern Scandinavian countries of Denmark, Iceland, Norway, Sweden and Finland maintained the highest average rate of about 228 per 100,000.

The CHD mortality rates among the English speaking countries, however, changed quite dramatically by 1980-84. The rates of the U.S., Canada and Australia ranged from 200 to 215 per 100,000 (mean = 207), while they ranged from 234 to 294 among the remaining countries, having an average of 260 per 100,000.

As will be discussed later, there is little question that the above CHD mortality profile illustrates distinctive biases, preferences, "fashions" or knowledges of those certifying cause of death in the various countries. While it is tempting to indicate, for example, that latitude is a major factor influencing CHD mortality, as some have suggested (Chapter 2), that "theory" is not supported by trends in Europe and it is most certainly not supported by the English speaking countries whose geographic distribution is much greater than that of the European countries.

CHD Mortality Trends. Figures 4-1 to 4-5 present male CHD mortality trends for most of the countries listed in the 1988 WHO Annual.[3273] A few countries are omitted because data for only the most recent years were available. Each Figure compares the U.S. with a set of other countries, there being no uniqueness about each set. Recalling the detailed discussion in Chapter 3, it should be emphasized that 1949 marked a most important change in the ICD which resulted in major, automatic increases in reported CHD mortalities. Thus, the trends subsequent to 1950 do not adequately illustrate the so-called "epidemic" but instead tend to focus on peaks and declines or, in some countries, increases.

The overall trends shown in Figures 4-1 through 4-5 are inconsistent with each other and demonstrate no systematic relationships with so-called "life-style" changes. As will be seen in the following section, CHD mortality rates do not at all correlate positively with the major risk factors among all the nations participating in the MONICA project. Furthermore, life-style changes are gradual, whereas 17 of the 36 countries represented in the figures exhibited unreasonable CHD mortality rate increases and/or decreases.

The islands of Ireland and Great Britain are illustrative of the strangeness of mortality trends. The overall trends of both Northern and Southern Ireland have been gradually upward, with Northern Ireland reporting significantly higher rates. But

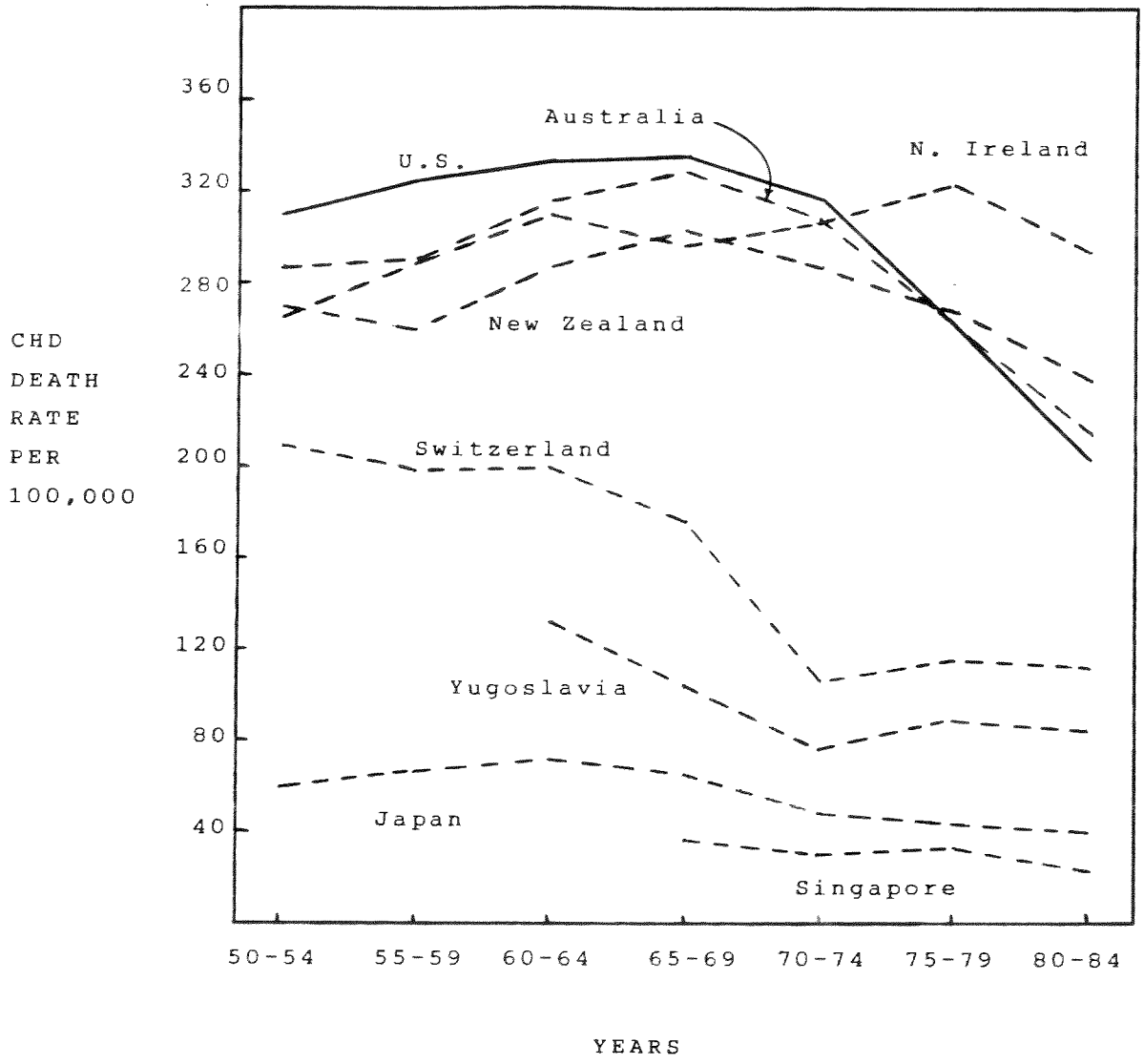

Figure 4-1. Age-standardized (world) male CHD death rates by year for the U.S., Australia, Northern Ireland, New Zealand, Switzerland, Yugoslavia, Japan and Singapore (adapted from World Health Statistics Annual,1988[3273])

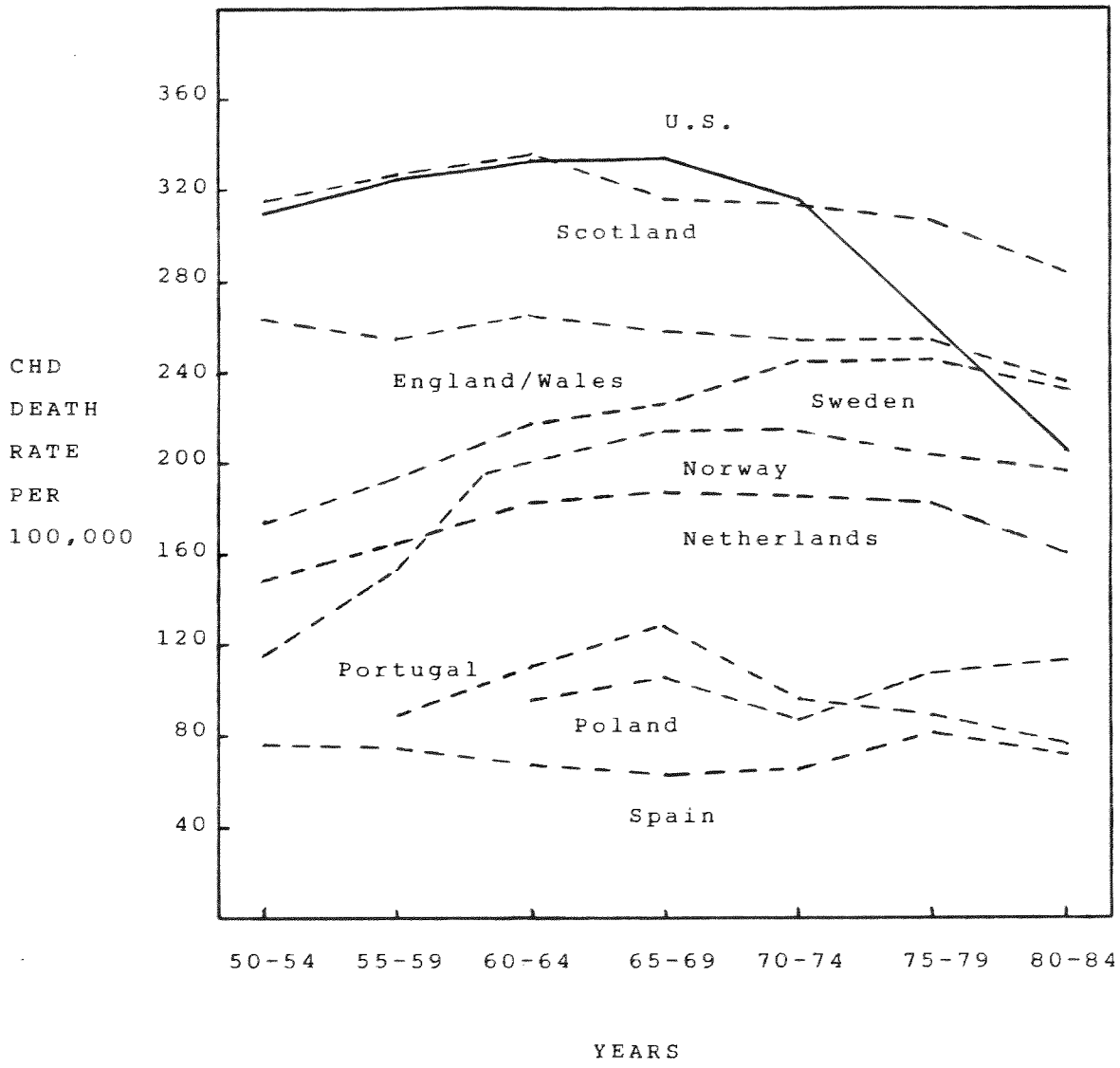

Figure 4-2. Age-standardized (world) male CHD death rates by year for the U.S., Scotland, England/Wales, Sweden, Norway, Netherlands, Portugal, Poland and Spain (adapted from World Health Statistics Annual, 1988[3273])

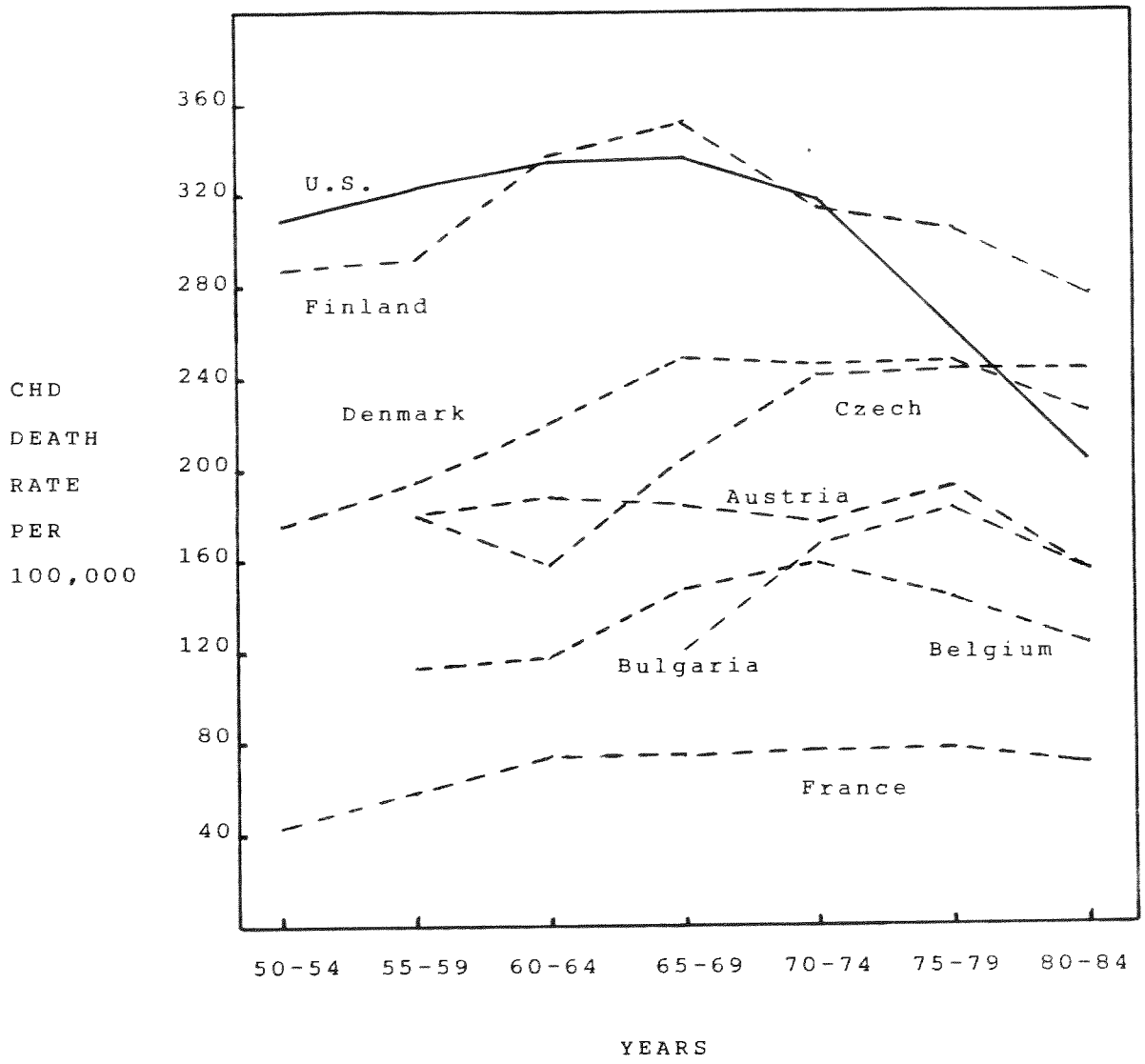

Figure 4-3. Age-standarized (world) male CHD death rates by year for the U.S., Finland, Denmark, Czechoslovakia, Austria, Bulgaria, Belgium, and France (adapted from World Health Statistics Annual, 1988 [3273])

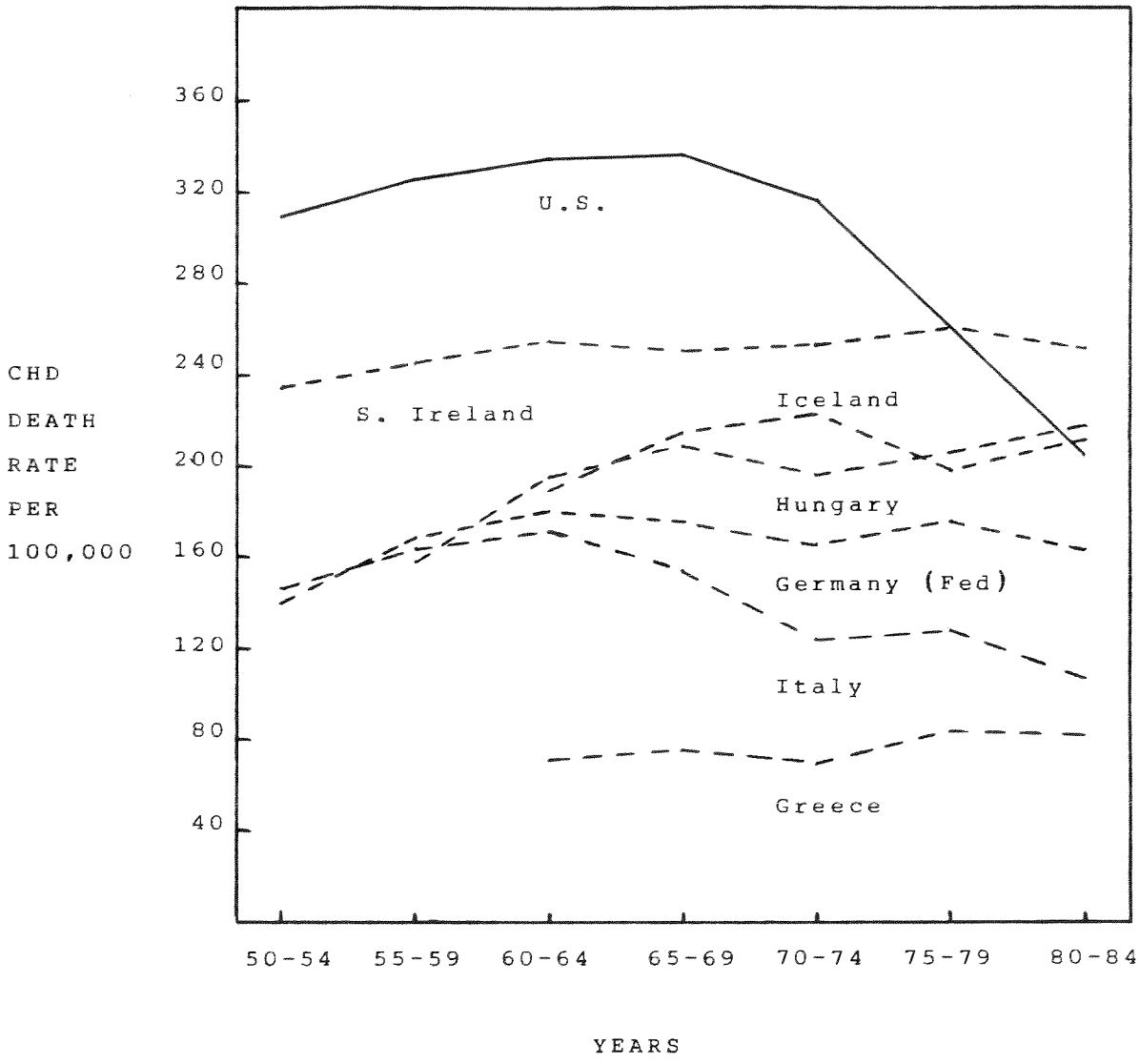

Figure 4-4. Age-standarized (world) male CHD death rates by year for the U.S., Southern Ireland, Iceland, Hungary, Germany, Italy and Greece (adapted from World Health Statistics Annual, 1988[3273])

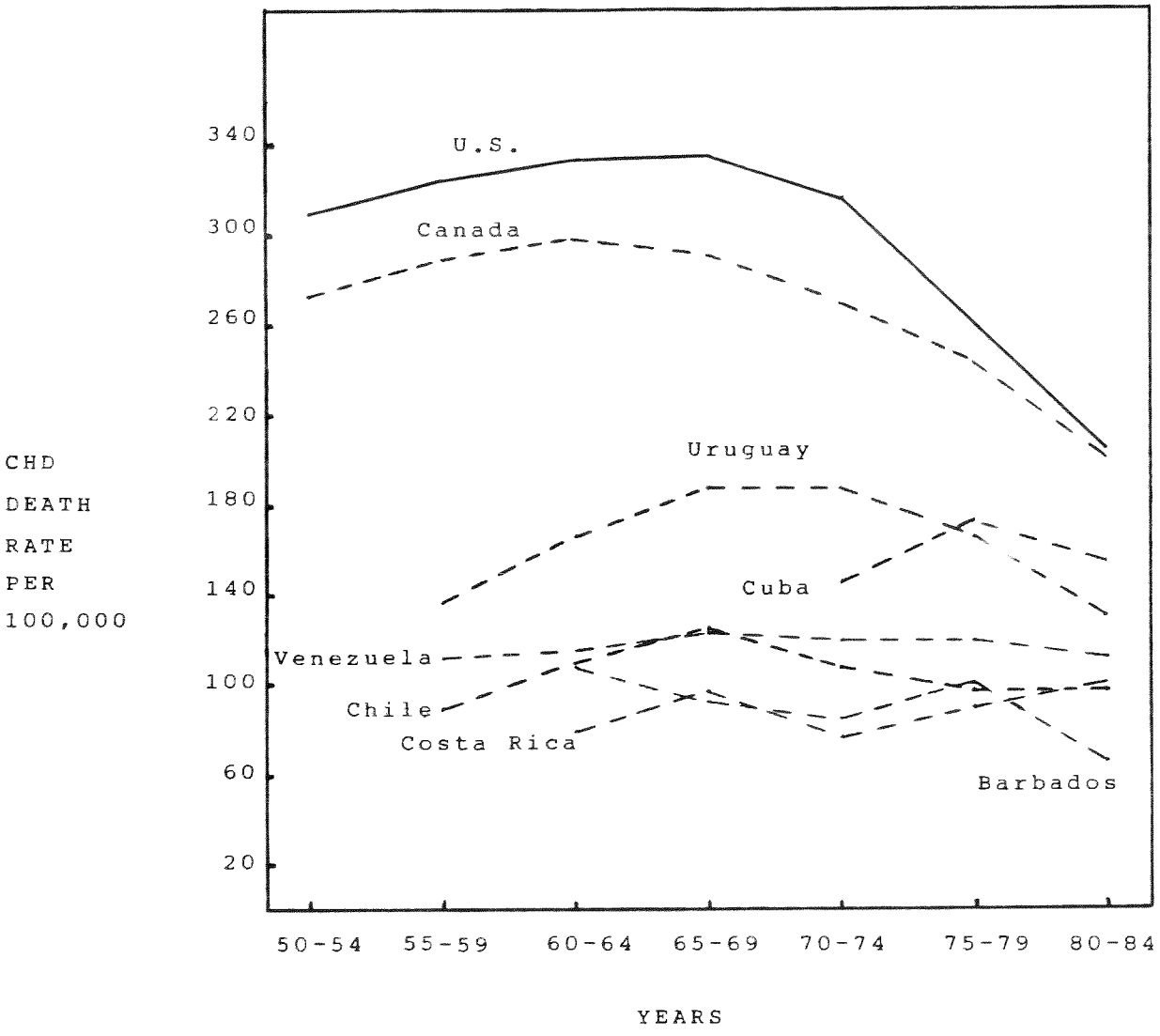

Figure 4-5. Age-standardized (world) male CHD death rates by year for the U.S., Canada, Uruguay, Cuba, Venezuela, Chile, Costa Rica and Barbados (adapted from World Health Statistics Annual, 1988[3273])

England/Wales and Scotland have shown gradually decreasing rates, with Scotland reporting significantly higher rates. There are no data in the literature that can adequately explain these unique trends and differences.

As will be discussed in detail in a following section, risk factor changes in Japan have correlated negatively with mortality trends and key risk factors in France are severe and yet mortality rates are very low.

There seems little doubt that much of the differences observed in rates and trends among countries was and is due to differences in diagnostic/death certification practices. Although the 1989 WHO annual[2797] admitted that "diagnostic fashions and the like will certainly affect the comparability of cause-of-death data," there was the suggestion that the reported rates and trends are generally valid. But in a 1987 WHO annual,[2840] there was greater emphasis placed on death certification problems. For example, it was stated that "...the much larger decline in IHD mortality [in the U.S.] suggests that some of the trend at least may well have arisen from internal reassignments within the heart disease group. ...the assertion that at least some of the rise in mortality from ischaemic heart disease in Southern and Eastern Europe is due to changing diagnostic and certification practices would seem to be supported by the data. Thus, in Romania, Spain and to a lesser extent Yugoslavia and Poland, the rise in ischaemic heart disease mortality is substantially greater than the rise (slight decline in Spain) observed for all heart diseases, suggesting that some transfer of deaths into ischaemic heart disease may have occurred."

The WHO annual continued elsewhere, "The comparability of patterns and trends of ischaemic heart disease mortality is certainly affected by differences in diagnostic practices among certifying physicians as well as the usage and precision of clinical, laboratory and autopsy findings. ...countries such as Poland, Romania, Yugoslavia, Spain and France report a relatively large proportion of heart disease deaths which are coded to non-ischaemic causes, which may well indicate a preference among physicians in these countries for less specific diagnoses other than ischaemic heart disease." In sum, while countries undoubtedly have different CHD mortality rates, the actual differences are probably no where near as great as reported statistics indicate.

Sex Differences. Figures 4-6 through 4-9 show the CHD mortality trends for males and females of the various countries. Two peculiarities are readily observed. First, with the exception of only Hong Kong (which is not, of course, a country), the differences in mortality rates between males and females were initially small or relatively small and progressively widened from the 1950s to the 1980s. Second, in most countries the rates for men increased during the 1950s and early 1960s; in a few, the rates remained relatively constant. Regardless, the rates for women either remained constant or decreased during that period. Only the rate of Norwegian females showed a consistent and significant trend upward during that period. These trends and differences again suggest diagnostic and death certification differences because they cannot be explained by "life-style" differences between the sexes.

Of no little importance is the fact that females worldwide did not participate in the so-called CHD "epidemic" which was most significantly launched by the 1949 ICD revision. Furthermore, if diet was an important risk factor, the CHD mortality trends among males and females would not be inconsistent because males and females typically consume the same diets within the same societies.

Life Expectancy. Figures 4-10 and 4-11 show the life expectancies of males 35-64 at age 65 for European, Americas, and Far East region countries for which both life expectancy[2797] and age-standardized CHD death rates[3273] were available. In addition to the fact that the life expectancy at age 65 in the U.S. is greater than the vast majority of European and Far East countries, only four countries had both higher

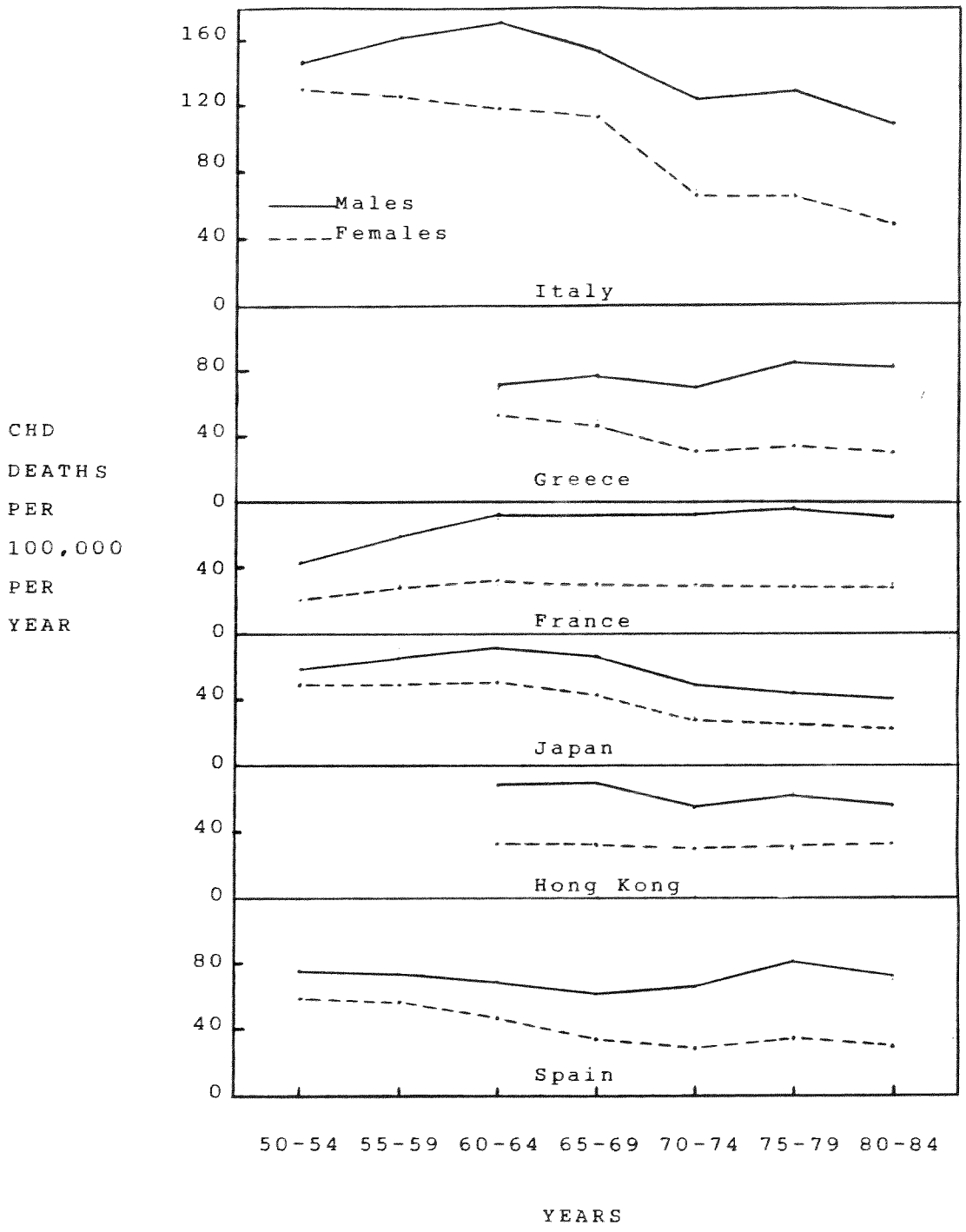

Figure 4-6. Age-standardized (world) CHD death rates by sex and year for Italy, Greece, France, Japan, Hong Kong and Spain (adapted from World Health Statistics Annual, 1988[3273])

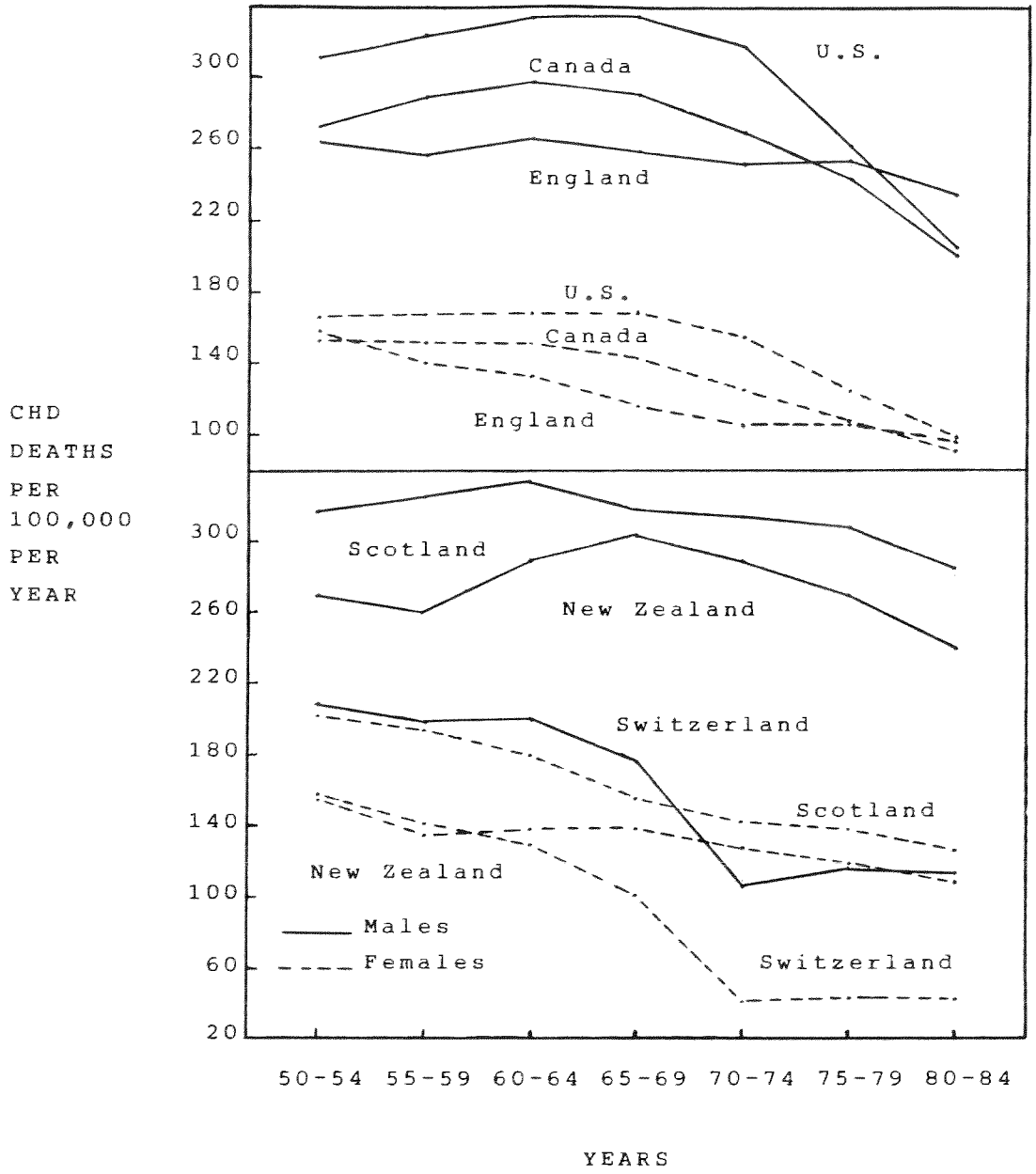

Figure 4-7. Age-standardized (World) CHD death rates by sex and year for the U.S., Canada, England, Scotland, New Zealand and Switzerland (adapted from World Health Statistics Annual, 1988[3273])

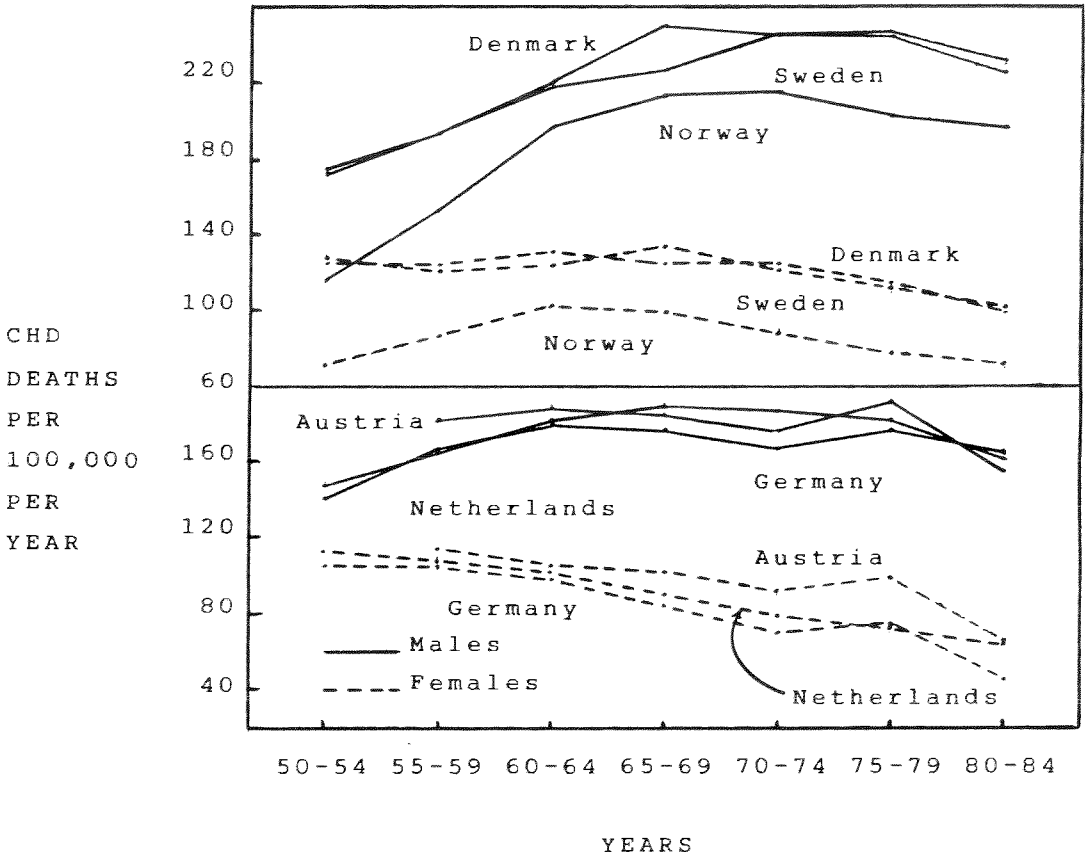

Figure 4-8. Age-standarized (World) CHD death rates by sex and year for Sweden, Denmark, Norway, Germany, Netherlands, and Austria (adapted from World Health Statistics Annual, 1988[3273])

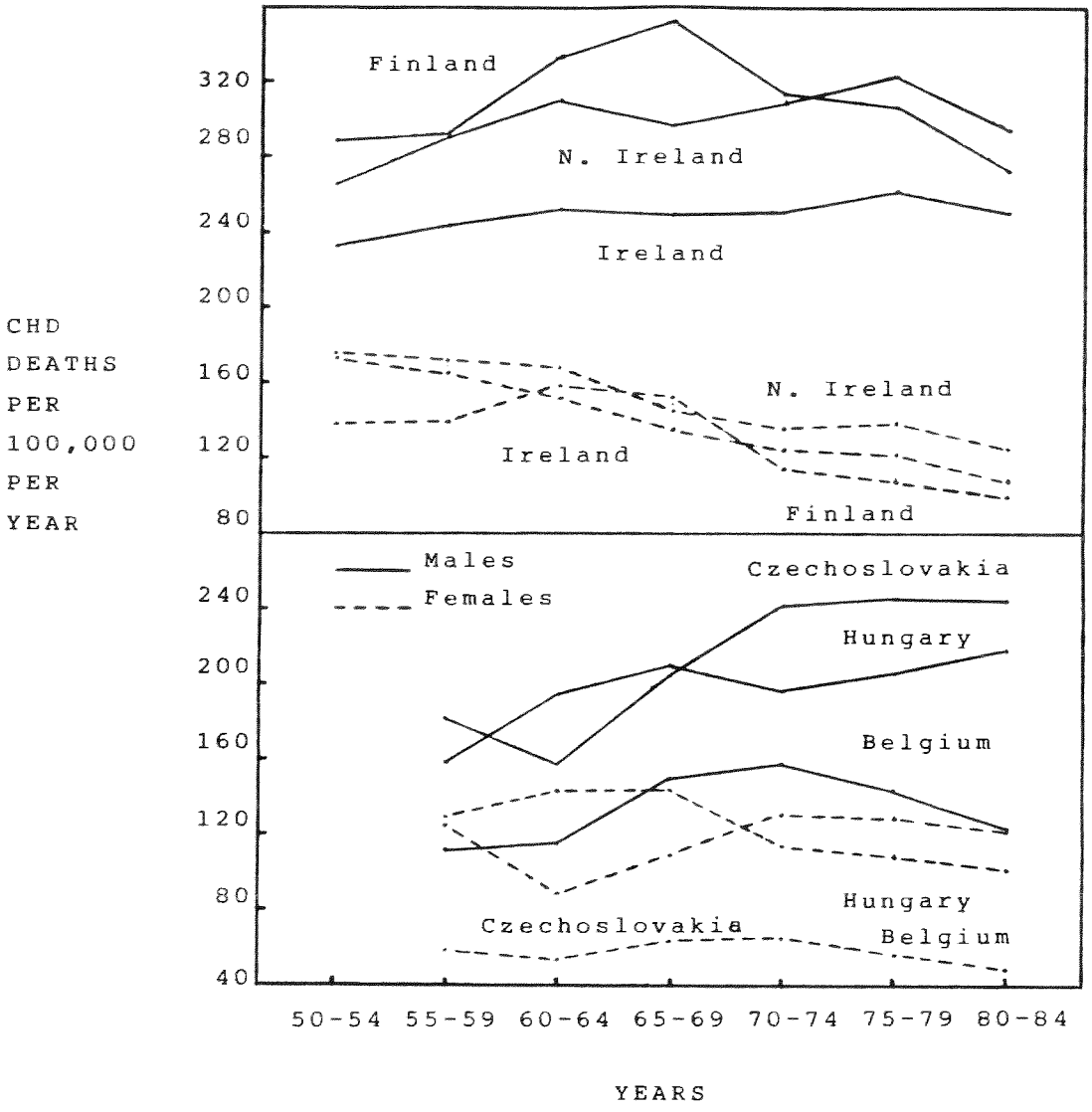

Figure 4-9. Age-standardized (World) CHD death rates by sex and year for Northern Ireland, Finland, Czechoslovakia, Hungary and Belgium (adapted from World Health Statistics Annual, 1988[3273])

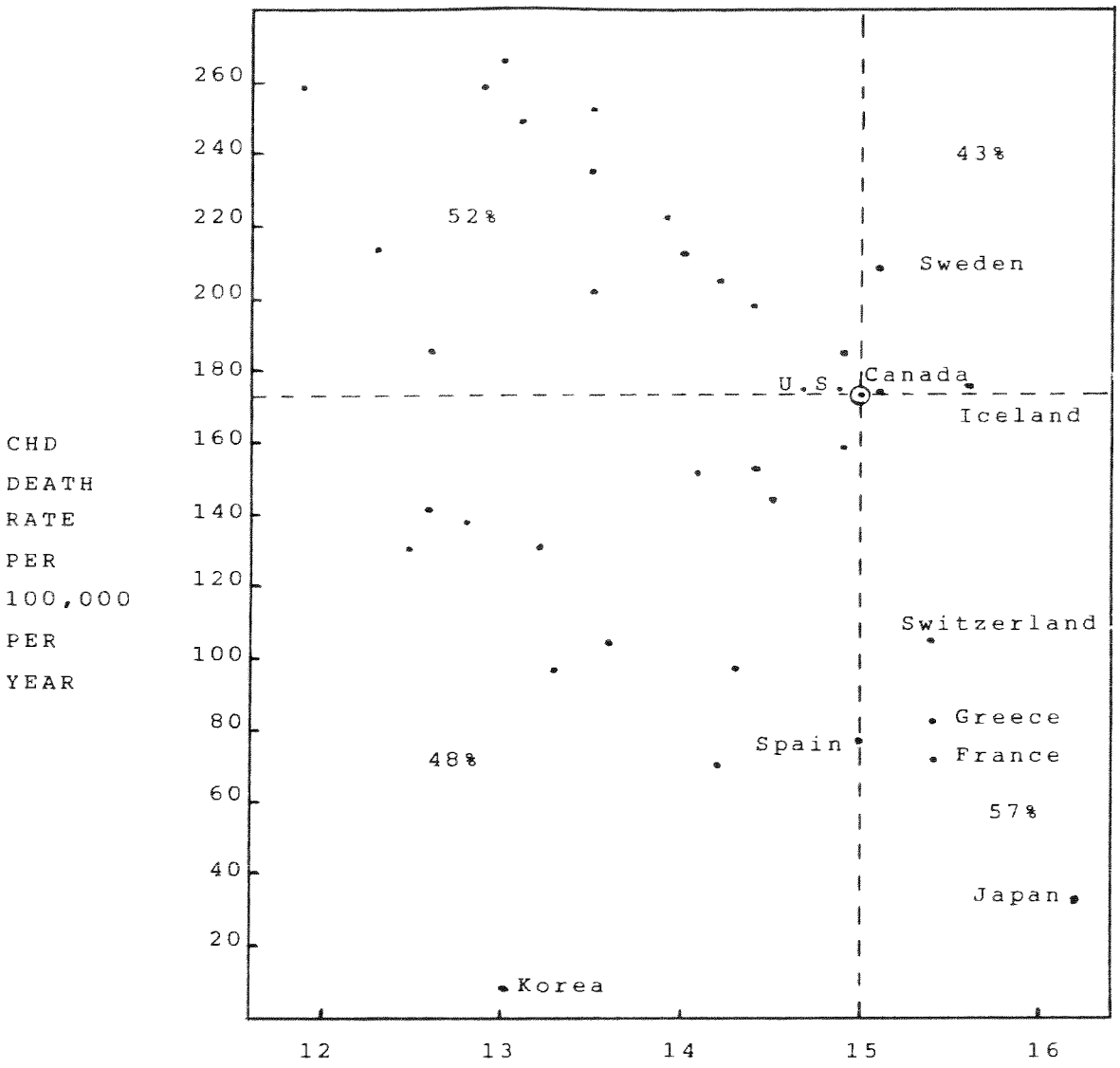

Figure 4-10. Life expectancy at age 65 by CHD death rate for males in the U.S. and 32 European and Far East countries (adapted from World Health Statistics Annual, 1988,[3273] 1989[2797])

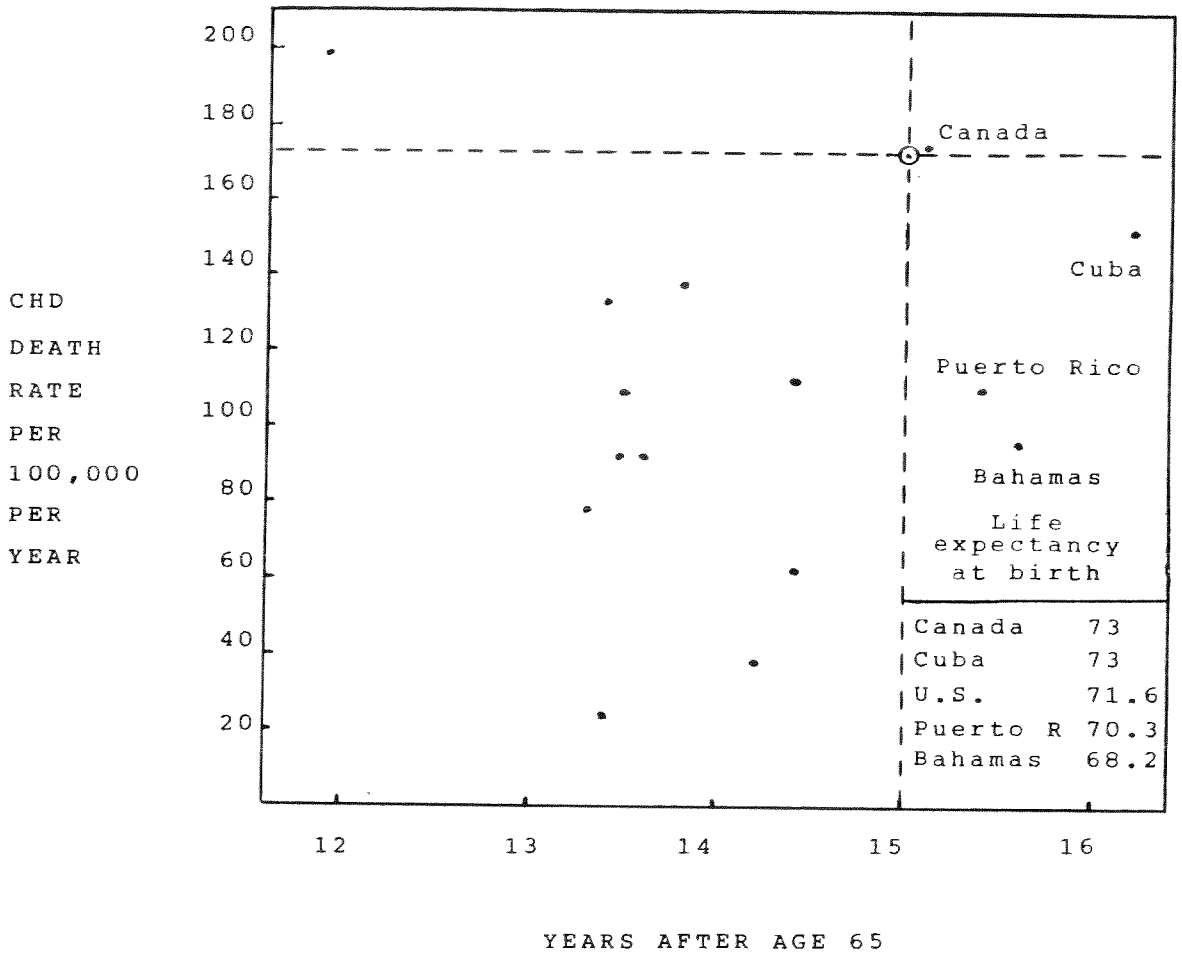

Figure 4-11. Life expectancy at age 65 by CHD death rate for males in the U.S. and 14 countries of the Americas (adapted from World Health Statistics Annual, 1988,[3273] 1989[2797])

expectancies and lower CHD mortality rates. As will be seen below, the males of three of these countries have a higher prevalence of cigarette smoking and higher blood cholesterol levels than do Americans. No risk factor data were obtained by WHO for the fourth, i.e., Greece.

For the region of the Americas, only three of the listed countries are purported to have life expectancies at age 65 that are greater than the U.S. and a lower CHD mortality rate. As has been emphasized elsewhere in these volumes, it is highly doubtful that any of these countries (U.S. and Canada excepted) record CHD deaths with an accuracy that is even remotely as accurate as the more economically advanced countries.

The MONICA Data. The MONICA project includes population samples of males and females between the ages of 35 to 64. In the 1989 WHO Annual the whole country mortality rates were compared to the rates obtained in the population samples of each country to determine whether they adequately represented each country.[2797] Subsequently, data from risk factor measurements, i.e., blood cholesterol levels, blood pressure levels and cigarette smoking prevalence were presented for the samples only. Not only are the MONICA data inconsistent with the risk factor philosophy, it will be seen that some key information is missing from certain countries which would have made the results even more inconsistent. Let us first address the mortality data.

The 1989 WHO Annual said, "The present analysis shows that, in most cases, the mortality observed in MONICA population [samples] reflects the country mortality very well, suggesting that contrasting mortality patterns within a country are not common. This is a most preposterous statement because not only are the differences between countries and samples and between samples rather substantial, it has long been known that there are large differences between regions within countries.

Table 4-1 presents the CHD mortality rates for each of the 26 countries and their respective MONICA samples for both males and females. The percent difference between country and sample ranged from -25.4% to +115.4% for males and the mean difference was 16.7%. The range for females was -35.3% to +62.8% and the mean was 10.3%. These differences can hardly be interpreted as "reflecting the country mortality very well." The discrepancies were substantial and exhibited themselves in all directions. For example, the samples greatly exaggerated the actual difference between the U.S. and Canada for males and greatly underestimated the difference for females. In some cases, the samples reversed the countries' rates, i.e., although the rate in Spain is greater than in France, the sample rate is lower than the sample rate of France. In effect, the sample rates were grossly inconsistent with whole country rates and it is absurd to state otherwise.

Two additional peculiarities were evident in the WHO data. The Japanese sample city was not named and the Iceland sample was called "Iceland" and its detailed data were identical to that listed under "whole country."

With regard to the "suggestion that contrasting mortality patterns within a country are not common," nothing could be further from reality. The fact that there were wide differences between whole country and sample CHD rates certainly indicates contrasting mortality patterns. Moreover, there were 12 countries listed in which two to five geographic samples were included. Eight and six of the countries showed radically different sample rates for males and females, respectively.

In effect, samples varied substantially within a country and the mean of the samples within a country varied substantially from the whole country itself.

Table 4-1

Comparison of whole country and MONICA sample CHD mortality rates[a] (World Health Statistics Annual, 1989[2797])

	Males			Females		
	Country	Sample	% Diff	Country	Sample	% Diff
Canada	187	222	+35	47	41	-12.8
U.S.	197	182	-7.6	61	48	-21.3
Belgium	131	101,166,180	+13.7	31	33,39,30	+9.7
Czech.	295	220	-25.4	73	48	-34
Denmark	199	195	-2.0	50	44	-12
Finland	317	296,357,456	+16.6	51	74,47,48	-10.5
France	79	78,102,105	+20.3	13	21,11,20	+33.3
Germ. Dem.	145	136,145,147 163,165	+11.3	35	49,30,40 35,44	+13.1
Germ. Fed.	164	151,153,170 176	-0.9	35	26,33,35 26	-14.3
Hungary	299	235,294	-11.5	82	86,71	+4.3
Iceland	206	b,c	--	39	b,c	--
Israel	159	169	+6.3	49	46	-6.1
Italy	115	92,122	-6.9	23	20,24	-4.3
Malta	184	c	--	51	c	--
Poland	219	172,180	-19.6	45	31,51	-8.9
Spain	89	68	-23.6	17	11	-35.3
Sweden	183	183,237	+14.8	35	40,41	+15.7
Switz.	112	103,114	-3.1	19	17,15	-15.8
U.S.S.R.	294	240,278,326 405,418	+13.4	85	40,70,80, 127,125	+4.0
N. Ireland	341	348	+2.0	93	88	-5.4
Scotland	336	380	+13.1	103	132	+28.2
Yugoslavia	143	308	+115.4	43	70	+62.8
Australia	197	159,231	-1.0	56	39,81	+7.1
China	c	49	--	c	27	--
Japan	29	33	+13.8	9	9[c]	0.0
New Zealand	246	231	-6.1	70	64	-8.6

a Age-standardized for ages 35-64.
b Listed as whole country, not sample.
c No data.
d City not named.

Figure 4-12 presents the male CHD mortality rates by blood cholesterol levels for 19 MONICA country samples. Blood cholesterol levels were apparently not measured for six other countries, i.e., Finland, France, Israel, Malta, Yugoslavia and Japan. Not only is it pointless to include these countries in the MONICA analyses without the most important data of all, cholesterol level, three of the countries are especially unique in having very low and very high rates of CHD mortalities. Iceland was also not included in Figure 4-10 because, as noted earlier, the sample data appeared to be, in fact, the country data.

With the exception of China, Figure 4-12 clearly demonstrates no relationship between blood cholesterol level and CHD mortality. Virtually all the remaining countries exhibited higher blood cholesterol levels than did the U.S. and yet 41% of those countries had lower CHD mortality rates.

Figure 4-13 plots the same blood cholesterol levels against the more accurate country CHD mortality rates. Iceland is now included, as is Japan and France whose blood cholesterol levels have been determined elsewhere.[2774,2790,2801] Now, all but China and Japan demonstrated higher cholesterol levels than did the U.S. and an equal number had higher and lower CHD mortality rates. As will be discussed in a subsequent section, the cholesterol level of Japanese has greatly increased over the last 20 years but its CHD mortality rate has decreased. All things considered, therefore, these data again demonstrate absolutely no relationship between cholesterol level and CHD mortality rate. This conclusion remains unchanged when a U.S. cholesterol level of 215 mg is used, reflecting a more accurate estimate of the U.S. male adult population.

Figure 4-14 duplicates Figure 4-13 for females. Again, with the exception of China and Japan, all of the remaining countries had higher cholesterol levels than did the U.S. and a disproportionate 68% had lower CHD mortality rates. Thus, these data argue even more strongly against the lipid hypothesis.

The MONICA data on cigarette smoking and blood pressure also show no relationship with CHD mortality for males and it is questionable whether the observed relationship between smoking and CHD mortality in females has any real meaning. The most relevant and simplified comparisons are those between the U.S. and the countries which yielded lower CHD mortality rates. With respect to males, 13 MONICA countries yielded lower mortality rates, i.e., Japan, China, France, Spain, Switzerland, Italy, Belgium, Yugoslavia, both German republics, Sweden, Malta and Canada. The 1989 WHO Annual indicated that 40% of American males smoke cigarettes and it failed to report the percentage of Japanese smokers. At the time of the risk factor measurements, the percentage of American male smokers was 32%,[2664] not 40%, and the percentage for Japanese males was a huge 70%.[2800,2801]

If we use the inflated WHO estimate of 40%, then a little more than half of the countries which had lower CHD mortality rates than the U.S. also had higher percentages of smokers. If we use the more accurate estimate of 32%, then all but Canada had higher percentages of smokers. In either case, cigarette smoking most certainly did not differentiate between the high and low CHD mortality rates.

The findings for American females were opposite to those for males. The 1989 WHO Annual listed 36.8% as the percentage of female smokers in the U.S. This figure is again inflated as reliable estimates place the percentage at 30%.[2800,2801] Even so, more American females smoke than the females from all but four MONICA countries. They also have higher CHD mortality rates than all but six MONICA countries. Of the six which had higher CHD rates, three had lower percentages of smokers. While these data are, of course, generally consistent with the risk factor

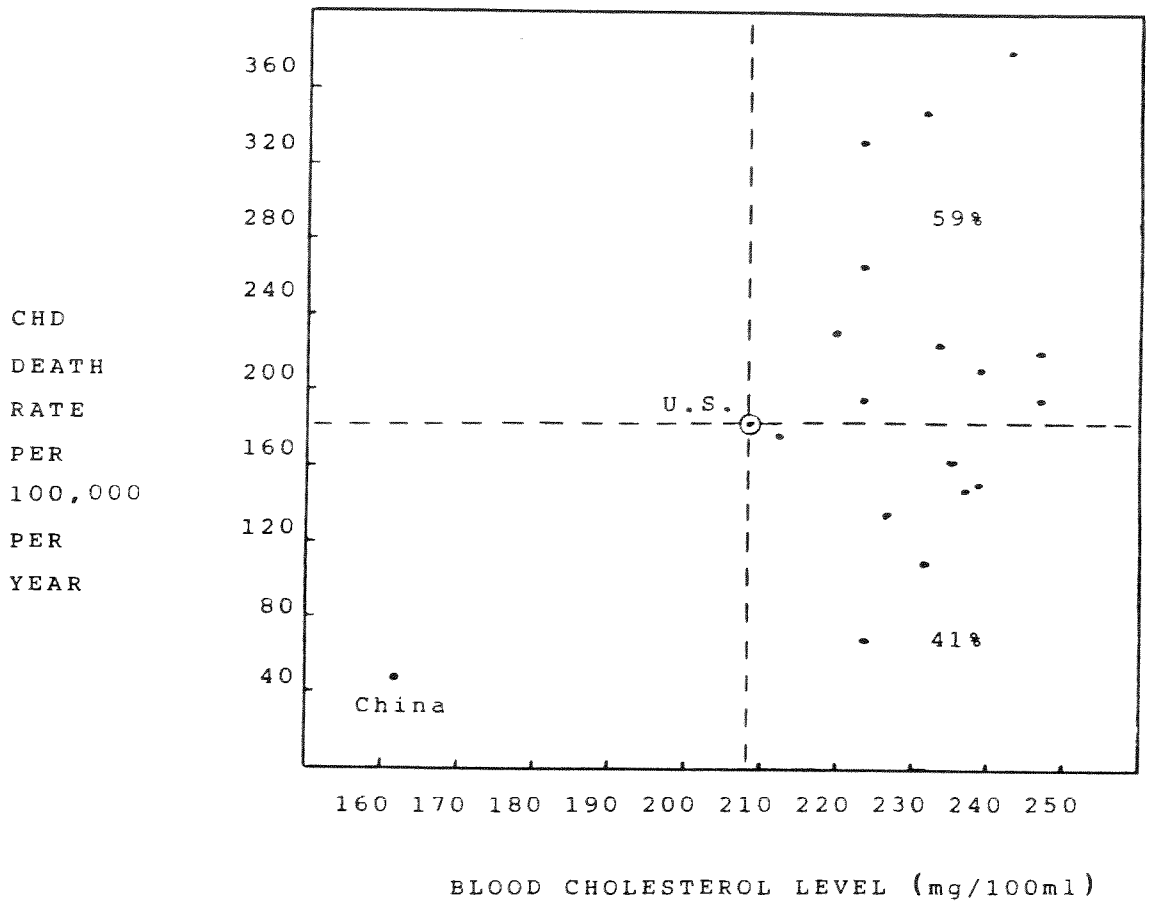

Figure 4-12. CHD mortality rates by blood cholesterol levels for 19 MONICA country male samples (adapted from World Health Statistics, 1989[2797])

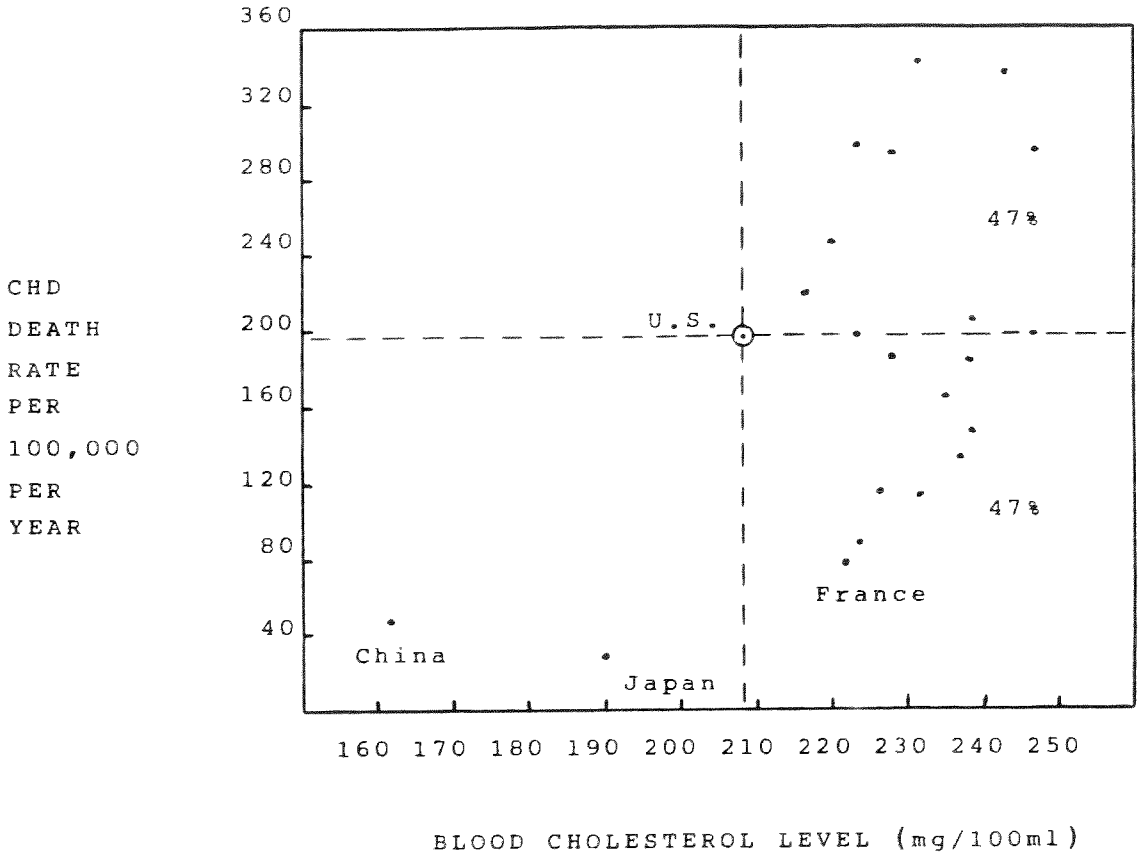

Figure 4-13. CHD mortality rates (whole country) by blood cholesterol levels for 22 MONICA country male samples (adapted from World Health Statistics Annual, 1989,[2797] Simons, 1989,[2774] Dolnick, 1990,[2790] Goto, 1985[2801])

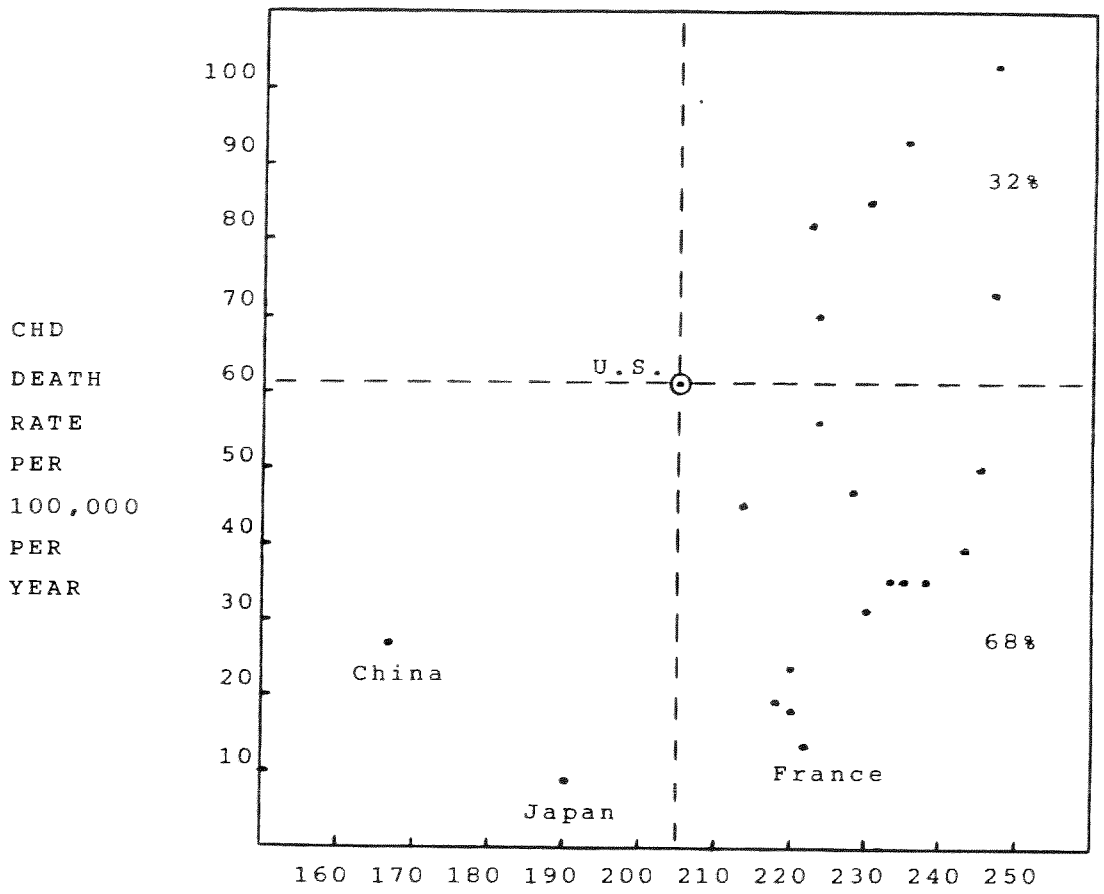

Figure 4-14. CHD mortality rates (whole country) by blood cholesterol levels for 22 MONICA country female samples (adapted from World Health Statistics Annual, 1989,[2797] Simons, 1989,[2774] Dolnick, 1990,[2790] Goto, 1985[2801])

concept, the learned reader by now recognizes that male findings are always deemed more important in view of their much higher CHD rates and that there frequently exist differences of this kind between the sexes. An overriding consideration is the fact that the CHD mortality rate has steadily decreased among females during the period in which female smoking increased. Trend data are vastly more relevant than a correlational slice in time, as will be seen below in the context of Japanese risk factor trends.

Of the 13 MONICA countries which had lower CHD mortality rates than U.S. males, only four had lower mean diastolic blood pressures (Spain, Switzerland, Belgium and Canada) and only two had lower mean systolic blood pressure (Spain and Canada). Moreover, only four MONICA countries had smaller percentages of males with diastolic blood pressures greater than 95 mm Hg (Spain, Switzerland, Belgium and Canada) and only one had a smaller percentage of males with systolic blood pressures greater than 160 mm Hg. These data again indicate very strongly no relationship between blood pressure and CHD mortality rate.[a]

The findings for females were much the same. Only six MONICA countries had lower diastolic blood pressures than American females and only two had lower systolic pressures. Furthermore, only seven and six countries had smaller percentages of females with diastolic and systolic blood pressures, respectively, greater than 95 mm Hg and they were smaller by only 1-3 and one percentage points, respectively.

In sum, the WHO data and, in particular, the MONICA data are clearly not supportive of the concept that cholesterol, blood pressure and cigarette smoking are important contributors to CHD mortality. Moreover, mortality trends do not correspond with risk factor change trends, where such data are available.

The following sections discuss a number of major populations in some detail which demonstrate trends and/or relationships inconsistent with the risk factor concept. Additional countries are subsequently reviewed as a group because they were all included in a special edition of a journal and biased interpretations were rampant.

The Japanese Model

The most frequent population comparison made by alliance members is that between the U.S. and Japan. The Japanese diet and reported low CHD mortality rates have been cited innumerable times as strong evidence supporting the diet-CHD hypothesis by such individuals as Levy,[1401,1846] Connor,[411,2436] Stamler,[539,561,1531] Glueck,[1136] Grundy,[499] Keys,[540,1082] Castelli,[1531] Naito,[1397] and Roberts,[788] as well as the AHA[517] and the American Health Foundation.[2634,b] But this support derives from inappropriate and incomplete analyses. For examples, consider the following statements:

"The fact that Japanese males have the lowest incidence of coronary artery disease among Western populations, despite a high prevalence of smoking and hypertension, perhaps illustrates the concept that low levels of plasma cholesterol are protective" (Witztum[2575]);

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[a] Blood pressures, like other risk factors, were not measured for the Japanese cohort but it is well known that hypertension is prevalent among the Japanese.

[b] Japan's Sakuta also maintained that Japan's low fat diet contributes to the prevalence of low cardiovascular rates but then stated that "malignant tumors, cardiovascular disease and stroke are the three cardinal causes of death in Japan."[2678]

"Fears of hazardous side effects of fat-modified diets appear to be unfounded since populations subsisting on Oriental and Mediterranean diets, which met the specifications of the recommended [Prudent] diet, are long-lived and have low CHD mortality" (Kannel and Stamler[1083]) [the fat content of the Mediterranean diet does not meet the recommended diet, being about 43% of calories[a]];

"Populations with low average serum cholesterol concentrations and low CHD morbidity and mortality, such as Italy and Japan, have higher life expectancy than the U.S. population" (American Health Foundation[2634]) [misleading, as will be seen];

"It turns out that the longevity of American men, once they reach 30, is among the lowest in the world. We have very poor life expectancy compared with the Japanese, Southern Italians, Portuguese, Greeks, etc." (Connor[2436]) [misleading, as will be seen]; and

"In Japan, CHD rates are low despite the fact that both cigarette smoking and hypertension are widely prevalent in the population" (Stamler[2635]). La Rosa[2396] and Leaf[2913] made almost the identical comment.

Table 4-2 presents principal life expectancy data of 1978 reported by Kannel, Stamler and their colleagues. Note first of all that Japanese men and women had life expectancies at birth of only 3.8 years and 1.3 years longer than American men and women, respectively. These are astonishingly small differences when it is recognized that (1) Japan has the lowest infant mortality rate in the world (5 per 1,000 live births) and the U.S. has one of the highest rates (10.1 per 1,000),[2647] and (2) Japan has essentially no poverty and excellent health care for its entire population, while there is widespread poverty in the U.S., with tens of millions of people having little or no health care and considerable malnutrition. Thus, not only is the life expectancy of Americans at birth only slightly lower than that of the Japanese, it achieves this level despite the lack of health care and massive malnutrition. In any event, the much greater infant mortality in the U.S. depresses the average life expectancy at birth but obviously has nothing whatsoever to do with the average American diet or any cardiovascular disease.

It should be emphasized that the U.S. proclivity toward the almost continuous acquisition of large numbers of (mostly) poor immigrants effectively assures a large poverty base, while Japan has essentially no immigration.

A second thing to note in Table 4-2 is that the initial life expectancy advantage of the Japanese progressively disappears with age. At age 65, after which most CHD mortality occurs, the life expectancy of males in Japan is a mere 7 months longer than in the U.S. and it is actually lower for females (10 months). This phenomenon is best illustrated in Figure 4-15 which shows the advantage in years of the Japanese (and Greeks and Italians) at birth and at ages 35, 45, 55 and 65. If the Japanese (or Greek or Italian) diet were protective against CHD and does extend life, the trends observed in Figure 4-15 would be increasing, not decreasing with age. That is an incontrovertible fact because the effects of diet are hypothesized to be accumulative over decades.

A third thing to note in Table 4-2 and Figure 4-15 is that the statements by Kannel and Stamler and the American Health Foundation regarding the Italian life expectancy are nothing less than fallacious. The Italian advantage is actually a disadvantage for women at all ages and for men beyond 45 years of age.

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[a] The 43%, cited by Keys,[282] contrasts with the average American diet of 37% and the Prudent diet's "less than 30%."

Table 4-2

A comparison of life expectancies at different ages between U.S., Japan, Greece and Italy, 1978 (adapted from Kannel et al.,1984[1083])

Males	0	35	45	55	65
U.S.	69.4	37.7	28.8	20.7	14.1
Japan	73.2	40.3	31.0	22.4	14.7
Greece	72.9	41.0	31.6	22.9	15.3
Italy	69.8	37.8	28.6	20.3	13.3
Females					
U.S.	77.3	44.4	35.1	26.5	18.6
Japan	78.6	45.0	35.5	26.3	17.8
Greece	77.6	44.8	35.2	26.0	17.5
Italy	76.1	43.3	33.8	24.8	16.5

Note: These data reflect 1978 values which is the period cited by many alliance members. Life expectancies at birth have increased in both the Japanese and American populations.[2683]

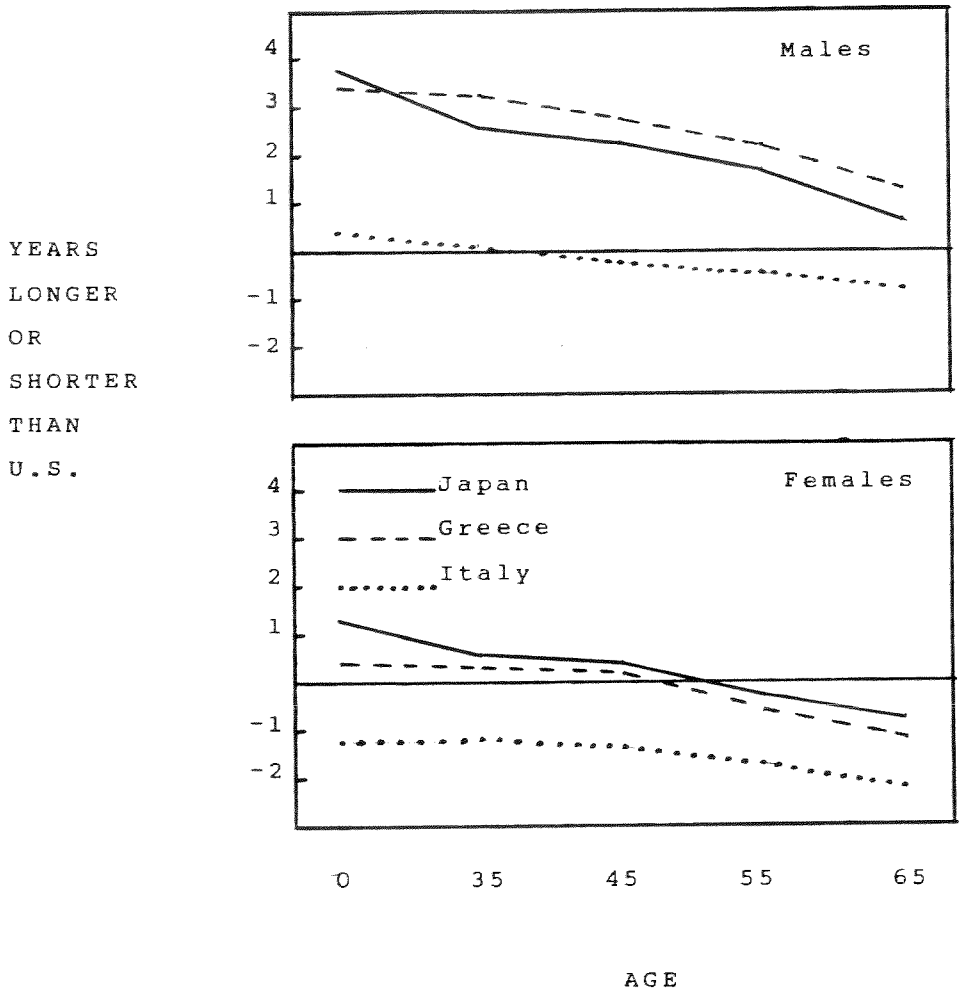

Figure 4-15. Years advantage or disadvantage of Japan, Greece, and Italy, relative to the U.S., at birth and ages 35-65 (adapted from Kannel et al., 1984[1083])

Finally, as is perfectly obvious in the figure, American women live longer than the women of Japan and Greece after age 45 and of the women of Italy at any age.

Not only do all of the data of Table 4-2 and Figure 4-15 provide strong evidence against the diet-CHD or diet-longevity hypothesis of the alliance, they actually provide evidence in favor of the American diet. The early life expectancy advantage of the Japanese, Greeks and Italians reflect better overall health care, while the decreasing trends thereafter reflect something other than health care because the overall health care systems in those countries remain intact, while medical care remains poor for millions of Americans, and other factors such as widespread malnutrition, homicides, and alcohol and drug addiction serve to reduce longevity among Americans. For example, a recent survey showed that 28% (63 million) of the U.S. population have no health insurance.[2812]

Let us now take a closer look at infant mortality and its influence on life expectancy at birth in the U.S. and Japan. Figure 4-16 shows infant mortality for the two countries from 1940 to 1980. As can be seen, mortality was far greater in Japan in 1940. However, it decreased rapidly thereafter, becoming superior to that of the U.S. by the mid-1960s. There are currently 500 more infant deaths per 100,000 live births per year in the U.S. than in Japan.

Figure 4-17 presents life expectancies at birth for males and females in the U.S. and Japan since 1900. Life expectancy was vastly greater in the U.S. in 1900 and maintained its advantage until the 1940s, after which Japanese life expectancy increased enormously. Life expectancies of males and females in Japan exceeded those of the U.S. in the 1960s and 1970s, respectively. Unfortunately, the United Nations data, from which Figure 4-16 and 4-17 derive, did not provide infant mortality and life expectancy data for the same years between 1940 and 1950, but the authors of that data made it clear that "The rapid increase in the expectation of life at birth in the early post-war years was closely related to the rapid decline in infant and child mortality."[2778] They cited Preston and Gardner's conclusion that income level was the single most important cause of the increase in life expectancy.

In sum, the life expectancy and infant mortality trends in the two countries demonstrate again that the superiority of the Japanese in longevity has nothing to do with diet. Although Kannel appears not to understand the significance of life-expectancy at adult ages vs life expectancy at birth, he did demonstrate such understanding much earlier in his career. In 1961 he said, "...no important reduction in morbidity and mortality from CHD has occurred. This is apparent in the relatively slight increase in life expectancy at age 40 which has been achieved in the past several decades, while life expectancy at birth has been substantially prolonged."[2093]

Considerable data are available which directly deny a relationship between diet and heart disease among the Japanese. For example, Levy[1806] and Levy and Feinlieb[1401] noted that the CHD mortality rate in Japan had decreased about 20% from 1969 to 1977 but made no mention of the fact that the Japanese diet had increased in the percentage of saturated and total fats. Kannel and Thom[1174] reported that the CHD mortality and diet trends in Japan were "anomalous," which is an anomalous way of saying that the trends were opposite to the diet-CHD hypothesis. Marmot and Smith[2595] also reported a CHD mortality decline in Japan from 1965 to 1986 but said nothing of dietary changes. Shimamoto et al.[1807] tracked a rural community of 7,030 persons in Japan from 1964 to 1983 and found no significant change in CHD mortality rates. (As will be seen below, Blackburn and Jacobs seemed to find their results most displeasing since they presented evidence against the lipid hypothesis.) Also using data

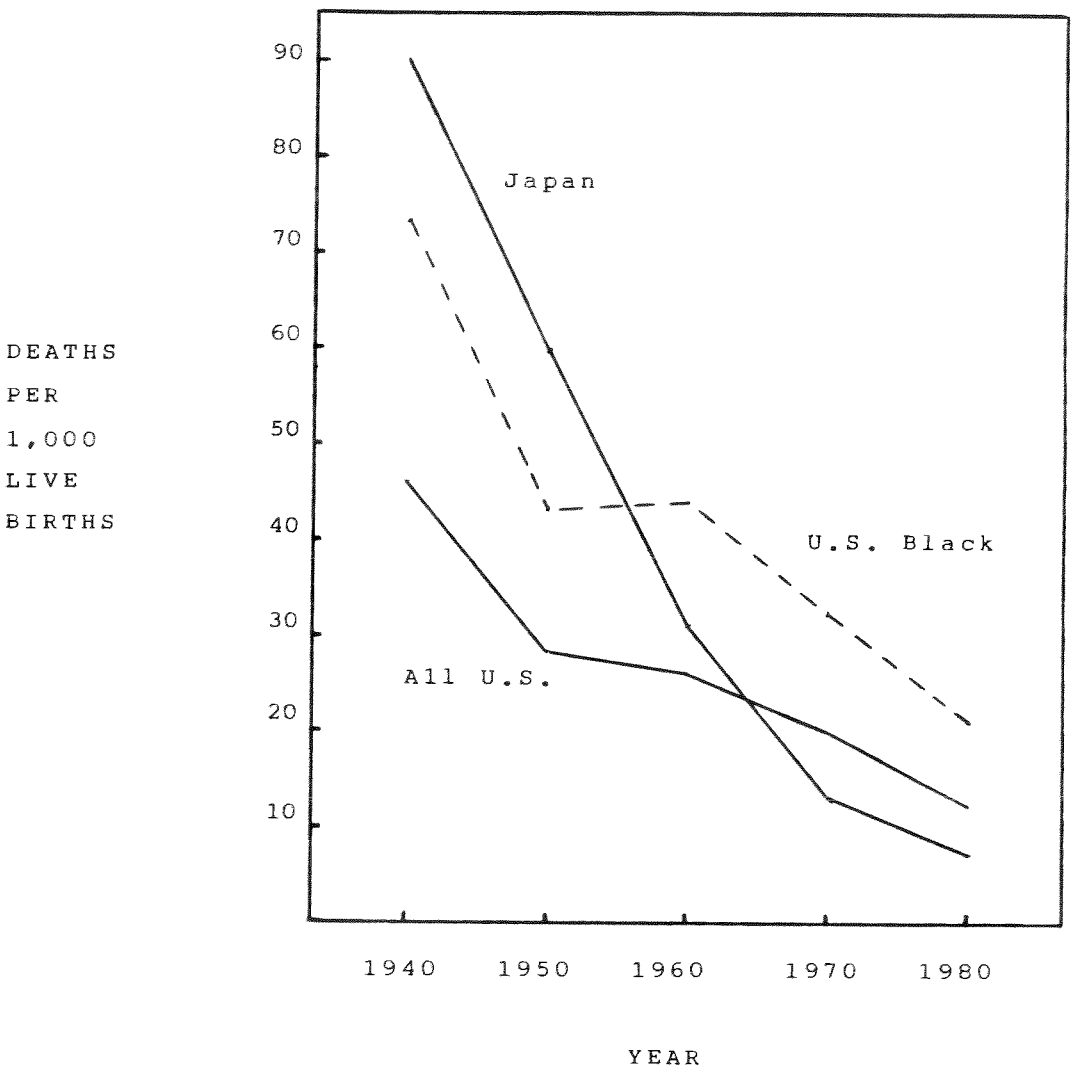

Figure 4-16. Infant mortality in the U.S. and Japan (adapted from the U.S. Public Health Service, 1989[2735] and United Nations, 1984[2578])

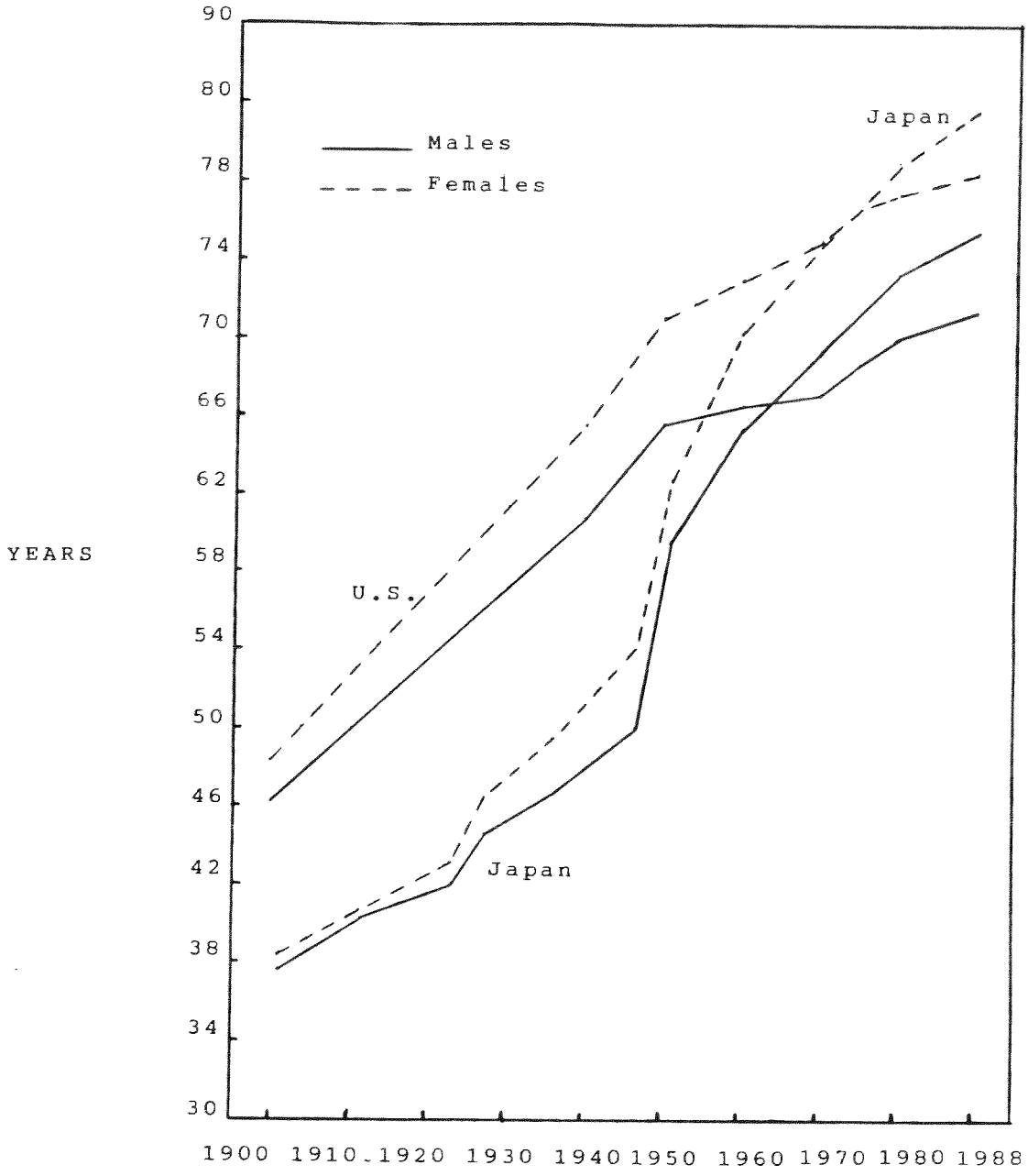

Figure 4-17. Life Expectancy at birth for males and females in the U.S. and Japan (adapted from U.S. Public Health Service, 1989,[2735] United Nations, 1984,[2578] Cimons, 1990[2683])

age-adjusted to the 1935 population, Kimura[3031] reported that CHD mortality "rates rose for those aged 70 and above but were unchanged or decreased for young and middle-aged groups" from 1960 to 1975.

Wen and Gershoff,[451] Keys et al.,[1082] Bidlock and Smith,[1771] Shimamoto et al.,[1807] Goto,[2801] Horibe et al.,[2800] and Kimura[3031] all reported relatively substantial increases in consumption of total fat, saturated fat and dietary cholesterol in Japan from the 1950s to the 1980s. Apparently the most recent study was the 1990 investigation by Lands et al.[2778] They reported that total fat and saturated fat increased from 11% to 25% and from 3% to 8% of total calories from 1960 to 1985. In noting that the Japanese diet was rapidly approaching that of the U.S., Lands et al. made a most peculiar statement, namely that "If valuable benefits are to come from a study of our diet differences, it must come soon--before the differences disappear." Could Lands et al. have missed the "valuable" information that has already derived from the Japanese people over the past 30 years, i.e., the fact that as the Japanese people transitioned from a high vegetarian diet to a more Western diet, their CHD mortality rate declined? What could be more decisive than that--especially since blood cholesterol levels have also increased rather substantially (Keys et al.,[1082] Shimamoto et al.,[1807] Leaf,[2682] Goto[2801]). For example, Goto[2801] cited surveys of large samples of Japanese. The first was conducted in 1961 by the Research Committee on Atherosclerosis in Japan. It yielded a mean blood cholesterol level of 176 mg (it was not reported separately for the sexes). A second survey was performed in 1980-81 by the Research Committee on Familial Hyperlipidemia in Japan. That survey obtained mean blood cholesterol levels of 190 mg for males and 192 mg for females. Thus, the Japanese levels apparently increased about 15 mg in a 20 year period. Goto and his colleagues obtained blood samples from smaller groups of males and females in 1983 and found mean levels to be 200 and 206 mg, respectively.

Apparently unhappy with Shimamoto et al.'s findings, Blackburn and Jacobs claimed that "neither the magnitude nor the duration of exposure to elevated atherogenic lipoproteins is as yet sufficient among the Japanese to be reflected in a major increase of coronary events."[1808] Such a statement is grossly inconsistent for several reasons. First, the alliance has repeatedly asserted that small differences in blood cholesterol levels lead to significant changes in CHD rates in relatively short periods (e.g., the 7.4 year LRC trial and the 5 year Helsinki II trial). Second, if long periods of time are necessary to cause changes, why, then, is the alliance encouraging the elderly population to sacrifice their desired foods and their money (for cholesterol-lowering drugs). Third, Blackburn and Jacobs ignore the fact that the Japanese CHD mortality rate has been declining for 20 years. Would they have readers believe that it takes more than 20 years of dramatic increases in consumption of fat and saturated fat to finally cause an acceleration of the atherosclerotic process? What of the studies by Blankenhorn and others who claim to have effected changes in one to two years?

The Blackburn and Jacobs statement was not even consistent with their own statements made subsequently in their article. For example, they said that "cholesterol levels were falling in the U.S., paralleling stroke decrease." Not only did the decline in stroke precede falling cholesterol levels by many years (Chapter 9) the magnitude of the reported (but dubious)[a] fall in cholesterol was only 2.8% and 3.6% for men and women, respectively, far less than that of the Japanese people. Thus, according to Blackburn and Jacobs, the effect of small blood cholesterol changes apparently have an immediate impact in the U.S. but large changes in Japan require more than 20 years.

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[a] See Chapter 3 of Volume 1 and the present volume for a detailed discussion of "falling" cholesterol levels in the U.S.

The left hand of the alliance ought to know what the right hand is doing. In 1988 NHLBI's Yusuf et al. reviewed 22 randomized trials and concluded that "a relatively short period of treatment in adult life can lead to an important reduction in coronary heart disease. A modest but more prolonged reduction in cholesterol level is likely, therefore, to lead to an important reduction in coronary heart disease..."[1594] It is certain that the Japanese experience is far longer than Yusuf's "short" or "modest" period of treatment and it is equally certain that the blood cholesterol increase of perhaps 20 to 25 mg is greater than the reduction seen in the U.S. population.

Leaf[2681,2913] recently also published a most misleading statement, i.e., "In Japan recently there has been an increase in fat intake, as its diet becomes more Westernized. This increase has been associated with an increase in the public's average cholesterol levels, which in turn has been associated with a rise in CHD." Leaf[2913] made a similar remark a year earlier. Note that Leaf said "CHD," not CHD mortality which has been decreasing. The rise in CHD in Japan, like the U.S., is unquestionably due to the aging of both populations, as well as increasing awareness of and diagnostic capabilities for detecting CHD. For example, Horibe et al.[2800] noted that the percentage of persons over 65 years in Japan was increasing at a greater rate than the total population.

Castelli[2955] presented a similar misleading statement, i.e., "apparently with a change in fat intake from 20 to 30 g 15 to 20 years ago to almost 60 g a day now in the metropolitan areas of Japan, coronary disease is on the rise." Thus, the logic of Castelli, Leaf and others is as follows: The CHD mortality rate in the U.S. is decreasing because fat intake is decreasing but the CHD morbidity rate in Japan is increasing because fat intake is increasing. They simply ignore the facts that CHD mortality is also decreasing in Japan and that morbidity is apparently increasing in the U.S. Also, Castelli suggests that an increase of fat intake in Japan to 60 g per day is sufficient to initiate an increase in CHD. If so, then the Prudent diet which he promotes should have no benefits since it has at least (30% of 2600 calories) 87 g.

The heart disease and stroke mortality rates in Japan, as reported in a United Nations[2578] report, are shown in Figure 4-18.[a] With the exception of the perturbation during the 1950s the heart disease death rate has remained almost constant from 1935 to 1960. As life expectancy among the Japanese reached the level of the U.S. around 1960 (Figure 4-17), their heart disease death rate initiated a gradual decline. One cannot help but suspect, therefore, that CHD mortality in Japan has always been under-reported and under-reporting may occur today as well. Three investigators have provided evidence of this likelihood, Keys, McMichael and Stehbens.

Commenting on the low CHD mortality rates observed for Japan in his Seven Countries study, Keys[1082] said, "A possibility concerns missed diagnosis in Japan, especially in such rural areas as provided the two Japanese cohorts in this study."

Another important factor which probably plays a role in Japanese vital statistics (as well as those of other countries) is that which McMichael[2435] referred to as "diagnostic fashion" before the 1977 U.S. Senate Select Committee on Nutrition and Human Needs. He said, "The medical profession in giving advice to patients is apt to

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[a] The report did not indicate whether "heart disease" represented all heart diseases or CHD. It is perhaps academic in view of the fact that the rate reported was so low it hardly matters.

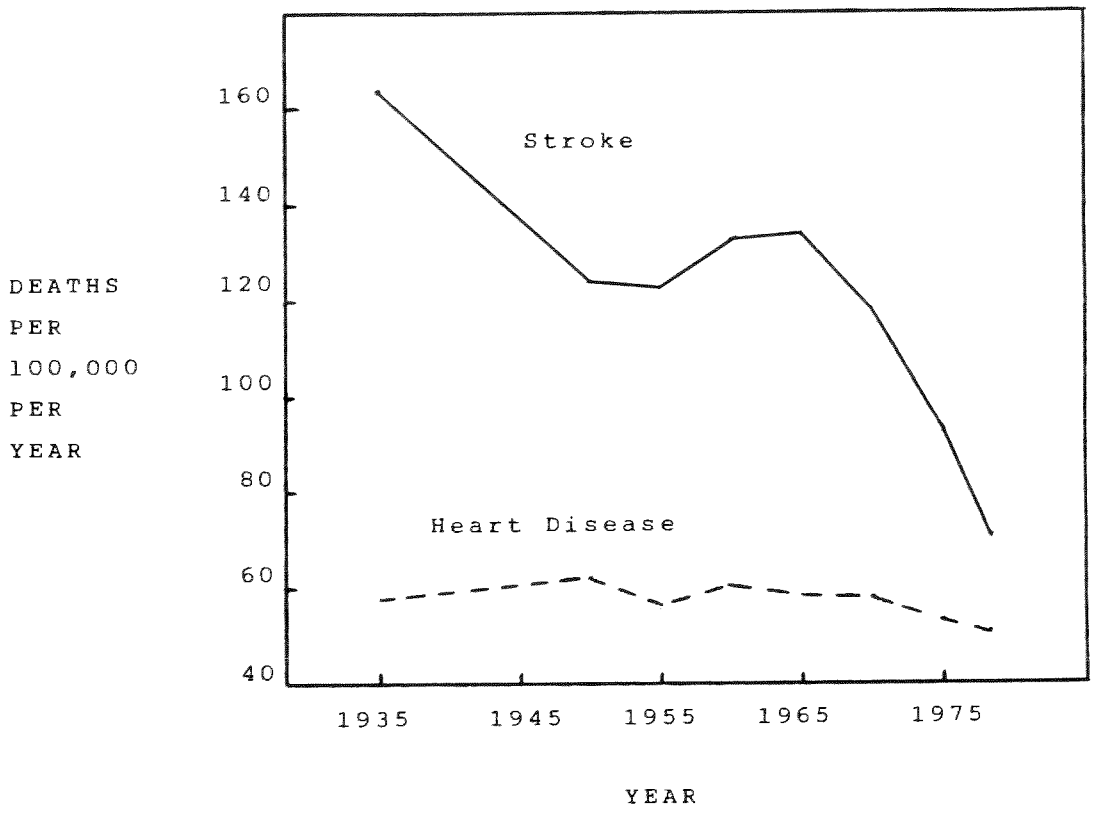

Figure 4-18. Age-adjusted mortality rates due to stroke and heart diseases in Japan (adapted from United Nations, 1984[2578])

follow fashions. I have been a doctor for 50 years this year, and I have seen all sorts of things come and go. If you had done a Gallup poll (such as has been conducted in Oslo[a] 15 years ago, as to whether doctors treated MI with anticoagulants, you would have had the same high percentage saying yes. And yet that effort has now faded out, it was dangerous and the results were problematic, and indeed often negligible. so the profession follows fashions and this is why you get an answer like this of considerable approval to what is for the moment a fashionable regime under trial."[2435]

For example, Stehbens reported in 1987 that "The high incidence [of cerebral hemorrhage in Japan] is now attributed to diagnostic fashion"[426] and speaking at the Cedars Sinai Hospital on March 28, 1989 Stehbens stated that "In Japan, death from cerebral hemorrhage was regarded as evidence of intelligence in the family. Death from heart disease was undersirable. Nearly 50% of death certificates were not signed by a medical practitioner. These figures were not verifiable as even today the autopsy rate is only 3%."[2190] Stehbens[3330,3331] also cited Kurtzke and Kurland,[3332] Kurland et al.[3348] and Carruthers[3333] as indicating the social desirability of having stroke on one's death certificate in Japan. (Interestingly, Kurtzke and Kurland published their comments in a 1970 NHLI document.) Carruthers emphasized that "In Japan, it has long been considered dishonourable to die of an affliction of the heart, but honourable to succumb to one affecting the brain. Thus, part of the apparently low incidence [of CHD] may be due to differential reporting of the causes of sudden death by physicians not wishing to cast dishonour on the family name." As will be seen later in this chapter, Japanese physicians certify deaths before examination of autopsy findings, indicating the desire to select a death of choice.

According to the 1988 World Health Statistics Annual[3273] the CHD death rate in the U.S. is five times greater than in Japan. If this difference reflected a true advantage, it would be reflected in a much higher life expectancy at middle-ages. But it is not. The only meaningful conclusions to be drawn, therefore, are the following: (1) either many CHD deaths are erroenously and/or purposely reported as stroke or other causes; or (2) the Japanese are genuinely dying more frequently than in the U.S. of diseases other than CHD, thus necessarily depressing CHD rates. Neither case represents a more favorable state-of-affairs in Japan than in the U.S.

In sum, the evidence supporting the Japanese diet as a protection against CHD or early death is not only thoroughly nonexistent, the available evidence actually leads to opposite conclusions. If one uses the alliance's "logic," which takes account of current life expectancy and ignores all factors influencing it, then one can conclude that (1) American males at age 65 will increase their life expectancy by 3.5 months by assuming a diet midway between the American and Japanese diets early in their lives and that (2) American women at age 65 will shorten their lives by 5 months with the same dietary change. If the reader finds this reasoning silly, he/she is unquestionably correct, but that is the level of logic employed routinely by the alliance. Rather than being a model for risk factor intervention, Japan actually refutes such intervention. Japanese males have cholesterol levels around 200 mg, represent the most prolific cigarette smokers in all developed countries[2800,2801] (70.1% of all males smoked in 1982), and have a high prevalence of hypertension.[2801]

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[a] Referring to a 1977 University of Oslo survey of some 200 physician researchers around the world which indicated that 99% of the researchers believed that there was a connection between diet and heart disease.

Other Models

France. While the alliance focuses attention on the current diet and CHD mortality rates in Japan and ignores trends, infant mortality and life expectancies at different ages, it ignores altogether the French population which completely denies the diet-CHD hypothesis. The French consume more fat, more saturated fat and more dietary cholesterol than do Americans and they have higher blood cholesterol (about 222 mg).[2774,2790] Cigarette consumption in France is also equal to that in the U.S.[2074,2790] Yet, CHD mortality in France is the second lowest among industrialized countries.[2790] As emphasized by Dolnick,[2790] Ducimetiere et al.[2818] and Tunstall-Pedoe,[1572] the low CHD rates are not due to inaccuracies in death certifications to any substantial degree. And while a French prospective study indicated that a blood cholesterol-CHD gradient existed in the French, the French population had a lower incidence of major CHD than the U.S. populations even after adjustment for known risk-factor levels."[2818,a] Dolnick asked the question, "If something in the French diet is protecting French hearts, why isn't France swarming with researchers trying to find out what's going on?"[2790] He cited Tunstall-Pedoe as replying that "Unfortunately, a national excess of disease is a greater spur to research than is a deficit." But such a reply was quite erroneous in view of the fact that the U.S. has expended considerable sums of money investigating innumerable populations with low CHD rates and has undertaken a very large study in mainland China in recent years (see below). But since France provides considerable negative evidence linking fat, saturated fat and dietary cholesterol with CHD, it is simply ignored like hundreds of other "anomalies." Investigation of the French "lifestyle" would be an acceptance of negative evidence and an admission that something other than diet was the primary cause of CHD.

It is true that there is a relationship between blood cholesterol level and CHD rates in France but just as such relationships in the U.S. are weak and reflective of only a small percentage of the population, the relationship observed in France is equally weak. The most important consideration by far is the fact that the French diet is everything opposite to that espoused by the alliance and the French CHD mortality rate is everything desired by the alliance. One further item of interest is the observation by Tunstall-Pedoe[1572] that CHD rates are higher among the upper classes in France than among the lower classes. As will be seen below, the opposite observation was reported by Campbell for mainland Chinese.

China. A major epidemiologic study of mainland and Taiwan Chinese is in progress and a large monograph of results thus far has apparently been published. This writer has found one journal article and four nonjournal articles addressing the study and they leave a great deal to be desired with respect to consistency and accuracy. For example, in her discussion of the China study, Anne Moffat's[2793] article in Science in 1990 was replete with errors and/or misleading statements. She said that "In a typical U.S. diet, animal fat provides 40% to 45% of the calories." Even total fat, let alone animal fat, does not exceed 37%. Roberts[3344] said that total fat consumption in the U.S. represented 40% of calories.

The one journal article, published in 1990, was co-authored by T. Colin Campbell.[3319] They emphasized that "Within China neither plasma total cholesterol nor LDL cholesterol was associated with cardiovascular diseases." Furthermore, "The results indicate that geographical differences in cardiovascular disease mortality within China are caused primarily by factors other than dietary or plasma cholesterol." Note

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[a] The strength of the French gradient was not presented by Ducimetiere et al.[2818] but it is probably no stronger or meaningful than that observed in the U.S.

that since blood cholesterol level was not associated with these diseases, it follows that fats and animal fats were irrelevant because their importance lies in their association with blood cholesterol levels.

Campbell was the author of two nonjournal articles published in 1989.[2791,2792] He indicated that "intakes of nutrients were obtained over a 3 day period by directly measuring food consumption for the entire household, then calculating intakes with the use of Chinese food composition tables. The problems of seven or fewer day diet records are discussed elsewhere and will not be repeated here. However, the reader should keep them in mind in the following discussion.

Cholesterol levels in mainland China were said to range from 88 mg to 165 mg. Campbell reported that CHD "risk in China continues to decline to an almost negligible level when plasma cholesterol levels are low." Moffat[2793] cited Campbell as saying that "...there is no threshold of plasma cholesterol below which CHD mortality is constant." Note that these statements are in distinct contradiction to those made in the journal article discussed above, published two years later.

Apparently the "major" finding of the China study, according to the nonjournal articles, was a correlation between meat consumption and CHD, essentially identical to that observed in the many between population studies performed many years earlier. Campbell concluded that "a diet rich in protein, particularly animal protein, may have the greatest potential for enhancing risk for these [CHD, cancer and diabetes] diseases."[2792] In addition to the fact that the alliance now seems to be placing protein, as well as fat, on the forbidden list of nutrients (it is doubtful that coronary arteries differentiate between animal and plant protein), Campbell's correlation between meat consumption and CHD is equally as confounded as were the many between population studies before it. Meat is the luxury of the wealthier classes and the wealthier classes enjoy greater access to physicians and hospitals and, therefore, more accurate diagnosis of diseases. Campbell noted that CHD rates were higher in the "industrially developed areas with greater income and literacy" but did not address the death certification accuracy issue. In view of the immense Chinese population and the low standard of living, it is doubtful that most deaths in rural areas were directly certified by physicians. Thus, Campbell and his colleagues were likely dealing with CHD mortality statistics generated by medically untrained individuals. And even if all deaths <u>were</u> certified by physicians, it is not likely that more than a very small percentage of deaths in rural areas were diagnosed correctly because the vast majority of deaths undoubtedly occurred outside of hospitals and without prior exposure to physicians.

In a third nonjournal article, Campbell[3320] indicated that "Average cholesterol levels at our survey sites in China ranged from about 100 to 200, although other data show much higher levels for Chinese individuals living in urban areas. But even in the 100-to-200 range, the higher their cholesterol, the greater their risk of heart disease..." Not only does this statement contradict the journal article, the range of blood cholesterol levels reported (100-200 and "much higher levels") was quite different than expressed earlier, i.e., 88 mg to 165 mg, or at a 1988 Senate hearing, according to Roberts,[3344] i.e., 90 to 175 mg.

One can only wonder how Campbell can contradict himself so profoundly on such important issues on a single study within so short of time. Nevertheless, one must accept the journal article over the nonjournal articles and thus, one must conclude that blood cholesterol, ergo fats and cholesterol, were not related to cardiovascular diseases. However, it is humorous to note that the emphasis on "no thresholds" in the nonjournal articles indicates tht CHD is still present at cholesterol levels of about 100 mg. If such a state-of-affairs was true, it reduces the angiographic studies (Chapters

6 and 7) to silliness since they purport to show regression at cholesterol levels of 200 to over 300 mg.

Moffat cited Bruce Ames as indicating that "China is the perfect place to do epidemiology."[2793] Such a statement is impossible to accept for three reasons. First, Japan is a far superior country "to do epidemiology" because it is vastly more advanced, unquestionably has far more accurate vital statistics and has greatly altered its diet over the last 20 to 25 years. There is an abundance of data already available to evaluate the diet-disease relationship, whereas trends in China will be exceedingly slow because the increase in standard of living (and changes in diet) will be exceedingly slow.

Second, for reasons already indicated earlier, France is a superior country "to do epidemiology" because it seems (according to the alliance) to be doing all the wrong things and getting all the right results.

And third, there are wide differences in heart disease mortality rates among the 9 major regions (and indeed among the 50 states) within the United States.[2736] What is the purpose of conducting a large study of individuals from different regions of China or any other country when epidemiologists can compare the diets of inhabitants of say, the Middle Atlantic region with the Mountain region, having mortality rates of 388 and 219 per 100,000, respectively, or Pennsylvania with Alaska or New Mexico, having mortality rates of 405, 89 and 193 per 100,000, respectively? Clearly, the alliance does not really believe that these rate differences are associated with dietary differences. Otherwise, NHLBI/AHA would surely conduct between region or state studies.

It is submitted that investigations of regions within China cannot produce any more useful data than studies of regions within the U.S. They both have the same major problem, namely that different regions have entirely different capabilities to compile accurate cause of death statistics. If a medical diagnostic examination were given to a group of physicians, a group of nurses, a group of physiologists, and a group of chemists, would the reader believe that each would score equally well on the exam? Similarly, if such an examination were given to a group of Beverly Hills physicians, a group of Burgaw, North Carolina physicians, a group of Santa Rosa, Guatemala physicians and a group of Foping, China physicians, would the reader believe that each would score equally well on the exam? If not, how can anyone take seriously studies which compare the diets and CHD rates among regions of China which vary in terms of prosperity, medical sophistication and frequency of exposure to physicians?

As noted by Kesteloot et al.,[2168] "the very low prevalence of myocardial infarctions in the People's Republic of China is generally acknowledged, but precise and objective data are difficult to obtain." Also, like Japan the stroke mortality rate is extremely high in China[2744,2819] which provokes two considerations. First, the alliance maintains that diet and blood cholesterol levels are associated with all cardiovascular diseases. Clearly, high stroke rates in China and Japan discredit the notion that high cholesterol levels are related to stroke. Second, there is the suspicion that stroke is, to a large extent, the fashionable and desired way to die (on certificates) in China, as well as Japan. In any event, as enunciated by Shi et al.,[2819] "Epidemiologic evidence has consistently linked low total serum cholesterol levels with intracerebral hemorrhage in Japan, the People's Republic of China, and more recently in North America."

India. Malhotra and Majumbar[2275] indicated that Indians in India have lower CHD rates than Europeans, while Indians in Britain have higher rates than Europeans and strangely attributed such differences to diets. Even if the Indians completely adopted

the British diet, what logic would suggest that their CHD rates would be three times greater than white Englishmen, as reported by Reaven.[2789]

The low reported CHD death rates in India are not surprising because virtually all poor countries have low reported rates. It is doubtful that more than a small percentage of deaths in India are directly certified by physicians or medically trained personnel. It is doubtful that anyone has any idea of the true CHD mortality rates in India or dozens of other poor countries.

Attributing the high CHD mortality rates of Indians in Britain to diets is emphatically quashed by the fact that they have lower blood cholesterol levels, lower intakes of saturated fat and lower smoking rates than white Englishmen.[2789,3147] Reaven maintained that these Indians were best described as exhibiting "syndrome x," having one or more of the following characteristics: a higher incidence of noninsulin-dependent diabetes mellitus, lower levels of HDL, high triglycerides, central obesity and hypertension, relative to white Englishmen.[a] However, this theory is dubious for at least three reasons. First, how does one explain that Indians with very low CHD rates suddenly contract "syndrome x," and high CHD rates after moving to England, particularly as their diets remained more similar to their homeland than to England's? If "syndrome x" characterizes Indians in England, it should also characterize Indians in India, unless one can prove that only a genetically unique set of Indians move to England.

Second, as will be seen below, "syndrome x" appears to have the opposite affect on Mexican Americans.

And third, one cannot legitimately set aside the fact that the Indians in England have fewer major "risk factors" and consume less of the alliance's proclaimed most dangerous food, saturated fat, and explain the contradiction with a contrived "syndrome x."

Certainly one reason why the Indians in England have higher CHD rates than Indians in India is because of the higher standard of living in England. India has one of the lowest life expectancies among major countries and it is logical to assume that Indians would live longer (and thus increase the frequency of CHD) in a country with more food and better health care. Moreover, one would naturally expect the superior health care system in England to increase the apparent CHD rate among Indians via more accurate death certifications. However, this explanation cannot account, of course, for the presumed fact that the CHD rates of Indians in England are much higher than white Englishmen.

Scotland. Da[2593] cited the Scottish Heart study of 10,359 men and women from 22 geographically different districts. Although blood cholesterol levels were high in all districts, they were not related to standardized mortality ratios which varied from 51 to 136. Although Da attributed the high rate of CHD to the prevalence of high cholesterol levels, he simultaneously noted that the CHD mortality was declining in Scotland, a fact inconsistent with the high cholesterol levels.

Mexican Americans. In 1990 Mitchell et al.[2460] reported findings from the San Antonio Heart study and indicated that Mexican American men have lower cardiovascular mortality rates than non-Hispanic white men, even though their total cholesterol levels are slightly higher, their HDL levels are lower and they have higher prevalence of diabetes mellitus, obesity, hypertension and smoking, essentially the

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[a] But, according to Reaven, "not all patients have every abnormality."[2789] Thus, "syndrome x" could characterize many populations besides Indians living in England.

"syndrome x" profile. Mexican American women demonstrated similar profiles with the exception of having a low rate of smoking. Because the percentage of diabetes was about 2.5 times greater among the Mexican American men and women and because Mexican Americans historically have consumed high carbohydrate diets, there seems little doubt that the latter contributed to the former. In any event, essentially nothing in the San Antonio Heart study conforms to the alliance's risk factor concept.

Switzerland. Kannel and Thom[1174] observed that CHD mortality decreased 13% and 40%, respectively, for men and women in Switzerland between 1951 and 1976, despite the fact that the consumption of animal fats per capita increased by 20%. Kannel and Thom also noted that smoking increased among women and remained constant among men during that period.

England. It was mentioned in Volume 1 that there was no change in blood cholesterol levels in England during the last 12 years, although CHD mortality decreased significantly.[1409,1454] Morris added the fact that saturated fat consumption decreased from 50.9 g to 40.6 g to 14.3 g per day during that period. And Kannel and Thom[1174] also indicated that cigarette smoking declined during that period.

Greece and Yugoslavia . Keys[2839] indicated that his surveys showed that the diets in Greece and Yugoslavia were low in saturated fats and cholesterol in the late 1950s but increased "dramatically" thereafter. In the short period from 1960 to 1970 blood cholesterol had increased from 205 mg to 235 mg in Greece. Despite the so-called atherogenic trends, the WHO data presented earlier clearly show that CHD mortality trends in these countries have been sharply downward since 1960, consistent with the trends in Japan.

Aravanis et al.[2951] also compared the Seven Countries cohort in Crete in 1960 with a similar group in 1982. Cholesterol level increased from 203 mg to 214 mg, the percentage of smokers increased from 57% to 74% and body fatness increased "strikingly." Aravanis et al. concluded that "there is nothing in the risk profile of these middle-aged men to suggest that they are at low risk for CHD."

Denmark. Figure 4-3 showed that the CHD mortality trend in Denmark was quite low in 1950 and then sharply increased until the late 1960s, after which it remained almost constant for 15 years. The CHD rate in 1950 was a little more than half of that of the U.S. in 1950 but surpassed the U.S. by 1980. How real are these trends and how do they reflect dietary changes?

It is sometimes said by Danes themselves that the Danish people live to eat, rather than eat to live. The present writer has experienced the Danish diet in homes quite distant from one another. It appears to be a diet far richer in fats, saturated fats and cholesterol than that of the U.S. In fact, former NHLBI director, Theodore Cooper,[2688] acknowledged that in 1975 Denmark exhibited about half the CHD mortality rate as that of the U.S., although Danes consumed more calories, more fat and saturated fat than did Americans. Why, then, has the Danish CHD mortality rate been constant from the late 1960s to the late 1970s and then been decreasing since that time?

With regard to the CHD "epidemic" in Denmark from 1950 to the late 1960s, Keys[540] pointed out that "Even in such a medically sophisticated country as Denmark, a study of autopsy findings in the late 1950s indicated that CHD deaths were under-reported in the vital statistics by some 30 to 40%. If one adds 40% to the 1950 mortality rate, one can account for virtually all of the "epidemic." Keys stated that under-reporting had also occurred in other countries such as Norway. Indeed, as was emphasized in Chapter 3, under-reporting was unquestionably the major reason why

CHD mortality rates appeared low in many countries and then appeared to increase in epidemic proportions as knowledge, diagnosis capabilities and fashions changed.

Eskimos. Volume 1 addressed the notion that primitive Eskimos have high fat diets and low CHD mortality rates and it was concluded that Eskimos rarely live long enough to contract overt CHD and that cause of death statistics associated with Eskimos are highly dubious. In this light it is interesting to review an inconsistent 1990 statement by Middaugh and then note the comments made by Keys in the 1950s and then again in 1973.

Middaugh[2569] examined 13,534 Alaskan death certificates from 1980 to 1986. He reported that Alaskan natives had a lower age-adjusted CHD mortality rate than other Alaskans (162 vs 242 per 100,000) but a much higher death rate from other causes (954 vs 619). He concluded that "These suggest that Alaskan Natives have less cardiovascular disease than other populations." He then went on to say that "limitations of death certificates are well known. No data exist about their accuracy in Alaska or the correlation of recorded causes of death with autopsy results."

In 1957[276] Keys said, "The few primitive Eskimos...eat a diet which is as fat as, and possibly on occasion even fatter than, that of the U.S. Armed Forces. The primitive Eskimo does does not know his own age, but it is known that anything beyond the age of 30 years is considered 'old' and that only a few primitive Eskimos ever reach age 50. Perhaps there are a total of 100 such men in the world Eskimo population. In any case, there is no evidence at all as to the frequency of atherosclerosis among Eskimos, let alone among the primitive Eskimos."

In another article in 1959 Keys[569] said, "Though Eskimos are an exceedingly small group of atypical people, their bizarre manner of life excites the imagination, including that of medical writers, who have been want to endow them with a remarkable freedom from some of the ills that beset the rest of us. Since the popular picture of the Eskimo sees him happily gorging on blubber, it is a short step to conclude that he eats a very high fat diet but suffers no CHD. The fact is that nothing is really known about the incidence of CHD among Eskimos. According to Ehrstrom, arteriosclerosis is common among them, reaching an incidence of 29% in North Greenland, but the evidence is dubious, particularly in regard to atherosclerotic heart disease. In any case, we could not expect a high incidence of CHD among primitive Eskimos because few of them attain an age when they would be likely victims of the disease." Keys also noted that the Eskimo diet contained about 45% protein, compared to the 13-14% protein in the American diet.

Ignoring his logic with regard to age and other comments, Keys[2838] completely reversed his argument in a 1973 article. He (and his associates) said that "The data reported by Bang et al.[452] show that the Eskimos have significantly lower levels of cholesterol, triglycerides, and total lipids than comparable, normal Danish people." (Keys neglected to say, however, that the cholesterol levels of the Eskimos were higher than those of Americans.) The incidence of CHD is considered to be very low among Eskimos. According to data presented by Bang et al. only three cases of CHD were reported between 1963 and 1967 in a district of 1,350 individuals.

Why did Keys first indicate correctly that Eskimos do not live long enough to contract CHD and then later omit the age qualification and claim that they have low CHD rates? The answer is that in 1973 Keys was promoting high polyunsaturated fat diets as a means of reducing blood cholesterol levels (see Chapter 10) and "Eskimos are the only people believed to habitually consume a diet rich in polyunsaturated fats." Thus, the higher fat content of the Eskimo diet (than the American diet) could be "explained" by the fact that it is heavily polyunsaturated.

Distorted Models

In 1985 a special issue of Cardiology was published which contained 11 articles describing CHD mortality and risk factor trends in 11 countries. Clearly, the intention was to demonstrate that risk factor changes caused the CHD mortality trends because the data were completely unsupportive of such relationships and yet most authors and an editorial introducing the articles claimed otherwise. Most of the articles exhibited some of the worst scientific analyses and reporting this writer has encountered during the preparation of this review and the editorial yielded a highly distorted summary of the articles as well.

The editorial indicated that the period of interest was "the past 20 or 15 years," thus, 1970 to 1985. But since mortality statistics are never current, the general period was the 1970s, give or take two years. As will be seen, restricting analyses to this period rather than to a broader period leads to very misleading conclusions. for example, CHD mortality undertook a strong decline among Italian men in the early 1960s, leveled off in the 1970s and then decreased again in the early 1980s. Thus, the overall trend was overwhelmingly downward and the plateau in the 1970s was little more than a perturbation, seen frequently in mortality statistics over time. However, by ignoring the trend before 1970, the authors (and the editorial) implied that the overall CHD mortality trend in Italy was upward.

A second major distortion of the data pertained to sex differences. In all cases, except one, CHD mortality trends among women were either downward or constant and greatly differed from those for men in direction and/or onset. Thus, when authors interpreted risk factor trends to explain CHD mortality trends for men, they totally ignored the fact that their interpretations made no sense at all with respect to women. But his is not unusual because the alliance has always ignored the fact that a CHD epidemic never occurred for women in the U.S. and yet they are told, for example, that if they consume the same "rich" diet that they have always consumed (with no increase in CHD mortality), they will suffer increased CHD mortality. Of course, this statement defies logic but that is precisely the logic employed by the alliance.

The editorial was authored by Pyorala, Epstein and Kornitzer.[3215] They said that "The contributors to this special issue have been chosen because there exists, in their respective countries, information which may help to understand the prevailing--either declining or rising--CHD mortality trends." On the contrary, as will be seen, some of the countries had almost no relevant data relating risk factors with CHD and countries were omitted for which excellent data were available, e.g., Japan, France, England, etc.

Pyorala et al. indicated that "Among the 11 countries selected for the reports included in this issue of the journal, 7 countries--the U.S., Australia, New Zealand, Finland, Norway, Belgium and Israel--have definitely shown a declining CHD mortality trend for working-age men during the 1970s, whereas in 4 countries--Sweden, Poland, Italy and Spain--the prevailing trend during the 1970s has been a rise in male CHD mortality." This statement is misleading because for men (1) the overall trend in Italy was downward before and after the 1970s, (2) the CHD mortality rate in Spain was effectively constant from the mid-1960s through the early 1980s, and (3) Sweden exhibited a decline after the mid-1970s. The WHO data presented in Figures 4-6 and 4-8 confirm these trends. Poland was shown by the authors to demonstrate a CHD increase during the 1970s but no data were found in WHO statistics to reveal what the overall trend might have been.

Pyorala et al. continued, "A trend toward better dietary habits has without any doubt prevailed during the 1970s in 6 of the 7 countries with declining CHD mortality trends and information available from several countries indicates that these dietary

changes have been accompanied by decreased in the population mean levels for serum cholesterol. In the 4 countries with rising CHD mortality trends [actually only one] no definite improvement has occurred in dietary habits and, on the basis of limited information available, population mean levels for serum cholesterol appear to have been rising in 3 of these countries." This statement is so utterly false that there can be no doubt that Pyorala intended to support the diet-CHD hypothesis at any cost. Like alliance members, Pyorala et al. ignored the fact that dietary changes occurred long before the CHD changes occurred and often were negatively correlated with CHD trends.

Almost no blood pressure measurements over time were available and those that were available tended to be negatively correlated with CHD trends. Yet, Pyorala noted that antihypertensive drug therapy had increased during the 1970s and they therefore "assumed that an improvement has occurred in hypertension control also in those countries from which the reports in this issue do not give corresponding documented evidence." Not only are assumptions tenuous, hypertension control per se does not necessarily indicate protection against CHD (see Chapter 9).

Finally, Pyorala et al. said that "Prevalence of smoking, particularly among men, has been decreasing in 6 of the 7 countries with declining CHD mortality trends and remained unchanged in 1 of them. Information concerning trends in smoking habits in the 4 countries with rising CHD mortality trends [actually only one] is scanty and not necessarily applicable to the whole population. In actuality, smoking prevalence trends were often nonpredictive negatively correlated with CHD trends, particularly for women.

The following subsections briefly review the relevant data presented by the 11 sets of authors, and demonstrate that the risk factor changes were predominantly uncorrelated or negatively correlated with CHD mortality trends. The reader is urged to examine the appropriate overall CHD mortality trend data for both males and females in Figures 4-1 through 4-9 when reading the review of a specific country.[a] As noted earlier, all authors presented CHD trends only for a restricted period.

United States. Although Chapter 3 discussed at great length the lack of correspondence between risk factor and CHD trends in the U.S., it is useful nevertheless to see once again how factual data become distorted in a series of articles purporting to determine whether risk factors are predictive of CHD mortality.

The author of the U.S. article was Stamler.[3204] He was the only author who discussed CHD trends before the 1970s, give or take 2 years. He maintained that CHD mortality increased from 1940 to 1967 and then decreased, corresponding to dietary hypertension control and smoking changes. He neglected to tell readers, however, that the dietary changes were initiated several decades before the decline, hypertension control was minimal prior to the decline and per capita consumption of cigarettes did not decline significantly until many years after the decline began. He also neglected to inform readers that the relationship between CHD and risk factor changes were either negative or nonexistent for women since women did not experience an increase in CHD mortality during the period in which the "terrible lifestyle" of Americans was presumably killing men at an epidemic rate.

In short, Stamler completely distorted the trend data, a habit he has exercised in literally dozens of articles.

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[a] The WHO annual did not provide long-term data for Poland and did not distinguish between male and female trends in Australia.

Israel. Goldbourt and Neufeld[3213] indicated that there was a substantial reduction in CHD mortality in both males and females after 1974. After examining risk factor trends they concluded that "Changes in CHD mortality were not accompanied by putatively anti-atherogenic trends in eating habits" and "Little, if any, change in serum cholesterol levels and cigarette smoking habits have been observed."

Thus far, neither the U.S. nor Israeli trends supported the risk factor-CHD mortality relationship.

Poland. Rywik and Kupse[3212] reported that there was a strong upward CHD mortality trend among men in Poland from 1970 to 1978, with a slight decreasing trend thereafter. A similar but weaker trend occurred among women. The authors indicated that "The increasing trend in CHD mortality observed over a considerable part of the analyzed time period seems to be an artifact or an effect of changes in the method of classification of causes of death. This trend has been noted already since the 1950s, when the relevant statistical data were obtained for the first time." They noted that there was much error in death certifications and said, "frequently the direct cause of death and not the underlying cause of death is entered erroneously into the death certificate."

The authors indicated that animal fat consumption began to increase in the 1960s and 1970s but this trend could not be considered the cause of the mortality that was already on the increase for 10 years or more. They said, "It is doubtful whether changes in the diet of the population could cause parallel changes in mortality." They also reported that the Polish Trial on CHD Prevention indicated a slight (3.5%) reduction in blood cholesterol, an increase in blood pressure and a slight decrease in cigarette consumption over a 6-year period among 40-59 years.

All in all, Rywik and Kupse admitted that diet was not related to the CHD mortality trends and evidence associated with risk factors was predominantly unsupportive of the risk factor-CHD relation. Thus, three of the studies yielded negative results.

Italy. Menotti et al.[3214] compared CHD mortality and risk factor trends between 1970 and 1979. They indicated that mortality continued to increase throughout the 1970s, implying that it had been increasing before the 1970s as well.

Examination of Figure 4-6 from WHO data shows that the mortality trend in the 1970s was nothing more than a brief plateau preceded by strong declines for men (10 years) and women (20 years) and followed by similar declines. While Menotti et al. concentrated on the plateau, seeking to explain it in terms of risk factors, they should have focused on the overall trend which was much more reflective of what was going on in Italy.

In another article Nicolosi et al.[3159] pointed out that animal fat consumption in Italy had been increasing continuously since 1951 and as much as 172% by 1985. However, Menotti et al. omitted the early data and implied that the animal fat consumption trend began in 1964, obviously to "explain" the observation that CHD mortality did not decrease during the 1970s. (In actuality, it showed an almost imperceptible increase). Using the whole period of increasing animal fat consumption, one can only conclude that such consumption was negatively correlated with CHD mortality.

Since no national samplings of blood cholesterol levels were available, Menotti et al. cited the measurements taken from the two Italian cohorts of the Seven Countries study. They reported that mean cholesterol levels of these men increased from 202

mg in 1960 to 222 mg in 1970. While this trend is consistent with the cited animal fat consumption trend, it is also negatively correlated with the CHD mortality trend.

Menotti et al. also cited the two Italian cohorts as demonstrating no change in cigarette consumption from 1960 to 1970. They omitted national statistics which showed that cigarette consumption in Italy increased from 1951 to 1985,[3159] again presenting a negative relation with the CHD mortality decline.

Menotti et al. also indicated that blood pressures remained constant in the two Italian cohorts from 1960 to 1970.

While Menotti et al. suggested that risk factor trends explained the CHD trend in the 1970s, the overall risk factor trends were generally negatively related to the mortality trends, representing a fourth country that did not conform to the risk factor-CHD relation.

Spain. Although data on hypertension trends in Spain were inadequate, Vintro and Sans[3205] indicated that the two other major risk factors for CHD have increased considerably since the late 1950s and early 1960s. Available data show that blood cholesterol levels increased from about 218 mg in 1968 to about 246 mg in 1978. Cigarette consumption increased linearly from 1957 to 1980, a total of 146%. A figure of Vintro and Sans showed a small increase in CHD mortality from 1968 to 1973 in women and a similar increase in men from 1968 to 1974, after which the rates remained constant until 1977. They concluded that the "adverse" trends in risk factors would lead to much greater increases in CHD mortality rates. But if that were true, the CHD mortality trends should have increased after 1973, not stabilized.

WHO data on Spain were presented earlier in Figure 4-6. Vintro and Sans' selection of the period 1968 to 1977 was most misleading. Figure 4-6 shows that CHD mortality among men has not changed much since 1950 and the short rise after 1965 was followed by decreasing trends after 1975. The trend among women was downward from 1950 to 1970 and the rise thereafter was very brief and totally inconsequential. In effect, the CHD mortality trends in Spain are fully inconsistent with the blood cholesterol and smoking trends.

Vintro and Sans acknowledged that blood cholesterol levels in Spain were high (by world standards), while CHD rates were low (by world standards) but, although this discrepancy was prime evidence of a lack of association between cholesterol level and CHD in Spain, they devoted only one (curious) sentence to this most important observation, i.e., "The mean values for serum cholesterol which we have observed in our studies on industrial populations of Catalonia are higher than those expected on the basis of observed death rates from CHD."

In explaining the CHD mortality increase from 1968 to 1974 Vintro and Sans used an illogical argument to claim that the trend was real rather than due to changes in CHD knowledge and death certification practices. All cardiovascular death rate decreased among women and remained constant among men during that period, indicating that the reported increase in CHD must have been accompanied by a reported decrease in other cardiovascular disease suggesting changes in death certification practices. Yet, Vintro and Sans indicated the opposite illogical argument, i.e., "The absence of changes in total cardiovascular mortality in Spain [men only] with a simultaneous reduction of the mortality from chronic rheumatic heart disease suggests, however, that the increase in CHD mortality is a true phenomenon."

Spain represented the fifth country to show no positive relation between risk factors and CHD mortality.

Finland. Pyorala et al.[3206] indicated that in 1959 the mean cholesterol level in East Finnish men was less than 5% higher than in men from West Finland and yet their reported CHD morality rate was a huge 50% higher. By 1974, the difference in CHD rates still persisted but the difference in blood cholesterol levels virtually dissolved.[a] These facts alone say very little for the blood cholesterol-CHD relation.

The authors' data showed an essentially constant CHD mortality rate among females since 1950, with a slight downward trend after 1967. The male CHD mortality rate peaked about 1965 and remained constant until 1971, after which it began its decline. Like so many other countries, there was no reported CHD epidemic among women which also argues against a diet-CHD hypothesis.

Although Pyorala et al. did not provide blood cholesterol data for women, they did indicate that the diet was such as to produce high levels in women as it did in men. But despite the fact that CHD mortality in men peaked in 1965 and remained constant for six years and then declined, reported blood cholesterol levels remained very high (283 mg and 266 mg in East and West Finnish men) through 1969. Reduced cholesterol levels were not recorded until 1974, three years after the decline began. Moreover, the levels in 1974 (256 mg and 260 mg in East and West Finnish men) were still very high by world standards and higher than those observed in other countries during their "epidemics." It does not make much sense to say that a mortality decline is associated with a cholesterol level of 260 mg, while simultaneously saying that a lessor level is associated with an increasing mortality.

Nearly 60% of Finnish men smoked cigarettes from 1960 to 1965 and that percentage dropped to about 45% by 1970 and and to 40% by 1975. This trend did precede and parallel the CHD trend. However, the fact that the association has not been found in other countries, including the U.S., presents more an anomaly than evidence for a real cause and effect phenomenon.

The use of antihypertensive drugs was relatively rare during the period in which the CHD mortality peaked and then initiated a decline. Significant use of drugs occurred after the decline began, indicating again a failure to demonstrate a logical relation between a risk factor and CHD.

Since blood cholesterol trends were available, a discussion of food consumption trends is of little importance. However, it is useful to note a contradiction by Pyorala et al. They said that "The per capita consumption of fat increased during the 1950s reaching its peak around the year 1960." They presented a figure that showed that fat consumption clearly did not peak in 1960 or even 1970. In fact, it increased almost linearly from 1950 to 1979, with the bulk of the increase occurring after 1960.

In sum, the Finnish risk factor trend data present evidence that is predominantly unsupportive of the risk factor-CHD relation, although the authors suggested otherwise. Thus, six countries cannot be said to be supportive of the relation.

Norway. Thelle[3207] reported that CHD mortality among women had decreased steadily since 1960, while men continued to experience an increase up to 1975, after which a steady decline occurred. No population cholesterol levels were given but Thelle indicated that subjects in the Tromso Heart study showed a cholesterol reduction of 15 mg from 1974 to 1979. Not only is a 15 mg drop in 5 years for the population of Norway highly unlikely, it is not consistent with dietary trends, i.e., Thelle said, "So far the public data available does not show any major dietary changes occurring in the Norwegian population." Moreover, the reported reduction in the

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[a] In 1976 McMichael[2164] cited Punsar and Karvonen as observing this fact.

Tromso study cannot explain the CHD mortality decline among women which was initiated 15 years earlier.

Cigarette consumption trends were also in the opposite direction to the mortality trends. The percentage of female smokers almost doubled (23% to 42%) from 1956 to 1982, while CHD mortality declined. The percentage of male smokers decreased 12% (65% to 53%) during the CHD mortality increase (1956 to 1976) and another 13% (53% to 40%) during the subsequent mortality decline (1976 to 1982).

No data on hypertension or treatment for hypertension were given.

In sum, the evidence presented by Thelle did not support the diet-CHD hypothesis and it most certainly did not support the risk factor concept insofar as cigarette smoking in concerned. The blood cholesterol level measurements were restricted to a small group over a very short period of time and, according to the authors, not accompanied by dietary changes in the population. Therefore, Norway must be considered as the seventh country that failed to conform to the risk factor-CHD relation.

Belgium. Kornitzer[3208] indicated that CHD mortality increased in men from 1958 to 1968, after which it declined. Effectively no increase was observed in women, although a decline was reported after 1968, simultaneously with men.

Kornitzer provided no data concerning population risk factor trends. However, estimates derived from a series of small studies were presented. Blood cholesterol levels were said to have been 249 mg in 1965, 234 mg in 1973 and 234 mg in 1978. While Kornitzer suggested that this trend was consistent with the CHD trends, it was not. CHD mortality continued to increase during the period in which cholesterol levels were said to have dropped 15 mg and mortality continued to decrease after 1973 when cholesterol levels were said to have stabilized at 234 mg. These inconsistencies were also observed for the female mortality trend.

Blood pressure measurements in a series of studies from 1965 to 1978 showed no changes whatsoever, again reflecting no relation with CHD mortality trends.

Cigarette consumption among males was said to have decreased from 72% in 1968 to 49% in 1978. This trend was consistent with the CHD mortality decline. However, as with cholesterol measurements, the cigarette consumption data were obtained on a very restricted age group of middle-aged men and are not necessarily reflective of population trends. Also, Kornitzer omitted smoking trend data for women, suggesting that, like so many other populations, cigarette consumption increased during the CHD mortality decline.

Kornitzer's discussion of dietary changes in Belgium consisted of five sentences and was highly misleading. For example, he said that butter and soft margarines decreased and increased, respectively, and that saturated oils decreased during the 1960s and 1970s. It will be recalled from Chapter 3 that this trend occurred long before and during the U.S. CHD epidemic and it is very likely to have occurred also in Belgium. If so, the trend data presented by Kornitzer would be meaningless. Furthermore, the key dietary variable is animal fat, not simply butter, and any discussion omitting animal fat consumption has no relevancy to the diet-CHD relation.

Belgium becomes the eighth country to yield data generally unsupportive of the risk factor-CHD relation.

Sweden. Welin et al.[3209] reported that CHD mortality among middle-aged men increased from 1968 to 1980 and remained constant among middle-aged women. The WHO data presented earlier in this chapter (Figure 4-8) shows that CHD mortality

increased in the entire male population from 1950 to 1980 and then initiated a decrease thereafter. During the same period, females experienced a constant mortality rate until 1970 and then began a steady decline.

Despite these varying mortality trends, no changes in risk factors were observed. Welin et al. stated that "No major changes have taken place in Sweden explaining the increasing mortality from CHD" [in men but not in women]. Studies showed that mean cholesterol levels and blood pressures remained constant during the male "epidemic" and the percentage of male cigarette smokers declined somewhat. No comparable data were presented for females.

(In another report Malmros[3335] indicated that Swedes were officially recommended to consume less fat, less saturated fat and more polyunsaturated fat, beginning in 1968. Many low-fat products entered the marketplace and considerable polyunsaturated fatty acids were integrated within many food items such as margarines, margarine cheese. Malmros asked, "What has been the effect of these food trends? Has the mortality from ischemic heart disease fallen in the same way as it has in the U.S., for example?" He then said, "Unfortunately, it has not. On the contrary, among men it has, if anything, increased.")

In sum, Sweden represents the ninth country whose CHD mortality trends cannot be explained by the alliance's risk factors.

Australia. Figure 4-1 showed that CHD mortality among males in Australia increased sharply until the 1965-69 period and then undertook a steep decline. In their discussion of risk factors and mortality trends, like so many other authors, Hardes et al.[3210] focused only on the CHD decline since 1968. They also presented little actual data on risk factor changes, preferring instead to report a few (misleading) generalities. For example, they indicated that cigarette consumption increased during the "epidemic" but "between 1968 and 1977-1978 there has been a slight decrease in consumption in the age group 35-74 with an increased consumption in younger age groups, particularly women. Since no data were presented, one must conclude that the reported "slight" decrease was indeed insignificant and could not, therefore, account for much, if any, of the CHD mortality decline.

Hardes et al. offered no data whatsoever regarding trends in blood cholesterol or hypertension. And like other authors, they devoted only a few sentences to food consumption trends and presented only a few selected trends. For example, they indicated that meat consumption decreased after 1958, while butter and margarine decreased and increased, respectively, after 1951, resulting in an overall decline in animal fats. Incredibly, the authors suggested that these trends were consistent with the CHD mortality decline when, in fact, they preceded the decline by 15 years, the period in which the Australian CHD "epidemic" occurred.

New Zealand. Beaglehole and Jackson[3211] reported that CHD mortality had been declining in New Zealand since 1968 but that was only true for men. The WHO data (Figure 4-7) show that the decline for women began at least in 1955. The authors indicated that there had been a decline in consumption of animal fats since 1965. The implication was that this trend began in 1965 but the authors did not say that. Had it begun in 1965, it could not explain the mortality decline for women that was initiated in 1955. Had it begun earlier to account for the female mortality trend, it would then be incapable of explaining the male mortality trend. After all, it would be nonsense to say that an animal fat trend had an immediate effect on females but required a 13-year lag for effects to show for men.

Beaglehole and Jackson stated that no national data were available for either blood cholesterol or blood pressure measurements over time. However, they used data from

three small studies conducted in 1964, 1975 and 1982. Blood cholesterol level in 1982 was said to be 6% and 15% higher than in 1975 and 1964, respectively (no actual cholesterol levels were reported). The authors noted that these "populations were not strictly comparable." Indeed, they were not comparable at all. The 1964 and 1975 studies were of different rural populations and the 1982 study was of an urban population. Not only was the 1982 study an unpublished thesis, suggesting that it consisted of a very small and unique population, Rywik and Kupse[3212] reported in their article on Poland that urban males exhibited blood cholesterol levels that were 17% higher than rural dwellers. In short, Beaglehole and Jackson presented no reliable and adequate data on the subject of blood cholesterol trends.

In attempting to positively correlate blood pressure trends with CHD trends, Beaglehole and Jackson reported that 55% of hypertensives were on drugs in 1982 in Auckland, compared to 30% in Napier in 1973. Not only was this an improper comparison, the percentages must be considered estimates since the number of hypertensives cannot be determined without measuring the entire population. But in any event, the matter is irrelevant because their data were for a period that was at least five and 18 years after the male and female mortality declines began, respectively.

Beaglehole and Jackson used similar after-the-fact data on cigarette consumption to "explain" mortality declines. They reported that the percentage of male and female cigarette smokers decreased by 5% and 3%, respectively, from 1976 and 1981, a period that was 8 to 21 years after the beginning of the CHD mortality declines.

The most objective conclusion to be derived from the New Zealand data is that they do not support the risk factor-CHD relation. Beaglehole and Jackson noted that "the data are less than ideal" and "in the absence of regular monitoring of risk factor levels using comparable methods in large defined populations it is not possible to be completely confident as to the role of these risk factor reductions." As emphasized in Chapter 1, "not possible to be completely confident" really means no confidence at all. The only data of consequence offered by Beaglehole and Jackson were the food consumption trends and they were probably incomplete and unable to explain the fact that the male and female CHD mortality declines started many years apart.

Comments. The above 11 studies presented vasty more evidence against than in support of the risk factor-CHD relation. It is a grotesque distortion of reality to say that they supported the relation, as most of the authors and the editorial by Pyorala would have readers believe. As with alliance members in general, it seems not to disturb many epidemiololgists whether a major change in a risk factor occurs 5, 10, or even 20 years before, or many years after a major change in mortality. Moreover, they seem totally unperturbed by the fact that risk factor changes cannot explain female mortality rates simply because almost every major population in the world has shown no CHD "epidemic" among women and because CHD downturns among women have occurred at widely different points in time from those of men. It is clear that such epidemiologists have a charter to support the risk factor concept and do so at the expense of rational scientific reasoning. Criteria for "evidence" changes from study to study and even within a single study for different risk factors and for the two sexes.

Summing Up

Despite the repeated assertions by the alliance that population studies provide evidence of a relationship between diet, blood cholesterol-level and CHD, the bulk of the evidence, and certainly the most important evidence, thoroughly rejects that hypothesized relationship. Almost all of the alliance's evidence derives from between-population studies which correlate food availability and/or mean blood cholesterol levels with reported CHD rates. Not only are such studies thoroughly confounded by

numerous uncontrolled variables, such as differences in compiling accurate statistics and in diagnosing CHD, they also reveal remarkable inconsistencies. For example, Simons[2774] recently presented his 19 between nations study of 40-69 year-old men in which he reported a correlation of .67 between blood cholesterol level and CHD mortality. When one examines Simons' scatterplot, the correlation (which explains less than 50% of the variance as it is) appears meaningless. Many of the countries had identical blood cholesterol levels but wildly different CHD rates. For example, Japan, Yugoslavia and Israel had blood cholesterol levels of 198 mg, 199 mg and 199 mg, respectively, but had CHD mortality rates of 70, 195 and 310 per 100,000. The mean cholesterol levels in Poland, Canada and the U.S. were 211 mg, 208 mg and 212 mg but their respective CHD rates were 275, 380 and 390. Similarly, the cholesterol levels of France, Italy, Switzerland, Belgium, Hungary and Australia ranged from 222 mg to 230 mg but their respective CHD rates were 130, 203, 225, 255, 403 and 420.

No objective scientist can ignore these "discrepancies" in favor of an overall correlation, even if the latter were much higher. Moreover, the discrepancies associated with diet and CHD are far too extensive to dismiss as well. Interestingly, Hegsted and his colleagues,[408] long time alliance members, admitted in 1965 that "it should be emphasized that the differences in the levels of serum cholesterol of various population groups cannot be adequately explained by differences in fat intake."

As far back as 1956 Keys[280] made a most informative statement that was universally ignored subsequently by alliance members, i.e., "The vital statistics for mortality rates by cause are generally less reliable in countries in which IHD is reported to be relatively uncommon." If one recognizes that CHD was also reported to be relatively uncommon in the U.S. at one time (while "other" heart diseases were common), Keys' statement effectively explains both the "epidemic" and the major differences in rates between, at least, most countries.

BETWEEN POPULATIONS

Field Studies

The Seven Countries Study. The word "landmark" has often been used by alliance members to describe Ancel Keys' Seven Countries study, commonly cited as proof that the American diet is atherogenic.[2889,3361] As will be seen, the dietary assessment methodology was highly inconsistent across cohorts and thoroughly suspect. In addition, careful examination of the death rates and associations between diet and death rates reveal a massive set of inconsistencies and contradictions. We first turn to the dietary assessments.

The study included 16 cohorts of men in 7 countries. According to a 1989 article by Keys and his colleagues,[2293] "detailed data on food consumption patterns have been published only for 9 of the 16 cohorts," citing two references in foreign languages. In a 1986 article Keys et al.[617] cited 5 papers published in the Dutch journal, Voeding, that was not available in the huge UCLA biomedical library. Thus, attempts to understand how the surveys were conducted were based on "summaries" presented by Keys and his co-workers in several English papers. It was, to say the least, annoying trying to "decode" these discussions since they contained numerous contradictions.

In his 1970 report of the 10-year follow-up of the study, Keys[493] said that "Except with the U.S. railroad men, the dietary studies involved seven-day records with weighing of all foods eaten by men representing statistical subsamples of the cohorts. Repetitions of these seven-day surveys covered seasons of the year. Nutrients consumed were measured by chemical analysis [of duplicate food items] as well as being caculated from tables of food composition." The American cohort was subjected to a highly inaccurate method of assessment, i.e., a 24-hour recall of foods eaten.

Keys admitted that this method would yield a "substantial amount" of error, so "adjustments" were made, based on visits to the homes of 50 (2% of cohort) men and "prolonged examination of details with the wives." Not only was it likely that this additional analysis did not eliminate much of the error, Keys also admitted that error could be up to 10% at the group level, even with the arbitrary elimination of many subjects because their estimates were "incredible." The estimated total and saturated fat consumed as a percentage of total calories were 40% and 18%, respectively, both considerable exaggerations over those observed in many larger surveys conducted in the U.S. which have shown values of 36% and 13-14%, respectively (Chapter 3). The erroneous values obtained by Keys by quite dubious methods completely distorted the entire results and conclusions of the Seven Countries study.

Keys' claim that surveys were conducted during the different seasons was quite misleading. Multiple surveys were conducted in only 8 of the 16 cohorts and the percent of calories as fat was found to vary an average of 15% across seasons. Since Keys used the averages across seasons for these cohorts and the single survey values for the remaining 8 cohorts, it was simply not appropriate to compare all cohorts as though they were based on the same standards--but Keys did make such comparisons.

Contrary to the suggestion in the early part of Keys' discussion, chemical analysis of duplicate foods was not accomplished for all but the U.S. cohort. Later in his report he indicated that such analyses were not performed for 3 of 5 cohorts in Yugoslavia and as will be seen below, one of three Italian cohorts.

While Key's 1970 article implied that all but the American cohort involved surveys in which all foods were weighed before eating, such was not the case, as indicated in a 1986 article by Keys et al.[617] In that article they admitted that the Rome, Italy cohort's diet was also assessed by the highly inaccurate recall method (interview-questionnaire). However, they implied that chemical analyses were performed for all other cohorts which, as noted above, was not true.

In yet another article by Keys[2839] it was admitted that chemical analyses were performed on only "some" of the foods in the two Japanese cohorts. Thus, no chemical analyses or partial chemical analyses occurred for six of the 16 cohorts. Keys also noted another variation in methodology, i.e., in some cohorts duplicates of each meal were apparently put together before the meal was eaten, while in others "equivalent composites" were constructed at the end of the 7 days, based on the weights of the foods determined during the week. Unquestionably, this variation introduced another source of error.

A 1989 article by Keys et al.[2293] not only presented additional data suggesting further sources of error, it also introduced several contradictions. With regard to the latter, they falsely stated that the American and Roman cohort men "weighed and recorded their food consumption." What motivated them to put forward such a falsehood, particularly in view of all previous statements? Keys could not have been more emphatic in a 1979 article, i.e., "recording the weights of all foods eaten...was not done in the U.S. where only a dietary interview was possible with railroad employees."[2839] Since it is highly unlikely that the 1989 statement was an "inadvertent mistake," e.g., it was repeated not once but twice elsewhere in their article, it seems certain that it was purposely intended to artificially strengthen a serious weakness of their study. By now there were probably few, if any, researchers knowledgeable about the details of the dietary surveys.

In their 1989 article Keys et al. said that three dietary surveys were conducted in Crete but Keys[493] earlier indicated that only two were performed. And while Keys[617] indicated that all surveys involving the record method include trained

dietitians who supervised the weighing of foods, why were the data from so many subjects discarded?[2293] Why also were some foods weighed before cooking and others after cooking?[2293] And why did some men supply insufficient data and/or fail to weigh foods as directed?[2293] If supervision did occur, it was clearly inadequate.

The data from a number of subjects were discarded because they were only for 4 to 6 days, rather than the planned 7 days. If 4 to 6 days were inadequate, why were the one-day data from the U.S. cohort considered valid?

Also in their 1989 article Keys et al. indicated that the surveys of all cohorts were not accomplished in the same year and some occurred 5 to 11 years after the first survey. This is flatly inexcusably scientifically.

Finally, the 1989 article indicated that of the original 12,770 men in the Seven Countries study 9,719 comprised the 14 cohorts who were assessed by the diet record method. But the diets of only 419 were actually assessed, yielding an average sample size of 3.3%. Even given that the survey methodology was accurate, which it most certainly was not, such small samples must have been unrepresentative of their respective cohorts. At minimum, by chance alone, they must have been unrepresentative of at least several cohorts.

It is almost inconceivable that the Seven Countries study was performed with such scientific abandon. It is also dumbfounding how the NHLBI/AHA alliance ignored such sloppiness in their many "rave reviews" of the study. It is not sufficient to merely assume that the above noted sources of variation provided few or no errors in the dietary data. On the contrary, such massive variations could not help but promote errors. And there were apparently other errors. For example, there was suggestion in the Keys et al.[2293] article that "extreme values" were observed in the dietary data and subsequently eliminated. In summary, the diet-CHD relationship reported for the Seven Countries study cannot be taken seriously by the objective and critical scientist. The study can be used, moreover, as an example of how not to collect food consumption data.

In an article unrelated to the Seven Countries study, Keys et al.[988] indirectly criticized his own dietary collection procedure and data. He said, "It might seem...that little of quantitative value can be secured in studies on free-living people, with estimates based only on food diaries', shopping lists, interviews with dietitians, recollections of what was eaten and about how big were the portions, and final computation from tables of 'average food composition' that necessarily ignore the large natural variations from place-to-place, time-to-time and sample-to-sample. Such crude methods cannot provide reliable details for individuals but when applied with care it is hoped that they may yield reasonable approximations for group averages of cooperative people who have frequent, repeated contact with supervising dieticians." Note that Keys et al. emphasized that with "frequent" and "repeated" diet samples obtained by dietitians it is hoped that they may yield reasonable approximations for group averages. Obviously, his Seven Countries study did not meet his own requirements for even ("may") adequate dietary sampling. In fact, in another article, Keys[2839] made it clear that diets in the Seven Countries cohorts changed quite drastically in some of the countries which presumably had the lowest CHD mortality rates. He said, "Blood cholesterol increased in Yugoslavia, Italy and Greece in the first five years and still more in the 10 year examinations. (For example, Nicolosi et al.[3159] reported that blood cholesterol levels in the Italian cohorts increased from 202 mg in 1960 to 222 mg in 1970.) The same men on the island of Crete changed from an average of 205 mg in 1960 to 235 mg in 1970. The changes in food are even more dramatic, from an average of small portions of meat once or at most twice a week in 1957 and 1960 to meat 4 or 5 times a week, butter or a butter margarine mix in the shops where nothing like that was seen a few years ago, ice cream often taking place of dried

fruits and nuts... Similar changes are observed in the villages of Italy and Yugoslavia."

It is noteworthy that Livingstone et al.[2697] recently compared energy intake, as measured by the seven day weighed dietary record, with energy expenditure, as measured by the doubly labeled water technique. They found that recorded energy intakes were underestimates of actual intakes and concluded that studies correlating diet with health probably yield biased interpretations. Similarly, Freudenheim et al.[2972] correlated food intakes with 1, 2, 3 and 7 day dietary records. They found that "Measurement of one, two, three or seven days of dietary intake per person...did not permit quantification of individual intake...," although they reported that "mean intake for a group can be estimated using one diet record or one 24-hour recall, provided that a sufficiently large group is sampled." By no means did Keys and his colleagues use "sufficiently large groups" in the Seven Countries study.

An interesting study which relates to the Seven Countries study is that conducted by Dougherty et al.[2257] They obtained seven day dietary records of small groups (20, 21 and 21) of male farmers in Italy, Finland and the U.S., three countries used in the Seven Countries study. Dougherty found that the total fat and saturated fat, as percentages of total calories, were much lower in the Italian cohort than in the U.S. cohort (32% vs 40% and 8.7% vs 17.4%, respectively), and yet the blood cholesterol levels of the Italians were much higher, i.e., 213 mg vs 191 mg. On the other hand, the Finnish cohort's intake of total fat and saturated fat was nearly identical to those of the U.S. cohorts (39% vs 40% and 22.1% and 17.4%, respectively) and yet the blood cholesterol levels of the Finnish cohort were substantially higher than those of the U.S. cohort (242 mg vs 191 mg, respectively). These results say very little for the importance of diet to blood cholesterol levels among nations and also run counter to some of the findings in the Seven Countries study.

Turning now to death rates and the associations between diet and death rates, Keys et al.[3190] reported that the percentage of total calories as saturated fat correlated .84 with CHD mortality. While this correlation might seem impressive, it is, in fact, an excellent example of the absurdity of epidemiological correlations which the alliance seems unable to fathom.

The first table presented by Keys et al. showed the all-cause and CHD death rates for the 16 cohorts at the end of 10 years. While neither Keys et al. nor others seemed disturbed by these data, the U.S. cohort data almost jumped off the page. Listed were death rates of 574 and 1,088 for CHD and all-causes, respectively. Thus, CHD constituted 53% of all deaths, a proportion that was 61% higher than that found among white males nationwide, i.e., 33%.[1940,a] Interestingly, the proportions for the remaining six countries (averaging across cohorts within a country) were almost identical to those computed by this writer from WHO[2825] statistics for the 1965-1969 period. We do not know how Keys et al. arrived at this U.S. cohort death rate but it is grossly unrepresentative of the U.S. as a whole and of U.S. states and regions. Thus, it is clear that the basic death rate data that Keys et al. used for the U.S. cohort were either wholly incorrect or derived from a peculiar group of individuals not observed in U.S. vital statistics. If we assumed that the all-cause death rates are correct (and they are also overestimates compared to U.S. and WHO statistics for these countries), the U.S. CHD rate should have been approximately 359, not 574.

As previously noted, Keys et al. reported a correlation of .84 between the percentage of total calories as saturated fats and CHD mortality. Table 4-3 shows their principal data from which the correlation was computed. The cohorts are shown in the same order as presented by Keys et al., an order that appears random but, in actuality, may have been accomplished to disguise the enormous discrepancies. Table 4-4 shows those discrepancies by pairing cohorts with similar staturated fat intakes. For example, the U.S.-Slavonia pair presented a saturated fat intake difference of 4% of calories but a CHD mortality difference of 168%. Not only is the saturated fat estimate for the U.S. cohort higher than typically reported for Americans (see Chapter 3), even if the estimate were valid, it is preposterous to believe that such a small difference in saturated fat would lead to a 168% increase in CHD mortality.

All the remaining pairs of cohorts in the table present highly similar or identical intakes of saturated fat but radically different CHD mortality rates. Of the 32 pairs shown, only six revealed CHD rate differences below 50% and 4 of those represented inverse relationships, i.e., the higher the saturated fat, the lower the CHD rate. Fourteen of the cohort pairs revealed CHD mortality rate differences of more than 100%, ranging as high as 3122%. Moreover, nearly half of the cohort pairs showed inverse relationships.

The correlation between saturated fats and all-cause mortality was substantially less than that for CHD mortality (.47 vs .84). A similar table of discrepancies for all-cause mortalities was not constructed because it should be more than obvious that even more discrepancies would be evident. However, it is worth noting that seven cohorts had higher all-cause mortality rates than did the U.S. cohort and four of these presumably consumed lower amounts of saturated fats, averaging under 10% of total calories. The remaining three had saturated fat intakes only slightly higher than that of the U.S. cohort. In addition, four other cohorts had all-cause mortality rates slightly lower than that of the U.S. cohort but had much lower saturated fat intakes, averaging 7.3%.

Keys et al. said that "We do not claim that the results reported here prove a cause-and-effect relationship between diet fats and mortality. Indeed, despite the relatively high correlation observed, Table 4-4 shows that it is totally meaningless. If a cause and effect relationship existed between saturated fat and CHD, there would be very few inconsistencies between pairs and the magnitude of the inconsistencies would

[a] The proportion existing in 1960, roughly the peak of the CHD epidemic in the U.S. WHO data for the 1965-1969 period showed a proportion of 34%.[2825]

Table 4-3

Death rates and saturated fat consumption in the Seven Countries study (adapted from Keys et al., 1981[3190])

Cohort	% calories as sat. fat	Death rate[a] All	CHD
Belgrade	12	509	288
Crevalcore	10	1241	248
Dalmatia	9	758	86
E. Finland	22	1727	992
Corfu	7	764	144
Ushibuka	3	1248	66
Crete	9	543	9
Montegiorgio	9	1080	150
Zutphen	19	1175	420
Rome	8	1027	290
Slavonia	14	1477	214
Tanushimaru	3	1006	88
U.S.	18	1088	574
Velika	9	1078	80
W. Finland	19	1318	351
Zrenjanin	10	1101	152

a Per 10,000 per 10 years.

Table 4-4

Pairs of cohorts having similar saturated fat consumption but different CHD death rates (derived from Table 4-3)

Cohort	% sat. fat	CHD rate[a]	Diff.	Cohort	% sat. fat	CHD rate	Diff.
E. Finland	22	992	182%	Montegiorgio	9	150	88%
W. Finland	19	351		Velika	9	80	
W. Finland	19	351	20%	Montegiorgio	9	150	1567%
Zutphen	19	420		Crete	9	9	
W. Finland	19	351	-64%[b]	Dalmatia	9	86	856%
U.S.	18	574		Crete	9	9	
Zutphen	19	420	-37%	Velika	9	80	789%
U.S.	18	574		Crete	9	9	
U.S.	18	574	168%	Rome	8	290	-36%
Slavonia	14	214		Slavonia	14	214	
Slavonia	14	214	-35%	Rome	8	290	-17%
Belgrade	12	288		Crevalcore	10	248	
Belgrade	12	288	89%	Rome	8	290	-91%
Zrenjanin	10	152		Zrenjanin	10	152	
Crevalcore	10	248	63%	Rome	8	290	-93%
Zrenjanin	10	152		Montegiorgio	9	150	
Crevalcore	10	248	65%	Rome	8	290	-237%
Montegiorgio	9	150		Dalmatia	9	86	
Crevalcore	10	248	188%	Rome	8	290	-263%
Dalmatia	9	86		Velika	9	80	
Crevalcore	10	248	210%	Rome	8	290	-3122%
Velika	9	80		Crete	9	9	
Crevalcore	10	248	2656%	Rome	8	290	101%
Crete	9	9		Corfu	7	144	
Zrenjanin	10	152	77%	Corfu	7	144	-67%
Dalmatia	9	86		Dalmatia	9	86	
Zrenjanin	10	152	90%	Corfu	7	144	-80%
Velika	9	80		Velika	9	80	
Zrenjanin	10	152	1589%	Corfu	7	144	-1500%
Crete	9	9		Crete	9	9	
Montegiorgio	9	150	74%	Tanushimaru	3	88	33%
Dalmatia	9	86		Ushibuka	3	66	

[a] Per 10,000 per 10 years.

[b] Minus signs indicates inverse relation.

be relatively slight. But quite the opposite occurred in the Seven Countries study. The inconsistencies are many and the magnitudes, including reversals, are enormous. Even if the dietary data were valid, and the previous discussion indicated that at least much of those data were not, Tables 4-3 and 4-4 demonstrate that there is no meaningful relationship between saturated fat and CHD or total mortality. The correlations observed were merely artifacts of some overall ordering that was undoubtedly influenced by uncontrolled variables. For example, it has been stressed elsewhere in this volume that higher CHD rates and saturated fat intakes tend to occur in the more prosperous countries which can afford the food products associated with saturated fats and which have greater capabilities of diagnosing CHD. It is doubtful that Keys and his associates were unaware of the massive discrepancies in their study because their table was clearly arranged to hide them. If one were to simply order either the saturated fat percentages or the CHD death rates of Table 4-3 from highest to lowest or vice-versa, the discrepancies would immediately become observable. Further, if one orders the cohorts according to country, the discrepanices immediately become observable as well, although not nearly as many are easily detectable as with the ordering of all cohorts. For example, Table 4-5 shows 9 discrepant pairs within countries, three of which indicate inverse relationships. The U.S. and Netherlands are not represented in this table because they involved only one cohort.

In sum, the Seven Countries study was a landmark investigation, a glaring example of scientific incompetence or extremely biased reporting--or perhaps some of each. The biases are everywhere. For example, in Key's 1953 between countries study,[279] when all fats were believed to elevate blood cholesterol, he reported a perfect relationship between total fat consumption and CHD mortality. When the Seven Countries study was initiated, it was recognized that only saturated fats elevated blood cholesterol. Hence, Keys and his associates subsequently reported a high correlation between saturated fats and CHD mortality rates but found no relationship between total fats and CHD. As indicated in Volume 1, Keys always manages to find the relationships that are in vogue at the time--even if they are opposite to what he reported in earlier studies. In any event, there never was any justification for conducting the Seven Countries study in the first place. Because the CHD mortality rates have long been known to vary tremendously between states and between regions, there was no point in conducting a more costly and cumbersome study between countries where medical sophistication and death certification systems were substantially different and where many other variables were left uncontrolled.

An observation from John McMichael should be noted. Speaking before the 1977 Senate Select Committee on Nutrition and Human Needs, he stated that "If you eliminate East Finns from the Seven Countries study, the relationship of CHD to cholesterol is much less convincing."[2435] The East Finns were unique in that not only did they consume huge amounts of food, including fat, they were also extremely hard-working lumberjacks. McMichael also observed that "most of the coronaries occurred around the middle average level of blood cholesterol. So there is no indication you get more coronary artery disease at high levels."

Despite the many insurmountable problems of the Seven Countries study, particularly the pathetically inaccurate assessment of diets in the American cohort and the obviously inflated CHD rate for that cohort as induced from the much too high CHD/all-cause ratio, the 1989 AHA/NHLBI joint statement (reviewed in Chapter 1) indicated that the study "provides the strongest evidence [available] that diets high in saturated fatty acids increase the risk of coronary heart disease."[2500,3349] If this study provides the best evidence available, then all other studies can be automatically discarded as providing no evidence whatsoever. The alliance's ignoring of the glaring flaws and unconditional acceptance of the study's results reflects either gross incompetence or purposeful deception.

Table 4-5

Pairs of cohorts within countries having similar saturated fat consumption (derived from Table 4-3)

Cohort	% sat. fat	CHD rate	Difference
Finland			
E. Finland	22	992	182%
W. Finland	19	351	
Italy			
Crevalcore	10	248	65%
Montegiorgio	9	150	
Montegiorgio	9	150	-93%
Rome	8	290	
Greece			
Crete	9	9	-1500%
Corfu	7	144	
Japan			
Tanushimaru	3	88	33%
Ushibuka	3	66	
Yugoslavia			
Slavonia	14	214	-35%
Belgrade	12	288	
Belgrade	12	288	89%
Zrenjanin	10	152	
Zrenjanin	10	152	77%
Dalmatia	9	86	
Zrenjanin	10	152	90%
Velika	9	80	

The Ireland-Boston Diet-Heart Study. Volume 1 indicated that the Ireland-Boston Heart study yielded no significant evidence supporting the diet-CHD hypothesis. However, the study continues to be cited by the alliance as supporting the hypothesis. Therefore, a more detailed critique of that investigation follows.

The Ireland-Boston Heart study was designed to control hereditary factors by comparing pairs of brothers living in either Boston or Ireland. It was apparently assumed from vital statistics that the CHD death rate in the U.S. cohort would be significantly greater than that in the Ireland cohort and that this difference could be related to various factors such as diets. The concept was a good one but the conduction and analyses of the study bordered on the absurd.

Brown, Hegsted, Stare and others published a 42 page description of the Ireland-Boston study in 1970.[437] Some 1,154 brothers were enrolled in the study. The Boston brothers were urban dwellers and workers, whereas the Irish brothers were predominantly farm workers. Thus, at the outset, the study design was already confounded by at least two (and possibly more) uncontrolled variables. Farm workers are involved in vastly more physical activity than urban workers and it is commonly believed that the latter undergo considerably more psychological stress. Such subject selection should never have been accepted by Brown et al.

The Boston brothers were all over 20 years of age when they moved to Boston. Since atherosclerosis is known to originate in childhood, 376 additional men were selected who were unrelated to the brothers but were born in the U.S. from parents who were born in Ireland.

Brown et al. noted that food disappearance data showed that in 1960-62 "a total of 3486 calories [were] available per capita per day with fat providing 34% of total calories" in Ireland, while in the U.S. "3,127 calories were available per capita per day of which 41% (142 g) was from fat." Since it is well-known that actual consumption, particularly of fats, is significantly lower than that indicated by availability data (Chapter 3), the authors should have been suspicious about their acquired dietary data discussed below.

Two extraordinary facts can be observed with respect to the dietary data. First, despite a 42 page report, Brown et al. did not indicate any details whatsoever about their technique for acquiring dietary information from subjects other than to say that "a careful dietary history [via interviews] was taken by a nutritionist." Thus, it is not known whether the data represented 24 hour recalls, seven day estimates or whatever. Second, dietary data were purposely obtained on "samples of adequate size," rather than all subjects. Since the final report of this study (discussed below) excluded all subjects for which dietary data were not taken, 371 subjects or 25% of all subjects, what was the point of enrolling these subjects in the first place?

Table 4-6 presents the estimated principal nutrient intakes of the Boston and Irish brothers as reported by Brown et al. Dietary surveys of this vintage indicate that the American male consumed an average of about 2600 calories, 110 g of fat, 36-37% of total calories as fat, 14% of total calories as saturated fat, about 4-5% as polyunsaturated fat and under 500 mg as cholesterol. As can be seen in the table, the Boston brothers were said to consume quite different amounts of these nutrients. Thus, either the method of estimating intakes was in considerable error or the subjects selected were atypical. If the former was the case, there is no reason to assume that the error was constant across all nutrients and across both the Boston and Ireland cohorts. In other words, one cannot assume that overestimates and underestimates were the same for all subjects.

Table 4-6

Nutrient	Boston	Ireland
Total calories	3075[a]	3768
Total fat (g)	135[a]	159
% calories	39[b]	38
Saturated fat (g)	59[a]	77
% calories	17[a]	18
Monounsaturated fat (g)	52	58
% calories	15	14
Polyunsaturated fat (g)	8.6	9.2
% calories	2.5[c]	2.2
P/S ratio	1.59 [0.15][d]	1.18 [0.12][d]
Carbohydrates (g)	293	436
% calories	38	46
Cholesterol	844[a]	894

[a] Substantially greater than typical American male diet.
[b] Somewhat greater than typical American male diet.
[c] Somewhat lower than typical American male diet.
[d] Simple observations of polyunsaturated and saturated fat intakes indicate that their P/S ratio were computed erroneously. Correct values are in brackets.

It is not known how Brown et al. computed P/S ratios for the two cohorts but it is quite clear that they are grossly incorrect.

Brown et al. reported that their data revealed no real differences between the two cohorts with regard to the primary nutrients established by the alliance to be contributors to atherosclerosis. They said, "The major similarities noted are that fat provides approximately the same percent of total calories (about 38%) and that a similar percent of total calories is provided by saturated fatty acids." Indeed, the difference between cohorts in total and saturated fats was only 1%. Moreover, the difference between cohorts in monounsaturated and polyunsaturated fats was also 1% or less. These small differences should be recalled when the final report on this study is discussed below.

The reader should also specifically note that the authors neither converted the cholesterol intakes from absolute amounts to amounts per 1,000 calories consumed, as was done in their subsequent final report, nor even devoted a single sentence to cholesterol intakes. This omission must be taken as an admission by the authors that the difference in intakes was trivial. The Irish brothers consumed 5.9% more cholesterol than did the Boston brothers but when the intakes are converted to amounts per 1,000 calories, the Boston brothers consumed 15.6% more cholesterol. Since this percentage is twice as large as the percentage (7.3%) subsequently classified as "significant" in the final report, it is quite clear that they altered their criteria of importance in order to produce "positive" findings from an expensive and long-running study.

Finally, it is noteworthy to mention that three other cohorts of Irishmen (2 urban and 1 rural) were enrolled in the study for purposes of comparison with the Irish farm workers. Although the four Irish cohorts had widely different cholesterol levels of 211 mg, 213 mg, 232 mg and 244 mg, they had essentially identical diets. Strangely, Brown et al. referred to these differences as "slight" but did indicate that they "do not seem to be related to any differences in the fat or cholesterol composition of the diet."

The 20-year follow-up of the Ireland-Boston Diet-Heart study was published by Kushi, Stare and their co-workers.[472] As will be seen, these authors transformed the study from a between countries to a within population survey, having found no significant results from the former.

Table 4-7 presents a breakdown of subjects included and excluded in the 20-year follow-up. With the exception of the first row, the top third of the table is not important because many of these subjects and data were excluded. Kushi et al. indicated that 567 Irish, 572 Bostonian and 369 other Americans were enrolled at baseline. These numbers are lower than the numbers provided by Brown et al., i.e., 575, 579 and 376, respectively. Kushi et al. failed to mention the loss of 22 men, let alone the reasons for their exclusion.

As indicated earlier, 25% of the subjects listed in the top third of the table were excluded from the study for the reasons given in the middle third but overwhelmingly because of no diet history. Since the study was designed for 500 pairs of brothers, it is incomprehensible why these subjects were excluded. Two points are relevant. First, the diet histories of these subjects were purposely not taken at baseline; the original investigators indicated that a three-fourths sample was quite "adequate to allow meaningful comparisons." Second, other studies such as the Seven Countries study, involved smaller samples of dietary data and yet included the entire cohorts in diet-mortality analyses. Thus, it would seem that alliance members employ arbitrary and inconsistent criteria for inclusion and exclusion of subjects. Kushi et al. did not discuss this issue and gave the impression that the dietary data on the excluded subjects somehow was lost, i.e., "Men were excluded from the analysis presented here

Table 4-7

Subjects included and excluded in the 20-year Ireland-Boston Diet-Heart study follow-up (adapted from Kushi et al., 1985[472])

	Ireland	Boston	First Generation
Enrolled at baseline	567[a]	572[a]	369[a]
Known to be deceased	196	186	64
Death certificates found	174	168	60
Died of CHD or IHD	53	67	28
Subjects excluded	177	186	148
Lost	20	46	40
No diet history	142[b]	136[b]	93[b]
No serum cholesterol data	10	4	8
No cigarette data	5	0	1
Subjects included	390	386	225
Known to be deceased	143	150	41
Death certificates found	127	135	38
Died of CHD or IHD	41	54	15

[a] These numbers are lower than the numbers indicated by Brown et al., i.e., 575, 579 and 376, respectively.

[b] Diet histories were purposely not taken from these subjects at baseline, begging the question--why were they even enrolled at baseline if they are going to be excluded from mortality, blood cholesterol, etc., analyses.

if information was missing for one or more of the following reasons: ...there was no dietary information for them..."

The bottom third of Table 4-7 lists the data upon which the 20-year between countries analysis was based. Although there appears to be a greater number of CHD/IHD deaths among the Boston brothers, the difference between cohorts was not statistically significant. Moreover, since the data were based on death certificates, the difference observed in this study could very well have been due to the differences between the countries in recognizing/diagnosing CHD. It has been emphasized in Volume 1 and the present volume that the more economically advanced a country, the more sophisticated and advanced its medical system and the higher the CHD mortality rate. Neither Brown et al. nor Kushi et al. demonstrated that the accuracy of death certificates, particularly with respect to CHD, was the same or even remotely similar for the Boston and Ireland cohorts. Would anyone truely believe, for example, that the dead Irish farmers were diagnosed by physicians with the same knowledge, expertise and diagnostic equipment as Boston physicians who completed the death certificates for the Boston brothers?

Although the difference in CHD mortalities between cohorts was not significant, the matter is not academic because it represents a major problem of all between countries studies and is essentially ignored by the alliance. Therefore, even if the difference was significant, it still could not be concluded scientifically that it was real and not due to differences in death certificate accuracy.

The between countries analyses can be summarized by a few statements by Kushi et al. "None of these differences in mortality approached statistical significance, even after adjustment for other risk factors, including systolic blood pressure, serum cholesterol level, cigarette smoking, and the modified Hegsted dietary-lipid score. The absence of statistically significant differences between cohorts in mortality from CHD contrasted with the many significant differences in dietary and other risk factors. The pattern of nondietary risk factors generally followed the mortality patterns, with the average level of each risk factor highest for the Boston brothers. [However, the differences were generally trivial, particularly blood cholesterol, i.e., 2.6 mg.] There were many significant differences in dietary habits among the three cohorts at baseline, including the markedly higher energy intake in the Irish brothers. However, only a few of the dietary variables mirrored the mortality rates from CHD. The Boston brothers had the highest dietary cholesterol levels, modified Hegsted dietary-lipid scores, and animal-foods scores, and the lowest vegetable protein and total-carbohydrate intakes and vegetable-foods score."

The last sentence in the above paragraph is both misleading and irrelevant. The Boston brothers did not consume more dietary cholesterol but actually 94 mg less per day than the Irish brothers. The Hegsted score, discussed in detail in Chapter 5, is a contrived equation that forces highly variable and perhaps curvilinear data into a regression line and should not be used in place of raw dietary data in an experiment or prospective study. Third, an animal foods score per se has no scientific relationship with either blood cholesterol or CHD. Rather, it is the saturated and unsaturated components of animal and vegetable foods that relate to cholesterol and CHD. And fourth, vegetable protein and vegetable-foods scores also have no scientific relationship with blood cholesterol or CHD independent of their saturated and unsaturated fat components. It is simply ludicrous to suggest to the reader that these findings indicate even the slightest relationship between diet and CHD mortality.

Table 4-8 show the principal dietary data presented by Kushi et al. and they yield an entirely different picture than painted by the authors in their text. As can be seen, saturated fat intake was significantly higher in the Irish brothers and monounsaturated and polyunsaturated fats were significantly lower--precisely the opposite to that predicted by the alliance's lipid hypothesis. Moreover, the dietary

Table 4-8

Dietary and nondietary measures of the Ireland-Boston cohorts (adapted from Kushi et al., 1985[472])

	Ireland	Boston
Nondietary variables		
Blood cholesterol	215.9	218.5
Systolic BP (mm Hg)	134.7	139.3[a]
Diastolic BP (mm Hg)	82.8	86.9[a]
Cigarettes (packs/day)	1.72	1.89[a]
Relative weight (% standard)	100.5	106.7[a]
Dietary variables		
Total calories	4033	3099[a]
% calories as		
Protein	13.5	16.6[a]
Fat	37.6	38.9[a]
Animal	33.3	32.4
Vegetable	4.3	6.5[a]
Saturated	17.7	16.9[a]
Monounsaturated	17.8	19.4[b]
Polyunsaturated	2.1	2.6[a]
Carbohydrate	47.1	38.9[a]
Cholesterol (mg/1000Kcal)	233	273[a]
Total Cholesterol (mg)	940	846[a]

[a] Significantly different from Irish brothers.

[b] These values were not given by Kushi et al. but appear to be significantly different, judging by the significance achieved in the other dietary variables.

cholesterol intake of the Irish brothers was higher than that of the Boston brothers. There is no scientific basis for converting absolute intake to amount per 1,000 calories consumed but such a conversion resulted in an apparently greater intake by the Boston brothers.

After suggesting that the dietary data supported the mortality trends when they did not, Kushi et al. stated that "since mortality rates for CHD did not differ significantly among the three cohorts, the cohorts were combined" and they proceeded to conduct a within population analysis. Table 4-9 presents the dietary intakes of those who did and did not die of CHD.

Before discussing Kushi et al.'s analysis of their data, note that of the 891 men listed under the category "No CHD death," 224 (25%) had died of unspecified causes. It is inappropriate to include these subjects in the diet comparison because a large number of them are likely to have had or could have had relatively advanced coronary atherosclerosis. In any event, a nonCHD death cannot be scientifically interpreted to indicate no serious atherosclerosis. Therefore, regardless of Kushi et al.'s interpretations of their data, the results were so badly confounded, no interpretation is even minimally meaningful.

Apparently not recognizing (or ignoring) the confounded nature of their results, Kushi et al. interpreted Table 4-9 as follows. "Those who died consumed significantly less total carbohydrate and fiber than those who did not die, and also tended to consume less starch and vegetable protein." Not only is this statement incorrect, i.e., "those who did not die" included the above noted 224 individuals who did die, it must be again emphasized that there is no scientific evidence that carbohydrates or starch per se, or fiber are related to CHD, independent of lipids. It is therefore irrelevant and meaningless to suggest that they influence CHD.

Kushi et al. also stated that "Cholesterol consumption was also significantly greater among those who died from CHD." Whether absolute or converted amounts of dietary cholesterol are considered the differences of 18-21 mg per day is so small, only the highly biased lipid enthusiast would suggest that it has clinical importance.

The fact is that the diet compositions of those who died and did not die of CHD were effectively identical. Moreover, the fact that all those results were badly confounded renders the entire analysis a meaningless exercise.

It is to be noted that lipid enthusiasts always attempt to show that blood cholesterol distinguishes between those who do and do not die of CHD. While blood cholesterol levels were presented for the original cohorts, they were conspicuously absent in Kushi et al.'s within population analyses. This omission must have been purposeful and the only reason for purposely omitting blood cholesterol levels would be to omit evidence against the lipid hypothesis.

In their discussion, Kushi et al. said, "The associations reported here between diet and death from CHD can only be viewed as suggestive. We had no information about individual subjects between the initial examination during the early 1960s and the ascertainment of vital statistics some 20 years later. It is not known whether these men made important changes in their diets during the years after they were first seen. The interpretation of the associations thus assumes that the initial patterns of relative dietary content and other risk factor held constant." Not only was that assumption highly tenuous on common sense grounds, there is abundant evidence that populations and individuals do change their diets over time quite substantially. Major food trends over time have been indicated by USDA availability studies. Dietary changes in subpopulations were amply demonstrated in the Seven Countries study by Keys and his

Table 4-9

Nutrients consumed by those who did and did not die of CHD in the 20-year follow-up of the Ireland-Boston Diet-Heart study (adapted from Kushi et al., 1985[472])

Nutrient	No CHD death (n = 891)	CHD death (n = 110)	Significant?
Total calories	3,355	3,208	No
% Calories as			
Protein	15.5	15.2	No
Fat	38.5	39.4	No
Animal	31.7	32.8	No
Vegetable	6.8	6.7	No
Saturated	16.9	17.4	No
Monounsaturated	18.9[a]	19.4[a]	No
Polyunsaturated	2.7	2.6	No
Carbohydrate	42.7	41.2	Yes
Cholesterol (mg/1,000 Cal)	248	266	Yes
Total Cholesterol (mg)	832	853[a]	?
Fiber (g/1,000 cal)	0.81	0.75	Yes

[a] None given by Kushi et al.

colleagues (Volume 1). Anyone who has lived as an adult for 20 years has surely observed major changes in food consumption at home and at restaurants. It is simply inconceivable that Kushi et al. could make such an assumption. Despite the fact that their analysis was based on substantial flaws, confounded data, untenable assumptions and, sufficient by itself, totally unimpressive data, Kushi et al. concluded that "Overall, these results tend to support the hypothesis that diet is related, albeit weakly, to the development of CHD." What else could they say? Alliance members must always interpret results as supportive of the diet-CHD hypothesis.

As a footnote, Kushi et al. neglected to note that subjects contracting CHD in the Framingham and Honolulu Heart studies consumed less dietary cholesterol and slightly less fat and saturated fat than did subjects who were free of CHD.[903]

The NI-HON-SAN Study. A prospective study was undertaken in 1965 to compare the death rates and risk factors of Japanese males living in Japan, Honolulu and San Francisco. It was referred to as the NI-HON-SAN study and its purpose was to compare populations unconfounded by "genetic, environmental and cultural variation between countries and by differences in the observational techniques used from one country to another."[3396] However, it seems obvious that only genetics were held relatively constant. Certainly there were substantial environmental and cultural differences between the three geographic regions. More importantly, as will be discussed later, perhaps the most significant factor of all was uncontrolled, i.e., different people and different techniques were used to measure risk factors and assess cause of death. It is also likely that morbidity assessments also varied somewhat. In fact, the NI-HON-SAN study and the continued follow-on of the Honolulu cohort (Honolulu Heart Program) was so replete with methodological flaws, it is not far behind the Seven Countries study as a model of how not to conduct a prospective study. Before critiquing the NI-HON-SAN study, however, it is useful to discuss a study by NHI (Gordon[3397]) which appeared to be the seed from which the NI-HON-SAN study grew.

Small pilot studies are often conducted before a full-scale program is undertaken in order to determine feasibility and likely outcomes. Gordon's report, which examined the mortality statistics of Japanese males living in Japan, Hawaii and the U.S., appeared to provide the basis for the NI-HON-SAN study. However, Gordon's data base appeared to contain substantial errors and her analyses and conclusions left much to be desired.

One glaring flaw suggesting an erroneous data base was the difference in total mortality rates between white and Japanese Americans in 1950. The white mortality was reported to be 21% greater than the Japanese American rate (37% greater for ages 55 and over). These differences are highly unlikely to be real and probably reflect errors in tabulating the population of Japanese in America. A similar but updated paper by Gordon[3398] in 1967 provides additional evidence for questioning the data base. That paper showed the all-cause death rate to increase slightly (1,042 to 1,099) among all white Americans and to decrease greatly among Japanese Americans (899 to 646). According to her data, therefore, the total mortality of all white Americans in 1960 was 70% higher than all Japanese Americans. Her data also indicated that the total death rate of white Americans was 71% higher than of Japanese living in Hawaii. Incredibly, Gordon simply accepted these data without questions, even though it must have been evident that they had to be in gross error.

The above discussion indicates that none of Gordon's analyses regarding differences between Japan, Hawaii and the U.S. was correct because her data base was wholly incorrect. Nevertheless, it is useful to present further problems with her analyses.

The 1957 report showed that the all cardiovascular death rate was effectively identical for all ages of Japanese males living in Japan, Hawaii and the U.S. Since all cardiovascular diseases are said by NHLBI/AHA to be due to the same underlying cause, i.e., arterial atherosclerosis, and since diet was said to be a cause of atherosclerosis in the early 1960s, it was illogical to propose that dietary differences could be the cause of these opposite trends in CHD and stroke and to initiate the NI-HON-SAN study which, of course, was intended to demonstrate that diet affected atherosclerosis development.

Other flaws in Gordon's data base are easily seen. For example, the all cardiovascular death rate in Hawaiian Japanese and U.S. Japanese in 1950, ages 55-64, were 795 and 808 per 100,000, respectively, almost identical to that of Japanese in Japan (793), but in 1960 they both decreased precisely 42%, while the Japan rate increased 10%. Similar but somewhat less outrageous trends occurred for the remaining age groups. This massive difference between the Japanese and American populations is again not likely to have occurred, particularly in the space of only 10 years.

Another flaw can be seen in the arteriosclerotic heart disease mortality rate presented in Gordon's 1967 report. While the reported CHD mortality epidemic in the U.S. occurred throughout the 1950s, her data showed that the rate decreased in Japanese Americans rather substantially. These opposite trends cannot be explained by diet unless one assumes that Japanese Americans moved increasingly toward vegetarianism during the 1950s, an assumption that is likely to be the opposite to reality.

Gordon's 1967 report also showed that stroke mortality among Hawaiian Japanese was the lowest among the three populations, not intermediate as will be emphasized repeatedly in follow-up reports of the NI-HON-SAN study. Yet another discrepancy was related to differences between males and females. Native born Japanese American males were reported to have much higher CHD death rates than foreign born Japanese Americans in 1960, while the opposite was reported for females. These opposite trends again make no sense and cannot be explained by dietary differences.

In short, Gordon's data base can only be adequately explained by admitting that much of the mortality statistics is more influenced by changing diagnostic fashions and requests of "next of kin" than anything else. Gordon apparently anticipated criticisms of her naive interpretations and offered the following. "The first instinct of experts in vital statistics is to appeal to a difference in medical certification in such a case, the classic 'reporting artifact.' This is a possibility, of course, but against it must be weighed the frequency with which a 'stroke' can be recognized and described quite unequivocally."[3398] While it is certainly true that stroke can be diagnosed accurately after death, it is equally true that CHD cannot without an autopsy. And as emphasized elsewhere in this volume, cause of death on death certificates is influenced by (1) family members who wish certain causes to be used instead of others, e.g., cardiac arrest instead of drug overdose, and (2) a complete lack of knowledge about the deceased, leaving the task to guessing or selecting "fashionable" causes. Earlier in this chapter evidence was presented that the Japanese culture considers stroke to be the more desirable and CHD the less desirable certification of death.

A rational analysis of mortality statistics would have led NHI to not conduct the NI-HON-SAN study. But such was not the case and it will be seen that the study was also performed with scientific abandon.

Next to the Framingham study, the NI-HON-SAN/Honolulu Heart Program was (and is) the best example of salami-slicing, discussed in Chapter 9. Many authors published many articles containing bits and pieces of the results from these studies. However,

seven will suffice here to demonstrate that the studies were flawed to the extent that the results were entirely meaningless.

The Japanese, Hawaiian and California samples used in the NI-HON-SAN study consisted of 2,141, 8,006 and 1,844 men, respectively, ages 45-64.[3396] The follow-up periods were 6, 2 and 4 years, respectively.[584] The 6 year period for the Japan cohort was said to "compensate for the smaller sample at risk." However, the California cohort was the smallest of all but was followed for only 4 years.

The mean blood cholesterol levels of the Japan, Honolulu and San Francisco cohorts were reported to be 182, 218 and 225 mg, respectively.[1534,1795,a] However, these values were in error for two reasons. First, measurements of all subjects were performed without regard to a fasting period. More importantly, the Japan cohort was measured in Japan, while the Honolulu and San Francisco cohorts were assessed in San Francisco.[1795] An interlab reliability check showed that the San Francisco lab averaged 7 mg higher values for the same blood samples than the Japan lab but there was no statement by the authors that they adjusted the cholesterol values to compensate for the inherent variability. It would appear, therefore, that all analyses involving the Japanese cholesterol value were in error. Since study results depended so much on cholesterol values, it was scientifically inexcusable to use two different laboratories and not to adjust the values when it was known that there was significant interlab variability.

Estimates of the nutrients typically consumed by the three cohorts were obtained by interviewing subjects and asking them what they ate during the last 24 hours. The authors maintained that "it is believed that the...24-hour recall...method, practical for use with a very large sample size, yields results suitable for this kind of epidemiologic study."[550] However, not only is it effectively impossible to assess nutrient intakes with an accuracy level "suitable" for an epidemiologic study, they obtained data that should have convinced them that their method was inadequate. For example, they obtained 7-day nutrient intake estimates (still inadequate for long-term studies) and correlated these data with the 24-hour recall data. Although they obtained correlations of 0.4 to 0.6, meaning that one technique could explain only 16% to 36% of the variation in the second technique, they absurdly concluded that these very low correlations "indicate reasonably good agreement." The fact is that they were apparently shackled with the 24-hour recall method by design and attempted to justify its use by improperly interpreting correlation coefficients.

Not only was the California cohort size small compared to the other cohorts, the authors also obtained dietary intake estimates from a very small proportion of the cohort (9.7%), while estimates were obtained on nearly 100% of the other cohorts. Thus, yet another bias was introduced in a study that already was becoming burgeoned with biases.

Examination of the obtained dietary data also reveals some very obvious errors that should have been easily detected by "experts" purporting to be knowledgeable of nutrition and the dietary habits of Americans. Table 4-10 shows the most relevant data from the study.[550] One only has to look at the percent of calories as saturated fat for the Honolulu and San Francisco cohorts to see that these data are grossly in error.

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[a] Kagan et al.[567] plotted the cholesterol levels in figure form and showed the Japanese cohort to have a cholesterol level a few milligrams lower than reported by Nichaman.

Table 4-10

Estimated intakes of selected nutrients in the NI-HON-SAN cohorts (adapted from Kato et al., 1973[550])

Nutrient	Japan	Honolulu	San Francisco
Total calories	2,164	2,275	2,262
Total fat (g)	37[a]	85	95
Saturated fat (g)	16	59	66
Unsaturated fat (g)	21	26	29
Cholesterol (mg)	464	545	533
% calories as fat	15	33	38
% calories as sat. fat[b]	7	23	26
cholesterol/1,000 cal.[b]	214	240	236

[a] Numbers were rounded.

[b] Not calculated by authors but calculable from data.

Many surveys in the U.S. over the last 25 years have shown that Americans do not consume more than about 14% of calories as saturated fat (see Chapter 3). Japanese Americans, whether in Hawaii or San Francisco, most certainly would not consume greater amounts. Hence, the values listed in the table for the Hawaiians and San Franciscans, i.e., 23% and 26%, respectively, are, without a doubt, at least twice as great as the amounts normally consumed and probably more than twice as great.

The above noted surveys have also shown that total dietary fat among American adults averages about 36% of calories. Thus, the values listed for the Hawaiian and especially the San Francisco cohort are probably several percentage points in excess of reality.

U.S.D.A. data indicate that the total per capita availability of dietary cholesterol in the U.S. was about 540 mg at the time the NI-HON-SAN was initiated and the above national surveys indicate that males 40-69 years consumed an average of about 460 mg per day. Thus, the values listed for the Honolulu and San Francisco cohorts, whose diets were by no means completely westernized, were clearly much too high and it seems probable that the value listed for the Japan cohort was also too high.

While one might argue that even significant error is tolerable in an epidemiological study if it is random--since relative differences between cohorts are of most importance, not absolute amounts consumed--the evidence presented above largely suggests that there was substantial bias with regard to the nutrients most often related to the atherosclerotic disease, namely fat and saturated fat. When we acknowledge also that the diets in the San Francisco cohort were only sampled and the fact that the 24-hour recall correlated poorly with a "validity" test via a 7-day food survey, one cannot have any faith whatsoever in the NI-HON-SAN dietary data.

Kato et al.[550] computed correlations between dietary nutrients and blood cholesterol levels within each of the three cohorts. Table 4-11 presents the correlation coefficients for the relevant nutrient intakes. Kato et al. claimed that this "correlational analysis showed consistent and positive relationships between serum cholesterol level and dietary intake of saturated fat...and dietary cholesterol." The word "consistent" is hardly appropriate in view of the fact that the correlations were so close to zero. These nutrients could not explain more than 0% to 2.9% of the variance in blood cholesterol, regardless of the statistical significance achieved. The authors did acknowledge that the correlations were "relatively small" and "emphasize the importance of other, perhaps nondietary factors." However, they did not draw that conclusion while making between cohort comparisons.

The reader should also note that the authors used absolute levels of dietary cholesterol, rather than cholesterol per 1,000 calories. Kushi et al. in the previously discussed Boston-Ireland study and Shekelle et al. in the to-be-discussed Western-Electric study insisted that cholesterol per 1,000 calories consumed was the proper unit. However, one soon learns from the literature that the alliance's "proper" unit is always that which shows statistical significance.

Thus far, we have seen that there was bias introduced in measuring blood cholesterol across the three cohorts and that the measurement of dietary nutrient intakes was accomplished by a known unreliable and highly inaccurate technique. And none of the authors expressed the least bit of concern about these errors. It is not surprising, therefore, that they were also unconcerned about the fact that mortality and morbidity were assessed differently for each cohort.

The subjects in Japan were examined initially and "the majority were examined and followed up during three successive 2 year periods of risk between 1965 and 1972."[568] However, because the Japan cohort was followed for 6 years, subjects surpassing 68 years of age at the end of two and four years were eliminated to maintain the same

Table 4-11

Correlation coefficients between blood cholesterol and nutrient intake (adapted from Kato et al., 1973[550])

Nutrient	Japan	Honolulu	San Francisco
Total calories	.11[a]	.06[a]	.00
Saturated fat (g)	.15[a]	.07[a]	.07
Cholesterol (mg)	.12[a]	.04[a]	.14
% calories as fat	.13[a]	.12[a]	.12
% calories as sat. fat	.15[a]	.10[a]	.17[a]
cholesterol/1,000 cal.	___[b]	___[b]	___[b]

[a] Statistically significant.

[b] Not computed.

age range across cohorts. Thus, the sample decreased in size over time. The average follow-up period was 5 years.

The written protocol for determining nonfatal CHD in the Japan cohort was presumably the same as that used for the Honolulu cohort.[568] In view of all the other variation existing in the NI-HON-SAN study, it is doubtful that standardized diagnostics were indeed followed without variation. However, in the absence of specific evidence to the contrary, this critique gives the authors the benefit of the doubt on this issue. Cause of death statistics, on the other hand, are quite another matter. Worth et al.[1794] made it clear that Japanese physicians "customarily completed death certificates without benefit of autopsy reports, i.e., even though about 33% of deaths were followed by autopsies, the autopsy reports were not used to certify the actual cause of death. Worth et al. indicated that "while there still might be differences in accuracy of certification between autopsied and non-autopsied cases, there is no reason to believe these differences are large." This is a remarkable statement in view of the fact that CHD is almost impossible to diagnose accurately without autopsies.

Worth et al. presented a sample of 327 deaths for which autopsy and death certifications were available. The autopsy reports indicated that 4.6% of the deaths were due to CHD. This is about half of that reported in the World Health Organization Statistics Annual[3273] for the appropriate age group during the 1965-1969 period. Similarly, the autopsy reports indicated an 18% rate of strokes, while the WHO Annual listed about 24%. Thus, the Japanese cohort was uniquely peculiar because the autopsy reports greatly underestimated cardiovascular death rates in Japan which themselves probably underestimate the true rates in Japan, as discussed previously in this chapter.

The NI-HON-SAN investigators provided evidence that the Japan cohort was indeed peculiar.[567,1794,3396] It derived from a population of 100,000 persons in the Hiroshima and Nagasaki cities who were already involved in a long-term study by the Atomic Bomb Casualty Commission to investigate the delayed effects of radiation. Since apparently a large percentage of the cohort was exposed to radiation, it is perhaps not surprising that 77% of the autopsies showed causes of death other than cardiovascular diseases. In any event, selection of the Japan cohort was totally inappropriate because of its underlying radiation problem.

The custom of not using autopsy reports to certify causes of death in Japan is rarely, if ever, analyzed by alliance members and deserves further discussion here. The question is, what possible reason could there be for rejecting objective evaluations and retaining subjective opinions? It seems more than obvious that physicians wished to base cause of death on factors other than actual causes of death. It was emphasized earlier in this chapter that stroke is a culturally preferred legal cause of death, while CHD is undesirable. Clearly, certifications of death were heavily influenced by "next of kin," a custom that is not at all invisible in the U.S.

Contrary to Japan custom, death certifications in Honolulu are "customarily" accomplished <u>after</u> physicians receive autopsy reports. And since a greater percentage of cohort deaths were autopsied in Honolulu than in Japan (50% vs 33%) the sum total is that the death certificates in Honolulu <u>must</u> have been considerably more accurate than those in Japan. Worth[1794] noted that of 580 autopsies performed in Hawaii, 20% of the deaths were attributed to CHD, nearly 4 1/2 times more frequent than that reported in the Japan cohort autopsies.

In keeping with the alliance's policy to treat U.S. cohorts in international studies with substantially less scientific vigor than for foreign cohorts, no follow-up exams were performed on the San Francisco cohort. Instead, questionnaires were mailed to

subjects after 2 and 4 years.[584] Medical records were obtained for all persons who indicated on their questionnaires that they might have CHD. Needless to say, this was an extremely poor way to conduct a between countries study and must have contributed error over and above that inherent in the examinations. The likelihood is that the questionnaire/follow-up method underestimated CHD events, but it is impossible to know in what direction the bias actually occurred.

Like Hawaii, death certifications in San Francisco occurred after autopsy reports were received by physicians--when autopsies were performed. According to Worth et al.[1794] 55% of the San Francisco cohort was autopsied. Robertson et al.[584] made an interesting statement, i.e., "For cohort decedents with suspected CHD, copies of death certificates, clinical information relating to terminal illness and autopsy findings were sent to the mortality reviewer." The implication of this statement is that no information about deaths were sent to the reviewer if the investigators did not suspect CHD. One would hope that the reviewer would have all available data on all decedents.

Having now discussed the rather uncontrolled and occasionally naive methods of measuring blood cholesterol levels, nutrient intakes and CHD endpoints, we now turn to the reported relationships between these variables. As will be seen, it is most appropriate to first examine total mortality rates. Table 4-12 presents the data published by Worth et al.[1794] in 1975. They represent the total enumerated men in the three cohorts and not the number that participated in the NI-HON-SAN study. As can be seen, the total annual mortality rate in the Japan group was 16.5 per 1,000 persons, more than twice the rates in Honolulu (7.5) and San Francisco (8.1) which were nearly identical. It is astonishing that the NI-HON-SAN investigators acknowledged the differences in total mortality rates and yet focused entirely on CHD rates as though they reflected greater benefits of the Japanese lifestyle, while the higher total mortality rate was of no consequence.

The CHD mortality rate in Japan was only slightly lower than that in Honolulu and 50% of that in San Francisco. The slight difference between the Japan and Honolulu rates clearly does not correlate with the wide differences in blood cholesterol levels and diets discussed earlier.

Table 4-13 shows the combined fatal and nonfatal CHD events and rates in the NI-HON-SAN study for each of the cohorts. Since morbidity was assessed by questionnaire in San Francisco, it was compared to similar questionnaire data used in the Hawaii cohort. Thus, comparisons in the study were those between Japan and Honolulu and between Honolulu and San Francisco. The annual event rate and CHD death rate in the Japan cohort were reported to be about 50% lower than those in Hawaii and the latter were about 26% and 43% lower than those in San Francisco, respectively. The NI-HON-SAN investigators insisted that the differences were real and systematically ruled out the possibility that there were any diagnostic errors. All indications are that CHD is under-reported in Japan and over-reported in the U.S. In particular, it is probable that the CHD death rate was under-reported in Japan. However, there is no way to determine the extent of error that occurred in the study and we will, therefore, assume in the following discussion that the data in Table 4-13 are valid.

To place these data in a perspective that most people can appreciate, they indicate that over a 20-year period Hawaiians would have 2.8% more CHD events that would Japanese and that San Franciscans would have 2% more CHD events that would Hawaiians. These are not terribly impressive differences, especially when we consider them in the context of the "big picture." Robertson et al.[584] chose not to do this and concluded that "some change in environmental or living habits has altered susceptibility to the disease." Let us consider a prospective study in which 100% of a

Table 4-12

Annual mortality rates per 1,000 men in Japan, Honolulu and San Francisco (adapted from Worth et al., 1975[1794])

Cause of death	Age at death	Japan[a]		Honolulu[b]		San Francisco[c]	
		No.	Rate	No.	Rate	No.	Rate
All causes	50-54	95	9.4	89	4.5	13	3.3
	55-59	150	13.9	89	7.6	26	13.9
	60-64	302	24.5	134	13.7	18	14.8
	Total	547	16.5[d]	312	7.5[d]	57	8.1[d]
CHD	50-54	4	0.4	22	1.1	5	1.3
	55-59	15	1.4	20	1.7	9	4.8
	60-64	26	2.1	38	3.9	6	4.9
	Total	45	1.4[d]	80	1.9[d]	20	2.9[d]

[a] Total enumerated men = 9,329.
[b] Total enumerated men = 11,148.
[c] Total enumerated men = 2,180.
[d] Calculated by the present author.

Table 4-13

Fatal and nonfatal CHD events in the NI-HON-SAN study (adapted from Robertson et al., 1977[584])[a]

	Number in chart	Person years at risk	CHD events[a]	Annual rate per 1,000	CHD deaths	Annual rate per 1,000
Japan	3,096	9,908	16	1.6	4	0.4
Honolulu	7,705	15,410	47	3.0	13	0.8
Honolulu	7,705	15,410	44	2.8	13	0.8
San Francisco	___[b]	7,172	27	3.8	10	1.4

a Myocardial infarctions and CHD deaths.
b Not given.

cohort's subjects died of cancer. Which of the following poses the most important scientific question:

"What environmental or lifestyle factors were involved that caused the total elimination of CHD in this cohort?;" or

"What environmental or lifestyle factors were involved that caused such a high cancer rate?"

Robertson et al. and other alliance members would, of course, select the first question, although it is clearly the least appropriate by far. In this respect, it is noteworthy that the NI-HON-SAN investigators apparently did not publish all-cause death rates for the specific cohorts. The reason for this omission is undoubtedly because it would have been embarrassing to suggest that lower blood cholesterol levels and vegetarian diets led to lower CHD rates when the same data can be associated with higher all-cause rates. It will be recalled (Table 4-12) that the larger enumerated groups showed a 100% greater all-cause death rate in Japan than in Honolulu or San Francisco. Not only is this finding far more important than differences within subdivisions of all-cause deaths, it also provides one reason for the observed CHD differences. If the Japanese died much more frequently than Americans of causes other than CHD, then it is unimpressive that their CHD rates would be lower.

It was indicated earlier that the Japan cohort was composed of individuals exposed to radiation emitted from the nuclear explosions in Hiroshima and Nagasaki. Some 85% of the subjects involved in the two U.S. cohorts were second generation immigrants. Thus, selection of the Japan cohort was, in reality, a biased selection because it had a greater likelihood of sustaining higher cancer rates. It is virtually impossible to comprehend the statement by Robertson et al. that "The cohort in Hiroshima and Nagasaki is considered appropriate for comparison with the Japanese resident in Hawaii and California."

It was noted earlier that the mean blood cholesterol levels for the Japan, Honolulu and San Francisco cohorts were 182 mg,[a] 218 mg and 225 mg, respectively. Marmot et al.[1534] admitted that "The fact that...the California Japanese have a higher CHD prevalence indicates that differences in serum cholesterol do not completely account for the Japan-Hawaii-California differences in CHD prevalences." Indeed, the word "completely" is quite misleading. The difference of 7 mg between the Honolulu and San Francisco cohorts is simply too small to explain anything. Marmot et al. also pointed out that "at equivalent levels of cholesterol, California Japanese still have higher CHD prevalence." (They also said that "at equivalent levels of blood pressure, the high California prevalence persists.") Marmot et al. concluded that "These facts, plus the near universality of smoking in Japan, suggests that conventional risk factors only partly explain the observed gradient in CHD." In reality, most of the important data regarding risk factors did not support the hypothesis that differences in CHD events were due to risk factor differences and it was inappropriate to suggest that such differences were even "partly" supportive, just as it is inappropriate to suggest that 10 "tails" in 100 tosses of a coin "partly" supports the notion that the coin is biased toward falling on "tails."

If risk factor differences could not at all account for CHD differences between Honolulu and San Francisco, it would be scientifically dubious to claim that they account for the differences between the Japan and Honolulu cohorts. But that is precisely what Robertson et al.[568] concluded. To use the coin tossing analogy again,

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[a] Recall that this value should have been adjusted upward by at least 7 mg.

if a coin lands on "heads" once and "tails" once in two tosses, it is illogical to conclude that the "heads" occurrence does not support the biased coin hypothesis but the "tails" occurrence does provide support.

Of considerable importance, but given very little visibility, was a finding cited by Carruthers[333] attributed to Marmot. Carruthers reported that "studies by Dr. Michael Marmot of Japanese living in San Francisco have clearly shown that the results of the NI-HON-SAN study are more likely due to social changes than dietary ones [and thus blood cholesterol variations]. He found that those who lived according to Japanese tradition as well as eating the Japanese diet had the same low incidence of CHD as those living in Japan. If, however, with disruption of the family-support system, even though they kept to traditional Japanese food, heart attack rates went up to those experienced by the rest of the population of San Francisco." This trend could be real or merely due to an acceptance of death certification "fashion" in the U.S. It most certainly cannot be attributed to diet.

In sum, despite the fact that the NI-HON-SAN investigators suggested that their between populations study was well-designed and analyzed, it was, in fact, replete with design flaws, including inappropriate selection of cohorts, uncontrolled and/or unstandardized diagnostic techniques, exceedingly poor and unreliable methods for determining nutrient intakes, and inappropriate use of two laboratories with known interlab unreliability to measure blood cholesterol levels. And like other between population studies such as the Seven Countries and the MONICA investigations, the continental U.S. cohort was poorly conceived because it was much smaller than the other cohorts, was not subjected to follow-up exams, and was totally inadequately assessed for nutrient intakes. It is amazing that so many profound conclusions are drawn suggesting that high CHD rates in the U.S. are due to high fat and saturated fat intakes and to high levels of blood cholesterol from studies in which U.S. cohorts are so very poorly represented and assessed. In the 1991 report by the NCEP's Expert Panel[3361] Carleton et al. presented the following totally distorted "review of the NI-HON-SAN study."

"Other epidemiologic studies have also observed high correlations between dietary saturated fatty acids and CHD. In this vigorous and detailed study, prevalence rates of CHD were found to be lowest in Japan and highest in California [note no mention of all-cause death rates]. Further, CHD rates in the three populations were correlated with blood cholesterol levels [but cholesterol did not discriminate between two of the populations]. There was a particularly high correlation between percent of calories from dietary saturated fatty acids and CHD rates in these populations [totally false]." so much for an "objective" evaluation by the NHLBI/AHA alliance.

The Honolulu portion of the NI-HON-SAN study continued as a standard prospective study. It is discussed later in this chapter as a within-populations study.

The Intersalt Study. The notion that high intakes of salt cause high blood pressure has never been scientifically established. Thus, the Intersalt study, comprised of 52 population groups from 32 different countries, was conducted in the hope of providing such scientific evidence.[2771] After the study was published an article in Internal Medicine News stated that "Results from a multicenter, international study of 32 countries have confirmed that populations with a low salt intake have little or no hypertension."[2676] Also, Stamler[2109] stated that the Intersalt study produced "abundant, rich, and precise confirmation" of the relation between sodium intake and blood pressure. But such statements were highly inaccurate descriptions of the results of the Intersalt study. For example, Bennett and Gilbert[2675] pointed out that "A significant positive correlation between a high level of sodium excretion and elevated blood pressure was identified at only 8 of 52 study sites. At two centers, increased sodium excretion was associated with lower blood pressure. Overall, the study showed

that a change of only 2/0.1 mm Hg in blood pressure would be predicted by a change of 100 mmol (3860 mg) in sodium excretion. Even this minimal change would have disappeared if four centers whose enrollees with an extremely low sodium intake had been excluded from the analysis." Indeed, Massie[2109] indicated that the Intersalt study showed that a blanket salt restriction is like "using a sledgehammer to hammer a pin."

After adjustment for other key variables, sodium excretion was significantly associated with systolic blood pressure within only 8 centers and with diastolic blood pressure within zero centers.

The authors of the Intersalt study presented no correlations between diastolic or systolic blood pressure and sodium excretion between centers after adjusting their data for other key variables. Observation of their scatterplots suggested that the correlations were quite small. Much of their "positive" results depend on four unique groups, i.e., two Brazilian Indian populations, a Papua New Guinean population and a Kenyan group. The authors admitted that these groups "substantially influenced associations in linear regression and Pearson correlation analyses."

There were six U.S. cohorts in the Intersalt study, including blacks, whites and orientals. The rank order correlations between these groups with respect to sodium excretion and diastolic and systolic blood pressure were .26 and .26, respectively, indicating that sodium excretion accounted for no more than 6.8% of the variance.

The Intersalt authors drew the following erroneous or misleading conclusions: (1) sodium excretion was significantly related to blood pressure in individual subjects within centers; and (2) sodium excretion was positively associated with blood pressure across all 52 centers but not across 48 centers when the four peculiar cohorts are excluded. They indicated that two-sided "conservative" statistical tests were used on the data to ensure significance but one can only wonder why they applied statistical tests at all because they interpreted their results as though "positive associations" were synonymous with "significant." Moreover, a few significant findings were given far greater weight than many nonsignificant findings.

In a separate report, Stamler et al.[3238] indicated that "sodium excretion was significantly and independently related to the systolic blood pressure of individuals." The implication of this statement was that such a finding was observed at all 52 centers. Stamler et al. completely omitted the fact that the significant relationship was observed for only 8 of the 52 centers. They also indicated that the association between sodium excretion and blood pressure was "not as strong or consistent for diastolic pressure" when, in fact, no significant associations were observed for any of the 52 centers. Stamler also reported that "Across populations, the level of sodium excretion correlated with the slope (increase) of blood pressure..." They subsequently admitted, however, that significance was not achieved when the above noted rare Indian/native populations were excluded from the pooled results. Not only were these populations not representative of Western countries, Stamler et al. admitted that they "strongly influenced the cross-center associations.

In keeping with his inclination to elevate positive results and ignore negative findings, even when the latter dominate the former, Stamler concluded that in the U.S. the "Average sodium intake should be reduced substantially over time."

In effect, the Intersalt study should have been interpreted as providing no evidence of a practical association between salt intake and blood pressure. Not only were associations few in number and weak in magnitude, as Bennett and Gilbert emphasized, even if all associations were significant, the results have no practical applications.

McGregor[2083] emphasized that recommendations on salt intakes are based on animal and epidemiological evidence, not on experimental evidence. Dustan[2109] noted that adding or subtracting salt from the diets of most hypertensives or normotensives has not been adequately shown to increase or decrease blood pressure, respectively.

Typical of epidemiologic studies was that of Gleiberman.[1121] She compared 27 populations and found a strong correlation between salt intake and blood pressure. But she listed a sizeable number of confounding factors that "render the comparison of epidemiological observations problematic." She pointed out that blood pressure instruments were different in different countries, methodologies were different, measurements were taken at different times during the year, sample selections were biased and methods of salt intake assessment "present further difficulties." Glieberman also observed that when the same populations were studied by different investigators, "wide differences in blood pressure levels" were obtained. Further, she acknowledged notable exceptions to the overall association, i.e., some populations have low intakes but high blood pressure and some have high intakes and low blood pressure.

A 1991 study published by Vartiainen et al.[3237] compared subpopulations in China, the U.S. and East Finland. Oriental diets typically have very high levels of salt so it was not surprising that the authors reported that the Chinese cohort had a high intake of salt. Yet, the cohort had the lowest levels of systolic and diastolic blood pressures.

WITHIN POPULATIONS

CHD Within the U.S.

Wide differences in CHD death rates between states and regions have long been known. For example, Sauer and Enterline[3156] presented an analysis of such differences in 1958. They concluded that the differences were real but did not attempt to explain their cause. Moreover, they failed to present a convincing case, although aspects of their discussion seemed reasonable.

During the 1975 FTC-NCEN trial a defense lawyer asked former NHLBI director Theodore Cooper to explain the wide differences in CHD mortality rates between divisions, regions and states of the U.S.[2688] Cooper first indicated that he had essentially no knowledge of the subject, cited no studies on the subject and then speculated that the reason for the differences was differences in diet, using the terms "I think" and "may." He said, "I could not be definitive here. I am just beginning to look into these kinds of differences in states and in a multifactorial analytical way in trying to get better data. But some of it, in my opinion, is due to the lifestyle, specifically. I think so, I think so. I think there are studies, say in the Southeastern United States, where if you do certain population studies, the diet pattern is different and it may have differences."

When a person is confronted with data that run counter to his position, he often rambles incoherently in an effort to extricate himself from an embarrassing situation. Cooper's statement was a perfect example. Part of it was totally illogical. For example, his last sentence says, in effect, "I think there are studies...where if you do certain population studies..." How can "there be studies where if you do certain population studies?"

In reality, each state and region of the U.S. has a different political system, a different medical system and different medical knowledges, fads and fashions, not unlike the differences observed between countries. It does not make sense, therefore, that adequate studies of between states and between regions should be excluded in favor of innumerable between country studies. This was emphasized by biostatistician

Lew[2732] in 1962. He said, "It should be noted that the variation in death rates from CHD within the U.S. are almost as great as those between the U.S. and countries reporting low death rates from this cause. An investigation of the reasons for the wide differences in death rates from CHD within the U.S. might well precede appraisals of the international differences in death rates from CHD. Yet, in the course of reviewing the literature, this writer found very few articles discussing CHD mortality differences and only one article relating diet with regions. And most of these articles presented extremely brief discussions. For example, in 1970 Stamler[561] stated that "sizeable differences exist among the major regions and the 50 states of the U.S.A. in mortality rates for premature CHD. For the states, these differences were almost 100% in 1959-61 for white males and females age 45-64. Even greater differences were recorded for nonwhites." He devoted a total of 4 sentences to the topic. Levy and Feinleib[1401] devoted 5 sentences to the topic, indicating that "marked regional differences can be noted."

Perhaps the most thorough discussion of regional differences was presented by Feinleib et al.[2810] in 1988. They said that the purpose of their paper was "to present regional data on morbidity and mortality from CHD in the U.S. in a manner that may permit analyses of possible causal relations between trends in medical care and the decline in CHD mortality." Note that although the alliance has attributed the CHD mortality decline to risk factor control to a far greater extent than to medical intervention, relating risk factor differences with regional CHD differences was conspicuously absent as a goal of Feinleib et al.

Feinleib et al.'s charts indicated that the 1980 CHD mortality rate of males 55 years and older was the highest in the Middle Atlantic states, followed by the East South Central states, the East North Central states, the New England states, the South Atlantic states, the West North Central states, the West South Central states, and the mountain and Pacific states (about the same).[a] Since this ranking appeared to correlate with population density, this writer computed the densities for the 9 regions by dividing the populations by the respective land areas (excluding lakes, rivers, etc.).[b] The Spearman's rho (rank) correlation was found to be .87. Although a correlation was not computed for females, it appears from Feinleib et al.'s charts that it would be almost identical with that for males. Thus, these data are consistent with most studies comparing countries, i.e., the more medically sophisticated a country (or region), the higher the CHD mortality rate.

Probably the most important studies on this topic were conducted in 1964 and 1965 by Borhani and Hechter[2982] and Hechter and Borhani,[3025] discussed in more detail in Chapter 9. These investigators noted that the CHD mortality decline in California began 11 years before the national decline was initiated (1953 vs 1964) and long before the population was influenced by AHA or government bodies. The CHD mortality rate also declined in Utah during the 1950s and it remained almost constant in the nation's most populated state, New York (an actual decrease was observed for females). Hechter and Borhani also reported that there were wide CHD mortality rates between California counties and that these rates were randomly distributed throughout the state.

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[a] These rankings were reported by Havlik and Feinleib[2796] to be somewhat different for the 1970 time frame, suggesting different dates of the CHD decline and rates of decline.

[b] Population figures were for 1977, about three years earlier than Feinleib et al.'s CHD data, but the densities are not likely to have changed much during that short period of time.

A more recent study by Rayland et al.[3009] uncovered yet another finding that conflicts with the risk factor concept. They found that the CHD decline occurred before 1950 in many states for specific age groups. For example, among 45-54 year old males, the decline occurred in 1931 (Maryland), 1941 (California) and 1949 (Montana). Among 55-64 year old females, the decline began between 1910 and 1945 in seven states.

Lew[2732] was obviously correct. With the huge differences in CHD mortalities between U.S. regions, states and even counties, it makes no sense at all to ignore or trivialize these differences and spend greater sums of money and time attemptimg to correlate risk factors with CHD among nations where the uncontrolled variables are much greater.

It was reported in Chapter 3 that Lew[2732] attributed lower CHD rates in some U.S. regions to an educational lag in the recognition of CHD as a cause of death. "The lag has naturally been greatest in those parts of the U.S. where medical standards and facilities have been the poorest. The same situation has probably been responsible for a substantial part of the differences in death rates from CHD between the medically backward and the medically advanced countries.

The only data found relating diets with U.S. regions was that of Eleanor Pao[2811] who presented a paper at a 1986 NHLBI sponsored conference. She noted that the USDA conducted nationwide food consumption surveys in 1965 and 1978 but indicated (strangely) that 1965 dietary data were available only for males in the southern and north-central regions. (One can only wonder why data for the other regions were not available 21 years after the survey was conducted.) Pao's data were restricted to fat intakes and showed that fat consumption as a percentage of total calories was higher in the southern region than the north-central regions.

Pao did not relate the fat consumption data to CHD mortality rates. Also, she did not define the north-central or southern regions but indicated that they represented half of four geographic regions. If one assumes that her four regions were identical to the four regions discussed in detail by Feinleib et al.[2810] (in addition to the 9 regions noted earlier), then Feinleib et al.'s CHD mortality data do not correlate at all with Pao's fat intake data. Results such as these have probably discouraged the alliance from conducting more extensive between regions and between states analyses. Kannel and Thom[1174] stated that "An attempt to correlate geographic differences in coronary mortality with geographic differences in risk factor levels was not successful" but they did not cite a single reference for the "attempt."

Before departing from this subject, it is useful to mention a correlation this writer computed between the CHD death rate and the suicide death rate among the regions from NCHS data.[2736] The rank correlation was -.97, meaning that the lower the CHD death rate the higher the suicide death rate. Thus, if one wishes to live in a low CHD region in the hopes of reducing his changes of dying from CHD, he should move to a high suicide rate region. Of course, this correlation is not causal and, of course, this recommendation is ludicrous but no more so than the literally thousands of correlations published and seriously accepted by alliance members.

The Framingham Study

Although the Framingham study is generally placed on a pedestal and at times almost worshipped by the public and research community alike, the data emerging from the study are no where near as scientifically "clean" as the public and research community are led to believe. While it is impossible for an observer such as this writer to determine precisely the error likely to be involved in Framingham data,

principally because the Framingham study has received so little critique by those intimately familiar with it, there are, nevertheless, certain indicators which suggest that Framingham data or presented Framingham data are not at all representative of even Framingham residents who are not involved in the study.

Problems associated with the study may be categorized as (1) methodological, (2) analytical, (3) presentational and (4) interpretational error. The first problem can generate error independent of the investigators, while the latter ~~two~~ three problems can be or are definitely generated by the study investigators.

Methodological Error. Since its inception a major methodological flaw was designed into the Framingham study which is purposely avoided in a proper scientific study. Most, if not all, of the Framingham data is confounded. As pointed out by Werko[2913] 14 years ago, a humanitarian policy virtually assured that the Framingham study would produce confounded results. To illustrate the effects of this policy, consider the basic design of a Framingham study and all prospective studies.[a]

Subjects are examined at so-called baseline in terms of known or potential risk factors and then are followed for some arbitrary period of time. Correlations or some similar associative measures are then computed to determine the strength of the relationship between levels of risk factors and the occurrence or absence of clinical CHD. For these relationships to be meaningful, the original baseline measures must remain stable for at least some significant period of time. For example, if the follow-up period is five years, the stability must remain for at least three to four years and possibly longer. Otherwise, the endpoints would be correlated with fleeting and unrepresentative measures of risk factors. This "natural" problem is compounded by the fact that the Framingham investigators effectively promote instability. That is, when subjects are determined to have "abnormally" high blood cholesterol levels or hypertension at baseline, such information is transmitted to the subjects' physicians. This procedure was documented in an early Framingham report by Kannel et al.[2093]

> "Upon completion of each examination a diagnosis was made using uniformly applied criteria as indicated below. An abstract of the findings was sent to the personal physician indicated by the subject. No medical advice was provided to any participant beyond encouragement to visit his physician if the need was indicated."

While such subjects and their physicians may not have acted on that information, the likelihood is that many, if not the majority, did act on it, particularly as Framingham investigators have established considerable credibility, rightly or wrongly. Although the disclosure of subjects' health status to their physicians may be considered to be an ethical necessity, it is a scientifically atrocious procedure. The entire 40-year Framingham program was and is designed to produce confounded results and Framingham investigators neither attempt to determine the extent of confounding or even address the problem.

As discussed elsewhere in this volume, little stability has been found in prospective investigations, such as the Seven Countries study, where risk factor measurements have repeatedly been made during follow-up periods. Regardless of whether or not Framingham subjects purposely altered their blood cholesterol levels after baseline, there is considerable evidence that levels did (and do) change significantly. This was evident in a 1966 article by Kahn and Dawber[3040] who determined the strength of the relation between CHD and blood cholesterol level measured at baseline and subsequent examinations. The very fact that they performed such an exercise at all indicated that blood cholesterol levels must have changed importantly. The fact that "Among

[a] The concept of studies within a study is addressed below.

men, the only [but most important] coronary disease category for which discrimination was substantially improved by using cholesterol measurements obtained after the first value was coronary heart disease death" indicates that cholesterol levels changed a great deal. (Note that this quote implies that later measurements also improved discrimination of other categories, although not "substantially.") The levels also changed among women since "cholesterol measures were consistently associated with a moderate improvement in risk discrimination over the original cholesterol value."

Although admitting that blood cholesterol levels were changing after baseline, Kahn and Dawber drew a most dubious and unreasonable conclusion, i.e., "On the basis of the present report, it would be premature to judge whether a long-term prospective study of coronary disease benefits sufficiently from periodic cholesterol measurements in the study population to justify the effort involved." In effect, knowing that blood cholesterol levels had changed over a relatively short period of time, Framingham investigators nevertheless went on to correlate baseline measures with CHD events over periods of 10, 20 and even 30 years. There is absolutely no question that the changing cholesterol levels produced errors in the Framingham data and the magnitude of the error undoubtedly increased with time.

Further (albeit indirect) evidence of changing cholesterol levels in the Framingham study was presented by NHLI statisticians in 1971. Truett and Sorlie[3041] developed a rather elaborate mathematical model which generated quite obvious "if-then" statements. To illustrate, assume that after following the Framingham cohort for 10 years, some subjects developed CHD (Group A) and some did not (Group B). If the difference between the two groups in cholesterol levels increased from baseline to the CHD event, then later cholesterol measurements would clearly be more predictive of the event than a baseline measure. If, on the other hand, the difference decreased, then the baseline measurement would be the best predictor.

This writer cannot understand why numerous pages of algebraic equations were necessary to arrive at conclusions that were more than obvious a priori. Moreover, since the purpose of the model was to determine the effects of successive measurements on prediction of CHD, it is dumbfounding why the model itself was published but not its application to Framingham data. In any event, the very fact that NHLI undertook this effort again indicates that blood cholesterol levels were indeed changing over time.

Perhaps even more basic than changing cholesterol levels over time is the accuracy of measurements taken at baseline. Volume 1 presented a wealth of evidence showing that blood cholesterol varies tremendously within individuals from day to day. With this in mind Dawber[3001] offered a most curious and unreasonable observation, i.e., "Although the Framingham study utilized only one [blood cholesterol] determination at initial examination, and this measurement quite accurately classified the population, in retrospect it would have been better to have performed several tests before a classification was made." In the first place, since several tests were not performed, Dawber could not logically draw the conclusion that the one measurement "quite accurately classified the population." In the second place, if the single measurement did indeed "quite accurately classify the population," why would it "have been better to have performed several tests before classification." If one reads between the lines, Dawber was really saying that several tests should have been performed because we have all learned that single tests yield highly inaccurate results. But, in fact, Dawber had to say that their single test "quite accurately classified the population" because anything less would be an admission that decades of follow-up studies were based on inaccurate data at entry.

The U.S. distribution of cholesterol levels shows a gradual increase in LDL to age 64 in men, e.g., the 95th percentiles for 35-44, 45-54, 55-64 and 65-74 age groups are 206 mg, 211 mg, 217 mg and 217 mg, respectively.[1066] The same percentiles for the

Framingham males are 176 mg, 203 mg, 228 mg and 226 mg. Thus, with the exception of 35-44 year-olds, the Framingham population reveals higher cholesterol levels for the age groups of most importance. The reader is also referred to Chapter 3 which provides further evidence that the Framingham blood cholesterol distributions were different from the U.S. population. Whether the higher cholesterol levels observed in Framingham subjects were due to peculiarities of this subpopulation or to different cholesterol measurement instruments/techniques or to both is unknown.

Werko[2913] discussed a number of other methodological problems with the Framingham study. For example, he pointed out that the Framingham subject population exhibited distributions of blood pressure, blood cholesterol, weight and smoking that were different from those of the Framingham community and other U.S. studies. Moreover, the CHD mortality rate of the Framingham population was different from that of the Framingham community and "there was a rather marked difference in cardiovascular and total mortality between those agreeing and those disagreeing to participate in the study." These and other problems effectively assure that the Framingham group was and is not a representative sample of the U.S. population. Yet, "...research workers of all kinds have used the Framingham data as if it represented the male population not only in the USA, but in the whole Western industrialized part of the world."

Analytical Error. One of the most peculiar analytic methods employed by Framingham investigators is the fact that the program consists of a large number of individual studies with different subgroups of subjects, follow-up periods and methods of analysis. Even Henry Blackburn criticized this method of conducting the program.[2044] As noted by Werko, "This makes it impossible for those outside the study to compare the published results from one time period to another. It is also impossible to compare the conclusions reached with those arrived at in other studies."

The original Framingham population consisted of 1,976 males who responded to the Framingham investigators' request to participate and 312 volunteers. Significant differences between the responders and volunteers were subsequently found but the combined group was analyzed as though it were a representative sample of the Framingham community.[2913] The effects of drop-outs on individual study results were never determined. In addition, all of the subjects in the individual studies who developed cardiovascular disease were subsequently dropped from the program, yielding progressively more biased (unrepresentative) samples over time.

The overall sample size was relatively small initially. The peculiar method of chopping up this sample into smaller subgroups with even smaller subgroups representing a very wide range of ages may have enabled the investigators to generate hundreds of journal articles (and hundreds of publications on personal resumes) but it is not the most scientifically acceptable way to conduct a prospective study.

Werko emphasized that "The tendency has been to use more and more elaborate statistical methods and less of the primary figures in consecutive publication..." Indeed, the 1957 Dawber et al.[2348] 4-year follow-up report used the simple Chi square test to determine the significance of the differences in CHD rates for different blood cholesterol levels. In the 1961 6-year follow-up report, statistical tests were apparently used but they were not mentioned (Kannel et al.[2093]). No statistical tests were described and few or no references to "significance" were made in the 8, 10 and 12-year follow-up reports (Kagan et al.,[2728] Kannel,[1885] Kannel et al.[554]).

Statistical test results without the mention of the tests themselves were also presented in the 1971 14-year follow-up study (Kannel et al.[1376]). It appears that regression analyses were introduced in this report as well, although the authors failed to give the reader even a modest description of their statistical analyses. For

example, they said that "...a more detailed examination of the relation of serum cholesterol to risk of coronary heart disease, using a more sophisticated type of analysis, is required. First, the relationships of serum lipids to coronary heart disease do not vary with the type of coronary heart disease so far as can be judged from the available data. The net contribution of cholesterol and ...[VLDL]...lipoprotein is about the same for uncomplicated angina as it is for other coronary heart disease. Cholesterol, as indicated by the size of the coefficient in Table 2, carries most of the weight as a contributor to coronary heart disease in men, whether manifested as angina or some more serious form of the disease." Thus, they began discussing coefficients without describing what they were or how they were derived.

Somewhat later in their article Kannel et al. said, "A discriminant analysis was also made of the relation of various lipids measured in the study to incidence of coronary heart disease after 8 years. The net effect of each of the lipids, including cholesterol, phospholipid, and the lipoprotein fractions..., was assessed. According to this analysis the dominant effect was assigned to serum cholesterol, with an insignificant contribution of the other lipids. In multivariate discrimination involving a number of highly correlated variables, however, a slight statistical advantage in one of these variables will lead to a marked depression of the discriminant weights assigned to the other variables." Again, Kannel et al. introduced the terms "discriminant analysis," "multivariate discrimination" and "discriminant weights" without defining them or indicating their derivation.

Two articles were published in 1977 by Gordon, Castelli, Kannel and their co-workers. The first appeared in May and introduced the terms "univariate and multivariate logistic regression coefficients" and again failed to adequately define them.[453] Statements such as "likelihood ratios of the logistic functions indicate how well the various risk functions fit the actual data" must surely have failed to penetrate the cerebrums of most readers. In an August report a logistic function was defined as an equation which used logarithms.[523] While statistician Tavia Gordon undoubtedly knew what she was doing, it is doubtful that either Castelli, Kannel or the typical reader had more than a cursory understanding of such equations, logs, regression, etc.

By 1979 tables of logistic regression coefficients were appearing regularly in articles by Kannel and Castelli.[1046] In 1981 the entire data set was composed of four tables of regression coefficients. Gordon et al. defined their analysis as follows: "The analytical method used is that of logistic regression in which the parameters are estimated by the method of maximum likelihood. This has been generally found to fit the data satisfactorily. The regression co-efficients are tabled in a standardized form (i.e., multiplied by the SD of the variable), which allows for a direct comparison of the strength of the relationship of each of the endpoints with HDL and LDL cholesterol and triglyceride levels." None of the statistical terms were defined and it is unlikely that the nonstatistician reader had any idea what Gordon et al. were talking about.

The presentation of reams of regression coefficients continued in subsequent articles by Castelli and/or Kannel.[1091,1096] In a 1986 article Castelli and Anderson[1531] presented a table of "univariate and multivariate logistic regression coefficients" and said nothing of their derivation. In another 1986 article Castelli et al.[261] introduced additional terms such as "proportional hazards models," "estimates of relative risk" and cited statistical books and articles instead of defining them. Consider, for example, the following: "Estimates of relative risk due to various risk factor differences are calculated by taking the exponential of the product of the associated regression coefficient from the proportional hazards model and the difference between the 80th and 20th percentiles of the sex-specific risk factor distribution." Similar presentations were given in later articles (Kannel[787,964,1448,3239]).

In 1986 Greenland et al.[3017] demonstrated that "standardized regression coefficients, correlations, and path co-efficients have no meaningful biologic or public health interpretations as measures of effect. We therefore recommend that their use be avoided in epidemiologic analysis." Indeed, regression analysis in general has greatly distorted the results of the Framingham study and that is undoubtedly the reason why such analyses have been repeatedly performed.

Chapter 3 discussed in detail the fact that a relatively large percentage of sudden deaths, including heart attacks cannot be attributed to atherosclerosis. The Framingham investigators are well aware of this fact. For example, Kannel et al.[3015] reported that 60% of the subjects in both the Framingham and Albany studies who died suddenly exhibited no prior evidence of CHD. Also, all of the subjects who died suddenly demonstrated no relationship with cholesterol level. Kannel et al. observed that "The proportion of sudden deaths attributed to CHD...varies widely, particularly in autopsy series." Yet, knowing all these facts the Framingham investigators have always included all sudden deaths as CHD events in their data analyses.

Despite its apparent preeminence among prospective studies, it is perhaps not fully appreciated how small the Framingham investigation really is. It is also easy to lose sight of the facts that Kannel and others recognized early on that blood cholesterol level was not a predictor of CHD at the individual level and that the relationship between cholesterol and CHD at the group level was very weak below 300 mg which comprises the vast majority of individuals. Regression equations and all of the mathematical chicanery used to support them cannot alter these basic facts. The combination of small numbers of subjects, small numbers of CHD events, weak to exceedingly weak relationships between cholesterol and CHD, not to mention the fact that a significant number of events (e.g., some MIs and sudden deaths) probably had little or nothing to do with atherosclerosis, presents an unimpressive data set that has been completely exaggerated by use of what might appear to be sophisticated statistical analyses but which are, in reality, rather simplistic and elementary "models" of the human system. The reader is urged to review Werko's[2913] discussion of this topic as it relates to the Framingham study.

Presentational Error. The most sensible and scientific way of showing a relationship between two variables is to plot one variable against the other, using equal interval scales. In the cholesterol-CHD case, the vertical scale typically represents the CHD death or "event" rate, e.g., events per thousand per year. This scale may be numbered 5,10, 15, 20 or 10, 20, 30, 40 or some similar sequence in which the distances between pairs of numbers of equal magnitude are identical. The horizontal scale represents the cholesterol scale. Ideally, this scale would range from about 100 mg to about 400 mg and would be numbered 120, 125, 130, 135 or some similar sequence of equal intervals. However, because the number of subjects in a study is usually relatively small and the variability in CHD events among subjects having the same cholesterol levels is very great, the scientifically acceptable way of scaling cholesterol levels is to use intervals of 10, 15 or 20 mg. For example, 100-119, 120-139, 140-159, etc. Since each interval is the same length, just as is the CHD event rate scale, the plotted linear or curvilinear relationship between the two variables will be a true representation of reality.

Unfortunately, Framingham investigators have seldom published true relationships between cholesterol level and CHD rate. The rate scale has often been replaced by "morbidity ratio" or "relative risk" scales. The cholesterol scale has typically been distorted by using a wide array of unequal intervals and a wide array of numbers of intervals. For example, in the first 4-year follow-up of the Framingham subjects, Dawber et al.[2348] used a scale having only 3 intervals, i.e., < 225, 225-259 and ≥ 260

mg. It is virtually impossible to generate a true relation between CHD rate and cholesterol level with such a scale.

In the 6-year follow-up Kannel et al.[2093] also used a scale having only 3 intervals and it was composed of different intervals, namely < 210, 210-244 and ≥ 245 mg. In the 8-year follow-up by Kagan et al.[2728] 6 intervals were used, < 200, 200-219, 220-239, 240-259, and ≥ 260 mg. However, CHD event rates were replaced with morbidity ratios.

The use of morbidity ratios continued in the 10-year follow-up (Kannel et al.[1885]) but not the (mostly) equal interval cholesterol scale used in the 8-year follow-up. Instead, two different scales were employed for different figures. One was a quartile scale, which, of course, was a completely unequal interval scale and the authors even failed to indicate the actual cholesterol intervals, i.e., the scale was numbered 1, 2, 3 and 4. The second scale was again composed of 3 intervals and they were yet a third version of the scale, i.e., < 180, 180-199 and 200-225 mg. Note that each interval was also different from the other.

The 12-year follow-up by Kannel et al.[554] presented yet a different cholesterol scale, while maintaining the morbidity ratio scale. Their cholesterol "scale" was composed of two intervals, combined Quartiles 1 and 2 vs Quartile 4. Not only were actual cholesterol levels not given, Quartile 3 was arbitrarily ignored.

The 14-year follow-up by Kannel et al.[1376] again presented different cholesterol scales. In one case Quartile 1 was compared with Quartile 4 and the two intermediate quartiles were dropped. In a second case, all quartiles were compared. In the third case, the most acceptable scale of all was used, i.e., < 180, 180-199, 200-219, 220-239, 240-259, 260-279, 280-299, and 300 mg. However, morbidity ratios were still used rather than event rates.

In 1977 Gordon et al.[453] presented the first 4-year follow-up of subjects with respect to HDL and CHD. CHD rate, rather than morbidity ratio, was used as the vertical scale. The cholesterol scale was also comprised of acceptable intervals, i.e., < 25, 25-34, 35-44, 45-54, 55-64, 65-74 and ≥ 75 mg. It is noteworthy to mention, however, that only 9% of the Framingham population fell within the first and last two intervals. Thus, only four of the intervals were relevant to 91% of the Framingham population. Although these data were presented again in much later articles by Castelli and Anderson[1531] in 1961 and by Castelli[2750] in 1988, neither indicated what the follow-up periods were, suggesting that they wanted the reader to believe they were long follow-ups.[a] One must question the stability of the HDL-CHD relationship reported for the 4-year follow-up since it was apparently never reported for longer follow-ups.

Subsequent reports published from 1977 to 1987 were dominated by tables of regression coefficients, relative risk values and repetitions of previous figures (Gordon et al.,[523] Kannel et al.,[1046] Gordon et al.,[581] Wilson et al.,[1096] Kannel,[1091] Castelli and Andersen,[1531] Castelli et al.,[261] Wilson et al.[1366]). All of these reports were redundant with each other and/or previous articles. But in 1987 Kannel published two partially redundant articles which presented perhaps the most important data relating blood cholesterol with CHD.[787,964] The vertical scale was a CHD event rate scale and the cholesterol scale contained five intervals, with the three intermediate intervals

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[a] Castelli[2750] cited a previous article of his[261] as the source of the HDL-CHD relationship but that article contained no such data.

being equal. These data, shown in Chapter 3 (Figure 3-26) and based on a 30-year follow-up, reveal an exceedingly weak relationship between cholesterol and CHD for cholesterol levels up to 294 mg.

Following the two revealing Kannel articles were more reports containing old and redundant data, with considerable emphasis placed on 3-dimensional bar graphs which are poor ways of showing relationships between 3 variables (Kannel,[823,1448,2893] Castelli,[2750] Levy et al.,[2549] Castelli et al.[2292]).

Interpretational Error. As previously noted, Framingham investigators seemed to be reasonably objective in their early reports but subsequently exhibited stronger and stronger biases. The use of such terms as "powerful" to describe an exceedingly weak relationship has been commonplace. One kind of bias exhibited was the process of reinterpreting data in order to appear consistent with the current position of the alliance. For example, since the 1984 Consensus Conference the alliance, via the NCEP, has emphasized the measurement of total cholesterol and, partially because of inherent inaccuracy of measurements and partially because of difficulty of "treatment," has deemphasized the measurement of HDL. The NCEP's position was "chiseled in stone," so to speak, with the publication of its report by the Expert Panel in January 1988. It was said that "Serum total cholesterol should be measured in all adults 20 years of age and over."[1066] In an appendix the Panel did indicate that HDL should be measured in all patients who have first been found to have high total cholesterol but the very short discussion devoted to this measurement and what to do with it was a reflection of its attitude to focus almost exclusively on total cholesterol and its so-called atherogenic component, LDL.

The decision to focus on total cholesterol in the late 1980s can be seen in the interpretation of Framingham data. Framingham investigators time and again emphasized in the 1970s and most of the 1980s that total cholesterol was not related to CHD in those over 50 years of age. Consider the following statements in chronological order:

1977 - "At these [49 to 82 years] ages, total cholesterol per se is not a risk factor for CHD at all."[453]

"A number of studies...have found that total serum cholesterol...is a diminishing CHD risk factor in older men and apparently no longer a CHD risk factor for men over 65."[523]

1979 - "For persons older than age 50 the serum total cholesterol has little predictive value."[1046]

1983 - "We now also know that the impact of cholesterol diminishes with age; beyond age 65 it is difficult to show any relation at all."[1091]

1984 - "The impact of serum total cholesterol wanes with advancing age and beyond 55 no longer predicts CHD."[1083]

1986 - "It [total cholesterol] no longer predicts the risk in those aged over 50 years."[1531]

1987 - "The total cholesterol level is a particularly useful indicator for CHD in younger persons, but it loses some of its strength after age 55, especially among men."[1366]

"Its [total cholesterol] tends to wane with age, but remains a significant predictor of CHD in elderly women."[787]

The relation between total cholesterol and CHD "is now further confirmed by 30 years of follow-up in the Framingham study and extended to elderly patients of both sexes."[964]

Note that in 1987 the Framingham investigators began to reinterpret the same 30-year data. While total cholesterol had no relation to CHD in those over 50 years in 1986, it merely "loses some of its strength" in early 1987, "tends to wane with age, but remains a significant predictor of CHD in elderly women" later in 1987 and becomes a full predictor in "both sexes" in the same year. Obviously, the investigators, who had previously been promoting the HDL-CHD relationship for the elderly, reinterpreted their data to conform to the NCEP's focus on total cholesterol. (This topic is also discussed in Chapter 9.)

Summing Up. Whether one wishes to believe it or not, the Framingham investigators have presented a prolific array of figures and tables and most have been designed to deceive rather than to reveal. Simple, straightforward relationships based on CHD rates and equal interval cholesterol scales have generally been avoided in favor of far less informative but seemingly (to the reader) "significant" data. And despite the fact that alliance members unequivocally define LDL as the atherogenic element of blood cholesterol, this writer has never observed a figure or table among Framingham reports which shows CHD rate as a function of a multiple, equal interval cholesterol scale. One gets the distinct impression that every attempt was made by Framingham investigators during the 1950s to evaluate and present their data objectively and thoroughly. However, objectivity and thoroughness soon gave way to presentations which best supported the lipid hypothesis.

The Framingham study could have been a great prospective investigation. Instead, NHLBI and/or the Framingham investigators created substantial methodological problems at the outset and progressively used the study to promote dogma rather than honestly investigate the antecedent causes of CHD. Although often referred to as a "landmark" investigation, it is, in reality, a highly confounded and very messy scientific study conducted by individuals who probably know little about statistical analysis but who apparently instruct statisticians to present considerable sophisticated but irrelevant statistical shenanigans. When Framingham director, William Castelli, claims that the study has uncovered more than 200 risk factors for CHD, the trained scientist should at once become suspicious of the meaningfulness of all these associations, particularly as no one as yet has proven that a single risk factor causes CHD. The trained scientist should also be suspicious of the fact that Framingham investigators apparently never publish the actual correlations observed between cholesterol level and CHD rate.

The Western-Electric Study

The Chicago Western-Electric study was another example of what can be called, pure and simple, bad science, designed and conducted by naive investigators and subsequently analyzed and documented by naive and biased investigators. Strong words perhaps but easily supported. The blood cholesterol levels and diets were determined for 1900 middle-aged men in 1957-1958 and again one year later. The men were then followed for 19 additional years, after which the investigators correlated dietary nutrients with 19-year risk of CHD. This was bad science because all of the results and conclusions were based on the assumption that diets (and presumably cholesterol levels) remained constant over the 19-year period. Even if the authors did not know then what is well known today that diets and blood cholesterol levels change considerably over time, it would still be bad science because a scientist simply cannot draw rigorous conclusions based on assumptions. In fact, one should not even conduct

a study that requires such assumptions. At minimum, examinations and diet assessments should have been performed periodically to avoid the need for assumptions.

The Western-Electric study was particularly bad science because the investigators knew from the second year examinations and diet assessments that blood cholesterol levels and diets were, in fact, changing substantially. They nevertheless averaged the two sets of blood cholesterol levels and diets and naively assumed that all these measures would henceforth be constant for the next 19 years. It is virtually impossible to account for such naive reasoning.

No matter how bad a study is, the fact that it is published in a scientific journal gives it an aura of credibility in the eyes of the medical community. It is for that reason that a more detailed critique of the Western-Electric study follows. At the outset, however, it should be clear to any scientist that the study actually deserves no further attention. If Shekelle et al.'s[1339] statement that the Western-Electric study was "...the most precise and convincing study to date" is taken seriously, then virtually all within population dietary surveys must be rejected because there is almost nothing scientifically satisfactory about their study. Such a statement is, in fact, an insult to the intelligence of the professional scientist.

The description, analyses and interpretations of results of the Western-Electric study were spread over a number of papers and it is not certain that all of the important information was published even at that.[a] However, there is ample information to find substantial fault with the study.

Like the Framingham study, the Western-Electric study was initially designed with a built-in confounding factor, i.e., results of "most" individuals' examinations were sent to their personal physicians,[487,3002] although "No therapeutic suggestions were made" by the study authors. While the main report of findings, (Shekelle et al.[487]), published in 1981, had nothing to say about the possible impact of the data sent to physicians, a 1982 report by Shekelle et al.[3082] indicated that 344 (18% of the total) subjects had systematically changed their diets from the first to the second examinations. Incomplete information was presented with respect to the directional changes made by all 344 subjects. Shekelle et al. did say, however, that 84 men with initial cholesterol levels of 300 mg or greater had reduced their intakes of lipids after the first examination and 42 of these "did so on the advice of a physician."[b] Thus, the data presented indicated that diets had changed partially because of the study design and there is no telling the full impact of this design flaw because influences by personal physicians after the second examination could have been substantial.

Stamler[3002] indicated that the reduced lipid intakes of the 84 men who had a cholesterol level at or above 300 mg at entry was such that "there was no longer a relationship between dietary lipids and serum cholesterol in the first follow-up year--clearly an artifact produced by the study." Of course, this was not an artifact produced by the study but rather one introduced by the investigators themselves.

Related to the personal physician influence, another unanswered question is whether or not other "risk" factors had changed after the first or second examination because of the information sent to these physicians. For example, reductions in hypertension or cigarette smoking could have, directly or indirectly, altered blood cholesterol levels.

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[a] 487,1313,1339,1357,1565,2278,3082

[b] Shekelle et al. did not indicate why the other 42 had reduced their intakes.

Although not mentioned in their 1981 report, Shekelle et al.[3082] indicated in their 1982 report that their cohort contained 302 subjects who had cholesterol levels at or above 300 mg at entry. These constituted 15.9% of the entire cohort, approximately four to five times the percentage observed in other population studies. Regardless of the technique they used, it is clear that their blood cholesterol measurements were wholly or partially in error.

The dietary data collected at the two exams were unquestionably in gross error and that error was compounded by Shekelle et al.'s conversion of the data into "diet scores" via the Keys et al. and Hegsted et al. equations. Before discussing the dietary data, the reader should be aware that these equations are highly imprecise and should never have been used for the purposes of the Western-Electric study. Yet, they are the very core of the analyses from which Shekelle et al. would draw their conclusions. A very detailed discussion of the equations, the data used to develop them, the rationale underlying them, and their inherent errors is presented in Chapter 5.

In describing their dietary data, Stamler[1565] said, "In this study, habitual diet of the men was assessed not by a 24-hour recall or by a short questionnaire, but by an in-depth interview covering the prior 28 days, with cross-checks, requiring about 60 minutes per man. This was done twice for these men, at the original survey in 1958 and at the first annual re-exam one year later. This method not only served to characterize the nutrient intakes of each man with a degree of precision and validity not achieved previously in cardiovascular epidemiologic studies, it also yielded valuable information on reproducibility of nutrient intake and influence of the original exam on eating pattern."[1565]

While the above quote was obviously designed to impress the reader, it was, in reality, merely a gathering of impressive words having no scientific foundation. For example, it is preposterous to think that an accurate determination of nutrient intakes over a 28 day period can be made in a 60 minute interview, no matter how "in-depth" it is. Even if individuals were able to recall exactly what they ate each of the previous 28 days, which they most certainly could not, they could not possibly estimate with any degree of accuracy the exact quantities of each item, especially the amount of fat (e.g., how much was lost during the cooking of each piece of meat?).

Stamler and Shekelle's use of the terms "precision" and "validity" suggest that they do not fully understand them.[a] In the first place, their technique was not validated empirically at all so a discussion of validity was quite inappropriate. In the second place, repeating a subjective measurement instrument may yield a high reliability (precision) correlation but that correlation has nothing to do with the validity of the instrument. Third, the reliability correlations observed in the study were rather low, being .44, .57, .65 and .66 for polyunsaturated fat, saturated fat, dietary cholesterol, and total energy intake, respectively. These correlations explained only 19% to 40% of the variance observed in the intake distributions and only 19% to 32% for the two critical lipids, polyunsaturated and saturated fats. Fourth, these correlations were computed for 82% of the men "who reported no reported systematic change in diet between the two periods."[487] Thus, the uncomputed reliability correlations for the entire cohort would undoubtedly have been exceedingly low.

Keys[2839] noted that recording the kinds and approximate amounts of foods eaten for a series of days by the interview technique is fairly good with highly intelligent and cooperative subjects, but "It would be unrealistic to expect similar dedicated and

[a] The fact that Shekelle and Stamler published correlations to 3 decimal places is yet another indication of the alliance members' lack of understanding of statistics. The third decimal place has no practical or statistical significance at all.

intelligent cooperation in other samples." One can imagine the inaccuracies inherent in the Western-Electric study where subjects were not likely to be dedicated and they were asked to recall foods eaten for 28 days. The Western-Electric subjects kept diaries of foods eaten and Keys emphasized that the interview "histories indicated more food eaten than was recorded in the diaries; some of the men admitted that they were sometimes embarrassed to put down how much they had eaten." He said, "It must be emphasized that one problem with the history dietary method is that what is recalled is subject to the personal psychology of the subject."

Both the Framingham and the Western-Electric studies used the Burke procedure. In 1975 Blackburn[2691] referred to this procedure as "fuzzy" and indicated that he would not expect the Western-Electric study to show a relationship between diet and cholesterol or CHD for that reason. Stehbens recently said that "Even if short term assessments of diets are accurate, they are of no consequence since individual diets vary qualitatively and quantitatively within wide limits during a lifetime." Attempts to correlate the dietary content of fat or other constituents from one or two weeks with the incidence of CHD or even the severity of atherosclerosis that develops over a lifetime are unacceptable scientifically. Indeed, as was shown earlier in this chapter, Keys and his colleagues reported large changes in diet (and blood cholesterol levels) within the first 10 years of the Seven Countries study.

Because diets had changed substantially from the first to the second examination, Shekelle et al. averaged both sets of dietary data "to provide base-line estimates for intake of saturated fatty acids, polyunsaturated fatty acids, and dietary cholesterol individually and as summarized by the formulas of Keys and Hegsted." After having observed large enough dietary changes in only 5% of the study duration to force the need to compute averages, it is astounding that Shekelle et al. could possibly believe that diets were then "fixed" for the remaining 95% of the study duration. In fact, words cannot express how utterly foolish it was for Shekelle et al. to ignore the obvious and run their study beyond the first year. The entire study results were based on a totally untenable assumption about what the participants consumed through 19 years.

Although there is no doubt that the dietary data collected in the Western-Electric study were grossly in error, further distorted in the process of converting them to "diet scores" and, in any event, changed substantially over time, Shekelle, Stamler and colleagues insist that their study proves that diet is related to CHD. Yet, in other articles, these investigators have expressed something less than certainty. For example, two years before the 1981 publication of the Western-Electric study Stamler[1313] said, "...it is very difficult to overcome the problems that exist with respect to the validity of nutritional data collected in individuals. ...due to intra-individual variation the number of measurements, both of dietary variables and serum cholesterol, especially the former, has been inadequate to estimate the true means of individuals." More recently, Shekelle and Stamler[2278] admitted that "over so long a period, dietary habits may change" and that "such changes would tend to obscure a true association between diet and risk of disease." In fact, such changes would render initial dietary data arbitrary and completely meaningless, even if they were accurate for the time, and they were not.

It is of interest (and some humor) to note that in an entirely different context, Stamler and his co-workers[93] attempted to minimize the importance of a possible low cholesterol/high cancer association among six prospective studies with the following argument: "The interval between measurements [of cholesterol] and death was often long (more than 5 years in half the cases), so that dietary habits and cholesterol levels might well have changed in the meantime." Since the Western-Electric follow-up was nearly four times longer than the above prospective studies, it is incredible that

Stamler and Shekelle can so readily assume that dietary changes of consequence did not take place in their study.

Although discussed at length in Volume 1 and elsewhere in this volume, it is nevertheless useful to always remind the reader that endpoint data are always likely to be in error in prospective studies where many independent physicians using different criteria, are involved in certifying causes of death. Anywhere from 20 to 40% of the deaths classified as due to CHD could be incorrect, either because some other disease was the true cause or because subjects died of myocardial infarctions that were unrelated to atherosclerosis. Shekelle et al., the Framingham investigators and other prospective study researchers always assume that the endpoint data are precise when everyone knows that they involve substantial error. It is not sufficient to claim that such error is random. When there are many sources of error in a study, random error of 20-40% cannot be dismissed so lightly by the objective scientist.

The basic results of the Western-Electric study are presented last in this critique because their only importance lies in the fact that they have frequently been cited by the alliance as proof that diet affects the development of CHD. In view of the foregoing, they can only be a complete hodgepodge of errors.

In their 1984 report Shekelle et al. concluded that "the composition of the diet affects serum cholesterol concentration and risk of coronary disease in middle-aged, American men."[487,a] Olson[1722] objected to their conclusion, noting that saturated fats correlated with blood cholesterol but not with CHD rates, while dietary cholesterol and polyunsaturated fat correlated with CHD death rate but not with blood cholesterol. The fact is that the correlation between dietary variables and blood cholesterol was .08 which is, for all practical purposes, zero. Shekelle et al. recognized this state-of-affairs but did not consider it terribly important, i.e., "The correlations between dietary variables and serum cholesterol concentration in our study were small--a general finding among studies reporting positive results."

It is also objectionable that Shekelle et al.'s converted total cholesterol intake to the intake per 1,000 calories consumed. As was observed in the Boston-Ireland study, this conversion resulted in the Boston brothers consuming more cholesterol per calories consumed, although the Irish brothers consumed almost 100 mg more cholesterol per day. As is discussed elsewhere in this volume, there is no unequivocal scientific basis for this conversion.

Characteristically, Shekelle et al. did not present actual intakes of cholesterol. However, if one uses the reported mean energy intake of 3,183 calories, the mean cholesterol intake would then have been 766 mg per day. This value is about 200 mg higher than the per capita availability for cholesterol in 1960, as computed by the USDA (Figure 3-15). It may be noted also that the total energy value of 3,183 calories is also slightly higher than the USDA data (Figure 3-13) and 600 to 700 calories higher than that reported for middle-aged men in the NHANES I survey (Table 3-4). Since the USDA data are known to be substantial exaggerations of what people actually eat, this is yet another reason for rejecting the dietary data compiled by Shekelle et al.

It is universally recognized that saturated fat has a far more profound effect on blood cholesterol than does dietary cholesterol. It therefore follows that if the lipid hypothesis is correct, variations in saturated fat should have a far greater influence on

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[a] Blood chlesterol values from the first exam correlated only .66 with those from the second exam.[3082] The reader can imagine what the correlations might be 3, 5, 10 or more years later.

CHD mortality than variations in dietary cholesterol. Yet, low, medium and high consumption of saturated fat in the Western-Electric study did not result in significantly different CHD mortality rates. This finding alone should lead anyone to question the presumed observed relationship between dietary cholesterol and CHD mortality.

In sum, the Western-Electric study was bad science from beginning to end but even worse science has been exhibited in the many positive interpretations of the study by alliance members in innumerable "review" articles. Such members close their eyes to the many obvious flaws and simply regurgitate Shekelle et al.'s conclusions.

The Honolulu Heart Program

The Honolulu Heart Program was a follow-on of the Honolulu cohort in the NI-HON-SAN study. The same baseline data obtained during the original examinations of these subjects were used to correlate later with CHD rates. For example, Table 4-14 shows the most relevant nutrient intakes from three tables presented by Yano et al.[767] in a 6-year follow-up and relates them to different CHD conditions. Subtable 3 indicates that saturated fat intake for the four CHD conditions ranged from 55 g to 60 g per day, consistent with the earlier presented Table 4-10 which listed a mean of 50 mg across all CHD conditions. Subtables 1 and 2, however, show saturated fat intakes of slightly more than half of 59 g and 12 to 13% of total calories. The reader may recall that the NI-HON-SAN investigators claimed that the Honolulu cohort consumed 23% of total calories as saturated fat, an amount that is absurdly high for white Americans, let alone Japanese Americans. Clearly, the data in Subtables 1 and 2 are closer to the truth and it is dumbfounding why Yano et al. presented contradictory data in their article.

When nutrient intakes were expressed in absolute amounts, no significant differences were found between intakes and any of the CHD manifestations. However, the authors maintained that the percentages of total calories as fat and saturated fat in the CHD death plus MI condition were significantly higher than those in the non-cases group. While statistical significance may have been achieved, common sense should lead one to conclude that the absolute differences were much too small (2% for fat and 1% for saturated fat) to have been the factor differentiating between CHD and no CHD. Moreover, as emphasized elsewhere in this volume, it is well-established that fat per se is not related to CHD either by scientific evidence or by theory. Therefore, the 2% difference in total fat intake is not only miniscule, it is also irrelevant. Yano et al. acknowledged that the relation between saturated fat intake and CHD was "weak" but suggested that it might be stronger if a more accurate measure of nutrient intakes had been taken instead of the 24-hour recall method employed. Of course, the relationship might also have been in the opposite direction as well with a more accurate technique. There is no scientific basis for suggesting that either outcome is more likely.

In the same year that Yano et al. published their report, Reed et al.[2820] reported results from autopsies on some of the men who died in the Honolulu Heart Program. Some 481 men died and autopsies were performed on 226. However, for some unexplained reason the extent of coronary and/or aortic atherosclerosis was determined for only 137 persons and correlated with blood cholesterol level. Reed et al. indicated that cholesterol correlated 0.24 and 0.35 with severity in the aorta and coronary artery, respectively. Not only is the selection of only 137 from the total of 226 autopsies a suspicious procedure, similar to other dubious procedures in the Honolulu study, these correlations nevertheless were quite low, explaining only 5.8% and 12.3%, respectively, of the variance due to cholesterol. It must be emphasized that such low correlations cannot possibly be used as scientific evidence of a cause-effect relation between cholesterol and atherosclerosis.

Table 4-14

Selected data from three tables presented by Yano et al. (1978[767])

Table 1	Non-Cases	CHD death + MI	Acute CI	Angina
Total fat (g)[a]	86	85	80	87
Saturated fat (g)[a]	32	31	30	31
Cholesterol (mg)[a]	549	521	557	587

[a] No significant difference between nutrient and any CHD event.

Table 2

% calories as fat	33	35[a]	31	34
% calories as sat. fat	12	13[b]	12	12
Cholesterol/1,000 cal.	Not given			

[a] 35% said to be significantly greater than 33%.
[b] 13% said to be significantly greater than 12%.

Table 3

Total fat (g)	Not given			
Saturated fat (g)[a]	60	56	58	56

[a] No significant difference between nutrient and any CHD event.

The original Honolulu cohort that undertook a baseline examination involved 8,006 men. However, 301 were found to have CHD and the investigators excluded them from follow-up studies. Thus, the above study by Yano et al. consisted of 7,705 men. In a 9-year follow-up study that related blood cholesterol with CHD and total mortalities, however, the 301 men were not excluded. In this follow-up, Kagan et al.[71] reported that CHD mortality increased as blood cholesterol increased. The authors stated that "The serum cholesterol-to-CHD relationship constitutes an important link in the diet-heart hypothesis and this finding has led to extensive efforts to alter nutrient composition in Western countries."

Kagan et al. also showed an identical relationship between blood cholesterol and cancer mortality, but in the opposite direction, i.e., cancer mortality was highest at the lowest blood cholesterol levels and progressively decreased as cholesterol increased. The authors did not describe the negative relation in this fashion. They said, "The prominent upward trend of cancer mortality in the lower range of serum cholesterol is disquieting," suggesting that there was no trend at higher cholesterol levels. The summation of all data demonstrated that total mortality was optimum between 210 mg and 269 mg cholesterol and increased below 210 mg and above 270 mg. Therefore, while the alliance recommends cholesterol levels below 200 mg, one of their prime prospective studies indicated that the safest levels were between 210 mg and 269 mg.

Three years later (1984) Yano et al.[3395] published a 10-year follow-up report in which the 301 originally diagnosed men with CHD were again excluded from analyses. They indicated that men diagnosed as having CHD demonstrated a mean cholesterol level 12.9 mg higher than those presumably free of CHD. Not only was this difference rather small, it should be recalled from Chapter 3 that the Framingham data showed that much of the difference between CHD cases and noncases was due to a relatively few subjects with very high blood cholesterol levels who disproportionately affected the mean of the distribution of cholesterol levels of the CHD cases. If these few subjects were removed, it is likely that the difference between cases and noncases in the Honolulu Program would be less than 5 mg and possibly disappear altogether. In any event, the difference reported was in itself wholly unimpressive.

Another 10-year follow-up report was published in 1984 by McGee et al.[484] In addition to excluding the 301 men with CHD at baseline, these investigators also excluded 160 men with cancer and stroke at baseline. If such exclusions were appropriate, why were they not accomplished in previous analyses? But most astonishingly of all, McGee et al. excluded 502 men who they said (during the baseline examinations) either could not recall what they had eaten during a 24-hour period or indicated that what they had eaten was atypical of their usual diets. Since these 501 men (and the 160 cancer an stroke cases) were not excluded in the 1978 follow-up by Yano et al.[767] which compared CHD with non-CHD cases in terms of diets, one can only criticize what appears to be a continuous and arbitrary process of excluding different subsets of men in the Honolulu study. The differences between all-CHD and non-CHD cases in fat intake (34.7% of calories vs 33.3%) and saturated fat intake (12.7% vs 12.3%) were claimed to be statistically significant, although they were clearly of no practical importance whatsoever. Similar differences in the 1978 follow-up without the additional exclusions did not reach significance. Unlike the earlier report, McGee et al. also claimed that the difference between all-CHD cases and non-cases in dietary cholesterol intake (257 mg per 1,000 calories vs 242 mg) was also significant, although it was again trivial in a practical sense. Thus, it seems more than apparent that the investigators omitted data from the cohort for the sole purpose of finding statistical outcomes supporting the lipid hypothesis.

McGee et al.[3393] published another 10-year follow-up report in 1985 that was both revealing and misleading. They again excluded the same 963 individuals as in their earlier article and plotted the total, cancer, stroke and CHD death rates by fat,

saturated fat and cholesterol intakes. Total, cancer and stroke death rates decreased as dietary fat and saturated fat increased. On the other hand, CHD death rate generally increased as total fat and saturated fat increased. However, the authors used a greatly expanded vertical scale for the CHD and stroke figures which totally exaggerated the relationships. If one plots the CHD and stroke mortality data on the same vertical scale used for the total mortality relation, the CHD and stroke relationships will be seen to be essentially flat across the intake range. For example, the death rate differences between the highest and lowest intakes of fat (0.05%) and saturated fat (1.5%) over a 10-year period were rather trivial. Moreover, such differences become completely meaningless because the relation between fat, saturated fat and total mortality were strongly in the opposite direction. Nevertheless, McGee et al. concluded that "The data from the Honolulu Heart Program have supported the diet-heart hypothesis," although they acknowledged the "dilemma" regarding total mortality. In keeping with the alliance's mumbo-jumbo language, instead of concluding that there were "no overall benefits from a low fat diet," they should have indicated that there was overall harm in low fat diets.

Another autopsy study of men dying in the Honolulu Heart Program was published in 1987. Reed et al.[3369] presented results for 230 and 226 men who "had gradable" coronary arteries and aortas, respectively. These authors gave their readers baffling contradictions. While concluding that blood cholesterol was a significant predictor of atherosclerotic severity, they also admitted that when the relation "was adjusted for selection bias," there was no significant relation between cholesterol level and atherosclerosis. And, in fact, when the relation was not adjusted, the only significant effect was found below 187 mg, not between 188 mg and above. Furthermore, unlike the earlier autopsy study, Reed et al. omitted the reporting of correlation coefficients, strongly suggesting that they were even smaller than observed in the earlier study.

Even though their basic data indicated an extremely weak relationship between cholesterol levels and atherosclerosis severity, the authors seemed alarmed that "None of more than 25 measures of dietary patterns and 24-hour dietary intake was associated with atherosclerosis in any statistical model." They added, "We have no explanation why the reported intakes of nutrients and types of diet were not associated with atherosclerosis scores." Lest the reader overlook a most important observation, this latter statement referred to the fact that atherosclerosis severity was the same for those consuming a Japanese diet as for Western diets even though the blood cholesterol levels of these groups were substantially different. This finding was also emphasized by Rosenman[1337] in Internal Medicine News. But it is dumbfounding why Reed et al. were surprised that dietary intakes did not correlate with atherosclerosis. All of the previous reports found weak to nonexistent relationships between dietary intakes and either blood cholesterol level or CHD events.

In sum, the Honolulu Heart Program represents one of dozens of studies that purport to support the diet-CHD and lipid hypotheses but, in fact, provide abundant data to the contrary. Yano et al.[2817,2820] recently summarized the study's results thusly, because low cholesterol levels are associated with high all-cause mortalities, involving increased rates of cancer, stroke, etc. "The ideal range of cholesterol values corresponding to minimum death risk in men aged 50 to 71 was 200-220 mg." Thus, while the alliance is encouraging all Americans to reduce their cholesterol levels below 200 mg, and preferably to 150 mg or lower, the Honolulu investigators are encouraging Americans to maintain their levels above 200 mg. Consistent with their habit of distorting facts, the NCEP's Expert Panel[3361] devoted one (false) sentence to the Honolulu Heart Program in its 1991 report, i.e., "Still other epidemiologic studies showing a correlation between CHD and intake of saturated fat have been...the Honolulu Heart Program..."

The Lipid Research Clinics Prevalence Study

Gordon, Rifkind and their co-workers[2773] published the results of a diet-blood cholesterol analysis of the LRC Prevalence study. They reported that saturated fat intake in grams correlated .00 or slightly negatively with LDL and total cholesterol, respectively, in both men and women. The percentage of calories as fat correlated .04 to .09 with LDL and total cholesterol in both men and women. The percentage of calories as saturated fat correlated .04 to .07 with total cholesterol and LDL in both men and women. And total calories correlated negatively with LDL and total cholesterol in both men and women.

These utterly trivial findings were viewed by Gordon et al. as confirmation of results from between population studies. However, their subsequent discussion was quite rational and it is suspected that, in view of their more current statements on changing the American diet, they would not like to be associated with that discussion today. They said, "But how important and meaningful are the cross-sectional relations we have noted. Expressed in the form of simple correlation coefficients, none of the specific nutrients measured in the LRC Prevalence study accounts for more than 1% of the total variance of the lipids considered. The weakness of the noted relations may be partly explained by the unreliability of the 24 hour recall, but even after allowance is made for that, only a small proportion of the lipid variance within the LRC population is explained by diet. Even if we allow for all...extraneous sources of variation, probably less than 10% of the variance in lipid levels from person to person can be explained by the dietary variables we have considered. Thus, the LRC data suggest, as do all similar data from other populations, that dietary variation plays a minor role in interindividual variation in lipid levels, but that most of the variation in lipid levels between persons in general populations is attributable to nondietary factors."

Gordon et al. reported an additional interesting finding. They indicated that "The LRC observation that the more people eat, the lower their LDL or total cholesterol seems surprising. However, it is consistent with reports of other studies." The question is, then, why does it seem surprising?

Two years later, the US-USSR Steering Committee[1906] reported near zero correlations between key dietary nutrients (except alcohol) and HDL and LDL levels for the U.S. and U.S.S.R. cohorts in the LRC Prevalence study. Alcohol correlated .25 and .35 with HDL.

The Heart Disease Control Program

Stamler et al.[3045] published CHD and all-cause mortality statistics in 1960 for various racial/ethnic groups in the city of Chicago. The data were quite intresting in that they did not conform to many statements made by the alliance. Stamler et al. had almost nothing to say about these "anomalies" and, in fact, managed to introduce further confusion.

Table 4-15 presents the most relevant data from the Stamler et al. report. Despite its small size the table has many large inconsistencies. For example, Stamler et al. noted that "Chinese men had coronary disease rates slightly lower than those for the white population." These "slightly lower rates" were 32% for ages 45-54 and 18% for ages 55-64. These authors did not mention that white and Chinese female CHD rates were essentially identical or that the all-cause death rates for both Chinese males and females were considerably higher than white males and females, respectively. There is no way that diet can be used to explain these differences.

Table 4-15

CHD and all-cause deaths per 100,000 among three racial/ethnic groups in Chicago (adapted from Stamler et al.,1960[3045])

Group		Ages 45-54 Males	Ages 45-54 Females	Ages 55-64 Males	Ages 55-64 Females
CHD	White	330	67	830	267
	Chinese	225	67	682	252
	Japanese	137	40	391	140
All-Cause	White	1,006	547	2,353	1,292
	Chinese	1,533	721	3,442	1,477
	Japanese	712	487	1,761	986

Table 4-15 shows that the CHD and all-cause mortality rates among the Japanese were substantially lower than both whites and Chinese. Since alliance members, including Stamler, frequently have said that Japanese Americans have similar diets and cholesterol levels as white Americans, typically pointing to the Japanese, Hawaii and California Heart study,[a] clearly the data of Table 4-15 provide no support for the notion that diet influences CHD or all-cause mortality rates among the Japanese. Moreover, if one assumes that the Japanese in Chicago consumed vegetarian diets, one would have to assume that the Chinese did not, since the CHD and all-cause mortality rates for the two groups were quite different. However, it would be scientifically ludicrous to make such unsupported assumptions simply as an attempt to support the lipid hypothesis.

Other Studies

As indicated in the previous section Shimamoto and his co-workers published in 1989 the results of following two cohorts of Japanese men and women from 1963 to 1983.[1807] Animal fat consumption increased 113%, blood cholesterol levels increased 14% to 18% (for men and women, respectively) and blood pressure declined--but there was no change in CHD death rates. There was, however, a huge reduction in all-stroke mortality of 60%. Although they didn't collect alcohol consumption data, they noted that national data revealed a two-fold increase in alcohol consumption during that period. The authors suggested that the increased blood cholesterol levels may have caused the decline in stroke.

In 1970 Keys and Kimura[2755] correlated fat intakes with blood cholesterol levels in middle-aged farmers in Japan. The correlations for total fat and saturated fat were only .17 and .23, respectively. Thus, fat explained only 2.9% and 5.3% of the distribution of cholesterol levels.

Rose and Marmot[3412] reported a 7.5 year follow-up of 17,530 London male civil servants and found that the higher the social class, the lower the CHD mortality and the higher the blood cholesterol level. These findings, derived from one of the largest of all prospective studies (the Whithall study), were clearly opposite to that predicted by the lipid hypothesis.

Researchers of the LRC Prevalence study attempted to correlate dietary nutrients with blood cholesterol levels for middle-aged Russian and American men.[1906] The only correlation of any significance was the association between alcohol consumption and HDL, i.e., .25 to .35. Correlations between fatty acids and total or LDL cholesterol levels closely approached zero.

An Israeli study published by Kahn et al. in 1969 was included as one of many prospective studies in Volume 1 showing no relationship between diet and blood cholesterol in a large cohort of men.[520] In 1989 Keys criticized Kahn et al. because they "did not anticipate and allow for the great effects of intra-individual variation in the variables of concern, especially the dietary items."[2295] Kahn et al. obtained dietary data from a single questionnaire which requested the types and portions of foods consumed by a participant in a day, week or month. Keys maintained that dietary data must be collected over a period of time to yield reliable data. He indicated that Kahn et al. should have recognized their errors and published a new analysis. Since they did not, Keys felt obliged to perform this analysis himself and, in the process, "provide an object lesson in regard to dietary surveys and their evaluation." In view of the sloppy dietary surveys performed in the Seven Countries study, it is most odd that Keys considered himself the appropriate instructor for

[a] 550,557,567,584,1078

"object lessons" on conducting dietary surveys, even though his basic criticism is undoubtedly valid.

Keys also criticized Kahn et al. for taking only one blood cholesterol measurement from each participant. The present writer found no evidence from Keys' articles that more than one blood cholesterol measurement was taken at baseline in his Seven Countries study.

One cannot help but wonder why Keys did not also feel obliged to criticize Stamler and Shekelle's relating CHD with extremely old and limited dietary data, discussed earlier in this section. More than likely, criticism was withheld because "positive" findings were reported, no matter how inconsistent they may have been.

Finally, a 1982 study by Fehily et al. was another example of selective omissions of data leading to misleading implications.[1900] They obtained 7 days dietary data for 117 men and reported quantitative relationships between HDL levels and alcohol, saturated fat and fish intakes. The relationships were essentially flat across all but the highest intakes levels, i.e., those levels that exceed the typical American diet. For example, HDL increased only at the highest levels of alcohol or fish intake and decreased only at the highest saturated fat intakes, 15% to 19% of total dietary calories. Fehily et al. also stated that LDL level was positively associated with the percent of total calories from total fat but presented neither the quantitative relationship nor any discussion about LDL and saturated fat. Since they admitted obtaining total cholesterol and LDL levels but reported no data relating them with saturated fat, it is apparent that they also intended to deliberately mislead readers with selective omissions of unsupportive data--and the most important data at that.

Vegetarian Studies

Cholesterol Levels. Ten studies were reviewed in Volume 1 in which blood cholesterol levels of vegetarians and nonvegetarians were compared. Additional studies were subsequently found and all are briefly reviewed below. There is no question that vegetarianism per se reduces blood cholesterol levels. However, the absolute amount of reduction among free-living populations cannot be observed from these studies because of numerous methodological problems, one of which is the combination of too few subjects and atypical subjects, e.g., nonvegetarians who have unusual blood cholesterol levels, excessive intakes of calories, fat and cholesterol, etc. Improper "control" groups necessarily led to spurious differences between vegetarian and nonvegetarians.

The mean blood cholesterol difference between complete vegetarians (vegans) and nonvegetarians across seven studies was found to be 60 mg (Table 4-16). However, because of the above noted improper comparisons, this value is probably an overestimate of 10 to 15 mg.

The Hardinge and Stare[425] investigation demonstrated two major flaws. First, the blood cholesterol level of both vegans and nonvegetarians were much too high to be representative of their respective populations. Clearly, the cholesterol measurement instruments used by Hardinge and Stare were inaccurate and possibly unreliable as well. Second, examination of the dietary data presented by the authors reveals that the total calories, fat and cholesterol intakes of the nonvegetarians were grossly greater than those of the typical American, i.e., 3,720, 176 g and 914 mg, respectively. Thus, the selection of atypical subjects as "controls" served to exaggerate the blood cholesterol difference between the vegan and American diet. In sum, the Hardinge and Stare study was badly flawed methodologically and should not be taken seriously by anyone.

Table 4-16

Blood cholesterol levels of vegans and nonvegetarians

		Blood Cholesterol (mg/100 ml)			
Study	Date	Nonveg(n)	Vegans(n)	Difference	Problems
Hardinge[425]	1954	292 (30)	206 (25)	86	a,b,c,e,f
Ellis[2814]	1970	240 (12)	181 (12)	59	a,b,d,e,f
Burslem[1165]	1978	182 (78)	133 (56)	49	b,c,e,f
Sanders[2813]	1978	236 (22)	158 (22)	78	a,b,d,e,f
Knuiman[2427]	1982	212 (52)	146 (33)	66	a,d,e,f
Fisher[2428]	1986	177 (10)	135 (10)	42	a,b,d,e,f
Thorogood[1073]	1987	205 (1198)	166 (114)	39	d,e,f

[a] Too few subjects.
[b] Cholesterol measurements apparently inaccurate.
[c] Control subjects' diets contain far more fat than typical diet.
[d] No dietary data.
[e] More smokers among the nonvegetarians or information not given.
[f] Nonvegetarians were heavier or had more obesity or information not given.

Not only did the Ellis and Montegriffo[2814] investigation employ too few subjects to obtain stable results, they also apparently used atypical nonvegetarian subjects, since their mean blood cholesterol level was quite high, i.e., 240 mg. Additionally, the nonvegetarians were not completely matched with the vegans and 62% of them smoked as compared to 13% of the vegans. The authors also presented no dietary data which made it impossible to determine the significance of their results.

The Burslem et al.[1165] study also yielded results which were not representative of their respective populations. They compared 58 vegans who lived on Tennessee farms with 78 nonvegetarians at Washington University. One would expect farmers to have greater caloric intakes than nonfarmers but, in fact, the nonfarmers consumed slightly more. Moreover, the total caloric intakes of both nonvegetarians and vegetarians were quite low, under 2,300, particularly for these rather youthful groups (17 to 40 years). In addition, the percentage of total calories consumed as fat by the nonvegetarians was said to be 42%, again exceeding the typical American diet by about 17% (42% vs 36%). Finally, the blood cholesterol levels of both vegans and nonvegetarians appeared considerably lower than would be expected for this age group, suggesting problems of measurement accuracy and reliability.

The Sanders et al.[2813] investigation was again composed of two few subjects to yield stable results and the high mean blood cholesterol level of the nonvegetarians (235 mg) suggests that subjects and/or diets were atypical of their populations. No dietary data were presented.

The Knuimen and West[2427] study used vegans from Belgium and the Netherlands and nonvegetarians from the Netherlands. While these authors reported a 66 mg blood cholesterol difference between the groups, this value is again impossible to evaluate because dietary data were not presented.

The study by Fisher et al.[2428] compares 10 vegans, who were Seventh Day Adventists (SDAs) from New Hampshire, with a matched group of 10 nonvegetarians from the University of Massachusetts. The age range was 20 to 47 years and as can be seen in Table 4-16, the blood cholesterol levels of both groups were clearly not representative of their respective populations. The study employed too few subjects and was also confounded in that the nonvegetarian group included smokers, while the vegan group did not. No dietary data were given.

The final study listed in Table 4-16 is that of Thorogood et al.[1073] These investigators employed by far the largest groups of subjects and undoubtedly obtained the most stable and meaningful blood cholesterol levels of all seven studies. The age range was < 29 to > 60 years but most subjects within the groups were under 40 years. Unfortunately, this study again failed to provide dietary data. However, because the nonvegetarian group contained 1,198 subjects, we may feel reasonably satisfied that the group was representative of the population. The mean blood cholesterol level of 205 mg also appears to be realistic.

In short, the Thorogood et al. study is probably the only investigation that was satisfactory scientifically and yet it appears to have yielded an underestimate of the potential cholesterol reduction one could expect from a completely vegetarian diet. In any event, it is dumbfounding why researchers of the other six studies paid so little attention to design adequacy of their experiments and omitted rather important data.

Table 4-17 lists 17 studies which compared nonvegetarians with a variety of semi-

Table 4-17

Blood cholesterol levels of vegetarians and nonvegetarians

		Blood Cholesterol (mg/100 ml)				
Study	Date	Nonveg(n)	Veg(n)	Difference	Problems	SDAs
Hardinge[425]	1954	292 (30)	256 (30)	36	a,b,c,e,f	No
Walden[564]	1964	237 (433)	194 (145)	43	b,c,e,f	Yes
West[1164]	1968	204 (125)	185 (125)	19		Yes
Sacks[565]	1975	184 (115)	126 (115)	58	b,d,e,f	No
Hickie[842]	1975	199 (1399)	161 (183)	38	Teenagers	
Ruys[1162]	1976	201 (1456)	154 (105)	47	Teenagers	
Simons[2815]	1978	229 (38)	175 (20)	55	a,b,c,e,f	Yes
Webster[2340,g]	1979	212 (16940)	192 (779)	20	d,e,f	Yes
Gear[1163]	1980	251 (264)	212 (91)	39	b,d,e,f	No
Burr[1133]	1981	231 (215)	214 (85)	17	b,c,d,f	No
Fraser[2341,g,h]	1981	--------	206 (517)	50	b,d,e,f	Yes
Knuiman[2427]	1982	212 (52)	181 (56)	31	d,e,f	No
Liebman[2816]	1983	195 (18)	183 (36)	12	a	No
Fisher[2438]	1986	170 (15)	150 (15)	20	a,b,d,e,f	Yes
Thorogood[1073]	1987	205 (1198)	188 (1550)	17	d,e,f	No
Fraser[i]	1987	203 (160)	190 (160)	13	c,e	Yes
Fonnebo[2345]	1988	226 (16506)	189 (43)	37	e,f	Yes

[a] Too few subjects.
[b] Cholesterol measurements apparently inaccurate or atypical subjects.
[c] Control subjects' diets contain excessive fat than typical diet.
[d] No dietary data or insufficient data.
[e] More smokers among the nonvegetarians or information not given.
[f] Nonvegetarians were heavier or had more obesity or information not given.
[g] Means were not reported. Estimates were calculated from authors' graphs/tables showing means at different age groups.
[h] Compared group with another study of European nonvegetarians to derive the "about 50 mg" difference. This value, therefore, is subject to considerable error because of (1) improper comparison, and (2) the nonvegetarian value would be a spurious 256 mg.
[i] 2339,2342

vegetarians, i.e., varying in the quantity of animal food consumed.[a] Two of the studies involved teenagers and are not relevant to the present discussion but were nevertheless included in the table for general interest.

Most of the studies had methodological problems and/or provided insufficient data for interpreting results. For example, more than half of the studies compared SDA vegetarians with nonvegetarians who were not SDAs. In view of the fact that SDAs are a unique group of people who not only do not consume cigarettes, alcohol or coffee, but also apparently have a religiously derived, less emotionally stressful lifestyle than nonSDAs, comparisons of SDAs with nonSDAs produced scientifically confounded results. Cigarettes, alcohol and stress (and some say coffee) elevate blood cholesterol levels. The strength of a 6'4" 240 pound male vegetarian is greater than that of a 5'6" 120 pound male nonvegetarian but no one would attribute that greater strength to vegetarianism.

Almost all of the studies employing small numbers of subjects produced suspect data for various reasons, including improper matching of vegetarian and nonvegetarian groups on important variables. For example, the Simons et al.[2815] study compared a predominantly male nonvegetarian group with a predominantly female vegetarian group. Where data were provided, vegetarian subjects were generally leaner and/or consumed fewer calories and/or cigarettes. There was also significant evidence in some studies providing dietary data that nonvegetarians were consuming diets that contained considerably more fat and/or saturated fat than that contained in the typical diet.

Eight of the 15 studies also failed to provide dietary data. How can one truly assess the effects of a "vegetarian" diet when we do not know of what it is composed?

The substantial lack of control in the vegetarian studies undoubtedly resulted in the wide range of mean differences reported, i.e., 12 mg to 58 mg. The average of the mean differences is 31 mg. There were over 3400 vegetarian subjects included in the 15 studies and nearly half were involved in the Thorogood et al. investigation which yielded a cholesterol difference of only 17 mg. Although this difference certainly seems unusually small, it is difficult to argue against sample sizes of 1,198 and 1,550. Moreover, since the vegetarians in the Thorogood et al. study apparently were not SDAs, they may be more representative of free-living vegetarians than were the few selected subjects in some of the other studies. As noted by Liebman and Bazzarre,[2816] most vegetarians do not exclude red meat and chicken altogether and generally do not limit their consumption of other animal products such as eggs and dairy foods.

In view of the massive evidence that saturated fat significantly elevates blood cholesterol and that dietary cholesterol has little effect, it is surprising to note a relatively recent statement by Sacks, Castelli and their co-workers, namely, "One reason for the discrepant results between vegetarian and nonvegetarian groups may be that the low range of cholesterol consumption in vegetarians is the range in which dietary cholesterol has most of its [trivial] effects on serum cholesterol levels."[2426] Note the word "may" and compare that statement with that of Liebman and Bazzarre, i.e., "Although the vegetarian subjects were characterized by widely differing egg consumption levels, no relationships were observed between dietary or egg cholesterol intakes and plasma lipid levels."[2816]

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[a] A study by Sacks et al.[2426] was not included because they (1) did not include a nonvegetarian comparison group, and (2) compared vegetarian groups, each of which were evaluated many years apart.

Two additional studies were found which compared conventional diets with simulated vegetarian diets. Masarei et al. evaluated a lacto-ovo-vegetarian (meatless) diet relative to a usual omnivore diet and reported that it decreased blood cholesterol level by 10 mg (4.8%) and 7 mg (3.4%), respectively, in men and women. (It also decreased HDL levels.[2429]) They concluded that meat therefore played a small role in altering cholesterollevels. While this may be true, examination of the diets used by Masarei et al. give no indication that meat per se was the factor differentiating the diets. For example, the omnivore diet contained more total fat (8 g), more saturated fat (8 g), more cholesterol (58 mg), less polyunsaturated fat (10 g) and a much lower P/S ratio (.30 vs .66). Thus, the small differences observed in this study were undoubtedly due to these differences rather than to the fact that the omnivore diet contained meat.

The second study conducted by Cooper et al. compared a vegan diet with an omnivorediet in 15 free-living subjects in a crossover design.[2430] The vegan diet caused a reduction of 20 mg (12.5%) and an HDL reduction of 10%. Although this reduction must be considered modest, compared to population measurements, the study also suffers from exaggerated differences in nutrients. For example, the omnivore diet contained 650 (40%) more calories and 57 g (150%) more total fat. One might question the realism of the vegan diet of only 1590 calories in sustaining normal weight.

CHD Mortalities. While there have been ample investigations which show, quite unsurprisingly, that vegetarian diets significantly decrease blood cholesterol levels, studies evaluating the effects of vegetarian diets on mortalities continue to be few in number. One cannot help but wonder if available data from the many existing prospective studies are being shelved because they reveal no benefits of vegetarianism. For example, the blood cholesterol data shown in Table 4-17 associated with Fonnebo, were derived from the Tromso Heart study in Norway. The question is, why were not mortality statistics presented along with cholesterol measurements?

No new prospective studies comparing vegetarians with nonvegetarians have been found since publishing Volume 1. However, recent follow-ups or analyses of previous studies were discovered and are therefore reviewed here. One of the worst analyzed studies encountered during this writer's review of some 3,000 articles was the Seventh Day Adventists (SDAs) investigation. This study was first published as a six-year follow-up by Phillips et al. in 1978 and was discussed in Chapter 4 of Volume 1. Two articles describing various results of a 21-year follow-up of this study were published in 1984 and are reviewed here.

Kahn et al. presented total mortality rates as a function of the frequencies of consuming cheese, meat, milk, eggs and fat attached to meat.[2431] The total death rate decreased as the frequencies of consuming cheese, eggs, meat and milk increased. It increased 3.7% in that group which indicated that it ingested the fat attached to meat. These rates were not presented by Kahn et al.; they were computed from their data by this writer. Kahn et al. rather arbitrarily threw out most of their data and considered only subjects who indicated very infrequent or very frequent consumption of the various foods. They then computed "odds ratios" which showed that mortality increased as meat or poultry consumption increased (but not for cheese, eggs, milk or fat attached to meat). Kahn et al. concluded that "Although our results add some substantial facts to the diet-disease question, we recognize how remote they are from establishing, for example, that men who frequently eat meat or women who rarely eat salad are thereby shortening their lives."

Not only is it tenuous, to say the least, to relate weak dietary questionnaire data to subsequent mortality over a 21-year period, the analyses of Kahn et al. appear to

be post hoc, after finding that the overall data were opposite to that required by the lipid hypothesis. Furthermore, the fact that their analyses still showed no association between mortality and cheese, eggs, milk and fat attached to meat renders the meat-mortality relationship rather meaningless because the former foods contain far more fat, saturated fat and cholesterol than does meat per se. In effect, the Kahn et al. study is yet another example of negative results which are massaged and misinterpreted to support the alliance's proclamation that vegetarians live longer lives. The Kahn et al. study most certainly provides no such support.

Snowden et al. published the CHD, rather than the total mortality, data for the 21-year SDA study.[2343] Since they did not eliminate the intermediate frequencies of consumption data on meat, but did so with eggs, cheese and milk, this represents further evidence that both Kahn et al. and Snowden et al. based their results on arbitrary post hoc analyses and not on pre-planned analyses contingent on the design of their questionnaire. They computed relative risk ratios and concluded that CHD mortality increased as meat consumption increased. However, this writer computed rates from their data and found trivial increases of 0.04% and 0.01%, respectively, for males and females.

Snowden et al., like Kahn et al., also found no relationships between frequency of consumption of eggs, cheese and milk and CHD mortality "risk," and concluded that "our study shows that meat-consuming Adventists have a substantially higher risk of fatal IHD than vegetarian Adventists...(and)...adds substantial evidence that meat consumption is related to heart disease risk in free-living populations." However, this writer computed mortality rates from their data and obtained very trivial increases of 0.10% and 0.01%, respectively, for males and females.

Snowden et al. also concluded that "For men, nonvegetarianism had a significantly higher risk for fatal IHD than nonvegetarianism." Again, however, this writer computed mortality rates and found trivial differences, i.e., 0.1% for males and .01% for females.

One of the authors of the SDA study, Fraser, cited it in a 1988 article, claiming that "There seems little doubt that SDA men at least experience less total IHD than do others. The reasons for this are not necessarily clear."[2339] Dwyer also published an article in 1988, stating erroneously that Kahn et al. demonstrated that nonvegetarians have higher all-cause mortality rates than vegetarians.[2359] She also erroneously reported that "vegetarians tend to have high HDL cholesterol levels" but cited no evidence. Not only do the majority of vegetarian studies (where measurements were taken) show lower HDL levels among vegetarians, it is broadly known that high carbohydrate diets decrease HDL levels (see Chapter 9).

The overpowering motivation to show that diet is related to CHD and total mortalities is no better exemplified than in the above two studies. While Kahn et al. and Snowden et al. both used the term "substantial" to describe the effects of meat consumption on mortalities, it is more than obvious that "trivial" is a far more appropriate descriptor. It is also interesting that throughout their numerous post hoc analyses, they brushed aside their totally negative findings on foods which have much greater quantities of fat, saturated fat and cholesterol. Typical of other alliance analyses, they would apparently have clung to any "positive" finding and downplayed the importance of other findings.

To add to the peculiarities of the SDA study, Fraser et al. compared the diets of a sample of the SDAs with those of nonSDAs in 1987.[2342] The following year, Snowden cited the Fraser et al. study as showing that "Adventists had a lower intake of total fat, saturated fatty acids and monounsaturated fatty acids than did non-Adventists."[2344] But reference to the Fraser et al. article reveals that the Adventists

had only 2% less total fat, 0.9% less saturated fat and 0.3% less monounsaturated fat (in terms of total calories) than the nonvegetarians, hardly a difference worth emphasizing.

The Burr and Sweetnam[1134] prospective study that compared vegetarians with nonvegetarians was discussed in Volume 1. It was shown that the annual CHD death rate among vegetarians was only 0.01% lower than that of nonvegetarians. Yet the authors indicated that "A significant correlation was found between vegetarianism and mortality from IHD which was especially marked among men... These findings confirm other evidence of a lower mortality from heart disease among vegetarians." This conclusion was extraordinarily misleading. The IHD death rate among vegetarians after seven years was 1.22% and it was 1.33% among nonvegetarians. The difference between the two (0.11%) was determined to be significant. The all-cause death rates among vegetarians and nonvegetarians were 6.2% and 4.7%, respectively. The difference of 1.5%, nearly 14 times larger than the IHD difference was supposedly nonsignificant. Whether nonsignificance was indeed the case, such results were most peculiar to say the least. However, they get more peculiar with further analysis.

Table 4-18 presents the annual death rates for vegetarians and nonvegetarians as a function of sex and cause of death. As can be seen, the "marked" difference between vegetarian and nonvegetarian men in IHD was only .11%. And although the difference in all-cause death rate in the opposite direction, Burr and Sweetnam failed to emphasize that fact. Moreover, the IHD and all-cause death rates among females was actually slightly greater and substantially greater, respectively, in vegetarians than in nonvegetarians. Thus, these results are absolutely not supportive of the proposition that vegetarianism protects against either IHD or all-cause mortalities.

A small study by Ellis and Montegriffo[2814] included 26 vegans and 26 matched controls with mean ages of 42.7 years. Although the cholesterol level of the vegans was 59 mg lower than that of the nonvegetarians and although most of the nonvegetarians smoked, while vegans did not, there were no differences in the clinical states, including CHD, between the two groups.

The evidence against the presumed benefits of vegetarianism is further strengthened by two additional studies. Reiser and Shorland[1804] cited an autopsy study by Ruffer in 1921 of 800 vegetarians which revealed that atherosclerosis was just as prevalent among them as among nonvegetarians. More recently Ellis et al.[2948] performed what they believed to be the first determination of atherosclerosis in vegans. They compared 26 vegans with a matched group of nonvegetarians and found both groups to have the same degree of coronary atherosclerosis, regardless of age, despite the fact that the nonvegetarians had substantially higher blood cholesterol levels.

Despite the lack of evidence indicating beneficial effects of vegetarianism, some authors report otherwise. For example, Esrey claimed that "vegetarian populations not only have some of lowest cholesterol levels in the world, they also have low incidence of heart disease."[2232] And although Sanders et al.[2813] observed that "The few clinical studies made so far in Britain and the U.S. have not been able to identify any real differences in the health of vegans compared with omnivores," they nevertheless concluded that "a vegan-type diet may be the one of choice in the treatment of IHD, angina pectoris and other hyperlipidemias." Were it not for the fact that many CHD researchers use such "logic" routinely, that conclusion might be considered quite humorous.

EXERCISE AND CHD

The 10.5 year follow-up of the 12,138 MRFIT men by Leon presumably showed an absolute 1% lower CHD mortality rate among men who exercised moderately than

TABLE 4-18

Annual death rates of vegetarians and nonvegetarians as a function of sex (adapted from Burr & Sweetnam, 1982[1899])

	IHD	All-Cause
Male vegetarians	.22%	.93%
Male nonvegetarians	.33%	.88%
Female vegetarians	.14%	.86%
Female nonvegetarians	.10%	.54%

those who exercised very little.[1702] Not only is this difference small, two serious questions arise. First, since those who exercise tend to be nonsmokers, the variable of smoking must be extracted out before conclusions can be reached about the effects of exercise per se. Such information was not discussed by Leon. And second, why was the mortality rate for heavy exercisers not discussed by Leon?

A long-term Johns Hopkins study of 1,000 graduating students revealed that subsequent mortality among those who initially expressed interest in athletics wasabout twice as high as those who expressed no interest.[1700] Since no information was obtained on the actual level of exercise exhibited by the students, the value of this finding is highly questionable at best. A more important finding was reported in 1960, i.e., autopsies of 207 persons revealed no relationship between physical activity level and degree of atherosclerosis in the deceased.[1999]

The relationship between exercise and HDL is also questionable, at least for practical forms of exercise. Grundy et al. and Thompson et al. noted that mild exercise has little or no effect on HDL.[1803,1804] Authors typically provide little or no scientific evidence supporting vigorous exercise. For example, Grundy et al. suggested aerobic exercise to "try to raise HDL."[1803] And York stated that a half hour of aerobic exercise per day "may help keep the cardiologist away."[1697]

Like so many other epidemiological findings, the issue of exercise versus no exercise is usually imbedded in confounding variables. Even if regular exercisers exhibit lower mortality rates than nonexercisers, exercise per se may have nothing to do with such rates. It has been pointed out, for example, that "frequent exercisers also tend to be leaner, smokeless and take better care of themselves in general."[1706] Nelson cited Corday as concluding that "There's no evidence that exercise extends life."[2022]

A well-publicized 1989 study relating fitness with all-cause and CHD mortalities is discussed in Chapter 10 because it is more a demonstration of distortion of findings than it is an exposition of the influence of exercise on health. The present discussion is limited to a review of studies which related exercise to the levels of lipids. Some of these studies were recently reviewed by Cantwell and Price.[2299]

Of 22 studies, ten reported that exercise increased HDL,[a] nine showed no effects,[b] two showed conflicting results[c] and one did not measure HDL.[2300] No consistent profile emerged from these studies, e.g., the strenuousness of the exercise program generally did not differentiate between those showing HDL increases and those showing no effects. However, Superko reviewed investigations in 1986 which compared HDL levels in athletes and sedentary individuals.[2315] The HDL levels were higher in the athletes who participated in relatively strenuous exercises such as swimming, running, soccer and cross-country skiing. Interestingly, Lamon-Fava et al. observed that when exercise induces amenorrhea (suppression of menstruation) in women, HDL levels actually decline.[2250]

Of the 22 studies, only three reported that exercise reduced LDL levels.[2302,2303,2311]

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[a] 172,304,2301,2302,2304,2305,2306,2310,2312,2313

[b] 884,885,1373,1652,2303,2307,2308,2309,2316

[c] 2311,2314

Cantwell and Price described a previous study of theirs in which they measured the total cholesterol levels of 35 players on a major league baseball team.[2299] They found that 57% of the players had levels of 200 mg or higher. Since about 60 to 65% of the general population has levels of 200 mg or higher, their results would suggest little differences between athletes and nonathletes with regard to total cholesterol levels. It should be noted, however, that baseball is one of the least strenuous sports.

Powell et al. reviewed 43 studies associating exercise with CHD and concluded that "the inverse association between physical activity and incidence of CHD is consistently observed." Virtually all of the data presented by these investigators was in the form of relative risk ratios which made it impossible to determine rate difference between activity levels or the importance, therefore, of the relative risk ratios. It is notable, however, that most of the risk ratios hovered between 1 and 2, suggesting trivial rate differences. There were a number of < 1 risk ratios and "no relationships." It is also curious why the MRFIT results were not included since it was the largest of all cohorts assessing the effects of exercise. In any event, because Powell et al. chose to ignore actual CHD rate data, their review is effectively worthless.

The whole notion that exercise is protective against CHD is based on the highly confounded between-population "armchair" studies and the many subsequent preachings of Stamler and others that a "sedentary lifestyle" increases the risk of CHD. Stallones[3027] observed in 1980 that "The national mania for recreational jogging has not spread to large numbers of upper-middle-class men and women, both black and white, whose death rates are falling as rapidly as those of younger people." John McMichael[3403] emphasized that the evidence linking exercise with CHD is, if anything, negatively supportive and indicated that recommendations based on such evidence "does our profession little credit."

One of the more objective statements to emerge from the alliance was published in 1981 by the NHLBI Working Group.[3067] It said, "A regular program of sensible, reasonably vigorous, frequent, and sustained exercise can imrpove physicial fitness, appearance and mental well-being. Much less certain is whether physicial activity affects morbidity and mortality from atherosclerosis and, if it does, by what means."

AUTOPSY STUDIES

A perfect example of distortion by the alliance is related to the 1968 International Atherosclerosis Project (IAP) report authored by Scrimshaw and Guzman.[1080] This study reported correlations between total fat intake, animal fat intake, blood cholesterol level and severity of atherosclerosis as determined by autopsies of some 31,000 persons from 15 different populations. Correlations of .76 and .67 were observed between severity of atherosclerosis and blood cholesterol level and total fat intake, respectively. And because both cholesterol level and total fat correlated equally with atherosclerosis, obviously they correlated with each other with similar strength (.74). But the most important finding of all were near zero correlations (.07 and .07) observed between atherosclerosis and animal fat intake and between blood cholesterol and animal fat intake, respectively.[a]

The IAP report has rarely been cited in the literature, undoubtedly because it revealed an embarrassing zero association between animal fat intake and either atherosclerosis or blood cholesterol. This selective omission by the alliance represents

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[a] Scrimshaw and Guzman also reported small and nonsignificant correlations between sugar intake and either atherosclerosis or blood cholesterol.

one of its most frequent techniques of distorting the epidemiological research literature.

The only citations of the Scrimshaw and Guzman report found during the preparation of the present review document were those of Stamler and his colleagues.[a] In 1970 they stated that "the International Atherosclerosis Project represents the most comprehensive and systematic study of postmortem findings on aorta and coronary atherosclerosis in different populations. Its final report includes a valuable chapter on the relationship of nutrition to the disease. A highly significant correlation was found between intake of fat and severe atherosclerosis at autopsy." Since Stamler et al. did not mention the most important finding of all, i.e., no association between animal fat intake and atherosclerosis or blood cholesterol level, it is apparent that they deliberately intended to mislead readers, constituting a second frequent technique used by the alliance to distort the literature.

Stamler again cited the IAP in 1973 and again selectively omitted the zero animal fat correlation.[573] In 1978 and 1979 he cited the IAP again but then specifically stated that "Data on saturated fat and dietary cholesterol were not reported."[539,1313] Since animal fat is synonymous with saturated fat, Stamler thus transitioned from omitting important information to creating false information.

Stamler[3002] again reported only the relationship between total fat and atherosclerosis in the IAP in 1982.

In 1988 Stamler and Shekelle again cited the IAP and this time they specifically denied the existence of data. They said that "reliable data were not available on dietary lipid composition, hence no analyses were reported for either mean saturated fat or cholesterol intake and their relation to severe atherosclerosis."[1565] This and previous statements by Stamler et al. can be contrasted with one statement and tabular data (Table 4-19) presented by Scrimshaw and Guzman, i.e., "The findings...suggest that in most populations sources (types) of fat and of carbohydrate are not the primary factors in determining severity of atherosclerotic lesions."[1080]

Not only did Stamler et al. purposely abuse the process of objectively reviewing literature, his conclusions were still not consistent with the lipid hypothesis. Since monounsaturated and polyunsaturated fats have neutral and/or blood cholesterol-lowering affects, respectively, it is not logical to conclude that total fat is related to either blood cholesterol level or atherosclerosis, particularly when animal fat is specifically shown not to relate to blood cholesterol level and atherosclerosis. Most alliance members avoided the embarrassment of explaining the IAP's results. Stamler et al. chose to explain them by distortion and illogics. Moreover, in other contexts Stamler has used the opposite argument. For example, he said, "Reduction of all fats--without attention to composition of the diet--is not a scientifically sound or practically realistic approach to achieving sizable improvement in serum cholesterol-lipid-lipoprotein levels..."[3051] Indeed, reduction of all fats has no sustained effect on blood cholesterol level at all.

Solberg and Strong[3055] were also guilty of biased reporting of the IAP results. They said, "The ranking for raised lesions is positively and significantly correlated with the ranking by...the percentage of calories from dietary fat. The data conform to the hypothesis that geographic differences in extent of atherosclerosis can be explained in

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[a] It may be noted that Stamler et al. did not cite the original report by Scrimshaw and Guzman in these citations but rather a chapter by these authors in a book edited by McGill.

Table 4-19

Correlations between dietary components and atherosclerosis severity (adapted from Scrimshaw and Guzman, 1968[1080])

	Blood Chol.	% Calories from fat	% total fat from animal fat	sugar intake
Atherosclerosis severity	.76[a]	.67	.07	.32
Blood cholesterol level		.74	.07	-.07
% calories from fat			-.01	.27
% total fat from animal fat				-.25

[a] Blood cholesterol measurements derived from a variety of surveys conducted in the various populations, not from the subjects autopsied. It is doubtful that the mesurement techniques used across countries were strictly comparable and it is doubtful that those measured accurately matched the subjects autopsied.

part by differences in fat consumption..." But Solberg and Strong computed no correlation between raised lesions and animal fat consumption, although they reported the relevant raw data in the same table from which they calculated the correlation for total fat. This writer computed a negative correlation of -.17.

Despite the biased reporting, the IAP clearly did not support the diet-CHD relationship.

Stamler and apparently all other alliance members have omitted in their reviews many additional autopsy studies. The following authors reported zero to very weak correlations between blood cholesterol level and degree of atherosclerosis: Paterson et al.;[2087,2386] Mathur et al.;[2088] Lande and Sperry;[530] Feinleib et al.;[3366] Rhoads et al.;[3367] Okumiya et al.;[3368] Reed et al.;[3369] Sorlie et al.;[3370] Barboriak et al.;[3371] Cramer et al.;[3372] Solberg et al.;[3373] Marek et al.;[3374] and Mendez and Tejada.[3375] Not only did Reed et al.[3399] find a low correlation between total cholesterol and severity of atherosclerosis in the Honolulu Heart Program, it was even lower and nonsignificant for LDL, the alliance's one and only "atherogenic" lipoprotein. The authors also reported a nearly zero (-.09) correlation for the alliance's one and only "protective" lipoprotein. As emphasized by Ravnskov,[3365] the very low correlations found in these studies could not have any biologic significance. A particularly interesting study was that of Gore et al.[3300] who performed autopsies on 659 persons in Los Angeles and 260 individuals in Japan. They reported no significant differences between the countries in the degree of atherosclerosis for all ages. The authors stated, "In view of the comparatively low incidence of fatal coronary artery disease in Japan [as reported by death certificates] and the relatively low levels of serum cholesterol among the Japanese, it is surprising not to find more striking differences in the aorta between the U.S. and Japan." And, as noted earlier, Reiser and Shorland[1804] reported that 800 autopsies of vegetarians by Ruffer in 1921 revealed that atherosclerosis was as prevalent among them as among nonvegetarians. More recently, Ellis et al.[2948] found no differences in atherosclerosis between vegans and a matched group of nonvegetarians, regardless of age, and despite substantial differences in blood cholesterol levels.

Autopsies were performed on two population groups that were generally vegetarians, i.e., Bantus and Indians. Both Walker[2787] and Meyer et al.[2785] found less severe coronary atherosclerosis in Bantus than white men. However, they also reported that the Bantus suffer from high rates of other cardiovascular diseases, notably cerebral artery atherosclerosis and cryptogenic heart disease. Meyer et al. cited Laurie and Woods as saying that "There is enough evidence to refute the view that Bantu enjoy any relative freedom from atherosclerosis." Similarly, Kulangara and Subramanian[2786] autopsied 263 individuals from South India and found lesions on virtually all the aortas in those over 40 years of age and on 58% of the coronary arteries in the same age group, increasing to 100% in older age groups. The investigators also reported that the severity of atherosclerosis was similar to that seen in American whites in some Indian communities.

Another study, discussed in detail in Chapter 10, was the Pathological Determinants of Atherosclerosis in Youth (ADAY) study, headed by Robert Wissler.[3151,3406] The right coronary arteries of 390 males aged 15-34 years who had died of violent causes were related to risk factors, blood cholesterol level being obtained postmortem. Correlations between total cholesterol and severity of atherosclerosis were <u>not</u> reported, suggesting that no correlations were fund. Instead, Wissler et al. reported correlations for VLDL + LDL, i.e., .24 to .16 for two measures of severity. Correlations with HDL were again near zero, i.e, -.06 to .04. Thus, these correlations again demonstrated very little relationship between cholesterol level and atherosclerosis severity.

McMichael[2435] cited Fuster and Mayo as finding no association in 300 living patients between cholesterol level and severity of atherosclerosis as assessed by angiography. Similarly, Ravnskov[3365] cited Nitter-Hauge and Enge, and Fuster et al. as observing identical findings.

It is of interest to also note the reviews of others. While Beaver and Akins[2775] indicated that "most elderly persons have extensive atherosclerosis," McGill,[3323] Glueck[3245] and Van Itallie[3325] stated that autopsy data show no relationship between atherosclerosis and cholesterol or fat intake or obesity.

Even if a few studies have shown strong correlations between blood cholesterol levels and severity of atherosclerosis, they cannot transcend the many studies that have not. Moreover, ignoring the massive negative evidence will not strengthen the lipid hypothesis. But not only does the alliance ignore negative studies routinely, it also accepts very low correlations (0.05 to 0.3) as proof of a cholesterol-atherosclerosis cause and effect relationship (see Chapter 2). Such correlations indicate that cholesterol level has the capability of predicting the degree of atherosclerosis in < 1% to about 9% of a population. Knowing that some 21% of the population dies of CHD, one can guess with far more accuracy who will die of CHD than can be predicted by cholesterol level.

5. EXPERIMENTAL STUDIES ON DIET AND BLOOD CHOLESTEROL

"This effect of dietary cholesterol, like that of serum cholesterol, is quantitatively substantial, so that its avoidance or correction has by inference a potential to reduce substantially risks of CHD and other atherosclerotic disease."

(Jeremiah Stamler, 1988[1565])

"You can't say that reducing dietary cholesterol will reduce atherosclerosis."

(Myron Weisfeldt, AHA president, 1989[2543])

"The focus over the past few years has been mainly on cholesterol, yet the impact of dietary cholesterol on blood cholesterol is a very controversial issue. Some people are strongly affected by dietary cholesterol, but the majority of the population is not..."

(Claude Lenfant, NHLBI director, 1991[3267])

INTRODUCTION

In Volume 1 experimental data on diet and blood cholesterol were trichotomized into those derived from whole foods laboratory studies, liquid formula laboratory studies and free-living studies. In 1957 Van Itallie reasoned that liquid formula diets were preferable because of the difficulties of determining the exact contents of whole foods diets.[353] In the same year, Page et al. concluded that "formula diets...cannot be extrapolated to normal diets."[512] Indeed it has long been shown repeatedly that no matter what their content, liquid formulas result in cholesterol levels that are lower (and sometimes substantially lower) than they were during base diets with regular foods.[a] To this writer's knowledge, no one has determined why liquid formulas have this effect. A description of the content and method of preparation by Mattson et al.[1897] reveals nothing on this issue, unfortunately. But much more bewildering is the question of why many investigators have repeatedly used liquid formula diets when they knew that their results would not be generalizable to the population consuming whole foods. Because liquid formula study results have almost exclusively been used by the alliance as evidence of the so-called large effects of cholesterol and saturated fats on blood cholesterol, it appears inescapable that these distorted results were much preferred.

The studies most often cited by the alliance as showing that dietary cholesterol is significantly hypercholesterolemic are those of William Connor, critiqued in detail below.

DIETARY CHOLESTEROL

Additional Studies

Seven additional studies on dietary cholesterol were acquired since completing Volume 1. Katan et al. fed 504 mg, 504 mg and 860 mg to subjects in high (predominantly saturated) fat whole food diets to subjects whose base diet was approximately 115 mg.[1826] The mean blood cholesterol increase per 100 mg ingested

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[a] 331,340,343,402,415,700,717,874,948,1395,1755,1756,1757,1759

was 2.5 mg. Zanni et al. fed similar amounts (745 mg) to subjects in two moderate fat diets, one predominantly saturated and one predominantly polyunsaturated.[1827] The mean blood cholesterol increase per 100 mg ingested was 2.5 mg.

Fisher et al. fed 1,000 mg of cholesterol to subjects in either a predominantly saturated or polyunsaturated fat liquid diet.[1901] The mean blood cholesterol increase was 0.65 mg per 100 mg ingested. Miettinen et al. also fed 725 mg to subjects in a low fat diet.[1819] Neither the fatty acid composition nor the type of food (liquid or whole) were given in their brief report. The mean blood cholesterol increase was 2.4 mg/100 mg ingested.

Flaim et al. fed two groups of subjects identical diets having about 400 mg cholesterol.[2355] Four eggs were added to one diet and the other diet was adjusted to compensate for the nutrient content of the eggs. The mean blood cholesterol increase per 100 mg ingested was approximately 1.4 mg (the exact figure cannot be computed from their data). Cholesterol feeding also increased HDL 15.3%, while increasing total cholesterol only 8.6%.

The mean cholesterol increase per 100 mg ingested across the above five experiments is 1.9 mg, identical to that computed for whole foods studies in Volume 1.

Cooney et al. instructed free-living subjects to consume either (about) 250 mg cholesterol or (about) 1,000 mg cholesterol (from eggs) in diets containing red meats only or poultry and fish.[2174] Two subgroups of subjects (15 and 14) consumed the diets in different orders. The addition of eggs in one order resulted in a significant increase in blood cholesterol level, while such was not the case for the second order. However, the absolute increase per 100 mg ingested was low in either case, i.e., 0.4 mg and 2.2 mg. (These figures are approximate because exact dietary values were not given.)

Faber et al.[2703] evaluated the effects of dietary cholesterol on blood cholesterol among competitive body builders who did not participate regularly in aerobic exercise. These 76 subjects consumed slightly more fat (39.6% of total calories) and exactly the same saturated fat (13.9% of total calories) as the typical American. However, dietary cholesterol was three times the average, i.e., 1,443 mg. Yet, the mean blood cholesterol level of these men was only 183 mg and their total to HDL ratio was only 3.5.

Faber et al. compared two subgroups of subjects who consumed less than 1.5 eggs and more than 6 eggs per day. The dietary cholesterol amounts in these groups were 509 mg and 2,823 mg, respectively. Yet, their mean blood cholesterol levels were 176 mg and 189 mg, a difference of only 13 mg. Further, their total to HDL ratios were essentially identical, i.e., 3.5 and 3.4. Not only was 13 mg a small increase for a dietary increase of 2,314 mg, it was also partially due to the fact that the egg eaters had a somewhat higher saturated fat intake (14.6% vs 12.9% of total calories). Needless to say, the increase in blood cholesterol per 100 mg ingested was quite small, being less than 0.5 mg.

It is to be noted that many experiments over the last 56 years used egg yolks as the source of dietary cholesterol. The amount of cholesterol in a typical egg has been "officially" sanctioned to be about 274 mg in the USDA's Nutritive Value of Foods,[946] published in 1981 and apparently originally derived from USDA's Composition of Foods,[1110] published in 1963. Examination of the latter document reveals that two entirely different cholesterol values were given for the egg. For example, egg yolk was indicated to contain 1,500 mg cholesterol per 100 grams. Since the average yolk is said to be 17 g, it follows that it contains 255 mg cholesterol. On the other hand, the same document indicated that there was 550 mg cholesterol per 100 g of whole

eggs. Since the average egg is said to be 50 g, it follows that it contains 275 mg cholesterol, suggesting that 20 mg is contained in the white portion of the egg. But since the USDA document specifically noted that there is no cholesterol in the white portion, it would seem that we have a paradox. Which is correct, 255 mg or 275 mg?

In 1974 the USDA published Agriculture Information Bulletin No. 361 entitled, Fats in Food and Diet.[1797] This Bulletin listed 250 mg as the cholesterol content in either one egg or one yolk. Most experimenters apparently assumed 250 mg per egg, rather than 275 mg.

Recently the USDA evaluated the cholesterol content of a large nationwide sample of eggs and found the average large egg to contain about 213 mg.[1798,1907] Since there is no basis to suggest that the egg has lost some 60 mg cholesterol by natural evolution in such a short period of time, it seems quite likely that the reduction is due to more accurate cholesterol measurement instruments.[2261] For example, Okey analyzed eggs in 1944 and found that the cholesterol content was 2% of the weight of a yolk.[2092] Since the typical yolk weighs about 17 g,[946] her yolks apparently contained about 340 mg cholesterol. However, while a modest downward trend is certainly possible and perhaps even likely, it does not seem probable that it dropped from 340 mg to 213 mg. As is discussed elsewhere in this volume, early studies of vegetarians also reported much higher blood cholesterol levels than those reported in later studies, again suggesting more accurate measurement instruments.

Those who promote the fear of dietary cholesterol emphasize the quantities of cholesterol in foods and seem oblivious of their effects on blood levels. For example, AHA's Nutrition Committee member, Frank Franklin evaluated the "new" egg thusly, "whether you get hit with a 10-pound sledgehammer or a 20-pound hammer, you're still on the ground."[2260] And Bonnie Liebman of the Center for Science in the Public Interest said, "we haven't solved our cholesterol problem just by reanalyzing these foods."[2261] Obviously, neither Franklin nor Liebman are adequately knowledgeable of the literature to make such public statements. NHLBI director Claude Lenfant apparently has finally recognized what has been known for decades, namely that "Some people are strongly affected by dietary cholesterol, but the majority of the population is not."[3267]

A Critique of Connor's Three Experiments on Cholesterol

In the 1989 Food and Nutrition Board's "Diet and Health," it is stated that "Examples of vigorously controlled experiments include those reported by (William) Connor et al. (1961a, b, 1964). In each of these experiments, six men were placed on cholesterol-free and high-cholesterol diets that were either formula diets or carefully selected natural foods. Cholesterol was added as egg yolk. In all three experiments, substantial increases in serum total cholesterol resulted from the addition of egg yolk to the diet."[2070] We will see that a competent review of Connor et al.'s studies reveals that they were among the worst controlled and most irrelevant of all experiments conducted to date.

It was stressed in Volume 1 that because of well-known wide variations in human responses, a sufficient number of individuals should be included in experiments to adequately sample that variation. Connor's studies used only six subjects each and either one, two or three per specific dietary condition. This fact alone provides one basis for questioning the generalizability of his results. And it was noted above that Connor's studies involved liquid diets or, at minimum, liquid fats. Since it is also well-known that liquid diets produce results far different from those of whole food diets, this fact alone is also sufficient grounds for classifying Connor's studies as irrelevant. But we have not yet begun to describe the experimental design flaws in Connor's studies.

Table 5-1 depicts the four principal dietary conditions in Connor's first study.[362] The total dietary fat as a percentage of total calories was almost identical for all conditions but the specific compositions were quite different. For example, Group A not only had a large quantity of cholesterol in Period II and none in Period III, it had a significantly higher percentage (24%) of saturated fat. Furthermore, Period II was composed of all liquid foods, while Period III was composed of an unknown quantity of liquid foods. The same situation existed for Group B but in reverse. Therefore, because variation in cholesterol was thoroughly confounded with variations in saturated fats and diet type, Period II cannot be logically compared with Period III for either group.

Because saturated fat also varied significantly between Groups A and B, these groups also cannot be logically compared for either period.

Although insufficient data are given, there is also the possibility that the saturated fats in the egg yolk conditions were more hypercholesterolemic than those in the no-yolk conditions because of greater quantities of the three fatty acids generally considered to raise blood cholesterol, i.e., lauric, myristic and palmitic fatty acids.

Connor et al. claimed that "the amounts of saturated, monounsaturated and polyunsaturated fatty acids in the high cholesterol and cholesterol-free diets were similar, so that effects from differences in dietary fat were minimized."[362] As can be clearly seen in Table 5-1, they most certainly were not similar. Most of the effects observed in this experiment were undoubtedly due to the differences in saturated fats, not to differences in dietary cholesterol. The question is, why did Connor et al. not use identical fat compositions?

Connor et al.'s second study used all liquid diets and was also confounded.[321] Table 5-2 shows the four principal conditions in this experiment. Period I and II were said to have identical diets except for the 950 mg cholesterol in Period II. As can be seen in the Table, there was 22 g more of the oil (fat) in Period I than in Period II to compensate for the 22 g of yolk fat in Period II. However, when the stearic acid content of the diets is excluded (shown to be nonhypercholesterolemic before Connor's study by Ahrens et al.[776]), the 22 extra grams of oil in Period I increased the P/S ratio, while the 22 extra grams of egg yolk in Period II decreased the ratio. Thus, Period I and II were again confounded and cannot logically be compared.

Periods III and IV were not confounded since crystalline cholesterol was used and the fatty acid composition of the diets were indeed identical. However, the effect of this cholesterol was also minimal, i.e., 0.8 mg per 100 mg ingested. Connor et al. suggested that this effect "might" have been due to reduced absorption of crystalline cholesterol. While this "might" have been the case (and also might not), the higher effect between Periods I and II (7.3 mg/100 mg ingested) were undoubtedly due to variations in fatty acid concentrations. Further, as noted in Volume 1, cholesterol in liquid diets produces blood cholesterol increases about 100% higher than does cholesterol in whole food diets.

The third study by Connor et al. was again confounded and also obtained results at variance with essentially all other experiments, i.e., in his zeal to demonstrate "profound" effects of dietary cholesterol, he reported that the fatty acid composition of diets was relatively unimportant. It is of interest to note also that three of his six subjects were insulin-dependent diabetics.

Table 5-1

The fat and cholesterol compositions of the first Connor et al. experiment (1961,[362])

	PERIOD II (liquid)			PERIOD III (partially liquid)[b]		
	Sat.	Poly.	Chol.	Sat.	Poly.	Chol.
GROUP A[a]	27%	27%	2,783 mg	21.7%	26%	0
GROUP B	20%	26%	0	26%	27%	2,400 mg

[a] Each group composed of 3 men.
[b] Unknown quantity of peanut oil.

Table 5-2

The fat and cholesterol compositions of the second Connor et al. experiment (1961,[321])

FAT	PERIOD I NO CHOL	PERIOD II CHOL	PERIOD III NO CHOL	PERIOD IV CHOL
Yolk (g)	0	22	0	0
Oil (g)[a]	133	111	133	133
Chol (mg)	0	950	0	2,400[b]

[a] Saturated/unsaturated fatty acid compositions were the same across periods. The oil was a mixture of 60% peanut oil, 30% cocoa butter and 10% safflower oil.

[b] Crystalline cholesterol instead of egg yolk.

possibility that the experimental design was confounded, Connor et al. concluded that fatty acid composition was not very important. They would, of course, not make such statements today.

As can be seen in Table 5-3, Period I was said to be identical to Period IV except that they differed substantially in terms of P/S ratios. Yet the blood cholesterol difference between these periods was not very different, i.e., 11 mg. And it was essentially identical for Periods II and III which contained no cholesterol but also varied greatly in terms of P/S ratio. Rather than recognizing these findings as a major clue to the possibility that the experimental design was confounded, Connor et al. concluded that fatty acid composition was not very important. They would, of course, not make such statements today.

It is often the case that authors do not provide readers with sufficient methodological information to allow others to carefully analyze and replicate their experiments. Connor et al. also failed to provide the specific fatty acids associated with their diets. However, using the CRC Handbook of Chemistry and Physics[2107] which presents the fatty acid compositions of fats and oils, estimates of the compositions of Connor et al.'s diets were constructed. Excluding the nonhypercholesterolemic fatty acid, stearic acid, the four diets were found to have entirely different
percentages of saturated fats. Thus, Period I had a higher percentage (30%) of saturated fat, as well the addition of cholesterol, than Period II
which clearly would account for some or most of the blood cholesterol difference (38 mg or 5.2 mg/100 mg ingested) observed between the periods.

Similarly, Period IV was found to have a higher saturated fat content than Period III. The difference was smaller (22%) and so was the difference in blood cholesterol levels, i.e., 28 mg or 3.9 mg/100 mg ingested.

In summary, Connor et al.'s experiments were thoroughly replete with design flaws. If the authors of the Food and Nutrition Board's "Diet and Health" report were unable to detect these rather obvious flaws, particularly in view of today's knowledge on saturated and polyunsaturated fats, stearic acid, dietary cholesterol, etc., they were clearly too incompetent to "critically and thoroughly" review the literature. If they did detect the flaws, then they exhibited incredible bias by selecting the most irrelevant of experiments to prove that dietary cholesterol "substantially increases serum total cholesterol."[2070] It is not coincidental that the NHLBI/AHA alliance has repeatedly focused on Connor's studies in its "reviews."

It is noteworthy to mention that in his testimony before an FTC law judge in 1975 Connor[2436] indicated that his "studies were carried out with reputable and established methods of approach" and, at the same "trial," Stamler[2438] referred to Connor's experiments as "exquisite." When asked by a lawyer whether his studies used natural or formula diets, Connor said, "We used a mixture of diets. ...obviously formula diets should be taken to real foods as well and this has been done and similar results have been obtained." When asked whether the results of formula diets can be extrapolated to the use of natural foods, Connor said, "I think they can." However, not only was his testimony false, his colleagues at the trial contradicted him. For example, Theodore Cooper[2688] responded, "Yes, indeed" to the statement that Connor's metabolic ward study results could not be generalized to free-living subjects and Frederick Stare[2689] said that "Studies done with a formula feeding have little application to men." Perhaps the primary promoter of the diet-CHD concept himself, Ancel Keys, stated as long ago as 1957 that liquid formula diets "are not comparable to ordinary meat-potato-vegetable-fruit-bread" diets."[2954]

A Critique of the Hegsted et al. Experiment

The 1965 experiment by Hegsted and his coworkers[408] has been cited prolifically by alliance members as showing the importance of dietary cholesterol to blood cholesterol levels. They concluded that "Dietary cholesterol is obviously an important

Table 5-3

The fat and cholesterol compositions of the third Connor et al. experiment (1964,[322])

FAT[a]	PERIOD I CHOL	PERIOD II NO CHOL	PERIOD II NO CHOL	PERIOD IV CHOL
Chol. (mg)	729	0	0	725
Egg Yolk (g)	11			11
Beef fat (g)	16.5			5.6
Olive Oil (g)	35	35	44	50.5
Cocoa Butter (g)	45	55	5	3
Soybean (g)	5	20	30	20
Peanut Butter (g)			20	
Safflower Oil (g)			10	20
Total fat	112.5	110	109	110.1
P/S Ratio	.24	.25	1.69	1.53
Blood Chol.	213	175	174	202

[a] Although this was defined as a whole foods experiment, the foods of relevance are fats and most of the fats in this experiment were liquids.

variable in determining the serum cholesterol level. All recent work appears to support this conclusion. Our data indicate an essentially linear response to dietary cholesterol and an average increase of about 5 mg percent serum cholesterol for each 100 mg of dietary cholesterol although there is one aberrant value for olive oil" [Figure 5-1]. This value is consistent with the regression coefficients in Figures 2, 3 and 4 [coefficients of 5.6, 5.7 and 5.9, respectively] and is similar in magnitude to the response obtained by Connor et al."[321]

Hegsted et al.'s emphasis on the similarity between the presumed 5 mg increase in blood cholesterol per 100 mg ingested being "consistent with the coefficients in their regression equations contrasts with their statements two pages earlier in their report. They said, "...as has already been indicated, the size of the regression coefficients depends upon the other variables included in the equation. Snedecor has explained why this is true. These equations are primarily descriptive of the information from which they are derived. Should new variables be included, such as a dietary carbohydrate component [or the elimination of a variable, such as monounsaturated fatty acids], the regression coefficients for the fatty acid might be expected to change. It is somewhat hazardous to attach as much functional significance to the regression equations as Keys et al.[716] have done." The question is, why did Hegsted et al. attach functional significance to their equations two pages later? Also, their expression, "might be expected to change," is peculiar since they went into great detail showing that the coefficients do indeed change dramatically (see later section on multiple regression equations) with the addition and subtraction of variables. It is of interest to note in this regard that the equation ultimately selected by Hegsted et al. for general use did not contain any of the above noted cholesterol coefficients which they compared with the 5 mg/100 mg formula. Rather, their selected equation yielded a cholesterol coefficient of 6.8. Hence, a second question--why did they not cite this coefficient in support of their formula?

In arriving at the 5 mg/100 mg formula, Hegsted et al. were highly selective in the use of their data. Had they used all their relevant data, they would have derived a completely different formula. Table 5-4 presents 25 of their 36 diets which were identical or nearly identical in saturated and polyunsaturated fat but varied in dietary cholesterol. In view of the conclusions of Hegsted et al., Keys et al. and others that neither stearic acid nor acids with less than 12 carbons affect blood cholesterol, the saturated fat shown in Table 5-4 is composed of only lauric, myristic and palmitic acids, thereby presenting a more accurate composition of blood cholesterol-affecting fatty acids. The quantities shown are percentages of total dietary calories.

The top half of Table 5-4 presents the data from which Hegsted et al. computed their formula of a 5 mg change in blood cholesterol for a 100 mg change in ingested cholesterol. There were a total of 13 different comparisons (from 11 diets) which yielded a mean change of 3.8 mg/100 mg ingested. When the sixth diet is eliminated, which yielded a change in the opposite direction to that expected, the mean change was 4.6 mg/100 mg ingested.

The bottom half of Table 5-4 shows 9 additional comparisons (from 14 diets) ignored by Hegsted et al. Note that the variations in saturated and polyunsaturated fat compositions were effectively identical to those of the top half of the table and, in any event, were too small to produce differences of consequence. While there was one so-called "aberrant" result in the top half of the table, there were four such results in the bottom half. The mean change in blood cholesterol for all comparisons in Table 5-4 was 9.1 mg/100 mg ingested. When all the negative values are omitted, the mean change was 15.1 mg/100 mg ingested. Thus, the conclusion by Hegsted et al. that their data showed a 5 mg increase in blood cholesterol for each 100 mg ingested is simply not true. All of their relevant data indicated a 9.1 mg to 15.1 mg increase per 100 mg, depending on the inclusion/exclusion of "aberrant" results.

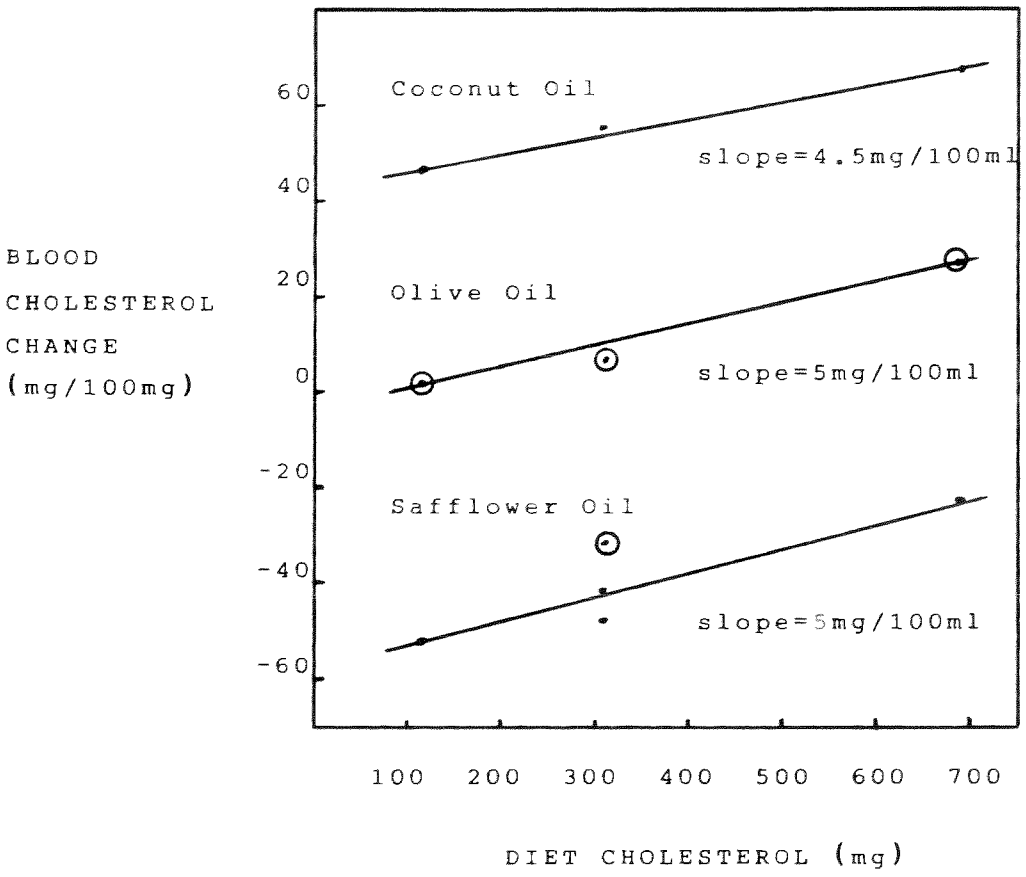

Figure 5-1. Blood Cholesterol change with increases in dietary cholesterol (adapted from Hegsted et al., 1965[408])

Table 5-4

Identical diets in the Hegsted et al. experiments which varied in the amount of dietary cholesterol (computed from Hegsted et al., 1965[408])

	Sat. Fat[a]	Poly Fat[a]	Diet Chol(mg)	Blood Chol. Change(mg)	Change per 100 mg ingested
Comparisons presented by Hegsted (excluding the value denoted by an asterisk)	3.8	25.8	116	-52	5 comparisons (5.8, 2.1, 6.8, 5.0, 5.3)
	3.7	26.0	306	-41	
	3.8	24.9	306	-48	
	4.7	24.9	686	-22	
	4.8	4.8	116	+1	5 comparisons (-16.8, 3.2, 15.5, 4.7)
	5.2	4.9	306	-31*	
	5.2	4.9	306	+7	
	6.1	5.1	686	+28	
	26.1	1.1	116	+46	3 comparisons (5.3, 2.9, 3.7)
	26.1	1.3	306	+56	
	26.1	1.6	686	+67	
Other relevant comparisons	4.8	4.8	116	+1	2 comparisons (-20, -7)
	3.4	3.0	306	-37[b]	
	3.4	3.0	306	-14[b]	
	9.6	2.0	306	-2	2 comparisons (2.6, 20.6)
	9.1	1.5	437	+32	
	10.7	3.2	437	+25	
	13.8	1.2	306	+41	5 comparisons (-3.3, -2.5, -3.1, 27.5, 2.5)
	12.9	2.7	489	+35[b]	
	14.5	2.3	529	+34[b]	
	14.3	5.7	529	+46	
	15.1	3.4	529	+38	1 comparison (91.3)
	16.1	2.0	552	+59	
	12.3	10.6	437	+9	1 comparison (38.5
	12.5	9.4	489	+29	

a Percentage of total dietary calories.
b Directional change opposite to expected.

The issue of aberrant results requires further discussion. It is well-known that the response to dietary cholesterol varies enormously among individuals and, most likely, within individuals. In 1986 Hegsted admitted that "extremely large differences in serum cholesterol response have been reported at comparable differences in cholesterol intake."[2721] He cited, for example, a study by Bronsgeest-Schoute et al.[483] in which 16 of 44 subjects in his experiment showed an increase of up to 20 mg in blood cholesterol after the removal of eggs from their diets. Hegsted reasoned that "Whatever the response to eggs may be, it is not likely that removal of eggs actually causes an increase in serum cholesterol." But such a statement is quite inconsistent with numerous observations, including his own. Of the 25 relevant diets in Table 5-4, 20% produced blood cholesterol changes opposite to that expected.

In the study cited by Hegsted (Bronsgeest-Schoute et al.), 36% of the subjects gave "wrong" responses. In fact, this writer observed numerous instances of such "wrong" responses in the process of evaluating more than 50 different experiments in Chapter 5 of Volume 1. In calculating the maximum response to dietary cholesterol, this writer considered "wrong" responses as zero responses. This tactic biased the mean response upward. However, the fact that significant numbers of subjects or groups show unexpected responses indicates clearly that they are real. They may not be explainable as yet, but they cannot be ignored as chance occurrences. If experimenters wish to generate formulas for use in the general population, they most certainly should use means based on all their data.

Hegsted et al. used only 40% of their relevant diets in generating their 5 mg/100 mg ingested formula. Were it not for the fact that the alliance typically ignores much of the relevant existing data, this tactic might be considered shocking. Instead, it is merely routine. Of course, as was shown in Volume 1, the mean blood cholesterol response to dietary cholesterol is well under 5 mg/100 mg ingested. Since all of Hegsted et al.'s data reveal a mean of 9.1 mg to 15.1 mg, one must seriously question their experiment in general. As will be noted in a later section of this chapter, the use of oils as the predominant fat in their diets may have had something to do with their often peculiar findings.

A Critique of the Mattson et al. Experiment

The 1972 Mattson et al. experiment is also one of the few studies cited by the alliance as demonstrating that dietary cholesterol has "a major role in determining blood cholesterol levels."[368] It was one of only five experiments cited by the Food and Nutrition Board's 1989 report, "Diet and Health."[2070] In addition to the fact that the experiment involved liquid formula diets which rendered it nongeneralizable to the American diet, it presented other problems as well.

Mattson et al. placed 70 male prisoners on a partial cholesterol-free and then a wholly cholesterol-free formula diet for 21 days. Subsequently, the subjects were divided into four groups and fed different amounts of cholesterol. They indicated that the diet contained four feedings per day with 470 calories per feeding. The total number of calories per day was therefore only 1880. Although this number is about the same as that typically involved in female diets, it is about 720 calories less than the typical male diet. Mattson et al. indicated, surprisingly, that the subjects gained an average of 3.1 pounds over the 42 day period. This fact alone leads one to suspect that liquid formula diets affect individuals differently than whole foods diets.

Unlike Connor's studies discussed earlier, the Mattson et al. experiment appeared to maintain constant fatty acid compositions, while varying dietary cholesterol. However, all fatty acids derived from oils, except for the small amount included in the eggs which were in powder form. These forms of fats (and perhaps cholesterol) undoubtedly produce the peculiar effects on blood cholesterol, compared to whole foods.

Mattson et al. did not provide the composition of the subjects' diets prior to the experiment which made it impossible to contrast the fatty acid/cholesterol compositions of the diets and properly assess subsequent decline in blood cholesterol during the cholesterol-free diet. Although this was not considered necessary to contrast the subsequent four diets varying in dietary cholesterol amounts, it was important in gaining an appreciation for the differences between liquid and whole food diets in influencing blood cholesterol levels.

Instead of randomizing the 70 subjects into the four cholesterol groups after the 21 day cholesterol-free period, Mattson et al. committed two cardinal experimental errors. First, they inexcusably eliminated "an equal number of subjects with the highest and lowest cholesterol values." They neither allowed the reader to observe the cholesterol range and note the levels omitted nor provided any rationale whatsoever to justify this action. In effect, they purposely transformed a presumably random sample of men from a prison institution into a biased sample.

Second, while it is clear that they did not randomly assign the remaining 56 subjects to the four cholesterol groups, it is not completely clear how the assignment was made. They said that "The decrease in serum cholesterol level while they were on the cholesterol-free diet was the primary basis for group assignment." However, they continued, "Secondary bases for assignment to groups were body weight and the absolute serum cholesterol level." This hazy description of assignment leaves much to be desired and is suggestive of bias, whether intended or not. One cannot lose sight of the fact that the authors were apparently employees of Procter and Gamble which also apparently funded the study. Procter and Gamble had much to gain from studies showing dietary cholesterol to increase blood cholesterol since their products were in competition with those of the dairy, egg and meat industries, all of which produced most of the cholesterol-laden foods.

Distributing 14 subjects to each cholesterol group on the basis of three assignment variables meant that only about 4.7 subjects, on the average, were assigned per variable. Twelve subjects subsequently dropped out of the experiment and they did so differentially among the groups. Thus, the control group lost 4 subjects (29%), the lowest cholesterol group lost 3 subjects (21%), the second highest cholesterol group lost 2 subjects (14%) and the highest cholesterol group lost one subject (7%). Not only was there a distinct bias across the groups, i.e., the lower the cholesterol group, the smaller the number of subjects, the two lowest cholesterol groups must have been significantly altered in terms of the assignment variables.

Mattson et al. computed a regression equation from their data and indicated that the relationship between dietary cholesterol and blood cholesterol was linear. The equation, i.e., blood cholesterol change = 1.60 + 0.118 mg cholesterol/1,000 calories), yielded the blood cholesterol rate change 13.4 mg/100 mg ingested per 1,000 calories, a seemingly quite impressive rate. (However, when it is calculated in terms of the 1,880 calorie daily diet, the rate reduces to 6.5 mg/100 mg ingested.) Figure 5-2 provides an accurate representation of a figure they presented which shows their regression line. Note that they misplotted one of their points. Their second point should have been at the open circle position, rather than at their solid dot position. The proper points now form an almost perfect accelerating function, precisely the opposite trend as has been typically observed (see, for example, the plot of 48 values from 16 different experiments by Hegsted in 1986[2721]). Granting the fact that the (positively accelerating) function implies an absurd relationship between dietary and blood cholesterol, it nevertheless represents more accurately the observed means (see a later section on multiple regression equations).

Calculating a blood cholesterol rate change from the Mattson et al. tabular data illustrates the accelerating function. The four groups ingested 0.106 mg, 212 mg and

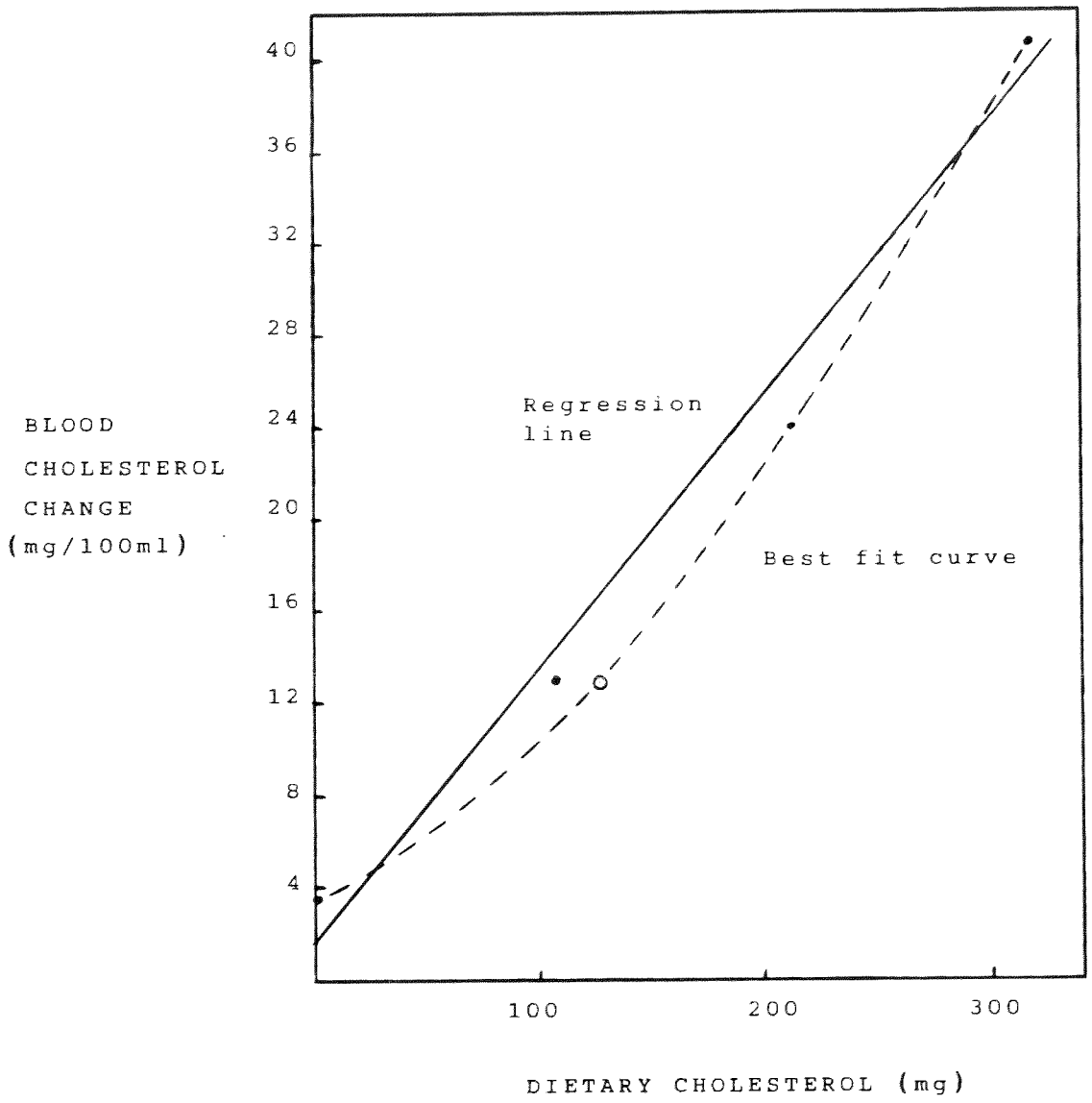

Figure 5-2. Relation between dietary cholesterol and change in blood cholesterol (adapted from Mattson et al., 1972[368])

317 mg cholesterol per 1,000 calories per day. In terms of the 1880 calorie diet, the absolute amounts per day were 0, 199 mg, 399 mg and 596 mg, respectively. The mean blood cholesterol levels of these groups were 3.4 mg, 13 mg, 23.8 mg and 40.5 mg, respectively, yielding blood cholesterol rate increases of 4.8 mg, 5.1 mg and 6.2 mg. Note that the Mattson et al. regression equation "straightened" the actual means to yield a value higher than all three individual rate changes.

Mattson et al.'s discussion seemed devoid of a critical understanding of the literature. They wrongly criticized Keys et al.'s regression equation which predicted a (correct) negatively accelerating function. They stated, "it is unlikely that any relationship either linear or curvilinear, will hold at extremely high levels of cholesterol intake." But in his plot of the results of 16 studies Hegsted showed a clear curvilinear (negatively accelerating) function well within the amounts ingested in their experiment.

Mattson et al. presented the very strong impression that dietary cholesterol was much more important in influencing blood cholesterol than was fatty acid composition. They cited Hegsted[408] as showing that saturated and polyunsaturated fatty acid produced "significant" changes but also cited one of the three Connor studies critiqued earlier[322] and a study by Erickson et al.[331] (see below) as showing "the role of fatty acid composition to be minor relative to that of the dietary cholesterol level." They continued, "At the typical United States level of dietary cholesterol of 700 mg/day, dietary fat must have a P/S ratio of 7 to bring about a significant lowering of blood cholesterol." In addition to the fact that the 700 mg/day was about 175 mg to 200 mg more than studies have shown to be the average consumption, Mattson et al.'s statement that the P/S ratio must be 7 to lower blood cholesterol level was quite absurd and need not be discussed further.

In sum, the Mattson et al. study left much to be desired in terms of design, analysis, interpretations of results and an understanding of the state-of-the-art. Moreover, they did not even address the possibility that their liquid formula diet might affect blood cholesterol differently than would whole foods diets. In view of the sponsor's vested interests in finding important effects of dietary cholesterol, the problems and potential biases in this study cannot be dismissed and their results cannot be taken seriously.

The Erickson et al. study cited above was an earlier experiment by essentially the same authors.[331] Although this liquid formula diet study produced two comparisons yielding blood cholesterol rate changes of 3.2 mg and 3.6 mg/100 mg ingested, a little more than half the value reported in the later Mattson et al. study, it is of interest to describe a serious flaw in the study which led to the false conclusion that dietary cholesterol, not fatty acid composition, was important in affecting blood cholesterol.

Erickson et al. gave five diets to small groups of men. The fatty acid compositions of these diets are shown in Table 5-5. Rows 3 and 4 indicate the total saturated and polyunsaturated fat quantities in each diet, from which they computed the P/S ratios found in Row 5. The diets contained no cholesterol. The subsequent blood cholesterol levels were nonsignificantly different. Erickson et al. concluded that "The diets used in this study afford a rigorous test of the concept that blood cholesterol is a function of the P/S ratio of the dietary fat, since comparisons were made among P/S ratios of 0.1, 0.7, 1.5 and 1.6. We found that a high ratio, 1.6, or an extremely low ratio, 0.1, resulted in essentially identical plasma cholesterol levels. These results are thus incompatible with such a concept."

Table 5-5

Fatty acid compositions of the 5 diets used by Erickson et al. (1964[331])

	Diet (grams per 100 grams)				
Fatty acid	A	B	C	D	E
Palmitic	5.5	5.9	7.3	7.2	10.2
Stearic	2.7	2.8	6.2	6.3	12.7
All saturated	8.2	8.7	13.5	13.5	22.9
All polyunsaturated	13.3	13.0	9.1	9.3	2.1
P/S ratio 1	1.6	1.5	.7	.7	.1
P/S ratio 2	2.4	2.2	1.3	1.3	.2
Blood cholesterol	193	188	190	188	195

Several studies were published prior to the 1962 Erickson et al. study which showed that stearic acid had no effects on blood cholesterol.[a] It can be seen in Table 5-5 that the amount of stearic acid was the same in the first two diets, the same in the second two diets, although greater than in the first two, and much greater in the fifth diet. When stearic acid is not considered in calculating P/S ratios, Row 6 shows that the differences between the ratios were even greater than those calculated by Erickson et al. Palmitic fatty acid increased and polyunsaturated fatty acid decreased quite substantially from the first to the fifth diets. The question is, why did such diets produce the same blood cholesterol levels?

The answer to the above question cannot be found in the Erickson et al. report. If the compositions of the diets and the resulting blood cholesterol levels were as shown in Table 5-5, the authors managed to obtain findings that run contrary to a large body of evidence. There is no question that palmitic acid and polyunsaturated acids are hypercholesterolemic and hypocholesterolemic, respectively. These processes have been recently confirmed with whole food diets (Reiser et al.[877]), as well as with liquid formula diets (Bonanome and Grundy[1395]). The only conclusion of consequence that can be drawn from the Erickson et al. study is that it produced highly erroneous results by chance or there existed certain experimental biases not detectable in reading their report. In either event, the study results cannot be considered more than scientific curiosities.

In sum, both the Mattson et al. and Erickson et al. studies appear to be heavily biased, whether intentional or unintentional, and most certainly should not be selected by the alliance or anyone else as "models" for demonstrating the relationship between dietary lipids and blood cholesterol.

Equations Predicting Blood Cholesterol Changes from Dietary Cholesterol Changes

It was emphasized in Volume 1 and elsewhere that dietary cholesterol has a negligible effect on blood cholesterol level and this fact has been known since the early (1933) work of Okey and Stewart.[346] Nevertheless, dozens of additional experiments were conducted and equations were developed for predicting the magnitude of the effect of dietary cholesterol. In 1962 Anderson et al. (including Keys) concluded that the increase in blood cholesterol "appeared to be a linear function of the square root of the (added) cholesterol in the daily diet."[1840] Hence the formula,

$$\Delta C = \sqrt{C_D} \qquad (1)$$

where ΔC is the change in blood cholesterol level and C_D is the difference between the base and new dietary cholesterol amounts per 1,000 calories ingested. Equation 1 would thus predict that the addition of 200 mg cholesterol to a base diet of 2600 calories with 200 mg cholesterol would increase blood cholesterol by

$$\Delta C = \sqrt{\frac{200}{2600}} = 8.8 \text{ mg},$$

which is equal to 4.4 mg per 100 mg ingested.

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[a] 375,713,714,1309

In 1965 Keys and his colleagues published two papers in which new analyses led to a different equation.[333,351] They computed a regression equation using the data from five experiments (Grande et al.,[351] Beveridge et al.,[349] Steiner et al.,[319] Connor et al.,[362] Erickson et al.[331])

$$\Delta C = -2.3 + 1.73 \left(\sqrt{C_2} - \sqrt{C_1} \right) \qquad (2)$$

where C_1 is the base dietary cholesterol per 1,000 calories per day, C_2 is the new dietary cholesterol, and -2.3 and 1.73 are constants. Since the equation generates a line which intersects the Y axis below the origin, Keys et al. chose to force it through the origin by eliminating the constant -2.3 and altering the slope somewhat, i.e., changing the constant 1.73 to 1.5,[a]

$$\Delta C = 1.5 \left(\sqrt{C_2} - \sqrt{C_1} \right) \qquad (3)$$

Equation 3 now predicts that the addition of 200 mg cholesterol to a base diet of 2600 calories with 200 mg cholesterol would increase blood cholesterol by

$$\Delta C = 1.5 \left(\sqrt{153.8} - \sqrt{76.9} \right) = 5.6 \text{ mg},$$

which is equal to 2.8 mg per 100 mg ingested, and considerably lower, relatively speaking, than that predicted from Equation 1.

Three major problems underlie Equation 3. First, four of the five studies used in the regression analysis involved liquid formula diets. As emphasized time and again, formula diets affect blood cholesterol levels differently from whole foods and, therefore, are inappropriate for use in prediction equations.

Second, the Beveridge et al. study used a diet period of 8 days and Keys et al. assumed that the full effect of the new cholesterol intake had not taken place. They therefore adjusted upward, in a most arbitrary manner, Beveridge et al.'s reported blood cholesterol levels an average of 43%.

Third, Keys et al. noted that the Connor et al. study was confounded because the conditions having the higher amounts of cholesterol also had higher amounts of saturated fat. They again arbitrarily adjusted Connor et al.'s reported blood cholesterol downward by 7.5%, (see the detailed analyses of Connor et al.'s three experiments on dietary cholesterol in the previous section).

Of the 20 different diets employed in the five experiments, Keys et al. adjusted 8 (40%) of the reported blood cholesterol levels. In addition, they did not use one of Beveridge et al.'s 7 dietary conditions, for some reason. One also must question why Keys et al. did not use data from other experiments. In sum, the Keys et al. regression analysis consisted of so many problems, it would appear that the data were forced into a condition which produced an artificial equation and correlation (r = .95).

In 1984 Keys stated that he found Equation 3 to be acceptable when applied against 39 experiments. (In actuality, there were 15 experiments which yielded 39 diet conditions.) Two years later (1986) Hegsted said that Keys' equation "does not appear to provide a good prediction of the observed values."[2721] He first added his 9 values computed from his highly questionable [illegible] experiment to Keys' 39 values and computed an exponential equation. (The mean of his 9 values was 11.9 mg/100 mg

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[a] It is possible that the 1.73 constant in Equation 2 was an unintentional error and was intended to be 1.53, in which case the slope was not altered.

ingested, compared to a mean of 6.0 mg/100 mg ingested for Keys' 39 conditions.) This procedure immediately biased the overall results towards a single experiment. Hegsted then eliminated 8 conditions (4 experiments by Keys' Brongeest, Schonfeld and Buzzard) on the untenable and inexcusable grounds that they were "low responses" to dietary cholesterol (mean of 2.5 mg/100 mg ingested) and computed a second equation. Of course, this procedure again further biased the overall results towards his single experiment.

Hegsted then threw out 10 more conditions (5 experiments by Keys, Beveridge et al., Steiner, Mistry and Schonfeld) on the equally untenable grounds that the dietary cholesterol amounts were "high intakes." (They ranged from 463 mg to 1605 mg, yielding 5.1 mg/100 mg ingested) and computed a third exponential equation. This procedure again biased the overall results towards his single experiment. Thus far, Hegsted eliminated 18 conditions which produced a mean of 4.5 mg increase in blood cholesterol per 100 mg ingested and added his 9 conditions which yielded a mean of 11.9 mg/100 mg ingested.

Hegsted then simplified the third exponential equation to derive a linear equation, i.e.,

$$\Delta C = 0.097\ C_D \qquad (4)$$

where C_D is the difference in cholesterol amounts between two diets per 1,000 calories per day. Using the same example as before, Equation 4 predicts that the addition of 200 mg cholesterol to a base diet of 2600 calories with 200 mg cholesterol would increase blood cholesterol by

$$\Delta C = 0.097\ (76.9) = 7.5 \text{ mg}$$

which is equal to 3.7 mg per 100 mg ingested.

The equations of Keys et al. and Hegsted have been cited and used by numerous other researchers without regard to the fact that they are inconsistent with the experimental data. They (particularly that of Hegsted) were derived by most unscientific manipulations and selections of data. One study used by both Keys and Hegsted was not even an experiment but rather a field study of primitive Mexican Indians. As shown in Volume 1, the average blood cholesterol increase per 100 mg ingested across all solid food experiments was found to be 1.9 mg and it was 4.2 mg across liquid formula experiments. Since the above equations were based on both solid and liquid diets, they predict values that are <u>between</u> solid and liquid blood cholesterol outcomes and they both, therefore, exaggerate the true effects of dietary cholesterol on blood cholesterol.

On the other hand, despite the wide use of the above equations, both of which predict less than a 4 mg increase in blood cholesterol level per 100 mg ingested, many alliance members have published much higher values without indicating how they arrived at such values.

It may be noted that the 1989 Food and Nutrition Board's "immensely, thorough and comprehensive"[1976,1977] review of the diet-CHD literature presented the equations of Keys et al. and Hegsted and accompanied them with a comprehensive <u>three</u> sentences. The Board did <u>not</u> indicate whether the equations were valid, useful or even consistent with one another (which they are not).

On Absolute vs Relative Amounts of Dietary Cholesterol

Some members of the alliance argue that the amount of dietary cholesterol per unit of calories ingested is the proper measure of intake and not the absolute amount ingested. Suppose we have three male subjects, Slim, Fatso and Big John. Slim is 6 feet tall, of average weight and consumes 2,600 calories and 500 mg cholesterol per day. Fatso is 5 feet 8 inches, considerably overweight and consumes 3,500 calories and 600 mg cholesterol per day. And Big John is 6 feet 6 inches, of average weight and consumes 3,500 calories and 600 mg cholesterol per day. Although Fatso and Big John consume 100 mg cholesterol more than Slim, they actually consume less cholesterol (171 mg) per 1,000 calories ingested than Slim (192 mg).

There is some logic to the suggestion that Slim may be consuming more cholesterol than Big John but it is difficult to conceive of a rationale which suggests that Slim is consuming more cholesterol than Fatso. Fatso has more fat cells but a smaller frame and probably a smaller arterial blood network. Would Stamler and his colleagues actually conclude that Fatso's cholesterol intake is preferable to that of Slims? If so, what is the scientific basis for this assertion?

In general, the effects of dietary cholesterol on blood cholesterol levels are independent of the fat composition of the diets and there is no evidence that they are not independent of the number of calories in the diet. It is conceivable that they may be related to the height/frame dimensions of individuals, based on the simple concept that "larger" persons have larger blood networks and therefore can consume more dietary cholesterol than can "smaller" persons and maintain the same blood cholesterol levels. However, it is likely that there are many factors, including genetics, which influence the amount of cholesterol absorbed from the diet and discussions of all such factors are entirely speculative and not very fruitful. Suffice it to say that measuring cholesterol intake as a function of a given unit of calorie intake distorts the intake and there is no scientific justification for this distortion.

The same argument does not hold for fatty acids because the effects of saturated, monounsaturated and polyunsaturated fatty acids are not independent. Therefore, for example, measuring saturated fatty acid intake as percentage of total calories or total fats makes sense. On the other hand, given the same fatty acid compositions, the evidence indicates that total fats as a percentage of total calories is not a meaningful measurement.

DIETARY FATS

Fatty Acids

Introduction. According to the Encyclopaedia Britannica, the generic term for all oils, fats and waxes is "oil," which defines all "substances having the common property of being greasy fluids, either at the ordinary temperature, or at temperatures below the boiling point of water."[1275] All oils are comprised mostly, if not entirely, of compounds of carbon and hydrogen. They are all combustible and insoluble in water.

A class of oils is known as fatty (fixed) oils and fats. They are composed primarily of triglycerides, a formation of three fatty acid molecules with one molecule of glycerol. All fats are edible. With few exceptions, all fatty oils are also

edible if properly purified.[a] Figure 5-3 shows the molecules of four of the most common fatty acids, stearic, oleic, linoleic and linolenic. Each has a carboxyl end (COOH), followed by a straight chain of 18 carbon atoms. When all carbon atoms are connected by single bonds, each atom beyond the carboxyl structure is connected to a pair of hydrogen atoms and the entire chain is referred to as a saturated fatty acid. A fully saturated acid with 18 carbon atoms is called stearic acid.

When a single double-bond occurs in a carbon atom chain, a hydrogen atom is missing on each side of the double-bond but only on one side of the molecule. The loss of a pair of hydrogen atoms defines this chain as a monounsaturated fatty acid. Also, the location of the double-bond from the methyl end of the chain is referred to as the omega (W) number. Since the double bond occurs after the ninth carbon atom, this chain is called an W-9 fatty acid. The monounsaturated fatty acid shown in Figure 5-3 is oleic acid, because it has 18 carbons. The third chain shown in Figure 5-3 has two double-bonds and, therefore, two missing pairs of hydrogen atoms. Such chains are referred to as polyunsaturated fatty acids. Because the first double-bond occurs after the sixth carbon atom, this chain is also classified as an W-6 fatty acid. A fatty acid with 18 carbons and two double-bonds is called linoleic acid. The fourth chain shown in the figure has three double-bonds and three pairs of missing hydrogen atoms. It is also a polyunsaturated fatty acid and because it has 18 carbons, it is called linolenic acid. It is part of the W-3 class of fatty acids. Some fatty acids have as many as six double-bonds. They occur in small quantities in fish oils.

The fatty oils are characterized as being more unsaturated than fats. The double-bonds of unsaturated fatty oils are more readily attacked by oxygen (oxidation) than are single bonds.[391,1799] Thus, the more unsaturated the fatty acids, the greater the oxidation. Curiously, this oxidation (drying) process produces a "tenacious" film from highly unsaturated vegetable oils such as linseed, tung and hempseed but much less tenacious films from highly unsaturated marine animal oils.[1275] Soy bean, corn, cottonseed, sesame and rapeseed, all commonly consumed as foods, are considered semi-drying oils. The non-drying oils (e.g., olive oil) also oxidize but far too slowly for commercial use in paints and varnishes.

It is often said that cooking oils are not chemically altered by heat. It is true that these oils are generally not affected by temperatures under 250 C. However, they do oxidize in the presence of air and the simultaneous application of heat (and light) accelerates the oxidation process,[391,1800] leading to the formation of semi-solid and eventually solid substances.[1275] Prolonged heating at high temperatures reduces the number of unsaturated fatty acids (via polymerization), thereby reducing the P/S ratio.[2576]

While the chemical composition of fats in humans and animals are primarily genetically determined, they are affected by the type of fatty oil or fats consumed. The hydrolyzed triglycerides absorbed into the intestine are recombined to form triglycerides which have similarities with the fatty oils and fats consumed. For example, Eskimos consume large quantities of marine oils and their fat resembles blubber oil.

Common Fatty Acids. The general literature focused on fatty acids and triglycerides typically provide no estimates of their total numbers. It is clear, however, that they are quite large. For example, one source indicated that cow's milk alone contained at

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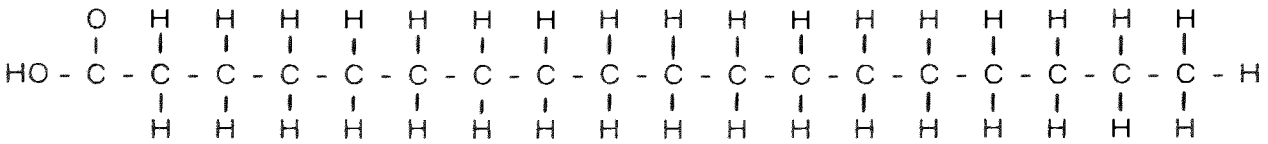
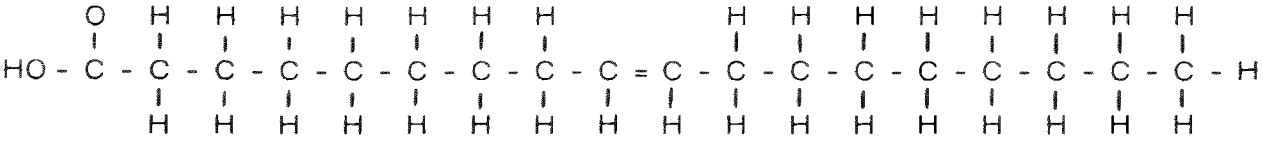
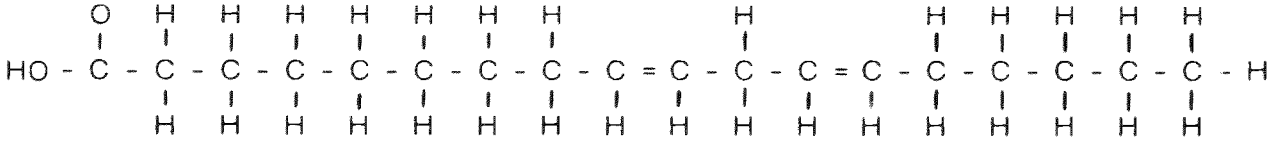
[a] One exception is castor oil (derived from the castor bean) which is nevertheless consumed therapeutically. Also, while the plants (seeds) from which oils are extracted contain vitamins and minerals, the expressed oil does not.[2163]



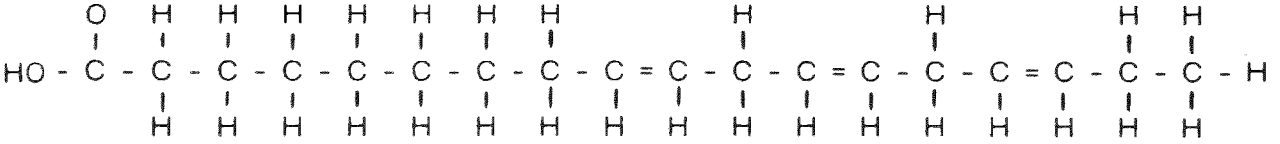
STEARIC ACID ($C_{18}H_{36}O_2$)--SATURATED



OLEIC ACID ($C_{18}H_{34}O_2$)--MONOUNSATURATED



LINOLEIC ACID ($C_{18}H_{32}O_2$)--POLYUNSATURATED



LINOLENIC ACID ($C_{18}H_{30}O_2$)--POLYUNSATURATED

FIGURE 5-3. Molecules of four common fatty acids varying in degree of saturation (adapted from Ensminger et al.[1800]).

least 64 different fatty acids.[2108] And since all may bind with glycerol to form triglycerides, the number of possible triglycerides is obviously very large. On the other hand, relatively few fatty acids comprise the bulk of fatty acids in foods.

Table 5-6 and 5-7 show the fatty acid compositions of common animal and vegetable fats. As can be seen, land animals are primarily composed of three saturated and one monounsaturated fatty acids, namely, myristic, palmitic, stearic and oleic acids. Since only lauric, myristic and palmitic acids are considered hypercholesterolemic, they comprise the total saturated fatty acids shown in Column 7 of the tables.[a] Interestingly, when the nonhypercholesterolemic stearic acid is dismissed, the percentage of saturated fatty acids in marine animals is not substantially lower than that of land animals (with the exception of butter) as people are commonly led to believe. Furthermore, when it is recognized that people consume only a small part of the fat in retail cuts of meat (Volume 1), the differences in saturated fatty acids between land and marine animals approaches insignificance.

Marine animals contain considerably less monounsaturates and considerably more polyunsaturates than do land animals. Moreover, some of the fish oils are very highly unsaturated, as previously noted, associated with chains of 20 to 24 carbons.[391]

Most vegetable oils are characterized as being low in saturates (an exception is cottonseed oil), with small quantities of palmitic acid and even smaller quantities of stearic acid. With the exception of rapeseed oil and olive oil, vegetable oils have large amounts of both monounsaturates (oleic) and polyunsaturates (linoleic). Olive and one variety of safflower oil are almost completely composed of monounsaturates.

The four tropical oils present unique fatty acid profiles. Palm kernel and coconut oils have substantial amounts of lauric acid and about equal amounts of myristic, palmitic and short-chained (4-10) fatty acids. While these oils are more saturated than all other foods, it is questionable whether they are much more hypercholesterolemic than is meat. For example, the short-chained acids are not hypercholesterolemic and if lauric acid has neutral effects, as suggested by Hegsted et al.,[408] the hypercholesterolemic profile of these fatty acids would be quite similar to that of meat. The 1989 Food and Nutrition Board Report included the following statement: "There has been little or no investigation of the metabolic effects of these fatty acids since 1965, and the role of lauric acid (C12) remains uncertain."[2070] In view of the fact that NHLBI controls most research funds and also created the staff of the Food and Nutrition Board, it is obvious that the uncertainty surrounding lauric acid has, for some reason, been purposefully maintained by the alliance.

The saturated fats of cocoa and palm oils are exclusively palmitic and stearic acids. While not having any short-chained and little lauric acids, they do have large amounts of monounsaturates. Palm oil is the only tropical oil having a significant amount of polyunsaturates, i.e., 9.3%.

Hardness and Hydrogenation. The only fatty acids that are solid at room temperature are those saturated acids having 14 or more carbon atoms. All other saturated and unsaturated acids are liquid at room temperature. Whether a fat or an oil is solid or liquid depends on their total fatty acid compositions. For example, milk fat has a

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[a] Although it is well known that stearic acid is not hypercholesterolemic, it is not clear in the literature whether lauric acid has significant effects. For example, Grande et al.[419,718] reported significant effects, while Hegsted et al.[408] observed "little or no effect." In any event, with the exception of two tropical oils (palm kernel and coconut), lauric acid's presence in common foods is quite minimal.

Table 5-6

Fatty acid composition of vegetable fats[1]
(percent of total fat)

	SATURATED					MONOUNSATURATED			POLYUNSATURATED		
Fatty Acid	Lauric	Myristic	Palmitic	Stearic	Total Sat.[2]	Palmitoleic	Oleic	Total Mono.	Linoleic	Linolenic	Total Poly.
Carbons	12:0	14:0	16:0	18:0	12-16	16:1	18:1	16-22	18:2	18:3	18+
Corn	0.0	0.0	10.9	1.8	10.9	0.0	24.2	24.2	58.0	0.7	58.7
Cottonseed	0.0	0.8	22.7	2.3	23.6	0.8	17.0	17.8	51.5	0.2	51.9
Olive	0.0	0.0	11.0	2.2	11.3	0.8	72.5	73.7	7.9	0.6	8.4
Peanut	0.0	0.1	9.5	2.2	14.7	0.1	44.8	46.2	32.0	0.0	32.0
Rapeseed	0.0	0.0	4.8	1.6	5.2	0.5	53.8	55.5	22.1	11.1	33.3
Safflower[3]	0.0	0.1	6.2	2.2	6.9	0.4	11.7	12.1	74.1	0.4	74.5
Safflower[4]	0.0	0.0	4.8	1.3	4.8	0.0	75.3	75.3	14.2	0.0	14.2
Sesame	0.0	0.0	8.9	4.8	9.4	0.2	39.3	39.7	41.3	0.3	41.7
Soybean	0.0	0.1	10.3	3.0	10.6	0.2	22.8	23.3	51.0	6.8	57.9
Sunflower[5]	0.0	0.0	5.4	3.5	6.6	0.2	45.3	45.4	39.8	0.2	40.1
Sunflower[6]	0.0	0.0	5.9	4.5	5.8	0.0	19.5	19.5	65.7	0.0	65.7
Cocoa	0.0	0.1	25.4	33.2	26.5	0.2	32.6	32.9	2.8	0.1	3.0
Coconut[7]	44.6	16.8	8.2	2.8	83.7	0.0	5.8	5.8	1.8	0.0	1.8
Palm	0.1	1.0	43.5	4.3	45.0	0.3	36.6	37.0	9.1	0.2	9.3
Palm Kernel[8]	47.0	16.4	8.1	2.8	78.6	0.0	11.4	11.4	1.6	0.0	1.6

1 U.S. Department of Agriculture Handbook No. 8-4
2 Total cholesterol-raising acids (lauric, myristic, palmitic).
3 High linoleic.
4 High oleic.
5 Low linoleic.
6 High linoleic.
7 Carbon chains 6-10 = 14.1%.
8 Carbon chains 6-10 = 7.2%.

Table 5-7

Fatty acid compositions of animal fats[1]
(percent of total fat)

	SATURATED					MONOUNSATURATED			POLYUNSATURATED		
Fatty Acid	Lauric	Myristic	Palmitic	Stearic	Total Sat.[2]	Palmitoleic	Oleic	Total Mono.	Linoleic	Linolenic	Total Poly.
Carbons	12:0	14:0	16:0	18:0	12-16	16:1	18:1	16-22	18:2	18:3	18+
Beef	0.9	3.7	24.9	18.9	29.5	4.2	36.0	41.8	3.1	0.6	4.0
Butter	2.3	8.2	21.3	9.8	31.8	1.8	20.4	23.4	1.8	1.2	3.0
Milk, cow's[3]	2.9	8.9	23.8	16.7	35.6	1.8	29.6	31.4	2.9	0.5	3.4
Mutton	0.0	3.8	21.5	19.5	25.3	2.3	37.6	40.6	5.5	2.3	7.8
Pork	0.2	1.3	23.8	13.5	25.3	2.7	41.2	45.1	10.2	1.0	11.2
Chicken	0.1	0.9	21.6	6.0	22.6	5.7	37.3	44.7	19.5	1.0	20.9
Duck	0.0	0.7	24.7	7.8	25.4	4.0	44.2	49.3	12.0	1.0	12.9
Egg[4]	0.0	0.0	25.0	8.0	25.0	0.0	50.0	50.0	10.0	2.0	15.0
Turkey	0.0	0.9	20.6	6.2	21.5	6.0	35.9	42.9	21.2	1.4	23.1
Human fat[4]	1.0	4.0	23.0	5.0	28.0	5.0	43.0	48.0	14.0	1.0	8.0
Milk, human[4]	7.0	8.5	21.0	8.0	36.5	2.5	36.0	38.5	7.0	1.0	3.4
Cod liver[5]	0.0	5.8	8.4	0.6	14.2	20.0	2.5[6]	22.0	27.0	1[6]	63.0[7]
Herring[5]	0.0	7.3	13.0	0.0	20.3	4.9	0.0	4.9	0.0	20.7	74.0[7]
Menhaden[5]	0.0	5.9	16.3	1.2	22.2	15.5	0.0	15.5	0.0	29.6	60.3[7]
Sardine[5]	0.0	5.1	14.6	3.2	19.7	11.8	8.9[8]	20.7	8.9[8]	0.0	27[7]

1 U.S. Department of Agriculture Handbook No. 8-4
2 Total cholesterol-raising acids (lauric, myristic, palmitic).
3 National Dairy Council.[2108]
4 Robinson and Lawler.[391] USDA Handbook 8-1[1798] report 37% oleic acid.
5 Weast et al.[2107] (CRC Handbook of Chemistry).
6 Goodnight et al.[1830]
7 Mostly long-chain fatty acids.
8 Weast et al. indicated a sum of 17.8% for both linoleic and linolenic. Thus, each acid was assigned half that amount here.

significant amount of short chained saturated fatty acids, producing a soft fat. Coconut and palm kernel oils have a substantial amount of short chained fatty acids, thus yielding oils.

Fats are essential to baked foods, although in their pure form they are colorless, odorless and tasteless.[2290] They acquire distinctive colors, flavors and odors from the absorption of other substances. Because fatty oils readily become rancid via oxidation, causing foods to acquire disagreeable odor and taste, and because they are oils, causing foods to lose their shape and become limp, naturally solid saturated fats, such as lard, have historically been used in baking. The highly saturated tropical oils have also been used, sometimes lightly hydrogenated. However, with the new fear of tropical oils generated by the alliance (see section on tropical oils), food manufacturers are rapidly replacing these oils with other more heavily hydrogenated oils.

The hydrogenation process has been used throughout most of this century, principally to convert vegetable oils into hard margarines but secondarily to give longer shelf life to vegetable oils (slow the progress of rancidity).[a] Very light hydrogenation primarily reduces the number of double bonds in polyunsaturated fatty acids. It generally converts few or no monounsaturates into saturates. At the other extreme, very heavy hydrogenation can convert an oil into a completely saturated fat. For example, complete hydrogenation of linolenic or linoleic acids (each having 18 carbons) results in the saturated stearic acid. Since there are a large number of margarines on the market varying in hardness, they also vary in terms of percentages of saturated fatty acids, ranging from about 9% to as much as 28%.[2157] Of most concern about hydrogenation, however, is not the increase in saturates and/or the decrease in unsaturates but rather the introduction of unnatural fatty acid molecules (recall Chapter 1). The current partial hydrogenation process converts some natural "cis" unsaturated fatty acids into unnatural "trans" acids, as exemplified in Figure 5-4. The natural unsaturated fatty acid folds back upon itself at each double-bond, whereas the trans form tends to remain relatively straight.[2445]

The American diet is now loaded with trans fatty acids because so much of the food contains partially hyrogenated fats. One popular fat is canola (Puritan) oil, derived from rapeseeds. Rapeseed oil originally contained a highly toxic (erucic) fatty acid that killed many people[2603] but that acid has since been genetically bred out of the oil.[2601,2602,3389] However, because of its significant content of highly oxidizable linolenic acid, partial hydrogenation is necessary to eliminate it. In the process, substantial trans acids are produced.

Linoleic, linolenic and arachidonic acids are called "essential" fatty acids. However, because arachidonic acid is synthesized from linoleic acid and the purpose of linolenic acid is effectively unknown, linoleic acid is apparently the only essential fatty acid of importance in foods.[391,1799] When linoleic acid is transformed from cis to trans forms by hydrogenation it no longer can function as an essential acid, although it is utilized as a food substance. Most sources indicate that essential fatty acid deficiency is nonexistent, suggesting that very small quantities are necessary.[391] However, some recent evidence from rat feedings is suggestive of negative physiological effects of hydrogenated fatty acids, particularly reproductive functions.[2444]

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[a] Antioxidants (e.g., Vitamin E) are often generally added to vegetable oils.[391]

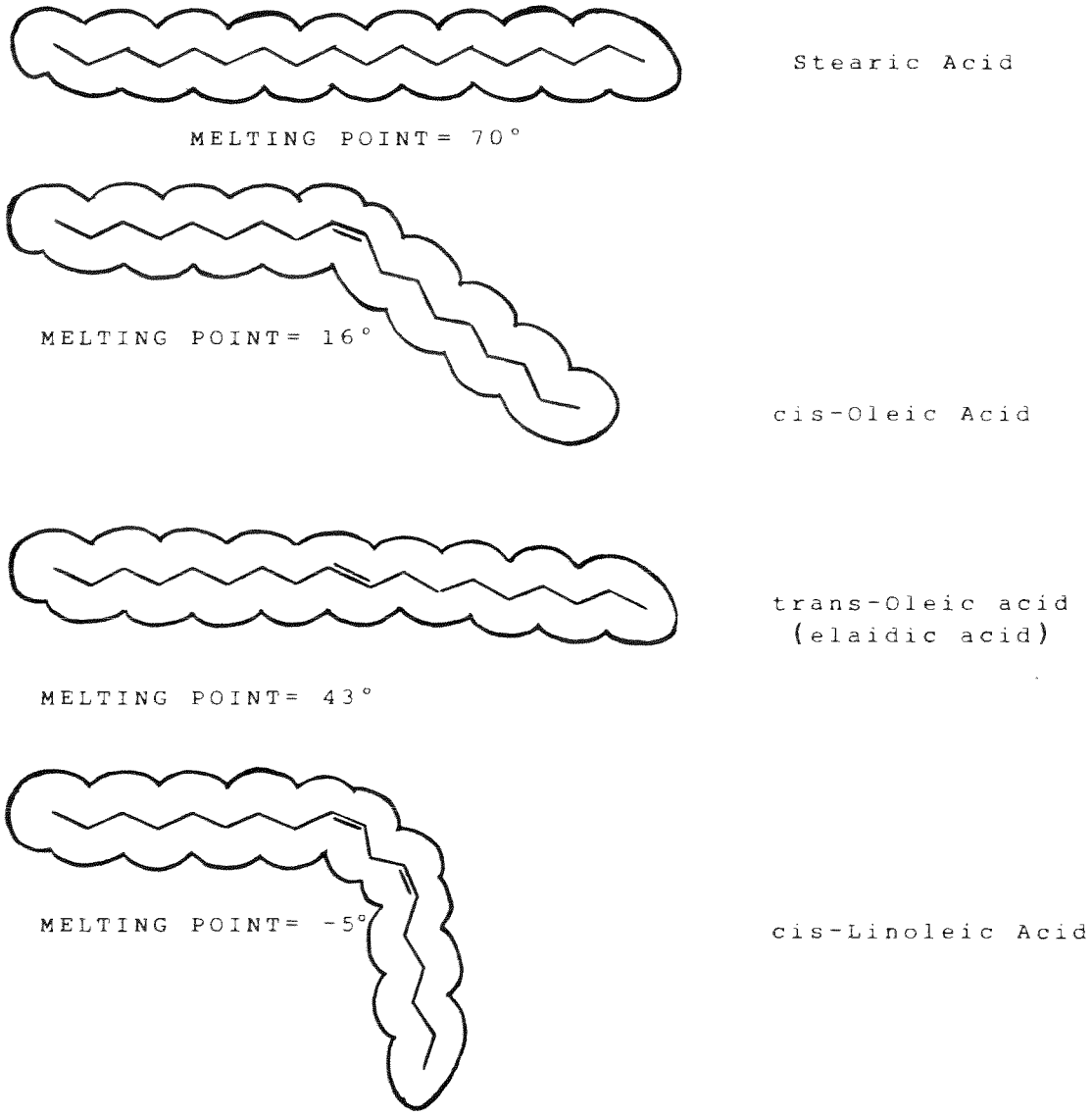

Figure 5-4. Physical characteristics of common forms of fatty acids with 18 carbons (adapted from Vance and Vance, 1985[2445])

Fat Absorption. Short chained fatty acids of less than 14 carbon atoms enter the intestinal mucosa and are subsequently absorbed into the portal vein,[391,712] where they travel (with albumin) directly to the liver. The glycerol associated with these free fatty acids also enters the portal circulation. The longer chained fatty acids are reconstituted as triglycerides and then enter the lymph circulation. Interestingly, Ahrens observed that "unsaturated acids are hydrogenated in part during absorption from the gut, presumably by bacteria."[712] No other references were found which confirmed this observation, however.

Because cholesterol and fats are hydrolyzed mostly in the small intestine, this fact has led to the ileal bypass operation which removes part of this intestine (see Chapter 9). Liquid fats are hydrolyzed more rapidly than solid fats[391] which adds confusion to the observed fact that liquid formula diets depress blood cholesterol levels relative to solid foods diets. Apparently, cholesterol and fats are absorbed into the intestinal epithelium at about the same rate. However, cholesterol is subsequently released much more slowly than fats, accounting for the fact that peak activity in the blood of cholesterol ingestion may require 2 to 3 days but only 3 to 4 hours for fat.[2544]

The Liver. In addition to forming VLDL (and ultimately LDL) and HDL, the liver can transform one fatty acid into another by changing the number of carbon atoms in the chain and by introducing one double bond in saturated fatty acids to yield a monounsaturated acid.[391] The liver hydrolyzes triglycerides and resynthesizes them and it also forms triglycerides from free fatty acids. The free fatty acids may derive from the intestine via the portal vein or from adipose tissue via the epinephrin stimulated hydrolysis of triglycerides.[2271]

The Hydrogenation of Fatty Acids

Introduction. In 1957 Ahrens[712] and Van Itallie[353] cited Sinclair[1747] as hypothesizing that the increased consumption of partially hydrogenated oils after World War I might be a cause of the reported increased incidence in CHD. Based on discussions by Kinsell and Michaels[1748] and Ahrens et al.,[340] it was hypothesized that the factors underlying such a cause could be the two chemical effects of the hydrogenation process, i.e., (1) destruction of some essential fatty acids (simultaneously reducing and increasing, respectively, the polyunsaturated and monounsaturated fatty acid components of the fat) and (2) the production of unnatural isomers, cis-trans and trans-trans. Both types of isomers were known to be unable to replace cis-cis linoleic acid in essential fatty acid deficiencies. Thus, Sinclair proposed that the CHD increase might be due to a decrease in the essential fatty acids in the so-called Western diet.

Kinsell and Sinclair suggested that the cholesterol-lowering effects of vegetable oils were due to their content of essential fatty acids.[874,a] Although such a suggestion was subsequently found to be incorrect,[b] there nevertheless lingered the possibility that the chemical transformations occurring during the hydrogenation process might be harmful to health. First, hydrogenation might somehow affect the ability of the oils to reduce blood cholesterol levels. Second, the unnatural isomers might have one or

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[a] Because of the effects of linoleic acid on blood cholesterol levels, apparently via the excretion of steroids,[2324] Kinsell et al. concluded that "the prescription of a low-fat diet is biologically unsound."[2323]

[b] 343,714,716,875

more harmful effects on the body. With regard to the latter, Van Itallie cautioned that "...since the possibility has not been excluded that some of the substances formed during the hydrogenation may be harmful, their status should be promptly and thoroughly investigated."[353] As will be seen, such substances have been neither "promptly" nor "thoroughly investigated." In fact, there strongly appears to have been a concerted effort to avoid research on the unnatural isomers by the NHLBI/AHA alliance.

The above discussion suggests three issues in need of specific analysis: (1) the matter of reducing essential fatty acids by hydrogenation; (2) the question of whether or not hydrogenated oils are hypercholesterolemic; and (3) the question of whether the unnatural isomers emerging from hydrogenation may be harmful to health. These issues are independently discussed below.

Essential Fatty Acids. Sinclair's proposal that the increased incidence in CHD might be due to the reduction of essential fatty acids in hydrogenated products seems quite untenable. Prior to the increased use of the hydrogenation process, the consumption of polyunsaturated fats was exceedingly low. Not only did unhydrogenated oils progressively increase in the diet, hydrogenated oils also contributed increased amounts of essential fatty acids despite hydrogenation. In other words, there was an obvious and strong positive correlation between consumption of essential fatty acids and the CHD incidence.

The Effects of Hydrogenated Fats on Blood Cholesterol

At the outset, it must be said that it is illogical to suggest that hydrogenation has no effects on blood cholesterol level if one accepts the recognized facts that saturated fats increase cholesterol levels and polyunsaturated fats decrease such levels. The only question worthy of discussion is whether or not hydrogenation has practical effects.

A cursory examination of the literature associated with the effects of hydrogenated oils on blood cholesterol levels leaves the impression that such effects are minimal or nonexistent. For example, Hunter and Applewhite, representatives of the Institute of Shortening and Edible Oils, stated in 1988 that "The combined results (of relevant studies) indicate that replacement of hydrogenated fat with unhydrogenated fat in the diet is of little value in reducing serum lipid levels."[1746] It should be noted that if this statement were a fact, then NHLBI/AHA's contention that the CHD "epidemic" was largely caused by the increased consumption of saturated fat would be untenable, since the increased saturated fat in the American diet during the first half of this century was entirely (not partially) due to hydrogenated oil products (see Chapter 3 on food consumption trend studies).

One reason for the impression that hydrogenated products are not hypercholesterolemic is undoubtedly due to the poor quality of the relevant research and perhaps the even poorer quality of the interpretations of the results of that research. A second reason is the fact that the NHLBI/AHA alliance seldom addresses hydrogenated fats when it links saturated fats with CHD. And a third reason is the fact that most of the published literature is extremely old, suggesting that the issue has long been resolved in favor of the hydrogenation process.

In 1964 Erickson et al.,[331] an employee of the Procter and Gamble Company, cited five studies which supposedly demonstrated that partial hydrogenation is

hypercholesterolemic[a] and another six studies (including their own) which reported no hypercholesterolemic effects.[b] As will be seen, their assessment was both misleading and incorrect.

A Summary of Studies. Since Erickson et al. recognized five studies showing hydrogenated fats to be hypercholesterolemic, this review will be restricted to those studies cited by Erickson et al. as reporting no effects of hydrogenation, as well as their study and three additional investigations not included in their review.

The earliest study cited by Erickson et al. was that of Beveridge and his co-workers in 1958.[412] These investigators fed a liquid diet containing 35% of total calories as butterfat to subjects. Subsequently, carbohydrates representing 25% of total calories were replaced with hydrogenated corn oil for half the subjects and unhydrogenated corn oil for the remaining half. The latter additions produced the same changes in blood cholesterol levels.

The Beveridge et al. experiment cannot be said to have answered anything. In addition to being a liquid diet study, results of which have always been peculiarly different from those of whole foods studies, as noted previously, the diet was absurd in being composed of 60% of total calories as fat, with the base fat being very heavily saturated with 35% of calories as butterfat. Since both diets contained about 23% of calories as saturated fats, already about 64% more than the typical American diet, it is not very likely that the additional hydrogenated or unhydrogenated corn oil will make much difference, particularly as partial hydrogenation alters the polyunsaturated and monounsaturated fatty acid compositions, rather than the saturated fat content. In sum, this study was quite poorly designed to evaluate the effects of hydrogenated fats on blood cholesterol levels.

Erickson et al. cited a second study by Beveridge (and Connell), performed in 1962.[409] These investigators conducted two experiments comparing hydrogenated margarines with unhydrogenated corn oil. They reported no effects of 8 margarines in the first experiment and indicated that only three of 8 margarines in the second experiment produced significantly higher cholesterol levels than did the corn oil. They concluded that hydrogenation was not important. Such a conclusion, however, was poorly conceived for several reasons. First, the study again used liquid diets and its results absolutely cannot be generalized to the population consuming whole foods.

Second, like the earlier Beveridge study, the first experiment in the present study involved margarines being added to a diet already containing 10% of total calories as saturated fats. The variation among all the margarines in saturated fats was very narrow.

Third, in the second experiment wherein the total saturated fats in the margarine diets were only 5.9% to 8.5% of total calories, the average cholesterol level produced by the margarine diets was 31 mg higher than that produced by the corn oil diet. In effect, the results of the two experiments were quite contradictory and made no sense whatsoever.

As noted by Enig, the amount of saturated fat in commercial margarines varies dramatically, in some cases, nearly 30%.[1744] Beveridge and Connell used margarines

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[a] 343,375,418,545,1855

[b] 409,412,700,1853,1854,1962

of very similar saturated fat content. Based on the results of numerous other experiments, these investigators should have found effects in their first experiment because of the wide variations in polyunsaturated fat content. In any event, one of the two experiments clearly demonstrated that hydrogenated margarines are hypercholesterolemic, compared to unhydrogenated corn oil and this study, therefore, cannot be placed in the category supporting the notion that hydrogenation has no effects on cholesterol.

The third study cited by Erickson et al. was the first (1962) experiment published by Procter and Gamble (McOsker et al.[700]). These investigators also concluded that hydrogenation has no effects on blood cholesterol levels in another liquid diet experiment. However, such a conclusion cannot be drawn from their data. They compared 5 hydrogenated fat diets with one unhydrogenated fat diet but failed to disclose the specific saturated fatty acids in all diets. For example, they listed the combined palmitic and stearic acids for all diets, but since it is has long been known that stearic acids are not hypocholesterolemic, it is impossible to determine which, if any, of the diets had higher amounts of palmitic acid. Moreover, the polyunsaturated content of the diets varied substantially, with the unhydrogenated fat diet having 47% to 352% more polyunsaturates, amounts that vastly exceed the differences between most hydrogenated and unhydrogenated fats.

It is of interest to note, however, that one of McOsker et al.'s diets not only had significantly more palmitic/stearic acids, it was the only diet listed as having a significant amount of myristic/lauristic acids. This diet produced a cholesterol level 10% higher than that of the unhydrogenated fat diet. Therefore, based on the data given and omitted, this study provides evidence for and none against the proposition that hydrogenated fats are hypercholesterolemic.

The fourth study cited by Erickson et al. was conducted by Wilcox and Galloway in 1961.[1853] They compared a hydrogenated cottonseed oil and a hydrogenated lard diet with an unhydrogenated lard diet. At the outset, it is most peculiar why Wilcox and Galloway chose cottonseed and lard as fats to be evaluated for the effects of hydrogenation since both are highly saturated to begin with. It is of interest, in this regard, that they omitted information on the saturated and monounsaturated fatty acid content of the diets. Nevertheless, the hydrogenated fat diets produce slightly higher cholesterol levels than their unhydrogenated counterparts (2.5% for the cottonseed diets and 6% for the lard diets).

Morse and his co-workers conducted the fifth study in 1962 cited by Erickson et al.[1854] They compared a partially hydrogenated corn oil diet with a diet having a mixture of liquid corn oil and partially hydrogenated soy and cottonseed oils. These diets reduced cholesterol levels by almost identical amounts. However, since no specific compositions of the fatty acids were provided in this study, and since both diets had unknown quantities of hydrogenated fats, it is again impossible to draw any conclusions from the results. On the other hand, Morse et al. did indicate that one diet had a P/S ratio of .6, while the other was 1.45. Since the former would normally produce a much higher blood cholesterol level than the latter, the only conclusion to be drawn from this information is that either the ratio variation was due exclusively or almost exclusively to the dominance of stearic acid in the high P/S ratio diet, or Morse et al. obtained results totally inconsistent with dozens of other experiments. In any event, this study again cannot be used as evidence for or against the proposition that hydrogenated fats raise blood cholesterol level.

The final study cited by Erickson et al. was that of Grasso et al., published in 1962.[1852] The results of this experiment not only were opposite to that attributed by Erickson et al., i.e., a hydrogenated soy oil diet yielded a cholesterol level nearly 13% higher than did an unhydrogenated vegetable oil, the compositions of the diets were,

for all practical purposes, identical. Both had 12% saturates and the hydrogenated fat diet had only 2% fewer polyunsaturates and 2% more monounsaturates. Moreover, the validity of this study approached zero because there were only two subjects participating and both had serious dysfunctions, i.e., one had hypothyroidism and the other was a diabetic.

In summary, none of the six studies cited by Erickson et al. can be considered as providing unconfounded evidence that hydrogenated fats do not raise cholesterol levels and some, in fact, provide evidence to the contrary. The fact that extremely important information was selectively omitted from some of the articles leads one to suspect that at least some of the studies were conducted with pre-conceived biases.

The 1964 Erickson et al. study itself yielded results which are highly questionable, to say the least. First, they compared two pairs of hydrogenated and unhydrogenated diets, each pair having almost identical fatty acid compositions, and found that they produced identical effects on blood cholesterol levels. That outcome, of course, is hardly surprising. Second, one of these pairs of diets contained nearly 100% more saturated fat than the other pair and only 31% less polyunsaturated fat. Yet, both pairs affected blood cholesterol levels identically. Thus, while attempting to prove that hydrogenated fat does not elevate cholesterol level, which the study emphatically did not, the results were totally inconsistent with a large body of research findings. It should be mentioned finally that Erickson et al. used liquid formula diets.

Three additional experiments should be mentioned. A 1957 study by Anderson et al. found that a hydrogenated safflower oil diet produced a higher (9.3 mg) cholesterol level than an unhydrogenated diet of the same oil.[1856] Since this study was published as an abstract with few details, the importance of the reported difference cannot be determined.

Mattson et al. compared two diets in which the fatty acid compositions were essentially identical.[1857] The difference between the diets was that the hydrogenated fat in one diet contained substantial quantities of trans isomers, while the hydrogenated fat in the second diet consisted of only cis acids. The fact that both diets affected cholesterol levels the same is not surprising and the study would ordinarily be considered irrelevant to the present discussion. However, because both diets contained hydrogenated fats, it is curious that one contained virtually no trans isomers.

A final study to be mentioned was the 1982 investigation by Laine et al.[1914] They found that hydrogenated corn oil raised blood cholesterol level 6.2% higher than unhydrogenated soy oil, despite the fact that the compositions of both fats were only slightly different. Thus, both diets had 8% saturated fats and the unhydrogenated fat diet had only 3% more polyunsaturates than the hydrogenated oil diet.

The Effects of Unnatural Isomers on Health. This issue is discussed in Chapter 8.

Conclusions. Since an abundance of experiments have shown that saturated and polyunsaturated fats raise and lower blood cholesterol levels, respectively, it is, as noted at the outset, illogical to state or hypothesize that hydrogenation has no effects. Fatty acid compositions can be designed to suggest that hydrogenation per se has no effects but such manipulations hardly constitute scientific evidence. Some of the studies cited above were either purposely designed to mislead readers and/or they were poorly reported in scientific journals. There is no question that hydrogenating a given fat will increase its ability to raise blood cholesterol levels. The more it is hydrogenated, the greater its ability.

Apparently the most recent study on this subject was published in 1990 by Mensink and Katan.[2859] They compared three diets having identical amounts of calories, protein, carbohydrates, total fat and polyunsaturated fat. Two of the diets also had identical amounts of saturated and monounsaturated fat. The only difference between these diets was that one had all of its monounsaturated fatty acids as Cis isomers (the "Oleic diet"), while the other diet contained 10.9% of total calories as trans isomers ("Trans diet"). The resulting mean blood cholesterol levels of subjects in the Oleic and Trans groups were 172 mg and 182 mg, respectively, suggesting that the Trans isomers increased blood cholesterol levels.

The third diet administered by Mensink and Katan was the same as the Oleic diet except that it had twice the amount of saturated fat and a little more than half of the monunsaturated fat. The mean blood cholesterol level of subjects consuming this "saturated fat diet" was reported to be 193 mg, suggesting that Trans fatty acids have perhaps half the cholesterol-lowering effects as saturated fatty acids.

The Mensink and Katan study appeared to be well-designed theoretically. However, there was a procedural problem of no little importance and there were at least two peculiarities observable in their results. With regard to the procedural problem, although all food was either served the subjects in the presence of the experimenters (lunch) or prepackaged with preparation instructions for home consumption (breakfast and dinners), the results of the study were based on the assumption that all subjects ate all of the foods given to them and resisted consumption of all other foods away from the experimenters. Scientific conclusions should not be based on assumptions, particularly as experimental subjects are notorious for exhibiting a variety of non-compliance levels when not monitored. It is almost a certainty that significant noncompliance occurred and the matter is not satisfied by another assumption, i.e., that the degree of noncompliance was distributed equally among the groups. While the amount of error is argumentative, it can never be resolved. The most that can be drawn from the study is that trans fatty acids per se probably elevated blood cholesterol somewhat but the actual amount remains unknown.

One peculiarity of the Mensink and Katan study is that the mean blood cholesterol levels of the females were substantially (9%) higher than were those of males, although the mean ages of the groups were essentially identical. Since mean blood cholesterol levels of females are typically significantly lower than those of males below the age of 45, the total discrepancy is considerable. While this discrepancy does not directly diminish the significance of their basic findings, it nevertheless is a bothersome outcome.

A second peculiarity is the selection of percent of total calories as saturated fat used in the three diets. None of the three diets remotely simulated the typical American diet. The oleic and trans diets contained 30% less saturated fat than is typically consumed in the U.S. and the saturated fat diet was 39% higher than that in the typical diet.[a] This range served to exaggerate the differences that would be observed in more realistic dietary changes. If the saturated fat diet were adjusted to simulate the American diet, the difference between the trans and saturated fat diets, with respect to mean blood cholesterol levels, would have been only about 5 or 6 mg, rather than 11 mg, and possibly less if monounsaturated fat does indeed lower blood cholesterol similarly to polyunsaturated fat (see below).

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[a] The fact that the study was conducted in the Netherlands is irrelevant because we are concerned about American diets and changes that can be realistically expected.

A third peculiarity of the Mensink and Katan study is that the saturated fat diet had a saturated to unsaturated fat ratio of 1.07, while that of the oleic diet was 0.33. One would expect a much larger difference in blood cholesterol level than the 12% observed.

As emphasized in Volume 1 and elsewhere, there has long been considerable evidence indicating that liquid formula diets produce peculiarly different effects on blood cholesterol than whole food diets. It is incomprehensible why some experimenters have repeatedly employed liquid diets in the face of this knowledge and perhaps even more incomprehensible why they insist that their results are generalizable to the American diet. They are unequivocally not generalizable.

Monounsaturated vs Polyunsaturated Fats

Volume 1 summarized the many studies which evaluated the effects of various types and quantities of fatty acids on blood cholesterol level. Much previous research indicated that polyunsaturated fat has a depressing effect on cholesterol, while monounsaturated fat seems to have neutral effects. A 1985 study by Mattson and Grundy[717] found no significant difference between diets differing in monounsaturates and polyunsaturates. It is worth noting, however, that the polyunsaturated diet yielded a somewhat lower mean cholesterol level.

A 1989 study by Mensink and Katan[2646] also evaluated the relative effects of monounsaturates and polyunsaturates. They concluded that "a mixed diet rich in monounsaturated fat was as effective as a diet rich in polyunsaturated fat in lowering LDL cholesterol." This was a strange conclusion in view of the fact that their monounsaturated fat diet yielded a significantly greater cholesterol depression than did the polyunsaturated fat diet.

The above two studies did show agreement with respect to demonstrating that both monounsaturates and polyunsaturates depress cholesterol levels but they were not in agreement in terms of the relative effects of the two fatty acids. Moreover, both studies suffered from unknown effects of procedural problems. The Mensink and Katan results were again based on the assumption that all subjects conformed perfectly to food preparation and eating instructions away from the laboratory. The Mattson and Grundy study used liquid formula diets.

In view of the fact that these studies reported results quite different from many previous studies, it would be well to see additional studies with tighter experimental control employing whole foods.

The Tropical Oil Fiasco

Introduction. The hysteria generated by the first elements of the alliance's NCEP included the proposal for congressional bills which would require all foods with saturated fats to be labeled as such. Although tropical oils (palm, palm kernel, coconut and cocoa butter) are highly saturated fats, they have been used sparingly in manufactured foods and represented a very small part of the American diet. Nevertheless, the Center for Science in the Public Interest (CSPI), a dubious consumer organization, demonstrated an eager willingness to join the alliance's bandwagon and "fingered tropical oils as cardiovascular time bombs" in late 1986.[1925]

The CSPI's announcement motivated the soybean industry to mount an advertising campaign (tropical oils are "hazardous to your health") to encourage food manufacturers to replace tropical oils with soybean oil.[1923,1925] While the soybean industry virtually dominated the cooking oil market, i.e., about 80% of $2 billion in sales, its revenues were eroding with the growing importation of Canadian rapeseed oil

(Procter and Gamble's Canola oil).[1925,a] Such ads naturally provoked Malaysia and the Philippines, the leading exporters of palm oil and coconut oil, respectively.[1922] Although only about 4% of Malaysia's exports went to the U.S., the Malaysians were concerned that the American reaction might impact on their sales in other countries.[1921]

Apparently triggered by the anti-tropical oil advertising, Phil Sokolof, a wealthy recovered heart attack victim, founded and totally funded the "National Heart Savers Association."[1916,3000] On November 1, 1988 he placed ads in major U.S. newspapers entitled, "The Poisoning of America."[2230,b] He urged Americans to avoid purchasing foods containing palm or coconut oils or lard. Subsequently, the major food manufacturers announced that they would remove both tropical oils and animal fats from their products. Another Sokolof ad appeared on March 1, 1989 which announced this fact.[2238] Thus, the Sokolof ads probably did more for the soybean industry than did their own campaign. According to the Malaysia Trade Commissioner, palm oil exports to the U.S. dropped about 26% before Sokolof's ads.[1924] That value may approach 100% in the near future.

On February 2, 1989 the Malaysian Oil Palm Growers' Council placed full page ads in major U.S. newspapers entitled, "The facts about palm oil."[1919] Among other things the ads indicated that palm oil (1) has "positive anti-thrombotic properties" and (2) "reduces blood cholesterol." With regard to the latter, 12 unnamed experiments (or 8 experiments having 12 sub-experiments) were cited as proof that palm oil depresses cholesterol levels.

The Malaysian ad angered Bonnie Liebman of CSPI who declared that "It's the most deceptive ad I've seen as 12 years as a nutritionist."[1915] While Liebman was quite correct, her anger was nevertheless unjustified because CSPI's initial attack on tropical oils reflected little knowledge of the true relationship between diet and CHD. Ironically, Scott Grundy, co-author of three of the studies cited in the Malaysian ad, called it deceptive. As noted in Chapter 5 and elsewhere, most of his experiments were deceptive simply because they used liquid diets.

Finally, the California Medical Association joined the bandwagon in 1989 by instituting a "comprehensive education program aimed at curbing the public's use of oils high in saturated fats."[1733]

Statement of the Problem. Like so many other issues, it is difficult to obtain an accurate estimate of the per capita consumption of tropical oils. As emphasized in Volume 1, figures used by many researchers and medical writers are typically based on USDA "availability" data and do not realistically account for wastage. Charles Mitchell of CSPI reported that tropical oils represent 3% of the total fat in the American diet.[1918] A spokesperson for the United Coconut Association of the Philippines, Carl Levin, offered the value of 5%[1923] and AHA spokesperson, John LaRosa, held that it was 7%.[1916] Since this report has cited evidence indicating that

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[a] The soybean industry is developing a new soybean with a saturated fat content comparable to rapeseed.[2617]

[b] Sokolof had previously placed full page ads in major newspapers which spewed the usual NHLBI/AHA dogma such as the erroneous "For every 1% you lower your cholesterol, you reduce your risk of heart attack 2%."[2231]

LaRosa sometimes has difficulty in reporting facts accurately, an average of the first two estimates, i.e., 4%, may be used for the present discussion.[a]

The typical American diet consists of about 110 g of fat. Four percent of 110 g is equal to 4.4 g, a very insignificant amount by itself.[1915,1917,1924] Most of this 4.4 g is comprised of palm, coconut and cocoa oils. Averaging across data presented in seven different studies/sources, these oils are approximately 50%, 93% and 60% saturated, respectively.[b] However, it seems generally accepted that only lauric, myristic and palmitic acids are hypercholesterolemic.[408,419,718] Therefore, the valid saturation percentages for palm, coconut and cocoa oils are about 46%, 77% and 24%, respectively. Assuming equal consumption, the 4.4 g of tropical oils per day consists of about 2.2 g of hypercholesterolemic fat. This amount represents 2% of total fat and 0.76% of total calories. As will be seen, this amount is totally insignificant.

Charles Mitchell of CSPI stated that "If the recommendation is to cut back on saturated fat, every little bit helps."[1918,3000] Such a response reflects little understanding of the combined effects of various fatty acids. For example, all vegetable oils contain hypercholesterolemic fatty acids. Why, then, does Mitchell not recommend that they be eliminated from the diet? If the answer is that these saturated fatty acids are dominated by the associated unsaturated acids, it must be logically concluded that the very small amounts of tropical oils in the American diet are similarly dominated by all other fats. Even if they represented the "deciding" fat in one's diet, 2.2 g of saturated fat, along with 2.2 g of noncholesterolemic or hypocholesterolemic fat, cannot have more than a minor effect on blood cholesterol levels, as indicated by dozens of experiments (Volume 1). Certainly the "benefits" of removing tropical oils from foods will be totally insignificant compared to the costs involved, including the major disruptions of the economies of such countries as Malaysia and the Philippines.

Tropical Oil Experiments. Several experiments have compared diets whose fats consisted exclusively of palm oil with diets in which either polyunsaturates or monounsaturates predominated. These diets were extremely unrealistic because they far exceeded the saturated or polyunsaturated fats in the typical American diet. Most relevant would have been diets having a few grams of palm or coconut oil more or less than currently existing in the American diet in order to determine the importance of such tropical oils on blood cholesterol levels. However, these extreme diets may permit the derivation of a reasonable estimate of their importance by interpolation.

Tables 5-8 through 5-13 provide pertinent data from six studies which used palm or coconut oils. Three of these studies permit direct comparisons between a palm oil diet and a diet high in polyunsaturates.[717,879,1914] The mean composition of the palm oil diets was (% of total calories) as follows:

PALM OIL DIET			HIGHLY POLYUNSATURATED DIET		
SAT	MONO	POLY	SAT	MONO	POLY
18.7%	16.4% +7	3.9%	5.6%	11.3% -16	22.3%

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[a] In 1990 the FDA's Park and Yetley[2929] indicated that tropical oil consumption in the U.S. was less than 4% of total fat, less than 2% of total energy and constituted less than 8% of all dietary saturated fat.

[b] 322,335,714,717,877,1395,1822,1975

Table 5-8

Fat composition of diets used by Mattson and Grundy[717]

	% of total fats (% of total calories)			
Fatty Acid	Diet 1[a]	Diet 2[b]	Diet 3[c]	Typical Diet
Saturated	49.7 (20)	8.6 (3)	11.2 (5)	(14)
Monounsaturated	40.0 (16)	73.4 (29)	14.7 (6)	(16)
Polyunsaturated	10.1 (4)	17.9 (7)	73.3 (29)	(7)
Cholesterol level	224 mg	197 mg	191 mg	-

a Palm oil.
b High oleic safflower oil.
c High linoleic safflower oil.

Table 5-9

Fat compositions of diets used by Bonanome and Grundy[1395]

	% of total fats (% of total calories)			
Fatty Acid	Diet 1[a]	Diet 2[b]	Diet 3[c]	Typical Diet
Stearic	4.7 (20)	42.9 (21)	2.2 (4)	(14)
Other saturated	46.3	8.35	5.7	(14)
Oleic	38.8 (15.5)	39.4 (15.6)	79.7 (32)	(16)
Linoleic	9.9 (4)	8.9 (3.6)	12.4 (5)	(7)
Cholesterol level	202 mg	173 mg	181 mg	

a Palm oil.
b Completely hydrogenated soybean oil plus safflower oil.
c High oleic safflower oil.

Table 5-10

Fat composition of diets used by Ahrens et al.[879]

	% of total fats (% of total calories)		
Fatty Acid	Diet 1[a]	Diet 2[b]	Diet 3[c]
Saturated	48 (19.2)	34 (13.6)	10 (4)
Monounsaturated	42 (16.8)	46 (18.4)	36 (14.4)
Polyunsaturated	10 (4)	12 (4.8)	54 (21.6)
Cholesterol level	201 mg	189 mg	180 mg

[a] Palm oil.
[b] Lard
[c] Corn oil.

NOTE: Compositions are averages of several brands used.

Table 5-11

Fat compositions of diets used by Laine et al.[1914]

Fatty Acid	% of total fats (% of total calories) Diet 1[a]	Diet 2[b]
Saturated	46 (17)	21 (7.9)
Monounsaturated	44 (16.3)	36 (13.5)
Polyunsaturated	10 (3.7)	43 (16.2)
Cholesterol level	194 mg	162 mg

a Palm oil.
b Corn oil.

Table 5-12

Fat compositions of diets used by Anderson et al.[335]

	% of total fats (% of total calories)			
Fatty Acid	Diet 1[a]	Diet 2[b]	Diet 1[c]	Diet 2[c]
Saturated	59 (20.7)	14.8 (5.2)	59 (20.7)	14.8 (5.2)
Monounsaturated	25 (8.8)	15.6 (5.5)	25 (8.8)	15.6 (5.5)
Polyunsaturated	16 (5.6)	69.6 (24.4)	16 (5.6)	69.6 (24.4)
Cholesterol level	158 mg	122 mg	167 mg	130 mg

a Two parts palm oil and one part coconut oil.
b Safflower oil.
c Identical to Diets 1 and 2 except for added cholesterol.

Table 5-13

Fat composition of diets used by Grande et al.[718]

	% of total fats (% of total calories)		
Fatty Acid	Diet 1[a]	Diet 2[b]	Typical Diet
Saturated	18 (5.2)	30 (8.7)	(14)
Monounsaturated	59 (17)	24 (7)	(16)
Polyunsaturated	23 (6.7)	46 (13.3)	(7)
Diet Cholesterol	154 mg	159 mg	
Cholesterol level	225 mg	227 mg	

[a] 73% olive oil and 27% safflower oil.
[b] 61% safflower oil and 39% palm oil.

NOTE: A 3rd diet used by Grande et al. is not presented here because it contained an incomparable amount of dietary cholesterol.

The mean difference in cholesterol levels between these diets was 29 mg. The saturated fat in the palm oil diets averaged about 34% higher than that in the typical diet and the polyunsaturated content averaged about 44% lower. Similarly, the saturated fat in the polyunsaturated diet averaged about 60% lower than that in the typical diet and the polyunsaturated fat averaged about 218% higher.

Let us now consider the impact of removing 4.4 g of palm oil from the current diet and replacing it with safflower oil. If we consider saturated fats to have twice the effect on blood cholesterol as polyunsaturated fats (often accepted by the alliance but the exact formula will have little effect on the present analysis), we can compute positive (cholesterol raising) and negative (cholesterol lowering) values or indices for the above diets. For example, for the palm oil diet, 18.7% is 4.7% higher than the typical diet and 3.9% is 4.1% lower. These percentages translate to +4.7 + 2.05 or 6.75. Similarly, the polyunsaturated fatty diet yields values of -8.4 - 7.6 = -16. Since the blood cholesterol difference between these two indices was 29 mg, we can plot them as end points of a 29 mg cholesterol scale, as shown in Figure 5-5. Drawing a line through these points causes an intersect with the zero point on the index scale, representing the index for the typical diet.

Since 4.4 g is 1.5% of total calories of the typical diet (2600 calories), we need to compute an index for exchanging 1.5% of safflower oil for palm oil. This index turns out to be -1.1. Plotting this point in Figure 5-5 indicates a theoretical reduction in blood cholesterol level of slightly more than 1 mg. This change is not only trivial, it would remain trivial if it is in error by a few hundred percent.

Anderson et al. conducted a study similar to the above experiments except that the percentage of total calories as fat used was less than those used in the above three studies.[335] The saturated fat diet composition was 20.7-8.8-5.6 and the polyunsaturated diet was 5.2-5.5-24.4. These compositions yield indices of +7.4 and -17.5, respectively. If they are plotted along the extrapolated line in Figure 5-5, they will yield a predicted blood cholesterol difference of 31 mg. The actual difference reported by Anderson et al. was 36 mg.

Two experiments by Mattson and Grundy and Bonanome and Grundy compared palm oil diets with diets dominated by monounsaturates.[717,1395] The average compositions of their diets were 20-15.75-4 and 3.5-35.5-6, respectively. Computing indices from these diets (ignoring the monounsaturates again) yields values of +7.5 and -10. These points along the line in Figure 5-5 produce a predicted cholesterol difference of a little more than 21 mg. The actual mean difference observed in the two studies was 24 mg.

Finally, Grande et al. compared a diet whose fat was composed of 39% palm oil and 61% safflower oil with a diet dominated by monounsaturates.[718] However, dietary fat was only 29% of total calories, making this study seemingly quite incomparable to the above studies. However, the diet compositions (8.7-7-13.3 vs 5.2-17-6.7) produced indices if -8.4 and -8.7 which would predict a cholesterol difference of about 1 mg. Grande et al. reported an actual difference of 2 mg.

In Conclusion. The above analysis is not intended to suggest that the above formula developed for generating Figure 5-5 has any level of generality for predicting the differences in cholesterol levels for all fat diets. In fact, it is certain that it is far too simple to have generalized predictive power. However, given a set of highly similar conditions, it should provide reasonable, albeit limited, predictive power. It was employed in the present discussion only to provide an approximate numerical value for the expected impact on blood cholesterol of removing a few grams of tropical oils from the American diet. As indicated earlier, the total disruption of the domestic and international economies is an extremely high price to pay for an

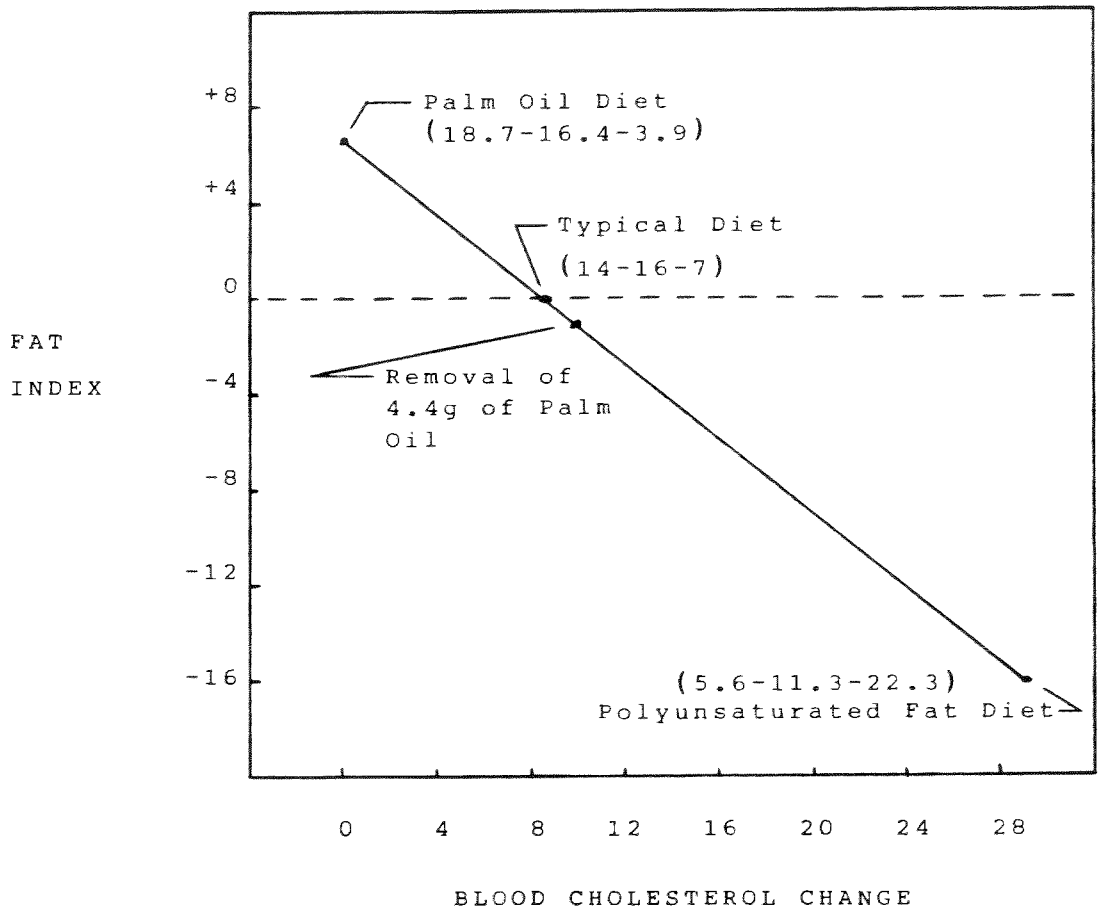

Figure 5-5. A fat index based on fatty acid composition of fats.

essentially unmeasurable "benefit." It is yet another example of major decisions being driven by major ignorance of the scientific data.

Unfortunately, money may not be the only principal effect of the removal of tropical oils from the diet. Likely replacement fats will be hydrogenated vegetable oils, increasing the already growing amount of trans isomers in the American diet.

While CSPI and others worry about 4.4 g of tropical oils in the American diet, Hill pointed out that Polynesians consume a heavily saturated fat diet composed of 56 g of coconut oil, as well as meat and fish, and yet demonstrate a negligible incidence of CHD.[1763] Scott Grundy's reply to Hill was that "...coconut oil, with it's high content of lauric acid, may not be as hypercholesterolemic as other fats that are rich in palmitic acid. Thus, it may not be surprising that Polynesians are less coronary prone than might appear at first glance."[1770] If AHA's Grundy is uncertain regarding the hypercholesterolemic ability of coconut oil, why are his associates (e.g., Castelli[1802] and Connor[1825]) recommending that it be eliminated from the American diet? And if it is hypercholesterolemic, why the low incidence of CHD among Polynesians?[a]

Finally, Scarbrough, deputy director of the FDA's Office of Nutrition and Food Sciences, was cited by Burros as stating that the "FDA's evaluation of consumption data has conclusively demonstrated that these oils are relatively minor contributors of saturated fats to the American diet."[2228]

Equations Predicting Blood Cholesterol Changes from Dietary Fat Changes

Both Keys et al. and Hegsted et al. developed equations for predicting the effects of dietary fats on blood cholesterol levels. Keys et al. apparently introduced the first equation in a one-page mid-1957 article, based on data they were currently extracting from on-going experiments.[315] Of 58 available comparisons (i.e., pairs of diets), they excluded 13 comparisons which included corn oil "because of evidence of the peculiarity of this oil," and four comparisons involving sardine oil "because the polyethenoids in fish oils are so different from those in the other food fats." The remaining 41 comparisons resulted in the multiple regression equation,

$$\Delta C = 2.73 (\Delta S) + .01 (\Delta M) - 1.31 (\Delta P) \qquad (5)$$

where ΔC is the change in blood cholesterol level, ΔS, ΔM and ΔP are the changes in the saturated, monounsaturated and polyunsaturated fatty acids in the diet, respectively, in terms of total dietary calories, and 2.73, .01 and -1.31 are the coefficients associated with those acids. The authors did not disclose the constant which is involved in a multiple regression equation.

Because the contribution of the ΔM term was considered negligible, the equation was recomputed without the ΔM term, resulting in

$$\Delta C = 2.74 (\Delta S) - 1.31 (\Delta P) \qquad (6)$$

Equation 6 was then applied to the comparisons involving corn oil and sardine oil. It gave "satisfactory predictions" for the sardine oil comparisons but overestimated the effects of corn oil by an average of 10 mg.

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[a] Grundy did not express uncertainty in 1983, i.e., it has been "shown that coconut oil raises the plasma cholesterol to about the same degree as butter fat."[1822]

Keys et al. concluded that saturated fatty acids have "about twice as much effect on the serum cholesterol level as do the poly-ethenoids which, moreover, act on the opposite direction."

In late 1957 Keys et al. presented a more lengthy article and it would appear that it was more or less redundant with the earlier article except for a detailed presentation of data. While the earlier paper reported 58 dietary comparisons, of which 41 were used to construct the regression equation, the later paper reported the availability of 64 comparisons. However, they again indicated that all but 41 comparisons were excluded in the process of generating the equation which was,[a]

$$\Delta C - 1.68 + 2.76 \Delta S + 0.05 \Delta M - 1.35 \Delta P \qquad (7)$$

The coefficient associated with ΔM and the constant were considered negligible contributors. A new equation was computed which was identical to Equation 6 above. (It is not known whether this was a more detailed presentation for the derivation of Equation 6 in the earlier article or a re-computation of similar data.)

Keys et al. then plotted the sardine oil and Japanese coal miner comparisons and reported that they fell almost exactly on the regression line. However, the equation overestimated blood cholesterol levels for the comparisons involving corn oil by an average of 11 mg and for the comparisons involving coconut oil by an average of 26 mg.

Keys et al. conducted an experiment in 1958 to verify their earlier findings that monounsaturated fatty acids had no direct effects on blood cholesterol levels.[405] This study of three comparisons supported the elimination of the ΔM term in Equation 8.

In 1959 Keys et al. computed another regression equation involving 10 comparisons (including corn oil) from their late 1957 study,[716] three comparisons from their 1958 study[405] and six new comparisons. It was said to predict the corn oil comparisons "satisfactorily" if 6 mg was added to the predicted change. Keys et al. stated that the coefficients in this equation were not significantly different from those of Equation 6 and so they pooled the 19 comparisons with the old 41 comparisons to generate

$$\Delta C = 2.73 \Delta S - 1.30 \Delta P \qquad (8)$$

When they used the corrected ΔC values for the corn oil comparisons, the equation became

$$\Delta C = 2.68 \Delta S - 1.23 \Delta P \qquad (9)$$

One comment by Keys et al. is of further interest. They described their equation as showing that it takes a "little more than 2 g of linoleic acid to counter the effect of 1 g of saturated fatty acid such as stearic or palmitic acid. Thus, the authors were not yet aware that stearic acid was not hypercholesterolemic.

In a series of four articles in the same journal issue in 1965 Keys et al. continued further development of their equation. In the first article[719] they cited their late 1957 equation, minus the second decimal place in the ΔS and ΔP terms, i.e.,

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[a] In addition to excluding 13 corn oil and four sardine oil comparisons, Keys et al. also excluded three coconut oil comparisons and three comparisons derived from Japanese coalminers.

$$\Delta C = 2.7 \ \Delta S - 1.3 \ \Delta P \qquad (10)$$

They computed another regression equation with 13 new comparisons and obtained C = 3.07S - 1.76P. They then replaced the new coefficients with the old coefficients (2.7 and -1.3) and reported that they produced ΔC values that were not significantly different from those obtained from the new coefficients. "Accordingly, there is no reason to change the previous coefficients and we prefer $\Delta C = 2.7 \ \Delta S - 1.3 \ \Delta P$."

In accounting for the discrepancies associated with corn oil comparisons, Keys et al. said, "For each 10% of calories supplied by corn oil, perhaps it is reasonable to estimate an average fall of about 2 to 3 mg cholesterol of serum independent of the effect of the fatty acid in the corn oil" (implying that corn oil contained some hypocholesterolemic substance besides polyunsaturated fatty acids). "Plant sterols are ubiquitous but they are ingested in only minute amounts except in special experiments and by the few persons who deliberately incorporate great amounts of some oils, notably corn oil, in the diet."

The second 1965 article by Keys et al. noted that their studies and that of Connor et al. in 1964[322] showed that the effects of dietary cholesterol were independent of the fat composition of the diet.[333] They therefore combined Equation 3 in the previous section with Equation 10 above, i.e.,

$$\Delta C = 1.5 \left(\sqrt{C_2} - \sqrt{C_1} \right) + 2.7 \ \Delta S - 1.3 \ \Delta P \qquad (11)$$

The third 1965 article by Keys et al. focused on the problems of assessing diets in individuals and groups of individuals and noted that "careful" group assessments can provide reliable results, whereas individual assessments are plagued with a number of problems.[988] This study is discussed in more detail in Chapter 4 as it relates strongly to prospective studies which correlate diets with cholesterol levels and CHD mortalities.

Equation 10 overestimated changes in blood cholesterol when diets contained cocoa butter, beef fat, coconut oil and butter fat. Their fourth 1965 article focused on the reasons for these discrepancies.[1309] They said, "There is good reason to believe that, in the diet, fatty acids with fewer than 12 carbons have much less effect on serum cholesterol than the longer chained saturated fatty acids." The smaller carbon chain acids are "absorbed in the intestine capillaries and the hepatic portal system rather than via the lymphatics. It is reasonable, therefore, to suggest exclusion of such short-chain fatty acids from the S term in estimations." Reference to Tables 5-4 and 5-5 reveals that coconut oil contains about 91% of total fat calories as saturated fatty acids. About 14.6% of these acids are composed of those containing less than 12 carbon atoms. A small amount of these short chain acids are also contained in butter fat. Thus, if such fatty acids are not hypercholesterolemic, their inclusion in Equation 6 would, of course, produced inflated ΔC values.

Keys et al. recomputed a regression equation using 63 previous comparisons and 11 new comparisons from experiments by Connor et al.[322] and Erickson et al.,[331] excluding stearic acid in the ΔS term. They obtained $\Delta C = 1.1 (2.05 \ \Delta S' - \Delta P)$ which they simplified to

$$\Delta C = 1.2 (2 \ \Delta S' - \Delta P) \qquad (12)$$

where $\Delta S'$ is composed only of lauric, myristic and palmitic acids. The fats most affected by this equation are cocoa butter, beef, pork and mutton fat, butter fat and milk, all of which have relatively large amounts of stearic acid (Tables 5-4 and 5-5) and all of which are the alliance's targeted harmful foods.

In 1972 Grande et al. observed that their Equation 12 predicted that a diet having twice the polyunsaturated fatty acids as saturated fatty acids would have a zero effect on blood cholesterol level.[718] They conducted an experiment which involved four diets having polyunsaturated to saturated fat ratios of 2.5/1, 1/1.1, 1/1.7 and 1/1.8 (where saturated fats involved only 12 - 16 carbon chains). The first diet contained only 4.5% of total calories as fat. The second diet contained 12.7% as fat and the third and fourth diets contained 29% as fat. Thus, not only did the first two diets have P/S ratios radically different from 2/1, they were also extremely low in total fats. Yet, the blood cholesterol levels of subjects in each of the four diets were insignificantly different, i.e., 225 mg with a range of 221 mg to 228 mg. Unexplainably, Grande et al. concluded that "It follows from our results that dietary fats having a proportion of polyunsaturated glycerides twice that of saturated glycerides of 12 to 16 carbon atoms can be isocalorically exchanged for each other, for monoene fatty acid glycerides and for carbohydrates...without causing significant changes of serum cholesterol concentration.

Grande et al.'s results also do not support the notion that low fat diets are preferable to high fat diets insofar as blood cholesterol levels are concerned.

Hegsted and his colleagues computed their own multiple regression equation in 1965 after completing a dietary experiment which yielded 36 comparisons.[408] That equation was

$$\Delta C = 2.32S + 0.32M - 1.46P + 6.51C + 0.83 \qquad (13)$$

where S, M and P have identical definitions as in the Keys et al. equation and C is a change of 100 mg dietary cholesterol per day, assuming a 2,600 calorie diet. As Keys et al. observed, neither the M term or the constant contributed anything and so the equation was recomputed without those terms, i.e.,

$$\Delta C = 2.16S - 1.65P + 6.77C \qquad (14)$$

The correlation associated with this equation was reported to be .94 which thus explained 88% of the blood cholesterol variation.

Hegsted et al. then computed additional regression equations which examined the individual contributions of the various saturated fatty acids. Although their data indicated that only myristic and palmitic acids were of importance, with myristic acid being about 3.7 times more important than palmitic acid, they concluded that the overall correlation was only "slightly superior" to that of Equation 14 and, therefore, provided no basis for departing from that simpler equation.

While Keys and his co-workers were convinced that the effects of dietary cholesterol were independent of the fatty acid composition, Hegsted seemed to both agree and disagree. For example, they noted that the coefficient of dietary cholesterol varied as much as threefold in equations which involved different sets of variables. They said that "This is due to the fact that the variables are not independent and that the coefficients are inter-related." But later they stated, "There appears to be little or no interaction between the dietary oils and dietary cholesterol" and blood cholesterol response to dietary cholesterol "was independent of the effects induced by dietary fat."

Twenty-one years later (1986), Hegsted reverted to the interdependency concept. "When Keys et al. developed their original equation $\Delta C = 2.74\ \Delta S - 1.31\ \Delta P$, they ignored the effects of changes in dietary cholesterol. It is agreed that the effects of dietary cholesterol are small compared to the effects of dietary fat but, whatever the effects of dietary cholesterol were in those studies, their effects are accounted for in

the coefficients of ΔS or ΔP, or both. Thus, when the effects of dietary cholesterol, independently determined, were simply added to the above multiple regression equation to yield $\Delta C = 1.3 (2 \Delta S - \Delta P) + 1.5 (\sqrt{C_2} - \sqrt{C_1})$, dietary cholesterol effects are apparently included in both parts of the equation." Hegsted's point was well-taken but it did not address the specific issue of independence. As will be discussed in the next section, the regression equation itself forces an interdependence between variables when such interdependence may not actually exist in the real world.

Several things are most peculiar about the Hegsted et al. data. As emphasized by the authors, as well as Keys et al.[1309], Horlick,[713] Malmros,[714] Erickson et al.,[331] Ahrens et al.,[375] and more recently, Reiser[877] and Bonanome and Grundy,[1395] stearic acid has essentially no effect on blood cholesterol. Similarly, Hegsted agreed with Keys et al.,[1309] Hashim et al.[415] and Grande et al.[718] that saturated acids with 10 carbons or less have no effect on blood cholesterol as well. Only 50% of the total saturated fats in the control diet was composed of lauric, myristic and palmitic acids, while the experimental diets contained as little as 31% and as much as 82%. The total saturated fats varied from as little as 3.6% to as much as 32.3% of total dietary calories but it was not true that the so-called hypercholesterolemic fatty acids increased proportionally with the increase in total saturated fatty acids. In fact, a rank order correlation between the two was nearly zero (rho = -.02). It would be strange, therefore, for Hegsted et al. to obtain a correlation of .94, given no effects of stearic acid and fatty acids of less than 10 carbons.

In computing an equation concerned with the individual effects of the various fatty acids, Hegsted et al. obtained coefficients of 0.66 and 0.49 for saturated fatty acids of 10 carbons or less and stearic acid, respectively. These positive coefficients combined (1.15) comprised 61% of the coefficient for polyunsaturated fatty acids. In other words, if the equation can be considered valid, the "insignificant" saturated fatty acids alone would nullify the effects of 61% of dietary polyunsaturated fatty acids, a not so insignificant effect. These findings explain the discrepancies discussed in the above paragraph but they also run counter to the accepted opinion that stearic acid and short carbon chain fatty acids have no effects on blood cholesterol level. This issue is of no little importance in view of the fact that red meats have continuously been targeted by the alliance as hypercholesterolemic, although 30% to 51% of their fat is composed of stearic acid (see Table 5-5). Also, 26% of the saturates in butter is composed of stearic and short chain acids.

Because a multiplicity of regression equations yielded radically different coefficients for dietary cholesterol, the true effects of dietary cholesterol on blood cholesterol cannot be determined from Hegsted et al.'s equations. The actual effects of dietary cholesterol in the Hegsted et al. experiment were discussed in the previous section entitled Dietary Cholesterol.

Finally, the results of Hegsted et al. confirm the findings of Keys et al. that fatty acid composition is the factor influencing blood cholesterol, not total fat. The lack of reduction in blood cholesterol with a substantial reduction of dietary fat and the hypocholesterolemic effect of polyunsaturated fatty acids led Hegsted et al. to conclude that "the most effective practical diets for lowering the serum cholesterol should be those relatively high in total fat with (a) a small proportion of myristic and palmitic acids, particularly myristic acid, (b) a high proportion of polyunsaturated acids, and (c) a small amount of dietary cholesterol."

Hegsted revised the dietary cholesterol component of his equation in 1986.[2721] It was discussed in the previous section, Dietary Cholesterol. Suffice it here to say that the term 6.77C became 0.097C, where C is the difference in cholesterol intake in terms of mg per 1,000 calories.

A Theoretical Flaw

The equations of Keys and Hegsted, used prolifically by many alliance members, clearly indicate that for every one unit of saturated fat ingested, two units of polyunsaturated fat are required to maintain a constant blood cholesterol level. This "principle" was recently applied by Swain et al.[2627] in their argument that oat bran does not reduce blood cholesterol levels (see a later section of this Chapter). They said, "Oat bran contains, in addition to fiber, more fat than refined wheat. However, since the fat had twice as much polyunsaturated as saturated fatty acids, no alteration in serum cholesterol or low-density lipoprotein cholesterol levels would be expected from the fat content of oat bran." In effect, they (and Keys and Hegsted) are saying that a food substance with a P/S ratio of 2.0 has no effect on blood cholesterol. Of course, we know that this cannot be true.

The typical American diet contains about 14% and 7% of total calories, respectively, as saturated and polyunsaturated fats (the exact amounts are not critical for the present discussion). Such a diet yields a P/S ratio of 0.5. As the P/S ratio increases (the AHA diet ratio is 1.0), blood cholesterol level decreases. This relationship has been amply demonstrated in numerous experiments and there is probably no one who would suggest that it is not a fact. How, then, can a food substance with a P/S ratio of 2.0 have no effect on blood cholesterol when that ratio obviously increases the overall ratio in a person's diet? The answer, of course, is that it must have an effect.

To use an extreme example, the typical American diet contains 14%, 16% and 7% of total calories as saturated, monounsaturted and polyunsaturated fats, respectively, (P/S = 0.5). Suppose we now feed a group of individuals a diet containing 7%, 16% and 14% of calories as saturated, monounsaturated and polyunsaturated fats, respectively (P/S = 2.0). Everyone would agree that blood cholesterol would decrease substantially, despite the fact that the polyunsaturated fat was only twice the quantity of the saturated fat. One might argue that we, in fact, altered the P/S ratio by a factor of four instead of two. And indeed we did. But let us now simply increase the total dietary fat by 6%, of which saturated and polyunsaturated fats constitute 2% and 4%, respectively. The new P/S ratio would be 0.69 instead of 0.50. Everyone should also agree that this diet would decrease blood cholesterol as well, though not dramatically so.

If we substract 6% of the fat from the typical diet, where the 6% is again composed of 2% saturated and 4% polyunsaturated, the new P/S ratio would be 0.25 instead of 0.50. Everyone should again agree that this diet would increase blood cholesterol.

One may wish to pursue the reasons why the equations appear to have some predictive capability at the group (but not at the individual) level, while recognizing the truth inherent in the above discussion. However, it suffices to know that blind application of the equations leads to conclusions that are quite opposite to reality.

Problems with Regression Equations

Mathematics is generally referred to as an exact science. The presentation of equations in the biological sciences, therefore, may imply to the naive reader that a physiological process operates in some precise, predictable fashion when, in fact, it does not. In determining the validity and meaningfulness of the multiple regression equations computed by Keys et al. and Hegsted et al., one needs to have some minimum understanding of such equations and their derivation. Some of the following discussion is derived from Guilford.[2722]

In Chapter 2 of Volume 1 the definition of correlation was given and the meaningfulness of correlations varying in strength was discussed. Figure 5-6 shows a hypothetical scatterplot of two variables, X and Y. Let us assume that Y is a measure of blood cholesterol and X is a measure of saturated fat intake. In general, as X increases (i.e., saturated fat is added to the base diet), Y also increases (blood cholesterol goes up). Similarly, as -X increases (i.e., saturated fat is subtracted from the base diet, -Y decreases.

A mathematical relationship between X and Y is denoted by the correlation coefficient and a regression line. The correlation coefficient, varying from 0.0 to 1.0, (positive or negative), is a measure of the strength of the relationship between X and Y. If we found that every time we increased saturated fat by a specific amount, say 10 g, we always found blood cholesterol to rise 1.5 times (in mg), all plotted points between X and Y would fall on a straight line and the correlation would be 1.0. But even though most of the points in Figure 5-6 do not fall along a straight line, a straight line can nevertheless be computed which indicates the average or general relationship between X and Y. Without getting into the details of computing this line it is sufficient to say that it is the statistical "best fit" to all the points in the scatterplot.

The best fit line is described by a "regression" equation which takes the form $Y = a + bX$, where "a" is a constant and "b" is a coefficient (weighting) of X. In actuality, the simplest mathematical description of a line in a scatterplot is $Y = bX$. If "b" were determined to be 2, then for each unit of increase in X, Y would increase two units because $Y = 2(1) = 2$. This two unit vertical movement for one unit horizontal movement describes the slope of the line. Thus, the constant "b" determines the slope.

When $X = 0$, Y also equals zero. This means that the equation $Y = bX$ can only describe lines with various slopes which always pass through the origin ($X = 0$, $Y = 0$) of the scatterplot. Therefore, the constant "a" is added to indicate where the line passes through the Y axis. In other words, it moves the same sloping line upwards and downwards. In computing regression equations with physiological functions, we rarely observe a line passing through the origin. That is simply because there is more than one variable affecting another variable. In the saturated fat, blood cholesterol example, we can, of course, remove all saturated fat from a person's diet and thus achieve a zero point. But blood cholesterol level would not remotely approach zero. Thus, we could never conduct an experiment which allowed us to compute a regression line that passes through the origin. On the other hand, the origin is often not of interest in any event. What we generally are most interested in is the slope, i.e., we want to know, for example, how much blood cholesterol (Y) will increase when we increase dietary saturated fat (X) by a certain amount. Therefore, investigators typically dismiss or ignore the constant "a."

An extremely important point to note is that the regression equation describes a line which generally indicates the slope and height of a distribution of measurements. As can be seen clearly in the scatterplot of Figure 5-6, most of the measurement points do not come close to falling on the line, which means that the equation does not hold true for individuals. Rather, it generally describes, for example, the expected response of a group of individuals when all their measurements are combined. And how well it does this depends on the strength of the association between X and Y, i.e., how close all the measurement points come to a straight line. The strength of an association is determined by the correlation coefficient, r. Squaring the correlation yields the variance which describes the percentage of one set of measurements (Y) that is explained by a second set of measurements (X). For example, in Figure 5-6 the correlation between X and Y is .30. The variance, therefore, is $.30^2$ or .09, which

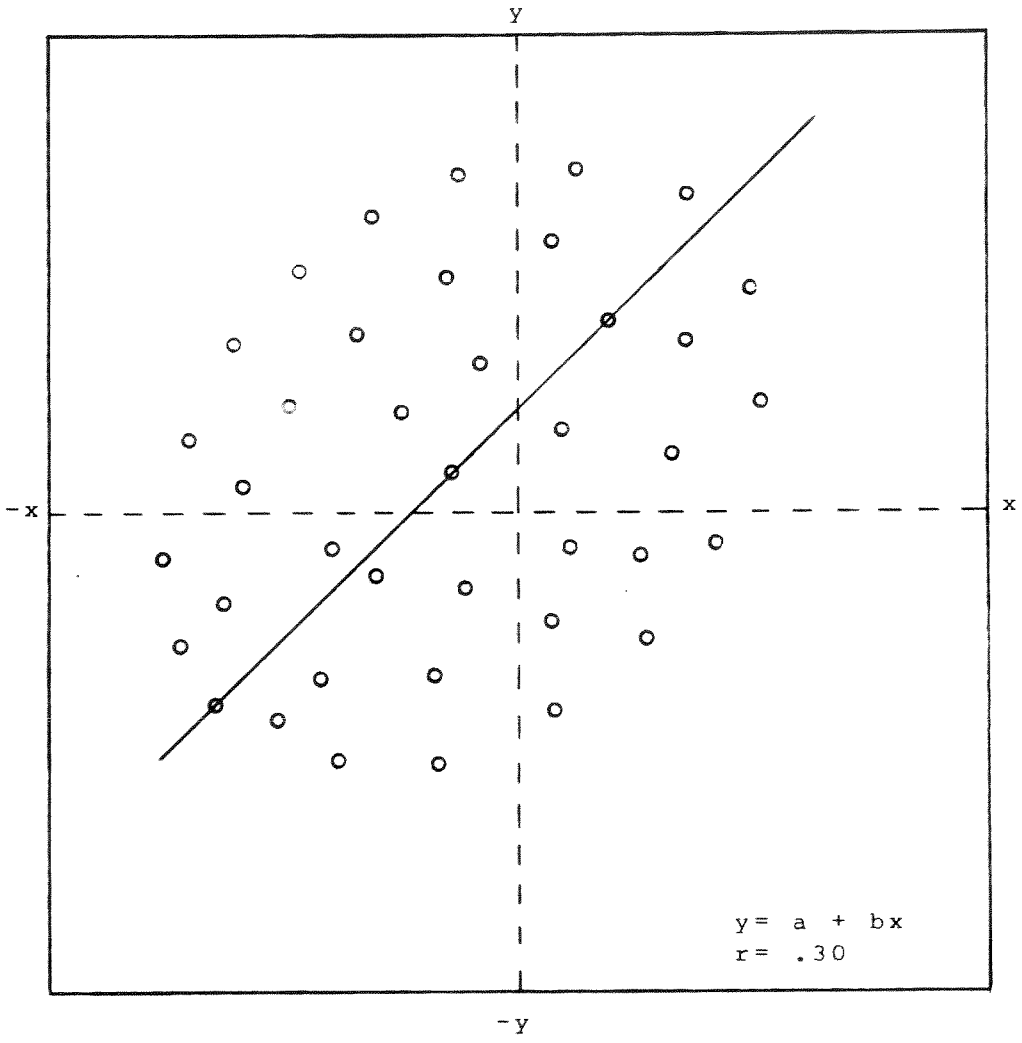

Figure 5-6. Hypothetical scatterplot of two variables, x and y, and the "best fit" regression line.

is 9%. This means that because there is so much variation from the straight line in Figure 5-6, Y accounts for only 9% of the variation in X and, similarly, X accounts for only 9% of the variation in Y. If all the points in the scatterplot fell on the straight line, the correlation would be 1.0 and the variance would be 1.00 or 100%, meaning that all Y measurements would determine exactly all (100% of) X measurements because there would be no variation about the straight line.

One should never lose sight of the fact that an equation is not a description of how individuals will respond. In fact, where correlations of .70 or less occur, most of the individuals in a group will respond differently from that predicted by the equation and the differences will be radical in many individuals. Many processes in physics and chemistry operate in precise and unvarying ways so that equations describe perfectly a process no matter how many times it is measured. Although the human body also operates in precise ways, there are so many unknown variables operating differently in each individual that we cannot obtain the same response from two or more individuals even when we treat them all in the same exact way, e.g., feed them all 50 g of saturated fat. An equation does not take account of this variability. An equation is borrowed from an exact science and applied to an inexact science. It does not in the least make the inexact science any more exact. It merely makes it appear more exact.

In effect, it is naive and totally incorrect to apply a regression equation to individuals because it will almost invariably predict a wrong response to a given treatment.

Thus far we have discussed equations which relate two variables. Now we wish to discuss equations which relate three or more variables. Although they involve different computations, they have similar meanings as the two variable situation. The equation is again a "best fit" line which generally describes a group of measurements having considerable variability about that line. The only difference is that the equation has additional terms. For example, a three variable multiple regression equation is $X_1 = a + b X_2 + c X_3$, where X_1 is the dependent variable (e.g., blood cholesterol level), X_2 and X_3 are independent variables (e.g., saturated fat and polyunsaturated fat, respectively) and "b" and "c" are the slopes of X_2 and Y_3. With regard to the latter, "b" is the slope of X_2 when the effects of X_3 are held constant and "c" is the slope of X_3 when the effects of X_2 are held constant. If "b" and "c" were computed to be 2 and -1 respectively, then we could say that one unit of polyunsaturated fat (X_3) would have one-half the affect on blood cholesterol than one unit of saturated fat. The negative sign of X_3 indicates that polyunsaturated fat decreases blood cholesterol. Therefore, the equation indicates that one unit of saturated fat increases blood cholesterol level twice as much as one unit of polyunsaturated fat decreases the level. According to these "b" and "c" coefficients or weightings, two units of polyunsaturated fat and one unit of saturated fat would result in no change in blood cholesterol level.

All of the problems associated with interpreting a two-variable regression equation and a correlation with respect to individuals are exactly the same as those associated with interpreting a multiple regression equation and a multiple correlation. There are, however, some additional concepts to consider with regard to multiple correlation. While there is only one correlation between two variables, there is a correlation between the dependent variable and each independent variable and a correlation between independent variables involved in a multiple correlation. The relationship between all of these correlations in a three variable situation is indicated by the equation,

$$R = \sqrt{\frac{r_{12}^2 + r_{13}^2 - 2r_{12}r_{13}r_{23}}{1 - r_{23}^2}} \qquad (15)$$

where R is the multiple correlation, r_{12} and r_{13} are the correlations between the dependent variable X, and independent variables X_2 and X_3, respectively, and r_{23} is the correlation between the two independent variables X_2 and X_3.

Examination of Equation 15 reveals some very fascinating facts. For example, if there is a zero correlation between the two independent variables (r_{23}), then the entire right term in the numerator and the entire denominator are eliminated and the multiple correlation is then the square root of the sum of the two squared correlations relating the independent variables with the dependent variable.

Table 5-14 presents 15 different sets of intercorrelations in order to demonstrate their effects on the multiple correlation. In examples 1, 2 and 3 the between independent variable correlation is zero. Thus, as the remaining correlations increase size, the multiple correlation (R_{123}) also increases in size. Interestingly, r_{12} and r_{13} need only be .71 each in order to achieve a multiple correlation of 1. Of course, this is almost impossible to achieve because (1) individual correlations of that magnitude are rare and (2) seldom will r_{23} be zero. In examples 4, 5 and 6 a small r_{23} reduces the multiple correlation somewhat and increases the size of r_{12} and r_{13} necessary to achieve a multiple correlation of 1.0. As r_{23} increases in size (examples 7, 8 and 9), the multiple correlation decreases rapidly.

The first fact to be derived from Equation 15 and Table 5-14 is that the strongest multiple correlation can be obtained when the correlations with the dependent variable are high and the between independent variable correlation is as low as possible.

Examples 10 and 11 illustrate the same decreasing multiple correlation trend as r_{23} increases when both r_{12} and r_{13} are relatively high. But Example 12 shows that the multiple correlation increases with a very high r_{23} when r_{12} and r_{13} are <u>different</u> and one is relatively small. Note that in Examples 11 and 13 r_{12} and r_{13} are the <u>same</u> and even though they are larger in Example 11 than Example 12, Example 12 yields a larger multiple correlation because r_{12} and r_{13} are different and one is relatively small. In this specific case, a high r_{23} is beneficial.

Examples 14 and 15 show that a negative R_{23} contributes substantially to a multiple correlation when r_{12} and r_{13} have positive signs. But when either r_{12} or r_{13} have negative signs (Examples 16 and 17), the negative r_{23} depresses the multiple correlation. Finally, if all intercorrelations are negative (Example 18), the multiple correlation is greatly augmented (compare Examples 14 and 18).

All of the above examples can be explained rather simply. When two independent variables are correlated with each other, this means that they are partially redundant or overlapping and, therefore, partially duplicate each other. Even though they each may correlate independently with the dependent variable with a coefficient of .5, for example, the fact that they partially duplicate each other means that when both are correlated simultaneously with the dependent variable, the total coefficient is less than .5 + .5. In effect, the coefficient is .5 + .5 <u>minus</u> the part contributed by the duplication.

When the correlations between the dependent and independent variables are different and one is low, a high correlation between the two independent variables has the opposite effect. This is because the low correlation contributes little directly to the multiple correlation but, through its high correlation with the second independent variable, indirectly contributes to the multiple correlation.

With the foregoing knowledge in hand, let us now re-examine the Keys et al. and Hegsted et al. regression equations. First, there is enormous variability among

Table 5-14

Effects on the multiple correlation of different sets of intercorrelations

Example	r_{12}	r_{13}	r_{23}	R_{123}	R^2_{123}
1	.1	.1	0	.14	.02
2	.3	.3	0	.42	.18
3	.71	.71	0	1.0	1.0
4	.1	.1	.1	.13	.018
5	.3	.3	.1	.40	.163
6	.73	.73	.1	1.0	1.0
7	.1	.1	.5	.11	.013
8	.3	.3	.5	.35	.12
9	.87	.87	.5	1.0	1.0
10	.5	.5	.5	.57	.333
11	.5	.5	.9	.51	.26
12	.5	.3	.9	.61	.37
13	.3	.3	.9	.31	.095
14	.5	.3	.5	.50	.25
15	.5	.3	-.5	.81	.65
16	.5	-.3	-.5	.50	.25
17	-.5	+.3	-.5	.50	.25
18	-.5	-.3	-.5	.81	.65

individuals in their response to the various fatty acids and cholesterol and there is considerable variation within the same individual over time. Keys et al. and Hegsted et al. constructed their equations from specific sets of data. Keys et al. discarded considerable data because such data simply added too much variability to their correlational matrix. One can always generate an equation with a high multiple correlation by selection of the "right" data. As noted in Volume 1, Keys always seemed to produce near perfect relationships in experiments and prospective studies.

The Hegsted et al. Equation was also based on highly selected data, namely, the data from only their single experiment. Granting the fact that it was a large experiment, it was still only a single experiment. Most experiments undoubtedly vary somewhat in terms of biases that differentially affect results. For example, some studies used completely liquid formula diets. Others used conventional foods. It is a known fact that these diets affect blood cholesterol levels differently. Now while Hegsted et al. used whole foods, almost all of the fat involved in their diets was comprised of vegetable oils. Even though most of these oils were embedded in conventional type foods, they were still oils and it cannot be assumed that they caused blood cholesterol responses identical to that of animal fats, even if the fatty acid compositions were the same. After all, no one can explain to this day why liquid formula and whole foods diets have differential effects.

Second, the construction of a regression equation from one set of data must be validated against other sets of data. Regression equations in the biological sciences are notorious for failing to demonstrate generality when applied to other data. This is due to the enormous variation between and within individuals, noted earlier. When an equation is computed from a sample of people and diets, it is based on a sample of the total variability existing in the world. Thus, when it is applied to another sample, that sample is likely to contain variability that is not in the first sample. If we now construct a new regression equation to account for the variability in both samples, the regression equation simultaneously has greater generality than the first equation but even less application to the individual or even subgroups of individuals. Of course, this process can be repeated to gain more and more generality and less and less specificity. In actual fact, there really is no optimum point in this process because the total variability is so great it thoroughly overwhelms a regression equation. After all, a regression equation is a highly simplified linear function which accounts for only a few of perhaps dozens of variables that are operative simultaneously.

Although Keys et al. re-computed new regression equations with new sets of data and although both Keys et al. and Hegsted et al. re-computed new formulas for the blood cholesterol-dietary cholesterol relationships with new sets of data, this writer has not encountered systematic validation studies of their equations. But, as noted above, it really does not matter because neither initial nor 10th generation equations will have any utility at the individual level or much utility at the group level. Although both Keys et al. and Hegsted et al. strongly emphasized that their equations could not be used at the individual level, and although their equations have inadequate generality to be applied routinely, these important facts seem to have been ignored by some alliance members who use the equations as though they were precision instruments. For example, Stamler and Shekelle said that the Keys et al. and Hegsted et al. "equations permit relatively precise predictions of the effects of dietary lipid change on serum cholesterol in groups of people."[1565]

A third important consideration is that just as a multiple regression equation artificially transforms or squeezes a distribution of highly variable responses into a linear response relationship, each time variables are subtracted or added or a different set of subjects, etc. are used, the coefficients for the various variables change rather dramatically. This fact was clearly noted by Hegsted et al. and again illustrates that the equation cannot determine the true effects of, for example, saturated fats, on blood cholesterol. To demonstrate this process, Hegsted obtained coefficients of 2.32,

0.32, -1.46 and 6.51 for saturated fat, monounsaturated fat, polyunsaturated fat and dietary cholesterol, respectively. Note that the coefficient for saturated fat was 1.6 times larger than that of polyunsaturated fat and 28 times smaller than that of cholesterol. But when each saturated fatty acid was included as a separate variable, the summation of the coefficients for all saturated fatty acids was 9.94 which was 5.3 times larger than that of polyunsaturated fat and 1.7 times larger than that of cholesterol. Thus, not only did the coefficients change drastically, we have a case where the sum of the (saturated fatty acid) parts is far greater (4.3 times) than the whole (all saturated fatty acids combined). But this apparent paradox is due to the artificiality of the mathematical process, not to a physiological process because, in either case, subjects ingested all of the saturated fatty acids.

The fact that Keys et al. and Hegsted et al. obtained sufficiently different coefficients for saturated (2.7 vs 2.16) and polyunsaturated (1.2 vs 1.65) fatty acids is another example of the influence of different sets of data. For example, for a 5% increase and 4% decrease in total calories as saturated fat and polyunsaturated fat, respectively, the Keys et al. equation predicts an 8.3 mg increase in blood cholesterol, while the Hegsted et al. equation yields 4.2 mg, a twofold difference. If one argues that the absolute difference is small and unimportant, then it would follow that this dietary change (which is really quite significant) also produces a small and unimportant increase in blood cholesterol.

In sum, the computation of multiple regression equations might have been a useful theoretical exercise had they not been taken seriously by researchers such as Stamler and Shekelle.

CHOLESTEROL PLUS FAT

Experiments

In 1960 Horlick compared two diets with comparable amounts of protein.[1855] One diet had 45% fat, 41% carbohydrate and 512 mg cholesterol and the second had 4% fat, 80% carbohydrate and 28 mg cholesterol. These diets produced a blood cholesterol difference of 40 mg, about 20 mg less than was observed in his earlier (1957) study[713] which compared similar diets.

The Connor Cholesterol/Saturated Fat Index

Zilversmit proposed a "cholesterol index" (CI) in 1979 to describe the blood cholesterol raising or reducing effects of a given food. The equation is as follows:[2424]

$$CI = 1.01 (S - 0.5P) + 0.05C \qquad (1)$$

where S = saturated fat in grams, P = polyunsaturated fat in grams and C = cholesterol in milligrams. This equation essentially weights saturated fat as a unit, polyunsaturated fat as one-half unit and cholesterol as one-twentieth of a unit.

Zilversmit indicated that a "prudent diet" contains an average of 2,400 calories which includes 26.7 g (10%) each of saturated and polyunsaturated fat and 300 mg cholesterol. Inserting these values in Equation (1) yields an index of 28.5. Multiplying this index by 3.51 gives an index of 100. Thus, indices for other foods would include the 3.51 factor and they would range below and above the prudent index of 100.

$$CI = [1.01 (S-0.5P) + 0.05C] \, 3.5 \qquad (2)$$

Zilversmit indicated that Equation (1) "is essentially the same as that proposed by Whyte and Havenstein"[318] in 1976. However, several readings of the 1976 article failed to reveal such an equation. Whyte and Havenstein presented no equations whatsoever but did indicate that they used equations by Keys et al.[1309] and Mattson et al.[368] to compute the cholesterol lowering and raising effects of various foods.

In 1986 Connor et al. "developed the cholesterol/saturated fat index (CSI),"[2425]

$$CSI = (1.01S) + (0.05C) \qquad (3)$$

which is identical to Zilversmit's Equation (1) without the polyunsaturated fat factor. The elimination of the polyunsaturated fat factor was based on the AHA's recommendation to limit consumption of such fat to less than 10% of calories. Since polyunsaturated fats currently constitute about 7% of total calories, Connor et al. treated that factor as a constant. It is strange, however, that Connor et al. retained the .01 decimal place for the saturated fat factor since it has a completely trivial effect on the CSI and the weights for the saturated fat and cholesterol factors were only estimates at the outset.

Connor et al. stated that "The CSI per 1000 Kcal...correlated well (r= .78) with mortality from ischaemic heart disease in men aged 55 to 64 from 40 countries." Of course this is true simply because the index parallels the saturated fat disappearance data of between population studies which, in turn, were already shown to parallel the CHD rates. Moreover, the NHLBI/AHA alliance has long incriminated saturated fat and dietary cholesterol as being atherogenic. Thus, Connor et al.'s correlational exercise was superfluous to say the least.

In illustrating the utility of their index, Connor et al. stated that "It is particularly instructive to compare the CSI of fish with that of 20% fat beef. A 100 g portion of cooked fish contains 66 mg cholesterol and 0.2 g of saturated fat. This contrasts with 96 mg cholesterol and 8.1 g saturated fat in 100 g of 20% fat cooked beef. The CSI for 100 g fish is 4, whereas that of an equal portion of beef is 13." However, this "instruction" is quite misleading for two reasons. First, according to the USDA Nutritive Value of Foods,[946] fat-trimmed whole beef contains only 3.6 g saturated fat and 89 mg cholesterol per 100 g, substantially less than the above example, yielding an index of 8.1. Second, the reason why retail ground beef is heavy in fat is because the fat is added to the beef after grinding. Much of this fat is lost in the cooking process.

To have practical meaning the CSI index should have a "base" value representing the prudent diet, as shown by Zilversmit, in order to compare other calculated values. For example, using Zilversmit's values of 2400 Kcal, 26.7 g saturated fat and 300 mg cholesterol, the CSI yields an index of 41.7. This index is more than five times larger than the 8.1 value computed for 100 g, meaning that an individual could consume per day the equivalent of five times the saturated fat and cholesterol found in 100 g whole beef.

Not only is the concept of a saturated fat/cholesterol index rather meaningless, in view of the fact that this document has presented ample evidence which argues against the importance of saturated fat and cholesterol in atherogenesis, the index itself is not at all an accurate representation of the relative importance of saturated fat and cholesterol in raising blood cholesterol. Equation (3) gives the impression that cholesterol is much less important (one-twentieth) than saturated fat to the Connor et al. index. But this impression derives from not recognizing that saturated fats are measured in grams, while cholesterol is measured in milligrams. For example, the typical diet of 2600 calories contains 40 g (14% of total calories) saturated fat and 500 mg cholesterol. The contributions of these nutrients to the CSI index are 40 and

25, respectively, indicating that saturated fat has only 1.6 times the effect of cholesterol in raising blood cholesterol. Since the experimental data in Chapter 5 show that 500 mg cholesterol contributes about 9.5 mg to blood cholesterol and that vegans have cholesterol levels about 55 mg lower than omnivores, there is a very large discrepancy between 9.5 mg and 55 mg. Even allotting 10 mg of this 55 mg value to the effects of increased polyunsaturates (which is probably an overestimate because the total fat in vegans' diets is generally much lower than in omnivores), the ratio of saturated fat to cholesterol (35.5 to 9.5) is far greater (3.7) than that shown in the Connor et al. index.

Equations often take on the image of mathematical exactness, as noted earlier, to those unfamiliar with the data that were used to generate the equations. If the Connor et al. index were generally accepted as a routine means of measuring the atherogenic characteristics of food, it would be an example of the "triple blind leading the blind," i.e., an incorrect equation applied to foods which are weakly related to blood cholesterol levels (across practical ranges) which, in turn, are weakly related to CHD. It is hardly an example of sophisticated science.

ALCOHOL

Ernst et al.[1908] and others[1906] reported a positive association between alcohol consumption and HDL level in the LRC prevalence study in 1980. Fehily et al. found a similar relationship in 117 men aged 44 to 60 years in 1982.[1900] Lin[1881] and Miller[1909] observed in 1989 identical relationships in the Second National Health Nutrition exam and a large survey of 4,860 men in England, respectively. These studies were entirely consistent with a large body of evidence presented in Volume 1.

In addition to the large number of studies showing benefits of alcohol consumption to CHD presented in Volume 1, two studies were reported in 1990 and one in 1991. Handa et al. found that moderate drinkers (101 to 300 ml alcohol per week) had less severe stenosis than nondrinkers among 212 men who underwent angiography.[2641] They also indicated that heavy drinkers exhibited less stenosis but nonsignificantly so.

In a retrospective controlled study of 2,301 New Zealanders clinically free of cardiovascular diseases, Jackson reported that drinkers had a 30 to 36% reduction in fatal or nonfatal cardiac events. Not only were there benefits for both men and women, the effects were "greatest in individuals who consumed one to 5 drinks a day, but were present among subjects who drank as many as 8 drinks per day."[2738] Interestingly, Jackson attributed the benefits of alcohol not to augmented HDL but rather a "likely antithromboembolic" effect.

Finally, a large prospective follow-up study of 51,529 men also found a negative relation between alcohol intake and CHD (Rimm et al.[3411]).

Despite the massive evidence that has now accumulated, the alliance steadfastly recommends against the consumption of alcohol for therapy against heart disease, e.g., Grundy, Rifkind and Cleeman.[1803] Others completely distort scientific findings. For example, an article by Davidson was most misleading and inconsistent. He stated quite erroneously that "considerable controversy persists...regarding the possible advantages of light alcohol consumption, usually defined as less than 1 oz (two drinks) per day."[1788] On the contrary, the research literature could hardly be more emphatic in showing protective effects of light alcohol consumption (Volume 1). Davidson continued, "in heavy drinkers--such as drinking six or more drinks per day, or being registered with temperance boards [poor association]--coronary artery disease mortality is increased." As shown in Volume 1, the evidence regarding heavy consumption is ambiguous but is more suggestive of protection against CHD than anything else. Finally, Davidson said that "at mild to moderate levels of intake...evidence suggests no

elevation of the CHD risk." Note that Davidson stated that such intakes suggest "no elevation of CHD risk," rather than saying that there is a decrease in risk which is the common finding. Thus, Davidson would have his readers believe that the effects of alcohol consumption vary from no benefits to increased risk of CHD, almost exactly opposite to what has been observed repeatedly.

OAT BRAN/MEAL STUDIES

Introduction

In 1963 DeGroot and his colleagues[1833] reported that the consumption of rolled oats decreased blood cholesterol levels. A number of studies have since reported similar results. These findings led food manufacturers to increase the number of food products containing oats. For example, five new oat products were introduced in 1987, 44 were introduced in 1988 and 218 entered the market in 1989.[2854,2855]

Connor[2844] and Weisfeldt[2856] recently suggested that cereal manufacturers have been overly enthusiastic and guilty of giving the public misinformation about oat products, respectively. In view of the fact that the alliance has been enthusiastically propagandizing the public and industry with misinformation and contradictions for decades, it is rather hypocritical to accuse industry of capitalizing on the oat bran/meal studies. Even now, as Sacks[2854] maintains that "the data showing that oat bran lowers cholesterol is quite soft," his fellow alliance member, Castelli,[2849] holds that oat products do indeed independently lower blood cholesterol "3-5%."

Let us briefly review the relevant studies. We will see that most leave much to be desired in terms of scientific control, particularly that of Sacks and his co-workers[2627] who erroneously claimed that their experimental design "was intended to overcome the limitations of other designs previously used."

A Summary of Research Studies[a]

DeGroot et al.[1833] were apparently the first investigators to evaluate the effects of oats in a 1963 experiment. They "asked" 21 males, ages 30-50 years, to consume daily 300 g of a bread containing 140 g of rolled oats in place of regular bread. Not only was 300 g more than half (66%) of a one pound loaf of bread, much more than is typically consumed, the investigators had no way of knowing how much of the experimental bread the subjects actually ate. DeGroot et al. indicated that blood cholesterol decreased from 251 mg to 223 mg after three weeks, for a percentage reduction of 11.2%. However, their data showed that cholesterol had been decreasing during a three week baseline period. Moreover, cholesterol was still decreasing when the oat consumption period was terminated. Thus, the reduction reported was not based on stable results.

DeGroot et al. also noted that rolled oats have a higher polyunsaturated fat content than other cereals. Their studies with rats indicated that about half of the effects of oats was due to those fats. They also observed that fecal fat and bile acid excretion increased with oatmeal consumption but not cholesterol excretion.

Eighteen years later (1981) Kirby et al.[1834] conducted a controlled experiment employing only 8 subjects. All but one subject had vascular disease and all had blood

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[a] The reader may also wish to consult the recent review by Anderson and Gustafson.[2358]

cholesterol levels above 260 mg. The subjects consumed two identical diets differing only in that one contained 94 g of oat bran. The experimenters presumably accounted for the additional polyunsaturated fat content of oats. After 10 days on the oat bran diet the mean cholesterol dropped from 269 mg to 234 mg, for a percentage reduction of 13%. On the one hand, this percentage may have been lower had the diet period continued; Kirby et al. admitted that 10 days was not sufficient to determine maximal effects. On the other hand, the mean baseline cholesterol measurement before the oat bran diet was 269 mg, while it was only 256 mg before the control period. This discrepancy of 13 mg suggests that the actual reduction during the test period was somewhat exaggerated due to substantial variations in "normal" cholesterol levels.

Like DeGroot et al., Kirby and his associates also found that there was increased fecal excretion of fat and bile acids but not cholesterol during oat diets.

Judd and Truswell[1831] conducted a controlled experiment in late 1981 and they also accounted for the amount and type of fats in rolled oats. They fed 10 young men and women 125 g rolled oats and reported that blood cholesterol decreased from 202 mg to 187 mg (7.4% reduction). Fecal fat and bile acid, but not cholesterol, excretion also increased during the experimental diet.

In 1984 Anderson and his colleagues published three reports of oat feeding studies. One study (Storch et al.[2841]) involved the addition of muffins containing 53 g of oat bran to subjects consuming their regular diets. Blood cholesterol decreased 12.4%, from 185 mg to 164 mg. The remaining two studies were laboratory controlled and involved hypercholesterolemic men (Anderson et al.[2099,1836]). In both investigations, 100 g of oat bran reduced blood cholesterol 19% and 23%. Fecal fat and bile acid secretions were gain found to increase with oat bran feeding.

A 1986 study by Van Horn et al.[1829] was poorly conceived, insofar as investigating oat bran is concerned. A large number of subjects were asked to follow the AHA diet at home for several weeks. At the end of 6 weeks, they were instructed to make and eat oat bran or oatmeal foods according to recipes provided by the investigators. These recipes called for 60 g of oat bran or oatmeal per day. The oat foods were to replace equal amounts of carbohydrates in the AHA diet. Blood cholesterol levels dropped only 5.2% during the AHA diet only (208.4 mg to 197.6 mg). They decreased another 2.4%, relative to a control group, during the AHA plus oat diet. Much discussion was presented by Van Horn et al. concerning possible reasons for these rather undramatic results. Unquestionably the most important and perhaps the only relevant reason was the likelihood that subjects did not faithfully follow the AHA diet and even less so for the oat supplemental AHA diet, particularly as subjects were required to follow recipes. The authors acknowledged this possibility but focused predominantly on other factors.

Another free-living dietary study was performed by Gold and Davidson.[1898] They distributed oat bran muffins to a group of students and asked them to consume the muffins in place of other carbohydrates. If consumed, the daily dose of oat bran was a mere 17 g. Mean blood cholesterol decreased 5.3% (179 mg to 169.5 mg).

A final study was published in 1990 by Sacks and his colleagues (Swain et al.[2973]) and it purported to prove that oat bran has no independent ability to reduce blood cholesterol. Swain et al. conducted another free-living experiment in which subjects were asked to consume 100 g of oat bran or wheat per day. Blood cholesterol decreased from 186 mg to 172 mg in both the oat bran and wheat conditions. The authors concluded that "oat bran has little cholesterol-lowering effect and that high-fiber dietary grain supplements reduce serum cholesterol levels about equally, probably because they replace dietary fats." (Note the word "probably," which reflects the fact that Swain et al. really did not know what their subjects had eaten during the study.)

David Jenkins[2849] referred to the Swain et al. investigation as "a nicely done little study." In his editorial accompanying the Swain et al. article, Connor[2844] called it "a well-thought-out study" and "a superbly conducted study."[a] The University of California, Berkeley, Wellness Letter[2846] also called it "a well-designed study." And Blankenhorn[2842] said, "This is clear evidence. People who substitute oat bran for bacon and eggs are going to come out ahead." As will be seen, these remarks demonstrate once again that alliance members and their supporters do not have stringent criteria for conducting scientifically sound research. The flaws were clearly noted by others. For example, Ernest Schaeffer[2849] said that Swain et al. "should have given the subjects all of their food, not allowed them to prepare the bulk of it for themselves. That is the correct way to conduct a controlled study..." In his review in the British Medical Journal, Wheaton said that "The dietary assessments [the primary data in the study] were crude and inconsistent." And Kritchevsky[2853] perhaps summed it up best of all, i.e., he called it a "bad study."

Before discussing the problems of the Swain et al. study in more detail, it is useful to compare free-living studies of oat feedings with those of egg feedings. In Volume 1 a number of free-living studies investigating the effects of dietary cholesterol were reviewed. Subjects ate their usual diets but were instructed at a certain point to add one, two or three eggs to their diets. These studies were biased toward showing effects because an egg contains a large amount of cholesterol (213 mg) and proportionally more saturated fat (20% of calories) than exists in the usual diet (about 14%) and yet it only has about 85 calories. A little more than one slice of bread fulfills the calories of a single egg. The fact that egg feeding in those studies resulted in statistically insignificant increases in blood cholesterol levels (about 1.4 mg per 100 mg ingested) not unlike laboratory studies (about 1.8 mg), indicated that the free-living studies were relatively "clean" experimentally.

Oats are not nearly as palatable a food as eggs and they are not nearly as digestible, yielding a measure of discomfort when consumed in quantity. Subjects in some of the above studies admitted that they did not consume all of the oat foods required. It is very possible that they did not consume as much as they said they did. This possibility is supported by the fact that the five free-living studies yielded much smaller cholesterol reductions, on the average, than did the four laboratory experiments (Table 5-15).

Commenting on his free-living study, Sacks[2850] stated that "A number of...major studies did not have a low-fiber-control group, so you could not distinguish the effect of oat bran from the substitution of fat in the diet." But on the contrary the previous <u>controlled</u> studies by Kirby et al.,[1834] Judd and Truswell[1831] and Anderson et al.[2099] maintained constant saturated and polyunsaturated fats in the diet of control and oat bran conditions. Moreover, because the Swain et al. study was a free-living one, the authors did not have any control of what their subjects ate, so they could not conclude with <u>any</u> degree of scientific assurance that oat bran's effects were due to that product's replacement of saturated fats in the diet, rather than to the soluble fiber itself.

It is incredible that Sacks and his colleagues placed so much credibility in the dietary data collected. The differences observed between high fiber and low fiber

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[a] Connor and Connor[1825] established their bias the year before the Swain et al. study was published, i.e., "In man, all the fiber-feeding studies in the literature provide little evidence that dietary fiber (as contained in high fiber foods) is hypocholesterolemic."

Table 5-15

Controlled Experiments	Date	Oat Base	Baseline Chol. (mg)	Cholesterol Reduction (%)	HDL Change (%)
Kirby[1832,1834]	1981	94	269	-13	None
Judd[1831]	1981	125	202	-7.4	None
Anderson[2099]	1984	98	280	-19	None
Anderson[1836,a]	1984	100	Hyper	-23	-20
Free-Living Experiments				15.6	
DeGroot[1833]	1963	140	251	-11.2	ND
Storch[2841]	1984	53	185	-12.4	ND
VanHorn[1829]	1986	37	198	-2.4	None
Gold[1898]	1986	17	179	-5.3	None
Swain[2973]	1990	100	186	-8.1	None

[a] Cited by Anderson and Gustafson.[2358]

conditions in terms of saturated and polyunsaturated fat were unquestionably smaller than the errors that are inherent in the subject-generated dietary data. This is like comparing two correlations which vary in terms of a third decimal place when we know that they are in error at the first decimal place.

Wheaton[2843] emphasized a further important point. "...when the authors calculated the expected change in serum cholesterol concentration [according to the Keys equation] they compared values for fat intake derived from two different types of dietary record--a food frequency questionnaire [before the experimental diets] and a four day record [during the experimental diets]--so like was not compared with like."

A final consideration of the subject-generated, dietary data relates to estimated total calories consumed. The subjects reported that they consumed 2,065 calories at baseline and 2,429 and 2,315 calories during the high and low fiber diets, respectively. Thus, the experimental diets presumably contained 364 and 250 more calories per day, respectively, than during baseline diets. When one realizes that over a six week period these excess calories amounted to 15,288 and 10,500 calories, respectively, one must conclude that the dietary data contain gross inaccuracies because subjects in the high and low fiber diets gained only 2.2 and 1.5 ounces.

Other Research[a]

Three additional studies were recently reported briefly in the Medical Tribune and Internal Medicine News. Horowitz[2851] cited Maren Hegsted as conducting a laboratory controlled experiment which showed a 7% reduction in blood cholesterol with either oat bran or rice bran. The baseline cholesterol levels of the subjects ranged from 199 to 252 mg. Horowitz also cited Wendy Demark-Wahnefried as conducting a free-living study with subjects having cholesterol levels of 250-280 mg. Although she found no effects of a 50 g supplement of oat bran, she nevertheless concluded that "there is a component in oat bran that acts to lower cholesterol." It is perhaps worthy to note that the Hegsted and Demark-Wahnefried studies were funded by rice growers and the Quaker Oats Company, respectively.

The third study, performed by Linda Van Horn,[2852] was another free-living experiment. Some 53 g of instant oats per day was reported to have reduced blood cholesterol in middle-aged subjects 12.3 mg.[b]

The Physiological Mechanisms of Oats

Although it would appear that oats do indeed have hypocholesterolemic effects, the studies conducted to date do not permit an accurate estimate of their cholesterol-lowering per unit of ingestion. There is suggestion, however, that the reduction may be only a few percentage points for dosages considered practical for ingestion or likely to be ingested, e.g., one ounce (29 mg) per day. Even this amount is probably optimistic because few people will likely consume an oat containing product virtually every day.

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[a] Anderson et al.[1394] recently reported a significant reduction in blood cholesterol level with the ingestion of psyllium mucilloid, a prime ingredient in anti-constipation fiber agents. Bell et al.[2356] also reported a small reduction with psyllium.

[b] Other studies evaluating oat bran were confounded by other factors. For example, Chen and Andersen[2100] combined oat bran with beans. The subsequent reduction in blood cholesterol could not, of course, necessarily be attributed to oat bran.

The above discussion notwithstanding, it is of interest to know the mechanisms by which oat products lower blood cholesterol. As described by Anderson and Chen,[1835] oats contain fiber, that part of plant foods which is not digestible in the small intestine. The fiber in oats is water-soluble, whereas it is water-insoluble in other plants such as wheat. Some water-soluble fibers typically swell (gel) in the presence of water and this process may result in a slowing of their transit time through the small intestine.

Swain et al. indicated that "It has...been proposed that water-soluble fibers, but not insoluble fibers, have hypolipidemic properties, in part, because they can bind bile acids and promote the excretion of sterols."[2627] By itself, this statement reflects little understanding of the state of knowledge because, as noted in the previous section, a number of studies, including the early DeGroot et al. experiment, have shown that oat consumption does not increase excretion of cholesterol, although it does promote excretion of fat and/or bile acids. Moreover, the fact that beans lower blood cholesterol but do not promote excretion of bile acids led Anderson et al.[2099] to suggest that the loss of bile acids per se may not be relevant.

Since water-soluble fiber slows down the absorption process, it has also been suggested that this process may also reduce cholesterol absorption.[1835,2845] But even so, dozens of studies (Volume 1) have amply demonstrated that dietary cholesterol has little influence on blood cholesterol.

Soluble fiber is abundantly fermented by the microflora in the colon, resulting in the formation of numerous short-chain fatty acids.[1834,2845] However, it is not known what role these absorbable fatty acids play, if any, in the reduction of blood cholesterol.

In sum, given that water-soluble fiber, such as that in oats, does indeed reduce blood cholesterol, the mechanisms by which it accomplishes this process are still unknown. Many people recommend high fiber diets[2847] but side effects of such diets should be recognized. For example, cases of intestinal obstruction have been observed from persons consuming excessive amounts of oat bran muffins.[2845] Also, the more soluble fiber is consumed, the more water is needed to prevent severe constipation and the fewer important minerals and trace elements are absorbed.[2848]

WEIGHT REDUCTION, FAT AND BLOOD CHOLESTEROL

Since its first dietary recommendations in 1961[517] the AHA has repeatedly urged Americans to reduce their obesity and fat consumption on the grounds that both of these factors individually and in combination reduce blood cholesterol levels. The AHA's rationale since 1961 is as follows:

> "...reduction of the total calorie intake, by decreasing the amount of ordinary fat in the diet, usually causes reduction of the blood cholesterol concentration. Avoidance of excessive fat in the diet also helps avoid obesity because one gram of fat provides 9 calories, while one gram of protein or carbohydrates provides only 4 calories."

While these remarks suggest that the benefits of reduced calories can only be achieved by the reduction of fat, the AHA statement qualified the above remarks by the following two sentences:

"Most persons in the U.S. who are overweight will find it profitable to reduce their total caloric intake. Reducing the amount of fat in the diet is one way to do this."

The AHA statement also indicated that

"...the blood cholesterol concentration may also be reduced by controlling the amount and type of fat in the diet without altering caloric intake."

The 1988 report of the NCEP Expert Panel[1066] effectively regurgitated the AHA's rationale through the years, i.e.,

"Total fat intake in...therapeutic diets should not exceed 30% of total calories. The purpose of decreasing total fat is twofold--to facilitate reduction of saturated fatty acid intake and to promote weight reduction in overweight patients by substituting foods of lower caloric density."

Of course, followers of the AHA also ape their recommendations and reasoning, sometimes introducing errors in the process. For example, Alexander Leaf[2913] said, "The adoption of a diet with reduced levels of total and saturated fat reduces the likelihood of obesity. Saturated fat, of course, does not have fewer calories than monounsaturated or polyunsaturated fats.

The alliance's arguments are naive, unscientific in nature and contrary to the empirical evidence compiled over more than 30 years. It is well known that fat per se is not related to blood cholesterol and there is no evidence that the reduction of fat in the diets of obese individuals will not be accompanied by an excess consumption of carbohydrates and/or proteins, thereby maintaining or even increasing obesity.

As early as 1957, Stare et al.[3291] maintained that "it is questionable whether a decrease in the serum cholesterol that is induced by weight reduction can be maintianed after caloric equilibrium has been reestablished."

In 1959 Olson[1480] observed that

"The effect of weight loss upon the serum cholesterol has been disappointing. Although transient decreases in serum cholesterol and phospholipids following initiation of diet therapy have been noted, in most cases the serum lipids begin to return to pre-treatment levels before body weight has reached a plateau and by the time the subject is in caloric equilibrium again at a new (and lower weight), the serum lipids have returned to their control values."

Pollack[3020] reiterated Olson's observations in 1960.

The originator of the Prudent Diet was Norman Jolliffe. In 1961 he and his colleagues[3030] reported a modest (11%) reduction in blood cholesterol level in men using a diet that was slightly more severe than the AHA's Phase I diet. In 1962 Jolliffe[3021] noted that previous studies showed that blood cholesterol levels rose to their original levels after weight reduction. He demonstrated that a low-fat "Prudent Reducing Diet," with a relatively low P/S ratio, followed by a much higher fat diet, with a high P/S ratio resulted in weight and cholesterol loss, followed by a sustainment of the weight and cholesterol levels. In other words, they showed that caloric reduction was necessary for weight loss and temporary cholesterol loss, while a change in fat composition was necessary for the sustainment of cholesterol loss.

Also in 1962 Ende[2824] reported most interesting findings. He found that the complete elimination of food resulted in blood cholesterol increases in men and women

of all ages over a 72 hour period. It could not be determined whether the cholesterol rise was due to the body's need for additional cholesterol or to the physiological and psychological stress associated with the starvation process.

Wolf and Grundy[2958] presented further evidence that weight reduction per se is subsequently followed by a return of blood cholesterol to original levels in 1983. However, they seemed not to comprehend the reason for this phenomenon and they appeared unaware of the previous studies cited above.[a] Thus, it is not surprising that in 1984 Grundy's[3034] discussion of the rationale underlying the AHA's Prudent Diet was devoid of an understanding of the relationship between blood cholesterol and weight/fat per se reduction (see section on Scott Grundy, Chapter 10). His rationale was not at all consistent with the accumulated experimental evidence.

Two years later Grundy[336] compared a high (40%) fat diet (P/S = 1.7) with the low (30%) fat AHA Phase I diet (P/S = 1.0) and reported that both yielded identical blood cholesterol levels, i.e., 175 mg. These diets were also compared with a very low (20%) fat AHA Phase II diet (P/S = 1.0) having 150 mg of cholesterol lower than the first two diets. This latter diet was found to yield a blood cholesterol level significantly different from those of the first two diets. But again, Grundy et al. seemed not at all aware of the most important finding of their study, namely, that blood cholesterol remained the same whether total fat was 40%, 30% or 20% of calories.[b] They again did not cite or discuss the research discussed earlier and merely concluded that "the diet recommended for the general public [Phase I] appeared as effective for lowering of cholesterol levels as diets containing more polyunsaturates or more carbohydrates." Note that they did not say "as diets containing less fat." The only reasons that can be advanced for Grundy's repeated avoidance of the issue of fat per se versus fat composition in reducing weight and blood cholesterol are (1) complete ignorance of previous research on the subject, or (2) the need to protect and perpetuate AHA's long-time recommendation to reduce total fat in the diet. Although the first reasons cannot be discounted, the second reason seems the more likely in view of the AHA's almost religious fervor to appear consistent over the years.

In sum, weight reduction does not result in sustained blood cholesterol reduction and the reduction of fat per se does not result in lowered blood cholesterol. Moreover, the assumption that total fat calorie reduction among obese individuals is unproven and, as discussed elsewhere in this volume, probably false. In the first place, fat moves more slowly through the stomach than carbohydrates or proteins, sustaining longer the feeling of satiety. In the second place, obesity is caused by the desire for food (calories) and not necessarily specific foods. Finally, much of the obesity in the U.S. has historically been associated with the excess consumption of carbohydrates. Therefore, ignoring this fact and focusing on fat per se makes no sense at all. But then, much of the AHA's rationale in general makes no sense.

NIBBLING VS GORGING

Although the terms "nibbling" and "gorging" seem somewhat out of scientific character to describe different rates of food consumption, they have been accepted in the literature and, therefore, will be used here. Gwinup et al.[3023] were apparently the first to compare three rates of consumption in terms of their effects on blood

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[a] Another related article published by Kesaniemi and Grundy[2959] in 1983 also indicated a lack of awareness of relevant previous research.

[b] Theoretically, their 40% diet should have yielded a somewhat lower cholesterol level than the other diets since it had a higher P/S ratio.

cholesterol level in humans. They served three regular meals per day to 5 subjects for 14 days. Subsequently the same quantity and types of foods were distributed to the subjects in 10 smaller meals over a period of 18 hours. Then the same quantity and types of food were served the subjects in a single meal per day for 14 days.

Gwinup et al. reported that nibbling (10 meals) yielded the lowest blood cholesterol levels and gorging (1 meal) produced the highest levels, with the 3-meal per day showing intermediate cholesterol levels.

Keys[2839] was apparently unaware of the Gwinup et al. study and stated the following in 1979: "The idea that the frequency of eating may be consequential part from what is eaten came from experiments on animals in which 'nibbling' over a protracted period of time resulted in lower serum cholesterol levels than 'gorging' the same amount of food in a short time. ...we were unable to confirm this in controlled trials with middle-aged women." Note that Keys implied more than one experiment.

Jenkins et al.[2967] compared a 3-meal with a 17-meal a day diet in seven men in 1989. Each diet was followed for two weeks. Blood cholesterol levels were significantly lower during the 17-meal than during the 3-meal diets.

While nibbling may indeed lower blood cholesterol relative to less frequent eating patterns, the above studies were unimpressive in their power. Five and seven subjects per experiment were more suitable as "pilot" studies than as scientific experiments to be published in journals. Moreover, the Jenkins et al. study was another in which subjects consumed most of the pre-packaged foods at home and their results, therefore, were again based on the assumption that subjects followed instruction perfectly, an assumption that is never likely to be tenable.

The Jenkins et al. study also yielded a pattern of results similar to many other studies in which the primary variable was found to produce significant results, while another variable presented results contrary to other studies but the authors ignored them. For example, an editorial in the British Medical Journal stated that "The [Jenkins et al.] diet studied was a good example of a 'Prudent' diet. So the diet was such that the decrease in serum cholesterol concentrations was predictable."[2967] It is true that the total cholesterol level for the 3-meal Prudent diet did decrease 7 mg, compared to the cholesterol level on the subjects' usual diets, but the mean LDL level actually increased 3 mg and HDL decreased 2 mg, hardly the expected and desirable outcome of consuming the Prudent diet. It is, as usual, dumbfounding why Jenkins et al. ignored this trend and why the editorial failed to differentiate between total cholesterol and the two lipoproteins considered most important in atherogenesis.

MISCELLANEOUS DIETS

In 1958 Olson et al.[1780] compared a low protein (25 g) diet with a normal protein (100 g) diet. The fat remained the same in both diets but the former had more carbohydrates than the latter to compensate for the lower amount of protein. Olson et al. reported that the low protein diet reduced blood cholesterol levels in 9 hypercholesterolemics from 311 to 267 mg--44 mg. On the other hand, very recently Newbold[2886] placed 7 patients with food allergies on a high protein/fat diet composed primarily of rib steaks and attached fat and secondarily of raw vegetables and fruit and a small amount of vegetable oil. The mean cholesterol level of the subjects fell from 263 mg to 189 mg, a difference of 74 mg. In view of the fact that it is well known that protein per se has little or no effects on blood cholesterol, the apparently opposite findings of the above studies suggest that uncontrolled variables were active,

especially in the Newbold study where presumably considerable saturated fat was consumed.[a]

LONG-TERM EFFECTS OF DIETS

Most dietary experiments do not provide evidence regarding the effects of certain diets over the long term. It is generally assumed that the effects observed over a few weeks will remain constant over many months or years. This issue is unresolved but most certainly should be investigated because certain outcomes could have enormous impact on dietary recommendations.

Some provocative findings were reported by Brunner et al. in 1979 but were seemingly overlooked.[2029] They placed 26 Yemenite Jews on a seven month high fat diet that contained more than twice the calories (4,553) than in their normal diets. The high-fat diet was also high in saturated fatty acids (P/S = .4), compared to their normal diets (P/S = 1.1), and contained nearly twice the amount of dietary cholesterol (911 vs 512). Subsequently, the subjects reverted to their normal low-fat diets for three months and then resumed the high-fat diet once again for two months.

Figure 5-7 shows the blood cholesterol trends of Brunner et al.'s subjects over the 12-month period. The high-fat diet produced a continuous rise in cholesterol level over a full five months from an initial 150 mg to a final 199 mg. While Brunner et al. maintained that the subsequent low-fat and high-fat diet periods yielded predictable decreases and increases in cholesterol levels, they failed to note the rather large downward trend during the last two months of the initial high fat period. Although the low-fat diet was initiated after the seventh month, the trend during the 8th and 9th months was a perfect extrapolation of the trend during the previous two months.

The Brunner et al. study clearly presents provoking questions. For example, does it actually require many months in free-living populations for cholesterol levels to finally stabilize after switching to a high-fat diet? Also, would cholesterol levels have continued to drop had the subjects remained on the high-fat diet? Unfortunately, these questions may never be answered fully because lengthy experiments are rarely conducted.

THE KEYS AND HEGSTED EQUATIONS: A SOBERING THOUGHT

It was emphasized earlier in this chapter that despite the prolific use of the Keys and Hegsted equations, they are oversimplifications of the real world and cannot help but yield substantial error from application to application. Those equations were based on saturated fat, polyunsaturated fat and dietary cholesterol. If one accepts the relatively new information as facts that (1) some saturated fats are not hypercholesterolemic, (2) monounsaturated fats depress blood cholesterol, (3) trans isomers of monounsaturated fats increase blood cholesterol, (4) alcohol increases blood cholesterol, (5) oat bran decreases blood cholesterol, (6) complex carbohydrates decrease HDL levels, (7) the frequency of eating affects blood cholesterol, and (8) smoking increases blood cholesterol, then the equations are not only oversimplifications of reality, they are absurd oversimplifications.[b] Yet, alliance members will continue to use the equations oblivious or uncaring of their gross inaccuracies.

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[a] The Newbold report was a description of clinical case findings and did not present specific dietary data.

[b] Yet to be fully determined are other foods which are said to alter cholesterol levels, e.g., coffee.[1911,2571,2581,2684]

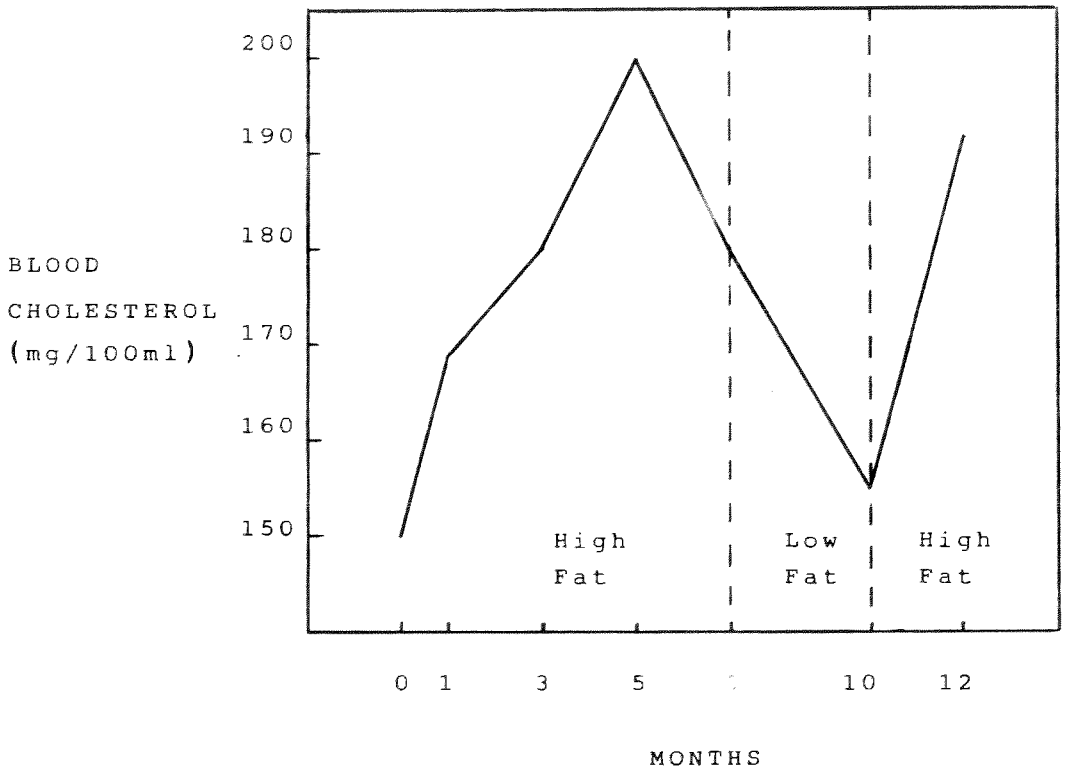

Figure 5-7. Cholesterol levels of Yemenites on high fat, low fat and high fat diets (adapted from Brunner et al.,[2029])

In Volume 1 we summarized the dozens of experiments previously performed that compared different diets containing different types and quantities of fatty acids. Although it was clear that high polyunsaturated fat diets decreased and high saturated fat diets increased blood cholesterol levels, one could generally not find a predictable functional relationship between the quantities of fats used and blood cholesterol changes. This was undoubtedly due, in large part, to the great variety of diets used by experimenters who unwittingly allowed variables noted in the immediately above paragraph to vary uncontrolled, producing a large array of confounded results.

Finally, regression equations are notorious for being unable to describe adequately a new set of data after being developed from an old set of data when applied to psychological or physiological problems. The Keys and Hegsted equations are being used indiscriminately by many individuals who have no real understanding of regression equations and their limitations.

6. CLINICAL TRIALS

"It is our opinion that the encouraging results of our own trial, even when buttressed by concordant observations in two other primary prevention studies, are not sufficient grounds for aggressive efforts to change the U.S. diet."

(Seymour Dayton and Morton Pearce, Veterans' Hospital Diet Trial, 1969[2541])

"Dear Senator McGovern: Thank you for providing me with a copy of your committee's publication entitled 'Dietary Goals for the U.S.,' and for the invitation to comment upon these issues. The main reservation I would have is that...more radical restriction of saturated fat and cholesterol might very well be even more efficacious."

(Seymour Dayton, Senate Select Committee Hearings, 1977[2708])

INTRODUCTION

Chapter 6 of Volume 1 reviewed 33 conventional clinical trials which attempted to reduce CHD mortality and/or morbidity rates with diets or cholesterol-lowering drugs. It also reviewed 8 trials which used angiograms as the means of assessing benefits of treatments. The present Chapter focuses primarily on how the alliance distorts clinical trial findings. As will be seen, these distortions derive from various techniques such as erroneous reviews, selective omissions of data and completely illogical, irrational and obviously biased reasoning. This chapter also addresses angiographic trials purporting to show regression of atherosclerosis. (Chapter 7 presents a detailed discussion of regression and the massive evidence and logic that argues against the reported findings.)

CONVENTIONAL CLINICAL TRIALS

The following sections critique the follow-up studies on the Multiple Risk Factor Intervention Trial (MRFIT), the Coronary Drug Project (CDP), the Minnesota Coronary Survey and the Stockholm trial. Additional critiques of the Oslo Diet/Smoking trial, the Veterans trial, the POSCH trial, and the DART trial are also presented.

Before initiating the review the reader would do well to recall or reread the discussion presented in Chapter 3 ("Cholesterol and CHD Events"). While it is always assumed that all diagnoses of CHD events and deaths are valid, we all know that they are subject to gross error, particularly the certification of deaths. Moreover, a substantial percentage of myocardial infarctions are not found at autopsy to be related to thrombi or substantial atherosclerosis. And since the only hypothesized relationships between blood cholesterol and CHD is between blood cholesterol and atherosclerosis, a large percentage of the fatal and nonfatal myocardial infarctions and sudden deaths occurring in trials are used erroneously as endpoint data. Although the alliance and its followers would deny this fact rather vigorously, there are abundant supportive data presented in this volume and elsewhere.

Another important point was emphasized by Stehbens.[3316] Clinical trials have frequently used subjects with very high blood cholesterol levels, many of which are familial hypercholesterolemics (FH). Since many or most FH subjects have a lipid storage disease superimposed on their natural atherosclerotic vessels, these individuals undoubtedly constitute a confounding factor in the data base. Symptomatic fatal and nonfatal ischemia due to lipid storage disease in men under 60 years of age, the age group typically used in trials, is clearly not representative of symptomatic atherosclerosis occurring after age 60.

It is often the case that what one does not know does not bother one. Clinical trial reports give the illusion of accuracy because authors do not even suggest that their endpoint statistics may be in error. Although we all know, for example, that death certification is often based on guesses and what is fashionable at the time, all deaths in clinical trials are assumed to be 100% correctly diagnosed.

Finally, one must always be cautious of biases, even when authors maintain that their trials were thoroughly blinded and randomized. One cannot help but note the enormous inclinations of authors to find positive results. No matter what the data reveal, they are almost always strongly interpreted in favor of the lipid hypothesis. The data from some studies, particularly from mainland Europe, report such incredible effects of cholesterol lowering that they simply cannot be believed. In sum, clinical trials are costly and time-consuming. It would appear that negative findings from such investments are intolerable to both the authors and the funding agencies. Hence, the findings are almost invariably positive--even when they look negative to the reader. The tell-tale signs that "something has been extracted from nothing" are not only visible in reports of clinical trials, they are evidence in the simple fact that there is a never-ending conduction of trials, i.e., if so many trials have produced such an abundance of positive findings, why is it necessary to conduct so many more trials?

Minnesota Coronary Survey

Chapter 6 of Volume 1 reviewed the Minnesota Coronary Survey which was a four-year follow-up published in 1975.[555] In 1989, 14 years later, Frantz et al. published a 4.5 year follow-up whose results were identical to the original report.[2350] Although blood cholesterol level was lowered about 14% in a diet group relative to a control group, there were virtually no differences between groups in CHD or all-cause death rates. Much post hoc analyses revealed no positive effects of diet treatment whatsoever in this randomized and blinded trial. It is curious that Frantz et al. were motivated to publish so little additional data so many years after the trial was terminated.

Stockholm Trial

Another strangely delayed report of an old clinical trial was published in 1988 by Carlson and Rosenhamer.[2263] Although they referred to this document as a "final report," it covered the same period of time (5 years) as did a 1980 report, reviewed in Chapter 6 of Volume 1.[840] This study was an unblinded secondary prevention trial which employed both clofibrate and nicotinic acid as the cholesterol-lowering treatment. The trial began with 279 treated and 276 control subjects and ended up with 144 treated and 145 control subjects. Some 107 subjects withdrew from the study but were nevertheless included in the analyses. Blood cholesterol was lowered 13% in the treated group, relative to the control group.

The article by Carlson and Rosenhamer was poorly organized and written and omitted some important information. There were also indications that their mathematics were occasionally in error. Nevertheless, the results presented little bases for debate because Carlson and Rosenhamer concluded that "the beneficial effect of treatment in IHD deaths appeared to be related to the degree of triglyceride lowering but not to that of serum cholesterol." Because this study was unblinded, none of its results can be taken seriously. Carlson and Rosenhamer recognized this design flaw but insisted that it was unavoidable because of the side effects of nicotinic acid. Because cholestyramine has very pronounced side effects, how was it then that the LRC trial (Chapter 7) was blinded?

The MRFIT Study

A 10.5 year follow-up of the MRFIT study was published in 1990.[2723] The MRFIT Research Group concluded that "After an average of 10.5 years of follow-up, mortality rates for coronary heart disease, cardiovascular disease, and all causes were lower for SI (treated group) than UC (control group) men by 10.6%, 8.3% and 7.7%, respectively. In summary, the 10.5-year MRFIT mortality findings provide support for early intervention on cholesterol, smoking and blood pressure for the primary prevention of CHD." But as we shall see, such a conclusion was partially false and grossly misleading.

The Research Group first briefly reviewed principal findings of the MRFIT study after its termination in February of 1982. The differences between treated and control groups in total and LDL cholesterol levels were 4.6 mg and 3.9 mg, respectively. There were no significant differences between groups in mortalities due to CHD, all cardiovascular diseases or all causes after an average period of 6.9 years. The Research Group concluded that "We have shown that it is possible to apply an intensive long-term intervention program against three coronary risk factors with considerable success in terms of risk factor changes. It may be relevant that multifactor intervention received a less than optimal test owing, in part, to unexpected declines in risk factor levels and, in part, to lower-than-expected mortality in the UC group. In regard to the former, the UC men thus constituted to a considerable extent a 'treated' group."[471] Indeed, many alliance members attributed the lack of treatment effects to the very small difference between groups in blood cholesterol level. For certain, differences of 4.6 mg in total cholesterol (2%) and 3.9 mg in LDL cholesterol could not possibly have produced different CHD or total mortality rates.

The 10.5 year follow-up was not only based on the same trivial cholesterol differences noted above for the first 6.9 years, but also on apparently no differences between groups during the next 3.8 years. This latter assumption must be considered tenable because (1) subjects were not treated beyond 6.9 years and (2) cholesterol measurements were not obtained on subjects beyond 6.9 years. Thus, the average cholesterol differences between groups during the entire 10.5 years must have been on the order of 3.3 mg and 2.6 mg for total and LDL cholesterol, respectively. It is simply preposterous to consider these values as being even remotely capable of differentially influencing CHD and total mortality rates. Yet, the MRFIT Research Group did just that. It will be recalled from Chapter 4 that Blackburn did not think that a much larger difference occurring in Japan over more than twice the period of time was sufficient to alter CHD trends.[1808] Thus, alliance members consider very small differences sufficient when the outcome favors the lipid hypothesis and very large differences insufficient when the outcome does not favor the hypothesis.

Table 6-1 presents the 10.5 year follow-up data. While the MRFIT Research Group explicitly stated that the mortality rates for CHD, cardiovascular disease and all causes were lower in the treated group by 10.6%, 8.3% and 7.7%, Table 6-1 shows that the actual rate reductions were 0.37%, 0.36% and 0.25% over the 10.5 year period (and 0.04%, 0.03% and 0.06% per year). Thus, the Research Group authors computed "relative differences" but called them rate differences in their text. In view of the fact that the relative differences were inflations of the actual rate differences by factors of 28.6, 23 and 30.8, this "oversight" is no little error. Either the authors did not understand the difference between relative differences between numerators and rate ratios or they purposely intended to deceive their readers.

In evaluating the 3.8 year follow-up data independently, the authors said that there were no significant differences in CHD or cardiovascular deaths but a significant difference in all-cause deaths. Interestingly, while they presented a detailed breakdown of categories of deaths for the entire 10.5 year period where no significant

Table 6-1

	Control Group (n = 6438)		Treatment Group (n = 6428)		Rate Differences[a]	
	Total	Rate	Total	Rate	10.5 yrs.	Annual
CHD deaths	226	3.51%	202	3.14%	0.37%	0.0352%
Cardiovascular deaths	290	4.50%	266	4.14%	0.36%	0.0343%
Total deaths	537	8.34%	496	7.72%	0.25%	0.059%

[a] None of the rate differences were significant.

differences were observed, they provided no such data for the 3.9 year period, where some significance was purported to have been achieved.

With regard to this latter finding, three points should be made. First, the annual rate difference in all-cause deaths was only 0.18%. Second, regardless of the difference, it cannot possibly be attributed to the blood cholesterol differences between groups which were trivial during the 6.9 year period and apparently zero during the 3.8 year period. And third, this post hoc analysis of subgroups of data was emphatically cautioned against by the same authors in their 1982 report, namely, "The overall results do not show a beneficial effect on CHD or total mortality from this multifactor intervention. These results are accompanied by an apparent heterogeneity of effects among sizable subgroups, but there must be caution in reaching conclusions from such subgroup data."[471] It is unfortunate that the authors could not follow their own advice. It is unfortunate also that alliance members ignore the trivial decrease in blood cholesterol but claim it contributed to the decreased mortality. For example, Glen Griffin, editor of Post Graduate Medicine, said, "You may recall that some skeptics have used the initial unimpressive U.S. MRFIT study findings to pooh-pooh the benefits of eating a low-cholesterol, low-fat diet. But now the 10 1/2 year results of the study are in and show a 24% lower heart attack death rate..." In effect, Griffin considered the results "unimpressive" during risk factor control and apparently impressive after control was terminated. He also falsely claimed a 24% reduction in CHD death rate when, in fact, it was a mere 0.37% over the 10.5 year period.

In summary, despite the massive effort and intense desires by the alliance to show benefits of risk factor control, the MRFIT study was a failure in general and in specific, i.e., its overall results were unimpressive and its principal target results (CHD and cardiovascular mortalities) were substantially unimpressive. Moreover, whatever minor effects one may wish to accept cannot be attributed to the alliance's key risk factor, blood cholesterol level.

As usual, unfortunately, the media transform negative findings into positive ones. Gina Kolata of the New York Times published the following statement one day after the above report was published: "A study of more than 12,000 middle-aged men found that those given help to stop smoking, lower their blood pressure, lose weight and go on cholesterol-lowering diets substantially cut their risk of heart attack."[2724] Kolata completely botched the job of reviewing the article accurately. For example, she claimed that the treated group had a 24% lower heart attack rate than did the control group. Not only was the actual rate reduction only 0.37% over the entire 10.5 year period, the heart attack category was only one of two categories subsumed under the primary endpoint, CHD. The second category was "other ischemic heart disease" which is more related to atherosclerosis and blood cholesterol than is heart attack and, according to the alliance's presentation, showed a nearly 12% increase in the treated group. Thus, Kolata was guilty of publishing selective and misleading data, as well as totally erroneous rate information. Kolata cited NHLBI director, Claude Lenfant, as saying, "We feel vindicated." Only the alliance can feel vindicated by negative, nonsignificant and/or trivial findings.

The Coronary Drug Project

Table 6-2 shows the principal data presented in the 1975[490] and 1986[1374] reports on the Coronary Drug Project (CDP). The top half of the table presents the percentages of total deaths for all six groups, CHD deaths and nonfatal MIs for the three groups completing the trial, and the blood cholesterol reductions in the niacin and clofibrate groups, relative to the control group. As is obvious, there were no significant differences between groups in total or CHD death rates during the trial. Authors of the 1975 report indicated that there were significantly fewer nonfatal myocardial infarctions in the niacin group (but not the clofibrate group) than in the

Table 6-2

6.2 Year Trial

Fatal and nonfatal Events	Control	Niacin	Clofibrate	Low Estrogen	High Estrogen	Dextro-Thyroxine
Total deaths (%)	28.0	26.1	28.2	28.8	29.0	27.8
CHD deaths (%)[a]	19.2	18.6	17.2	--	--	--
Nonfatal MI (%)[a]	13.8	10.1	13.1	--	--	--

15-Year Follow-Up

Total deaths (%)	58.2	52.0	57.8	59.7	58.3	57.0
CHD deaths (%)	41.3	36.5	--	--	--	--

[a] Based on 1975 report which covered a period averaging more than 5 years but less than 6.2 years.[490]

control group. However, the MIs in the niacin group were more severe than in the

The average blood cholesterol reduction in the niacin and clofibrate groups, relative to the control group, were 9.9% and 6.5%, respectively.

Authors of the 1975 report drew the following conclusions: "There is no evidence of significant efficacy of clofibrate with regard to total mortality and cause-specific mortality. There is no evidence of efficiency of niacin with regard to total mortality and cause-specific mortality. Because of the excess incidence of arrhythmias, gastrointestinal problems, and abnormal chemistry findings in the niacin group, great care and caution must be exercised if this drug is to be used for treatment of persons with CHD."[490]

While the authors of the 1986 report will subsequently speak of a "lag" in the effects of niacin and, in another context, beneficial effects of the elimination of the niacin treatment, the reader should recognize the overriding findings of the trial itself, i.e., no beneficial effects were observed during the trial while subjects were treated with cholesterol-lowering drugs. In fact, three of the drug groups were terminated early in the trial (1.5, 3.0 and 4.7 years) because of "excess" numbers of deaths, nonfatal MIs and cancer,. It is scientifically unjustified to dismiss all of these negative findings and accept only positive findings. It is particularly unjustified to dismiss the results of the low-dose estrogen-treated group which completed a 4.7 year trial period (94% of the length of the Helsinki II trial).

Alliance members were quick to rationalize the results of the 1975 trial report. William Connor, for example, said in 1975 that the outcome was entirely "predictable" because the cholesterol lowering was minimal.[2436] But not only did the niacin group achieve a greater reduction than did the cholestyramine group in the LRC trial, the often publicized "2% reduction in CHD events for a 1% reduction in blood cholesterol" should have resulted in all groups achieving greater benefits than the control group.

Former NHLBI director, Theodore Cooper, indicated in 1975 that the negative results were due to the fact that all the CDP subjects had advanced atherosclerosis. "It is my opinion that at certain stages in the disease...it will not be reversible by manipulation of the serum cholesterol."[2688] Stamler and Dipalma presented a similar argument, i.e., "There is little doubt that long-term therapy with any of these agents for patients who have recovered from MI is not worth the risk involved."[1351]

The bottom half of Table 6-2 shows the total death rates after 15 years for all six groups and the CHD death rates for the control and niacin groups only. It is clear from these data that the death rates of all drug groups, except the niacin group, were not different from the control group. The authors of this study, Canner et al., indicated that total mortality in the niacin group was significantly lower than in the control group. While this difference cannot be disputed, the difference between the two groups in CHD death rates most certainly can be disputed. For example, during the trial there were apparently uniform criteria used to diagnose cause of death. But after the trial cause of death was determined by death certificates from different geographic regions (e.g., states) and from physicians with widely different knowledges, equipment, exposure to patients, etc. The completely uncontrolled nature of measuring this endpoint casts doubt on the validity of the CHD mortality data. It is interesting, in this regard, that while Canner et al.'s data suggested that the difference between groups in CHD mortality was statistically significant, this apparent fact was not mentioned in their text.

It is also interesting that while the LRC authors would later place far greater emphasis on nonfatal than fatal events, Canner et al. indicated that no data were collected during the follow-up with respect to nonfatal MIs.

In contrast to the outcome of the actual trial, alliance members all praised the benefits of niacin on extending life expectancy (see "Reviews of Clinical Trials"), including Stamler, who was a co-author of the follow-up report.

In addition to the fact that it is scientifically inexcusable to present follow-up results of selected trials (and groups within trials) but not those of all trials, there are a number of problems underlying the apparent difference in mortality between the niacin and control groups. Some were noted by Canner et al. but none are ever mentioned by alliance members who "review" the study.

Canner et al. maintained that the "likely explanation [for the long-term survival benefit with niacin] stems from the cholesterol-lowering effect of niacin, which was superior to that of the other drugs studied in the CDP. Thus, it is possible that a 10% reduction in serum cholesterol, maintained over 5 to 8 years may have significantly slowed the progression of coronary atherosclerosis." (Note the words "possible" and "may.") If such an explanation were valid, then favorable mortality trends after 15 years should have been exhibited by all of the other drug groups because, although they did not have quite the cholesterol reductions as did the niacin group, they did show reduction of consequence. It is illogical not to generalize the argument to the other groups, particularly since alliance members heavily promote the concept that "for each 1% reduction in cholesterol level, there is a 2% reduction in CHD." This formula cannot be justifiably applied only to selective data which "prove" it correct.

In view of the early mortality/cancer rates which occurred in the dextrothyroxine and estrogen groups, resulting in the termination of these groups, it could be argued that the side effects of these drugs overwhelmed the benefits of their cholesterol-lowering effects. However, the fact that those groups showed no greater total mortalities than the control group after 15 years indicates that his argument is incorrect. Canner et al. confirmed this observation.

The reverse argument can be applied to the niacin group, i.e., it is an essential vitamin and its beneficial effects may have derived from that fact. Cholesterol-lowering may have been a side effect which had nothing to do with increased life expectancy. This writer doubts the validity of this explanation but it is, in fact, a more logical explanation than attributing cholesterol-lowering benefits to niacin but not to clofibrate, dextrothyroxine and estrogen.

Canner et al. presented two curious and somewhat inconsistent explanations for the fact that differences between the niacin and control groups did not emerge until after six years. First, they said, "While a time lag in development of beneficial trend in mortality as a consequence of lowering serum cholesterol and slowing coronary atherosclerosis is to be expected, it seems surprising that his lag--for niacin treatment--is of the magnitude of 6 years or more. Both the niacin data during the CDP and the cholestyramine data from the LRC trial show about a 2 to 3 year delay before the development of a beneficial trend in nonfatal MI. Because the atherosclerotic processes underlying nonfatal and fatal MI presumably are similar...it is puzzling that an additional 3 years of serum lipid-lowering seems to be required for a beneficial trend in mortality. However, it is possible that initially, niacin prevents primarily milder, nonlife-threatening infarction. This is suggested by unpublished data from the CDP; among patients with interim nonfatal MI, those in the niacin group had greater subsequent mortality during the treatment phase of the trial than did patients in the placebo group. Thus, although patients receiving niacin experienced nonfatal MI less frequently than did patients receiving placebo, their nonfatal infarctions were

more severe than those of the placebo group, suggesting that milder MI may have been prevented by niacin. Then, as the favorable lipid-lowering effect of niacin on the coronary arteries increased over time, more severe life-threatening infarction may have been prevented."

The concept that niacin initially prevents milder MIs (niacin patients had more severe but less frequent MIs) and later prevents more severe MIs is not only grossly speculative, it is scientifically unsound. The alliance maintains without equivocation that cholesterol deposition on the artery wall from the blood is the cause of CHD and that the higher the cholesterol level, the greater the deposition and the greater the risk of CHD. It is simply ludicrous to suggest, therefore, that a reduction in blood cholesterol and in the deposition of cholesterol in the arteries, would "initially" protect against "mild" MIs but not "severe" MIs. A slower rate of cholesterol deposition should delay all degrees of MI initially and during the long term, if the lipid hypothesis is valid. The hypothesis is quite inconsistent with the reasoning of Canner et al. Moreover, Cornfield and Mitchell (of the National Heart Institute) emphasized in 1969 that epidemiologic data, including unpublished Framingham data compiled by Gordon and Ederer, indicated that "the relationship between cholesterol value and event rate is essentially the same for all three endpoints [angina pectoris, nonfatal myocardial infarction and CHD death.]

The authors continued, "As an alternative explanation for the 6 year lag, there may have been counterbalancing adverse effects of niacin while patients were taking the drug; the beneficial lipid-lowering effect may be manifest only after the drug is discontinued. The significantly higher incidence of atrial fibrillation and other cardiac arrhythmias in the niacin group may be a possible mechanisms for this explanation." This is again a highly speculative explanation and not very reasonable. For example, if niacin did produce adverse effects with respect to heart disease and total mortality, those effects should also have carried over to the follow-up period. Further, if their explanation were true, niacin should be eliminated as a cholesterol-lowering drug because (1) it would have no overall beneficial effects during use and (2) it would be inefficient to use it on an on-and-off manner. Since cholesterol-lowering drugs tend to be used for life, it is not likely that patients would be told of niacin's lack of effect during use, given that Canner et al.'s explanation were true.

The whole concept of "lag" is unreasonable, as indicated in Chapter 3. If the lipid hypothesis is valid, then the effects of lipid lowering should be observable within perhaps months after initiation when taken by patients with advanced disease. If the niacin and control groups were highly comparable in terms of the average degree of advanced atherosclerosis, then a reduction in lipid deposition via cholesterol-lowering should delay all MIs, on the average, in the niacin group during the trial. The fact is that the results of the CDP study, including the follow-up, present more data in conflict with the lipid hypothesis than they do in concert. In their attempts to explain peculiar findings, Canner et al. were seemingly unaware that their explanations were not reasonable extrapolations of the lipid hypothesis.

More likely explanations for the observed findings were presented by Canner et al. under the topic, "other explanations." For example, they indicated that no data were available to ascertain whether the niacin group received better medical and/or surgical treatment of their coronary heart disease. However, they rejected this possibility on the grounds that "patients in the niacin group had a nearly 50% lower incidence of cardiovascular surgery than did placebo-treated patients, also, most categories of cardiac medications were prescribed less frequently for niacin than for placebo-treated patients during the trial. There is no reason to expect these patterns to have changed drastically after the trial was over." Not only is this information (given more as an afterthought than anything else) explosively important, their assumption of unchanging patterns adds fuel to the fire. If, as indicated earlier, the niacin and control groups were initially comparable in terms of average degree of atherosclerosis, why, then was

there twice as much cardiovascular surgery among the control patients and why were those patients more frequently prescribed cardiac medications? Given that all patients were treated equally, with the exception of the drug niacin, why did control patients require far more cardiovascular surgery and more cardiac medicines? This question is most profound because it suggests that the groups (1) were not initially comparable and/or (2) were differentially treated. Moreover, if these patterns continued, as assumed by Canner et al., they would again support the concept that the control group was composed of patients with more severe disease, on the average, than the niacin group.

The fact that the groups were randomized does not dismiss the above logic. Randomization increases the probability of comparability but it does not guarantee comparability. Part of the reason why groups differ significantly in response to a treatment is because they differ significantly at the outset, although that fact may not be visible in terms of the standard characteristics normally reported, such as age, weight, cholesterol level, etc. Aside from the fact that all patients suffered an MI before participating in the CDP, it is probably impossible to determine the comparability of the groups with respect to the degree of atherosclerosis. In any event, Canner et al.'s final bit of information demands examination and could very well explain all of the differences observed between the groups.

Unfortunately, the peculiar and inconsistent results of the Canner et al. study have been totally ignored by the alliance, a tactic that artificially reinforces the belief in the lipid hypothesis at the expense of more scientific explanations.

The Oslo Diet/Smoking Trial

The Oslo Diet/Smoking trial is an excellent example of a study whose results are impossible to be believed by rational thinkers. The study's design and results were highly inconsistent with those of many other trials and provoke more anger than praise. Let us first briefly summarize previous diet trials.

Three U.S. primary (Diet-Heart study,[1071] MRFIT[471,474] and Minnesota Survey[555]) and one mixed primary/secondary (Veteran's Hospital[454]) trials were conducted whose durations were 4 to 7 years.[a] The total number of treated subjects in these trials was over 12,300. Cholesterol-lowering diets produced no significant beneficial effects in terms of CHD events, CHD deaths or total mortality, despite the fact that blood cholesterol levels were reduced in excess of 10% in three of the trials.

Three British secondary (Research Committee,[485] Rose[495] and Research Committee[466]) and the large WHO collaborative trial[847] also failed to show benefits of cholesterol-lowering by diet among 9,483 treated subjects. The early (1972) Helsinki primary trial,[1145] the early (1970) Oslo secondary trial[480] and an early (1965) mixed primary/secondary trial (Hoed[491]) did report positive findings but, not so surprisingly, all were unblinded studies and two were also not randomized. In sum, cholesterol-lowering by diet in scientifically acceptable trials has consistently failed to reduce CHD events, CHD mortality or total mortality in a treated population of nearly 22,000 men. How, then, did the very small Oslo Diet/Smoking trial achieve significant results on all three endpoints? It should be emphasized at the outset that, as shown in Volume 1, mainland European trials have generally reported an abundance of positive findings, while U.S. and British trials have generally shown an abundance of negative findings. This dichotomy is undoubtedly due to the fact that mainland European investigators failed to eliminate biased diagnoses by blinding the diagnosticians.

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[a] The Anti-Coronary Club is not included in this review because it is recognized to be grossly flawed scientifically.

Although the Oslo Diet/Smoking trial authors claimed that their trial was blinded, there is strong evidence in their own report that suggests otherwise. We shall address this all important issue first.

Hjermann et al. stated that "all [cardiovascular events] were diagnosed by two cardiologists who were not involved in the study and did not know to which group the men belonged."[849] However, elsewhere in their report Hjermann said, "One of us (I. Hjermann) talked for 10-15 minutes individually to the men in the intervention group about the risk-factor concept and the purpose of the study. One of us (I. Hjermann) re-examined subjects in the intervention group every 6 months and control subjects every 12 months. Follow-up included a short clinical examination with special emphasis on cardiovascular symptoms, body weight, blood pressure, serum cholesterol and triglyceride levels, and a 12-lead resting ECG. At each follow-up the men in the intervention group were asked about their eating and smoking habits. A cholesterol curve was made for each man and shown to him." Thus, it is quite clear that at least one of the principal investigators was intimately knowledgeable of the treated and control subjects and of their cardiovascular symptoms. If the study was truly blinded, Hjermann would not have been involved in the examination process. The fact that he knew who the treated subjects were, talked individually to them and examined sufficient grounds to define this trial as unblinded and, therefore, probably biased like most of the previous mainland European trials. As we examine this study in more detail we shall see that its results were quite improbable.

The numbers of subjects in the treated and control groups were 604 and 628, respectively. Hjermann et al.[849] indicated that "with a mean starting cholesterol level of 329 mg, a sample size of 615 in each group would give a 60% chance of discovering a 50% fall in [CHD] incidence at the 5% level of significance."[a] Not only did they explicitly state that cigarette smoking was not considered in the calculation of sample size, they also apparently used no expected blood cholesterol reduction value in their calculations. Without such a value, the above quote has no meaning whatsoever. Since they reported a relative CHD reduction of 47%, it would appear that their "calculations" were after-the-fact. For example, in their 1981 report Hjermann et al. indicated that the blood cholesterol reduction of treated subjects, relative to the control subjects, was 13%. But in their 1985 report, Holme et al.[846] said it was 10% and "...it can be predicted that a 10% reduction in serum cholesterol is associated with at least a 50% reduction in CHD incidence based on the control group regression, whereas the observed difference in CHD incidence in fact was 47%." Thus, their "prediction" was after-the-fact.

The Oslo study was initiated in 1972. The year before the NHLBI Task Force[705] determined that 24,000 to 115,000 subjects would be necessary for 7 to 10 years to show a significant reduction in CHD events by diet, assuming a 10% reduction in cholesterol levels. These estimates represent 20 to 93 times larger sample sizes than that used in the Oslo study which showed a 50% relative reduction in CHD events. Although many alliance members have repeatedly stated during the Oslo trial and after it was completed that a diet trial is not feasible, they readily and unabashedly cite the Oslo study as evidence supporting the diet-CHD relationship. For example, the 1985 NHLBI Workshop,[492] which included such individuals as Lenfant, Rifkind, LaRosa, Castelli and Blankenhorn, concluded that (1) "a double-blind trial of diet intervention was not feasible, and therefore a test using a drug to lower cholesterol was undertaken [the LRC trial], and 9 paragraphs later (2) they cited the Oslo study and stated that "serum cholesterol levels dropped by 10% and coronary events were significantly less in the experimental group." Since these two statements are wholly

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[a] Relative, not absolute, percentage decrease.

inconsistent, either the alliance has been thoroughly wrong on this issue for many years or the Oslo trial was not, in fact, blinded at all--or both. In any event, Lenfant and his colleagues seemed oblivious of the contradiction inherent in the Workshop report.

One can only wonder how trial investigators compute their sample size requirements. For example, the LRC protocol report[503] indicated that given a 24% differential in cholesterol levels--2.4 times greater than that presumably assumed and obtained by Holme et al.--a sample size of 1900--over 3 times greater than that employed in the Oslo trial, was required.

Because cholesterol reduction in the LRC trial was 8.5% and the relative reduction of CHD events was 17%, Rifkind[500] claimed that for each 1% reduction in cholesterol we can expect a 2% reduction in CHD events. The cholesterol and relative CHD event reductions in the Helsinki II trials were 10% and 34%, respectively, yielding a 3.4% reduction in CHD for each 1% reduction in cholesterol. Using the same "logic" for the Oslo study, there was nearly a 5% reduction in CHD events for each 1% reduction in cholesterol. This would imply to the naive reader that if we reduce our blood cholesterol by a mere 20%, we can 100% eliminate CHD. For example, suppose a control group had a CHD frequency of 100 after 5 years. Then reducing the cholesterol level of the treated group would reduce risk by 100%, i.e., eliminate the entire 100 CHD events.[a] Of course, this is absurd but that is precisely the way the alliance's risk concept works.

Although undoubtedly biased and fabricated the reported Oslo study results supported the alliance's lipid hypothesis. Interestingly, alliance members have devoted little discussion to the study in reviews, have apparently never reviewed it critically and have often reviewed it erroneously. The study was not mentioned or referenced in the Consensus Conference report[1845] and it was referenced but not mentioned in the Expert Panel's report.[1066] Naito[1397] reviewed "the evidence that lowering blood cholesterol reduces heart mortality and morbidity" but omitted the Oslo study. In four relevant articles by Gotto, zero sentences,[1369] one sentence[2886] and three sentences[1425,2527] were devoted to the Oslo trial.

Castelli[1302] devoted two sentences to the Oslo trial and committed an error, i.e., he indicated that the treated group's cholesterol level was reduced 15% when, in fact, it was reduced 10%. Purporting to "update" the 1970 Inter-Society Commission for Heart Disease Resources report, Kannel, Stamler and others[1083] gave the Oslo study four sentences and committed two errors. They claimed that the treated group's cholesterol level was 13% lower than the control group's and that this difference resulted in a 47% lower "incidence" of CHD events. The 47% reduction was the relative difference between the groups, not the reduction in incidence or rate. The 1989 Food and Nutrition Board's report[2070] devoted five sentences to the Oslo study and almost completely botched its review. For example, it cited Hjermann et al.[849] as indicating that the Oslo trial was 7.5 years when, in fact, it was 5 years. Furthermore, Holme et al.'s[846] 1985 report described an 8.5-10 year follow-up but it was not cited by the Board. The Board also indicated that the diet treatment decreased the "incidence" of CHD by 47% when, in fact, the reduction was 2.6%. Finally, the Board stated that "Total mortality in the experimental and control groups was 26/1000 and 38/1000, respectively ($p = .25$). Since this difference did not

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[a] Although control of cigarette smoking was also a factor in the Oslo study, "...the net differences in smoking or quit rates between the groups were too small to explain much of the differences in CHD incidence."[846]

remotely approach statistical significance, as evidenced by the p value, it can be inferred that the presentation of this statement was intended to mislead statistically unsophisticated readers.

The Veteran's Diet Trial

As shown in Volume 1 this trial demonstrated no significant benefits of dietary changes on either CHD events or total mortality. Dayton and Pearce[2541] indicated that there had been only three primary prevention trials using diet to lower blood cholesterol. These were the Anti-Coronary Club, the Helsinki I trial and the Veteran's trial. Despite emphasizing in considerable detail the importance of randomization and blindedness in clinical trials, Dayton and Pearce "reviewed" the Anti-Coronary Club and Helsinki I trials without mentioning the fact that they were both nonrandomized and unblinded. They concluded that "Each of the three trials has reported a more favorable clinical outcome in the experimental group." Not only can the Anti-Coronary Club and Helsinki I studies be classified as scientific garbage, it is impossible to fathom how the treated group in the Veteran's trial can be considered to have yielded a "more favorable clinical outcome when its total mortality was only slightly lower (174 vs 177) than that of the control group and trend data indicated that nonCHD deaths were progressively increasing and decreasing in the treated and control groups, respectively, after the fourth year of the 8 year plus trial. There was no opposite trend for CHD deaths.[a]

Since the alliance associated diet with atherosclerosis and atherosclerosis with CHD, it is pertinent to review the autopsy studies of Dayton et al.[454] on those subjects who died in the Veteran's trial. They concluded that "There is no evidence of a diet-related difference among any of the characteristics graded" with respect to coronary arteries. The same is true of combined data for the total aorta plus the common iliac arteries. There was no difference between the two groups in lipid concentration of the aorta, circle of Willis, coronary atheroma, or uncomplicated aortic atheroma." And there was "no difference between the two groups...in calcium concentration of the aorta..." In addition, "abundance of cholesterol, triglyceride, and phosphatide in the lipid of aortic tissue was also the same in both groups" and "this was also true of coronary and aortic atheromata and of circle of Willis."

A most interesting aspect of the results of the Veteran's trial was that associated with fatal and nonfatal myocardial infarctions and sudden deaths due to CHD. First, there were 51 and 42 fatal and nonfatal infarcts in the control and treated groups, respectively, but because infarcts were counted instead of the number of men suffering infarcts, there were actually only 44 and 36 men in the control and treated groups who had infarcts.[454] And since the number of fatal infarcts was identical for both groups, namely 24, the groups therefore differed by only 8 nonfatal infarcts, a most insignificant difference for an 8 year trial of 846 middle-age and elderly men.

Dayton et al.[454] reported that there were 27 and 18 "sudden deaths due to coronary disease" but the criteria for this diagnosis was anything but satisfactory. They said, a "case was construed to be sudden death due to coronary heart disease (a) if death were either instantaneous or unwitnessed and an autopsy showed severe coronary atherosclerosis and no other apparent cause of death; or (b) if death occurred instantaneously in a man previously free of apparent life-threatening disease and no autopsy was done. Neither of these criteria were sufficient to assure that death was due to atherosclerosis. The criterion of "severe atherosclerosis" does not necessarily

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[a] In their May 1969 article Dayton and Pearce indicated that the experimental group had the highest number of total deaths.[2541]

mean complete occlusion and both the first and second criteria could describe a death due to other causes, e.g., coronary artery spasms independent of significant atherosclerosis. Note particularly that the second criterion includes "a man previously free of apparent life-threatening disease" which obviously implies free of severe atherosclerosis as well as severe cancer, etc.

Dayton and Pearce[2541] reported that there were a total of 70 deaths due to all "acute atherosclerotic events" in the control group and 48 in the treated group. These events included acute MI, sudden death due to CHD, cerebral infarct, amputation for gangrene, ruptured aneurysm and miscellaneous. Not only were 73% and 88% of these events, respectively, acute MI and sudden death, discussed above, Dayton and Pearce admitted that "in ten of the control and in nine of the experimental cases, the atherosclerotic complication appeared to be a partial cause of death." Unfortunately, they did not indicate which cases those were. It seems clear that death due to "amputation for gangrene" (3 cases in the control group and none in the treated group) was due to the amputation procedure rather than to gangrene. As noted elsewhere in this volume, a similar argument can be directed toward deaths due to the other "atherosclerotic events."

In the last analysis, if the autopsy data could not in the least differentiate between treated and control subjects with respect to the degree and severity of atherosclerosis, only differences observed between the groups, whether they be MIs or athlete's feet, cannot be attributed to differences in atherosclerosis. If one wishes to cling to the notion that reducing blood cholesterol reduces MIs, he cannot employ atherosclerosis as the intermediate step, insofar as the Veteran's trial is concerned.

Although they have made opposite statements elsewhere, Dayton and Pearce[2541] presented a more honest appraisal of their study in 1969, i.e., "It is is our opinion that the encouraging results of our own trial, even when buttressed by concordant observations in two other primary prevention studies, are not sufficient grounds for aggressive efforts to change the U.S. diet."

The WHO Cooperative Trial

The WHO Cooperative trial which used clofibrate as the cholesterol-lowering agent generated some of the strongest evidence against the lipid hypothesis. However, it has sometimes been "reviewed" as providing supportive evidence. For example, in his 1989 review Stanford's Superko[2335] concluded that "these results are intriguing and suggest that prevention of coronary events by cholesterol reduction can increase life expectancy." And although Gotto[2527] acknowledged in 1988 that the clofibrate group suffered "an overall increase in mortality" he maintained that "the trial's initial hypothesis--that the reduction of plasma cholesterol would reduce CHD incidence--was confirmed. A 9% decrease in cholesterol was linked with a 20% decrease in nonfatal MI." It is because of these flagrantly bad interpretations of the WHO trial that the study is discussed here in more detail.

The WHO investigation was the largest cholesterol-lowering trial conducted, being composed of three groups having a total of 15,744 subjects.[3001] The experimental group consisted of men with high cholesterol levels who received the clofibrate drug. A control group of high cholesterol men received a clofibrate-like capsule which contained olive oil. A second control group of men with low cholesterol also consumed the olive oil capsule. Subjects derived from Edinburgh, Budapest and Prague and ranged from 40 to 69 years of age. The trial was double blinded and subjects participated for a mean duration of 5.3 years. However, mortality data continued to be gathered for an additional 4.3 years.

An author of the WHO reports, J.A. Heady, indicated in 1973 that "No toxic effects [of clofibrate] have been reported and the side effects associated with it are quite small--an important consideration not only from the ethical, but also from the design point of view, since side effects can nullify the 'blindness' of a trial."[464] It is emphasized in Chapter 7 that the drug used in the LRC trial, cholestyramine is notoriously objectionable, having many unpleasant side effects.

The mean cholesterol levels of the clofibrate and two control groups at entry were 249,242 and 181 mg, respectively.[461] Cholesterol reduction in the clofibrate group relative to the control groups, ranged from 8.8% to 9.7% during the active part of the trial, slightly greater than that achieved in the LRC trial.

Table 6-3 presents the pertinent results of the WHO trial. Although there were significantly fewer nonfatal myocardial infarctions during the trial, the fatal infarction rate was actually slightly higher. Using relative risk terms, nonfatal infarctions were reduced 25% and fatal infarctions were increased 6%. The absolute percentages, however, were only 0.83% and 0.04%. In effect, the use of clofibrate had essentially no practical benefits whatsoever.

Deaths due to CHD and nonCHD were consistently higher in the clofibrate group than in its comparable control group. The most important criterion of a trial's success is all-cause mortality. Using relative risk terms again, the clofibrate group demonstrated all-cause death increases of 47% and 25%, respectively, for the in-trial period and in-trial plus follow-up period. Of course, the absolute increases were considerably smaller but the point is that cholesterol lowering in this trial most certainly had harmful, not beneficial effects on the health of the participants.

Two additional observations are of interest. First, the difference between the two high cholesterol groups in all-cause deaths diminished during the 4.3 year follow-up. This trend suggests that as cholesterol levels increased in the experimental group, the all-cause death rate decreased. Second, the mortality rate differences between the two control groups for the in-trial and trial plus follow-up periods were 0.06% and 0.18%, respectively. Yet, the mean difference between the groups in cholesterol level was a huge 66 mg. This represents a mere 0.027% reduction in CHD deaths per 10 mg reduction in blood cholesterol. Looking at it in terms of Rifkind's "formula," for every 1% decrease in blood cholesterol level, there was a 2.5% reduction in CHD deaths. But in absolute and practical terms, for every 1% decrease in blood cholesterol level, there was an infinitely trivial 0.0067% reduction in CHD death rate.

In sum, the WHO cooperative demonstrated no real or practical advantages of low cholesterol on CHD mortality, either via cholesterol lowering or naturally occurring differences. It is impossible for objective scientists to conclude that this trial provided evidence supporting the lipid hypothesis or lipid lowering.

THE POSCH SECONDARY TRIAL

Sponsored by NHLBI, the Program on the Surgical Control of the Hyperlipidemias (POSCH), reported in 1990, was a trial which determined the cholesterol-lowering effects of partial ileal bypass surgery on subsequent mortality and morbidity.[3058] Although the 24 authors of this study, led by Henry Buchwald, concluded that "Partial ileal bypass produces sustained improvement in the blood lipid patterns of patients who have had a myocardial infarction and reduces their subsequent morbidity due to coronary heart disease," this study yielded unimpressive results and was also scientifically flawed in many ways, as will be seen.

Some 838 patients were said to be randomized to a surgical (n = 421) and a control (n = 417) group. However, in view of the fact that randomization was "within 18 strata based on the total plasma cholesterol level, the lipoprotein phenotype, and the

Table 6-3

Nonfatal myocardial infarction and deaths per 1,000 per year from various causes (adapted from the Committee of Principal Investigators, 1978,[461] 1980[1661])

		Control Groups	
Myocardial Infarctions	Clofibrate	High Chol.	Low Chol.
Nonfatal MI	4.6[a]	6.2	1.7
Fatal MI	1.3	1.2	0.6
Total	5.9[a]	7.4	2.3
Deaths in Trial			
CHD	1.3	1.2	0.6
NonCHD	4.2	2.4	2.9
All-causes	5.7	4.0	3.7
Deaths in 9.6 Years			
CHD	3.2	2.9	1.1
Stroke	0.6	0.4	0.3
Cancer	2.6	2.1	2.0
Accidents/Violence	0.6	0.6	0.5
All nonCHD	4.9	3.7	3.7
All-causes	8.1	6.6	4.8

[a] Significantly lower than high cholesterol control group.

extent of coronary artery disease determined arteriographically," it is clear that "matching" was as predominant as randomization in the construction of the two groups. Therefore, the study could at best be described as partially randomized and this fact is of no little importance, i.e., it is likely to have created systematic errors. For example, one of the strata was "extent of coronary artery disease as determined arteriographically." As was discussed in Volume 1 (and later in this Chapter) determining the extent of atherosclerosis angiographically is fraught with problems and heavily dependent on subjective judgments. While pure randomization tends to ensure equality, matching the groups on the basis of judgments tends to introduce inequalities. This writer has no faith, therefore, that the control and surgical groups were adequately randomized.

Incredibly, Buchwald et al. stated that "All analyses are based on randomization assignment (intention-to-treat), whether or not the treatment was actually carried out." They went on to say that "Of the 421 patients assigned to surgery, 22 refused to undergo the operation but were nonetheless included in the surgery group for purposes of statistical assessment." In effect, 5.2% of their treatment group did not receive treatment but they nevertheless included it as though it were treated. This was an absolutely astonishing procedure that defies the very foundations of scientific principles. The only conceivable reasons for including these subjects would be (1) to artificially inflate group size, and/or (2) to include data in the treatment group that are favorable to the lipid hypothesis (see below).

Buchwald et al. indicated that another 5.5% of the treatment group underwent reversal of the ileal bypass surgery between 2 and 11 years after the initial operation because of serious complications. Thus, the actual size of the treated group over the 10 year follow-up period was about 7% smaller than that used in the statistical analyses. Conversely, the investigators included about 29 persons in the treated group that were either not treated or only "temporarily" treated. It is interesting, in this regard, that in their review of other clinical trials they cautioned that "The recent reports of observations made after the period of a clinical trial [cited the 15 year follow-up of the Coronary Drug Project and the 10 year follow-up of the MRFIT] must be viewed with circumspection." Certainly, one must question the results of a treatment group in which a substantial percentage were not treated.

Some 9.3% of the total number of subjects were women. While it seems probable that they were distributed equally to the control and treatment groups, no discussion of their distribution was presented by Buchwald et al. In fact, there was no differentiation at all between the sexes in their report, a most surprising omission in view of the fact that mortality and morbidity is typically much higher among men than women.[a]

Over the course of the 10-year follow-up control subjects increasingly used cholesterol-lowering drugs until 31.5% were using them by year 10. In contrast, only 3.7% of the treated subjects used such drugs at that point. This differential "treatment" produced one baffling outcome and one unknown but certainly confounding event. With regard to the former, the mean cholesterol level of the control group at baseline was 250 mg and 240 mg at 10 years, the point of maximum use of cholesterol-lowering drugs. The difference between 250 and 240 mg is exceedingly small and not reflective of the fact that nearly a third of the subjects were taking "at least one cholesterol-lowering medication."

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[a] Elsewhere, it was indicated that cholesterol reductions in men and women were almost identical.[1724]

With respect to the confounding event, as noted in Volume 1 and Chapter 8 of this volume, cholesterol-lowering drugs have side effects, some of which can be quite serious. As will be seen below, the treatment group suffered significantly more nonCHD morbid events than controls and the difference was probably an underestimate because the cholesterol-lowering drugs in the control group undoubtedly contributed some morbidity. In particular, the ileal bypass operations and cholesterol-lowering drugs typically increase the frequency of gallstones and the need for associated surgery. In effect, the "control" group seemed not to enjoy the so-called benefits of the drugs, i.e., cholesterol-lowering and reduced CHD events, but probably suffered their side effects.

Another factor which operated against the equality of the two groups, discussed below in another context, is the fact that more control subjects were found to have gallstones at baseline than treatment subjects (131 vs 101). This would be an unlikely occurrence had proper randomization been accomplished.

Thus far we have a treatment group, about 15% of which were effectively control subjects and a control group, about 7% of which were effectively treated subjects (within the first 5 years). Although this might seem to bias the trial against finding differences in CHD events, the outcome may very well have been the opposite. Again, the question must be asked--why would untreated subjects be included in a treatment group? In any event, all of the foregoing indicates that the treatment and control groups were badly flawed by improper randomization and analysis, and the uncontrolled factor of taking cholesterol-lowering drugs.

According to Buchwald et al., "The primary endpoint of the trial was death due to any cause. A secondary endpoint was cause-specific death. Other secondary endpoints were recurrent myocardial infarctions, whether confirmed or suspected..." and other "soft" endpoints such as angina. Their results showed no significant differences between groups in either total deaths or CHD deaths. Therefore, the trial failed to demonstrate significant benefits of cholesterol-lowering with respect to their primary and principal secondary endpoints. And since no independent analysis of their third endpoint was performed, nonfatal myocardial infarction, it has to be assumed that it also did not significantly differentiate between the treatment and control groups.

Like the LRC authors, Buchwald et al. then combined the fatal and nonfatal MI's and reported that the treated group had significantly fewer such events than did the control group, i.e., 30% vs 19.5% over a mean follow-up period of 9.7 years. Assuming a "clean," unconfounded and properly randomized trial, this study demonstrated that reducing blood cholesterol via a major operation by about 50 mg resulted in the reduction in total deaths of only (14.9% - 11.6% ÷ 9.7 years =) 0.34% per year and in CHD "events" (30% - 19.5% ÷ 9.7 years =) 1.1% per year. The reader should recall and acknowledge that this was not a clean, unconfounded and properly randomized trial. But even taking the results as is, the reductions in mortality and CHD "events" are remarkably small "benefits," for the enormous financial, health and psychological costs paid by the treated subjects. Let us now examine the health costs.

Before discussing the side effects of the ileal bypass operation it is important to note two subtleties in the reporting of results by Buchwald et al. While fatal and nonfatal endpoint events were discussed in terms of the entire 9.7 years, the side effects were presented in terms of annual rates. This procedure had the psychological effect of making the differences in endpoints look large and making the differences in side effects look small--all consistent with the need to support the lipid hypothesis and belittle the associated side effects of lowering cholesterol. A second subtlety is that the discussion of side effects by Buchwald et al. gives the impression that side effects were assessed for only the first 5 or 6 years of follow-up, begging the question--why not the full 9.7 years? It simply is not clear whether the analyses included the total follow-up period or just 5 or 6 years.

Buchwald et al. indicated that the "principal side effect of the ileal bypass operation was diarrhea." The surgery patients reported "more than 3 bowel movements per day, whereas the control-group patients had fewer than 1.5 movements per day. ("More than" and "fewer than" are also curious ways of reporting quantitative data.) Chronic diarrhea is, of course, unpleasant, unhealthy and not without financial costs associated with visits to physicians and medications. The investigators said, "During the first five years of follow-up, 6 to 8 percent of the surgery group had watery or frothy stools, as compared with 0 to 1 percent of the control group."

While diarrhea may have been the principal side effect in terms of frequency, it most certainly was one of the least important side effects observed. For example, the rate of kidney stones per year was 4% in the treatment group and only 0.7% in the control group (38.8% vs 6.8% for the 9.7 year trial), a significant difference. In addition, it was noted earlier that more control subjects than treatment subjects had gallstones at baseline. "Of the 286 control-group patients and 320 surgery-group patients whose gallbladder was found to be free of gallstones at baseline or immediately after partial ileal bypass surgery, 4 control-group patients and 14 surgery-group patients underwent cholecystectomy during the first five years of follow-up and an additional 10 control-group patients and 40 surgery-group patients had gallstones that were detected by oral cholecystography or ultrasonography. The difference between the groups in the five year rate of gallstone formation was significant." But what of the incidence of gallstones and cholecystectomies during the entire 9.7 years?

Buchwald et al. indicated that 57 treatment patients had bowel obstructions and 15 required surgical repair. Since no data were given for control subjects, apparently only the treatment group suffered bowel obstructions.

Of the total 421 treatment subjects (but in reality only 399 who actually had the ileal bypass), 23 required a reversal of the procedure, 10 (more than controls) required cholecystectomies (within the first five years) and 15 required surgery for bowel obstructions. Thus, the ileal bypass procedure required that (48 ÷ 399 =) 12% of the group subsequently undergo major surgery.

Buchwald et al. indicated that "Coronary-artery bypass grafting was performed in 137 control-group patients and 52 surgery-group patients," suggesting that atherosclerosis progressed more rapidly in the control group or that atherosclerosis was a greater problem in that group at baseline. Each of these possibilities is equally plausible. Probably more plausible is the possibility that more control subjects chose to undergo bypass grafting. It must be recognized that bypass operations are elective surgeries and alternatives to medical treatment or no treatment at all. In view of the fact that the treatment greatly lowered blood cholesterol, it is likely that treatment subjects were more confident that they were pursing a preventive approach than were control subjects. Thus, this likelihood alone could easily account for the difference between groups in electing to have bypass grafts. In any event, the incidence of such operations is not a measure of the effectiveness of the cholesterol-lowering.

Finally, pre- and post-operative angiographs were made of all patients in the study as another means of assessing the benefits of cholesterol-lowering. Nearly all of the changes that were observed by subjective judgments were associated with the degree of progression. The "scores" for regression indicated that slightly more regression occurred in the treatment group than in the control group. This rather unimpressive difference was viewed by Buchwald et al. as follows" "This apparent regression, however, may represent random variation in the arteriographic evaluation."

The investigators concluded that "Partial ileal bypass was chosen as the intervention in this study because of its powerful capability in lowering lipid levels and its acceptable morbidity." It is mindboggling how Buchwald et al. could draw such a

conclusion. The absolute "benefits" of treatment were unimpressive and they were obtained at a very high cost, i.e., at least 447 major surgeries and numerous chronic ailments and suffering associated with diarrhea, kidney stones, gallstones, etc. Interestingly, the investigators indicated that "the precise role of this intervention in the treatment of hypercholesterolemia remains uncertain." (Chapter 8 addresses this issue more specifically.)

Buchwald[3060] was far more exuberant in his subsequent interaction with the Associated Press. He said his study "offers the strongest justification for marked lipid intervention that has ever been offered" and "is a very powerful study and should, except for certain people who will never be satisfied, end the cholesterol controversy." He continued, "It is eminently logical to extend all cholesterol-lowering therapy, including this, to patients with high cholesterol who have not had a heart attack." One can only wonder what a boon this would be to surgeons in this country in which about 60% of the population has "high cholesterol," according to the alliance.

WHO Multifactorial Trial

The WHO Multifactorial trial was another example of authors attempting to draw positive conclusions from mostly negative results. This trial involved nearly 50,000 men in 66 factories in the United Kingdom, Belgium, Italy and Poland, half of which were given advice and promotional materials regarding cessation of smoking, weight reduction, cholesterol-lowering (by diet), daily exercise and control of hypertension (by drugs). The remaining half served as controls.

Four-year follow-up data were presented in 1983 by the WHO Collaborative Group.[3328] Overall, fatal and nonfatal CHD and all deaths were said to have decreased 7.4%, 3.9% and 2.7%, respectively, as a result of the interventions. However, as Volume 1 emphasized, positive results tend to emerge exclusively from mainland European countries but not the United Kingdom. This trial was no different. While CHD events and all-cause deaths were reported to have decreased in Belgium, Italy and Poland, they had increased in the United Kingdom. This result alone suggests that diagnostic bias was the reason for the differential results. However, there were other peculiarities that provided little bases for assuming that any of the results were associated with risk factor changes.

Table 6-4 shows the percentage reduction in risk factors and incidence/mortality at each of the four centers. The first thing to note is that the only differences found to be statistically significant were the total CHD incidence and all cause death rates in Belgium, i.e., the intervention presumably reduced incidence 24% and all-cause deaths 17%, relative to controls. These reductions are more than remarkable when it can be seen that risk factors were hardly reduced at all. Based on numerous other studies, there is no way that reductions in blood cholesterol, cigarette smoking and blood pressure by 0.9%, 3.7% and 1.3% could lead to such large reductions in CHD events and all-cause deaths.

The most substantial reduction of a risk factor among the four centers was cigarette smoking at the U.K. center. All other risk factors were also reduced, albeit trivially, and yet CHD incidence and all-cause death rates increased.

In sum, an examination of Table 6-4 reveals that risk factor changes in direction and/or magnitude were not at all consistent with changes in CHD incidence and all-cause death rates. It is highly doubtful that the physicians performing diagnostics in the mainland European centers were blinded. In any event, the data make little scientific sense and do not deserve further discussion.

Table 6-4

Percent reduction in risk factors and in incidence/mortality at each center (adapted from WHO Collaborative Group, 1983[3328])

	U.K.	Belgium	Italy	Poland
		% Change in risk factors		
Cholesterol	-0.4	-0.9	-4.8	-1.0
Cigarettes/day	-15.6	-3.7	-5.5	-5.9
% Smokers	-4.5	-1.7	+2.3	+1.3
Weight	-0.4	+0.2	-1.9	-1.0
Systolic BP	-1.6	-2.3	-4.1	-0.6
		% difference in incidence/mortality[a]		
Fatal CHD	+8	-21	-30	-20
Total CHD	+5	-24[b]	-14	-20
All deaths	+14	-17[b]	-6	-22

[a] Between intervention and control group.

[b] Significant at .05 level.

THE DART STUDY

The Diet and Reinfarction trial (DART)[2297] was a 2-year secondary trial that evaluated the effects of various diets on death and myocardial reinfarction. Some 2,033 men recovered from myocardial infarction were randomized into groups receiving different dietary advice. Half of the subjects were advised to consume at least two weekly portions of fish and the remaining half were given no advice pertaining to fish. Half of each of these two groups were advised to reduce their total fat intake to 30% of total calories and the remaining halves received no such advice. Finally, half of each of these four groups were advised to increase their intake of fiber, while the remaining halves were not so advised. At six months and two years questionnaires were administered to subjects to determine their degree of compliance with the above advice.

Subjects given fat advice were found to have lowered their total fat from 35% to 32% of total calories. Their P/S ratios were nearly twice those of the subjects who received no fat advice. These subjects' cholesterol levels decreased only 2.8% and there were no significant differences in total deaths, CHD deaths or CHD events between the two groups. There also were no significant differences between the groups receiving and not receiving fiber advice, although the former apparently consumed twice the fiber than the latter. However, the authors indicated that the group receiving fish advice had significantly fewer all-cause deaths, significantly fewer CHD deaths, and nonsignificantly fewer CHD events than did the group receiving no fish advice. The rate differences for these endpoints were 3.5%, 3.7% and 2.1%, respectively.

The authors, Burr et al., presented percent surviving curves for the fish and no fish advice groups over the two-year trial. These curves were identical through the first 65 days and then they separated in an accelerated manner, i.e., about 50% of the difference between the two groups in total deaths for the entire two years had already occurred 62 days after the curves separated (4.2 months into the trial) and 90% had occurred by 187 days (8.4 months). Effectively the total difference between the groups had occurred by 10 months into the trial; thereafter the difference between the two groups remained constant.

Burr et al. concluded that "The results suggest that fatty fish (and fish oil)[a] reduces mortality in men after MI, by about 29% [actually, a rate decrease of 3.5%] during the first 2 years. The effect appeared early in the trial, and it may be questioned whether it is likely that a dietary change would act so quickly. At the start of the second world war IHD mortality in Norway fell sharply within a year of a sudden change in the national diet which included a rise in fatty fish intake; mortality rose again within a year of the end of the war, when dietary habits returned to their previous pattern. Fish oils appear to have a favorable effect on clotting mechanisms and blood platelets, and reduce the rate of restenosis in the coronary artery within 3 to 4 months of angioplasty."

Burr et al.'s reference to the Norwegian CHD mortality rates during and after World War II as a basis for explaining the rapid effect of fish on longevity is totally untenable for several reasons. As indicated in Volume 1, most prospective studies have not shown benefits of fish consumption over many years, let alone a few months. For example, Burr et al.'s use of Norway flies in the face of a 10-year Norwegian study[1319] which found that a community consuming nearly three times the amount of fish as another community had a higher CHD mortality rate. Second, it was also

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[a] Some of the subjects in the fish advice group elected to consume fish oil capsules.

noted in Volume 1 that deaths due to other causes, i.e., infectious diseases, war (bombings, combat), etc., increased in the European countries during the war and these deaths naturally reduced the overall CHD mortality rate. Surely,, researchers must recognize that large numbers of military and civilian casualties occur during wartime and must, therefore, depress the CHD mortality rate.

The majority of randomized and blinded studies investigating the effects of fish oil supplements on restenosis have demonstrated little or no benefits (Chapter 6, Volume 1) and these and other studies led the FDA to consider banning the sale of fish oils in 1990. Thus, Burr et al. presented a biased "review" of such studies. The amount of fish consumed by Burr et al.'s "fish advice" subjects was a mere 43 g per day, representing 0.35 g of EPA per day. These amounts could not have much affect on platelet aggregation. Moreover, one 5 grain daily aspirin tablet equals the effect of about 19 g per day of EPA, 54 times the amount consumed by Burr et al.'s subjects, and yet all of the largest aspirin trials have not shown that aspirin reduces the all-cause death rate.

In short, Burr et al.'s results are not believable and can at best be considered inconsistent with the majority of studies. It is also worth noting that the authors found no significant differences between groups on all CHD events but indicated that "We decided at the outset that total mortality would be the primary endpoint and we calculated that 2,000 subjects would be required to detect a 30% reduction in total mortality...at $p < 0.5$." Elsewhere in this volume, alliance members are cited who maintain emphatically that the LRC and Helsinki II trials were not large enough to detect significant differences on total death rates, despite the fact that these trials contained twice the number of subjects than were involved in the Burr et al. trial. We again have an example of post hoc rationalizing and inconsistent logic in explaining study outcomes.

Goldstein[2671] also noted that the small amount of fish consumed in the Burr et al. study "is not enough to cause an antiplatelet effect." Riemersma et al.[2672] also maintained that an antithrombotic effect cannot be used to explain Burr et al.'s results "because nonfatal myocardial infarctions increased in the fish advice group" [49 vs 33].[a]

Skrabanek[3280] touched a nerve. He said, "As the study was about the prevention of myocardial infarction, it is strange that no percentage reduction is mentioned in the summary for this endpoint. The reason? It would not be statistically significant." Burr and Fehily[2674] replied that "Our study was not just 'about the prevention of MI.' The predetermined primary endpoint was all-cause mortality and we see this as the most appropriate endpoint in all such trials." But while it <u>should</u> indeed be the most appropriate endpoint in all CHD clinical trials, the dietary variables were all accepted to be associated, directly or indirectly, with myocardial infarctions and it is strange, therefore, that the primary endpoint was not the reduction in reinfarctions. Burr et al.'s results are presented in such a way that one cannot determine the number of fatal MIs in his groups but we can see that there were more nonfatal MIs in the fish advice group. We must agree with Skrabanek, therefore, that the difference between groups in all MIs was probably small and nonsignificant; the fish advice group may even have suffered the <u>greater</u> number of MIs. Although Burr et al. reported that 78

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[a] Burr et al. argued that their effect was not likely due to a reduction in saturated fat but Hornstra[2623] indicated that it may have been in view of the fact that the P/S ratio doubled in the fish advice group. However, studies of cholesterol-lowering (which is what saturated fat is all about) have at best shown small reductions in CHD events but no significant differences in total or CHD deaths, precisely the opposite to that reported by Burr et al.

CHD deaths occurred in the fish advice group, while 116 occurred in the no advice group, many of these deaths may have been of the sudden death variety and not necessarily MIs. This possibility is supported by the fact that Burr et al. did not respond to this aspect of Skrabanek's criticism.

REVIEWS OF CLINICAL TRIALS

Biased reviews of clinical trials are rampant. For example, Mishkel discussed only the LRC, Helsinki II and Blankenhorn et al. trials and the niacin group of the CDP trial. He simply omitted all other trials.[2336] Garber et al. reported that the LRC, Helsinki II, niacin (CDP), WHO, MRFIT, Veterans and (multiple risk factor) Oslo trials "have shown that cholesterol reduction lowers both the incidence of and mortality from coronary heart disease."[2265] In point of fact, none of those trials revealed significant reductions in CHD deaths and/or all-cause mortalities, and some did not show significant reductions in CHD incidence. Muldoon[2642] emphasized this point in a letter to the editor, i.e., Not a single clinical trial presented by the authors show such an effect. In their defense, Garber et al.[2643] cited Yusuf and Cutler as showing that "pooled analysis of the LRC-CPPT and other primary prevention trials shows that cholesterol-lowering drugs significantly reduce the coronary heart disease death rate as a separate endpoint. In the Wadsworth Veterans Administration primary prevention trial of diet, the reduction in mortality from CHD was statistically significant without pooling." But such a defense is untenable. Yusuf and Cutler's "pooled analysis" does not and cannot alter the fact that not a single trial showed significant reductions in either CHD or total mortalities. Moreover, it is suggested that Garber et al. read the Veterans trial report a little more carefully; they will find their statement to be totally incorrect.

To illustrate how trivial findings are exaggerated by alliance members, Garber et al. stated that there was a "large but insignificant fall in all-cause mortality" in the Oslo Diet/Smoking trial.[2265] Muldoon[2642] noted that the actual difference between the treated and control groups was only 0.8% Garber et al.[2643] replied that it was an "impressive" difference but they chose to use the relative reduction value of 32% rather than the absolute value of 0.8%.

In view of his legitimate criticisms, it is strange that Muldoon et al.[2927] subsequently reviewed six trials and committed similar errors of reasoning. The six trials were selected because they (1) were randomized primary trials, (2) had experimental and control groups, (3) lowered blood cholesterol in the experimental group, and (4) yielded total and cause-specific mortality data. They were the L.A. Veterans trial,[454] the Minnesota Coronary Survey, the WHO Clofibrate trial, the Dorr et al.[843] (Upjohn Company) trial, and the LRC and Helsinki II trials. The Veterans trial included many men who had had myocardial infarctions or showed other evidence of CHD at entry so it was by no means a pure primary trial. And while the Dorr et al. trial appeared to fulfill all of Muldoon et al.'s criteria, it must be considered questionable because it is the only study of a long line of trials which showed that treatment reduced total mortality as well as CHD mortality and was funded and conducted by the Upjohn Company, to say the least, a highly vested interest group. In pooling the four drug trials and the two diet trials separately, Muldoon concluded that "pharmacologic treatment, but not diet, lowered mortality from coronary heart disease significantly" [$p < 0.04$, one-tailed]. Not only would this conclusion be reversed if an appropriate two-tailed test had been used, it was also entirely dependent on the dubious Dorr et al. study which accounted for nearly 50% of the difference between the four treatment and control groups.

Although Muldoon[2642] had previously criticized Garber et al. for using relative reduction between treatment and control groups, Muldoon et al. reported that "The

observed 15% [relative] reduction in deaths from coronary heart disease [in the six trials] is clinically significant." The absolute reduction was only 0.23%. The authors did emphasize, however, that treatment in the six trials did not influence total mortality.

The so-called "Expert Panel" of the National Cholesterol Education Program stated in 1988 that "The issue of whether lowering LDL-cholesterol levels by dietary and drug interventions can reduce the incidence of CHD has been addressed in more than a dozen randomized clinical trials."[1094] However, the Panel devoted four sentences to only three of the trials, i.e., the LRC[500] and Blankenhorn trials[760] and the niacin group in the CDP trial.[1374]

A 1989 review by Superko was particularly peculiar.[2335] He first discussed the WHO and CDP trials and concluded that "these results are intriguing and suggest that prevention of coronary events by cholesterol reduction can increase life expectancy." Of course, life expectancy was not increased in the WHO trial or in all five groups of the CDP trial. The fact that the niacin group of the CDP showed a significantly lower all-cause mortality 9 years after the trial was terminated cannot supercede all of the negative results from both trials.

Superko then "reviewed" the LRC and Helsinki II trials and concluded that cholesterol-lowering reduces CHD "events" but omitted the fact that life expectancies were unaltered. He also misleadingly reported that "no significant adverse medical effects were detected with the long-term use of the bile-binding resin" in the LRC trial.

It is interesting that in 1975, when the CDP was recognized by the alliance to have failed to show benefits of cholesterol lowering, former NHLBI director, Theodore Cooper, was asked, "Could a reasonable scientist, a reasonable practitioner extrapolate from the results of secondary prevention to primary prevention?"[2688] Cooper replied, "A reasonable scientist would not." Now that one of the CDP groups shows significant effects, despite no treatment for 15 years, it is now apparently reasonable to extrapolate those results--but, of course, not the negative results from the other CDP groups.

In 1989 Rifkind said, "Although many...trials have been conducted, often with encouraging results, it is only recently that conclusive data have become available. Several clinical trials have been reported and provide impressive evidence that cholesterol lowering is beneficial in a variety of contexts."[2032] He cited the LRC and Helsinki II trials but did not mention that they showed no improvement in life expectancy whatsoever. On the other hand, he cited the CDP niacin group as showing greater life expectancy but ignored the results of the other CDP groups. Rifkind also cited the MRFIT screened cohort but said nothing of the MRFIT trial itself which, of course, was a failure.

In 1983 Stamler[3036] published a review article entitled, "Pharmacological Trials: Primary and Secondary Prevention of Coronary Heart Disease." Of the many drug-induced blood cholesterol-lowering trials that had been conducted, Stamler discussed only the European WHO primary trial[3001] which used clofibrate and the U.S. Coronary Drug Project Secondary trial[490] which employed several types of drugs. He omitted a European primary trial[461] and five European[a] and two American[843,1125] secondary trials. In his abstract Stamler referred to his article as a "brief review." Indeed it

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[a] 462,463,496,497,840

was. He did not even mention his own secondary prevention trial in which estrogens were used. Although he considered his estrogen study successful in 1963,[1125] he would probably hope that no one would remember that the trial was ever performed.

In 1984 Castelli[2955] stated that "Although many people say they are unimpressed by the results of such trials, in every single trial there was a decrease in the subsequent rates of coronary heart disease that was proportional to the decrease in total cholesterol; with as low as a 1% fall in cholesterol, there was a fall of 2 to 3% in the subsequent rates of coronary heart disease." The very fact that his statement is utterly absurd warrants its inclusion in this section. For starters, the cholesterol reductions in the LRC,[500] Helsinki II[1056] and WHO clofibrate trials were 8.5%, 8.5% and about 9.3%, respectively. The CHD "event" rate decreases in these studies were 1.7%, 1.4% and 0.53%, respectively. So much for Castelli's knowledge of rates and/or mathematics.

Another example of biased and improper reviews was published by Barbara Dwyer in Cardio magazine.[2264] For example, she stated that "numerous primary prevention trials leave no doubt that lipid control hinders development of CHD." She listed 8 references in support of that statement. Three of the references were articles on the same LRC trial. A fourth reference was a Framingham study article and was not, therefore, a clinical trial at all. A fifth reference was the MRFIT trial which failed to show a relation between CHD and cholesterol reduction. A sixth reference was the 6-year follow-up of the cohort screened for the MRFIT trial and also was not, therefore, a clinical trial at all. A seventh reference was a discussion by Robert Levy, not a trial. The eighth reference was the Helsinki II trial. Thus, Dwyer's "numerous" trials involved three trials within 8 references and one was a complete failure and two showed no benefits of lipid lowering on overall mortality.

In "reviewing" secondary prevention trials, Dwyer cited the 15 year follow-up of the niacin group of the Coronary Drug Project (CDP) which was a prospective follow-up, not a trial. Dwyer failed to note that the CDP itself was a total failure. Dwyer also cited the Stockholm Ischemic Heart Disease Secondary Prevention study, even though that trial was unblinded. Finally, she cited as evidence the pharmaceutical company financed Blankenhorn et al. trial.

Curiously, Dwyer listed 9 articles in her references (30 to 38) which were never cited in her article. Eight of these articles described unsuccessful diet and drug trials.[a]

Gotto's position is quite representative of that of the alliance, i.e., "Clinical trials provide strong evidence for the lipid hypothesis."[1341] Others thoroughly disagree (Oliver;[1734] Lancet editorial[1810]). In 1988 McCormick and Skrabanek reviewed a number of clinical trials in Lancet and concluded that there is "no experimental evidence to support the notion that intervention programs prevent coronary heart disease or reduce overall mortality."[1597] Subsequently, four letters were published in Lancet that were highly critical of McCormick and Skrabanek's review. One was written by Geoffrey Rose who accused those authors of "distortion" and "selective review."[2096] Such terms are particularly interesting because they are most descriptive of the alliance's behavior. Rose claimed there was a 7.4% reduction in CHD deaths in the WHO trial treated group, employing the LRC and Helsinki II authors' method of determining differences. McCormick and Skrabanek correctly replied that the proper

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[a] Chapter 9 also discusses the 1989 National Research Council's "review of clinical trials."

statistic was the rate difference, which was only 0.1% in the WHO trial.[1713] They also pointed out that the total mortality rate difference was zero, a fact ignored in Rose's letter.

A second letter was written by M.P.H. Doublet Stewart who accused McCormick and Skrabanek of "selecting" the evidence to be reviewed and "falsifying" it.[2096] He argued that the LRC, Helsinki II and WHO trials showed significant reductions in CHD events, that the niacin treated group in the Coronary Drug Project (CDP) showed a significantly lower all-cause mortality and that the Blankenhorn et al. study proved that cholesterol-lowering causes regression in lesions. In so doing, Doublet Stewart himself ignored a large number of unsuccessful trials, not to mention the fact that the above trials left much to be desired in terms of beneficial results and conclusions. With regard to the latter, why is it that Doublet Stewart claims success for one group in the CDP 9 years after treatment was ceased and ignores four other groups which showed no beneficial effects of cholesterol-lowering?

A third letter was written by Christopher Birt who, interestingly, defended perhaps the most confounded and ill-designed "trial" of all, the North Karelia Project, and apparently had no other criticisms of McCormick and Skrabanek's review.[2097] As indicated in Volume 1, the North Karelia Project was so badly designed and the data were so poorly analyzed, it should not be necessary to discuss it in any detail. Incredibly, Birt noted that one of the North Karelia Project's investigators, Salonen, subsequently published a statement absolving himself of statements made about the success of the Project. Birt merely used the term "noteworthy" to describe Salonen's statement that "In my judgment the data do not justify the conclusion that the program caused the decline in CHD."[834]

The fourth letter was written by Peter Croft and, insofar as this writer can determine, appeared only to criticize McCormick and Skrabanek for demanding "proof of causality."[2098] This writer would be curious to know how Croft would feel about the importance of "proof" in a court of law in which he is wrongly accused by Scotland Yard of being a murderer.

In 1989 Gunning-Schepers et al. more or less acknowledged that McCormick and Skrabanek were correct but nevertheless argued that intervention programs are useful because some people will receive benefits and none will be harmed.[1812] Their philosophy was based on the alliance's "group risk" concept (Chapter 3). As an analogy, Gunning-Schepers et al. said that "The fact that only a small proportion of those exposed will actually get poliomyelitis has never been an argument to deny a generation the benefits of vaccination." As far back as 1956 Katz, Stamler and Pick presented the same argument, i.e., although only a relatively small percentage of people may be affected by diet and cholesterol level, they recommended dietary and hygienic changes for everyone "which can do no harm."[1884] While appearing relevant, these arguments are not at all appropriate. First, the exact cause and prevention of poliomyelitis are precisely known, while the cause and prevention of atherosclerosis are clearly not known. Second, numerous tests have shown that, with the exception of a very small percentage of people, vaccinations for poliomyelitis are harmless, while numerous trials have yielded considerable evidence of harm and unpleasant side effects associated with cholesterol-lowering drugs and certain diets (Chapter 8 in this and Volume 1). Third, one or two painless vaccinations can hardly be compared to a lifetime of undesirable foods or drugs, both of which--particularly drugs--will cost Americans billions of dollars. And fourth, a major recommended dietary change has already proven to be a serious mistake (e.g., high intakes of polyunsaturated fats) and another may soon be so classified (e.g., high carbohydrate intakes lower HDL), and with all the clinical experiences with cholesterol-lowering drugs, it can hardly be said that they "can do no harm."

As noted in Volume 1, the only U.S./British clinical trial which showed a significant reduction in CHD deaths was the Dorr et al. study.[843] It was funded by the Upjohn Pharmaceutical company and it used the drug, colestipol, manufactured by Upjohn. Moreover, the only U.S./British trial which presumably showed a deceleration in growth or a regression of atherosclerosis was the Blankenhorn et al. study.[760] It was also funded by the Upjohn company and it also used colestipol. The NHLBI/AHA alliance would probably say that these associations were merely coincidental. The alliance would probably say also that it is merely coincidence that the chairman of Upjohn is Theodore Cooper the former director of NHLBI who ruled out the conduction of a large diet trial and instead launched the LRC drug trial which, in turn, launched the NCEP and a growing demand for cholesterol-lowering drugs.

Virtually no one denies the fact that the great bulk of evidence indicates that cholesterol-lowering does not reduce total mortality rates. The only apparent justification for the enormous financial and health costs involved in a nationwide intervention program, as noted in Chapter 2, is the huge financial gains to be made by the medical, pharmaceutical and certain food industries.

ANGIOGRAPHIC CLINICAL TRIALS

As of this writing, the result of three new angiographic trials and a four-year follow-up of the Blankenhorn et al.[760] study were published in 1989 and 1990. Like nearly every angiograph study published earlier, authors of these trials reported an abundance of positive results, typically much greater than observed in conventional clinical trials. Prior to reviewing these studies, it is important to consider three serious problems which render all of them suspect.

Qualifiers

While one would like to believe that all scientists are competent, honest and objective, we all know that they are not. A large number of medical researchers are not academically trained in the scientific methods, analyses and the presentations of logical discussions. Equally important, there may well be more conflicts of interest among medical researchers than among researchers of all other sciences combined. The reason is that there are extremely rich pharmaceutical industries which, one way or another, continuously give money to researchers involved in the evaluation of their drugs. As noted in Chapter 9, most of this money is in addition to grants from other agencies such as the AHA or NHLBI. These conflicts of interest are so pervasive in medical research that it is astounding that anyone can take the results of most of that research seriously, particularly as it almost always "proves" the great efficacy of each and every drug evaluated. It will be recalled from a previous section that of the 27 conventional clinical trials on cholesterol-lowering, only one reported that treatment reduced both CHD and all-cause death rates. That trial, authored by Dorr et al.[843] and presumably randomized and blinded, was funded and conducted by the Upjohn Company, makers of the drug used in the study.

In a related study, Schulman et al.[3321] supposedly evaluated the cost-effectiveness of various cholesterol-lowering drugs (lovastatin, niacin, cholestyramine, colestipol, gemfibrozil and probucol). Of 115 studies using these drugs, Schulman et al. chose 58 which "met the criteria" for the study. They concluded that niacin and lovastatin were more efficient than the remaining drugs. While one might wish to consider it coincidental that the study was funded by Merck and Company, the maker of lovastatin and, of course, niacin (since all pharmaceutical companies manufacture this vitamin), it would indeed be naive to do so.

Money influences researchers and it is naive to blindly accept the results of any study in which there is a financial arrangement between a drug company and the

researcher(s). Both the original Blankenhorn et al.[760] study and its four-year follow-on study[3085] were supported by the Upjohn Company, makers of the drug evaluated. Kane[3086] and two of his co-authors received funds from Merck, Sharp and Dohme and Upjohn, makers of the drugs evaluated in their angiographic trial. Brown et al. indicated no arrangements with drug companies (although this does not mean there were none) but their angiograms also did not reveal impressive effects of rather massive cholesterol-lowering. The Ornish trial,[3421] although composed of extremely few subjects and appeared to have a low overhead, was indicated to have more than 17 financial supporters, including the Quaker Oats Company, a company with vested interests.

This writer cannot accept as scientific evidence the results of any study in which the researchers received pay, honoraria, "consultation" fees, travel/hotel expenses, etc., etc.[a] This writer also questions the integrity of prominent NIH members who seemingly go out of their way to praise cholesterol-lowering drugs, and then eventually become highly paid staff members of the drug industries which make these drugs.[b] This volume, particularly Chapter 10, provides ample evidence that alliance members have frequently and purposely misled readers and often fabricated "facts." It is doubly important, therefore, to question studies in which conflicts of interest are clearly in evidence.

A second major problem is that while the angiographic study authors consider their results "conclusive" and rarely, if ever, suggest that their assessments of stenosis are anything but precise, other researchers knowledgeable of angiograms severely criticize their use on the grounds that they are read with considerable judgment inaccuracies. For example, in 1990 Loscalzo[2981] presented a rather penetrating critique of even quantitative (computerized) angiogram assessments, i.e., angiography "has serious shortcomings. Radiocontrast agents define only the luminal outline of a vessel. Since the percent change in the diameter of the lumen depends critically on the adjacent segment chosen as a "normal" reference, the absolute luminal diameter cannot be measured with confidence because the 'normal' reference segment may be atherosclerotic as well. Smooth and concentric involvement of this segment with atherosclerosis may artificially decrease the estimated narrowing produced by the eccentrically involved narrowed segment under consideration. With long-awaited improvements in methods such as utrasonography, computed tomography, and especially vascular magnetic resonance imaging, precise identification of the true lumen, the normal vessel wall, and the true wall of the atheromatous vessel segment will be possible.

"Many other factors besides the architecture of a static lesion contribute to the clinical importance of a coronary lesion. Very early in atherogenesis, dysfunction of the endothelium may lead to paradoxical vasoconstruction in response to vasodilative simuli, and in more advanced lesions such adverse alterations in vasomoter tone may also affect the appearance of the lesion and the resulting interpretation of its clinical importance. Abnormal vasoconstruction cannot be distinguished readily without the routine administration during angiography of direct vasorelaxants of coronary smooth muscle that act independently of the endothelium (such as organic nitrates); and as

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[a] As will be noted in Chapter 9, NEJM's Arnold Relman indicated that "Everybody's doing it."

[b] As will be seen in Chapter 9 and well-known to many, many medical researchers, these "services" often amount to essentially nothing whatsoever and are merely fancy names for "I'll scratch your back, if you scratch my back."

shown in forearm vasculative responses in patients with elevated LDL cholesterol levels, every direct vasorelaxation may be impaired in some persons."

"Another important issue is the discordance between the type of lesion most likely to regress during lipid-lowering therapy and the type of lesion most likely to produce acute coronary syndromes. In the study by Brown and colleagues,[3087] the greatest degree of regression was noted in the lesions that were initially the most stenotic. Ambrose and colleagues[3003] [and Little[3153]], however, have shown that these very stenotic lesions are not the ones most likely to produce an acute coronary syndrome; lesions of much less severity (mean stenosis, 34 percent) are more commonly found to be the culprits in patients with acute Q-wave myocardial infarction. Thus, the benefits of lowering lipid levels to the clinical outcome in these patients may not be related solely to the direct regression of lesions, but rather to improvements in vascular function. Furthermore, considering the length of time required for marked regression of atherosclerotic lesions to occur, the clinical benefits of lipid-lowering therapy in the comparatively short study of Brown and colleagues cannot simply be the result of a direct reduction in the size of lesions likely to produce acute coronary syndromes."

An excellent critique of the angiographic assessment technique was recently presented by Stehbens.[3316] He said, in part, "Angiography has inherent potential sources of error, being a crude mode of assessment revealing only the lumen silhouette and little information about the wall. It does not demonstrate the degree of intimal thickening, medial atrophy or mural ectasia. Gross alterations in the silhouette in short term studies are usually caused by spasm, thromboembolism, thrombolysis, ulceration or repair, but do not reveal the nature of the lesion." Stehbens stressed that "It is difficult to comprehend [how] significant regression of the profound architectural and degenerative changes of advanced atherosclerosis could ensue. When arterial trauma and bacterial aneurysms undergo healing, remnants of pre-existing tissue can be recognized within the fibrous scar tissue and neo-intima but no architectural regression occurs." This is a most important point. Clinical trials using subjects with familial hypercholesterolemia may show regression via "lipid resorption and dissolution of foam cells analogous to regression in cholesterol-fed rabbits" but this is a regression of the overlaying lipid storage problem, not the underlying atherosclerotic disease.

Petch[3078] stated that "The information [from angiograms] has to be interpreted with caution for several reasons, including procedural differences among studies; observer error; the pitfalls of coronary arteriography and its occasional lack of correlation with necropsy findings; the uncertain part played by coronary vasospasm; and, most important, the bias introduced by studying a selected population."

Robert Vogel[1859] presented a short but scathing attack in 1989 on the use of angiograms as means of measuring stenosis. He said, "The popular practice of estimating the degree of coronary artery stenosis by subjective visual assessments of a patient's angiogram has no place in modern interventional cardiology and should be crossed off the list." He went on to say that "we're putting numbers on that are just plain incorrect."

How is it that lipid hypothesis promoters see angiograms as precise means of assessing stenosis, while others see them as imprecise? How can there be such divergent opinions on such a relatively simple issue, especially when studies clearly show that angiogram assessments are unreliable?[3157] If we dig into this matter, we will find that lipid hypothesis promoters were more cognizant of the shortcomings of angiograms in other contexts. For example, while NHLBI director Levy[288] and others were convincing the 1977 Senate Select Committee on Nutrition and Human Needs that a low-fat, low-cholesterol diet would probably solve the CHD problem in the U.S., he

was asked for his opinion of the Pritikin diet which had received much attention nationwide. Perhaps because the Pritikin diet was viewed as "competition" for the alliance's Prudent diet, Levy presented a relatively severe critique of Pritikin's use of angiograms as means of assessing his diet's effects on atheromas. He said, "Interpretation of regression of atherosclerotic plaques by angiography has proven in many studies to be very difficult because of precise requirements of standardization of the technique as well as in quantifying the lesions. It is particularly difficult to obtain exactly the same view of the specific lesions in the coronary arteries on repeat films and this carries over to the identification of lesions found in the coronary arteries on autopsy." He continued, "While the drastic dietary program would be likely to lower plasma cholesterol, it would not be possible to accept the evidence [angiograms] as proof of reversal of atherosclerotic lesions."

An interesting critique of angiographic assessment of atherosclerotic change over time was presented by Blankenhorn and Sanmarco,[1979] before they undertook their own angiographic study which was published in 1987. The critique is interesting because after describing a series of serious problems of angiography, they effectively dismissed those problems in their praise of a previous study which suffered from those problems. Blankenhorn and Sanmarco correctly indicated that high dropout rates of angiographic studies bias results and make it difficult to know what the real effects of cholesterol reduction are on the average or individual patient. They noted that in the study by Kuo et al.[857] 60% of the subjects were dropouts.

They correctly pointed out that the same (not advanced) x-ray equipment should be used on pre- and post-treatment examinations. Otherwise, differences in film quality can bias assessments. In the Kuo et al. study, more advanced equipment was used in their second examination of patients.

Blankenhorn and Sanmarco emphasized the importance of angular accuracy on repeat angiograms, i.e, the angle must be matched as closely as possible on the two angiograms. It is not possible to position patients so that all views are identical, but the matching must be close. They pointed out that there were "sufficient differences in position [in the Kuo et al. study] that determination of lesion change is risky..."

Blankenhorn and Sanmarco indicated that "Films must be read systematically and all lesions evaluated rather than directing attention to 'significant' lesions. Angiographers tend to disregard lesions which do not appear to affect blood flow, and changes in these lesions may be overlooked. ...Kuo's paper shows what may be increasing plaque size in the main marginal branch of the circumflex coronary artery; or it could be vessel rotation so that plaque originally in front has moved to a more lateral position on the second examination. It is not possible to decide between these alternatives without considering all available views in the cineangiogram."

Despite the above criticisms of the Kuo et al. study, all of which render the results of that study highly suspect, Blankenhorn and Sanmarco concluded in their final paragraph that "The films presented by Kuo and co-workers are encouraging examples of apparently stable vessels over 3-4 years. We are impressed by these findings. We do not wish to have our comments on technical details of angiography detract from the importance of this pioneering effort." Indeed, their conclusion sounded very much like—"Don't let facts interfere with your thinking."

In addition to discussing other problems with angiography, angiograms and their interpretation, Blankenhorn and Sanmarco indicated that "Accuracy of coronary angiography must be evaluated by comparing films with postmortem findings. Little is known about accuracy of film interpretation, since the number of patients examined postmortem in the immediate postmortem period has not been large. However, it is possible to analyze change in lesions without knowing their absolute size." They went on to say that "Human readers encounter problems with consistent and precise

evaluations of plaque size, a process central to evaluation of atherosclerosis treatment."

The comments in the immediately above paragraph are somewhat inconsistent and somewhat misleading. In the first place, if "little is known about accuracy of film interpretation" because of a lack of postmortem validation, then statements such as "it is possible to analyze change in lesions" have little meaning. It is typically the case that changes in lesions are very small during angiographic trials and humans do not excel in their abilities to accurately estimate very small changes in size. Because of this limitation, the use of several readers of angiograms will not necessarily improve accuracy. Rather, a group will merely average the error of the individuals.

Additional constraints of angiogram assessments discussed by Blankenhorn were cited by Malinow.[3219] He said, "There are methodologic difficulties in comparing films recorded years apart. Techniques must assure that the films are identical in several respects, including magnification, position, ratio of film density of background tissue to that of the contrast material in the vessel, timing in relation to the cardiac cycle or to the pulse wave, arterial blood pressure, vascular tone, and heart rate. In practice, interpretation of images of stenosis must exclude changes associated with spasm, thrombosis, vascular ectasia, and arterial rotation." Malinow very importantly pointed out that the emphasis on the relatively few studies purporting to show regression are often totally divorced from "numerous studies in which regression was not observed." This massive selective omission presents a massive distortion of all scientific data.

Perhaps the overall problem confronting an individual reviewing angiographic trials can be summarized in one sentence presented by Galbraith et al.[1141] in 1978, namely, "Previous studies indicate that coronary angiography is a reliable diagnostic procedure, but interobserver variability in the clinical interpretation of angiograms remains a problem in achieving optimal results." The question is--how can angiography be reliable if interobserver variability remains a problem. The two parts of this sentence are contradictory. And let us not forget that reliability is an essential but insufficient condition for achieving accuracy. Until angiography readings are thoroughly validated with postmortem findings, angiography may never be legitimately accepted as a means of accurately assessing the condition of atheromas.

A third major problem with angiographic studies is that while their results may seem impressive when divorced from all other literature on the blood cholesterol-CHD literature, they often present perplexing contradictions when discussed in the light of other literature. Since this issue is addressed in detail in Chapter 7, suffice it here merely to draw attention to its principal concern. Angiographic studies always report a slowing of progression following cholesterol-lowering and usually report regression, no matter what the baseline and on-trial cholesterol levels were. As will be seen below and in Chapter 7, as much as 53% of the patients of the treated group in one study was reported to have shown regression when blood cholesterol was lowered from 378 to 261 mg. Moreover, 38% of the control subjects were purported to have shown regression with a cholesterol-lowering from 366 to 335 mg. Virtually any regression at all at cholesterol levels of 261 to 335 mg defies massive literature produced by the alliance which maintains that all cholesterol levels above 200 mg are atherogenic.[a] One simply cannot reconcile the two; one or the other set of data must be wrong, whether purposely fabricated or generated by unconscious bias via improper controls, e.g., poor randomization and/or blinding procedures. As this writer emphasized in Volume 1, I have never in nearly 32 years of research observed the kind of bias that

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[a] It is acknowledged that a small percentage of patients may exhibit spontaneous regression in some lesions over a 12-month period or more.

is so obvious in the medical literature. In fact, it is almost impossible not to detect at least several examples of bias in a single article. Review articles are often saturated with bias.

It is also important to point out that authors of angiographic studies often suggest that angiograms are more sensitive measures of CHD development than are the harder endpoints (deaths, nonfatal heart attacks) over much longer periods of time. As will be discussed in a concluding section of this chapter, the evidence indicates that soft endpoints correlate highly with hard endpoints. If atherosclerosis ultimately leads to death, as the alliance has repeatedly claimed, then lesion development clearly must correlate highly with death rate. And because infarctions often occur in people with little or no atherosclerosis and when they do occur in people with substantial atherosclerosis, they are typically not associated with the most severe lesions, it must be acknowledged that angiographic studies are, in fact, less sensitive assessments of CHD event risk.

With the above discussion hopefully clearly in mind, we now turn to the most recent angiographic studies which have received much medical and public attention.

The Blankenhorn et al. Trial

The 2-year Blankenhorn et al.[760] (CLAS I) angiographic trial was published in 1987 and reviewed in Volume 1.[a,b] The preliminary results of the 4-year follow-up (CLAS II) were presented in the Medical Tribune in 1989[2513] and the final results were published by Cashin-Hemphill et al.[3085] in 1990. It was reported that a colestipol-niacin treated group showed more nonprogression (52% vs 15%) and more regression (18% vs 6%) than did a control group. In their abstract, they concluded that "These results confirm CLAS I findings and indicate that regression can continue for 4 years. They reaffirm the need for early initiation of vigorous long-term lipid lowering therapy in coronary bypass subjects." At the end of their text, they stated that "Divergence of progression and regression rates also continued from CLAS I to CLAS II, with significant benefits from drug therapy in native coronary arteries and bypass grafts."

Because the CLAS II study was supported, in part, by the makers of colestipol, the Upjohn Company, this writer cannot accept its results as scientific evidence for anything. The fact that it suffered from all the problems discussed in the previous section, should render it at least highly suspect to objective readers.

To illustrate further problems with the CLAS II study, let us assume that there were real and practical differences between the treated and control groups. If the treatment did, in fact, slow progression and increase regression, it would follow, therefore, that the treated subjects in CLAS II should show improvement over the

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[a] Rifkind[865] referred to the 2-year Blankenhorn et al. results as "conclusive" at a press conference but later in print indicated that cholesterol-lowering in that study "may have caused regression of coronary plaques."[1803]

[b] Not noted in Volume 1 was a comment by Levin,[1712] i.e., "the study did not separate drug therapy from niacin treatment, confounding the results with two interacting variables, cholesterol treatment and vitamin treatment." While this may seem to be a minor flaw, in view of all other considerations, it cannot be dismissed as unimportant. After all, the niacin group but not the clofibrate group of the CDP presumably resulted in lower post-trial mortality than a control group, although they both lowered blood cholesterol.

same treated subjects in CLAS I, since they benefitted from a 100% extension of time at the same reduced blood cholesterol level. But such was emphatically not the case.

Figure 6-1 shows Cashin-Hemphill et al.'s distributions of "global" change scores at the end of CLAS I and CLAS II for the 56 drug-treated subjects. The negative scores represent judgments of degrees of regression and the positive scores indicate judgments of degrees of progression. Zero indicates no change. At the end of CLAS I, 9 subjects were judged as showing regression, while 10 were so judged at the end of CLAS II. One must classify this "improvement" as considerably less than impressive. Some 23 subjects were judged to show no change at the end of CLAS I, while only 19 were so judged at the end of CLAS II. This clearly represented the opposite of improvement. Finally, 24 subjects were judged to show progression at the end of CLAS I, while 27 were so judged after CLAS II. Again, this represented the opposite of improvement. Thus, with the exception of <u>one</u> additional subject purporting to exhibit regression, virtually <u>all</u> of the trends from CLAS I to CLAS II were toward progression. Although this finding is most important, the authors had almost nothing to say about it, e.g., "The drug-treated group response was more variable at 4 than at 2 years and was slightly shifted toward progression." This "slightly shifted toward progression" might easily be overlooked for what it really means, namely, that continued cholesterol reduction by the huge amount of 62 mg did not stop overall progression.

It is submitted that the results of the drug-treated group from CLAS I to CLAS II offer no evidence that massive reduction of blood cholesterol prevents atherosclerosis. Moreover, as is shown in Chapter 8 the mean blood cholesterol level in the drug-treated group was already within the low range of numerous prospective studies in which <u>total</u> mortality rates increase. Further reductions would increase the risk of death from all causes.

An important implication of Cashin-Hemphill et al.'s findings is that the American diet is not the cause of CHD. There are no safe diets, let alone acceptable diets that will reduce blood cholesterol levels by 62 mg or more. Since the drug-treated group showed increased progression with a decreased cholesterol level of 62 mg, it follows that dietary changes cannot prevent progression of atherosclerosis.

In order to demonstrate inconsistencies from one angiographic study to another, consider the control group's progress from CLAS I to CLAS II. Presumably because of the cholesterol-lowering diet that was consumed by both drug-treated and control groups, the mean cholesterol level of the control group was 14 mg (5.8%) lower than at baseline. Despite this reduction, the percentage of subjects showing no progression or regression dropped from 36% to 13% from CLAS I to CLAS II. Also, the percentage of subjects showing progression increased from 60% to 83%. Therefore, there was clearly a substantial worsening or atherosclerosis associated with an "improvement" of blood cholesterol level. Of course, it can be argued that the worsening would have been greater had the 14 mg not been last. But when we find that much regression and nonprogression is reported in other studies where on-trial cholesterol levels are higher than those in the control group in the CLAS II study, one must conclude that something is transpiring that defies scientific reasoning.

Finally, it is amusing to point out that reported regression in the drug-treated group increased from 16% to 17.9% from CLAS I to CLAS II, while it increased from 4.3% to 6.4% in the control group. In evaluating virtually all clinical trials, the alliance employs the "risk" concept which is based on relative rather than absolute differences. Using the alliance's risk concept, therefore, the above changes indicate that regression increased 49% without drug treatment and only 12% with drug treatment. Of course, Cashin-Hemphill et al. did not note the fact that regression in the control group increased more than in the drug group either relatively (49% vs 12%) or absolutely (2.1% vs 1.9%).

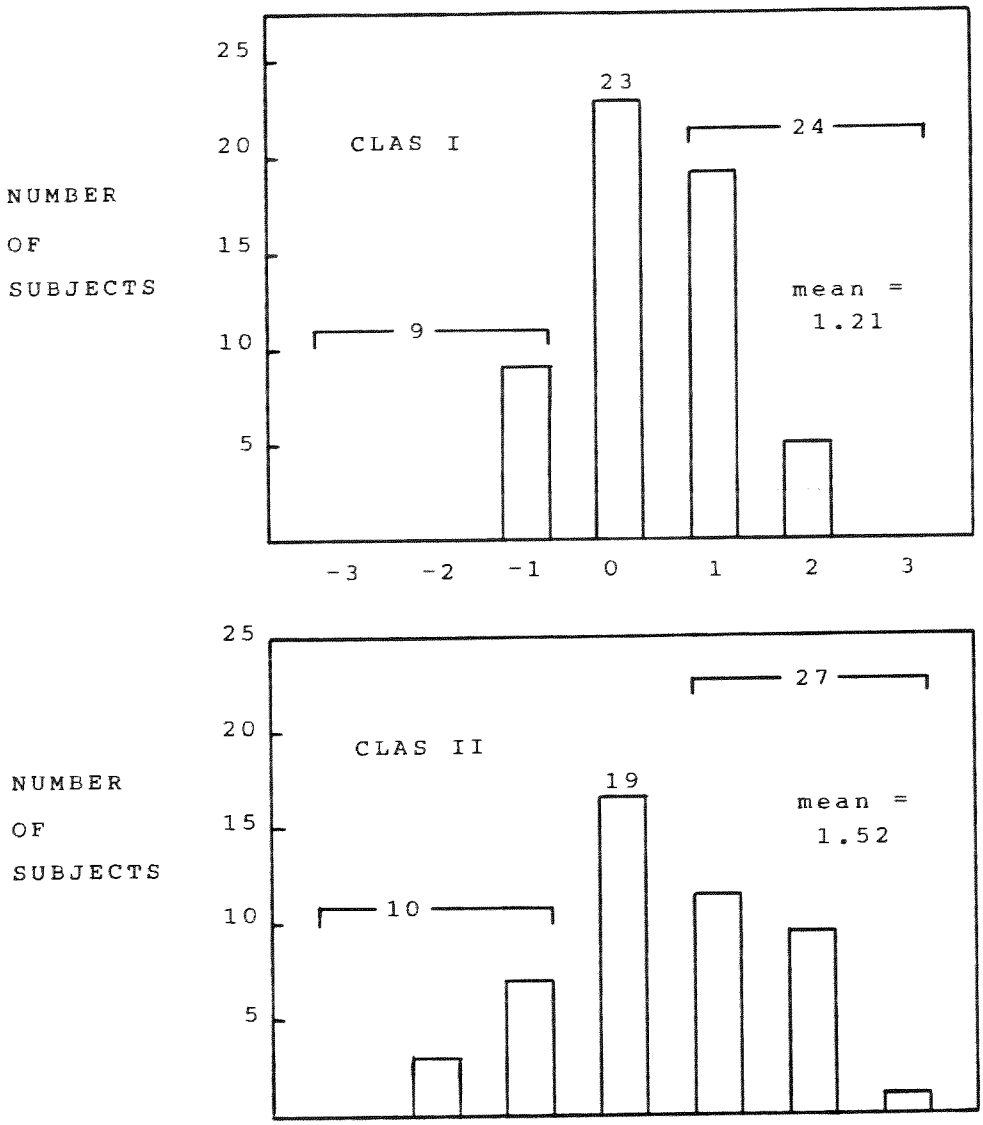

Figure 6-1. Distributions of "global" change scores at the end of CLAS I and CLAS II periods (adapted from Cashin-Hemphill et al. 1990[3085])

Although not directly relevant here, it is nevertheless useful to summarize a 1990 study by Blankenhorn[2705,2898,2926] which reported a 2-year follow-up of his control group, associating diet with subsequent development of atherosclerosis. It illustrates the faith he places on recognized unreliable data. Based on a single 24 dietary recall, he jumped to the monumental conclusion that reducing total fat, not saturated fat and cholesterol, differentiated between the men with respect to new fatty deposits, as indicated by follow-up angiograms. It is incredible that he can correlate an unreliable method of assessing the development of fatty deposits with an even more unreliable method of assessing diet. It is also incredible how alliance members can conclude that diet is the principal cause of atherosclerosis but differ so profoundly on the dietary nutrients that supposedly are atherogenic. Most alliance members maintain that saturated fat is the prime promoter of atherosclerosis, such as Keys, and other members such as Stamler and Connor, hold that the primary culprit is cholesterol. Now Blankenhorn concludes that the atherogenic factor is total fat, not specific lipids, even though total fat per se has no influence on blood cholesterol levels.

The Kane et al. Trial

Kane et al.[3086] compared a group of treated subjects with various combinations of colestipol, niacin and lovastatin with a control group via pre- and post-treatment angiograms. The 72 subjects in both groups were instructed to consume a prudent-like diet. In addition, the authors' Committee on Human Research requested that control subjects be offered cholesterol-lowering drugs in order to satisfy medical ethics. Forty-four percent of the control group elected to take colestipol. Thus, this study more or less represented a comparison of two groups which differed in the amount of cholesterol-lowering drugs they consumed.

Blood cholesterol levels decreased from 366 to 335 mg in controls and from 378 to 261 mg in treated subjects. The percentages of subjects showing regression (53% vs 38%) and regression and no change (73% vs 47%) were reported greater in the treated than in the control group. Also, the percentage of subjects showing progression were said to be much greater in the control than in the treated group (53% vs 27%). Thus, although not discussed at all by Kane et al. who focused all their attention on the differences between groups, their data showed that 47% to 73% of both groups exhibited regression or no change with what the alliance would classify as highly herogenic cholesterol levels, i.e., 261-335 mg.[a] Since spontaneous regression and stabilization occurs only in a small percentage of subjects, these data are totally inconsistent with everything that is known about regression and progression of atherosclerosis and yet, Kane et al. completely ignored the import and implications of these findings. They simply concluded that "Our observations taken together with those of Blankenhorn et al. and Brown et al. indicate strongly that therapy directed at atherogenic hyperlipidemia of diverse origins is effective, validating the lipid hypothesis."

It is noteworthy to mention one peculiarity of Kane et al.'s discussion on selection and randomization of subjects. Subjects selected had not undergone bypass or angioplasty operations. In addition, Kane et al. said that "No...patient developed symptoms or electrocardiographic evidence of coronary heart disease during the trial." Yet, they also said that "patients with...multiple infarcts were excluded." This latter statement strongly implies, of course, that patients with single infarcts were included.

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[a] The mean change during the trial was toward regression in the treated group (still inconsistent with a mean cholesterol level of 261 mg) and toward progression in the control group. Regardless of these overall trends, the fact remains that Kane et al.'s assessment technique yielded an unexplainable percentage of subjects showing regression or no change in both groups.

Such an implication provokes three questions. How many subjects with infarcts were included in the study and why was there no discussion about their distribution within the treatment and control conditions? Third, how is it that Kane et al. classified infarcts as something other than CHD, contrary to the alliance's definitions?

Finally, three of the authors of the study, Kane, Malley and Havel received "honoraria" and/or "consultation" fees from Merck, Sharp and Dohme and Upjohn Company, makers of the two principal drugs (lovastatin and colestipol, respectively) used in their study. Again, this fact alone is sufficient, in the present writer's view, to completely reject the results of the study.

The Brown et al. Trial

Brown et al.[2513,3087] compared two groups treated with cholesterol-lowering drugs (one with lovastatin and colestipol and the other with niacin and colestipol) with a control group. As nearly all authors of angiographic studies, Brown et al. reported that the treated groups exhibited more regression and less progression than did the control group. It was difficult, however, to determine the magnitude of these differences because the authors' quantitative descriptions were not perfectly clear. The authors concluded that "In men with coronary artery disease who were at high risk for cardiovascular events, intensive lipid-lowering therapy reduced the frequency of progression of coronary lesions, increased the frequency of regression, and reduced the incidence of cardiovascular events."

In his review of the Brown et al. trial, Lascalzo[2981] qualified these results by saying that "...it must be emphasized that the extent of the change in luminal diameter measured in this study was small, and statistical significance was achieved only by virtue of the power and precision of the computerized edge-detection techniques used to assess the coronary angiograms." The implication is that had computerized techniques not been used, differences between groups would not have been observed. This is most interesting in view of the massive reduction in blood cholesterol achieved, i.e., 93 mg and 61 mg in the two treated groups and in view of the fact that other studies have always reported differences with noncomputerized techniques. It would seem that differences are always reported, no matter what techniques are used.

The luminal diameter changes reported by Brown et al. were--2.6%, 0.6% and 1.8% for the control, colestipol/lovastatin and niacin/colestipol groups. Assuming that these differences were real, as indicated by Loscalzo they were quite small. Indeed, the ost of the daily consumption of two drugs and the total reductions of cholesterol levels achieved do not indicate that they were cost-effective. And it must also be re-emphasized that unless tens of millions are placed on drugs, much smaller reductions in cholesterol can be expected by dietary changes and, therefore, much smaller changes in luminal diameters.

Some 146 men were initially randomized to the three experimental groups, theoretically yielding 48.7 persons per group. Since 46 in the control group completed the study, while only 38 and 36 of the treated groups did so, it is clear that the high dropout rates (22% and 26%) in the treated groups may have strongly biased all of the results obtained.

The reader may recall Loscalzo's critique of computerized angiograph assessment techniques in an earlier section. It can be further added that the application of a computer only comes after standard angiograms are obtained, which are subject to all problems previously discussed, and after humans manually trace the borders of lesions onto "standard forms." The slightest error in making these tracings could easily have a profound effect on the final results.

The Brown et al. study was apparently not supported by funds from pharmaceutical companies and the authors indicated no financial arrangements with such companies, although the absence of that information does not mean, of course, that one or more of the authors do not have such arrangements.

The Ornish Trial

The Ornish trial consisted of subjecting a set of subjects to "lifestyle" changes, i.e., a very low fat, high carbohydrate diet, regular moderate aerobic exercise, stress management training, group support activities and the cessation of smoking. The trial consisted of only 41 subjects for a period of one year, but the results from 29 subjects were announced early and given much favorable publicity.[a] Although Ornish indicated that the average percent diamter stenosis decreased in the experimental group and increased in the control group, and that the greater the adherence to the lifestyle changes, the greater the regression, contrary to the lipid hypothesis, the amount of regression did not correlate with the amount of cholesterol reduction. This was a most significant finding that was not discussed in Ornish's paper when all subjects had completed the 1-year program (below).

Shapiro et al.[2897] cited an experimental participant of the Ornish study, Robert Royall. Prior to entering the study Royall presumably followed the AHA diet for one year and his physician noted that one of his arteries had stenosed from 37% to 77% during that period. Royall then entered the Ornish program and was said to feel better "almost immediately" after starting the program. His blood cholesterol dropped from 360 mg to 250 mg, producing a "dramatic change" in his artery. There is effectively nothing believable about Shapiro et al.'s description. It is highly doubtful that Royall's artery would have increased its blockage from 37% to 77% in one year on any diet. If Royall felt better "almost immediately" after starting Ornish's program, it could not possibly be due to the diet or cholesterol reduction because changes in stenosis do not occur "almost immediately." Finally, it is impossible to rationalize that a "dramatic [favorable] change" in an artery [regression] can occur with a cholesterol level of 250 mg, considered a "high risk" level by Ornish's fellow alliance members.

The 1-year report for all subjects in the trial was published in mid-1990 by Ornish et al.[3421] Subjects for the study were patients who had already undertaken angiograms for other reasons. Some 94 subjects, aged 35-75 were selected but only 48 agreed to participate. Of the 48, seven subjects were subsequently eliminated because follow-up data were said to be "not available," one control and 6 experimental subjects. While this may be true, it is not unique among clinical trials that subjects are eliminated after all results are in. It is most suspicious, moreover, that almost all of the dropouts occurred in the experimental group and for reasons unrelated to the lifestyle changes. For example, it was said that the entry anigogram for one experimental subject "was lost."

Subjects completed a 3-day diet diary at baseline and again one year later in order to determine compliance with the prescribed diet that consisted of 10% fat, 70-75% carbohydrates and a P/S ratio of > 1. While it has been emphasized in Chapter 4 that accurate estimates of nutrient intakes cannot be obtained with 3-day observation periods or the diary method, the matter is academic because the relevant variable was the reduction in blood cholesterol which, of course, could be measured more accurately.

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[a] 2513,2556,2687,3422

Ornish et al. claimed that the mean percent diameter stenosis decreased from 40% to 37.8% in the experimental group and progressed from 42.7% to 46.1% in the control group. It was also reported that the experimental subjects experienced less frequent and less severe chest pains after one year, while the control subjects experienced more frequent and more severe pains.

Recognizing that the "lifestyle" changes in the study were quite severe and demanding, particularly the diet, Ornish et al. concluded that "The point of our study was to determine what is true, not what is practicable." They indicated that the alliance's Prudent Diet of 30% fat was "not sufficient to bring about regression."

Taken at face value, the Ornish et al. study would appear to present significant evidence supporting the lipid hypothesis. But upon close analysis there are many aspects of the trial that lead one to question the validity of the results. First, it has been discussed at length that first and second angiograms are not directly comparable for a number of reasons, whether or not they are "quantified," and we will not dwell further on this factor.

Second, randomization is generally not effective with very small groups and can lead major differences between groups at baseline. For example, the groups were not equal in males and females. The experimental subjects were younger (56.1 years) than the control subjects (59.8 years). The mean percent diameter reduction in the control subjects at baseline was greater (42.7%) than that of experimental subjects (40%). It was noted that there was only one smoker in the experimental group at baseline but no mention was made of the number of smokers in the control group. Thus, there is the strong suggestion that the groups were quite different in terms of smoking habit at baseline. One can also only wonder why Ornish et al. made an issue out of "stopping smoking" when only one of the 22 experimental subjects smoked at baseline. The investigators also "excluded from analysis 33 lesions that were 100% occluded at aseline," but failed to mention their distribution between the groups.

Third, although Ornish et al. indicated no correlation between degree of progression-regression and cholesterol reduction in their preliminary findings, they selectively omitted this topic in their final report. This omission strongly suggests that a zero correlation was still observed and, if so, the case for the lipid hypothesis is severely weakened. There seems no doubt that had a strong correlation existed, Ornish et al. would surely have made note of it.

Fourth, it is exceedingly well known and documented that a low-saturated fat, high carbohydrate diet reduces HDL substantially. Yet, in the Ornish et al. trial HDL was presumably unaffected by the extreme diets undertaken by the experimental subjects. This discrepancy with dozens of other studies cannot be dismissed lightly and should have been discussed by Ornish et al., but it was ignored.

Fifth, 42% of control subjects were reported to exhibit overall regression and 47% were said to show regression or no change in percent occlusion. This was a most curious and unexplainable finding and it suggests substantial error in the quantitative assessment of angiograms. Spontaneous regression has been seen for small percentages of subjects but never for nearly half of a group of subjects. Again, Ornish et al. omitted a discussion of this discrepancy.

Sixth, alliance members in recent years have stressed the importance of HDL and, as noted elsewhere in this volume, Framingham investigators maintain that HDL and particularly the total cholesterol to HDL ratio are the most important predictors of atherosclerosis development. Yet, not only did control subjects have a much higher mean HDL level (50 vs 37.4 mg), they had a slightly lower mean total: HDL ratio (4.9

vs 5.2). Ornish et al. again omitted a discussion of these findings and thus an explanation for a major discrepancy between their results and those of Framingham.

Finally, the Ornish et al. trial was another small study that was designed with built-in confounders. Even setting aside the problems discussed above, it is not possible to say what variable contributed to the outcome, given that the outcome was a true reflection of the independent variables.

All things considered, the Ornish et al. study involved numerous serious problems which the authors meticulously avoided discussing and which others ignored. For example, NHLBI director Lenfant erroneously claimed that the study "offers strong scientific evidence that life-style changes alone can actually reverse the progression of atherosclerotic plaques in coronary arteries." [96] The evidence was at best weak and highly questionable.

It is interesting that Ornish et al. suggested that their "therapy" was probably not practical. Indeed, even if it were proved beneficial, it is not likely that the vast majority of people would come close to tolerating it, particularly the Pritikin-type vegetarian diet. Even Allan Chait, the 1990 Chairman of the AHA Nutrition Committee, said that "people who go into these programs for the rest of their lives are essentially going to become slaves to their arteries. It would be difficult for them to lead normal lives in American Society."[2895] While undoubtedly correct, it is also suspected that the AHA is not pleased to have its Prudent Diet usurped by the Pritikin Diet. As noted in an earlier section, the former NHLBI director, Robert Levy, severely criticized the Pritikin Diet (and angiogram assessment of atherosclerosis changes) in 1977.

Some Comments

In his letter to the editor Attarian[3246] noted that Kane et al.'s report stated that there was "a strong but not statistically significant" difference with regard to regression vs progression but later indicated that treatment "did indeed result in improvement." In addition to the fact that it is a contradiction to say that a difference is "strong" and "nonsignificant," Kane[3246] employed the usual alliance escape tatic by stating that "The study was not designed to detect changes in the incidence of new coronary events." Kane noted that the Brown et al. study did report a significant reduction in coronary events. Thus, if a reduction is found, it is prominently displayed and if a reduction is not found, well, the study was not designed to detect a reduction.

Attarian also noted that the Cashin-Hemphill et al. report indicated "no significant differences in major medical events experienced over the 4-year period." Blankenhorn[3247] responded with the usual explanation that his study "was not designed to test effects on clinical events."

In reviewing the above angiographic studies, one must recognize that while the authors themselves imply that their results were accurate, the previous discussion indicates that considerable inaccuracies must have occurred but will never be addressed. Chapter 7 discusses in detail a number of reasons why blood cholesterol lowering is not likely to cause regression and why studies showing regression conflict with other data that are prominently and continuously promoted by the alliance. However, it is useful to note here two technical findings and one theoretical consideration. If a very large study comparing vegetarians with nonvegetarians over many years shows no differences in CHD mortality rates (Chapter 4) how can we take seriously these exceedingly small angiographic studies which purport to show a slowing of progression and an increase in regression with (during therapy) cholesterol levels that are higher than those of vegetarians? It is not logical.

In the discussion prior to reviewing angiographic studies it was emphasized that two specific investigations found that thrombi form more frequently in the least occluded arteries than in the most occluded. This finding, if generally true, is monumentally important because it would logically follow that the degree of atherosclerosis has little or nothing to do with myocardial infarctions and, therefore, the slight changes in progression and regression purported to have occurred in angiographic study patients could not possibly have much to do with infarctions or sudden deaths.

Clinical trials, particularly angiographic trials, typically involve subjects with familial hypercholesterolemia. Chapter 2 presented considerable pathologic evidence indicating that familial hypercholesterolemia (and diet induced hypercholesterolemia in animals) produces a lipid storage disease superimposed on true atherosclerosis. While the alliance rather feebly attempts to deny this likelihood, they nevertheless effectively support the concept, albeit indirectly, by referring to the experimental disease as "atherosclerosis-like." If a lipid storage disease is superimposed on true atherosclerosis, and much evidence supports this concept and none denies it, then the results of most clinical trials may have been associated with variations in lipid storage disease and not atherosclerosis. This is a theoretical notion that cannot be dismissed by the objective scientist.

REVIEWS OF ANGIOGRAPHIC TRIALS

Superko cited 11 angiographic trials as having "design problems" but indicated that three additional trials were "controlled studies."[2335] These trials were conducted by Duffield et al.,[639] Blankenhorn et al.760 and Brensike et al.[839] The Brensike et al. study was funded by NHLBI and found no significant effects of cholesterol lowering. Duffield et al. and Blankenhorn et al. did report significant benefits of cholesterol lowering but the results of these trials are heavily clouded by the fact that they were funded by the drug companies (Bristol-Myers and Upjohn, respectively) whose drugs were used in these trials. Superko failed to mention this potential bias and also stated that the Brensike et al. results were significant when, in fact, they were not. Moreover, Superko failed to note that the Duffield et al. study involved only a small number of subjects. Despite all the "design problems," lack of significance and/or potential biases, Superko drew the untenable conclusion that "It is abundantly clear that reduction of elevated LDL cholesterol results in...a reduction in the rate of progression of coronary atherosclerosis."

Gotto,[1341,2035] Horlick,[1930] Rifkind,[2032] Grundy,[1803] Blankenhorn,[1717,2039,2706] Kuo,[2850] and Dwyer[2264] have also cited the nonsignificant results of the Brensike et al. study as evidence that cholesterol lowering decelerates progression and/or increases regression. Horlick's citation was uniquely contrary to fact, i.e., he referred to the study as "providing sound scientific evidence that reducing the plasma cholesterol level reduces the risk of coronary events and is associated with regression or arrest of lesions."[1732]

Gotto,[1341,2035] Rifkind,[2032] Blankenhorn et al.[2705] and Dwyer[2264] also cited the Arntezenius et al. study[853] as evidence (known as the Leiden Intervention trial), even though the trial was neither randomized nor blinded and had no control group. It is simply inexcusable to infer anything from a study employing no control group.

It is of interest to briefly summarize the repetitive reviews of one researcher, e.g., Blankenhorn. While he has apparently published numerous redundant articles throughout medical journals, the following are probably representative of the lack of comprehensiveness, objectivity and accuracy of all his articles.

Blankenhorn and Kramsch[1717] "reviewed" only the Duffield et al.[639], Brensike et al.[839] and the Blankenhorn et al.[760] studies in a 1989 article. In another 1989 article, Blankenhorn again cited the Duffield et al. and Brensike et al. studies as supportive evidence and referred to the Duffield study as "controlled."[2039] He also cited the Cohn et al.[867] study and, of course, his own, which he said was "The first coronary angiographic trial to show a statistically significant treatment effect on coronary atherosclerosis." And in a 1990 article Blankenhorn[2706] omitted the Duffield et al. and Cohn et al. studies (as well as others) but cited his own trial and those of Brensike et al. and Arntezenius et al.

One can only wonder why Blankenhorn includes different subsets of angiographic trials in each of his "reviews." Could it be that these variations bypass the typical journal's criterion that an article for publication cannot be published elsewhere?

OTHER ANGIOGRAPHIC STUDIES

A number of small studies have been conducted which have evaluated restenosis rates following angioplasty or bypass operations. At the outset, it must be emphasized that each suffers from the problem of measuring restenosis by angiograms. Potential bias due to lack of blindedness also appears to be a problem in some studies.

Some of the studies involved the lowering of cholesterol levels after surgery, while others merely associated existing cholesterol levels with restenosis rates. And still others involved the feeding of fish oil supplements.

The results of studies associating cholesterol levels with restenosis rates have been mixed. For example, Banka et al. and Holloman each lowered blood cholesterol in small groups of angioplasty patients.[2573] Banka et al. reported that cholesterol-lowering via lovastatin resulted in a lower restenosis rate that was observed in control subjects, while Holloman found no benefits from use of the same drug. The latter also reported that blood cholesterol levels were exactly the same in restenosis as in nonrestenosis groups and that HDL was higher in the restenosis group.

Bergelson[2572,2573] did not lower blood cholesterol but they reported that the mean level of a group showing restenosis was higher than that of a group not showing restenosis (211 vs 200 mg). On the other hand, the results were confounded because the restenosis group contained a larger number of smokers (66.5% vs 48.4%). In addition, the cholesterol levels of females showing restenosis were the same as those showing no restenosis.

As noted elsewhere in this volume, by far the most important study of this genre, if for no other reason because of its size, DeBakey[2326] reported that there was no correlation between cholesterol level and rate of restenosis in grafts among a large number of patients. Additionally, in England Wiseman et al.[2195] found that cholesterol levels were significantly lower in accelerated grafts than in grafts that remained patent.

Clinical trials feeding W-3 fish oil supplements to patients after angioplasty have also yielded mixed results.[2165,2166,2670] Positive results were reported by Dehmer et al.,[2322] Milner et al.[2668] and Slack et al.[2669], and negative or no effects were

obtained by Reis et al.[2321] and Grigg et al.[2667,a]

It is clear that the aggregate of findings thus far does not support the concepts of blood cholesterol-lowering or fish oil supplements in depressing restenosis rates. There seems to be a general consensus that the benefits of fish oils are dubious and they are not officially recommended by the alliance.[b] However, Connor and Castelli advocated the consumption of fish oils at a 1987 teleconference sponsored by a fish oil-producing drug company.[1179] More recently, Connor[1920] said that "We now have strong evidence relating omega-3s to a decreased incidence of coronary heart disease." Others agree (Blackburn,[1934] Fisher[1753]). As indicated in Volume 1, this writer was unable to locate the "strong evidence" noted by Connor and apparently the FDA was unable to locate it as well. In July 1990 the FDA banned the sale of fish supplements, saying that "At the present time, there is inadequate scientific evidence to support health claims on fish oils or to support claims that these ingredients have an effect on the risk of coronary heart disease."[2558] The ban was subsequently lifted but apparently reluctantly.

BLINDEDNESS, RANDOMIZATION AND VESTED INTERESTS

In Volume 1 the Helsinki diet clinical trial, conducted by Miettinen et al.[1145] was described as "such a poorly designed study it is astounding that it was ever conceived, let alone conducted." These investigators gave a cholesterol lowering diet to patients in Hospital A for six months, and then to Hospital B for the next six months. They claimed that the CHD death rate was significantly lower in Hospital A than B when A received the special diet but was not significantly lower in Hospital B than A when B received the diet. Subjects were clearly not randomized in this study and there was clearly no single or double-blind procedures. Moreover, while other trials of many years of duration have not been able to demonstrate significant differences in CHD mortality, Miettinen et al. would have his readers believe that significant differences were observable after only six months of diet treatment.

The Hospital study was perhaps the worst trial ever conducted, defying virtually all scientific principles associated with proper experimentation. It was severely criticized in considerable detail by Halperin, Cornfield and Mitchell[431] (Halperin and Mitchell being representatives of NIH and NHLBI, respectively). Most alliance members have not cited this Finnish study in their reviews of clinical trials.[c] But those that did cite the study reviewed it favorably. The American Health Foundation,[424] Glueck,[543] and Dayton et al.[454] matter-of-factly indicated that the study's diet "decreased the incidence of coronary events." Grundy et al.[499] said that the diet "produced a decrease in serum cholesterol and an apparent decrease in CHD mortality rates." The Inter-Society Commission[552] and Basil Rifkind et al.[500] stated that the study produced "encouraging" results. In three different articles, Stamler referred to the Helsinki I trial results as "decidedly positive,"[539] "encouraging,"[2939] "decidedly encouraging"[1313] and "meaningful."[2938] Hegsted[2692] and Blackburn[2691] called it a "well-designed" trial

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[a] It has been known for some time that erucic acid of denatured rapeseed oil has serious toxic effects.[2601,2602,2603] While most of this acid is removed during food processing, cetoleic acid has similar toxic effects and it is abundant in fish oils.

[b] 978,1066,1754,2165,2251

[c] A number of "reviewers" cited the study as demonstrating that diet lowers blood cholesterol but did not mention the trial's results.[754,1136]

and the latter told an FTC law judge that "Randomized procedures were generally proper." Most absurd of all was Goldberg's[1398] description, i.e., "quite impressive."

In the ideal world scientists would be objective observers of nature and honest reporters of facts. But we do not live in an ideal world and the objectivity and honesty of many epidemiologists leave a great deal to be desired. A recent statement by Feinstein is most apropos. He indicated that there are often "absent or low scientific standards in epidemiologic studies of cause-effect relationships." Epidemiologists "do not seem upset by investigators making changes in control groups after the results have been analyzed, by large numbers of studies with unresolved and unreconciled contradictions, by the infrequent precautions against ascertainment bias, by statistical maneuvers that are substituted for a true dose-response curve, or by the credulous acceptance of erroneous death certificate diagnoses."[2245]

Cornfield and Mitchell[488] emphasized in 1969 the inevitable biases that occur when trials are not blinded. Unblinded trials tend to report "marked effects [of treatments] on such softer endpoints as angina pectoris and nonfatal myocardial infarction, but not on the hard endpoint of death," illustrating the ease with which bias can influence the diagnoses of nonfatal events but not fatal events. They pointed out that this outcome is inconsistent with epidemiological evidence and cited unpublished Framingham data of Tavia Gordon and Fred Ederer of NHI which showed that the relationship between cholesterol value and event rate is the same for soft and hard endpoints. Cornfield and Mitchell politely attributed the inconsistent findings to the fact that the studies were not blinded. The term "politely" is used because the underlying reason for the findings is bias, not the mere fact that a study was unblinded. And that bias may occur by conscious or unconscious acts.

Cornfield and Mitchell also pointed out that "The only safe way known to assure...comparability [among groups before a treatment is given one group] is by random allocation. Substitutes, such as matching, assume either that all important determinants are accounted for by the matching variables. It remains to be demonstrated that matching on known risk factors could eliminate selection effects."

In 1973 Mitchell and Jesse[3225] reiterated the obvious biases demonstrated in unblinded and nonrandomized trials and concluded that "All the studies conclusively [underline added] demonstrated the critical need for random allocation of patients to the treated or the control group and the necessity for the double-blind design..."

In their report on the Veterans' Diet rial in 1969, Dayton et al. stressed that "Although the importance of randomization of subjects and of the double-blind technique has been abundantly emphasized in the literature, these arguments have seemingly been more persuasive to biomathematicians than to physicians."[454] Indeed, many clinical trials were not blinded and/or randomized. Some kinds of trials are still being conducted today that are not blinded and/or randomized. While many readers assume or pretend that such trials are conducted and analyzed objectively and honestly, even, for example, when investigators are being paid by or own stock in drug companies whose drugs are being tested in the trials, medical science and the health of a nation should not depend on assumptions. With few or no exceptions, clinical trials that are not blinded and randomized should not be funded, particularly by public monies, and should never be accepted for publication in scientific journals.

There is a wealth of research literature which clearly demonstrates that whenever bias is permitted in an experiment, bias is highly likely to affect the study's outcome. There is no rational reason to avoid these procedures except to permit authors to consciously or unconsciously bias their results. It is not coincidental that almost every medical study reports "positive" results, even though there may be great contradictions between studies. Investigators are motivated to obtain "positive" results to satisfy (1)

funding agencies, whether a drug company or NHLBI/AHA, and (2) journal editors, who tend to reject articles that do not show "significant effects." The epidemiologist who accepts the results of unblinded and nonrandomized studies not only exhibits a poor sense of scientific discipline, he/she effectively encourages the continued conduction of such trials.

Unfortunately, the fact that trial investigators claim that their trials were blinded and randomized is no guarantee that they were blinded and randomized. While such a statement may seem overly distrustful and unjustified, there is abundant evidence to support it. First, as shown throughout this volume, particularly Chapter 8, many of the most prominent alliance members have repeatedly reported false information in their reviews of previous literature, often presenting numerous distortions in a single article. While one may wish to classify these manipulations as inadvertent errors, the fact that they are always systematically in one direction, rather than randomly distributed between two directions, indicates that they were purposeful manipulations. Thus, it would be extraordinarily naive to assume that at least some manipulations are not also being made on the data from clinical trials.

Second, of the 8 angiographic trials discussed in Volume 1, only two were reported to have shown both a slowing of progression and regression of atherosclerotic plaque, i.e., Duffield et al.[639] and Blankenhorn et al.[760] both of these trials were funded by pharmaceutical companies (Bristol-Meyers and Upjohn, respectively) whose drugs were used in those studies. Moreover, the only U.S./British trial that reported significantly lower CHD and total mortalities from cholesterol-lowering was funded by the Upjohn Company which "tested" its own drug. That trial was also reported to be blinded and randomized (Dorr et al.[843]). In addition, the so-called blinded and randomized Helsinki II trial was either heavily or completely funded by the Warner-Lambert Company, makers of the drug used in that study.[1056] The Cashin-Hemphill et al.[3085] and the Kane et al.[3086] angiographic trials were affiliated with drug company money. It is not known whether the authors of the Brown et al.[3087] or the Ornish[2513,2556,2687] angiographic trials had financial arrangements with drug companies but, in any event, the former published unimpressive findings with respect to cost-effectiveness and the latter conducted a multi-variable study yielding confounded results. Moreover, all angiographic studies have been relatively small where even small manipulations of data could have major impact on outcomes.

The only trial of real consequence that was apparently blinded and randomized, not funded by a drug company and yielded at least some significant treatment effects was the LRC study. As emphasized in Chapter 7 of both volumes of this review, those significant effects were produced, at minimum, by questionable and unethical statistical analyses after the data were examined. Further, that trial was not free of potential influence by drug companies. Although most alliance members and non-alliance researchers recommended a diet trial (Chapter 7), a drug trial was instead approved and promoted by the then NHLI director, Theodore Cooper, who subsequently became the chief executive of Upjohn. In addition, pharmaceutical companies not only influence NHLBI's National Cholesterol Education Program by being on NCEP's coordinating committee, one must know that these high-profit oriented companies are not funding most of the NCEP's campaign for nothing.

If one wishes to risk his/her own health on the results of critical studies which are not blinded or randomized or are funded by companies with extreme vested interests or whose authors receive money directly or indirectly from such vested interests, that is his/her prerogative, of course. But it is quite another thing to risk the health of the American population. The whole purpose of this review is to show that the health of the American people <u>is</u> being compromised by medical researchers and agencies who neither abide by scientific ethics nor by the Hippocratic oath. In view of the massive manipulations and distortions that occur routinely, one must be suspicious of any

clinical trial that purports to support the lipid hypothesis, particularly since they yield many subtle contradictions. One contradiction that makes all "positive" clinical trials suspect is the fact that the results of large vegetarian studies do not show benefits of lipid-lowering, so why do very small clinical trials always demonstrate that lipid-lowering is beneficial?

NEW TRIALS

A new clinical trial designated as the Cholesterol Reduction Seniors Program (CRISP) has been funded by NHLBI.[2523,3094,3266] Some 400-500 men and women over the age of 65 will be given lovastatin for one year. If no serious side effects are observed, a full-scale trial of 5,500 subjects will be conducted.

As shown in Chapter 8, there is evidence that lovastatin can cause liver function changes, cataracts and increases in blood levels of Lp(a). The 1989 president of AHA referred to lovastatin as "potentially toxic." Yet, this drug is already the frequently prescribed cholesterol-lowering drug in the U.S.

The CRISP trial is representative of both the strength of the alliance's conviction regarding the benefits of cholesterol-lowering and its "shoot first and ask questions later" policy. While it has indicated for years that cholesterol lowering has been "conclusively" proven to reduce CHD events and that the LRC and Helsinki II trial findings can be generalized to women and all ages, clearly it has no faith in its own conclusions. Moreover, the alliance has successfully encouraged the elderly for years to consume cholesterol-lowering drugs and yet it is only now that side-effects are to be systematically determined.

POSTSCRIPT

The alliance has spent billions of dollars on research related to the cholesterol-CHD relationship and all of its members have repeatedly stated since 1984 that the relationship has been conclusively established. Yet, the research has continued unabated, with hundreds of millions of dollars being spent on conventional and unconventional trials. For example, Ornish et al.[3421] pointed out in 1990 that "over twenty clinical trials <u>are</u> being carried out to determine whether the progression of coronary atherosclerosis can be modified." Almost all of this research has focused on drugs as the cholesterol-lowering agent. In those few studies which have used diets, none have been free of confounding variables and most were quite small and unimpressive. If as the alliance claims, the data "overwhelmingly" indicate that cholesterol-lowering will substantially reduce CHD rates, why is it necessary to continue conducting study after study at taxpayers' expense? Moreover, if as the alliance claims, the data "overwhelmingly" indicate that dietary changes will substantially reduce CHD rates, why are dietary changes constantly rejected in trial after trial in favor of drugs?[a] The answers to these questions, of course, is that the alliance does not believe its own propaganda and is repetitively attempting to obtain evidence that it <u>will</u> find convincing. The constant conduction of trials speaks for itself. Chapter 7 discusses in detail the illogical rationale used by the alliance to use drugs instead of diets as cholesterol-lowering agents in clinical trials.

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[a] Although the Ornish et al.[3421] trial <u>did</u> use a cholesterol-lowering diet, it also involved the manipulation of other variables, so that diet per se could not be independently assessed.

7. THE "CONCLUSIVE" TRIALS

"I don't think that surgery patients are a good model for understanding atherosclerosis."

(Claude Lenfant, commenting on DeBakey's findings which showed no relationship between blood cholesterol level and degree of restenosis in 15,000 bypass patients, 1987[677])

"For the first time, we are presented with evidence regarding regression of lesions in humans."

(Claude Lenfant, commenting on Blankenhorn et al.'s angiographic trial with 162 bypass patients, 1987[859])

LIPID RESEARCH CLINICS (LRC) TRIAL

The following letter was published in Lancet on February 28, 1987, authored by Edward R. Pinckney and the present writer:[505]

"Sir - while preparing a review of published work on diet, serum cholesterol, and heart disease we read a 1984 Lancet editorial that states, correctly, that a two-tailed statistical test is essential to test the effects of a drug. The authors of the Lipid Research Clinics Program (LRCP) trial stated that a one-tail test was appropriate, yet your editorial claims that the LRCP results "strongly" suggest that energetic cholesterol reduction can reduce the high risk of coronary heart disease (CHD), perhaps by up to half. You seem to be saying that the difference between the placebo and drug groups though statistically insignificant, is convincing.

"The LRC protocol,[503] published in 1979, concluded that 'the most appropriate trial of the efficacy of cholesterol lowering would be dietary study' and 'it was essential to be sure that any one observed beneficial effect of cholesterol lowering was a real one. Therefore, alpha was set at .01 rather than the usual .05.' However, the project became a drug study, not a diet study, and the level of significance was reduced to .05. Moreover, a one-tailed test was used despite the fact that a two-tailed test is required when there is likelihood that a drug may increase or decrease mortality. Such a likelihood was more than supported by findings from previous clinical trials in which drug-treated groups suffered equal or greater CHD mortalities and/or equal or greater morbidities than did control groups. To compound the misuse of a one-tailed test and the post hoc changing of the statistical analysis plan, the investigators avoided conventional statistical tests which also would have yielded insignificance.

"One finding that was significant, by conventional statistical tests, was the fact that more gastrointestinal cancers, and deaths due to gastrointestinal cancers, occurred in the drug-treated group than in the placebo group. Yet, the investigators had nothing to say about this observation in their reports, and the project's director even belittled this finding elsewhere when he said: 'As for cancer, we did report (in the tables) a slight increase in GI cancers in the cholestyramine-treated group.' Thus, the investigators brushed aside an important and significant finding while raising to prominence an insignificant one.

"The LRCP study has been much criticized. In response to many critical letters submitted to the Journal of the American Medical Association, on which the LRCP study was reported, a JAMA editorial essentially admitted that the study was improperly analyzed. 'It may surprise some readers and contributors to learn that

statistical reviewers for The Journal seldom advocate rejection of a submitted article solely on the basis of faulty statistical analysis of data.' Thus the U.S. government, via the National Heart, Lung and Blood Institute, has launched a nationwide program to alter the diet of Americans, based on a study (costing $150 million of public money) that had a faulty statistical analysis. What is more, the statistical defects were known to the trial's organizers and to the journal that published their results."

The following is the response of the "Lipid Research Clinics Program Investigators" to the above letter, undoubtedly headed by Rifkind.[2443] The present writer's comments are interspersed within brackets. The reader should note particularly how Rifkind et al. side-stepped important criticisms, made false statements or shifted a reader's attention away from a central issue:

"Sir - The letter from Dr. Pinckney and Dr. Smith contains erroneous and misleading statements about the Lipid Research Clinics (LRC) Coronary Primary Prevention Trial (CPPT). Without reopening the debate on statistical issues that we have addressed previously at length, we would like to respond on the following points." [Thus, Rifkind et al. refused to respond to our major criticism that they changed their alpha level from .01 to .05 after the results were known. Moreover, they most certainly did not "previously" address this issue satisfactorily. In fact, Rifkind elsewhere denied an accusation by L'Abbe et al.[2455] that alpha was changed from .01 to .05. L'Abbe et al. cited the following statement from the LRC protocol report:

"Since the time, magnitude, and cost of this study make it unlikely that it could ever be repeated, it was essential to be sure that any observed beneficial effect of cholesterol lowering was a real one. Therefore, alpha was set at 0.01 rather than the usual 0.05."[503] Rifkind and his colleagues replied that "The statement cited by Drs. L'Abbe, Detsky and Logan was taken from a published description of the procedure for estimating a sample size sufficient to provide the LRC-CPPT with the statistical power to test this hypothesis. The intent of this statement was to explain to the reader the rationale for setting alpha equal to .01, rather than .05 in these computations. Its intent was not to dictate in advance the criteria for assessing the insignificance of the study's outcome."[2443] Rifkind et al. obviously attempted to explain their way out of a dilemma but could not do so successfully because the protocol statement was absolutely clear in stating the reason why an alpha of .01 was selected to determine significance. Elsewhere in the protocol report the selected alpha and the reason for selecting it were again reiterated, i.e., "A significance level alpha = 0.01 was chosen as the standard for showing a convincing difference between treatment groups."[503] Note the phrase, "for showing a convincing difference."

"(1) In their initial paragraph, Pinckney and Smith cite a 1984 Lancet editorial as advising two-tailed testing for all drug trials, and wonder how this position can be reconciled with The Lancet's endorsement of the CPPT's conclusion that lowering raised cholesterol levels reduces the risk of coronary heart disease (CHD). That editorial distinguishes between trials aimed at testing 'a scientific hypothesis' (e.g., the so-called cholesterol hypothesis, relating reductions in plasma cholesterol levels and CHD risk and trials aimed at 'evaluating a therapy,' and acknowledges the appropriateness of a one-tailed test in the former category. Since the CPPT was designed as a test of the cholesterol hypothesis and used cholestyramine therapy only as the most feasible way to obtain the necessary reduction in cholesterol levels, the editorial does not contradict itself." [Rifkind et al.'s attempt to justify a one-tailed test was simply inadequate. In view of results from previous trials showing negative effects of drugs, such as clofibrate and estrogens, three hypotheses, not one, should have been addressed and would have been addressed by objective scientists, e.g., that cholesterol-lowering drugs (1) increases mortality/morbidity, (2) decreases mortality/morbidity, and (3) has no effect on mortality/morbidity. To select only the first of these hypotheses is to ignore previous findings and bias the results in favor of

the selected hypothesis. The protocol report acknowledged previous findings in the statement, "In some trials a further problem has been the occurrence of significant morbidity and mortality associated with the use of cholesterol-lowering agents."[503] A few months after the LRC results were published, an NHLBI workshop was held. Statistician Richard Kronmal argued that a two-sided test should have been applied to the LRC data. Max Halperin subsequently concluded that "in the end, the resolution regarding inference would depend on consensus rather than a statistical test."[492] Such a comment, while undoubtedly consistent with the alliance's reasoning, demonstrated a profound rejection of scientific analysis principles, something Rifkind did not find foreign, e.g., he elsewhere stated that "I do not feel that to be a shade on one side or the other of a probability value is important to the final result."[756] One can only imagine the consequences of such an attitude. Initially, hundreds of studies would be published with authors presenting "important" findings, even though their results were a "shade" shy of statistical significance. Later, hundreds of other studies would be equally embraced, even though their results were a shade and one-half or two shades shy of statistical significance. The ease with which Rifkind casts aside scientific principles reflects his clinical background and neither an understanding nor an allegiance to the discipline of science. In addition, the cholestyramine therapy was certainly not "the most feasible way to obtain the necessary reduction in cholesterol levels." The reduction observed in the LRC trial was 8.5%, relative to the control group, and substantially less than had been reported in diet trials, including the National Diet Heart Study.]

"(2) In their next paragraph, Pinckney and Smith recite a series of allegations concerning manipulation of the data analysis so that the CPPT outcome would appear more favorable than it was. We will not respond here to their allegations concerning significance testing; our position on these issues, as explained elsewhere in great detail, has not changed. [Rifkind et al. again brushed aside criticisms with the inadequate excuse of "having explained" them elsewhere.] "However, their statement that 'the project became a drug study, not a diet study' (and the implication that this was somehow improper) requires a response. This statement was based on part of a sentence from the first page of the 1984 CPPT results paper (the 1979 CPPT design paper was incorrectly given as the source): 'the most appropriate trial of the efficacy of cholesterol lowering would be a dietary study.' [True, the citation was incorrect but the substance and the general source, NHLBI, <u>were</u> correct.] "Pinckney and Smith should have pointed out that the paper went on to say: 'However, the 1971 National Heart and Lung Institute Task Force on Arteriosclerosis recommended against conducting a large-scale, national diet-heart trial in the general population, because of concern regarding the blinding of such a study, the large sample size and the prohibitive cost.. Accordingly, the LRC-CPPT was initiated in 1973 as an alternative test of the efficacy of reducing cholesterol levels... The use of the drug cholestyramine resin permitted a double-blind design. Thus, the CPPT <u>from its</u> outset used cholestyramine as the means for attaining a plasma cholesterol differential between randomized treatment groups." [Not only did Rifkind et al. say essentially the same thing as did Pinckney and this writer--with more historical details--their argument for using a drug rather than diet was completely untenable, as shown in Volume 1 and particularly in the next section of this chapter.]

"(3) Next, Pinckney and Smith incorrectly state that the excess of gastrointestinal cancers in the cholestyramine group was 'significant, by conventional statistical tests.' We reported in 1984 that there were 21 such cancers (6 buccal cavity/pharynx, 2 oesophagus, 6 colon, 4 rectum, 3 pancreas) in the cholestyramine groups and 11 (1 oesophagus, 1 stomach, 6 colon, 2 rectum) in the placebo group. Setting aside the question of whether conventional statistical tests are appropriate when such pathologically disparate cancers are grouped post hoc, the conventional statistical test for a four-fold table gives $X^2 = 3.1$ (2.5 if the continuity correction is used.) Although this result was not significant at the $p = .05$ level, it was not merely

'brushed aside.' Whereas Pinckney and Smith allege that 'the investigators had nothing to say about this observation in their reports,' the 1984 CPPT results paper indicates otherwise: 'The small numbers and the multiple categories prevent conclusions from being drawn. [Suffice it here to say that the difference between groups in the study with respect to CHD deaths was only 8, one more than the difference in GI cancer deaths. Yet, Rifkind et al. did not conclude that 8 was a "small number." Indeed, they emphasized a "24% reduction in definite CHD death," implying that the difference of 8 was statistically significant when it was not. Using Rifkind et al.'s mathematical reasoning, there was a 700% increase in GI cancer deaths in the treated group. Also, Rifkind's contention that we grouped cancers "post hoc" is erroneous because, as emphasized, an increase in GI cancer cases should have been an hypothesis to be tested before the trial began, based on previous trials. Moreover, Rifkind stated elsewhere that "Without a doubt, cholestyramine is a drug that resides in the GI tract, and animal experiments indicate that it may promote cancer there."[191] Thus, in no way could such an analysis be construed as "post hoc." However, we do admit to having made one error which, unfortunately, was carried forward in Volume 1, i.e., the present writer calculated (ironically) incorrectly a simple Chi square test which erroneously led to our conclusion that there were significantly more GI cancers in the treatment group. That is probably the most important error committed in Volume 1, although it has essentially no impact on any conclusions reached. Rifkind and his associates would not admit to the many errors they commit almost routinely.]

"(4) Finally, Pinckney and Smith state that 'In response to many critical (of the CPPT) letters...a JAMA editorial essentially admitted that the study was improperly analyzed.' That editorial published 1 1/2 years after the CPPT results, is a general article on statistical review and does not comment, even indirectly, on the statistical analysis (or any other aspect) of the CPPT. We are at a loss to see how this article can be construed as an editorial disclaimer of the CPPT. [As noted in Volume 1, there were a great many criticisms of the LRC analyses throughout the medical literature. This fact alone indicates that the LRC analyses must have been less than satisfactory and JAMA editors would not likely have been oblivious of this criticism. Therefore, when two critical letters were published in JAMA on June 7, 1985, it is not surprising that JAMA also published simultaneously an editorial indicating that they seldom reject an article solely on the basis of faulty statistical analyses. While Rifkind et al. would have readers believe that the editorial and critical letters were coincidentally published at the same time one and one-half years after the CPPT results, coincidence seems unlikely. Moreover, the editorial was a disclaimer for all articles published in JAMA, ergo a disclaimer for the LRC trial as well.]

"We suggest that the readers of The Lancet refer directly to the CPPT reports and to the other sources cited by Pinckney and Smith, rather than accept at face value their representation of what these sources say, before drawing their own conclusions. [We strongly agree with this suggestion. Many performed this task and that is precisely why so many criticisms of the LRC analyses were published.][a]

It is important to note that the criteria changing and statistical shenanigans of Rifkind et al. were strongly pointed out by Henry Buchwald and his colleagues,[3326] themselves authors of an NHLBI sponsored clinical trial (Chapter 6). In 1989 they said, "During the course of this trial, the LRC-CPPT changed from two primary response variables, coronary heart disease death and definite, non-fatal myocardial infarction, to the combined endpoint of coronary heart disease death plus definite, nonfatal myocardial infarction. More controversially, the LRC-CPPT adopted a revised

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[a] A few excerpts from the Rifkind et al. letter were omitted because they were not central to the issues addressed.

standard for statistical significance--a one-sided p-value of 0.05 (equivalent to a more standard two-sided p-value of 0.1) at trial termination and abandoned its originally specific significance level of $p < 0.01$." Thus, Rifkind's denial of that which even strong supporters of NHLBI can easily observe makes it all the more certain that Rifkind is anything but an objective scientist.

According to the LRC protocol report, a total "population of 3550 men followed for 7 years would be sufficient to test the benefits of lipid lowering at the desired [.01] significance and sensitivity."[503] In actuality, 3606 men were employed and the trial period averaged 7.4 years. Thus, these "excesses" served to increase the chances of achieving significant findings. The theoretical sample size was also based on the expectation that "The average rate of participants discontinuing the medication was projected to be 5% per year."[503] Since the report of findings indicated that only 27% of the participants had stopped taking the drug at the end of the seventh year, this also served to increase the power of the study to achieve significance.

The sample size was also based on the expectation that "The interval between initiation of intervention and maximum reduction of coronary risk was arbitrarily assumed to be 3 years."[503] Although the report of findings did not present complete data on this subject, it did indicate that the differences between the drug and placebo groups after the first and seventh years were 13.4% and 7.4%, with the average being 8.5%. Therefore, it appears that "maximum reduction of coronary risk" occurred after only one year, again increasing the power of the study to achieve significance.

The sample size was also based on "a very simplistic statistical analysis that merely compares two incidence rates while ignoring such information as the time of the occurrence of the event. If one uses a more sophisticated model...smaller estimates of minimal sample size are obtained."[503] Since a "more sophisticated model" was indeed used in data analysis, this procedure again served to increase the chances of achieving significance.

Of potentially great importance was the fact that CHD "events" in the LRC trial included deaths that probably were not related to atherosclerosis and thus blood cholesterol level. A primary end point of the trial was "Definite atherosclerotic coronary heart disease death," which included either or both of the following categories:[500]

A. "Death certificate with consistent underlying or immediate cause plus either of the following:

   1. Preterminal hospitalization with definite or suspect myocardial infarction

   2. Previous definite angina or suspect or definite myocardial infarction when no cause other than atherosclerotic coronary heart disease could be ascribed as the cause of death

B. Sudden and unexpected death (requires all three characteristics):

   1. Deaths occurring within one hour after the onset of severe symptoms or having last been seen without them

   2. No known nonatherosclerotic acute or chronic process or event that could have been lethal

   3. A 'unexpected' death occurs only in a person who is not confined to his home, hospital, or other institution because of illness within 24 hours before death."

The reader will note first that the primary end point was defined as "Definite atherosclerotic CHD death" and yet included definite or suspect myocardial infarction in Subcategories 1 and 2 of Category A. Not only is "suspect" not the same thing as "definite," there was absolutely no evidence presented to indicate whether the definite or suspect myocardial infarctions were due to atherosclerosis. It has been emphasized elsewhere in this volume that even alliance members admit that as much as 50% of all MIs is not due to atherosclerosis. Category A, therefore, undoubtedly included irrelevant deaths, i.e., not related to atherosclerosis.

As for Category B, the reader is referred to Chapter 3 and 4 which indicated that ample evidence is available, including Framingham data, which demonstrates unequivocally that blood cholesterol is not even weakly related to sudden deaths. Thus, all sudden deaths included in the LRC data base were also irrelevant.

Despite all the "padding" in the study, it was still necessary for the LRC investigators to reduce the initially selected .01 level of significance to the .05 level in order to show a significant difference in CHD "event" rate between the drug and control groups. In fairness, it must be said that the 8.5% difference in cholesterol level between the drug and control groups was only one-third of the projected 24%. Nevertheless, it was unethical and wrong to reduce the significance level because, if nothing else, it was an admission that their results were marginal at best.

Finally, it is useful to reemphasize the ludicrous manner by which Rifkind et al. calculated the CHD event reduction in the LRC trial. They said, "...at 7 years of follow-up the event rate was 8.6% in the placebo group and 7.0% in the cholestyramine groups, a reduction of 19%."[500] They therefore calculated the event percentages of each group and then calculated the percentage difference between the percentages. To illustrate the absurdity of this procedure, consider three hypothetical clinical trials having 100, 1000 and 100,000 men in both treatment and control groups, as shown in Table 7-1. Assume one CHD event in the treatment group in each trial and 2, 4 and 8 events in the control groups as shown. Despite the fact that the event rates become progressively larger in the control groups from Trial 1 to Trial 3, relative to the treatment groups, the rate differences become progressively smaller because the number of subjects greatly increases from 100 to 100,000. Yet, Rifkind et al.'s method of calculating differences would show progressively larger rate differences. In Trial 3, for example, Rifkind et al.'s difference would be no less than 100,000 times greater than the actual rate difference.

The correct event rate difference in the LRC trial was 8.6% - 7% = 1.6%. Objective and unbiased scientists would have reported this difference as the true rate difference. Of course, neither researchers, practicing physicians nor the public at large would have been impressed with such a difference and so Rifkind et al. chose to emphasize their grossly distorted version.

In 1990 Rifkind[3221] indicated that cholestyramine caused a "small increase in HDL" and that "Upon careful analysis, we found that the decrement in LDL and the increment in HDL independently accounted for these favorable effects" [reduced CHD events]. The small increase, relative to the control group, was indeed small, i.e., 1.2 mg, and it is doubtful that "careful analysis" would show that this increment independently accounted for part of the already tiny 1.6% difference in event rates between groups. One almost needs a microscope as it is to observe differences between groups. Now he suggests that 1.6% can be dichotomized into the independent effects of total and HDL cholesterol.

Table 7-1

Rifkind et al.'s method of determining
CHD event rate percentage reduction

		Treatment	Control	Rate Difference	Rifkind's Difference
Trial 1	N	100	100		
	Events	1	2		
	Event rate	1%	2%	1%	100%
Trial 2	N	1000	1000		
	Events	1	4		
	Event rate	0.1%	0.4%	0.3%	300%
Trial 3	N	100,000	100,000		
	Events	1	8		
	Event rate	0.001%	0.008%	0.007%	700%

It may be noted that Rifkind based his much publicized "2% reduction in CHD events for 1% reduction in total cholesterol" on his (erroneous) observation that there was a 19% reduction in CHD events for an 8.5% reduction in total cholesterol.[a] If HDL did indeed have a meaningful impact on that 19%, then Rifkind's erroneous observation becomes doubly erroneous. If it did not have a meaningful impact, then it is ridiculous to pretend that it did. Rifkind cannot have it both ways.

What is most important in a trial is whether or not an observed positive difference between treatment groups is cost-effective. If one wishes to use relative risk ratios in order to appear impressive, one must eventually employ rates to calculate whether or not a treatment is cost-effective. While a complete cost-effectiveness analysis of the LRC results will not be performed in this review, even a cursory examination will reveal that the LRC study results would be extremely costly to achieve in practical settings. For example, 1906 subjects treated for 7.4 years would entail a total drug cost of about $28,208,800. Since there was an excess of 32 CHD events in the control group, the cost per event saved (in drug costs alone) was $881,525. To this must be added the costs of periodic visits to physicians, blood cholesterol measurements, other medications to combat side effects of cholesterol-lowering drugs and surgeries and early deaths due to drug-induced or drug-facilitated diseases such as gallstones and cancer. Only by the excruciatingly irrational reasoning of NHLBI and AHA can it be concluded that these costs are justifiable.

Of course, Rifkind et al. would respond by suggesting that the same results could be obtained by the Prudent Diet. In the LRC report of results they said, "The LRC was not designed to assess directly whether cholesterol lowering by diet prevents CHD. Nevertheless, its findings, taken in conjunction with the large volume of evidence relating diet, plasma cholesterol levels, and CHD, support the view that cholesterol lowering by diet also would be beneficial."[500] But such a stance not only represents wishful thinking, it also reflects a failure to acknowledge that all scientifically acceptable diet trials have produced results contrary to their "large volume of evidence." At minimum, the LRC trial was a failure. At maximum, it was highly unimpressive. But the NHLBI/AHA alliance does not measure success and failure by conventional scientific means. Rather, the alliance defines success and failure by proclamations.

WHY A DRUG TRIAL?

Introduction

In 1960 an Executive Committee on Diet and Heart Disease was put together to evaluate the feasibility and potential utility of conducting a large-scale trial in which blood cholesterol is lowered by a special diet.[725,3018] Former AHA president Irvine Page was chairman of the Committee which concluded after two years of study that a diet-heart study was necessary to provide the definitive evidence for promoting societal dietary changes. The Committee also determined that about 100,000 men would be required for the trial over a four to five year period. However, because it was not known whether a double-blind diet study could be conducted, the Committee recommended that a small-scale feasibility study be conducted first.

The feasibility study, headed by six principal investigators including Irvine Page and Jeremiah Stamler, was initiated in late 1962 and a final report was published in

[a] It would appear that NHLBI's statistician Jerome Cornfield introduced this concept in 1962. Using Framingham data he reported that "A 1% difference in serum cholesterol is associated with a 2.66% difference in risk at all levels of serum cholesterol." Not only is "risk" unrelated to "rate," the later Framingham data certainly did not confirm Cornfield's equation with respect to "risk" as well.

1968.[725] The authors recommended that diet-heart studies "should be planned and put into operation as soon as possible." Participants would involve 47,000 to 58,000 men aged 40-59 or 45-59 at entry with blood cholesterol levels of 250 mg or higher. Although the feasibility study established that a double-blind design was possible, the authors recommended that only the assessment of end point events be blinded for practical reasons.

The authors acknowledged the possibility that during a diet-heart trial the control group might undergo modification of their risk factors, because of the influence of AHA and National Heart Institute programs. As with the Framingham study (Chapter 4) the authors recommended that "Data concerning the risk findings of all participants should be made available to their personal physicians." Thus, while perhaps ethically desirable, this recommendation would have had the potential for reducing or eliminating differences between diet and control groups with respect to risk factors, particularly cholesterol levels. The question is, therefore, why recommend a study that is specifically designed to be a failure?

The Diet-Heart study authors suggested an alternative approach to a diet only study, i.e., in addition to consuming a special diet, the experimental group could be treated for obesity, hypertension, cigarette smoking and physical inactivity. Thus, while the authors initially maintained that a definitive diet-heart study was necessary, they nevertheless recommended a study in which the diet question could in no way be answered.

Eliciting little attention was the fact that although the Diet-Heart study was a feasibility investigation, it nevertheless collected end point data. The Diet-Heart study authors had little to say about this issue except that "The observed overall coronary heart disease incidence rate for the three feasibility studies was 0.5% per year, one-half the anticipated rate." While they did not differentiate between the diet and control groups, the implication is that differences were minimal or perhaps even in the opposite direction as predicted.

In 1968 Page and Brown[3079] published an editorial in the journal Circulation urging the National Heart Institute to conduct a "major definitive study of the effect of diet on the primary prevention of myocardial infarction." But Donald Frederickson, the director of the National Heart Institute, appointed a Diet-Heart Review Panel in 1968 to evaluate the Diet-Heart Feasibility study results and other data and recommend the next logical steps in the diet-heart question. The panel was chaired by Edward Ahrens and included William Connor and Seymour Dayton. The Panel's report, published in 1969, indicated that "It is not proven that dietary modification can prevent arteriosclerotic heart disease in man" and that this question "cannot be answered in experimental animals but only in man."[3018] They believed that the best test of the diet-heart issue would derive from a double-blind primary prevention trial in the open population. However, because of "greater difficulty in accomplishment," the Panel recommended two more "economical" trials. These included a secondary prevention trial in an open population and primary trial in a closed population. Double-blind designs were recommended "for the sake of obtaining more nearly conclusive results." The Panel also estimated that the ideal large primary trial of five years would require about 57,000 men and would cost about $20 to $380 million.

In the year that the Panel's report was published Ivan Frantz[2962] noted that "Few controversies have divided the medical community for such a long time as has the sterol hypothesis. The inordinate delay in undertaking a study of sufficient size to settle the controversy once and for all is due to the cost in dollars and in scientific man-hours. We keep hoping that 'the indispensable ordeal' can somehow be finessed. Perhaps a new discovery will miraculously deliver us from it. If it does not, some

courageous group with control over the necessary resources will eventually make the unpleasant decision."

In 1970 the Inter-Society Commission, whose staff included Jeremiah Stamler, William Connor and Thomas Dawber, strongly urged that "a special Committee be established at a high level of the Federal Government to develop coordinated plans for large-scale, long-term trials to determine the effect of various interventions, particularly diet modification, on the rates of premature atherosclerotic diseases in the U.S." The Commission cited the National Diet-Heart study and the Diet-Heart Review Panel reports.

There is no indication that the Frederickson-appointed Diet-Heart Review Panel had any influence on the National Heart and Lung Institute's research plans.[a] It seems to have been outrightly rejected because the new NHLI director, Theodore Cooper, formed yet another "Task Force" in mid-1970 to essentially duplicate the Panel's efforts and to recommend entirely different studies. The fact is that Cooper was never in favor of a large diet trial. When a Senate Committee approved the conduction of such a trial in June 1968, Cooper expressed "reservations" even then.[3313] Wall Street Journal columnist Jerry Bishop[1995] reported that the NHLI was under great budget constraints in 1970 which led to the rejection of the so-called "costly" diet-heart trial. However, not only was Cooper against such a trial in 1968, there was an abundance of direct and indirect evidence that indicated that the diet-heart trial was rejected for the principal reason that NHLI simply had no faith in the diet-CHD relationship. In particular, two studies were published in 1969 and 1970 that offered negative support and provided more fuel for Cooper's antagonistic position. The Veterans diet trial report,[454] appearing in 1969, indicated that a special low-saturated fat, low-cholesterol diet did not significantly reduce CHD events. Such results confirmed the findings of earlier randomized and blinded diet trials conducted in Europe.[466,485,495] Authors of the Veterans trial, Dayton and Pearce, stated that "The results of our own trial, even when buttressed by concordant observations on two other primary prevention studies, are not sufficient grounds for aggressive efforts to change the U.S. diet."[2541]

Of equal impact was the Framingham diet study published in 1970.[274] This study demonstrated virtually no relationship between dietary nutrients consumed by Framingham participants and subsequent CHD incidence. There is no question that the accumulated evidence, topped by the Veterans trial and the Framingham Diet study, had a profound effect on NHLI and its Task Force in 1970, although neither addressed these studies explicitly.

The Task Force's report was published in June 1971.[705] Selected excerpts follow:

"...recommendations concerning diet are based on personal impressions and fragmenting evidence rather than a scientific proof.

"Intuitively, it would seem prudent to decrease the incidence of hyperlipidemia in the population of the U.S. by controlling diet. However, this would be a formidable venture if it were to involve changing the diet of the entire nation. Indeed, before advocating such a major revolution in diet, the Tack Force concluded that convincing evidence should be sought that lowering the levels of lipids in blood reduces morbidity and mortality from arteriosclerosis.

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[a] The NHI became the NHLI in 1969.

"...the Task Force concluded that there is considerable uncertainty that a meaningful answer could be obtained or that the [proposed diet-heart] could be carried through to completion.

"The Task Force chose instead to recommend, for the present, more limited trials of diet, such as that which is currently being supported by the NHLI in Minnesota, using a closed population. [This "Minnesota Survey" trial[555] would be classified in 1976 as another failure to demonstrate the benefits of dietary changes on CHD.]

"Clinical trials using...drugs...are currently underway. Particularly noteworthy is the Coronary Drug Project which the NHLI is conducting...[This trial[49] would be classified in 1975 as another failure to demonstrate that lowering blood cholesterol reduces CHD incidence.]

"Within the NHLI Intramural Program, a study has been initiated of 250 patients with elevated levels of blood cholesterol. Half of the subjects will be treated using a combination of diet plus the cholesterol-lowering drug cholestyramine; the other half will receive only the diet. [This study would be published in 1984, failing to demonstrate significant benefits of cholesterol-lowering.]

"Currently under development by the NHLI is a third program which, at present, involves six cooperating groups called Lipid Research Clinics. These clinics will assemble a population of patients with hyperlipoproteinemia. The Task Force urges that this program be expanded as expeditiously as possible to include clinical trials of treatment in order to determine whether correction of the blood-lipid abnormality by diets and drugs will modify morbidity and mortality from coronary heart disease. [This recommendation led to the MRFIT study which was published in 1982 as yet another failure and to the LRC trial which was published in 1984, showing dubious significant but unimpressive results.]

"Finally, the Task Force believes the coordinated national effort should be related to the experiences that are being gained outside of the U.S. For example, a primary trial of long-term treatment with clofibrate, a lipid-lowering drug, is now underway in Edinburgh, Prague, and Budapest under the aegis of the World Health Organization. Important data have already begun to be gathered. The Edinburgh study has shown that there are no important toxic effects of clofibrate...[This WHO trial[461,1661] would be published in 1978 and 1980, not only representing another failure but also revealing higher death rates with clofibrate use.]"

Rationale for Rejecting a Diet-Heart Trial

In view of the fact that NHLI rejected the recommendations by the authors of the National Diet Heart feasibility study and the Diet-Heart Review Panel, it is more than apparent that NHLI handpicked Task Force members who would also reject those recommendations. The rationale used by NHLI, as expressed through the Task Force may very well be the best example of illogical, inconsistent and outrightly absurd reasoning demonstrated by the alliance. Incredibly, despite its absurdity, this writer was not able to find a single article whose author(s) contested the alliance's rationale.

The rejection of the Diet-Heart study was said to be based on "three convictions."

(1) "...one might well fail to obtain the desired definitive scientific answer from this huge undertaking.

(2) "the managerial problems of carrying out a well-controlled study with such a large free living population (estimates ranging from 24,000 to 115,000 individuals) in a country where an average of 18% of the total population move annually, and for the lengthy period of time (7-10 years) required to obtain a sufficient number of clinical events in the study population world make the study difficult to complete.

(3) "in view of these uncertainties, the projections of manpower and dollar costs (ranging from $500 million to more than one billion dollars) for such a study are formidable."

The first "conviction" was almost humorous. In view of all research data, there is no doubt that NHLI had no confidence whatsoever in even a very large diet trial showing benefits of cholesterol-lowering by diets. As will be seen, all other reasons given for rejecting the trial were undoubtedly created to justify that rejection.

The second "conviction" addresses several points which the Task Force discussed in greater detail. These are critiqued below.

The third "conviction" appears to have been an arbitrarily generated, inflated cost. All estimates to that time were substantially lower. The National Diet-Heart study[725] investigators indicated that a large diet-heart trial was economically "feasible." The 1970 Inter-Society Commission for Heart Disease Resources report estimated the cost to be $70 to $80 million. Blackburn[2691] said the cost would range "anywhere from $50 to $100 million." And the Diet-Heart Review Panel[3018] estimated the cost to be $20 to $380 million. The Task Force report presented no cost analyses or rationale of any sort to arrive at the figure of $500 million to $1 billion. As will be seen, this figure was a total exaggeration of reality.

More specific reasons given for rejecting the large diet trial follow. One reason was the presumption that cholesterol-lowering by diet would be insufficient to induce a significantly lower incidence in CHD cases. Levy[1846] and the LRC design protocol report[503] subsequently concurred with that argument. But all such arguments were completely unsupported by previous clinical trials. As emphasized in Volume 1, previous diet trials, including the National Diet Heart feasibility study, achieved lower blood cholesterol levels than did previous drug trials. And, of course, the LRC drug trial, which the NHLI, via the Task Force, recommended over the diet trial, would later prove to have reduced blood cholesterol level to a significantly less extent than did the Diet-Heart feasibility study. Therefore, this reason for rejecting the diet trial ran wholly contrary to the existing scientific evidence. Very importantly, if NHLI did not honestly believe that cholesterol-lowering by diet in a well-controlled trial could result in a significantly reduced incidence in CHD, how could NHLI expect the American population to alter its diet sufficiently to produce such results? In an official statement to the press[2500] in 1989 and to the medical world[3349] in 1990 the AHA and NHLBI maintained that Americans can easily reduce their blood cholesterol levels by 10% using the AHA recommended diet, thereby reducing CHD events by 20%. Thus, it would seem, the public can do something in an uncontrolled situation that NHLBI could not in a highly controlled trial.

A second reason given was that it would be difficult to complete a 7-10 year trial in a country where 18% of the population moves annually. Of course, this argument was pure smokescreen because it was equally applicable to the subsequently selected LRC drug trial that was also designed for 7-10 years. In fact, the proposed diet trial would have had fewer problems because it was designed for five years, not 7-10 years.

A third reason given was concern about "the inevitable high dropout rate when individuals are required to adhere to vigorous dietary prescriptions for many years." Levy also later used this argument.[1846] Not only is this argument partially redundant

with the second argument discussed immediately above, it is likely that the dropout rate would have been substantially less with a diet trial, where free food would be supplied for many years, than with the subsequently selected drug trial, where subjects would be subjected to a most obnoxious substance (cholestyramine) and all its highly unpleasant side effects. Consider a participant's likely answer to the following question: would you rather consume a drug several times daily for seven years that will probably cause one or more unpleasant side effects (vomiting, bleeding, diarrhea, nausea, rash, abdominal pain, flatulence, heartburn, anorexia, arthritis, muscle and joint pains, headaches, anxiety, dizziness, gallstones, etc.) or would you rather consume pleasant food for five years that we will provide you free of cost? It is, frankly, absurd to think that the dropout rate would be higher in the diet trial, especially since all alliance members insist repeatedly that low-saturated fat, low-cholesterol diets can be just as palatable as the typical American diet.

A fourth reason given was the presumption that the diets of control subjects might approach those of the treated subjects over time, due to national diet changes encouraged by such "health" agencies as NHLI and AHA. But this argument is invalid for two reasons. First, there were no indications in 1973 (the initiation of the LRC drug trial) that health agencies had had any major impact on the diets of most Americans. In fact, the huge National Cholesterol Education Program, launched 12 years later in 1985, was solid testimony to the fact that most Americans had been uninfluenced by previous recommendations of NHLI and AHA. It is true that the American diet was changing gradually but, as shown in Chapter 3, that trend had been underway long before the establishment of the National Heart Institute and the first recommendations by the AHA. Second, given the possibility that major dietary changes might occur, due to perception by subjects for a need to reduce blood cholesterol levels, it is more likely that control subjects in a drug trial would have altered their dietary habits. According to the National Diet-Heart feasibility study authors, subjects could not distinguish between the experimental and control diets so why would control subjects be concerned? On the other hand, while the LRC authors would later claim that the LRC study was double-blinded, it is highly unlikely that the drug subjects were blinded because of the numerous and obnoxious side effects of cholestyramine which they had to tolerate. In fact, by the LRC authors own admission, the drug subjects reduced their consumption of the required amount of cholestyramine by an average of 30% to 37% during the entire seven year trial.

A fifth reason given the Task Force was that subjects treated with diet "would most likely modify other risk factors." This is an incredibly silly argument because it is clearly equally applicable to subjects treated with drugs.

A sixth reason given was totally redundant with the above fifth reason and this reflects both the sloppiness and desperation of the Task Force's presentation. It was said that control subjects in a diet trial would likely improve other risk factors such as smoking and hypertension because of national health programs. Of course, this "argument" is again equally applicable to control subjects in a drug trial.

Based on their analysis, investigators of the National Diet-Heart study[725] concluded that 47,000 to 58,000 men would be required for five years. The Diet-Heart Review Panel[3018] offered seven designs most of which required 30,000 to 219,000 men for five years. The NHLI Task Force[705] estimated that the required number of men would be 24,000 to 115,000 for 7 to 10 years. These estimates were apparently reinterpreted subsequently by other alliance members. For example, Stamler[1313] who co-authored the National Diet-Heart study report, claimed that the needed sample size would be 40,000 to 400,000. Grundy[499] indicated it would entail 60,000 for "at least 10 years." And Levy presented two different estimates in two different articles, i.e., 50,000 to 150,000 for 10 to 15 years[288] and 30,000 to 150,000 for 10 to 30 years.[1846] These

wildly different interpretations suggest a disregard for facts and an emphasis on the need to convince readers that the diet trial was not feasible.

It is to be noted that the above estimates of required numbers of subjects were generated and "created" after-the-fact, i.e., after the National Diet-Heart feasibility study was completed, giving the impression that the required number was unknown before the feasibility study. Such was decidedly not the case. The National Heart Institute approved the conduction of a large diet trial involving 100,000 men in 1962, pending the success of the feasibility study. This fact can be found in the first paragraph of the National Diet-Heart study Final Report,[725] published in 1968, and in an editorial in Circulation by Irvine Page[2925] four years earlier. Thus, the failure of the feasibility study to show positive effects of diet changes (as well as the negative Framingham diet study results and previous diet trials), not the number of subjects needed for the main study, was undoubtedly the only relevant concern.

Task Force Recommendations

The Task Force stated that "A definitive test of this hypothesis [i.e., lowering blood cholesterol reduces CHD incidence] in the general population is needed. However, such a test presents formidable problems since it would require a large population young enough so that arteriosclerosis is still relatively limited, and one that would adhere to a standardized diet, or drugs, or both, for a period of approximately 7 to 10 years. Before embarking on such a massive undertaking, it would be desirable to carry out more modest clinical trials in target populations at high risk of arteriosclerosis. As described earlier in this report, several such trials are currently under way both in the U.S. and abroad. In addition, other trials should be initiated to supplement those on-going efforts."

The "other trials" recommended by the Task Force were multifactor prevention trials in which blood lipids, cigarette smoking and hypertension would be manipulated in subjects who were hypercholesterolemic, smokers and hypertension. The Task Force also recommended that the existing six Lipid Research Clinics should be expanded to increase the number of patients with hypercholesterolemia and conduct "clinical trials of treatment in order to determine whether correction of the blood lipid abnormality by diets and drugs will modify morbidity and mortality from CHD. It is clear that expansion of the Lipid Research Clinics will also make it possible for them to conduct primary prevention trials in 'high risk' patients." Thus, although not describing the recommended trials in detail, obviously the MRFIT and the LRC trials were the ultimate derivatives of these general recommendations.

If one takes the above statements literally, the Task Force set aside a "definitive" test of the lipid hypothesis and recommended instead "more modest clinical trials" which, by definition were not definitive. Therefore, the ultimate results of the LRC trial should not have been described as "conclusive" by Rifkind and others. More importantly, the setting aside of a definitive trial in favor of first conducting more modest trials in view of the fact that several other modest trials were already underway suggests that the Task Force considered many modest undefinitive trials to be more cost-effective than one definitive trial. Such reasoning was profoundly irrational.

Lest the reader think that too much may be made of semantics, let it be emphasized that the illogical, inconsistent and general abuse of semantics have served the alliance well in justifying every step taken toward the initiation of the NCEP, despite the accumulation of an otherwise insurmountable body of unsupportive scientific evidence.

A few months after the Task Force's report was published, Theodore Cooper spoke at the 1971 AHA annual meeting.[2085] While the large scale diet trial was rejected by the Task Force and NHLI, Cooper stated, "my...recommendation is that the test of the lipid hypothesis using the usual clinical end points be extended to a large scale trial in patients at high risk because of their lipid characterization. Such trials should strive for maximal lowering of lipids by any method available, effective, appropriate to the patient situation, and safe, be it diet, drugs, surgery, or any combinations thereof. The test is therefore not of diet or drugs or surgery, but rather it is a test of a lipid hypothesis. This distinction is most important. As you know, the Institute has been urged to endorse and undertake a national study of the effect of alteration of the diet on the cause of heart disease. All diet studies that have been initiated or proposed would be expected to reduce lipid levels to some extent. We now know that the reduction from a single dietary regimen would not be expected to constitute optimal metabolic management in all patients. Thus, in my opinion, a diet-heart study alone is not an adequate test of the lipid hypothesis."

In view of the fact that Cooper selected the single factor LRC drug trial, the above argument is illogical. While suggesting that a drug trial would be a test of the lipid hypothesis but a diet trial would not, which would be absurd, Cooper also absurdly suggested that a single dietary regimen would not constitute an optimal therapy but a single drug therapy would be optimal.

Not only did Cooper maintain erroneously that diet changes could not lower blood cholesterol levels sufficiently, Manttari et al.[3004] made the same claim in justifying the use of a drug in the Helsinki II trial. Would anyone seriously believe that the Warner-Lambert Pharmaceutical Company would have funded the Helsinki II trial if diet were selected as the sole means of reducing cholesterol levels?

Despite his attempt to suggest that his focus was on the lipid hypothesis rather than diets or drugs, it is clear from his arguments that he wanted to avoid a diet trial at all costs. Most importantly, the accumulated evidence from clinical trials to date, including the National Diet-Heart feasibility study, showed that diets reduced blood cholesterol levels to a greater extent than did drug trials. And, as indicated earlier, if a large well-controlled clinical trial on diet could not demonstrate significant effects on CHD end points, how can the alliance expect the entire American population to change its diet to the extent supposedly necessary to show health benefits?

Even though Rifkind[3339] knew or should have known that diet clinical trials achieved greater cholesterol-lowering than drug trials, he reported during the 1984 LRC press conference that the LRC study used a "potent" cholesterol-lowering drug. This "potent" drug did not reduce cholesterol as much as did the diets used in the Diet-Heart Feasbility study. The fact that subjects may not have continuously taken the full recommended dosage is irrelevant.

Of equal importance is the argument by Cooper (as well as by the Task Force,[476,705] Levy[1846] and Rifkind[3339]) that a drug trial could be increased in power by using only middle-aged men with very high blood cholesterol levels. Of course, this procedure could have been applied to a diet trial as well and, in fact, it was recommended by the National Diet-Heart study investigators[725] as a means of reducing sample size. But the impression given by Cooper and others was that it was somehow uniquely an advantage of conducting a drug trial.

Cooper continued, "Elevated blood cholesterol, elevated blood pressure, and cigarette smoking have been repeatedly reported as prime 'risk factors' for CHD. It seems reasonable to extrapolate these observations to practical prevention by advocating a program which includes elimination of cigarette smoking along with

reduction of serum cholesterol and control of blood pressure. Since all these measures seem prudent and sensible, perhaps even obvious, do we need to have a multifactor clinical trial? This is my...recommendation.[a]

Cooper indicated that the drug trial, the MRFIT trial and a hypertension trial (involving the young, women and blacks) could be conducted simultaneously for "less than $112 million over a 7-10 year period."[1996,2085] Of course, the cost of the drug and MRFIT studies alone turned out to be $265 million, undoubtedly higher than would have been the cost of a definitive diet trial.[b]

Some Additional Gobbledygook

To illustrate further inconsistencies and fabrications by the alliance, consider the topic of blindedness. The National Diet-Heart study investigators (which included Jeremiah Stamler) concluded that "The double-blind design achieved its objectives splendidly" and that a large scale diet trial is "economically feasible."[725] Yet, much later Stamler[2939] told his readers that "large-scale unifactor diet-heart primary prevention trials could not readily be performed double-blind with free-living Americans, except at very great cost. In effect, Stamler simply accepted "party line," a behavior he has shown repeatedly for decades. In his 1984 discussion of the LRC drug trial, Rifkind[755] fraudulently told his readers that there was a "virtual inability to devise a double-blind [diet] study." And Robert Levy switched tracks in different contexts. In 1981 Levy[1846] agreed that a "double-blind design could be maintained" in a diet trial but when he discussed the Oslo diet trial in 1984 he said, "Unfortunately, because it was a diet study, it could not be blinded."[698]

The FTC-NCEN legal trial in 1975 was discussed in detail in Chapter 2. Testifying under oath at this trial Henry Blackburn said that the 1971 Task Force report indicated that a large diet trial "would not be tested in our time because of the constraints of the sample size and cost...and the other difficulties in testing it as a single factor hypothesis in high risk middle-aged Americans."[2691] [Note the emphasis on "single factor hypothesis."] Our leaders have decided that national priorities are such that we can't undertake the single factor trial and they proposed an alternative, a very practical public health one that you know about, related to the end point of coronary mortality. That is, the MRFIT trial."

Blackburn discussed such things as drop-out rates, confidence values, etc., all concepts equally valid to any type of clinical trial, single or multi-factored. Then he said, "That is why we really don't seriously consider single cause interventions for these reasons or certain dietary items specifically in experimental studies. This is out of the question, not only from the design standpoint but from the very practical matter that you can't do a pure and simple single factor trial on diet...because you modify diet and it is liable to influence a person's smoking habit or how much exercise he gets. Anything that affects health behavior en masse will end up being a multi-factor trial so that is why the decision was made for the MRFIT."

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[a] Note the term, "my recommendation," as opposed to the "Task Force's" or NHLI's" recommendation. While Zukel et al.[3345] indicated that Cooper "approved" the Task Force's recommendations, all evidence indicates that the Task Force "adopted" Cooper's recommendations.

[b] Cooper would later testify at the Senate Select Committee on Nutrition and Human Needs that a diet-heart trial was prohibited by "economic factors and practical management factors."[2186]

Two related questions emerge after reading Blackburn's testimony on his subject. Could he, as an "expert witness," not have known that the Task Force recommended the single factor LRC drug trial, as well as the MRFIT? And could he, as an "expert witness," not have known that the LRC trial had already been underway for two years prior to his testimony? In effect, Blackburn's arguments were poor interpretations of the Task Force's report which, in turn, was comprised also of poor reasoning.

Theodore Cooper's testimony at the FTC-NCEN trial was even more dumbfounding.[2688] He said the Task Force "indicated from practical reasons both size and cost of the [diet-heart] study, for the ability to maintain people in the study and follow them for long enough periods of time for what the design criteria might be, the definitive trial on primary prevention becomes a largely impractical thing and if you were then to intervene in addition with medications which over a period of time began to show some toxic effects or other bad effects, then you have an ethical problem so they said for practical reasons that perhaps the further steps ought to further pursue a secondary trial." Thus, this statement clearly indicated that a primary prevention trial was rejected in favor of a secondary trial, even though the recommended and selected MRFIT and LRC trials were both primary trials and were already underway for three and two years, respectively, when Cooper made this statement. (Elsewhere in his testimony Cooper acknowledged that an LRC drug trial was currently being conducted but he was not questioned with respect to his contradictory testimony.)

Although Cooper said that a "definitive trial on primary prevention becomes a largely impractical thing," he later testified that "there were several unresolved problems and that trials ought to be continued, studies continued and definitive trials attempted to resolve the problems." Thus, he effectively said that a definitive primary trial ought to be conducted even though it is largely impractical. And it is to be observed also that Cooper's statement about introducing medications in a trial, their toxic effects and the associated ethical problem is nothing less than baffling, particularly as his LRC study was wholly based on (cholesterol-lowering) medications.

All things considered, there can be no doubt that NHLI rejected a definitive diet trial for one reason only, namely because Cooper and his colleagues did not believe that diet changes would affect CHD rates. All of the arguments presented comprised rhetoric designed to hide this fact. Maintaining their contradictory stance many alliance members such as Rifkind[500] and Levy[698] simultaneously claim that a diet trial is not feasible in one context and yet eagerly cite the diet trials conducted previously in the U.S. and Europe in another context. If diet trials are not feasible, how is it that so many have been conducted?

As a postscript, Irvine Page, former president of the AHA and director of the National Diet-Heart feasibility study, offered the following comments in 1980 on the Task Force's rejection of a diet trial: "...the planned clinical experiments [MRFIT and LRC trials] aimed at testing the hypothesis that lowering plasma cholesterol slows atherogenesis, have for the most part been ill planned and financed. The great opportunity to do it properly [i.e., conduct a large-scale diet trial], once offered to the U.S. Public Health Service, was rejected by an 'expert' committee, whose judgment in retrospect does not appear to have been expert."[104] Indeed, neither Cooper nor the Task Force exhibited intelligent behavior which could be described as "expert."

The reader may recall that the Diet-Heart feasibility study authors estimated that a definitive trial could be conducted within a five year period. The Task Force subsequently transformed that period into one of seven to ten years. In 1981 the NHLBI Working Group[3067,3068] reached the pinnacle of absurdity by claiming that a diet trial would require decades. The Working Group stated,

"A direct test of the role of dietary lipids in the etiology of atherosclerotic disease would involve randomizing thousands of newly weaned infants to two groups, one to subsist for decades in a diet rich in cholesterol and saturated fat, and the other on a diet low in these constituents. Both groups would require the same caloric balance and all other aspects of lifestyle held constant in a like fashion. The end point would be incidence and mortality from atherosclerotic disease in the two groups in middle-age. Clearly, this test of etiology is not feasible, either practically or ethically."

The Working Group also said that "...an insoluble problem that exists in regard to all unifactor trials is that of self-imposed multiple changes in lifestyle by participants, whether it be intervention in diet, smoking cessation, exercise, or modification of type A behavior. Such single factor trials are not feasible." But two paragraphs later in a different context the Working Group boasted about NHLBI's single factor LRC trial, i.e., "In the U.S., a primary prevention trial is in progress concerning the ability of the drug cholestyramine to reduce CHD risk as a result of middle-aged men with hyperlipoproteinemia."

The Working Group's "reasoning" was so completely irrational that it is worthwhile listing the names of the group's members here:

Alfred P. Fishman	John Ross, Jr.
Sidney Blumental	Russell Ross
Lawrence S. Cohen	David C. Sabiston, Jr.
M. Bernadette Garvey	Revel A. Stallones
Edgar Haber	Jeremiah Stamler
David A. Hamburg	James F. Toole
Henry C. McGill, Jr.	Donald B. Zilversmit
Alex V. Nichols	John B. Dunbar
M. Jeanne Pontious	Jay Moskowitz

Whether true or not there is an old saying that there is a fine line between intelligence and madness. Perhaps too much "expertise" caused the Working Group to cross that line.

CHD "EVENTS," CHD MORTALITY AND TOTAL MORTALITY

In their reviews of the LRC and/or Helsinki II trials, alliance members stress the difference between treatment and control groups in CHD "events" (i.e., fatal and nonfatal MI) but rarely mention the more important fact that the differences in CHD deaths and total deaths were negligible (e.g., Goodman,[2034] Hunninghake,[2152] Rifkind,[2032] Grundy[2036]). Long before any important clinical trials were conducted, Katz, Stamler and Pick[3201] stated in 1956 that "such evaluations require several years of assay, since the sole reliable criterion for assessing the efficacy of a given regimen is its effect on the duration of survival" [underlines added]. In 1977 Stamler emphasized that "...all causes of mortality is the acid test...because...(the)...concordance among trends of CHD, cardiovascular and all-causes mortality rates strongly supports the conclusion that the decreases reported in CHD mortality rates are real, not spurious."[1600] In 1981, Robert Levy was more explicit. He said, "The bottom line in a chronic disease prevention program is not awareness or treatment, but change in mortality."[1846] And with respect to trials published before the LRC and Helsinki II studies, Levy argued that "The problem with all these trials is that none of them have shown a difference in heart attack or death rate in the treated group. Only when soft end points were used in fact was there any subjective difference."[288]

But neither the large MRFIT, the LRC nor the subsequent Helsinki II and Physicians' Aspirin studies showed changes in mortality as a result of treatment. As pointed out by Fries et al., the combined total deaths in the treatment groups in all four studies were virtually identical to those in the control groups, i.e., 488.[1813]

A common argument used by the alliance to "explain" the lack of differences observed in total mortalities is that the studies were not designed to show such differences. For example, Horlick stated in 1989 that "None of the trials reported thus far was designed to examine total mortality."[1930] Glueck said, "The controlled clinical trials [LRC, Helsinki and CDP niacin group] on lowering LDL and/or raising HDL were designed solely to assess CHD morbidity and mortality and had neither the sample size, power, nor duration of follow-up sufficient to allow a statistically significant assessment of whether and to what degree cholesterol lowering might reduce all causes of mortality. Thus, it is statistically inappropriate to belabor these trials for their lack of demonstration of a reduction of all causes of mortality."[2565] And Gotto repeated the argument, "It was not possible to reach significant conclusions about all causes of mortality because of the limitations of the number of subjects enrolled and the length of the study."[2035,a]

Probably the most dramatic attempt to deceive both physicians and the public at large was that of DeWitt Goodman who "debated" Robert Olson on a 1989 McNeil/Lehrer News Hour broadcast.[2506] Describing the principal American clinical trials Olson said, "These studies show a small change in nonfatal heart attacks but no change in all-cause mortality, no change in longevity." Goodman replied, "I'm sorry that Dr. Olson misunderstands, and misinterprets the evidence. The clinical trials were designed to show a reduction in heart attacks, but not overall death rate." Olson then said, "That's simply not true" and Goodman responded, "It <u>is</u> true."

The three principal American trials, all funded and supervised by NHLBI, were the CDP, the MRFIT and LRC studies. The CDP Research Group reported in 1975 that "The <u>primary</u> end point or response variable established for determination of drug efficacy in the project was <u>total mortality</u>." Sherwin et al.[3043] emphasized that death was the recommended end point, not heart attacks per se, because "it was felt that biases might arise in the ascertainment of nonfatal events." The MRFIT Research Group stated during (1976,[476]) and after (1982,[471] 1986,[474]) the trial that the <u>primary</u> end point was <u>total CHD mortality</u> and that a secondary end point was <u>total mortality</u>. And the 1979 protocol report for the LRC trial clearly indicated that one of the two <u>primary</u> end points was <u>total CHD mortality</u>.[503] Therefore, contrary to what Gotto, Horlick, Rifkind, Goodman and others would have readers believe, the American clinical trials were indeed designed primarily to assess total mortality and/or total CHD mortality. The above statements about end points are in the medical literature for all to see. It may seem harsh to call these individuals fabricators but the only alternative is to classify them as incredibly unknowledgeable in that which they profess to be expert.

Table 7-2 provides some relevant data on the four major trials. In addition, similar data are presented for a trial in England in which "treatment" was advice to subjects to consume more fish and less red meat. (The purpose of including this trial will be evident below.) It is clear that the selection of end points was not related to trial duration or number of subjects. It is also well known that none of the trials showed

[a] But Gotto,[1341] Rifkind,[2032] Blankenhorn[2039] and many others were quick to praise the niacin group in the CDP trial as showing a decrease in overall mortality 9 years after treatment was stopped, despite the fact that the niacin group was much smaller than treatment groups in the LRC, Helsinki and MRFIT studies.

Table 7-2

Slective findings and characteristics
from five clinical trials

	Primary End Points				
	Nonfatal MI	Fatal MI	Total Mortality	Duration(yrs)	Number of Treated Subjects
CDP[490]			Yes	6.2	1,101-1,119
MRFIT[471]		Yes		7.0	6,438
LRC[500]	Yes	Yes		7.4	1,906
Helsinki II[1056]	Yes	Yes		5.0	2,051
Burr[2297]			Yes	2	1,015

significant effects of cholesterol lowering on the primary end points. While the authors of the LRC and Helsinki II trials maintain that the primary end point (singular) was the combined end points of fatal and nonfatal MI, the LRC protocol report[503] clearly states otherwise and the Helsinki II trial report[1056] also refers to three primary end points, i.e., fatal MI, nonfatal MI and cardiac death.

The Burr et al. trial provokes more amusement than it does scientific interest. It is reviewed in detail in Chapter 6 but is mentioned here to illustrate the inconsistencies with which "end points" are chosen. Fish consumption, of course, has been promoted by some as a protection against CHD. Burr et al.,[2297] however, found no benefits of fish consumptionadvice with respect to CHD but reported that such advice reduced total mortality. The authors insisted that "We decided at the outset that total mortality would be the primary end point." Such a contention is most certainly unlikely.

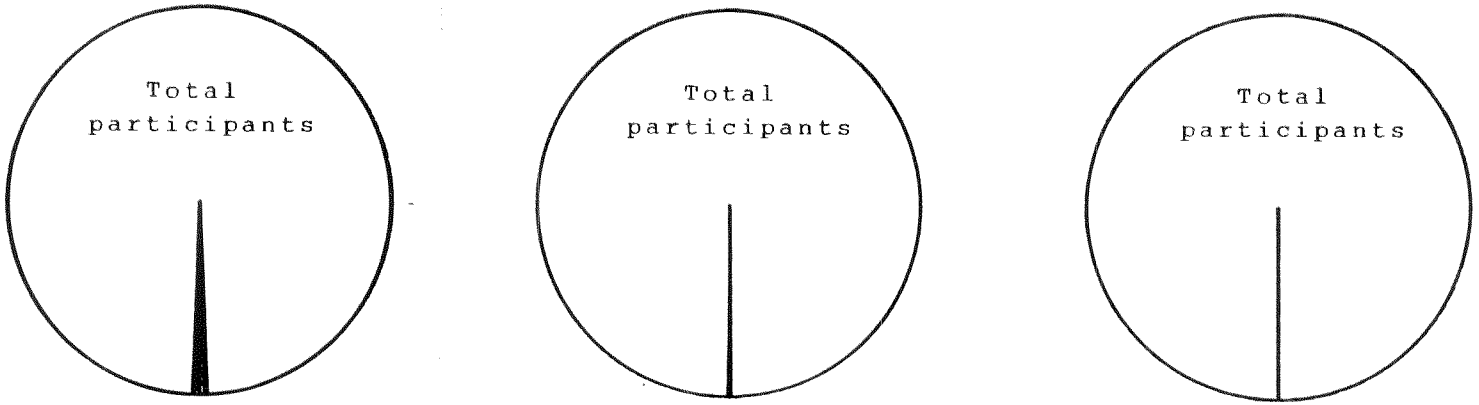
Like so many other aspects of the diet-CHD research program, end points are quite obviously frequently changed to fit the outcomes of studies. There is documented proof of that fact. When data reveal no effects whatsoever among subgroupings, end points are not changed (because there is nothing to gain) but the study is then described as inadequate in terms of duration, number of subjects, cholesterol lowering, etc. to observe expected effects.

In two large randomized groups, one would expect the total death rate to be statistically identical in both groups, given no differential treatment or given an ineffective treatment. If a treatment is given to one group which reduces CHD deaths significantly, that reduction should be reflected in a difference in total deaths between groups. It is true that the total death rate difference will not be statistically significant unless the difference between CHD deaths is quite large, but it nevertheless should correspond closely with the difference in CHD deaths. For example, if a treatment affects only CHD and reduces the number of CHD deaths by, say 50, then the total deaths in that group should be roughly 50 fewer than in the comparison.

The fact is that the trials defined as "conclusive" by the alliance, i.e., the LRC and Helsinki II studies, reported a combined reduction of 13 CHD deaths and a 0.0 reduction of total deaths. Neither values are of any statistical consequence in terms of total participants (7,887) and total duration (12.4 years). Thus, the "conclusive" trials were effectively dependent almost entirely on differences in the soft end point of nonfatal CHD "events." Not only is this outcome representative of the criticisms of many researchers, it is also representative of Levy's criticism of previous trials.

Since the difference in total deaths between treated and control groups in the combined LRC and Helsinki II trials was 0.0, there is no statistical evidence that a significant difference would emerge in a group of 100,000 or even a million participants. And even if a significant difference did emerge, it would likely have no practical consequences whatsoever.

Figure 7-1 shows rather dramatically the exceedingly small differences between treatment and control groups in the combined LRC and Helsinki II trials with respect to CHD events, CHD deaths and total deaths. No objective scientist would consider such differences worth the cost and side effects of taking cholesterol-lowering drugs. The cost of drugs alone for the two trials amounted to about $32,618,148, assuming $1,920 per year per person for cholestyramine and $540 per year per person for gemfibrozil. That figure represents more that $32 million per no lives saved and about $544 thousand per CHD event saved. Rather than conclusively demonstrating that cholesterol-lowering by drugs reduces CHD events, these trials conclusively



(a) CHD EVENTS (b) CHD DEATHS (c) TOTAL DEATHS

Figure 7-1. Difference between treated and control groups in (a) CHD events, (b) CHD deaths and (c) total deaths in the combined LRC and Helsinki II trials.

demonstrated that cholesterol-lowering has trivial effects on CHD and no effects on total mortality.

Finally, the total lack of scientific ethics exhibited by the LRC and Helsinki II trial authors in "interpreting" the results of these studies was outrightly shameful. Although not presenting a scathing attack, a 1989 article by Brett[2969] provided a clear example of their attempts to "weasel" their way out of a dilemma that virtually all trial investigators have confronted, namely the failure to find differences in total death rates between treated and control groups. He said, "Curious language was employed to explain the general failure of these drug trials to influence mortality. For example, the Helsinki authors, reflecting on the increased mortality rates among patients treated with clofibrate in a previous study, stated that 'the excess of deaths diverted attention from the principal study finding...incidence of coronary heart disease.' To consider an excess of deaths a diversion is to advance an odd point of view.

"The interpretation of insignificant or almost significant differences between small numbers is also noteworthy. For example, the statistically insignificant reduction in coronary deaths in the LRC trial (38 among the controls vs 30 among the patients treated with drugs) was nevertheless labeled 'a 24% reduction in risk' without qualification. On the other hand, another outcome of the LRC study was an excess of violent and accidental deaths among the treated patients (4 in controls vs 11 in treated patients; the tone of the language here was strikingly different: 'Since no plausible connection could be established between cholestyramine treatment and violent or accidental death, it is difficult to conclude that this could be anything but a chance occurrence.' Oddly enough, a similar trend occurred in the Helsinki study (4 violent or accidental deaths in controls vs 10 inpatients treated with drugs). The authors acknowledged that this trend 'has also been observed in other studies,' and then simply concluded that this outcome 'has been interpreted to be a chance finding.' Even when an unfavorable finding reached statistical significance and might plausibly have been explained by the known side effects of a drug (e.g., 81 gastrointestinal operations in the gemfibrozil group vs 53 in the placebo group in the Helsinki study: $P < .02$), it was barely acknowledged by the authors."

Unfortunately, the lack of scientific ethics of authors is paralleled by the lack of ethics of journal editors and reviewers because, in the last analysis, it is they who allow biased and incompetent articles to be published. This issue is addressed in Chapter 9.

REGRESSION

In reviewing the literature associated with the regression of human atherosclerotic plaque, one cannot help but recognize that it is a perfect model for all diet-blood cholesterol-CHD literature. It is composed of horrendously biased reviews. Alliance members accept nonsignificant findings from studies. They accept results from unblinded and/or nonrandomized studies and even studies without control groups. They classify results as "conclusive" when, in fact, such results are really quite puny and questionable. And very importantly, they contradict themselves in the process of "reviewing" literature and seem neither to recognize their contradictions nor detect the illogics of their discussions in the context of other epidemiological studies. Let us first address the subject of contradictions.

Contradictions

In Volume 1 it was pointed out that alliance members have concluded en masse that there is no blood cholesterol threshold below which atherosclerosis does not occur and that regression in atherosclerotic plaque occurs with the lowering of blood

cholesterol. These diametrically opposed conclusions cannot be reconciled by any reasonable logic and yet alliance members seem wholly unperturbed by that fact. Consider the following quotes from Volume 1 and additional literature:

"The relationship between serum cholesterol and CHD is not a threshold one,...but rather is a continuously graded one..." (Jeremiah Stamler)[263]

"The continuous relationship between cholesterol (and LDL cholesterol) levels and the incidence of coronary heart disease clearly demonstrates that no single level of cholesterol separates those at risk from those who are not." (Robert Levy)[1427]

"There is no threshold in cholesterol concentration below which there is no risk of disease..." (Herbert Naito)[243]

"It would appear that the higher the [cholesterol] level, the higher the risk; the lower the level, the lower the risk." It "is continuous, graded and strong." (William Kannel)[1091,1448]

"Arterial lesions occur even when cholesterol concentrations are low. Nonetheless, the rate of progression of atherosclerosis in people with cholesterol levels of 150 mg to 200 mg is relatively slow." (Scott Grundy)[1167]

"Since Japanese men...[have a low]...level of serum cholesterol...[and]...show a distinct gradient of CHD risk by cholesterol levels the suggestion of a critical level for CHD risk becomes even less plausible. We must admit to a certain regret that there does seem to be a gradient of CHD risk at low levels of serum cholesterol." (William Kannel and Tavia Gordon)[2638]

The immediately above quote by Kannel and Gordon effectively dismisses the almost hopeful and certainly speculative 1989 statement by Rifkind, i.e., "a threshold perhaps occurs at cholesterol levels of between 100 and 150 mg."[2032] Indeed, Kannel et al.[2935] left no room for regression when he said, "Since atheromas are encountered throughout the range of lipids common to Western civilization,...we must assume that given enough time everyone has enough lipid to produce atheromas."

It is to be emphasized that the above quotes clearly indicate that no level of cholesterol is completely safe and that the very best that can be obtained from cholesterol lowering is a reduction in the rate of progression. None of the above quotes allow for the concept of regression because regression not only requires a regenerative function which would give cholesterol powers that are rarely, if ever, observed in physiology, namely, a regenerative function at the other extreme. It is difficult to conceive of a body substance that is not degenerative at both extremes, e.g., hormones, vitamins, etc. Therefore, not only are arguments stressing no thresholds in the the cholesterol-CHD relationship wholly inconsistent with arguments stressing regression at low cholesterol levels, the hypothesized regression concept demands a physiological function that has probably never been observed in medicine.

Alliance members remain unperturbed by these contradictions, either because they are scientifically incompetent to recognize them or because they wish to promote the cholesterol-lowering philosophy at any cost including scientific integrity. It is difficult to determine which of these explanations is the more accurate in the writings of alliance members because they easily discuss the no threshold and regression concepts without the slightest suggestion that they recognize that the concepts are inconsistent with one another. The following provide examples of quotes from the same articles by prominent alliance members.

"...the relationship of serum cholesterol to CHD in the U.S. population is graded and not a threshold relationship." "...atherosclerosis regression, as indicated by perceptible improvement in overall coronary status, occurred in 16.2% of the treated subjects versus 2.4% of the untreated individuals." (Herbert Naito)[1352]

"The evidence indicates that the cholesterol mortality association is continuous, graded and without a threshold." "...the use of colestipol-niacin therapy, diet alone, and cholestyramine resin have demonstrated that reduction of low-density lipoprotein (LDL) and/or elevation of high-density lipoprotein (HDL) can either retard the progress of atherosclerosis or induce its regression." (Charles Glueck)[2886]

"Studies have not revealed any threshold levels of LDL below which atherosclerosis becomes unapparent." "Recent studies suggest that atherosclerosis tends to regress in men when plasma lipid levels are substantially reduced." (American Health Foundation report authored by Antonio Gotto, Jeremiah Stamler, David Blankenhorn and others)[2634]

Alliance members cite angiographic trials as producing evidence that reducing cholesterol levels induces regression.[a] The study most prolifically cited is that of Blankenhorn et al. who used as subjects patients who had recently undergone bypass surgery. At a 1987 press conference following the publication of the Blankenhorn et al. trial, NHLBI director, Claude Lenfant, said, "For the first time, we are presented with evidence regarding regression of lesions in humans."[859] (His subordinate, Basil Rifkind, said that the trial was the "first conclusive study with clear-cut results in humans."[865]) Yet, in the same year DeBakey and his colleagues published a study which showed no relationship between cholesterol level and degree of restenosis in 1400 bypass patients but Lenfant argued that "I don't think that surgery patients are a good model for understanding atherosclerosis."[677] Thus, it is evident that surgery patients represent good models if the results support the lipid hypothesis and bad models if they do not support it. There is simply no other explanation for Lenfant's contradictory statements.[b]

In Volume 1 eight angiographic studies were reviewed in which relatively small numbers of subjects were given cholesterol-lowering diets and/or drugs. Table 7-3 presents pertinent characteristics and results of those trials, as well as baseline and on-trial blood cholesterol levels. As can be seen, the upper two studies involved no control groups (and thus no blindedness) and therefore cannot be scientifically used to assess the effects of cholesterol lowering on progression or regression. Yet, the authors of these studies claimed that they demonstrated a slowing of progression and even regression of atherosclerosis. The next two studies were presumably blinded but not randomized and this writer would not classify them as scientifically acceptable as well.

The lower four trials were presumably blinded and randomized but there is still the possibility of bias because of the fact that three were funded by highly vested interest groups, i.e., drug companies. Moreover, of the two studies showing positive results, the Duffield et al. trial involved too few subjects to be taken seriously.

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[a] They also cite animal studies but Chapter 2 stressed that the induced disease in animals is not true atherosclerosis but rather a lipid storage disorder.

[b] DeBakey and his colleagues published similar findings in 1964.[128] In 1975 the former NHLBI director, Theodore Cooper, also criticized that study on the grounds that surgery patients were not good subjects to evaluate the blood cholesterol-heart disease issue.[2688]

If the above criticisms were not enough to dismiss all or most of the angiographic studies as evidence supporting the lipid hypothesis and, in particular, regression, the reader should then note the baseline and on-trial blood cholesterol levels of subjects which participated in the studies. In the six trials which reported a slowing of progression the mean baseline and on-trial cholesterol levels were 302 mg and 232 mg, respectively. And in the four trials which reported regression the mean baseline and on-trial cholesterol levels were 309 mg and 231 mg, respectively. If one accepts the alliance's frequently espoused contention that atherosclerosis progresses with cholesterol levels as low as 150 mg, e.g., "plasma cholesterol concentrations above 150 mg are unnecessarily high and put patients at risk for arterial deposition and its consequences" (Rifkind[2032]), it is therefore ridiculous to simultaneously accept data suggesting that progression is slowed and regression occurs in groups whose mean cholesterol levels is 231 mg, approximately 11 to 15 mg higher than the mean level of the U.S., already branded as being predominantly atherosclerosis-prone.

While one might argue that the effects on progression and regression may have occurred at the lower end of the distribution, there is evidence that this was not the case. For example, in the Blankenhorn et al. trial, the only study that met minimum scientific design criteria and achieved positive results, the mean cholesterol level on trial in the treated group was 180 mg. Although Blankenhorn et al (should have but) did not correlate cholesterol levels with stenosis measurements, they did present results for "low" and "high" on-trial cholesterol subgroups, i.e., 165 mg and 189 mg, respectively. Their "global" stenosis score was virtually identical for both subgroups, indicating that their presumed positive effects occurred in the upper part of the cholesterol distribution as often as in the lower part.

The cholesterol-lowering in the partially reported trials of Brown and Ornish should also be mentioned. Brown lowered the mean cholesterol levels in two groups of subjects from 270 mg to 210 mg and 181 mg, respectively.[2513] He reported that 35% of the subjects in each group showed regression, indicating no difference between groups with a cholesterol difference of almost 30 mg. This observation takes on greater significance when we recall Rifkind's formula (now cited hundreds and perhaps thousands of times in the media): for each 1% fall in cholesterol level, there is a 2% fall in CHD incidence. Thus, there was an 11% greater fall in cholesterol in one group than in the second group but there was not a 22% (or even 1%) greater fall in CHD incidence.[a]

In the one-year diet study by Ornish the cholesterol levels of 12 subjects were lowered from 227 to 136 mg.[2556,2687] Ornish reported that the mean percent diameter of stenosis regressed 3.6% but, very importantly, there was no correlation between the amount of cholesterol lowering and the amount of regression, a fact that is incompatible with the lipid hypothesis.

Since it is well-established that atherosclerosis occurs abundantly in populations having blood cholesterol levels as low as 150 mg and that heart attacks occur almost equally across the 150 mg to 250 mg spectrum, it is illogical to claim that regression occurs at levels far greater than 150 mg and even far greater than 200 mg. Such claims are tantamount to suggesting that virtually any reduction in cholesterol levels promotes regression, a concept that is totally contrary to the position long held by the alliance. Prominent members of the alliance such as Rifkind and Castelli indicated that "safe" cholesterol levels are below 150 mg. The suggestion, therefore, that

[a] While overt CHD events are certainly different from covert CHD events, there should be an exceedingly high correlation between the two if the alliance's contention is true that nearly all MIs are dependent on extensive atherosclerotic occlusion.

Table 7-3

Blood cholesterol levels at baseline
and on-trial in 8 angiographic trials

Trial	Date	Results: Slowed Progression	Results: Regression	Cholesterol Level(mg): Baseline	Cholesterol Level(mg): On Trial
No control group and therefore not blinded as well					
Kuo[857]	1979	Yes	Yes	413	270
Arntezenius[853]	1985	Yes	Yes	266	239
Not randomized					
Nash[856]	1982	Yes	No	279	222
Nikkiles[852]	1984	Yes	No	297	244
Blinded and randomized					
Duffield[639,a,b]	1983	Yes	Yes	311	234
Blankenhorn[760,a]	1987	Yes	Yes	246	180
Cohn[867,a]	1975	No	No	260	251
Brensike[839]	1984	No	No	310	256
			Mean	298	237

[a] Funded by a drug company.

[b] Only 11 and 23 subjects in experimental and control groups, respectively.

regression occurs at 180 mg, 210 mg, 239 mg and even 270 mg, as has been reported, simply cannot be reconciled with either the preachings of the alliance or the existing body of evidence.

Finally, it should be noted that angiographic studies not concerned with cholesterol lowering treatments have reported relatively large percentages of subjects showing spontaneous regression. For example, Kramer found that up to 15% of 385 patients observed over 37 months showed regression of lesions,[1766] almost as great as was reported by Blankenhorn et al. for their drug-treated group.

Vegetarianism

While the alliance spends billions of dollars over decades attempting to demonstrate that reducing blood cholesterol will reduce incidence of CHD and even cause regression of atherosclerotic plaque, it gives relatively little attention to "natural" experiments occurring in many countries, i.e., vegetarian groups within populations. While it is difficult to determine how many vegetarians exist in the U.S., it is likely that the number far exceeds the largest of all clinical trials. Nevertheless, this writer found only 17 articles on vegetarian studies in more than five years of literature search (see Chapter 4 for a review of those studies). Only four groups of vegetarians were compared with nonvegetarians with respect to CHD rates and three involved Seventh Day Adventists (SDA). As noted in Chapter 4 of Volume 1 and the present volume, analyses of the SDA studies were inexplicably bad. Moreover, SDAs are poor societal models of vegetarianism because of unique confounders such as their religiously-induced emotional state and lifestyle, e.g., almost all abstain from smoking, caffeine, etc. However, despite these confounders and despite the poor analyses of these groups, substantial CHD incidence was reported, although less than that exhibited in the general population. The point is that vegetarianism is effectively the Prudent diet carried to its limit and the SDA studies showed that CHD incidence was still very much in evidence, even with the elimination of smoking.

Probably the only study of vegetarians that is relatively free of confounders was that of Burr and Sweetnam in England.[1134] The annual CHD mortality rates among 4,685 vegetarians and 6,238 nonvegetarians were 0.174% and 0.190%, respectively, yielding a difference of 0.16%. Not only is this difference trivial, female vegetarians had a somewhat higher CHD mortality than nonvegetarians (0.04%) and male vegetarians had a higher all-cause mortality than nonvegetarians (0.22%). Thus, these results provide absolutely no evidence that vegetarianism protects against CHD or all-cause mortality and they derive from by far the most acceptable scientific study to date.

While most investigators have attempted to impress and influence practitioners and the public at large with respect to the fact that vegetarianism does indeed reduce blood cholesterol levels, they systematically avoid presenting the far more important findings that vegetarianism does not eliminate or even have practical effects on CHD mortality. This writer does not truly know what <u>really</u> goes on in the blood cholesterol-lowering angiographic trials but it is clear that their results do not conform to the real world. If CHD incidence cannot be shown to be eliminated or very substantially reduced in real vegetarian populations, it is ridiculous to place any value on very small angiographic studies which report regression even though cholesterol levels are typically much higher than those found in actual vegetarians. It is again a demonstration of pure illogical reasoning.

Atherosclerosis Development in the Young

As noted by Ross, atherosclerosis is initiated during childhood with fatty streaks.[1559] These fatty streaks are observed in the aortas of infants immediately

after birth and increase in number thereafter. These observations have been reported by many alliance members, e.g., Kannel et al.[2935] and McGill.[3032] The International Atherosclerosis Project found in over 23,000 autopsies that fatty streaks and raised lesions were already observable in the coronary arteries of 15 to 24 year-olds in virtually every one of the 19 populations studied.[2436] Very importantly, although the percentage of cases per population was under 20%, it is of interest to know that the differences between population groups were quite small.

The population groups varied greatly in terms of consumption of saturated fats and cholesterol. In fact, the Project found no correlations between animal fat consumption and either blood cholesterol levels or the degree of artery occlusion.[1080] Scrimshaw and Guzman concluded that "...in most populations sources of fat and of carbohydrates are not the primary factors in determining severity of atherosclerotic lesions."

In sum, the antecedents of atherosclerosis appear very early in life, long before habitual diets are formed and, in any event, among all populations including those consuming very low saturated fat and cholesterol diets. These data also provide evidence that such dietary lipids do not initiate atherosclerosis. It follows, therefore, that reduction in consumption of such lipids will not induce regression of atherosclerosis.

While alliance members would like everyone to believe that cholesterol reduction in subjects with clinical atherosclerosis leads to regression of lesions, let us not forget that alliance members used the opposite argument to explain the failure of secondary intervention trials to show benefits of cholesterol-lowering diets or drugs. For example, in discussing the failed CDP, Theodore Cooper[2688] said, "It is my opinion that at certain stages in the disease...it will not be reversible by manipulation of the serum cholesterol." Similarly, Hegsted[2692] stated that "...it would seem clear that dietary modification of atherosclerotic men in their 40s and 50s or older should not be expected to have much effect. Authors of the 1971 NHLI Task Force[705] held that secondary trials have failed because "the disease was so far advanced that it is not reasonable to expect an improvement in prognosis. Even in those dietary trials carried out with older subjects free of clinical disease, it is known that in most subjects arterial lesions have progressed to the irreversible stage." And Thomas Dawber[3001] observed in 1980 that "Although a dramatic discovery by which the atherosclerotic process could be reversed is conceivable, the possibility is not great, especially in long-standing disease. Once scarring and calcification have developed, the disease may well be irreversible. ...it is unlikely that efforts to change blood lipids at advanced age would be worthwhile."

In conclusion, despite reports of regression by cholesterol lowering, several lines of evidence indicate that such reports must be inaccurate or simply chance occurrences. The lines of evidence can neither be dismissed nor reconciled logically with the reports of regression. To do so would be analogous to suggesting that flying saucers <u>do</u> exist and come from Mars when we know for certain that no life of any kind exists on Mars. It may be noted that one of the most well-known promoters of the diet-CHD hypothesis, Robert Wissler, very recently admitted that "atherosclerosis develops at an accelerated rate in <u>some</u> individuals with little or no increase in any of the generally accepted risk factors" and that "the concentric inflammatory lipid-laden lesions that involve sustained endothelial injury <u>often</u> are not capable of beneficial regression, even though substantial quantities of lipid may be removed from them"[3406] [underlines added]. Referring to the Glossary of Mumb-Jumbo in Chapter 1 will suggest that the words "some" and "often" actually mean "most" and "always," respectively.

The final report of the Physicians' Health Study Research Group on Aspirin was published in 1989.[2351] The results were essentially identical to those published in 1988. While the authors maintained that "there was a statistically significant, 44% reduction in the risk of MI that included significant benefits of aspirin for both fatal and nonfatal events," that figure was 47 times larger than the actual rate reduction of 0.93%. This rate reduction led to the statement that "our trial demonstrates conclusively a benefit of aspirin in reducing the incidence of first MI."

The authors admitted that there was "no reduction in the risk of mortality from all cardiovascular causes." In fact, the death rates were identical (0.15% vs 0.15% for the aspirin and control groups, respectively). Similarly, the all causes death rates were also effectively identical (0.39% vs 0.41%).

An editorial published in the same issue of JAMA in which the aspirin study appeared offered a rather inconsistent description of the study's results. For example, Fuster et al. observed that "although the rate of nonfatal MI was reduced by 44%, the absolute risk reduction was less than two events per thousand per year. There are clear problems in reporting risk reduction as a percentage when the absolute prevalence of events is low."[2352,a] Yet, they concluded that "Given the available data, it now seems reasonable to advocate the use of aspirin in a dose of 160 to 325 mg a day in patients with clinical manifestations of CHD" and that "aspirin appears to be beneficial in the protection of first MI, at least in men over the age of 50."

Letters to the editor criticizing the aspirin study were submitted by Khaw, Kaplan and Bader. Khaw pointed out that while there was a statistically significant difference between the aspirin and placebo groups in fatal MI and other ischemic heart disease (34 vs 53, respectively), there were more sudden deaths in the aspirin group (22 vs 12) and such deaths are typically included as CHD events in other studies.[2607] For example, sudden deaths were classified as CHD in the LRC trial.[500] Inclusion of sudden deaths results in a nonsignificant difference between groups (56 vs 65 in aspirin and placebo groups, respectively).

The aspirin study authors did not respond to Khaw's criticism but did respond to a similar comment by Kaplan. The latter stated that "Aspirin does not reduce the risk of death from heart disease, it only alters the distribution among categories."[2608] Although the aspirin study authors arbitrarily divided the deaths into subgroups to yield significance, they said, "We believe that Kaplan's suggestion that inferences be drawn among the subgroups is potentially very misleading."[2610] Strangely, it was the aspirin study authors, not Kaplan, who drew inferences among the subgroups and it is indeed "potentially very misleading" to do so. This is simply another example of how alliance members inconsistently select data from their findings which satisfy their preconceived beliefs.

Bader's letter stated that "In the absence of a significant difference in overall mortality or mortality from cardiovascular disease between aspirin takers and controls, the early termination of the aspirin component of the Physicians' Health study by the Data Monitoring Board of the Steering Committee was unfortunate. There was no compelling reason to terminate."[2609] The Steering Committee replied, "We disagree with Bader's assertion that the trial could have been extended for a few more years with relative ease to answer the question of cardiovascular mortality. Besides the ethical issue of withholding the results of a conclusive statistically extreme benefits of aspirin with respect to first MI, the rate at which cardiovascular mortality end points were occurring precluded answering this question definitively until the year 2000 or

[a] Fuster et al. apparently meant "fatal and nonfatal," rather than simply "fatal."

beyond."[2610] In addition to their highly exaggerated term "extreme benefits," their recognition that it would take 11 or more years to determine whether aspirin reduced mortality was, in effect, an admission that there is little evidence that aspirin reduces mortality.

The lack of differences observed between groups in life expectancy is common to most clinical trials investigating cholesterol-lowering but seemingly not at all bothersome to Hennekens et al. or other other authors. The lack of a difference between groups with respect to total cardiovascular deaths and the increased incidence of stroke with aspirin usage led Horton and Kendall to recommend caution regarding the use of aspirin as a preventive therapy.[2319] Hennekens et al. also implied caution by stating that "The doctor is in the best position to weigh the risks and benefits" of aspirin usage.[2246,2351] Unfortunately, the typical physician is probably not in the best position for such advice because he/she rarely reads the research literature and understands it less.

The generally negative benefits seen in the Physicians' study above are reinforced by a recent study published by University of Southern California (USC) researchers, headed by Paganini-Hill and her co-workers.[2442] They followed elderly persons for 6.5 years and reported that 1,579 previously healthy daily aspirin users sustained 40% increased risk of all cardiovascular diseases than a comparable group of 7,756 nonaspirin users. They recommended against the daily consumption of aspirin. Hennekens, director of the Physicians' study, criticized the USC researchers and accused them of being "far off base." Although all clinical trials have indicated no benefits of aspirin on total mortality and most trials have indicated little or no benefits on CHD, Hennekens stated that "the totality of evidence is that aspirin reduces the risk of heart attack."[2442] It is to be noted, moreover, that an FDA advisory committee concluded that aspirin "should not be used routinely as a preventive measure" by healthy people after reviewing Hennekens' study.

8. CHOLESTEROL MEASUREMENT, METHODS AND HARM IN REDUCING IT AND THEORIES OF CAUSATION

"Studies suggest that total plasma cholesterol levels of 110 to 150 mg may be physiological for human beings."

(Basil Rifkind & Claude Lenfant, 1986[253])

"Plasma cholesterol concentrations above 150 mg are unnecessarily high and put patients at risk for arterial deposition and its consequences."

(Basil Rifkind, 1989[2032])

"But whether cholesterol as low as 150 holds any dangers is unknown."

(Basil Rifkind,1989)[a]

"I do not think the case for cholesterol reduction has been proved to the degree we all would prefer."

(Basil Rifkind, 1989[2523])

INTRODUCTION

This chapter extends Volume 1's discussion on the measurement of cholesterol, mass cholesterol screening, the cost-effectiveness of reducing cholesterol and the side effects of cholesterol-lowering drugs. A large section is devoted to the relationships found in major prospective studies between low cholesterol levels and cancer and/or all-cause mortality. The potential harm of consuming trans fatty acids is addressed. Finally, the evolution of thought regarding the causation of CHD and, in particular, atherosclerosis, is discussed.

THE MEASUREMENT OF BLOOD CHOLESTEROL

As noted in Volume 1 many factors, including the measurement instruments themselves, contribute to the errors and variations in the cholesterol level of a single individual.[b] Some of the factors that degrade cholesterol levels are actually promoted by the alliance. For example, the reduction of dietary cholesterol reduces HDL,[1819,1827,1903] as does the reduction of alcohol and increase in carbohydrate consumption (Volume 1). Some of the most commonly prescribed anti-hypertensive drugs, such as thiaside diuretics and non-selective beta-adrenergic blocking agents also lower HDL.[1864] And some prominent alliance members recommend regular consumption of fish oils, although they generally elevate cholesterol levels[1699] (also Volume 1).

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[a] Attributed to Rifkind by Jean Carper, Washington Post.

[b] Not noted in Volume 1 was anabolic steroids, used by many athletes; regular use elevates total cholesterol levels.[2122]

A 1989 NHLBI report stated that, "unfortunately...the reliability of cholesterol measurements...in public screening programs are often inadequate."[1696] But as discussed in Volume 1, the same state-of-affairs occurs in physicians' offices, independent laboratories and hospitals.[a] Not only are cholesterol measurement instruments inaccurate, the most common fingerstick devices "consistently give higher blood cholesterol readings than venous blood measures,"[1731] as much as 8.5%.[2361] In fact, William Kannel reported in 1988 that the fingerstick devices (enzyme method) can typically yield cholesterol values as much as 20% higher than the more accurate chemical method.[1383,1448]

The most serious problem of cholesterol measurement has always been instrument calibration. In Volume 1 it was noted that the National Bureau of Standards and the College of American Pathologists have recently been providing reference (blood) materials to allow test instruments to be calibrated to the same blood sample. However, not only is it unknown how many physicians buy and use these materials, there is considerable question as to their ability to improve measurement accuracy. For example, consider a recent statement by Naito. "The CAP reference materials with target values are the best that we have at the present, but do not represent state-of-the-art material. The technology for developing these types of materials is at least 30 years behind the times.[b] Many reference materials are no longer in their native state as serum or plasma. Reference materials with high concentrations of bilirubin, hemoglobin or vitamin C may interfere with the cholesterol assay. Other factors, e.g., added stabilizers, anti-microbial agents, lyophilization, etc., also may affect results."[1783]

In the past, blood samples sent simultaneously to many labs by CAP and others have revealed remarkably wide variations in measurements. One of the most recent surveys was that of Holman et al. who sent samples to 10 labs, consisting of three teaching and five community hospitals and two commercial labs.[2585] They estimated that 12% of patients would be misidentified as high risk despite the fact that 8 of the labs used National Bureau of Standards quality controls.

Recognizing that screening instruments are unreliable, the FDA recommended that individuals having their cholesterol measured by such devices should ask the following questions: "What are your quality controls?; Are you running control samples?; what do you do when the readings are off? and; is a clinical chemist supervising this test?" Not only is it naive to think that individuals will indeed ask such questions, it is also naive to think that screening personnel will provide accurate answers. They may not even know the answers.

Myers and Cooper, Centers for Disease Control, made similar recommendations to physicians regarding the laboratories they use, i.e., "Physicians should know about the labs they use and be able to assess the level of quality assurance these facilities provide. Physicians should inquire about the lab's day-to-day precision and find out if the lab meets at least the 5% CV precision goal recommended by the NCEP Lab Standardization Panel."[2361] Again it seems unlikely that physicians will either ask precise questions of labs or receive valid answers. After all, if a lab's cholesterol

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[a] Posnick cited a 1987 CAP survey of 2,000 elite laboratories as finding good measurement accuracy but also cited experts as indicating that they are not representative of the average lab.[2193]

[b] If we take Naito literally, not only is the desired technology 30 years in the future, the materials presently in use are not even current "state-of-the-art."

measurements are inaccurate or if the lab is unaware of its accuracy, is it likely to reveal such information to physicians and risk loss of business?

Alliance members often use the terms "precision" and "accuracy" with considerable abandon when discussing cholesterol tests. Precision (or reliability) is used to indicate the degree to which an instrument yields the same value time and again for the same blood sample. Accuracy (or validity) denotes the degree to which an instrument yields the true cholesterol value of a blood sample. If an instrument is accurate, it is also precise, but if it is precise, it is not necessarily accurate. A cholesterol test instrument must be both precise and accurate in order to avoid subsequent unnecessary fear and intervention. As discussed in Volume 1 of this review, accuracy is still a major problem with cholesterol test instruments. The alliance is aware of this state-of-affairs but utters a series of inconsistent statements regarding this matter. For example, the NCEP's Naito[2528] claimed that "precision is not a major problem with most of today's desktop systems, unless they are improperly calibrated." Since he is a member of NCEP's Laboratory Standardization Panel, Naito should know that calibration affects "accuracy," not "precision." Naito continued, "In the past, there weren't any protocols for calibration, and physicians got by because they developed their own reference range. With today's uniform cutoff points for high- and medium-risk levels, however, individual reference range no longer can be used." Of course, cutoff points also have nothing to do with calibrating an instrument and thus its accuracy.

Bachorik[3164] was inconsistent in assessing desktop analyzers. He said, "the past few years...has led to the development of small, portable or semi-portable instruments that can accurately measure cholesterol concentrations in the physician's office or at other nonlaboratory sites... Most of these instruments do not require daily calibration and can be operated by individuals who lack formal laboratory training." He then said that "The desktop cholesterol analyzers, if properly calibrated and used by trained operators, can provide fairly accurate and precise cholesterol measurements." Subsequently, Bachorik elevated "fairly accurate" to "accurate" again, i.e., "Desktop cholesterol analyzers can provide accurate and precise cholesterol measurements if..."

Recent studies confirm that cholesterol measurements are still intolerably inaccurate, regardless of the optimism. For example, McGuire[3160] reported as much as 20% variability between instruments and within a given subject. In an editorial in the Journal of the American Medical Association, Belsey and Baer[3163] concluded that "only by improved technology will we be able to reach the point that an individual can know their 'cholesterol number' with a fair degree of confidence."

The issue can be no better illustrated than by the personal experience of Jeffries,[3129] a hospital laboratory director. While visiting a cholesterol instrument manufacturer, she had a cholesterol test at her host's urging. The value obtained was 284 mg, some 34 mg higher than a value she had obtained prior to embarking on a low-fat, low-cholesterol diet ("almost completely eliminating eggs and red meat"). The following day she had another test done with her laboratory instrument and the value mysteriously dropped 54 mg.

And while many alliance members are encouraging physicians to measure HDL, they also know that most instruments in the country cannot measure HDL with any adequate degree of accuracy. For example, Peter Wilson,[3223] Framingham investigator indicated in late 1990 that "At a community hospital laboratory, you would typically get an error of 7 to 10% for total cholesterol. In terms of HDL, the answer is more difficult. Even under the best conditions, the laboratory error will be greater than it is for total cholesterol."

With effectively universal recognition that cholesterol measurement is inaccurate, it is nothing less than astonishing that Grundy, Rifkind and Cleeman can tell their readers that "In recent years, methods for rapid and accurate measurement of serum cholesterol have become widely available."[1803] (Most recently Grundy[3083] said that "A critical need for the future is improvement of measurement of lipoprotein risk factors. Methods of lipid measurements are improving steadily, but much progress still is needed." In other words, accuracy is still intolerable.) And while most alliance members agree that a HDL measurement accuracy in most laboratories is intolerable,[a] Castelli maintains that it should be measured anyway,[1809] and the NCEP guidelines call for its measurement also in "patients" at high risk for CHD.[2456]

MASS CHOLESTEROL SCREENING

Adults

The U.S. Preventive Services Task Force, created by the Secretary of Health in 1984, concluded in 1989 that there was "insufficient evidence" to support the concept of screening cholesterol levels of all adults.[1937] In the same year the congressional Office of Technology Assessment (OTA) reported that cholesterol screening for the elderly would cost Medicare about $5.4 billion and would likely have little effect on death rates. The OTA estimated the total cost to the nation to be about $14.3 billion.[2161]

The Committee on Nutrition of the Pediatrics Society also announced its opposition again in 1989 to the screening of children above the age of two, recommended by the NCEP guidelines.[1718] The Committee maintained that (1) measurement error is too great, (2) many measurements would be necessary because of large day to day variations, (3) it would be difficult for a growing child to remain on a strict diet or drug regimen and (4) diets or drug treatments could be deleterious to growth and development.

Many investigators in the U.S. and abroad have considered indiscriminate screening of all Americans to be questionable and uneconomical.[b] Scott argued that many screening programs are being operated "irresponsibly."[1727] A 1989 NHLBI report said that there is poor quality control in cholesterol screening programs.[1696] The report indicated that more than 25% of all those screened will likely be misclassified. And Richard Kusserow, a HHS Department Inspector General, examined 71 public screening programs in 11 states and reported at a congressional hearing in 1989 that "an alarming number of cholesterol screenings were conducted by inadequately trained people who did not follow guidelines.[2466] He cited unsanitary conditions, lack of instrument calibration and improper use of instruments. Yet, the screening programs in and out of physicians offices are increasing substantially, despite the "irresponsibility" and lack of measurement accuracy. Robert Rej of the New York Department of Health said, "currently published data for analyzers in extra-lab settings indicate that performance is inferior--often markedly inferior--to that obtained in a routine clinical lab setting. Impression may be more than 4-fold greater than that contained in clinical labs."[2586] And there is apparently no forthcoming lows to federally regulate public screening programs.[2591]

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[a] 1760,1792,1803,1809,1864,2456

[b] 1939,2197,2383,2384,3414

The AHA issued a statement in response to the criticisms and expressed concern about the screening programs which Kusserow described as "staggering sloppiness."[2531] NHLBI's Rifkind[3161] also acknowledged the irresponsible mass screening programs. The AHA absolved itself of any responsibility by stating that the mass screening programs "are not part of the medical care system." Perhaps not, but they were certainly stimulated by the medical care system by the mass fear campaign generated by AHA and NHLBI.

It was indicated in Volume 1 that some 100 million cholesterol tests were performed in 1986.[596,1005] That number doubled in 1987 at a cost of $3 billion.[1005] It was also noted in Volume 1 that NHLBI does not officially sanction mass screening and yet it recommends that physicians measure every patient's cholesterol level, regardless of the purpose of his/her visit. The NCEP campaign has most certainly resulted in mass screening in one form or another. For example, patient visits for cholesterol tests have increased 9 times since 1983.[2589] Also, the NCEP encourages every American to "know your cholesterol level."

Unfortunately, information reaching the homes of millions of people present a distorted and confusing picture of cholesterol testing. For example, a 1990 article in Better Homes and Gardens indicated that "Many cholesterol tests are no more accurate than the 30-day weather forecast."[3162] Having said that, the author then went on to say that "Public screenings, like those offered at malls and health fairs, can be quite accurate."

Judith Wagner, OTA project director, also emphasized that NHLBI's recommendations to physicians and the public effectively promote mass screening.[2161] Thus, NHLBI/AHA encourage mass cholesterol testing, knowing full well that the instruments used in most laboratories and screening programs are inaccurate, and simultaneously criticizes the programs for having poor quality control. In reality, NHLBI/AHA are probably not at all concerned about the low quality of the mass screening programs because, if they were, they would include warnings in their massive communications to the public via the NCEP.

Some of those opposed to mass screening recommend measurements only on those who have recognized risk factors. For example, Macnair said that "In such subjects it should amount to professional negligence not to measure blood pressure and lipids."[2383] However, this issue is rather academic in view of the fact that 200 million tests are already being administered per year. Moreover, as was emphasized in Volume 1 nearly the entire male population has one or more of the risk factors accepted by the alliance.

O'Keefe et al. pointed out that about 40% to 50% of the U.S. population may be told to lower their cholesterol levels, according to NCEP guidelines.[a] Since the NHLBI report indicated misclassifications in excess of 25%, these figures indicate that if all Americans are screened, some 30 million will be misclassified.[b] A large number of these individuals could be placed on drugs. Vogel pointed out that 250,000

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[a] It was reported in 1989 that the 240 mg cut off point applied in Britain would result in nearly half of the middle-aged men being earmarked for cholesterol-lowering therapy.[1811] Little and Horlick indicated a similar percentage for Canadians with the 200 mg cut point[2363] but Yale said that the percentage probably exceeds 60%.[2318]

[b] Laemmle et al. observed that 14.5%, 46.7% and 17.6% of 897 subjects within the total cholesterol classifications of <200 mg, 200-239 mg and >240 mg, respectively, were misclassified, according to the NCEP guidelines.[2166]

Americans were on cholesterol-lowering drugs in 1981 and the number is currently running at 1.23 million.[1868] He estimated that the number will reach 3 million by 1995. O'Keefe et al., however, suggested that the figure could be much higher.[1887]

All things considered, it is incomprehensible that a true scientist could utter the recent statement made by the NCEP's James Cleeman, i.e., "The (NCEP) guidelines go exactly where the science is now."[1760]

Garber et al.[2265] summed it up thusly, blood cholesterol level's "Value as a screening test...is limited by four sources of uncertainty. First, its role as a predictor of risk in elderly persons is not well defined. Second, because many clinical laboratories produce inaccurate cholesterol measurements, the relation between the reported cholesterol value and the reference standard is unknown. Third, there is little direct evidence about the efficacy of cholesterol reduction in women, young persons, or elderly persons. Finally, clinical trials in patients with established CHD suggest that overall survival benefits may be observed many years after the initiation of therapy, but this finding has yet to be confined in asymptomatic, nonsmoking persons with hypercholesterolemia."

All things considered, it is incomprehensible that anyone could utter the recent statement made by the NCEP's James Cleeman, i.e., "The [NCEP] guidelines go exactly where the science is now."[1760] As admitted by AHA's 1989 president Myron Weisfeldt,[3091] the guidelines are completely arbitrary and the effects of following them are completely unknown to the alliance.

Children

Some physicians promote the screening of all children above the age of two.[824,1647,3172] Garcia noted rather dogmatically that "The evidence supports routine screening of all children."[3172] It would appear, however, that the majority of researchers agree that the screening of children is not justified, including the alliance's Gotto,[1000] the American and Canadian Pediatrics Societies[1719,3173] and others.[3103,3104]

Two particularly important facts are either unrecognized or ignored by those promoting the screening of children. First, studies have demonstrated that the cholesterol levels of adults cannot be predicted by the levels observed in childhood.[3104,3165,3171] The highest correlation of .61 observed indicates that the children's levels explained only 37% of the variance associated with the adults' levels. Second, both physical and psychological harm are likely outcomes of screenings. As noted by Lauer and Clarke,[3104] a large percentage of children would be misclassified and subjected to unnecessary treatment. Newman et al.[3103] indicated that "Screening and interventions to lower blood cholesterol levels for millions of children would be expensive, could lead to labeling and family conflicts and may cause malnutrition and increased noncardiovascular mortality." Rowe[3123] reported that chronic diarrhea and depressed growth are effects of low-fat diets in children. Pugliese et al.[3200] also observed depressed growth. Nevertheless, the Intersociety Commission[552] recommended dietary fat reductions for all ages, including infants and children.

When one fully recognizes that (1) the relationship between blood cholesterol level and CHD is extremely weak in adults as a group and totally nonpredictive in adult individuals and (2) a child's cholesterol level is a poor predictor of his adult level, it is scientifically and clinically unreasonable to subject the nation's children to cholesterol tests. However, there seems little doubt that such will eventually be the case because the overall trend in the U.S. is towards multiple cholesterol tests for all

Americans, regardless of benefits. The benefits to the medical industry, however, are clear--$5 to $6 billion a year.

ON THE LOGIC OF FASTING

The question of fasting or no fasting before cholesterol measurements are taken has apparently never been answered adequately. While many writers make definitive statements on this issue, they seldom cite data which support their statements. Very few studies were found during the preparation of this review and those that were found leave much to be desired. For example, Castelli et al. measured cholesterol levels in subjects 3, 6, 9 and 24 hours after consuming three different meals and found no differences in levels during the 24 hours period.[1883] Close examination of their study, however, reveals peculiar implications. First, the three test meals were exclusively fat (safflower oil), protein or carbohydrate. Theoretically, each of these meals should depress cholesterol levels relative to a normal diet. Why didn't Castelli et al. evaluate a saturated fat diet, the very substance that the alliance focuses mostly on as the dietary cause of CHD?

The implication is that a recent diet of neutral or hypocholesterolemic foods has little effect on cholesterol levels over a 24 hour period. However, Castelli et al. indicated that their subjects were given a fat free meal the night before the test day. Therefore, the measurements after the three neutral or hypocholesterolemic test meals were compared with a measurement taken (probably 12 hours) after a fat-free meal. If the fat-free meal depressed cholesterol levels prior to the test meals, it is not likely that the test meals would have depressed them further. In sum, this study seemed designed to eliminate the possibility of determining the recent effects of meals.

A second study was cited in Volume 1. Cohn et al. fed subjects a liquid formula meal and measured cholesterol levels 3, 6, 9 and 12 hours afterward.[1665] They reported no changes in total cholesterol during the 12 hour period although HDL, VLDL and LDL levels changed. However, since Cohn et al. failed to describe the composition of the meal given to subjects, this study proved virtually nothing.

Castelli,[1802,1883] Cohn et al.,[1665] Kannel,[1783] Naito,[1783] Gotto,[154] Donaldson[1791] and others maintain that fasting is not necessary for measuring total cholesterol. But a recent discussion on the subject by Baer was both contradictory and suggestive of effects after all.[1913] He cited Gerald Cooper as saying that "Recent meals stimulate chylomicron formation but have little or no effect on the blood concentration of cholesterol even though its concentration is affected by the diet over a long period of time." Baer then went on to say, "...very low density lipoproteins (VLDL) are synthesized by the liver and are part of the series of lipids that are formed over a protracted period of time from the diet. These are normally unaffected by recent meals." But two sentences later Baer stated, "but VLDL may also be influenced by a recent meal."

Most writers indicate or imply that all VLDL forms in the liver. Hence, Baer's emphasis is on the time it takes for a meal to cause the formation of VLDL from the liver. However, West maintains that about 15% of all VLDL is created in the intestine.[1793] This would account for Baer's final sentence above and provide the necessary basis for concluding that a recent meal does, in fact, influence blood cholesterol levels. It is to be noted that Robert Levy also maintained that VLDL originates in the intestine as well as the liver.[1427]

To some extent the entire discussion above is somewhat academic. Since everyone agrees that diet affects blood cholesterol levels, even if the effects lag a meal by a longer period than 12 hours, the problem of measuring "normal cholesterol" remains.

For example, suppose that it takes four days for a very high saturated fat meal to exert its influence on blood cholesterol levels. If so, one needs to be concerned about what an individual ate four days earlier. The same concern should be expressed whether the lag period is 48 hours or one week. No matter what the lag period, a given measurement will be affected by previous meals. Since the whole idea of fasting to begin with was to obtain a normal or steady-state cholesterol measurement, the knowledge that a very recent meal may not significantly affect the measurement does not resolve the problem in the least, i.e., it does not ensure a steady-state measurement. Unless a person's diet is effectively constant with respect to nutrient compositions, there is no such thing as a steady-state measurement. And that is undoubtedly one reason why many measurements are necessary to derive a subject's mean level. To suggest that a 12 hour fasting period is not necessary to obtain a "normal" cholesterol measurement reflects little understanding of this issue.

THE COST EFFECTIVENESS OF TREATING HYPERCHOLESTEROLEMIA

In 1985 Steinberg estimated that the total CHD costs to the nation, including medical care and lost production, was about $60 billion.[264] In 1989 the U.S. Preventive Services Task Force and the AHA/NHLBI Joint Statement reported estimates of $80 and $100 billion, respectively.[1766,2500]

Without a doubt, the costs are horrendous and growing at an alarming rate, not because of a CHD epidemic but because the population is aging and modern society, through medicare and other widespread insurance programs, has permitted more and more people access to the services of hospitals and physicians. Whereas most people simply lived with their heart disease symptoms and subsequently died without treatment in decades past, in recent times they have accessed medical care only because insurance programs provided the needed funds. For example, hundreds of thousands of people undergo very costly angioplasty and bypass operations each year. Most of these people could not possibly afford these operations were it not for the availability of insurance programs. Moreover, physicians' and hospitals' fees could not possibly have grown so rapidly in recent times were it not for insurance programs.

In effect, as noted by former NHLBI director, Theodore Cooper, heart disease has been the number one killer disease in this country since the turn of the century[2085] but it has only been in recent decades (mostly after 1940) that society developed affordable means of treating it medically, i.e., medical insurance. It is naive and irrational to ignore this factor because, along with an aging population and inflationary increase in physicians' and hospitals' fees, it explains all or nearly all the reasons why the nation's bill for heart disease is close to $100 billion annually.[a] It will continue to grow until society decides that medical care fees are no longer affordable even by insurance, i.e., the combination of taxes earmarked for medicare and private medical insurance, a point which has already been reached by many Americans.

The Office of Technology Assessment issued a report in 1989 which indicate that 47% to 57% of the nation's elderly would be treated with diets and drugs if the NCEP guidelines are followed, yielding a projected cost to Medicare of $1 to $5.4 billion per year. For example, 60% of all cholesterol-lowering drugs are being taken by those

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[a] The spiraling costs of medical care, a subject far to complex to discuss here, have evolved in large part, because insurance companies have always paid "prevailing" fees of physicians and hospitals, permitting the latter to frequently increase their fees which then become "prevailing" fees, etc.

over 60 years of age.[2726] Elsewhere in these volumes the total cost of the NCEP program to the American public is estimated to be about $60 billion per year.

The alliance maintains that the NCEP will reduce medical care and losses in production costs but the evidence indicates the costs will actually increase substantially. For example, a number of models have been used to predict the costs of medical therapy and life extensions of cholesterol-lowering. Recently, Davenport and Whittaker indicated the cost of medical therapy for men aged 65 to 69, having cholesterol levels of 265 mg, is $777,600 per year of life saved.[1910,a] Weinstein and Stason[3236] estimated the pharmacological cost, based on the LRC trial results, to be $126,000. Kelly[3242] calculated a cost of $50,510 to $108,826, depending on the type of cholesterol-lowering drug used, for men age 40 at entry with cholesterol levels above 265 mg. Not only are these costs prohibitive, they are also unquestionably underestimates because the basic statistical data from clinical trials indicate virtually no decrease in overall mortality with cholesterol-lowering. Prospective studies such as Framingham and the MRFIT screened cohort are often used in developing cost-effectiveness models but trial results are the more relevant data. One cannot consider CHD deaths alone because as detailed elsewhere, at least half of CHD deaths are not related to atherosclerosis and total mortality is, after all, the bottom line.

The alliance continuously ignores the overall effectiveness element. For example, Bassler objected to a Naito projection that cholesterol-lowering "may save approximately 300,000 lives annually."[1935] He pointed out that "because the trials show that lowering cholesterol always raises overall mortality, how can we justify the continued use of those drugs and diet?" Naito replied that overall mortality "tended to remain unchanged" due to "an increased number of noncoronary events" and concluded that "Personally, I doubt that this is due to the lowering of a person's cholesterol per se."[1936] Thus, Bassler's conclusion, based on scientific clinical trial data, is defined as "unsound scientific judgment" by Naito and "Personally, I doubt" apparently <u>is</u> sound scientific judgment. The admission by Naito that no change in overall mortality has occurred in trial after trial cannot be followed logically by the inference that 300,000 lives can be saved annually--unless wishful thinking is also defined as sound scientific judgment.

Even assuming that diet does reduce CHD (and there is no evidence that it does) and assuming that cholesterol-lowering does not increase total mortality (and the evidence indicates that it does), the expected average blood cholesterol reduction from the NCEP would not likely be more than 10% and would probably be closer to 5% or 7%. Not only would this reduction have a trivial effect on CHD, based on the blood cholesterol-CHD relationships observed in the Framingham and MRFIT data, it would, at best, delay but not eradicate medical costs because CHD would decelerate but not cease progression or regress. Any small savings that might accrue from this delay would likely be compensated for by increased costs a few years later, due to CHD, cancer, etc.

The indirect goal of the NCEP is to put cardiologists, particularly surgeons, out of business. On the contrary, this writer predicts that key indicators of the prevalence of CHD, bypass, angioplasty, etc. operations, will increase in frequency as the NCEP program proceeds. The evidence emphatically indicates that the worst case scenario is inevitable, i.e., the $60 billion NCEP costs will be added to the current costs of $100 billion.

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[a] Kelly also reported costs ranging from $642 to $2,536 for dietary therapies.

Finally, the concept of treating everyone to protect those at risk should be addressed. It is abundantly clear in these volumes that most people who contract CHD have low to moderate blood cholesterol levels, meaning that cholesterol level cannot predict the occurrence of CHD at the individual level. Thus, the alliance recommends that everyone should be treated in order to guarantee that those at real risk will be treated. Alliance members liken this process to programs which eradicate infectious diseases (but see Chapter 1). Unfortunately, the problems of heart disease and infectious diseases are not even remotely similar in either a technical or economic sense. The causes of the infectious diseases were discovered to be specific bacteria, whereas the cause of atherosclerosis is still unknown but thought to be multifactored. And when we say multifactored, the alliance means multi-multifactored. For example, Castelli stated in 1990 that "The Framingham study has pinpointed as many as 200 factors associated with increased risk of the disease."[2598] Because "associations" are the rule in physiological processes, we may someday exceed 1,000 factors. The risk factor concept has evolved into an absurd "Dow" indicator of CHD causes.

Of equal importance is the fact that some infectious diseases were eradicated for life by the administration of simple, inexpensive vaccines. The cost of the blood cholesterol tests alone (a series over time) will vastly exceed the cost of a vaccine. The "treatment" costs in terms of drugs and special foods, as well as repetitive visits to physicians, will cost an individual anywhere from several hundred to as much as $4,000 per year for life. Moreover, many tens of millions of people will sacrifice for life many of the foods they enjoy.

In sum, to suggest that the NCEP is similar to programs aimed at eliminating infectious diseases is tantamount to suggesting that a mountain cabin is similar to the Empire State Building. There simply is no comparison whatsoever.

THE POTENTIAL HARM OF REDUCING BLOOD CHOLESTEROL

Low Blood Cholesterol

Chapter 8 of Volume 1 presented an imposing list of studies which found higher rates of cancer mortalities at lower levels of blood cholesterol. It is evident, moreover, that while some studies did not show such a relationship, some of those did show an inverse or U-shaped relationship with all-causes mortality. In addition, the high cancer/all-cause mortality and low cholesterol relation may have been disguised in some studies by the use of specific cholesterol scales. A most dramatic example of this latter concern will be shown below in relation to the data collected from the large cohort of MRFIT screenees.

Although the distinction between cancer and all-cause is certainly important scientifically, it is clinically irrelevant whether a person with low cholesterol has a greater chance of dying from cancer or other noncardiovascular causes than persons with higher cholesterol levels. As will be seen, however, the alliance has made a serious attempt to discredit the low cholesterol-high mortality problem by ignoring the all-cause mortality issue and emphasizing that the low-cholesterol-cancer relationship is "inconsistent" because it does not occur in all studies or in most women.

The Denial

In 1979 Gotto, Stamler, Blankenhorn and others[2634] published a statement on behalf of the American Health Foundation. It said, in part, "The possibility has been raised that very low plasma cholesterol concentrations could lead to cancer risk and to deleterious effect on growth and nervous system formation. Most population studies lend no support to the possibility of excess risk from noncardiovascular causes,

including cancer." But such a conclusion was blatantly false. Stamler himself co-authored a 1974 article[93] in which the data from six prospective studies were pooled, including the Seven Countries, Framingham, Chicago Gas Company, Western Electric Company, Whitehall (London) and Minnesota Businessmen studies. The conclusion reached was that a definite relationship existed between low-cholesterol and colon cancer.

The Admission

The growing concern over the low-cholesterol and cancer relation was evidenced shortly after the Gotto et al. statement in an NHLBI workshop dedicated to this topic. The two day workshop was held in February 1980 and NIH published a summary statement of the meeting in July 1980.[2694] The reader should particularly note the candidness and objectivity of the statement, as well as a more detailed summary statement by Manning Feinleib,[1816] and then observe how they both subsequently published opposite statements.

The July 1980 NIH statement admitted that some studies showed a relationship between low cholesterol levels (< 180 mg) and cancer and "Toward this end epidemiologists from NHLBI and the NCI will continue to review data from studies in progress. It is common observation in medicine that physiological measurements have particular ranges of values that correlate with health and longevity, whereas values greatly above or below that range are accompanied by pathological correlates of varied kinds. It may turn out that the lowest end of the blood cholesterol distribution (levels below 180 mg) may not be optimal from the standpoint of overall mortality, even as the upper end of the distribution is disadvantageous from the standpoint of cardiovascular disease mortality."

Feinleib's review of the workshop proceedings was published in 1981. He said that "much of the data presented showed an inverse relationship between cancer mortality and cholesterol among men and a U-shaped relation between total mortality and cholesterol." (Note the phrase, "much of the data.") Feinleib emphasized that "The tendency for most epidemiologists...to think in terms of monotonic risk functions is also generally sound so long as one is concerned with a relatively specific disease outcome. However, when the totality of disease outcomes is considered, the rule tends to be for a U- or J- shaped relationship. Why should cholesterol levels behave any differently?" Why, indeed, should cholesterol levels behave any differently?

Feinleib reasoned that "the 'ideal' cholesterol level does not lie at either extreme of the distribution but somewhere towards the mean. From several directions, the indication is that for optimal mortality rates the ideal cholesterol may be somewhat below that of the average U.S. level but probably not at the very low levels advocated by some."

More Denial

In the same year that Feinleib's article was published, another workshop was held which was sponsored by the National Cancer Institute, as well as NHLBI. NIH again quickly published a brief summary statement in August of 1981 which "reviewed" both the 1980 and 1981 workshop findings.[2998] NIH said that of eight epidemiologic studies examined during the first workshop, only "the data from three of the studies presented (Framingham, Puerto Rico and Honolulu) suggested such a relationship, but the others did not."

In 1982 Robert Levy[2964] and Feinleib[95] published independent summaries of the two workshops. Levy noted that eight studies were evaluated in the first workshop, i.e.,

Framingham Heart study
Honolulu Heart study
Puerto Rico Heart Health study
Chicago Peoples Gas Company study
Chicago Western Electric Company study
Chicago Heart Association Detention Project
The AHA Pooling Project
Yugoslavian Cardiovascular Disease study

Like the NIH statement, Levy claimed that "only three of these studies--Framingham, Honolulu, and Puerto Rico--suggested that very low cholesterol levels (under about 180 mg) were associated with a statistically significant increase in cancer mortality; this association only occurred in men. No relationship between cholesterol levels and cancer mortality for either sex was evident in the other five studies reviewed. The other studies disclosed no significant association between serum cholesterol and cancer mortality." (Note the triple redundancy in the above three sentences and the emphasis twice on the word "significant."

Feinleib's summary of the first workshop was similar to that of Levy and diametrically opposite to his paper published in the previous year. He said, "Whereas three of the studies reviewed at that time did suggest such a [inverse] relationship [between cholesterol and cancer], the others did not. And in those studies suggesting that low serum cholesterol might increase cancer risks, there were several inconsistencies." Thus, Feinleib completely contradicted the interpretations and conclusions of his 1982 article, suggesting rather strongly that NHLBI and NCI decided that their program could not tolerate an inverse relationship. Clearly, if such a relationship were well-known to the public, few would be anxious to lower their cholesterol levels. NHLBI and the Cancer Institute eliminated this threat merely by re-writing history.

The Evidence

Let us now examine the eight studies ourselves. Despite Feinleib's statement that there were "inconsistencies" in the Framingham, Puerto Rico and Honolulu studies, in fact, there were no inconsistencies in these studies with respect to the inverse relationship in men.

Figure 8-1 shows relevant data for the Framingham study. The bottom part of the figure was published by Williams et al.[1285] The inverse relation between all cancers and cholesterol is clearly evident. The upper part of the figure was published by Feinleib[1816] in his first workshop review article in 1981. He cited Williams et al.[1285] as his source but, in fact, Williams et al. presented no such data in table or figure form in their article. However, it must be assumed that these data are legitimate. All of the data in Figure 8-1 show cancer death rates to be higher below 190 mg than at higher levels of cholesterol. The all-cause death rate was also observed to be higher below 190 mg than at levels up to 279 mg. Although not shown in the figure, Williams et al. reported that non-colon cancers death rates were higher among women at cholesterol levels below 190 mg than at all higher levels.

Sorlie and Feinleib[1191] published another relevant article in 1982. They noted that both cancer incidence and death rates among men were inversely related to cholesterol. Although not statistically significant, they also reported that the highest rates also occurred among women with cholesterol levels below 190 mg.

When the low-cholesterol, cancer relation became generally known by the medical

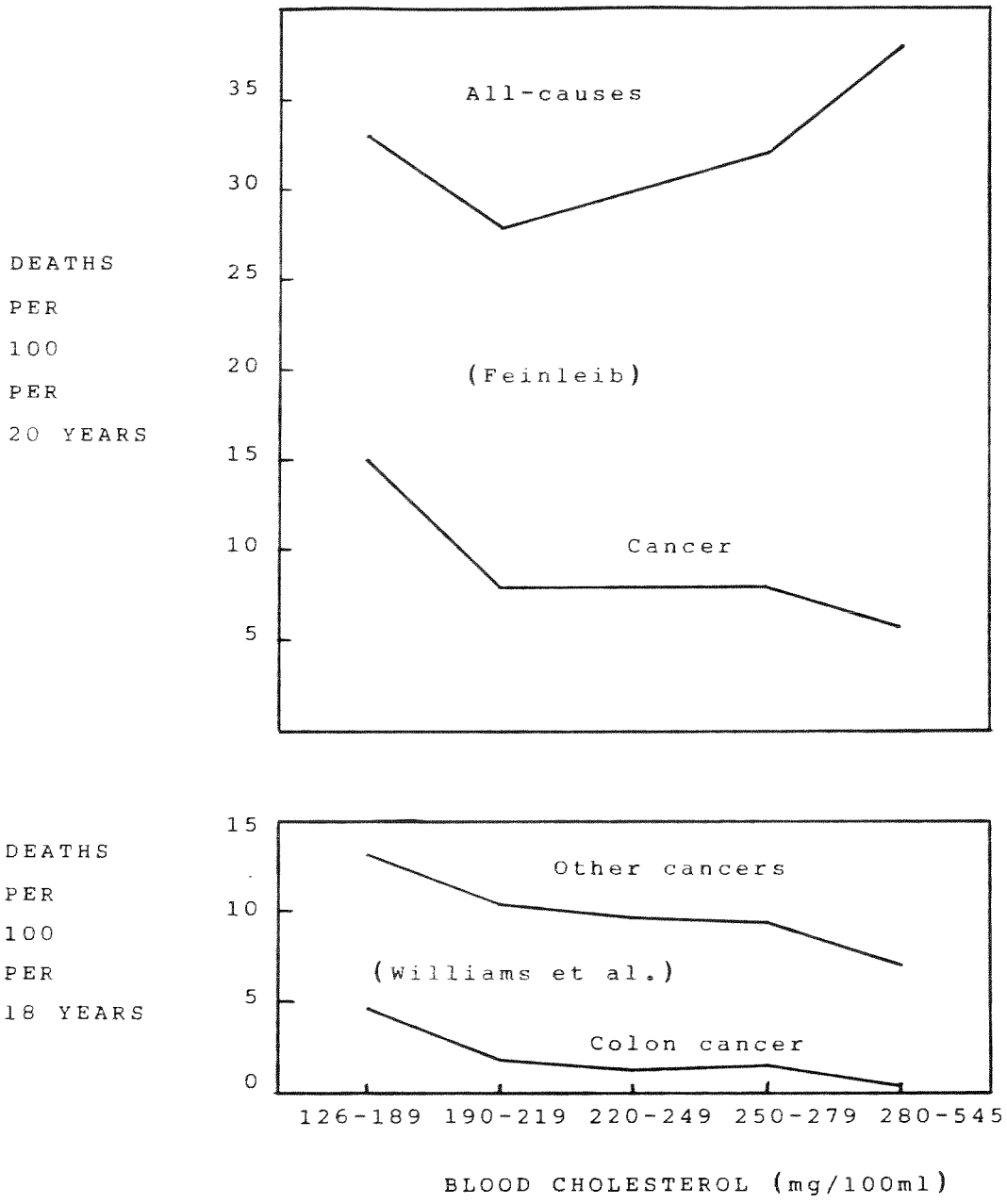

Figure 8-1. All-cause and cancer death rates in men in the Framingham study (adapted from Feinleib,1981[1816] and Williams et al.,1981[1285])

community in 1981, Lilienfeld[3008] wrote, "We should not become so specialized in our research endeavors with respect to one disease entity so that other entities are ignored. Prospective studies in cardiovascular diseases have been in progress for many years. This possible relationship of cancer to cholesterol may have been ascertained earlier." Indeed, there is strong evidenced that Framingham investigators withheld the cholesterol, cancer/all-cause relations from the public and medical community for at least 10 years. For example, Rose and Shipley[68] noted in 1980 that a 1970 technical report of a 16-year Framingham follow-up contained data showing that both all-cause and non-CHD death rates were higher at cholesterol levels below 205 mg than at higher levels.[a] Interestingly but not so surprisingly, 1970 was the year that the Framingham diet study was also published as a technical report--and was never subsequently published in the open literature (journals). Rose and Shipley constructed Figure 8-2 "from the detailed reference tables of the Framingham study" technical report.

In sum, the Framingham data are quite consistent in showing that cholesterol levels below 190 to 205 mg are associated with high all-cause, cancer and non-CHD death rates. While the associations may be weaker in women, the primary focus of the alliance's attention has always been on men because of low CHD rates among women and of weak relationships between cholesterol levels and CHD among women.

The inverse relationship with cancer was clearly observed in the Honolulu Heart Program by Kagan et al.[71] in 1981 (Figure 8-3). And, as can be seen, a clear U-shaped function was evident for all-cause mortality. The authors stressed that these relationships held strongly during the length of the 9-year follow-up.

Garcia-Palmieri et al.[72] also reported a strong inverse relationship between cholesterol and cancer in the 8-year follow-up of the Puerto Rico Heart Health Program (Figure 8-4). And they also found that this relation remained strong for the length of the follow-up. Unfortunately, these authors did not report all-cause mortality rates.

Rather than being "inconsistent," as Feinleib indicated, the above three studies were quite consistent. Now let us turn to the remaining five studies which Feinleib indicated showed no inverse relationship between cholesterol and cancer.

The Yugoslavia Cardiovascular Disease study, as reported by Kozarevic et al.,[74] did not present a functional relationship between cholesterol and cancer. However, the authors did find that low blood cholesterol level at baseline was related to both high cancer and all-cause death rates over the seven year follow-up. Moreover, Kozarevic et al. reported a strong inverse relation between cholesterol and all-cause mortality, as can be seen in Figure 8-5. Thus, contrary to the Workshop's conclusions, this study most certainly supported the concept that low cholesterol levels are related to high rates of cancer and/or all-cause mortality.

At this point, half of the eight studies "reviewed" by the Workshop clearly revealed strong evidence indicating that low cholesterol levels are harmful to health.

The Chicago Peoples Gas Company study showed positive relationships between cholesterol and cancer and all-cause mortality.[73] However, the data from this study

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[a] Authored by Kannel and Gordon[3062] and entitled, "Some characteristics related to the incidence of cardiovascular disease and death."

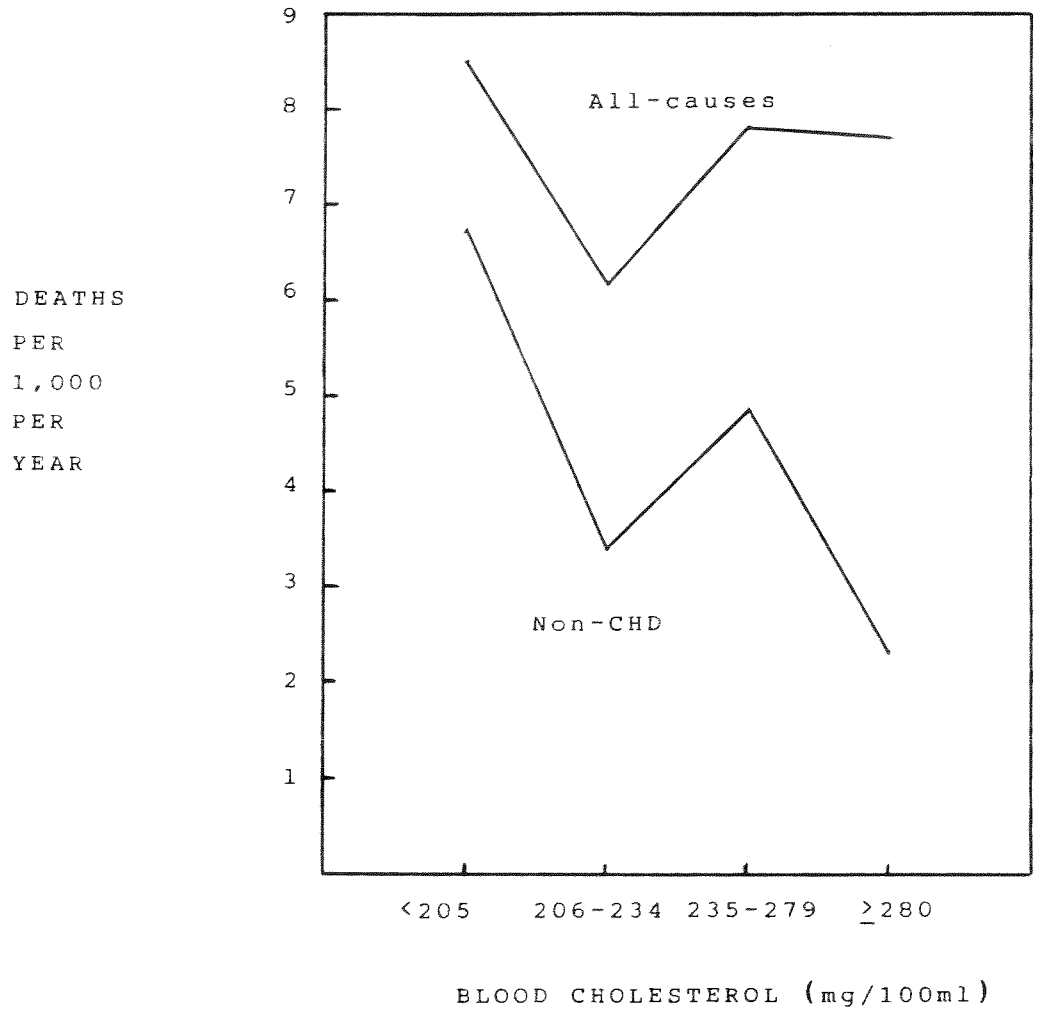

Figure 8-2. All-cause and non-CHD death rates by cholesterol levels in the Framingham study (adapted from Rose and Shipley, 1980[68])

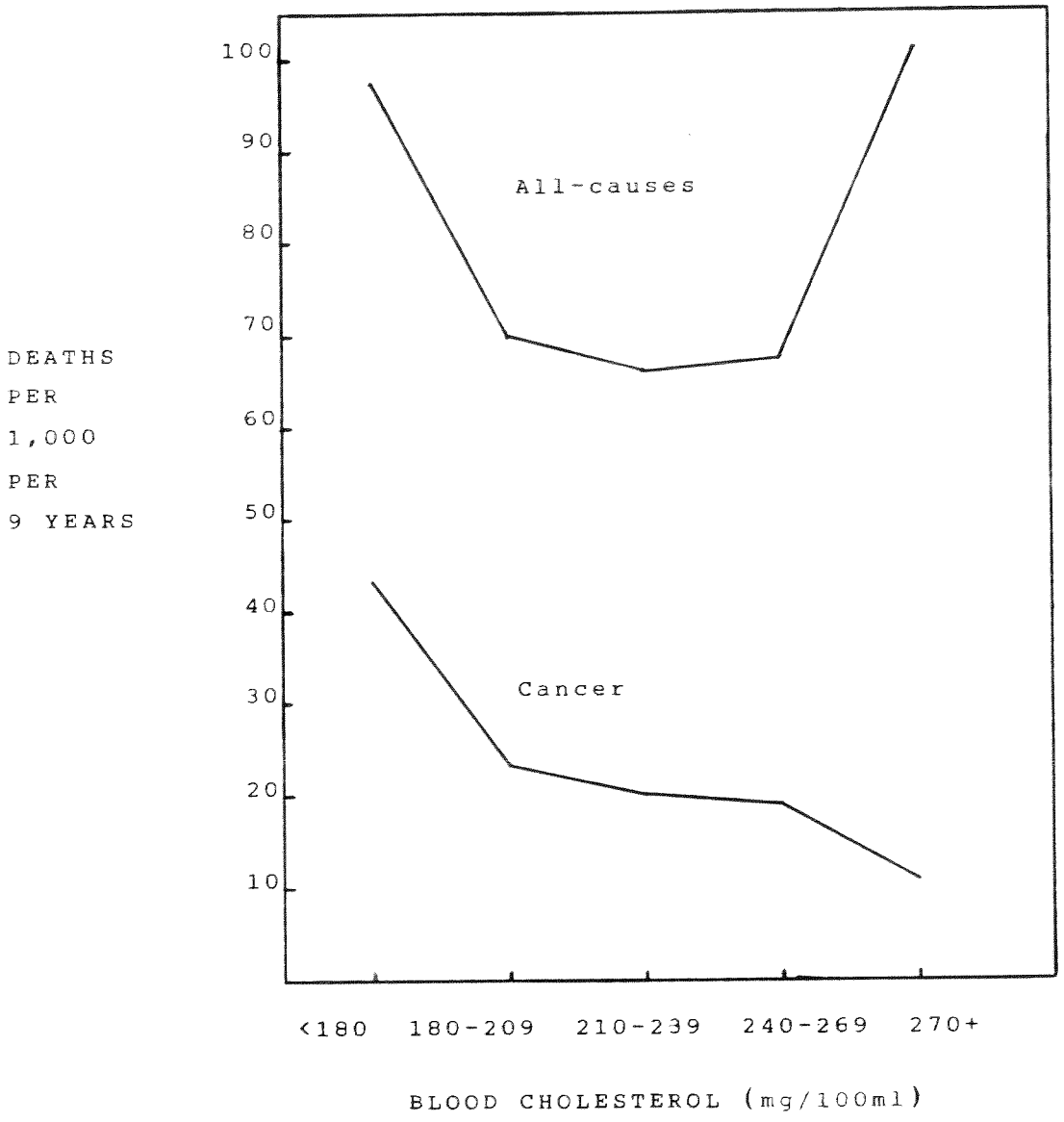

Figure 8-3. All-cause and cancer death rates by cholesterol levels in the Honolulu Heart Program (adapted from Kagan et al., 1981[71])

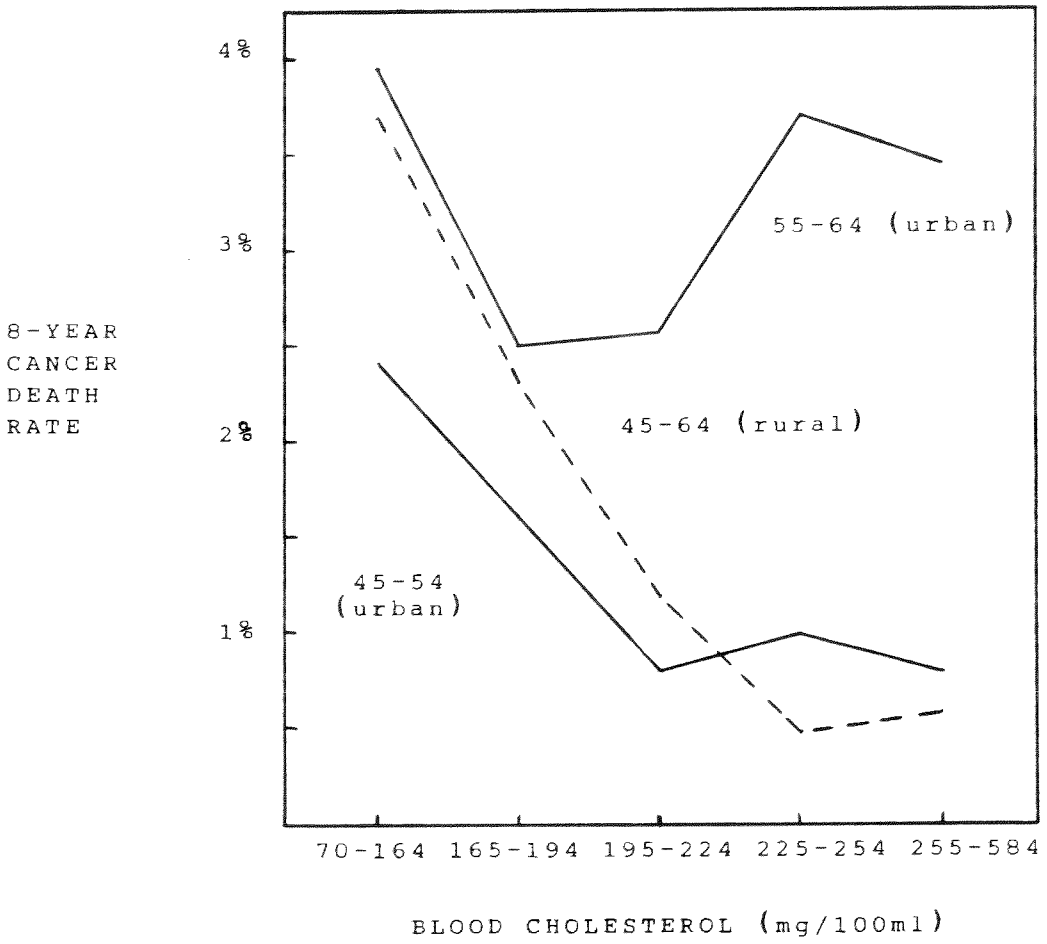

Figure 8-4. Cancer death rate by blood cholesterol in the Puerto Rico prospective study (adapted from Garcia-Palmieri et al., 1981[72])

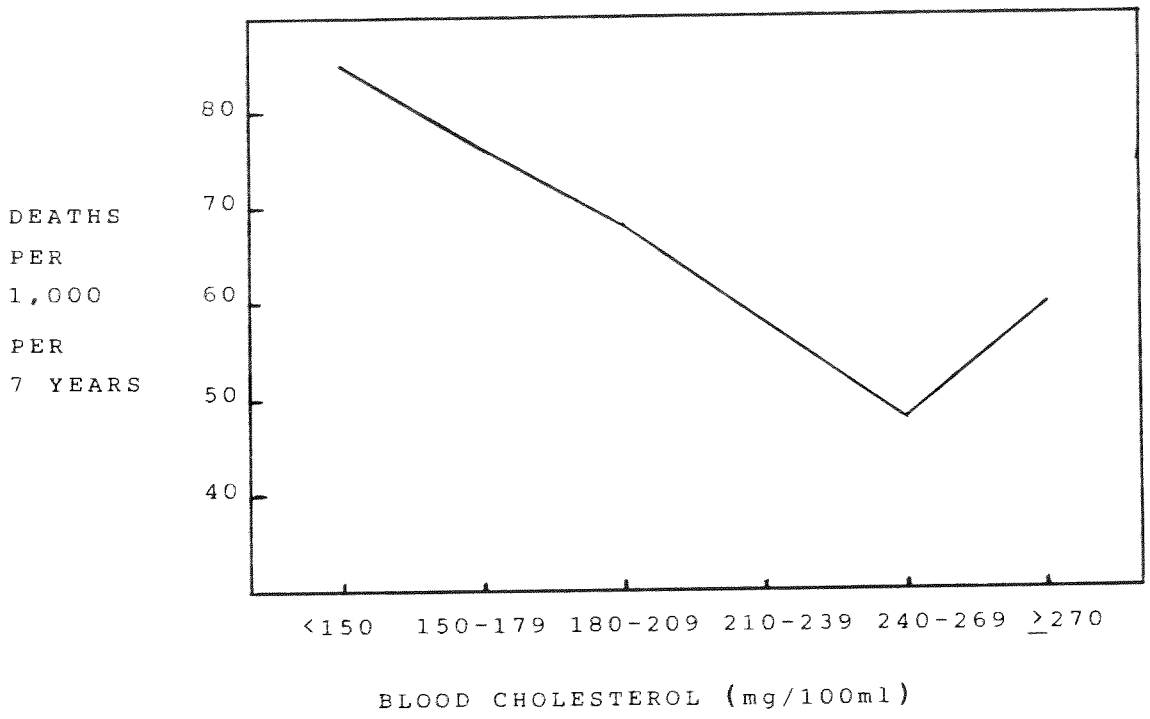

Figure 8-5. All-cause death rate by cholesterol levels in the Yugoslavia Cardiovascular Disease study (adapted from Kozarevic et al., 1981[74])

are suspect to begin with because they also revealed a highly inconsistent relation between cholesterol and CHD. For example, CHD mortality decreased as cholesterol level increased from ≤ 200 to 245 mg, increased from 245 to 270 mg and then decreased beyond 270 mg. In effect, the 18-year follow-up of this study did not support the results of most prospective studies, so the fact that it did not support the inverse relation between cholesterol and cancer and/or all-cause mortality should be not unexpected.

The Chicago Western Electric Company study reported positive relationships between cholesterol and CHD and all-cause mortality rates but not between cholesterol and cancer.[73] Thus, this study presented results almost completely opposite to those of the Chicago People's Gas Company study with respect to CHD and cancer. However, they were more consistent with those of other prospective studies and so this study should be recognized as legitimately unsupportive of the inverse relation.

The Chicago Heart Association Detection Project in Industry produced yet another set of results which contrasted with those of the other two Chicago studies. Cholesterol was inconsistently related to CHD, unrelated to cancer and demonstrated a weak but apparent U-shaped relation with all-cause mortality. It is noteworthy that death rates for cancer, CHD and all-causes were higher at cholesterol levels ≤ 184 mg than at 185-203 mg. This study is at least supportive of the low-cholesterol, high cancer and/or all-cause death rate and, it may be observed, it contained more than twice the number of subjects (6,890) as those that participated in both of the other Chicago studies (3,132).

The last of the eight studies was the AHA Pooling Project but as most everyone knows, it was not an independent investigation, being composed of five studies, three of which have already been discussed, i.e., Framingham and the two Chicago utility studies. The only relevant and independent contribution of the Pooling Project to the present discussion was that of two remaining studies known as the Albany and Tecumseh investigations, having a combined subject pool of 3,063. This writer found no data related to cancer or all-cause mortality rates in the Pooling Project Final Report[519] but all-cause mortality data were reported in the 1977 Senate Select Committee on Nutrition and Human Needs. All-cause death rate formed a strong U-shaped function with blood cholesterol in both of these investigations.

In summary, by far the bulk of the material reviewed in the first NHLBI Workshop demonstrated that cancer and/or all-cause mortality was high or highest at the low blood cholesterol levels. Feinleib's 1981 paper reflected this state-of-affairs but his 1982 paper completely distorted it.

Denial and Distortion

Seventeen studies were "reviewed" in the second Workshop.[95] Both Levy[2964] and Feinleib[95] admitted that eight of these studies showed an inverse relation between blood cholesterol and cancer mortality in men. These were

Framingham Heart study
Stockholm Prospective study
Twin Cities Businessmen study
Seven Countries, Northern Europe
Hypertension Detection and Follow-up Program
Israeli Civil Servants study
Evans County study
Hiroshima-Nagasaka study.

Apparently in an attempt to bias the Workshop, four studies which were included in the first Workshop were notably absent in the second, namely

Honolulu Heart Program
Puerto Rico Heart Health study
Yugoslavia Cardiovascular Disease study
Chicago Heart Association Detection Project.

All of these studies provided modest to strong support of the low-cholesterol, high cancer and/or all-cause mortality relationships. It is more than evident, therefore, that the Workshop's personnel selected a specific set of studies which would permit them to conclude that the majority (9 to 8) of studies opposed the low cholesterol, high cancer and/or all-cause mortality concept.

The studies purported to show no negative effects of low cholesterol were

Tecumseh
Kaiser Permanente
Western Collaborative
Seven Countries, Southern Europe
U.S. Railroad
Oslo
Lipid Research Clinics
Western Electric
Kiryat Yovel.

It is impossible to address most of these studies because Feinleib provided no references and indicated that "most of the data reported at the Workshop were preliminary and not yet published." However, as will be seen below, the Lipid Research Clinics study[2639] subsequently reported a strong inverse relationship between blood cholesterol and cancer and a U-shaped function with all-cause mortality. In addition, Keys[82] will report in 1985 that virtually all seven of the countries in his Seven Countries study showed higher cancer death rates among men who had low cholesterol levels at entry.[a] Finally, Hiatt and Fireman[975] will report in 1986 that an inverse relation between cancer and cholesterol exists for both men and women in the Kaiser Permanente study.

It is most interesting that Feinleib[95] included 9 additional studies not considered by the Workshop. Six of these studies supported the low cholesterol, high cancer and/or all-cause death rate relationship (Puerto Rico,[72] Honolulu,[71] New Zealand Maoris,[77] Whitehall,[68] Paris Government Workers,[69] and Malmo, Sweden[78]). Of the three studies which Feinleib claimed did not support the relationship, the Yugoslavian study and the Chicago Heart Association Detection Project did indeed provide supportive evidence as discussed earlier. Only the Chicago Gas Company failed to support the relationship and it may be recalled that this study also failed to show a consistent relation between cholesterol and CHD as well.

Feinleib concluded, "While there is inconsistent but confirming evidence of a possible increase in cancer risk at very low cholesterol levels (below 180 mg) in men,

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[a] The Italian Research Group[3050] subsequently published a 25-year follow-up of the two Italian cohorts of the Seven Countries study and, despite the growing concern over the inverse relation between cholesterol and cancer and total mortality, this group failed to report data on these relationships, although they listed the percentages of cancer and total deaths.

the magnitude of this risk is generally modest when present. Physicians can feel confident in advising reduction of blood cholesterol levels for all persons with higher than average levels."[95] Not only did he ignore the all-cause death rate threat at low cholesterol levels, he erroneously belittled the importance of the potential harm of low cholesterol levels.

More Evidence

Substantial evidence supporting the low-cholesterol, high cancer/all-cause death rate appeared in the 1980s. It is informative to initiate the review of this evidence with the findings from the large cohort of individuals screened for the MRFIT study because it is clear that a concerted effort was made by alliance members to initially cover-up these findings and to subsequently belittle their significance.

MRFIT Screened Cohort. Figure 8-6 shows both Kannel et al.'s[527] 1986 presentation of the all-cause death rates in the screened cohort and Iso et al.'s[1866] presentation in 1989. Kannel et al. plotted the data in terms of unequal cholesterol intervals, i.e., quintiles (dashed curve), while Iso et al. plotted the same data in equal intervals (solid curve). It is abundantly clear that the quintile scale completely obliterated the true relationship between total mortality and cholesterol level, namely, a U-shaped function which is clearly observable in Iso et al.'s data. This is precisely what we indicated might be the case in Volume 1 of this review.

Kannel et al. not only attempted to diminish the importance of low cholesterol levels by the use of quintiles, they also suggested that it was an artifact arising from the existence of cancer among individuals at the time of cholesterol measurement. Acknowledging that the total death rate in the first cholesterol quintile was higher than in the second quintile, they stated that "It reflects a somewhat higher cancer mortality rate at low cholesterol levels" and indicated that another report (uncited by Kannel et al. but discussed below) demonstrated that "the inverse relationship between serum cholesterol and cancer diminishes with duration of follow-up, suggesting that a reduced cholesterol level is more likely to be a consequence of cancer than a cause."

In a later (1988) article Kannel[1383] again discussed these data and said, "At cholesterol values below 160 mg, there appears to be an excess mortality." But note that in his 1986 figure (Figure 8-6) the rate increase occurred below 182 mg, not 160 mg. Kannel continued, "Examination of the MRFIT screening cohort data showed that the association between low serum cholesterol level and the incidence of cancer does not persist beyond five years of follow-up." While his 1986 statement suggested that the inverse relationship "diminished" over time, his 1988 remark clearly indicated that it disappeared before the total follow-up period of six years. As we shall see, Kannel and his colleagues completely distorted the facts.

The presentation of Iso et al. dramatically demonstrated that all-cause mortality formed a very strong U-shaped relationship with blood cholesterol in the screened cohort. In 1987 Sherwin et al.[92] published data relating the cancer death rate with cholesterol in that cohort. Figure 8-7 shows death rates for the total follow-up period, for the first two years, and for six or more years after cholesterol measurements were made. They reported that "Mortality follow-up revealed a significant excess of cancer in the lowest decile of serum cholesterol level during the early years of follow-up [bottom curve of Figure 8-7] which attenuated over time [top curve]. These findings are consistent with the inference that the association between low serum cholesterol level and cancer is at least in part due to an effect of preclinical cancer on serum cholesterol level." Not only did Sherwin et al. not deny that a relationship exists between low cholesterol and cancer, as indicated in their qualification--"at least in part"--it can be seen in Figure 8-7 that the relationship was clearly not attenuated over time. The cancer death rate increase below 200 mg (the

cholesterol level below which the alliance recommends all Americans achieve) was 4.4 per 1,000 for the $\geq$ 6 year period, while it was about 3.2 per 1,000 for the < 2 year period. Thus, the relationship strengthened, not attenuated, with time.

How can Sherwin et al. interpret a growing relationship as a decreasing relationship? Simple, they avoid rates and focus on meaningless relative risk ratios. They said, "During the first two-year period the risk in the lowest decile was 2.1 times higher than the average risk in deciles 2 through 10; during the second, third, and fourth periods, the risk in the lowest decile was 1.5, 1.2 and 1.3 times higher than the average risk in deciles 2 through 10." Their analyses clearly show how relative risk ratios totally distort facts. For example, Sherwin et al. noted that the bottom curve in Figure 8-7 shows a two to one ratio between the first decile and the average of deciles 2 through 10. This ratio is large primarily because the rates were low. To illustrate, consider the first two deciles in the upper and lower curves. Six over three (lower curve) is a higher ratio (i.e., 2) than 13.9 over 9 (upper curve, i.e., 1.5) but clearly the rate difference is higher in the upper curve than in the lower curve. Thus, relative risk ratios can and do actually transform a negative trend into a positive trend.

It is of interest to note that Stamler was a co-author of the Sherwin et al. article. In his 1986 report in which he presented CHD death rates as a function of cholesterol level, Stamler[263] plotted rates in terms of a six year period, rather than one year. This tactic magnified the differences between low and high cholesterol levels by a factor of six and was consistent with the alliance's desire to promote the importance of cholesterol to CHD. It is obvious, however, that the alliance fears an inverse relation between cholesterol and total mortality and, accordingly, Sherwin et al. reported their rates in terms of one-year, rather than six year intervals, thereby minimizing the differences between low and high cholesterol levels. The present writer converted Sherwin et al.'s annual rates to six year rates in order to permit proper comparison with Figure 8-6.

Lipid Research Clinics Prevalence Study. Figure 8-8 presents the relationships between cholesterol and cancer and all-cause death rates among men in the LRC Prevalence study as reported by Cowan et al.[2639] Clearly, the cancer death rate was highest at the lowest cholesterol interval and the all-cause death rate was higher at the lowest cholesterol interval than at both the second and third intervals. It is suspected that the rates at the low end of the cholesterol scale might be even more impressive were a more appropriate equal interval scale used instead of a quartile scale. Examination of the data over time led Cowan et al. to conclude that "the inverse relation in men is not due to pre-existing disease."

Similar relationships were not observed among women in the study.

Hypertension Detection and Follow-up Program. Morris et al.[972] reported that the Hypertension Detection and Follow-up Program "demonstrated a weak inverse relation between serum cholesterol and cancer mortality incidence." They also indicated that the relationship persisted over time, ruling out the notion that preclinical cancer was the cause of the low cholesterol levels at entry. Figure 8-9 shows that the inverse relationship with all cancers was quite strong, despite Morris et al.'s attempt to suggest otherwise, and, with the exception of lung cancer, the inverse relation was continuous across the entire cholesterol spectrum.

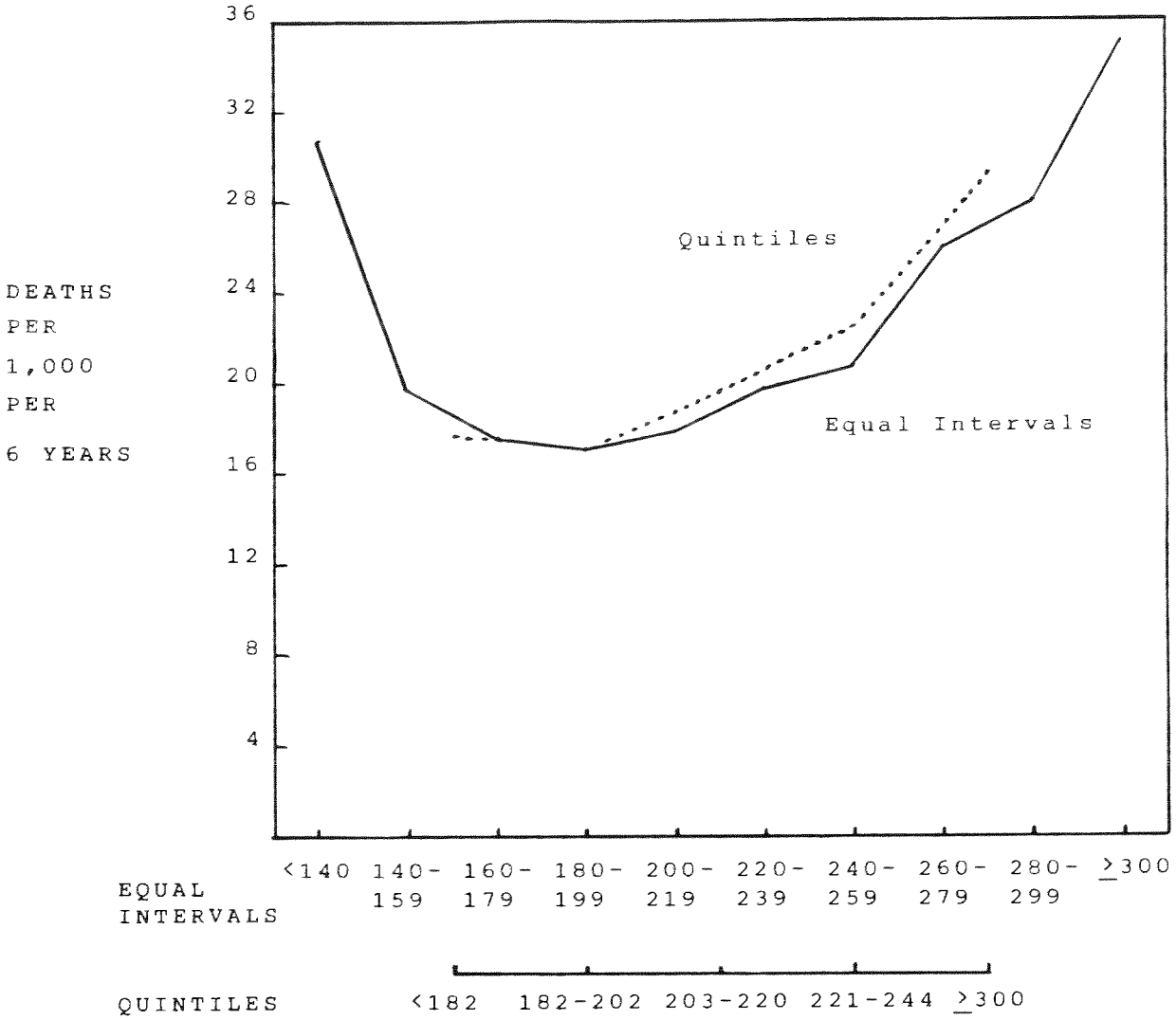

Figure 8-6. All-cause mortality rate in the MRFIT screened cohort plotted by quintiles and equal intervals (adapted from Kannel, 1986[527] and Iso et al., 1989[1866])

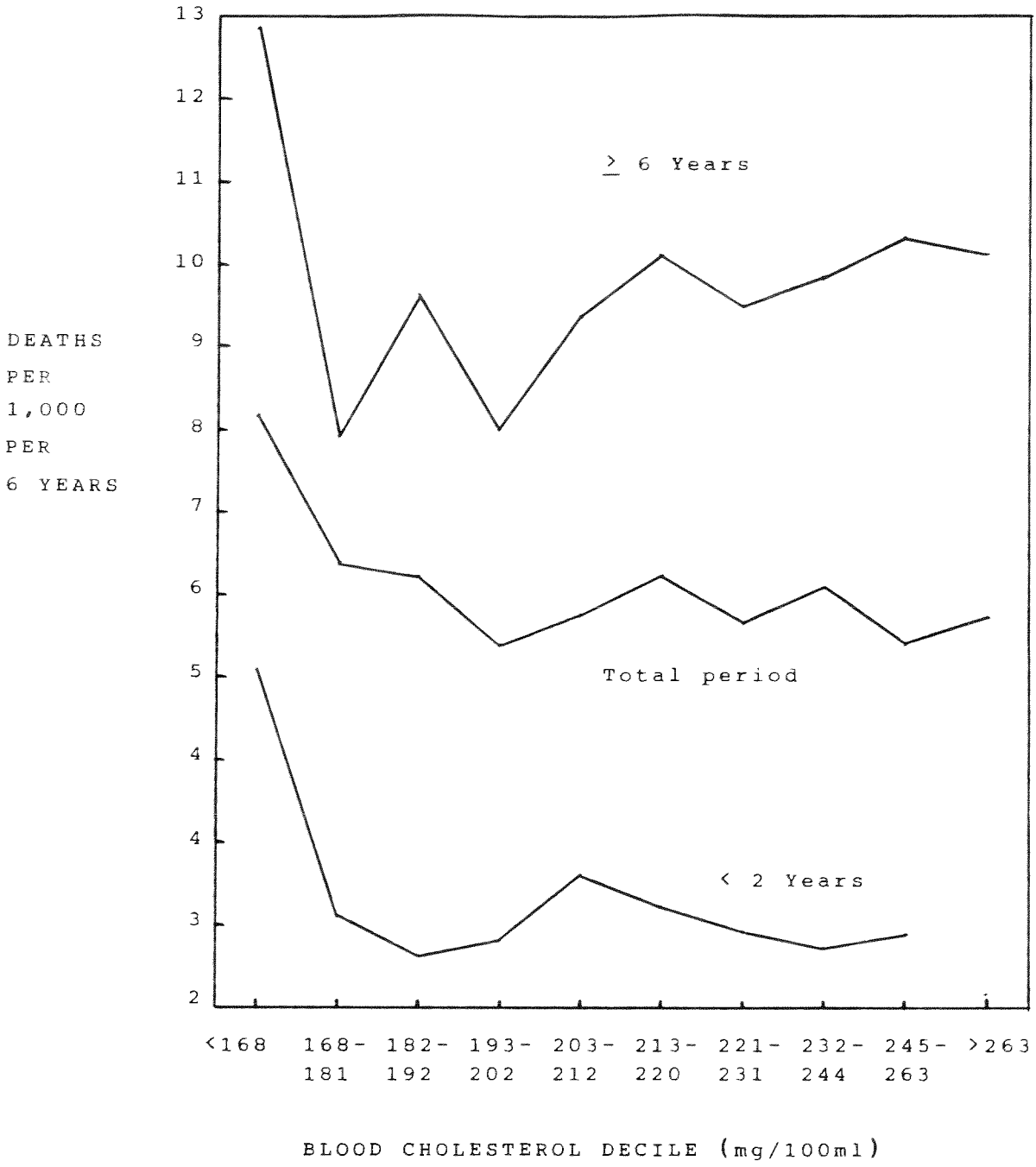

Figure 8-7. Cancer death rate by cholesterol level and by time from cholesterol measurement in the MRFIT screened cohort (adapted from Sherwin et al., 1987[92])

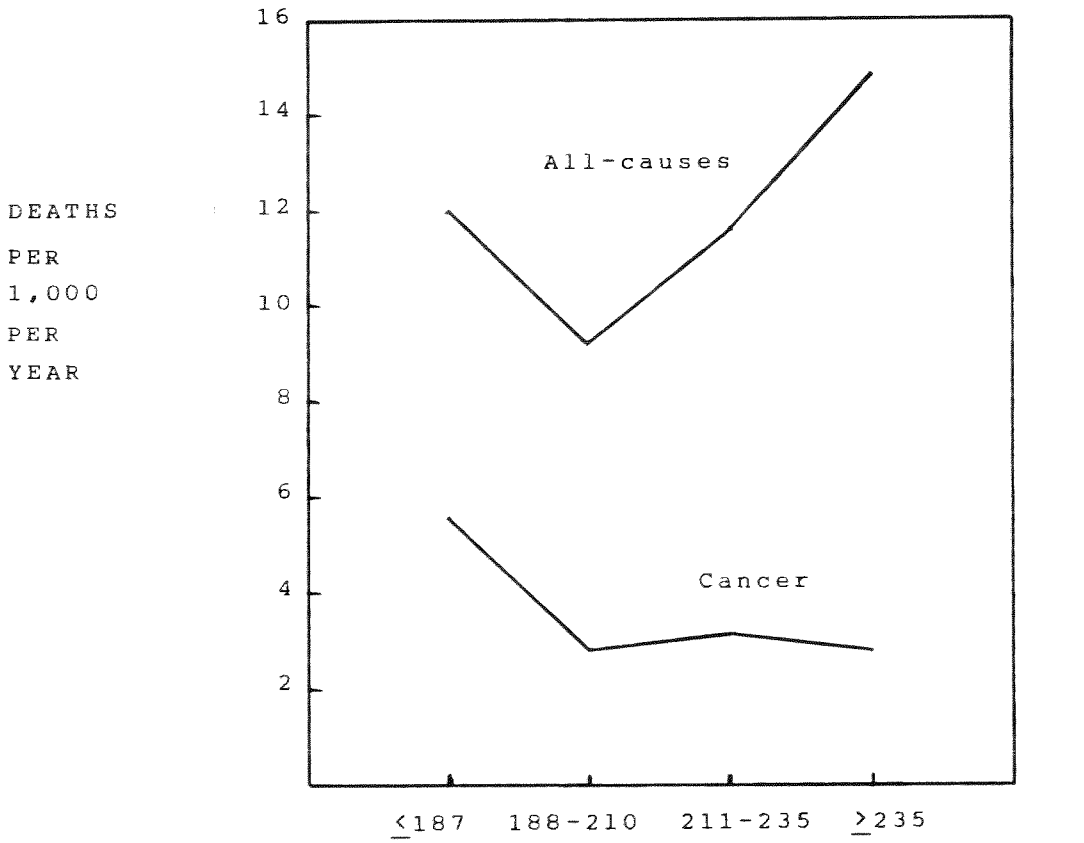

Figure 8-8. All-cause and cancer death rate by cholesterol levels in the Lipid Research Clinics Prevalence study (adapted from Cowan et al., 1990[2639])

The reader may note that the rate difference between the highest and lowest cholesterol levels for "other cancers" was 13 per 1,000 per 5 years. This would translate to 15.6 per 6 years. This difference was far greater than that observed by Stamler et al.[263,a] for CHD in the 6-year follow-up of the MRFIT screened cohort. Since Stamler et al. called their relationship "powerful," while Morris et al. referred to theirs as "weak," it is clear that alliance members do not hesitate to use the terms "powerful" and "weak interchangeably, depending on whether or not the outcome is consistent with their preconceived beliefs.

Rancho Bernardo Study. Wingard et al.[67] reported higher cancer and all-cause mortality rates at the lowest cholesterol interval than at intermediate intervals. Figure 8-10 shows the inverse relationship held for three of four intervals for all-cause mortality and for all intervals for cancer mortality. Although these relationships cannot be considered substantial, they are nevertheless nontrivial and confirm the findings of many other studies.

Kaiser Permanente Medical Care Program. Figure 8-11 presents the cancer-cholesterol relationship for the Kaiser Permanente study as reported by Hiatt and Fireman.[975] These investigators indicated that the trend was significant for females but not for males, opposite to that observed in most studies. However, in view of the fact that nearly every major study has revealed an inverse relation between cancer and cholesterol, the trends in the Kaiser Permanente study are clearly supportive of the inverse relation, whether or not statistical significance was achieved for males.

The above comments notwithstanding, the results of this study are not directly comparable with those of other studies because both fatal and nonfatal cancer incidence was included, whereas only fatal cancer rates were used as endpoints in other other studies.

Honolulu Heart Program. It will be recalled that Kagan et al.[71] reported a very strong inverse relation between cholesterol level and cancer and a U-shaped relation between cholesterol and all-cause mortality for a 9-year follow-up of the Honolulu Heart Program (Figure 8-3). Figure 8-12 shows the results of a 10-year follow-up by Reed et al.[2820] but rather than death rates, these investigators chose "incidence" rates, obviously a combination of fatal and nonfatal rates. Therefore, these results are again not directly comparable with those of other studies. The fact that Kagan et al. showed a strong inverse relation for cancer deaths, while Reed et al. reported no relation whatsoever for total cancer incidence indicates that the weak relationship reported by Hiatt and Fireman[975] for the above Kaiser Permanente study was very likely due to the inclusion of nonfatal cancers.

A letter to the editor in 1990 by Benfante and Reed[2832] confirmed previous findings in an 18-year follow-up, i.e., the relation between total mortality and cholesterol is U-shaped and "Deaths due to cancer, hemorrhagic stroke, and other causes account for the higher mortality rates below 189 mg and this pattern persists after cancer deaths during the first 5 years of follow-up were removed from the analysis." This statement strongly suggests that the inverse relation between cancer

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[a] It would appear that if all cancers were combined, the difference in death rates between the highest and lowest cholesterol levels would be very similar to that observed by Stamler et al. for CHD.

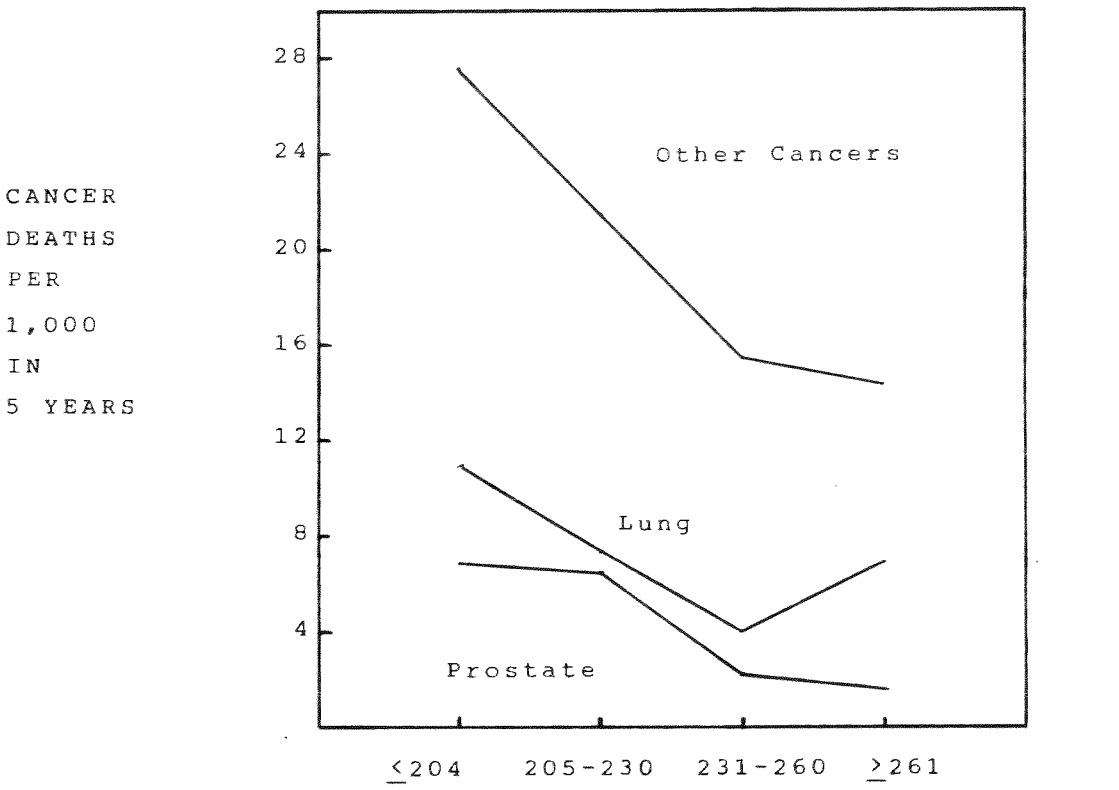

Figure 8-9. Cancer death rates by site in the Hypertension Detection and Follow-up Program (adapted from Morris et al., 1983[972])

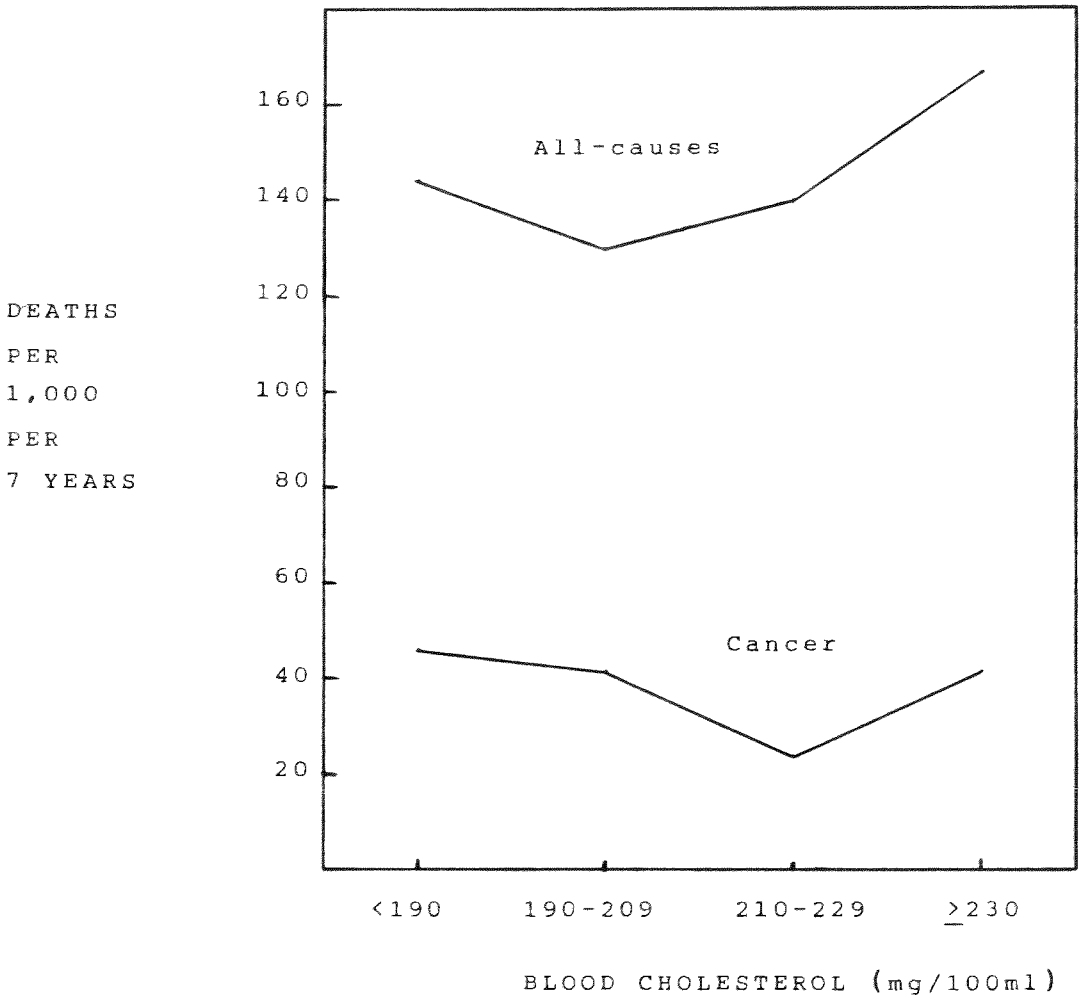

Figure 8-10. All-cause and cancer death rates in the Rancho Bernardo study (adapted from Wingard et al., 1984[67])

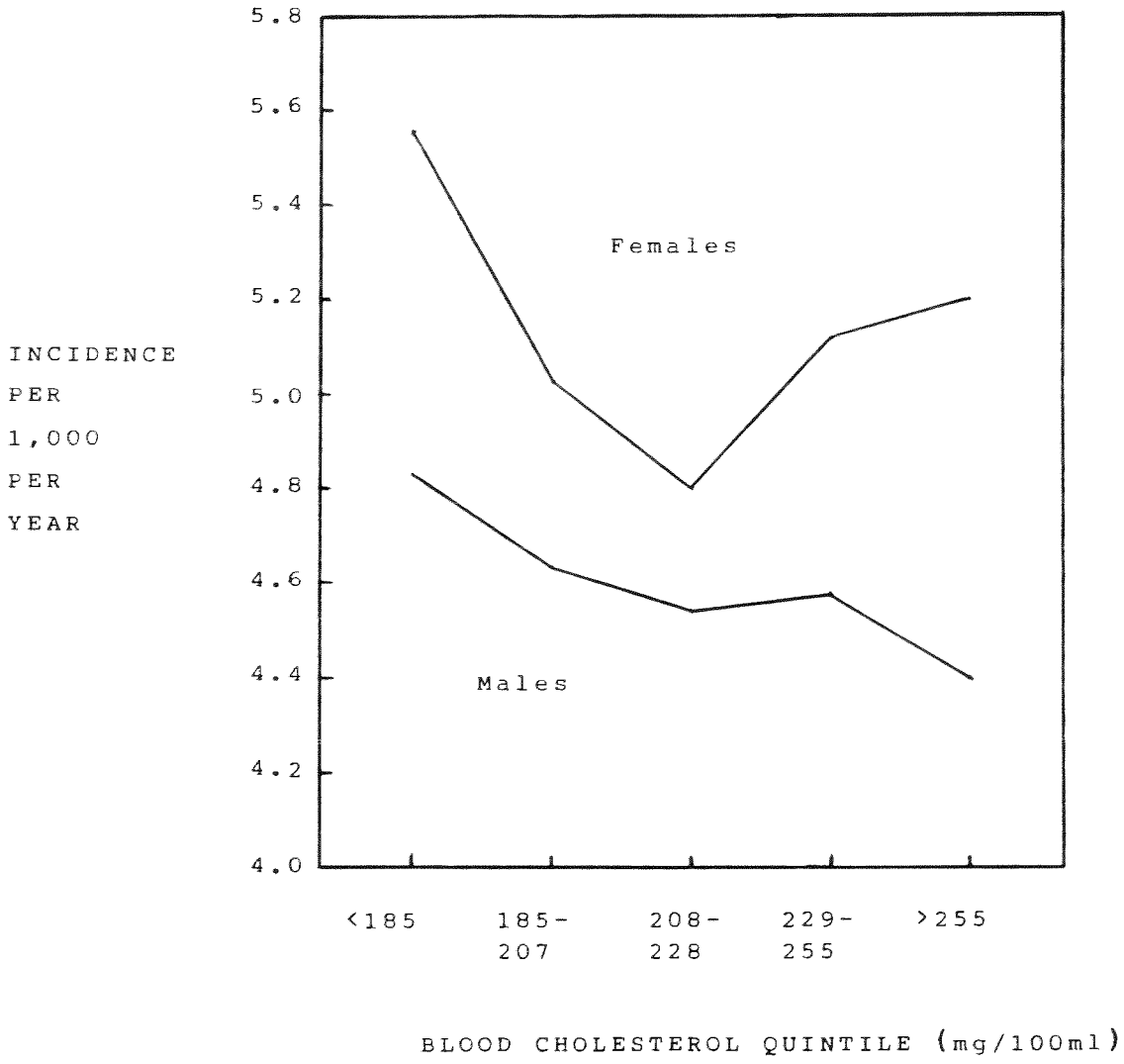

Figure 8-11. Incidence of cancer by cholesterol level for males and females in the Kaiser Permanente Medical Care Program (adapted from Hiatt and Fireman, 1986[975])

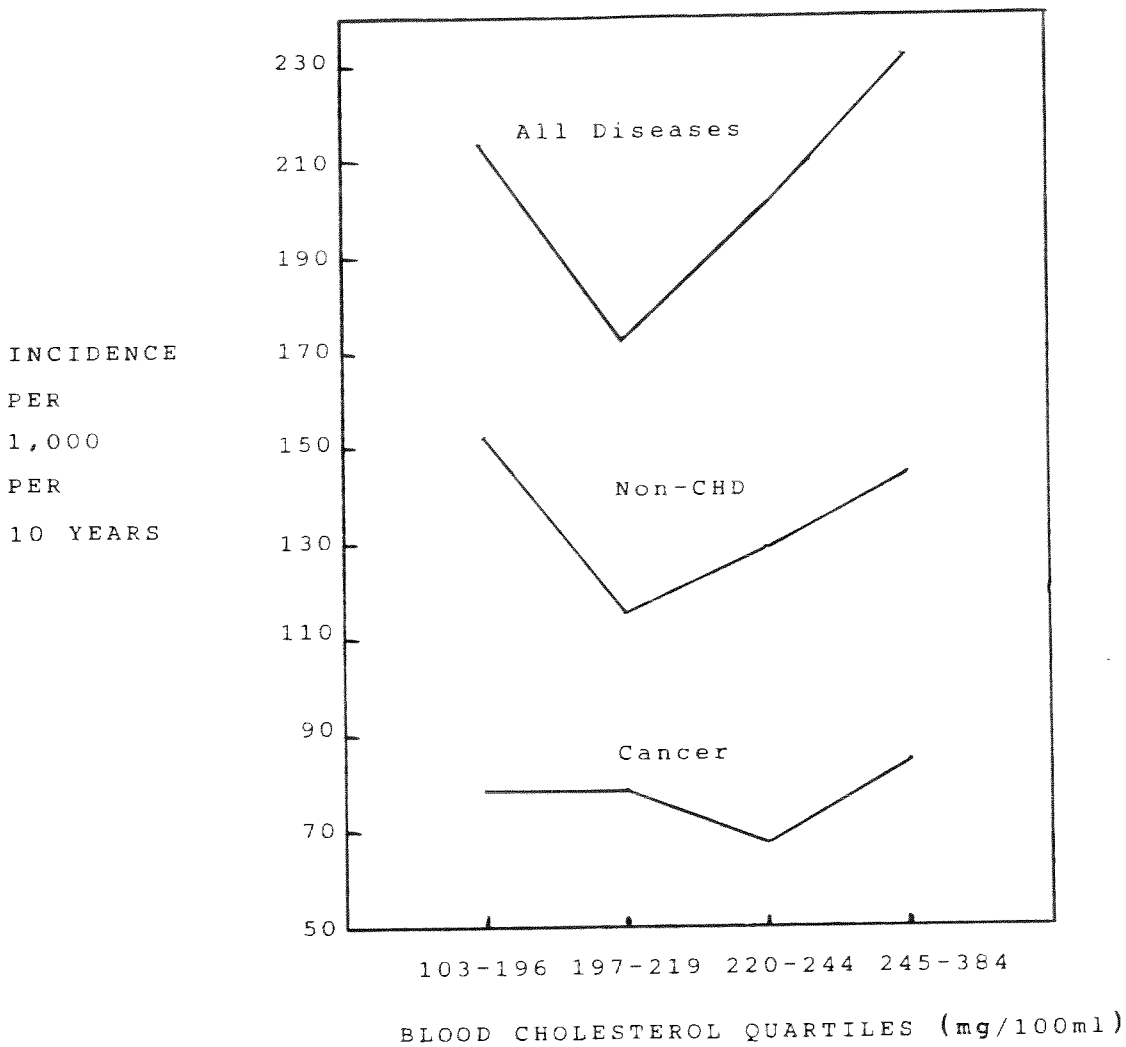

Figure 8-12. All-diseases, non-CHD and cancer incidence in the Honolulu Heart Program (adapted from Reed et al.,1986[2820])

cholesterol is U-shaped and "Deaths due to cancer, hemorrhagic stroke, and other causes account for the higher mortality rates below 189 mg and this pattern persists after cancer deaths during the first 5 years of follow-up were removed from the analysis." This statement strongly suggests that the inverse relation between cancer mortality and cholesterol observed in the 9-year follow-up was also observed in the 18-year follow-up.

Whitehall Study. Rose and Shipley[68] reported similar findings for the large English Whitehall study. As can be seen in Figure 8-13, inverse relationships were evident for both cancer and non-CHD death rates and a U-shaped function was observed for all-cause death rates. While the trends appear to be weaker than those in previously discussed studies, this is largely because they were computed for one year periods, unlike the multiple year periods used by most other investigators.

Renfrew and Paisley Survey. Isles et al.[1860] presented similar results for the Renfrew and Paisley Survey in England. It is to be noted that their results, shown in Figure 8-14, are also given in one year, rather than multiple year, periods. The inverse relation between cancer and cholesterol level was continuous and, unlike most other studies, the all-cause death rate was highest at the lowest cholesterol interval and constant at the remaining intervals.

Israeli Ischaemic Heart Disease Study. Figure 8-15 shows the all-cause and cancer death rates by cholesterol level in the Israeli Ischaemic Heart Disease study. Yaari et al.[973] concluded that "Total mortality seems to be raised only in the top quintiles of serum cholesterol (an apparent 'J' relation). There is no evident association between cancer mortality rates and cholesterol concentrations." However, it is clear that the cancer death rate trend over the first three quintiles is identical to the all-cause death rate trend. Classifying one trend as real and the other as not real is illogical. In fact, the inverse relation between cancer and cholesterol level is evident for four of the five quintiles; only Quintile 4 deviates from the overall trend. In any event, the Israeli study presented trends consistent with nearly every major prospective study, i.e., cancer and/or all-cause death rates were higher at low cholesterol levels than at intermediate levels. A subsequent longer follow-up by Goldbourt et al.[1098] again revealed higher all-cause death rates at low cholesterol levels than at intermediate levels.

Paris Prospective Study. Cambien et al.[69] reported that the cancer-death rate in the Paris Prospective study was inversely related to blood cholesterol level. As can be seen in Figure 8-16, the relationship was continuous. Although these investigators claimed that "This association is not likely to represent an etiologic link between low cholesterol and cancer," they admitted that their claim was "not conclusive."

NHANES I Epidemiologic Follow-up Study. Schatzkin et al.[3216] reported that cancer incidence and mortality was higher among both men and women with the lowest cholesterol levels than in those with higher levels in the 10 year NHANES I Epidemiologic Follow-up Study (Figure 8-17). They concluded that "It may be premature to dismiss the inverse relation between serum cholesterol and cancer simply as a preclinical marker of disease."

Additional Studies. Many other studies have provided support for the low cholesterol, high cancer and/or all-cause mortality relationships but most did not present their data in terms of death rates.[70,850,977] Some of the studies consisted of relatively few subjects.[974,1875,1886] Of considerable importance is the Seven Countries study, i.e., Keys et al.[82] noted that "In all 7 countries the men who died of cancer had lower cholesterol levels at entry than did their group means." They stressed that this

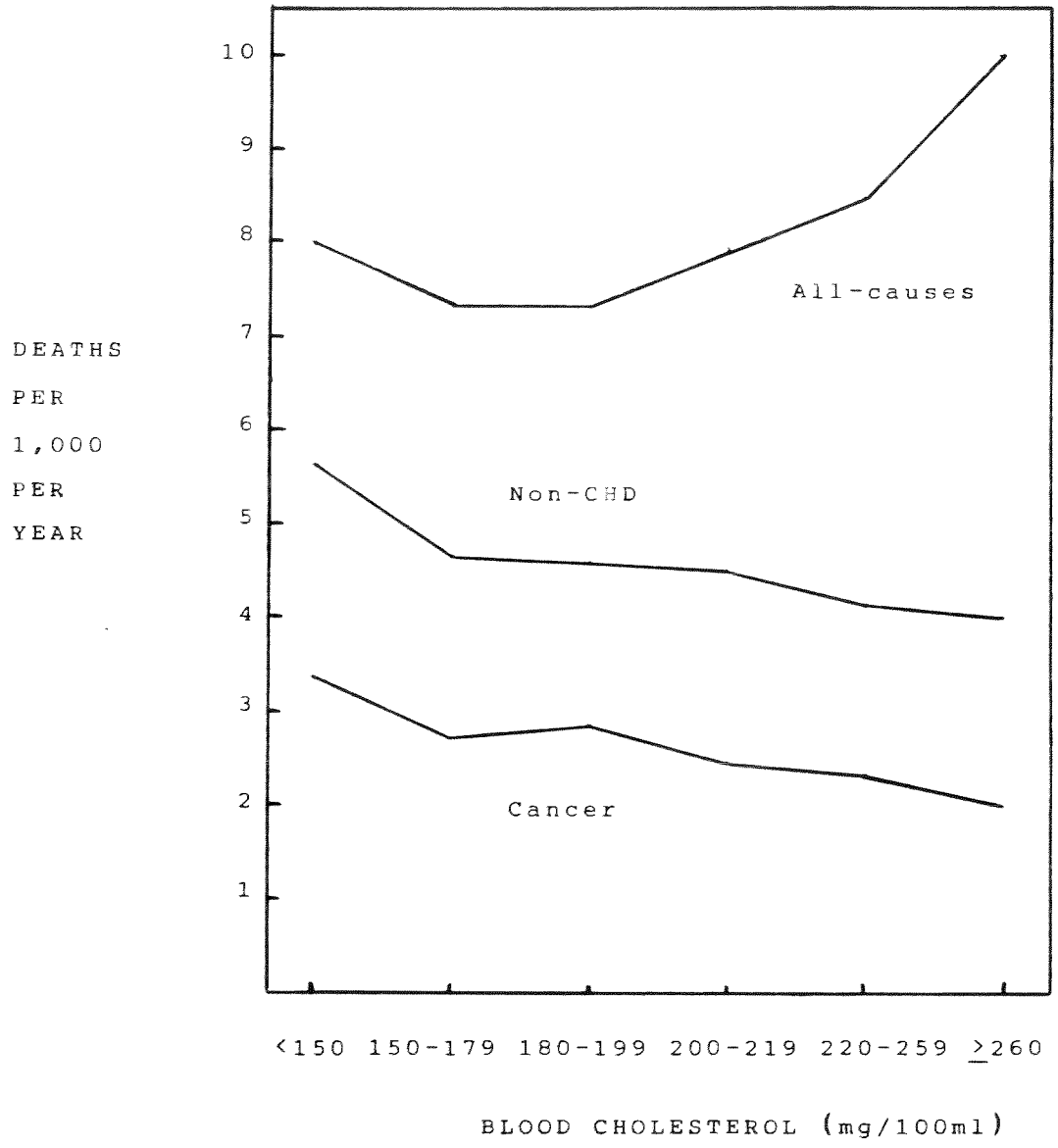

Figure 8-13. Age-adjusted all-cause and cancer death rates by cholesterol levels in the Whitehall study (adapted from Rose and Shipley, 1980[68])

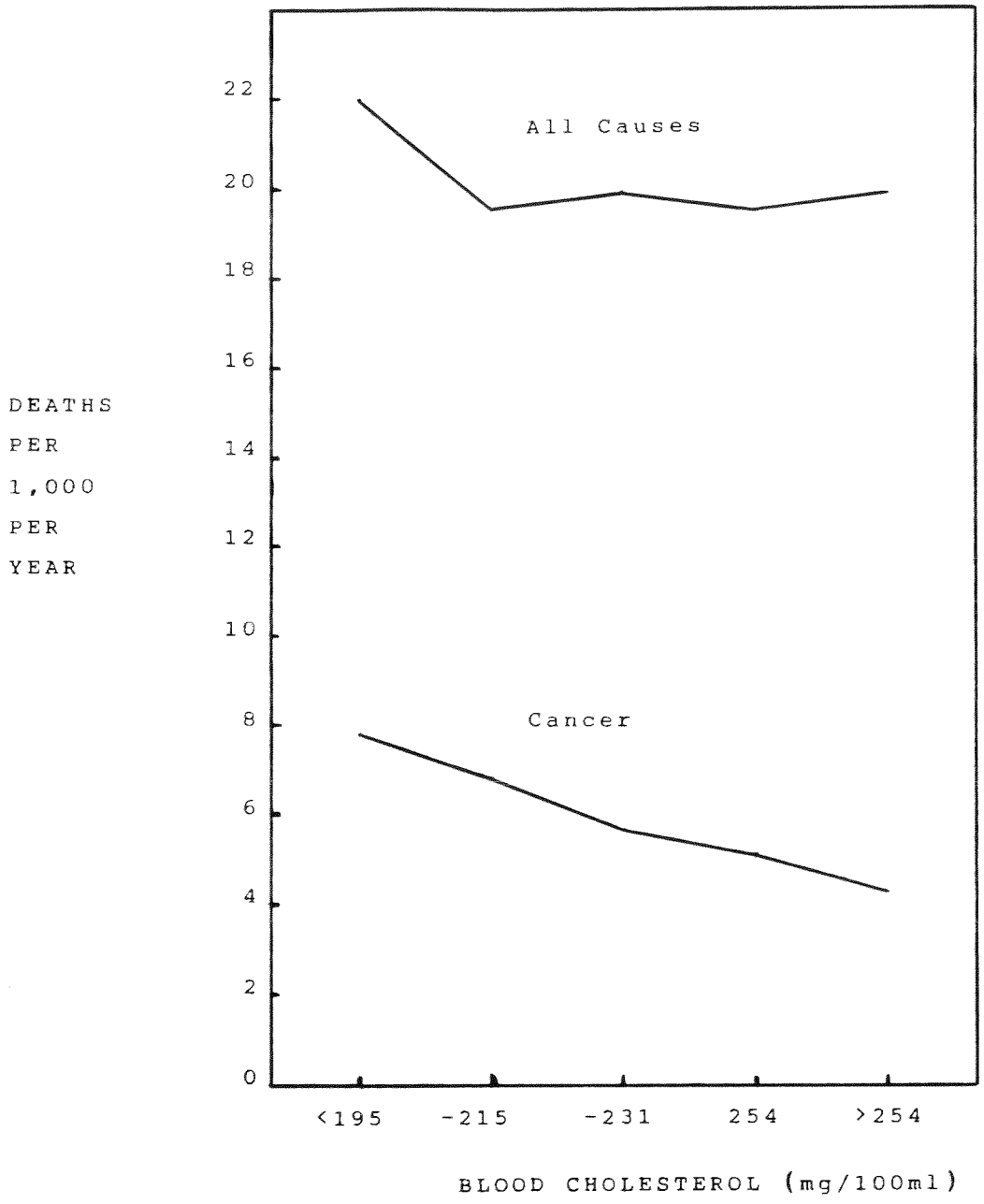

Figure 8-14. All-cause and cancer death rates by blood cholesterol level in the Renfrow and Paisley Survey (adapt- Isles et al., 1989[1860])

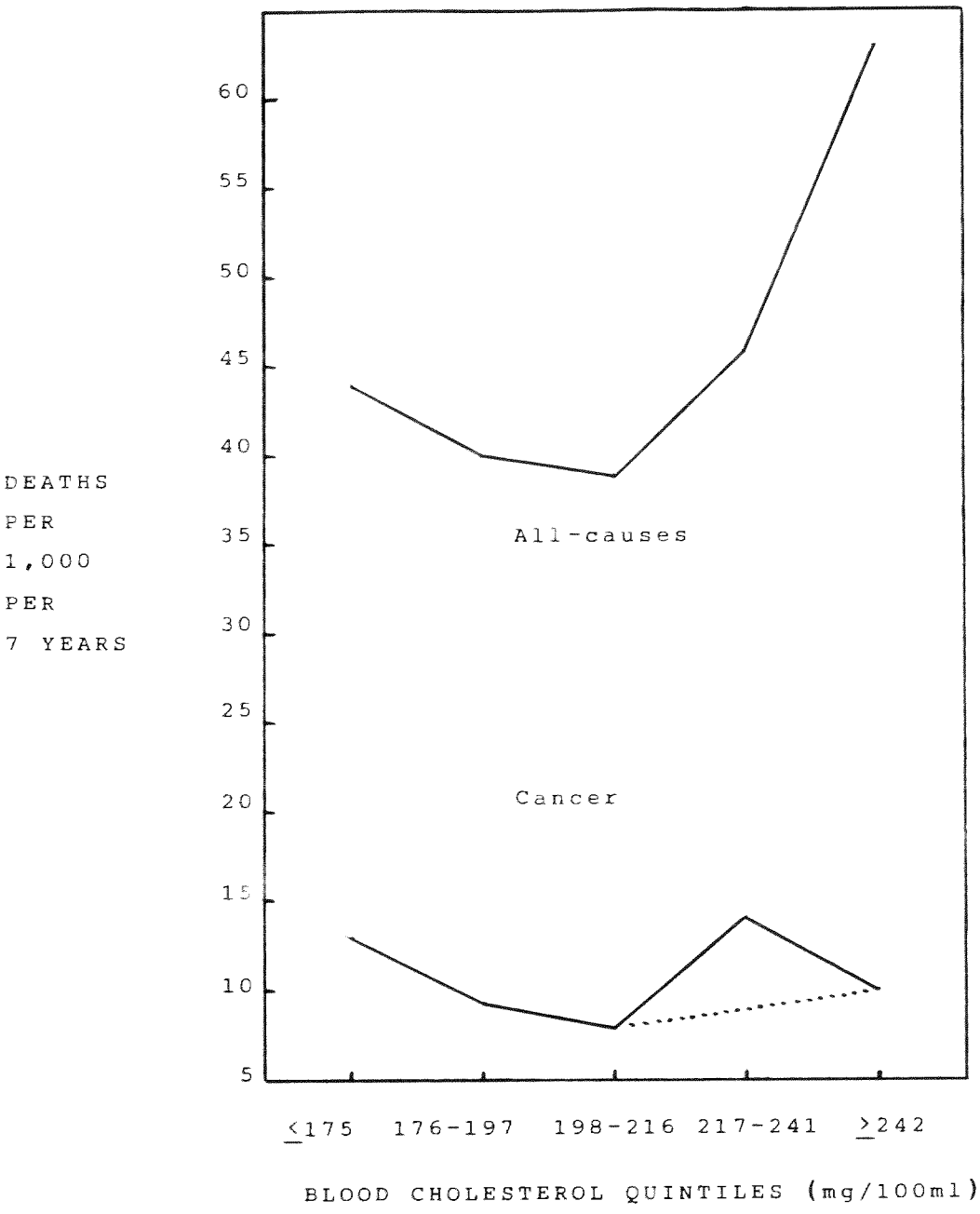

Figure 8-15. Age-adjusted cancer and all-cause mortalities by cholesterol levels in the Israeli Ischaemic Heart Disease study (adapted from Yaari et al., 1981[973])

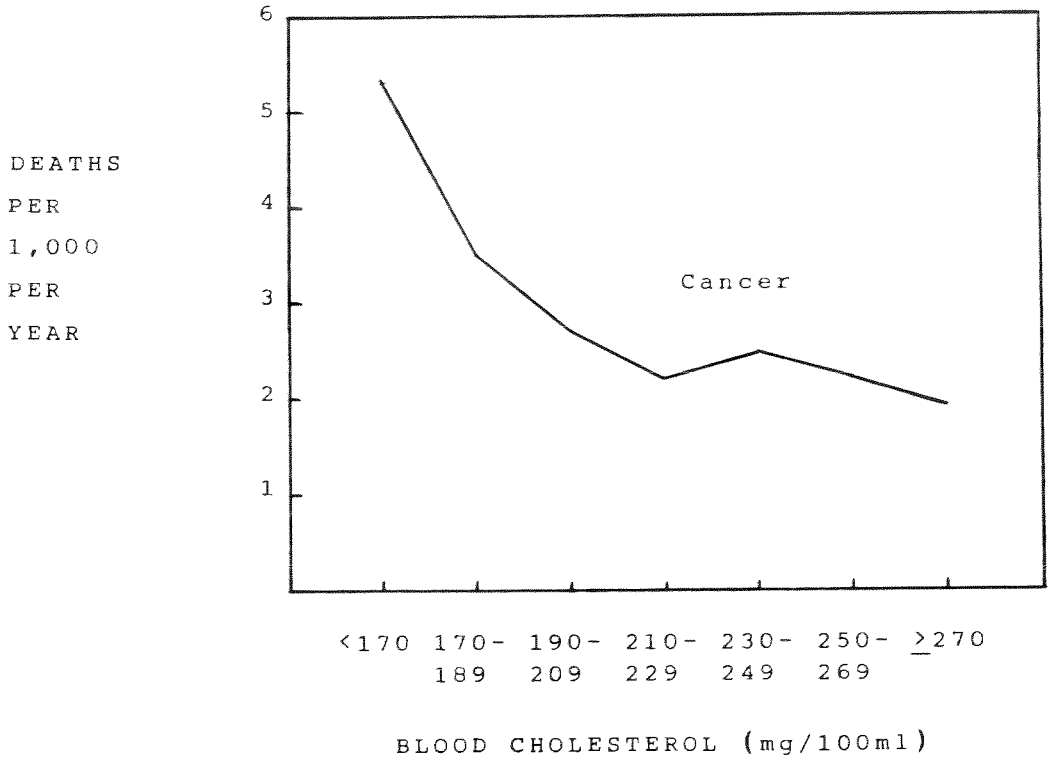

Figure 8-16. Cancer death rate by cholesterol levels in the Paris Prospective study of Coronary Heart Disease (adapted from Cambien et al., 1980[69])

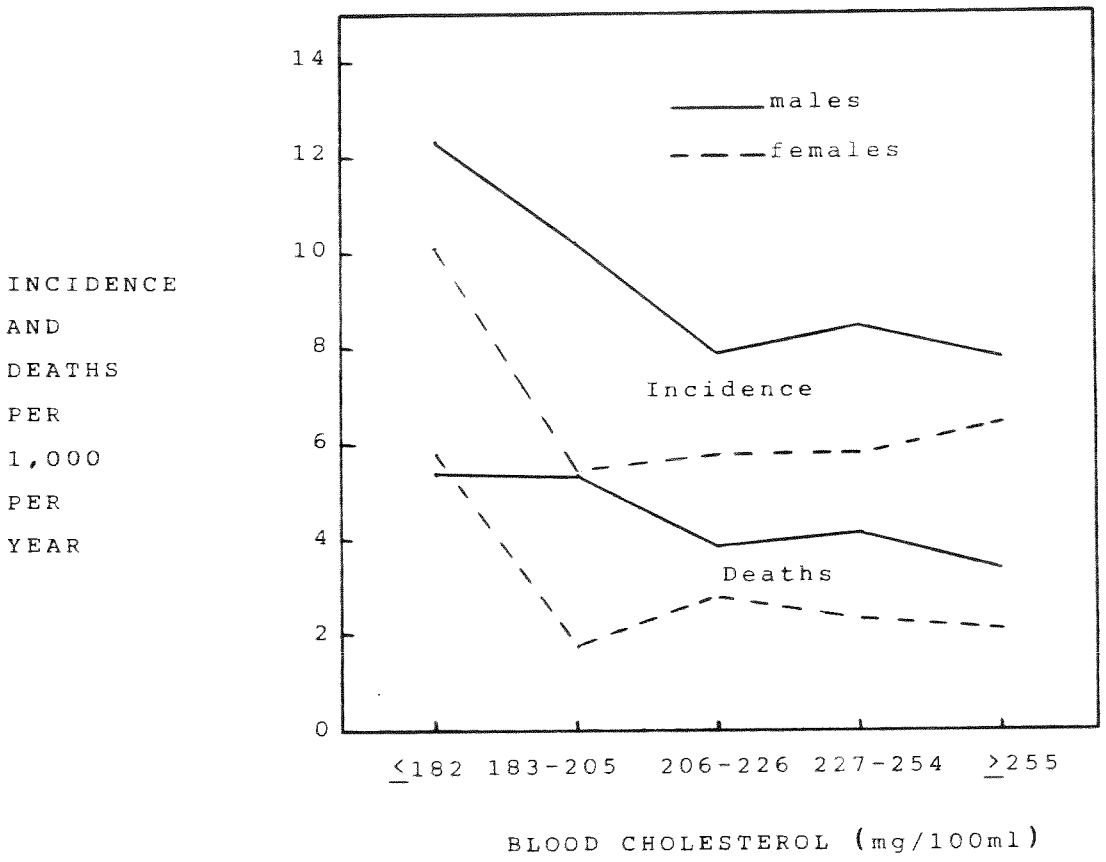

Figure 8-17. Cancer incidence and death rate by cholesterol levels in the NHANES 1 Epidemiologic Follow-up study (adapted from Schatzkin et al., 1987[3216])

relationship held over a 15 year period even when the first five years of data were eliminated. Also, a Danish study by Agner and Hansen[3166] reported that total mortality was greater in the lowest cholesterol quintile than in the remaining quintiles.

Negative Findings. It is evident from all of the foregoing that nearly every major study has revealed evidence of harm associated with low cholesterol levels. Some studies have not provided such evidence but one can easily find fault with most of them. For example, some studies[971,3006,3057] compared small numbers of cancer patients with "matched" controls. As emphasized in Volume 1, matching leaves much to be desired in assuring that groups are equal, especially when matching only considers sex and age. One study compared patients with adenomas with "matched" controls and reported that they had higher, not lower, cholesterol levels.[94] Not only are adenomas not cancer, these results are opposite to the general finding that cancer patients have lower cholesterol levels than noncancer patients.[a]

Two important investigations were prospective studies conducted in England. Shaper et al.[2162] and Meade et al.[1293] reported no increase in death rates at the lowest cholesterol levels. However, the former presented their data in quintiles and the latter used the even more distorted scale of tertiles. The lowest cholesterol interval of these studies lumped all levels below 212 mg and 216 mg, respectively. Not only does a large percentage of the adult male population fall below these levels, as shown with the MRFIT screened cohort, the true relationship between low cholesterol levels and cancer or total mortality can easily be washed out by using such broad intervals. As presented by their authors, therefore, these studies cannot be used to support or deny the inverse relation between cholesterol and mortality.

The Illogical and Inconsistent Arguments

A major argument used by the alliance against the concept that low cholesterol levels are associated with high rates of cancer is exemplified in a statement by Feinlieb, i.e., "Given the long latency period of many forms of cancer, changes in lipid metabolism that may be reflected in serum cholesterol levels might long antedate any clinically detectable symptoms of the disease."[95] He said the panelists at the 1981 workshop sponsored by NHLBI and NCI "concurred that the correlations observed [among studies] did not substantiate any direct cause and effect relationship between low blood
cholesterol levels may serve as a 'marker,' possibly genetic, and in only small numbers of male individuals in any given population." Feinleib continued, "Some of the studies attempted to allow for this [long latency period] by excluding from statistical consideration those subjects who developed cancer up to 10 years after their blood lipid determinations; however, the apparent relationship persisted. While these data seem to exclude low cholesterol levels as being secondary to an occult cancer, the lead time for a polyp to convert to a cancer could by 10 or 15 years or more."

Of course, Feinleib's argument could and should be applied to the cholesterol-CHD relationship as well because the latency period for CHD symptoms is typically much longer than that for cancer. It was amply shown in the Framingham study that the closer to the exhibition of clinical signs of CHD that blood cholesterol measurements are made, the more valid they are in predicting CHD (Chapter 4). Consistent with Feinleib's argument that the low cholesterol, high cancer mortality involves "only small numbers of male individuals," among those having high cholesterol levels there is also only a small number of male individuals with high cholesterol levels who die of CHD. It is foolish and illogical to invoke these arguments for the cancer case and not for

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[a] 971,2829,3006 and virtually all the studies discussed in previous sections.

the CHD case, particularly as there is no scientific proof that cholesterol causes CHD as well. If cancer alters lipid metabolism during its early states, resulting in low blood cholesterol levels which "mark" the disease, it is equally plausible that early atherosclerosis alters lipid metabolism which then serves to "mark" that disease. Certainly, it would be consistent with the "injury repair" theory of atherogenesis held by some investigators. In view of the fact that cholesterol is only statistically associated with either CHD or cancer and has essentially no predictive capacity at the individual level, the most logical conclusion to be drawn is that cholesterol is neither a cause of nor a marker for either disease insofar as the vast majority of people are concerned.

The alliance's argument that cancer is not caused by low cholesterol levels but rather induces low levels is a direct contradiction to their arguments of cancer and cholesterol in between population studies. For example, Grundy[3034] indicated in 1984 that between populations studies show that populations with high fat and cholesterol intakes (and, therefore, high cholesterol levels) have higher cancer rates. Kannel[1091] introduced the same argument in 1983. Thus, depending on the context in which they speak, cancer is caused by high cholesterol levels and also causes low cholesterol levels. It should not be difficult to see that such reasoning is completely irrational.

Sidney and Farquhar[2963] concluded in 1983 that clinical trials predominantly reveal no evidence of a low cholesterol, high cancer relation. It should be obvious, however, that clinical trials are generally not good vehicles for testing the relation. In the first place, the mean cholesterol difference between treated and control groups has usually been only 10% or less which is hardly the same thing as comparing individuals with cholesterol levels below 180 mg with those 30, 40 and 50 mg above 180 mg in prospective studies. In the second place, most clinical trials have used subjects with high cholesterol levels so that treated groups did not, in any sense, exhibit low cholesterol levels.

Because clinical trials subsequent to 1983 did offer evidence of a low cholesterol, high cancer relation, it is interesting to note a very recent argument by Yusuf et al.[2257] which attempted to diminish its significance. They said, "We...are concerned by the observed excess in non-CHD mortality in several trials. We found the external and internal evidence that supports this to be weak because there is (1) little epidemiologic, experimental, or mechanistic evidence to support a claim of excess non-CHD mortality, (2) no relationship between the intensity of lowering the level of cholesterol and excess non-CHD deaths, other than gallstones, with the fibric acid derivatives. We cautiously concluded that while one cannot completely dismiss an adverse effect of lowering cholesterol levels, the observed increase in non-CHD is consistent with chance."

Yusuf et al.'s argument is completely untenable on several grounds. As observed by Basinsky et al.[2256] the excess in non-coronary heart disease mortality recurs in trial after trial (and prospective study after prospective study), not just in several trials as Yusuf et al. would have readers believe. Second, lack of epidemiologic, experimental or mechanistic evidence is no more relevant than is the lack of evidence explaining thrombus and spasm. Third, since there is no relationship between blood cholesterol level and CHD for the vast majority of individuals, the fact that no relationship exists between the intensity of lowering the level of cholesterol and excess non-CHD deaths is not surprising. Non-CHD deaths include widely different causations, e.g., cancer, suicides/accidents, etc. which may confound the derivation of some kind of monotonic relation. (As amply demonstrated earlier, the intensity-mortality relation certainly can be seen in prospective studies.) And fourth, the use of the term "chance" as an explanation for all undesirable findings by the alliance is fast becoming irrational and boring.

Yusuf was far more candid and objective in responding to a query by a New York Times reporter regarding higher mortality at low cholesterol levels. He said, "I can't fully explain it and it worries the hell out of me."[203]

Hegsted also used poor reasoning to downplay the importance of low cholesterol levels in a letter to the editor. He said it is a "well-established fact that it is precisely those populations that consume a low-fat, cholesterol-lowering diet, which have a low mortality from the cancers typifying the populations that consume a high-fat, Western type diet. If diets that lower serum cholesterol increase risk of cancer of the bowel, breast and so on, these cancers should be rampant in the many populations that consume such diets."[2216] At the outset, it is not a well-established fact that low-fat and high-fat diets cause low and high rates of cancer. The highly confounded between population studies simply cannot be legitimately defined as producing "well-established facts." In addition, cancers might be rampant in those generally poor and/or primitive populations if (1) their life expectancies were long enough to allow the degenerative cancer diseases to kill more people, and (2) their death certification process were wholly conducted by physicians rather than lay attendants.

Another fallacy in comparing populations is that the alliance assumes that every individual in the world, regardless of genetic structure, requires the exact same amount of cholesterol to satisfy his/her physiological needs. Such an assumption cannot be tenable. As was emphasized in Volume 1, variability (primarily from genetics) is the essence of human beings. This variability includes different physiological needs. This discussion is elementary and should not be necessary but it is because the alliance is locked onto the notion that variation with respect to cholesterol, is the exception, rather than the rule.

Hegsted continued, "Within any group on similar diets, there are very large differences in serum cholesterol concentrations, and in every group studied there have been large differences in the response of serum cholesterol to dietary modification.[a] There is no evidence...that individuals with low serum cholesterol concentrations were consuming diets differing from those of others in the group. Indeed, the low serum levels were unlikely to be diet-related since very restricted diets are needed to yield such low cholesterol values in normally responsive individuals. It is much more likely that these were non-responders or poor responders, with respect to serum lipids, to the usual high-fat, high cholesterol diets. Susceptibility to disease, perhaps especially the major chronic disease, is affected by both genetics...and the environment. Therefore, for reasons unknown, these poor responders or nonresponders are likely to be especially susceptible to some cancers. In view of epidemiological evidence, especially from investigations of immigrants which show an increasing frequency of cancer as a Western type diet is adopted, these susceptible individuals may be those most likely to benefit, with respect to cancer, from consumption of a prudent diet that lowers serum cholesterol."

The above six sentences comprise a montage of speculation, bad assumptions and incredibly poor logic. For example, it is completely speculative and without scientific

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[a] This statement is true but it is a quite different view than that expressed by other prominent alliance members. For example, Connor[2436] said that for 5% of the population heredity is more important than diet in affecting cholesterol but "For the other 95% of the population, the dietary influence is paramount." Also, Levy[1276] maintained that "in individual subjects around the world, it can be shown that the cholesterol level, although clearly in part under genetic control, is greatly affected by environmental factors, especially diet."

foundation to state that poor responders or nonresponders to high-fat diets "are likely to be especially susceptible to some cancers." (This writer knows of no evidence, moreover, that poor or nonresponders to high-fat diets are exclusively individuals with low blood cholesterol levels.) Second, just as immigrants to Western countries enjoy all the economic advantages of those countries, including high fat diets, so do they become part of more sophisticated medical diagnostic/death certification systems which detect and record types of deaths more accurately than do the systems from whence they came. That is a much greater likelihood than is the assumption that a Western diet promotes cancer. And third, it is preposterous to say that individuals (poor responders) who are not affected by fat and cholesterol should therefore be placed on a low-fat, low-cholesterol diet.

As illogical and inconsistent as Hegsted's letter was, Shekelle and Stamler said, "We agree with Professor Hegsted."[2217]

Kannel's[1091] reasoning on this subject also leaves much to be desired. In noting an inverse relation between cancer and cholesterol in 1983 he said, "The findings are inconsistent and paradoxical because they can be demonstrated only for men. Moreover, an examination of diet to colon cancer indicates that a high-fat diet seems to predispose. This tends to discredit a causal relationship between low cholesterol and colon cancer."

Like Grundy and many others, Kannel places great credibility on the confounded data from the between population studies, although his choice of words suggests that such data might be spurious, e.g., "a high-fat diet seems to predispose." The reader may note also that Kannel, Hegsted and many other alliance members tend to use high fat and high saturated fat interchangeably. Blood cholesterol level is their primary concern and there is abundant evidence that cholesterol level is affected by the composition of fat, not the amount of fat.

The fact that the inverse relationship may not exist for women is neither inconsistent nor paradoxical. If all significant relationships observed for men were "discredited" because similar relationships were not observed for women, a tremendous amount of world-wide data, including much of that of Framingham, would be thrown out instead of promoted by the alliance. Differences between the sexes have been observed in great quantities and are capped by the fact that the reported CHD death rate trend among white women exhibited no epidemic during the period in which the reported rate among men increased substantially.

In "updating" the Intersociety Commission for Heart Disease Resources report, Kannel et al.[1083] stated one year later that "Epidemiologic studies often show a quadratic relation of serum cholesterol to overall mortality with an excess of deaths at both extremes. Since some excess mortality at low serum cholesterol appears to persist even after removal of proximate mortality, it is not likely that occult terminal illness is entirely responsible." They went on to say that low cholesterol levels, i.e., below 180 mg, are not consistent with "overall health status." On the other hand, W. Virgil Brown elected to exaggerate the cholesterol level of danger. In 1990 he said, "There is no question that cross-sectional studies in many different populations have shown that persons with extremely low total cholesterol levels do less well than those with slightly higher total cholesterol levels."[3223] Apparently, Brown considers 180-210 mg "extremely low" because the majority of the studies previously described show higher cancer and/or total death rates to be higher below this range.

In general, alliance members continuously stress the need to reduce blood cholesterol levels and downplay or ignore the possibility and indeed the likelihood that the risk of cancer will be increased. Virtually all of the alliance's key members have said that the relationship between blood cholesterol and CHD mortality is continuous,

and graded without a threshold, e.g., Stamler,[263] Levy,[1427] Naito, [243] Kannel [1448] Grundy[1167] and Tyroler.[2743] In noting a continuous curve even in the relatively low-cholesterol Japanese population, Kannel and Gordon said, "We must admit to a certain regret that there does seem to be a gradient of CHD risk at low levels of serum cholesterol."[2638]

The alliance specifically recommends, therefore, that Americans reduce their blood cholesterol levels as much as possible. The following are typical statements:

"For most individuals hypercholesterolemia is present with levels over 180 mg." (Connor and Connor,[411])

"...hypercholesterolemia probably refers to any plasma total cholesterol level above 180 mg." (Witztum,[2575])

"studies suggest that total plasma cholesterol level of 110 to 150 mg may be physiological for human beings." (Rifkind and Lenfant,[253])

Optimum [cholesterol] values for prevention of coronary disease and atherosclerosis are probably 140 to 180 mg." (Castelli et al.[1273]).

Herbert Naito cited NHLBI guidelines as indicating that heart attack victims, as well as many others, should lower their cholesterol levels below 130 mg.[1359]

The NCEP's James Cleeman recommended that Americans lower their cholesterol to "around 120 or 130."[2379]

"It occurs to me that the norm for the human species for serum cholesterol in adults is probably about 160 mg." (Kane[1872])

"The real problem is to find people who need to lower their cholesterol and define a goal for them. I define it as 150." (W.V. Brown[249])

"We need a target goal and I think it should be the ratio of total cholesterol to HDL cholesterol of 4.5 and an LDL below 150. The only exception would be those people with total cholesterol below 150. For those people, we don't care what the HDL is." (Castelli[1259])

"Data from Framingham and MRFIT suggest that biologic normal is more like 150 mg." (Vogel[186])

"A population mean level of plasma cholesterol of 160 $\pm$ 30 mg...[is indicated]...to be desirable for coronary disease prevention." (American Health Foundation in 1979[2634])

"There is substantial evidence from the laboratory and experimental animals to indicate that it is optimal to maintain the serum cholesterol concentration at 150 mg." (American Health Foundation in 1980[1310])

"Plasma cholesterol concentrations above 150 mg are unnecessarily high and put patients at risk for arterial deposition and its consequences." (Rifkind[2379])

"...it is clear that the lower the total cholesterol level, the lower the risk of coronary disease and all-cause mortality." (Kannel[1532])

"At the moment the only guide would seem to be--the lower the better." (Daniel Steinberg[3037])

"With regard to plasma cholesterol levels, the lower the better." (Grundy[1167])

"The lower the better, may indeed be the only proper response to the question, 'how low should cholesterol be?" (Davenport and Whittaker[1910])

Most of the above statements were made after the accumulation of most of the studies reviewed earlier. Also, it can be seen that these recommendations were for cholesterol levels to be as low as possible or at least close to or below 150 mg. They can be contrasted with a 1985 statements by Keys et al. who acknowledged that cancer mortality was higher below 170 mg in all of the countries of his Seven Countries study, i.e., "such levels would rarely be approached even by drastic dietary modifications."[82] Thus, while one alliance member doubts that Americans can bring their levels below 170 mg, other members are urging that they do so. But lest we get hung-up on 170 mg, let us recall that some studies indicate that 180 to 200 mg may be dangerous.

Castelli[1273] essentially denied all the evidence in 1987. He said, "With the exception of cancer deaths in older men, there is no age group in either sex for which subjects with lower cholesterol levels have significantly increased overall mortality, CVD mortality or cancer mortality." Two years later, he indicated that if you follow the alliance's advice, "you will live a little longer."[2487] LaRosa[2484] also maintained in 1989 that "Your chances of a long, healthy life are much higher if your cholesterol is low."

It is useful to repeat one of Rifkind's statements presented earlier and introduce two additional statements he made, all uttered in 1989. "Plasma cholesterol concentrations above 150 mg are unnecessarily high and put patients at risk for arterial deposition and its consequences."[2032] Shortly after this comment was made, the Washington Post's Carper asked Rifkind to respond to the fact that total mortality has been increasingly found to be higher at low cholesterol levels than at moderate levels. Rifkind was cited as saying that "...whether cholesterol as low as 150 holds any dangers is unknown."[2379] And elsewhere Rifkind said, "I do not think the case for cholesterol reduction has been proved to the degree we all would prefer."[2523]

In 1990 Grundy[2740] indicated that physicians should tell all patients, including those with low cholesterol levels, that "You still need to follow this general [Prudent] diet."

In effect, Rifkind, Grundy and their alliance colleagues advise Americans to get their cholesterol levels as low as possible while simultaneously ignoring the now mountainous evidence that such advice will likely cause considerable harm.

Two final observations are relevant. Reiser and Shorland[1804] indicated that "it is unbiological and unreasonable that an essential blood constituent should be toxic at all levels," as stressed by the alliance.[a] Second, a Newsweek Magazine article cited a man who had a heart attack and then a bypass operation.[2712] He then went on a rigid diet which resulted in his cholesterol dropping to 120 mg. While this "story" undoubtedly suggested to millions of readers that a 120 mg cholesterol level is healthy,

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[a] Reiser[3137] had made a similar statement in 1978 in response to a statement by Cornfield[3136] which implied that all blood cholesterol levels cause CHD.

Hazzard[1765] observed that "...preliminary analysis of various prevalence surveys indicates that a total cholesterol that drops below 120 is as good a predictor as any we have of impending death."[a]

The astonishing response or, better yet, lack of response to the evidence is perhaps no better exemplified than a short statement by W. Virgil Brown, i.e., "These data are real, but we do not know what they mean."[957]

Low Fat Diets

It has been emphasized elsewhere that low fat diets are typically synonymous with high carbohydrate diets which reduce HDL proportionally more than they do total cholesterol. This fact makes the Prudent Diet a contradiction of recommendations. Reaven also considers such diets potentially harmful to some people because they also increase triglycerides and either blood sugar or insulin.[2169] Of even more importance is the increasing evidence that high carbohydrate diets are associated with increased rates of gallstones. For example, a 1990 editorial stated that "The consensus is that generally raised serum triglyceride levels [except from alcohol] are positively associated with gallstones."[2616] A recent study in Chili, for example, showed that gallstone disease afflicts 55% of the women and 30% of the men, all of whom consume high carbohydrate diets, particularly legumes."[2739]

It is interesting that during the period in which diet was being correlated with cholesterol levels and CHD in the Framingham study, 427 persons were recorded as having gallbladder disease and correlations were computed for dietary fat, protein and cholesterol but no data or analysis was presented for carbohydrates.[3047]

Webb observed that the dispute over the merits of high carbohydrate diets will continue until research is more conclusive.[2169] But, unfortunately, the dominance of the lipid hypothesis in the eyes of the alliance will not likely lead to conclusive research because if a high carbohydrate diet is proven harmful, the alliance's entire program will be groundless.

In the early part of this chapter it was noted that many researchers recommend reducing the fat, particularly saturated fat, and cholesterol content of the diets of children who exhibit what they or the alliance considers high blood cholesterol levels. It was also noted that pediatric societies are generally against such recommendations because of possible harm to normal functioning and growth. In this regard, it is useful to examine what nature has provided for the smallest child of all, breast milk. In 1960 the American Academy of Pediatrics[2986] reported that the fat content of breast milk was 48% of total calories (identical to that in cow's milk).[b] Of the total fat, almost 48% was found to be saturated (8.3% stearic acid). Almost exactly the same compositions were reported in studies nearly 20 years later. For example, Nayman et al.[2976] found total fat to be 54% and saturated fat to be 43% of total fat (7% stearic acid). These and many other studies leave no doubt that a high fat diet is necessary for proper growth in a rapidly developing infant. And since rapid growth occurs long after the arbitrary 2 years of age that some have selected as the time to

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[a] Littenburg[1939] also cautioned that low cholesterol may be associated with a higher CHD death rate among the elderly.

[b] Even such animals as the Gray whale produce milk with a high fat content, i.e. 40%.[3185]

alter diets, there is no scientific basis for assuming that the high fat content of breast milk is not a dietary requirement for proper growth for many childhood years.

The composition of breast milk with respect to types of fatty acids is another matter. Insull and Ahrens[2985] observed that breast milk tends to resemble the maternal diet. Sanders et al.[2813] also reported that the breast milk of vegans contained 31% less saturated fat than that of omnivores, excluding stearic acid. On the other hand, Patterson et al.[2987] found no change in the composition of fatty acids in women consuming low saturated or high saturated fat diets. They also found no change in the cholesterol level in breast milk. Similarly, Read et al.[1965] compared the compositions of breast milk obtained from four groups (Tanganyikans, Bedouins, Jordanians and Lebanese) whose diets varied substantially in total fat and kind of fat (animal vs vegetable). They reported that these diets yielded milk having remarkably similar compositions. In fact, the group having the lowest fat content (Tanganyikans) produced the highest level of saturated fat. Their results were replicated in a follow-up study, confirming the finding that a high carbohydrate diet yields a high composition of saturated fatty acids.[2989]

It would appear, therefore, that nature considers a high fat, high saturated fat diet to be optimum for growth and proper functioning of infants and we have no reason to believe that that diet is not also optimum for at least young children. Before the advent of the diet-CHD dogma breast milk was universally considered to be the perfect food for children.[a] It is now being questioned because of the inordinate obsession with blood cholesterol. In this regard, it is important to note that the polyunsaturated fat promotion by the alliance beginning in the 1960s apparently led to the development of infant formulas in the early 1970s with high concentrations of vegetable and polyunsaturated fats.[3224]

Cholesterol-Lowering Drugs

In his testimony before an FTC law judge, Blackburn[2691] said, "We all know that long-term ingestion of drugs is likely to be toxic. There is no such thing as a non-toxic drug." It was emphasized in Volume 1, however, that most alliance members omit side effects, particularly the more dangerous effects, when describing cholesterol-lowering drugs in articles. In many cases, their praising of such drugs appears to be associated with financial relationships with drug companies.

The sales trends for cholesterol-lowering drugs are most interesting and thought-provoking. The number of prescriptions written for each of eight drugs in the years 1978, 1983 and 1988 were reported by Wysowski et al. and are presented in Table 8-1. The downward trend of clofibrate, once the dominant drug by far, undoubtedly reflects the negative experiences with the drug in a number of clinical trials. The same can be said of dextrothyroxine. As of 1988 lovastatin, gemfibrozil, cholestyramine and probucol held 94% of the market. However, it was clear that lovastatin was on its way to dominating the market. For example, according to a 1989 statement by Merck and Company, lovastatin had already held a 56% share of the market at that time, being prescribed for more than 1.2 million people in the U.S. alone.[2590] By 1990 the percentage rose to 60%.[3174] Simvastatin, the next generation of lovastatin, is not yet approved by the FDA but is being used or will be used in many other countries.

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It should be recognized that before the advent of the "bottle," children were nursed for a number of years.

The most interesting aspect of Table 8-1 is the sharp downward trend in drug sales from 1978 to 1983 and then the huge upward surge, an average increase of 80% per year. There is little question that the widespread publicity given to the LRC trial and the cholesterol "consensus" conference held in early and late 1984, respectively, launched the upward surge. It seems clear that prior to those events physicians did not feel strongly about a cholesterol-CHD connection. It is almost as if the alliance's NCEP was designed to increase cholesterol-lowering drug sales. One cannot help but get the impression that many key alliance members were actually promoting, in a marketing sense, these drugs. A review of the literature reveals innumerable articles in journal "supplements" sponsored by drug companies in which alliance members praised cholesterol-lowering drugs.

As one might expect, cholesterol-lowering drugs are predominantly being prescribed to those who potentially will gain the least from such drugs, i.e., women (59%) and those over 60 years of age (59%). Wysowski et al.[2726] cited Sempos, Fulward and Haines as indicating that 40 million Americans age 20-59 and 24 million Americans age 60 and over are candidates for such drugs. The amount of profits to be made from the sales of such drugs to 64 million Americans is so great, concepts of medical ethics and CHD suppression seem trivial by contrast. A 1987 remark by W.V. Brown is informative, i.e., cholesterol-lowering "drugs are underutilized at the moment, but we expect them to be overutilized in the future."[1710] Indeed. Overutilization is synonymous with unnecessary and/or inappropriate utilization and this state-of-affairs is and will continue to be attributable to Brown and other members of the alliance. The overutilization will come about because many people will find the cost of drugs more tolerable than sacrificing desirable foods and, as pointed out by Palumbo,[2468] the likely diet and exercise changes in the majority of Americans will not depress their cholesterol levels to that recommended by the alliance's guidelines.

With the exception of niacin, cholesterol-lowering drugs are expensive and most of the people consuming them are least able to afford them, as well as least likely to benefit from them. Often overlooked are the indirect costs, i.e., costs associated with visits to physicians to monitor drug's performance and adjust dosages.[3125] And since side effects are common, additional laboratory tests are performed and additional drugs are prescribed to counteract the side effects. In effect, drugs are needed to counter the effects of cholesterol-lowering drugs which will probably provide no benefits to patients in the first place.

Clofibrate and Cholestyramine. Dietary fats produce a complex of solvents which participate in maintaining bile acids in solution.[2334] Both are absorbed and travel to the liver. Bile acid resins, such as cholestyramine and clofibrate, bind to the solvents as well as to the cholesterol in the bile and facilitate their excretion in the feces. The subsequent shortage of solvents causes bile acids in the gallbladder to precipitate into gallstones.

Table 8-1

Cholesterol-lowering drug prescriptions
(adapted from Wysowski et al., 1990[2726])

Drug	Date Introduced	Prescriptions (millions[a]) 1978	1983	1988
Clofibrate	1967	3.56	1.05	0.45
Cholestyramine	1967	0.18	0.26	2.21
Dextrothyroxine	1967	0.39	0.16	0.05
Nicotinic acid	1974	0.17	0.20	1.02
Colestipol	1977	0.01	0.05	0.29
Probucol	1977	0.09	0.37	1.26
Gemfibrozil	1982	--	0.46	3.79
Lovastatin	1987	--	--	3.84

a Numbers are rounded to nearest 10,000.

Clofibrate was used in the large WHO clinical trial. In 1969 two of the trials staff members said that the drug was selected because "The drug is considered to be exceedingly safe."[3134] However, higher mortality occurred in the clofibrate-treated subjects in that trial, with cancer being the major contributor. As a result of this trial and other findings, the FDA forced the manufacturer in 1979 to indicate on clofibrate's label its limited benefits and its risk of cancer and gallstones.[2015] Some years later, although acknowledging the results of the WHO trial, Schaefer and Levy[3022] nevertheless recommended clofibrate "who cannot be effectively treated with diet and other hypolipidemic drugs."

And, as was shown in Volume 1, cholestyramine is also associated with increased frequency of gallstones and gastrointestinal cancer in both animal and human studies. With regard to the latter, NHLBI's LRC clinical trial, published in 1984, provided the most important evidence. The LRC director, Rifkind, referred to that evidence as "chance" findings unrelated to cholestyramine.[191] In 1989 Goldstein emphasized that there were 11 new GI cancers and one death from these cancers in the control group and 21 new GI cancers and 8 deaths in the cholestyramine group, a finding not unexpected from animal research.[2649] James Weir of the Warner-Lambert Company, makers of cholestyramine, replied that "we believe he [Goldstein] has unfairly extrapolated from animal test results."[2650] In addition to the fact that the alliance has been extrapolating prolifically from animal research for decades, Goldstein's primary concern were the GI cancers found in the LRC trial. Interestingly, Rifkind's reply was far different from his original defense of cholestyramine. He and Gordon said, "the observation of excess cancers in the organ system directly exposed to cholestyramine resin was a matter of concern."[2651] Despite the dangers, Hunninghake holds that "the long-term safety of resins has now been established"[2035] and Castelli claimed that the resins are "the safest drugs."[2553]

Gemfibrozil. Current regulations require that gemfibrozil labels also carry warnings of risk for cancer, gallbladder disease, appendicitis, etc.[2127] The label specifically states that "The potential benefit of gemfibrozil in treating type IIa patients with elevations of LDL cholesterol only is not likely to outweigh the risks."[2107] Yet, Gotto stated that "In my opinion, gemfibrozil should be considered appropriate therapy for patients with mild to moderate primary hypercholesterolemia of either type IIa or type IIb."[2104]

Two clinicians also independently reported incidents of confirmed gemfibrozil-induced headaches.[2103,2104]

Lovastatin. Tobert, an employee of the manufacturer of lovastatin, reported very few side effects in a trial apparently conducted by his company consisting of 744 patients. He specifically stated that there was "no evidence of an effect of lovastatin on the lens."[2106] On the other hand, Mieczkowski and Holahan obtained evidence that lovastatin does cause cataracts.[1806] Tobert admitted that a small percentage of patients developed serious liver changes and other side effects.[2106] Tan[2570] and others[3177,3178] have reported that lovastatin causes skeletal muscle injury (sharply elevated creatine kinase level) in some patients taking the drug. And because many physicians prescribe two or more cholesterol-lowering drugs simultaneously, it is noteworthy to mention that complete heart block and/or renal damage or failure have occurred with the combination of lovastatin and gemfibrozil.[2661,3105,3177] Of great potential importance also are the recent findings of Kostner et al.[2515] and Jurgens et al.[1874] which showed that lovastatin therapy increased Lp(a) levels 33% and 140%, respectively (see later discussion of Lp(a) in this chapter).

The WHO trial demonstrated that clofibrate is by no means "exceedingly safe" as was once thought.[3134] In keeping with the inconsistencies of alliance members, Rifkind indicated caution in prescribing lovastatin until long term data have been accumulated, while Grundy said, "Even in the absence of proof by clinical trials, it's not unreasonable to consider use of this drug."[3130]

Niacin. Additional side effects of niacin reported in the literature include myopathy, in the form of leg cramps and painful muscles, and "serious hepatitis."[2337] Hepatotoxicity can occur with doses of over 3 g niacin per day and one person was observed to have a complete liver failure a few days after taking a sustained release preparation of niacin.[2320] Also, there is evidence that niacin interferes with the control of blood sugar in non-insulin-dependent diabetics, raising blood sugar as much as 16%,[3176,3178] and increases the level of uric acid, elevating the potential for gout.[3176]

Comment

Anyone even somewhat familiar with side effects of cholesterol-lowering drugs knows that gallstones are a relatively frequent problem. Gallstones can be slowly dissolved by orally taken bile acid agents.[2469] Since many alliance members own stock in drug companies (Chapter 9), we would anticipate greater investments in companies manufacturing the bile acid agents as more and more millions of people are encouraged to take cholesterol-lowering drugs.

The Ileal Bypass: Medieval Butchery?

Chapter 6 reviewed the POSCH Trial in which cholesterol-lowering was accomplished by partial ileal bypass. Apparently the first ileal bypass operation to exclusively lower blood cholesterol was performed by Buchwald and Varco in 1963.[2905] By 1964 a number of patients had had the operation and Buchwald indicated that "To date there have been no untoward after-effects of the operation." Buchwald et al.'s 9.7 year trial published in 1990 demonstrated considerable "untoward after-effects," although they astonishingly claimed them to be "acceptable."[3058] To briefly summarize those after-effects, 399 subjects underwent the ileal bypass, itself a major surgery, of course, and 48 of these subjects subsequently underwent major surgeries to reverse the bypass, remove gallbladders and repair bowel obstructions. In addition, the bypass patients suffered chronic diarrhea, more kidney stones and gallstones and considerably more bowel obstructions. When the cost and misery of all this (and probably more that was not reported, as will be seen) is contrasted with the "benefits" of absolute reductions of 0.34% total deaths per year and of 1.1% CHD "events" per year, it is difficult to conclude that the ileal bypass operation is cost-effective, unless, of course, the analysis considers physician/hospital income as the measure of effectiveness and patient loss as the measure of cost.

This writer has not made a concerted effort to determine all the side effects of ileal bypass operations. It is noteworthy that the 1971 NHLBI Task Force[705] indicated that "surgical mortality has been 1%...(and that)...side effects are minimal with good surgery." Assuming that the Buchwald et al. trial involved only "good" surgery, then we can conclude that "minimal" side effects means "substantial side effects." The Task Force went on to say that "in the hand of other surgeons with fewer cases more serious side effects occurred." Thus, we can conclude that the average ileal bypass operation in the country can be expected to yield more serious side effects and probably higher surgical mortality than that revealed in the POSCH trial. The Task Force also noted that "The ability to absorb Vitamin B12 is nearly lost, and this vitamin must, therefore, be supplemented parenterally. Very importantly, minerals are lost with chronic diarrhea, particularly potassium, the loss of which can cause cardiac

arrhythmias and the addition of which (pills) can cause ulcers.[3059] And more water must be consumed because so much is lost through lack of absorption.

In 1964 Buchwald indicated that the protocol for the ileal bypass operation restricted its use to patients with cholesterol levels within the 300 to 600 mg range.[2905] Apparently that protocol was subsequently ignored or set aside because his POSCH trial involved individuals whose mean cholesterol level was only 250 mg.

The NHLBI Task Force indicated that "surgical therapy for the hyperlipidemias should be considered an experimental procedure to be undertaken with utmost caution." However, NHLBI approved and funded the POSCH study only a few years after this statements was published. During the conduction of the POSCH trial, Kannel, Castelli and Gordon[1046] stated that "...ileal bypass hardly constitutes an acceptable solution to the problem" [of reducing blood cholesterol level], indicating once again that alliance members contradict each other on rather important issues.

There does seem to be justification for the ileal bypass operation in cases of very high cholesterol levels, as suggested by Buchwald's early protocol. Starzl et al.[2991,2994] reported in 1974 that a portacaval shunt substantially reduced the cholesterol level of a 12-year old girl who had already suffered an infarction and exhibited chest pains and all the signs of Type IIa hypercholesterolemia, presenting a blood cholesterol level of 769 mg pre-operatively. The girl soon died and Starzl et al. guessed that she succumbed to "an acute cardiac arrhythmia" since there were no thromboses found at autopsy.

Mitchell and Levy[2992] indicated that "The medical treatment of choice [for Type IIa hypercholesterolemia] is a combined regimen of a low-fat, low-cholesterol diet with a high P/S fatty acid ratio; a bile-acid sequestrant such as cholestyramine; and nicotinic acid to the limits of tolerance," rather than a surgical procedure. However, Bowers[2993] noted that diet and drugs were ineffective in reducing the girl's cholesterol level and Mitchell and Levy should have known that their recommendations could not possibly reduce a cholesterol level of 769 mg by 500 mg or more.

Because the exceedingly high blood cholesterol levels lead to a fatal "lipid storage disease," as described elsewhere in this Volume, the ileal bypass operation seems quite justified. However, to use this procedure on subjects with cholesterol levels under 300 mg, and perhaps under 350 mg, is, in this writer's opinion, medieval butchery, more commonly called "unnecessary surgery" by media critics.

What will be next? How about removing part of the liver to slow the production of VLDL? How about undergoing dialysis once a week to remove VLDL and LDL from the blood? How about giving people artificial hearts, thereby eliminating the problem altogether?

TRANS FATTY ACIDS

Introduction

Prior to the 1968 AHA statement on diet and CHD Fred Kummerow participated on the AHA's Committee on Nutrition and indicated a need for the public to be aware of the unnatural trans isomers which existed in relative abundance in hydrogenated oils. The AHA apparently concurred because the original 1968 statement read, in part, "Of this total (fat), polyunsaturated fats which are not hydrogenated should comprise twice the quantity of saturated fats. Partial hydrogenation of polyunsaturated results in the formation of 'trans' forms which are less effective than 'cis,cis' forms in lowering cholesterol concentrations. It should be noted that many currently available

shortenings and margarines are partially hydrogenated and many contain little polyunsaturated fat of the natural 'cis,cis' form."[1740]

The AHA initiated distribution of the 1968 statement but soon stopped after receiving a letter from the Institute of Shortening and Edible Oils. The medical director of AHA, Campbell Moses, wrote the following letter to Kummerow:

"Dear Fred:

Enclosed is another copy of the diet and heart disease statement, together with the criticism of recommendation 2 offered by the Institute of Shortening and Edible Oils. I have talked with Dr. Fred Mattson about this criticism and he believes it is entirely valid and that the statement, as printed, is inappropriate.[a] I must confess that I think our recommendations are not as accurate as they should be, particularly with regard to partial hydrogenation..."[1695]

The final 1968 statement omitted all references to hydrogenation and trans fatty acids.[1740] Thus, Moses demonstrated favoritism toward the edible oils industry while continuing to reject criticisms from the egg industry, even though there was probably more scientific evidence incriminating hydrogenation than eggs.

Kummerow submitted a letter to Senator George McGovern, Chairman of the 1977 Senate hearings on nutrition and human needs, pointing out that the trans fatty acids in the American diet were being ignored because of the collusion between the AHA and the Institute of Shortening and Edible Oils and that neither AHA nor NIH were funding any research on the possible harmful effects of hydrogenated fats.[1739] McGovern apparently ignored his letter.

Twelve years later the Food and Nutrition Board's Diet and Health report devoted three sentences to trans fatty acids. "Effects of trans fatty acids isomers have been observed in laboratory animals (reviewed by Kritchevsky, 1982; Senti, 1985). These isomers are not metabolized in the same way as the cis isomers. However, at dietary intakes similar to those consumed by humans, and with a small proportion of linoleic acid in the diets, the trans fatty acid isomers appear to have no deleterious health effects (Jackson et al., 1977; Kritchevsky, 1983; Regee et al., 1984)."[2070]

The key word to note in the report's conclusion (third sentence) is "appear." As emphasized by Kummerow,[1739] Enig[1827] and Kinsella et al.,[1862] the potential effects of trans acids on health are not known because research has been sparse and almost exclusively centered on rats.[b] Also, studies have generally been inadequately designed. Not only has AHA and NIH purposely avoided funding research on trans acids, they have also ignored their existence when determining the composition of the American

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[a] Mattson was an employee of Procter and Gamble, a major manufacture of foods employing vegetable oils. Procter and Gamble was on the AHA's board of directors.[692]

[b] Kummerow observed that "Animal models fed such (hydrogenated) fats deposit more fat in their hearts than those fed natural unhydrogenated fats."[1738]

diet, e.g., the NHANES II survey.[a] Enig indicated that the NHANES II survey omitted estimates of trans fatty acids and presented fatty acid compositions of hydrogenated foods before they were hydrogenated.[1749,1827] In view of the facts that the American diet is replete with trans fatty acids and that the alliance refuses to fund adequate research on their potential effects on health, one cannot but suspect that the alliance's actions again reflect the interests of specific food manufacturers. In a U.S. Department of Health and Human Services report published in 1989 the LSRO director, Kenneth Fisher, acknowledged receipt of information from Enig but declared in the report that "Data on trans fatty acid content in a wide variety of foods are not available in the NNMS (survey). In view of the conclusions that current levels of intake (in conjunction with current levels of intake of linoleic acid) have no significant deleterious effects..., there is little urgency in modifying the USDA nutrient databases in regard to trans fatty acid composition of foods or in monitoring the intake of trans fatty acids in national surveys."[2446] Thus, the LSRO accepted data from Enig and then declared that such data did not exist. This tactic clearly suggests that the LSRO was operating on behalf of the edible oils industry, rather than the American people.

In view of the above, it is interesting to quote a passage from the 1989 Food and Nutrition Board's "Diet and Health," i.e., "Most evidence indicates that these [trans] isomers, in the quantities usually consumed in the U.S. diet, do not influence serum cholesterol concentrations. There may be other effects unrelated to lipid and lipoprotein metabolism. These possibilities deserve careful attention and additional investigation."[2070] Unfortunately, these are politically hollow words because the alliance has had decades to give "careful attention" to the potential harm from trans isomers.

Sources of Hydrogenated Oils and Trans Isomers

Partially hydrogenated oils are everywhere. They can be found in shortenings, salad and cooking oils, doughs, crusts, crackers, cookies, pastries, snack chips, margarines, donuts, candies, imitation cheeses and puddings.[1742,1827] They are used prolifically in deep fried foods, e.g., chicken, fish, shrimp and french fries. Margarines have 16 to 70 percent of their fatty acids as trans acids and salad oils range from 8 to 17 percent.[1694,1862] Shortenings contain 14 to 60% trans acids.[1862] Enig analyzed the trans acids of 500 retail foods and offered the data to the Life Science Research Office (LSRO) of the Federation of American Societies for Experimental Biology.[1743] The LSRO ignored the data, however.

Estimates of the percentage of total fats as trans acids in the American diet have been given as 5 to 15% by Enig[1742,2157] and 5 to 10% by Kinsella et al.[1862,b] The Institute of Shortening and Edible Oils' Hunter suggested an estimate of 7.5%.[1717,1746] Hunter and Applewhite have been exceedingly defensive in discussions focused on the percentage of trans acids in the American diet and, simultaneously claim that they are harmless. They maintained that "The Institute believes that there is no documented justification for including trans acids with (or without) saturated fatty acids as part of nutrition labeling."[1746] Sampugna et al. responded to that statement with the following: if the Institute believes that trans acids are harmless, "why do they so

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[a] 1741,1744,1749,1827

[b] A very recent report by Enig et al.[2974] indicated a mean consumption of 13.3 g per day per person, roughly 12 to 13% of total fat consumed.

vehemently and so frequently attack researchers whose findings suggest that the consumption of trans fatty acids is greater than the values that industry reports?"[2153]

Morgan[2662] cited David Kluvfeld as saying in 1990, "Food companies like trans fatty acids because they can be like a brick at room temperature. They are stable, and solid, just like saturated fats." Between 5 and 60% of the vegetable oil can be transformed into trans acids. Morgan also noted a comment by Randall Wood, i.e., "processors can still advertise the fact that they're using an unsaturate. They don't have to say a thing about the trans fatty acid content."

Effects of Trans Fatty Acids on Health

Because partial hydrogenation almost exclusively affects polyunsaturated fatty acids and because linoleic acid is the most common polyunsaturate in fatty oils, the essential linoleic acid is largely destroyed in either of two ways. It is transformed into either a trans or cis monounsaturate or a trans isomer of linoleic acid. In both cases, it no longer functions as an essential fatty acid. Apparently no one knows how much linoleic acid is required by the body and it is doubtful that anyone really knows how much cis linoleic acid is consumed in the diet. And since little or no research is being performed to acquire this information, the edible oils industry is given a free hand to produce unlimited quantities of hydrogenated foods.

Animal research indicates that trans fatty acids alter the properties of cell membranes and related enzyme activities.[1741,1743,1862] Such effects can reduce the ability to metabolize chemical carcinogens.[1743] Another contributor to cancer was indicated by Douglass: "What normally happens is that the curved cis form has its hydrogen atoms close enough together to resonate into pi-electrons and pi-electrons clouds. This allows them as cell wall components to oxygenate themselves well. However, when trans forms are used in cells walls, the hydrogen atoms are further apart so they do not resonate, thereby decreasing oxygenation and contributing to cancer and heart disease."[1694]

Enig stressed that trans fatty acids alter the immune response and decrease the response of red blood cells to insulin.[1741,1743] In their review of experimental research, Kinsella et al. indicated that trans acids affect hemostatic and hemotological properties of the blood and can decrease prostaglandin production.[1862] They also pointed out that trans acids suppress growth and cause liver changes in the presence of a linoleic acid deficiency. Enig observed that the negative effects of trans acids appear minimal with normal intakes of saturated fatty acids but increase as the saturate intakes decrease.[1749] Thus, the alliance's Prudent Diet not only suppresses HDL levels via the increase in carbohydrates (Chapter 9), it also enhances the negative effects of trans isomers via the decrease in saturated fats.

THE CAUSE OF CORONARY HEART DISEASE

The Evolution of Thought: Medical Textbooks

Some old 20th century medical text books were reviewed to determine the changing state-of-knowledge about the causation of atherosclerosis. They are followed by more

recent articles.[a] The oldest text reviewed was published in 1926 and authored by McCrae.[2783] It will be recalled from Chapter 3 that the International Classification of Diseases (ICD) did not include "coronary artery disease" or any rubric resembling that term until the 1930 revision. Angina pectoris was included in the 1900 and 1910 and 1920 revisions. In keeping with this differentiation in the ICD, McCrae also treated angina pectoris as a separate disease in his text but nevertheless related it to atherosclerosis. He cited Heberden as coining the term angina pectoris in 1768 which meant "disorder of the breast." He also cited Jenner as associating angina pectoris with coronary artery disease. McCrae indicated that angina pectoris was "a disease of the better classes" from stress and "not an affliction of the working class." He listed a number of theories as to why angina pectoris occurs, including the theory that it is triggered by insufficient blood flow to the cardiac muscle. He concluded that "No generally accepted explanation of the phenomenon of the attack has been offered."

McCrae devoted little text to coronary artery disease but did acknowledge its existence and stated that "Thrombosis of the coronary arteries occurs usually in middle-aged or elderly people" whose vessels are sclerotic. Little or no discussion was devoted to the atheromas but substantial attention was given to the collateral circulation. He cited Pratt as showing that "the vessels of Thebesius, which open from the ventricles and auricles into a system of fine branches and thus communicate with the cardiac capillaries and coronary veins, may be capable of feeding the myocardium sufficiently to keep it alive even when the coronary arteries are occluded." He was apparently not aware of the circulation that develops during the course of atherosclerosis development.

The fifth revision of the ICD in 1939 included both angina pectoris and diseases of the coronary arteries. As exemplified in a 1942 text book by Adams,[2782] angina pectoris was now viewed as a symptom, i.e., "Angina pectoris is presumably due to ischemia of the myocardium; flow of blood through the coronary arteries is insufficient to meet the requirements of the moment," brought by atherosclerosis or other specific causes. Adams continued, "Atherosclerosis of the coronary arteries is a common cause of heart disease and beyond middle life, occurring rarely before the age of forty but frequently beyond fifty. Recent work of Blumgart and his associates...has conclusively shown that extensive narrowing or even obstruction of one or more of the major coronary arteries may exist without seriously hampering cardiac efficiency. They explain this apparent inconsistency by the fact that extensive collateral circulation can and often does develop; an area of the myocardium deprived of blood supply by vascular narrowing or obstruction may receive adequate nutrition through anastomatic vessels reaching it from the same major artery poximal to the point of obstruction or from some other unaffected artery. If the arterial disease progression slowly enough to permit adequate collateral circulation to develop, blood supply to the myocardium may be sufficient for ordinary needs for many years."

Adams offered no explanation of the cause of atherosclerosis but did devote considerable discussion to the cause of myocardial infarctions. He said, "The common and dangerous complication of coronary heart disease [note the use of the modern term, CHD] is the syndrome which has been incorrectly termed coronary thrombosis or coronary occlusion. It may be brought about in 2 ways: (1) prolonged myocardial ischemia in the absence of a fresh occlusion, as in a case of existing coronary artery disease when added strain is imposed; or (2) coronary artery occlusion due to fresh

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[a] Although early investigators such as Virchow[2978] considered atherosclerosis the result of chronic inflammatory response in the mid 1800s, a theory accepted by many today, it will be seen that it was not discussed by many medical writers during the first 50 years of the present century.

thrombosis or subintimal hemorrhage. In the latter instance, the episode is likely to begin when the patient is at rest. The obstruction may occur in the vessel which normally supplies the affected area or in a distant vessel which has, by means of collateral circulation, become its source of supply."

The year (1949) in which the seventh ICD revision introduced the term "Arteriosclerotic heart disease, including coronary disease," Rehberger[2780] published his text. He defined coronary sclerosis as "an arteriosclerosis (atheroma) or a thickening of the wall of the smaller vessels or arterioles due to chronic hypertension; it is usually both. Infarction of the left ventricle may occur in the atheromatous form and produce pulmonary edema or sudden collapse. The hypertensive form is accompanied by cardiac hypertrophy. Heredity, obesity, diabetes, and chronic nephritic predispose to coronary sclerosis, which commonly occurs in old age but may occur much earlier. Causes of myocardial infarctions include coronary thrombosis, coronary embolism, rupture of an atheromatous abscess in the wall of a coronary artery, hemorrhage into such an abscess, and prolonged local ischemia resulting from coronary narrowing plus overwork."

By 1952 epidemiologists such as Keys had convinced many medical people that the American "lifestyle" was the cause of CHD. That attitude was reflected in medical books in the 1950s. For example, in discussing the possible approaches to solving the heart attack problem, Marriott[2779] said, "Advance may come with improved treatment, but it seems more likely to be achieved by determining and avoiding the cause of those degenerative changes in the arteries which lead to coronary disease... It seems not unlikely that our whole way of life may be at serious fault." Yet, he later indicated that "We know absolutely nothing which has a definite preventive effect on the development of arteriosclerosis."

Patterson[2784] also published a book in 1952 but had nothing to say about "lifestyle." In fact, he demonstrated no faith in any of the many theories existing at that time, e.g., "The factor, or factors, responsible for the initiation of the arteriosclerotic process in man is still obscure. Little is to be gained from a detailed examination of the various theories that have been advanced over the last fifty years..." In particular, Patterson indicated that the hypercholesterolemic theory that originated with Anitschkow and remains the love of the NHLBI/AHA alliance, was substantially flawed. He said that "an injury [to the intima] must be postulated as otherwise the disease process would be diffusely spread throughout the arterial system instead of being focal in its distribution." Although he stated that blood lipid level may "play some part in the progression of the arteriosclerotic process," he stressed that high cholesterol levels do not produce atherosclerosis in some animal species and that many humans suffering the end-stage of atherosclerosis do not have high blood cholesterol levels. "Furthermore, the production of coronary occlusion with MI appears to result from factors which often have no relationship to the level or character of the blood lipids at the time of the catastrophe."

Patterson also discussed at length the collateral circulation, noting that the anastomatic circulation only develops in the presence of atherosclerosis, i.e., it "develops when and where it is needed." If the arteries are gradually narrowed by disease, anastomatic channels of some magnitude are found about the points of stenosis, and there only. He continued, "there is reason to believe that they may compensate for narrowing or occlusion to a degree sufficient to enable the heart to meet the demands of the ordinary activities of life."

While Patterson referred to the artery disease as arteriosclerosis, two years later Clark[2781] used the term, atherosclerosis, to more correctly describe the atheromas. It is clear that he did not believe that the causation of atherosclerosis was known. He said, "Atherosclerosis often is traceable to a disturbance of the glandular system, and,

most frequently, to faulty body metabolism. Control of diet and proper exercise is often as important as any medicine used. Some of the newer theories lay the blame on the manner in which the body handles the fatty substance, cholesterol." But he concluded that "No one knows the primary cause of hardening of the arteries."

In 1959 Holman et al. evaluated the filtration and local formation hypotheses associated with the pathogenesis of atherosclerosis.[2171] They concluded, in part, that "The evidence against filtration is more or less conclusive. The size, shape, distribution, and general appearance of the early lesion cannot be explained on the basis of filtration. On the experimental side two masses of data are, to say the least, difficult to reconcile with concepts of filtration. The first of these has to do with the time interval between cholesterol feeding and the first appearance of lesions. Despite the fact that the blood cholesterol level and the level of the other blood lipids starts to rise within a few days after starting the cholesterol feeding, months must go by before lesions begin to make their appearance--and there is no strict correlation between the height of blood cholesterol level and the extent and degree of lesions. While, in general, it can be stated that some elevation of the blood cholesterol level is prerequisite for lesions, everyone who has worked with experimental animals has encountered some animals that do not get lesions, and the vast majority of humans with atherosclerotic lesions have no known hypercholesterolemia or hyperlipemia. The other mass of data is even more damning to the filtration hypothesis. There are several examples of hypercholesterolemia] and hyperlipemia that have been dissociated from arterial lesions of any kind. Alloxan diabetes, detergents, and sifter's lipid mobilizing factor are all known to produce marked sustained hyperlipemia and hypercholesterolemia with no ensuing arterial lesions of any kind."

Holman et al. indicated that the most impressive evidence derives from the study of hundreds of aortas and coronary arteries from populations all over the world. "Practically everyone beyond the age of 3 years has shown some degree of fatty streak of the aorta...and the similarity in the pattern of development of fatty streaks in regard to age in various parts of the world has been striking. It is difficult to believe that each of these persons has consumed too many calories, too much fat, too little protein, too much or too little animal fat, or too much or too little unsaturated fat or that each has had hypertension or some other disturbance that could have left scattered 'scars' in the arterial wall that predisposed to differential filtration."

Indeed, in examining the autopsied material from the International Atherosclerosis Project, Tejada et al.[2436] found fatty streaks and raised lesions in coronary arteries of 15-24 year-olds in virtually all 19 populations studied, ranging from New Orleans white men to Durban Bantus. by age 55 all populations exhibited substantial cases of fibrous plaques, complicated lesions and calcified lesions. The most severe atherosclerosis occurred in populations with enormously different diets. As noted in Volume 1 investigators of the Project found essentially zero correlations between animal fat consumption and either atherosclerosis severity or blood cholesterol.[1080] Tejada et al. reported substantial variability in atherosclerosis severity within and between populations with considerable overlap of distributions.

Holman et al. went on to say that "Much confusion has arisen from translation of data among various species of animals and failure to keep proper perspective on the various stages of atherosclerosis. For example, reference is frequently made to the fatty streaks in the aorta and coronary arteries of cholesterol-fed rabbits or chickens with the inference that these data might be pertinent to clinical coronary artery disease in man. Not only does this type of reasoning ignore interspecies caution but it refers the first stage of atherogenesis in one species to the fourth stage of atherosclerosis in another species. Even if the enzyme systems and other mechanisms for lipid transport in the two species were the same--and there is ample evidence that they are not--there still remains the probability that lipid transport has little or no effect on the final episode (complication of one or more strategically located fibrous

plaques by hemorrhage or thrombosis) that precipitates the clinical coronary artery disease."[2171]

Holman and his colleagues emphasized a most important point, i.e., "The usual sequence of events in human atherosclerosis--fatty streak, fibrous plaque, complication, disease--has not yet been produced in experimental animals, and the applicability of these experimental vascular lesions which have been produced to humans is not clearly established."[1821] Indeed, they are not even vaguely established.

An interesting observation by Page[3080] in 1969 is worth noting in the present context. He indicated that "It is not wholly clear why some elderly persons can have extensive coronary atherosclerosis without ischemic heart disease. Perhaps the best explanations are (1) the narrowing of the lumen occurs slowly enough to allow collateral circulation to develop and (2) much of the atherosclerosis in older people is of the calcific variety, usually associated with widening rather than narrowing of the lumen."

In a 1989 article entitled, "Recent concepts on the pathogenesis of atherosclerosis," Haust devoted one-half page to a review of theories.[2175] He maintained that all theories are compatible with the concept of "injury and repair," including the lipid hypothesis which proposes that blood lipids both injure the intima and subsequently "repair" it by accumulating within it. In describing the three major theories Haust employed five sentences, each of which was qualified by the word "may," e.g., "Factors from the lumen may injure the endothelium directly..."[a]

Yet, Katz, Stamler and Pick stated in 1956 that "Atherosclerosis is a reversible disease. This conclusion is based on extensive data collected in rabbit, chick, dog and man."[1884] And Castelli and Griffin made the following profound statement in 1988: "unquestioned evidence (indicates) that coronary artery disease is preventable."[1802]

An interesting concept was proposed by Ravenholt in 1980.[2170] "Degenerative cardiovascular disease and cancer are ordinarily viewed as two distinctly different diseases--because one originates within blood vessels and the other originates within almost all tissues except blood vessels--but it may be more useful to consider them as manifestations of the same fundamental disease process; malignant cellular evolution. Thus, we have 'malignant' atheromas within blood vessels and malignant neoplasms in other tissues." While this proposal does not offer anything new with respect to the specific pathogenesis of atherosclerosis, the classification of atherosclerosis as a type of cancer has intriguing implications and offers new avenues of exploration.

It must be evident to the objective observer that although we know a good deal more about the anatomic and chemical structure of atherosclerosis than we knew 65 years ago, our knowledge of the pathogenesis of atherosclerosis, particularly the initiating and sustaining factor(s), has advanced insignificantly. There are many who have committed themselves to the lipid hypothesis, of course, but that hypothesis will never be proven to be correct, if for no other reason, because it has been shown innumerable times that blood cholesterol level cannot predict who will and will not eventually develop clinical atherosclerosis.

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[a] Buja presented essentially the same description with one sentence and one "may."[1798]

The Suspension of Thought

Perhaps the dominant thought that has prevailed for 15 to 20 years, much to the frustration of objective researchers, was described rather simply in 1975 by Henry Blackburn.[2733] He asserted that there are two schools of thought about the cause of atherosclerosis, namely the "academic view" and the "pragmatic view." The academic view was said to consider atherosclerosis and CHD as being "largely due to a metabolic abnormality" that is predominantly caused by genetic defects. Blackburn said that the academic view considers the conquering of atherosclerosis to be tied to understanding and altering the mechanisms of lipid metabolism.

The pragmatic view was said to consider atherosclerosis the result of the "manifestations of a way of life," with genetics playing a minor role. He stated, "The consistency and congruence of evidence from clinical, laboratory and epidemiologic studies indicate that serum lipids, primarily serum cholesterol, and arterial blood pressure and cigarette smoking are universally strong influences on the rise of the disease and that they probably are causally related to CHD." According to the pragmatic view, we can conquer atherosclerosis by changing our bad behaviors to lower blood cholesterol and blood pressure, and eliminate smoking. (Recall that the Japanese have high prevalences of smoking and high blood pressure and their cholesterol levels are now nearly as high as in the U.S. and yet their CHD death rate is exceedingly low.)

First and foremost, Blackburn did not so much as acknowledge the existence of the point of view of many prominent researchers, including Duff, that atherosclerosis is not a metabolic-derived disease. Thus, rather than describe existing schools of thought, he effectively suspended thought on the subject.

Second, he equated atherosclerosis with CHD, seemingly not cognizant of much data, including that from Framingham, which clearly indicates that CHD includes disorders other than atherosclerosis, enunciated by his mentor Ancel Keys on more than one occasion (Chapter 3).

Third, the terms "academic" and "pragmatic" appear to be wholly inappropriate as discriptors of his two "views" because they typically refer to theoretical (academic) and practical (pragmatic) approaches to resolving the same problem. Blackburn, however, used the terms to define different problems. The academic view was said to consider atherosclerosis a metabolic disorder, while the pragmatic view was said to consider atherosclerosis a disease of lifestyle and not a disorder at all. If the academic view were correct, the pragmatic approach could not logically work because practical dietary changes would not depress blood cholesterol levels to that recommended by the "pragmatists and all other risk factors" described by the pragmatists as contributing to a bad lifestyle would be, by definition, irrelevant.

Finally, in his article Blackburn criticized the American lifestyle on the basis of insufficient and, therefore, erroneous information. While he alleged that a CHD mortality epidemic was taking place in the U.S. in 1975, it had actually been declining for 12 years. Moreover, all-cardiovascular disease mortality, which the "pragmatists" also attribute to lifestyle, had been declining for at least 35 years.

In short, Blackburn's discussion was a reflection of a disorder that has afflicted most "pragmatists," i.e., the ostrich syndrome.

Many prominent physicians objectively acknowledge that the cause of atherosclerosis is still unknown. For example, DeBakey[677,1255] emphasized in 1987 and 1988 that "The underlying cause of atherosclerosis is unknown" and "...we still do not understand its cause." In an apparent dismissal of the "lifestyle" causation hypothesis, Canadians

Gotlieb and Koo[2585] very recently summed it up thusly, "Understanding the processes that promote [endothelial] injury leading to disruption of vessel wall homeostosis is important for developing rational methods of preventing and treating atherosclerosis."

The Distribution of Atherosclerosis

As described by DeBakey[2560,2561,2562] atherosclerotic occlusive disease occurs predominantly in one or more of four major arterial beds. These are the (1) coronary bed, (2) major branches of the aortic arch, (3) visceral arterial branches of the abdominal aorta, and (4) terminal abdominal aorta and its major branches (feeding the legs). In all beds atherosclerosis usually (but not always) occurs in the proximal or midproximal portions. Very importantly, there is a tendency for some people to develop occlusions in one bed and not the other.[677] DeBakey reported that only 5.7% of a large group of patients had the disease in more than one arterial bed.[2562]

Of particular interest is the rate of progression of atherosclerosis as a function of age and arterial bed.[2561,2562] Slow and moderate rates tend to occur most often in the coronary arterial bed, while moderate and rapid rates tend to occur most often in the aortic arch and the terminal abdominal aorta and its major branches. Moreover, atherosclerotic progression occurs much more rapidly in younger than older patients[2560] and younger patients are more likely to develop new disease in the same or another arterial bed.[2562] Bypass patients over 65 years tend to have slow to moderate progression.[2560] DeBakey noted that "it is not generally appreciated that after surgical correction of the original well-localized process some patients show no evidence of further progression of the disease in other parts of that arterial bed," leading to the inference that "Atherosclerosis is not necessarily a continuously progressing disease and may even be self-limited."[2561] Indeed, it has long been noted that some lesions do not progress at all.[3231]

DeBakey observed that 25% or more of bypass patients has no identifiable risk factor.[2561] Moreover, the survival rate of patients with cholesterol levels above 261 mg was the same as that of patients with cholesterol levels below 180 mg.[2560]

DeBakey indicated that he was "convinced that atherosclerosis represents a number of distinctively different clinical and anatomicopathologic patterns with various rates of progression." He believes that "much of the confusion about etiology, diagnosis, treatment, and prevention stems from the failure to recognize these widely different patterns, which may indeed represent different entities. For example, certain epidemiologists tend to represent all forms of atherosclerosis as a single entity without regard for their distinctly different patterns or rates of progression. Even in such studies concerned with clinical manifestations of one arterial bed (for example, coronary artery disease, so often used for this purpose), the researchers have failed to recognize the widely different patterns and rates of progression.[2561] A perfect example of DeBakey's concern is the fact that the alliance typically promotes the lipid hypothesis as being applicable to all cardiovascular diseases. The alliance praises the low-fat oriental diet because of the presumed low rates of coronary atherosclerosis in those populations but then appears oblivious to the fact that another cardiovascular disease, stroke, is the primary and secondary killer of Chinese and Japanese, respectively.[2744]

Coronary Atherosclerosis

Figure 8-18 depicts the coronary arterial bed which consists of the left and right coronary arteries and their branches. The figure also illustrates common locations of occlusive disease, as indicated by dark patches. The proximal and midproximal

locations of the disease are considered good candidates for bypass grafts, whereas occlusions at more distant locations tend not to be treatable by surgery.

Of considerable importance is the fact that atherosclerosis tends to be localized. As noted by Burch and Phillips[2947] and Freis,[2946] the blood flowing through all the vessels of the body has the same level of cholesterol and yet the disease occurs at very specific sites. Even Kannel et al.[2935] recognized this fact long ago, i.e., in 1971 they said, "Although lipids may influence the overall rate of deposition of atheromas in the intima of arteries, it is quite clear from the distribution of lesions that local factors must play a role." Kaunitz[2975] also emphasized this point several years later. He said, "it is difficult to explain the spotty distribution of the lesions if one assumes that we are dealing with a generalized disturbance of lipid metabolism."

As pointed out by McMillan,[3231] "The lesions of atherosclerosis in the adult are pleomorphic. They may be rich or poor in lipid, rich or poor in fibrous tissue, cells or ground substance, and complicated or uncomplicated." McMichael[210] emphasized that lipid deposition occurs in only 50% of all arterial lesions. These facts also imply that local factors must be necessary for the initiation and/or progression of lesions.

A most important observation relating to atherosclerosis development is rarely, if ever, discussed in the general epidemiologic literature and only once, to this writer's knowledge, has it been exposed to the public. Within a few years after receiving a heart transplant, the majority of patients exhibit rather severe coronary atherosclerosis.[3150,3169] In some cases, severe atherosclerosis occurs within a few months after the transplant. It is virtually certain that neither diet nor blood cholesterol nor any other of the alliance's risk factors has anything to do with this phenomenon. Because immune system depressants are routinely used in heart transplant patients to protect against rejection, it is thought that the rapidly developing atherosclerosis may be due to bacterial or viral infections. In any event, the phenomenon poses no threat to the alliance because its catch-all concept--multifactorial causation--allows for literally hundreds of causes of coronary atherosclerosis.

Genetics and Genetic Variation of LDL

Despite vast quantities of data from human dietary experiments which show wide variations in blood cholesterol levels among individuals consuming the exact same diet, some alliance members simply proclaim that genetics is not very important in determining blood cholesterol levels. For example, Connor testified before an FTC law judge in 1975 that diet was of "paramount" importance for 95% of the population.[2436] And in 1976 Glueck and Connor cited geneticist Arno Motulsky, chairman of the 1989 Food and Nutrition Board's Committee on Diet and Health, as concluding that "most persons with hypercholesterolemia do not appear to have a genetic basis for their disorder."[1136] Yet, at a 1987 International Life Sciences Institute conference on diet and Health Motulsky emphasized the great genetic variability of humans and stressed that blood pressure levels are under strong genetic control. (He did not relate cholesterol level with genetics but simply said that everyone should be on the Prudent diet, suggesting that genetics was of minor importance.)

Although in 1973 Stamler did recognize the fact that "Even when individuals are placed on a single uniform diet in a metabolic ward, the range of serum cholesterol remains wide,"[573] he nevertheless seemed reluctant to attribute such variations to genetics. For example, he said, "The specific mechanisms of the large interindividual differences in serum cholesterol response to diet of a population remain a mystery. Undoubtedly, they have a genetic basis, as evidenced by the fact that they are already present in umbilical cord blood."

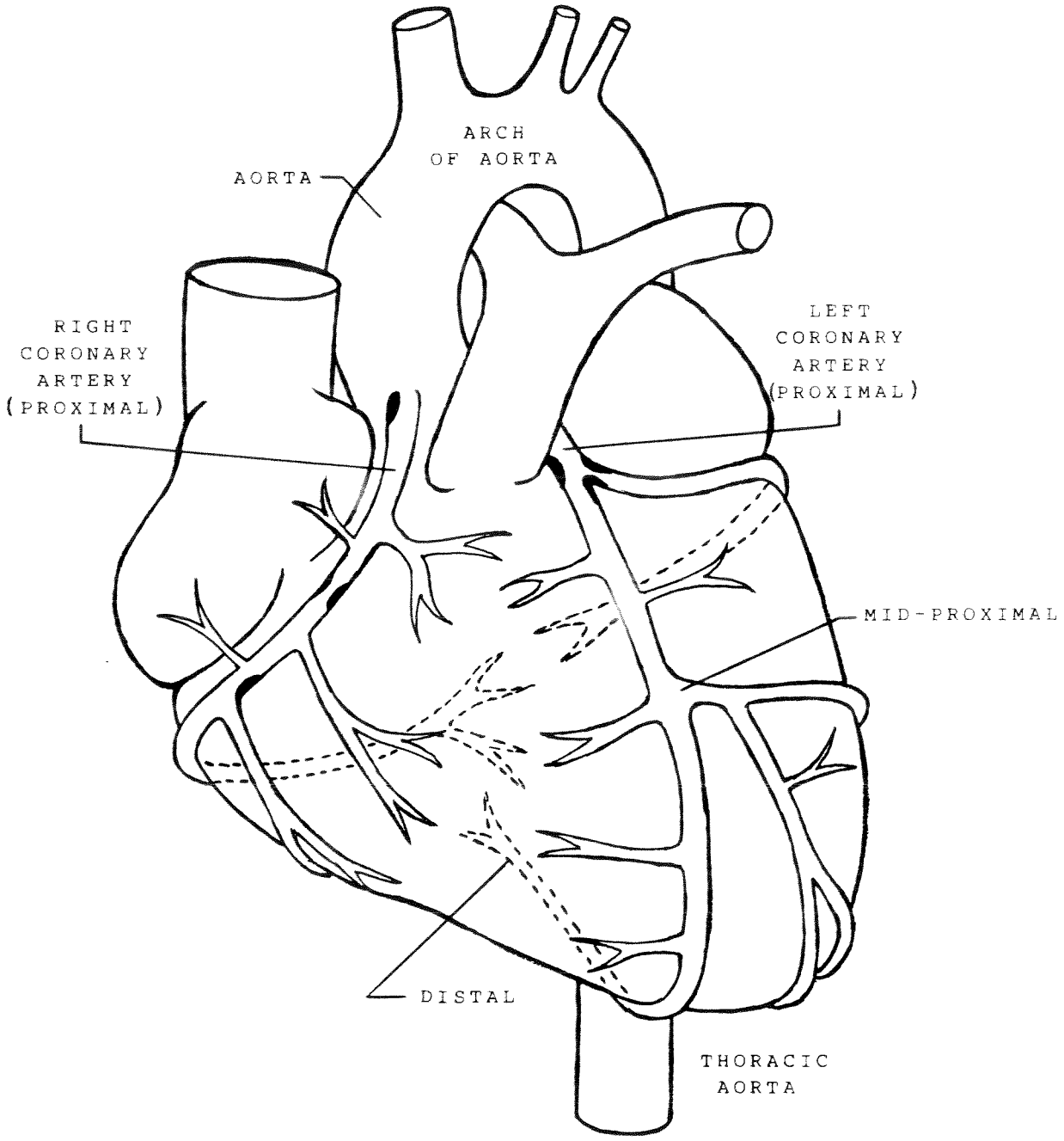

Figure 8-18. The coronary arterial bed, with examples of atherosclerotic occlusive disease (adapted from DeBakey,[2562,2565] Gray,[2741] Langley and Cheraskin[2742])

To ponder the "specific mechanisms of the large interindividual differences in serum cholesterol" is a strange endeavor in view of the fact that large individual differences are commonplace for almost all human characteristics. Why should cholesterol be any different?

Grundy also seemed reluctant to focus directly on genetics. In discussing reasons why cholesterol increases with age, he indicated that one explanation would be an increasing production of LDL and a decreasing fractional clearance of LDL, both of which "might be explained by an age-dependent decline in the activity of LDL receptors."[262] "Age-dependent" sounds very much like genetics to this writer.

One of the strongest promoters of the Prudent diet is Basil Rifkind. Yet, in a rather detailed review of the literature in 1982 with colleagues Segal and Schull, he found much evidence in support of a genetic basis for cholesterol level and very little in support of an environmental influence. They said, "Genetic factors contribute importantly to variation in total cholesterol and triglyceride levels, as well as to that in the different classes of lipoproteins. Most studies reveal nontrivial correlations between parents and offspring, on the one hand, and siblings, on the other. But the contribution shared environments make to these correlations seems unclear. One notes, however, that virtually all of the studies we have cited, as well as many uncited, fail to find significant spouse correlations in serum cholesterol. This argues against a strong environmental influence."[2747] Rifkind et al. reached such a conclusion without even addressing the massive numbers of dietary experiments which clearly show strong genetic influences.

"Family history of CHD" is a risk factor for CHD, although not given the ranking it deserves by the alliance. In actuality, it is probably the most important determinant of CHD. For example, Jorde et al.[2567] reported in 1990 that family history accounted for 53% of the CHD cases in 1,058 adults. Myerson and Santello[1718] related family history with blood cholesterol level in children. They divided the children into two groups having cholesterol levels above and below 170 mg. They reported that 50% of the children with a family history of CHD had cholesterol levels below 170 mg, suggesting that family history correlates poorly with cholesterol levels in children. They also found that 64% of the children who had cholesterol levels above 170 mg did not have a family history of CHD.

While the main thrust of the alliance focuses on diets and drugs to lower blood cholesterol levels, increasing efforts are being directed toward factors considered to be completely genetic in origin, in particular, Lp(a), dense LDL and mutated LDL.

Lp(a) is apparently an LDL particle with an extra protein, apo(a), bound to its apo B-100 protein.[2393] It was identified in 1963 by Berg[2387,2394] and later discovered in atherosclerotic lesions by McLean et al.[2387]

Almost everyone has some level of Lp(a).[2387,2392] Although it presumably averages less than 15% of the total blood cholesterol,[1036] it apparently ranges from less than 1 mg to more than 100 mg.[2387] It is considered strongly associated with the degree of atherosclerosis.[a] Of substantial interest is the report that unlike LDL, Lp(a) does not increase with age and is not correlated with levels of LDL.[2599]

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[a] 173,1028,1032,1036,2329,2387,2394,2599,3126

Lp(a) is genetically based and not affected by variations in diet.[a] Most investigators indicate that it is not affected by drugs,[1032,2329,2387] although some report that niacin[2392] and neomycin[2393] or both[1472] may lower it somewhat, while lovastatin apparently greatly increases it[1874,2515] or has no effect.[2600]

The role of Lp(a) in atherosclerosis is not known[2393] but is suggested that it may promote thrombogenesis by interfering with the dissolution of blood clots.[2392] Being structurally similar to plasminogen,[2329,2387, 2393,2479] it is hypothesized that Lp(a) may inhibit the action of plasmin[2387] or its precursor, plasminogen.[2387,2393]

According to Krauss, there are at least four types of LDL particles which are characterized by size and and density.[2390] The larger buoyant types are labeled LDL-I and LDL-II. The smaller and denser types are called LDL-III and LDL-IV. The larger LDL particles are presumably predominant in most people but about one-third of the population are said to have a predominance of the smaller particles. There is some evidence that the smaller, dense particles are associated with higher rates of CHD. As with Lp(a), the dense particles appear to be genetically based and independent of diet. However, Krauss elsewhere indicated that drug and diet therapy reduced levels in some individuals, although he cited no references for this assertion.[2622]

Finally, a recent British/American study provided evidence suggesting that an inherited mutation of the gene for apo B-100 may increase blood cholesterol levels, as well as susceptibility to CHD. However, current knowledge defines no physiological role for the mutant at present.

Oxidation

It was noted in Chapter 2 that most of the rabbit studies involved oxidized cholesterol.[282] When pure cholesterol was used, the atherosclerosis-like disease was not induced, even though hypercholesterolemia was induced.[2178,b] These observations led a number of investigators to consider the possible link between oxidation products and atherosclerosis. Experimental evidence was subsequently found which indicated that lipid peroxides can induce endothelial cell injury[2447] and such peroxides were also found to be higher in CHD patients than in healthy patients.[2272] Interestingly, Stringer et al. reported that the level of lipid peroxides is not correlated with the alliance's risk factors, such as total cholesterol, hypertension, smoking, diabetes, etc.[2272]

At least two concepts have been formulated. One concerns the specific oxidation of LDL in vivo and the other involves oxidized cholesterol and/or fatty acids in vivo or consumed by diet. The first concept has been described by Steinberg as follows: "The earliest recognized gross lesion in atherosclerosis is the fatty streak composed of 'foam cells', i.e., cells loaded with cholesteryl esters. Normal monocytes and monocyte derived tissue macrophages in culture cannot be converted to foam cells by

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[a] 173,1032,1381,2392,3126

[b] Alternatively, the ingestion of antioxidant by rabbits inhibits LDL oxidation and thus induced atherosclerosis.[2482] Apparently, this process was observed from use of the cholesterol-lowering drug, probucol, which was originally manufactured as an antioxidant.[2483]

incubation with even very high concentrations of LDL. It is postulated that the circulating LDL must first undergo some kind of modification and that it is the modified LDL that is taken up more rapidly to generate foam cells. Some studies suggest that LDL undergoes an oxidative modification which then allows it to be taken up by the macrophage."[2389,a] For example, it apparently has been shown in culture that scavenger receptors on macrophages easily take up oxidized LDL.[2332,2535] Although Carew notes that "this observation does not prove oxidized LDL causes atherosclerosis,"[2332] others have taken less conservative stands. For examples, Hazzard indicated that oxidized cholesterol appears to be toxic to the arterial endothelium"[2292] and Schwartz et al. stated that "oxidized LDL clearly plays a key role in atherogenesis."[2333] Jialal presented a somewhat confusing description of the process. "Recently, it has been demonstrated that LDL can be oxidatively modified by cells such as endothelial cells. This oxidized LDL appears to be recognized by the same class of scavenger receptors. Oxidized LDL appears to inhibit cholesterol esterfication and is unlikely to promote as much foam cell formation as other modified lipoproteins, such as acetyl-LDL. However, there is no evidence for the existence of acetyl-LDL in vivo."[2391]

An excellent review of the concept linking oxidized lipids to atherosclerosis was recently presented by Addis and Park.[2178] They believe that considerable evidence exists which suggests that lipid oxidation products initiate the atherosclerotic lesion and promote the growth of plaque, although one is apparently not dependent on the other, i.e., oxidation products could be the initiators of the lesion, while cholesterol itself could be involved in the development of plaque.

Addis and Park noted that definitive human absorption studies have not been conducted to determine whether the potentially damaging lipid oxidation products are created in vivo, consumed in the diet or both. However, in studies of rats and pigeons, dietary cholesterol oxidation products have been seen to damage the endothelium, while pure cholesterol apparently had no effect.[b] They also noted that the effects of cholesterol oxidation products are apparently independent of the level of blood cholesterol.

Addis and Park also reported that linoleic acid hydroperoxides have similar effects as cholesterol oxidation products.

Addis and his colleagues point out that all lipid containing foods are susceptible to oxidation but the most important are those that are dehydrated , (e.g., powdered eggs, powdered cheeses, chicken, turkey and beef), subjected to high temperatures (e.g., foods fried in frying oils) or cooked and stored (e.g., cooked uncured meats).[2179,2180,2181] Similar findings were reported by Swedish investigators Nourooz-Zadeh and Appelqvist.[2612,2613,2614,2615] In addition, they indicated that fresh butter contains only traces of cholesterol oxides but that the quantities increase with storage or heating.[2613]

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[a] Ocana mildly criticized Steinberg's discussion for limiting the oxidation concept to in vivo considerations.[2529] Steinberg subsequently agreed that oxidized products in the diet may also play a role in atherogenesis.[2530]

[b] Rats and pigeons are considered to be good models for human atherosclerosis, while rabbits are not.

Infections

Volume 1 addressed the growing interest in the possible role of the herpes virus in the development in atherosclerosis. Here we merely wish to present a 1984 statement by McGill,3032 namely, "...the same techniques of molecularbiology that have contributed so much to our knowledge of lipoprotein metabolism, lipoprotein-cell interactions, and monocyte functions recently have yielded evidence of both herpesvirus and cytomegalovirus infection of cells in human atherosclerotic lesions. Both viruses are notorious for ubiquity, latency, chronicity, and ability to transform cells. It is easy to hypothesize that viral infection in the vicinity of a juvenile fatty streak could stimulate lipid accumulation, neurosis, proliferation, or other responses that could accelerate the progression of a fatty streak to a fibrous plaque. These observations may be pieces of the puzzle of atherosclerosis, or they may belong to some other puzzle concerned with viral biology. We must be alert to either outcome [underlines added].

Heart Attacks

It was emphasized in Volume 1 that although there is general agreement that blood clots and/or coronary spasms cause heart attacks, current knowledge cannot explain how and why these events occur. In his historical review of explanatory concepts of heart attacks, Rosenfeld noted that it was known early on that a "high proportion of individuals with normal cholesterol levels experienced infarctions.[2387] Freis[2946] emphasized this point in 1969 and it has been verified repeatedly in many prospective studies, including Framingham.

With regard to spasms, Feldman suggested that vasoconstriction could be important in cases where luminal narrowing is severe.[2328] He reported that sometimes a coronary segment is chronically "supersensitive to vasoconstriction stimuli which results in a spasm. However, most spasms appear to be independent of vasoconstriction or, at least, caused by an independent mechanism. There is no explanation as to why and how spasms occur in normal or nearly normal arteries.

In any event, the reader should recall discussions in Chapter 3 and elsewhere which emphasize that (1) 50% or more of sudden deaths, attributed to heart attacks, occur with little or no major atherosclerosis, (2) autopsy studies reveal that most heart attacks occur from events in the least severely diseased arteries[3153] and (3) "clinical studies...have shown that the mechanism of sudden cardiac death in most patients is an electrical alteration, usually ventricular fibrillation, and that most patients resuscitated from sudden cardiac death do not develop diagnostic evidence of myocardial infarction."[3128] Kaunitz[2975] also pointed out that heart attacks "frequently precede rather than follow coronary thrombosis." Further, Framingham data (Chapter 4) reveal no relationship between rate of sudden death and cholesterol level.

The alliance has made it abundantly clear on numerous occasions that its principal concern is with "premature" fatal and nonfatal heart attacks. By definition, "premature" refers to men, most of which have neither clinical nor subclinical atherosclerosis. But individuals such as Castelli[1179] draw highly misleading and erroneous conclusions from statistics associated with "premature" attacks. For example, in observing that less than half of the heart attacks occur in men with significant atherosclerosis, he stated that "About half of the deaths that are from heart attack or stroke are brought about by atherosclerosis." To show the error of this conclusion, consider the following close analogy: suppose that 50% of all men were pure vegetarians and 50% were omnivorous. If half of all heart attacks occur among omnivores and, therefore, half occur among vegetarians, the only scientific conclusion to be reached is that the occurrence of heart attacks is independent of the consumption of animal foods. Castelli would conclude that 50% of all heart attacks

are caused by the consumption of animal foods and that the other 50% are caused by "other factors." But we can use the exact same logic to conclude that 50% of all heart attacks are caused by vegetarianism and that the other 50% are caused by "other factors." The statistics associated with the degree of atherosclerosis and heart attacks occur equally often among atherosclerotic and nonatherosclerotic individuals and, therefore, are independent of atherosclerosis.

Heparin

During the preparation of this volume a copy of an intriguing letter-to-the-editor in the New England Journal of Medicine was submitted to this writer by the author, Alexander Schulman.[2185] The letter stated, in part, "As a middle-aged general surgeon who has recently undergone coronary bypass graft surgery, I have looked for ways of preventing further atherosclerosis. I was dismayed to realize that there are no medications available to prevent atherosclerosis. I searched the literature...and learned that much had been published but apparently ignored about heparin as an antiatherosclerotic agent--an action that is totally separate from its antithrombotic effect."

"Ten studies in animals conducted before 1971 emphasized the role of heparin and heparin fractions in preventing atherosclerosis. Five clinical trials, whose results were published between 1956 and 1987, all reported reductions in cardiac deaths with the long-term use of very low doses of heparin. To my knowledge, there are no studies that contradict these findings."

"There is concern that heparin may cause bleeding, osteoporosis and rarely, thrombocytopenia. Such concern is valid with respect to the dosages needed for its antithrombotic effect, but these complications have been almost nonexistent when low dosages, such as 10,000 units every other day, were used to combat atherosclerosis."

Although medications per se are not central to this document, an exploratory examination of heparin's potential as an antiatherosclerotic agent seems appropriate. It must be emphasized, however, that the following discussion is based almost entirely on the reviews of two authors, Jaques[2176,2177] and Engelberg.[2182,2183,2184] A few critical comments are reserved for the summation of this topic.

Heparin is a complex set of substances that naturally occurs in all animals and constitutes the strongest of all biological acids. It was prepared as a drug in the 1930s and, because of its anticoagulant activity, has been used prolifically in vascular surgeries to prevent intravascular clotting and venous thrombosis. Commercial heparin contains over 100 different chemical substances but only about 25% to 35% of these substances produce anticoagulant activity.

The administration of heparin activates the release of many enzymes into the circulation. One such enzyme, diamin oxidase, is released from the intestinal mucosa and reduces the rate of dietary fat absorption. Another enzyme, lipoprotein lipase, hydrolyzes triglycerides in chylomicrons and VLDL particles into free fatty acids and glycerol and constitutes the major means of removing triglycerides from the blood. In the process, HDL levels increase and LDL levels decrease.

When significant quantities of heparin are in the blood, there is an ever present danger of hemorrhage due to substantial anticoagulant activity. In the normal individual, endogenous heparin is typically isolated from the circulation, i.e., it is rapidly taken up by the endothelium after secretion so that dangerous concentrations in the blood do not occur. The heparin concentration in the endothelium has been shown to be 1,00 times greater than the level observed in the blood, indicating that the endothelium is the target organ. And therein presumably lies the important effects of heparin, insofar as CHD is concerned. Normal endothelium has a high negative

electrostatic charge. The reduction of this charge, resulting from endothelial damage, apparently can generate the formation of a thrombus. Heparin restores the negative charge, thereby reducing the likelihood of thrombus formation. This process is supplemented by other endothelial level actions such as the activation of antithrombin, fibrinolysin, etc.

Because heparin has predominantly been used as an anticoagulant and because it is generally viewed to be only an anticoagulant, relatively little research has been devoted to its use for CHD. Yet, the original investigators of heparin focused on its negative charge on the endothelium and its corresponding protection against thrombus.

The goal of heparin treatment is to achieve a high level in and on the endothelium, while maintaining a low concentration in the blood. This apparently can be accomplished by inhaling heparin, i.e., it "reaches endothelium almost directly and the concentration is kept low in the general circulation and the storage in macrophages, etc. for later transfer to endothelium means that administration can be spaced at wide intervals."[2177]

As with any treatment, the ultimate effectiveness of heparin must be determined by clinical trials. Therefore, a brief examination of the fire clinical trials cited by Schulman was performed. Two of the trials were not blinded[2448,2452] and it appears that a third was also not blinded and apparently had no control group.[2451] A fourth was blinded but the authors stated that "The low degree of statistical significance found necessitates great caution in the interpretation of our results."[2449] Unfortunately, the journal containing the fifth trial[2450] was not found. In keeping with criteria established in this review, it must be concluded that the efficacy of heparin treatment has yet to be satisfactorily demonstrated by clinical trial.

One final comment seems appropriate. Both Engelberg and Jaques emphasized the relevancy of heparin to atherosclerosis. It would appear that their entire discussions focus directly or indirectly on thrombus, not arterial lesions and plaque. The primary effect of heparin is said to be the maintenance of a negative electrostatic charge on the endothelium to prevent formation of thrombus. There are comments regarding the slowing of fat absorption and the clearance of triglycerides from the blood stream but neither activity would be expected to impact on the initiation or development of atherosclerosis.

Philosophy and Common Sense

It has been established without a doubt from countless prospective studies that the relationship between blood cholesterol level and CHD is weak and only observable statistically at the group level. Moreover, with the exception of specific subgroups, notably those with exceedingly high cholesterol levels, e.g., 350 mg and over, CHD events occur as frequently below the mean population level as above. These facts are well documented in the literature and cannot be disputed legitimately. What, then, of the ramifications of the two principal conclusions drawn from these facts?

One conclusion holds that a weak correlation between cholesterol level and CHD events indicates a non-causal relationship. While this conclusion must be more correct than incorrect, it fails to explain the additional fact that very high blood cholesterol levels are much more strongly related to CHD events than low or moderate levels. However, as discussed at length in Chapter 2, the concept of a "lipid storage disease" can easily dispense with that single discrepancy. Moreover, substantial pathological evidence provides scientific support for that concept. Perhaps to the surprise of many, the non-causal conclusion and the lipid storage disease concept can explain virtually all findings from both prospective studies and clinical trials. With regard to the latter, such trials have typically employed males with atypically high blood

cholesterol levels and yet the absolute reduction in CHD event rates has generally been quite minimal (e.g., under 2% in both the LRC and Helsinki II trials), suggesting that the lipid storage disease concept is more applicable than is the general lipid hypothesis. The latter concept demands that a very substantial absolute reduction in CHD events should have occurred in the LRC and Helsinki II trials, e.g., 8 to 10% in the 7.4 year LRC trial.

The non-causal conclusion, of course, explains a mass of data that do not support the lipid hypothesis, in particular, the negative or zero correlations between fat and saturated fat consumption trends in the U.S. and many other countries and CHD mortality trends (Chapters 3 and 4).

The second conclusion drawn from the previously noted facts is that, despite the weak relationship between blood cholesterol and CHD, the alliance has chosen to call it "powerful" and causal in nature. Whether "weak" or "powerful" the alliance does recognize that the relationship is statistical and nonpredictive at the individual level. It dispenses with the low correlational relation by invoking the multifactorial concept, i.e., what the lipid hypothesis cannot explain can be explained by other factors. In medicine, such an explanation is generally indefensible scientifically, but it is not a logical impossibility, i.e., based on the history of diseases it is unlikely but not impossible that atherosclerosis is caused by many factors. But the multifactorial concept, in fact, weakens, not strengthens, the lipid hypothesis. Blood cholesterol level cannot be a powerful risk factor, by definition, if many other factors are independent causes of atherogenesis, as the alliance maintains.

In addition to the fact that neither cholesterol nor any of the other risk factors can explain the many "anomalies" occurring in the world, e.g., fat consumption and CHD mortality trends, the high prevalence of smoking and hypertension among the Japanese and yet the low prevalence of CHD mortality, etc., the cholesterol component itself becomes suspect with closer scrutiny of the data. Let us consider two important points. First, it is a given fact that alliance members universally incriminate LDL as the atherogenic culprit and it is a given fact, based on numerous analyses of prospective studies, that LDL is atherogenic at all but perhaps extremely low levels, e.g., < 80 mg. It has been emphasized in Chapters 1 and 3 that the presentation of graphic and quantitative relationships between LDL and CHD have been meticulously avoided by the alliance. Of all the numerous Framingham reports, this writer found only two graphic presentations and they were distorted by the use of "relative risk" and "morbidity ratio endpoints," rather than CHD event rate.

Figure 8-19 was reconstructed from a bar graph published by Castelli et al.[2292] in 1989.[a] Because of the use of relative risk instead of rate,the quantitative relation between LDL level and CHD is virtually impossible to determine. Since Castelli et al. used rates to illustrate relationships between CHD and total cholesterol and HDL, as well as other factors, it is more than obvious that their intention was to hide the weak relation between LDL and CHD rate. Even so, the figure provides enough clues to detect that weakness. A risk ratio of 1.0 is typically used to represent the lowest CHD rate observed. Why, then, did Castelli et al. break tradition and arbitrarily use another rate as 1.0? The relative risk difference between the lowest and highest LDL levels was only 0.85. Knowing that relative risk greatly

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[a] The same figure was presumably previously published by Castelli et al. in a 1988 Canadian journal.

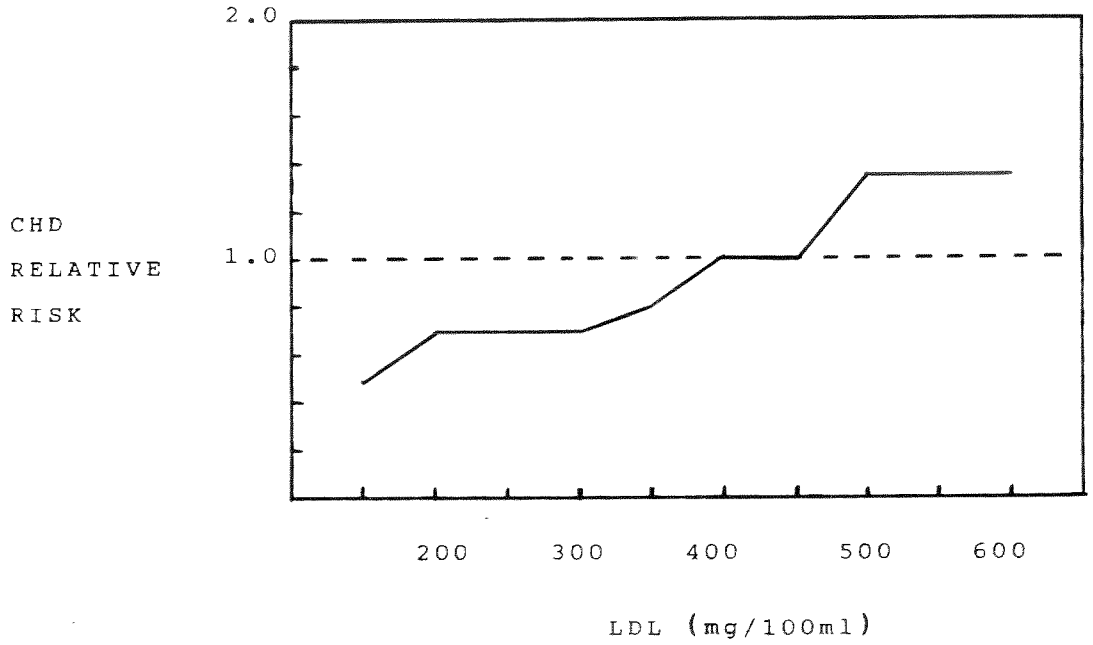

Figure 8-19. CHD relative risk by LDL level (adapted from Castelli et al., 1989[2292])

exaggerates rates, this risk difference reflects a very small rate difference that is unquestionably trivial from a clinical point of view. Finally, LDL was labeled "Sf 0-20 Mg/dl (LDL)" in the Castelli et al. figure. We do not know the significance of the Sf 0-20" term since "mg/dl" was also used. If the scale given indeed represents mg/dl (or mg/100 ml), and there is no reason to indicate otherwise, then it is clear that most of the scale involves LDL levels that occur in only a fraction of the population. For example, Abbott et al.[2957] showed that the 95th percentile of the LDL distribution in the Framingham male population ranged from 203 mg to 226 mg for 35 to 74 year-olds. This means that the curve in Figure 8-19 beyond 226 mg represents only 5% of that male population. (If we use more accurate U.S. data, i.e., survey data presented in NHLBI's 1988 Expert Panel report,[1066] the cut point would be 217.) Because the number of persons diminishes rapidly towards the extremes of normal distributions, there is little doubt that most of the curve shown in Figure 8-19 involves less than 1% and possibly less than 0.5% of the population.

In sum, the data presented by Castelli et al. provide no evidence of the importance of LDL level for anyone other than those suffering from extreme familial hypercholesterolemia, a condition causing the lipid storage disease, rather than atherosclerosis. This state-of-affairs explains the reason why Framingham reports redundantly present CHD-total cholesterol relationships and redundantly exclude CHD-LDL relationships. The lack of LDL importance poses a dilemma for the alliance that cannot be explained logically. If LDL level is not important, there is no other lipoprotein to be incriminated except VLDL. Furthermore, total cholesterol is predominantly LDL and HDL. Since HDL's relation with CHD is negative, it makes no sense to choose total cholesterol as the primary predictor of CHD because (1) high HDL levels (considered beneficial) contribute to high total cholesterol levels, and (2) if LDL is unimportant as an independent predictor, how can it become important by being combined with so-called "good" cholesterol, i.e., HDL? If the proportion of HDL to LDL was exactly the same in all persons, one or the other or total cholesterol would yield the same predictive capability. But the proportions vary. Clearly, if LDL is atherogenic and HDL is anti-atherogenic, the use of total cholesterol as the primary predictor of CHD is absurdly illogical. Alliance members surely must recognize this dilemma, although they do not acknowledge it.

The second important point with respect to the cholesterol component relates to how LDL is supposed to cause or promote atherosclerosis. Considerable recent laboratory work has just about convinced all alliance members that LDL per se cannot initiate atherosclerosis. As noted in a previous subsection, Steinberg[2389] described the problem thusly, "The earliest recognized gross lesion in atherosclerosis is the fatty streak composed of 'foam cells,' i.e., cells loaded with cholesterol esters. Normal monocytes and monocyte derived tissue macrophages in culture cannot be converted to foam cells by incubation with very high concentrations of LDL. It is postulated that the circulating LDL must first undergo some kind of modification and that it is the modified LDL that is taken up more rapidly to generate foam cells" (underlines added).

The three Steinberg sentences are loaded with important implications. First, Steinberg indicated that normal LDL level per se is irrelevant with regard to atherogenesis. Second, when Steinberg said that "It is postulated that circulating LDL must first undergo some kind of modification..." the word "postulated" means "assume," indicating that the process is not scientifically established. Third, Steinberg's use of the term, "some kind," again indicated scientific uncertainty. Finally, Steinberg's use of the term, "more rapidly," is strange in view of his contention that unmodified LDL cannot be taken up at all. While a modified LDL may indeed eventually be proven to take part in foam cell development, there is nothing inherent in the entire concept that (1) explains why atheromas are highly localized, and (2) necessitates that high LDL levels are more atherogenic than low levels.

In summary, the lipid hypothesis support derives primarily from prospective studies showing low correlations between total cholesterol and CHD. Secondary support comes from animal experiments and between population studies. As amply shown in Volume 1, the results of between population studies can easily be explained by other factors and, as shown in Chapter 2 of this volume, the results of animal studies (and human studies involving familial hypercholesterolemics) can easily be explained by the lipid storage disease concept, backed-up by pathologic evidence. We are left, therefore, with the low correlations found in prospective studies and the unexplainable dilemma that LDL plus HDL is a better predictor, albeit weak in an absolute sense, than LDL alone. The lipid hypothesis runs contrary to a great mass of data, particularly CHD mortality and morbidity trends. Not only did the CHD mortality rate peak and initiate a decline while the same fat/saturated fat and cigarette consumption trends continued, there is increasing evidence that CHD morbidity is increasing despite all of the population-wide interventions promoted by the alliance since about 1970. The lipid hypothesis, as formally defined, simply defies philosophical reasoning and just plain common sense. While those who promote it claim to be scientists, they are no more scientists than is a truck driver a physician simply because he decides to play doctor with medical text book in hand.

Looking for the Real Cause

Bristol-Myers Squibb Company announced in 1990 that it will contribute $36.8 million over five years toward cardiovascular research at Massachusetts General Hospital.[2658] The hospital indicated that scientists from all over the world will be recruited to perform research on the molecular and genetic aspects of cardiovascular disease. Could it be that Bristol-Myers knows that the current cholesterol fad will go away and is funding for the future?

The purpose of this review was not to speculate on the true cause of atherosclerosis but rather to appraise the vast evidence accumulated thus far, Despite the repeated assertions of alliance members, the true cause of atherosclerosis has not been scientifically established. Moreover, those who claim that "lifestyle" changes can prevent the development of atherosclerosis cannot explain the extremely important fact that the disease is initiated in early infancy among all populations of the world. The disease is logically preventable but a sound theoretical basis has not been presented and, as this review shows, the evidence clearly does not support an empirical basis. Atherosclerosis still must be classified as a natural degenerative disease, not unlike the general degeneration that occurs in the aging process.

When NHLBI and AHA eventually recognize and accept reality, medical scientists will be able to direct their energies to more productive areas of research. Those who currently harbor genuine interest in the true cause of atherosclerosis would do well to read the work of a New Zealand pathologist (William Stehbens[3261]). He has devoted decades to researching and understanding the engineering properties of vessel walls as a function of vessel architechture, biochemical disturbancies, the frequency and amplitude of vibrations and the variations in blood pressure. Stehben's hemodynamic theory of mechanical fatigue (degeneration), first proposed in 1958,[3424] has vastly more scientific support than does the lipid hypothesis. Although it offers no immediate promise for prevention, it does offer progress. As noted in Chapter 1, the outgoing 1980 AHA president Thomas James expressed the philosophy that should be every scientists's posture, i.e., "The truth is exciting enough."

9. SOME MAJOR ISSUES

"Admittedly, our ability to explain changes in mortality in terms of its causes and the reasons for the trends is seriously limited. Such an undertaking is hazardous considering changing 'fashions' in death certificate and nosological rules."

(William Kannel and Thomas Thom, 1979[2877])

"There is no unequivocal explanation as to why CHD mortality had risen so high in the first place, nor is it clear why mortality for stroke, hypertension, and all cardiovascular diseases have been declining since 1940 or earlier, antedating antihypertensive therapy. In fact, no one has yet established a convincing fit of trends for any risk factor with cardiovascular mortality trends."

(William Kannel and Thomas Thom, 1984[1174])

The data are "substantial enough to suggest that the beneficial changes that have taken place in...risk factor levels...have indeed contributed to the decline in mortality."

(William Kannel and Thomas Thom, 1984[1174])

"I think it is reasonable to infer that the continuing and marked decline in coronary heart disease mortality in the U.S. since the late 1960s is related to improvements in nutrition and serum cholesterol as well as other risk factors."

(William Kannel, 1988[1383])

THE FALL OF THE CARDIOVASCULAR MORTALITY RATE

Introduction

As noted elsewhere in this volume, alliance members such as Stamler, Keys and Connor originally believed that the so-called CHD "epidemic" was caused entirely by dietary excesses. Connor maintained that the excess was cholesterol, while Keys held that it was any kind of fat. Stamler repeatedly incriminated "rich diets," high in fat and cholesterol. Somewhat later saturated fat was labeled as the principal dietary contributor to CHD, cholesterol was a distant secondary contributor and total fat was considered important because it presumably promoted obesity (although high starchy carbohydrate diets may be more obesity-promoting). By this time, CHD was considered a multi-factorial disease but diet maintained a primary causation.

Alliance members generally do not attempt to correlate risk factor or so-called "lifestyle" changes with the reported rise in CHD mortality during the "epidemic." The reason for this omission is simple. There are no adequate trend data associated with blood cholesterol levels or blood pressures before 1950, cigarette consumption trends correlated poorly and food consumption trends were precisely opposite to those proclaimed by the alliance.

But while alliance members related risk factors to the "epidemic" at a very general level, they have produced numerous redundant articles which related changes in risk factors to the CHD mortality decline and often accompanied their discussions with quantitative (albeit highly misleading) information. However, as was shown in Chapter 3 regarding food consumption trends, their discussions are more notable for what they omit than for what they include. Most interestingly, the discussions initially indicate that it is difficult or impossible to correlate risk factor changes with the CHD decline

but subsequently attempt to convince readers that observed risk factor changes can be and probably were responsible for most or all of the CHD mortality decline. Let us first consider some of their initial and more objective comments.

In 1979 Kannel and Thom[2877] said, "Admittedly, our ability to explain changes in mortality in terms of its causes and the reasons for the trends is seriously limited. Such an undertaking is hazardous considering changing fashions in death certificates and nosological rules. Mortality from hypertensive disease and its major sequela, stroke, began a steady decline long before the introduction of effective antihypertensive medications and continues despite general undertreatment" [Note particularly the last phrase, i.e., "continues despite general undertreatment."] In 1981 Levy[1846] indicated that "It is difficult to attribute the ebb and flow of CHD mortality to specific events. Many possible factors could be responsible for it. ...it is possible to define a multitude of changes that many have contributed to the CHD decline..."

These authors indicated even greater reservations in 1984 articles. Kannel and Thom[1174] said, "There is no unequivocal explanation as to why CHD mortality had risen so high in the first place, nor is it clear why mortality for stroke, hypertension, and all cardiovascular diseases have been declining since 1940 or earlier, antedating antihypertensive therapy. In fact, no one has yet established a convincing fit of trends for any risk factor with cardiovascular mortality trends." Levy and Feinleib[1401] reported, "The reasons for the [CHD] decline in the U.S. are still speculative..." And NIH's Brody and Schneider[3012] emphasized that "These declines in mortality from heart disease and stroke are largely unexplained."

A particularly interesting statement was made by Levy[2806] in 1979, i.e., "Since 1968, the decline in CHD death rate has occurred in both men and women, has occurred in every age range, and has occurred in our minority and majority populations. Any explanations which are put forth to explain the decline in mortality must be cognizant of the fact that the decline has been seen in our entire population." As will be seen below, Levy and other alliance members did <u>not</u> even attempt to explain this state-of-affairs because it is more than obvious that it could not be due to risk factor control. As emphasized by Mitchell,[919] all segments of society could not be similarly affected by such control. For example, he said, "I remain unconvinced that a poor black woman living in Washington is likely to have changed her lifestyle or been offered the advances in blood-pressure control and coronary care to the same extent as a young, affluent white man from Scarsdale."

Despite the above statements, the same authors and many others have not hesitated to convince readers that risk factor control was responsible for the CHD and stroke mortality declines. In 1982, Kannel said that the CHD decline coincided with improvements in the major cardiovascular risk factors."[519] In 1981 Levy concluded that "both primary prevention through lifestyle changes and improved treatment regimens have played a role in the decline."[1846,a] In their 1984 article, Kannel and Thom said that the data are "substantial enough to suggest that the beneficial changes that have taken place in...risk factor levels...have indeed contributed to the decline in mortality."[1174] And in their 1984 article, Kannel, Stamler and others[1083] concluded that "The recent declines in deaths due to CHD and cardiovascular disease are at least partially a result of widespread changes in lifestyle and improvement in health behavior. Factors likely contributing to this decline include better detection and control of hypertension, reduced cigarette smoking in middle-aged men, reduced saturated fat and cholesterol consumption in the national diet, a resultant decrease in

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[a] Yet, at the end of his article, Levy said, "Only when we truly understand atherogenesis will we be able to effectively prevent or retard its occurrence."

serum cholesterol, and in increased level of leisure exercise." They also said that "The rapid rise and subsequent decline in coronary disease mortality over the past three decades testifies to powerful environmental influences... The scientific basis for the assertion that atherosclerosis and its clinical manifestations are largely a product of lifestyle is well established." Since Kannel et al. cited a 1981 NHLBI workshop as the "scientific basis," obviously they equated consensus opinion with scientific evidence.

Ignoring the actual evidence, alliance members appear to have generated scripts to ensure consistency and convince readers. Consider, for examples, the following recent statements: "It is a reasonable inference, given all the facts, that the positive changes in lifestyles and risk factors among Americans have contributed, at least in part, to the decline so far registered in the coronary mortality rates" (NHLBI Working Group[3068]); "It is a reasonable inference that the steady and marked decline in CHD mortality in the U.S. since the late 1960s...is related to the improvements in nutrition and serum cholesterol distribution, as well as in other risk factors" (Stamler[263]); It is a reasonable inference, given all the facts, that the positive changes in lifestyles and risk factors among Americans relate causally to the decline so far registered in the coronary mortality rates" (Stamler[3033]); "It can be reasonably inferred that the steady and marked declines in death rates in the U.S. from coronary heart disease, stroke, all cardiovascular diseases, and all causes since 1968 are related to reductions in these [hypercholesterolemia, hypertension and cigarette smoking] risk factors" (Stamler and Stamler, 1984[2939]); "We can reasonably speculate that the steady and marked decline in CHD mortality rates...over the last two decades can probably be attributed, in part, to decreases in the cholesterol concentration of the general population" (Naito[1352]); "I think it is reasonable to infer that the continuing and marked decline in coronary heart disease mortality in the U.S. since the late 1960s is related to improvements in nutrition and serum cholesterol as well as other risk factors" (Kannel[1383]); the decline in CHD mortality "has coincided with improvements in the levels of predisposing risk factors in the general population" (Kannel[392]); the "attempt to modify risk factors almost certainly has contributed to the declining death rate from heart disease in the U.S." (Grundy, W.V. Brown et al.[980]); and "In the past 15 years or so there has been a 40% decline in the incidence of coronary disease mortality in the U.S. This decline is probably attributable to many factors...[including]...implementation of preventive measures, such as decreases in cigarette smoking, treatment of high blood pressure, and dietary fat modification" (Rifkind[2032]).

Levy also said that "The weight of evidence thus seems to indicate that risk factor modification has played a major role in the recognized decrease in cardiovascular mortality rates."[698] And Levy and Kannel absurdly attributed this cardiovascular mortality decline to the "discovery" of risk factors in the Framingham study even though the decline began before any follow-up data were collected in that study. They wrote, "during the past two decades, the incidence of mortality from cardiovascular disease has declined dramatically in the U.S. It is safe to say that the pioneering work of the Framingham study has contributed to this momentous change..."[1532] Elsewhere, Kannel wrote that there has been a "dramatic downturn" in CHD mortality over the Framingham 40 years and "We would like to think that some of the work done in the Framingham study has contributed to this,"[1932] even though the CHD death rate had stabilized and initiated a downturn by the time the early Framingham data were published, let alone acted upon. There is simply no way that Framingham could have been responsible for the CHD mortality decline.

One of the most absurd statements of all was that of Levy, i.e., "If we...just evaluate the changes in cholesterol, smoking habits and blood pressure control, one can calculate that risk factor change alone could explain the entire decline in CHD mortality over the last 10 years [1971-1981]."[1846] Others have similarly made equally absurd statements and two pairs of authors can be cited as examples. In 1984

Goldman and Cook wrote, "Using reasonable assumptions gathered from the published literature, we estimated that more than half of the decline in ischemic heart disease mortality between 1968 and 1976 was related to changes in lifestyle, specifically to reductions in serum cholesterol levels and cigarette smoking."[2353] This "estimate," based on "reasonable assumptions" was translated in 1988 by Ernst and LaRosa thusly: "analysis of factors influencing the decline in CHD attributes 30% to reductions in plasma cholesterol."[2227]

Writing on behalf of the AHA's Nutrition Committee, Grundy et al.[980] stated that "The average cholesterol level of the population has decreased continually since the mid-1960s, probably due to changes in dietary habits and increased exercise. This attempt to modify risk factors almost certainly has contributed to the declining death rate from heart disease in the U.S." Yet, official statements by the AHA from 1961 to 1986 stated that "current" American diets contained 40% fat, 15-20% saturated fat and 5-8% polyunsaturated fat, indicating no change whatsoever in the American diet since the mid-1960s.[a] The NHANES I and 2 surveys also demonstrated no dietary trends (Chapter 3). Thus, Grundy et al.'s remarks were both inconsistent with previous AHA statements and contrary to fact.

Finally, citing no more evidence than his predecessors, Hiatt stated in 1989 that "heart disease deaths are plummeting. Diet, decreased cigarette smoking, treatment of high blood pressure, exercise seem to be most responsible for the drop."[2496]

As much as the alliance would like physicians and the public at large to believe that the Framingham study and/or risk factor control were responsible for some or all of the cardiovascular and CHD mortality declines, it decidedly was not the case. Historical events are clear and to deny them is tantamount to rewriting history.

Chapter 3 amply demonstrated that food consumption trends in this century were not at all related to the CHD mortality "epidemic" or decline. Although not directly relevant to the central topic of this review, subsections below show that trends in the alliance's two other major risk factors, cigarette smoking and hypertension also do not correlate properly with the CHD or stroke mortality trends. Prior to initiating those discussions, however, two most important points need to be addressed, namely mortality vs morbidity trends and the CHD mortality decline in the U.S. and California.

Mortality vs Morbidity Trends. An extremely important issue is whether or not CHD morbidity is paralleling the CHD mortality decline. If it is not, then discussions of risk factor control become totally and unequivocally meaningless. This issue was introduced at least 12 years ago at an NHLBI conference and has periodically been addressed by Kannel and others.[b]

In 1982 Kannel stated that "The decline in CHD mortality reverses an earlier epidemic rise persisting into the 1960s. Unfortunately,...there are no comparable data trends in morbidity. This is important, since a reduction in mortality without a decline in attack rate indicates better medical care was responsible, while a reduction in both suggests environmental influences."[519] Feinleib presented the identical argument. He said, A decrease in incidence reflects a change in primary prevention factors, whereas a decrease in case fatality is the result of improvements in treatment of the disease after it has taken hold. Assessment of the causes of the decrease in cardiovascular mortality must therefore take these 2 factors into account. The

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[a] See discussion on AHA dietary recommendations for the AHA statement references in Chapter 2.

[b] This issue was the partial subject of a 1980 Lancet editorial.[2836]

evidence to date, therefore, does not give a clear indication of the trends in cardiovascular disease incidence, and thus the question of the role of prevention in the decrease of CHD mortality remains unresolved."[689]

Also in 1984 Kannel, Stamler and others, "updating" the 1970 Inter-Society Commission report, repeated the argument, "Unfortunately, there is inadequate information as to whether the declines in mortality have been accompanied by improvements in the prevalence, incidence, or case fatality rates. Thus, it is not possible to ascertain with confidence whether the declines in cardiovascular mortality reflect a reduction in the frequency of attacks or an improvement in life expectancy after an attack."[1083]

And again in 1984 Kannel and Thom re-emphasized the point but subtlety added one word (underlined), "It is still essentially unknown, however, whether this decline is occurring in the incidence of new cases or whether there has been a change in the prognosis, severity, case fatality and survivorship after development of cardiovascular disease. Without knowing if the incidence or severity of coronary attacks is declining along with mortality one cannot be certain that improvement with respect to risk factor levels, health habits, or other types of primary prevention have contributed to the mortality decline.[1174] As will be seen, the use of the term "severity" provided a way out of a potential dilemma, i.e., how do you justify the continued emphasis on risk factors if CHD incidence increases or remains the same as mortality decreases?

The above statements strongly suggest that no data whatsoever were available for evaluating the potential dilemma but, in fact, some data were available from the Framingham study and Kannel and the alliance were aware of them over a decade ago. For example, Kannel and Thom[2827] noted in 1979 that Framingham mortality trends tended to mimic national trends. And while there existed no adequate national morbidity trends, the Framingham data indicated no declines in coronary attacks for men or women and no declines in stroke for men and most age groups of women. They concluded most strangely, "stroke, as well as for CHD, The Framingham incidence trends do not entirely parallel the falling mortality trends." Thom and Kannel reported the same trends again in 1981.[2826]

Note that Kannel and Thom did not say that CHD and stroke incidence had increased. They merely said that they did not decrease. In 1989 Kannel announced that 30 years of Framingham data revealed that all cardiovascular diseases, including CHD and stroke, had increased in frequency.[1842,a] In 1990, Kannel and his colleagues published specific data confirming the fact that CHD morbidity had increased rather substantially from 1950 to 1980.[2894] Thus, the above statement that "The Framingham incidence trends do not entirely parallel the falling mortality trends" was almost opposite to reality. There was a very strong negative correlation between mortality and morbidity. (The National Centers for Disease Control issued a press release on April 28, 1989 revealing that heart disease was also on the increase nationwide, as exemplified by increased rates of hospitalization.[1862,2219,2262] While this statistic does not prove that heart disease is actually increasing, it is certainly suggestive.) But ignoring his 1982 logic, as well as Feinleib's, Kannel concluded that "The improved case fatality rates for stroke and cardiovascular disease in general, despite the rising incidence and prevalence of these diseases, strongly suggest that

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[a] Prior to Kannel's recent announcement, Castelli informed HeartBeat Magazine that "We will soon be releasing statistics showing that the second generation (of Framingham) is running a 20% lower heart attack rate."[2044] This is yet another example of Castelli's apparent inability to know what is going on in his own project.

better medical care may be a factor, but the occurrence of less severe disease due to improvement in some major risk factors cannot be excluded."[a]

The latter part of this conclusion is, of course, absurd. It makes no sense at all to suggest that improvements in risk factors have led to an increased incidence of the disease, regardless of severity. If risk factors comprise the cause of the disease, then their reduction should reduce, not increase, its frequency. In fact, risk factor reduction should logically lead to a reduction in both incidence and severity. But since Kannel and other alliance members have committed themselves fully to the risk factor concept, they must always explain all positive and negative findings in ways which protect the concept, no matter how illogical such explanations may be. In their 1990 article Kannel and co-workers[2894] said, "Our data do not prove that the improvements in risk factors [from 1950 to 1980] caused the decline in cardiovascular mortality. We can conclude only that risk factors and mortality improved concurrently." But, of course, their own, as well as national, data clearly indicated that this was absolutely not true. CHD mortality increased from 1950 to 1963 and morbidity increased during the entire 30 years.

It should be clear to the reader that the mortality/morbidity issue is extremely crucial and one would assume that a legitimate program to eradicate CHD would include an assessment of whether or not CHD morbidity is increasing, remaining constant or decreasing. The question is, therefore, what is NHLBI doing to resolve the issue? The NHLBI held a conference in 1978 which addressed the decline in CHD mortality. The proceedings of that conference were published in 1979.[2796] In 1988 the proceedings of an NHLBI workshop held in 1986 were published.[2803] The Foreword of that document was written by Claude Lenfant.[2802] He stated that the 1978 conference "concluded that the decline was real, and that both primary prevention and better clinical care had contributed to, but did not fully explain, the decline. As a consequence, the conference strongly recommended that the Institute collect the data necessary to assess whether the incidence of the disease has changed." Lenfant continued, "By and large, the recommendations of the 1978 conference have been implemented, but in one instance we have been slow--namely, to initiate a study to measure incidence rates. Such a study is now in progress, but it will take years to obtain data that can be extrapolated to the whole nation."

In view of the massive changes that the alliance is indirectly forcing upon society, including diets, cholesterol-lowering drugs and antihypertensive drugs, it is unconscionable that NHLBI has been "slow" to obtain data which would determine trends in CHD incidence. Twelve years have passed since that conference, a period in which substantial and sufficient data could have been accumulated. It is not known what study Lenfant was referring to but a World Health Organization (WHO) project known as MONICA is presumably collecting such data during the period 1984 to 1993 in 26 countries. However, the latest WHO World Health Statistics annual is 1989 but only presented initial data obtained during the start-up of MONICA. Those data are discussed in Chapter 4. It is to be noted that while there are multiple centers in other countries participating in MONICA, data from the U.S. is being obtained only from a sample of 1,402 persons in Stanford, California, although the WHO document is not perfectly clear on this point. For example, it is stated that "The total population aged 25-64 being monitored is 15 million. The populations included in the present report are listed in ...[a table]...in which a summary of the population size, sample size, participation rate and survey period is given." The population size was listed as 84,600 but the sample size was 1,402. The latter figure does not appear to represent even a modest effort to determine CHD incidence trends in the U.S.

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[a] This quote was derived from the writer who interviewed Kannel.

The Start of the Mortality Decline. Authors attempting to relate CHD mortality trends with risk factor trends must, of course, know when the so-called epidemic peaked and subsequently began its decline. Alliance members have access to all mortality data and to analysts who specialize on such statistics. It may seem surprising, therefore, that they differ so significantly on this issue, sometimes with themselves. For example, former NHLBI director Levy[698,2806] chose 1969 as the year of the decline, as did Feinleib[689] and Gordon and Thom.[533] Current NHLBI Director Lenfant[2802] selected 1968, as did Cooper et al.[2825] Others reported that the decline began in 1964, e.g., Beaglehole et al.,[585] Kannel and Thom[1174] and Thom and Maurer.[2799] Note that Thom was associated with both 1964 and 1969.

The late 1960s have been favored by many because it allows better cause and effect relations between the 1964 Surgeon General's report on smoking and the CHD decline. However, NHLBI's own data betray them and some of their contributors have shown that the year of decline was, at most, 1964. The clarity of the decline is somewhat obscured by influenza epidemics which artificially increase CHD mortality. As noted by Rosenberg and Klebba[2830] at an NHLBI conference in 1979, the most severe epidemic occurred in 1963, the year in which CHD mortality reached its peak. An epidemic of lessor consequence struck the year before as well. Since the CHD mortality rates were lower in nonepidemic years 1961 and 1964, before and after the two epidemic years, it is clear that the mortality rate actually peaked between 1961 and 1963. This led Rosenberg and Klebba to conclude that "the downturn in mortality from IHD began in 1964 or earlier." These authors also cited a March 1974 National Center for Health Statistics report that pinpointed 1964 as the year of the decline.

What is important to recognize is that regardless of whether the decline occurred in 1962, 1963 or 1964, the mortality rate had clearly ceased its upward climb by 1962 and it is this year that must be considered, as well as the beginning of the downward trend. If there were a several year spread between peak and decline, as implied by Levy and Lenfant, which there was not, two questions, rather than one, require answers, namely, "What caused the epidemic to cease and what caused the mortality rate to decline? As will be seen, alliance members will attempt to explain the decline, in part, on the 1964 smoking report, but they obviously could not use that explanation for the epidemic cessation that preceded the report.

The CHD Mortality Decline in California. In 1981 Thom and Kannel[2826] told their readers that the declines [in CHD and stroke mortalities] are not only uniform across...demographic regions, according to the Division of Analysis of the NCHS, they are also fairly uniform for virtually all geographic areas in the nation. The decline may have begun sooner in certain areas of the country especially among white women." Such a statement was partially incorrect and wholly misleading.[a] Chapter 4 presented ample evidence from alliance members themselves indicating that there were substantial state and regional differences in the CHD "epidemic" and decline.[b] The most deviate region was California. This state undertook a CHD mortality decline long before the U.S. as a whole. In fact, its decline occurred at about the same time that the epidemic was initiated nationwide. Not only were "risk" factors essentially unknown at that time, cigarette consumption was high, detection and treatment of hypertension was almost nonexistent and everyone was eating what Stamler has referred to dozens of times, the "rich" American diet. It is submitted that the California mortality data are unequivocally and totally unexplainable by the risk factor concept and, for that reason, they are never discussed by Kannel and his fellow alliance members, although the data are certainly well known.

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[a] Noted also by Davis et al.[3027]

[b] 561,1401,2688,2732,2810

Winkelstein[3005] reported that the nationwide CHD mortality decline began "around 1970" and indicated that "It is not usually recognized that the downturns in IHD mortality were noted a decade earlier than 1970 in New York and California." Such a statement is typical of the laxity among so many researchers in ensuring accuracy of reporting. The U.S. CHD decline occurred in 1964, not "around 1970," and, as will be seen, the California CHD decline occurred in 1953 not 1960, as implied. Moreover, there was no decline in New York until 1969, although the rates during the 1960s were barely upwards.

Borhani and Hechter[2982] were apparently the first to recognize that CHD mortality rates in California had been falling for some time. They compared the 1950 rate with that of 1960 and found rates dropped across all age groups and both sexes. The present writer computed an average decline of 16.9% and a range of 12.5% to 19.7%. In 1965 Hechter and Borhani[3025] showed that the CHD rates among California counties varied dramatically for both males and females, i.e., 236-436 per 100,000 and 29-141 per 100,000, respectively. A thorough analysis revealed that these rates varied randomly within the state, defying any recognizable pattern.

Figure 9-1 shows the crude CHD death rates for California[3010] and the U.S. Age-adjusted data were not found in the Vital Statistics of California. However, as will be seen below, the trends exhibited in Figure 9-1 for both males and females mimic very closely those for age-adjusted trends for white males. These data and those presented below indicate that the CHD decline in California apparently began in 1953. Of most significance is the fact that the California and U.S. trends were quite dramatically in the opposite directions.

Not only is the California CHD mortality trend a complete embarrassment to the alliance, other states pose embarrassments as well. For example, the CHD mortality decline in Utah also occurred in the 1950s and the rate in the most populated state, New York, was almost constant throughout the 1950s.[3025] In fact, the rate among females actually decreased during that period, while that among males increased slightly. Figure 9-2 shows the age-adjusted rate trends for white males for New York and California.[2984]

As much as the alliance would like to make people believe that the California, Utah and New York trends were probably due to risk factor changes--if confronted with this issue--it is doubtful that 100 alliance members working together could mount a risk factor argument that would convince anyone except the most devout believers in the lipid hypothesis. However, Stamler would probably not hesitate to explain Figure 9-2 as an example of the effects of differing diets. Thus, he would likely say that Californians had a "rich" diet in 1950 and New Yorkers had a "very rich" diet; New Yorkers maintained their "very rich" diet over the next 17 years, while the diets of Californians became blander and blander. Then, in 1968 New Yorkers got the word. They changed their diets rapidly and, as can be seen in the Figure, their CHD mortality rate began a rapid descent. Silly? Yes, but not more than a few microns different from a large number of explanations by Stamler of the CHD "epidemic" and subsequent decline.

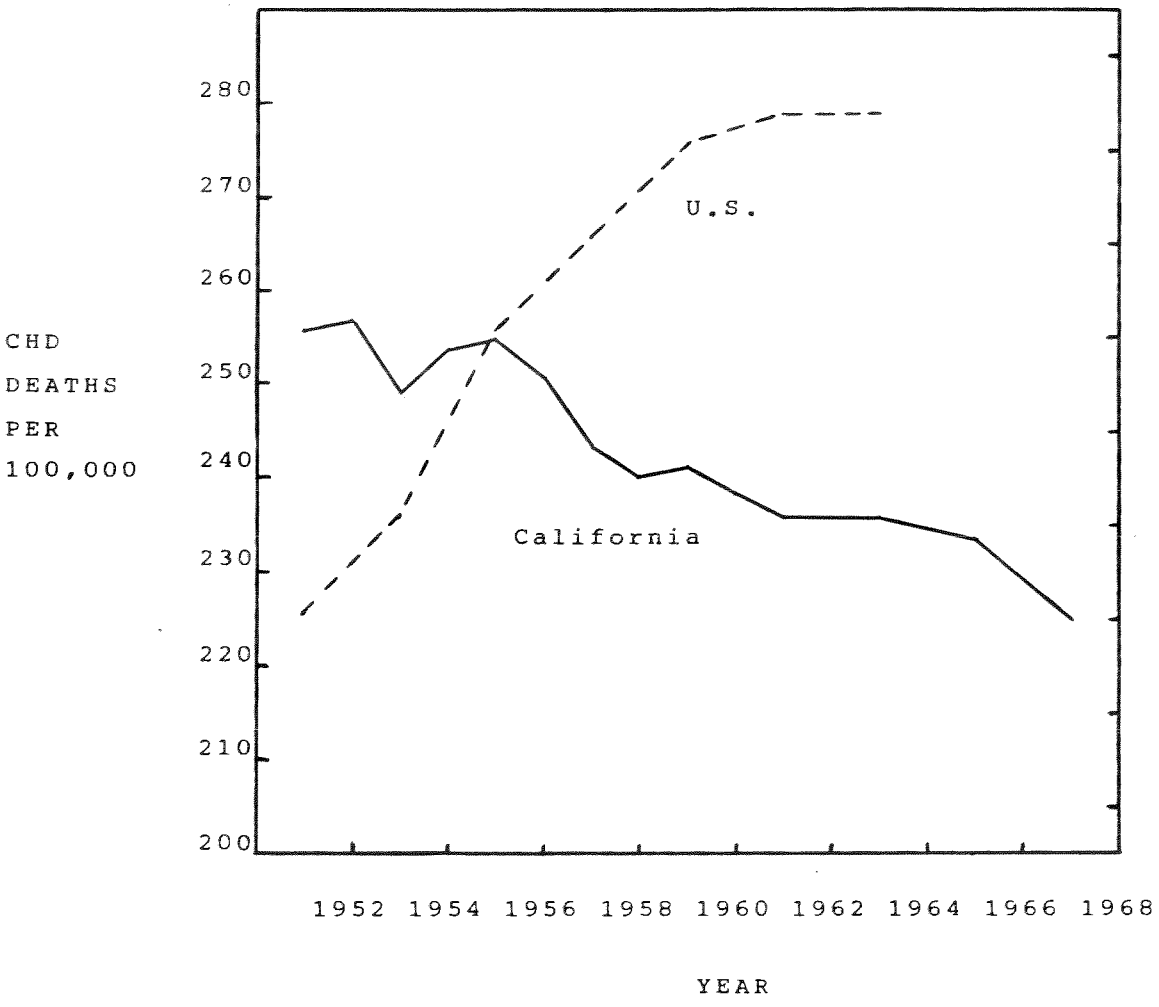

Figure 9-1. Crude CHD death rate trends for California and the U.S. after 1951 (adapted from California Public Health Statistics Reports,[3010] and Grove and Hetzel, 1968[1949])

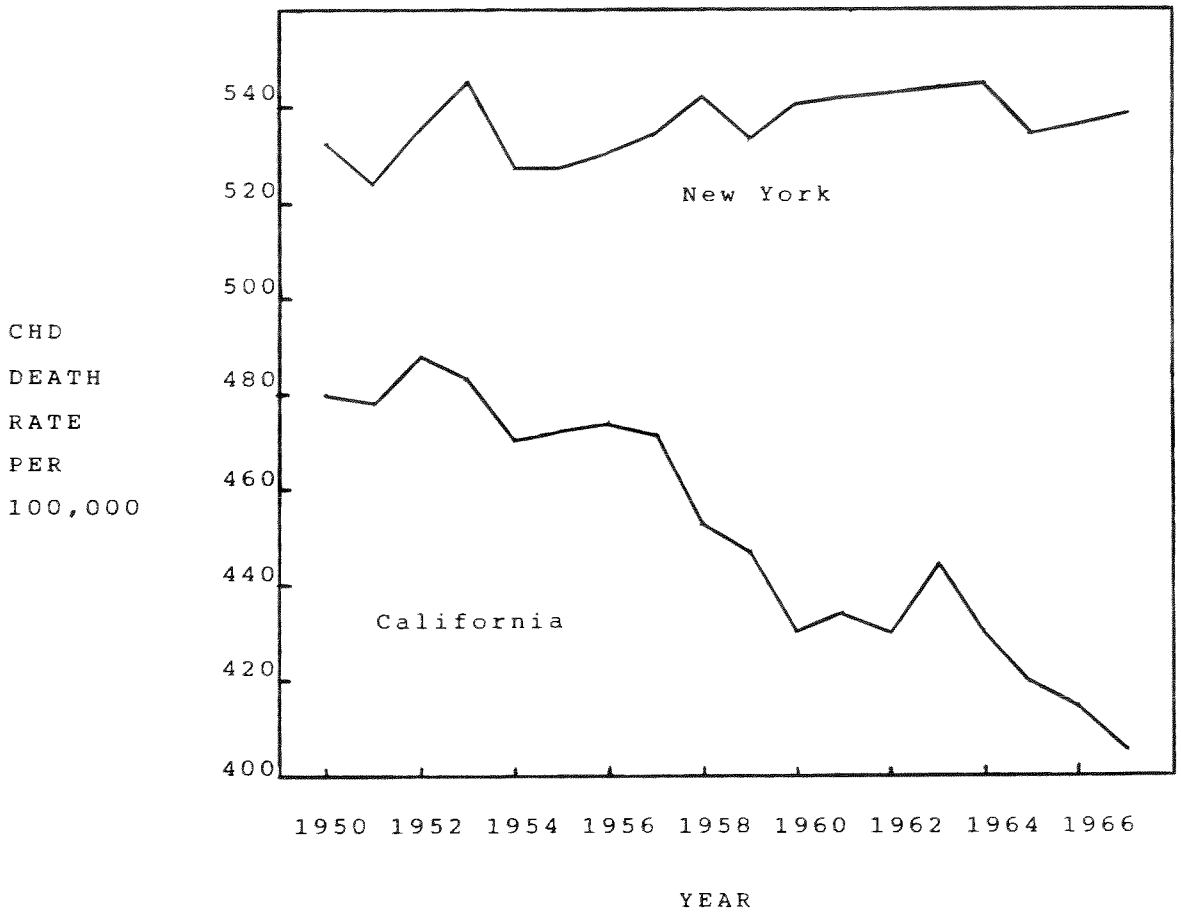

Figure 9-2. Age-adjusted CHD mortality for California and New York white males from 1950 to 1967 (adapted from Kim et al., 1983[2984])

Hypertension

CHD and Stroke Mortality Declines. Figure 9-3 shows the CHD mortality decline during the 8th and 9th ICD revisions by race and sex. The dotted lines in the trends connect the years 1968 and 1978, during which period the 8th revision was in effect. With the exception of the years 1972 and 1973, the trends during the 8th revision were effectively linear. Two factors apparently created the perturbations in 1972 and 1973.

In 1978 NHLBI sponsored the Conference on the Decline in Coronary Heart Disease mortality. The proceedings of that conference were published in 1979, edited by Havlik and Feinleib.[2796] One of the papers at the conference analyzed the CHD mortality decline and was discussed earlier, i.e., Rosenberg and Klebba pointed out that the influenza epidemics which occurred in various years with various severities partially obscured the true declining CHD mortality trend during the 1960s and 1970s because influenza tends to increase the mortality rate among those with CHD. The years 1971 and 1974 were nonepidemic years and the CHD rates associated with these years fell on or near the dashed lines shown in Figure 9-3. However, 1972 and 1973 were epidemic years of some consequence and the result was a temporary slowing of the CHD mortality rate. Thus, the one perturbation in the linear trends seen in Figure 9-1 was due to influenza influences. Trends after these epidemics soon resumed the slopes that occurred in whites before the epidemics and somewhat later in nonwhites.

A second factor that apparently contributed to the perturbations occurring in 1972 and 1973 was discussed by Wing et al.[2986] The overall CHD mortality trend was influenced by the fact that the mortality rate was increasing in some states while it was decreasing in most others. Wing et al. noted that part of the unusual variation that occurred in the 1972 region was due to the fact that the final states which had heretofore been increasing in CHD rates had finally initiated their descents.

The slopes during the 9th ICD revision were effectively linear and identical to those during the 8th revision for white and nonwhite males. They were also linear but somewhat less steep for white and nonwhite females.

The use of effective antihypertensive drugs began in the 1950s but it was not until the 1970s that they became a significant treatment for hypertension. This surge was initiated by the launch of NHLBI's National High Blood Pressure Education Program (NHBPEP) in 1973, the year in which the influenza-provoked perturbation peaked. As will be seen later, alliance members have claimed that the steep downward trend in the CHD mortality following 1973 was caused by the NHBPEP. But not only is this claim clearly false, if one choses to use it, one should also explain the CHD mortality decline deceleration before 1973 and why it decelerated again after 1975. The fact is that the overall trends shown in Figure 9-3 are remarkably linear and demonstrate absolutely no influence of the NHBPEP and the rising use of antihypertensive drugs after 1973. This fact is particularly evident in the white male and female trends which, after all, represent the bulk of the U.S. population and the primary focus of attention in prospective studies and clinical trials.

The present author found no literature which described the actual frequency of use of antihypertensive drugs before and after 1973. However, Baum et al.[3232] reported

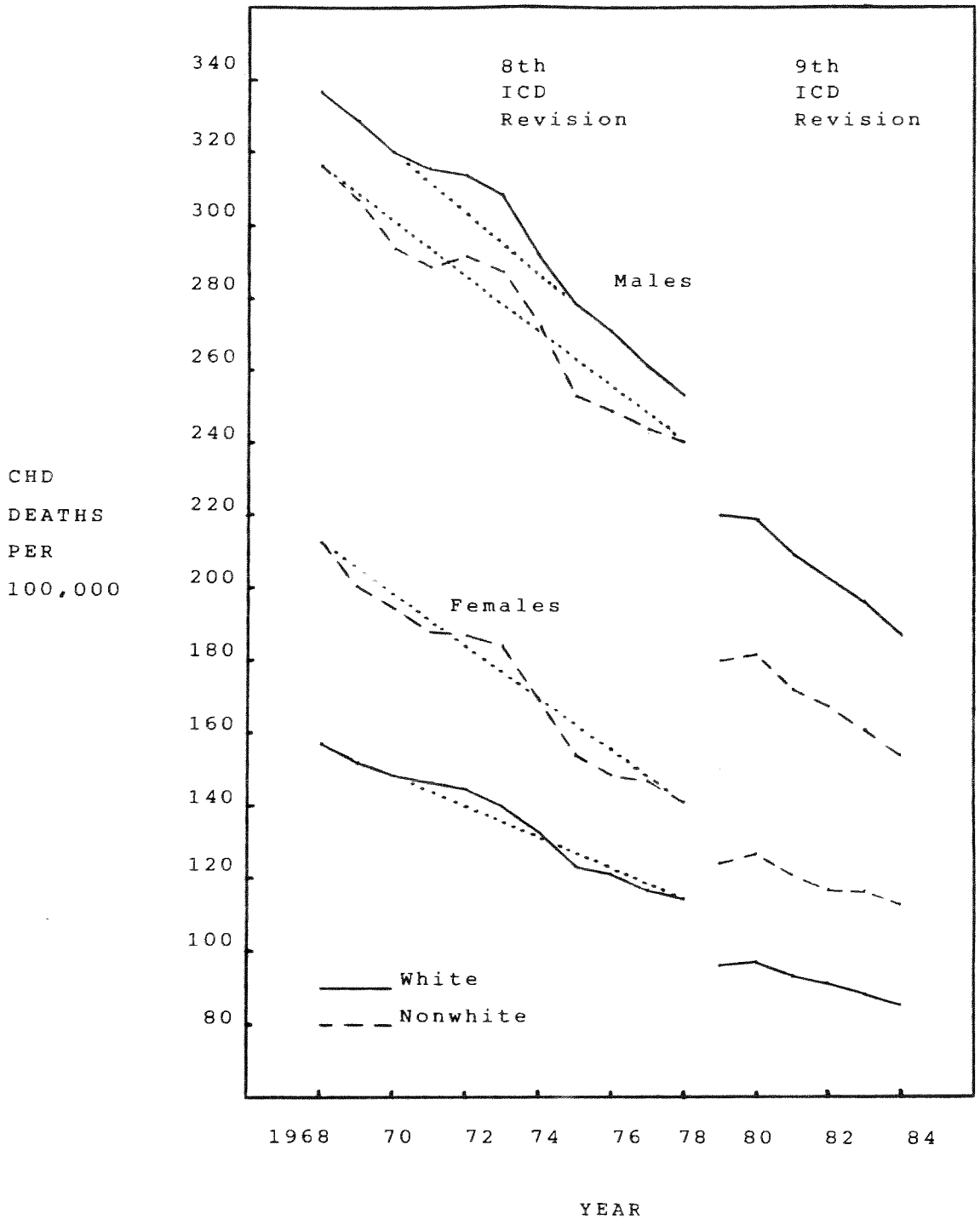

Figure 9-3. Age-adjusted CHD mortality decline by sex and race (adapted from Higgins and Luepker, 1988[2798])

that the number of all drug prescriptions increased 14% from 1971 to 1973 and then decreased almost as much from 1973 to 1979. These trends, of course, were opposite to those that would be expected with a (NHBPEP) nationwide program to place large numbers of Americans on antihypertensive drugs.

Figure 9-4 shows the age-adjusted stroke mortality trend from 1949 to 1984 for all races and sexes. As a first level analysis, one can draw (dotted) lines which connect the first and last years of ICD revisions. These data indicate that the stroke mortality trends were essentially linear during the 6th and 7th ICD revision periods, with the latter having a steeper slope. And with the exception of the years 1972, 1973 and 1974, the 8th revision also conforms to a linear function and, like the 7th, exhibits a steeper decline than its predecessor.

Figure 9-5 presents the age-adjusted stroke mortality trends for 35-74 year-olds by sex and race. This age range was selected by Cooper, Stamler and their colleagues in 1978 as being the most representative of trends.[2825] As can be seen, the trends were linear for white males and females, with an indication of a slight influence from the influenza epidemics of 1972 and 1973. The overall trends for nonwhites were also linear and also yielded an indication of a slight influence of the influenza epidemics. However, the nonwhite trends showed a rather large perturbation between 1970 and 1972. This writer did not interrogate the literature for the likely reasons for this perturbation and Cooper et al. had nothing to say about it. However, they used it indirectly to suggest that the trends after 1973 were uniquely downward.[a] In their description of the trends after 1967 they said, "This downward slope persisted into the 1970s, with a more steeper descent over the last several years. The percent decline...is particularly striking for nonwhite males and females." But, in fact, there was clearly not a steeper descent over the last several years among the whites and the apparent steeper descent among nonwhites after 1973 was a continuation of the original descent in 1968 and 1969 and appeared steeper because of the temporary perturbation from 1970 to 1972. But as will be seen below, alliance members ignored the perturbation and claimed that the NHBPEP caused a steep downward reduction in the stroke mortality rate.

It may be noted that the large differences in stroke mortalities between whites and blacks are apparently not due to racial differences per se because blacks in other parts of the world, e.g., Africa, presumably have lower rates and severities of hypertension.[2772]

Hypertension and CHD. Prospective studies such as the follow-up of the MRFIT screened cohort[263] indicate a positive association between blood pressure and CHD. Thus, it would seem logical that the reduction in hypertension would lead to a reduction in CHD mortality. However, there is broad evidence and widespread recognition that the reduction of hypertension with antihypertensive drugs does not reduce mortality or morbidity due to CHD and, in fact, sometimes increases these rates.[b] Indeed, after examining 30 years of Framingham data, Kannel and others admitted that myocardial infarctions, sudden deaths and even stroke increasedincidence whether or not hypertensive therapy was given to participants.[1842,1877,1878,2215] But instead of emphasizing that hypertensive therapy

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[a] Other alliance members repeated this error. For example, Levy[2977] said, "The mortality rate from stroke...has declined approximately 36% over this period [since 1948], with the steepest decline occurring in the last 5 1/2 years" [1973 to 1979].

[b] 833,1762,1779,1815,1842,2082,2084,2192,2514,2522,2568,2577,2644,2755,3116,3138

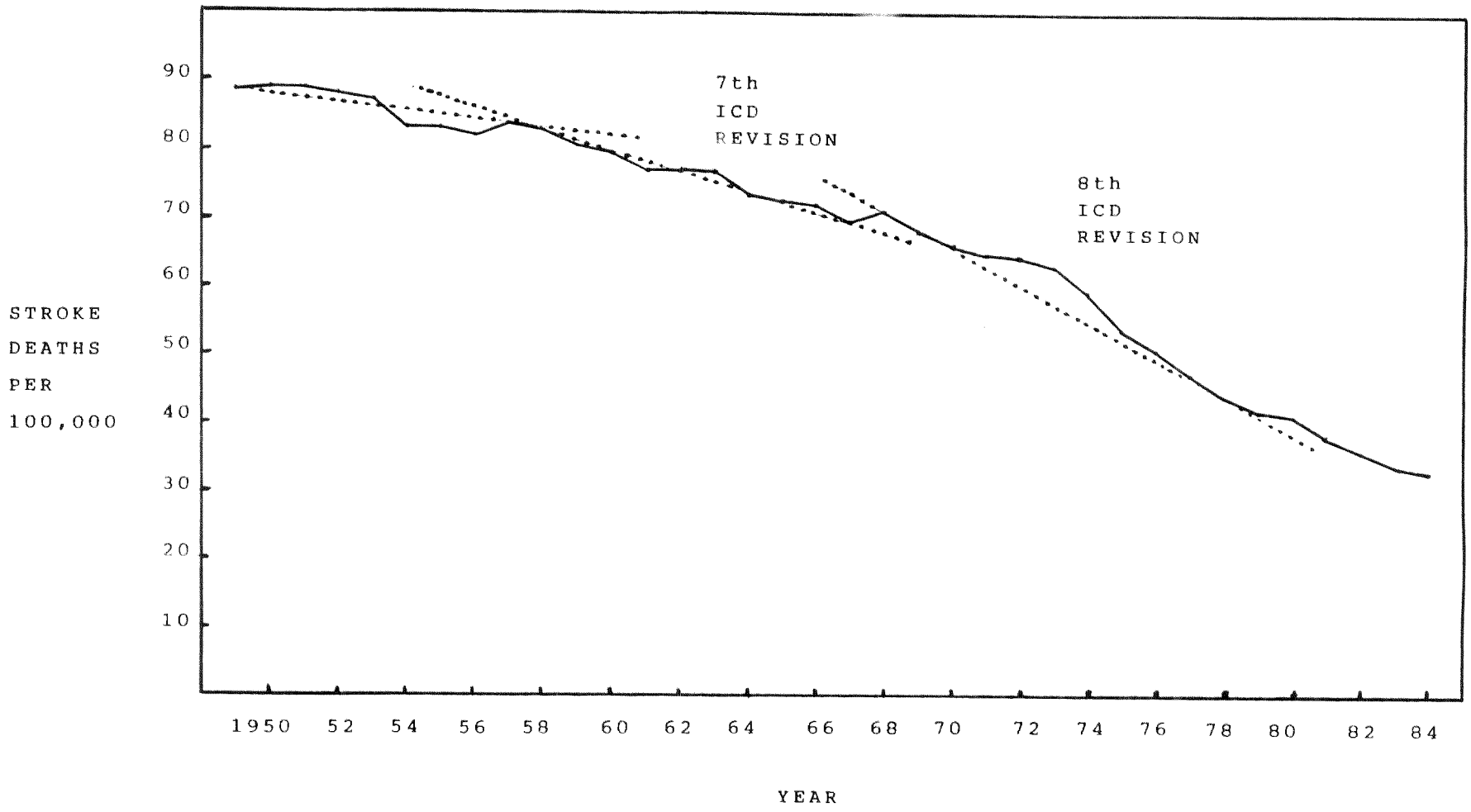

Figure 9-4. Age-adjusted stroke mortality decline by ICD revision (adapted from Higgins and Leupker, 1988[2798])

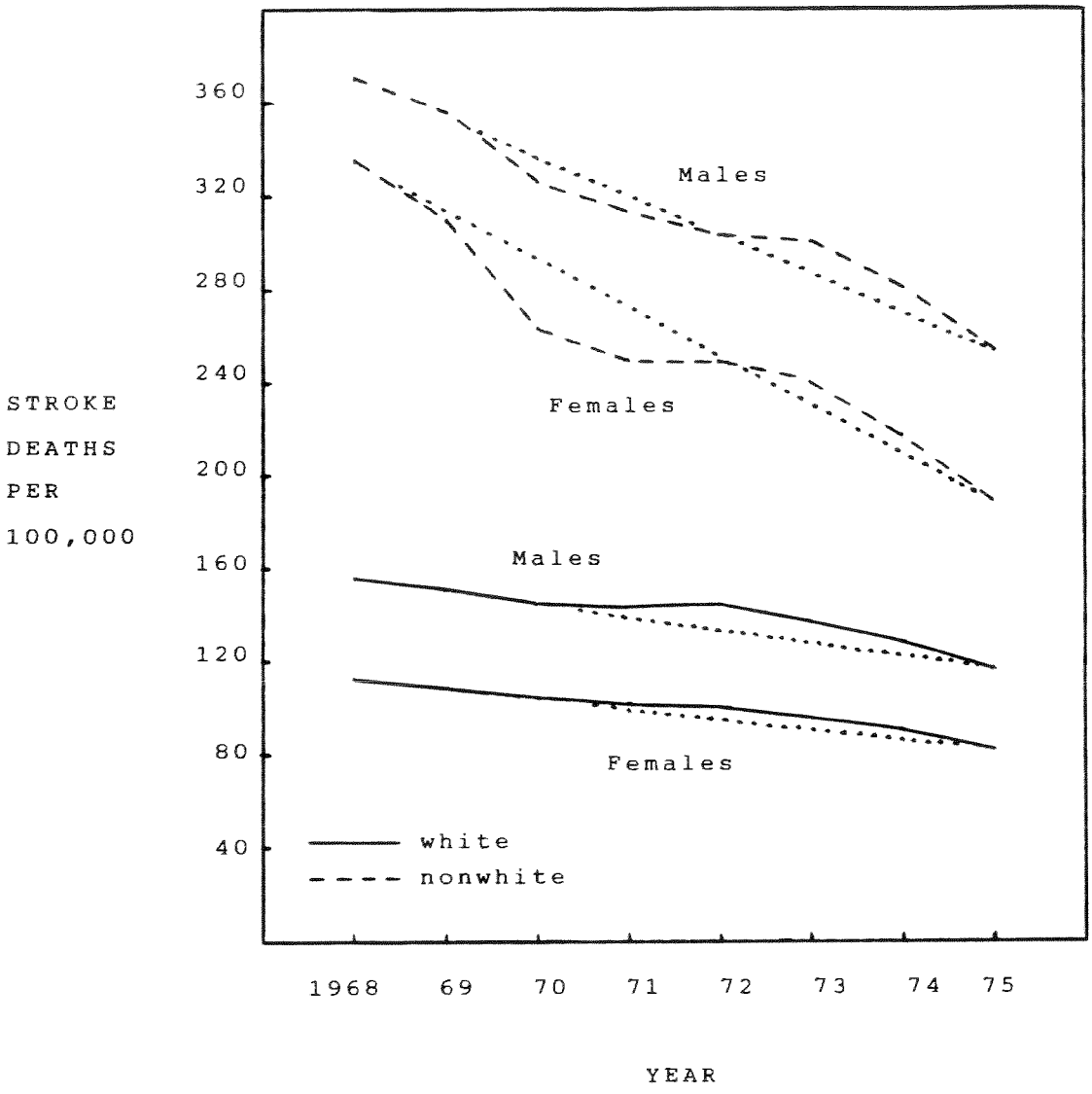

Figure 9-5. Age-adjusted stroke mortality decline by sex and race for 35-74 year-olds (adapted from Cooper et al., 1978[2825])

was ineffective, Kannel indicated that it did no harm[1842] and had "trivial benefits with respect to CHD.[2679] A review of the Framingham study published in Contemporary Internal Medicine said, "it is now becoming clear that drug treatment itself may be an important risk factor for sudden death."[2215]

To illustrate how trivial findings become distorted and exaggerated, consider the Hypertension Detection and Follow-up Program Trial (HDFP). This trial randomized 10,940 persons to two groups, one receiving "optimum" antihypertensive treatment for high blood pressure (Stepped Care, SC) and the other receiving "Customary Care in the community" (Referred Care, RC).[3108] Thus, there was no conventional control group. During the 5-year study period, all subjects were partially or fully examined annually. The SC subjects were also seen at least every four months. All RC subjects having a diastolic blood pressure of 90 mg Hg or higher were encouraged to see their physicians for treatment. In effect, then, the HDFP represented a study of two groups varying in the degree to which participants received antihypertensive treatment for high blood pressure. Theoretically, the groups would have been effectively identical had the RC subjects followed the advice given by the HDFP investigators. As it turned out, about 75% of SC and 52% of RC subjects received antihypertensive therapy during the study. Also, 59% and 37% of the subjects in the SC and RC groups, respectively, had maintained the goal blood pressure or achieved lower levels.

In the 1979 report the HDFP Cooperative Group indicated that there were 131 and 148 CHD deaths in the SC and RC groups, respectively. It was said that "Extensive work remains to be done on cause-specific mortality, taking into consideration all available data (multiple causes of death on death certificates, autopsy, clinical, coroner-medical examiner, and hospital data); the...[current]...findings...are solely from the nosologist's 'blind' single-cause coding of death certificates, i.e., based on a preliminary analysis of mortality. For these reasons, no tests of statistical significance are given for the specific causes of death." The Cooperative Group did note, however, that the SC group had a significantly lower number of all-cause deaths (349) than did the RC group (419). The Cooperative Group concluded that "These findings...indicate that the systematic effective management of hypertension has a great potential for reducing mortality for the large numbers of people with high BP in the population, including the millions with 'mild' hypertension.

Using the risk concept, the Cooperative Group said that there was a 16.9% "reduction in mortality for...[the]...SC Group." However, the actual rate reduction was only 1.32% over the 5-year period, a most unimpressive "benefit" from all the drug-taking including its costs and side-effects.

In a 1986 report the Cooperative Group[3259] introduced a series of articles on the HDFP. The Group indicated that the HDFP showed that extensive antihypertensive drug treatment reduced CHD mortality by 10.4% and CHD mortality and morbidity by 16.4%, citing Borhani et al.[3258] as evidence (see below). The Group concluded that "The HDFP study results summarized above and documented in the following articles demonstrate conclusively the beneficial effects of vigorous treatment of mild hypertension...in reducing morbidity and mortality."

The Borhani et al.[3258] report revealed that the 10.4% reduction in CHD deaths cited by the Cooperative Group amounted to only a 0.28% reduction in rate over 5 years and an annual reduction of a mere 0.056%. Similarly, the annual reduction of all-cause mortality was 0.25%. Thus, these results were considerably less impressive than the Cooperative Group and others would have readers believe. It is noteworthy to mention also that the total numbers of CHD deaths listed in the Borhani et al. report for the SC and RC groups were identical to those listed in the original 1979 Cooperative Group report, suggesting that the "extensive work" needed to determine specific causes of death in this study was either not accomplished or conflicted with

the original data and was rejected.[a] In view of the many complexities involved in determining actual cause of death, discussed at length elsewhere in this volume, it is highly unlikely that "extensive work" by a number of physicians using all data and established criteria would have come to the exact same conclusion for all deaths as did the single nosologist. It just does not happen this way. Yet, that is apparently what the Cooperative Group and supporters expect readers to believe.

Although the difference between groups in all-cause mortality rates was small, the difference that can be attributed to antihypertensive therapy was even smaller. The SC group had 26 fewer noncardiovascular deaths than did the RC group which amounted to 37% of the difference in all-cause deaths.[b] When these irrelevant deaths are eliminated, the difference in all-cause deaths reduced to 0.16% per year.

A most important result of the HDFP noted by Kuller et al.[3110] and others[3117] was the relationship between antihypertensive therapy and CHD mortality in white men, the chief target group of most prospective studies and clinical trials engaged in CHD research. The CHD mortality rate was actually slightly higher (1.74%) in the SC group than in the RC group (1.69%). This finding was due to a higher rate of CHD death among those white men who had CHD symptoms at baseline. This result for white males is identical to that found in the much larger MRFIT trial.[471] Kuller et al.also emphasized that there was virtually a zero difference between the SC and RC white male groups in all cardiovascular diseases, whether or not CHD symptoms were present at baseline. The only difference between these groups favoring the SC cohort was noncardiovascular deaths and those were not related to blood pressure problems. As indicated earlier, "something" other than antihypertensive therapy was operating to reduce mortality (and probably morbidity) in the HDFP. In any event, the HDFP did not yield evidence indicating that mass antihypertensive drug treatment has practical (cost-effective) benefits with respect to either CHD or all-cause death rates, particularly for white males. Since white men comprise the primary target population of the alliance, this critique does not constitute inappropriate post hoc analyses.

In view of the above substantial and consistent evidence, as well as the fact that the CHD mortality decline has been almost perfectly linear, during which period antihypertensive drug therapy progressively increased in frequency, it is dumbfounding how anyone can suggest that this therapy reduced the CHD mortality rate. But that is precisely what alliance members maintain. For example, Gillum, Folson and Blackburn[2696] indicated that the "declining population levels of blood pressure seem likely to have contributed to the decline in CHD mortality..." And in their discussion of risk factors, Gordon and Thom[533] stated that "A more plausible explanation for the recent CHD mortality decrease lies in the continuing amelioration of hypertension. There has been a long term decline in mortality from hypertension and hypertensive heart disease. It is entirely logical to anticipate that the waning force of hypertension would also lead to a reduction in CHD mortality." However, not only is there no evidence in the mortality trends of Figure 9-3 that the NHBPEP, initiated in 1973, had any effect whatsoever on the CHD mortality trends, Gordon and Thom's subsequent discussion suggested that they really did not believe that hypertension control was effective, i.e., "...if an amelioration of hypertension accounts for the recent decline in CHD mortality, it is difficult to explain the extended period before

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[a] A 1988 report by Curb et al.[3109] of NIH suggested that the "extensive work" was not accomplished--or not reported.

[b] Cressman and Gifford[3260] suggested that the reduced noncardiovascular deaths in the SC group "was due, at least in part, to the extra care provided to these patients."

1968 during which CHD mortality was still rising while hypertension mortality was declining."[a]

With so much talk in the literature about reducing hypertension in the U.S., it is almost humorous to note a 1981 statement by Thom and Kannel, i.e., "...it is not clear why prevalence [of hypertension] has not declined in the face of long-term use of antihypertensive medication."[2826]

A common explanation for the lack of effects (or negative effects) of antihypertensive drugs on CHD, as exemplified by Castelli,[2555] and Denker and Pollock,[833] is that these drugs elevate blood cholesterol levels, thereby blunting the beneficial effects of lowering blood pressure. Moser[2514,2754] is strongly opposed to this explanation on the grounds that cholesterol increases have been relatively small (e.g., 5% to 7%) and occurred only in short-term trials. He pointed out that cholesterol actually decreased from baseline in trials lasting more than a year. Ames,[2522] on the other hand, is a strong advocate of the explanation and he believes it is the only reasonable explanation for the observed results. He noted that when the cholesterol levels of both controls and treatment subjects in long-term trials are examined, the levels of controls also decreased over time and more so than did the levels of treated subjects. Thus, antihypertensive therapy, notably diuretics and beta-blockers, do, in fact, raise blood cholesterol somewhat, relative to untreated subjects.

Of course, the totality of Volume 1 and this volume indicates that his writer cannot agree with Ames that the relative differences in cholesterol levels observed in the studies accounted for the failure to find CHD benefits. Others have offered alternative explanations. For example, Krone and Nagele[2084] and Northcote[2082] cited studies which showed that reducing diastolic blood pressure below 85 to 90 mg Hg resulted in greater rates of myocardial infarctions than when the blood pressure was maintained over 90 mm Hg. Cruickshank[3112] and Mittila et al.[3139] reported an inverse correlation between blood pressure and mortality. A recent study in Sweden reported that "widely used [diuretic] drugs for high blood pressure may increase the risk of diabetes and heart attacks."[2220] And an editorial in Lancet cited studies showing that the diastolic blood pressure of treated hypertensive patients can fall to 30 to 40 mm Hg or less during sleep, increasing the likelihood of ischemia.[1815] Moreover, many studies have found that high blood pressure did not increase total mortality in the elderly.[b]

Because antihypertensive effects on CHD tend to be either negative or neutral, the explanation of Albertson may be particularly relevant. "We know that coronary thrombosis is the proximate event in most MIs and probably in many sudden deaths. But hypertension may not have anything to do with coronary thrombosis."[2568] He pointed out that diuretics deplete total body potassium, increase uric acid, and produce hyperglycemia and hyperinsulinemia, as well as elevate cholesterol. Weinberger also emphasized that diuretics cause a decrease in potassium and magnesium, leading to increased rates of sudden deaths.[2192] He warned that diuretics are particularly dangerous in the elderly.[2226]

It is important to stress that widespread use of antihypertensive drug therapy occurred without benefit of data demonstrating clinical efficacy. For example, in 1969 Morris and Gardner[3134] stated that "We urgently need to know whether reduction of

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[a] Thom and Kannel repeated this argument and counter-argument in a subsequent article.[2826]

[b] 3112,3114,3139,3140,3141,3142,3143,3144

mild hypertension before or in early middle-age will reduce the subsequent incidence of CHD." More explicitly, 1989 AHA president Myron Weisfeldt[3091] said, "With regard to high blood pressure I would point out that in truth we still know relatively little about the importance of high blood pressure in the elderly and its treatment. ...when we adopted a blood pressure of 140/90 as a guideline for normalcy and abnormalcy, and in a sense for drug treatment, we had little or no evidence about the appropriateness of these guidelines or the appropriateness of the treatment of high blood pressure in the elderly."

Yet, despite all of the negative evidence and the admission by Weisfeldt, the use of antihypertensive drug therapy continues to increase, especially in the elderly, and such therapy continues to be promoted. For example, Epstein[3113] recently said, "Blood pressure in the elderly should be reduced..." And in his promotion, NHLBI's Jeffrey Cutler[2220] asserted that "Diuretics are the only drugs tested and shown in large trials to reduce stroke, and they are also cheap, and relatively free of disturbing side effects." Apparently, Cutler does not consider sudden deaths and heart attacks as "disturbing side effects." (See next section for additional side effects of antihypertensive drugs.)

As will be seen below, discussions of risk factors and their effects are somewhat academic in view of the apparent fact that the incidence of heart attacks and strokes are increasing in the U.S., despite the declining mortalities.

Hypertension and Stroke

Clinical trials have apparently shown that the reduction of hypertension decreased the mortality and morbidity due to stroke and congestive heart failure.[a] This writer has not analyzed the relevant studies to confirm the reports of others, primarily because stroke is of only peripheral importance to this review. Their reviews are therefore assumed to be accurate, although such an assumption has proven to be almost always erroneous in other areas of this review. Regardless, we are primarily interested in the last analysis in what takes place in the real world, namely the effects of antihypertensive therapy on national stroke mortality trends. Also, while most investigators simply conclude that clinical trials confirm the benefits of antihypertensive drugs, Applegate's[2759] review noted that three of five major trials with the elderly failed to demonstrate statistically significant results, suggesting again that the alliance has probably exaggerated the benefits of such drugs on the incidence of stroke.

Kannel indicated that "cerebrovascular and hypertensive cardiovascular disease mortality has been declining since 1928, antedating effective antihypertensive treatment."[519] Cooper, Stamler and their colleagues extended the decline to an even earlier year, i.e., "Death rates from stroke have been declining in this country since at least 1920."[2825] It is important to emphasize at this point that the stroke mortality decline began 60 to 70 years ago without medical intervention of any sort and long before stroke was associated with "risk factors." Thus, arguments by the alliance which attempt to convince readers that antihypertensive therapy has been effective in reducing the rate of stroke mortality must demonstrate a clear and significant change in the mortality rate trend and associate that change with known interventions. They must also explain why stroke mortality was declining for decades without medical intervention or changes in their accepted risk factors.

Despite the fact that the stroke mortality decline initiated many years before the advent of antihypertensive drugs and has been sustained in a function that does not

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[a] 1815,2084,2514,2522,2577,2611

reflect effects of medical intervention at all, alliance members nevertheless insist that antihypertensive drugs accelerated the decline. For example, 1977 AHA president, Harriet Duston[3301] said, "The death rate from stroke...has fallen a striking 50% in the last 20 years [1957-1977], and we think this is primarily due to a greater awareness of the problem of hypertension...and the fact that this condition can be effectively treated with drugs. Kannel and Thom maintained that "The dramatic deceleration around 1973, when major strides were being made in the detection and control of hypertension stands as testimony to the efficacy of control of hypertension in primary prevention of cardiovascular catastrophes."[1174] Kannel, Stamler and others said, "Hypertension control in particular is believed to have contributed greatly to the decline in cardiovascular mortality, particularly that mortality attributable to stroke and cardiac failure."[1083] Moser stated that "Great progress has been made in the management of hypertension over the past 30 to 35 years, with a dramatic decrease in stroke death rate.[2754] And Walker said, "Cerebrovascular mortality...began to decline much earlier (1952), after rising slightly from 1941 to 1951. ...the greatest reduction has occurred since 1963 with the most striking decrease in 1975, probably reflecting success of the current nationwide effort to treat hypertension more effectively."[2699,a]

Not only did the above authors (and many others) fail to present sound evidence in support of their conclusions, they did not seem very knowledgeable of the actual stroke mortality trends, particularly Walker whose article was an editorial in the New England Journal of Medicine. For example, (see Figure 9-4) the cerebrovascular mortality decline occurred many years earlier than he specified and it did not rise from 1941 to 1951. It rose from 1948 to 1949 as a result of the 6th ICD revision, but that was, of course, artifactual. Similarly, 1963 did not represent a year after which a unique decline occurred and there was certainly no "striking decrease in 1975." Levy[2834] maintained that "the steepest decline has occurred since the beginning of the NHBPEP in 1972 (a different date). He continued, "In five years the program has become the most exciting example of successful disease prevention." High praise for an unmeasurable effect.

Elsewhere, Levy[698] said, "Before the beginning of the NHBPEP, death from stroke was decreasing at approximately 1%/year, with a slight increase to 1.5% in the early 1970s. Since the inception of the program, the rate of decrease has risen to > 5%/year. Thus, the evidence indicates that the 49% decrease in stroke mortality rate over this period [1973-1984] can be attributed in large part to the improved attention to, and treatment of, hypertension." The reader is encouraged to review Figure 9-5 and its accompanying discussion to see how misleading was Levy's statement.

If an examination of Figures 9-4 and 9-5 and the accompanying discussion does not suffice to completely convince readers that antihypertensive drug therapy has had little or nothing to do with the stroke mortality decline, it is noteworthy to mention that a detailed investigation by Klag et al. found no relationship between the stroke trend after 1973 and the increased use of antihypertensive drugs.[1876] Moreover, in their review of population studies they found that the "majority of strokes occur in normointensives and in borderline hypertensives." To these may be added the following facts. In 1989 Kannel reported that stroke has increased in frequency during 30 years of Framingham experience[1842] and the Centers for Disease Control announced in the same year that hospitalizations for stroke had increased 51% from 1970 to 1986.[2756] (However, the actual increase appears to be 37% because there was an artifactual increase as a result of the 9th ILCD revision in 1979.

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[a] Levy[2834] said the steepest decline occurred since the beginning of the NHBPEP in 1972.

As Kannel illogically explained that increasing CHD morbidity and decreasing CHD mortality may be due to a reduction in "severity" of CHD, Wolf offered the same illogics with regard to stroke, i.e., there may be "a lessening in stroke severity with better control of hypertension."[1878] Again, how can one reason rationally that risk factor control leads to a greater incidence of a less severe disease?

The overall effects of antihypertensive drugs are badly clouded by the failure of researchers to thoroughly and objectively evaluate the positive and negative aspects of studies. Researchers constantly overemphasize certain outcomes and underemphasize other outcomes. For example, the Veterans Administration trial, reported in 1970, has been widely held as proving the worth of diuretics with respect to stroke, and having no negative effects on CHD.[2644] But while the difference between groups in CHD events was nearly zero, there were almost twice the number of CHD deaths in the treated group than in the untreated group.

Moser indicated that there are "at least" 50 antihypertensive drugs available today.[2079] In his review of the development and use of many such drugs, beginning in the 1940s, it would appear that only the diuretics which emerged in the late 1950s have sustained the years and proved effective in reducing hypertension. Most other drugs were either relatively ineffective, toxic or had undesirable side effects. One gets the distinct impression that there are no good drugs, all things considered, although Moser indicates otherwise.

Northcote concluded that of all the drugs available, diuretics and beta-blockers are the only drugs which have been shown to reduce mortality and morbidity with respect to stroke and congestive heart failure.[2082] While there is now substantial evidence that diuretics increase MIs and sudden deaths, especially in the elderly, Massie, nevertheless, recommended the use of those drugs for the elderly.[2611] And while beta-blockers are not sufficiently effective in reducing hypertension in the elderly, which, after all are the principal recipients of all drugs, they yield a substantial number of side effects such as fatigue, insomnia, nightmares, impotence, aggravated asthma or chronic bronchitis, increased peripheral vasoconstriction (worsening symptoms of peripheral artery disease), increased triglycerides and total cholesterol and decreased HDL.[2079,2082]

A comment by Oliver in 1986 regarding the U.K. Medical Research Council hypertension trial is most appropriate. "The recent results of the...trial in 17,354 men, 35 to 64 years old, over a period of five years (85,000 patient-years) produced no benefit on CHD incidence and only prevented one stroke in 850 mildly hypertensive patients (diastolic blood pressure 90 to 109 mm Hg). At the same time between 20% and 25% of the healthy men treated with a diuretic or beta-blocker developed adverse reactions sufficient to require their withdrawal from the trial. In other words, the risk of controlling the risk of mild-to-moderate hypertension is greater than the uncontrolled risk."[1734]

In another recent study Psaty et al.[3044] observed a most serious "withdrawal syndrome" of hypertensives treated with beta-blockers, i.e., a "transient" increased risk of myocardial infarction in patients with no prior history of CHD.[a]

Let us now summarize a few important phenomena that everyone accepts and then apply a little common sense. Everyone recognizes that stroke mortality had been steadily decreasing for many decades before the advent of antihypertensive drugs and

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[a] Side effects of antihypertensive drugs are many and some are serious to fatal. Reviews of side effects for various types of drugs can be found elsewhere.[3117,3118,3119,3120,3121,3122,3123]

the NHBPEP. Moreover, if one accepts the concept that the NHBPEP did accelerate the decline somewhat (although Figures 9-4 and 9-5 indicates that it did not), it is clear from Figures 9-4 and 9-5 that stroke mortality would have achieved the level obtained by current widespread drug usage a few years later at most. What are the ramifications of this outcome?

Undoubtedly, Levy and others would say that many lives were saved. However, the mortality trend data indicate that the absolute percentage reduction in deaths, if any, is quite small. But more importantly, the end result is by no means the same. In one case, the medical industry will have millions of people on antihypertensive drugs for the next 100 years. In the other case, stroke mortality would be insignificant without drugs and no one would require such drugs in the future. In effect, the medical industry will perpetuate an enormous cost to society for a service that will be completely irrelevant and unnecessary. Moreover, the side-effects of drugs will add an additional cost. As noted by Wilhelmsen,[2945] "The problem of drug-induced side effects is of special importance as a great number of people have to be treated in order to save relatively few lives." This becomes outrageous when we consider the fact that even fewer or no lives will be saved.

Cigarette Smoking

The alliance claims that cigarette smoking is a cause or promoter of all cardiovascular diseases. It's sister organizations also claim that cigarette smoking is a cause or promoter of lung cancer. Although cancer is not directly relevant to this review, it is nevertheless useful to show how the two groups use opposite criteria in linking cigarette smoking with these diseases and, in the process, contradict each other and themselves. By careful selection of specific data and the omission of other more important data, the alliance and its sister organizations have apparently convinced most physicians and the public that the cardiovascular and lung cancer mortality trends can be explained by the cigarette smoking trends. As will be seen, no such relationships can be shown when all of the data are analyzed.

In keeping with the proclivity of alliance members to compare different populations having numerous confounding variables, Friedman[3028] correlated the per capita consumption of cigarettes per state (estimated from annual state cigarette tax revenues) with the reported CHD mortality rates. The correlation in 1960 was .55. As emphasized in Volume 1, such correlations have essentially no meaning whatsoever. To illustrate one such inconsistency, Friedman showed California and New York to be nearly the highest per capita consumers of cigarettes and yet they were among the very few states whose CHD mortality rates were declining, rather than increasing, in 1960 and prior to 1960. Stallones[3027] agreed with this position, i.e., "Little information is available about regional variations in cigarette smoking, but a concordance between such variation and the geographic pattern of the mortality from IHD also does not seem likely."

Cardiovascular Diseases. Although cardiovascular diseases include abdominal and peripheral artery diseases as well as CHD and stroke, emphasis here is on the latter two diseases which define by far most of the cardiovascular deaths.

It is true that epidemiologic studies have shown that cigarette smokers have a higher blood cholesterol level than nonsmokers and apparently demonstrate higher "risk" of CHD, stroke and lung cancer. For example, Craig et al. reviewed 56 studies on smoking and found cholesterol levels in smokers to be about 8.3 mg, on average,

higher than in nonsmokers.[2248,a] And Wells reviewed 10 epidemiological studies and reported that the elevations in CHD risk among men and women smokers were 31% and 23%, respectively.[2199] But knowing what we know about "relative risk," these increases were probably trivial in terms of rate differences.

The practical effects of smoking on the probability of stroke are also subject to debate. Shinton and Beevers recently reviewed 32 studies and reported that the overall relative risk of stroke due to smoking was 1.5.[1880] Although these researchers listed the number of strokes occurring in each study, they failed to provide the number of individuals at risk, making it impossible to determine the importance of the relative risk values reported. However, they did indicate that "The overall excessive relative risk of 50% is modest by epidemiological standards..." We can safely say, therefore, that "modest" translates to "trivial."

It is also important to recall a statement by Ahrens before the 1977 Senate Select Committee, i.e., "Smoking doesn't lead to coronary disease or cancer in all smokers, but only a small percentage of them. The key question is 'which ones.'"[2435]

Most of the epidemiological data, therefore, is not impressive in condemning cigarette smoking as a major cause of CHD or stroke. The "acid test," however, is what has happened in the real world. In order to demonstrate a possible causation of the CHD or stroke mortality declines, it must be shown that the cigarette consumption decline was significant and occurred just prior to a parallel decrease in mortality. (The terms "possible" is used because even given such a state-of-affairs, a cause-effect relationship is still not proven.)

At the outset, we can dispense with the notion that cigarette smoking influenced the stroke mortality rate for three reasons. First, examination of Figure 9-4 shows that stroke mortality was decreasing continuously and linearly during the period (up to 1963) in which cigarette consumption greatly increased. Second, there was no observable, unique decline in stroke mortality after 1963 when cigarette consumption leveled off and declined slightly (Figures 9-4 and 9-5). And third, by far the most important declines in (per capita) consumption of cigarettes did not occur until after 1980, a point after which the decline in stroke mortality slowed, rather than accelerated.

Figure 9-6 presents the per capita consumption of cigarettes, the percentage of male and female smokers and the CHD mortality trends. The Surgeon General's Report on Smoking and Health was announced to the public in 1964 but while CHD mortality began its decline in 1964, cigarette consumption actually increased during a two year period following that announcement and remained above or at the 1964 level for four years. Subsequent to 1968, cigarette consumption decreased a few percentage points and then increased slightly. In the 11 years following the Surgeon General's report, the mean cigarette consumption was a mere 1.2% lower than it was in1964.

The only year after 1964 that cigarette consumption declined below the 1964 level

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[a] Wells cited Svenson et al. and Garland et al. as finding no differences in cholesterol levels, blood pressure or other risk factors between nonsmokers living with smokers and nonsmokers living with nonsmokers.[2199] One must also remember that nonsmokers tend to exercise more than smokers so the 8.3 mg difference observed may be due to exercise, as well as to smoking.

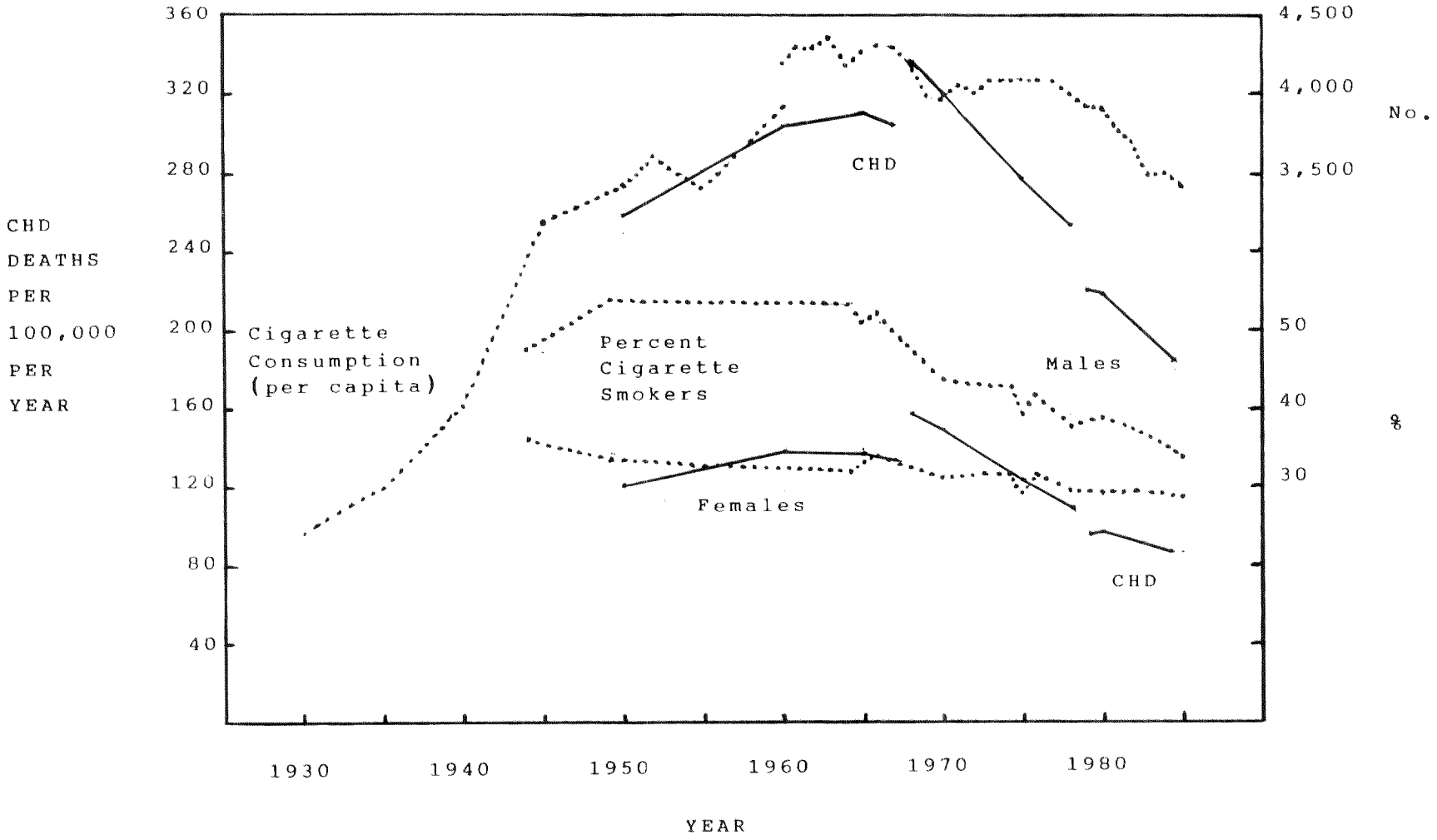

Figure 9-6. Age-adjusted CHD mortality rates by sex, per capita cigarette consumption (upper right)scale and percent of population as smokers (lower right scale) (adapted from Higgins and Leupker, 1988, NHLBI Working Group, 1981,[3068] Center for Disease Control, 1987[2828] and U.S. Statistical Abstracts)

was 1969, a full six years after the CHD mortality decline began. This fact indicates unequivocally that the former could not possibly have caused the latter. Moreover, the fact that cigarette consumption remained at a constant plateau for 12 years, while CHD mortality declined 23%, excludes completely even the possibility that the mortality decline was influenced even a small amount by cigarette consumption trends.

Some have maintained that the growing use of filter cigarettes after the Surgeon General's report was published may have impacted CHD rates. However, a Framingham report by Castelli et al.[3402] indicated that filter cigarettes had no influences on CHD rates.

It is important to emphasize that these data do not reveal even the slightest hint of an association between cigarette consumption and CHD mortality. While the subsequent discussion will include arguments by some alliance members that the percentage of smokers in the population decreased after the Surgeon General's report was announced, such arguments cannot override the per capita consumption trends for the following reasons. The alliance claims that, like cholesterol, the relationship between cigarette smoking and CHD mortality is graded and continuous, in effect, that CHD is dose-related to smoking. Thus, even though the proportion of cigarette smokers diminished (among men) after 1964, the fact that per capita consumption increased means that the remaining smokers became heavier smokers. If the CHD mortality rate decreased in the former, the same logic would demand that the CHD mortality rate increased in the latter. If anything, there should have resulted in a slight increase in CHD mortality from 1964 to 1967 which, of course, there was not.

A second reason is that the decrease in the proportion of smokers after the Surgeon General's report occurred exclusively in males. As can be seen in Figure 9-6, the percentage of female smokers was almost constant from 1964 through 1976 and yet, CHD mortality among females declined throughout that period. This point was also emphasized by Stallones.[3027]

A final consideration is that the data bases for determining percentage of smokers were derived from relatively small samples and, as noted by Stern,[2833] there is evidence that "systematic under-reporting" of cigarette smoking occurs.

In effect, it is absolutely unreasonable and literally beyond wishful thinking to claim that the CHD mortality decline was due, in part, to changes in cigarette consumption and/or proportions of smokers. But, as will be seen, alliance members have frequently made such claims because they are simply incapable of admitting that the real-world evidence runs counter to their studies and dogma.

Thom and Kannel[2826] more or less suggested in 1981 that the cigarette consumption trends were not consistent with the CHD mortality trends but they minimized the inconsistencies by distorting the facts and misleading readers. They said, "Between 1965 and 1978 the proportion of cigarette smokers decreased 35% among men and 10% among women." The National Health Interview Survey was the only agency which conducted surveys in 1965 and 1978 and they showed reductions of 26.6% among men and 11.1% among women.[3004] Thus, they overestimated the male reduction by 8.4% and underestimated the female reduction by 1.1%. More importantly, Thom and Kannel chose the period 1965 to 1978 to maximize the apparent reduction in smokers. Had they chosen the period 1964 (Surgeon General's report) to 1976, there would have been a reduction of 21% among males and <u>increase</u> of 1.6% among females, substantially different from what they projected to readers. This is a vastly more important period because it more accurately associates smoking trends with the initiation of the CHD mortality trends.

Thom and Kannel indicated that "the proportion of heavy smoking did not decline," a most misleading statement in view of the fact that heavy smokers among men and women almost doubled during their period of analysis.[2664,3011,3073]

In a 1984 article Kannel and Thom[1174] reported a smaller reduction in male smokers and a larger reduction in female smokers over a slightly longer period (1965-1980), i.e., 25% (instead of 35%) for men and 14% (instead of 10%) for women. Again, the National Health Interview Surveys showed reductions of 25% and 11.7% for males and females, respectively.[2828] Kannel and Thom discussed the same inconsistencies described in their 1981 article and concluded that "...an attempt to match trends in cigarette smoking by age, race and sex with the reversal in CHD mortality trends have not strongly linked the two." Indeed, such a statement is misleading because the two trends were not linked at all.

Stamler[579] attempted to show a correlation between cigarette consumption and CHD but his own data betrayed him. He reported that "a downward trend [in per capita cigarette consumption] has been recorded since the publication in 1964 of the landmark report to the Surgeon General on Smoking and Health," although his data, like Figure 9-6, showed that cigarette consumption was higher during the three years following the report. He claimed that there was a "sharp downturn in per capita consumption of cigarettes in 1967-69." But, as previously noted, that "sharp downturn" was a temporary reduction of a few percentage points and it was followed by a small increase in consumption for several years.

Stern[2833] referred to the slight decline in 1964 as a "sharp, though transient, drop" and said that "A steeper, more sustained decline occurred between 1968 and 1979 when anti-smoking commercials on radio and television were required by the FCC under the Fairness Doctrine. When these commercials were discontinued in 1970, per capita consumption rebounded, although it has remained well below its 1963 peak." But even a cursory examination of Figure 9-6 reveals that it was not at all "well below its 1963 peak" as much as 12 years later and only slightly lower than that occurring in the year of the Surgeon General's report.

Suppose cigarette consumption remained almost constant from 1963 to 1975, which it did, and suppose that subsequent consumption progressively decreased 30% to 1980. One can say <u>legitimately</u> that consumption decreased 30% from 1963 to 1980 but that is a misleading statement because the total drop occurred between 1975 and 1980, not between 1963 and 1980. Because specific cigarette consumption and CHD mortality trends do not correspond during the majority of the latter's decline, most alliance members have chosen to use misleading statements and/or the weaker "percentage of smokers" data to convince readers. For example, in 1981 Levy said that "since 1963, the per capita consumption of tobacco has declined by over 29%."[1846] In 1984 Levy and Feinleib reported that "since the appearance of the Surgeon General's report in 1963, there have been marked changes in the cigarette smoking habits of Americans. By 1975, the proportion of men smoking cigarettes had declined by 25%, from 53% in 1964 to 39% in 1975."[1401] Note that they omitted per capita consumption data <u>and</u> female smoking trends.

Mason et al.[2346] reported a 43% to 33% drop in smoking prevalence among "adults" from 1966 to 1980. Gillum, Folsom and Blackburn selected periods well after the 1964 CHD mortality decline as evidence that "the decrease in cigarette smoking likely was a contributor to the decline in CHD mortality."[2696] They cited the National Health Interview Survey as showing that smoking rates fell 3.6% to 38.3% in men and 2.6% to 29.4% in women between 1976 and 1980."

Fiore and his colleagues[1737] from the Centers for Disease Control devoted an entire article to cigarette smoking trends in the U.S., indicated that smoking was "the

single most preventable cause of premature death in the U.S.," and yet omitted smoking trend data that would support or deny that contention, i.e., their trend data were between 1974 and 1985. They also did not present per capita consumption data.

Alliance members also exaggerate small differences. For example, Kannel and Thom[1174] said, "It is noteworthy that before the Surgeon General's Report on Smoking and Health in 1964 there was a general and rapid rise in mortality from CHD. Subsequent to 1964, CHD mortality declined promptly and rapidly." In actuality, the four years before the Surgeon General's report saw a CHD mortality increase of only 2.7% and the four years following the report saw a reduction of only 2.1%. Not only can these changes not be considered "prompt and rapid," there was no association between these changes and cigarette consumption changes which, after all, is the only association of relevance.

It may be recalled from Chapter 3 that because major changes in the American diet greatly preceded the CHD mortality decline, alliance members called upon a wide variety of physiological latency periods in an attempt to reconcile the huge discrepancies. In effect, the alliance accepted the untenable assumption that a change in blood cholesterol level (via a change in diet) required a latency period of as many as 30 years for its effects to be observed on mortality trends, even though they maintain (contradictorily) that cholesterol is dose-related to CHD. Because the downturn in the percentage of male smokers and the extremely brief and shallow downturn in per capita consumption of cigarettes coincided with the decline in CHD mortality, the latency concept is nowhere to be found in the alliance's discussions and, instead, its members speak of "prompt and rapid" changes in mortality rates to changes in cigarette consumption rates. As we will see, the long latency period will once again be called upon to explain the discrepancy between changes in cigarette consumption and changes in lung cancer mortality trends.

The 1981 NHLBI Working Group[3067] emphasized that "persons who cease smoking experience a rapid decline in their risk of atherosclerotic disease." If one carefully examines Figure 9-6 one can see that the significant and continuous decline in per capita consumption of cigarettes began in 1978. The sudden downward trend from a horizontal trend cannot be seen to have any affect whatsoever on the CHD mortality trend which was well underway before the change in per capita consumption of cigarettes. While one can overlook this major discrepancy in an effort to convince others that the cigarette smoking and CHD declines were associated, the discrepancy is scientific evidence against a cause-effect association.

Finally, it is noteworthy that Robinson et al.[1703] followed 978 patients with first myocardial infarctions who entered a hospital from 1980 to 1985. They observed that "...smokers had a better prognosis than non-smokers."

Lung Cancer. Formal recognition of the possible relation between cigarette smoking and lung cancer apparently occurred in the early part of this century. However, it is generally acknowledged that the first serious research on this issue was begun in the 1940s and 1950s by such investigators as Wynder and Graham[3064] and Levin et al.[3063] While these investigators reported that smoking prevalence was higher in lung cancer patients than in "control" patients, it is often overlooked that the differences between the two groups were often not very substantial. A study of lung cancer among Chinese in Hong Kong is a very recent example, i.e, 92% of lung cancer patients smoked, but a very large 73% of matched control subjects without lung cancer also smoked.[2952]

In 1957 the U.S. Surgeon General issued the first government statement on smoking and health.[3038]

"The public Health Service feels the weight of the evidence is increasingly pointing in one direction; that excessive smoking is one of the causative factors in lung cancer."

That was followed in 1959 by another statement, i.e.,

"The weight of the evidence at present implicates smoking as the principal factor in the increased incidence of lung cancer."

While the above statements were something less than emphatic, the 1964 Surgeon General's report left no doubt that the government fully believed that cigarette smoking was harmful to health. For example, the report said, in part,

"Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction... The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking."

The reader should particularly note the implications of the last sentence which virtually everyone accepts in one context and rejects in another. Let us re-phrase the sentence to leave no doubt what it means. The longer a person smokes and the more cigarettes per day a person smokes (both relate to "dose") the greater the probability of his developing lung cancer. When smoking is discontinued, the probability of developing lung cancer then diminishes. This statement clearly describes a continuum whereby an increment in smoking and an increment in nonsmoking gradually increases, and decreases, respectively, the probability of developing cancer.

There is no doubt that there must be a lag or latency period between the initiation of smoking in first-time smokers and the development of lung cancer, assuming that cigarette smoking does indeed cause lung cancer. Clearly the lag period must vary in length since some people develop lung cancer at a very early age and some develop it at a very old age. However, because lung cancer is universally considered to be a smoking dose-related disease (a continuum) and because the chances of lung cancer development diminishes upon the cessation of smoking, the latency concept is totally inconsistent with the dose concept after the original latency is traversed and the increase in lung cancer mortality rate is initiated. For example, suppose 50% of a population has been smoking for 30 years and that the lung cancer mortality rate has been increasing for 5 years. If the dose concept is accepted, it is totally illogical to then say that a significant reduction in smoking (say, 50% to 40% in 5 years) will require another 25 years for this decline to be reflected in the lung cancer mortality rate. Theoretically, the decline should be observable one year after the smoking decline begins. More likely, two or three years would be required to transcend the perturbations in vital statistics which are influenced by a host of factors. Put in the words of the Surgeon General (and the alliance in general), when a significant proportion of the population ceases to smoke, "the risk of developing lung cancer diminishes." Thus, the development of lung cancer will be delayed or eliminated in this group and those effects should be observable in the annual statistics, not 20 to 25 years later.

It is hoped that the reader fully comprehends that a latency period is a logical prelude to a dose-related disease before the disease emerges but an illogical construct afterwards. The alliance either does not understand this logic or it simply ignores it in order to "explain" mortality trends in terms of risk factor trends. Latency periods were assumed to be fairly short in the 1970s when cigarette smoking was on the decline and the alliance was certain that lung cancer mortality would soon decline. For example, Gio Gori, deputy director of the National Cancer Institute, stated in 1976 that "If everybody stopped smoking today, we would not conquer lung cancer

immediately. It would take about 10 years."[2936] Because lung cancer mortality continued its strong upward climb during the 1980s, despite long-term downward trends in smoking, latency periods were then assumed to be 20 or more years (e.g., Horm and Kessler[3029]). Let us now examine the actual mortality and smoking statistics.

Figure 9-7 presents three sets of data. The solid curves depict the age-adjusted lung cancer mortality rate trends for males and females since 1930. The upper dotted curve indicates the per capita consumption of cigarettes during the same time period. And the lower dotted curves show the percentage of males and females who smoked cigarettes since 1944. Not shown are two additional trends. First, filter-tipped cigarettes emerged in the 1960s and low-tar and low-nicotine cigarettes appeared in the 1970s.[3011] Both theoretically diminished "slightly" the development of lung cancer.[3005,3011,3069] However, a simultaneous trend took place which tended to reduce or eliminate the benefits of the low-yield cigarettes, i.e., the percentage of heavy smokers almost doubled from 1965 to 1980.[2664,3011,3073] One author guessed that the heavy smoking trend was due to low-tar smokers compensating for the low-tar by smoking more cigarettes.[3073] Another author guessed that the heavy smoking trend suggested "that the bulk of the smoking cessation [after 1965. See Figure 9-7] may have been among lighter smokers."[3011] Although there is apparently no evidence to support either guess, the matter may be somewhat academic because overall lung cancer mortality rates should be more a reflection of per capita consumption than of the percentage of smokers. Nevertheless, it is worthwhile noting how the alliance has used the various trends to explain the lung cancer trends.

One cannot determine from Figure 9-7 the exact "latency" period between exposure and disease because the per capita consumption and the lung cancer curves are based on different dimensions. Thus, the vertical distance between the two curves is arbitrary and that distance obviously greatly affects the horizontal distances as well. On the other hand, the overall trends at given points in time can be compared. For example, the per capita consumption curve was upward until 1965, after which it undertook a slight decline until 1975 and then began a steeper decline. Lung cancer mortality among males, although continuing to increase, appears to be approaching an asymptote. Even if we assume that it will begin to decline by 1990, the dose-related concept is simply incompatible with the fact that 25 years was required for a reduction in smoking to cause a reduction in lung cancer mortality, particularly as the percentage of smokers and the amount of tar and nicotine also diminished. The fact is that the lung cancer mortality trend cannot be explained by the per capita consumption trend. To assume that it does is tantamount to saying that if all smokers ceased smoking in 1965, there would still be no leveling off and downward trend in lung cancer mortality until 1990 because of the latency period. It seems unlikely that anyone would agree with this alternative and certainly it is incompatible with the concept that smoking cessation diminishes the risk of lung cancer. Thus, it is illogical, inconsistent and boring to suggest that the per capita consumption trend explains the lung cancer mortality trend by attributing a very wide time differential to a hypothetical and untenable latency period.

It is not known whether alliance members are unaware of the illogics of their arguments or whether they simply ignore logic altogether in order to preserve the risk factor concept. Consider, for example, the following statement by McGinnis, Shopland and Brown, all from the U.S. Department of Health and Human Services: "Current incidence rates for smoking-related diseases tend to be a function more of past than current levels of tobacco consumption because of the long latency period between onset of exposure and disease. The decline in smoking prevalence since 1964 are beginning to be reflected in lower mortality rates for the leading smoking related killers."[2664] Since McGinnis et al. published their article in 1987, they apparently accepted a latency period of 23 years for "the leading smoking related killers" which are, according to the alliance, CHD and lung cancer. Their statement is completely dumbfounding because it is universally recognized that the CHD mortality rate

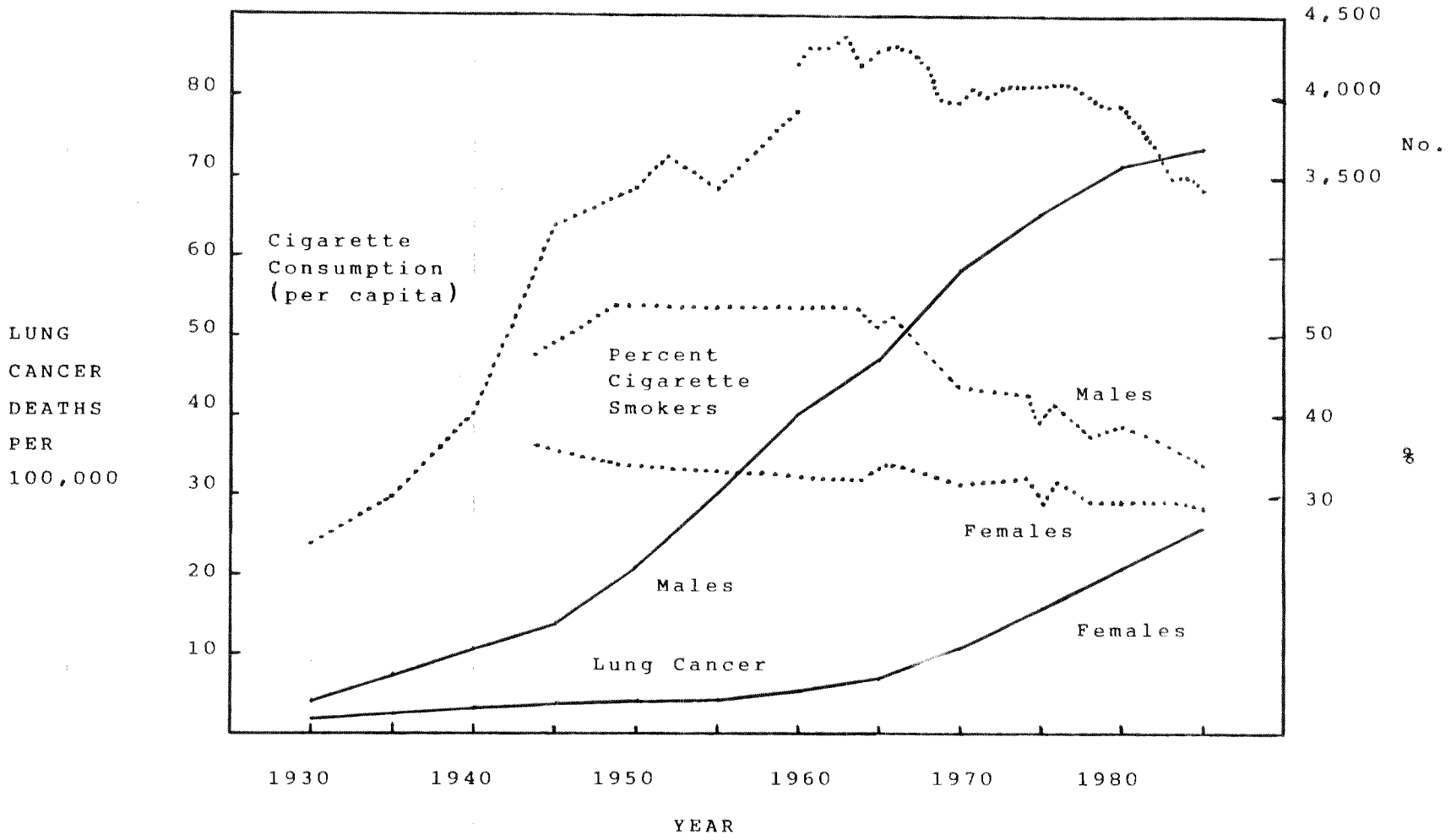

Figure 9-7. Age-adjusted lung cancer mortality rates by sex, per capita cigarette consumption (upper right scale) and percent of population as smokers (lower right scale) (adapted from American Cancer Society, 1990,[2835] NHLBI Working Group, 1981,[3068] Centers for Disease Control, 19872828 and U.S. Statistical Abstracts)

initiated a decline in 1964, not 23 years later. Moreover, while a deceleration of the lung cancer mortality occurred during the 1980s (Figure 9-7), there is not yet a mortality decline as indicated by McGinnis et al. A simple examination of Figures 9-6 and 9-7 reveals that one absolutely cannot claim a latency period for both CHD and lung cancer and, although a latency period is the only possible explanation for the fact that lung cancer mortality continues to rise 20 years after the decline in smoking, it is a scientifically untenable explanation.

Warren Winkelstein[3005] calculated lung cancer mortality increases of 6.7%, 4.6% and 2.2% for the succeeding periods, 1950-59, 1960-69 and 1970-77, respectively, and concluded that "the time trend in age-adjusted lung cancer mortality in men appears to reflect the declining per capita exposure to tobacco tar while the time trend in women does not." In addition to the fact that Winkelstein's third period was shorter than his first two periods, which yields improper comparisons, if the reader will align a ruler from the 1950 point on the male curve in Figure 9-7 to the 1975 point, he/she will note that the "curve" between those points is as much a straight line as is ever observed in vital statistics. Moreover, even though the death rate increase was linear through that period, the percentage increase declined simply because the denominators used to calculate percentages become larger as the death rate increases. For example, if the death rate increase is constant at 10 per 100,000 per decade, then the percentage increase from 40 to 50 is 10 ÷ 40 = 25% and the percentage increase from 50 to 60 is 10 ÷ 50 = 20%. Thus, it is misleading to focus on percentage increases when, in fact, the absolute increase remains constant (or even increases).

In a 1977 MMWR report[3069] it was stated that "In women, whose cigarette consumption has been rising rapidly in the past 30 years [1947-1977], lung cancer mortality continues to rise at an increasing rate." Again, examination of Figure 9-7 shows that lung cancer mortality in 1977 was not "rising at an increasing rate (implying acceleration), but rather rising at a constant rate. In addition, another MMWR report[2828] published 10 years later in 1987 presented all smoking surveys conducted from 1944 to 1986. The dotted lines in Figure 9-7 represent a plot of those surveys as presented by the MMWR report and, as can be seen, there is no indication of a "rapid rise" in cigarette consumption among women during the period 1947-1977. In fact, the surveys conducted by a number of different agencies, all show that the percentage of female smokers actually declined somewhat during that period. It is true that the percentage of heavy female smokers (i.e., 25 or more cigarettes per day) increased from 13 to 23% from 1965 to 1985,[2664] but it is also true that the quantity of tar and nicotine absorbed per cigarette decreased during that period. Thus, these counter trends more or less neutralized each other.

Horm and Asire[3071] examined the lung cancer mortality trends from 1969 to 1978 and noted that the death rate increased for all age groups except 35-44 in men and for all age groups in women. They concluded that "If these trends continue, the data suggest that the total incidence rates for men and women will be equal by the year 2000." One need only glance at Figure 9-7 to know that their prediction is a little more likely to be realized than being struck by lightning. The lung cancer mortality rate among men would have to decrease by 33% and the rate among women would have to increase 100% over the next 9 years for that prediction to come true.

The implication in Horm and Asire's statement is that the decrease and increase in mortality among women and men, respectively, for the age group 35-44 would result in major trend changes from 1978 to 2000 as that age group progressed to the older age groups. But such major trend changes are by no means inevitable or even likely to occur simply because of the specific trends observed for one age group for one short period of time. The lung cancer death rate is very low for the 35-44 age group and the slightest change among females can cause a small positive or negative "trend." For example, the mortality rates for females were 6.8, 6.4, 6.9 and 6.7 for the years 1975, 1976, 1977 and 1978, respectively. While the overall trend from 1969 to 1978

was up a total of 1.1 per 100,000, it was essentially constant for the last four years. These data hardly provide a solid basis for their prediction.

Figures 9-8 and 9-9 show the lung cancer mortality rates for males and females by age group and by decade.[2735] These data derive from the U.S. Vital Statistics and are somewhat different from those presented by Horm and Asire and those by the American Cancer Society (Figure 9-7) because the latter age-adjusted their data to the 1970 population, while the U.S. Vital Statistics data are adjusted to the 1940 population. However, these different adjustments do not affect overall trends. As can be seen, with the exception of the two oldest groups, the death rates among males under 74 years appear to have asymptoted through the 1980s. A definite downward trend can be observed for 35-44 year-olds but, as already noted, the rates are so low that the trend is not very meaningful and it cannot be assumed that the same trend will be reflected in the older ages as time passes.

The mortality trends among females are somewhat inconsistent. The upward climb during the 1970s and/or 1980s is modest for the 85 + group, steeper for the 75-84 group, steeper yet for the 65-74 group, then considerably less steep for 55-64 and 45-54 groups and essentially constant for the 35-44 group. While one can speculate what these inconsistencies mean, they cannot be adequately explained in terms of cigarette consumption trends. For example, Figure 9-7 shows that the percentage of female smokers has decreased only slightly since 1964. However, if one selects 1965 as a starting date, a somewhat greater decrease is apparent. Studies by the National Health Interview Survey from 1965 to 1987 provided trends for age groups. Figure 9-10 shows that the percentage of women who smoke has been decreasing among women under 65 years of age over the last 13 to 22 years. If we assumed that cigarette smoking is a dominant cause of lung cancer, and that a latency period is required, then these trends would predict that lung cancer mortality among females will decrease by the year 2000, not increase substantially as suggested by Horm and Asire. But no such trend is underway. In actual fact, the totality of Figure 9-10 and 9-7 clearly demonstrates an inverse relationship between cigarette consumption and lung cancer mortality.

Winkelstein[3005] not only accepted a long latency period as an explanation of why changes in lung cancer mortality do not soon follow changes in cigarette smoking, he also seemed oblivious of female smoking trends. In 1985 he said, "We believe that the evidence presented here...conclusively indicates that declines in lung cancer mortality are occurring in young American men as a result of the decreased prevalence of smoking among them and the reduction in the average tar content of American cigarettes. The decline will be extended to older age groups if successive cohorts continue the downward trend in smoking. Furthermore, there is reason to believe that the same trend can be realized among women if the downward trend in smoking prevalence can be extended to them." As can be clearly seen in Figure 9-10, smoking trends among all women under 65 have been downward since 1965.

In discussing smoking trends, one must not lose sight of the fact that many young people quit smoking after some initial "experimental" period and some people initiate the smoking habit years later.[a] Therefore, the smoking behaviors of youthful groups cannot possibly be an accurate barometer of the behaviors of older groups in the forthcoming decades. For example, a 1986 survey of Rhode Island public high school students revealed that a considerably higher percentage of females smoked than did

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[a] It may be noted in Figure 9-10 that the percentage of persons who smoke decreases with age after 34 years. A large survey by Hammond and Garfinkel[3065] obtained the same findings in 1961.

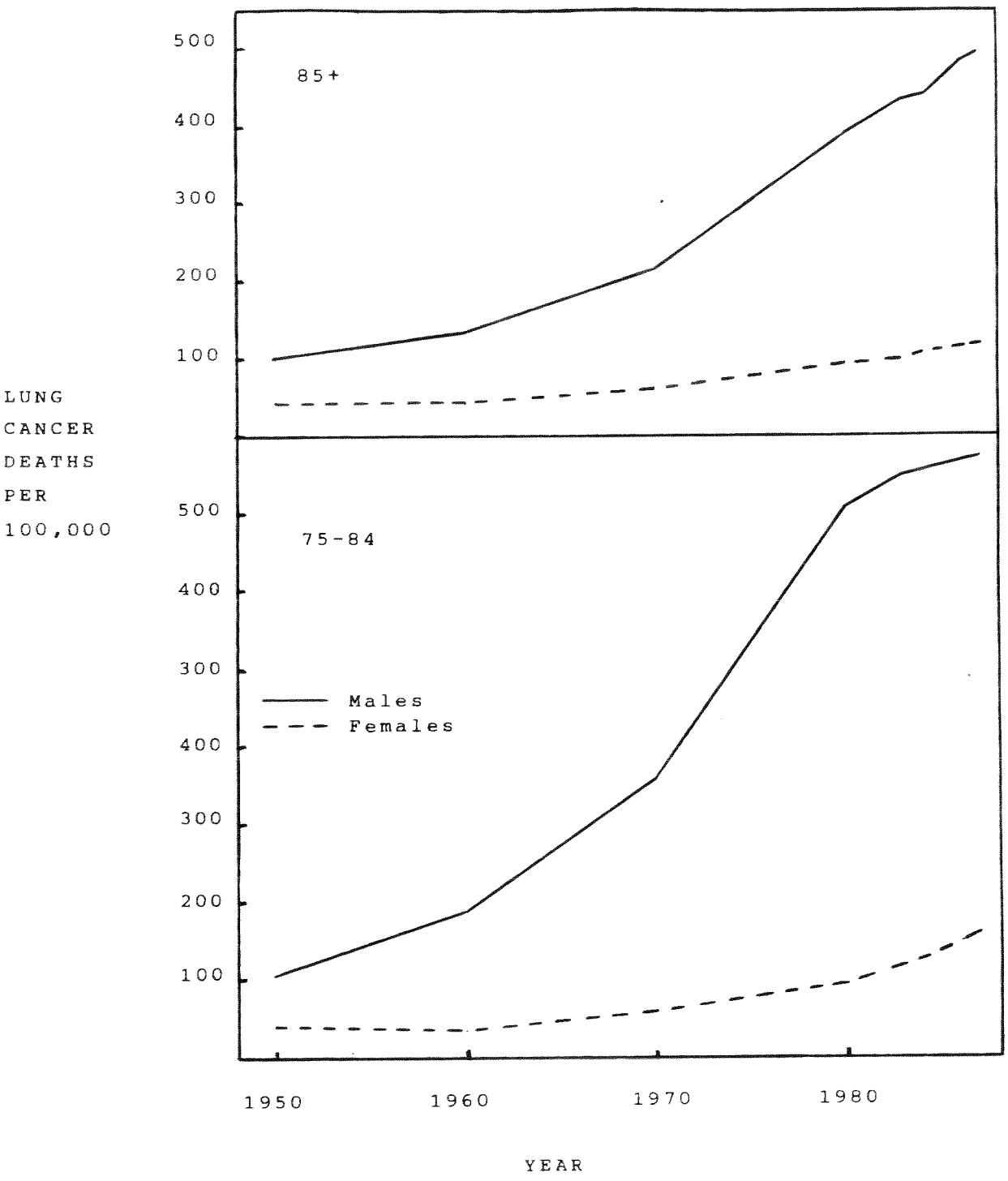

Figure 9-8. Lung Cancer mortality by age group in white males and females over age 74 (adapted from National Center for Health Statistics, 1989[2735])

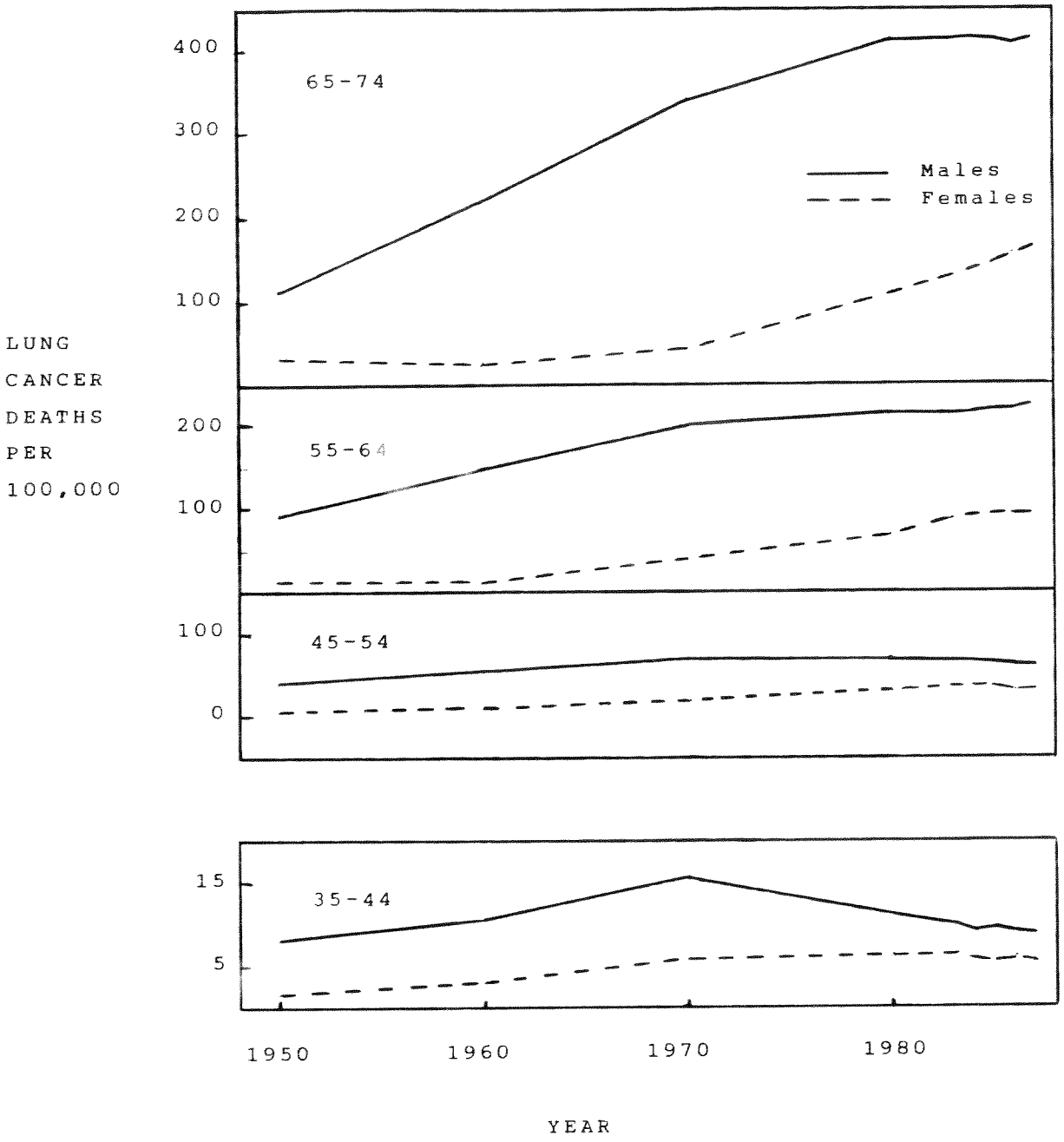

Figure 9-9. Lung cancer mortality by age group in white males and females 35 to 74 years (adapted from National Center for Health Statistics, 1989[2735])

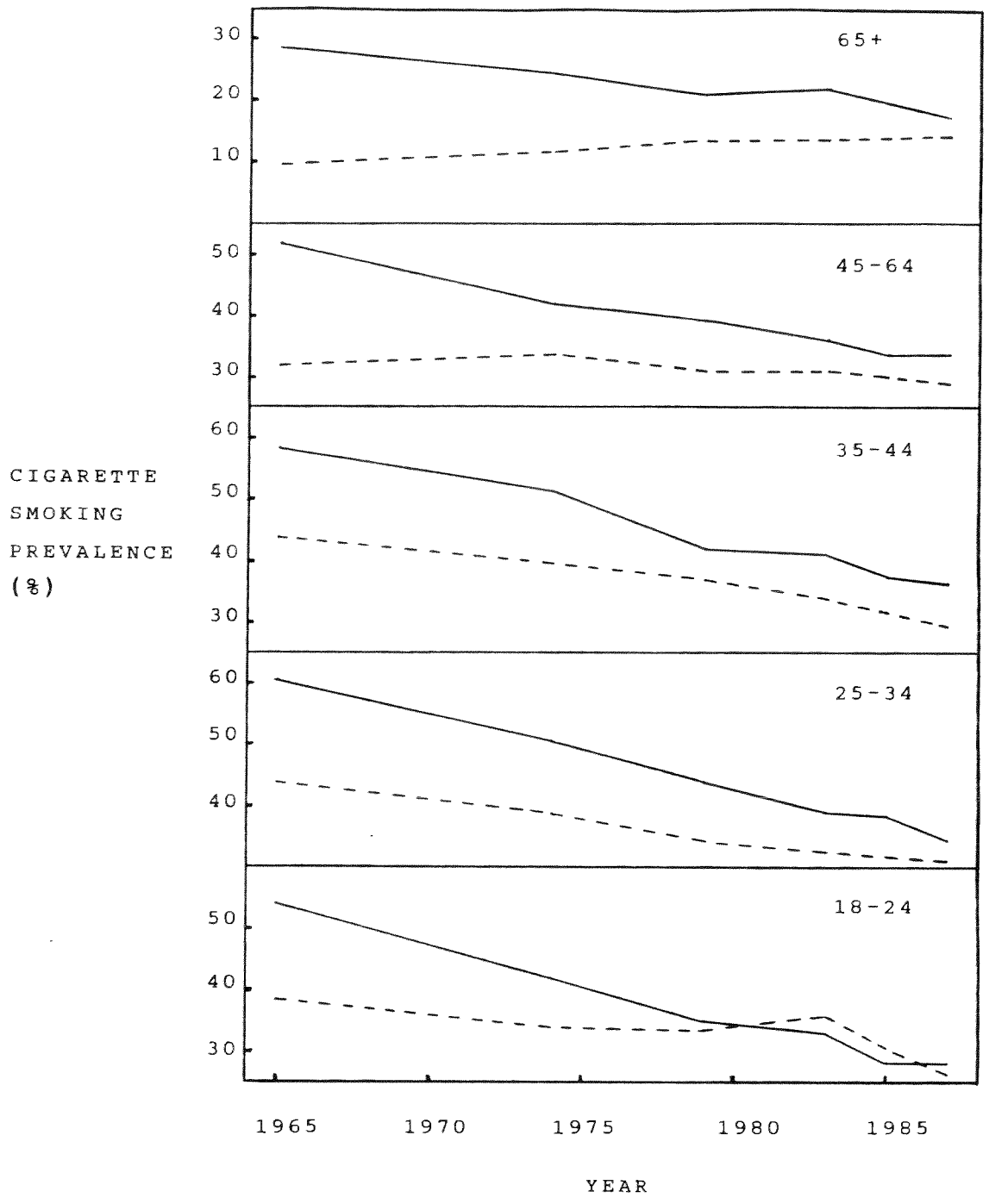

Figure 9-10. Percentage of the population who smoke cigarettes by sex and year (adapted from National Center for Health Statistics, 1989[2735])

males (26.5% vs 17.5%).[3070] A slightly higher smoking habit among 18-24 year-olds in recent years can also be seen in Figure 9-10. However, if the trend among 18-24 year-olds over the years were a predictor of trends in the coming decades, then one should see identical proportions of smokers for 25-34 year-olds at, say, 1980 as for 18-24 year-olds at 1975.

The reduction of smoking among males is much steeper than that of females for all age groups but this trend would be expected since a much higher percentage of males smoked before the population was told of the dangers of smoking. This differential change is quite common in human behavior.

Figure 9-7 shows that per capita cigarette smoking has decreased about 22% since the peak year of 1963 and the trend continues downward. In addition, the percentages of males and females who smoke have been declining since about 1965. Yet, the lung cancer mortality rates continue upward for both sexes. The minimum latency periods that can be used (albeit illogically) to explain this discrepancy is more than 20 years and may eventually become 30 years. One wonders how long this period must become before even the alliance recognizes the absurdity of it all. One also wonders why the alliance ignores the fact that almost twice as many Japanese males smoke than American males and yet have slightly more than half the lung cancer mortality.[2800,2835]

A Final Comment. As indicated earlier, the results of retrospective and prospective studies--and even clinical trials--cannot override real-world facts. And the real-world facts do not in the least suggest that changes in the so-called major risk factors have yielded observable changes in relevant mortality rates. Moreover, the accumulating evidence that CHD and cancer morbidities are increasing, rather than decreasing, completely obliterates the notion that benefits are being derived from long-term reductions in risk factors. The many attempts by the alliance to interpret the real-world data in ways which make them appear to support the risk factor concept are obvious examples of incompetence or extreme bias, neither one of which belongs in the field of medical science. One such recent attempt by Assistant Secretary for Health James Mason and Deputy Assistant Secretary for Health Michael McGinnis[2942] is a case in point. They said, "During the 1980s, death rates declined for three of the leading causes of death among Americans: heart disease, stroke, and motor vehicle crashes. Much of our progress is attributable to reductions in risk factors. The more than 40% decline in heart disease mortality since 1970 reflects dramatic increases in high blood pressure detection and control, the decline in cigarette smoking and increasing awareness of the role of blood cholesterol and dietary fat. Stroke death rates, which dropped by more than 50% in the same period, also reflect gains in hypertension control and declines in smoking." Not only is this statement false, it is also poorly conceived. First, the reduction in motor vehicle crashes has nothing to do with medicine or the Department of Health and Human Services and is, therefore, an irrelevant topic. Second, heart disease mortality is not affected by "increasing awareness of the role of blood cholesterol and dietary fat." And third, dietary fat per se does not increase blood cholesterol level or accelerate the development of CHD. Of course, as the foregoing sections have shown, the CHD, stroke and lung cancer trends absolutely cannot be explained by changes in risk factors.

BLOOD CHOLESTEROL AND CHD IN WOMEN

In 1989 the AHA held the first Conference on Women and Heart Disease.[2717,2751] In describing the conference for Internal Medical World Report, Odom Fanning[2751] called CHD among women, the "silent epidemic," despite the fact that the CHD mortality rate among women is now (1987) 76.9 per 100,000, 33% lower than it was in 1949 (114.6) when the ICD introduced the modern definition of CHD and provoked the so-called (on paper) epidemic. This fact, together with a statement at the conference by 1988 AHA president, Bernadine Healy, i.e., "Heart disease has been the number one

killer of women for 81 years,"[2517] clearly indicate that there was no CHD epidemic among women in the past and there most certainly is no "silent epidemic" today.

Fanning cited Castelli as saying that "one of the greatest myths of American medicine is that cardiovascular disease is an affliction of men but not women. This 'sexual bias' may stem from the fact that very few women develop the manifestation of cardiovascular disease before menopause." This writer is aware of no such myth. It was perhaps created by Castelli at the conference to initiate a fear campaign among women. Knowledge of CHD rates among women and time of onset have been known within the medical community for decades.

Before discussing the relationship between blood cholesterol and CHD in women, a realistic examination of the CHD lag in women should be addressed. Robert Levy told Senator McGovern's Senate Select Committee on Nutrition and Health in 1977 that women lagged men in overt CHD by at least 10 years.[288] More recently, many authors have reported that angina pectoris, heart attacks and sudden deaths typically occur 10 to 20 years later in women than in men (e.g., Glazer,[115] Hartz,[2745] Hazzard,[2360] Perlman,[2752] Weis et al.[2748]). After 30 years of following Framingham women, Kannel reported that "Women lagged men in incidence by 10 years for CHD in general" and that "for MI and sudden death women had a 20-year advantage over men."[787] Hazzard[2360] pointed out that the extra years were even enjoyed by women with familial hypercholesterolemia. Sullivan also noted this advantage in menstruating women "heterozygous for FH in the face of grossly elevated cholesterol."[2254] (Sullivan earlier had introduced the concept of iron loss via menstruation as a possible protective factor against CHD[2253]).[a] Perlman stressed that CHD mortality among women "remains a rare event before 65 years of age.[2752] Thus, most women enjoy all the middle-age years and enter the elderly years without symptomatic CHD.

Bush reported a statistic which appears ominous when divorced from the above information. She said, "The probability of a woman's dying of cardiovascular disease is one in two."[2751] Let us state further that the probability of a woman dying of all-causes is one in one. Although this latter statistic is far more ominous, one might laugh it aside with the response, "of course." However, when one readily accepts the concept that death is the inevitable outcome of old age, it should not be terribly difficult to accept the concept that cardiovascular death is the likely outcome of old age.

While it has always been a goal to prolong life, the prolongation of life today is a far different matter than that pursued 30, 50 or even 70 years ago. In the early decades of this century, large number of people died of various diseases prior to experiencing middle and old ages. Today, the vast majority of people reach and exceed middle-age. The life expectancy of women is currently nearing 80, an age that is usually permeated with a variety of physical, physiological and/or neurological problems and that typically prevents one from enjoying most of the normal pleasures of life. If blood cholesterol-lowering can delay the onset of overt cardiovascular disease, and by now the reader should reject that notion, the best that could be expected from a "campaign against CHD in women" would be to increase life expectancy to perhaps 83 or 84 years and thus a few years of uncomfortable and unpleasurable life.

In men CHD eliminates 5 to 15 years of productive and pleasurable life. Conquering CHD would theoretically protect those years. But beyond 75 years for both men and women the problem of medicine is not so much the conquering of

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[a] Alternatively, others such as Bush, proposed that higher levels of HDL, produced in menstruating women, comprise the protective factor.[2461]

degenerative diseases as it is the conquering of degeneration itself. Somewhere this writer read that bypass operations do not necessarily increase the remaining years of life but rather increase the life in the remaining years. Unless medicine can increase the life in the elderly, there is little point in increasing their years.

In any event, it has been amply shown in Chapter 8 and elsewhere that atherosclerosis occurs in all populations including vegetarians. Those who insist that therapy will delay the onset of overt CHD and thus reduce the nation's costs associated with this disease do not think logically. Once the initial (theoretical) delay has occurred, the costs will be even greater for both CHD and cancer because greater numbers of people will have reached, and will continue to reach, the elderly ages. Those who claim that atherosclerosis can be reversed cling to questionable angiographic studies and ignore real world data which show that atherosclerosis progresses in all populations, regardless of their diets or cholesterol levels.

Even without reviewing the evidence linking blood cholesterol with CHD in women, the above discussion indicates that a campaign to engulf American women has highly suspicious signs of ulterior motives, principally the motive of increasing the medical industry's income. Why, for example, would Castelli say that "Virtually all of the heart attacks that occur in American women under the age of 40 occur in those whose cholesterol and triglyceride levels place them in the upper decile of an age-matched group of women,"[1642] when he also emphasized that "In the Framingham Heart study, only six of 1,600 premenopausal women died of CHD."[2751] His second statement clearly indicates that CHD is essentially nonexistent in women under about 45 to 50, so what is the point of his first statement?

Blood Cholesterol and CHD

The principal data relating blood cholesterol with CHD in women derive from the Framingham study. Figure 9-11 shows the CHD morbidity ratio as a function of cholesterol level after 14 years of follow-up at Framingham. Castelli and Anderson indicated that "the total cholesterol level was an important and independent predictor of CHD in those aged under 50 years...[but]...it no longer predicts the risk in those aged over 50 years."[1531] But the reader should note that the significance associated with those under 50 years was due entirely to those having cholesterol levels above 279 mg, representing a very small percentage of the female population. The morbidity ratio remains at or below 100 across most of the female cholesterol range. Of course, one can compute a regression equation which yields a highly significant coefficient (slope) but such a coefficient would be spuriously influenced by the morbidity ratios of the two highest cholesterol intervals and would not at all be representative of perhaps 90% of the cholesterol range (and female population).

Kannel published the cholesterol-CHD relationship for women after 30 years of Framingham follow-up (Figure 9-12, ignoring the dashed curve for the moment). The reader should note that Kannel's cholesterol scale used intervals of 30, rather than the 20 used by Castelli and Anderson, and he also eliminated an interval at the low end. This procedure accomplished two things. First, if the CHD rate at the lowest end of the first very large interval (84 mg) is lower than at the upper end of the interval (204 mg), then collapsing that entire range into one interval will result in a steeper apparent slope from that interval to the next (205-234). But that is an artifactual slope, generated by improper scaling.

Second, the first interval comprises about 45% of the American female population. This means that one of the five cholesterol intervals used by Kannel represented 45% of the population and the remaining four intervals represented the remaining 65%. But, of course, there is more exaggeration to come.

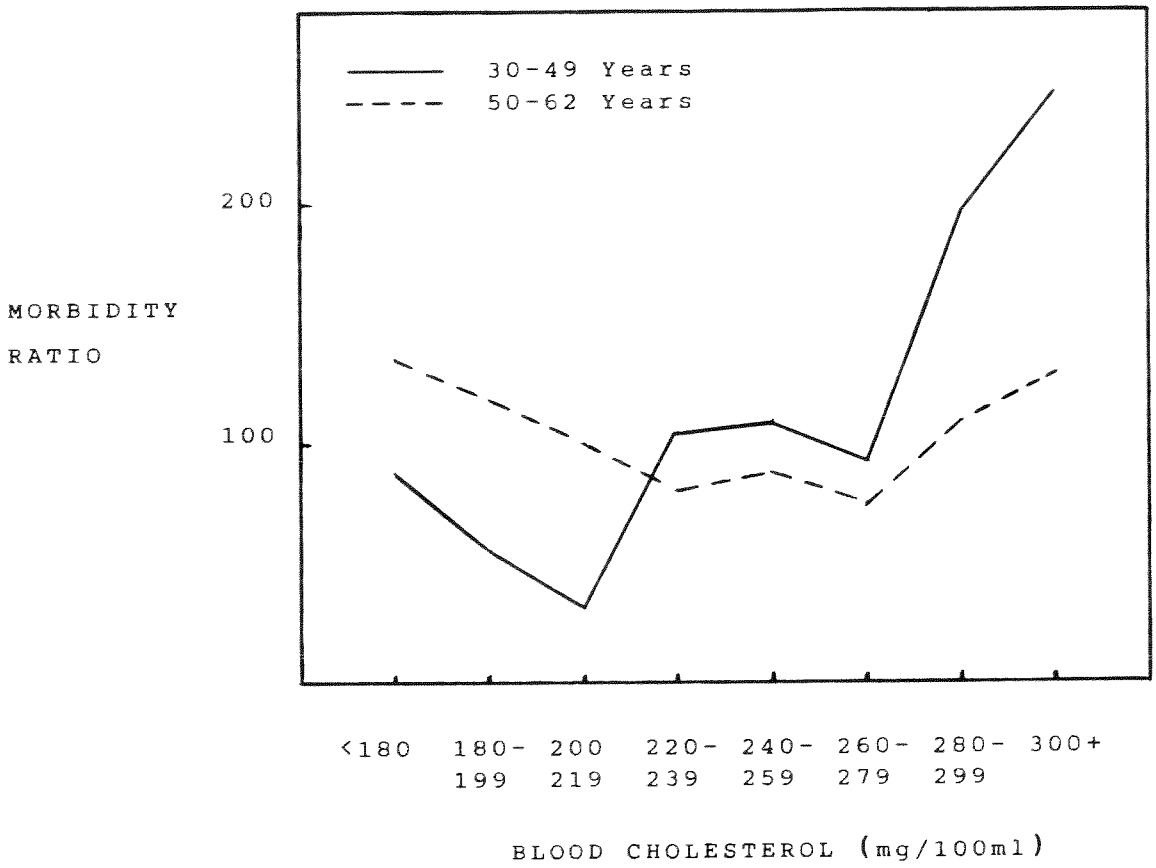

Figure 9-11. CHD morbidity ratio by cholesterol level in women after 14 years (adapted from Castelli and Anderson, 1986[1531])

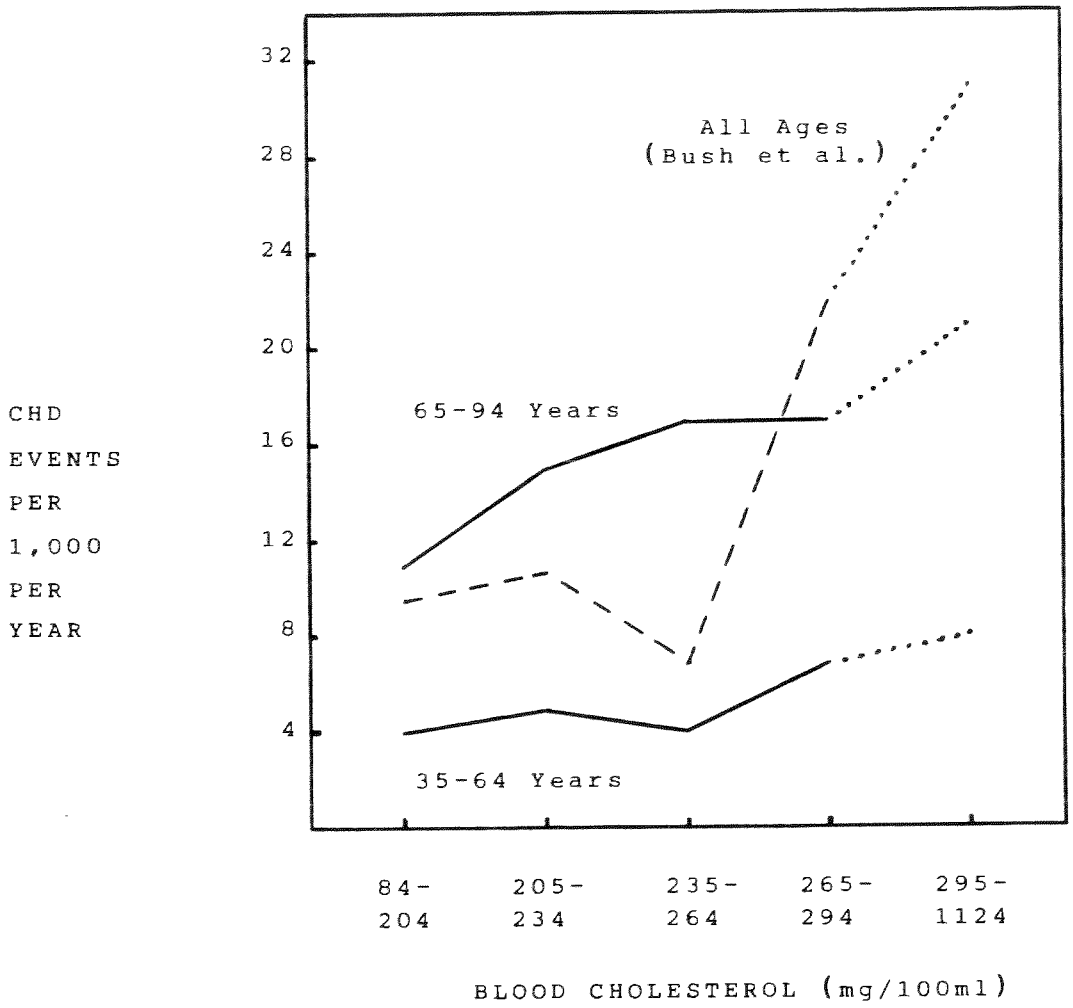

Figure 9-12. CHD event rate by cholesterol level in women after 30 years (adapted from Kannel, 1987[787] and Bush, 1988[1618])

The final interval used by Kannel was not only the result of collapsing many equal intervals into one, greatly exaggerating the slope, it also represented 5% of the female population. What we have, therefore, are essentially no differences in CHD rates among women across 90 to 95% of the cholesterol range (about 180 mg to 294 mg).

The dashed curve in Figure 9-12 was produced from data published by Trudy Bush.[1618] While she referred to her data as deriving from Framingham, it is clear that they are wildly different from the data presented by Framingham investigators. It is apparent that her data are incorrect.

In 1989 Castelli et al.[2292] published the same 30 year follow-up data of Framingham but presented the data in terms of five age groups, rather than the two groups used by Kannel (Figure 9-13). Castelli et al. also used a cholesterol scale that suggests they used the midpoints of Kannel's intervals, rather than disclose the entire interval. It should be remembered, therefore, that the 280 mg point on the scale represents the interval, 265 to 294.

Unless one deals with large amounts of data, e.g., data from 20,000 people, we can expect some ups and downs in curves along a dimension that is theoretically continuous and either upwards or downwards. That is the statistical nature of small amounts of data. With that thought in mind and ignoring the final interval of > 294 mg, there is no real evidence in Figure 9-13 that the CHD rate increases with increases in blood cholesterol.[a] For all practical (and clinical) purposes, the "curves" for the two youngest groups of women are effectively flat. One cannot focus on the slope from 250 mg to 280 mg in the 55-64 age group as evidence, and simultaneously dismiss the zero slope below 250 mg. One also cannot focus on the slope from < 205 mg to 250 mg in the 75-84 age groups as evidence and simultaneously dismiss the even greater downward slope beyond 250 mg.

One of the five curves (ages 65-74) conforms to the lipid hypothesis but even that curve has little more relevancy than those below it. In fact, the entire set of curves comprise little more than an academic issue for two reasons. First, Castelli indicated that most myocardial infarctions occur in women whose cholesterol levels are between 200 and 250 mg. Thus, the very high CHD rates that occur at the very high cholesterol levels are based on small numbers of events and small percentages of women.

Second, all the rates shown in Figure 9-13 were based on relatively small numbers of events. Although Framingham investigators publish a virtual flood of articles, they typically omit data that allow readers to determine the practical importance of their figures, CHD rates, etc. For example, Framingham women were 30 to 59 years old at entry. After 30 years, these women should have been 60 to 89 years old. Yet, Kannel's Figure involves ages 35 to 94. The 30 year follow-up, therefore, is apparently composed of several "studies" of varying lengths during the 30 years. In any event, Kannel provided some clues. He indicated that over the 30 years 574 of 2,873 women developed "manifestations" of CHD (angina, myocardial infarction, coronary insufficiency and sudden death). Thus, only 20% of the women presumably developed overt signs of CHD. More remarkably, 55% of these "diseased" individuals were classified as having angina. Only 195 (6.8%) of the 2,873 women had myocardial infarctions in 30 years and only 196 (6.8%) died of "coronary" problems, of which 73 (2.5%) were sudden deaths.

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[a] The final interval includes rates for those with very high blood cholesterol levels, including familial hypercholesterolemia. As emphasized in Volume 1 and elsewhere in this volume, there is good evidence that these high cholesterol levels produce a "lipid storage," problem, not true atherosclerosis.

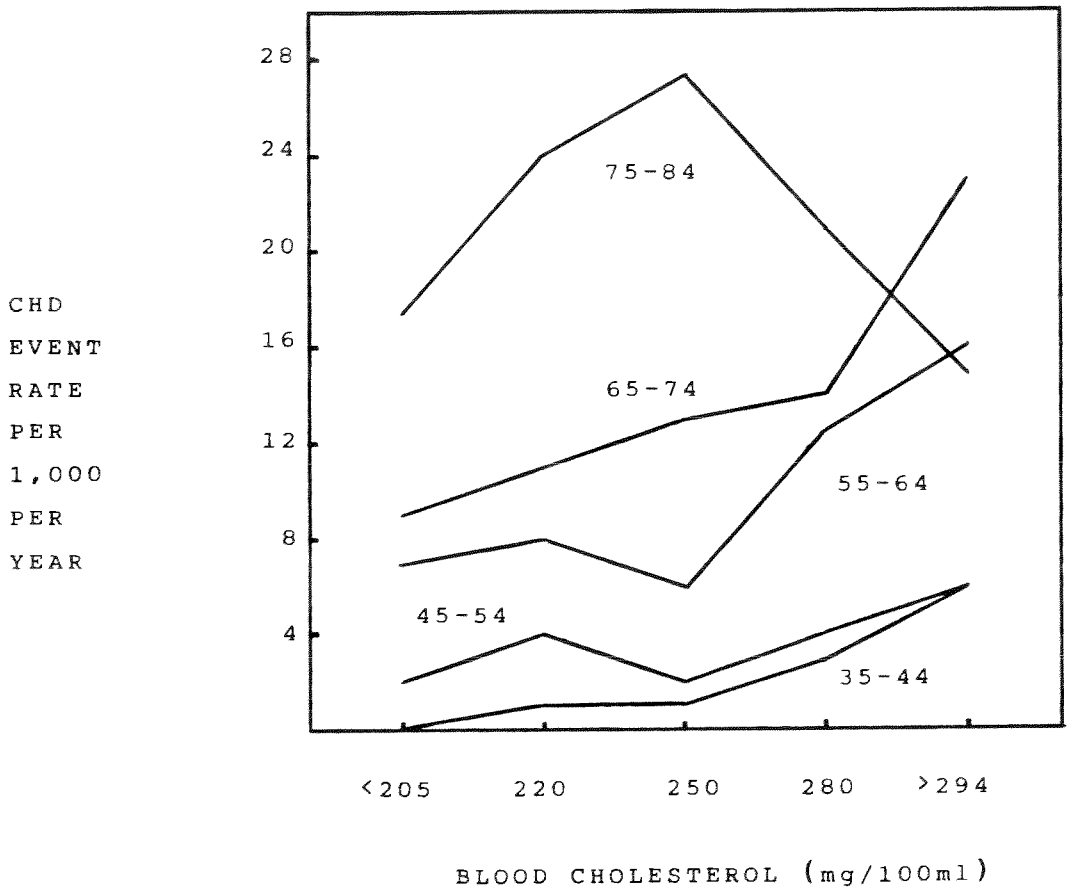

Figure 9-13. CHD event rate by cholesterol level in women after 30 years (adapted from Castelli et al., 1989[2292])

Since Castelli[2751] indicated in 1989 that only six of 1,600 premenopausal women had died of CHD in the Framingham study, and since menopause typically occurs about age 50, this means that the number of deaths occurring in the lower two age groups of Figure 9-13 was six, which, statistically speaking, is essentially zero. Thus, about 190 of the total deaths occurred in approximately 1,273 women aged 50 to 94, a remarkably low 15%.

Even though the number of CHD events was low and the CHD death rate was extremely low, they were unquestionably exaggerations based on the assumption that atherosclerosis was the necessary cause of all cases. As discussed elsewhere in this volume, autopsy studies have shown that atherosclerosis is not the underlying cause of myocardial infarctions or sudden deaths in a relatively large percentage of cases. The Framingham investigators have indirectly defined infarctions as atherosclerosis without autopsy verification by assuming a relationship between cholesterol and infarctions. Similarly, their definition of sudden death was somewhat arbitrary, i.e., "This was considered to be due to CHD when it was documented to have occurred in a matter of minutes and was attributed to no other cause by the physician who completed the death certificate and when no other cause of death was suggested by prior medical history."[2093] Therefore, it is probable that about one-third to one-half of the CHD deaths were not caused by atherosclerosis per se.

Let us summarize some key points. Anderson et al.[1273] acknowledged that there is no significant association between cholesterol level and either overall or cardiovascular disease mortality in women younger than 50 after 30 years of Framingham observations. Castelli[2751] acknowledged that very few women develop CHD before menopause. Perlman[2757] emphasized that "It has...been well established that he total serum cholesterol level...is not predictive of heart disease in women once they pass menopause." Bush[1618,1783] acknowledged that no relation between LDL and CHD in women can be clearly demonstrated and, indeed, admitted that it was nonexistent in the Lipid Research Clinics Prevalence study. Yet, Kannel[787] maintained that there is a "powerful" relationship between cholesterol and CHD in women, Bush[1618] held that "it seems clear that total cholesterol is an important predictor of coronary disease in women," and Robert Knapp[1786] stated that "The importance of LDL cholesterol and heart disease risk is similar in women and men." Thus, alliance members seem to pay very little attention to their own data.

An interesting way of illustrating the insignificance of cholesterol on CHD mortality in women was recently documented by Khaw and Rose. "To prevent one death from CHD within five years estimates of the numbers of people who would have to be screened over the five years and of those who would subsequently be treated ranged from 137,320 and 20,600, respectively, for women age 25-34."[2194]

Finally, the reader is encouraged to review Figure 3-23 (Chapter 3) which shows the distributions of blood cholesterol levels for persons with and without CHD. These figures have been published many times by Framingham investigators and they always exclusively involve men. The failure to show similar distributions for women indicates strongly that the distributions, for all practical purposes, overlap almost completely. Framingham investigators almost always omit data that argue against the lipid hypothesis.

Other Risk Factors

Perlman followed nearly 12,000 women for 15 years and reported that the strongest predictors of cardiovascular mortality among women before menopause were smoking, high blood pressure and diabetes.[2752] Beard et al. examined the records of all women in Rochester diagnosed as having CHD from 1960 to 1982.[2757] They indicated that

smoking, hypertension and diabetes were the major risk factors.[a] On the other hand, Glazer[115] indicated that cigarette smoking, hypertension and obesity did not correlate with sudden death in women.

Although often emphasized as one of three major risk factors for CHD by many alliance members, the Framingham study has repeatedly demonstrated little or no influence of smoking on CHD rates.[261,964] A recent article by Castelli et al.[2292] showed that the CHD rate remained exactly the same for nonsmokers and smokers who consumed up to two packs a day. The rate increased substantially beyond two packs a day but this rate is difficult to evaluate because it involved an interval of 2 to 4.5 packs a day, over twice as great as all the remaining four intervals presented by Castelli et al. This suggests that the rate associated with three packs a day may not have been much different than for 40 or fewer cigarettes.

As indicated earlier in this chapter, we are ultimately concerned with real-world mortality and morbidity trends, not associations within prospective studies. It was shown that the beginning of the CHD mortality decline occurred during the peak years of cigarette consumption in the U.S. Moreover, Kannel admitted that the CHD decline among women has been equal to that among men "despite an increase in cigarette smoking "among women."[787] Indeed, an analysis of consumption trends by McGinnis et al.[2664] also revealed that cigarette smoking increased somewhat among women while their CHD mortality rate declined.

Despite her contention that blood cholesterol is an important risk factor, Bush acknowledged that "little is known about risk factors for women."[1618]

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[a] Stampfer[2758] stated in an editorial that Beard et al. "were unable to assess the influence of other risk factors such as blood cholesterol. However, Beard et al. did not report such a statement in their article and they did indicate that blood work had been done on the women.

Estrogen Use

Estrogen use is only of peripheral relevance to the diet-cholesterol-CHD relationship and associated research, therefore, was not reviewed in depth. It would appear that the researchers who conclude that "risk" of CHD is decreased with menopausal use[a] outnumber those who suggest no benefits.[b] Further, there seems to be consensus that oral contraceptives increase the "risk" of CHD,[1618,2751,2753] although there are dissenters.[2621] It is noteworthy that Framingham investigators found a relation between estrogen use and CHD "risk" only when the data were adjusted for cigarette use.[3193] When such an adjustment was made, the relation dissolved. The most recently published study, the 10-year follow-up of the Nurses' Health study, reported positive results of postmenopausal estrogen.[3417] However, while the authors indicated that individual confounders did not reach significance, although they were in evidence (e.g., obesity, smoking, etc.), they failed to display their results when adjusted for all confounders simultaneously.

Clouding the picture even further are the many studies showing an increase in breast and endometrial cancers with postmenopausal therapy.[3418] Disagreement seems to center on the magnitude of the effect, not the effect itself. For example, a review by the Centers for Disease Control[2737,3419] in 1991 indicated that the increase in breast cancer was significant, while a review by Dupont and Page[3364] in the same year suggested that the effect was not "appreciable."

In overviewing many of these studies, this writer found it impossible to determine the practical implications of results because (1) meaningless risk ratios are often the only dependent variables published (e.g., Barrett-Connor and Bush[3248]), (2) many studies are not free of confounding variables, and (3) potential benefits with respect to CHD events are countered by increased rates of breast and endometrial cancers. It is truly questionable whether postmenopausal estrogen therapy is beneficial, all things concerned, or cost-effective. DeBakey[2235] recently concluded that "It's unclear whether estrogen replacement therapy really helps..." As noted by Goldman and Toseteson,[3418] randomized clinical trial of estrogen replacement therapy is really necessary to resolve a messy controversy. But like so many other scientifically unresolved issues, long-time and widespread use of a medication often occurs in the absence of scientific proof of costs and benefits, as well as harm. The sales of the leading drug, premarin, have increased from about $140 million to nearly $600 million from 1986 to 1990 and are expected to approach $800 million by 1994.[3420]

The explanation for the beneficial effects of estrogen in postmenopausal women is that the hormone increases HDL and decreases LDL. The explanation as to why it increases risk as an oral contraceptive is that the doses of estrogens necessary to suppress ovulation increase LDL and sometimes decrease HDL. Relevant data from the Framingham study were presented by Abbott et al.[2957] in 1983. Figures 9-14 and 9-15 show the LDL and HDL levels, respectively, of women who were and were not, taking estrogens before and after menopause. (Male levels are also shown for further comparison.) Contrary to the above "explanations," it can be seen that estrogen use has little effect on LDL levels before age 50 but increases the levels after that age.

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[a] 1618,2507,2508,2509,2511,2512,2619,2751,3101,3191,3192,3417

[b] 2296,2509,2510,2511

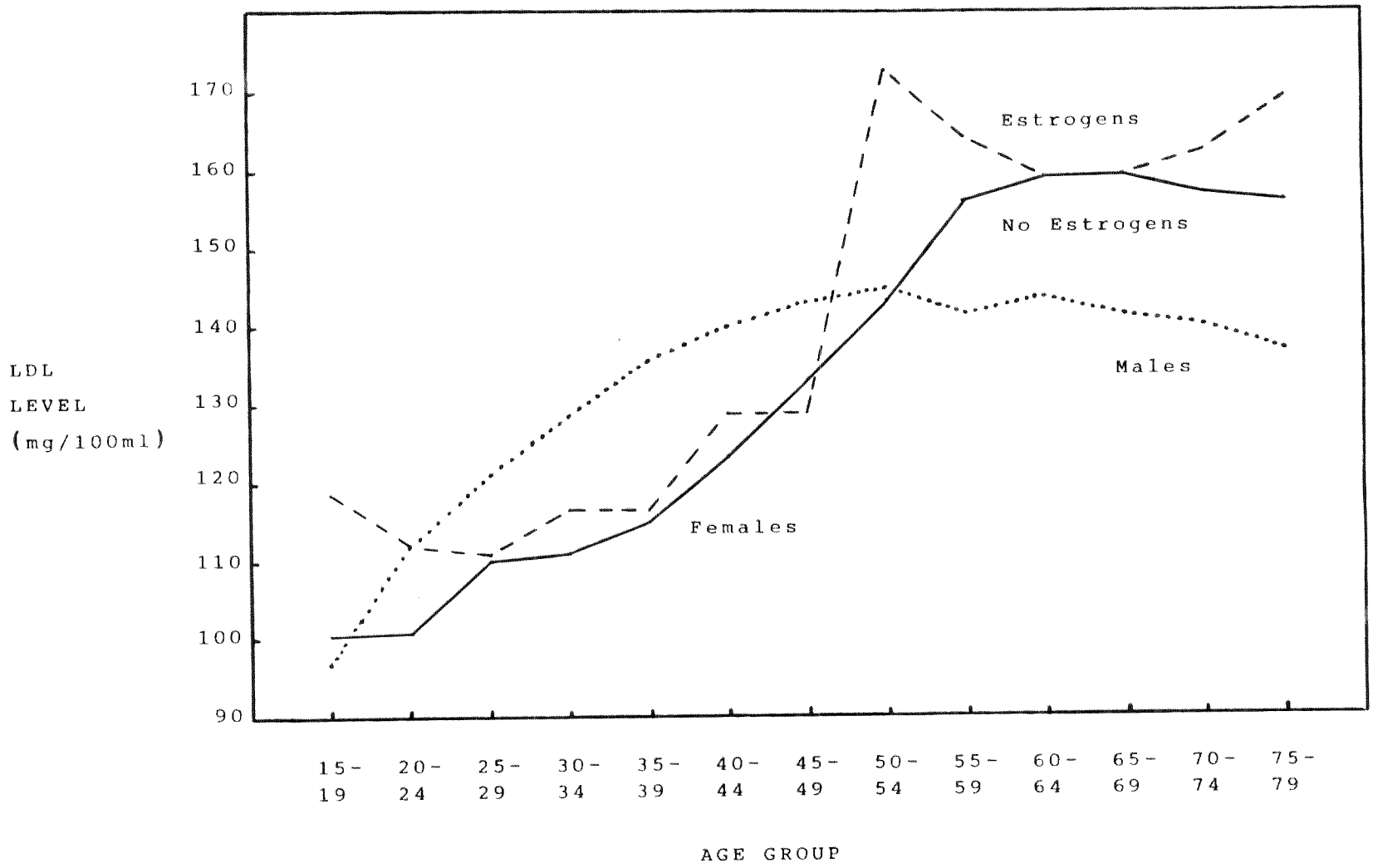

Figure 9-14. LDL cholesterol level by age, sex and use of estrogen hormone (adapted from Abbott et al., 1983[2957])

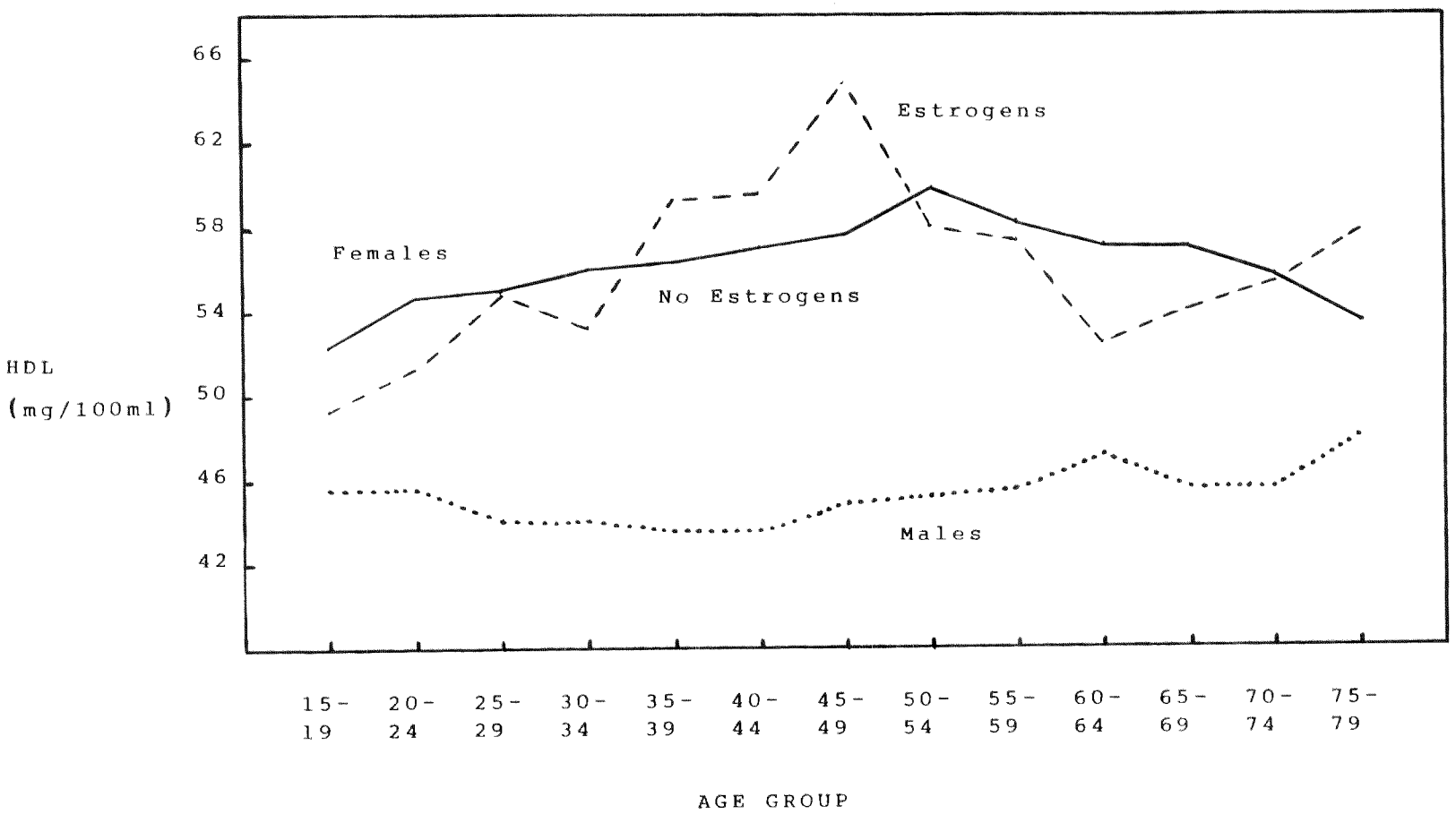

Figure 9-15. HDL cholesterol level by age, sex and use of estrogen hormone (adapted from Abbott et al., 1983[2957])

The effects of estrogen use on HDL levels are quite peculiar. If the data of Abbott et al. can be taken seriously, it would appear that estrogens increase HDL levels up to age 49 and then decrease the levels thereafter. Insofar as lipids are concerned, therefore, the Framingham data provide negative evidence that estrogens are beneficial after menopause and inconsistent evidence regarding their effects before menopause. A smaller study by Krauss et al.,[3270] however, reported opposite results with respect to postmenopausal estrogen use.

Regardless of the outcome of the many studies investigating estrogen use, as has been shown with other risk factor, vital statistics data do not support the basic perception that CHD rates accelerate as a result of loss of estrogen following menopause. The reader is referred to Figure 1-4 which shows that the CHD death rate curve for females by age is absolutely identical to that for males, although displaced by a decade. If one concludes that the rise in CHD rates after the 45-54 age period is due to loss of estrogen, what is the reason for the increased acceleration after the 55-64 age period? Also, what is the explanation for the identical accelerated trends in men? Because the male and female curves are identically shaped, it is more logical to conclude that menopause has no unique effect on women with respect to CHD mortality rates.

BLOOD CHOLESTEROL LEVEL AND THE ELDERLY

In early 1977 Gordon, Castelli, Kannel and others reported that "At these [49 to 82] ages, total cholesterol per se is not a risk factor for coronary heart disease at all."[453] They cited a 1966 article by Gofman et al. and were obviously referring as well to their own Framingham data. In late 1977 the same authors said, "A number of studies...have found that total serum cholesterol...is a diminishing CHD risk factor in older men and apparently no longer a CHD risk factor for men over age 65."[523] In 1979 Kannel, Castelli and Gordon indicated that "For persons older than age 50 the serum total cholesterol has little predictive value."[1046] In 1983 Kannel wrote, "We now also know that the impact of cholesterol diminishes with advancing age; beyond 65 years it is difficult to show any relation at all."[1091,a] And in 1984 Kannel et al. said, "The impact of serum total cholesterol wanes with advancing age and beyond 55 no longer predicts CHD."[1083] (Note that the above statements indicate cutoff ages of 49, 50, 55 and 65.)

In all of the above articles, the Framingham investigators presented no tables or figures showing the observed relationship between total cholesterol and CHD events. In 1986, however, Castelli and Anderson did present such a figure (Figure 9-16) and stated that "Although the total cholesterol level was an important independent predictor of CHD in those aged under 50 years, it no longer predicts the risk in those aged over 50 years."[1531] Figure 9-16 clearly shows no cholesterol-CHD relationship in women and no relationship in men up to 280 mg.

1987 marked the year in which the Framingham investigators began interpreting their data in opposite ways. For example, in two 1987 articles, Kannel[787,964] presented relevant data for 65 to 94 year-olds and concluded that "The serum total cholesterol is a powerful risk factor for CHD in both sexes. Its impact tends to wane with age, but remains a significant predictor of CHD in elderly women."[787] The

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[a] As late as 1989 Levy, Kannel, Castelli and others reported that the cholesterol differences between CHD and nonCHD cases after four years of follow-up were only 6 mg for men and 5 mg for women.[2549]

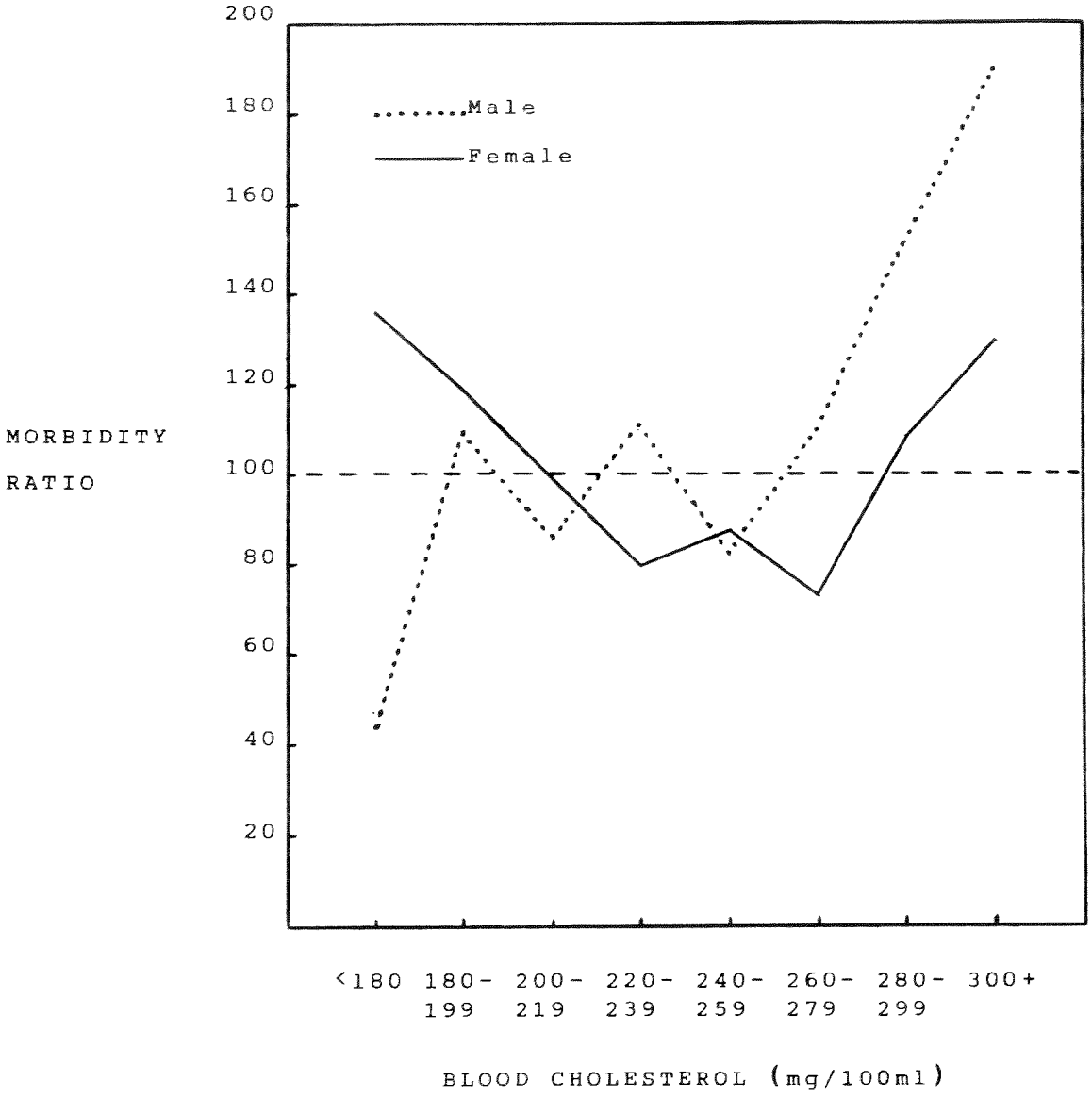

Figure 9-16. Risk of CHD event in men and women aged 50-62 years at entry after 14 years (adapted from Castelli and Anderson, 1986[1531])

reader should note that this statement implies that total cholesterol was not a significant predictor in elderly men. Figure 9-17 shows Kannel's Framingham data (ignoring the Honolulu curve, for the moment). As can be seen, the CHD event rates across the three middle equal cholesterol intervals (205 mg to 294 mg) were essentially flat. The slopes at both ends, particularly the upper end, were largely due to the spurious influence of CHD rates at the extremely low and extremely high cholesterol levels. Not only would the CHD rates likely have remained relatively constant somewhat beyond 294 mg, the issue is quite academic because only a very small percentage of the population has cholesterol levels beyond 294 mg. Thus, Kannel's data clearly showed no practical relationship between cholesterol level and CHD for the vast majority of elderly American men and women.

In the following year Kannel[1383] issued some mumbo-jumbo which suggested that total cholesterol was both a predictor and nonpredictor of CHD for the elderly. Note the subtle implications of the following statement: "...the impact of the total cholesterol concentration declines with advancing age, a decline more apparent among men than women, and the waning effect of current cholesterol values with advancing age might be interpreted as suggesting that serum cholesterol values in persons beyond 65 have no relevance concerning CHD mortality beyond that age. However, this does not appear to be the case. Partition of the total cholesterol into its atherogenic LDL and protective HDL components restores its predictive capacity." If "its" refers to total cholesterol, then Kannel effectively said, "total cholesterol is not predictive but if we partition it into LDL and HDL particles, the predictive capacity of total cholesterol is restored." Of course, such a statement would indicate an illogical outcome. If, on the other hand, "its" refers to cholesterol per se, then Kannel would be admitting once again that total cholesterol has no predictive capacity in the elderly.

Kannel continued, "Furthermore, if the serum cholesterol level is examined in a middle-aged person in relation to CHD occurring beyond age 65, there is a strong predictive connection." Of course, this is a preposterous statement because "serum cholesterol" has no predictive capacity at the individual level and Kannel was one of the first investigators to publish this fact.[1885]

Castelli et al. continued the reinterpretation process in their 1989 article. They said, "As the population ages in Framingham and more data become available, serum cholesterol has emerged as a primary risk factor in patients older than 65 years."[2292] Castelli et al. presented their 30 year data in 3-dimensional block diagrams of many age groups which did not reveal trends as clearly as curves. This writer therefore constructed a set of curves for the age groups of interest. Figure 9-18 presents those curves. The reader should first note that the cholesterol scale is not composed of intervals and no data were given in the text of Castelli et al. to indicate whether the points along the scales represented the means of intervals. It is certain, however, that intervals were used to produce their figure.

The most important observation to be made from Figure 9-18 is that, contrary to what Castelli et al. would have readers believe, there is effectively no rational relationship between total cholesterol level and CHD events for men up to at least 280 mg. And while there is an upward trend among the 64 to 74 year-old women, the trend among 75-84 year-olds is most decidedly not consistent with the lipid hypothesis. Moreover, as noted earlier, the upward surge in three of the curves after 294 mg is an artifact brought about by collapsing the high CHD rates of the extreme cholesterol levels with those of lower rates closer to 300 mg. The downward trends below 220 mg are likewise artifacts of the same collapsing process. Furthermore, the CHD rates beyond 294 mg constitute less than 5% of the population. It is ludicrous to publish

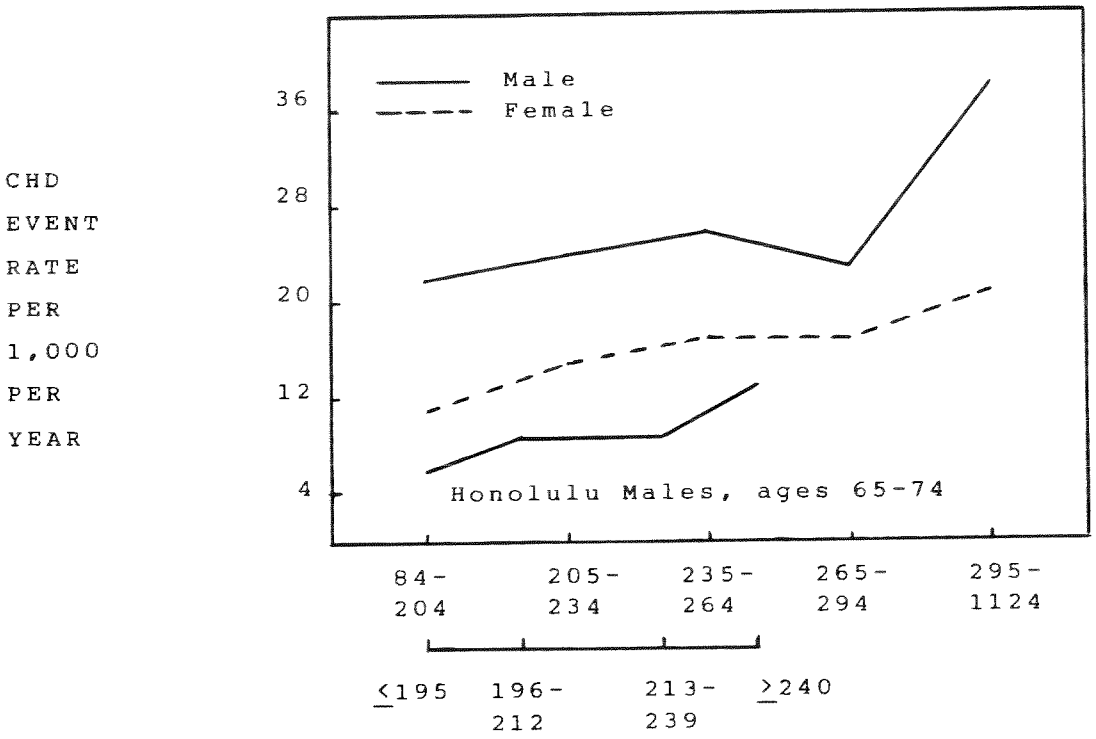

Figure 9-17. CHD event rate in men and women aged 65-94 years at entry after 30 years (adapted from Kannel,1987[787] and Benfante and Reed, 1990[2563])

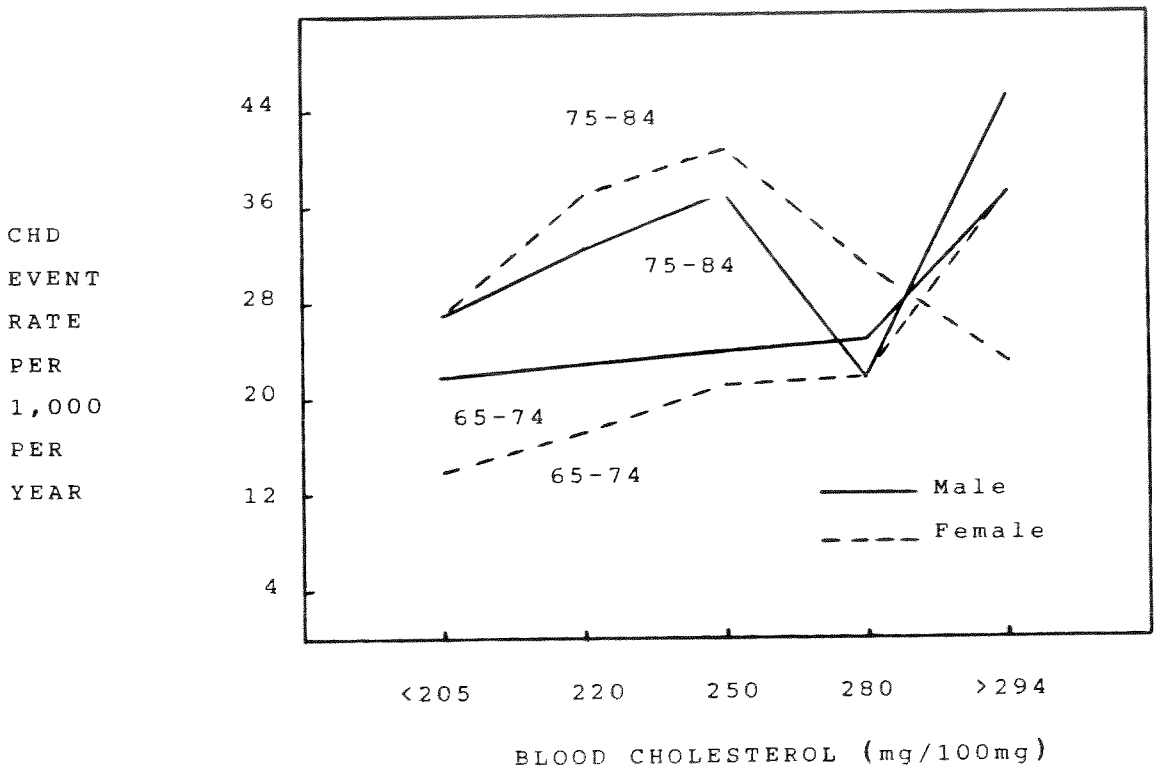

Figure 9-18. CHD event rate in men and women aged 65-84 at entry after 30 years (adapted from Castelli et al., 1989[2292])

such data and claim that they represent proof that total cholesterol is an important risk factor in the elderly. They are less impressive than the data presented in Figure 9-14 which Castelli and Anderson admitted did not reveal a predictive relationship.

In 1990 Benfante and Reed reported the 12-year follow-up of the Honolulu Heart study and concluded that "The results suggest that serum cholesterol level is an independent predictor of CHD, even among men older than 65 years."[2563] Their data for men aged 65-74 at entry are shown in Figure 9-17 below the Framingham data. Like the Framingham curves, the Honolulu curve shows essentially no relationship until the cholesterol interval, $\geq$ 240 mg. And as before, this upward surge is again an artifact of the collapsing of all intervals beyond 240 mg. Moreover, the lower end of the cholesterol scale was accompanied by a higher all-cause mortality than at levels of 200 mg to 220 mg.

Many other studies in the U.S. and Europe have also shown that the relationship between cholesterol levels and CHD mortality greatly diminishes or disappears altogether among persons over 50 or 55 years of age.[a] One exception was that of Barrett-Connor et al.[3170] who claimed that cholesterol was related to CHD mortality after age 50 in both men and women. However, they presented their data in terms of deceptive risk ratios, not rates, and their key comparison was the upper quintile of cholesterol against the lower four quintiles. These statistical maneuverings were undoubtedly accomplished to hide a very weak relationship, particularly over the first four quintiles. It is interesting that they gave CHD death rates as a function of age groups but meticulously avoided the use of rates in relating cholesterol with mortality.

For a discussion of the weak relationship between HDL and CHD among the elderly, the reader is referred to Chapter 3.

New York Times reporter, Gina Kolata, cited 1989 AHA president, Myron Weisfeldt, as saying that he would recommend cholesterol-lowering diets to the elderly despite the fact that the benefits of "cholesterol-lowering in older patients is based on inference."[2523] He indicated some conservatism regarding the use of drugs with older patients, however. Framingham director, William Castelli, is much less conservative, of course, i.e., "the rules for cholesterol [lowering] should be tougher the older you get," implying that he would prescribe both cholesterol-lowering drugs and diets for the elderly.[2660] Rifkind also maintained that "the elderly should pay more attention to their cholesterol,"[2660] as did Lenfant.[2837] Perhaps DeWitt Goodman made the most irresponsible statement of all, i.e., "We now have evidence that clearly supports the conclusion that the elderly will live longer and better by lowering cholesterol."[2837] Virtually all researchers know that cholesterol-lowering has never been shown to extend the lives of anyone, regardless of age. And Aronow and Kafonex and Kwiterovich made almost identical statements, i.e., "Age per se should not be a reason for failing to treat hyperlipidemia"[2270] and "old age per se should not prohibit medications."[2777] Indeed, as was shown in Chapter 8, 59% of all cholesterol-lowering drugs are currently being prescribed for individuals over 60 years of age (Wysowski et al.[2726]).

Diametrically opposed to alliance members are not only the basic research data but also such prominent individuals as past AHA president Thomas James, recently retired Surgeon General C. Everett Koop and the Mayo Clinic's P.J. Palumbo. James said, "one of the saddest things is to see patients who are in their 70s or 80s and who are terrified by what they are eating. Their obsession with diet and cholesterol is a national tragedy."[2523] Koop recently stated that "I think the worst thing about the

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[a] 3166,3167,3168,3169,3243,3244,3245

cholesterol effort in this country is that it has frightened about 30 million (senior) people that don't have to be frightened at all."[2441] Palumbo emphasized that "we have seen patients in their 80s who are literally starving themselves to get down to a cholesterol level of 200 mg."[2660] James agreed that there is evidence of malnutrition among the elderly because of their cholesterol obsession.

Palumbo indicated that "The NCEP is weighted toward treatment of individuals older than 60 years,"[2695] despite the fact that there are no data relating treatment of hypercholesterolemia in the elderly. And since diet and exercise are not likely to reduce cholesterol levels to less than 240 mg and certainly not to less than 200 mg...are we, therefore, justified to go beyond diet and treat patients older than 60 years with medications that have potential risks that may outweigh the benefit?" Others, such as Peter Lamy, have called for a "nutrition liberation" for the elderly.[2677,a]

Finally, it is worth noting the contradiction observed by Moser and Gorlin,[3338] i.e., "We find it difficult to reconcile statements in JAMA by Drs. Anderson, Castelli and Levy that 'there is no association between cholesterol levels at age 60 years and cardiovascular death' and the personal communication from Dr. Castelli to Drs. Ginsberg and Goodman..., that elevated cholesterol is significantly associated with risk of cardiovascular disease in persons over 60 years old, and in fact, over 65."

The absurdity and weakness of the alliance's position is exemplified by the total disagreement exhibited by some of the most prominent medical spokespersons in the country. It is also exemplified by the fact that NHLBI is currently planning an 8-year clinical trial of cholesterol-lowering with men and women over 60 and 68 years of age, respectively.[2660] If the evidence of the efficacy of lowering cholesterol in the elderly is so convincing as the alliance maintains, why the need for a costly trial to obtain redundant evidence? Obviously, this issue is simply another case of the alliance's prescribing treatment for the American public before the treatment has been even adequately evaluated.

The NHLBI trial with an elderly cohort will apparently use lovastatin as the cholesterol-lowering drug, according to Basil Rifkind.[2523] In this regard, it is noteworthy to mention that AHA president Weisfeldt said he would tend to avoid putting a man under age 40 on such a drug because "These drugs are potentially toxic."[2523] If they are toxic in men under 40, they most certainly will be toxic in men and women over 40.

OBESITY AS A RISK FACTOR

Anything that correlates with CHD significantly can be classified as a risk factor. Chapter 2 noted that the alliance has accumulated hundreds of such factors, one of which is obesity. The designated importance of this factor is a prime example of the alliance's "transformation process," i.e., the elevation to risk stardom of very weak and inconsistent raw data.

At the outset, it should be emphasized that obesity ranks last among the primary risk factors of importance to the alliance. For example, the NCEP Expert Panel[1066] ranked it tenth among 10 risk factors listed. Since the present document has shown

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[a] In the years (e.g., 1975) when Frederick Stare was a strong supporter of the diet-CHD hypothesis, he said, "Anybody who gets to the age of 70 should quit worrying about their diet."[2689] He also indicated that those over 60 "probably" need not be concerned about diet.

that the blood cholesterol-CHD relationship is very weak and nonpredictive of CHD at the individual level, it follows that the relationship between obesity and CHD must be extremely weak, no matter what researchers claim it to be in discussions independent of other risk factors.

As early as 1953 Keys[279] downplayed the importance of obesity as an independent contributor to CHD. In 1975 he reviewed numerous studies which revealed little or no relationship between obesity and CHD when other variables, particularly blood pressure, we recontrolled. He said, "It is remarkable that the view that overweight is a major risk factor for CHD has been widely accepted the world over in spite of the fact that the American Insurance Company reports have been substantially the only evidence for this, an increasing body of persuasive evidence either denies the purported relationship or indicates that the relationship is slight and may be explained by the association of hypertension with obesity in some people."

Van Itallie[2915] interpreted the literature somewhat different. He said, "The evidence connecting obesity with an increased risk of developing CHD is both consistent and substantial, deriving from case studies and prospective population investigations." Of 5 studies cited by Van Itallie, two were the same study, i.e., Framingham, and all had been classified by keys as not showing a relation between obesity and CHD. Van Itallie did concede, however, that the strength of the relation is "considerably weakened" when other factors are controlled." Elsewhere, Van Itallie and Hirsch[3325] indicated that "Autopsy data provide no confirmation of an independent association between obesity and atherosclerotic disease."

In 1979, Kannel, Gordon and Castelli[2918] indicated that "...despite many studies over the past several decades, we are still uncertain about its [obesity] causes and biological consequences." They found extremely low correlations between relative weight and blood cholesterol for both males and females and concluded that "weight gain does not explain more than a small fraction of the variation in...atherogenic traits..."

The original 1970 Intersociety Commission[552] report observed that longer term prospective studies "suggest that the association between overweight and CHD risk may be largely attributable to the increased proneness of overweight men to hypertension, hyperlipidemia and diabetes." In the 1984 "update" of the 1970 report Kannel et al.[1083] reported that "Obesity is associated with an excess of CHD, particularly angina pectoris and sudden death, largely as a consequence of its relationship to atherogenic risk factors."

The 1971 NHLBI Task Force[705] maintained that the relationship between obesity and CHD "appears to apply to the extremely obese. The increased risk in obese individuals may be related to the higher incidence of hyperlipidemia, hypertension and diabetes." The 1981 NHLBI Working Group[3067] presented a similar position, i.e., "a great deal of the [obesity] effect is due to the fact that obesity increases the likelihood of hypercholesterolemia, hypertension, and diabetes. Obesity alone does not affect longevity unless the individual is markedly overweight."

In 1984 Levy and Feinleib[1401] cited the Framingham study as showing that obesity is and is not an independent risk factor for CHD. They indicated that the effect does not appear until after many years of follow-up. In 1987 Garrison[1462] presented a rather curious and contradictory statement. He said, "Despite the overwhelming evidence that body fatness is a major precursor of the established CV [cardiovascular] disease risk factors, there are still pitfalls in analyzing and presenting the relationship between obesity or body fat level and CV disease; therefore, medical science will

probably continue to produce seemingly contradictory messages on this issue. (Note that Garrison referred to CV disease, rather than CHD.)

In 1989 Phillips and Shaper[3281] reviewed 11 prospective studies and compared CHD events for obese and nonobese men, all of which were hypertensive. They presented the endpoint data in terms of relative risk ratios, rather than rates. This writer computed weighted mean risk ratios for CHD, i.e., 1.04 and for all cardiovascular diseases, i.e., 0.95. Knowing that relative risk ratios greatly exaggerate rate ratios, 1.04 and 0.95 reflect virtually zero relationships between obesity and CHD and all cardiovascular diseases among hypertensive men.

Other studies offer no support to the concept that obesity per se is a risk factor. For example, a large intervention study in the United Kingdom reported that body mass index was not related to fatal or nonfatal myocardial infarction.[3007] And both Keys[540] and Van Itallie[2790] noted that autopsy studies consistently show no relationship between obesity and atherosclerotic disease. Keys also observed that angiographic investigations confirmed the autopsy findings.

With particular respect to women Burkman[3283] recently reviewed studies associating obesity with CHD and found that the relationship has ranged from none to weak, i.e., "Most have found either no relationship or at best a weak relationship." A very recent study by Manson et al.[3282] indicated that the CHD event rate did increase with relative weight in 145,886 women. However, the effect was almost totally due to the heaviest subgroup and the rate difference between this and the leanest subgroup was only 0.074%, when adjustments were made for age and smoking. Manson et al. did not present rates when hypertension and diabetes were controlled but indicated that the independent effects of obesity were "attenuated" when these variables were factored out. Indeed, their data indicated that both diabetes and hypertension greatly increased from the leanest to the heaviest subgroups, leaving little room for effects due to obesity per se.

In keeping with the alliance's proclivity toward proclamations, rather than adherence to scientific evidence, the NCEP "Expert Panel" report[1066] proclaimed that "Obesity...is an independent risk factor for CHD." And because of the associations between obesity and other "risk factors," Grundy[3083] recently concluded that "control of obesity may move to the head of the list for overall reduction of CHD risk by dietary modification."

Lest the reader gain the impression that all obese individuals are hypercholesterolemic, hypertensive, diabetic, etc., it should be emphasized that such is emphatically not the case. In fact, only a relatively small percentage of obese individuals have such conditions.

In sum, as noted at the beginning of this discussion, if obesity is indeed an independent risk factor for CHD, it must be of very minor importance. Thus, if an individual is not diabetic, hypercholesterolemic, or hypertensive, there can be no practical consequences of weight loss insofar as cardiovascular diseases are concerned. Of course, this writer would not condone obesity in general but personal attitudes do not comprise a relevant data base for this volume. Moreover, there seems to be virtually no scientific justification for condemning conditions from light to moderate overweight.

BIOMEDICAL RESEARCH FRAUD

Fraud has always existed in biomedical research, as it has in virtually all disciplines, but it appears to have risen above some tolerable threshold in recent years. Writers began giving it serious attention in 1987 as a result of some rather dramatic

incidents.[2130,2145,2147] In particular, John Darsee of Harvard and Robert Slutsky of the University of California at San Diego were caught grinding out fake data and publishing masses of articles in very short periods of time. And because Darsee and Slutsky shared their articles with a large number of co-authors,[2132] it is obvious that collusions were taking place, suggesting trends rather than isolated corrupt individuals. A conclusion reached at the 1987 National Conference of Lawyers and Scientists was that scientific fraud was increasing. The question posed was whether the exposed "bad apples" represented the "tip of the iceberg."[2124]

The growing fraud and obvious conflicts of interest, not so surprisingly, captured the interest of the U.S. Congress and investigations into fraud in biomedical research have been underway for some time.[a] Feder and Stewart indicated that fake data and sloppy research constitute hundreds of millions of wasted dollars each year.[2146] Representative Ted Weiss concluded that "Researchers having financial interest in the outcome of federally funded research represent unequivocal conflicts of interest."[2072,2073] Peter Budetti, aide to the House Subcommittee investigating fraud, said that biomedical research has its own pork barreling, i.e., an arrangement whereby "senior scientists are virtually assured funding and get papers accepted for publication because of who they are rather than their contribution to the work."[2149]

There is little doubt that money is the primary, if not only, factor underlying the increase in fraud. Leary suggested that the roots of the current problem can be found more than a decade ago within the government's new policy of encouraging industry to assume part of the financial burden of biomedical research.[2143] This resulted in more opportunities for both scientists and universities to increase their revenues. Leary cited Minsky as observing that "over the last decade the scientific community has become as much a world of business as scholarship. If you make the ethics of science the same as Wall Street, you're going to corrupt science." Rubenstein pointed out that a university environment was created which not only tolerated fraud, it also nurtured it.[2137]

Rather than admit to the obvious, the "establishment" predictably denies that fraud has been increasing, as exemplified in the following. Science Editor Daniel Koshland, Jr. said that "There is no evidence of an increased percentage of fraud in science."[2129] Writing an editorial in the Journal of the American Medical Association, Patricia Woolf claimed that fraud is "infrequent."[2151] Arthur Rubenstein of the Institute of Medicines stated that "cases of misconduct are rare events."[2138,2141] The editor of Human Pathology claimed that "Fraud in scientific publications is relatively rare."[2125] And deputy director of NIH, William Raub, maintained that fraud is "extremely rare."[2126] Clearly these statements are defensive in nature and not at all descriptive of the true state-of-affairs. As noted by Greenberg, the scientific establishment isn't keen on cleaning house or even looking closely for malfeasance.[2146]

When conflicts of interest began to surface as a public concern, NIH vigorously defended its policy which, in effect, was no policy at all, i.e., it left fraud investigation to the universities and provided no guidelines on how these institutions would carry out their investigations.[2124,2031] As recent as 1986, NIH's Raub stated that the whole process of giving grants was not in "need of fundamental change."[2126] Strangely, he said that researchers "...will admit incompetency but say 'I am not a crook.'"[2145]

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[a] 2072,2073,2134,2143,2149

Fearing interference in the research environment, the New England Journal of Medicine's Angel and Relman emphasized that government should stay out of the investigatory process and let universities handle their own cases of misconduct.[2136] This is, of course, the age-old position taken by institutions which have knowingly allowed themselves to become corrupt. In effect, "if we're doing something bad with public funds, let us detect and correct it." It is interesting that universities allow an independent organization (NCAA) to police their athletic programs which have little impact on society but vigorously oppose a monitoring of their research programs which involve many billions of public dollars.

Conflicts of Interest

As noted in Volume 1, conflicts of interest abound in biomedical research and they include many prominent individuals who participate in NHLBI/AHA programs.

William Roberts, Editor of the American Journal of Cardiology, recently stated in an editorial that "I have heard of physicians involved in clinical trials owning large amounts of stock in the company whose drug they are investigating. Some particularly prominent physicians occasionally advise pharmaceutical companies, and are paid large fees for doing so, and large lecture fees for speaking publicly on the drug(s) produced by the company these advise."[1927]

The American College of Cardiology held a special session on bioethics at its 1989 meeting.[2072] One speaker, DeMaria, noted that current congressional hearings have uncovered "eminent" cardiologists with conflicts of interest. Another speaker, John Williams, said, "We now receive invitations to attend special symposiums dealing with drug Z to treat condition Y and the symposium is sponsored by the maker of the drug. Monetary offers are made in order 'to help defray financial loss from attendance.' Or we receive an invitation to a well-known resort, and 'please bring spouse.' 'The afternoons will be free.' In neither case are we being asked to present information or to participate in the symposium." And a third speaker, Klocke, frankly conceded that "conflict of interest 'possibilities' are very much more frequent...than they have been."

One of the most common conflicts of interest is the endorsement of a product, however subtle. For example, Merck, Sharp and Dohme, makers of lovastatin, issued a press release in 1989 which stated that "The following physicians were involved in clinical investigations of mevacor (lovastatin). They have agreed to be available for media interviews..."[2031]

Carlos Ayers
Carlos Dujovne
Robert Eckel
Barry A. Effron
Elaine B. Feldman
Waldo R. Fisher
Alan Fogelman
A. David Goldberg
Anne Goldberg
Ira Goldberg
Ronald Goldberg
Antonio Gotto
Philip Greenland
Scott Grundy
Richard J. Hauel
Don Hunninghake
Roger Illingworth
Philip A. Kern
Robert H. Knopp
Peter O. Kwitervich
John LaRosa
Robert S. Lees
Valery Miller
Charles Nugent
Lawrence D. Rink
Paul Samuel
Gustav Schonfeld
Evan A. Stein
Daniel Steinberg
Neil J. Stone.
Elliot J. Sussman
Joseph Witztum

It is quite likely that they are all being paid for this "agreement" which is effectively an endorsement. At least one of these physicians, Daniel Steinberg, had apparently represented Merck, Sharp and Dohme before the FDA to solicit approval of the drug.[3378]

Scott[3188] reviewed many ways in which physicians receive monies or gifts from drug companies in the apparent hopes that they will prescribe the companies' drugs or will find the drugs "effective" in experiments. One popular way was revealed at the Veterans Administration. One drug company gave "honorariums" and "gratuities" to 32 physicians, one of which received as much as $50,000. Scott cited Goldfinger of Harvard as observing that "The assumption that one can accept the blandishments without any risk of being compromised is incredibly naive, but even if it were true, would that make it right? Indeed, isn't it a bit sleazy to take the corsage without at least yielding its sender a place on one's dance card?"

Fraud and Peer Review

The Darsees and the Slutskys are dramatic and blatant cases of fraud and the establishment would have others believe that fraud is only the faking of data. According to Webster's dictionary, fraud is much more general than that, being "Something said or done to deceive." Defensive statements regarding the frequency of fraud are dramatically opposite to the facts and even to the present activities of the establishment. For example, the First International Congress on Peer Review in Biomedical Publication, sponsored by the American Medical Association, was held in Chicago in May of 1989. Some 250 journal editors and several major newspapers attended. As noted by Sun, "The fact that such a meeting was held at all demonstrates how uncomfortable the scientific community has become with some parts of the peer review process."[2147] Altman indicated that the editors reached "Consensus that the peer review system works in most cases,"[2148] while Sun maintained that "At the conclusion of the conference, no one even approached a consensus on anything."[2147] James Sammons was cited by Kalsner and Kalsner as saying that the peer review process was subjected to "intense scrutiny."[2201]

Journal editors are more defensive regarding the peer review system than they are of any apparent desire to improve it. For example, Science's Koshland stated that "We must recognize that 99.9999 percent of reports are accurate and truthful"[2129] and that there is no need for a "fundamental change in procedures."[2145] The New England Journal of Medicine's Relman said that he "can't agree there's been a breakdown in science's quality assurance system"[2153] The Journal of Laboratory and Clinical Medicine's Daniel thinks that the peer review system does "an outstanding job of applying objectivity and the standards of science."[1721] Of course, little improvement in the peer review system can be expected when editors themselves are blind to the obvious.

A 1987 editorial in the New York Times noted, "If the quality controls aren't detecting even outright fraud, how well do they sift out garbage?" Blatant fraud cases represent the extreme. "Careless science and manipulated data are probably far more common and science's quality control system may also be letting in a lot of garbage."[2144] Stewart and Feder found an average of 12 errors in each of the 18 papers published by Harvard's Darsee.[2132] In reviewing over 4,000 papers on diet, blood cholesterol and coronary heart disease, the present writer found it almost impossible not to observe at least a few errors in most research reports. In fact, some forms of deception literally saturate the literature.

Sun concluded that the peer review "system is riddled with bias, particularly on the part of reviewers. Journals favor studies with 'positive' rather than 'negative' results and researchers pad their resumes by spreading the results of a single experiment over several publications."[2147] Sun cited the editor of Archives of Otolaryngology, Byron Baily, as tracking 1000 authors chosen at random. Some 201 of these authors published 644 articles which had duplicate parts of their original articles. Thirty-three percent of the 644 articles were highly similar to the original articles, 40% were

essentially slight "up-dates" of original articles and 20% were the result of "salami slicing," i.e., spreading parts of one study over several journal articles.

Pinckney observed that there has been "a growing tolerance of sloppy-even fraudulent--research practices."[2141] Wade pointed out that "mediocre articles can easily evade the present quality control system."[2139] He emphasized that "quantity is routing quality." And Martin noted that "some of our leading journals have established a policy to accept frankly incomplete manuscripts if they are judged scientifically exciting. These same journals often reject well-documented work under the pretext that it lacks sufficient general interest."[2130] He described it thusly," Give us your half-baked ideas and spare us the boring details."

Drummond Rennie and his colleagues of JAMA said, "...we cannot be sure how much peer review is a game of chance."[1729] He asked, "Is a paper rejected because an editor does not like a topic or thesis and selects reviewers who will reject it?" Marcia Angel of NEJM frankly admitted such a practice. She said, "reviewer bias is not necessarily bad" and indicated that she sometimes purposely sends papers to reviewers with known biases.[2147] Many journals publish editorials that strongly support the lipid hypothesis (e.g., Postgraduate Medicine,[1784] Human Pathology,[2225]). Such bias unquestionably plays a role in rejecting anti-lipid hypothesis articles. In view of the facts that the lipid hypothesis has vastly more unsupportive than supportive evidence and that anti-lipid hypothesis articles are few and far between, it is clear that journal editors and reviewers are defining the state-of-the-art by biased selection of articles.

Although Williams reported that some 435 articles have been published which discussed the peer review process,[2135] JAMA's Rennie and the American Medical News recently pointed out that the process itself has never been evaluated scientifically.[1729,2140]

The reasoning of editors is sometimes dumbfounding. For example, NEJM's Relman stated that "scientists are not expected to believe the author's interpretations of his results are necessarily correct or that his experimental design is sensible or that his methods are correct. But if the research is on the face of it plausible, and the methods seem appropriate, and the results not obviously self-contradictory or impossible, then there is no way to detect fraud."[2028] If reviewers do not have appropriate expertise in how to <u>logically</u> interpret results, design proper experiments, understand the theory and use of statistics, etc., why do editors employ them as reviewers? A person who <u>judges</u> the quality of contributors should obviously have the <u>qualifications</u> to be a judge.

More recently, Relman stated that "we're all interested in the truth, but it's mostly what happens after publication of a study that determines truth."[2147] While there is some validity to this statement, it is highly misleading because the biases exhibited by editors and reviewers demonstrate that truth is <u>not</u> their goals at all. Rather, <u>they</u> select what is and is not truth by virtue of their power to accept and reject manuscripts. Garbage may eventually be determined to be garbage but it may remain as apparent truths for many years.

A recent Lancet editorial included an equally dumbfounding remark, i.e., "Peer review works best if you do not ask too much of it."[2142] What is too much? Judging by the literature this writer has read, it is clear that very little is asked of peer review. An old adage seems appropriate, namely, it is a case of the blind leading the blind.

Perhaps JAMA's George Lunberg topped them all with a recommendation that is more naive than it is workable. He stated that "the editorial process has to be held to the same scrutiny at least as the authors who submitted the articles for our scrutiny."[2149] Since editors have the power to accept and reject articles, what editors will publish articles or letters which criticize them? How else can the editorial process be held to the same scrutiny?

Of very great importance to the selection bias problem in journals is the influence of drug advertising. While journal editors would vigorously deny that drug advertising affects the selection of articles to be published, it is well-known that advertising is the financial backbone of nearly all publications and must influence editors. As long ago as 1969 Edward Pinckney told a U.S. senate Subcommittee that a "most unwholesome relationship" exists between the AMA and the drug industry and indicated that "the AMA today virtually exists more for the benefit of pharmaceutical companies than it does for its membership."[2173] The acceptance of "misleading ads" is indicative of a greater interest in money than in quality and a willingness to do whatever is necessary to appease drug manufacturers.

As noted elsewhere in this volume, this writer has felt the sting of rejection by John Archer of JAMA, David Sharp of Lancet and Arnold Relman of NEJM. The whole purpose of Diet, Blood Cholesterol and Coronary Heart Disease: a Critical Review of the Literature is to provide the scientific community and others with comprehensive and critically reviewed data that the mainline journals refuse to publish. Paul Friedman recently stated that, "Luckily, most cases (of fraud) have not had impact on how doctors treat patients."[2137] In view of the fact that most doctors are now "treating" millions of patients with cholesterol levels above 200 mg on the basis of fraudulent literature, Friedman's statement is devoid of any sense of reality.

John Bailar, president of the Council of Biology Editors listed several requirements that reviewers should impose on authors.[2145] They all reduce to one concept, namely, honesty in reporting a study. The following is a list the present writer would hope that any scientific journal would impose on authors:

1) A full description of methodology, allowing the reader to (1) replicate the study if desired and/or (2) see logical associations between specific procedures and results obtained;

2) A presentation of sufficient data, statistics (means, standard deviations, ranges, correlations, etc.), significance test results, etc. to allow readers the same opportunity as the author to evaluate the results;

3) A requirement to draw logical conclusions from the results and to avoid selection of an illogical conclusion or a single logical conclusion from confounded data which can yield two or more equally logical conclusions;

4) A requirement to stop describing nonsignificant results as anything more than chance findings;

5) A requirement to "critically" review both sides of a controversy when presenting literature reviews. Noncritical reviews of selected literature, commonplace in the diet-CHD articles, are effectively worthless.

A specific statement by Relman in response to Wade's criticism should be emphasized. He said, "Journalists ought to avoid overheated rhetoric lest they destroy public confidence in vital institutions that have served society well."[2153] Institutions generally do nothing without protracted and heated criticisms, including formal investigations. Their first order or business is defending themselves and it is only

when such defending behavior appears to be failing in the face of continued criticism that institutions then agree to make changes. As to Relman's concern over the loss of public confidence, there is strong suggestion that the continued publication of fraud and garbage is better than risking the loss of public confidence. Finally, in view of the massive garbage published on the diet-CHD issue which has resulted in a monumentally enormous financial, emotional and physiological impact on the population, there is no way that journals "have served society well" in the last 20 to 30 years. The only real benefits can be seen in the growth in profits of the pharmaceutical industry.

Relman[3132] recently said that "I wish and hope that all practicing physicians would have the competency and scientific knowledge to read critically all articles appearing in journals dealing with new discoveries. But I don't think it is realistic. The fact is that most physicians are not in a position to make independent critical judgments, particularly when it is in a field they are not expert in. So they must rely on the judgments of their colleagues." But while Relman readily passes judgment concerning the scientific incompetency of practicing physicians, he simply does not understand or is unwilling to accept the fact that such incompetency extends to journal editors and reviewers as well. The latter are certainly more competent than practicing physicians but they are still insufficiently competent to maintain a high quality of articles. They do not know that the current quality is mediocre because they do not have the competency to detect the mediocrity. And since they reject the notion that they lack sufficient competency, the quality of journal articles is not likely to improve for many years to come. In fact, it is unlikely that journals will make any fundamental changes in how they do business. Journal personnel are highly influenced by their prime financial supporters, namely drug companies. They are obviously influenced by NIH and AHA. Pork barreling will continue and the dogma of NHLBI/AHA will continue through manuscript selection bias process. In short, the first International Congress on Peer Review in Biomedical Publication was probably little more than yet another facade, designed to look like something is being accomplished when, in fact, there are no real intentions to change anything. Although journals are intended to be scientifically free, they are clearly among the most biased and politically controlled institutions in the nation.

Examples of Common Fraud

The diet-CHD literature is decimated with redundant reviews of all sizes which, to say the least, inaccurately reflect the actual state-of-the-art. Two reviews were selected for evaluation here to illustrate how both editors and alliance members commit an abundance of fraud in single publications. The first review was published in 1988 by William Roberts, editor of the American Journal of Cardiology and a staff member of NHLBI.[1595] The second review was published in 1989 by the National Research Council's Food and Nutrition Board, staffed by alliance members.[2070] It is entitled, "Diet and Health."

Roberts stated that "...only in recent years has sufficient evidence accumulated to indicate without reasonable doubt that cholesterol plays a major role in the development of atherosclerotic plaques, and, therefore, symptomatic fatal atherosclerotic coronary artery disease." He listed the following seven factors and presented brief discussions of each:

(1) "Feeding high-cholesterol diets to certain nonhuman animals produces atherosclerotic plaques similar to those occurring in humans."

Key words in factor #1 are "certain" and "similar." Plaques are not formed in animals which metabolize cholesterol like humans and the plaques formed in the other "certain"

animals do not comprise the same hard plaque that occurs in the human disease. In short, Roberts presented a highly biased and deceptive summation of animal studies.

(2) "Cholesterol is found in both experimentally induced atherosclerotic plaques in nonhuman animals and in plaques in humans."

This statement is most certainly true and has been known since the early part of this century. However, it proves virtually nothing with respect to diet or blood cholesterol level, i.e., it provides no scientific evidence supporting the lipid hypothesis. (It is also curious why Roberts used the term "nonhuman animals.")

(3) "Atherosclerotic plaques large enough to produce clinical problems occur only in persons having serum or plasma total cholesterol levels > 150 mg for long periods of time."

In addition to the fact that this statement is false, nearly all populations in the world which have cholesterol levels below 150 mg have very short life expectancies. In addition, prospective studies such as the MRFIT follow-up of screened men clearly show CHD mortalities below 150 mg. One might advise Roberts to contact his fellow editor, Glen Griffin of Postgraduate Medicine, who recently underwent a bypass operation, despite the fact that his cholesterol level had been "under 150 mg."[1784]

(4) "The higher the blood total cholesterol level the greater the chance of having symptomatic and fatal atherosclerotic disease."

As emphasized elsewhere, this statement is totally false. One can say that when large groups of individuals are considered, there is tendency for CHD mortality to increase with increasing blood cholesterol level. However, this group phenomenon is due to a specific minority of individuals within that group. Factor #4 is not true for the vast majority of individuals within the group and this fact is well known to the alliance, as discussed elsewhere.

(5) "The higher the serum total and LDL cholesterol levels, the greater the extent of the atherosclerotic plaques."

Roberts cited the International Atherosclerosis Project as concluding that "the mean serum total cholesterol level correlated positively with the severity of the atherosclerotic plaques" and that "the severity of the atherosclerotic plaques also correlated positively with the percent of dietary calories from fat." Not only did Roberts fail to mention that the Project found no correlation between animal (saturated) fat consumption and either blood cholesterol level or plaque severity (opposite to the alliance's diet-CHD hypothesis), he also failed to mention other autopsy studies which revealed no association between cholesterol level and plaque severity (see Chapter 4). Furthermore, Chapter 3 reveals that LDL has not been adequately shown to be related to CHD in the Framingham study.

(6) "Lowering the blood total cholesterol and LDL cholesterol levels decreases the chances of fatal or nonfatal atherosclerotic disease."

Roberts cited the LRC[500] and Helsinki II[1056] trials as evidence for this statement. Chapters 7 in both volumes of this review amply demonstrate the weaknesses of these studies. Suffice it here to say that, like all alliance members, Roberts carefully omitted the most important finding from these trials, i.e., cholesterol-lowering reduced all-cause mortalities by zero percent.

(7) "Atherosclerotic plaques regress when high blood cholesterol levels are lowered."

Roberts cited irrelevant animal studies and the two angiographic studies by Brensike et al.[836] and Blankenhorn et al.[760] The former study found no statistically significant regression, indicating that Roberts attributes importance to statistically nonsignificant findings. With respect to the Blankenhorn et al. study, the reader is referred to Chapter 7. However, it is useful to emphasize two observations. First, the Blankenhorn et al. study was funded by the pharmaceutical company supplying the cholesterol-lowering drugs used in the study. Second, atherosclerosis is highly prevalent in vegetarian and other populations whose cholesterol levels are much lower than those existing in the Blankenhorn et al. study, rendering their results highly suspect.

Roberts concluded his review by stating that "There is no longer any controversy about cholesterol's role in atherosclerosis." Key members of the NHLBI/AHA alliance have uttered almost the exact statement many times in recent years. Again, such statements would not be repeated so many times if they described a true state-of-affairs. They are, in effect, designed to convince readers of yet another fallacy, i.e., that the research community is now in complete agreement.

Arno Motulsky, Chairman of the committee which prepared the 1989 Diet and Health report, described the document as follows: "By drawing from the vast and diverse epidemiologic and laboratory data base, the Committee has attempted to ensure a comprehensive and critical review."[1976] DeWitt Goodman, Vice-chairman of the Committee, said that "What's special about this report is not that it's all new but that it's immensely, thoroughly documented."[1977] Both of these statements are not only false, the review was neither comprehensive nor critical. It was, however, extremely biased. Since it would require at least 200 pages to adequately address all of the deceptions presented in Diet and Health, the following discussion presents only several examples.[a]

A most important segment of the literature is that which comprises experimental studies on dietary cholesterol. Over 50 such experiments were published but Diet and Health reviewed only five, all of which were irrelevant because they involved liquid formula diets (see Chapter 5 for a detailed critique of these studies). In his criticism of Thomas Moore's Atlantic Monthly article, NHLBI director Lenfant[3380] said that the Diet and Health report "exhaustively reviewed" dietary studies. Apparently, therefore, Lenfant considers a review of 10% of the relevant literature as "exhaustive."

The Diet and Health report indicated that "Animal foods in general were related to CHD risk and total deaths in Seventh-Day Adventists (Phillips et al., 1978)." As discussed in Chapter 4, the Phillips et al. study reported highly inconsistent and contradictory findings. For example, while nonvegetarian males exhibited a higher CHD mortality than vegetarian males, the opposite finding was reported for females. Thus, the Food and Nutrition Board selectively omitted this information. Further, the animal eating subjects in the Phillips et al. study had a much lower CHD death rate than that of the general population, indicating that nondietary variables were the primary causes of the CHD death rate differentials.

In its general conclusions, the Board stated that "Epidemiologic data suggest that consumption of fish is associated with a reduced risk of CHD (Kronhout et al., 1985; Shekelle et al., 1981)." In their review section, however, they cited three studies which did not find relationships between fish consumption and CHD death risk. Thus, they drew their conclusion from the lessor amount of evidence. Further, the Kronhout et al. and Shekelle et al. studies were replete with problems and produced results

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[a] The Diet and Health report was funded primarily by private companies which have or may have vested interests in its contents, e.g., the Kellogg Company via its derived W.K. Kellogg Foundation.[2075]

inconsistent with the lipid hypothesis (see Chapter 4 of both volumes for a detailed discussion of the Shekelle et al. study and Chapter 5 of Volume 1 for a discussion of the Kronhout et al. study). Finally, there were additional studies not cited by the Board which did not support the conclusion that fish consumption reduces risk.

The Board also concluded that "There is clear evidence that the total amounts and types of fats and other lipids in the diet influence the risk of atherosclerotic cardiovascular diseases..." Yet, in the only between nations study considered acceptable to the Board, Keys' Seven Countries study, the Board's review section noted that the cohort having the lowest risk of CHD and total death also had diets very high in total fats (40% of calories).

The Board stated that "The results of studies of individuals within populations have in general been somewhat inconsistent and inconclusive." On the contrary, numerous within population studies have produced exceedingly consistent findings. The fact that they demonstrate no relationships between diet, blood cholesterol and CHD led the Board to the illogical conclusion that they were, therefore, "inconsistent and inconclusive."

The Diet and Health report included a mere 1 1/2 pages of text on a "review" of dietary clinical trials, most of which was devoted to two diet trials, the Veteran's Administration trial[454] and the Helsinki I trial."[1145] While the Board gave the reader the impression that both trials showed that diet was related to CHD, the Veterans trial yielded nonsignificant results and the Helsinki I trial was both unblinded and incredibly confounded (see Chapter 6). The authors of the Veterans trial stated in 1969 that "The results of our own trial, even when buttressed by concordant observations in two other primary prevention studies, are not sufficient grounds for aggressive efforts to change the U.S. diet."[2541]

The remaining 1/2 page of the Board's review of clinical trials briefly described the MRFIT,[474] the Goteborg[491] the WHO multi-factor trials[847] and the Oslo diet trial.[480] The Board indicated that three multi-factor trials demonstrated no effects of treatment but that the Oslo trial did show that cholesterol-lowering reduced CHD incidence. The Board failed to note, however, that the Oslo trial was unblinded.

Despite the overpowering negative results observed in the dietary clinical trials, the Board concluded that the "results of clinical trials strongly support the concept that lowering total cholesterol levels reduces incidence of CHD."

In summary, the Food and Nutrition report is a grotesque imitation of a "comprehensive and critical" review. The Board omitted large amounts of relevant and important literature, only rarely reviewed a study critically and repeatedly drew inappropriate conclusions.

Summing Up

Denying the existence of massive amounts of garbage in the literature may be called the ostrich technique. It merely perpetuates the problem. In 1988 Harvard drafted new guidelines which were intended to ease the "publish or perish rule."[2133] The guidelines warned against the publication of incomplete studies, salami slicing, etc. Hopefully, all universities will adopt such guidelines and provide means of enforcing them but it seems unlikely.

Apparently concerned about potential government regulation of their research "business," some universities began developing rules in 1989 with the intentions of eliminating conflicts of interest.[2143] Simultaneously, NIH developed guidelines to eliminate conflicts of interest among nongovernment researchers who receive grants

from that agency.[2150] These guidelines were submitted to a House Subcommittee investigating conflicts of interest and were intended to prohibit researchers and members of their immediate families from having financial interests in the companies whose products they are evaluating. "The high-tech industry (food and drug industries) is full of the kind of arrangement that the new guidelines would affect."[2298]

Representative Ted Weiss was pleased with the guidelines which were announced on September 15, 1989.[3272] Arnold Relman also agreed with the guidelines and indicated that the New England Journal of Medicine would henceforth require its authors to disclose financial holdings in companies whose drugs are the subject of their research. He said, "I believe it is very important for our society to be able to count on the unbiased, uninfluenced, dispassionate scientific judgment of academic investigators when it comes to biomedical technology. If the whole academic biomedical enterprise simply becomes a business, society has lost something essential. What can you absolutely trust?"[3111] (But did Relman maintain this stance subsequent to the guidelines being rejected?)

The guidelines were immediately attacked by drug companies, scientists, universities and investors who submitted in excess of 700 letters to NIH.[2587,2588,2682] One such letter was written by David Korn, vice-president and dean of Stanford University, the fifth largest recipient of NIH grants in 1988 of nearly $104 million: "I have found it impossible to conjure up effective measures that would protect us against conflict situations other than to continue to depend on individual integrity and to introduce policies and procedures of full and timely disclosure. To go beyond this point, in my judgment, is futile and will accomplish little else other than to stifle research activity and rapid transfer of the fruits of that research to the public benefit."[2588] It is difficult to believe that an educator could make such an astoundingly naive statement. Not only does his statement suggest that conflicts of interest should be protected, educators are perhaps the premier antagonists of "individual integrity." How many teachers, for example, eliminate all surveillance of students during examinations and leave the outcome to "individual integrity?"

The letter writing onslaught apparently resulted in the new Secretary of Health ordering NIH to dump their proposed guidelines.[2587,2725] He said, that the guidelines would result in a "regulatory burden" on researchers. He directed NIH to develop less constraining guidelines and indicated that they should go through the time-consuming process of being published in the federal register and allowing a period of time to pass for industry response. In effect, the massive conflicts of interest will continue to flourish, drugs will undoubtedly be praised by researchers who are motivated more by their financial interests in the drugs than by the efficacy of the drugs.

The general idea of ensuring by government regulations that universities spend taxpayers monies properly seems to particularly disturb the editorial staff of Science. On July 13, 1990 Daniel Koshland[3133] asserted, "History shows such a [medical research] system can be destroyed by excessive suspicion or excessive neglect. A spirit of compassionate skepticism is needed to make it work." Several months later (February 8, 1991) an editorial by Philip Abelson[3186] said, "In a world where uncertainty and danger will always be a part of living, the need to foster competence in research and development should be obvious. But apparently Congress and the administering agencies have lost sight of this goal. In an effort to ensure impeccable use of public funds, they have piled law after law and regulation after regulation on all those conducting research. Many of these laws and regulations are applicable to the universities. They have given rise there to administrative bureaucracies and to diversion of scientists from their creative efforts." But as will be seen below, the regulations seemed not to have diverted university officials from creative fraud.

One year after Stanford's Korn severely criticized NIH for imposing guidelines and not allowing "individual integrity" to oversee research activities, and 8 and one months after Koshland's and Abelson's editorials, respectively, a federal audit of Stanford's medical research charges to the government revealed perhaps the most outrageous fraud ever perpetrated by a university upon American taxpayers. It was estimated that Stanford may have overcharged the government in fraudulent overhead expenses as much as $200 million during the 10 years in which Donald Kennedy has been the university's president.[3084] Among the many fraudulent charges were,[a]

depreciation on Stanford's 72-foot yacht
Kennedy's university house
university-owned residences
enlarging Kennedy's bed
liquor
flowers
refurbishing a grand piano
cedar closet for Kennedy's house
Kennedy's post-wedding reception
fruitwood commode
furnishings, including antiques
administrative costs associated with a profitable shopping center owned by Stanford.[b]

When representative John Dingell began congressional hearings on Stanford's abuses of research overhead spending on March 11, 1991 Stanford had already withdrawn $690,000 in charges to the government but insisted it had done nothing wrong. Kennedy said, "We fully expect Stanford to emerge from the vigorous scrutiny now underway a stronger and more effective institution in serving the public interest."[3180] Prior to the audit, however, it was clear that Stanford was serving the interest of Stanford more than those of the public.

The following day (March 12) Kennedy issued a warning that a crackdown on the charges by universities could seriously affect medical research. "I would hate to see a quick legislative or administrative fix that in effect throws the baby out with the bathwater."[3181] Kennedy acknowledged that the university should not have charged the government for some things but said that they were "quantitatively small errors." While the theft of $100 constitutes a felony, apparently Kennedy did not consider fraudulent charges dwarfing $100 a crime at all.

In overviewing the many fraudulent overbillings by Stanford, Representative Dingell asked, "And where was the [Stanford] Board of Trustees while all of this was happening? They were at Lake Tahoe on a retreat costing $45,250 that was also subsidized by the taxpayers."[3182] Dingell used such terms as "great incompetence," "rascality" and "outlandish charges" to describe Stanford's officials. Kennedy admitted that such charges as those associated with the Stanford yacht were "mistakes" but denied that they were purposely intended to defraud the government.

But despite the denials, the overcharges were, of course, purposely intended to defraud the government. What else could they be? Only the dumbest of persons would consider such charges legitimate overhead costs, particularly as there were many and varied over a long period of time. When Kennedy had trouble explaining some of

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[a] 3084,3180,3181,3182,3183

[b] By September 1991 improper billings were still being uncovered, e.g., $1,300 per year unkeep of a campus mausoleum.[3415]

the billings at the congressional hearings, such as for silverware that was already owned by Stanford, Representative John Bryan said, "It is really a disappointment to me to see the president of a fine university stonewalling the committee like a common politician."[3182]

Speaking before the Stanford University Alumni Association, Kennedy finally fully acknowledged Stanford's wrongdoings and publicly apologized.[3183] He said the abuses were "highly embarrassing" and that "I owe you an expression of deep regret and apology that we have not met our historical standards in this affair. I take full responsibility for the management of the institution, and I am sorry it has let you down." Not only did Kennedy apologize to the wrong people, it is clear that he did so only after it was certain that Stanford had been caught red-handed in long-term fraudulent activities. Yet, he still maintained that such activities were the result of "poor judgment" when greed was obviously a far more accurate explanation. He said, "We pursued what was permissible under the rule, without applying our more customary standard of what was proper."[3183] This statement effectively admits that they were engaging in unethical ("improper") practices. (Kennedy announced his resignation in July 1991 as Stanford's president.[3416])

There will hopefully be substantial fall-out from the Stanford scandal. For example, during the congressional hearings, Caltech withdrew more than $500,000 it billed the government from 1987 to 1990.[a] Of that amount, $80,000 was for a retreat by school trustees and entertainment. A spokesman for Caltech suggested that there was no wrongdoing but that it would have "taken hours sifting through minutiae" to justify the charges."[3182] If we assume "hours" to be 10, then it would appear that Caltech did not consider $50,000 per hour was worth the time.

According to a March 11, 1991 article, there was renewed discussion concerning rules governing federal monies for university research.[3182] One can only wonder how much waste and corruption must be uncovered before the government finally establishes rules that will protect taxpayers' monies from being so outrageously abused by universities. When one fully recognizes the abundance of conflicts of interest and the purposeful misappropriations of massive amounts of taxpayers' monies occurring routinely at major universities, only the naive could possibly conclude that the medical research conducted by universities has somehow remained free of fraud. Indeed, this writer has found evidence of widespread fraud.

THE MEDIA

Introduction

If the evidence against the diet-CHD hypothesis is so strong, why is it not known to the public and physician practitioners? That is a question this writer sought to answer. The following subsections discuss personal experiences with the press and medical journals and the level of objectivity exhibited by popular syndicated physician columnists. With regard to the latter, special attention is devoted to Frederick Stare, one of the earliest and most prolific promoters of the diet-CHD hypothesis.

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[a] Harvard, Massachusetts Institute of Technology and Michigan University also withdrew $500,000, $731,000 and $5.9 million, respectively, at the time of this writing.[3311,3312,3413]

Personal Experiences

We are told repeatedly that one reason why America is a great and free country is because we have a great and free press. But great and free to who? Certainly not to the public. In the course of researching the literature and preparing the present review, this writer observed innumerable times that the press has been anything but free with respect to the diet-CHD issue. As evidence supporting these observations, consider what the press has published on the issue and consider the receptivity of the press to information that departs from the AHA's dogma.

Hundreds of newspapers have regularly published syndicated physician columnists Frederick Stare, Jean Mayer and Lawrence Power for three decades and each has spewed the dogma of AHA with such incredible frequency they appeared to be little more than mouthpieces for the AHA. Not one of them demonstrated a scientific understanding of the literature. In addition, thousands of other articles were published periodically which essentially repeated the same dogma in more detail. Rarely, if ever, were articles published which even suggested that there were valid scientific arguments against the notion that diet was a cause of CHD.

The press always prides itself as disseminating all the news no matter what. If a president is ejected from office in the process of giving the public all the facts, that can't be helped, we are told. But why has not the press disseminated all the facts on the diet-CHD issue? Could it be that it was simply unaware of all the facts? To answer these questions, this writer wrote informative letters (some quite lengthy) to Walt Bogdanich and George Melloan of The Wall Street Journal, Lawrence Altman of The New York Times, Curt Supplee of The Washington Post, Harry Nelson and Robert Steinbrook of The Los Angeles Times, and Andy Furillo of The Los Angeles Herald-Examiner. Not one of these reporters even so much as acknowledged receipt of the letters. In addition, a letter was submitted to syndicated columnist Jack Smith, requesting that he give this writer permission to quote material from his 1970 article which poked fun of the verbiage in a 1970 Framingham report.[a] Smith also did not acknowledge receipt of the letter.

If each of the above reporters/writers were independently asked why they did not respond, he would probably say that he never received such a letter. But say what you will about the U.S. Postal Service, it is not likely that it failed to deliver one of the letters, let alone 8. And this is not the end of the story.

Letters were sent to television reporters George Will, David Frost and Russ Nichols. None responded but an assistant to Will at least acknowledged receipt, albeit with disinterest.[2110]

Letters to the editor were submitted to the Magazines McCall's, Family Circle and Redbook. Neither McCall's nor Family Circle acknowledged receipt of the letters and Redbook rejected it. The latter's response is partially reproduced here because it provides some insight into why the public gets an unbalanced view from the press.[2111]

Dear Dr. Smith:

"In articles such as we publish at Redbook, authorities have to be cited. The experts and institutions which Redbook quotes are the ones which are shaping and establishing our national health and nutrition policy."

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[a] No permission was necessary, of course. The purpose was to determine Smith's position today as a member of the press.

"We appreciate and respect the detailed concern you have voiced. We also urge you to share them with the people and institutions you challenge and question."

Sincerely,
Margaret E. Happel
Food and Nutrition Editor

The magnitude of the naivete inherent in the second sentence is so great, it is nothing less than bewildering.

A very detailed letter was submitted to Joseph R. Botta, science editor of Consumer Reports, describing the counter-arguments to the diet-CHD issue and offering as much or as little material as desired. Beyond the "thank you for your interest" verbiage. Botta's reply was, "We follow this issue quite closely and prefer to conduct our own research into it."2112

A 5,000 word article was submitted to Peter Bloch of Penthouse Magazine, summarizing the entire diet-CHD story. The article was neither acknowledged nor returned.

Perhaps saddest of all was the reaction of the American Association of Retired Persons (AARP), representing individuals most likely to be subjected to costly cholesterol-lowering drugs. A personal friend of this writer and a significant employee within the AARP approached the executive editor of the AARP's Modern Maturity Magazine, John Wood, about an article presenting the other side of the diet-CHD story. The friend assured Wood of this writer's credibility but he apparently decided that the millions of readers of Modern Maturity should not be exposed to both sides of the diet-CHD issue.

A detailed summary of Diet, Blood Cholesterol and Coronary Heart Disease was offered for publication in the British medical journal Lancet and the American journals New England Journal of Medicine and the American Journal of Clinical Nutrition. David Sharp of Lancet rejected the summary because it was "far too thorough and exhaustive."2113 The editor of the New England Journal of Medicine, Arnold Relman, rejected it because "it is much too massive for our use."2114 Albert Mendeloff, editor of the American Journal of Clinical Nutrition, said that "It appears that you have already published it and have it copyrighted, therefore it cannot be published in the Journal. If you wish to send us the larger document and have it considered as a book for review, we will be happy to have it reviewed."2115 Since the summary was a technical report, it could have been published in any journal and the copyright issue was not a constraint at all because permission to publish the summary was given to Mendelhoff. In any event, the large document was sent to Mendelhoff. Several months later he wrote that "two experts" had read the document and that "They advise our listing the volume, but believe, since it is essentially a compilation of work by many scientists, that it is not necessary to provide a journal review of the document."2550 That rationale was so illogical and ludicrous, one cannot help but speculate about hidden motives for refusing to review the document. In view of the fact that many food and drug manufacturers are experiencing large profits from the NCEP and that 22 of the sustaining members of Mendelhoff's journal are major food and drug manufacturers (e.g., Procter and Gamble, Quaker Oats Company, Hoffmann-LaRoche, Inc., Miles Laboratories, etc.), it seems likely that a review of the document was rejected because it was not in the best interests of these food and drug manufacturers. While such a likelihood would certainly be denied by Mendelhoff, he would also be hardpressed to explain his rejection rationale. After all, most medical books are, in large part, compilations of the research of others.

The large document was also sent to only one publisher of medical books, Hemisphere Publishing Corporation, because of the nature of the subsequent rejection. An editor[3184] of Hemisphere wrote,

Dear Dr. Smith:

I regret to advise you that our Editorial Board's decision is one to decline your publishing proposal due to marketing constraints because of this very controversial topic. This is in no way a reflection on the merits of your book. We believe it to be a worthwhile work, however, our publications are primarily targeted to physicians, libraries, and the general medical community, who invariably are fully in accordance with the views of the AHA as well as the National Heart, Lung and Blood Institute. It would, therefore, be counter productive for us to publish such a volume and would not enhance your aim which is to refute their findings.

It was apparent that all publishers would maintain the same stance. There was only one voice permissible on CHD research, that of the NHLBI/AHA alliance.

It is possible, of course, that this writer was so incompetent he was universally perceived as such. That does not seem to be a likely explanation because very prominent physician researchers gave high praise to this writer's documents. For example, Great Britain's Michael Oliver stated that "Much of what you have written needs to be published in a mainline journal and, for that matter, republished since the message needs reinforcement."[2116] True pioneers of the diet-CHD research program, Edward Ahrens and George Mann referred to the summary document as "momentous"[2117] and "an outstanding review,"[2118] respectively. Very recently, long-time diet-CHD researcher Raymond Reiser kindly referred to the large document as a "magnum opus."[2119] Compliments were also received by many lessor known individuals.

We may not wish to go so far as to say that the NHLBI/AHA alliance "controls" the press and scientific medical journals but it would seem that only the naive would deny that they are, at minimum, strongly influenced.

The following subsections provide numerous examples of what and how the media communicate to the public. The "what" is NHLBI/AHA dogma and the "how" is nonscientist physicians and reporters, neither of which actually read the scientific literature. Just as a professional football organization would not think about hiring a nonphysician to perform surgery on its players, it is likewise unthinkable that (particularly wealthy) newspapers, TV channels, etc., would hire nonscientists to interpret and report scientific findings. But that is precisely what they do. While the "M.D." may appear impressive beside a syndicated columnist's name, it is usually a guarantee that he neither reads nor fully understands the scientific literature.

Syndicated Physician Columnists

In the early period in which the AHA was establishing its presence and position on the diet-CHD issue, i.e., 1958 to 1966, some syndicated medical columnists such as Alvarez[a] and Molner[2045,2046] exhibited skepticism about the importance of diet to CHD. Frederick Stare was initially skeptical before 1958 but promoted AHA's dogma in his columns until about 1972, at which time his Harvard colleague, Jean Mayer, took over the column. Lawrence Lamb and Lawrence Power also published columns in the 1970s and 1980s.

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[a] 2047,2048,2049,2050

Six 1970 columns of Lamb were reviewed.[a] All repeated the dogma of AHA but three were of particular interest for other reasons. In a 1972 column he indicated that the egg industry expressed anger with him for recommending limited consumption of eggs.[2052] Amazingly, he said, "At issue here is not even the question of whether the AHA and many of the leading nutritionists...are correct, but your right to know what the scientific bodies have recommended." He went on to say, "I shall continue to report what our scientists have found, not because of the old journalistic adage of the truth no matter who it hurts, but the truth because of who it helps--the millions of daily readers of this column." Note that his argument initiated with reporting the AHA's recommendations, right or wrong, then altered his stance by indicating that he and the AHA speak only the truth.

In a 1974 column he reported that egg cartons contained the following statements: "Research indicates eating eggs will not increase serum cholesterol in the average person if they are not gaining weight and; "Research indicates high levels of serum cholesterol are not correlated with high risk of heart attack in most people."[2054] Although both statements were either nearly or fully correct, Lamb concluded that "Examples like this one lead me to think that consumers really do need a watch dog in terms of food and health."

In a 1978 column Lamb indicated that a survey of researchers world-wide revealed that 99% believed there was an association between diet and heart disease. The question is, why is a survey necessary if the facts are clear? Obviously, clinical judgements were surveyed and Lamb equates such judgements as facts, just as he viewed AHA's dogma.

Jean Mayer's columns were not only indistinguishable from Stare's, they were often indistinguishable from each other. For example, a column in 1978[2156] was, with the exception of a few words, exactly the same as one published in 1975.[96] Throughout the 1970s and 1980s Mayer repeatedly recommended the reduction in total fats, saturated fats and cholesterol and the increased consumption of polyunsaturated fats.[b] With boring regularity, he cautioned his readers to consume no more than two eggs per week.

Like other syndicated columnists, Mayer was especially critical of the egg industry for defending itself. In at least two columns in 1974 he criticized the National Commission on Egg Nutrition (an egg industry agency) for advertising that "There is absolutely no scientific evidence that eating eggs, even in quantity, will increase the risk of heart attack," even though that ad was scientifically correct.[160,1980] In the same year a Mayer column was cited by Elzinga as suggesting that egg cartons should have the warning, "eating eggs is dangerous to your health."[1988]

In a 1976 column Mayer said that "cholesterol is a fat[2154] but several years later he said it "is part of the lipid family, which also includes fats."[2155]

Particularly bad reporting was demonstrated in a 1984 Mayer column.[2158] In discussing the results of the LRC trial, Mayer stated that diet trials could only produce a blood cholesterol reduction of 5%, necessitating a huge, costly trial to obtain statistically significant results. Quite obviously, Mayer had no knowledge of the subject because previous diet trials depressed blood cholesterol levels more than did drug trials, including the LRC study.

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[a] 2051,2052,2053,2054,2055,2056

[b] 96,101,127,160,183,1716,1978,1979,1980,1981,1982,1988,2154,2155,2156,2158

Lawrence Power's columns were also relatively indistinguishable from Mayers', principally because they also faithfully promoted AHA's dogma.[a] He also repeatedly warned his readers to greatly reduce their consumption of eggs. One particular quote in 1979 on this subject was especially interesting, i.e., "The largest, best-designed and best controlled feeding studies have demonstrated that two egg yolks a day raise blood cholesterol levels--but not in everybody."[108] This writer has no idea what "large" studies to which Power was referring. As noted in Volume 1 almost all "large" studies have found nonsignificant effects of eggs on blood cholesterol levels.

In 1978 Power[135] defined polyunsaturated fats as "friendly" fats and indicated that Americans had "been eating less of them for the past 50 years" which, of course, was absolutely opposite to reality. Eight years later Power[3322] said, "Over much of this century, people in developed countries have been the unwitting participants in nutrition experiments of unprecedented scale. One of the experiments has involved the manipulation of edible oils and their addition to our diet. Food technology has given us edible oils in abundance, but at unnatural levels of dietary concentration. The new research is beginning to indicate that the polyunsaturated fats in such vegetable oils, including the oils of soybean and safflower seeds, are contributing to recurring, painful inflammatory states such as headache, arthritis and phlebitis. Our diet is awash in...polyunsaturated vegetable oils." No where in Power's 1986 article was the word "friendly" associated with polyunsaturates.

Frederick Stare is an enigma of monumental proportions. Through his prolific writings he has undoubtedly influenced millions of people hundreds of times over a period of more than 30 years. For many of those years he repeated the dogma of AHA faithfully. For the remainder, he has preached almost entirely opposite philosophies. And during the entire period, he appeared willing to endorse any industry and any product in return for financial rewards. Were it not for his significant impact on Americans, this report would not devote special attention to his writings. Because of his key role in promoting the diet-CHD relationship, it seems important to describe at least some of his history.

It will be recalled in Chapter 2 that Stare was one of the authors of a 1957 report to the AHA which concluded that there was no evidence to associate diet with CHD.[512] Elsewhere he wrote, "Should you start eating more meat, and particularly more animal fat? That depends on what you like to eat, how much you want to spend for food, and how carefully you watch your weight."[2063]

One year later he co-authored a public statement which described the presumed importance of controlling risk factors.[539] And in 1961 he was one of five authors of the first AHA statement recommending that Americans reduce their intake of cholesterol and saturated fat and "substantially" increase the ingestion of polyunsaturated fats.[517,b] For many years thereafter in his syndicated column he warned readers that saturated fats and especially eggs were contributors to heart disease.[1983,1984,1985,c] And like the AHA's Campbell Moses and others, he ridiculed the 1970 Framingham report which revealed no association between diet and CHD.[1987]

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[a] 28,108,111,112,135,198,207,298,299,1715,2159,2160

[b] Elsewhere in the same year Stare said that total calories in th diet were more important than the type of fat.[2058]

[c] In 1967 Stare claimed that researchers who still doubt the CHD-cholesterol relationship are not keeping up with medical advances.[2057]

An attempt was made to obtain every column published by Stare in the Los Angeles Times in the year 1969. Apparently 38 columns were published, of which 74% promoted one or more AHA recommendations.[a] In fact, the column appeared to be little more than a promotional arm of the AHA. Stare recommended or implied the reduction in consumption of red meats 9 times, of saturated fats 21 times, of eggs 13 times, of dietary cholesterol in general 13 times, and of salt 7 times.[b] He also recommended increased consumption of polyunsaturated fats 11 times.

In one 1969 column he stated, "To my knowledge, I've never heard of too much polyunsaturated fat for man..."[1959] Yet, in 1957, in answering the question, "Do high polyunsaturated fat diets cause any ill effects?, he had answered, "Any drastic changes in the accustomed diet could lead to unforeseen metabolic disturbances--a good reason to always be careful about recommending drastic changes in the diet until an abundance of convincing evidence is available on all points involved."[3291] In another article Stare described USDA Prime beef as the highest quality grade, followed by Choice and Good, without noting that the higher grades of beef were associated with higher contents of fat and saturated fat.[1968]

Three 1969 columns provided readers with different implications. "Chocolate is a perfectly good food for children and adults and like most other foods, can be a component in the diet in reasonable amounts."[1968] "Chocolate contains no cholesterol but is a potent source of saturated fat."[1971] "The fat of the cocoa bean (chocolate) is rich in saturated fat and this type of fat favors the formation of cholesterol by the body tissues."[1974]

Stare continued to recommend dietary changes in 1972[106] and 1973.[389] In the latter year he accused "a few researchers" who disagreed with him and the AHA and indicated that they "foster confusion among practicing physicians who, after all, have the responsibility of treating patients." Stare would soon reverse his philosophy and probably produce more confusion than any other individual in the country.

After many years of claiming that a CHD epidemic occurred in this country, caused in large part by diets, Stare co-authored a book in 1983 which made the following statements: "Beyond the bounds of logic is the popular premise that America is now in the midst of an 'epidemic' of noninfectious 'killer diseases.' The favorite corollary is that most of these 'killers' are allegedly related to faulty nutrition." "...mortality from coronary heart disease has decreased about 30% in the last 30 years."[1948] In point of fact, there was no popular premise that a CHD epidemic was occurring in 1983 and mortality from coronary heart disease had been decreasing since 1963, not 1953 as implied in their statement.

Contrary to many years of recommending dietary changes, Stare indicated agreement with the 1980 Food and Nutrition Board's report (rejected by NHLBI and AHA) and stated that "Other than recommending weight control, we feel it is premature to suggest basic and specific nutrient changes in the diet of healthy Americans. There is no reason to believe that normal consumption of eggs, meat and dairy products as part of a balanced, varied diet, poses any hazard to healthy members of the general population."

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[a] 1941-1945, 1952-1974

[b] With regard to salt reduction, Stare strongly indicated that a "drastic" reduction was necessary to lower blood pressure.[1944]

Of unique interest Stare presented a list of descriptors on "how to spot a nutritional quack." Five of these descriptors follow:

(1) "The quack always has something to sell: a course of lectures, vitamin preparations, tonics, nature foods, diet plans, reducing machines, natural cosmetics, books..." Stare has been selling his advice throughout the media prolifically for decades.

(2) "The quack usually claims to be a 'medical expert' or a 'leading nutritionist,' and is often the president or director of an important sounding (if nonexistent) 'scientific society.'" Stare always reminds his reader that he is professor of nutrition at the prestigious Harvard University, although he has been retired for many years.

(3) "The quack...suggests that everyone is suffering from poor nutrition." In a 1969 column Stare said, "If one considers tooth decay, osteoporosis,, coronary heart disease, obesity and iron deficiency anemia as examples of poor nutrition (which I think they are), there is considerable malnutrition among all economic levels of our society."[1944]

(4) "The quack distorts scientific data to suit his own ends." Since Stare interpreted the same scientific evidence on diet and CHD in the 1980s far differently than in the 1960s and 1970s, there is every suggestion that he has distorted the data "to suit his own ends."

(5) "Similarly, the quack puts together his own unscientific data." The present discussion on Stare provides ample examples of how he "puts together his own unscientific data."

In 1986 Stare published a letter-to-the-editor in FDA Consumer in which he said, "far too much emphasis to the hazards of saturated fat and dietary cholesterol and not enough to the hazard of too many calories" is given by the magazine.[2061] And in 1989 he maintained that blood cholesterol "plays only a minor part in this (CHD) disease" and "Many Americans have developed an unnecessary cholesterol-phobia brought on by undue emphasis on cholesterol in food and in the blood."[1946]

Stare probably reached the peak of his departure from AHA philosophy with his letter-to-the-editor in the Journal of the American Medical Association in 1989.[1928] "The cholesterol factor is of minor importance as a risk factor in cardiovascular disease" (implying that diet's effects on cholesterol must also be, at most, minor). "The NCEP...aided by the AHA and now the AMA is, in my opinion, most unfortunate because it gives undue emphasis to a minor risk in cardiovascular disease and thus a false hope to millions of individuals."[a] He also criticized TV's Arthur Ulene for capitalizing on his TV fame by selling health education materials on the air on CHD.[b]

It is difficult to know exactly when Stare switched positions on diet and CHD and there is evidence that he takes both positions when it "suits his own ends." For example, it has been shown that his writings from 1983 to the present have recommended no fundamental changes in the diets of "healthy Americans" and emphasized that blood cholesterol level is a minor factor in CHD. Yet, in 1986 he

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[a] Yet, Stare testified under oath at the 1975 FTC-NCEN trial that blood cholesterol was one of three significant risk factors for cardiovascular disease.[2689]

[b] AMA spokesperson Seekins[1929] and Ulene[2460] accused Stare of expressing an opinion on blood cholesterol that was not shared by the NCEP's Expert Panel and "the majority of the experts."

...ssumably prepared a "review" of studies for Procter and Gamble Company which strongly associated diet with CHD and, in particular, suggested that Procter and Gamble's Puritan Oil would decrease the risk of CHD.1372,a The "review" was replete with false or misleading information. For example, he cited 11 studies as providing data associating fat and saturated fat with increased risk of CHD. In fact, 8 of those studies had nothing to do with relating any kind of fat with CHD. He also cited 8 studies as providing evidence that unsaturated fats are associated with a reduced risk of CHD. In fact, virtually none of those 8 studies provided any empirical evidence showing that unsaturated fats reduce CHD risk.

Stare's promotions and endorsements of a wide variety of products lends considerable insights into the apparent ease with which he promotes both sides of the diet-CHD issue. While at Harvard University, Stare solicited and obtained many millions of dollars from a wide array of food and drug industries. Table 9-1 lists the companies which were "large regular donors to Dr. Frederick J. Stare's nutrition department" as of 1978, according to Hess.2059 In the same year, Representative Benjamin Rosenthal reported that "some eminent nutritionists have traded their independence for the food industry's favors."2062 He cited a CSPI study which said, "One can only come to the conclusion that industry grants, consulting fees and directorships are muzzling, if not prostituting nutrition and food science professors."

Harvard was specifically singled out as the worst offender.b

Indeed, Stare promoted almost everything and, according to other writers, for lucrative fees.

In 1976 FDA hearings on proposed food supplement regulations, Stare testified on behalf of the Cereal Institute, Corn Products Co., the Pharmaceutical Manufacturers Association, National Biscuit Co., Kellogg Co. and the Sugar Association.2068 He said that the cereals (which contained as much as 70% sugar) were nutritionally better than old-fashioned breakfasts.2059 In his media presentations, he said, "There is no convincing evidence that in the average American diet decreasing the intake of sweets will lessen tooth decay."2065 In his syndicated column he said he had eggs for breakfast in Moscow but would have preferred (apparently the sugar laden) cereals to the eggs.1987

Some of Stare's pronouncements include: DDT and other pesticides are harmless in ...oods; the DES food supplement for cattle is harmless; and red dye #2 is ...armless.2059 Murray and Tarr quoted Stare as saying, "Eat your additives: they are ...od for you. All current information points to the fact that they present no hazards ...en if you eat artificially colored foods in quantity everyday."2067 Pinckney and ...nckney pointed out that Stare has written on behalf of the National Fisheries ...titute such erroneous statements as fish has less cholesterol than milk.39 ...ewhere, he recommended the consumption of fish twice a week.1321

More recently Stare has publicly stated that fast foods have "substantial nutritional ...e"2060 and has written on behalf of the beef industry.1946 In 1989 his name was

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...though a Procter and Gamble pamphlet mailed to physicians, Stare's name was ... as the author, followed by "Puritan Oil Press Conference, August 1986."

...special audit of Stare's Harvard department the year before revealed that the ...ment misused $132,000 of federal grant money. Stare was determined to be ...sible for this abuse.2065

Table 9-1

Food and drug industry donors to
Stare's nutrition department
(from Hess, 1978,[2059])

Ajinomoto Company of New York
(a monosodium glutamate marketer)
Amstar Corporation
Beatrice Foods
Beech-Nut, Inc.
Campbell Institute for Food Research
Carnation Company
Coca-Cola Company
Continental Can Company
Council for Tobacco Research
CPC International
E.R. Squibb & Sons
Foundation Funds of Norton Simon
(food packer)
General Electric Foundation
Gerber Products Company
Grocery Manufacturers of America
H.J. Heinz Company Foundation
Hoffman-LaRoche (pharmaceuticals)
International Sugar Research Foundation
John A. Hartford Foundation
(the A & P parent fund)
Kellogg Company
Kraftco
Lever Brothers Company
Marion Laboratories
MEDCOM, Inc.
Miles Laboratories
Monsanto
Nabisco, Inc.
National Biscuit Co. Foundation
National Canners Association
National Fisheries Institute
Nestle Foundation
Nutrition Foundation*
Oscar Meyer & Co.
Pepsico Foundation
Perdue, Inc.
Pfizer, Inc.
Procter & Gamble
R.T. French Company
Richardson-Merrell
Searle Laboratories
Smith Kline & French Laboratory
Standard Brands
Star Kist Foods
Stouffer Foods
Sugar Association
Swift and Co.
Thomas J. Lipton Foundation
Tuna Research Foundation
United Brands Foundation
United Fruit Company Foundation
United States Brewers Assoc.

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* Supported by Armour & Co., Abbott, Inc., American Sugar Refining Co., Baker Laboratories, Campbell Soup Co., Gelatin Co., Coca Cola Co., Continental Baking Co., General Foods Corp., General Mills Co., Gerber Products Co., H.J. Heinz Co., Kellogg Co., Libby, McNeil & Libby, Knox Gelatine, Merck & Co., National Biscuit Co., National Dairy Prod., Nestles Co., Inc., Pepsi-Cola Co., Pet Milk Co. and more.[2064]

listed on a full-page newspaper ad which stated, "There is no scientific evidence that residues in food from regulated and approved use of pesticides have been the cause of illness or death in either adults or children."[1947]

Although Stare refused to disclose his "consulting fees from companies, he did admit in 1970 that he had been receiving fees for "15 or 18 years."[2066] Yet, when asked in 1975 during the FTC-NCEN trial whether he received fees for his consulting work with industries, Stare testified, "I would say essentially none. Essentially none. I can't honestly say that I have never accepted an honorariam but I am on no firm basis."

Frederick Stare is not merely an example of conflict of interests, he is one massive conflict of interests. Yet, newspaper columnist Marion Burros quoted him as saying, "I really honestly feel I have not reduced my credibility."[2066]

Nonphysician Columnists/Writers

Many journals send advance copies of issues to the media with the constraint that media articles must be withheld until the day the issue is actually published. According to Driscoll, "This allows journalists time to write and edit their copy. When used properly, this system works well."[2659] As will be seen, the system does not work well because journalists are journalists and they can no more analyze and interpret scientific medical articles than they can scientific physics articles. Typically, they assume medical articles are flawless and regurgitate the authors' findings and conclusions. They also introduce errors in the process.

Jane Brody, the "Personal Health" columnist of the New York Times wrote in her November 11, 1986 column, "The dozens of letters I have received in response to recent columns on fats and cholesterol in foods indicated that many readers remain uncertain about how to choose a heart-healthy menu."[21] As we will see, it is effectively impossible not to be confused by her columns because they are not only contradictory, they frequently provide totally incorrect information.

In her November 5, 1986 column Brody said, "Cholesterol...is usually, although not always, associated with fat. Thus, whole milk...contains seven times as much cholesterol as fat-free skim milk."[19] In the first place, cholesterol is predominantly in the muscles of animals, not in the fat; milk products are the exception. In the second place, according to the USDA's Nutritive Value of Foods,[946] whole milk has three times, not seven times the content of cholesterol and the absolute amounts are not large, i.e., 33 mg vs 10 mg.

Also in her November 5, 1986 column Brody said that "It is not advisable to consume large amounts of polyunsaturated fats because, while they lower the damaging LDL and VLDL cholesterol in the blood, they also reduce the protective HDL cholesterol."[19] But one month later (December 10, 1986) she said, "Experts recommend substituting unsaturated liquid vegetable oils (corn, safflower, sunflower, soybean [all polyunsaturated] and olive oils, for example) for saturated fats. Unsaturated oils in the diet help to lower cholesterol levels in the blood."[20]

Brody also gave readers confusing and conflicting information in her December 10, 1986 column regarding fish fat. She maintained that "Fish oil capsules cannot be taken to counter the unhealthy effects of a typical American high-fat diet" and then said that "Fatty fish are recommended because fish fat is largely unsaturated and contains [polyunsaturated] fatty acids shown to protect against heart disease and cancer."[20]

After encouraging readers to increase their consumption of polyunsaturated fats, Brody warned readers of the dangers of polyunsaturates in her March 11, 1987 column, i.e., "A...problem results from overconsumption of polyunsaturates, which can interfere broadly with immune responses. Too much total fat, particularly too many polyunsaturates, can also promote the growth of cancers of the breast, colon and prostate. ...a wise consumer would stick to a low-fat diet and keep consumption of polyunsaturates at a minimum level."[2207]

In a column probably published in 1988, Brody said, "The studies by dozens of scientists also show that polyunsaturated fats, which have been widely recommended as replacements for artery clogging saturated fats, can, when consumed in amounts now common in American diets, impair normal immunological responses. This impairment, in turn, might increase the risk of developing certain infections or even cancer. Researchers say that polyunsaturates, even when consumed at the recommended level of 10 percent of total calories, could be hazardous"[2453] [The AHA recommends less than 10%, not 10%]. But in the March 15, 1988 issue of Family Circle Brody again pushed polyunsaturates. "Polyunsaturated fats help lower cholesterol levels in the blood and, thus, offer protection against heart disease. ...you'll want to look for a margarine that lists a higher proportion of polyunsaturates than saturates."[2241]

In the same Family Circle article Brody appeared to promote fish oil capsules when she said, "Fish oils often contain a type of fatty acid called omega-3--shown to be especially useful in lowering blood cholesterol and triglycerides."[2241] As noted in Chapter 5, moderate amounts of omega-3 fish oils appear not to reduce LDL levels and may, in fact, increase them when high levels of triglycerides are decreased.[121,1195]

In the October-November 1988 issue of Modern Maturity Brody said, "Try to use as little fat as possible and, when fat is added, primarily use vegetable oils such as olive, corn oil and safflower oil, and margarine,"[2229] most of which is polyunsaturated fat. Brody also gave the impression that only carbohydrates were healthy foods. In addition to saying, "Try to use as little fat as possible," she said "A three-ounce serving of lean meat or skinless poultry is adequate for a meal. Excess protein in itself is now considered a potential health hazard."

But by far the most blatantly false information given to Modern Maturity readers was her statement that "While 20% of the calories in a typical steak, roast or burger come from protein, the remaining 80% come from fat, and most of that fat is cholesterol-rich, artery clogging saturated fat."[2229] The following data from the USDA's Nutritive Value of Foods[946] show that Brody's statement contains several major errors. First a sirloin

	---Percent of total calories---			
Meat	Protein	Fat	Sat. Fat	Cholesterol (mg)
Lean sirloin	59	36	16	25.6/oz
Sirloin + fat	38	56	24	25.7/oz
Lean hamburger	37	63	24	24.7/oz
Reg. hamburger	33	66	25	25.3/oz

steak with the outer layer of fat (which few people consume), has twice the percentage of total calories as protein than indicated by Brody. Removal of the outer layer of fat shows a ratio of protein to fat that is almost the opposite to that expressed by Brody, i.e., 1.64 vs her 0.25. Her percentages of protein and fat were also way off the mark for regular and lean hamburger and would be even further off

the mark for extra lean hamburger and especially for hamburger ground from chuck or round steaks trimmed of their outer layers of fat, consumed by many people.

It is noteworthy to mention that there is not much difference between lean and regular hamburger because the values were based on cooked patties, where much fat is automatically separated from the lean meat.

Contrary to Brody's remarks, beef fat is not "cholesterol-rich." In fact, as can be seen above (differences between lean and lean plus fat) and as should be known by health "experts," fat has very little cholesterol. Cholesterol principally resides in meat cells and that is the reason why beef, fish, and chicken have similar quantities of cholesterol per unit weight. And contrary to Brody's remarks, "most" of the beef fat is not "artery clogging saturated fat." Some 38 to 44% of the fat in the above meat cuts is saturated fat and only little more than half of that saturated fat raises blood cholesterol. The reader will recall from Chapter 5 that the saturated fatty acid, stearic acid, does not elevate cholesterol.

In sum, Brody could hardly have been more inaccurate in her "expert" communications to the nation's senior citizens.

Despite her sloppy, inconsistent and erroneous reporting, Ernst Wynder, president of the American Health Foundation said, "When it comes to preventive advice, she is more on target than most doctors," and Robert Barnett, editor of American Health, said, "She has done more than any other journalist to bring accurate information about nutrition and health to the public."[2554]

Marlene Cimons[2653] of the Los Angeles Times and Gina Kolata[2652] of the New York Times published columns on February 28, 1990 describing the recommendations of the 1990 NCEP Panel Report. Cimons told her readers that the average American diet contains 13% saturated fat, while Kolata said it was 15-16%. Kolata maintained that the NCEP recommended that Americans eliminate all saturated fat from their diets, while Cimons reported that saturated fat should constitute less than 10% of total calories. Kolata also cited the Panel as saying that "unsaturated fats, which, like butter, are solids at room temperature, should constitute no more than 10 percent of the calories consumed. The average American diet obtains 13% of its calories from these fats. Finally, Cimons indicated that an egg contains 213 mg cholesterol and Kolata reported that it contains 274 mg.

Kolata was incorrect on each of the above statements, representing a combination of sloppy reporting and inadequate knowledge.

An article by Sterne[2596] in Heart to Heart, edited by Antonio Gotto, included the following three sentences: "While fat is generally considered bad for us, some fat is necessary in the diet. [This essentially says that "fat is necessary but bad for us.] A good suggestion when shopping for margarines is that the ratio of polyunsaturated to saturated fats should be 2:1 to 3:1. It is better to avoid partially hydrogenated fats when possible." It is never possible to purchase margarines that are not partially hydrogenated because all margarines are partially hydrogenated and a magazine purporting to give advice on such a subject should know that elementary bit of information.

Beatrice Trum Hunter is a book author and the food editor of Consumer's Research magazine. She requested and received a "review" copy of this writer's book, "The Cholesterol Conspiracy," in January or February of 1991. Three months later (May 1990), she published an article in Consumers' Research entitled, "Food health claims: fact vs fiction."[3379] Some of the material in her article bore an uncanny resemblance to excerpts from this writer's book. Much of the remaining material was scientifically

incorrect. Moreover, Hunter's point of view or "message" reversed itself in the course of her article. Let us first examine some of the material that appears to have been derived from this writer's book.

On the cover of the book is a quote by George Mann, i.e., "saturated fat and cholesterol in the diet are not the cause of coronary heart disease. That myth is the greatest deception of this century, perhaps of any century." Hunter used that quote in her article and also placed it in a separate "box" for emphasis. The first sentence in the text of the book was the statement. "For the vast majority of people, diet has little practical effect on their blood cholesterol levels." In her article, Hunter wrote, "for the vast majority of people, diet has little practical effect on the individual's blood cholesterol level." The only difference between the two sentences was the replacement of "the individuals" for "their."

Hunter briefly described a number of topics that were covered in detail in the book but were not known to those who had not read the research literature in depth. For examples, the health risks associated with very low blood cholesterol levels, the fact that NHLBI undertook a campaign in 1985 to change the American diet despite no direct proof of its efficacy, the fact that the campaign will cost Americans huge amounts for cholesterol tests, drugs and higher priced special foods, the fact that food consumption and CHD mortality trends in the U.S. and in other countries are not positively correlated, etc.

With regard to publishing incorrect information, consider the following. Hunter said, "There is general agreement that most Americans eat too much fat." Since fat per se does not elevate blood cholesterol, since some populations (e.g., Greeks, French, Danes) which consume more fat than the American population have low mortality rates, and since obesity can be the result of overconsumption of carbohydrates as much or more than the overconsumption of fat, this statement is without any scientific support whatsoever.

Hunter indicated that the Framingham study began in 1948 "with some 28,000 adults who were monitored over a period of years." Anyone who is familiar with the literature, as Hunter would have her readers believe, would know above all else that the Framingham study began with about 5,000 participants, not 28,000. Such a glaring error in a relatively short article should have been detected during her proof-reading, given that she knew the correct number, which she apparently did not.

Hunter said, "Investigations have shown that hydrogenated fats are saturated fat equivalents." The knowledgeable person knows, of course, that almost all hydrogenated fats are partially hydrogenated and do not have anywhere near the saturated fatty acid content of "saturated fat." Moreover, their content of trans isomers in no way makes them equivalent to saturated fatty acids. Additionally, even if hydrogenated fats were highly or completely hydrogenated, all of the saturated fat would be stearic acid and, therefore, not a factor in elevating blood cholesterol.

Hunter maintained that restaurants that make French fries from vegetable oils rather than beef fat "will increase the intake of saturated fat equivalents from the partially hydrogenated vegetable oils that are used." This, of course, is impossible because the oils are only lightly hydrogenated and have substantially lower cholesterol raising saturated fatty acids, than there are in beef fat.[a] She continued, "In addition, the amount of long-chain fatty acids--considered unfavorably by some medical

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[a] Light hydrogenation also produces fewer trans acids than partial hydrogenation and such acids do not elevate cholesterol to the extent that lauric, palmitic and myristic do.

researchers--plus the saturated fat equivalents will increase in the French fries..." Hunter clearly has no real understanding of this topic as hydrogenation, whether light, partial, or complete, does not increase the long-chain fatty acids.

Finally, Hunter begins her discussion on diet and heart disease by emphatically indicating that there is no connection between the two. She said, "The conventional slogans are that fat and cholesterol are bad. The less fat and cholesterol one eats, the better for one's health. By cutting down on fat and cholesterol, one lowers the risks of heart disease and cancer. Don't you believe it.!" For 4 1/2 columns of her article she indicated that there was no evidence to support the diet-CHD relationship, just as was stressed in the book. Then, in the second half of her fifth column she strongly suggests that saturated fat is harmful (see above discussion). In her sixth and final column she wrote the following contradictory statements. "It is time for Americans to challenge...the official dietary recommendations... Perhaps the soundest advice was given in a report by the U.S. Surgeon General in 1988...[which stated that] 'Development of the major chronic disease conditions--coronary heart disease, stroke, diabetes, or cancer is affected by [in part]...diet...an important component.'" Thus, Hunter effectively criticized the dietary recommendations and then described them as the "soundest advice." She simply did not know that the Surgeon General's report was written and sponsored by the same individuals and groups (NHLBI and AHA) who produced the dietary recommendations she criticized.

In a 1991 book by Jane Heimlich entitled, "What your doctor won't tell you,"[3386] food "expert" Hunter was cited several times. In one citation she described the effects of hydrogenation, i.e., "Hydrogenation is then bubbled through the oil in the presence of nickel, platinum or some other catalyst... The heating of the oil ruins its original character, with destruction of all vitamins and mineral factors as well as an alteration of proteins." Oils, of course, have none of the common vitamins, little or no minerals and certainly no proteins, so heating oils cannot destroy or alter what they do not have.

In summary, the reporting by Brody and others has been grossly in error, misleading and contradictory. It is inexcusable for one to pretend to be an authority on health, food and nutrition or reporter of facts on such issues and simultaneously publish information which reflects not only an obvious lack of knowledge but also a disregard for consistency and accuracy.

Before departing from a discussion of how the media has so confused and misled the population, it is useful to reproduce part of a March 3, 1990 editorial in the New York Times, a reaction to NHLBI's announcement that all Americans, not simply those "at risk" for CHD, should consume the Prudent Diet. The reader may be amused by two characteristics of the editorial. First, it apparently wishes to impress us all with its "vast" vocabulary, caring little whether it is communicating properly with the average person (underlines and bracketed definitions were added by this writer). Second, the editorial goes to great lengths to ridicule NHLBI's recommendations, while simultaneously advising its readers to accept them.

> "The Federal Government felt moved this Lenten week to get up in the pulpit and urge its flock to discipline their diets. It admonished [cautioned, warned] every citizen above 2 years of age to eat less fat and more spinach. The sermon is probably salubrious [favorable to health], but the sanctimony [sacredness] can be taken with a modicum [small amount] of salt."
>
> "A group that has little doubt of its own wisdom is the National Cholesterol Education Program, the public voice of the National Heart Lung and Blood Institute. One of its committees now says that people should take less than 30 percent of total calories from fat, and less than 10 percent from saturated fatty acids."

"These are moderate recommendations, and far more likely to be right than wrong."

"Dr. Richard Carleton, the chairman of the cholesterol panel, argues that 38 different professional organizations endorse his panel's conclusions. Their message, he says, is: 'Let's not confuse. Let's coalesce. Let's speak with the same voice.'

"But that's not how science works. Eminent authorities can err en masse, especially when they coalesce and suppress confusion. The premature release of the Salk polio vaccine is just one example close to home. The cholesterol panel may be right, but its methods are those of puffery [very flattering publicity], not science.

"In listening to dietary advisers, there is one good policy: Eschew [avoid] fats, fads and excessive certainty."

The final sentence tells it all; despite all of its "colorful" rhetoric, it also advises Americans to "eschew fats" because it "is probably salubrious," "may be right" and "more likely to be right than wrong." While NHLBI and NCEP may not have liked the "colorful" rhetoric, they most certainly must have been pleased that the Times transmitted their propaganda faithfully.

A Final Comment

DeWitt Goodman stated in 1989 that "Mass media handling of biomedical issues, especially matters of diet and other behaviors perceived to be under an individual's personal control, often can be outrageously wrong, misleading, or merely irrelevant, but most of what has been said about cholesterol has been refreshingly cool in presentation and accurate in content."[1698] In view of the fact that Goodman and other alliance members have made many hundreds of fraudulent statements, it is virtually impossible for the media to have presented accurate information to the public. In fact, media discussions of diet, cholesterol and CHD cannot be better described than "outrageously wrong, misleading or irrelevant." To illustrate this situation, consider the 1988 NHLBI/AHA survey[2244] which was a follow-up to the 1983 and 1986 surveys. While nearly 80% of those surveyed agreed that reducing blood cholesterol would have a "large effect" in preventing CHD, knowledge of cholesterol was no better than that observed in the 1983 survey. For example, 67% of the sample didn't know the food sources of cholesterol. Such a state-of-affairs exemplifies the fact that the massive print, radio and TV "stories" directly or indirectly funded by the NHLBI/AHA alliance and food and drug manufacturers have been anything but "accurate in content."

"Scientists" such as Goodman, Connor and many other alliance members who mislead other scientists and the public and, at the same time, accuse other scientists of being misleading, illustrate not only the pervasive fraud in both the scientific and lay literature but also the fact that the entire CHD research program is controlled by fraudulent or highly incompetent scientists or both.

Perhaps this discussion can be capped by a brief description of HeartBeat Magazine. The editors state that "HeartBeat does not endorse any medical treatment, nor does it encourage you to undertake treatment on your own."[2043] The spring 1989 issue contains 46 pages, of which 35% were advertisements of foods containing low salt, low fat, low cholesterol and high-fiber and of aspirin and drugs. Of the five articles in the magazine, one described the Framingham study, suggesting that the NCEP is essentially based on that study, another indicated that diets and drugs can reverse atherosclerosis, another presented low salt, low saturated fat and low cholesterol

recipes, and a fourth recommended daily aspirin consumption because it "may help your heart." So much for the editors' nonendorsement policy!

INDUSTRY

The media and medical journals were not the only institutions unresponsive to information counter to that spewed by AHA and NHLBI. The industries presumably hurt the most by the cholesterol hysteria were also relatively unresponsive. This writer sent letters and summary documents to executives of the beef and dairy industries. Only the beef industry executive acknowledged receipt of the summary document and he indicated little interest. More than a year later the National Live Stock and Meat Board requested a "review" copy of Volume 1 of the present critical review. In early 1990 Volume 1 was favorably reviewed in the Board's newsletter, "Food and Nutrition News."[2708] However, no member of the beef industry subsequently contacted this writer, even though the data in Volume 1 were strongly supportive of the beef industry.

The egg industry's disinterest was particularly interesting because it was probably the hardest hit by the cholesterol hysteria. For example, egg consumption has steadily decreased since about 1950. The average number of eggs consumed per year in 1989 was about 235 per person, down 40% since 1950 and even 23% lower than in 1910.[2437] Egg producers' financial losses in 1988 were the highest in the 17 years that the U.S. Department of Agriculture began recording such data. Let us see how the egg industry responded to these losses.

It will be recalled from Chapter 2 that in the early 1970s the egg industry formed a group called the National Commission on Egg Nutrition (NCEN) whose responsibility was to promote eggs and attempt to halt slumping sales.[2377,2379] Among its advertisements was, "There is absolutely no scientific evidence that eating eggs in any way increases the risk of heart attack." Although that ad was scientifically true, the AHA president, Richard Ross, filed a complaint with the FTC, requesting that such advertising be prohibited.[3264,a] Chapter 2 described the FTC-NCEN trial which led to a ruling that NCEN must cease linking egg consumption with heart disease.[2370] Thus, it was subsequently legal for the AHA and other health groups to publicly make scientifically unsupported claims but illegal for NCEN to publicly make scientifically supported claims.

As a result of the AHA's victory over NCEN, the latter apparently decided that "if we can't lick them, then we'll join them." NCEN gave way to the Egg Nutrition Center (ENC) which now promotes AHA's dogma in its newsletter, "Nutrition Close-up,"[2438] and in its advertising, particularly in medical journals.[2477] However, ENC's articles and ads focus on the "badness" of saturated fat (of which the egg contains very little) and downplay the importance of dietary cholesterol (of which the egg has a great deal).

Prior to having reviewed the FTC-NCEN trial testimonies, this writer wrote a letter in October 1987 to Al Pope, president of the United Egg Producers, one parent of ENC.[2478] A number of documents were enclosed and substantial data were offered which indicated that dietary cholesterol had little practical influence on blood cholesterol. Pope did not reply to that letter and instead sent it to Pam Peterson, apparently a public relations representative of ENC. Several months later Peterson wrote a letter to this writer without indicating serious interest in the data offered to

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[a] The NCEN's Hendrik Wentink noted that Ross would later testify before McGovern's hearings on health and nutrition that the cause of CHD was unknown.

Pope.[2499] Nevertheless, this writer naively sent a letter on April 6, 1988 to Peterson and enclosed several tables of data that derived from Volume 1 of this review.[2501] Neither Peterson nor any one else of ENC acknowledged receipt of the letter and data, although it was determined in late 1989 that they did indeed receive them.

On May 2, 1988 this writer offered similar data to Louis Raffel, president of the American Egg Board, another parent of the ENC.[1705] Although this writer offered the data free of charge, Raffel's brief reply indicated no interest in the data and said, "I'm not sure I understand what you think the American Egg Board can do for you since you do not want monetary reimbursement."[2709]

Upon receiving copies of various letters between this writer and the egg industry, Charles Chao, an executive of the California Egg Industry, submitted a letter in June 1988 to Pope which read, in part, "Dr. Russell L. Smith is trying to be a friend to our industry and we don't even have the courtesy to treat his efforts with a gracious attitude. The answers he has received from the egg people are shameful and unexplainable."[2710] Apparently, Chao received no reply to his letter either.

In August of 1989 Cathey McCharen, vice-president of ENC, purchased a copy of Volume 1 of this review and there ensured a brief interchange of letters in which McCharen seemed displeased with this writer's strong negative attitude towards NHLBI and AHA but simultaneously described Volume 1 as "very important."[a] When this writer offered on November 14, 1989 to try to convince the FTC that the scientific evidence did not show a relationship between the consumption of eggs and CHD, no further correspondence was received from McCharen.[2717] Not only did McCharen avoid mentioning the "very important" Volume 1 in ENC's Nutrition Close-up newsletter, this writer began accumulating evidence that ENC, the American Egg Board and the United Egg Producers were effectively promoting the dogma of their former enemy, the AHA, obviously in the hopes of gaining some kinds of concessions. For example, a United Egg Producers' publication in early 1989 announced that McCharen, Pope and Raffel met with the National Cholesterol Education Program (NCEP) Committee and offered "suggestions regarding the draft recommendations to the general population."[1735] The publication went on to say that "The egg industry has supported the NCEP's educational efforts" and that "The NCEP has been successful in raising the awareness and getting the medical community to treat elevated cholesterol levels. Yet, one of our worst fears is coming true because of that increased awareness--the message in advertising is focusing on "no cholesterol."

What is dumbfounding is that it was all entirely predictable. Of course the food industries' advertising is focusing on "no cholesterol." AHA members have relentlessly incriminated dietary cholesterol, particularly eggs, for 30 years. Even more dumbfounding is that ENC employs a seven member "scientific advisory panel" and of the seven, three are long-time diet-CHD promoters--Christakis, LaRosa and Schonfeld. While ENC (at least overtly) accepts AHA's recommendations to the public which, in part, call for the reduction in consumption of eggs, LaRosa stated in Redbook magazine in 1988 that "dietary cholesterol can lead to heart disease even if it doesn't raise a person's blood cholesterol level."[1617] Thus, while LaRosa was apparently being paid by ENC to be an advisor, he was telling the public that even a little bit of dietary cholesterol can cause heart disease. Yet, ENC's McCharen[2623] published an article in 1990 claiming that ENC's "scientific advisors [including LaRosa] are also convinced that there is no scientific evidence for the recommendation of 'less than' 300 mg cholesterol per day or restriction of eggs for the general healthy public."

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[a] 2711,2712,2713,2714,2715,2716,2717

During 1989 this writer had conversations with the scientific staffs of a number of well-known companies and relatively large industries. All experienced fear of AHA and rather than join forces to combat that organization, they have chosen to join the bandwagon, more or less, and fight among themselves. For example, when the Kellogg Cereal Company ran an ad that suggested that an egg breakfast may contribute to heart disease, the American Egg Board president, Louis Raffel, sent a letter of protest to the Kellogg Company president, G.D. Robinson. Together with maintaining that the cholesterol in eggs has little influence on blood cholesterol, Raffel said, "In addition to our policy decision not to disparage other food products, the U.S. Department of Agriculture strongly discourages each agricultural commodity from making negative statements about any other agricultural commodity."[2718]

But the egg industry does indeed make negative statements, albeit indirectly, about other agricultural commodities.[2477] While downplaying the importance of dietary cholesterol in eggs, the ENC's ads promote the fear of saturated fats, which, of course, are prominent nutrients in almost all meat and dairy products, as well as many other products such as chocolate and baked foods.

The National Live Stock and Meat Board also (at least overtly) accepts AHA's recommendations to the public but defends red meats on the grounds that it contains little saturated fat when trimmed and cooked.[2719] The National Dairy Board (at least overtly) accepts AHA's recommendations but defends dairy products. The Board said, "There is an important place for dairy products in the foods you choose, even if your doctor has placed you on a cholesterol-lowering diet. A major reason for this is that dairy products are the chief source of calcium in the American food supply, and you probably know how important calcium is."[2720] The Board emphasized, "Keep calcium up and cholesterol down" and presented data showing that dairy products contain lower amounts of cholesterol and/or fat than do meat and eggs.

In effect, the AHA has divided and conquered the egg, meat and dairy industries and is undoubtedly amused at how each defends itself hopelessly and accuses the other of being the real culprit in heart disease. And although none of these industries have anything to do with heart disease, they are apparently unwilling to use the mountainous scientific evidence that supports them. The present writer has heard rumor that the beef industry has taken a "fit, not fight" position, i.e., it intends not to fight the diet-CHD promoters but rather to scientifically alter the beef we eat by reducing its saturated fat and cholesterol. Thus, the beef will "fit" the AHA's and NHLBI's recommendations. It would appear that the egg and dairy industries have taken the same position. Given that the lipid hypothesis is still king in another 10 years, real foods in the American diet will be replaced by what a group of biochemists at the University of Maryland call "funny foods," i.e., deranged foods. Like the high polyunsaturated fat diet debacle, virtually no one within the AHA and NHLBI seems to care whehter or not such foods may be harmful.

10. ALLIANCEDEGOOK

"With regard to high blood pressure I would point out that in truth we still know relatively little about the importance of high blood pressure in the elderly and its treatment. I am sure you again will recall that when we adopted a blood pressure of 140/90 as a guideline for normalcy and abnormalcy, and in a sense for drug treatment, we had little or no evidence about the appropriateness of these guidelines or the appropriateness of treatment of high blood pressure in the elderly. This is a situation exactly analogous to that of cholesterol."

(Myron Weisfeldt,[3091] 1989 AHA President)

INTRODUCTION

The term "gobbledegook is defined in Webster's dictionary as "unclear, wordy jargon." It is most frequently used to describe the speeches of politicians who often cleverly avoid saying anything meaningful and/or say what is useful at the time, despite the fact that it may be contradictory to their previous statements. The literature on diet, blood cholesterol and CHD is virtually saturated with statements made by alliance members which are either contradictory, illogical, irrational or simply false. In some cases, they clearly did not know what they were talking about or paid little attention to adhering to evidence. In other cases, their statements were inconsistent with or virtually contradictory to statements made by themselves or others elsewhere. In still other cases, it is clear that their statements were designed to mislead readers. In all such cases, their communications can be best described as alliancedegook.

The purpose of this chapter is not to make alliance members look incompetent or fraudulent. Rather, the purpose is to provide evidence that they are incompetent and/or fraudulent. Much alliancedegook can be seen throughout Volumes 1 and 2. In a sense, therefore, this chapter represents an exclamation point for the two volumes. Exemplifying the overall problem was William Castelli's criticism of Thomas Moore's 1989 book, "Heart Failure." He attempted to discredit Moore by saying that "He obviously doesn't have a scientific background."[2485] It is apparent from the many articles by Castelli and other alliance members that they also have little or no academic training in the discipline of science and their on-the-job training has left much to be desired. It is often said that a little knowledge can be dangerous in the wrong hands and it is painfully obvious that it has been extremely dangerous in the hands of the alliance because it is costing the American people tens of billions of dollars, immeasurable anguish, needless sacrifice and, most likely, the health of large numbers of people who are on cholesterol-lowering drugs, excessive fish oils and/or aspirins, and/or malnourishing and/or high polyunsaturated fat diets.

The following subsection presents examples of alliancedegook on a variety of topics related to the diet-blood cholesterol-CHD hypothesis. Subsequently, several recent studies are critiqued as examples of "How not to interpret data." They are not unique but rather represent typical ways in which alliance members fail to use objective, scientific principles in analyzing and interpreting their own data. Then, separate discussions of 12 of the most prominent diet-CHD promoters are presented which provide examples of how they contradict themselves, think irrationally, mislead readers and re-write history. Finally, a brief discussion is presented regarding the diet-cancer relationship to show that it is also based on the same confounded associations that the alliance uses to promote the diet-CHD relationship.

The Rise and Fall of CHD Mortality

The most logical argument used by the alliance for concluding that the CHD mortality decline since 1963 is real is that it is substantial, sustained and accompanied by declines in mortality rates from all heart diseases, all cardiovascular diseases and all-causes. Cooper, Stamler and others[2825] stated in 1978 that

> "The magnitude and consistency of the decline in CHD mortality since 1968 argues forcefully for a real, rather than artifactual, break in the pattern of this disease in the U.S. Changes in diagnostic categories, assignment of death certificates, and other inaccuracies in the method of measurement can be of only limited importance in influencing this trend given the parallel decline in deaths from other CV diseases and all causes."

In 1979 Kannel and Thom[2827] focused on the last factor, namely that

> "...the decline now covers at least nine years. But, more importantly, the rate of death from all causes combined is also falling. This is to be expected when the decline in the leading cause of death is real. Evidently, significant reassignment of coronary death to other rubrics have not occurred."[a]

And in their "update" of the 1970 Inter-Society Commission report, Kannel, Stamler and others[1083] said,

> "The marked decline in coronary heart disease and cardiovascular mortality has been paralleled by a decline in mortality from all causes, as would be expected with an abatement of the leading determinants of death."

The above quotes provoke two considerations. First, while their argument was most certainly strong, such logic was never applied by them or other alliance members to the so-called CHD epidemic, during which mortalities from all heart diseases, all cardiovascular diseases and all causes were also declining, not increasing. This fact, by implication, indicates that the alliance knew the CHD epidemic was artifactual.

Second, the above quotes strongly imply also that if the mortalities due to all heart diseases, all cardiovascular diseases and all-causes remained the same or increased during the CHD decline, then this outcome would indicate that physicians were merely reassigning CHD deaths to other rubrics. This implication again indicates that the alliance knew that the CHD "epidemic" was due to reassignment, rather than to a real increase in CHD mortalities. It would be totally naive to think that they did not know. It is reflected in the fact that their discussions of the "epidemic are invariably short and/or nonanalytical and never question the validity of the reported CHD mortality data and that their discussions of the CHD mortality decline are lengthy and highly analytical.

Knowing the CHD "epidemic" was artifactual and acknowledging that fact are, of course, two entirely different things. If the alliance acknowledged that the "epidemic" was an artifact, it could not attribute the high CHD mortality during all of the 20th century to "rich" diets, cigarette smoking or any other "lifestyle" factors and the NCEP would thus be a costly but meaningless program, which, of course, it is. Two sentences written by Lenfant[2802] in 1988 reflect the alliance's dilemma.

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[a] Kannel and Thom repeated this statement in 1984.[1174]

"With recognition as a disease entity came recognition of its [CHD] prevalence."

That sentence essentially describes the fact that the prevalence of CHD grew gradually as recognition of it grew gradually, as exemplified in the periodic changes in the ICD. However, two sentences later, Lenfant disregarded that historical process and suggested a true epidemic of a disease that was universally known and detected in 1900, i.e.,

"...the proportion of all deaths attributed to heart disease had increased from 8% in 1900 to 27% in 1950.

Jeremiah Stamler, Levy and Feinleib (and many others) have steadfastly maintained that there was a great CHD epidemic in the U.S. from 1900 to 1962.

"The industrialized countries are indeed being ravaged by an epidemic of coronary disease especially among males." (Stamler[573])

"By 1940, coronary artery disease was the leading cause of death in the United States." (Levy and Feinleib[1401])

In 1976, Theodore Cooper, speaking before the Senate Select Committee as an Assistant Secretary for Health, also referred to CHD as "the modern epidemic."[2186] However, in a more objective and less political mood as NHLBI director in 1972 he said,

"It may be that coronary heart disease is seen by the public [and researchers] as a relatively new disease. In actual fact, heart disease has been the number one killer in the United States since at least 1910."[2085]

And in 1989 former AHA president, Bernadine Healy, dealt another blow to the epidemic notion by saying that

"Heart disease has been the number one killer of women for 81 years."[2517]

In 1988 Griffin and Castelli published a book entitled, "Good Fat, Bad Fat," and made the following statement:

"75% of the people in North America have fat plugging their coronary arteries--and the problem gets worse every day."[1667,a]

Virtually everyone recognizes that CHD mortality has been on a steep decline since the mid 1960s. As detailed in Chapter 3 of the first and present volume, alliance members have unanimously held that the decline is primarily due to risk factor control. If so, then Griffin and Castelli's remarks describe a trend that is opposite to reality. On the other hand, if Griffin and Castelli are correct, then risk factor control has obviously had no influence on the prevalence and incidence of the atherosclerotic disease. The alliance cannot have it both ways.

To illustrate the alliance's position and lack of conviction thereof, consider the following remarks by the 1981 NHLBI Working Group,[3067] i.e.,

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[a] Castelli described this condition somewhat differently in another 1988 article, i.e., "The Framingham studies have shown that 75% of Americans over the age of 65 have lesion on their carotid echoes."[1642]

"The continuous and substantial decline in mortality rates from CHD in the U.S. is probably due to changes in multiple determinants [risk factors] of the disease. Identifying the mechanisms responsible for the decrease may help to accelerate the decline in CHD...

"Because of the continuing high toll of the atherosclerotic diseases in terms of premature illness, disability, and death--despite the decline in the death rates--clarification of the bases for the decline in mortality requires urgent attention."

Although the alliance is typically loath to admit that anything other than their primary risk factors is responsible for CHD, this statement almost bursts with the admission that it cannot explain the CHD mortality decline.

Control of Heart Disease

While some alliance members praise their emphasis on lifestyle changes as a principal cause of the decreasing CHD mortality trends, other alliance members are warning that the reason for the CHD mortality decline is unknown and/or the CHD prevalence and incidence are on the increase. For examples, Rifkind stated in 1989,

"We no longer have to view [CHD] as an inevitable consequence of aging but as a condition we can do something about. We can reduce it from the No. 1 cause of death to a condition of much less consequence."[2532]

Levy[2977] held that

"Not only is the declining death rate a clear sign that the battle against cardiovascular disease is being won but the absolute number of cardiovascular deaths also fell below 1 million in 1975 and 1976 for the first time since 1963."

And in 1990 the editor of Internal Medicine, Alfred Bollet, said,

"We are bringing under control the number one cause of death in this country. Attempts to determine the probable reasons for the declining mortality rate of ischemic heart disease all concern changes in individual life-styles..."[2906]

But NIH's Brody and Schneider[3012] said,

"In the last few decades, a sharp reduction in the age-specific and overall mortality rate from the two most common age-dependent disorders, heart disease and stroke, has occurred. These declines in mortality from heart disease and stroke are largely unexplained."

And two years after making his above statement, Levy[1846] indicated that

"Only when we truly understand atherogenesis will we be able to effectively prevent or retard its occurrence."

AHA's Scott Grundy stated in 1986 that

"CHD will remain the nation's leading cause of death for the next 25 years."[262]

While Grundy suggested that the reason why the CHD mortality rate will remain high for a long time was because of an aging population, Kannel and his colleagues showed that over a 30 year period, the incidence of both CHD and stroke has been increasing.[1842,2894]

"...the baseline prevalence of cardiovascular disease increased from 1950 to the 1970 cohort."

Finally, Weinstein[2892] emphasized in 1986 that under current conditions the

"CHD incidence, prevalence, mortality, and cost will increase by about 40% by 2010..."

With CHD incidence and prevalence thus apparently increasing in the U.S., it is astounding that Freeman[2196] would criticize Great Britain for being 10-15 years behind the U.S. in CHD prevention. He incorrectly concluded that Great Britain's CHD rates were "soaring while ours are falling."

Animal Experiments

"The attempt to extrapolate to man the findings from cholesterol experiments with rabbits and chickens can lead to absurdities" (Keys[279]).

"Those who deny their [animal experiments] relevance for man as a species must either deny the foundation of modern experimental medicine..."[a] (Stamler[2635]).

Causes of CHD

In 1956 Stamler and his colleagues were quite emphatic in defining atherosclerosis as a metabolic disease.

Atherosclerosis "is a metabolic disease, in which altered cholesterol-lipid-lipoprotein metabolism plays a critical and decisive (but not exclusive) role. Without deranged lipid metabolism, clinically significant atherosclerosis would occur but rarely, particularly in middle-age, regardless of the functional states of the cardiovascular system."[694]

In 1962 Stamler said,

"...diet may be viewed as an essential or necessary cause of atherosclerotic disease," i.e., for the large-scale occurrence of this disease in middle-age."[574]

Nine years later (1971) Kannel et al. indicated that

"Since atheromas are encountered throughout the range of lipids common to Western civilization, lipemia cannot yet be designated as an essential precursor."[2935]

In 1975 Stamler vehemently stated that he always defined atherosclerosis as multifactored.

"It is a multifactored disease, and everyone in the field doing meaningful thinking in research on it has recognized this since before I got into the field."[2438]

By Stamler's standards, William Connor was not doing meaningful research because he still maintained in 1975 that atherosclerosis was caused by diet, specifically cholesterol

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[a] Stamler's sentence was incomplete, i.e., it did not include an "or" alternative.

with enough fat to absorb the cholesterol.[2436] And by Stamler's standards, Stamler himself was not doing meaningful research in 1956.

But Stamler again repeated the so-called essentiality of diet in increasing blood cholesterol and thus CHD in 1978 and 1979.

> "...it is...reasonable and sound to designate 'rich' diet as a primary, essential, necessary cause of the current epidemic of premature atherosclerotic disease..."[539]

> "'rich' diet and resultant nonoptimal serum lipid-lipoprotein levels are apparently the primary essential causes of epidemic premature atherosclerotic disease..."[2635]

But in 1980 Framingham's Dawber presented the opposite view, i.e.,

> "...the factors involved [in atherogenesis] appear to be multiple rather than single etiologic components, no essential factor having thus far been identified."[3001]

William Castelli is director of the Framingham study and William Roberts is a staff member of NHLBI which sponsors the Framingham study.[a] One would think that there would be at least relatively close agreement between such individuals at this point in time with respect to the number of important risk factors. In 1989 Castelli said,

> "The Framingham study has identified several risk factors for cardiovascular disease including advancing age, hypertension, obesity, cigarette smoking, electrocardiographic left ventricular hypertrophy, elevated total and low levels of high-density lipoprotein cholesterol."[2549]

The following year he elevated "several" to 200 in a Reader's Digest article, i.e.,

> "The Framingham study has pinpointed as many as 200 factors associated with increased risk of the [CHD] disease."[2598]

But NHLBI's Roberts maintains the extreme opposite position, namely,

> "In my view, there are not 10 atherosclerotic risk factors, there is only 1--and that is an elevated (> 150 mg) serum total cholesterol and specifically an elevated serum LDL-cholesterol level."[2537]

Kannel et al.[1083] indicated that

> "Despite unwarranted skepticism the evidence linking cigarette smoking to CHD is formidable and meets the criteria for an etiological relationship. The findings are internally consistent, strong, graded..."

They then presented 18 year follow-up data from the Framingham study which showed that CHD "event" rate increased from < 20 cigarettes per day to 20 a day and then decreased with more than 20 per day for all age groups of men. And for the oldest

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[a] He is also editor of the American Journal of Cardiology.

group (65-74), the heaviest smokers had a far lower CHD "event" rate (4.2/1,000) than those who had quit smoking (15.3), those who smoked less than 20 cigarettes (13.7) and those who smoked 20 cigarettes per day (19). Perhaps Kannel et al. have different definitions of "internally consistent, strong and graded" than those commonly accepted for these terms.

Kannel et al. also made the following two statements on Pages 177A and 178A, respectively, of their article:

> "...Finnish loggers who perform strenuous labor, suffer the world's highest rate of myocardial infarction, numerous deaths due to CHD have now been documented in marathon runners and joggers. Despite acknowledged [?] benefits to patients with CHD, there is no evidence that exercise training improves prognosis."

> "Sustained physical activity appears to be associated with a reduced cardiovascular mortality and lower rates of fatal coronary attacks."

In discussing the decline in CHD mortality Kannel and Thom published the following statement which made no sense whatsoever:

> "Evidence that control of hypertension is an important contributor to the decline in mortality is especially strong because hypertension is one of the major risk factors for stroke, cardiac failure, and coronary heart disease."[1174]

How can evidence be strong just because hypertension is a risk factor?

Blood Cholesterol and CHD

In 1987 the chairman of the Laboratory Standardization Panel, NCEP, Herbert Naito, said,

> "No doubt, there are individuals who have none of the risk factors outlined here but who still face CHD, but this percentage remains small."[1352]

But one year later, Naito presented an entirely different profile, namely,

> "Among individuals undergoing bypass surgery at the Cleveland Clinic Foundation, about 35% demonstrate none of the known risk factors except for a hereditary predisposition to the disease."[1397]

Are we to believe that the percentage grew from "small" to "35%" in the course of one year? If so, almost all CHD deaths in 1990 should be due to nonrisk factors.

> "Epidemiologic data indicate that CHD risk escalates sharply at serum cholesterol levels above 200 mg" (Kannel, Stamler et al., 1984[1083])

> "One statistic that just jumped off the pages of our research reports was the average cholesterol count of those who suffered heart attacks: 240. The risk of having a heart attack increased significantly when the count rose above 200" (Castelli, 1990[2598]).

> The MRFIT screened cohort data "reinforced the suspicion that a cholesterol above 200 mg places an individual at risk" (LaRosa[1545]).

Examination of the Framingham and MRFIT data (Volume 1) clearly show that the CHD event or death rate does not sharply increase after 200 mg. Two hundred is

merely a point along a continuous curve in the MRFIT data and the CHD event rate is essentially flat in the Framingham data up to 294 mg.

Acknowledging that there was no gradient of CHD risk with blood cholesterol levels in a Yugoslavia population, Kannel and Gordon drew a highly speculative conclusion and implied that there was evidence to support it, i.e.,

> "...if we have reason to suspect (as we do) that the level of HDL-C in that population is high, then that would explain the lack of gradient."[2638]

Kannel and Gordon did not provide any evidence or otherwise substantive basis for "we have reason to suspect."

In 1990 Witztum published the following irresponsible statement:

> "Irrespective of what the primary event is that leads to initiation of atherosclerosis in any given individual, atherosclerosis cannot be sustained or become clinically significant without elevated LDL cholesterol levels."[2575]

Clinical atherosclerosis most certainly occurs in Americans with very low blood cholesterol (including LDL) levels and it occurs in virtually all populations of the world, including those having low cholesterol levels.

In 1979 the American Health Foundation also made an irresponsible statement. Ten years later it was partially repeated by Leaf.

> "Populations with low average serum cholesterol concentrations and low IHD morbidity and mortality, such as Italy and Japan, have higher life expectancies than the U.S. population. This is indirect evidence that mortality rates for common cancers, including colon cancer, are not higher in populations with low plasma lipid levels than in those with higher concentrations."[2634]

> "In societies in which the mean cholesterol levels are 3.9 mmol per liter [150 mg] or lower without the use of drugs, CHD is essentially unknown as a public health problem."[2685]

In addition to the fact that the vast majority of populations in the world with low blood cholesterol levels have lower life expectancies than do Americans, and thus die earlier of nondegenerative diseases, Italy and Japan being two of the few exceptions, it was shown in Chapter 4 that most and all of the American population exceeds Japan and Italy, respectively, in life expectancy at age 65, the most important measure of the importance of blood cholesterol level. Further, the fact that life expectancy at birth is greater in Japan and Italy is no evidence whatsoever of the relationship between low cholesterol and cancer (see Chapter 8).

It is exceedingly well known that blood cholesterol level is not predictive of CHD in individuals and it is even more well known that relationships between blood cholesterol level and CHD within specific populations cannot be detected. Yet, in 1984 Kannel, Stamler and others[1083] made the following fraudulent statement:

> "Within different societies the relation of serum cholesterol to subsequent individual risk of CHD has been examined, the strength and independence of the association established..." [Note that they imply a strong relation but actually do not indicate the strength at all.] "There is no doubt that the level of the serum cholesterol cholesterol is related to the rate of development of clinical CHD both within and among populations." [Again, the implication of strength but no actual indication of strength.]

The Strength of the Relation between Blood Cholesterol and CHD

As emphasized in Chapter 9 and elsewhere the blood cholesterol distributions of those who have and do not have overt CHD almost completely overlap, meaning that the vast majority of people with CHD have the same cholesterol levels as those without CHD. Kannel recognized in 1964 that a relation between total cholesterol and CHD was apparent at the group level but not at the individual level. He said,

> "Diagnosis of overt heart disease on the basis of lipid levels alone is simply not feasible."[1885]

Three years later in 1967, Kannel, Castelli and McNamara proclaimed that,

> "It is now possible, using ordinary procedures and simple laboratory tests, for an industrial health unit to identify among its employees those who are prime candidates for a 'heart attack.'"[554]

In 1977 Gordon, Castelli, Kannel and others elevated the predictability of total cholesterol to "powerful," i.e.,

> "A number of studies...have found that total serum cholesterol...is a very powerful risk factor for CHD in young men."[523]

But in 1982, two of the immediately above authors, Kannel and Gordon, demoted the importance of cholesterol.

> "Serum cholesterol is not a strong risk factor for CHD. There is, to our knowledge, no such truly powerful CHD risk factor."[2638]

In 1984 Kannel et al. presented a similar statement, i.e.,

> "Several personal characteristics are related to CHD risk; they include elevated blood lipids, high blood pressure, cigarette smoking, and impaired glucose tolerance. None by itself is strictly determinative."[1083]

In 1986 Castelli concurred.

> "Obviously, the total cholesterol value cannot accurately predict which patients have a lipid problem when the cholesterol levels are between 200 and 250 mg or even between 150 and 250 mg."[1531]

And in 1987 and 1988 Kannel and Castelli contradicted themselves and each other once again.

> "The serum total cholesterol is a powerful risk factor for CHD in both sexes" (Kannel,[787]).
>
> The cholesterol reading by itself is no clue to a healthy heart" (Castelli,[1567]).

In 1990 Naito and Kwak[2912] indicated that better markers than cholesterol levels are needed. They said, "Every year, patients with apparently no conventional risk factors for CHD suffer from angina pectoris, a myocardial infarction, or even die suddenly from heart failure with no warning. From the standpoint of diagnostic medicine, we need better diagnostic markers--markers with high diagnostic efficiency, high specificity and sensitivity, and high positive and negative predictive values."

If the cholesterol concentrations were a powerful or even a modest predictor of CHD at the individual level, alliance members would not spew the literature with the above gobbledegook.

Cholesterol Level and Plaque

> "Diet therapy alone usually lowers the serum total cholesterol and LDL-cholesterol levels only about 10%, and a reduction of this magnitude probably causes little to no disappearance of portions of atherosclerotic plaques" (William Roberts[2200]).

> "...the...extent of plaque reversibility appears to be roughly proportional to the extent of the lowering of the serum total and LDL-cholesterol levels" (William Roberts[2200]).

In 1987 Castelli said,

> "We want the ratio of total cholesterol/HDL cholesterol to be under 4.5 unless the person's total cholesterol is 150 or lower, in which case we don't care what his HDL-cholesterol is."[1302]

In the following year, Glen Griffin, editor of Postgraduate Medicine and co-author with Castelli of "Good Fat, Bad Fat," wrote,

> "I had decided when I saw the plaques in my parent's coronary arteries that I didn't ever want to go through this [a bypass operation]. So, I immediately began eating more fish and less meat. I cut down on eggs to a couple a week, and I had already quit eating liver when I was in medical school. I thought I was on a good prevention program to keep my coronary arteries from getting plugged up like this--and to avoid a heart attack. I wasn't.[1784]

Indeed, although Griffin's cholesterol level was "under 150 mg, although he still required a bypass operation and although he was living evidence of the failure of alliance-promoted dietary changes and low blood cholesterol levels to retard atherosclerosis development, he praised Castelli and promoted the Prudent diet. While Griffin might argue that his total to HDL ratio was high, that issue is irrelevant. Castelli clearly indicated that the ratio is unimportant when the total cholesterol is 150 mg or lower. Moreover, Griffin's long-time dietary profile was clearly consistent with the alliance's recommendations, as evidenced by his exceedingly low total cholesterol level of "under 150 mg."

When asked whether cholesterol-lowering will extend life in the elderly, Castelli said,

> "You may not live longer but you'll be less likely to have a heart attack prematurely."[2660]

But apparently DeWitt Goodman had information unavailable to Castelli and others.

> "We now have evidence that clearly supports the conclusion that the elderly will live longer and better by lowering cholesterol."[2837]

The Lag Between Blood Cholesterol Changes and CHD Changes

Many alliance members have emphasized that CHD mortality rates decreased in European countries during World War II when foods containing saturated fats were in short supply. For example, Keys said,

> "The Russian attack and the outbreak of World War II soon thereafter brought great hardship to Finland, including severe restrictions of some foods, notably fats. However,...there was a surprising decrease in the incidence of CHD... The occupation by the Germans brought similar food privation to Norway and within 2 years the mortality from CHD fell sharply..."[540,a]

But his former student and colleague, Henry Blackburn, does not think that a rise in blood cholesterol from 150 to 185 mg and a parallel reduction of CHD mortality and a large increase in dietary cholesterol and saturated fat consumption in the Japanese over a 20 year period were sufficient to cause an increase in CHD mortality.

> "...neither the magnitude nor the duration of exposure to elevated atherogenic lipoproteins is as yet sufficient among the Japanese to be reflected in a major increase of coronary events."[1808]

Yet, the MRFIT Research Group, of which Blackburn was a co-principal investigator, reported in 1990 that a cholesterol reduction of less than 5 mg over a 10.5 year period led to reductions in CHD rates.

> "After an average of 10.5 years of follow-up mortality rates for coronary heart disease, cardiovascular disease, and all causes were lower for SI [treated group] than UC [control group] men..."[2723]

Of course, the experimental subjects were also treated for cigarette smoking and high blood pressure as well. But, as noted in Chapter 9, antihypertensive drugs have not had a positive impact on CHD. Stamler (and many others) have stressed, moreover, that "CHD rates are low [in Japan] despite the fact that both cigarette smoking and hypertension are widely prevalent in the population."[2635]

In constrast to both Keys and Blackburn, Yusuf et al.[1594] claims that "a relatively short period of treatment [blood cholesterol-lowering] in adult life can lead to an important reduction in CHD."

One of the most commonest statements made by virtually all prominent alliance members over the last 6 years is: "for every 1% reduction in blood cholesterol, there is a 2% reduction in CHD." To say the least, this formula is more than slightly incorrect when applied to the Japanese trends. It is also opposite to the trends seen in many other countries (Chapter 4).

Blood Cholesterol and All Cardiovascular Diseases

Kannel et al.[1083] presented the following three statements on Pages 163A, 166A and 182A, respectively, of their article.

> "The relationship [between blood cholesterol and atherosclerosis] can be demonstrated for all clinical manifestations of atherosclerosis."

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[a] But an early AHA report (Page et al.[512]) indicated that the CHD decline in Norway preceded food shortages, as it did also in Britain.

"While CHD mortality has been shown to be clearly related to blood lipids and lipoproteins, their relationship to overall and noncardiovascular mortality is less clear. Only a weak and inconsistent relationship of atherothrombotic brain infarction to serum total cholesterol has been noted. In occlusive peripheral arterial disease the relationship is also weak."

"High blood pressure, elevated serum cholesterol, cigarette smoking (in some groups), ECG abnormalities, and diabetes are precursors common to the three major manifestations of atherosclerosis--coronary heart disease, acute brain infarction, and occlusive peripheral arterial disease."

The NHLBI/AHA alliance has indiscriminately associated blood cholesterol with all vascular diseases but particularly with coronary and cerebrovascular diseases. Yet, the evidence linking blood cholesterol with cerebrovascular and peripheral artery disease is essentially nonexistent. No associations were found in the Framingham and Honolulu studies, or the 5 year MRFIT follow-up study.[1600,1869,1873] Other studies reported similar results.[1704,1870,1871,a]

Fowkes reviewed some 20 studies which attempted to relate cholesterol level with peripheral atherosclerosis.[1762] He concluded that there was no cholesterol "profile" for peripheral atherosclerosis.

Most recently, Iso et al. related all stroke mortality with blood cholesterol after a six year follow-up of the large group of men screened for the MRFIT study.[1875] Unlike other investigators of this study, Iso et al. used an equal interval cholesterol scale. He found virtually no relationship between cholesterol level and all-stroke mortality.[b]

The Optimum Level of Blood Cholesterol

In 1984 Rifkind said,

"If you have 200 [mg level], are middle-aged and don't have any other risk factors, then you don't have much to worry about."[2014]

Two years later Rifkind and Lenfant indicated that

"Studies suggest that total plasma cholesterol levels of 110 to 150 mg may be physiological for human beings."[253]

In 1989 Rifkind essentially repeated the above statement, i.e.,

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[a] Heyman reported cholesterol level to be higher in stroke victims than "comparable controls" in 1961.[287] Such a finding is peculiar, however, in view of the fact that cholesterol levels typically drop considerably following infarctions.

[b] Iso et al. did suggest that one type of stroke may be associated with increasing blood cholesterol levels, while a second type may be associated with decreasing levels. Chen et al. found no relationship between cholesterol levels and CHD in 9021 middle-aged Chinese in Shanghai and admonished Iso et al. for differentiating between the two types of stroke on the basis of very few cases.[2457] Iso et al. subsequently agreed that his differentiation was tenuous.[2458]

"Plasma cholesterol concentrations above 150 mg are unnecessarily high and put patients at risk for arterial deposition and its consequences."[2032]

But when, in the same year, the Washington Post's Jean Carper pointed to research indicating that higher nonCHD death rates occur at low blood cholesterol levels, she said,

"Rifkind...foresees no hazards in getting cholesterol down between 170 and 180. But whether cholesterol as low as 150 holds any dangers, he says, is unknown."[2379]

Again in 1989 Rifkind elsewhere stated that

"I do not think the case for cholesterol reduction has been proved to the degree we all would prefer."[2523]

Kannel, Stamler and others presented the following two statements in 1984 on Pages 166A and 169A, respectively, of their article:

"It is important to establish optimal levels for cholesterol and lipoproteins since epidemiologic data do not indicate any critical value where CHD incidence abruptly escalates."

"Since epidemiologic data indicate that CHD risk escalates sharply at serum cholesterol levels above 200 mg,..."

Blood Cholesterol Level Increase with Age

The 1972 article by Connor and Connor[411] has been cited numerous times in these volumes because it was a key report cited in the 1972 Inter-Society Commission's report and because it was saturated with errors and false and/or unsubstantiated statements. The following is one such statement:

"In the American population there is a steady increase of the plasma cholesterol with age, which peaks in the age range of 45-55 years for men. Note that medical students at age 21 had a mean serum cholesterol of 181 mg. Twenty-five years later, given the typically American pattern of life, the mean serum cholesterol level would predictably rise to the 220-280 mg range."

There is absolutely no scientific basis for this statement and, in fact, it is opposite to the evidence. First, they imply that a constant "typical American pattern of life causes a progressive increase in blood cholesterol level over time. There is no evidence or theoretical basis for such an implication. Second, dietary surveys always show that calorie consumption decreases with age and the proportion of calories as fat does not increase with age. The NHANES surveys show that dietary cholesterol decreases slightly with age.

Elevating HDL and its Importance

In 1979 Kannel and Castelli said that

"...many measures required to lower CHD risk (e.g., weight reduction, exercise,

stopping smoking, and moderating alcohol intake) also raise HDL."[2731,a]

In 1983 Rifkind[3039] emphasized alcohol, i.e.,

> "We conclude that alcohol consumption and certain nutrients may determine HDL-C levels. The most consistent and strongest association involves alcohol consumption.

Rifkind noted that there were reports showing that carbohydrates reduce HDL (see Prudent Diet below) but indicated that

> "It is likely that the importance of sucrose and starch intake in explaining HDL-C level is probably not great."

(However, he presented a table which showed that carbohydrates correlated almost as strongly with HDL as did alcohol.)

But in 1989 Rifkind said that

> "There is no sure method of raising HDL levels. Advising patients to lose weight, increase exercise, and stop smoking may be pro forma, but these measures have varying results."[1686]

In the same year an ad appeared in the Journal of the American Medical Association (December 15) promoting a TV program hosted, in part, by Rifkind. Sponsored by the drug company, Parke-Davis, the program's subtitles were

> "How and why HDL clears coronary arteries" [and]
>
> "How to raise HDL."[2502]

In yet another publication in the same year, Rifkind stated,

> "It has been hypothesized that HDL is involved in the 'reverse transport' of cholesterol from peripheral tissues to the liver. The relevance of these reverse-transport pathways to the rate of deposition (or removal) of cholesterol in atherosclerotic plaques has yet to be established. It is difficult to determine whether low levels of HDL cholesterol have a direct etiologic role in atherosclerosis or serve only as a marker of a more fundamental metabolic disorder."[2459]

And then in 1990 Rifkind[3221] indicated that many studies including his LRC trial, demonstrated that HDL reduces the risk of CHD but said,

> "Our ability to increase HDL levels through lifestyle modifications is variable."

In the same 1990 article, Steinberg[3277] made the following two statements, one of which was inconsistent with the other and one of which was inconsistent with one of the above Rifkind statements.

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[a] Note the word "moderating" which means neither increasing nor decreasing intake. It is apparent that Kannel and Castelli avoided the word "increasing" because the alliance always recommends against increasing alcohol consumption.

"There is no doubt that those having a high HDL are strongly protected, for some reason, against atherosclerosis."

"But I don't think we have any data showing us that a high HDL will protect an artery against atherosclerosis."

Levy and Castelli recently expressed nearly opposite opinions regarding the importance of HDL to CHD. Castelli stated that it has been "proven definitively that raising HDL levels lowers the risk of heart attack."[1809] Contrarily, Levy held that "there is no absolute proof that raising HDL alone can lower a person's risk of heart disease."[1634]

Unfortunately, Castelli's apparent love affair with the press suggests that his recommendations may be received more frequently by the public than those of others. For example, newspaper reporter Doheny recently quoted Castelli as saying that "If your total cholesterol is 150 mg per deciliter of blood or higher, you should also ask your doctor to determine your level of HDL, the so-called good cholesterol believed to have protective effect against heart disease."[2284] Such a recommendation would impact on nearly the entire population since almost everyone has a cholesterol level of 150 mg or higher.

Measuring Cholesterol Levels

Prominent alliance members fully agree that HDL cannot be accurately measured in most laboratories throughout the country. For example, NCEP coordinator, James Cleeman, said in 1989 that "...the idea of measuring HDL in everyone does not seem warranted by the evidence, by the inaccuracy of measurement of HDL, and by the expense."[1760] NCEP's DeWitt Goodman stated in 1989 that "It's ridiculous to put so much emphasis on HDL levels at the national level because labs are not standardized and therefore test results will vary significantly."[1809] Stanford's Alan Garber[2265] said that "The striking variability in reported HDL levels indicates that routine HDL assays are highly imprecise." Their views were fully supported in 1989 and earlier by 1988 AHA president, Bernadine Healy, Scott Grundy, Basil Rifkind, Herbert Naito and others.[a] Yet, John LaRosa stated in 1989 that measurement of HDL...is readily available through most clinical labs...and is reasonably reliable."[2037] Ernst and LaRosa insisted that "Lipoprotein analysis should include measurement of HDL cholesterol."[2227] And William Castelli was cited by Nash as maintaining that "inconsistent measurements are no excuse for not measuring HDL."[1809]

Castelli[3131] holds that HDL measurement is most important in persons with cholesterol levels below 200 mg, whereas Gotto[3241] maintains that between 200 and 239 mg "is precisely where it's most useful to know what the patient's HDL is..." Castelli[1302] and Kannel[3241] insist that the assessment of the total to HDL cholesterol ratio is the most important cholesterol measurement but DeWitt Goodman[3241] asserts that "The [NCEP] Panel is opposed to using ratios, because you end up combining factors that cannot be combined."

Naito emphasized that "To measure HDL, patient must fast for 12 hours."[1792] Levy also indicated that a nonfasting HDL measurement is "questionable." [1427] Castelli told his readers, on the other hand, that "HDL cholesterol levels can be determined in a nonfasting blood sample."[1802] And William Kannel cited Naito as

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[a] 1439,1619,1654,1686,1760,1792,1803,1809,2038

saying, "Right now, nonfasting is adequate for...HDL."[1783] Garber et al. stated in 1989 that not only must a patient fast for HDL measurements, the measurements after fasting are still "highly imprecise."[2265]

In 1988 Kannel[1448] said,

> "Recently, desk-top instruments for screening, which measure total cholesterol from capillary blood obtained by fingerstick, have become available, greatly facilitating in-office evaluation of cholesterol concentrations. However, the data on the prognostic significance of serum cholesterol from prospective population studies were obtained with a chemical calorimetric method (Abell-Kendall). Different methods of determining serum cholesterol, although capable of producing reproducible results, may give average values that differ by 25-97 mg."

Yet, on the same page Kannel indicated that the NCEP

> "has been greatly abetted by the...further development of convenient, accurate, and economical fingerstick methods for measuring cholesterol."

In the same year Kannel stated elsewhere that

> "A normal total cholesterol reading of 220 mg by the chemical method can be classified at 265 mg with the enzyme [fingerstick] method, invoking needless active treatment."[1383]

To further compound the matter, one needs to be aware of starvation studies. While concern is always centered on specific meals which might raise or lower blood cholesterol levels, Ende[2824] demonstrated in the 1960s that starvation increases blood cholesterol more than specific foods. For example, he showed that in several groups fasting for 72 hours resulted in a blood cholesterol increase of 42 mg and 35 mg in young (21-35 years) males and females, respectively, and 25 mg in males 43-62 years. Thus, fasting per se apparently produces a reading that is abnormal for subjects who eat regularly.

Clinical Trials

Hegsted noted in 1978 that atherosclerotic lesions begin in adolescent boys but do not become a health problem until much later in their lives.

> "A definitive study to demonstrate the effect of diet upon CHD would require a study starting with adolescent boys, preventing hyper-cholesterolemia and atherosclerosis, and following them for a 20 or 30 year period."[2692]

This reasoning is applicable to drug trials as well since the effects on blood cholesterol levels of cholesterol-lowering drugs are identical to those of special diets. Hegsted's logic is dumbfounding.

However, although stressing the need for a 20 to 30 year period, Hegsted nevertheless indicated that

> "Most of the well-designed trials have shown an amelioration of CHD after dietary modification which lowered the serum cholesterol."

He cited the Dayton and Pearce Veterans study[454] which obtained nonsignificant results and two trials in Finland[1145] and Norway,[480] both of which were unblinded,

which is sufficient grounds for rejecting them. Moreover, the Finnish hospital study was unquestionably the worst designed clinical trial in medical history (see Volume 1).

In 1988 Perlman et al. stated that the

> "Risk factor intervention trials in men have demonstrated that lowering...serum cholesterol level, particularly LDL-C, can reduce mortality."[2752]

The authors cited the LRC and MRFIT trials as evidence, both of which clearly did not show reduced mortality from cholesterol-lowering. If there is one consistent finding among all the many clinical trials over the last 30 years, it is the fact that cholesterol-lowering does not reduce mortality.

By 1979 18 of the 26 conventional trials of cholesterol-lowering had been conducted. Kannel and Castelli said,

> "It must be admitted that the results achieved in trials to reduce CHD risk by drugs or diet designed to lower the serum total-cholesterol have been disappointing."[2731]

By 1988 eight additional trials were published, three of which were complete failures and another two of which were not blinded. The remaining three studies yielded quite small CHD "event" rate reductions via cholesterol-lowering. Yet, Castelli maintained that

> "Clinical trials that use diet or drugs to lower serum cholesterol levels have consistently shown a 2% reduction in the incidence of CHD for every 1% reduction in total serum cholesterol level."[2750]

Not only have the clinical trials <u>not</u> "consistently" shown such a relationship, admitted by Kannel and Castelli in their 1979 statements, there most certainly was not a 2% reduction in the <u>rate</u> of CHD, which is by far the most important measure of a treatment.

At the conclusion of their clinical trial, Seymour Dayton and Morton Pearce said,

> "It is our opinion that the encouraging results of our own trial, even when buttressed by concordant observations in two other primary prevention studies, are not sufficient grounds for aggressive efforts to change the U.S. diet."[2549]

But several years later, Dayton presented an entirely different interpretation of his trial results and made the opposite dietary recommendations.

> "Dear Senator McGovern: Thank you for providing me with a copy of your committee's publication entitled 'Dietary Goals for the U.S.,' and for the invitation to comment upon these issues. The main reservation I would have is that...more radical restriction of saturated fat and cholesterol might very well be even more efficacious. Our own trial strongly suggested that a diet reduced in content of saturated fat and cholesterol was effective in reducing complications of arteriosclerosis in men under the age of 65."[2708]

In 1984 Stamler[2939] said, "Trials of preventive intervention against...atherosclerotic disease are not, and cannot be, decisive tests on disease causation..." He cited a 1984 article by Castelli[2955] as the source for saying that "Although such research may contribute to understanding of disease etiology, it cannot be the critical, decisive test." While the NHLBI Task Force in 1971 essentially made such a statement in the process of recommending the "nondefinitive" MRFIT and LRC trials (Chapter 7), a

careful examination of the cited Castelli article revealed no such discussion. In any event, Basil Rifkind strongly disagreed with Stamler and the Task Force (as well as former NHLBI director Cooper) when he said that "...the LRC-CPPT is the first study to demonstrate conclusively that the risk of CHD can be reduced by lowering blood cholesterol"[200] and that "the outcome of the Helsinki Heart study is conclusive."[1170]

Total Fats and CHD

The AHA has long maintained that total fat intake, regardless of type, is strongly related to CHD. The NHLBI has since accepted this assertion and the Food and Nutrition Board has recently re-emphasized it in its "Diet and Health" report, namely, "There is clear evidence that the total amounts and types of fats and other lipids in the diet influence the risk of atherosclerotic cardiovascular disease..."[2070] Like so many other statements by the alliance, which are based far more on proclamation than evidence, the epidemiological and experimental evidence is very unsupportive of the alliance's position on total fat intake and there is absolutely no question that the alliance is aware of this state-of-affairs, as exemplified in the following discussion.[a]

Many early dietary experiments clearly demonstrated that very high fat diets composed predominantly of vegetable oils lowered blood cholesterol levels substantially (e.g., Kinsell et al.[328,363] Beveridge et al.,[348] Ahrens et al.[359]). AHA used these findings to encourage Americans to increase their consumption of polyunsaturated fats in its early statements to the public.

More recent studies have similarly shown that total fat is not related to blood cholesterol. For example, Baggio et al. reported that a 38% fat diet produced a substantially lower blood cholesterol level than did a 28% fat diet when the saturated and polyunsaturated fatty acids amounts were the same the high-fat diet contained more monounsaturated fat.[1782] Similarly, Grundy et al. showed that a 40% fat diet produced the same blood cholesterol levels as 30% and 20% fat diets when the percentage of saturated fatty acids remained equal to or less than the monounsaturates and polyunsaturates.[336,b]

With regard to epidemiological data, it is well known that populations living in the Mediterranean area (e.g., Greece) have high fat (40%) diets and low CHD death rates (e.g., Keys et al.,[282,493] Grundy,[978] Baggio et al.[1782]). The major fat in these diets is olive oil which is high in monounsaturates. Much of this knowledge derives from the Seven Countries study, probably the most frequently cited of all population investigations by the alliance.

Therefore, if the principal connection between diet and CHD is the former's influence on blood cholesterol, as the alliance has maintained for many years, then the alliance's position on total fat intake is inconsistent and untenable. But, as indicated earlier, the alliance must know this and the fact that it maintains an untenable position exemplifies its disregard for evidence and logic and its faith in proclamations.

The AHA generated its position on total fats from the 1953 population study of Keys[276] and a number of experiments conducted in the 1950s showing that fat-free diets lowered blood cholesterol levels (Volume 1). Apparently the AHA was not

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[a] For example, in considering the effects of monounsaturated fats, Grundy said, "it is not unreasonable to allow recommendations up to 35% calories from fat."[2480]

[b] Jones et al. found somewhat higher cholesterol levels in a 40% fat diet than a 20% fat diet but the differences were not significant.[1778]

scientifically competent to recognize that the population studies were highly confounded and it was not yet knowledgeable of the differential effects of saturated and polyunsaturated fats. The results from fat-free studies were not due to the loss of fat per se but to the fact that the typical diet contains three times as much saturated as polyunsaturated fats. Thus, a fat-free diet increased the P/S ratio from about .35 to 1.0. When experimental data first became available in the late 1950s, which elucidated the differential effects of the three fatty acids, the AHA should have altered its position on total fats--but it did not. Instead, it accepted both sets of data, although it ignored the not so subtle implications of the experimental data toward the position on total fats. Thus, the AHA encouraged the increased consumption of polyunsaturated fats, representing the apparent acceptance of the experimental data, and continued to recommend the reduction in total fat, representing the continued acceptance of the confounded population studies.

Speaking at a 1988 OB/GYN symposium, Edward Linn stated that "...the important point to emphasize to your patients is that it's really the total fat content, especially saturated fats, that we must be the most concerned about."[1787] In 1990 Ullman and Connor[3341] and Babayan and Blackburn[3343] made identical remarks. "It must be emphasized that to decrease serum cholesterol levels and the risk of coronary heart disease, both total and saturated fat intake must be decreased."[3341] "The real issue, and the key to educating the public, is the need for limitation of excessive caloric intake and the restriction of fat intake to not more than 30%."[3343] Of course, all of these statements derived from the AHA.

Illustrating the fact that the alliance's right hand is often unaware of what the left hand is doing, the NHLBI Working Group[3068] said that "At one time, investigators thought that the total amount of dietary fat was a major determinant for the concentration of serum cholesterol, and thereby, for atherosclerotic disease. This concept was modified when the effect of saturation was discovered. Because of the high calorie denisty of fat, total dietary fat is now considered important primarily in determining total caloric intake..." But NHLBI's Basil Rifkind[3081] cited Stephen in a 1990 article who purported to find that total fat intake rose from about 34% of total calories in the 1930s to 42% in the 1960s and then fell thereafter, suggesting a total fat-CHD relation.

Diet and CHD in the Framingham, Puerto Rican and Honolulu Studies

Dawber, Kannel and others[3334] published preliminary results of the Framingham Diet study in 1961. They concluded that

> "important degrees of variability with respect to fat intake probably do not exist owing to a lack of sufficient persons with 'low' fat intake (i.e., under 30% of calories derived from fat)."

In 1962 Kannel and his colleagues[2728] indicated that

> "Preliminary analysis of our diet sample shows no significant correlation between various dietary components and the serum cholesterol level. In our population, whose intake of calories, fat, cholesterol and other dietary components is high, a threshold level of some component, be it fat, cholesterol, or some other constituent, may have been passed, beyond which further increment is not associated with increment in serum cholesterol levels."

They cited Connor's[321] 1961 article as the source for this threshold level concept. Connor claimed that

"Six egg yolks with a cholesterol content of 1,425 mg did not cause a greater rise in the serum cholesterol than did two egg yolks with one third as much cholesterol. Perhaps all cholesterol above a certain amount is unabsorbed and passes out in the stool."

But such a statement was based not only on too few subjects (six), it did not clearly follow from Connor's data. The blood cholesterol increases of pairs of subjects consuming 475 mg, 950 mg and 1,425 mg of cholesterol were 66 mg, 63.5 mg and 77 mg, respectively. Certainly the 66 mg and 77 mg increases were correlated with the quantities of cholesterol consumed. The 63.5 mg increase could easily have been due to sampling error, i.e., too few subjects. No scientist should draw any conclusions from data derived from group sample sizes of two. But neither Connor nor Kannel were sufficiently trained scientists to recognize the importance of sample size.

Kannel published a technical report in 1970 which contained the final analyses of the Framingham Diet study.[a] He made the following statement:

"There is considerable range of cholesterol levels within the Framingham study group. Something explains this interindividual variation, but it is not diet. There is no discernible association between reported diet intake and serum cholesterol."[274,b]

He also reported that no relationship existed between diet and CHD. As noted in Chapter 2, the AHA's Campbell Moses dismissed the study results on the grounds that (1) there was insufficient variation among Framingham subjects in the consumption of fats and (2) the cholesterol intake was much lower than that of Americans in general.[2010] While William Connor agreed with the first part of Moses' argument, he maintained that the Framingham subjects had higher cholesterol intakes than the general population, i.e.,

"All subjects in Framingham had high intakes (of cholesterol and saturated fats) so that there was a failure to discriminate."[411]

And speaking before the 1977 Senate Select Committee, Antonio Gotto presented a similar criticism:

"The differences between the diets of individuals were not very great in that population."[1601]

The statements of Moses, Connor and Gotto bore no sensible relation to the Framingham Diet study data and the concept of a threshold in the effects of saturated fats and cholesterol on blood cholesterol is wholly inconsistent with the alliance's position, as will be seen, and unsupported by scientific evidence. Let us first examine the variations in nutrient intake.

Animal fat consumption ranged from 32% to 97% of total fats in men. Cholesterol consumption ranged from 250 mg to 1500 mg. These ranges were very wide and

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[a] This report was never published in a journal, suggesting that the alliance did not want this information to be widely known.

[b] Kannel[274] indicated that there was no relation between diet and CHD as well and a later article by Kannel and his colleagues[903] also reported no relationship between dietary cholesterol, saturated fat or total fat and CHD (see below).

closely corresponded to the AHA Prudent Diet at one extreme and an exceedingly high saturated fat and cholesterol diet at the other extreme. It is ludicrous to suggest that all subjects had high intakes of cholesterol and saturated fats and it is equally ludicrous to suggest that there was insufficient variation in intake. The reader should recall the alliance's emphasis on the importance of extremely small differences in intake of cholesterol and saturated fat in other studies.

A most amusing and yet insightful description of the Framingham Diet study report was published in 1970 by syndicated columnist Jack Smith. He quoted the report as saying,

> "It is important to be perfectly clear what these findings mean and what they do not mean. They mean that the Framingham study group diet (as measured here) is not associated with concurrent differentials in serum cholesterol level. It does not mean that the difference between Framingham and some other population (say the people of Japan) in serum cholesterol level is unrelated to differences between these populations in diet."[274]

Smith said, "Good enough. I think I have that. It's perfectly clear, once we work in behind those tricky double negatives. I can't quite not wonder, though, exactly what the people of Japan have to do with it. Medical researchers are always making irrelevant asides about people who live halfway round the world in some geographical haven that is free of civilization's ills. The Fru-Fru islanders have no sex frustrations; the hairy Ainu have no athlete's foot; the Eskimos have no colds."[2009]

If large variations in diet have no relationship to blood cholesterol levels or CHD in Framingham subjects, what indeed have the people of Japan got to do with it? Even a nonmedical, nonscientist writer can detect the irrelevancy and illogics of Kannel's "reasoning."

An argument often used by alliance members is that Framingham subjects and Americans in general consume cholesterol and saturated fat in amounts that exceed threshold levels, above which variations have no differential effects on either blood cholesterol levels or CHD. For example, Kannel et al.[2935] stated in 1971 that

> "Although Western populations show a wide range of serum lipid values, the population as a whole appears to be over the dietary threshold so that the correlation between nutrients in the diet and serum lipid values within the population is poor."[2935]

This argument is yet another example of the alliance's inability to reason logically--or with any degree of common sense. First and foremost, about 45% of the American population, as exemplified by the Framingham study, the MRFIT population and the Lipid Research Clinics study population, has cholesterol levels ranging from about 130 to 200 mg. Since this range is comparable to all nonwestern countries whose low-fat, low-cholesterol diets are praised by the alliance, obviously 45% of the American population cannot be over the "dietary threshold."

Not only is the premise that everyone is consuming a high-fat, high-cholesterol diet in the U.S. population totally false (and, as noted, Kannel observed that fact in his Framingham study), the threshold argument does not in the least explain the reasons for the extreme vairation in blood cholesterol levels which Kannel readily acknowledges. In fact, most of the lipid hypothesis promoters have stated time and again that the variation in blood cholesterol levels in the U.S. is mostly dependent on diet and only partially based on genetics. Epidemiologists have stressed over and over that the reason why the U.S. (and other Western populations) has higher cholesterol levels than other less advanced populations is because the U.S. consumes more

saturated fat and cholesterol. Probably the most recent statement by the alliance on this topic is the late 1990 article by Scott Grundy who said, "A fundamental hypothesis of the NCEP is that most hypercholesterolemia is of dietary origin" (Grundy cited the 1988 NCEP report[1066]). It is therefore utter nonsense to say that the relatively small blood cholesterol differences observed between populations (e.g., 20 to 50 mg in most cases) are due to dietary differences and, contrarily, that the huge differences (e.g., 200 mg plus) observed within a (Western) population are not related to dietary differences.

The implication of this argument is that if everyone is over a "threshold," with diet having no further effect, then the entire variation in cholesterol levels is due to one and only one factor, genetics. Yet, that is what the "threshold" argument demands.

If the above discussion were not enough to disassemble the threshold concept, the reader should recognize that numerous experiments have shown that the addition of saturated fats to the diets of subjects consuming their normal "rich" American diets elevates their cholesterol levels (Volume 1). Surely, Kannel et al. must be at least somewhat familiar with such experiments.

The threshold concept should not be a matter of discussion among grown men and women, let alone individuals purporting to be scientists.

Despite all of the above, Gotto[2527] published the following false statement:

> "Epidemiologic studies, such as...Framingham...showed that populations with low consumption of saturated fat...had virtually no atherosclerosis or CHD mortality."[a]

The report cited by Gotto was a 1971 article by Kannel et al.[1376] which had nothing to do with the diet and CHD relation and did not even contain the words "fat" or "saturated fat."

In 1981 Kannel et al.[903] reported that there were no differences observed between CHD and nonCHD subjects in the Framingham, Puerto Rican and Honolulu studies with respect to intakes of dietary cholesterol, total fat or specific fats and drew the following illogical conclusion:

> These data "would not lend to an alteration of currently recommended preventive diets that emphasize lowering fat intake, because in isocaloric diets the logical way to balance a decreased fat intake is to increase the consumption of foods containing starch."

The second part of this sentence is not an explanation for why the Framingham, Puerto Rican and Honolulu findings "would not lend to an alteration of currently recommended preventive diets that emphasize lowering fat intake" as implied. Moreover, given the desirability of lowering the fat intake, it is equally logical to increase the consumption of protein as it is to increase carbohydrates.

The following statement by Kannel, Stamler and others[1083] in 1984 is blatantly fraudulent and contradicts earlier statements by Kannel et al.[903]

> "Middle-aged male populations studied according to similar protocols in Puerto Rico, Hawaii, and Framingham show concordance between mean levels of saturated fat, cholesterol intakes, and serum cholesterol."

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[a] Gotto made a similar statement in another article.[1341]

This statement was undoubtedly designed to imply that there was a positive relationship between diet and blood cholesterol level in these studies when, of course, there was not. If the reader examines the statement carefully, all it really indicates is that the subjects in the three studies showed the same relationship between diet and blood cholesterol. Kannel et al. neglected to say that it was a zero relationship and did not cite references for the original studies, one of which was his own, cited earlier.[274,334,550]

Dietary and Blood Cholesterol

In 1933 Okey and Stewart reported a "slight" increase in blood cholesterol with large amounts of dietary cholesterol.[346] In 1949 Gutman stated that "studies in man of the effects of diets high in cholesterol...indicate that they have surprisingly little influence upon serum cholesterol levels."[1801] In their report to the AHA in 1957, Page et al. concluded that "In man, it seems likely that serum cholesterol concentration is virtually independent of the intake."[512] Very recently Schonfeld maintained that "The removal of cholesterol alone from diets, without changing other components, produces relatively modest effects on the concentrations of plasma lipids"[1777] and Anderson emphasized that "what proponents of the diet-health theory still fail or refuse to acknowledge is that cholesterol intake has little to do with serum cholesterol levels in the great majority of people."[2013] Writing in the Canadian publication, Rapport, Murry pointed out that experimental and epidemiological data convinced many countries to eliminate cholesterol from dietary guidelines. "The AHA has, since 1961, been unwavering in its advice to reduce cholesterol intake and has been joined in this by...many other American organizations. The advice to restrict dietary cholesterol has been almost exclusively a USA phenomenon."[1940]

Finally, it is of interest to cite a frustrated reader of Hospital Practice, as exemplified in his letter-to-the-editor. Melvin Goldberg wrote, "several times in the past...you have made remarks about eggs affecting serum cholesterol levels and being bad for the heart. This is pure mythology, but it has become so deeply embedded in everyone's consciousness that I feel I risk burning at the stake for saying otherwise."[2030] Goldberg conducted a review of the literature and found in all cases that egg consumption has never been shown to increase CHD incidence or significantly affect blood cholesterol level.

As was shown in Volume 1, the evidence supporting the above statements is enormous. Yet, core NHLBI/AHA members simply defy the evidence and publish statements which run completely contrary to the facts. And they usually cite few or no studies as supportive evidence. For example, Ernst and Levy[300] claimed that dietary cholesterol is "hypercholesterolemic," Connor[350] said that "Cholesterol consumed in the human diet is now known to have a great effect on serum cholesterol levels, and Stamler and Shekelle[1565] maintained that the effects of dietary cholesterol are "substantial." Katz, Stamler and Pick[1884] told their readers that "It is not true that cholesterol metabolism is uninfluenced by diet (cholesterol). All recent studies demonstrate the opposite." These authors, however, cited not one human dietary study.

As to the magnitude of the effects of dietary cholesterol, consider the following statements:

> "The average serum cholesterol can be expected to fall 5 mg for each 100 mg decrease in intake." (Kannel et al.[1083])

"Removal of all cholesterol from the diet would result in a cholesterol drop of 30 mg." (Castelli[1736])
[Since the average intake is about 500 mg, the rate would be 6 mg per 100 ingested.]

"Each 100 mg of dietary cholesterol raises plasma approximately 7 mg." (Grundy et al.;[499] Peters and Goroll[1027]).

"For each 100 mg of cholesterol ingested, plasma cholesterol will increase by something like 8 to 10 mg." (Goldberg[1398])

And William Connor's[1825] latest analysis indicates a blood cholesterol increase of 13 mg per 100 mg ingested. Thus, we have alliance members' estimates of 5, 6, 7, 8 to 10 and 13 mg per 100 mg ingested and all are gross exaggerations of the true value of about 2 mg in whole foods experiments.

In 1984 Kannel, Stamler[1083] and others made the following two statements on Pages 167A and 170A of their article:

"One hundred milligrams of dietary cholesterol (per 1,000 calories) causes a 5 mg increase in serum cholesterol" [Thus, for a 2,500 caloric diet, this statement indicates that a total of 250 mg dietary cholesterol causes a 5 mg increase in serum cholesterol.]

"It is recommended that dietary cholesterol be reduced from the current 400 mg/day for men to 250 mg/day. The average serum cholesterol can be expected to fall 5 mg for each 100 mg decrease in intake."

Thus, while it apparently takes 250 mg to raise blood cholesterol 5 mg, eliminating only 150 mg lowers blood cholesterol 5 mg, according to Kannel et al. Accepting these "premises" as valid (which, of course, they are not) one can lower blood cholesterol by eating more dietary cholesterol. To illustrate, consider an individual with a cholesterol level of 220 mg. He consumes 500 mg more cholesterol per day than usual. His blood cholesterol then rises to 230 mg. Subsequently, he eliminates 300 mg of dietary cholesterol and his blood cholesterol drops to 215 mg. Eureka, he increases his dietary cholesterol by 200 mg per day and decreases his blood cholesterol by 5 mg.

After recommending the AHA's Prudent diet for all patients, which includes the restriction of dietary cholesterol to less than 300 mg per day, Schaefer and Levy[3022] were asked, "Could you summarize your views about the role of dietary cholesterol?" Schaefer and Levy effectively sidestepped a discussion of the independent effects of cholesterol, i.e.,

"Most studies of hyperlipidemic or normolipidemic subjects on low-saturated fat, low-cholesterol diets show that if the diet is strictly adhered to, significant reductions in plasma cholesterol levels due to decreases in LDL levels can be achieved. Population studies also support this view. The amount of plasma cholesterol reduction depends on how the diet is modified, one should not only increase the dietary ratio of polyunsaturated to saturated fat but also restrict saturated fats and cholesterol. Patients may have to be followed on a long-term basis before a marked change can be seen."

To illustrate the alliance's dogmatic attitudes, consider a 1989 article by Connor and Connor.[1825] They said, "Over the past 25 years some 26 separate metabolic experiments involving 196 human subjects and patients have shown decisive effects of dietary cholesterol on human plasma cholesterol." However, they referenced only four

experiments, two of which were Connor's and all of which involved inappropriate liquid diets.[319,321,322,349] The tone of their discussion suggested that they were irritated by the fact others do not think that dietary cholesterol is important in elevating blood cholesterol. They said, "...attempts are still being carried out and are highly touted as showing that dietary cholesterol has no effect on plasma cholesterol levels. There is a recent review for those who wish to explore the subject more fully." That review was hardly recent, having been published 8 years earlier, and it was co-authored by Connor himself.[402] Moreover, that "review" was so brief and incomplete, it simply could not be classified as a review. In one-third of a small journal page it quickly mentioned 14 previous experiments, three of which were whole foods studies that found no significant effects of dietary cholesterol.

It is most curious to note that Connor was co-author of one of the 12 free-living studies reviewed in Volume 1 (Table 5-5).[402] That study yielded a blood cholesterol increase of 4.3 mg per 100 mg ingested, not only the highest of all other studies, but 3.5 times the average of the other studies. While such an outcome may be purely coincidental, it is consistent with Connor's highly deviant findings.

Although the alliance's statements on dietary cholesterol are totally erroneous, they are the only statements heard by the press and public. For examples, the following "information" was cited as deriving from John Robbins' Diet for a New America.[1926] "The rise in blood cholesterol from consuming 1 egg per day: 12%. The rise in heart attack risk from 12% rise in blood cholesterol: 24%." While both of these values are complete fabrications, readers are nevertheless led to believe that their chances of getting a heart attack will increase 24% with the daily consumption of one egg. It is difficult to believe that medical "scientists" would transmit such utter nonsense to the public.

Also heard by the press and the public was the following statement in the New York Times, attributed to cardiologist Louis Lange: "Doctors say the best way to lower cholesterol levels is to eat less cholesterol."[2255] Not even Connor or Stamler would agree with that statement today. And at least one alliance member seemed aware of the relevant literature prior to the great push to reduce everyone's consumption of dietary cholesterol, i.e., Daniel Steinberg[3037] stated in 1962 that "Dietary cholesterol...is in itself without much effect on serum cholesterol levels in man..."

While the Stamlers, Connors, LaRosas and others falsely attribute great importance to dietary cholesterol, the alliance's leaders seem to be shifting away from that position. For example, 1989 AHA president Myron Weisfeldt[2543] stated that "You can't say that reducing dietary cholesterol will reduce atherosclerosis." And in 1991 Claude Lenfant[3267] said, "The focus over the past few years [decades is more accurate] has been mainly on cholesterol, yet the impact of dietary cholesterol on blood cholesterol is a very controversial issue. Some people are strongly affected by dietary cholesterol, but the majority of the population is not--at least not to the extent that messages and information were focused on it."[a] Such a statement is an indirect admission that the alliance has greatly exaggerated the importance of dietary cholesterol and continues to do so, e.g., Willett and Sacks[3229] also stated in 1991 that "The most firmly established conclusion about dietary lipids is that the intake of cholesterol should be reduced. The optimal intake of cholesterol is probably zero."

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[a] This is in contrast to the 1989 AHA/NHLBI joint statement that said, "these studies demonstrate unequivocally that high intakes of dietary cholesterol will significantly raise serum cholesterol levels in the majority of people."[2500,3349] Note that AHA/NHLBI and Lenfant used "majority in the opposite manner.

(One year earlier Willett[2970] indicated that there was only one consistent finding regarding a specific dietary nutrient and CHD, i.e., "A strong protective effect of moderate alcohol intake.")

The Amount of Fat in the Diet

The most commonly published estimate of the total amount of fat in the American diet is 36% to 38% of total calories (e.g., Hegsted et al.,[408] Stare,[1372] Connor and Connor,[1825] Kim et al.,[1841] Ernst and LaRosa,[2227] Doheny,[2282] the 1988 Surgeon General's Report[2433] and the NHANES I and II population surveys.[2557] An NIH report indicated a value of 35% to 40%.[2288] Miller[2239] and Cohen and Spain[3346] reported values of 40% to 45% and the man claiming to have produced the most comprehensive report on diet and CHD (National Research Council's "Diet and Health"), Arno Motulsky was said to have indicated that the average American diet is 48% fat.[2075] The record goes to Katz, Stamler and Pick, however, who stated that the American diet consisted of 40% to 60% fat,[694] and that the average American business and professional man ingests almost 60% of his calories in the form of fats."[3201]

LaRosa and Karmally[3052] indicated in 1987 that the American diet contained 40% of calories as fat. Since Ernst and LaRosa[2227] (above) had said that the fat content was 37% in 1988, apparently his estimate varies with his co-authors.

The NHANES I and II population surveys revealed that the average American diet contained about 13.6% of total calories as saturated fat.[2557] The estimate of Hegsted et al.[408] was nearly identical, i.e., 14%, but Stare,[1372] LaRosa,[1709] LaRosa and Karmally,[3052] and Grundy were a little on the high side, namely, 16%, 14-18%, 17% and 13-16%, respectively. But Connor[1930] claimed the percentage was "well over 20% and Castelli[1802] said it was "between 50 and 70 g per day" (an average of 22% for a 2500 calorie diet).

Absolute vs Relative Amounts of Dietary Cholesterol

Some members of the alliance argue that the amount of dietary cholesterol per unit of calories ingested is the proper measure of intake and not the absolute amount ingested. Suppose we have three male subjects, Slim, Fatso and Big John. Slim is 6 feet tall, of average weight and consumes 2,600 calories and 500 mg cholesterol per day. Fatso is 5 feet 8 inches, considerably overweight and consumes 3,500 calories and 600 mg cholesterol per day. And Big John is 6 feet 6 inches, of average weight and consumes 3,500 calories and 600 mg cholesterol per day. Although Fatso and Big John consume 100 mg cholesterol more than Slim, they actually consume less cholesterol (171 mg) per 1000 calories ingested than Slim (192 mg).

There is some logic to the suggestion that Slim may be consuming more cholesterol than Big John but it is difficult to conceive of a rationale which suggests that Slim is consuming more cholesterol than Fatso. Fatso has more fat cells but a smaller frame and probably a smaller arterial blood network. Would Stamler and his colleagues actually conclude that Fatso's cholesterol intake is preferable to that of Slims? If so, what is the scientific basis for this assertion?

In general, the effects of dietary cholesterol on blood cholesterol levels are independent of the fat composition of the diets and there is no evidence that they are not independent of the number of calories in the diet. It is conceivable that they may be related to the height/frame dimensions of individuals, based on the simple concept that "larger" persons have larger blood networks and therefore can consume more dietary cholesterol than can "smaller" persons and maintain the same blood

cholesterol levels. However, it is likely that there are many factors, including genetics, which influence the amount of cholesterol absorbed from the diet and discussions of all such factors are entirely speculative and not very fruitful. Suffice it to say that measuring cholesterol intake as a function of a given unit of calorie intake distorts the intake and there is no scientific justification for this distortion.

The same argument does not hold for fatty acids because the effects of saturated, monounsaturated and polyunsaturated fatty acids are not independent. Therefore, for example, measuring saturated fatty acid intake as a percentage of total calories or total fats makes sense. On the other hand, given the same fatty acid compositions, the evidence indicates that total fats as a percentage of total calories is not a meaningful measurement (see On Total Fats).

The Consumption of Polyunsaturated Fat

The alliance was quick to recommend high polyunsaturated fat diets to Americans following early diet experiments until direct and indirect evidence began accumulating that such diets were harmful, possibly carcinogenic. In 1979 Stamler effectively denied that the alliance made these ill-fated recommendations and criticized those who bring up the issue. He said,

> "...recommendations by the American Heart Association, The Inter-Society Commission, the White House Conference on Nutrition, the Senate Select Committee and others have not been to eat a diet high in polyunsaturates. Therefore, it is time that critics of efforts to improve the lipid composition of the U.S. diet address the real issues and cease inserting the false issue of high polyunsaturated fat."[2635]

And in 1983 Stamler[3051] insisted that the AHA and its supporters had been consistent in their recommendations regarding the consumption of polyunsaturated fats, i.e.,

> "In terms of advice to the general public, the statement in 1961...by the AHA...emphasized reduced saturated fat and cholesterol intake and moderate (not high) ingestion of polyunsaturates. Thus, there is a clear record over 20 years in regard to advice to the public. The 'issue' of high polyunsaturates is in essence a non-issue."

The issue was important because the American people were told innumerable times by the alliance that polyunsaturated fats protected against CHD and there was considerable evidence that Americans were increasing their consumption of polyunsaturated fats, as indicated by the ever increasing availability of numerous brands of vegetable oils, shortenings and margarines. To this writer's knowledge, the alliance has never told the public that high consumption may be dangerous. Rather, it merely recommends limiting intake to 10% of total calories. Such a recommendation does not contradict earlier recommendations in the minds of Americans because there is a subtle omission of exceedingly important information.

Despite Stamler's statements of denial, he was one of the six authors of the first AHA recommendations to the public in 1961. That statement contained numerous comments indicating or suggesting that saturated fats were bad and polyunsaturated fats were good for health. It also contained two sentences that left no mistake about the desirability of "substantially" increasing dietary polyunsaturated fat, i.e.,

> "Substitution of polyunsaturated for a substantial part of the saturated fat in the diet may also be a valuable addition to this program."

> "It should be borne in mind that moderate amounts of fat, particularly those containing an appreciable quantity of the polyunsaturated type, are necessary for

good health."[517]

Stamler was a principal investigator of the National Diet-Heart feasibility study which used different diets containing 15 to 20% of total calories as polyunsaturates.[725,3076] These diets had P/S ratios of 1.5 to 2.0. One part of the study had a diet "very high in polyunsaturated fat, with a P/S ratio of 4.4. Stamler[3076] also recommended in 1968 a diet "high in polyunsaturated fatty acids" for overwieght persons with hypercholesterolemia. Stamler[2633] also prepared a pamphlet in 1977 entitled, Four keys to a healthy heart, in which he stressed that Americans should (1) increase consumption of vegetables because they have polyunsaturated fats, (2) use oils and modified shortenings which are high in polyunsaturated fats, (3) substitute soft margarines...for butter on toast or rolls because they are high in polyunsaturated fats, (4) use oils in salads because they are high in polyunsaturated fats, and (5) use oils rather than solid shortenings in cooking because they are high in polyunsaturated fats. There is no way that anyone would interpret Stamler's pamphlet as anything other than recommending a high polyunsaturated fat diet. Stamler[3075] also published a report in 1968 in which he recommended diets containing "10 to 15% of calories as polyunsaturated fat" for control of hypercholesterolemia.

A second author of the 1961 AHA statement, Frederick Stare, would subsequently recommend to the millions of readers of his syndicated column dozens and perhaps hundreds of times over many years to greatly increase their consumption of polyunsaturated fats (Chapter 9). In one column he said,

> "To my knowledge, i've never heard of too much polyunsaturated fat for man..."[1959]

Stare also prepared a pamphlet in 1969 that was distributed by the AHA. Both adults and "kids" were encouraged to consume "a diet low in saturated fats and cholesterol and high in polyunsaturated fats." He said that "every member of the family will be eating the kind of diet that is best for health."

In 1965 Hegsted, Stare and others told fellow physicians that

> "...the most effective practical diets for lowering the serum cholesterol should be those relatively high in total fat with (a) a small proportion of myristic and palmitic acids...(b) a high proportion of polyunsaturated acids..."[408]

Hegsted would later (1978) exclaim the opposite, i.e.,

> "...overconsumption of food but particularly fat...[is a]...contributor to the most important health problems of Americans..."[2692]

A third author of the original AHA recommendations, Ancel Keys, recommended as early as 1959 low-fat diets with P/S ratios greater than 1.0.[2920] And as late as 1973 he stated that

> "The recommended modifications for transforming the usual U.S. diet into a cholesterol-lowering diet are to reduce saturated fat and cholesterol intake and to increase polyunsaturated fat."[2838]

Keys recommended two diets, both of which exceeded 10% of total calories as polyunsaturated fats (11% and 14%). Keys also suggested that a high fat diet was fine for some countries but not for others. He said,

> "A policy of reducing fat intake to 30% or less of dietary energy should apply only to populations such as those of northern Europe and the U.S. where most

of the fat in the diet comes from meat and dairy products."[282]

In addition to the fact that trimmed meat is not a substantial contributor to dietary fat, Keys' statement clearly admits that relatively high fat diets per se are not harmful and implies that Americans could reduce their risk of CHD by consuming much more of the Greek fats, an implication directly opposite to the alliance's dogma. Keys also admitted that the Greek diet now consists of 43% of total calories as fat, approximately 6% higher than that in the American diet.[282]

The AHA's recommended diet derived from Norman Jolliffe who coined the term "Prudent Diet" during his conduction of the Anti-Coronary Club trial in the 1960s. This diet was composed of 30 to 33% fat and had a P/S ratio between 1.25 and 1.50, indicating the predominance of polyunsaturated fat.[467,469,2917]

In 1968 the AHA announced its latest dietary recommendations to the public. The statement read, "The ideal quantity of fat needed in the diet is not known, but an intake of less than 40% of calories from fat is considered desirable. Of this total, polyunsaturated fats should probably comprise twice the quantity of saturated fats."[662]

Van Itallie was also an apparent supporter of high polyunsaturated fats. He said,

> "It is now established that portable diets can be devised that are rich in polyunsaturated fatty acid content and provide the same proportion of fat to which Americans are accustomed."[2916]

In 1971 Kannel et al.[2935] recommended "for the bulk of the general population with more modest lipid disorders" a diet "that is low in saturated fat and high in polyunsaturated fat (P/S ratio greater than 1)."

The 1977 Senate Select Committee report not only recommended a high (10% of total calories) intake of polyunsaturated fat for everyone, (see Blackburn below) it recommended an absurdly high intake for those with familial hypercholesterolemia, i.e.,

> "Limit all meat to no more than 9 oz of cooked meat per day. Consume in some fashion 2 teaspoons of polyunsaturated fat for each oz of cooked meat."[1055]

If one could consume pure polyunsaturated fat, 18 teaspoons would represent about 75 g or 675 calories which is 26% of total calories, assuming a 2600 calorie diet. The most concentrated form of polyunsaturated fat is in safflower oil. But it would be necessary to consume 23.4 teaspoons of safflower oil to obtain 18 teaspoons of polyunsaturates. This amount of oil represents about 97 g or 34% of total calories.

In the same Senate Select Committee report, ex-AHA president Antonio Gotto, presented his "Help Your Heart Eating Plan." He said,

> "Diets can be prescribed to lower cholesterol which are nutritious, which provide adequate calories, nutrients, vitamins and minerals and which are free from known harmful effects. This is what I would consider to be--Prudent diet and one which we employ with our patients...in Houston."[1601]

The plan included 6 teaspoons of polyunsaturated oil per day and 6 teaspoons of soft safflower oil or corn oil margarine per day. Twelve teaspoons of oil represent about 50 g of fat or 17% of total calories in a 2600 calorie diet.

Although AHA member Scott Grundy and his colleagues indicated in 1982 that "while some replacement of saturated fats by polyunsaturates seems safe, it may be

prudent not to exceed 10% of total calories."[499] Yet, in 1985 he recommended a diet "rich in polyunsaturates," namely,

> "20% [of calories] as polyunsaturates."[687]

In 1986 Henry Blackburn said,

> "I've always been concerned about too much polyunsaturates. We know of no natural diets with 10% polyunsaturated fats, and we don't need that much."[1368]

Yet, in the Hearings before the Senate Select Committee on Nutrition and Human Needs in 1977 he praised the vegetable oil industry for its advertising claims that consuming vegetable oils reduces heart disease.[2707] He also noted that these [vegetable oil] products were successfully used by the National Diet-Heart Study, in the Minnesota Laboratory of Physiological Hygiene, and elsewhere, through the 1960s." The diets in the Diet-Heart Study, in fact, exceeded 10% of total calories as polyunsaturates. It may also be added that Blackburn was an author of the 1982 AHA statement noted above which recommended up to 10% of total calories as polyunsaturates.

In 1972 Connor and Connor recommended a diet high in polyunsaturates for lowering blood cholesterol. For example, they said,

> "If the P/S value...is greater than 1, the product in acceptable for use on this diet. Avoid butter and lard; use margarines, vegetable shortenings and oils."[411]

But three years later Connor indicated that he was against increasing the intake of polyunsaturates because

> "We shouldn't be trying to change the diet of the population before we know exactly what the given substance will do."[2436]

The American Medical Association[3257] published a book in 1982 in which it was recommended that fats and oils be consumed which have P/S ratios of 2 or higher.

Large amounts of polyunsaturated fats are still being recommended by some members of the alliance. For example, Kannel recently said that "...a diet designed to minimize the risk of coronary heart disease should emphasize restricted calories, less saturated fat and cholesterol, more fish oil and polyunsaturated fat..."[823] Moser recommended that people "Replace saturated fats (animal fats) with neutral fats (olive oil) or polyunsaturated fats (safflower, canola or corn oil)."[807] Alexander maintained that "As much as possible of the fat that is consumed should be obtained from polyunsaturates and fish."[209] Writing in the magazine Heart to Heart, edited and promoted to physicians by Gotto,[289] Sterne said, "A good suggestion when shopping for margarine is that the ratio of polyunsaturated to saturated fats should be from 2:1 to 3:1."[2596] The AMA's Council on Scientific Affairs recommended "10% or more [of total calories] derived from fats and oils rich in polyunsaturated fatty acids."[2890] Leaf maintained in 1989 that "Monounsaturated and polyunsaturated fatty acids are apparently not harmful and may even be beneficial in their effects on serum cholesterol levels..."[2913] As sources for this suggestion he cited the 26 to 34 year-old studies of Hegsted et al.[408] and Keys et al.[716] which recommended diets high in polyunsaturates and presented no evidence regarding the safety of high polyunsaturated fat diets.

The California Medical Association stated that "Whenever possible, use liquid vegetable oils such as corn, soybean, safflower, olive, or peanut in cooking instead of

butter or lard. A diet low in cholesterol relies on...polyunsaturated oils..."[1148] And writing in a 1990 issue of The Physician and Sportsmedicine, Duke University's Susan Kleiner urged, "we need to increase the amount of unsaturated fats in our diet by eating more vegetables and vegetable oils..."[2887]

Finally, perhaps the most prolific advice giver of all, Castelli, recommended a diet in 1988 containing 13 teaspoons of oil and margarine per day.[1802]

As indicated in Chapter 9, syndicated columnist Jane Brody (and many others) repetitively recommended that her readers increase, then decrease, then increase, then decrease, etc. their consumption of polyunsaturates. From whence does Stamler think she got her information? Very recently, Jane Hurley[3276] of the Center for Science in the Public Interest indicated that any margarine was good for health if it was low in saturated fat and contained 6 g or less fat per tablespoon, implying that there was no harm in a very high polyunsaturated to saturated fat ratio.

In sum, as noted by Bonnie Liebman,[1368] "For years, heart disease experts have urged consumers to eat fewer saturated fats--which tend to raise blood cholesterol--and more polyunsaturated fats--which lower blood cholesterol." She cited Franks Sacks as admitting that "In the past, our emphasis was to get people to use polyunsaturated fats instead of others." Indeed, in 1988 the Expert Panel of the NCEP readily admitted that "...very high intakes of linoleic acid were once advocated for cholesterol lowering..."[1094] and the 1989 alliance-controlled Food and Nutrition Board indicated that "High polyunsaturated fatty acid diets (i.e., more than 10% of total calories) are no longer recommended in the U.S. for lowering serum cholesterol in part because of concern about the longer-term safety of such diets."[2070] Therefore, while Stamler and the alliance would like people to forget that they heavily promoted high polyunsaturated fat diets without recognizing the possible harm, it cannot be forgotten because the effects of the promotion are still in evidence, consumption is still increasing and promotion is still ongoing. Moreover, some alliance members also promote the regular consumption of fish oils which are also highly concentrated polyunsaturated fats.

Meat and Fat

Alliance members frequently inform readers that beef is heavily laden with harmful fat. For example, Antonio Gotto said that

"Beef ranges from 8% to 45% fat after the fat has been removed."[1369]

Using trimmed round steak and sirloin steak as typical examples of beef cuts, total fat in the cuts is only 9% by weight, while protein is 31% by weight.[946] Although it is true that the total fat is 39% in terms of total calories, it is also true that 52% of beef fat is composed of unsaturated fatty acids and that 14.1% of the saturated fatty acids is comprised of stearic acid, a non-cholesterol raising acid. Thus, beef contains only 13% of total calories as cholesterol-raising saturated acids and it is partially countered by the accompanying unsaturated fats.

Although the alliance condemns total fat, as well as saturated fat, NCEP does so primarily because it presumably promotes obesity to a greater extent that do carbohydrates. Not only is this contention scientifically unproved, it has been stressed elsewhere in this volume that because fat and carbohydrates differentially influence hunger, fats may actually be the least obesity promoting. In any event, the relevant saturated fatty acids in beef are trivial. For example, if a person consumed one pound of beef per day, and few people come close to that amount, he would be consuming 5% of total calories as relevant saturated fatty acids in a 2600 calorie diet,

half of what is recommended by the alliance.[a]

The following excerpts derive from a letter-to-the-editor and a reply published in the American Journal of Cardiology in 1991. Reacting to an editorial by William Roberts, Mark Goldstein[3309] indicated that "The editor stated that animal flesh was never intended for human beings, who are natural herbivores." After noting that more than one-third of human teeth are incisor and canine teeth, Goldstein pointed out that "humans are not natural herbivores. We are omnivores."

Roberts[3310] replied that "Yes, most humans can and do eat animal flesh, and yes, some of our teeth are sharp, but these facts do not mean that we should eat meat (and kill animals to do so) and they do not mean that we are natural carnivores. Both human beings and the 100,000 cows, and the 250,000 pigs, and the 9 to 12 million chickens we kill every day in the USA would be better off if human beings did not think we were carnivores." In addition to the fact that Roberts' argument was more theological than philosophical, it also combined ignorance with hypocracy in a very few sentences. First, facts suggesting that humans were intended to eat meat should not be ignored in favor of no facts suggesting that humans should not eat meat. Second, Roberts' understanding of anthropology would make any novice anthropologist wince. Man was most certainly a natural carnivore long before he learned about agriculture and farming. Does Roberts honestly believe that primitive man always planted seeds and/or was always naturally supplied with sufficient eatable vegetation?

Third, Roberts' statement that "these facts do not mean that we should eat meat (and kill animals to do so)..." is curious. The phrase, "and kill animals to do so" is obviously redundant and undoubtedly intended to project his personal attitude rather than to offer scientific expertise.

Fourth, Roberts' contention that man "would be better off" if he did not eat meat is a completely biased and scientifically unsupported point of view and does not belong in a scientific journal.

And fifth, Roberts' concern with the well-being of animals in the satisfaction of one of man's basic and natural physiological drives is grossly hypocritical for a man who serves on the staff of NHLBI which continuously encourages and supports the needless slaughter of millions of animals under the guise of "studying atherosclerosis," particularly when it has been known for decades that experimentally induced "atherosclerosis" is not, in fact, human atherosclerosis. Roberts also said that "For humans to eat animal flesh is certainly 'deadly' to the animals we eat." He should be informed that for humans to dissect animals is equally "deadly" to the animals we dissect.

If Roberts is against the killing of animals for human purposes, he should resign from an organization that supports their mass slaughter. If Roberts is in favor of killing animals for medical purposes but not for food, he is simply another example of the abundant hypocracy that permeates the alliance.

Alcohol and CHD

The overwhelming evidence indicates that regular consumption of alcohol in moderation (and perhaps excessively) is associated with lowered incidence of CHD. Without apparent exception the alliance and its supporters recommend against

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[a] 6.4%, of total calories, assuming a 2,000 calorie diet.

consumption of alcohol beyond one or two drinks per day and present some rather poor rationale for this position. For example, Kannel[823] stated in 1987 that

> "Alcohol tends to raise triglyceride level, which may be atherogenic, but also raises HDL; however, the latter is not necessarily beneficial, since it mainly increases the HDL-3 rather than the beneficial HDL-2 subfraction. Whatever the mechanism involved, risk of CHD appears to be lowered by moderate alcohol intake despite adverse effects on blood pressures, triglyceride levels and cardiac rhythm."

Yes, no, yes, no!

In an editorial in the American Journal of Public Health Walter Willett stated,

> "Despite the prominence given to the relation between diet and CHD during the last 40 years, direct evidence is disappointingly meager. Only two consistent findings have emerged," [one of which is] "a strong protective effect of moderate alcohol intake."[2970]

But the 1981 NHLBI Working Group said,

> "Reports on the relation of alcohol ingestion to atherosclerosis and to clinical atherosclerotic disease are inconsistent."[3068]

Fish Oils

In 1987 Kannel reported that

> "...fish oils...influence the pace of atherogenesis." ...a diet designed to minimize the risk of coronary heart disease should emphasize...more fish oil...[823]

In the same year Castelli and Connor published similar statements, i.e.,

> "Certainly, in those with CHD or at high risk for CHD the consensus was that if a person could not eat adequate amounts of fish, supplements [of fish oil] should be given." (Castelli[1179])

> "If omega-3 fatty acids are desirable in fish for the general population, as I certainly think they are, then we have to translate that into fish oil supplementation for those who are unable or unwilling to eat fish." (Connor[1179])[a]

In 1988 the Expert Panel of the NCEP explicitly recommended against the consumption of fish oils.

> "The use of fish oil capsules as a supplement in a therapeutic diet for high risk cholesterol levels is not recommended here."[1066]

And in July 1990 the Food and Drug Administration banned the sale of fish oil capsules, saying that

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[a] The Castelli and Connor statements were made during a teleconference of four persons, funded by Warner-Lambert, manufacturers of fish oils. It seems likely that they were paid for their participation and that the resulting brochure of dialog was little more than an endorsement-type promotion of fish oils.

"At the present time, there is inadequate scientific evidence to support health claims on fish oils or to support claims that these ingredients have an effect on the risk of coronary heart disease."[2558]

However, the FDA later rescinded that ban, indicating that its statement to 67 industries which market fish oil was "inaccurately worded."[3061] The FDA indicated that advertising claims suggesting that fish oils are beneficial to heart disease are banned, not the fish oils.

The Prudent Diet

Seven studies were cited in Volume 1 as indicating that high carbohydrate diets depress HDL levels proportionally more than they do total cholesterol levels.[a] To this list may be added twelve more articles.[b] Scott Grundy's interpretation? In 1986 he said that a high carbohydrate diet

"...produces some disturbing effects on plasma lipoprotein levels, raising VLDL and lowering HDL."[262]

But four years later he said,

"a very restrictive low-fat diet will increase HDL marginally."[2597]

In 1966 Levy et al.[3217] conducted an experiment that showed that a high carbohydrate, low-fat diet disproportionately lowered HDL, thus raising the total-to-HDL ratio. During his tenure as NHLBI director, Levy[982] co-authored a report that presented similar experimental data for both normal and hypercholesterolemic men. The ratio increase among normals was small but this would nevertheless appear to be a negative trend since the mean cholesterol levels before the diet was quite low and, according to the alliance, not in need of reduction, i.e., 176 mg. The ratio increase among hypercholesterolemics was large.

Abbott, Garrison, Wilson and Castelli[3340] presented Framingham data relating HDL levels with LDL levels. They indicated that "Negative asssociations always occur, but the strength of the relationship depends on the sex and age group." However, observation of the figures presented by Abbott et al. clearly show that HDL is always positively associated with LDL in men up to an HDL of 49 mg. A negative association occurs thereafter with all but one age group. Moreover, Abbott et al. showed a very strong negative relationship between HDL and VLDL throughout the HDL range. These data are thus consistent with the high-carbohydrate, low HDL relationship.

Some 13 articles reported that polyunsaturated fats also lower HDL levels.[c] The effects of monounsaturated fats have yielded conflicting results.[d] However, Schonfeld

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[a] 373,450,590,978,1572,1607,1625

[b] 1790,1806,1820,1822,1823,1828,1848,1849,1850,1851,2028,2036

[c] 439,717,869,877,948,1607,1774,1775,1776,1825,1827,1901,2036

[d] 373,717,948,1395,1777,1782

provided evidence that HDL level is lowered proportionally more than total cholesterol when total fat is reduced.[1790]

Since the Prudent Diet calls for an increase in carbohydrates and polyunsaturates and a decrease in saturated fats and total fats, this diet operates to depress HDL unfavorably, the lipoprotein considered by some prominent alliance members to be the most important lipid factor in CHD.

One of the most important members of the alliance who contributed directly and indirectly to adoption and promotion of the Prudent Diet was Theodore Cooper, the former director of NHLBI, Assistant Secretary for Health and current chief executive officer of a cholesterol-lowering drug manufacturer, the Upjohn Company. During his testimony before Senator McGovern's Select Committee on Nutrition and Human Needs in 1976, the Senator asked, "Is it not a fact that looking at the problems of the American people as a whole that overconsumption may be as serious a problem of nutrition as underconsumption?" Cooper replied,

> "Particularly overconsumption of the wrong things, Senator [note emphasis on 'wrong things']. I would agree with that. Very often in the poor we see people who are plump who might be called obese, and people would then conclude that they do not have a deficiency because they look rotund, healthy in one sense of the word. But it is true that the consumption of high carbohydrate [high carbohydrate!] sources with the induction of obesity constitutes a very serious public health problem in the underprivileged and economically disadvantaged."[2186]

Also speaking before the Senate Select Committee, Mark Hegsted said,

> "What are the risks of reducing meat and fat and increasing carbohydrates? There are none that can be identified."[2434]

It is precisely this "very serious public health problem" discussed by Cooper, i.e., high carbohydrate diet, that is being promoted today as the Prudent Diet. The diet that was long condemned as unhealthy was referred to as "starchy." But starch is the abundant carbohydrate found in all of the foods now promoted in the Prudent Diet, namely, seeds, fruits, vegetables, fibers and roots of plants, including beans, corn, potatoes and rice. Instead of being called "starchy," they are now given the more colorful name, "complex carbohydrates." But a rose by any other name is still a rose.

With regard to obesity, Reiser and Shorland[1804] pointed out that "Fats slow the emptying time of the stomach and slow the absorption rate from the intestine, delaying hunger. Carbohydrates have the opposite effects, due, in part, to rapid emptying of the stomach," stimulating the hunger response. The AMA's Council on Foods and Nutrition had earlier described the physiological process in some detail.[2629] "Fat affects gastrointestinal motility, particularly gastric emptying. Fat in the duodenum acts to retard gastric motility and emptying time by stimulating the release of enterogastrone. Since enterogastrone inhibits hunger contractions and the psychic phase of gastric stimulation, its presence might be expected to decrease appetite. This inhibition may account for the satiety value of fat."

The alliance also emphasizes low-fat diets because it assumes that the replacement of high calorie fat will be equal (weight) amounts of low calorie carbohydrates. This assumption is hardly likely to be true and, in any event, national recommendations should not be based on assumptions. As emphasized by Van Itallie and Hirsch,[3325] "There is no evidence that the higher caloric density of fat...is itself repsonsible for undue weight gain."

High carbohydrate diets elevate blood sugar levels.[829,2192] According to Weinberger, elevated blood sugar promotes cardiovascular disease, congestive heart failure, claudication, stroke and CHD two to five times in both men and women.[2192] Nervi et al. also presented experimental evidence that legumes promote gallstones.[2464] Since high carbohydrate diets usually contain relatively large amounts of legumes, the incidence of gallstones could increase with greater consumption of the Prudent diet.

The Prudent Diet, as described by Grundy et al.[499] contains 30% of total calories as fat, 55% as carbohydrates and 15% as protein.[a] Newspaper reporter Burros recently told her millions of readers that the Food and Nutrition Board's report recommends that consumers ingest only 6 oz of meat per day.[2280] Six ounces of lean sirloin contains only 53 g (212 K cal) of protein which is only 8.2% of the protein recommended. The reason for recommending this small amount is not because of the fat associated with lean meat (which is very little) but because the high carbohydrate diet recommended also provides a significant amount of protein. In fact, it is almost impossible to consume a high carbohydrate diet and maintain a protein intake of only 15% of calories.

Table 10-1 shows some common foods recommended by the alliance in the proportions commonly eaten for breakfast, lunch and dinner. Note that the entire menu is only 1,284 calories or about one-half of the average calories consumed per day. Yet, it contains 98.5 g of protein, 31% of the calories in the table and already 15% of a 2600 calorie diet. The addition of any more dairy products and/or vegetables will raise the protein content substantially. Also note that the only dairy product in the table is nonfat milk and that no meat or cheese is represented in the breakfast or lunch meals, contrary to what is commonly consumed. For example, popular foods such as nonfat yogurt or nonfat cottage cheese would each increase the protein content of Table 10-1 by 13%.

Even a cursory evaluation of the American way of life should convince all but the alliance that a high carbohydrate, low protein, low fat diet will be unacceptable and therefore impossible to achieve by the vast majority of the American people.[b] However, Schaefer and Levy[3022] think otherwise. They said, "The average American diet contains about 36 to 40 percent [average = 38%] of calories as fat. Therefore, reduction of fat intake to 20 to 30 percent [average = 25%], as recommended by the AHA, is not a striking reduction for most people, especially if our diet is compared with that of some other societies." Reducing the fat intake from 38% to 25% would most certainly be a "striking reduction," i.e., 34%, and what diets other societies consume has nothing to do with whether or not a reduction in the American diet of 38% to 25% is "striking."

Finally, it is noteworthy to mention that NHLBI director Claude Lenfant, the chief promoter of the 30% fat Prudent diet, gave high praise to Dean Ornish's small angiographic trial which purported to show that a severe diet and reductions in other risk factors slowed progression and caused regression of atheromas.[2896] Subsequently, Ornish told the New York Times that Lenfant's Prudent diet has been repeatedly shown to be ineffective in altering the development of atherosclerosis.[3386] In turn,

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[a] Columnist Jane Brody absurdly recommended 70% or more carbohydrates as a "most effective cholesterol-lowering diet."[2470]

[b] The high carbohydrate diet, recommended for all Americans by the alliance, is, of course, not a suitable diet for diabetics. Grundy therefore recommended a high monounsaturated fat diet for noninsulin dependent diabetics but Stanford's Reavan indicated that such a diet has no scientific basis.[1805]

Table 10-1

Protein and calorie content of some recommended high-carbohydrate foods

Breakfast	Protein (g)	Calories
bran cereal (1 oz)	4	80
nonfat milk (1 cup)	8	85
bread (2 slices)	5	130
egg (1/2)	3	40
Lunch		
bread (2 slices)	5	130
peanut butter (1 Tbs)	5	95
Dinner		
lean sirloin (6 oz)	53	360
baked potato (1)	4	180
corn (1/4 cup)	1	34
bread (1 slice)	2.5	65
nonfat milk (1 cup)	8	85
	98.5	1,284

Allan Chait, chairman of the AHA Nutrition Committee, proclaimed Ornish's treatment totally impractical.[2895]

The P/S Ratio

Speaking before the 1977 Senate Select Committee on Nutrition and Human Needs, NHLBI director Robert Levy said,

> "Whereas the polyunsaturated/saturated fat diet ratio used to be .2 or .3, it is now higher, closer to 1.0."[288]

But four years later he said,

> "the polyunsaturated fat ratio used to be .1 to .2 but it is now closer to .4 to .5."[1846]

Clofibrate

Based on the results of the WHO Cooperative trial[3001] which found that cholesterol-lowering with the drug clofibrate yielded higher all-cause and CHD death rates than observed in control group, Stamler[3036] emphatically stated in 1983 that

> "There is thus no place for this drug in the primary prevention of atherosclerotic diseases in the general population or its sizable strata in the industrialized countries with hypercholesterolemia."

Prior to Stamler's statement, Kannel et al.[2935] recommended clofibrate and Lees and Wilson[3042] called it "outstanding." After Stamler's statement, Robert Levy3022 and Scott Grundy[3034] recommended clofibrate to physicians and Grundy indicated that it was "generally safe."

Dietary Fat and Cancer

Mary Enig and her co-workers analyzed food, CHD and cancer trends in 1978 and concluded that

> "We have examined the fat-cancer relationship...there is...an essentially strong negative or no correlation with animal fat to total cancer deaths, breast and colon cancer incidence."[221]

Cholesterol researcher Charles Glueck cited Enig et al. as

> "Underscoring epidemiological associations between saturated fat and carcinoma of the colon and breast,"[543]

implying that they observed a positive association, which they did not. Note also that Enig et al. used the term "animal fat," while Glueck transformed that term to "saturated fat."

Smoking, CHD and Lung Cancer

In 1988 Ockene[2804] made the following two inconsistent statements:

> "Estimates indicate that up to 30%, or 170,000, of all CHD deaths in the U.S. each year are attributable to cigarette smoking."

"Data limitations do not permit one to draw definitive conclusions about the affect of smoking cessation on the declining CHD mortality rate."

Breslow[2809] strangely equated both the CHD decline and the lung cancer increase with the Surgeon General's report on smoking in 1964 and the subsequent decline in smoking.

"The drop in CHD mortality beginning about the same time [as the smoking decline] is consistent with a role for cigarette smoking, as is the continuing climb in death rate from a lung cancer and other forms of chronic lung disease."

The decline in cigarette smoking occurred after the CHD mortality decline and lung cancer mortality is still on the rise 26 years after the smoking decline!

In Chapter 9 Stamler was cited as saying that the CHD mortality decline was paralleled by the smoking decline. He and his co-workers[2805] elsewhere said that

"There is a significant positive correlation between the slopes of per capita cigarette consumption for the years 1967-73 and the slopes of the CHD mortality rates for the 1969-75 period for men, for women and for both sexes combined."

In fact, however, there was a slight negative correlation according to their data (their Tables 20 and 22) which showed an increase in smoking from 1967 to 1973 (3,800 to 3,850 cigarettes per capita per year) and a decrease in CHD mortality from 1969 to 1975 (591 to 479 per 100,000).

The Costs of CHD

For decades alliance members have been claiming that atherosclerosis is preventable by lifestyle changes. One of the earliest claims was that of Keys, i.e., "It is abundantly clear that degenerative heart disease is not an inevitable consequence of aging, beginning in youth and progressing with the years, indifferent alike to medical efforts and improvement in living conditions."[279] In 1979 Wynder said that "Many of the cardiovascular diseases, and arteriosclerosis as well, are preventable."[2648] And very recently Myron Weisfeldt indicated that much heart disease is preventable."[2583]

Alliance members have also suggested or implied that the huge costs associated with atherosclerosis and cardiovascular diseases in general can be reduced or eliminated by changing lifestyles. In 1972 NHLI director Cooper[2082] indicated that the total costs of "circulatory" diseases was over $8 billion annually. In 1981 Levy[1846] reported that the total annual CHD cost was over $27 billion. The 1984 Consensus Conference presented a figure of $60 billion plus. And in 1989 Alexander Leaf[2913] cited the AHA as estimating the total annual cost of cardiovascular diseases to be $84 billion.

The argument by the alliance that "dramatic" changes in lifestyles since 1963 have resulted in the CHD mortality decline and that the huge costs of medical care can be substantially reduced by further lifestyle changes is nothing less than absurd and totally devoid of an understanding of what is actually happening. The age-adjusted cardiovascular and CHD mortality rates have decreased nearly 50% since 1963. More importantly, the total number of CHD deaths have decreased more than 20% since

1972.[a] Yet, the cost of cardiovascular disease has increased about 1,000% in that period. Natural inflation can only account for a small fraction of that increase. For example, the Consumer Price Index for all medical care rose from 34 in 1970 to only 139 in 1988.

The above trend data indicate that either the incidence and prevalence of CHD has actually been increasing, despite mortality trends, or greater numbers of people with CHD have entered the medical system for treatment or both. While it is certainly likely that more and more patients have entered the medical system since 1972, this trend cannot account for the huge increases in costs. Moreover, as noted elsewhere in this volume, there is evidence from the Framingham study that the incidence of both CHD and stroke have been increasing.

Given the hypothetical (but untrue) state-of-affairs that CHD morbidity is decreasing, it would also not materially affect the total costs. As emphasized by Leaf, "The goal of preventive care is to postpone the occurrence of chronic disease events."[1641,2913] Dawber[3001] indicated that "It simply is not likely that the diseases which affect the older members of our population can be prevented altogether. It is much more reasonable to hypothesize that the onset of these diseases can be delayed." Indeed, Grundy[262] admitted in 1986 that "CHD will remain the nation's leading cause of death for the next 25 years, because of the aging of our population, the number of new cases of CHD and corresponding mortality rates will actually increase." Because life expectancy beyond 65 is increasing, the hypothetical postponement of CHD events would merely postpone the costs, not reduce them. Once the initial postponement lag is traversed, the costs would begin increasing again.

Finally, if cardiovascular morbidity were decreasing, particularly since the downturn in CHD mortality, why have the number of cardiologists increased so tremendously? Figure 1-1 in Chapter 1 shows that while the cardiovascular death rate decreased about 40% from 1965 to 1985, the number of cardiologists increased 547% during that period,[2798] about 24 times greater than the U.S. population. The AMA's Council on Long Range Planning and Development projects the number of cardiologists to be 25,231 by the year 2010.[2798] Given current trends, the cardiovascular mortality rate should be about 35% of the 1965 level.

The evidence is rather overwhelming in indicating that the incidence of atherosclerosis has been increasing during the period in which cardiovascular disease mortality has declined and it is clearly reflected in the enormously increased direct and indirect costs and numbers of cardiologists. In fact, the costs are increasing at abnormal rates because of the increasing billions of dollars that are being spent on such wasteful endeavors as cholesterol tests, cholesterol-lowering drugs, special foods, etc. In point of fact, while the NCEP purports to decrease CHD costs, it is actually augmenting them by very substantial amounts.

The 1971 NHLI Task Force

The 1971 NHLI Task Force[705] clearly indicated that it was not known whether blood cholesterol-lowering would affect CHD development and that "more decisive evidence" was needed before "advocating" changes in the American diet.

> "...it is not known whether measures resulting in reduction of serum lipid and lipoprotein concentrations will also result in a lowering of the rate of

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[a] 1892-1896

occurrence of atherosclerotic clinical disease either in individuals with normal serum levels or in individuals with elevated levels."

"Although there is some evidence to support the popular belief that blood lipids are causally related to arteriosclerosis, and that a decrease in total and saturated fats in the diet may help to prevent the complications of arteriosclerosis such as heart attack and stroke, this evidence is scientifically not entirely convincing. Therefore, recommendations concerning diet are based on personal impressions and fragmentary evidence rather than on scientific proof." "On the basis of populations studies relating incidence of arteriosclerosis to levels of serum lipids it would seem desirable to undertake to reduce serum lipid levels in the population of the U.S. However, this is a formidable venture since it would require changing the diet of the entire population. In order to demonstrate whether intervention of such heroic proportions should be advocated more decisive evidence is needed that lowering of serum lipids at any given age by whatever means will indeed reduce morbidity and mortality from atherosclerosis."

But despite these statements the Task Force nevertheless approved the following statement to the public:

"Current data indicate that the average North American has higher than optimal blood cholesterol levels and ingests excessive calories, saturated fat and cholesterol. Pending confirmation by appropriate diet or drug trials, it therefore would appear prudent for the American people to follow a diet aimed at lowering serum lipid concentrations. For most individuals, this can be achieved by lowering intake of calories, cholesterol, and saturated fats. An attempt should be made to attain and maintain optimal weight through weight loss by balancing calorie intake and expenditures. In certain individuals with clearly elevated levels of serum cholesterol or trglycerides, close medical supervision with more vigorous attention to the diet and the use of drugs may be necessary."

HOW NOT TO INTERPRET DATA

Although innumerable studies have been critiqued in Volume 1 and the present volume, here we wish to specifically focus on how the alliance routinely misinterprets data. Sometimes the data are confounded but alliance members draw the conclusions that best fit their preconceived beliefs. Sometimes a result is statistically nonsignificant but nonsignificance is ignored and the result is treated as a "strong" finding. All too often, moreover, a study is so loosely controlled that the results are based more on assumptions than established facts. Finally, error-prone subjective measurement techniques (e.g., 24-hour diet recall surveys) are typically used to calculate nutrients consumed to two decimal places when the number immediately preceding the decimal is suspect.

Although a very large number of studies could be included in this discussion, the following were selected to represent the kinds of misinterpretations commonly committed. And because the misinterpretations are always systematically biased toward the risk factor-CHD hypothesis, it is clear that they are purposeful, rather than inadvertent.

The Wynder et al. Study

Ernst Wynder, president of the American Health Foundation, a principal agency of the alliance, conducted a cholesterol screening of 10,672 persons in 1986 with his colleagues.[2618] Cholesterol measurement was accomplished with a fingerstick (enzyme method) device which was known to be quite inaccurate (see William Kannel's

comments in Chapter 8). Among other things, Wynder et al. compared the blood cholesterol levels of those with and without prior medical history of cardiovascular disease (Table 10-2). the following is their interpretation of these data.

"Relative to participants with no medical history of other cardiovascular disease ["none' = 200], the average values for male diabetics were reduced by approximately 6 mg" ($P < .01$), whereas nondiabetic men with a history of either hypertension or myocardial infarction showed an average increase of 3 mg ($P < .05$). In women, no clear pattern is evident, although subjects with a prior infarction tended to show higher average levels than disease-free subjects. In general, therefore, these results indicate that cholesterol is reduced as a possible consequence of treatment for diabetes mellitus, but is increased in the presence of hypertension or, as is to be expected, prior myocardial infarction." In just three sentences Wynder et al. managed to distort and misinterpret their data beyond recognition.

First, the mean cholesterol level of diabetic men was 12 mg lower than that of men with no history of cardiovascular disease, not 6 mg. Further, such a finding should not have been taken seriously because (1) diabetic women tended to show the opposite trends and (2) diabetics tend to have higher blood cholesterol levels than nondiabetics in general. Second, emphasizing that nondiabetic men with a history of either hypertension or myocardial infarction showed an average increase of 3 mg over men with no cardiovascular disease history is nothing less than extraordinary. A difference of 3 mg can hardly be taken seriously. Moreover, given that it <u>were</u> important, how can Wynder et al. ignore the fact that subjects with <u>both</u> hypertension and myocardial infarction exhibited the same cholesterol level as men without cardiovascular disease? Does this mean that the more risk factors you have, the lower the cholesterol? That would seem to be the case with diabetics with myocardial infarction with and without hypertension but not diabetics with only hypertension.

The truth is that there were virtually no meaningful, consistent relationships between cholesterol levels and cardiovascular histories for either men or women and Wynder et al. were clearly attempting to create something from nothing.

<u>The Pekkanen et al. Study</u>

Pekkanen and his colleagues,2965 including Basil Rifkind, purported to analyze the importance of total cholesterol and lipoproteins as predictors of CHD and cardiovascular diseases (CVD) mortalities in men who had and did not have CVD symptoms at baseline.[a] Subjects were 2,541 men aged 40 to 69 years who were involved in the Lipid Research Clinics Prevalence study. The follow-up period was 10.1 years. The authors concluded that "The risk of death from both CHD and CVD increases with less favorable levels of lipids in both men with CVD at baseline and those without such disease." They also indicated that "The risk of mortality increases in a graded fashion according to lipid level."

The mean total cholesterol levels of the men with and without CVD at baseline were 220 mg and 210 mg, respectively. The mean LDL level was slightly higher among those with CVD at baseline (147 vs 141) but HDL levels were essentially the same (45.5 vs 46.3). Although Pekkanen had little to say about these baseline measurements, it is quite clear that the differences between those who had and did not have CVD symptoms were quite small. If one calculates the total to HDL cholesterol ratio from these values, the ratios are almost indistinguishable, i.e., 4.8 vs

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[a] Cardiovascular diseases were defined as all manifestations of CHD, including MI, abnormal ECG and angina pectoris.

Table 10-2

Age-adjusted mean cholesterol levels of those with and without medical history of cardiovascular disease (adapted from Harvis et al., 1989[2618])

Medical History	Mean Cholesterol (mg/100 ml) Men	Women
None	200	205
Diabetes mellitus	188	202
Diabetes/hypertension	201	205
Diabetes/MI	189	204
Diabetes/hyper/MI	186	226
Hypertension	203	208
Hypertension/MI	200	201
MI	203	217

MI = myocardial infarction

4.5. The authors' only relevant statement that "men with cardiovascular disease at baseline were older, had higher levels of total and LDL cholesterol..." was grossly misleading. In addition to the fact that cholesterol levels were nearly the same, HDL levels and total/HDL ratios were effectively the same. Moreover, the men with CVD at baseline were "older" by a mere 7 months.

Table 10-3 presents their data relating total cholesterol, LDL and HDL with CHD and CVD death rates. At the outset, these data are somewhat suspect simply because they are based on relatively few deaths. For example, there were only 42 and 25 CHD deaths occurring among the men with and without CVD at baseline, respectively. Similarly, there were only 61 and 51 CVD deaths occurring in those groups. Thus, the reliability of the death rates shown in the table is in doubt.

Examination of Table 10-3 reveals that most of the effects of cholesterol level occurred in the men who exhibited CVD symptoms at baseline. The CHD and CVD death rates greatly increased with increasing cholesterol and LDL levels among those who had CVD symptoms at baseline but such was not the case among the men who were free of CVD at baseline. In the latter group, the CHD death rate declined slightly as cholesterol and LDL levels increased through about 60% of the range of population cholesterol levels (< 200 through 200-239). Moreover, the CVD death rate increased slightly as total cholesterol increased from < 200 to 200-239 and <u>decreased</u> slightly as LDL level increased from < 130 to 130-159. These trends hardly justify the statement that "The risk of death from both CHD and CVD increases with less favorable levels of lipids."

The CHD and CVD death rates <u>did</u> increase with total and LDL cholesterol levels above 240 and 160, respectively. However, we again have another example of misleading scaling, i.e., it is simply improper to use a 3-interval cholesterol scale with one interval (e.g., $\geq$ 240) representing about 40% of the entire blood cholesterol range. It is very likely that the death rates did not increase much, if at all, at cholesterol levels of 250, 260, 270 or even 280 mg. One must always remember that when the alliance lumps all cholesterol levels above some modest level such as 240 mg together, there is an apparent need to demonstrate that the CHD death rate increases substantially at that modest level. In actuality, however, use of such a broad interval makes it impossible to determine where the increase actually begins. There was certainly no upward trend below 240 mg.

Equally important, the absolute differences in death rates between the 3 levels of cholesterol LDL and HDL are quite small. For example, consider LDL which the alliance claims is the atherogenic lipoprotein. The annual CHD death rate at or above 160 mg is 0.117% greater than that at or below 130 mg. What this literally means is that in order for one to reduce his chances of dying of CHD by 0.117%, he must lower his LDL from the highest level in the population to the lowest level. Only the alliance would consider a trivial increase in life expectancy for a huge decrease in LDL important.

Pekkanen et al. seemed to have problems with even simple interpretations of their data. For example, they said, "In our study, the estimated relative risks for the various plasma cholesterol and lipoprotein lipid levels were not significantly different for men with and men without preexisting cardiovascular disease, and there were no indications that the role of the lipid levels was more important in the men with preexisting cardiovascular disease." But such a statement is absurd because their data clearly show that the opposite state-of-affairs was true. As can be clearly seen in Table 10-3, the relative risk increases across cholesterol or lipoprotein levels were far greater among those with preexisting CVD than those free of CVD at baseline. For example, the top row in the table shows relative risk increases of (2.74 ÷ 0.65 =) 4.2 and (17.08 ÷ 1.64 =) 10.4 for the two groups. The remaining pairs of risk ratios are 3.0 vs 5.6, 2.5 vs 11.7, 2.4 vs 6.3, 2 vs 5.6 and 2.9 vs 5.1. Furthermore, only a blind

Table 10-3

CHD and CVD death rates as functions of lipid levels and condition at baseline (adapted from Pekkanen et al., 1990[2965])

Deaths /1000 per year (number)	No CVD at baseline			CVD at baseline		
CHD	0.65	0.55	2.74	1.64	9.09	17.08
CVD	1.66	1.98	4.98	3.90	11.30	21.83
Total Cholesterol	< 200	200-239	≥ 240	< 200	200-239	≥ 240
CHD	0.77	0.56	1.94	1.64	4.46	19.15
CVD	1.83	1.67	4.33	3.62	7.08	22.78
LDL	< 130	130-159	≥ 160	< 130	130-159	≥ 160
CHD	1.63	0.91	0.78	18.32	11.75	3.29
CVD	4.77	3.07	1.65	22.82	13.67	4.48
HDL	< 35	35-44	≥ 45	< 35	35-44	≥ 45

person could say that Table 10-3 provides "no indications that the role of the lipid levels was more important in the men with preexisting cardiovascular disease." The table, in fact, is loaded with such indications.

By denying that the effects of lipid levels were different for the two groups, Pekkanen et al. avoided the embarrassment of trying to reconcile that difference with the lipid hypothesis. The alliance maintains that cholesterol level is a "powerful" predictor of CHD among those free of CHD at baseline. Table 10-3 shows that it is a weak predictor at best and apparently only at very high cholesterol levels. The fact that the effects of lipid levels are observable almost entirely among those with preexisting CVD and are almost entirely unobservable among those free of CVD at baseline provides very little support for the lipid hypothesis and suggest, instead, that cholesterol level is more a response to CHD than a cause.

In sum, Pekkanen, Rifkind and their associates communicated two entirely different sets of information. One set was comprised of their figures and tables and the second set was their description/interpretation of these figures and tables. The latter bore little resemblance to the former.

The Ginsberg et al. Study

Henry Ginsberg and his co-workers[2636] published an experiment in the New England Journal of Medicine in 1990 which purported to compare the effects of the AHA's Step 1 diet and a monounsaturated fat enriched Step 1 diet on blood cholesterol as contrasted with the "average American diet."[a] They concluded that the Step 1 diet significantly reduced blood cholesterol, compared to the average diet, and that the monounsaturated fat-enriched diet "does not alter the beneficial effects of the Step 1 diet on plasma lipid concentrations." Despite the fact that this study had 9 authors, it was designed improperly and the data analyses/interpretations were improper, inadequate and highly misleading.

Thirty-six medical students consumed the "average" American diet for 10 weeks. Subsequently, one-third of the subjects switched to the Step 1 diet and another third switched to the monounsaturated fat-enriched Step 1 diet. The remaining third (controls) stayed on the "average" diet. Table 10-4 shows the relevant contents of the three diets.

At the outset, the study was purposely designed to exaggerate the differences between the average diet and the Step 1 diet because the Ginsberg et al. "average" diet was not, in fact, the average American diet. Most surveys, including the government's NHANES[2557] surveys show that the fatty acid compositions of the average American diet is quite different from that used by Ginsberg et al. In effect, Ginsberg exaggerated the saturated fat component by about 2.3% of total calories (a relative increase of 17%), increased the polyunsaturated fat by 2.7% and substantially reduced the monounsaturated fat. It may be noted that Table 10-4 contains the calculated intakes. In actuality, Ginsberg et al. intended the saturated fat intake to be an even greater exaggeration, namely 18% of calories.

Additionally, the fatty acid composition of the saturated fats in Ginsberg et al.'s "average" diet were different from the average diet. For example, Hegsted et al.[408] determined that the typical diet contains 0.25%, 0.96% and 5.65% of total calories as lauric, myristic and palmitic acids, respectively. Ginsberg et al.'s "average" diet contained 3.4%, 2.2% and 6%. Thus, their diet contained significantly more lauric and

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[a] Mary Enig[2928] contributed to the following critique.

Table 10-4

Composition of the average, AHA Step 1 and mono-enriched Step 1 diets (adapted from Ginsberg et al., 1990[2636])

% of Total Calories	Average diet	AHA Step 1	Mono-enriched AHA Step 1
Fat	37.2 (37)[a]	30.8	37.6
Saturated	15.9 (13.6)	9.4	9.2
Monounsaturated	11.7 (16.4)	11.0	17.9
Polyunsaturated	9.7 (< 7)	10.4	10.5
Cholesterol (mg)	389 (435)	280	215

[a] Values in parentheses are average values obtained in the NHANES surveys.[2557]

myristic acids than is presumably contained in the actual diet. Hegsted et al. concluded that myristic acid had the largest affect on blood cholesterol. Thus, another bias is evident in the Ginsberg et al. data.

Before initiating the experimental period, the mean blood cholesterol levels of the controls, Step 1 subjects and Step 1 plus monounsaturated fat were 177, 182 and 191 mg, respectively. Since it is generally known that the lower one's cholesterol level, the less it will be affected by cholesterol-lowering agents, another bias was built into the Ginsberg et al. study, i.e., it would be expected that the Step 1 diets would reduce blood cholesterol levels of subjects with initial cholesterol levels of 182 mg and 191 mg to a somewhat greater extent than of subjects with initial cholesterol levels of 177 mg.

We now have two built-in biases which can, and undoubtedly did, artificially create a larger difference between the Step 1 diets and the actual average American diet than would have occurred had the biases been eliminated.

The Step 1 and Step 1 plus monounsaturated fat diet decreased blood cholesterol levels 12.4 mg and 15.9 mg, respectively, relative to the control group. These values represent percentage reductions of 6.9 and 9.3, respectively. Thus, even with the built-in biases these reductions were not impressive. There is no question that had the biases been eliminated these reductions would have been lower, perhaps only 50% of those reported.

Figure 10-1 shows the blood cholesterol levels of the three groups on weeks 13, 15, 17 and 21, from which the mean levels were computed. Ginsberg et al. stated that "There was an increase in the plasma concentration of total cholesterol in all three groups at week 17 of the total study period. This change was qualitatively similar in all three groups and occurred at the time of midterm examinations." But note that they did not say "quantitatively" similar, a far more important consideration. The fact is that whatever caused the increase in blood cholesterol level affected the Step 1 diet more than it did the Step 1 plus monounsaturated diet and it affected the "average" diet more than it did the Step 1 diet and yet it had nothing to do with the diets. This confounding of results added yet another bias. Had the 17th week measurement been eliminated from the analysis, the differences between the groups would have diminished further.

Equally important, it is clear from the figure that differences between the groups were decreasing as the diet period progressed. By the 21st week the Step 1 diets yielded cholesterol levels only 5% lower than the control diet. When all the biases are accounted for, this difference would approach zero.

The cholesterol lipoproteins LDL and HDL did not decrease significantly in the Step 1 diet but Ginsberg et al.'s interpretation would suggest that the former reduction was important, while the latter was not. They said, "There was a nonsignificant trend toward a reduction in LDL cholesterol levels in the Step 1 diet" and "The plasma levels of HDL cholesterol did not change significantly in either the Step 1 or the mono diet group." The fact is that HDL did decrease, somewhat consistent with the results of numerous studies which replaced fat with carbohydrates. Thus, the already small difference between the control and Step 1 diets was due, in part, to a loss of so-called "good" cholesterol.

In their last paragraph Ginsberg et al. said, "the consumption of a diet consistent with Step 1 guidelines recommended by both the American Heart Association and the Adult Treatment Panel of the National Cholesterol Education Program can significantly reduce the plasma total cholesterol level in healthy young men." But such a conclusion most certainly could not be logically drawn from a study that was so

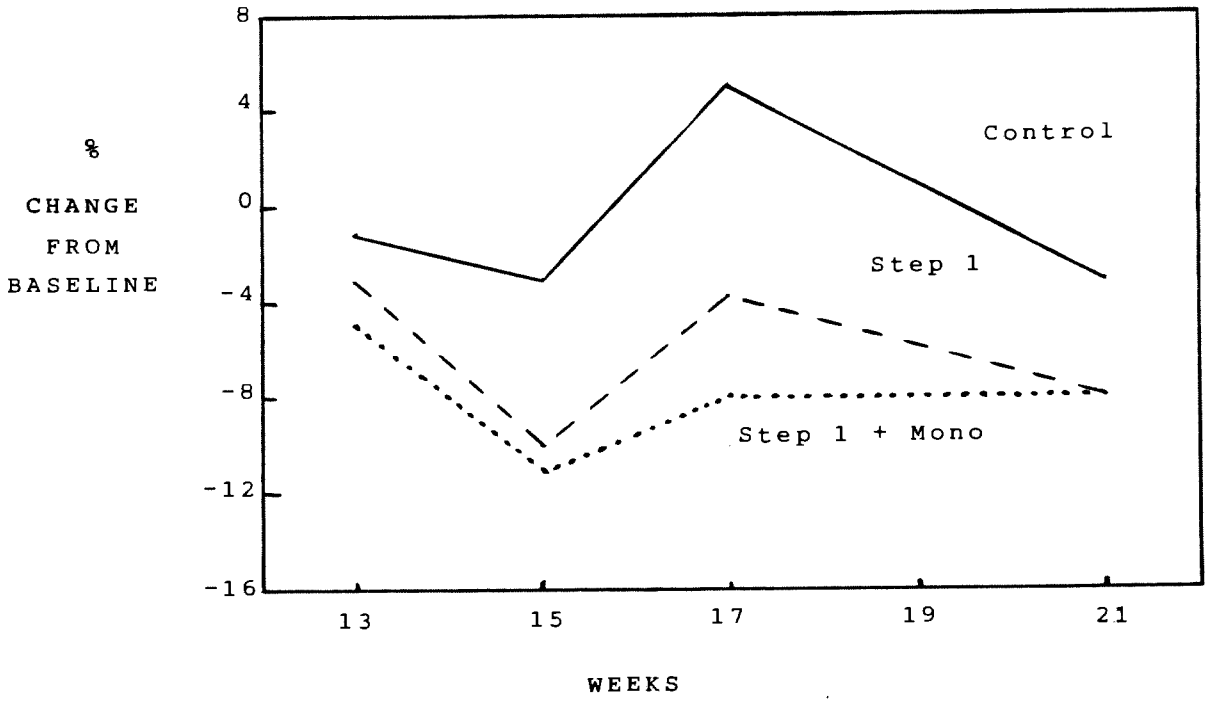

Figure 10-1. Cholesterol levels over time on the AHA's Step 1 and Step 1 plus monounsaturated fat diets (adapted from Ginsberg et al., 1990[2636])

scientifically flawed it should never have been accepted for publication in any journal, let alone the New England Journal of Medicine.

In keeping with the media's habit of passing erroneous medical information to the public as well as distorting it in the process, the Wall Street Journal's Waldholz[2655], said that "researchers compared blood cholesterol levels in young men who ate a typical American diet to those who ate a low-fat diet" and found the latter to reduce cholesterol 8%. Of course, Ginsberg et al. did not show that a low-fat diet per se was the reason for the cholesterol reduction. (A previous study by Wolf and Grundy[1822] also could not demonstrate a significant difference between a 40% and a30% fat diet but nevertheless concluded, "This study does not speak against a general recommendation for a decrease in fat intake in the population, but it does indicate the need for more investigation to provide a stronger foundation for such a recommendation." Indeed, there is virtually no scientific foundation for such a recommendation.)

In a 1987 letter to Edward Pinckney the editor of the New England Journal of Medicine, Arnold Relman, said, "all papers under consideration by NEJM are carefully reviewed for experimental design and statistical validity. If they are deficient we will not consider publication unless the problem can be--and is--remedied."[2940] The Ginsberg et al. study is but one of many published in NEJM which involved incredibly poor designs and statistical analyses.

The Blair et al. Study

Typical of the almost weekly epidemiological "discoveries" that are given wide news coverage by the media was the November 3, 1989 article by Steven Blair and his colleagues in the Journal of the American Medical Association which related "physical fitness" with all-cause mortality, cardiovascular disease, cancer, etc.[2440] While the authors claimed "a strong, graded and consistent inverse relationship between physical fitness and mortality in men and women," they also said that "The findings seem not to be due to confounding by age or other risk factors." The word "seem" should be kept in mind as this study is described below.

Some 10,224 men and 3,120 women, deemed healthy at baseline, were divided into five groups representing quintiles of physicial fitness, as determined by the length of time achieved on a treadmill test. Other variables measured were smoking status, body mass, blood pressure, blood cholesterol, blood glucose and family history of death from CHD. The subjects were then followed for an average of 8.4 years.

Table 10-5 (a) shows the overall findings for all-cause deaths among males (similar results were obtained for females). The authors claimed "a strong graded and consistent inverse relationship between physical fitness and mortality." We can, however, dispense with most of this relationship rather quickly on practical grounds. For example, over a 20-year period only 1.4% more men would be dead in Quintile 2 than Quintile 5. Most men probably would not find that benefit worth the cost of maintaining that fitness level over 20 years. Blair et al. also failed to provide the treadmill time ranges for the quintiles, so that it is virtually impossible to determine the magnitude and practical importance of the difference between Quintiles 1 and 2. Quintile "numbers" are meaningless. Fitness was the primary independent variable in the study and it was inexcusable, therefore, to omit recorded fitness values. As emphasized elsewhere in Volume 1 and the present document, quintiles are also unequal intervals and should be not be used to relate a dependent variable with an independent variable.

The mortality rate difference between Quintile 1 and the remaining quintiles is so great, it seems obvious that something other than fitness contributed to that

difference. Blair et al. indicated that the overall "trends remained after statistical adjustment for aging, smoking habit, cholesterol level, systolic blood pressure, fasting, blood glucose level, parental history of CHD and follow-up period." But while the authors presented data showing such adjustments one variable at a time, none were given that accounted for two or more variables simultaneously. This was particularly important for two variables because it is well-known that persons who exercise regularly tend to be nonsmokers and lean. It is probably also true that the least healthy in general exercise the least. Thus, one would expect a higher mortality rate in Quintile 1 because of higher prevalence of smokers, least lean individuals and least healthy individuals and not simply because of exercise per se. Although Blair et al. had no measure of "healthiness," we can examine the effects of smoking and obesity when each is averaged over the other.

Table 10-5 (b) and (c) show the death rates as functions of smoking habit and body masss, respectively. With regard to the latter, the higher the body mass index, the more lean the individual. For these analyses the authors combined Quintiles 2 and 3 and Quintiles 4 and 5. Although they offered no explanation for this procedure, it is apparent from the inconsistencies still observable in the table that the authors wanted to eliminate the more gross inconsistencies that distorted the "strong graded" trends. There were sufficient data for analysis by five quintiles and, moreover, what is the point of dividing the independent variable into quintiles and then collapsing them? In any event, it is quite clear that the very high mortality rate in Quintile 1 in Table 10-5 (b) was due, in large part, to the high prevalence of smokers. The huge dropoff of mortality in Quintile 1 from smokers to ex-smokers to never smokers clearly demonstrates the contribution of smoking. A less severe dropoff among smokers from Quintle 1 to the remaining quintiles could be due to variations in fitness but it seems more likely to be due to variations in leaness, i.e., since it is known that exercisers tend to be lean, it is likely that the higher the physical fitness measured among smokers, the greater the leaness.

If we just examine the trend for those who never smoked, the mortality reduction expected from the least fit to any other fitness level would be only 2% over a 20-year period. Not only is this again a very small benefit, it may be due, in part, to the possibility that Quintile 1 had a greater percentage of least lean individuals. Incredibly, Blair et al. provided no data to resolve these important issues.

The same confounding problem exists for Table 10-5 (c). Because the less lean a person is, the less likely he is to be fit, Quintile 1 is likely to contain a disproportionate percentage of least lean individuals, thus contributing to the higher mortality rates observed. We can again see that there was a huge dropoff in mortality in Quintile 1 from the least lean to the less lean categories, clearly demonstrating the importance of leaness. A less severe dropoff among the least lean from Quintile 1 to the remaining quintiles could be due to variations in fitness but it is equally or more likely to be due to a progressively lower prevalence of smokers and/or heavier smokers, i.e., the higher the fitness level among the least lean subjects, the more likely the lower the prevalence of smoking. It is, of course, impossible for the reader to know where the smokers and ex-smokers are in Table 10-5 (c), just as it is impossible to know where the least lean subjects are in Table 10-5 (b). The two variables are confounded with physical fitness.

A peculiarity of Table 2 is worth noting. Tables 10-5 (b) and (c) are simply the rearrangement of the same set of data involving 240 deaths. Yet, the lower subtable shows 7 higyher (and in some cases, much higher) death rates and only two slightly lower death rates than those in the upper table. It is difficult to understand how this can happen.

In the same issue of the Journal was an editorial by Koplan et al.[3152] They said, "An increasing body of evidence suggests that physical activity and physical fitness

Table 10-5

A summary of specific male findings from the Blair et al. physical fitness study (adapted from Blair et al., 1989[2440])[a]

	Fitness quintile[b]	Person years	Number of years	Age-adjusted death rates per 10,000 person-years[c]	
	1	14,515	75	64	
	2	16,898	40	25.5	Rate
(a)	3	17,287	47	27.1	Difference
	4	18,792	43	21.7	equals
	5	17,557	35	18.6	0.069%

[a] Findings for females were similar but much less pronounced.
[b] The higher the quintile, the higher the fitness.
[c] Because these rates are age-adjusted, they are not directly derivable from the data of Columns 2 and 3.

	Smoking habit	Fitness Quintile 1	2+3	4+5
	Current smokers	80	47	41
(b)	Ex-smoker	44	13	19
	Never smoked	26	16	16

	Body mass	Age-adjusted death rates per 10,000 person-years		
	< 20	155	55	38
(c)	20-25	46	26	15
	> 25	48	22	20

contribute to good health. Blair et al. provide evidence in this issue of JAMA that physical fitness is associated with lower rates of all causes of mortality as well as cardiovascular disease and cancer mortality." (The "increasing body of evidence" had previously been described by an NHLBI Working Group[3067] as being "uncertain.") Thus, not only did "peer review" fail to detect the many flaws in the Blair et al. study, JAMA also seemed intent on praising the flawed study without careful examination. In effect, while the news media informed all Americans that even a little exercise can greatly extend life, the Blair et al. study's results were badly confounded and incomplete and incapable of yielding that conclusion. It is worthy to note that Balir et al. included Kenneth Cooper who coined the term "aerobics," earns income from his Aerobics Center and "could benefit from a report that encourages the 90% of Americans who don't exercise to begin a moderate fitness program."[2454]

The Vartianen et al. Study

Vartianen et al.[3237] compared groups of men from China, the U.S. and East Finland.[a] Table 10-6 presents the primary data of interest. They concluded that "The differences we observed in diet, cholesterol level, and coronary heart disease mortality rates fit together well." Since blood pressures also "fit" in that model, why did they omit that fact? More importantly, had a Japanese cohort replaced the Chinese cohort, the same conclusion would have been drawn. However, since it was shown in Chapter 4 that the Japanese diet has become progressively "richer" and the Japanese blood cholesterol has become progressively higher over the last 30 years, while their CHD mortality rates have progressively decreased during that period, the diet and cholesterol elements of the relationship cannot be viewed as causal. Omitting trends, therefore, leads to highly misleading conclusions drawn from static "slices" in time.

Noting that the Chinese cohort had by far the highest stroke mortality rate, the authors stated that "Recent data from the Multiple Risk Factor Intervention Trial indicate an inverse association, for middle-age men, between intracranial hemorrhage and the combination of high blood pressure and low serum cholesterol level. This association may be related to high level of polyunsaturated fats in the diet, because there is evidence to suggest that these fatty acids can reduce platelet aggregation. We can only speculate about a possible association between...[the Chinese cohort's] high mortality rates for stroke and its comparatively high proportion of men who have both low serum cholesterol levels [under 160 mg] and high blood pressure..." The authors cited the Iso et al. study of the follow-up of the men screened for the MRFIT, not the trial itself. Moreover, in a response to a critique[2457] Iso et al.[2458] admitted in a subsequent letter-to-the-editor that the inverse association between intracranial hemorrhage and low serum cholesterol they had reported was, in fact, slight and nonsignificant. In addition, although the authors implied above that the Chinese cohort had high blood pressure, it actually had the lowest of the three groups. It would seem that the authors paid little attention to their own data, as well as to Iso et al.'s.

The authors stated that the "high mortality rates for stroke [in the Chinese cohort] may also arise from its high rates for smoking prevalence, since smoking is known to contribute to stroke mortality." However, the relationship between smoking and lung cancer is considered even stronger and yet the authors ignored the fact that the much higher smoking prevalence was associated with a much lower lung cancer mortality rate.

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[a] Data for women were also presented but the male data suffice to illustrate the point to be made.

Table 10-6

A comparison of death rates due to specific causes and risk factors between male cohorts in China, the U.S. and East Finland (adapted from Vartianen et al.,1991[3237])

Condition	China	U.S	E. Finland
CHD mortality	10	420	802
Stroke mortality	247	57	113
Lung cancer	77	141	158
Cholesterol level	158	216	241
Blood pressure - Dia.	80	84	86
Blood pressure - Sys.	124	129	145
% Smokers	66	42	36
Saturated fat (% energ)	7	13	20
Salt intake (grams)	18	--	14

Vartianen et al. did note that the Chinese cohort had a high intake of salt and yet the lowest blood pressures but this finding was not emphasized and contrasted to the statements made by other alliance members such as Stamler (see Chapter 4).

In summary, the data of Vartianen et al. run contrary to the position held by the alliance with regard to the causes of stroke and lung cancer and, without trend data, the association reported between CHD and diet remains dubious. Nevertheless, the authors viewed their data as strongly supportive of the diet-CHD relationship.

The PDAY Research Group Study

The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group,[3151] headed by Robert Wissler, evaluated the right coronary arteries of 390 males aged 15-34 years who had died of violent causes.[a] Correlations were computed for the associations between atherosclerotic measures (percentage of intimal surface area involved with lesions and raised lesions) and the variables of age, race, cholesterol level, and smoking. Table 10-7 "shows standardized multiple regression coefficients for age, race, VLDL + LDL and HDL concentrations, and smoking as predictors of percentage of intimal involvement with lesions in... Multiple correlations coefficient values incorporating all four variables as predictors of extent of lesions are small but statistically significant." Since five variables are clearly evident in the table, it is apparent that Wissler et al. combined VLDL + LDL with HDL as a single variable.

As emphasized in Volume 1, many factors affect blood cholesterol levels substantially, including fear, stress, loud noises, etc. The subjects under investigation were victims of violent deaths and since blood samples were taken postmortem, there is every likelihood that the blood cholesterol values obtained were more associated with the degree to which subjects perceived their impending deaths than anything else. Although Wissler et al. cited other studies as showing that "the cholesterol concentrations of postmortem blood of humans dying of natural causes...corresponds to premortem values up to 90 hours after death," the word "corresponds" suggests some level of imperfection and "dying of natural causes" is not the same as dying of violent causes. Mathur et al.[2088] reported postmortem cholesterol samples to be different beyond 16 hours after death. This issue was brushed aside much too hastily.

Another interesting observation one can make before examining the results of this study is that total cholesterol levels of the subjects, as well as VLDL + LDL and HDL levels, were presented in a separate table by the authors but total cholesterol was conspicuously absent as a variable in the multiple regression analysis. In view of the fact that total cholesterol is by far the predominant lipid measure used by the alliance in relating lipids to atherosclerosis, its absence suggests that it did not relate significantly to the extent of atherosclerosis.

Wissler et al. concluded that "The association of serum lipoprotein levels between 15 and 34 years of age with intimal surface involvement by atherosclerotic lesions of...coronary arteries strongly supports the view that control of hyperlipidemia will retard the progression of atherosclerosis in the young. The findings also provide strong evidence for the effects of smoking on atherosclerosis in the young and emphasize the importance of control of smoking in the long-range prevention of adult atherosclerotic disease."

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[a] The thoracic and abdominal aorta were also examined but need not be discussed here.

Table 10-7

Multiple regression coefficients relating independent variables with measures of atherosclerosis (adapted from Wissler et al.,1990[3151])

Variable	Percentage Surface area	Raised
Age	.321[a]	.261[a]
Race	0.97	-.053
VLDL + LDL	.243[a]	.162
HDL	-.057	.036
Smoking	.040	.056
R^2	.20	.13

[a] $p < .05$

Note, first of all, that the squared multiple correlations, encompassing all variables, were quite small for both atherosclerotic measures. At most, the combined variables explained only 13 to 20% of the variance associated with the atherosclerosis distribution and it can be seen that by far the largest contributor to these correlations was the age variable. Age should never have been included in the analysis because it is not a manipulable "risk factor" and serves only to greatly inflate the multiple correlation. Had age been eliminated, both squared correlations would probably have been under .10. Although contributing little, race also should not have been included in the analysis for the same reason.

The coefficients for HDL were extremely small and statistically nonsignificant. Moreover, the sign was positive for the raised lesion dependent variable, nullifying the coefficient for surface area. The coefficients for VLDL + LDL were also very small, although statistically significant.[a] Since the squared multiple correlations are small to begin with, the elimination of all variables except the lipid variables would result in a totally trivial squared multiple correlation. Wissler et al. completely distorted reality by claiming that these lipid-atherosclerosis relations "strongly supports the view that control of hyperlipidemia will retard the progression of atherosclerosis in the young."

Wissler et al. indicated that "The findings also provide strong evidence for the effects of smoking on atherosclerosis in the young..." As can be clearly seen in the table, the coefficients for smoking were again extremely small and statistically nonsignificant. In fact, they, like those for race and HDL, were so close to zero, it is absurd that they should be considered to be weakly supportive of anything, let alone strongly supportive.

The Wissler et al. study is a prime example of how the alliance routinely defines weak data as strong data. Statistical significance is ignored and any relationship, no matter how weak, is considered "strongly" supportive of the risk factor-CHD relationship.

The Small et al. Study

One of the most inane articles published in a scientific journal was that of Small et al.[3227] In one respect, it represents the perfect example of "experts" demonstrating little expertise. In another respect, it is a perfect example of the ineffectiveness of peer reviewers. And in still another respect, it is a perfect example of "doing things the hard way."

Small and his colleagues indicated that "fat in meat is present primarily in fat cells interspersed between muscle cells of the meat. There is almost no cholesterol ester in meat. Most of the free cholesterol is in the muscle-cell membranes within the meat and very little is in the fat itself. For this reason, it is difficult to extract the cholesterol from meat simply by cooking it and draining off the excess fat, or by subjecting meat by meticulous trimming. Although these two procedures are effective in diminishing the total amount of fat in meats, the fat that remains in the meat is largely saturated and the cholesterol is retained.

Small et al.'s process of removing fat and cholesterol from ground beef was referred to as "extraction." The method involves the stir-frying of the meat in vegetable oil (0.5 to 1.0 quarts per 2 pounds of beef) for about 10 to 15 minutes. This process, in addition to extracting out the solid fat of meat through its

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[a] The reader should be reminded that the coefficients in the table (excluding R^2) are not correlations but rather weightings representing the importance of each variable (see Chapter 5).

liquification, is said to replace some of the saturated fat in the meat with polyunsaturated fat. After cooking, the meat and oil are poured through a strainer to eliminate most of the oil and water. Then, one to two cups of boiling water are poured over the meat to eliminate more fat. Small et al. recommended the remaining meat for all recipes calling for crumbled ground beef.[a]

Pertinent data from the Small et al. study are presented in Table 10-8. Given lean ground beef having a fat content of 20.7% by weight, regular and extraction stir-frying resulted in the removal of 59% and 67.7%, respectively, of the fat, as shown in the upper part of the table. For a (before cooking) 6 oz serving the extraction process eliminated only 3 g more fat than the regular stir-fry method.

The bottom part of Table 10-8 presents the composition of the fats remaining after cooking by the two methods. Excluding stearic acid, which has no affect on blood cholesterol, the regular and extraction stir-frying resulted in 4.51 g and 2.17 g of saturated fat, respectively. Thus, the extraction process removed only 2.34 g more than did regular stir-frying. This difference amounts to 0.8% of a 2,600 calorie diet. Since the alliance "allows" 10% of total calories as saturated fats, 0.8% cannot possibly have much influence on blood cholesterol level one way or the other.

It is true that the extraction process resulted in a disproportionate increase in polyunsaturated fat. But this is hardly an improvement in view of the fact that polyunsaturates reduce HDL levels. Because the alliance has recommended the consumption of many other foods that are low in saturates and high in polyunsaturates, using the extraction process regularly would serve to push the total polyunsaturates beyond 10% of total calories, no longer recommended by the alliance. Equally important, the one fatty acid universally accepted by alliance members, monounsaturates, can be seen to be much higher in the meat cooked by the regular stir-fry method. In short, the extraction process may lower blood cholesterol level a few milligrams but it will also disproportionally lower HDL and add to the growing excess of polyunsaturates in the diet.

Small et al. also indicated that regular stir-frying resulted in the removal of 18% of the cholesterol, while the extraction method eliminated 39%. Since six ounces of beef containing 20.7% fat has approximately 148 mg cholesterol, the extraction process removed 31 mg more cholesterol than did the regular stir-fry method. In Volume 1 of this review a rise of 1.9 mg of blood cholesterol was calculated across experiments for an ingestion of 100 mg cholesterol. The extraction process, therefore, manages to reduce blood cholesterol a little more than one-half milligram, again hardly a spectacular effect for all the trouble.

Accompanying the Small et al. article in the New England Journal of Medicine was an editorial by Willett and Sacks[3229] referring to the extraction process as "ingenious" but impractical. They said, "...for now let's leave the meat intact. The financial and ecological costs of the ingenious process they propose need to be considered before it can be advocated on a wide scale." New York Times reporter Elisabeth Rosenthal, called the process a "relatively simple new method."[3149] And Gail Levey of the American Dietetic Association stated that "It is an elaborate procedure, but if somebody uses a lot of chopped meat, I think it's probably worth it."[3230]

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[a] The authors did recommend freezing all liquids in order to separate the beef broth and fat and subsequently use the broth as a seasoning. However, this is irrelevant to the issue at hand.

Table 10-8

Principal results from the Small et al. study
(adapted from Small et al.,1991[3227])

Beef type	% fat	% fat removed by Stir-fry	% fat removed by Extraction
Lean	20.7	59	67.7

Fat type	Grams fat left/6 oz serving Stir-fry	Grams fat left/6 oz serving Extraction
Saturated[a]	4.51	2.17
Monounsaturated	7.85	4.04
Polyunsaturated 0.40	4.47	

[a] Excluding stearic acid.

When one examines the blood cholesterol-CHD relationship from the Framingham study or the MRFIT screened cohort follow-up, the most that can be expected from the extraction process would be an extension of life by a few hours. But that is not what makes the Small et al. study uniquely inane. If one wishes to consume only very low fat ground beef, he/she has only to purchase it at the market. Apparently unknown to Small et al., Willett and Sacks, and others is the fact that ground beef is nearly fatless when it is first ground in the market. Fat is subsequently added by butchers to conform to the legal requirements for the various types of ground beef. For example, "regular" ground beef contains no more than 30% fat and "lean" and "extra lean" have progressively less fat added. One can select whole lean beef such as bottom round steak and have the butcher trim the outer layer of fat and then grind the lean at no cost. This ground beef has less fat after cooking than does Small et al.'s lean meat after the extraction process.[3228] Moreover, the cost is generally less and often much less, not only because of the savings in vegetable oils, but also because bottom round and whole round steak are frequently on sale at a price per pound substantially lower than the leaner ground beef varieties.

If physician researchers and dieticians must give advice on the preparation of meats, they should at least have rudimentary knowledge about meats. Small et al.'s "ingenious" process is analogous to concluding that the most speedy way to transport a person from Los Angeles to New York City is to fly a route that passes over Lima, Peru.

SOME LIPID HYPOTHESIS EVANGELISTS

The lipid hypothesis was initially promoted vigorously by the AHA and subsequently by Framingham investigators and then NHLBI. There are many alliance members who had adhered to the hypothesis with evangelistic fervor and there are many more who have been faithful followers, regardless of the massive accumulated negative evidence. This section is concerned with most of the key alliance members who have controlled the relevant research funds and/or were most responsible for literally brainwashing the medical community, the media and the public at large. Although they have been cited numerous times throughout Volume 1 and the present volume, here we wish to consider them independently and specifically focus on their capacities for scientific reasoning or, perhaps more appropriately, incapacities for scientific reasoning. Not all of the major promoters are included in this section, e.g., Basil Rifkind, simply because this volume would become altogether unmanageable. We therefore apologize to Rifkind and others who might feel slighted by this omission. (The reader may recall that Ancel Keys was discussed in Chapter 1 in keeping with his position as "leader" of the diet-CHD hypothesis.

The nonmedical researcher Senator McGovern heads the list of promoters because he officially brought the U.S. government aboard the AHA bandwagon during the Senate hearings in the 1970s. These hearings comprised typical government proceedings in which conclusions and recommendations appeared to precede testimony.

Senator George McGovern

As described in Chapter 2, Senator George McGovern chaired a Senate Select Committee which held hearings in 1976 and 1977 on Nutrition and Human Needs. These hearings effectively fused NHLBI and AHA and made the diet-CHD issue a government-sponsored national issue. Before the hearings were completed, McGovern published a document called "Dietary Goals for the U.S." During the 1977 hearings the Committee took testimony from many individuals, among whom were Norton Spritz and Robert Olson. The dialog between McGovern, Spritz and Olson is perhaps representative of the mentality of the hearings in general and of their lack of scientific objectivity.[2729] It will be recalled that McGovern was apparently convinced

of a diet-CHD relationship before the hearings began and conducted the hearings correspondingly. His goal was to do something now and not wait for conclusive proof of the diet-CHD hypothesis.

The interaction between McGovern, Spritz and Olson can be more fully appreciated if some additional background information is known. In 1959 Seymour Dayton (with Morton Pearce) conducted a clinical trial in which a special low-fat, low-saturated fat and low-cholesterol diet was given to a group of middle-aged men for 8 years. The trial was considered well-designed and executed but nevertheless failed to provide evidence that the diet reduced heart disease or extended life expectancy. In their final report they said, "we consider our own trial, with or without the support of other published data, to have fallen short of providing a definitive and final answer concerning dietary prevention of heart disease."[454] In another journal article in the same year they said, "It is our opinion that the encouraging results of our own trial, even when buttressed by concordant observations in two other primary prevention studies, are not sufficient grounds for aggressive efforts to change the United States diet."[2541]

In some post hoc analyses Dayton and Pearce observed that the death rate among the men consuming the special diet was somewhat lower in those under 65 but not in those over 65. However, they emphasized that such variations within a large group are common (and, of course, they are, as emphasized in Volume 1) and that one should not make an issue of them.

It may be noted that between Dayton's 1969 reports and 1977 the results of six other cholesterol lowering trials were published. Four of the studies, including the Coronary Drug Project, were conducted in the U.S. and Great Britain and all reported negative findings.[a] The remaining two were conducted in Helsinki, Finland and Oslo, Norway.[480,1145] Although authors of both of these trials reported positive findings, such findings cannot be taken seriously because neither trial was blinded and the Helsinki trial, probably the worst designed and conducted trial, was also not randomized. Thus, by 1977 a most imposing number of trial failures had accumulated.

In his testimony to the Committee, Spritz said that the Dayton trial was the "best study" which investigated the diet-heart disease hypothesis but still failed to show benefits of a cholesterol-lowering diet. McGovern interrupted Spritz to read a recent letter from Dayton. It read, "Dear Senator McGovern: Thank you for providing me with a copy of your Committee's publication entitled 'Dietary Goals for the U.S.' and for the invitation to comment upon these issues. The main reservation I would have is that a more radical restriction of saturated fat and cholesterol might very well be even more efficacious. Our own trial strongly suggested that a diet reduced in content of saturated fat and cholesterol was effective in reducing complications of arteriosclerosis in men under the age of 65." Thus, Dayton gave McGovern interpretations and conclusions that were precisely opposite to those he had published in two journals. Olson noted this fact but McGovern seemed oblivious to the contradiction.

McGovern said, "Now, it strikes me if you regard that doctor as the author of the best study and he is saying that as far as he is concerned we ought to go even further in recommending reductions in cholesterol and saturated fat intake, that this refutes your own case." Spritz replied, "The data that are most important and most relevant are mortality figures" and "There isn't one year in...the whole 8 years...where the group eating the test diet was doing better in terms of mortality than the group

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[a] 462,463,490,555

eating the usual diet." But McGovern apparently paid no attention to that fact and said, "You recommended him to this Committee as the author of the best study, and he is the man who says he endorses the dietary goals, endorses reduction in cholesterol as a means of reducing the risk factor involved in the heart diseases we are talking about here today."

Spritz tried a new approach. He said, "I have respect for his opinion. In the letter he is dealing with his opinion about what will happen if you put this diet into a national policy. I'm dealing with the data, that is, what he found in 8 years when he compared several hundred men. I think that is the thing to look at, not his overall feeling which is no better than my overall feeling."

Spritz discussed other trials on which drugs or diets were used to lower blood cholesterol and indicated that none showed that cholesterol-lowering over long periods increased life expectancy. He said, "This is a tremendous body of negative evidence that says that diet changes don't protect people from heart disease."

Seemingly oblivious to everything Spritz said, McGovern continued to repeat his illogical argument, namely, "I come back to the fact that you cite Dr. Dayton as the author of the kind of diet study that you have confidence in, and you are saying that his is one of the best studies, in your opinion, that has been done. Dr. Dayton, the author of the study which you say is well done, is recommending to this Committee that we should have gone beyond where we did in recommending reduction of cholesterol intake. Either he is a reliable witness or he isn't. You say he is. You say he is the author of one of the best studies you know of. Yet, when he writes this Committee that we didn't go far enough in calling for a reduction of cholesterol as a means of protecting the American population against heart disease, you challenge his recommendations. I don't follow that logic."

Olson then entered the discussion, probably to the delight of a very frustrated Spritz. He said, "You have to distinguish between Dr. Dayton's published words, and I have it quoted in my testimony, and his letter to you, Senator. He did report that the Los Angeles study [trial] did not note any decrease in total mortality [or CHD morbidity], and he cited an increase in malignant neoplasms in the group receiving the high polyunsaturated fatty acid diet. The study is, in fact, negative. There are investigators who are enthusiastic for change, and there are many investigators who are not enthusiastic for change. I think what we are trying to obtain in these hearings is a balanced view of the evidence.

Again, apparently paying no attention to or unable to understand the simple logic of Spritz and Olson, McGovern simulated the proverbial broken record. He said, "What I'm trying to get across is that the man you cite as the author of a careful study does recommend change, reduction in cholesterol." Olson responded, "he doesn't put that view forward to his colleagues in the medical community." And McGovern quickly replied, "He puts it forward in a letter to this Committee which I have read."

Olson tried another tactic. "In every single profession there are varied opinions on what should be done. In my opinion, Dr. Dayton is saying to you, 'Let's do the big experiment on the U.S. population.' I think that is not the appropriate way to go." McGovern said, "He says our own trial strongly suggested that a diet reduced in content of saturated fat and cholesterol was effective in reducing complications of arteriosclerosis in men under the age of 65." Then Olson responded, "Cancer is also a target for the 'Dietary Goals.' If you put into context the concluding statement in his paper, he admits that total mortality from the killer diseases was not changed in his study. That is all we can say on that point."

Clearly unable or refusing to acknowledge their arguments, McGovern dismissed the topic thusly, "I think we have made the point."

In summary, Dayton conducted a well-designed study which found that a special diet did not improve CHD morbidity or mortality and did not affect life expectancy after 8 years and he specifically and emphatically recommended against changing the American diet in two scientific articles. Nevertheless, in his letter to McGovern 8 years later he gave his opinion that the American diet should change. Senator McGovern readily accepted his opinion as fact and rejected his scientific trial data as, apparently, nonfacts.

Spritz and Olson must have been in need of aspirin following their debate with McGovern. Certainly this writer found it stressful just reading the few pages of dialog.

Robert Levy

At the 1977 Senate Select Committee hearings on nutrition and health Senator Percy asked Levy the following question: "May I ask you whether we know really what caused the [CHD] decline. More specifically, can we connect the decline in mortality with decreases in the incidence of the risk factors which you cited--elevated blood cholesterol, high blood pressure, cigarette smoking, and the other factors that Senator Kennedy mentioned?"[288] Levy said, "Yes, I think we can. ...it is certainly striking, that risk factor control, especially in the middle and upper class, has become dramatic, and with that we have seen the downturn in cardiovascular deaths."

Four years later Levy[1846] redundantly emphasized initially that it was essentially impossible to explain the CHD mortality decline. He said, "It is difficult to attribute the ebb and flow of the CHD mortality to specific events.[a] Many possible factors could be responsible for it. ...it is possible to define a multitude of changes that may have contributed to the CHD decline from 1968-1978. It should be evident that we have too many, rather than too few, possible explanations for the decline." But despite the "difficulty," Levy then strongly indicated that risk factor control was the reason for the decline, i.e., "Cardiovascular epidemiologists [meaning himself, Stamler, etc.] believe that even if we ignore the real impact of increased leisure exercise activities in American, and just evaluate the changes in cholesterol, smoking habits, and blood pressure control, one can calculate that risk factor change alone could explain the entire decline in CHD mortality over the last 10 years."

Levy noted that cardiologists disagreed with the risk factor philosophy and he then concluded, "Thus, it is not at all clear that primary prevention is the major cause of the decline." But that ebb was quickly followed by more flow, more ebb and more flow. "It is clear from the evidence of the past decade that we can control atherosclerosis or at least its cardiovascular sequellae. A focus on prevention implies a focus on the basic cause or causes of atherosclerosis, for until we understand the basic cause better we cannot hope to control it and thereby prevent its dreadful clinical sequellae. Only when we truly understand atherogenesis will we be able to effectively prevent or retard its occurrence. The decline in the CHD epidemic in the 1970s strongly suggests that we can control and eventually eradicate modern civilized man's most serious killer disease."

Noting that the CHD mortality rate initiated a decline after 1963, Levy[3102] asserted that after 1963 there was a decline in "the average American consumption of eggs, whole milk, butter, and animal fats and an increased ingestion of fats and oils of vegetable origin...," suggesting a cause and effect relation. Omitted was the fact that these food consumption trends began long before 1963.

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[a] As will be seen, Levy's discussion contained far more "ebb and flow" than did the CHD mortality trends.

At the 1977 hearings Senator McGovern asked Levy, "There is general agreement that reducing the cholesterol level, assuming it is in an elevated state is in the patient's interest?" Levy replied, "Most certainly, Senator. However, he later said, "Where the doubt exists is the question of whether lowering cholesterol will result in a reduced incidence of heart attack; that is still presumptive. It is unproven."

At the hearings Levy also said, "The problem, as I see it, where I sit in the NHLBI, is that we would like to demonstrate that cholesterol lowering is beneficial before we go out and do it on a massive scale." But he later indicated that "Now while we have not gone out aggressively to tell the average American patients what to do, we have aggressively educated the physician and the public-at-risk, those with high cholesterol, as what they can and should do about lowering their cholesterol. Some 3.5 to 4 million pamphlets and manuals have been distributed by the Institute in the last 6 years." Thus, Levy had been telling physicians and the public for 6 years to lower blood cholesterol levels before demonstrating, that cholesterol lowering was beneficial.

In his 1981 article Levy discussed the primary reasons why a proposed national diet-heart trial was rejected in favor of the LRC drug trial. "When the [National Diet-Heart feasibility study] results were analyzed in terms of the sample size calculations, it became obvious that with a cholesterol-lowering of only 10% and a dropout rate of 10% per year, a national diet heart primary prevention trial would require between 30,000 and 150,000 subjects and 1 to 3 decades." The subsequent LRC drug trial was able to reduce blood cholesterol levels even less, i.e., 8.5%, so why did it not also require 30,000 to 150,000 subjects for 1 to 3 decades? Levy went on to say that "The power of the [LRC] study is increased because these patients are at increased risk (their initial cholesterol levels are elevated). Furthermore, a bile acid sequestrant (cholestyramine) is added to the dietary prescription so that more than a 10% cholesterol-lowering is achieved." Of course, persons with elevated cholesterol levels could have been involved in the diet trial as well but Levy implied that such a procedure was valid only for a drug trial. Levy also implied that cholesterol-lowering in the treated subjects of the LRC was especially substantial because they were receiving both a cholesterol-lowering diet and a drug. But being director of NHLBI when the LRC trial was being connected, Levy knew very well that both the treated and control groups were receiving the same cholesterol-lowering diet.

In 1987 Levy[1057] indicated that the value of fish oil consumption "has not been demonstrated" and that "I have not prescribed fish oil capsules for any of my patients. But the following year he said, "Consumption of fish oils rich in omega-3 fatty acids can also help lower VLDL excess in some patients."[1541]

To illustrate Levy's understanding of statistical concepts, consider his description of alpha and beta errors. He said, "...they are common to all clinical trials, whether dealing with a rash or prevention of heart attacks. They deal with the fact that you want to see a measurable difference between the groups. They deal with the fact that you want the difference to occur more than by chance. You don't want it to occur 1 our of 2 times; you want it to occur 1 out of 20 times or less frequently. You want the results to be significant."[288] Those readers who understand what alpha and beta errors are must surely be chuckling this very moment. They may wish to shake their heads in dismay as well upon knowing that his and similar "expert" testimony was presented to Senator McGovern's Committee in 1977.

Antonio Gotto

Gotto[3357] published an article in early 1990 entitled "Clinical value of cholesterol screening" and almost everything in the article was either false or fraudulent. He said

that "portable analyzers have made screenings feasible at schools, religious institutions and shopping malls nationwide" but failed to mention that these analyzers are notoriously inaccurate or that persons operating the analyzers are typically incompetent.

Gotto said, "One of the first epidemiologic studies to connect elevated cholesterol levels with increased incidence of coronary artery disease (CAD) was the Framingham Heart study. [He cited the 1971 article by Kannel, Castelli, Gordon and McNamara.[1376]] After nearly 20 years of chronicling the cardiac histories of a large cohort of men in Framingham, Massachusetts, investigators had enough data to report that higher blood cholesterol levels were clearly associated with higher rates of CHD and that lower levels were associated with lower rates." He presented a figure (Figure 10-2) which he said derived from the 1971 report. Not only was the report a 14 year follow-up, not "nearly 20 years," Gotto's figure was not published in the Kannel et al. article in either figure or tabular form. Moreover, Gotto's figure resembles nothing that his writer has observed in the Framingham literature. (Gotto's figure was also published by the 1990 AHA/NHLBI joint statement, "The Cholesterol Facts,"[3349] discussed in Chapter 1.) He also gave the reader the impression that women were not in the Framingham study.

Gotto indicated that "The Multiple Risk Factor Intervention Trial (MRFIT) provides more recent evidence of the connection between cholesterol and CAD. [He cited Martin et al.[525]] They found a positive correlation between elevated cholesterol levels and death due to CAD began with cholesterol levels as low as 180 mg."

Figure 10-3 shows the figure presented by Gotto (dashed curve) which was attributed to Martin et al. The solid curves represent the actual original figure published by Martin et al. Gotto's curve is fabricated for several reasons. First, he expanded the vertical scale in order to yield a steeper climbing curve (but now shown in Figure 10-4). Second, the original curve shows a continuously decreasing function to 140 mg, while Gotto's curve erroneously extrapolates below 140 mg and suggests that a threshold was reached. Third, the final point on the Martin et al. curve is at the 310 mg level, while it was moved to the 280 mg level for the Gotto curve, fraudulently increasing the slope of the curve. Other points on the Gotto curve were also moved to the left to create the fraudulent curve. Fourth, Gotto purposely omitted the total mortality curve which shows that total mortality increases below 180 mg, regardless of the CHD mortality. This omission gave the reader the false impression that the lower the cholesterol the greater the health benefits. And finally, Gotto's figure was captioned "Multiple Risk Factor Intervention Trial," although the figure was derived from a follow-up of the men <u>screened</u> for the trial and had nothing to do with the trial itself.

Gotto continued, "Results of the 1984 Lipid Research Clinics Coronary Primary Prevention Trial (CPPT) provided the most compelling clinical evidence to that data of a connection between high lipid levels and premature death. The result was a 1 percent drop in total cholesterol levels and approximately a 2 percent drop in CHD risk. Total cholesterol in the men taking the drug was reduced, on average, by 9 percent more than those receiving a placebo. Moreover, coronary events occurred in 19% less of the treated group than in the placebo group." Of course the LRC trial did <u>not</u> provide evidence of a connection between high lipid levels and premature death--either CHD or total deaths. There was not a 2% drop in CHD even rate for a 1 drop in cholesterol. The event rate decrease was only 1.7% and the correct formula was a 0.2% reduction in CHD event rate for each 1% fall in cholesterol over a 7.4 year period.

Gotto said, "The Helsinki Heart study demonstrated that drug treatment could successfully lower elevated cholesterol and LDL levels, thereby reducing the risk for

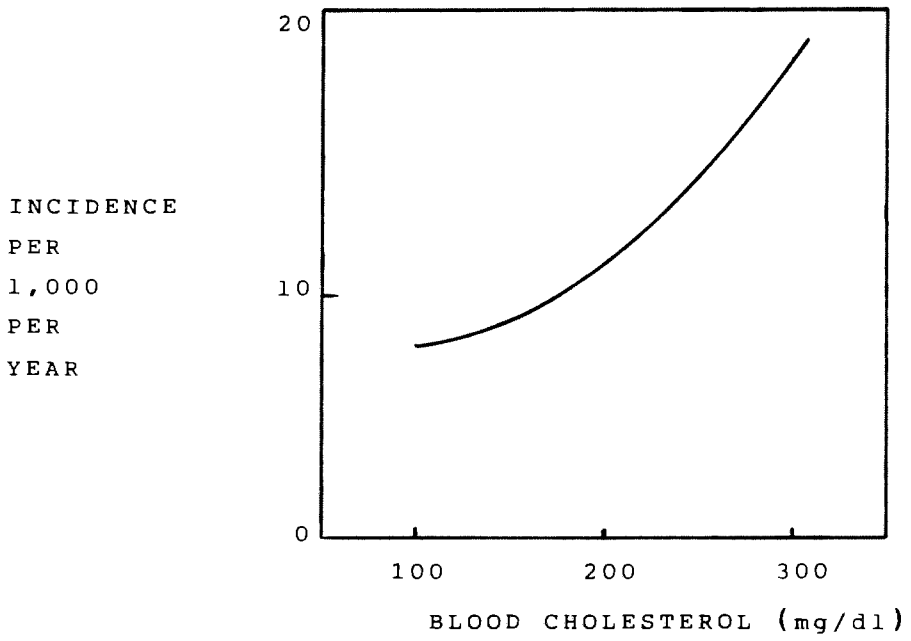

Figure 10-2. Purported CHD event incidence by cholesterol level in the Framingham cohort (adapted from Gotto,1990[3357])

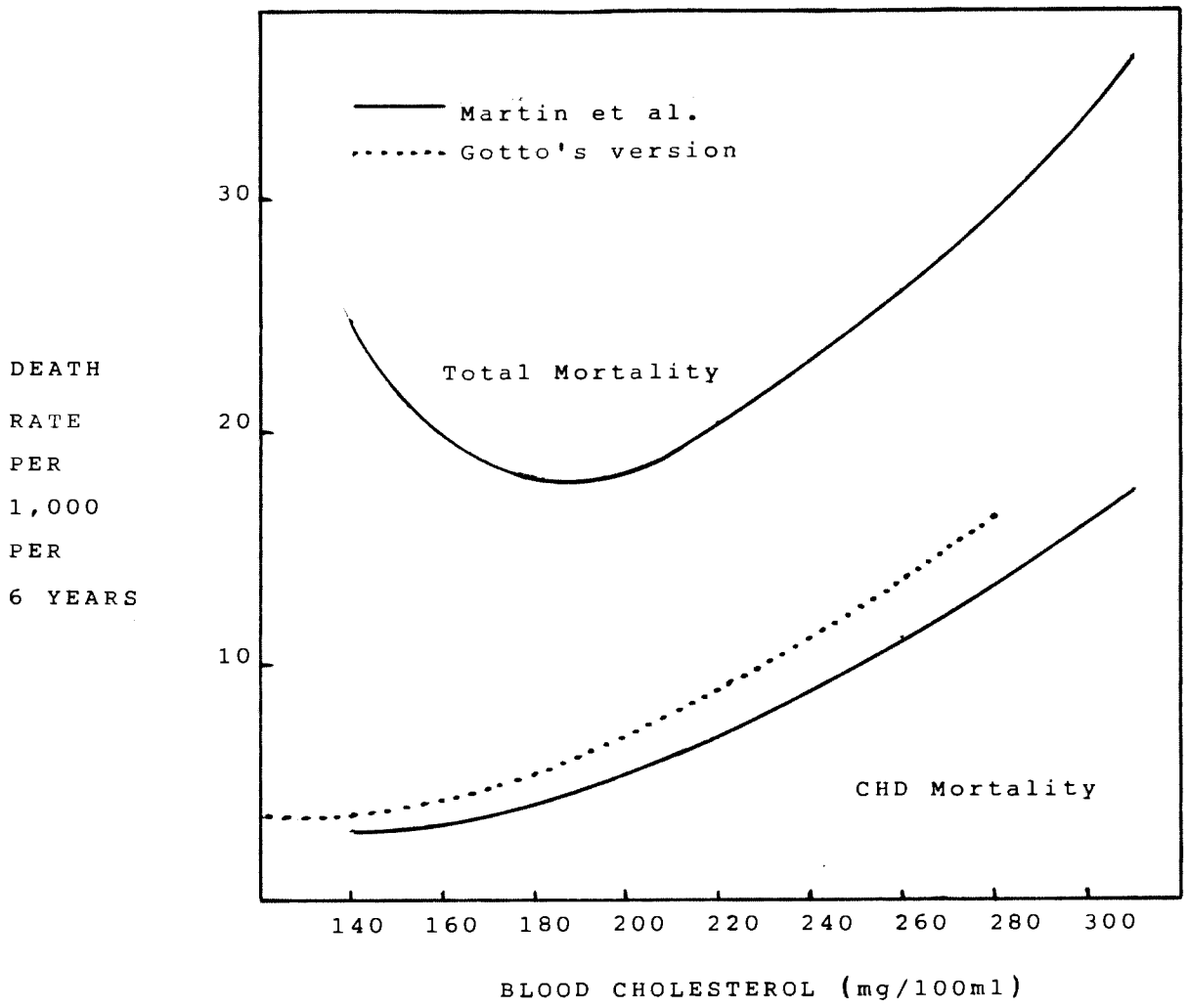

Figure 10-3. CHD Death rate by cholesterol level in the MRFIT screened cohort as described by original authors and subsequently by Gotto (adapted from Martin et al.,1986[525] and Gotto,1990[3357])

CAD. Applying the CPPT's 1:2 ratio of cholesterol-lowering to CAD reduction, the researchers expected the 8 percent reduction in total cholesterol to translate into 16 percent fewer coronary events in the group treated with gemfibrozil than in those taking a placebo. But the results of the Helsinki study were more dramatic: coronary events occurred in 34 percent less of those who had taken gemfibrozil than in those who had

not." This expectation was based on the "risk" concept which has no relation to rate. In actuality, the rate reduction in the treated group was 1.4% less than was observed in the LRC trial.

Gotto praised the Blankenhorn et al.[760] study as showing that cholesterol-lowering leads to regression even though the cholesterol levels in the treated subjects were higher than those in the MRFIT screened cohort cited by Gotto which showed increasing death rates.

Gotto cited the 15-year follow-up of the CDP and said that it "showed that men who had taken nicotinic acid during the project had experienced 11% fewer deaths than those who had taken a placebo." He did not mention the fact that those taking clofibrate did not show a reduction in deaths and he also implied that nicotinic acid had an effect when it was not administered.

Gotto apparently could not even indicate the correct data for the "official" initiation of the NCEP. "In 1987, when evidence supporting the lipid hypothesis was overwhelming, the NHLBI launched the National Cholesterol Education Program."

Speaking before the 1977 Senate Select Committee on Nutrition and Human Needs, Gotto[1601] introduced his "The Help Your Heart Eating Plan" that "will teach you that foods prepared with polyunsaturated fats are delicious and will help your heart." This diet was recommended for all adults. It included 6 teaspoons of polyunsaturated oil per day plus 6 teaspoons of safflower or corn oil margarine (high in polyunsaturates) per day. Twelve teaspoons of polyunsaturated oil are equal to about 50 g of fat or 17% of total calories in a male diet (2,600 calories) and 23% in a female diet (2,000 calories). Gotto emphasized that his diet was "free from known harmful effects."

Seven years later, Gotto[1369] buried his "Help Your Heart Eating Plan" and replaced it with "The Living Heart Diet" in which polyunsaturated fat was not to exceed 10% of total calories. He said, "A high ratio of polyunsaturated to saturated fat is only recommended for treatment of severe hypercholesterolemia, not for the general public." However, he clearly recommended a high polyunsaturated to saturated fat ratio for the public in 1977 and indicated that was "what I would consider to be a prudent diet."

William Castelli

With the exception of Jeremiah Stamler, probably no one spews more alliancedygook than does William Castelli, Framingham director. Consider first his "expert" knowledge regarding blood cholesterol levels and heart attacks. The reader should hold on to his/her hat because the following, although amusing, is highly confusing because of so many contradictions. We present first two of his statements in the 1970s (underlines added).

"Moderate[a] serum cholesterol elevations between 250 and 350 mg constitute the bulk of 'hypercholesterolemics' that appear to be predisposing to the abundance of coronary heart disease as it appears in the general population."[1376]

"...the bulk of coronary heart disease has been shown to arise out of the segment of the population with only modest[a] elevations of cholesterol..."[1046]

Castelli was fond of indicating the percentage of myocardial infarctions that occur between 150 and 200 mg, 200 and 250 mg, etc. With regard to 150-200 mg,

"About 20% of the heart attacks...occur in people who have cholesterol under 200."[2789]

"...half of the heart attacks in America occur at cholesterol levels between 150 and 200 mg."[1259]

He was particulary fond of the 200-250 mg range.

"Approximately 40% of patients who developed myocardial infarction...had serum cholesterol levels between 200 and 250 mg."[2750]

"...almost half the people who did get a heart attack had a cholesterol between 200 and 250 mg."[1302]

"...half of the myocardial infarctions...will occur...between 200 and 250 mg."[1531]

"...the majority of heart attacks occur in people whose total cholesterol level is between 200 and 250 mg."[1802]

The "bulk of the heart attacks in America occur at cholesterols between 200 and 250 mg."[1327]

We can conclude from the above that "40%," "almost half," "half," "the majority," and the "bulk" of the heart attacks occur at cholesterol levels between 200 and 250 mg," according to Castelli. Not only are these statements wildly inconsistent, one was an illogical conclusion, i.e.,

"Many physicians have argued that most of their patients with cholesterol levels between 200 and 250 mg will not have a heart attack. Although this may be valid, it is also true that half of the heart attacks they see in their practices will occur in these same patients."[1531]

Castelli effectively said that although most of the patients with levels between 200 and 250 mg may not have heart attacks, half of them will have heart attacks.

If we consider all of the foregoing 9 statements literally, about 150% of heart attacks occur at cholesterol levels between 150 and 350 mg. Of course, this is absurd but it is not inconsistent with Castelli's routine reasoning. Incidentally, in 1990 Internal Medicine News cited Castelli as saying that most people who die from CHD have total cholesterol levels in the range of 200 to 240 mg.[2597]

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[a] Of course, Castelli now considers these "moderate" elevations to be "very high" elevations.

Castelli also believes that 50% of all heart attacks occur below 250 mg--and 225 mg, i.e.,

> "...half of the myocardial infarctions occur in people with cholesterol levels below 250 mg."[1531]

> "One-half of all myocardial infarctions now occur in people whose serum cholesterol is 225 mg or less."[2462,a]

In the same article published in 1986, Castelli[1531] made the following three inconsistent statements:

> "About three quarters of the myocardial infarctions in our society occur in people whose cholesterol levels are between 150 and 300 mg."

> "In our society, half of the myocardial infarctions occur in people with cholesterol levels below 250 mg."

> "...half of the myocardial infarctions...will occur...between 200 and 250 mg."

The reader is encouraged to draw a cholesterol scale and then bracket off portions of that scale according to the above three statements to illustrate how important Castelli regards accuracy in his reporting.

What is the strength of the relationship between blood cholesterol and CHD? What measure of cholesterol is the most strongly related to CHD? The answers depend on which Castelli article one reads. In two different articles he said,

> "The cholesterol reading by itself is no clue to a healthy heart."[1567]

> "Obviously, the total cholesterol value cannot accurately predict which patients have a lipid problem when the cholesterol levels are between 200 and 250 mg, or even between 150 and 250 mg."[1531]

But in another article, he wrote

> "There is overwhelming agreement in the medical community that an elevated cholesterol is a cause of atherosclerosis."[1802]

And in the same article two paragraphs apart, Castelli[2955] said

> "The simple total cholesterol was powerfully related to the subsequent rate of coronary heart disease."

> "...the use of total cholesterol in individual cases is fraught with uncertainty."

With regard to the best measure of cholesterol, consider first the immediately above five statements, three of which indicate that total cholesterol is both a powerful and a weak predictor of CHD. The following statement suggests that total cholesterol is a better measure than HDL:

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[a] These statements contrast with Castelli's co-worker, William Kannel, who said that 50% of heart attacks occur below 240 mg![1701]

"Total cholesterol and HDL cholesterol levels are probably the most important risk factors. The total cholesterol level is a particularly useful indicator for CHD..."[1366]

But elsewhere Castelli said,

"...high-density lipoprotein is shown to be the most powerful single factor for predicting coronary heart disease risk in both sexes."__

"HDL is a more powerful risk factor than LDL, triglycerides, or total cholesterol."[1603]

And still elsewhere he said,

"...the ratio of total to high-density lipoprotein is as good as any other and represents a simple scale for the clincian to follow."[2955]

"...the best way to predict risk [of CHD] is to calculate a ratio of the total cholesterol to high-density lipoprotein cholesterol."[1531]

It is notable that although Castelli and the alliance in general agree that the atherogenic lipoprotein is LDL, it is seldom, if ever, referred to as a "powerful" or "best" predictor of CHD.

Consider now statements by Castelli to millions of New York Times readers on a subject in which he apparently knows almost nothing. "If you eat a hamburger made with Prime meat, you've blown your saturated fat [allotment for the day]. If you eat a hamburger with Choice, you've almost blown it. But if you eat a hamburger made with Select meat, you have one for breakfast, lunch and supper."[2294] Castelli went on to say that "Doctors don't know a thing about nutrition," apparently not recognizing that his hamburger statement was a perfect case in point.

In the first place, the amount of saturated fat or fat in general in hamburger is not at all related to (USDA grades) "Prime," "Choice" or "Select." It is typically ground from the lean trimmings of <u>all</u> beef carcasses and then ground fat is <u>added</u> to correspond with the designations, "regular" (no more than 30% fat), "lean" "extra lean" and "leanest" (progressively lower percentages of added fat). The hamburger may be ground from the trimmings from specific primal sections of a carcass such as the "sirloin" or "round" sections, but it is still trimmings to which fat is added. Prime, choice and select beef have nothing to do with how much fat is in ground beef, even though they represent progressively (slightly) lower amounts of fat in <u>whole</u> cuts of meat.

New York Times writer, Marion Burros said that "Ever since Castelli learned about the select grade last year [1988], beef has been back on his diet."[2294] In actuality, select beef is the same beef that has been sold in most markets for many years. In the 1960s and early 1970s most markets sold choice beef (from cattle "fattened" in small feedlets after months of range grazing). But when supplies dwindled and beef prices rose enormously in 1973, most markets ceased purchasing and selling USDA choice beef and began selling an ungraded beef that would ordinarily be graded "good" by the USDA. Since the term "good" had little consumer appeal, markets did not have the beef graded as "good" by the USDA and instead labeled the beef with their own "house brand" names, such as "premium beef," 4-star beef," etc. This saved the market (and consumers) about 10 cents per pound which the USDA charged for the grading process plus even more for switching from choice to good grades. It also eliminated almost completely the USDA from the meat grading business. Then on November 23, 1987, the USDA officially changed the name of "USDA Good" to "USDA

Select" and markets began selling USDA graded beef again because the term "select" had greater consumer appeal than "good."

It is an unfortunate fact that the media accept the statements of Castelli and other alliance members simply because they are classified as "experts," even though they have no expertise or exhibit no expertise on many subjects about which they speak or write. Castelli and others have left a trail of alliancedegook so wide, the Queen Mary could comfortably travel the path--sideways.

Let us now cite a few more statements by Castelli which lie somewhere between irrational and absurd. Although virtually all other alliance members agree that typical laboratories in this country cannot measure HDL with sufficient accuracy[a] and that measurements of HDL should not be performed, in any event, on nonfasting subjects.[1792,2265] Castelli insists that HDL measurements should be performed routinely[1809] and on nonfasting subjects.[1802]

Castelli said that everyone with a total cholesterol to HDL ratio of 4.5 or higher should have a complete lipoprotein analysis.[2462] Since he elsewhere reported that 67% of the American population has ratios above 4.5[1531] and since NHLBI estimated a complete lipoprotein analysis to cost about $300 each,[952] Castelli is effectively asking the American public to spend up to $48 billion on cholesterol tests alone. And that apparently does not include physician fees which, at a modest $100 per person, would entail another $16 billion.

In 1989 Castelli maintained that "serum cholesterol has emerged as a primary risk factor in patients older than 65 years."[2292] Yet, Surgeon General Koop, whose 1989 report was prepared and frequently cited by the alliance, also stated in 1989 that cholesterol level is not important in senior citizens. He said, "I think the worst thing about the cholesterol effort in this country is that it has frightened about 30 million [senior] people that don't have to be frightened at all."[2441,b]

Finally, it is noteworthy to mention a Procter and Gamble pamphlet (1987,[1054]), sent to health professionals, that was "reviewed for technical accuracy" by William Castelli:

"While excessive consumption of total dietary fat and saturated fat is associated with increased risk for CHD, certain unsaturated fats are linked to a reduced risk. Mediterranean countries where a relatively high intake of monounsaturated fat and low consumption of saturated fat correspond with low CHD mortality." They also cited the Eskimo study in which Eskimos have low CHD rates and high poly intakes. But they purposely neglect to say that these populations consumed as high or greater amounts of total fats as do Americans.

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[a] Goodman,[1809] Healy,[1439] Grundy,[1619] Rifkind,[1654] etc.

[b] To illustrate the fear generated by Castelli and others, Hazzard recently replied to a question concerning a 78 year-old women without CHD symptoms thusly: If "she is still concerned about her lipids, I would probably give her drug therapy."[1765] Note that the women is 78 and the fact that the recommended drug therapy was contingent on her concern, not on Hazzard's. In a similar question and answer column, Aronow recommended that a 75 year-old woman with a cholesterol level of 249 mg be placed on treatment whether or not she had CHD symptoms. "age should not be a reason for failing to treat hyperlipidemia."[2270]

William Kannel

In 1990 Kannel published an article entitled, "CHD risk factors: a Framingham update."[2893] He presented a figure showing "Eight year risk of cardiovascular disease per 1,000" as a function of blood cholesterol level. Because the vertical scale was actually a rate scale, it was improper to use the term "risk" as though it was interchangeable with rate, which it most certainly is not. It was also improper to use the term "cardiovascular disease" because Kannel's text was restricted to CHD and because there are ample data indicating that stroke and peripheral artery diseases are not related to blood cholesterol level. Finally, the CHD event rate ranged from about 1 per 1,000 at a cholesterol level of 175 mg to 4 per 1,000 at a cholesterol level of 335 mg. Although this cholesterol range was extremely broad, i.e., 160 mg, the rate difference between the lowest and highest levels was a mere 0.3%, hardly a basis for Kannel's claim that "high serum cholesterol is a powerful predictor of cardiovascular [CHD!] disease." For example, if a person reduced his blood cholesterol level by 40 mg, his likelihood of a CHD event over an 8 year period would be reduced by 0.08%, according to these data.

Rather than admit that LDL was effectively not related to CHD in subjects over 50 years of age, Kannel stated that "In the over 50 study group, HDL cholesterol, rather than LDL cholesterol, proved to be the more potent lipid indicator of risk. ...most striking is the power and independence of HDL as a predictor. In the elderly, at least, the protective effect of HDL cholesterol exceeds the atherogenic effect of LDL cholesterol." But rather than use a rate scale and a functional curve as he did for total cholesterol, he instead used a "relative risk scale as a function of 3 levels of LDL and 3 peculiar "intervals" of HDL, i.e., $\leq$ 25, $\leq$ 55 and $\leq$ 85 mg (in bar graph form). They were, in fact, not independent intervals and certainly not appropriate to demonstrate a functional relation. Clearly the use of a risk scale and such intervals was an indication that the relation between HDL and CHD was very weak and perhaps inconsistent. It is virtually impossible to determine the importance of the relation in terms of rates and that undoubtedly was Kannel's purpose of using a risk scale and peculiar HDL intervals. It should be noted, moreover, that Kannel's risk scale was labeled CHD, not cardiovascular disease as was the case in his first figure.

Kannel indicated that "hypertension is a powerful risk factor..." and this time showed not hypertension per se but "isolated systolic hypertension [over 160 but normal diastolic pressure] in yet another form, i.e., he used a rate scale vs the presence or absence of isolated systolic blood pressure. And while Kannel's first figure was labeled "risk of cardiovascular disease per 1,000" and the second figure was labeled "Relative risk of coronary heart disease," his third figure was labeled "Average annual risk of MI per 10,000." Myocardial infarction is one category of coronary heart disease and coronary heart disease is one category of cardiovascular diseases.

Kannel stated that "...it was convincingly shown in various studies that lowering elevated LDL cholesterol or total cholesterol values by diet or drugs reduces coronary morbidity and mortality. This statement, of course, is an absolute fabrication. Many diet trials have been conducted without success and no diet or drug trial has significantly reduced either CHD or total mortality. Kannel acknowledged this fact in 1983, i.e., he said "So far, the results of trials to reduce coronary risk by either drugs or diet have been rather unimpressive."[1091] The only diet trial published after 1983 was the Oslo Diet and Smoking Trial.[846,849] Kannel said, "In the Oslo Diet and Smoking Trial of 412 asymptomatic, hypercholesterolemic men, nonhypertensive subjects randomized to a low-saturated fat, low-cholesterol diet had a 35% lower prospective incidence of coronary disease over the five year study period. It was difficult to separate effects of diet and smoking cessation, however."

Three errors are evident in Kannel's statement. First, the Oslo authors reported a 47% reduction in CHD, not 35% (see Chapter 6). Second, neither the 35% nor the 47% refer to "incidence" but rather to "relative risk." And third, the Oslo authors stated that detailed analyses revealed that the trial's effects were almost entirely due to cholesterol-lowering.[a]

Kannel also briefly discussed the LRC and Helsinki II trials and again referred to relative risk reduction as rate reductions.

Kannel said, "Several studies have provided angiographic evidence that progression of the lesions could be made to slow down and possibly even regress." He cited the Blankenhorn et al. study and indicated that "During two years of treatment, coronary atherosclerosis was actually improved in about 16% of drug-treated patients, compared with less than 3% of the placebo group." But three sentences later he said, "The clinical and epidemiological evidence also confirmed that there was no threshold in the range of cholesterol values to be classified as 'safe' for coronary disease avoidance or 'unsafe' and to be reduced." In addition to this sentence being poorly constructed, it contradicts Kannel's interpretation of Blankenhorn et al.'s results, i.e., if there is no threshold below which CHD can be avoided, there cannot logically be regression from cholesterol lowering.

Kannel stated that, "Guided by population studies, we noted that serum cholesterol values of around 160 mg in general predicted low coronary mortality and long life expectancy." In view of the fact that prospective studies, including the huge MRFIT screened cohort, demonstrate higher all-cause death rates below 190-200 mg, Kannel's statement was both false and misleading.

Kannel said that "Drug treatment is recommended at total cholesterol levels of 240 mg and above..." Because the mean cholesterol level among adults is about 215-220 mg, this recommendation would involve about 40% of all adults.

In another recent article Kannel[1448] said, "Despite a progressive increase in all causes of mortality in relation to the total cholesterol value in serum, owing chiefly to coronary heart disease, the leading cause of death, serum cholesterol values < 160 appear to accompany an excess mortality. The increased mortality at low cholesterol values has been found to be related to cancer, particularly colon cancer. Analysis of the time course of this relationship suggests a cholesterol-lowering effect of subclinical cancer." Not only did Kannel republish Martin et al.'s MRFIT cohort results which showed that all-cause mortality began increasing below 190 mg, not 160 mg, he also fraudulently attempted to explain away the importance of the low-cholesterol-cancer association. As noted elsewhere in this volume and Volume 1, many studies have shown that the association persists after adjusting for the possibility of subclinical cancer. Kannel admitted this fact in an earlier article.[1083]

In the same article Kannel said, "...examination of serum cholesterol in middle age in relation to the occurrence of coronary heart disease beyond age 65 shows a strong effect. He presented a table which is reproduced as (a) in Table 10-9. The reader should note that while the text indicated "coronary heart disease," his table referred to "cardiovascular disease."[b] The correct table should have been (b) in Table 10-9

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[a] The validity of this statement is debatable but not relevant to this topic. What is relevant is Kannel's accuracy in "reviewing" the Oslo study.

[b] It is also curious, if not humorous, to note that the disease rate decreases at very high cholesterol levels.

Table 10-9

(a)

Risk of cardiovascular disease after age 65 by average serum cholesterol in middle age (adapted from Kannel,1988[1448])

Average serum cholesterol	Age-adjusted annual disease rate per 1,000
84-204	26.4
205-234	31.2
235-264	36.7
265-294	52.7
294-1124	43.9

(b)

Risk of coronary disease by serum cholesterol in men 65-94: 30-year follow-up (adapted from Kannel,1987[787])

Serum cholesterol	Age-adjusted annual rate per 1,000
84-204	22
205-234	24
235-264	26
265-294	23
294-1124	38

NOTE: Only data for male subjects were reproduced in these tables.

which was published by Kannel a year earlier.[787] Was this switch a mistake or purposeful? The latter seems likely because the correct table effectively shows no relationship between cholesterol and CHD up to 294 mg which, of course, would not support his text statement of a "strong effect."

Despite Kannel's statement of a "strong effect" and an incorrect table, two paragraphs later he said, "In the age group 50-80 years, the total cholesterol in serum was a poor predictor of coronary heart disease, because the impact wanes progressively with advancing age." Thus, it would seem, cholesterol has a "strong effect" on CHD and is also a "poor predictor" of CHD. Such reasoning, of course, is typical of alliance members.

In another 1990 article Kannel and his colleagues[2894] reported that although the CHD mortality rate had decreased in the Framingham population from 1950 to 1980, the prevalence of CHD actually increased quite substantially. In attempting to explain these opposite trends, they suggested that so-called favorable risk factor trends occurring since 1950 caused the mortality decline but were too slow to influence incidence. They said, "Little is known about the delay between changes in risk factor status in a population and changes in the incidence of disease and death. It is likely, however, that changes in risk factor status would have to begin at an early age in order to produce major reductions in the incidence of disease among 50-59 year-olds. It seems reasonable that a shorter time would be necessary for changes in risk factors in a population to lead to reduced mortality."

The above quote may very well be the most absurd statement ever uttered by medical "researchers." The notion that 30 years of risk factor changes can reduce CHD mortality but not effect the strongly increasing incidence of CHD is incredibly devoid of all rational thought. Moreover, the statement is opposite to that frequently espoused by alliance members with respect to clinical trials, i.e., they have argued time and again that risk factor changes reduce CHD incidence but not mortality in clinical trials because the latter endpoint requires more time than the former endpoint. In addition, if it takes decades to change incidence, how can that position be reconciled with the angiographic studies which purport to show regression after only one year of risk factor change?

In the same year Kannel made the following two contradictory statements in two different articles:

> "...the more severe the coronary artery atherosclerosis, the more likely was the [MI] attack to be fatal."[3016]

> "Older persons in general have more advanced coronary atherosclerosis, the most potent stimulus to the development of a collateral circulation. Older persons may for this reason be less subject to sudden death since their coronary collaterals protect them at the time of occlusion."[3015]

Scott Grundy

In 1986 Grundy[262] published a "state-of-the-art" review entitled, "Cholesterol and coronary heart disease." It was only seven pages of text and included only 50 references. Of the 45 references which involved persons as authors, 22% were Grundy's. At the outset, then, it was virtually impossible for Grundy's article to even resemble a state-of-the-art review of cholesterol and heart disease.

Like Gotto, Grundy presented a curve which was supposed to be derived from the MRFIT screened cohort data. However, instead of citing Martin et al.[525] as the source,he cited Stamler et al.[263] who presented tabular data but no figures. The only

table that could have been used by Grundy gave death rates as a function of 10 cholesterol deciles and their associated mean cholesterol levels. Grundy's figure was not a faithful representation of this table and his curve contained 11 plotted points, not the 10 decile points. But like Gotto's, his figure also exaggerated the upward slope of the MRFIT data and implied greater health benefits at low cholesterol levels because he also omitted the important total mortality curve.

Grundy stated that "The major population surveys reveal an additive, or even a multiplicative, interaction of the major coronary risk factors--plasma cholesterol level, smoking, and hypertension." Since it is well known that blood cholesterol level has no predictive capability at the individual level, statements suggesting that risk factors are additive or multiplicative in their effects are grossly misleading.

Grundy said that a group of epidemiologists in 1979 "proposed that ideal cholesterol levels for adults range from 130 to 190 mg." He cited as the source an article by Stamler[2635] and said that "According to MRFIT data, this range seems reasonable, because it is below the zone of markedly increasing risk." No where in the Stamler article was there a recommended range of 130 to 190 mg. However, another article by Barry Lewis,[2634] generated from the same conference that Stamler attended, did recommend a mean population cholesterol level of 160 mg with a suggested range of 100 to 220 mg. While Grundy considered this general range reasonable in view of the MRFIT data, the latter most emphatically indicated that total mortality is greater in this range than at higher levels.

Grundy stressed that "A reduction in the cholesterol level to 150 mg in such a patient (over 50 years) could delay the onset of CHD by as long as ten years." Indeed, the onset may be delayed forever because the patient may die of other causes first, according to the MRFIT data.

Grundy indicated that "...it may be useful to review the effects of different nutrients on cholesterol levels and on the metabolism of lipoproteins." Of the 60 plus experiments conducted on dietary cholesterol, Grundy cited only four studies, an irrelevant hamster study, one experiment by Hegsted et al.,[408] another experiment by Mattson et al.[368] and a nonexperiment by keys et al.[333] From these studies he claimed that "an increase in cholesterol intake from 250 to 200 mg will raise the plasma cholesterol level by an average of about 10 mg." This value is about twice the amount typically observed in whole food experiments (see Volume 1).

With respect to the effects of saturated, monounsaturated and polyunsaturated fats, on which dozens and dozens of experiments have been focused, Grundy cited a total of four studies, one of which was a nonexperiment and two others of which were his own studies. This, then, was Grundy's "useful review" of diet experiments.

Grundy cited five studies as demonstrating that dietary cholesterol causes CHD independent of its effects on blood cholesterol. These studies were critiqued in Chapter 4 and, as was emphasized, constituted some of the worst examples of scientific investigation this writer has encountered.

Grundy cited the LRC study as "strong evidence that lowering LDL concentration will reduce the risk of CHD." Cholesterol-lowering in that trial resulted in a 1.7% reduction of CHD events over a 7.4 year period.

He said that "38% of men dying of CHD [in the MRFIT screened cohort] had cholesterol levels over 245 mg at screening." but more important is the fact that 62% of the CHD deaths had cholesterol levels <u>below</u> 245 mg.

Grundy indicated that "since 15 to 20% of the population has hypercholesterolemia by the criteria of the cholesterol consensus conference, an enormous number of patients will be included" in the medical care system. In view of the fact that the "Expert Panel" redefined hypercholesterolemia in 1988 as above 200 mg, representing more than 60% of the adult population, Grundy's "enormous" becomes modest by contrast.

Grundy said that "Evidence from the MRFIT [screened cohort] demonstrates that most coronary deaths occurring before age 65 years are the consequence of the major risk factors--elevated plasma cholesterol, smoking and hypertension." As noted in Volume 1, and Chapter 3 of this volume, nearly all (79%) of the MRFIT screened cohort had one or more risk factors at baseline. The statement that "most coronary deaths are the consequence of the major risk factors" connotes absolutely no new information whatsoever.

Grundy told his readers that "Theoretically, a marked reduction in cholesterol levels in such [CHD] patients will retard the further development of atherosclerosis, and this possibility emphasizes the need for secondary prevention trials to test the efficacy of cholesterol-lowering in patients with established CHD." One can only wonder where Grundy has been since many secondary trials have been conducted without success.

Despite the jubilant claims by most alliance members that CHD is being conquered, Grundy stated that "CHD will remain the nation's leading cause of death for the next 25 years. [He will later say, "with little doubt, the next decade will see a massive effort to utilize these recent breakthroughs in cholesterol control for prevention of CHD."] A shift in peak incidence of CHD from late middle age to old age, because of a decline in other risk factors, should focus attention on the problem of mildly elevated plasma cholesterol levels as the major causative factor of CHD in older people." The implication of this statement is that the CHD mortality rate is currently higher in middle age than in old age. Such an implication is nonsense because there are reams of data showing that the CHD mortality rate has always been, is and will continue to be, higher for each succeeding age group.

Grundy said, "In several countries, such as Japan, where intakes of total fats, including saturated fats, are very low and carbohydrates are consumed as the major source of energy, plasma cholesterol concentrations and rates of CHD are relatively low. This is an argument for reducing intake of total fat and increasing carbohydrate intake." Not only is the Japanese experience evidence against such an argument (see Chapter 4), Grundy had earlier criticized a low (20%) fat diet and indicated that it produces "some disturbing effects on plasma lipoprotein levels, raising the VLDL concentrations and lowering the HDL level. Elsewhere in the same year Grundy did indeed recommend a diet of 20% of calories as fat for moderate hypercholesterolemia."[1167]

Grundy said that because of the harmful effects of high polyunsaturated fats "intakes of linoleic acid exceeding 10% of total energy intake are rarely recommended anymore." His use of the word "rarely" is questionable since he recommended one year earlier a diet "rich in polyunsaturates," i.e., "20% [of calories] as polyunsaturates."[687]

Grundy also said that "...the whole concept of using drugs for long-term primary prevention of CHD, when the risk ratio is increased only two to three times [200% to 300%] above baseline, is questionable." Yet, in the same article he indicated that "The availability of highly effective drugs, such as reductase inhibitors, offers the promise of simple pharmacological control of hypercholesterolemia. The recent and dramatic surge of interest in cholesterol-lowering drugs by the pharmaceutical industry supports the belief that use of these drugs will be widely accepted by the medical

community." And in the same year[1167] and in the year before[1278] Grundy recommended drugs for "many" patients with moderate hypercholesterolemia.

In addition to the many false and misleading statements, all of which are by no means presented here, Grundy's entire article was held together with a network of speculative "mays," "probablys," "seeminglys" and "apparentlys." "...high-density lipoproteins may accept cholesterol from extrahepatic tissues (and other sources) and transfer it to VLDLS (and LDLs)..." "...data from a much larger study, the MRFIT, seemingly void the strict threshold concept." This nonlinearity between severity of atherosclerosis and risk for CHD probably contributes to the curvilinear relationship between cholesterol level and risk for CHD." "...a plasma cholesterol level of 200 mg may induce a critical degree of coronary sclerosis by about age 70 years." "Although genetic factors certainly must contribute to many cases of primary hypercholesterolemia, diet is probably a significant factor for a large number of people." "...some people may be overly sensitive to excess dietary cholesterol, saturated fatty acids, or total calories and may respond with an unusually marked increase in their LDL levels." "The same mechanisms probably pertains to humans." "Not only does it [dietary cholesterol] increase the cholesterol content of chylomicron remnants, it apparently also raises plasma concentrations of beta-VLDL..." "...dietary cholesterol could be more atherogenic than revealed by its action on the fasting plasma cholesterol level." "The saturated fatty acids seemingly increases LDL levels by suppressing the activity of LDL receptors." "Other investigators support the concept that linoleic acid reduces the HDL cholesterol level, but this may happen only at high intakes." "...linoleic acid may be neutral in its effect on LDL receptor activity, and therefore the LDL-lowering action of linoleic acid may be mainly the consequence of its replacement for saturated fatty acids." "...they [omega-3 fatty acids] seemingly do not lower LDL levels more than other unsaturated fatty acids and apparently have little to offer for treatment of hypercholesterolemia." "The effects of carbohydrates on plasma triglyceride concentrations may be related to the caloric states of an individual." "If one is mildly to moderately overweight, high intakes of carbohydrates may substantially raise triglyceride levels, but if one's weight is on the low side of normal, carbohydrates may have little or no effect." "Marked hyperlipidemia in an obese person probably signifies a concomitant defect in the catabolism of VLDL or LDL..." "Obesity also reduces levels of HDL, and thus obese persons often demonstrate multiple abnormalities of lipoproteins, some of which may enhance atherogenicity."[a] Another way in which diet could augment risk for CHD..." "A high intake of dietary fat could also be atherogenic..." "All of these are potentially atherogenic mechanisms, but most remain in the realm of speculation..." "Although dietary modification overall may not be as potent as drugs for cholesterol lowering..." "The lower the better" for cholesterol levels "is probably the best philosophy." "...such a diet may help prevent CHD..." "Both saturated fatty acids and cholesterol seemingly reduce LDL-receptor activity." "...the recommendation to decrease intake of saturated fatty acids and cholesterol seems justified for most Americans." "...the high-monounsaturated diet overall appeared to be at least as good as..." "This approach seems prudent."

In 1987 Grundy et al.[3256] presented a figure showing the CHD risk ratio as a function of blood cholesterol level and, like Gotto (discussed earlier), cited the same 1971 Framingham report authored by Kannel et al.[1376] as their source. That figure was not in the Kannel et al. report and there were no data within the report that could have been used to generate Grundy et al.'s figure. Grundy et al. also presented a figure showing the CHD risk ratio by cholesterol level for the 6-year follow-up of

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[a] But not according to Keys and others (see section on obesity).

the MRFIT screened cohort. But rather than cite the original reports of that follow-up as source data, Grundy et al. cited the above 1986 Grundy "state-of-the-art" review article.[262] As source data for that figure they cited Stamler et al.[263] However, the latter published no such figure and Grundy et al.'s figure also could not be directly derived from their data. Moreover, Grundy et al. showed a ratio of less than 1.0 (0.7) in their figure, while Stamler et al., like the vast majority of researchers, used 1.0 as the lowest risk ratio. In fact, use of a less than 1 risk ratio is a totally arbitrary decision and gives the false illusion that that particular cholesterol level has a subnormal risk.

In 1984 Grundy[3034] presented the AHA's Phase I, II and III diets and subsequently indicated the rationale underlying them. The diets are:

	% fat	% Carbo	% Protein	Fat (%) Sat	Mono	Poly
Phase I	30	55	15	10	10	10
Phase II	25	60	15	8.3	8.3	8.3
Phase III	20	65	15	6.7	6.7	6.7

The rationale for using the low-fat, low-cholesterol diet for treatment of hypercholesterolemia is based on the following principles: "(1) It represents a reasonable extension of the diet recommended for the general public." [This is not really a principle and it has no scientific foundation.] "(2) It progressively decreases the major cholesterol-lowering constituents of the diet (i.e., saturated fats and cholesterol)." [This is absolutely not true. Fat per se is not related to blood cholesterol levels and this fact has been known for decades and was confirmed by a 1986 Grundy experiment.[336] Cholesterol alteration depends on fat composition and, as can be seen, the fat compositions of the three diets are identical. See section on Blood Cholesterol and Weight Reduction.] "(3) It precludes large intakes of polyunsaturated fats." [This is debatable. All diets have P/S ratios of 1.0, substantially higher than that of the typical American diet over this century. It is simply not known whether this ratio is harmful.] "(4) It facilitates weight reduction by removing foods of high caloric density." [This is an unproven assumption and conflicts with the historical knowledge that much of the obesity in the U.S. has been due to high carbohydrate diets, as discussed elsewhere in this volume.]

Grundy published another "review" in late 1990 that was replete with distortions, contradictions and senseless reasoning.[3083] A few examples follow. He said, "Although the available evidence fully justifies this [NCEP] program, its practical application to the American public has generated a series of new questions that must be explored. For example, it can be questioned whether reduction in coronary risk through lowering cholesterol levels extends to both sexes and all age groups." This is the classic "shout first and ask questions afterwards approach." The alliance is telling Americans of all ages above 2 to change their diets and take drugs, because "the available evidence fully justifies this," but "it can be questioned" whether reduction of cholesterol among women and the elderly is justified (about 70% of the total population). This is, of course, a contradiction. Moreover, the NCEP did not generate the question of whether it will be beneficial to lower cholesterol in women and the elderly. This question was well known long before the NCEP began.

Grundy indicated that "A low serum HDL cholesterol level has emerged as the strongest single lipid predictor of CHD."[a] He then indicated that "...a strong

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[a] Grundy cited Kannel et al. (1979[1046]) as the source for this statement. A review of that article revealed no such comment.

rationale for specific therapy of HDL cholesterol is lacking." Somewhat later Grundy presented the following two sentences, one sentence apart. "...high carbohydrate diets can raise serum triglycerides and lower HDL concentrations. The American Heart Association, NCEP, National Research Council and American Diabetes Association recommends that carbohydrates be used as the major replacement for cholesterol-raising fatty acids in the diet." In effect, Grundy said that low HDL is the most important lipid in the development of CHD but that there is no rationale for increasing it and everyone recommends a high carbohydrate diet which lowers it.

Grundy maintained that "The recommendation for a low-fat diet for prevention of CHD is well founded on epidemiologic data and likely will remain in place for many years." Indeed the AHA, of which Grundy is a member, has preached this gospel for nearly 30 years. But all alliance members know that it is not true and they frequently cite the Greeks as having high fat diets and one of the lowest CHD death rates in the world, albeit to promote the "goodness" of monounsaturated fats.

Claude Lenfant

The alliance makes major decisions behind closed doors and then holds contrived workshops and consensus conferences, and prepares literature "review" reports, all of which, naturally, fully support their pre-conceived decisions. While this writer had no "hands on" direct evidence of the above repetitive scenario, there is an abundance of indirect evidence and there are admissions by Key alliance members that the scenario is a true representation of the state-of-affairs. Let us consider the 1984 Consensus Conference and National Cholesterol Education Program (NCEP) as prime examples.

The alliance would have physicians and the public believe that there was a logical and unpredictable sequence of events which led to the NCEP. For example, when the LRC trial results were published in January 1984, they were considered "conclusive" and NHLBI held a mid-year workshop and an end of the year consensus conference, ostensibly to determine whether the sum total of all research to date sufficiently supported the lipid hypothesis and, if so, to make recommendations. The following discussion will show that the workshop and Consensus Conference Panel were instructed to make preplanned recommendations.

NHLBI director, Claude Lenfant, published an article in Circulation in May 1986 which provided part of the evidence indicating that the unannounced NCEP was operative in 1983 and that the Consensus Conference was nothing more than a facade.[2086] He wrote,

> "...in January 1984, the results of the NHLBI-sponsored Coronary Primary Prevention Trial (CPPT) were announced. Immediately after the announcement, the NHLBI began to develop plans to ensure the widest possible dissemination of the CPPT results. Included in the Institute plans was a national program modeled on the NHLBI."

This statement clearly and unequivocally indicates that NHLBI, at least, made the decision for an NCEP long before the Consensus Conference and, at most, was already running elements of the program, as will be seen.

Lenfant stated that,

> "Development of the NCEP proceeded in a careful, organized manner. First the need for a national program to educate the public and the health professional community was verified. Two surveys conducted before the release of the CPPT results, one of the public and the other of practicing physicians, provided important evidence of a need for an NCEP."

While Lenfant did not actually say that the surveys represented the first elements of the NCEP, the suggestion was strongly implied. For example, survey data were totally unnecessary for the formation and implementation of the NCEP. NHLBI already knew that physicians and the public were not unanimously in agreement that the diet-blood cholesterol-CHD relationship was important. There was really only one meaningful purpose of the surveys, namely to assess the impact on the public and physicians of the planned announcement of the LRC study and "conclusions" from the subsequent Consensus Conference.

Additional evidence supporting this contention was provided by Ronald Goor who was the first coordinator of the NCEP. The Medical Tribune reported that,

> "The [survey] study, detailed at the AHA meeting here [January 1985], was designed as the first step in a national campaign by the NHLBI and the AHA to enhance physician awareness of the importance of aggressive intervention in hyperlipidemia, and to get the American public to adopt a healthier diet, according to Ronald Goor,...coordinator of the NHLBI's program."[265]

The reader should especially note in the above quote that the survey "was designed as the first step in a national campaign." It is clear from this quote that NHLBI made the decision to form NCEP in at least 1983 and carried out, albeit quietly, the first step in the program, i.e., establish a baseline attitude of physicians and the public by which the NCEP campaign can later be assessed.

In his 1986 Circulation article, Lenfant went on to say that a workshop was held in June 1984 to discuss the LRC results and

> "to clarify and consolidate the scientific evidence to support the [NCEP] program. The conclusions of the workshop were reinforced by the statement of the December Consensus Development Conference."

One participant of that workshop was Beth Schuker who indicated that the 1983 survey "confirmed the need for a public education program and will serve as a baseline for developing these programs and tracking changes." (Note the word "will.)[492] Also at the workshop was Michael White who described the "mechanisms" of the National High Blood Pressure Education Program and stated that "a similar model could be adapted for disseminating CPPT results to professionals and the public."[492]

The Conference Panel of 14 people were handpicked by NHLBI and all were long-time promoters of the lipid hypothesis. According to Merz, "The NHLBI had asked the panel to use the data [LRC and other trial data] to formulate a plan to stave off coronary heart disease."[260] The panel's report included, in part,

> "...we are persuaded that the blood cholesterol levels of most Americans are undesirably high, in large part because of our high dietary intake of calories, saturated fat, and cholesterol. We recommend that the NHLBI provide the focus for the development of plans for a National Cholesterol Education Program."[1845]

Thus, NHLBI initiated the NCEP in 1983 and gave the public and physician practitioners the impression that it was conceived at the Consensus Conference after

rigorous analysis of existing data by leading experts.[a] As indicated in Chapter 2, there was considerable disagreement at the Conference but NHLBI's preconceived NCEP plan was ramrodded through as though there was a true consensus. Long-time advocate of the lipid hypothesis, Daniel Steinberg, was the Panel's chairman.

As a final note to this sad example of medical progress, Lenfant stated that,

> "The formal launch of the NCEP occurred with the inaugural meeting of the NCEP Coordinating Committee [in December 1985]. All of the development activities will be directed toward the dissemination and public acceptance of four basic tenets about cholesterol, namely (1) there is a clear association between cholesterol and coronary heart disease, (2) cholesterol is easy to measure, (3) everyone should know his or her cholesterol level, and (4) individuals with elevated blood cholesterol levels should do something about it."

The word "tenet" means an opinion, doctrine or principle that is accepted as valid. Since NHLBI was well aware of the fact that the relationship between blood cholesterol and CHD was effectively nonexistent for most people and only weak when group data are considered, and since NHLBI was well aware that most laboratories in the country at that time could not measure blood cholesterol accurately, the NCEP initiated as a brainwashing program, not as a health promoting program.

In 1987 the results of two studies were announced. Michael DeBakey indicated that no correlation between blood cholesterol level and rate of restenosis was observed after 30 years of evaluating 1,400 bypass patients. When asked for a response to this study, NHLBI director, Claude Lenfant said,

> "I don't think that surgery patients are a good model for understanding atherosclerosis."[677]

Yet, when Blankenhorn announced his findings of plaque regression in a cholesterol-lowering study comprised of far fewer bypass patients and partially funded by NHLBI, Lenfant fully approved of surgery patients as good models. At a press conference he said,

> "For the first time, we are presented with evidence regarding regression of lesions in humans."[859]

In defense of the NCEP at 1989 hearings called by Representative Henry Waxman, Lenfant said,

> The program "does not prescribe a medical regimen. We inform the public. We urge people to see their doctor."[2857]

Of course, this statement is completely false. As noted in Volume 1, the program was aimed equally at physicians and numerous "educational" and "treatment" guideline materials were sent to physicians by NHLBI and AHA. Everything that physicians know about cholesterol levels and the treatment of so-called high cholesterol levels was derived from the NCEP program. The NCEP was designed to frighten all Americans to see their doctors and simultaneously "teach" all physicians how to (1) measure blood cholesterol levels, and (2) determine and treat hypocholesterolemics (as

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[a] Many other alliance members promoted this false impression. For example, Gotto said, "That [LRC] study had a major effect on public and government attitudes. It led to the Cholesterol Consensus Conference and later on to the National Cholesterol Education Program."[1838]

defined and specified, respectively, by the alliance). Lenfant's statement was nothing less than a mockery of the two state-of-affairs.

Jeremiah Stamler

Jeremiah Stamler is one of the most prolific writers among alliance members. Yet, if one were to remove the redundancies within and between his many articles and also eliminate material that is either based entirely on opinions or runs contrary to reality, there would be little left to read. In a 1979 article Stamler[2938] said,

> "During the last 20 years, expert groups and public leaders have repeatedly advised Americans to pursue better lifestyles... The American people have been making changes. U.S. Department of Agriculture data indicate that per capita annual consumption of eggs, dairy fat and lard have decreased significantly. As a consequence, intake of total animal fat is down, despite increased consumption of meat, especially beef, so that both cholesterol and saturated fat per day are down modestly. On the other hand, use of vegetable oils and fats is up..."

The unquestionable implication in this statement is that these dietary changes took place since 1959 during the period that "expert groups and public leaders have repeatedly advised Americans to pursue better lifestyles..." Yet, Stamler presented tables and figures which clearly showed that the dietary changes were underway long before 1959. In fact, one of his figures showed dietary animal fat decreasing since 1909-1913.

Stamler presented the same illogical discussion of dietary trends in many other articles, sometimes with contradictory tables and figures and sometimes without.[a] Of considerable interest was his obvious bias before and after he recognized that CHD mortality was declining in the U.S. For example, in 1956 he and his colleagues[694] maintained that fat, milk, eggs, sugar had been increasing since 1910, correlating with the reported increase in CHD mortality (note that he did not mention animal fat per se trends). In 1962 he said,

> "...virtually our entire population is at risk, in that it habitually consumes a diet high in calories, total fats, saturated fats, cholesterol and refined carbohydrates."[574]

But after he recognized that CHD mortality was declining,[574] he stated that important and favorable dietary changes had been taking place since 1940 and 1950, the period in which he had previously indicated Americans were undergoing unfavorable dietary changes. Thus, he altered his "interpretation" of dietary trends to fit his knowledge of the CHD mortality trends.

As emphasized in Chapter 3, everyone agrees that CHD mortality statistics cannot be traced before 1939 and it is clear that most of the so-called "epidemic" occurred after 1948. The fact that dietary animal fats and vegetable fats have been decreasing and increasing, respectively, since the beginning of this century, it is obvious these trends greatly preceded both the epidemic and decline.[b] It is therefore illogical to draw the conclusion that animal fat, the principal carrier of saturated fat, caused both the CHD epidemic and its decline--but that is precisely what Stamler concluded, i.e.,

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[a] 539,1313,2635,2825,2938,2939,3002,3033,3051

[b] Dietary cholesterol remained nearly constant.

"...it is scientifically correct to designate diet high in cholesterol, saturated fat, and calories as the primary and essential cause of the epidemic of premature CHD in the U.S. and other western industrialized countries."

In effect, despite the data presented by Stamler and others, he nevertheless proclaimed that "it is scientifically correct" to incriminate saturated fat, etc.

One of the long-time common tactics of alliance members is the claim that the vast majority of research evidence supports their position, whether it be the diet-CHD hypothesis, the lipid hypothesis or the concept of multifactor causes of CHD. For example, the statement from the contrived 1984 Consensus Conference included the following passages:

"The evidence supporting a causal relationship between blood cholesterol levels and CHD comes from a wealth of congruent results of genetic, experimental, pathologic, epidemiologic and intervention studies. These data establish beyond any reasonable doubt the close relationship between elevated blood cholesterol levels and CHD."[1845]

Of course, the primary implication of that passage is that an incorrect diet is the cause of elevated cholesterol levels and thus CHD. But according to Stamler, the "wealth of congruent results" existed 11 years earlier in 1973, i.e.,

"A vast literature--clinico-pathologic, epidemiologic, and animal-experimental--exists on the relationship between nutrition and atherosclerosis. Extensive evidence is available from epidemiologic research on the significance of habitual diet in the etiology of the 20th century epidemic of coronary disease in the economically advanced countries."[573]

In fact, according to Stamler, there was "massive" evidence in 1966, i.e.,

"What rational basis is there for preventive measures? This question can be answered in full by drawing on massive findings of clinicopathologic, animal-experimental and epidemiologic research."[3019] (In support of this statement, he cited a previous Stamler article.)

In fact, according to Stamler this "extensive evidence" was available 22 years earlier in 1962.

"It has been unequivocally demonstrated that such abnormalities as hypercholesterolemia and hypertension, diabetes, and heavy cigarette smoking are associated with several-fold increases in risk of occurrence of coronary disease in middle-age. In addition, extensive data have been amassed on the contribution of multiple abnormalities to risk. The overwhelming evidence indicates that the disease is multifactorial in causation, with diet as a key essential etiologic factor."[574]

In fact, according to Stamler, the "extensive data," "abundant data" and "overwhelming evidence" were available 28 years earlier in 1956, about the time he initiated his career in epidemiology[694,3201] and before reliable and significant data were available from the Framingham study or similar studies.

"This fundamental metabolic concept of atherosclerosis rests upon an extensive foundation of knowledge. It is documented by abundant data accumulated by the three major investigative approaches to the atherosclerosis problem--the clinico-pathological, the epidemiological and the animal-experimental methods of research."[694]

"The fundamental [metabolic] theory of atherogenesis rests on an extensive foundation of research knowledge. It is documented by abundant data accumulated via the 3 major investigative approaches to unknown diseases processes--the clinico-pathological, epidemiological, and animal experimental research methodologies."[3201]

It is to be noted that Stamler's "extensive" and "abundant data" pointed essentially to a single cause of CHD in 1956. That same data mysteriously pointed to multiple causes only a few years later. In any event, Stamler and other alliance members[a] repetitively attempted to convince the medical community and the public with the use of superlative words, rather than superlative evidence.

An example of Stamler's "extensive" data leading to inappropriate and dangerous conclusions can be seen in a 1963 article. He said, "During the years 1949 to 1952, extensive evidence--clinico-pathologic, animal-experimental and epidemiologic--was accumulated relating extrogens to cholesterol-lipid-lipoprotein metabolism, and suggesting a possible protective effect of these hormones against clinical atherosclerotic coronary heart disease."[1125] He then reported the results of his secondary clinical trial in which 156 men were given estrogens for five years. Stamler maintained that his trial was both randomized and double-blind and that the estrogen treatment resulted in a 50% reduction in mortality as compared to a control group. He concluded that "The positive results of our investigation, with the approximately 50% or greater reduction in five year mortality rate, lead us to recommend mixed conjugated equine estrogens to the medical profession for use in the long-term management of myocardial infarction."

As most knowledgeable researchers know, three other clinical trials using estrogens on male subjects reported either opposite results[490,496] or no effects of the hormones.[496] Two of these trials were published in 1961 and 1962 and the third (Coronary Drug Project) was published in 1975. In the latter case, estrogen treatment was actually terminated long before the trial was scheduled to be completed because of its harmful effects. One can only wonder how many physicians took Stamler's advice and how many of their patients died prematurely because of that advice.

Because Stamler has frequently attempted to produce a treatise on the subject of "congruence" among the various types of studies, it is useful to discuss his argument to illustrate his less than modest grasp of scientific concepts. The following is the essence of his argument.[539]

"It has been argued that the total body of 'indirect' evidence--epidemiologic, clinical, pathologic animal experimental--permit only the formulation of hypotheses concerning man. Only 'direct' experiments, i.e., randomized controlled trials, permit the decisive testing of hypotheses and therefore the arrival at sound scientific conclusions concerning etiology. Based on this approach to the methodology of science, allusions are made, for example, to the diet-heart 'hypothesis,' thereby indicating that any concept of the etiologic role of diet in the causation of the disease is completely conjectural and tentative at this time.

"This reflects a basic misunderstanding of the methodology of science. Were it to prevail, the entire bodies of knowledge acquired in modern times by geology, astronomy and evolutionary biology would have to be classified as hypothesis rather than theory, since they rest almost exclusively on observational, rather

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[a] 376,499,552,980,1000,1094,1136,1276,2288,2433

than experimental, data. It would have to be the hypothesis of gravitation, not the theory of gravitation, the hypothesis of relativity, not the theory of relativity; the hypothesis of evolution, not the theory of evolution. In fact, sound methodology throughout the sciences recognizes the ability to arrive at valid conclusions concerning etiological relationships based on proper assessment of observational data."

"The terms hypothesis and theory both have precise meanings in the language of science. The Random House unabridged dictionary states 'A hypothesis is a conjecture put fourth as a possible explanation of certain phenomena or relations, which serves as a basis of argument or experimentation by which to reach the truth'; and 'A theory properly is a more or less verified or established explanation accounting for a known fact or phenomenon'."

"Given the vast body of consistent information from many research methodologies on the relationship between lifestyle and atherosclerotic disease, particularly diet and athero disease, it is inappropriate to use the term hypothesis in speaking about the general area of knowledge."

Unfortunately, in his need to impress readers with his apparent understanding of science and its methods, Stamler actually demonstrated almost no understanding whatsoever. First, he essentially classified experiment and observation as mutually exclusive methods of science. All methods of science, including experiment, involve observation and there are many ways to "observe" besides looking at a phenomenon. Experiments merely comprise one way in which observation is used.

Second, the sciences of geology, astronomy and evolution most certainly involve experimental, as well as other, observational techniques.

Third, apparently Stamler did not read his dictionary carefully because a theory is most emphatically neither always nor perhaps most frequently a "verified or established explanation accounting for a known fact or phenomenon." A theory may vary anywhere from totally verified to totally unverified. Although a theory may often contain many proven or unproven postulates or assumptions, it may also be--nothing more than an hypothesis. Moreover, any scientist should know these facts without resorting to a dictionary.

Fourth, in view of the fact that the diet-heart disease relationship was not proven at the time Stamler made the above statements and still is not proven to date, it certainly is appropriate to refer to it as an hypothesis or an unproven theory.

And fifth, the "vast body of consistent information," to which Stamler and his alliance colleagues so often refer, is consistent only by their judgments, not by the judgments of others. As shown throughout Volume 1 and the present volume, almost all animal research is nongeneralizable to humans and is irrelevant. The epidemiological (between population) studies are horrifically confounded with numerous uncontrolled variables and have generated highly spurious correlations based on economic development, i.e., the more developed a nation, the more animal foods it has to consume, the more capable it is to diagnose CHD and record such statistics, and the longer its people live--increasing the likelihood of dying of CHD. The 27 clinical trials (Volume 1) predominantly show no benefits of cholesterol-lowering on CHD and virtually no benefits on total mortality. And the prospective studies show that cholesterol levels cannot predict subsequent CHD development in individuals. Denying the truth of these facts is tantamount to admitting (1) considerable technical ignorance or (2) fraudulent messages to readers.

Throughout his career Stamler has maintained that diet is the primary and essential factor in atherosclerosis and that other risk factors may contribute to the disease but

are not necessary. Yet, he mimicked other alliance members in 1984 saying that a diet-heart trial was not feasible i.e.,

> "It has been determined that a unifactor diet-heart study adequate to provide definitive evidence is not feasible because of considerations of size, duration, adherence, confounding factors, and cost."[1083]

Since it was determined that a unifactor drug-heart study was feasible, it is obvious that Stamler also had no faith in a diet-CHD connection (see Chapter 7 for detailed discussion of the alliance's rationale for rejecting a diet-heart trial).

Stamler's biased reasoning is no better exemplified than in his 1983 article.[3051] In fact, his bias was so blatantly visible, it is difficult to understand why a journal would publish such nonsense. Stamler reported life expectancy at various ages for six countries, including the U.S., in an effort to demonstrate that the U.S. diet is harmful to longevity. Table 10-10 presents the relevant data from his table, i.e., life expectancy at birth, age 35 and age 65. As noted earlier in this volume, if diet affects life expectancy, it would demonstrate its effects the older a person becomes. Obviously, life expectancy at birth depends primarily on infant mortality rates, not something an infant has had little experience with, namely, diet.

Stamler said, "Note that Italian males have better life expectancies than U.S. males at all ages from birth thru age 35." But it is far more important to note that U.S. males had longer life expectancies than Italian males after age 35 and that U.S. females had longer life expectancies at all ages. Stamler then said, "Note that Greek males have much better life expectancies at all ages than U.S. males, in fact, better also than all the other European populations, including the Swedish." It is clear from the table that Swiss men outlive the Greek males at all ages, contrary to Stamler's assertion, and Swedish females also outlive Greek females at all ages as well. Moreover, while the Greek males do outlive U.S. males at all ages, Greek females do not outlive U.S. females. The reader may also be reminded that the Greek diet has a greater percentage of fat than the U.S. diet which is contrary to that recommended by the alliance.

Stamler continued, "Note further that Japanese males at most ages are second only to the Greeks in life expectancy; at birth they are the first in longevity." Again, the table clearly shows that Swiss males, whose diet is hardly vegetarian, greatly outlive Japanese males at all ages, contrary to Stamler's statement. Also, the Japanese males live only 7 months longer at age 65 than U.S. males and the U.S. females live 10 months longer than Japanese females at age 65.

Stamler concluded his incredibly poor analyses of Table 10-10 by saying, "...one thing is clear from these data, they lend no support to the thesis that the U.S. diet is optimal health-wise." It can be said with greater authority that they lend no support to the thesis that the Greek, Italian or Japanese diets are optimal as well. Furthermore, although half of his data were of females, he totally ignored them. Since females consume the same diets as males, and since U.S. females are equal to or superior to all other groups in life expectancy, Stamler's conclusion was simply irrational.

Stamler's reasoning has not only been irrational and premature, it is sometimes simultaneously humorous. For example, in discussing the small difference found between treatment and control groups in the MRFIT trial, Stamler said, "Detailed analyses indicate that this could have occurred by chance, but this is unlikely."[2939] And in 1984 he said,

Table 10-10

Life expectancy at various ages for six countries in 1978
(adapted from Stamler, 1983[3051])

Country	Men (age in years) 0	35	65
USA[a]	69.4	37.7	14.1
Switzerland	78.9	45.3	18.2
Sweden	72.5	39.6	14.3
Italy[b]	69.8	37.8	13.3
Greece	72.9	41.0	15.3
Japan	73.2	40.3	14.7
	Women		
USA[a]	77.3	44.4	18.6
Switzerland	72.0	39.5	14.2
Sweden	79.0	45.3	18.1
Italy[b]	76.1	43.3	16.5
Greece	77.6	44.8	17.5
Japan	78.6	45.0	17.8

[a] 1977 data
[b] 1975 data

"In the late 1950s, several investigative groups in the U.S. concluded that existing evidence warranted the design of controlled trials to assess whether change in diet, particularly lipid modification to lower serum cholesterol, is effective in the primary prevention of coronary heart disease."[2939]

Stamler cited 8 references, all of which were published between 1967 and 1982, 8 to 24 years after the "late 1950s," five of which were authored or co-authored by Stamler himself, a sixth of which was a WHO group, not a U.S. group, and a seventh of which was a National Conference on High Blood Pressure Education, not cholesterol lowering.

In 1981 Stamler boasted pompously that,

"we can be proud--in a healthy nonchauvinistic way--that we in the U.S. have generally given the lead and set the pace in the development of public policy on the primary prevention of CHD."

Had Stamler used the word "ashamed," instead of "proud," that statement would have been much more accurate.

Finally, it is worthwhile noting Stamler's description of the diet employed in his Coronary Prevention Evaluation Program which began in 1958. In 1960 he said the diet was "composed of 40-45 g unsaturated fat (largely from vegetable and fish oils, therefore high in polyunsaturated fatty acids) and 20-15 g saturated fat (low saturated fat)."[376] In 1966 he described the same diet as low in saturated fat but did not mention polyunsaturated fat[3288] and in 1968 he said the same diet was "moderate, not high in polyunsaturated fatty acids."[3287]

William Connor

Probably the most passionate promoter of the dietary cholesterol-blood cholesterol relationship is William Connor. Despite the fact that his early (1961,1964) dietary experiments were badly flawed and confounded (Chapter 5), Connor drew the conclusion that the effects of dietary cholesterol were "profound" and far more important than fatty acids.[321,322,362] In 1978 Connor presented a graph which showed that blood cholesterol increased 8 mg per 100 mg ingested.[1136] The graph was based on one of his experiments and one by Fred Mattson, both of which involved liquid diets.[321,368] Eleven years later in 1989 he presented another graph which showed that blood cholesterol increased 13.3 mg per 100 mg ingested.[1825] This value is three times the amount found in other studies using liquid diets and seven times the amount found in whole foods experiments (Table 5-2, Chapter 5, Volume 1).

As evidence supporting his latest graph Connor stated that "over the past 25 years some 26 separate metabolic experiments involving 196 human subjects and patients have shown decisive effects of dietary cholesterol on human plasma cholesterol..."[1825] However, he referenced only four experiments, two of which were his own and all of which involved liquid diets.[a] The tone of his discussion suggested that he was irritated by the fact that others do not think that dietary cholesterol is important. For example, he said, "...attempts are still being carried out and are highly touted as showing that dietary cholesterol has no effect on plasma cholesterol levels. There is a recent review for those who wish to explore the subject more fully."[1825] That review was hardly recent, having been published 8 years earlier, and it was co-authored by

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[a] 319,321,322,349. Interestingly, Connor omitted one of his studies.[362]

Connor himself.[402] Moreover, that review was so brief and incomplete it simply could not be classified as a review. In one-third of a small journal page it quickly mentioned 14 previous experiments, three of which were his own, 8 of which involved liquid diets (one of which was not even an experiment) and three of which were whole foods studies that found no significant effects of dietary cholesterol.

It is most curious to note that Connor was co-author of one of the 12 free-living studies reviewed in Chapter 5 (Table 5-5).[402] That study yielded a blood cholesterol increase of 4.3 mg per 100 mg ingested, not only the highest of all other studies but 3.5 times the average of the other studies. While such an outcome may be purely coincidental, it is consistent with Connor's highly deviant findings.

Connor's position on cholesterol absorption and synthesis is also contrary to the facts as well as the results of his own experiments. In 1972 he said,

> "The gut absorbs about 40% of the ingested cholesterol. In man, the total input from synthesis seems relatively constant in amount, so that the amount of dietary cholesterol absorbed into the body is superimposed upon the amount of cholesterol synthesized and this is additive."[411,a]

If this statement were true, then the consumption of 400 mg of dietary cholesterol should increase blood cholesterol about 160 mg since "about 40%" is absorbed and added to a constantly synthesized amount. The 160 mg value is about 21 and 9.5 times those actually observed in over 50 whole foods and liquid diet experiments, respectively, a totally preposterous exaggeration.

Incredibly, in another part of the same article Connor contradicted himself by saying that,

> "Four hundred mg dietary cholesterol per day has approximately the same effect on serum cholesterol levels as does 700 mg/day."

If synthesized cholesterol is constant and dietary cholesterol absorption is about 40%, this statement is illogical and, of course, it is totally contrary to the scientific evidence. Furthermore, synthesized cholesterol is highly variable in quantity, the absorption rate of dietary cholesterol is highly variable and the more dietary cholesterol is consumed, the greater the blood cholesterol (Volume 1).

A curious series of statements by Connor and his colleagues in the same article in 1982 are also of interest.[1830] "If dietary linoleic acid is at the level of 4 to 8% of the total calories, there is little indication that increasing it further would result in significant health benefits." Then, after discussing possible harmful effects of dietary linoleic acids, they said "...the expected benefits of modest increases of dietary polyunsaturated fat would far outweigh the possible risks outlined above." This statement was then followed by, "While linoleic acid intakes of up to 10% of the total calories would not be considered dangerous or even deleterious, only slight effects upon plasma lipid levels and platelet function may be expected.

In 1982 Connor[1830] stated that,

> "Clearly, use of fish oil supplements to substantially increase the intake of W-3 fatty acids (particularly eicosapentaenoic acid) would not be indicated at the present time except under experimental conditions."

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[a] Connor repeated much of this statement under oath at the FTC-NCEN trial in 1975.[2436]

But at a 1987 teleconference sponsored by a fish oil-producing drug company Connor[1179] advocated the consumption of fish oils. And in 1989 Connor[1920] was cited as saying,

> "We now have strong evidence relating omega-3s to a decreased incidence of coronary heart disease."

One year later the FDA banned the sale of fish oil supplements on the grounds that "At the present time, there is inadequate scientific evidence to support health claims on fish oils or to support claims that these ingredients have an effect on the risk of coronary heart disease."[2555] But making unsupported statements is routine for Connor. He once indicated that dietary cholesterol was the important nutrient in influencing blood cholesterol, not fat type and when he finally recognized that he was wrong, he advocated a diet high in polyunsaturated fat.[411] He eventually dropped that recommendation.

Daniel Steinberg

In 1962 Daniel Steinberg[3037] maintained that "About 50% of the men in the U.S.A will die of ischemic heart disease." Of course, that figure was almost twice the actual rate.

In 1970 Steinberg was the chairman of AHA's Council on Arteriosclerosis and a former staff member of NIH. (He would later become chairman of the 1984 Cholesterol Consensus Conference Panel.) He summarized the progress that had been made in an article in Circulation as follows (this writer's comments are inserted to provide "closure" of issues):[2727]

> "Over the past 25 years we have seen the amassing of the incontrovertible epidemiologic evidence from prospective studies as well as from retrospective studies that there is a very real association between blood cholesterol and atherosclerosis [although it is weak and nonexistent at the individual level]. We still don't fully understand [meaning = no understanding at all] the role of free fatty acids in atherosclerosis, but there is some reason [what reason?] to believe that they may [may!] contribute to hyperlipoprotenemia, that they may [may!] precipitate in travascular thrombosis, and they may [may!] even have a primary role in atherogenesis." [All of the above translates thusly: There is a weak relationship between blood cholesterol and atherosclerosis in groups but we have not obtained direct scientific evidence during the last 25 years with respect to the relation between free fatty acids and atherosclerosis or to the genesis of atherosclerosis in general.]
>
> "Today, the practitioner has a growing armamentarium of drugs that affect lipid metabolism. We hope to have an answer in the course of the next few years from the National Heart Institute--sponsored Coronary Drug Project as to whether the 4 drugs under study will prevent CHD." [The answer is that none of the drugs used reduced CHD during the trial,[490] two of the drugs--dextrothyroxine and estrogen--proved dangerous during the trial, a third drug--clofibrate--developed a world-wide history of dangerous side effects, i.e., cancer, heart attacks, gallstones, etc., and a fourth drug--nicotinic acid--produces numerous unpleasant side effects and possibly dangerous liver dysfunctions.]
>
> "The amount of cholesterol in the diet was at first not thought to make any difference and there was a prevailing dogma to that effect. It remained for Connor and Beveridge and others to establish that cholesterol does count." [As noted in Volume 1, the Connor[321,322,362] and Beveridge[349,356] studies employed

liquid formula diets which are known to yield results quite different from whole foods diets. Moreover, all of Connor's studies were poorly designed and produced confounded results. Even so, the Beveridge studies did not demonstrate much effect of dietary cholesterol, i.e., 2.7 mg/100 mg ingested in one study using up to 634 mg and 1.5 mg/100 mg ingested using amounts in excess of 800 mg.]

Steinberg briefly discussed experiments showing the differential effects of saturated and polyunsaturated fats and then continued,

> "All of these basic nutritional studies led up to the National Diet-Heart Feasibility study [which lowered blood cholesterol a greater extent than did cholestyramine in the LRC trial but found no effects], and should lead us soon to definitive primary prevention trials if the government lets us go ahead [The MRFIT[474] trial which failed to demonstrate benefits of simultaneously reducing blood cholesterol,smoking and high blood pressure and the LRC trial[500] which yielded trivial benefits of cholesterol lowering].

Meanwhile, we have the already very convincing, although not fully definitive results, of the studies of the New York Anti-Coronary Club [which was so bad, even William Castelli would later refer to it as "bad science"], of Leren and of Turpeinen in Scandinavia [In Volume 1 this writer wrote of the Turpeinen mental hospital trial, "such a poorly designed study it is astounding that it was ever conceived, let alone conducted." The trial was also severely criticized by NHLBI staff.[431] The Leren trial[480] was unblinded and therefore suspect.], of Dayton and Pearce in Los Angeles [yielding nonsignificant findings]. It is now good medical practice to treat--and I use the word advisedly--people who have definite hyperlipoproteinemia. In short, we have come in 25 years to the point where we are probably [probably!] preventing a disease that was considered to be an inevitable accompaniment of age not very long ago."

If Steinberg maintained even a modicum of objectivity during the preparation of his article, he could not possibly have come to the conclusion that "it is now good medical practice to treat...hyperlipoproteinemia." It is noteworthy, however, that he qualified his last sentence with the word "probably," indicating a significant degree of uncertainty.

While the above 1970 paper focused exclusively on blood cholesterol and diet, Steinberg's[2943] 1979 article indicated that,

> "...there is reason to believe that there is more than one cause of atherosclerosis... Atherosclerosis is, in fact, a disease of multiple interactive etiologies, and prevention may well require intervention along different lines."

It is interesting that Steinberg first said that "there is reason to believe" and then indicated emphatically that it was an established "fact" that atherosclerosis was a multifactorial disease. It is also interesting that he cited a 1962 article authored by himself as the source for the established fact. Steinberg then cited two articles by fellow AHA member Jeremiah Stamler as "documenting" and "discussing in detail" the risk factors in atherosclerosis.

Steinberg noted that the CHD mortality rate was on the decline "for reasons still uncertain." And while his AHA organization recommended in 1961 and continued to recommend in 1979 that Americans change their diets to lower blood cholesterol, Steinberg stated that

> "The question of whether correction of hyperlipidemia reduces risk is controversial."

He again cited the Veteran's trial and the two unblinded Scandinavian trials as evidence that,

> "...'the lipid hypothesis' is not without support from direct experimental testing in clinical trials."

Of course, if Steinberg could evaluate trials adequately, he would not have drawn such a conclusion.

Most interestingly, Steinberg described a case of familial hypercholesterolemia as the "best example of regression of atherogenesis in man" when, in fact, it appeared to be an excellent example of regression of what Stehbens called "lipid storage disease." Steinberg said,

> "Perhaps the best example of regression of atherogenesis in man is the child with homozygous familial hypercholesterolemia on whom Starzl and co-workers performed a portacaval shunt. Plasma cholesterol levels fell from over 800 to below 400. During the following year, skin xanthomata regressed almost completely and angina disappeared. The pressure drop across the aortic valve fell from 56 mm Hg to 10 mm Hg. Coronary angiography preoperatively showed extensive diffuse narrowing in the major vessels and the circumflex artery was not even visualized. A year later all three large vessels were visualized and there remained only three discrete areas of focal narrowing."

Clinical trials using angiography to evaluate the effects of blood cholesterol-lowering on artery narrowing, particularly those after Steinberg's 1979 article, have reported questionable evidence of regression and, in any event, the regression was slight and not seen in the majority of subjects. Moreover, as noted in Chapter 7 authors have reported no correlations between extent of cholesterol-lowering and degree of regression, in case Steinberg would argue that the boy's cholesterol was lowered much more than has been the case in clinical trials. Also, Steinberg emphasized that the "death rate from coronary heart disease is decreasing nationwide." Since no alliance member would suggest that blood cholesterol has decreased more than 10 to 15 mg in the population, such an argument by Steinberg would again be unsupported.

In a 1983 report, Steinberg[2944] cited a statement by G. Lyman Duff in a 1951 article.

> "So popular has this view [the lipid hypothesis] become that the casual reader of recent literature might wonder whether some authors conceive of an atherosclerosis so independent of the substratum of the vessel wall that it may occur in the absence of the blood vessels themselves."

He then went on to say that,

> "I hope that I am not one of those authors, but you can see that I would have felt uncomfortable presenting a Duff lecture in which the cells of the artery wall do not make an appearance. I am relieved to be able to assure you that they will appear."

Thus, it appears that Steinberg completely missed Duff's point. Duff did not suggest that the knowledgeable reader would conceive of an atherosclerosis independent of the vessel wall, based on the writings of lipid hypothesis enthusiasts. Rather, he was emphasizing that the enthusiasm exhibited for the hypothesis was far greater than the data would suggest, a description that most certainly characterized Steinberg.

In 1989 Steinberg[2700] published a similar but lengthier article that was glib, naive, arrogant and gloating. It was entitled, "The Cholesterol Controversy is over: why did it take so long?" Some excerpts follow:

> "The history of medicine is replete with examples of stout resistance to change. ...conservatism may cost lives by delaying the transfer to practice of interventions that could be life saving. My thesis is that there was such a delay in recognizing the importance of hypercholesterolemia and its management. ...there continued to be a great deal of resistance well after the cause-and-effect relation should have been evident. Even before clinical intervention studies provided the conclusive evidence, the cause-and-effect relation should have been easily read from the wealth of evidence at the biochemical, pathologic, epidemiologic, and clinical levels. Today the controversy is over [only because the alliance says it is over]. The [1984 Consensus] Conference panel, which I was privileged to chair, concluded unanimously that there was a cause-and-effect relation between hypercholesterolemia and CHD risk" [because the panel was selected by NHLBI who agreed with that thesis and because the panel was directed a priori to adopt that thesis in its report].

Although he mentioned no names, the "resistance" referred to by Steinberg was primarily that of NHLBI which represented the monetary and power base for atherosclerotic research. Other researchers who disagreed with the AHA obviously had no real impact on NHLBI's ultimate decision to join AHA's crusade. As to the cause-and-effect relation, Steinberg knows very well that the relation has been established only by the collective judgments of AHA and NHLBI members via the 1984 Consensus Conference; it has never been established scientifically. Moreover, Steinberg knows (or should know) that the blood cholesterol distributions of CHD and nonCHD subjects overlap almost completely, indicating, at most, that high blood cholesterol is only important to a relatively few.[a] If the higher the cholesterol, the higher the CHD, why does that relation not occur with the vast majority of people? Why has the Japanese CHD mortality rate declined during the last 20 years while the nation's cholesterol level climbed upward? Why does France have an extremely low CHD mortality rate, while having higher cholesterol levels than Americans? There are so many exceptions to Steinberg's rule that it is utterly foolish to speak of cause-and-effect relations.

Indeed, the history of medicine <u>is</u> replete with examples of stout resistance to change. The AHA is perhaps the best example in the entire history of medicine, adhering relentlessly to its dogma since 1961 in the face of a mountainous accumulation of negative findings. It succeeded because of its enormous power, not because of definitive and conclusive evidence.

Steinberg continued,

> "Once it became evident that the fatty streak was the precursor of many (or perhaps most) of the advanced lesions, it was easier to become interested in lipoproteins. In fact, we now know that lipoproteins can account for fatty streak formation independent of any loss of endothelial cells and that a high low-density lipoprotein (LDL) level may [may!] itself be sufficient to lead to a fatty streak [cites himself].

In addition to the fact that this statement demonstrates considerable uncertainty, its relevance is highly questionable. As shown in the International Atherosclerosis Project

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[a] And as discussed elsewhere in this volume, this importance may not be related to atherosclerosis per se but rather to Stehben's concept of "lipid storage disease."

by Tejada et al.,[2436] fatty streaks and raised lesions were found in 15-24 year-olds in all of the 19 populations studied. To repeat a statement from Chapter 8, Holman and his colleagues emphasized that "practically everyone beyond the age of 3 years has shown some degree of fatty streak of the aorta. It is difficult to believe that each of these persons has consumed too many calories, too much fat, too little protein, too much or too little animal fats or too much or too little unsaturated fat or they each has had hypertension or some other disturbance [hypercholesterolemia] that could have left scattered 'scars' in the arterial wall that predisposed to differential filtration."[2171] Furthermore, whether or not LDL may be involved in the development of the lesion, it does not necessarily follow that concentration level is important.

Steinberg went on to say,

> "Today I think [think!] we can all agree that atherosclerosis is a disease of multiple causality. In fact, it almost [almost!] certainly is not a single disease but more likely [likely!] a group of different (albeit related) diseases. [In effect, this statement really means that we can all agree to speculate that atherosclerosis is a group of diseases because there is no supportive scientific evidence.] The same end results--the atheroma--may [may!] stem from more than one initiating factor and be reached via different but probably [probably!] interacting pathways. In some patients hypercholesterolemia may [may!] indeed be the dominant cause; in others, for example, the Japanese with their very high incidence of cerebral atherosclerosis, hypertension may [may!] be the dominant cause; in still others, cigarette smoking may [may!] be the dominant cause (via mechanisms yet to be elucidated). [This entire paragraph is completely speculative and without a shred of scientific evidence.]

Steinberg said,

> "Within-country studies, including the Framingham study in the U.S., have often failed to demonstrate a significant correlation, although correlations are there to be found if looked for carefully" [cited Stamler and Shekelle article of 1988].

This implies two things. First, the Framingham investigators and almost all other within population researchers apparently were not "careful," according to Steinberg, and, second, Stamler and Shekelle's "careful" study was the relating of dietary data obtained in a one-hour interview to CHD mortality 19 years later, under the grossly naive and proven to be untenable assumptions that (1) nutrients and their quantities were accurately recorded in an interview, and (2) the individuals' diets remained constant for 19 years. (See Chapter 4 for a detailed critique of this study.)

Steinberg suggested that within population studies are not very important anyway because

> "The primary hypothesis is that risk is related to the plasma cholesterol level. Failure to find a good correlation between dietary composition and risk does not necessarily disprove the underlying hypothesis."

While this argument is, of course, valid, it must be continuously stressed that the lipid hypothesis is weakly supported by group data and not at all supported by individual data. Furthermore, the primary emphasis of the alliance's NCEP is to change everyone's diet, so it would seem to be a great deal more important to scientifically relate dietary composition with CHD risk than is apparent in Steinberg's philosophy. Also, it is interesting that Steinberg still refers to the "lipid hypothesis" since he earlier stated that the cause-and-effect relationship between cholesterol and CHD was firmly established.

Steinberg continued,

> "...the lipid hypothesis makes no sense at all if you accept the 95th percentile definition of normal...[because]...50% of the population is dying of CHD! Undoubtedly, then, many rejected the lipid hypothesis because so many patients were dying of CHD despite perfectly normal cholesterol levels."

It is amazing that Steinberg would emphatically (exclamation point) state that 50% of the population is dying of CHD when the figure is closer to 25%. Moreover, about half of this percentage comprises women who are generally quite elderly and, of the remaining 12.5%, most involve men beyond the age of 65 years.

Steinberg then went to to present highly misleading information by omitting the most crucial data.

> "Japanese plasma cholesterol levels are notably lower than those in the United States, as is CHD mortality, but both are higher in Japanese who have migrated to Hawaii and even more so in Japanese who have migrated to San Francisco. As the migrants acquire new dietary habits, their mean cholesterol levels go up and so do their death rates from CHD. Clearly, this is not genetic but environmental; probably [probably!] the major difference is the diet. Even this rather powerful epidemiologic lesson was not fully internalized by our profession at first."

Steinberg's logic is strikingly devoid of rational thought. Diet was <u>not</u> the only variable that differed between the three groups. Perhaps a dozen other variables were uncontrolled, including different medical systems, diagnostic capabilities and fashions. Vastly more important, as described in considerable detail in Chapter 4, the Japanese diet has greatly increased in fat, saturated fat and cholesterol during the last 20 years and yet the CHD mortality has declined during that same period. These trend data <u>in Japan</u> are opposite to the lipid hypothesis and completely overwhelm a small between population study with numerous uncontrolled variables. Hopefully, Steinberg will "fully internalize <u>this</u> rather powerful epidemiologic lesson," but it is doubtful because the alliance rejects all negative evidence.

> "If risk changes with shifts in cholesterol level, the MRFIT data predict that a relatively modest 17% drop in cholesterol level could lead to a 40% decrease in coronary death rate for men with cholesterol levels initially in the range of 221-244 mg."

Of course, this statement is absolutely false and it reflects how addicted even alliance members are to the concept of "risk." It is not synonymous with "rate" as Steinberg suggests. Also, a 17% drop in cholesterol level in those with initial cholesterol levels between 221-244 mg is an average of about 39 mg, hardly "modest." If we use Martin et al.'s[525] MRFIT data, we find that a 39 mg drop from an initial level of 230 mg will result in a mortality rate decrease of about 0.3% per six years or an annual rate decrease of 0.05%. Steinberg's 40% decrease is an exaggeration of reality by no less than a factor of 133.

The repetitive statement by Steinberg and many other alliance members that for every 1% drop in blood cholesterol, there is a 2% drop in CHD risk (implying to the population that it is a 2% drop in CHD rate) suggests the following: A man with an initial cholesterol level of 440 mg can be CHD-free with a 50% reduction in his blood cholesterol, resulting in a cholesterol level of 220 mg, which the alliance considers atherogenic. Also, a man with a cholesterol level of 280 can become CHD-free by reducing his cholesterol to 140 mg--and smoke like crazy, have high blood pressure, be obese, etc. If not, then the 2% for 1% "formula" is obviously not correct and the multifactorial explanation of CHD is also not correct.

"...it was commonly believed that diet would reduce cholesterol levels by only a very small percentage and that, therefore, the game was not worth the candle. In retrospect, that was, of course, a misconception. Depending on the starting cholesterol level (and the starting diet), one can expect a drop of 10-20%."

Apparently Steinberg is not familiar with either dietary experiments or vegetarian studies. A 20% decrease in cholesterol from an initial level of 230 mg is 46 mg, a few milligrams shy of that observed as the difference between pure vegetarians and those consuming the typical American diet and between the same individuals who first consume the typical diet and then consume a no animal product vegetarian diet. Is Steinberg so naive to think that the entire American population would be willing to become vegetarians?

In discussing the LRC trial, Steinberg said,

"Not only did the trial achieve significance in terms of CHD mortality..."

Of course, there was no significant difference between treated and untreated groups in either CHD or total mortality in the LRC trial.

Theodore Cooper

Theodore Cooper is not well represented in the relevant literature, having been director of the NHLI in the early 1970s and then moving on to higher political positions during the period in which massive numbers of articles were written on the subject of diet-blood cholesterol-CHD. In fact, Cooper[2688] said in 1975 that he had "very few, if any" publications related to the diet-cholesterol-CHD issue. Nevertheless, in the relatively few relevant articles that this writer was able to find that were written by Cooper, inconsistencies, errors and contradictions were quite evident.

Speaking before the 1971 AHA meeting Cooper said, "Looking at coronary artery disease from 1950 to 1970, one finds that there has been, particularly in the 35-44 year age group, a far from trivial percentage increase in the death rate due to arteriosclerosis of 12.4%." In the first place, the CHD death rate had been declining since 1963 so 1950-1970 was a strange period to discuss increases. In the second place, the increase in the CHD death rate for white males 35-44, which the alliance focuses on almot entirely, was only 6.2%, and the increase among white males 45-54 was only 2.9%. Both of these were quite minor and undoubtedly due to the major ICD change that took place in 1949 (Chapter 3).

Testifying on behalf of the FTC at the 1975 FTC-NCEN trial (Chapter 2), Cooper was asked, "Is there any scientific evidence that eating eggs increases the risk of heart attacks?" Cooper replied, "In my view, there is, particularly in certain-type people, yes." When asked to describe the evidence, Cooper said, "Let me make it clear here, I do not know of studies which purport to say that or have been studied specifically to say eating eggs was the variable against the incidence of heart disease. I didn't mean it in that sense."

Elsewhere a lawyer asked whether it had been scientifically proven if dietary modification can alter the CHD death rate. Cooper responded, "It has not been proven." "...the general conclusion that I would come to is that you can increase blood cholesterol substantially by increasing the intake of cholesterol. (Volume 1 indicated that the increase is about 1.9 mg per 100 mg ingested, averaged over many experiments in which whole foods were consumed.)

Early in his testimony a lawyer asked, "How much cholesterol is in the average egg?" Cooper replied, "40 to 60 mg." A few minutes later the lawyer informed

Cooper that the average egg had about 250 mg cholesterol. Cooper did not react to that correction. When the lawyer asked him how much one egg of 250 mg cholesterol would increase blood cholesterol in the average person Cooper said, "I would think one egg would make a small increase on the average American level in a normal individual." Thus, while he had indicated earlier that "you can increase blood cholesterol substantially by increasing the intake of cholesterol," he subsequently indicated that the addition of 250 mg would have a "small increase."

Most of Cooper's testimony indicated that he believed that diet was strongly related to CHD. When the lawyer pointed out that Denmark had one-half the CHD mortality rate as did the U.S. and yet consumed per capita more calories, more total fat and more saturated, Cooper replied, "I think the explanation is that there are many factors in the genesis of CHD and the potency of any of the factors varies under different conditions." Thus, Cooper used the standard argument in defense of all data that do not support the lipid hypothesis.

Cooper still talked about a CHD epidemic in 1975. He said, "there is one other group or types of studies that have been supported from time to time and these are the effects of exercise on heart disease, as a theory, of the sedentary way of life of the American public being a factor in our great increase in heart disease over the past 20 years." Not only did the CHD death rate begin its decline after 1963, 60% of those 20 years, nearly everyone but Cooper was aware of that fact. Yet, near the end of his testimony he acknowledged that CHD mortality had been declining for at least 8 years.

Speaking before the 1976 Senate Select Committee on Nutrition and Human Needs, Cooper[2186] uttered the following two inconsistent and/or contradictory statements: "Altered nutrition has tremendous potential in curbing CHD"; Changing the diet would lead to a "25% reduction in incidence of CHD"; and "...as a real preventative, I cannot give you a formula which will prevent heart disease by diet." (These statements may be contrasted with his emphatic "NO" answer to the question, "Can you assure Americans that if they alter their diets, they will avoid CHD?," asked at the FTC-NCEN trial.) One can only wonder how Cooper arrived at the rather precise figure of 25% without having some kind of a formula.

Elsewhere, Cooper[2633] indicated that "heart disease...(is)...preventable primarily by changes in individual behavior." This statement can also be contrasted with his emphatic "correct" answer to the question, "Doctor, it is a fact, I think, isn't it, that the cause of atherogenesis is still in this year of our Lord, unknown?," again asked at the FTC-NCEN trial."

As director of NHLBI in the early 1970s Cooper rejected the funding of a large diet-heart trial which nearly everyone recommended, including the AHA (Chapter 7), and replaced it with a cholesterol-lowering drug trial. It would seem that he has since been rewarded for that decision by an appreciative drug industry. He is now chairman of the board of the Upjohn Pharmaceutical Company.

John LaRosa

John LaRosa,[1545] chairman of the AHA's Nutrition Committee, presented "Introductory Remarks" at a symposium in 1988, presumably designed to update NCEP recommendations. In describing key historical events LaRosa initiated his lecture with his one and only accurate statement, namely that the LRC trial results were published in January of 1984. He then went on to say that

> "The publication of the LRC-CPPT results led to the National Institutes of Health Consensus Conference about 18 months later."

Since the Consensus Conference was held in December of 1984, LaRosa was apparently unable to guess the right year. He continued,

> "The Consensus Conference established guidelines for defining hypercholesterolemia by risk group, classified by decade of age..."

Although this statement is debatable, strictly speaking, the discussion below will provide evidence that the conference panel merely regurgitated preconceived guidelines.

LaRosa said,

> "Immediately following the Consensus Conference was the publication of the follow-up of the screened cohort for the Multiple Risk Factor Intervention Trial (MRFIT), involving the more than 300,000 men who had been screened for that trial."

Unless one defines "immediately" as 23 1/2 months later, and it is doubtful that anyone would, LaRosa was grossly in error. The screened cohort follow-up was published on November 28, 1986.[263]

LaRosa indicated that,

> "The important finding of this study was that cholesterol levels above 200 mg were predictive of increased risk of CHD, and the regression line was straighter than had been anticipated."

As indicated elsewhere, 200 mg was nothing more than a point along a continuous curve and did not represent a value beyond which the CHD death uniquely accelerated. As for the "regression line was straighter than had been anticipated," all regression lines are perfectly straight, by definition. Such a remark suggests that LaRosa does not know what a regression line is.

LaRosa then said that,

> "This [screened cohort study] led in turn to the establishment of the National Cholesterol Education Program."

In actuality, the NCEP was formally launched in November of 1985, one year before the screened cohort study was published.

Everyone makes errors but it is difficult to believe that LaRosa made so many gross historical errors inadvertently. There is strong suggestion that they were purposeful.

National Institutes of Health

A March 1990 article in the Medical Tribune observed,[3189]

> "From the fourth floor of National Institutes of Health ((NIH) building number 31, the National Cholesterol Education Program recommended last month that Americans reduce their cholesterol by an average of 10% by holding fat to less than 30% of their total calories. A visit to the six NIH restaurants on the first floor a couple of days later revealed the proof of the pudding: NIH does not practice what it preaches."[3]

Many fatty foods were displayed including a quarterpound cheeseburger having 937 calories, 55% fat and 21% saturated fat.

"Absent were such high-fiber foods as whole-grain breads, brown rice, and even a single serving of fresh fruit."

FOREIGNDEGOOK

Although the U.S. is unquestionably the most prolific producer of gobbledegook, other countries have made significant contributions. Examples from two countries follow.

Australians Dywer and Hetzel[2911] presumably set out to explain the CHD mortality decline in the U.S. in terms of diet and smoking trends. They erroneously used 1968 as the year of the mortality decline when it is well known to have occurred in 1964. They considered a "latent period for effect of 5 years" to be satisfactory and "concluded that the different patterns of CHD mortality...do correlate to some extent with changes in diet and cigarette smoking." However, not only did they use the wrong year for the mortality decline, their discussion was not consistent with their selection of a latent period. For example, they noted that the consumption of butter, milk and cheese, and eggs declined after 1935, 1946 and 1950, respectively, which yielded latent periods of 33, 22 and 18 years (assuming 1968 as the year of decline).

Dwyer and Hetzel indicated that there was a progressive rise in vegetable fat consumption since 1935, again a 38 year latent period. And while virtually all food consumption studies have shown that animal fat consumption has been decreasing for decades, Dwyer and Hetzel claimed that it increased up to 1970. If that were true, and it is not, their latent period for animal fat would be -2 years, (but actually -6 years) which, of course, is absurd.

Dwyer and Hetzel also showed cigarette consumption to decline rather trivially after 1963 and plateau several years later. Not only was there no latent period at all in this case, the cigarette consumption trend did not match at all the strong downward trend of CHD.

Writing for the Canadian Atherosclerosis Society, Simon Rabkin cited the 1986 Martin et al.[525] article on the men screened for the MRFIT and stated that "A study of more than 350,000 men aged 35 to 57 years in the U.S. revealed a continuous gradient of risk without evidence of a threshold serum cholesterol below which the disease would not develop; the relationship persisted for many decades after the initial measurement."[2274] The "many decades" was, of course, actually a 6-year period.

Most U.S. investigators agree that the Prudent diet lowers blood cholesterol about 10% or less.[a] Yet, the director of the lipid clinic at Victoria Hospital in Montreal, Ruth McPherson, told her readers that reducing dietary cholesterol from 500 mg to 250 mg, reducing saturated fat from 14% to 7%, increasing polyunsaturated fat to 10% and increasing complex carbohydrates will reduce blood cholesterol 7%, 15%, 5%, and 7%, respectively, for a total of 34%.[2362] Her dietary changes represent almost exactly the Prudent diet but her bottom line estimate was more than three times that typically observed.

The 1984 Cholesterol Consensus Conference was sponsored and controlled by the government via NHLBI. The 1988 Canadian Cholesterol Consensus Conference, whose chairman was Louis Horlick, was not sponsored or controlled by Canadian government.

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[a] 1066,1071,2200,2330

While the Canadian conference agreed tin large part with the conclusions and recommendations of the American conference, the Ontario Task Force on the Use and Provision of Medical Services did not and the Ontario Medical Association endorsed the Task Force's findings.

Horlick criticized the Task Forced and Ontario Medical Association (which Horlick admitted "includes many of the foremost Canadian experts among its membership") for coming "to a decidedly gloomy and negativistic opinion regarding our ability to influence the clinical course of asymptomatic hypercholesterolemia" and for "promulgating policy for physicians."[2471] Since the Canadian conference conclusions, were also promulgated, apparently Horlick did not believe that conclusions other than those derived from his conference deserved promulgation.

Speaking for the Task Force, Rasaiah suggested that Horlick's Conference Panel was not willing "to appraise the relevant evidence critically" and that the Task Force's "analyses are not 'gloomy' but a realistic prerequisite to policy formulation."[2473] Rasaiah presented a detailed example of how Horlick completely misinterpreted the results from the U.S.'s National Diet Heart study.

A recent British study discussed elsewhere in this volume indicated that giving fish consumption "advice" to a group of subjects led to a 29% reduction in all-cause mortality as compared to a control group, in recovered MI patients over a two-year period. There was no difference between groups in CHD deaths. The 29% reduction in all-cause mortality was the relative difference between groups. In actuality, the absolute difference was only 3%. Additionally, the study was not blinded and there was no evidence presented that "treated" subjects complied fully, partially or not at all with the "advice." Yet, the University of Guelph's Bruce Holub described the study thusly, "In a randomized controlled trial on secondary prevention of myocardial infarction the subjects eating fish at least twice a week had a 29% lower all-cause mortality rate because of a reduced rate of death from ischemic heart disease."[2524,a]

DIET AND CANCER

While cancer per se is not the subject of this review, it has been a topic of interest when related to low blood cholesterol levels and high polyunsaturated fat diets. Moreover, a cursory examination of the epidemiologic literature on cancer reveals a stunning similarity of "evidence" linking fat with cancer to that linking fat with CHD. In fact, the apparent need to link fat with disease is so pervasive, one gets the distinct impression that man would live to be 200 years if only fat were eliminated from the diet. In any event, it was considered useful to demonstrate that the data linking diet with cancer and the scientific reasoning of the epidemiologists who acquire and interpret those data are questionable. We shall first present an example of the hypothesized fat-colon cancer relation.

In November 1990 Walter Willett[2970] published an editorial in the American Journal of Public Health in which he said, "Despite the prominence given to the relation between diet and CHD during the last 40 years, direct evidence is disappointingly meager." He subsequently indicated that "For the last decade, public policy reports have focused on fat as the most important dietary cause of cancer in the U.S.; benefits from fat reduction have been anticipated for cancers of the breast, colon and prostrate. However, as described by Byers, recently accrued data have rendered these relations less rather than more clear." One month later Willett and his colleagues[3089] published a 6-year follow-up of a prospective study of 88,751 nurses aged 34-59 years.

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[a] New York Times columnist Jane Brody also told her readers that the fish advice resulted in a 29% reduction in all-cause mortality.[2526]

They concluded that "These prospective data provide evidence for the hypothesis that a high intake of animal fat increases the risk of colon cancer, and they support existing recommendations to substitute fish and chicken for meats high in fat." Not only does red meat have little more fat than fish and chicken when the outer layer of fat from beef and pork cuts is discarded, which it normally is, the Willett et al. study grossly distorted the effects of fat by using relative risk values rather than rates.

Table 10-11 presents the key data from the Willett et al. study, showing the relative risks and absolute annual colon cancer rates (computed by the present writer) for the quintiles of total, animal and saturated fat consumptions. The difference between quintiles of risk were said to be significant for each fat classification. The relative risk increases from first to fifth quintiles were 100%, 89% and 39%, respectively, for total, animal and saturated fat. The actual annual rate increases, however, were infinitely small by comparison and totally meaningless. The rate increase from the lowest to the highest total fat consumption was a mere 0.011%. The corresponding rate increases for animal and saturated fat were 0.016% and 0.005%, respectively. To more dramatically illustrate the complete triviality of these data, if one transitions from a very low saturated to a very high saturated fat diet, she would increase her annual rate of contracting colon cancer by five-thousandths of one percent. Apparently, however, Willett did not consider this evidence "meager," as he did previous evidence as described in his immediately preceding article.

The reasoning associated with the hypothesized relation between fat and breast cancer is doumbfounding. Schatzkin et al.[2402] cited animal studies and between nations studies as supporting the fat-breast cancer relation. They said that "breast cancer rates vary over more than a five-fold range between...countries with the highest and lowest rates." But examination of their data revealed that the actual rate range was only 1 per 100,000 to 24 per 100,000, 0.02%. Yet, the reported fat intake ranged from 25 g to 160 g per day. If one takes this relationship literally, then a reduction of a huge 50 g of fat per day (nearly half of that in the American diet), would result in a decrease in breast cancer rate of les than one one-hundredths of one percent.

Many authors have recently concluded that within population studies show weak and inconsistent relationships between fat consumption and breast cancer.[2402,2403,2408,2409] Among the more recent studies were the NHANES I survey, the Willett et al. nurses survey, a 30-year study of Navaho Indians and a one-year clinical trial. Some 5,485 women from the NHANES I survey were followed for 10 years. In 1958 Love[2407] reported that there was no statistically significant relationship between fat consumption and breast cancer.

Willett et al.'s[2404] survey of 89,538 nurses over a four year period revealed "no evidence of a positive relation between dietary total or saturated fat, linoleic acid, or cholesterol and the risk of breast cancer." While the range of fat intake among the nurses was only 30% to 45% of calories, Potter[2405] and Willett et al.[2406] stressed the fact that the range encompassed that which is recommended by NHLBI/AHA, as well as the highest consumers of fat in the industrialized world.

Gibbons[2398] followed 5,000 Navaho Indians for 30 years. Although their diets were unusually high in fat and "virtually" without fiber, green and yellow vegetables, Gibbons reported no breast cancer cases whatsoever and, in fact, only a few cases of other cancers.

In 1989 Cousins et al.[2401] published the results of a one-year clincial trial comparing a 23% fat diet with a high fat diet among women who had mammographic dysplasia in at least 50% of breast volume at entry. The low-fat diet resulted in no discernible differences in the extent of displasia.

Table 10-11

Consumption of fat and development of colon cancer
(adapted from Willett et al.[3089])

	Quintile				
	1	2	3	4	5
Total fat (g)	< 58	58-66	67-73	74-81	≥ 82
Relative risk	1.00	2.48	1.88	2.61	2.00
Rate (%)	0.017	0.037	0.027	0.037	0.028
Animal fat (g)	< 39	39-47	48-55	55-64	≥ 65
Relative risk	1.00	1.22	1.27	1.55	1.89
Rate (%)	0.023	0.026	0.026	0.032	0.039
Saturated fat (g)	< 23	23-25	26.28	29-32	≥ 33
Relative risk	1.00	1.09	1.28	1.81	1.39
Rate (%)	0.025	0.025	0.028	0.038	0.030

A raging debate has been in progress for some time concerning the merits of conducting a large clincial trial in which many women would be placed on a very low-fat diet for 10 years. The trial is said to require 13,000 treated women and 19,000 controls and is estimated to cost $130 million.[2399] Although a National Cancer Institute (NCI) pamphlet for consumers maintains that a low-fat diet "may" reduce the risk of breast cancer,[2399] an NCI panel simultaneously concludes that evidence linking fat with breast cancer is too weak to warrant the expenditure of $130 million.[2400] The panel expressed little faith that reducing fat intake from 40% to 20% would reduce the rate of breast cancer.

Of course, the debate is very reminiscent of the controversy surrounding the proposed diet-heart disease trial during the late 1960s and early 1970s. NHLI really did not believe then that a low-fat, low-cholesterol diet would reduce the incidence of CHD (see Chapter 7) and it is quite clear that NCI has no faith now in showing that such a diet will reduce the rate of breast cancer. Yet, NCI will probably continue to encourage American women to reduce their fat intakes. This pattern of reasoning is exemplified in the 1990 comments of Dimitri Trichopoulos.[2566] He said that evidence linking diet and cancer is less compelling than the public and many scientists are given to believe. He emphasized that the overall evidence linking particular nutrients with specific cancers is generally weak. Yet, he nevertheless recommended dietary changes!

The diet-breast cancer issue has recently achieved a level of notoriety that is incomprehensible. In January 1991 NCI's Edward Sondik[3194] said that there has been a "genuine" increase in breast cancer incidence "over the last 30 to 40 years" and "We really don't know what that's due to." Diet was said to be one possible explanation. In the same month Time Magazine[3195] ran a cover story that indicated that breast cancer incidence had increased from about 85 per 100,000 women to about 113 per 100,000, a rise of 33%. The incidence trend was referred to as an "epidemic."

In asking why the incidence rate of breast cancer is increasing, the magazine article ruled out birth control pills, smoking, alcohol, estrogen therapy and food additives as causes because dozens of studies have provided no evidence that they are important. The article also indicated that many researchers believe that high fat diets are the cause but "have little success in obtaining funds" to obtain "conclusive evidence via a clinical trial." Thus, despite the implication of a major epidemic of breast cancer, as dramatically portrayed by Time Magazine, NCI decided once again in December of 1990 not to fund a diet-breast cancer clinical trial, indicating the on-going lack of faith in the diet-breast cancer hypothesis.

More bad news for the fat-cancer promoters was reported in 1991 by Centers for Disease Control researchers.[3410] These investigators had followed 5,454 men and 7,876 women for 17 years after their diets were assessed in the NHANES I survey in 1971-75. No relationships were found between fat intakes and risk of breast, porstate or colon cancers.

Lost in the dust of those who always claim that reported increased incidences of diseases are epidemics, rather than the result of more thorough diagnostic/detection programs, is the rather overwhelming fact that breast cancer mortality has not changed one iota for decades. In 1978 Susan Devesa and Debra Silverman[3072] of NCI published an article in the Journal of the NCI. They said, "Among white females, both the incidence and mortality rates have remained fairly constant over the last 25 years."[a] That period ranged from 1953 to 1978. Yet, they presented breast cancer

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[a] A very slight increase among nonwhites was observable.

mortality rates from 1935 to 1978, a 39-year period in which the rates were as constant as anything could possibly be.

The American Cancer Society publishes "Cancer Statistics," an annual compilation of cancer mortality rates derived from the National Center for Health Statistics from 1930 to 1987. The 1991 pamphlet[3196] shows that breast cancer mortality has been perfectly constant from 1940 to 1986, a period of 46 years. Thus, there is certainly no breast cancer mortality epidemic and there was certainly no incidence epidemic up to 1978. There seems little doubt, therefore, that the publicized incidence epidemic is not much more than an artifact of the recent promotional efforts to encourage all women to have regular mammograms.

To cap the absurdity of the diet-cancer state-of-affairs, a recent study by Prentice and his colleagues,[3197] including Byar of NCI, concluded that reducing fat in the diet reduces estrogen levels which, in turn, reduces risk of breast cancer. Thus, one arm of the National Institutes for Health (NHLBI) encourages the use of estrogen in postmenopausal women to reduce risk of CHD, while another arm (NCI) suggests that a reduction of estrogen reduces risk for breast cancer, which predominantly occurs in older women. By now this writer cannot find this contradiction surprising.

A CLOSING THOUGHT

With the exception of the very small percentage of people who have extremely high blood cholesterol levels (over 350 mg), due to familial hypercholesterolemia, it is medically senseless to be concerned about the cholesterol levels of perhaps 97% to 98% of the population. There is, therefore, only one rational basis for the National Cholesterol Education Program--to create a huge new source of income for physicians, pharmaceutical companies, many food manufacturers and supporting industries. While such professions/industries would vigorously deny it, let us not forget that only they stand to gain from the program, namely $30 to $60 billion per year. Medical, scientific and business ethics have been set aside in the past for considerably smaller sums.

When this volume was completed, approximately 17,000 hours had been devoted to reviewing the literature. In the process many medical articles with little or no direct relevance to the diet-cholesterol-CHD relationship were also read. When it was all over, this writer sat back and pondered the preventive medicine dilemma facing the American people. The alliance instituted the National High Blood Pressure Education Program in the early 1970s using arbitrary systolic and diastolic cut-off points. Supposedly 60 million Americans became potential patients for life.[2259] Using cholesterol cut-off points that were also set arbitrarily, another 60 to 80 million Americans also became potential patients, many of which will be for life as well. Increasing millions of Americans will have their blood pressures and cholesterol levels checked routinely. Large numbers will take one or more antihypertensive drugs and one or more cholesterol-lowering drugs for life. Large numbers will also take one or more drugs for life to relieve the unpleasant and/or dangerous side effects of antihypertensive and cholesterol-lowering drugs. And millions of "patients" will purchase higher priced "low fat, and low cholesterol" foods for life. And because genetics plays a major role in establishing blood pressures and cholesterol levels, the reservoir of money will always be replenished by the sons and daughters and the grandsons and granddaughters of current patients.

The domain and cost of preventive medicine is broad and ever expanding. Women routinely consume birth control pills for decades and then are encouraged to take more estrogen pills after menopause for life to supposedly prevent premature CHD. Women are also encouraged to have periodic, expensive mammograms, although they have only a "fair degree of accuracy"[12] and evidence indicates that survival is the same whether

or not mammograms are taken. Virtually everyone is encouraged to have periodic dental x-rays, although rarely is an important cavity undetectable by eye.

This discussion could go on and on but will not. The typical reader is well aware of the trends. While one segment of society encourages Americans to avoid illegal drugs, another segment is dedicated to placing every man, woman and child on one or more legal drugs. The latter segment also promotes more and more use of x-rays for both diagnostic and treatment purposes. There is no such thing as a harmless drug or x-ray. Not only are these and other preventive techniques generating hundreds of billions of dollars, they are also creating diseases. Anyone having even a modicum of knowledge about the ionizing effects of radiation, for example, knows that accumulative doses of radiation can cause cancer, and that cancer will never be traced to any single or series of exposures. Similarly educated physicians know that some cholesterol-lowering drugs will eventually result in many patients undergoing surgery for gallstones.

This writer is most certainly not against the use per se of prescription drugs or potentially harmful diagnostic techniques. They are clearly valuable when used judiciously. However, greed and perhaps ignorance are leading to massive overuse and harm--a state-of-affairs quite inconsistent with the Hippocratic Oath.

Preventive medicine espoused by NHLBI is in reality continuous and costly treatment for life with a return of little or no benefits. There is evidence that witch doctors were technologically more advanced. If NHLBI and AHA had spearheaded a program to advance mathematics, rather than CHD research, 2 plus 2 would surely be something other than 4 today.

As NHLBI director in 1979 Robert Levy[2977] asserted, "The NHLBI is responsible for providing leadership, coordination and direction for a national research program aimed at the diseases of the heart, blood vessels, lungs and blood." History will eventually demonstrate that such leadership led to the enormous expenditures of public monies and little tangible progress toward the prevention or cure of atherosclerosis.

POSTSCRIPT

When this volume was being prepared for printing a review of this writer's lay book, The Cholesterol Conspiracy, appeared in the New England Journal of Medicine (October 24, 1991). The following is that review:

"THE CHOLESTEROL CONSPIRACY"
By Russell L. Smith, with Edward R. Pinckney. 389 pp. St. Louis, Warren H. Green, 1991. $37.50[a]

> "This book argues that American physicians have been duped by greedy drug companies and a misguided research establishment into believing that high levels of cholesterol are dangerous and require treatment. The American public is now suffering the consequences of this enormous hoax by having their diets unnecessarily modified, and many citizens are being subjected to unpleasant and dangerous treatments to lower their serum cholesterol levels. Are conspiratorial forces at work? The authors of this book would have readers believe that greed and subterfuge are behind the national preoccupation with cholesterol, and they go so far as to describe it as deception on a Hitlerian scale.

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[a] The publisher assured me that the price was $27.75.

"The reader is initially struck by the lengths to which the book goes in an attempt to authenticate its position. The appendixes and references make up more than 60 percent of the book's 375 pages. If the scholarly quality of a manuscript were a function of the number of references this would be a masterpiece (it contains more than 2500). In reality, it is only slightly more preposterous than tedious. However, it is an interesting book to read if one is looking for examples of how to apply quotations out of context (see appendix 17); misrepresent and misinterpret scientific data (see chapter 6); and introduce unsubstantiated, and potentially libelous, claims of conflict of interest (see chapter 3).

"Over the past four decades, we have learned a great deal about cholesterol and the part it plays in the pathogenesis of one of the most common causes of morbidity and mortality in this society at the present time. Undoubtedly, the treatment of hypercholesterolemia is warranted in patients who are at high risk and in people with familial histories of premature coronary disease. Many unsolved mysteries persist in this field, as pointed out by the authors of this book. For instance, can dietary modification really prevent the development of coronary artery disease in a given patient? What is the meaning of the failure to lower overall mortality in clinical studies such as the Lipid Research Clinics Trial and the Helsinki Heart Study, even though mortality from coronary disease decreased significantly? As physicians, we have an obligation to maintain a rigorous perspective in our approach to the prevention and treatment of coronary artery disease, and we can all benefit from a thorough and ongoing reexamination of the data on cholesterol.

"Unfortunately, this book, which is laced with paranoia and hearsay, does not contribute to this process."

DOUGLAS E. VAUGHAN, M.D.
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This writer submitted a letter to the Editor of the Journal rebutting the review. Since it is not known whether the journal will exercise fairness and publish the letter, a rebuttal is presented here.

Vaughan accused me of "applying quotations out of context." There is, of course, nothing wrong in publishing quotes out of context, providing that one does not alter the author's meaning. I did not alter authors' meanings and Vaughan presented no evidence that I did.

Vaughan accused me of misrepresenting and misinterpreting scientific data but he again cited not a single example of scientific data that I misrepresented or misinterpreted.

Vaughan accused me of introducing "unsubstantiated, and potentially libelous, claims of conflict of interest" and again offered not a single example as evidence. Moreover, while being impressed with the number of references, he nevertheless ignored them and erroneously stated that my claims were unsubstantiated.

Vaughan referred to the book as "slightly more preposterous than tedious but, you guessed it, again provided no basis for such meaningless descriptors.

Vaughan also said the book was "laced with paranoia and hearsay." In addition to the fact that he apparently does not know what the word "paranoia" really means, the content of the book is precisely opposite to hearsay, being prolifically referenced to the scientific literature.

In point of fact, Vaughan's criticisms of this writer's book best describe his own review--unsubstantiated, unsupported and unscientific nonsense that should not have been published in a journal purporting to be scientific. It is the perfect example of how the alliance operates. It criticizes others of the very things that it does routinely and it is seemingly unable to perceive its own hypocritical behavior.

Is Vaughan even capable of critiquing an in-depth book on this subject? Probably not, as exemplified in his statement that "mortality from coronary disease decreased significantly" in the Lipid Research Clinics and the Helsinki trials. If Vaughan is not knowledgeable of the basic findings from two of the most publicized studies in the last 40 years, how can we believe that he is knowledgeable of the many hundreds of lessor known studies? We cannot!

The primary contention of the book is that diet is not related to CHD for at least the vast majority of people. Although Vaughan called the book "preposterous," he nevertheless offered a statement that did not deny that contention. He said, "Many unsolved mysteries persist in this field, as pointed out by the authors of this book. For instance, can dietary modification really prevent the development of coronary artery disease in a given patient?"

Vaughan indicated that "Over the past four decades, we have learned a great deal about...the part it [cholesterol] plays in the pathogenesis" of atherosclerosis. It is impossible to understand how Vaughan and others can so blindly accept cholesterol as atherogenic when virtually every study shows that the relationship between cholesterol and CHD is extremely weak and that cholesterol level is far less capable of predicting who will and will not die of CHD than the simple act of guessing.

Finally, Vaughan stated that "As physicians, we have an obligation to maintain a vigorous perspective in our approach to the prevention and treatment of coronary artery disease, and we can all benefit from a thorough and ongoing reexamination of the data on cholesterol." But his blanket condemnation of The Cholesterol Conspiracy demonstrated that he is incapable of benefitting from a thorough and ongoing reexamination of the data on cholesterol because his mind is already closed. He pretends to be open-minded but has no intention of practicing what he preaches.

The actual letter submitted to the journal was shorter than the above rebuttal, conforming to the journal's requirements, i.e.,

"The the Editor: In his review of my book. The Cholesterol Conspiracy (Oct. 24), Douglas Vaughan accused me of "applying quotations out of context," "misrepresenting and misinterpreting scientific data," etc. The book was also said to be "Laced with paranoia and heresay." Since Vaughan provided not a single verifiable datum to prove I committed these heinous writing crimes, his meaningless diatribe does not belong in a scientific journal. Calling my book "preposterous," he admitted that the relation between diet and coronary disease is an "unsolved mystery," thus supporting the main contention of the book.

While stating "we can all benefit from a thorough and ongoing examination of the data on cholesterol," Vaughan revealed that he has no interest in data unsupportive of the lipid hypothesis. For example, it is well known that blood cholesterol has a very weak mathematical relation with coronary disease.[1] in 1964 Kannell et al.[2] admitted that "diagnosis of overt heart disease on the basis of lipid level alone is simply not feasible," and Castelli and Anderson[3] were even more explict in 1986, i.e. "obviously,

the total cholesterol value cannot accurately predict which patients have a lipid problem when the cholesterol levels are between...150 and 250 mg." When unique subsets of patients are excluded (e.g., familial hypercholesterolemics) the weak relation effectively dissolves.[4] In reality, we can guess with far greater accuracy (25%) than we can predict with cholesterol level (≤ 9%) who will die of the disease.

Well known pathologists (e.g. Duff,[5,6] Watanabe et al.[7] Stehbens[8-13]) have clearly shown that diet-induced and familial hypercholesterolemia-induced disease in animals and humans, respectively, are not conventional atherosclerosis. Thus, the primary population subset noted above is not even relevant insofar as conventional atherosclerosis is concerned. Moreoever, autopsy and unconfounded prospective studies show no differences in atherosclerosis severity and coronary mortality rate, respectively, between vegetarians and nonvegetarians,[14,15] and many other autopsy studies have shown zero to weak correlations between atherosclerosis severity and cholesterol level[16-31] or fat or cholesterol intakes.[32,33]

Although low-density lipoprotein is commonly called the atherogenic lipoprotein, why are correlations, or figures showing the relation, between that lipoprotein and coronary disease rate conspicuously absent in 40 years of Framingham reports?

The routine ignoring of hundreds of critical studies was the reason I wrote 2 large scieintific volumes (1,400+ pages, 3,400+ references)[34,35] and their derivative, The Cholesterol Conspiracy. Vaughan's perception of my book as "tedious" and "preposterous" reflects his rejection of data that disturbs his evangelistic faith in the lipid hypothesis. He is memerized by the "risk factor" concept, oblivious of its fundamental weaknesses, a fact even Kannel et al. admitted only several years ago.[36,37] Measuring everyone's cholesterol and treating the many millions whose levels are over 200 mg will reduce morbidity and mortality like a wingless 747 will fly. Finally. I would suggest that Vaughan consult a dictonary before accusing his next victim of paranoia and reread the lipid research clinics and Helsinki trial reports. They did not show a significant decrease in coronary disease mortality as he stated.

Russell L. Smith, Ph.D.
Vector Enterprises
Sherman Oaks, CA

The New England Journal of Medicine published a scathing and unsupported attack on The Cholesterol Conspiracy. We will now see if this Journal has the scientific fairness and ethics to publish my reply.

Finally, a letter from Howard Wayne[3426] pertaining to the misuse of angiography in the assessment of atherosclerosis development over time was received too late to be intergrated within Chapter 6 but is noted here because of its importance. He emphasized that a major reason why angiograms are inappropriate for such usage is that "we now know that remodeling of an artery occurs after it becomes partially obstructed. The lumen actually increases in size so that the obstruction appears to be, and actually is, proportionally less. But this is a naturally occurring phenomenon and has nothing to do with diet or drug treatment." Thus, any amount of arterial dilation must necessarily confound serial measurements.