Wendy Nielsen

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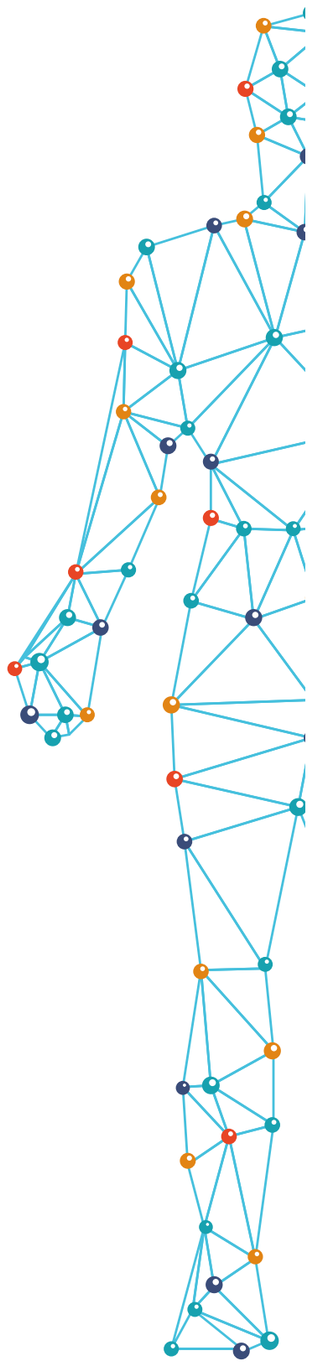
CANCER, CARBS AND CONTROVERSY

Thomas Seyfried, Dr. Eugene Fine explain how cancer is affected by sugar, insulin and inflammation.

BY BRITTNEY SALINE



Accounts of deadly tumors date as far back as 3,000 B.C. in ancient Egypt.

Yet despite centuries of study, cancer is—after cardiovascular disease—the world's second-leading cause of death, claiming more than 8 million lives in 2012 alone, a number that's expected to nearly double over the next 20 years.

Prevailing theories of most researchers and oncologists today dictate that cancer is thought of predominantly as a genetic disease, whereby damage to a cell's nuclear DNA turns the healthy cell into a cancerous one.

But what if we've only been studying a piece of the puzzle for all these years? What if cancer is just as much about what we put into our bodies as the genes we were born with?

Genetic or Metabolic?

Thomas Seyfried, a Boston College biology professor with a doctorate in genetics and biochemistry, disagrees with the idea that cancer is primarily a genetic disease.

"That's all misinformation," said the author of the 2012 book "Cancer as a Metabolic Disease."

It's not that cancer cells don't have mutations, he said. It's that—with a few exceptions—those mutations are not the cause of the disease but rather the effect, the result of damage to a cell's mitochondria, the "powerhouse" responsible for converting energy from nutrients into adenosine-5'-triphosphate (ATP) through cellular respiration.

What's causing the damage? In rare instances, Seyfried said, it can be genetic. However, he said mitochondrial damage is typically the result of environmental factors such as carcinogens, radiation and inflammation. While inflammation can be the result of things such as wounds or bacterial infections, it's also the consequence of repeated spikes in blood sugar driven by excess sugar and carbohydrate intake.

"What sugar will do is cause imbalances in metabolic hormones leading to systemic inflammation, and it's the systemic inflammation that is linked to higher risk for cancer," he said.

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Dominic D'Agostino agreed. He's a research partner of Seyfried's and an assistant professor in the Department of Molecular Pharmacology and Physiology at the University of South Florida.

"Carbs in and of themselves are not dangerous, per se, but when they're consumed in excess, especially over time, they contribute to more inflammation," D'Agostino said. "With chronic inflammation ... you're gradually damaging the mitochondria in the (organ) and preventing the (organ's) ability to use the mitochondria efficiently."

Once damaged, the mitochondria produce reactive oxygen species (ROS), cytotoxins that damage proteins, lipids and DNA in cells, causing mutations and setting carcinogenesis—cancer formation—in motion.

"So now we're getting something coming out of the damaged mitochondria that's facilitating further damage to the mitochondria and causing these mutations that everybody seems to be studying," Seyfried said. "So now what are we studying? We're studying downstream epiphenomena of the damage to the respiration."

Unable to respire, the damaged cells revert to aerobic glycolysis, an oxygen-free fermentation process whereby cells consume enormous amounts of glucose to generate energy for unbridled growth and proliferation, a process dubbed the "Warburg Effect" for its discoverer, biochemist and Nobel Prize winner Otto Warburg.

Mitochondria damaged by inflammation can also trigger the activation of oncogenes, genes that, when activated, cause a normal healthy cell to transform into a cancer cell.

"People say cancer's a thousand diseases, and this is the result of the gene theory," Seyfried said. "But they're all fermenting. They all have the same metabolic malady: They need glucose and glutamine to survive. Whether it's a colon tumor, whether it's a brain tumor, whether it's a breast tumor, they're all the same … if you look at it from the metabolic perspective, you see a singular disease of respiration."

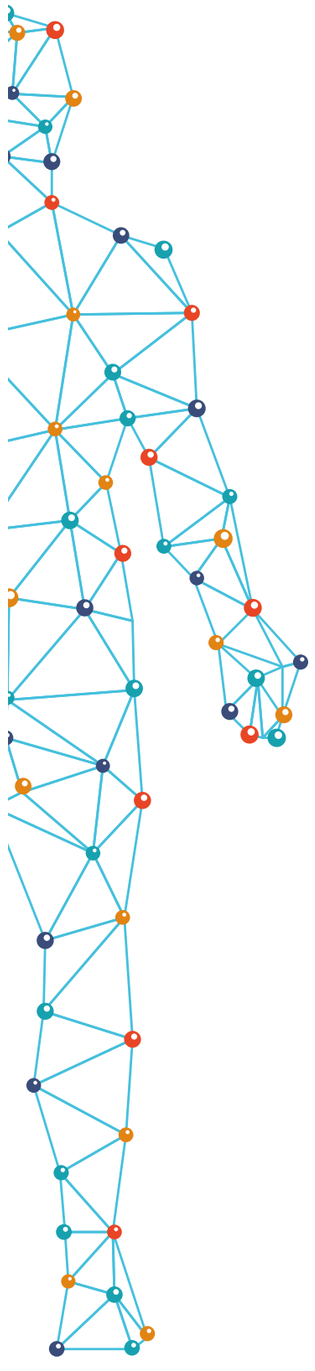
According to Seyfried, science has for decades focused on the symptom, not the cause.

"Why have we not made any major advances in cancer for the last 50 years?" he asked. "Because people are studying downstream epiphenomena. It's not that complicated. When you think (about cancer) as a mitochondrial metabolic disease, most of the complexity goes away."

Weapon of Choice

So how do we fight cancer?

The current standard of care typically calls for surgery, radiation therapy and/or chemotherapy. The problem with the latter two, however, is that while they may stall the disease's progress, the



Dominic D'Agostino

Dr. Eugene Fine

cancer tends to eventually return even stronger than before.

"Radiation causes cancer. Everybody knows this," Seyfried said. "So why do you take a patient and expose him to radiation? All because it kills the tumor cells better than it kills the normal cells. But the normal cells that survive are now put at risk for returning as a form of cancer."

Chemotherapy is well known to create a variety of adverse side effects such as depression, cardiovascular disease and digestive problems, Seyfried said.

"So what we have to ask is, 'Is there another way to treat cancer patients without poisoning and radiating them?'" he said.

According to Seyfried, the solution starts in the kitchen.

"(Cancer) uses glucose and glutamine," he said. "So if you can stop the glucose and glutamine entering into these tissues, the cells will die."

To limit the amount of available glucose and glutamine, Seyfried proposes the ketogentic diet, a "low-carbohydrate, high-fat diet that alters metabolism by increasing the level of ketone bodies in the blood," which has long been accepted by mainstream science and medicine as a safe and effective treatment for epilepsy.

Ketone bodies are an alternative fuel source created when low insulin levels force the body to break down fat for fuel instead of glucose. The human body will, on average, enter a state of ketosis at a carbohydrate intake level of about 50 grams per day, give or take depending on activity level.

The punch line is that while ketone bodies can replace glucose as fuel in healthy cells and even act as neuroprotectors by shielding neurons in the brain from free radicals, most tumor cells cannot use ketone bodies for energy. Ketones can also act as anti-inflammatories.

In 2014, Seyfried and D'Agostino tested the theory on mice inoculated with metastatic cancer. One group of rodents was given a diet of standard rodent chow for 21 days; another, the ketogenic diet. A third group was given the ketogenic diet with ketone ester supplementation, and still another was given the ketogenic diet, ketone supplementation and hyperbaric oxygen therapy. The increase in survival time compared to the control group was 44.6, 65.4 and 103.2 percent, respectively. Seyfried and D'Agostino's work complemented an earlier study in which researchers demonstrated that rodents fed a ketogenic diet with ketone ester supplementation experienced reduced tumor proliferation and increased mean survival time by up to 69 percent.

"So the ketones had changed the metabolic physiology of the animals in a way that prevented the growth and metastasis of the cancer," D'Agostino said.

D'Agostino compared the treatment to weeding a garden.

"The glucose is really like fertilizer to the soil, and you're sprinkling the soil with little pre-cancer cells, which are the seeds," he said.

"If you're on a ketogenic diet, the soil is almost devoid of the nutrients that allow the cancer cells to take root and grow. And in a way, if you produce nutritional ketosis and also lower blood glucose … it's almost like putting an herbicide on the soil that's specific to the cancer cells."

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About Insulin

Dr. Eugene Fine, a clinical professor at Albert Einstein College of Medicine in New York, New York, shares a perspective similar to Seyfried and D'Agostino's. While he, too, believes the ketogenic diet can be instrumental in the fight against cancer, Fine said it's more about inhibiting insulin than reducing blood glucose.

"Cancers are dependent on insulin signaling," he said.

If there are high levels of circulating insulin in the blood, insulin can bind to insulin receptors on cancer-cell membranes, activating signaling molecules that stimulate cell growth and proliferation.

"It sort of locks the cancer into a permanent growth mode," Fine said. "On the other hand, if you reduce the insulin signaling, at least you have the potential to slow the cancer growth somewhat."

High insulin also provokes the release of ROS, which Fine described as "chemical bombs inside of cells" that adipose tissue reacts to by "secreting toxic chemicals into the blood, … which then go around and wreak havoc in other tissues and are associated well as a mechanism of causing mutations in cells, including cancer."

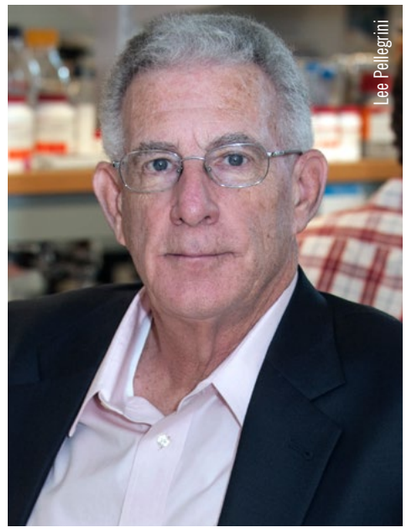
So how are insulin and insulin signaling reduced?

"Insulin secretion is inhibited most simply by restricting carbohydrate (CHO) ingestion, thus decreasing the dietary sources of glucose, the principal secretagogue for pancreatic insulin release," Fine et al. wrote in a 2012 study.

Like Seyfried, Fine also wanted to find an alternative to the standard of care.

"The problem is with all these mutations, you treat adults with toxic cocktails of five different chemical chemotherapeutic agents in order to fail treating them," he said. "What you do is you shrink

Adrienne Scheck



Thomas Seyfried

the tumor for a temporary period of time, but you can't possibly treat all of the variations."

In 2012, Fine conducted a small clinical trial with 10 patients with advanced, incurable cancers that remained progressive even after at least two standard treatment methods. After 28 days of consuming a ketogenic diet, all 10 patients became ketotic, some to greater to degree than others.

"The patients who had the most ketosis were the ones who had either stable disease or partial remission, and the ones who generally had the least amount of ketosis were the ones who had progressive disease," Fine said of the trial's findings. "We have found that ketone bodies directly inhibit cancer growth in all of the cancers that we've measured, and they don't inhibit the growth of control, normal cells."

Fine isn't suggesting we can fight cancer with our forks alone.

"I doubt that that would be the case," he said. "What I imagine is that there can be a role for a ketogenic diet to complement other forms of therapies to produce less toxicity, because if they synergize to produce greater efficacy, then you can reduce the dose of toxic drugs."

> "Perhaps even more important is that if our dietary habits changed in general, these same effects could be preventing cancers to begin with."
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> —Dr. Eugene Fine

Fine continued, speaking of lowering insulin, raising ketones in the blood and combining the ketogenic diet with non-toxic therapies: "So there are three parallel effects, and all of them could be having useful effects on inhibiting cancer growth. And perhaps even more important is that if our dietary habits changed in general, these same effects could be preventing cancers to begin with."

The Church of Gene Theory

So if the ketogenic diet can have such a profound effect on cancer, why aren't more people talking about it?

"It's very hard to change dogma," Seyfried said. "It's a religion. People who are devout in their religion, regardless of what that religion happens to be, how easy is it to change their view? It's impossible. This is what's happened to the cancer field."

But that's not the only reason, according to Seyfried.

"There's a vested interest in not knowing about it," he said. "Don't forget, think of the revenues that are generated from what we're doing today … all of this is sustaining momentum on the part of the pharmaceutical and academic industries. And what happens if someone comes along and says, 'Hey, it's not a genetic disease. It's a mitochondrial metabolic disease,' and you just got a $5 million grant to study the gene mutations in breast cancer? What are you gonna say, 'I'm gonna (give) my money back now'?"

Even if individual researchers are on board, garnering support—ideological and financial—presents a major challenge.

"You have to get funding for the clinical trial, you have to get buy-in from the university or the place that's doing the clinical trial, you gotta get all the oncologists on board, and they have to be enthusiastic about it," D'Agostino said.

And when funding usually comes from drug companies with an eye to supply the magic pill, donations for a diet-based cure are unlikely to come in a flood.

"Who pays for most of these trials?" Seyfried asked. "The pharmaceutical companies. Do you think the pharmacist is gonna step forward and say, 'Let's do a head-to-head, let's do a face-off,' … suppose the other thing works better, and it doesn't cost anything?"

A compromise might be needed to bring a ketogenic-diet-focused approach to cancer treatment into the mainstream, D'Agostino said.

"The first way to get this therapy recognized is to combine it with what's already accepted," he said.

Best of Both Worlds

Adrienne Scheck has been evaluating the combined approach for the last six years. A Barrow Neurological Institute associate professor of neurobiology with a doctorate in biology, Scheck has been studying the effects of the ketogenic diet as an adjuvant to radiation therapy and chemotherapy "because the traditional therapies aren't curing people," she said.

Describing cancer as the "perfect storm" of genetics, aging, and environmental and lifestyle factors, Scheck suggested the ketogenic diet can improve the efficacy of radiation.

"Every time a cancer cell divides, it can actually change its genetics," she said. "So some cells will actually get more sensitive and they'll die, but most of the cells will get changes that allow them to survive therapy … so if you can increase the sensitivity of the tumor cells to radiation, you can kill more of the cells, and if you can kill more of the cells, then you've got a better chance at eventually curing the tumor."

A low-carbohydrate, high-fat diet, she said, can also protect healthy cells from the radiation.

"The ketogenic diet is known to be neuroprotective," Scheck said. "So maybe the ketogenic diet will also help protect the normal brain from any damage that might happen from radiation. If that's the case, then the ketogenic diet might actually be sort of helping from two sides; it might be sensitizing the tumor and actually helping make the normal brain a little more resistant to any long-term damage."

In 2012, Scheck et al. published a study detailing the effects of the ketogenic diet on mice implanted with malignant glioma, brain tumors highly resistant to radiation and chemotherapy and near impossible to completely remove with surgery. The study analyzed four groups of rodents: one fed a standard diet, a second fed a ketogenic diet, a third fed a standard diet alongside radiation treatment, and a fourth fed a ketogenic diet alongside radiation therapy.

Animals fed the ketogenic diet survived longer than those fed a standard diet, and nine out of 11 mice given both the ketogenic diet and radiation therapy were cured of their tumors. Rodents on the standard diet quickly declined after the radiation therapy was completed.

"Thus, we propose that a more than additive and highly positive survival effect is seen through the (ketogenic) diet and adjuvant radiation therapy," the authors wrote.

Currently, Scheck is leading an ongoing human clinical trial combining the ketogenic diet with the traditional standards of care—radiation therapy and chemotherapy. Though it's too soon for conclusions, Scheck spoke positively of the preliminary results.

"It doesn't seem to be hurting (patients') quality of life; it's definitely not hurting any cognitive test that we've done," she said. "So it doesn't seem to be doing anything bad, and some of the patients have done quite well."

Of one patient who has seen significant tumor reduction since beginning the trail, Scheck said, "She's basically back to living a relatively normal life, and she's been doing well for a couple of years now."

Turning the Titanic

The work has just begun.

Though interest in cancer as a metabolic disease and the ketogenic diet as a therapy is growing—Fine has secured support to conduct another clinical trial later this year, over triple the size of the previous—support and funding for large-scale clinical trials continues to be a challenge.

Still, Seyfried maintains that we're on the "cutting edge."

"We have not yet developed the perfect cocktail or scheduling to completely resolve the cancer issue, but can it be done? Absolutely," he said. "This is not an insurmountable problem."

"It's a big ship you have to turn," D'Agostino said. "It's like turning the Titanic, and you have a little tiny rudder. And the little tiny rudder is the voice of people like us."

He continued:

"But we need to acknowledge the data that's out there now: basic science and metabolic physiology telling us that diet is a profound, big hammer for managing this."

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