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Why Glucose Restrictions Are Essential in Treating Cancer

Analysis by Dr. Joseph Mercola Fact Checked | July 31, 2022

STORY AT-A-GLANCE

- All cancer cells, regardless of tissue origin, use fermentation energy for growth. They ferment lactic acid from glucose in the cytoplasm, which also involves succinic acid fermentation using glutamine as a fermentable fuel
- Even when tumor cells appear to be making ATP and taking in oxygen, suggestive of normal respiration, their mitochondria are abnormal; hence, mitochondrial dysfunction is at the root of most cancers
- The true origin of cancer is damage to the respiratory function of your mitochondria, triggering compensatory fermentation, which is run by oncogenes. Oncogenes facilitate the entry of glucose and glutamine into the cell to replace oxidative phosphorylation
- Metastatic cancer cells are hybrid "rogue" macrophage cells — a mix of an immune system cell and a dysregulated stem cell with macrophage characteristics, which allows it to rapidly replicate and spread
- Press-pulse cancer treatment involves restricting the fermentable fuels — glucose and glutamine — in a cyclical fashion to avoid causing damage to the immune system
- A biopsy may not always be a good option as this procedure may actually cause the cancer to spread or turn a potentially benign situation into a malignant one

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Thomas Seyfried, Ph.D., professor in the biology department at Boston College, is a leading expert and researcher in the field of cancer metabolism and nutritional ketosis. His book, "Cancer as a Metabolic Disease: On the Origin, Management and Prevention of Cancer" is a foundational textbook on this topic, and in August 2016, he received the Mercola.com Game Changer Award for his work.

Here, we discuss the mechanisms of cancer and the influence of mitochondrial function, which plays a crucial role in the development and treatment of this disease. His **landmark cancer theory is available as a free PDF**.

Many of his views are now encapsulated in his most paper,[1] "Mitochondrial Substrate-Level Phosphorylation as Energy Source for Glioblastoma: Review and Hypothesis," published online December 27, 2018. He's also published a number of other papers[2,3,4] on the metabolic underpinnings of cancer.

> *"The paper … is a review and hypothesis paper identifying the missing link in Otto Warburg's central theory,"* Seyfried explains. *"[Warburg] defined the origin of cancer very accurately back in the 1920s, '30s, '40s and '50s in his work in Germany. Basically, he argued and provided data showing that all cancer cells, regardless of tissue origin, were fermenters. They fermented lactic acid from glucose as a substrate.*
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> *Even in the presence of oxygen, these cells were fermenting. This is clearly a defect in oxidative phosphorylation. The problem is that for decades, people said Warburg was wrong — mainly because we see a lot of cancer cells take up oxygen and make adenosine triphosphate (ATP) from within the mitochondria … People began to question, 'If cancer cells have normal respiration, why would they want to use glucose as a fermentable fuel?'*
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> *The whole concept became distorted … The cancer cells simply choose to ferment rather than respire. Now, of course, if you look under the electron microscope at majority of cancers, you'll see that the mitochondria are defective in a number of different ways. Their structures are abnormal. The*

numbers are abnormal. There are many abnormalities of mitochondria seen directly under electron microscopy. Clearly, Warburg was not wrong."

Why Biopsies Are Risky

Before we delve into the meat of how cancer actually occurs it would be good to review a diagnostic strategy that nearly all of us are offered when confronted with a cancer diagnosis. It is vital to understand that this may not be your best strategy and that for many it would be wise to avoid the biopsy.

Seyfried warns against doing biopsies, as this procedure may actually cause the cancer to spread. A tumor is basically a group of proliferating cells in a particular part of your body. For purposes of diagnosis, a small biopsy sample will often be taken to ascertain whether the tumor is benign or malignant.

The problem is that when you stab into the cancer microenvironment to remove a part of the tissue, it creates a wound in that microenvironment that in turn elicits the invasion by macrophages and other immune cells.

If you already have an acidic microenvironment, you run the risk of causing a fusion hybridization event in that microenvironment between your macrophages and cancer stem cells (as discussed below). This could turn a potentially benign situation into a malignant one, and if the tumor is malignant, stabbing into it could make a bad situation worse.

"The question is, what is the value of doing a biopsy in the first place? We take biopsies of breast tissue to get a genomic readout of the different kinds of mutations that might be in the cells. Now, if cancer is not a genetic disease and the mutations are largely irrelevant, then it makes no sense to do that in the first place. If the tumor is benign, why would you want to stab it? If the tumor is malignant, why would you ever want to stab it?

I came to this view by reading so many articles in the literature based on brain cancer, breast cancer, colon cancer, liver cancer showing how needle biopsies

have led to the dissemination of these tumor cells, putting these people at risk for metastatic cancer and death," Seyfried says.

In metabolic therapy you would not touch the tumor; you would not disturb the microenvironment. By leaving it alone, you allow the tumor to shrink and go away.

"When you start to look at this as a biological problem, many of the things that we do in cancer make no sense. We have, in brain cancer, people say, 'You have a very low-grade tumor. Let's go in and get it out.' What happens is you go in and get it out, and then the following year it turns into a glioblastoma.

How did that happen? Well, you disturbed the microenvironment. You allowed these cells that are marginally aggressive to become highly aggressive. Then you lead to the demise of the patient," Seyfried says.

"That happens significantly because it's called secondary glioblastoma arising from therapeutic attempt to manage a low-grade tumor. The same thing can happen with all these different organs. You stab breast tumors, you stab colon tumors, you run the risk of spreading the cells …

My argument is the following: If the patient has a lump, whether it's in the breast, in the colon, lung or wherever or a lesion of some sort, that should be the cue to do metabolic therapy.

Do metabolic therapy first. In all likelihood, it will shrink down and become less aggressive. Then the option becomes, 'Should we debulk completely rather than doing some sort of a biopsy?' We want to reduce the risk, because if we can catch the whole tumor completely, then we don't run the risk of spreading it …

In our procedure, you bring the body back into a very high state of metabolic balance, and then you strategically go and degrade the tumors slowly without harming the rest of the body.

Radiation, chemo and the strategies that we're using today don't do this. They're based on the gene theory of cancer that genetic mutations are causing the cell

cycle to grow out of control. Well, this is not the case. Again, a lot of these toxic procedures need to be rethought, reanalyzed in my mind."

Solving the Warburg Theory's Dilemma

In biology, structure determines function. This is an evolutionarily conserved concept. So, how can mitochondria be structurally abnormal in tissue, yet have normal respiration? As Seyfried notes, this doesn't make sense. Confusion has arisen in part because many study cancer in culture, and "make profound statements and comments regarding what happens in culture," Seyfried says.

"If you look at cancer cells in culture, many of them do take in oxygen and make ATP, but at the same time, they're fermenting. This was the conundrum. They called it the Warburg Effect. They're fermenting, but many people at the same time thought their respiration was normal.

This was the main problem with Warburg's theory. But Warburg clearly said in his papers [that] it's not the fact that they take in oxygen; it's how much ATP they can generate from oxidative phosphorylation, which is the normal respiratory capacity of the mitochondria."

As explained by Seyfried, if you measure ATP and look at oxygen consumption in tumor cells, it appears they're making ATP and taking in oxygen, therefore, their respiration is assumed to be normal. However, when you look at the tissues in cancer patients, the mitochondria are abnormal.

"What I and Dr. Christos Chinopoulos from Semmelweis University in Budapest, Hungary, who is the world-leading expert on mitochondrial physiology and biochemistry … realized [was] that the mitochondria of tumor cells are actually fermenting amino acids, glutamine in particular. They're not respiring. They're fermenting an alternative fuel, which is glutamine," Seyfried says.

Warburg's Cancer Theory Proves Correct

With this understanding, Warburg's theory can be proven correct — cancer arises from damage to the mitochondria's ability to produce energy through respiration in their electron transport chain.

The compensatory fermentation involves not only lactic acid fermentation, but also succinic acid fermentation using glutamine as a fermentable fuel. It's been known for decades that glutamine is a main fuel for many different kinds of cancers, but most people thought it was being respired, not fermented.

Seyfried and Chinopoulos' discovery confirms that cancer cells in fact have damaged respiration, and to survive, the cancer cells must use fermentation. The two most available fermentable fuels in the cancer microenvironment are glucose and glutamine. Hence, targeting glucose and glutamine is a crucial component of cancer treatment.

Without glucose and glutamine, the cancer cells will starve, as they cannot use ketones. The simplest approach to cancer then is to bring patients into therapeutic ketosis, and then strategically target the availability of glucose and glutamine.

> *"Basically, what we're saying [is] that mitochondrial substrate-level phosphorylation is a non-oxidative metabolism mechanism inside the mitochondria that would generate significant amounts of energy without oxidative phosphorylation,"* Seyfried says.

Genetic Mutations Are Not the Cause of Cancer

According to Seyfried, mitochondrial dysfunction is at the heart of nearly every type of cancer. Unfortunately, few oncologists have this understanding and many still believe cancer is the result of genetic defects. However, nuclear transfer experiments clearly show cancer cannot be a genetic disease.

> *"There's been no rational scientific argument that I have seen, to discredit the multitude of evidence showing that the [genetic] mutations are not the drivers but the effects [of mitochondrial dysfunction],"* Seyfried says.

"As a matter of fact, there's new information now where people are finding so-called genetic drivers of cancer expressed and present in normal cells, normal skin and also esophagus … This is another [issue] — how you get these so-called driver mutations in normal tissues. We're also finding some cancers that have no mutations, yet, they're fermenting and growing out of control.

There are a number of new observations coming out that challenge the concept that cancer is a genetic disease. And once you realize that it's not a genetic disease, then you have to seriously question the majority of therapies being used to manage the disease. This [helps] explain [why] we have 1,600 people a day dying from cancer in the United States.

Why do we have such an epidemic of suffering and death when we have been studying this disease for decades? Well, if you look at the massive amounts of scientific papers being written on cancer, you'll often find that they're structured around gene defects.

What I'm saying is that if cancer is not a genetic disease and the mutations are downstream epiphenomena, why would the field continue to focus on things that are mostly irrelevant to the nature of the disease? What I'm saying is very devastating, because I'm telling the majority of the people in the field that they're basically wasting their time …

I think we can drop the death rate of this disease by about 50% in 10 years if cancer is treated as a mitochondrial metabolic disease, targeting fermentable fuels rather than using toxic therapies that are focused on downstream effects.

Radiation is designed to stop DNA replication. DNA replication requires energy. If you pull the plug on their fermentable fuels, they're not going to be able to replicate anyway … All of the things that we're doing to treat cancer is basically approaching the disease from a misunderstanding of the biology …

We know viruses can cause cancer. We know radiation causes cancer. We know carcinogens cause cancer. We know intermittent hypoxia causes cancer. We

know systemic inflammation causes cancer. We know just getting older puts you at risk for more cancer.

We know there are inherited mutations in the genome that can cause cancer. But how are all these things linked through a common pathophysiological mechanism? The common pathophysiological mechanism is damaged through the structure and function of the mitochondria.

Every one of the issues … including inherited mutations, damage the respiration of a particular population of cells in a tissue. You look at the breast cancer gene (BRCA 1), for example. People will say, 'Cancer must be a genetic disease because you inherit a mutation that causes the disease.'

You only get the disease if that mutation disrupts the function of the mitochondria. Fifty percent of women who carry the mutation never get cancer or breast cancer because the mutation, for some reason, did not damage the mitochondria in that person."

So, to summarize, the true origin of cancer is damage to the respiratory function of the mitochondria, triggering compensatory fermentation, which is run by oncogenes. Oncogenes play a role by facilitating the entry of glucose and glutamine into the cell to replace oxidative phosphorylation.

Why and How Cancer Spreads

Seyfried also has a very different view on the biology of metastasis (the spread of cancer). He explains:

"We've looked at cancer stem cells in a number of our preclinical models … These guys grow like crazy in place. The tumor just keeps expanding, but it doesn't spread. It doesn't spread into the bloodstream or metastasize to various organs.

We discovered a very unusual cancer 20 years ago. It took us 10 to 15 years to figure out what it was. You can put a few of these cells anywhere in the mouse's body and within three to four weeks, this mouse is full of metastatic cancer. It made the cover of the International Journal of Cancer, when we published this back in 2008, but we had worked on the problem for years.

We couldn't figure out what it was that made these cells so incredibly metastatic. We found out that once we identified the biology of the cell, it turned out [it has] many characteristics in common with the macrophage, which is one of the most powerful immune cells in our body.

We said, 'Wow. Is this unique only to this kind of cell or do metastatic cancers in humans also express characteristics of macrophages?' We looked and we found that almost every major cancer that metastasizes has characteristics of macrophages. Then we said, 'Well, how could this possibly happen? Is it coming from the macrophage?'

A number of scientists ... have all clearly shown that there is some fusion hybridization character going on. In other words, macrophages, our wound-healing cells, they come into a microenvironment where you might find many proliferating neoplastic stem cells, but they don't have the capacity to metastasize.

It's only when the macrophages fuse with these stem cells that you have a dysregulated energy metabolism coming in this hybrid cell. This hybrid cell now has characteristics of both stem cells and macrophages.

The stem cell is not genetically equipped to enter and exit tissue. The macrophage, as a normal cell of your body, is genetically equipped to enter and exit tissue and live in the bloodstream. They're very strongly immunosuppressive. These are all characteristics of metastatic cancer."

Metastatic Cancer Is a Hybrid Cell Combination

According to Seyfried, metastatic cancer cells are essentially a hybrid, a mix of an immune system cell and a dysregulated stem cell, the latter of which could originate from a disorganized epithelial cell or something similar. In short, it's a hybrid cell with macrophage characteristics.

Macrophages are essential for wound healing and part of our primary defense system against bacterial infections. They live both in the bloodstream and in tissues, and can go anywhere in the body. When an injury or infection occurs, they immediately move in to protect the tissue.

> *"The metastatic cancer cell has many of those same properties,"* Seyfried explains, *"But the energy and the function of the cell is completely dysregulated, so it proliferates like crazy but has the capacity to move and spread through the body, so it's a corrupted macrophage. We call it a rogue macrophage."*

Like macrophages, metastatic cancer cells can also survive in hypoxic environments, which is why most angiogenic therapies are ineffective against metastatic cancer.

So, what do these metastatic hybrid cells need to survive? Both macrophages and immune cells are major glutamine consumers, and according to Seyfried, you can effectively kill metastatic cells by targeting glutamine.

Conventional Cancer Treatments Are Unnecessarily Deadly

However, it must be done in such a way so as to not harm the normal macrophages and the normal immune cells. In other words, it must be strategic. For this reason, Seyfried developed a "press-pulse therapy" for cancer, which allows the patient to maintain normal immune system function, while at the same time targeting the corrupted immune cells — the macrophage fusion hybrid metastatic cells — as well as inflammation.

> *"The therapies we are using to attempt to kill these [metastatic] cells put us at risk for having the cells survive and kill us. You can control these cells for a*

short period of time, but they can hunker down and enter into some sort of a slightly dormant state, but they reappear.

People say, 'Oh, these tumor cells are so nifty and smart they can come back at you.' The problem is you've never really challenged them on their very existence, which is they depend on fermentation to survive. If you don't target their fermentation, they're going to continue to survive and come back at you.

Many of the therapies that we use — radiation, chemo and some of these other procedures — are not really going after the heart of the problem. That oftentimes puts you at risk for the recurrence of the disease. Your body is already seriously weakened by the toxic treatments. And in the battle, you lose. If you are fortunate enough to survive … your body is still beat up.

You have now put your [body] at risk for other kinds of maladies … Why are we using such toxic therapies to kill a cell when we know what its weaknesses are? These are the paradigm changes that will have to occur as we move into the new era of managing cancer in a logical way."

A Strategic Approach to Killing Cancer Cells

To properly address cancer, then, you need to clean up the microenvironment, because the microenvironment will strategically kill cells that are dependent on fermentation while enhancing cells that aren't. At the same time, the microenvironment will also reduce inflammation.

"You also have to be very careful not to kill your normal and healthy immune cells, because they need glutamine too," Seyfried says. *"What we find is that when we strategically attack the tumor this way, it turns out that our immune cells are paralyzed.*

The cancer cells are killed, but the normal immune cells are paralyzed. They're not dying, they're just not doing their job. What we do is we back off the therapy a little; allow the normal immune cells to regain their biological capacity, pick up

dead corpses, heal the microenvironment, and then we go after the cancer cells again.

It's a graded response, knowing the biology of the normal cells and the abnormal biology of the tumor cells. This is a beautiful strategy. Once people know how you can play one group of cells off another, and how you can strategically kill one group of cells without harming the other cells, it really becomes a precision mechanism for eliminating tumor cells without harming the rest of the body.

You don't need to be poisoned and irradiated. You just have to know how to use these procedures to strategically kill the cells. Protecting normal macrophages is part of the strategic process. Killing the corrupted ones is part of the strategic process. Again, you have to put all of these together in a very logical path. Otherwise, you're not going to get the level of success that we should be getting."

The Press-Pulse Strategy

This strategy is what Seyfried calls "press-pulse treatment," and essentially involves restricting the fermentable fuels — glucose and glutamine — in a cyclical fashion to avoid causing damage to normal cells and tissues. Glucose is effectively restricted through a ketogenic diet. Restricting glutamine is slightly trickier.

The press-pulse strategy was developed from the concept of press-pulse in the field of the paleobiology. A "press" was some chronic stress on populations, killing off large numbers, but not everything, because some organisms can adapt to stress. The "pulse" refers to some catastrophic event.

The simultaneous occurrence of these two unlikely events led to the mass extinction of almost all organisms that existed on the planet. This was a cyclic event over many hundreds of millions of years. The geological records show evidence for this press-pulse extinction phenomenon.

"What we simply did was take that concept and say, 'Let's chronically stress the tumor cells.' They need glucose. You can probably kill a significant number of tumor cells by just stressing their glucose. That's the press. The press is different ways to lower blood sugar. You put that chronic stress on top of the population either by restricted ketogenic diets [or] therapeutic fasting. There are a lot of ways that you can do this.

Also, emotional stress reduction. People are freaked out because they have cancer, therefore their corticoid steroids are elevated, which elevates blood sugar. Using various forms of stress management, moderate exercise — all of these will lower blood sugar and contribute to a chronic press and stress on the cancer cells.

However, you're not going to kill all cancer cells if you just take away glucose. Because the other fuel that's keeping the beast alive is the glutamine. We have to pulse, because we can't use a press for glutamine targeting, because then you're going to kill your normal immune cells or impair them, and they are needed for the eventual resolution of the disease.

What we're going to do is we're going to pulse various drugs. We don't have a diet system that will target glutamine. Glutamine is everywhere. It's the most abundant amino acid in your body … But you have to use [the drugs] very strategically; otherwise they can harm our normal immune system and then be counterproductive ...

I think that once we understand how we can target effectively glutamine without harming our normal immune cells … this is the strategy that will make most of these other therapies obsolete ... It's cost-effective and non-toxic and it will work very well.

But we're still at the very beginning of this. We need to continue to develop the doses, timing and scheduling of those drugs that are most effective in targeting glutamine that can be done without harming the rest of the cells in our body."

If you would like to support Dr. Seyfried's research, please consider making a donation to the "Foundation For Metabolic Cancer Therapies." The donation tag is on the top row of the of the foundation site. This Foundation is dedicated to supporting Dr. Seyfried's studies using metabolic therapy for cancer management with 100% of the donated funds going directly to research on metabolic therapy for cancer.

Sources and References

- [1] ASN Neuro December 27, 2018
- [2] Cancer as a Metabolic Disease by Thomas Seyfried (PDF)
- [3] Carcinogenesis 2014 Mar; 35(3): 515–527
- [4] Frontiers in Cell and Developmental Biology 2015; 3: 43