# Tripping over the Truth: How the Metabolic Theory of Cancer Is Overturning One of Medicine's Most Entrenched Paradigms, Travis Christofferson

Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar.” -- Location108

inherited genetic mutations play a major role in only 5 to 7 percent of all cancers. -- Location110

It is hard to believe that after Ted Kennedy helped pass the National Cancer Act in 1971, he had no better treatment options for his brain tumor diagnosis almost forty years later. -- Location129

scientific evidence supporting the origin, management, and prevention of cancer with metabolic-based approaches was thoroughly documented in Professor Thomas Seyfried’s book Cancer as a Metabolic Disease. -- Location132

It’s safe to say that the evidence strongly supports the implementation of metabolic-based therapies in situations of managing advanced brain cancer and metastatic cancer, especially if the tumor expresses a prominent Warburg effect and thus expresses intense visualization with a PET scan, a sign of excess sugar consumption and cellular proliferation. -- Location141

Metabolic-based strategies include the use of drugs that target cancer-specific metabolism (such as hexokinase II) and signaling (such as PI3K/AKT/mTOR), and engineered ketogenic diets. -- Location145

***Nutritional ketosis impacts multiple tumor-promoting pathways by limiting glucose availability to the tumor, suppressing insulin and growth factor signaling.*** -- Location147

* Of particular relevance is the intersection of metabolism with epigenetic control and metabolic reprogramming of aberrant signaling pathways that promote the Warburg effect. -- Location149

This year, almost six hundred thousand Americans will die from cancer. -- Location219

One in two men and one in three women will be diagnosed in their lifetimes. -- Location220

the real death rates from cancer are the same today as they were in the 1950s. -- Location221

* Maybe we’ve mischaracterized the origin of cancer. Maybe cancer is not a genetic disease after all. -- Location233
* Maybe we are losing the war against cancer because scientists are chasing a flawed scientific paradigm, and cancer is not a disease of damaged DNA but rather one of defective metabolism. -- Location234
* The idea that cancer was metabolic did not come from Seyfried either. The original claim came from a remarkable German scientist named Otto Warburg in 1924. -- Location237

Warburg’s observation was this: -- Location242

* Cancer cells have a perverted method of generating energy. They truncate the conversion of glucose (sugar) into energy. -- Location243
* They depend much less on the efficient process of aerobic respiration, using oxygen to produce energy—instead relying much more on the ancient and highly inefficient pathway known as fermentation. -- Location243
* Summarized in a few words, ***the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar***.” -- Location247

cancer cells have damaged cellular organelles called mitochondria -- Location250

Typically each animal cell, including those of humans, has one thousand to two thousand mitochondria. -- Location250

* Mitochondria are thought of as the cellular power plants. -- Location251
* They generate energy through oxidative respiration, supplying the body with the energy it needs to function. -- Location252

The damaged mitochondria (later pages will show how the damage occurs in the first place), unable to generate enough energy for cellular survival, then send out emergency signals to the nucleus, a 911 call pleading for it to switch on emergency generators.

* Once this call is made and DNA responds, the entire complexion of the cell changes. -- Location252
* It begins to exhibit the hallmark features of cancer: uncontrolled proliferation, genomic instability (the increased probability that DNA mutation will occur), evasion of cell death, and so forth. -- Location255
* Damage to mitochondria happens first, then genomic instability, and then mutations to DNA. -- Location258

The therapeutic implications of the metabolic theory are that every type of cancer is treatable, because every type of cancer has the same beautiful, metabolic target painted on its back, regardless of the tissue of origin or type of cancer. -- Location327

**CHAPTER 1 -** How Cancer Became Known as a Genetic Disease

was clear that carcinogens were altering the cell and mutating a critical component that was responsible for controlling cellular division. Although the mutated component was unknown, cause and effect were established. A line was drawn from carcinogen to cancer. The theory would eventually become known as the somatic mutation theory of cancer. -- Location418

* theory linking carcinogens to damaged chromosomes became known as the SMT. -- Location469

A normal human cell typically obtains almost 90 percent of its energy through aerobic metabolism and the remainder through an anaerobic pathway. -- Location625

* Certain cells, such as muscle cells, can create energy without oxygen by generating lactic acid—but only briefly, when oxygen is absent or the muscles demand great amounts of energy. -- Location626
* Once oxygen becomes available or the activity stops, the cells resume the much more efficient method of making energy aerobically. -- Location627

To Warburg’s surprise, he found that cancer cells generated abnormal amounts of lactic acid. They were generating energy through the antiquated fermentation pathway. Even more surprising, they did it in the presence of oxygen. -- Location641

***This led to Warburg’s famous distinction: Unlike normal cells, cancer cells ferment glucose in the presence of oxygen, a characteristic now known simply as “the Warburg effect***.” -- Location644

Cancer cells were producing energy in a way that evolution had set aside as an auxiliary pathway, a highly inefficient generator that kicked in when the power went out. -- Location647

As Warburg continued his experiments, he found that cancer’s defective metabolism presented itself without exception in all types of tumor cells. -- Location649

***Warburg made another critical observation that hinted at why cancer cells were fermenting in the first place. He showed that when normal, healthy cells were deprived of oxygen for brief periods of time (hours), they turned cancerous. No other carcinogens, viruses, or radiation were needed, just a lack of oxygen.*** -- Location652

* This led him to conclude that cancer must be caused by “injury” to the cell’s ability to respire. -- Location654
* He contended that once damaged by lack of oxygen, the cell’s respiratory machinery (later found to be mitochondria) became permanently broken and could not be rescued by returning the cells to an oxygen-rich environment. -- Location655

“If you want to understand function, study structure.” -- Location716

The intricate operations of the cell are carried out by legions of workers called proteins. Proteins act as gateways, directing materials into and out of the cell, and also provide the cell’s supportive scaffolding. -- Location726

* They serve as catalysts, facilitating myriad chemical reactions that continuously generate energy and power in an almost inconceivable number of cellular processes. -- Location727
* Proteins function as intricate circuit boards within the cell. They constantly receive signals from the outside in the form of hormones or nutrients, and then relay the information through the appropriate channels, always adjusting and adapting. -- Location729
* It is proteins that dictate the structure of DNA itself, -- Location731
* Directed by a continuous dance between DNA and the environment, proteins dictate the three-dimensional architecture of DNA, allowing for specialization and adaptation. -- Location734
* In a hair follicle, for example, the gene encoding for the hair protein is exposed, but in a liver cell, it is wrapped up. -- Location735
* every protein is made of the same twenty-one amino acids. The different configurations, however, allow them to serve vastly different functions. -- Location745

***Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar.***” -- Location809

Secondary causes such as x-rays, dyes, tar, asbestos, and cigarette smoke were largely irrelevant. They only precipitated the prime cause: damaged respiration. -- Location811

**CHAPTER 2 -** Chemotherapy and the Gates of Hell

A series of experiments using mice confirmed Goodman’s and Gilman’s hypothesis: It was clear that the mustard compound significantly decreased the size of lymphoid tumors in the mice. -- Location967

Nitrogen mustard works by attacking DNA itself. -- Location991

Nitrogen mustard works by seeking out the nucleotide guanine and locking it into a permanent handshake with its partner cytosine. This prevents DNA from being able to unzip, thus effectively preventing cell division. -- Location997

Of course, nitrogen mustard is unable to distinguish a normal cell from a cancerous one, so it travels through the body indiscriminately locking the DNA of every cell it encounters and freezing it in place, like a parking attendant putting a boot on the wheel of a car. -- Location998

“Never run away from a fight. The farther you run, the more difficult it will be to fight back.” -- Location1173

**CHAPTER 3 --** Breakthroughs and Disappointments

Warburg was able to describe grossly what he believed to be the fundamental alteration in cancer cells: They fermented glucose in the presence of oxygen. But Warburg had failed to discover why or how cancer cells exhibited this effect. -- Location1316

***the faster a tumor grew and the more aggressive it was—the lower the overall number of mitochondria and the more it fermented glucose.*** -- Location1373

The tumor cells that exhibited a robust “Warburg effect” and grew the fastest invariably retained only about 50 percent of the mitochondria compared to normal tissue-matched cells. -- Location1379

in biology, structure equals function. Pedersen irrefutably showed that the mitochondria of cancer cells were structurally altered almost everywhere he looked. -- Location1383

Just like all forms of life use DNA as a blueprint of instructive code, life uses a single molecule, adenosine triphosphate (ATP) as the universal carrier of metabolic energy. -- Location1403

* ATP is generated by the cell in two pathways: fermentation (glycolysis) or aerobic respiration (mitochondrial energy generation utilizing oxygen). -- Location1409
* Glycolysis starts with one molecule of glucose and, through a series of ten steps, transforms it into two molecules of pyruvate. -- Location1410
* Once pyruvate is generated, the cell has a decision to make: It can take pyruvate and shuttle it into the mitochondria, where it will begin the respiratory energy cycle—the highly efficient process that employs oxygen to generate a staggering twenty-three molecules of ATP. -- Location1411
* Alternately, the cell can ferment pyruvate, an inefficient method of energy production that produces only two molecules of ATP and generates lactic acid, a waste product. -- Location1413
* A healthy cell might convert pyruvate to lactic acid for a good reason; a cancer cell could do the same for a bad one. -- Location1414

Your cells are remarkable, self-regulating chemical engines that constantly adjust for maximum economy. -- Location1425

As Bustamante and Pedersen discovered, rather than retaining a healthy cell’s exquisite ability to regulate the amount of glucose entering the fermentation pathway, the valves that regulated the flow in the cancer cell were stuck open. -- Location1426

* The protein that catalyzes the first step of glycolysis (converting glucose into glucose-6-phosphate by tagging it with a phosphate group) is called hexokinase, and it alone determined the how of the Warburg effect. -- Location1428
* The “cancerous” version of hexokinase is a vestige of the past, a result of the evolutionary process as it moved through time. -- Location1431
* The irreverent form of hexokinase, hexokinase II, however, ignores the signal to slow down and keeps the valve wide open, shoving as much glucose as it can down the fermentation pathway. -- Location1447
* The hyperactivity and overexpression of hexokinase II results in cancer cells that are bloated with glucose. Here was the contrast between normal and diseased tissue that had been needed for the diagnostic application of a PET scan. -- Location1466

PET scans are the only way to detect actively metabolizing tumors,” Pedersen said. -- Location1475

The images produced by a PET scan are a dramatic visualization of cancer’s grotesquely voracious appetite for glucose. -- Location1483

This was so inefficient that it took eight thousand pounds of ground pancreases to extract a single pound of insulin hormone. At Genentech, the human insulin gene was spliced into bacterial cells, subverting them into remarkably efficient insulin-producing machines -- Location1531

Genentech was fantastic at one aspect of pharmaceutical development, but it was not in the tricky, high-risk, high-reward business of developing new drugs—at least not until the company ran out of proteins to synthesize. -- Location1536

A normal breast cell might contain fifty thousand HER2 receptors on the surface of the cell. The breast cancer cells that “lit up” Ullrich’s probe contained up to 1.5 million receptors. -- Location1566

***The balance between cell growth and cell death is a tightrope the body must walk every day, with billions of cells condemned to death through apoptosis and billions of cells dividing to replace them***.

* If the tenuous relationship shifts too far toward cell death, degenerative conditions such as Parkinson’s disease, Alzheimer’s disease, and amyotrophic lateral sclerosis (ALS) can occur.
* If shifted too far toward growth, cancer might occur. -- Location1686

The laboratories of Pedersen and Colombini discovered that hexokinase II interacted with VDAC. When bound to hexokinase II, VDAC locked the gate, preventing the release of cytochrome c, thereby preventing apoptosis and effectively immortalizing the cell—one of the most salient and awe-inspiring qualities of the cancer cell. -- Location1689

However, unlike the overexpression of the oncogene HER2/neu, which occurred in only a fraction of cases of breast cancer, the overexpression of hexokinase II occurred in virtually every cancer cell. -- Location1692

In one fell swoop, the switch from normal hexokinase to hexokinase II not only allowed cancer cells to compensate for the energy lost due to loss of and damage to mitochondria, but also immortalized the cancer cell, turning it into a voracious, gritty, enduring version of a normal cell. -- Location1693

Pedersen’s lab then made another discovery in 2003. In addition to its hysterical consumption of glucose and its impediment of apoptosis, hexokinase II positioned itself perpendicularly to a protein called ATP synthasome, a rotating, machinelike protein that belched out the cellular energy currency, ATP. -- Location1695

* Hexokinase II’s positioning allowed it to steal ATP before it had the chance to escape, putting the cancer cell’s insatiable appetite for glucose before other cellular needs. -- Location1697

A single molecular transition to a parasitic isozyme was largely responsible for two hallmark features of cancer: the Warburg effect and the evasion of apoptosis. -- Location1702

It was in all of them, just as the PET scans had shown. -- Location1704

***In theory, 3BP could target any cancer that was “PET positive” (meaning that cancer was actively fermenting glucose via overexpressed hexokinase II).***

* Considering that this equated to about 95 percent of all cancers (the ones that were not PET positive were probably not growing, or growing very slowly), the implication was almost inconceivable. -- Location2100

**CHAPTER 4 --** Dark Matter

Well aware that the creative process flourishes with an uninhibited mindset, he had ping-pong tables installed in his lab and started a band with his coworkers. -- Location2175

Long before the malignant form of cervical cancer occurred, Papanikolaou noticed populations of premalignant cells burst through the confines of normal growth restraints. -- Location2193

As the data from TCGA were analyzed, researchers quickly realized that a tidy series of mutations simply wasn’t there, even though Vogelstein’s model suggested that was what they should see. -- Location2206

More alarming, the data failed to reveal any sort of consistent pattern. -- Location2207

It contained a degree of randomness that caught everyone by surprise. -- Location2207

For the SMT to work, mutational patterns that explained the origin of a given type of cancer had to be found—cause -- Location2223

Vogelstein knew that the SMT was in trouble. Enough data had been compiled to determine that his model of a series of sequential mutations as the cause of cancer could be scrapped. -- Location2242

A prominent researcher declared that intratumoral heterogeneity represented the most important clinical feature of the cancer genome and grimly described the targeted approach to cancer treatment this way: “When an old tree falls or is logged, many seedlings are poised to grow and take its place.” -- Location2351

The last member of the heterogeneity family is intermetastatic heterogeneity: the mutational heterogeneity observed between the cells in the primary tumor and the cells at distant sites where the tumor has metastasized. -- Location2353

beyond the obvious preventative measures like not smoking and avoiding other carcinogens, the only established way to reduce overall cancer rates was through caloric restriction or periodic fasting, a practice known to restore mitochondria, again linking cause to metabolism. -- Location2415

Weinberg’s hallmarks read as follows: Cancer cells

(1) stimulate their own growth,

(2) evade growth-suppressing signals,

(3) resist cell death (apoptosis),

(4) enable replicative immortality,

(5) induce the ability to grow new blood vessels enabling tumor growth (angiogenesis), and

(6) spread to distant sites (metastasis). -- Location2429

The humble scientist “called out” Weinberg for omitting the Warburg effect from his list of hallmarks. -- Location2445

but the one he omitted from this list is the Warburg effect. It is the oldest known property of cancer, and it is a characteristic of every cancer. -- Location2449

Weinberg thought there was enough evidence to justify the addition of two new “emerging” hallmarks.

1. The first was cancer’s ability to evade destruction by the immune system. -- Location2452
2. Weinberg called the second addition “reprogramming of energy metabolism”—another way of saying “the Warburg effect.” -- Location2454

**CHAPTER 5 --** Watson Reconsiders

The Truth in Small Doses: Why We Are Losing the War on Cancer and How to Win It. -- Location2522

**CHAPTER 6 --** Mitochondria: An Old Theory Is New Again

Humans have ten times as many bacteria in the gut than cells in the entire body. -- Location2605

* They manufacture vitamins, train the immune system, and keep unwelcome bacteria at bay. -- Location2605

Pedersen established that cancer cells had damaged and fewer mitochondria, proving Warburg’s contention that cancer cells fermented because they had to. -- Location2630

* Along with corroborating Darlington’s work showing that a wide swath of chemical carcinogens directly damage mitochondria, Pedersen showed that viruses could also. -- Location2658
* He provided evidence showing how viruses used the mitochondrial machinery for replication, and he referenced pictures of viral particles living within mitochondria. -- Location2659

The strange results raised another question: Why would restricting calories slow tumor growth? -- Location2724

* It was the reduced calories that had the antitumor effect.” -- Location2727
* But why would reducing calories in general affect tumor growth? -- Location2728
* When Seyfried summarized all his research in his 2012 book, Cancer as a Metabolic Disease, it took some time for people to take notice, but they did. -- Location2740
* According to Seyfried, the mutations at the heart of the SMT of cancer were downstream to the true cause: damaged mitochondria. -- Location2791
* Seyfried had noticed that simple caloric restriction shrank tumors, an observation that he could now justify through a theoretical framework. -- Location2995
* Caloric restriction drives down blood glucose, forcing cancer cells to ferociously compete with healthy cells for the fuel they so desperately crave. -- Location2996
* He modified the diet slightly, keeping overall calories restricted but eliminating carbohydrates in favor of fats, a modification that might put even more metabolic pressure on the cancer cells. -- Location2997
* With no carbohydrates, the body is jerked out of its preferred state of metabolic energy generation. It is forced to manufacture molecules called ketone bodies to take the place of glucose as a source of circulating fuel. -- Location2998
* Unlike glucose, ketone bodies burn oxidatively. They have to be metabolized in healthy, functioning mitochondria, which Seyfried knew, cancer cells don’t have many of. Metabolically, normal cells have other options, but cancer cells do not. -- Location3001
* If cancer was truly a disease of dysfunctional mitochondria, a dietary regimen that he coined the ***“restricted ketogenic diet” (R-KD),*** one that transitions away from utilizing glucose as an energy source to the use of ketone bodies, might have more impact than simple caloric restriction. -- Location3002
* Wilder’s regimen, which he termed the “ketogenic diet,” consisted of approximately one gram of protein per kilogram of body weight per day, with almost no carbohydrates and the rest of the calories consumed from fat. -- Location3011

produced a made-for-TV movie titled ***First Do No Harm*** starring his good friend Meryl Streep. He then started the Charlie Foundation, dedicated to training dieticians in hospitals to administer the ketogenic diet for epileptics, but his efforts encountered friction. -- Location3020

***Not only did the ketone bodies result in greater efficiency, but they showed a strange ability to drastically increase the amount of ATP produced inside the cell.*** -- Location3034

* He discovered that by widening a critical energetic gap in the electron transport chain, ketone bodies changed the intracellular landscape, effectively supercharging the cell. The metabolic transformation inspired him to dub the molecules “superfuel.” -- Location3035
* The brain consumes 20 percent of the energy we consume at any given time. Worse, while other tissues in the body can transition to burning fatty acids, the brain is hamstrung by the fact it can burn only glucose, leaving it uniquely vulnerable. -- Location3039
* a metabolic conversion during times of deprivation into a state of hyperefficiency, or ketosis. Because the brain could transition from burning glucose to ketone bodies, the molecules could rescue the brain from its metabolic plight, providing a backup fuel to feed its monstrous appetite. -- Location3042
* “The survival benefit is obvious; ketone bodies allow a normal-weight human to go from two to three weeks without food to about two months. -- Location3045

In addition to the well-known weight-loss benefits that Robert Atkins touted in the 1970s, ketosis was shown to potentially impact a host of neurological diseases, including Parkinson’s disease, Alzheimer’s disease, ALS, and brain trauma. -- Location3050

* Like a cleaner-burning fuel, ketone bodies appear to preserve, or even restore, damaged mitochondria. -- Location3056
* His ideas focused on maintaining the fidelity of the respiratory apparatus through exercise, respiratory vitamins (mostly B vitamins), and the avoidance of carcinogens (a practice that Warburg himself took to an extreme; in his later years he ate only food grown organically on his own land). -- Location3079
* He found that below the surface both caloric restriction and R-KD affected a vast swath of biochemical processes. -- Location3142
* He found that, mirroring the ability of ketone bodies to attenuate a host of seemingly unrelated neurological diseases, caloric restriction, too, affected many qualitative aspects of the cancer cell. -- Location3143
* He found the R-KD to be antiangiogenic—it choked off the production of new blood vessels supplying the tumor, as Rous had discovered almost one hundred years earlier. -- Location3145
* The diet was also proapoptotic, in that it facilitated orderly cell death. -- Location3146
* This was in sharp contrast to the chaotic cell death caused by chemotherapy and radiation, a disorderly process known to increase inflammation and fan the flames of malignancy. -- Location3147
* As practitioners of periodic fasting or caloric restriction had documented for years, the diet proved to be anti-inflammatory, a loosely defined process associated with initiating and driving cancer. -- Location3148
* When Seyfried looked further, the diet proved to be anti-invasive as well. -- Location3150
* The diet influenced hormones like IGF-1, implicated as fuel for tumor cells, attenuating its malevolent influence. -- Location3151
* Everywhere he looked, in every biochemical process subverted by cancer, the diet pushed back, pressuring the cells to a state of normality. -- Location3152

“All oncologists should know that dietary restriction is the nemesis of many cancers,” -- Location3153

In one experiment ketone bodies were added to one petri dish containing growing cancer cells and another containing normal cells. As expected, the cancer cells died or floundered along, barely able to grow, while the normal cells effortlessly transitioned to the new fuel. -- Location3156

The difference between the MRI taken the day she entered the hospital and the one in February was striking. Where there were once grotesque masses, there was nothing. In two and a half months, her brain was, as far as the MRI could tell, free of cancer. -- Location3184

The twofold benefit of the diet was backed by a series of studies. -- Location3211

Unable to make the transition to ketosis, cancer cells were put under tremendous pressure, as the fuel they craved was replaced by one they couldn’t consume. -- Location3213

* The missing and damaged mitochondria, Seyfried reasoned, was the Achilles’ heel of cancer cells. It left them metabolically hamstrung. His lab zeroed in on this weakness, bombarding the cell from every metabolic angle and capitalizing on its inflexibility. -- Location3215
* Veech worked out a biochemical map showing how entering ketosis translates into a differentiation between normal cells and cancer cells. -- Location3216
* The ketogenic diet, as he showed, supercharges normal cells, lifting them to a vigorous state of health. -- Location3217

In addition to bathing the cells in a superefficient fuel, ketone bodies do something else: They prepare normal cells to deal with free radicals—the hyperactive wrecking balls blamed for every malady from cancer and neurodegeneration to the mother of all disease, aging itself. -- Location3218

* In addition to the antioxidants people consume, cells manufacture an antioxidant called glutathione that alone is responsible for neutralizing the bulk of the free radical assault. -- Location3222
* As Veech noticed, ketone bodies dramatically tilt the ratio of armed glutathione (the antioxidant form) to unarmed glutathione, beefing up the cellular defense of healthy cells as they transition to ketone body metabolism. -- Location3224

As the transition to ketosis drives down blood glucose levels, a cancer cell had both its energy source and its capacity to prepare glutathione for battle against free radical assault taken away. -- Location3228

When administered to a cancer patient, R-KD makes healthy cells healthier and cancer cells sicker. -- Location3229

His 2012 manifesto, the work he claims “was his most important since the double helix,” is entitled “Oxidants, Antioxidants, and the Current Incurability of Metastatic Cancers,” -- Location3234

* First, the most important pathway to killing cancer cells is through apoptosis, and it appears that apoptosis in many cases is triggered by quick bursts of free radicals. -- Location3238
* Second, many current cancer therapies operate by inducing bursts of free radicals, thus triggering apoptosis. -- Location3239
* Most ROS is generated as a by-product of mitochondrial metabolism, so the damaged mitochondria in cancer cells are likely to “leak” much more ROS, leaving cancer cells in a precarious state of oxidative chaos. -- Location3241
* R-KD does the opposite. It cuts off the cancer cell’s ability to manufacture its most important antioxidant—glutathione—rendering it defenseless against most cancer treatments. -- Location3258
* As an added bonus, because R-KD affects cancer cells and normal cells differently, the diet forces healthy cells to manufacture more glutathione, thus preparing them for the corrosive effects that ROS-generating therapies collaterally imposes on healthy tissue. -- Location3260
* R-KD appears as a dream scenario: It sensitizes cancer cells to ROS, leaving them perched on the edge of a cliff, while it prepared the rest of the body to handle any additional ROS-generating therapies, thus minimizing treatment side effects. -- Location3261

Fasting is essentially the same as R-KD, it is the quickest route to ketosis. -- Location3269

The trial provided empirical evidence that fasting prepared normal cells to withstand a chemotherapeutic assault. -- Location3280

It seemed that in every scenario, entering ketosis enhanced other therapies while keeping toxic shrapnel from damaging healthy tissues. The diet appeared to slow cancer growth, but that alone did not appear to be R-KD’s strong suit. The way it prepares the therapeutic landscape makes it unique. -- Location3289

It was like primer to a painter or fertilizer to a gardener. It conditions the environment in which the cancer exists, enhancing other therapies while attenuating side effects. -- Location3291

When you see Dominic D’Agostino, you don’t think scientist. The University of South Florida professor has a passion for nutrition and fitness, and in a charity fundraiser, he broke the Guinness World Record for the most weight squatted in twenty-four hours (175,500 pounds in less than six hours, breaking the old record by more than 50,000 pounds). -- Location3305

* D’Agostino and his students excitedly documented the effects of increased oxygen pressure on different types of cells. -- Location3314
* He had already delved deeply into nutritional ketosis as a way to mitigate seizures and other side effects that SEALs might experience from oxygen toxicity. -- Location3318
* He knew the diet protected neurons from a variety of insults, so it was easy to connect the dots. -- Location3319
* “We did an experiment that showed ketones could kill cancer cells by themselves,” he said. -- Location3320
* The swirling observations led him to Seyfried’s 2010 journal article “Cancer as a Metabolic Disease.” The comprehensive theory Seyfried laid out tied everything D’Agostino had seen firsthand into a unified whole. -- Location3321
* while D’Agostino was observing the ROS-generating ability of hyperbaric oxygen chambers to explode cancer cells. -- Location3323

In addition to saturating pockets of tissue that may be hypoxic, hyperbaric oxygen generates ROS, the crucial element of most cancer therapies -- Location3324

In a mouse model of highly metastatic brain cancer, they measured the effect of R-KD plus hyperbaric oxygen. The results, published in the summer of 2013, gave testimony to the power of the simple union. -- Location3326

By themselves, R-KD and hyperbaric oxygen slowed tumor growth, but together, they eviscerated it. -- Location3327

The diet alone increased mean survival by 56.7 percent compared to the control mice, and when it was combined with hyperbaric oxygen, the mean survival jumped to 77.9 percent. -- Location3328

They envision treating patients with a “synergistic combination of nutritional ketosis, cancer metabolic drugs (like 3BP, DCA, and 2DG) and hyperbaric oxygen therapy (HBOT).” -- Location3331

It is possible that one day R-KD combined with HBOT could replace radiation altogether, especially considering that HBOT is able to target cancer anywhere in the body and radiation is not. -- Location3343

They say that R-KD combined with HBOT “could potentially kill tumor cells as effectively as radiation without causing toxic collateral damage to normal cells.” -- Location3345

Like R-KD with HBOT, 3BP appears to be a largely nontoxic therapy that could potentially treat any cancer that is PET positive, which equates to 95 percent of cancers. -- Location3352

**CHAPTER 7 --** Where Do We Go from Here?

Healthy cells can transition to accommodate ketosis, while cancer cells are left sputtering in their inflexibility. -- Location3462

All Dr. Ko needs to launch 3BP into a small trial is about $3 million. Trials for R-KD combined with HBOT also need about $3 million. -- Location3486

But it has turned out that most of the things that cause cancer, including tobacco smoke and asbestos, don’t cause mutations. Rather than modifying the genes themselves, smoke and asbestos alter the activity of genes through a collection of processes called epigenetics. -- Location3525

For example, the ketone body beta-hydroxybutyrate (BHB) has been found to inhibit the enzyme histone deacetylase in addition to being an energy substrate. -- Location3597

* This may account for BHB’s ability in vitro to slow the growth of cancer cells irrespective of the glucose concentration. -- Location3598
* BHB’s epigenetic modifying ability also may account for its known capacity to alter many important cancer pathways. -- Location3599
* The power of ketones in general continues to amaze researchers. In addition to the ability of BHB to protect against a multitude of disease processes, a 2014 study showed administration of BHB can increase the life span of the roundworm Caenorhabditis elegans by approximately 20 percent. -- Location3600
* The life extension was determined to be the result of epigenetic activity, specifically the inhibition of histone deacetylation by BHB, -- Location3602

In the VM-M3 mouse model of metastatic cancer, they tested the combination of the ketogenic diet, HBOT, and ketone supplementation. The treated mice exhibited decreased growth of both the primary tumor and metastatic spread to the lungs, kidneys, spleen, adipose tissue, and liver. -- Location3609

* Also, and more importantly, the treated mice lived 103 percent longer than controls, again illustrating the power of synergy with metabolic therapies. -- Location3611
* choking off both glucose and glutamine, cancer’s preferred fuels. -- Location3634

Today Jane has a Facebook page entitled “Jane McLelland’s Off-Label Drugs for Cancer,” where patients and survivors share their stories of using repurposed drugs.\* -- Location3656

Doing the math reveals that the addition of MSCT resulted in a 400 percent increase in survival compared with standard chemotherapy treatment, an incredibly meaningful number especially for this type of cancer: lung cancer has the highest mortality rate, killing 1.59 million people worldwide in 2012. -- Location3784

With our allotted time about to run out we spoke briefly about the exciting possibility of adding the new exogenous ketones to the MSCT protocol. -- Location3797

Today half of the people who contact us are interested in using the diet for other purposes,” said Jim Abrahams, founder of the Charlie Foundation. Their website ([www.charliefoundation.org](http://www.charliefoundation.org) ) contains an abundance of resources, from food suggestions to recipes to current clinical trials studying the ketogenic diet’s effect on cancer. -- Location3822

Since the ketogenic diet is high in fat, gradual initiation to the full plan is often better tolerated. -- Location3844

There are several programs that assist with achieving these goals. KetoDietCalculator ([www.ketodietcalculator.org](http://www.ketodietcalculator.org) ) is a mobile application and online program that I designed over twenty years ago, -- Location3851

Some of the lowest-carbohydrate whole foods that have the highest nutrient value are sprouted seeds from vegetables such as broccoli, cabbage, and radishes. -- Location3857

Digestive health is especially important to anyone with cancer, not only for assuring regularity but also for other reasons: Immune function is enhanced, brain metabolism is optimized, and glucose levels can also be improved. -- Location3860

Selecting foods that will encourage healthy gut microbes (bacteria) is the goal. Pre- and probiotics are necessary in the diet to make this happen. -- Location3861

Prebiotics foods are insoluble fibers, which provide food for gut bacteria. Low carbohydrate sources include Jerusalem artichokes, dandelion greens, garlic, asparagus, leeks, red onions, chicory root, and inulin powder. -- Location3863

Probiotic foods include cultured yogurt (Greek yogurt is highest in fat), apple cider vinegar, kimchee, and sauerkraut. -- Location3864

New evidence in human studies has shown that artificial sweeteners can alter gut microbes, encouraging the storage of fat instead of turning food into energy. -- Location3866

Checking your glucose level after consuming an alcoholic beverage is the best way to know what you can handle. -- Location3872

Dry red wines (such as merlot or pinot noir) cause a lower rise in glucose than white wines. -- Location3874

The high-fat content of a meal lowers the rate at which the wine is absorbed, leading to a delayed and lower rise in glucose. -- Location3874

It is essential during the fasting phase and during diet therapy to monitor blood glucose levels and ketones. -- Location3883

The state of ketosis causes a diuretic effect, resulting in weight loss from loss of body fluid, which may be 5–10 percent of body weight. -- Location3888

Keep carbs low (12–20 grams) and protein low but adequate (around 0.8–1.0 grams per kilogram of ideal body weight). The amount of fat you need will be dependent on your degree of calorie restriction (if any). -- Location3915

Vegetables The emphasis here should be on nonstarchy choices. When possible, choose organically raised foods.

* Asparagus
* Broccoli
* Brussels sprouts
* Cabbage
* Cauliflower
* Celery
* Cucumbers
* Greens (for sautéing)
* Kale
* Mushrooms
* Salad greens
* Spinach
* Zucchini

After you are keto-adapted, you can add back in limited amounts of these foods:

* Garlic
* Onions
* Peppers
* Tomatoes -- Location3925

To reach ketosis, you’ll need to limit your intake of fruits and berries. Wait until you’re keto-adapted before adding limited amounts of low-sugar berries or fruit back into your diet. Even then, always combine them with fats to lower their impact on blood glucose and insulin. -- Location3936

Whenever possible, choose meats from pasture-raised or free-range animals. -- Location3938

Note that even uncured bacon and sausage usually contain nitrates “naturally occurring in celery juice” (or beet powder). -- Location3941

* Beef
* Lamb
* Pork (including limited amounts of bacon and sausage)
* Poultry
* Seafood (such as wild-caught fish, tinned fish, and shellfish)
* Wild-game meats • Eggs (preferably free range or high in omega-3) -- Location3943

Milk is not keto-friendly because it is high in lactose (milk sugar). -- Location3947

Limit dairy intake and choose products from animals that have been pasture raised.

* Butter, clarified butter, or ghee
* Cheese (limited amounts of hard cheeses such as cheddar or Parmesan, or soft, high-fat cheese such as Brie)
* Heavy whipping cream
* Cream cheese
* Sour cream (cultured, without added starches or fillers) -- Location3950

Research your favorites to evaluate the pros and cons of each.

* Almonds
* Brazil nuts (limit these to 2–3 per day)
* Coconut meat, unsweetened
* Hazelnuts
* Macadamias (good choice—highest in fat; lowest in carbs and protein)
* Pecans (also a good choice)
* Walnuts (high in omega-3 but also high in omega-6—keep it reasonable)
* Chia seeds
* Flaxseeds (rich in healthy omega-3 and fiber—grind and store in the refrigerator)
* Hemp hearts/seeds (also a good plant source of omega-3) -- Location3957

Avocados And Olives These two foods deserve a special mention. Both are high in healthy monounsaturated fats. -- Location3965

Both can also help to boost the fat content of a meal. For example, ½ of an average Haas avocado provides 2 teaspoons (approximately 10 grams) of fat with little carb or protein. -- Location3966

Fats And Oils Keto diets are very high in fat, so quality, composition, and balance are important. Look for cold-pressed organic varieties and avoid all heat-extracted and refined -- Location3970

Animal fats and lard

* Butter or ghee (if dairy is included in the diet)
* Coconut oil and MCT or C8 oil derived from coconuts or red palm
* Omega-3 fish oils, either as fresh fish (such as sardines or wild-caught salmon) or in purified supplements (krill and fish oil—make sure these include DHA/EPA) • Olive oil (extra virgin for dressings) -- Location3974

Salad dressings and mayonnaise—preferably homemade using olive oil

* Buttery spreads such as Earth Balance or MELT Organic
* Other oils based on personal preferences (such as avocado or macadamia) -- Location3979

Spices, Flavorings, And Seasonings These items add variety and interest to your meals. Some also have health benefits as anti-inflammatories or aid in maintaining blood glucose control. -- Location3984

***Importance of Fasting Intermittent fasting is yet another important metabolic strategy for general health improvement as well as for cancer. There are many variations on this theme, but the pattern that is easiest to follow and that may enhance your efforts the best is daily fasting of 14 to 16 hours, which involves eating all your food for the day within an 8 to 10-hour window***. -- Location4041

***The Glucose/Ketone Index Calculator*** -- Location4046

* We recently developed the Glucose Ketone Index Calculator (GKIC) to assess the potential therapeutic effects of various low-carbohydrate and ketogenic diets (KDs) for management of cancer.\* -- Location4047
* The GKIC is a simple tool that measures the ratio of blood glucose to blood ketones and can help monitor the efficacy of metabolic therapy in clinical trials for malignant brain cancer or for any cancer that expresses aerobic fermentation. -- Location4049
* GKI values of 1.0 or below are considered therapeutic, -- Location4050

Hyperbaric oxygen therapy can also be considered another pulse disturbance in elevating oxidative stress -- Location4063

The normal cells readily transition to ketone body metabolism for protection against oxidative stress damage and oxidative stress. -- Location4064

**APPENDIX B --** List of Practitioners

Doctors Familiar with Metabolic Cancer Therapies -- Location4071

* Dr. Mark Renneker, UCSF (mark.renneker@ucsf.edu)
* Dr. George Yu, George Washington University, Washington, DC ([george.yu8@gmail.com](mailto:george.yu8@gmail.com))
* Dr. Helen Gelhot, St. Louis, MO area ([helengelhot@charter.net](mailto:helengelhot@charter.net))
* Dr. Simon Yu, St. Louis, MO ([simonyumd@aol.com](mailto:simonyumd@aol.com))
* Dr. Greg Nigh, Portland, OR ([drnigh@naturecuresclinic.com](mailto:drnigh@naturecuresclinic.com))
* Dr. Robert Elliott, Baton Rouge, LA (relliott@eehbreastca.com) -- Location407
* Dr. Kara Fitzgerald, Hartford, CT ([kf@drkarafitzgerald.com](mailto:kf@drkarafitzgerald.com))
* Dr. Ian Bier, Portsmouth, NH ([ian@hnnhllc.com](mailto:ian@hnnhllc.com))
* Dr. Neal Speight, North Carolina ([nespeight@gmail.com](mailto:nespeight@gmail.com))
* Dr. Ouriana Stephanopoulos, University of Kansas, Kansas City (ostephanopoulos@kumc.edu) -- Location4077