Nature Wants Us To Be Fat

Richard Johnson, MD

Chapter 1 The Power of Fat

Animals and humans fare better if they carry a moderate level of fat. These fat stores aid pregnancy. They aid survival in times of food scarcity.

“Nature wants us to have sufficient fat to survive situations that are rough. To nature, obesity is not unnatural; it is not a disease. Fat is powerful, beneficial, and beautiful- at least in the right setting.”

Chapter 2 Secret Reasons It Helps to Be Fat

“We now have our first clue to the cause of obesity: fat has a purpose. Fat provides calories to animals when they cannot find food. It is a safeguard during times of trouble and can be critical for survival.”

“Fat provides a way to store calories when food is not available, but there are certainly other things that an animal needs to survive. One of the most important is water.”

Johnson discusses what is called “metabolic water,” the water produced in the body during metabolism. Metabolic water is produced through metabolism of fat.

“Storing fat is only one approach to an anticipated food shortage; another is to reduce the energy you use. Starving animals, for example, reduce how much energy they use while they are resting, to compensate for energy used while foraging, so that overall, they burn less energy than an animal that is not starving.”

This is similar to what happens with animals preparing for hibernation. They slow energy use even before hibernation begins.

Part of the survival response in times of food scarcity is to decrease the uptake of glucose in the body with the notable exception of the brain. For glucose to be taken up by muscle and the liver, insulin is required. The brain does not require insulin, thus what glucose is available in the blood can readily supply the brain.

“So we see that animals that become obese in nature activate a series of survival responses that include foraging for food, lowering their metabolism, becoming insulin resistant, and increasing fat storage not only in adipose tissues, but also in liver and blood. This constellation of findings has been observed over and over in hibernating animals including bears, squirrels, and marmots, as well as for birds preparing for long-distance travel, and clearly contributes to their survival during periods of food shortage.”

“A similar constellation of signs is observed in *people* who are overweight or obese, referred to as **metabolic syndrome**. Metabolic syndrome usually refers most specifically to obesity that is most prominent around the abdomen (called “central obesity”) in combination with insulin resistance. It is frequently accompanied by increased triglycerides in the blood, as well as a reduction in “good” cholesterol (HDL cholesterol) and mild elevations in blood pressure. Fatty liver is also common. Today, one-fourth of adults have metabolic syndrome.”

The issue is that for animals, the period of “metabolic syndrome” ends at the end of hibernation or at the end of migration. Most commonly, for humans it continues and worsens over time.

The highly choreographed sequence whereby animals build up fat stores in preparation for times of scarcity Dr. Johnson calls the **survival switch.** In many of us this switch has been activated but is never reversed. “The survival switch has become a **fat switch.”**

Chapter 3 The Survival Switch

The survival switch is turned on by fructose. Fructose is the dominant sugar in fruit and honey, and is bonded together with glucose to form sucrose. Dr. Johnson talks about animals preparing for hibernation, and birds preparing for migration by fattening up on fructose containing foods.

Johnson got into all of this because of an interest in uric acid. He and his lab figured out that elevated uric acid can cause high blood pressure. He also began to look into why uric acid levels had increased in more recent times. **Through his and other’s research, he figured out that sugar, particularly fructose and raise uric acid levels.** “This led me to wonder if fructose intake might increase blood pressure through its ability to raise uric acid levels.” It did.

Johnson found that blocking uric acid production blocked the increase in blood pressure. Surprisingly, blocking uric acid also blocked some of the weight gain, insulin resistance, and a rise in triglycerides- all the hallmarks of metabolic syndrome. He wanted to know why.

The basic question that he pursued was if fructose caused metabolic syndrome. And if so, how. **It became clear that excessive fructose did cause all the features of metabolic syndrome including fatty liver, elevated blood pressure, insulin resistance, and reduced HDL cholesterol.** Also noted was lowered energy metabolism after meals. This was especially noteworthy in those animals and humans that consumed fructose in a liquid form.

Interestingly, fructose intake strongly stimulated appetite after a few weeks of a larger intake**. Animals that got the fructose did not gain weight if their calories were restricted, but they still developed insulin resistance, elevated triglycerides, and increased blood pressure. What this showed is that excess fructose intake stimulated appetite. It made the animals very hungry.**

In another experiment, rats were given either sucrose or starch for their carbohydrate. The sucrose fed rats developed diabetes and fatty liver, even in a situation where they were calorie restricted.

Johnson wanted to know why fructose drove hunger. What Johnson’s group found is that lab animals given a high-fructose diet became leptin resistant. Leptin is a hormone released by fat cells that tells the brain that we are full. Eating a high-fructose diet for several weeks to months will cause leptin resistance. Hunger increases because you never feel full.

If an animal consumes a diet that is high in fat while they are leptin resistant from a high-fructose diet, they will gain weight. An animal given a high-fat diet while not on fructose and not leptin resistant will self-regulate their food and maintain a more normal weight. “This is the likely explanation for why popular high-fat, low-carb diets do not cause obesity.”

The liver is fully responsible for fructose causing obesity and metabolic syndrome even though fructose is also metabolized in the kidneys and intestines.

One of the peculiarities of fructose metabolism is that its metabolism is distinctly different that metabolism of glucose. To metabolize glucose and fructose, a certain amount of energy is used up to start the process. This energy comes from ATP, the energy currency of the cell. **When glucose is in abundance, the metabolism will slow if ATP is getting too low, allowing the cell to catch up.**

Fructose metabolism is quite different. If there is excessive fructose, there is no brake on the process. ATP is used up. ATP is converted to ADP in this process. ADP in turn is converted into AMP, which is then converted into uric acid. ATP falls precipitously if a lot of fructose is present.

The intracellular uric acid causes oxidative stress of the mitochondria, impairing their function. Uric acid also impairs the body’s ability to burn fat, thus fat is produced and stored.

The drop in ATP is perceived as an emergency. Hunger is stimulated to rebuild ATP levels. With the oxidative stress in the mitochondria, the food that is eaten when hungry under this condition is converted more readily to fat.

Characteristics of the Survival Switch

The survival switch has several characteristics which include the following:

- **Hunger** Hunger is driven by low ATP levels. This simulates starvation. The accompanying leptin resistance prevents us from feeling full. It is the leptin resistance which develops over time that is more responsible for stimulating food intake and weight gain.
- **Craving** Craving is driven by fructose metabolism in the intestines and possibly in the brain.
- **Foraging behavior** This behavior aids in the search for food in unfamiliar areas. It contributes to risk taking, impulsiveness, rapid decision making, and aggression.
- **Increased food intake** This is driven by hunger and craving, and achieved by foraging behavior.
- **Reduced resting metabolism** This allows the body to conserve energy when not needed for foraging. It likely comes from changes in mitochondrial function.
- **Fat accumulation** Increased production and reduced burning of fat results in fat accumulation. This is caused by oxidative stress at the mitochondrial level, most especially in the liver. This fat supplies a source of stored energy and of metabolic water.

- **Glycogen accumulation** This is produced in the liver along with fat and supplies water and energy. The water comes from the blood and is stored with the glycogen.
- **Thirst** As glycogen is produced, water is removed from the blood to be stored with the glycogen. This triggers thirst.
- **Insulin Resistance** This is linked to mitochondrial oxidative stress (along with fat accumulation per Lou Cantley and Richard Shulman).
- **Increased Blood Pressure** Increases in blood pressure are driven in part by uric acid accumulation. This maintains circulation in the case of dehydration or low availability of salt.
- **Salt Retention** This is driven by the effects of uric acid on the kidneys. Increased salt can support circulation.
- **Low Grade Inflammation** This is likely driven in part by uric acid. It may provide some defense against infection
- **Reduced Oxygen Needs** Moving away from oxidative phosphorylation toward aerobic glycolysis decreases the need for oxygen.

Chapter 4 Why We Are Becoming Fat

"Our love affair with fructose has deep roots, for fructose saved our shared ancestors from extinction more than once. **At least two times in our history, our survival was linked not simply with fructose, but with lifesaving genetic mutations that gave us a winning combination: the ability to store *more* fat from *less* fructose.**

The first of these mutations was the loss of the ability to make vitamin C. This mutation happened far back in mammalian evolution. Vitamin C acts as an antioxidant and would be expected to dampen the survival switch by protecting mitochondria from oxidative stress. Less vitamin C means more fat storage.

The second mutation was in an enzyme called uricase that breaks down uric acid. This mutation leads to generally higher levels of uric acid, again causing activation of the survival switch and much greater fat accumulation for a given amount of fructose intake.

Uric acid levels in primates that had the gene that metabolizes uric acid measured 1-2mg/dL. In primates with the mutation, the levels were 3-4 mg/dL. In a hunter/ gatherer tribe in the Amazon, the average levels of uric acid were about 3 mg/dL.

The average uric acid level for the researchers testing the Amazonian tribe was 5 mg/dL.

Increasing vitamin C intake decreases the risk of metabolic syndrome.

Johnson goes on to discuss the development of commercialized sugar and the relationship between sugar, tooth decay, and obesity.

Sugar intake has skyrocketed since the early 1800's. In 1800, the average sugar intake in England was 18 pounds per person per year. In the US, average sugar intake in 1893 was 60 pounds per year. By 1970, it was 95 pounds per year. With the introduction of high fructose corn syrup, consumption increased to an average of 130 pounds of

sucrose and fructose per year by the year 2000. Sucrose and high fructose corn syrup account for 15-25% of calories today.

Chapter 5 An Unpleasant Surprise: It's Not Just Fructose

"Our big discovery was that there is *another* major source of fructose that can trigger the survival switch, and thus cause obesity and metabolic syndrome: the fructose *that our bodies make*."

The pathway in the body that converts glucose into fructose is called the *polyol pathway*. In this pathway, glucose is converted into sorbitol, then on the fructose. It was thought for a long time that this pathway was minimally active and responsible for only a minor amount of fructose in the body. This turned out to not be the case. **When the body is flooded with glucose, this pathway is activated.**

"It was a major breakthrough, simultaneously exhilarating and depressing. It is not just the fructose we eat that causes obesity; it is the fructose we make. What is more, glucose, a major component of the carbohydrates in our diet, could be converted to fructose in our body. **Yes, there was a little evidence that glucose itself could cause some obesity, for the animals that received glucose but whose fructose production or metabolism was blocked still gained some weight compared to mice on normal diet. However, much of the weight gain, and almost all of the insulin resistance and fatty liver, that follows from high intake of glucose appears due to the fructose that the body makes from the glucose."**

The usual theory as to why sugar causes obesity is that excess sugar intake causes high levels of insulin and insulin resistance. What Johnson's group figured out is that a high sugar intake, *but with the ability to metabolize fructose blocked* did not cause weight gain or insulin resistance. They did not develop fatty liver either.

"The cause of metabolic syndrome is fructose." This is either directly, as fructose, or from excess levels of glucose activating the polyol pathway leading to conversion of the glucose into fructose.

The polyol pathway is also activated by dehydration. Conversion of glucose to fructose makes for a source of metabolic water.

Low blood pressure activates this pathway as well. The generation of fructose helps us to hold onto salt.

Low blood oxygen levels also activate this pathway.

The uric acid generated by fructose metabolism also activates the polyol pathway, amplifying the survival switch.

Salt and the survival switch

Excess salt intake- enough to make an animal somewhat dehydrated and thirsty will trigger the polyol pathway, and over time, cause enough of an excess production of fructose to trigger obesity in lab mice. All the features of metabolic syndrome are also

triggered. In mice modified to not be able to metabolize fructose remained lean on the same high salt diet.

“In other words, almost all of salt’s negative health effects were a consequence of salt stimulating fructose production. Even the well-know effect of salt on blood pressure appears to depend on fructose.”

Apparently one study in humans lasting only five day, subjects were given a high salt diet. By the end of the five days the subjects had signs of insulin resistance. In a Japanese study, people who ate a high salt diet were much more likely to develop diabetes and fatty liver. In another study people who are overweight are about 30% more likely to be dehydrated as based on blood tests.

Vasopressin: The Fat Hormone

“Mild dehydration stimulates the development of obesity, and people with obesity show signs of dehydration. A high-salt diet is one way to trigger dehydration, and our studies showed that this, in turn, stimulates fructose production and fat formation.”

Vasopressin acts to reduce loss of water from the kidneys. Fructose stimulates storage of fat which makes metabolic water available.

“Fructose, as it turns out, directly stimulates the production of vasopressin.”

One of the questions that has been asked is if being better hydrated can help prevent obesity. It appears that the answer is yes. Staying hydrated keeps vasopressin low which leads to less activation of the polyol pathway and less production of fructose.

Umami and Obesity

The umami flavor comes from the presence of glutamate. Our taste for umami can be markedly enhanced by the presence of AMP, a breakdown product of ATP. AMP is converted to IMP before being converted to uric acid.

“These substances, AMP (adenosine monophosphate) and IMP (inosine monophosphate), are present in high amounts in foods such as lobster and other shellfish, dark fish (mackerel, anchovies, and tuna), organ meats such as liver, and foods containing yeast (including several cheeses). Beer is especially high in umami, not because of the alcohol content, but because brewer’s yeast is rich in glutamate as well as AMP and IMP.”

These is good evidence that foods high in umami can cause obesity. The thought is that they do so by activating the survival switch by engaging the energy depletion pathway.

Chapter 6 The Bread-and-Butter Diseases of Humankind

Gout and hyperuricemia

Recall that before the uricase mutation took hold, uric acid levels ranged from 1-2 mg/dL. With the uricase mutation it rose to 3-4 mg/dL. **"However, the introduction of the Western diet, and especially alcohol and foods rich in sugar and umami, has pushed uric acid even higher, so that the average levels today are 5-6 mg/dL- and the uric acid of as many as 20 million people in the US is even higher. These elevated levels (>6 mg/dL in women and >7 mg/dL in men) are sometimes referred to as *hyperuricemia*, and people with hyperuricemia are the ones most likely to develop gout."**

For Johnson, elevated uric acid is a consequence of the survival switch in overdrive.

What is more troubling is that **there is good evidence that elevated uric acid can itself trigger the survival switch in a kind of feed-forward mechanism**

Type 2 Diabetes: Endgame of Insulin Resistance

Activation of the survival switch by fructose triggers insulin resistance. Sugar can even directly damage the insulin producing cells of the pancreas.

"Sugar is not the only food associated with diabetes risk, but as we've seen, sugar is not the only food that turns on the survival switch, even if it is its major driver. It is therefore not surprising that high-glycemic carbohydrates, including foods such as rice and potatoes, also increase the risk for diabetes, although not as strongly. The same is true for red meat, beer, and other umami foods, and for high-salt diets. All of these suggest that type 2 diabetes is an unwanted gift of the fat switch."

Hypertension, Heart Failure, and Stroke

"…volunteers develop an immediate rise in blood pressure after they are given fructose, whereas this is not observed with glucose or water."

The rise in blood pressure is related to increases in uric acid, which in turn is related to increased intake of fructose. Allopurinol, a uric acid blocking drug, abolishes the increased blood pressure in response to fructose.

Salt is also related to increases in blood pressure. Increased salt concentration in the blood triggers the production of fructose and the production of vasopressin.

"While the survival switch's release of uric acid and vasopressin is what increases blood pressure in the short term, there is evidence that another system eventually takes over."

Activation of the survival switch causes low grade inflammation in the kidneys- important regulators of blood pressure. This inflammation is self-perpetuating. It causes the kidneys to retain salt. This in turn helps create high blood pressure.

Liver Disease

"In the 1970s, doctors began to see a new type of liver disease that has since increased dramatically throughout the world. Today it is the most common cause of liver failure and the need for a liver transplant. The disease is called non-alcoholic fatty liver disease, sometimes referred to as NAFLD."

The fatty liver gradually worsens causing low grade inflammation. Over time this inflammation gradually destroys the lever by causing cirrhosis, a progressive scarring process.

Several bits of evidence point directly to sugar, especially fructose consumption as a direct cause of fatty liver. **Most people who developed NAFLD had a history of drinking excessive amounts of high fructose corn syrup laden soft drinks. Most had excess uric acid and the features of metabolic syndrome.**

Biopsies of the livers of patients with NAFLD had a marked increased expression of an enzyme involved in fructose metabolism (fructokinase) and chronic depletion of ATP in the liver cells, a hallmark of activation of the survival switch.

Chronic Kidney Disease

Chronic kidney disease is especially frequent in people with metabolic syndrome. The two most common causes of CKD are diabetes and hypertension. CKD may be one of the results of activation of the survival switch.

There is also some evidence that fructose may directly cause CKD. "The kidney, along with the liver and brain, metabolizes fructose, and the resultant uric acid causes local inflammation and oxidative stress. We have found that high-fructose diets can cause kidney damage over time and can also accelerate preexisting kidney damage. We have also found that the kidney can make fructose via the polyol pathway, especially in the setting of diabetes, and this can lead to kidney damage too- likely part of why diabetes causes kidney disease."

Activation of the survival switch elevates uric acid levels. Elevated uric acid can predict the development of CKD.

Atherosclerosis, Heart Attacks, and Sudden Death

Low grade inflammation is a feature of cardiovascular disease. Activation of the survival switch activates low grade inflammation. When this activation is chronic, it is possible that it plays a role in development of cardiovascular disease though no good studies have been done on the relationship between the survival switch and CVD.

Cancer

"Fructose is cancer cells' preferred fuel, for it support tumor growth under these low-oxygen conditions."

Johnson notes that when cancer cells metastasize, they land in a low oxygen environment because a vascular support system is not in place yet.

"Some cancer cells, such as metastatic colon cancer, pancreatic cancer, and breast cancer, particularly like fructose as a fuel, and this may explain why these cancers are more common in individuals with obesity."

"Researchers are also evaluating whether products of fructose metabolism, such as uric acid and lactic acid, may have a role in stimulating tumor growth and spread."

Chapter 7 How the Survival Switch Affects Our Mind and Behavior

Sugar can cause an addiction. It is a true addiction in that it stimulates the same parts of the brain as heroin, and, if given an opioid blocker such as naloxone, the person addicted to sugar will go into withdrawal.

There is an especially close relationship between sugar and alcohol. Both fructose and alcohol can cause fatty liver. Heavy drinkers have an inordinate craving for sweets. A history of alcoholism in parents, especially the father is associated with a stronger than usual craving for sugar in children. Sugary alcohols are especially addicting.

One way that alcohol activates the survival switch is by causing dehydration and subsequent activation of the polyol pathway. In mice that were genetically unable to metabolize fructose, giving the mice alcohol did not cause fatty liver disease. Recall that alcoholic fatty liver and non-alcoholic fatty liver look identical. In mice that were unable to metabolize fructose, their rate of alcohol consumption was about 1/4th the amount that would ordinarily be consumed on average.

“Alcoholism is a sugar disorder. The sedating effects of alcohol are due to the alcohol itself. However, the craving for alcohol and its ability to cause liver disease both stem from its stimulation of fructose production, which then turns on the survival switch.”

Because alcohol induces fructose production, it explains the connection between alcohol intake and metabolic syndrome. This is especially true with beer consumption because of the umami-rich yeast in beer.

Johnson describes another mutation which allowed our primate precursors to metabolize alcohol. This mutation happened about 10 million years ago. It increased the ability to metabolize 40-fold. **This gave another source of fructose- alcohol induced dehydration activating the polyol pathway, causing the conversion of glucose to fructose.**

Behavioral Disorders

Besides stimulation of hunger and thirst, raising blood pressure, creating low-grade inflammation, and maximizing storage of fat, the survival switch triggers various behavioral changes.

“This cluster of behaviors- impulsivity, exploratory behavior, rapid decision-making, novelty-seeking, and risk-taking- is collectively referred to as the *foraging response.”*

Fructose intake by healthy volunteers was associated with more immediate hunger and a desire for high-calorie foods as compared to glucose intake. There was decreased activity in the area of the brain associated with will power (per-frontal cortex).

“…higher uric acid levels were associated with aspects of foraging behavior, including impulsivity, novelty-seeking, risk-taking, and decreased ability to deliberate (think before acting).”

Some of these qualities associated with the foraging response are characteristics of leaders, explorers, entrepreneurs, and adventurers. But a fine line separates these behaviors from ADHD, bipolar, mania, etc.

Attention Deficit/ Hyperactivity Disorder

Johnson makes the case the ADHD is related to sugar intake and elevated levels of uric acid. He cites several studies which show that the more sugar a person takes in, the more likely there will be an issue with ADHD. The past studies that were done used sucrose rather than fructose. Johnson admits that the information he is presenting is correlation. This does not necessarily prove causation. He proposes several ways of testing the hypothesis.

Bipolar Disorder

Similarly to ADHD, Johnson presents some correlative evidence that suggests a relationship between sugar, especially fructose intake and bipolar disorder. **Interestingly, lithium helps reduce uric acid. Several trials of adding allopurinol to lithium showed benefit in bipolar disorder.**

"One particularly fascinating piece of evidence is the finding that individuals with bipolar disease make fructose in their brains. Specifically, studies of spinal fluid from these patients found high levels of fructose, as well as sorbitol, the substance in the polyol pathway from which fructose is made."

Johnson suggests that the depressive phase might be related to ATP depletion.

Aggression

Dr. Johnson talks about various correlations between sugar intake and aggressive behavior. These are correlations.

Cognition and Dementia

Risk factors for Alzheimer's disease includes heavy intake of foods known to trigger the survival switch such as sugar, high-glycemic carbohydrates, and salt. Diabetes and obesity are implicated in Alzheimer's as well. Fructose is heavily implicated in diabetes and obesity so it begs the question if fructose intake can cause Alzheimer's.

"The brains of Alzheimer's patients show elevated fructose levels, with amounts four to six times higher than those found in brains from individuals of similar age and sex who did not have Alzheimer's. *The highest elevations were found in regions classically affected by the disease*. There is also evidence that much of this fructose is being made in the brain via the polyol pathway. As in bipolar disorder, high amounts of sorbitol, the precursor to fructose, have also been found."

ATP is decreased. AMP is cleared rather than being converted back to ATP. The enzyme responsible for this process is up to twice as high in patients with Alzheimer's as compared to age-matched controls.

"Fructose may be causing resistance to the effects of insulin not only in muscle and liver, but also in the brain, and it is this that may be the root cause of Alzheimer's."

The question is why nature would set things up this way. Johnson speculates that as part of the survival switch there will be less inhibition and more willingness to explore, to look for food- foraging behavior. These are helpful in the short run perhaps but living in this state chronically may well cause damage to the brain.

Uric Acid Paradoxes

There are several apparent paradoxes regarding uric acid elevation, dementia, intelligence, and creativity.

One suggestion is that elevated uric acid is associated with genius and achievement. Uric acid has similarities to caffeine and that uric acid may act as a stimulant. Loss of the uricase enzyme may have beneficial effects on brain function. Studies were done to look at whether high uric acid was associated with higher intelligence. These studies were negative. However, some studies suggested that higher uric acid were associated with the being high achievers and with doing better on exams. Another study found that those in the top level of uric acid in high school did better in school and were more likely to go to college, to date more, to be more confident, and to spend more time in leisure activities.

Johnson suspects that the association with dementia on the one hand and high achievement on the other may reflect the amount of time spent with the survival switch activated through life. In the short term, activation of the survival switch and the connection to foraging behavior- rapid response time, openness, modest risk-taking, exploratory behavior, and novelty-seeking, might be very beneficial. What he wonders about are the long-term implications of being in this state for prolonged periods of time.

Another paradox is that Alzheimer's patients frequently have low uric acid levels. "This is a little easier to understand, as numerous studies have shown that Alzheimer's patients often lose substantial weight in the months before they are diagnosed. Since the concentration of uric acid in the blood is largely driven by food intake, it is to be expected that these patients' uric acid level would be low at the time of diagnosis."

Chapter 8 Understanding Sugar in Our Diet

In this chapter, Dr. Johnson looks at the prevalence of sugar in the modern American diet.

"One study of over 85,000 packaged foods showed that 68 percent of them contained fructose, glucose, or combined fructose-glucose caloric sweeteners. According to the American Heart Association, the average person takes in the equivalent of twenty-two teaspoons of added sugar…a day, accounting for 15-20 percent of their overall caloric

intake.” In poor people this can be much more because of the relatively lower cost of high-sugar foods.

Dr. Johnson notes that there are multiple names for the variants of added sugars.

Question 1. Do we need to consider the amounts of sugar (and especially fructose) in fruits and vegetables?

With regard to the survival switch, the source of the switch is largely under the control of the liver. Some amount of fructose is metabolized in the intestinal wall. It is the fructose beyond this that gets transported to the liver for processing. **Foods with a small amount of fructose will have the fructose cleared by the intestines.**

Fruits have more fructose than most other foods. “However, whole fruits contain substances that tend to block the effects of fructose, such as vitamin C, plant compounds known as flavonoids, potassium, and fiber.” Dr. Johnson recommends eating smaller portions of fruits that are high in fructose and choosing fruits that are lower in fructose to begin with. (Recall too that modern fruits have been bred to be particularly sweet.)

Dr. Johnson recommends limiting fruit juices, fruit drinks and fruit smoothies. They have too much fructose or added sweeteners to be healthy.

Question 2. Is there any difference between consuming added sugars in drinks and eating added sugars in food?

The survival switch is activated by a fall in ATP levels in the liver. When sugars are taken in as drinks often in a very short period of time, **the liver is overwhelmed by the fructose triggering a very strong drop in ATP levels thereby activating the survival switch.**

People rarely drinks soft drinks or eat sugary desserts slowly.

Question 3. Is there a reason it felt as if I could eat sugar with impunity when I was young, and now it seems so easy to gain weight from almost anything I eat?

There are metabolic changes as we age. Another aspect though is that the more fructose one eats, the more efficient we become at absorbing it. We can upregulate the absorption of fructose when we are exposed to a lot of it.

In one study: “**We compared how well fructose was absorbed and metabolized in lean children, children with obesity, and children with obesity who had fatty liver, and the findings were striking. The lean children did not absorb the fructose very well and metabolized it slowly. In contrast, the obese children absorbed fructose much more easily, and the children who were both obese and had fatty liver absorbed and metabolized fructose to an even greater extent.”**

“The good news is that there’s an easy fix. This increased sensitivity can be reversed by eliminating fructose from your diet for five days to two weeks.”

Question 4. Are artificial sweeteners safe? Will using them help me to lose weight?

"Takeaway: Use artificial sugars with caution, if at all. They do not cause weight gain on their own, but they also do not block craving for sugar and may encourage it."

Question 5. I understand that soft drinks are bad, but what about sports drinks?

Properly formulated sports drinks are fine to use if you are exercising heavily and sweating profusely. A good sports drink has glucose and a bit less fructose along with salt. The amount of fructose is such that it will be metabolized in the intestinal wall. A bit of fructose helps glucose to absorb. Too much glucose is problematic, as is having more fructose than glucose.

Question 6. There are some reports that sugar can improve performance. How is that possible, given the evidence that sugar impairs school performance?

There are studies showing that sugar can increase mental performance. The studies were done in children. They used glucose, not sucrose or fructose. Kids not eating breakfast do worse in school. Glucose can prevent this. Too much glucose can make things worse though. "Consistent with these findings, a randomized study showed that adolescents receiving a low-glycemic breakfast performed better on standard tests assessing working memory and attention than children receiving a high-glycemic breakfast or no breakfast at all."

Dr. Johnson's takeaway: "Low blood sugar worsens mental performance, but so does high blood sugar. Be sure to eat breakfast, but steer clear of cereals with high glycemic indexes!"

Question 7. Are some people resistant to the effects of fructose-containing sugars? What are the potential causes of sugar resistance?

"In individuals of any age who do not eat a lot of fructose-containing sugars, **the systems for absorbing and metabolizing fructose are not 'turned on.'** As a result, when they do eat sugar, they have a relatively mild metabolic response."

"Another common reason is that young and/or athletic individuals tend to have healthier mitochondria. Their healthier energy factories are more resistant to the fructose-driven oxidative stress that triggers the survival switch."

Another group of people that seem to be resistant to high levels of sugar intake consumed large quantities of epicatechin containing cacao beverages. Epicatechin will lower triglycerides and decrease inflammatory markers in people with metabolic syndrome. It also protects the liver cells from the oxidative stress caused by fructose intake.

Question 8. Is there a way to block our craving for sugar?

The single best way to reduce sugar cravings is to markedly decrease or preferably eliminate all added sugars and sugar substitutes for several weeks. The first days will be difficult, but then become progressively easier. **It is best to reduce alcohol as well.**

You can sometimes appease your sugar craving by eating some whole fruit, drinking water, or eating vegetables or a salad.

Chapter 9 The Optimal Diet for Blocking the Fat Switch

In this chapter, Dr. Johnson reiterates the purpose of the survival switch and how it works. He then goes on to make dietary recommendations.

"To help protect animals as risk of death from starvation, dehydration, suffocation, and other threats to survival, nature developed a biological response…that we have named the survival switch. The primary way this switch is activated is by eating or making fructose; dehydration and elevations in blood glucose "turn on" the body's ability to make fructose. Ingesting foods that are rich in umami can also activate this biologic switch, as these foods stimulate the production of uric acid, which has a critical role in fructose's effects. The importance of this pathway is why we, and many other species, have developed specific tastes for sweet, salty, and savory foods."

"The effects of the switch are quite powerful. First, it stimulates craving and impulsivity while reducing willpower, which helps drive foraging for food and water even in dangerous situations. It causes leptin resistance in the brain, so that we remain hungry even after we eat and therefore take in more food than we need, which allows us to build up our fat stores."

Other effects include developing insulin resistance, increased blood pressure, inflammation, and mitochondrial oxidative stress.

The consequences of all of this is that we accumulate fat, burn less fat, and we shift energy production to a more primitive system that doesn't use oxygen (aerobic glycolysis).

One of the most pertinent points that Dr. Johnson makes is that this switch is best only engaged for limited periods of time. The modern diet keeps this switch activated.

The big three- Carbohydrates, fat, and protein

Good Carbs and Bad Carbs

The carbohydrates to be concerned about are the fructose-containing sugars, such as sucrose and high fructose corn syrup (HFCS), and carbohydrates that cause a significant rise in blood sugar.

Dr. Johnson discusses ***glycemic load***, a measure of a combination of glycemic index- a measure of the tendency of a food to raise blood sugar, along with a measure of how much is typically eaten at a meal. If you eat only a small amount of a high glycemic food

the effect will, of course, be different from eating a large amount of a high glycemic index food.

Instant oatmeal, cornflakes, baked potato, white rice, white bread, pancakes, bagels, sweet corn, and spaghetti all have a high glycemic load. A high glycemic load is 20 or above. (Tables of glycemic load are available online.)

Dr. Johnson recommends that people use continuous glucose monitors to get a sense of how they respond to various foods. Everyone is different in how they respond to any given food. (Doing this for 4-6 weeks is an excellent way to track your unique response to foods that you eat.)

“I personally have found this device to be useful in identifying what specific foods raise my blood glucose levels (and therefore have the potential to activate the switch) and also for identifying when I am susceptible to low blood glucose levels (<60 mg/dL), which can lead to light-headedness and confusion (the latter of which can occur during exercise, fasting, or restricting carbohydrate intake).”

“A good goal is to maintain glucose levels between 70 and 110 mg/dL for most of the day. Glucose levels are expected to rise following a meal, but the level of glucose one to two hours after eating should be less than 140 mg/dL and ideally less than 120 mg/dL. While we do not know the specific glucose level in the liver or blood that triggers the survival switch, maintaining blood glucose levels in this range will certainly minimize the production of fructose in response to carbohydrate intake.”

Good Fats and Bad Fats

Fat does not activate the survival switch. Animals given a high fat diet without the added sugars stayed leptin sensitive and adjusted their food intake to keep their weight at a good place. On the other hand, if the survival switch is already activated, fat intake will result is rapid weight gain. The best diet to make and animal (and a human) obese is a high sugar, high fat diet.

“On a low-carbohydrate diet (and therefore a diet that is low in fructose and high-glycemic carbohydrates), the survival switch is turned down, and you are less hungry. Therefore, even though your diet may be high in fat, you will not gain weight. This is also why a low-fat diet only results in weight loss if you also include calorie restriction as part of the diet, whereas on a low-carb diet, calorie restriction (i.e., avoiding fat) is not required. *Fructose is the criminal. Fat is only the accomplice.*”

Dr. Johnson talks about the beneficial effects of omega 3 fatty acids, saying that they may block the negative effects of fructose.

Good Proteins and Bad Proteins

Dr. Johnson has the opinion that red meat is not good for you because of the levels of some of the umami substances and because of the potential for formation of TMAO during cooking. He prefers poultry and most fish, dairy, and vegetable proteins including beans.

Dr. Johnson talks about various diets, noting especially how hard it is to maintain most of them for any length of time. He introduces his own recommendation, suggesting a diet that is closer to the standard diet in terms of macronutrient composition. He has specific recommendations for protein amounts and types, types and quantities of fat and carbohydrate. He discusses salt and water, umami foods, and dairy.

Alcohol should be considered to be a type of sugar in terms of how it is handled in the body. He recommends coffee, tea, and dark chocolate. He recommends 500-1000mg of vitamin C daily.

The Switch Diet

Sugar:

- Reduce sugar to 10% of calories, aiming for 5% or less long-term.
- Eliminate sugary drinks entirely

Carbohydrates

- Reduce high-glycemic carbohydrates
- Emphasize whole grains, low-glycemic vegetables, and high fiber foods
- Limit fruit to 3-4 servings per day, separated; Have ½ servings of high-glycemic fruits
- Avoid dried fruit, fruit juices, fruit syrups, and fruit concentrates

Protein

- Limit high-umami proteins (red meats, organ meats, and shellfish)
- Emphasize fish, poultry, dairy, and vegetable proteins.

Fat

- Emphasize monounsaturated and omega-3 fats.
- Saturated fats can account for up to 10% of total fat intake

Salt

- Reduce salt intake to 5-6 grams daily
- Limit processed foods, as they are often high in salt9 as well as sugar).

Water

- Drink 8 ounces of water 6-8 times daily

Dairy

- Dairy is generally recommended, especially milk
- Butter and cheese are fine if LDL cholesterol levels are controlled
- High-umami cheese should be limited

Coffee, Tea, and Chocolate

- Coffee and tea are recommended
- Dark chocolate is encouraged

Alcohol

- Reduce or eliminate alcohol
- If you want to drink alcohol, sip rather than drinking quickly, and alternate with water

Vitamin C

- Take a vitamin C supplement daily

Lowering Uric Acid

If your uric acid levels are high (>6 for women and >7 for men), the first thing to do is to work with your diet. Dr. Johnson discusses the possibility of using medication to lower elevated uric acid levels, even if you do not suffer from gout because of the effect of uric acid on the survival switch.

“The diet outlined here is aimed at preventing weight gain and improving overall health. And while this dietary advice may incidentally lead to weight loss, it is not specifically aimed at helping you lose weight. Let’s turn to that next.”

Chapter 10 Restoring Your Original Weight and Improving Your Healthspan

“The primary problem is that, when you have been overweight or obese for a while, your body begins to think of your current weight as normal. Indeed, it wants to keep you at that weight. This means that when you go on a diet and begin losing weight, your body responds by reducing how much energy it uses. This decrease in metabolism minimizes your weight loss. You may also get hungrier, which drives you to eat more to regain the weight you have already lost.”

“When you fast for an extended period, the energy you need decreases in response, sort of like it does for an animal that is hibernating. Since you are using less and less energy to function, weight loss slows down over time. For all the good things associated with fasting, it is still not enough.”

Important points about the cause of mitochondrial dysfunction and what is needed for repair

When we eat fructose, uric acid is produced which causes oxidative stress to the mitochondria. “This in turn reduces production of ATP while shunting the calories from fructose into storage as fat and glycogen. The process allows us to build up stores of energy for times when food is not available.”

This oxidative stress can be damaging to the body, both to the mitochondria and to the rest of the body. In a more natural setting, this damage is relatively short-lived, and the mitochondria recover. “We, in contrast, are turning on the survival switch full blast for years and years. What was meant to be a temporary depression of energy production by the mitochondria for survival purposes becomes a permanent one, with dire consequences.”

With chronic oxidative stress the mitochondria undergo structural changes. They become smaller and their energy production decreases, even when the survival switch is not activated. "This resets the metabolism, lowering energy production and use as weight increases. Because your body now thinks the higher weight is the normal weight, it sees weight loss as a threat to your survival and responds by altering your metabolism further."

Fructose causes more oxidative stress to the mitochondria than other nutrients.

"…curing obesity is easiest if it is caught early before there is permanent damage to the mitochondria. Indeed, my personal experience has been that it is much easier to treat obesity in children and adolescents, and can be done simply by diet to reduce intake of foods that can activate the switch. This is because younger people still have plenty of functioning mitochondria."

The key for people who have damaged their mitochondria is to rehabilitate them.

"This approach focuses primarily on blocking continuous activation of the survival switch. Second, we want to proactively stimulate the repair of the energy factories, or, even better, increase the production of mitochondria to replace the ones we have lost."

One low tech way to check mitochondrial function is to check gait speed. Here you walk normally (for you), counting the steps. Walk a known distance. To do this you could measure out 50 feet or so, then get up to your comfortable speed and start counting the number of step and the number of seconds to go through that 50 feet. Calculate your feet per second rate. Gait speed varies from 2-6 feet per second. People who could use some mitochondrial help will have a speed under 4 feet per second. Don't try to walk fast with this test. Walk your normal walk.

"Studies have shown that natural gait speed correlates with the quality of your mitochondria…" "A reduced pace has been associated with increased fatigue and low ATP levels in skeletal muscle."

Blocking the fat switch

A study was done where patients were put on a moderately low salt diet (6 grams per day) along with a low fructose diet. The numbers of mitochondria in the white blood cells increased dramatically. Intermittent fasting will also decrease activation of the survival switch.

Stimulating mitochondrial growth: Lessons from superhumans

This section discusses elite athletes. It is informative to see how this group of people generate energy.

Johnson talks about the work of physiologist Inago San Millan. "His work (as well as that of others) has demonstrated that top international athletes- which he has referred to as 'superhumans'- have superb energy factories and, as a result, posses something he refers to as 'metabolic flexibility,' the ability to move back and forth between using fat and carbohydrates for energy. For example, when working out at low or moderate intensity, these athletes primarily burn fat, but when working out at full exertion, they

primarily burn carbohydrates. In contrast, people with obesity are metabolically *in*flexible. They cannot burn fat very well, they can only exercise for short periods of time, and their oxygen consumption is only about one-third of the elite athlete's-suggesting that their energy factories, which require oxygen to function, are working less hard."

Lactate is generated in the metabolism of glucose. Individuals with healthy mitochondria can use lactate as fuel. Elite athletes can exercise a long time before lactate builds up because they are very efficient at utilizing it as fuel. By contrast, those with obesity have trouble using lactate. It builds up more rapidly.

So, how quickly lactate builds up is a proxy measure of the health of the mitochondria. And, high lactate can impair mitochondrial function, similar to uric acid.

Interestingly, fructose metabolizes to lactate much more than glucose does, with up to 25% of fructose being converted in this way.

Increasing your energy factories

"What is the best type of exercise to improve mitochondrial function? Many studies have examined this. First, **it needs to be an endurance type of exercise**, such as walking, exercising on a treadmill, swimming, or cycling, as opposed to a non-endurance exercise such as weightlifting. Second, **it is most effective if you are either fasting or do not eat any carbohydrates before the exercise**. Third, **the exercise has to be sustained for at least an hour, and be done at least three or four times a week**. This is because it takes some time to activate the process of mitochondrial growth, and exercising less than thirty minutes at a time rarely achieves this."

"Exercise intensity also matters. As Inago showed, **once you start to accumulate lactate in your blood, not only do you begin to feel fatigued, but the high lactate levels block the mitochondria's ability to burn fat, resulting in an inability to continue exercising. So, the trick for our purposes, is to find an exercise where you can last an hour without accumulating lactate. This varies dramatically among individuals. People with poor mitochondrial function, like those with long-standing obesity or metabolic syndrome, have to exercise at a much lower speed than weekend or competitive athletes."**

How do you know how hard to go? How do you know if you are going too easy?

The technical way is to test your lactate levels. Lactate testing is available with test strips.

"The simplest (and the one that Inago recommends) is considering the intensity of your breathing and your ability to talk. The right exercise intensity should allow you to maintain a conversation, but with some degree of difficulty. If you can speak and breathe while exercising almost as well as you can at rest, then you are going too easy. If you can't maintain a conversation, then you are exercising too hard."

"Exercise is often categorized by zones based on heart rate. The level of exercise that is optimal for improving your mitochondria is referred to as Zone 2…and generally

corresponds to light intensity characterized by a heart rate approximately 70 percent of your maximum healthy heart rate."

Johnson says that the 70 percent figure is poorly validated. He mentions in a footnote that a common formula is to estimate your maximum heart rate by subtracting age from 220, then multiplying by 0.7.

(A note from RJH: In a podcast with Peter Attia and Phil Maffeltone, Maffeltone suggests using a formula of 180 minus age, then modifying it upwards by 5-10 points if you are in good shape, or downward by 5-10 points if you are more metabolically ill or deconditioned.)

Intermittent fasting can stimulate mitochondrial biogenesis, as can supplements containing epicatechin found in dark chocolate and bitter cocoa. Green tea contains a less potent variant called epigallocatechin which also stimulates mitochondrial biogenesis.

On the flip side, supplements of NAC, alpha lipoic acid, and vitamin C (all are antioxidants) interfere with the rebuilding of mitochondria. The point here is to not overdo the antioxidants, especially when you are exercising.

(A note from RJH: One article I read noted that short bursts of oxidant stress were helpful in stimulating mitochondrial repair and activating mitochondrial protection mechanisms.)

Another benefit of better mitochondrial function: Blocking the effects of aging

In this section Dr. Johnson discusses the effects of chronic, excessive sugar intake on life span, cardiovascular disease mortality, and dementia.

"Our group found provocative evidence suggesting that the chronic production of fructose in our body may contribute to aging as well. As we have learned, our bodies can make fructose from the glucose in carbohydrates, even if the carbohydrates do not contain fructose.'

In a mouse study, mice were bred such that they could not metabolize fructose. These mice had normal organs as compared to aged-matched mice who could metabolize fructose.

A plan to lose weight and keep it off

"The first step of an effective weight-loss plan is to stimulate fat burning. Since we burn fat only when we need additional energy, we need to reduce the energy we obtain from our diet. All diets aimed at weight loss involve calorie restriction. However, the most successful diets *also* always involve turning down the switch, for tis helps minimize hunger and the foraging response that occurs when the switch is turned on. This is why diets focused primarily on calorie restriction, but in which sugar and high-glycemic carbohydrates are allowed, are doomed to fail as soon as the calorie restriction ends. **This is also why diets that *restrict* sugar and high-glycemic carbohydrates can cause weight loss even without specifically restricting calories.** By dimming the switch, these diets reduce hunger, so calorie restriction

occurs naturally. In addition, **turning down the switch allows one to burn fat more effectively…one of the actions of the switch is to block the burning of fat…"**

"The second step is to block the reduction in metabolism that the body uses to compensate for the weight loss and keep us at our current weight. As mentioned, when we have been overweight for a long time, our energy factories are working at reduced capacity, and this is associated with the body's perception of overweight as the new normal. When this happens, we respond to weight loss by reducing our metabolism, so that the amount of food that once kept us at a stable weight now causes weight gain. This process causes almost all dietary plans to fail. **To overcome this, we have to prevent further injury to these energy factories by dimming the switch while we both stimulate the production of new energy factories and increase our energy output."**

So, exercise- not to burn calories, but to stimulate mitochondrial growth and repair. Turn down the switch by changing the type of food you eat. Dr. Johnson recommends starting with a low-carb or keto diet. These diets restrict sugar and carbs- our main sources of fructose. By turning down the switch, appetite is naturally decreased. The foraging response goes away. Get enough water, especially when you are taking in salt. Keep the salt to a more reasonable level (which is easy to do if you are avoiding packaged foods). Keep umami foods to a low level. You might want to practice time-restricted eating, keeping your food intake to a relatively shorter window during the day.

Typically, it is hard to stay with a strict keto or low-carb diet for a long period of time. At some point you may want to change to a more Mediterranean diet or investigate Dr. Johnson's Switch Diet, described above.