

A Special Interview with Dr. Richard Johnson

By Dr. Joseph Mercola

DM: Dr. Joseph Mercola

RJ: Dr. Richard Johnson

Introduction:

DM: Welcome, everyone. This is Dr. Mercola, and today I'm joined by Dr. Richard Johnson who is the chief of the Division of Renal Diseases and Hypertension at the University of Colorado. He's published hundreds of articles and two books: *The Sugar Fix* and *The Fat Switch*, which we're going to talk about today.

The Fat Switch is really in the media quite a bit now. Dr. Johnson's getting quite a few interviews from the conventional media about this topic on sugar, because it discusses fructose's impact on your body, its potential for toxicity, and the ways to balance it out. Interestingly, the *The Fat Switch* is published by Mercola.com.

So, welcome and thank you for joining us today, Dr. Johnson.

RJ: Thank you, Dr. Mercola. It's really great to be here.

DM: I'm wondering if you could comment on and define fructose a bit, because many of our viewers are not going to be as adept to the biochemistry – and the connection with sugar. Because you talked about sugar initially and it's great to have that historical background, but if you can combine that with respect to the glucose, fructose, and the dangers of fructose as high-fructose corn syrup relative to just plain sugar.

RJ: Yeah, you're absolutely right. We should probably go through the definitions. Table sugar is also known as sucrose. And sucrose contains one molecule of fructose and one molecule of glucose bound together. We call it a disaccharide. But one sucrose molecule actually has a fructose and a glucose molecule bound to it. Sucrose or table sugar is basically about 50 percent fructose. When you eat this sucrose, the sucrose gets metabolized in the intestines to free fructose and free glucose that you then absorb.

High-fructose corn syrup is the other major source of fructose. And high-fructose corn syrup consists of a mixture of fructose and glucose mixed freely together. There's a little bit in most things like soft drinks. There's a little bit more fructose than glucose. It's not exactly a 50-50 ratio, but the ratio can vary depending upon which food.

Because it's free fructose and free glucose, it may have slightly different characteristics that we can talk about a little bit later. But these are the two key ways that people are being exposed to fructose. They make up the vast majority of fructose that we see. It's probably...

DM: Excuse me.

RJ: Yeah, go ahead.

DM: When you mentioned free fructose, can you expand on that? It's just not bound together in that bond, is that correct?

RJ: Right. What I mean by free fructose is it's just fructose and glucose mixed together. They're not bound together.

There are some differences, like high-fructose corn syrup is basically a liquid. It can be mixed into fluids very easily. It tends not to crystalize like sucrose can.

I don't know if you remember the old days where you'd open up a candy bar, and you'd see crystals inside it if it was old, because that was the sugar or sucrose crystalizing. Or the ice cream you might take out of the freezer, and you open it up and you see crystals on the top. That was from the sucrose. With high-fructose corn syrup, it doesn't crystalize. It's cheap. You can mix it very easily into foods. It has a long shelf life.

People have liked it. And the food industry has learned that people love sugar, you know. Even babies love sugar. They'll prefer sugar water over milk. All animals like sugar – basically almost all. The food industry has figured this out, that if they can add just small amounts of sugar or high-fructose corn syrup to foods, it often makes people feel that it tastes better. It's like put in crackers. *[Laughs]* And it's put in foods you've never think of can have a little bit of high-fructose corn syrup or sugar. You have to read carefully the labels. Then try to figure out how much is in there. *[Laughs]* We've been exposed to a lot of this fructose.

I should mention that natural fruits also have fructose. In my original book, *The Sugar Fix*, I was quite concerned about that, because it was another source of fructose. And we can show that fructose does a lot of bad things.

But the good news is we've done subsequent studies, and we've been able to show that natural fruits, although there's some fructose there... First, it's only small amounts. It's like four to eight grams compared to a Coca-Cola or a soft drink that can have 20 grams. Secondly, there are so many wonderful things in natural fruits like vitamin C, antioxidants, resveratrol, flavonols, quercetin, and all these things that actually neutralize some of the effects of fructose.

Because of that, natural fruits do not seem to have the same degree of risk. Now, if you sit down *[Laughs]* in front of the couch and you eat hundreds of, you know, a bowl of grapes or something like that, you may get into a little bit of trouble. If you drink fruit juice that is concentrated and has several – three or four – fruits, and you drink it fast, so that you get a big dose of fructose *[Laughs]* in a very short time, that may overwhelm the benefits of the antioxidants.

DM: Isn't the...

RJ: Dried fruits, which we all love, actually are pretty much pure fructose, because the drying process removes a lot of the good things. I don't recommend drinking a lot of fruit juice, which should be limited. And I don't recommend eating dried fruits.

The American Pediatric Association has linked fruit juice with obesity in children. We probably should limit the fruit juices to four to six ounces a day for most people.

DM: The other component, too, especially with the fruit juice is the fact that it's in liquid, because there's apparently some additional toxicity in the liquid version versus the solid. And of course, it's liquid. It doesn't have the fiber in it also.

You are not just spreading previously known information. One of the greatest reasons why the media has contacted you for your insights on this story is because you are a real pioneer in this area. I'm convinced; there's no doubt in my mind that our readers and viewers would love to hear the process, the story that you went through, and the epiphanies that you had in really discovering this, because it really wasn't through the traditional researcher approach. It's a fascinating story. I'm wondering if you can expound on how you came through this in developing the book *The Fat Switch*.

RJ: You're totally right. I've realized from my discussions with many people that there's more than one approach to try to figure out the cause of a disease. Most of us as scientists have focused just on pure medical science like molecular biology, physiology, and genetics. These are incredibly important tools and have a critical role in helping us figure out diseases. But actually, there's a much bigger field to select from that can help us. For example, there is the field of comparative physiology, which is a complicated phrase and which means study in animals in nature.

You want to know something different? *[Laughs]* For example, most animals have learned how to become fat and how to become thin. They do it in a tightly regulated way. Whales will get fat in the Arctic in preparation for going to their breeding grounds in Baja, Mexico and other places. Hibernating mammals will double their weight and fat in the fall in preparation for winter. Insects have to get fat to survive living as a pupa in the cocoon. Birds will get very fat prior to long-distance migration.

I realized that I can learn by reading the studies about these animals. As I read them, I had another insight, *[Laughs]* which, you know, actually had not been appreciated before. That is that these animals develop all the features of metabolic syndrome that we do. They get fat. They're visceral fat goes up. They get fatty liver. The triglycerides go up in their blood. They get insulin-resistant. Horses get insulin-resistant as they get fat. Birds get insulin-resistant, as they get fat. Mammals, when they prepare for hibernation, get insulin-resistant. It's a normal process. It's not a disease.

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This is how animals store fat. It's part of the fat storage syndrome. I've actually proposed (and it's in press) that the metabolic syndrome really should be called the fat-storage condition, because it's just a fat storage.

The question is when these animals do it, how do they do it? One of the interesting things is that when we're studying fructose, we found that the key enzyme – there was a key enzyme activated. We talked about fructokinase, but that activated another enzyme. When we activate that enzyme in cells, they accumulate fat. When we block it, they block fat.

Then we looked at hibernating mammals in the paper. This one's not in press yet; it's actually just being submitted. But we can show that animals used the same switch – the fat switch – to become fattened in the fall, and then to burn fat in the winter. The switch is turned on and off almost like a clock. We can show it in the animal. And guess what turns on the switch? Fructose turns on the switch. *[Laughs]*

DM: *[Laughs]*

RJ: I mean, it's exactly that enzyme. Guess what's turned off in obese people? That enzyme. In fact, we now know that enzyme's turned off. I'm sorry; I've said it incorrectly. The enzyme that makes you fat is turned on in obese people. And the enzyme that makes you lean is turned off. Even drugs like Metformin, which is the most common drug used for diabetes and it causes weight loss, is probably working on this switch. And we've got evidence for that. But no one really had realized that there is a switch.

This is why the book is called *The Fat Switch*, because basically there is a switch that turns on and off. It looks to me like it's universal to all animals. This book is a story of that. It includes taking animals, looking at them, and trying to figure out why they're becoming fat and thin.

Then our discovery process, which was kind of – it was a detective story. One of the ways we've learned about what was turning on the switch was ironic. We have figured that if we wanted to make an animal turn on the switch, we should actually restrict its food. First, it will burn its carbohydrates, and then it will burn its fat, but eventually...This is all programmed, but it doesn't. Once all the fat's gone, it's like an alarm signal. When that alarm signal occurs, the animals are going to want to re-accumulate fat like big time and quickly.

That's how we discovered or one of the ways we discovered there was a switch. We studied; we looked at the literature for what was going on in that phase. Then we looked at it in terms of our animals with our studies with fructose. We saw that there was some parallel things going on, some things that were similar. That's what triggered our ability to discover the switch.

Then once we *[Laughs]* realized that there was this switch, we asked, "Why are people becoming obese?" Now we realized it was related to the sugar intake. The book includes a big section on history of the introduction of sugar, and how it was linked with obesity. I got to tell you I love Google.

DM: *[Laughs]*

RJ: Google Scholar is one of the greatest things that's ever happened, because you can ask through Google Scholar. You can pull old manuscripts from *[Laughs]* 800 A.D., 1400 A.D., and there it is on your screen. You can read it. You realize that probably very few people have ever read that. Now they have Search functions, too, so you can actually search a 900-page book for sugar cane or something like that, and you can find it.

By doing that I had really interesting discovery. I found that many, many people in the past have linked sugar intake with obesity, going all the way back to the Sanskrit writings of Sushruta, the Indian physician who first described obesity and diabetes in 300 A.D. People didn't realize it, but he actually linked it with sugar himself. *[Laughs]* The linkage of sugar with obesity turns out to be a part of the detective story.

The last part was connecting in with the evolutionary aspects. There's a very famous evolutionary biologist in London – in the Natural History Museum. His name is Peter Andrews. He trained with Richard Leakey. He's like a world expert on human evolution. It turned out that there were certain mutations that occurred.

For example, we don't make vitamin C. We also have higher uric acids than most other animals. When we look at when these mutations occurred, we could see that they actually occurred during periods of human famine, and that these were probably mutations that allowed us to become fatter in response to fructose than other animals. We're much more sensitive to sugar than most animals. It's because of these mutations.

Then I was able to work *[Laughs]* with a spectacular scientist who helped resurrect those extinct genes. We're able to basically prove that when we lost these genes, we became more sensitive to sugar. The story is kind of a grand story. It puts these all together. Then out of it comes the discovery that this pathway is probably important not just in obesity, but in a lot of other diseases like celiac disease, food allergies, and kidney disease. It's a pretty grand story. It's referenced. It has a lot of figures. It tells a story few others have told.

DM: This incredible fat switch that you've discovered through your pretty novel process is really not necessarily bad or dangerous by itself. It's actually highly useful in the animal kingdom. It's just that through a variety of circumstances that you very well-articulated in your book has actually been used to make us sick and ill and massively increases chronic degenerative disease and obesity. It's not necessarily a bad switch. It has its useful utility.

RJ: Absolutely right. Survival requires being able to store food in preparation for periods of food shortage and starvation. All animals had to learn how to regulate their weight.

Normally, their weight is kept very, very stable. Animals don't want to get fat, they don't want to get thin. They keep their weight stable. But they have actually learned that to prepare for periods of time when there isn't much food around, how to accumulate weight. They have to become leptin-resistant, so that they can eat more than they would normally. They have to slightly reduce their energy output, so that the food gets transferred into fat.

It's actually a normal process that animals use. They trigger it different ways. But one of the ways you can trigger it, interestingly, is by diet. Historically, it was kind of linked with fruit. I told you that fruit's healthy. But fruit's healthy for us, because we tend to eat fruits that are not super ripe. But as a fruit really ripens, it actually becomes sweeter. The good things like vitamin C actually go down. Really, really ripe fruit actually does increase fat.

We know this: orangutans will get fat to wait for the fruiting of the trees. Then they will go there and eat massive amounts, so that they can, you know, store fat. It's actually been shown that they do when they do that. There's a really interesting fish called the Pacu fish. Joe, did you know that there are fish that eat only fruit?

DM: *[Laughs]* I was not aware of that. No.

RJ: *[Laughs]* Yeah. In the Amazon River, there are some fish that only eat fruit. One of the most famous ones is called the Pacu fish. It looks like a toothless *[Laughs]* piranha. It's a big fish. Every spring, the rains fall, and the Amazon River swells.

The Amazon, which is normally, you know, certain distance wide, will suddenly flood into the jungle. And for a short period of time, the whole jungle will be inundated for thousands of square kilometers. These fish have timed it to go in there. I should even say, the fruit trees have timed it to drop their fruit into the water. Right about that time, a very, kind of rotting fruit falls into water.

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It's very high in sugar content. The fish come in there, and they eat all the fruits. They help the fruit trees by dispersing the seeds. In turn, they get all that fruit. They dramatically increase their fat content.

Then as the waters recede, the Pacu fish goes back into the river – I mean as the river recedes. It will quit eating for three to five months, maybe even six months, before the inundation comes again and the cycle recurs. They use this period of time to get really fat. They're fat. They get huge fatty liver. Then they consume all their fat for survival when there's no food around.

There are a lot of examples of this, where animals have used fructose, for example, to get fat. The hummingbird drinks nectar. Nectar is basically sugar. During the day, they eat and take up so much nectar. Their liver becomes so creamy white. It's the whitest, fattest liver of all birds. But because of their high metabolism, during the night they start burning off all the fat. In fact, they burn it all off, they'll go into torpor, where they'll drop their metabolism and just sit there very quietly until the morning when they wake up and try to get more sugar.

This is something that a lot of animals do. And we can learn from that. Our approach was to try to look for parallels – you know, how we can learn from this. Actually, it's my hope that as we figure out how to reverse the switch and how to cure obesity, that this will also be very helpful to animals in the wild, where we'll be able to use our knowledge to help them under certain circumstances. I also actually hope to help the animals in the zoo. There are a lot of zoos where animals are actually becoming fat. I've worked with several wildlife conservatory people who are involved in these projects to try to help them.

Also, horses can get into trouble through fructose. We believe that diseases like founder disease, which killed great animals like Secretariat, we can benefit and help these animals and horses based upon our studies.

DM: It's fascinating work. I mean that you have discovered this major discovery, this fat switch that can be absolutely utilized not only in the treatment of animals but certainly for humans. We could take this knowledge, this information, and extrapolate it for different strategies to be effective. We'll talk about some of these strategies.

But there's one specifically that we haven't discussed previously (which has become popular in many circles), called intermittent fasting, where someone will stop eating after dinner, and typically engage in 12- to 18-hour fast. It's not a two- or three-day fast.

I'm wondering, with your understanding of the fat switch and the way it works... The theory of that is you're basically consuming your glycogen store. It forces your body to metabolize the fat that's in your system and, by doing so, better gear up that machinery to do that.

Really, in reality it's more likely to replicate what our ancestors were exposed to. They didn't have access to a refrigerator 24/7 or convenience stores to get food. I'm wondering what your thoughts are on intermittent fasting as a tool, in light of your discovery of the fat switch, to allow people to optimize their ability to obtain an ideal body fat.

RJ: Well, you're absolutely right that if you want to burn fat, intermittent fasting is a pretty good way to do it. Normally when you fast, there's a short period of time where you're burning glycogen, which is the carbohydrates stored in your liver and other tissues but particularly in the liver. While there's glycogen around, it's hard to burn fat, because the body will preferentially burn glycogen. The wonderful thing is glycogen gets burned off fairly quickly, but it takes six to eight hours before it's really burned or before it's completely removed. It takes a little bit longer in people who are obese.

If you eat a dinner early, for example, at 5:00 PM, then you decide not to eat afterwards until the morning, by two or three in the morning the glycogen is gone. Now the body burns fat. You are burning fat while you are sleeping. It's a great move. Whereas if you stay up until midnight and you're eating little chips and things like this that are keeping your glycogen stores up, you may never burn the glycogen at all. By the time you wake up in the morning, you still have glycogen in your liver. You've burned no fat.

Another thing that comes out of this (actually there's work at the university here that confirms this) is that if you exercise in a fasting state like in the morning, you will be burning fat.

DM: *[Laughs]*

RJ: But if you exercise at the end of the day or one hour before you have some kind of snack, you'll probably just be burning the glycogen. It's great to exercise, okay?

DM: Uh-huh.

RJ: Exercise at either time. *[Laughs]* It's wonderful. But if you want to burn fat, you should do it on a fasting stomach. This is one of the things that is important. Now having said this, if this fat switch is turned on, it's going to be a battle. Because as soon as you finish exercising, you're going to be really hungry.

I had a friend who had a weight problem. He and I climbed Mt. Rainier, you know, 14,000 feet. When we got back down, we probably had burned 3,000 calories *[Laughs]* trying to get to the top. But then we went to a restaurant where I think he ate 4,000 calories. *[Laughs]*

DM: *[Laughs]*

RJ: I have this great insight that exercise is a wonderful thing, but we really need to learn how to turn off the fat switch as well. If we can turn off the switch, exercise, and do these kinds of things, we're much more likely to keep the weight off and stay healthy.

DM: Well, thank you for confirming that. It's something I've been applying personally. I'm considering making major revisions to the program. Because the traditional view is that breakfast is the most important meal of the day. You got to have a good breakfast. The reality is maybe one of the most important meals not to eat. Because if you combine that with the fast that you've

had from sleeping, then you're able to enter into this phase where you're far more effectively able to burn the fat and really get down to those stores to optimize your body fat.

RJ: Yeah. Or another way to do this would be to consider exercising in the morning.

DM: Uh-huh.

RJ: And then just having a modest breakfast after that. Then I think it's important... I have a feeling we're eating too much for dinner, really. We would probably do better to reduce the amount we eat for dinner. You do want energy during the day while you're really working. I think that breakfast is okay, but you just want to exercise before breakfast. It's pretty much in alignment with what you're saying.

DM: Okay, just a little refinement. We're still under the discovery phase to optimize the details. But there are some other aspects of your discovery of the fat switch that have some benefits. I'm wondering if you could expand on those. Some of them are still in process. What can people do or what does the research suggest that we can benefit from knowing how the fat switch works?

RJ: Well, one of the key things is, obviously, it looks like fructose is one of the main ways we turn on the switch. It's primarily from sugars and high-fructose corn syrup.

The first rule, if you want to not gain weight or to reduce the risk for obesity, is just cut back on the sugars. I think you can get *The Sugar Fix*, which actually details all the amounts of the fructose in different foods. Or you can just kind of take the simple approach of reading the labels and trying to avoid the foods that have lots of sugar and fructose in it. Don't get trapped by it saying "low-fat," meaning it's healthy. Because if they say "low-fat," they could actually be high-sugar.

First thing is try to reduce your sugar intake, high-fructose corn syrup intake, by half to a third.

The second thing is – and this paper again is not yet published, so stay tuned. But we discovered that under certain circumstances, the body can make its own fructose. I hate to say this. *[Laughs]* It isn't just from the fructose we eat. Fructose can be made from carbs.

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We've done a study where we gave mice glucose in the water and where they drank a huge amount of it. They ate a lot of glucose. If you put glucose in the food, they don't get metabolic syndrome, but they're not eating so much. But when you put it in water because it's sweet, they drink a lot. And they actually take in a lot of glucose. What we discovered is that under certain circumstances – and this is one of them – the animals start to make fructose from the glucose. You know, I've told you before that normally starch doesn't cause obesity. And it doesn't in these animals.

But if you put glucose in the water, they started getting fatty liver and insulin resistance and all the features of metabolic syndrome. It puzzled us until we discovered that they were converting the glucose to fructose in their liver. When we gave glucose in the water to animals that couldn't metabolize fructose, they did not get fatty liver, they did not get insulin resistance, and they had minimal weight gain compared to the controls.

There are circumstances where carbs can be converted to fructose even when there's no fructose in the carbs. I think – we don't know this for sure, but I believe that some people, particularly those who are very insulin-resistant, may actually be converting some of their carbs to fructose.

The way I interpret this now, based upon the data we have, is that if you want to not gain weight, the most important thing is to reduce sugar, fructose intake from the diet. But if you're really overweight, the old low-carb diet may be a good way to go, because it will reduce the fructose intake. It will also reduce carbs that may be playing a role, under certain circumstances, in making fructose in the body. But the interesting thing is that it's still the fructose that's doing it.

DM: Interesting. That is fascinating. Because it appears that glucose is a relatively safe carb, assuming it's not converted to fructose.

RJ: Right, exactly. It looks like in normal, healthy, young people, it's not being converted to fructose. But we do have some evidence that under conditions – one of them would be insulin resistance, or if you're overweight – you may be converting some of the carbs to fructose.

The way I recommend is if you want to not gain weight, just reduce the sugar and fructose content. If you are overweight and you want to lose weight, you may have to restrict all carbs until we get better ways to do this.

DM: That's terrific.

RJ: The other thing to mention is that our work identified other foods that could cause obesity. The big one was beer. Because beer also, when it metabolizes, it generates a lot of uric acid in the cell. As I mentioned, that seems to play a role in this switch.

It's well-known that people who drink lots of beer can develop a beer belly. Well, beer belly is actually [*Laughs*] a form of visceral obesity. It's abdominal obesity. Many of these people who drink beer also get high-blood pressure. They get elevated triglycerides. They get fatty liver. In some, they basically develop a type of metabolic syndrome.

I believe that the overwhelming factor driving the obesity epidemic is sugar, but that there are individuals who are getting obese other ways. One of them is through beer and perhaps some other ways, too. But this will be the two main culprits.

DM: I want to expand on that uric acid component for a moment. You had mentioned previously and your newer research suggests that (fruits) are beneficial and healthy in moderation.

RJ: Right.

DM: But you want to avoid fruit juices and dried fruits. I'm wondering if someone was to over-consume even healthy fruit that wasn't necessarily overripe, would using your blood uric acid level be a way to monitor for the negative potential impacts of excessive fruit consumption?

RJ: Yeah. You know, serum uric acid has recently emerged as a major predictor for obesity, diabetes, high blood pressure, and fatty liver. There are so many studies now, and they're all showing the same thing. There's like 15 studies or 20 studies showing that an elevated uric acid in your blood dramatically increases your risk for high blood pressure. There are others that

show that it increases the risk for fatty liver. There are others that show that it increases the risk for diabetes.

You're absolutely right. We actually believe that elevated uric acid turns on the enzyme that helps convert the carbs to fructose. Most people who are obese and insulin-resistant have a high uric acid. We think that's the reason that they're converting the carbs to fructose.

DM: Getting back to your book, when I first read it, it's very compelling. It's almost like a novel or a detective story. I was just really fascinated with your writing style and ability to present a very compelling story about something that many of us know a lot about. But it was just so interesting, because you really used the process of your own discovery, or wrote it as you were discovering it yourself – almost. It was very compelling.

I'm wondering, too. I mean you're a legitimate researcher professionally. You're a physician at an accredited major university. You're publishing research in the peer-reviewed journals. On the other hand, you're a maverick. I mean, the message you have isn't widely accepted or adopted yet at this point. I'm wondering what type of response other professionals in your community are giving you with this information.

RJ: I get such a mixed response. *[Laughs]* You will not believe it. There are different factions that may be very much wed to their own hypotheses or longstanding dogma, so that it can be a very difficult time. I can have reviews where people just really say, "This is a fantastic research." I can also have reviews where people are very challenged by what we're writing.

One of the things that's happened is when there's a lot of controversy, there's lots of questions. When there are lots of questions, it takes a lot longer to get a paper published, because they want you to prove it nine different ways. But, you know, I'm willing to take on that challenge *[Laughs]*, because the science is very compelling.

I'll give you an example of one of the big challenges that we've had and which is now being appreciated. As I mentioned, people are eating more and exercising too little. But we think that it's driven by the body, not so much by the culture. That's not saying the culture doesn't accelerate it, but we think it's the changes in the body that make you want to eat more and exercise less.

But one of the striking and amazing discoveries with fructose is that even if you control the intake, so that an animal is not eating so much extra food, they still develop features of metabolic syndrome. The metabolic syndrome is really a form of pre-diabetes. You become insulin-resistant. You get fatty liver. Your blood pressure goes up. You have high triglycerides. And everyone thought that that had to be associated with actual massive weight gain or obesity.

But when we take animals and we pair **[inaudible 38:37]**: one group is getting a number of calories that an animal would normally eat, but it's high in fructose. Another group will get the same amount of food – exactly the same amount of food *[Laughs]*, but with a different carbohydrate like glucose.

It's the fructose-fed rats that developed metabolic syndrome. Suddenly they get fatty liver. They get visceral fat. Their blood pressure goes up. Their triglycerides are high. They actually

developed all these features, whereas the glucose-fed rats don't. And they're eating the same number of calories.

When we first published this, this was a challenge for people, because they said, "Well, listen. You shouldn't be getting fatty liver, unless you're eating more. You shouldn't be getting fat, unless you're eating more." But here, we're eating the exact same number of calories.

We even did a study two years ago that was even more *[Laughs]* remarkable. We took laboratory animals, and we put them on a diet. We gave them 90 percent of what they normally eat. But one diet had 40 percent sugar. Now remember, some kids are eating 30 percent of their diet as sugar right now.

DM: Uh-huh.

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RJ: These rats were laboratory rats who are eating a diet of 40 percent sugar. The control rats were eating the same in starch. What was amazing was that the sugar-fed animals developed fatty liver – like massive fatty liver – and even became diabetic. The control animals did not.

There's something special about fructose, that it's not just a calorie. This led us to try to figure out why. And it was a detective story *[Laughs]*, Dr. Mercola. It really was a detective story. It was like a big challenge to figure out how fructose was causing diabetes and obesity through a mechanism that didn't really require excessive calorie intake.

What we did (and there was a literature on this, but no one really had been studying this at all) was to look at what fructose does when it's metabolized. Fructose is a sugar. It's just like glucose. But when it's metabolized, it's very different from glucose.

There is an enzyme in the cell. I know it's always bad to give the name of a biochemical target, but there is an enzyme called fructokinase. This is the enzyme that metabolizes fructose. It's unlike any other sugar enzyme or anything like that. I think that when you metabolize food, you have to use some energy to metabolize food. I mean, in order to make energy, you have to use a little energy in the process.

All cells, when they metabolize food, whether it's fat or sugar, they use some energy in the process. But fructose is distinct in using so much energy to make energy that for a short while the cell becomes energy-depleted. When it loses its energy, it suddenly quits functioning normally. It starts to develop an inflammatory response. There is a process called oxidative stress that occurs in the cell. It's this process that's critical.

The way we prove that was we took animals that did not have that fructokinase enzyme. They metabolized fructose through other ways, and they did not get the metabolic syndrome. Even though they were ingesting fructose, they were safe from its effects. We could show that it was due to this energy depletion that was occurring in the cell.

It's a pretty exciting story. There have been several additional things that came out. We tried to figure out how the energy depletion actually caused the cell to accumulate fat.

We found that when the energy is depleted, a substance called ATP, which is basically the currency used by our body to make... It's our energy source. The ATP levels fell. The ATP that had been consumed broke down. Suddenly, we started forming a substance called uric acid. Uric acid is the substance that we know can cause the disease gout, but it's been long associated with obesity. But everyone thought it was elevated in people with obesity, because obese people get gout. It wasn't really thought that the uric acid might have a role in obesity.

This was a big challenge again, because no one really wanted to believe that. But what we were able to show is that uric acid can actually stimulate fat accumulation in cells through this process of working on the mitochondria where the ATP is made. It's a long answer [Laughs], Dr. Mercola. But basically, it's because of the way fructose is metabolized that you get these changes.

DM: Our last interview was about two years ago or a little bit over two years ago. Since then, we're excited at that time for you to share the information on a lot of the research that you were doing, but couldn't discuss because it was in process and had yet to be published. Now it's published and you've written a book, I'm wondering if you can update us on that journey and explain what's happened since then.

RJ: Well, there's been a lot of work done in the last two years on fructose from our group as well as from others. It's becoming more and more of a central stage issue that it could have a role in the epidemic of obesity. There have been several big discoveries, I think, in the last several years that are in some respects changing the way we think about what causes obesity. If you like, I can kind of go through some of these.

DM: Oh sure, yeah, let us. I think everyone would be interested hearing about these updates.

RJ: Yeah.

DM: It's such a pervasive topic. It affects just about the large percentage of the population. It's really hidden; most people aren't aware of the implications.

RJ: The obesity epidemic, of course, is just striking everywhere, you know, all over the world. It's affecting the young as well as the old. Most people have thought that the obesity epidemic is simply due to our culture. In our culture, we have these very large meals given to us. We get seconds. We get seconds on drinks. We get larger and larger drinks. People used to have seven-ounce Cokes, and then it was 12-ounce, 16-ounce, 20-ounce – the idea that bigger portions are driving up the increased intake.

Likewise with Internet, TV, telephones, escalators, elevators, and people are exercising less. It's been thought for a long time that the reason we're getting obese is we're eating too much and exercising too little. And this is driven by our culture. What we've been learning in the last few years is it is true: we are eating too much. We are exercising too little. But it's not driven by our culture. It's actually driven by changes that are occurring in our body. We now know, for example, that the reason people are eating more is that they're becoming leptin-resistant.

People who are obese frequently cannot control their appetite. Leptin is a hormone that controls appetite. When you become resistant to leptin, you suddenly start eating more, because you can't control your appetite. We also know that people are exercising less not because the TV is so

good or because the iPhone *[Laughs]* is so fun to play with. But rather, they're exercising less because they have less energy. They have less energy, and this can be shown by measuring energy in the muscle or the tissues. We can measure the energy as ATP, and that tends to be low in people who are obese.

They actually did a study a number of years ago where they took children who are watching TV a lot. They were watching almost 20 to 25 hours of TV a week. The hypothesis was: well, if we take the TV away, they're going to exercise more. They randomized half of the children to only watch half the TV they normally watch. They have little monitors on the TV, so they could really measure this accurately.

What they found was that when they reduced the amount of TV by half in the one group – and the other group continued watching their usual 25 hours *[Laughs]* of TV a week – the kids that reduced their TV in half, the theory was they would increase their physical activity. But they didn't. Actually *[Laughs]*, their physical activity went down.

It's not about watching TV that makes you exercise a little. It's the fact that the culture's responding to us. Because we're tired, the TV – the people who make TV programs know this. They actually make the TV really exceptionally great, so we'd want to watch it. The reason people keep bringing these larger and larger portions isn't because it's our culture, food is inexpensive, and so forth. It's because they know we want more, because we can't control our appetite.

What's particularly striking is that normally we regulate weight very well. Animals regulate weight very tightly. It's actually hard to make an animal obese permanently. You can force-feed it, and it will get real big. But you quit feeding it, it will come right back down to its normal weight. You can starve an animal, and it will lose weight. Sure. But as soon as you let it do its thing, it will eat, and gain its weight right back to where it's supposed to be.

There was something that's causing a change, where we're gaining weight from losing our control of appetite and by reducing our energy in our tissues. One of the things that does that is fructose. When we take an animal and we put fructose in the water and let it drink the fructose, suddenly it no longer regulates its weight tightly.

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It becomes leptin-resistant. This is one of the things that our group showed, that if you give fructose to an animal, they become leptin-resistant. They can't control their appetite. In fact, we even took the fructose away from them after they were leptin-resistant. We gave them a high-fat diet. They couldn't control how much they ate a lot more than the control animals. It turns out that this leptin resistance can persist even when you take the fructose away at least for a while.

We also found that when you give fructose to animals, it reduces the energy production in the liver. The amount of ATP that's being produced goes down. There's a block in the ability to oxidize fat. When you can't oxidize fat, the fat accumulates. *[Laughs]* When you can't oxidize fat, you can't produce as much energy as you need, because that's how you get energy – one of the ways. Suddenly, you have less energy, you have more fat, and you're hungry more. It's a bad combination, because together it's driving this epidemic.

DM: Well, thank you for expanding on it and doing this research to help identify these issues. I'm wondering, though, with respect to the cultural components that you've mentioned earlier, the issue of the cost of fructose. Because it would seem to me that a big portion of the changes that have occurred biochemically and metabolically are related to the massive amount of fructose in the diet, and that seems to be what happened in the mid-70s when it became so cheap it produce.

RJ: Absolutely.

DM: Then it's further worsened by the subsidies that the United States government has to the corn crops. Corn is cheap as can be. Then they have it even cheaper to extract this fructose.

RJ: You know, we can actually look at this indirectly. You can even go farther back. There have been studies done in England. Actually in England, sugar was actually pretty expensive for a long time. In the early 1800s, for example, it was still pretty expensive. There was a tax on sugar that kept people from being able to buy a lot. They kept reducing the sugar tax throughout the 1800s. Then they repealed it completely in 1874. Associated with that, sugar intake started going up dramatically. Then it continued to go up dramatically through the early 1900s.

In 1900, only [*Laughs*] three percent of 50-year-old men were obese. It started increasing to 10 to 15 percent by 1950 to 1960. It started... Then, you're absolutely right. In the early 1970s, high-fructose corn syrup was introduced. When it was introduced, there started to be a dramatic increase in overall fructose intake. There was about 20 to 30 percent increase in total fructose intake between about 1975 and today. With that has been a marked increase in obesity that parallels that rise.

DM: A lot of the physiology around this has to do with insulin and this even more important hormone leptin. I'm wondering if you can comment on some of the misconception about insulin resistance that people might have and confuse and impair their ability to appreciate what's going on here.

RJ: Well, insulin is an incredibly important hormone. It moves glucose in the cells for metabolism. It is involved in some fat accumulation. A lot of people have thought that the reason for the obesity epidemic is just recurrent stimulation of insulin levels. But our work's showing that starch, which stimulates insulin, doesn't cause metabolic syndrome. It suggests that it's not insulin per se. We believe that the key problem is insulin resistance, not insulin itself. When the tissues become resistant to insulin, insulin levels go up as well. It's under those circumstances that you see fatty liver, visceral fat, and obesity.

Interestingly, the glucose studies we did really showed that. Because when we gave glucose, insulin is stimulated. It was only through fructose (the glucose that was being converted to fructose) that we saw the insulin resistance.

The insulin resistance, when we gave glucose to animals that could not metabolize fructose, they were completely safe. They had high insulin levels, but they had no fatty liver, they had no insulin resistance, and they were protected from obesity. It isn't the insulin itself that's the problem; it's insulin resistance. And insulin resistance appears to be truly driven by fructose.

If you become insulin-resistant from carbs, it's presumably because the carbs are being converted to fructose in your body, or because you're actually eating fructose as a main component of your carbs.

DM: Now, the other component is leptin. I'm wondering if you can comment on leptin and its role in this whole process relative to insulin. Is it even more important? It's not something we hear a lot about. But certainly, it's emerging as a key role and player.

RJ: Many years ago, Jeff Friedman discovered that if you knock out leptin so that a mouse couldn't have any leptin at all, he'd become hugely fat. You may remember the cover of *Nature* magazine where he shows a balance. He has one mouse [Laughs] on one side and it's a leptin-resistant mouse. I mean, a leptin knockout. He's like hugely fat. And he has like two or three mice on the side. They still don't keep up with him. [Laughs] The balance is swinging in favor of the one big fat mouse.

Leptin is like a really important hormone that controls appetite. If you don't have leptin, you're going to get really fat. Or if you get resistant to leptin so that the leptin doesn't work, it's kind of like not having leptin. You get really fat.

What's become evident is that people who are getting fat often have leptin resistance. It's very, very common. You can show that, because they have high blood levels of leptin when they shouldn't. It's kind of like high insulin levels in people who shouldn't have high insulin. That kind of mean that the tissues are resistant, and so the body tries to make more leptin or more insulin to compensate.

But the leptin resistance, because these people can't control their appetite, they tend to eat more. Over time, they will gain weight. Leptin resistance is really important.

What's striking is that when we fed animals fructose, which we did with Phil Scarpace, these animals became leptin-resistant. There's data in humans that if you feed fructose to humans for several months, their blood leptin start to go up higher than expected and higher than the controls. That suggests that leptin resistance is developing in them. It probably takes several months; it doesn't occur overnight. You won't see it in a study that's done for only two weeks. It does take time to see.

DM: Okay, well, thank you. Now, another observation you made is the connection between fructose and dehydration. I'm wondering if you can expand on what you've found, and what was going on with that component.

RJ: One of the big discoveries of our group is that fructokinase – this enzyme that when it's activated it seems to be responsible for causing the changes in the liver, the fatty liver, the insulin resistance – it's really driven by this particular enzymatic reaction, which then activates the fat switch. What we found is when that enzyme was metabolized in fructose, the cell became inflamed. In the liver, the cell actually starts to reduce inflammatory mediators and oxidative stress. It's associated with low-grade injury to the cell.

When we discovered that, we started saying to ourselves, "What about the other sides of the body where this enzyme is present?" It turns out that the enzyme isn't present everywhere. It's only present in some certain important areas. It's in the hypothalamus, which controls appetite.

It's in the isle itself of the pancreas where insulin is controlled. It's in the intestinal wall where it's very important in permeability. And it's in the kidney. Because I'm a kidney *[Laughs]* doctor, I said, "Let's study it in the kidney."

We found that when fructose was metabolized by tubular cells in the kidney, suddenly there was injury to the tubule. Then we started looking for conditions where this would occur.

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We found that if we gave very high doses of sugar to animals, they would develop injury in their tubules. And I told you that under certain circumstances, the body can make its own fructose.

We started studying certain kidney diseases. We found, to our amazement, that there are certain situations where the kidney tubule will make fructose from glucose. The tubules are particularly important, because when you make urine, you're filtering the blood to make urine. Initially, the filtrate has a lot of glucose. It has the same glucose concentration as blood, but it all gets reabsorbed in one side. That's where this enzyme is.

Under certain conditions like dehydration or *[inaudible 1:00:57]* and cardiovascular surgery, you can get a change in this tubule, or suddenly it starts to make fructose. We've discovered that this actually may be driving the number of kidney diseases.

One of the reasons I've been interviewed (I just got interviewed on NBC a few days ago) is there's an epidemic of kidney disease occurring in Nicaragua. Also, there's an epidemic occurring in Sri Lanka. There are reports of excessive kidney failure occurring in Egypt and the Philippines. It's becoming a major world health issue.

In some of these areas in Nicaragua, maybe 10 to 15 percent of the young men are developing kidney disease. They're mainly people working out on the sugar cane fields and the agricultural communities under the very hot sun where the temperature's extremely high. These people are getting dehydrated. They're losing five or six pounds in the course of the day. We know that, theoretically, that can activate these enzymes in the kidney. Suddenly, it might be responsible for causing kidney damage there.

They've been looking for pesticides, heavy metals, and toxins. They haven't found them as a cause. Now the current theory is it might be dehydration.

One of the sad things is that many of these people are hydrating themselves with sugared solutions, very highly sugared solutions like fruit juices, to which they're adding sugar *[Laughs]*, or soft drinks. Here we have a perfect storm. They're dehydrated. The tubules are now converting the glucose to fructose anyway. Then we get them highly sugared solutions where they're getting more fructose. And we think it could be playing a role in this epidemic.

We don't know for sure if it is causing this epidemic. But it is a good hypothesis, and it's currently – I think – the favorite hypothesis. We've been funded to go down to Nicaragua to try to figure out what's going on and to see if we can help.

DM: That's very exciting. Hopefully, you'll be able to make a dent in that illness for them. One of the items that you've mentioned previously a few times was metabolic syndrome. I'm

wondering if you could comment on the connection between metabolic syndrome, uric acid, kidney disease, and fructose, and all that's intertwined.

RJ: Yes. Metabolic syndrome, as I've mentioned, is very common. We call it "a cluster of signs." Basically, people will have insulin resistance or impaired glucose tolerance. They'll have elevations in their blood lipids or fats like serum triglycerides. They'll have a reduction in HDL cholesterol. They'll have elevated blood pressure. And they'll have visceral obesity or abdominal obesity.

This cluster of signs was noted as early as the 1920s. These signs are frequently associated. These people often have fatty liver. It was noted in the 1920s that these people also have high uric acid. In fact, a high uric acid is seen in the vast majority of people with metabolic syndrome. Likewise, if you have a very high uric acid, you have high risk for having features in metabolic syndrome. They should be considered almost part of the syndrome.

As I've mentioned, we've got evidence that uric acid may actually have a role in causing the metabolic syndrome. This is still very *[Laughs]* controversial. But if we take animals with metabolic syndrome and we lower uric acid, we can improve the metabolic syndrome. We can improve the insulin resistance. We can block some of the inflammation that's going on in the fat. We can reduce fat in the liver. We can reduce blood pressure. This has become a very hot topic.

Now, we're not sure that the typical drugs being used today to lower uric acid in humans, if we can get all those same benefits, because we have to lower the uric acid inside the cell, not just in the blood. In our animal models, we're using a little bit higher doses than people are typically using. But having said that, we have run a number of clinical studies, and we've found that like obese children who get drugs like allopurinol, we can lower their blood pressure.

We've done two studies. One had really been done by [\[inaudible 1:05:55\]](#). Interestingly, he had an effect on weight in these kids as well. Other people have shown that lowering uric acid can improve other features of metabolic syndrome. There are some pilot studies showing that it can improve insulin resistance. It's raising the *[Laughs]* specter that serum uric acid may be an important blood test to perform on people, because we know it can certainly predict if you're at risk.

Also, for developing features of metabolic syndrome, there's now some evidence that lowering it could be beneficial. But clearly, we need big clinical trials to prove this. It's looking promising that this is important.

DM: Yeah, it looks to be, at least from what you've shared with me before, even a more important risk factor than total cholesterol.

RJ: Probably.

DM: I'm wondering if you could just briefly comment on the ranges that one might look for in their blood tests. This is a blood test that's relatively inexpensive any doctor can do for anyone watching this. All commercial labs do it. There are different levels that are considered optimum. It's just like there's a Goldilocks range. Too low is also not as good as too high.

RJ: Right. That's correct. Back 50 years ago, the normal levels of uric acid in people were like four or five – even three was a relatively normal level. Today, because of the Western diet and all the sugar we're eating, the normal levels are in the five to six ranges. The range has been increasing. What the lab calls "normal" now is not what was *[Laughs]* called normal 30 years ago.

But what we do know is that uric acid levels greater than seven are really considered elevated by all standards. They really start to significantly increase the risk for kidney disease, hypertension, insulin resistance, and metabolic syndrome – all of those. It's just so clear. There's so much data, and it's overwhelming.

But interestingly, our studies have suggested that the risk with uric acid begins around 5.2 to 5.5. There are a lot of people who have too high uric acid based upon our studies.

At this point, you can try to reduce your uric acid by reducing sugar. There are certain foods like beer, as we've mentioned, that is very *[Laughs]* potent at raising uric acid. There are certain umami-type foods like organ meats, liver, and shellfish that can raise uric acid. Watch some of these foods. I wouldn't eat shrimp every day (even if you can afford it), because it can raise uric acid. We do think that some of these foods could have a little bit of an influence. But we still believe the overwhelming mechanism is through sugar and high-fructose corn syrup.

DM: I'm particularly curious about a low-sugar approach to optimize your uric acid levels. In your perspective, is it possible to have two little carbohydrate? If you're going under 50 grams a day of total carbohydrate, could that be counterproductive and actually stimulate a rebound that actually raises uric acid levels?

RJ: You know, it's well-known that when you go on a very severe low-carb diet, that there's at least a short period of time where uric acid goes up in the blood.

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DM: Uh-huh.

RJ: We don't really know the implications of this. It seems to be short-term. But it's also true that if you have low-fat stores and low-carb stores, if you get any protein breakdown like with exercise, you're going to get a rise in uric acid as well. We do want to have some carbohydrate and fat stores just for the normal metabolism. We don't want to be completely, you know, glycogen-free *[Laughs]* and fat-free.

DM: *[Laughs]*

RJ: I'll tell you. This is totally an anecdote, but it does tell a story. I remember going to the gym, and there was this guy who was so muscular and had no body fat. I mean almost none. It was just pure muscle. He was very good with his diet. He was incredible.

Then he got pneumonia, and he just happened to get a bad form of pneumonia. It just knocked him out because he had no fat stores. He had no carbs. He started breaking down proteins. He was hospitalized, and you know, he started breaking down proteins. He was really sick. His

muscle mass went away fairly quickly before he got better. Thankfully, he got completely better. He's back to being a *[Laughs]* muscular guy.

But I realized, being involved in this care, that it's not a terrible thing to have a little bit of fat stores and a little bit of carbs. Because when you get ill, you want to rely on them for a bit.

For example, it's been shown that caloric restriction allows an animal to live longer. It's true. But you feed them every day their certain amount of food. But if they miss their food for a while, they actually are much more vulnerable to dying.

It's very good to be lean, athletic, and low fat stores, but you don't have much reserve if you get sick. That's the problem. More food is restricted from you. That's the only problem. One of the things that happens is that uric acid goes up under those conditions of protein breakdown.

DM: Oh, thank you for that answer and sharing that story, which helps really emphasize the point that there is this Goldilocks – this fine balance. That if we go to an extreme, likely it's going to be almost equally as counterproductive or maybe even worse. Because if you don't have these reserves, you could die prematurely from something that would relatively be easily addressed if you had enough reserves.

RJ: Yeah. That's probably why in our past, people actually appreciated obesity and wanted people to be obese, especially the women who help keep the baby healthy during pregnancy. I think there was a time when obesity was viewed as an advantage.

DM: Sure. Well, I think, as I understand it, there are really two things you can optimize for: one is fertility and the other is for fitness. They are divergent goals. *[Laughs]*

RJ: Yeah.

DM: You really can't have both. *[Laughs]*

RJ: *[Laughs]* Hopefully, you'll get a little bit good for both.

DM: With fitness, it's longevity.

RJ: But you're right.

DM: You can't....

RJ: Marathon runners, ballet dancers, and so forth, many of them have amenorrhea – the women. I mean they don't have a menstrual period, because they're so thin.

DM: Uh-huh.

RJ: They can't maintain their normal hormone balance.

DM: In closing, are there any other points that you'd like to emphasize in the book or things that we haven't touched on at this point?

RJ: I just want to thank you, Dr. Mercola. Because you know, many, many years ago when I was just studying fructose for the first time, I would go to the website and try to read about it. I

found your website. That was the first time. I read your analysis of fructose, and it got me thinking a lot about fructose. You actually had a big play in initiating my interest in it. As I started studying it, I realized that we needed to do more research on the topic. So, I just want to thank you for inviting me to be on your show, and for supporting and publishing my book on your website. I'm very grateful to you. Thank you very much.

DM: Well, I really appreciate that and the opportunity to have an impact on a great brain like yourself who's made some amazing discoveries. It's going to have such an enormous influence of the health of the culture.

I mean, this *Fat Switch* is just phenomenal. And anyone who's watching this, I strongly encourage you to pick up a copy of the book, because it's just really... It's not only loaded with good information with which we've touched upon here, but it's also just a fascinating read. It's just as I mentioned earlier it's like a detective novel. It's very compelling. It's very hard to put down. That is the danger. *[Laughs]* If you have limited time you may not want to get it, because you're just going to be engaged in it so much.

But again, I thank you for all that you've done and will continue to do in helping us understand the details of this really important topic.

RJ: Thank you.

[END]