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Reductive Stress — The Hidden Culprit of Chronic Disease

Analysis by Dr. Joseph Mercola | April 07, 2024

STORY AT-A-GLANCE

- Reductive stress has a significant yet underappreciated role in biological health, contradicting conventional biological education
- Reductive stress, which results from an imbalance in the cell's electron flow that leads to a surplus of NADH, is a primary cause of oxidative stress that leads to virtually every degenerative disease and the most common causes of death
- Reductive stress leads to oxidative damage by causing a bottleneck in mitochondrial electron transport
- Elevated NADH levels, a hallmark of reductive stress, alter your body fat composition by promoting the conversion of saturated fats to monounsaturated fats. This highlights the intricate relationship between diet, cellular energy balance, and fat physiology
- Strategies for mitigating reductive stress and improving metabolic health include dietary adjustments to favor glucose burning, reduce fat intake, and manage blood glucose levels through selective protein and carbohydrate sources

In this interview, Brad Marshall explains how reductive stress works, and why it's so bad for your health. Understanding reductive stress is an important topic because it's fundamental to optimizing your biology. It's a fundamental biological principle that is not widely appreciated or even understood, as it contradicts almost everything we've been taught about biology.

"I went to Cornell University for molecular biology, and I'm a boy from the country. I'm from upstate New York. My grandparents were farmers. I grew up in rural America, went to Cornell and learned genetics," Marshall says.

"After school, I went to Memorial Sloan Kettering Cancer Center and worked in a tissue culture lab and cloned genes and learned the art of molecular biology in the lab. After that, I went to the French Culinary Institute because I love to cook, I'm interested in food ...

From there, I went on and worked at the Berkeley Drosophila Genome Project for the Gene Ontology project. There, I was involved more in the software side of things.

The Drosophila (fruit fly) genome had just been sequenced and we were building software to help biologists parse through all of this data and annotate what are genes? What are these genes involved? What do we know about these genes and how do we keep track of all of that? …

At that point, I did what appeared to be kind of a strange move, but I moved back to upstate New York, bought a farm and started raising hogs because, like I said, I'm also really interested in food ...

I was interested in reducing my polyunsaturated fat (PUFA) intake and had come from reading work on the Weston A. Price website and the work of Sally Fallon. That was 2004 ..."

Fat Saturation and Reductive Stress Go Hand-in-Hand

While raising pigs, Marshall noticed that the consistency of the fat was dependent on what he fed them. Genetics also made a difference. And, indeed, when researching the literature about pig farming in the late 1800s, he discovered that this was well-known back then.

Foods high in linoleic acid (LA), such as chufas and peanuts result in soft, oily fat that that cannot be sliced properly, because it accumulates in fatty tissues. To firm up the fat, they would feed them starch during the eight weeks before slaughter.

As noted by Marshall, "most things that you eat in your diet don't accumulate." Extra protein, for example, doesn't change the protein composition of your muscle fibers. But the PUFAs in your diet does bioaccumulate and alters the composition of fat throughout your body.

> *"I'd been reading the work of Peter Dobromylskyj who writes the blog Hyperlipid, and he was talking a lot about reactive oxygen species (ROS) production in the mitochondria.*
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> *When we burn calories, we inevitably wind up creating these reactive oxygen species, which is interesting to me as a biologist, because I was taught in college that reactive oxygen species are bad. They do damage and hurt the cells.*
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> *And then I start reading his blog and he's saying, 'Well, no, they're actually important signaling molecules, and they affect insulin signaling and the energy in and energy out of the cells.' I thought that was interesting.*
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> *And so, I've just gone down that rabbit hole, and now I realize that this whole topic of reductive stress, NAD+ and NADH and fat saturation are all joined at the hip. You can't separate these topics. They're all connected."*

What Is Reductive Stress?

Reductive stress, put simply, means you have too many mobile electrons in the cell. Calories are energetic electrons found in fat and carbohydrates. They're mostly carbon and hydrogen, but carbohydrates have oxygen as well. As explained by Marshall:

> *"The calories in food are just electrons between the carbon and the hydrocarbon bonds … Those electrons between the carbon and the hydrogen,*

that's where the energy is. And so, we have these systems where the electrons flow through the cell, and we use that electron flow to create ATP, and the ATP moves our body.

The electrons move on electron carriers, which are things like NAD. NAD, when it has electrons, is NADH, and when it loses the electrons, it's NAD+. You want a balance of NAD+ and NADH. Then the electron flow works.

What happens is, we get too many electrons in the system. We get too many NADH and not enough NAD+. And that can happen because we're allowing too much fuel into the system. That's usually why it happens. To use an analogy, cars used to have carburetors. A carburetor takes in fuel and air and mixes the fuel and the air together.

If you get the right amount of fuel and the right amount of air, it burns cleanly and the engine runs. But if you get too much fuel and not enough air, that's called a rich fuel-to-air mixture. It's too rich, it's too much fuel, and it doesn't burn cleanly. And that's essentially what's happening with reductive stress.

That's essentially what's happening with metabolic syndrome. People might've heard of it as energy toxicity, or people might've heard of hypoxia or pseudo hypoxia. They're all similar concepts. In our bloodstream we have glucose, fats, amino acids, and they can all get used for fuel.

If they're too high, they're all going into the mitochondria together, and you get those carriers that move the electrons around. You can think of them like taxis. If all of the taxis are full of people and you're the next one trying to get in a taxi, there are no taxis left.

The taxis are all full. That's reductive stress. It means that the electrons that are waiting to get burned have nowhere to go, and it builds up. And suddenly you have, whatever, a crowd of angry people, and it's not working. And so, it really is just electron flow."

Now, reductive stress does cause damage, because you now have a surplus of electrical negative charge, and that can cause secondary oxidative stress. So, fundamentally, it's the cause of most oxidative stress. So, oxidative stress is not caused directly by free radicals. Rather, oxidative stress is caused by a surplus of electrons in the mitochondrial electron transport chain.

Reduced Versus Oxidized Molecules

Again, NADH is the reduced version of NAD. It's reduced because it carries negatively charged electrons. So, it's a redox molecule. In the mitochondria, the NADH donates its electrons to other molecules in the electron transport chain.

> *"Think about it like a cab. Either you've got a passenger or you don't. When you've got a passenger, when you've got the electrons, you're the reduced version. You drop that passenger off, you drop those electrons off, you can pick up another electron again.*
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> *And there's just a network of these things, picking up electrons, dropping them off. When you have the electron, you're reduced. Drop the electron off, you're oxidized,"* Marshall says.

On a side note, I've been promoting grounding (earthing) popularized by Clint Ober. Ober is a wonderful soul, a genuine human being, full of love, but he doesn't understand how grounding works. He believes that your body is picking up electrons from the surface of the earth, but it's the exact opposite. It reduces reductive stress.

How Does Reductive Stress Cause Damage?

The goal is to get rid of the extra electrons and to move the electrons through the electron transport chain. When this works, your body produces ample energy without excessive ROS.

The problem arises when you're not taking those electrons from that fuel and efficiently move them through the system. That's when you get reductive stress, which in turn causes oxidative stress. How does that happen? Marshall explains:

> *"The NADH carries electrons to the electron transport chain. That makes the ATP which runs your body. But the first step of that is the NADH hands a pair of electrons off to Complex I. If you have too much NADH, this is called electro pressure. You've got too much of this NADH, and you've only got so much of this Complex I.*
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> *If you've got six molecules of NADH all trying to hand their electrons off to the Complex I at the same time, they can't all make it through. You essentially have a bottleneck. And these electrons, they want to move to the next thing because they're in this very energetic state, and they want to jump. And if there's not enough throughput for them all to get off, then some of them will come back out. They're not going to make it into Complex I.*
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> *That's what creates superoxide, which is a free radical, an ROS. The superoxide starts that chain of what potentially can lead to oxidative damage. Now, it doesn't necessarily lead to oxidative damage. In fact, it can be helpful.*
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> *But if the reason that you're generating superoxide is because you have too much NADH, and all the electrons are being funneled towards Complex I and you're generating superoxide there, that's bad, because you're going to generate so much superoxide there that your antioxidant systems are going to become overwhelmed. You're going to have this long-term increase in superoxide and hydrogen peroxide."*

Understanding Oxidation

For clarity, the reason superoxide is being generated is because there's oxygen in the mitochondria. Superoxide is an oxygen molecule with one additional electron. Oxygen is

supposed to be there because the energy is created through oxidative phosphorylation. That's why we convert fuel so much more efficiently than bacteria.

So, oxygen is there waiting to be used. The electrons are designed to be transferred through the electron transport chain. If the electron transport chain is backed up, the surplus electrons will attack oxygen directly, which is what creates the free ROS.

When we say that something is “oxidized,” it means it lost an electron or a pair of electrons. The reason we call it oxidation is because oxygen is extraordinarily electrophilic. It loves electrons.

When electrons go through Complex I the correct way, ATP is generated and at the end of the electron transport chain they join with oxygen, converting the oxygen to water. This is what you want. But if you have too many electrons, they’ll spill out and prematurely bind with oxygen, thereby creating ROS. It also decreases your mitochondria's ability to generate energy, and that's the crux of almost every single disease we have.

Connecting the Dots

Another important factor in energy production is pyruvate dehydrogenase. Pyruvate dehydrogenase is the limiting factor in burning glucose. It converts glucose into acetyl-CoA, and that's a crucial step. You can't burn glucose oxidatively if pyruvate dehydrogenase isn't working. And while it's working, it's making superoxide.

Glucose has six carbons and there's an enzyme that breaks glucose down into two molecules of 3 carbon pyruvate. Ideally, pyruvate should be burned in the mitochondria, but it can't do it directly. It must be converted to acetyl-CoA, and the enzyme that does it is pyruvate dehydrogenase.

If this conversion doesn’t happen, the pyruvate backs up and forms the reduced version of pyruvate — lactate — which is a problem. Lactate is elevated in cancer. It’s also elevated when you have low NAD. So, pyruvate and lactate are what's called a redox pair. So, you want to keep lactate low. You want to be able to oxidatively burn glucose.

“What happens is — and this is the part that connects all the dots — there is an enzyme in the mitochondrial membrane called NNT, and it uses the superoxide to regenerate NAD+. When everything is functioning, the more reactive oxygen species that you can produce, the higher your metabolic rate can go.

So, when you create reactive oxygen species and that oxygen becomes superoxide and ultimately is converted back to water, you're still burning oxygen. That's still metabolic rate. The electrons are still making their way back to oxygen. We have this circuit in the mitochondria that can do that, when things get a little overheated, it's like a pressure relief valve, this NNT.

And so, that's a neat trick. The problem comes when you have this buildup of acetyl-CoA in the mitochondria. That's the second part of this reductive stress. All of our foods are converted to acetyl-CoA. Glucose, fat and a lot of amino acids are converted to acetyl-CoA.

If you have too much of all these fuels flooding into the mitochondria all at the same time, you get this buildup of acetyl-CoA. And then, there's this process that happens called acetylation. That's where you have all these enzymes working away, and these acetyl groups, if they build up too high, can jump onto the enzymes, causing them to stop working.

One of the first enzymes to get acetylated is NNT, the kind of magical enzyme in the mitochondrial matrix that converts the reactive oxygen species into NAD+. When that gets acetylated and turns off, now you've lost that safety relief valve. Now, acetyl-CoA and NADH builds up even more because NNT isn't working.

That's when you have the real train wreck. When NADH builds up, you're having frank oxidative damage. But that oxidative stress and that damage started with rising NADH levels. When NADH levels rise, the metabolism slows down a bit. The acetyl-CoA can't be burned fast enough. Those levels rise. Then you get acetylation, and now you've got real problems.”

Unlocking the Secret to Boosting Your Energy

When you get acetylation, you reduce the efficiency and the ability of your mitochondria to produce cellular energy. So, you get fatigued. Your brain doesn't have the energy it needs. Your immune system is impaired. Every process in your body needs energy, and if your mitochondria aren't producing it, you're going to be impaired, sometimes quite seriously.

It's this chronic mitochondrial dysfunction that, typically, causes metabolic inflexibility, which is when your body cannot efficiently burn glucose in your mitochondria.

> *"The key thing to understand is, the process of oxidative stress begins with reductive stress. It begins with too much NADH, too much acetyl-CoA. And that just leads to slowing everything down. The other enzyme that gets acetylated very quickly is succinate dehydrogenase, which is Complex II.*
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> *That's the FADH2, the other main input of electrons into the mitochondria. When acetyl-CoA levels build, Complex II gets turned off, and then the whole system slows down. You can't efficiently create ATP, you can't send electrons through the system, and you've got all kinds of problems."*

How to Become a More Efficient Glucose Burner

One of the key take-homes from this is that if you want to be optimally healthy, you want to burn glucose in your electron transport chain of your mitochondria, and one of the best ways to ensure that is to increase carbs and lower your fat intake.

As explained by Marshall, when you eat a meal, insulin is released. When you consume a meal that generates a lot of insulin, it suppresses the release of free fatty acids from your fat cells. Those free fatty acids are what cells import and burn in the mitochondria.

> *"Essentially, what the insulin is doing is it's kind of telling the fat to get out of the way because you can't efficiently burn fat and glucose at the same time*

> *because of the Randle cycle. The burning of fat will displace your ability to burn glucose,"* Marshall explains.
>
> *"So, insulin lowers the amount of fat that can enter the mitochondria. Interestingly, it also lowers the amount of branched-chain amino acids that are circulating."*

Marshall struggled with elevated blood glucose in the mornings and, as an experiment, he swapped muscle meat and protein from grains for bone broth and pork rinds.

> *"Papers have shown there's this competition between branched-chain amino acids that are high in muscle meats and grains, and glycine that is high in connective tissues, collagen, gelatin,"* he says.

Within about two weeks, his fasting blood glucose was reliably right around 80, which is optimal. He was consuming about 600 grams of mostly starch and some sugars, primarily sucrose from whole fruit.

The problem with pure fructose, such as agave nectar, is it doesn't activate insulin, and without the insulin signaling, your body won't be able to burn that fructose. So don't eat agave nectar. Sucrose, however, does generate an insulin response, as does starch.

Fat Burns in the Flame of Carbohydrate

As noted by Marshall, many traditional cultures eat high-starch diets and have very high metabolic rates. That's an important point. If your metabolic rate is low and you're eating plenty of healthy carbs, it could be that your fruit intake is too high and you need more starchy foods.

> *"When you eat a lot of starch and glucose, and you look at what happens in the mitochondria when you're burning the glucose efficiently, it lowers NADH. You get high NAD+ and low NADH when you are actively burning glucose,"* Marshall says.

"I think the reason for that probably has to do with what I said before. The pyruvate dehydrogenase generates ROS, and NNT replaces the NAD+. But it doesn't really matter why. The point is, if you're actively burning glucose, you'll have high NAD+ availability, and that's what you need to run your metabolism. Those electrons need to go somewhere, and they want to go to NAD+ …

There is an old saying in the medical literature: Fat burns in the flame of carbohydrate. You can find this in the 1920s, 1930s if you search PubMed. I think the reason for that is that when you're burning carbohydrates, you're increasing the amount of NAD+, and fat requires a lot of NAD+ to burn.

Fat requires a lot of oxygen to burn basically, and NAD+ is essentially playing the role of oxygen in the mitochondria. It's oxidizing the fat. And so, I think burning carbohydrates generates enough NAD+ that you can burn fat more efficiently and more cleanly."

How Elevated NADH Affects Your Fat Composition

Elevated NADH also affects your fat composition. There's an enzyme called SCD1 that converts saturated fat in your body to monounsaturated fat, and that enzymatic reaction uses NADH. So, if you are in reductive stress, which means you have elevated NADH, you're going to convert a lot of your saturated fat into monounsaturated fat. Again, that's because you have surplus electrons that are looking for a home and they find this home on that enzyme.

Monosaturated fat is soft, while saturated fat is firm. And, recall the discussion about pig fat, the way to make it firmer is by increasing starch. If you have mostly saturated fat in your body, you're going to have high NAD+ availability and a fast metabolic rate.

Why High LA Is Associated With Decreased Diabetes Risk

Paradoxically, reputable researchers have shown that high LA levels are associated with a decreased risk of diabetes. Biologically, this made little sense to me, considering LA is

the most significant metabolic toxin in your diet, until Marshall explained it.

When you're in reductive stress and you high NADH, the activity of desaturase enzymes increases. SCD1 converts stearic acid to oleic acid. But another one called delta-6 desaturase or D6D puts a third double bond into LA (which has two double bonds), and that's the limiting step in LA's conversion to arachidonic acid.

Arachidonic acid gets built into cell membranes, and once it's released, it can oxidize. So, when you're in reductive stress, you start converting LA to arachidonic acid that then becomes oxidized 5-HETE, 12-HETE and 15-HETE, which are associated with disease, including cardiovascular disease.

> *"The 5-HETE, 12-HETE and 15-HETE feed back and activate PPAR-α and aryl hydrocarbon receptor, and they in turn increase the amount of these desaturase enzymes that we're making,"* he says.
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> *"So, you have this huge feedback loop where the polyunsaturated fat is getting oxidized, and that is a signal to convert more of your saturated fat into monounsaturated fat. So, the pattern that predicts diabetes, heart disease, obesity is low saturated fat, especially low stearic acid, low linoleic acid, because that's all getting oxidized.*
>
> *If you have high monounsaturated fat and low polyunsaturated fat, that's actually a really bad sign. That doesn't mean that you should run out and start swilling soybean oil because the polyunsaturated fat is part of the system that is creating the problem.*
>
> *It's just that it burned as part of the process. It's not the thing that accumulates really. And in fact, it's sort of the opposite. There are breeds of pigs that we've selected to remain very lean, and if you take one of these hogs and feed them sunflower oil or sunflower seeds … the lard was something like 54% linoleic acid. So, these lean breeds of hogs just accumulate the linoleic acid, they don't oxidize it.*

Whereas if you look at a fatty breed of hog like a Mangalitza, when you feed them linoleic acid or other vegetable oils, they convert all that linoleic acid to monounsaturated fat and they remain much lower. That's the difference between the hog that remains metabolically healthy and the hog that becomes obese and probably insulin resistant — the metabolically healthy hog isn't oxidizing the linoleic acid.

And of course, one of the main reasons why that hog would oxidize the linoleic acid is that it's in reductive stress, because the reductive stress drives the desaturation of those fats in the first place. It drives the activity of delta 6 desaturase, and that's really the key gating step that is predictive in humans of diabetes and results in that pattern of low stearic acid, high oleic acid, and low linoleic acid."

While high LA is associated with decreased diabetes, if this process continues, problems will eventually occur.

Measuring Your Redox Balance

In the interview, Marshall explains how we intend to measure the cellular redox balance of patients by testing redox pairs like pyruvate and lactate, which reflect the redox of the cytoplasm, and acetoacetate and beta-hydroxybutyrate, which reflect the redox of the mitochondria. Why is this important? Marshall explains:

"In the mitochondria, you want to have high NAD+ because that's where your metabolism is happening. That is going to tell you how fast your metabolic rate's going to go, et cetera. Whereas in the cytoplasm, that's where desaturase reactions are taking place and lactate is being produced.

If you have high NADH in the cytoplasm, that's when you start oxidizing your linoleic acid, that's when you start converting stearic acid to oleic acid and that's when you start creating the 5-HETE and the 12-HETE.

So, you want to know what's happening in both places, and it's complicated. There's interplay back and forth between both of them and if the mitochondria are overwhelmed and spitting out tons of reactive oxygen species, then the cytoplasm can also get oxidized. So, you really want to know both."

Also, when you have high NADH in your cytoplasm, you're going to activate the SCD1 enzyme that reduces LA. It lowers it, which superficially feels like a good thing, but it's not, because it's taking the LA out of your fat stores, causing it to oxidize, and it's the oxidized metabolic byproducts, the breakdown products, that cause the most damage.

Ideally, you want to excrete LA very slowly. Provided you have good liver function, it will attach to glucose and be excreted in your urine without getting oxidized. This is a slow process, so you must be patient. If the LA is released to rapidly, you'll end up with severe damage that will raise your risk for chronic diseases such as cancer and heart disease.

More Information

To learn more, please listen to the interview in its entirety. You may need to listen to it several times, even, to really understand it. Once you do, however, the answers to many of your health problems will become that much clearer.

In the interview, we also discuss the potential problems of branched-chain protein (red meat) and the benefits of collagen or gelatin, which are high in the amino acids glycine, proline and hydroxyproline. Importantly, glycine helps to directly eliminate reductive stress.

We also review the benefits of stearoylethanolamide (SEA) supplementation. SEA is a natural compound your body makes from stearic acid in your adipose tissues. So, your blood level of SEA is reflective of the stearic acid levels of your adipose tissues. As you progress towards metabolic syndrome, diabetes, obesity and heart disease, your stearic acid levels drop.

Ideally, your SEA level should be around 8%. The average now is only around 3% to 3.5%, which helps explain why about 95% of Americans are metabolically inflexible. SEA also

helps regulate your cannabinoid system.

If you want to dive deeper into molecular biology, be sure to check out Marshall's YouTube channel, **Fire in a Bottle**.

The Best Nutrition Course Is NOW Available for You!

I have very good news to announce. Very shortly I will be sending out invites to train individuals interested in becoming one of my health coaches. My health coaches will be some of the best trained coaches on the planet because they will understand how biology works and how to correct it to optimize health.

Many will apply but only a few will be accepted. Once they are accepted, they will be allowed to enroll in my nutritional biochemistry course at no charge. This course is based on the concepts of the late Dr. Ray Peat who popularized bioenergetic medicine. That's a fancy word for optimizing diet choices to maximize cellular energy production.

Poorly functioning mitochondria is pervasive and probably exists in 98% of the population. Diligent application of the principles outlined by Doctor Peat will help your mitochondria recover so they can produce the amount of energy they were designed to. This is important because your body needs energy to activate its intrinsic healing capacity.

The foundation for the nutritional biochemistry course that will be taught to our health coaches is from a course that Ashley put together. It took her more than one year to write this course, and in my view, it is the best health course I've ever seen in my life.

I only wish I had this course when I first started practicing medicine. It would have been a game changer. It's hard to imagine how many additional hundreds of millions of people I could have helped with this knowledge. Not to worry though as the knowledge is now available for you.

If you are seriously interested in understanding how your body works, and more importantly, what specific actions you can take to guide it to working the way it was

designed to, then **this is the course you need to take**.

You can enroll for the course on her website. Please understand that I take no commissions from recommending this course. All the funds go directly to Ashley. She is probably the most knowledgeable farmer on the planet when it comes to health. This is why she can produce some of the healthiest food possible. But you may realize that farmers don't earn very much, so you can support her mission to provide the world with healthy food by **purchasing her course**.

I would encourage you to seriously consider taking advantage of the wealth of knowledge that has taken her many years to compile and make available to you in an easy to learn format.