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Crucial Facts About Your Metabolism, Part 2

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STORY AT-A-GLANCE

- What medicine refers to as "oxidative stress" is actually reductive stress resulting in the production of free radicals. Once you understand this process, it becomes easier to understand how to optimize your health
- According to the rate-of-living theory, the higher your metabolic rate — which means the quicker the electrons move from food toward oxygen, which is the final acceptor of electrons — the faster you'll age because there'll be higher oxidative stress. But deeper analysis reveals the exact opposite appears to be the case
- The truth is, the higher your metabolic rate, the slower you age, because high metabolism creates fewer reactive oxygen species (ROS)
- Your metabolism is high when electrons move rapidly and easily through the mitochondrial electron transport chain. When electrons are impeded from moving forward, they can back up, leak through the mitochondrial membrane and start moving backward, where they combine with oxygen to create excessive ROS

In this video, which is the second half of our two-part interview, Georgi Dinkov and I continue our discussion about the biochemistry of human metabolism and the process of aging. Part one can be viewed on my Substack site.

We begin by reviewing a complex concept that is not understood by any health experts, and that is the concept of reductive stress, which plays a crucial role in accelerated aging. As it turns out, what science refers to as "oxidative stress" is actually secondary

to reductive stress resulting in the production of excess free radicals. Once you understand this process, it becomes easier to determine the best ways to combat it.

Rate-of-Living Theory

To understand this, you first need to understand what oxidation and reduction reactions are. Dinkov explains:

> *"Rate-of-living theory underpins this whole concept of oxidative stress. Currently, pretty much every doctor will tell you that the higher your metabolic rate — which means the quicker the electrons move from food towards oxygen, which is the final acceptor of electrons — the faster you'll age because there'll be higher oxidative stress. You'll be producing a higher amount of reactive oxygen species (ROS).*
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> *But if you look at the actual data, and this is even in the medical books, it turns out it's the exact opposite. ROS are generated from oxygen, but it's actually when you're NOT shuttling the electrons fast enough towards oxygen.*
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> *And, when these electrons [from food] build up in various chunks of this process, whether it's in the Krebs cycle or the electron transport chain, you have to do something with them.*
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> *If you look at what a reactive oxygen species is, you'll see that it's actually oxygen that has been reduced, in other words, oxygen that has gained an electron. Now, an electron, by its nature, is a reductive species. Basically, a food is a donor of electrons, a reductant.*
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> *Oxygen is an acceptor of electrons, an oxidant. So, if you have a buildup of electrons, this means that you are in a state of excessive reduction, or at least higher than optimal.*
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> *So, your body has to do something with them. You're giving the body electrons, either from food or through lipolysis, or the cortisol-generating amino acids*

from your muscles. Ultimately, all of these things get converted to energy, and the way energy works is, it's a flow of electrons.

So, electrons, ideally, should be paired at the very end with oxygen through Complex 4 of the electron transport chain. If that does not happen, then these electrons can attack oxygen molecules [moving through the metabolic chain] and reduce them by an electron or two, [which] generates these very reactive species."

Rephrased Summary

To reiterate, when electrons cannot move forward in the metabolic chain, they can build up. At a certain point, the buildup becomes toxic to that specific step, causing the electrons to be shuttled backward, where they encounter oxygen molecules.

Molecular oxygen is always present, but it's only useful if it's used at the last step, which is the cytochrome C oxidase. At any other point, oxygen coming into interaction with these electrons is asking for trouble. When the electrons build up in Complex 1 or 3, which is usually the case, then the excess electrons leak through the mitochondrial membrane and start combining with molecular oxygen, creating excess ROS in the process.

However, these oxygen species are not oxidative. They're not oxidizing agents anymore. They have accepted either one or two electrons, so they're actually a reductive species such as hydroxyl or superoxide anions.

Combined, hydroxyl radicals and superoxide anions are responsible for approximately 90% of the ROS generated, and both are single electron reductive agents. This means they can attack and damage DNA, various enzymes and important tissues like the inner mitochondrial membrane and cardiolipin.

But hydroxyl radicals and superoxide anions are not oxidants. They're a reduced form of oxygen, so they're highly reactive and can wreak a lot of havoc, but the very reason they're present is because there was an excess of electrons to start with, and an excess

of electrons is, by definition, a reductive state. So, in short, only when you're in a reductive state can you have oxidative stress and subsequent production of ROS.

For some reason, this reductive state became termed "oxidative stress," as if oxygen was the cause of it, but oxygen by itself does not do much damage, provided the electrons, the reductants, are flowing or moving appropriately. Basically, oxygen is an innocent bystander in this process. The real culprit is excess electrons buildup.

The Easier the Flow of Electrons, the Less Oxidative Stress

What this all means is that the higher your metabolic rate, the more easily these electrons flow from food to oxygen and the less oxidative stress you're going to have. The slower your metabolic rate, the greater the buildup of electrons, which combine with oxygen to create ROS or oxidative stress. Again, it's not truly oxidative stress but damage caused by excess reductive stress, meaning too many unpaired electrons. Dinkov continues:

> *"The determining factor for most of the creation of the ROS is the NADH to NAD+ ratio. NADH being the reduced form and NAD+ the oxidized form. This ratio also controls the speed of metabolism of carbohydrates because the rate limiting step is pyruvate dehydrogenase.*
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> *When you're in the oxidized state, in other words, NAD+ predominates, then pyruvate-dehydrogenase works well and electrons flow through the Krebs cycle and the electron transport chain ...*
>
> *When NADH predominates, you have too many electrons ... that are not meeting oxygen properly. This buildup of electrons creates these bottlenecks, either in Complex 1 or Complex 3, mostly ... Then something has to happen with these electrons. Two things can happen. One is increased synthesis of the ROS. Second, your body uses these extra electrons to synthesize fats.*
>
> *So, you can view obesity, or at least extreme obesity, as a desperate mechanism to get rid of electrons that are coming from food but are not getting processed*

properly. In other words, you're not combusting the food properly. So, what happens with it? Well, you store it. That's the only thing that the body can do.

And, by the way, whenever you have obesity or severe overweight, you always have high amounts of ROS, because those are the only two things that the body can do with the extra electrons. It cannot simply evaporate them, though there's some research on grounding that [shows] you can help get rid of the excess electrons [that way].”

Antioxidants Aren’t the Best Answer

So, again, when you have an excessive buildup of electrons, which by definition is a reductive state or a state of reductive stress, your body can dissipate the electrons either by synthesizing fats or creating ROS. Your body must then deactivate these ROS to avoid excessive damage.

A number of enzymes and antioxidants can do this. But the whole point is, why bother taking these substances if the whole problem, from the very beginning, was a low basal metabolic rate, i.e., the metabolic process was not working as fast as it should have to avoid electron buildup?

Paradoxically, the way to get rid of “oxidative stress,” or more correctly reductive stress, is to increase oxidation, i.e., to increase your metabolic rate. This will prevent the ROS from being generated in the first place. Continuously taking antioxidants merely masks the problem.

As noted by Dinkov, “The solution is to improve metabolism, so the electrons go where they should be going and don't build up.” How to improve your metabolic rate is at the heart of the late Ray Peat’s work, which Dinkov has studied extensively.

Best Supplements for Reductive Stress

To reduce this reductive stress (improperly referred to as oxidative stress), you can take oxidizing quinines such as vitamin K2 and/or methylene blue.

Methylene blue (MB) is the parent molecule for hydroxychloroquine. In its oxidized form, MB is dark blue. Its reduced form is colorless and is now being used in antiaging skin care products. The active form you want to use is the oxidized, blue form, but even if you took the reduced form, reduced MB tends to easily grab oxygen from the environment to become oxidized again.

What makes MB so universally useful is that most people have serious reductive stress secondary to excessive LA in their diets, so, if there's a block anywhere in the electron transport chain, methylene blue simply transfers the electrons straight to oxygen, bypassing the obstruction.

As a result, your cells can generate more energy. Methylene blue can serve as an emergency oxidant not only in the electron transport chain but in the Krebs cycle. It can accept electrons and allow them to continue moving. For all these reasons, methylene blue appears to be a fantastic solution for reductive stress.

Methylene blue is also augmented and works synergistically with near-infrared radiation, so you can further boost the benefits by combining it with sun exposure or a near-infrared sauna. Also, combined with red light, methylene blue creates singlet oxygen species that kill viruses and bacteria.

Methylene blue is classified as a drug and to get USP human grade typically requires a prescription so it can be purchased legally at a compounding pharmacy. There are companies that sell the USP grade but it is illegal and you would need to see their third party testing to confirm it was tested for purity. Doses are typically 5-10 mg/day for most unless they are sick then can increase to 50 mg.

Niacinamide is also useful for reducing reductive stress, as it increases NAD+ by providing fuel for the rate limiting enzyme for creating it, NAMPT. Methylene blue in combination with niacinamide is particularly potent at reducing reductive stress and increasing energy.

Biohacks for Obesity

At present, a clear majority of people are overweight or obese and metabolically inflexible. This goes to the point of not being metabolically efficient, which is what we're talking about. Strategies that will increase your metabolic rate and address obesity include the following, each of which is discussed in greater detail in the interview:

- Avoid PUFAs as much as possible, as they are the primary contributor to reverse electron flow that shuts down your metabolism and increases reductive stress. PUFAs damage cardiolipin, which prevents it from binding with Complex 4. Once that Complex is dysfunctional, even if all the others are working, you'll get a buildup of electrons.

- A daily aspirin regimen (325 mg per day).

- Niacinamide, 50 mg three times a day. Niacinamide activates pyruvate dehydrogenase (PDH), which is the throttle for the Randle switch, discussed in **Part 1 of this interview**.

  Niacinamide is also a precursor for NAD+. According to Dinkov, research shows that ATP levels have an almost perfect correlation with NAD+. So, the higher your NAD+, the higher your ATP synthesis and the better your metabolism works. Niacinamide is also a required cofactor to convert cortisol into the inactive (and far less dangerous) form of cortisone.

  Ideally, also take magnesium half an hour or so after the niacinamide. If your ATP output is low, the magnesium cannot bind to the ATP, and in its free ionic form, magnesium is rapidly excreted. Taking niacinamide will raise NAD+ and hence ATP, allowing your body to more effectively use the magnesium.

- Drink organic black coffee, and if you get jittery, you probably don't have enough glycogen in your liver, so drink your coffee or take a caffeine tablet with some food or some glycine, beta-alanine or taurine, all of which are GABA agonists.

- Optimize your cellular melatonin production by getting regular sun exposure or using a near-infrared sauna.

Vitamin E

Another supplement that most people need is vitamin E. That's going to limit the oxidation of PUFAs such as LA into mutagenic and carcinogenic metabolites. The kind you want is the "dextro," not the "levo" kind, and you want primarily alpha, including D-alpha-tocopherol.

According to Dinkov, vitamin E has also been shown to have an antagonistic relationship with estrogen, which plays a significant role in many chronic diseases, including certain cancers. The tocopherol isomers are also moderately strong aromatase inhibitors.

> *"So, basically, by taking vitamin E, whatever estrogenic effects are out there, even from nonperoxidized PUFA, or if you're producing too much estrogen for whatever reason, if you have endocrine disruptors which are capable of binding and activating the estrogen receptor just like estrogen does, tocopherol will block some of that,"* Dinkov says.
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> *"It's really a versatile molecule that has genomic steroid-like effects, but it mimics progesterone, which is also the main anti-estrogen in the body for females, testosterone and the dihydrotestosterone being the main anti-estrogens in the body of males.*
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> *Tocopherol will have most of these effects. And it probably has much fewer side effects than taking steroids. The daily needs have been shown to correlate perfectly with your intake and storage of PUFAs, so the daily need, the real RDA, of vitamin E is about 2 mg of vitamin E for every gram of PUFA consumed, which means, if you're consuming 50 grams of PUFA, you need 100 mg vitamin E to combat its peroxidative and estrogenic potential.*
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> *Most people are used to measuring the vitamin E in units. If you take the vitamin E dosage in milligrams and multiply by 1.5, you get the dosage in international*

units."

Animal Protein and Longevity

Dinkov also dives deep into the science behind protein needs. He recommends 80 to 120 grams of protein a day for muscle maintenance, which is lower than many others. Typically, if you want to build muscle, experts will recommend twice that.

Dinkov, however, stresses the need for collagen, as it contains higher amounts of specific amino acids with anti-inflammatory and other healing properties. These include glycine, proline, hydroxyproline and alanine.

Red meat is higher in amino acids that induce inflammation: methionine, histidine, tryptophan and cysteine. On a side note, Dinkov points out that aspirin inhibits the absorption of methionine, cysteine and tryptophan from food. He believes a single baby aspirin with a meal would suffice to inhibit absorption of these proinflammatory amino acids. He also discusses other benefits of aspirin, so for more details, listen to the interview in its entirety.

According to biologist Ray Peat's work, amino acids in their free state have many hormone-like functions. For example, during stress, cysteine and tryptophan are released in large quantities, and these amino acids have antimetabolic effects. Other amino acids act as nerve-modifiers, triggering excitation or inhibition, while others, especially glycine, have cell-protective, anti-stress effects.

As such, many degenerative and inflammatory diseases can be ameliorated by eating more collagen and gelatin-rich foods. Red meat, on the other hand, contains far higher levels of the antimetabolic amino acids cysteine and tryptophan, which you want less of if you struggle with degenerative and/or inflammatory conditions.

Life extension studies have shown that restricting tryptophan or cysteine alone produces greater life extension than what is achieved in most calorie restriction studies, which is rather remarkable.[1]

More Information

You can check out Georgi's blog at **www.haidut.me** or **follow him on Twitter**. He also has hundreds of videos on **YouTube** on a plethora of topics. A major sampling of Ray Peat's work is also available for free on these two sites: **wiki.chadnet.org/Ray-Peat** and **RayPeat.com**.