The Weston A. Price Foundation

Sulfur Deficiency

JULY 2, 2011 BY STEPHANIE SENEFF, PHD (HTTPS://WWW.WESTONAPRICE.ORG/AUTHOR/SSENEFF/)

Read this in:
Español (https://www.westonaprice.org/es/health-topics/deficiencia-de-sulfuro/)

Print post

A Possible Contributing Factor in Obesity, Heart Disease, Alzheimer's and Chronic Fatigue

Obesity is quickly becoming the number one health issue confronting America today, and has also risen to epidemic proportions worldwide. Its spread is associated with the adoption of a Western-style diet. However, I believe that the widespread consumption of food imports produced by U.S. companies plays a crucial role in the rise in obesity worldwide. Specifically, these "fast foods" typically include heavily processed derivatives of corn, soybeans and grains, grown on highly efficient mega-farms. Furthermore, I will argue in this essay that one of the core underlying causes of obesity may be sulfur deficiency.

Sulfur is the eighth most common element by mass in the human body, behind oxygen, carbon, hydrogen, nitrogen, calcium, phosphorus and potassium. The two sulfur-containing amino acids, methionine and cysteine, play essential physiological roles throughout the body. However, sulfur has been consistently overlooked by those addressing the issues of nutritional deficiencies. In fact, the National Academy of Sciences has not even assigned a

minimum daily requirement (MDR) for sulfur. One consequence of sulfur's limbo nutritional status is that it is omitted from the long list of supplements that are commonly artificially added to popular foods like cereal.

UNAPPRECIATED DEFICIENCIES

Sulfur is found in a large number of foods, and, as a consequence, it is assumed that almost any diet would meet the minimum daily requirements. Excellent sources are eggs, onions, garlic, and leafy dark green vegetables like kale and broccoli. Meats, nuts, and seafood also contain sulfur. Methionine, an essential amino acid, is found mainly in egg whites and fish. A diet high in grains like bread and cereal is likely to be deficient in sulfur. Increasingly, whole foods such as corn and soybeans are disassembled into component parts with chemical names, and then reassembled into heavily processed foods. Sulfur is lost along the way, and so is the awareness that this loss matters.

Experts have recently become aware that sulfur depletion in the soil creates a serious deficiency for plants,[17] brought about in part by improved efficiency in the U.S. agricultural industry, which has steadily consolidated into highly technologized mega-farms.

It is estimated that humans obtain about ten percent of their sulfur supply from drinking water. Remarkably, people who drink soft water have an increased risk of heart disease compared to people who drink hard water.[2] Many possible reasons have been suggested for why this might be true, and just about every trace metal has been considered as a possibility.[3] However, I believe that the real reason may simply be that hard water is more likely to contain sulfur.

SULFUR AND OBESITY RATES

The ultimate source of sulfur is volcanic rock, mainly basalt, spewed up from the earth's core during volcanic eruptions. It is generally believed that humans first evolved in the African rift zone, a region that would have enjoyed an abundance of sulfur due to the heavy volcanic activity there.

The three principal suppliers of sulfur to the Western nations are Greece, Italy and Japan. These three countries also enjoy low rates of heart disease and obesity and increased longevity. In the United States, Oregon and Hawaii, two states with significant volcanic activity, have among the lowest obesity rates in the country. By contrast, the highest obesity rates are

found in the midwest and in southern farm country: the epicenter of the modern agricultural practices (mega-farms) that lead to sulfur depletion in the soil. Among all fifty states, Oregon has the lowest childhood obesity rates.

Hawaii's youth are faring less well than their parents, however: while Hawaii ranks as the fifth from the bottom in obesity rates, its children aged ten through seventeen weigh in at number thirteen. As Hawaiians have recently become increasingly dependent on food imports from the mainland, they have suffered accordingly with increased obesity problems.

In her recently published book, *The Jungle Effect*,[25] Dr. Daphne Miller devotes a full chapter to Iceland in which she struggles to answer the question of why Icelanders enjoy such remarkably low rates of depression, despite living at a northern latitude, where one would expect a high incidence of Seasonal Affective Disorder. She points out, furthermore, their excellent health record in other key areas: "When compared to North Americans, they have almost half the death rate from heart disease and diabetes, significantly less obesity, and a greater life expectancy. In fact, the average life span for Icelanders is amongst the longest in the world." While she proposes that their high fish consumption, with associated high intake of omega-3 fats, may plausibly be the main beneficial factor, she puzzles over the fact that former Icelanders who move to Canada and also eat lots of fish do not also enjoy the same decreased rate of depression and heart disease.

In my view, the key to Icelanders' good health lies in the string of volcanoes that make up the backbone of the island, which sits atop the mid-Atlantic ridge crest. Dr. Miller pointed out that the mass exodus to Canada was due to extensive volcanic eruptions in the late 1800s, which blanketed the highly cultivated southeast region of the country. This means, of course, that the soils today are highly enriched in sulfur. The cabbage, beets and potatoes that are staples of the Icelandic diet are likely providing far more sulfur to Icelanders than their counterparts in the American diet provide.

TWO MYSTERIOUS MOLECULES

Now comes the difficult question: why does sulfur deficiency lead to obesity? The answer, like much of biology, is complicated, and part of what I theorize is conjecture.

Sulfur is known as a healing mineral, and a sulfur deficiency often leads to pain and inflammation associated with various muscle and skeletal disorders. Sulfur plays a role in many biological processes, one of which is metabolism. It is present in insulin, the essential hormone that promotes the utilization of sugar derived from carbohydrates for fuel in muscle and fat cells. However, my extensive literature search has led me to two mysterious molecules found in the blood stream and in many other parts of the body: vitamin D_3 sulfate and cholesterol sulfate.[35]

Upon exposure to the sun, the skin synthesizes vitamin D_3 sulfate, a form of vitamin D that, unlike unsulfated vitamin D_3, is water soluble. As a consequence, it can travel freely in the blood stream rather than encapsulated inside LDL (the so-called "bad" cholesterol) for transport.[1] The form of vitamin D that is present in both human milk[19] and raw cow's milk[2] is vitamin D_3 sulfate (pasteurization destroys it in cow's milk).

Cholesterol sulfate is also synthesized in the skin, where it forms a crucial part of the barrier that keeps out harmful bacteria and other microorganisms such as fungi.[35] Cholesterol sulfate regulates the gene for a protein called profilaggrin, by interacting like a hormone with the nuclear receptor ROR-alpha. Profilaggrin is the precursor to filaggrin, which protects the skin from invasive organisms.[31,24] A deficiency in filaggrin is associated with asthma and arthritis. Therefore, cholesterol sulfate plays an important role in protection from asthma and arthritis. This explains why sulfur is a healing agent.

Like vitamin D_3 sulfate, cholesterol sulfate is also water-soluble, and it too, unlike cholesterol, does not have to be packaged up inside LDL for delivery to the tissues.

Here I pose the interesting question: where do vitamin D_3 sulfate and cholesterol sulfate go once they are in the blood stream, and what role do they play in the cells? Surprisingly, as far as I can tell, nobody knows. It has been determined that the sulfated form of vitamin D_3 is strikingly ineffective for calcium transport, the well-known "primary" role of vitamin D_3.[29]

However, vitamin D_3 clearly has many other positive effects (it seems that more and more are being discovered every day), and these include a role in cancer protection, increased immunity against infectious disease, and protection against heart disease. Researchers don't yet understand how it achieves these benefits, which have been observed empirically but

remain unexplained physiologically. However, I strongly suspect it is the sulfated form of the vitamin that instantiates these benefits, and my reasons for this belief will become clearer in a moment.

One very special feature of cholesterol sulfate, as opposed to cholesterol itself, is that it is very agile: due to its polarity it can pass freely through cell membranes, almost like a ghost.[30] This means that cholesterol sulfate can easily enter a fat or muscle cell. I am developing a theory which at its core proposes an essential role for cholesterol sulfate in the metabolism of glucose for fuel by these cells. Below, I will show how cholesterol sulfate may be able to protect fat and muscle cells from damage due to exposure to glucose, a dangerous reducing agent, and to oxygen, a dangerous oxidizing agent. I will further argue that, with insufficient cholesterol sulfate, muscle and fat cells become damaged, and as a consequence become glucose intolerant, unable to process glucose as a fuel. This happens first to muscle cells but eventually to fat cells, as well. Fat cells become storage bins for fats to supply fuel to the muscles, because the muscles are unable to utilize glucose as fuel. Eventually, fat cells also become too disabled to release their stored fats. Fatty tissue then accumulates on the body.

SULFUR AND GLUCOSE METABOLISM

In order to understand my theory, you will need to know more about glucose metabolism. Skeletal muscle cells and fat cells break down glucose in the presence of oxygen in their mitochondria, and in the process they produce ATP, the basic energy currency of all cells. A glucose transporter called GLUT4 is present in the cytoplasm of muscle cells, and it migrates to the cell membrane upon stimulation by insulin. GLUT4 essentially acts as a key that unlocks the door, letting glucose into the cell, but, like a key, it only works when it's inserted in the membrane.

Both glucose and oxygen, unless they are carefully managed, can cause harm to the cell's proteins and fats. The glucose enters the cell within special cholesterol-rich sites in the cell wall called lipid rafts.16 This is likely orchestrated to protect the cell wall from damage,

because extra cholesterol allows the vulnerable lipoproteins in the cell wall to pack more tightly and reduce their risk of exposure. In muscle cells, myoglobin is able to store additional oxygen, bound to an iron molecule safely sequestered in an interior cavity within the myoglobin protein.

Sulfur is a very versatile molecule, because it can exist in several distinct oxidative states, ranging from +6 (in the sulfate radical) to -2 (in hydrogen sulfide). Glucose, as a powerful reducing agent, can cause significant glycation damage to exposed proteins, leading to the formation of Advanced Glycation End Products (AGE's) that are extremely destructive to health: they are believed to be a major contributor to heart disease risk.[4] I hypothesize that, if sulfur (+6) is made available to glucose as a decoy, the glucose will be diverted into reducing the sulfur rather than glycating some vulnerable protein such as myoglobin.

In searching the Web, I came across an article written in the 1930s about the striking ability of iron sulfate, in the presence of the oxidizing agent hydrogen peroxide, to break down starch into simple molecules, even in the absence of any enzymes to catalyze the reaction.[5] The article pointedly mentioned that iron works much better than other metals, and sulfate works much better than other anions. In the human body, starch is first converted to glucose in the digestive system. The muscle and fat cells only need to break down glucose. Thus, their task is easier, because the iron sulfate is now starting from an intermediate breakdown product of starch rather than from starch itself.

Where would the iron sulfate come from? It seems to me that the cholesterol sulfate, having hopped across the cell membrane, could transfer its sulfate radical to the myoglobin, whose iron molecule could provide the other half of the formula. In the process, the sulfur molecule's charge would be driven down from +6 to -2, releasing energy and absorbing the impact of the reducing effects of glucose, and therefore serving as a decoy to protect the proteins in the cell from glycation damage.

When the cell is exposed to insulin, its mitochondria are triggered to start pumping both hydrogen peroxide and hydrogen ions into the cytoplasm, essentially gearing up for the assault by glucose. If cholesterol sulfate enters the cell alongside the glucose, then all the players are available.

I conjecture that cholesterol sulfate is the catalyst that seeds the lipid raft. Iron sulfate is then formed by bonding the iron in the heme unit in myoglobin to a sulfate ion provided by cholesterol sulfate. The cholesterol is left behind in the cell wall, thus enriching the newly forming lipid raft with cholesterol. The hydrogen peroxide, provided by the mitochondria

upon insulin stimulation, catalyzes the dissolution of glucose by the iron sulfate. The pumped hydrogen can pair up with the reduced sulfur (S-2) to form hydrogen sulfide, a gas that can easily diffuse back across the membrane for a repeat cycle. The oxygen that is released from the sulfate radical is picked up by the myoglobin, sequestered inside the molecule for safe travel to the mitochondria. Glucose breakdown products and oxygen are then delivered to the mitochondria to complete the process, which ends with water, carbon dioxide and ATP, all while keeping the cell's cytoplasmic proteins safe from glucose and oxygen exposure.

If I'm right about this role for cholesterol sulfate both in seeding the lipid raft and in providing the sulfate ion, then this process breaks down miserably when cholesterol sulfate is not available. First of all, the lipid raft is not formed. Without the lipid raft, the glucose can not enter the cell. Intense physical exercise can allow glucose to enter the muscle cells even in the absence of insulin.[27] However, this will lead to dangerous exposure of the cell's proteins to glycation (because there is no iron sulfate to degrade the glucose). Glycation interferes with the proteins' ability to perform their jobs, and leaves them more vulnerable to oxidation damage. One of the important affected proteins would be myoglobin: it would no longer be able to effectively carry oxygen to the mitochondria. Furthermore, oxidized myoglobin released into the blood stream by crippled muscle cells leads to painful and crippling rhabdomyolysis, and possible subsequent kidney failure. This explanation accounts for the observation that sulfur deficiency leads to muscle pain and inflammation.

METABOLIC SYNDROME

The metabolic syndrome is a term used to encapsulate a complex set of markers associated with increased risk to heart disease. The profile includes (1) insulin resistance and dysfunctional glucose metabolism in muscle cells; (2) excess triglycerides in the blood serum; (3) high levels of LDL, particularly small dense LDL, the worst kind; (4) low levels of HDL (the "good" cholesterol) and reduced cholesterol content within the individual HDL particles; (5) elevated blood pressure; and (6) obesity, particularly excess abdominal fat. I have argued previously that this syndrome is brought on by a diet that is high in empty carbohydrates

(particularly fructose) and low in fats and cholesterol, along with a poor vitamin D status.[35] While I still believe that all of these factors are contributory, I would now add another factor as well: insufficient dietary sulfate.

I have described in a previous essay my interpretation of obesity as a condition driven by a need for abundant fat cells to convert glucose to fat because the muscle cells are unable to efficiently utilize glucose as fuel. With sulfur deficiency comes the answer as to why muscle cells would be defective in glucose management: they can't come up with enough cholesterol sulfate to seed the lipid raft needed to import the glucose.

An alternative way to overcome a muscle cell's defective glucose metabolism is to exercise vigorously, so that the generated AMPK (an indicator of energy shortage) induces the GLUT4 to migrate to the membrane even in the absence of insulin.[27] Once the glucose is inside the muscle cell, however, the iron-sulfate mechanism just described is dysfunctional, both because there's no cholesterol sulfate and because there's no hydrogen peroxide. Additionally, with intensive exercise there's also a reduced supply of oxygen, so the glucose must be processed anaerobically in the cytoplasm to produce lactate. The lactate is released into the blood stream and shipped to the heart and brain, both of which are able to use it as fuel. But the cell membrane remains depleted in cholesterol, and this makes it vulnerable to future oxidative damage.

Another way to compensate for defective glucose metabolism in the muscle cells is to gain weight. Fat cells must now convert glucose into fat and release it into the blood stream as triglycerides, to fuel the muscle cells. In the context of a lowfat diet, sulfur deficiency exacerbates the problem. Sulfur deficiency interferes with glucose metabolism, so it's a much healthier choice simply to avoid glucose sources (carbohydrates) in the diet; i.e. to adopt a very low-carb diet. Then the fat in the diet can supply the muscles with fuel, and the fat cells are not burdened with having to store up so much reserve fat.

Insulin suppresses the release of fats from fat cells.[32] This forces the fat cells to flood the bloodstream with triglycerides when insulin levels are low, that is, after prolonged periods of fasting, such as overnight. The fat cells must dump enough triglyceride into the bloodstream

during fasting periods to fuel the muscles when the dietary supply of carbohydrates keeps insulin levels elevated, and the release of fats from the fat cells is repressed. As the dietary carbs come in, blood sugar levels rise dramatically because the muscle cells can't utilize them.

The liver also processes excess glucose into fat, and packages it up into LDL, to further supply fuel to the defective muscle cells. Because the liver is so preoccupied with processing glucose and fructose into LDL, it falls behind on the generation of HDL, the "good" cholesterol. So the result is elevated levels of LDL, triglycerides, and blood sugar, and reduced levels of HDL, four key components of the metabolic syndrome.

The chronic presence of excess glucose and fructose in the blood stream leads to a host of problems, all related to glycation damage of blood stream proteins by glucose exposure. One of the key proteins that gets damaged is the apolipoprotein, apoB, which is encased in the membrane of the LDL particles. Damaged apoB inhibits the ability of LDL to efficiently deliver its contents (fat and cholesterol) to the tissues. Fat cells again come to the rescue, by scavenging the broken LDL particles (through a mechanism that does not require apoB to be healthy), taking them apart, and extracting and refurbishing their cholesterol. In order to function properly, the fat cells must have intact apoE, an antioxidant that cleans up oxidized cholesterol and transports it to the cell membrane for delivery to HDL particles.

FAT CELLS, MACROPHAGES, AND ATHEROSCLEROSIS

While diligently converting glucose to stored fats, the fat cells are awash in glucose, which damages their apoE through glycation.[20] Once their apoE is damaged, they can no longer transport cholesterol to the membrane. Excess cholesterol accumulates inside the fat cells and eventually destroys their ability to synthesize proteins. Concurrently, their cell membranes become depleted in cholesterol, because they can no longer deliver it to the membrane.[34] A fat cell that has deteriorated to this degree has no choice but to die: it sends out distress signals that call in macrophages. The macrophages essentially consume the dysfunctional fat cell, wrapping their own membrane around the fat cell's membrane that is now barely able to hold its contents inside.[8]

Macrophages are also principal players in the fatty streaks that appear along the sides of major arteries leading to the heart, and are associated with plaque build-up and heart disease. In a fascinating set of experiments, Ma and others[22] have shown that the sulfate ion attached to oxidized forms of cholesterol is highly protective against fatty streaks and

atherosclerosis.

In a set of in-vitro experiments, they demonstrated diametrically opposite reactions from macrophages to 25-hydroxyl cholesterol (25-HC) versus its sulfoconjugate 25-hydroxyl cholesterol sulfate (25-HC3S). Whereas 25-HC present in the medium causes the macrophages to synthesize and store cholesterol and fatty acids, 25-HC3S has the exact opposite effect: it promotes the release of cholesterol to the medium and causes fat stores to shrink. Furthermore, while 25-HC added to the medium led to apoptosis and cell death, 25-HC3S did not. I suggest that the sulfate radical is essential for the process that feeds cholesterol and oxygen to the heart muscle.

MUSCLE WASTING DISEASES

I recently came upon a remarkable article in a 1997 issue of FASEB[11] which develops a persuasive theory that low blood serum levels of two sulfur-containing molecules are a characteristic feature of a number of disease conditions. All of these diseases are associated with muscle wasting, despite adequate nutrition. The authors have coined the term “low CG syndrome” to represent this observed profile, where “CG” stands for the amino acid “cysteine,” and the tripeptide “glutathione,” both of which contain a sulfhydryl radical “-S-H” that is essential to their function. Glutathione is synthesized from the amino acids cysteine, glutamate and glycine, and glutamate deficiency figures into the disease process as well, as I will discuss later.

The list of disease conditions associated with low CG syndrome is surprising and very revealing: HIV infection, cancer, major injuries, sepsis (blood poisoning), Crohn’s disease (irritable bowel syndrome), ulcerative colitis, chronic fatigue syndrome and athletic over-training.

This paper fills in some missing holes in my theory, but the authors never suggest that sulfur deficiency might actually be a precursor to the development of low CG syndrome. I think that, particularly with respect to Crohn’s disease, chronic fatigue syndrome and excessive exercise, sulfur deficiency may precede and provoke the muscle wasting phenomenon. The

biochemistry involved is complicated, but I will try to explain it in as simple terms as possible.

I will use Crohn's disease as my primary focus for discussion: an inflammation of the intestines, associated with a wide range of symptoms, including reduced appetite, low-grade fever, bowel inflammation, diarrhea, skin rashes, mouth sores and swollen gums. Several of these symptoms suggest problems with the interface between the body and the external world, for example, a vulnerability to invasive pathogens. I mentioned before that cholesterol sulfate plays a crucial role in the barrier that keeps pathogens from penetrating the skin. It logically plays a similar role everywhere there is an opportunity for bacteria to invade, and certainly a prime opportunity is available at the endothelial barrier in the intestines. Thus, I hypothesize that the intestinal inflammation and low-grade fever are due to an overactive immune system, necessitated by the fact that pathogens have easier access when the endothelial cells are deficient in cholesterol sulfate. The skin rashes and mouth and gum problems are a manifestation of inflammation elsewhere in the barrier.

Ordinarily, the liver supplies cholesterol sulfate to the gall bladder, where it is mixed into bile acids, and subsequently released into the digestive system to assist in the digestion of fats. If a person consistently eats a lowfat diet, the amount of cholesterol sulfate delivered to the digestive system from the liver will be reduced. This will logically result in a digestive system that is more vulnerable to invasion by pathogens.

The sulfate that's combined with cholesterol in the liver is synthesized from cysteine, therefore insufficient bioavailability of cysteine will lead to a reduced production of cholesterol sulfate by the liver. This will, in turn, make it difficult to digest fats, likely, over time, compelling the person to adhere to a lowfat diet. Whether lowfat diet or sulfur deficiency comes first, the end result is a vulnerability to infective agents in the intestines, with a consequential heightened immune response.

Dröge[11] further discusses how a reduction in the synthesis of sulfate from cysteine in the liver leads to increased compensatory activity in another biological pathway in the liver, one that converts glutamate to arginine and urea. Glutamate is highly significant because it is produced mainly by the breakdown of amino acids (proteins in the muscles), for example, by

muscle wasting. The muscle cells are triggered to cannibalize themselves in order to provide adequate glutamate to the liver, mainly, in my view, in order to generate enough arginine to replace the role of sulfate in muscle glucose metabolism. (These activities in the liver and muscles are circular and mutually supportive.)

Arginine is the major source of nitric oxide (NO) and NO is the next best thing for muscle glucose metabolism in the absence of cholesterol sulfate. NO is a poor substitue for SO_4^{-2}, but it can function in some of the missing roles. As you will recall, I propose that cholesterol SO_4^{-2} accomplishes a number of important things in muscle cells: it delivers oxygen to myoglobin, it supplies cholesterol to the cell membrane, it helps break down glucose, it protects the cell's proteins from glycation and oxidation damage, and it provides energy to the cell. NO can help in reducing glycation damage, as nitrogen can be reduced from +2 to 0 (whereas sulfur reduces from +6 to -2). It also provides oxygen, but it is unable to transfer the oxygen directly to myoglobin by binding with the iron molecule, as is the case for sulfate. NO does not supply cholesterol, so cholesterol deficiency remains a problem, leaving the cell's proteins and fats more vulnerable to oxidative damage. Furthermore, NO itself is an oxidizing agent, so myoglobin becomes disabled, due to both oxidation and glycation damage. The muscle cell, therefore, engages in mitochondrial oxidation of glucose at its own peril: better to revert to anaerobic metabolism of glucose to decrease the risk of damage. Anaerobic metabolism of glucose results in a build-up of lactic acid, which, as explained in Dröge[11] further enhances the need for the liver to metabolize glutamate, thus augmenting the feedback loop.

Furthermore, if I'm right about cholesterol sulfate seeding lipid rafts, then, with a cholesterol sulfate deficiency, the entry of both glucose and fat into the muscle cell is compromised. This situation leaves the cell with little choice but to exploit its internal proteins as fuel, manifested as muscle wasting.

In summary, a number of different arguments lead to the hypothesis that sulfur deficiency causes the liver to shift from producing cholesterol sulfate to producing arginine (and subsequently nitric oxide). This leaves the intestines and muscle cells vulnerable to oxidation damage, which can explain both the intestinal inflammation and the muscle wasting

associated with Crohn's disease.

The immune system depends upon abundant cholesterol to defend against severe stress. I have previously argued that high serum cholesterol is protective against sepsis. It is worth repeating here the abstract from Critical Care,[38] which studied changes in blood cholesterol levels following trauma, infection and multiple organ failure: "Hypocholesterolemia is an important observation following trauma. In a study of critically ill trauma patients, mean cholesterol levels were significantly lower (119 ± 44 mg/dl) than expected values (201 ± 17 mg/dl). In patients who died, final cholesterol levels fell by 33 percent versus a 28 percent increase in survivors. Cholesterol levels were also adversely affected by infection or organ system dysfunction."

Thus, many of these conditions/diseases that lead to muscle wasting may do so because cholesterol (and therefore cholesterol sulfate) is depleted from the blood serum. This results in the same feedback loop between the liver and the muscles that I discussed with regard to C rohn's disease. I think it's plausible that the muscle wasting associated with all of these conditions is caused by this same feedback mechanism.

I have discussed the role cysteine plays in providing sulfate to the liver. But what is the role of glutathione, the other sulfur-containing protein that's depleted in low GC syndrome? Muscle cells ordinarily contain significant levels of glutathione, and its depletion leads to mitochondrial damage.[23] Patients undergoing surgical trauma have been found to exhibit reduced glutathione levels in their skeletal muscles.[21] It is tempting to speculate that cholesterol sulfate provides the sulfur needed for glutathione synthesis, so that the deficiency would be explained by the reduced availability of cholesterol following the immune system's heightened response to surgical trauma. Glutathione is a potent antioxidant, so its deficiency will further contribute to dysfunction of the muscle cell's mitochondria, therefore greatly impairing its energy supply.

There is a growing awareness that glutathione deficiency may play a role in many diseases. Whether the problems that arise are just due to insufficient supply of the glutathione molecule itself, or whether a more general sulfur deficiency is the root cause, is perhaps hard to say, but provocative nonetheless.

IN CONCLUSION

Modern lifestyle practices conspire to induce major deficiencies in cholesterol sulfate and vitamin D_3 sulfate. We are encouraged to actively avoid sun exposure and to minimize dietary intake of cholesterol-containing foods. We are encouraged to consume a high-carbohydrate, lowfat diet which, as I have argued previously,[34] leads to impaired cholesterol uptake in cells. Fortunately, correcting these deficiencies at the individual level is easy and straightforward. If you just throw away the sunscreen and eat more eggs, those two steps alone may greatly increase your chances of living a long and healthy life.

SIDEBARS

IS THE SKIN A SOLAR-POWERED BATTERY FOR THE HEART?

The evidence is quite compelling that sunny places afford protection from heart disease. A study described in a 1996 issue of QJ Med.[14] provides an in-depth anaylsis of data from around the world showing an inverse relationship between heart disease rates and a sunny climate and a low latitude. For instance, the cardiovascular-related death rate for men between the ages of 55 and 64 was 761 per 100,000 men in Belfast, Northern Ireland, but only 175 in Toulouse, France. While the obvious biological factor that would be affected by sunlight is vitamin D, studies conducted specifically on vitamin D status have been inconclusive, with some even showing a significant increased risk for heart disease with increased intake of vitamin D_2 supplements[12].

I believe, first of all, that the distinction between vitamin D_3 and vitamin D_3 sulfate really matters, and also that the distinction between vitamin D_2 and vitamin D_3 really matters. Vitamin D_2 is the plant form of the vitamin. It works similarly to D_3 with respect to calcium transport, but it cannot be sulfated. Furthermore, apparently the body is unable to produce

vitamin D_3 sulfate directly from unsulfated vitamin D_3 [19] (which implies that it produces vitamin D_3 sulfate directly from cholesterol sulfate). I am not aware of any other food source besides raw milk that contains vitamin D_3 in the sulfated form. So, when studies monitor either vitamin D supplements or vitamin D serum levels, they're not getting at the crucial

aspect for heart protection, which I think is the serum level of vitamin D_3 sulfate.

Furthermore, I believe it is extremely likely that vitamin D_3 sulfate is not the only thing that's affected by greater sun exposure, and maybe not even the most important thing. Given that cholesterol sulfate and vitamin D3 sulfate are very similar in molecular structure, I would imagine that both molecules are produced the same way. And since vitamin D_3sulfate synthesis requires sun exposure, I suspect that cholesterol sulfate synthesis may also exploit the sun's radiation energy.

Both cholesterol and sulfur afford protection in the skin from radiation damage to the cell's DNA, the kind of damage that can lead to skin cancer. Cholesterol and sulfur become oxidized upon exposure to the high frequency rays in sunlight, thus acting as antioxidants to "take the heat," so to speak. Oxidation of cholesterol is the first step in the process by which cholesterol transforms itself into vitamin D_3. Sulfur dioxide in the air is converted nonenzymatically to the sulfate ion upon sun exposure. This is the process that produces acid rain. The oxidation of sulfide (S-2) to sulfate (SO_4^{-2}), a strongly endothermic reaction[15], converts the sun's energy into chemical energy contained in the sulfur-oxygen bonds, while simultaneously picking up four oxygen molecules. Attaching the sulfate ion to cholesterol or vitamin $D_3$is an ingenious step, because it makes these molecules water-soluble and therefore easily transportable through the blood stream.

Hydrogen sulfide (H_2S) is consistently found in the blood stream in small amounts. As a gas, it can diffuse into the air from capillaries close to the skin's surface. So it is conceivable that we rely on bacteria in the skin to convert sulfide to sulfate. It would not be the first time that humans have struck up a symbiotic relationship with bacteria. If this is true, then washing the skin with antibiotic soap is a bad idea. Phototrophic bacteria, such as Chlorobium tepidum, that can convert H2S to H2SO4 exist in nature[39,36], for example in sulfur hot springs in Yellowstone Park. These highly specialized bacteria can convert the light energy from the sun into chemical energy in the sulfate ion.

Another possibility is that we have specialized cells in the skin, possibly the keratinocytes, that are able to exploit sunlight to convert sulfide to sulfate, using a similar phototrophic mechanism to C. tepidum. This seems quite plausible, especially considering that both human keratinocytes and C. tepidum can synthesize an interesting UV-B absorbing cofactor,

tetrahydrobioptin. This cofactor is found universally in mammalian cells, and one of its roles is to regulate the synthesis of melanin,[33] the skin pigment that is associated with a tan and protects the skin from damage by UV-light exposure.[9] However, tetrahydrobiopsin is very rare in the bacterial kingdom, and C. tepidum is one of the very few bacteria that can synthesize it.[37]

Let me summarize at this point where I'm on solid ground and where I'm speculating. It is undisputed that the skin synthesizes cholesterol sulfate in large amounts, and it has been suggested that the skin is the major supplier of cholesterol sulfate to the blood stream.[35] The skin also synthesizes vitamin D_3 sulfate upon exposure to sunlight. Vitamin D_3 is synthesized from cholesterol, with oxysterols (created from sun exposure) as an intermediate step (oxysterols are forms of cholesterol with hydroxyl groups attached at various places in the carbon chain). The body can't synthesize vitamin D_3 sulfate from vitamin D_3 [19] so it must be that sulfation happens first, producing cholesterol sulfate or hydroxy-cholesterol sulfate, which is then optionally converted to vitamin D_3sulfate or shipped out "as is."

Another highly significant feature of skin cells is that the skin stores sulfate ions attached to molecules that are universally present in the intracellular matrix, such as heparan sulfate, chondroitin sulfate, and keratin sulfate[26]. Furthermore, it has been shown that exposure of the melanin-producing cells (melanocytes) to molecules containing reduced sulfur (-2) leads to suppression of melanin synthesis,[7] whereas exposure to molecules like chondroitin sulfate that contain oxidized sulfur (+6) leads to enhancement of melanin synthesis.[18]Melanin is a potent UV-light absorber, and it would compete with reduced sulfur for the opportunity to become oxidized. It is therefore logical that, when sulfur is reduced, melanin synthesis should be suppressed, so that sulfur can absorb the solar energy and convert it to very useful chemical bonds in the sulfate ion.

The sulfate would eventually be converted back to sulfide by a muscle cell in the heart or a skeletal muscle (simultaneously recovering the energy to fuel the cell and unlocking the oxygen to support aerobic metabolism of glucose), and the cycle would continually repeat.

Why am I spending so much time talking about all of this? Well, if I'm right, then the skin can be viewed as a solar-powered battery for the heart, and that is a remarkable concept. The energy in sunlight is converted into chemical energy in the oxygen-sulfur bonds, and then transported through the blood vessels to the heart and skeletal muscles. The cholesterol

sulfate and vitamin D_3-sufate are carriers that deliver the energy (and the oxygen) "door-to-door" to the individual heart and skeletal muscle cells.

Today's lifestyle, especially in America, severely stresses this system. First of all, most Americans believe that any food containing cholesterol is unhealthy, so the diet is extremely low in cholesterol. Eggs are an excellent source of sulfur, but because of their high cholesterol content we have been advised to eat them sparingly. Second, as I discussed previously, natural food plant sources of sulfur are likely to be deficient due to sulfur depletion in the soil. Third, water softeners remove sulfur from our water supply, which would otherwise be a good source. Fourth, we have been discouraged from eating too much red meat, an excellent source of sulfur-containing amino acids. Finally, we have been instructed by doctors and other authoritarian sources to stay out of the sun and wear high SPF sunscreen whenever we do get sun exposure.

Another significant contributor is the high carbohydrate, lowfat diet, which leads to excess glucose in the blood stream, which glycates LDL particles and renders them ineffective in delivering cholesterol to the tissues. One of those tissues is the skin, so skin becomes further depleted in cholesterol due to glycation damage to LDL.

SULFUR DEFICIENCY AND ALZHEIMER'S DISEASE

With an aging population, Alzheimer's disease is on the rise, and it has been argued that the rate of increase is disproportionately high compared to the increase in the raw number of elderly people.[37] Because of a conviction that the amyloid beta plaque, which is a signature of Alzheimer's, is also the cause, the pharmaceutical industry has spent hundreds of millions, if not billions of dollars pursuing drugs that reduce the amount of plaque accumulating in the brain. Thus far, drug trials have been so disappointing that many are beginning to believe that amyloid beta is not the cause after all. Recent drug trials have shown not only no improvement, but actually a further decline in cognitive function, compared to placebo. I have argued elsewhere that amyloid beta may actually be protective against Alzheimer's, and that problems with glucose metabolism are the true culprit in the disease.

Once I began to suspect sulfur deficiency as a major factor in Americans' declining health, I looked into the relationship between sulfur deficiency and Alzheimer's. Imagine my surprise when I came upon a web page posted by Ronald Roth, which shows a plot of the levels of various minerals in the cells of a typical Alzheimer's patient relative to the normal level (http://www.acu-cell.com/dis-alz.html (http://www.acu-cell.com/dis-alz.html)). Remarkably, sulfur is almost non-existent in the Alzheimer's patient's profile.

To quote directly from that site: "While some drugs or antibiotics may slow, or if it should happen, halt the progression of Alzheimer's disease, sulfur supplementation has the potential of not only preventing, but actually reversing the condition, provided it has not progressed to a stage where much damage has been done to the brain. One major reason for the increase in Alzheimer's disease over the past years has been the bad reputation eggs have been getting in respect to being a high source of cholesterol, despite the fact of dietary intake of cholesterol having little impact on serum cholesterol, which is now also finally acknowledged by mainstream medicine. In the meantime, a large percentage of the population lost out on an excellent source of sulfur and a host of other essential nutrients by following the nutritional misinformation spread on eggs. Of course, onions and garlic are another rich source of sulfur, but volume-wise, they cannot duplicate the amounts obtained from regularly consuming eggs."

Why should sulfur deficiency be so important for the brain? I suspect that the answer lies in the mysterious molecule alpha-synuclein, which shows up alongside amyloid-beta in the plaque, and is also present in the Lewy bodies that are a signature of Parkinson's disease.[28] The alpha-synuclein molecule contains four methionine residues, and all four of the sulfur molecules in the methionine residues are converted to sulfoxides in the presence of oxidizing agents such as hydrogen peroxide.[13] Just as in the muscle cells, insulin would cause the mitochondria of neurons to release hydrogen peroxide, which would then allow the alpha-synuclein to take up oxygen in a way that is very reminiscent of what myoglobin can do in muscle cells. The lack of sufficient sulfur would directly impact the neuron's ability to safely

carry oxygen, again paralleling the situation in muscle cells. This would mean that other proteins and fats in the neuron would suffer from oxidative damage, leading ultimately to the neuron's destruction.

I have argued elsewhere that biologically pro-active restriction in glucose metabolism in the brain (a so-called type-III diabetes and a precursor to Alzheimer's disease) is triggered by a deficiency in cholesterol in the neuron cell membrane. Again, as in muscle cells, glucose entry depends upon cholesterol-rich lipid rafts, and, when the cell is deficient in cholesterol, the brain goes into a mode of metabolism that prefers other nutrients besides glucose.

I suspect that a deficiency in cholesterol would come about if there is insufficient cholesterol sulfate, because cholesterol sulfate likely plays an important role in seeding lipid rafts, while concurrently enriching the cell wall in cholesterol. The cell also develops an insensitivity to insulin, and, as a consequence, anaerobic metabolism becomes favored over aerobic metabolism, reducing the chances for alpha-synuclein to become oxidized. Oxidation actually protects alpha-synuclein from fibrillation, a necessary structural change for the accumulation of Lewy bodies in Parkinson's disease (and likely also Alzheimer's plaque).[13]

SULFUR AS A PROTECTIVE AGENT AGAINST RADIATION DAMAGE

Sulfur-containing biological molecules like glutathione and the amino acids cysteine and methionine play an important role in redox (oxidation/reduction) reactions by tempering the damaging effects of reactive oxygen species (ROS); that is, by acting as potent antioxidants.[1] Closely related to this role in protecting from oxidation damage associated with aerobic metabolism is the potential role of sulfur in protection from radiation damage due to sun exposure, radiation treatments for cancer, or radiation exposure following a nuclear reactor meltdown.

An awareness that sulfur protects against ionizing radiation dates back to at least 1949.[10] An enlightening article from 1983[5] showed, via experiments conducted at very low temperatures, that sulfur's reaction to radiation is a secondary effect. The associated primary effect is ionization of oxygen, producing the highly reactive species, O_2^-, Sulfur then responds by

binding to the O_2^- and thus preventing other molecules from reacting adversely with it.

Through an extensive review of the research literature on the response of human skin to the radiation in sunlight, I have come up with a theory for how sulfur could be intimately involved not just in preventing harm from sunlight, but rather by contrast in harnessing the sun's energy and putting it to good use. I propose that sulfur, readily available from the active cysteines in an enzyme called (inappropriately) endothelial nitric oxide synthase (eNOS), reacts with two O_2^- ions produced by sunlight exposure to produce the highly stable and useful anion, sulfate. This reaction would take place in a cavity formed by two abutting molecules of eNOS (that is, an eNOS dimer). A positively charged zinc atom centered in the cavity[8] draws in the two O_2^- ions to combine them with a nearby sulfur atom attached to a cysteine residue, to form a sulfate anion SO_4^{-2}. The sulfate, then, in a subsequent reaction, combines with cholesterol to form cholesterol sulfate, a prominent component of the outer layers of the skin (and also of hair, feathers, fur and fingernails).

An article that appeared in 2002 on the effects of irradiation treatment on aortic endothelial cells[4] revealed that irradiation induces expression of another "inducible" nitric oxide synthase, iNOS. My belief is that the purpose of the iNOS in this case is identical to the purpose of eNOS in the skin: to mop up anticipated O_2^- radicals produced by the radiation, and to convert them to sulfate. The authors showed that if the cells are supplied with the substrate to produce nitric oxide, L-arginine, then this causes them to initiate a programmed cell death reaction called apoptosis. What happens is that the L-arginine binds to the iNOS (and the eNOS as well) and deflects these enzymes towards producing nitric oxide rather than sulfur dioxide. Unfortunately, under the right circumstances, nitric oxide can turn into the highly reactive species ONOO − (known in the vernacular as "oh, no!")[9]and this can make the cell non-viable.

A highly significant fact that supports a primary role for the NOS's in producing sulfate is that red blood cells have an abundance of eNOS, but they are very careful to keep out its substrate L-arginine.[6] This act has puzzled researchers, but the answer becomes clear when you realize that red blood cells are strong producers of cholesterol sulfate,[11]as well as major carriers of oxygen. This makes them a prime candidate for using eNOS to convert oxygen to sulfate (taking advantage of sunlight as a catalyst), and then shipping it to the tissues via the carrier molecule cholesterol sulfate. This action would both protect the red blood cell from

oxidative damage and reduce the risk of damage due to oxygen exposure in other cells, as the oxygen supply contained in the sulfate constitutes safe transport of oxygen to these cells. I have little doubt that this is a productive (but overlooked) mode of oxygen transport in the body.

The sulfur in cysteine plays a crucial role in protecting proteins from radiation damage. In experiments conducted in the late 1950s[3], it was shown that proteins needed to contain only half a percent of cysteine by weight to be immune to any damage to the other amino acids in the protein. Proteins containing no cysteine produced complex irradiation spectra indicating that diverse chemical reactions had taken place.

An article from Nature in 1962[2]showed that sulfur has a remarkable ability to protect macromolecules in colloidal suspensions against cross-linking upon exposure to radiation. The effect was much larger than what the authors would have expected, given their understanding of possible mechanisms, so there is still something mysterious about sulfur's protective role. Since molecules in the blood serum are in some sense a colloidal suspension, this behavior has relevance to protection from ionizing radiation of proteins like serum albumin, which contains significant amounts of cysteine.

The best source of sulfur is the protein from animal products such as meat, fish and eggs. Sulfur is becoming depleted from the soil, so vegetables contain even less sulfur than they used to. It is therefore highly likely that vegetarians suffer from sulfur deficiency, which could affect their susceptibility to damage from radiation exposure.

1. G . Atmaca, "Antioxidant Effects of Sulfur-Containing Amino Acids," *Yonsei Medical Journal*, Vol. 45, #5, 776-788, 2004.

2. A . Charlesby, et al., "Radiation Protection with Sulfur and Some Sulfur-containing Compounds," *Nature*, Vol. 194, 782, May 26, 1962.

3. W.Gordy and I. Miyagawa, "Electron spin resonance studies of mechanisms for chemical protection from ionizing radiation," *Radiation Research*, Vol. 12, 211-229, 1960.

4. M. Hirakawa, M. Oike, K. Masuda, and Y. Ito, "Tumor Cell Apoptosis by Irradiation induced

Nitric Oxide Production in Vascular Endothelium," *Cancer Research*, Vol. 62, 1450 1457, 2002.

5. H-S Kim and C. Alexander, Jr, "ESR Study of the Requirements for Sulfur Radical Formation in irradiated 6-MeMPR," *J. Korean Physical Society*, Vol 16, No 2, 186-189, 1983.

6. P . Kleinbongard, et al., Red blood cells express afunctional endothelial nitric oxide synthase. *Blood*, Vol. 107, No. 7, 2943-2951.

7. L .A. Kormarnisky, et al., "Sulfur: Its Clinical and Toxicologic Aspects," *Nutrition*, Vol. 19, 54-61, 2003.

8. H. Li, et al., "Crystal structures of zinc-free and -bound heme domain of human inducible nitric-oxide synthase. " *J. Biol. Chem.* Vol. 274, 21276-21284, July, 1999.

9. M.L. Pall, Nitric oxide synthase partial uncoupling as a key switching mechanism for the NO / ONOO − cycle. *Medical Hypotheses* Vol. 69, No. 4, 821-5, 2007.

10. H.M. Patt, et al., "Cysteine protection against x-radiation," *Science* Vol. 110, 213, 1949.

11. C .A. Strott, Cholesterol Sulfate in Human Physiology: What's It All About? (2003) 44 *J Lipid Res* 1268-1278.

References

1. Magnus Axelson, "25-Hydroxyvitamin D3 3-sulphate is a major circulating form of vitamin D in man," *FEBS Letters* (1985), Volume 191, Issue 2, 28 October, pp 171-175; doi:10.1016/0014-5793(85)80002-8.

2. T. Crawford and Margaret D. Crawford, “Prevalence and Pathological Changes of Ischaemic Heart-Disease in a Hard-water and in a Soft-water Area,” *The Lancet* (1967) 4 February.

3. Biorck, G., Bostrom, H., Widstrom, A. “Trace Elements and Cardiovascular Diseases” *Acta Med. Scand.* (1965) 178, 239.

4. Brownlee M, Cerami A and Vlassara H. “Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications.” *N Engl J Med* (1988) 318: pp. 1315-1321.

5. W. R. Brown, “The hydrolysis of starch by hydrogen peroxide and ferrous sulfate.” *J. Biol. Chem.* (1936) 113: 417-425.

6. N Le Boulch, L. Cancela and L. Miravet, “Cholecalciferol sulfate identification in human milk by HPLC,” *Steroids* (1982) Volume 39, Issue 4, April, pp 391-398; doi:10.1016/0039-128X(82)90063-0

7. Cho SH, Na JU, Youn H, Hwang CS, Lee CH, Kang SO, “Sepiapterin reductase producing L-threo-dihydrobiopterin from Chlorobium tepidum.” *Biochem J* (1999) 340 (Pt g2);497-503. PMID: 10333495

8. Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E, Wang S, Fortier M, Greenberg AS and Obin MS. “Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans.” *J Lipid Res* (2005) 46: pp. 2347-2355.

9. Gertrude-E. Costin and Vincent J. Hearing, “Human skin pigmentation: melanocytes modulate skin color in response to stress,” *The FASEB Journal* (2007), 21:976- 994; doi: 10.1096/fj.06-6649rev.

10. Heuy-Ling Chu, Bor-Sen Wang and Pin-Der Duh, “Effects of Selected Organo-sulfur Compounds on Melanin Formation,” *J. Agric. Food Chem.* (2009) 57 (15), pp 7072-77; DOI: 10.1021/jf9005824.

11. Wulf Dröge and Eggert Holm, “Role of cysteine and glutathione in HIV infection and other diseases associated with muscle wasting and immunological dysfunction,” *FASEB Journal* (1997) Vol. 11, November, pp. 1077-1089.

12. Marie-Claude Drolet, Marie Arsenault, and Jacques Couet, “Experimental Aortic Valve Stenosis in Rabbits,” *J. Am. Coll. Cardiol.* (2003) Vol. 41, pp. 1211-1217.

13. Charles B. Glaser, Ghiam Yamin, Vladimir N. Uversky, and Anthony L. Fink, “Methionine oxidation, a-synuclein and Parkinson’s disease,” *Biochimica et Biophysica Acta* (2005) Vol. 1703, pp. 157-169.

14. D.S. Grimes, E. Hindle, and T. Dyer, “Sunlight, cholesterol and coronary heart disease.” *Q. J. Med*. (1996) 89:579-589.

15. Simon L. Hockin and Geoffrey M. Gadd, “Linked Redox Precipitation of Sulfur and Selenium under Anaerobic Conditions by Sulfate-Reducing Bacterial Biofilms,” *App and Envrmnl Microbiology* (2003) Dec., p. 7063-72, Vol. 69, No. 12; DOI: 10.1128/AEM.69.12.7063-72.2003.

16. Inoue, M., Chiang, S.H., Chang, L., Chen, X.W. and Saltiel, A.R. “Compartmentalization of the exocyst complex in lipid rafts controls Glut4 vesicle tethering.” *Mol. Biol. Cell* (2006) 17, pp 2303-11.

17. Joseph Jez, “Sulfur: a Missing Link between Soils, Crops, and Nutrition.” *Agronomy Monograph #50*. (2008) American Society of Agronomy, Inc.

18. Katz IR, Yamauchi T, Kaufman S. “Activation of tyrosine hydroxylase by polyanions and salts. An electrostatic effect.” *Biochim Biophys Acta.* (1976) Mar 11;429(1):84-95.

19. Dilnawaz R. Lakdawala and Elsie M. Widdowson, “Vitamin D in Human Milk,” *Lancet* (1977) Volume 309, Issue 8004, 22 January, pp 167-168.

20. Yong Ming Li and Dennis W. Dickson, “Enhanced binding of advanced glycation

endproducts (AGE) by the ApoE4 isoform links the mechanism of plaque deposition in Alzheimer's disease," *Neuroscience Letters* (1997), Volume 226, Issue 3, 155-158; doi:10.1016/S0304-3940(97)00266-8.

21. J L Luo, F Hammarqvist, K Andersson, and J Wernerman, "Skeletal muscle glutathione after surgical trauma." *Ann Surg.* (1996) April; 223(4): 420-27.

22. Yongjie Ma, Leyuan Xu, Daniel Rodriguez-Agudo, Xiaobo Li, Douglas M. Heuman, Phillip B. Hylemon, William M. Pandak and Shunlin Ren, "25-Hydroxycholesterol-3-sulfate regulates macrophage lipid metabolism via the LXR/SREBP-1 signaling pathway," *Am J Physiol Endocrinol Metab* (2008) 295:1369-1379; doi:10.1152/ajpendo.90555.2008. 23. Martensson, J., and Meister,A., "Mitochondrial damage in muscle occurs after marked depletion of glutathione and is prevented by giving glutathione monoester." *Proc Natl Acad Sci U S A,* (1989) 86:471-475.

24. John A. McGrath and Jouni Uitto "The filaggrin story: novel insights into skin-barrier function and disease," *Trends in Molecular Medicine* (2008) Volume 14, Issue 1, 20-27.

25. Dr. Daphne Miller, *The Jungle Effect*, HarperCollins Publishers, New York, New York, Paperback edition, 2009.

26. Leonard M. Milstone, Lynne Hough-Monroe, Lisa C. Kugelman, Jeffrey R. Bender and John G. Haggerty, "Epican, a heparan/chondroitin sulfate proteoglycan form of CD44, mediates cell-cell adhesion," *Journal of Cell Science* (1994) 107, 3183-3190.

27. E.O. Ojuka, T.E. Jones, L.A. Nolte, M. Chen, B.R. Wamhoff, M. Sturek, and J.O. Holloszy, "Regulation of GLUT4 biogenesis in muscle: evidence for involvement of AMPK and Ca2+," *Am J Physiol Endocrinol Metab* (2002) Vol. 282, #5, May.

28. Olivares D, Huang X, Branden L, Greig NH, Rogers JT. "Physiological and Pathological Role of Alpha-synuclein in Parkinson's Disease Through Iron Mediated Oxidative Stress; The Role of a Putative Iron-responsive Element," *Int J Mol Sci* (2009) 10:1226-60.

29. Lorraine E. Reeve, Hector F. DeLuca, and Heinrich K. Schnoes, "Synthesis and Biological Activity of Vitamin D3 Sulfate," *Jrnl Biol. Chem.* (1981) Vol. 256., #2. Jan 25, pp. 823-826.

30. W. V. Rodriguez, J. J. Wheeler, S. K. I.imuk, C. N. Kitson, and M. J. Hope, "Transbilayer Movement and Net Flux of Cholesterol and Cholesterol Sulfate between Liposomal Membranes" *Biochemistry* (1995) 34, 6208-6217.

31. Sandilands A, Sutherland C, Irvine AD, McLean WH, "Filaggrin in the frontline: role in skin barrier function and disease," J Cell Sci. (2009) May 1;122(Pt 9):1285-94.

32. Scoppola A, Testa G, Frontoni S, Maddaloni E, Gambardella S, Menzinger G and Lala A. "Effects of insulin on cholesterol synthesis in type II diabetes patients," *Diabetes Care* (1995) 18: pp. 1362-1369.

33. Schallreuter KU, Wood JM, Pittelkow MR, Gutlich M, Lemke KR, Rodl W, Swanson NN, Hitzemann K, Ziegler I, "Regulation of melanin biosynthesis in the human epidermis by tetrahydrobiopterin." *Science* (1994) 263(5152);1444-6. PMID: 8128228.

34. S. Seneff, G. Wainwright, and L. Mascitelli, "Is the metabolic syndrome caused by a high fructose, and relatively low fat, low cholesterol diet?" *Archives of Medical Science* (2011), Vol. 1, pp.8-20.

35. Charles A. Strott and Yuko Higashi, "Cholesterol sulfate in human physiology: what's it all about?" *Journal of Lipid Research* (2003) Volume 44, pp. 1268-1278.

36. Wahlund, T. M., C. R. Woese, R. W. Castenholz, and M. T. Madigan, "A thermophilic green sulfur bacterium from New Zealand hot springs, Chlorobium tepidum sp." *Nov. Arch. Microbiol.* (1991) 159:81-90.

37. M. Waldman, MD, 9th International Conference on Alzheimer's and Parkinson's Diseases (2009) Abstract 90, Presented March 12-13.

38. Robert F Wilson, Jeffrey F Barletta and James G Tyburski,"Hypocholesterolemia in Sepsis

and Critically Ill or Injured Patients" *Critical Care* 7:413-414, 2003. http://www.medscape.com/viewarticle/511735_2 (http://www.medscape.com/viewarticle/511735_2).

39. Aubrey L. Zerkle, James Farquhar, David T. Johnston, Raymond P. Cox, and Donald E. Canfield, "Fractionation of multiple sulfur isotopes during phototrophic oxidation of sulfide and elemental sulfur by a green sulfur bacterium," *Geochimica et Cosmochimica Acta* (2009) Volume 73, Issue 2, 15 January 2009, pp 291-306; doi:10.1016/j.gca.2008.10.027.

This article appeared in *Wise Traditions in Food, Farming and the Healing Arts*, the quarterly journal of the Weston A. Price Foundation, Summer 2011 (http://www.westonaprice.org/get-involved/journal-summer-2011-salt-and-sulfur/).

About Stephanie Seneff, PhD

Stephanie Seneff, PhD received her Bachelor's degree in Biology with a minor in Food and Nutrition in 1968 from MIT. She received her Master's and PhD degrees in Electrical Engineering and Computer Science in 1979 and 1985, respectively, also from MIT. Since then, she has been a researcher at MIT, where she is currently a Senior Research Scientist in the Department of Electrical Engineering and Computer Science, and a Principal Investigator in the MIT Computer Science and Artificial Intelligence Laboratory. Throughout her career, Dr. Seneff has conducted research in diverse areas including human auditory modeling, spoken

dialogue systems, natural language processing, human language acquisition, information retrieval and summarization, computational biology, and marine mammal socialization. She has published over one hundred fifty refereed articles on these subjects, and has been invited to give keynote speeches at several international conferences. She has also supervised numerous Master's and PhD theses at MIT. She has recently become interested in the effect of drugs and diet on health and nutrition, and she has written several essays on the web articulating her view on these topics. She is the first author of two recently published nutrition-related journal papers, one on the metabolic syndrome and one on Alzheimer's disease. Two papers on theories related to cholesterol sulfate are currently under review. Stephanie will give an all-day workshop on metabolism at Wise Traditions 2011.