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How Statins Really Work Explains Why They Don't Really Work.

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1. Introduction

The statin industry has enjoyed a thirty year run of steadily increasing profits, as they find ever more ways to justify expanding the definition of the segment of the population that qualify for statin therapy. Large, placebo-controlled studies have provided evidence that statins can substantially reduce the incidence of heart attack. High serum cholesterol is indeed correlated with heart disease, and statins, by interfering with the body's ability to synthesize cholesterol, are extremely effective in lowering the numbers. Heart disease is the number one cause of death in the U.S. and, increasingly, worldwide. What's not to like about statin drugs?

I predict that the statin drug run is about to end, and it will be a hard landing. The thalidomide disaster of the 1950's and the hormone replacement therapy fiasco of the 1990's will pale by comparison to the dramatic rise and fall of the statin industry. I can see the tide slowly turning, and I believe it will eventually crescendo into a tidal wave, but misinformation is remarkably persistent, so it may take years.

I have spent much of my time in the last few years combing the research literature on metabolism, diabetes, heart disease, Alzheimer's, and statin drugs. Thus far, in addition to posting essays on the web, I have, together with collaborators, published two journal articles related to metabolism, diabetes, and heart disease (Seneff1 et al., 2011), and Alzheimer's disease (Seneff2 et al., 2011). Two more articles, concerning a crucial role for cholesterol sulfate in metabolism, are currently under review (Seneff3 et al., Seneff4 et al.). I have been driven by the need to understand how a drug that interferes with the synthesis of cholesterol, a nutrient that is essential to human life, could possibly have a positive impact on health. I have finally been rewarded with an explanation for an apparent positive benefit of statins that I can believe, but one that soundly refutes the idea that statins are protective. I will, in fact, make the bold claim that nobody qualifies for statin therapy, and that statin drugs can best be described as toxins.

2. Cholesterol and Statins

I would like to start by reexamining the claim that statins cut heart attack incidence by a third. What exactly does this mean? A meta study reviewing seven drug trials, involving in total 42,848 patients, ranging over a three to five year period, showed a 29% decreased risk of a major cardiac event (Thavendiranathan et al., 2006). But

because heart attacks were rare among this group, what this translates to in absolute terms is that 60 patients would need to be treated for an average of 4.3 years to protect one of them from a single heart attack. However, essentially all of them will experience increased frailty and mental decline, a subject to which I will return in depth later on in this essay.

The impact of the damage due to the statin anti-cholesterol mythology extends far beyond those who actually consume the statin pills. Cholesterol has been demonized by the statin industry, and as a consequence Americans have become conditioned to avoid all foods containing cholesterol. This is a grave mistake, as it places a much bigger burden on the body to synthesize sufficient cholesterol to support the body's needs, and it deprives us of several essential nutrients. I am pained to watch someone crack open an egg and toss out the yolk because it contains "too much" cholesterol. Eggs are a very healthy food, but the yolk contains all the important nutrients. After all, the yolk is what allows the chick embryo to mature into a chicken. Americans are currently experiencing widespread deficiencies in several crucial nutrients that are abundant in foods that contain cholesterol, such as choline, zinc, niacin, vitamin A and vitamin D.

Cholesterol is a remarkable substance, without which all of us would die. There are three distinguishing factors which give animals an advantage over plants: a nervous system, mobility, and cholesterol. Cholesterol, absent from plants, is the key molecule that allows animals to have mobility and a nervous system. Cholesterol has unique chemical properties that are exploited in the lipid bilayers that surround all animal cells: as cholesterol concentrations are increased, membrane fluidity is decreased, up to a certain critical concentration, after which cholesterol starts to *increase* fluidity (Haines, 2001). Animal cells exploit this property to great advantage in orchestrating ion transport, which is essential for both mobility and nerve signal transport. Animal cell membranes are populated with a large number of specialized island regions appropriately called lipid rafts. Cholesterol gathers in high concentrations in lipid rafts, allowing ions to flow freely through these confined regions. Cholesterol serves a crucial role in the non-lipid raft regions as well, by preventing small charged ions, predominantly sodium (Na+) and potassium (K+), from leaking across cell membranes. In the absence of cholesterol, cells would have to expend a great deal more energy pulling these leaked ions back across the membrane against

a concentration gradient.

In addition to this essential role in ion transport, cholesterol is the precursor to vitamin D3, the sex hormones, estrogen, progesterone, and testosterone, and the steroid hormones such as cortisol. Cholesterol is absolutely essential to the cell membranes of all of our cells, where it protects the cell not only from ion leaks but also from oxidation damage to membrane fats. While the brain contains only 2% of the body's weight, it houses 25% of the body's cholesterol. Cholesterol is vital to the brain for nerve signal transport at synapses and through the long axons that communicate from one side of the brain to the other. Cholesterol sulfate plays an important role in the metabolism of fats via bile acids, as well as in immune defenses against invasion by pathogenic organisms.

Statin drugs inhibit the action of an enzyme, HMG coenzyme A reductase, that catalyses an early step in the 25-step process that produces cholesterol. This step is also an early step in the synthesis of a number of other powerful biological substances that are involved in cellular regulation processes and antioxidant effects. One of these is coenzyme Q10, present in the greatest concentration in the heart, which plays an important role in mitochondrial energy production and acts as a potent antioxidant (Gottlieb et al., 2000). Statins also interfere with cell-signaling mechanisms mediated by so-called G-proteins, which orchestrate complex metabolic responses to stressed conditions. Another crucial substance whose synthesis is blocked is dolichol, which plays a crucial role in the endoplasmic reticulum. We can't begin to imagine what diverse effects all of this disruption, due to interference with HMG coenzyme A reductase, might have on the cell's ability to function.

3. LDL, HDL, and Fructose

We have been trained by our physicians to worry about elevated serum levels of low density lipoprotein (LDL), with respect to heart disease. LDL is not a type of cholesterol, but rather can be viewed as a container that transports fats, cholesterol, vitamin D, and fat-soluble anti-oxidants to all the tissues of the body. Because they are not water-soluble, these nutrients must be packaged up and transported inside LDL particles in the blood stream. If you interfere with the production of LDL, you will reduce the bioavailability of all these nutrients to your body's cells.

The outer shell of an LDL particle is made up mainly of lipoproteins and cholesterol. The lipoproteins contain proteins on the outside of the shell and lipids (fats) in the interior layer. If the outer shell is deficient in cholesterol, the fats in the lipoproteins become more vulnerable to attack by oxygen, ever-present in the blood stream. LDL particles also contain a special protein called "apoB" which enables LDL to deliver its goods to cells in need. ApoB is vulnerable to attack by glucose and other blood sugars, especially fructose. Diabetes results in an increased concentration of sugar in the blood, which further compromises the LDL particles, by gumming up apoB. Oxidized and glycated LDL particles become less efficient in delivering their contents to the cells. Thus, they stick around longer in the bloodstream, and the measured serum LDL level goes up.

Worse than that, once LDL particles have finally delivered their contents, they become "small dense LDL particles," remnants that would ordinarily be returned to the liver to be broken down and recycled. But the attached sugars interfere with this process as well, so the task of breaking them down is assumed instead by macrophages in the artery wall and elsewhere in the body, through a unique scavenger operation. The macrophages are especially skilled to extract cholesterol from damaged LDL particles and insert it into HDL particles. Small dense LDL particles become trapped in the artery wall so that the macrophages can salvage and recycle their contents, and this is the basic source of atherosclerosis. HDL particles are the so-called "good cholesterol," and the amount of cholesterol in HDL particles is the lipid metric with the strongest correlation with heart disease, where *less* cholesterol is associated with increased risk. So the macrophages in the plaque are actually performing a very useful role in increasing the amount of HDL cholesterol and reducing the amount of small dense LDL.

The LDL particles are produced by the liver, which synthesizes cholesterol to insert into their shells, as well as into their contents. The liver is also responsible for breaking down fructose and converting it into fat (Collison et al., 2009). Fructose is ten times more active than glucose at glycating proteins, and is therefore very dangerous in the blood serum (Seneff1 et al., 2011). When you eat a lot of fructose (such as the high fructose corn syrup present in lots of processed foods and carbonated beverages), the liver is burdened with getting the fructose out of the blood and converting it to fat, and it therefore can not keep up with cholesterol supply. As I said before, the fats can not be safely transported if there is not

enough cholesterol. The liver has to ship out all that fat produced from the fructose, so it produces low quality LDL particles, containing insufficient protective cholesterol. So you end up with a really bad situation where the LDL particles are especially vulnerable to attack, and attacking sugars are readily available to do their damage.

4. How Statins Destroy Muscles

Europe, especially the U.K., has become much enamored of statins in recent years. The U.K. now has the dubious distinction of being the only country where statins can be purchased over-the-counter, and the amount of statin consumption there has increased more than 120% in recent years (Walley et al, 2005). Increasingly, orthopedic clinics are seeing patients whose problems turn out to be solvable by simply terminating statin therapy, as evidenced by a recent report of three cases within a single year in one clinic, all of whom had normal creatine kinase levels, the usual indicator of muscle damage monitored with statin usage, and all of whom were "cured" by simply stopping statin therapy (Shyam Kumar et al., 2008). In fact, creatine kinase monitoring is not sufficient to assure that statins are not damaging your muscles (Phillips et al., 2002).

Since the liver synthesizes much of the cholesterol supply to the cells, statin therapy greatly impacts the liver, resulting in a sharp reduction in the amount of cholesterol it can synthesize. A direct consequence is that the liver is severely impaired in its ability to convert fructose to fat, because it has no way to safely package up the fat for transport without cholesterol (Vila et al., 2011). Fructose builds up in the blood stream, causing lots of damage to serum proteins.

The skeletal muscle cells are severely affected by statin therapy. Four complications they now face are: (1) their mitochondria are inefficient due to insufficient coenzyme Q10, (2) their cell walls are more vulnerable to oxidation and glycation damage due to increased fructose concentrations in the blood, reduced cholesterol in their membranes, and reduced antioxidant supply, (3) there's a reduced supply of fats as fuel because of the reduction in LDL particles, and (4) crucial ions like sodium and potassium are leaking across their membranes, reducing their charge gradient. Furthermore, glucose entry, mediated by insulin, is constrained to take place at those lipid rafts that are concentrated in cholesterol. Because of the depleted

cholesterol supply, there are fewer lipid rafts, and this interferes with glucose uptake. Glucose and fats are the main sources of energy for muscles, and both are compromised.

As I mentioned earlier, statins interfere with the synthesis of coenzyme Q10 (Langsjoen and Langsjoen, 2003), which is highly concentrated in the heart as well as the skeletal muscles, and, in fact, in all cells that have a high metabolic rate. It plays an essential role in the citric acid cycle in mitochondria, responsible for the supply of much of the cell's energy needs. Carbohydrates and fats are broken down in the presence of oxygen to produce water and carbon dioxide as by-products. The energy currency produced is adenosine triphosphate (ATP), and it becomes severely depleted in the muscle cells as a consequence of the reduced supply of coenzyme Q10.

The muscle cells have a potential way out, using an alternative fuel source, which doesn't involve the mitochondria, doesn't require oxygen, and doesn't require insulin. What it requires is an abundance of fructose in the blood, and fortunately (or unfortunately, depending on your point of view) the liver's statin-induced impairment results in an abundance of serum fructose. Through an anaerobic process taking place in the cytoplasm, specialized muscle fibers skim off just a bit of the energy available from fructose, and produce lactate as a product, releasing it back into the blood stream. They have to process a huge amount of fructose to produce enough energy for their own use. Indeed, statin therapy has been shown to increase the production of lactate by skeletal muscles (Pinieux et al, 1996).

Converting one fructose molecule to lactate yields only two ATP's, whereas processing a sugar molecule all the way to carbon dioxide and water in the mitochondria yields 38 ATP's. In other words, you need 19 times as much substrate to obtain an equivalent amount of energy. The lactate that builds up in the blood stream is a boon to both the heart and the liver, because they can use it as a substitute fuel source, a much safer option than glucose or fructose. Lactate is actually an extremely healthy fuel, water-soluble like a sugar but not a glycating agent.

So the burden of processing excess fructose is shifted from the liver to the muscle cells, and the heart is supplied with plenty of lactate, a high-quality fuel that does not lead to destructive glycation damage. LDL levels fall, because the liver can't keep up with fructose removal,

but the supply of lactate, a fuel that can travel freely in the blood (does not have to be packaged up inside LDL particles) saves the day for the heart, which would otherwise feast off of the fats provided by the LDL particles. I think this is the crucial effect of statin therapy that leads to a reduction in heart attack risk: the heart is well supplied with a healthy alternative fuel.

This is all well and good, except that the muscle cells get wrecked in the process. Their cell walls are depleted in cholesterol because cholesterol is in such short supply, and their delicate fats are therefore vulnerable to oxidation damage. This problem is further compounded by the reduction in coenzyme Q10, a potent antioxidant. The muscle cells are energy starved, due to dysfunctional mitochondria, and they try to compensate by processing an excessive amount of both fructose and glucose anaerobically, which causes extensive glycation damage to their crucial proteins. Their membranes are leaking ions, which interferes with their ability to contract, hindering movement. They are essentially heroic sacrificial lambs, willing to die in order to safeguard the heart.

Muscle pain and weakness are widely acknowledged, even by the statin industry, as potential side effects of statin drugs. Together with a couple of MIT students, I have been conducting a study which shows just how devastating statins can be to muscles and the nerves that supply them (Liu et al, 2011). We gathered over 8400 on-line drug reviews prepared by patients on statin therapy, and compared them to an equivalent number of reviews for a broad spectrum of other drugs. The reviews for comparison were selected such that the age distribution of the reviewers was matched against that for the statin reviews. We used a measure which computes how likely it would be for the words/phrases that show up in the two sets of reviews to be distributed in the way they are observed to be distributed, if both sets came from the same probability model. For example, if a given side effect showed up a hundred times in one data set and only once in the other, this would be compelling evidence that this side effect was representative of that data set. ***Table 1 shows several conditions associated with muscle problems that were highly skewed towards the statin reviews.***

Side Effect	# Statin Reviews	# Non-Statin Reviews	Associated P-value
Muscle Cramps	678	193	0.00005
General Weakness	687	210	0.00006
Muscle Weakness	302	45	0.00023
Difficulty Walking	419	128	0.00044
Loss of Muscle Mass	54	5	0.01323
Numbness	293	166	0.01552
Muscle Spasms	136	57	0.01849

Table 1: Counts of the number of reviews where phrases associated with various symptoms related to muscles appeared, for 8400 statin and 8400 non-statin drug reviews, along with the associated p-value, indicating the likelihood that this distribution could have occurred by chance.

I believe that the real reason why statins protect the heart from a heart attack is that muscle cells are willing to make an incredible sacrifice for the sake of the larger good. It is well acknowledged that exercise is good for the heart, although people with a heart condition have to watch out for overdoing it, walking a careful line between working out the muscles and overtaxing their weakened heart. I believe, in fact, that the reason exercise is good is exactly the same as the reason statins are good: it supplies the heart with lactate, a very healthy fuel that does not glycate cell proteins.

5. Membrane Cholesterol Depletion and Ion Transport

As I alluded to earlier, statin drugs interfere with the ability of muscles to contract through the depletion of membrane cholesterol. (Haines, 2001) has argued that the most important role of cholesterol in cell membranes is the inhibition of leaks of small ions, most notably sodium (Na+) and potassium (K+). These two ions are essential for movements, and indeed, cholesterol, which is absent in plants, is the key molecule that permits mobility in animals, through its strong control over ion leakage of these molecules across cell walls. By protecting the cell from ion leaks, cholesterol greatly reduces the amount of energy the cell needs to invest in keeping the

ions on the right side of the membrane.

There is a widespread misconception that "lactic acidosis," a condition that can arise when muscles are worked to exhaustion, is *due to* lactic acid synthesis. The actual story is the exact opposite: the acid build-up is due to excess breakdown of ATP to ADP to produce energy to support muscle contraction. When the mitochondria can't keep up with energy consumption by renewing the ATP, the production of lactate becomes absolutely necessary to *prevent* acidosis (Robergs et al., 2004). In the case of statin therapy, excessive leaks due to insufficient membrane cholesterol require *more* energy to correct, and all the while the mitochondria are producing *less* energy.

In in vitro studies of phospholipid membranes, it has been shown that the removal of cholesterol from the membrane leads to a nineteen fold increase in the rate of potassium leaks through the membrane (Haines, 2001). Sodium is affected to a lesser degree, but still by a factor of three. Through ATP-gated potassium and sodium channels, cells maintain a strong disequilibrium across their cell wall for these two ions, with sodium being kept out and potassium being held inside. This ion gradient is what energizes muscle movement. When the membrane is depleted in cholesterol, the cell has to burn up substantially more ATP to fight against the steady leakage of both ions. With cholesterol depletion due to statins, this is energy it doesn't have, because the mitochondria are impaired in energy generation due to coenzyme-Q10 depletion.

Muscle contraction itself causes potassium loss, which further compounds the leak problem introduced by the statins, and the potassium loss due to contraction contributes significantly to muscle fatigue. Of course, muscles with insufficient cholesterol in their membranes lose potassium even faster. Statins make the muscles much more vulnerable to acidosis, both because their mitochondria are dysfunctional and because of an increase in ion leaks across their membranes. This is likely why athletes are more susceptible to muscle damage from statins (Meador and Huey, 2010, Sinzinger and O'Grady, 2004): their muscles are doubly challenged by both the statin drug and the exercise.

An experiment with rat soleus muscles in vitro showed that lactate added to the medium was able to almost fully recover the force lost due to potassium loss (Nielsen et al, 2001). Thus, production and release of lactate becomes essential when potassium is lost to the

medium. The loss of strength in muscles supporting joints can lead to sudden uncoordinated movements, overstressing the joints and causing arthritis (Brandt et al., 2009). *In fact, our studies on statin side effects revealed a very strong correlation with arthritis, as shown in the table.*

While I am unaware of a study involving *muscle* cell ion leaks and statins, a study on *red blood cells* and *platelets* has shown that there is a substantial increase in the Na+-K+-pump activity after just a month on a modest 10 mg/dl statin dosage, with a concurrent decrease in the amount of cholesterol in the membranes of these cells (Lohn et al., 2000). This increased pump activity (necessitated by membrane leaks) would require additional ATP and thus consume extra energy.

Muscle fibers are characterized along a spectrum by the degree to which they utilize aerobic vs anaerobic metabolism. The muscle fibers that are most strongly damaged by statins are the ones that specialize in anaerobic metabolism (Westwood et al., 2005). These fibers (Type IIb) have very few mitochondria, as contrasted with the abundant supply of mitochondria in the fully aerobic Type 1A fibers. I suspect their vulnerability is due to the fact that they carry a much larger burden of generating ATP to fuel the muscle contraction and to produce an abundance of lactate, a product of anaerobic metabolism. They are tasked with both energizing not only themselves but also the defective aerobic fibers (due to mitochondrial dysfunction) and producing enough lactate to offset the acidosis developing as a consequence of widespread ATP shortages.

6. Long-term Statin Therapy Leads to Damage Everywhere

Statins, then, slowly erode the muscle cells over time. After several years have passed, the muscles reach a point where they can no longer keep up with essentially running a marathon day in and day out. The muscles start literally falling apart, and the debris ends up in the kidney, where it can lead to the rare disorder, rhabdomyolysis, which is often fatal. *In fact, 31 of our statin reviews contained references to "rhabdomyolysis" as opposed to none in the comparison set. Kidney failure, a frequent consequence of rhabdomyolysis, showed up 26 times among the statin reviews, as opposed to only four times in the control set.*

The dying muscles ultimately expose the nerves that innervate them to toxic substances, which then leads to nerve damage such as neuropathy, and, ultimately Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, a very rare, debilitating, and ultimately fatal disease which is now on the rise due (I believe) to statin drugs. People diagnosed with ALS rarely live beyond five years. ***Seventy-seven of our statin reviews contained references to ALS, as against only 7 in the comparison set.***

As ion leaks become untenable, cells will begin to replace the potassium/sodium system with a calcium/magnesium based system. These two ions are in the same rows of the periodic table as sodium/potassium, but advanced by one column, which means that they are substantially larger, and therefore it's much harder for them to accidentally leak out. But this results in extensive calcification of artery walls, heart valves, and the heart muscle itself. Calcified heart valves can no longer function properly to prevent backflow, and diastolic heart failure results from increased left ventricular stiffness. Research has shown that statin therapy leads to increased risk to diastolic heart failure (Silver et al., 2004, Weant and Smith, 2005). ***Heart failure shows up 36 times in our statin drug data as against only 8 times in the comparison group.***

Once the muscles can no longer keep up with lactate supply, the liver and heart will be further imperilled. They're now worse off than they were before statins, because the lactate is no longer available, and the LDL, which would have provided fats as a fuel source, is greatly reduced. So they're stuck processing sugar as fuel, something that is now much more perilous than it used to be, because they are depleted in membrane cholesterol. Glucose entry into muscle cells, including the heart muscle, mediated by insulin, is orchestrated to occur at lipid rafts, where cholesterol is highly concentrated. Less membrane cholesterol results in fewer lipid rafts, and this leads to impaired glucose uptake. Indeed, it has been proposed that statins increase the risk to diabetes (Goldstein and Mascitelli, 2010, Hagedorn and Arora, 2010). ***Our data bear out this notion, with the probability of the observed distributions of diabetes references happening by chance being only 0.006.***

Side Effect	# Statin Reviews	# Non-Statin Reviews	Associated P-value
Rhabdomyolysis	31	0	0.02177
Liver Damage	326	133	0.00285
Diabetes	185	62	0.00565
ALS	71	7	0.00819
Heart Failure	36	8	0.04473
Kidney Failure	26	4	0.05145
Arthritis	245	120	0.01117
Memory Problems	545	353	0.01118
Parkinson's Disease	53	3	0.01135
Neuropathy	133	73	0.04333
Dementia	41	13	0.05598

Table 2: Counts of the number of reviews where phrases associated with various symptoms related to major health issues appeared, besides muscle problems, for 8400 statin and 8400 non-statin drug reviews, along with the associated p-value, indicating the likelihood that this distribution could have occurred by chance.

7. Statins, Caveolin, and Muscular Dystrophy

Lipid rafts are crucial centers for transport of substances (both nutrients and ions) across cell membranes and as a cell signaling domain in essentially all mammalian cells. Caveolae ("little caves") are microdomains within lipid rafts, which are enriched in a substance called caveolin (Gratton et al., 2004). Caveolin has received increasing attention of late due to the widespread role it plays in cell signaling mechanisms and the transport of materials between the cell and the environment (Smart et al., 1999).

Statins are known to interfere with caveolin production, both in endothelial cells (Feron et al., 2001) and in heart muscle cells, where they've been shown to reduce the density of caveolae by 30% (Calaghan, 2010). People who have a defective form of caveolin-3, the version of caveolin that is present in heart and skeletal muscle cells, develop muscular dystrophy as a consequence (Minetti et al., 1998). Mice engineered to have defective caveolin-3 that stayed in the cytoplasm instead of binding to the cell wall at lipid rafts

exhibited stunted growth and paralysis of their legs (Sunada et al., 2001). Caveolin is crucial to cardiac ion channel function, which, in turn, is essential in regulating the heart beat and protecting the heart from arrhythmias and cardiac arrest (Maguy et al, 2006). In arterial smooth muscle cells, caveolin is essential to the generation of calcium sparks and waves, which, in turn, are essential for arterial contraction and expansion, to pump blood through the body (Taggart et al, 2010).

In experiments involving constricting the arterial blood supply to rats' hearts, researchers demonstrated a 34% increase in the amount of caveolin-3 produced by the rat's hearts, along with a 27% increase in the weight of the left ventricle, indicating ventricular hypertrophy. What this implies is that the heart needs additional caveolin to cope with blocked vessels, whereas statins interfere with the ability to produce extra caveolin (Kikuchi et al., 2005).

8. Statins and the Brain

While the brain is not the focus of this essay, I cannot resist mentioning the importance of cholesterol to the brain and the evidence of mental impairment available from our data sets. Statins would be expected to have a negative impact on the brain, because, while the brain makes up only 2% of the body's weight, it houses 25% of the body's cholesterol. Cholesterol is highly concentrated in the myelin sheath, which encloses axons which transport messages long distances (Saher et al., 2005). Cholesterol also plays a crucial role in the transmission of neurotransmitters across the synapse (Tong et al, 2009). *We found highly skewed distribution of word frequencies for dementia, Parkinson's disease, and short term memory loss, with all of these occurring much more frequently in the statin reviews than in the comparison reviews.*

A recent evidence-based article (Cable, 2009) found that statin drug users had a high incidence of neurological disorders, especially neuropathy, parasthesia and neuralgia, and appeared to be at higher risk to the debilitating neurological diseases, ALS and Parkinson's disease. The evidence was based on careful manual labeling of a set of self-reported accounts from 351 patients. A mechanism for such damage could involve interference with the ability of oligodendrocytes, specialized glial cells in the nervous system, to supply sufficient cholesterol to the myelin sheath surrounding nerve axons. Genetically-engineered mice with defective oligodendrocytes

exhibit visible pathologies in the myelin sheath which manifest as muscle twitches and tremors (Saher et al, 2005). Cognitive impairment, memory loss, mental confusion, and depression were also significantly present in Cableâ€™s patient population. Thus, his analysis of 351 adverse drug reports was largely consistent with our analysis of 8400 reports.

9. Cholesterol's Benefits to Longevity

The broad spectrum of severe disabilities with increased prevalence in statin side effect reviews all point toward a general trend of increased frailty and mental decline with long-term statin therapy, things that are usually associated with old age. I would in fact best characterize statin therapy as a mechanism to allow you to *grow old faster*. A highly enlightening study involved a population of elderly people who were monitored over a 17 year period, beginning in 1990 (Tilvis et al., 2011). The investigators looked at an association between three different measures of cholesterol and manifestations of decline. They measured indicators associated with physical frailty and mental decline, and also looked at overall longevity. In addition to serum cholesterol, a biometric associated with the ability to synthesize cholesterol (lathosterol) and a biometric associated with the ability to absorb cholesterol through the gut (sitosterol) were measured.

Low values of all three measures of cholesterol were associated with a *poorer* prognosis for frailty, mental decline and early death. A reduced ability to *synthesize* cholesterol showed the strongest correlation with poor outcome. Individuals with high measures of all three biometrics enjoyed a 4.3 year extension in life span, compared to those for whom all measures were low. Since statins specifically interfere with the ability to synthesize cholesterol, it is logical that they would also lead to increased frailty, accelerated mental decline, and early death.

For both ALS and heart failure, survival benefit is associated with elevated cholesterol levels. A statistically significant inverse correlation was found in a study on mortality in heart failure. For 181 patients with heart disease and heart failure, half of those whose serum cholesterol was below 200 mg/dl were dead three years after diagnosis, whereas only 28% of the patients whose serum cholesterol was above 200 mg/dl had died. In another study on a group of 488 patients diagnosed with ALS, serum levels of

triglycerides and fasting cholesterol were measured at the time of diagnosis (Dorstand et al., 2010). High values for both lipids were associated with improved survival, with a p-value < 0.05.

10. What to do Instead to Avoid Heart Disease

If statins don't work in the long run, then what can you do to protect your heart from atherosclerosis? My personal opinion is that you need to focus on natural ways to reduce the number of small dense LDL particles, which feed the plaque, and alternative ways to supply the product that the plaque produces (more about that in a moment). Obviously, you need to cut way back on fructose intake, and this means mainly eating whole foods instead of processed foods. With less fructose, the liver won't have to produce as many LDL particles from the supply side. From the demand side, you can reduce your body's dependency on both glucose and fat as fuel by simply eating foods that are good sources of lactate. Sour cream and yogurt contain lots of lactate, and milk products in general contain the precursor lactose, which gut bacteria will convert to lactate, assuming you don't have lactose intolerance. Strenuous physical exercise, such as a tread machine workout, will help to get rid of any excess fructose and glucose in the blood, with the skeletal muscles converting them to the much coveted lactate.

Finally, I have a set of perhaps surprising recommendations that are based on research I have done leading to the two papers that are currently under review (Seneff3 et al, Seneff4 et al.). My research has uncovered compelling evidence that the nutrient that is most crucially needed to protect the heart from atherosclerosis is cholesterol sulfate. The extensive literature review my colleagues and I have conducted to produce these two papers shows compellingly that the fatty deposits that build-up in the artery walls leading to the heart exist mainly for the purpose of extracting cholesterol from glycated small dense LDL particles and synthesizing cholesterol sulfate from it, providing the cholesterol sulfate directly to the heart muscle. The reason the plaque build-up occurs preferentially in the arteries leading to the heart is so that the heart muscle can be assured an adequate supply of cholesterol sulfate. In our papers, we develop the argument that the cholesterol sulfate plays an essential role in the caveolae in the lipid rafts, in mediating oxygen and glucose transport.

The skin produces cholesterol sulfate in large quantities when it is

exposed to sunlight. Our theory suggests that the skin actually *synthesizes* sulfate from sulfide, capturing energy from sunlight in the form of the sulfate molecule, thus acting as a solar-powered battery. The sulfate is then shipped to all the cells of the body, carried on the back of the cholesterol molecule.

Evidence of the benefits of sun exposure to the heart is compelling, as evidenced by a study conducted to investigate the relationship between geography and cardiovascular disease (Grimes et al., 1996). Through population statistics, the study showed a consistent and striking inverse linear relationship between cardiovascular deaths and estimated sunlight exposure, taking into account percentage of sunny days as well as latitude and altitude effects. For instance, the cardiovascular-related death rate for men between the ages of 55 and 64 was 761 in Belfast, Ireland but only 175 in Toulouse, France.

Cholesterol sulfate is very versatile. It is water soluble so it can travel freely in the blood stream, and it enters cell membranes ten times as readily as cholesterol, so it can easily resupply cholesterol to cells. The skeletal and heart muscle cells make good use of the sulfate as well, converting it back to sulfide, and synthesizing ATP in the process, thus recovering the energy from sunlight. This decreases the burden on the mitochondria to produce energy. The oxygen released from the sulfate molecule is a safe source of oxygen for the citric oxide cycle in the mitochondria.

So, in my view, the best way to avoid heart disease is to assure an abundance of an alternative supply of cholesterol sulfate. First of all, this means eating foods that are rich in both cholesterol and sulfur. Eggs are an optimal food, as they are well supplied with both of these nutrients. But secondly, this means making sure you get plenty of sun exposure to the skin. This idea flies in the face of the advice from medical experts in the United States to avoid the sun for fear of skin cancer. I believe that the excessive use of sunscreen has contributed significantly, along with excess fructose consumption, to the current epidemic in heart disease. And the natural tan that develops upon sun exposure offers far better protection from skin cancer than the chemicals in sunscreens.

11. Concluding Remarks

Every individual gets at most only one chance to grow old. When you

experience your body falling apart, it is easy to imagine that this is just due to the fact that you are advancing in age. I think the best way to characterize statin therapy is that it makes you grow older faster. Mobility is a great miracle that cholesterol has enabled in all animals. By suppressing cholesterol synthesis, statin drugs can destroy that mobility. No study has shown that statins improve all-cause mortality statistics. But there can be no doubt that statins will make your remaining days on earth a lot less pleasant than they would otherwise be.

To optimize the quality of your life, increase your life expectancy, and avoid heart disease, my advice is simple: spend significant time outdoors; eat healthy, cholesterol-enriched, animal-based foods like eggs, liver, and oysters; eat fermented foods like yogurt and sour cream; eat foods rich in sulfur like onions and garlic. And finally, say "no, thank-you" to your doctor when he recommends statin therapy.

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