

# Cholesterol: Myths and Truths

By Chris Masterjohn

## Debunking the Myths About Cholesterol

The idea that cholesterol is the cause of heart disease has been repeated so many times over the last half century that most people assume it to be true without a second thought.

We are told to avoid eating nutritious, cholesterol-rich foods like butter, liver and egg yolks in order to avoid the ravages of a high blood cholesterol level, even though these foods do not raise blood cholesterol levels in most people, and when they do, they primarily raise "good" cholesterol.

Now that statins, the cholesterol-lowering drugs, have begun to bring in a bonanza of profits for pharmaceutical companies, any new disease that can be pinned on cholesterol represents a chance to broaden the scope of profits ever more wide.

The result? Alzheimer's disease is now blamed on cholesterol and statins are now hailed by some as the solution. Stroke is likewise blamed on cholesterol and the solution is the same. Does the scientific evidence back it up? Or is it just another "cholesterol myth?"

## Myths and Realities

The truth is that there is some kernel of truth in every myth.

Virtually no one in the research community believes anymore in the simplistic form of the cholesterol hypothesis of heart disease that this hypothesis took when it ascended to its present position of dominance over the course of the 1960s through the 1980s.

At one time, the cholesterol hypothesis went something like this: arteries are like pipes; cholesterol is like gunk. The more gunk there is, the more the pipes get clogged up. When they get so clogged up that blood can't flow through them, a heart attack ensues.

Now, the cholesterol hypothesis goes something like this: arteries are complex biological systems and heart disease is a disorder of inflammation and oxidative stress; when cholesterol levels get out of control, the cholesterol causes inflammation and oxidative stress. It decreases the functioning of the artery's best friend -- nitric oxide -- and "activates" white blood cells that start the inflammatory process. Because the body cannot protect high levels of cholesterol from oxidative stress, the cholesterol gets oxidized and accumulates in the blood vessel wall. When the white blood cells get loaded up with oxidized cholesterol, they make more pro-inflammatory chemicals that eventually lead to the destabilization of the plaque. The plaque ruptures, a clot forms, and a heart attack ensues.

So the question is: is this second hypothesis really the same hypothesis as the first?

It might seem like it the way I have written it, but I have focused every sentence on cholesterol. What happens when we consider that each stage of the process has nothing uniquely to do with cholesterol?

Free radicals and inflammation of any kind hurt nitric oxide functioning. Bacteria and immune cells specific to them -- many of them oral pathogens found primarily in gum disease -- inhabit arterial plaque, and are sure to play a role in initiating inflammation. Oxidized lipoproteins are indeed harmful -- but it is not the cholesterol, hidden deep within the core of the particle, that is the problem! It is primarily the phospholipids and the proteins on the surface of the lipoprotein that oxidize. And it is polyunsaturated fatty acids within those phospholipids that are vulnerable. Vitamins, minerals, phytochemicals, and antioxidants of both the plant and animal kingdoms protect against oxidation and suppress inflammation, stabilize plaque and regulate clotting.

Is cholesterol involved in heart disease? Yes. But does its place in our understanding of heart disease today resemble the centrality of its place in the old hypothesis? No.

Yet in the mass media version of science, the old myth remains triumphant. It is simple, believable, and good for selling drugs.

But when regular folks like us want to figure out what a healthy diet is, the cholesterol hypothesis in its simplistic and mythical form obscures the issue. Is the egg yolk a health food because it is nutritious? Or a danger because it is high in

cholesterol? What about liver and organ meats? Is virgin coconut oil a health food because it is rich in antioxidant polyphenols and low in polyunsaturated fats that are vulnerable to oxidation? Or is it a danger because it is high in saturated fat, which raises cholesterol levels?

In order to understand the truth about these questions, we have to debunk the myths.

This section of Cholesterol-And-Health.com is dedicated to exposing commonly perpetrated myths about cholesterol, and is fully documented with research from peer-reviewed journals.

## Myth: Cholesterol Causes Stroke

*September 20, 2007*

by Chris Masterjohn

Stroke is the third leading cause of death in the United States<sup>1</sup> and the single greatest cause of disability in most developed countries.<sup>2</sup> The American Heart Association states that high cholesterol levels contribute to stroke and lists this disease as the second most important reason for avoiding cholesterol-rich foods such as butter, egg yolks and organ meats.

Does cholesterol really cause stroke -- is this a myth or a reality?

### Different Strokes

Through the early 1990s neither epidemiological studies<sup>4</sup> nor controlled trials of cholesterol-lowering drugs were able to generate any evidence for an association between cholesterol levels and the risk of stroke.

In fact, a 1995 report in which researchers pooled together the results of 45 prospective cohort studies involving over 450,000 people found that the risk of stroke slightly declined with increasing cholesterol levels -- though the effect was so small that it could easily have been due to chance.

It would soon become evident, however, that the failure to find any association between cholesterol and stroke resulted from the failure to differentiate between the two major categories of stroke: hemorrhagic and ischemic. Hemorrhagic stroke occurs when a blood vessel ruptures, whereas ischemic stroke occurs when a blockage closes off the flow of blood within the vessel.

Studies that have differentiated between these two forms have shown that cholesterol is associated with a decreased risk of hemorrhagic stroke -- less common but more deadly -- and an increased risk of ischemic stroke.

### Finding the Correlations

The Honolulu Heart Study enrolled 8,000 Japanese American men between 1965 and 1968, measured their cholesterol levels, and followed them for fifteen years. In 1980, the researchers running the study published a six-year follow-up report in which serum cholesterol had no association with ischemic stroke; as cholesterol levels increased, however, the risk of hemorrhagic stroke declined. In 1994, the fifteen-year follow-up report showed that high cholesterol (over 213 milligrams per deciliter or mg/dL) was indeed associated with an increased risk of ischemic stroke. Those with cholesterol levels under 213 had a 2.5 chance of ischemic stroke over 10 years while those with cholesterol levels over 240 had a 3.2 chance of ischemic stroke over the same length of time.

The Multiple Risk Factor Intervention Trial (MR FIT) confirmed these findings in over 350,000 men. Those with cholesterol levels under 160 had three times the risk of hemorrhagic stroke as those with higher levels, while those with levels over 200 had a higher risk of ischemic stroke than those with lower levels. Between 200 and 240, the risk increased only 20 percent, but levels over 280 were associated with 2.5-fold increase in risk.

The Eastern Stroke and Coronary Heart Disease Collaborative Research Group confirmed the findings in eastern Asian countries as well. The group pooled the results of 18 prospective studies conducted in China and Japan involving nearly 125,000 people. For every 23-point drop in serum cholesterol, the risk of ischemic stroke decreased by 23 percent and the risk of hemorrhagic stroke increased by 27 percent.

## Shifting the Balance: Ischemic vs. Hemorrhagic Stroke

Thus, it began to become clear that as cholesterol levels go up, the risk of ischemic stroke goes up and the risk of hemorrhagic stroke goes down. Some authors have suggested that because over 90 percent of strokes in the US are ischemic, our best bet to avoid stroke is to eat a low-fat, low-cholesterol diet so we can reduce our risk of the most common form.

The data indicate, however, that our ratio of ischemic to hemorrhagic strokes is so high only because our cholesterol levels are so high. In Japanese American men living Hawaii, whose cholesterol levels are between those of Japanese living in Japan and mainland Americans, hemorrhagic stroke constitutes 25 percent of all strokes. In China and Japan, where serum cholesterol levels correspond to the bottom two thirds of the range of western levels, hemorrhagic stroke constitutes 42 percent of all strokes.

Victims of hemorrhagic stroke suffer greater neurological deficits, are more likely to be institutionalized, and are four times more likely to die within thirty days than victims of ischemic strokes. A recent comparison of the two types showed that only 7 percent of ischemic stroke victims died within this period of time, whereas fully 28 percent of hemorrhagic stroke victims died.

So a cholesterol-lowering diet should merely shift our risk from a less deadly to a more deadly form of stroke. Yet there is an even larger flaw in the reasoning. Conventional wisdom would have us believe that if high cholesterol is associated with ischemic stroke, so is a diet high in animal fat. But the conventional wisdom is wrong.

## Eat Your Cholesterol: Animal Fat Intake Associated With a Decreased Risk of Ischemic Stroke

In the Honolulu Heart Study, the risk of ischemic stroke *decreased* as the intake of total and saturated fat went up.<sup>12</sup> Among stroke fatality victims who also had heart disease, there was no relationship between any dietary factors and the amount of atherosclerosis in the blood vessels supplying the brain. Among the others, atherosclerosis of the large arteries was associated with a decreased intake of animal protein and total fat and an increased intake of carbohydrate; atherosclerosis of the small arteries was associated with a decreased intake of fish.

The Framingham Heart Study followed 800 men over the course of 19 years and found a decreased risk of ischemic stroke associated with an increased intake of total, monounsaturated and saturated fat.

Studies since this time have occasionally shown no relationship between the intake of animal fat and the risk of ischemic stroke, but most have continued to show a decreased risk of this disease associated with an increased intake of animal fat and fish.

## Does High Cholesterol *Cause* Ischemic Stroke?

It is a fundamental principle of science that correlation does not prove causation. Thus, the correlation of high cholesterol with the risk of ischemic stroke does not prove that the high level of cholesterol causes the increased risk. If, however, interventions that specifically increase or decrease cholesterol levels without affecting other variables are able to increase or decrease the risk of ischemic stroke, this would represent powerful evidence for causation. Is this the case?

## Cholesterol-Lowering Drugs and the Risk of Stroke

Early trials with cholesterol-lowering drugs were less than promising. A 1993 report pooled together the results of 13 trials conducted between 1966 and 1992 involving over 45,000 men. Cholesterol lowering had no association with the risk of stroke. It tended to decrease the risk of fatal stroke and increase the risk of nonfatal stroke, but the magnitudes of these differences were only strong enough to be distinguished from the effects of chance in trials using the drug clofibrate. Treatment with this drug more than doubled the risk of fatal stroke. The only trial that distinguished between the risk of ischemic and hemorrhagic stroke used a similar drug called gemfibrozil; treatment with this drug increased the risk of fatal hemorrhagic stroke by a factor of five.

The results of later trials with statins were more impressive. A 2004 report that pooled together the results of 120 lipid-lowering trials, including 24 using statins, showed that treatment with statins lowered the risk of stroke by 18 percent, due almost entirely to a decrease in ischemic stroke. The reduction in LDL correlates to the reduction in atherosclerosis of the carotid artery -- a main artery supplying the brain -- and to the reduction in the risk of stroke.

## Statins, Rho, and Nitric Oxide

Although some would argue that the old cholesterol-lowering drugs were less effective than statins simply because they were less effective at reducing cholesterol, the fact is that statins do a lot more than lower cholesterol, and their efficacy against ischemic stroke cannot by any means be construed as evidence that high cholesterol causes ischemic stroke -- even when this efficacy correlates with the degree of total or LDL cholesterol reduction.

Statins decrease the activation of Rho through the same mechanism through which they decrease cholesterol levels. Their ability to decrease the activation of Rho correlates with their ability to decrease cholesterol levels. As explained in the this article, Rho activation suppresses the levels of nitric oxide made by the blood vessel wall, which increases the risk of atherosclerosis.

By inhibiting the activation of Rho, statins greatly increase the amount of nitric oxide made by the blood vessel lining. This results in a great reduction in the magnitude of stroke and its residual neurological effects in laboratory animals. There is also further evidence that statins protect against stroke by increasing the body's ability to dissolve blood clots independently of both nitric oxide and cholesterol.

## Is Cholesterol Irrelevant?

It would be a mistake to assume that, because statins clearly have protective effects against stroke that do not involve cholesterol, cholesterol itself must be entirely irrelevant. Most likely, the level of LDL is a loose indicator of the level of *oxidized* LDL.

When the phospholipids and proteins at the surface of an LDL particle oxidize, that LDL particle can accumulate in atherosclerotic plaque and depress the production of nitric oxide. Likewise, a high level of sugar in the blood can damage this LDL by a process called "glycation," which also makes it accumulate in atherosclerotic plaque and depress the production of nitric oxide.

Selective filtering of LDL from the blood of patients with very high cholesterol -- most of which is oxidized -- appears to improve nitric oxide production and blood flow. Unfortunately, researchers have only tested the effect of this treatment on these parameters in small, uncontrolled trials.

It appears -- though this can't be proven beyond a shadow of a doubt -- very likely that oxidized and glycated LDL contributes to the disease process that lies behind ischemic stroke. How important these factors are compared to the myriad others that affect the process of inflammation and oxidative damage, however, we cannot quantify.

Whether and how low cholesterol causes the increased risk of hemorrhagic stroke with which it is associated is still an open question. Animal experiments have shown that diets high in animal fat and cholesterol reduce the incidence of stroke in rats with high blood pressure. In humans, the association of low cholesterol with hemorrhagic stroke primarily exists among those with diastolic blood pressure above 90 millimeters mercury (mm Hg). It is possible, then, that cholesterol protects against hemorrhage by strengthening and stabilizing the blood vessel walls, especially when they need extra strength to withstand the constant onslaught of high blood pressure.

## What's for Dinner?

If we look at the science objectively, it appears that both high and low cholesterol levels will increase the risk of stroke. In the MR FIT trial, stroke mortality was lowest between 180 and 200, increased somewhat below 180 and above 240, and was the highest below 160 and above 300. So it makes sense to use exercise, and proper control of chronic infections (which increase both cholesterol levels and Rho activation) to maintain moderate cholesterol levels. In all likelihood, however, the association between high cholesterol and ischemic stroke is, if causal, due primarily not to LDL itself but to oxidized and glycated LDL -- so maintaining good antioxidant status should take the lead role.

As discussed above, ischemic stroke and atherosclerosis of the blood vessels that lead to the brain appear to be associated with a low intake of animal protein and fat, a low intake of fish, and a high intake of carbohydrate. In the Diet and Reinfarction Trial (DART), subjects who reduced their total fat intake from 35 percent of calories to 32 percent of calories and doubled their polyunsaturated-to-saturated fat ratio from 0.4 to 0.8 *doubled* their risk of dying of stroke.

The research tells us that, with respect to stroke, animal foods are our friends, and refined carbohydrates and vegetable oils are our enemies.

Is cholesterol involved in stroke? Yes. Does it *cause* stroke? Low and high cholesterol may both play contributory roles, but do not have the final word. Should we avoid eggs, butter and organ meats in order to lower our risk of stroke? Absolutely not -- that is the myth that has no grounding in scientific reality.

# Myth: Eating Cholesterol-Rich Foods Raises Blood Cholesterol Levels

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by Chris Masterjohn

The myth goes something like this: arteries are like pipes; cholesterol is gooey, sticky gunk. When you eat cholesterol, it winds up in your blood. If the cholesterol level in your blood gets too high, it starts caking up the pipes. Thus, if you don't want your pipes clogged, don't eat foods rich in cholesterol.

Such is the basic logic behind advice to avoid eating nutrient-dense foods like liver and [egg yolks](#).

## Eating Cholesterol Does Not Raise Blood Cholesterol Levels

The truth is, however, that there is no direct connection between the amount of cholesterol you eat and the concentration of cholesterol in your blood. In most people, eating cholesterol has little or no effect on this amount. In about 30 percent of the population, eating cholesterol does in fact increase the concentration of cholesterol in the blood -- but it increases the "good" cholesterol.

To put it in more scientific terms, eating cholesterol "results in a less atherogenic lipoprotein profile."

## Egg-Feeding Intervention Trials

In a recent review,<sup>1</sup> cholesterol researcher Dr. Maria Luz Fernandez of the University of Connecticut's Department of Nutritional Sciences summarized the results of a number of studies testing the effects of egg consumption on blood cholesterol levels. In children aged 10-12, in men aged 20-50, in premenopausal and postmenopausal women, in whites and hispanics, the same basic finding persists: two or three eggs per day has little or no effect on the blood cholesterol levels of over two thirds of the population.

Less than a third of the population, by contrast, are termed "hyperresponders." When these people eat egg yolks, their cholesterol levels do go up. LDL, the so-called "bad cholesterol," and HDL, the so-called "good cholesterol" both go up equally, so there is no change in the ratio of LDL to HDL, or of LDL to total cholesterol, both of which are considered better measures of the risk of heart disease than the total concentration of cholesterol.

## LDL Particle Size

Moreover, the actual number of LDL particles do not change at all; they just get bigger. When your doctor measures your blood cholesterol level, the lab reports it by weight. In America, this is usually in milligrams per deciliter. When your "cholesterol level" is high, this means that in a given measure of blood volume (such as a deciliter or a tenth of a liter) the total number of cholesterol-carrying lipoprotein particles *weigh more*. This could mean that you have more particles, or it could mean that the particles weigh more because they are carrying more cholesterol.

According to research that Dr. Fernandez cites in her review, it is the small, dense LDL particles that raise the risk of atherosclerosis, while the large, buoyant LDL particles are safe. This may be because small, dense LDL particles are much more vulnerable to oxidation. People whose LDL is primarily small and dense have three times the risk of heart disease as people whose LDL is primarily large and buoyant.

In the egg-feeding studies, egg consumption makes the LDL particles of the "hyperresponders" get bigger, not more numerous. When they get bigger, they become less subject to oxidation and accumulation in atherosclerotic plaque.

## Busting the Myth

In over two thirds of the population, then, egg consumption leads to little or no change in cholesterol at all. In less than a third of the population, total cholesterol goes up, but both the ratio of LDL to HDL and the total number of LDL particles remains the same; the LDL particles just get bigger and safer.

If arteries were like pipes and cholesterol was like gunk, more gunk would just clog up the pipe -- but arteries are nothing like pipes and cholesterol is nothing like gunk. Consider the myth busted.

# Myth: One High-Saturated Fat Meal Can Be Bad

## Why you don't need vegetable oil in your carrot cake and milk shake to protect your arteries.

By Chris Masterjohn  
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Newspapers the world over have recently declared that a single meal rich in saturated fats will disrupt the functioning of your arteries and contribute to the inflammation of your blood vessels, following an Associated Press story by Joe Milicia.<sup>1</sup> Milicia reported on a recent study<sup>2</sup> published by a team of researchers led by Dr. Stephen J. Nicholls of the Australian Heart Research Institute in the *Journal of the American College of Cardiology* entitled, "[Consumption of Saturated Fat Impairs the Anti-Inflammatory Properties of High-Density Lipoproteins and Endothelial Function.](#)"

The news article quoted the Kansas City cardiologist Dr. James O'Keefe as claiming the study showed that "when you eat [saturated fat], inflammation and damage to the vessels happens immediately afterward." Of course, the study showed no such thing.

Dr. Nicholls, the lead author of the study, was quoted in the article as saying the study showed the "need to aggressively reduce the amount of saturated fat consumed in the diet." The AP article then clarified for us that this meant reducing our intake of beef, pork, lard, poultry fat, butter, milk, cheeses, coconut oil, palm oil and cocoa butter, and replacing them with safflower oil, sesame oil, sunflower seeds, corn and soybeans. Wow! This study had the power to make sweeping conclusions about over 15 different foods! But in reality, of course, the study showed no such thing.

The study has already been widely criticized on the internet. Some of the criticism has been good; some has been rather poor. My own view is that this was a well-designed and interesting study; the authors of the report, however, unfortunately made unjustified conclusions from their data in the report itself, and the press articles further sensationalized the story and distorted the study's findings, making rather hysterical claims, unfortunately with the support of the study's lead author.

You may be surprised to find out that arterial function was actually better after the coconut oil meal than the safflower oil meal! Or that, contrary to the claims of the Associated Press article, the authors never measured inflammatory components in the subjects' blood. Or further, that they provided absolutely no evidence that different types of fatty acids, such as saturated or unsaturated, had anything to do with their findings!

In fact, they completely overlooked an alternative explanation that has substantial evidence in the scientific literature to support it: the differences they observed between the anti-inflammatory effects of the different diets may have been due largely or entirely to the difference in vitamin E content of the diets rather than the type of fatty acids present in the oils.

So, let's take a look at what the researchers actually found, and what it might actually mean.

## One High-Saturated Fat Meal: The Real Story

The researchers fed fourteen adults a meal of carrot cake and a milk shake on two separate occasions. In half of the meals, the food was made with coconut oil, which is about 90% saturated fat, while in the other half, the food was made with safflower oil, which is about 75% polyunsaturated fat.

Both oils were non-hydrogenated, organic, unrefined and virgin (David Celermajer and Jason Harmer, personal communication).

Each subject received each of the two types of meals on separate occasions after an overnight fast. Half of them received the safflower oil meal first and the coconut oil meal second, while the other half received the coconut oil meal first and the safflower oil meal second, to ensure that the order in which they received the meals did not affect the result. The two meals were separated by a month, to ensure that the first meal had as little an effect as possible on the second meal. Finally, the researchers were blinded to which meals the subjects were receiving, to minimize the effect of bias on the collection of the data.

The researchers took three types of measurements before the meals were fed and at 3 hours and 6 hours after the meals were fed. The first type of measurement they took was the levels of various constituents in the subjects' blood: total cholesterol, LDL, HDL, triglycerides, insulin, and free fatty acids.

The second type of measurement they took was of various parameters of blood flow. For example, they tested the amount of blood flowing through the subjects' forearms at each point, and they tested the subjects' "vascular reactivity." That is, they used pressure to stop blood flow through an artery in the arm and then tested how quickly and to what extent the artery reacted once the pressure was released by dilating to increase the return of blood to the blood-deprived area. With this type of test, the more the blood vessel dilates when pressure is released, the better shape it's believed to be in.

Finally, the researchers extracted HDL from the subjects' blood at each time point. Then, they incubated endothelial cells from human umbilical veins with the HDL at various concentrations. After the incubation period, they added an inflammatory chemical called TNF-alpha to the cells, which stimulates the production of adhesion molecules such as ICAM-1 and VCAM-1, which are believed to play a role in the adhesion of plaque to arteries. HDL has been shown to inhibit the expression of these inflammatory molecules, and the researchers conducted this part of the study to see if how you eat can affect *how much* potential HDL has to inhibit the expression of presumably harmful adhesion molecules. The researchers *claimed* to generate two findings:

- Flow-mediated dilation, or the ability of blood vessels to dilate and return blood flow after being occluded with pressure, decreased more strongly after the coconut oil meal than after the safflower oil meal. From this, they concluded that "consumption of saturated fat impairs . . . endothelial function."
- When cells were incubated with HDL taken from subjects after they ate the coconut oil meal, the expression of the inflammatory adhesion molecules ICAM-1 and VCAM-1 in response to TNF-alpha stimulation was *increased* compared to cells incubated with HDL taken from fasting subjects. By contrast, when cells were incubated with HDL taken from subjects after they ate the safflower oil meal, the expression of inflammatory molecules in response to TNF-alpha stimulation was *decreased* compared to cells incubated with HDL taken from fasting subjects. From this, the authors concluded that "consumption of saturated fat impairs the anti-inflammatory properties of high-density lipoproteins."

Although both of these conclusions are more conservative than the statements written in the Associated Press article, neither of them are justified by the study.

Let's take a closer look at each.

## Coconut Oil and Flow-Mediated Dilation: Harmful or Helpful?

The researchers claim that consumption of the saturated fat meal impaired flow-mediated dilation -- that is, it hurt the ability of blood vessels to dilate and return blood flow to an area from which blood flow had been stopped with pressure. The researchers did indeed show that at the 3-hour mark the decline in flow-mediated dilation was almost twice as great in the coconut oil group as it was in the safflower oil group.

Yet as Anthony Colpo, author of [\*The Great Cholesterol Con\*](#) has already [pointed out](#), the flow-mediated dilation was actually *higher* in the coconut oil group than in the safflower oil group at every point along the way!

The reason? When the subjects were fasting, those who were about to eat the coconut oil meal had 33% better flow-mediated dilation than those who were about to eat the safflower oil meal. Even at the 3-hour point, when flow-mediated dilation had declined the most, it was still 9% *higher* in the coconut oil group than the safflower oil group!

There are two ways we could look at this. **Figure 1** shows the changes that took place in flow-mediated dilation three and six hours after the meals, relative to the flow-mediated dilation before the meals (called "baseline"). You can see for both the coconut oil meal and the safflower oil meal, flow-mediated dilation declined substantially at the 3-hour mark.

**Figure 1.** *Percent change in the degree of flow-mediated dilation compared to baseline values.*

<b>Group</b>	<b>Baseline</b>	<b>3 hours</b>	<b>6 hours</b>
Safflower Oil	No change.	17% lower.	8% lower.
Coconut Oil	No change.	32% lower.	10% lower.

Now let's look at it another way. Figure 2 compares the relative degree of flow-mediated dilation between the coconut oil group and the safflower oil group. Surprise, surprise -- the flow-mediated dilation is *higher* (a good thing) in the *coconut oil* group at every single time point during the study!

**Figure 2.** *Comparison of the degree of flow-mediated dilation in the coconut oil group to that in the safflower oil group at three time points.*

<b>Baseline</b>	<b>3 hours</b>	<b>6 hours</b>
33% higher in coconut oil group.	9% higher in coconut oil group.	29% higher in coconut oil group.

Thus, we have to ask: is consumption of coconut oil rather than safflower oil the reason for the greater *decline* of flow-mediated dilation in the coconut oil group? Or is the reason for this decline the simple fact that the people who ate the coconut oil started out with a higher value of flow-mediated dilation in the first place, and therefore, so to speak, had more to lose?

There are two reasons that the latter might be true: first, the decline in flow-mediated dilation after a meal might not be a function of the flow-mediated dilation before the meal; second, a randomly high sampling error for the flow-mediated dilation before the meal could result in what's called "regression to the mean," which is explained below.

In the first case, it could be that eating carrot cake and drinking a milkshake, regardless of whether it is made with safflower oil or coconut oil, depresses flow-mediated dilation to a certain point regardless of fasting levels of flow-mediated dilation. For example, eating the meal might depress flow-mediated dilation to about 5%, regardless of whether the person's fasting level of flow-mediated dilation was 6% or 9%, in which case a person with a higher fasting level would experience a greater decline simply by virtue of the higher fasting level.

Thus, the coconut oil group, who by random chance had a 33% higher fasting rate of flow-mediated dilation, would exhibit a greater relative decline than the safflower oil group for no other reason than that they started off with substantially better flow-mediated dilation in the first place!

The authors themselves admitted a very similar explanation in the journal article, writing that "it is possible that 'regression to the mean' may have contributed to some of the FMD [flow-mediated dilation] reduction observed after consumption of the saturated fat." The concept of "regression to the mean" is essentially this: if by random sampling error an initial value tends to be higher than the mean, a second value will tend to be closer to the mean. Thus, a decline in values could result simply from the first value being randomly high.

And of course that's exactly what we saw here. Yet was this caveat noted in the press? Of course not. Instead, we were told that when we eat saturated fat, "damage to the vessels happens immediately afterward," and thus we must "aggressively reduce the amount of saturated fat consumed in the diet."

No one warned us that if when fasting, by random sampling error we happen to have a higher-than-average value of flow-mediated dilation, "damage to the vessels happens immediately" after we eat due to "regression to the mean." No one warned us that we must "aggressively reduce the amount of random sampling error" lest we suffer statistical arterial dysfunction with one, single meal.

## Does Coconut Oil Cause Inflammation?

Contrary to the Associated Press report's claim that "fewer inflammatory agents were found in the arteries" after the safflower oil meal than before it, the researchers did not measure any type of inflammation in the people consuming the meals. Instead, they incubated isolated umbilical vein endothelial cells with HDL taken from these subjects at various time points before and after the meals, and then stimulated these isolated cells to produce inflammatory adhesion molecules by adding a compound called TNF-alpha to the cells, and measured whether the HDL isolated after the different meals had a different ability to lower the amount of adhesion molecules released after stimulation with the TNF-alpha.

The researchers found that cells incubated with the HDL isolated from subjects after they had eaten the coconut oil meal produced *more* adhesion molecules (ICAM-1 and VCAM-1) after stimulation with TNF-alpha than cells incubated with HDL isolated from fasting subjects, and that cells incubated with HDL isolated from subjects after they had eaten the safflower oil meal produced *fewer* adhesion molecules after stimulation than cells incubated with HDL isolated from fasting subjects.

There are a number of problems with the large leap of logic it takes to conclude from this that a meal rich in saturated fat causes inflammation. First, others have already questioned how relevant this finding with isolated cells is to how our arteries actually function within us. After all, we are neither test tubes nor Petri dishes, but complex organisms with many different chemical and electrical feedback systems that do not exist in laboratory dishes. The researchers could have directly measured the levels of ICAM-1 and VCAM-1 in the subjects' blood, but that is not what they chose to study.

Second, the researchers *only* studied the anti-inflammatory potential specifically of HDL. The researchers could have incubated the cells with whole plasma to measure the total anti-inflammatory capacity of the blood, but they chose not to, for the simple reason that they were only trying to answer one small question about HDL and not look at the bigger picture (David Celermajer, personal communication). Virgin coconut oil is rich in very powerful polyphenols,<sup>5</sup> some types of which have been shown to decrease expression of TNF-alpha and adhesion molecules, and which are carried by water-soluble proteins in the blood and not by HDL. Thus, virgin coconut oil's contribution to the anti-inflammatory capacity of the blood could be primarily in the non-HDL fraction, whereas safflower oil's contribution to the anti-inflammatory capacity of the blood might be primarily in the HDL fraction. We simply do not have enough knowledge at this point to say for sure.

The only way to determine the effect of safflower oil and coconut oil on the total anti-inflammatory capacity of the blood is to perform the experiment by incubating the cells with whole plasma. The only way to determine the effect of safflower oil and coconut oil on the actual level of inflammation in the people consuming the oils is to measure the inflammatory compounds being directly produced in their blood. This study did neither.

Finally, and most importantly, the researchers provided no evidence whatsoever that the effects they observed were due to the type of fat. They simply *assumed* that the difference they observed between safflower oil and coconut oil was due to the fact that coconut oil is high in saturated fat and safflower oil is high in unsaturated fat. In doing so, they overlooked a very interesting hypothesis that could explain their results and that has substantial support in the scientific literature.

## An Alternative Hypothesis: Vitamin E

The difference between safflower oil and coconut oil does not stop at the relative saturation of their fatty acids. Figure 3 shows the difference in vitamin E content between the two oils. Safflower oil is 77 times higher in alpha-tocopherol and 47 times higher in total tocopherols.

**Figure 3.** Typical tocopherol (vitamin E) content of coconut oil and safflower oil.  
Source: (Enig, 2000).

<b>Tocopherol</b>	<b>Coconut Oil</b>	<b>Safflower Oil</b>
Alpha-tocopherol	5 mg/kg	387 mg/kg
Beta-tocopherol	--	--
Gamma-tocopherol	--	174 mg/kg
Delta-tocopherol	6 mg/kg	240 mg/kg
Total tocopherols	11 mg/kg	801 mg/kg

Is it plausible that the difference in vitamin E content of the oils could account for the difference in the expression of adhesion molecules in the isolated cells? Absolutely.

A recent review of alpha-tocopherol's role in regulating gene expression listed the suppression of the gene that codes for ICAM-1 as one of its functions. In fact, Chinese researchers performed a very similar experiment to the one we've been discussing, where they incubated endothelial cells taken from human umbilical veins with vitamin E instead of HDL. They found that incubating the cells with alpha-tocopherol, gamma-tocopherol and mixed tocopherols all inhibited the ability of oxidized LDL to induce ICAM-1 expression in the cells in a dose-dependent manner.<sup>12</sup> Another group found vitamin E to reduce both ICAM-1 and VCAM-1 in the heart cells of rats.

Vitamin E suppressed ICAM-1 and VCAM-1 levels *in vivo* in rabbits, although the effect on VCAM-1 was not statistically significant. In humans, the combination of vitamins E and C, but not vitamin C alone, decreased blood levels of ICAM-1 after six months. When the supplementation was stopped, blood levels of ICAM-1 returned to their initial levels. A similar effect was seen on VCAM-1, but it was not statistically significant. Unfortunately the researchers did not study the effect of vitamin E alone.

Vitamin E travels in the blood associated with lipoproteins, including HDL. When endothelial cells are incubated with vitamin E-enriched HDL, they selectively take up vitamin E from the HDL at ten times the rate at which they take up the HDL particles themselves. It is therefore reasonable to suggest that the high vitamin E content of safflower oil led to an enrichment of the subjects' HDL particles with vitamin E, which was then taken up by the endothelial cells where it suppressed the expression of adhesion molecules.

Yet one question remains: why would the HDL taken from subjects after they ate the coconut oil meal be less effective at suppressing the expression of adhesion molecules than HDL taken from subjects when they were fasting? From what I can find, data is very limited on the effects of eating a meal on the distribution of vitamin E in the blood. The one study I've found so far suggests that the fraction of vitamin E in HDL actually declines temporarily after a meal when the meal is relatively low in vitamin E, but rises if the meal is high in vitamin E. It may be, then, that the vitamin E content of HDL declined after the coconut oil meal not because of the coconut oil itself but because any low-vitamin E meal reduces the amount of vitamin E in circulating HDL, while the safflower oil added enough vitamin E to the meal to make the vitamin E content of HDL rise.

The only way to actually know would be to directly measure the vitamin E content of the HDL particles after the meal. Although the researchers who conducted the study we've been discussing measured the amount of protein, phospholipid, triglyceride and cholesterol in the HDL particles that they extracted, they unfortunately did not measure the amount of vitamin E in these particles.

This is, of course, a hypothesis. I have not shown conclusively that the effects observed in the study must have been due to vitamin E; I have simply shown this is a plausible explanation. Further research would be needed to confirm or refute my hypothesis.

Likewise, it is an unconfirmed hypothesis that the effect observed was a result of the consumption of saturated fat. This unfortunately did not stop the researchers from titling their paper "*Consumption of Saturated Fat Impairs the Anti-Inflammatory Properties of High-Density Lipoproteins and Endothelial Function*" as if they had actually shown this to be the case.

## So Which Oils Should We Eat?

If it turns out to be true that the difference in protective effect of HDL in the test tube was in fact due to the high vitamin E content of safflower oil and the low vitamin E content of coconut oil, that does not mean we should avoid coconut oil. It doesn't even mean we should eat safflower oil!

It simply means that coconut oil is not a good source of vitamin E. Coconut oil is still the best source of medium-chain fatty acids that boost metabolism and support the immune system, and virgin coconut oil is rich in powerful antioxidant polyphenols.

Polyunsaturated fatty acids such as those found in safflower oil actually deplete the body of vitamin E and thereby increase the body's need for vitamin E -- this is basic textbook biochemistry. Safflower oil may raise the amount of vitamin E in lipoproteins immediately after a vitamin E-rich meal, but what is the long-term effect on vitamin E status of a high intake of polyunsaturated fats?

It makes sense then that the best way to obtain vitamin E would be from sources that are high in vitamin E but low in polyunsaturated fat. Palm oil is an excellent example of such a source.

Palm oil is only 9% polyunsaturated, compared to safflower, which is 75% polyunsaturated. In terms of absolute amount of vitamin E, palm oil has a somewhat lower level of alpha-tocopherol, more than double the gamma-tocopherol, and large amounts of tocotrienols, which are another important part of the vitamin E complex that are completely absent in safflower oil. The combined absolute value of tocopherol and tocotrienol forms of vitamin E is 46% higher in palm oil than safflower oil.

When one takes into account the high polyunsaturated fat content of safflower oil, which increases the need for vitamin E, the advantage of more saturated palm oil becomes obvious: the ratio of vitamin E to polyunsaturated fatty acids in palm oil is *12 times* the same ratio in safflower oil!

Yet newspapers the world over carrying the Associated Press article told us to reduce our intake of palm oil and other saturated fats "aggressively."

## Drawing Conclusions: One Meal High In Saturated Fat is Not So Bad

We've been told that this study shows that when "you eat [saturated fat], inflammation and damage to the vessels happens immediately afterward." We've been told that it shows we must "aggressively reduce the amount of saturated fat consumed in the diet." We've been further told to throw out the beef, pork, lard, poultry fat, butter, milk, cheeses, coconut oil, palm oil and cocoa butter, replacing all these fats with safflower oil, sesame oil, sunflower seeds, corn and soybeans.

This is all on the basis of a study that couldn't differentiate the effect of coconut oil from the effect of random sampling error on flow-mediated dilation and showed people consuming coconut oil to have *better* flow-mediated dilation at all time points than people consuming safflower oil.

It is on the basis of a study that could not differentiate between the effects of saturated fats and the effects of low-vitamin E meals on the capacity of HDL to prevent inflammation in a Petri dish.

It is on the basis of a study that told us nothing about the amount of inflammation going on within the people consuming the meals, who are much more complex than globs of cells in a Petri dish.

Further research should uncover whether the effects seen in the test tube are due to vitamin E, to saturated or unsaturated fats, or to other causes entirely, and what relevance these observations in the test tube have for real, living people.

In the mean time, I'm going to continue cooking with CLA-rich clarified butter, and continue eating vitamin E-rich red palm oil and polyphenol-rich virgin coconut oil and extra virgin olive oil. I will continue to get my essential fatty acids from animal sources including butterfat, egg yolks from pasture-raised chickens, organ meats, cod liver oil, and fatty fish, so I can obtain the most benefit from the hormone precursors and structurally useful essential fatty acids while not overdosing on peroxide-promoting, free radical-generating, vitamin E-depleting polyunsaturates from vegetable oils like safflower oil.

Whoever's going to convince me to do otherwise has a bit more work to do.

## Notes

1. [One internet blogger](#) has claimed that the small sample size (14 people) and the short duration of the study "alone render it meaningless," and further criticized the researchers for "fail[ing] to completely isolate the effects of either fat type because they fed a high-fat, high-sugar mixed meal concoction that would not be replicated in a real world experience."

I would certainly like to see the study repeated in the context of a more nutritious and less refined meal, but the researchers effectively controlled for the sugar, flour, milk and other parts of the meal by keeping them the same and varying only the oil with which the food was made. While a larger sample size would be better and a longer study would be easier to understand the implications of, neither a small sample size nor a short duration make the study "meaningless."

Researchers conduct statistical analyses that determine whether their study has the statistical power to conclude that a correlation they've observed is real. Since these researchers did observe some findings that were statistically significant, this shows *ipso facto* that their sample size was sufficiently large to generate the conclusion that those particular correlations were real.

This is, of course, different than drawing an inference about what the correlation means from the data. This is more of an art, and subject to error. The blogger cited above misses the more important point that the researchers, doctors who were interviewed in the press, and journalists were careless in interpreting the *meaning* of the results.

2. This finding has been brushed aside by several authors because the difference between the two meals did not reach statistical significance.<sup>4,5</sup> In the context of this study, "statistically significant" means that the authors performed statistical tests showing that the likelihood their finding was due to chance was 5% or less.

Actually, the decline in flow-mediated dilation after the coconut oil meal did indeed reach statistical significance. The difference between the coconut oil and safflower meals were close to significance: an 8% likelihood the finding was due to chance. This is good reason to be less sure of the data and to be more cautious in interpreting it, but it doesn't somehow make the finding disappear into thin air or become irrelevant. Setting the significance level at 5% is simply an arbitrary convention.

3. If you've read Anthony Colpo's article, my numbers might confuse you at first because Colpo presented the data as absolute change in percentage points, reporting changes of 0.9% and 2.2%, whereas I'm reporting the relative change in dilation. Thus, my numbers are much larger.

Here's the difference: The researchers tested the change in the diameter of the blood vessel after the pressure they applied to restrict blood flow was released. When the pressure is released, the diameter increases to rush blood to the area that has been deprived of blood. Among the various groups, the change in diameter ranged from a 4.3% increase in diameter to a 6.9% increase in diameter. Before the coconut oil group ate their meal, the average increase in blood vessel diameter after restriction was 6.9%. At three hours following the coconut oil meal, the average increase in blood vessel diameter after restriction was 4.7%. Colpo reported this as a 2.2% decline by subtracting 4.7% from 6.9%. I reported it as a 32% decline by dividing 4.7% by 6.9%, then subtracting this figure from 100%, showing the *relative* decline as a percentage of the baseline value.

This strikes me as a much more valuable figure, because the absolute percentage of increase in blood vessel diameter is small. Reporting absolute percentage change, by contrast, does not give us any sense of the importance of the change. If we expected a blood vessel to double in diameter, which would be an increase of 100%, then it might be relatively unimportant if the diameter increases by 97.8% instead of 100%. Why? Because the additional volume of blood that can be transferred in a given section of the blood vessel to compensate the tissues for previous oxygen deprivation would only be about 4.4% lower. By contrast, if we expect the blood vessel diameter to increase to a maximum of, say, 10%, then an absolute reduction of 2.2% to 7.8% dilation is suddenly much more profound. In this case, the additional volume of blood that can be transferred in a given section of the blood vessel would be 39.2% lower. Cells that are starving for oxygen to whom compensatory additional oxygenated blood is supplied at an almost 40% lower rate probably don't care that the absolute change is only 2.2%!

4. The only study I could find on the effects of a meal on the distribution of vitamin E between the various lipoproteins in the blood<sup>6</sup> *seems* to show, but does not show conclusively, that *eating a meal*, in and of itself, either reduces the total amount of vitamin E in the blood or causes it to shift from HDL and LDL to other lipoproteins, while the vitamin E content of the meal compensates for this effect, such that a low-vitamin E meal would reduce the amount of vitamin E carried in these lipoproteins and a high-vitamin E meal would raise it.

After a meal containing 18 mg of alpha-tocopherol, the alpha-tocopherol content of HDL declined at three hours, and bottomed out after six hours, after which it rose. After a meal containing 27 mg of alpha-tocopherol, the alpha-tocopherol content of HDL bottomed out at three hours instead of at six hours, after which it rose, although it did not reach baseline values until at about 9 hours. After a meal containing 25 mg of gamma-tocopherol, the gamma-tocopherol level of HDL decreased slightly at three hours, but was raised beyond baseline levels at six hours. After a meal containing 51 mg of

gamma-tocopherol, the gamma-tocopherol of HDL began increasing immediately or at least before the first postprandial measurement at three hours, with no initial decrease.

These results suggest two things:

- First, although gamma-tocopherol is present in HDL in smaller amounts than alpha-tocopherol (in the fasting state, there was roughly five times as much alpha-tocopherol than gamma-tocopherol in the HDL), it accumulates specifically in HDL more readily after a meal than does alpha-tocopherol. This is suggested because 25 mg of gamma-tocopherol accumulated in HDL more quickly and to a greater degree than 27 mg of alpha-tocopherol.
- Second, there is a general trend for a low-vitamin E meal to reduce the amount of vitamin E in HDL and a high-vitamin E meal to raise the amount of vitamin E in HDL. This is suggested because raising the amount of alpha-tocopherol from 18 mg to 27 mg reduced the amount of time for which the alpha-tocopherol level of HDL was reduced, and raising the gamma-tocopherol from 25 mg to 51 mg changed the trend from a reduction of the gamma-tocopherol level of HDL at three hours to an increase of this level at three hours.

It should be kept in mind that the reduction is occurring specifically in HDL, IDL and LDL. Vitamin E is initially transported by chylomicrons when it is absorbed, and all of the meals substantially increased the amount of vitamin E being carried by chylomicrons in the blood.

Unfortunately, we can't draw any conclusive implications from this study for the following reasons:

- First, the researchers reported some of the measurements as a combination of HDL, IDL and LDL measured together, and other measurements for HDL and LDL measured separately. Since the trends for HDL and LDL matched each other closely when measured separately, it is *probably* valid to assume that the trends showed for HDL, IDL and LDL measured together reflect the trends for HDL alone, but it is also possible that this is invalid.
- Second, the researchers combined the high dose of gamma-tocopherol with the low-dose of alpha-tocopherol, and vice versa. We can't discern from the study whether the amount of alpha-tocopherol affects how much gamma-tocopherol accumulates in the HDL and vice versa.
- Third, the researchers only looked at alpha-tocopherol and gamma-tocopherol. Safflower oil contains roughly 30% of its vitamin E as delta-tocopherol (see **Figure 3**), which was not measured in the study.

Nevertheless, as far as the data go, it is *plausible* that the low-vitamin E coconut oil meal reduced the total tocopherol content of the HDL fraction by virtue not of any specific attributes of coconut oil but by virtue of the effect of eating a meal *per se*, and that the high-vitamin E safflower oil meal increased the total tocopherol content of the HDL fraction by virtue of its high tocopherol content.

5. My hypothesis makes several testable predictions, allowing researchers to confirm or refute the hypothesis:

- The experiment should be repeated, and the total tocopherol levels of the HDL fractions should be analyzed after they are extracted. If the HDL extracted after the safflower oil meal is not higher in vitamin E than the HDL extracted after the coconut oil meal, this would completely refute my hypothesis. If the HDL taken after the coconut oil meal is not lower than that taken from the same subjects in the fasting state but nevertheless fails to inhibit adhesion molecule expression as well as HDL taken from the same subjects in the fasting state, this would partially but not completely refute my hypothesis.
- The total tocopherol and individual tocopherols of the HDL particles should be analyzed, and it should be determined whether the difference in any of the individual tocopherols or in the total tocopherols can account for the difference in adhesion molecule expression. If the difference in vitamin E cannot account for any of the difference in adhesion molecule expression, this would completely refute my hypothesis. If the tocopherol concentration of the HDL could account for some or all of the difference in adhesion molecule expression, this would be consistent with my hypothesis, but would not confirm it, because the tocopherol could simply be a marker for dietary intake of unsaturated fatty acids.
- In order to dissociate the effect of dietary vitamin E from that of dietary unsaturated fatty acids, the experiment could be modified in several ways. First, purified fatty acids that are devoid of vitamin E could be fed. Vitamin E could also be supplemented at various doses in various subgroups. This has the benefit of completely eliminating the confounding effect of vitamin E. It has the drawback of potentially failing to replicate the effect of natural fatty acids within their natural content as they are found in unrefined oils for any number of unforeseen reasons.
- Another way to dissociate the effect of dietary vitamin E from that of dietary unsaturated fatty acids would be to use different mixes of unrefined oils to achieve either a standardized fatty acid composition and differing vitamin E contents or a standardized vitamin E content with differing fatty acid compositions. This has the benefit of eliminating any unforeseen confounding factors introduced by refining oils and purifying fatty acids, and the drawback of being unable to completely eliminate vitamin E and other constituents and thereby perfectly isolate the effect of fatty acids. Here is one example of how this type of standardization could be achieved:

- 100 grams of palm oil yields an almost identical fatty acid composition to a combination of 50 grams of olive oil and 50 grams of coconut oil if we consider saturation only and disregard chain length. The two mixtures are identical in proportion of monounsaturated fat (39 grams), while the former yields 52 grams of saturated fat and 9 grams of polyunsaturated fat and the latter yields 54 grams of saturated fat and 7 grams of polyunsaturated fat. By contrast, the total vitamin E content of the former would be 117 mg, while the total vitamin E content of the latter would be only 8 mg. 100 grams of olive oil would provide only 16 grams of saturated fat and only 13 mg of vitamin E.
- If HDL isolated from subjects consuming unrefined palm oil was no more or less effective than HDL isolated from subjects consuming the mixture of unrefined coconut oil and unrefined olive oil, but was *less* effective than HDL taken from subjects consuming unrefined olive oil alone, it would strongly refute my hypothesis that dietary vitamin E is more important than the saturation of dietary fat. If, on the other hand, the HDL isolated from subjects consuming unrefined palm oil was much more effective than both the HDL isolated from subjects consuming the mixture of coconut oil and olive oil and the HDL isolated from subjects consuming olive oil alone, it would strongly refute the hypothesis that the saturation of dietary fat is most important and strongly support my hypothesis that the dietary vitamin E is most important.
- In order to completely dissociate the direct effect of vitamin E content of HDL particles from its potential role as a marker for other effects on HDL composition mediated by the degree of unsaturation of dietary fats, HDL particles could be artificially enriched with tocopherols or a combination of tocopherols and tocotrienols. If the variation in adhesion molecule expression by cells incubated in different sources of HDL particles can be completely accounted for by the degree of artificial enrichment of the HDL particles with vitamin E, this would support my hypothesis. If the variation in vitamin E content of the HDL particles could not account for the variation in adhesion molecule expression, it would refute my hypothesis.

We need to maintain perspective, though, and realize that this question is merely of academic interest, and has no practical relevance for which oils we should consume in our diet. Just because one oil increases the anti-inflammatory capacity of HDL more than another oil does not mean that it increases the total anti-inflammatory capacity of all of the constituents of the blood more than the other oil. Furthermore, adding an inflammatory cell signaling compound such as TNF-alpha to a Petri dish does not approximate the much more complex conditions that the cells lining our blood vessels experience.

Nevertheless I would like to see the answers to the questions I have raised in this article. To my knowledge, these are original research suggestions, but it is possible that others have already raised them elsewhere.

# Part I: Debunking the Myth

## Myth: Cholesterol Causes Alzheimer's Disease Part I: Debunking the Myth

*by Chris Masterjohn*  
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Cholesterol is widely blamed for causing Alzheimer's disease. Yet little is known about the relationship between cholesterol and Alzheimer's, and one hypothesis, described below, is that cholesterol *protects the brain* from Alzheimer's.

It is unsurprising that, when one of the most booming industries is the sale of cholesterol-lowering drugs, just about every disease under the sun would be pinned to cholesterol. The more diseases blamed on cholesterol, the more profits generated by the sale of cholesterol-lowering drugs.

But is it *true* that cholesterol causes Alzheimer's disease? Or, on the other hand, could you actually *harm* your brain by reducing its cholesterol content through drugs or a low-fat, low-cholesterol diet? And if cholesterol isn't to blame, what *does* cause Alzheimer's, and what is the best way to protect ourselves from it?

These questions and more, are all answered below.

## Let's All Blame Cholesterol

Headlines blaming cholesterol for Alzheimer's disease abound. A Google search for "cholesterol and the brain" turns up such titles as "[Cholesterol central to brain disease.](#)" and "[Cholesterol bad for brain, too.](#)"

One study bragged that by using statins, cholesterol-lowering drugs, medical researchers could reduce the amount of cholesterol in the brains of Alzheimer's patients with *normal cholesterol levels* by an average of 21.4 percent. Without studying whether this drop in cholesterol resulted in improved memory or other cognitive effects, the study celebrated the ability to reduce normal levels of brain cholesterol based on the dubious notion that cholesterol is "involved" in the formation of amyloid plaques, a hallmark of Alzheimer's disease.

Since the brain, being only 2% of the body's weight, yet containing a full 25% of its cholesterol, relies on cholesterol as so necessary and central to its function, it is not very surprising that cholesterol would be "involved" in any brain disorder.

Yet there is an enormous gap between showing "involvement" of cholesterol and the conclusion that it is a good thing to lower normal brain cholesterol levels by over 20 percent. It is also quite clear that *neurons* are "involved" in Alzheimer's disease. Yet no one is jumping on the bandwagon to push pharmaceutical drugs that *reduce the number of brain cells*.

One website recommends adopting a "[brain-healthy diet](#)" by "reduc[ing] your intake of foods high in fat and cholesterol." As we will see below, this is *anything but* a "brain-healthy diet."

## Alzheimer's Disease: Some Background

Before we approach the question of whether cholesterol causes (or protects against) Alzheimer's disease, sometimes abbreviated "AD," some background information about this disease is necessary.

Alzheimer's disease was named after Alois Alzheimer, who was a psychiatrist with a specialty in neuropathology, and was the first to show what was going on *physically* in the brain of someone with what we now call Alzheimer's. In 1907, he presented his findings from the autopsy of his patient, Auguste D., who had been admitted to an asylum for "delerium and frenzied jealousy of her husband."

Alois Alzheimer noted two things about the condition of Auguste's brain, to which he attributed her mental degeneration: "miliary bodies," which we now call "amyloid plaques," and "dense bundles of fibrils," which we now call "neurofibrillary tangles." This was a bold claim at a time when the connection between the physical and the mental was being explored but not yet fully accepted, and in 1910, Alzheimer's mentor, Emil Kraepelin, named the disease after him.

The amyloid plaques are made up of a peptide (a peptide is a fragment of a protein) called "beta-amyloid," which is formed by the cleavage of amyloid precursor protein (APP) by an enzyme called "gamma-secretase." The tangles, on the other hand, are primarily composed of a protein called "tau," which forms tangles when it is hyper-phosphorylated. The plaques exist on the outside of cells, while the tangles exist on the inside of cells.

The pathology of Alzheimer's disease is very complex, and an attempt is made here to make it simple, while still remaining accurate. The most important pieces of the puzzle to remember at this point are these four:

**APP:** APP is the precursor of beta-amyloid.

**Beta-amyloid:** Beta-amyloid forms plaques deposited outside the cells of the brain, which are found in Alzheimer's disease.

**Gamma-secretase:** Gamma-secretase cleaves APP, yielding beta-amyloid.

**Tau:** Tau is a protein that, when hyper-phosphorylated, forms the "neurofibrillary tangles" that are found inside cells in the brains of Alzheimer's patients.

The connection between cholesterol and Alzheimer's disease rests on what is called the "amyloid hypothesis," and a somewhat dubious connection between cholesterol and beta-amyloid.

## The Amyloid Hypothesis

The amyloid hypothesis of Alzheimer's disease was proposed in 1984 when the structure of beta-amyloid was discovered by Glenner and Wong. The amyloid hypothesis holds that the accumulation of beta-amyloid is the driving force behind amyloid plaques, neurofibrillary tangles, synapse loss (synapses are the connections between neurons), and neuronal cell death. Accumulation is held to occur when the production of beta-amyloid exceeds its clearance from the brain or degradation by enzymes.

## The Cholesterol-Alzheimer's Hypothesis

In this article, I will refer to the idea that high serum or brain cholesterol is a driving force behind Alzheimer's, and that lowering of serum or brain cholesterol through diet or drugs can prevent Alzheimer's, as the "cholesterol-Alzheimer's" hypothesis.

The cholesterol-Alzheimer's hypothesis depends on the amyloid hypothesis, which is controversial in itself. Here is an excerpt from a [Science Daily News Release](#):

"Brain cholesterol is involved in the formation of amyloid plaques, one of the hallmarks of Alzheimer's disease. Amyloid plaques are waxy buildups that harm brain cells.

"This class of drugs [statins] may be potentially beneficial in the treatment of Alzheimer's disease,' said Dr. Gloria Vega, professor of clinical nutrition and the study's lead author.

"If we limit cholesterol synthesis in the brain, we may be able to decrease the production of amyloid plaques."

Note that this reasoning relies on two assumptions: 1) high cholesterol levels cause the buildup of amyloid plaques, and 2) it is the buildup of amyloid plaques that drive the neural pathology and cognitive deficits in Alzheimer's disease.

If the cholesterol-Alzheimer's hypothesis is true, it would predict the following:

- There should be a clearly defined relationship between serum or brain cholesterol levels and levels of beta-amyloid
- High serum or brain cholesterol should be a risk factor for Alzheimer's disease
- Intervention studies modifying cholesterol levels should not only modify Alzheimer's-related pathology, but should increase or reduce Alzheimer's pathology in direct proportion to the effects on cholesterol, called a "dose-response" relationship. A hypercholesterolemic diet should induce or worsen both physical and cognitive AD-related pathology in proportion to the increase in cholesterol levels, and statins should not only improve the physical and cognitive pathology of Alzheimer's, but they should do so in direct proportion to their effectiveness in lowering brain cholesterol.

Despite the wide-spread blaming of cholesterol for Alzheimer's and the celebration of statins as a possible cure, none of these turn out to be true. The amyloid hypothesis remains highly questionable and unconfirmed; cholesterol's relationship to amyloid levels is inconclusive; high cholesterol is not a true risk factor for Alzheimer's; and, statins do not appear to inhibit amyloid plaques at reasonable doses and can even cause neuronal cell death at high doses.

## Problems With the Amyloid Hypothesis

While it is true that the accumulation of amyloid plaques are a universal hallmark of Alzheimer's disease, it does not necessarily follow that they are the primary *cause* of Alzheimer's disease. There in fact are many other signs of pathology, including the rapid destruction of certain fatty acids and proteins involved in synapse formation. Possibilities outside the conventional amyloid hypothesis include:

- beta-amyloid is an irrelevant byproduct of other damage
- beta-amyloid accumulation represents an increased burden on the Alzheimer's brain, but is secondary to more primary causes of degeneration
- beta-amyloid is a byproduct of a neuroprotective mechanism designed to protect against the damage of Alzheimer's
- beta-amyloid is itself involved in a protective mechanism, or is otherwise necessary, but factors entirely separate from its production cause it to form fibrillary plaques, which may contribute an additional harmful burden

## Scant Evidence in Favor...

According to a review published February, 2005, in *Cell*, by Rudolph E. Tanzi and Lars Bertram, "Twenty Years of the Alzheimer's Disease Amyloid Hypothesis: A Genetic Perspective," most of the evidence "confirming" the amyloid hypothesis to date has been associations of Alzheimer's disease with genes that are, in turn, associated with a phenotype that includes amyloid plaques.<sup>3</sup>

Yet such associations are not confirmations of the hypothesis. An association of Alzheimer's with a particular phenotype is merely an association, and does not help us understand causation, any more than an association of fire men with burning buildings "confirms" that fire men are the cause of fires. This is especially true because, as discussed in *Part II* of this article, the gene mutations associated with AD all have neurodegenerative effects *independent* of amyloid plaques.

In 2003, a study by Hock et al., attempted to improve cognitive deficits by treating Alzheimer's patients with beta-amyloid immunizations, reasoning that antibodies against beta-amyloid would carry beta-amyloid out of the brain for elimination. Many of the subjects already had endogenous antibodies to beta-amyloid, but the ones whose antibody levels increased significantly over time after immunization performed better on mental examinations than did those whose levels did not significantly increase.

Ten of the thirty test subjects experienced little change in the level of antibodies after immunization, and the rate of increase in the level of these antibodies was never measured in the test subjects prior to immunization. Test subjects who were immunized but did not experience a subsequent rise in antibodies had a *worse* rate of decline on cognitive tests than than the averages reported in the literature.

The authors of the study regarded it as "the *first* successful clinical evidence for a central role of beta-amyloid in causing cognitive decline and dementia in AD patients." (My Italics.) Yet the authors themselves concluded that the evidence was decidedly *against* the antibodies carrying beta-amyloid out of the brain. More importantly, they did not include a control group that was not immunized! Thus, there was no evidence that the immunizations were what caused the antibody levels to rise, and the authors admitted they didn't know the mechanism by which the antibodies improved mental performance.<sup>4</sup>

#### SIDEBAR

Another interesting note: The authors only found a relationship when they used their *own* unverified method for measuring antibodies. Using the standard ELISA method, they found no relationship at all. Without providing any evidence that their method was superior to the standard ELISA, they went on to make outrageous claims.

Yet most journalists and doctor's would have only read the summary of this study or a review that cited it, nor would they typically have read Dr. Alexei Koudinov's letter on the financial conflict of interest of one of the author's of this study.

In the aforementioned review, Tanzi and Bertram cite a study in which aged rhesus monkeys developed tau phosphorylation and neuronal loss after having pre-assembled beta-amyloid fibrillary plaques injected into their brains. Young rhesus monkeys, on the other hand, did not, and aged monkeys did not respond to *soluble* beta-amyloid injection. This appears to support a causal role for beta-amyloid fibrillary plaques in the development of other forms of Alzheimer's-related pathology.

Yet, the fact that only pre-formed fibrillary plaques and not soluble beta-amyloid caused pathology are evidence *against* the amyloid hypothesis's claim that it is *accumulation* of beta-amyloid that leads to the formation of amyloid plaques and general AD-related pathology. And, as we will see below, there are many more examples where beta-amyloid appears to be independent of other AD-related pathology and not causal.

### ...And Considerable Evidence Against

While the amyloid hypothesis relies mostly on genetic associations that do not confirm causality, there are many pieces of evidence that contradict the simplistic picture where beta-amyloid deposits are the cause of all other neurodegeneration in Alzheimer's.

One recent study found that changing the amount of DHA, an omega-3 fatty acid abundant in the brain, in the diet of mice that possessed Alzheimer's-related genes, was able to modulate a great deal of the physical pathology and also the cognitive deficits in the mice, independent of the genetically related beta-amyloid accumulation.

Mice that possess the genes to express amyloid plaques do not exhibit neurofibrillary tangles. This suggests that, contrary to the amyloid hypothesis, amyloid plaques are not sufficient to cause the development of neurofibrillary tangles.

A study designed to test whether different forms of beta-amyloid were more or less important to the formation of amyloid plaques found that a particular form consisting of 42 amino acids was necessary for the formation of plaques. Yet it also found "massive" deposition of amyloid plaques in these mice *without* neuronal loss, tangles, or a general appearance of Alzheimer's. This further indicates that, although amyloid plaques are involved in Alzheimer's, they are not the "cause."

One study knocked out the gene for the enzyme presenilin-1 (PS1) in mice. PS1 and PS2 are building-blocks of the gamma-secretase enzyme, which cleaves APP into beta-amyloid, so knocking out PS1 should diminish the accumulation of amyloid plaques. As it turned out, knocking out PS1 diminished amyloid plaques *and* caused mild impairment of memory.

But with the loss of both PS1 *and* PS2, the result was "strongly impaired LTP [long-term potentiation, necessary for memory], spatial and contextual memory deficits, and, after some time, massive loss of synapses, dendrites, and neurons. Remarkably, this neurodegeneration was accompanied by increased Tau phosphorylation . . . "

In this case, decreasing beta-amyloid proved disastrous to the brains of the mice, *and* resulted in the phosphorylation of tau, which is what is believed to generate the neurofibrillary tangles. PS1 and PS2, which make up the gamma-secretase enzyme, also have many other functions in the nervous system. So, while the study definitely doesn't establish a causal relationship between lack of beta-amyloid and neural degeneration, it certainly calls into question whether beta-amyloid is the driving force behind synapse loss, tau phosphorylation, and the other forms of neurodegeneration that occur in its *absence*.

## Is Beta-Amyloid a Result of Neuro-*Protection*?

Considerable evidence indicates that beta-amyloid is a byproduct of *protective* mechanisms. If this is true, it could be that other, more primary, causes of Alzheimer's pathology occur first, and then beta-amyloid accumulation is a result of the brain's self-defense against Alzheimer's-related pathology.

One interesting observation is that Alzheimer's-related pathology occurs in Down's Syndrome patients, but not until *middle-age*. In this case, it is clear that degeneration occurs *before* the deposition of amyloid plaques and other outward manifestations of Alzheimer's-related pathology.

As Bothwell, et al., pointed out in 2000, APP, the precursor to beta-amyloid, is widely preserved across species, which is highly suggestive that it fulfills a function critical to survival. As pointed out by Kounnas, et al, Mattson showed APP to be neuroprotective, Koo showed APP to increase in response to aging, and Abe showed APP to increase in response to neuronal injury.

All these seem to suggest that APP production, and therefore beta-amyloid with it, would increase in response to damage being done to the brain, whether by aging, diet and environment, or genetic defects. This suggests that the beta-amyloid accumulation in Alzheimer's may be a secondary byproduct of a *protective* response to damage.

## The Cholesterol-Alzheimer's Hypothesis Bites the Dust

The cholesterol-Alzheimer's hypothesis relies heavily on the amyloid hypothesis, which remains controversial and has been shown in the preceding section to be seriously questionable. Nevertheless, recent research allows us to evaluate the cholesterol-Alzheimer's hypothesis directly on its own merits, or, rather, its own demerits.

Earlier in the article, we established three criteria for the cholesterol-Alzheimer's hypothesis to meet:

- A direct relationship between cholesterol levels and beta-amyloid should be conclusively shown.
- High brain or serum cholesterol should be a risk factor for Alzheimer's.
- A hypercholesterolemic diet should worsen Alzheimer's in direct proportion to its cholesterol-raising effects, and cholesterol-lowering statins should lower the risk of Alzheimer's in direct proportion to their ability to lower cholesterol.

Are these true? As it turns out, no. Not at all.

The cholesterol-Alzheimer's hypothesis assumes that there is a positive correlation between cholesterol levels and beta-amyloid production. Yet this assumption was based on what reviewer Benjamin Wolozin referred to in *Neuron* as "highly perturbed systems," in 2004, writing that, "it remains to be seen whether true *in vivo* alteration of cholesterol alters beta-amyloid."

*Strike one* for the cholesterol-Alzheimer's hypothesis.

## SIDEBAR

The term *in vivo* refers to phenomena that occur in natural living organisms. *In vivo* evidence is distinguished from *in vitro* evidence, which occurs in a highly manipulated laboratory setting where cells or chemicals isolated from a living organism are used. *In vitro* evidence allows us to have greater control over conditions, but it must always be paired with *in vivo* evidence showing that the findings are relevant to natural living organisms.

A February 2005 review in the pages of *Molecular Neurobiology* analyzed the data available to date and determined cholesterol levels *not* to be a risk factor for AD. According to the authors:

"Studies were reviewed that have examined cholesterol levels in Alzheimer's patients and control subjects, including prospective studies, and based on that review, the conclusion is reached that the majority of studies do not support elevated cholesterol levels in serum and brain as a risk factor for Alzheimer's disease."

*Strike two* for the cholesterol-Alzheimer's hypothesis.

The authors go on to write that analyzing cholesterol levels into specific sub-categories might be more helpful in identifying risk. This is an important point, because high cholesterol levels are often associated with confounding factors. For example, familial hypercholesterolemia involves a dysfunction of LDL receptors. On the one hand, cholesterol levels in the blood increase because they cannot be received into cells, and on the other, the absence of properly functioning LDL receptors could be causing other problems. Such a dynamic could cause some studies to misidentify a problem as resulting from high cholesterol, rather than a more specific defect of receptors, or even a *deficiency* of intracellular cholesterol.

In Alzheimer's for example, it has been established that the LDL receptor-related protein, or LRP, is responsible for eliminating beta-amyloid from the brain. But it is *also* responsible for bringing apolipoprotein-E-associated cholesterol into cells. Thus, a deficiency or dysfunction of LRP could be a third factor that results in *both* increased free brain cholesterol and increased beta-amyloid. Some studies might mistakenly conclude that the high cholesterol level caused the high beta-amyloid level, when the two were actually coincidental.

In addition, it would also be possible to mis-associate the increased free cholesterol with a negative effect in the brain, when it is actually an inability of the cholesterol to exercise its own *positive* effect in the cells, due to the defect in its receptor.

The cholesterol-Alzheimer's hypothesis has failed our first two criteria. A clear link between cholesterol and beta-amyloid has not been demonstrated. When studies are reviewed together, they do not suggest high cholesterol as a risk factor for AD.

Now for the final nail in the coffin. The third prediction of the cholesterol-Alzheimer's hypothesis is that intervention studies modifying cholesterol should be able to induce or worsen AD through a hypercholesterolemic diet and to ameliorate it through cholesterol-lowering statin drugs. False, and false.

Of the two available studies measuring beta-amyloid changes in response to hypercholesterolemic diets in rodents, one 1998 study found a hypercholesterolemic diet to *lower* beta-amyloid in proportion to the *rise* in cholesterol, and a 2000 study found the opposite.

Unfortunately, neither study measured synapse loss, neuronal cell death, neurofibrillary tangles, or any other Alzheimer's-related pathology, which we know can occur independent of beta-amyloid plaques in animals. Nor did either study measure cognitive function of the mice. Thus, neither of these conflicting studies were good measurements of Alzheimer's disease.

Studies with rabbits have been ignored for this article because rabbits are herbivorous and their response to cholesterol is not analogous to that of an omnivore.

There is only one study indexed for Medline that has studied the effect of a hypercholesterolemic diet on any aspect of cognition in animals. This 2004 controlled study found a hypercholesterolemic diet fed to pregnant rats to *preserve cognitive functioning* in rat pups exposed to anoxia as measured by a linear maze and a Morris water maze. A 1995

human study found that feeding eggs as a source of dietary cholesterol was helpful to elderly whose memory was impaired.

Thus it has never been established that a hypercholesterolemic diet can induce or worsen Alzheimer's disease, and available research suggests that raising cholesterol is generally helpful in improving or preserving cognitive function, not deteriorating it.

What about statins?

Hoglund et al., made three unsuccessful attempts to try to reduce beta-amyloid with statins. In their 2005 report,<sup>22</sup> they cite epidemiological studies that showed statin use to result in a lower risk of AD. However, this study did not group the patients by statin dosage, so it was impossible to see if there was a dose-response effect. In addition to this criticism, which the authors note, epidemiological studies are not true "evidence," in that they can be used to *generate* hypotheses, but never to *confirm* them.

They go on to cite cell culture and animal studies that showed that cholesterol was correlated with beta-amyloid and that decreasing cholesterol with statins decreased beta-amyloid; however, they rightly criticized these studies as "exceeding clinically relevant doses many times over."

Both clinical and animal studies evaluating the effect of statins on APP are cited as contradictory.

The authors published three studies on the effect of statins on beta-amyloid. In the first study, simvastatin was used on AD patients and found to have no effect on beta-amyloid. The second study used simvastatin or atorvastatin on hypercholesterolemic, and found no effect on beta-amyloid. The third study used simvastatin on AD patients and analyzed their cerebro-spinal fluid for a particular AD-related pattern of beta-amyloids, and found no effect.

Not only was there *not* an effect on beta-amyloid, but there was a significant reduction of total plasma and LDL cholesterol, and there was a significant reduction in biomarkers for brain cholesterol levels. Thus, we know the dose of statin was high enough to reduce brain cholesterol levels, yet still did not effect beta-amyloid levels.

*Strike three.* The cholesterol-Alzheimer's hypothesis has struck out.

Cholesterol has not been conclusively tied to beta-amyloid, nor is it a true risk factor for Alzheimer's, and modulating both serum and brain cholesterol through hypercholesterolemic diets and statins does not modulate Alzheimer's-related pathology consistent with the failed cholesterol-Alzheimer's hypothesis.

It is interesting to note that in the report of the study cited above, after failing to control beta-amyloid through statins three times, the authors suggested studying higher dosages of statins, even though they had established their own dosages to be effective in reducing cholesterol.

Yet according to a recent German report, high doses of statins inhibit the growth of dendrites and axons, which form the connections between neurons, and induce neuronal apoptosis, which is a fancy way of saying they make brain cells commit suicide.

Since cholesterol is vital to the brain and is the limiting factor in the formation of synapses, it is unsurprising that drugs lowering brain cholesterol could damage neurons.

In fact, Iwo J. Bohr has recently presented the hypothesis that cholesterol is *protective* against Alzheimer's disease!

## **Cholesterol Is the Brain's Best Friend**

That cholesterol plays a central role in the development and maintenance of the brain and nervous system is reflected by the fact that the human brain makes up only two percent of the body's weight, yet contains nearly 25 percent of its cholesterol.

Over the last five years, new research has been elucidating the role of cholesterol in the brain and highlighting its vital importance. For example, in 1997 it was discovered that an unknown factor secreted by glial cells, which grow alongside neurons, was the limiting factor allowing the growth of synapses, which are the connections between neurons.

In 2001, this unknown "glial factor" was identified as cholesterol. In the absence of the glial secretion, the neurons formed few and inefficient synapses. When the glial secretion was supplied intact but deprived of cholesterol, it was ineffective. When neurons deprived of this glial secretion were exposed to a solution of cholesterol, synapse formation increased by *twelve times*. Synapses formed in the presence of the cholesterol-containing glial secretion were highly efficient and highly functioning.

Cholesterol has also been discovered to play an important role in forming what are called *lipid rafts*, areas in the plasma membrane of cells that anchor certain proteins important to cell signaling.

A 2004 study found that several of the proteins anchored in these lipid rafts are responsible for stimulating and guiding the growth of nerve axons. Depriving the membrane of cholesterol selectively inhibited the effect of attractive signaling proteins, which destroyed the axon's ability to grow in the proper direction.

Thus, cholesterol is the limiting factor in the ability to form synapses and for nerve growth per se, and is also essential to the regulation of that growth, so that synapses form properly and in the right places.

## Is Cholesterol *Protective* Against Alzheimer's Disease?

On June 10, 2005, Ivo J. Bohr's new hypothesis was released from peer review and published in *Lipids in Health and Disease*, hypothesizing that cholesterol is a protective factor in Alzheimer's disease.

As background, Bohr cites a hypercholesterolemic diet as protective of cognitive function in rats and a high cholesterol level's association in humans with lower mortality and a better outcome following a first stroke. He also points out that Alzheimer's patients have *lower* levels of cholesterol in serum, brain membranes, and in lipid rafts, and that Alzheimer's has been related to the downregulation of a gene involved in cholesterol synthesis.

Bohr's hypothesis is that APP plays a role in bringing in apolipoproteinE-enriched cholesterol into cells, which is a protective response to neuronal damage. Since AD pathology targets a type of nervous system receptor called "cholinergic receptors," and these receptors are cholesterol-dependent, as aging or other forms of stress damage the cholinergic receptors, the need for cholesterol in the brain is increased.

According to Bohr's hypothesis, a higher demand for cholesterol will cause APP metabolism to increase, and would result in greater beta-amyloid accumulation. The increased demand for cholesterol could be generated both by aging or other oxidative damage, or due to a deficiency in the ability to bring it into cells. One specific form of the gene for apolipoprotein E referred to as the epsilon-4 allele, for example, makes the brain less efficient at bringing cholesterol into its cells.

### SIDEBAR

Note: Dr. Alexei Koudinov, founder and editor of the scientific journal *Neurobiology of Lipids* has informed me of several articles in which a similar hypothesis was presented earlier. These will be reviewed and this article will be changed to properly credit Dr. Koudinov.

Is Bohr's hypothesis correct? More testing is needed. But one thing is clear: far from it being established that cholesterol causes Alzheimer's, the precise opposite may well just turn out to be true. If it is, depriving the brain of cholesterol through a low-fat, low-cholesterol diet or cholesterol-lowering drugs, could have the potential to make Alzheimer's disease *worse*.

## A Radical High-Fat Diet May Protect Against Alzheimer's

While many authors, contradicting all available scientific evidence, will advocate a "brain-healthy diet" as one that is low in fat and cholesterol, it is ironic that the one diet that has a substantial body of evidence showing its benefits to patients of neurological diseases is the low-fat diet's antithesis: the ketogenic diet.

In a 2003 review in *Nutrition Reviews*, Dr. Theodore B VanItallie and Thomas H Nufert outlined the history of the ketogenic diet, the evidence supporting its effectiveness, and the case for testing its possible therapeutic value for Parkinson's disease and Alzheimer's disease.

The ketogenic diet was first reported as effective in treating epilepsy in 1924, after it had been proposed three years earlier by Woodyat and Wilder of the famous Mayo Clinic. The ketogenic diet is, gram for gram, 80 percent fat, which results in a diet that supplies 90 percent of its calories as fat, five percent as carbohydrate, and five percent as protein.

The ketogenic diet causes a large increase in the circulation of ketones. Certain ketones protect neurons in the brain from excitotoxic effects, and they supply a more efficient form of energy to the brain than glucose, especially in certain neurological disorders, such as Alzheimer's, where glucose metabolism is impaired in the brain and localized insulin resistance has taken hold.

Among epileptic patients who adhere to the ketogenic diet, 40 percent experience greater than 90 percent reduction in seizures, and an additional 40 percent experience 50 to 90 percent reduction!

The ketogenic diet is difficult for patients to adhere to, but its therapeutic value is undeniable. It has been proven to be clinically effective, and research on the benefits of ketones to the brain has accumulated in the near-century since its first clinical use.

Conversely, there is no evidence to support any such dramatic clinical reversal of a neurological disease with a low-fat diet or low-cholesterol diet.

VanItallie and Nufert make the case that a ketogenic diet should be tried for therapeutic effectiveness in Alzheimer's disease: Alzheimer's has been linked to insulin resistance in the brain, and a ketogenic diet can restore metabolic efficiency in such cases. Most strikingly, the addition of beta-hydroxybutyrate, a ketone, to cell cultures protects them from harmful effects of beta-amyloid fragments.

Once again, not only are the recommendations of the cholesterol-Alzheimer's hypothesis not supported by science, but sound scientific research appears to support just the opposite: an extremely *high-fat* diet may be therapeutic in Alzheimer's disease.

## Concluding Remarks: Cholesterol, the Unsung Hero

While it is widely popular (and profitable) to blame Alzheimer's disease on cholesterol, and thereby advocate a low-fat, low-cholesterol diet to prevent Alzheimer's, and the use of statin drugs to prevent or treat Alzheimer's, the connection has been exposed as nothing more than myth.

The cholesterol-Alzheimer's hypothesis claims that high cholesterol causes the accumulation of beta-amyloid, and that the accumulation of beta-amyloid is the driving force behind all Alzheimer's-related pathology.

Yet cholesterol has not been conclusively linked to beta-amyloid, and some studies suggest an inverse correlation between the two. That beta-amyloid accumulation is the driving force behind Alzheimer's-related pathology has yet to be demonstrated, and is called into question by animal experiments that show many AD-related pathologies to take place independent of beta-amyloid.

In the midst of the anti-cholesterol hysteria, research continues to show that cholesterol is the most vital and important substance in our brains. It is cholesterol that allows our neurons to form synapses so that we can learn, remember, and think. Cholesterol appears to be important to the brain's reaction to nerve damage, and its most important role in Alzheimer's disease may be as a *protective* factor.

Cholesterol truly is the unsung hero of the brain.

## Just what *does* cause Alzheimer's?

So if cholesterol isn't the culprit, what is? Are there dietary measures we can take to protect ourselves? Are there lifestyle choices we can make to protect ourselves?

Yes. While cholesterol is not one of them, there are many factors in Alzheimer's, some of which are controllable, some of which are not, that have been demonstrated with varying degrees of conclusiveness by real science to play a central role.

# Myth: Cholesterol Causes Alzheimer's Disease

## Part II: The *Real* Causes of Alzheimer's Disease

by Chris Masterjohn Published August 5, 2005.

In Part I of this article, it was shown that the cause of Alzheimer's disease (AD) is not high cholesterol, contrary to a growing myth-- a myth that provides a great service to the producers of cholesterol-lowering drugs, but does very little to increase our understanding about the truth of Alzheimer's Disease.

So what *does* cause Alzheimer's disease? The truth is that there is more that we do *not* know than that we *do* know.

However, there has been a great deal of research on Alzheimer's that has uncovered genetic, dietary, environmental, and lifestyle factors that unquestionably play a role in causing Alzheimer's, and yield some practical steps we can take to protect ourselves from the disease.

Genetics plays a major contributing factor to the cause of Alzheimer's. Yet animal experiments show that the effect of certain AD-related genes can be modified by diet, and some of the most strongly related genes are only found in five percent of Alzheimer's patients.<sup>1</sup>

There is strong evidence that depletion of the omega-3 fatty acid DHA -- found in quality egg yolks, some fish, and [cod liver oil](#) -- is a primary causal factor in Alzheimer's-related pathology, and insulin resistance appears to also play a role, both of which are modifiable through diet.

Since DHA depletion occurs through, and itself also aggravates, a very high rate of oxidation in the brain, this suggests that dietary antioxidants would be helpful in preventing Alzheimer's. Taken together, it appears that eating a diet rich in traditional whole foods of both animal and plant origin, low in vegetable oils and excessive amounts of carbohydrates would strongly protect against Alzheimer's.

### Are Genetics the Cause of Alzheimer's?

There are many genes that have been studied in relation to Alzheimer's disease, but there are a few that stand out.

#### The ApoE4 Allele As the Cause of Alzheimer's

Apolipoprotein E (apoE) is an essential molecule to the brain that is involved in the transport of cholesterol and other lipids. There are several different forms of the gene for apoE, and one of them, epsilon-4, (apoE4) is correlated with Alzheimer's disease.

The epsilon-4 allele of apoE is very common. To date, meta-analysis from the [Alzheimer's Research Forum](#) shows that it is present in about 13 percent of the population, but 36 percent of the Alzheimer's population.

Although apoE4 occurs nearly three times as frequently in Alzheimer's populations than in the general population, neither one nor two copies of the allele is either necessary or sufficient to cause Alzheimer's disease.

Although beta-amyloid aggregation is higher in the presence of the epsilon-4 allele, that is not the end of the story.

When apoE4 is added to neurons in cell culture, isolated from any effects on or of beta-amyloid, it inhibits the growth of axons and dendrites, whereas the other forms of apoE enhance the growth of axons and dendrites, relative to a straight lipoprotein medium.

Why is this?

First, it is important to understand the significance of apoE in the brain.

In 1997, it was found that some factor in the secretion of glial cells, which grow alongside neurons, was responsible for the ability to form synapses, which are the connections between the axon of one neuron and the dendrites of another. For four years it remained unknown what this mystery "glial factor" was, but in 2001 it was identified as apoE-enriched cholesterol.

Without the glial secretion, neurons formed few and inefficient synapses. With it, they formed many efficient synapses. The measurements of the unknown factor matched apoE, which is responsible for transporting cholesterol and other lipids from glial cells to neurons.

But isolated ApoE did not have the effect of the mysterious and elusive "glial factor," nor did some of the non-cholesterol lipids it carried, which even proved toxic to neurons at high doses. Isolated *cholesterol*, on the other hand, *did*.

Exposing glial-deprived neurons to a solution of isolated cholesterol increased their synapse formation by *twelve times*. Producing a cholesterol-free glial secretion with a statin drug abolished the effect of the glial factor.

Thus, apoE's primary benefit to the nervous system appears to be its delivery of cholesterol to neurons, which is necessary for synapse formation.

Dr. Iwo Bohr has suggested that apoE4 is less able to efficiently deliver cholesterol to neurons, and that this characteristic contributes to its causal role in Alzheimer's disease.

Dr. Bohr cites Lane and Farlow, who observe that apoE4 is less efficient at transporting free fatty acids, and notes that apoE4 is associated with a higher level of cholesterol, which may indicate that cholesterol is not being internalized into cells efficiently.

Yet a 1998 study by Zhong-Sheng et al. appears, at least at first glance, to contradict this.

They compared the effect of apoE3 to that of apoE4 on neuronal cell culture, incubating both forms of apoE in beta- very low-density lipoprotein (beta-VLDL), and found that apoE4 was slightly *more* efficient at delivering cholesterol to cells, although apoE3, not its associated cholesterol, was retained within the cell at several times the amount that apoE4 was retained. This appeared to occur because apoE4 was quickly released from the cell, not because it was broken down within the cell.

Even still, apoE3 enhanced dendrite and axon growth, while apoE4 inhibited dendrite and axon growth.

This appears to suggest that while cholesterol is the limiting factor in the formation of *synapses*, internalized apoE might be the limiting factor in the initial *growth* of the axons and dendrites. It is unknown *why* there is a difference between the two forms of apoE in this matter, but there are several (speculative) possibilities:

- apoE or one of its breakdown products is needed by the cell to deliver cholesterol to lipid rafts in the membrane, which are known to be necessary signaling molecules involved in the growth of dendrites and axons (My suggestion)
- apoE is released into the cytosol (the inside of a cell) where it complexes with other proteins necessary for axon and dendrite growth (Suggested by Zhong-Sheng et al.)

It is important to be careful of drawing conclusions from this study. Since this study was *in vitro*-- using isolated cells rather than a living organism-- it utilized conditions that would not occur in a living organism. For example, both forms of apoE were only incubated with VLDL, and not other lipoproteins, such as chylomicrons, IDL, LDL, and HDL.

This, in fact, is *critical* to evaluating the observation of whether or not apoE4 is *less* or *more* efficient at delivering cholesterol to cells.

Lane and Farlow note that apoE4 has a preferential affinity to bind to high-triglyceride lipoproteins like chylomicrons and VLDL, as opposed to low-triglyceride lipoproteins such as LDL, IDL, and HDL. While they are making a different point, this observation bears an important corollary that has gone unnoticed:

- High-triglyceride lipoproteins are also *low-cholesterol* lipoproteins!

According to Figure 2.10 in Dr. Mary Enig's book, *Know Your Fats*, excluding HDL, there is an inverse relationship between cholesterol and triglyceride percentage of a lipoprotein. The following data is derived from this table, but excludes irrelevant information:

	Chylomicrons	VLDL	LDL	IDL
Triglyceride %	84-89	50-65	30	7-10
Cholesterol %	4-15	15-25	30	42-50

As you can see, apoE4, by binding to high-triglyceride lipoproteins, is also preferentially binding to *low-cholesterol* lipoproteins.

Thus, in a living organism, it appears that apoE4 is less effective than other forms of apoE at delivering cholesterol to cells because it prefers lipoproteins that have less cholesterol.

This is consistent with the observation that cholesterol levels are higher in people bearing the apoE4 allele, possibly due to deficient internalization of that cholesterol, and supports Dr. Bohr's hypothesis.

ApoE4 has other effects as well. It is less efficient at delivering DHA to neurons, the importance to Alzheimer's of which will be discussed below, and which may be related to its association with insulin resistance.

Is ApoE4 the "cause" of Alzheimer's? As Tanzi and Bertram note,<sup>1</sup> even carrying two copies of the allele is not sufficient to cause Alzheimer's, nor is carrying even one copy necessary to cause Alzheimer's. Therefore, there must be dietary and/or environmental (or other genetic) factors that interact with ApoE4's ability to contribute to the cause of Alzheimer's.

Lane and Farlow note that apoE4 has many of the same effects as a high-carbohydrate diet, and review evidence showing that apoE4 is least common in populations with a long history of agriculture, and most common in present hunter-gatherer populations, ranging from four percent in Israel to 40.7 percent among African Pygmies.

It may well be that apoE4 is only a harmful gene *if* it is accompanied by a high-carbohydrate diet that one's ancestors have not partially adapted to by weeding out the apoE4 gene.

## APP Mutations as the Cause of Alzheimer's

Since amyloid precursor protein (APP) is the precursor of beta-amyloid, one may intuitively jump to the conclusion that its role in Alzheimer's disease is primarily related to this particular function.

Yet a study, discussed below, by Takahishi et al. showed a very different problematic characteristic of a common APP-related mutation.

APP has many roles, and is both secreted from the cell and exists inside the cell. When APP is located inside the cell, it binds to an enzyme called heme oxygenase (HO).

HO protects cells by transporting iron, an oxidizing agent, out of the cells, and is also responsible for the production of bilirubin, which is an antioxidant with neuroprotective effects.

APP695, which is a mutant form of APP associated with familial Alzheimer's disease (FAD), has a significantly *greater* effect at inhibiting HO than the "regular" form of APP. This provides an explanation for how this mutation could contribute to Alzheimer's in addition to or even despite its relation to beta-amyloid.

As we will see below in the section on DHA, a high oxidation rate in the brain appears to contribute a much greater proportion to the cause of Alzheimer's disease than does the formation of amyloid plaques, through the massive oxidation and depletion of DHA, an essential fatty acid, and the proteins that form synapses. We will also see that harm done through this oxidation can be largely controlled through diet.

## Presenilin Mutations as the Cause of Alzheimer's Disease

Presenilins (PS), which include presenilin-1 (PS1) and presenilin-2, (PS2), are important to both the nervous system and the entire body for many different reasons. They also happen to be subunits of the gamma-secretase enzyme, which cleaves APP into beta-amyloid.

Therefore, mutations in the presenilins associated with Alzheimer's disease could be regarded as circumstantial evidence favoring the amyloid hypothesis.

Yet, it turns out that a more in-depth look at the relation of PS1 and PS2 to the neuropathology seen in Alzheimer's disease paints a very different picture.

Research into the possibility of using presenilin-inhibitors as drugs to treat Alzheimer's should be regarded as yet another nail in the coffin of the amyloid hypothesis, which, as Dr. Koudinov has tirelessly pointed out, is being supported by researchers who continually violate institutional standards in failing to disclose information about their conflicting financial interests.

The amyloid hypothesis would predict that inhibiting presenilins would, in turn, inhibit gamma-secretase-- which cleaves APP into beta-amyloid-- which would, then, decrease the production of beta-amyloid.

The amyloid hypothesis holds that decreased production will lead to decreased accumulation, and thus decreased formation of amyloid plaques. This would result in a decreased neurofibrillary tangles and the other characteristics of Alzheimer's that are all supposedly caused by beta-amyloid accumulation.

So, drugs that inhibit presenilins should be a prime candidate for Alzheimer's.

Yet a study by Marjaux et al. proved quite otherwise. Knocking out PS1 in mice specifically in the brain led to a decrease in beta-amyloid, along with *mild memory impairment*.

The absence of both PS1 and PS2 led to "strongly impaired LTP [long-term potentiation, necessary for memory], spatial and contextual memory deficits, and, after some time, massive loss of synapses, dendrites, and neurons. Remarkably, this neurodegeneration was accompanied by increased Tau phosphorylation . . ."

The increase in tau phosphorylation is "remarkable" because excessive tau phosphorylation is what leads to neurofibrillary tangles. The amyloid hypothesis would have predicted that decreasing beta-amyloid accumulation would *decrease* the chance of developing tangles, and prevent the neurodegeneration seen above, yet the precise opposite took place.

While this study does not necessarily show a causal role in a deficiency of beta-amyloid for the associated results, it certainly calls deeply into question whether beta-amyloid is the cause of Alzheimer's-related neurodegeneration that occurs in its *absence*.

However, it also cannot be ruled out that decreasing beta-amyloid was in itself harmful. Dr. Koudinov has reviewed studies showing positive effects of beta-amyloid, and showing that beta-amyloid corrects the neurodegenerative effects of cholesterol deficiency, and that this positive effect is abolished by cholesterol-lowering drugs.

Since the presenilins have so many important functions, it is likely that PS mutations related to Alzheimer's disease decrease the ability of PS to perform its important functions, which could possibly even include positive effects of beta-amyloid.

## Genetic Determinism?

The apoE4 allele is the most common among Alzheimer's patients, being present in about 36 percent of cases, yet it is neither sufficient nor necessary to cause Alzheimer's disease.

On the other hand, the mutations in APP, PS1, and PS2 are present in only five percent of AD cases. Although they account for only a small portion of Alzheimer's disease, Tanzi and Bertram regarded them as "fully penetrant" in a recent review, their presence guaranteeing the development of Alzheimer's disease.

Yet this should remain an open question. As will be discussed in the next section, the neurodegeneration in mice with APP mutations can be controlled dietarily. Since deficiencies of DHA and other dietary factors are nearly universal in modern societies due to changes not only in *what* we eat, but also how that food is produced, studies may be missing important environmental factors that regulate the expression of these genes simply because they are not varied in the populations we study.

Additionally, studies with rodents invariably come to the impossibility of reconciling the standard cereal-based lab chow with the fact that a single wild population of mice or rats that has invented agriculture has yet to be found.

## DHA-Depletion as the Cause of Alzheimer's

While the studies reviewed in Part I of this article that fed hypercholesterolemic diets to rodents, one inducing, the other decreasing, amyloid deposits, didn't bother to measure the *cognitive function* of the rodents, the story is different for DHA. And while the results of cholesterol-feeding have been contradictory, the story is again different for DHA.

Docosohexaenoic acid (DHA) is an omega-3 polyunsaturated fatty acid found in such foods as cod liver oil, fatty fish, and egg yolks from chickens raised on pasture. Considerable evidence of various kinds indicates that DHA deficiency plays a causal role in Alzheimer's disease.

## Human Evidence

Low dietary intake of DHA is a risk factor for Alzheimer's disease, and low serum levels are likewise correlated with occurrence of Alzheimer's as well as the degree of progression of dementia. Brain levels of DHA in the hippocampus are considerably deficient in patients with Alzheimer's disease. Additionally, supplementing with DHA improves memory in the elderly.

## Animal Evidence

Animal experiments demonstrate conclusively that both the pathological hallmarks of Alzheimer's disease as well as mental functioning can be modified in rodents by modifying dietary intake of DHA.

A 2004 study found that supplementing with DHA reversed the effects of beta-amyloid infusion on memory errors in an 8-arm radial maze. The study inserted an osmotic pump into the brains of these rats to allow a constant infusion of aggregated beta-amyloid to enter the brain in two groups of rats, one with DHA supplementation, the other without. A third group was fed DHA group but not given beta-amyloid infusion, and a fourth, control group had neither DHA supplementation nor beta-amyloid infusion.

Obviously conclusions from this study must be drawn hesitantly and conservatively, since there is no way to know how closely having an osmotic pump inserted into one's brain with a constant influx of beta-amyloid approximates natural conditions of Alzheimer's. It would have been interesting to have a control of another substance pumped into the brains of rats, to compare to the effect of aggregated beta-amyloid.

Nevertheless, not only did DHA protect from the effects of beta-amyloid infusion, but the DHA brain-pump group performed better on cognitive tests than even the control group!

One interesting point is that the beta-amyloid infusion only had reproducibly negative effects on cognitive impairment when aluminum chloride was added to the infusion, which causes beta-amyloid to aggregate.

Not only is this evidence *against* the claim of the amyloid hypotheses that amyloid plaques are merely the product of accumulation of beta-amyloid, but the fact that aluminum was being infused into the brains of these rats should raise a red flag to anyone eager to blame memory impairments on the beta-amyloid.

Of course, neither the aluminum used nor the fact that non-aggregated beta-amyloid had no reproducible effect were noted in the abstract.

### **SIDEBAR**

It's actually quite common for critical points to be left out of a summary (abstract). For example, an abstract might claim that a study found a correlation between animal fat intake and breast cancer, when the full text shows that the people who had ate the most animal fat had lower rates of breast cancer than people who ate more.

But an Associated Press reporter reads the abstract, and then a major newspaper writes a story based on the AP report, and then a journalist for a local newspaper or news program give you the story, having no idea what it actually found.

A 2005 study found that dietary DHA decreased the level of insoluble beta-amyloid and amyloid plaques, but did not influence the level of soluble beta-amyloid, and cognitive effects were not measured. It is particularly surprising that the authors referred to beta-amyloid as the "causal factor" in Alzheimer's disease when the level of soluble beta-amyloid was not associated with the degree of plaque in this study, and the same group of researchers published a study in 2004 showing DHA to regulate massive dendritic pathology by mechanisms that were independent of beta-amyloid!

The most enlightening animal study of DHA's relation to Alzheimer's was this 2004 study by the above authors.<sup>20</sup> In this study, they explicitly state that memory loss has a greater correlation with the degeneration of dendrites than it does with plaques or tangles.

In Alzheimer's disease, there is a 70-95 percent loss of debrin through oxidation, which is a protein that regulates another protein, actin, in the dendritic spine, and a 17 percent loss of another synaptic protein, synaptophysin.

Depleting mice that had a human APP-mutated gene associated with Alzheimer's disease (called "transgenic" mice) of dietary DHA caused an 85% loss of debrin, and a rapid depletion of brain DHA, which makes up 15 percent of the brain and concentrates at synapses.

DHA also caused the cleavage of actin into fractin, which is associated with Alzheimer's pathology. Supplementing the diet restored entirely both the debrin and actin, and restored the brain DHA level.

DHA-depletion also caused learning deficits in the mice with the AD-related gene, as measured in a water maze, which was restored by adding DHA back into the diet. Mice without the AD-related gene did not have such a high depletion rate of brain DHA levels nor the other pathology.

The authors noted that DHA-depletion also caused the loss of a subunit of an enzyme called P13-kinase, which is involved in insulin signaling, the dysfunction of which has been associated with Alzheimer's disease.

Beyond a certain aging point, the transgenic mice began to develop some cognitive defects even when fed DHA. The authors rightly pointed out that it is unknown whether earlier intervention with DHA during development may have had a more profound effect.

It should also have been noted that, in a disease notably related to insulin resistance, to which a cereal-based diet could contribute both through an autoimmune mechanism and through a supply of excessive carbohydrates, similar experiments should be performed that attempt to approximate a diet natural to a wild member of the species.

In any case, it is quite clear from both human and animal studies that DHA-deficiency contributes to at least a portion of the cause of Alzheimer's, and that modifying it dietarily modifies the pathology of Alzheimer's.

## Insulin Resistance as the Cause of Alzheimer's Disease

Considerable evidence indicates that insulin resistance plays a role in the development of Alzheimer's disease. Insulin is responsible for bringing glucose into cells, and prolonged, chronic, high levels of insulin can lead to insulin resistance, where insulin is incapable of exerting its effect on cells.

### Human Evidence

Type 2 diabetes is characterized by insulin resistance. Population studies indicate that Type 2 diabetics have two to three times the risk of Alzheimer's disease as the general population.

In a commentary in *The Lancet*, Mark Strachan reviewed research showing that, on the one hand, insulin has a profound effect improving memory, and on the other, high blood levels of insulin are associated with increased memory *decline*.

This indicates that insulin resistance leads to cognitive dysfunction because of insulin's inability to carry out its proper function.

It has been hypothesized that high-carbohydrate diets could lead to Alzheimer's disease through chronic over-exposure of cells to insulin signaling, which accelerates cellular damage in cerebral neurons, and can cause insulin resistance.

Indeed, this is highly suggested by the frequency of AD-related genes across different populations. The apoE4 allele, for example, is nearly three times more frequent among Alzheimer's populations than the general population, yet this gene appears to be selected against by populations with a long history of high-carbohydrate diets. The following table shows the frequency of the apoE4 allele in various populations, with data supplied by a review by Lane and Farlow.

#### **Agriculturalists Hunter-gatherers**

Greek 6.8% African Pygmies 40.7%  
Turks 7.9% Papuans 36.8%  
Mayans 8.9% Inuits 21.4%  
Arabs in  
Northern Israel 4%

As can be seen above, and as pointed out by Lane and Farlow, the lowest frequencies of the apoE4 allele are found in populations with a long history of agriculture, and the highest frequencies are found in long-time hunter-gatherer populations.

High-carbohydrate diets and the apoE4 allele alike share many problematic characteristics including the depression of lipid metabolism. It appears that the combination of a high-carbohydrate and the apoE4 allele leads to disastrous health consequences not limited to Alzheimer's.

In consequence, populations with a long history of agriculture have successfully weeded out the gene-- through a history of carbohydrate-induced fatal disease-- while individuals in modern societies disconnected from the pattern in which their ancestors have traditionally eaten are now succumbing to these diseases because of these dietary factors.

## Animal Evidence

Animal experiments verify a role for insulin resistance as a contributing cause of Alzheimer's disease. A 2004 study found that diet-induced insulin resistance in mice with an AD-related APP mutation caused a decrease in the P13-kinase enzyme, which also occurs under DHA-depletion (discussed earlier), increased amyloid plaque burden, and caused impairment of performance in a water maze. Interestingly, the insulin resistance also caused a relationship to appear between gamma-secretase activity (which forms beta-amyloid) and AD-related pathology, which seems to indicate that it is *insulin resistance* that might cause beta-amyloid to become harmful.

Another 2004 study found that mice with the same gene mutation were inherently insulin-resistant, at least on the diet they were fed. By eight months the transgenic mice (the mice who contained the human APP mutation) demonstrated poor glucose tolerance, and by thirteen months they became hyperinsulinemic. This result was avoided by a drug that increases insulin sensitivity.

Oddly, the authors of the first study claim to have induced insulin resistance with a high-fat (60 percent), low-carbohydrate (20 percent) diet. This is interesting, because in the second study, insulin resistance developed on the standard diet, which, according to macronutrient data on Dyet Inc.'s website is a low-fat (15 percent), high-carb (65 percent) diet.

Additionally, the website of the supplier of the diets in the first study, Research Diets Inc., even claims itself that its high-*carbohydrate* diet is used to induce insulin resistance. The induction of insulin resistance by a high fat diet could be an aberration caused by the particular strain of mice.

Or, it could be a result of the fact that the fats in the diet are processed by extrusion into pellets, which is a high-pressure, high-heat process that would cause major damage to the unsaturated fats with toxic byproducts, possibly including trace amounts of trans fats, which are known to contribute to insulin resistance.

Additionally, that apoE4 is seen less often in agricultural societies than hunter-gatherer societies indicates that it is the high-carbohydrate diets made possible by agriculture that are the culprit, rather than high-fat diets. Evidence also suggests that extremely high-fat, ketogenic diets would be beneficial to Alzheimer's.

It must be emphasized that the healthful alternative to a high-carbohydrate diet that improves insulin sensitivity is *not* a high-*protein* diet. A high-protein diet is metabolically similar to a high-carbohydrate diet because nearly half of the amino acids in most protein foods are glucogenic, meaning they convert readily to glucose, which is sugar. The healthful alternative is a high-*fat* diet.

It has been a great disservice to public understanding that diets such as the Atkins diet are referred to as "high-protein," when such diets, properly done, are high-fat diets. The attempt of many ill-informed consumers to try to do low-carb diets *and* low-fat diets at the same time has no doubt led to many negative health effects as the result of excessive protein consumption.

## Oxidation as a Cause of Alzheimer's Disease

Thus far in this article we've seen that oxidative damage in the brain is a central feature of Alzheimer's disease. For example, the APP695 mutation discussed above decreases anti-oxidant activity in the brain, and DHA-depletion, also discussed above, causes massive oxidation of important synaptic proteins.

As Lane and Farlow point out, low intake of antioxidants is a risk factor for Alzheimer's disease, one population study found that cholesterol is only a major risk factor for Alzheimer's disease if it is accompanied by high transferrin, which transports iron, an oxidative agent, and Alzheimer's disease is characterized by a higher rate of oxidation in the brain.<sup>36</sup>

Since oxidative damage is determined by:

- a low antioxidant status
- a high consumption of oxygen
- a low capacity for regeneration<sup>6</sup>

it would be a sensible precaution against Alzheimer's disease to increase antioxidant consumption and to decrease excess consumption of easily oxidized substances. This translates to an increased intake of fresh, unrefined, unprocessed fruits and vegetables, avoiding excessive cooking, which destroys anti-oxidants, and decreasing intake of polyunsaturated fat.

While DHA, a polyunsaturated fat, is protective, it is also true that DHA is only one of many polyunsaturated fats, and that modern diets tend to be deficient in DHA while being enormously excessive in other polyunsaturated fats from vegetable oils.

Polyunsaturated fats contain many double-bonds, which are targets for oxidation, whereas monounsaturated fats contain only one double bond, and saturated fats contain no double bonds.

Therefore, a prudent, anti-oxidative diet should include a high saturated fat to unsaturated fat ratio, and a minimum of polyunsaturated fat, providing it is sufficient in DHA.

## Other Causes of Alzheimer's Disease

There is much more to be known about Alzheimer's than we know now. However, research increasingly is implicating other factors in Alzheimer's disease, including the accumulation of toxic metals in the brain and excitotoxicity (the death of neurons by excessive excitation) of glutamate.

These factors also interact with genetics, since apoE is responsible for sequestering heavy metals in the brain as well as protecting against the excitotoxic effect of glutamate, while apoE4 is less efficient at both than other forms of apoE.

However, since both of these factors are highly regulated in the body by complex mechanisms, more research needs to be done to determine exactly what dietary and environmental risks are. Still, it makes sense to take reasonable precautions by avoiding exposure to aluminum and other heavy metals, and avoiding intake of MSG, a source of excitotoxic glutamate.

Another factor may be engagement in stimulating activity. In a 2002 study reported in the Journal of the American Medical Association, it was found that, after adjusting for age, sex, and education, a 1-point increase on a test of cognitive activity translated to a 33 percent reduction in the risk of Alzheimer's disease. This suggests that another protective measure we can take is to simply stay active: read, write, listen to music, and so on.

Although, it seems possible that this could be a reflection of decreased cognitive activity in people predisposed to Alzheimer's. And thus, it becomes a chicken-and-egg problem. Nevertheless, engaging in stimulating activity is clearly a positive thing to do regardless, and could in fact be protective.

Finally, Dr. Kilmer McCully, who did ground-breaking and revolutionary work connecting a protein-derivative, homocysteine, to heart disease, has informed me that there is a growing interest in the relationship between homocysteine and Alzheimer's.

Elevated homocysteine levels are associated with Alzheimer's. Homocysteine levels become elevated through a deficiency of B vitamins, largely a result of modern processing of vegetables and the disappearance of liver from the modern menu.

## Conclusions: Causes of Alzheimer's Disease

Even though many are advocating a low-cholesterol, low-fat diet to prevent Alzheimer's, based on the dubious notion that cholesterol causes beta-amyloid accumulation, which, in turn, causes Alzheimer's disease, the use of this deceptive and out-dated model shouldn't prevent us from taking real, science-based precautions against Alzheimer's disease.

It appears highly evident that DHA-depletion, insulin resistance, increased oxidation, and perhaps activity levels and homocysteine levels, are all controllable factors that are partial causes in the development of Alzheimer's disease.

Genetics plays a factor, but genes are clearly only part of the picture. It makes sense to increase our consumption of fresh fruits and vegetables, saturated fats, and sources of DHA such as egg yolks from pastured chickens and cod liver oil, and to decrease our consumption of carbohydrates and most polyunsaturated fatty acids. A high-fat diet may help by preventing insulin resistance and by contributing neuro-protective ketone bodies as well.

Medium-chain triglycerides (MCTs) are also effective in increasing ketone bodies regardless of other dietary factors, so the addition of coconut oil to the diet, the best food source of MCTs, might also be a protective factor.

Naturally, avoiding processed foods or cooking materials that contain metals like aluminum and excitotoxins like MSG are also reasonable precautionary measures.

And lastly, staying active appears to protect against Alzheimer's, reminiscent of the old adage, "use it or lose it."

In addition to fish and fish oils, DHA is available from pasture-raised animal products. Since modern supermarkets usually do not contain such beneficial foods, local farms are often the best way to procure them. [EatWild.com](http://EatWild.com) will help you find sources of pasture-fed animal products in your area. And our page on liver and cod liver oil will assist you in finding the highest quality cod liver oil.

Cholesterol is not the cause of Alzheimer's disease. But, given it's relation to mental performance, a lack of it may contribute to the maintenance of outdated and thoroughly refuted scientific theories.