A R T I C L E

Cholesterol, longevity, intelligence, and health.

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The biological meaning of cholesterol is just starting to be explored.
Everything that doctors know about cholesterol is wrong.
New information about cholesterol is clarifying important issues in physiology and pathology.

Medical magazines and television stations like to propagate the idea that cholesterol is bad stuff, and as a result, that cliche is known to almost every American. Recent journal articles have promoted the idea that "the lower the serum cholesterol is, the better" it is for the health of the patient.

The theory that heart disease is "caused by cholesterol" has gone through several stages, and most recently the use of the "statin" drugs has revived it in a radical way. One consistent theme for fifty years has been that people should eat more polyunsaturated fat and less saturated fat, to lower their cholesterol, and to avoid butter, cream, eggs, and "red meat," because they contain both saturated fat and cholesterol. Often, medical attention is focused on the fats in the atheroma, rather than on the whole disease process, including clotting factors, vascular spasms, heart rhythm, viscosity of the blood, deposition of calcium and iron in blood vessels, and the whole process of inflammation, including the reactions to absorbed bowel toxins.

Almost 100 years ago, some experiments in Russia showed that feeding rabbits cholesterol caused them to develop atherosclerosis, but subsequent experiments showed that rabbits are unusual in responding that way to cholesterol, and that even rabbits don't develop atherosclerosis from cholesterol if they are given a supplement of thyroid (Friedland, 1933). By 1936, it was clear that hypercholesterolemia in humans and other animals was caused by hypothyroidism, and that hypothyroidism caused many diseases to develop, including cardiovascular disease and cancer. There was already more reason at that time to think that the increased cholesterol was a protective adaptation than to think that it was maladaptive.

The strange idea that cholesterol causes atherosclerosis was revived in the 1950s when the vegetable oil industry learned that their polyunsaturated oils lowered serum cholesterol. (Many other toxins lower cholesterol, but that is never mentioned.) The industry began advertising their oils as "heart protective," and they enlisted some influential organizations to help in their advertising**:** The American Dietetic Association, the American Heart Association, the US Dept. of Agriculture and FDA, and the AMA. Besides the early rabbit research, which didn't make their case against cholesterol and might actually have had implications harmful to their argument (since Anitschkow had used vegetable oil as solvent for his cholesterol feedings), the oil industry helped to create and promote a large amount of fraudulent and unscientific work.

The death rate from heart disease in the United States began increasing early in the twentieth century, and it reached its peak from about 1950 to 1975, and then began declining. During the decades in which the death rate was rising, consumption of animal fat was decreasing, and the use of vegetable oil was increasing. In the southern European countries that have been said to show that eating very little animal fat prevents heart disease, the trends after the second world war have been the opposite--they have been eating more animal fat without an increase in heart disease.

The correspondence between heart disease and consumption of saturated fat and cholesterol is little more than advertising copy. If

people were looking for the actual causes of heart disease, they would consider the factors that changed in the US during the time that heart disease mortality was increasing. Both increases in harmful factors, and decreases in protective factors would have to be considered.

The consumption of manufactured foods, pollution of air and water, the use of lead in gasoline, cigarette smoking, increased medicalization and use of drugs, psychosocial and socioeconomic stress, and increased exposure to radiation--medical, military, and industrial--would be obvious things to consider, along with decreased intake of some protective nutrients, such as selenium, magnesium, and vitamins.

But those harmful factors all had their defenders**:** Who defends socioeconomic stress? All of the social institutions that fail to alleviate it. In 1847, Rudolph Virchow was sent to Poland to study the health situation there, and when he returned, the highly regarded anatomist, physiologist and pathologist announced that the Poles wouldn't have a health problem if the government would stop oppressing them, and institute economic reforms to alleviate their poverty. The reforms weren't made, and Virchow lost his job. Other harmful factors, such as seed oils, degraded foods, and radiation, have specific, very well organized and powerful lobbies to defend them.

Despite the growing knowledge about the dangers of polyunsaturated fats, many medical articles are still advocating the "official" heart protective diet (e.g., "**...** diets using nonhydrogenated unsaturated fats as the predominant form of dietary fat," Hu and Willet, 2002).

Some dogs alertly look at the thing a person is pointing at, other dogs just sniff the pointing finger. The publicists who disregard the complete nutritional and ecological situation, to focus on cholesterol and fat in the diet, are like the finger sniffers.

Recent articles in the medical and lipids journals are praising the 1950 work of J. W. Gofman, and the 1914 rabbit studies of N. N. Anitschkow, as the research that revealed cholesterol to be the cause of heart disease. Anitschkow and his co-workers, however, understood that their experiment hadn't explained human heart disease, and John Gofman, about 50 years after publishing his work on the lipoproteins, has done some large studies that could be crucial in disproving the doctrine that has become almost a national religion.

He has shown that mortality from both heart disease and cancer corresponds very closely to the population's exposure to medical services, and specifically to medical radiation. During the peak years of heart disease mortality, medical x-rays gave very large doses of radiation with each exposure, and the population was also exposed to radioactive fallout from atomic bomb testing (explosions from 1945 to 1963 produced a peak of heavy fallout that persisted through the 'sixties and into the 'seventies).

Around 1971, someone noticed that the commercial cholesterol being used in feeding experiments was oxidized, that is, it wasn't really cholesterol. Comparing carefully prepared, unoxidized cholesterol with the oxidized degraded material, it was found that dietary cholesterol wasn't necessarily atherogenic (Vine, et al., 1998).

Dietitians often recommend eating poached salmon, rather than "red meat," to lower cholesterol. Experimenters have measured the toxic oxidized cholesterol in different foods prepared in a variety of ways. Steaming salmon produced several times as much oxidized cholesterol as frying it, because of the longer cooking time that allowed the polyunsaturated fatty acids to break down, producing toxins such as acrolein and free radicals that oxidize the cholesterol and other components of the fish. The toxic cholesterol content of the steamed salmon was much higher than that of beef cooked at a high temperature.

When oxidized polyunsaturated oils, such as corn oil or linoleic acid, are added to food, they appear in the blood lipids, where they accelerate the formation of cholesterol deposits in arteries (Staprans, et al., 1994, 1996).

Stress accelerates the oxidation of the polyunsaturated fatty acids in the body, so people who consume unsaturated vegetable oils and fish will

have some oxidized cholesterol in their tissues. The constant turnover of cholesterol in the tissues tends to lower the proportion of the toxic oxidized degradation products of cholesterol, but in hypothyroidism, the use of cholesterol is slowed, allowing the toxic forms to accumulate.

Many antioxidant nutrients act like a thyroid supplement did in the 1934 rabbit experiments, preventing atherosclerosis even when extra toxic cholesterol is given to the animals. People who eat seafood get much more selenium in their diet than people who eat nothing from the sea, and selenium is one of the extremely protective nutrients that prevent atherosclerosis in animal experiments with excess cholesterol.

It is well established that several antioxidant nutrients are protective factors in heart disease. The medical establishment has expended a great amount of money and time in the last 60 years fighting the use of vitamin E or selenium for treating or preventing heart disease, though many physicians now take vitamin E themselves. But people who study free radical chemistry recognize that polyunsaturated fats are highly susceptible to oxidation, and that saturated fats tend to slow their degradation, acting to some extent as antioxidants. Several experiments and observations have shown that cholesterol itself can protect against damaging oxidation of polyunsaturated fats, protecting DNA and other vital components of the cell. A consistent program to prevent the oxidation of cholesterol would have to include all of the vitamins and minerals that are involved in antioxidant defense, avoidance of nutrients that exacerbate the destructive oxidations, and an effort to normalize the hormones and other factors, such as carbon dioxide, that have protective effects against free radical oxidation. A low level of cholesterol might increase susceptibility to the oxidants.

The steroids in general, especially those produced in large amounts, progesterone and DHEA, are important parts of the antioxidant defenses. Cholesterol, either that produced internally by the cell, or taken in from the blood stream, is the precursor for all the steroids in the body. Several of the major steroid hormones are antiinflammatory, and cholesterol itself is antiinflammatory. (Mikko, et al., 2002; Kreines, et al., 1990). Cholesterol also protects against radiation damage, and many forms of toxin (saponins, cobra venom, chloroform--W.G. MacCallum, *A Text-book of Pathology,* 1937, Saunders Co.; many more recent studies show that it protects blood cells against hemolysis--breakdown of red blood cells--caused by heat and other harmful agents; e.g., Dumas, et al., 2002, Velardi, et al., 1991). Cholesterol, vitamin E, progesterone, and vitamin D are considered to be "structural antioxidants," that prevent oxidation partly by stabilizing molecular structures. One of the basic functions of cholesterol seems to be the stabilization of mitochondria, preventing their destruction by stress. Serious stress lowers ATP, magnesium, and carbon dioxide. When ATP and intracellular magnesium are decreased, cholesterol synthesis increases.

During stress, free fatty acids are released from the tissues, and circulating in the bloodstream they are highly susceptible to oxidation. They contribute to the formation of the age pigment, lipofuscin, which is an oxygen-wasting substance that's found in the atheroma plaques in the damaged blood vessels. Iron and calcium accumulation adds to the tissue damage.

The hemolysis which is promoted by polyunsaturated fats and an imbalance of antioxidants and oxidants, releases iron and heme into the blood stream. The incidence of atherosclerosis is increased when the body iron stores are high (Kiechl, et al., 1997), probably because of its role in lipid peroxidation and lipofuscin formation.

Especially when the lining of the blood vessel is too permeable, because of the influence of polyunsaturated fats, prostaglandins, estrogen, etc., the heme and iron will enter the endothelial cells, where the iron will catalyze the formation of free radicals, and the heme will be broken down by the enzyme heme oxygenase, into biliverdin, iron, and carbon monoxide, which can contribute to the oxidative stress of the cells. Carbon monoxide makes the blood vessel lining more permeable, allowing fats and fibrinogen to enter the cells (Allen, et al., 1988).

Although cholesterol is protective against oxidative and cytolytic damage, the chronic free radical exposure will oxidize it. During the low cholesterol turnover of hypothyroidism, the oxidized variants of cholesterol will accumulate, so cholesterol loses its protective functions.

When the metabolic pathways of the steroid hormones were being worked out, an experimenter perfused an isolated ovary with blood. When the amount of cholesterol in the blood pumped into the ovary was increased, the amount of progesterone in the blood leaving the ovary increased proportionately. In the healthy organism, cholesterol is constantly being synthesized, and constantly converted into steroid hormones, and, in the liver, into the bile salts that are secreted to emulsify fats in the intestine. Thyroid hormone and vitamin A are used in the process of converting cholesterol into pregnenolone, the immediate precursor of progesterone and DHEA. Anything that interfered with these processes would be disastrous for the organism. The supply of cholesterol, thyroid and vitamin A must always be adequate for the production of steroid hormones and bile salts. When stress suppresses thyroid activity, increased cholesterol probably compensates to some extent by permitting more progesterone to be synthesized.

In very young people, the metabolic rate is very high, and the rapid conversion of cholesterol into pregnenolone, DHEA, and progesterone usually keeps the level of cholesterol in the blood low. In the 1930s, a rise in the concentration of cholesterol was considered to be one of the most reliable ways to diagnose hypothyroidism (*1936 Yearbook of Neurology, Psychiatry, and Endocrinology,* E.L. Sevringhaus, editor, Chicago, p. 533). With aging, the metabolic rate declines, and the increase of cholesterol with aging is probably a spontaneous regulatory process, supporting the synthesis of the protective steroids, especially the neurosteroids in the brain and retina.

Many people refer to the structural importance of cholesterol for "membranes," and often imply that the membranes are just at the surface of the cell (the plasma membrane). But in fact cholesterol is found in the nucleus in the chromosomes, bound to DNA and in the nuclear matrix that governs the activation of genes, and in the mitotic spindle, which regulates separation of the chromosomes during cell division**:** without sufficient cholesterol, cells divide irregularly, producing aneuploid daughter cells (i.e., they have an abnormal number of chromosomes). Aneuploidy is now coming to be recognized as an essential feature of cancer cells. A significant amount of cholesterol was recently discovered to bind to hemoglobin, suggesting that it will be found in association with many other types of protein, when it occurs to anyone to look for it. Osmotic regulation, which is closely involved in cell division and other functions, appears to require cholesterol synthesis.

Around 1985, a big study in Hungary showed that lowering cholesterol with drugs caused a huge increase in the cancer death rate. Hundreds of publications appeared in the U.S. saying that wasn't possible, because low cholesterol is good, the lower the better. The extreme increase in cancer mortality in the Hungarian study was probably the result of the drug that was commonly used at that time to lower cholesterol, but the pattern of mortality in that study was approximately the same pattern seen in any group with very low cholesterol. In the last 20 years, there have been many studies showing that lowering cholesterol increases mortality, especially from cancer and suicide, and that people with naturally low cholesterol are more likely to die from cancer, suicide, trauma, and infections than people with normal or higher than average cholesterol.

The increased mortality from accidents and suicide when cholesterol is lowered is reminiscent of the problems seen in progesterone deficiency, and it's very likely that a deficiency of the neurosteroids accounts for it. A deficiency of progesterone and other neurosteroids (the steroids synthesized by the nerves themselves) causes depression of mood and impaired learning ability, among other neurological changes. As was the case with cancer, the pharmaceutical industry continues to deny that their anticholesterol drugs cause suicide, depression, and dementia, but there is a large amount of evidence from human as well as animal studies showing that mood and intelligence are depressed by lowering cholesterol. Simply injecting cholesterol into animals can improve their learning ability. In the Framingham heart study of 1894 people extending over a period of about 20 years, people with cholesterol naturally in the "desirable" range, below 200 mg.%, scored lower on "verbal fluency, attention/concentration, abstract reasoning, and a composite score measuring multiple cognitive domains" than those with higher cholesterol (Elias, et al., 2005).

After the age of fifty, low cholesterol is clearly associated with an increased risk of dying from a variety of causes. A study of old women indicated that a cholesterol level of 270 mg. per 100 ml. was associated with the best longevity (Forette, et al., 1989). "Mortality was lowest at serum cholesterol 7.0 mmol/l [=270.6 mg%], 5.2 times higher than the minimum at serum cholesterol 4.0 mmol/l, and only 1.8 times higher when cholesterol concentration was 8.8 mmol/l. This relation held true irrespective of age, even when blood pressure, body weight, history of myocardial infarction, creatinine clearance, and plasma proteins were taken into account."

The next step in studies of this sort should be to see how the combination of extra thyroid with adequate cholesterol influences longevity. The rising cholesterol that commonly occurs with aging is probably only partial compensation for declining thyroid function, and by optimizing all of the protective factors, radical changes in the aging process may be possible.

In the roundworm C. elegans, which is now a very popular animal for testing aging theories, because its genes and cells have been thoroughly "mapped," it was recently found that adding a gene that simply allows it to synthesize cholesterol, rather than depending on food for its sterols, increased its life span by as much as 131% (Lee, et al., 2005). That would be like increasing the human lifespan to about 175 years. These worms are also more resistant than normal to radiation and heat stress.

The cells of the thymus are extremely sensitive to radiation and other stressors, and their enrichment with cholesterol inhibits lipid peroxidation, DNA degradation, and death in response to radiation (Posokhov, et al., 1992).

Many high altitude regions of the world have high levels of background radiation, from minerals as well as cosmic rays, so it has been dogmatically believed that mortality from cancer and heart disease would increase with altitude, but the reverse is true. Because oxygen at lower pressure displaces less carbon dioxide from the blood, the body is able to retain more carbon dioxide at high altitude. Carbon dioxide protects against free radicals, and also helps to deliver oxygen to tissues, to maintain efficient energy production, and to prevent cellular stress. One study found 18 times higher incidence of hypertension in low altitude populations than in high altitude people (Fiori, et al., 2000). For many years, these principles have been applied in treating atherosclerosis and other degenerative diseases, in high altitude health resorts. Even a short period of hypoxic treatment can improve the body's ability to eliminate atherogenic lipid peroxides, possibly by improving the stress-resistant functions of the liver (Meerson, et al., 1988; Aleshin, et al., 1993; Kitaev, et al., 1999).

I think editors of medical journals generally see themselves as the purveyors of enlightenment, i.e., as the pushers of the stylish and prestigious doctrines. (Selectivity of evidence to serve the received doctrine is the commonest form of scientific dishonesty.) But because their mental framework is culturally narrow, they sometimes publish things which later could turn out to be embarrassing (if inconsistency could embarrass such types).

The recent discovery that the size of the LDL particle is a predominant factor in the development of atherosclerosis is one of those things that the editors and medical professors should find embarrassing.

Smaller lipoprotein particles have a greater surface area exposed to the oxidative factors in the serum, and so are more rapidly degraded into toxic substances. People with larger LDL particles are remarkably resistant to heart disease, and the drug companies are looking for a way to turn their lipoproteins into products. But the conditions that govern the size of the LDL particles are physically and chemically reasonable, and are causing confusion among the doctinaire.

There have been several studies in India showing that consumption of butter and ghee is associated with a low incidence of heart disease; for example, according to one study, people in the north eat 19 times more fat (mostly butter and ghee) than in the south, yet the incidence of heart disease is seven times higher in the south. A study in Sweden found that the fatty acids in milk products are associated with larger LDL particles (Sjogren, et al., 2004).

In a 35 day study, when butter (20% of the calories) was compared to various kinds of margarine (with more trans fatty acids) in a similar quantity, the LDL particles were bigger on the butter diet (Mauger, et al., 2003). But in a study of the habitual diet of 414 people, large LDL particles were found to be correlated with increased intake of protein, animal fat, and trans fatty acids (Kim and Campos, 2003).

In a study of the effect of dietary cholesterol on the atherogenicity of the blood lipids, 52 people were given either an egg diet (with 640 mg. of extra cholesterol per day) or a placebo diet for 30 days. Those whose LDL increased the most on the high cholesterol diet had the largest LDL particle size (Herron, et al., 2004). They concluded that "these data indicate that the consumption of a high-cholesterol diet does not negatively influence the atherogenicity of the LDL particle." A similar study in Mexico found that "Intake of 2 eggs/d results in the maintenance of LDL:HDL and in the generation of a less atherogenic LDL in this population of Mexican children" (Ballesteros, et al., 2004).

The estrogen industry tried to get into the heart disease business several times over the last half century, and they are still trying, but the issue of estrogen's harmful effects on LDL particle size is getting some attention. Estrogen clearly decreases the size of the LDL particles (Campos, et al., 1997). The LDL particles also get smaller at menopause, and in polycystic ovary syndrome, and in preeclamptic pregnancies, all of which involve a low ratio of progesterone to estrogen. But there are still journals publishing claims that estrogen will protect against heart disease, by reducing the atherogenic response in increasingly mysterious ways. Occasionally, people have argued not only that estrogen is the factor that protects women against heart attacks, but that androgens predispose men to heart disease. One of their arguments has been that androgens lower HDL, the "good" form of cholesterol. However, there are many studies that show that testosterone and DHEA (Arad, et al., 1989) are protective against atherosclerosis. The LDL particle size is increased by androgens, and postprandial triglyceridemia is decreased (Hislop, et al., 2001).

The studies in the 1930s that showed the protective effects of thyroid hormone against atherosclerosis and heart disease have sometimes been interpreted to mean that the thyroid is protective ***because*** it lowers the cholesterol, but since cholesterol is protective, rather than harmful, something else explains the protective effect. Ever since the time of Virchow, who called atherosclerosis ***arteritis deformans,*** the inflammatory nature of the problem has been clear to those who aren't crazed by the anticholesterol cult. We are all subject to a variable degree of inflammatory stimulation from the endotoxin absorbed from the intestine, but a healthy liver normally prevents it from reaching the general circulation, and produces a variety of protective factors. The HDL lipoprotein is one of these, which protects against inflammation by binding bacterial endotoxins that have reached the bloodstream. (Things that increase absorption of endotoxin--exercise, estrogen, ethanol--cause HDL to rise.) Chylomicrons and VLDL also absorb, bind, and help to eliminate endotoxins. All sorts of stress and malnutrition increase the tendency of endotoxin to leak into the bloodstream. Thyroid hormone, by increasing the turnover of cholesterol and its conversion into the protective steroids, is a major factor in keeping the inflammatory processes under control.

In hypothyroidism, the pituitary secretes more TSH to activate the thyroid gland, but TSH itself has a variety of pro-inflammatory actions. The C-reactive protein (CRP), which is recognized as a factor contributing to atherosclerosis, is increased in association with TSH. CRP activates mast cells, which are found in the atheroma plaques, to produce a variety of pro-inflammatory substances, including histamine.

The belief that cells are controlled by a plasma membrane, and that cholesterol's main function is to participate in that membrane, has led to a culture that treats cholesterol physiology with little curiosity. A different perspective on the cell starts with a recognition of the lipophilic nature of the structural proteins (not "membrane proteins," but things like cytoskeleton-cytoplasmic ground substance, spindle, centrosome-centrioles, nuclear matrix, etc.), with which lipids interact. Modifying an extremely complex system, the living substance, cholesterol participates in complexity, and must be investigated with subtlety. I suspect that the

physiological meaning of cholesterol has to do with movement, stability, differentiation, memory, and sensitivity of the parts of the cells, that is, with everything physiological.

The functions of cholesterol parallel the functions of other sterols in plants and other types of organism. Its functions have been refined and extended with the development of other steroids, such as progesterone, as biological requirements have evolved, but cholesterol is still at the center of this system. To deliberately interfere with its synthesis, as contemporary medicine does, reveals a terrible arrogance.

Many participants in the cholesterol-lowering cult believe that they have succeeded in hijacking our science culture, but when the patents on another generation of their drugs have expired, the cult could begin to fade away.

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