Ray Peat's Newsletter

"Twenty morons at the right places can kill a science." **Erwin Chargaff quoted by Gilbert Ling***

Cholesterol in Context: Part I

I decided to write about cholesterol again because the US government and most medical doctors continue to say absurd things about it. Individuals can protect themselves by refusing to swallow their toxic misinformation, but our common environment is being degraded in many ways by the consequences of this massive deception.

It's useful to know something of the forces that have gone into creating the cholesterol demon of popular culture, but the essential thing is to recover the main line of investigation of cholesterol's role in the development of life and consciousness.

Several people in the 1930s and '40s showed that hypothyroidism caused atherosclerosis, and that thyroid supplementation corrected it. In people whose thyroid gland was removed, their serum cholesterol increased as their rate of metabolism slowed, and when they were given desiccated thyroid to normalize their metabolic rate, their serum cholesterol was immediately correspondingly normalized. In the early 1930s, Broda Barnes showed that heart disease developed in hypothyroid people, not in people whose metabolism was properly maintained by the thyroid hormone.

Later, many experimenters, building on older observations, showed that the rising cholesterol had a defensive function. For example, when the amount of cholesterol flowing into an ovarian artery was increased, the amount of progesterone flowing out of an ovarian vein increased proportionally, as the raw material was converted to the product. A major function of the thyroid hormone is the conversion of cholesterol into steroid hormones, including the "bile salts," but that function has to be considered in relation to structural and energetic processes that are affected by both thyroid and cholesterol.

According to an old edition of W.G. MacCallum's pathology textbook, "It has been shown that certain lipoid substances, especially cholesterine, can act as inhibiting or neutralizing agents toward such haemolytic poisons as saponin, cobra poison, etc., through forming with them an innocuous compound. Hanes showed that the relative immunity of puppies from chloroform poisoning is due to the large amount of cholesterin esters in their tissues. When artificially introduced into the tissues of adult animals a similar protection is conferred."

One of the strangest things about cholesterol research is that there have been so few studies of the general physical interactions of cholesterol with proteins, in contrast to the obsessive study of its *in vitro* interactions with fats.

Since then, numerous publications have described cholesterol's effect in protecting red blood cells from factors that would normally cause them to disintegrate. These protective effects involve the intrinsic qualities of the cells themselves, not just as the "neutralizing" function that Hanes referred to.

In the 1930s, while it was being shown that hypothyroidism caused serum cholesterol to increase, and also increased the risk of dying from

infectious disease and of developing heart disease or cancer, two investigators examined the relation of atherosclerosis to the blood's cholesterol content, and found that there was no correlation between them, regardless of age (Landé and Sperry, 1936). The development of the cholesterol culture, and its claims to the contrary, in the following decades has been reviewed by Uffe Ravenskov and Malcolm Kendrick.

The billions of dollars that have been spent to promote sales of anticholesterol drugs and foods can account for the public's fear of cholesterol, but there were deeper factors in the biomedical culture that made it easy for many researchers to ignore or deny the fact that cholesterol in the blood doesn't cause hardening of the arteries.

In the 1960s, the "lipid bilayer cytoplasmic membrane" was a craze, and the physical properties of cholesterol and saturated fatty acids were popularly used to explain everything in terms of "membrane fluidity." (Between January, 1964 and the present, PubMed lists more than 37,000 entries for "lipid bilayer.")

Cholesterol is a waxy substance, with a melting point (198.4 F, 148 C) far higher than that of even the saturated fatty acids, and the image of these hard frozen substances affected the way many seemingly intelligent researchers approached their thinking about cholesterol's functions in the organism.

In *in vitro* experiments with thin layers of oily substances, saturated fats and sterols are less mobile than polyunsaturated fats, and this simple fact has motivated thousands of people to explain problems in every kind of organ and tissue in terms of the accumulation of these "hard fats," or a deficiency of the fluid polyunsaturated fats.

The actual physical stiffness of whole cells and their surroundings is very important. For example excitotoxicity (Fang, et al., 2014), and other forms of energy depletion can stiffen cells, and prolonged energy depletion and inflammation lead to degenerative changes—tissue calcification, fibrosis, and invasive, disorganized cell movement, for example. These stress related stiffenings of the cell substance and matrix have nothing directly to do with the local quantity of cholesterol.

Hypothyroidism, leading to energy depletion and increased stress hormones, causes increased rigidity of various cells that have been examined, including red blood cells and brain cells (Tacconi, et al., 1991). The stiffer cells are also more fragile and disintegrate more easily. The stiffness of red blood cells in hypothyroidism increases the viscosity of the whole blood, and changes in blood proteins contribute to this.

The fact that hypothyroidism usually involves an increase in cholesterol along with the increased rigidity and viscosity often leads the "lipid bilayer" people to explain those changes as a result of the increased absorption of cholesterol by the red cells, reducing the "fluidity of the membrane." The experiments that showed the protective anti-hemolysis effect of cholesterol conflict with this, because stiffer red cells are more fragile.

When the cholesterol content of red blood cells is experimentally lowered, they become more rigid, and restoring the normal amount of cholesterol restores their flexibility (Murphy, 1962). The *in vitro* behavior of simple mixtures of cholesterol with fats simply doesn't correspond with the way cholesterol affects living cells.

One of the strangest things about cholesterol research is that there have been so few studies of the general physical interactions of cholesterol with proteins, in contrast to the obsessive study of its *in vitro* interactions with fats. In the body, the adipose tissues with a high fat content maintain a much lower cholesterol content than the muscle tissues. This is partly because muscles produce more cholesterol than fat tissue does, but also because the structural proteins of cells have a high affinity for cholesterol. In effect, fat and proteins are mutually soluble.

I think it's correct to think of protoplasm as a complex kind of solution of proteins, water, cholesterol and other lipids, nucleic acids, ATP, and smaller amounts of other substances, with a viscosity that varies as small changes of solutes modify the balance of cohesive forces. Because of its molecular shape and hydrophobicity, cholesterol acts as both a lubricant and a stabilizer of this complex system. It decreases cell rigidity by increasing protein mobility (Ayee and Levitan, 2016).

In bacteria and fungi and plants, stability is more important than flexibility. Like the thyroid

hormone, cholesterol is uniquely associated with animals; plants and fungi use slightly different sterols. Its resistance to oxidative damage allows tissues to function safely at relatively high body temperature in the presence of intense oxidative reactions, as in the brain. The red blood cell's mechanical stability and flexibility are essential for effectively fulfilling its various functions in circulation, allowing it to pass undamaged through narrow capillaries, and it has also served as a useful model for understanding these physical properties in cells of other types, including nerve cells, muscle cells (Hissa, et al., 2013, 2017), white blood cells (Saha, et al., 2017), endothelial cells (Byfeld, et al, 2004), kidney cells (Khatibzadeh, et al., 2012), lens cells (Borchman and Yappert, 2010) and cancer cells (Morachevskaya, et al., 2007).

Many "authoritative sources" describe cholesterol as the precursor to bile acids and steroid hormones, and also as a component of a cell membrane which serves in place of plants' rigid cell wall. This membrane, for more than 50 years, has been described as a semi-permeable lipid bilayer, reinforced by cholesterol, interrupted here and there by protein pores, channels, pumps, receptors, and various attachment sites. This "cell-wall-equivalent" is often said to have tensile strength, as well as a chemical barrier function, that keeps a cell from losing its "plasma" which is enclosed and retained by the membrane.

When a drop of water is on an oily surface it doesn't spread, because of its strong cohesive forces, and the oil's lack of those forces. When a drop of oil falls onto water, it spreads, becoming extremely thin. Benjamin Franklin estimated that a teaspoonful of olive oil spread over about half an acre of a pond. Oil has very weak cohesive forces, and effectively no tensile strength.

The fact that cholesterol strengthens cells, keeping them from disintegrating under stress, obviously has nothing to do with a lipid bilayer membrane. That membrane doctrine has made it seem paradoxical that the loss of cholesterol should make cells stiffer, while weakening them. Gilbert Ling has, for 65 years, pointed out the numerous "paradoxes" confronted by the advocates of the lipid boundary membrane, but the membrane doctrine continues to govern most biomedical thinking, including theories of cholesterol's role in the diseases of aging.

About 40 years ago, someone noticed that the commercial cholesterol used for research was contaminated by oxidation, and that pure cholesterol didn't produce the same toxic effects. Lipid peroxidation was observed in atherosclerotic plaques, and the breakdown products of polyunsaturated fats such as hydroxynonenal, malondialdehyde, and acrolein (from EPA, arachidonic acid, and other highly unsaturated fats in the affected blood vessel are known to attract white blood cells such as macrophages, which accumulate in the plaques.

The age pigment, ceroid or lipofuscin, that's derived largely from PUFA and associated with the macrophage "foam cells" in the plaque, accumulates iron (Lee, et al., 1998), and by catalyzing oxidation, creates local hypoxia, leading to lactic acid production, contributing to an inflammatory process. The products of lipid peroxidation, such as azelaic acid (Riad, et al., 2018), along with lactate, lead to the calcification of tissue.

Several observers have demonstrated that a protein that can remove excess cholesterol and other lipids from arteries, ABCA1 (ATP-binding cassette transporter or CERP (cholesterol efflux regulatory protein), is degraded by polyunsaturated fatty acids. "These findings raise the possibility that an increased supply of unsaturated fatty acids in the artery wall promotes atherogenesis by impairing the ABCA1 cholesterol secretory pathway in macrophages" (Wang and Oram, 2002, 2005).

Paul Cullen, et al. (1997, 2005) found that the foam cells found in atherosclerosis plaques contain ". . . cholesterol esters, principally cholesteryl eicosapentaenoate, cholesteryl docosahexaenoate, cholesteryl arachidonate, cholesteryl linoleate and cholesteryl oleate." The oxidation of these fatty acids produces acrolein and related compounds which block the ability of cells to regulate cholesterol (Shao, et al., 2005).

Combined with the unstable polyunsaturated fats, cholesterol can't perform its normal functions. The unstable polyunsaturated fats inactivate the corrective (ABCA) protein that removes the damaged form of cholesterol from

cells, while they activate the enzyme (ACAT) that forms that toxic form of cholesterol (Johnson, et al., 1983).

Several pharmaceutical companies have recognized that a drug to inhibit the enzyme that forms cholesterol esters would be profitable, but trials in which the experimental drug increased heart disease have dampened their interest. It has already been established that progesterone inhibits ACAT in a variety of tissues (Miller and Melnykovych, 1984; Batetta, et al., 2001), probably as part of its positive feedback effect on its own production, increasing the amount of its own precursor ("… regulation of the ACAT reaction may significantly modulate rates of progesterone biosynthesis." Veldhuis, et al., 1985). It's significant that progesterone has the opposite effect on this enzyme in the liver ("… progesterone alone increases the hepatic ACAT activity, but given in combination with estrogen progesterone does not have the same effect on hepatic ACAT activity," Miller and Melnykovych, 1984), since the liver's ability to secrete cholesterol is essential for making cholesterol available to steroid-forming tissues, such as the ovary and adrenal glands. Progesterone, which has many functions that protect against PUFA, also increases a related regulatory protein, ABCA2, that regulates cholesterol and is highly expressed in the brain (Davis, et al., 2004).

The healthy young brain contains a very large amount of cholesterol, almost all in the pure, non-esterified or "free" form—more than 99.5%, according to Orth and Bellosta (2012, citing Björkhem and Meaney, 2004). The aging, degenerating brain contains an increasing amount of esterified cholesterol, and some experiments show that inhibition of ACAT, preventing that accumulation, is protective (Bryleva, et al., 2010;). The local anesthetics lidocaine, benzocaine, tetracaine, and dibucaine inhibit this enzyme (Bell, et al., 1982).

In the 1960s, the famous "heart protective diet," based on a belief that PUFA were both essential and beneficial, was tested on a group of 846 veterans. The diet of half of the men contained corn oil rather than other fats, while the others were given a more typical diet with what they called "saturated" fats, which weren't very saturated. The number of double bonds, the degree of unsaturation, in a fat can be measured by the amount of iodine they bind. The fats in the control diet had an iodine number of 55; butter's iodine number is less than 40, coconut oil's less than 10. The control group contained fewer non-smokers, and more heavy smokers. After 8 years, the number of fatal heart attacks was the same in both groups, but there were seven deaths from cancer in the experimental group, and only two in the control group. While there is still great reluctance to acknowledge the carcinogenic nature of PUFA, results such as this have motivated the drug industry to consider using their ACAT inhibitors (blocking the attachment of PUFA to cholesterol) for treating cancer.

The polyunsaturated fatty acids, by being combined with the normally protective cholesterol, convert it into a sort of toxin, a disorganizing factor, leading to neurodegeneration, hardening of the arteries, cataracts, chronic kidney disease, and cancer.

When the diet lacks the polyunsaturated fatty acids, the liver synthesizes saturated fatty acids, and exports its cholesterol mainly in combination with palmitate, which doesn't promote lipid peroxidation, or in the non-esterified "free" form. A lifetime of accumulating PUFA progressively degrades the liver's protective functions, but those functions can gradually be restored by providing carbohydrates and saturated fats without the polyunsaturated fats, along with some of the factors that have been depleted along with free cholesterol, especially pregnenolone and progesterone.

In the next newsletter, I intend to talk about a line of thinking about cholesterol that has been submerged by the food and drug industries and their accomplices in government.

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