Ray Peat's Newsletter

"Those who have the privilege to know, have the duty to act." ***Albert Einstein***

Cholesterol in Context

Part II: A Formative Medium

"The experts" used to speak of cholesterol as a waxy substance that causes atherosclerosis, but now they always add that it's also an essential material that's needed for making cell membranes, bile acids, and steroid hormones. That common way of describing cholesterol is hardly an improvement.

From about the middle of the 19th century, the word "protoplasm" was used to describe the jelly-like living substance, and the word colloid (glue-like, resembling gelatin) began to be used around the same time, along with the older word emulsion, to describe the living material. The complex physical and chemical properties of various artificial colloids and emulsions were increasingly studied in comparison to living protoplasm. Between 1900 and 1950, these comparisons led to important new insights into bioelectricity and metabolism, and the ability of cells to regulate their interactions with their environment.

In the 1920s, a Dutch chemist, H. G. Bungenberg de Jong, found that when solutions of different polymers, such as gelatin and acacia gum, were mixed, they separated into two phases, almost like oil and water, with one phase containing a higher concentration of the two polymers, and less water, than the other phase. He called this spontaneous rearrangement of dissolved polymers "coacervation," meaning "clumping together." When various salts were added, the ions were non-randomly distributed between the two phases, and an electrical potential difference was maintained between the two phases.

A change in the concentration of a single salt could cause the proportion of solid and liquid phases to change. Changing temperature, pressure, or pH, could change the balance of the phases, altering the distribution of ions or other dissolved substances. For example, in a particular coacervate, lowering the temperature slightly causes the solids to be slowly dissolved, leaving a single liquid phase; with a return to the original temperature, the solid phases reappear, along with an unequal distribution of the dissolved substances.

> **It is evident that, at present, we are not going to give up the mass faith in scientific technology that is the religion of modern times; and yet we cannot continue with it, as it has been perverted. So I look for a "New Reformation."**
>
> **Paul Goodman**

The coacervate systems behave in even more complex ways when they contain more than two kinds of polymer, for example when they contain protein, polysaccharides, and nucleic acids, as well as fats or other lipids, sugars, and salts. Any change, anywhere in the system, causes a holistic adjustment of the whole system, that can involve changes of structures and their affinities.

The coacervation process permits compartmentalization and specialization of functions within cells, but a few substances, along with water, are ubiquitous in the living state; cholesterol is one of those.

The maintenance of a non-random distribution of ions and other solutes, and the existence of an electric potential difference, were the reasons that some people had postulated the existence of a semi-permeable membrane around cells. The work of Bungenberg de Jong and his colleagues showed that no membrane was needed to explain those properties of living cells.

Modifying an extremely complex system, the living substance, cholesterol participates in complexity, and must be investigated with subtlety.

To many people, this perspective made it clear that important aspects of the living substance could be understood holistically in terms of its structural reactions to the physical environment that could contribute, alternatively, to maintaining an equilibrium, or to growing, or to degenerating.

In the 1940s, use of the new electron microscope failed to show the barrier membrane around cells that some people had postulated. Gilbert Ling, who developed the "Ling-Gerard glass microelectrode," showed why he believed that the electrode was registering a phase potential, rather than a membrane potential. Ling, D.N. Nasonov, A.S. Troshin, and others showed not only that the postulated regulatory cell membrane was unnecessary, but that it was impossible. The surface of a cell is the boundary between phases, and within a cell there are slight variations in phase, but (except in the case of vacuoles) there is no place for the watery solution supposedly enclosed by a barrier membrane.

By the 1950s, a model of the living cell had become official, in which the cell was controlled by the inherited blueprint in the DNA, and operated through the chemical reactions produced by enzymes in a watery solution, acting on materials that they encountered through random collisions with dissolved substances. Biochemistry, as a profession if not a science, was based on the assumption of random diffusion of substrates and enzymes in a watery solution. It was considered ridiculous to suggest that emulsifying cells and suspending their enzymes in water might not accurately reflect what happens in living cells.

From the perspective of people who knew the parallel histories of cytology and coacervate research, the gene-membrane-random-solution model of the cell seemed insane and/or stupid, but that model was effectively kept in its dominant place by the disregard for reality of those who control the institutions of culture.

While the idea of the living substance as a special *condition of being* makes it possible to understand health and sickness pragmatically and to investigate the organism's interactions with its environments coherently, the chemical and pharmaceutical cartels wanted a model of the cell and organism that would rationalize the sale of specific substances to treat discrete diseases by acting on identified receptors or enzymes. The idea that atherosclerotic heart disease is caused by cholesterol and can be prevented by poisoning the enzyme that makes cholesterol is the most profitable achievement of that paradigm. The billions of dollars gained from the statins have strengthened the place of the industry's marketing paradigm in our culture, and the phrase "cholesterol is needed for cell membranes" is a crucial part of that paradigm.

The case against science is straightforward: much of the scientific literature, perhaps half, may simply be untrue. Afflicted by studies with small sample sizes, tiny effects, invalid exploratory analyses, and flagrant conflicts of interest, together with an obsession for pursuing fashionable trends of dubious importance, science has taken a turn towards darkness.

Richard Horton
(editor-in-chief, the Lancet)

With aging, the organism's reduced functionality is paralleled by structural changes. The steady decrease of tissue water content is one of

the most noticeable features of aging. It has been known for several decades that the production of progesterone and DHEA decreases steadily with aging, and in recent years it has been noticed that when aged skin is exposed to sunlight it produces only half as much vitamin D as young skin does. Old skin has about half as much cholesterol as young skin, so it isn't surprising that those substances derived from it are reduced.

In old skin and other organs, including the brain, the synthesis of cholesterol decreases with aging (Ghadially, et al., 1996; Stange, et al., 1984), although modified, combined forms of it accumulate (sulfate and fatty acid esters). The increased effects of cortisol, and decreased effects of thyroid hormone, with aging contribute to the decreased cholesterol synthesis with aging (Henze, et al., 1981; Rosenberg, et al., 1986).

The characteristic opacity of aged skin is the result of an accumulation of layers of dead cells on the surface. While the vital underlying skin cells contain much less cholesterol than normal, the inert cells contain an increased amount of cholesterol sulfate. When the skin's free cholesterol content is increased experimentally, the skin regains its ability to shed the dead superficial cells. When it's lowered experimentally, as with a statin, the skin takes on the structure and appearance of old skin. Aging seems to be a state of cholesterol starvation.

In allowing skin cells to shed naturally, cholesterol is activating a proteolytic enzyme and restoring the skin's normal barrier function and acidic pH. At the same time it's affecting many other processes, including mitochondrial respiration (Kaufmann, et al., 2006). The well known side effect of the statins, rhabdomyolysis (muscle cell disintegration) is known to involve damage to the mitochondria. Exercise, placing a large energy demand on muscle, increases the risk of damage when a statin is present.

Low serum cholesterol has been associated with depression, suicide, violence, and increased cancer mortality. Since statins enter the brain, and inhibit the synthesis of cholesterol there, decreased mitochondrial function is undoubtedly a factor in the mental side effects that they can produce. In animals, the statins are known to cause birth defects when they are given during pregnancy, and mitochondrial damage to the embryo is probably one of the mechanisms.

The few people who have warned about some of the harmful effects of the statins have suggested that it's the reduced production of coenzyme Q10, ubiquinone, that impairs the mitochondrial energy function. However, there is evidence that the amount of cholesterol corresponds to the mitochondria's ability to produce ATP (Ziolkowski, et al., 2010; Ferreira, et al., 2003).

"At every step in the process, there is room to distort results, a way to make a stronger claim or to select what is going to be concluded," and there is an "intellectual conflict of interest that pressures researchers to find whatever it is that is most likely to get them funded."

Dr. John P.A. Ioannidis

More than 250 proteins are specifically adapted to binding cholesterol. These include the proteins of the cells' structural, "skeletal," proteins, such as the microtubules that form the mitotic spindle, sorting the chromosomes appropriately during cell division, and also the proteins and DNA of the chromosomes, and the nuclear matrix, and the filaments that control cell shape and movement, the light transmitting fibers of the lens, and proteins that govern special functions of muscle contraction, nerve conduction, and secretion.

Cholesterol's functions are similar in many ways to those of progesterone. In the pregnant uterus, for example, progesterone's relaxing function is backed up by cholesterol (Smith, et al., 2005). In the brain, excitation of nerves by glutamic acid is controlled by the uptake protein which binds this transmitter, and this protein's function depends on cholesterol; reduction of cholesterol prolongs nerve excitation (Butchbach, et al., 2004).

About 60 years ago, Carl Lindegren, in *Theory of the Body Pattern*, showed ways in which changes in the centrosome of the ovum, and the cytoskeleton that it organizes, can cause abnormalities in the structure of the body. At that time, the culture of biology was completely devoted to the idea that the blueprint of the body was entirely contained "in the genes," that is, "coded in the DNA." Experimenters had transplanted nuclei from one phylum of animal into the egg cytoplasm of another phylum with a different body plan, demonstrating that at least the main scheme of the body pattern is governed by the cytoplasm, but even now the culture is only reluctantly starting to think about the implications of this holistic view of the organism.

The apparent endemicity of bad research behavior is alarming. In their quest for telling a compelling story, scientists too often sculpt data to fit their preferred theory of the world. Or they retrofit hypotheses to fit their data. . . . Our love of "signifcance" pollutes the literature with many a statistical fairy-tale.

Richard Horton

There is renewed interest in the primary cilium, a little projection that nearly all our cells have, which is derived from the centriole after cell division is completed, and the cell settles into its differentiated functions. This cilium is a sense organ, keeping the cell aware of its orientation and location in the body. For example, the primary cilia of the cells lining blood vessels all point toward the heart, whether they are in veins or arteries; they are oriented in relation to the big picture.

The gene system involved in embryonic development, stem cells, and cancer, acts through the primary cilium (Rohatgi, et al., 2007), and the "hedgehog" family of morphogenic proteins requires the attachment by an ester bond of a cholesterol molecule to the protein, that permits it to be guided to the appropriate place of action to control differentiation of cells in the right pattern. The development of a new pattern is guided by the orientation already existing in the centrosome-cilium-cytoskeletons.

Within the cell nucleus, there is a highly organized substance, the nuclear matrix, that interacts closely with the rest of the cytoskeleton, permitting DNA to be expressed according to the cell's need as it responds to its environment. Cholesterol and other lipids are essential for the specific highly organized interactions between DNA and the rest of the cell (Albi and Villani, 2009).

When cultured cells are experimentally "cholesterol starved" they are unable to complete the mitotic process, and are arrested in a tetraploid state, with twice the normal number of chromosomes (Martínez-Botas, et al., 1999). In this arrested state they are unstable and, if cell division resumes, likely to form aneuploid (abnormal number of chromosomes) cancer cells The tetraploid state becomes frequent in aging skin; one of the effects of ultraviolet light is to inhibit the formation of cholesterol. Aging and premature death of the skin cells is a better outcome than cancerization; both can be produced by cholesterol deprivation.

Cholesterol is involved in the maintenance of stem cells and the control of their maturation into functioning cells. A "cholesterol chelator," cyclodextrin, which interferes with cellular cholesterol, causes cardiac stem cells to mature into functioning heart muscle cells: "β-CD performed its function by increasing the free intracellular cholesterol (Shi, et al., 2017).

Another group using a cyclodextrin to reduce the accumulation of the age pigment lipofuscin, found that the cyclodextrin increased cholesterol synthesis (Gaspar, et al., 2017).

Excitatory transmission appears to contribute to the loss of cholesterol in the brain during aging; the amount of cholesterol in synapses decreases with aging (Sodero, et al., 2011). Although excitatory (glutamatergic) stimulation lowers brain cholesterol, environmental enrichment (meaningful experience) increases it (Levi, et al., 2005), and also reverses the age-related decline in the neurosteroids derived from cholesterol (Rossetti, et al., 2015).

In the brain, the accumulation of cholesterol esters (at the expense of free cholesterol) increases with age and contributes to neurodegeneration. Intervention to liberate cholesterol from the fatty acids has a nerve-protecting effect in a worm model of Parkinson's disease (Zhang, et al., 2017). A great increase in cholesterol esters, relative to free cholesterol, has been seen in the chromosomes of cancer cells (Struchkov and Strazhevskaia, 1989; Struchkov, et al., 2002).

The "age pigment," lipofuscin, is produced by oxidation of polyunsaturated lipids. The polyunsaturated fatty acids, that accumulate with age, have been known for about 80 years to be the main source of this material. These fatty acids inhibit the synthesis of cholesterol (Kuroda and Endo, 1976), and increase its conversion to cholesterol esters (Spector, et al., 1980). At birth, there is a very low concentration of cholesterol ester, and the proportion remains low until about the age of 20, when growth slows, and beyond the age of 20, the cholesterol esters accumulate at about five times the rate of cholesterol accumulation. After the age of 40, the cholesterol esters become the main component of the lipids of blood vessels (Smith, 1974). The accumulation generally increases with age in other tissues, and the proportion seems to correlate with loss of function in viral disease and cancer as well as in aging. An increase of the esterification rate in the serum is a predictor of heart disease and sudden death (Tanaka, et al., 2013).

The enzyme responsible for the harmful ester formation is activated by highly polyunsaturated fatty acids (Johnson, et al., 1983). It has been suggested that the statins might act by way of the "essential fatty acids" (Das, 2001).

Although healthy tissues usually produce enough cholesterol for their own needs, the glands that secrete large amounts of steroid hormones take up considerable amounts of cholesterol from the blood, absorbing low density lipoprotein (LDL) cholesterol in proportion to their need. In an experiment with blood-perfused ovaries, it was found that the amount of progesterone secreted varied with the amount of LDL cholesterol in the blood. The increased serum cholesterol in stress is an important protective adaptation.

In a study of several hundred people in their seventies, it was found that in those whose baseline total cholesterol was 195-244 mg/dL, "…each 10-mg/dL increase in the 1988-to-1991 change in non-HDL-C was associated with an adjusted mortality odds ratio (OR) of 0.67…" (Karlamangla, et al., 2004).

Those who have the power to act seem to think somebody else should act first.

Richard Horton

During the last 65 years, industry-generated recommendations to replace saturated fats in the diet by polyunsaturated fats, to "control cholesterol," have been based on propaganda science, not objective science. With the passing of the generations that were indoctrinated with the ideas of random biochemical reactions, random mutations, semipermeable lipid bilayer membranes made of cholesterol and essential fatty acids with membrane pumps, a synthesis of the fragmentary insights about life that were achieved in the last century has become possible.

Besides eliminating polyunsaturated fats (n-3 and n-6) from the diet to reduce the formation of cholesterol esters and to reduce the decline of cholesterol synthesis with aging, supplementing with progesterone is a way to reduce the formation of esters (Synouri-Vrettakou and Mitropoulos, 1983; Miller and Melnykovych, 1984; Jeng and Klem, 1984; Mulas, et al., 2011; Anchisi, et al., 2012). Lidocaine is another inhibitor of cholesterol ester formation (Bell, 1981; Bell, et al., 1982) that is probably useful in some degenerative conditions.

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