Ray Peat's Newsletter

Medical genetics and immunology: Islands of fantasy in a sea of ignorance

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Implications of inflammation

It has become widely accepted that inflammation has a central role in several major diseases--atherosclerosis, cancer, Alzheimer's disease, diabetes and obesity, Parkinson's and Huntington's disease, asthma, epilepsy, for example--so understanding the nature of inflammation has gained special importance. For thousands of years, inflammation has been defined by the presence of swelling, redness, increased heat, and pain.

Is the inflammation the main cause of the disease, or is it instead, a response to the disease process? Not long ago, the medical profession began to see inflammation as an important part of the healing process, reflecting the actions of both an innate immunity and a learned immunity, and before that, it was seen, like fever, as the problem to be relieved, with "allopathic" treatments.

Soon after good microscopes were developed, Rudolf Virchow described the collection of white blood cells in infected areas and tumors, and suggested that their accumulation was a consequence of the damage to blood vessels and congestion, caused by tissue damage. They were incidental to the inflammation. A generation later, Elie Mechnikoff, who had studied the orderly and meaningful movements of cells in the developing embryos of a great variety of organisms, saw that the collection of white cells around a foreign material was intentional; in the case of the embryos of starfish, the white cells were part of the organism's digestive system. When he introduced rose thorns into the tissues of water fleas, the wandering cells engulfed and dissolved them. He reasoned that the pus that surrounds a thorn in a person's finger represents the same process--a protective eating and destruction of the harmful material.

For the Greeks and Romans, the pus of an abscess was "laudable," but by Mechnikov's time, pus had become identified with the presence of infectious microorganisms. Disinfectants were used to prevent the infections that could produce pus. However, by the end of the 19th century, sterile extracts of microorganisms were found to be able to produce the inflammatory signs of infection. Virchow's observation of white blood cells in cancers could be considered as an early recognition of sterile inflammation, but the term came into use later, and has appeared intermittently in the literature for many years. The concept has become more important as researchers have explored the interactions between the supposedly primitive, non-specific "innate immunity," and the supposedly more highly evolved specific adaptive immunity.

Trauma, prolonged interruption of blood supply, chemical injury, radiation injury, and signals from nerves are among the things that can cause sterile inflammation.

Although the concept of sterile inflammation has been in the medical literature for a long time, the influence of the drug industry has helped to keep it from entering significantly into medical education. In 1976, I was talking to a recent graduate of Stanford's medical school, and when I mentioned sterile inflammation, she interrupted, saying "there's no such thing, inflammation means that there's an infection." When the involvement of inflammation in neurological disease or atherosclerosis is mentioned, most physicians probably infer that this is evidence of a hidden infection or a mysterious new organism. It could be, but to assume that is to neglect the many other possible causes.

Mechnikov's idea of intentionality, goal directed behavior, in the wandering cells was antagonistic to the most powerful trend in science,

the doctrine of randomness in a mechanistic, deterministic view of matter. Following Descartes, the mechanistic materialists saw living organisms as machines, in which each part interacts mechanically with adjoining parts, and consciousness was something essentially distinct from the living substance of the organism. But as early as the 18th century, some researchers were thinking of the brain as an integrating center, not only for perception and movement, emotion and thought, but even for sickness and health.

The mechanistic materialists labeled such holistic thinking as anthropomorphizing or vitalism. Explanations were considered to lack "objectivity" if they related to a purpose; students were taught to avoid "teleological" explanations, if they wanted to be real scientists. However, from the time of Pasteur and the adoption of mass vaccination, the body's reactions to alien material were concretized in the concept of an "immune system," which existed for the purpose of defending against infections. It's important to remember what scientific knowledge about the nature of life was at that time—almost nothing that people believed at that time about how our bodies come into being, how they produce chemical changes, or how they move and sense, is now recognized as true. But the basic idea of an "immune system" has hardly changed in 100 years.

Although Mechnikov shared the 1908 Nobel Prize with Paul Ehrlich, Ehrlich's Nobel lecture expressed an extremely reductionist view of the organism, almost comical when juxtaposed to Mechnikov's lecture. According to Ehrlich, it was necessary for science to differentiate "the concept of the cell into that of a great number of separate, individual functions." In that lecture he talked about lock-and-key interactions, and receptors on cells. This was the course taken by science in the following century.

Mechnikov's goal directed phagocytes were accepted as part of the immune system that increasingly focused on Ehrlich's highly specific antigens and antibodies. Although the immune system was understood to have the purpose of defending the organism by destroying germs, it was put into an "objective" reductionist mechanistic scheme by giving it its own evolutionary explanation, through the natural selection of random changes in genes which, through time, became a very complicated machine that happened to kill germs, by strictly local molecular interactions. The germ killing, antibody forming immune system was thought to have evolved bit by bit, along with the evolution of the complex nervous, reproductive, and digestive structures and functions that distinguish mammals and people from sponges and roundworms, each feature the result of random changes that were preserved by natural selection.

By the 1960s, because of the ability through "vaccination" to create antibodies that would bind even to newly synthesized substances, the earlier idea of a simply genetically programmed immune system had to be abandoned, because the number of possible antibodies would have required a tremendous amount of DNA, that wouldn't fit inside a cell. New genetic explanations were invented to explain the ability of the immune system to adapt flexibly to unexpected new diseases. This was achieved by the idea of the immune system as a microcosm of evolutionary history, in which hypermutable genes could in a very short time evolve the new sequences needed to produce novel antibodies to destroy novel pathogens. It was still random, but very fast, and the cells that were selected, and stimulated to multiply, formed a clone, the way a mutant cancer cell formed a clone, supposedly giving each tumor its unique genetic individuality.

In an international immunology symposium at the University of Oregon in 1969, a few famous immunologists presented their recently developed theory about immunity, based on the neodarwinian theory of evolution as the result of random changes that are preserved by natural selection. The day after a description, to a large audience, of an experiment demonstrating clonal selection, in which specific immune cell clones were killed in a culture dish, and shown to stay dead, while other clones survived, an assistant professor of developmental biology described, to a small group of students, an experiment in which he had replicated that demonstration of clonal selection, and then repeated the same conditions, but with different concentrations of cells in the dish. With a sparse

cell population in the dish, his results were the same as those described in the earlier lecture, but when he increased the cell population to a certain point, the missing "clones" reappeared.

In the absence of a whole organism, but with a quorum of their peers, the cells were able to reconstitute a full repertoire of sensitivity. My impression as he described the experiment was that it implied that each cell had to have a knowledge of the type of organism it belonged to, rather than just being committed to expressing certain genes for the rest of its life. A few weeks later I met the professor in the hall and asked if he was publishing the experiment, and he said he hadn't written it up yet. I watched for it in the next few years, but never saw anything by him that related to it. Ten years later, a few other people began questioning the clonal deletion theory of self tolerance, but the many changes that have been made subsequently have been essentially to preserve the mechanistic randomness of the theory, and the doctrine that it is a system specifically evolved for fighting microbes. The goal-directedness introduced by Mechnikov was kept for the system as a whole, but the intentionality was reduced to random changes.

This doctrine of a separately evolved, and evolving, immune system provided no insight into the phenomenon of sterile inflammation, and it's that kind of inflammation, which lacks intelligible goal-directedness, that has become so important for understanding the chronic and degenerative diseases, and aging.

Before someone thinks of a mechanistic-neodarwinist theory of sterile inflammation, I want to propose a very different approach. Life is very adaptable, but it isn't infinitely adaptable. Life, in its highly complex forms, whether mollusk, mammal, fungus, or phanerogam, has many common features, and each type has a range of environments that are more or less suitable. The neodarwinian ideology inclines many biologists to assume that an organism's present form represents its best adaptation to its present environment, or to its recent past environments. This leads to arguments that "we evolved to eat ...," or to live in certain ways. But experiments in which animals become more intelligent and live longer when they are put into an environment which never existed in nature imply that organisms have their own internal principles that allow them to become more than they or their ancestors ever were, if they have the right environment.

The intrauterine environment permits injuries to be repaired, mostly without inflammation or scarring, and when some of those features, such as high carbon dioxide and sugar content are provided postnatally, inflammation and scarring can be prevented or reduced.

When prenatal environments are modified, the development of the animal's brain and metabolism is affected, affecting the course of that animal's life, and influencing subsequent generations. The wrong balance of prenatal nutrients can decrease the metabolic rate and increase obesity, or a better balance can increase brain development and alertness. When a young animal's early life is enriched with stimulation and opportunity for exploration, its brain development is improved (increased cortical thickness and enzyme activity), and those changes are passed on to subsequent generations, with cumulative effects if the improved environment continues to be available.

The prenatal absence of inflammation corresponds to conditions that are providing energy and other conditions necessary for a very high rate of metabolism, with minimal stress. Generalizing from an understanding of gestation, we could say that inflammation, and the failure of tissue maintenance, occurring later in life is the result of a gap between the energy that's available and the demands that are made on the organism or on a particular tissue.

This approach to understanding inflammation suggests why it contributes to degenerative processes, and suggests potential remedies, but it also offers a new perspective on the processes that are called innate and acquired immunity. The boundaries of what used to be called an immune system have been expanding and becoming blurred, as the interactions of nerves, hormones, nutrition, tissue repair, reticulo-endothelial system, phagocytosis, and wandering or stem cells come to be understood in more detail.

Jamie Cunliffe and Polly Matzinger have been developing a new understanding of the immune

system, centered on the idea that tissue damage is the main issue, rather than the distinction between self and nonself antigens. They recognize that the old model, especially the "adaptive immune system," is failing to explain things, and they are giving more weight to things such as inflammation that had been attributed to an "innate immune system," but what they are describing might better be described as an alert, intelligent organism maintaining itself.

This new orientation would make "stem cells" part of the "immune system," since they sense danger or tissue damage, and adapt to repair it. The wandering white blood cells, rather than being the end product of a particular clone, are able to transform themselves when they find themselves in new situations, becoming a different kind of cell. The signals that cause them to go where they are needed are related to inflammation, but this is exactly where immunology and stem cell research need to direct their attention. These signals are strongly influenced by environmental conditions.

One of the important features of the intrauterine environment is that it is steadily very warm, and that means that the fats which are synthesized from sugar will be relatively saturated. If sugar is deficient, which is common as a result of maternal hypoglycemia in the third trimester of pregnancy, free fatty acids from the mother's tissues and her diet will provide energy for the fetus.

The brain requires a high level of sugar for optimal growth, so maternal undernutrition or hypoglycemia will increase the ratio of the baby's body weight to its brain weight, and will change various other features of metabolism and structure. If the mother's fats are highly unsaturated, they can be turned into the pro-inflammatory prostaglandins during stress, and hypoglycemia during the third trimester is highly stressful for the fetus. Besides causing injury to the fetus during this time, producing inflammation and potentially scarring and granuloma or fibroma formation, the prostaglandins activate the stress hormones, such as corticotropin release hormone, which is a trigger for stimulating the birth process, and so tend to cause premature delivery.

These polyunsaturated fats, which are clearly alien to the gestational process, interfering in so many ways with optimal development, are present in the mother's tissues and foods because of the type of environment she occupies. If she ate only foods from a warm climate, where plants and animals produce mostly saturated fats, the fetus wouldn't be subjected to the anti-regenerative, pro-inflammatory, anti-developmental effects of the fatty acids and prostaglandins. The polyunsaturated fatty acids, prostaglandins, and inflammation, clearly encroach on the process of gestation, altering the subsequent life of the exposed individuals, causing them to adapt to the world by metabolizing less energy; they continue to constrain development throughout the lives of those who continue to be exposed to them.

The figures for premature births and low birth weight in recent decades suggest the importance of the issue. While adults are getting fatter, more underweight babies are being born. In affluent countries, while the adults' body size has increased during this time, their head circumferences haven't. These changes are similar to those seen in animals fed increased amounts of polyunsaturated fats. Besides being the precursors for the prostaglandins, the polyunsaturated fatty acids amplify inflammation and stress in a variety of other ways.

The prostaglandins are, in adults as they are in the fetus, central to the scarring, fibrosis, and failure of regeneration that are considered to be normal for mammals when they are injured or are aging. The failure of regeneration in a phylum of animals is closely related to their susceptibility to forming tumors. Cancer can be considered as a form of dystrophy, a consequence of tissue atrophy, a failure to keep regenerating. An example of this antagonism would be the experiment in which parts were cut off salamanders, allowing them to grow a new tail or leg, but when a tumor was grafted on where a tail was amputated, the tumor was converted into a tail, by the animal's "regenerative environment."

Before the recognition that adult tissues all contain stem cells, most biologists thought of the organism as being made up of "adult cells," that would last for a large part of a normal life span. Tissues were examined microscopically after they had been killed and hardened chemically, and it didn't occur to most researchers to think of the

image under the microscope as a single frame from a moving picture. G. Zaijecek has done experiments that reveal "cell streaming" in tissues normally thought of as static, such as the liver, pancreas, or the cornea of the eye. It has been recognized for a long time that when the cells of the adrenal cortex are regenerating they "stream" away from the outer capsule, changing their form and function as they go. Zajicek has showed evidence that a similar transformation of function occurs in the pancreas, with acinar cells turning into islet cells as they migrate (Zajicek, et al., 1990).

The innervation of some regenerating epithelial tissues, such as the bladder, skin, and cornea, has been studied in considerable detail, and it's fairly well known that the sensory nerves have complex "trophic" or sustaining effects in these tissue. For example, if sensory nerves are destroyed in an area of the skin, that area becomes thin and shiny. Since some of Pavlov's earliest studies, nerves have been known to have a trophic function on the tissues they innervate. In some tissues–bladder, stomach, heart, liver–complex chemical signals are known to be released by the sensory nerves, but the presence of nerves in other tissues, such as the cortex of the adrenal gland (Heym, et al., 1995), hasn't been so well studied, though all such tissues are known to have nerves. In animals such as salamanders, nerves are known to be involved in the regeneration of lost parts. Nerves are intrinsic parts of cancers, too.

About 50 years ago, a study of the production of blisters produced by hypnotic suggestion found that the blister fluid contained ATP, which had been released by sensory nerves, at the spot that had been touched by what the subject believed was a lighted cigarette. ATP also appears in the fluid of a blister caused by heat, but this example showed how important the sensory nerves are, for things beyond sending messages to the brain. Both ATP, and one of its breakdown products, adenosine, activate some enzymes involved in inflammation. ATP activates the MMP proteinase enzyme that dissolves extracellular matrix, which is a basic step in tissue remodeling, and it also activates a phospholipase which releases arachidonic acid, and the cyclooxygenase enzyme, COX-2, which converts arachidonic acid to prostaglandins.

Besides activating the enzymes to break down the extracellar structure, ATP stimulates cell division and angiogenesis, all of which are normal parts of tissue maintenance. In the bladder, stretching causes the epithelial cells to release ATP, which stimulates sensory nerves; in this situation, the epithelial cells are acting as sense organs, and the ATP acts as a neurotransmitter. It has a similar effect in the breast, in relation to milk ejection (Bowler, et al., 2001). In other tissues, such as bone, mechanical forces also release extracellular ATP, and in this situation it seems to be an important anabolic stimulus to bone growth and repair (Furuya, et al., 2004).

ATP is increasingly recognized (Burnstock, 2007) as a basic neurotransmitter or cotransmitter, but it is something more important and basic than that: it's a constant signal of any cell's presence to neighboring cells. If the concentration of ATP varies too much, it indicates that something is wrong. If a cell is injured or fails to produce enough energy, it leaks ATP. During oxygen deficiency, the leaking ATP causes vasodilation, increasing circulation, and in the respiratory center, it stimulates breathing (Buttigieg and Nurse, 2004; Conde, et al., 2012).

In the prenatal environment, lacking polyunsaturated fatty acids from the environment, ATP is involved in the orderly development of the organism, adjusting rates of growth in a coordinated way. This system, that can be seen in embryology and the early stages of gestation, has all the properties of a self-regulating control system, with a built-in intention to develop in a certain direction. The intention that Mechnikov saw in the phagocyte, is in the whole organism. Cells that will later be thought of as part of "the immune system" are present at the very early stages of embryonic development, participating in its coming into existence. There is no genetic "blueprint" that is being read out for either the organism as a whole or for an immune system that has evolved to deal with infectious challenges. The system creates and discovers its potential, in a unique way, responding to what its environment provides it.

Not long ago, following the cult of the "Weismann barrier," it was believed that oocytes were "read out" at an early stage of development, from a genetic blueprint that would never be accessible again. That doctrine lasted for 100 years, until someone tested it (Johnson, et al., 2004, 2005; Bukovsky, et al., 2005; White, et al., 2012). As they showed, the embryo and the adult are intentional unities, able to improvise in surprising ways, but genetics and immunology have created fragmentary, mechanistic descriptions of them.

During development, the coordinated growth and functioning of the system is affected by the chemicals in the environment that the organism encounters. The prostaglandins reflect a particular ecosystem in which plants produce certain unsaturated fatty acids, but biomedical ideologues have idealized them, following the doctrine that this is the environment that we evolved to live in. This is very much like the nutrition professor at Oregon State University who taught students that white bread should be included in the diet because God gave it to us.

Lacking PUFA and prostaglandins, extracellular ATP would activate constructive pathways, tending to create a new equilibrium, without producing all of the harmful effects of the prostaglandins. As unstable polyunsaturated fats accumulate in the tissues with aging, they increasingly promote vicious circles of stress (some of those were described in Fats, Functions & Malfunctions).

Recognizing a mismatch between the organism's potentials and the present environment, and suggesting ways to improve the environment, isn't anything new, and a limited form of it has been institutionalized in various offices of occupational health and safety, traffic safety, and pollution control, but it conflicts with the other well-institutionalized attitude, that people must be changed to conform to the situation as it is. Eugenics, sterilization, vaccination, health education, and publicity campaigns explaining why cancer, heart disease, and obesity are caused by choices the individual makes, are well financed and supported by large organizations.

The idea of autoimmunity epitomizes this general situation, in which reductionist theories are invoked to explain why a person is causing his own sickness. If antibodies evolved to attack microbes, then the immune system has become defective when it produces antibodies against its own tissue. But if the system of wandering cells, complement, antibodies, etc., has to do with development and maintenance of the organism, the presence of antibodies and other "immune" factors would be expected whenever a tissue is damaged.

Simply twisting a piece of cartilage has been shown to make it antigenic, and many other things causing sterile inflammation cause antibodies to appear. Strokes or other brain injuries cause antibodies to be produced. The presence of auto-antibodies has been found to facilitate the recovery from an aseptic inflammatory condition of the brain, accelerating healing and re-vascularization (Hofstetter, et al., 2003). Intravenous immunoglobulin has a long history of use to reduce inflammation (Nimmerjahn and Ravetch, 2008), and it has been tested as a treatment for heart failure, producing anti-inflammatory effects (Aukrust, et al., 2006).

Components of the complement system and C-reactive protein, which are increased by tissue injury, are involved in the anti-inflammatory clearance of dying cells (Gershov, et al., 2001).

The presence of the "essential fatty acids" is an important factor in the allergenicity of transplanted tissues (Schreiner, et al., 1988), which might be expected, from the role of the prostaglandins in creating inflammation whenever a tissue is stressed.

Many types of evidence indicate that environmental PUFA and prostaglandins produced from the "essential" fatty acids are required for inflammation to progress to degeneration. The n-9 polyunsaturated fatty acids (the kind that we can make from saturated fat or sugar) seem to be positively protective against inflammation. For example, rats fed a diet with 2% hydrogenated coconut oil for two weeks had lower levels of IL-6 and C-reactive protein than when a small amount of arachidonic acid and docosahexaenoic acid (DHA) were added. Mead acid (20:3n9) was lower in the group with the PUFA supplement,

and the inflammatory reaction to endotoxin was greater in the supplemented group (Ling, et al., 2012).

Many of the things that can be achieved by vaccination and treatment with safe anti-inflammatories such as aspirin could be done better by long-term changes of diet, and by taking into account the interactions of the hormones, especially progesterone, estrogen, and thyroid, with nutrients and stressors. But much more than that is needed: The nature of the relationships between environmental factors and the body's reactions has to be clarified, so that the processes of healing and regeneration can more closely resemble the prenatal condition, possibly even continuing in adulthood the "pedomorphic" process, realizing human potentials that haven't previously been seen.

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