Ray Peat's Newsletter

Natural forces within us are the true healers of disease. **Hippocrates**

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Arthritis, Autoimmunity, & Aging

For several decades it has been known that women are from 2 to 10 times more likely than men to be affected by an autoimmune disease, such as rheumatoid arthritis or systemic lupus erythematosis, SLE, and that the incidence of autoimmune disease increases with aging. Most physicians believe that autoimmune diseases are chronic and progressive, and that, on average, they shorten life by several years. It's very common for an autoimmune disease in one organ to be associated with an autoimmune problem in one or more other organs. The incidence of heart disease and several types of cancer is higher in people with SLE or rheumatoid arthritis.

According to the National Institutes of Health, 23.5 million people in the US suffer from an autoimmune disease, based on studies of 24 different "autoimmune diseases." The NIH says that the prevalence is increasing; it has recently been called "an epidemic" and an "explosion." Many researchers have listed from 80 to more than 100 diseases that they consider to be "autoimmune."

The idea of autoimmune disease can be traced back to Paul Ehrlich's theory of immunity, and his idea of a therapeutic "magic bullet" has dominated the medical approach to treating the autoimmune diseases. In the theory, the immune system's normal function is to destroy pathogens by a specific "lock and key" interaction, and errors in the system cause it to attack tissues of the "self," rather than "not-self" substances. In both cancer and autoimmunity, the dominant theory has been that particular genes are causative, with varying roles ascribed to environmental factors such as viruses, toxins, and mutagens.

Treatments for rheumatoid arthritis have overlapped with treatments for cancer, using cytotoxic-immunosuppressive chemicals such as methotrexate, gold salts, and glucocorticoid hormones, or radiation, to destroy the cells that damage "self" tissues. Because of the brain damage and other effects of those treatments, special antibodies have been developed to block the natural inflammation-promoting substances such as tumor necrosis factor and interferon, but treatment with these can cost $2000 per month, and they don't correct the basic problem. They are sold with the warning that they can increase susceptibility to deadly infections.

The embryologist Elie Metchnikoff looked at immunity as an aspect of the organism's maintenance of its own integrity. The role of phagocytes in shaping an organism, such as turning a tadpole into a frog, was guided by the identity of the whole organism, and the elimination of pathogens followed the same principle. Although the idea of a guiding organismic field that was held by most embryologists disappeared in the 1950s, in the 1990s a similar holistic view appeared in Matzinger's "danger theory" and Cunliffe's "morphostasis" or damage theory of immunity, in which destruction of pathogens isn't "the purpose" of the "immune system," but a side effect of maintaining organismic integrity.

From that perspective, "protective autoimmunity" isn't a contradiction in terms, and the "diseases of autoimmunity" look very different.

The ability of organisms to defend themselves against the infinite variety of alien substances puzzled geneticists for many years, until they decided that accelerated mutation in the immune cells could explain the ability to make an infinite number of magic bullet-, lock-and-key-, antibodies. A requirement, in that point of view, was that these changes had to be random; there could be no intelligent behavior in the white blood cells,

something that had been implied in Metchnikoff's phagocyte behavior.

The "field" idea of the 20th century biologists—Alexander Gurwitsch, Charles Child, Paul Weiss, and others—was understood as the conditions that permitted the cells of the organism to achieve and maintain a functional unique identity. Gurwitsch explored the role of weak light emissions from cells, Child saw metabolic gradients as the basis of the generation and maintenance of a unified form, with its polarities, and Weiss included the organism's relation to its environment as one of the components of the organismic field.

Each organism in its development is constantly making decisions as it interacts with the world, and these decisions affect its structure, and constitute its uniqueness. Individual cells coming into being in the organism experience the unique conditions of their unique place in the organismic field, and their reactions to their place in the field modify the field. The ways that they sense their surroundings and organize appropriate responses have been ignored and/or denied by reductionist biologists, but they are the focus of attention for those who are taking a new look at "immunity." When a cell is understood to be sensing and responding to its unique situation, it's appropriate to view it as making intelligent generalizations and making appropriate decisions.

One of the important "sense organs" of cells (white blood cells, cells in mucous membranes, endothelial cells, even brain cells) is the "Toll-like receptor," TLR, which can cause cells to produce inflammatory cytokines, including interleukins, tumor necrosis factor TNF, and interferon. The TLRs have a central place in autoimmunity as well as immunity in the original sense, but they were discovered as the crucial factor in establishing the dorso-ventral, back-front, polarity in the developing fruit fly embryo. They translate position into cellular differentiation. The fact that they occur throughout the organism, even in nerve cells in the brain, rather than just in the "immune white blood cells," is consistent with Metchnikoff's view, in which "immunity" is a side effect of maintaining the coherence of the organism.

The integrity of an organism depends on everything being in its proper place, and when the integrity is disrupted, appropriate reactions occur, to restore the pattern. With small local disturbances of the field, the irritant will just be removed and degraded, with local adjustments of cell metabolism, but with larger disruptions, the entire organism will respond, with exchange of substance and information regionally and systemically, until the field becomes stable.

Recent studies are showing that location can determine whether or not endogenous proteins provoke an inflammatory reaction. (Arneth, 2010, 2012; Midgley and Beresford, 2011; Zheng, et al., 2011). Traditionally, the pattern recognized immunologically was a molecular structure, such as a protein and a material bound to the protein, but now the meaningful patterns include complex situations, the position of substances within the organismic context.

The traditional reductionist approach to immunology that has dominated for 100 years has given certain meanings to the components of what they call the immune system—antibodies, phagocytes, cytokines, etc. Biologists who are interested in the holistic processes of growth, development, and regeneration have found different meanings in those things. For example, Polezhaev showed that phagocytosis is an integral part of the cell differentiation process in tissue regeneration. In the early embryo, where there are no pathogens, TNF and interferon are present, acting as regulators of cell development and differentiation (Li, et al., 2014). Estrogen participates in the embryonic definition of the dorso-ventral polarity (Carroll, et al., 2014). In the absence of pathogens, these "signals of inflammation" are morphogens, links in the organismic field.

The toll-like receptor has been identified in simple animals such as flies, worms, and sponges, but estrogen is associated with even the simplest single cell organisms, such as Tetrahymena, so its functions in the organismic field are probably even more general than those of the TLR.

When the organism is injured, the system's "morphogens" are called into action; if no foreign organism is responsible for the injury, the reaction is called "sterile inflammation." In a healthy young organism, the repairs are made to restore the field's integrity, and the "inflammatory"

signals subside. However, if the organism lacks the necessary resources of substance and energy, the distortion of the field persists, potentially aggravating the deficiencies, leading to a state of chronic inflammation and degeneration. When there is no injury, the same signals guide the continuing processes of renewal.

One basic question is "what does injury mean to the organism?" With a general answer to that question, we can think about the organism's possible restorative responses, as they relate to "immunity," as well as to "autoimmunity" and regeneration and aging.

Highly organized multicellular organisms depend on the high metabolic efficiency made possible by the use of oxygen. During cell division to replace lost or damaged cells, this oxidative metabolism is suspended, and then is restored to allow the new cells to differentiate and take their place in the organismic field. The field, the organism's integrity, is sustained by organized respiratory metabolism, and it can be interrupted by mechanical trauma, excessive stimulation, poisons, etc., or by the absence of oxygen, of glucose, or of substances that specifically neutralize the inflammatory signals. All of these forms of injury activate aromatase, the enzyme that converts testosterone to estrogen, and estrogen activates the primitive processes that support cell division.

If "injury" effectively means "hypoxia with activation of estrogenic processes," then we can see that, in outline, the healing recovery process will involve various means for restoring tissue oxidative metabolism. Seeing a local injury in the context of the organism's life as a whole, we can see it as a parallel to the rising formation of estrogen that prepares the egg and the uterus lining for pregnancy with local hypoxia, followed by a shift to progesterone production and a generously renewed supply of oxygen. The estrogen-progesterone polarity of pregnancy exists in the adult tissues, as the polarity of growth and maturation, of inflammation and normalization.

Almost as soon as purified estrogen was available for research in the 1930s its ability to produce inflammation, cancer, miscarriages, and convulsions was recognized, but after 1941 the US pharmaceutical industry conspired to promote it as a cure for cancer and hundreds of other medical problems, including miscarriages and arthritis. Estrogen's essential role in the autoimmune inflammatory diseases has been apparent for several decades, but the industry's control of the FDA, the medical journals, and the universities has made people explain away their perceptions. Women whose rheumatoid arthritis began shortly after they started using estrogen often insisted on continuing it or even increasing the doses, because they and their doctors believed the claims in the medical journals. When they could be convinced to take a vacation from the estrogen treatment, their recovery was usually quick and complete.

In the 1970s, after I had learned to think of progesterone as the antagonist of estrogen, rather than as merely its complement during gestation, I suggested that some people with swollen, red, painful stiff joints try applying some progesterone topically. The first woman who tried it was in menopause, and her ratio of estrogen to progesterone was 1 to 1, many times higher than it should be. Her index finger that had looked like a stiff red sausage became flexible, painless and normal a few days after dipping it into a solution of progesterone in olive oil. Over the next ten years I saw similar immediate, complete, and permanent recoveries in a series of people who had been diagnosed with either rheumatoid or "osteoarthritis." At that time osteoarthritis was treated as a separate disease resulting from the wear and tear of aging, even though it was much more prevalent in women, and was associated with excessive estrogen.

There are many reasons for an imbalance between estrogen and progesterone. With aging, the amount of aromatase in the ovaries increases (Shaw, et al., 2015), but the failure to form the progesterone-producing corpora lutea at menopause causes a sudden decrease in progesterone, leaving a relative excess of estrogen. In rats, removal of the ovaries doesn't lower estrogen (Dimitrijević, et al., 2013; Stanojević, et al., 2015), but it does lower progesterone. Ovaries are a minor part of the body's estrogen production, but a major part of its progesterone production. The adrenal glands, brain, and skin can produce progesterone, but the ovaries are specialized to

produce large amounts of it, using the abundant cholesterol in the blood stream as its raw material. Injury to the ovaries, or systemic stress, tends to decrease the production of progesterone, while the body's production of estrogen is increased. Endotoxin absorbed from the intestine during stress promotes many inflammatory reactions, and activates aromatase (Christeff, et al., 1987, 1991, 1992).

It's hard to imagine how it would be possible for an "estrogen deficiency" to occur, but very easy to see why an excess of estrogen is so common. When the body's anabolic hormones, especially the thyroid hormone T3, are decreased, more events become stressful. Because of the inefficient use of glucose in hypothyroidism, fatty acids are mobilized from the tissues, and these contribute to stress and inflammation. In the autoimmune diseases, free fatty acids are consistently high. Besides contributing to the energy deficiency of hypothyroidism, the free fatty acids promote the effects of estrogen, and increase the formation of the inflammatory prostaglandins, which activate aromatase. Since estrogen increases lipolysis and elevates free fatty acids, and promotes their conversion to prostaglandins, this process initiated by stress easily becomes a self-sustaining vicious circle.

These components, hypothyroidism, accumulated polyunsaturated fatty acids, and unopposed estrogen, are basic components of all the autoimmune diseases. Progesterone happens to intervene at every stage of this process, tending to interrupt it. Sugar's ability to lower free fatty acids and to activate the thyroid hormone make it another important normalizing factor in stress and inflammation. Niacinamide and aspirin, by reducing free fatty acids, prostaglandins, and nitric oxide, and increasing cell energy, are very helpful in correcting the problems that lead to the "autoimmune diseases."

Since the 1950s, it has been recognized that antibodies produced by B cells are central to the autoimmune process. With aging and stress, the regulatory thymus gland shrinks (from about 35 grams around puberty to about 5 grams at age 70), while the more stable B cells are maintained at about the same level, or even increased. Without a functioning thymus, the antibodies bound to antigenic material become a problem (for example activating mast cells and platelets), rather than being just part of a corrective process.

Current therapies reduce inflammation by eliminating one or more components of the B cell antibody system. The reduced inflammation can permit some restorative processes to work, but the drugs aren't curative. A more biological approach would be to reduce exposure to the factors that damage the thymus or over-excite the B cells. Some of the factors that cause atrophy of the thymus gland include cortisol and other glucocorticoid hormones, estrogen, prostaglandins, polyunsaturated fatty acids, lipid peroxidation, nitric oxide, endotoxin, hypoglycemia, and ionizing radiation. Progesterone and thyroid hormone support restoration of the thymus gland, providing protection by opposing all of those agents of atrophy. An increase of sugar in the diet can correct some of the metabolic changes of aging (Missios, et al., 2014). Proliferating thymic cells are energized by sugar, their senescence is activated by fat metabolism.

Drugs that are currently used with some success for treating diseases that aren't thought of as "autoimmune," such as memantine used in Alzheimer's disease, will probably be useful in the "autoimmune diseases," that is, in diseases that involve estrogen and inflammation, including cancer.

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