Ray Peat's Newsletter

Every component of the organism is as much of an organism as every other part. Barbara McClintock

Inflammation, adaptation, and aging

For 100 years, schools and universities have taught that inflammation is an essential and benign part of our immune system, and until recently leading medical schools were teaching that inflammation implies infection, explicitly claiming that if there is inflammation, a biological pathogen must be present. If the 20th century contemporary alternative view of inflammation itself as a pathological response that doesn't necessarily indicate the presence of pathogenic organisms was mentioned, it was virulently rejected as unscientific nonsense. In recent years, this alternative view has been slowly moving into the mainstream, while the unfounded dogmatic official view of inflammation is quietly disappearing from research publications. There are, however, powerful forces in society committed to the old view.

For example, when news reports have described the painful inflammation many people experience following a vaccination, drug company agents have responded "that's good, it means the vaccine is working." (Actually, the immediate inflammatory reaction is usually caused by an adjuvant; any specific reaction to the antigenic material develops more subtly.)

The doctrine that inflammation is a necessary part of immunity, leading to destruction of the pathogen, affects the way diseases are treated. In the case of sickness associated with corona virus infection, all attention is being given to stopping the multiplication of the virus, and all of the effective anti-inflammatory treatments have been disparaged. The fraudulent Lancet article last spring on hydroxychloroquine, with coordinated FDA action, was intended to discourage the empirical treatment of symptoms, in support of the government-pharmaceutical campaign to vaccinate everyone in the world. (Recently, a Lancet article reporting that supplemental vitamin D reduced covid mortality by 60% was retracted by the editors.)

> **It is the habits and manner of life and the conditions in which its ancestors lived that have in the course of time fashioned its bodily form, its organs and qualities."**
>
> **Jean-Baptiste Lamarck**

The ACE2 enzyme, which is one of our basic means of reducing inflammation, is widely seen as the door through which the virus enters cells, and therefore as something to be blocked to protect against the virus. The virus can enter cells that lack the ACE2 enzyme (Hojyo, et al., 2020), but the important facts are that cellular inflammation promotes viral replication, and that the ACE2 enzyme prevents inflammation. Poor nutrition, aging, and other stresses weaken our antiinflammatory defenses, leading to chronic systemic inflammation, and preexisting inflammation favors viral replication, allowing the virus's toxic spike protein to dangerously interfere with our natural antiinflammatory system; the consequence can be the "cytokine storm" and multiple organ failure.

If inflammation doesn't have the essential protective immune function that has been

attributed to it, and can have such a destructive role in aging and stress, why do we have genes for the factors that contribute to inflammatory reactions? Biologists usually say that any trait found in an organism is the result of natural selection, and the presumption is that it has been beneficial at some time in our history. This presumption tends to support the complex stories that textbooks tell about the role of inflammation in disease and immunity.

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There is a very large feature of all vertebrates and at least some invertebrates and plants that relates to the question of immunity and viral infection. After the completion of the Human Genome Project, it was discovered that our "genes," the DNA that codes for proteins, make up only 2 to 3% of our DNA, and that 8% of our DNA has features showing that it represents the essential genes for producing retroviruses, and that another 40% of our DNA also represents sequences characteristic of retroviruses. This DNA has been called the genomic dark matter. A large part of it consists of mobile genetic elements, transposons.

In the 1940s, Barbara McClintock discovered that plants under stress can move their genes around to improve adaptation by producing more variation in the offspring. Rather than admit that McClintock had discovered an aspect of the creativity of life, they felt that the adaptive flexibility she had discovered was intolerably alien to their mechanistic understanding of life.

McClintock's recognition of stress-induced genetic adaptability was completely unacceptable to the dogmatic genetic determinism that was firmly in control of the research establishment, so she became almost invisible for 30 years, until the genetic engineering industry revived her work, with great publicity and prizes, so that they could claim that their genetically modified organisms were no different from the organisms that modified their own genes.

It has been discovered that McClintock's "jumping genes" come from the "viral" part of our DNA, but this information hasn't led to a general reconsideration of whether their origin is really viral. Rather, the main effect has been to darken the reputation of these agents of adaptive change. On the Cold Spring Harbor Laboratory (former home of the eugenics movement) website there is the statement "Half of your genome started out as an infection; if left unchecked, some parts of it can turn deadly all over again." As with inflammation, our intrinsic nature is given the blame for some of our worst problems.

These parallels aren't just trivial coincidences, they have been created in line with a consistent ideology of control, by a few very powerful organizations. Denial that the conditions of life are relevant to health has been their main theme, from the eugenics movement in the last century to the current fraudulent information about viral diseases.

According to the doctrine of natural selection, changes in organisms occur randomly, and environmental conditions allow some of those random variants to thrive, while it eliminates the unfit individuals. This ideology justified sterilization or euthanasia of those judged to be unfit, and it has used state power to suppress, not only the Lamarckian epigenetic idea that better conditions could be assimilated by the organism and its descendants, but also many of the efforts to eliminate disease by improving nutrition and eliminating poverty.

A simple shift of perspective can solve some old puzzles, such as how millions of species of viruses came to exist, since viruses can't reproduce themselves without the organisms they infect, and why our cells would retain such an immense amount of useless or harmful DNA, if our DNA has evolved by the elimination of the parts that didn't contribute to fitness. McClintock's work has led to an answer to those questions, as well as a basis for understanding the intelligence of epigenetics and the inheritance of adaptations. The dark DNA functions during embryonic development, mediating effects of the intrauterine environment on the expression of the

structural and regulatory proteins making up the organism. There is no reason to think of it as useless, and this means that there is no reason to believe that any of it originated as an infective disease.

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The study of exosomes, the particles the size of small viruses, which transmit useful (or harmful) information between cells, has revealed their similarity to the particles of DNA that bacteria use to transfer new information, such as resistance to antibiotics, to other bacteria. The exosome particles can carry the DNA of mobile genetic elements, and as they leave the body in its secretions, including sweat and saliva, they can carry genetic information to other individuals of the same species, or to very different types of organism.

The genetic dogma has insisted that our DNA works like a computer with "read only memory"—information flows from DNA to RNA and from RNA to proteins, but never in the reverse direction. The existence of reverse transcriptase in human cells shows that the dogma was wrong in the case of copying the information of RNA to DNA. James Shapiro's work with bacteria shows that they—supposedly one of the simplest organisms—have a read-write genome, and by understanding their situation, are able to modify their genes to adapt to problem situations. It's increasingly obvious that we have abilities similar to bacteria, with the dark DNA being part of this adaptive system.

The basic outlines of our human form and functions come into existence during gestation, in a very controlled environment. The sequential appearance of many different kinds of cell arranged in different patterns requires the interactions of cells with each other and with their surroundings. In responding to their changing conditions, cells are secreting regulatory proteins, cytokines, under the guiding influence of the transposons (Deverman and Patterson, 2009; Jachowicz, et al., 2017; Nishihara, 2019, 2020), controlling the expression of proteins of specialized cell structures and metabolism.

The healthy mother's physiology, interacting with her environment, is constantly adjusting the intrauterine conditions, regulating temperature, providing oxygen and sugar, regulating carbon dioxide level and essential nutrients while excluding major toxins. The course of the baby's development can be disturbed if the mother is malnourished or poisoned or experiencing inflammation, as from an infection, chronic stress, or vaccinations. A failure of energy, caused by hypoglycemia or interference with the use of oxygen, stops the formative developmental processes, and the constructive actions of the cytokines can become destructive, causing inflammation, probably accounting for a large portion of birth defects (Yockey and Iwasaki, 2018).

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In the well controlled gestational conditions, a local tissue injury can heal without leaving a scar (Olutoye, et al., 1996). Later in life, depending on the person's conditions of life, and on the extent to which some of the intrauterine conditions have been preserved, a similar injury might heal quickly with minimal scarring, or it might fail to heal, or it might produce massive scarring. The cytokines, and their regulating non-coding DNA, have varying effects, depending on whether there is sufficient energy to continue their preferred course of development, or whether stressful conditions demand the radical changes that can destabilize the chromosomes, leading development in a very different direction, that might produce offspring more suitable to the hostile environment.

Prolonged exposure to environmental conditions that are far from the perfect conditions of healthy gestation results in a systemic inflammatory state, and this chronic inflammation leads to the degenerative processes of aging, with a failure of the tissue restorative processes.

The loss of stem cells, and the accumulation of senescent cells that should have been replaced from the stem cell reserve, is a general feature of aging, though tissues differ in the rate of stem cell loss, according to their special stresses. Intrauterine conditions, including low oxygen and high carbon dioxide, are ideal for the functioning of stem cells, and in the mature individual, stem cells are maintained in areas with lower oxygen pressure. (Ivanovic, et al., 2004; Jeanne, et al., 2009; Hammoud, et al., 2012; Vlaski, et al., 2014), Bone marrow is a tissue with a generally low oxygen content, and it provides a continuing supply of new cells that circulate to other tissues. In cell (mouse embryonic fibroblasts) culture experiments, growth under 20% oxygen, similar to the atmosphere, caused rapid aging, while growing under 3% oxygen the cells didn't senesce. At 1% oxygen, stem cells don't divide, while at 3% they divide without losing their stem cell properties.

When cells are respiring vigorously, all of the oxygen reaching the mitochondria is immediately used, so the oxygen concentration near the respiratory enzymes is close to zero. If something interferes with the mitochondrial oxygen consumption (for example lack of thyroid hormone or the presence of too much polyunsaturated fat, or nitric oxide, or carbon monoxide), the local oxygen concentration increases, because it isn't being used. The hypoxic and quiescent stem cells are activated by the local increase of oxygen, and begin dividing and differentiating. If the damaged cells are removed, stem cells can replace them; otherwise, experiencing the conditions interfering with efficient oxygen use, they will tend to produce a tumor.

A failure of efficient oxidative energy leads to an increase of inefficient glycolysis, and the rapid use of glucose creates a local deficiency of glucose, activating the formation of the growth factor VEGF which stimulates the formation of new blood vessels (Park, et al., 2001; Dantz, et al., 2002). The retina of the eye normally experiences a low oxygen environment; an excessive amount of oxygen, such as the treatment given premature babies, produces inflammation and stimulates the formation of new blood vessels, and often causes blindness. Caffeine, which can restore respiratory energy production (for example by inhibiting nitric oxide formation), inhibits the formation of VEGF and consequently inhibits neovascularization and prevents the retinopathy of prematurity. In other tissues, similar effects of caffeine can inhibit cancer growth.

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The premature baby, suddenly leaving its low oxygen, high CO2, sugar rich environment, and experiencing the extreme new environment of a hospital incubator, is an extreme example of the way that our normal adaptive reactions can become destructive when misdirected by an unfavorable environment. The normal person, living many years in an environment with limited amounts of the most supportive factors, and varying amounts of many harmful factors, experiences a gradual accumulation of the tissue changes that are produced by the misdirected adaptive factors. Cytokines that were constructive under the conditions of gestation, become pro-inflammatory, profibrotic, and harmful in a variety of ways, for example promoting the neovascularization of age-related macular degeneration or of rosacea or of tumor growth.

In childhood and maturity, vigorous oxidative metabolism can maintain some of the essential protective factors of gestation, including adequate levels of glucose and carbon dioxide, good temperature regulation, and avoiding overproduction of superoxide and lactate. In these conditions, the cytokines can contribute to adaptation and continuing development. As inhibitors of oxidative metabolism such as polyunsaturated fats

accumulate in the tissues, the dominance of protective factors decreases, and the cytokines become more likely to produce inflammation.

As chronic inflammation progresses to fibrosis and loss of normal tissue functions, the conditions of stress increase the likelihood that the transposable elements will be activated (Andrenacci, et al., 2020), increasing chromosomal instability and physiological malfunctions.

Many years ago Gaetan Jasmin (1956, 1968) showed that low blood glucose intensifies abnormal inflammatory reactions, and that increasing blood glucose minimizes dangerous anaphylactoid reactions. It's the oxidation of glucose (producing carbon dioxide), which is favored by warmth and the right amount of insulin, that can prevent inflammation (Razavi Nematollahi, et al., 2009; Gogitidze, et al., 2010; Dandona, et al., 2010; Wright, et al., 2010). Too much insulin causes hypoglycemia, promoting inflammation; diabetics who suffer nocturnal asthma attacks can solve the problem by reducing the bedtime dose of insulin. Nocturnal asthma has been prevented by having a nighttime glass of milk or other snack to sustain blood sugar (Caplin, 1976.)

Regular exercise is often recommended for decreasing chronic inflammation, despite the fact that prolonged strong muscle contraction produces inflammatory cytokines. It turns out that the increased temperature produced by muscle activity has antiinflammatory effects that outweigh the effects of the contraction-induced cytokine. Simply keeping the body temperature up can provide those benefits of exercise (Hoekstra, et al., 2020), as long as the level of glucose is maintained.

The role of our endogenous DNA mobile elements in stress, aging, and inflammation, and their structural similarity to viruses, suggests that substances that are helpful for stress-induced inflammation could be helpful for viral infections, and vice versa. All of the effective treatments for Covid-19 have had antiinflammatory effects—angiotensin blockers, cinanserin (a serotonin blocker), antihistamines, naringenin, hesperidin, fisetin and other flavonoids (Clementi, et al., 2021; Bellavite and Donzelli, 2020; Mishra, et al., 2020; Jo, et al., 2020), progesterone (Jakovac, 2020), and calcium channel blockers (Solaimanzadeh, 2020; Jayaseelan VP and Paramasivam, 2020).

These substances reduce intracellular calcium and increase carbon dioxide in relation to oxygen and lactate, with the effect of reducing random and meaningless excitation and activation of tissues, making energy available for purposeful organized activities of the organism.

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