Ray Peat's Newsletter

"The problems we face today cannot be solved by the minds that created them" Albert Einstein

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"In the last few months cardiac hormones (i.e. atrial natriuretic peptides) have been shown for the first time to decrease the size of infarcts after acute myocardial infarctions and to cure 80% of human pancreatic cancers and two-thirds of human breast cancers in athymic mice without any surgery. Even the human pancreatic cancers that were not cured had their volume decreased to less than 10% with each of four cardiac hormones and with vessel dilator to less than 2% compared to untreated animals. None of the treated human pancreatic cancer animals died of cancer – they lived a normal lifespan and died of old age."

"In the past year the mechanism of how cardiac hormones cure cancer(s) has been largely elucidated in cancer cells: They target the RAS/RAF-MEK 1/2-ERK 1/2 kinase cascade by inhibiting up to 98% of the activation (phosphorylation) of both MEK 1/2 and ERK 1/2 and block completely the stimulation of ERK by mitogens such as epideral growth factor resulting in decreased DNA synthesis within the nucleus of the cancer cell.

Cardiac hormones (i.e. atrial natriuretic peptides) consist of a family of peptides which are synthesized and then stored as three different prohormones, i.e., 126 amino acid (a.a.) atrial natriuretic peptide (ANP), 108 a.a. brain natriuretic peptide (BNP) and 103 a.a. C-natriuretic peptide (CNP) prohormones. Within the 126 a.a. ANP prohormone are four peptide hormones i.e. ANP, long acting natriuretic peptide (LANP), vessel dilator, and kaliuretic peptide with blood pressure lowering, natriuretic, diuretic and/or kaliuretic (i.e., potassium excreting) properties."

David Vesely, 2008

Peptides, coherent adaptation, and some terminal diseases: *The roles of thyroid, progesterone, calcium, salt--issues of energy and inflammation; towards an organismic paradigm for medicine*

In the last 50 years, huge numbers of people have probably suffered needlessly and died prematurely because of a mistaken bio-medical ideology. Much of that ideology has been deliberately imposed by a corrupt drug industry, which effectively controls the regulatory agencies, major medical journals and texts, and the way the mass media treat scientific ideas.

Scientific reductionism fosters specialization, and specialization leaves the "big picture" susceptible to manipulation by those with financial and political power.

The practice of medicine is still based on mechanistic biological doctrines, but some of the coherent holistic approaches that disappeared after the second world war are being vindicated by recent research.

In treating heart disease, it's common to prescribe one drug to modify the heart's contractions, another drug to modify the kidneys' handling of water and sodium, another drug that modifies the tension of the blood vessels, and a drug to inhibit blood clotting. In treating cancer, drugs to kill tumor cells are often combined with drugs to treat the side effects of the toxic drugs, and other drugs to treat symptoms produced by the cancer. Each drug has its particular "indications," and the whole process seems to be logical and rational, as long as the doctor participates in the mechanistic culture that describes the organism and each drug's effect on the organism.

Epilepsy, diabetes, osteoporosis, depression, boils, arthritis, insomnia, etc., all have their special mechanisms and special drugs.

When a practicing physician is confronted by a patient who is trying to think about the problem coherently, in terms of things that were known in 1940 or that have been recently discovered, it's extremely unlikely that the physician will take the time, or have the mental flexibility, to consider the patient's perspective.

There is nothing in the present medical culture that would allow a physician to consider that a common substance such as progesterone, or thyroid, or calcium, or sugar, might be able to prevent or alleviate or cure some or all of the conditions mentioned above. But there are some clearly established facts that have the potential of radically changing medical culture.

The idea of cell renewal ("tissue streaming") with coordinated multiplication of stem cells and safe dissolution (apoptosis) and recycling of mature cells has now reached mainstream biology, despite some occasional lip-service to the "Hayflick limit," which submerged the idea of continuous tissue renewal for 40 years. The idea of tissue-specific regulators of cell division (e.g., W.S. Bullough's chalones) was incompatible with the Hayflick doctrine that mature cells were incapable of dividing, and with the cancer doctrine, that only genetic mutant cells were able to continue dividing beyond the Hayflick limit of 50 divisions. But now, there is great interest in studying the many specific and general factors that regulate stem cells, differentiation, and apoptosis in the mature animal.

Some of these basic regulatory systems that have been ignored for so long turn out to be processes that we have in common with all forms of life.

Every cell contains proteolytic enzymes that break down enzymes and other proteins as new proteins are made. These changes allow the cell to adapt to changes in its environment, such as different energy sources. During stress, these enzymes are activated so that new systems can be quickly formed to meet the stress. When the stress is so intense that the cell is unable to adapt, enzymes of this sort break down the cell's structure, and the synthesis of new proteins stops, causing the cell to decompose in an orderly way. More intense and sudden stress can cause a less orderly kind of cellular death, but the proteolytic enzymes participate in that kind of dissolution too, though the peptide fragments produced are different.

Bacteria growing in colonies function in some ways like multicellular organisms, and the adaptive processes, including cell dissolution when the supply of food is depleted, allow the events in an individual cell to contribute to the regulation of the colony (Ben Jacob, et al., 2004). The peptide fragments that regulate bacterial colonies also influence the interactions between bacteria and more complex organisms, because stress-induced proteolysis is a universal feature of life, and very different organisms respond in similar ways to certain kinds of fragmented proteins.

The injury-induced alarm reactions that activate proteolytic enzymes in complex organisms typically release peptide fragments that are toxic to bacteria (possibly in a sort of "excitotoxicity"), and prevent their growth and invasion, while at the same time they stimulate wound healing and local cell division; if the local injury is serious enough, an amplified inflammatory reaction can involve the whole organism, its white blood cells and adaptive antibody production and hormonal and nervous reactions.

This kind of "innate immunity" is something we have in common with all forms of life. Coupled to the alarm/inflammatory system, there are more specific protective systems of regulatory peptides, that happen to be called "natriuretic peptides," although they do much more than regulating the kidneys' handling of sodium. They were first discovered in the atria of hearts, and so were called "atrial natriuretic peptide," ANP, but then peptides with similar structure and effects were found in the brain, and called "brain natriuretic peptide," BNP, and the next type to be discovered was called CNP.

Very similar peptides occur in mollusks, insects, reptiles, plants, and mammals, apparently in all multicellular organisms, and their functions in those organisms haven't been clarified, but their

universality has stimulated interest in exploring their multiple functions.

Many immunologists think of "innate immunity" as a primitive system that serves to activate the "higher" "adaptive immune system" of vertebrates. A major difference between these two systems is supposed to be the absence of memory in the innate system. In the 1950s, experimenters applied a little copper sulfate to the leaf of a plant, in a concentration just high enough to injure the tissue it touched. Then several days later, application of a highly diluted solution of the same chemical was found to cause an intense reaction and injury. The plant's "primitive" immune system demonstrated memory. "Stress memory" in plants is now more widely recognized (Goh, et al., 2003). Recent evidence (Bouché, et al., 2003; Baluška, et al., 2004; Bais, et al., 2004; Wipf, et al., 2002) supports J. C. Bose's early work showing nerve-like functions in plants.

In 1908, Ilya Mechnikov (also written Elie Metchnikoff) and Paul Ehrlich shared the Nobel prize for physiology or medicine, for their work on immunity.

Ehrlich is considered a pioneer in chemotherapy. His early work using synthetic dyes to stain bacteria and blood cells led him to the idea of a "magic bullet," in which a toxic substance (such as certain of the dyes that were being produced by the German chemical industry) would selectively kill a particular pathogen. His ideas led eventually to the current theory of using monoclonal antibodies as "magic bullets" to kill cancer cells.

Mechnikov was investigating embryology, trying to understand the principles by which an animal develops, when he realized that nutrition, especially the process of intracellular digestion of proteins, was a guiding force in the development of the organism, and later, considering the process of phagocytosis, he saw that this same principle was centrally involved in the organism's resistance to injury and infection. From seeing the place of cellular digestion and nutrition in the growth and survival of the organism, he extended his studies to the problem of the factors that influence the organism's resistance, for example why poor people are especially susceptible to infectious disease, and how toxins absorbed from the intestine weaken resistance to infections, and contribute to aging.

Acquired immunity, existing after recovering from an infection or being vaccinated, was well known to Mechnikov (he worked with Pasteur, for example), but he didn't make the extreme distinction between innate and adaptive immunity that is now often made.

For Mechnikov, the movement of cells from connective tissues into the blood, and from the blood into the endothelial and connective tissues, destroying harmful extraneous material or cells that were no longer useful, was an integral physiological process, influenced by the nervous system, to form and sustain the organism.

Although some of his contemporaries saw cellular immunity as a sort of mechanical and autonomous system (and some denounced him as a "vitalist" because of the intelligence he saw in cellular behavior), Mechnikov insisted that the processes of immunity were integral organismic processes, in which the nervous system had an essential role. Over the years, there have been many demonstrations of the brain's importance in the inflammatory process, but even the most recent studies that have found that "neuropeptides" appear to function as part of the "innate immune system" haven't achieved the comprehensive view of the organism that Mechnikov had.

Contemporary immunology and medicine see the immune system largely as Ehrlich saw it, as a specialized killing system. Like Ehrlich, few medical immunologists are interested in the similarities between plants and animals, because they see the human immune system as a unique thing evolved to more effectively destroy things which are "not-self."

The alternative view, that has grown out of Mechnikov's work, sees that the adaptiveness of plants and invertebrate animals gives us an essential perspective on our own biology. Growth, regeneration, stem cells, learning, and aging, have to be taken into account when thinking about infections, vaccinations, and the "autoimmune" diseases. We, humans and vertebrates generally, have a very intense energy metabolism that requires a powerful circulatory system that

supports a complex nervous system, but the similarities of the immune systems of the different phyla are in some ways more important than the differences. Learning or imprinting is something that can occur in any kind of cell, and the importance of the "simple" regulatory peptides of the innate immune system is now starting to be recognized in medicine.

All of our tissues, when damaged, can produce inflammation, stimulate growth, and signal to the rest of the organism that something is wrong. All, or most, of our tissues are also able to produce substances, the "natriuretic peptides," that restore stability, by reducing inflammation, inhibiting abnormal growth, increasing phagocytosis, and balancing energetic and synthetic metabolism and structural processes, including cellular differentiation, throughout the body.

The existence of these peptides in the other multicellular organisms, and the discovery that they act on pathogens (Krause, et al. 2001) as well as on the consequences of injury, suggests that they can be considered as part of the "immune system," but that recognition needn't detract from their roles in developmental, reproductive, and other basic biological processes. In the tradition of Mechnikov, it would be better to describe them as "morphostatic peptides," referring to Jamie Cunliffe's view of immunity, or "morphogenic peptides," to acknowledge that development never stops.

Cells that were once thought to cause autoimmune destruction are now known to be involved in repair and regeneration (Hofstetter, et al., 2003). Antibodies, rather than being just germ-killing proteins, or destructive autoantibodies, have many other functions, including the regulation of inflammation and regeneration (del Barco, et al., 2008; Bieber, et al., 2001; Schwartz, 2000). Phagocytes, besides eliminating foreign matter and exhausted cells, are considered to be "antigen presenting" cells that guide the adaptive immune system, but they also have an important role in guiding regeneration and differentiation of stem cells.

L.V. Polezhaev showed that processes similar to embryonic induction, guided by phagocytes, are involved in the organism's responses to damaged tissues. For example, when a piece of killed muscle tissue was enclosed in a porous capsule that permits molecules, but no cells, to diffuse through it, and implanted subcutaneously, it had no inductive effect on surrounding cells. But when the pores of the capsule allowed cells to enter, skeletal muscle formed where the dead tissue had been, and tissue resembling heart muscle formed outside the capsule. Phagocytosis had been essential for the induction to occur. The ingested material guided the differentiation of the surrounding cells.

The phagocytosis function isn't limited to the blood cells commonly called phagocytes; even nerve cells can ingest particles and fragments of damaged tissues. Polezhaev believed that fats were an inmportant factor in stimulating regeneration, and recent research shows that saturated fats and unsaturated fats have very different effects on the antigen presenting cells (Shaikh, et al., 2008). The innate immune system is probably impaired as a result of the cumulative toxicity of the polyunsaturated fats, contributing to the problems of aging.

Unsaturated fatty acids inhibit phagocytosis (Guimaraes, et al., 1991, 1992; Costa Rosa, et al., 1996; Virella, et al., 1989; Akamatsu, et al., 1990), and accumulate with aging. Phagocytosis decreases with aging, while other immune functions may increase. The age pigment, lipofuscin, consisting largely of oxidized polyunsaturated fats, impairs the phagocytic function even before it becomes grossly visible. The highly oxidizable n-3 polyunsaturated fats (Virella, et al., 1989) appear to be the most harmful to immunity against infections such as tuberculosis (Paul, et al., 1997).

ANP activates the phagocytic processes, while inhibiting inflammation (Borán, et al. 2008; Vollmar, et al., 1997).

The use of one of these nontoxic natriuretic peptides (BNP) as a drug for treating heart failure has possibly been helpful (Mohammed, et al., 2008), and now others have been discovered to be very active against cancer (Vesely, et al., 2006, 2008), but it shouldn't be necessary to wait for their availability as drugs, since their secretion can be induced by ordinary physiological means. Mechnikov and his contemporaries concentrated

mainly on trying to reduce the absorption of bacterial toxins from the intestine to preserve or restore the basic defensive and restorative processes, but in the last century new approaches have become possible.

Since these peptides were called "natriuretic" because of their effects on salt and water regulation, it seems reasonable to consider them in situations in which there are problems with the regulation of water and salt. Premenstrual syndrome, preeclampsia or pregnancy hypertension, congestive heart failure, brain swelling and seizures all involve disturbances of salt and water regulation, but the mechanical medical tradition has almost always substituted beliefs for facts.

Because of beliefs about cell physiology, most medical publications have argued for sodium restriction in those situations, but the evidence is clear that **inadequate salt retention** is usually their outstanding pathological feature.

Progesterone has been an effective treatment in all of those conditions, and it increases the ability of the kidneys to retain sodium. Progesterone increases ANP, and together they prevent sodium loss. (Because of this, it would be better to think of ANP as an *anti*natriuretic, rather than a natriuretic, peptide.) Each of them helps to prevent excessive vascular permeability (leakiness), and to inhibit the secretion of the antidiuretic hormone (ADH, or vasopressin) from the pituitary. ADH causes sodium loss, water retention, vascular leakiness, and constriction of arterioles, increasing blood pressure while decreasing the delivery of oxygen to the tissues, and increasing the tendency of blood to clot inappropriately.

Drugs to antagonize ADH are available, and are sometimes used to treat heart failure; these drugs help to **increase** sodium retention. Aldosterone antagonists (synthetic variations of progesterone) are also used to treat heart failure; they cause sodium to **decrease.** Progesterone, and the ANP it stimulates, would inhibit both ADH and aldosterone, regulating sodium and blood pressure and improving kidney function, while (like digitalis) progesterone strengthens the heart's contraction. The reason progesterone isn't used seems to be that no drug company promotes its use.

Estrogen is often recommended to "protect the heart," and even to treat heart failure, but it lowers ANP, increases ADH/vasopressin, causes water retention and sodium loss, vascular leakiness, and (like aldosterone) weakens the heart's contraction. Part of estrogen's action on capillaries results from increasing the vascular permeability factor (VPF), which is now called vascular endothelial growth factor (VEGF). This growth factor contributes to degenerative problems including diabetes, glaucoma, arthritis, atherosclerosis, and cancer, and blocking it can cause cancers to regress. ANP blocks the production and vascular action of VEGF (Pedram, et al., 2006). Both ANP and BNP protect against excessive permeability (Klinger, et al., 2006).

Thyroid hormone, like progesterone, also increases ANP, and, probably acting through increased carbon dioxide, is essential for regulating sodium and water. Hypertonic sodium chloride and increased carbon dioxide, in themselves, increase the formation of ANP. Caffeine is another substance which inhibits VEGF, while increasing ANP.

When an imbalance of these hormones allows too much sodium to be lost, and too much water to be retained, the phagocytic cells swell, and their autophagic and phagocytic activity is impaired, making the organism more susceptible to infection. Simply correcting the osmotic balance by supplementing salt can improve immune function (Junger, et al., 1994), as it stimulates respiratory metabolism, and increases carbon dioxide and body temperature. Increased carbon dioxide promotes tissue remodeling, lowers stress, and increases the synthesis of ANP (Kukacka, et al., 2007).

ANP protects against stress-induced excitatory effects of calcium (Green, et al., 2007; *Kuribayashi*, et al., 2006; Tian and Yang, 2006; Yoshioka, et al., 2000; Wang, et al., 1993).

Intracellular calcium overload is an essential feature of heart failure and hypertrophy (Malyshev Ilu, Meerson, 1990). Both vitamin D and vitamin K require carbon dioxide for disposing of calcium properly, preventing its toxicity. When carbon dioxide is inadequate, for example from simple hyperventilation or from hypothyroidism, calcium

is allowed to enter cells, causing inappropriate excitation, sometimes followed by calcification.

Keeping an optimal level of carbon dioxide (for example, when adapted to high altitude) causes calcium to be controlled (Arkhipenko, et al., 1992), resulting in lowered parathyroid hormone (PTH), an effect similar to supplementing with calcium, vitamin D, and vitamin K. (E.g., Nicolaidou, et al, 2006.) The contribution of PTH to inflammation and degeneration is just being acknowledged (e.g., Kuwabara, 2008). It suppresses phagocytosis (Esposito, et al., 1988; Smogorzewski, et al., 2001), probably by causing calcium overload, but in other situations it stimulates proliferation of lymphocytes and T cells (Klinger, et al., 1990; Adachi, et al., 1990).

The thyroid hormone, producing carbon dioxide, helps to sustain the level of ionized calcium (Lindblom, et al., 2001). In a vitamin D deficiency, or a calcium deficiency, the parathyroid hormone increases, and this hormone can contribute to many inflammatory and degenerative processes, including heart failure (Smogorzewski, 1995; Halapas, et al., 2006; Sugimoto, et al., 2008) and cardiac hypertrophy (Liu, et al., 2008). ANP and PTH have opposite effects on cellular calcium handling, and increasing the oral intake of calcium increases ANP (Halabe, et al., 1990), but lowers PTH.

Consuming enough calcium and vitamin D to keep the parathyroid hormone suppressed (and to support ANP) is important to protect against the degenerative conditions.

In organisms with a lower rate of metabolism, the regulatory substances are more closely associated with the organisms' structure, but in homeothermic animals with a high rate of metabolism, nerves and circulating hormones serve to reinforce the basic processes of immunity, allowing the whole organism to adapt coherently to sudden changes in its situation. These hormonal and nervous systems have "polarities" that are analogous to those of the innate peptide system, i.e., one side to defend and alarm and promote growth, another side to restore coherence and functions. The defensins are balanced by the "natriuretic peptides," while estrogen, VEGF, and ADH are balanced by progesterone and thyroid, and by the osmolarity, carbon dioxide, and heat that they sustain. The antimicrobials accelerate healing, but they also stimulate tumor growth, when they aren't balanced by the opposing systems.

Mechnikov was right in seeing bacterial toxins from the intestine as a cause of aging, and he was on the right track in trying to introduce a more beneficial bacterial ecology into the intestine by using sour milk. The lactobacilli do have some protective effects, but the lactic acid that they produce turns out to function as an alarm signal, which accelerates the same aging processes that the other bacterial endotoxins produce.

When these simple physical and chemical factors are well balanced, metabolism renews the structure of the organism, directing the differentiation of new cells and adjusting the composition of the intercellular substance, according to the type of stress the organism is experiencing.

Mechnikov's emphasis on the developmental, formative nature of the immune system, combining embryology and nutritional physiology with immunity, created the foundation for the understanding of regeneration and stem cell functions. Wandering cells can become structural parts of the fixed tissues and organs (Rohde, et al., 2007), or they can remove debris and call for more phagocytic cells, or they can signal for replacement stem cells and guide their differentiation.

Local-systemic interactions, in which local events cause systemic changes, and systemic events cause local changes, have been neglected and misinterpreted, especially where the "immune system" is concerned.

The recent renewal of interest in inflammation as a basic cause of chronic and degenerative disease, is a first step toward an integral therapeutic system, even though the systemic restorative processes are still being neglected.

Bacterial endotoxins are probably the central problem, but polyunsaturated fats, heavy metals, and extraneous hormones interact with them, extending their toxic actions.

Reducing the toxic factors, relative to the restorative factors, should be the aim, rather than looking for another drug.

When even a natural, endogenous substance is used as "a drug," the way it is conceptualized and

named is likely to reinforce the mechanical models of the organism, and those models are always inadequate. If we see health problems as events in an organism's adaptation to a problematic environment, the focus is shifted to the defects in the environment that might be remedied.

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