

Ray Peat's Newsletter

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

Copyright 2009

Raymond Peat P.O. Box 5764 Eugene OR 97405

July 2009

Not for republication without written permission.

"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 epidermal 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 chalone) 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 important 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 *antinatriuretic*, 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 Iu, 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.

REFERENCES

- Biochem Biophys Res Commun. 1990 Feb 14;166(3):1088-94. **Parathyroid hormone-related protein is a possible autocrine growth inhibitor for lymphocytes.** Adachi N, Yamaguchi K, Miyake Y, Honda S, Nagasaki K, Akiyama Y, Adachi I, Abe K.
- Immunol Rev. 1993 Aug;134:5-19. **Chronic rejection in experimental cardiac transplantation: studies in the Lewis-F344 model.** Adams DH, Russell ME, Hancock WW, Sayegh MH, Wyner LR, Karnovsky MJ.
- Biochem Biophys Res Commun. 1990 Mar 30;167(3):1001-8. **Effects of temperature and osmolality on the release of atrial natriuretic peptide.** Agnoletti G, Cornacchiari A, Ferrari R, Harris P.
- J Invest Dermatol. 1990 Sep;95(3):271-4. **Suppressive effects of linoleic acid on neutrophil oxygen metabolism and phagocytosis.** Akamatsu H, Komura J, Miyachi Y, Asada Y, Niwa Y.
- Endocrinology. 1992 Mar;130(3):1753-5. **Atriopeptin: an endogenous corticotropin-release inhibiting hormone.** Antoni FA, Hunter EF, Lowry PJ, Noble JM, Seckl JR.
- Kardiologia. 1992 Jun;32(6):57-61. **[Effects of adaptation to periodic hypoxia on Ca²⁺ pump of the cardiac sarcoplasmic reticulum and its resistance to endogenous damaging factors]** Arkhipenko IuV, Sazontova TG, Rozhitskaia II, Meerson FZ.
- Trends Plant Sci. 9, 26-32, 2004. **How plants communicate using the underground information superhighway.** Bais, H.P. et al.
- Biologia (Bratisl.) 59 (Suppl. 13), 1-13, 2004. **Root apices as plant command centres: the unique 'brain-like' status of the root apex transition zone.** Baluška, F. et al.
- J Urol. 2007 Feb;177(2):751-6. **Atrial natriuretic peptide attenuates hypoxia induced chemoresistance in prostate cancer cells.** Bell EN, Tse MY, Frederiksen LJ, Gardhouse A, Pang SC, Graham CH, Siemens DR.
- Trends Microbiol. 2004 Aug;12(8):366-72. **Bacterial linguistic communication and social intelligence.** Ben Jacob E, Becker I, Shapira Y, Levine H.
- BMJ. 2000 Jun 17;320(7250):1622A. **Antibodies can repair damaged myelin in model of MS** Berger A.
- Trends Neurosci. 2001 Nov;24(11 Suppl):S39-44. **Humoral autoimmunity as a mediator of CNS repair.** Bieber AJ, Warrington A, Pease LR, Rodriguez M.
- Hum Exp Toxicol. 1995 Jul;14(7):615-6. **Cross talk between the immune system and the nervous system in response to injury: implications for regeneration.** Blakemore WF. MRC Cambridge Centre for Brain Repair, UK.
- Glia. 2008 Mar;56(4):394-411. **The ANP-cGMP-protein kinase G pathway induces a phagocytic phenotype but decreases inflammatory gene expression in microglial cells.** Borán MS, Baltrons MA, García A.
- Bose, J.C., *The Nervous Mechanism of Plants*, Langmans, Green and Company, 1926.
- Trends Cell Biol. 13, 607-610, 2003. **GABA signaling: a conserved and ubiquitous mechanism.** Bouché, N. et al.
- Nat Immunol. 2005 Jun;6(6):558-64. **The nervous system and innate immunity: the neuropeptide connection.** Brogden KA, Guthmiller JM, Salzet M, Zasloff M.
- J Clin Endocrinol Metab. 1990 Feb;70(2):349-52. **The influence of gender, age, and the menstrual cycle on plasma atrial natriuretic peptide.** Clark BA, Elahi D, Epstein FH. "...ANP levels in young women average approximately twice those in young men...."
- Biochem Mol Biol Int. 1996 Nov;40(4):833-42. **The effect of N-3 PUFA rich diet upon macrophage and lymphocyte metabolism and function.** Costa Rosa LF, Safi DA, Guimarães AR.
- Fertil Steril. 1988 Nov;50(5):743-6. **Atrial natriuretic peptide, plasma renin activity, and aldosterone in women on estrogen therapy and with premenstrual syndrome.** Davidson BJ, Rea CD, Valenzuela GJ. "Estrogens are known to increase the renin-angiotensin-aldosterone system and to produce fluid retention, while atrial natriuretic peptide (ANP) induces an increase of the urinary output and tends to return the fluid balance to normal."
- Expert Rev Neurother. 2008 May;8(5):819-25. **Boosting controlled autoimmunity: a new therapeutic target for CNS disorders.** del Barco DG, Berlanga J, Penton E, Hardiman O, Montero E.

Life Sci. 1999;64(25):2341-50. **Dual effect of female sex steroids on drug-induced gastroduodenal ulcers in the rat.** Drago F, Montoneri C, Varga C, László F.

Int J Artif Organs. 1988 May;11(3):159-60. **Toxicity in uremia. 2. Correlation between PTH levels and impaired aspecific immunity.** Esposito R, Romano-Carratelli C, Lanzetti N, Hohenegger M, Pluvio M, Capodicasa G, Nuzzo I, Giordano C.

J Endocrinol. 1991 Dec;131(3):R9-12. **Atrial natriuretic peptide is a physiological inhibitor of ACTH release: evidence from immunoneutralization in vivo.** Fink G, Dow RC, Casley D, Johnston CI, Lim AT, Copolov DL, Bennie J, Carroll S, Dick H.

Plant Cell Environ. 2008 Aug 19. [Epub ahead of print] **Molecular mechanisms underlying plant memory in JA-mediated defence responses.** Gális I, Gaquerel E, Pandey SP, Baldwin IT.

Proc Natl Acad Sci U S A. 1973 Aug;70(8):2457-61. **Growth inhibition and morphological changes caused by lipophilic acids in mammalian cells.** Ginsburg E, Salomon D, Sreevalsan T, Freese E. "Human (HeLa, Chang liver, L-132, and Intestine 407) and other mammalian (XC, SV3T3, and chick-embryo) cells in tissue culture are at least as sensitive to inhibition by lipophilic acids and nitrite as bacteria."

Plant J. 2003 Oct;36(2):240-55. **Stress memory in plants: a negative regulation of stomatal response and transient induction of rd22 gene to light in abscisic acid-entrained Arabidopsis plants.** Goh CH, Nam HG, Park YS.

Brain Res. 2004 Jul 30;1016(1):33-9. **The role of carbon monoxide and nitric oxide in hyperosmolality-induced atrial natriuretic peptide release by hypothalamus in vitro.** Gomes DA, Reis WL, Ventura RR, Giusti-Paiva A, Elias LL, Cunha FQ, Antunes-Rodrigues J

J Biol Chem. 2007 Nov 23;282(47):34542-54. **Epub 2007 Sep 24. Atrial natriuretic peptide attenuates elevations in Ca²⁺ and protects hepatocytes by stimulating net plasma membrane Ca²⁺ efflux.** Green AK, Stratton RC, Squires PE, Simpson AW.

Biochem Int. 1992 Jun;27(1):9-16. **Metabolic and functional changes in macrophages of rats fed polyunsaturated or saturated fatty acid rich-diets during ageing.** Guimarães AR, Costa Rosa LF, Safi DA, Curi R.

Biochem Int. 1991 Feb;23(3):533-43. **Effect of polyunsaturated (PUFA n-6) and saturated fatty acids-rich diets on macrophage metabolism and function.** Guimarães AR, Costa Rosa LF, Sitnik RH, Curi R.

ANZ J Surg. 2008 Jun;78(6):432-6. **Macrophages, more than just scavengers: their role in breast development and cancer.** Gyorki DE, Lindeman GJ.

Metabolism. 1990 Feb;39(2):209-12. **Atrial natriuretic factor levels in renal stone patients with idiopathic hypercalciuria and in healthy controls: the effect of an oral calcium load.** Halabe A, Wong NL, Wong EF, Sutton RA. "Ionized calcium is a stimulator for the release of several peptide hormones. Atrial natriuretic factor (ANF) is a peptide hormone released from atrial tissue in response to atrial distension or volume expansion. In the present study, we have examined the effect of an oral calcium load in healthy controls and renal stone patients with idiopathic hypercalciuria."

In Vivo. 2006 Nov-Dec;20(6B):837-44. **The PTHrP/PTH.1-R bioregulation system in cardiac hypertrophy: possible therapeutic implications.** Halapas A, Diamanti-Kandarakis E, Kremastinos D, Koutsilieris M.

Int J Cancer. 2005 May 1;114(5):713-9. **Antimicrobial protein hCAP18/LL-37 is highly expressed in breast cancer and is a putative growth factor for epithelial cells.** Heilborn JD, Nilsson MF, Jimenez CI, Sandstedt B, Borregaard N, Tham E, Sørensen OE, Weber G, Stähle M.

J Allergy Clin Immunol. 2004 Jan;113(1):79-85. **Mechanism of bronchoprotective effects of a novel natriuretic hormone peptide.** Hellermann G, Kong X, Gunnarsdóttir J, San Juan H, Singam R, Behera S, Zhang W, Lockey RF, Mohapatra SS.

Expert Opin Biol Ther. 2007 Sep;7(9):1449-61. **The role of cathelicidin and defensins in pulmonary inflammatory diseases.** Herr C, Shaykhiev R, Bals R.

J Neuroimmunol. 2003 Jan;134(1-2):25-34. **Autoreactive T cells promote post-traumatic healing in the central nervous system.** Hofstetter HH, Sewell DL, Liu F, Sandor M, Forsthuber T, Lehmann PV, Fabry Z.

Circ Shock. 1994 Apr;42(4):190-6. **Hypertonic saline enhances cellular immune function.** Junger WG, Liu FC, Loomis WH, Hoyt DB.

Endocrinology. 2002 Mar;143(3):846-52. **Inhibition of cyclooxygenase-2 by natriuretic peptides.** Kiemer AK, Lehner MD, Hartung T, Vollmar AM.

Circ Res. 2002 May 3;90(8):874-81. **Inhibition of p38 MAPK activation via induction of MKP-1: atrial natriuretic peptide reduces TNF-alpha-induced actin polymerization and endothelial permeability.** Kiemer AK, Weber NC, Fürst R, Bildner N, Kulhanek-Heinze S, Vollmar AM.

Kidney Int. 1990 Jun;37(6):1543-51. **Effect of parathyroid hormone on human T cell activation.**

Klinger M, Alexiewicz JM, Linker-Israeli M, Pitts TO, Gaciong Z, Fadda GZ, Massry SG.

Exp Cell Res. 2006 Feb 15;312(4):401-10. **Natriuretic peptides differentially attenuate thrombin-induced barrier dysfunction in pulmonary microvascular endothelial cells.** Klinger JR, Warburton R, Carino GP, Murray J, Murphy C, Napier M, Harrington EO. "Previous studies have described a protective effect of atrial natriuretic peptide (ANP) against agonist-induced permeability in endothelial cells derived from various vascular beds." "We conclude that ANP and BNP protect against thrombin-induced barrier dysfunction in the pulmonary microcirculation by a cGMP-independent mechanism, possibly by attenuation of RhoA activation."

Cancer Res. 2008 Jan 1;68(1):249-56. **Natriuretic peptide receptor a as a novel anticancer target.** Kong X, Wang X, Xu W, Behera S, Hellermann G, Kumar A, Lockey RF, Mohapatra S, Mohapatra SS.

Eur J Pharmacol. 1993 Jul 20;238(2-3):417-9. **Alpha-atrial natriuretic peptide attenuates ethanol withdrawal symptoms.** Kovács GL.

Eur J Med Res. 2001 May 29;6(5):215-8. **Human natriuretic peptides exhibit antimicrobial activity.** Krause A, Liepke C, Meyer M, Adermann K, Forssmann WG, Maronde E.

Gen Physiol Biophys. 2007 Jun;26(2):133-42. **Protein remodeling of extracellular matrix in rat myocardium during four-day hypoxia: the effect of concurrent hypercapnia.** Kukacka J, Bibova J, Ruskoaho H, Pelouch V.

Brain Res. 2006 Feb 3;1071(1):34-41. Epub 2006 Jan 26. **Neuroprotective effect of atrial natriuretic peptide against NMDA-induced neurotoxicity in the rat retina.** Kuribayashi K, Kitaoka Y, Kumai T, Munemasa Y, Kitaoka Y, Isenoumi K, Motoki M, Kogo J, Hayashi Y, Kobayashi S, Ueno S.

Osteoporos Int. 2008 Sep 30. **High prevalence of vitamin K and D deficiency and decreased BMD in inflammatory bowel disease.** Kuwabara A, Tanaka K, Tsugawa N, Nakase H, Tsuji H, Shide K, Kamao M, Chiba T, Inagaki N, Okano T, Kido S.

Endocrinology. 2007 Jan;148(1):332-6. Epub 2006 Sep 28. **Atrial natriuretic peptide, a regulator of nuclear factor-kappaB activation in vivo.** Ladetzki-Baehs K, Keller M, Kierner AK, Koch E, Zahler S, Wendel A, Vollmar AM.

Horm Res. 2001;55(2):81-7. **Decreased levels of ionized calcium one year after hemithyroidectomy: importance of reduced thyroid hormones.** Lindblom P, Valdemarsson S, Lindergård B, Westerdahl J, Bergenfelz A.

J Int Med Res. 2008 Sep-Oct;36(5):942-50. **Rat parathyroid hormone 1-34 signals through the MEK/ERK pathway to induce cardiac hypertrophy.** Liu X, Xie R, Liu S.

Kidney Int Suppl. 2001 Feb;78:S195-6. **Dysfunction of polymorphonuclear leukocytes in uremia: role of parathyroid hormone.** Massry S, Smogorzewski M.

Biull Eksp Biol Med. 1990 Mar;109(3):227-9. **[Adaptation to stress exposure prevents the**

arrhythmogenic and contractile effects of the "calcium paradox"] Malyshev Iu, Meerson FZ.

Rev Cardiovasc Med. 2008 Summer;9(3):151-8. **Nesiritide in acute decompensated heart failure: current status and future perspectives.** Mohammed SF, Korinek J, Chen HH, Burnett JC, Redfield MM.

Endocrinology. 1990 Jan;126(1):466-71. **Stimulation of rat atrial natriuretic peptide (rANP) synthesis by triiodothyronine and thyroxine (T4): T4 as a prohormone in synthesizing rANP.** Mori Y, Nishikawa M, Matsubara H, Takagi T, Toyoda N, Oikawa S, Inada M.

Cancer Res. 1992 Apr 1;52(7 Suppl):2067s-2070s. **Calcium, vitamin D, and colon cancer.** Newmark HL, Lipkin M. "Calcium contributes to the progression of epithelial cells through all phases of the proliferative cycle and into stages of cell differentiation; intracellular concentrations of calcium that are required for cell renewal, however, are lower than those required for epithelial-cell differentiation." "In rodent models, increased dietary calcium inhibited hyperproliferation of colon epithelial cells induced by increased levels of fatty acids or bile acids present in the colon. When carcinogens induced hyperproliferation of colon epithelial cells the hyperproliferation was decreased by added dietary calcium, and in several animal models the occurrence of carcinogen-induced carcinomas of the colon decreased with increased dietary calcium." "Decreased levels of ornithine decarboxylase also were reported in human and rodent colon mucosa exposed to increasing levels of calcium." "In epidemiological studies, several investigators reported inverse correlations between levels of dietary calcium intake and the incidence of colon cancer. Extrapolation of the data have suggested a protective effect of total calcium intakes above 1500 to 1800 mg/day."

Eur J Pediatr. 2006 Aug;165(8):540-5. **The effect of vitamin K supplementation on biochemical markers of bone formation in children and adolescents with cystic fibrosis.** Nicolaidou P, Stavrinadis I, Loukou I, Papadopoulou A, Georgouli H, Douros K, Priftis KN, Gourgiotis D, Matsinos YG, Doudounakis S.

Metabolism. 1997 Jun;46(6):619-24. **Influence of n-6 and n-3 polyunsaturated fatty acids on the resistance to experimental tuberculosis.** Paul KP, Leichsenring M, Pfisterer M, Mayatepek E, Wagner D, Domann M, Sonntag HG, Bremer HJ.

J Biol Chem. 2002 Nov 15;277(46):44385-98. Epub 2002 Sep 3. **Deciphering vascular endothelial cell growth factor/vascular permeability factor signaling to vascular permeability. Inhibition by atrial natriuretic peptide.** Pedram A, Razandi M, Levin ER. "Vascular endothelial cell growth factor (VEGF) was originally described as a potent vascular permeability factor (VPF) that importantly contributes to vascular pathobiology." "Thus, ANP acts as an anti-permeability factor by inhibiting the signaling functions of VPF that we define here and by preserving the endothelial cell TJ functional morphology."

Cardiology. 1991;78(4):317-22. **Plasma levels of atrial natriuretic peptide are increased in normotensive**

postmenopausal women as a function of age. Portaluppi F, Bagni B, Cavallini AR, Calisesi M, Valpondi V, Montanari L, Mollica G.

Stem Cells. 2007 Jul;25(7):1746-52. Epub 2007 Mar 29. **Immune cells mimic the morphology of endothelial progenitor colonies in vitro.** Rohde E, Bartmann C, Schallmoser K, Reinisch A, Lanzer G, Linkesch W, Guelly C, Strunk D.

Mol Vis. 2004 Jul 15;10:450-7. **Atrial natriuretic peptide in the vitreous humor and epiretinal membranes of patients with proliferative diabetic retinopathy.** Rollin R, Mediero A, Martinez-Montero JC, Roldán-Pallarés M, Suárez-Leoz M, Vidal-Fernández P, Cortés-Valdés C, Fernández-Cruz A, Fernández-Durango R.

Histol Histopathol. 2006 Jul;21(7):775-83. **Cardiac natriuretic peptides: hormones with anticancer effects that localize to nucleus, cytoplasm, endothelium, and fibroblasts of human cancers.** Saba SR, Vesely DL.

Science. 1988 May 20;240(4855):1032-3. **Essential fatty acid depletion of renal allografts and prevention of rejection.** Schreiner GF, Flye W, Brunt E, Korber K, Lefkowitz JB.

Prog Brain Res. 2000;128:259-63. **Autoimmune involvement in CNS trauma is beneficial if well controlled.** Schwartz M.

Proc Natl Acad Sci U S A. 2005 Oct 4;102(40):14452-7. Epub 2005 Sep 22. **C-type natriuretic peptide inhibits leukocyte recruitment and platelet-leukocyte interactions via suppression of P-selectin expression.** Scotland RS, Cohen M, Foster P, Lovell M, Mathur A, Ahluwalia A, Hobbs AJ.

Inflamm Res. 2008 Dec;57(12):558-563. **Exploring the complex relations between inflammation and aging (inflamm-aging): anti-inflamm-aging remodelling of inflamm-aging, from robustness to frailty.** Sergio G.

Scand J Immunol. 2008 Jul;68(1):30-42. **Differential effects of a saturated and a monounsaturated fatty acid on MHC class I antigen presentation.** Shaikh SR, Mitchell D, Carroll E, Li M, Schneck J, Edidin M.

Life Sci. 1988;42(11):1173-80. **Effect of sodium ion on atrial natriuretic factor release from rat hypothalamic fragments.** Shibasaki T, Naruse M, Naruse K, Yamauchi N, Kim YS, Masuda A, Imaki T, Demura H, Ling N, Inagami T, et al.

Miner Electrolyte Metab. 1995;21(1-3):55-62. **PTH, chronic renal failure and myocardium.** Smogorzewski M.

Heart. 2008 Nov 10. **Serum Intact Parathyroid Hormone levels predict hospitalization for heart failure.** Sugimoto T, Tanigawa T, Onishi K, Fujimoto N, Matsuda A, Nakamori S, Matsuoka K, Nakamura T, Koji T, Ito M.

Dokl Akad Nauk SSSR. 1984 Sep-Oct;278(1):253-6. **[Stress-induced decrease in body resistance to tumor growth and the prevention of this phenomenon by central inhibitory metabolites]** Sukhikh GT, Meerson FZ, Mikhaleva II.

Anticancer Res. 2006 Nov-Dec;26(6B):4143-8. **Atrial natriuretic peptide and long acting natriuretic peptide**

inhibit ERK 1/2 in prostate cancer cells. Sun Y, Eichelbaum EJ, Wang H, Vesely DL.

Artif Organs. 2001 Feb;25(2):99-108. **Better correction of metabolic acidosis, blood pressure control, and phagocytosis with bicarbonate compared to lactate solution in acute peritoneal dialysis.** Thongboonkerd V, Lumlertgul D, Supajatura V.

Neuroscience. 2006;139(4):1211-20. **C-type natriuretic peptide modulates glutamate receptors on cultured rat retinal amacrine cells.** Tian M, Yang XL.

Ann. Bot. (Lond.) 92, 1-20, 2003. **Aspects of plant intelligence.** Trewavas, A.

J Investig Med. 2008 Dec 16. **Cardiac and Renal Hormones: Anticancer Effects In Vitro and In Vivo.** Vesely DL.

J Investig Med. 2009 Jan;57(1):22-8. **Cardiac and renal hormones: anticancer effects in vitro and in vivo.** Vesely DL.

Clin Immunol Immunopathol. 1989 Aug;52(2):257-70. **Depression of humoral responses and phagocytic functions in vivo and in vitro by fish oil and eicosapentanoic acid.** Virella G, Kilpatrick JM, Rugeles MT, Hyman B, Russell R.

Eur J Pharmacol. 1997 Jan 29;319(2-3):279-85. **Effects of atrial natriuretic peptide on phagocytosis and respiratory burst in murine macrophages.** Vollmar AM, Förster R, Schulz R.

Lung Cancer. 2008 Jan;59(1):12-23. **The host defence peptide LL-37/hCAP-18 is a growth factor for lung cancer cells.** von Haussen J, Koczulla R, Shaykhiev R, Herr C, Pinkenburg O, Reimer D, Wiewrodt R, Biesterfeld S, Aigner A, Czubyko F, Bals R.

J Physiol. 1993 Jan;460:427-41. **Mechanisms underlying chemoreceptor inhibition induced by atrial natriuretic peptide in rabbit carotid body.** Wang WJ, He L, Chen J, Dinger B, Fidone S.

Clin Invest Med. 1997 Aug;20(4):211-23. **Effect of progesterone therapy on arginine vasopressin and atrial natriuretic factor in premenstrual syndrome.** Watanabe H, Lau DC, Guyn HL, Wong NL.

Trends Biochem. Sci. 27, 139-147, 2002. **Amino acid/neurotransmitter transporters are highly conserved between fungi, plants and animals.** Wipf, D. et al.

J Neurochem. 2000 Feb;74(2):633-40. **Cyclic GMP/cyclic GMP-dependent protein kinase system prevents excitotoxicity in an immortalized oligodendroglial cell line.** Yoshioka A, Yamaya Y, Saiki S, Kanemoto M, Hirose G, Pleasure D.

Sheng Li Xue Bao. 1991 Dec;43(6):580-3. **[Effect of ANP on estradiol and progesterone production by rat ovarian cells]** Zhao YL, Wang JH, Cheng CP. "The results showed that 0.1-10 ng/ml ANP promoted progesterone production in a dose dependent manner. alpha-ANP also enhanced progesterone production by granulosa cells, but not estradiol."