Ray Peat's Newsletter

Imagination is more important than knowledge. Knowledge is limited. Imagination encircles the world. **A. Einstein**

Copyright 2015 **Raymond Peat P.O. Box 5764 Eugene OR 97405** **July 2015**

Not for republication without written permission.

Imprinting and Aging

Many things have been found to change the rate of aging, but they have generally been ignored, forgotten, or denied. In the last several years many biologists have said that restriction of calories is the only proven means of significant life prolongation. The popularity of that opinion can be traced to the "rate of living" or "wear and tear" theory that was popular early in the 20th century. A few experimenters found that restriction of particular substances, rather than calories, could account for the life prolonging effects of a restricted diet.

Some of the substances in foods that shorten the life span are toxins, such as cadmium and arsenic, an excess of iron (Klang, et al., 2014; Massie, et al., 1993), phosphate (Bergwitz, 2012, Kuro-o, 2010) and the amino acids methionine, cysteine, and tryptophan.

Many experiments have found that increased amounts of some nutrients, especially niacinamide and vitamin E, have produced distinct increases in longevity in animal studies. The ratio of phosphate to calcium and vitamin D regulates "klotho," a very important anti-aging protein.

The intestine is a source of toxins, and some studies have found considerable life extension by keeping the intestine free of bacteria. At the beginning of the 20th century, Elie Metchnikof (The Nature of Man, 1894, Prolongation of Life; Optimistic Studies, 1907) believed, basing his ideas on comparative biology, that intestinal toxins caused aging by disrupting the immune and endocrine systems' functions in tissue maintenance and renewal. He noticed that the intestine of short-lived herbivores such as rabbits had a strong odor of putrefaction and a great variety of bacterial species, but that the intestines of long-lived birds such as parrots and ravens had no unpleasant smell, even when he had fed the ravens with rotting meat, and contained only a few species of bacteria.

Metchnikoff's ideas about intestinal toxins as a source of sickness and aging were widely attacked in US medical journals. In 1907 he wrote "Even at present there are critics who regard me as incapable of sane and logical reasoning."

There have been many experiments involving the manipulation of hormones to change the rate of aging. W.D. Denckla's experiments showed great life span extension from removal of the pituitary gland. The presence of the gland slows oxygen consumption with aging, its removal prevents that slowing. Other experimenters have found that reducing the amount of oxygen in the atmosphere extends the life span, supporting the observation that the prevalence of the degenerative diseases is lower at higher altitudes. Long lived species have greater amounts of carbon dioxide and bicarbonate in their blood (Muradian, 2013).

In the first half of the 20th century there was a growing consensus that x-rays and other ionizing radiation accelerated the aging process, but after 1950, the military-medical complex began promoting the idea that x-rays didn't cause cancer and heart disease, and could even slow the aging process. Something similar happened regarding estrogen and polyunsaturated fats; at first they were seen to synergize with the harmful effects of radiation, then the industries promoted the opposite belief.

Until recently, Clive McCay's experiments with grafting young animals to old animals were generally forgotten, but he showed that the maximum life span could be approximately doubled. Experiments of this sort have resumed,

with a focus on finding a product in the young animial's blood that can be sold as a product. Harvard has patented a molecule, GDF-11, which activates cell renewal.

Alexis Carrell's experiments with chicken hearts demonstrated immortalization of an organ, by frequently renewing the plasma in which the tissue was maintained. Han Selye designed an experiment in which an animal's own plasma and lymph renewed a bit of connective tissue isolated in an implanted glass tube, and found that the repeated removal of fluid from the chamber kept that tissue from aging, while the rest of the animal aged normally

Other experimenters found that tissues repeatedly grafted from old animals into younger animals were apparently immortalized (or renewed with each transplantation), while retaining their normal function and structure through as many as ten normal life spans. Removing an old dog's plasma and replacing it with a salt solution restored the dog to youthful vitality, suggesting that simple dilution of something in the aged internal environment can be beneficial.

These observations, as a group, show that aging involves systemic physiological processes very different from "wear and tear," but something in the culture of science and medicine has created a reluctance to consider the problem holistically, to think about the nature of the living organism that responds in those ways.

Although farmers have generally recognized that plants and animals are altered by changes in the weather or their food supply, the doctrine of genetic determinism had until recently caused many people to insist that the environment and diet of a pregnant woman couldn't affect the development of her baby. While animal experiments in the 1950s and '60s were showing that the size and proportions of the body were influenced by the conditions of the mother during gestation, and that those changes could be passed on for generations, the official medical doctrine [illegible] mobilize its energy in the normal way. In old age, a relatively small stress can be deadly, because the organism is unable to produce the energy needed to respond to the stress. Learned helplessness is coming to be seen as a form of "imprinting," involving various epigenetic medicine, because some of the conditions that made them possible haven't changed.

Ideas of stable inheritance in biology, from 19th century Weissmanism to 20th century neo-darwinism were paralleled in physics by the philosophy of atomic determinism, a "clock-work universe," which would follow universal laws while inevitably "running down." Analyzing the amount of energy, in the form of fire, used in a steam engine to produce work, and the amount of heat produced by friction as the engine did its work, it was realized that the system would always lose some usable energy as heat, so that a "perpetual motion" machine was impossible in principle. The total amount of energy stayed the same (the first law of thermodynamics), but the amount of usable energy always decreased (second law of thermodynamic).

These laws were useful for mechanical engineering and chemistry, but the physicists were so pleased by the simplicity of that way of thinking that they applied it to the whole universe, including the interior of stars. When they were criticized, they became rude. Applying their understanding of Kant's philosophy and Darwin's evolution theory, they said that their opponents were suffering from the inheritance of a primitive philosophy that made their brain unable to grasp the new true science. Around the beginning of the 20th century, this attitude was widely shared in the "scientific" culture. Ludwig Boltzmann, Ernst Mach, and Arthur Eddington all expressed it.

The universe, in this "new" view, is running down, from a beginning state of absolute order and unlimited available energy (a complete absence of entropy), to a future state of absolute disorder and complete entropy. Eddington wrote: "The law that entropy always increases--the second law of thermodynamics--holds, I think, the supreme position among the laws of Nature."

"The chain of deductions from this simple law have been almost illimitable; and it has been the interested and active condition. The hormones and other chemicals that can correct learned helplessness increase the production and effective use of energy and relieve the physiology of stress, which has led to the unfavorable "imprinted" or developmental changes.

the final taking away of a dimension that did it. I will tell you what is stopping you. You are using a conception of space which must have originated many million years ago and has become rather firmly embedded in human thought. But the space of physics ought not to be dominated by this creation of the dawning mind of an enterprising ape."

This attitude was immediately taken up by the anti-Darwinists at the beginning of the 20th century who created neo-darwinism and genetic determinism, with their "immortal germ line," and the "mortal soma" doctrine that made the "wear and tear" theory of aging seem plausible.

Any change in the immortal genes had to be random, because while entropy can only increase, order decreases. In 1956, this was formalized as the Central Dogma of molecular biology, that information flows only from DNA to RNA and from RNA to protein.

Embryologists and developmental biologists continued to think in terms of fields creating forms, of emergent features, and "epigenetic" effects, until government defunding and other events submerged that kind of thinking after about 1950. The "War on Cancer," that was declared in 1971, funded studies based on the idea that cancer was "genetically determined," caused by (unpredictable) changes in the DNA of a single cell. That project's failure to produce results in more than 40 years has led to a reconsideration of the idea that cancer is a metabolic and developmental problem, involving the same principles that govern normal development.

If cancer can now be seen as an epigenetic problem of development, then maybe aging, which progressively increases the tendency to develop cancer, can be productively treated as a systemic metabolic problem that steers development into blind alleys.

In "learned helplessness," an animal will die in a situation that a normal animal could easily endure, because it fails to mobilize its energy in the normal way. In old age, a relatively small stress can be deadly, because the organism is unable to produce the energy needed to respond to the stress. Learned helplessness is coming to be seen as a form of "imprinting," involving various epigenetic factors such as modification of DNA by attaching methyl groups in specific gene-regulating locations (van der Doelen, et al., 2015; Nikolova and Hariri, 2015; Bodden, et al., 2015; Sterrenburg, et al., 2011). Although the state of helplessness can persist indefinitely, a single experience of escape is all that's necessary for the animal to regain its normal ability to escape and to mobilize its energy to survive stress.

In aging, expression of genes is broadly inhibited by a general increase in DNA methylation. Because of the involvement of similar epigenetic modifications of gene expression, aging can be thought of as a type of imprinting that involves features similar to learned helpless, in which the organs and tissues, including the brain, are unable to mobilize the energy needed for ordinary adaptive processes.

At the opposite philosophical extreme from genetic determinism is the (e.g., Whiteheadian) view of the body as a unique substance that's always in process of development, in free interaction with everything in its environment. Our language and culture tend to instill some "Platonic" ideas of determinism, rigid categories and timelessness, but early life stress--during gestation and early childhood--sets the organism on a course of inadaptability and exaggerated susceptibility to stress, resembling a chronic mild degree of helplessness, which makes it easier to conform to the impositions of the culture.

The characteristic outlook toward the future, in this stress-induced state, is that it will be just more of the same, and that efforts to improve it are futile. The opposite attitude, recognizing that the complexity of interactions is always creating new possibilities, sees multiple possibilities and imaginatively makes choices that are likely to lead to a future of further possibilities and choices.

In animal studies, an enriched environment is one of the things that can promote change of the brain and behavior from the hopeless condition to the interested and active condition. The hormones and other chemicals that can correct learned helplessness increase the production and effective use of energy and relieve the physiology of stress, which has led to the unfavorable "imprinted" or developmental changes.

The balance between methylation and demethylation is influenced by both general and local conditions, including the abundance of methyl donors and the redox balance, with a reduced state (higher ratio of GSH to GSSG, a shift away from oxidation) and hypothyroidism increasing methylation. Other factors include intracellular pH, and energy. (Jump, et al., 1987; Wong, et al., 1989; Sui and Li, 2010; Holz-Schietinger and Reich, 2015; Huang, et al., 2012; Niedzwiecki, et al., 2013; van der Wijst, et al., 2015). These factors are involved in adapting to the environment, and mediate the effects of the environment on the genes.

The blood and lymph are the internal environment, *milieu intérieur*, that cells constantly interact with and depend on for the substances and signals that they need to survive and function. Since it changes with the states of the organism and its external environment, it will reflect the processes of enrichment and renewal, stress and degeneration, regeneration and aging. These fluids, and the nervous system, control the processes of adaptive imprinting.

The kidneys, lungs, and intestine interact closely in maintaining this watery internal environment. Foods and intestinal bacteria produce adaptive reactions, but some of those adaptive reactions, that are effective for the moment, limit the range of future adaptations.

Stressed, imprinted, and inefficient kidneys increase stress imprinting systemically. Chronic kidney disease accelerates aging, and with aging there's a steady decrease of kidney function.

Several of the effective anti-aging methods involve exchange and dilution of the blood serum or lymph, implying that something responsible for the syndrome of aging is present at increased concentration in old age. Other anti-aging methods are closely related to the function of the kidneys or intestine, implying that the aged kidneys are removing less of the senescence-producing factors (senectogens), and/or that the aged intestine is producing more. Failing kidneys damage bowel function, leading to increased production of toxins.

Early life stress increases vasopressin (the antidiuretic hormone), and serotonin, and these are involved in life-long behavioral effects, including increased depression, aggression and anxiety. A variety of types of stress, especially if prolonged, increase vasopressin, including maternal separation, forced swimming, suspension by the tail, pain, and exposure to bacterial endotoxin, cadmium, and probably organophosphates. Hypoglycemia, histamine, serotonin, estrogen, and parasympathetic nervous activity are among the endogenous factors that increase vasopressin.

Stress affects gene methylation to increase production of vasopressin. Antagonists to vasopressin can reverse the learned helplessness produced by stress. Vasopressin is responsible for the intestinal bleeding of stress, causing constriction of the bowel blood vessels, and damages the barrier function of the bowel, and also the blood brain barrier and generally increases vascular leakiness.

Chronic exposure to vasopressin damages the kidneys, causing abnormal growth and fibrosis, as it does in the heart. The increased collagen synthesis is at least partly dependent on the increased nitric oxide production caused by vasopressin. Increased nitric oxide is also responsible for the reduced body temperature and lower metabolic rate produced by vasopressin.

The lower metabolic rate is useful during sleep and torpor/hibernation, but when vasopressin is increased in the daytime the effect is to reduce adaptability, as in aging.

Since darkness is stressful, sleep, with reduced urine formation and reduced calorie requirement, is convenient, though longer light exposure, with less need for sleep, probably slows aging processes. High altitude raises the threshold for vasopressin secretion, increasing the metabolic rate, and this probably contributes to the lower incidence of degenerative diseases at high altitude.

Stressed cells shed increasing quantities of microvesicles or exosomes containing proteins, RNA, and DNA into the blood and lymph, and these can be taken up by other cells. The process extends the idea of a "synapse" to include a substantial relationship between cells even in remote parts of the body. This communication, intensified by stress, extends the idea of "epigenetics" far beyond the mere modification of genes and histones, to include transfer of genetic

material between cells. In the highly stressed states, it's likely that the blood platelets, which normally carry a considerable amount of vasopressin, release it along with the granules and microvesicles that they shed.

The food industry is promoting the use of various gums and starches, which are convenient thickeners and stabilizers for increasing shelf-life, with the argument that the butyric acid produced when they are fermented by intestinal bacteria is protective. However, intestinal fermentation increases systemic and brain serotonin, and the short-chain fatty acids can produce a variety of inflammatory and cytotoxic effects. Considering the longevity and stress-resistance of germ-free animals, choosing foods (such as raw carrots or cooked bamboo shoots or cooked mushrooms) which accelerate peristalsis and speed transit through the bowel, while suppressing bacterial growth, seems like a convenient approach to increasing longevity.

In the years following the publication of Mechnikoff's book in the US, there was a campaign in medical journals to deny the validity of his idea of life-shortening "auto-intoxication" from the bowel. Warnings about the dangers of laxatives and enemas became common, and it was argued that a daily bowel movement wasn't necessary. Max Gerson's use of enemas in cancer therapy was ridiculed. Finally, the FDA banned the sale of cascara as a laxative. Recently, the kidney industry has been realizing that the bowel is the source of the major toxins of uremia, so there might be a gradual change of attitude toward the intestine in medicine generally.

Avoiding hypoglycemia and optimizing sugar oxidation reduces stress and especially vasopressin (Heisler, et al., 1994), protecting the ability to produce progesterone and testosterone. Hypoglycemia increases growth hormone and liberates free fatty acids from storage. Growth hormone has been known for a long time to produce insulin resistance, and the mechanism for that involves increasing free fatty acids and strongly inhibiting the crucial enzyme for oxidizing glucose, pyruvate dehydrogenase (PDH).(Nellemann, et al., 2013.) Aging involves these same changes. Free fatty acids in the blood are mainly bound to albumin, and when these fatty acids are unsaturated they contribute to kidney damage and albumin leakage into the urine.

Since the long-lived dwarf mice, lacking growth hormone, have been studied, it has been known that increased growth hormone decreases longevity, and decreased growth hormone extends it. "Animal models of congenital GH [growth hormone] deficiency have remarkably increased life span and humans with congenital GH deficiency may have decreased rates of age-related diseases such as diabetes and cancer" (Chertman, et al., 2015).

The anti-aging protein klotho is inhibited by vasopressin and aldosterone (Tang, et al., 2011). Klotho allows the kidneys to pass phosphate into the urine, while growth hormone has the opposite effect, causing the retention of phosphate (Schmid, et al., 2013), one of the most important "uremic toxins." Vasopressin increases tissue calcification by causing the uptake of phosphate (Nishiwaki-Yasuda, et al., 2007).

Meats, legumes, nuts, and grains have an extremely high ratio of phosphate to calcium. Milk, cheese, and cooked leaves have a good ratio of calcium to phosphate. Calcium's anti-inflammatory effects help to reduce the inflammatory/excitatory effects of phosphate.

Estrogen decreases kidney function in various ways, including increases of vasopressin and nitric oxide, increased cortisol and growth hormone, and inhibition of pyruvate dehydrogenase, with a shift away from sugar oxidation to increased fat mobilization and oxidation. Stimulating intestinal activity, for example with unfermentable fiber, helps to reduce estrogen and cortisol, while increasing progesterone. Progesterone and thyroid hormone are protective for the kidneys.

Choosing foods rich in B vitamins helps to maintain glucose oxidation, and supplementing niacinamide can be especially helpful by decreasing the level of free fatty acids in the blood. Sugar, from ripe fruit, and milk or other calcium-rich food, and progesterone are other things that protect kidney function by reducing free fatty acids.

Parathyroid hormone is a "partial agonist" to vasopressin in kidney (Carney and Dirks, 1988),

and its excess is a serious problem in chronic kidney disease. Parathyroid hormone in the "upper normal" range contributes to hardening of the arteries (Buizert, et al., 2013), and it's associated with other aging problems, including osteoporosis and frailty (Tajar, et al., 2013). Larger intake of calcium in the diet, and lower phosphate, can prevent the increased parathyroid hormone in aging.

In general, things that are favorable for good cell functioning decrease the harmful effects of increased hormonal activities.

REFERENCES

Miner Electrolyte Metab. 1999 Jul-Dec;25(4-6):384-90. Nitric oxide/L-arginine in uremia. Aiello S, Noris M, Remuzzi G.

Nephrol Dial Transplant. 2012 Sep;27(9):3399-406. Dietary phosphate modifies lifespan in Drosophila. Bergwitz C.

Front Behav Neurosci. 2015 Mar 3;9:47. Benefits of adversity?! How life history affects the behavioral profile of mice varying in serotonin transporter genotype. Bodden C, Richter SH, Schreiber RS, Kloke V, Gerß J, Palme R, Lesch KP, Lewejohann L, Kaiser S, Sachser N.

J Clin Endocrinol Metab. 2013 Oct;98(10):E1583-90. PTH: a new target in arteriosclerosis? Buizert PJ, van Schoor NM, Simsek S, Lips P, Heijboer AC, den Heijer M, Deeg DJ, Eekhoff EM.

Miner Electrolyte Metab. 1988;14(2-3):142-5. Effect of parathyroid and antidiuretic hormone on water and calcium permeability in the rat collecting duct. Carney SL, Dirks JH.

Growth Hormone in Aging. Chertman LS, Merriam GR, Kargi AY. In: De Groot LJ, Beck-Peccoz P, Chrousos G, Dungan K, Grossman A, Hershman JM, Koch C, McLachlan R, New M, Rebar R, Singer F, Vinik A, Weickert MO, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2015 May 4.

Neuroendocrinology. 1994 Sep;60(3):297-304. Vasopressin mediates hypoglycemia-induced inhibition of luteinizing hormone secretion in the ovariectomized rhesus monkey. Heisler LE, Tumber AJ, Reid RL, van Vugt DA.

Biochim Biophys Acta. 2015 Jun;1850(6):1131-9. De novo DNA methyltransferase DNMT3A: Regulation of oligomeric state and mechanism of action in response to pH changes. Holz-Schietinger C, Reich NO(2).

Cancer. 2012 Oct 15;118(20):4969-80. Helicobacter pylori induces promoter methylation of E-cadherin via interleukin-1? activation of nitric oxide production in gastric cancer cells. Huang FY(1), Chan AO, Rashid A, Wong DK, Cho CH, Yuen MF.

J Biol Chem. 1987 Jan 15;262(2):778-84. Chromatin structure and methylation state of a thyroid hormone-responsive gene in rat liver. Jump DB, Wong NC, Oppenheimer JH.

Aging (Albany NY). 2014 Nov;6(11):975-91. Iron promotes protein insolubility and aging in C. elegans. Klang IM, Schilling B, Sorensen DJ, Sahu AK, Kapahi P, Andersen JK, Swoboda P, Killilea DW, Gibson BW, Lithgow GJ.

Mech Ageing Dev. 2010 Apr; 131(4): 270–275. A potential link between phosphate and aging – lessons from Klotho-deficient mice Kuro-o, M.

Mech Ageing Dev. 1993 Apr;67(3):227-37. Inhibition of iron absorption prolongs the life span of Drosophila. Massie HR, Aiello VR, Williams TR.

Biogerontology. 2013 Dec;14(6):687-91. "Pull and push back" concepts of longevity and life span extension. Muradian K

Acta Physiol (Oxf). 2013 Oct 21. Growth hormone-induced insulin resistance in human subjects involves reduced pyruvate dehydrogenase activity. Nellemann B, Vendelbo MH, Nielsen TS, Bak AM, Høgild M, Pedersen SB, Biensø RS, Pilegaard H, Møller N, Jessen N, Jørgensen JO.

Epigenetics. 2013 Jul;8(7):730-8. Blood glutathione redox status and global methylation of peripheral blood mononuclear cell DNA in Bangladeshi adults. Niedzwiecki MM1, Hall MN, Liu X, Oka J, Harper KN, Slavkovich V, Ilievski V, Levy D, van Geen A, Mey JL, Alam S, Siddique AB, Parvez F, Graziano JH, Gamble MV.

Trends Cogn Sci. 2015 Jul;19(7):366-73. Can we observe epigenetic effects on human brain function? Nikolova YS, Hariri AR.

Endocr J. 2007 Feb;54(1):103-12. Vasopressin stimulates Na-dependent phosphate transport and calcification in rat aortic smooth muscle cells. Nishiwaki-Yasuda K, Suzuki A, Kakita A, Sekiguchi S, Asano S, Nishii K, Nagao S, Oiso Y, Itoh M.

J Endocrinol. 2013 Nov 1;219(2):R37-57. Growth hormone and Klotho. Schmid C, Neidert MC, Tschopp O, Sze L, Bernays RL.

PLoS One. 2011;6(11):e28128. doi: 10.1371/journal.pone.0028128. Chronic stress induces sex-specific alterations in methylation and expression of corticotropin-releasing factor gene in the rat. Sterrenburg L, Gaszner B, Boerrigter J, Santbergen L, Bramini M, Elliott E,

Chen A, Peeters BW, Roubos EW, Kozicz T.

Steroids. 2010 Dec;75(12):988-97. Effects of perinatal hypothyroidism on regulation of reelin and brain-derived neurotrophic factor gene expression in rat hippocampus: Role of DNA methylation and histone acetylation. Sui L, Li BM.

Age Ageing. 2013 May;42(3):352-9. The association of frailty with serum 25-hydroxyvitamin D and parathyroid hormone levels in older European men.

Tajar A, Lee DM, Pye SR, O'Connell MD, Ravindrarajah R, Gielen E, Boonen S, Vanderschueren D, Pendleton N, Finn JD, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Huhtaniemi IT, Kula K, Lean ME, Punab M, Wu FC, O'Neill TW.

Am J Physiol Renal Physiol. 2011 Oct;301(4):F745-50. Downregulation of Klotho expression by dehydration. Tang C, Pathare G, Michael D, Fajol A, Eichenmüller M, Lang F.

Growth Horm IGF Res. 2003 Oct;13(5):282-6. Growth hormone enhances proinflammatory cytokine production by monocytes in whole blood.

Uronen-Hansson H, Allen ML, Lichtarowicz-Krynska E, Aynsley-Green A, Cole TJ, Höidén-Guthenberg I, Fryklund L, Klein N.

Epigenetics. 2015 Aug 3;10(8):671-6. Local chromatin microenvironment determines DNMT activity: from DNA methyltransferase to DNA demethylase or DNA dehydroxymethylase. van der Wijst MG, Venkiteswaran M, Chen H, Xu GL, Plösch T, Rots MG.

Dev Psychopathol. 2015 Feb;27(1):123-35. Early life adversity and serotonin transporter gene variation interact to affect DNA methylation of the corticotropin-releasing factor gene promoter region in the adult rat brain. van der Doelen RH, Arnoldussen IA, Ghareh H, van Och L, Homberg JR, Kozicz T.

Mol Endocrinol. 1989 Apr;3(4):645-50. Thyroid hormone-, carbohydrate, and age-dependent regulation of a methylation site in the hepatic S14 gene. Wong NC, Schwartz HL, Strait K, Oppenheimer JH.

****