# Ray Peat's Newsletter

*What is now proved was once only imagin'd.*

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## Homeostasis and Aging

### Thyroid mysteries and minerals: Cramps, excitotoxicity, dementia, and CO2

Blood perfusion of the brain and heart and muscles is increased by carbon dioxide, which is logical, considering that carbon dioxide ordinarily rises during metabolic activation. But the kidneys don't have this simple response to carbon dioxide, and this seems to be because of the special role of carbon dioxide in homeostasis and kidney function.

Blood flow to the kidneys is regulated by nerves and hormones. Parathyroid hormone and growth hormone cause vasodilation in the kidney, and increase its blood flow. The increased flow tends to produce a more dilute, hypotonic urine. In the kidneys, carbon dioxide's effects are much more complex than just regulating blood flow, and the kidneys maintain a remarkably high concentration of $CO_2$, causing some people to argue that they concentrate it from the blood.

About 88 years ago, W. F. Koch (who is known for his cancer therapy) studied the parathyroid hormone and its relation to tetany (prolonged muscle contraction) and convulsions, and was able to demonstrate that the major minerals, sodium, potassium, magnesium, and calcium are to some extent interchangeable in alleviating the tetany and convulsions produced by removal of the parathyroid gland, though magnesium was the most effective. This work was ignored by those who wanted to establish a simple relationship between "one gland, one hormone, one mechanism, one symptom or disease." A. J. Carlson's group promoted the idea that the parathyroid hormone's function was simply to increase the amount of calcium in the blood, and that it was calcium which prevented tetany. This doctrine has had far-reaching consequences.

The view which has come to dominate twentieth century biology is that organisms were assembled by a simple-minded watchmaker named Natural Selection, and that they can be understood by reducing them to their simple parts, the way we understand a watch or a motor. A polar opposite to that view would be that nature is infinite, but knowable. To understand Koch's step from tetany to cancer isn't possible within the conventions of ordinary "medical endocrinology," but Koch assumed that nature hadn't learned its methods in medical school. Koch postulated, early in the century, that electrons and free radicals were involved in the most important biological processes—respiration, movement, immunity, regeneration, etc. He was probably the first person to apply the subtleties of organic chemistry (such as the activation of chemical groups by nearby groups) to biology. (Electronic induction.) Albert Szent-Gyorgyi, a Hungarian aristocrat, recognized the complexity of nature and tried to work out a detailed scientific explanation for the ideas postulated by Koch. Szent-Gyorgyi, following Koch's interest in free radical color changes and fluorescence, understood that certain biological pigments represented special *interactions of electrons and photons with proteins,* and that muscle contraction wasn't just "a mechanical process," but probably involved all of the processes that distinguish life from death.

***Books by William Frederick Koch:***
***Cancer and its Allied Diseases, 1926.***
***Natural Immunity, 1934.***
***The Chemistry of Natural Immunity, 1939.***
***The Survival Factor in Cancer and Viral Infections, 1955, 1958.***

For both Koch and Szent-Gyorgyi, contraction, respiration, and cancer were life processes that required understanding the interactions of water, electrons, and proteins. Practically all other biologists ridiculed their interest in water and electrons.

(One of Szent-Gyorgyi's major projects in studying the role of respiratory energy in muscle contraction involved a strain of goat that suffers from myotonia, or chronic and generalized excessive muscle tension. I suspect that Koch's work with tetany led him in this direction.)

Szent-Gyorgyi found that progesterone and estrogen have antagonistic effects on the heart, and explained progesterone's similarity to digitalis by suggesting that it helps the cells to "build structure." The structure that he referred to in the muscle cell was the structure made up of "structured water" and proteins and regulatory substances. Carbon dioxide's concentration affects the structural energy content of the protein-water system, and this effect can nicely account for many of the mysteries of cellular heat production, including the negative heat observed in certain stages of nerve and muscle activity. Szent-Gyorgyi used a variety of electron/photon/chemical interactions to demonstrate that intracellular water has special structural properties. This line of thinking led him to a view of ionic regulation (1957) similar to Gilbert Ling's, and probably contributed to Linus Pauling's similar ideas (1960). (Szent-Gyorgyi never publicly acknowledged his respect for Koch's work, since he was obviously aware of the great dangers from the coalition of the medical-pharmaceutical establishment, the FBI, and organized crime, which drove Koch out of the United States. During the decade in which Koch operated his clinic in Detroit, it was the only large city in the U.S. in which cancer mortality declined; while cancer mortality in Los Angeles was rising by 30%, in Detroit it was declining by 20%. Immediately after the Koch episode, the same alliance conspired against Andrew Ivy and the Durovic brothers to steal the anticancer drug they called Krebiozen, but in Koch's case, they couldn't figure out just what to steal, so they tried to kill him or put him in jail. A. J. Carlson, incidentally, had a prominent role in the conspiracy against Ivy.)

Instead of receptors and effectors, locks and keys, motors and pumps, all built up arbitrarily by natural selection, the coherent view of the organism is that the **fundamental properties of matter are used and amplified and focussed by processes of tuning and balancing.** It is the "subtle reactivity" of the living system which maintains the adaptive organization of energy and structure. Part of the reactivity of the organism is the flexibly interactive metabolism, which adaptively distributes substance and energy. Ordinary metabolism, by *adjusting the affinities of the cell substance,* can account more rationally for the processes that are called "homeostatic" than the hypothetical apparatus of "pumps" and "channels," which are biology's *deus ex machina,* proposed whenever needed.

The doctrine of "one gland-one action" caused people to focus on the low blood calcium which occurs in the tetany which is brought on by removal of the parathyroid gland (which sometimes killed patients when their thyroids were removed, along with the associated parathyroids). By the 1920s, surgeons were careful about avoiding damage to the parathyroids to avoid tetany, but tetany kept occurring. They began leaving part of the thyroid gland, too, but tetany still occurred in a significant portion of patients. In fact, tetany is a risk following other operations, such as removal of the gall bladder. A new explanation for post-thyroidectomy tetany was invented, "the hungry bone syndrome," based on the idea that hyperthyroidism robs the bones of calcium, and that the bones begin stealing calcium from the rest of the body when the gland is removed. However, animal experiments show that it is only synthetic thyroxin which causes bone to lose calcium, and that the natural thyroid hormone, $T_3$, stimulates bone growth; also, euthyroid patients can experience tetany following removal of their thyroid.

**Practically any kind of poisoning causes cells to take up calcium from the blood,** so the finding of hypocalcemia in association with tetany might permit people to confuse effect with cause!

Tetanic associated ↓ Calcium

(1) Guanidine + methylguanidine + Ammoniaque = Convulsion en agissant sur les recepteurs des ac. aminé excitatrice

The doctrine of hypocalcemic tetany led to the practice of treating tetany with intravenous calcium solutions; for example, veterinarians often treat cows' "grass tetany" with large intravenous doses of calcium. The treatment works, but the tetany is now attributed to a magnesium deficiency (since magnesium supplementation works better, as Koch discovered), and excessive ammonia produced in the cow's rumen can contribute to the magnesium deficiency. The facts that have grown up in veterinary research have a strong parallel to Koch's ideas presented around 1912.

Koch found that the **convulsions produced by removal of the parathyroid glands were associated with the development of nephritis and the appearance of the toxic substances, guanidine and methylguanidine.** These compounds, and ammonia, are now known to produce convulsions by acting on the "excitatory amino acid receptors." These excitatory receptors release calcium into the cytoplasm, activating many cell processes, including the liberation of fatty acids and the breakdown of proteins. When these "receptors" are activated, the cells' energy requirement increases, and glucose is consumed more rapidly. Whenever these "receptors" are activated, magnesium will protect the cell from the "toxic" excitation. Effective antidotes to the excitotoxins have been based on their blocking of these "receptors." Amantadine is now known for its neuroprotective activity, as well as its anticholinergic and antiviral effects. In the 1950s, toxins based on the guanidine group (e.g., phenformin) were introduced to treat diabetes, because they can lower blood sugar, but they were later withdrawn because they killed the patients too quickly.

Carbon dioxide, produced by respiratory use of glucose, suppresses glycolysis, and so spares sugar. Carbon dioxide is also combined with ammonia, detoxifying it into urea. Although it hasn't been determined, I suspect that Koch's "toxic amines" are detoxified by their direct combination with carbon dioxide, which spontaneously reacts with amines to form carbamino groups. When there isn't enough carbon dioxide to combine with ammonia, the ammonia can combine with ketoglutarate, from the Krebs cycle, interfering with respiration at the same time that it produces the excitatory glutamic acid. Ammonia, in chronic poisoning, rather than producing convulsions, produces stupor and coma, and at this point, its combination with glutamic acid to produce glutamine is probably important as a defense against seizures, eliminating both ammonia and glutamic acid.

Hyperventilation, in which too much carbon dioxide is "blown off," causes tetany, and in susceptible people, can cause convulsions. Hyperventilation causes constriction of the bronchial muscles and thickening of mucus, producing symptoms of asthma. It causes contraction of blood vessels in the heart, weakening the pumping action, while blood vessels in the general circulation also constrict, raising blood pressure and reducing circulation. Hyperventilation commonly causes arrhythmia, and thickens the blood. The loss of carbon dioxide reduces brain circulation, creating complex paresthesias and stroke symptoms. "Hyperventilation" is a relative term, and refers to the amount of carbon dioxide which is lost from the blood. Heavy, rapid breathing at high altitude or in the presence of a carbon dioxide-rich atmosphere, doesn't necessarily constitute hyperventilation.

Water, proteins, oxygen, and minerals, are all crucially regulated by carbon dioxide. The enzyme, carbonic anhydrase, which is regulated by hormones (including the parathyroid hormone) and nerves, accelerates the interchange between carbon dioxide and bicarbonate, each of which has special functions. Bicarbonate is more soluble in water, but carbon dioxide is more soluble in living substance and fats. Carbonic anydrase is active in regions which regulate fluids, such as the kidney, the gut, the eye, and the vestibular apparatus of the inner ear.

Carbon dioxide limits the electrical depolarization of nerves and muscles, a phenomenon first discovered by Gilbert Ling. This prevents the over-excitation and exhaustion of brain cells and muscle cells, including the heart. The presence of carbon dioxide limits the formation of lactic acid. This explains the "lactate paradox" of high altitude exertion (lactic acid isn't produced during hypoxic exercise, since carbon dioxide is retained

by the Haldane effect, in which the low oxygen pressure fails to displace all of the carbon dioxide carried in the blood cells), and it explains why lactic acid tends to be always present in the blood in hypothyroidism, diabetes, and obesity—insufficient carbon dioxide is produced, and lactic acid is produced even without oxygen deprivation or stress. This aerobic glycolysis, the production of lactic acid in the presence of oxygen, was defined by Otto Warburg as the characteristic cancer metabolism. The "respiratory defect" in which the Pasteur effect (suppression of lactic acid formation in the presence of oxygen) fails to operate, consists largely of the failure to produce carbon dioxide in the mitochondria.

Simple hyperventilation causes muscle spasms and paresthesia (prickling of the skin), in an experiment anyone can perform in a few minutes. When a large amount of carbon dioxide is blown off, the blood's pH increases very slightly, because of systemic adjustments. The "calcium deficiency" theory of tetany would suggest that increased alkalinity of the blood decreases the "availability" of ionized calcium, and that (somehow) the "decreased availability of ionized calcium" interrupts a relaxed state of the nerves and muscles. At least, that's the explanation that I have heard many times, though I am stating it in a way that makes it sound fairly crazy. (See Stadler, et al., 1995.) But, in fact, everywhere calcium is studied, it is an activator, an excitant, a goad to activity, when it enters the cytoplasm. The evidence is that hyperventilation, which changes the serum concentration of bicarbonate, magnesium, potassium, chloride, and phosphate, does not change the serum calcium concentration, while it does *increase the intracellular calcium content.* (Fujimoto, et al., 1987; Stadler, et al., 1995.)

The combination of the calcium ion, $Ca^{2+}$, with the bicarbonate ion, $HCO_3^-$, forms a very soluble complex ion with a single positive charge. In the saliva, there is more carbon dioxide than in the mouth, and this situation is believed to explain the fact that calcium which is dissolved in the saliva tends to be deposited in an insoluble form as it loses its solublizing bicarbonate, and the insoluble form contributes to dental plaque. (Presumably, this physical principle would account for the deposition of calcium in the walls of blood vessels or in any tissue which is relatively deficient in carbon dioxide.) Similarly, when serum bicarbonate decreases, the calcium escapes from its soluble complex, and in effect the available calcium—the forms of calcium which are not bound to bicarbonate--has *increased,* exactly the opposite of what the Carlson school has argued.

Calcium, which is released into the cytoplasm by the excitotoxins, triggers the release of fatty acids, the activation of nerve and muscle, and the release of a variety of transmitter substances, in a cascade of excitatory processes, but at the same time, it tends to impair mitochondrial metabolism, and progressively tends to accumulate in mitochondria, leading to their calcification death, which is also promoted by the antirespiratory effects of the unsaturated fatty acids and the lipid peroxidation they promote. Iron and calcium both tend to accumulate with aging or stress, and both promote excitatory damage; bicarbonate contributes to keeping iron in its inactive state, and probably has a similar effect against a broad spectrum of excitatory substances. Histamine release, nitric oxide, and carbon monoxide are broadly involved in excitotoxic damage, and carbon dioxide tends to be protective against these, too.

Besides the simple excitotoxic killing of nerve cells, the processes which impair carbon dioxide production set in motion the long degenerative process that ranges from diabetic lacticacidemia to dementia. In Alzheimer's disease, brain respiratory metabolism is inhibited, creating a carbon dioxide deficiency with an excess of lactic acid and ammonia. Both Alzheimer's disease and multiple sclerosis involve depressed brain metabolism combined with an inflammatory process. In any inflamed tissue, the enzyme beta-glucuronidase is activated, and this enzyme releases estrogen within the irritated cell, activating another sequence of neurotoxic processes.

In Alzheimer's disease, two other outstanding features are the tangles of microtubular material left where cells have disintegrated, and the amyloid plaques, which often form in

extracellular spaces and around blood vessels. One of the forms of amyloid (amyloid is named for its "starchy" appearance in stained slides) is produced from the normal protein, transthyretin, which carries vitamin A and thyroid hormone, when this protein is "glycosylated," by the addition of sugar molecules. In this glycosylated form, it resembles a mutant protein, and binds to the extracellular matrix. This glycosylation can occur spontaneously and quickly, in the absence of enzymes to catalyze it, when there is too much glucose present, and when the protein's amino groups (usually lysines) are not protected by being combined with carbon dioxide (as carbamino groups). The carbamino groups form rapidly when there is an abundance of carbon dioxide, but also rapidly decompose in the absence of carbon dioxide, allowing the protein to be structurally degraded by the addition of sugar molecules.

Reactions very similar to these occur when the products of lipid peroxidation attach themselves to proteins.

Similar reactions, reflecting metabolic and energetic conditions, can alter the structure and organization of the neurotubules, leading to cell death and the formation of the characteristic neurofibrillary tangles.

W. F. Koch also found that excessive coagulation was produced in the toxic antirespiratory state. Carbon dioxide, probably by controlling the availability of calcium, is an important protection against abnormal clotting. The prevention of clotting by carbon dioxide is thought to be part of the explanation for its protective effect against oxygen deprivation. (Pak and Sverchkova, 1987.) Hyperventilation causes increased vascular permeability, leading to hemoconcentration when a large portion of the blood's water escapes into the tissues. Vascular spasm, increased viscosity of the concentrated blood, and disturbed coagulation processes undoubtedly contribute to a wide range of health problems, including stroke, heart attack, and multiple sclerosis.

Since permanent high altitude residents chronically retain a larger amount of carbon dioxide in their tissue, I have looked for data on the incidence of degenerative brain disease among high altitude populations. In Kashmir, a house-to-house study of more than 66,000 people found that nearly one percent of the population suffered from some neurological impairment, such as cerebral palsy, epilepsy, mental retardation or stroke. But no cases of Alzheimer's disease or multiple sclerosis were found. In India, the incidence of these diseases is much lower than in the U.S., but their *absence* in Kashmir is remarkable.

If excess lactic acid in the brain tissue is characteristic of Alzheimer's disease and multiple sclerosis, then the "lactate paradox" suggests that a slightly higher retention of carbon dioxide in the brain of Kashmir residents would **counteract chronic excitotoxic effects, suppressing the stress metabolism** which leads to the degenerative brain diseases. Experimentally increased carbon dioxide tends to decrease intracellular calcium, and to decrease brain excitability.

Cancer, the classical disease of extreme "aerobic glycolysis," is also negatively associated with increased altitude. Mortality from heart disease, too, decreases with increasing altitude, and the role of carbon dioxide in heart function is very clear.

The neuroprotective steroids, progesterone and pregnenolone, and magnesium and carbon dioxide all protect against excitoxicity and the related excess of intracellular calcium, while promoting normal calcification. The thyroid hormone happens to promote the production of these steroids and carbon dioxide, and the retention of magnesium. By the simple process of avoiding the antithyroid substances, especially the polyunsatured fatty acids, the degenerative processes discussed here will be minimized. Cyanide, another common component of foods (usually in the bound form as cyanogenic glycosides, in seeds, sprouts, nuts, and grains), has specific antagonisms to carbon dioxide, thyroid, and respiration.

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