Ray Peat's Newsletter

A change of meaning is a change of being. *David Bohm*

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Problems of Metabolic Energy and Efficiency

Metabolism has been neglected as much by psychiatry as by oncology. Metabolism, an organized process of chemical changes, is always relevant, but the tradition of diagnosing illnesses has developed procedures of abstraction that too often omit the most relevant processes and patterns. When a doctor sells you a diagnosis, you are buying a social philosophy and a view of reality—or at least a philosophical booster shot.

Since the 1950s, biology in the US has been dominated by the ideology of logical atomism and reductionism, in which understanding of a system rests on knowledge of clearly and fully defined parts that constitute the system—atoms, molecules, genes, enzymes, pumps, motors, receptors, hormones, etc. A good reductionist would reason that, if the nature of the whole is to be deduced from the properties of the parts, those properties should be studied comprehensively, understanding how they react to specific environments. But it was that sort of knowledge that Bertrand Russell and the logical atomists/artificial intelligence philosophers realized would make reductionism impossible—if the nature of a substance is qualified by its relations, understanding it objectively requires a holistic and historical, empirical knowledge.

With their ideal science consisting of the ability to make predictive assumptions from general principles, it was natural for them to see organisms in terms of computable information. Until nearly the end of the century, growth and development were said to be specified and realized by the information in the genes—that information coded in DNA became the information in enzymes and hormones and receptors, and each of those constituted computable information. An outstanding product of that kind of biology was genetic engineering.

Genetics was originally an attempt to understand the origins of traits, and to define us by our limitations, our inheritance of unchanging traits. The "eugenics" ideal persists in our culture, although the name was changed for public relations purposes. Their (Mendel's, Weismann's, Morgan's, Lorenz's) philosophy of biology was simultaneously a philosophy of society.

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Adaptive physiology (dismissing the doctrine of timeless traits) is concerned with where we are going, what we are becoming, and what our possibilities are. The subject that it investigates requires attention to context and temporal processes.

Medical diagnosis—of the "scientific" sort—has been heavily influenced by the reductionist-determinist culture, and treatments are chosen according to the way the problem is understood. In the last several years, new information has shown that many, if not most, standard diagnoses and treatments are based on false assumptions, and are causing unnecessary harm. Because of the fatalistic implications of the theory behind the diagnoses, receiving certain diagnoses can cause depression, anxiety, or panic, and especially a sense of helplessness. If a diagnosis assumes that a disease is caused by a gene or a virus, when it is actually caused by something in the person's environment that could be changed, the diagnosis effectively colludes with the harmful environment.

The substitution of information for energy, the abstraction of the world, led to theories of aging and death of organisms as resulting from the inevitable, "entropic," loss of information, the degradation of DNA through somatic mutations, produced by oxidative damage, and to a theory of the fate of the universe as an entropic "heat death." If the death of an organism results from the damage caused by the random oxidation which is inevitable when we get our energy from oxidation, then antioxidants are good, and the existence of a powerful antioxidant system in cancer would seem illogical; as a result of that orientation, the facts about cancer metabolism (derived from the simplest as well as the most technologically advanced measurements) were simply denied, even by intelligent, well educated people. The idea that "cancer cells don't have enough electrons" encouraged people to use very inappropriate treatments. Exactly the same ideological approach to thinking about human physiology is leading to dangerously inappropriate treatments for psychoses, strokes, dementia, and respiratory, kidney, and heart disease, as well as many less serious but disabling conditions.

The organism's metabolism is a single, integrated process, in which each part has to adapt to conditions in the other parts. Our nerves contain chemical receptors that detect changes in the metabolic chemicals in the blood, permitting the organism to make adaptive changes. Every kind of cell releases carbon dioxide into the blood, in proportion to its metabolic rate, and its best known effect is to stimulate breathing, increasing the absorption of oxygen by the lungs in proportion to the metabolic rate.

Between its formation and its exhalation, CO_2 participates in many essential processes, including the stabilization of the energy producing system. When there isn't enough CO_2, the conversion of glucose to lactate increases, as an inefficient alternative source of energy, and then to supplement the rapidly consumed glucose, the use of the amino acid glutamine for energy increases, with ammonia as a byproduct. Both lactate and ammonia stimulate breathing, which can be life-saving if a simple lack of oxygen was the reason for the lack of CO_2; however, if the lungs have a normal supply of oxygen, increased ventilation resulting from ammonia and lactate will cause a further decrease of CO_2.

Since CO_2 relaxes smooth muscle, cells that are working and consuming oxygen and glucose (producing CO_2 in proportion to their activity) cause nearby blood vessels to relax and expand, delivering more oxygen and glucose in proportion to the increased need. When CO_2 is decreased, blood vessels constrict, limiting the supply of glucose and oxygen. With restricted blood supply, cells have to resort to locally stored glycogen for glucose, and to the breakdown of internal proteins for glutamine.

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In hypothyroidism, with lowered oxidative metabolism, the organism is never far from stress and hyperventilation, with the chronic production of lactate and ammonia. The inefficient metabolism of diabetes has similar effects. Diabetes and hypothyroidism are very closely related, since the use of glucose is required for the activation of the thyroid hormone, which is required for the efficient use of glucose. Besides ammonia and lactate, other stress related substances can also increase the drive to breathe more, depleting the essential CO_2—endotoxin, acetylcholine, serotonin, hydrogen sulfide, nitric oxide, carbon monoxide, angiotensin, and estrogen, for example.

Hypothyroid people, with low production of CO_2, are very susceptible to stress-induced hyperventilation, and they are often in a state of physiological hyperventilation. They are susceptible to over-production of ammonia (De Nardo, et al., 1999; Marti, et al., 1988) and lactate (Zarzeczny, et al., 1996), and to psychosis, especially depression and mania. The low metabolic rate that defines hypothyroidism has often been reported in psychoses and dementia (Wolberg, 1935; Gibbs and Lemcke, 1923).

If we neglect the coherent interactions of these essential properties of the organism, our attempts to prevent or cure sickness will fail.

The weak oxidative metabolism in hypothyroidism makes it easy to enter a state of reductive stress, with a shift toward a higher concentration of NADH and lactate. When the demands on a healthy organism are very intense or prolonged, stress hormones will block the thyroid action, causing this reductive shift to occur, activating the basic survival processes of cell renewal or reproduction. Reductive stress activates multiple layers of restorative processes (alternatives to the protective functions of carbon dioxide) to stimulate breathing, increase circulation, provide energy and materials for renewing cell structures. Prostaglandins, cytokines, estrogen, and nitric oxide are produced in coordinated ways, and cellular behaviors are changed defensively. The structures of the cell skeleton are modified, as the reductive chemistry changes protein disulfides to sulfhydryls, changing shapes and, most importantly, the solvent properties of the cell material.

When the crisis is overcome, and the environment is adequate, a healthy animal quickly restores its normal thyroid function, but incomplete resolution of problems leaves traces, changes in tissues and behaviors, that can accumulate. Residues, such as increased endorphins and changes of digestive patterns can cause the balance of the reductive substances to linger, causing a slight tendency to hyperventilate, and to be slightly deficient in carbon dioxide.

Since carbon dioxide has stabilizing effects in the brain, including the relaxation of blood vessels, the loss of carbon dioxide causes vasoconstriction, deficient delivery of oxygen and glucose to the brain, leading to a decreased metabolic rate. Schizophrenia, bipolar (manic depressive) psychosis, and Alzheimer's dementia involve a generally reduced metabolic rate, but in Alzheimer's disease the brain's use of sugar is decreased more than that of oxygen. Energy deprivation, caused by insufficient glucose or oxygen, causes immediate swelling of cells, and is associated with excitation; the ammonia associated with energy deprivation and excess excitation contributes to swelling (Kline, et al., 2012; Bosoi, et al., 1990; Mrsulua, et al., 1990; Kogure, 1984).

Several types of mental problem are associated with edema of the brain—an excess of water, or the presence of water that is functionally abnormal, less constrained, as measured by MRI. MRI can also directly measure the redox balance, NAD/NADH, of the brain, and it has been found that schizophrenics and manic depressives have lower ratios, that is, their cells are less well oxidized. Before any mental impairment develops, people who later develop Alzheimer's disease, experience reductive stress (Lloret, et al., 2016).

Glucose deprivation, by causing glutamine to be used as fuel, increases the formation of ammonia, and ammonia (through an excitatory effect on cells and direct activation of enzymes) promotes the glycolytic use of glucose, producing lactic acid even in the presence of oxygen and perpetuating the scarcity of glucose. Starvation shifts the electronic balance of cells away from oxidation, toward reduction, decreasing the ratio of NAD/NADH and of pyruvate/lactate, probably because of this self-destructive by-passing of the oxidative system.

This shift to a reductive, glucose wasting metabolism in the presence of oxygen is what Otto Warburg called the cancer metabolism. It's also the metabolism of an ailing brain, failing lungs and heart, and it parallels the metabolisms of aging and reproduction. Warburg recognized that the chemically reduced state coordinated the dedifferentiated cellular state that characterizes cancer, and the reductionists have identified a protein, hypoxia inducible factor (HIF) that activates the expression of genes that are characteristic of the glycolyzing cancer metabolism. This stabilization of a reduced balance in the presence of oxygen has been called pseudohypoxia.

There are several important mechanisms that are involved in perpetuating a pseudohypoxic state, and they can operate in a single tissue or organ, as well as in a generalized way throughout the organism. **The thing that is often overlooked is the coherent overlapping interaction of the structural sulfhydryl redox system (-SH, -SS-), the redox regulation of gene expression, the glycolytic and oxidative energy metabolisms, regulation of pH and ionic selectivity, osmolarity, and solvent properties, especially the hydrophobic/hydrophilic balance.**

The organism's homeostasis consists of a situational equilibrium of all of these properties, with our food assimilation, respiration, activity, and excretion being adjusted as needed. If we neglect the coherent interactions of these essential properties of the organism, our attempts to prevent or cure sickness will fail.

The hypoxia inducible factor increases many enzymes that promote the reductive state—aromatase (Samarajeewa, et al., 2013), prostaglandin synthase/cyclooxygenase (Xing, et al., 2015), the enzymes of glycolysis (Marin-Hernandez, et al., 2009), glutaminolysis (Kappler, et al., 2017), and glutamatergic excitation (Hsieh, et al., 2017), for example. Two of the enzymes that it activates, angiotensin converting enzyme (ACE) and carbonic anhydrase, have fundamental roles in shaping metabolism. Angiotensin II, the peptide produced by ACE, increases blood pressure and water retention and activates the pituitary and adrenal stress hormones, especially aldosterone. Both angiotensin and aldosterone activate carbonic anhydrase. It seems that any chemical that causes contraction of blood vessels also activates carbonic anhydrase (Puscas, et al., 2001). When the carbonic anhydrase in the wall of the blood vessel is activated, it converts the acid CO2 to bicarbonate, raising the pH of the cell, increasing its excitability. The alkaline shift in pH (the shift that becomes chronic in cancer cells) increases the excitation and energy expenditure of any type of cell.

These shifts toward pseudohypoxia, alkalinity, excitation, water retention, and inefficient energy production can be seen, either locally or systemically, in all of the chronic and degenerative conditions that are now known to involve inflammation. Stress modifies our breathing, causing a vicious cycle, in which the lactate and ammonia produced when stimulation exceeds our oxidative capacity stimulate more intense breathing, causing more carbon dioxide to be lost, reducing oxidative efficiency and increasing the formation of ammonia and lactate.

Considering the crucial role of CO2 in preserving the integrity of cells, there should be more attention to using it therapeutically—bag breathing (rebreathing expired air until the oxygen in the bag is uncomfortably depleted), bathing in it (using a bag or tub of pure CO2), using carbogen (5% CO2 in oxygen) in hospitals and for emergency resuscitation, and using carbonic anhydrase inhibitors such as acetazolamide in more situations, including psychiatric. Direct use of carbon dioxide is likely to be helpful in all the situations that are known to be benefitted by acetazolamide, without the risk of allergy to that drug—traumatic brain edema, mountain sickness, osteoporosis, epilepsy, glaucoma, hyperactivity (ADHD), inflammation, polyps of the intestine, and arthritis. Diabetes, cardiomyopathy (Torella, et al., 2014), obesity (Arechederra, et al., 2013), cancer, dementia and psychosis are also likely to benefit.

Because of their role in producing and maintaining pseudohypoxia, and stimulating hyperventilation, there should be more attention to measuring the presence of ammonia and lactate in the blood, breath and urine. Hospitals regularly record a patient's rate of breathing, but without measuring at least the amount of CO2 in the exhaled air, the simple respiration rate doesn't mean very much.

Other things that should be taken into account in any therapy are the light environment and the intestinal flora (endotoxin activates HIF), the cycles of sleep and activity, and the quality of environmental stimulation. Among the common inhibitors of carbonic anhydrase are the mildly oxidizing flavonoids such as apigenin and fisetin, some polyphenols, vitamin B1, vitamin D (Mras, et al., 2012), progesterone (partly by blocking the activation by estrogen and aldosterone), and emodin.

The being of matter is its meaning; the being of ourselves is meaning; the being of society is its meaning. The mechanistic view has created a rather crude and gross meaning which has created a crude and gross and confused society.

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