Ray Peat's Newsletter

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Optimizing respiration

In a given situation, people who eat more are healthier and live longer than those who eat less--their bodies burn calories vigorously. In one study, fat people were found to be able to maintain their weight on only 700 calories per day, about a third of a normal calorie intake. In animal studies, too, the fast-metabolizers live longer than the animals that don't burn calories so fast. When animals are fed a calorie-restricted diet, and live longer than their *ad lib* fed relatives, people like to say that their "metabolic rate is depressed," but that isn't true: the under-fed animals are *smaller* than the *ad lib* eaters, but **each gram of their tissue burns energy at a higher rate.**

The biological value of the antioxidants is that they allow oxygen to be used productively, rather than destructively. When something interferes with the normal, productive use of oxygen, there is a great increase in the destructive forms of oxidation, such as lipid peroxidation, and the antioxidative reserves become crucial. That is, decreased respiration of the productive sort tends to increase the destructive use of oxygen.

Respiration in the ordinary sense is breathing, the exchange of gases between the animal and its environment.

Tissue respiration refers to the absorption of oxygen from the blood by cells, or, more exactly, to the exchange of gases between cells and their environment. Plants and other organisms respire in ways that are biochemically very similar to our tissue respiration.

Not all the oxygen we consume is put to good use, and we sometimes produce exhalations of gases other than carbon dioxide and water vapor.

Optimizing respiration means increasing the uses of oxygen that provide energy and increase functional capacity, while decreasing the forms of oxidation that impair functioning and decrease the production of useful energy.

In general, things which are associated with energy-producing respiration (such as thyroid hormone, carbon dioxide, coconut oil) also have roles as "antioxidants."

In 1895 Magnus-Levy demonstrated that hypothyroid people have abnormally low heat production, and that their heat production could be brought up to normal by giving them thyroid substance. In 1926, Otto Warburg showed that the respiratory enzyme, containing the heme group, is inhibited by carbon monoxide, which binds to that enzyme, as it does to hemoglobin. Warburg also showed that visible light restores the activity of the respiratory enzyme by dissociating it from the carbon monoxide. Beginning in the 1930s, many substances were found that blocked respiration and

Under stressful conditions, people may exhale measurable amounts of pentane, ethane, isoprene, carbon monoxide, and other substances with potential toxicity.

In hyperventilation, so much carbon dioxide is lost in the breath that our tissue respiration is impaired, creating a partial "tissue suffocation."

If cells consume oxygen without producing carbon dioxide generously, a situation analogous to hyperventilation/tissue suffocation exists.

Oxygen deprivation is one of the signals that stimulates the production of new red blood cells, and this involves the production of porphyrin, heme, and hemoglobin.

The elimination of heme by oxidation produces carbon monoxide, which can block the respiratory production of energy.

The heme group (of hemoglobin and the respiratory enzymes, for example) is the iron-binding oily molecule that interacts with oxygen, and it is called a porphyrin. There is a long history of investigating the interactions of porphyrin metabolism with estrogen (L. C. Strong, "Sex differences in pigment content of Harderian glands of mice," *Proc. Soc. Exp. Biol. Med. 50,* 123-125, 1942), with cancer (e.g., F. H. J. Figge, *et al., Cancer Res. 2,* 335-342, 1942), with diet, and with excess iron. Estrogens are known to cause porphyria (R. D. Levere, *Blood 28,* 569-572, 1966), and to exacerbate the symptoms and biochemical disturbances in people with subclinical porphyria. Sometimes symptoms occur premenstrually, during the time of increased estrogen production--the term "ovulocyclic porphyria" has been in use for a long time. Puberty therefore increases the susceptibility to symptomatic episodes. Jaundice in pregnancy and in oral contraceptive users is probably a closely related phenomenon. (H. F. von Oldershausen, *Deutsch. Med.J. 19,* 394-403, May 15, 1968.)

Porphyrin synthesis begins at an important cross-over point of protein and carbohydrate metabolism. Succinyl CoA and amino levulinic acid can enter the Krebs cycle or the porphyrin pathway. Protein catabolism feeds into these pathways. Increased protein catabolism or blockage of oxidative consumption of Krebs cycle fuel--for example by poisoning--makes these precursors available to enter the porphyrin pathway. Stress-induced oxidation of heme can eliminate feedback control, but the *specific* outcome can be modified in many ways.

Low blood sugar, most often caused by hypothyroidism, and diabetes--which involves poor absorption of sugar by cells--both tend to lower the respiratory quotient, the amount of carbon dioxide produced in relation to the amount of oxygen used. High carbohydrate diets, sometimes with insulin, have been used to treat porphyria (Perlroth, et al., Waxman, et al.). The use of carbon dioxide inhalation in psychiatry has many metabolic justifications, one of which might be the importance of carbon dioxide in glucose regeneration. It is also essential for detoxifying ammonia. Whenever a symptom is relieved by glucose, I think we should suspect that thyroid and carbon dioxide might be deficient.

Many serious long-range consequences of excess heme/porphyrin production and metabolism are currently being investigated, suggesting that the criterion of "twice the upper limit of normal" excretion that was recently proposed by a government agency, for recognizing that a problem exists, could allow far more serious problems to develop over time, that on the surface might seem unrelated to porphyria. I consider any porphyrin excess to be a serious indicator of physiological stress. **The ramifications of disturbed heme metabolism, resulting from exogenous factors, are far-reaching. For example, G. Y. Kennedy, at the Cancer Research Laboratory, University of Sheffield, observed that a porphyrin shortened the time required to induce tumors, and porphyrin derivatives have been proposed to be "cancer hormones."** The carbon monoxide produced in the breakdown of heme inhibits many enzymes. The consequences of slight excesses in porphyrin metabolism just haven't been investigated, because of the genetic dogmatism that denies that the person's environment could be at fault.

The synthesis of heme/porphyrin, and the production of red blood cells, are stimulated by a lack of oxygen, or by toxins such as arsenic and iron, which cause oxidative stress. Emphysema, high elevation, sluggish circulation, and nocturnal breathing problems can cause enough oxygen deficiency to stimulate the formation of new red blood cells. Newborn babies often have polycythemia, as a result of limited prenatal oxygen supply. At a certain point, the continued production of red blood cells can make the blood so viscous that this viscosity impairs circulation through capillaries, and creates a vicious circle, stimulating the formation of more red blood cells. Men are more likely than women to have polycythemia rubra vera, possibly because testosterone is anabolic to the bone marrow, and estrogen tends to slow blood cell formation (females of all species are relatively "anemic," compared to males, partly because their blood is more dilute), but I think the greater ability of men's marrow to respond proliferatively to hypoxia is influenced by many factors, including

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increased mucopolysaccharides in the skin (O. Braun-Falco, *Derm. Wschr. 136,* 1085, 1957). This is reminiscent of hypothyroid myxedema; it has been suggested that mucopolysaccharides can act as a matrix for calcification (W, C. Johnson, et al., *J. Invest.Derm. 43,* 453, 1964). Estrogen stimulates the formation of collagen (Loeb, et al.), and increases its age-like properties, and progesterone opposes some of these pro-aging effects on connective tissues. Mere lack of oxygen stimulates collagen formation (Chvapil, et al.), and the opposing effects of estrogen and progesterone on tissue oxygenation can account for many of the tissue changes they produce.

Oxygen deprivation causes tissues to retain calcium (and iron), as does estrogen in many cases, being similar to aging in promoting cellular uptake of calcium. Since the porphyrins strongly bind metals, it has been suggested that they may have a role in mediating the deposition of metals in stressed tissues. Paroxysmal vasospasm occurs in about 90% of scleroderma patients, and estrogen and adrenalin are known to synergize in producing vascular spasm; **hypothyroidism normally involves elevations of both estrogen and adrenalin.**

The porphyrins break down into bilirubin, which also poisons mitochondrial respiration (Zetterstrom and Ernster).

I have known women who developed scleroderma after beginning the use of estrogen, and who were reluctant to stop, because they had been told that estrogen would protect them from osteoporosis and heart disease. Men who have had a diagnosis of scleroderma have told me that with the use of thyroid and magnesium supplements, epsom salts baths, and topical progesterone and vitamin E, their symptoms regressed. I suspect that carbon dioxide produced in mitochondria is the main factor in removing calcium from them.

Polymyositis sometimes leads to calcification, and **this would be expected if the problem is related to mitochondrial respiration, as is now generally thought to be the case;** thyroid and magnesium are often the factors needed to normalize mitochondria and prevent calcification. In general, fatigued cells take up calcium and lose magnesium.

Many people get minor bony excrescences (bone spurs, osteophytes, exostoses, hyperostoses) during puberty or menopause, or at other times of hormone imbalance, which often disappear spontaneously. This would have very little to do with the severe oxygen deficiency states in which collagen synthesis is overstimulated and general calcification occurs. Growth hormone and prolactin imbalances have been suspected to have a role in some of these growths, and cortisol--which is is active in several aspects of bone metabolism--is probably involved (all of these hormones are elevated by estrogen, and hypothyroidism is often responsible.) Progesterone, thyroid, bromocriptine, and other things are available to normalize the pituitary, when that is malfunctioning. The bone spurs that develop during times of fluctuating thyroid function, might also be promoted by rapid changes in calcium and carbon dioxide levels. (The description of bone mineral as "apatite" leads many people to forget its carbonate content.)

In general, lactic acid in the blood can be taken as a sign of defective respiration, since the breakdown of glucose to lactic acid increases to make up for deficient oxidative energy production. Normal aging seems to involve a tendency toward excess lactic acid production, and age-pigment is known to activate the process. Eliminating respiratory toxins (such as unsaturated oils, estrogenic and antithyroid substances, lead, and excess iron) is the most obvious first step to take when there is excess lactic acid formation. Carbon dioxide supplements have been shown experimentally to reduce residual lactate production. Many people experience exhilaration when they go to very high altitudes, and it is known that people generally burn calories faster at high altitude. **It has been found that, during intense exercise (which always produces a lactic acid accumulation in the blood), a lower peak accumulation of lactate occurs at high altitude, and this seems to be caused by a reduction in the rate of glycolysis, or glucose consumption.** (B.Grassi, et al.) Since there is less oxygen at high elevation, and since oxygen is used to consume lactic acid, this effect is the opposite of what many people expected. In some sense, respiration becomes more efficient at high altitude. Youth and increased

times supported the process by helping to stabilize the high energy metabolism of the brain, and even by stabilizing the "energized" state of water that supports brain efficiency. Roman Schmitt has proposed that, 66 million years ago when dinosaurs became extinct and mammals began their rapid evolution, "at that time hydrothermal venting went wild," releasing huge volumes of carbon dioxide and other substances into the atmosphere.

Antarctic ice cores show there were large increases in atmospheric carbon dioxide in relatively recent times: 10,200, 11,600, and 12,900 years ago, and two broad peaks in carbon dioxide release occurred just 4,200 and 7,700 years ago. (Figge and White.) Local or regional increases in carbon dioxide from volcanism could have more continuous effects on brain development.

In times of lower atmospheric carbon dioxide, our Krebs cycle still produces it internally, and the rapid development of the brain during gestation takes advantage of the high concentration of carbon dioxide in the uterus. (These ideas make me doubt the safety of the rapid breathing encouraged by some obstetricians.)

A weakened ability to oxidatively produce energy can lead to the maladaptive over-production of collagen, porphyrins, red blood cells, and other tissues and substances, which in turn can lead to many adaptive and maladaptive changes. I think skin and mucous membranes provide a good illustration of the way respiratory potential influences structure: Estrogen-increased keratinization is opposed by vitamin A, which increases the proportion of active, differentiated cells.

Changes that begin as functional adaptive processes can lead to structural and anatomical changes that contribute to functional derangements. *If we look at small anatomical structures such as capillaries, we can see that our anatomy is in flux, adjusting structures to meet changing needs.* After every experience of stress or trauma, we have to reconstitute ourselves. When this rebuilding lags, defects accumulate. Rosacea, diabetes, and systemic lupus erythematosa are examples of conditions that progress from functional to anatomical abnormalities.

Our organization is built on the basis of interacting structures and functions. Adequate respiration depends on adequate structures, and adequate structures require adequate respiration.

Anatomical structures, tubes, spheres, and sheets of cells, create gradients and fields as materials move through them, in relation to which cells organize themselves. Changes in simple electrical fields can cause radical changes in the behavior of cells. Changes in respiration cause many changes in chemical and electrical gradients, and the intensity of respiration is known to be a central factor in the development and preservation of biological form. Child's work on the developmental importance of metabolic gradients (summed up in *Patterns and Problems of Development,* 1941) has been confirmed and refined, despite the immense effort that has been spent on genetic mystification of the processes that create and maintain form.

The quality of the developing brain of the fetus, the deterioration of the aging immune system, and hundreds of other processes are governed by the quality of respiration.

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J Surg Res 1984 Jul;37(1):63-68 Evidence for aerobic glycolysis in lambda-carrageenan-wounded skeletal muscle. Caldwell MD, Shearer J, Morris A, Mastrofrancesco B, Henry W, Albina JE "Classically, increased lactate production in wounded tissue is ascribed to anaerobic glycolysis although its oxygen consumption has been found to be similar to normal tissue. This apparent inconsistency was studied in a standardized isolated perfused wound model. Male Sprague-Dawley rats were wounded (group W) with intramuscular injections of lambda-carrageenan and fed ad lib.; not wounded and pair fed to the decreased food intake of the wounded animals (group PFC); or not wounded and fed ad lib. (group ALC). After 5 days, the hindlimbs of animals from each group were either perfused using a standard perfusate with added [U-14C]glucose or [1-14C]pyruvate or assayed for the tissue content of lactate and pyruvate. In addition, the effect of a 30% hemorrhage on the tissue lactate and pyruvate concentration was examined. **Wounding increased glucose uptake and lactate production by 100 and 96%, respectively, above that seen in ALC animals.** Oxygen consumption was unchanged by wounding (5.74, 5.14, and 5.83 mumole/min/100 g in W, PFC, and ALC, respectively). Glucose and pyruvate oxidation were also unaltered among the groups. Hemorrhage resulted in a comparable increase in lactate and pyruvate in tissue from wounded and pair-fed control animals (above those concentrations found in tissue harvested without preexisting hemorrhage). As a consequence, the same relationship in L/P ratio was maintained after hemorrhage. Taken together, these results confirm the **presence of aerobic glycolysis in wounded tissue** (unchanged oxygen consumption, glucose, and pyruvate oxidation). In addition, pyruvate dehydrogenase activity in the wound was apparently the same as that found in muscle from pair-fed control animals."

Food Chem Toxicol 1984 Aug;22(8):615-621 Effect of orally administered food-grade carrageenans on antibody-mediated and cell-mediated immunity in the inbred rat. Nicklin S, Miller K "Experiments were performed to investigate the immunological consequences associated with the persorption of poorly degradable carregeenans from the diet. Using an inbred strain of rat it was demonstrated histochemically, by the carrageenan-specific Alcian blue staining technique, that **small quantities of food-grade carrageenans given at 0.5% in drinking-water for 90 days could penetrate the intestinal barrier of adult animals. This apparently occurred via an intact mucosa in the absence of inflammatory or pathological lesions. The carrageenan was demonstrated in macrophage-like cells present within the villi and lamina propria of the small intestine.** The oral administration of kappa, lambda or food-grade carrageenans did not affect local (biliary) or antibody responses to gut commensal microorganisms, or to orally-administered sheep erythrocytes. However, when sheep red blood cells were administered parenterally the ensuing anti-sheep red blood cell haemagglutinating antibody response was temporarily suppressed in carrageenan-fed rats. lambda-Carrageenan and iota-carrageenan both significantly (P less than or equal to 0.01 and P less than or equal to 0.05, respectively) reduced the mid-phase (14-28 days) haemagglutinin response; kappa-carrageenan (L100) was less effective but caused significant depression at day 21 (P less than or equal to 0.01). Individual responses were, however, within the control range 35 days after sheep erythrocyte administration, thus indicating the temporary nature of this effect. Although carrageenan administration depressed the anti-sheep erythrocyte antibody response, it did not affect T-cell immune competence as measured by the popliteal lymph node assay for graft-versus-host reactivity."

J Nutr 1986 Feb;116(2):223-232 Effects of certain dietary fibers on apparent permeability of the rat intestine. Shiau SY, Chang GW "Apparent intestinal permeability was determined indirectly by orally administering a poorly absorbed dye, phenol red, to rats and measuring its recovery in feces and in urine. Increased apparent permeability was recognized by increased dye recovery in urine and by an increased ratio of urinary to fecal dye recovery. Guar gum, pectin, carrageenan type I (80% kappa, 20% lambda), carrageenan type II (iota) and cellulose were each fed at levels of 5 and 15% (wt/wt) of the diet for 31 d to male Fischer 344 rats. The average initial weight of rats was 230 g. Rats fed 15% guar gum gained significantly less weight than most of the other rats (P less than 0.05). Phenol red recovery was measured at 2 and 4 wk after the beginning of the experiment. **At 2 wk urinary recoveries of phenol red were high in rats fed fiber-free and carrageenan type II diets, indicating increased apparent permeability.** By 4 wk, adaptation had apparently taken place." "These data are consistent with the hypothesis that intestinal permeability to foreign substances may be altered considerably by diet."

Pathologe 1993 Sep;14(5):247-252 [Persorption of microparticles].[Article in German] Volkheimer G "Solid, hard microparticles, such as starch granules, pollen, cellulose particles, fibres and crystals, whose diameters are well into the micrometre range, are incorporated regularly and in considerable numbers from the digestive tract. Motor factors play an important part in the paracellular penetration of the epithelial cell layer. From the subepithelial region the microparticles are transported away via lymph and blood vessels. They can be detected in body fluids using simple methods: only a few minutes after oral administration they can be found in the peripheral blood-stream. **We observed their passage into urine, bile, cerebrospinal fluid, the alveolar lumen, the peritoneal cavity, breast milk, and transplacentally into the fetal blood-stream. Since persorbed microparticles can embolise small vessels, this touches on microangiological problems, especially in the region of the CNS.** The long-term deposit of embolising