Ray Peat's Newsletter

That which we must learn to do, we learn by doing. Aristotle

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Nitric oxide, degenerative processes, and the medical marketplace

Vitamin K, vitamin A, niacinamide, progesterone, and some other substances with broad and powerful protective effects, block nitric oxide. Observations such as these are leading to new ways of understanding the physiology of stress and aging, but they are being ignored or denied by many influential people and institutions. I think a close examination of the issue will reveal some important facts about our organisms, and also about our medical culture.

When I was studying reproductive aging, around 1970, I noticed that the changes occurring in the aging uterus (including collagen deposition and "age pigment," lipofuscin) were similar to changes produced in any tissue by excess estrogen, excess polyunsaturated fats, vitamin E deficiency, ionizing radiation, or oxygen deprivation. The failure of energy production by oxidative metabolism was a common feature of aging and these other conditions.

Looking for things that can interfere with the use of oxygen, I knew that Keilin and Warburg had identified cyanide (CN-), carbon monoxide (CO), and hydrogen sulfide (H2S) as inhibitors of the respiratory enzyme. At that time, cyanide was already suspected to be produced endogenously, since our mitochondria produce the enzyme, rhodanese, that detoxifies it. Hydrogen sulfide, also produced endogenously, is quickly detoxified by a healthy liver. Carbon monoxide, known to be produced in the body from hemoglobin, and increased by stress, can accumulate in the body since it isn't easily detoxified, so it seemed to be a likely mediator of the stress-induced respiratory failure.

Until the mid-1980s, nitric oxide (NO) was known mainly as a toxic free radical in smog. Its inhibition of the respiratory enzyme paralleled the effects of CN-, CO, and H2S, so when it was discovered that it is produced by enzyme actions in the body, many people began investigating its toxic effects, and by the mid-1990s it was found to be involved in the development of diabetes and several other diseases. The production of a small amount in blood cells and the vascular epithelium is harmless, since it prevents oxygen from being consumed by the blood and vessel lining, allowing it to be used by the respiring surrounding cells.

Some conditions associated with increased nitric oxide: *Age pigment (lipofuscin); aging; albuminuria; anxiety; arthritis; asthma; autoimmunity; blood-brain barrier damage; brain degenerative conditions (ALS, Alzheimer's, Huntington's, Parkinson's, multiple sclerosis); brain trauma; cancer; cataracts; celiac disease; colitis; constipation; chronic fatigue; dengue virus infection; depression; diabetes; DNA damage; ebola virus infection; edema; excitotoxicity; glaucoma; heart failure, arrhythmia; herpes; irritable bowel disease; keloids; leaky gut; macular degeneration; malaria; sarcoidosis; shock (septic, traumatic, hemorrhagic); strokes; restraint stress; tau protein hyperphosphorylation; varicose veins; vibration.*

Nitric oxide had been identified as a vasodilator, and meanwhile, in the late 1980s and early

1990s, nitroglycerin (glyceryl trinitrate) which had been used for a long time as a vasodilator to relieve heart pain, was being sold as a topical treatment for male impotence, causing vasodilation and engorgement of the penis.

The nitrate (converted to nitric oxide) was known to act by increasing the formation of the "second messenger," cyclicGMP (Kukovetz and Holzmann, 1983) by activating the enzyme guanylyl cyclase, the same enzyme that is activated by testosterone (and also by progesterone, pregnenolone, and DHEA) (Vesely, 1979).

Nitroglycerin's effects on the heart were only momentary, with serious side effects, and Pfizer was looking for a better vasodilator, which directly increased the cyclicGMP. They originally thought of sildenafil, Viagra, as a drug for heart patients, but it turned out to work better for producing prolonged erections. Though it worked by preventing the breakdown of cGMP, it was generally considered to be a substance that increased the effect of nitric oxide.

The extreme commercial success of Viagra caused a shift of attention from the toxic effects of nitric oxide, to its role in virility and relaxing blood vessels. Even though Viagra acts on cGMP which is also increased by testosterone, the culture that developed after the mid-1990s began treating nitric oxide the way the drug industry had earlier taught researchers to treat estrogen--if something good happens in the body, it must be caused by NO, and if NO has an effect in the body, that effect must be good.

In the early years of estrogen research, medical observations had led most doctors to suspect that estrogen excess led to breast and uterine cancer, to blood clots and other vascular problems, to miscarriage, and to nervous and emotional problems such as seizures and depression that were more frequent around menstruation. But when 13 large drug companies decided to sell estrogen to treat menopause, and pressured the FDA to approve its sale for that purpose, suddenly the major journals were flooded with thousands of articles claiming that estrogen was an effective treatment for hundreds of diseases, mostly in women.

The saturation of the culture with false health claims about estrogen created the opportunity to sell estrogen ointments to grow hair on bald heads, and estrogen creams to plump up sagging faces. Building on their successful sales of estrogen to women, the estrogen industry began promoting the idea that it would prevent heart disease in men, but since men aren't protected by the large amount of progesterone that women have, some of the test subjects died of heart attacks and that stopped, for a while, the attempt to sell estrogen to men.

In the early years of investigating the functions of nitric oxide, its role in the malfunction or death of stressed cells in the pancreas, brain, and lung could be clearly demonstrated, and people were beginning to test substances that inhibited nitric oxide to protect tissues from damage caused by stress. The meaning of nitric oxide for the drug industry hadn't been formulated yet.

Already in 1993 (Chaves, et al.), nitric oxide was found to be rapidly increased in the uterus by estrogen, causing the uterus to almost double its weight in a few hours from the absorption of water. The association of the supposedly "heart protective" estrogen with the vasodilating nitric oxide soon put nitric oxide oxide into a privileged place in the medical economy.

The mystique of nitric oxide became powerful. Someone noticed that kids from Mexico City developed asthma when they went to the beach in Acapulco, and that the symptoms stopped when they returned to the polluted city, suggesting that nitric oxide was responsible (ignoring the effect of altitude). It became common to treat newborn pulmonary hypertension with inhaled nitric oxide, because it seemed obvious that opening constricted arteries in their lungs would improve oxygenation of their blood.

The amount of research proposing new ways to deliver nitric oxide itself to patients seems to be increasing, and a variety of products intended to increase the body's synthesis of nitric oxide are being sold. Some of these products are being promoted by professors of medicine, with the involvement of their universities.

We now seem to be in the "hair growing" and "wrinkle cream" phase of the nitric oxide culture. "If nitric oxide increases blood flow," they reason, "it must make hair grow and wrinkles disappear; and, in the brain, more circulation produced by nitric oxide must slow aging and prevent dementia. If nitric oxide promotes collagen synthesis, that must be good for the skin." They also claim that it helps to build bigger and better muscles, to reduce fatigue, to improve endurance and increase immunity, strengthen bones, and prevent heart disease and cancer. Nitric oxide has started to sound as good as estrogen.

Endotoxin, for example absorbed from the intestine during stress, can cause pulmonary hypertension, and septic (endotoxin) shock, with low systemic blood pressure, can involve pulmonary hypertension. Endotoxin greatly increases nitric oxide, especially in the lungs, and it can alter the response of blood vessels to nitric oxide (Boer, et al., 2015; Bonartsev, et al., 2004). I think prenatal exposure to endotoxin is probably responsible for most prenatal pulmonary hypertension (Mandell, et al., 2015).

In shock (with elevated nitric oxide), the use of oxygen is blocked, so the blood stays saturated with oxygen, yet pulmonary hypertension accompanies the systemic hypotension of shock. The use of a high oxygen concentration or hyperventilation for resuscitating newborns causes constriction of the pulmonary artery. The reduced production of CO2 during shock causes platelets to release their bound serotonin load, but excess oxygen in the lungs impairs their normal ability to destroy serotonin. Serotonin, besides increasing vasoconstriction, stimulates cell division and collagen synthesis. Providing a more physiological gas mixture, containing some carbon dioxide, might be appropriate, since carbon dioxide relaxes blood vessels. Providing carbon dioxide transcutaneously improved pulmonary circulation in an animal study (Yamaguchi, et al., 2015).

Pulmonary hypertension also occurs in adults, especially women, several times as often as in men, and is usually fatal within a few years. Increased exposure to estrogen and serotonin is known to increase the incidence in women; the use of SSRI antidepressants during pregnancy is known to cause PH in the baby. The "erectile dysfunction" drugs Viagra and Cialis, which inhibit the breakdown of cGMP, are being prescribed to women with pulmonary hypertension, despite some evidence suggesting that cGMP might already be too high.

The use of nitric oxide for treating pulmonary hypertension is deflecting interest from generally safe substances, such as magnesium, oxybutyrate, pentoxifylline, progesterone, DHEA, testosterone, and thyroid hormone, and directing attention away from the various factors that cause the pulmonary hypertension of adults as well as newborns.

Thromboxane, released from platelets which make it from a fatty acid, is a factor in pulmonary hypertension, and free fatty acids, produced by stress, have many toxic effects in the lungs; endotoxin increases lactate, thromboxane, and free fatty acids, as well as nitric oxide and circulating cGMP (Schuller, et al., 1992). Testosterone, which relaxes arteries (giving it a role in pulmonary circulation as well as penile circulation), doesn't inhibit the breakdown of GMP. Since the Viagra-type drugs do inhibit its breakdown, a significant controversy has developed, with some publications arguing against the use of testosterone to enhance virility.

The use of nitric oxide or Viagra to treat pulmonary hypertension is based on a misunderstanding of the nature of the disease. There is an "autoimmune" aspect to it (nitric oxide seems to be a factor in the other main autoimmune conditions), and in both newborns and adults, "tissue remodeling" is occurring, degrading the structure and function of the lungs. The cells are stimulated to divide rapidly, and to alter their form and interactions, forming new contractile and fiber-producing cells, and to produce a different sort of extracellular matrix, containing more collagen, leading to pulmonary fibrosis. In pulmonary hypertension, all the cellular components of the blood vessels in the lungs are metabolizing inefficiently, oxidizing fatty acids while producing lactate, as if they lacked oxygen. This is similar to the metabolism of cancers and of neurodegeneration, a metabolism of inflammation and fibrosis

(Ryan and Archer, 2014; Fang, et al., 2012; Pavlides, et al., 2010).

The synthesis of collagen, which can become excessive in aging and chronic inflammation, is, in good health, an adaptive process. Pressure and friction cause the soles of our feet and the palms of our hands to thicken and develop calluses, and this is a process that involves increased nitric oxide. Pressure, stretching, and vibration cause cells to form increased amounts of nitric oxide, and in those situations it's often appropriate to increase the production of collagen, and to adjust the extracellular matrix to resist the stresses.

Collagen synthesis is closely related to the regulation of cells' most basic defensive reactions. Vitamin C is best known for its prevention of scurvy, in which it is needed for the hydroxylation of the amino acid proline in the formation of the collagen molecule, to prepare it for secretion to form extracellular filaments. In normal cells in a resting state, most of the vitamin C inside cells is in the oxidized state, dehydroascorbate. It is when cells are sensing an oxygen deficiency that collagen is formed, and in this state, there is a shift away from the dehydroascorbate form to the reduced form, which acts as the cofactor, activating the enzyme.

The hydroxylation of proline leading to collagen synthesis normally occurs just in the specialized fibroblasts. When a stress is more intense and prolonged, lack of oxygen shifts the action of other proline hydroxylase enzymes, in every type of cell, allowing the hypoxia inducible factor, HIF, to accumulate, reorganizing cells' metabolism to produce lactic acid, rather than carbon dioxide.

The living state requires a flow of electrons, ultimately from sugar, eventually to oxygen, forming water and carbon dioxide. Depending on the cells' level of stimulation and work, the flow can be very fast or very slow. In stress, the flow must accelerate to respond to the changed needs, and this means that both supply and removal of electrons must be increased. Cells store some glucose internally in the form of glycogen, because glucose can't always be provided quickly enough by diffusion from the blood, and when oxygen can't be supplied quickly enough, glucose by itself can temporarily supply energy.

When the energy flow is disturbed at either end, defensive reactions shift the redox balance toward more of the reductants, with lactic acid increasing relative to pyruvic acid, ascorbate relative to dehydroascorbate, and NADH relative to NAD+. In starved rats, the cytoplasmic NAD+/NADH ratio decreased from the normal 725 to 528, and in diabetes to 208 (Williamson, et al., 1967).

The nitric oxide radical itself has a short existence, allowing an adaptation such as vasodilation to last only as long as the need for it continues. Similarly, the formation of collagen is appropriately situational--calluses gradually disappear when they aren't needed. Metabolic alterations, though, tend to become self-sustaining. The stress metabolism can spread within a single organ by the diffusion of lactic acid, which is a stress signal that can rouse the organism to correct the localized problem, for example by producing a fever. If the organism's resources aren't adequate, the problem can become chronic. Chronic exposure to lactate and the stress hormones causes degeneration of all the tissues.

Nitric oxide, by blocking oxygen use, creates a state of "pseudohypoxia" or reductive stress, and hypoxia can increase the production of nitric oxide (He, et al., 2007; Giusti, et al., 2008; Thompson, et al., 2009; Martinez-Romero, et al., 2012). It is commonly believed that nitric oxide is synthesized only by the enzyme nitric oxide synthase, from arginine, because that fits a theory that it is a well-controlled essential part of our physiology. However, there are several (animal and human) enzymes that can form nitric oxide from other materials, including nitrite and nitrate. For example, in the absence of oxygen, hemoglobin reduces nitrite to nitric oxide. Other reductive enzymes can convert nitrate (the most oxidized of the three) to nitrite.

This means that in reductive stress, the amount of nitric oxide formed will depend partly on the amount of nitrate and nitrite in the body fluids, not just on the amount of arginine that's taken up by certain cells. Besides nitrate and

nitrite that are ingested in some foods, the body's normal metabolism of arginine into nitric oxide will increase the amount of nitrite and nitrate in the body in proportion to the amount of stress.

The vicious cycles of stress operate at numerous levels. For example, nitric oxide lowers the production (Haluzik, et al., 1998) of testosterone and the thyroid hormone, T3, both of which directly relax blood vessels. In their absence, blood pressure tends to be higher, and hypothyroidism can increase the production of nitric oxide (Carreras, et al., 2001).

When hypertension is associated with increased nitric oxide, it is likely to be explained as a compensatory reaction (del Castillo, et al., 1995; Dubey, et al., 1996; Merta, et al., 2003; Vaziri, et al., 1998) rather than a cause.

To counter such arguments, many experiments have been done, that demonstrate the harm that is done by increasing nitric oxide, and the protective effects of blocking its formation or actions. I'll write about some of those in the next newsletter.

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