Ray Peat's Newsletter

. . . how soon we Shall have a change for the better I cannot Prophecy. ***William Blake***

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Antioxidants and formative fields: Disruptors & stabilizers

During the 20th century, the simplifying biological insights of W.F. Koch, Otto Warburg, and Albert Szent-Gyorgyi were dismissed as unscientific by the medical culture because their concern with metabolic processes conflicted with the reductionist ideas of established medicine, in which sickness was to be explained as the result of defects in molecules and genes. When the idea of "the gene" was concretized in 1953 by the description of the DNA molecule's structure, molecular reductionism was confirmed as the ruling ideology.

At the end of the century, there was a growing realization of the commercial possibilities in cloning and stem cells (which had been declared impossible by the reductionists), and so the less rigidly deterministic ideas of epigenetics, of metabolic causes of diseases other than diabetes, and of "developmental fields" began to reappear in medicine, but (with the guidance of government and industry) in a new reductionist form.

In the middle of the century, it was known that cancer cells have a powerful antioxidant capacity, and that their high reducing capacity, that protects them from toxic oxidants, is also crucially involved in their tendency to proliferate continuously. This is a general metabolic feature of cancer cells of all kinds.

James Watson, co-discoverer of the structure of the DNA molecule, and probably the most extreme reductionist in the US, has recently discovered that this antioxidant excess of cancer might be important. He warns that the use of antioxidant supplements could be harmful, by blocking the reactive oxygen species, ROS, which normally kill stressed cells. Most of his attention is given to the use of drugs to reduce cancer cells' antioxidant defenses--that is, he proposes new ways to chemically kill cancer cells.

Cells are protected against reactive oxygen species, such as those produced by lipid peroxidation and radiation, for example by inactivating them with a donated electron from ascorbate or vitamin E, or by combining a reducing molecule such as glutathione, GSH, with them. Many of the toxic ROS are produced by the cells' own respiratory apparatus, during stress, so that an even more basic "antioxidant" function is to suppress the formation of ROS, instead of destroying them after first creating them.

When the mitochondrial oxidation of glucose is functioning intensely, under the influence of thyroid hormone, few toxic free radicals are produced, but when something interferes with that intense use of oxygen to convert sugar to carbon dioxide, the ROS are produced more intensely. Suffocation, cyanide (Borle and Barsic, 1995), nitric oxide (Liu, et al., 2014), and carbon monoxide (Akyol, et al., 2014) increase damaging ROS. Ethyl alcohol, unsaturated fatty acids, and radiation are other things that inhibit mitochondrial respiration while increasing ROS.

When the mitochondria are respiring actively, besides not producing the toxic ROS, which Watson thinks are protective against cancer, they are performing another kind of oxidation, which regulates all cell processes, creating a complexly organized metabolism that allows cells to perform their normal functions, while inhibiting inappropriate proliferation. Oxidation does prevent cancer, but it does it by creating a formative field, continuing the developmental process that created the organism.

Embryologists have always been aware that life's self-organizing processes are something unique, that will require the discovery of

something beyond the known mechanical principles of non-living material. Early in the 20th century, the reductionists declared that it was unscientific to look for explanations of life other than chemical and physical processes, as those were understood at the time. Reductionists found it very hard to accept that organization was essentially different from disorganization. Applying information theory to matter has gradually made it obvious to most people that meaningful patterns such as cybernetic systems are significantly more than the sum of their (previously known) parts. The parts become something more when they work in the system.

In physics, a field is a definite (but mysterious) thing, the region around a material thing in which a particular force influences other things--a gravitational field influences other masses, an electrical field influences other charged things. Reductionists have tried to deny biological fields, by creating the straw-man of a "vital force," exactly analogous to the fields of the physicists, and observing that such a thing has no testable meaning. However, a biological field is simply a region that shows the effects of certain influences, and it can refer to a cell, a group of cells or tissues, an organ, an organism, or a larger system. For example, cells, organisms, and ecosystems are influenced by the earth's gravitational field, and also by its electromagnetic fields. Tissues are under the influence of pressures, tensions, pulsations, and electrical and chemical processes.

Cells exert influences on their environment, and in turn are influenced by their environment. Metabolism, which is essential for an organism's development and interactions with the world, is a "field," and the pattern of metabolism reflects, and affects, the organism's structure and the way it relates to the world.

To be concerned with "field effects" in biology is to be open to investigating the complexities of any issue, as opposed to the old doctrine that cells are simply unrolling the properties determined by a genetic blue-print. Those who claimed that life is genetically determined had ulterior motives, and those motives have outlived radical genetic determinism.

Medicine, as it begins to shift away from genetic determinism, is confronted by the fact that a metabolic view of health and sickness incorporates a recognition that the environment, and social institutions, should be evaluated according to their influence on metabolism. The risk of identifying important institutions as major pathogens makes it seem easier to create a muddle of gene testing and pharmacological research, instead of clarifying problems and finding the simplest solutions.

Warburg's "respiratory defect" description of cancer was first misrepresented as "eating sugar feeds cancer growth," and now the newer claim is that "sugar causes cancer." The reasoning is wrong, but it's consistent with the 200 year old mistaken belief that sugar causes diabetes, and with the fact that diabetics are especially susceptible to cancer. Diabetics are relatively unable to oxidize glucose, they produce lactate in the presence of oxygen, and may synthesize fat inappropriately. Diabetes is relevant to cancer exactly because of their shared inability to oxidize sugar and lactic acid.

Starvation creates an inability to oxidize glucose, resembling diabetes, because it increases free fatty acids in the blood, which are oxidized for energy instead of sugar. Many kinds of experiment have demonstrated that starvation stimulates the growth of tumors (Sauer, et al., 1986). In the absence of glucose, tumors preferentially derive their energy from the oxidation of fat, but they cause the breakdown of tissue proteins, to convert to fat and to use for growth. The presence of free fatty acids caused by a tumor causes "insulin resistance," and a tumor bearing animal can produce ketones with relatively normal blood glucose, as in diabetes.

The presence of lactate in a cell indicates that the cell's balance is reductive, rather than oxidative. The ratio of lactate to pyruvate in a cell is an indicator of the degree of reductive stress. Other indicators of the oxidative-reductive ("redox") balance in a cell are the ratio of NAD+ to NADH and of reduced to oxidized glutathione, GSH/GSSG. When a healthy cell is dividing, it momentarily shifts into a highly reduced state, with a large excess of sulfhydryl (SH) groups, and

a decrease of the disulfide bonds, including some of those involved in stabilization of proteins; the dividing healthy cell momentarily produces lactate, corresponding to its highly reduced condition.

Lactate, besides being an indicator of the cell's state, is itself a reductant. For many years it was known to be a promoter of inflammation, an antioxidant, and a stimulator of new blood vessel formation, but huge amounts of money and time were spent looking for proteins in tumors that could account for those features--their stimulation of blood vessel growth, promotion of inflammation, and protection against oxidants--while failing to consider the meaning of their continuous aerobic production of lactate.

Local production of lactic acid stimulates tissue renewal and repair, calling up resources from the surrounding tissues, or from the organism by activating a stress response. Within a cell, the conversion of pyruvate to lactate increases pH, increasing the cell's excitability, causing its water content to increase, and changing its affinity for adsorbed subtances (from potassium to sodium, for example). In the space surrounding stressed cells or cancer cells, lactic acid lowers the pH. Exposure to extracellular acidity creates "stemness" in cells, and increases their proliferation and motility (Fiaschi, et al., 2013).

Stress and inflammation lead to the production of lactate, and exposure of tissues to lactate activates processes that, if allowed to continue, will amplify the stress and inflammation. Cancer is a clear case of the amplification of inflammation. A protein called hypoxia-inducible factor, HIF, activates the enzymes cancer cells need to thrive in a poor environment, while it inactivates the enzyme system that's crucial for oxidizing glucose, pyruvate dehydrogenase (PDH). HIF is central to the establishment of aerobic glycolysis, and glucose deprivation is one of the important factors in the induction of HIF. Lactate (Polet and Feron, 2009), and more significantly, an excessively "antioxidant" (reduced) environment in the cell activate HIF (Haddad, et al., 2000). Oxygen deprivation, ionizing radiation, and estrogen are other things that activate HIF.

The composition and arrangement of the extracellular matrix affects the functions of cells, and stress affects the cells' ability to maintain it properly. For example, lactate (partly by increasing HIF) promotes the formation of collagen, and over time excess lactate promotes tissue fibrosis, accelerating the changes that occur with aging. Over-production and hardening of collagen reduces the cells' access to oxygen, sugar, and other nutrients, progressively decreasing the ability of cells to respond to stress.

When stress has activated HIF, most of the available glucose will be converted to lactate, maintaining the low-glucose, high-lactate conditions that produced the HIF, and the HIF of the glucose-deprived cells will shift fuel consumption toward the use of glutamine (Corbet, et al., 2014), and toward the use of some of the fuel for the synthesis of fatty acids (Menendez, et al., 2005), which will then be oxidized for energy production. This wasteful system of cell metabolism is supported by the stress hormones, that break down healthy tissues, converting amino acids to glutamine. The fatty acids that are mobilized from the tissues have effects similar to HIF, inhibiting PDH, preventing the oxidation of glucose.

When the system fails to restore efficiency to the disturbed tissue, the reductive excess becomes more intense and generalized, with increased production of HIF and other alarm or danger signals, including nitric oxide and the inflammatory cytokines. HIF, NOS, and other products of the disturbed cells cause fatty acids and amino acids to be released from tissues throughout the body. The fatty acids contribute to the inhibition of PDH, with a shift in fuel use systemically, and changes in the balance of nerve activity and hormones, and damage to the immune system. The increased serum lactate itself, in an individual with cancer, blocks the proliferation and function of T cells (Fischer, et al., 2007).

The healthy body is able to interrupt the process by supporting the maturation of the newly produced cells, and providing increased nutrients and oxygen through the newly formed blood vessels. Thyroid, cholesterol, pregnenolone, DHEA, progesterone, glucose and carbon dioxide

help to reverse the inefficient inflammatory metabolism.

If lactic acid is seen as a primary disruptor of fields, first in the cell with increasing pH, then in the surrounding extracellular spaces with decreasing pH, and systemically causing nervous, hormonal, biochemical and behavioral shifts in the organism, then carbon dioxide can be seen as the primary stabilizer of fields. It inhibits the formation of lactic acid, lowers the intracellular pH, stabilizes mitochondrial oxidative metabolism, has protective effects on protein structure, improves blood flow, and stabilizes nervous and hormonal systems and behavior. It can protect against nitric oxide and other mediators of inflammation (Dunlop, et al., 2014).

If the oxidative metabolism of a cell is compared to a flame, lactic acid is the smoke that's produced when there isn't enough oxygen, or when the temperature is too low. Both a cell and a flame produce carbon dioxide when nothing interferes with their oxidation. Interestingly, the effects of smoke on cells resemble those of lactate, producing inflammation, cancer, impaired oxidation, and damaged extracellular matrix. A smokeless, hot flame is called an oxidizing flame, because it converts the fuel completely to carbon dioxide, and, for example in a welding torch, can oxidize metal surfaces. A smoky flame is called a reducing flame, because it can donate electrons to oxidized metal.

Healthy cells, with a high ratio of oxidized NAD+ to reduced NADH, are analogous to an oxidizing flame. Ascorbic acid, in itself a reducing substance, is oxidized when it's introduced into a healthy cell, becoming dehydroascorbate (DHA), a relatively oxidizing material. In the functioning cell, DHA oxidizes the sulfydryl groups of newly formed proteins, stabilizing them, and preventing their degradation. In a stressed cell, proteins are misfolded, and quickly degraded.

In a cancer cell, the metabolism is strongly shifted in the direction of reduction, and ascorbic acid reflects this, being maintained in a reduced state (Romanovich and Basieva, 1979). The reduced state of ascorbate is involved in the reactions of HIF that promote collagen synthesis (Szarka and Lorincz, 2014). The excessive production of collagen contributes to the disorganization of the tissue field.

The accelerated protein degradation resulting from this type of (reductive) stress prevents cellular maturation and differentiation, one of the features of cancer, but probably also a factor wherever stem cells fail to mature into functional replacement cells.

The oxidation of fat contributes to the under-oxidized stress reaction, and blocking fat oxidation protects cells from the protein-misfolding stress reaction (Tyra, et al., 2012). A normally protective antioxidant, N-acetyl cysteine, in this situation blocks the protective effect of inhibiting fat oxidation. In patients with heart failure, the protective effect of inhibiting fatty acid oxidation (for example, with niacinamide supplements) is already well known. Since the unfolded protein response is now considered to be a factor in Alzheimer's and Parkinson's disease and diabetes (Delic, et al., 2012), among other chronic diseases, the inhibition of fat oxidation, and supporting sugar oxidation, now seems to be appropriate for preventing or treating any age-related degenerative disease.

The promotion of cancer growth by fasting isn't seen early in life, but appears in adulthood (Sauer and Dauchy, 1987), corresponding to the increasing quantity of stored fat, and probably to changes in its quality, i.e., the increased proportion of polyunsaturated fats with aging. Besides the generally stress-promoting effects of free fatty acids, the polyunsaturated fatty acids are converted, during stress, to prostaglandins and related inflammation-promoting substances. Bacterial endotoxin from the intestine is a chronic stress, increasing exposure to nitric oxide and the various danger signals that promote inflammation and aerobic glycolysis.

Besides selecting a diet that minimizes intestinal inflammation and free fatty acids, and that provides essential amino acids without an excess of cysteine, tryptophan, and arginine, the safe antiinflammatory supplements vitamin E, aspirin, niacinamide, vitamins K and D, thyroid hormone, progesterone, pregnenolone, DHEA, and coffee help to decrease the susceptibility to stress-induced aerobic glycolysis. Drugs such as

lidocaine and other local anesthetics, anticholinergics and antihistamines such as atropine, scopolamine, diphenhydramine, and cyproheptadine, acetazolamide (a carbonic anhydrase inhibitor, to protect against increased intracellular pH), and dichloroacetate, DCA, to activate the oxidation of glucose (by pyruvate dehydrogenase, PDH), should be considered for treating the conditions that involve continuing aerobic glycolysis. Niacinamide, by lowering free fatty acids, can also increase PDH (Wieland, et al., 1971), and fructose, in the form of fruits, is another safe promoter of pyruvate dehydrogenase.

REFERENCES

Redox Rep. 2014 Sep;19(5):180-9. The role of reactive oxygen species and oxidative stress in carbon monoxide toxicity: an in-depth analysis. Akyol S, Erdogan S, Idiz N, Celik S, Kaya M, Ucar F, Dane S, Akyol O.

Fiziol Zh Im I M Sechenova. 1995 Feb;81(2):47-52. [The unknown physiological role of carbon dioxide]. [Article in Russian] Baev VI, Vasil'eva IV, L'vov SN, ShugaleÄ- IV.

Cell Calcium. 1995 Apr;17(4):307-15. Chemical hypoxia increases cytosolic Ca2+ and oxygen free radical formation. Borle AB1, Barsic M.

Cancer Res. 2014 Aug 1. pii: canres.0705.2014. [Epub ahead of print] The SIRT1/HIF-2Î± axis drives reductive glutamine metabolism under chronic acidosis and alters tumor response to therapy. Corbet C, Draoui N, Polet F, Pinto A, Drozak X, Riant O, Feron O.

Free Radic Biol Med. 2012 May 1;52(9):2000-12. Oxidative protein folding and unfolded protein response elicit differing redox regulation in endoplasmic reticulum and cytosol of yeast. Delic M, Rebnegger C, Wanka F, Puxbaum V, Haberhauer-Troyer C, Hann S, KÃ¶llensperger G, Mattanovich D, Gasser B.

Curr Pharm Des. 2012;18(10):1319-30. Multiple biological activities of lactic acid in cancer: influences on tumor growth, angiogenesis and metastasis. Dhup S, Dadhich RK, Porporato PE, Sonveaux P.

Free Radic Biol Med. 2014 Apr;69:35-49. Therapeutic hypercapnia prevents inhaled nitric oxide-induced right-ventricular systolic dysfunction in juvenile rats. Dunlop K, Gosal K, Kantores C, Ivanovska J, Dhaliwal R, Desjardins JF, Connelly KA, Jain A, McNamara PJ, Jankov RP.

Autoimmunity. 1994;19(3):193-8. Nicotinamide decreases nitric oxide production and partially protects human pancreatic islets against the suppressive effects of combinations of cytokines. Eizirik DL, Sandler S, Welsh N, Bendtzen K, Hellerstrm C.

Cell Cycle. 2013 Jun 1;12(11):1791-801. Carbonic anhydrase IX from cancer-associated fibroblasts drives epithelial-mesenchymal transition in prostate carcinoma cells. Fiaschi T, Giannoni E, Taddei ML, Cirri P, Marini A, Pintus G, Nativi C, Richichi B, Scozzafava A, Carta F, Torre E, Supuran CT, Chiarugi P.

Blood. 2007 May 1;109(9):3812-9. Inhibitory effect of tumor cell-derived lactic acid on human T cells. Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, Gottfried E, Schwarz S, Rothe G, Hoves S, Renner K, Timischl B, Mackensen A, Kunz-Schughart L, Andreesen R, Krause SW, Kreutz M.

Mol Cell Biol. 1993 Aug;13(8):4609-17. Cooperative DNA binding of the human HoxB5 (Hox-2.1) protein is under redox regulation in vitro. Galang CK, Hauser CA.

Am J Physiol. 1982 Oct;243(4):H619-27. NAD/NADH: redox state changes on cat brain cortex during stimulation and hypercapnia. Gyulai L, Dora E, Kovach AG.

J Biol Chem. 2000 Jul 14;275(28):21130-9. Antioxidant/pro-oxidant equilibrium regulates HIF-1alpha and NF-kappa B redox sensitivity. Evidence for inhibition by glutathione oxidation in alveolar epithelial cells. Haddad JJ, Olver RE, Land SC.

Biochemistry. 1995 Oct 17;34(41):13443-52. Thiol dependence of nitric oxide synthase. Hofmann H, Schmidt HH.

Mol Cell Biol. 2012 May;32(10):1893-907. Glucose oxidation modulates anoikis and tumor metastasis. Kamarajugadda S1, Stemboroski L, Cai Q, Simpson NE, Nayak S, Tan M, Lu J.

Arch Biochem Biophys. 2003 Sep 15;417(2):183-93. Redox pacing of proteome turnover: influences of glutathione and ketonemia. Lockwood TD.

J Cell Biochem. 2005 Apr 1;94(5):857-63. Does endogenous fatty acid metabolism allow cancer cells to sense hypoxia and mediate hypoxic vasodilatation? Characterization of a novel molecular connection between fatty acid synthase (FAS) and hypoxia-inducible factor-1alpha (HIF-1alpha)-related expression of vascular endothelial growth factor (VEGF) in cancer cells overexpressing her-2/neu oncogene. Menendez JA, Vellon L, Oza BP, Lupu R.

Anesthesiology. 2010 Jul;113(1):116-25. Hypercapnic acidosis reduces oxidative reactions in endotoxin-induced lung injury. Nichol AD(1), O'Cronin DF, Naughton F, Hopkins N, Boylan J, McLoughlin P.

Int J Oncol. 2014 Jun;44(6):2077-84. HIF-1α activation under glucose deprivation plays a central role in the acquisition of anti-apoptosis in human colon cancer cells. Nishimoto A, Kugimiya N, Hosoyama T, Enoki T, Li TS, Hamano K.

J Intern Med. 2013 Feb;273(2):156-65. Endothelial cell metabolism and tumour angiogenesis: glucose and glutamine as essential fuels and lactate as the driving force. Polet F, Feron O.

Vopr Onkol. 1975;21(10):34-6. Ascorbic, keto and hydroxy acid metabolism in the cell nuclei of certain tumors. [Article in Russian] Romanovich EA, Basieva FI. The authors report the results of studies on the content of ascorbic acid, pyruvic acid and the activity of malate dehydrogenase decarboxylizing (MDHD) in cell nuclei of uterine fibromyoma, glandular hyperplasia of the endometrium with epithelial proliferation, common ovarian cyst and solid cancer. It was shown that due to the glycolysis inhibited respiration an oxidated form of ascorbic acid is absent in every case, whereas the MDHD activity is not manifested. The amount of a reduced form of ascorbic and pyruvic acid in benign tumors is at the control level, but in malignant growth these indices are markedly increased.

Antioxid Redox Signal. 2010 Jan;12(1):15-25. The role of dehydroascorbate in disulfide bond formation. Saaranen MJ, Kara. AR, Lappi AK, Ruddock LW.

Cancer Res. 1986 Jul;46(7):3469-75. Stimulation of tumor growth in adult rats in vivo during an acute fast. Sauer LA, Nagel WO, Dauchy RT, Miceli LA, Austin JE.

Cancer Res. 1987 Feb 15;47(4):1065-8.Blood nutrient concentrations and tumor growth in vivo in rats: relationships during the onset of an acute fast. Sauer LA, Dauchy RT.

Cell Biochem Funct. 2008 Oct;26(7):801-7. Hypercapnia protects erythrocytes against free radical damage induced by hypoxia in exposed rats. Skoumalova A, Herget J, Wilhelm J.

Protoplasma. 2014 May;251(3):489-97. The role of ascorbate in protein folding. Szarka A, Lorincz T.

Mol Biol Cell. 2012 Mar;23(5):811-9. Inhibition of fatty acid oxidation enhances oxidative protein folding and protects hepatocytes from endoplasmic reticulum stress. Tyra HM, Spitz DR, Rutkowski DT.

Archives of Biochemistry and Biophysics, 1971, 143(2), 593-601. Active and inactive forms of pyruvate dehydrogenase in rat heart and kidney: Effect of diabetes, fasting, and refeeding on pyruvate dehydrogenase interconversion. Wieland O, Siess E, Schulze-Wethmar FH, Funcke HGV, Winton B.

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