Ray Peat's Newsletter

"The cure of human cancer will be the resultant of biochemistry of cancer and of biochemistry of man." Otto Warburg

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100 Years of Cancer Metabolism

Since around 1950, the culture of biology and medicine in the U.S. has been re-engineered in ways that make it incompatible with older ideas on the same subjects, the way new computers are designed so that they can't use old programs. Many people are now writing about "cancer metabolism," especially Otto Warburg's 1923 discovery of cancer's "aerobic glycolysis," but most of them are taking his ideas out of context, to make them fit into the idea that the prime cause of cancer is a genetic defect, whose metabolic consequences might make it possible to kill the mutated cells without harming the rest of the organism.

When Warburg observed the production of large amounts of lactic acid by cancer cells in the presence of oxygen, and described it as "impaired respiration," with an absence of the "Pasteur effect," he was placing the cancer problem exactly at the center of the question of the nature of life. One of the implications of his idea was that cancer was a basic adaptive survival process of cells, exactly the sort of thing that would suggest that a "precisely targeted poison" would fail.

In Greece more than 2000 years ago, there was already a general understanding of metabolism, in which breathing was seen to be required for maintaining consciousness, vital heat production, assimilation of foods, and organization of functions. The details of oxidative metabolism were mostly unknown until the second quarter of the 20th century, and are still being worked out.

In Louis Pasteur's time, the leading chemists believed that fermentation, the production of alcohol from sugar, was produced by lifeless catalysts, activated by oxygen. Pasteur, without knowing any of the details of cell physiology, was able to show that fermentation was an internal process of living organisms, and that they did this in the absence of oxygen. In the presence of oxygen and sugar, the yeast grew without producing alcohol—respiration inhibits fermentation. (The Pasteur Effect that Warburg referred to is the suppression of lactic acid production from glucose in the presence of oxygen.)

> ***"No way can be imagined that is scientifically better founded to prevent and cure a disease, the prime cause of which is an impaired respiration. Neither genetic codes of anaerobiosis nor cancer viruses are alternatives today, because no such codes and no such viruses in man have been discovered so far; but anaerobiosis has been discovered."***
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> **Otto Warburg**

Pasteur's work was good physiological chemistry, but the mechanists called it "vitalism," and thought it was unscientific. For the next fifty years, a lot of effort was invested in the elimination of "vitalism" from biology, and some important discoveries (such as MacMunn's respiratory pigments in the 1880s) were neglected because they didn't fit into mainstream biology. In the 1920s, David Keilin in England rediscovered the respiratory pigments, and tried to explain their function by suggesting that there were particles in cells that acted as general oxidative catalysts, the way a platinum surface might.

One of the most interesting discoveries of Keilin's was that in living tissue the respiratory pigments are in a dynamic equilibrium between oxidation and reduction. Intense stimulation, by

consuming the oxygen locally, would cause them to become fully reduced, as electrons accumulated, and when resting tissue was supplied with an excess of oxygen, the pigments faded, with their nearly complete oxidation. Cyanide and carbon monoxide, by shifting the balance toward an excess of electrons, produced the same color change as intense stimulation and muscle contraction.

Warburg, around the same time, suggested that his "respiratory enzyme" might be acting on particles that served as catalysts, the way charcoal might. This was the work for which he received the 1931 Nobel Prize, not the insightful, but holistic, study of cancer metabolism. It wasn't until the late 1930s that the important idea of a respiratory chain was integrated with the recent recognition of ATP as an "energy transfer molecule" and the elaboration of the citric acid ("Krebs") cycle which provides fuel for oxidative energy production. Essential parts of the respiratory chain weren't discovered until the 1950s.

A little before Warburg's study of cancer metabolism, W.F. Koch, a professor of physiological chemistry in Detroit, had expressed his opinion that cancer, allergy, and susceptibility to infections resulted from defective tissue oxidation. Some of his articles were published in international journals, but newspaper articles describing cancer cures made Koch famous throughout Europe and America.

Koch had been a student of Moses Gomberg, who in 1900 had produced the first stable free radical (the triphenylmethyl radical). During the years of Koch's study at the University of Michigan (1905 to 1914), chemists and physicists were exploring the properties of carbonyl (C=O) groups and their interactions, trying to explain the unusual reactivities and colors of molecules containing these groups. While he was at the university, Koch lived with the family of a professor of homeopathy. From Koch's language, it's clear that he had assimilated the best contemporary knowledge of physical chemistry, and his holistic approach—treating the patient rather than the disease—reflected his familiarity with homeopathic medicine.

When Koch began applying his ideas to the treatment of cancer patients, in 1916, the existence of Gomberg's free radical was still questioned by the majority of chemists; it was only in the early 1930s, when free radical chemistry began to have industrial uses, that the possibility of stable free radicals came to be widely recognized by academic chemists. When Koch used the idea of electronic resonance within molecules, and between molecules, and in cells and organisms, to describe his therapeutic method, most physicians had no idea of what he was talking about. To some, the idea of catalyzing free radical oxidations in a patient sounded crazy and dangerous. The FDA invested considerable time and expense in demonizing Koch and his dangerous oxidative theory of treatment. I think Otto Warburg and Albert Szent-Gyorgyi were among the few who thought that Koch might be talking about something real. Szent-Gyorgyi acknowledged having "the highest respect" for Koch's work, but he was clearly aware of the dangers involved in premature holism.

In the 1950s and 1960s, Szent-Gyorgyi began talking openly about life processes in terms of a very precise balance between oxidation and reduction which kept systems of electrons in cells in a special free-radical-like state, oscillating between "donor" and "acceptor" molecules. He believed that a deficiency of the naturally occurring oxidative dicarbonyl molecule methylglyoxal might be a cause of cancer.

There is still interest in his theory, for example "The anti-cancer effect of methylglyoxal is now well established in the literature" (Pal, et al., 2016), but that molecule can also be toxic, depending on the condition of the cell. When the cell is healthy, methylglyoxal will be just one of many factors being created in the right place at the right time. The more volatile molecule glyoxal was one of Koch's reagents.

Early in his research Szent-Gyorgyi believed that vitamin C was one of the catalysts supporting oxidative metabolism in animals. The ordinary ascorbic acid (which contains one carbonyl group, activated by its conjugation with double bonded carbons) is, in the cell, oxidized to dehydroascorbate, a tricarbonyl, with a relatively stable free

radical intermediate state, semidehydroascorbate. The oxidized form greatly predominates in healthy cells, but in cancer cells the reduced form is increased. This corresponds to the generally less oxidized state of cancer cells, or of normal cells that are in an excessively excited state, relative to the availability of oxygen.

In his 1937 Nobel lecture, Szent-Gyorgyi began by saying "A living cell requires energy not only for all its functions, but also for the maintenance of its structure. Without energy life would be extinguished instantaneously, and the cellular fabric would collapse." Many years later he explained that he saw cell structure as an integral conductive/semiconductive system, and cellular movement and other functions, as consequences of the flow of energy through that system.

In the 1940s he was exploring the role of ATP in muscle contraction, and observed that muscle can contract without splitting ATP (Szent-Gyorgyi, 1949). Gilbert Ling's work shows that it's the electron-withdrawing effect of ATP that explains its effects, rather than its internal bond energy. In physics, the idea of cooperative phase transition is familiarly used to explain water's change of state during freezing and melting, but the reductionist ideology that is so conspicuous in science makes biologists reluctant to see it in the changes of state that occur in living cells. The idea that the bond energy of ATP is used to power muscle contraction, by causing little levers to move, is intimately associated with the belief in membranes, pumps, and random diffusion of enzymes and their substrates. To the mechanist, cells, organisms, and consciousness are just statistical abstracts of molecular events, and cancer is neatly explained as the product of random genetic mutations.

The way energy flows through a system depends on the conductive and catalytic condition of the system, and the condition of the system depends on the flow of energy. When a cell is stressed, stimulated beyond its ability to respond with increased respiration to produce the energy needed to return to its resting state, the stress itself is a relatively reducing state, like the cytochrome color shift Keilin saw when muscles contracted or were poisoned.

The reduced state leads to increased production of lactate, which produces enough energy to keep the cell alive, but the lactate contributes to the stressed redox shift in the cell that produces it, as well as in the surrounding cells.

The new reductionist interpretation of Warburg's idea is that the shift to aerobic glycolysis and lactate production is the result of a genetic change that centers on increasing glucose use, but in reality glucose deprivation is one of the things that can lead to the shift to aerobic glycolysis, with the lactate then being derived from the breakdown of tissue protein instead of glucose. V.S. Shapot found that providing both glucose and oxygen to rats with Ehrlich ascites cancer could produce the Pasteur effect, inhibiting glycolysis and restoring cellular respiration (Tagi-zade and Shapot, 1971). The ability of glucose to reduce excitation in other situations probably involves the increased oxidative state; an important part of the cancer physiology is overexcitation of the brain, especially the hypothalamus, and just increasing the level of blood glucose can lower that excitation (Shapot, et al., 1983).

When cells are dangerously overstimulated, oxygen and glucose are depleted. In the absence of oxygen, or when the ability to use oxygen is blocked, glucose is converted to lactate, and when glucose is depleted, glutamine is converted to lactate. With a limited supply of oxygen but an unlimited supply of lactate, the cell's metabolic reactions are shifted toward a reduced, electron-rich, state. This state inhibits the oxidation of glucose by blocking the enzyme pyruvate dehydrogenase, supporting the formation of lactate. These are internal processes of stressed cells, that can be interrupted when the organism provides corrective factors to restore oxidation.

When the organism as a whole is overburdened, with stress physiology passing into the "learned helplessness" or shock states, its metabolism shifts in the direction of reductive, "pseudohypoxic" metabolism, in which the nervous system suppresses oxidative metabolism, and the blood serum's components reflect the reduced state of the cytoplasm, with shifts in lactate/pyruvate, the ketone body ratio, increased

free fatty acids, and changes in hormones and other regulators.

White blood cells and stem cells move from the blood stream into the tissues that are producing lactate, and the lactate prevents them from leaving, blocks the normal cytotoxic and phagocytic functions, and causes them to secrete inflammation-promoting substances, aggravating the local stress and inflammation. Histamine, nitric oxide, and prostaglandins contribute to the movement of cells into inflamed tissue.

In the first reactions to injury, the inflammatory changes activate enzymes that support undifferentiated growth. The active thyroid hormone, T3, is destroyed locally by a specific deiodinase, prostaglandins are produced by cyclooxygenase, estrogen by aromatase, and nitric oxide by its synthase. These enzymes are activated by chemical reduction of their disulfide groups, converting them to thiols, and can be inhibited by appropriate oxidants. In a healthy organism, those oxidants are available.

In a healthy cancer-resistant organism, the new cells function as phagocytes and stem cells, supporting repair and regeneration, and the normally reconstructed tissue begins to respond to signals that guide its integration into the organism. These signals include hormones, nutrients, nerve activity, and even nucleic acids circulating in microvesicles or exosomes.

During aging, the proportion of unsaturated fat in the body increases, and during stress and inflammation when free fatty acids are released into the blood stream they interfere with oxidative metabolism, while amplifying the inflammatory-carcinogenic processes, providing arachidonic acid, which activates nitric oxide synthesis (Priante, et al., 2005) and is the precursor for prostaglandin synthesis and activator of excitatory processes including protein kinase C (PKC), which is another redox-sensitive regulatory protein. (Chu, et al., 2004).

Weight loss is often the first symptom that a person notices before a cancer is diagnosed. In cancer, as in sepsis, trauma, and aging, there is a shift toward the oxidation of fat rather than glucose. The flooding of the body with free fatty acids shifts the whole body more strongly toward the pseudohypoxic state of reductive stress, and produces resistance to thyroid, insulin, and cortisol.

In starvation, hypoglycemia leads to increased growth hormone secretion (Goldstein, et al, 2011) and an adaptively decreased rate of metabolism, but in the metabolism of a cancer patient, the growth hormone-induced shift to fat oxidation and hypoglycemia fails to decrease energy expenditure. Inflammatory signals contribute to the growth hormone increase, interfering with insulin and the efficient use of glucose. Cellular starvation, beginning with the tumor focus of metabolic inefficiency, increases inflammation, shifting the fuel metabolism, creating pseudohypoxia, in a vicious progression.

The cell-quieting effect of sugar oxidation probably involves the greater production of carbon dioxide with a shift of the electronic balance toward a more oxidized and coherent state. Aging itself involves a metabolic shift in the direction of cancer metabolism, with a relative inability to reduce energy expenditure in the basal, fasting state, and with increased fat oxidation, decreased glucose oxidation (Al-Jaouni, et al., 2002). The nature of sleep changes with aging, with a decrease of the restorative deep "slow wave" sleep in old age; this is probably an example of the progressive inability to fully restore the high energy resting state of cells.

With stress and aging, the body's equilibrium on average is less oxidized, and this affects the so-called antioxidants in food. Phenolic groups typically have estrogenic and antioxidant effects. Several of the polyphenols and flavonoids in plants, that are known to be protective against cancer, contain several hydroxyl groups and only one activated carbonyl, and can function as antioxidants and interact with "estrogen receptors." However, like vitamin C, they can be oxidized to produce arrays of multiple activated carbonyls, with strong electron withdrawing (oxidative) effects (Son, et al., 2010). Their interactions with the body's oxidative systems have hardly been studied, but fisetin and a few others are known to be pro-oxidants in the body.

Salicylic acid, aspirin's main metabolite, is a phenolic acid, and its metabolic effects have been

studied in a little more detail. The fact that the inflammation-promoting enzymes, aromatase, cyclooxygenase, and nitric oxide synthase, which are inhibited by an oxidizing environment are also inhibited by aspirin, would strongly suggest that aspirin and salicylic acid are functioning as pro-oxidants. In studies with yeast, aspirin is a pro-oxidant (Farrugia, et al., 2013), and inhibits the fermentation of glucose (Balzan, et al., 2004). The "reducing power," GSH/GSSG, is lowered by aspirin (Sapienza and Balzan, 2005). When the yeast is grown in acetate, glycerol, or ethanol, aspirin doesn't lower the reducing power as much as when glucose is the fuel. Glucose is a relatively pro-oxidant fuel.

Aspirin's protective effects in cancer are now well known, but its use in treating cancer patients is very limited. Cancer's intrinsically high antioxidant reducing power, and the counteracting beneficial pro-oxidant effects of ascorbic acid, flavonoids, and aspirin, have taken a long time to be recognized. For more than 50 years, the public has been very conscious of the biological dangers of free radical oxidation, and the protective effects of antioxidants.

Oxidative damage, such as lipid peroxidation, is a seriously harmful phenomenon. Aspirin and the bioflavonoids are powerfully protective against lipid peroxidation and the DNA mutations and protein damage triggered by the most toxic free radical, the hydroxyl radical. They can act directly as hydroxyl radical scavengers, so it has been assumed that this is the way they work in cells, but their main action there seems to be by improving the oxidative state of the cell.

Some radicals are produced in mitochondria, but effective mitochondrial oxidation of glucose minimizes that source of radicals. The most important source of hydroxyl radicals during stress is the ferrous ion, a reduced form of iron, for example the iron released when heme oxygenous degrades heme and produces carbon monoxide. Carbon monoxide, or hypoxia, increases the cell's reductive power, keeping iron in the reduced state that produces hydroxyl radicals (Zhang and Piantadosi, 1992). When the cell is in a reduced state, vitamin C is one of the reductants reacting with iron to produce hydroxyl radicals (Hara, et al., 2009). Like aspirin, the antioxidant/pro-oxidant flavonoids typically increase mitochondrial respiration and reduce inflammation.

When cancer metabolism increases the amount of lactate in the blood, increased breathing lowers the carbon dioxide in the blood (Gargaglioni, et al., 2003), and the loss of CO2 affects metabolism and physiology at all levels. When CO2 is increased, the redox balance of the cell is shifted in the direction of oxidation (Mel'nychuk, et al., 1977), the use of glucose for growth and fat synthesis is inhibited, and the Krebs cycle is activated (Mel'nychuk, et al., 1978).

Inescapable cellular excitation shifts cells into the characteristic cancer-like metabolism, and various anesthetics (e.g., propofol, a general anesthetic, and lidocaine, a local anesthetic) have been found to reduce tumor proliferation and inflammation. Lidocaine can be used systemically in small doses, even by transdermal absorption. Opioids stimulate cancer growth and metastasis, but they are still often used. (Byrne, et al., 2016.)

In severe prolonged stress, the body's stress-limiting parasympathetic nervous system can become counter-productive, promoting excitotoxicity, inflammation, and tumor growth. Although it's known that the growth and invasiveness of several types of cancer are stimulated by muscarinic cholinergic signals (including organophosphate insecticides), there seems to be little interest in using belladonna or atropine for treatment. Anticholinergic drugs can alleviate some of the symptoms of cancer, as well as contributing to a restoration of normal metabolism. Histamine and serotonin are other metabolic cancer promoters for which there are safe antagonists.

Progesterone affects all of the features of cancer metabolism in the right way.

The belief that the only way to eliminate cancer is to kill "every malignant cell" including the "cancer stem cells" was based on the belief that cancer is the result of genetic changes. Even as people are moving away from absolute genetic determinism and are recognizing that there is such a thing as cancer metabolism, they are still focusing on the need to kill the cancer cells, using a

combination of surgery, radiation, and chemotherapy.

Recently, an article in the New York Times Sunday Magazine (Sam Apple, "Starving the Beast," May 15, 2016) about the new interest in killing cancer metabolically, quoted James Watson, of DNA fame, as saying "I never thought, until about two months ago, I'd ever have to learn the Krebs cycle. Now I realize I have to." A thorough understanding of the Krebs cycle could lead to an interest in the Pasteur effect, and a reconsideration of the nature of cancer.

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