

# Lactate vs. CO<sub>2</sub> in wounds, sickness, and aging; the other approach to cancer

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## Glossary

**Aerobic glycolysis**, the conversion of glucose to lactic acid even in the presence of oxygen. The presence of oxygen normally restrains glycolysis so that glucose is converted to carbon dioxide instead of lactic acid.

**Anaerobic glycolysis**, the increased conversion of glucose to lactic acid when the supply of oxygen isn't sufficient, which is a normal event during intense muscle action.

**"Warburg Effect"** refers to Otto Warburg's observation that cancer cells produce lactic acid even in the presence of adequate oxygen. Cancer cells don't "live on glucose," since they are highly adapted to survive on protein and fats.

**Pasteur Effect**, the normal response of cells to restrain glycolysis in the presence of adequate oxygen.

**Crabtree Effect**, observed originally in yeast, refers to the inhibition of respiration in the presence of glucose. This occurs in cancers (e.g., Miralpeix, et al., 1990) and in rapidly proliferating normal cells (e.g., Guppy, et al., 1993).

**"Cancer metabolism"** or stress metabolism typically involves an excess of the adaptive hormones, resulting from an imbalance of the demands made on the organism and the resources available to the organism. Excessive stimulation depletes glucose and produces lactic acid, and causes cortisol to increase, causing a shift to the consumption of fat and protein rather than glucose. Increased cortisol activates the Randle effect (the inhibition of glucose oxidation by free fatty acids), accelerates the breakdown of protein into amino acids, and activates the enzyme fatty acid synthase, which produces fatty acids from amino acids and pyruvate, to be oxidized in a "futile cycle," producing heat, and increasing the liberation of ammonia from the amino acids. Ammonia suppresses respiratory, and stimulates glycolytic, activity.

The presence of lactic acid in our tissues is very meaningful, but it is normally treated as only an indicator, rather than as a cause, of biological problems. Its presence in rosacea, arthritis, heart disease, diabetes, neurological diseases and cancer has been recognized, and recently it is being recognized that suppressing it can be curative, after fifty years of denial.

The influence of politics on science is so profound that neither historians nor scientists often care to consider it honestly and in depth.

From the 19th century until the second quarter of the 20th century, cancer was investigated mainly as a metabolic problem. This work, understanding the basic chemistry of metabolism, was culminating in the 1920s in the work of Otto Warburg and Albert Szent-Gyorgyi on respiration. Warburg demonstrated as early as 1920 that a respiratory defect, causing aerobic glycolysis, i.e., the production of lactic acid even in the presence of oxygen, was an essential feature of cancer. (The formation of lactic acid is normal and adaptive when the supply of oxygen isn't adequate to meet energy demands, for example when running.)

Many people recognized that this was likely to be the key to the "cancer problem." But in the US, several factors came together to block this line of investigation.

The world wars contributed to the isolation of German scientists, and Warburg, of the famous Jewish banking family, continued his work in Germany with the support of the government, despite his open opposition to Nazism. In the years after the war, nothing positive could be said in the US about his work on cancer.

The metabolic interpretation of disease that had been making progress for several decades was suddenly submerged when government research financing began concentrating on genetic and viral interpretations of disease.

If an apparently non-infectious disease couldn't be explained on the basis of an inherited tendency---insanity, epilepsy, diabetes, toxemia of pregnancy, and cancer, for example---then genetic changes occurring in the individual, as a result of chance or a virus, were invoked. Nutrition and other conditions of life were until fairly recently said to have no influence on health if the person consumed sufficient calories and a minimum amount of the essential vitamins, minerals, and protein. The cult of genetic determinism was so powerful that it wasn't affected by the facts.

In 1932, a pediatrician, Alexis Hartmann (with M. Senn) in St. Louis, injected intravenously a solution of sodium lactate into patients with metabolic acidosis, and several of them survived---despite the fact that some of them were already suffering from an excess of lactate. The subsequent widespread use of lactate solutions in hospitals has contributed to the general denial of its toxicity.

Hartmann and Senn used racemic lactate, that is, a mixture of D-lactate and L-lactate. Our own tissues produce mostly L-lactate, but they can produce small amounts of D-lactate; larger amounts are produced by diabetics. Intestinal bacteria can produce large amounts of it, and it has many toxic effects. Methylglyoxal can be formed from either form of lactate, and it is an important factor in the glycation of proteins. It can also be formed from MDA, a product of lipid peroxidation. Protein glycation is an important factor in diabetes and aging, but glucose, rather than lactate and polyunsaturated fats, is commonly said to be the cause.

About 50 years ago, lactate was known to induce the formation of new blood vessels, and for a much longer time it has been known to cause vasodilation and edema. In 1968, it was shown to stimulate collagen synthesis.

Normally, collagen synthesis and neovascularization are caused by lack of oxygen, but lactate can cause them to occur even in the presence of oxygen. Maintenance of a normal extracellular matrix is essential for normal functioning and cellular differentiation. Abnormally stimulated collagen synthesis probably accelerates tumor growth (Rajkumar, et al., 2006).

Nervous and hormonal factors can cause lactate to accumulate, even without prior damage to the mitochondria (e.g., B. Levy, et al., 2003). Psychological, as well as physical, stress and overactivation of glutamate receptors can cause harmful accumulation of lactate in the brain (Uehara, et al., 2005). Rather than just being "associated with" tissue damage, lactate directly contributes to the damage, for example in the brain, causing nerve cell loss by increasing the release of excitotoxic glutamate (Xiang, et al., 2004). When a panic reaction is produced by sodium lactate, the reduction of protective neurosteroids appears to contribute to the excitatory state (Eser, et al. 2006); this would make the brain more susceptible to damage.

Lactate increases blood viscosity, mimics stress, causes inflammation, and contributes to shock. Lactated Ringer's solution contributes to the tissue damage caused by shock, when it's used to resuscitate shock victims (Deree, et al., 2007, 2008): it contributes to the inflammatory processes associated with shock, unlike the use of hypertonic saline and other solutions. Lactate contributes to diabetes, inhibiting the ability to oxidize glucose. It promotes endothelial cell migration and leakiness, with increased vascular permeability factor (VPF or vascular endothelial growth factor, VEGF) (Nagy, et al. 1985): this can lead to breakdown of the "blood-brain barrier."

In the brain, lactate can cause nerve damage, increasing intracellular fat accumulation, chromatin clumping, and mitochondrial swelling (Norenberg, et al., 1987).

The lactate in peritoneal dialysis solution impairs differentiation and maturation of (immune, monocyte derived) dendritic cells; according to the authors of the study, "These findings have important implications for the initiation of immune responses under high lactate conditions, such as those occurring within tumor tissues or after macrophage activation" (Puig-Kröger, et al., 2003).

Lactate also causes macrophages and synovial fibroblasts to release PGE<sub>2</sub>, which can contribute to inflammation and bone resorption (Dawes and Rushton, 1994). This is the prostaglandin known to activate the formation of estrogen (Haffty, et al., 2008).

Hartmann's lactated solution has been widely used in hospitals for resuscitation and for patients after heart surgery and other stressful procedures, but until recently only a few people have objected to its use, and most of the objection has been to the use of racemic lactate, rather than to lactate itself. In recent years several studies have compared hypertonic saline (lacking the minerals considered essential since Sydney Ringer formulated his solution around 1885), and have found it in some cases superior to the "balanced" lactate solution. Even hypertonic glucose, without minerals, has produced good results in some studies.

A solution containing a large amount of lactate has been used for peritoneal dialysis when there is kidney failure, but several studies have compared solutions using bicarbonate instead of lactate, and found that they don't cause the severe damage that always happened with the traditional solution.

While Warburg was investigating the roles of glycolysis and respiration in cancer, a physician with a background in chemistry, W.F. Koch, in Detroit, was showing that the ability to use oxygen made the difference between health and sickness, and that the cancer metabolism could be corrected by restoring the efficient use of oxygen. He argued that a respiratory defect was responsible for immunodeficiency, allergy, and defective function of muscles, nerves, and secretory cells, as well as cancer. Koch's idea of cancer's metabolic cause and its curability directly challenged the doctrine of the genetic irreversibility of cancer that was central to governmental and commercial medical commitments.

Albert Szent-Gyorgyi respected Koch's work, and spent years investigating the involvement of the lactate metabolites, methylglyoxal and glyoxal, in cell physiology, but since the government's campaign against Koch was still active when Szent-Gyorgyi came to the U.S., he worked out many of the implications of Koch's work relating to cellular oxidation without mentioning his name.

Lactate formation from glucose is increased when anything interferes with respiratory energy production, but lactate, through a variety of mechanisms, can itself suppress cellular respiration. (This has been called the Crabtree effect.) Lactate can also inhibit its own formation, slowing glycolysis. In the healthy cell, the mitochondrion keeps glycolysis working by consuming pyruvate and electrons (or "hydrogens") from NADH, keeping the cell highly oxidized, with a ratio of NAD<sup>+</sup>/NADH of about 200. When the mitochondrion's ability to consume pyruvate and NADH is limited, the pyruvate itself accepts the hydrogen from NADH, forming lactic acid and NAD<sup>+</sup> in the process. As long as lactate leaves the cell as fast as it forms, glycolysis will provide ATP to allow the cell to survive. Oxygen and pyruvate are normally "electron sinks," regenerating the NAD<sup>+</sup> needed to produce energy from glucose.

But if too much lactate is present, slowing glycolytic production of ATP, the cell with defective respiration will die unless an alternative electron sink is available. The synthesis of fatty acids is such a sink, if electrons (hydrogens) can be transferred from NADH to NADP<sup>+</sup>, forming NADPH, which is the reducing substance required for turning carbohydrates and pyruvate and amino acids into fats.

This transfer can be activated by the transhydrogenase enzymes in the mitochondria, and also by interactions of some dehydrogenase enzymes.

The enzyme, fatty acid synthase (FAS), normally active in the liver and fat cells and in the estrogen-stimulated uterus, is highly active in cancers, and its activity is an inverse indicator of prognosis. Inhibiting it can cause cancer cells to die, so the pharmaceutical industry is looking for drugs that can safely inhibit it. This enzyme is closely associated with the rate of cell proliferation, and its activity is increased by both cortisol and estrogen.

The first biochemical event when a cell responds to estrogen is the synthesis of fat. Estrogen can activate transhydrogenases, and early studies of estrogen's biological effects provided considerable evidence that its actions were the result of the steroid molecule's direct participation in hydrogen transfers, oxidations and reductions. E.V. Jensen's claim that estrogen acts only through a "receptor protein" which activated gene transcription was based on his experimental evidence indicating that estrogen doesn't participate in oxidation and reduction processes in the uterus, but subsequently his claim has turned out to be false.

Glycolysis is very inefficient for producing usable energy compared to the respiratory metabolism of the mitochondria, and when lactate is carried to the liver, its conversion to glucose adds to the energy drain on the organism.

The hypoglycemia and related events resulting from accelerated glycolysis provide a stimulus for increased activity of the adaptive hormones, including cortisol. Cortisol helps to maintain blood sugar by increasing the conversion of protein to amino acids, and mobilizing free fatty acids from fat stores. The free fatty acids inhibit the use of glucose, so the stress metabolism relies largely on the consumption of amino acids. This increases the formation of ammonia, yet the combination of glycolysis and fat oxidation provides less carbon dioxide, which is needed for the conversion of ammonia to urea. Ammonia stimulates the formation of lactate, while carbon dioxide inhibits it.

Starving an animal with a tumor increases the stress hormones, providing free fatty acids and amino acids, and accelerates the tumor's growth (Sauer and Dauchy, 1987); it's impossible to "starve a tumor," by the methods often used. Preventing the excessive breakdown of protein and reducing the release of fatty acids from fat cells would probably cause many cancer cells to die, despite the availability of glucose, because of lactate's toxic effects, combined with the energy deficit caused by the respiratory defect that causes their aerobic glycolysis. Recently, the intrinsically high rate of cell death in tumors has been recognized. The tumor is maintained and enlarged by the recruitment of "stem cells." These cells normally would repair or regenerate the tissue, but under the existing metabolic conditions, they fail to differentiate properly.

The extracellular matrix in the tumor is abnormal, as well as the metabolites and signal substances being produced there, and the new cells fail to receive the instructions needed to restore the normal functions to the damaged tissue. These abnormal conditions can cause abnormal differentiation, and this cellular state is likely to involve chemical modification of proteins, including remodeling of the chromosomes through acetylation of the histones (Alam, et al., 2008; Suuronen, et al., 2006). The protein-protective effects of carbon dioxide are replaced by the protein-damaging effects of lactate and its metabolites.

The ability of lactic acid to displace carbon dioxide is probably involved in its effects on the blood clotting system. It contributes to disseminated intravascular coagulation and consumption coagulopathy, and increases the tendency of red cells to aggregate, forming "blood sludge," and makes red cells more rigid, increasing the viscosity of blood and impairing circulation in the small vessels. (Schmid-Schönbein, 1981; Kobayashi, et al., 2001; Martin, et al., 2002; Yamazaki, et al., 2006.)

The features of the stress metabolism include increases of stress hormones, lactate, ammonia, free fatty acids, and fat synthesis, and a decrease in carbon dioxide. Factors that lower the stress hormones, increase carbon dioxide, and help to lower the circulating free fatty acids, lactate, and ammonia, include vitamin B1 (to increase CO<sub>2</sub> and reduce lactate), niacinamide (to reduce free fatty acids), sugar (to reduce cortisol, adrenaline, and free fatty acids), salt (to lower adrenaline), thyroid hormone (to increase CO<sub>2</sub>). Vitamins D, K, B6 and biotin are also closely involved with carbon dioxide metabolism. Biotin deficiency can cause aerobic glycolysis with increased fat synthesis (Marshall, et al., 1976).

A protein deficiency, possibly by increasing cortisol, is likely to contribute to increased FAS and fat synthesis (Bannister, et al., 1983), but the dietary protein shouldn't provide an excess of tryptophan, because of tryptophan's role as serotonin precursor--serotonin increases inflammation and glycolysis (Koren-Schwartz, et al., 1994).

Incidental stresses, such as strenuous exercise combined with fasting (e.g., running or working before eating breakfast) not only directly trigger the production of lactate and ammonia, they also are likely to increase the absorption of bacterial endotoxin from the intestine. Endotoxin is a ubiquitous and chronic stressor. It increases lactate and nitric oxide, poisoning mitochondrial respiration, precipitating the secretion of the adaptive stress hormones, which don't always fully repair the cellular damage.

Aspirin protects cells in many ways, interrupting excitotoxic processes by blocking nitric oxide and prostaglandins, and consequently it inhibits cell proliferation, and in some cases inhibits glycolysis, but the fact that it can inhibit FAS (Beynen, et al., 1982) is very important in understanding its role in cancer.

There are several specific signals produced by lactate that can promote growth and other features of cancer, and it happens that aspirin antagonizes those: HIF, NF-kappaB, the kinase cascades, cyclin D1, and heme oxygenase.

Lactate and inflammation promote each other in a vicious cycle (Kawauchi, et al., 2008).

The toxic mechanism of bacterial endotoxin (lipopolysaccharide) involves inappropriate stimulation (Wang and White, 1999) of cells, followed by inflammation and mitochondrial inhibition. The stimulation seems to be a direct "biophysical" action on cells, causing them to take up water (Minutoli, et al., 2008), which is especially interesting, since estrogen's immediate excitatory effect causes cells to take up water.

Hypoosmolarity itself is excitatory and anabolic. It stimulates lipolysis and fat oxidation (Keller, et al. 2003), and osmotic swelling stimulates glycolysis and inhibits mitochondrial respiration (Levko, et al., 2000). Endotoxin causes hyponatremia (Tyler, et al., 1994), and a hypertonic salt solution is protective, lactate solutions are harmful. Other stresses and inflammations also cause hyponatremia.

One of the effects of endotoxin that leads to prolonged cellular excitation is its inhibition of the glucuronidation system (Bánhegyi, et al., 1995), since this inhibition allows excitatory estrogen to accumulate.

In women and rats, antibiotics were found to cause blood levels of estrogen and cortisol to decrease, while progesterone increased. This effect apparently resulted from the liver's increased ability to inactivate estrogen and to maintain blood sugar when the endotoxin stress was decreased.

Now that hog farmers' use of antibiotics to stimulate growth has been discouraged, they have sought vegetables that have a natural antibiotic effect, reducing the formation and absorption of the intestinal toxins. The human diet can be similarly adjusted, to minimize the production and absorption of the bacterial toxins.

In 2007, two Canadian researchers announced that they were investigating the drug dichloroacetate, which blocks glycolysis, stopping the production of lactic acid, as a cancer treatment, with success. The drug (dichloroacetate) has toxic side effects, but it is useful in several other conditions involving over-production of lactic acid. Other drugs that inhibit glycolysis have also shown anticancer effects in animals, but are in themselves very toxic. On the theoretical level, it would be better to inhibit only aerobic glycolysis, rather than inhibiting enzymes that are essential for all glycolysis.

Since endotoxemia can produce aerobic glycolysis in an otherwise healthy person (Bundgaard, et al., 2003), a minimally "Warburgian" approach--i.e., a merely reasonable approach--would involve minimizing the absorption of endotoxin. Inhibiting bacterial growth, while optimizing intestinal resistance, would have no harmful side effects. Preventing excessive sympathetic nervous activity and maintaining the intestine's energy production can be achieved by optimizing hormones and nutrition. Something as simple as a grated carrot with salt and vinegar can produce major changes in bowel health, reducing endotoxin absorption, and restoring constructive hormonal functions.

Medical tradition and inertia make it unlikely that the connection between cancer and bowel toxins will be recognized by the mainstream of medicine and government. In another article I will describe some of the recent history relating to this issue.

It's nice that some cancer researchers are now remembering Warburg, but unfortunately they are usually just fitting the fact of cancer's aerobic glycolysis into the genetic mutant cell paradigm, thinking of the respiratory defect as just another opportunity for killing the evil deviant cancer cell, rather than looking for the causes of the respiratory defect. Warburg, Koch, and Szent-Gyorgyi had a comprehensive view of biology, in which the aerobic production of lactate, resulting from a respiratory defect, itself was functionally related to the nature of cancer.

A focus on correcting the respiratory defect would be relevant for all of the diseases and conditions (including heart disease, diabetes, dementia) involving inflammation and inappropriate excitation, not just for cancer.

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