Ray Peat's Newsletter

Beware of paper biophysics. **Otto Warburg**

Lactate, metabolic regression, & political-medical implications

Cellular differentiation: *In an early embryo, cells are interchangeable, but aa it grows, cells in different locations progressively become more specialized; this involves limiting the accessibility of DNA to the genes that are needed for making the proteins that are used for the specialized structures and functions. The process by which a cell becomes specialized in order to perform a specific function, as in the case of a liver cell, a blood cell, or a neuron. There are more than 250 general types of cells in the human body.*

Dedifferentiation: *The loss of specialized functions and structures by cells or tissues. This can result from injury or stress, as during cell culture, or it can occur in an organized way when a cell experiences changes in its environment; for example, an epithelial cell from a sheep's mammary gland dedifferentiated when it was placed in an ovum whose nucleus had been removed, giving it the ability to develop into the cloned sheep, Dolly.*

Redifferentiation: *Changing from one differentiated state to another differentiated state, sometimes following dedifferentiation to a stem cell-like state.*

By the 1960s, when I started studying biology at the university, the average person knew quite a bit about lactic acid, such as the fact that a deficiency of vitamin B2 causes an excess of lactate to be produced, and that lactic acid can cause the growth of blood vessels in the corneas or whites of the eyes, but the medical profession was already relegating information of that sort to the category of "lore," not to be taken seriously. Observations of metabolic events seemed trivial compared to the new discoveries about DNA.

Democratic ideologies rejected biological determinism, and argued that the nature of an organism is essentially influenced by the environments that it interacts with.

In 1970, in a talk at the university, Harry Rubin mentioned that he was hoping to discover the gene for the "angiogenic" factor (assumed to be a protein) that supports the growth of cancer, and a year later, in Boston, Judah Folkman announced a similar research project, that received huge financial support from industry, because of its great potential as a basis for a new kind of drug. In the last 16 years these angiogenesis inhibitors have been worth tens of billions of dollars to the drug industry, without a noticeable change in cancer mortality—they forgot to consider that normal tissues need to keep making new blood vessels. The protein they chose to block, *as well as several others with similar effects,* are proteins that are induced by lactate originating in the tumor, but relevant information of this sort never appears in the news or in medical journals.

Before commercial interests began changing the culture to suit their needs, literate cultures generally supported the interests of those in power by inculcating belief in the unchangeableness of human nature and the necessity of social

hierarchy. As the study of biology advanced, the old cultural factions emphasized the eternal fixity of inherited traits, and joined forces with new economic interests to promote the doctrine of genetic determinism (Allen, 1997). At the same time (late 19th to mid-20th century), democratic ideologies rejected biological determinism, and argued that the nature of an organism is essentially influenced by the environments that it interacts with.

The determinists generally followed Descartes in seeing the body as a machine, but they argued that the machine could be completely explained by its genes, and sometimes argued that the genes controlled all its functions, making a soul or mind unnecessary. The dissenters from that view saw the nature of life (and of existence in general) as an open question, to be answered by studying how it comes into being, how it functions, and what happens during its survival and disintegration.

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Metabolism's essential meanings of change and interaction put it at the center of non-determinist biological thinking, and cause the other, genetic and mechanistic, style of thinking to keep it in the background. Around 1950, powerful cultural forces (especially the US government) began massively supporting the genetic explanation for everything, cutting support to those who continued to explore the meaning of life in terms of its energy and metabolism. The futile "War on Cancer" looked for the cause of cancer in viruses and mutant genes, and denied that metabolism could be relevant. The Human Genome Project and the application of genetic engineering to virology, immunology, and other branches of medicine involved a similar belief in the irrelevance of metabolism.

Otto Warburg and Albert Szent-Gyorgyi shared a general view of life, in which simple life forms could be sustained by glycolysis (forming lactic acid), while oxidative metabolism, with its capacity to extract many times more energy from a given amount of fuel, is necessary to produce and maintain more complex forms of life. Both of them understood cancer to involve a regression to a primitive form of energy metabolism, glycolysis, which produces lactic acid rather than carbon dioxide. (When glycolysis occurs despite the presence of oxygen, it's called aerobic glycolysis.)

Warburg showed that in cancer, cellular respiration fails to suppress the production of lactic acid, as it does in normal cells, and that cancer can develop as a result of prolonged oxygen deprivation (with the associated lactic acid production). He observed that anything (including carcinogenic chemicals and radiation) that interferes with oxidative metabolism can lead to a series of changes**:** inflammation, followed by fibrosis, followed by atrophy and death, or sometimes instead of cell death, some of the cells become cancerous, losing their fixed identity as a differentiated element of a specific kind of tissue, and regress, dedifferentiate, to a primitive lactate-producing metabolism with a tendency to migrate to new locations.

Szent-Györgyi, ten years younger than Warburg, recognized the importance of his work, and began a long project of attempting to understand what it is about oxidative metabolism that not only suppresses the formation of lactic acid, but that accounts for the properties of differentiated life. He believed that it was the movement of electrons in the cell substance that animated cells, and that in the living state there are characteristic differences in the force with which the cell substance manages its electronic system. In the primitive, dedifferentiated state, pyruvic acid is the electron acceptor, turning into lactic acid, and in the fully differentiated state, oxygen is the more powerful electron acceptor, making possible a more intense energy flow (through several intermediate steps), at higher voltage.

The ratio of lactate to pyruvate, as a reduction-oxidation pair, affects the ratio of all the other reduction-oxidation pairs in the cell, such as NADH/NAD+ and reduced and oxidized glutathione, GSH/GSSG. The sulfhydryl, -SH, groups on the cysteines of cellular proteins behave similarly, and when the balance shifts toward oxidation, cysteine groups bond to each

other with -SS- links. One implication of this is that an excess of lactate can reduce the organized structure of the cell, because some of the disulfide, -SS-, groups in protein form rigid connections within and between proteins, and the conversion of some of these to -SH groups will increase the fluidity of the cytoplasm, at the same time that the changes modify the function of enzymes. Analogous sulfhydryl/disulfide reactions affect the viscosity of mucus and bread dough.

When the system is dominated by the more powerful electron acceptor, oxygen, complex structures are stabilized—similar to the way vacuum wrapping turns a loose powder into a firm lump. During excitation, or irritation or inflammation, the cell reacts as if the vacuum seal were broken, and the structure becomes looser, until the electron acceptors can reestablish the electron-deficient state.

Reproduction, beginning with the ovum, requires the same regressive metabolism, the production of lactic acid even when oxygen is available, that characterizes tumor metabolism and wound healing. The ovum itself requires oxidative metabolism for its own energy production, but produces lactate to regulate proliferation and growth and to modify the surrounding tissues. During implantation of the ovum in the uterus, lactate released by the ovum helps to activate the cells in a small area on the uterus. When a woman isn't pregnant, unopposed estrogen can cause lactate to appear in the lining of the uterus, leading to endometriosis (Horne, et al., 2019).

Starting with the structure of the ovum, there are metabolic gradients, differences in the degree of oxidation and reduction, at all stages of development, and these differences in electron affinity can be detected as electrical fields and currents. The importance of these gradients and fields in the development of the organism, and in healing and regeneration, has been known since early in the last century, but beginning in the 1950s research in these areas was defunded, in favor of the genetic determinist idea that there is a blueprint of the organism "in the genes," and that this blueprint explains everything in growth, health, and sickness, and that medicine must concentrate on correcting errors in the blueprint.

When the organism is understood as an on-going process of development, sustained by appropriate metabolic energy, rather than as a pre-determined machine, the parallels between the generative process in the embryo and the healing processes in later life offer a guide to protective and therapeutic practice.

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Dedifferentiated, stem-like cells, are created in areas of injury or chronic stress, where lactic acid is being formed. In the 1950s and '60s, L.V. Polezhaev showed that even mature neurons in the brain are stimulated to divide by the presence of injured, degenerating nerve cells. Daniel Mazia, Katsuma Dan, and others during the same period were showing that the proteins responsible for cell division become highly reduced, showing a high concentration of -SH groups, in preparation for the cell cleavage leading to embryonic development, and others showed that glycolysis is needed for this process. The structural proteins, microtubules, that form the "mitotic apparatus" that Dan and Mazia studied, are essential parts of the glycolytic system, working closely with the enzymes that produce lactate, and a reducing environment stabilizes them and supports their function.

For example, the process that starts a process of inflammation, activation of the "inflammasome," is promoted by a reducing environment, and involves the formation of microtubules**;** things that shift the balance toward oxidation decrease inflammation and cause the microtubules to dissolve.

The activated cells that produce and secrete lactate will transmit their regressed metabolic state to neighboring cells along with the lactate, unless the lactate is diluted and carried away in the blood. The amount of lactate in the blood, and the ratio of lactate to pyruvate, affects the metabolism of all cells in the body. For example,

a more reduced state of the blood will cause the liver to convert lactate to glucose, an energetically wasteful process that, while it lowers the amount of lactate, depletes the body's energy reserves. The metabolism of every part of the body is affected by the redox state of the blood (Nocito, et al., 2015).

Activation of cells causes them to take up calcium from their environment, and lactate has a binding, chelating effect on calcium, keeping it inside cells. Exposing blood vessels to lactate causes them to retain calcium (Zhu, et al., 2019; Yamaguchi, et al., 1984), which is itself excitatory, and prolonged and repeated lactate exposure promotes the synthesis of collagen, and the retention of fatty acids and cholesterol, producing atherosclerosis. (Shantha, et al., 2013; Mongraw-Chaffin, et al., 2012) Vascular smooth muscle cells activated by lactate proliferate and migrate, contributing to the formation of atherosclerotic plaques (Kim, et al., 2017; Bennett, et al., 2016). Under the influence of lactate and their new surroundings, they take on new forms and functions.

Recognizing that the ratio of lactate to pyruvate in the body fluids affects the redox balance of every cell in the body, and that this balance affects in a highly systematic way the metabolism and structure of all parts of the body, the value of knowing more about lactate is evident.

More than 100 years ago extreme shock was known to suppress oxygen consumption; extreme nerve stimulation was found to be part of the cause. A high level of lactate in the blood is an outstanding feature of shock, and, since the discovery that nitric oxide can be formed in the body, a high level of nitric oxide has been recognized as a feature of shock, contributing to the loss of blood pressure. The reducing environment of lactic acid domination produces the reduced thiols, -SH groups, that activate nitric oxide synthesis. Lactate and nitric oxide suppress oxygen consumption by interfering with respiratory enzymes including cytochrome oxidase, but also by decreasing the energy supply, inactivating the enzymes responsible for consuming lactate/pyruvate, the pyruvate dehydrogenase complex.

In the state of shock, lactate is suppressing the use of oxygen everywhere in the body, so there is no way to remove the lactate. In this situation, the accumulation of lactate inside the cells that produce it can slow or stop glycolysis, preventing the production of ATP as well as lactate. This is why shock causes a rapid fall in body temperature, and can quickly cause death. In good health, one of the important functions of carbon dioxide is to inhibit lactate formation, which helps to limit its production to the amount that can be oxidized, in a self regulating process. The production of lactate is potentially involved in many vicious cycles, which are normally prevented by the intervention of the whole body's oxidizing capacity, restoring balance to the oxidizing predominance.

About 50 years ago, someone proposed that nerve cells in the brain require lactate for energy, and that even lactate produced by skeletal muscles could be used by the brain. A few people have kept arguing for that hypothesis, at the same time that others are arguing that lactate isn't essential for cancer, or that it's antiinflammatory, or that it's essential for immunity, or for healing an injured brain, etc. Added to the historical antagonism of the pharmaceutical-medical industry to Warburg's discoveries, this new wave of publications is intensifying the confusion about lactate's functions.

If it's recognized that the ratio of lactate to pyruvate in the body fluids affects the redox balance of every cell in the body, and that this balance affects in a highly systematic way the metabolism and structure of all parts of the body, the value of knowing more about lactate will be evident.

It's true that lactate, while normally activating and amplifying inflammation, as in arthritis, can in certain situations turn off the immune system. The very high lactate in tumors can change the cytolytic T cells from tumor-destroying to inflammation promoting cells. When incoming cells experience the high lactate concentration near the

tumor, their own energy production is suppressed, as in shock. The result is that immigrant cells, instead of correcting or dissolving the defective cells, accumulate and dedifferentiate, taking on different forms and functions.

This ability to excite or to inhibit, depending on the surrounding energy economy in the organism, is operating in the brain during daily cycles of waking and sleeping, and in gradual processes such as the development of dementia. The recent demonstration of redifferentiation of heart cells to form stem cells when exposed to lactate (Ordoño, et al., 2020) probably has parallels in the maintenance of all tissues, including the brain—under the right conditions, metabolic regression supports constructive renewal.

The healthy sleeping brain increases its glycogen stores, and the excited, waking brain reduces the stores, while also reducing glucose and increasing lactate. Histamine, which can cause insomnia, activates the breakdown of glycogen, and GABA, which stops neural excitation, increases glycogen (Pennington and Pentreath, 1987). Fully excited neurons expend energy at a very high rate, and in this momentary state can use both oxidative metabolism and aerobic glycolysis, emitting lactate into their surroundings. The astrocytes associated with them can absorb lactate, and are able to convert it back to glucose by gluconeogenesis, and can secrete that glucose for use by neurons. In periods of rest, both astrocytes and neurons can convert lactate to glucose, and can store glucose as glycogen.

The lactate revisionists, who concentrate on its utility to a fully healthy organism, have neglected to assimilate the evidence of the metabolic complexity and adaptability of the various kinds of brain cell. Their arguments (deriving mainly from sports medicine) distract attention from the effects of increasing lactate in the systemic circulation on brain metabolism. Lactate easily crosses the "blood brain barrier," so an excess in the general bloodstream produced by stress or sickness will increase the energy burden on brain cells, resulting in a sense of fatigue or excitation.

Chronic exposure to a slight excess of lactate will cause progressive deterioration of blood vessels in the brain as it does in other parts of the body, and similar proliferating, migrating, and functional changes will occur. Developmentally, the changes of the neurodegenerative diseases under the influence of the regressive metabolism are analogous to the changes that occur in arthritis, cancer, kidney and liver disease. More intense and prolonged lactate exposure, which will occur wherever the body can't intervene to correct the metabolism, can account for the desensitizing and blocking that occur in dementia; lactate suppresses glycolytic as well as oxidative energy production. Shock, immunosuppression, and dementia involve massive suppression of the local ability to produce energy from glucose.

Our basic anti-glycolytic factor is carbon dioxide, which can be quickly delivered to the glycolyzing areas, suppressing glycolysis and restoring oxidative energy production.

Senescent cells accumulate in the body with age, and as they lose their normal functions, they shift to the regressed glycolytic metabolism, and begin emitting inflammatory signals, as well as lactate, into their surroundings, inducing senescence in the nearby cells (da Silva, et al., 2019). In the 1960s Leonard Hayflick believed that he had discovered an intrinsic aging mechanism in cells, a "limit" that made it impossible for a human or animal cell to divide more than 50 times. It didn't occur to him that events in a laboratory culture dish might not be relevant to the function of a cell in its normal place in an organism. Cells in culture quickly (Bittles and Harper, 1984) begin reorganizing in relation to their liquid and plastic or glass environment, and they begin reverting to the basic glycolytic metabolism, beginning to produce lactate; prolonged exposure to lactate accelerates the process. While exposure to lactate can cause a shift from oxidative to glycolytic metabolism (Kozlov, et al., 2020), addition of pyruvate can prevent that, by increasing the ratio of NAD/NADH (Kim, et al., 2018).

Lactate's involvement in processes of renewal are reminiscent of estrogen's related effects, but

luckily there is no powerful lactate industry analogous to the estrogen industry to inappropriately promote it. Its effects in cell renewal depend on brief and local shifts in its concentration, and those are restorative, rather than degenerative, only when the whole system can easily limit the duration and extent of those shifts. Trying to design drugs for suitably specific actions on the formation of lactate would be even harder than the anti-angiogenesis projects turned out to be in the 1970s.

Our basic anti-glycolytic factor is carbon dioxide, which can be quickly delivered to the glycolyzing areas, suppressing glycolysis and restoring oxidative energy production. The body's production and delivery of CO2 is naturally regulated by many substances, including nutrients, hormones and neurotransmitters, and by many drugs. Learning to identify and use the things that favor CO2, and to avoid things that shift the balance harmfully toward lactate, should be protective against many chronic ailments and aging. The "lactate paradox" at high altitude (less lactate is produced during stress) is a reflection of a better carbon dioxide economy, and it corresponds to many health benefits, some of which can be approximated at lower altitudes.

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