Ray Peat's Newsletter

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"The basic texture of research consists of dreams into which the threads of reasoning, measurement and calculation are woven." **Albert Szent-Györgyi**

Carcinogenic Metabolism

The recent "pandemic" has shown how little evidence is needed to create belief among the majority of "scientists" and doctors. (They are accustomed to taking the opinion of the "authorities" as evidence, so no actual evidence is needed to adopt a belief if it's the consensus of the authorities.) Since the early 20th century, the biological consensus in genetics and evolution has demonstrated a similar herd effect, in which the believability of a doctrine is based on factors other than evidence and careful reasoning. Neodarwinism, mechanistic materialism, and genetic determinism form a paradigm of biological knowledge that has been able to ignore vast amounts of accumulated evidence.

The belief that cancer is a genetic disease, caused by inherited or mutated genes, and that its treatment requires killing the tumor cells or "cancer stem cells," has failed to reduce the death rate from cancer, and in some cases increasing diagnosis and treatment have increased mortality. Evidence that has been generally ignored shows clearly that the developing cancer, and factors causing it to develop, cause genetic changes and mutations, and that the causes of cancer include the metabolic changes occurring in stress, aging, inflammation and degeneration, in addition to extrinsic chemical mutagens and radiation.

The killing technologies—surgery, radiation, chemotherapy—that seemed rational in the mechanistic paradigm, have failed massively through the entire 20th century, and have nothing to offer for a biological approach to cancer therapy. The tendency of cancer to recur in the same site after treatment has been traced to the inflammation provoked by the radiation, surgery, and chemotherapy, not necessarily to "cancer stem cells" that survived the treatment.

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People tend to support ideas that rationalize their activities and place in society, and oppose any views that would devalue their beliefs and weaken their social economic influence. For more than 100 years, the idea of an organism's general biological resistance has been neglected because of a belief (originating with the drug industry) that each disease has a unique identity that can be defined precisely, and that very specific chemical treatments can be found for each disease. The pharmaceutical industry has powerfully promoted this idea, comparing their "magic bullet" chemotherapy to the natural precision of our antibody system—asserting that specific drug therapy and vaccinations can promote health by eliminating diseases. The power and wealth of the drug industry rests on that ideology of the nature of health,

and would be weakened by a belief that health is the result of natural immunity, a basic biological resistance to all sorts of harm. The culture is so deeply indoctrinated with the mechanistic medical doctrine that most people are afraid to question a diagnosis of cancer, and the treatments that are prescribed.

150 years ago, there were two main views of biology, one in which life is endlessly adapting to its environments, and one in which life is a composite of immutable traits. People who occupy a favored place in society like to think that their own situation is determined by their immutable excellent traits, and that less favored people are in their situation because of less desirable traits. Although the great majority of cancers have clear environmental causes (Epstein, 1982), the carcinogenic pollution caused by governments and large corporations is ignored, putting the blame on the defective genes of the victims. However, low social-economic status affects the person's biological nature, and is carcinogenic, and that effect has been increasing in recent decades (Singh and Jamal, 2017). The mechanistic ideology behind the current understanding of cancer discourages constructive biological actions that could quickly alleviate the cancer problem.

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Ordinarily, cells are able to rest when their actions aren't needed, and efficient oxidative energy production allows them to accumulate energy and other resources in readiness to act. The energy reserves are essentially connected to the resting state. The depletion of energy, by glucose deprivation or oxygen deficiency, forces the cell into activity—seizures brought on by hypoglycemia are an example of that; muscle cramps and insomnia result from similar low energy conditions. The depletion of energy by excessive stimulation can lead to a self-maintaining vicious circle, in which fatigue and energy depletion interfere with rest and restoration. **Nitric oxide, formed as a result of energy deprivation** (Cárdenas, et al., 2000)**, and heme oxygenase, caused by glucose deprivation (Chang, et al, 2002), are major factors in the development of cancer.**

Cancer's outstanding feature is its inability to turn itself off. In the 19th century, Pasteur recognized a regulatory process in yeast, in which the presence of oxygen stopped the fermentative process. Otto Warburg, c. 1923, observed that this process which occurs in normal animal tissues, is absent in all kinds of cancer. He observed that the cancer continues to consume oxygen, but that there is some defect in the process, keeping it from suppressing the formation of lactic acid.

Warburg observed that cancers are hypoglycemic, because their rapid conversion of glucose to lactate exceeds the ability of blood vessels to deliver glucose, and that they are hypoxic or anoxic, for the same reason—their consumption of oxygen exceeds the capacity of the blood supply. He demonstrated that prolonged oxygen deprivation could cause normal cells to become cancerous. The implication of his work is that cancer stimulates its own growth, and that the inflammation-promoting effects of lactate are crucial for its development and properties, and its destructive effects on the host organism. Considering that lactate suppresses immunity, stimulates the formation of new blood vessels and promotes metastasis, the Warburg effect gives an accurate picture of the physiological and environmental nature of cancer.

However, it's important to consider how other regulatory processes throughout the organism are affected by lactate, in ways that can support the development of cancer, because they provide many opportunities for intervening to slow or reverse the process of cancerization.

Lactate is an activator of growth hormone and heme oxygenase and tends to increase glutamate and cellular excitation and inflammation, while reducing CO2 formation. Glutamate increases growth hormone (Luger, et al., 1992), which promotes oxidation of fatty acids, and reduces oxidation of glucose; the resulting decrease in

CO_2 leads to increased production of lactate. Dietary fat, like free fatty acids from lipolysis, increases glutamate and lowers the oxidation of glucose (the "Randle cycle").

The excitatory amino acids, including glutamate, cause cells to take up calcium; if the calcium is retained, the cell stays in an excited state. Increasing glucose has been found to protect against glutamate excitatory damage, by increasing the cells' ability to extrude the excitatory calcium (Nakashima, et al., 1996). This is probably another example of the Randle cycle, allowing cells to reduce fatty acid oxidation by increasing glucose oxidation, resulting in the formation of carbon dioxide and carbonic acid, which takes some calcium along as it streams out of the cell. The oxidation of glucose to carbon dioxide has stabilizing effects on cells, favoring the anti-excitatory effects of GABA, and reducing the action of glutamate; CO_2's effects are generally calming.

The excitatory effects of glutamate and the increased intracellular calcium generally stimulate proliferation of cells. Estrogen's excitatory effects support those processes. The inhibitory transmitter, GABA formed by decarboxylating glutamate, tends to reduce excitation and (in many cases) proliferation, and is supported by the calming effects of progesterone.

Close observation of the development of cancer of the intestine revealed that the appearance of a small area of cancer was surrounded by a larger area, in which the cells nearest the cancer center were precancerous, with a gradient of abnormality starting with merely inflamed cells at the periphery, increasing in abnormality (including mutated genes) according to their closeness to the cancer center. This has been described as the cancer field, suggesting that something emitted from a centre of inflammation has led to changes in adjoining cells. The idea of random mutations as the source of cancer simply can't explain this concentric gradient. The idea of random mutations has been progressively discarded over the last several decades, with good experimental reason (Monroe, et al., 2022).

The reductionists' adopting of the doctrine of randomness to explain radioactive nuclear decay and genetic mutations is a natural consequence of a narrow focus on local causal interactions---"what is there besides atoms?" Any patterns that may be visible in larger contexts will be automatically excluded. When it affects medical theories and treatments, the assumption of randomness leads certainly to dead ends.

Supportive, corrective therapy has nothing in common with the ruling paradigm of cancer treatment—it is reinforcing the organism's state of health, rather than attacking the disease of cancer.

In the development of a cancer field, the sum of stresses and irritations will lead to overproduction of lactate in some cells, with excitatory, inflammatory consequences. These consequences lead to the synthesis of nitric oxide and carbon monoxide (produced by heme oxygenase), and these are genomic destabilizers, leading to mutations. These mutations tend to favor cell survival in the particular harmful conditions, especially the local hypoxia and hypoglycemia produced by inflammation and excitation.

The rapidly dividing highly mutating cells of an expanding tumor don't live long, but they are replaced by the surrounding inflamed degenerating cells under the influence of hypoxia, lactic acid, and multiple excitatory signals. The complex of local cellular reactions to stress constitute the cancer field, and this progressively expands, unless conditions change. If the carcinogenic environmental factors are replaced by favorable conditions, a reversal of the inflammatory metabolic reactions can occur. The highly defective cancer cells aren't replaced in the absence of the excitatory-inflammatory signals from surrounding cells. Spontaneous regression of tumors can't be observed when treatment immediately follows diagnosis.

In the physiology of a tumor-bearing animal, there's a close parallel in the antagonism between fat oxidation and glucose oxidation, and the antagonism of lactate and CO_2. The oxidation of

fatty acids consumes oxygen without producing as much CO2 as the oxidation of glucose does; the lower production of CO2 increases the production of lactate; higher lactate favors the oxidation of fat. **Adding CO2 to the system by any means favors oxidation of glucose.**

Opposing the corrective effects of oxygen, CO2, and glucose, common excitatory, tumor-promoting agents produced at increased levels in tumors include histamine, serotonin, nitric oxide, carbon monoxide and free iron from activated heme oxygenase, lactate, ammonia, and cytokines, especially tumor necrosis factor and interleukins 1 and 6.

A common misinterpretation of Warburg's work has led to the idea of starving cancer by withholding sugar from the diet. That increases the tumor's consumption of protein and fat, leading to the conversion of the body itself to fuel to support the cancer growth, creating immunodeficiency and intensified stress. Diabetes was originally known as a wasting disease, quickly leading to death because of the inability to oxidize sugar, with increased lactate production and generalized inflammation**.** Depriving the diabetic person of the sugar they crave accelerates the conversion of their tissues to fuel, with greatly increased free fatty acids in the serum, blocking the oxidation of glucose. Increased serum free fatty acids are associated with both diabetes and cancer (Zhang, et al., 2020; Li et al., 2021).

Hysteresis is a general phenomenon in which an effect lags behind its cause—for example, it takes less energy to maintain a flow of electricity than to start it; it describes the inertia of the system. Cancer demonstrates this property—a continuing stress gradually leads to an accumulation of functional and structural changes that sustain the stressed condition, such as changes in the extracellular environment as well as intracellular processes. For example, the presence of lactate modifies the extracellular matrix in ways that increase lactate formation (Sullivan, et al., 2018). An important factor in creating functional and metabolic inertia is a phosphate transfer enzyme that creates a general pattern of activation, the kinase called mTOR (mechanistic target of rapamycin).

A bacterial fungicidal antibiotic, rapamycin, originally used to treat candidiasis, was found to be immunosuppressive, and is used to prevent rejection of kidney transplants. The mTOR enzyme inhibited by rapamycin has been found to promote growth, inflammation, fibrosis, and cancer growth, and to accelerate aging. Lactate promotes the activation of mTOR, and mTOR activates aerobic glycolysis, the defining feature of cancer.

Interrupting the vicious circles of cancerization is essential for the survival of the organism. There are many substances that can inhibit the inflammatory, degenerative processes acting at multiple levels, and these substances tend to be synergistic, so that a great number of substances can be safely used at the same time. This kind of supportive therapy has nothing in common with the ruling paradigm of cancer treatment—it is reinforcing the organism's state of health, rather than attacking the disease of cancer.

Things that favor the production of CO2 rather than lactate include CO2, sodium bicarbonate and acetazolamide, flavonoids such as apigenin and fisetin (Constantin, et al., 2010; Shan, et al., 2017; Zhao, et al., 2021), thyroid hormone, progesterone, and lidocaine (Karniel and Beitner, 2000),

Some of the things that inhibit mTOR include caffeine (Zhou, et al., 2010), aspirin (Din, et al.,2012), lidocaine (Zhang, et al., 2021), vitamin D (Al-Hendy, et al., 2016), and flavonoids.

Things that increase intracellular calcium tend to increase mTOR (Amemiya, et al., 2021). Radiation (ultraviolet and ionizing radiation) increases mTOR, and this effect can be reduced by flavonoids (Bridgeman, et al., 2016). mTOR is one of the factors in the radiation bystander effect, which is responsible for prolonged damage of other unirradiated cells in the organism (Verma and Tiku, 2022).

Many of the flavonoids are known as "antioxidants," but, like ascorbic acid/dehydroascorbate, inside the functioning cell they become beneficial oxidative catalysts. In excessive doses they might act as reducing agents. Ascorbic acid itself in some situations increases mTOR (Moretti, et al.,

2014). It's safest to get the flavonoids from food, rather than supplements.

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