Carbon Monoxide: Cancer Hormone?

Listed under Ray Peat. Theme

From the original article. Author: Ray Peat.

When I started graduate school in biology at the University of Oregon, cell "membrane" research was a thriving business, almost as lucrative as genetics. Years earlier, I had been intrigued by Linus Pauling's suggestion that anesthetics might act by "structuring" the water in nerve cells, and in trying to understand the physiology of hearing, I had concluded that the "unit discharge" (all-or nothing) idea of nervous transmission left almost everything unexplained. As a result, I concentrated on the organized internal complexity of structure in cells, and found no reason to believe that cells were bags of randomly acting enzymes enclosed in an "amazing membrane" which contained an array of pumps that regulated the composition of the enclosed fluid. When people produced pictures of"membrane pores," I thought they should also have to explain why pores of the same size appear when distilled water is frozen and photographed by the same techniques. If a red blood cell, when etched awa y microscopically looks like a sponge, how can a hypothetical membrane on the surface be all-important? Why did it take so long for electron microscopists to produce images of the membrane, when their microscopes were producing fine images, and why did it take several decades for them to decide how thick these membranes should be? Reading the history of the theory of the "plasma membrane," I decided that it was almost perfectly irrelevant to biology, because dead cells, as in hair, can demonstrate the same ionic gradients that were the reason for believing in the regulatory membrane.

Many people think of the membrane inside an egg shell when they hear people talk about the "cell membrane," but the standard lipid bilayer membrane to which so much importance is given should evoke an image of the iridescent sheen that can be seen on puddles when a trace of oil spreads over the surface. This spreading of oil over a mass of water is precisely the physical model that lies behind the membrane theory. But the proteins making up the cell have a great affinity for fats - the cell is far from being the watery mass that the theory says needs to be separated from its environment by an oily film.

When electron microscopes became available, people expected to see the cell membranes they believed in. But in the first pictures, no membranes were visible. After many trials, methods were found to create the appearance of a membrane on cells, but for more than 20 years microscopists were arguing over the thickness of the membrane. The images showed membranes that were as thin as 20 Angstrom units, or as thick as 300 Angstroms. After 30 years, their thickness was decided to be between 60 and 100 Angstrom units. Osmium, which is the standard material used for producing images of cell membranes, was already in medical use for creating "false membranes" on burned or ulcerated tissue. How do you suppose this material came to be used to reveal the membranes which theory required, but ordinary techniques didn't show?

I believe fats are important in carcinogenesis, but not because of any theoretical membrane function. They have regulatory functions, and I think it is important to avoid associating the idea of "regulation" with the misleading idea of "membranes."

Around the same time, I read the history of genetic thinking, and found that Weissmanism, which formed the basic orientation for contemporary thinking in genetics, was ludicrously mistaken. The technical definition of the "gene" has quietly changed over the last couple of generations, but the term has kept its mystique, which leads people to feel that they have explained something when they can identify "its gene." The mystique carries so much weight, that it is customary to accept

conclusions regarding "genetic causation" without ordinary statistical support.

At the time I began studying biology at the University, the brain was explained in terms of genes and membranes, with emphasis on membranes, and cancer was explained by genes and membranes, and the dominant thought was that a genetic defect caused a membrane defect, which caused the abnormal behavior of cancer cells. To an outsider, the idea sounded as defective then as it does now, but rhetoric is very important in science, and it was rhetorically persuasive to most scientists.

I have been hearing people say "we don't know what causes cancer, but we are certain it's genetic." John Gofman, in his new book, (1) argues that 75% of breast cancer is caused by exposure to radiation, and expresses annoyance that so many people seem to forget that radiation is well established as an important cause of the disease. He quotes a statement from a fund-raising appeal: "What's worse, even the best doctors have no idea what causes breast cancer or how to cure it." (The 75% figure might sound high at first, until you realize that the incidence of breast cancer in the U.S. has doubled since 1970.)

Samuel Epstein says that the National Cancer Institute and American Cancer Society are indifferent to or ignorant of cancer prevention. (2) He cites exposure "to chemical and radioactive carcinogens (notably large scale emissions and discharges from civilian nuclear reactors)" as known causes of breast cancer, and mentions "the cancer establishment's exploitation of women as scientific guinea pigs as evidenced by: their deliberate exposure of some 300,000 women without warning to high dose mammography in the 1970s; their failure to recognize the carcinogenic hazards of current `low dose' mammography...." Epstein also mentions that "exogenous estrogens synergize the carcinogenic effects of irradiation..."

So, we could reverse the popular claim of the cancer establishment, and say that most of the causes of breast cancer are now known.

Since the 1950s, when Gofman worked for the government and was himself a "radiation apologist," I have followed his work, and have admired his ability to free himself from mistaken views, even when doing so was costly to his career. He now holds the establishment view regarding the nature of cancer: He says it "is now considered to be a genetic disease. It is thought that a tumor develops in stages from a single cell, as the cell and some of its descendants accumulate a set of several `genetic lesions.'"

I am strongly inclined to doubt this part of the establishment view, too. I have mentioned some of the evidence against it in a previous newsletter For many years, histologists studying carcinogenesis in animals have seen diffuse changes in cells throughout the area which has been irradiated or chemically treated, where the cancer will appear. The uniformity of the precancerous tissue shows either that the "genetic lesion" isn't random, or that it is already invasive, though not yet cancerous. If we want to emphasize the "genes," we will say that certain genes are very susceptible to mutations, and that, once a mass of precancerous mutated cells exist, it is likely that other mutations will occur in those cells, "promoting" them from a precancerous to a cancerous state. But the outstanding feature of genetic mutations, which geneticists have insisted upon, is that they are different from physiological changes in being random. The very idea of "promotion," which is now an accept ed part of the doctrine, violates the traditional idea of what a mutation is. This issue has been coming up repeatedly in connection with the ideas of the cancer gene, the cancer virus, or the viral cancer gene: The gene (or virus) "is activated by the carcinogens or radiation," which amounts to saying that something - e.g., radiation or chemicals or hormones - causes cancer, leaving the cancer gene unable to explain anything.

In fact, the well-accepted tumor "promoters," estrogen (3) and unsaturated fatty acids, turn out experimentally to be fundamental carcinogens, as well as promoters. Phorbol esters, famous as experimental tumor promoters, activate a particular cellular system, which is also activated by unsaturated fatty acids, and by various hormones. Unsaturated fatty acids are now clearly identified as a "target" of ultraviolet radiation damage in skin cells, and increasingly they are seen to be involved in toxic injury and stress injury. Radiation absorbed anywhere in a cell can start a peroxidation chain reaction, causing widespread damage, which can include the inactivation of

important enzymes, including those known as "membrane pumps. " (4) These same chain reactions might also cause breaks in the DNA chain, producing mutations, but that is a separate question. If the antioxidant defenses and the energy reserves of the cell are depleted, permanent damage is very likely. People who see the c ell as being "essentially its genes" have denied that low-level radiation causes cancer, because they think about direct interactions between rays and genes. Even though most of the evidence has been deliberately suppressed and "lost" by the U.S. government, it is now very clear that low doses of radiation are carcinogenic.

The reason people want to say that cancer is "genetic" is simply that cancer cells have a stable identity which is propagated as they multiply. They, unlike the cells they derive from, are immortal, in the sense that they go on dividing, and don't mature into anything. They are said to be "dedifferentiated" cells, that are more like the cells of an embryo than like the cells of the tissue where they grow.

If cancer cells could mature into cells like those they came from, they would just be like any cell in the tissue-repair process. The cells we know as cancer are somehow stabilized in a relatively undifferentiated state, they inherit that state from the cells that precede them. It is reasonable to consider that genes might have something to do with being stuck in a condition of undifferentiated growth.

But there are many situations in which established, undifferentiated cancer cells have differentiated in the laboratory, under special conditions. This proves that, in those cases, the cancer was not a genetically caused thing, since the conditions didn't undo any mutation. For example, leukemia cells have differentiated after they were treated with DMSO or dimethyl formamide, for cold storage. Melanoma cells have reverted to a more differentiated type under the influence of the ophylline and testosterone. In one very interesting experiment, cells from a malignant tumor were combined with the cells of an embryo, and the mixed cells grew into a mature animal which was a mosaic, showing inheritance from four parents - that is, the cancer cells were just as good as healthy embryonic cells, and just needed the right environment to mature.

So, to me it seems that the real question is, "what can cause the stabilization of cells in the undifferentiated state, yet allow for certain conditions occasionally to restore the mature state?"

Some of the earliest cancer research demonstrated that tumor cells can be transplanted successfully into certain hosts, and not into others. This led many people to think about the various factors that might make some individuals resistant to cancer, and others susceptible. The immune system and hormones were found to be complexly involved in susceptibility. It occurred to some people that the cancer itself might produce a special hormone, that affected the host organism in a way that tended to allow the tumor to keep growing.

When extracts of cancers were injected into healthy animals, some of them became sick, and were inclined to develop cancer. Several lines of investigation led to the belief that pyrroles and porphyrins, related to heme (the iron-binding pigment in hemoglobin and various oxidative enzymes), might be a "cancer hormone," but the idea lacked charm, and didn't catch on.

I made extracts from aged uterine tissue, thinking it might contain estrogen, and found that when I injected it into a hamster, it seemed to cause secretion of porphyrin from the animal's eye. This led me to get interested in the hormonal significance of the porphyrin pigment, and it was known to be related to estrogen excess and cancer susceptibility. (5, 6)

Two of cancer's most mysterious features are its respiratory defect, identified by Otto Warburg, in which it converts glucose to lactic acid even in the presence of oxygen, and its resistance to lipid peroxidation. Lipid peroxidation is intimately involved in the control of cell division and aging, and in susceptibility of cells to elimination by the immune system, so cancer's antioxidative capacity seems to be closely related to its "immortal" nature. Iron (either free or bound to heine) is known to catalyze lipid peroxidation, but its presence in cancer cells simply supports their growth, rather than causing peroxidation.

Warburg discovered that light desorbs carbon monoxide and cyanide from respiratory pigments. In

trying to understand light's effects on respiration, it occurred to me that it might be desorbing those, or other toxins that bind to and inhibit the respiratory enzymes. Cancer cells lack the ability to detoxify cyanide, so it has seemed possible that cyanide might contribute to the respiratory defect of cancer; bowel bacteria can produce small amounts.

But carbon monoxide is always being produced in the body, by the enzyme heme oxygenase, which is involved in the breakdown of hemoglobin. Carbon monoxide, by binding to heme-iron, inhibits lipid peroxidation, (7) as well as inhibiting the respiratory pigments in the mitochondria.

Warburg observed that depriving growing cells of oxygen was sufficient to cause some of them to turn into cancer cells.

Anything which causes oxygen deprivation stimulates the formation of heme. (8)

If the breakdown of heme occurs in cancer cells, that is, if heme oxygenase can be demonstrated in them, then the conditions exist for a stable, heritable but non-genetic state which, as a result of the carbon monoxide which is produced in heme metabolism, combines a respiratory defect with resistance to lipid peroxidation. Heme oxygenase is induced by a variety of stresses, especially oxidative stress, (9, 10) and is known to exist in at least some cancers." (11) I think it will turn out to be a universal feature of cancer.

Heme could function as a systemic toxin, if produced in cancer cells in abundance, since it would be metabolized in the liver, with production there of abnormally large amounts of carbon monoxide. Liver abnormalities have long been recognized as an important feature of cancer.

And carbon monoxide, produced by a large tumor, would certainly be a systemic toxin. It could also account for the "regional cancerization" which has been reported to occur in the area immediately around a tumor, in which normal cells seem to be modified by the cancer as if by an inductive agent. These observations have always been discounted by the genetic dogmatists.

The relation between estrogen and porphyrin (which can be seen in some types of porphyria), and their association with cancer susceptibility, probably is a consequence of estrogen's interference with blood oxygenation, which would tend to cause exaggerated production of heine in various tissues. A sensitive instrument is now available, which can measure carbon monoxide in the breath; this could become an important diagnostic instrument.

Besides using light to desorb toxins from the heme group, there are probably various ways to directly inhibit the formation of heme. For example, ethyl alcohol inhibits heine formation (12) (the "hemeless" ring sideroblast is often considered to be a sign of alcoholism). Alcohol is superior in many ways to morphine for pain control in cancer patients, and if carbon monoxide produced by heme breakdown turns out to be a factor in cancer's persistence, alcohol might become an important factor in the prevention or treatment of cancer. It would be necessary to use a highly purified form of vodka, free of estrogen and other carcinogens. Except for bowel and liver cancer, the alcohol should be taken transdermally or intravenously. Anti-inflammatory and antihistamine agents, magnesium, progesterone, pregnenolone and other substances could be used to support oxidative metabolism.

The material used in heme synthesis is diverted from energy production. Useless heme production would contribute to cancer's energy-depleting effect on the organism.

Although carbon monoxide production by cancer cells will seem merely an incidental feature to the genetic dogmatists, I think it offers the opportunity for a unifying perspective on cancer, explaining both its systemic effects (immune suppression, wasting, and adrenal activation, for example) and its cellular features, including the respiratory defect, dedifferentiation, resistance to killing by lipid peroxidation, and - in some ways the most important feature - its stability, which has led so many people to call it a "genetic disease." Metabolic stress does cause chromosomal damage and mutations, but without the intrinsic resistance to lipid peroxidation, these defects would lead to the cells' death.

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