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DISCUSSION

AN ANALYSIS OF WARBURG'S VIEW ON THE ORIGIN OF CANCER CELLS

FERDINAND RODER

In an article which, translated from German, appeared in *Science* Otto Warburg (9) advances the proposition that injury to respiration followed by increased fermentation is the cause of the origin of cancer cells. He claims that there is today no other explanation that reduces this vital process to physics and chemistry. Notwithstanding the high regard due to Warburg on account of his achievements in the field of metabolism, his view on the origin of cancer cannot be left unchallenged. It is the purpose of this paper to show that Warburg's explanation of the origin of cancer is contradicted by the following facts:

1) The combination of impaired respiration and increased fermentation is not a characteristic of cancer. It is found in seeds and in unfertilized eggs and in leaves of plants during the night when their stomata are closed and, thus, their oxygen supply is reduced with the entailed accumulation of organic acids. It is further found in most fruits if they are placed in an oxygen free atmosphere, in which they continue to respire and are able to survive unharmed for months. And it is present in injured muscle, in wounds, burns, in inflammations of any kind and in the normal cells of the brain, the retina and the jejunal mucosa under anaerobic conditions.

2) The real characteristics of cancer are not explained by Warburg's view. They are: a) the fact that cancer originates from a single cell; it is not understandable how oxygen lack can affect only one, or at the most a few cells in a host of cells, b) the fact that cancer develops not at the site of greater cell damage but at some distance from it, that is, at the site of lesser damage. This has been found in experiments on animals after injections of benzpyrene had been given; c) the properties of cancer cells by which they are recognized, namely, hyperchromatosis, increased size of the cells and of their nuclei, indistinctness of the cell membranes and, clinically, the extreme hardness of cancerous tissue; d) the invasiveness of cancer; e) the phenomenon known as "contact spread"; f) the production of cancer in the ways commonly observed in man, that is, by heat, ultraviolet light, hormones, repeated proliferative inflammations and from benign growths such as papillomas, fibroids and nevi (moles). None of these qualities peculiar to cancer is mentioned, none of them is explained. This is understandable. If a problem concerning certain cells is considered from a single point of view instead of being viewed in all its aspects, from every side or angle, the essential qualities of those cells are necessarily out of view and cannot be considered.

3) The examples selected by Warburg are supposed to prove a causal relationship between damage to respiration by irritants (or by respiratory poisons) and the origin of cancer. The first two examples offered by Warburg as evidence, namely, the effect of oxygen lack on embryonal tissue and the effect of intermit-

tent oxygen deprivation on heart fibroblasts in tissue culture, do not provide a basis for generalization and the interpretations of these examples are not tenable if the following facts are taken into consideration: Irritants cause an increase of local blood circulation accompanied by an increased oxygen supply. This effect is visible with the naked eye on the skin if the latter was exposed to physical irritants like rubbing, heat or ultraviolet rays or to chemical irritants such as mustard or other rubefaciens. The increase in blood circulation by irritants was demonstrated by Cohnheim 79 years ago microscopically on the mesentery, the tongue and on the web of the feet of frogs. Oxygen lack has never been shown to lead to cancer *in vivo*, its uniform effect on normal cells is degeneration. This is evident in all kinds of degenerative inflammations, which derive their name from that characteristic, in angiospastic diseases, in thrombosis and embolism, in atherosclerosis or, in brief, in a vast number of pathological disorders. Thus, the contention that "circulatory disturbances" or oxygen deficiency lead to cancer is not supported by any other fact, which certainly would have been named if it existed. The only just and justifiable conclusion that can be drawn from Goldblatt's experiments, their description and his statements (2) is that "fibroblasts grown *in vitro* and submitted to repeated periods of anaerobiosis *sometimes* become neoplastic." (As can be seen from Goldblatt's description of the experiments made, this occurred in a few out of a number of more than 500 observed cases.) Furthermore, it was stated explicitly by Goldblatt at the end of his discussion that "it must nevertheless be recognized that in all three experiments (that is, in his own and in those of Gey and Earle) the changes may have been induced, as Earle has stated with regard to his own findings, 'by some unrecognized agent of unknown source.' "

The third example presented by Warburg as evidence, namely, the carcinogenic effect of urethane in small doses, does not add another, separate or independent proof, as is evident from Warburg's remark that it makes no difference "whether oxygen is withdrawn from the cell or whether the oxygen is prevented from reacting by a poison." His assertion that "the physicochemical mechanism by which urethane and other indifferent narcotics inhibit cell respiration was cleared up in 1921" is in sharp contrast to Heilbrunn's statement made in 1956 (3) that an effort should certainly be made "to interpret that enigma of enigmas, the fact that dilute solutions of anaesthetics may act as stimulating agents. Furthermore, Warburg's assertion has been contradicted by the facts that small doses of narcotics (such as ethylen, chloroform, ether, etc.) have been used in horticulture for quite some time, that is since the beginning of this century, for breaking dormancy, for promoting growth, in ripening and after-ripening and, thus, in processes that are inconsistent with the concept of poisoning as well as with that of injuring because they stimulate respiration instead of depressing it.

4) In a recent publication covering extensive investigations of his own and of others on the metabolism of cancer cells, G. Schmidt (8) comes to the conclusions that the biological end oxidation must take the same way as in normal cells and that the intensive glycolysis of cancer cells cannot be an energy substitute for respiration. His latest experiments reveal that ascites tumors have a large surplus

in cytochrom and in cytochrom oxidase in comparison with their actual respiration, which theoretically would make possible an oxygen consumption corresponding to the physiological intake of a maximally working heart muscle!

5) Regardless of these results, which invalidate Warburg's views on the relation between respiration and fermentation, it must be realized that Warburg's explanation of excessive fermentation is the basis of his conception of the origin of cancer cells and that the explanation of this vital process, given by him, does not reduce it to physics and chemistry, but is rather of that kind of which Newton said: "To tell us that any kind of matter is endowed with a certain occult faculty by which it acts and produces manifest effects is to tell us nothing."

6) It is very difficult to understand why precancerous cells should be more readily killed than cancer cells, since the former, being not yet cancer cells, are less different from, and more like, normal cells in their properties, actions and reactions. Likewise incomprehensible is Warburg's statement that the continual discovery of carcinogenic agents may hinder necessary preventive measures and thereby become responsible for cancer cases. It is obvious that the continued discovery of such agents is at present the only way to prevent cancer because only specific knowledge of potentially dangerous agents makes it possible to caution against their use. Knowledge of a common underlying cause tells us nothing about the various factors which may help to produce a certain effect. Where would medicine stand today if after the discovery of the common cause of all infectious diseases by Pasteur a suggestion of this kind had been adopted and the continual discovery of miscellaneous, infection-causing agents had been given up because "it can be harmful."

7) "There is only one common cause into which all other causes of cancer merge, the irreversible injuring of respiration." But no explanation is given why impairment of respiration is irreversible only in cancer and why, even in cancer, reversibility of injuries to respiration has been evidenced in some cases by regression of the tumor.

8) The assigning of effects to insufficient causes, faulty generalizations and analogies are not the only fallacies to which all reasoning is liable. Many statements would cease to seem controversial if it were not for undefined or insufficiently defined terms. Whereas in an experiment every precaution is taken to guard against possible errors by testing beforehand all reagents and tools which will be used, similar care is not always taken in mental experiments, as in the conception of hypotheses, where mental tools, scientific terms, are used, and sufficient care is not exercised when these terms are of such general currency as "cause". "Cause", in its complete meaning, denotes that event which is always followed by the same reality provided that no factor is present which is capable of rendering the causal relationship inoperative or ineffective. Awareness of that criterion for the establishment of a causal relationship led Koch to the formulation of his third postulate which states that a causal relationship between an organism and a disease can be established only if the inoculation of the organism in pure culture into suitable animals always reproduces the pathologic condition. Causal relationship means constant relationship, no event can be called the cause

of a process unless it is regularly followed by that process. Warburg's explanation does not specify the hidden, underlying cause of impairment of respiration neither in general nor in the particular instance of cancer, it does not reveal the underlying mechanism of impairment of respiration which, depending upon unknown and, therefore, unexplained conditions, causes a chain of consequences that leads either to degeneration or to cancer.

9) Warburg's "further" and last argument that no physicochemical explanation of the origin of cancer exists today is not warranted. An explanation of this kind does exist. It was published by me in 1929 (4) and 1944 (5). Its premise was that the living cells contain a surplus of oxygen. Evidence for the validity of this premise was set forth by me in the article, "The Dynamics of Cell Respiration and Growth and the Immediate Cause of Cancer," (5) and was subsequently furnished by an incidental observation made by D. Bronk in the course of experiments with the oxygen electrode, which led him to the following conclusion: "Obviously, there is in the brain a very short reserve of oxygen, so necessary for the continued activity of nerve cells." (1)

The premise of a physical storage, the existence of oxygen in colloidal dispersion besides its presence in molecular dispersion, made it possible to explain on strictly physicochemical grounds not only the two basic processes of life, impairment of respiration and its temporary increase during work and growth of the cells but also all known characteristics of cancer and, furthermore, the unexplained phenomena of the stimulating effect of small doses of narcotics (6) and of unspecific resistance to pulmonary tuberculosis. (7) It was that premise that led me in 1929 to the conclusion that not oxygen lack, but deficiency of oxygen activation is an essential *part* of the mechanism that converts an aerobic cell into an anaerobic cell. (4b) And it was that premise from which I arrived by deduction at the conclusion and the postulate that the living cells must contain ultra-microscopic particles of varying size and specific weight which consist of lipoids, proteins and enclosed oxygen. (See the diagram in the article: Zur Theorie der Zellatmung (4a). Particles corresponding to this description, except for the postulated oxygen content, were discovered and described by Claude and Lazarrow a decade later and named microsomes. However, no explanation of their origin and function has, thus far, been given although "they are integral and without doubt important components of the living protoplasm" (Claude) and no reason has been given why they are of different size and of varying specific weight in spite of constant chemical composition, why they appear as luminous discs under dark ground illumination, which is contrary to the law that hydrophilic colloids are not readily detectable in the ultramicroscope and contrasts with the nonrefractive character of the glycogen granules and mitochondria, why their respiration is of the same order of magnitude as that of the mitochondria, which carry the bulk of the respiratory enzymes, and why their respiratory quotient falls off with time. All these peculiarities of the microsomes as well as their origin and function are not explainable on the basis of the time-honored concept that the colloidal system of the living protoplasm consists only of solid and liquid

phases; they become explainable on the basis of the concept that the cells contain a surplus of oxygen.

It seems appropriate to close this discussion with a quotation from an editorial that appeared in the same issue as Warburg's article: "We can make grave errors—if we say we have the answers now—and thus doom man for a long time to the chains of authority, confined to the limits of our present imagination. It has been done so many times before. It is our responsibility as scientists—to teach how doubt is not to be feared but welcomed and discussed and to defend this freedom as our duty to all coming generations."—(R. P. Feynman.) It is deplorable that modern medicine is interested only in new data and in statistics and not in philosophy of science. If this had been the case, more attention would have been paid to the wise words of two eminent scientists: "The progress of biology has probably been checked by the uncritical assumption of half-truths. If science is not to degenerate into a medley of ad hoc hypotheses, it must become philosophical and must enter upon a thorough criticism of its own foundations." (Whitehead.) "Si les faits acquis à l'observation postérieurement à la construction de l'hypothèse sont reliés par elle aussi bien que les faits qui ont servi à la construire, si surtout des faits prévus comme conséquences de l'hypothèse reçoivent des observations postérieures une confirmation éclatante, la probabilité de l'hypothèse peut aller jusqu'à ne laisser aucune place au doute dans un esprit éclairé." (Cournot, *De l'Enchaînement.*)

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