OTTO WARBURG: "ON THE ORIGIN OF CANCER CELLS"

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ON FEB. 24, 1956, there appeared in **Science,** the weekly publication of the American Association for the Advancement of Science, a translation from the German of an article by Dr. Otto Warburg[1] entitled "On the Origin of Cancer Cells." Biochemists are agreed that, while this is a controversial article, it will remain a lasting and extremely valuable contribution to cancer biochemistry. It separates much of the wheat from the chaff of cancer research, and focuses in unequivocal fashion on distinct and fundamental metabolic differences between cancer and noncancer cells. Its central theme was developed thirty years ago; the data upon which the theme is based are unassailable.

This group, perhaps more than many others in dentistry, works intimately with the cancer problem. The sense of futility and lack of understanding which has continually been with workers in this field is slowly lifting and is being replaced by an expectancy that this problem may be solved in the forseeable future. For this reason, it has been decided to review with you the article entitled "On the Origin of Cancer Cells." We will note, in so doing. how it. is within dentistry's power to contribute greatly to a solution of the cancer problem.

First, let us consider Warburg's own summary of his researches (covering literally thousands of carefully planned and executed experiments) carried out during a thirty-year period ; then we can discuss in some detail the concepts involved.

"Cancer cells originate from normal body cells in two phases. The first phase is the irreversible injuring of respiration. Just as there are many remote causes of plague—heat, insects, rats-but only one common cause, the **plague bacillus, there are a great** many remote causes of cancer-tar, rays, arsenic? pressure, urethane-but there is only one common cause into which all other causes of cancer merge, the irreversible injuring of respiration.

"The irreversible injuring of respiration is followed, as the second phase of cancer formation, by a long struggle for existence by the injured cells to maintain their structure, in which a part of the cells perish from lack of energy while another part succeed in replacing the irretrievably lost respiration energy by fermentation energy. Because of the morphological inferiority of fermentation energy the highly differentiated body cells are converted by this into undifferentiated cells that grow wildly-the cancer cells."

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Let us now consider in some detail the meaning of these paragraphs. Apparently, an understanding of the terms respiration and fermentation is involved. We shall review some cell biology as a beginning. To live, a cell must have energy. Without energy (or calories) there is no life. The energy that is available to living cells ultimately comes from the sun's rays. During photosynthesis, plants store this energy in the chemical bonds of sugars and starches which we consume. As our digestive and circulatory processes make these foodstuffs available to our cells: the chemically stored energy is released by the activity of intracellular protein catalysts known to us as enzymes.[2]

To say that a cell requires energy in order to live implies much more than the simple analogies which are sometimes made, comparing this situation to the requirements of a machine for gasoline or other fuel. A machine, like a cell, is composed of parts. Supply energy, and the parts function. Remove energy, and the parts do not function, but it still remains a machine. Now consider a cell. Not only does it require energy for such a function as movement, as in the case of the muscle cell, but it requires energy to synthesize its own protoplasm. It also requires energy to synthesize and metabolize products essential to its life. In fact, it requires energy for all the vital activities which are brought together under the headings of growth, maintenance, repair, and function. Without energy, in contrast to a machine, the cell disintegrates, for energy is essential in maintaining cell morphology. Consider the delicate membrane which surrounds the cytoplasmic contents of the cell. This is a highly oriented structure and its integrity, as well as the passage of materials through and across it, depends upon adequate energy supply to the cell. The nucleus, the so-called regulator, similarly requires energy to maintain itself. Dispersed throughout the cytoplasm are small rodlike bodies or grana about 3 microns long and 0.5 micron in diameter, known as mitochondria. These occupy a special position in the cell's life, to which reference will be made later, and these too require energy for function and to maintain themselves." Thus, we can now realize that to maintain its structural and functional integrity and its bioarchitecture, the cell must have energy, that is, calories.

Now let us consider how the cell goes about obtaining its calories. The substance most easily utilized for energy supply by the cell is carbohydrate. What is the fate of a universal carbohydrate metabolic fuel, such as glucose? There are two main processes by which the cell may break down glucose to liberate stored energy. One of these is termed respiration, and predominates in the presence of adequate oxygen supply.* In this process, glucose is completely burned to CO, and H_2O, and 6 molecules of oxygen are consumed per molecule of glucose oxidized. The second process is termed glycolysis, and it is most vigorous in the absence of oxygen.[5] Although it may operate under conditions of adequate oxygen supply, usually glycolysis is depressed when sufficient oxygen is available. During glycolysis in the absence of oxygen, glucose is split to lactic acid. Such anaerobic glycolysis is also known as *fermentation.* A comparison of the energy released during the two processes reveals that,

per molecule of oxygen consumed, aerobic respiration liberates approximately seven times more energy from the glucose molecule than does the entire anaerobic glycolytic process.

Within the cell, respiration is known to occur almost exclusively in the mitochondria. The enzymes which mediate aerobic respiration are structural units built into and on the grana or mitochondria. The enzymes which catalyze glycolysis, on the other hand, are found in solution in the cytoplasm, so that we see a fundamental difference in the occurrence and distribution of the protein enzymes which mediate these two processes.[3] Now, when we speak of the burning or oxidation or degradation of glucose by body cells, it is obvious that we do not refer to the same sort of process that occurs outside the living cell. To oxidize glucose completely to CO, and H_2O outside the living cell, without enzymes. we would have to heat the glucose in concentrated acid For many hours at boiling temperature, a situation obviously incompatible with life. The cell, on the other hand, manages this remarkable feat at body pH and temperature, with intracellular protein enzyme catalysts. Enzymes arc among the most efficient catalysts known to man. For example, 0.1 mg. crude invertase, an enzyme which splits cane sugar, can split, as much cane sugar at room temperature in one-half hour as concentrated hydrochloric acid can in twenty-four hours, while *0.1* mg. crude lactase, an enzyme which splits milk sugar, can split as much milk sugar in ten minutes as concentrated hydrochloric acid can in three weeks. Another important fact to remember is that the burning of glucose in the cell is not an explosive event like the ignition of gasoline in an engine, with immediate dissipation of the energy as heat and power. In the body, to be sure, some of the chemical energy liberated is dissipated immediately as heat, but the burning process is very carefully regulated in space and time by bioarchitectural factors, and most, of the energy liberated is taken up in a particular type of chemical bond involving the phosphate group. These chemical bonds are, in fact, little energy packets manufactured by the cell which permit the body to store thn energy in a usable and transportable form. Such chemical packets of energy are known as high-energy phosphate bonds and are designated by the symbol, ~P. A. very important metabolite containing such bonds is adenosine triphosphate, or ATP. Ultimately, it is the lesser ability of glycolysis to generate ATP, as compared with the efficiency of respiration to do so, that explains the more abundant availability of' energy to the cell as a result of aerobic respiration. This may be due, in part, to the fact that the most efficient high-energy phosphate bond formation is always found to occur within the cell mitochondria.

The type of high-energy phosphate bond formation we are considering is called *oxidative phosphorylntion,* and its name indicates what it is. *Phosphorylation* means attachment of the phosphate group to a molecule, and *oxidative* means that this attachment occurs via an oxidative process. It is the energy liberated by the oxidative process which is locked in the high-energy bond of the attached phosphate group. We may illustrate these relationships as follows: In the case of inorganic phosphate (say, calcium phosphate), very few calories are required to bind the calcium and phosphate in a chemical bond.

When this bond is split, very few calories are liberated. With the ordinary type of organic phosphate bond, approximately 3,000 calories are required for formation and 3,000 calories are liberated when the bond is split. To form the metabolically important high-energy phosphate bond of the type found in ATP, approximately 11,000 to 13,000 calories are needed, and the same number of calories are liberated when the bond is disrupted. Now, once ATP is formed during oxidative phosphorylation, it may be transported anywhere throughout the cell and used by cells as, when, and where it is required. Intracellular enzymes will split off the high-energy phosphate groups, or transfer them, and liberate the calories of the bond for support of vital processes.[6] At this level, morphology and biochemistry merge as one, and the dictum of the old anatomists that structure is function is reborn at cellular molecular levels.

The over-all cellular metabolic picture involved here is that of the enzymatic splitting of large, more complex organic molecules into smaller, simpler ones, with liberation of energy at various stages, and channeling of such energy into cell systems for the performance of vital functions, and preservation of structural integrity of the cell. Within the cell, these processes react and interact in systems within systems, and phases within phases, and with an exquisite organization and regulation which orients the various concurrent diverging and converging processes in time and space and permits an integration without which cells must surely destroy themselves. Now let us briefly summarize what has been presented thus far :

1. Cells require energy to live (that is, for growth, function, maintenance, and repair) and for preservation of structural or bio-architectural relationships of cell components.

2. Energy for the above is ultimately derived from the sun, and is liberated from the chemical bonds of foodstuffs via intracellular enzymes.

3. There are two main pathways within the cell by means of which energy is released-respiration and fermentation (anaerobic glycolysis) . Relationships between these processes are listed in Table I.

TABLE I. A COMPARISON OF CERTAIN FEATURES OF RESPIRATION AND FERMENTATION

RESPIRATION	FERMENTATION
1. Burns glucose completely to CO, and H_2O $C_6H_{12}O_6 + 60_2 \rightarrow 6CO_2 + 6H_2O$ + Energy	1. Splits glucose to lactic acid $C_6H_{12}O_6 \rightarrow 2C_3H_6O_3$ + Energy
2. Yields approximately 624,000 calories per glucose mole (48-P)	2. Yields approximately 26,000 calories per glucose mole (2-P)
3. Enzymes localized in mitochondria	3. Enzymes diffused in solution in cytoplasm
4. Efficient coupling to oxidative phosphorylation, that is, generation of ATP	4. Poor coupling to oxidative phosphorylation, that is, generation of ATP

Note: $\sim$P = High-energy phosphate bond. See text for definition of oxidative phosphorylation.

With the preceding as background, we are now in a position to examine the development of the thoughts expressed by Dr. Warburg in his article. We shall digress momentarily to insert a brief historical note.

In 1914 Otto Warburg performed experiments in which he showed that when liver cells were lysed and disrupted by water, the intracellular grana, or particles, or mitochondria which could be centrifuged down contained nearly all the cell's respiratory activity. He also showed that this respiration could be inhibited by narcotics and other chemicals. More recent researches have extended our knowledge of these small bodies to the extent that they are regarded by many as autonomous, respiring bodies within the cell, and capable of dividing, of reproducing, and of transmitting genetic material. Tt is as such that they are considered in the above article.

Warburg has pioneered in, and devoted much of his entire career to, the study of cell respiration. His early researches were marked by the discovery of a hemoglobin-like respiratory enzyme which enables all cells (including those of oral tissues) to utilize molecular oxygen. For this work he received the Nobel Prize in medicine in 1932.

During the 1920's and early 1930's Warburg became interested in the cancer problem. In a biochemist's orientation, cancer is a problem in cell metabolism. It is regarded as the result of a point of departure from normal enzymatic processes of cell metabolism. One of the goals of the biochemist is to find this point of departure. Warburg asked two questions. First, how does the metabolism of a rapidly growing tissue differ from that of a tissue at rest? Where should one look? His answer was that the metabolism of a rapidly growing tissue must differ from that of a tissue at rest, in the nature and rapidity of those processes responsible for yielding energy for building tissue substance. He then asked whether the regularity and orderliness of nontumor growth and the disorganized nature of tumor growth were each expressions of a different metabolism. It was his opinion that in the answers to these questions lay the answer to the cancer problem.

We will now consider some points regarding metabolic studies of tumors. In studying the metabolism of a tissue, one must know its cellular composition. Liver, for example, would yield a relatively homogeneous population of parenchymal cells. Heart would yield a relatively homogeneous population of cardiac muscle syncytia. Solid tumors, however, are mixed-cell populations, and contain both malignant and nonmalignant metabolic variants. In recent years a technique has been evolved for yielding almost pure cultures of malignant cells. This technique is the ascites tumor cultivation technique.[7] It involves inoculation of a solid tumor mince into the peritoneal cavity of experimental animals. In certain instances, some of these solid tumors will begin to develop as freely growing cells in the fluids of the peritoneum. By means of serial transplants, a situation may be developed wherein the peritoneal cavity becomes an almost pure culture of malignant cells growing freely in ascitic fluid. One is then able to deal with almost homogeneously malignant cell populations. Data from metabolism experiments will now apply to a single cell type.

Now to Dr. Warburg's present article. The first topic discussed is "Energy of Respiration and Fermentation." It is pointed out that both processes produce energy, and both synthesize ATP, through which the energy of respiration and fermentation is then made available for life.

Ascites tumor cells consume about 7 cu. mm. oxygen per milligram dry tissue per hour via respiration, and also produce 60 cu. mm. lactic acid per milligram dry tissue per hour during fermentation. As we shall see later when we examine the actual data, converted to energy equivalents, this means that this cancer cell obtains approximately as much energy from fermentation as from respiration. A normal adult liver or kidney cell, on the other hand, obtains about 100 times more energy from respiration than it does from fermentation.

"The Injuring of Respiration" is next discussed. The damage to respiration must be irreversible, since the respiration of cancer cells never returns to normal. Also, the damage must not be too great, lest the cells die. When respiration is damaged, it forms too little ATP. This may be the result of diminished oxygen consumption, or oxygen consumption may remain at normal levels but respiration may become uncoupled from oxidative phosphorylation and ATP is not generated.

One method for the damaging of respiration is removal of oxygen. Another is the use of respiratory poisons, such as arsenious acid, hydrogen sulfide and its derivatives, or urethane. All these agents are known to produce cancer.

The experiments of Goldblatt and Cameron are also discussed. These investigators exposed heart fibroblasts in tissue culture to intermittent oxygen deficiency for long periods and finally produced transplantable malignant cells. In Warburg's opinion, "probably chronic intermittent oxygen deficiency plays a greater role in the formation of cancer in the body than does the chronic administration of respiratory poisons."

Next, the "grana" previously referred to are discussed. It is pointed out that "the autonomy of the respiring grana, both biochemically and genetically, can hardly be doubted today." In connection with the grana, it is also stated that x-rays and carcinogenic hydrocarbons may produce cancer by virtue of their effects on grana, that is, inhibition of respiration.

The "Increase of Fermentation" is the next topic discussed.

"When the respiration of body cells has been irreversibly damaged, cancer cells by no means immediately result. For cancer formation there is necessary not only an irreversible damaging of the respiration but also an increase in the fermentation-indeed such an increase of the fermentation that the failure of respiration is compensated for energetically."

This occurs over a long period of time, and many cell divisions are necessary. In support of the above, the work of Dean Burk, an eminent biochemist at the National Institutes of Health, is cited. Burk showed that if part of the liver of a healthy rat is cut out, the liver regenerates very rapidly, more rapidly even than a rapidly growing tumor. However, no increase in fermentation was associated with this growth. On the other hand, when hepatomas were induced by feeding rats butter yellow (a carcinogenic dye) as the tumors developed, fermentation increased slowly.

There is then a latent period following damage to respiration, during which many cell divisions occur and fermentation energy slowly replaces the

loss of respiration energy, which (latter event) is the driving force for the increase in fermentation. This also explains why the latent period of tumor formation in rats is less than that, of man, that is, the average normal fermentation rate of rat cells is higher than that of human cells. Therefore, the selective process begins at a higher initial fermentation level in rats and hence is completed more quickly.

We now come to a discussion of "Structure and Energy."

"Why are the body cells dedifferentiatcd when their respiration energy is replaced by fermentation energy?"

It is because, as was shown earlier, the ATP synthesized during respiration involves more structure than that synthesized by fermentation. Although, as an example, equivalent amounts of ATP might be synthesized by both processes and represent equal total amounts of energy, the energy does not have the same morphologic potential.

"Thus it is as if one reduced the same amount of silver on a photographic plate by the same amount of light, but in one case with a diffused light and in the other with a patterned light. In the first case a diffuse blackening appears on the plate, but in the second case, a picture appears; however, the same thing happens chemically and energetically in both cases."

In 1876 Pasteur noted that yeasts, which can also respire and ferment, could not maintain their structure permanently by ferrnentation alone; they would degenerate to bizarre forms. If, however, they were exposed to oxygen for a short time, they would rejuvenate.

"This, therefore, is the physicochemical explanation of the dedifferentiation of cancer cells. If the structure of yeast cannot be maintained by fermentation alone, one need not wonder that highly differentiated body cells lose their differentiation upon continuous replacement of their respiration with fermentation.

"I would like at this point to draw attention to a consequence of practical importance. When one irradiates a tissue that contains cancer cells, as well as normal cells, the respiration of the cancer cells, already too small, will decline further. If the respiration falls beneath a certain minimum that cells *need* unconditionally, despite their increased fermentation, they die; whereas the normal cells, where respiration may be harmed by the same amount, will survive because, with a greater initial respiration, they will still possess a higher residual respiration after irradiation. This explains the selective killing action of x-rays on cancer cells. But still further: the descendants of the surviving normal cells may in tho course of the latent period compensate the respiration decrease by fermentation increase and, thence, become cancer cells. Thus it happens that radiation which kills cancer cells can also at the same time produce cancer. Both events take place from harmed respiration ; tho killing by the harming of an already harmed respiration ; the carcinogenesis by the harming of a not yet harmed respiration."

The next topic is "Maintenance Energy." Studies with the ascites tumor cells have shown that cancer cells require much less energy to keep them alive than they do for growth, Thus, when deprived of all energy supplies at 37.5° C. for twenty-four hours all the cancer cells died, but when supplied with only one-fifth of the growth energy they remain alive and transplantable. This is of importance, since it explains that when cancer cells multiply very rapidly so that energy supply and nutrition become a problem, they may still remain viable.

Another phenomenon of interest is discussed under the heading of "Sleeping Cancer Cells."

"Since the increase in fermentation in the development of cancer cells takes place gradually, there must be a transitional phase between normal body cells and fully formed cancer cells. Thus, for example, when fermentation has become so great that dedifferentiation has commenced, but not so great that the respiratory defect has been fully compensated for energetically by fermentation, we may have cells which indeed look like cancer cells but are still energetically insufficient. Such cells, which are clinically not cancer cells, have lately been found, not only in the prostate, but also in the lungs, kidney, and stomach of elderly persons. Such cells have been referred to as 'sleeping cancer cells.' "

"The sleeping cancer cells will possibly play a role in chemotherapy. From energy considerations, I could think that sleeping cancer cells could be killed more readily than growing cancer cells in the body and that the most suitable test objects for finding effective killing agents would be the sleeping cancer cells of skin-that is, precancerous skin."

There are two points of interest, which may be inserted here. First, carcinoma in situ may be explicable on such a basis. Second, it takes no stretch of the imagination to realize that the many precancerous lesions occurring in the oral cavity may also come into this category. You are all aware of the situation with respect to detection of such lesions by alert clinicians. It would seem that dentistry has here an opportunity to contribute greatly to fundamental studies of the cancer problem in human beings.

Now let us examine some of the data presented by Dr. Warburg in support of his contentions. The metabolic activities of cells and tissues are expressed quantitatively as metabolic quotients, or Q values. This, as we shall see, refers to metabolic activity per milligram dry tissue per hour. At times, appended to the Q will be found a subscript, referring to the substance being measured, and a superscript, referring to the atmosphere in which the metabolic activity occurs.

In Table II, taken from Dr. Warburg's paper, we see some representative Q values, which are defined as follows :

Q_{O_2} = cubic millimeters O_2 consumed per milligram dry tissue per hour during aerobic respiration.

$Q_M^{N_2}$ = cubic millimeters lactic acid (Milchesäure) formed per milligram dry tissue per hour in nitrogen (anaerobic atmosphere during fermentation.

$Q_{ATP}^{O_2}$ = cubic millimeters ATP formed per milligram dry tissue per hour as a result of respiration.

$Q_{ATP}^{N_2}$ = cubic millimeters ATP formed per milligram dry tissue per hour as a result of fermentation.

$Q_{ATP}^{O_2} + Q_{ATP}^{N_2}$ = total ATP synthesis from respiration and fermentation.

In the first column of the table we see that there has been damage to the over-all oxygen consumption of the cancer cells, the values being 7 cu. mm. O_2 compared to 15 for normal cells. In the second column it is evident that anaerobic glycolysis of fermentation is twenty-five times more rapid in embryos

TABLE II

CELLS	Q_{O_2}	$Q^{N_2}_{M}$	$Q^{O_2}_{ATP}$	$Q^{N_2}_{ATP}$	$Q^{O_2}_{ATP} \div Q^{N_2}_{ATP}$
Liver	15	1	105	1	106
Kidney	15	1	105	1	106
Embryo (very young)	15	25	105	25	130
Cancer	7	60	49	60	109

than in the normal tissues listed, while the cancer cells are twice as active as the very rapidly growing embryos and sixty times as active as the liver and kidney. In the third column we see that energy available to the cells from respiration is the same with all the normal tissues, but that it is halved for the ascites cells. The fourth column is very interesting. When we compare it with column 3, we see that normal adult cells obtain 105 times more utilizable energy (ATP) from respiration than they do from fermentation. The rapidly growing embryo obtains about four times more energy from respiration than from fermentation. The cancer cells obtain more energy from fermentation than from respiration. But, as we see in column 5, the total utilizable energy is about the same for the cancer cells as for the liver and kidney, while the rapidly growing embryo has a greater total energy availability than all the other listed cell types in this table. Thus, we see that cancer cells have about as much energy available as normal body cells, but that the ratio of fermentation energy to respiration energy is much greater than in the normal cells. Such high fermentation energy is not available for maintaining normal structure.

Now you will note that in the above instance over-all respiration in the ascites cell is about one-half that in the normal cells. This need not be the case, and indeed it often is not the case. Some tumors may have as high an oxygen consumption as normal cells, or perhaps slightly higher. The important fact to remember in these cases, according to Warburg, is that oxidative phosphorylation is uncoupled from respiration in these tumors and ATP synthesis in the mitochondria does not occur.

We may now reconsider the two paragraphs with which this discussion was opened. They are taken from the summary of Dr. Warburg's article, and serve to condense, in his own words, the outstanding features of the material that has been discussed.

"Cancer cells originate from normal body cells in two phases. The first phase is the irreversible injuring of respiration. Just as there are many remote causes of plague-heat, insects, rats-but only one common cause, the plague bacillus, there are a great many remote causes of cancer-tar, rays, arsenic, pressure, urethane-but there is only one common cause into which all other causes of cancer merge, the irreversible injuring of respiration.

"The irreversible injuring of respiration is followed, as the second phase of cancer formation, by a long struggle for existence by the injured cells to maintain their structure, in which a part of the cells perish from lack of energy while another part succeed in replacing the irretrievably lost respiration energy by fermentation energy. Because of the morphological inferiority of fermentation energy the highly differentiated body cells are converted by this into undifferentiated cells that grow wildly-the cancer cells."

Before concluding, it should be noted that Dr. Warburg's ideas have been opposed. The most recent detailed opposition has come in a review article by Dr. S. Weinhouse (of the Lankenau Hospital Research Institute and the Institute for Cancer Research in Philadelphia) entitled "Oxidative Metabolism of Neoplastic Tissues, " appearing in ***Advances in Cancer Research*** (vol. 3, p. 270, 1955). This article was written before the current " Origin of Cancer Cells. " A key point in Dr. Weinhouse's refutation is the high oxygen consumption found in many tumors, which, it is claimed, negates the possibility of damaged respiration. It would appear that this objection can be met by the phenomenon of uncoupling of oxidative phosphorylation which was stressed earlier. This does not detract from some other points made by Dr. Weinhouse, which will not be discussed now. Let the score be balanced, however, by pointing out that other eminent workers in this field are reporting confirming evidence for the Warburg hypothesis.

I would like to close with a brief statement concerning Dr. Warburg. As members of a profession which began as an art but is rapidly gaining in the search for its science, we-all of us--stand indebted to the genius of this man whose mental powers have illuminated and molded modern biology. He has truly been called "the artisan of cell chemistry."

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