

# **The Prime Cause and Prevention of Cancer**

with two prefaces on prevention

Revised lecture at the meeting of the Nobel-Laureates on June 30, 1966  
at Lindau, Lake Constance, Germany

by  
Otto Warburg  
Director, Max Planck-Institute for Cell Physiology, Berlin-Dahlem

English Edition by Dean Burk  
National Cancer Institute, Bethesda, Maryland, USA

The Second Revised Edition  
Published by Konrad Triltsch, Würzburg, Germany  
1969

## **Preface to the Second Revised German Edition of the Lindau Lecture**

(The way to prevention of cancer)

Since the Lindau lecture of June 1966 many physicians have examined - not unsuccessfully - the practical consequences of the anaerobiosis of cancer cells. The more who participate in these examinations, the sooner will we know what can be achieved. It is a unique aspect of these examinations that they can be carried out on human patients, on the largest scale, without risk; whereas experiments on animals have been misleading many times. The cure of human cancer will be the resultant of biochemistry of cancer and of biochemistry of man.

A list of selected active groups of respiratory enzymes will soon be published, to which we recently added cytohemim and d-amino-Levulinic acid, the precursor of oxygen-transferring hemins. In the meantime commercial vitamin preparations may be used that contain, besides other substances, many active groups of the respiratory enzymes. Most of these may be added to the food. Cytohemim and vitamin B 12 may be given subcutaneously. (A synonym of "active group" is prosthetic" group of an enzyme.)

---

There exists no alternative today to the prevention of cancer as proposed at Lindau. It is the way that attacks the prime cause of cancer most directly and that is experimentally most developed. Indeed millions of experiments in man,

through the effectiveness of some vitamins, have shown, that cell respiration is impaired if the active groups of the respiratory enzymes are removed from the food; and that cell respiration is repaired at once, if these groups are added again to the food. No way can be imagined that is scientifically better founded to prevent and cure a disease, the prime cause of which is an impaired respiration. Neither genetic codes of anaerobiosis nor cancer viruses are alternatives today, because no such codes and no such viruses in man have been discovered so far; but anaerobiosis has been discovered<sup>8</sup>.)

---

What can be achieved by the active groups, when tumors have already developed? The answer is doubtful, because tumors live in the body almost anaerobically, that is under conditions that the active groups cannot act.

On the other hand, because young metastases live in the body almost aerobically, inhibition by the active groups should be possible. Therefore we propose first to remove all compact tumors, which are the anaerobic foci of the metastasis. Then the active group should be added to the food, in the greatest possible amount, for many years, even for ever. This is a promising task. If it succeeds, then cancer will be a harmless disease.

---

Moreover, we discovered recently <sup>a)</sup> in experiments with growing cancer cells in vitro that very low concentrations of some selected active groups inhibit fermentation and the growth of cancer cells completely, in the course of a few days. From these experiments it may be concluded that de-differentiated cells die if one tries to normalize their metabolism. It is a result that is unexpected and that encourages the task of inhibiting the growth of metastases with active enzyme groups.

a) In press in Hoppe-Seylers Zeitschrift für Physiologische Chemie 1967. 10 g riboflavin per ccm or 10 g d-Aminolevulinic acid inhibit in vitro growth and fermentation completely but inhibit respiration less. As expected, ascites cancer in vivo is not cured.

---

As emphasized, it is the first precondition of the proposed treatment that all growing body cells be saturated with oxygen. It is a second precondition that exogenous carcinogens be kept away, at least during the treatment. All carcinogens impair respiration directly or indirectly by deranging capillary circulation, a statement that is proved by the fact that no cancer cell exists, the respiration of which is not impaired. Of course, respiration cannot be repaired if it is impaired at the same time by carcinogens.

---

It has been asked after the Lindau lecture why the repair of respiration by the active groups of the enzymes was proposed as late as 1966, although the fermentation of the cancer cell was discovered as early as 1923. Why was so much time lost?

He who asked this questions ignored that in 1923 the chemical mechanism of enzyme action was still a secret of living nature alone<sup>1)</sup>. The first active group of an enzyme, "Iron, the Oxygen-Transferring Part of the Respiratory Enzyme" was discovered in 1924<sup>2)</sup>. There followed in two decades the discoveries of the O<sub>2</sub>-transferring metalloproteins, the flavoproteins and the pyridinproteins, a period that was concluded by the "Heavy Metals as Prosthetic Groups of Enzymes"<sup>3)</sup> and by the "Hydrogen Transferring Enzymes"<sup>4)</sup> in 1947 to 1949.

Moreover, during the first decades after 1923 glycolysis and anaerobiosis were constantly confused, so that nobody knew what was specific for tumors. The three famous and decisive discoveries of DEAN BURK and colleagues<sup>5)</sup> of the National Cancer Institute at Bethesda were of the years 1941, 1956 and 1964: first, that the metabolism of the regenerating liver, which grows more rapidly than most tumors, is not cancer metabolism, but perfect aerobic embryonic metabolism; second, that cancer cells, descended in vitro from one single normal cell, were in vivo the more malignant, the higher the fermentation rate; third, that in vivo growing hepatomas, produced in vivo by different carcinogens, were in vivo the more malignant, the higher the fermentation rate. - Furthermore, the very unexpected and fundamental fact, that tissue culture is carcinogenic and that a too low oxygen pressure is the intrinsic cause were discovered<sup>6-8)</sup> in the years 1927 to 1966. - Anaerobiosis of cancer cells was an established fact only since 1960 when methods were developed<sup>7)</sup> to measure the oxygen pressure inside of tumors in the living body.

This abridged history shows that even the greatest genius would not have been able to propose in 1923, what was proposed at Lindau in 1966. As unknown as the prime cause of cancer was in 1923 was the possibility to prevent it.

---

Life without oxygen in a living world that has been created by oxygen<sup>9)</sup> was so unexpected that it would have been too much to ask that anaerobiosis of cancer cells should be accepted at once by all scientists. But most of the resistance disappeared when at Lindau it was explained that on the basis of anaerobiosis there is now a real chance to get rid of this terrible disease, if man is willing to submit to experiments and facts. It is true that more than 40 years were necessary to learn how to do it. But 40 years is a short time in the history of science<sup>10)</sup>.

Wiesenhof über Idar-Oberstein, August 1967 OTTO WARBURG

---

Two years after the Lindau lecture LINUS PAULING (Science Vol. 160, Page 265, 1968) proposed to control mental diseases by adding to the food the active groups of respiratory enzymes. But here the experimental basis was lacking. No mental disease is known so far, the prime cause of which is an impairment of the respiration of brain cells.

---

### **Preface to the First edition** (Prevention of endogenous cancer)

Most experts agree that nearly 80% of cancers could be prevented, if all contact with the known exogenous carcinogens could be avoided. But how can the remaining 20%, the endogenous or so-called spontaneous cancers, be prevented?

Because no cancer cell exists, the respiration of which is intact<sup>1</sup>, it cannot be disputed that cancer could be prevented if the respiration of the body cells would be kept intact.

Today we know two methods to influence cell respiration<sup>1</sup>. The first is to decrease the oxygen pressure in growing cells. If it is so much decreased that the oxygen transferring enzymes are no longer saturated with oxygen, respiration can decrease irreversibly and normal cells can be transformed into facultative anaerobes.

The second method to influence cell respiration in vivo is to add the active groups of the respiratory enzymes to the food of man. Lack of these groups impairs cell respiration and abundance of these groups repairs impaired cell respiration - a statement that is proved by the fact that these groups are necessary vitamins for man<sup>2</sup>.

To prevent cancer it is therefore proposed first to keep the speed of the blood stream so high that the venous blood still contains sufficient oxygen; second, to keep high the concentration of hemoglobin in the blood; third to add always to the food, even of healthy people, the active groups of the respiratory enzymes; and to increase the doses of these groups, if a precancerous state<sup>3</sup> has already developed. If at the same time exogenous carcinogens are excluded rigorously, then most cancers may be prevented today.

These proposals are in no way utopian. On the contrary, they may be realized by everybody, everywhere, at any hour. Unlike the prevention of many other diseases the prevention of cancer requires no government help, and no extra money.

Wiesenhof, August 1966 OTTO WARBURG

---

## **The Prime Cause and Prevention of Cancer** (Revised Lindau Lecture)

By OTTO WARBURG  
(Director, Max Planck Institute for Cell Physiology, Berlin-Dahlem, Germany)

English Edition by DEAN BURK\*), National Cancer Institute, Bethesda, Maryland

\*) Note by DEAN BURK: Adapted from a lecture originally delivered by O. Warburg at the 1966 annual meeting of Nobelists at Lindau, Germany. O. Warburg won the Nobel Prize in Medicine in 1931 for his discovery of the oxygen transferring enzyme of cell respiration, and was voted a second Nobel Prize in 1944 for his discovery of the active groups of the hydrogen transferring enzymes. Many universities, like Harvard, Oxford, Heidelberg have offered him honorary degrees. He is a Foreign member of the Royal Society of London, a Knight of the Order of Merit founded by Frederick the Great, and was awarded the Great Cross with Star and Shoulder ribbon of the *Bundesrepublik*. His main interests are Chemistry and Physics of Life. In both fields no scientist has been more successful.

There are prime and secondary causes of diseases. For example, the prime cause of the plague is the plague bacillus, but secondary causes of the plague are filth, rats, and the fleas that transfer the plague bacillus from rats to man. By a prime cause of a disease I mean one that is found in *every* case of the disease.

Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar. All normal body cells meet their energy needs by respiration of oxygen, whereas cancer cells meet their energy needs in great part by fermentation. All normal body cells are thus obligate aerobes, whereas all cancer cells are partial anaerobes. From the standpoint of the physics and chemistry of life this difference between normal and cancer cells is so great that one can scarcely picture a greater difference. Oxygen gas, the donor of energy in plants and animals is dethroned in the cancer cells and replaced by an energy yielding reaction of the lowest living forms, namely, a fermentation of glucose.

The key to the cancer problem is accordingly the energetics of life, which has been the field of work of the Dahlem institute since its initiation by the Rockefeller Foundation about 1930. In Dahlem the oxygen transferring and hydrogen transferring enzymes were discovered and chemically isolated. In Dahlem the fermentation of cancer cells was discovered decades ago; but only in recent years has it been demonstrated that cancer cells can actually *grow in the body almost with only the energy of fermentation*. Only today can one submit, with respect to cancer, all the experiments demanded by PASTEUR and KOCH as proof of the prime causes of a disease. If it is true that the replacement of

oxygen-respiration by fermentation is the prime cause of cancer, then *all* cancer cells without exception must ferment, and no normal growing cell ought to exist that ferments in the body.

An especially simple and convincing experiment performed by the Americans MALMGREN and FLANEGAN confirms the view. If one injects tetanus spores, which can germinate only at very low oxygen pressures, into the blood of healthy mice, the mice do not sicken with tetanus, because the spores find no place in the normal body where the oxygen pressure is sufficiently low. Likewise, pregnant mice do not sicken when injected with the tetanus spores, because *also in the growing embryo no region exists* where the oxygen pressure is sufficiently low to permit spore germination. However, if one injects tetanus spores into the blood of tumor-bearing mice, the mice sicken with tetanus, because the oxygen pressure in the tumors can be so low that the spores can germinate. These experiments demonstrate in a unique way the anaerobiosis of cancer cells and the *non-anaerobiosis* of normal cells, in particular the *non-anaerobiosis of growing embryos*.

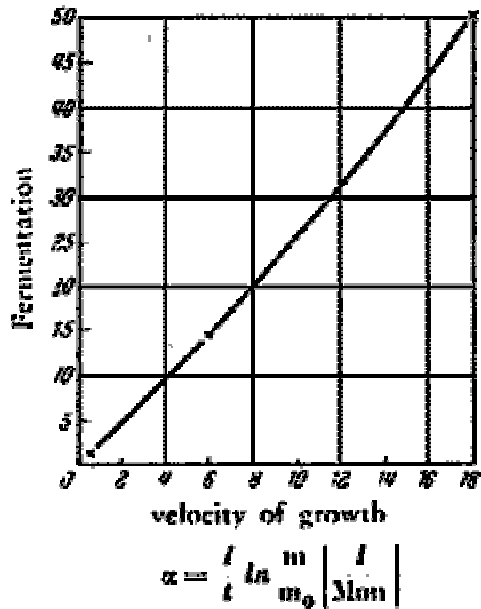
### **The Fermentation of Morris Hepatomas**

A second type of experimentation demonstrates a quantitative connection between fermentation of tumors and growth rate of tumors.

If one injects rats with cancer-inducing substances of different activities, one can create, as HAROLD MORRIS of the National Cancer Institute in Bethesda has found, liver cancers (hepatomas) of very different degrees of malignancy. Thus, one strain of tumor may double its mass in three days, another strain may require 30 days. Recently DEAN BURK and MARK WOODS 3), also of the National Cancer Institute, measured the *in vitro* rates of anaerobic fermentation in different lines of these hepatomas, and obtained a curve ([Fig. 1](#)) that shows a quantitative relationship between fermentation and growth rate, and therefore between fermentation and malignancy, in these various tumor strains. The fermentation increases with the malignancy, and indeed the fermentation increases even faster than the malignancy.

Special interest attaches to the fermentation of the most slowly growing hepatomas, because several investigators in the United States believed that they had found \*) that such tumors had no fermentation; that is that anaerobiosis cannot be the prime cause of cancer.

\*) For example see C. H. BÖHRINGER SON, Ingelheim am Rhein, the factory Work-Journal "Das Medizinische Prisma", Vol. 13, 1963. Here a lecture of VAN POTTER (Madison, Wisconsin) is reprinted where owing to the slow-growing Morris-tumors anaerobiosis as prime cause of cancer is rejected and the lack of "intracellular feeding back" is claimed to be the real cause of cancer.



**Fig. 1.** Velocity of growth and fermentation of the Morris-Hepatomas, according to DEAN BURK and MARK WOODS

DEAN BURK and MARK WOODS saw immediately from their curves that in the region of the zero point the rate of fermentation was so small that it could no longer be measured by the usual gross methodology employed by the aforementioned workers, whereas in the same region the smallest growth rate was always easily measurable. BURK and WOODS saw, in other words, that in the region of the zero point of their curves the growth test was more sensitive than the *usual* fermentation test. With refined and adequate methods for measuring fermentation of sugar (glucose) they found, what any physical chemist after a glance at the curve would realize, that even the most slow-growing Morris hepatomas fermented sugar.

The results of DEAN BURK and MARK WOODS were confirmed and extended by other workers with independent methods. PIETRO GULLINO, also in Bethesda, developed a perfusion method whereby a Morris hepatoma *growing in the living animal* could be perfused for long periods of time, even weeks, by means of a single artery and single vein, and the blood entering and leaving any given tumor could be analyzed. GULLINO found with this method that the slow-growing Morris hepatomas always produced fermentation lactic acid during their growth. This was in contrast to liver, where, as known since the days of CLAUDE BERNARD, lactic acid is not produced but consumed by liver; the difference between liver and Morris tumors *in vivo* is thus infinite (+ vs. -). GULLINO further found that tumors grow *in vivo* with diminished oxygen consumption. In summary, GULLINO's findings indicate that the slow-growing Morris hepatomas are partial anaerobes. SILVIO FIALA, a biochemist at the University of Southern California, found that not only did the slow-growing hepatomas produce lactic acid, but also that the number of their oxygen-respiring grana was reduced.

The slow-growing Morris hepatomas are therefore far removed from having refuted the anaerobiosis of tumors. On the contrary, they are the best proof of this distinctive characteristic. For forty years cancer investigators have searched for a cancer that did not ferment. When finally a non-fermenting tumor appeared to have been found in the slow-growing Morris tumors, it was shown to be a methodological error.

### **Transformation of Embryonic Metabolism into Cancer Metabolism**

A third type of experiment, from the institute in Dahlem with coworkers GAWEHN, GEISLER and LORENZ, is likewise highly pertinent. Having established that anaerobiosis is that property of cancer cells that distinguishes them from all normal body cells, we attacked the question, namely, how normal body cells may become transformed into anaerobes (6)7)8).

If one puts embryonic mouse cells into a suitable culture medium saturated with physiological oxygen pressures, they will grow outside the mouse body, *in vitro*, and indeed as pure aerobes, with a pure oxygen respiration, without a trace of fermentation. However, if during the growth one provides an oxygen pressure so reduced that the oxygen respiration is partially inhibited, the purely aerobic metabolism of the mouse embryonic cells is quantitatively altered within 48 hours, in the course of *two* cell divisions, into the metabolism characteristic of fermenting cancer cells. [Fig. 2](#) illustrates the very simple experimental procedure involved.

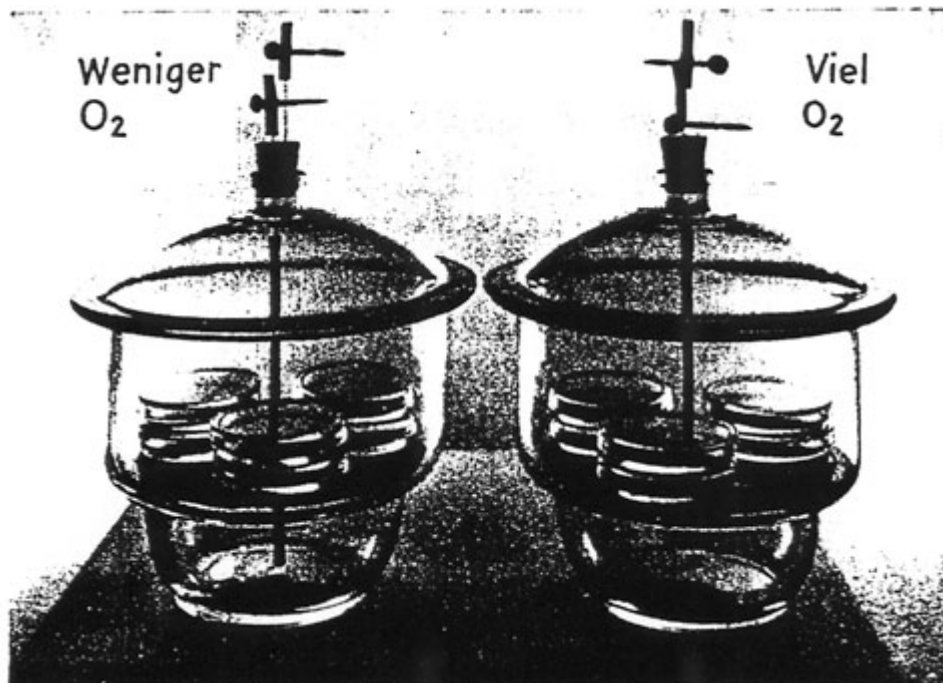
If one then brings such cells, in which during their growth under reduced oxygen pressure a cancer cell metabolism has been produced, back under the original high oxygen pressure, and allows the cell to grow further, the cancer metabolism *remains*. The transformation of embryonic cell metabolism into cancer cell metabolism can thus be irreversible, an important result, since the origin of cancer cells from normal body cells is an irreversible process. It is equally important that these body cells whose metabolism has thus been transformed into cancer metabolism now continue to grow *in vitro* as facultative anaerobes. The duration of our experiments is still too limited to have yielded results of tests of inoculation of such cells back into mice, but according to all previous indications such cells will later grow as anaerobes upon transplantation into animals.

In any case, these experiments belong to the most important experiments in the field of cancer investigation since the discovery of the fermentation of tumors. For cancer metabolism, heretofore, measured so many thousand of times, *has now been induced artificially in body cells* by the simplest conceivable experimental procedure, and with this artificially induced cancer metabolism the body cells divide and grow as anaerobes (*in vitro*)\*).

\*) The experiments were at once repeated, when they were published, of course without acknowledgment. See for example Th. Goodfriend, D. M. Sokol and N. O. Kaplan, J. molecular Biol. 15, 18, 1966.

In recent months we have further developed our experimental arrangements so that we can measure manometrically the oxygen respiration and fermentation of the growing mouse embryonic cells *during* the metabolic transformation. [Fig. 3](#) shows the experimental arrangement. We find by such experiments that 35 percent inhibition of oxygen respiration already suffices to bring about such a transformation during cell growth<sup>\*\*</sup>). Oxygen pressures that inhibit respiration 35 percent can occur at the end of blood capillaries in living animals, so that the possibility arises that cancer may result when too low oxygen pressures occur during cell growth in animal bodies.

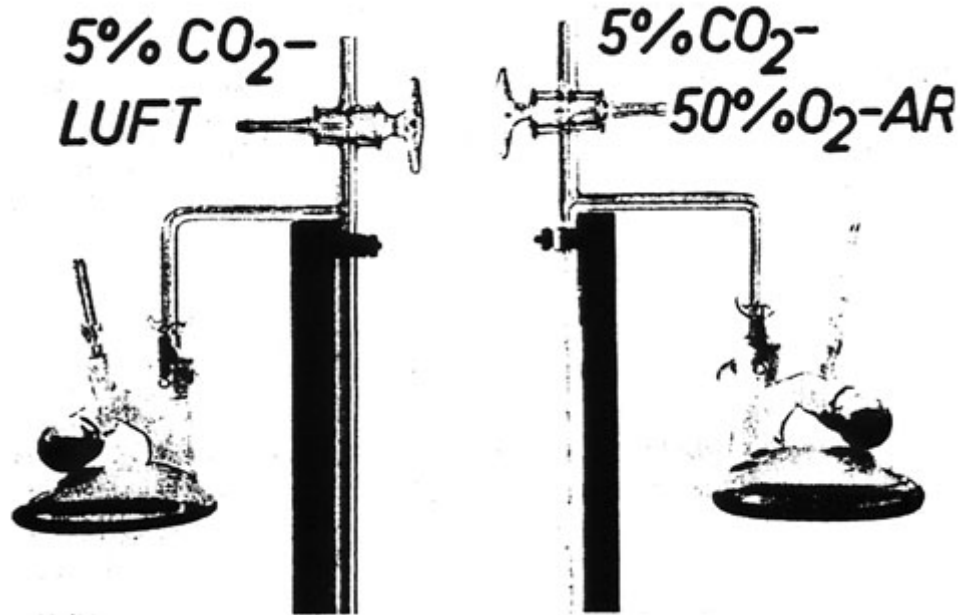
\*\*\*) These experiments show, like the curve of Dean Burk and Mark Woods in Fig. 1, that it is more correct to designate tumor cells as "partial anaerobes" rather than "facultative anaerobes". A body cell is transformed into a tumor cell if only a part of the respiration is replaced by fermentation.



**Fig. 2.** Method to transform embryonic metabolism into cancer metabolism by decreasing the oxygen pressure

The induction of cancers by solid materials injected into animals is a further experimental indication of this possibility. If one implants discs of solid substances under the skin of rats, the discs will soon be surrounded by capsules of living tissue that will be nourished with blood vessels from the hypodermis. Sarcomas very frequently develop in these capsules. It is immaterial whether the solid discs are chemically plastics, gold, or ivory, etc. What produces the cancer is not the chemical nature of the solid discs, but the special kind of blood

nourishment supplied to the tissue encapsulating the discs. This blood provision varies with the site and in adequacy within a given animal, and induces cancer from the low oxygen pressure in the encapsulating disc.



**Fig. 3.** Method to measure manometrically respiration and fermentation during the transformation of embryonic into cancer metabolism<sup>\*)</sup>

<sup>\*)</sup> The vessels are not shaken, because shaking inhibits growth. Therefore, the oxygen pressure in the liquid phase at the bottom of the vessels is much lower than in the gasphase. For example, when the oxygen pressure in the gas phase was 2000 mm H<sub>2</sub>O it was at the bottom of the vessels 130 mm H<sub>2</sub>O. (O. Warburg, A. Geissler and S. Lorenz, Zeitschr. Für Naturforschung 20b, 1070, 1965.)

## Thermodynamics

If a lowered oxygen pressure during cell growth may cause cancer, or, more generally, if any inhibition of respiration during growth may cause cancer, then a next problem is to show *why* reduced respiration induces cancer. Since we already know that with a lowering of respiration fermentation results, we can re-express our question: Why does cancer result if oxygen-respiration is replaced by fermentation?

The early history of life on our planet indicates that life existed on earth before the earth's atmosphere contained free oxygen gas. The living cells must therefore have been fermenting cells then, and, as fossils show, they were undifferentiated single cells. Only when free oxygen appeared in the atmosphere - some billion years ago - did the higher development of life set in, to produce the plant and animal kingdoms from the fermenting, undifferentiated single cells.

What the philosophers of life have called "*Evolution créatrice*" has been and is therefore the work of oxygen.

The reverse process, the dedifferentiation of life, takes place today in greatest amount before our eyes in cancer development, which is another expression for dedifferentiation. To be sure, cancer development takes place even in the presence of free oxygen gas in the atmosphere, but this oxygen may not penetrate in sufficient quantity into the growing body cells, or the respiratory apoenzymes of the growing body cells may not be saturated with the active groups. In any case, during the cancer development the oxygen-respiration always falls, fermentation appears, and the highly differentiated cells are transformed to fermenting anaerobes, which have lost all their body functions and retain only the now useless property of growth. Thus, when respiration disappears, life does not disappear, but the *meaning* of life disappears, and what remains are growing machines that destroy the body in which they grow.

But why oxygen differentiates and why lack of oxygen dedifferentiates? Nobody would dispute that the development of plants and animals and man from unicellular anaerobes is the most improbable process of all processes in the world. Thus there is no doubt, that EINSTEIN descended from a unicellular fermenting organism - to illustrate the miracle, molecular O<sub>2</sub> achieved. But according to the thermodynamics of Boltzmann, improbable processes require work to take place. It requires work to produce temperature differences in a uniformly temperatured gas; whereas the equalization of such temperature differences is a spontaneous process that does not require work. It is the oxygen-respiration that provides in life this work, and dedifferentiation begins at once when respiration is inhibited in any way. In the language of thermodynamics, differentiation represents a forced steady state, whereas dedifferentiation - that is, cancer - is the true equilibrium state. Or, illustrated by a picture: the differentiated body cell is like a ball on an inclined plane, which, would roll down except for the work of oxygen-respiration always preventing this. If oxygen respiration is inhibited, the ball rolls down the plane to the level of dedifferentiation.

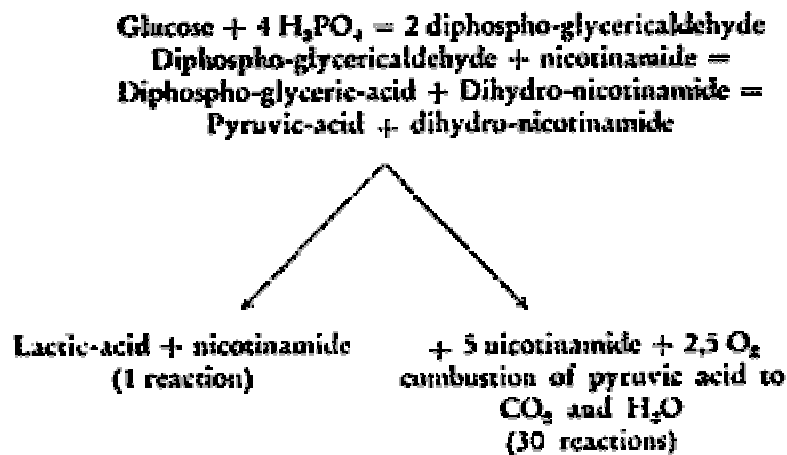
But why respiratory energy and not fermentation energy can differentiate, whereas in general, for example in growth, respiratory energy and fermentation energy are equivalent? Obviously, there would be no cancer if there were not this discrimination of fermentation energy, that is, *if fermentation like respiration could differentiate*. Then, when respiration is replaced by fermentation, fermentation would take over differentiation, and a high state of differentiation would be maintained even in the fermenting body cells.

## **Chemistry**

Physics cannot explain why the two kinds of energy are not equivalent in differentiation; but chemistry may explain it. Biochemists know that both respiration energy and fermentation energy do their work as phosphate energy, but the ways of phosphorylation are different. If one applies this knowledge to carcinogenesis, it seems that only oxidative phosphorylation but not fermentative phosphorylation can differentiate, a result, that may in future explain the mechanism of differentiation.

Yet Biochemistry can explain already today why fermentation arises, when respiration decreases. [Figure 4](#) shows that the pathways of respiration and fermentation are common as far as pyruvic acid. Then the pathways diverge. The endproducts of fermentation is reached by one single reaction, the reduction of pyruvic acid by dihydro-nicotinamide to lactic acid. On the other hand, the endproducts of the oxidation of pyruvic acid, H<sub>2</sub>O and CO<sub>2</sub>, are only reached after many additional reactions. Therefore, when cells are harmed, it is probable that first respiration is harmed.

In this way the frequency of cancer is explained by reasons of probability.



**Figure 4**

**To sum up:**

1. Impairment of respiration is frequent than impairment of fermentation because respiration is more complicated than fermentation.
2. The impaired respiration can be easily replaced by fermentation, because both processes have a common catalyst, the nicotinamide.
3. The consequence of the replacement of respiration by fermentation is mostly glycolysis, with death of the cells by lack of energy. Only if the energy of fermentation is equivalent to the lost energy of respiration, is the consequence anaerobiosis. Glycolysis means death by fermentation, anaerobiosis means life by fermentation.

4. Cancer arises, because respiration, but not fermentation, can maintain and create the high differentiation of body cells.

To conclude the discussion on the prime cause of cancer, the virus-theory of cancer may be mentioned. It is the most cherished topic of the philosophers of cancer. If it were true, it would be possible to prevent and cure cancer by the methods of virology; and all carcinogens could be eaten or smoked freely without any danger, if only contact with the cancer virus would be avoided.

It is true that some virus-caused cancer <sup>b)</sup> occur in animals, but no one sure human virus-cancer has been observed so far, whereas innumerable substances cause cancer without viruses in animals and man. Thus viruses do not meet the demands of Pasteur, that is must be possible to trace the prime cause in every case of the disease. Therefore science classifies viruses as remote causes of cancer, leading to anaerobiosis, the prime cause, that meets the demands of Pasteur.

b) The chicken Rous sarcoma, which is labeled today as a virus tumor, ferments glucose and lives as a partial anaerobe like all tumors. O. WARBURG, *Bioch. Zeitschrift* 160, 307, 1925; F. WIND, *Klinische Wochenschrift*, Nr. 30, 1926.

Many may remember how anaerobiosis as prime cause of cancer was recently disputed emphatically, when one single cancer - the slow Morris hepatomas - was believed (wrongly) to lack in fermentation. In contrast the virus theory is adhered to although all cancers of man are lacking in virus-origin. This means the surrender of the principles of Pasteur and the relapse into bygone times of medicine.

### **Applications**

Of what use is it to know the prime cause of cancer? Here is an example. In Scandinavian countries there occurs a cancer of throat and esophagus whose precursor is the so-called Plummer-Vinson syndrome. This syndrome can be healed when one adds to the diet the active groups of respiratory enzymes, for example: iron salts, riboflavin, nicotinamide, and pantothenic acid. When one can heal the precursor of a cancer, one can prevent this cancer. According to ERNEST WYNDER <sup>3)</sup> of the Sloan-Kettering Institute for Cancer Research in New York, the time has come when one can exterminate this kind of cancer with the help of the active groups of the respiratory enzymes.

It is of interest in this connection that with the help of one of these active groups of the respiratory enzymes, namely nicotinamide, tuberculosis can be healed quite as well as with streptomycin, but without the side effects of the latter <sup>c)</sup>. Since the sulfonamides and antibiotics, this discovery made in 1945 is the most important event in the field of chemotherapy generally, and encourages, in association with the experiences in Scandinavia, efforts to prevent cancer by dietary addition of large amounts of the active groups of the respiratory enzymes. Since there can scarcely be overdosage, such experiments can do no harm.

c) V. CHORINE: *C. R. sci. Paris*, 220, 150 (1945). – H. FUST and A. STUDER, *Schweizerische Z. für allgemeine Pathologie*, Band 14; Fasc 5 (1951).

I would like to go further and propose always making dietary additions of large amounts of the active groups of the respiratory enzymes after successful

operations when there is danger from metastatic growths. One could indeed never succeed in redifferentiating the dedifferentiated cancer cells, since during the short duration of human life the probability of such a back-differentiation is zero. But one might increase the respiration of growing metastases, and thereby inhibit their fermentation, and - on the basis of the curve of DEAN BURK and MARK WOODS obtained with the Morris hepatomas - thereby inhibit the growth of metastases to such an extent that they might become as harmless as the so-called "sleeping" cancer cells in the prostates of elderly men.

### **A Second Example of Application**

The physicist MANFRED VON ARDENNE has recently attacked the problem of the therapy of cancer. ARDENNE discovered that cancer cells owing to their fermentation, are more acid – inside and on their surface – than normal cells and hence are more sensitive to high temperatures. On this basis, he and his medical colleagues have treated cancer patients, after surgical removal of the primary tumors, by raising the body temperature of the patients to about 109° Fahrenheit for an hour, in the hope that the metastases will then be killed or their growth so slowed up as to become harmless. It is not yet decided whether this idea can be described as a practical success. But the provisional work of ARDENNE is already of great significance in a field where hopes of conventional chemotherapy have been dimmed but might be brightened by combination with extreme or moderate hyperthermy.

A third application. According to an estimate by K. H. Bauer of the Cancer Institute in Heidelberg, at least one million of the now living twenty five million male inhabitants of West Germany will die of cancer of the respiratory tract; still more will die from other cancer. When one considers that cancer is a permanent menace, one realizes that cancer has become one of the most dangerous menaces in the history of medicine.

Many experts agree that one could prevent about 80% of all cancers in man, if one could keep away the known carcinogens from the normal body cells. This prevention of cancer might involve no expenses, and especially would require little further research to bring about cancer prevention in up to 80 percent<sup>\*</sup>).

<sup>\*</sup>) Since this estimate was published, some thought 80% even to low. Yet prevention remained taboo and early diagnosis was the only consolation that was offered.

Why then does it happen that in spite of all this so little is done towards the prevention of cancer? The answer has always been that one does not know what cancer or the prime cause of cancer be, and that one cannot prevent something that is not known.

But nobody today can say that one does not know what cancer and its prime cause be. On the contrary, there is no disease whose prime cause is better known, so that today ignorance is no longer an excuse that one cannot do more about prevention. That prevention of cancer will come there is no doubt, for man wishes to survive. But how long prevention will be avoided depends on how long the prophets of agnosticism will succeed in inhibiting the application of scientific knowledge in the cancer field. In the meantime, millions of men must die of cancer unnecessarily.

---

### **Literature to Preface of Second Edition:**

1. WILLSTAETTER, WIELAND and EULER, Lectures on enzymes at the centenary of the Gesellschaft Deutscher Naturforscher. Berichte der Deutschen Chemischen Gesellschaft, 55, 3583, 1922. The 3 lectures of the 3 chemists show that in the year 1922 the action of all enzymes was still a mystery. No active group of any enzyme was known.
2. OTTO WARBURG, Biochem. Zeitschrift, 152, 479, 1924.
3. OTTO WARBURG, Heavy Metals as prosthetic groups of enzymes, Clarendon Press, Oxford, 1949.
4. OTTO WARBURG, Wasserstoffübertragende Fermente, Verlag Werner Sanger, Berlin, 1948.
5. DEAN BURK, 1941. On the specificity of glycolysis in malignant liver tumors as compared with homologous adult or growing liver tissues. In Symposium of Respiratory Enzymes, Univ. of Wisconsin Press. pp. 235-245, 1942. DEAN BURK, Science 123, 314, 1956. Woods, M. W., Sandford, K. K., Burk, D., and Earle, W. R. J. National Cancer Institute 23, 1079-1088, 1959. DEAN BURK, Burk, D., Woods, M. and Hunter, J. On the Significance of Glucolysis for Cancer Growth, with Special Reference to Morris Rat Hepatomas. Journ. National Cancer Institute 38, 839-863, 1967.
6. O. WARBURG und F. KUBOWITZ, Bioch. Z. 189, 242, 1927; H. GOLDBLATT und G. CAMERON, J. Exper. Med. 97, 525, 1953.
7. O. WARBURG, 17. Mosbacher Kolloquium, April 1966. Verlag Springer, Heidelberg, 1966.
8. O. WARBURG, K. GAWEHN, A. W. GEISSLER, D. KAYSER and S. LORENZ, Klinische Wochenschrift 43, 289, 1965.
9. O. WARBURG, Oxygen, The Creator of Differentiation, Biochemical Energetics, Academic Press, New York, 1966.
10. O. WARBURG, New Methods of Cell Physiology, Georg Thieme, Stuttgart, and Interscience Publishers, New York, 1962.

### **Literature to Preface of First Edition:**

1. OTTO WARBURG, A. W. GEISSLER, and S. LORENZ: ber die letzte Ursache und die entfernten Ursachen des Krebses. 17. Mosbacher Kolloquium, April 1966. Verlag Springer, Heidelberg 1966.
2. Any book on vitamins, such as Th. Bersin. Biochemie der Vitamine. Akad. Verlags.-Ges. Frankfurt 1966.
3. ERNEST L. WYNDER, SVEN HULTBERG, FOLKE JACOBSSON, and IRWIN J. BROSS, Environmental Factors in Cancer. Cancer, Vol. 10, 470, 2057.