The Prime Cause and Prevention of Cancer - Part 1

with two prefaces on prevention

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

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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 cytohemin 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. Cytohemin 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[8].)

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 [a]) 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[1]). The first active group of an enzyme, "Iron, the Oxygen-Transferring Part of the Respiratory Enzyme" was discovered in 1924[2]). There followed in two decades the discoveries of the O_2-transferring metalloproteins, the flavoproteins and the pyridinproteins, a period that was concluded by the "Heavy Metals as Prosthetic Groups of Enzymes"[3]) and by the "Hydrogen Transferring Enzymes"[4]) 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[5]) 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[6-8]) in the years 1927 to 1966. - Anaerobiosis of cancer cells was an established fact only since 1960 when methods were developed[7]) 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 [9]) 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[10]).

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[1] , 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[1]. 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[2].

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[3] 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)

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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 if 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 scientists has been more successful.

There are prime and secondary causes of diseases. For example, the prime cause of the plaque is the plaque bacillus, but secondary causes of the plaque are filth, rats, and the fleas that transfer the plaque 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 is 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.

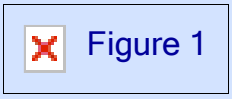

Fig. 1. Velocity of growth and fermentation of the Morris-Hepatomas, according to DEAN BURK and MARK WOODS

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 pint 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, GEISSLER 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 and 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, and 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[**]). 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.

Figure 2

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 king 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.

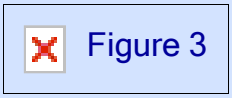

Fig. 3. Method to measure manometrically respiration and fermentation during the transformation of embryonic into cancer metabolism*)

*) 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_2O it was at the bottom of the vessels 130 mm H_2O. (O. Warburg, A. Geissler and S. Lorenz, Zeitschr. Für Naturforschung 20b, 1070, 1965.)