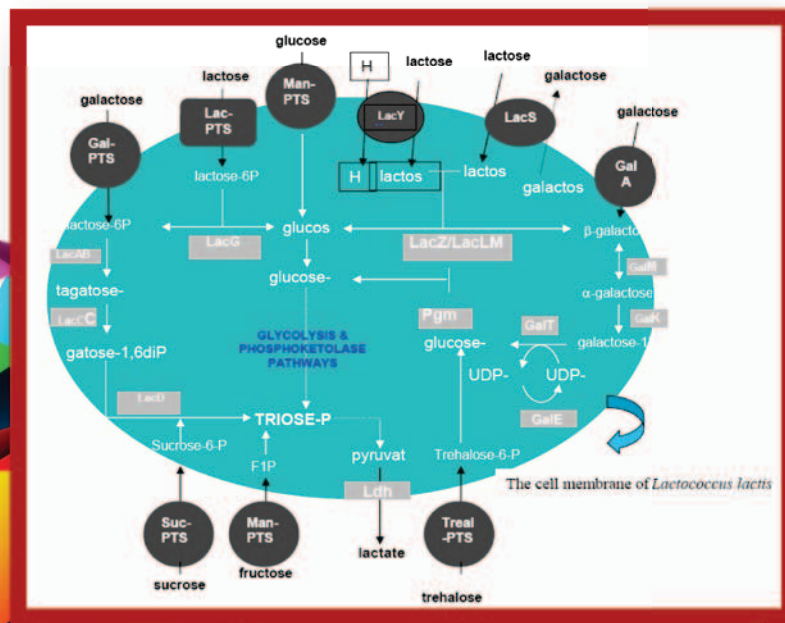


GLYCOLYSIS

*Regulation, Processes
and Diseases*



Paul N. Lithaw
Editor

BIOCHEMISTRY RESEARCH TRENDS SERIES

NOVA

Chapter II

**The Cancer-Hypoxia/Decreased
Respiration-Glycolysis Connection:
New Insights from Nobel Prize-winner,
Otto Warburg, MD, PhD**

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Abstract

Everyone of true conscience must admit that over the last 30 years insufficient progress has been made in the “war to cure cancer.” Otto Warburg, M.D., Ph.D., showed decades ago that development of cancer had a singular, prime cause. Each and every time cells (and tissues) were deprived of oxygen for a sufficient period of time, cancer developed. Furthermore, he clearly showed that the distinguishing feature of all cancer cells is the increase of anaerobic glycolysis and concurrent decrease of respiration—not merely excessive cell divisions. The significant increase in glycolysis observed in tumors has been verified today, yet few oncologists or cancer researchers understand the full scope of Warburg’s work and its great importance. Without the use of Warburg’s seminal discovery, cancer can never be truly cured—merely treated—although ineffectively, because when cancer returns from “remission,” as is often the case, the patient has a high probability of death; treatments are ineffective. Extensive references to Warburg’s original research are given.

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Introduction

Any intelligent fool can make things bigger and more complex. It takes a lot of genius and a lot of courage to move in the opposite direction.

—Albert Einstein, 1879-1955

This paper is about the incredible discovery of Nobel Prize-winner Otto Warburg, M.D., Ph.D., regarding cancer's *prime* cause—chronic systemic, cellular hypoxia (lack of oxygen), and cancer's *prime* characteristic—the ratio of respiration to fermentation (anaerobic glycolysis).

It is important to understand that Dr. Warburg always used actual *real-life* results as the basis of any scientific theory or explanation, *allowing the theory to fit the facts*. Unfortunately, this rarely happens with today's cancer researchers. They have it backwards—attempting to force the facts to fit their genetically based theories when their misguided theories do not fit the facts.

Significant glycolytic activity is a fundamental property of any tumor cell. Few oncologists today are familiar with Dr. Warburg's seminal work in this area; not surprisingly, progress both in preventing cancer and making significant improvements in treating the disease are lacking. Given the trillions of dollars spent on cancer research over the last 4 decades, there has been surprisingly little accomplishment compared to the great strides made, for comparable dollars spent, in other fields such as microelectronics and medical imaging technology.

Without understanding cancer's direct relationship with anaerobic glycolysis, I fear oncological treatments will continue to fall short of maximum effectiveness.

I am choosing to extensively reference Warburg's seminal work, specifically "The Metabolism of Tumours: Investigations from the Kaiser Wilhelm Institute for Biology"[1].

Glycolysis and Respiration

Throughout this paper we will use the term "glycolysis" to mean anaerobic (without oxygen) glycolysis with the end product of lactic acid. In humans, energy can be gleaned in two ways: through glycolysis or through cellular respiration. Glycolysis is the first step of each, although glycolysis does not require oxygen in any step of its chemical reactions.

When sufficient cellular oxygen is both plentiful and can be utilized, glucose is oxidized to pyruvate, which then enters the Krebs cycle. With insufficient cellular oxygen, the dominant glycolytic product is lactate. This latter process is known as anaerobic glycolysis.

Energy generation from stearic acid, the most commonly found fatty acid in triglycerides in the human body, can only occur in the mitochondria[2]. However, mitochondria can also beta-oxidize fatty acid molecules to form 2-carbon segments of acetyl-coenzyme A (acetyl-CoA) molecules, and the entire fatty acid molecule is broken down in this fashion. From each acetyl-CoA molecule split from a fatty acid, a total of 4 hydrogen atoms are released, and

these are ultimately oxidized in the mitochondria to form large amounts of ATP—146 molecules from each molecule of stearic acid. This chapter will *not* focus on this pathway; cancer cares little about it.

Glycolysis occurs in the cytoplasm of the cell, not in a specialized organelle, such as the mitochondrion, and is the *one common metabolic pathway found in all living things*. Glycolysis is simply the splitting of glucose into 2 molecules of pyruvic acid; it then proceeds via fermentation to produce 2 net molecules of ATP, along with waste products. There are many types of fermentation but we will only concern ourselves with lactic acid fermentation because this is applicable to humans and cancer metabolism.

Cellular respiration (with oxygen) does not produce lactic acid; the pyruvate is completely broken down to CO₂ and H₂O, with vastly more energy cogeneration than glycolysis. Three molecules of O₂ are required for each molecule of pyruvic acid, and the end of cellular respiration produces a net 36 molecules of ATP per molecule of glucose after processing in the Krebs cycle and the electron transport chain. Cellular respiration may also be termed *aerobic* glycolysis.

In 1910, Dr. Warburg published the following: (1) “The *most important and completely unexpected result* of the present investigation is the proof that the plasma-membrane *as such and not because substances pass in or out* through it, plays an *important role* in the oxidative metabolism of the cell. (2) In section II this was *proved unquestionably*” (emphasis added).¹

Dr. Warburg’s discovery shows that it is the cell membrane itself that is key to proper physiologic functioning. Each of us has approximately 100 trillion cells, each containing a (bi)lipid membrane. As Dr. Warburg states, this important result—the membrane itself—was “completely unexpected.”

Dr. Warburg proved decades ago in Germany, and it was confirmed by researchers in the United States, that when hypoxia—systemic oxygen deprivation—with 35% less cellular oxygen transfer occurs for a sufficient amount of time, cancer results.

Who Was Nobel Prize Winner Otto Warburg?

Dr. Warburg earned his doctorate in chemistry at the Berlin University in 1906 after initially studying under the great chemist, Emil Fisher. Warburg then studied medicine and earned his Doctor of Medicine at Heidelberg University in 1911.

How Significant is Otto Warburg?

We may gather some idea of the importance of Dr. Warburg’s work by what his colleagues said of him. In 1931, Dr. Warburg was awarded the Nobel Prize in “Physiology or Medicine.” Professor E. Hammarsten of the Royal Caroline Institute, a member of the Nobel Committee, said this to Dr. Warburg in his presentation speech: “Your bold ideas, but above

¹ Although this experiment was performed with developing sea-urchin eggs and the “plasma-membrane” likely referred to what is termed the “fertilization-membrane,” the insight is extraordinary.

all, your keen intelligence and *rare perfection in the art of exact measurement* have won for you exceptional successes, and *for the science of biology some of its most valuable material.*” In 1966, Dean Burk at the American National Cancer Institute said of Otto Warburg: “His main interests are Chemistry and *Physics of Life*. *In both fields no scientist has been more successful.*”

Chronology of Tumor and Cancer Discoveries

- The metabolism of tumors (1923-1925)
- The chemical constituent of the oxygen transferring respiratory ferment
- Origin of cancer cells (1956)
- Production of cancer metabolism in normal cells grown in tissue culture (1957-1968)
- Facultative anaerobiosis of cancer cells (1962-1965)
- Prime cause and prevention of cancer (1966-1969).

Dr. Warburg was one of the first cancer researchers. His insights and discoveries were incredible. Uniquely, despite his early successes and honors, Dr. Warburg continued to make major fundamental discoveries throughout his later years as well, capping off an amazingly fruitful 60-year career in research.

What Is Cancer?

While discussing the evils of cancer with a colleague, I realized how to simply explain what cancer really is. First let me state what it is *not*. It is *not an invader* in our bodies like a viral or bacterial infection. It is *not a genetic distortion* determined to kill us. It is *not an evil genius malcontent* buried deep within us waiting to strike its unsuspecting host. Cancer is none of these things.

Cancer is the body, at the cellular level, attempting to survive by reverting to a primitive survival mechanism. Surprisingly, it's that simple.

Hypoxia = Cancer

Over 80 years ago, Dr. Warburg proved that a 35% reduction in oxygen caused any cell to either die or turn cancerous. An amazing experiment by the Americans Goldblatt and Cameron in 1953 further confirmed this cancer/hypoxia connection[3], which was described by Warburg thus: “...[Goldblatt, an M.D. and Cameron] exposed heart fibroblasts in tissue culture to intermittent oxygen deficiency for long periods and finally obtained transplantable cancer cells. In the control cultures that they maintained without any oxygen deficiency, no cancer cells resulted”[4].

This experiment was conducted over a 2½-year time frame. The results were meticulously tabulated, and the conclusions rock solid. Dr. Warburg's work was extensively referenced in these scientists' paper, since his findings were very well known at that time.

Significantly, Goldblatt and Cameron also verified Dr. Warburg's finding (published in 1925)[5] *that a "respiration-impacted," destined-to-become cancerous cell could be stopped if it was oxygenated early enough.* In Goldblatt and Cameron's paper (p.527), it was reported:

...The length and frequency of exposure of the different [normal] cultures to nitrogen [cutting off oxygen] were varied greatly at first, in order to determine the periods that would prove *definitely injurious* in greater or less degree, but from which most of the *cultures recovered readily after the return to aerobic* [oxygenated] *conditions* were 15 minutes of nitrogen twice in 24 hours, for 3 successive days with an interval of 11¼ hours between successive exposures.

It was found that even after exposure to nitrogen for ½ hour, 3 times in every 24 hours, for 7 consecutive days, with an interval of 7½ hours between successive exposures, recovery could still occur, although the injury was great; *but recovery was slower and less certain* after such long periods of anaerobiosis [oxygen deprivation]; and *some of the cultures did not recover.* (Emphasis added.)

The authors also noted that once damage was too great to the cell, then no amount of oxygen would return the cell's respiration back to normal—it was forever doomed to a cancerous life.

In 1955, two other American scientists and physicians, Malmgren and Flanigan, again confirmed these findings, publishing them in the medical journal, *Cancer Research*[6]. An especially clever and convincing experiment added to the long list of experiments clearly demonstrating that *oxygen deficiency is always present when cancer develops.* These physicians referenced Dr. Warburg's work on p. 478 of their publication.

Dr. Warburg analogized Malmgren and Flanigan's results with the development of cancer cells in his *Prime Cause and Prevention of Cancer* lecture[7]:

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 [low oxygen] of cancer cells and the non-anaerobiosis [normal oxygen] of normal cells,* in particular the non-anaerobiosis of growing embryos.

Note: Rats and mice have much shorter lives than humans, so results, both good and bad, occur much faster, making them very useful in medical experiments.

We will focus more on the extensive use of physiology than of biochemistry in the cancer/glycolysis analysis.

The Metabolism of Cancer Cells

Dr. Warburg's ground-breaking paper, titled "The Metabolism of Carcinoma Cells," was published in the United States in *The Journal of Cancer Research* in 1925[5]. The paper was delivered as an address to the Rockefeller Institute in 1924, and much of this information had already been published in Germany in 1923.

Here are some of Dr. Warburg's glycolytic cancer findings that all oncologists and cancer researchers should be aware of: "...The result was *not* what we had anticipated ... *glucose brought the respiration to a standstill...*" Here it should be noted that cancerous tumors prefer sugar above all other metabolic fuels, and sugar stopped normal respiration. This effect does not occur in normal cells. Further, Warburg said, "In general it has been found that only tissue with unimpaired glycolytic activity is an integral property of the tumor cell. The conclusion drawn from this is that *glycolytic activity is an integral property of the tumor cell.*" Here, Dr. Warburg defined the fundamental property of any cancer tumor: its respiration is highly compromised. Finally, Warburg noted, "...The ratio splitting metabolism-oxidation metabolism for benign tumors is, however, displaced a long way in the direction of the oxidative metabolism. Malignant tumors produce three to four times more lactic acid per molecule of oxygen consumed than do benign tumors."

Here we are given tremendous insight into the difference between benign and cancerous tumors, and a key analytical tool to easily measuring the degree of malignancy.

Otto Warburg's Research

Dr. Warburg didn't play language games or use weasel words in reporting his results. He stated his findings definitively, based on extremely thorough and meticulous experimentation. Because he rarely used qualifying words to describe his findings, his anticancer discoveries and results offer sharp, definitive conclusions. He spent almost 60 years investigating cancer and he repeated experiments as many as 100 times before publishing. He did not draw conclusions lightly and he did not publish them until he was sure—which is why he was able to state them in definite terms. In contrast to the irresponsible tone so prevalent today, Dr. Warburg always held himself accountable for what he published. With Warburg's work, there was no need for the ubiquitous "new research shows..." that the old research was wrong and in need of correction. That is also why virtually *nothing he published was ever shown to be wrong later*—it was not just that he was sure, but that his conclusions were based upon unassailable science consistently repeated around the world.

As mentioned earlier, Professor E. Hammarsten of the Nobel Committee, in presenting Dr. Warburg with his Nobel Prize in 1931, made reference to Dr. Warburg's "...*rare perfection in the art of exact measurement...*" People may not have always agreed with his findings, but if they disagreed, they had no methodological basis for their disagreement.

Dr. Warburg even warned us decades ago that the cause of cancer would not be found in genetics—that research in this area would waste precious time and allow many more needless cancer mortalities..

Cancer is not Genetic

In his 1998 book, *“One Renegade Cell: How Cancer Begins,”* author Dr. Weinberg presents an excellent summary, much of it quite technical, of the previous few decades of “advancement” in the fight against cancer[8]. The author is a professor of biology at MIT and former director of the Oncology Research Laboratory at the Whitehead Institute in Cambridge, Massachusetts.

The problem with modern cancer researchers’ utter failure to find the *prime* cause of cancer or a valid means of preventing either the initial inception of the disease or a recurrence after remission has been their gradual shift from concentration on practical research to exploring academic and theoretical questions. Many of today’s cancer researchers seem to live in a dream world where pet theories may be explored for years without leading to any real solutions to disease. Regarding the huge effort to explain cancer with genetics, Dr. Weinberg stated, “...Something was very wrong. The notion that a cancer developed through the successive activation of a series of oncogenes had lost its link to reality”[8].

Dr. Weinberg exposes and details failure after failure of cancer researchers to find cancer’s cause or cure. More to the point, Dr. Weinberg states on page 67 that *cancer-causing “genes” are recessive—not dominant as everyone assumed!* On page 90 he reveals that “[F]ewer than one DNA base in a million appears to have been miscopied.” Thus, the prime cause of cancer is *not* a genetic mutation. On page 95, Dr. Weinberg shares his opinion that the genetic discoveries made thus far are “sterile”—the prime cause of cancer is not “genetic.”

On page 153, in the section, “Conquering Cancer by Preventing It,” Dr. Weinberg states “We must *address the ultimate roots of cancer* before we make substantial reductions in cancer incidence. *Genes and proteins will help us little here.*” How much clearer can Dr. Weinberg make it that cancer is not genetically based?

Weinberg clearly makes the point that all the modern research roads over the past 30 years geared toward finding the cause of cancer have led nowhere.

The Genetic Fallacy is Exposed Again—Internationally

The following article was published internationally via the excellent Internet publication *Medical News Today*, in an article titled “Cancer Comes Full Circle”[9], which refers to an article published in *Nature*[10]:

‘This study demonstrates how structure and function in a tissue are intimately related, and how loss of structure could itself lead to cancer,’ says Mina Bissell, who pioneered the view that *a cell’s environment is as important as its genes* in determining the formation and progression of tumors.

...But a number of investigators, including Bissell and her colleagues, have shown that the genetic alterations of oncogenes are not, as once believed, sufficient in themselves to cause cancer. Even activated oncogenes require changes in the tissue structure to produce cancer. (Emphasis added.)

Herein lies the cry to look elsewhere than genetics for the roots of cancer, and we reiterate that Dr. Warburg has already given us that key: glycolysis. Once again, a cry to look at the tissue structure is made. Tissue physiology can show us that glycolysis rather than respiration dominates in cancer.

Confirmation that Cancer Increases with Lack of Oxygen

An article in the cancer medical journal, *Radiotherapy and Oncology*, makes Dr. Warburg's #1 fact clear[11]:

After a median follow-up of 19 months (range 5-31 months), Kaplan-Meier-life table analysis showed *significantly lower survival and recurrence-free survival* for patients with a median pO₂ of ≤ 10 mm Hg *compared to those with better oxygenated tumors* (median pO₂ > 10 mmHg).

The Cox proportional hazards model revealed that the *median pO₂* and the clinical stage according to the FIGO are *independent, highly significant predictors of survival and recurrence-free survival*.

We conclude from these preliminary results that *tumor oxygenation* as determined with this standardized procedure appears to be a new independent prognostic factor influencing survival in advanced cancer of the uterine cervix. (Emphasis added.)

Benign versus Cancerous Tumors

What differentiates a cancerous tumor from a non-cancerous (benign) tumor? The cells of both tumors demonstrate essentially the same “mindlessness”—lost cellular intelligence. It's all a matter of degree of respiration impairment. Dr. Warburg had already verified and published this fact in 1925 in *The Journal of Cancer Research*[5]. Dr. Warburg's paper makes it quite clear:

Thus the quantitative difference between malignant and benign tumors becomes a qualitative one, when we pass from benign tumors to normal growth. The respiration of normally growing tissues suffices to bring about the disappearance of the glycolysis-products, whereas in tumors the *respiration is too small for this. This, then, is the difference between ordered and disordered growth*.

...From the embryonal type of metabolism there has again arisen the tumor type—benign or malignant, *depending on the duration of the oxygen deficit*.

In this manner [adding higher degrees of cyanide to curtail respiration] we obtain from the embryonic type of metabolism the tumor type—the benign tumor type when the concentration of cyanide is low [less impacted respiration]; the malignant type, when it is high [highly impacted cellular respiration].... [T]here has again arisen the tumor type—benign or malignant, depending upon the duration of the oxygen deficit.

Dr. Warburg's genius was unprecedented in making these seminal discoveries regarding the metabolism of cancer.

Dr. Warburg clarifies this in his own words:

The most important fact in this field is that *there is no physical or chemical agent with which the fermentation of cells in the body can be increased directly*; for increasing fermentation, a long time and many cell divisions are always necessary. The *mysterious latency period* of the production of cancer is, therefore, nothing more than the time in which the *fermentation increases after a damaging of the respiration*. This time differs in various animals; *it is especially long in man and here often amounts to several decades*, as can be determined in the cases in which the time of the respiratory damage is known—for example, in arsenic cancer and irradiation cancer. (Emphasis added.)

Warburg makes the startling statement that you cannot make a cell increase its fermenting capability unless lack of oxygen is at the root of the process.

Another landmark Warburg paper titled, "The Metabolism of Tumors in the Body,"[12] published by The Rockefeller Institute for Medical Research in New York in 1928, provides additional insight by stating *all tumors so far tested behave fundamentally alike*. Although this statement was already published in the *Journal of Cancer Research* paper three years before in 1925, it is worthy of repeating this important fact. Further, the authors state, "The tumor cell is more versatile than the normal cell as far as the obtaining of energy is concerned. *It can choose between fermentation and respiration*, while the normal cell is confined to respiration." This makes cancer cells much harder to kill than normal cells, and explains why prevention is so important, so that cancer never has a chance to start to develop.

A top biochemistry textbook in use in 1979 at MIT, where I matriculated, discussed the decreased aerobic (respiration)/increased anaerobic (glycolysis) relationship found with cancer cells[13]. On page 849 it states, "The rate of oxygen consumption of cancer cells is somewhat below the values given by normal cells. However, *malignant cells tend to utilize anywhere from 5 to 10 times as much glucose as normal tissues and convert most of it into lactate....*" Note that more glucose is required because of the lack of oxygen utilization for energy.

Lactic Acid Burn: A "Do-It-Yourself" Test

If you have ever worked out with weights, then you have likely already experienced "lactic acid burn." It is a burning sensation that comes from lactic acid buildup in your muscles, produced when they *ferment glucose for energy*—much in the same way that a cancer cell does. "Lactic acid burn" becomes a *problem of the past* when cellular oxygenation is increased.

Do lactic acid levels really increase in the blood if you have cancer? Yes. This fact was published back in 1925 by Dr. Warburg in his cancer journal article[5]. Current researchers also confirm the increase in lactic acid.

In investigating the relationship between lactate levels and human cervical cancer, Walenta et al.[14] found that the *metastatic spread* of uterine cervix carcinomas and neck cancers were closely correlated with lactate concentration in the primary lesion. However, the authors also noted that lactate concentrations were *significantly higher* ($p = .001$) in tumors *that had spread metastatically* (mean \pm SD, 10.0 ± 2.9 micromol/g; $n = 20$) compared to malignancies in patients in which metastases *did not occur* (6.3 ± 2.8 micromole/g; $n = 14$). Furthermore, the survival probabilities of patients that had low tumor lactate values were *significantly higher* compared to patients with high tumor lactate concentrations. The authors concluded, “Tumor lactate content may be used as a prognostic parameter in the clinic. Furthermore, these findings are in accordance with data from the literature showing the *presence of hypoxia in cervical tumors is associated with a poorer survival rate.*” (Emphasis added.)

In discussing aerobic glycolysis, Lu et al.[15] note that all cancer cells display *high rates of aerobic glycolysis*, a phenomenon historically known as the Warburg effect, but add “the relevance of the Warburg effect to cancer cell biology has remained obscure.” In their study, they discovered that the ability of *glucose to stimulate* HIF-1 (hypoxia-inducible Factor 1), a factor which *increased with lack of oxygen in cancer*, increased in parallel with the growth of the cancer, tumor development, tumor angiogenesis, and poor prognosis. Moreover, this effect could not be mimicked by using the glucose analog, 2-deoxyglucose, suggesting that *the metabolism of glucose was required for this effect to occur.*

This 2002 cancer study makes it clear that Dr. Warburg is still known—*cancer’s high glycolysis is termed the “Warburg effect”—but cancer researchers still have no idea how to make use of his discovery practically*, as evidenced by the second point above. These researchers found that HIF-1 responds directly to low oxygen, and is *stimulated* by glucose. In 2002, the Department of Biochemistry and Molecular Biophysics at the University of Arizona stated that the “aerobic glycolysis phenotype,” first described by Otto Warburg in 1924, might be central to the process of carcinogenesis itself.

Schwickert et al.[16] also stated the same result: the higher the lactic acid the greater the spreading of the cancer. An Italian study[17] once again stated the same result, with those patients having *higher lactic acid levels also having the highest rates of cancer recurrence after treatment.* Druml et al.[18] also discussed how the *increased lactic acid comes from the leukemic cells themselves* and no other cause or other source. The fact that cancer causes an increase in lactic acid is well known.

Researchers from the Harvard Medical School and Massachusetts General Hospital’s Department of Radiation Oncology also showed that low pH always comes from lactic acid as well as other by-products[19]. Their research confirms the above results.

I want to make this confirmation quite clear, so there is no misinterpretation. *Increased lactic acid output from cancer cells can always be used as a cancer marker.*

The bottom line is to keep cellular oxygenation levels high. In this fashion, as Dr. Warburg so clearly discovered, cancer can never start. Lactic acid levels naturally remain low when you are cancer-free and rise consistently, depending on how aggressive the cancer becomes. Although lactic acid levels increase primarily in the tumor tissue itself, lactic acid levels rise in the blood, too—and it is easy to have it measured.

Is Anaerobic Glycolysis (Running on Sugar) Really Significant for a Cancerous Cell?

Yes, it is. There is a drastic difference between cancerous and non-cancerous cells, and this difference is the greatest such difference. Dr. Warburg stated on p.151 of *The Metabolism of Tumours*:

Blood forms per hour a quantity of lactic acid equivalent to 0.1% of its dry weight, as compared with 12.4% formed by the tumour. The glycolytic action of the carcinoma tissue is *124 times greater* than the glycolytic action of *blood*.... Hence, carcinoma tissue forms *200 times as much lactic acid* as a resting frog's muscle and *8 times as much* lactic acid as a working frog's muscle working at maximum normal capacity[1]. (Emphasis added.)

As you can see, there is a significantly more lactic acid formation from cancerous tissue. Even muscle, which uses sugar as its prime fuel under intense physical exertion, *still produces a significant eight times less lactic acid than cancerous tissue*.

Furthermore, it is an easy experiment to show that all animal cells can run without oxygen to a certain extent (although not efficiently). However, with oxygen, most animal cells do not use glycolysis, as Warburg states on p. 60:

The first case occurs when we are working under anaerobic conditions. Any animal cells serve as experimental material, since all animal cells glycolyse [utilize significant sugar as prime metabolic fuel] under anaerobic conditions.... The second case arises when we are working under aerobic conditions with cells which do not glycolyse aerobically. This is the case with most normal animal tissues.

Louis Pasteur was the father of the field of stereochemistry, the “pasteurization” process, the “germ theory” (explaining the cause of most infectious disease)—one of the most important discoveries in medical science—a pioneer in the treatment of rabies, and founder of a revolution in verifiable science by demanding, “*Do not put forward anything that you cannot prove by experimentation.*” His work became the foundation for the science of microbiology and a cornerstone of modern medicine. *He understood the connection between cancer and —lack of respiration— and it was well known in 1861.* Dr. Warburg[20] described the significance of one of Pasteur's discoveries[21]:

As is well known, Pasteur found that respiration ‘inhibits’ fermentation. If he placed cells, which fermented under anaerobic conditions, in oxygen, the respiration, which now began caused either the diminution or the disappearance of the fermentation. Respiration and fermentation are thus connected by a chemical reaction I call the ‘Pasteur reaction’ after its discoverer.

It is not so much the inhibition of fermentation itself, which is characteristic of the Pasteur reaction, but rather the relationship between the inhibition of the fermentation and the respiration, i.e. the quotient: (anaerobic fermentation – aerobic fermentation) / respiration.

Warburg also commented that the quotient, which O. Meyerhof (another of Warburg's protégées and a Nobel Prize-winner) was the first to determine in the case for muscle, was purely an experimental quantity—i.e., it was based on real-life results—and independent of any theory. This means that there is no way to theoretically determine or guess that this result indeed occurs. *If a cancer scientist or researcher wasn't informed about this discovery, there is no way he or she would find it from other fields independently.*

Detailed Excerpts from Dr. Warburg

In this section, I provide cancer discoveries, taken from a speech Warburg gave at the 1966 Nobel-Laureates Conference in Lindau, Germany. The name of the address was “The Prime Cause and Prevention of Cancer”^[7]²:

But, even for cancer, there is only one main 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.

Comment

Normal cell respiration is replaced by energy production through the fermentation of sugar. This means that carbohydrates are utilized as cancer's prime fuel instead of proteins or fats. Cancer cells grow from the fuel of carbohydrates. When a cell cannot get the oxygen it requires, then it turns to fermentation of sugar for its energy. Next, Warburg noted:

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....

Comment

Dr. Warburg makes a very clear statement: cancer has *no* genetic basis and *no* viral basis that he could find. Nothing has changed since he made this statement over 40 years ago. But regardless of this groundbreaking insight, even today most medical institutions continue to look for the answers in the wrong areas. Thus, Warburg adds:

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

² English Edition by Dean Burk, National Cancer Institute, Bethesda, Maryland, USA.

Comment

Here, Dr. Warburg makes it perfectly clear that there is *no* cancer cell whose cell respiration is intact; therefore, cancer should be preventable if cellular respiration can be kept intact.

It is important to note that these facts regarding cell respiration are fundamental and apply to *all* cancer cells. Dr. Warburg states that *no cancer cell exists that has fully intact oxygen respiration. All cancer cells share this unique characteristic:*

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*.

Comment

Once sufficient oxygen-deficiency damage is done to a cell, it *cannot ever be repaired*. There is a “point of no return.” Therefore, Dr. Warburg’s amazing finding implies that *cancer prevention is the key*. Damaged cells only become cancerous because they have fermentation to turn to instead of dying. Then, they live and multiply, spreading the cancer. Warburg adds:

All normal cells meet their energy needs by the *respiration of oxygen*, whereas *cancer cells* meet their energy needs in great part by *fermentation*. From the standpoint of chemistry and physics 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 forms*, namely a *fermentation of glucose*.

Comment

Cancer cells are so different from normal cells that a greater difference cannot be imagined. Oxygen gas is relegated to a lower importance in cancer cells. Cancer cells thrive on sugar—the fuel of fermentation. Thus, Warburg says:

Cancer cells can actually grow in the body almost with only the energy of fermentation.

In the mouse, if 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 in 48 hours in the course of two cell divisions*.

Comment

Researchers must be wary of animal studies; however, in this case a direct human analogy is appropriate. Dr. Warburg’s amazing experiments showed how quickly cells could

enter the highway to cancer (although it takes them a long time to become fully cancerous *in the human body*—often *several decades* compared to “test tube” experiments conducted outside the body [i.e., *in vitro*]). Although this occurred in a mouse, the analogy with humans is correct—human cancer cells require little energy to live and oxygen-deprived cells replicate quickly. On irreversibility, Warburg noted:

If one increases to the original high oxygen pressure, and allows the cell to grow further, the cancer metabolism *remains*, it’s an irreversible process.

Comment

It is of paramount importance to understand that cancer is an *irreversible transformation*. At all costs it must be prevented. Once you have a cancer cell, there is no returning it back to normal. It is impossible. That’s why it is termed irreversible. On the cause of transformation, Warburg said:

We find by experiment about *35% inhibition of oxygen respiration* already suffices to bring about such a transformation during cell growth.

Comment

Only about *one-third less* oxygen transfer to a cell causes *irreversible cancer cells to form*. For maximum anti-cancer support, we need to fully oxygenate our cells, so possible glycolytic action potential never fully occurs. Dr. Warburg makes this clear. This is the cellular analogy of being choked to death:

In any case, during the *cancer development the oxygen-respiration always falls, fermentation appears*, and the highly differentiated cells are transformed to fermenting aerobes, which have lost all their body functions and retain only the now useless property of growth.... The meaning of life disappears.

Comment

Cancer *always* shows itself by non-availability of oxygen. A cancer cell lacks intelligence; it is a useless, “mindless, growing machine.” On the chemistry, Warburg noted:

The end-products of fermentation [the metabolic process associated with cancer] are reached by one single reaction. On the other hand, the end-products of the oxidation of pyruvic acid [the metabolic process of normal, healthy cells] are only reached after many additional reactions. Therefore, when cells are harmed, it is probable that first respiration is harmed.

Comment

Normal cell respiration is significantly more biochemically complicated than simple fermentation of sugar. Cancer cells prefer the easier fermentation route to live, in part, because there is no “intelligence” left in these cells to direct a complicated oxygen-breathing mechanism. The cancerous cell loses its ability to function in a normal, healthy way, because it has become dumb. Dr. Warburg points out that it is likely that the first harm to the cell that occurs is likely to be the harm to its respiration.

Dr. Warburg spoke eloquently at the German Central Committee for Cancer Control[4]³:

What was formerly only qualitative now becomes quantitative. What was formerly only probable has now become certain. The era in which the fermentation of the cancer cells or its importance could be disputed is over, and no one today can doubt that we understand the origin of cancer cells if we know how their large fermentation originates, or, to express it more fully, if we know how the damaged respiration and the excessive fermentation of the cancer cells originate.

Why Wasn't this Information Known Earlier?

Dr. Warburg continued:

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 of the National Cancer Institute at Bethesda (USA) 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 in the years 1927 to 1966. Anaerobiosis of cancer cells was an established fact only since 1960 when methods were developed to measure the oxygen pressure inside of tumors in the living body.

At first, one would think that it is immaterial to the cells whether they obtain their energy from respiration or from fermentation, since the energy of both reactions is transformed into the energy of adenosine triphosphate, and yet adenosine triphosphate = adenosine triphosphate. This equation is certainly correct chemically and energetically, but it is *incorrect morphologically*, because, although *respiration takes place for the most part in the structure of the grana [mitochondria], the fermentation enzymes are found for a greater part in the fluid protoplasm*. The adenosine triphosphate synthesized *by respiration therefore involves more [cell] structure* than the adenosine triphosphate

³ Otto Warburg was director of the Max Planck Institute for Cell Physiology, Berlin-Dahlem, Germany. This article is based on a lecture delivered at Stuttgart on May 25, 1955 before the German Central Committees for Cancer Control. Translation by Dean Burk, Jehu Hunter, and WH Everhardy at the National Institutes of Health (USA).

synthesized by fermentation. 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 diffused light and in the other with 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. Just as the one type of light energy involves more structure than the other type, *the adenosine triphosphate energy involves more structure when it is formed by respiration than it does when it is formed by fermentation.*

Comment

In other words, normal cell respiration takes place in the presence of a more differentiated cell structure; a cancer cell's fermentation involves less structure. Warburg continued:

Moreover, *it was known for a long time* before the advent of crystallized fermentation enzymes and oxidative phosphorylation that *fermentation—the energy-supplying reaction of the lower organisms—is morphologically inferior to respiration. Not even yeast, which is one of the lowest forms of life, can maintain its structure permanently by fermentation alone; it degenerates to bizarre forms.* However, as Pasteur showed, it is rejuvenated in a wonderful manner, if it comes in contact with oxygen for a short time. “I should not be surprised,” Pasteur said in 1876 in the description of these experiments, “if there should arise in the mind of an attentive hearer a presentiment about the causes of those great mysteries of life which we conceal under the words youth and age of cells.” *Today, after 80 years, the explanation is as follows: the firmer connection of respiration with structure and the looser connection of fermentation with structure.*

This, therefore, is the physicochemical explanation of the de-differentiation 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.

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 de-differentiation 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.”*

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.*

Physics cannot explain why the two kinds of energy [glycolysis vs. respiration] are not equivalent in differentiation; but chemistry may explain it. Biochemists know that the results of both respiration and fermentation are stored in ATP; indeed, the basic mechanism of ATP creation is the same, but the reactions used to generate ATP

molecules are *quite 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.... The *pathways* of respiration and fermentation *are common as far as pyruvic acid*. Then the pathways diverge. The endproducts of fermentation [are] reached by one single reaction, the reduction of pyruvic acid by dihydronicotinamide to lactic acid. On the other hand, the endproducts of the oxidation of pyruvic acid, H₂O and CO₂, 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.

Conclusion: How Cancer Occurs and How to Stop Cellular Respiration Reverting to Glycolysis

Heart attacks can stem from lack of oxygen. As Warburg discovered, so does cancer. Most normal, healthy cells get most of their energy by using oxygen in a process called “respiration.” This can be contrasted with the way cells utilize energy *without* sufficient oxygen, called “fermentation,” or glycolysis. Fermentation of sugar provides a way for cells to keep going energetically even in the presence of partial oxygen deprivation. In the presence of oxygen deficiency, cells that cannot obtain enough energy through fermentation perish. But the cells that succeed in utilizing fermentation exhibit their innate will to survive; these are the ones that do not die from the oxygen deficiency.

As directed by nature, in using this alternative source of energy, our cells are fulfilling their primary mission, which is to stay alive and reproduce. This takes place on all levels for all living things, and in the case of oxygen deficiency, cells are struggling to survive in a hostile environment of humans’ own making. That’s right; we unknowingly have forced our own cells to become cancerous.

After it begins, the disease worsens, since most humans hosting it never feel the cancer growing and so we do not take corrective measures. Once it shows up in lab tests, you have been hosting the cancer cells for years.

Nature has given every cell the potential to survive without oxygen, through fermentation. If that potential is not developed enough, then the cell will die when the oxygen drops below the 35% threshold. If none of our cells could run without oxygen, they would die immediately with no possible chance of future survival. Chronic deficiency of oxygen damages the mitochondria (energy producers) of the cell, so the cell, if it can, reverts to the ancient energy source of fermentation of sugar. A cancer cell running on fermentation can stay alive (without growing) with just 20% of a normal cell’s energy.

But one major problem is that this method is very inefficient. The cells that *can run on fermentation without oxygen* stay alive and become more prevalent as the other cells die. But there is a huge price to be paid: lack of cellular intelligence. Regarding cancer, anaerobic glycolysis leads to life but not to intelligence, and over time, if not stopped so that cellular respiration dominates, often death.

Can cellular oxygenation levels stay high so glycolysis never occurs? Yes. With today's science it is known how to guarantee maximum cellular oxygenation. This is the subject of a future paper.

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