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## WHAT IS CANCER?

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*Cancer is said to have countless causes—a genetic cause, a cause linked to abnormal protein production, an environmental cause, and a host of other factors. In view of the fact that unlike other medical conditions such as heart disease, diabetes, stroke and others in which the death rates in the last 50 years have plummeted—as much as 70 percent—the death rate of cancer in the last half century has remained unchanged. This is in all likelihood due to our misleading conception of what cancer is. The present paper defines cancer—for the first time—as a **normal body process** which serves as a “protective” device to the body but which, when called upon by the body to a greater extent than possible, becomes the body’s nemesis, ushering in the disease we know as cancer. While it is conceded that there are many changes associated with malignant change—genetic, mutational DNA and abnormal protein and dozens of other “components”—this paper proposes that the primary cause of cancer is not any of these changes, but energetics: that malignant change is a function primarily of energy metabolism.*

*Abstract.* In 1931 Otto Warburg received the Nobel Prize for his demonstration that cancer cells utilize a process known as glycolysis as their chief means of energy production, rather than the more energy-efficient oxidative respiration, as in normal cells. The author later demonstrated that glycolysis acted in a two-fold manner in cancer: as a source of energy production for the tumor, as proposed by Warburg, *and* as a pacemaker for cancer cachexia—the weight loss and bodily debilitation causally associated with more than two-thirds of all cancer deaths. The present paper proposes that glycolysis serves a much more vital and deep-seated process to the overall integrity—and, paradoxically, downfall—of the body. In the present paper the author proposes that cancer is a *normal body process*, invoked as a temporary adjustment by the body to offset

the development of oxidative stress—resulting from the oxygen environment and our oxygen-based metabolism—and its destructive effects on tissue health, aging (senescence) and cellular and whole-body mortality.

This normal body process acts to dissipate ambient energy (ATP), necessary to the maintenance of *oxidative stress*, through the protective action of glycolysis and involves the body's formation of “transitional” tissues, which although morphologically normal (i.e., normal in appearance under the microscope), are metabolically “cancerous,” undergoing glycolysis as their major means of energy production, but not to the extent found in cancer cells. These “transitional” tissues serve as reservoirs of glycolysis, to be activated by the body at any time and could thus ‘come and go,’ i.e., regress to normal body function or progress to morphologically recognizable cancer tissue. Thus when ATP availability is sufficiently decreased due to adequate glycolytic output, these tissues ‘regress’ to normal metabolic function.

But if ambient energy is not sufficiently lowered to offset the effects of oxidative stress, these “transitional” tissues no longer regress—their output of glycolysis is no longer “temporary”—but progress to frankly malignant tissue with *maximal glycolytic activity*. Once formed, however, malignant tissue—invasive and metastatic—takes on properties of its own and constitutes an imminent threat to life.

It is suggested that effective cancer control may lie with therapy of the metabolic shift to glycolysis in normal cells, rather than with therapy aimed exclusively at the tumor.

In 1968 I proposed that cancer cachexia was the product of a whole body energy-wasting circuit composed on the one hand of glycolysis in the ‘cancer compartment’ of the body and gluconeogenesis in the ‘normal compartment’ of the body (chiefly the liver and kidney cortex).<sup>1</sup> Specifically it was postulated that in the anaerobic breakdown of glucose to lactic acid (glycolysis) in tumors, a net 2 ATP molecules per glucose molecule were yielded to the tumor, but synthesis of glucose, via gluconeogenesis, from the resulting lactic acid (Cori cycle<sup>2</sup>)—as well as from citrate, succinate, propionate and others—required the utilization of the equivalent of 6 ATP molecules derived from *normal* host sources. Thus the equivalent of at least 14 ATP was “lost” to the body economy with each specific recycling (based on 2 equivalents of “lactate” being recycled to glucose): 2 ATP molecules *to* the cancer cell and 12 ATP molecules *from* normal host tissues. This recycling process represents under abnormal or unusual circumstances a major biosynthetic pathway capable of synthesizing up to 200 grams or more of glucose per day in the adult,<sup>3,4</sup> which exceeds total minimum daily body requirements; the only thermodynamic prerequisite for activation of this recycling process is that lactate from the glycolyzing tumor enter the blood, which multiple studies have repeatedly confirmed.<sup>4,5</sup>

It was further specified<sup>1</sup> that glycolysis and gluconeogenesis do not generally occur in the same tissues and were in general opposite—i.e., reverse—processes (metabolic pathways). However there were exceptions to this generality, the most important being the conversion of pyruvate to phosphoenolpyruvate (PEP). In glycolysis this conversion (PEP to pyruvate) proceeds directly, i.e., as a one-step process, catalyzed

by the enzyme *pyruvate kinase*. In gluconeogenesis this conversion (pyruvate to PEP) is a two-step process catalyzed by the enzymes *pyruvate carboxylase*, which converts pyruvate to oxalacetate, and *phosphoenolpyruvate carboxykinase (PEP CK)*, which converts oxalacetate to phosphoenolpyruvate (PEP). Thus it becomes possible to inhibit gluconeogenesis without inhibiting glycolysis, an important theoretical consideration, since many normal tissues (brain, red blood cells, skeletal muscle, others) depend on glycolysis for a portion of their energy supply. And since most gluconeogenic precursors enter the gluconeogenic pathway at the level of oxalacetate, inhibition of gluconeogenesis at phosphoenolpyruvate carboxykinase (PEP CK) is suggested as a means of inhibiting the energy loss sustained in the recycling process and therefore as a means of inhibiting cancer cachexia—associated with more than two-thirds of all cancer deaths<sup>6,7</sup> and termed perhaps the most devastating aspect of malignancy.

In later papers it was shown that all three body substrates—carbohydrates, protein and fats—participate in this energy-wasting metabolic circuit. Protein chiefly from peripheral muscle breakdown under the influence of cancer enters the gluconeogenic pathway as amino acids at the level of oxalacetate; and fats enter this pathway as glycerol at the level of triosephosphate. All exact significant amounts of energy from normal host sources in their recycling to glucose.<sup>8,9</sup>

Glycolysis in cancer therefore acts in a two-fold manner: as a source of energy production (growth) to the tumor *and* as a pacemaker for cachexia, i.e., as a source of lactate that initiates a progressive energy loss in the host through marked stimulation of gluconeogenesis. And while various substances, cytokines and others, have been proposed as the actual causative agents<sup>10</sup> of cancer cachexia, it should be borne in mind

that no matter what the cause, cancer cachexia must proceed via a thermodynamic process.

The important consideration is that in cancer a mechanism operates to deplete the body of ambient energy.

#### “Transitional” Cancer

In 1966 a study was published utilizing freshly obtained human colon carcinoma and measuring the differential glycolytic rates of each cellular type within the tissue without actually destroying the original intercellular relationships and architectural integrity of the tumor mass, nor subjecting this tissue to harsh physical or chemical treatment. This was accomplished by a combination metabolic, histologic and mathematical experimental approach.<sup>11</sup>

This study disclosed a spectrum of glycolytic values for various tissue and cellular elements within these solid tumors, with frank carcinoma (cancer) being the highest and corresponding to previously reported values obtained by differential experimental approaches,<sup>12,13</sup> and normal mucosa at least 5 cm. distant from the lesion being the lowest. Specifically it was found that frank carcinoma had a glycolytic rate of 23.8 – 40.6 ul lactic acid per mg. dry weight tissue per hour, whereas normal mucosa at least 5 cm. distant from the lesion had a glycolytic rate of only 4.3 – 9.0 ul lactic acid per hour. Benign polyps, whether villous or adenomatous, had values similar to those of normal mucosa; malignant polyps, villous or adenomatous containing *in situ* carcinoma, were similar to those of frank cancer.

The surprising finding of this study was that the morphologically normal-appearing mucosa immediately adjacent to the invasive cancer had a glycolytic value approaching that of frank cancer—18.75 ul lactic acid/hr—far more than that of the mucosa 5 cm. distant from the lesion. Thus, from a point of view of lactic acid elaboration (glycolysis), this microscopically normal-appearing mucosa adjacent to the lesion was metabolically almost identical to frank carcinoma, i.e., was already metabolically “cancerous.” For that reason this tissue was named “transitional” mucosa (i.e., transitional carcinoma).

The presence of “transitional carcinoma” in human colon cancer was confirmed 34 years later by a team of investigators led by Isaiah Fidler,<sup>14</sup> using different parameters of neoplastic expression than glycolysis. Freshly obtained surgical specimens of human colon cancer were analyzed by immunochemistry for Ki-67 labeling index, epidermal growth factor receptor, transforming growth factor- $\alpha$ , vascular endothelial growth factor, basic fibroblast growth factor, interleukin-8, and vascular density in morphologically normal-appearing mucosa and hyperplastic mucosa *adjacent* to the frank, cancerous lesion, as well as in normal-appearing mucosa distant from the lesion. It was found that the expression of these factors was significantly higher in the mucosa adjacent to the lesion than in the distant mucosa and was in fact similar to their expression in the tumor itself. For this reason this adjacent tissue was given the same nomenclature as in the previously referenced study with glycolysis<sup>11</sup>—“transitional” mucosa. Whether this mucosa adjacent to colon cancer represented a precursor lesion or a response to the growing cancer is unclear; however, this “transitional” mucosa produced high levels of pro-angiogenic molecules, which contribute to the angiogenesis of human colon carcinoma.

Thus, from various experimental directions it has been demonstrated that, at least in human colon tissues, it is possible that morphologically normal-appearing tissue can be expressing metabolic and other biochemical characteristics of frankly malignant tissue.

#### Temporary or Permanent?

Can these “transitional” changes in normal tissue be temporary or must they be permanent? That is, can they ‘come and go’, or are they progressive, until reaching morphological identification as frank malignancy? And—need these changes occur in tissues adjacent to malignancies or can they occur in tissues *de novo*?

Metabolic and/or physiologic changes—“adjustments”—are common within the body. Generally these “adjustments” are temporary and act to aid the body; but if these adjustments become progressive and “permanent,” they can turn markedly destructive. That is, the same devices the body calls upon that serve constructive ends, may, if allowed to progress, prove to be catastrophic.

In heat physiology, for example, as a result of exposure to high environmental heat extremes, the body calls upon—as a temporary measure—the development of a massively increased blood circulation to the skin which acts to bring needed fluid to the sweat glands, which in turn prevents or deters body heat storage by the cooling effect of evaporation of sweat; concomitantly the body develops an increased venous blood pressure, increased heart rate and increased cardiac output. But this “cooling effect” due to the massively increased skin circulation is but temporary, for if the threat of increased environmental heat energy remains undiminished—if the temporary adjustment of a massively increased skin circulation becomes permanent—the sweat glands eventually cease to function (fail) and the greatly enlarged skin circulation acts as a heat exchanger, bringing ever more *ambient* heat from the environment to the internal organs: to the brain, to the kidneys, to the liver; at the same time increasing venous blood pressure and cardiac output lead to high output cardiac failure. And suddenly the skin turns from cherry red to ashen grey, the cardiac output falls, and the body is plunged into *heat stroke*, which is very often fatal.<sup>15,16</sup> Thus physiological adjustments called upon as a temporary measure—especially those to an environmental threat—if allowed to become permanent, can bring on catastrophic consequences.

The question of temporary vs. permanent adjustment now calls attention to the finding of incidental cancers in the body. These are cancers that are found unexpectedly at post-mortems and by other means,<sup>17</sup> that have never become clinical or been diagnosed during a patient’s lifetime. These clinically silent malignancies occur with surprising frequency in the prostate gland—estimated to vary between 15 percent and 70 percent with rising population age<sup>18</sup>—but can occur in the thyroid, breast, colon, cervix and other tissues. The findings of incidental cancer, in view of morphologically normal-appearing “transitional” cancer herein described, suggest the possibility of the existence of “transitional” cancer of different tissue types within the body, both in association with frank malignancy and *de novo*, which too have remained occult or undetected. While *de novo* “transitional” tissue may be extremely difficult to detect experimentally, a hint as to its existence—and nature—may be gained by a consideration of *spontaneous regressions*.

Spontaneous regressions are the occurrence of an unanticipated complete regression within the body of a clinically identifiable malignant tumor mass to its normal

tissue of origin. Spontaneous regressions are extremely rare and their cause of regression is unknown. However, if there is a process within the body that can cause a frankly malignant tumor mass to undergo a complete regression to its normal tissue of origin, it is equally likely that a similar process may cause “transitional” cancer tissue—not yet morphologically malignant—to undergo regression from its newly acquired abnormal metabolic—i.e., “transitional”—functions to those functions associated with normal tissue of origin. In such a manner it would be at least theoretically possible for “transitional” tissue exhibiting metabolic aspects of cancer while morphologically normal—or disease entities themselves—to ‘come and go’.

In this regard it is generally known, and confirmed in many recent studies,<sup>19</sup> that during early embryonic and fetal development tissues utilize glycolysis as a major pathway of energy production, and as development proceeds this pathway is in time replaced by normal oxidative respiration. Thus early embryonic and fetal tissue exemplify the same kind of energy production as found in human “transitional” mucosa—glycolytic or cancer energy production—that can regress, i.e., proceed in the direction of “normal” energy production.

But not only can metabolically ‘abnormal’ tissues ‘lose’ their abnormalities—i.e., their aberrancies disappear—the body affords examples of entire disease entities that can be “temporary,” i.e. that ‘come and go.’ Diabetes is a classical example of this phenomenon. This disease is known to be precipitated by a number of factors, including genetic or hereditary influences, overweight, physical and psychological trauma, and many others. But this disease can also regress—disappear—totally. Examples of such regression include the diabetes of pregnancy; following the end of pregnancy this disease frequently disappears. A significant, dietary weight loss, with and without exercise, may cause this disease to fade. And for unknown reasons this disease may totally vanish.

But diabetes and the appearance of “transitional” tissues in the body have another remarkable similarity. In diabetes insulin production fails. Insulin allows glucose to get into the cells for energy production. If there is not enough insulin, glucose from the blood cannot get into the cells and instead spills out in the urine. Thus blood glucose is *lost* in the urine. That is, energy in the form of glucose is *diverted away* from the body.



Like in “transitional” tissue and frankly cancerous tissues, diabetes is acting to *rid the body of ambient energy*.

### Cancer Is a Normal Body Process

It is postulated that the diversion of energy from the body by the formation of “transitional” tissues (as well as a loss of glucose, as in diabetes), represents a metabolic *adjustment* which guards against the buildup of ambient energy (ATP) in the body; moreover, that the body makes this adjustment as a *temporary* measure, until ambient energy levels are perceived to be at “equilibrium”; at this time the “transitional” tissue returns to normal metabolic function. This process can be repeated. But if these adjustments are not temporary but are *allowed to become permanent*, the “transitional” tissue does not recede but goes on to become frankly, morphologically cancerous—invasive and metastatic—leading to organ dysfunction and the mortality of organ failure. While at the same time host energy loss due to increasing glycolysis and lactic acid production from functionally glycolytic (“transitional”) tissues and the recycling of peripheral protein breakdown products and other intermediates via gluconeogenesis becomes massive, leading to cachexia—weight loss, bodily debilitation—associated with the majority of all cancer deaths.<sup>7</sup>

Thus, it is proposed that the primary ‘defect’ in cancer is a normal body process that the body invokes—as a temporary adjustment—which acts to dissipate ambient energy in the body, i.e., to regulate ambient energy (ATP and ATP-equivalent) levels. This “adjustment,” not only occurring in tissues *adjacent* to frankly malignant tumors but in tissues without such proximity, can ‘come and go.’ However, when this adjustment is not temporary, but becomes *permanent*, a panoply of changes takes place, resulting in the appearance of morphologically recognizable islands and masses of frankly malignant tissue—tumors—which take on properties of their own and become the full-blown disease entity which we today call cancer.

Of course, this hypothesis generates—as well as solves—certain problems. The prime question it generates is whether *de novo* “transitional” tissue can occur by itself, i.e., not in adjacency to a frankly malignant tumor mass—and then, as a one-way step, proceed and/or regress either to frank malignancy or normal tissue. The occurrence of

false positive PET scans followed by negative biopsy, in the proximity of cancer and in normal tissues,<sup>20-22</sup> presents strong evidence for this. The “false positive” indicates rapid glucose uptake (i.e., glycolysis) in the tissue under examination, but normal appearance under the microscope. While this evidence is “indirect,” it is nevertheless strongly consistent with the existence of *de novo* “transitional” tissue.

One of the ‘problems’ this hypothesis solves is the question of how the presence of a relatively small amount of malignant tissue in the body—as in some cancers<sup>23</sup>—can produce profound cancer cachexia. The answer is that the amount of “malignant” tissue is not small. There is a large component of accompanying tissue—whether “adjacent” to the lesion or not—that is in the “transitional” stage, i.e., not yet morphologically identifiable as cancer but undergoing a glycolytic—‘cancerous’—metabolism, producing copious amounts of lactic acid and stimulating host energy loss (and profound wasting) via gluconeogenesis.

The presence of “transitional” tissue can also explain another enigma—the frequency of recurrence at anastomotic sites, following a tumor resection in which the borders are declared “free” from cancer. In this instance, the borders (formerly in proximity to the resected tumor mass), although indeed “normal” in appearance under the microscope, are already metabolically malignant and serve as a forerunner to a morphologically identifiable recurrence.

More importantly, the questions must be asked: Why does the body “want” to rid itself of ambient energy? What is the *threat* of too much energy in the body? What function, if any, does enhanced glycolysis serve in the body?

#### Oxidative Stress, ATP and Telomeres

Oxidative stress is the biological stress and damage induced on living systems—enzymes, proteins, membranes, especially DNA—by *reactive oxygen species* (ROS), such as free radicals and peroxides, brought about by increased cellular oxidant output in the face of reduced ability of biological systems to detoxify these reactant molecules. These substances cause significant damage to tissues and organ systems, have been linked to many disease syndromes, including strokes, heart attacks and neurodegenerative disorders and can importantly affect the aging process and life span.

The production of ROS—oxidative stress—arises from oxidative phosphorylation, the initiating step of oxidative respiration, the metabolic pathway that efficiently produces relatively large amounts of ATP—ambient energy—for cellular needs (32 ATP per molecule of glucose metabolized). During oxidative phosphorylation, electron transfer results in a mitochondrial proton flow and the formation of reactant oxygen molecules.<sup>24</sup> Although oxidative respiration is a vital part of metabolism, ROS in the form of free radicals, peroxides and other reactive oxygen substances are elaborated. Evidence indicates that this ambient energy—ATP—may provide the energy necessary for ROS production in various living systems and be an important determinant for apoptosis (cell death).<sup>25-27</sup> Thus ambient energy levels are linked to oxidative stress and resulting tissue damage and dysfunction.

Telomeres are repeating DNA sequences located at the ends of chromosomes. With each cell division the telomeres become shorter. When the telomeres become too short, the cells stop dividing and cell death ensues. Telomeric length—shortening—is thus associated with senescence and the aging process as well as with cellular and whole-body mortality.

Oxidative stress—in the form of reactive oxygen species (ROS)—is well known to have deleterious consequences on telomeric length and therefore tissue function. Chronic oxidative stress, for example, compromises telomeric integrity and enhances the onset of senescence in human endothelial cells<sup>28</sup>; this same factor accelerates telomeric loss and contributes to senescence in both human cellular and in whole-body systems.<sup>29,30</sup>

### Oxidative Stress and Glycolysis

The phenomenon of glycolysis in cancer tissue has been identified as one of the fundamental questions of tumor biochemistry “not yet fully understood.”<sup>31</sup> It has been ascribed as the chief means of energy production in cancer cells (known as the Warburg effect<sup>13</sup>) and as part of a whole-body metabolic circuit important in the production of cancer cachexia.<sup>1,8</sup> Recent evidence, moreover, indicates glycolysis might also serve another vital body function: as a protection against cellular and systemic oxidative stress. Cells in culture expressing high glycolytic rates almost totally abolish *reactive oxygen species* (ROS) formation.<sup>31</sup> Pyruvate, an end-product of aerobic glycolysis, is an effective

scavenger of ROS.<sup>31</sup> Aerobic glycolysis in proliferating cells minimizes oxidative stress during the cell cycle when cell division occurs, preserving cell division and cell immortalization.<sup>32</sup> Enhanced glycolysis renders cells resistant to oxidative stress, modulating cellular and organism senescence with significant increases in life span.<sup>31-33</sup>

### Cancer, Senescence and Immortality

This paper presents—in particular, the body’s evolution of glycolysis and functionally glycolytic (“transitional”) tissue—essentially as a normal process which the body invokes as a protective device to offset the destructive effects of the oxygen environment in which we live.

Oxidative stress—an inevitability of our oxygen-based metabolism—exerts markedly injurious effects on tissue and organ systems, on aging and on mortality itself. In the form of *reactive oxygen species* (ROS), oxidative stress and its damaging effects extend to all tissues, particularly to the telomeres and cell division, with important consequences on senescence and life span. But oxidative stress seems to be at least partially dependent on ambient energy—ATP—to fuel ROS production. And in lessening ambient energy levels, among other mechanisms,<sup>31-33</sup> glycolysis acts to counter the availability of these cell-damaging molecules.

Glycolysis by itself, instead of making available 32 ATP per glucose molecule for general cellular needs by oxidative respiration, produces only 2. And in conjunction with gluconeogenesis—and the nearly obligatory recycling of tumor-produced lactate to glucose—glycolysis *removes* 14 ATP from the general body economy with each glucose molecule metabolized (2 ATP *to* the glycolyzing tissue, 12 ATP *from* normal body energy pools). The loss of ATP to the body economy as a consequence, can become considerable. Thus, in making less ATP available for elaboration of ROS, glycolysis functions as an effective inhibitor of oxygen stress in the body.

To what extent can glycolysis be invoked by the body as a defense against oxidative stress? Other than frank cancer tissue, the body—seemingly—has but one choice: the elaboration of “transitional” tissue. As discussed, these are tissues in proximity to a cancerous lesion that appear normal morphologically but are already metabolically “cancerous,” undergoing glycolysis as their major means of energy

production, as well as expressing other metabolic and biochemical characteristics of frankly malignant tissue. Are these “transitional” tissues real? The two previously referenced studies<sup>11,14</sup> indicate the affirmative. These two studies, one completed 34 years after the other, using the same investigational tissue—freshly obtained human colon tumor tissue—and employing totally unlike experimental procedures, found almost identical results: namely, that the morphologically normal-appearing tissue adjacent—i.e., in close proximity—to the cancerous lesion, metabolically more closely resembled the cancerous lesion than the same normal-appearing tissue distant from the lesion. Each study independently named this adjacent tissue “transitional.” That these almost identical results could be a random “coincidence” is only a remote possibility.

Does *de novo* “transitional” tissue exist? That is, not in association with any cancerous lesion? This is an important question, for if so, such tissue could serve as reservoirs of glycolysis and be activated by the body at any time. Previous evidence for the existence of *de novo* “transitional” tissue in the body has been set forth—principally in the form of false positive PET scans followed by negative biopsy—indicating rapid glycolysis (F<sup>18</sup> 2-deoxyglucose uptake) in the tissue examined, but normal appearance under the microscope. Although false positives occur in tissues exhibiting hyperplasia, granulomas and in other inflammatory conditions, false positive PET scans in the proximity of cancer and in normal tissues—which can be high in incidence<sup>21</sup>—constitute strong presumptive evidence of the presence of *de novo* “transitional” tissue in the body; and, thus, that this tissue can ‘come and go.’

But to answer this question more particularly, the transition between a morphologically normal and a morphologically malignant cell must be considered.

Does a normal cell become cancerous in one step? That is, at one moment is it totally normal and the next, totally malignant? The findings presented in this paper, namely, that it is possible that morphologically normal-appearing tissue under the microscope can be expressing metabolic characteristics of frankly malignant tissue, suggests that the likelihood is greater that a normal cell reaches malignancy *through intermediate stages* rather than “turns” malignant at once.

But, if so, such intermediate stages constitute *de novo* “transitional” tissue—which would seemingly be applicable to many, if not all, cancers. Thus the probability is

high that *de novo* “transitional” tissue plays a key role—actually is a *sine qua non*—to the development of definitive cancer.

Moreover, if increased glycolysis via the development of “transitional” tissues represents a normal process invoked by the body as a temporary adjustment, which acts to regulate ambient energy levels in restraint of oxidative stress, the implication, as previously discussed, is that these tissues ‘come and go.’ Thus when ATP availability is sufficiently decreased, these tissues “regress” to normal metabolic function.

But if ambient energy is not sufficiently lowered to offset the effects of oxidative stress, these “transitional” tissues no longer regress—their output of glycolysis is no longer “temporary”—but go on to form tissues with maximal glycolytic capacity, i.e., frankly, morphologically identifiable malignant tissue. Once formed, however, malignant tissue, invasive and metastatic, takes on properties of its own and constitutes an imminent threat to life.

Since this paper identifies a “normal body process”—the shift to glycolysis in normal tissues—to be the primary “defect” in cancer and this shift’s “aberration” to result in tumor formation, the question arises as to which aspect of tumorigenesis may provide a potentially more effective basis for cancer therapy: the metabolic ‘shift’ or the tumor?

For the past 50 years the attention of the medical profession has been focused on the *tumor*. But all attempts to treat the tumor—to kill the tumor and therefore wipe out the disease—have in general been futile. During the past 50 years the death rate from this disease has reportedly hardly budged, decreasing at the most 5 percent overall, and in the major cancers not decreasing at all.<sup>34</sup> Cytotoxic chemotherapy, the major weapon to defeat cancer in the last 50 years, has succeeded in killing cancer cells, but in killing normal cells, too, and has been itself a cause of cancer mortality.

Effective cancer control may lie, rather, with therapy of the ‘shift’ to glycolysis, than with tumor therapy, potentially obviating such developments as drug resistance and major drug toxicity. In this regard it is recognized that not only can the “metabolic shift to enhanced glycolysis” provide a basis for cancer treatment but that discovery of the regulatory mechanism(s) underlying this metabolic shift may be essential to the future development of anti-cancer therapy.<sup>33</sup>

It is here theorized that cancer is a normal process invoked by the body as a protective device against tissue damage, senescence and death. It is the most exquisite of paradoxes that the more the body calls upon glycolysis to combat oxidative stress, the more likely it is that the body's protective mechanism will lead to its almost certain confrontation with death.

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