



One of the interesting observations in the prostate/multiple vitamin study was that there was an even higher risk for developing advanced prostate cancer among the frequent supplement users if there was a strong family history of prostate cancer. The implication here was that those individuals who were aware that there was a strong family history of prostate cancer were making the conscious choice of using high doses of multiple-vitamins as a means to lessen their risk of developing cancer. The study clearly showed that One-A-Day and Stress-Tab supplements were ineffective in reducing the risk for developing prostate cancer and did not lessen the chances for localized prostate cancer becoming metastatic. My question is, if an individual has a strong family history of prostate cancer, and if such an individual was strongly motivated to use multiple vitamins, wouldn't that confound the study by placing a higher number of patients likely to develop advanced prostate cancer in the frequent-supplement user category? Men who have a strong family history of prostate cancer are the most likely individuals to develop advanced prostate cancer. The aforementioned statistics do not separate out men who had strong family histories of prostate cancer.

One final concern is the question about the value of One-A-Day supplements and Stress-Tabs. As a practitioner involved in a preventive medical practice, I have some question as to what these supplements offer patients. The supplements do enable individuals to have the minimal daily recommendation of vitamins and minerals, if not even higher dose levels than what is recommended. However, I generally advocate the use of an "advanced" multiple-vitamin mineral preparation that includes vitamins and minerals that increase bio-availability and are "energetically" enhancing. Generally, these supplements include green food, enzymes, energy-conferring co-factors, and amino acids. In addition, I almost never advise an individual to supplement any vitamins and minerals without recommending supplementation of omega-3 and omega-6 fatty acids. Understandably, most of the individuals participating in this study never saw a nutritional or medical consultant about the use of their supplements. The study may provoke some argument from nutritionally oriented practitioners that synthetic off-the-shelf multiple vitamin preparations offer little benefit for treatment and prevention.

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1. Lawson, KA, Wright, ME, Subar, A, Mouw, T, Hollenbeck, A, Schatzkin, A, Leitzmann, MF. Multivitamin use and risk of prostate cancer in the National Institutes of Health – AARP diet and health study. *J National Cancer Inst.* 2007; 99(10):754-764. Available at: <http://jnci.oxfordjournals.org/cgi/content/full/99/10/754>. Accessed May 12, 2007.

Applying Warburg's Ideas in Practice

One of the most surprising developments in modern cancer research has been the reemergence of the ideas of Prof. Otto H. Warburg (1883-1970). Warburg was one of the most famous cell biologists and cancer researchers of the twentieth century. Starting in the mid-1920s, he made fundamental discoveries about the nature of respiratory enzymes. (The elucidation of the citric acid cycle was finally achieved by his student, Hans Krebs.) Warburg was awarded the Nobel Prize in 1931 for his discovery of the nature of cellular respiration. According to his biography at the Nobel Prize website, his discoveries "opened up new ways in the fields of cellular metabolism and cellular respiration," which incidentally have had a major impact on cancer research (www.nobelprize.org).

Warburg believed that the metabolism of cancerous tissues differed from that of normal tissues, notably in terms of the way that these tissues generate energy (ATP) from glucose. The cancer cell relies heavily on glycolysis, a less efficient and evolutionarily less advanced means of energy generation similar to the fermentation of yeast. Normal cells, by contrast, generally rely on a process called oxidative phosphorylation, which takes place in specialized organelles in the cells, called mitochondria. Cancer cells will use glycolysis even in the presence of oxygen, a phenomenon therefore known as "aerobic glycolysis," or, more colloquially, "the Warburg effect."

According to a recent article at the website of the National Cancer Institute (NCI), Dr. Warburg believed that aerobic glycolysis lay at the root of cancer's development, "but his theory never caught on" (NCI 2006). This statement made me smile, because Warburg was vehemently and often personally attacked by his many enemies, who did their best to kill his theory in the postwar period.

In fact, one can still find such anachronistic attacks on Warburg at the Quackwatch.org website. According to them, Warburg's research "never showed that oxygen use by normal and cancer cells was different. By 1960, research had identified nearly all energy-producing metabolic pathways in both normal and cancer cells and showed that energy-producing systems in normal cells were the same as those found in cancer cells." This astonishingly incorrect statement was written less than a decade ago.

Today, the Warburg effect is regarded as a scientific fact and, among other things, forms the basis of the billion-dollar PET scan industry. According to Craig Thompson, scientific director at the Abramson Family Cancer Research Institute, the renewed interest in Warburg's ideas "gives us a number of new avenues to investigate to see whether it can be exploited for therapeutic benefit." The NCI author similarly adds: "A growing cadre of researchers is now delving deep into cancer cells' energy-production machinery, with the hope of finding effective ways to short-circuit it."

Indeed, the "Warburg effect" offers many opportunities for specifically targeting cancer based on its peculiar metabolism. Two recent experiments have tried to do just that. They are in fact attempting to repair the defective mitochondria of cancer cells, with some apparent success in animal systems.

Some of the most interesting new treatments emerging for cancer are attempts to apply the "Warburg effect" in practice. At the beginning of 2007, there was an international flap over the discovery that a substance called dichloroacetate (DCA) could

greatly inhibit the growth of cancer. In February, a blogger at the American Cancer Society website wrote: "There is the medical equivalent of a tsunami wave building out there, only we don't know where this one is going to land." He was referring to DCA, whose role in cancer had been announced in a January 2007 article in *Cancer Cell* and in a press release from their institution, the University of Alberta.

Starting from the premise that cancer cells have a "unique metabolic profile" (aerobic glycolysis, or the Warburg effect), the researchers argue that this fact may confer resistance to apoptosis (programmed cell death). This resistance occurs because cancer cells have a high mitochondrial membrane potential and a low expression of the K⁺ channel Kv1.5. It is known that the common chemical dichloroacetate (DCA) inhibits the mitochondrial pyruvate dehydrogenase kinase (PDK). The application of DCA thus has the remarkable effect of shifting metabolism from (cancerous) glycolysis to normal glucose oxidation. It also activates the Kv channel in cancer cells, but not in normal tissue. DCA has been found to induce apoptosis, decrease cell proliferation, and inhibit tumor growth, all without significant toxicity in animal systems. It is also orally available and altogether represents a very promising anticancer agent. In animal experiments, DCA shrank the size of tumors by up to 75%.

In a June 2007 follow-up letter to his supporters, Evangelos D. Michelakis, MD, who directs DCA research at the University of Alberta, wrote that he and his colleagues were considering moving this research "from the laboratory to the level of a clinical trial." However, they note that "this is a very challenging endeavor since it is not supported by the pharmaceutical industry." They are nonetheless hoping to move forward with a "clinical trial that can address both efficacy and safety of this potential treatment....despite the fact that dichloroacetate has been used in humans for over 20 years [for certain rare non-malignant conditions, ed.] the appropriate dose for cancer patients remains unknown."

When news of DCA first broke in January 2007, there was near-hysteria, and some people started to make it available to patients over the Internet. The British journal *New Scientist* described it as a "New Cheap Drug That Kills Tumors." I was as excited as anyone by the prospects of DCA, however, some of the early publicity for the drug was undoubtedly premature and excessive. I therefore sent a letter to the editor of *New Scientist* in which I warned of some potential downsides to the therapy (Feb. 3, 2007). In the intervening months, I am happy to report, DCA has continued to generate a great deal of well-deserved interest. For example, in April, James G. Pan and Tak W. Mak wrote a review article in *Science* with the title, "Metabolic Targeting as an Anti-Cancer Strategy; Dawn of a New Era?" Pan and Mak state that "These observations provide intriguing insights into the plasticity of tumor metabolism that may offer new opportunities for therapeutic intervention" (Pan 2007). Let us hope that it will.

3-BrPA: Another Agent that Stops Aerobic Glycolysis

Another promising agent that works via the Warburg effect is 3-bromopyruvate (3-BrPA), a potent inhibitor of cell energy (ATP) production. The effects of this compound were brought to light by the work of Young Ko, and her colleagues at Johns Hopkins Medical Institution, Baltimore. In 2002, they reported on their direct intra-arterial delivery

of 3-BrPA to liver-implanted rabbit tumors. This off-the-shelf chemical inflicted "a rapid, lethal blow to most cancer cells therein." In addition, Ko and colleagues noted that the systemic delivery of 3-BrPA suppressed metastatic tumors that arose in the lungs of these same animals.

"In both cases, there is no apparent harm to other organs or to the animals," they wrote. Thus, the intra-arterial delivery of agents like 3-BrPA "directly to the site of the primary tumor, followed by systemic delivery only when necessary, may represent a powerful new strategy for arresting the growth of liver and other cancers while minimizing toxic side effects" (Geschwind 2002). It was an extraordinary effect, even for an animal experiment.

The appearance of such an astonishing paper from one of America's top research hospitals should have brought down the Jericho walls of resistance to radically new ideas. Instead, there was silence from the medical-industrial complex, particularly the pharmaceutical industry. Here's one possible reason: Dr. Ko has estimated the equivalent human dose of 3-BrPA at 70 cents per day, or around \$20 per month. Competing new "targeted" drugs such as Avastin, Herceptin, and Erbitux, sell for thousands of dollars per month. Avastin costs \$100,000 per year and out-of-pocket expenses run to \$10,000 to \$20,000 (*New York Times*, Feb. 15, 2006). A single treatment cycle of Zevalin is reported to cost \$30,000. Do the math.

According to an article at www.law.com, Dr. Ko states her belief that this premier medical school and its scientists have blocked her cancer work. In June 2005, Dr. Ko sued Johns Hopkins and four colleagues, claiming that she was discriminated against and her research was impeded, because she is an Asian woman with a successful project. Basically, she claims that her colleagues stole her research. It is a story of such skullduggery that it makes the narratives I related in *The Cancer Industry* pale in comparison.

In court papers, Hopkins officials state that they declined to renew Ko's three-year contract "in view of her lack of collegiality, cooperation, insubordination, and her hostile and insulting attacks directed at...senior faculty members." The upshot, however, is that 3-BrPA, one of the most intriguing laboratory findings in years, remains undeveloped and unavailable to patients. Without a doubt, 3-BrPA has a long way to go before it can be used in humans. Meanwhile, that work has been severely hampered by the infighting at Hopkins, and it is no surprise that the www.clinicaltrials.gov website lists no human tests with that agent. There is something dysfunctional about a system that promotes expensive and minimally effective cancer treatments but puts every imaginable roadblock in the way of testing such promising and inexpensive agents as dichloroacetate and 3-bromopyruvate.

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American Cancer Society (ACS) blogger on DCA: <http://www.cancer.org/asp/blog/Comments.aspx?id=130>

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On the social milieu of Otto Warburg's work, see my newsletter available at: http://www.cancerdecisions.com/031404_page.html.

Pan JG, Mak TW. Metabolic Targeting as an Anticancer Strategy: Dawn of a New Era? *Science STKE.* 2007(381):14

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