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#### INTRODUCTION

Louis Pasteur observed two types of energy production in the world of single cells. The most primitive form of energy production is anaerobic and does not use oxygen. This process is also called fermentation and is utilized in manufacture of beer and wine. This is considered a more primitive form of energy production.

The second form of energy production noted by Pasteur is aerobic which means that it utilized oxygen. This process is also called respiration. It is the form of energy production used by most multicellular organisms.

## OTTO WARBURG

Otto Warburg greatly admired Louis Pasteur. He became convinced that a defect in energy metabolism was central to the development of cancer. He believed this because of the nonspecific nature of the disease.

Warburg won a Nobel Prize in 1931 for his discoveries relating to energy production in cells. One of his observations was that cancerous cells can live and develop in the absence of oxygen. Today the ability of cancer cells to ferment glucose even in the presence of oxygen is known as "the Warburg effect."

Warburg had a Jewish father and lived in Germany throughout the Second World War. In 1935 Hitler had a polyp removed from his vocal cords. Afterwards, it is believed, he feared the development of cancer. This probably saved Warburg's life. He was the most prominent cancer researcher in Germany during the Second World War. Hitler turned a blind eye to his Jewish ancestry and ordered him to continue his research on cancer.

In 1944, Warburg was nominated for a second Nobel Prize by Albert Szent-Gyorgyi, the scientist who isolated vitamin C, for his discovery of the involvement of nicotinamide (vitamin B3) and flavin in fermentation. Flavin is a yellow pigment found in enzymes and vitamin B2. Hitler forbade Germans from accepting Nobel Prizes in 1937.

Warburg showed that normal body cells turned to cancer cells when they are deprived of oxygen for even a few hours time. There was no need to introduce carcinogens, radiation, or viruses to achieve this transformation. This led Warburg to conclude and promote the idea that the creation of cancer cells was due to a defect in cellular energy metabolism which later came to be identified with the mitochondria or energy factories of the cells.

Warburg never gave up his conviction that the primary cause of cancer was alterations in glucose metabolism and energy production. In 1966 at age 82 near the end of his life Warburg summarized his belief about cancer as he discussed primary and secondary causes of cancer. He said, "Cancer, above all other diseases, has countless seconday causes. Almost anything can cause cancer, but even for cancer, there is only one prime cause. The prime cause of cancer is the replacement of oxygen in normal body cells by fermentation of sugar."

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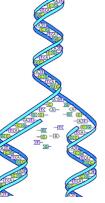
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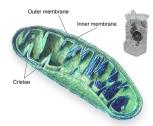
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# THE DNA HYPOTHESIS

Percivall Pott was the first scientist to show that cancer could be caused by an environmental carcinogen. In 1775 Pott associated chimney soot as a direct contact carcinogen leading to scrotal cancer in chimney sweeps. The primary carcinogen in chimney

soot is also a prime suspect in various cancers caused by smoking cigarettes. Pott's work resulted in the Chimney Sweepers Act of 1788 which sought to reduce the risk of cancer among the young boys who were working





## Mitochondria

as chimney sweeps.

In 1966 Francis Peyton Rous was awarded a Nobel Prize for his work showing that viruses could cause cancer. In 1911 a woman walked into the Rockefeller Institute in New York City carrying a chicken with a large tumor on its breast. Rous surgically removed the tumor, sliced it into pieces and placed it into the bodies of other chickens which subsequently developed cancer. Later Rous filtered out bacteria and cancer cells showing that viruses were causing the cancers.

In 1953 James Watson and Francis Crick discovered the structure of DNA. It became obvious that the DNA stored information. The scientific community moved away from Warburg's focus on the mitochondrial origin of cancer and concluded that defects in the DNA caused by chemical carcinogens, viral infection, or radioactivity.

It did not take long to trace the cancer-causing virus Rous had found in chickens to a defect in a specific gene triggered by the virus. It was named src for sarcoma. This gene was found to regulate kinases, key signaling molecules in the cell. The viral version of the src gene was stuck in the on position causing cells to divide over and over again. Science began a largely fruitless search of DNA for the cause of cancer.

The association of cancer with DNA led to chemotherapeutic treatments targeted at preventing replication of DNA. These treatments kill cancer cells, but they also have a devastating effect on healthy cells. In other words, the treatments are not specific.

## WARBURG CONTINUES

Pete Pedersen of Johns Hopkins worked in a laboratory run by Albert Lehninger. Leninger had discovered that mitochondria were the site of the cells' energy production. He also knew Warburg personally. Like a dog after a stick, Pedersen became fixated on the metabolism of cancer cells. He found that the cancers that grew the fastest and were most aggressive had a smaller number of mitochondria and fermented more glucose. Tumor cells that grew the fastest invariably had about half the mitochondria of normal body cells.

Mitochondria of cancer cells were also abnormal in structure. They were missing important internal membranes and had abnormal protein and lipid content. Pedersen has discovered why the Warburg effect takes place. In 1977 Pedersen and a graduate student, Ernesto Bustamante, identified a chemical messenger, mitochondrial hexokinase, responsible for pushing cells into utilization of fermentation for energy production.

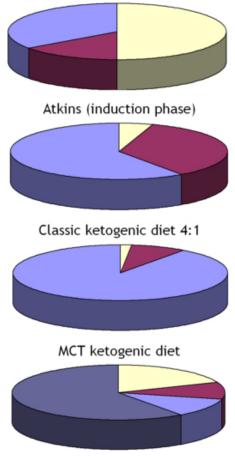
Hexokinase exists in four different forms (isozymes). The cancer cell produces vastly more hexokinase II, normally present in only tiny quantities in the normal cells of the body. This form of the enzyme forces glucose down the fermentation pathway and ignores the regulatory signals of the cell to slow down.

The fact that cancer cells stuff themselves with glucose due to high levels of hexokinase II became the basis for the PET scan, one of the most accurate means of identifying where cancer tumors exist in the body. A glucose molecule is combined with a fluoride molecule. This "tagged glucose" (FDG or gluorodeoxyglucose) can be easily detected by the PET scan. The PET scan is utilized in virtually every cancer center in the world and provides powerful illustration of the voracious appetite of cancer cells fir glucose.

Hexokinase II binds with a protein called VDAC preventing suicide of cancer cells (apoptosis) and making cancer cells immortal. Hexokinase II also positions itself in the cell in such a way that it can steal ATP (the energy produced by the cell).

In 1991 a brilliant South Korean scientist, Young Hee Ko, came to work in Pedersen's laboratory. She discovered that a molecule called 3BP (3-bromopyruvate) could enter the cell and mortally damage hexokinase II. Ko demonstrated that this compound was much more effective than traditional chemotherapeutic agents at killing cancer cells in virtually every type of cancer cell tested. Over 100 tissue studies demonstrated the effectiveness of the compound against

Typical American diet



🗆 Carbohydrate 🔳 Protein 🔲 Fat LCT 🔲 Fat MCT

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Sa 4	×
50 5	×

cancer cells.

Ko then tested the compound on rabbits. The compound killed cancer cells in living rabbits without killing the animals. Rat studies produced similar results.

Ko also was able to successfully treat one human subject with her compound. At this point the promising new compound became tied up in legal battles and politics.

Bert Vogelstein at Johns Hopkins University achieved recognition when his laboratory identified mutations of the p53 gene in cancer. Mutations of p53 are the most common of all alterations in the DNA of cancer cells affecting over 50% of cancers. In 2003 Vogelstein was recognized as the most frequently cited scientist in the world during the previous 20 years.

Voelstein's research led to the concept of intratumoral heterogeneity. In other words, most tumors have a wide variety of different mutations for cell to cell making treatment with a single drug almost impossible. In 2008 Voelstein linked a mutated oncogene direcly to defective energy production. In 2006 metformin which alters energy metabolism in diabetics was shown to reduce cancer risk.

Research on the energy metabolism of cancer cells appears to be bearing fruit, while targeting changes in the DNA has met with only limited success.

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https://commons.wikimedia.org/wiki/ File:Ketogenic\_diets\_pie.png

## CALORIC RESTRICTION

Caloric restriction and fasting have been repeatedly shown to reduce the risk of cancer and retard cancer growth in both animals and humans. These practices promote improved energy production and rejuvenation of mitochondria in cells.

Barrett and associated wrote, "Calorie restriction (CR) is the most effective and reproducible intervention for increasing lifespan in a variety of animal species, including mammals. CR is also the most potent, broadly acting cancer-prevention regimen in experimental carcinogenesis models."

Dr. Thomas Seyfried was drawn to research fats. His particular focus was on gangliosides which look like a blooming flower on the outer membrane of cells. These fats relay signals and are central to cell to cell communication. They constitute 6% of all the phospholipids in nerve cells.

When Seyfried fed these lipids to animals with tumors he was surprised to see a slowing of the growth of the tumors. A grant to study gangliosides as a cancer treatment found that the primary reason these lipids slowed cancer development was because they decreased appetite and promoted caloric restriction. Seyfried concluded that many of the drugs being tested to treat cancer did nothing more than make animals and people lose their appetites. The question was why caloric restriction inhibited cancer.

In 2012 Seyfried published Cancer

*as a Metabolic Disease*. It this book he argues that epigenetic signaling travels from damaged mitochondria to the nucleus of the cell altering the expression of the genes which have the potential to cause cancer. This signaling by the mitochondria is called the "retrograde response."

The signals from the damaged mitochondria alter the energy production of the cell from aerobic metabolism to fermentation of glucose as a source of energy for the cell.

In other words, the mitochondria are sending a message to the DNA of the cell: "We cannot produce energy in a normal way and need to alter the functioning of this cell to ferment glucose. Let's become a cancer cell." The changes in the DNA are secondary to damage to the energy producing mitochondria and the messages they send to the DNA of the cell.

Seyfried's hypothesis is supported by research conducted by Warren Schaeffer. Shaeffer placed the DNA of cancer cells into normal cells. The DNA tended become normal. He then placed normal DNA into cancer cells. The normal DNA was altered by the damaged mitochondria. The researchers wrote, "...we have found evidence to support the theory that the cytoplasm from a normal cell can suppress tumorigenicity."

The implications are enormous. It shifts the focus of cancer treatment and prevention from the DNA to the energy production of the cell in the mitochondria. The key to addressing cancer becomes focusing on the energy production of the cell in the mitochondria.

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# KETOGENIC DIET AND CANCER

A ketogenic diet tends to put pressure on cancer cells. It upregulates glutathione in normal cells, but not in cancer cells. This makes normal cells more resistant to oxidative damage and cancer cells less resistant.

In a study by Seyfried and associates the combination of a ketogenic diet and hyperbaric oxygen increased the survival time of mice with systemic metastatic cancer by 77.9%. The ketogenic diet alone increased survival time by 56.7%

Safdie reported in 2009 that fasting decreased the side effects of chemotherapy without interfering with the effectiveness of the treatment.

Fasting and a ketogenic diet decrease insulin levels and IGF-1 (insulin-like growth factor 1). Both of these substances increase the risk of developing cancer

There is one flawed study by Lisanti which suggests that ketones fuel cancer growth. A reference is provided (livinlavidalowcarb) which evaluates this study.

It appears that fasting and a ketogenic diet may not be effective in curing cancer, but they can be useful adjuncts to other treatments that interere with the ability of cancer cells to utilize oxygen or treatments that place oxidate stress on cancer cells. A number of food substances such as allium and cruciferous vegetables have proven anti-cancer properties. These nutrients could be incorporated into a ketogenic dietary regimen as well. As far as I know, no one has conducted a test along these lines.

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