A Genius and a Mistake

Max Planck scientist Otto Heinrich Warburg, biochemist, physician and Nobel laureate, would have celebrated his 125th birthday on October 8, 2008. It was he who discovered that industrial and car exhaust gases can trigger cancer. And Warburg firmly believed he had discovered even more: the prime cause of cancer. Today, 38 years after his death, the Warburg hypothesis is still as relevant as ever, and always makes a good headline.

"I discovered the quantum chemistry of photosynthesis and finally, in the field of medicine, the prime cause of cancer." This is how Warburg himself summed up his great scientific career. He is now considered to be the father of modern biochemistry: biologists have him to thank for enlightening the world about photosynthesis and cellular respiration.

The scientist derived the eponymous hypothesis from his observations in the field of cancer research: healthy cells generate energy by breaking down sugar – using oxygen in the process. Cancer cells, on the other hand, produce energy by fermentation. So they convert nutrients without the use of oxygen, even if oxygen is available. A life without oxygen – this, according to Warburg, is the prime cause of cancer.

This conjecture still keeps scientists busy to this day. In 2006, the Berliner Zeitung rejoiced: "Late recognition for a lateral thinker: Cancer is an abnormality of the metabolism, said Otto Heinrich Warburg back in 1924. It now turns out he may have been right." A team of scientists led by Michael Ristow from the Institute of Nutrition at the University of Jena has successfully proven the Warburg hypothesis. The majority of scientists considered it to have been disproved.

Even as a young man, Otto Heinrich Warburg, born in 1883, was keen to solve the cancer problem. But cellular respiration and photosynthesis also occupied the scientist all his life. Warburg went about his research in a different way than his fellow scientists: he was not content with the chemical model. He insisted on proving his conjectures on the physiological object. But the objects on which he carried out his tests – sea urchin eggs – were not even recognized as scientific test objects. Still, Warburg cared nothing for the opinions of anyone else – and he was successful. As it turned out later, the sea urchin egg, as a small and easily examined system, was indeed highly suited to his research purposes. Warburg discovered that the oxygen consumption of a sea urchin egg increased dramatically following fertilization – an observation that was later to occupy him again in his work on cancer research.

Photo: Archives of the MPS, Berlin-Dahlem

Otto Warburg in his lab at the Max Planck Institute for Cell Physiology in Berlin-Dahlem. The picture was taken in the 1960s.

The scientist demonstrated the presence of physiologically effective iron in the eggs and noticed that their respiration accelerated when iron was added. From this, Warburg concluded that iron plays an important role in cellular respiration – the process by which food is broken down by the body's own metabolic processes and energy is produced. He later succeeded in verifying this hypothesis. Another thing he discovered is that copper, iron and vitamins contribute substantially to enzyme function: Warburg described the catalytic role of iron porphyrins in biological oxidation.

He won the Nobel Prize in Medicine in 1931 for his discovery of the nature and mode of action of the respiratory enzyme. Warburg had been put forward for the prize back in 1927 for his research papers on the metabolism of cancer cells. But the Nobel Prize Committee voted against him, having honored the Dane, Johannes Fibiger, for his theory in cancer the previous year. Fibiger had identified Spiroptera carcinoma (a form of gastric tumor in rats that was apparently caused by nematodes of the species *Spiroptera*) and declared cancer in general to be an infectious disease – one of the most spectacular and, at the time, highly acclaimed scientific errors, as was subsequently revealed.

When Otto Heinrich Warburg was eventually set to be awarded the prize in 1931, he heard about it in passing in his lab. His wry comment was "It's high time." He was particularly delighted with a report in the Frankfurter Allgemeine Zeitung, in which his discovery was presented in a manner relevant to housewives in their kitchens at home: "If you drizzle a sugar cube with blood, plant ash or an iron(II) chloride solution from the pharmacy, the sugar will burn with a translucent flame, whereas without the addition of iron, it will merely caramelize."

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Otto Heinrich Warburg would surely be delighted to know that his theory on the cause of cancer is currently experiencing a renaissance. After more than eighty years, Warburg's hypothesis seems to be awakening from its scientific slumber. Scientists have detected signs that cancerous growth and energy metabolism are more closely intertwined than was previously thought.

The Royal Swedish Academy of Sciences wanted to honor Warburg with the Nobel Prize again: this time for proving that nicotinamide and various flavins were contained in coenzymes and acted as hydrogen carriers during biological oxidation. But Hitler had issued a decree forbidding Germans from accepting a Nobel Prize – thus preventing Warburg from doing so.

In the meantime, the momentousness of the many different cancers had been recognized. Scientists from across the globe were working hard to solve the problem. What they were looking for was a carcinogen as the perpetrator of all the evil. Time and again, the media carried sensational reports claiming that the cause of cancer had finally been found. Undeterred, Otto Warburg continued his research in his lab at the Kaiser Wilhelm Institute for Biology in Berlin-Dahlem, which was incorporated into the Max Planck Society in 1953.

Warburg believed that searching for the cause of cancer in a pathogen was absurd. He was convinced that the cause of cancer was to be found, not outside the body, but inside it – in the chemical reactions within the cells. He speculated that, when cancer cells start to grow unchecked, they ought to require more oxygen – just like the sea urchin eggs given added iron. This assumption reflected Warburg's fundamental research approach, which involved attributing life processes to physical and chemical processes. This notion was frowned upon in those days, with most scientists attempting to prove that diseases were infections.

Contrary to Warburg's assumption, however, his experiments showed that the difference between normal cells and cancerous cells lay not in any increase in respiration, but in their fundamentally different type of energy supply. "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," as the researcher noted in 1924 – and the Warburg hypothesis was born.

Warburg was adamant that diseases had different causes. He called these the "secondary" and "prime" causes. He illustrated this using the plague as an example: the prime cause of the plague is the plague bacillus, but secondary causes of the plague are rats and the fleas that transfer the plague bacillus from rats to humans. "What the plague bacillus is to the plague," said Warburg, "the fermenting body cell is to cancer."

The scientist was aware that cancer could have many causes – and that even time itself was capable of causing cancer. Warburg identified cancer-causing substances, was a vehement proponent of a tobacco ban, and urged people to limit the pollution of the air caused by fumes. But nobody listened. And he took part in the race to find a drug to treat cancer. Late in life, he still believed that the way to treat cancer would be found in the anaerobiosis of cancer cells. His idea was that supplements in food, such as the iron found in respiration enzymes, along with certain vitamins, could sustain – and even reinstate – cell respiration, thus rendering them suitable as a cancer therapy. But his search was to prove fruitless.

Even so, Warburg's cancer research inspired other scientists and doctors – above all, practitioners of alternative medicine. Methods such as cancer multistep therapy and oxygen therapy, as well as certain dietary regimes, were developed following the Warburg hypothesis. However, most orthodox medical practitioners and scientists reject these methods, as they consider their very basis to be erroneous and because there is no convincing proof that they work.

The proponents of these therapies, on the other hand, feel vindicated by a paper published in 2006. They interpret the findings of scientist Michael Ristow from the University of Jena as proof of the Warburg hypothesis. Ristow modified colon cancer cells such that they produced unusually high quantities of frataxin – a protein that activates cell respiration to an inordinately high degree. According to the scientist, the cancer cells that were forced to allow cellular respiration to take place grew much more slowly and formed smaller lesions than did regular cancer cells. Ristow says: "Even possible metabolic causes of cancer are something we should not lose sight of in our research."

Axel Ullrich, Director at the Max Planck Institute of Biochemistry in Martinsried, sees things differently. Among the treatments for which the distinguished cancer researcher laid the foundations are two cancer medications – the breast cancer drug Herceptin and the drug Sutent, which can be used to combat renal cell cancer and tumors in the gastrointestinal tract. In his interpretation, the fact that cancer cells obtain energy from fermentation has more to do with molecular genetics.

"Today, it is generally established that cancer arises as a result of cells that have lost their genetic stability. This, in turn, leads to an accumulation of chromosomal changes and mutations in the cell genome," says Ullrich. "The change in the cellular energy metabolism is a consequence of these genetic defects, but it is definitely not the reason why malignant tumors develop and grow."

The fact that Otto Heinrich Warburg's hypothesis on the origin of cancer was mistaken does nothing to diminish his great service to biochemistry. And he was certainly conscious of his successes: in January 1938, the Times carried an obituary for him – 32 years early. But it wasn't the fact that they'd mixed him up with a distant relative that annoyed Warburg. What really got him was the fact that this death notice misappropriated some of the important results of his research work. Nevertheless, he had fun accepting the condolences personally.

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