Harald zur Hausen (1936–) [1]

By: Kim, Grace

Harald zur Hausen studied viruses and discovered that certain strains of the human papilloma virus (HPV), a sexually transmitted disease, can cause cervical cancer, in Europe during the twentieth and twenty-first centuries. Zur Hausen spent his research career identifying the viruses that cause diseases, particularly cancer-causing viruses (oncoviruses). He primarily focused on HPV and cervical cancer. Zur Hausen hypothesized that HPV was cancerous and discovered that two strains, HPV 16 and 18, caused cervical cancer. That discovery led to improved diagnosis of cervical cancer and the later development of the HPV vaccines, Gardasil and Cervarix. In 2008, zur Hausen won the Nobel Prize in Physiology or Medicine[2].

Zur Hausen was born in 11 March 1936 in Gelsenkirchen-Buer, Germany. Growing up, he and his family survived World War II despite the frequent bombing of their hometown. Zur Hausen attended elementary school in Gelsenkirchen-Buer, Germany, but his education was interrupted in 1943 when schools closed due to the frequent bombing. After the end of World War II, in 1946, at the age of ten, he attended secondary school. In 1950, his family moved to Northern Germany, and he finished his high school education there, graduating in 1955.

After graduating from high school, Zur Hausen began his study of medicine at the University of Bonn[3] in Bonn, Germany, in 1955. He remained there until 1957 when he moved to continue his education at the University of Hamburg in Hamburg, Germany. Zur Hausen spent a year at the University of Hamburg before moving again to the Medical Academy in Düsseldorf, Germany, in 1958. In 1960, he graduated from the Medical Academy with his medical degree. Zur Hausen then spent two years working as a medical intern to receive a license to practice medicine in Germany. He worked in surgery and internal medicine, but spent most of his time as an intern in obstetrics and gynecology.

After his medical internship, zur Hausen pursued a career in research rather than as a physician. He began working in the medical microbiology and immunology department at the University of Düsseldorf in 1962. Zur Hausen received basic research training in the fields of bacteriology and virology through his study of the effects of the vaccinia virus in mouse[4] cells. Zur Hausen found that the virus caused mutations in cells' chromosomes, the structures that carry DNA, but he couldn't explain why they caused those mutations. Zur Hausen later said that he had limited resources for furthering his research education because studying bacteria and viruses was just beginning in Germany during the 1960s. While zur Hausen searched for research opportunities, he married his first wife in 1964, and they had a son, Jan Dirk, a year later.

In 1965, Zur Hausen became a post-doctoral researcher in the United States. Zur Hausen moved to the US to work at the Children's Hospital of Philadelphia in Philadelphia, Pennsylvania. There, he worked under the guidance of Werner Henle and Gertrude Henle, a team of virologists studying the Epstein-Barr virus (EBV). It can cause several diseases, including mononucleosis, an infection characterized by fever, sore throat, and fatigue. In the 1960s, though, scientists had recently discovered the virus in Burkitt's lymphoma cells. Burkitt's lymphoma is a cancer of the fluid that contains white blood cells (lymph). The Henles and their research team were working to develop diagnostic tests for EBV using blood samples (serological tests) in addition to determining if EBV caused Burkitt's lymphoma. The research team hypothesized that EBV acted as an oncovirus, or a virus that causes cancer, by maintaining a persistent infection in the lymphatic cells. A persistent virus infection means that the virus has inserted itself into the cell and remains there for a long time. Viruses in a cell replicate there and then infect other cells. The Henles hypothesized that EBV lingered in some lymphatic cells, slowly transferring the virus to other cells.

While zur Hausen expressed interest in studying EBV, he had little experience with the required research procedures. Zur Hausen worked with a different virus, the adenovirus, to familiarize himself with lab procedures. The adenovirus most commonly causes respiratory illness, though it can also lead to infections of the bladder or digestive system. The Henles taught zur Hausen how to use a method, nucleic acid hybridization, to identify and analyze DNA, as well as how to use other methods to detect viral DNA in sample cells. Using those methods, zur Hausen looked for chromosome mutations in human cells infected with the adenovirus. He also analyzed chromosomal differences in human lymphoblastoids, which are immature cells that eventually become different types of white blood cells.

While still working on his research with the adenovirus, zur Hausen began researching EBV. He analyzed Burkitt's lymphoma cells using an electron microscope[5], which bounces electrons off a specimen to create a high quality image of that specimen. When he did so, he discovered EBV in the cancerous cells. Zur Hausen's analysis further supported the hypothesis that EBV played a significant role in Burkitt's lymphoma. Zur Hausen's second son, Axel, was born in 1967.

In 1969, zur Hausen accepted a research position at the Institute for Virology at the University of Würzburg[6] in Würzburg, Germany. He led an independent lab group and continued to research EBV. He hypothesized that EBV DNA existed in all Burkitt's lymphoma cells but did not replicate and spread new virus copies as the Henles hypothesized. Zur Hausen proposed the virus only became activated in certain cells. While at the Institute of Virology, zur Hausen determined that there EBV DNA

was present in the DNA of Burkitt's lymphoma cells, even if it was not causing diseases like mononucleosis. Rather, EBV-infected lymphatic cells lived longer than uninfected cells, enabling them to grow and reproduce more than normal, a sign of cancer. He showed that viruses, as genetic information within human tumor cells, can initiate tumor growth by potentially modifying the genes [7] of the host cells.

In 1972, zur Hausen accepted a chairman position at the Institute of Clinical Virology in Erlangen-Nüremberg in Erlangen, Germany. During his time as chairman, zur Hausen began to study the causes of cervical cancer. Scientists had hypothesized that herpes-simplex 2 virus (HSV-2), a sexually transmitted infection that commonly results in genital warts, caused cervical cancer. Researchers had agreed that genital warts were most often caused by sexually transmitted infections. Scientists then demonstrated the presence of HSV-2 DNA in cervical cancer tumor cell samples, leading some to hypothesize that HSV-2 caused cervical cancer. Zur Hausen conducted his own research experiments using nucleic acid hybridization to search for HSV-2 DNA in cervical cancer tumor samples.

However, when zur Hausen looked for HSV-2 DNA in cervical cancer tumor samples in 1976, he found inconsistent results. Not all tumor samples contained HSV-2 DNA, leading zur Hausen to question whether or not the HSV-2 caused the cervical cancer. After failing to produce evidence of HSV-2 DNA in tumor samples, zur Hausen began investigating another sexually transmitted infection as the cause of cervical cancer, the human papilloma virus (HPV). Zur Hausen reviewed medical reports of women with HPV-caused genital warts developing cervical cancer. The medical reports linked HPV-caused genital warts to cervical cancer. Using those findings, zur Hausen published his theory that HPV caused cervical cancer 1976. A year later in 1977, zur Hausen moved to the Institute for Virology and Immunology at the University if Freiburg in Freiburg, Germany. Also in 1977, zur Hausen's third son Gerrit was born.

From 1977 onward, zur Hausen confirmed his theory that HPV causes cervical cancer. When he published his hypothesis that HPV caused cervical cancer in 1976, zur Hausen theorized that genital warts caused by HPV infections led to cervical cancer. In 1980, he and his research team cloned HPV DNA, using it as a template to analyze HPV DNA found in in samples. From 1980 through 1982, zur Hausen and his research team analyzed genital wart samples and discovered two new types of HPV in the samples, HPV 6 and 11.

After isolating and cloning [8] HPV 6 and 11 DNA, zur Hausen and his research team searched for HPV 6 and 11 DNA in cervical cancer tumor samples. If they found HPV 6 and 11 DNA in cervical cancer tumor samples, then the research team could conclude that HPV 6 and 11 caused cervical cancer. While the research team found some HPV 6 and HPV 11 DNA in the cervical cancer tumor samples, the DNA was not abundant. In 1983 and 1984, Zur Hausen instead discovered two new HPV strains, HPV 16 and 18, in the cervical cancer tumor samples.

In 1984, zur Hausen moved to *Deutsches Krebsforschungszentrum* (the German Cancer Research Center) in Heidlberg, Germany. He also divorced his first wife and married Ethel-Michele de Villiers, one of the members of his research team. Zur Hausen and his research team continued investigating genital wart samples and cervical cancer samples. They found that HPV 6 and 11 were prevalent in genital wart samples, whereas HPV 16 and 18 were prevalent in cervical cancer samples.

In 1986, zur Hausen contacted pharmaceutical companies to create an HPV vaccine. Zur Hausen later recalled that pharmaceutical companies rejected his vaccine proposals due to concerns that the vaccines may not be profitable for the companies and that there were more pressing health concerns than HPV. Nevertheless, zur Hausen continued his research on HPV. He conducted molecular research on HPV, refining the new molecular DNA techniques while simultaneously conducting research in clinical settings to explain how HPV develops and infects humans [9]. He also investigated the incidence and prevalence of HPV DNA in cervical cancer patients from around the world.

During the late 1980s, scientists used molecular techniques, like the polymerase chain reaction (PCR), to obtain genetic information from samples more efficiently. Using those techniques, many researchers all around the world found HPV DNA in many types of tissue samples. Those findings weakened zur Hausen's claim that HPV caused cervical cancer. Zur Hausen later argued that because many such techniques were new, lack of training and cross-contamination led to incorrect results.

When zur Hausen first published his hypothesis that HPV caused cervical cancer in the 1970s, few supported his findings. Most scientists argued instead that HSV-2 caused cervical cancer. As zur Hausen continued his research on HPV and cervical cancer in addition to the progress of laboratory techniques, the academic community shifted its research to focus on HPV rather than HSV-2. In 2006, zur Hausen wrote a book on his research findings, *Infections Causing Human Cancer*.

After years of research on HPV and cervical cancer, zur Hausen received many awards for his contributions to the field of oncovirus research. Those included the Robert Koch Prize in 1975, and the William B. Coley Award for Distinguished Research in Basic and Tumor Immunology in 2006. In 2008, zur Hausen won the Nobel Prize in Physiology or Medicine[2] for discovering the two strains of HPV that caused cervical cancer. He shared the prize with the researchers who discovered HIV (the human immunodeficiency virus), Francoise Barre-Sinoussi and Luc Montagnier [10]. Zur Hausen's Nobel Prize in Physiology or Medicine [2] was controversial. Swedish police conducted an anticorruption investigation to determine if AstraZeneca, a pharmaceutical company involved in the development of the HPV vaccine, influenced two members of the Nobel Prize selection committee. Charges were never brought after the investigation.

Although he retired from his directorship at the German Cancer Research Center in 2003, he continued to conduct research there. By 2016, he was studying the correlation between eating red meat and colorectal cancer.

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