Alfred G. Knudson

(1922–2016)

Cancer geneticist whose insights launched the search for tumour-suppressor genes.

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After years of observing children with the rare eye cancer retinoblastoma, Alfred Knudson proposed an explanation for how two different forms of it arise. His 'two-hit' hypothesis led to the realization that the loss of gene function, not just the activation of a cancer-causing gene, could cause cancer.

Knudson, who was born in Los Angeles, California, in 1922, died on 10 July, aged 93. After completing a bachelor of science degree at the California Institute of Technology (Caltech) in Pasadena in 1944, he earned a medical degree from Columbia University in New York City in 1947, and a PhD in biochemistry and genetics in 1956, also at Caltech. Knudson then spent years treating children in medical centres in California and New York.

During the 1950s and 1960s, cancer epidemiologists were preoccupied with trying to understand the environmental causes of the disease. In a 1953 paper, cancer biologist C. O. Nordling noted that in developed nations, the incidence of cancer seemed to increase with age (C. O. Nordling *Br. J. Cancer* **7,** 68–72; 1953). Nordling's proposal that the occurrence of cancer needed the accumulation of at least six sequential mutations was ultimately proved wrong. But his idea that cancer is caused by a certain number of 'hits' to the genome paved the way for Knudson's key insight.

Knudson had the foresight to focus on inherited tumours in childhood, which were relatively easy to study. The tumours could be counted and the early occurrence of the disease meant that there were fewer confounding factors to grapple with, such as the random genetic mutations that occur throughout life.

During his years in the clinic, Knudson had noticed that children with the hereditary form of retinoblastoma often developed multiple tumours in both eyes. By contrast, people with the 'sporadic' form developed a single tumour in only one eye. Also, in cases of hereditary retinoblastoma, the tumours typically occurred before the child was five; in sporadic cases, they occurred later in development.

On the basis of these observations, Knudson proposed that in hereditary retinoblastoma, one copy of the gene involved is mutated in the germ line (in reproductive cells such as eggs and sperm) and the other copy is mutated in somatic (non-reproductive) cells during the first few years of life, thus the cancer forms earlier. And because the germline mutation affects all somatic cells, these children are more prone to developing multiple tumours in both eyes. He argued that people who develop the other form are born with two normal alleles, both of which must become mutated in two 'sporadic' events in somatic cells, so the cancer develops later in life.

Knudson published his hypothesis in 1971 (A. G. Knudson *Proc. Natl Acad. Sci. USA* **68,** 820–823; 1971). He subsequently applied the same logic to other inherited tumours, such as Wilms' tumours (a type of kidney cancer) and those of the adrenal glands.

In 1983, cancer geneticist Webster Cavenee, then at the University of Utah in Salt Lake City, proposed that the genetic 'hits' in Knudson's mathematical models must be recessive, because the development of cancer happens only when both gene copies are mutated or lost. Using a technique called restriction fragment length polymorphism, Cavenee compared the DNA of tumours to that in normal tissues taken from people with retinoblastoma. He showed that the loss of heterozygosity (caused by a loss of the second, previously unaffected allele) led to cancer. (W. K. Cavenee *et al. Nature* **305,** 779–784; 1983).

Knudson's two-hit cancer hypothesis had a huge impact. Until this point, cancer was thought to be caused by the activation of oncogenes. Now the search was on for tumour-suppressor genes — whose loss of activity or function causes cancer. Knudson won the 1998 Albert Lasker Clinical Medical Research Award for his work on the genetic basis for cancer.

Knudson made other significant contributions through his leadership of one of the oldest cancer centres in the United States: the Fox Chase Cancer Center in Philadelphia, Pennsylvania. Joining in 1976, he spent 40 years there. He served as president (1980–82), scientific director (1982–83) and director of the centre's Institute for Cancer Research (1976–82).

The achievement of which he was most proud was giving Irwin Rose, a biochemist who joined the centre in 1963, US$50,000 so that Rose could extend the stay of two visiting scientists from Israel. Rose and these scientists, Avrum Hershko and Aaron Ciechanover, won the Nobel Prize in Chemistry in 2004 for discovering ubiquitin-mediated protein degradation. Cells use this process to break down and recycle protein; it has aided the development of several cancer drugs.

Alfred was a very supportive and approachable mentor, whose lack of patience for science that merely repeated the work of others kept everyone in his sphere striving for the new. He will be missed. ■

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