ALFRED G. KNUDSON

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Alfred G. Knudson was born in Los Angeles, California in 1922 to parents who worked with numbers and brought about his lifelong interest in math. Caltech was his "neighborhood school" and a natural choice for college. Although intending to study physics, he switched to biology because he thought all the problems in physics had been solved and realized that genetics had the same solid foundation as physics and chemistry. At Caltech, he trained with the legendary genetics professors Thomas Hunt Morgan and Alfred Sturtevant, and interacted with Ed Lewis—then a graduate student—and later with James Watson and Renato Dulbecco.

After graduating from Caltech in 1944, WWII prompted Al to join the Navy in order to support his training as a physician. Morgan suggested Columbia University for medical school, and Al applied with letters of recommendation from Morgan and Al's other Nobel Prize–winning Caltech professors, Linus Pauling and Carl Anderson. There he became very interested in the study of malignancies of children and had the foresight to think that such tumors were relatively easy (or easier) to study. He received his M.D. from Columbia in 1947. Al did his residency in pediatrics at New York Hospital and Memorial Sloan Kettering Cancer Center, allowing him to combine genetics and medicine. While at Memorial Sloan Kettering, he had a life-changing experience as the only full-time physician in a small unit of 20 children with cancer.

During the Korean War, Al spent two years as "a pediatrician in an Army uniform" to "pay back" the support he received by the Navy to attend medical school. He was stationed at Fort Riley, Kansas, caring for 1,500 newborn children and young adults on the base. Since he felt that "science was passing him by," and that medical students should be capable of understanding basic science if they wanted to understand pathogenesis and mechanisms of disease, he returned to Caltech with his wife and children to earn a Ph.D. in biochemistry and genetics, where he received support as a fellow of the John Simon Guggenheim Memorial. This training and his decision to study malignancies in children because of their "simplicity" were at the basis of his most important scientific contribution. What was striking about Al was his ability to carefully observe cancer in children and to formulate his hypothesis based on those observations and mathematics.

Al's first academic position was at the City of Hope Medical Center as Chairman of the Department of Pediatrics (1956–1966) and later as Chairman of the Department of Biology (1962–1966). There, in 1965, he published a still-relevant textbook, *Genetics and Disease*, in order to

"present . . . significant advances in terms of the human diseases familiar to the clinician, while suggesting . . . that genetics contributes to unifying our concepts of disease." This continued the theme of his scientific life and led to his decision to study pediatric cancer, since inherited cases were known and factors other than genetics were minimal.

During 1966–1969, he helped to establish the medical school and became the Associate Dean for Basic Sciences at the State University of New York at Stony Brook. In 1969, he moved to the MD Anderson Cancer Center in Houston, where he was Associate Director of Education, Professor of Biology and Pediatrics, and later, Dean of the Graduate School of Biomedical Sciences and Professor of Medical Genetics. At MD Anderson, using the detailed records of children treated for retinoblastoma, he developed his two-hit theory. He observed that children with familial retinoblastoma developed very early multiple tumors in both eyes, while patients with sporadic (non-familial) retinoblastoma developed a single tumor later and only in one eye. His interpretation was that children with hereditary (familial) retinoblastoma already carry a mutation in one of the two retinoblastoma genes (cells are diploid) from a parent. A second mutation leads to the loss of function of the gene causing the malignancy. In patients with the sporadic form of retinoblastoma both mutations are acquired in the somatic cells. His hypothesis was that retinoblastoma was caused by "two mutational events. In the dominantly inherited form, one mutation is inherited in the germinal cells and the second occurs in somatic cells. In the nonhereditary from, both mutations occur in somatic cells."[1] Later he applied the same logic to the study of other hereditary tumors, such as Wilms tumors and tumors of the adrenal glands.

In 1970 he moved to the University of Texas in Houston as Dean of the Graduate School of Biomedical Sciences. Thus, he was Dean when he developed and wrote the paper on his two-hit hypothesis of the pathogenesis of retinoblastoma, which was published in the *Proceedings of the National Academy of Sciences of the United States of America*.[2] This is curious since he did not have a particular admiration for most bureaucrats such as university deans and presidents. I remember him asking me, "Do you remember the name of university deans or presidents? Probably not, but you remember the name of the great scientists there!"

1 A. G. Knudson, "Mutation and Cancer: Statistical Study of Retinoblastoma," *Proceedings of the National Academy of Sciences of the United States of America* 68 (1971): 820–23.

2 Ibid.

In 1976, two important professional and personal events occurred (or "two hits" as a friend of his once said): he joined Fox Chase Cancer Center in Philadelphia, where he became Director of the Institute for Cancer Research (1976–1984) and President (1980–1982), and married Anna Meadows in 1976, whom he had met a few years earlier while he was a member of the External Advisory Committee in Oncology at the Children's Hospital of Philadelphia (CHOP). Anna, who was a fellow at the time, was interested in the etiology of childhood cancer; she told Al that she fell in love with his two-hit paper before she fell in love with him.

Al's two-hit hypothesis was proven to be true through the work of Webster Cavenee, then at the University of Utah, in 1983. Cavenee showed that the "two hits" in Knudson's model were correct, and that cancer develops when both copies of the gene are mutated or lost. Through the study of loss of heterozygosity of the retinoblastoma (Rb) gene, Cavenee showed that the loss of the normal gene led to the development of cancer.[3] The Rb gene was later cloned and characterized by Stephen Friend and colleagues.[4] All these findings led to the definition of tumor suppressor genes, the function of which must be lost in order to lead to tumor development. This was a very important discovery, since before these findings most of the scientific community believed that cancer was caused just by the activation of oncogenes. Such a discovery jump-started investigation into tumor suppressor genes.

Al stayed at Fox Chase for nearly 40 years, semi-officially retiring as Distinguished Scientist and Senior Advisor to the President in 2014, but continuing to work on manuscripts. He held positions of Director of the Institute for Cancer Research (1976–1983) and President (1980–1982) and established the Molecular Oncology Program, later defined by David Livingston as the "left ventricle of the Center," to which he recruited many colleagues. At Fox Chase, Al and his colleagues identified a germline mutation of the tuberous sclerosis 2 tumor suppressor gene, *Tsc2*, as the genetic determinant of renal carcinoma in the Eker rat. He worked with Michael Vilenchik on mutagenesis by ionizing radiation and implications for tumorigenesis and, over the last decade,

3 W. K. Cavenee, T. P. Dryja, R. A. Phillips, W. F. Benedict, R. Godbout, B. L. Gallie, A. L. Murphree, L. C. Strong, and R. L. White, "Expression of Recessive Alleles by Chromosomal Mechanisms in Retinoblastoma," *Nature* 305 (1983): 779–84.

4 S. H. Friend, R. Bernards, S. Rogelj, R. A. Weinberg, J. M. Rapaport, D. M. Albert, and T. P. Dryja, "A Human DNA Segment with Properties of the Gene that Predisposes to Retinoblastoma and Osteosarcoma," *Nature* 323 (1986): 643–46. Friend was Anna Meadows' resident at CHOP and had numerous conversations with both Anna and Al prior to cloning and characterizing the Rb gene.

his team worked closely to characterize gene expression changes in one-hit cells from genetically susceptible persons for cancer prevention.

Among his numerous prizes and honors were the Charles S. Mott Prize from the General Motors Cancer Research Foundation (1988), the Medal of Honor from the American Cancer Society (1989), the Gairdner International Award (1997), the Albert Lasker Award for Clinical Medical Research (with Janet D. Rowley and Peter C. Nowell; 1998), the Distinguished Career Award from the American Society of Pediatric Hematology/Oncology (1999), the Kyoto Prize (2004), and the AACR Lifetime Achievement Award (2005). He was an elected member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society. He served as President of the American Society of Human Genetics (1978) and was an inaugural fellow of the AACR Academy (2013).

Al believed it was very important to have original ideas and did not have much admiration for herd science. All the many discussions I had with him were on "original" science, trying to avoid what we now call "herd science," which has proliferated in the large swaths of scientific literature. He disapproved of "science that merely repeated the work of others," something that was evident in his groundbreaking research.

Al was extremely approachable, humble, without pretention, and loved to talk about science, particularly with young scientists and physicians. He had a boundless intellectual curiosity that extended well beyond genetics and medicine into astronomy, geology, pedagogy, and the nature of the universe, as well as passionate interests in art, music, and travel. He thought that his greatest achievement at the Fox Chase Cancer Center, of which he was extremely proud, was facilitating the work of Irwin Rose, an outstanding biochemist who joined Fox Chase in 1963. As President of Fox Chase, Al provided $50,000 to Rose in order to extend the stay at Fox Chase of two scientists who were visiting from Israel: Avrum Hershko and Aaron Ciechanover, who together with Rose discovered the process of ubiquitin-mediated protein degradation. This discovery led to the development of several anticancer drugs. Rose, Hershko, and Ciechanover received the Nobel Prize in Chemistry in 2004.

Al was a visionary and luminary, predicting a solution to the genetics of cancer before technologies for gene cloning were developed, shedding light on an entire field, and providing guidance to innumerable cancer clinicians and scientists all over the world. He was an outstanding, original, and imaginative scientist and a wonderful human being with whom it was a great pleasure to share ideas and friendship.

In addition to his wife Anna, he is survived by his daughters Linda, Nancy, and Dorene, his stepchildren Elizabeth, Brian, and Adam, 10 grandchildren and step-grandchildren, and five great-grandchildren. We all miss him.

Elected 1991

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