

In Memoriam: Lloyd W. Law (1910–2002)

Lloyd W. Law, Ph.D., died on October 28, 2002 at age 91. Dr. Law conducted important basic studies in mouse leukemia that laid the foundation for combination chemotherapy.

Dr. Law, a native of Ford City, Pennsylvania, earned his undergraduate degree in 1931 from the University of Illinois. Upon graduation, he taught biology in Charleston, Illinois for 3 years. He was awarded an Austin Fellowship, given to high school teachers for furthering their education in science, and in 1934, he was accepted at Harvard University in the Genetics Department whose Chief was William E. Castle. Dr. Law's thesis work dealt with the inheritance of genes that controlled the size of mice and established his lifelong interest in the genetics of the mouse. He earned his Ph.D. from Harvard in 1937.

While at Harvard, Dr. Law met George Beadle, who invited him to do postgraduate work in his new laboratory at Stanford University. At Stanford, Dr. Law worked on feeding a factor that changed the eye color of adult flies. This was the beginning of a fascination with chemical substances that modified genes. The next year, at the invitation of C. C. Little, he moved to Bar Harbor, Maine, to join the staff of The Jackson Laboratory. Here he resumed his interest in mice but now began to study cancer in mice, a subject he would never abandon.

Dr. Law began inducing tumors by injecting mice with azo compounds that induced sarcomas, hepatomas, and occasionally "leukemias" (the name used for tumors of hematopoietic origin), which became particularly interesting and opened a new field to him. At this time (1938–1939), John J. Morton and his assistant G. Burroughs Mider visited The Jackson Laboratory and described their intriguing new discovery that painting the skin of DBA mice with methylcholanthrene led to the rapid development of leukemias in a high percentage of the mice in 2–3 months. Dr. Law immediately repeated the work, and from that point forward, mouse leukemia became his primary research focus.

In 1942, Dr. Law joined the Air Force as a physiologist and pilot instructor. He rose to the rank of Captain. That year, he also married Bernette Bohlen, an artist who had come to The Jackson Laboratory to help with medical illustrations. In 1946, Dr. Law returned to Bar Harbor to resume his work. He set up a laboratory devoted to mouse leukemia using newly developed transplant lines, but there was now a new direction and interest. He began treating leukemic mice with chemotherapeutic agents, adrenal cortical extracts and urethane. At the urging of Walter Heston, he moved to the NCI¹ in Bethesda, Maryland in 1947, where he established leukemia research at the NCI.

The age of the antimetabolites in leukemia was rapidly expanding. Sidney Farber in Boston showed that remissions could be induced in childhood leukemia by folic acid antagonists (*e.g.*, amethopterin). George Hitchings and Gertrude Elion began producing antagonists in purine biosynthesis. Joseph Burchenal at Sloan Kettering used transplantable AKR leukemias, and Dr. Law studied the responses of DBA/2. The folic acid antagonists did not inhibit the AKR leukemias, but Dr. Law's famous L1210 cell line was sensitive to amethopterin and 8-azaguanine mercaptopurine. Lloyd and Joseph Burchenal independently discovered that leukemic lines could become resistant to amethopterin and the antipurines. Dr. Law showed that L1210 amethopterin-resistant cells were still responsive to 8-azaguanine.

Amid great discussion at the time about whether these drugs in-

duced resistance in the leukemic cells or whether preexisting resistant cells were selected out in drug-treated mice, Dr. Law applied the Luria-Delbrück fluctuation test to the development of resistance in L1210 to amethopterin and showed that the original tumor contained both sensitive and resistant cells in varying proportions. Amethopterin alone would be inadequate to eradicate most leukemic populations, and a second antimetabolite, working on different enzymes in purine pyrimidine biosynthesis, would be required to inhibit the amethopterin-resistant cells. From this came the concept of combination chemotherapy, using antimetabolites affecting purine and pyrimidine biosynthesis, and the idea that resistance to one agent occurred independently of the other because each involved an independent metabolic pathway. With the opening of the Clinical Center at the NIH in 1953–1954, and the arrival of clinicians (James Holland, Gordon Zubrod, Emil Frei, and Emil Freireich) interested in treating acute leukemia of childhood, Dr. Law's research became the basis of numerous discussions on the concept of combination chemotherapy.

Dr. Law's interest in mouse leukemia extended now into mechanism and pathogenesis. He was ever aware that the L1210 model was only part of the constellation of mouse leukemias and that other model systems existed that should be exploited. The NCI recognized his abilities and created the Leukemia Studies Section within its Laboratory of Biology devoted to leukemia research. The Laboratory of Cell Biology was established in 1970 to allow the expansion of Dr. Law's research program, and he became its Chief from 1970 to 1990. At one point, that laboratory became one of the largest at NCI and attracted many eminent scientists to work and train there. Dr. Law continued his interest in cancer chemotherapy with that group and expanded his research program to study tumor immunology. Soon he was at the forefront of that field as well.

Later, Dr. Law became fascinated with the Stewart/Eddy polyoma virus and focused on the immunity of the polyoma virus into the 1970s. He pioneered the concept of common tumor antigens and tumor-specific antigens and established effective immunization protocols whereby mice could be protected against subsequent challenge by one or more types of tumor cells. He retired as Lab Chief in 1990 and became Scientist Emeritus.

The NCI honored Dr. Law on his 90th birthday in 2001 with a symposium on combination chemotherapy. Among the participants were Joseph Burchenal, James Holland, Emil Frei III, and Emil J. Freireich. He continued his frequent visits to NIH during that time, and his colleagues always welcomed him for energetic discussions of their research. He continued his insightful comments at each such occasion until his death.

Throughout his career, Dr. Law served on numerous advisory committees and received many awards, including the AACR Richard and Hinda Rosenthal Award in 1957, the AACR G. H. A. Clowes Memorial Award in 1965, and the G. B. Mider Lectureship in 1970. In 1967, he was elected president of the AACR, and he was elected an Honorary Member in 1987. He was also elected an Honorary Member of the European Association for Cancer Research.

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¹ The abbreviation used is: NCI, National Cancer Institute.