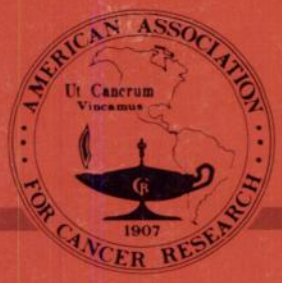
February 15, 1988



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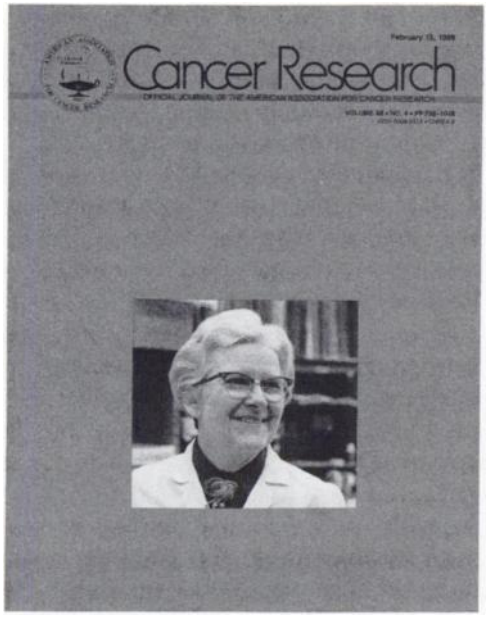
COVER LEGEND



Elizabeth Cavert Miller, who succumbed at 67 to metastatic kidney cancer on October 14, 1987, was an exceptional person. Members of the cancer research community, and indeed scientists from many disciplines around the world, recognize that her contributions to the metabolism of chemical carcinogens and to related topics are unrivaled.

She received a B.S. degree in Biochemistry from the University of Minnesota in 1941. As a WARF Scholar, she received her M.S. and Ph.D. degrees in Biochemistry at the University of Wisconsin in 1943 and 1945, respectively, under the direction of Carl A. Baumann. In 1942, she married James A. Miller, a fellow graduate student. After 2 years of postdoctoral work at the McArdle Laboratory for Cancer Research, she advanced through the professorial ranks and became Professor of Oncology in 1969. During this time she raised two daughters while working part time in the laboratory. Subsequently, she became Associate Director of the McArdle Laboratory in 1973, WARF Professor of Oncology in 1980, van Rensselaer Potter Professor of Oncology in 1982, and WARF Senior Distinguished Research Professor in 1984.

A 1947 paper in *Cancer Research* coauthored by the Millers entitled, "The Presence and Significance of Bound Aminoazo Dyes in the Livers of Rats Fed *p*-Dimethylaminoazobenzene," is a classic example of careful, thorough work and perceptive interpretation. For the first time it was recognized that a carcinogenic molecule had been metabolically modified to react covalently with a critically important component of a living cell. Shortly thereafter, working independently, Elizabeth Miller, utilizing the fluorescent properties of benzo(*a*)pyrene, reported the formation of protein-bound derivatives of the hydrocarbon in mouse skin. This project was undertaken prior to the availability of isotopically labeled carcinogenic hydrocarbons and was the first report of the covalent binding of a polycyclic aromatic hydrocarbon to a cellular macromolecule.

The Millers and their associates were the first to discover that the majority of chemical carcinogens require metabolism to reactive electrophilic forms that combine with nucleophilic atoms in cellular macromolecules, especially DNA, to initiate the processes that are involved in carcinogenesis. They also found that carcinogens are inactivated in the body in several ways. Furthermore, they demonstrated that the extents of these activations and inactivations could be greatly altered by the coadministration of many carcinogenic as well as noncarcinogenic chemicals. Thus the induction of the oxidases of the endoplasmic reticulum as a consequence of the administration of certain foreign chemicals to rats and mice was discovered. This finding played an important role in the development of the field of the cytochrome P-450 oxidases. These observations by the Millers have been among the most important discoveries in the entire history of cancer research as well as for understanding how countless numbers of plant constituents, hormones, drugs, and many foreign substances are detoxified and sometimes activated. A whole new era of pharmacology and toxicology research resulted from their original findings.

After establishing the generalization that the ultimate carcinogenic metabolites of chemical carcinogens are strong electrophilic reactants, the husband and wife team and their associates demonstrated that an ultimate carcinogenic electrophile can be mutagenic in a bacterial system. Thus, the basis was established for the use of mutagenesis assays, utilizing a source of activating enzymes, as a prescreen for potential carcinogenic activity of chemicals.

Other highlights in the career of Miller together with her husband and their associates include the characterization of the nucleic acid- and protein-bound derivatives of several chemical carcinogens in rat and/or mouse liver. There remained the question of the chemical structure of the ultimate electrophilic metabolite prior to *in vivo* covalent interaction with the nucleophilic atoms of the informational macromolecules. By careful and insightful research, it was demonstrated that sulfuric acid esters are the major carcinogenic metabolites of several alkenylbenzenes and aromatic amine derivatives.

Elizabeth Miller contributed countless hours to the American Association for Cancer Research and its

journal. From 1954 through 1964 she was the Scientific Editor and sole Associate Editor of *Cancer Research*. She served on several committees of the AACR, was twice elected to the Board of Directors (1957–1960 and 1974–1977), and was elected president for the 1976–1977 year. Her Presidential Address, published in *Cancer Research* in 1978, had been cited more than 650 times by mid-1987 according to *Science Citation Index*.

In addition, she served on many grant review as well as policy committees of the NIH and American Cancer Society. She had served on the Board of Directors of the American Cancer Society since 1980 and was appointed to the President's Cancer Panel of the National Cancer Institute in 1978. She was a member of the Advisory Committee to the Director, National Institutes of Health, 1984–1987.

Because of the importance of the fundamental discoveries that were made by this husband and wife team, they received the unique honor of concurrent election to membership in the National Academy of Sciences in 1978. The awards that they received, too many to list completely, included the following: Bertner, Papanicolaou, Bristol-Myers, FASEB Life Sciences, and the General Motors Mott Award. They were acclaimed internationally.

In addition, Elizabeth Miller, known as Betty to her many friends, worked tirelessly and effectively for the welfare of the McArdle Laboratory for Cancer Research and the University of Wisconsin. She served as Associate Director of the Laboratory from 1973 until she resigned only a few months before her death. In this capacity she helped all of the members of the Laboratory in countless ways. Together with her husband, Jim, she taught many graduate students and postdoctoral fellows the joys of scientific research by instilling in them enthusiasm for research. Both were patient yet demanding of the highest standards. One of Betty's greatest joys was the accomplishments of her former associates after they left her laboratory.

Betty was devoted to her two daughters, Linda and Helen. They grew up in a loving, caring family that took the time to go on canoeing and camping trips together and to learn the beauties of nature. The girls were encouraged to develop their talents to the fullest; Linda is a Ph.D. candidate in textile art, and Helen is an assistant professor of Botany-Ecology at the University of Kansas.

Betty excelled as a wife and mother as well as a scientist and administrator. She was very competent, modest, and helpful—an exemplary human being in every way.

Roswell K. Boutwell
Van R. Potter