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ELIZABETH CAVERT MILLER
1920—1987

JAMES A. MILLER
1915—2000

A Biographical Memoir by
BY ALLAN H. CONNEY, MIRIAM C. POIRIER,
YOUNG-JOON SURH, AND FRED F. KADLUBAR

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Biographical Memoir

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Elizabeth C. Miller

James A. Miller

ELIZABETH CAVERT MILLER

May 2, 1920–October 14, 1987

JAMES A. MILLER

May 27, 1915–December 24, 2000

BY ALLAN H. CONNEY, MIRIAM C. POIRIER,
YOUNG-JOON SURH, AND FRED F. KADLUBAR

James and Elizabeth Miller were a rare husband-and-wife team elected jointly to membership in the National Academy of Sciences in the same year, in 1978. Their wish was to have one memoir written for both.

JAMES A. MILLER AND ELIZABETH C. MILLER discovered and developed the important unifying concept that most carcinogenic and mutagenic chemicals are not carcinogenic or mutagenic per se but that these compounds must undergo metabolism to reactive electrophilic metabolites that exert their effects by covalently binding to critical sites on cellular macromolecules (DNA, RNA, and protein). James and Elizabeth Miller were the first to point out that “as a general class, chemical carcinogens would appear to be potential mutagens, and the mutagenicity of a chemical carcinogen in a given system will depend on its extent of conversion to electrophilic reactive form(s) and on the access of these active form(s) to the genetic material in the mutagenicity system under study.” These discoveries and novel concepts initiated a new era of modern toxicology and were the basis of (1) rapid mutagenicity tests (the Ames test and others) for the screening of potential human carcinogens, (2) research on

chemically induced mutations in protooncogenes and tumor suppressor genes, (3) large person-to-person differences in the sensitivity of people to environmental carcinogens (interindividual differences in the metabolism of carcinogens to their active forms), (4) formation of macromolecular adducts as indicators of cancer risk in molecular epidemiology, and (5) international laws regulating carcinogens in the diet and the environment.

EARLY LIFE OF ELIZABETH C. MILLER

FROM J. A. MILLER (1993,1)

Elizabeth Cavert Miller ("Betty") was the second daughter of Mary Elizabeth Mead (1890-1976) and William Lane Cavert (1887-1977). Her parents grew up on farms in Charlton, Saratoga County, New York, not far from Schenectady.

Elizabeth Miller was born into a well-educated family. Her father graduated from Union College in Schenectady after attending high school in that city. Betty's father was attracted to agricultural economics. After graduating from Union College in 1910, he attended Cornell Agricultural College in Ithaca and in 1912 obtained a B.S. degree in farm management. Betty's mother graduated from Vassar College in 1912 and studied home economics at Columbia University until 1914.

Betty's parents were married in 1914 and settled in St. Paul, Minnesota, where her father obtained an M.S. degree in farm management at the University of Minnesota. He joined the Agricultural Extension Division of this university as a specialist in the management of farms and continued his studies in agricultural economics. In 1929 Betty's parents took the children to Cornell University at Ithaca for a year while her father completed his Ph.D. degree in agricultural economics. The family returned to St. Paul, and in 1935

Betty's father became the chief statistician and then director of research in farm management at the Farm Credit Administration, District 7, in St. Paul. He retired from this position in 1957.

Elizabeth Miller grew up and received some of her elementary education in St. Paul. Because of the Great Depression the family moved in 1930 to the nearby town of Anoka, Minnesota, where they had a large garden to aid their budget. Betty helped raise turkeys and chickens and sold chicken eggs as part of her chores. She early absorbed the elements of economics and thrift from her parents, especially from her father. She completed her elementary education and graduated from high school in Anoka in 1937. Her parents saw no reason that women should not be educated as fully as men and made every effort to support their children in attending the University of Minnesota. Betty was an excellent student and had become interested in chemistry through a stimulating teacher in high school. Her father felt she should major in home economics at the University of Minnesota, but she chose instead agricultural biochemistry as a major and economics as a minor. The Department of Agricultural Biochemistry at the University of Minnesota was highly rated at that time. The chair of this department was Professor Ross A. Gortner, an outstanding scientist. He was a family friend and became Betty's mentor. Professor Michael Sandstrom in the department hired Betty to do analyses during the summers and encouraged her to continue in biochemistry in graduate school. She had the highest grade-point average in the entire College of Agriculture and received several scholarship prizes during her undergraduate years. She was also honored by election to Phi Beta Kappa.

Elizabeth Miller considered several universities for graduate work in biochemistry and finally chose the illustrious Department of Biochemistry at the University of Wisconsin in

Madison. The Research Committee at the university awarded her a Wisconsin Alumni Research Foundation (WARF) Scholarship. She arrived in Madison in the fall of 1941 and immediately encountered a sex bias in that the Department of Biochemistry would not accept her for graduate study in biochemistry alone. The department was finding it difficult at that time to find suitable jobs for their male Ph.D. graduates. As a result, they offered Betty a joint program in biochemistry and home economics. She decided to try this for a year and soon demonstrated her skills in course work and research.

In 1941 James A. Miller ("Jim") was a teaching assistant in charge of the laboratory class of the main graduate course in biochemistry. Jim recalled noticing Betty in the first period of that class. She had a way of showing her complete attention to any important matter at hand and executing it with care and dispatch. Jim paid a lot of attention to Betty and got to know her well. She was not finding her graduate research in a joint biochemistry-home economics program very interesting. Jim interceded with his major professor, Carl Baumann, to take her as a graduate student. This succeeded, and Betty started research on the metabolism of the vitamin pyridoxine in mice under Professor Baumann.

Jim soon realized that Betty was a very intelligent and wonderful young lady, and he fell in love with her and was shocked to find that she was already engaged. Her fiancé was in graduate school at the University of Iowa, so Jim had the advantage of location and time to pursue his case. After a few more months Betty became willing to go on dates with Jim. Jim indicates that the most important event in his entire life occurred early in the summer of 1942 when Betty broke her engagement and accepted Jim's proposal of marriage. This distressed Betty's parents, who felt that things had moved too fast. Furthermore, Jim and Betty wanted to marry soon and

did not want a big wedding. Betty's parents finally agreed to a simple wedding at home on August 30, 1942, with only a few guests. Her parents eventually accepted Jim graciously. Betty had started to smoke cigarettes in college, and her father heartily disapproved of this habit. Since Jim did not smoke, Betty simply stopped smoking and never took up the habit again. This considerably hastened Jim's acceptance by her father.

EARLY LIFE OF JAMES A. MILLER

FROM J. A. MILLER (1998)

James A. Miller ("Jim") was born on May 27, 1915, in Dormont, Pennsylvania, near Pittsburgh to a middle-class family as the fifth of six sons. His parents had only an eighth-grade education, but they greatly respected higher education. They also imbued their sons with a strong work ethic. As was the custom in the early 1900s, the first three sons had only one or two years of high school and then sought jobs. In the 1920s an older brother and Jim completed high school. Jim's early boyhood was a happy one, and with gifts of erector and chemistry sets he became interested in science as early as he could remember.

A dark period in Jim's family life occurred in the 1920s when his family endured four deaths in a period of six years. His oldest brother died from pneumonia, as did his mother's sister who lived with them. Next, his younger brother was killed by a car near their home. Worst of all, his mother died from a stroke in 1929 at the age of 49. From the evident chance occurrence of these deaths Jim became and remained an agnostic in religious matters. His father lost his job in 1930 and was seriously ill for several years. The four remaining brothers stayed together during Jim's years in high school and supported him in his efforts to go to college.

Jim graduated from high school in 1933 in the depth of the Depression and with few prospects of attending college. During the two years after high school, Jim was lucky to get a job as a timekeeper of piecework in a welding shop in a steel mill. He enjoyed the work because it was science in action, but this job lasted only six months until the work had been completed. Jim used the money earned from this job to take evening classes for the first year of college at the University of Pittsburgh. Then he was fortunate to get a job funded by the National Youth Administration to assemble reagents for the freshman chemistry class at the University of Pittsburgh. In 1935 with the help of his brothers, Jim enrolled in an honors course in chemistry at the university.

Another lucky break grew out of his job in his freshman year. Professor Hjort, whom Jim worked for in this job, shared an office with a professor of biochemistry named Charles Glen King. Professor King was well known at the time, for he and a graduate student had recently isolated the first vitamin (vitamin C) to be obtained in a pure state. As it turned out, Professor King needed help in his animal room, which was an old army barracks near the chemistry school. He chose Jim for this work. With this job and help from his brothers he was able to complete his college career. The animal work required only about 20 to 25 hours a week while he was completing his course work. Jim developed skills in cleaning cages and mixing diets for many guinea pigs, rats, mice, and one dog. An important opportunity in learning also opened for Jim in Professor King's efforts to get research grants (before NIH). With a grant from a local department store foundation, King was able to support several Ph.D. research associates. Happily, among these was Max O. Schultze, who had just obtained his Ph.D. at the famous Biochemistry Department in the School of Agriculture at the University of Wisconsin at Madison. Jim learned a lot

about the rigors of biochemical research from Max. In this wonderful research atmosphere Jim resolved early that he would make the most of his course work and the research going on around him. Jim graduated in 1939 in chemistry from the University of Pittsburgh with highest honors. On considering graduate work for the Ph.D. degree, Max advised Jim to apply to the Biochemistry Department at Madison. Jim was awarded a Wisconsin Alumni Research Foundation Scholarship in Biochemistry.

In the fall of 1939 Jim arrived in Madison to start graduate work. He joined in research with Professor Carl Baumann, a young assistant professor of nutritional biochemistry. Baumann needed help with studies on the effects of diet on the liver tumor-producing activities of 4-dimethylaminoazobenzene (DAB) in rats. Baumann was collaborating with Professor Harold Rusch in the Medical School in studies on this and other chemical carcinogens. In 1940 the McArdle Laboratory for Cancer Research was established with Professor Rusch as its director. In 1940 Jim became a teaching assistant and conducted the graduate laboratory course in biochemistry. It was in that course that Jim met and fell deeply in love with Elizabeth ("Betty") Cavert, a WARF scholar in biochemistry from the University of Minnesota. Jim and Betty were married in August 1942. She became a graduate student under Professor Baumann. They hoped to find university positions near each other once they had their Ph.D.s.

Jim obtained his Ph.D. in 1943 on the fluorescent properties of the polycyclic aromatic hydrocarbons. He had also started to study the metabolism of 4-dimethylaminoazobenzene in rats. Betty obtained her Ph.D. in 1945 on the toxicity of high-protein diets in mice deficient in vitamin B₆. In 1944 Professor Rusch offered Jim an instructorship in the McArdle Laboratory to start a program on chemical carcinogenesis. After Betty obtained her Ph.D., Rusch got

her a postgraduate fellowship in cancer research. Eventually, Betty and Jim started their work together with Rusch's full support. Their joint careers were entirely at McArdle for 45 years, and they ascended the academic ladder with the support of Professor Rusch.

Jim and Betty avoided having children for 10 years while they concentrated on their research. After that they decided to have children. They raised two daughters. Both of them went to the University of Wisconsin for their B.S. degrees. Linda obtained a master's degree from the University of Wisconsin-Menomonee in her art work and is now a fiber artist and fabric expert residing in Schofield, Wisconsin. Helen obtained her Ph.D. in botany from Duke University and is now a professor of botany-ecology at the University of Kansas at Lawrence. Sadly, in October 1987 Betty died prematurely of renal cancer. On recovering from that terrible loss, Jim married Barbara Butler in December 1988. Barbara had been Betty's assistant for nine years. Shortly after marrying Jim, Barbara received a Ph.D. in Near Eastern studies from the University of Michigan at Ann Arbor.

PERSONAL COMMENTS ABOUT THE MILLERS FROM
COLLEAGUES AND STUDENTS

Comments at Memorial Services for Elizabeth Miller and James Miller

HENRY C. PITOT (OCTOBER 25, 1987)

Betty and I started out in the administrative field as actors, she as Acting Director of the McArdle Laboratory and I as Acting Dean of the Medical School. When Harold Rusch resigned from the Directorship of the McArdle Laboratory, my colleagues asked me to assume his duties and gave me the right to choose my associate. One makes few really outstanding correct decisions in one's time on this earth. The decision to ask Betty Miller to assist me in the administrative duties of the McArdle Laboratory was one of the best decisions I have or ever will make. Dr. Rusch, the first director

and founder of the McArdle Laboratory, once told me that he viewed the position as one of service, service to one's colleagues, in order to insure that the best science and cancer research would come from their work. I never knew whether Harold counseled Betty in the same way, but her approach to departmental administration was the epitome of Harold's advice, one of service to her colleagues. She was concerned that the science at the McArdle Laboratory be of the highest caliber, and she let this be known to all her colleagues, including myself, in ways that were quite understandable. By her constant urging, her insistence on detail, and striving for the very best from all of us, she not only fostered the scientific excellence for which the McArdle Laboratory has been characterized, but she also, with her husband Jim, made discoveries which are at the very foundation of our understanding of how chemicals cause cancer, as well as, of our future ability to prevent cancer in the human which is caused by such agents.

VAN RENNELAER POTTER (OCTOBER 25, 1987)

The succession of honors that have come to Betty and Jim as a husband and wife team is almost unparalleled in the annals of science, yet I have never heard either one of them make an assertive self-serving statement. When speaking of their findings neither of them has ever used the personal pronoun I.

How sad it is that Jim and Betty can never share the Nobel Prize, which they unquestionably deserve, because the prize is given only to living persons.

There is only one woman, to my knowledge, whose career as a wife and research partner is comparable to that of Elizabeth Miller in the terms that I have described. That woman was Marie Sklodowska Curie, the daughter of a Physics professor at the University of Warsaw, Poland. Since women were barred from attending that University, Marie Sklodowska came to Paris in 1891 at the age of 24 to study physics with Professor Antoine Henri Becquerel and with Pierre Curie. She was married to Pierre Curie 4 years later. Together they discovered radioactivity. Marie and Pierre Curie shared the Nobel Prize with Professor Becquerel in 1903. Tragedy struck only 3 years later when Pierre Curie was run over and killed by a wagon with runaway horses.

Marie Curie continued to do research and was the sole awardee of a second Nobel Prize in 1911 for isolating pure radium. She had discovered radium, and polonium, which she named after her homeland, back in 1898 when she was working with her husband and Professor Becquerel.

Marie died of anemia at the age of 67, a victim of the radioactivity she had studied, just as Betty Miller died at age 67, a victim of the disease she had studied.

HOWARD TEMIN (OCTOBER 25, 1987)

The tragedy of Betty Miller's untimely death from the disease she had spent her life trying to understand and prevent makes it especially important to honor her life. In her life, Betty accomplished an incredible amount in cancer research and at McArdle in her quiet, efficient, unflappable way. She did all this while raising two delightful daughters and maintaining a close family life and home—a difficult juggling act for anyone.

Betty accomplished on her own merits. It seemed to me she would want to be remembered as a scientist who was also a woman and not as a woman scientist. Certainly at staff meetings she was impatient with attempts to use sex in judging people.

As I was asked more often to give general talks at national meetings, I used to go to the seventh floor (we were in the new building by then) to check with Betty and Jim various points about carcinogenesis and cancer in general for by then I realized that the world's authorities were right here in McArdle. I had many more interactions with Betty when she became Associate Director, and I had more administrative responsibility. I marveled at how she got everything done, but always seemed to have time to listen to problems and to give advice. Many times I walked first to the seventh floor to be told by Jim that Betty was upstairs and then up to her little office on the tenth floor. I would knock and she would say come in, looking up from a clutter of papers she was working on. I would ask if she had a few minutes, and she would always put aside her work to talk to me about grant preparation or other McArdle business. I always left reassured or redirected.

When I think about the reasons I have stayed here in Wisconsin, I realize that a major reason has been the people here like Betty Miller who had

stayed at Wisconsin. Betty had an intense institutional loyalty to McArdle, the University of Wisconsin-Madison, Jim, her family, cancer research, and science in general. She expressed her loyalty by her actions to further the well being of all around her in a selfless and unassuming way and a willingness to do some unglamorous jobs.

We are all diminished by Betty's passing. I especially will greatly miss having Betty's level headed advice, and I will use her example and memory as a guide.

VERONICA M. MAHER (OCTOBER 25, 1987)

I was not officially a graduate student of the Millers, nor were they officially on my committee for my Ph.D. in molecular biology while I was at McArdle. But Betty played an important role in my scientific career and in my life—a role I did not recognize for a long time. And when I graduated, she was willing to escort me to the stage for my diploma in the absence of my major professor, Dr. Szybalski.

When I began my doctoral studies in 1964, I had never heard of the term "role model." It was not until years later that I considered the term—what came to mind were the several role models I was privileged to have—women who spoke to me through their actions—their lives. One of these surely was Betty Miller.

When I began my graduate studies at McArdle, she was there on the staff—a fully trained, very capable scientist, equal in ability and stature with other members of the staff. And so it never entered my mind that there was anything unusual about a women scientist being in charge, entrusted with major responsibilities, the principal investigator of scientific research programs, securing major outside funding, directing graduate students, and so on. Therefore, later on, it never entered my mind that I would not begin my own career as a principal investigator, in charge of my own independent laboratory. Only later did I come to realize that other women did not have such an example.

When I attended major scientific meetings, there was Betty Miller. Sometimes she was the organizer of the meeting. Always she was an earnest participant, attending every session, asking critical key questions—even giving

the Presidential address—always very professional, very prepared, a *standard bearer*, a role model.

ROSSELL K. BOUTWELL (OCTOBER 25, 1987) (WITH MINOR REVISION)

Helen and Linda (the Miller's children) tell me that when they were young they thought they had a typical mother. She did everything that their friends' mothers did. There was one difference; the lullaby they heard after goodnight kisses was the sound of the typewriter. We, at the lab, found Betty the same as always; her research continued unabated, she supervised such things as the Department's open store-room, and led the Department seminar-journal club based on her knowledge of current literature. In one of the weekly seminars, Betty presented a paper she had read on the toxicity of the substitution by fluorine of a hydrogen atom in an amino acid (*JBC*, 188: 91-95, 1951). The conception by Dr. Heidelberger of fluorouracil as an anticancer agent much later was a consequence of that seminar.

I frequently saw Helen and Linda helping their mother provide food and water for the laboratory animals on the major holidays; Betty did this so that the animal caretakers could enjoy those holidays with their families. This act was so very typical. Betty had several priorities, all equal. Among these was the well-being of the people associated with the Millers. Particularly in the case of those who came from abroad, she made certain of their housing and that their basic needs were met. Assuring the proper care of the experimental animals was as important as her love and care for her family.

A recent highlight for Betty and Jim was the family trip to the Galapagos Islands and Ecuador, a gift in 1985 from their former students. Betty and Jim marveled at the unique flora and fauna of the islands that earlier had a major impact on Darwin. Betty snorkeled, and she rode on the rooftop of a train car through the mountains of Ecuador while clinging to the cat-walk, the only mature passenger from the U.S. to brave the challenge. Betty's sense of adventure remained strong.

ALLAN H. CONNEY (OCTOBER 25, 1987 AND JANUARY 14, 2001)

I had the good fortune of working as a graduate student with Betty and Jim Miller from 1952 to 1956. During this period and for the years that followed, Betty and Jim have been my parents in science. They taught me how to do

research, and I first experienced the joys of discovery with them. Both Betty and Jim tried very hard to instill their high standards into my research, even though they most certainly found me to be a very difficult student. The dedication of Betty and Jim's life to research and the high standards that were set by them inspired their students to set high standards for their own work. It was common for us to work in the laboratory on Saturdays, Sundays, and holidays. Betty and Jim served as role models, and they taught us by their example to dedicate our lives to research and to strive for excellence. Betty and Jim trained many students who then went on to make their own contributions to science.

When I was a graduate student, my normal working habits resulted in several experiments each week, and each experiment generated lots of dirty glassware that I rinsed and placed in sulfuric acid/dichromate cleaning solution. However, I was not always prompt in cleaning up my glassware, and my lab bench often had dirty glassware on it, even though Jim had given several gentle suggestions that I should keep my lab bench neat. One Saturday morning, when I came to work, I was greatly distressed to find Jim cleaning my glassware and my lab bench. When I tried to take over the glassware cleaning job, Jim simply said that he could handle it himself. This approach to teaching good housekeeping practices made a lasting impression on a young student and was a part of Jim's teaching by example.

After the untimely death of Betty, Jim married Barbara Butler, a former lab assistant in Jim and Betty's lab. Although Jim did not forget Betty, he was very much in love with Barbara, and she was a very important part of Jim's life in his later years.

NORMAN DRINKWATER (JANUARY 14, 2000)

Like many others, I feel extremely lucky to have been Jim's student. Seventy eight of us have had the opportunity to work in the Miller laboratory as graduate students or post-doctoral fellows. I first met Jim when he and Betty hired me as an undergraduate assistant in 1973 and was their graduate student from 1975 to 1980. Jim was a truly exceptional mentor, a wise and faithful counselor and teacher who brought out the very best in each of us. He was also extremely patient. When I, and two others nearly blew up the lab in a particularly foolish attempt to purify some chemical solvent, his only comment later was "it really is a good idea to check Fieser before setting up

that sort of thing.” “Fieser,” referring to the lab’s well-thumbed copy of a compendium of organic syntheses. As students, we would sometimes enter our regular research meetings with them, our arms full of notebooks, chart recorder tracings, and paper towels with scrawled notes, with a slight mixture of confusion and dread, but were invariably greeted by Jim’s “What do you have?” Jim’s great smile and the twinkle in his eye instantly communicating both his love of science and his confidence that we would ultimately learn how to do it well. The remarkable thing is that Jim’s enthusiasm for us and what we were doing was there for all of us and always, even when we hit those bad patches of several months of failed experiments. We always left those meetings, after being nudged in the right direction, gently or firmly as the need arose, feeling smarter and better able to do science.

ADDITIONAL COMMENTS FROM FORMER STUDENTS

MIRIAM POIRIER (AUGUST 2008)

The beginnings of my research career were as a graduate student in the Miller lab, where I was largely directed by Jim. At many difficult junctures, and sometimes when I was close to tears, Jim would listen to all of the details of my experiment and provide me with several possible solutions to the problem. He did not mince words when he considered that sloppy technique was a contributing factor, but he had a clarity of thought that allowed recreation of an experiment in his head, and he was adept at problem solving or suggesting new directions. In the process we graduate students learned experimental creativity, hypothesis validation, and a scientific caution that has sometimes been expressed as “beating a dead horse”. His exquisite sense of optimal experimental design is among the most valuable gifts that Jim gave to his students, and for that I have been profoundly grateful every day of my research career.

I did not finish the PhD but left the Miller lab with an MS degree. Several years later, as the mother of three small children, when I expressed my desire to finish the degree, Jim and Betty were completely supportive. It was then that I realized how important a friend and mentor Betty had been and would be to me. In subsequent years Betty and I frequently met at meetings, and I always delighted in her wisdom and friendship. Jim’s support was something I enjoyed and treasured for the remainder of his life, even after Betty’s passing and when he was married to Barbara. From scientific

recommendations, to critical advice in my decision to go to the Galapagos shortly before he passed away, Jim was always the cheery voice on the other end of the phone line. I felt I had lost a treasured friend when he was no longer with us.

Were it not for the training given by Jim and Betty Miller, the scientific careers and contributions of many talented scientists would not have been possible, and biomedical research would be substantially the poorer for it. Perhaps the best tribute that any of us can give the Millers is to continue their tradition of quality scientific discovery and mentoring, because we all do stand on the shoulders of those who have gone before us.

YOUNG-JOON SURH (SEPTEMBER 2008)

It has been a great privilege to be the last student of Jim and Betty Miller. I learned not only good science, but also a virtue of life from them. I am proud to be a member of Miller's academic pedigree, which has kept me pursuing the high standards that Jim and Betty maintained during their academic careers.

FRED F. KADLUBAR (AUGUST, 2009)

I was fortunate to be a postdoctoral fellow for Elizabeth and James Miller from 1973 to 1976. Besides being exemplary scientists and role models, they were the best mentors I have ever encountered. Unlike some of us, I kept my lab spotless. **I had to** as I was working with radioactive, highly colored azo dyes. You could easily see 100 dpm. But I came to the lab as a Texan schooled in intimidation. Betty and Jim showed me the error of my ways in that and in several other areas. They always showed their postdoctoral fellows a better approach, and they treated them with respect even if the lessons were sometimes difficult. My own terminology is that they were experts in behavioral modification, and I learned much about how to manage a laboratory. They were even kind to me when I introduced them to jalapeño peppers two weeks after I had joined the laboratory, i.e., I still had a job.

Another quality that I never forgot and adopted accordingly was their willingness to stop what they were doing and talk about your science at any time, weekdays or weekends. That was always the most important thing. You never had to make an appointment and their door was always open.

We did use Fieser in what turned out to be an explosive pentane distillation. Fieser just neglected to say to use diluted sulfuric acid. When you use concentrated sulfuric (like we did) and permanganate, you form Mn_2O_7 , a green solid that detonates on contact with air. But Betty handled this very calmly, used the expertise of the bomb squad; and I still had a job.

CONTRIBUTIONS TO SCIENCE

James and Elizabeth Miller provided the first demonstration of the metabolism of a foreign chemical to intermediates that covalently bind to macromolecules. They found that administration of hepatocarcinogenic aminoazo dyes to rats resulted in the covalent binding of dye metabolites to protein in the liver (they observed a tightly bound pink color in well-washed trichloroacetic acid precipitates of protein) (1947). Little or no covalent binding occurred in nontarget tissues that were refractory toward tumorigenesis by these dyes. In this early study the Millers also looked for the covalent binding of azo dye to DNA, but no pink color in DNA extracts was observed. Jim Miller pointed out later that they had missed the covalent binding of azo dye to DNA because the azo dye-DNA adduct did not have a pink color in acid (1998). The Millers found that factors influencing the *in vivo* binding of aminoazo dyes to protein also influenced the dye's hepatocarcinogenicity. These studies led the Millers to suggest that covalent binding of aminoazo dye metabolites to liver protein was required for the dye's carcinogenicity. This line of research was extended to carcinogenic polycyclic aromatic hydrocarbons. Betty Miller applied benzo[a]pyrene to mouse skin and reported on the covalent binding of metabolites of the hydrocarbon to protein in the skin (1951). This research by the Millers on two different classes of carcinogens provided the first evidence that the carcinogenicity of foreign chemicals was related to the covalent binding of

their metabolites to cellular macromolecules. An excellent review of these early studies appeared in (1953,1).

Starting in 1948 Jim Miller pioneered in research on the properties and regulation of enzyme systems that metabolize foreign chemicals. Jim was the first to demonstrate the oxidative metabolism of a foreign compound in a cell-free system by liver enzymes that were later identified as endoplasmic reticulum-associated cytochromes P-450 (1948,1). Jim Miller went on to provide the first demonstration of the metabolism of a foreign chemical by an NADPH-dependent enzyme in liver microsomes (1949,1). In this study he showed that liver microsomes reduced the azo linkage of 4-dimethylaminoazobenzene and that NADPH was required for catalytic activity.

Jim Miller showed that riboflavin-adenine dinucleotide was required for azo dye reductase activity (1949,2), and these results provided a mechanistic explanation for the protective effect of riboflavin on the carcinogenicity of aminoazo dyes (1948,2). These observations indicated that one chemical (a dietary vitamin) may alter the carcinogenicity of a second chemical by influencing its enzymatic metabolism. An additional pioneering study by Jim and Betty Miller indicated that several other dietary substances could influence the metabolism of a foreign chemical (1954). Subsequent studies by other investigators have shown that numerous dietary substances can influence the metabolism and action of drugs, carcinogens, and other foreign chemicals. It is now known that dietary factors can influence the metabolism of many foreign chemicals in human beings.

From 1953 to 1957 Jim Miller continued to make fundamental discoveries on the properties of enzyme systems that metabolize foreign chemicals. Jim discovered that the N-demethylation of an aminoazo dye by liver homogenate was an oxidative process requiring NADP, NAD, and the oxidizable

substrate hexose diphosphate (1953,2). This study, which suggested the requirement of reduced pyridine nucleotide and oxygen for the N-demethylation reaction, provided the frame of reference for important subsequent investigations by Bernard Brodie and his associates (Brodie et al., 1955) and by the Millers (1957,1,2) that demonstrated the oxidative metabolism of drugs and carcinogens by liver microsomes and also demonstrated that NADPH and oxygen were required for activity. It is now known that NADPH-dependent microsomal enzyme systems catalyze the oxidative metabolism of many foreign chemicals, and factors that influence the activity of these enzymes will alter the action of foreign chemicals. The Millers described the solubilization of the aminoazo dye N-demethylase system with deoxycholate, and they also made the important incidental observation that the demethylase system was inhibited by carbon monoxide (1957,1). Although the Millers did not pursue this line of research further, their early observations on the enzymatic metabolism of carcinogens helped pave the way for the discovery, purification, and characterization of the carbon monoxide-binding cytochrome P-450 enzymes that play such an important role in the metabolism of drugs, environmental chemicals, and endogenous substrates.

The Millers discovered that foreign chemicals could induce the synthesis of liver microsomal enzymes that metabolize the compound administered and other foreign chemicals (1957,2; 1956). The induction of these enzymes is important pharmacologically, for it leads to an accelerated biotransformation of drugs and other environmental chemicals *in vivo* and so alters the toxicity of drugs and environmental chemicals. The induction of microsomal enzymes has been shown to alter the carcinogenicity of chemicals that are metabolized by these enzymes. The initial discovery of microsomal enzyme induction by the Millers has broad significance, since several hundred substances, including drugs, steroids, insecticides,

food additives, industrial chemicals, and various other environmental pollutants can induce the synthesis of microsomal enzymes; and it is known that these substances can influence the metabolism of drugs and chemical carcinogens in humans. It should also be noted that studies on enzyme induction by the Millers were among the first on adaptive gene regulation by environmental stress in a eukaryotic system.

The Millers were the first to demonstrate metabolism of a chemical carcinogen to a chemically reactive species by a cell-free enzyme system (1958). In this study they demonstrated the NADPH-dependent liver microsomal metabolism of an azo dye to intermediates that were covalently bound to macromolecules. This study was an early precursor of the Ames test involving the metabolic activation of chemicals to mutagens.

The Millers were the first to demonstrate the biotransformation of a chemical to a more carcinogenic metabolite. They demonstrated the metabolism of 2-acetylaminofluorene via N-hydroxylation (a new metabolic reaction) to a metabolite that was more carcinogenic than the parent molecule (1960, 1961). The Millers found that the N-hydroxylated metabolite was further metabolized to highly reactive esters with even greater toxicity (1970,1; 1977,1). These discoveries by the Millers provided the first demonstration of proximate and ultimate carcinogenic metabolites and pointed out that metabolism is not always via detoxification pathways, but that metabolism of foreign chemicals may result in enhanced toxicity. In an important study V. M. Maher, W. Szybalski, and the Millers demonstrated directly that certain chemically reactive metabolites and derivatives of carcinogens were mutagenic, and the frequency of mutations was directly related to the amount of carcinogen bound to DNA (1968). In a series of discoveries the Millers elucidated the molecular events leading to the metabolic activation of 2-

acetylaminofluorene (see above), aminoazo dyes (1970,1; 1975; 1976,1,2), aflatoxin B₁ (1973,1; 1977,2), safrole (1973,2; 1985; 1983), estragole (1985; 1981,1), and ethyl carbamate (1982; 1993,2) to chemically reactive metabolites that react with macromolecules in cells. The later studies were the start of research on the metabolic activation of important naturally occurring carcinogens in our diet. Studies on the metabolic activation of several structurally diverse carcinogens led to the important unifying concept by the Millers that most carcinogenic and mutagenic chemicals are not carcinogenic or mutagenic per se but that these compounds must undergo metabolism to reactive electrophilic intermediates that exert carcinogenic and other toxic effects by covalently binding to critical sites on DNA, RNA, and protein (1969; 1977,3; 1984). The discovery by Jim and Betty Miller that most chemical carcinogens must undergo metabolism to highly reactive electrophilic intermediates (ultimate carcinogens) prior to exerting their carcinogenic effect has laid the foundation for subsequent research indicating a relationship between the mutagenicity of chemicals after metabolic activation and carcinogenicity.

From 1968 to 1971 the Millers pointed out that with appropriate metabolic activation, chemical carcinogens that are inactive per se would have mutagenic activity (1968; 1970,2; 1971). They also demonstrated that several ultimate carcinogens (esters of N-hydroxy-2-acetylaminofluorene, N-hydroxy-4-monomethylaminoazobenzene, and N-hydroxyaromatic amides) are potent mutagens (1968; 1970,2; 1971). Jim and Betty Miller pointed out that "as a general class, chemical carcinogens would appear to be potential mutagens, and the mutagenicity of a chemical carcinogen in a given system will depend on its extent of conversion to electrophilic reactive form(s) and on the access of these active form(s) to the genetic material in the mutagenicity system under

study" (1970,2). Research by the Millers on the metabolism of carcinogens to reactive metabolites provided the foundation for the later development of rapid mutagenicity tests by Ames and others that indicate which compounds undergo metabolism to mutagens and thereby pose a cancer risk.

Starting in 1966 Jim and Betty Miller contributed extensively to the characterization of DNA adducts that result from the metabolic activation of several chemical carcinogens and from the direct application of ultimate carcinogens (1977,3; 1984; 1966; 1977,4; 1981,2; 1987). This work on the covalent binding of chemically reactive electrophilic ultimate carcinogens to specific sites on DNA has stimulated much additional research by others on the covalent binding of carcinogens to DNA both in experimental models and in human subjects. In addition, the Millers work provided an important frame of reference for the more recent studies on the activation of protooncogenes and the inactivation of tumor suppressor genes by chemical carcinogens that are metabolized to mutagens. It is of interest to note that Jim and Betty Miller headed one of the first three groups that reported the presence of an activated protooncogene in tumors that were induced by chemical carcinogens. In this study the Millers demonstrated that structurally different chemical carcinogens produced different activating mutations in the c-Ha-ras protooncogene (1986). These results strongly suggested that protooncogene activation is an early event in chemical carcinogenesis.

The significance of the discoveries of James and Elizabeth Miller is manifested by the role of these discoveries in fostering several new areas of research with contemporary significance, including:

- development of short-term tests (Ames test and others) for the identification of potential mutagens and carcinogens: design of safer drugs, industrial chemicals, and environmental chemicals that are used for the benefit of humankind. Research by the Millers has helped prevent exposure of people to mutagens and carcinogens.
- mechanisms and regulation of metabolism of drugs, chemical carcinogens, and environmental pollutants (properties and regulation of the cytochrome P-450 enzymes: drug-drug and drug-carcinogen interactions; diet-carcinogen interactions; environmental factors influencing drug and carcinogen metabolism). Research on factors that influence foreign compound metabolism has had an important impact on the environmental sciences and in clinical pharmacology. This research has led to a more rational approach to human drug therapy and to the prevention of toxicity induced by drugs and other foreign chemicals.
- person-to-person differences in biotransformation of environmental carcinogens to toxic metabolites (helps explain why some people exposed to a carcinogen develop cancer whereas others do not).
- use of covalently bound adducts of environmental carcinogens as biomarkers and as an index of human exposure and metabolic activation.
- activation of cellular protooncogenes and inactivation of tumor suppressor genes by carcinogens that are metabolized to chemically reactive mutagens.
- eukaryotic gene regulation by environmental stress.

In summary, James and Elizabeth Miller discovered that foreign chemicals are metabolized to carcinogenic metabolites, and they also made seminal discoveries related to the enzymology and regulation of foreign compound metabolism. These discoveries initiated a new era of modern toxicology that has had a major impact on the environmental sciences.

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CHRONOLOGY ELIZABETH C. MILLER

ACADEMIC POSITIONS (ALL AT THE McARDLE LABORATORY)

1945-1947	Finney-Howell Postdoctoral Fellow
1947-1948	Instructor of Oncology
1949-1959	Assistant Professor of Oncology
1959-1969	Associate Professor of Oncology
1969-1980	Professor of Oncology
1972-1973	Acting Director
1973-1987	Associate Director
1980-1982	WARF Professor of Oncology
1982-1987	Van Rensselaer Potter Professor of Oncology
1984-1987	WARF Senior Distinguished Research Professor of Oncology
1987	Emeritus Professor of Oncology

SELECTED PROFESSIONAL ACTIVITIES

1954-1964	Assistant Editor, Scientific Editor, and Associate Editor of <i>Cancer Research</i>
1957-1960, 1974-1977	Member, Board of Directors, American Association for Cancer Research (President, 1976-1977)
1968-1972	Member, Pharmacology B Study Section, NIH
1971-1972	Chair, Pharmacology B Study Section, NIH
1972-1975	Member, Scientific Advisory Board, National Center for Toxicological Research
1973-1976	Member, Council for Research and Clinical Investigation Awards, American Cancer Society
1975-1976	Chair, Council for Research and Clinical Investigation Awards, American Cancer Society
1978-1980	Member, U.S. President's Cancer Panel, National Cancer Institute
1981-1984	Member, Council of the National Academy of Sciences
1984-1986	Member, Mott Committee and Awards Assembly, General Motors Cancer Research Foundation

1984-1987 Member, Advisory Committee to Director,
National Institutes of Health

HONORS

1973 Distinguished Alumni Award, University of Minnesota
 1978 Member, National Academy of Sciences
 1978 Griffuel Award, Association pour le Developpement
de la Recherche sur le Cancer, Paris, France
 1980 Honorary Member, Japanese Cancer Association
 1981 Fellow, American Academy of Arts and Sciences
 1982 Doctor of Science (Honorary),
Medical College of Wisconsin
 1983 Fellow, Wisconsin Academy of Sciences, Arts and Letters

HONORS AWARDED JOINTLY TO JAMES A. AND ELIZABETH C. MILLER

1962 Langer-Teplitz Award for Cancer Research, Chicago
Cancer Foundation
 1965 Lucy Wortham James Award for Cancer Research,
James Ewing Society
 1971 Bertner Foundation Award, M. D. Anderson Hospital
and Tumor Institute
 1973 Wisconsin National Division Award,
American Cancer Society
 1975 Papanicolaou Award, Papanicolaou
Institute for Cancer Research
 1976 Rosenstiel Award for Basic Medical Research,
Brandeis University
 1977 National Award in Basic Sciences,
American Cancer Society
 1978 First Founder's Award, Chemical Industry
Institute of Toxicology
 1978 Bristol-Myers Award in Cancer Research
 1978 Gairdner Foundation Award, University of Toronto
 1979 Federated American Societies of Experimental Biology
3M Life Sciences Award

- 1979 Louis and Bert Freedman Foundation Award,
New York Academy of Sciences
- 1980 Mott Award, General Motors Cancer Research Foundation
- 1981 Allan D. Bass Lectureship, Department of Pharmacology,
Vanderbilt University
- 1982 IBM-Princess Takamatsu Cancer Research Fund Lecturers
in Japan
- 1985 Honorees, Third International Symposium on Biological
Reactive Intermediates, University of Maryland
- 1986 Research Recognition Award, Samuel Roberts Noble
Foundation, Ardmore, Oklahoma

CHRONOLOGY JAMES A. MILLER

ACADEMIC POSITIONS (ALL AT THE McARDLE LABORATORY)

1943-1944	Finney-Howell Postdoctoral Fellow
1944-1946	Instructor in Oncology
1946-1948	Assistant Professor of Oncology
1948-1952	Associate Professor of Oncology
1952-1980	Professor of Oncology
1980-1982	Wisconsin Alumni Research Foundation (WARF) Professor of Oncology
1982-2000	Van Rensselaer Potter Professor of Oncology
1984-2000	WARF Senior Distinguished Professor of Oncology
1985-2000	Professor Emeritus of Oncology

SELECTED PROFESSIONAL ACTIVITIES

1950-1955	Biochemistry Study Section, National Institutes of Health
1960-1969	Food Protection Committee, National Research Council
1961-1968	WHO Committee on Evaluation of Carcinogenicity of Food Additives
1965-1968	Board of Directors, American Association for Cancer Research
1967	National Cancer Institute Committee on the Evaluation of Current Research and Training in Chemical Carcinogenesis
1968-1972	Research Advisory Council, American Cancer Society
1969-1970	Program Committee, 10th International Cancer Congress
1969	Advisory Panel on Carcinogenicity, Commission on Pesticides and Their Relationship to Environ- mental Health, U.S. Department of Health, Education, and Welfare
1968-1969	Committee on Evaluation of Safety of Non- nutritive Sweeteners, National Research Council

- 1969 Panel on Non-Psychiatric Effects of Drugs of Abuse, National Institute of Mental Health
- 1971-1975 Cancer Research Center Review Committee, National Cancer Institute
- 1970-1973 Core Committee on Chemical Carcinogenesis, Smithsonian Institution
- 1972-1976 Advisory Panel on Carcinogenesis, National Cancer Institute
- 1972-1975 Colon Cancer Segment, Carcinogenesis Program, National Cancer Institute
- 1972-1976 Council on Analysis and Projection, American Cancer Society
- 1977 Review and Evaluation Committee on the Carcinogenicity of Chlordane and Heptachlor, National Research Council
- 1978-1981 Board of Scientific Consultants, Memorial Sloan-Kettering Cancer Center
- 1979-1981 Associate Editor, *Cancer Research*
- 1979-1983 CIDAC-Carcinogenesis Advisory Board, Franklin Research Center
- 1980 Life Sciences Advisory Board, Los Alamos National Laboratory
- 1980-1983 Scientific Board of Visitors, Oklahoma Medical Research Foundation
- 1980-1983 Advisory Board, Environmental Cancer Information Center, City University of New York.

HONORS

- 1969 G. H. A. Clowes Award and Lectureship, American Association for Cancer Research
- 1978 Member, National Academy of Sciences
- 1980 Appointment as Wisconsin Alumni Research Foundation Professor of Oncology, University of Wisconsin
- 1980 Medalist Award, Intra-Science Research Foundation

- 1980 First Annual Award Lecture, Laboratory of Nuclear Medicine and Radiation Biology, University of California, Los Angeles
- 1980 Honorary Member, Japanese Cancer Association
- 1981 Fellow, The American Academy of Arts and Sciences
- 1982 Appointment as Van Rensselaer Potter Professor of Oncology, University of Wisconsin
- 1982 Doctor of Science (Honorary), Medical College of Wisconsin, Milwaukee
- 1983 Walter Huber Lecture, British Association for Cancer Research, York, England
- 1983 Fellow, Wisconsin Academy of Sciences, Art, and Letters
- 1984 Appointment as WARF Senior Distinguished Research Professor
- 1985 Appointment as Professor Emeritus of Oncology, University of Wisconsin

HONORS AWARDED JOINTLY TO JAMES A. AND ELIZABETH C. MILLER

- 1962 Langer-Teplitz Award for Cancer Research, Chicago Cancer Foundation
- 1965 Lucy Wortham James Award for Cancer Research, James Ewing Society
- 1971 Bertner Foundation Award, M. D. Anderson Hospital and Tumor Institute
- 1973 Wisconsin National Division Award, American Cancer Society
- 1975 Papanicolaou Award, Papanicolaou Institute for Cancer Research
- 1976 Rosenstiel Award for Basic Medical Research, Brandeis University
- 1977 National Award in Basic Sciences, American Cancer Society

- 1978 First Founder's Award, Chemical Industry
Institute of Toxicology
- 1978 Bristol-Myers Award in Cancer Research
- 1978 Gairdner Foundation Award, University of Toronto
- 1979 Federated American Societies of Experimental Biology
3M Life Sciences Award
- 1979 Louis and Bert Freedman Foundation Award,
New York Academy of Sciences
- 1980 Mott Award, General Motors Cancer Research Foundation
- 1981 Allan D. Bass Lectureship, Department of Pharmacology,
Vanderbilt University
- 1982 IBM-Princess Takamatsu Cancer Research Fund Lecturers
in Japan
- 1985 Honorees, Third International Symposium on Biological
Reactive Intermediates, University of Maryland
- 1986 Research Recognition Award, Samuel Roberts Noble Foun-
dation, Ardmore, Oklahoma

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