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## In Memoriam

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### Robert Warwick Miller



Robert W. Miller, a distinguished cancer and birth defects epidemiologist, who was a charter member and president of the Teratology Society (1970), died February 23, 2006 at the age of 84. At the time of his death, Dr. Miller was serving as Scientist Emeritus in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute (NCI). He was the first director of the Cancer Epidemiology Branch that was created by the NCI in 1961. Dr. Miller was born in New York City in 1921. He received his undergraduate and medical degrees from the University of Pennsylvania. He trained in pediatrics at the Buffalo Children's Hospital and in radiation biology and radiation medicine at the University of Rochester, Case Western Reserve, and Duke Universities.

I first met Dr. Miller when I was a third-year medical student at the University of Rochester in 1951. He was a volunteer attending on the Pediatric wards because he was a Captain in the U.S. Army (1951–1953) and was assigned to the Atomic Energy Project at the University of Rochester. He was an excellent pediatrician, very attentive and responsible to the patients under his supervision. We both never forgot one patient on the Pediatric Inpatient Service who was admitted with a diagnosis of acute rheumatic fever. She was treated with penicillin and aspirin and gradually improved and was discharged home on prophylactic penicillin. I called Bob several months later when this young girl was readmitted with acute fulminating rheumatic fever with myocarditis and died. When Bob found out that the girl's doctor in southern New York State did not place her on prophylactic penicillin he actually had tears in his eyes and could not believe that a physician could have made such an incompetent decision that cost a child her life.

Our paths crossed many times because of common assignments and, of course, common interests. We were together in Washington when I was in the Army and assigned to the Walter Reed Army Institute of Research and he was assigned to the National Academy of Sciences. We spent time together in Japan when he was the head of the Pediatric section of the Atomic Bomb Casualty Commission (ABCC) in Hiroshima. We were colleagues because of our membership in the Teratology Society and the National Council for Radiation Protection (NCRP).

While he was at the University of Rochester, he expressed his concern over the frequent use of fluoroscopy for examining young children, which led to a heated interdepartmental conference that resulted in more conservative radiological procedures, especially for children. Dr. Louis Hempelmann was at the meeting and launched his landmark study into the risk of thyroid cancer after radiotherapy of the infant thymus, and in 1953 Dr. Miller published one of the earliest reviews on the potential hazards to children from excessive medical X-ray exposures (Miller, 1953). When he was

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working in Hiroshima, he examined hundreds of children born in the months after the atomic bomb detonation and established that exposure to radiation during pregnancy increased the incidence of mental retardation and small head circumference in the offspring (Miller and Blot, 1972). He determined that there was a dose-response relationship: the greater the exposure, the greater the risk of the mental retardation and microcephaly. This experience piqued his interest in epidemiology, which led to his earning a doctorate in public health at the University of Michigan in 1961 with Dr. Thomas Francis, Jr. Dr. Francis had been the leader of the now legendary three-member Francis Committee (that also included Dr. Miller's friend, Seymour Jablon) that in 1955 essentially saved ABCC from scientific collapse by formulating a unified plan that became the blueprint of the future research program at ABCC, later known as the Radiation-Effects Research Foundation.

When he arrived at the NCI in 1961, he was ready to use his talents and training to make major contributions by studying the etiology of congenital malformations and cancer. He was an amazingly observant investigator. Some of his personal observations were humorous. He would tell you that the manufacturers of striped ties always put the stripes in the same direction. He believed that a skin cancer that he developed on his thigh was due to a nickel key holder that he always carried in his right pants pocket, although he never published this observation. When he was in China, he noted that the Chinese men had a higher incidence of cancer of the esophagus. He attributed this increased incidence to the fact that the "man of the house" was served first and was exposed to the hottest foods (Miller, 1978). He was always looking for associations on which he could establish reasonable hypotheses to test. Many of his discoveries were made with chart reviews before the desktop computer was a common entity. I think that one of his many great discoveries was the description of the genetic syndrome of Wilm's tumor, congenital aniridia, and hemi-hypertrophy, published in the *New England Journal of Medicine* in 1964 (Miller et al., 1964). It kindled his life-long interest in the etiological association between birth defects and cancer and the syndrome should have been named Miller's Syndrome.

During his career at NCI, which spanned 45 years, he laid the groundwork for understanding the patterns of childhood cancer and the risk factors involved. His studies linked specific types of childhood cancer with congenital malformation syndromes (Miller, 1968). He provided new insights into the genetic underpinnings of cancer. In particular, his work on retinoblastoma, Wilm's tumor, and familial multiple-cancer syndromes was instrumental in the subsequent discovery of cancer susceptibility genes and opened new avenues of research in molecular and cellular biology.

Throughout his career, Dr. Miller called attention to the importance of the alert clinician whose observations often provided the initial clues to the causes of cancer, birth defects, and other conditions. I always attributed the term "alert physician" to his cleverness with words and phrases (Miller, 1977). The effectiveness of this approach was recognized when he was asked to organize a Princess Takamatsu international symposium in Tokyo entitled "Unusual Occurrences as Clues to Cancer Etiology," and to edit the proceedings, which described the history of many key discoveries in the field. In calling attention to the value of astute clinical observations, he was fond of quoting Yogi Berra, who said, "you can observe a lot by watching." At the NCI, Dr. Miller created an epidemiological research program with a strong clinical and interdisciplinary focus, and he recruited and trained a series of young physicians and scientists, many of whom have become leaders in the field. He also advised and participated in many high-visibility projects precipitated by major environmental threats around the world, including studies of populations heavily exposed to radioactive fallout (Chernobyl, Marshall Islands), dioxin (Seveso, Italy), and Agent Orange (Vietnam). In 1979-1980, he served concurrently as the NCI Director of International Affairs, where he developed a series of binational agreements and workshops that encouraged collaborative research with scientists from other countries. I was fortunate to attend two of these workshops in Japan. Dr. Miller was respected by the Japanese scientists, and he ran these conferences like a symphony orchestra conductor. On one occasion, a Japanese scientist presented a questionnaire that he had developed that was 14 pages long for physicians to complete who were caring for cancer patients. I complemented the scientist and said that in the USA you could never get physicians to complete such a lengthy form. Dr. Miller pulled me aside to tell me in private that the scientist had been working on the questionnaire for 20 years and had not yet put it into actual use. As a Fellow of the American Academy of Pediatrics, Dr. Miller served for several years as Chairman of the Committee on Environmental Hazards, where he evaluated the risks from early-life exposures to various environmental toxins. He was instrumental in establishing the annual Practitioner Research Award to honor pediatricians whose office-based research had been exemplary. For his contributions to the Academy, he received the Outstanding Service Award in 1999.

Dr. Miller was not an individual who sought scientific confrontations. However, he would become very upset with poor science and bad scientists. Two examples come to mind. Dr. Miller's experience in Japan and his training in pediatrics and epidemiology led him to question the magnitude of the correlation of prenatal diagnostic X-rays and childhood cancer reported by Dr. Alice Stewart at Oxford University. Because no excess leukemia was seen following prenatal exposures from the atomic bomb, he doubted whether tumors of embryonic origin, such as neuroblastoma, could be induced by pelvimetry X-rays during the last weeks of pregnancy. He was also puzzled by the finding that every childhood cancer was increased by the same relative amount when such a wide range of relative risks of cancer were seen following childhood and adult exposures (Miller and Boice, 1997). He did not believe the magnitude of the leukemia risk of Alice Stewart's investigations or conclusions and neither did John Boice or I, and all three of us expressed our separate opinions.

In 1984, Otake and Schull reported that mental retardation following radiation exposure in Hiroshima and Nagasaki was a stochastic effect. They said that there was no threshold. After a meeting at the NCRP with Dr. Schull, Dr. Miller, Dr. Monson, Dr. Winick, and I attempted to convince Dr. Schull that his conclusions did not make biological sense and neither did the data support his views. Although Dr. Schull was not convinced following that meeting, he eventually came to the conclusion that mental retardation was a deterministic effect with a threshold and confidence intervals.

Dr. Miller was an exemplary example for the trainees in his division. He was meticulous and steadfast in making certain that scholarship and high ethical standards were essential features of every project and publication. He trained

many scientists and physicians in the magic of epidemiology, including Dr. Fred Li, Dr. Joseph Fraumeni Jr., and Dr. John Mulvihill, three of his stars.

Dr. Miller served for many years as Clinical Professor of Pediatrics at the Georgetown University School of Medicine. He received the NIH Director's Award in 1993, and the Distinguished Graduate Award from the University of Pennsylvania School of Medicine in 2002. His scientific accomplishments were also recognized when he received posthumously the first NCI Lifetime Achievement Award for "his visionary leadership and mentorship in cancer epidemiology over a 45-year career at the National Cancer Institute." The award was presented to his wife, Holly Miller, at a memorial service that was held on April 29, 2006 at the National Institutes of Health.

Robert Miller was a kind, gentle, and modest scientist and human being. Although he was very humorous, actually very funny, he rarely laughed vigorously at his own stories and jokes. He left the laughing up to others. He rarely told off-color stories and when he did, they lost their raunchiness. I remember on one occasion when I visited Hiroshima, I complained to him that solicitors on the Ginza in Tokyo would pester you to accompany them to a brothel. I asked Bob: "How do you respond?" He taught me the Japanese phrase that turned out to be very effective: "I just finished."

After Bob was married to Holly, he explained to me that because of her Japanese ways, she would never be able to drive in the United States, because she was not assertive enough. Little did he know! Holly offered to come to our apartment in Washington and prepare a typical Japanese dinner, *sukiyaki*. It was a beautiful, artistic dinner. During the after-dinner conversation, Bob mentioned that they were looking at homes in the area and Bob mentioned that he liked a two-story home near the NIH. This unassertive young woman blurted out "I want a rancher," to Bob's surprise. Holly did learn to drive and she was a good driver, which became a necessity after Bob had part of his leg amputated following an allergic reaction to heparin. He had met Holly, who was a nurse at the ABCC, in Hiroshima. They were married 51 years at the time of his death.

Holly also was not an exuberant laugher except on one Sunday morning when we were invited for brunch at the Millers. We had already left Walter Reed and Washington and were in Philadelphia. When we arrived with our four children, Holly had prepared a luscious brunch of lox and bagels, and the children ate heartily, except for Deborah. She was a little over 3 years old and the youngest of our children. She just kept staring at Holly. Holly said to Debby, "Aren't you going to eat?" Debby replied, "I did not know you were Jewish." Holly really laughed out loud.

On the home front, Holly and Bob were a team. They were very devoted to each other. They respected and admired each other's accomplishments. You do get to know someone after 51 years.

Those of us who had a long friendship with Robert Warwick Miller know what a great scientist and human being he was. This gentle, kind man accomplished so much without being political, which is an unusual accomplishment at the NIH. His contributions to science are in periodicals and texts, but his contribution to mankind is in the hearts and minds of his colleagues and friends.

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