
Living History Autobiography: Clinical Genetics: Key to Cancer Etiology

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INTRODUCTION

Whatever my contribution to genetics, it was not by long-range planning. I prefer to think short term, building on all previous experience as I address the next opportunity. Fortunately, when I came to the National Cancer Institute (NCI) in 1961, it was enough to have a broad mission. Mine was to find causes of human cancer through peculiarities in its occurrence—observational research, otherwise known as epidemiology. On being interviewed for the position as Chief of the Epidemiology Branch, I pledged not to study anything being addressed by others. I was accepted anyhow, there being no other applicants for the year-long vacancy. My research approach was applied to several fields (see Special Activities below) including the clinical genetics of cancer.

EARLY YEARS

My path to medicine began at birth. My parents from Manhattan went to Brooklyn on September 29, 1921, where I was delivered by my father's second cousin, a surgeon who owned a hospital there. My parents' high regard for him strongly influenced me to become a physician. During the first World War, my mother had been an ambulance driver for the Beekman Street Hospital in downtown Manhattan. Had she been born 70 years later, she may well have become a physician.

My father, born in Chelsea, Massachusetts, became an orphan early in life. During the war, a high point in his experience, he was a sergeant in the American Expeditionary Force in Europe. The canvas cover of his canteen had an ink-written list of the places he had been and the action he had seen, including Château-Thierry and Belleau Wood. (His helmet, upside down and mounted on a stand, was used as a planter in our living room.) Upon his return to civilian life he became a New York-based buyer of women's clothing for out-of-town stores that did not have buyers of their own.

A key figure in our lives was my mother's widowed father who came each night for dinner at our house. He

owned a chain of 25 shoe stores begun about 35 years earlier with start-up funds from my grandmother—saved from her household allotment. He was a great friend of his grandchildren and sponsored our school tuitions during the Great Depression.

One of my earliest memories is the birth of my brother, Bruce, when I was four. I could not understand why my mother was in the hospital, so on her return, as she stood near the unmade bed, I asked her to explain where babies come from. She said the mother lays an egg. "Where?" "In the bed." As I tugged down the bedclothes, she drew me away saying my father would explain later. They bought me a book, which did not make clear that the male organ had more than one function, so I remained puzzled.

I tried unsuccessfully to teach Bruce to read when he was three years old. My grandfather had a greater influence. He had given us a few shares of a low-price gold stock that did poorly, but it stimulated Bruce to learn how to read the stock price each day. He is now a stock broker.

My life as an apartment-dweller began near the 72nd Street entrance to Riverside Park, a huge playground. A concrete roof was being finished atop the New York Central railroad tracks on which a park and promenade were placed. It ran along the Hudson River for four miles. Across the river were the Palisades of New Jersey. When the fleet visited New York, the river was filled with battleships, and we visited when one of them had open house.

Cars were still cranked to start. The policeman at the intersection stood on a little platform and turned a stop-go signal by hand. There were double-decker buses and open-air street-cars in the summer, with running boards for the conductors. Bottled milk delivered daily to our door was transported by wagons drawn by horses with rubber horseshoes (an anti-noise measure).

We often visited the nearby Museum of Natural History and were awed by the war canoe that occupied the center of a large hall and was powered by the paddles of life-size wooden Indians. When I was 13, we moved to the East Side near the Metropolitan Museum of Art, where the most impressive sights were the Hall of European Arms and Armor, and the Egyptian crypts with mummies in them.

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My grammar school was co-educational until the fifth grade, when the girls stayed on and the boys went to a different school. There I skipped one grade in which fractions and decimals were taught, so I had to figure them out for myself. At the end of the sixth grade some of us were given the option of transferring to a junior high school near Columbia University where we would cover 3 years of school work in 2. We were trusted with girls in the class once again.

I was assigned to Stuyvesant High School on the basis of where we lived. It later developed an excellent reputation for science, but during my time there the classes were unruly and the teachers were terrible. Tough kids made us do their assignments in mechanical drawing and then stole the instruments. The English teacher read a newspaper while we sat in class with nothing to do. We had to take showers in a big room full of shower-heads and paid a nickel for the towel. After a year I transferred to Horace Mann, a country day school in Riverdale, just beyond the end of the Broadway subway line. It was a wonderful place, where English and writing were particularly well taught, and everyone could participate in sports and other after-school activities. I was very thin, so I went out for track, a non-contact sport. At graduation my family was amazed to see me receive my letter for track, a major sport, alongside the muscular shot putters and discus throwers. At track meets, they got up at intervals for a brief test of strength, while I ran my heart out in the mile and half-mile races.

I went to the University of Pennsylvania, where, as a pre-medical student, I majored in chemistry, a bad choice, and took all the literature courses possible. To fill in a two-credit course in my senior year, I selected art appreciation: paintings since the Renaissance. It surpassed everything else I studied in college, and it brought out my lifelong interest in art.

MEDICAL SCHOOL AND HOSPITAL TRAINING

World War II started as I was applying to medical school. I did not apply to the University of Pennsylvania until my rarely seen pre-medical advisor called me in and suggested that I do so. I took the hint, and, because of the war, classes began in March 1943. In our ninth week, we were given the option of entering the military, which would pay our expenses, or remain civilians on reserve in the Medical Administrative Corps and pay our own expenses. Most of us chose a military service—the Army in my case because my myopia, even though corrected by glasses, would have barred me from the Navy.

We went to an Army camp to be outfitted and indoctrinated as Privates. Most schools allowed the Army students to live on their own, supported by their military allowance for food and housing. Our school put us in barracks (fraternity houses) and screwed dining tables to the basketball court so we could be fed there. At first I was in a fraternity house with three roommates and a bathroom that everyone in the house used all night long. Sleep was impossible. The Captain of our

unit, an Assistant District Attorney from New York, said if I could find a vacancy elsewhere I could move. I found another house in which the two people in one room were from Philadelphia and lived at home.

In college we had learned the fundamentals of genetics, but in medical school, the only memorable reference to the subject concerned blood groups ABO and Rh, as taught in physiology. Medical school instilled in us an approach to medicine that encouraged innovation, as one can appreciate today from essays by Comroe [1977], a former member of the faculty, on how discoveries in basic sciences have led to advances in clinical medicine.

Because experience in medical procedures was downplayed (“you will learn that in the first week of your internship”—as we did), I mistakenly interned in the non-academic division of Kings County Hospital in Brooklyn. We were too much on our own there because some of the residents, who had just returned from the war, were in a resting phase. However, the variety of experience and self reliance we gained were immense.

Competition for residency training was keen because of the returning wartime physicians. Also, in medical school our exposure to pediatrics was brief and my attraction to the field did not come until that rotation at the end of my internship. After a short intermission as an intern at the Kingston Avenue Hospital for Contagious Diseases in Brooklyn, I managed to secure a residency beginning on January 1, 1948 at Buffalo Children's Hospital. Teaching there had been in a low state academically, and the new Chairman, Mitchell I. Rubin from the faculty of the University of Pennsylvania, had been recruited to elevate it. He sought housestaff from leading departments around the country to begin in the middle of the academic year, which matched my need. He proved to be a superb teacher of clinical pediatrics. It was a surprise to hear him lecture 2 years after I left Buffalo and realize that I had even adopted some of his speaking style.

RADIATION BIOLOGY

Upon finishing my residency training in 1950, I did not feel finished. Subspecialization was just beginning in those post-war years, but I did not want to devote my life to one organ system. So when an announcement from the Atomic Energy Commission (AEC) appeared for 1 year of postdoctoral training to educate a few physicians about radiation effects, it seemed broad enough biologically and novel. All organs could be studied in this swashbuckling new field. The deadline had already passed, but I was accepted for the program anyhow. In June 1950, just as the Korean War began, I was sent to Western Reserve University for a few months of animal research in radiobiology and then to Duke University for classroom work. Duke provided my first real exposure to human genetics—through C. Nash Herndon, an early medical geneticist, who travelled twice weekly from Bowman-Gray School of Medicine in Winston-Salem to Durham to teach our class of eight. Another excellent course was in biostatistics taught by

Bernard Greenberg of the University of North Carolina School of Public Health.

MILITARY SERVICE

I had been ejected by the Army at the end of my third year in medical school when the vision standard was raised. It was lowered again for the Korean War. My draft notice arrived as the course at Duke ended in February, and the AEC had me assigned as a Captain in the Army to the Atomic Energy Project of the University of Rochester. There, as a New Yorker leery of dogs, I took my turn in bleeding about a dozen of them a day after they had been irradiated, as we sought therapy that would reduce mortality from acute radiation sickness. Teaching pediatrics claimed part of my time—ward rounds and clinics, where I learned that the Radiology Department insisted on fluoroscoping each child under 2 years of age for whom a chest *film* had been ordered. (The Chairman said that young children squirmed too much for a film, and besides, the residents need the practice.) The child's exposure from fluoroscopy was much greater than that from a film, especially when the radiology resident kept his foot on the pedal as he showed the child's mother what he was seeing. After I mentioned this on ward rounds, the housestaff began to write on X-ray requisitions, "Film only, no fluoroscopy," which led to a confrontational conference involving pediatricians, radiobiologists, and the Chairman of Radiology. There we presented a premature infant who, in the first month of life, had had seven diagnostic fluoroscopies for atelectasis plus 75 R to shrink the thymus. The session led Louis Hempelmann, one of those present, to evaluate the risk of thyroid cancer after radiotherapy of the infant thymus. This treatment was routinely used to protect against sudden infant death, known then as thymus staticolymphaticus [Simpson et al., 1955]. An excess of thyroid cancer was found, and Louis added to the findings in follow-up studies over the next 30 years [reviewed by Miller and Koszalka, 1993].

The session led me to write a review on the potential hazards to children from medical radiation exposures, which included a section on the possible accumulation of germline genetic effects and a question about the role of cellular genetics in carcinogenesis [Miller, 1953]. The theme of the paper was that radiological exposures of children should be minimized to save their margin of safety for later unavoidable exposures. No attention was paid to this subject until 3 years later when the same points were made in reports by authoritative committees of the United States National Academy of Sciences [1956] and the British Medical Research Council [1956].

HIROSHIMA

As my military tour (as a unit of one) in Rochester neared its end, I learned that two faculty members were going for short assignments to the Atomic Bomb Casualty Commission (ABCC) where late effects of ex-

posure to the atomic bomb were being studied in Hiroshima and Nagasaki. The idea of combining my knowledge of pediatrics and radiation effects in a field study for a year was appealing, so I applied and was accepted as chief of the ABCC Hiroshima children's clinic. It was a joyous time, for there was so much to see and do. It was like being 7 years old again and discovering many fascinating things around me. Japanese signs in English were still quaint. Food stores carried cans of "Genuine Indian Curry," which depicted an American Indian on the cover. Inscribed in the wood of a lakeside gazebo we saw the amorous declaration, "Shigeki roves Nobuko," an example of the usual problem with "r's" and "l's." A story-teller rode through downtown Hiroshima on a bicycle with a picture frame mounted on the rear. He stopped at intervals and slid pictures into the frame as he told stories to a crowd of children who bought candy in return.

At the clinic, a tape recorder played children's songs throughout the day. We checked five Japanese pediatricians after they examined the children—about 4,400 during my time there. The youngest had been exposed to the bomb in utero. The 1954 staff, young and collegiate, aged together and have long been retired.

I stayed on an extra 6 months to finish my work and the courtship of my wife, Haruko, a nurse at ABCC. We were married at the U.S. consulate in Kobe on February 21, 1955 and returned to Hiroshima until the end of May, during which time I wrote up the effects of the A-bomb on children in the first decade after exposure. We timed our arrival in the United States to the date for the annual meeting of the Society for Pediatric Research in the expectation that my report would merit presentation. It concerned small head size and mental retardation among the group exposed in utero, and leukemia in others exposed as children. The paper was rejected (not mainstream pediatric research?), although the publication has been much cited [Miller, 1956].

We made Rochester our base as I sought an academic position. No one needed a pediatrician who was well informed about radiation effects. In my effort to widen my horizon, I had become too narrow. The advice that I train for another 3 years in pediatric radiology evoked a near-lethal shudder.

NATIONAL ACADEMY OF SCIENCES

Time to ponder my future came with an offer to serve as a Professional Associate in the ABCC office at the National Academy of Sciences, which was responsible for the studies in Japan. My stay was on a month-to-month basis and lasted 2 years. My function was to recruit staff and provide medical advice on ABCC to R. Keith Cannan, a biochemist who was the Chairman of the Division of Medical Sciences. Dr. Cannan was a wonderful medical administrator and scientist. He attended parts of most meetings, followed their progress closely, and brought committee reports up to his high standard. The experience taught me about chairing committees to bring out their creativity, which served

me well in a long series of United States-Japan workshops on cancer etiology, 1981–1996 [Miller, 1996a].

My work in Japan had crystallized my interest in epidemiology, present since birth in my instinctive search for patterns in designs, disease occurrence, or clustering of any sort. When I explained this interest to Dr. Rubin toward the end of my residency, he took action by introducing me to a visiting virologist, who was unfamiliar with non-infectious disease epidemiology.

Thomas Francis, Jr., Professor of Epidemiology at the University of Michigan, visited Dr. Cannan as a new key advisor on ABCC. There had been a large number of advisors on clinical medicine, but epidemiology was not their forte. (It took a biochemist to recognize the need.) The ABCC was saved from scientific collapse in 1955 by the three-member Francis Committee, which formulated a unified research program of excellent design that is still in place today.

By a fortunate coincidence, James V. Neel, Professor of Human Genetics, also at the University of Michigan, visited Dr. Cannan at that time to discuss plans to extend a portion of the Genetics Program he had headed at ABCC. Now he and William J. Schull were planning a follow-up of inbred children and a matched sample of outbred children who had been among the non-exposed group in the earlier genetics study. The new study needed a Chief of Pediatrics to help plan and execute the examination of about 7,400 children, 6–12 years of age, in Hiroshima and Nagasaki. It was agreed that I would spend a year in the Master of Public Health course in Dr. Francis' Department at the School of Public Health as the Neel-Schull study was planned, to be followed by a year each with them in Hiroshima and Nagasaki collecting data, and another year with Dr. Francis writing a dissertation for a doctorate in public health. Being in a classroom again full-time was awful, as expected, but Jim Neel is a superb epidemiologist and leader, and on-the-job education about genetics could be incorporated in my future career. My dissertation concerned ocular abnormalities, the most frequent clinical effect among children whose parents were cousins [Miller, 1963a].

NATIONAL CANCER INSTITUTE

Upon completion of these 4 years, the best opportunity for my interests proved not to be in the study of birth defects as expected but in cancer etiology at the National Cancer Institute. Cancer epidemiology was not a hot topic then, and there was no competition for the position as Chief of the Epidemiology Branch. My knowledge of the subject was limited, which seemed an asset in forming a fresh approach. At the interview for the position, I promised Michael B. Shimkin, Associate Director for Field Studies and Statistics, that I would look for entirely new ventures. These studies proved to be in two main categories: the link between cancer and congenital anomalies, and pediatric cancer epidemiology. We also made studies of adult cancers, especially occupational, e.g., lung cancer among arsenic-exposed hardrock miners [Wagoner et al., 1963] and among Japanese who manufactured mustard gas during the war [Wada et al., 1968].

WILMS TUMOR AND ANIRIDIA

The link between cancer and congenital anomalies began with the thought that if childhood leukemia occurred excessively in Down syndrome, might other childhood cancers be excessive in children with other congenital anomalies? Wilms tumor seemed a good bet because it was embryonal in nature, had an early age peak, and several case reports had appeared concerning its occurrence in children with congenital hemihypertrophy. All the clearances needed for such studies today were not needed then. Approval from the appropriate clinician was all that was required to review hospital series of medical records.

My wife and I started at Children's Hospital in the District of Columbia. It had a small number of Wilms tumor cases, but one of the children had "large pupils that do not react to light," according to the pediatric resident's physical examination. The consultant in ophthalmology set the record straight by diagnosing congenital aniridia, which, because of absent irises, cannot react to light. We extended the study to five other hospitals and reviewed 440 hospital charts, 6 of which were for children with aniridia, 3 others with hemihypertrophy, and others with more than the usual number of genitourinary-tract anomalies [Miller et al., 1964]. In 1972, Knudson and Strong reviewed the literature on Wilms tumor and showed that the pattern of findings was similar to that of retinoblastoma and fit the hypothesis of a two-hit event, one before and the other after conception. Both neoplasms were associated with birth defects; those in children with retinoblastoma proved to be due to a deletion of a D chromosome, as it was called then. We knew to look for a deletion in the Wilms tumor-aniridia syndrome but had no laboratory available to make the study. Riccardi et al. [1978] showed that the deletion was in the short arm of chromosome 11. From these observations in particular, the concept of tumor suppressor genes emerged. It applies, as we now know, to a wide variety of common adult cancers but was uncovered initially by study of the link between uncommon childhood neoplasms and congenital anomalies. Cloning of the genes responsible opened a huge research area for molecular and cellular biology.

To the chart reviews we added demographic data on mortality-childhood cancer registries had not yet been established. At that time, before advances in therapy, childhood cancer mortality was so high that it almost equaled incidence. We studied most of the childhood cancers in this way.

We kept track of case reports on hemihypertrophy and childhood cancer, and realized that it occurred excessively not only with Wilms tumor but also with hepatoblastoma and adrenal cortical carcinoma [Miller, 1966]. It also occurred as a multiple primary neoplasm in some children *without* hemihypertrophy [Miller, 1968a]. In 1964 Beckwith and Wiedemann independently described the syndrome (as distinguished from hemihypertrophy alone) that now bears their names in which other birth defects occur as well as these neoplasms [reviewed by Sotelo-Avila et al., 1980]. The gene (*WT-2*) has been mapped to chromosome region 11p15, and that for Wilms tumor with aniridia to

chromosome band 11p13 (*WT-1*) [reviewed by Hastie, 1994]. A gene for familial Wilms tumor (*FWT1*) has been reported in chromosome region 17q12-21 [Rahman et al., 1996].

TRILATERAL RETINOBLASTOMA

Our study of hospital records for retinoblastoma demonstrated an excess of osteosarcoma around the knee, not attributable to radiotherapy for the eye tumor [Jensen and Miller, 1971]. Osteosarcoma occurs not only as a second primary neoplasm in the same child but also separately in relatives [Hansen and Cavenee, 1987]. In monitoring children with cancer for unusual occurrences at the National Children's Medical Center (under its old name we had encountered our first case of aniridia there), a member of our staff found a child with bilateral retinoblastoma and a pineal tumor. It occurred to me that the pineal tumor might be due to ectopic retinal cells, and that the diagnosis was trilateral retinoblastoma. We quickly found two other cases (with unidentified cell type) in the literature, and others, unpublished, when word of the disorder spread [Bader et al., 1980; Bader et al., 1982]. The diagnosis was confirmed by Lorenz E. Zimmerman of the American Registry of Ophthalmic Pathology at the Armed Forces Institute of Pathology. Before long he had studied 27 such cases (unpublished teaching handout, 1982), and 6 cases were reported by Kingston and her associates [1985] in Great Britain. Two of the patients in our series also had tumors of the cheek that were retinal in origin, an instance in which tumorigenesis demonstrated the presence of cells left behind during embryologic development.

It seemed to me that if studies looking backward for the causes of disease are termed "retrospective," and those looking forward for the development of disease after a specific exposure are "prospective," why not "laterospective" searches for collateral disease, such as cancer and congenital anomalies? The term did not catch on in the U.S., but Noboru Kobayashi, Professor of Pediatrics at Tokyo University, has used it ever since.

DOWN SYNDROME AND LEUKEMIA

Before I arrived in Bethesda, an expert committee of epidemiologists proposed that NCI initiate a 12-hospital retrospective study of childhood leukemia, to seek evidence of environmental influences, especially radiation exposure. The 2 year data collection was completed before I arrived, and my task was to analyze it. Looking over the case abstracts showed that, although everyone used the same questionnaire, the nurses who conducted the interviews had emphasized different questions, e.g., dental X-rays in one instance and shoe fluoroscopy in another. It was impossible to analyze the environmental data, but two genetic observations could be made. Among 459 children with leukemia, 5 had sibs with Down syndrome, an excess that was barely significant statistically. Among their 1,000 sibs about 1.5 children with Down syndrome were expected as compared with 5 observed [Miller, 1963b]. This finding,

never replicated, suggested that a chromosomal mechanism in common could account for meiotic non-disjunction in Down syndrome and leukemia in their sibs. This work led to my review of radiation, chromosomes, and viruses in the etiology of childhood leukemia [Miller, 1964]. Epidemiologic evidence for the leukemogenic effects of radiation and chromosomal anomalies (Down syndrome and chromosomal breakage syndromes) was strong, whereas evidence for horizontal viral spread of childhood leukemia had been sought but not found. Review of the literature on causes of death in Down syndrome through 1969 demonstrated that the peak for leukemia was at age 1 year as compared with 4 years in the general population. No excess of other cancer was found [Miller, 1970].

ATAXIA-TELANGIECTASIA AND LEUKEMIA

The other genetic observation from the 12-hospital study concerned early evidence, from Peterson, Cooper, and Good [1965], that non-Hodgkin lymphoma occurred excessively in immunodeficient children, including those with ataxia-telangiectasia (AT), and they predicted that acute lymphocytic leukemia (ALL) would also be excessive. We wondered if the 12-hospital study might have such a case, but AT had been too recently defined for the diagnosis to be well known. A search for a child with cerebral palsy and ALL led to two deceased sibs in Oregon with ALL and "Friedreich's (?) ataxia." A call to Frederick Hecht in Portland led to the diagnosis of AT in a third sib, and a family photograph showed ocular telangiectasia in the deceased sib who was old enough to have this manifestation. Hecht found that the surviving sib had chromosomal instability [Hecht et al., 1966], and several years later an unsolicited communication from Current Contents notified me that our report was my most frequently cited publication (because of the description of chromosomal instability).

NEUROFIBROMATOSIS-1 (NF-1) AND CHILDHOOD LEUKEMIA

The literature disclosed that 17 cases of leukemia had occurred in children with NF-1. We telephoned other cancer centers and found 12 unreported cases, bringing the total to 29. The distribution by cell type was unusual because of the predominance of myelogenous leukemia, chronic or acute [Bader and Miller, 1978]. No one could think of a reason for this excess in a neuroectodermal disorder until a small gene (*EV12A*) for leukemia was found in the midst of the large gene for NF-1 when it was cloned [Cawthon et al., 1990; Wallace et al., 1990]. The association of rhabdomyosarcoma with NF-1 was also described by members of my Branch, with a major role played by Joann Bodurtha, on elective with us while a medical student at Yale [McKeen et al., 1978].

RUBINSTEIN-TAYBI SYNDROME AND NEOPLASIA

By 1989 Jack H. Rubinstein of Cincinnati Children's Medical Center had amassed case histories of 574 chil-

dren with Rubinstein-Taybi syndrome (RTS) (broad thumbs and characteristic facial anomalies). He thought there might be an excess of neoplasia among them. Patricia Siraganian of my staff and I helped him evaluate his data, which suggested an excess of certain benign or malignant tumors [Siraganian et al., 1989]. By 1995, he and I had ascertained enough additional cases to strengthen the suggestion of an association of RTS with neural tumors and benign developmental tumors, e.g., choristoma, dermoid cyst, and pilomatricoma [Miller and Rubinstein, 1995]. The gene at 16p13.3 had already been cloned and was reported to be the gene for CREB binding protein, which may account for the congenital anomalies and tumors in RTS [Petrij et al., 1995].

PANCREATIC CYSTIC FIBROSIS AND ILEAL ADENOCARCINOMA

My rule of thumb is that chance does not explain the occurrence of three pairs of rare associated diseases. In searching various sources for cancer in cystic fibrosis (CF) of the pancreas, we found a third patient with ileal carcinoma at age 30, among the small number of long-term CF survivors. The first two cases had been published, and the third was in an abstract of papers presented at the annual meetings of the CF Foundation over the previous 20 years. The search was made because virologists had isolated the *met* oncogene on chromosome 7, near the locus for the *CF* gene. No cancer excess has been found. A large number of duodenal adenocarcinoma and lymphoma has been reported in non-tropical sprue, an observation that suggests the small bowel cancers were related to steatorrhea and malabsorption in both diseases and not to the *CF* gene [Siraganian et al., 1987].

CANCER DEATHS IN SIBS

In 1964 Brian MacMahon, Professor of Epidemiology at Harvard, suggested that we obtain copies of death certificates on all children who died of cancer in the United States to be linked to their birth certificates in a search for clues to cancer cause. We created, in effect, a registry of about 50,000 death certificates, 1960–1969 [Miller, 1971a], but the birth certificates were beyond us with regard to procurement and scope of the study. We re-coded the diagnoses by cell type, instead of using the too-broad codes of the WHO International Classification of Diseases (ICD). This made it possible for Fraumeni and Glass [1970] to report the rarity of Ewing sarcoma in blacks, a diagnosis formerly unobtainable because the ICD code combined all forms of bone cancer. Another publication [Miller, 1969] concerned associated diagnoses of congenital anomalies, including aniridia with Wilms tumor recorded by a physician in Plum Creek, Pennsylvania, before the syndrome had been described in the literature. We had extracted the mothers' maiden names from the death certificates, and when we alphabetized and matched on the children's surnames, along with other death certificate information, we found excesses of deaths among sibs [Miller, 1968b; Miller, 1971b]. Of greatest interest were

six pairs of sibs, both of whom had brain tumors, or one had brain tumor and another had soft-tissue sarcoma or osteosarcoma. We know now that these families had Li-Fraumeni syndrome, the clinical signs of which were described independently the following year by other members of my Branch [Li and Fraumeni, 1969a,b]. We also know that this syndrome accounted for the findings in our 1967 study of medical records for 62 children with adrenocortical carcinoma, 2 of whom had astrocytoma and 2 had sibs with adrenocortical carcinoma [Fraumeni and Miller, 1967]. Two other children in the series had congenital hemihypertrophy, 9 had hamartomas, and 5 had genitourinary tract abnormalities, all of which are associated not with LFS, but with Wiedemann-Beckwith syndrome [Sotelo-Avila et al., 1980].

The registry showed the deaths of 5 young sib-pairs among 270 children with Letterer-Siwe disease, 1960–1964, evidence of the lethal nature of this familial form of histiocytosis [Glass and Miller, 1968]. Five pairs of same-sex twins had died of leukemia under age 6 years, adding to the five pairs of same-sex twins previously described by MacMahon and Levy [1964], suggestive of a genetic mechanism. There was an odd phasing out of concordance with age. When new laboratory techniques became available they showed that the mechanism was not genetic but due to *transplantation* of leukemic cells from one monozygotic twin to the other through their circulation in common during intrauterine life [Changanti et al., 1979; Mahmoud et al., 1995]. This explained why concordance for leukemia was highest in the first year of life and disappeared by age 7 years.

In addition to these genetic studies, the resource was used for a series of descriptive studies (e.g., type-specific cancer deaths by single year of age [Miller and Dalager, 1974] cancers in the newborn [Fraumeni and Miller, 1969] and in the first year of life [Bader and Miller, 1979], and follow-up studies, as after the use of a vaccine that may have been contaminated with a carcinogen [Sever and Miller, 1971]).

EXCESS OF RARE CANCERS IN WERNER SYNDROME

One of our greatest opportunities to link a genetic disorder with cancer came by chance. Under the United States-Japan Cooperative Cancer Research Program, Dr. Haruo Sugano of the Cancer Institute in Tokyo and I have coordinated 31 workshops on cancer etiology since 1981 [Miller, 1996a]. In 1994, as we prepared for a workshop on cancer clusters, Dr. Sugano happened on a note in a Tokyo medical newsletter concerning a nearby rheumatologist's study of cancer in the Werner premature aging syndrome (WS), more common in Japan than elsewhere due in part to inbreeding. The author, Dr. Makoto Goto, was invited to speak to Dr. Sugano's group and then to the workshop. For his research he had no assistance or funds, so several of us offered to help him take accurate inventory of 127 case histories concerning neoplasia in WS, and I reviewed the literature on non-Japanese patients with WS (34 cases). This 2-year task showed that the ratio of carci-

noma to non-epithelial cancers was 1 to 1 instead of 10 to 1 as found in the general adult population. The difference was due to a marked excess in the Japanese WS patients of soft-tissue sarcoma, osteosarcoma, melanoma of the feet or mucosa (very rare sites), myeloid leukemia and its precursors, thyroid carcinoma, and benign meningioma. Non-Japanese had excesses of osteosarcoma, soft-tissue sarcoma, and benign meningioma but not of the other neoplasms seen in the Japanese, perhaps due to differences in mutations. Cloning of the gene at chromosome site 8p12 was reported [Yu et al., 1996] on the same day that our report was published [Goto et al., 1996].

At our next United States-Japan seminar, which concerned genetic syndromes with high risk of cancer, it was shown that different arrays of cancers occur in other hereditary chromosomal disorders with congenital anomalies (Bloom syndrome, Fanconi syndrome, and ataxia-telangiectasia), and that the Li-Fraumeni family cancer syndrome bears some resemblance to WS in its excess of osteosarcoma and soft-tissue carcinoma but not in the other four cancers most often seen in LFS. Also, unlike WS, LFS has no systemic disorders. These peculiarities of occurrence should be explained now that the gene for Werner syndrome has been cloned, and its mechanism of action can be determined.

PAGET DISEASE OF BONE AND OSTEOSARCOMA

The excess of osteosarcoma (OS) in WS drew our attention to other genetic disorders with high risk of osteosarcoma. The peak in the incidence of OS among the elderly, particularly in males in Western countries, has been attributed to Paget disease of bone (PDB). Our pathologist co-author, Dr. Yuichi Ishikawa, mentioned that PDB was rare in Japanese, which led us to obtain OS incidence data for males, 1973–1993, from the Osaka Cancer Registry and NCI's Surveillance, Epidemiology, and End-Results Program. The incidence was virtually identical until age 55 years when it rose to a peak in the United States but not in Japan [Ishikawa et al., 1996]. A PDB gene has been tentatively mapped to chromosome area 6p21.3 [McKusick, 1994].

RACIAL DIFFERENCES IN CANCER RATES

The yield of new information from the United States-Japan workshops was fueled largely by racial differences in cancer occurrence. A workshop on cancer incidence under age 30 years documented that the rates were very low in Japan for Ewing sarcoma, non-Hodgkin lymphoma of the B-cell type, Hodgkin disease, testicular cancer, and melanoma [Miller and Sugano, 1987; Miller, 1996b]. Low rates for melanoma in Japan are due not to skin pigmentation as in blacks but in part to sun avoidance and the rarity of dysplastic nevi, a genetic precursor [Hara et al., 1992]. In any event, waiting rooms in Japanese cancer hospitals must have substantially fewer young adults than do United States hospitals. The differences in rates await explanations from laboratory research.

INTERNATIONAL CHILDHOOD CANCER STUDY

In 1970 the International Union Against Cancer (UICC) established a ten-member Committee on Childhood Cancer, the mission of which was to promote international collaboration in pediatric oncology. As co-chair, I suggested a recent case series from as many countries as possible of findings in children with cancer, including the diagnosis, cell type, and unusual occurrences such as the presence of congenital malformations. By mail we received information from almost 60 countries on about 37,000 children with cancer. Among the remarkable observations was a near-absence of neuroblastoma in central Africa, possibly due to an environmental influence that enhances the usual regression of microscopic foci of neuroblastoma cells normally in the fetal adrenal gland [Miller, 1989]. Also, skin carcinoma in Tunisia accounted for 11% of all childhood cancers, equal to the frequency of Wilms tumor plus neuroblastoma in the United States. The children had xeroderma pigmentosum (XP) and were the subjects of laboratory research, but the marked excess of childhood skin cancer in North Africa had not been documented. Another finding, still unexplained, was the high rates of retinoblastoma in several countries, especially India and Pakistan [Miller, 1977].

CHILDHOOD CANCER ETIOLOGY NEWSLETTER

The Committee met in Amsterdam in 1972 to review the findings and to plan for the future. We met for 1 day, in conjunction with the annual meeting of the International Society of Pediatric Oncology (SIOP). To encourage clinicians to think about cancer etiology, I volunteered to prepare a Newsletter for members of the Society and others. Almost every month for 10 years I abstracted about eight new publications of etiologic interest and mailed the summaries to 1,000 people. The second issue passed along the information that a second case had been reported in which a severe acute radiation reaction had occurred after conventional radiotherapy for lymphoma, a neoplasm that occurs excessively in AT. The Newsletter arrived in Birmingham, England, just after Dr. Jillian Mann had observed a case there. She consulted with Dr. David G. Harnden, a basic scientist at the hospital, whose group obtained skin fibroblasts from the patient, irradiated them, and found diminished survival in culture [Taylor et al., 1975]. This represented a genetic-environmental interaction, later shown to be due to defective DNA repair of X-ray damage, analogous to the DNA repair defect in XP after UV damage [Paterson et al., 1976]. In collaboration with Dr. Malcolm C. Paterson, who discovered the DNA repair defect in AT, my Branch sought similar defects in families with syndromes that predisposed to cancer. We found nothing to match the defects in AT and XP.

The small grant to hold the meeting in Amsterdam was from the Virginia chapter of the American Cancer Society. By way of thanking its members, I wrote twice to describe these developments but received no reply.

THE ALERT CLINICIAN

Throughout my career I have called attention to the role of the alert clinician in causal research. Nearly every human carcinogen and teratogen was first described by an alert observer [Miller, 1978a]. The same is true of syndrome delineation, so important in human genetics.

The Japanese in a sense honored this concept by asking me to take the lead in organizing non-Japanese participants for the 18th annual international Princess Takamatsu Cancer Symposium in 1987. The subject, *Unusual Occurrences as Clues to Cancer Etiology*, concerned the histories of key discoveries and subsequent laboratory research. Early observations, which often are not recorded or fade from memory, were brought to life by about 20 people who were involved in these studies from the beginning. Among the speakers were Arthur L. Herbst on a rare form of cervical/vaginal cancer in young women whose mothers were treated early in pregnancy with diethylstilbestrol, Yukio Nishimoto on an epidemic of respiratory-tract cancer in Japanese who manufactured mustard gas during World War II, Gregory O'Connor on the pathology of African lymphoma at the same time Burkitt was discovering the neoplasm clinically, Alfred G. Knudson, Jr. on tumor suppressor genes, and David T. Purtilo on the X-linked lymphoproliferative syndrome [Miller et al., 1988]. The Princess held a dinner for us at her villa, a high point in my career.

CONFRERES

Joseph F. Fraumeni, Jr., who had just finished his residency in clinical oncology at Memorial Hospital in New York, joined us in 1962, a year after I arrived at NCI. He participated in ongoing studies, spent an academic year at the Harvard School of Public Health (Master's degree in Epidemiology), and began to originate research of his own, a notable early contribution in genetics being a report on urinary bladder cancer in a man and his three sons, in which he sought a metabolic explanation [Fraumeni and Thomas, 1967]. In 1974 he convened a conference on Persons at High Risk of Cancer, the proceedings of which were widely read [Fraumeni, 1975]. It was followed in 1982 by his classic textbook on epidemiology, now in its second edition [Schottenfeld and Fraumeni, 1996].

Frederick P. Li joined us in 1967 after clinical training in internal medicine at the University of Rochester and Bellevue Hospital in New York. He had taken a year off in medical school to participate in established epidemiologic studies as he travelled the world. While getting started under our guidance in an epidemiologic study of the causes of death in chemists, he spent his evenings studying for a Master's degree in demography at Georgetown University.

Two years after he arrived at NCI he went to a dinner party where he heard that a child with cancer and a strong family history of cancer had been admitted to the NIH Clinical Center. The next morning Fred went to the ward and obtained the pedigree. He and Joe Fraumeni found three more such families in a series of

medical records already under study of children with rhabdomyosarcoma [Li and Fraumeni, 1969a,b]. A registry of such families was established and the disorder, now known as the Li-Fraumeni syndrome due to a germline mutation of p53 [Malkin et al., 1990], was shown to consist of soft-tissue sarcoma, osteosarcoma, breast cancer, brain cancer, leukemia, and adrenocortical cancer under 45 years of age [Li et al., 1988].

Fred went to various Harvard-affiliated hospitals for 3 years of fellowships in internal medicine and oncology, and remained in our Boston Field Station for the remainder of his 24-year Public Health Service career. In Boston's highly competitive environment he made a large number of astute observations about cancer etiology, inborn or environmentally induced. One of the most interesting was a 3,8 translocation in familial renal cell carcinoma [Cohen et al., 1979].

John J. Mulvihill joined us in 1970 after his internship in pediatrics at the University of Washington. Two years later, stimulated by our Veterinary Section, which had created a multicenter epidemiology registry for cancer and other diagnoses in domestic animals, he published a main article in *Science* on their congenital and genetic diseases [Mulvihill, 1972].

He went to Johns Hopkins for a 2-year residency in pediatrics. All of the clinical training of our staff outside NIH was sponsored by the Public Health Service, which was possible then. Soon after his return to Bethesda, he took the lead in convening a landmark conference on the genetics of human cancer, the proceedings for which advanced the development of interest in this field [Mulvihill et al., 1977].

We had long been convinced that von Recklinghausen neurofibromatosis (NF-1) could provide important clues to carcinogenesis. There was little interest in NF-1 until John organized a symposium on the subject in 1979. Research into the disease and its neoplasia flourished after the meeting and publication of its proceedings [Riccardi and Mulvihill, 1981], aided by the activities of the National Neurofibromatosis Foundation led by Lynn Courtemanche, a young nurse with the condition.

SPECIAL ACTIVITIES

China 1977

My most extraordinary trip was for 22 days to the People's Republic of China in 1977 with a 12-person Delegation sponsored by the National Academy of Sciences (NAS). Our objective was to learn as much as we could about cancer research in China just after the Cultural Revolution had ended. Fortunately our group was strong in etiology, and being in China then allowed us to explore this unknown place, rich in etiological observations and opportunities [Miller, 1978b]. We learned of pigs and people with high rates of nasopharyngeal carcinoma (the latter related to their HLA haplotype) near Canton, ducks and people with liver cancer due to chronic hepatitis in Shanghai, and, in Lin County, chickens with gullet cancer and people with so much esophageal cancer that it doubled their total for all other cancer. I was shown extensive hand-drawn pedigrees of family clusters of esophageal cancer, with very

few women in the family tree. Where were they? The deaths were ascertained from tombstones, and women did not merit them.

Just before we left China we learned about the tin mines where workers had an epidemic of lung and skin cancer, presumably due to radon and arsenic exposure. The chest surgeon who accompanied us on the entire trip had told us there were no occupational cancers anywhere in China. We asked who was in charge of the tin-mine study and were told that it was the chest surgeon.

Then a member of our group, a geographer born in Shanghai, challenged our hosts to make county maps showing the cancer rates (as my NCI group had already made for the United States). The next day they brought the map of one Province, which they had not planned to show us. We later learned that they had already completed the map for all of China, done during the Cultural Revolution, when research was forbidden. Fred Li went to Beijing for 3 months in 1979 to help prepare the English version of their monumental book of cancer maps.

Dioxin in Seveso, Italy

Earlier that year, I was a member of a four-person group sent by NAS to Seveso, Italy to assist in plans for follow-up of people exposed to a toxic cloud of dioxin from a runaway reaction in a chemical factory. The town had been closed and clean-up workers wore protective clothing. Domestic rabbits, birds, and other wildlife had died, but the only effect in humans then was chloracne, in children who had played in the cloud as it came to earth. We recommended the establishment of an International Steering Committee to advise annually on follow-up studies, of which I was a member for its 5-year duration. There were two memorable developments: 1) when a laboratory test was developed, the highest blood levels of dioxin in stored specimens were in children who had had chloracne—up to 56,000 ppt 2 weeks after exposure [Moccarelli et al., 1991]; and 2) the arrest of the Committee chairman, an Israeli, as a Soviet spy who used teratology as a cover and is still in jail.

Air Force Agent Orange Study

In 1984, I was appointed chairman of a high-level advisory committee to oversee the Air Force study of the effects of Agent Orange on flight crews who had served in Vietnam. It was a sensitive assignment that no one wanted. We met at Brooks Air Force Base in Texas to avoid publicity that would have bedeviled us in civilian setting. The study was well done and the reports were published promptly. No finding of note turned up during my 5 years with the Committee. I tried to resign after 3 years but was too valuable it was said. Then after 5 years, I was removed by an act of Congress. Senator Daschle of South Dakota changed the charter for our committee to state that the chairman (in order to be trusted) must not be a government employee. The Under Secretary for Health posed with me for a photograph, but I never received the print.

Hiroshima Again

My link to the Atomic Bomb Casualty Commission and its successor, the Radiation Effects Research Foundation, continued for 35 years. In 1971, when the exchange rate for the dollar fell against the yen, ABCC was unable to meet its expenses. My Branch at NCI was able to provide the needed funds through a 3-year contract that called for, among other things, the establishment of tumor tissue registries in Hiroshima and Nagasaki. These registries provide histologic material for a surveillance that has become a foundation for cancer incidence studies there ever since. Over the years I served on various advisory committees to ABCC, the best of which was the Science Council, 1980–1989. It met in Japan, where my wife could visit her family.

For the centennial anniversary of Roentgen's discovery of X-rays, I was invited by the editor of Radiation Research to prepare a review of adverse effects since then [Miller, 1995]. It was more than 40 years since I had opened my career on the subject. During the same time, my chapter on radiation injury had appeared in each edition of Nelson's Textbook of Pediatrics. The idea for the chapter was passed on to Dr. Nelson by a book company representative who had asked me what might improve the textbook.

Chernobyl

In 1987 and 1989, I was a member of Delegations for the Department of Energy to discuss with Soviet scientists their follow-up studies of people exposed to fallout from Chernobyl. We met in Moscow and Kiev. Chernobyl was the third area I visited that had been evacuated because of contamination, the other two being Seveso and the Love Canal in Niagara Falls, where 82 chemicals had been buried in the abandoned canal, and a school for 400 children built on top. As a result of our second visit to Chernobyl, NCI played an active role in follow-up studies, but I withdrew early because of intense international competition for a piece of the action, and the struggle to work collaboratively with the Soviets. (Endocrinologist in Kiev: "Your suggestion is not practical—to examine 1,000 children with high thyroid doses as compared with an appropriate sample of lightly exposed children. In the Soviet Union we must examine all 151,000 children in the region.")

Marshall Islands

In 1957 I was invited to join a Brookhaven group to examine the Marshall Islanders who had been exposed to fallout from a weapons test on Bikini. My assignment would be to examine children who had been exposed, mainly on the atoll of Rongelap. I had to decline because the date conflicted with the start of my training at the University of Michigan. Besides, I thought, nothing will be found among only 32 children. In the ensuing years, two exposed as infants developed myxedema and were of short stature, and among older children 18 developed neoplasms: 13 thyroid nodules, 4 thyroid carcinoma, and 1 leukemia [Merke and Miller, 1992].

In 1989 I was invited again, this time to advise the three-judge Nuclear Claims Tribunal about which

members of the population of 45,000 should be compensated for late radiation effects, from a fund of 45 million dollars. Only 82 people on two atolls had received more than 0.20 Gy (20 rads), a dose too low to produce a detectable increase in cancer in the Japanese survivors of the atomic bomb [Miller, 1995]. At the end of my week there, I typed up my medically-based recommendations, the influence of which is difficult to sense after changes in the members of the Tribunal and political pressures to extend the list of eligibles. It was interesting though, and I learned what an atoll looks like—a two-lane circle of road at sea level around a blue lagoon, with not much room for people at the edges of the road.

American Academy of Pediatrics

To me, the best aspect of the American Academy of Pediatrics is its large number of committees to deliberate important matters concerning child health and pediatricians. Among those on which I served were the Committee on Environmental Hazards (CEH) (10 years, 6 as chairman) and the Council on Pediatric Research (13 years as a member or consultant). Perhaps my most lasting contribution was to introduce the establishment of an annual Practitioner Research Award. The idea started in CEH as an alert practitioner award, but, although the cost was low, we were told there was no money to fund it. The Council on Pediatric Research had more clout. The concept was modified to apply to office-based research. The Practitioner Research Award, first given in 1986, gained immediate prestige. In addition to honoring practitioners, the research, significant and diverse in subject-matter, set examples for all pediatricians.

MARRIAGE AND HOME LIFE

After almost 42 years of marriage, my wife and I are closer than ever. She worked for 27 years, most of it as a research technician in an NCI laboratory of chemical carcinogenesis. Japanese often say that the best marriage involves an American husband, a Japanese wife, and a U.S. home. It was certainly so for us.

Holly loves music, especially opera. Often, after the first few notes are sung, she can identify the performer and the opera. She, who knew little English when she arrived here, is a political junky. She watches extended versions of both conventions for President (on PBS) and loves political commentary. She keeps an up-to-date account of our income and expenses, reads a novel a week, and the daily New York Times. Her devoted support has made my career possible.

My favorite activity is street-walking, exploring cities. The teratologist, Josef Warkany, a good friend, asked me during a visit to Japan if he should visit Hakone National Park. He loved my reply, "It's only scenery." Exploring cities is probably related to my neural pathways for observational research—always screening for something new. Reading the New Yorker magazine is in the same category because of the diversity of the contents. In trying to predict if people going to Japan would like it, I asked what they thought of the New Yorker. The correlation was high.

When I worked at the National Academy of Sciences, an elderly lady called the operator and said she would like to talk to someone about willing her body to science when she died. "Just a minute," the operator said, "and I'll connect you with Personnel." I sent the anecdote to the New Yorker, which sent me \$25 and published it three weeks later in the Talk of the Town.

Washington is filled with museums and we visited them often. We have a modest collection of works on paper by the Ashcan School (American, 1925–1940) and contemporary Japanese woodblock prints. A love of architecture led us to have a board-certified architect replace a screened porch over the garage with a splendid sunny room with a beamed cathedral ceiling, a large built-in bookcase to match, and windows the length and width of Japanese scrolls with a view of flowers and shrubs in place of paintings. It is a country place of peace and quiet that we reach by crossing our living room.

A SUMMING UP

Our emphasis has always been on medical as contrasted with statistical studies. The program has been fitted to the talents of the Branch members, who followed their own creative instincts guided by senior staff. Thus, as the staff changed, research emphasis of the Branch changed. However, creativity in observational research is rare among physicians. Aided by the military draft of physicians, who could discharge their obligation in the Public Health Service at NIH, we had ample young people with excellent early training. All the 2-year people were productive while with us, but most fell silent after they left. The problem appeared to be two-fold: few clinicians have a sustained interest in our style of research, and even if they did, there were virtually no suitable positions for them at academic institutions. Grant-funding usually requires hypotheses to be tested, whereas we were trying to develop new hypotheses based on our own clinical observations. Fortunately, at NIH grant funds were not needed, although peer review every 4 years now stresses hypothesis testing.

The end of the draft brought the end of new recruits. This scarcity plus health problems led me to retire but I continue to work as a Scientist Emeritus. I have as many opportunities as ever for innovative research, through the use of disease registries and other data at hand. The data are essentially off-the-shelf, and the supply is substantial.

In 1975 the leaders in cancer research at NCI and elsewhere believed that most cancer was due to environmental causes, knowledge of which would lead to prevention and early detection. We were urged to abandon our work because the rare disorders we were studying "were not a public health problem, and, besides that, you cannot fix genetics." We stayed put, which time has shown was the right thing to do.

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