

CHRONICLE

LIVING HISTORY

One of the monumental discoveries in medicine during the last century was that recorded by Farber et al. in 1948. The team at the Boston Children's Hospital found that a simple compound administered systemically to children with leukemia caused a remission of the thitherto universally lethal disease.

Members of that research team who were then Fellows were asked recently to record their impressions of those heady days. What was it like to see peripheral blood smears, loaded with lymphoblasts, clear with the administration of aminopterin?

To be present at such epochal moments in the advance of medicine and science comes but once in a lifetime. Drs. Wolff, Mercer, and Sylvester have graciously consented to let us share in their recollections. An additional echo of those days is provided by Prof. Ravindranath who, by chance, met one of the first patients cured of leukemia 45 years before.

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Editor-in-Chief

First Light on the Horizon: The Dawn of Chemotherapy

James A. Wolff, MD*

Key words: childhood cancer; antimetabolites; chemotherapy; treatment of leukemia

Prior to the end of World War II the management of patients with either acute or chronic leukemia was essentially that of supportive care. Neither surgery nor radiation therapy (RT), the standard forms of treatment for cancer, were applicable to acute leukemia, and RT had a limited role in the chronic leukemias. Whole-blood transfusions were given, although not routinely, when anemia became severe. Chemotherapy, which had been introduced for infectious diseases such as malaria and syphilis by the beginning of the Twentieth Century, had virtually no impact on the treatment of leukemia or malignant solid tumors. Chemical agents (colchicine, arsenic, benzol) had been tried without success in chronic myelogenous leukemia. Haddow reported the use of urethane in chronic myelogenous leukemia in 1946, the same year in which the beneficial effects of nitrogen mustard derivatives in adults with lymphomas was reported. In 1947, at a time when the mortality for childhood leukemia was 100%, a group at the Boston Children's Hospital, headed by the late Dr. Sidney Farber, a pediatric pathologist, initiated a number of clinical trials for the treatment of

leukemia in children. Various folic acid antagonists were utilized. The impetus for these studies arose from multiple observations.

Folic acid deficiency was known to be associated with bone marrow inhibition. Moreover, in 1944 Leuchtenberger and his colleagues in the Department of Pathology at the Mount Sinai Hospital in New York City reported that a "fermentation I. Casei factor" inhibited growth of Sarcoma 180 transplanted in female Rockland mice [1]. A year later the same group showed complete regression in one-third of single spontaneous breast carcinomas in mice treated with intravenous injections of "fermentation I. Casei factor" [2]. At the time it was thought that this substance was folic acid. Later, Hutchings and his group

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at the Lederle Laboratories showed that the agent contained in the extract was a conjugate of folic acid, pteroyltriglutamic acid (teropterin). Subsequent work at Mount Sinai Hospital showed that pteroylglutamic acid (folic acid) was not effective in producing regression of these breast cancers [3]. Moreover, Farber had himself found that administration of folic acid had “accelerated the leukemia process.” Finally, a report by Heinle and Welch [4] in 1948 stated that administration of folic acid was attended by rapid hematologic and clinical relapse in three patients with chronic myelogenous leukemia.

Although the evidence that antagonists of folic acid inhibited proliferation of leukemia cells was fuzzy at the time, Farber enlisted the help of Hutchings and other chemists at the Lederle Laboratories. One of them, Y. Subbarow, quickly synthesized a number of folic acid conjugates with antimetabolite effect, and the first clinical trial of pteroylglutamic acid conjugates by the Farber team was soon published in December, 1947 [5]. They reported observations in 90 patients with advanced malignant disease, of whom 41 were children and 49 were adults. All subjects were treated with pteroyldiglutamic acid (dioplerin) or pteroyltriglutamic acid (teropterin). Eleven of these patients had acute leukemia. In these subjects bone marrow biopsies performed before and after therapy showed “no evidence of pancytopenia or agranulocytosis.” Adult patients “experienced improvement in energy, appetite and well-being.” It was concluded that the substances were nontoxic and warranted further investigation.

Following the initial clinical trial, Farber joined with Dr. Louis K. Diamond, a pediatric hematologist, Drs. Robert D. Mercer and Robert F. Sylvester (Research Fellows in Pathology and Tumor Research), and myself (Research Fellow in Pediatric Hematology) to form a team. Its mission was to investigate the effects of folic acid antagonists in children with acute leukemia, which had not yet been stratified at that time into morphologic types. These patients therefore included children with acute myelocytic as well as acute lymphocytic leukemia. The first child in this study began treatment on December 3, 1947. Between that time and April 15, 1948, 16 children with acute leukemia were treated with 4-aminopteroylglutamic acid (aminopterin) intramuscularly. These children were all seriously ill at the start of treatment. Ten of them showed significant clinical, hematologic, and pathologic evidence of improvement lasting several months. Six of the sixteen had poor responses. Because of the reluctance of referring physicians to treat acute leukemia, recruitment of patients was difficult and became moreso as severe toxic effects became apparent. The investigation also met considerable resistance from the house staff, who were not accustomed to managing such severely ill children. The first report of these studies [6] on June 3, 1948, gave detailed data of temporary

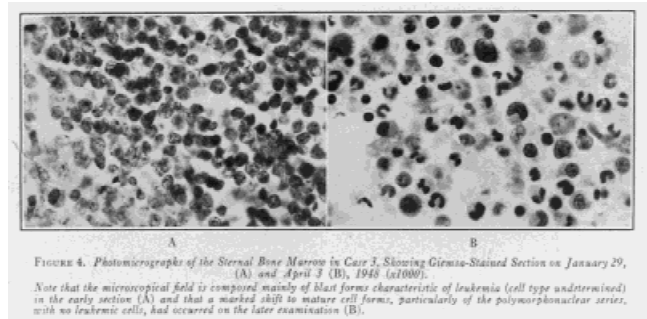


Fig. 1.

remissions in five children. Figure 4 of that report shows striking improvement in the bone marrow in one of these children (Fig. 1).¹ The authors suggested a search for other folic acid antagonists that might be less toxic and even more effective than aminopterin.

Publication of the results of treatment with aminopterin aroused widespread interest throughout the world. The Boston Children's Hospital became the mecca for a number of investigators interested in childhood leukemia. Conferences were arranged for visitors to familiarize themselves with the details of treatment. Early in 1948, another folic acid antagonist, 1-4-diamino-N-10 methylpteroylglutamic acid (originally labeled a-methopterin, later methotrexate), became available to the Boston investigators. Their subsequent studies showed that this drug was less toxic and even more effective than aminopterin. The Farber group's experience with folic acid derivatives was recognized quickly as a paradigm in the search for other agents to combat childhood leukemia. The Boston Children's Hospital continued to play a leading role in this endeavor. Farber, with great energy and foresight, had established the Children's Cancer Research Foundation (CCRF) in 1947, when he introduced the first research program in chemotherapy devoted to childhood cancer. The "Jimmy Fund" became the fundraising arm for the CCRF. The CCRF charter was expanded in 1969 to provide services for patients of all ages, and was renamed the Sidney Farber Cancer Institute in 1947 in honor of its founder, one year after his death. Nine years later, it became the Dana Farber Cancer Institute, as it is known today.

On reflection, the passage of 50 years has not diminished for me the heady excitement that accompanied Farber's ground-breaking experiments. By and large, the program had the enthusiastic support of our colleagues at our institution, then known as the Boston Children's Hospital. A few nay-sayers, as may be expected, advanced arguments that overemphasized the potential of

toxicity. Despite an early undercurrent of disapproval from these sources, the fairly obvious benefits to be derived overruled any objection. For me, there were, moreover, many satisfactions in addition to the realization, even back then, that very likely we had started down a path that would benefit future generations of children. One of these was the opportunity to study the sequence of events in the evolution of remission in patients with acute leukemia. With the help of Betsy Gallatin, our accomplished research technician, we outlined in great detail the changes that occurred after chemotherapy in both the peripheral blood and the bone marrow. These proved to be similar to those seen in the rare child who underwent a brief remission spontaneously or as a result of febrile infection. After leaving the Boston Children's Hospital for the Babies Hospital in New York City, we were greatly helped by this knowledge in our further investigations.

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BIOGRAPHIC NOTE

Dr. James Wolff was the only one of the three Fellows involved with this initial and epochal research who continued in hematology/oncology. He left Boston to join the Babies Hospital staff in New York City, a unit of the College of Physicians and Surgeons of Columbia University. Steadily, over the years, he built an academic unit in pediatric hematology/oncology that proved to be one of the fertile training grounds for specialists in this field. He was one of the original members of the National Wilms Tumor Study Committee as well as being a principal investigator in what has become the Children's Cancer Group. His contributions to clinical research as well as the outstanding clinical service organized at Babies Hospital earned him steady promotions on the academic track and he became a tenured Professor of Pediatrics at Columbia in 1972. He continued in that capacity until his retirement in 1981, after which he became Director of the Valerie Fund Center for Blood Diseases and Cancer in Children at the Overbrook Hospital in Summit, New Jersey. That institution is a Columbia University affiliate. He remained in that capacity for seven years and is now fully retired and divides his time between Florida and Edgartown, Martha's Vineyard.

His contributions to the welfare of children were recognized by the formation in 1991 of the James A. Wolff Professorship in the Department of Pediatrics at Columbia. He was also awarded the Distinguished Alumnus Award by the Babies Hospital in 1996.

ADDENDUM

Dr. Louis K. Diamond, aged 97 years and considered by many the Father of Pediatric Hematology, died on June 24, 1999.

Further Reflections

Robert Sylvester, MD*

One reason for our excitement during this early work was the possibility that we were involved in genuinely "new" science. The principle of biological antagonism had only recently been elucidated, particularly with respect to the treatment of bacterial infections with sulfonamides, and the prospect that this same phenomenon might show promise in the treatment of neoplastic disease was intriguing indeed.

Resistance to our line of investigation is not surprising in light of the general agreement within mainstream pediatrics at that time that minimal support for children with leukemia was the treatment of choice for this heretofore rapidly and universally fatal disease. Lack of support by our colleagues was, however, frustrating to say the least, and it is to Dr. Farber's lasting credit that he was able to press on in spite of the opposition.

There was a lot of media attention when the work was first presented at the Children's Hospital in early April, 1948, and I remember how careful and thorough Dr. Farber was in his briefing of the press in an attempt to avoid sensational reporting. Of course, and despite his care, when the papers came out the next morning, leukemia had been "cured in Boston."

I finished in Dr. Farber's laboratory in July, 1948, and became the Chief Resident in Pediatrics at the Children's Hospital in Columbus, Ohio. I thereafter joined an established practice in Columbus and was appointed Clinical

Instructor in the Department of Pediatrics at Ohio State University. Then, another Boston Children's alumnus recruited me in 1961 to take over his practice in the small college town of Granville, Ohio. This was only about an hour away from Columbus Children's, so I was able to continue with my interests there. With others, I became interested in the emerging subspecialty of adolescent medicine.

My participation in this particular episode in the development of oncology was almost accidental, but I have always looked back on it with a feeling of satisfaction that we were able to add some impetus to a vital movement in medicine, which continues to grow and gain strength.

EDITOR'S NOTE

Dr. Sylvester taught and provided primary pediatric care in central Ohio for 40 years. He was appointed Clinical Professor of Pediatrics in the Medical School of the Ohio State University in 1976. He retired in 1988 and now lives on Sanibel Island in Florida.

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The Team

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One aspect of the "dawn of chemotherapy" has never been freely discussed. It concerns the interdepartmental relationships within Boston Children's Hospital, which at times threatened the entire effort.

The chemotherapy treatment team consisted of Dr. Louis K. Diamond, head of hematology, and his associate Dr. James Wolff, who were concerned with the more scientific aspects of changes in the blood and bone marrow. Dr. Sidney Farber, Chief of Pathology, recruited Dr. Robert Sylvester and me to manage clinical aspects of patient care. Both of us were Board-qualified in general

pediatrics. Dr. Farber was in charge of the whole group, and our clinical team reported directly to him.

Follow-up examinations were carried out in the vestibule to the lavatory in the pathology building, with patients and their families waiting in the halls. We sharp-

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ened our own bone marrow needles. Patients were admitted to Children's Hospital when appropriate. Surprisingly, these comparatively crude arrangements functioned well.

Our problems, territorial as well as social, were related to the attitude of the house staff of the medical service of which Dr. Charles Janeway was the chief. The house staff objected to the idea of "pathologists" treating patients. The fact that Dr. Sylvester and I were well-trained clinicians made no impression on them.

In retrospect it is easy to understand the objections and hostility of the house staff. At this time the mortality rate of children with leukemia was virtually 100%. The general philosophy of care was, "Let them die in peace." To obtain repeated blood samples and to examine the bone marrow seemed to some to be cruel. Dr. Janeway was flooded with complaints.

At the peak of this unrest, Dr. Janeway called me into his office. In his gentle and wise manner, he discussed every aspect of the situation, taking into account my own conviction that Dr. Farber was making real progress and that the antifolics were helpful. I do not know what Dr. Janeway said to the house staff, but soon their attitude changed for the better, perhaps because, at about this time, we began to see favorable changes in the bone marrow. One child went into complete remission. The bone marrow looked so normal that one could dream of a cure, but of course that was not to be so easily achieved.

Other problems during this time were related to the emotional impact of caring for large numbers of very sick

children. It was not possible to care for these youngsters on a daily basis without developing strong bonds of affection. Each death was intensely depressing. I was often required to attend the autopsy of one of these children, a particularly difficult experience. On some weekends my wife and I retreated to Cape Cod, where the sound and sight of the waves on Vineyard Sound would restore my emotional equilibrium.

My recollections of this period and my experience are mixed. It was the beginning of a very important direction in the treatment of the malignant diseases. Clinical studies are carried out in a vastly more scientific fashion today, but, despite its difficult beginnings, history has vindicated our early efforts.

EDITOR'S NOTE

Dr. Mercer completed his Research Fellowship in 1949. He then joined the Faculty at the Western Reserve University and shortly thereafter founded the Department of Pediatrics of the Cleveland Clinic Foundation, of which he became the Chairman. He remained there to become a national figure in pediatrics and the first recipient of the Outstanding Achievement Award granted by the Ohio Chapter of the American Academy of Pediatrics in 1983, the year of his retirement. He and his wife have since then been active in environmental and other civic affairs in the Florida community they have made their home.

Forty-five-Year Follow-up of a Childhood Leukemia Survivor: *Serendipity or Karma?*

Yaddanapudi Ravindranath, MBBS*

More and more children with cancer are being cured, and follow-up of long-term survivors becomes more important and at the same time more complex. As childhood cancer survivors become adults and become more mobile, over time contacts with the treating physician become less frequent. On the other hand there are unexpected pleasures when long-term survivors surface in the most unexpected places.

In 1979, while still a young faculty member at the Children's Hospital of Michigan in Detroit, I was gathering data for a paper on long-term survivors of childhood ALL [1]. Dr. Wolf Zuelzer, one of the early pioneers in the treatment of childhood leukemias, by then had one of the largest collections of leukemia survivors, treated on his composite cyclic therapy (CCT) [2,3].

Contacting and talking to the survivors and their families was a great thrill to me as a neophyte in leukemia studies, and I can recall the enthusiasm of many at the other end of the telephone as well. One parent, mother of the longest known survivor at that time (about 25 years from diagnosis), however, wanted us to leave her child alone (he had suffered enough) and would not give the now adult survivor's contact phone number or the address. I

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was of course rather disappointed and wondered if I would even know him. It was so near and yet so far!

I had pretty much given up hope of personally seeing some of these long-term survivors, but, having spent quite some time reviewing these charts, the names stuck in my mind. Then, on one glorious sunny summer afternoon of 1998, at a golf outing, I heard the name again. There was a putting contest, and he had qualified. I had goose bumps and a lump in my throat. I was quite certain that this must be the person whose chart I had reviewed some 20 years back. The last name was a bit uncommon, it was a fund-raising event in support of research for childhood cancer, and I thought it would be too much of a coincidence that there was another young man in the Detroit area with the same name, who would also be interested in supporting a cancer research program at the Children's Hospital. With great trepidation and choking with emotion, I approached the man who could be one of the longest known survivors of childhood leukemia. I had to be careful of his reaction as well, for I suspected he had no knowledge of his past tryst with destiny, and I was not sure how I should broach the subject. Yes, it was he!! He was not aware of what he had had, but he remembered being a patient at Children's, remembered the "back pokes" for the bone marrows, and vaguely recalled the name Zuelzer. He was diagnosed at age 5 years 7 months on October 13, 1952 (by Dr. Ruth Heyn at the University of Michigan). Initial Hb was 7.5 g/dl; WBC was 3,450/ μ l; and a marrow aspirate showed 93.8% stem cells (blasts). Remission had been induced with cortisone and maintained with aminopterin 0.5 mg daily (with some interruptions) until August 10, 1953, when the aminopterin was stopped. He was seen periodically until July, 1957, and then he was "lost to follow-up." A 10-month treatment and 45-year survival—very cost efficient indeed. In Zuelzer's concept the leukemic lympho-

blasts were "lymphoid stem cells [present day pre-pre-B]," hence the name *acute stem cell leukemia*, and by current BFM terminology he is a steroid "good responder." He is married, though without children, is in good health, and is a successful small business owner.

Was it only *serendipity*¹ that I should find him after his being "lost to follow-up" for so many years? I think it was our *karma* that we should meet, and it is my *dharma* to write of it.

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¹*Serendipity* is derived from an Arab name for the island nation Sri Lanka, "*serendib (-p)*," itself a corruption of "*Simhaladvipa*," a Sanskrit name for Sri Lanka (Encyclopedia Britannica). *Serendip(-b)ity* was coined by Horace Walpole (1754) from the title of the fairy tale "The Three Princes of Serendip," who were always making discoveries, by accident and sagacity, of things they had not actually been seeking. (Oxford English Dictionary). *Karma*, in Hinduism and Buddhism, is the sum of a person's actions in one of his or her successive states of existence, regarded as determining his or her fate in the next; hence necessary fate and destiny, following as effect from cause (Oxford and Webster's dictionaries). *Dharma*, in Hinduism, is social custom regarded as one's duty, essential function, conduct appropriate to one's essential nature—of a king to punish and protect, of a Brahman to study and pray, or in "modern times" of an academician to study and write, etc. (modified from Webster's dictionary).