Emil Frei III, MD:  
In Memoriam (1924–2013)

"Tackle a big problem and stay with it"—advice from Emil Frei II to Emil Frei III

Emil Frei III (Tom) was probably the most admired American cancer researcher of his generation. His death marks the end of an amazing journey in oncology, a field that was in its infancy in February 1955 when he arrived at the National Cancer Institute (NCI, Bethesda, MD). During his long career, he contributed importantly to the cure of childhood leukemia, Hodgkin’s disease and other lymphomas, breast cancer, and other malignancies. It would be appropriate to state that his work and that of his colleagues has saved and will save millions of lives throughout the world. Born in St. Louis, Tom Frei grew up in a deeply religious family, surrounded by artists and musicians. The family business was the Emil Frei Art Glass Company, founded by his grandfather and managed by his father; his mother was a concert pianist and music reporter. The quantitative approach he loved most were mathematics and science, even though there were no scientists in the family to guide him. He was greatly influenced by books about science, including the classic book on epidemiology, *Rats, Lice, and History* by Hans Zinsser.

Tom started at St. Louis University (St. Louis, MO) as an art student, but the Navy drafted him and sent him to Colgate (Hamilton, NY), where he enrolled in an accelerated premed program. This enabled him to go to Yale Medical School (New Haven, CT) and earn his MD degree in 1948, after only 2 years. At Yale, he met Elizabeth Smith, a nurse, who became his wife and mother of their 5 children. He had an internship at St. Louis University, followed by a short period in private practice before being drafted back into the Navy when the Korean War broke out. As a medical officer serving 2,500 men in a destroyer squadron in the Far East, he learned about general medicine, wounds, parasitic, venereal, and respiratory diseases, and psychiatry.

He yearned to do medical research and had his first chance when he left the military in 1953 and took a medical residency at Washington University in St. Louis (St. Louis, MO). It was there that Dr. C. Gordon Zubrod took him under his wing as they investigated a new type of respiratory infection caused by a pleura-pneumonia–like organism. They worked out the nature of the infection in the ear canal of the rat and how to cure it with a new antibiotic, tetracycline. Tom credited this and subsequent experience with Dr. Zubrod (after both had moved to NCI) with teaching him about rigorous measurement in clinical research and the importance of the laboratory in bringing science to the bedside.

When Tom arrived at the NCI in 1955 at the age of 31 years, he decided to focus on the treatment of leukemia. Quantitative studies on leukemia were lacking; the relative response rates to two known chemotherapeutic agents, methotrexate and 6-mercaptopurine, were unknown; and no one had defined partial and complete responses. The quantitative approach his chief Dr. Zubrod encouraged had been started at NCI and later continued at Roswell Park (Buffalo, NY) by Dr. James Holland. They standardized the meaning of remission, required each trial to have a specific objective, specified patient eligibility with respect to age, kind of leukemia, stage of the disease and other factors, and defined measures of disease activity.

The NCI was a special place in the mid-20th century. The field of oncology was new and chemotherapy was in its infancy. There were excellent biologists on campus in Drs. Lloyd Law and Abraham Goldin, and the military draft enabled recruitment of outstanding young doctors into the Public Health Service. Furthermore, most established hematologists shunned leukemia patients because the disease was invariably fatal. But Tom heeded his father’s advice to him as a young man to "tackle a big problem and stay with it." He was "totally committed to the position that science could solve the cancer problem."

Two months after Tom was appointed as chief of the Leukemia Service, he was joined by Dr. Emil J Freireich, fresh from his Boston hematology fellowship and full of self-confidence. When Emil Freireich first introduced himself, Tom was taken aback. “You don’t have to assume that name to get a job with me.” Thereafter, Emil Frei reverted to his former nickname, "Tom" (from his confirmation name after St. Thomas Aquinas), which he had acquired to avoid confusion with two other living family Emil’s, and J Freireich (no period) was J. (They continued to get each other’s mail.) There followed a most amazing collaboration by these two young men as they discussed, planned, and argued

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daily, and systematically constructed attacks on the deadly leukemia problems of uncontrollable bleeding, bacterial and fungal infections, brain and other organ infiltration by leukemic cells, and bone marrow failure. Their prospective clinical trial designs in childhood leukemia were used to determine that two drugs were better than one, that platelet levels were related to bleeding, that using fresh blood or (later) isolated platelets could stop bleeding, proving the value of serial bone marrow testing, and other issues that required quantitative measurement. Indeed, it was not until 1955 that complete remission was defined by bone marrow examination.

There was a sense of urgency that nourished ideas for new studies by Tom and J as they forged novel stratagems to apply to the children and adults who were under their care in the newly constructed NCI Clinical Center. As a father and as a young doctor, Tom was extremely compassionate in his care of patients, understanding what they and their parents were experiencing. He was acutely sensitive to the additional pain he might be inflicting in the course of conducting protocol research that required frequent blood drawing, bone marrow examinations, and lumbar punctures. J was more impatient to try something new even before preclinical testing because he knew what it meant to do nothing for these children. These tactical arguments were also conducted on the ward in front of young doctors who would have to implement the difficult procedures on their patients.

Although the lessons were often painful, it was important role modeling for the clinical associates assigned to the Leukemia Service for a month at a time. Those of us who were fortunate enough to be clinical associates in the mid-1950s were almost the same age as our mentors at NCI, and some actually had more formal medical training. Many of the trainees were inspired to continue their careers in hematology/oncology, which resulted in seeding academic centers with new oncology leaders in the years that followed. Importantly for morale, the pioneering studies on patients with leukemia were being conducted despite clinical scorn, even contempt, from certain famous hematologists who were even overtly critical of the aggressive studies conducted on children who had no hope of cure. Such hostility (“let these children die in peace”) was hard to bear given what we knew that patients and their families did endure. Clinical research in the United States in general owes much to the training opportunities at the National Institute of Health (NIH; Bethesda, MD), perhaps more than anywhere else to the National Cancer Institute.

The critical work in achieving complete remissions depended on a series of chemotherapy trials begun at NCI and largely conducted by the Acute Leukemia Group B (ALGB), which Tom chaired from 1955 to 1963, and subsequently by Jim Holland when Tom moved from NCI to Houston. The insight of using multiple drugs having different mechanisms of action and toxicities permitted the use of full doses of each to produce additive and possibly synergistic responses. They also determined that continuing chemotherapy after patients had achieved remission greatly increased the duration of the remission, which in turn increased survival.

Their most courageous leap came when J and Tom decided to combine four active drugs—vincristine, methotrexate (amethopterin), 6-mercaptopurine, and prednisone (VAMP), something that had never been done and that would not be permissible today. Seventeen patients were treated with VAMP; 3 stayed in long-term remission or cure. Those who remitted stayed in remission for a median of 150 days. And, with extensive subsequent refinement and treatment of the brain at St. Jude’s (Memphis, TN) and elsewhere, the cure rate achieved by the ALGB and others is now around 80%. The principles discovered in acute lymphocytic leukemia using combination chemotherapy were also successfully applied to treating patients with Hodgkin’s disease and non-Hodgkin’s lymphomas with the MOPP program with Drs. DeVita, Cannelos, and others. The drugs and doses have since been modified with considerable success for patients having a number of other malignant disorders, and the use of combination chemotherapy remains the mainstay in cancer chemotherapy.

In 1965, Tom moved to MD Anderson Cancer Center (Houston, TX) as director of clinical research and chairman of experimental therapeutics. Then, in 1972 he joined what is now the Dana-Farber Cancer Institute (Boston, MA) as physician-in-chief and became its director until 1980. His contributions continued with discoveries for improved survival for patients with osteogenic sarcoma, breast cancer, and lymphomas. During his career in Bethesda, Houston, and Boston he successfully trained a generation of leaders in clinical cancer research.

He published more than 500 articles in scientific and professional journals and, with Dr. Holland, he coauthored the influential Cancer Medicine, now going into its ninth edition as the primary textbook in oncology. Tom received numerous awards and honors in recognition of his scientific contributions. Among these was the Albert Lasker Medical Research Award; Fellow, American College of Physicians; General Motors Charles F. Kettering Award; Armand Hammer Award; first NIH Distinguished Alumni Award; Member, Institute of Medicine; Elected Fellow, American Academy of Arts and Sciences. He received the American Association for Cancer Research (AACR) Inaugural Lifetime Achievement Award and less than a month before he died was named an inaugural Fellow of the AACR. The respect, admiration, and affection of basic and clinical cancer researchers may best be exemplified by Tom being elected President of both the AACR and the American Society of Clinical Oncology.

Tom was married to Liz Frei until her death in 1986. He married Adoria (Brock) Frei in 1987; she died in 2009. In his later years, Tom suffered from Parkinson’s disease. He is survived by his five children, Mary, Emil IV, Alice, Nancy, Judy, and their spouses, and his 10 grandchildren.

Emil Frei III was truly loved by all in the cancer community. I like to visualize him perfectly dressed as an Indian swami at our 1957 Halloween party. Tom played the part to the hilt! His broad smile, gentle humor, and roaring laughter will continue to play on for those privileged to have known him.

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Correction: Emil Frei III, MD: In Memoriam (1924–2013)

In this article (Cancer Res 2013;73:4597–8), which appeared in the August 1, 2013 issue of Cancer Research (1), the title contained a typographic error. The correct title is: Emil Frei III, MD: In Memoriam (1924–2013). The online version of the article has been corrected and no longer matches the print version. The publisher regrets this error.

Reference


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