Emil J. Freireich, a founding father of medical oncology, died on February 1, 2021, at age 93, in Houston, TX, his home since 1965. His legacy is immense.

Three personality traits defined Freireich: optimism, audacity, and imagination. Robert Kennedy once said: “Some men see things as they are and ask why. I dream of things that never were and ask why not.” Freireich represented this spirit, questioning conventions and rejecting hopelessness. He emphasized that all knowledge is transitional and highly dynamic, and that most of what is medical truth today will be obsolete soon. Fortunately for humanity and for cancer research, these three attributes, controversial at times, revolutionized cancer treatment and saved the lives of millions of patients over the 65 years of Freireich’s medical prominence.

Born to Hungarian immigrants in 1927, Freireich lost his father at the age of 2 and survived in hopeless surroundings. While he experienced desperation firsthand, he was an eternal optimist. In his 1997 oral history (preserved at the NCI), he recounted, “People born in that era.... lived through one of the greatest economic dislocations in the history of our species—the Great Depression of 1929.... There was no work, no jobs, no money, and no food... we all grew up believing that the whole world was this jungle...worried about food, shelter, safety. We used to get beat up [and] robbed, we used to steal, we were hungry.” But Freireich survived and became one of the greatest giants in cancer research.

Where others saw insurmountable difficulties, he saw opportunity. “Humans cannot live without hope. Hopelessness is the greatest trauma a person has to suffer,” he said. When others, seeing a terminal leukemia patient, urged Freireich to quit and let the patient die in peace and with dignity, he offered hope and often delivered on his promise. To the mantra of “letting patients die with dignity,” he responded, “There is even greater dignity in fighting for one’s life.” Through innovative care, he miraculously cured hundreds of patients whom others deemed terminal. Should he then not, according to the church’s edicts, be canonized? And Freireich had infinite kindness. When he heard that one of the MD Anderson faculty, John Benvenuto, was dying from terminal pancreatic cancer in Tampa, FL, Freireich traveled to see him, paid on his credit card $5,000 (in 1986) for his air ambulance flight travel back to MD Anderson, and directed his care. Benvenuto lived another 10 years.

Freireich’s audacity led him to defy traditions and conventions, and this caused him a lot of trouble. He said he was almost fired three times during his NCI tenure (1955–1965) because of the controversies surrounding his “radical” work. Perhaps this was accentuated by his imposing personality.
and, at times, unfiltered, confrontational approach. Vincent DeVita, who joined the NCI in 1963, recalled that many of the clinical associates “had been warned by their professors not to get too close to Freireich. [The NCI, they said] was a good place to stay out of Vietnam but stay away from Freireich.”

At the dawn of medical cancer research, there were no guiding rules, and the established traditionalists borrowed from other disciplines and threw the “dogmas” at Freireich when criticizing his work. So Freireich created his own principles, what he called “Freireich’s Laws.” Observing the inevitable deaths of children with leukemia, he treated them with two-, then three-, and then four-drug chemotherapy combinations. The medicine eminences criticized his work as immoral and reminded him of the medical axiom, “Primum non nocere” (first, do no harm). Freireich retorted (Law No. 5; the Physician’s Creed): “Primum non nocere fails to do the possible and the necessary. The physician’s admonition must clearly be: Do what can possibly be done and, perhaps more important, do that which is necessary.” “First do no net harm,” Daniel Sokol clarified in a 2013 British Medical Journal article (1).

Freireich and his colleagues conducted the first randomized trials in leukemia. In those early days, the control arm delivered the expected terrible results. Freireich became deeply concerned about the “experimentation” aspect, that patients in the control arm were not receiving what might often be a better treatment—thus no “equipoise” in the two treatments offered. He collaborated with Edmund Gehan, Peter Thall, and Elihu Estey to develop statistical methodologies that evaluate treatment benefit without the need for randomization: rigorously matched historical controls, multivariate analyses, Bayesian statistics, and others. He also rejected “experimental therapy” (benefit only to the experimenter) in favor of “investigational therapy” (mutual benefit to the patient and the investigator), leading to Freireich’s Law No. 1 (Clinical Investigator’s Creed), “The primary beneficiary of clinical research is the patient participating in that research;” and Freireich’s Law No. 6, “The best patient care is clinical research.” A corollary to this was his questioning the convention that a phase I evaluation aims only to define toxicity, emphasizing that it must evaluate efficacy as well. Today, several cancer drugs have been approved on the basis of efficacy in phase I trials.

Freireich’s avant-garde research paved the way to the cure of many cancers. In recognizing his work, people often highlight the two original discoveries at the NCI. The first was his discovery of the association between low platelet counts and bleeding in children with leukemia, and that the bleeding could be stopped with fresh blood transfusions. This led to the invention, in collaboration with IBM engineer George Judson, of the first continuous-flow cell separator, through which fresh platelets could be collected (2). Still, patients were dying because the leukemia was not eradicated. This led to his second discovery of the role of multiagent chemotherapy to cure childhood acute lymphoblastic leukemia.

But his contributions were as significant, if not more so, after he moved to MD Anderson in 1965. Freireich and Emil Frei III were recruited to this little known “Research and Tumor Institute” focused on cancer surgery and radiation, and established the Department of “Developmental Therapeutics,” or DT, the first large-scale comprehensive chemotherapy program. They were the magnets that attracted like-minded researchers who were inspired by them and who believed that cancer is curable. Basic science and clinical research fused to form the first clinical-translational research department in the world. Freireich was the first clinical-translational researcher, even before the discipline had a name.

At its peak, DT was a constellation of the most diverse group of cancer researchers, who developed much of the early research in cancer. Many of the early chemotherapy drugs such as cytarabine, Adriamycin (doxorubicin), and cisplatin were developed during this period. These became components of many curative regimens in cancer: cytarabine-anthracyclines in leukemia, CHOP (cyclophosphamide-Adriamycin-vincristine-prednisone) in lymphoma, FAC (5-fluorouracil-Adriamycin-cyclophosphamide) in breast cancer, and many others.

After Gerald Bodey described the association between neutropenia and infections, he and Freireich conceived the idea of using empiric antibiotics for fever and neutropenia (without waiting for positive cultures). This, and platelet transfusions, drastically reduced the two most common causes of death during cancer therapy, infections and bleeding, and allowed the safer use of intensive chemotherapy in hematologic and solid tumors as well as the implementation of stem cell transplantation.

One of Freireich’s priorities since the early years at MD Anderson was to train physician–scientists. In 1966, he created a fellowship program in medical oncology (before it was a recognized board-certification specialty). He believed that clinician–scientists would not only work in a laboratory but also deliver direct patient care. This was a monumental legacy as he educated and trained several generations of oncologists, many of whom took the experiences to near and far places, built new cancer programs, and helped hundreds of thousands of patients with cancer.

Freireich was the epitome of “I am MD Anderson.” His death leaves us and the world of cancer care and research much diminished. Michael Keating said, “We were lucky to be observers and participants in his life—a life wonderfully led.” Perhaps not that of a saint but of a great man nonetheless.

REFERENCES
Honoring Emil J. Freireich: A Visionary Medical Cancer Researcher—March 21, 1927–February 1, 2021

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