Emil J. Freireich 1927–2021

Emil J. Freireich, MD, died on 1 February 2021, at the age of 93, in Houston, Texas, his home since 1965. The child of Hungarian immigrants, he was born on 16 March 1927 in Chicago. His father died during the Great Depression, leaving the family poverty-stricken. Raised in very difficult conditions, Dr. Freireich emerged from destitution to become a Promethean pioneer in cancer research.

Two characteristics defined him throughout his life: eternal optimism, and defiance of established norms. Believing that hopelessness is the greatest trauma a person has to suffer, through his seminal contributions to oncology he gave hope in abundance to thousands of patients over the course of his career.

First encouraged to pursue a college education by his high-school physics teacher, he set himself the goal of one day becoming a doctor. He earned his bachelor's degree from the University of Illinois-Champaign in 15 months, waiting tables and working a variety of odd jobs to pay his tuition. After earning his medical degree from the University of Illinois College of Medicine at Chicago in 1949, he completed his training in internal medicine at Cook County Hospital and Presbyterian Hospital, before accepting a hematology fellowship at the Massachusetts Memorial Hospital in Boston, where he studied anemia. There he not only discovered his true passion for studying blood disorders, but also found the love of his life: Haroldine Lee Cunningham, a nurse, whom he married in 1953.

His career in cancer research began two years later when the National Cancer Institute (NCI) hired him as a senior investigator and director of its leukemia program. His first ground-breaking observation was that patients with leukemia were dying from excessive bleeding caused by insufficient platelets and required transfusion of fresh whole blood to survive. In collaboration with IBM, he then developed the first-ever continuous-flow blood-cell separator, which extracted platelets and white blood cells from whole blood. The platelets, transfused into patients with leukemia, stopped their fatal bleeding.

In 1955, the established dogma was that unlike 'allogeneic' cancers such as choriocarcinoma that arise from the 'foreign' fetus and are curable with methotrexate, 'syngeneic' tumors were curable only with surgical removal or irradiation.

Emil J. Freireich, MD. Credit: Photo by Wyatt McSpadden.

When Dr. Freireich started investigating methotrexate–prednisone as a couplet regimen for childhood acute lymphocytic leukemia and subsequently added a third and fourth drug, the medical establishment reacted with horror, questioning the veracity and ethics of his work. Dr. Freireich, however, was undeterred. He was famous among his contemporaries for proposing numerous aphorisms known as 'Freireich's laws', which he formalized in a lecture at the 1976 annual meeting of the American Society for Clinical Oncology following his receipt of the David A. Karnofsky Memorial Award. The fifth of these challenged the fundamental principle in medicine attributed to Hippocrates, '*primum non nocere*' (first do no harm). Dr. Freireich's view, which he adopted as his own 'Physician's Creed', was that doctors have an obligation to treat where possible: *primum non nocere* fails to do the possible and the necessary. Despite enormous skepticism from the then-prevailing experts, he forged ahead with his research and designed the concept of the multidrug regimen that paved the way to the cure of most children with acute lymphocytic leukemia, the first ever of many cancers now curable with medical therapies.

In descriptions of Dr. Freireich's phenomenal accomplishments, emphasis is commonly placed on his early successes at the NCI. But these were only the first chapter of a long career of contributions, which took off when he arrived, together with Emil 'Tom' Frei III, MD, at MD Anderson, then a little-known research institute, in 1965. Over the next 15 years, they built the single largest entity devoted to cancer research and therapy: the Department of Developmental Therapeutics. Attracted by his larger-than-life personality, infectious enthusiasm, charisma, tremendous research vision, defiance of norms, and great (and at times outrageous) sense of humor, dozens of physicians who would themselves become luminaries in cancer research were enticed to join the department. At its peak in 1975–1979, the department included the largest and most eclectic group of cancer researchers who shared some of his great qualities and were determined to cure cancer.

Dr. Freireich and his faculty developed many of the early curative chemotherapy regimens, including CHOP, FAC for breast cancer, CYVADIC for melanoma and sarcoma, and others. Later, Dr. Freireich partnered with Gerald Bodey, who identified the association between low neutrophil counts and infections, to create the concept of early empiric antibiotic therapy, without the delay of waiting for positive blood cultures, for fever and neutropenia in cancer. This revolutionary step massively reduced mortality from infections in neutropenic patients and, together with platelet transfusions, allowed the expansion of intensive chemotherapy not only in leukemia but across all cancers and in stem-cell transplantation.

When Dr. Freireich and the NCI group conducted the first randomized trials in cancer, he soon realized that patients receiving placebo or conventional care in the control arm might not be benefiting as much from the trial. Dr. Freireich believed that the primary beneficiary of clinical research is the patient participating in that research, making this the first of his laws, which he dubbed the 'clinical investigator's creed'. With this in mind, he collaborated with Edmund Gehan, who created the first survival curves in cancer, and later with Peter Thall and Elihu Estey, to develop methodologies that allowed the recognition of a treatment benefit without the need to resort to randomized trials, such as

rigorously matched historical controls, multivariate analysis and Bayesian designs.

Many of Dr. Freireich's students and mentees spread all over the world, creating new dedicated cancer-research centers. But others, including myself, decided to remain at MD Anderson, to continue leukemia research and care with Dr. Freireich, at the renowned cancer center he helped create. When his Department of Developmental Therapeutics evolved naturally into several multidisciplinary tumor-specific departments in 1979–1980, Dr. Freireich continued to lead the leukemia-research program and to inspire cancer experts across the institution. He served on the MD Anderson faculty full-time for 50 years from 1965 to 2015, and later part-time, but still came to work daily, until March 2020, when the COVID-19 pandemic hit. After a 55-year career filled with achievements, happiness and fulfilment, he died in February 2021 among his leukemia-research family at MD Anderson, cared for by his colleagues. Dr. Freireich leaves behind a legacy of groundbreaking science and an indelible mark on all those who had the fortune and privilege of knowing him, training under him and thriving because of him. Although we mourn his death, we also celebrate the trailblazing scientist whose revolutionary work paved the way for modern cancer care and research. ❐

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