

This Week's Citation Classic

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Hersh E M, Bodey G P, Nies B A & Freireich E J. Causes of death in acute leukemia: a ten-year study of 414 patients from 1954-1963. *J. Amer. Med. Ass.* **193**:105-9, 1965. [National Cancer Institute. Acute Leukemia Service. Medicine Branch, Bethesda, MD]

Major causes of death in acute leukemia were infection in 70% of patients and hemorrhage in 52%. In 38% of the patients there was more than one cause of death. Striking changes took place during the ten-year study period. Fatal hemorrhage declined to nearly half the early rate, and fatal staphylococcal infection from 23.5% to 3.1%. At the same time, fatal infections due to fungi increased from 8.2% to 23.2%. [The SC® indicates that this paper has been cited over 235 times since 1965.]

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"When we joined the leukemia program at the NCI as clinical associates in 1962, we became aware of the grim prognosis of acute leukemia patients. At that time the remission rate for adults was 10%, and their survival was one year. For children the remission rate was barely 50%, and their survival was less than one year.

"Rather than being discouraged, Emil J. Freireich, chief of the leukemia program, pointed out that this situation was a challenge for clinical research. Data gathering, data analysis, and the use of conclusions from analyzed data to formulate testable hypotheses could result in improved therapy for this disease.

"In 1963, after completing a difficult year caring for patients receiving experimental therapy for acute leukemia (we lost 70 children that year), Gerald P. Bodey, Boyd A. Nies, and I began to review the 414 patients seen at the NCI over the preceding ten years. The data were tabulated and analyzed completely by hand, this preceding the era when biostatistical and computer support were readily available to the clinical investigator.

"The important conclusions of the study were as follows: The most common cause of death was host defense failure and the resultant infection, hemorrhage as a cause of death had declined drastically concurrent with the development of platelet transfusion therapy; few patients died of leukemia (i.e., infiltration of vital organs with malignant cells) but rather from the complications of the disease and/or its treatment.

"This was one of the first clinical studies specifically to evaluate the causes of death in malignant disease and served as a prototype for subsequent similar studies. It proved that supportive care can have a major effect on the course of malignant disease. Most important was the observation that leukemia patients often do not die of the direct effects of the disease. These implications have influenced developments in supportive care, antibiotic therapy, chemotherapy, and immunotherapy. Today the majority of patients with leukemia enter complete remission and 50% of children and 20% of adults are apparently cured.

"Publication of the paper was not easy. It was submitted to and rejected by the *Journal of Clinical Investigation* and the *Annals of Internal Medicine* before its acceptance by the *Journal of the American Medical Association*.

"The study also had a profound effect on my own career. It prompted an interest in host defense mechanisms in cancer, clinical cancer immunology, and immunotherapy which remain my main research interests and have become major components of cancer research.

"Finally, the professional relationships which resulted in this paper have remained remarkably intact during the last 17 years. Freireich, Bodey, and I still work together at the University of Texas M.D. Anderson Hospital. Freireich as chairman of the department of developmental therapeutics, Bodey as chief of chemotherapy and the Clinical Research Center, and myself as deputy department chairman and chief of immunology Nies is in the private practice of oncology in California. For all of us it continues to be an exciting journey."