

This Week's Citation Classic®

Aur R J A, Simone J, Hustu H O, Walters T, Borella L, Pratt C & Pinkel D.
Central nervous system therapy and combination chemotherapy of childhood lymphocytic leukemia. *Blood* 37:272-81, 1971.
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Treatment combining multiple antileukemic agents, cranial irradiation, and simultaneous intrathecal methotrexate for childhood acute lymphocytic leukemia produced a 50-percent 17-year leukemia-free survival. It established definitely the curability of this disease. This study was duplicated many times over, has resisted challenges, and has also served as a model for more recent improvements. [The SCJ® indicates that this paper has been cited in over 230 publications.]

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Acute lymphocytic leukemia (ALL) is the most common malignancy affecting children. As a drug-responsive neoplasm, ALL has been a testing ground for the development of concepts in cancer therapy that have broad potential application.¹ In 1962 an all-out combat against ALL was initiated, utilizing the concept of "total therapy"—the combination of all known effective agents given for induction, intensification, and maintenance of remission. Combination chemotherapy to overcome initial resistance and to inhibit emergence of acquired resistance was the cornerstone.² Specific treatment of clinically inapparent meningeal leukemia was administered early in remission to overcome the problem of inadequate diffusion of methotrexate and mercaptopurine into cerebrospinal fluid. Treatment was stopped after two to three years of continuous complete remission to avoid excessive toxicity and to test whether the leukemia was suppressed or cured. Most important, a radical intention was adopted—cure instead of palliation.

In early exploratory studies (1962-1965), several ideas emerged. First, this type of therapy, although toxic, was feasible. Next, a 90 percent remission could be attained, and median hematological remission extended to two years. Most meaningful, a

significant proportion of children could remain free of leukemia without apparent risk of relapse after cessation of therapy. ALL was probably curable.^{3,4} In a 1965-1967 comparative study, in which no preventive CNS therapy was given, low-dosage continuation chemotherapy resulted in more frequent and earlier meningeal relapse than high-dosage continuation chemotherapy. This suggested that the level of systemic therapy has a significant influence on meningeal leukemia.⁵

A 1967-1968 pilot study ("total therapy" study V), incorporating more intensive chemotherapy and a higher dose of cranial irradiation, resulted in a 50 percent cure rate. Of 31 children who achieved complete remission, 19 survive free of leukemia 17 years later and none has experienced relapse in the past 13 years. The results of this study have been confirmed by countless other pediatric cancer centers and cooperative groups, including the Childhood Cancer Centre at the King Faisal Specialist Hospital & Research Centre.^{1,6}

Joseph Simone, an active coworker in the "total therapy" program, defined nicely the role of the individuals involved with the "total therapy" studies.⁷ He said, "Our visionary was Donald Pinkel, without whom our leukemia studies would not exist.... [If] Aur is the heart of our group, then my role has been to provide pedestrian support and locomotion."

There are two closing notes that I believe have important implications. First, "total therapy" study V came to me because the other members of the St. Jude staff, junior and senior, did not want it. The ongoing "total therapy" study IV⁵ had discouraged everyone because of its gloomy progress. Second, our manuscript was submitted to the *New England Journal of Medicine* and was rejected because it described a new and experimental approach that might endanger the patients if the physicians were neither familiar nor skillful with the therapy. The manuscript was hurriedly adapted to the specifications of *Blood*, submitted on September 10, 1970, and was published in March 1971 with minimal revisions. The receptivity and prompt action by the editorial board of *Blood* brought us a great feeling of fulfillment and, for children and adults with ALL, created a real opportunity for cure.

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6. Aur R J A. Childhood cancer center at the King Faisal Specialist Hospital and Research Center in Saudi Arabia. *Amer. J. Pediat. Hematol. Oncol.* 7:396-8, 1985.
7. Simone J V. Childhood leukemia as a model for cancer research. *Cancer Res.* 39:4301-7, 1979.

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