In discussing the clinical management of leukemia, it would appear desirable to review briefly the pathology and the signs and symptoms of the disease. Leukemia is primarily a disease of the blood and blood-forming organs. The normal marrow is made up of three separate components: the myeloid elements which produce the polymorphonuclear leukocytes of the peripheral blood; the erythroid elements which produce the red cells and hemoglobin; and the megakaryocytes which produce platelets. In leukemia, the marrow is invaded by abnormal neoplastic cells, which may arise from any cell type, with replacement of the normal elements. This results in a lack of the three normal types of cells in the blood which in turn can produce various symptoms of the disease. The lack of polymorphonuclear leukocytes, which are the main line of defense against infection, leads to increased susceptibility particularly to the pyogenic organisms with pyogenicomia, infection of small skin scratches and cuts, and bacteremia. The lack of adequate levels of red cells and hemoglobin diminishes oxygen transport to the tissues and engenders symptoms of anemia such as lassitude, easy fatiguability, and dyspnea on exertion. The deficiency of platelets causes a hemorrhagic diathesis with petechiae, ecchymoses, epistaxes, and the various symptoms of gastrointestinal, urinary, and cerebral bleeding. The ability of these neoplastic cells which have replaced the normal elements both in the marrow and in the blood to invade tissue leads to other signs and symptoms of the disease such as splenomegaly, hepatomegaly, lymphadenopathy, and subperiosteal and other osseous involvement with consequent pain in bones and joints. Localized tumor masses and skin infiltration may occur, and in certain types of leukemias, particularly the acute monocytic variety, infiltration of the gums is common.

The predominant signs and symptoms in a given case depend a great deal on the type of leukemia. In the chronic myelocytic form, for example, where the peripheral blood usually has a high percentage of myelocytes and mature polymorphonuclear leukocytes, the symptoms of infection are uncommon. Often the platelet count may be elevated, and bleeding is less of a problem. In the early stage before treatment or in the terminal stages, the replacement of the erythroid elements of the marrow lead to anemia. Infiltration of myelocytes and other young forms of the white cell series into the spleen causes enlargement of that organ and the liver, but enlargement of lymph nodes is relatively rare until late in the disease.

In chronic lymphocytic leukemia, by contrast, the predominant signs are usually infiltration and enlargement of lymph nodes and often splenomegaly. Skin infiltrations are more common. Anemia in the early stages is not too frequent a finding, but a lowered resistance to infection and an increased tendency to petechiae and ecchymoses frequently occur.

It is in acute leukemia, however, that the manifestations of a deficiency of all normal formed
elements are most apparent. Thus, in this form of the disease, lack of resistance to infection, severe anemia, severe hemorrhagic diathesis, ulcerations of mucosa and gums, and infiltrations of nodes, spleen, and other tissues are common. Since leukemia is by very definition a widespread systemic disease at the time the diagnosis is made, the forms of treatment that may be curative for localized cancers such as surgery and obliterative radiation are not effective. The physician is then forced to rely on the techniques of chemotherapy and palliative radiation.

We are living now in an age of chemotherapy, and if more time is spent in this review on chemotherapeutic agents than on radiation, it will be because the author feels that the discipline of chemotherapy holds more promise for the future control of leukemia than does treatment with ionizing radiation.

In the past 20 years most of the infectious diseases of protozoal, bacterial, and rickettsial etiologies have surrendered to chemotherapy. Considerable progress in the treatment of leukemia has also been made in the past decade. The difficulties of the chemotherapy of leukemia as contrasted to infectious disease, however, are quite obvious. For instance, sulfanilamide is an antimetabolite of p-aminobenzoic acid (PABA). The chemical similarity is so close that the antimetabolite is able to enter the same enzyme systems as the normal metabolite, but once there the chemical difference is just sufficient so that the reaction can go no further and the whole enzyme system is blocked. In the use of the sulfonamides in the treatment of infections caused by hemolytic streptococci, for example, the chemotherapist is dealing with a particularly advantageous situation. The streptococcus requires PABA for its nutrition and therefore is inhibited by its antimetabolite, sulfanilamide. The patient, on the other hand, has no requirement for PABA and therefore is not harmed by its antimetabolite. In addition to this qualitative difference in requirements, there is also the factor of the patient's resistance to the infection which will serve to eliminate the occasional organisms which are refractory to the antimetabolite. Unfortunately, in leukemia at the present time we know of no qualitative difference between normal and neoplastic cells to exploit, nor can we rely on the factor of host resistance to destroy the few leukemic cells which even in the most favorable cases may withstand the antimetabolite. There are, however, certain quantitative differences in the nutritional requirements of normal and leukemic cells, particularly in the acute leukemias, which may be used to the advantage of the patient. In addition, there are certain compounds with so-called radiomimetic effect, and others which, for lack of more precise knowledge as to mode of action, we term general cell poisons. These agents are of value mainly in the chronic leukemias.

With all the agents used in the treatment of leukemia, the margin between therapeutic dose and toxicity is small, and careful clinical management is essential.

In chronic myelocytic leukemia there are many types of treatment that yield excellent results in the early stages, causing fall in total leukocyte count, decrease in the immature forms, rise in hemoglobin, decrease in size of liver and spleen, and general subjective improvement. No matter how satisfactory the response in the early stages to any of these agents, however, eventually the patient's disease becomes resistant to the specific therapy employed, and at that time it is usually resistant also to most other forms of therapy. The average survival time of patients with chronic myelocytic leukemia is between 3 and 3½ years (27, 36, 41), and up to the present time the statistics have not shown a marked increase in survival time by any of the forms of therapy. Although in most of these series there is no actual prolongation of time of survival, there is a marked increase in the useful and comfortable life span of the patient, and with the appropriate form of therapy the patient can usually be kept in good condition throughout the course of his disease until a few weeks before death.

Ionizing radiation either by the use of localized x-ray to the spleen, total body spray, or by the oral or intravenous administration of radioactive phosphorus remains the most widely employed and thoroughly studied form of treatment, but it obviously can only be employed in cooperation with qualified radiologists. Radiation therapy is usually given over the spleen at doses of 50 r to 100 r daily, alternating anterior and posterior ports, until a total of between 300 and 600 r has been given (9). This amount is usually sufficient to achieve a remission characterized by a fall of the total leukocyte count to near normal levels, decrease in the percentage of immature forms in the peripheral blood, rise in hemoglobin, decrease in size of the spleen, and increase in general wellbeing. In some cases, however, it may be necessary to give higher total dosage. Osgood (40), using titrated regularly spaced total-body irradiation, has reported very satisfactory results in the therapy of leukemia and feels that most of the beneficial effects of such therapy are related to the fact that
the leukemic process is kept under continuous control by these repeated small doses of radiation. Preliminary reports from this series seem to show a definite increase in the mean survival time.

Radioactive phosphorus was first used in the treatment of chronic myelocytic leukemia by Lawrence et al. (33). It was originally thought that, since there was greater pick-up of phosphorus by the more rapidly growing cells of leukemia, P³² would give specific irradiation to these cells. This specificity, however, is not of a high enough order to make P³² much more satisfactory than total-body irradiation. It is usually given either orally or intravenously in a dose of 1/10 mc/kg of body weight (11). Excellent remissions may be produced with this technic with little or no radiation sickness, but its use is limited to institutions having the necessary facilities for handling radioactive isotopes.

The first chemotherapeutic agent to be used in the treatment of chronic myelocytic leukemia was arsenic, as employed by Lissauer in 1865 (35). When given orally in the form of Fowler’s solution, 5 drops 8 times daily, increasing 1 drop per day until a top dose of 20 drops 3 times daily has been reached or toxic symptoms have intervened, this agent will cause good remissions in chronic myelocytic leukemia (32). Unfortunately, the toxic symptoms of nausea and vomiting in some patients are so pronounced that they cannot tolerate enough of this drug to develop remissions of their disease.

Another agent which has been reported to be beneficial in this form of the disease is benzol, which is administered in doses of 4 cc. daily by mouth in olive oil. This drug has been studied mostly by the Hungarian school of Koranyi (32) and Kalapos (29) and is rarely used in this country.

Urethan was discovered in 1946 by Paterson et al. (43) to produce quite satisfactory remissions in patients with chronic myelocytic leukemia. The usual dose of 3 gm. daily by mouth will, in a period of approximately 30 days, produce a fall in white count, a rise in hemoglobin, and a general improvement in the patient’s condition. Again, as with arsenic, this drug causes a certain amount of nausea and vomiting and also drowsiness which may limit the patient’s ability to tolerate adequate amounts of the drug.

A third group of chemotherapeutic agents which are very useful in this form of the disease stems from the work done during World War II on vesicant war gases. Nitrogen mustard, methylbis(β-chloroethyl)amine (HN²), when given in a total dose of 0.4 mg/kg of body weight intravenously, will also cause remissions, often lasting as long as 6 months (24, 28, 31). The nausea and vomiting accompanying the injection of nitrogen mustard rarely last over 24 hours, so that the patients can almost always tolerate this form of therapy. The fact that the drug is generally given in isolated courses, however, does not tend to allow smooth control of this disease. For this reason, orally administered agents such as triethylenemelamine (TEM) (4, 30, 34) or 1,4-dimethylsulfonyloxybutane (Myleran) (23, 25, 26) tend to give better control of the disease. TEM is usually given in doses of 2.5–5 mg. daily for 2 consecutive days each week until the white count reaches normal levels, and then maintenance therapy is carried on according to the patient’s need. Myleran is generally given in doses of 4–6 mg. daily until such time as the white count reaches normal levels, and then the drug is continued at this dose or at slightly lower levels indefinitely to keep the patient in remission. Because of the variations in the gastrointestinal absorption of TEM and the occasional nausea and vomiting which follow its use, Myleran is now preferred by some hematologists.

The folic acid antagonists which have such a remarkable effect against acute leukemia in children are without practical value in the treatment of chronic myelocytic leukemias, but the purine antagonist, 6-mercaptopurine (6-MP) (6), will cause good remissions in a very high percentage of patients with this disease. This drug is generally given orally at 2.5 mg/kg of body weight and must be continued at this dose, or slightly lower levels, even after the white count reaches normal levels. If therapy is stopped, in most cases the white count will rise precipitously within 4 weeks. This drug, also, in contrast to the previously mentioned agents, has occasionally shown effect in causing temporary remissions even in the acute terminal stage of this disease, but in contrast to the early stage, the remissions are very short-lived, lasting from 1–3 months, despite continuous therapy with mercaptopurine.

Chronic lymphocytic leukemia may occasionally be an exceedingly benign disease, particularly in the elderly patient. In such cases, no therapy may be indicated for considerable periods of time. In the average patient, however, the treatment of choice is local x-ray therapy to the involved nodes (10), although Osgood (40) has reported good results by titrated regularly spaced total body irradiation or P³².

It may be of considerable biochemical interest that many of the chemotherapeutic agents that are so useful for the treatment of chronic myelo-
cytic leukemia, such as arsenic, benzene, Myleran, and mercaptopurine seem to be without beneficial effect in the chronic lymphocytic form. The nitrogen mustard type agents are useful, however, with TEM being the drug of choice, since, by the gradual use of the drug over a long period of time, the correct dosage may be achieved with less danger than with the use of HN\textsuperscript{2} in short courses. The dosage of TEM used in this form of the disease is approximately half of that used in the chronic myelocytic form. Urethan may also be of some value.

ACTH and cortisone have been shown by Pearson et al. (44) to be useful in the treatment of chronic lymphocytic leukemia, particularly in those cases in which there is an associated thrombocytopenia or hemolytic anemia. These investigators feel that in chronic lymphocytic leukemia, in contrast to acute leukemias, resistance to the hormones develops slowly, and the patient may be maintained for long periods of time on hormone therapy alone.\footnote{O. H. Pearson, personal communication.} In this form of the disease, as with the chronic myelocytic variety, although considerable palliative effects may be achieved, it is difficult to state that any real increase in survival time follows the use of the various therapeutic agents (12, 37), although again Osgood's group feels that some increase in survival time may be achieved with P\textsuperscript{32} and total body spray x-ray (40).

In the acute leukemias, in contrast to the chronic leukemias, we have agents which can cause a definite prolongation of survival time. Here radiation is of no value except occasionally in the treatment of certain localized manifestations of the disease, and the clinician must rely on chemotherapeutic agents alone. The first practical use of antimetabolites in the treatment of leukemia was the demonstration by Farber et al. (20) that 4-aminopteroylglutamic acid (Aminopterin) was effective in producing remissions in children with acute leukemia. These classic studies have since been corroborated by many investigators (47). The most commonly utilized drugs are Aminopterin (49), at a dose of 0.25–0.5 mg. daily by mouth, and A-methopterin (48), at a dose of 2.5–5 mg. daily by mouth. The first signs of toxicity of the folic acid antagonists usually appear as ulcerations of the buccal mucosa. These are covered with a yellowish exudate and surrounded by a reddish areola and are frequently painful. They in themselves are not dangerous, but they may be precursors of ulcerations farther down the gastrointestinal tract. The latter may be dangerous in a patient who already has a bleeding diathesis. The usual plan of therapy in children with acute leukemia is to administer the drug orally daily until such time as a remission occurs, as evidenced by return of the marrow to normal function, or until definite signs of toxicity appear (Chart 1). If toxicity occurs, therapy is discontinued temporarily for a period of 7–10 days, until the signs subside, and then started again at a somewhat lower dosage and continued until a remission is achieved. In the absence of a remission, if the patient is in reasonably good condition, therapy is usually continued for at least 2 months and occasionally longer at increased dosage even to the point of mild toxicity, in the hope of obtaining a remission. Once a remission has been achieved, the patient may be continued on maintenance dosage of the drug or treatment may be discontinued entirely. If an intermittent schedule is used, however, sternal marrow aspirations should be done every 2 weeks during the period of remission, as it is only by this technic that the first signs of a relapse may be detected. In this way, therapy can be reinstated and the marrow returned to normal before any deterioration in the patient's clinical condition is seen (5).

Compilation by Farber (18) of the results reported at the Second Conference on the Folic Acid Antagonists in 1951 (47) showed that 68 per cent of 425 children with acute leukemia treated with the antifolies were considered as having been improved by therapy. In our own experience (2), 30–50 per cent of children will have good clinical and hematological remissions from these drugs, and others will have some degree of clinical improvement. Children whose disease has become resistant to cortisone or 6-MP may still be expected to respond to the antifolies. There are many other folic acid antagonists, but none seem to have any particular advantage over Aminopterin and A-methopterin.

Another type of antimetabolite, the purine antagonist, 6-mercaptopurine, will bring about remissions in a high percentage of children with acute leukemia and also occasionally in adults with this disease. The synthesis of mercaptopurine by Elion, Hitchings \textit{et al.} (14) was the result of a long-term program of study of possible antagonists of precursors of nucleic acid. This compound has been shown to be a purine antagonist in \textit{L. casei} (15), but studies in animals have shown that neither the toxic manifestations nor the antileukemic effects can be reversed by simple purines\footnote{J. H. Burchenal, unpublished observations.} (7). Its tumor-inhibiting action in mice was first demonstrated by Clarke \textit{et al.} in Sarcoma 180 (7). In patients, mercaptopurine is generally given at a dosage of 2.5 mg/kg of body
weight in a single dose daily by mouth. In our experience, there is little or no toxicity in children at this dosage level. Prolonged treatment in adults or at higher doses in children may produce evidence of bone marrow depression and oral and gastrointestinal toxicity. At least 3 weeks of therapy and often up to 6 or 8 weeks are needed before remissions are achieved. Maintenance therapy at the same dose is usually employed, and remissions usually last from 2 to 10 months. In platelets to normal levels, and return to normal percentage of polymorphonuclear leukocytes in the peripheral blood after 4 weeks of continuous therapy. 6-Mercaptopurine will produce remissions in patients who were either initially resistant to A-methopterin or cortisone; and similarly in patients responding at first to mercaptopurine and then developing resistance, A-methopterin or cortisone will frequently produce remissions. In contrast to the folic acid antagonists, 6-mercaptopurine appears to have a beneficial effect on monocytic leukemia and to work almost equally well on leukemias with high or low total leukocyte counts. It also has considerable value in adults with this disease.

The hormones, ACTH, cortisone, and hydrocortisone, are also of value in the management of acute leukemia (21, 44). Cortisone can be given either orally or intramuscularly, with the usual dose in a child being 100–200 mg. daily and in adults 100–400 mg. daily, given in divided doses every 6 hours. ACTH can be given as Acthar gel intramuscularly or in aqueous solution by con-

![Chart 1. The course of leukemia in a 2½-year-old child treated with aminopterin and A-methopterin](image-url)
constant intravenous drip. By the latter technic 25 mg/day is usually sufficient for children and 50 mg. for adults. If Acthar gel is given, the dose should be somewhat higher. Undesirable side effects of the administration of these hormones are sodium retention and consequent water retention, and edema, hypertension, Cushing's facies, hypokalemia, increase in susceptibility to infection, and occasional psychic changes. These compounds have an advantage over the antimetabolites in that they act much more rapidly, but the disadvantage is that the remissions are usually of considerably shorter duration. They will produce remissions in 50–70 per cent of children with acute leukemia and in a smaller percentage of young adults (46), and are frequently active in patients whose disease has previously developed resistance to mercaptopurine or A-methopterin. If the patient is over the age of 30, it is rare, however, to have really good remissions with the use of these agents.

The folic acid antagonists, the purine antagonists, and the hormones are all usually employed eventually in a given patient, and it cannot be said that any one is the best agent for the treatment of acute leukemia. With these several compounds available, however, one is faced with the question of which agent to use first in a given patient. Since the hormones act more rapidly than the antimetabolites, but generally cause shorter remissions, we have evolved the following plan of therapy (3): If the patient is acutely ill and it appears unlikely that he will survive the 8 weeks necessary for either class of antimetabolites to exert their effect, he is started on cortisone by mouth or ACTH by constant intravenous drip. Once he has been brought into remission, or

![](chart.png)

**CHART 2.**—The course of acute leukemia in a 2½-year-old child treated with various chemotherapeutic agents. P-165 refers to azaserine.
resistance to the first appears, and holding the hormones, ACTH and cortisone, in reserve for exacerbations of the disease which do not appear to be controlled by the antimetabolites.

The lack of cross-resistance between the folic acid antagonists, the purine antagonists, and the steroids has been utilized in the treatment of patients, as can be seen in Table 1. The first series of figures show 218 cases taken from Tivey’s (53) article on untreated leukemias of children. The second column is from 154 patients treated with the folic acid antagonists and the steroids by the Chemotherapy Service at Memorial Center. The third group of 49 patients consists of all the children with acute leukemia whose treatment was initiated at Memorial Center between July 1, 1952, when mercaptopurine first became available for the treatment of acute leukemia in addition to the folic acid antagonists and steroids, and April 1, 1953. Although the last group of patients is admittedly small, the improvement in the percentage of 12-month survivors from 5 per cent to 29 per cent to 52 per cent demonstrates the advantage of the addition of a third type of antileukemic agent to the armamentarium of the clinician. Although it is true that many of Tivey’s earlier cases did not have the benefit of as much antibiotic and transfusion therapy as did the other two series, the fact that in his untreated series 50 per cent of the patients survived less than 3.9 months from the start of their disease, in the second series 8.9 months, and in the last series, using all three types of agents, 50 per cent had survived over 12 months after the start of their disease, would indicate that at least some progress is being made.

So much for the agents which are of proved value in the clinical management of leukemia. I would like now to mention a few other compounds which in preliminary clinical studies have shown some effect on the leukemic process; but first I would like to dilate a bit on the difficulties of the clinical investigator engaged in the evaluation of new chemotherapeutic agents.

Although there is usually good correlation between pharmacological data in dogs and man, unexpected and qualitative differences occasionally occur. For this reason, clinical studies are usually begun at a dosage level of one-tenth of that estimated from the dog data to be the maximum tolerated daily dose. If, as happened with one compound recently, the dog is much more sensitive to the toxic action of the drug than man, as much as 6 months’ time may be lost in the cautious gradual approach to the correct dosage in the patient. In addition, unrelated, intercurrent disease may also alter the patient’s response to an agent.

Once the maximum tolerated dose is determined, one must then study adequate numbers of leukemias to evaluate the drug. Two acute leukemias morphologically identical, giving similar histories and similar physical findings, may be biochemically different and react differently to a given compound. In a previously untreated child with acute leukemia, the clinical investigator usually does not feel justified in testing an unknown compound when there are already three types of known agents which stand a good chance of benefiting the patient temporarily. The patients whose disease has become resistant to all the conventional agents are frequently too ill to allow time for adequate dosage of the new compound.

In studying chronic myelocytic leukemia in the adult, the patient in the early stages, when his disease might respond to a new antileukemic agent, is usually leading too active and useful a life to be hospitalized; and in the terminal acute stage, when he can be hospitalized, he will usually not respond to any therapy.

The difficulties of clinical evaluation are increased many times when a combination of two or more agents are used, since the optimal dosage of each must be determined and the effects compared to those achieved when either drug is used alone. Thus, differences in drug tolerance, the heterogeneity of the human disease, and psychological and sociological factors combine to make the clinical evaluation of chemotherapeutic agents vastly more complex than the study of such drugs against mouse leukemia.

Among the new compounds currently being investigated clinically in various laboratories, triethylene phosphoramide (19, 52) and triethylene thiophosphoramide (50), as well as 1,3-bis ethyleneiminosulfonyl propane (42), a compound chemically related to both Myleran and TEM, have been shown to have a beneficial effect in the chronic leukemias by various investigators. A
colchicine derivative, Demecolcin, has also been reported to have antileukemic effects in patients by Moeschlin (39).

Among the antimetabolites, 2,4-diaminoo-5-(5'4'-dichlorophenyl)-6-methylpuridine (17) has at toxic doses produced occasional remissions in children with previously untreated acute leukemia. Its toxicity at therapeutic levels, however, and its lack of effect in A-methopterin-resistant disease, deprive it of practical value.

Similarly, Modest et al. (38) have studied clinically six different dihydrotiazines, but, although they possess some antileukemic activity, certain undesirable side effects prevent them from being practical agents at the present time.

Among the purine analogs, a similar lack of spread between toxic and therapeutic dosage exists with 6,6-diaminopurine. Although rare remissions in both acute leukemia and the chronic myelocytic form have been achieved, this does not appear to be a practical agent alone for the management of any type of leukemia.

6-Mercapto-2-aminopurine (thioguanine), synthesized by Elion et al. (14), and 6-chloropurine, synthesized by Bendich et al. (4), however, have both brought about remissions in chronic myelocytic leukemia at nontoxic doses. The former has not as yet had adequate clinical trial in acute leukemia, but 6-chloropurine has produced remissions in one previously untreated adult. It has been ineffective so far in children whose disease has already become resistant to mercaptopurine.

Preliminary studies have shown that O-diazacyl-L-serine (azaserine) (1, 13, 51) will occasionally produce partial temporary remissions in children with acute leukemia, but relapses occur within a month despite continued therapy at full dosage (16).

It would appear to the author that in the future the greatest hope of controlling leukemia lies in chemotherapy, but until something more than quantitative differences are discovered between normal and leukemic cells, it is doubtful whether any single agent will have sufficient specificity to control the disease. The answer to this may well be combination therapy, employing several compounds for the sequential inhibition at different levels of a single metabolic pathway essential for the leukemic cell. To date, combinations of A-methopterin and cortisone, or A-methopterin and mercaptopurine have not, however, demonstrated any marked synergistic effect in patients (3). Even mercaptopurine and azaserine, despite the striking results in animals reported by Clarke et al. (8), have shown suggestive additive effect in only a small percentage of children with acute leukemia.

More effective combinations should be sought empirically by screening technics or somewhat more rationally by studying the biochemical reactions inhibited by the folie acid antagonists and other potent antileukemic agents. By synthesizing, screening, and evaluating clinically, alone and in combination, analogs of the products of such reactions, and through the effort now being put into the study of this disease in this country and throughout the world, it should be possible in the not too far distant future to bring the efficacy of the clinical chemotherapy of leukemia to a level comparable to that obtained in the treatment of infectious disease.

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