Acute Leukemia
In Adults, 1977

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In the last decade, considerable progress has been made in the understanding, diagnosis, classification and treatment of acute leukemia. Now known to be a malignant disorder of the blood forming organs, acute leukemia is characterized by progressive accumulation of primitive blood cells that have lost the capacity for normal maturation. This accumulation impairs the production of normal blood elements by the bone marrow, resulting in anemia, neutropenia, thrombocytopenia and, if uncontrolled by treatment, death usually from infection or hemorrhage. Formerly, the diagnosis of acute leukemia in an adult was followed shortly by death. Today, modern treatment can result in complete remission of the disease in most adults, with some patients surviving for prolonged periods of time.

Incidence
The incidence of acute leukemia steadily increased in this century, until the 1960s, when a leveling off in the rising curve was noted.1 Although much of the increase can be attributed to greater access to medical and diagnostic facilities, a modest true increase probably occurred. Ninety percent of patients with acute myelogenous leukemia (AML) are adults, one-third of whom are over 60 years old. However, adults account for only 20 percent of patients with acute lymphoblastic leukemia (ALL). As in other neoplastic diseases, incidence increases with age.2

Etiology
Many tantalizing clues to the cause of acute leukemia have been uncovered and are being actively pursued. Racial
variation has been noted, for example, in Japanese, who exhibit a low incidence of leukemia. A genetic influence is illustrated by a slightly increased incidence (four- to seven-fold) in the first-degree relatives of patients. More impressive, however, is the high likelihood (10-20 percent) that a monozygotic twin of a sibling with leukemia will develop the disease.\(^3\) The second twin will have leukemia of a similar morphological type, usually lymphoblastic, occurring at a similar, typically young age. Other high-risk factors include congenital disorders associated with abnormal chromosome patterns, such as Down’s syndrome (15-fold), Fanconi’s anemia and Bloom’s syndrome. Congenital and acquired immunodeficiency diseases also predispose to leukemia, perhaps through a deficiency in immunosurveillance.\(^4\)

Radiation exposure has been incriminated as a causative agent of leukemia in studies involving radiologists, atomic blast survivors and patients treated with radiation for ankylosing spondylitis and other disorders.\(^5\) Diagnostic radiology, except when greatly excessive, and radioactive therapy for hyperthyroidism have not been shown to be leukemogenic. However, diagnostic abdominal radiology in a pregnant woman may increase the risk of leukemia in the offspring by a factor of 40 percent.\(^6\)

Benzene is the only established leukemogenic chemical, and patients recovering from benzene-induced bone marrow aplasia often develop some form of acute leukemia. In addition, a number of patients treated with melphalan for multiple myeloma have developed acute leukemia.\(^7\) Factors other than the drug may be responsible; for example, prolonged survival in a patient responding to melphalan, which may alter the natural history of myeloma, can allow a “natural” terminal leukemic transformation to become manifest. The result, however, has been a heightened awareness that chemotherapeutic agents may be leukemogenic on the basis of their proven ability to cause chromosomal damage and prolonged suppression of immune function.

\[\ldots\text{ possible virus particles have been found in blast cells of patients.}\]

Interest in viruses as a causative factor in human leukemia has been heightened by the discovery of reverse-transcriptase (an RNA-directed DNA polymerase) in the cells of patients with acute leukemia.\(^8\) This enzyme has also been associated with RNA tumor viruses in animals. Using the electron microscope, possible virus particles have been found in blast cells of patients with acute leukemia.\(^9\) Geographic or social clustering of the disease has been investigated, but without definite conclusion as to its significance. Thus, while viruses are a well-known cause of leukemia in animals, their role in human leukemogenesis remains conjectural.

Pathophysiology of Acute Leukemia

The concept of acute leukemia as a disease characterized by rapid proliferation of cells must be modified. It is now established that there are fewer leukemic blasts in the process of division than normal myeloid precursors, and that the time taken for cell division is shorter in leukemic than in normal cells.\(^10\) The primary problem appears to be an uncontrolled proliferation and continued accumulation of primitive cells that have lost

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the capacity to mature. Bone marrow of patients with acute leukemia grown in semi-solid agar demonstrates a relative lack of cells capable of maturation but, frequently, a persistence of cells with some residual proliferative capacity.11

Leukemia appears to arise by some genetic alteration or mutation in the hematopoietic stem cell, giving rise to an abnormal clone of cells that proliferate and accumulate in the bone marrow. Normal bone marrow contains 750 billion cells, 95 percent showing some degree of maturation. At the diagnosis of acute leukemia, there are 1,000 billion primitive leukemic cells, with little evidence of residual normal marrow elements. In 30 to 50 percent of patients, a chromosomal abnormality, sometimes detectable in early red cell, megakaryocyte and white cell precursors, and is associated with loss of proliferative control and inability to differentiate into normal cells. An increase in leukemic cells prevents the production of normal blood cells by the bone marrow and causes anemia, neutropenia and thrombocytopenia.

**DIAGNOSIS**

**Presenting Features**

The diagnosis of acute leukemia based on signs and symptoms alone is frequently difficult. (Table 1.) The most common presenting complaints—fa-

| TABLE 1. PRESENTING FEATURES OF ADULT ACUTE LEUKEMIA |
|-------------------------------------------------------|
| **Frequency** | **Symptoms** | **Signs** |
| Common complaints, non-specific | Fatigue, malaise, weight loss, fever | Signs of anemia, weight loss, fever |
| Less common complaints, suggestive of leukemia | Infection: refractory, recurrent | Ulcerative pharyngitis, gum hypertrophy |
| | Bleeding: skin, gums, uterus | Purpura, bruises, retinal hemorrhages |
| | Pain: splenic, sternal, periarticular | Enlarged liver and spleen, sternal tenderness, presence of lymph nodes (X-ray = wide mediastinum) |
tigue, malaise, weight loss and fever—
are non-specific and may indicate many other illnesses. Patients with acute leukemia usually look ill, but some can feel surprisingly well despite advanced disease, and a few are diagnosed following routine blood work.

Leukemia rarely is a cause of anemia, and is usually suspected only when iron, folate and vitamin B-12 deficiency states have been excluded. Persistent refractory anemia, however, is more often seen in patients with leukemia and so-called pre-leukemic states (see page 11); bone marrow aspiration is indicated.

**The most common presenting complaints—fatigue, malaise, weight loss and fever—are non-specific...**

Fever in patients with leukemia is generally not associated with clinical evidence of infection. But if infection is present, usually in the oropharynx or lung, response to therapy is less satisfactory than expected and recurrence more common. Neutropenia and impaired neutrophil function contribute to this pattern.

Bleeding manifestations are usually attributable to a low platelet count and impaired platelet function and are, therefore, difficult to distinguish from other thrombocytopenic disorders. However, petechiae, skin bruising, epistaxis, gum bleeding and menorrhagia are common and, if associated with a low platelet count or atypical cells in the peripheral blood, should suggest leukemia and the need for bone marrow aspiration. Hemarthrosis, extensive bruising and prolonged bleeding from a wound are suspicious of a coagulation disorder; this occurs only in the promyelocytic form of acute leukemia, which is characterized by disseminated intravascular coagulation with hypofibrinogenemia.13 Catastrophic cerebral hemorrage, due to leukostasis in the small cerebral blood vessels and disruption of the vessel wall, is a serious risk in patients who have platelet counts less than 25,000 and high white blood counts (greater than 100,000/cc. mm.) with a predominance of blast cells.14

Gum infiltration, manifest as purplish hypertrophic tissue, perhaps accompanied by infection and offensive breath, is uncommon, but when present may point to acute leukemia with a monocytic component, as does perirectal pathology. Skin infiltration is usually violaceous and papular, and is also more often seen in patients with monocytic leukemia.

Spread to the central nervous system, termed meningeal leukemia, is an uncommon presenting feature that usually occurs late in the disease, especially in patients with acute lymphoblastic leukemia. (See page 22). Chloromas or tumors of blast cells are also uncommon at presentation, but can occur at any site, for example, the breast or spine. Bone pain, particularly periaxicular, is also seen more frequently in patients with lymphoblastic disease. Sternal tenderness, usually exquisite and localized, is experienced by two-thirds of patients.

An enlarged liver or spleen and the presence of lymph nodes are more common in patients with ALL than AML (75 percent versus 50 percent). Lymph nodes are firm and discrete. X-ray of the chest may show mediastinal widening caused by lymph nodes or thymic enlargement.

**Laboratory Findings**

The diagnosis of acute leukemia is suggested by peripheral blood examination, especially if pancytopenia or immature cells are noted. Normocytic, normochromic anemia with a low reticulocyte count is usually present, although erythroleukemia is characterized by macrocytic cells and dysplastic nucleated red blood cells in blood films.
Leukemia developing in a patient with a history of sideroblastic anemia is associated with hypochromic, microcytic anemia. The white blood cell count can be low, normal or high; one in four patients has a white blood count greater than 50,000/cm. on presentation. Neutropenia and thrombocytopenia are usual. Severe thrombocytopenia (less than 50,000/cm.) is present in 40 per cent of patients. (Table 2.) Another characteristic feature of acute leukemia is the presence of blast cells in the peripheral blood in small or, more often, large numbers. Occasionally, a hiatus exists between the primitive and mature white cells with a deficiency in the myelocyte and metamyelocytic stages.
locyte stages, although a deficiency of all maturing granulocytic cells is more common. Leukemoid reactions usually maintain evidence of an orderly stepwise maturation in the white cell series.

Serum uric acid is elevated in half the patients with acute leukemia; an elevated serum lactic dehydrogenase, presumably due to ineffective hemopoiesis, is typical. Disturbances in serum proteins are common, but nonspecific.

Serum muramidase (lysosome) is a specialized study that may be valuable in differentiating the morphological types of leukemia. A very high level is associated with acute monocytic and myelomonocytic leukemia, normal to
high levels with myeloblastic leukemia, and normal to low levels with lymphoblastic leukemia. A fairly constant correlation between serum levels and clinical activity is found in most patients with elevated levels at diagnosis.\textsuperscript{15}

In summary, it is essential that any abnormality of blood counts should be assessed with a differential white cell count and blood film. This gives a clue to the diagnosis of many serious blood disorders or suggests the need for bone marrow examination.

**Bone Marrow Examination**

Bone marrow aspiration usually provides many hypercellular particles that, when smeared, leave hypercellular trails on the slide. Reproducible estimates of cellularity are provided by making histological sections on clotted marrow aspirate (clot-section). Occasionally, marrow aspiration does not obtain particles and a trephine needle biopsy is necessary. The major indications for this procedure include: (1) extreme hypercellularity; (2) hypoplasia in patients with smoldering leukemia; (3) a prior history of myelofibrosis in patients who develop leukemia; and (4) leukemia-induced fibrosis of the marrow de-novo.

Differential count of the nucleated cells on the bone marrow smears usually shows 60 to 90 percent blast cells, with decreases in erythroid precursors, mature white cells and megakaryocytes. The first step in classification is to separate acute lymphocytic leukemia (Fig. 1) from non-lymphocytic forms (Fig. 2), initially by standard Romanowsky or

| TABLE 2. |
| --- |
| PERIPHERAL BLOOD COUNTS ON PRESENTATION OF ACUTE LEUKEMIA |

| Test              | Range                  | Percent of Patients |
|-------------------|------------------------|---------------------|
| Hemoglobin        | <10 gm./100 ml.        | 60                  |
| White Blood Count | <5,000/cu. mm.         | 30                  |
|                   | 5,000-10,000/cu. mm.   | 15                  |
|                   | 10,000-50,000/cu. mm.  | 30                  |
|                   | >50,000/cu. mm.        | 26                  |
| Platelet Count    | <50,000                | 40                  |
|                   | <150,000               | 85                  |
| Blast Cells Present | -                     | 90                  |
Wright stains of blood and marrow smears and, if necessary, by special stains. The differentiating factors are listed in Table 3. The presence of Auer rods is virtually diagnostic of acute myeloid leukemia and a large number of heavily granulated cells, monocytoid cells, or dysplastic erythroid cells virtually excludes the diagnosis of lymphocytic disease. Coarse granules or block-positivity on PAS stainings suggest lymphoid disease; erythroblasts often show a positive PAS stain in patients with erythroleukemia. Sudan black or peroxidase-positive staining of primitive cells indicate myelogenous origin. Alphanaphthol acetate will stain cells with esterase activity, especially monocytic cells. Using a combination of standard and special stains, classification of dis-

| ALL                                      | AML                                      |
|------------------------------------------|------------------------------------------|
| • High nuclear-cytoplasmic ratio        | • More cytoplasm                         |
| • 1-2 nucleoli                          | • 2+ nucleoli                            |
| • Clumped chromatin                     | • Fine lace-like chromatin                |
| • Homogenous cell population             | • More heterogeneous cell population     |
| • Round nuclei                          | • Auer rods present (20-30%)             |
|                                          | • Granules in primitive cells            |
|                                          | • Megaloblastosis and red cell dysplasia (erythroleukemia) |
|                                          | • Folded, indented nuclei (myelomonocytic) |
| • Course granules or block-positive on PAS stains | • Positive erythroblasts (erythro-leukemia) on PAS stains |
|                                          | • Sudan black, peroxidase-positive       |
|                                          | • Esterase-positive on alpha-naphthol acetate stains (myelomonocytic forms) |
| • High leukocyte alkaline phosphatase   | • Low leukocyte alkaline phosphatase     |
ease is possible in 80 to 90 percent of patients. Cells from the remaining patients are morphologically undifferentiated and show negative special staining reactions; they are classified as acute undifferentiated leukemia. Electron-microscopy, if available, is a useful tool in differentiating AML from ALL.

Another group of patients includes those with "hairy-cell" leukemia, so named because the cells have cytoplasmic villous projections, which are visible on stained, living or electron-microscopic preparations. Such cells show

tartrate-resistant acid phosphatase activity in the cytoplasm. This diagnosis is important because patients usually follow an indolent course for long periods of time. Splenectomy often improves the peripheral blood picture, but response to those chemotherapeutic agents used in acute leukemia is disappointing.

Accurate classification of adults with acute leukemia, although desirable, is not essential. Most physicians initially use similar chemotherapeutic regimens to treat adult patients with both AML and ALL. Subsequent decisions regarding chemotherapy, however, are influenced by the morphologic diagnosis, for example, the use of L-asparaginase in patients with ALL.

**Serum muramidase (lysosome) is a specialized study that may be valuable in differentiating the morphological types of leukemia.**

**Special Studies**

*Cyto genetic analysis* of the chromosome constitution of marrow cells in acute leukemia is most useful, since 30-50 percent of patients have an abnormal chromosome pattern that disappears when the leukemic cell population is depleted and when normal cell regeneration occurs in complete remission. The chromosome abnormality will return when the disease relapses. Most reports suggest that patients with a normal chromosome pattern have a slightly higher response rate and, therefore, longer survival. Deletion of chromosomes, especially losses of D and E groups, is associated with a poor prognosis.

Additional chromosomes are usually found in patients with acute lymphoblastic leukemia, whereas in those with acute myeloblastic leukemia, deletions and additions of chromosomes or combinations of these patterns are all seen. Abnormal chromosome findings in patients with refractory anemia suggest that the patient is likely to develop acute leukemia.

If bone marrow cells are cultured in semi-solid agar, various growth patterns are evident. For example, there may be no growth at all, small or large clusters of cells or larger cell collections called colonies. A correlation has been made between good response to treatment and growth of small clusters on culture.

If bone marrow is cultured in the presence of tritiated thymidine, cells synthesizing DNA are labeled. The *labeling index* (percentage of cells labeled with radioactive thymidine) is usually lower in leukemic blasts than in normal blasts. Patients with very low labeling indices have poor response to therapy, while those with high labeling indices usually have a rapid but transient response to therapy.

**Differential Diagnosis**

Many patients will have a clinical picture similar to acute leukemia. For example, the anemic features of the disease are not distinctive; fever and malaise can be caused by a multitude of infectious diseases, and identical bleeding manifestations can be the result of any thrombocytopenic state. Persistence of these symptoms, failure of infections to respond normally to antibiotics or any clinically significant bleeding should be investigated by a complete blood exami-
nation, including blood film and differential white blood cell count.

The major clinical challenge is the differentiation of acute leukemia from infectious mononucleosis, which is also characterized by fever, pharyngitis, splenomegaly and lymphadenopathy. The distinction can usually be made on assessment of the atypical lymphocytes in the peripheral blood smear in mononucleosis, positive heterophile antibody tests and a rising titer of antibody against the Epstein-Barr virus.

Leukemoid reactions with immature cells in the peripheral blood can also be seen in disseminated carcinoma, lymphoma and other marrow infiltrative disorders. Myeloproliferative syndromes such as myelofibrosis can cause a similar blood picture, as well as marked enlargement of the spleen. Trephine biopsy with reticulin and collagen stains is often necessary to differentiate these disorders from leukemia. Other conditions to be ruled out include the megakaryoblastic anemias, aplastic anemia, systemic lupus erythematosus and hypoproliferation from any cause.

Leukemoid reactions generally show only a few blasts in the peripheral blood with more mature cells predominating. Leukocyte alkaline phosphatase activity is usually elevated in leukemoid reactions, but low or normal in acute leukemia. Bone marrow aspiration, trephine biopsy for histological section and culture for acid-fast bacilli and fungi usually provide definitive diagnostic evidence.

**Pre-Leukemia and Smoldering Leukemia**

Certain diseases, such as Down's syndrome, can be considered pre-leukemic in view of the increased risk of leukemia in these patients. Other disorders—the myeloproliferative syndromes, multiple myeloma, paroxysmal nocturnal hemoglobinuria, sideroblastic anemia and benzene-associated aplastic anemia—
al diseases that with some regularity develop into acute leukemia late in the course of the illness, can also be termed pre-leukemic. The same is true of chronic granulocytic leukemia, which is characterized by the development of terminal acute leukemia in 60 percent of patients, and of lymphoma, which can also have a late leukemic phase.

Most often, however, the term pre-leukemic is used to describe a group of patients, usually over 50 years of age, with dysplastic bone marrows and some evidence of failure to produce one of the normal blood elements. Such patients usually develop an obviously leukemic blood picture late in the course of disease. The clinical picture is very variable. The bone marrow is generally hypercellular, but may be hypocellular. An increase in blast cells, usually from five to 30 percent, or the presence of atypical monocytes in the bone marrow is often evident. Myeloid hyperplasia may be the only abnormal bone marrow feature. Splenomegaly may or may not be present. The labeling index is usually low, indicating a slowly proliferative state. In summary, the picture is that of 'non-diagnostically abnormal' bone marrow, with evidence in the peripheral blood of failure to produce normal blood elements. Many of these usually older patients will develop increasing evidence of acute leukemia if followed. Some die of bleeding or infection without further evidence of leukemia, and some die of incidental causes without further progression of disease. However, if an abnormal chromosome pattern is noted on cytogenetic analysis, the risk of developing leukemia is higher.18

In our opinion, such patients should not be treated for leukemia until evidence of progressive disease is present (for example, greater than 50 percent leukemic cells in a hypercellular bone marrow and/or a white cell count of more than 50,000/cm.) or until life-threatening infection or bleeding com-
complications demand intervention. These patients respond very poorly to conventional therapy. The chance of response is probably best when the leukemic cells are proliferating, since current chemotherapeutic agents are most effective on dividing cells. Other patients should receive only supportive care with packed red cell and platelet transfusions and antibiotic therapy as indicated.

TREATMENT

The management of the patient with acute leukemia is one of the most challenging exercises in internal medicine. Agents used in treatment have many and diverse toxicities, and complications that arise during therapy can involve any organ system. The psychological support of the patient and his family are of utmost importance. The most exciting part of this challenge, however, is that with optimal care, a number of patients can achieve remissions of several years duration, with chemotherapy discontinued after the first 18-24 months. Metticulous attention to the day-to-day management of the patient is essential, placing considerable responsibility on the staff.

Who and When to Treat

Urgent treatment is required for two groups of patients: (1) those with a high circulating blast cell count (greater than 25,000/mm.), in whom the risk of fatal intracranial hemorrhage increases with the height of the blast cell count and with time; and (2) patients with acute progranulocytic leukemia or acute myeloblastic leukemia who have evidence of a coagulation disorder.

In the former category, cell division can be promptly arrested by treatment with intravenous hydroxyurea (1 gm./m.²) or continuous intravenous infusion of cytosine arabinoside (Ara-C). If available, leukapheresis using a continuous-flow cell separator will help to quickly decrease the peripheral blood count. In the latter group of patients, the release of thromboplastic material from the primitive cells may cause intravascular coagulation and consumption of clotting factors. Characteristic features are hypofibrinogenemia and elevated fibrin split products with prolongation of prothrombin time and partial thromboplastin time. Effective chemotherapy will usually restore these parameters to normal in 10 to 14 days, although transient worsening can occur soon after initiation of treatment.

On the other hand, patients with a high leukemic infiltrate, that is hypercellular bone marrow and 60 to 90 percent primitive cells, should be treated when the diagnosis is established, but delays of a few days are probably not harmful.

... with optimal care, a number of patients can achieve remissions of several years duration ...

There is also no urgency to initiate treatment in patients with a hypocellular or normocellular bone marrow and a relatively low percentage of leukemic cells (10 to 50 percent). Observation of disease by weekly bone marrow aspirations and regular blood counts should soon determine if the leukemia is progressive, in which case treatment should be initiated, or if it is non-progressive, in which case only supportive care is necessary until progression is noted. Severe thrombocytopenia (less than 20,000/cu. mm.), causing hemorrhage and granulocytopenia (less than 1,000/cu. mm.) associated with repeated serious infections, is a sufficient reason to initiate treatment.

The management of elderly patients in whom response to therapy is less satisfactory can usually be decided after a
TABLE 4.
RESPONSE RATES IN ADULT ACUTE LEUKEMIA
FOR SINGLE AGENT AND COMBINATION CHEMOTHERAPY

| Agent or Combination                  | Percent CR rate |
|---------------------------------------|-----------------|
| Mercaptopurine                        | 10-20           |
| Methotrexate                          | 10-20           |
| Vincristine                           | 5-10            |
| Prednisone                            | 10-15 (Mostly ALL) |
| Cyclophosphamide                     | 5-10            |
| POMP*                                 | 40              |
| Ara-C (5-day infusion)                | 40              |
| Daunorubicin                          | 40-50           |
| OAP (5-day infusion)**                | 38              |
| OAP (10-day)                          | 51              |
| DOAP (daunomycin + OAP)               | 50-60           |
| COAP (cyclophosphamide + OAP)         | 50-60           |
| AD-OAP (adriamycin + OAP)             | 60-70           |
| VP (vincristine + prednisone)         | 19 (40% ALL, 16% AML) |
| Ara-C + thioguanine                   | 56 (Non-lymphocytic) |

*POMP (mercaptopurine, vincristine, methotrexate and prednisone)
**Ara-C, vincristine, prednisone

Frank discussion with the patient and his family on the likelihood of response and the natural history of the disease. Accuracy of information at this time is essential. Some patients, usually the minority, will elect not to be treated, whereas the remainder will choose to have a chance at complete remission. While the rate of remission is lower (30-40 percent in patients over 50 years of age with op-
ternal therapy), older patients who achieve complete remission have the same duration of remission and survival as younger patients.

Remission Induction by Chemotherapy

The natural history of acute leukemia is well defined. More than 50 percent of untreated patients will die in less than three months. 90 percent in less than one year. Spontaneous remissions are rare, usually occurring in children. Farber, in 1948, demonstrated the clinically useful antileukemic action of aminopterin and efforts to discover and define other chemotherapeutic agents have continued from that time. The rewards are most apparent in childhood leukemia, where 20-50 percent of patients now have a reasonable chance of cure. Early grounds for optimism are now also being seen in adult acute leukemia; progress has come on many fronts, such as new chemotherapeutic agents, immunotherapy and improved supportive care.

Two most significant factors in remission induction therapy have been, first, the development of cytosine arabinoside (Ara-C) and the anthracycline antibiotics, daunomycin and adriamycin, and second, the successful blending of these and earlier chemotherapeutic agents into combination regimens. (Table 4.) Single agents and their response rates in adult leukemia are listed in Table 4. Anthracycline antibiotics and Ara-C—agents with the highest response rates—form the basis of most modern regimens.

Present Chemotherapy Regimens

By the mid 1960s, several agents such as 6-mercaptopurine, methotrexate, vincristine and prednisone were available with remission rates as single agents of five to 20 percent. A major advance was made when these drugs were combined into a regimen, POMP, designed to exploit the additive cytotoxic effects without causing additive toxicity, as individually the target organs of toxicity of each agent varied. Complete remission rates of 40 percent in adults with leukemia were obtained. Complete remission (CR) is defined as:

- no clinical evidence of leukemia;
- normal peripheral blood counts;
- less than five percent blasts in a normal cell, well-differentiated bone marrow.

Anthracycline antibiotics and Ara-C—agents with the highest response rates—form the basis of most modern regimens.

Cytosine arabinoside’s killing action is limited to cells synthesizing DNA during the cell cycle. The Southwest Oncology Group, which has been studying the most advantageous method of administration, has found that continuous infusion of Ara-C is more effective than intermittent injections, and that five-day infusions achieve a higher CR rate than two-day infusions (38 percent versus 20 percent). Vincristine and prednisone were added to Ara-C (OAP); 10-day infusions (10-day OAP) were shown to be superior to five-day infusions, not only in terms of remission rate (51 percent versus 38 percent) but also remission duration and survival. The addition of daunomycin (DOAP) and cyclophosphamide (COAP) to OAP raises the complete remission rate to 50-60 percent. A pilot study combining adriamycin to OAP (AD-OAP) carried out at the M.D. Anderson Hospital achieved complete remission in 70 percent of patients.

In the most recent Southwest Oncology Group (SWOG) study on chemotherapy of acute leukemia (CIAL), patients with greater than 30,000 blast cells, organ failure and acute progranulocytic leukemia were initially treated
The remaining patients were initially treated with vincristine and prednisone alone (VP) until remission occurred or until progression or lack of continued improvement was noted. VP-failures would then begin on adriamycin and seven-day Ara-C infusions. The response rate to VP alone was 19 percent (16 percent for AML versus 40 percent for ALL). Overall, the CR rate was 60 percent with a higher response noted in patients under 50 years old (73 percent) than in older patients (43 percent). Figure 3 shows comparative survival, computed by life-table analysis for the Southwest Oncology Group studies on five-day OAP, 10-day OAP and CIAL. The addition of adriamycin to OAP has been shown to improve response rates and survival for patients in both young (less than 50 years) and older age groups. Patients are randomized to receive or not receive immunotherapy with BCG, which is introduced when the patient is in CR. Results of this method of maintaining remission are not yet available.

Patients being treated by Acute Leukemia Group B are obtaining similar good results with daunomycin and Ara-C. Several other investigators in the United States, Europe and the United
TABLE 5.
TOXICITY OF AGENTS USED IN MANAGEMENT OF ADULT ACUTE LEUKEMIA

| Drug                        | Classification           | Myelosuppression |
|-----------------------------|--------------------------|------------------|
| Cytosine arabinoside (Ara-C)| Pyrimidine analogue      | +                |
| Adriamycin                  | Anthracycline antibiotic | + (severe with daunomycin) |
| Daunomycin                  |                          |                  |
| Mercaptopurine              | Purine analogue          | +                |
| Thioguanine                 |                          |                  |
| Methotrexate                | Folate antagonist         | +                |
| Vincristine                 | Periwinkle alkaloid      | -                |
| Prednisone                  | Glucocorticoid           | -                |
| L-asparaginase              | Bacterially-produced enzyme | -              |

Kingdom have reported 50-60 percent CR rates with similar combinations. Clark at Memorial Sloan-Kettering Cancer Center has accumulated a large experience with Ara-C by intravenous injection every 12 hours, combined with oral administration of 6-thioguanine, a purine analogue related to mercaptopurine. In this regimen, Ara-C and thioguanine are administered until bone marrow hypoplasia is induced. The overall CR rate in patients with non-lymphocytic leukemia is 56 percent in this series.

Thus, using modern aggressive chemotherapy, most patients with acute leukemia, especially younger patients, can expect to achieve remission. The major challenge remains the improvement of remission duration.

Toxicity
All effective regimens in acute myelogenous leukemia are myelosuppressive and are, therefore, likely to be complicated by life-threatening infection and bleeding. (Table 5.) Ara-C is relatively free of side-effects, other than myelosuppression, although febrile reactions can be seen following injection, as can symptoms and signs of enterocolitis after prolonged high-dose courses.
| Other Toxicity                                                                 | Comments                                                                 |
|-------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Fever, nausea                                                                 | Best as continuous I.V. infusion                                          |
| Vomiting, alopecia, stomatitis, cardiac damage                                | Avoid extravasation; restrict total adriamycin dose to 550 mg./m² and daunomycin to 500–750 mg./m² |
| Nausea, vomiting, diarrhea                                                    | Occasional cholestatic jaundice; mercaptopurine-allopurinol interaction |
| Nausea, stomatitis, diarrhea                                                  | Hepatic dysfunction; cirrhosis with chronic use                           |
| Neurotoxicity, alopecia, constipation, abdominal pain                         | Avoid extravasation                                                      |
| Indigestion                                                                   | Other side effects uncommon with short courses                           |
| Fever, allergy, fatty liver, diabetes, pancreatitis, fall in clotting factors | Principally used in ALL                                                  |

The anthracycline antibiotics, adriamycin and daunomycin, share the adverse reactions of vomiting, alopecia and stomatitis. Daunomycin is more likely to cause severe marrow hypoplasia. In both agents, toxic cardiomyopathy can lead to a picture of congestive heart failure, usually at cumulative doses of 550 mg./m² for adriamycin and 500–750 mg./m² for daunomycin. However, these levels are much higher than usually needed to induce complete remission and only occur when patients are maintained on these drugs or receive them during repeated remission induction following relapse. If the cumulative doses of the anthracyclines are kept below these levels, the risk of cardiomyopathy is about five percent. In addition, if treatment is stopped before the sum of the Q.R.S. voltages in the six standard limb leads of the EKG has fallen to 30 percent below the pre-anthracycline EKG tracing, protection from clinically significant cardiac damage should be further improved. Assessment of an EKG prior to each administration of adriamycin or daunomycin is mandatory. These agents cause very severe chemical cellulitis if extravasation occurs, often resulting in ulceration requiring skin grafting. Vincristine shares
Mercaptopurine and thioguanine can rarely cause cholestatic jaundice. The effect of mercaptopurine, but not thioguanine, is increased three-to-four-fold, if given in conjunction with allopurinol, which decreases the hepatic inactivation of mercaptopurine. Methotrexate also produces transient abnormalities in liver function and can result in hepatic fibrosis and cirrhosis, especially if given on a chronic daily basis.

Vincristine, L-asparaginase and prednisone, useful predominantly in acute lymphoblastic leukemia, result in no significant myelosuppression. (Table 5.) Vincristine can cause peripheral neuropathy, alopecia, constipation and abdominal pain. L-asparaginase is often followed by febrile and allergic reactions of immediate and delayed hypersensitivity type, as would be expected after the injection of a foreign protein. This reaction can generally be circumvented by changing the type of L-asparaginase from that derived from Erwinia species to that produced by E-coli and vice versa. Fatty liver, diabetes, pancreatitis and falling clotting factors are common side-effects of asparaginase. Further descriptions of the modes of action and toxicity of these chemotherapeutic agents can be obtained in pharmacology and oncology texts.35-36

Remission Maintenance by Chemotherapy

Maintenance therapy is necessary in adult acute leukemia. The strategy is ill defined, however, since the continued killing effect of therapy on leukemic cells is impossible to determine when the patient is in remission and there is no evidence of disease on clinical or bone marrow examination. Lack of efficacy can only be demonstrated by relapse of the patient.

After inducing a remission with adriamycin, Ara-C, vincristine and prednisone (AD-OAP), it is our practice to give another three courses of the same combination at a reduced dose, sufficient to prevent life-threatening marrow suppression. Adriamycin is then omitted and maintenance continued with OAP. A balance is necessary, giving doses of Ara-C as high as possible but without causing the absolute granulocyte count to fall below 500/cu. mm. or the platelet count below 100,000/cu. mm. OAP has been found to be a well tolerated, predictable regimen and patients who receive it remain in excellent health. Once remission is achieved, BCG is administered weekly by scarification in an attempt to boost the host defenses against leukemia; BCG has been shown to prolong remission and survival.37 Other groups are exploring combined chemoinmunotherapy maintenance programs with similar encouraging results.38 (See page 19 for details.)

Many other maintenance programs, several employing chemotherapeutic agents not used in remission induction therapy, have been explored but the optimal approach has not been established. Remission duration is usually short, that is, less than 18 months.

Late Intensification

In 1970, we adopted a new approach to remission maintenance since, despite continued maintenance therapy, relapses continued to occur with more than half the patients relapsing during a 12-month period after remission. Patients who have been in remission for more than one year are now being treated with three courses of combination therapy, using agents to which their tumor cells have not been exposed. The most commonly used regimen has been POMP.39 The doses of the first course are the same as those used in remission induction therapy. Dosages of the second and third courses are increased, depending on the extent of toxicity to the preceding course, especially infection, mucositis and hepatic dysfunction. After discon-
Continuing chemotherapy, all but seven patients were maintained on BCG immunotherapy. More than 50 patients have now been treated in this fashion and it is predicted from life-table analysis that only 30 percent will relapse in the first 12 months, most of these relapses occurring in the first six-month period. It is further predicted that as many as two of three patients will continue in unmaintained complete remission from two to four years. Comparison with a closely matched historical control group who continued to receive maintenance chemotherapy discloses that those receiving late intensification had a markedly prolonged duration of remission. (Fig. 4.)

Immunotherapy
An important advance in the management of patients with acute leukemia is the development of immunotherapy. Tumor-associated antigens, not present on normal blast cells, have been unequivocally demonstrated on leukemic cells. In 1969, Mathé utilized the principle, which had been developed in animal models, that antitumor immunotherapy works best when the tumor load is low. He treated groups of children who had been in remission for two years with BCG by scarification and irradiated tumor cells, in an attempt to boost nonspecific and specific antileukemic immunity. The results were encouraging, with half the patients remaining in complete remission and off chemotherapy for prolonged periods of time. A matched control group receiving no chemotherapy or immunotherapy showed poorer results. This study remains the only series in which the beneficial effect of immunotherapy in lymphoblastic leukemia was clearly demonstrated, but it provided the stimulus for further research in both myeloblastic and lymphoblastic disease.
Those studies that revealed no benefit, however, have applied different strains of BCG by different methods and have not used tumor-specific immunotherapy techniques.

In acute myelogenous leukemia, the situation is quite different. Hersh has shown that pretreatment immunocompetence and recovery of immunocompetence following intensive remission induction therapy correlated with a good response rate and long remission duration and survival. \(^{42}\) Several groups have now shown that administration of BCG to increase immune reactivity is associated with longer remission and prolongation of survival. This finding is consistent whether or not specific antitumor immunotherapy was also used. Gutterman's study from this institution demonstrated significant prolongation of median remission duration from 50 to 91 weeks in adult leukemia when BCG was added to maintenance therapy with OAP. \(^{37}\) (Fig. 5.) This prolongation is more significant in patients with AML. Similar encouraging results have been shown with MER, a methanol extraction residue of BCG. \(^{38}\)

Further intriguing observations have arisen in a group of patients treated at Memorial Sloan-Kettering Cancer Center with an antipseudomonas vaccine, which was given in an attempt to de-
crease pseudomonas infection. The anti-infective effect was not marked, but several patients treated with this vaccine have had very long remissions.\textsuperscript{13} The role of autologous or allogeneic leukemia cells or leukemic cell extract in inducing specific antileukemia immunity, although appealing, is at the present time ill-defined and under active investigation.\textsuperscript{43}

Bone Marrow Transplantation

Bone marrow transplantation is being increasingly used as treatment for patients who have failed induction chemotherapy or have relapsed. The leukemic cells are eradicated with a combination of 1000 rads whole body irradiation and high-dose chemotherapy, for example, cyclophosphamide. The problems in allogeneic transplants are graft rejection, graft versus host disease and, to a lesser degree, recurrent leukemia. Immunological reactions do not occur in identical twins, in whom transplantation is an excellent strategy. Transplantation is limited to those who have a closely related donor (HL-A compatible and mixed lymphocyte culture nonreactive).

We are using autologous transplantation, thus broadening the applicability of transplantation beyond the scope of allogeneic transplants. When patients have been in remission for four-six months, marrow is aspirated and separation techniques used to remove as many residual leukemic cells as possible. The marrow is then frozen and stored. If the patient relapses, he is prepared as for an allogeneic transplantation, but his own stored marrow is infused. This technique is intellectually attractive since there is no immune rejection, but transplantation of residual leukemic cells may be a problem.

\textbf{SUPPORTIVE CARE}

\textbf{Bleeding}

Hemorrhage is closely correlated with thrombocytopenia\textsuperscript{44} and to a large extent can be prevented or controlled by platelet administration.\textsuperscript{45} When the platelet count is below 20,000, the risk of bleeding increases steeply and prophylactic platelet transfusions are indicated. Eventually, many patients become refractory to random transfusions, but transfusions from first-degree relatives can often prevent or circumvent this situation. Bleeding associated with disseminated intravascular coagulation and decreasing clotting factors, as in acute granulocytic leukemia and sepsis, is a difficult problem. There is no definite evidence that replacement therapy with plasma fractions or heparin given in high or low doses is effective in acute leukemia. However, if initial plasma transfusions do not stop bleeding, cautious use of heparin is probably indicated. Of course, control of the initiating factor, that is, leukemia or sepsis, is the single most important factor in management.

\textbf{Infection}

Infection is the major complication encountered in induction therapy of acute leukemia, and is related to the degree and duration of neutropenia.\textsuperscript{46} Sepsis, pneumonia and soft tissue infections, including perianal infections, are most common. Staphylococcus aureus, a major pathogen before the introduction of semi-synthetic penicillins, is now of minor concern. Fungal infections, especially from Candida species, remain a significant problem in that 20 percent of patients have disseminated fungal infections at the time of death.\textsuperscript{47}

Fever in neutropenic patients is an indication for urgent antibiotic therapy; sepsis carries a high mortality rate in the first 24 hours, if patients are not treated promptly with effective antibiotics. Good coverage of likely pathogens is provided by a combination of (A) carbenicillin, which cures 80 percent of all pseudomonas infections and is given
in a dose of 30 gm./day, and (B) gentamicin, which is effective against other gram-negative bacilli, and is administered intravenously at a dose of 1 mg./kg. every six hours. The administration of aminoglycoside antibiotics, such as gentamicin and Amikacin, in twice the conventional daily dose by continuous infusion has been investigated, and improved cure rates, especially in neutropenic patients, are being obtained.48 If the infection fails to respond, granulocyte transfusion, usually using cells from the patient’s relatives, has been shown to be a very useful treatment modality.49 Continued failure to respond indicates the possibility of less common infections, especially fungi and to a lesser extent pneumocystis carinii, toxoplasma, cytomegalovirus and mycobacterial disease. Sulfamethoxazole-trimethoprim is effective in the protozoal diseases mentioned and in bacterial infections that do not respond to first-line antibiotic therapy.50 Common sites of fungal infections are the oropharynx and esophagus, which respond well to amphotericin B, as well as the lung and disseminated sites, which usually respond poorly unless the patient goes into remission.

Protected Environment

Plastic bubble isolators (Life-island) and laminar air flow rooms have been used for more than a decade to provide an environment with few pathogens for acute leukemia patients who are receiving chemotherapy. To achieve the low-pathogen state, it is also necessary to administer oral non-absorbable antibiotics, such as gentamicin, vancomycin and nystatin, thus reducing endogenous microbial flora of the gastrointestinal tract.51 It is now established that isolation and microbial suppression, can significantly decrease the incidence of infection.52 This relative freedom from infection permits the administration of higher doses of chemotherapy, which in turn achieves a slightly higher remission rate in some series and prolongation of remission duration and survival.53 In most instances, patients tolerate the isolation well, both physically and psychologically. In protected environments, patients less than 60 years old have achieved complete remission rates of 80 percent using a combination of adriamycin, Ara-C, vincristine and prednisone.

Fever in neutropenic patients is an indication for urgent antibiotic therapy; septicemia carries a high mortality rate in the first 24 hours.

Meningeal Leukemia

Central nervous system involvement is an uncommon presenting feature in acute leukemia, especially in adults. However, one study found an incidence of 21 percent at autopsy.54 Clinical signs and symptoms occur in 40 percent of patients with ALL and 6.5 percent of those with AML; usually after the patient has been in remission for more than six months. This suggests that the longer the duration of remission, the higher the incidence of CNS disease—a pattern that has been established for childhood leukemia. Half the patients were still in hematological remission when CNS involvement was diagnosed. This is attributed to the failure of antileukemic therapy to cross the blood-brain barrier and sufficiently control disease in the area.

Cranio-spinal irradiation and intensive intrathecal therapy with methotrexate and Ara-C, which have been effective in children, have not been systematically studied in adults. After clinical disease has been detected, therapy generally controls meningeal disease clinically until death, usually shortly thereafter of hematologic relapse. Cure of meningeal disease has been documented in some patients at autopsy.
PROGNOSTIC FACTORS

Many factors influence the likelihood of achieving complete remission in adult leukemia. The best known and most important is the age of the patient. Elderly patients have decreased immunological competence and their leukemic cells often have a low labeling index. In addition, they are less able to tolerate severe infection.

Infection at the time of diagnosis has a major adverse effect on prognosis. A diagnosis of ALL has a minor beneficial effect on the likelihood of obtaining a remission. However, the various morphological subtypes of acute myelogenous leukemia have not been consistently shown to affect response.

The pattern of growth of leukemic cells in agar culture has been correlated with response; a higher response rate was achieved in patients whose bone marrow grew with a pattern of small clusters of leukemic cells. A slightly higher response rate is also noted in patients with normal chromosome patterns, as compared to those with abnormal patterns especially with deletions of D and E groups.

FUTURE PROSPECTS

Major improvements in the treatment of leukemia will depend on the development of new effective chemotherapeutic agents. Rubidazone, 5-azacytidine, ifosfamide and guanazole are promising, but still in the developmental stage. Rubidazone, an anthracycline related to adriamycin and daunomycin, has resulted in a 57 percent complete remission rate in one French series; similar encouraging results have been achieved in previously treated patients at our institution. Steady progress in all aspects of supportive care is occurring with improved white cell and platelet transfusion techniques, following the realization of the importance of the histocompatibility factors.
compatibility system (HL-A) in matching donor and recipient. New antibiotics for infection and better methods of administration are being introduced.

If the survival curves of patients treated at various time periods are analyzed, a steady improvement in survival can be noted. (Fig. 6.) It is now anticipated that several patients in complete remission who are maintained with carefully monitored chemioimmunotherapy and late intensification chemotherapy followed by further immunotherapy can remain disease-free, without chemotherapy, for several years. Although advances in the methods of inducing remission in older patients and maintaining remission are urgently needed, a pessimistic approach to adult acute leukemia is a thing of the past. Hopes for curing a significant proportion of these patients are now realistic, with further improvements expected in the next few years.

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