Childhood Leukemias

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DONALD PINKEL

Introduction

Since its initial recognition 150 years ago, leukemia has been the focus of remarkable research activity and consequent progress. The drama of its manifestations, its frequency in children, its commercial importance in animal husbandry, its usefulness in understanding hematopoiesis, and its ready adaptability as a model for other human cancers are among the reasons for this attention. But perhaps more important for the current generation of its students was the discovery 25 years ago that the most common variety of leukemia could be cured in approximately one-half of children, the first generalized cancer to be cured and the first autologous cancer to be cured with chemicals.[1] This chapter summarizes the history of the study of leukemia, particularly childhood leukemia, with regard to description, causation, and treatment. It concludes with comments about the lessons taught by this history.

Description of leukemia

Although the first description of a patient with leukemia was published in 1827,[2] it was not until 1845 that Virchow[3] in Germany (Fig. 1.1) and Bennett[4] and Craigie[5] in Scotland, in separate case reports, recognized it as a distinct disease, "white blood." Two years later, Virchow introduced the term "leukemia" for this entity and proceeded on a series of investigations that were summarized in 1856.[6] He distinguished leukemia from leukocytosis and described two types: splenic, associated with splenomegaly, and lymphatic, associated with large lymph nodes and cells in the blood resembling those in the lymph nodes. The following year, acute leukemia was described by Friedreich,[7] and in 1878 Neumann[8] established the existence of myelogenous leukemia. The close relation between lymphomas and leukemias was defined by Turk[9] in 1903.

Ehrlich's introduction of staining methods in 1891 allowed the differentiation of leukocytes and identification of leukemia cell types.[10] Splenic and myelogenous leukemias were soon recognized as the same disease, originating from a myeloid precursor. Eventually the leukemic myeloblast, monoblast, and erythroblast were identified. It also became apparent that some acute leukemias were marked only by abnormal leukocytes in the blood, not leukocytosis. By 1913, leukemia could be classified as chronic lymphocytic, chronic myelogenous, acute lymphocytic, myeloblastic or monocytic, or as erythroleukemia.[11] Not only did these advances result in refined classification of leukemia, but they shed light on the nature of normal hematopoiesis as well. The prevalence of acute leukemia during childhood, especially between ages 1 and 5 years, was noted in 1917.[12]

Progress in the description of leukemia has continued to parallel the development of new technologies, such as special staining, electron microscopy, chromosomal analysis, immunophenotyping, and molecular genotyping. With use of electron microscopy, platelet peroxidase staining, and monoclonal antibody reactivity to a platelet glycoprotein, CD41, acute megakaryocytic leukemia became a well-defined entity.[13] Although some hematologists and many chemotherapists lumped all childhood acute leukemias into one category as late as the 1960s, the discovery that acute lymphoid and acute myeloid leukemias responded differently to prednisone and methotrexate made it necessary to use the new technologies to clearly distinguish them.

After the discovery in 1960 of the Philadelphia chromosome in adult chronic myeloid leukemia and the later introduction of banding techniques, many nonrandom chromosomal abnormalities were found to be associated

Fig. 1.1. Rudolf Virchow, the father of leukemia research, established leukemia as a medical entity in the years 1845 to 1856. He also classified leukemia by its pathologic anatomy and cell morphology and postulated its cellular origin.

with specific types of acute leukemia.[14,15] Application of DNA probing and amplification methods resulted in molecular genotyping of leukemias, both for diagnosis and for detection of residual cells of the leukemia clone.[16]

In 1973, Borella and Sen[17] (Fig. 1.2) demonstrated that in some children with acute lymphoid leukemia, the leukemic lymphoblasts were of thymic origin. They further showed that T-cell leukemia was clinically as well as biologically unique.[18] As monoclonal antibodies to leukocyte cell surface antigens were developed, further immunophenotypic classification of leukemia cell population became possible.[19]

Currently, leukemia is classified as acute or chronic, lymphoid or myeloid as in the 19th century (see Chapter 2). However, the morphology of acute leukemia is subclassified into three lymphoid varieties and eight myeloid. Myelodysplastic syndromes such as monosomy 7 syndrome and juvenile myelomonocytic leukemia are also recognized. Immunophenotyping of leukemia cells with monoclonal antibodies separates the lymphoid lineage into early and late B-precursor, B-cell, and T-cell (see Chapter 7). It also helps to distinguish anaplastic lymphoid from myeloid cell types and to classify the eight myeloid types, and contributes to identifying the rare biphenotypic variety. Genotypic classification by chromosomal analysis, fluorescent in situ hybridization, DNA probing, and polymerase chain reaction techniques allows molecular genetic definition of leukemias (see Chapters 9, 10, and 11). Because leukemia is now recognized as a molecular genetic disorder and the most effective acute leukemia drugs disrupt molecular genetic processes, this approach to cell characterization may be the ultimate descriptive method. With use of recent technology, it has become clear that the most frequent form of acute leukemia in children is B-precursor cell, often with excessive chromosomes or expression of novel hybrid genes such as *ETV6-CBFA2 (TEL-AML1)*, *E2A-PBX1*, or *BCR-ABL* (190 kb) and, in young infants, often demonstrating rearrangement of the *MLL (HRX)* gene.[20,21]

Fig. 1.2. Luis Borella identified thymic cell leukemia, introducing immunophenotyping of leukemia and initiating its classification by biological function in addition to morphology.

During the past 25 years, the importance of describing the leukemia host has also become more apparent. Not only such features as age, gender, and disease extent, but also ethnicity, nutrition, socioeconomic status, and accompanying syndromes and diseases have been correlated with type of leukemia and outcome of treatment.[22–27] For example, children with trisomy 21 (Down) syndrome have a high incidence of leukemia, especially acute megakaryocytic leukemia.[26] They also have twice the cure rate of other children with acute myeloid leukemia when treated with chemotherapy.[27] The extra 21 chromosome introduces not only increased vulnerability but also better curability. Host genetic polymorphism, with regard to enzymes such as thiopurine methyltransferase that make available, activate, or detoxify antileukemia drugs, may also be important.[28,29] Malnutrition, poverty, and underprivileged ethnicity are associated with low cure rates.[22–25]

In summary, the history of the past 150 years illustrates that progress in the comprehension of leukemia has paralleled the continued application of new ideas and technology to its description by creative, industrious, and practical clinical investigators.

Causation of leukemia

Since leukemia was recognized 150 years ago, the search for its causation has followed several approaches: infectious, genetic, physical, and chemical. Pursuit has been vigorous and often marked by heated controversy. Over time it has become apparent that all approaches may be correct and that leukemia results from numerous causes, often interacting, varying from cell type to cell type and from one patient to another.

Infectious causes

When "white blood" was identified, some observers considered it the result of severe inflammation, but the new technology of blood microscopy revealed that the white cells of leukemic leukocytosis appeared different from those of inflammatory leukocytosis. However, interest continued in an infectious etiology. Ellerman and Bang's[30] transmission of fowl leukemia by cell-free extracts in 1908, suggesting a viral causation, was a landmark finding that led to extensive searches for the virus etiology of all leukemias, both in animals and humans, throughout the 20th century. In 1951, a mammalian leukemia virus was first demonstrated by Gross[31] (Fig. 1.3) by injection of newborn mice with cell-free filtrates from leukemic mice. Subsequently, several leukemia-producing viruses were isolated from cats, cattle, gibbon apes, and humans with adult-type T-cell leukemia.[32–35] All were characterized as retroviruses. In addition, two large DNA viruses of the herpes group were associated with leukemia: Marek's disease virus in birds and Epstein-Barr virus (EBV) in B-cell lymphoma/leukemia of African children (Burkitt lymphoma).[36,37] Extensive attempts to identify leukemia viruses in children with B-precursor, T-cell, myeloid, and temperate zone B-cell leukemia have been unsuccessful.[38] However, the critical experiments that led to identification of murine and feline leukemia viruses, injection of newborn of the same species, cannot be performed.

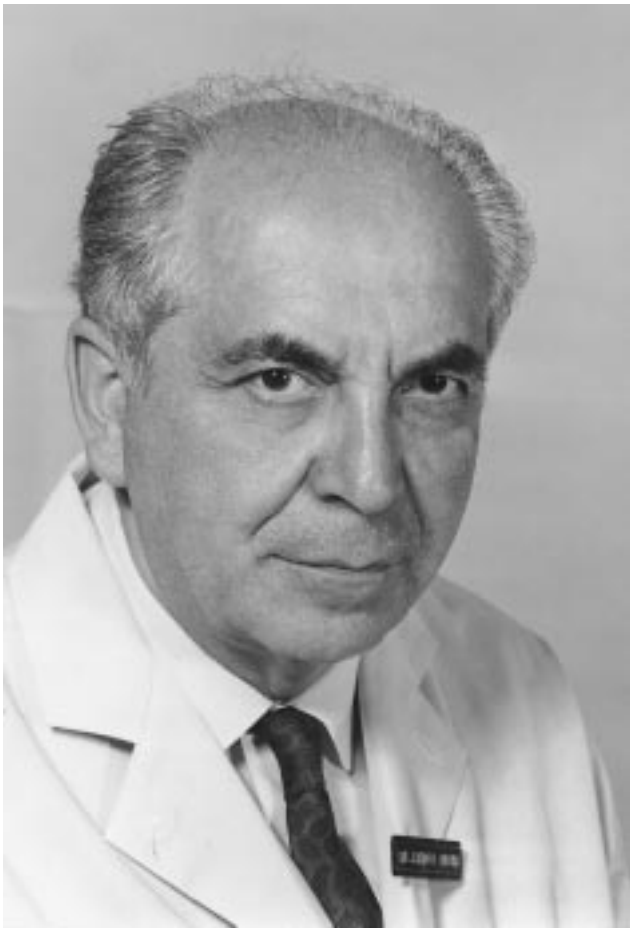

Fig. 1.3. Ludwik Gross described the first mammalian leukemia virus in 1951, initiating research efforts that led to study of the molecular pathology of leukemia.

Despite the failure to identify leukemia viruses other that EBV in children with leukemia, some epidemiologic characteristics have been interpreted in favor of an infectious cause. In 1917, Ward[12] reviewed 1457 cases of acute leukemia and concluded that the weight of evi-

dence was against infection. In 1942, Cooke[39] collected information on children with acute leukemia from 33 American pediatric services (a harbinger of pediatric cooperative studies) and demonstrated a sharp peak in incidence between ages 2 to 5 years, paralleling peaks in measles and diphtheria incidence. He concluded that acute infections were a factor in causing childhood leukemia. Lending weight to an infection hypothesis was the report by Kellett[40] in 1937 of a concentration of cases in Ashington, England. He suggested that an infection, possibly widespread but of low infectivity, might be the causative agent. Subsequent instances of temporo-spatial proximity of children with leukemia were reported from Erie County, New York; Niles, Illinois; and Northumberland and Durham, United Kingdom,[41–44] but study elsewhere has failed to confirm significant aggregation or other evidence of communicability.[45,46] Also cited to support the infection hypothesis was the lower incidence and younger age of acute leukemia in children of lower income families.[41] It was speculated that this could fit the pattern of infectious diseases such as paralytic poliomyelitis where, because of early exposure and maternal immunity, disease tends to occur at an earlier age and less frequently in underprivileged children. Recently, Kinlen and colleagues[47] described excessive leukemia and non-Hodgkin lymphoma rates in children living near large rural construction sites. They suggested that the high risk was related to unaccustomed mixing of rural and urban people and was evidence for an infective process. Greaves and associates[48,49] have further modified and expanded Kellett's hypothesis based on newer understanding of the biology of childhood leukemia and international epidemiologic data. In summary, infectious causation of childhood leukemia has been demonstrated for EBV-associated B-cell lymphoma/leukemia but remains only a hypothesis for other forms.

Physical causes

Although ionizing radiation probably induced leukemia in Marie Curie, its leukemogenic effects in radiologists only became quantitated in 1944.[50] In 1955, studies of Japanese children who survived atomic bombing demonstrated a marked increase in acute leukemia, both lymphoid and myeloid.[51] In the same year, Simpson et al.[52] reported that children who received neonatal thymic irradiation had an increased risk of thymic lymphoma and acute leukemia as well as thyroid carcinoma. Numerous subsequent studies of prenatal and childhood exposure to diagnostic radiography and medical radiation for benign disease yielded evidence that low-dose radiation can be a factor in the causation of childhood leukemia.[53,54] Action was taken in the 1960s and 1970s to reduce fetal, neonatal, and childhood exposure to ionizing radiation. Medical radiation for neonatal thymus, tinea capitis, acne, benign tumors, and even some malignancies was eliminated. Shoe store fluoroscopes were removed, medical and dental radiology equipment and protection upgraded, and diagnostic radiography, especially by fluoroscope, was reduced or replaced with ultrasound imaging.

Chemical causes

In 1928 Delore and Borgomano[55] reported a patient with acute leukemia associated with benzene intoxication. Subsequently, numerous reports confirmed that benzene can produce myelodysplasia and acute myeloid leukemia.[56,57] A dose-response relationship was recently found in China.[58] Although the hazards have been occupational and the victims adults, the significant yield of benzene in cigarette smoke—three times greater in sidestream than in mainstream smoke—and in automobile exhaust raises the question of whether parental smoking and automobiles are causative factors of leukemia in children.[59]

The advent of cancer chemotherapy in the 1950s and its extension in the 1960s and 1970s led to the appearance of secondary leukemia both in children and adults. Alkylating agents and drugs that bind topoisomerases, especially etoposide and teniposide, were found to be leukemogenic in children, most often producing acute myeloid leukemia with distinctive chromosomal and molecular genetic abnormalities.[60,61] The question of whether small environmental concentrations of agents with similar activities can be responsible for some cases of de novo childhood leukemia with similar genetic findings needs to be answered.

Genetic causes

A genetic cause of leukemia was first suggested in 1896 by Hartenstein[62] who observed lymphoid leukemia in a cow and its mother and speculated that it was hereditary. In 1931, strains of mice with high frequencies of leukemia/lymphoma were identified,[63] and by 1935 an inbred strain with a 90% incidence of lymphoid leukemia was produced.[64] Extrinsic nonhereditary factors were postulated to explain the 10% failure of this inbred strain to develop leukemia. The evidence for a possible genetic

basis of murine leukemia led to studies of familial incidence in humans. A 1937 report[65] of three families with multiple cases was followed by a large study by Videbaek[66] in Denmark comparing families of patients with leukemia and families of healthy persons. A significant difference was found and a genetic hypothesis proposed. An institution-based study in Boston in 1957[67] did not support Videbaek's findings, but the author acknowledged three families with multiple cases of acute leukemia, two with parental consanguinity, and suggested a recessive gene in these families. Although leukemia in twins was described in 1928,[68] the high concordance rates for leukemia in like-sex and monozygous twins were uncovered in 1964 by MacMahon and Levy.[69] Recent studies by Ford et al.[70] using genetic markers indicate that twin concordance probably results from intrauterine metastases from fetus to fetus.

In addition to increased familial incidence and twin concordance, the increased risk of leukemia in children with constitutional chromosome abnormalities further supported a genetic hypothesis. The report of a child with Down syndrome and acute lymphoid leukemia in 1930[71] and subsequent similar reports led to a national survey in 1957 by Krivit and Good[26] that demonstrated the high incidence of leukemia in this trisomy disorder. In the past 40 years, childhood leukemia has become associated with numerous constitutional genetic disorders, including primary immunodeficiency diseases, chromosome instabilities, and inherited cancer syndromes.[72]

Observation of the distinct Philadelphia chromosome associated with chronic myeloid leukemia by Nowell and Hungerford[14] in 1960, and Rowley's discovery[15] that it resulted from a 9;22 chromosomal translocation in 1973, were followed by identification of numerous nonrandom chromosomal abnormalities associated with biologically distinct leukemias and hybrid genes. In 1982, the human homologue of the Abelson murine leukemia virus protooncogene *abl* was found to be relocated from chromosome 9 to 22 in chronic myeloid leukemia, to form its characteristic hybrid gene, *BCR-ABL*.[73] In the same year the human homologue of an avian leukemia oncogene (*myc*) was identified on the region of chromosome 8 that is translocated in B-cell lymphoma of children.[74] By the mid-1980s, there was a clear consensus that leukemia was a somatic genetic disorder of hematopoiesis.[75] Although the ultimate causation of most childhood leukemias remains unknown, the establishment of a genetic mechanism, recognition of the role of homologues of animal leukemia virus oncogenes in human leukemia cells, and the knowledge that ionizing radiation and chemical leukemogens modify genetic DNA appear to reconcile the four historical approaches to causation.

Treatment

Palliative treatment

Because of the diffuse nature of leukemia and its catastrophic manifestations, physicians began to treat patients with chemicals shortly after it became recognized as a disease entity. In 1865, Lissauer[76] reported a patient with leukemia whose disease remitted after she received Fowler's solution (arsenious oxide); arsenicals became a standard but marginally useful palliation.

With the discovery of roentgen rays in 1896, interest turned to their clinical application in cancer therapy. In 1903, Senn[77] reported the response of leukemia to irradiation, and this modality, applied most often to the spleen, largely replaced arsenious oxide as a palliative measure, especially in chronic leukemia. When radioactive nuclides became available in 1940, radioactive phosphorus came into use for chronic myelogenous leukemia and polycythemia vera.[78]

Based on pathology reports of hematosuppression in mustard gas victims on the Western Front in World War I[79] and at the Bari harbor disaster in World War II,[80] nitrogen mustard was synthesized and tested in animals and then patients with lymphoma and leukemia in 1943.[81,82] Temporary partial remissions were produced, but toxicity was considerable, especially in patients with acute leukemia.

The chemical identification of folic acid in 1941[83] as an essential vitamin, its synthesis in 1946,[84] and the reversal of megaloblastosis by its administration[85] raised the question of whether it might be useful in the treatment of acute leukemia. In 1947, when Farber (Fig. 1.4) and colleagues gave folic acid (pteroylglutamic acid) to children with acute leukemia, Farber was impressed that it might have produced acceleration of the leukemia.[86,87] Subsequently, a 4-amino antimetabolite of folic acid, aminopterin, synthesized by Seeger et al.,[88] was provided to Farber and given to children with acute leukemia. Many of the children developed complete clinical and hematologic remissions that lasted for several months.[86] The era of specific leukemia therapy had begun!

A year after the report of remissions with aminopterin, a 1949 conference on the newly isolated adrenocorticotrophic hormone (ACTH) revealed that it produced prompt although brief remissions of acute lymphoid

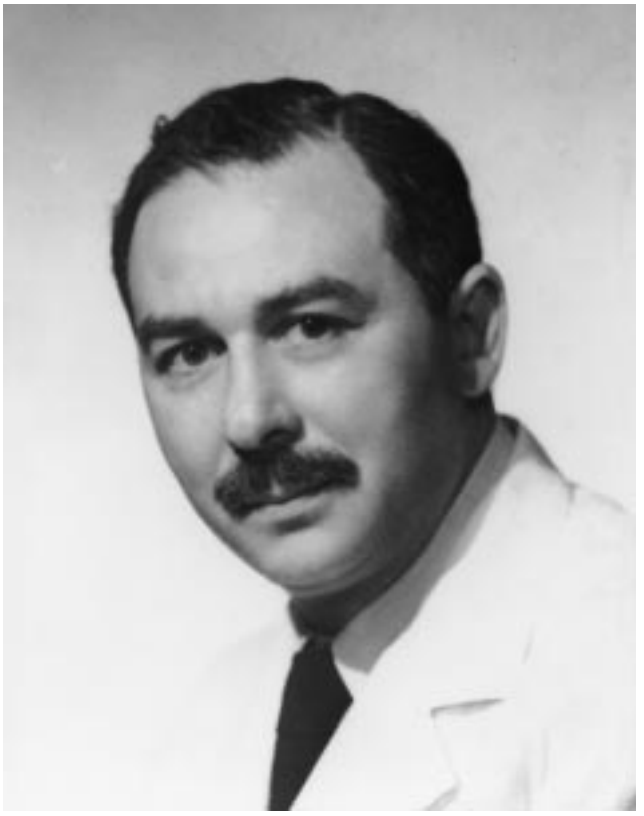

Fig. 1.4. Sidney Farber and his colleagues discovered that a synthetic antifolate, 4-amino-pteroylglutamic acid, produced remissions of childhood leukemia. This introduced antimetabolite chemotherapy and began the research leading to cure of many children with leukemia.

Fig. 1.5. Gertrude Elion, working with George Hitchings, used understanding of purine metabolism to develop three drugs important to children with leukemia: mercaptopurine, allopurinol, and acyclovir.

leukemia.[89] Cortisone and its synthetic analog, prednisone, had similar activity and soon replaced ACTH.

Unlike the folate antagonists, the purine antimetabolites 6-mercaptopurine and thioguanine resulted from a lengthy study of purine metabolism, purine analog synthesis, and structure-activity relationships by Elion and Hitchings[90] (Fig. 1.5) in the 1940s and early 1950s. In 1953, a report by Burchenal and associates[91] that 6-mercaptopurine produced remissions in patients with acute leukemia, especially children, promptly led to its use in sequential and combination chemotherapy with a corticosteroid (usually prednisone) and methotrexate, the 4-amino-N^{10}-methy1-folate analog that succeeded aminopterin.[87] The enthusiasm generated by the discovery of three effective drugs for childhood acute leukemia in 5 years was dampened, however, by the realization that virtually all of the patients eventually died of resistant leukemia or its complications.[87] This led to a fixed notion among most pediatricians and hematologists that temporary remissions and prolongation of survival in comfort were the most one could expect from leukemia chemotherapy.

In 1959, a pro-drug analog of nitrogen mustard, cyclophosphamide, with less toxicity for platelet production, was introduced and later shown to have value in lymphoid leukemia.[92] In 1962, vincristine, an alkaloid from the periwinkle plant with a unique mode of action, was shown to produce complete remissions of childhood lymphoid leukemia resistant to other agents.[93] But, as with all the other agents, remissions were temporary and relapse with resistant leukemia ensued.

Curative therapy

The first cure of leukemia was described in 1930 by Gloor,[94] who treated an adult with arsenious oxide, mesothorium, irradiation, and blood transfusions from two siblings (presaging current myeloblation and peripheral blood stem cell transplantation?). In 1964, Burchenal and Murphy[95] collected 36 cases of 5-year cures of treated childhood acute leukemia by a questionnaire survey of hematologists. Zuelzer[96] reported a 3% 5-year cure rate in children with acute lymphoid leukemia who received cyclic chemotherapy with prednisone, methotrexate, and mercaptopurine. A 5% 5-year cure rate was reported by Krivit et

al.[97] for sequential or cyclic chemotherapy of acute lymphoid leukemia with these agents in a Children's Cancer Group study. Stimulated by the studies of Skipper et al.[98] and Goldin et al.[99] in treating mouse leukemia with chemotherapy, leukemia Study Group B[100–102] used two-drug combinations and National Cancer Institute investigators used four-drug combinations that yielded similar low cure rates in patients with acute lymphoid leukemia.[103,104] The failure to achieve a significant cure rate in these courageous attempts reinforced the prevailing pessimism about leukemia therapy. Persons who continued to advocate anything beyond palliation were looked upon with skepticism, if not scorn, into the early 1970s.

In 1962, St. Jude Children's Research Hospital was opened in Memphis, Tennessee, with a mandate to seek prevention or cure of childhood leukemia. The St. Jude investigators defined several specific obstacles to the cure of childhood acute leukemia.[75] First was drug resistance: initial, as demonstrated by the high proportion of patients who failed to experience remission on single-drug treatment; and acquired, as indicated by eventual relapse in most children despite continued drug administration. The second obstacle was clinically isolated meningeal relapse that occurred with increasing frequency as systemic chemotherapy became more effective and hematologic remissions lasted longer. Meningeal relapse was thought to be due to the inadequate diffusion of methotrexate and mercaptopurine through the blood–cerebrospinal fluid barrier with consequent proliferation of leukemia cells in the leptomeninges. The third obstacle was the overlapping toxicity of antileukemia drugs, especially hematosuppression, immunosuppression, and mucositis, and thus the dilemma of limiting dosage or risking treatment-related death. However, the greatest obstacle was a pessimism that inhibited thoughts of curing patients with leukemia.

A curative approach to children with acute lymphoid leukemia was initiated in 1962. It consisted of four treatment phases: remission induction, intensification or consolidation, preventive meningeal treatment, and prolonged continuation therapy.[105,106] The main features were the administration of combination chemotherapy for induction, intensification and continuation chemotherapy, the use of different drug combinations for induction and continuation, preemptive irradiation of the cranial or craniospinal meninges, elective cessation of chemotherapy after 2 to 3 years, and most important, the objective of cure rather than palliation.

The pilot studies from 1962 to 1965 were fraught with considerable difficulty, including the emergence of *Pneumocystis carinii* pneumonia due to immunosuppression and the inadequacy of low-dose craniospinal irradiation to prevent meningeal relapse.[105–107] However, longer complete remissions were achieved than previously and 7 of 41 children became long-term leukemia-free survivors after cessation of therapy, a higher rate than previously reported, justifying the notion that acute leukemia could no longer be considered incurable. A fourth study compared full-versus half-dosage continuation chemotherapy and demonstrated that, despite its toxicity, full dosage was required to achieve longer remission.[108] It was clear from this experience that more capability in prevention and control of infection, especially with *Pneumocystis carinii* and the herpesviruses, was required.

With this information, another pilot study was inaugurated in December 1967, in which intensity of continuation chemotherapy was increased and higher-dose cranial irradiation combined with intrathecal methotrexate was used to treat the leptomeninges.[1] Within 6 months, the superiority of this regimen was apparent, and a randomized comparative study of meningeal irradiation was initiated.[109] Both the pilot study and the subsequent randomized study demonstrated a 50% cure rate for children with acute lymphoid leukemia who had received multiple agent chemotherapy and effective preventive meningeal therapy.

Since 1970, many institutional and collaborative groups throughout the world, using the same four phases of treatment but with modifications of drug selection and dosage schedules, have confirmed the curability of acute lymphoid leukemia in children.[20] Intrathecal methotrexate alone failed to prevent meningeal leukemia in one study.[110] However, Sullivan and associates[111] demonstrated that repeated administration of three drugs intrathecally during remission induction and continuation therapy was equivalent to meningeal irradiation for this purpose. Radiotherapy and its adverse sequelae could be avoided in most patients.

In the 1980s and 1990s, improved cure rates of up to 70% were reported.[20, 112] National surveys in the United States and United Kingdom demonstrated marked reduction in childhood leukemia mortality.[113, 114] Much of this improvement was related to more positive attitudes and greater clinical skill with experience, a remarkable increase in hematology-oncology medical and nursing specialists, better means of prevention and treatment of infection, more availability and use of blood components, earlier diagnosis and treatment, increased governmental and private health insurance coverage, improved childhood nutrition, and, in some instances, patient selection.

But the discovery and judicious introduction into treatment of additional antileukemia drugs was also important. These included cytarabine, a synthetic pyrimidine antimetabolite (1968),[115,116] daunorubicin, a natural DNA-intercalating anthracycline antibiotic (1967),[117] asparaginase, an enzyme synthesized by bacteria that lyses the essential amino acid asparagine (1970),[118] and the epipodophyllotoxins etoposide and teniposide, topoisomerase-binding agents derived from the mandrake root.[119] Modification of drug schedules, such as the intravenous administration of methotrexate in high dosages with delayed leucovorin rescue, was another factor.[120] The definition of subtypes of acute lymphoid leukemia and the successful targeting of specifically designed chemotherapy in children with T-cell and B-cell leukemia or otherwise at high risk of relapse with B-precursor leukemia therapy programs have been important also.[121,122]

From the beginning of leukemia chemotherapy the morphologic differences in response to chemotherapy were apparent. Although occasional patients with acute myeloid leukemia experienced remissions with 6-mercaptopurine or thioguanine, a 50% remission rate was first achieved in 1967 when thioguanine was combined with cytarabine.[123] Further improvement followed the introduction and inclusion of daunorubicin and etoposide. By intensive administration of these drugs, accompanied by considerable supportive therapy, it became possible in the 1980s to cure approximately 25% to 30% of unselected children with acute myeloid leukemia.[124]

In 1957, Barnes and Loutit[125] administered lethal doses (LD_{98}) of total-body irradiation to leukemic mice with or without subsequent homologous bone marrow transplants. The mice that received marrow homografts tended to survive without leukemia but died of a wasting disease; those that did not receive grafts had recurrence of leukemia. This led the investigators to suggest that the grafts had an antileukemic effect and stimulated similar experiments in humans. With the introduction of human leukocyte antigen (HLA) typing and matching,[126] Thomas and colleagues[127] achieved successful treatment of leukemia by myeloablation with total-body irradiation and chemotherapy and subsequent marrow transplantation from an HLA-compatible sibling. Evaluation of the efficacy of this procedure relative to intensive chemotherapy alone for acute leukemia has been hindered by patient selection and lack of randomized comparative studies.[128] Also, the sequelae of the procedure in children, such as chronic graft-versus-host disease, multiorgan impairment, and growth failure, often preclude true cure (i.e., restoration of the capacity for normal growth, development, and health as well as freedom from leukemia). On the other hand, experience demonstrated that some types of leukemia were not curable by chemotherapy alone. Replacement of bone marrow by myeloablation and histocompatible transplant was successful in eliminating chronic myeloid leukemia[129] that otherwise was only palliated by chemotherapy with myleran[130] or hydroxyurea.[131] The same was true for some cases of juvenile myelomonocytic leukemia, myelodysplasia/myeloid leukemia associated with chromosomal monosomy 7, and acute myeloid leukemia that failed to respond to intensive chemotherapy or relapsed despite it.[132–134] Evidence, again from non randomized comparisons, was reported that suggested an advantage of marrow transplantation in eliminating leukemia from children with acute lymphoid leukemia who develop hematologic relapse during chemotherapy,[135] But this remains controversial.

In the 1980s, a new class of agents, biological response modifiers, became available. One of them, alpha interferon, was shown by Talpaz and colleagues[136] in 1986 to produce remissions of chronic myeloid leukemia, some complete, both hematologic and cytogenetic, and enduring.[137] Children with adult-type chronic myeloid leukemia had similar responses.[138] This offered an alternative to myeloablation and marrow transplantation.

The conclusion in the 1980s that leukemia was a genetic disorder and observations that drugs effective in curing leukemia modified DNA suggested that chemotherapy might focus on genetic targeting.[75, 139] In 1988, Huang et al.[140] reported the differentiation of acute promyelocytic leukemia with resultant complete remission after administration of all-trans-retinoic acid (tretinoin). Subsequently, the genetic defect in acute promyelocytic leukemia was linked with an abnormal intranuclear retinoic acid receptor.[141] When tretinoin was combined with conventional cytotoxic chemotherapy, the cure rate was significantly increased.[142] This was the first instance of successful differentiation-inducing therapy of a human cancer, the first successful use of a vitamin to treat a human cancer, and the first specific targeting of a therapeutic agent to a cancer-associated gene rearrangement. This discovery was a major stimulant to searching for other methods of genetic targeting in the leukemias associated with specific gene rearrangements, as described in other chapters of this text.

In summary, the past 34 years of clinical investigation to identify curative treatment of childhood leukemia have

been a mixed success with wide variations in cure rates. These variations not only reflect differences in leukemia cell morphology, immunophenotype, and genotype, as well as the extent of leukemia, but also in the economic status, ethnicity, residence, and nutrition of the patients. The cost and complexity of curative leukemia therapy severely limit its usefulness, placing it beyond the reach of the majority of the world's children who need it.[143] Another and perhaps increasing problem are the serious adverse late sequelae of treatment with alkylating agents, anthracyclines, epipodophyllotoxins, radiotherapy, and allogeneic transplantation of hematopoietic cells, discussed elsewhere in this text (see Chapter 24).

Supportive therapy

During the 100 years between Virchow's establishment of leukemia as an entity and the advent of alkylating agents, comforting the patient with narcotics and human empathy was the first consideration. When ionizing radiation was introduced in 1903, it became an important palliative agent for relieving local bone pain and obstructive masses as well as reducing white blood cell counts.[77] Since chemotherapy was introduced in the 1940s, radiation has remained important for palliation of painful lesions as well as for curative therapy in management of extramedullary relapse in the meninges and testes and in myeloablation prior to marrow transplantation.[127, 144, 145]

In 1828, Blundell[146] reported a successful direct blood transfusion in a woman with postpartum hemorrhage. However, severe reactions discouraged further use. Landsteiner's[147] identification of human blood groups in 1901 enabled safer blood transfusion. During World War I, Rous and Turner[148] discovered that a citrate dextrose solution and cold would preserve red blood cells. Robertson,[149] an American Army surgeon who had recently worked with Rous,[150] used this solution and packing boxes containing ice to preserve human red blood cells for prompt transfusion of wounded soldiers near the battlefront.

For children with acute leukemia, the introduction of the hospital blood bank in 1937 was the first step in prolonging their lives.[151] By the late 1940s, blood transfusions together with the newly available antibacterial agents became generally accepted as a way of maintaining life while families tried to adapt to the prognosis and begin their grieving.

In 1954, with the advent of plastic blood transfusion and transfer bags and the use of the refrigerated centrifuge, platelet transfusions became available to control thrombocytopenic bleeding.[152,153] This resulted in a remarkable reduction in hemorrhage as a cause of death. Platelet transfusions also provided time for antileukemia drugs to produce remission, especially in patients with acute myeloid leukemia, and this led to increased rates of remission induction. Finally, the availability of platelet transfusions allowed administration of higher or more prolonged dosages of hematosuppressive agents because one could tide patients through periods of drug-induced thrombocytopenia.

When effective chemotherapy was first employed in acute leukemia, rapid lysis of leukemia cells often resulted in serious and occasionally fatal metabolic disturbances, especially in florid leukemia with high white blood cell counts or massive organ involvement. The introduction of allopurinol, a synthetic inhibitor of xanthine oxidase, along with skillful fluid and electrolyte therapy, did much to solve this problem.[154]

As children survived longer in remission, the immunosuppression caused by chemotherapy was more evident. Varicella became a major problem, particularly with prednisone therapy.[155,156] Many children died of severe disseminated varicella and others had treatment interrupted for long periods with consequent increased risk of relapse. With recognition that varicella and herpes zoster were caused by the same virus, plasma from adults convalescing from zoster was used both for treatment and for prevention in recently exposed children. After convalescent plasma was found effective for prevention or modification, varicella-zoster immune globulin (VZIG) was prepared and demonstrated to be effective also.[157] The availability of VZIG and education of parents and teachers about the hazard of varicella zoster infection were a major advance in reducing mortality, morbidity, and treatment interruption in exposed children. However, the third contribution of Gertrude Elion to children with leukemia, the introduction of acyclovir in 1980, was perhaps more important.[158,159]

Shortly after intensive multiagent therapy was introduced for acute leukemia at St. Jude Children's Research Hospital, a peculiar pneumonia began to appear in many of the children. At first it was called "St. Jude pneumonia" and thought to be related to drug toxicity, viral infection, or both. However, postmortem study of the lungs and pulmonary needle aspiration in patients and methenamine silver nitrate staining revealed *Pneumocystis carinii* organisms.[160] An institutional epidemiologic study performed in collaboration with the federal Communicable Disease Center (CDC) indicated that the disease was solely related to immunosuppression

of the patients and not to contagion.[161] Again, this disease became a major limiting factor in treating children with acute leukemia because of its occurrence during remission, its mortality and morbidity, and the consequent interruption of chemotherapy, especially in critical early months of treatment. Pentamidine isethionate was used to treat infantile Pneumocystis pneumonia in Europe but it was unavailable in the United States.[162] It had to be imported from France with Food and Drug Administration approval for each diagnosed case. Subsequently, the CDC obtained an investigational new drug permit that not only expedited therapy, but eventually was the mechanism by which the acquired immunodeficiency disease syndrome was recognized in San Francisco. Finally, the brilliant studies of Hughes and colleagues,[163] first in mice and then in patients, demonstrated the value of trimethoprim and sulfamethoxazole (cotrimoxazole) not only in treatment but, more important, in prevention of the disease.

Early in the combination therapy of acute leukemia, severe and sometimes fatal bacteremia, particularly with gram-negative bacteria, especially *Pseudomonas aeruginosa*, was a major obstacle.[164] Bodey and associates[165] showed that neutropenia was the major reason for these infections, although mucositis was an important contributor. They identified critical levels of neutrophils for control of the infections and demonstrated the need for prompt initiation of appropriate antibiotics in patients with fever and severe neutropenia. As effective aminoglycoside antibiotics became available in the 1960s and were used appropriately, mortality and morbidity due to gram-negative bacteremia declined, resulting again in better survival of children with acute leukemia. Infections with resistant gram-positive cocci have become a problem in the past 20 years, prompting the greater use of vancomycin in patients with staphylococcal or enterococcal infections and neutropenia.[166]

The immunosuppression and mucositis due to chemotherapy, radiation, and poor nutrition in children with leukemia also encouraged serious and sometimes fatal mycoses.[167] The introduction of amphotericin B in 1958[168] and of fluconazole in 1990[169] represented significant advances in controlling these infections. However, some mycoses such as aspergillosis and mucormycosis remain resistant to treatment and are major causes of mortality, especially in children with prolonged neutropenia who are receiving extensive antibiotic therapy (see Chapter 25).

Psychosocial issues became more important as children began to survive longer. Farber and associates[87] recognized early the need for "total care" of children with acute leukemia. In 1964, Vernick and Karon[170] introduced truthfulness in communicating with the children. Anticipating the significance of survival quality, Soni and Colleagues[171] pioneered longitudinal study of the neuropsychological consequences of acute leukemia and its treatment. Other late effects have also been studied extensively with the goal of defining the human cost/benefit ratio for each element of leukemia therapy (Chapter 24).

Lessons from the history of leukemia

The value of history is not just in savoring the past but in appreciating how it illuminates the present and guides us into the future. Several lessons can be learned from the study of the history of leukemia, particularly childhood leukemia. One is the importance of heeding new facts and listening to new ideas and hypotheses. At each point in the history of leukemia there have been instances of lost time and opportunity because of unreasoned resistance to innovation. Ten years after Virchow's description of leukemia and its verification by others, its existence was still denied by many. Videbaek's 1947 report of familial risk of leukemia was largely rejected on statistical grounds, although the risk became apparent subsequently. In 1958, 8 years after his pivotal discovery, Gross was still criticized for describing the viral etiology of a mouse leukemia; in fact, the director of a large cancer research center threatened to dismiss anyone who tried to initiate study of leukemia viruses. Twenty years elapsed between the establishment of a battlefront blood bank and the first blood bank in an American hospital. When antifolate and antipurine drugs were first introduced, many hematologists and pediatricians refused to prescribe them because they were "too toxic." Into the 1960s some parents were advised and students taught to withhold chemotherapy from childhood leukemia patients: "let the children die in peace." Throughout the 1960s proposals to treat childhood acute lymphoid leukemia with curative intent, using combination chemotherapy and radiotherapy, were turned aside by leaders of cooperative pediatric leukemia groups, even when presented with promising pilot data. In 1996 there was persistent resistance to using new knowledge of the biology and pharmacology of acute lymphoid leukemia to select treatment.[172] It is important for physicians and scientists to be open to new thinking that challenges conventional wisdom and ways.

Another lesson is the significance of the case report describing a patient and what the patient taught the physician. Virchow's case report of leukemia in 1845,

Lissauer's description of a patient whose leukemia responded to arsenious oxide, Brewster and Cannon's observation of leukemia in a child with Down syndrome, and Gloor's patient who was cured of leukemia after arsenious oxide, mesothorium, irradiation, and sibling blood transfusions eventually led to detailed knowledge of leukemia morphology and biology, curative therapy, and study of genetic mechanisms.

A third lesson is the need to encourage rather than dampen speculation in spoken and printed discussion. Kellett's idea that the residential aggregation of leukemia cases in Ashington might reflect an infectious agent, widespread but of low infectivity, remains viable, although statistical significance of time-space clustering is dubious. Equally important, however, is the need to clearly identify speculation and to require adequately controlled, scientifically sound investigations before drawing conclusions. Many children with acute leukemia were subjected to BCG injection on the basis of an uncontrolled study before appropriate investigations demonstrated its lack of efficacy.[173–175] The relative value and risk/benefit ratio of allogeneic bone marrow transplantation for children with most types of acute leukemia remains undefined because properly randomized prospective comparison with optimal treatment omitting marrow transplantation has not been performed.[128]

The most important lesson is the need to encourage original investigator-initiated research of leukemias by clinicians and scientists working together, exchanging ideas and coordinating clinical observations with biological experimentation. For example, after Gross heard a lecture by Gilbert Dalldorf on the use of newborn mice to identify coxsackievirus, he switched to newborn mice as subjects of his experiments and discovered the first mammalian leukemia virus. Farber's impression that folic acid accelerated leukemia encouraged development of antifolates and the first effective treatment for childhood leukemia. Robertson's knowledge of red blood cell preservation gained at the Rockefeller Institute enabled him to initiate blood banking on a Belgian battlefront. Borella's observation that children with thymomegaly had a more aggressive lymphoid leukemia and his identification of thymic cell leukemia as a distinct entity led to immunophenotyping and initiated classification of leukemia by biological function.

It is also important that clinical and laboratory researchers be free to think independently and to pursue goals as they see fit with minimal intervention by managers and committees. There is an anecdote that an accomplished senior leukemia researcher was asked by a site visit committee for his 5-year plan. He is said to have responded: "Five years? I don't know what I will do this afternoon. I haven't looked at my mice today."

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