Childhood Leukemias

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1 Historical perspective of leukemia

1.1 Introduction

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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 30 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.

1.2 Description of leukemia

Although the first description of a patient with leukemia was published in 1827,2 it was not until 1845 that Virchow3 in Germany (Fig 1.1) and Bennett4 and Craigie5 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. He also proposed his cellular theory of the origin of leukemia, a concept basic to current understanding of the disease. The following year, acute leukemia was described by Friedreich,7 and in 1878 Neumann8 established the existence of myelogenous leukemia. The close relation between lymphomas and leukemias was defined by Turk9 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

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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 (ALL and AML) 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 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 It also became possible to use archived neonatal Guthrie blood spots to trace back the fetal origin of many childhood leukemias.17–24

In 1973, Borella and Sen25 (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.26 As monoclonal antibodies to leukocyte cell surface antigens were developed, further immunophenotypic classification of leukemia cell populations became possible.27

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.28–30 Recently, the World Health Organization published a new classification of leukemia based on the advice of numerous experts.31,32

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Whether its complexity will be justified by more precise diagnosis, better understanding and improved prognosis is uncertain.

During the past 30 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.–39 For example, children with trisomy 21 (Down) syndrome have a high incidence of leukemia, especially acute megakaryocytic leukemia.38 They also have twice the cure rate of other children with acute myeloid leukemia when treated with chemotherapy.39 The extra 21 chromosome introduces not only increased vulnerability but also better curability. Hispanic youngsters have a high frequency of acute promyelocytic leukemia.40 Host genetic polymorphisms with regard to enzymes such as thiopurine methyltransferase that make available, activate, or detoxify antileukemic drugs are important.41,42 Genetic polymorphisms may also play a role in susceptibility to leukemia among persons exposed to environmental leukemogens or prone to dietary deficiency of folic acid.43,44 Malnutrition, poverty, and underprivileged ethnicity are associated with low cure rates.33–37 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 this disease by creative, industrious, and practical clinical investigators.

1.3 Causation of leukemia

The search for the causation of leukemia 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 and varying from cell type to cell type and from one patient to another. Recent studies suggest that childhood leukemia is initiated during fetal life. Rearrangements of either leukemia-associated genes or immunoglobulin heavy-chain genes in childhood leukemia cells have been identified retrospectively in stored neonatal Guthrie blood spots.17–24 However, the frequency of leukemia-associated gene rearrangments, such as TEL-AML1, in surveys of blood spots far exceeds the incidence of childhood leukemia. This indicates that the gene rearrangement alone is insufficient to cause leukemia. Other factors must be contributory.

1.4 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’s45 transmission

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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 Gross46 (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. 47–80 All were characterized as retroviruses. These single-stranded RNA viruses produce DNA polymerase and integrase, which reverse transcribe the viral RNA genome to DNA and integrate it into the cellular genome. This can result in neoplastic transformation of the cell with or without virus production. In addition, two large DNA viruses of the herpes group were associated with leukemia: Marek disease virus in birds and Epstein–Barr virus (EBV) in B-cell lymphoma/leukemia of African children (Burkitt lymphoma).51,52 Since both EBV-positive and EBV-negative B-cell lymphoma/leukemia have comparable gene rearrangements and postulated mechanisms of leukemogenesis, it is doubtful that the virus is causative.53 Extensive attempts to identify leukemia viruses in children with B-precursor, T-cell, myeloid, and temperate zone B-cell leukemia have been unsuccessful.54 However, the critical experiments that led to identification of murine and feline leukemia viruses, injection of newborn of the same species, cannot be performed.

Despite the failure to identify causative leukemia viruses in children with leukemia, some epidemiologic characteristics have been interpreted in favor of an infectious cause. In 1917, Ward12 reviewed 1457 cases of acute leukemia and concluded that the weight of evidence was against infection. In 1942, Cooke55 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 Kellett56 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 temporospatial proximity of children with leukemia were reported from Erie County, New York; Niles, Illinois; and Northumberland and Durham, United Kingdom,57–60 but study elsewhere has failed to confirm significant aggregation or other evidence of communicability.61,62 Also cited to support the infection hypothesis was the lower incidence and younger age of acute leukemia in children of lower income families.57 It was speculated that this could fit the pattern of infectious diseases such as paralytic poliomyelitis, in which early exposure and maternal immunity contribute to the appearance of disease at an earlier age and less frequently in underprivileged children. More recently, Kinlen and colleagues63 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 infectious process.

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Greaves and associates64,65 have further modified and expanded Kellett's hypothesis based on a newer understanding of the biology of childhood leukemia and international epidemiologic data. In summary, infectious causation of childhood leukemia remains only a hypothesis.

1.5 Physical causes

Although ionizing radiation probably induced leukemia in Marie Curie, its leukemogenic effects in radiologists only became quantified in 1944.66 In 1952, studies of Japanese children who survived atomic bombing demonstrated a marked increase in acute leukemia, both lymphoid and myeloid.67 Subsequently, Simpson et al.68 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.69,70 The most recent evidence suggests that low-dose radiation induces a transmissable genetic instability in hematopoietic stem cells.71 This results in diverse chromosomal aberrations in their progeny many cell divisions later.

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. However, as long as nuclear weapons continue to exist, radiation remains a potential cause of leukemia.

1.6 Chemical causes

In 1928, Delore and Borgomano72 reported a patient with acute leukemia associated with benzene intoxication. Subsequently, numerous reports confirmed that benzene can produce myelodysplasia and acute myeloid leukemia.73,74 A dose–response relationship was recently found in China.75 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.76 Smith has proposed that the phenolic metabolites of benzene are converted to quinones that produce DNA strand breaks, topoisomerase # inhibition and mitotic spindle damage in hematopoietic cells.77

In recent years folic acid deficiency has become associated with the causation of childhood leukemia. An unconfirmed case control study in Australia78 suggested a protective effect of maternal folate supplementation against the risk of childhood B-precursor ALL. In both

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children and adults, genetic polymorphism of 5,10–methylenetetrahydrofolate reductase, resulting in loss of this enzyme's activity, appears to reduce the risk of some forms of ALL.44 The suggested mechanism is the increased availability of methyl groups from the folate cycle for conversion of uracil to thymine. This reduces the possibility of uridine incorporation into DNA and consequent genomic instability. Transfer of methyl groups by way of the folic acid cycle is essential to purine synthesis and the suppression of untimely gene expression as well as the methylation of uracil to form thymine. Defects in the folic acid cycle produced by dietary deficiency, impaired absorption or transport, antifolate agents, genetic polymorphism or exposure to nonphysiologic methylating agents, such as the pesticide methyl bromide, might contribute to the pathogenesis of leukemia.

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 topoisomerase #, especially etoposide and teniposide, were found to be leukemogenic in children, most often producing acute leukemia characterized by MLL gene fusions.79,80 This observation of the role of topoisomerase binding is consistent with the Smith hypothesis77 for the mechanism of benzene leukemogenesis. A recent study demonstrated that children who had acute leukemia with MLL fusion genes were more likely to have low function of an enzyme that detoxifies quinones.43 Another study revealed an association between this leukemia genotype and maternal exposure to certain drugs and pesticides.81 These data suggest that both maternal exposure to potential leukemogens and fetal genetic polymorphisms might contribute to the induction of childhood leukemia.

1.7 Genetic causes

A genetic cause of leukemia was first suggested in 1876 by Hartenstein,82 who observed lymphoid leukemia in a cow and its mother and speculated that it was hered-itary. In 1931, strains of mice with high frequencies of leukemia/lymphoma were identified,83 and by 1935 an inbred strain with a 90% incidence of lymphoid leukemia was produced.84 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 the familial incidence of human leukemia. A 1937 report85 of three families with multiple cases was followed by a large study by Videbaek86 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 195787 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 1928,88 the high concordance rates for leukemia in like-sex and monozygous twins were uncovered in 1964 by MacMahon and Levy.89 Recent studies by Ford et al.18 using genetic markers indicate that twin concordance probably results from intrauterine metastases from fetus to fetus.

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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 193090 and subsequent similar reports led to a national survey in 1957 by Krivit and Good38 that demonstrated the high incidence of leukemia in this trisomy disorder. Over the past 40 years, childhood leukemia has become associated with numerous constitutional genetic disorders, including primary immunodeficiency diseases, chromosome instabilities, and inherited cancer syndromes.91

Observation of the distinct Philadelphia chromosome associated with chronic myeloid leukemia by Nowell and Hungerford14 in 1960, and Rowley's discovery15 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 proto-oncogene abl was found to be relocated from chromosome 9 to 22 in chronic myeloid leukemia, to form its characteristic hybrid gene, BCR-ABL.92 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/leukemia of children.93 By the mid-1980s, there was a clear consensus that leukemia was a somatic genetic disorder of hematopoiesis.94 More important, these translocations became models of the two general mechanisms of leukemogenesis by chromosome/gene rearrangements. The BCR-ABL hybrid gene gives rise to a BCR-ABL fusion protein with excessive and promiscuous tyrosine kinase activity.95 This leads to the activation of myriads of proteins along several signaling pathways and reduced cell adhesion, increased mitoses and inhibition of apoptosis – conditions favorable to leukemogenesis, either chronic myeloid or acute lymphoblastic. The second mechanism is exemplified by the translocation of the MYC oncogene of chromosome 8 to the immunoglobulin heavy-chain region of chromosome 14.96 The consequence is remarkably increased expression of the MYC gene, whose translation product dimerizes with the normal MAX protein. This drives cell replication at the expense of differentiation. B-cell lymphoma and/or leukemia results.

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. The more recent insights about genetic polymorphisms, folic acid and the consequences of leukemia-associated gene rearrangements have introduced new potentials for the prevention and treatment of childhood leukemias.

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1.8 Treatment

1.8.1 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, Lissauer97 reported a patient with leukemia whose disease remitted after she received Fowler 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, Senn98 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.99 Based on pathology reports of hematosuppression in mustard gas victims on the Western Front in World War I100 and at the Bari Harbor disaster in World War #,101 nitrogen mustard was synthesized and tested in animals and then patients with lymphoma and leukemia in 1943.102,103 Temporary partial remissions were produced, but toxicity was considerable, especially in patients with acute leukemia.

The chemical identification of folic acid in 1941104 as an essential vitamin, its synthesis in 1946,105 and the reversal of megaloblastosis by its administration106 raised the question of whether it might be useful in the treatment of acute leukemia. In 1947, Farber (Fig. 1.4)107,108 and colleagues gave folic acid (pteroylglutamic acid) to children with acute leukemia and were impressed that it might have produced acceleration of the leukemia. Subsequently, a 4-amino antimetabolite of folic acid, aminopterin, synthesized by Seeger et al.,109 was provided to Farber for use in children with acute leukemia. Many of them achieved complete clinical and hematologic remissions that lasted for several months.107 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 leukemia.110 Cortisone and its synthetic analogue, 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 analogue synthesis, and structure-activity relationships by Elion and Hitchings111 (Fig. 1.5) in the 1940s and early 1950s. In 1953, a report by Burchenal and associates112 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-N10-methy1-folate analogue that succeeded aminopterin.108 The enthusiasm generated by the discovery of three effective drugs for childhood acute leukemia in 5 years was dampened, however, by

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the realization that virtually all of the patients eventually died of resistant leukemia or its complications.108 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 prodrug analogue of nitrogen mustard, cyclophosphamide, with less toxicity for platelet production, was introduced and later shown to have value in lymphoid leukemia.113 In 1962, vincristine, an alkaloid from the periwinkle plant with a unique mode of action, was shown to induce complete remissions of childhood lymphoid leukemia resistant to other agents.114 But, as with all the other agents, remissions were temporary and relapse with resistant leukemia ensued.

1.8.2 Curative therapy

The first cure of leukemia was described in 1930 by Gloor,115 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 Murphy116 collected 36 cases of 5-year cures of treated childhood acute leukemia by a questionnaire survey of hematologists. Zuelzer117 reported a 3% 5-year cure rate in children with ALL who received cyclic chemotherapy with prednisone, methotrexate, and mercaptopurine. A 5% 5-year cure rate was reported by Krivit et al.118 for sequential or cyclic chemotherapy of ALL with these agents in a Children's Cancer Group study. Stimulated by the studies of Skipper et al.119 and Goldin et al.120 in treating mouse leukemia with chemotherapy, Leukemia Study Group B121–123 used two-drug combinations and National Cancer Institute investigators124,125 used four-drug combinations that yielded similar low cure rates in patients with ALL. 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 in 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.94 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 antileukemic drugs,

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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 ALL was initiated in 1962. It consisted of four treatment phases: remission induction, intensification or consolidation, preventive meningeal treatment, and prolonged continuation therapy.94,126–128 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, pre-emptive 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.126–128 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 study129 compared full versus half-dosage continuation chemotherapy and demonstrated that, despite its toxicity, full dosage was required to achieve longer remission. 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 study1 was inaugurated in December 1967, in which the intensity of continuation chemotherapy was increased and higher-dose cranial irradiation combined with intrathecal methotrexate was used to treat the leptomeninges. Within 6 months, the superiority of this regimen was apparent, and a randomized comparative study of meningeal irradiation was initiated.130 Both the pilot study and the subsequent randomized study demonstrated a 50% cure rate for children with ALL 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 ALL in children.28 Intrathecal methotrexate alone failed to prevent meningeal leukemia in one study.131 However, Sullivan and associates132 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 75% were reported.28,133 National surveys in the United States and United Kingdom demonstrated marked reduction in childhood leukemia mortality.134,135 Much of this improvement was related to more

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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 antileukemic drugs was also important. These included cytarabine, a synthetic pyrimidine antimetabolite (1968),136,137 daunorubicin, a natural DNA-intercalating anthracycline antibiotic (1968),138 asparaginase, an enzyme synthesized by bacteria that lyses the essential amino acid asparagine (1967),139 and the epipodophyllotoxins etoposide and teniposide, topoisomerase-binding agents derived from the mandrake root.140 Modification of drug schedules, such as the intravenous administration of methotrexate in high dosages with delayed leucovorin rescue, was another factor.141 The definition of subtypes of ALL and the successful targeting of specifically designed chemotherapy in children with T-cell or B-cell leukemia or those otherwise at high risk of relapse with B-precursor leukemia have been important also.142,143

From the beginning of leukemia chemotherapy, the morphologic differences in response to chemotherapy were apparent. Although occasional patients with AML experienced remissions with 6-mercaptopurine or thioguanine, a 50% remission rate was first achieved in 1967 when thioguanine was combined with cytarabine.144 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 AML.145 More recent reports are more optimistic.146,147

In 1957, Barnes and Loutit 148 administered lethal doses (LD98) 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,149 Thomas and colleagues150 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.151 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. Treatment with very high dosage chemotherapy and radiotherapy and histocompatible

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hematopoietic transplant was often successful in eliminating chronic myeloid leukemia152 that otherwise was only palliated by chemotherapy with myleran153 or hydroxyurea.154 Success was reported in some cases of juvenile myelomonocytic leukemia, myelodysplasia/ myeloid leukemia associated with chromosomal monosomy 7, and AML that failed to respond to intensive chemotherapy or relapsed despite it.155–157 Evidence, again from non-randomized comparisons, was reported that implied an advantage of hematopoietic transplantation in eliminating leukemia from children with ALL who develop hematologic relapse during chemotherapy. 158

However, recent comparisons employing more acceptable analysis of results indicate no advantage over aggressive chemotherapy in children with ALL in first relapse and children with ALL that demonstrates rearrangements of the 11q23 chromosomal region.159–161 For children with newly diagnosed AML 6-year event-free survival is similar whether treated with transplant or chemotherapy. 147,162

In recent years the original concept of hematosuppression and transplant proposed by Barnes and Loutit148 has been rediscovered. Transplants are viewed as immunotherapy and success dependent on graft versus leukemia reaction, not myeloablation.163 Moderate chemotherapy without radiotherapy is often used instead of “megatherapy.” This reduces treatment-related mortality and morbidity and may improve eventual outcome. In the 1980s, a new class of agents, biological response modifiers, became available. One of them, alpha interferon, was shown by Talpaz and colleagues164 in 1986 to produce remissions of chronic myeloid leukemia, some complete, both hematologic and cytogenetic, and enduring.165 Children with adult-type chronic myeloid leukemia had similar responses.166 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.94,167 In 1988, Wang and colleagues (Fig. 1.6).168 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.169 When tretinoin was combined with conventional cytotoxic chemotherapy, the cure rate was significantly increased.170 This was the first instance of successful differentiation-inducing therapy for a human cancer, the first successful use of a vitamin to treat a human cancer, and the first specific targeting of a thera-peutic 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.

With the introduction of molecular diagnostic technology in the 1990s, it became possible to classify most childhood leukemias genetically.28–30 For example, TEL-AML1+ leukemia resulting from a t(12;21) translocation can only be identified by molecular technology in

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most cases.29 The advantage of genetic classification quickly became clear when Druker and colleagues171 showed that BCR-ABL leukemia, whether myeloid or lymphoid, could be effectively treated by blocking the tyrosine kinase activity of the BCR-ABL fusion protein. The agent currently used, imatinib mesylate, has replaced hematopoietic transplantation and alpha interferon as initial therapy for chronic myelocytic leukemia.172 It is also included in the treatment of BCR-ABL+ ALL. Although Southern blotting, the polymerase chain reaction and fluorescent in situ hybridization have been the mainstays of molecular genetic analysis of leukemia, the introduction of microarray techniques has been an important recent advance.173 With this method, one can predict the likely response to chemotherapy as well.

In summary, the past 40 years of clinical investigation to identify curative treatment of childhood leukemia have met with mixed success, as demonstrated by the wide variation in cure rates. This lack of uniformity reflects not only differences in leukemia cell biology and the extent of leukemia, but also the economic status, ethnicity, residence, nutrition and constitutional genetics 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.174 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 Chapters 30 and 31).

1.8.3 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.98 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 hematopoietic transplantation.150,175,176 In 1828, Blundell177 reported a successful direct blood transfusion in a woman with postpartum hemorrhage. However, severe reactions discouraged further use. Landsteiner's178 identification of human blood groups in 1901 enabled safer blood transfusion. During World War I, Rous and Turner179 discovered that a citrate dextrose solution and cold would preserve red blood cells. Robertson,180 an American Army surgeon who had recently worked with Rous,181 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.182 By the late 1940s, blood transfusions together with the newly available antibacterial agents became generally accepted as a way of maintaining life while

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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.183,184 This resulted in a remarkable reduction in hemorrhage as a cause of death. Platelet transfusions also provided time for antileukemic drugs to produce remission, especially in patients with AML, leading 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 leukemic 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, together with skillful fluid and electrolyte therapy, did much to solve this problem.185 More recently, recombinant urate oxidase (rasburicase) was developed as a more potent drug than allopurinol in the prevention and treatment of hyperuricemia.186 As children survived longer in remission, the immunosuppression caused by chemotherapy was more evident. Varicella became a major problem, particularly with prednisone therapy.187,188 Many children died of severe disseminated varicella, while 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.189 The availability of VZIG and the 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.190,191

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 Jungs and pulmonary needle aspiration in patients and methenamine silver nitrate staining revealed Pneumocystis carinii organisms.192 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.193 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 the critical early months of treatment. Pentamidineisethionate was used to treat infantile Pneumocystis pneumonia in Europe, but it was unavailable in the

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United States.194 It had to be imported 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 (Fig. 1.7) and colleagues,195 first in rats 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.196 Bodey and associates 197 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 bester survival of children with acute leukemia. Infections with resistant gram-positive cocci have become a problem in the past 25 years, prompting the greater use of vancomycin in patients with staphylococcal or enterococcal infections and neutropenia 198

The immunosuppression and mucositis due to chemotherapy, radiation, and poor nutrition in children with leukemia also encouraged serious and sometimes fatal mycoses.199 The introduction of amphotericin B in 1958.200 and of fluconazole in 1990.201 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 32).

Psychosocial issues became more important as children began to survive longer. Farber and associates.108 recognized early the need for "total care" of children with acute leukemia. In 1964, Vernick and Karon 202 introduced truthfulness in communicating with the children. Anticipating the significance of survival quality, Soni and Colleagues 203 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 Ieukemia therapy (Chapter 30).

1.9 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,

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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. In 1958, 8 years after his pivotal discovery, Gross was still criticized for describing the viral etiology of a mouse leukemia. 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 medical students taught to withhold chemotherapy from childhood leukemia patients: "let the children die in peace" 201 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 important knowledge of leukemia biology and treatment.

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.205-207 The relative lack of value and unfavorable risk/benefit ratio of hematopoietic transplantation for children with most types of acute leukemia has taken decades to clarify because proper comparison with optimal treatment omitting transplantation was not performed initially.

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 Coxsackie virus, 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

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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.

The long-term advantage of scientific freedom often exceeds the short-term gain of tightly restricted research. The late Robert Guthrie illustrates this. Assigned to provide microbiological assays of experimental antileukemic drugs, he deviated when he conceived the notion of using such an assay to screen heel-stick blood spots of newborn for high phenylalanine levels. His purpose was early detection of phenylpyruvic oligophrenia so that mental retardation could be prevented by dietary deletion of phenylalanine.17 In Order to continue this research, Dr. Guthrie was compelled to resign his position for a lesser one elsewhere. Not only did his work result in to day's highly successful neonatal screening programs, but 45 years later "Guthrie spots" are used to Crack fetal origins of leukemia. Good research benefits all eventually. 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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