Neoplastic Diseases of the Blood

FOURTH EDITION

EDITED BY

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The editors dedicate the fourth edition of this work to our families, to the hundreds of fellows we have trained, and to the thousands of patients we have had the privilege to care for over the decades.

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Preface

The fourth edition of *Neoplastic Diseases of the Blood* is long overdue, as evidenced by the tremendous progress made in our understanding of the nature of hematologic malignancies and their treatment since the third edition appeared in 1995. The fourth edition is current and up to date, draws heavily on recent references, and is designed, as were the previous editions, to be a readable encyclopedic resource for established hematologists and oncologists as well as for Fellows in those disciplines. Six new chapters are included in this edition, and all other chapters have been extensively revised and updated. The new chapters concern the epidemiology of chronic leukemias, molecular biology and cytogenetics of chronic myeloid leukemia, myelodysplastic syndromes, cytokines and signal transduction in multiple myeloma, umbilical cord stem cell transplantation, and HLA typing in hematopoietic cell transplantation. Some 112 authors from 4 continents, more than 50 new to this edition, have contributed their expertise to this work. This edition is divided into the same five sections found in earlier editions, each the primary responsibility of an editor: Chronic Leukemias and Related Disorders (John M. Goldman), Acute Leukemia (Peter H. Wiernik), Myeloma and Related Disorders (Robert A. Kyle), Lymphoma (Peter H. Wiernik), and Supportive Care (Janice P. Dutcher). Dr. Goldman is a new editor for this edition, and those of us who have served as editors previously are delighted to have him join us.

Our sincere hope is that patients with hematologic malignancies will benefit directly from this new edition. That hope is what drives us to take on and complete the huge task that is the creation of this book.

We wish to thank the publisher, Cambridge University Press, for assisting us in every way possible through all phases of the development of the book. Special thanks to Heidi Steinmetz Lovette, Editor, Medicine, and Dr. Richard Barling, Director, Medical and Professional Publishing, for guidance and support. Both were instrumental in bringing this project to completion.

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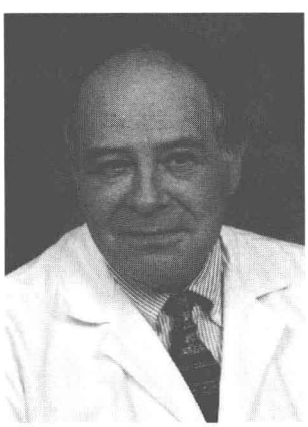

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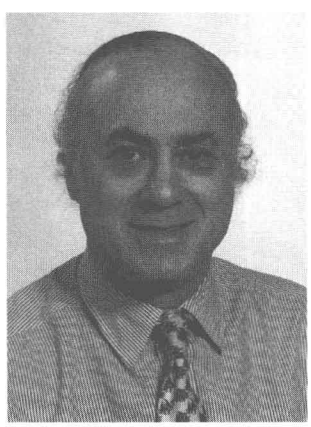

John M. Goldman

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SECTION ONE

Chronic Leukemias and Related Disorders

1

A History of the Chronic Leukemias

John M. Goldman and Myrtle Y. Gordon

Although chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) can be grouped together for some purposes, they differ in many ways, CML being a disease with well-defined progressive stages (chronic phase; acceleration; transformation) occurring in middle life, whereas CLL is a relatively indolent disease involving mainly the elderly. Whereas CML has well characterized molecular features, which can reasonably be assumed to be related to its pathogenesis, the cause of CLL is virtually unknown. The observations that have led to our current state of knowledge and ability to treat patients are the subject of this chapter (Table 1–1). Recent reviews on the history of CML have also been provided by Piller in 1997[1] and Geary in 2000.[2]

DEFINITIONS, CLASSIFICATION, AND CHARACTERIZATION

The recognition that the leukemias are an extremely heterogeneous group of diseases has developed progressively since the condition was first described and owes much to technological development over the past 150 years or so. Thus, the distinctions between the chronic and acute and between the myeloid and lymphoid leukemias did not emerge for some time. The postmortem characteristics of the blood first attracted the attention of the early observers of leukemia. According to Gunz and Henderson,[3] the first accurate description of leukemia was probably made by Velpeau in 1827,[4] although it is likely that leukemia had been seen as early as 1811.[5] This was followed by the observations of Donne[6] and of Craigie.[7] Nevertheless, the recognition of leukemia as a distinct entity is attributed to the virtually simultaneous reports of Bennett in Scotland[8] and Virchow in Germany[9] in 1845. These classic cases involved John Meredith, a 28-year-old slater from Edinburgh and Marie Straide, a 50-year-old cook, in Berlin. Both patients had been unwell for 1.5 to 2 years and their condition had progressively worsened, with increasing weakness, bleeding, and other problems. In both cases the remarkable features at autopsy were the large size of the spleen and the consistency of the blood, in particular the white cell content. Virchow used the term "weisses Blut" to describe the predominance of white cells in the blood and later, in 1847, proposed the term "Leukaemie." Bennett suggested "leucocythaemia." The first diagnosis of leukemia in a living patient was made by Fuller in 1846,[10] by which time Virchow had documented a further nine cases. The first reported case of leukemia in America was in a 17-year-old seaman in Philadelphia in 1852;[11] this was followed by several case reports, mainly from the Boston area.

Early attempts to distinguish different forms of leukemia included Virchow's distinction between splenic and lymphatic leukemias, each of which was associated with particular types of white blood cells.[12] This division is broadly equivalent to myeloid and lymphoid leukemias, with the important observation by Neumann in 1870[13] that the cells responsible for the so-called splenic leukemia were actually made in the bone marrow. Until 1889, when Ebstein first used the term "acute leukemia" on clinical grounds,[14] the disease was considered to be a chronic one. Ebstein also recognized the difference between *de novo* acute leukemia and "acutization" of the chronic disease. It rapidly became apparent that a diagnosis of acute leukemia carried an implication of very short-term survival, whereas patients with chronic leukemia could survive for a little while longer.

The next contribution to the description of the leukemias was provided by Ehrlich in Germany, who developed methods for staining blood cells in 1891.[15] This revealed immediately the differences in morphology between granulocytes and lymphocytes, a distinction that had previously been based only on microscopic examination of unstained granular and agranular cells with different nuclear shapes. Although these early studies provided the foundation for the morphological classification of the myeloid and lymphoid leukemias, they did not permit the discrimination of T cells and B cells. This information was not available until the 1960s.

Table 1–1. Milestones in the History of Chronic Leukemia

1845	Recognition of leukemia as a disease entity (probably CML)
1846	First diagnosis of leukemia in a live patient
1865	First therapy of CML: Fowler's solution
1891	Development of methods for staining blood cells
1895	Discovery of X-irradiation
1924	Recognition of CLL as a distinct clinical entity
1934	Malignant nature of leukemia established experimentally
1946	First effective chemotherapy for leukemia—nitrogen mustard
1960	Identification of the Philadelphia chromosome (22q$^-$)
1966	Realization that CLL is a disease of cell accumulation
1966	Introduction of leukapheresis in the treatment of CML
1973	Recognition of the reciprocal nature of the (9;22) translocation
1978	Introduction of autografting for CML
1982	First routine use of allografting for CML
1984	First description of the BCR gene in CML
1990	Demonstration that the *BCR-ABL* gene could cause a CML-like disease in mice.
1999	Introduction of the ABL tyrosine kinase inhibitor into clinical practice as treatment for CML

Abbreviations: CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia.

The first person to appreciate the role of the bone marrow may possibly have been William Shakespeare, when he wrote "Thy bone is marrowless, thy blood is cold." In 1878 Neumann realized that the leukemias originated in the bone marrow[16] and added myelogenous leukemias to the splenic and lymphatic leukemias described by Virchow. Ehrlich[15] identified a primitive cell type that he thought was ancestral to the lymphoid and myeloid cell lineages, and thereby probably made the first reference to the concept of a hemopoietic stem cell. The view that there are distinct hemopoietic cell lineages was later supported by Naegeli in 1900,[17] when he distinguished between myeloblasts and lymphoblasts.

During the late nineteenth and early twentieth centuries, many new terms were conjured up to describe a variety of leukemias, and there was some confusion over the relationship between different types of lymphoid neoplasm. However, Turk in 1903 recognized that there was a close connection between lymphoid leukemias and lymphomas (lymphosarcomata) and grouped together the chronic and acute leukemias and the lymphomas as the "lymphomatoses,"[18] a term that is roughly equivalent in meaning to the modern "lymphoproliferative disorders." Until the 1930s, however, there was controversy about the relationship between leukemia in particular and cancer in general. The malignant nature of the leukemias was only established when the disease was induced in rodents by the intramedullary injection of tar and other chemical carcinogens.[19,20] Descriptions of leukemic cells increased in sophistication with the development of special stains and phenotypic markers. The development of these tools led to the detailed definition of the chronic myeloid and lymphoid leukemias and to the description of the various types of transformation or "blast crisis" that ensue in CML. Nevertheless, the divisions made early on between myeloid and lymphoid and between chronic and acute leukemias were remarkably similar then to those used today.

The study of cytogenetics developed during the 1950s, and in 1956 the number of human chromosomes in each normal cell was established as 46. The discovery of the Philadelphia (Ph) chromosome in 1960 by Nowell and Hungerford[21] provided a marker that proved to be pathognomonic for the disease and heralded a new era. With this marker, it was possible to demonstrate that CML is a clonal disorder originating in a hemopoietic stem cell. Moreover, the development of clonogenic assays for hemopoietic progenitor cells in the 1970s enabled Fialkow and colleagues[22] to demonstrate the clonal origin of leukemic progenitor cells from different lineages by study of individuals who were heterozygous for the isoenzymes of glucose-6-phosphate dehydrogenase (G6PD).

During the 1970s much attention was paid to the kinetics of leukemic cells, and it was generally concluded that the proliferating granulocytic compartment divides less actively in CML bone marrow than in normal bone marrow. A variety of indices were established to describe granulopoiesis in CML, and the likelihood that there was an element of residual regulation of granulopoiesis became appreciated.[23,24]

De Klein et al.[25] found that the Ph translocation involved the movement of the normal human counterpart of the murine *v-abl* oncogene from chromosome 9 to chromosome 22, and one year later the reciprocal translocation of genetic material from chromosome 22 to chromosome 9 was identified.[26] The translocation results in the formation of a fusion gene, *BCR/ABL,* on chromosome 22. Because of variability in the breakpoints in the *BCR* gene and the relative constancy of the ABL breakpoint, exon 2 of the *ABL* gene can be linked upstream to exon 2 of BCR (b2a2 junction) or to exon 3 of BCR (b3a2 junction). Both rearrangements result in the production of hybrid messenger RNA and a hybrid BCR/ABL p210 protein tyrosine kinase.[27] With today's molecular technology, it is possible to detect very small numbers of cells expressing the *BCR/ABL* gene using the polymerase chain reaction (PCR),[28] and this has obvious implications for the monitoring of disease and the management of patients. However, the biological effects of p210 expression in CML remain an enigma and a major challenge to cell and molecular biologists.

Chronic lymphocytic leukemia is an acquired B-cell disorder whose clonal origin can now be demonstrated by detecting unique rearrangements of immunoglobulin genes by Southern blot hybridization. The recognition of CLL as a distinct clinical entity can be dated back to the turn of the century. Several authors provided case reports and clinical data that distinguished CLL from lymphoma. Osler in his text *The Principles and Practice of Medicine*[29] recounted his experience of the disease at the Johns Hopkins Hospital in Baltimore, where CLL accounted for 22 percent of all leukemias and survival times of 3 to 11 years were noted. In 1924, Minot and lsaacs[30] published the first comprehensive clinical report on a series of 80 patients, which according to one author,[31] marked the formal emergence of CLL as a distinct and well described clinical entity.

There followed 50 years of definition and clinical description of CLL, which assisted clinical hematologists in their diagnosis, understanding, and treatment of the disease. Some of the most important contributions of this era were made by Galton in 1966[32] and Dameshek in 1967,[33] who realized that CLL is a disease of cell accumulation as a result of a reduced cell death rate, rather than a proliferative disease.[34] This reduction in cell death rate is thought to be due to suppression of apoptotic mechanisms[35] and may be associated with dysfunction of the p53 gene. The tumor suppressor gene BCL-2 also is known to inhibit apoptosis, and small lymphocytic malignancies, including CLL, express moderately high levels of the corresponding bcl-2 protein.[36]

It was not until 1972 that the presence of immunoglobulins on the surface of CLL cells was first demonstrated, thus confirming CLL as a disease of B lymphocytes.[37,38] Thereafter the development of methods for detailed immunological phenotyping led to an accurate description of the phenotype of CLL cells, which are arrested at an intermediate stage of B-cell differentiation.[39,40] Cytogenetic studies revealed that there is no "marker" abnormality in CLL equivalent to the Ph chromosome in CML, but several structural chromosome abnormalities occur consistently in varying proportions of cases. It is now widely recognized that there is an inverse correlation between the extent of chromosome abnormalities and survival in CLL.[31]

The precise etiology of CLL remains uncertain but studies identifying a tendency for CLL to occur in families suggest that