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白血病

Leukemia

Seventh Edition

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Leukemia

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PREFACE

The first edition of this textbook appeared in 1958 as a monograph written entirely by William Dameshek and Frederick Gunz. It was authoritative and almost totally anecdotal. Very little science, preclinical or clinical, was included. Rather, there was extensive review of the "state of the art" concerning the diagnosis, pathogenesis, and treatment of the group of diseases under the rubric *leukemia*. As presented, it reflected both the extent of knowledge of the disease and the mode of medical education of that period. The two authors, a famed Boston professor and his not-yet famous associate (a visiting scholar from New Zealand), provided their readers with the sum of their knowledge and experience with the disease(s). The book was enthusiastically received, and it stimulated many young physicians to enter the then sparsely populated fields of hematology and oncology and young scientists to seek to unravel the mysteries of this poorly understood disorder.

The progress made since that time is the subject of the current volume. No two individuals could possibly provide the perspective and summarize the knowledge to the extent that Dameshek and Gunz succeeded in doing in 1958. The current seventh edition has three editors and 47 authors. Other differences are yet more striking. Virtually every chapter in this seventh edition contains data not available in 1958. Even much of the history chapter could not have been written then; it was in the process of being made. The clonal nature of leukemia was only speculative at that time, before the recognition of the Philadelphia chromosome. The existence of both T and B lymphocytes was not yet domesticated. Diagnosis depended solely on clinical features and stained blood smears. Treatment was based on a handful of drugs, and "cures" were so infrequent that a worldwide survey could identify fewer than 100 5-year survivors. As a consequence, most medical personnel, and to an even greater extent the public at large, considered the diagnosis of leukemia a death sentence, and whether to subject a patient to antileukemia drug thereapy was widely debated and heatedly contested. Even patients who achieved remission often found themselves ostracized by friends and schoolmates and were denied employment or admission to college. Surgical procedures were postponed or rejected on the basis of the poor prognosis perceived for the disease.

Currently for the majority of patients the situation is markedly different. Curative treatments exist, supportive measures ensure a degree of succor to almost all, and society recognizes and encourages the reintegration of leukemia patients into society. Over the last four decades, diagnostic, therapeutic, and prognostic maneuvers have been derived from rigorously controlled, prospective clinical studies of large numbers of patients. Recently there has been a second paradigm shift, from empirically based management to diagnosis and treatment plans derived directly from molecular genetic knowledge. Although these specifically targeted therapies are so far restricted to only a few forms of leukemia, their success encourages optimism for future progress in this group of diseases so recently regarded with despair.

This edition is dedicated to all those whose energies and dedication, or suffering and courage, have united to make this progress possible; and to those in the twenty-first century who continue to strive toward the goal of eradication or prevention of leukemia for all patients.

Edward S. Henderson, M.D.
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PREFACE TO THE FIRST EDITION

LEUKEMIA, like cancer and poliomyelitis, has been classed as one of the "dread diseases." Without doubt, it represents the most important single problem in hematology. In the United States alone it kills at least 10,000 annually, many of them bright, active children or intelligent men and women in their prime of life. Most statistics indicate that the disease is on the increase, particularly in the last three decades of life. Whether or not this is actually true or due simply to more case studies and better recognition, there can be no question regarding the seriousness of the problem and the necessity to cope with it by all available means.

There have been many thousands of articles written about leukemia but the paucity of books on the subject is amazing. Forkner's text of 1938 was encyclopedic in its scope and for many years remained almost the only central source. The enormous resurgence of interest in the disease, brought about in large measure by the possibility of achieving at least temporarily beneficial results with various chemicals, has led to a quest for more precise knowledge of the disease: its character, the nature of the leukemic cell, the pathophysiology of such features as the anemia, hyperuricemia, the hemorrhagic state, etc. Etiologic factors, previously unknown, have come to the surface, and today there is great talk of the viruses and much statistical evidence for the leukemogenic effects of ionizing radiation. The empirical nature of most of our therapy, even that with the newer antimetabolic and cytotoxic agents, and its eventually unsatisfactory characteristics, have naturally led to an increasing inquiry into the more fundamental aspects of cellular growth and proliferation.

What is leukemia? Is it a reactive disturbance, or is it neoplastic? Does it represent a cellular reaction to an infectious or other agent, or does a harmful mutation take place, leading to an abnormal type of unusually rapid leukocyte proliferation? The leukemic cell seems to have some rather characteristic features as we examine it, but when one tries to analyze it feature by feature, chemical by chemical, the apparent differences between normal and leukemic cells become less and less pronounced. Perhaps this is why, in treating leukemia, we are always limited by what the chemical or other agent does to the *normal* cells; the action upon both leukemic and normal cells is so much alike.

This work on leukemia is limited almost entirely to a consideration of *human* leukemia. Not that mouse leukemia and fowl leukemia are not important; they are of utmost importance, particularly from the investigational aspect. We present in this monograph a rather personal account, not only of our own interests in this field but of what we think the practitioner (internist, pediatrician, pathologist and clinical pathologist) may be interested in. The work is by no means encyclopedic nor is it a textbook, although sometimes, as in the clinical descriptions, it must partake of some of the features of the latter. There is probably more emphasis on certain aspects than on others, again an indication of our special fields of interest: etiologic agents, the myeloproliferative syndromes, therapy. Nevertheless, we believe that there is presented in these pages a fairly comprehensive picture of the present state of our knowledge (some might say "ignorance") of leukemia. We realize full well that this is but an interim report and that perhaps in a short time, whether it be a year or a decade, a revolution in understanding and control of the disease may well take place. Actually, the fact that one has a difficult time in defining leukemia may in itself be somewhat hopeful. Since there is no complete certainty that the condition is malignant, nor even what "malignancy" is, it is altogether possible that leukemia may eventually turn out to be a deficiency state or an immunologic reaction or a response to an infectious agent. Again, what we learn from leukemia, with its readily available blood and tissue cells, should certainly be of considerable value in the understanding of neoplastic disease in general.

This work could never have been completed without the help of many individuals. From our patients we have learned a great deal, particularly in courage and forbearance. From out colleagues, who have come to work with us from many lands and many parts of this country, we have gleaned much valuable information, and the give-and-take of our daily discussions has been of utmost value. We may single out a few who have worked with us on specific problems in this field: Drs. Mario Baldini, Boston; Luis Bergna, Buenos Aires; Marvin Bloom, Buffalo; Edmund W. Campbell, Boston; Jyoti Chatterjea, Calcutta; William H. Crosby, Washington, D.C.; Solomon Estren, New York; Henry Goldenberg, Toronto; Norma Granville, Hartford; Zacharias Komninos, New York; William McFarland, U.S. Navy, Bethesda, Maryland; Carlos Mesa Arrau, Santiago, Chile; Enrique Perez Santiago, San-

turce, Puerto Rico; Anthony Pisciotta, Milwaukee; Jack Rheingold, Washington, D.C.; Martin Rosenthal, New York; Fernando Rubio, Jr., Boston; Richard H. Saunders, Rochester; Laurence I. Schwartz, New York; Jay Silverberg, Pittsburgh; Karl Singer, deceased; Mario Stefanini, Boston; Asuman Unugur, Istanbul; Louis Weisfuse, Long Island, New York; Leda Zannos, Athens, Greece.

In addition, we wish to acknowledge with thanks the help of the following individuals, all of New Zealand: Drs. G. C. T. Burns, A. F. Burry, A. J. Campbell, A. M. Goldstein, R. F. Hough, J. B. Jameson, G. L. Rolleston, D. T. Stewart, and Messrs. S. E. Brooks and K. A. Donaldson.

Our secretarial staff headed by Miss Joyce Rock and including Mrs. Arlene Morris, Mrs. Mildred Seagraves and Miss Zelda Cushner, has somehow triumphed over a mountainous collection of drafts, copies, bibliographies, illustrations, made all the more complex by the half-world separating the two authors. Among our many technicians over the years, we must particularly note Mrs. Irma B. Mednicoff and Mrs. Louise D'esy Choinski.

Special thanks are due to Dr. H. Edward MacMahon, Professor of Pathology, Tufts University School of Medicine, and his staff for their cooperation in providing most of the photomicrographs of sections in the text (except those otherwise cited); Dr. Alice Ettinger, Radiologist, New England Center Hospital, for her continued interest in our work, and for supplying most of the x-ray illustrations used in the text; Dr. W. J. Mitus of our laboratory, for his aid in the histopathologic and histochemical sections; Professor Y. Kawakita of Kumamoto City, Japan, for his meticulous illustrations done while he was with us in Boston; Dr. Joseph Beard of Durham, North Carolina, who reviewed the section on viruses and with whom we had several profitable discussions on this important subject; Dr. Charles Congdon of Oak Ridge National Laboratories, Oak Ridge, Tennessee, who examined the section on reactions to x-rays and with whom we have collaborated in a bone marrow transplantation project; Dr. Wayne Rundles of Durham, North Carolina, who reviewed the sections on multiple myeloma and urethane and supplied several excellent electrophoretic patterns of serum and urine; Dr. Marcel Bessis, of Paris, who generously allowed the use of some of his extraordinary electron micrographs; and to Dr. Leon Dmochowski of Baylor University, Houston, Texas, who supplied electron micrographs showing viruses in leukemic cells from different animal species and humans. Mr. Tuckerman Day compiled the index.

We acknowledge with appreciation the help of our wives, Mrs. Ruddy Dameshek and Mrs. Joan P. Gunz, whose patience was undoubtedly strained at times while their husbands toiled over an ever-demanding manuscript. To our long-time secretary, Mrs. Edith M. Florentine, we extend thanks for her constant cooperation, particularly in unearthing pertinent clinical data.

Finally, we cannot fail to acknowledge the generous support throughout the years of the American Cancer Society, Inc., the American Cancer Society (Massachusetts Division), the National Cancer Institute of the United States Public Health Service, the Medical Research Branch (Division of Biology and Medicine) of the United States Atomic Energy Commission, the Damon Runyon Memorial Fund for Cancer Research, Inc., and of generous private donors. Among these may be listed Mr. E. Calvin Fowler, of Chattanooga, Tennessee (deceased May 29, 1958), Mr. E. Stanley Wright of Worcester, Massachusetts, the Greenbaum Family of Boston (in honor of Mrs. Sarah Greenbaum, deceased), and the Rho Pi Phi Ladies Auxiliary, of Boston. We are indebted to the Schering Corporation and to its Vice-President and Medical Director, Dr. Edward Henderson, for their generous contributions of large amounts of prednisone (Meticorten) and their financial aid in defraying the cost of the colored plates.

William Dameshek
Frederick Gunz

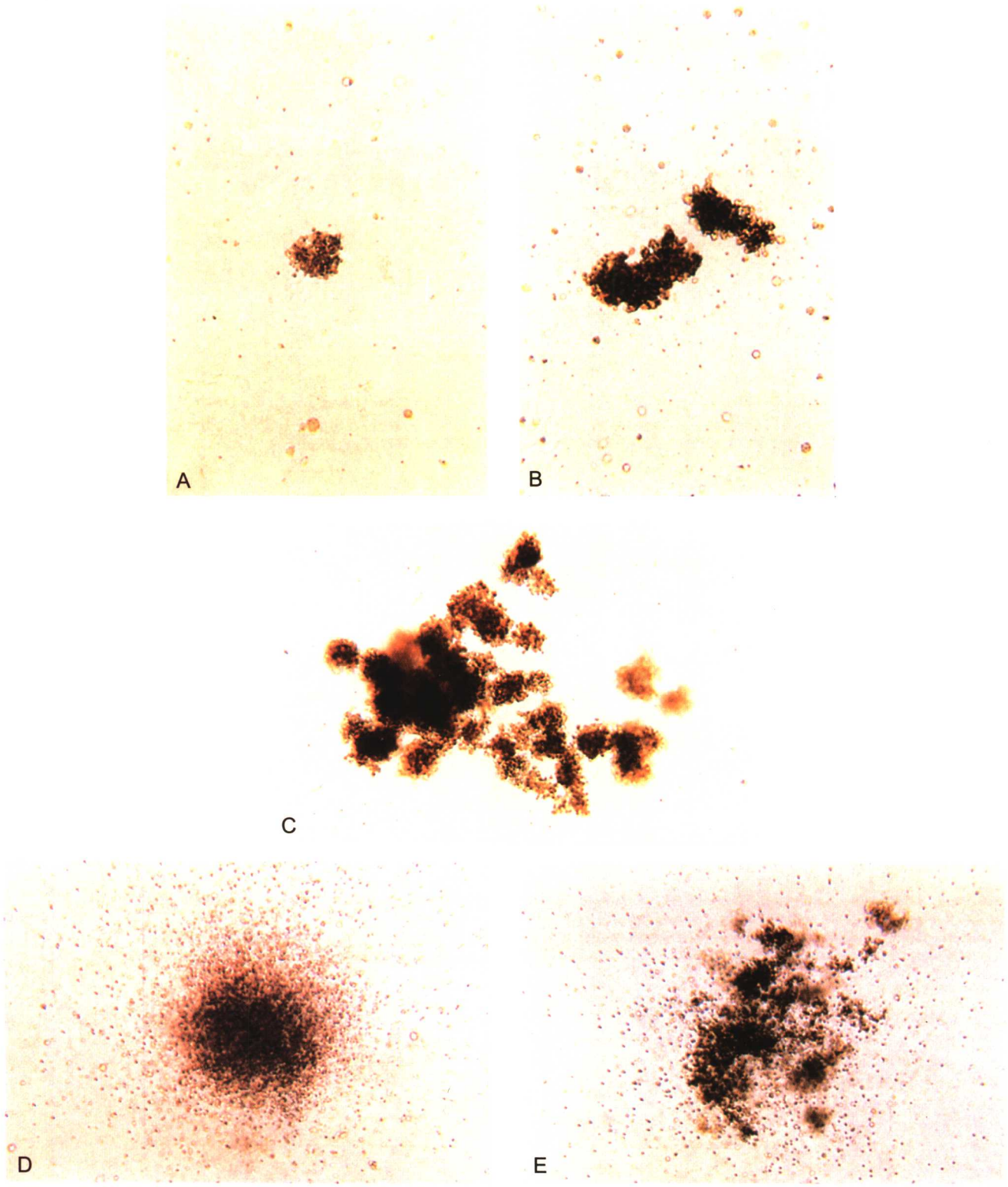

FIGURE 3–3. Photomicrographs of various types of hematopoietic colonies containing single or multiple lineages of differentiating blood cells. The colonies were photographed in the living state in the cultures in which they were generated. *A*, Typical CFU-E–derived colony. *B*, Typical BFU-E–derived colony. *C*, Typical primitive BFU-E–derived colony. *D*, Typical CFU-GM–derived colony. *E*, Typical CFU-GEMM–derived colony. All colonies shown at the same magnification.

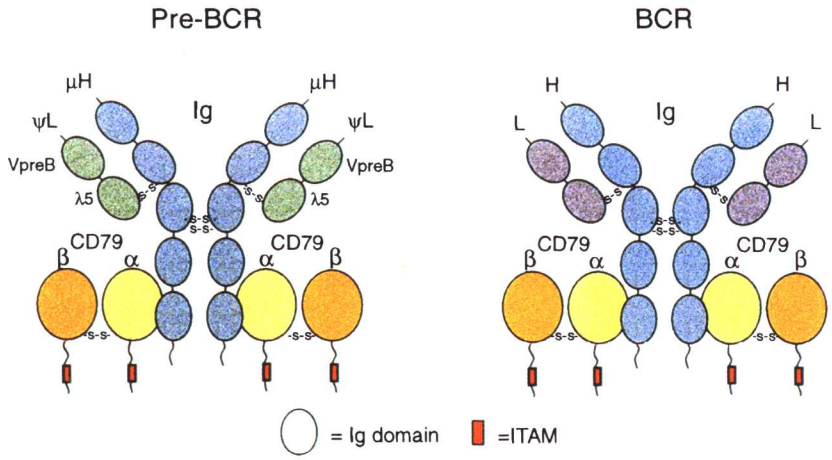

FIGURE 4–3. Molecular composition of the pre-B-cell receptor (pre-BCR) and B-cell receptor complexes. In the pre-BCR complexes, μH chains are associated with ψL chains. In BCR complexes, H chains are associated with L chains (either κ or λ). Signal transduction is mediated by CD79 molecules, which contain immunoreceptor tyrosine-based activation motifs in their cytoplasmic domains.

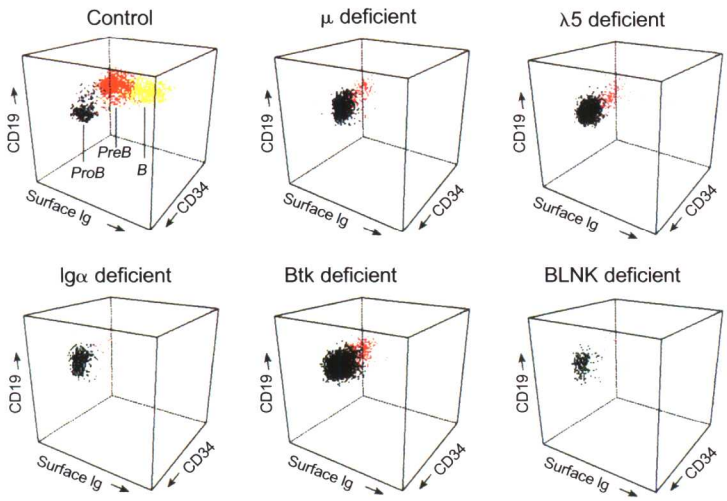

FIGURE 4–4. Block in B-cell differentiation in patients with agammaglobulinemia. Flow cytometric analysis of the immunophenotype of $CD19^+$ B cells in a bone marrow of a healthy individual shows three distinct cell subpopulations: $CD34^+$ surface Ig^- (pro B), $CD34^-$ surface Ig^- (pre-B), and $CD34^-$ surface Ig^+ (immature and mature B). The immunophenotype of patients with agammaglobulinemia caused by different genetic abnormalities is shown. Note that the main block in B-cell differentiation in all patients is at the transition between pro-B and pre-B cells.[88, 101, 102, 154, 159]

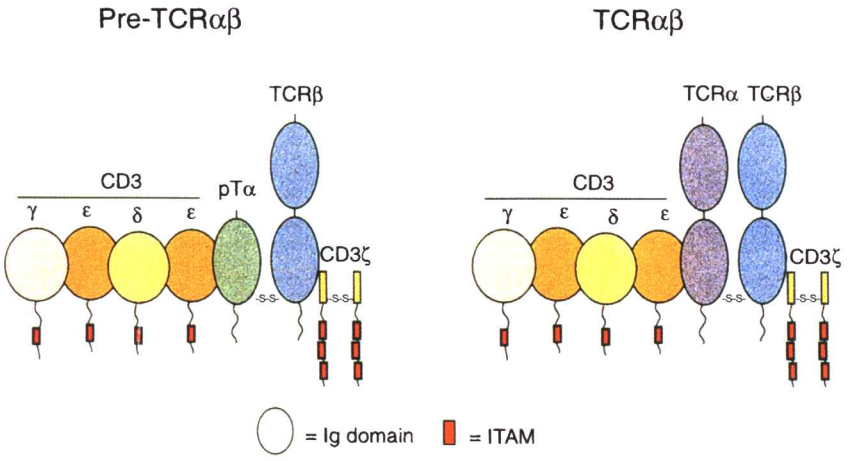

FIGURE 4–7. Molecular composition of the pre-T-cell receptor αβ (pre-TCRαβ) and T-cell receptor αβ (TCRαβ) complexes. TCRβ chains are associated with pTα chains in the pre-TCRαβ complexes and with TCRα chains in the TCRαβ complexes. Signal transduction is mediated by CD3 molecules, which contain immunoreceptor tyrosine-based activation motifs in their cytoplasmic domains.

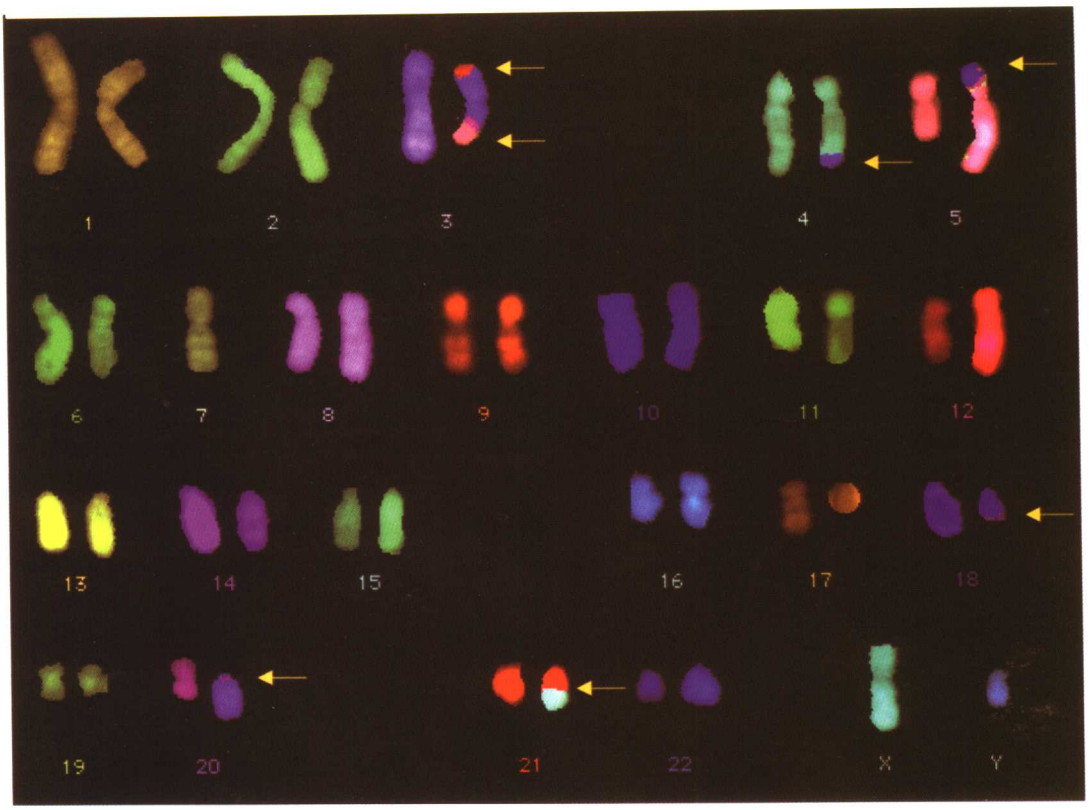

FIGURE 5–1. M-FISH analysis of a case of AML. The karyotype was analyzed as follows: 46,XY,del(5)(q22-q35),inv(8)(q13q24)/45,idem,-7/45,idem, -7,-12,+mar1/45,idem, der(3)(21qter->21q2::3p2->2q2::20?::5p1->5pter)der (4)(4pter->4q31::3p2->3pter) der(5)(5qter->5p1::20?::18q21->qter)-7der(18)(18pter->18q21::20?) der(20)(p10 or q10->q11 or p11::3q2->3pter)der(21)(21pter->21q2::4q31->4qter)/46,XY. (Courtesy of Deborah Lillington.)

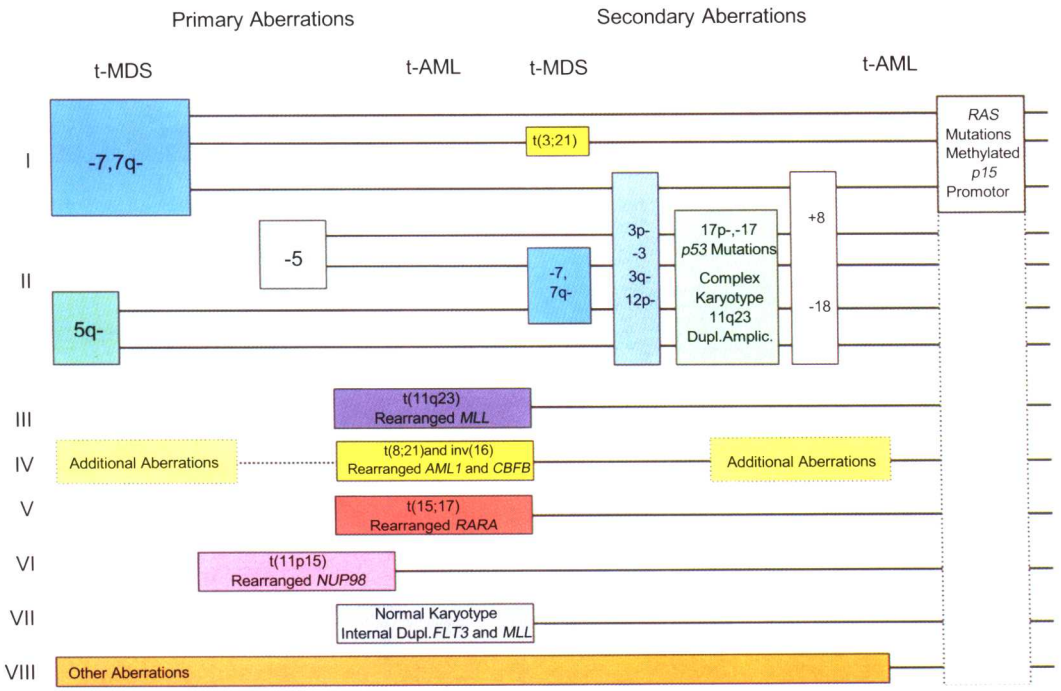

FIGURE 9–4. Model of genetic pathways in the genesis of treatment-related AML and MDS.

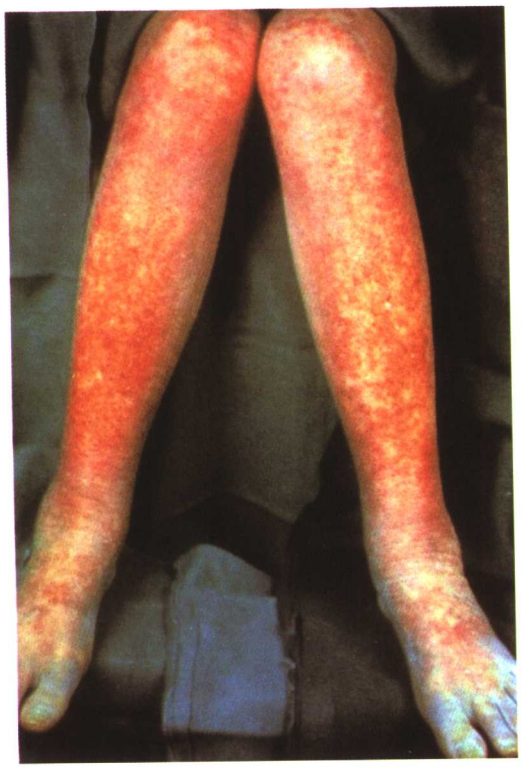

FIGURE 11–1. Petechial hemorrhages in a patient with severe thrombocytopenia.

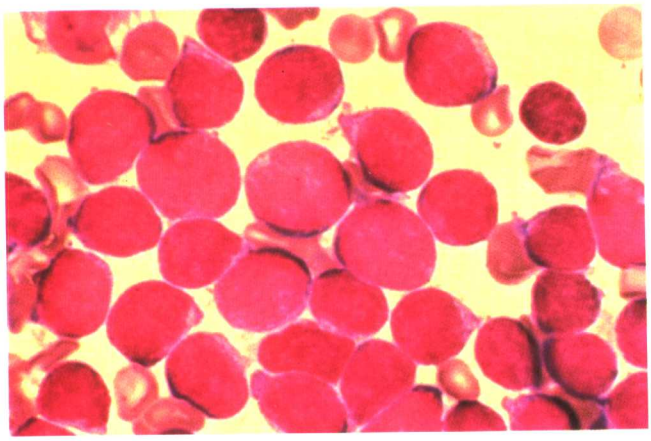

FIGURE 11–2. Acute lymphoblastic leukemia, FAB-L1 morphology. Note scant cytoplasm.

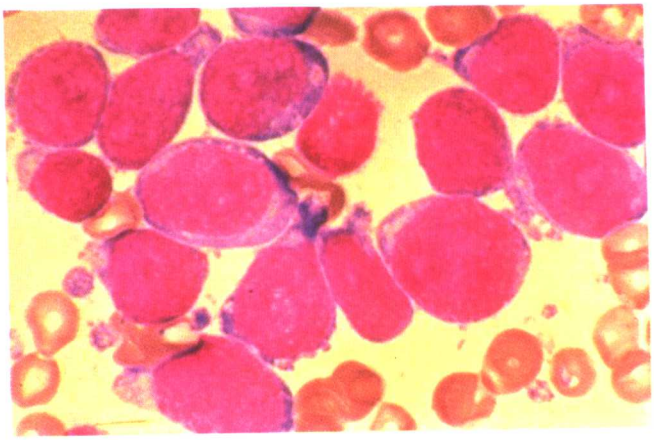

FIGURE 11–3. Acute lymphoblastic leukemia, FAB-L2 morphology. Cells have variable size and a lower nuclear-to-cytoplasmic ratio than L1 blasts.

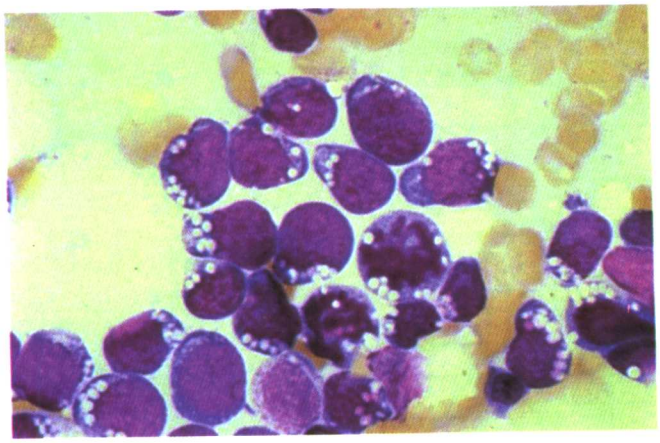

FIGURE 11–4. Burkitt cell leukemia, FAB-L3 morphology. Cells typically have deeply basophilic cytoplasm with numerous vacuoles. Most of these are cytoplasmic. Note the presence of a cell in metaphase, not an uncommon finding in this highly proliferative leukemia.

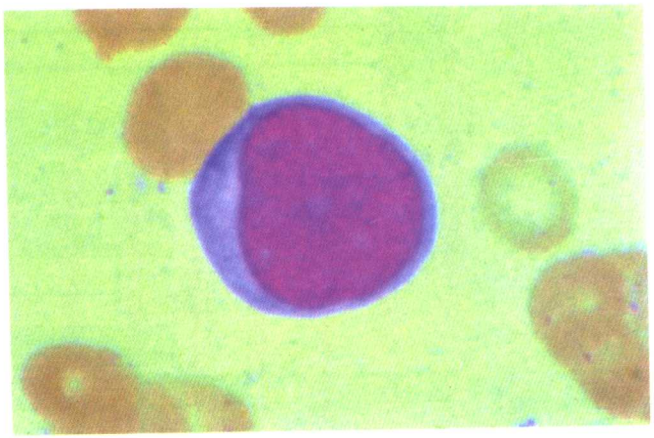

FIGURE 11–5. Type I myeloblast. Note nucleolus, noncondensed chromatin, and absence of cytoplasmic granules.

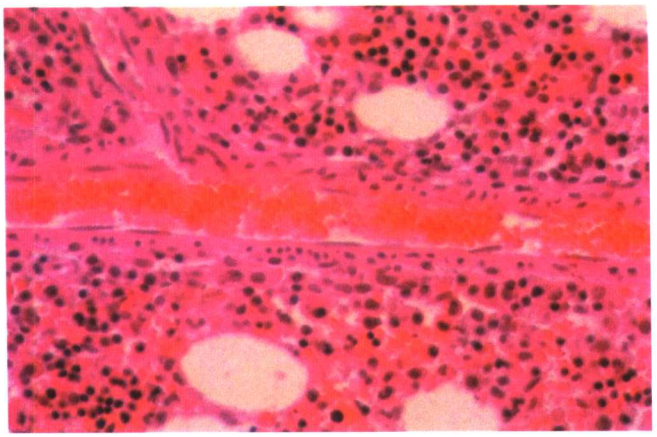

FIGURE 11–6. Bone marrow biopsy; type II myeloblast; similar to type I myeloblast but with slightly more cytoplasm containing a few azurophilic granules.

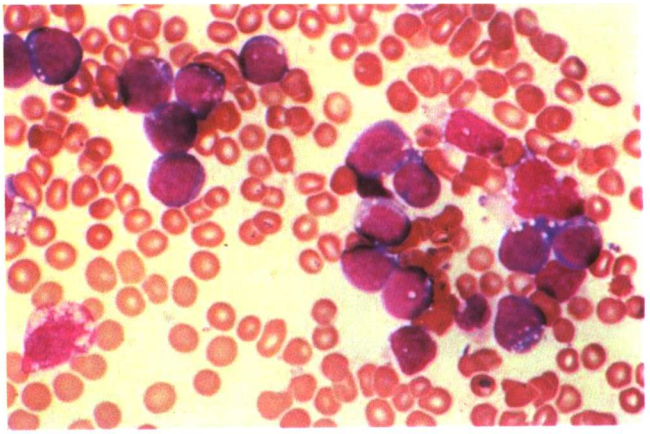

FIGURE 11–7. Undifferentiated acute myeloblastic leukemia (FAB-M0). Note the similarity to Burkitt cell leukemia (FAB-L3), ALL-L2, and acute megakaryocytic leukemia (FAB-M7). Diagnosis depends on the results of immunologic, cytogenetic, and molecular studies.

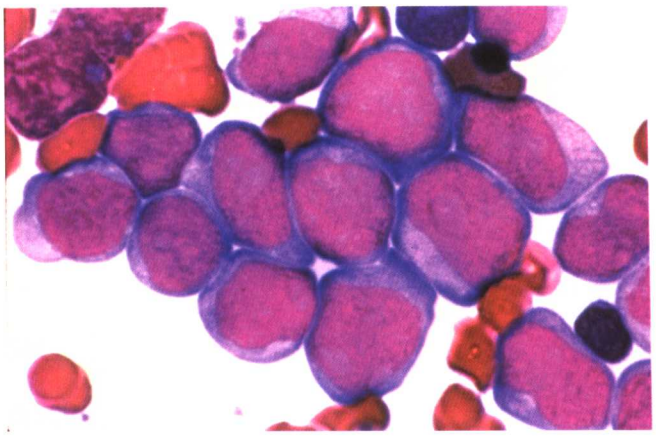

FIGURE 11–8. Acute myeloid leukemia, FAB-M1. Note many type I and few type II myeloblasts and little maturation in this bone marrow smear.

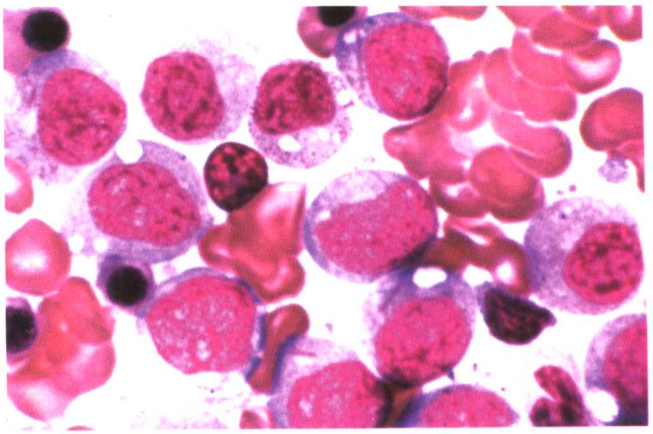

FIGURE 11–9. Acute myeloid leukemia with t(8;21)(q22;q21). This bone marrow exhibits FAB-M2 morphology with type II myeloblasts and some granulocytic maturation. Note the long, fine, and somewhat tubular-appearing Auer rods in four of the blasts characteristic of t(8;21) leukemia.

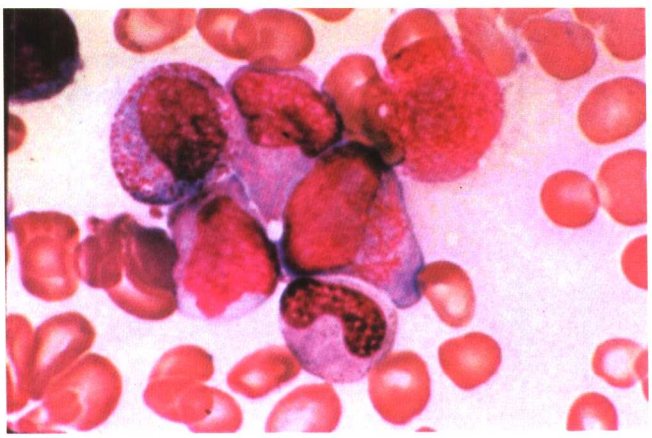

FIGURE 11–11. Hypergranular acute promyelocytic leukemia (FAB-M3). Note the indented nucleus, perinuclear clear zone ("haupt"); abundant cytoplasm containing abnormally large, "succulent" azurophilic granules; and multiple Auer rods, some appearing to be in bundles (faggots).

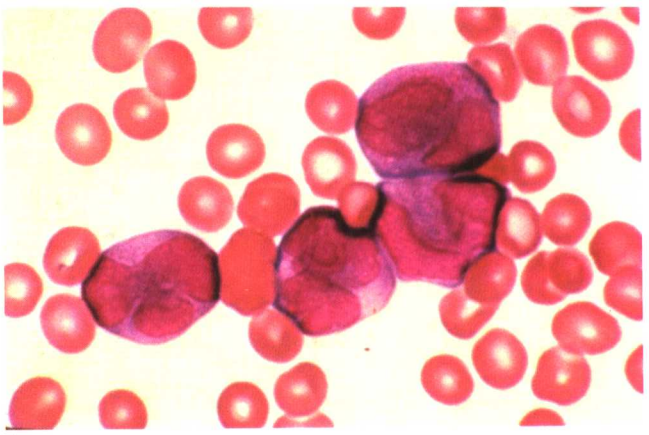

FIGURE 11–13. Microgranular acute promyelocytic leukemia, FAB AML-M3var. The large granules noted in Figure 11–11 are absent. The diagnosis can be suspected on the basis of the nuclear appearance with indentation and some chromatin condensation; however, it must be confirmed by cytogenetics or molecular detection of a translocation involving the *RARA* gene.

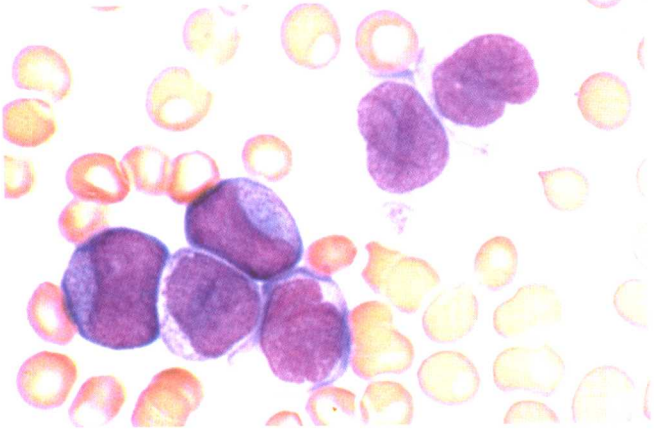

FIGURE 11–14. Acute myelocytic leukemia (FAB AML-M4) bone marrow. This category is typified by nearly equal numbers of myeloblasts and monoblasts plus promonocytes.

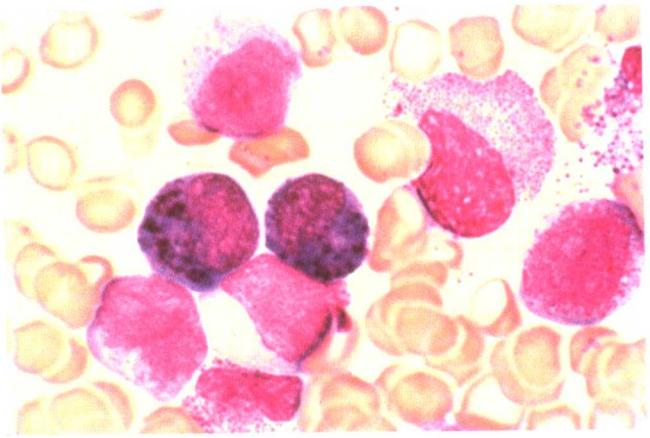

FIGURE 11–15. AML-M4 with abnormal eosinophils. This is classified as AML-M4Eo by the FAB Group. It is associated with cytogenetic aberrations involving chromosome 16, typically inv(16)(p13;q11).

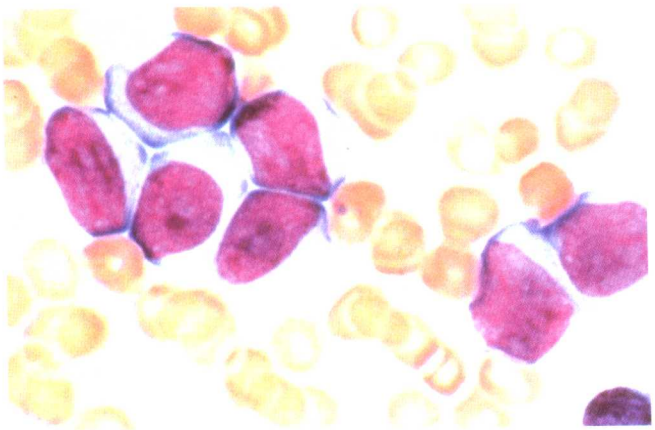

FIGURE 11–16. Acute monoblastic leukemia, FAB AML-M5a. Note the absence of mature monocytes and of granulocytic cells.

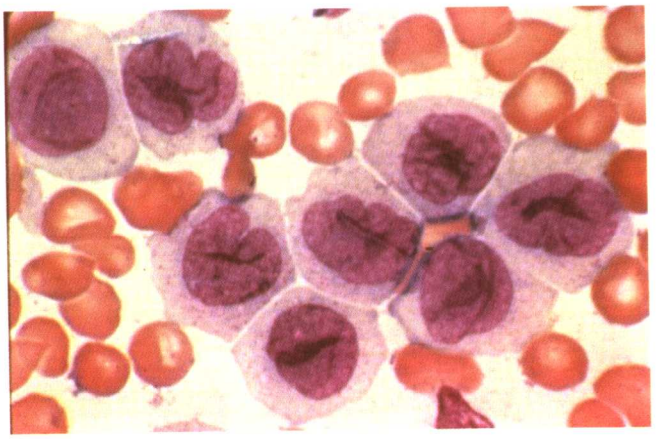

FIGURE 11–17. Acute monocytic leukemia, FAB AML-M5b. Smear consists primarily of partially differentiated monocytic cells, most promonocytes, with few blasts or granulocytic cells.

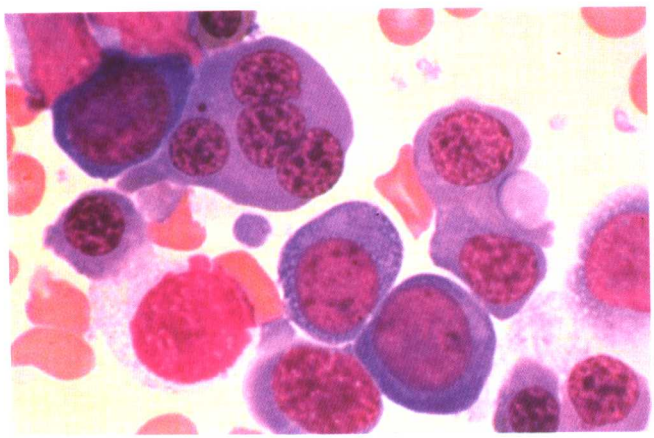

FIGURE 11–18. Acute erythroid leukemia, FAB AML-M6. Note the markedly dyspoietic erythroid precursor cells and the presence of excessive numbers of both erythroblasts and myeloblasts.

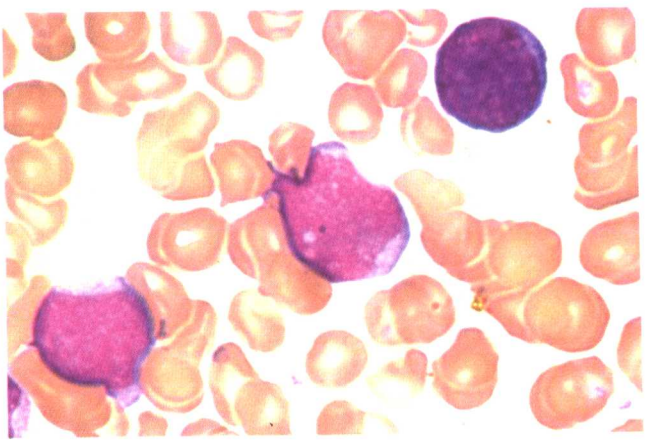

FIGURE 11–19. Acute megakaryocytic leukemia, FAB AML-M7. Peripheral blood smear containing a heterogeneous but poorly differentiated population of blast cells. Definite diagnosis depends on antigen phenotyping with use of antiplatelet membrane antigen reagents and/or platelet peroxidase staining and ultrastructural analysis (immunoelectron microscopy).

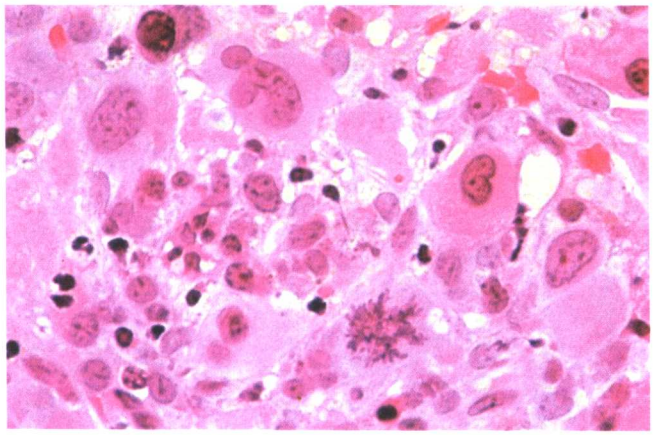

FIGURE 11–20. Acute megakaryocytic leukemia, bone marrow biopsy specimen revealing markedly increased numbers of megakaryocytes and fibrosis.

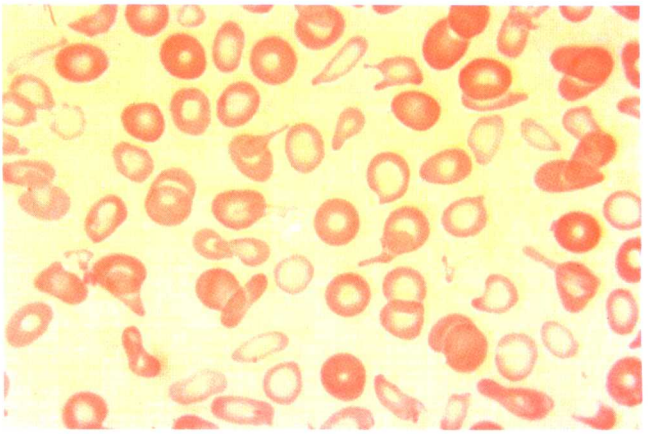

FIGURE 11–21. Peripheral blood smear from a patient with the refractory anemia form of myelodysplastic syndrome. Anisocytosis and poikilocytosis are striking, and neutrophils tend to be hypogranular.

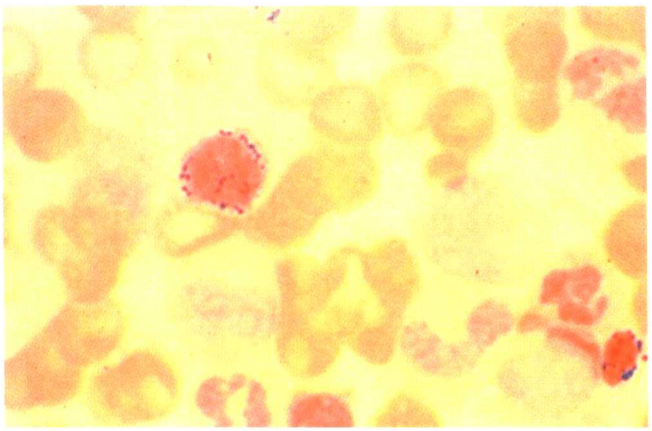

FIGURE 11–22. Refractory anemia with ring sideroblasts (iron stain of bone marrow aspirate).

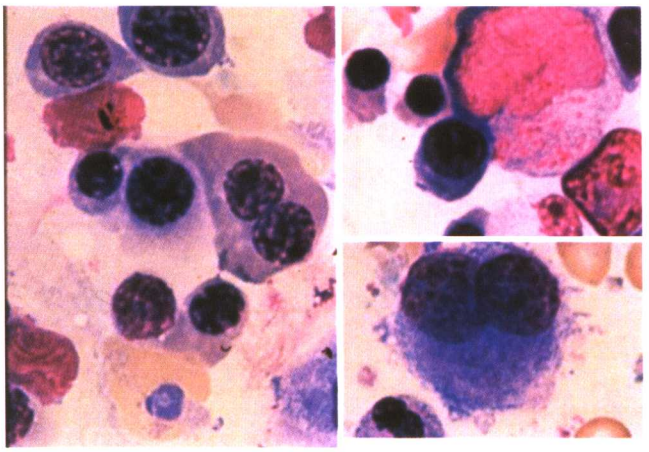

FIGURE 11–23. Composite of marrow cells from a patient with refractory cytopenia with multilineage dysplasia. Clockwise from top right: myelocyte, micromegakaryocyte, and multiple dysplastic erythroid precursors.

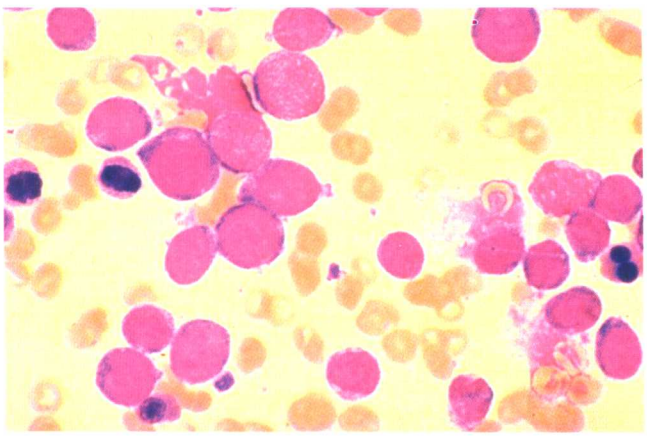

FIGURE 11–24. Refractory anemia with excess blasts. Both increased myeloblasts and dysplastic erythroid precursors are prominent.

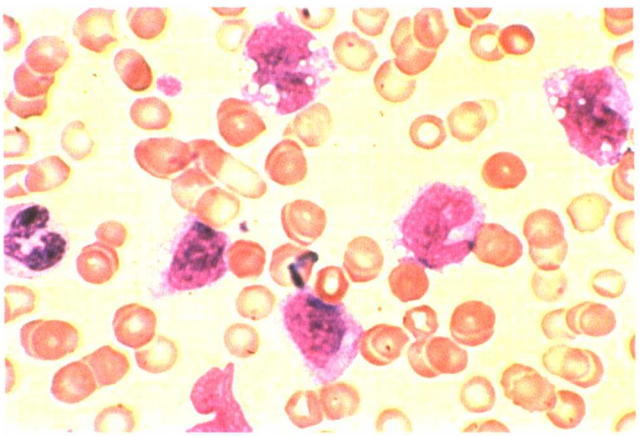

FIGURE 11–25. Chronic myelomonocytic leukemia. Note many monocytes and dysplastic mature neutrophils with hypogranulation. This is classed as a myelodysplastic syndrome by the FAB Group and as a myeloproliferative/myelodysplastic disorder by the WHO Committee.

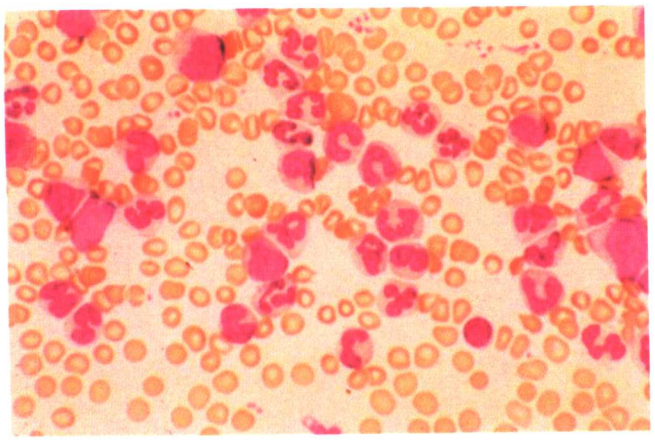

FIGURE 11–26. Chronic myelogenous leukemia, chronic phase. Myelocytes and banded and segmented neutrophils are present. Two Pelger-Huët cells (with bilobed nuclei) are also seen.

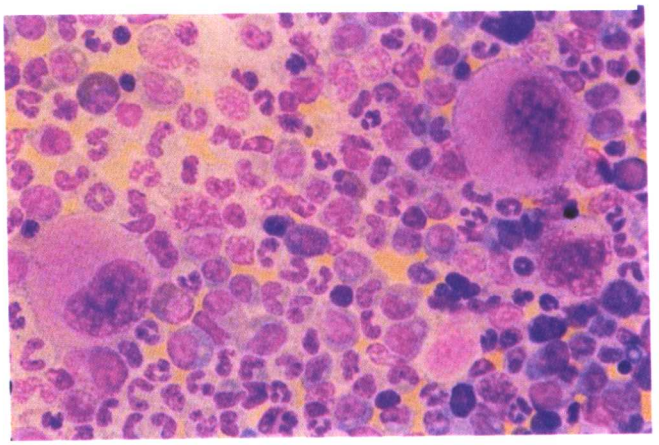

FIGURE 11–27. Chronic myelogenous leukemia, chronic phase, bone marrow biopsy specimen. Marked hypercellularity is seen with increased numbers of dysplastic megakaryocytes, and all stages of granulocytic differentiation are apparent.

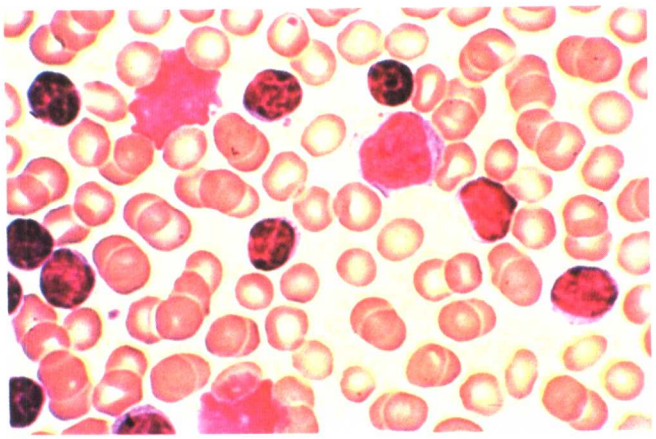

FIGURE 11–28. Chronic lymphocytic leukemia, B-cell type. Bone marrow aspirate shows small lymphocytes with condensed nuclear chromatin. Also present are several typical smudge cells. The T-cell type may resemble this or may have more T-cell characteristics.

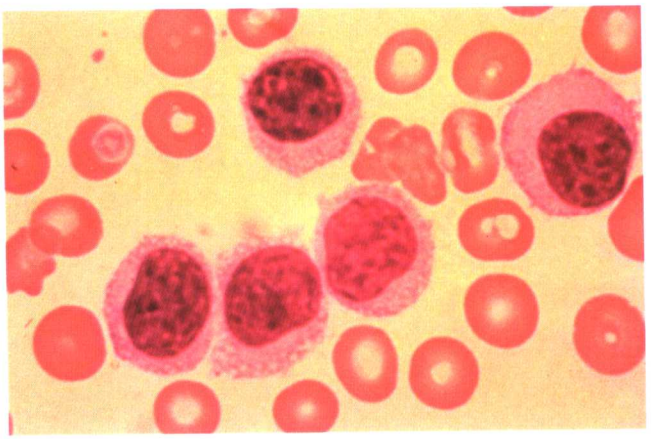

FIGURE 11–29. Hairy cell leukemia. Peripheral blood smear stained with Wright-Giemsa contains hairy cells.

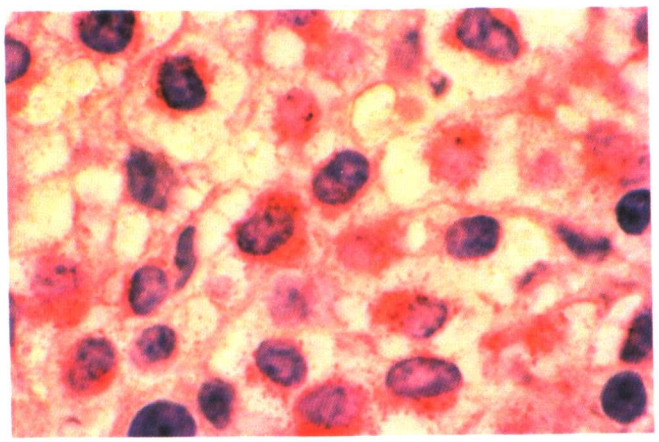

FIGURE 11–30. Hairy cell leukemia. Bone marrow biopsy specimen exhibits tartrate-resistant acid phosphatase staining of hairy cells. Note the wide separation of the hairy cells.

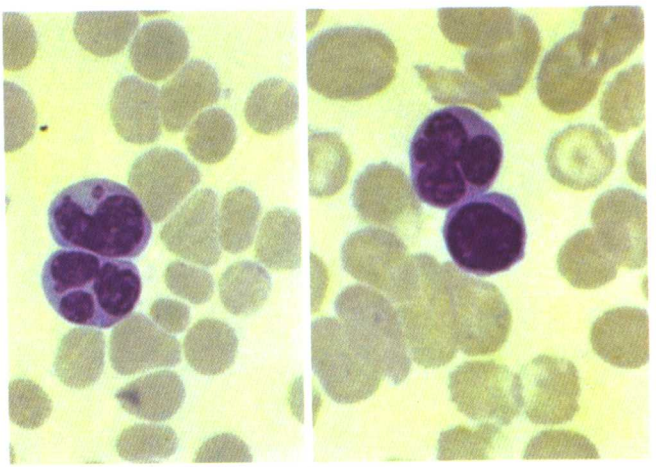

FIGURE 11–31. Adult T-cell leukemia/lymphoma. Peripheral blood contains characteristic malignant T cells with multilobed nuclei (cloverleaf or flower cells).

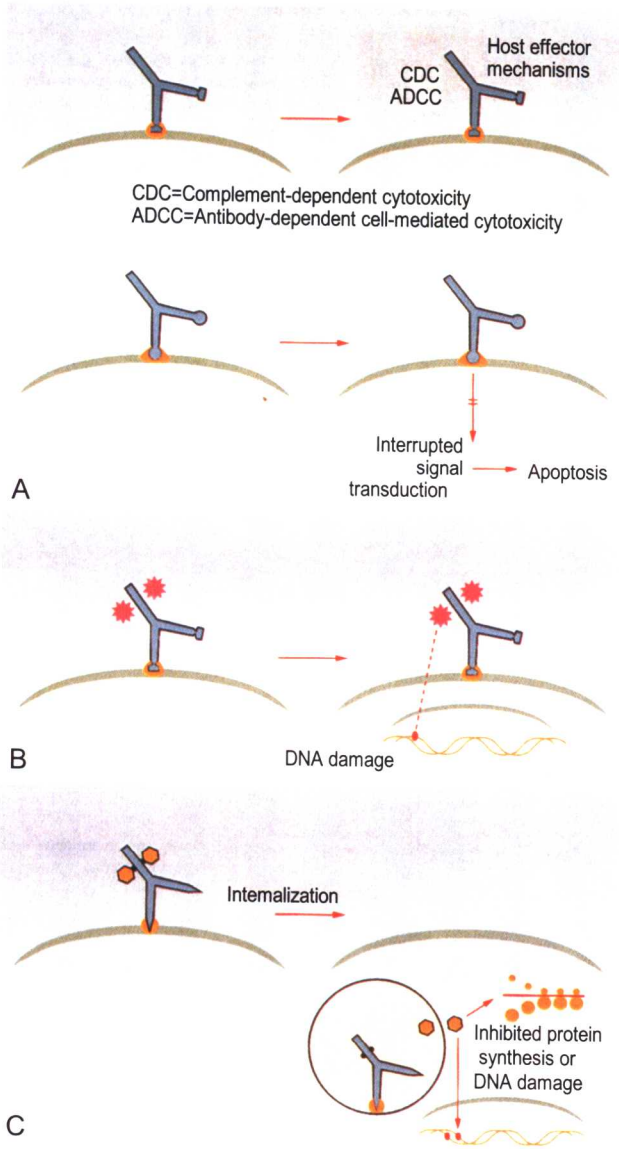

FIGURE 18–1. Antibody-targeted tumor killing, three mechanisms of action. *A*, Unconjugated monoclonal antibody: Binding of antibody initiates killing of target cells by complement-dependent cellular cytotoxicity or antibody-dependent cellular cytotoxicity in the top panel. Antibody binding (e.g., anti-CD20 antibody) interrupts cellular signal transduction, resulting in apoptosis in the lower panel. *B*, Monoclonal antibody linked with radioisotopes: Depending on the antigen targeted, radiolabeled antibody remains on the surface of the cell (CD45) or is internalized (CD33). Radiation induces DNA damage and cell death. In the instance of CD33, the radioisotope is delivered to the cell's interior. In the case of CD45, radiolabeled antibody remains on the cell surface. *C*, Both approaches damage DNA and lead to cell death. Monoclonal antibody linked with antitumor agents: Antibody-bound chemotherapy or toxin is internalized. Interaction with DNA or ribosomal protein synthesis results in cytotoxicity.

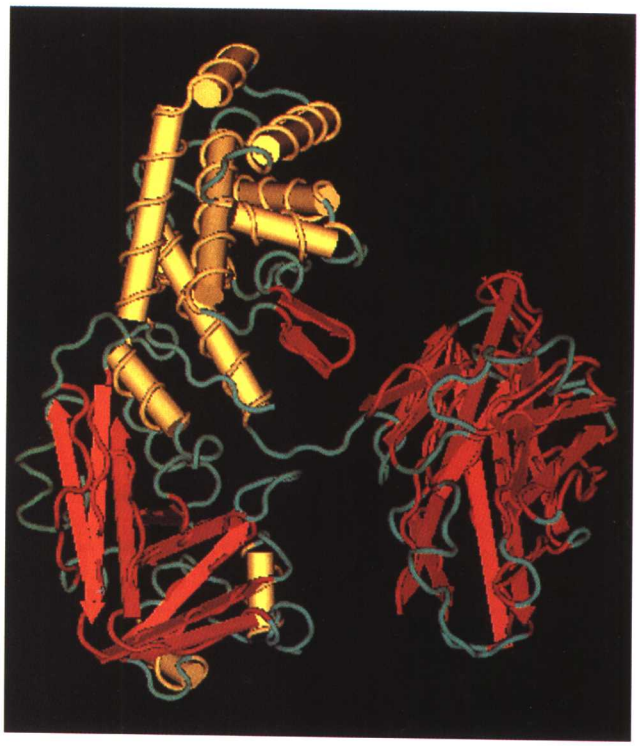

FIGURE 18–2. Ribbon drawing of α-carbon backbone of diphtheria toxin (DT) with domains in different colors. (From Choe S, Bennett MJ, Fujii G, et al: The crystal structure of diphtheria toxin. Nature 1992;357:216.)