

## PREFACE

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The chronic leukemias and lymphomas represent a biologically diverse group of neoplasms characterized by relatively indolent natural history and distinct clinical features. Clinically identified by inexorable tumor progression with a propensity for an accelerated phenotype, these chronic hematologic disorders are also often associated with immune-related complications such as autoimmune thrombocytopenia, hemolytic anemia, pure erythrocyte aplasia, and dermatologic manifestations. These distinct clinical manifestations not only shed light on the immune response to these diverse neoplasms, but may also provide insight into disease biology. The purpose of *Chronic Leukemias and Lymphomas: Biology, Pathophysiology, and Clinical Management* is to describe the unique features of these chronic hematologic neoplasms—with a special emphasis on their biologic features—and to provide insights into clinical manifestations and potential targets for treatment in this new period of antineoplastic pharmacology.

Chronic lymphoproliferative neoplasms are often characterized by clonal expansion of cells demonstrating defects in apoptosis. Distinct cytogenetic and molecular abnormalities provide sensitive markers of disease, allowing for assessment of mechanisms of proliferation and cell death for a given cell population. Although the biology of malignant neoplasia is typically portrayed as a result of impairment in cellular differentiation coupled with a defect in cellular proliferation, the chronic lymphoproliferative disorders are considered models for defects in the phenotype of programmed cell death. In chronic lymphocytic leukemia, failed programmed cell death appears to be the principal disorder immortalizing the malignant precursor cell and its progeny. Presumably, molecular alterations that inhibit cell death promote the slow clonal expansion characteristic of the disease. Similar impairments of apoptosis have been described in follicular lymphomas suggesting unique targets for such therapies as the purine nucleoside analogs and monoclonal antibodies. These chronic lymphoproliferative diseases are to be contrasted with Hodgkin's disease and large cell lymphomas, disorders whose biology more closely reflects the biology of aggressive malignant neoplasias, and are also well described in this text.

In the new era of targeted therapy, another susceptible molecular feature of clonal neoplasia has been identified in chronic myelogenous leukemia. Long considered the paradigmatic myeloproliferative disease, chronic myelogenous leukemia is characterized by a distinct molecular lesion, the *bcr-abl* gene whose

product confers a proliferative phenotype to the clone. Now a licensed drug, STI-571 (Gleevec) takes advantage of this unique molecular lesion, leading to a high rate of cytogenetic remission.

The other myeloproliferative disorders presumably have similar defects in cell replication. Like the chronic lymphoproliferative neoplasms, myeloproliferative diseases have a variable tendency to evolve to an accelerated phase characterized by impaired cell maturation and rapid clinical deterioration. This molecular and clinical evolution may not be inevitable, assuming that effective therapy can be initiated in the early, relatively benign clinical phase of the disease.

In the last decade, a confluence of basic and clinical research results has led to a more complex view of these so-called “indolent neoplasms.” These results have also led to remarkable developments in therapy. Studies in the last ten years have led to completely different, and unanticipated, forms of therapy including unique small molecules targeted at specific genetic lesions, pro-apoptotic drugs, monoclonal antibodies, and adoptive immunotherapy. The new forms of treatment are designed to address these chronic diseases according to their unique susceptibilities, and in the process will lead to an improved understanding of the evolution of malignant neoplasia.

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