The hematologic malignancies, broadly defined as the "leukemias," are cancers that cross socioeconomic and gender lines and affect persons of every age group. Nearly 22,000 individuals in the United States will die of these malignancies each year, and the associated personal and economic loss is great.

The term "leukemia" actually refers to a family of blood cancers, each having a distinct pattern of symptoms and cytology and each differing in age of onset, prognosis, and therapeutic options. The acute leukemias -- acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) -- have been recognized for their rapid clinical progression when untreated and are diagnosed by the identification of primitive, poorly differentiated hematopoietic precursors (blasts) in the blood and bone marrow. The chronic leukemias are more heterogeneous and also include myeloid and lymphoid disorders. Chronic myelogenous leukemia (CML), a relatively indolent disorder that is most common in young adults, is characterized by a proliferation of mature and immature myeloid precursors. CML gives rise to high peripheral blood white counts and splenomegaly. The chronic lymphoid leukemias, of which chronic lymphocytic leukemia (CLL) and hairy cell leukemia are the most common, are generally disorders of mid to late adulthood. They are usually indolent but, in many cases, may not be curable with conventional therapy. Patients will have variable numbers of circulating malignant lymphoid cells. The degree of splenomegaly, lymphadenopathy, and bone marrow involvement will depend on the subtype of leukemia diagnosed.

While the myelodysplastic syndromes are often not considered under the heading of "leukemia," they share many of the same cytogenetic and molecular abnormalities as AML. Approximately half of patients with myelodysplasia will develop AML within a few years of diagnosis, and hence this disorder has been referred to as "preleukemia" in the past. Myelodysplasia is a syndrome of bone marrow failure, with morphologically and functionally abnormal myeloid precursors showing failure to mature appropriately. In many instances, the distinction between AML and myelodysplasia is blurred, further supporting the close association between these entities.

Of all the malignancies, the leukemias have perhaps been the object of the most intense and extensive basic science investigations. It has been suggested that this was a natural evolution, since malignant cells in single-cell suspensions could be readily retrieved without invasive surgical procedures. These cell suspensions could be purified and grown in vitro, allowing for relatively pure populations of tumor cells and the establishment of cultured cell lines. The identification of hematopoietic growth factors, first in cultured supernatants and later in purified form, has allowed the systematic evaluation of cell growth kinetics and differentiation and has opened the door for tumor biologists and geneticists.

With the recognition that many subtypes of leukemia are characterized by reproducible karyotypic abnormalities, a tremendous growth in the field of cytogenetics has been realized. In this issue of Cancer Control, Peter Papenhausen, PhD, and his colleagues explore the rapidly expanding area of cytogenetic and molecular abnormalities that are currently recognized as diagnostic or prognostic variables in acute and chronic leukemia and myelodysplasia. While classical karyotypic analysis remains the mainstay of cytogenetics, new techniques that utilize concomitant molecular probes (FISH and comparative genomic hybridization) are proving to be powerful adjuncts to basic biologic and clinical investigations.

The chromosomal abnormalities that were identified by classical cytogenetics have become the focus of many molecular biologists. The majority of genes that have been cloned from these breaksites are known to be involved in cell proliferation, cell death, or cell differentiation. These so-called "oncogenes" are critical components in the multiafactorial pathway leading to the development of a malignancy, and correlates have been found in nearly all animal species and human tissues. The discovery of oncogenes has truly revolutionized cancer biology and is probably the major factor responsible for the marked growth in the fields of molecular biology and diagnostic hematopathology. The molecular identification of translocation breaksites, or immunologic identification of the associated chimeric proteins, is becoming common practice in the clinical and laboratory evaluation of patients with leukemia. More accurate subtyping and classification of the acute and chronic leukemias has been made possible by the recognition that the leukemic cell morphology is closely related to the molecular genotype. Cytogenetics has also proven to be one of the most important and reproducible prognostic variables in the evaluation of patients with both acute and chronic leukemia. Factors such as growth fraction, DNA ploidy, immunophenotype, and multidrug resistance are closely related.

As advances in molecular biology have been immediately translated into advances in diagnosis, the impact on treatment is only beginning. One of the first examples of "targeted leukemia therapy" occurred somewhat through serendipity. Acute promyelocytic leukemia (APL) is characterized by a chromosomal translocation involving chromosomes 15 and 17, at the site of the retinoic acid receptor gene. Today, the use of all-trans-retinoic acid, which greatly improves long-term remissions of APL, has become the standard of care for treatment of APL. Another example of a therapeutic intervention evolving in response to basic science investigations is the development of pharmacologic agents aimed at reversing multidrug resistance. This followed the identification and characterization of several cytosolic and membrane proteins that could impart a drug-resistant phenotype to tumor cells. Clinical trials in this area continue to receive critical attention. Meanwhile, pharmacologists and tumor biologists continue to work toward the identification of critical cell pathways in oncogenesis, so that the dream of "oncogene-targeted drug discovery" can eventually be realized.

As new information has been generated through laboratory investigations, so too has progress been made in the therapy of these malignancies. Myelodysplasia remains difficult to treat. Patients are often elderly, and the abnormal bone marrow cells are frequently resistant to conventional chemotherapy. Significant mortality and morbidity result from persistent and recurrent infections, as well as bleeding. More accurate diagnoses, combined with the development of better prognostic scales, have helped to select patients most likely to require immediate intervention. Supportive care, including the use of hematopoietic growth factors, remains the mainstay of treatment. Clinical trials that involve multidrug resistance reversal and intensive chemotherapy are ongoing. Bone marrow transplantation is still considered to be experimental in this disorder, with few eligible patients in view of their advanced age at diagnosis.

Advances in chemotherapy have included refinement of the dosage and timing of cytotoxic agents, as well as the development of less toxic regimens for high-dose therapy with stem cell rescue (both autologous and allogeneic stem cell transplantation). In this issue, Ruben Saez, MD, reviews the role of conventional and high-dose therapy for AML and provides some guidelines for therapeutic decision making at the time of diagnosis and relapse. New agents also have been investigated, and several have shown promise in affecting the outcome, either by increasing remission induction rate or prolonging the asymptomatic phase. Interferon has been shown to help eliminate Philadelphia chromosome-positive cells from the bone marrows of patients with CML, and it most likely can prolong the duration of chronic phase. Cures have been realized after allogeneic bone marrow transplantation in this disease, and posttransplant therapies are under investigation in an attempt to ameliorate transplant-related morbidity/mortality, as well as relapse rate. The discovery of the nucleoside analogs and the institution of trials of fludarabine and 2-CdA in the chronic lymphoid leukemias have provided the first demonstrations of complete remission in these disorders. Whether this can eventually be translated into a durable remission or cure remains to be seen. The advent of these agents is perhaps the most significant therapeutic advance yet seen in these lymphoid leukemias.
As diagnosis and research applications become complex and more technically advanced and as therapy becomes more intense, it is increasingly more important to remember the patient as an individual person. It can be easy to lose the human side of medicine in a quagmire of technology. Quality-of-life issues are gaining increased prominence, patient tolerance of chemotherapy is improved due to the effective use of analgesic and antiemetic medications, and the psychosocial aspects of repeated or prolonged hospitalization are being addressed. National and local support groups are being formed, and hospitals and cancer centers are providing a forum to address patient and family concerns during and after treatment. In this issue, Donna Corwin Moss, MA, CSW, describes the role of leukemia support groups and provides an insight into the contributions of national organizations such as the Leukemia Society of America. Other areas of ongoing investigation revolve around the issues of posttherapy morbidity. While patients are now frequently cured of their leukemia, postchemotherapy or radiation therapy-induced cognitive or sensory disorders, infertility and sexual dysfunction, and growth retardation are emerging as important issues.

We have come a long way in our understanding of hematologic cancer. Still, many unresolved issues remain. This issue of *Cancer Control* can touch on only a few of these important topics. It is our hope that advances in biology, diagnosis, treatment, and patient satisfaction with outcome will continue into the next century.

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