T cells. The activated macrophages phagocytose blood cell progenitors in the marrow and formed elements in the peripheral tissues, while the "stew" of mediators released from macrophages and lymphocytes suppress hematopoiesis and produce symptoms of systemic inflammation. These effects lead to cytopenias and a shock-like picture, sometimes referred to as "cytokine storm" or the systemic inflammatory response syndrome (Chapter 4).

Familial forms of HLH are associated with several different mutations, all of which impact the ability of cytotoxic T cells and NK to properly form or deploy cytotoxic granules. How these defects lead to HLH is not known. One idea with some experimental support is based on the premise that cytotoxic T cells keep immune responses in check by lysing antigen-bearing dendritic cells or activated macrophages; if this regulatory mechanism fails, hyperactivation of the immune system and the clinical syndrome of HLH ensue. Unbridled HLH is associated with extremely high levels of inflammatory mediators such as interferon-γ, TNFα, IL-6, and IL-12, as well as soluble IL-2 receptor. Some "sporadic" cases in adults also prove to have mutations in the same set of genes, while in other adult-onset patients the cause is unknown. The most common trigger for HLH is infection, particularly with Epstein-Barr virus (EBV).

Clinical Features. Most patients present with an acute febrile illness associated with splenomegaly and hepatomegaly. Hemophagocytosis is usually seen on bone marrow examination, but is neither sufficient nor required to make the diagnosis. Laboratory studies typically reveal anemia, thrombocytopenia, and very high levels of plasma ferritin and soluble IL-2 receptor, both indicative of severe inflammation, as well as elevated liver function tests and triglyceride levels, both related to hepatitis. Coagulation studies may show evidence of disseminated intravascular coagulation. If untreated, this picture can progress rapidly to multiorgan failure, shock, and death.

Treatment involves the use of immunosuppressive drugs and "mild" chemotherapy. Patients with germline mutations that cause HLH or who have persistent/resistant disease are candidates for hematopoietic stem cell transplantation. Without treatment, the prognosis is grim, particularly in those with familial forms of the disease, who typically survive for less than 2 months. With prompt treatment, with or without subsequent hematopoietic stem cell transplantation, roughly half of patients survive, though many do so with significant sequelae, such as renal damage in adults and growth and mental retardation in children.

Neoplastic Proliferations of White Cells

Malignancies are clinically the most important disorders of white cells. These diseases fall into several broad categories:

- *Lymphoid neoplasms* include a diverse group of tumors of B-cell, T-cell, and NK-cell origin. In many instances the phenotype of the neoplastic cell closely resembles that of a particular stage of normal lymphocyte maturation, a feature that is used in the diagnosis and classification of these disorders.
- *Myeloid neoplasms* arise from early hematopoietic progenitors. Three categories of myeloid neoplasia are recognized: *acute myeloid leukemias*, in which immature progenitor cells accumulate in the bone marrow; *myelodysplastic syndromes*, which are associated with ineffective hematopoiesis and resultant peripheral blood cytopenias; and *chronic myeloproliferative disorders*, in which increased production of one or more terminally differentiated myeloid elements (e.g., granulocytes) usually leads to elevated peripheral blood counts.
- The *histiocytoses* are uncommon proliferative lesions of macrophages and dendritic cells. Although "histiocyte" (literally, "tissue cell") is an archaic morphologic term, it is still often used. A special type of immature dendritic cell, the Langerhans cell, gives rise to a spectrum of neoplastic disorders referred to as the *Langerhans cell histiocytoses*.

Etiologic and Pathogenetic Factors in White Cell Neoplasia: Overview

As discussed see in the following sections, the neoplastic disorders of white cells are extremely varied. Before we delve into this complexity, it is worth considering a few themes of general relevance to their etiology and pathogenesis.

Chromosomal Translocations and Other Acquired Mutations. **Nonrandom chromosomal abnormalities, most commonly translocations, are present in the majority of white cell neoplasms.** Many specific rearrangements are associated with particular neoplasms, suggesting a critical role in their genesis (Chapter 7).

- **The genes that are mutated or otherwise altered often play crucial roles in the development, growth, or survival of the normal counterpart of the malignant cell**. As a consequence, certain mutations are strongly associated with specific tumor types, so much so that is some instances they are required for particular diagnoses. In some instances, the mutation produces a "dominant-negative" protein that interferes with a normal function (a loss of function); in others the result is an inappropriate increase in some normal activity (a gain of function).
- **Oncoproteins created by genomic aberrations often block normal maturation, turn on pro-growth signaling pathways, or protect cells from apoptotic cell death**. Figure 13-4 highlights some of the more common or better characterized oncogenic events that serve as oncogenic driver mutations in particular kinds of white cell malignancies.
  - Many oncoproteins cause an arrest in differentiation, often at a stage when cells are proliferating rapidly. The importance of this block in maturation is most evident in the acute leukemias, in which dominant-negative oncogenic mutations involving transcription factors are often present that interfere with early stages of lymphoid or myeloid cell differentiation.
  - Other mutations in transcriptional regulators seem to directly enhance the self-renewal of tumors cells,