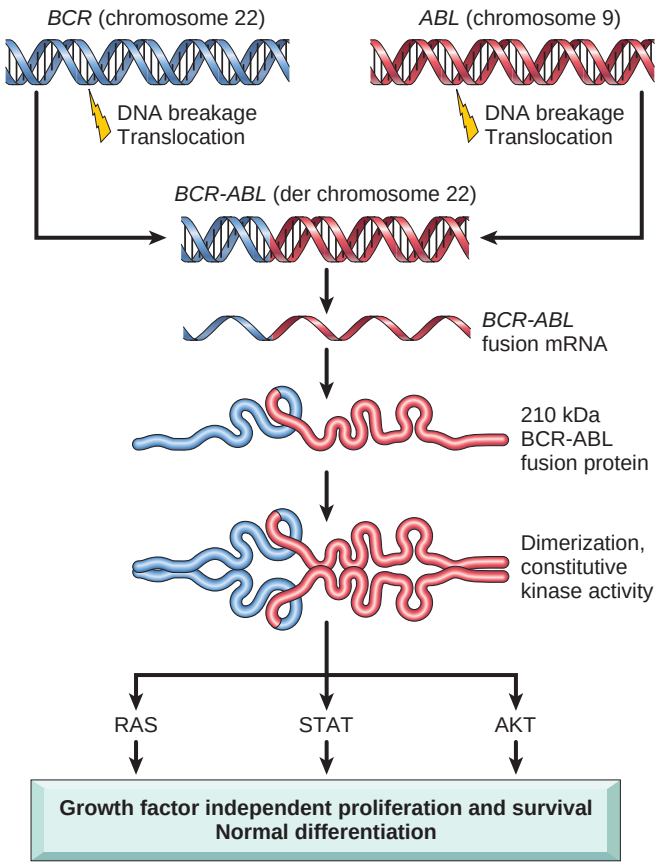

Figure 13-32 Pathogenesis of chronic myeloid leukemia. Breakage and joining of *BCR* and *ABL* creates a chimeric *BCR-ABL* fusion gene that encodes a constitutively active BCR-ABL tyrosine kinase. BCR-ABL activates multiple downstream pathways, which drive growth factor-independent proliferation and survival of bone marrow progenitors. Because BCR-ABL does not interfere with differentiation, the net result is an increase in mature elements in the peripheral blood, particularly granulocytes and platelets.

in CML is usually 210 kDa in size. In more than 90% of cases, *BCR-ABL* is created by a reciprocal (9;22)(q34;q11) translocation (the so-called *Philadelphia chromosome* [Ph]). In the remaining cases the *BCR-ABL* fusion gene is formed by cytogenetically complex or cryptic rearrangements and must be detected by other methods, such as fluorescence in situ hybridization or polymerase chain reaction (PCR)-based tests. The cell of origin is a pluripotent hematopoietic stem cell.

Pathogenesis. Tyrosine kinases are normally regulated by ligand-mediated dimerization and autophosphorylation, which creates an activated kinase capable of phosphorylating other protein substrates (Chapters 3 and 7). The BCR moiety of BCR-ABL contains a dimerization domain that self-associates, leading to the activation of the ABL tyrosine kinase moiety. The ABL kinase in turn phosphorylates proteins that induce signaling through the same pro-growth and pro-survival pathways that are turned on by hematopoietic growth factors, including the RAS and JAK/STAT pathways. For unknown reasons, BCR-ABL preferentially drives the proliferation of granulocytic and megakaryocytic progenitors, and also causes the abnormal release of immature granulocytic forms from the marrow into the blood.

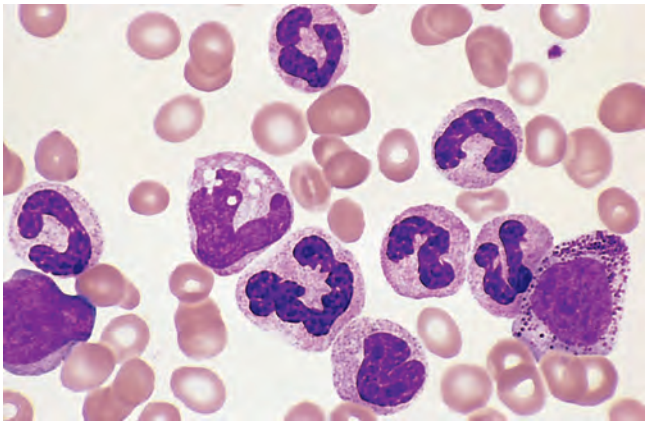

Figure 13-33 Chronic myelogenous leukemia. Peripheral blood smear shows many mature neutrophils, some metamyelocytes, and a myelocyte. (Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Tex.)

MORPHOLOGY

The marrow is markedly **hypercellular** because of massively increased numbers of maturing granulocytic precursors, which usually include an elevated proportion of eosinophils and basophils. Megakaryocytes are also increased and usually include small, dysplastic forms. Erythroid progenitors are present in normal or mildly decreased numbers. A characteristic finding is the presence of scattered macrophages with abundant wrinkled, green-blue cytoplasm so-called sea-blue histiocytes. Increased deposition of reticulin is typical, but overt marrow fibrosis is rare early in the course. The blood reveals a **leukocytosis, often exceeding 100,000 cells/mm^3** (Fig. 13-33), which consists predominantly of neutrophils, band forms, metamyelocytes, myelocytes, eosinophils, and basophils. Blasts usually make up less than 10% of the circulating cells. Platelets are also usually increased, sometimes markedly. The spleen is often greatly enlarged as a result of extensive extramedullary hematopoiesis (Fig. 13-34) and often contains infarcts of varying age. Extramedullary hematopoiesis can also produce mild hepatomegaly and lymphadenopathy.

Clinical Features. CML is primarily a disease of adults but also occurs in children and adolescents. The peak incidence is in the fifth to sixth decades of life. There are about 4500 new cases per year in the United States.

Figure 13-34 Chronic myeloid leukemia (spleen). Enlarged spleen (2630 gm; normal: 150 to 200 gm) with greatly expanded red pulp stemming from neoplastic hematopoiesis. (Courtesy Dr. Daniel Jones, Department of Pathology, MD Anderson Cancer Center, Houston, Tex.)