or a lymphoid-lineage stem cell. In the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3, the myeloid stem cell further differentiates into daughter cells of its named lineages (see Fig. 45-1). The lymphopoietic stem cell becomes a pre-B cell or a prothymocyte (pre-T cell) and leaves the marrow for further maturation.

Erythroid Lineage

Primitive erythroid precursors arising from the myeloid stem cell are called burst-forming unit–erythroid cells. These cells then differentiate into erythroid colony-forming unit (CFU-E) cells, which are the committed progenitor cells of erythrocytes. CFU-E cells express receptors for erythropoietin (EPO), an 18-kD molecule produced by renal interstitial cells in response to low oxygenation states or anemia. EPO upregulates proliferation of CFU-E cells and promotes their maturation into proerythroblasts and reticulocytes, which begin to synthesize hemoglobin (see Table 45-2).

Granulocyte and Monocyte Lineages

Human GM-CSF acts early in the hematopoietic pathway to regulate maturation of the CFU-GEMM stem cell. Differentiation of this myeloid precursor into specific committed progenitors occurs under the direction of granulocyte CSF (G-CSF) and monocyte CSF (see Table 45-2). Granulocyte CFU cells undergo sequential transformation into easily recognizable myeloblasts, myelocytes, and eventually early polymorphonuclear neutrophils with their characteristic polysegmented nuclei. Monocyte CFU cells, in contrast, retain a single nucleus as they mature from monoblasts to promonocytes to monocytes and sometimes to macrophages.

Other Lineages

Eosinophils and basophils develop from CFU-GEMM cells under the influence of IL-5 and IL-3 plus IL-4, respectively. The acquisition of their specific granular contents helps in distinguishing their precursors from those of early monocytes.

The development of platelets is morphologically distinct from the other lineages. CFU-GEMM cells differentiate into megakaryocyte CFU cells, so named because the cells cease cell division early but not nuclear replication. Megakaryocytes are the only cells in the body with the capacity to double their DNA content (i.e., endomitosis). Over the course of several cell cycles, the maturing megakaryocyte eventually acquires several times the nuclear content of other cells in preparation for its eventual dissolution into platelets with a fraction of the cytoplasm of other hematopoietic cells. Two growth factors, thrombopoietin (TPO) and IL-11, increase platelet counts by promoting megakaryocyte development (see Table 45-2).

Stem Cell Plasticity

Provocative data have challenged the conventional paradigm of hierarchical HSC differentiation. Experts have proposed that HSCs dedifferentiate into more immature progenitors and can cross lineages and transdifferentiate into nonlymphohematopoietic cells such as myocytes, hepatocytes, gastrointestinal epithelial cells, and neurons.

Whether this plasticity of HSCs is an intrinsic property of adult stem cells or is caused by contaminating cells of other populations, fusion of hematopoietic cells with other tissue cells, or artifacts introduced by ex vivo stem cell isolation techniques remains controversial. Nevertheless, the suggestion that adult HSCs may be a dynamic, renewable resource for tissue repair and regeneration holds great promise.

PRIMARY HEMATOPOIETIC FAILURE SYNDROMES

Diseases of the HSC that disrupt the normal regulated pattern of stem cell development can result in underproduction of mature progeny (i.e., aplastic anemia), overproduction of mature progeny (i.e., myeloproliferative disease), or failed differentiation with the production of excess immature forms (i.e., myelodysplasia and acute leukemia). *Hematopoietic failure*, defined as the inability of HSCs to produce normal numbers of mature blood cells, manifests clinically as peripheral pancytopenia (i.e., decreased production of all blood cell lineages).

Although marrow dysfunction producing pancytopenia can result from several hematologic and nonhematologic causes (Table 45-3), primary bone marrow failure disorders are characterized by a profound impairment of the ability of the HSC to replenish the stem cell pool. Rarely, marrow failure syndromes result from intrinsic HSC defects. In most cases, these disorders are the result of extrinsic damage to normal HSCs. The most common treatment modalities for primary hematopoietic failure disorders are exogenous growth factor administration and stem cell transplantation.

Growth Factors in Clinical Use

Discovery of the factors that influence normal hematopoiesis led to important therapeutic applications for patients with defects in hematopoietic cell production. The finding that committed hematopoietic cells of each lineage can be stimulated to proliferate and differentiate by specific cytokines (see Table 45-2) has been clinically useful.

Advances in DNA technology led to the synthesis and purification of recombinant human (rh) proteins with similar biologic activity in vivo. Administration of these products to patients enabled successful manipulation of mature cells in the peripheral

TABLE 45-3 DIFFERENTIAL DIAGNOSIS OF PANCYTOPENIA

Primary bone marrow disorders
- Aplastic anemia
- Congenital aplastic anemia syndromes
- Fanconi's anemia
- Shwachman-Diamond syndrome
- Congenital dyskeratosis
- Acquired aplastic anemia
- Hypocellular myelodysplastic syndrome
- Myelofibrosis
- Paroxysmal nocturnal hemoglobinuria
- Acute leukemias: acute lymphocytic leukemia, acute myeloid leukemia
- Hairy cell leukemia

Systemic diseases with secondary bone marrow effects
- Metastatic solid tumor to marrow
- Autoimmune disorders: systemic lupus erythematosus, Sjögren's syndrome
- Nutritional deficiencies: vitamin B_{12}, folate, alcoholism
- Infections: overwhelming sepsis from any cause, viruses, brucellosis, ehrlichiosis (mycobacteria)
- Storage diseases: Gaucher's disease, Niemann-Pick disease
- Anatomic defects: hypersplenism