along particular lineages. Some of these cells are referred to as *colony-forming units* (CFUs) (Fig. 13-1), because they produce colonies composed of specific kinds of mature cells when grown in culture. From the various committed progenitors are derived the morphologically recognizable precursors, such as myeloblasts, proerythroblasts, and megakaryoblasts, which are the immediate progenitors of mature granulocytes, red cells, and platelets.

HSCs have two essential properties that are required for the maintenance of hematopoiesis: pluripotency and the capacity for self-renewal. Pluripotency refers to the ability of a single HSC to generate all mature blood cells. When an HSC divides, at least one daughter cell must self-renew to avoid stem cell depletion. Self-renewing divisions occur within a specialized marrow niche, in which stromal cells and secreted factors nurture and protect the HSCs. As one might surmise from their ability to migrate during embryonic development, HSCs are not sessile. Particularly under conditions of marked stress, such as severe anemia or acute inflammation, HSCs are mobilized from the bone marrow and appear in the peripheral blood. In fact, HSCs used in transplantation are now mainly collected from the peripheral blood of donors treated with granulocyte colony stimulating factor (G-CSF), one of the factors that can mobilize a fraction of marrow HSCs from their stem cell niches.

The marrow response to short-term physiologic needs is regulated by hematopoietic growth factors through effects on the committed progenitors. Because mature blood elements are terminally differentiated cells with finite life spans, their numbers must be constantly replenished. In current models of hematopoiesis, some divisions of HSCs give rise to cells referred to as *multipotent progenitors*, which are more proliferative than HSCs but have a lesser capacity for self-renewal (Fig. 13-1). Division of multipotent progenitors gives rise to at least one daughter cell that leaves the stem cell pool and begins to differentiate. Once past this threshold, these newly committed cells lose the capacity for self-renewal and commence an inexorable journey down a road that leads to terminal differentiation and death. However, as these progenitors differentiate, they also begin to proliferate more rapidly in response to growth factors, expanding their numbers. Some growth factors, such as stem cell factor (also called *KIT ligand*) and FLT3-ligand, act through receptors that are expressed on very early committed progenitors. Others, such as erythropoietin, granulocyte-macrophage colony-stimulating factor (GM-CSF), G-CSF, and thrombopoietin, act through receptors that are only expressed on committed progenitors with more restricted differentiation potentials. Feedback loops involving these lineage-specific growth factors tune the marrow output, allowing the numbers of formed blood elements (red cells, white cells, and platelets) to be maintained within appropriate ranges (Table 13-1).

Many diseases alter the production of blood cells. The marrow is the ultimate source of most cells of the innate and adaptive immune system and responds to infectious or inflammatory challenges by increasing its output of granulocytes under the direction of specific growth factors and cytokines. By contrast, many other disorders are associated with defects in hematopoiesis that lead to deficiencies of one or more types of blood cells. Primary tumors of hematopoietic cells are among the most important diseases that interfere with marrow function, but certain genetic diseases, infections, toxins, and nutritional deficiencies, as well as chronic inflammation from any cause, can also decrease the production of blood cells by the marrow.

Table 13-1 Adult Reference Ranges for Blood Cells*

Cell Type	
White cells ($\times 10^3/\mu L$)	4.8-10.8
Granulocytes (%)	40-70
Neutrophils ($\times 10^3/\mu L$)	1.4-6.5
Lymphocytes ($\times 10^3/\mu L$)	1.2-3.4
Monocytes ($\times 10^3/\mu L$)	0.1-0.6
Eosinophils ($\times 10^3/\mu L$)	0-0.5
Basophils ($\times 10^3/\mu L$)	0-0.2
Red cells ($\times 10^3/\mu L$)	4.3-5, men; 3.5-5, women
Platelets ($\times 10^3/\mu L$)	150-450

*Reference ranges vary among laboratories. The reference ranges for the laboratory providing the result should always be used.

Tumors of hematopoietic origin are often associated with mutations that block progenitor cell maturation or abrogate their growth factor dependence. The net effect of such derangements is an unregulated clonal expansion of hematopoietic elements, which replace normal marrow progenitors and often spread to other hematopoietic tissues. In some instances, these tumors originate from transformed HSCs that retain the ability to differentiate along multiple lineages, whereas in other instances the origin is a more differentiated progenitor that has acquired an abnormal capacity for self-renewal (Chapter 7).

MORPHOLOGY

The bone marrow is a unique microenvironment that supports the orderly proliferation, differentiation, and release of blood cells. It is filled with a network of thin-walled sinusoids lined by a single layer of endothelial cells, which are underlaid by a discontinuous basement membrane and adventitial cells. Within the interstitium lie clusters of hematopoietic cells and fat cells. Differentiated blood cells enter the circulation by transcellular migration through the endothelial cells.

The normal marrow is organized in subtle, but important, ways. For example, normal **megakaryocytes** lie next to sinusoids and extend cytoplasmic processes that bud off into the bloodstream to produce platelets, while red cell precursors often surround macrophages (so-called *nurse cells*) that provide some of the iron needed for the synthesis of hemoglobin. Processes that distort the marrow architecture, such as deposits of metastatic cancer or granulomatous disorders, can cause the abnormal release of immature precursors into the peripheral blood, a finding that is referred to as **leukoerythroblastosis**.

Marrow aspirate smears provide the best assessment of the morphology of hematopoietic cells. The most mature marrow precursors can be identified based on their morphology alone. Immature precursors ("blast" forms) of different types are morphologically similar and must be identified definitively using lineage-specific antibodies and histochemical markers (described later under white cell neoplasms). Biopsies are a