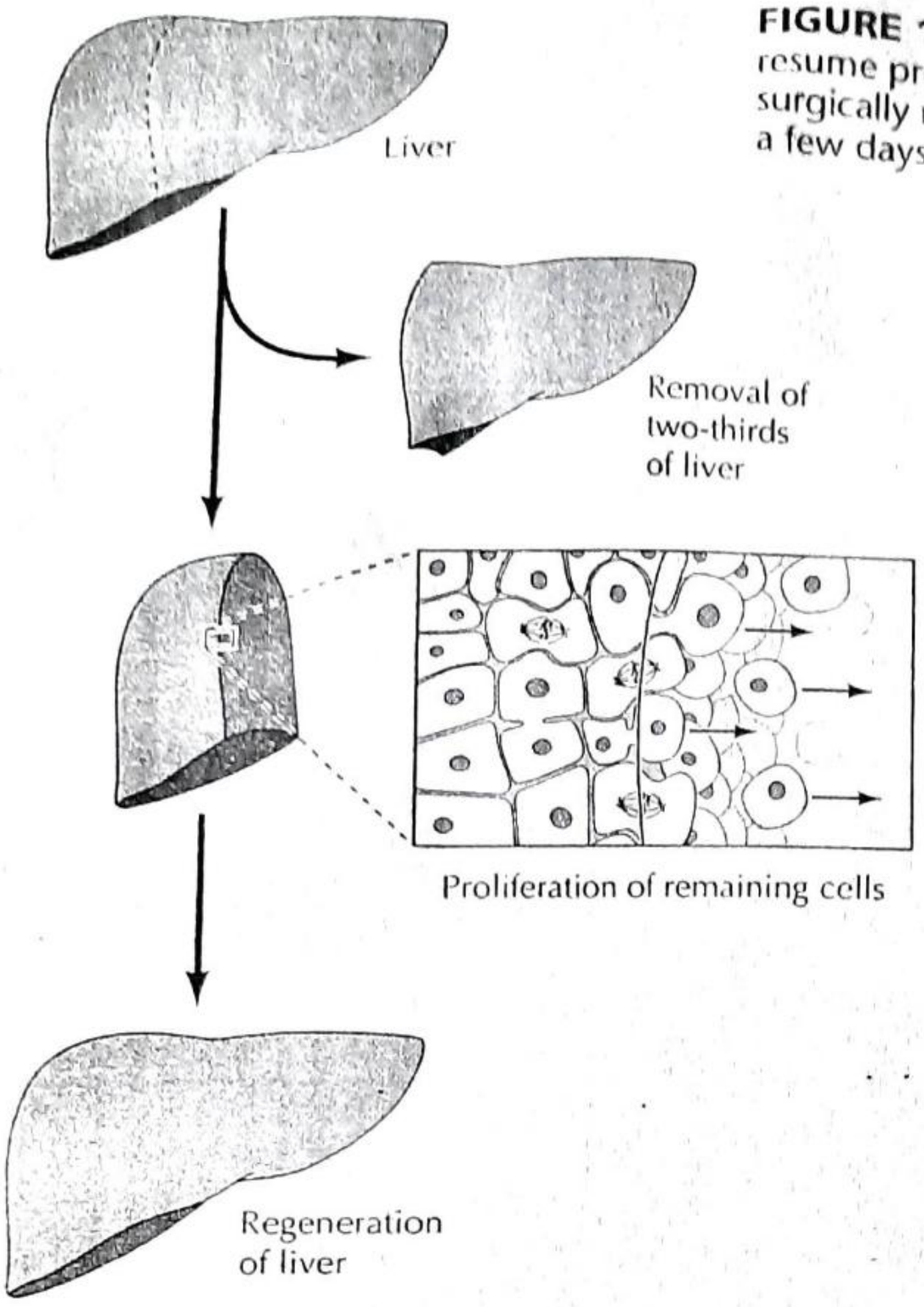


FIGURE 17.16 Liver regeneration Liver cells are normally arrested in G_0 but resume proliferation to replace damaged tissue. If two-thirds of the liver of a rat is surgically removed, the remaining cells proliferate to regenerate the entire liver in a few days.

The epithelial cells of some internal organs are also able to proliferate to replace damaged tissue. A striking example is provided by liver cells, which are normally arrested in the G_0 phase of the cell cycle. However, if large numbers of liver cells are lost (e.g., by surgical removal of part of the liver), the remaining cells are stimulated to proliferate to replace the missing tissue (**Figure 17.16**). For example, surgical removal of two-thirds of the liver of a rat is followed by rapid proliferation of the remaining cells, leading to regeneration of the entire liver within a few days.

Stem Cells

Most fully differentiated cells in adult animals, however, are no longer capable of cell division. Nonetheless, they can be replaced by the proliferation of a subpopulation of less differentiated self-renewing cells called **stem cells** that are present in most adult tissues. Because they retain the capacity to proliferate and replace differentiated cells throughout the lifetime of an animal, stem cells play a critical role in the maintenance of most tissues and organs.

The key property of stem cells is that they divide to produce one daughter cell that remains a stem cell and one that divides and differentiates (**Figure 17.17**). Because the division of stem cells produces new stem cells as well as differentiated daughter cells, stem cells are self-renewing populations that can serve as a source for the production of differentiated cells throughout life. The role of stem cells is particularly evident in the case of several types of differentiated cells, including blood cells, sperm, epithelial cells of the skin, and epithelial cells lining the digestive tract—all of which have short life spans and must be replaced by continual cell proliferation in adult animals. In all of these cases, the fully differentiated cells do not themselves proliferate; instead, they are continually renewed by the proliferation of stem cells that then differentiate to maintain a stable number of differentiated cells. Stem cells have also been identified in a variety of other adult tissues, including skeletal muscle and the nervous system, where they function to replace damaged tissue.

Stem cells were first identified in the hematopoietic (blood-forming) system by Ernest McCulloch and James Till in 1961 in experiments showing that single cells derived from mouse bone marrow could proliferate and give rise to multiple differentiated types of blood cells. Hematopoietic stem cells are well-characterized and the production of blood cells provides a good example of the role of stem cells in maintaining differentiated cell populations. There are several distinct types of blood cells with specialized functions: erythrocytes (red blood cells) that transport O_2 and CO_2; granulocytes and macrophages, which are phagocytic cells; platelets (which are fragments of megakaryocytes) that function in blood coagulation; and lymphocytes that are responsible for the immune response. All these cells have limited life spans ranging from less than a day to a few months, and all are derived from the same population of hematopoietic stem cells. More than

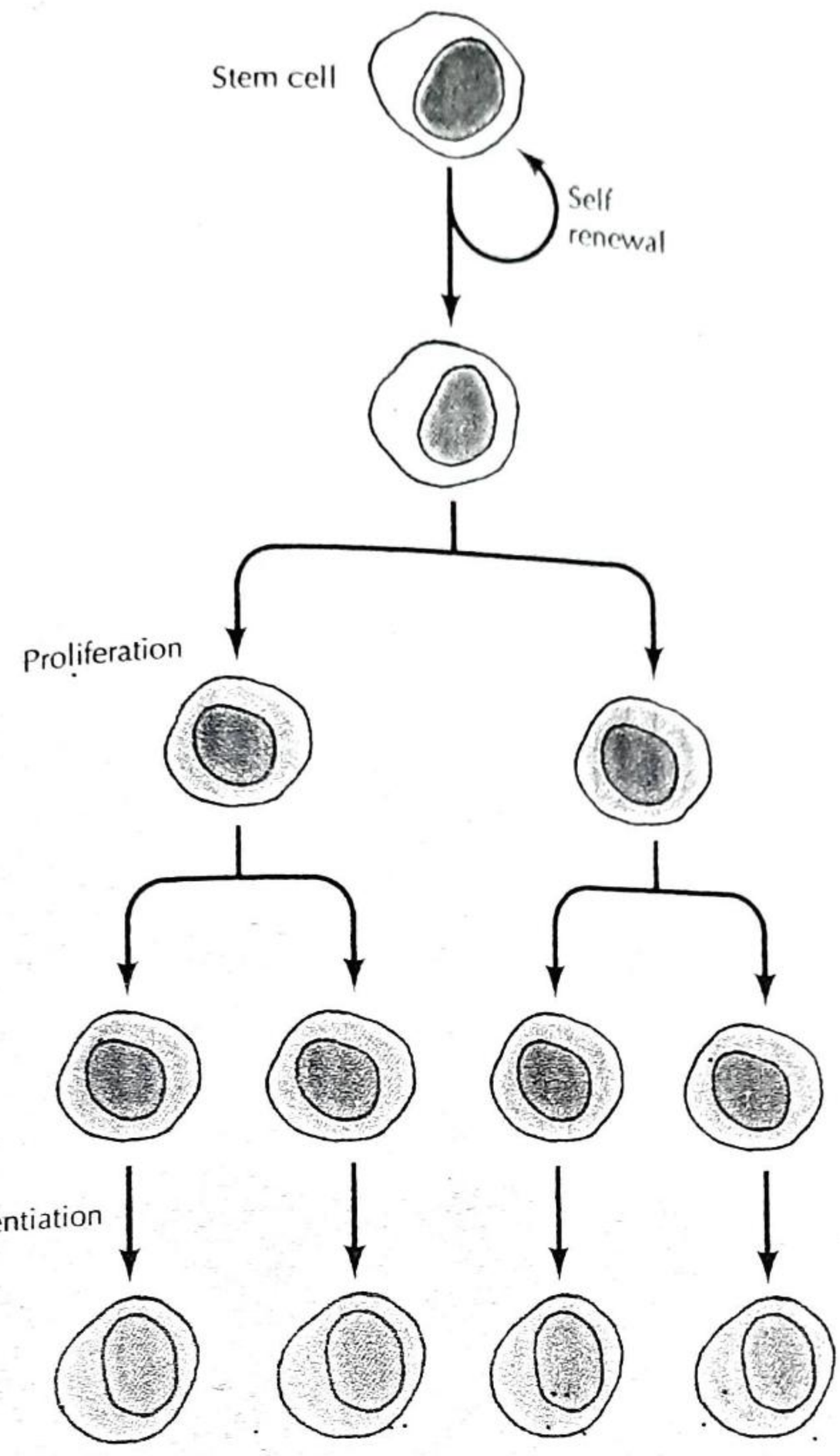


FIGURE 17.17 · Stem cell proliferation Stem cells divide to form one daughter cell that remains a stem cell and a second that proliferates and then differentiates.

100 billion blood cells are lost every day in humans, and must be continually produced from hematopoietic stem cells in the bone marrow (**Figure 17.18**). Descendants of the hematopoietic stem cell continue to proliferate and undergo several rounds of division as they become committed to specific differentiation pathways that are determined by growth factors that channel precursor cells along specific pathways of blood cell differentiation. Once they become fully differentiated, blood cells cease proliferation, so the maintenance of differentiated blood cell populations is dependent on continual division of the self-renewing hematopoietic stem cell.

The intestine provides an excellent example of stem cells in the self-renewal of an epithelial tissue. The intestine is lined by a single layer of epithelial cells that are responsible for the digestion of food and absorption of nutrients. These intestinal epithelial cells are exposed to an extraordinarily harsh environment and have a lifetime of only a few days before they die by apoptosis and are shed into the digestive tract. Renewal of the intestinal epithelium is therefore a continual process throughout life. New cells

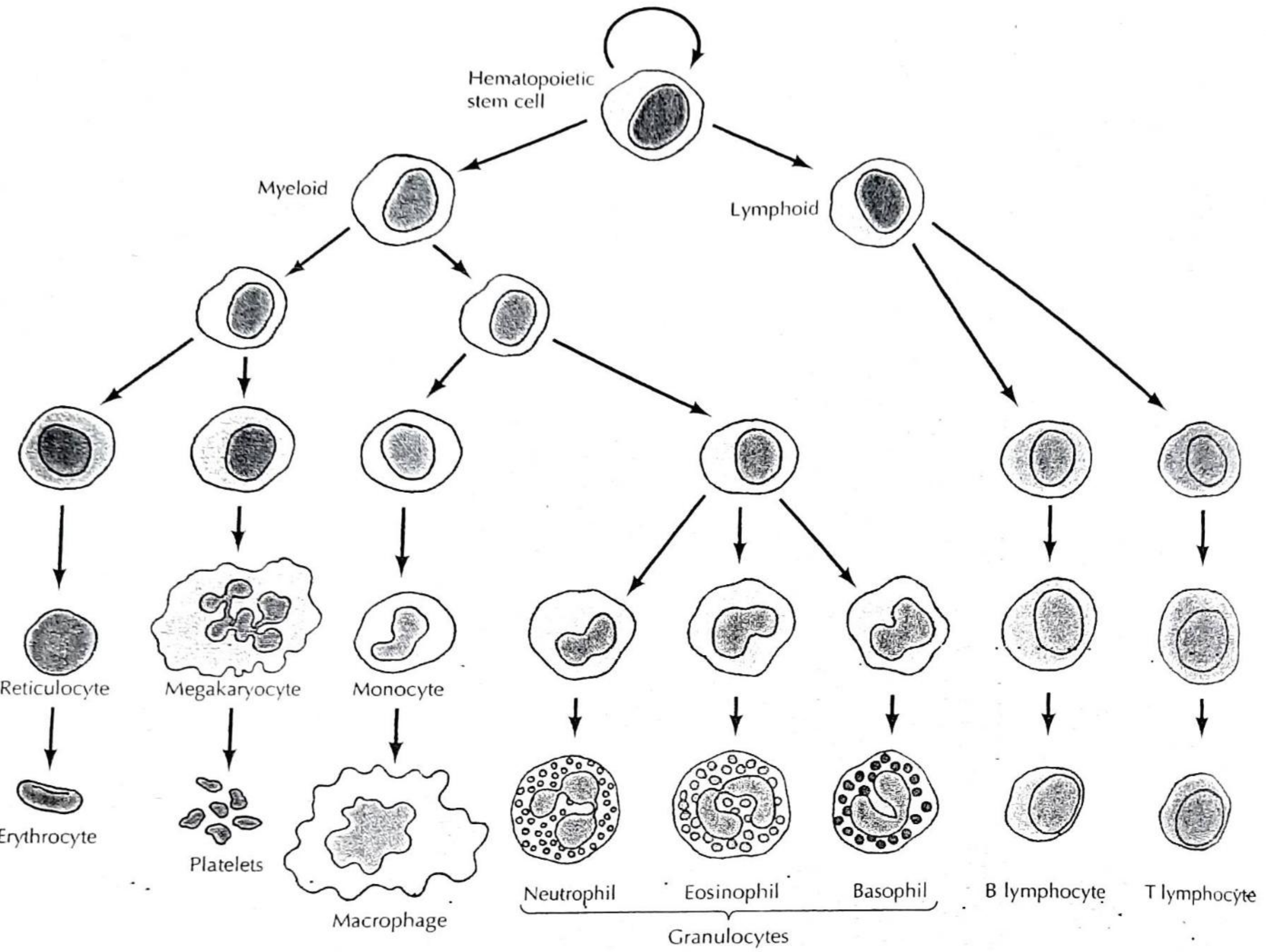
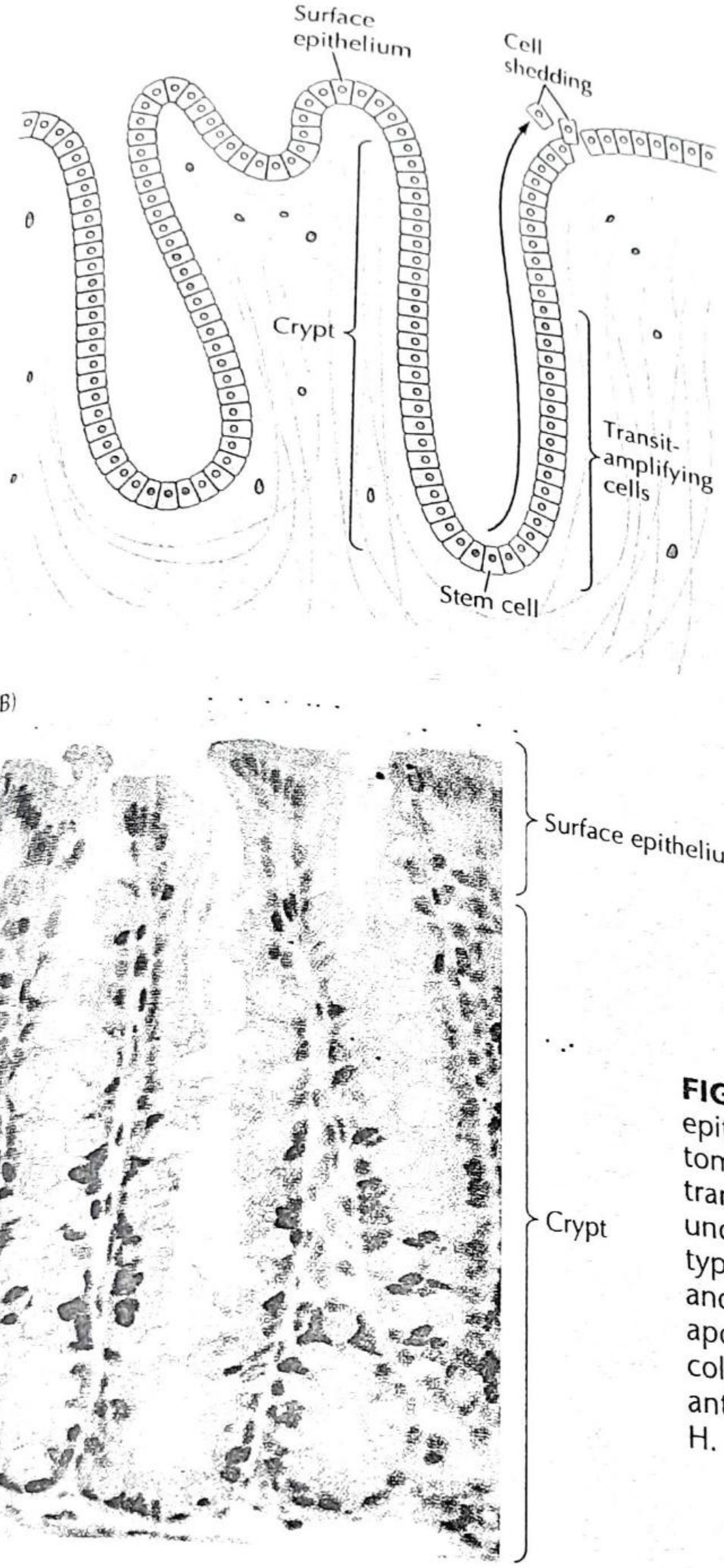


FIGURE 17.18 Formation of blood cells All of the different types of blood cells develop from a hematopoietic stem cell in the bone marrow. The precursors of differentiated cells undergo several rounds of cell division before they differentiate.

are derived from the continuous but slow division of stem cells at the bottom of intestinal crypts (**Figure 17.19**). The stem cells give rise to a population of transit-amplifying cells, which divide rapidly and occupy about two-thirds of the crypt. The transit-amplifying cells proliferate for three to four cell divisions and then differentiate into the three cell types of the colon surface epithelium: absorptive epithelial cells and two types of secretory cells, called goblet cells and enteroendocrine cells. The small intestine also contains a fourth cell type, Paneth cells, which secrete antibacterial agents. Each crypt contains approximately six self-renewing stem cells, which can give rise to all of the different types of cells in the intestinal epithelium.

Stem cells are also responsible for continuous renewal of the skin and hair. Like the lining of the intestine, the skin and hair are exposed to a harsh external environment—including ultraviolet radiation from sunlight—and are continuously renewed throughout life. The skin consists of three major cell lineages: the epidermis, hair follicles, and sebaceous glands, which



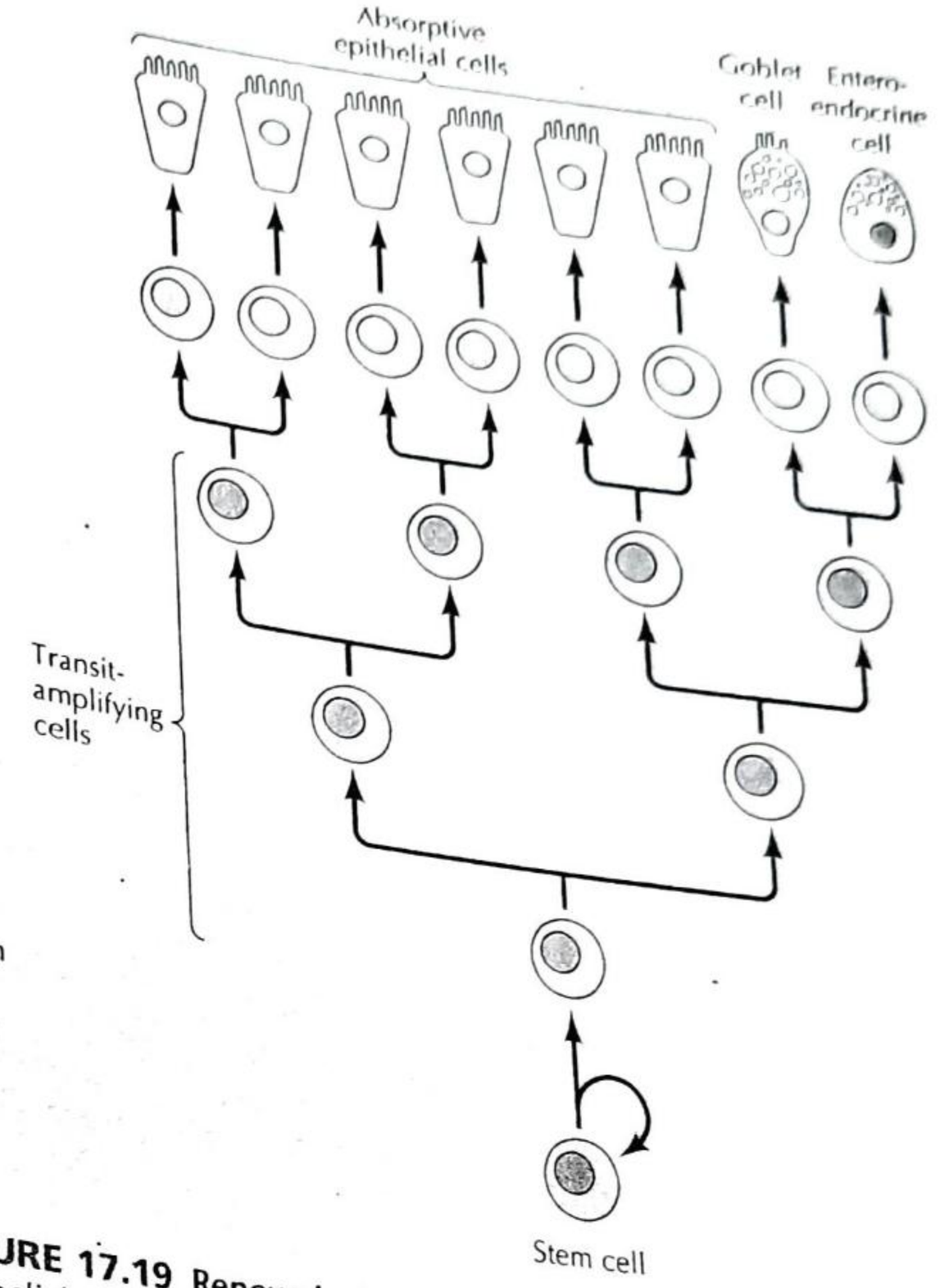


FIGURE 17.19 Renewal of the intestinal epithelium (A) Colon epithelial cells are renewed by division of stem cells located at the bottom of the intestinal crypt. The stem cell gives rise to a population of transit-amplifying cells, which occupy about two-thirds of the crypt and undergo three to four divisions before differentiating into the three cell types of the surface epithelium (absorptive epithelial cells, goblet cells, and enteroendocrine cells). The surface epithelial cells continually undergo apoptosis and are shed into the intestinal lumen. (B) Micrograph of a colon crypt and surface epithelium. Proliferating cells are stained with antibody against a cell cycle protein (brown nuclei). (From F. Radtke and H. Clevers, 2005. *Science* 307: 1904.)

release oils that lubricate the skin surface. Each of these three cell populations is maintained by their own stem cells (**Figure 17.20**). The epidermis is a multilayered epithelium, which is undergoing continual cell renewal. In humans, the epidermis turns over every two weeks, with cells being sloughed from the surface. These cells are replaced by epidermal stem cells, which reside in a single basal layer. The epidermal stem cells give rise to transit-amplifying cells, which undergo three to six divisions before differentiating and moving outward to the surface of the skin. The stem cells responsible for producing hair reside in a region of the hair follicle called the bulge. The bulge stem cells give rise to transit-amplifying matrix cells,

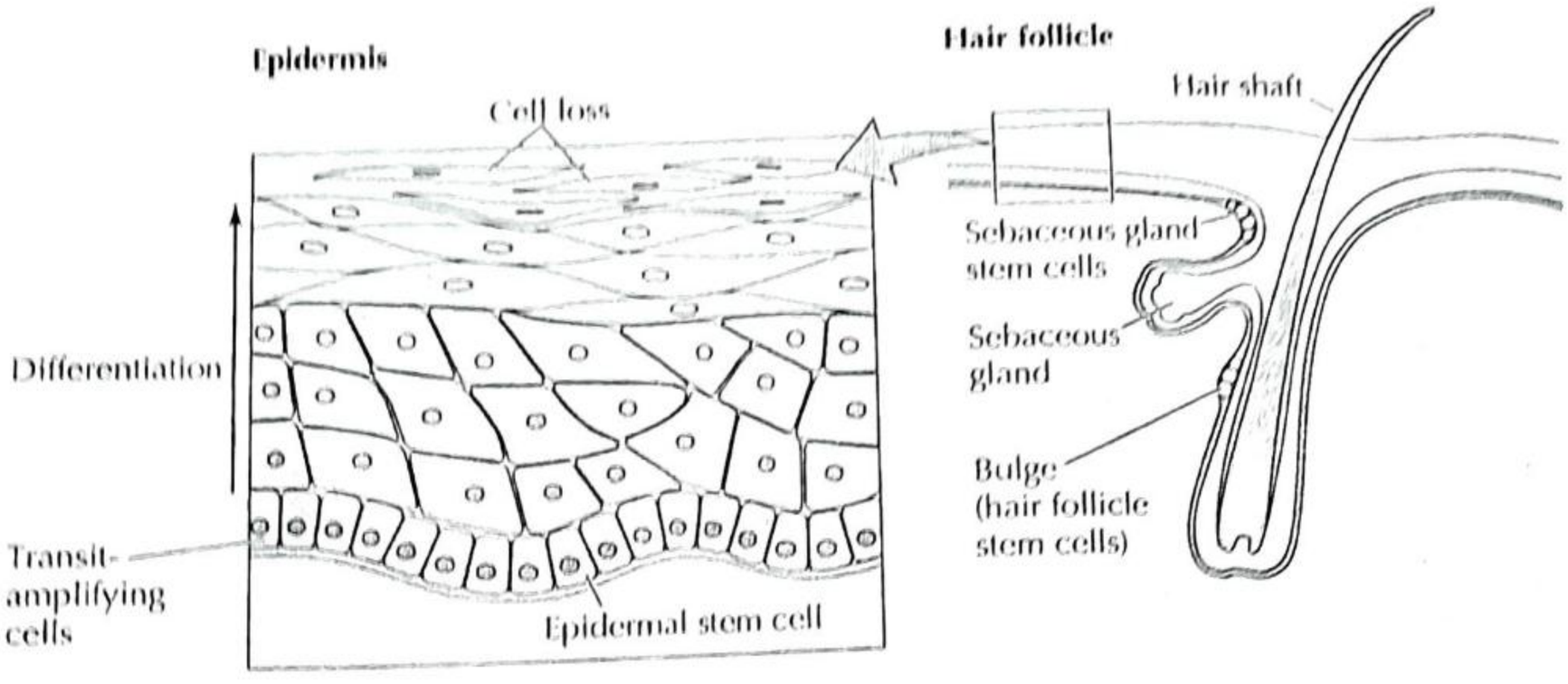


FIGURE 17.20 Stem cells of the skin The epidermis consists of multiple layers of epithelial cells. Cells from the surface are continually lost and replaced by epidermal stem cells in the basal layer. The stem cells give rise to transit-amplifying cells, which undergo several divisions in the basal layer before differentiating and moving to the surface of the skin. Stem cells of hair follicles reside in a region beneath the sebaceous gland called the bulge, and distinct stem cells of the sebaceous gland reside at its base.

which proliferate and differentiate to form the hair shaft. Finally, a distinct population of stem cells resides at the base of the sebaceous gland. It is notable that, if the skin is injured, stem cells of the bulge can also give rise to epidermis and sebaceous glands, demonstrating their activity as multipotent stem cells from which both skin and hair can be derived.

Skeletal muscle provides an example of the role of stem cells in the repair of damaged tissue, in contrast to the continual cell renewal just described in the hematopoietic system, intestinal epithelium, and skin. Skeletal muscle is composed of large multinucleated cells (muscle fibers) formed by cell fusion during development (see Figure 12.21). Although skeletal muscle is normally a stable tissue with little cell turnover, it is able to regenerate rapidly in response to injury or exercise. This regeneration is mediated by proliferation of satellite cells, which are the stem cells of adult muscle. Satellite cells are located beneath the basal lamina of muscle fibers (**Figure 17.21**). They are normally quiescent, arrested in the G_0 phase of the cell cycle, but are activated to proliferate in response to injury or exercise. Once activated, the satellite cells give rise to progeny that undergo several divisions and then differentiate and fuse to form new muscle fibers. The continuing capacity of skeletal muscle to regenerate throughout life is due to self-renewal of the satellite stem cell population.

Stem cells have also been found in many other adult tissues, including the brain and heart, and it is possible that most—if not all—tissues contain stem cells with the potential of replacing cells that are lost during the lifetime of the organism. It appears that stem cells reside within distinct microenvironments, called **niches**, which provide the environmental signals that maintain stem cells throughout life and control the balance between their self-renewal and differentiation. Stem cells are rare in adult mammalian tissues, however, so the precise identification of stem cells and their niches represents a major challenge in the field of stem cell biology. For example, although the role of stem cells in maintenance of the intestinal epithelium has long been recognized, the intestinal stem cells at the base of the crypt (see Figure 17.19) were only recently identified by studies of Hans

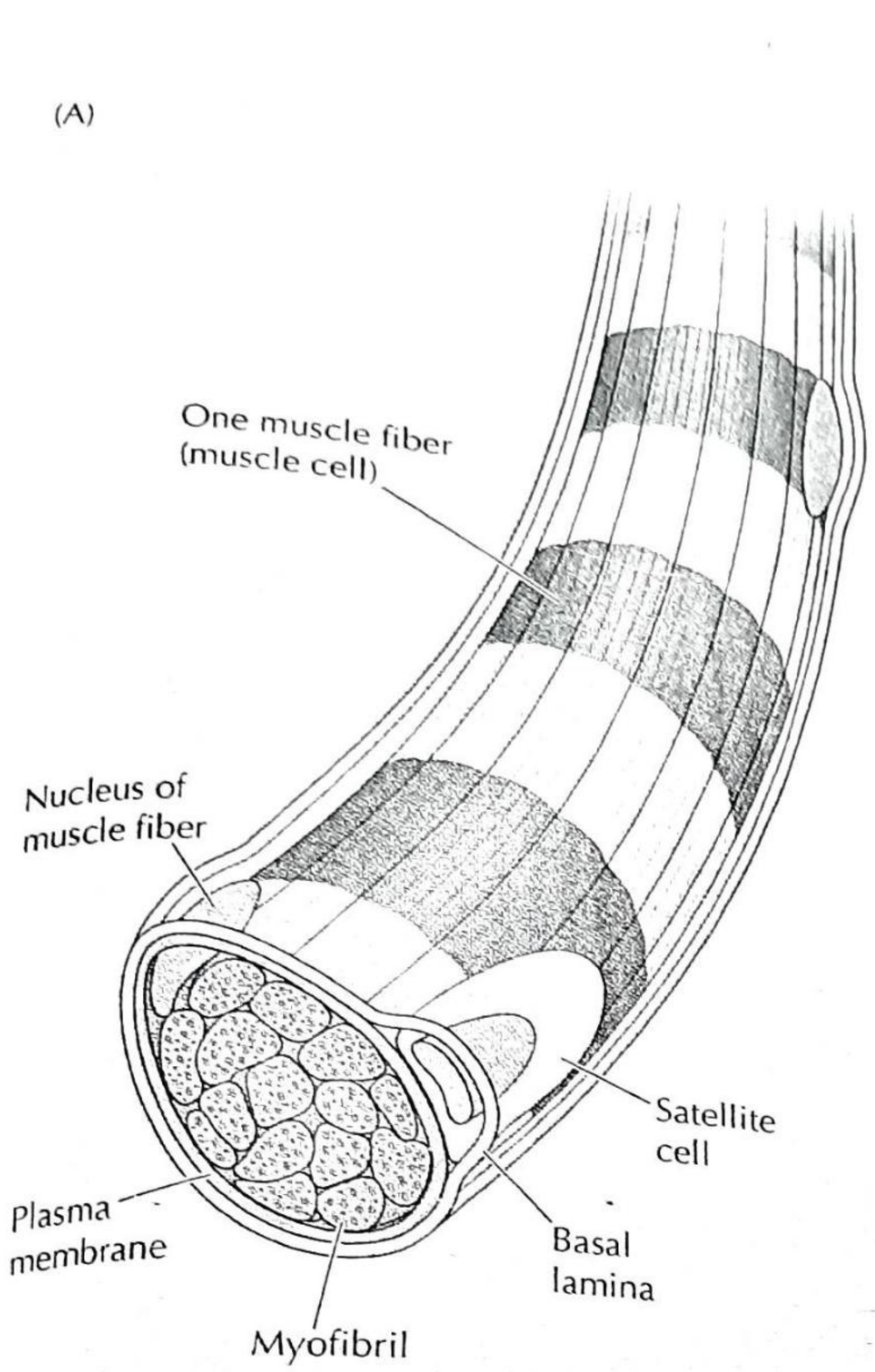


FIGURE 17.21 Muscle satellite cells (A) The stem cells of skeletal muscle are the satellite cells, located beneath the basal lamina of muscle fibers. (B) Electron micrograph showing a satellite cell and the nucleus of a muscle fiber. (From S. Chargé and M. Rudnicki, 2003. *Physiol. Rev.* 84: 209; courtesy of Sophie Chargé and Michael Rudnicki.)

Clever and his colleagues in 2007. Signaling by the Wnt pathway (see Figure 15.44) plays a major role in controlling the proliferation of these stem cells, and it is thought that Wnt polypeptides secreted by fibroblasts of the underlying connective tissue are responsible for intestinal stem cell maintenance. Wnt signaling is also involved in regulation of several other types of stem cells, including stem cells of the skin and hematopoietic system. In addition, signaling by the TGF-β, Hedgehog, and Notch pathways (see Figures 15.41, 15.43, and 15.45) play important roles in stem cell regulation, although the precise roles of these factors in regulating different types of stem cells within their distinct niches remains to be understood.