as disseminated intravascular coagulation, hypotensive shock, and metabolic disturbances including insulin resistance and hyperglycemia. This clinical triad is known as *septic shock*; it is discussed in more detail in Chapter 4.

KEY CONCEPTS

Systemic Effects of Inflammation

- Fever: cytokines (TNF, IL-1) stimulate production of prostaglandins in hypothalamus
- Production of acute-phase proteins: C-reactive protein, others; synthesis stimulated by cytokines (IL-6, others) acting on liver cells
- Leukocytosis: cytokines (colony-stimulating factors) stimulate production of leukocytes from precursors in the bone marrow
- In some severe infections, septic shock: fall in blood pressure, disseminated intravascular coagulation, metabolic abnormalities; induced by high levels of TNF and other cytokines

Excessive inflammation is the underlying cause of many human diseases, described throughout this book. Conversely, defective inflammation is responsible for increased susceptibility to infections. The most common cause of defective inflammation is leukocyte deficiency resulting from replacement of the bone marrow by leukemias and metastatic tumors, and suppression of the marrow by therapies for cancer and graft rejection. Inherited genetic abnormalities of leukocyte adhesion and microbicidal function are rare but very informative; these are described in Chapter 6, in the context of immunodeficiency diseases. Deficiencies of the complement system are mentioned earlier and are described further in Chapter 6.

We next consider the process of *repair,* which is a healing response to tissue destruction caused by inflammatory or non-inflammatory causes.

Tissue Repair

Overview of Tissue Repair

Repair, sometimes called healing, refers to the restoration of tissue architecture and function after an injury. (By convention, the term *repair* is often used for parenchymal and connective tissues and *healing* for surface epithelia, but these distinctions are not based on biology and we use the terms interchangeably.) Critical to the survival of an organism is the ability to repair the damage caused by toxic insults and inflammation. Hence, the inflammatory response to microbes and injured tissues not only serves to eliminate these dangers but also sets into motion the process of repair.

Repair of damaged tissues occurs by two types of reactions: regeneration by proliferation of residual (uninjured) cells and maturation of tissue stem cells, and the deposition of connective tissue to form a scar (Fig. 3-24).

- **Regeneration.** Some tissues are able to replace the damaged components and essentially return to a normal state; this process is called *regeneration*. Regeneration occurs by proliferation of cells that survive the injury and retain the capacity to proliferate, for example, in the rapidly dividing epithelia of the skin and intestines, and in some parenchymal organs, notably the liver. In other cases, tissue stem cells may contribute to the restoration of damaged tissues. However, mammals have a limited capacity to regenerate damaged tissues and organs, and only some components of most tissues are able to fully restore themselves.
- **Connective tissue deposition (scar formation).** If the injured tissues are incapable of complete restitution, or if the supporting structures of the tissue are severely damaged, repair occurs by the laying down of connective (fibrous) tissue, a process that may result in scar formation. Although the fibrous scar is not normal, it provides enough structural stability that the injured tissue is usually able to function. The term *fibrosis* is most often used to describe the extensive deposition of collagen that occurs in the lungs, liver, kidney, and other organs as a consequence of chronic inflammation, or in the myocardium after extensive ischemic necrosis (infarction). If fibrosis develops in a tissue space occupied by an inflammatory exudate, it is called *organization* (as in organizing pneumonia affecting the lung).

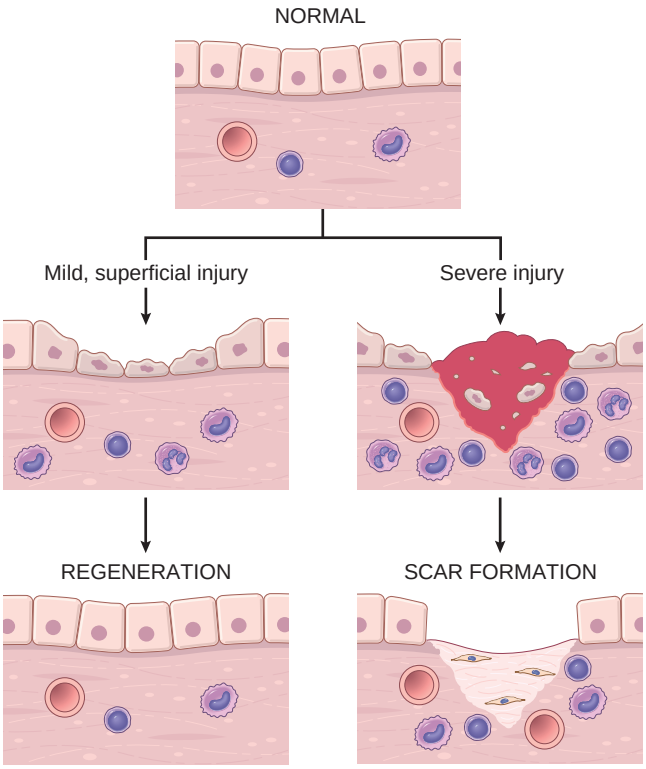

Figure 3-24 Mechanisms of tissue repair: regeneration and scar formation. Following mild injury, which damages the epithelium but not the underlying tissue, resolution occurs by regeneration, but after more severe injury with damage to the connective tissue, repair is by scar formation.

After many common types of injury, both regeneration and scar formation contribute in varying degrees to the ultimate repair. Both processes involve the proliferation of various cells, and close interactions between cells and the extracellular matrix (ECM). We first discuss the general