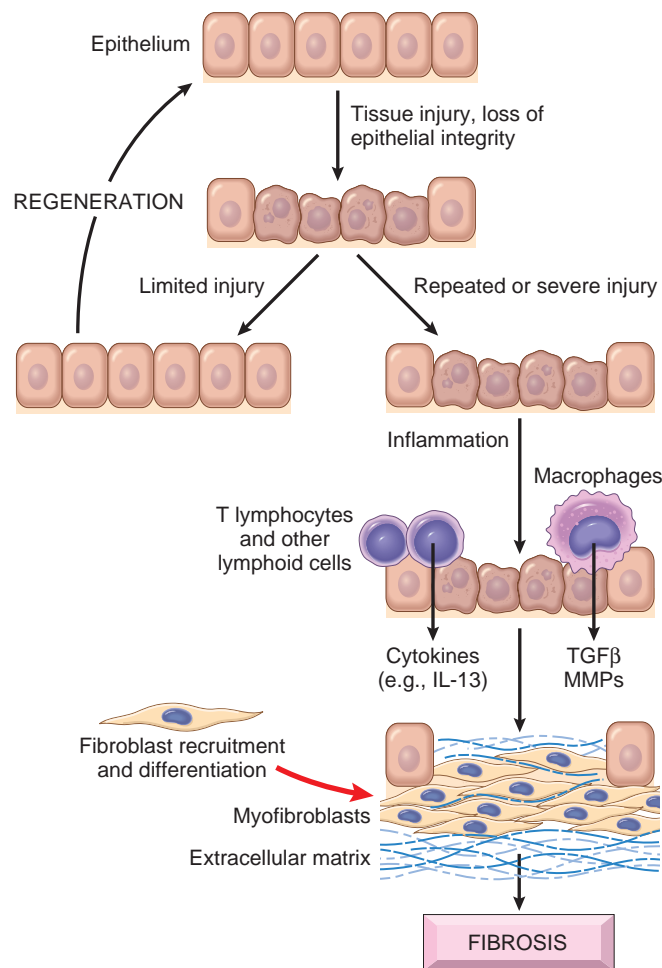


modifications of collagen fibers (cross-linking, increased fiber size) after collagen synthesis ceases. Wound strength reaches approximately 70% to 80% of normal by 3 months but usually does not substantially improve beyond that point.

### Fibrosis in Parenchymal Organs

Deposition of collagen is part of normal wound healing. The term *fibrosis* is used to denote the excessive deposition of collagen and other ECM components in a tissue. As already mentioned, the terms *scar* and *fibrosis* are used interchangeably, but *fibrosis* most often refers to the abnormal deposition of collagen that occurs in internal organs in chronic diseases. The basic mechanisms of fibrosis are the same as those of scar formation in the skin during tissue repair. Fibrosis is a pathologic process induced by persistent injurious stimuli such as chronic infections and immunologic reactions, and is typically associated with loss of tissue (Fig. 3-31). It may be responsible for substantial organ dysfunction and even organ failure.



**Figure 3-31** Mechanisms of fibrosis. Persistent tissue injury leads to chronic inflammation and loss of tissue architecture. Cytokines produced by macrophages and other leukocytes stimulate the migration and proliferation of fibroblasts and myfibroblasts and the deposition of collagen and other extracellular matrix proteins. The net result is replacement of normal tissue by fibrosis.

As discussed earlier, the major cytokine involved in fibrosis is TGF- $\beta$ . The mechanisms that lead to the activation of TGF- $\beta$  in fibrosis are not precisely known, but cell death by necrosis or apoptosis and the production of reactive oxygen species seem to be important triggers of the activation, regardless of the tissue. Similarly, the cells that produce collagen under TGF- $\beta$  stimulation may vary depending on the tissue. In most organs, such as in lung and kidney, myofibroblasts are the main source of collagen, but stellate cells are the major collagen producers in liver cirrhosis.

Fibrotic disorders include diverse chronic and debilitating diseases such as liver cirrhosis, systemic sclerosis (scleroderma), fibrosing diseases of the lung (idiopathic pulmonary fibrosis, pneumoconioses, and drug-, radiation-induced pulmonary fibrosis), end-stage kidney disease, and constrictive pericarditis. These conditions are discussed in the appropriate chapters throughout the book. Because of the tremendous functional impairment caused by fibrosis in these conditions, there is great interest in the development of antifibrotic drugs.

### Abnormalities in Tissue Repair

Complications in tissue repair can arise from abnormalities in any of the basic components of the process, including deficient scar formation, excessive formation of the repair components, and formation of contractures.

- Inadequate formation of granulation tissue or formation of a scar can lead to two types of complications: wound dehiscence and ulceration.** Dehiscence or rupture of a wound, although not common, occurs most frequently after abdominal surgery and is due to increased abdominal pressure. Vomiting, coughing, or ileus can generate mechanical stress on the abdominal wound. Wounds can ulcerate because of inadequate vascularization during healing. For example, lower extremity wounds in individuals with atherosclerotic peripheral vascular disease typically ulcerate (Chapter 11). Nonhealing wounds also form in areas devoid of sensation. These neuropathic ulcers are occasionally seen in patients with diabetic peripheral neuropathy (Chapters 24 and 27).
- Excessive formation of the components of the repair process can give rise to hypertrophic scars and keloids.** The accumulation of excessive amounts of collagen may give rise to a raised scar known as a *hypertrophic scar*; if the scar tissue grows beyond the boundaries of the original wound and does not regress, it is called a *keloid* (Fig. 3-32). Keloid formation seems to be an individual predisposition, and for unknown reasons this aberration is somewhat more common in African Americans. Hypertrophic scars generally develop after thermal or traumatic injury that involves the deep layers of the dermis.
- Exuberant granulation** is another deviation in wound healing consisting of the formation of excessive amounts of granulation tissue, which protrudes above the level of the surrounding skin and blocks reepithelialization (this process has been called, with more literary fervor, *proud flesh*). Excessive granulation must be removed by cautery or surgical excision to permit restoration of the