sic (e.g., infection) or intrinsic to the injured tissue, and systemic or local:

- **Infection** is clinically one of the most important causes of delay in healing; it prolongs inflammation and potentially increases the local tissue injury.
- **Diabetes** is a metabolic disease that compromises tissue repair for many reasons (Chapter 24), and is one of the most important systemic causes of abnormal wound healing.
- **Nutritional status** has profound effects on repair; protein deficiency, for example, and particularly vitamin C deficiency, inhibits collagen synthesis and retards healing.
- **Glucocorticoids (steroids)** have well-documented anti-inflammatory effects, and their administration may result in weakness of the scar due to inhibition of TGF-β production and diminished fibrosis. In some instances, however, the anti-inflammatory effects of glucocorticoids are desirable. For example, in corneal infections, glucocorticoids are sometimes prescribed (along with antibiotics) to reduce the likelihood of opacity that may result from collagen deposition.
- **Mechanical factors** such as increased local pressure or torsion may cause wounds to pull apart, or dehisce.
- **Poor perfusion,** due either to arteriosclerosis and diabetes or to obstructed venous drainage (e.g., in varicose veins), also impairs healing.
- **Foreign bodies** such as fragments of steel, glass, or even bone impede healing.
- **The type and extent of tissue injury** affects the subsequent repair. Complete restoration can occur only in tissues composed of stable and labile cells; even then, extensive injury will probably result in incomplete tissue regeneration and at least partial loss of function. Injury to tissues composed of permanent cells must inevitably result in scarring with, at most, attempts at functional compensation by the remaining viable elements. Such is the case with healing of a myocardial infarct.
- The **location of the injury** and the character of the tissue in which the injury occurs are also important. For example, inflammation arising in tissue spaces (e.g., pleural, peritoneal, synovial cavities) develops extensive exudates. Subsequent repair may occur by digestion of the exudate, initiated by the proteolytic enzymes of leukocytes and resorption of the liquefied exudate. This is called *resolution*, and in the absence of cellular necrosis, normal tissue architecture is generally restored. However, in the setting of larger accumulations, the exudate undergoes organization: granulation tissue grows into the exudate, and a fibrous scar ultimately forms.

Selected Clinical Examples of Tissue Repair and Fibrosis

So far, we have discussed the general principles and mechanisms of repair by regeneration and scar formation. In this section we describe two clinically significant types of repair—the healing of skin wounds (cutaneous wound healing) and fibrosis in injured parenchymal organs.

Healing of Skin Wounds

This is a process that involves both epithelial regeneration and the formation of connective tissue scar and is thus illustrative of the general principles that apply to healing in all tissues.

Based on the nature and size of the wound, the healing of skin wounds is said to occur by first or second intention.

Healing by First Intention

When the injury involves only the epithelial layer, the principal mechanism of repair is epithelial regeneration, also called *primary union* or *healing by first intention.* One of the simplest examples of this type of wound repair is the healing of a clean, uninfected surgical incision approximated by surgical sutures (Fig. 3-29). The incision causes only focal disruption of epithelial basement membrane continuity and death of relatively few epithelial and connective tissue cells. The repair consists of three connected processes: *inflammation*, *proliferation* of epithelial and other cells, and *maturation* of the connective tissue scar.

- Wounding causes the rapid activation of coagulation pathways, which results in the formation of a blood clot on the wound surface (Chapter 4). In addition to entrapped red cells, the clot contains fibrin, fibronectin, and complement proteins. The clot serves to stop bleeding and acts as a scaffold for migrating cells, which are attracted by growth factors, cytokines, and chemokines released into the area. Release of VEGF leads to increased vessel permeability and edema. As dehydration occurs at the external surface of the clot, a scab covering the wound is formed.
- Within 24 hours, neutrophils are seen at the incision margin, migrating toward the fibrin clot. They release proteolytic enzymes that begin to clear the debris. Basal cells at the cut edge of the epidermis begin to show increased mitotic activity. Within 24 to 48 hours, epithelial cells from both edges have begun to migrate and proliferate along the dermis, depositing basement membrane components as they progress. The cells meet in the midline beneath the surface scab, yielding a thin but continuous epithelial layer that closes the wound.
- By day 3, neutrophils have been largely replaced by macrophages, and granulation tissue progressively invades the incision space. As mentioned earlier, macrophages are key cellular constituents of tissue repair, clearing extracellular debris, fibrin, and other foreign material, and promoting angiogenesis and ECM deposition. Collagen fibers are now evident at the incision margins. Epithelial cell proliferation continues, forming a covering approaching the normal thickness of the epidermis.
- By day 5, neovascularization reaches its peak as granulation tissue fills the incisional space. These new vessels are leaky, allowing the passage of plasma proteins and fluid into the extravascular space. Thus, new granulation tissue is often edematous. Migration of fibroblasts to the site of injury is driven by chemokines, TNF, PDGF, TGF-β, and FGF. Their subsequent proliferation is triggered by multiple growth factors, including PDGF, EGF, TGF-β, and FGF, and the cytokines IL-1 and