consists of both hypertrophy and hyperplasia of proximal duct cells. The mechanisms underlying this response are not understood, but likely involve local production of growth factors and interactions of cells with the ECM. The extraordinary capacity of the liver to regenerate has made it a valuable model for studying this process, as described below.

Restoration of normal tissue structure can occur only if the residual tissue is structurally intact, as after partial surgical resection. By contrast, if the entire tissue is damaged by infection or inflammation, regeneration is incomplete and is accompanied by scarring. For example, extensive destruction of the liver with collapse of the reticulin framework, as occurs in a liver abscess, leads to scar formation even though the remaining liver cells have the capacity to regenerate.

Liver Regeneration

The human liver has a remarkable capacity to regenerate, as demonstrated by its growth after partial hepatectomy, which may be performed for tumor resection or for living-donor hepatic transplantation. The mythologic image of liver regeneration is the regrowth of the liver of Prometheus, which was eaten every day by an eagle sent by Zeus as punishment for stealing the secret of fire, and grew back overnight. The reality, although less dramatic, is still quite impressive.

Regeneration of the liver occurs by two major mechanisms: proliferation of remaining hepatocytes and repopulation from progenitor cells. Which mechanism plays the dominant role depends on the nature of the injury.

- **Proliferation of hepatocytes following partial hepatectomy.** In humans, resection of up to 90% of the liver can be corrected by proliferation of the residual hepatocytes. This classic model of tissue regeneration has been used experimentally to study the initiation and control of the process.

  Hepatocyte proliferation in the regenerating liver is triggered by the combined actions of cytokines and polypeptide growth factors. The process occurs in distinct stages (Fig. 3-25). In the first, or *priming*, phase, cytokines such as IL-6 are produced mainly by Kupffer cells and act on hepatocytes to make the parenchymal cells competent to receive and respond to growth factor signals. In the second, or *growth factor*, phase, growth factors such as HGF and TGF-α, produced by many cell types, act on primed hepatocytes to stimulate cell metabolism and entry of the cells into the cell cycle. Because hepatocytes are quiescent cells, it takes them several hours to enter the cell cycle, progress from G_0 to G_1, and reach the S phase of DNA replication. Almost all hepatocytes replicate during liver regeneration after partial hepatectomy. The wave of hepatocyte replication is followed by replication of nonparenchymal cells (Kupffer cells, endothelial cells, and stellate cells). During the phase of hepatocyte replication, more than 70 genes are activated; these include genes encoding transcription factors, cell cycle regulators, regulators of energy metabolism, and many others. In the final, *termination*, phase, hepatocytes return to quiescence. The nature of the stop signals is poorly understood; antiproliferative cytokines of the TGF-β family are likely involved.

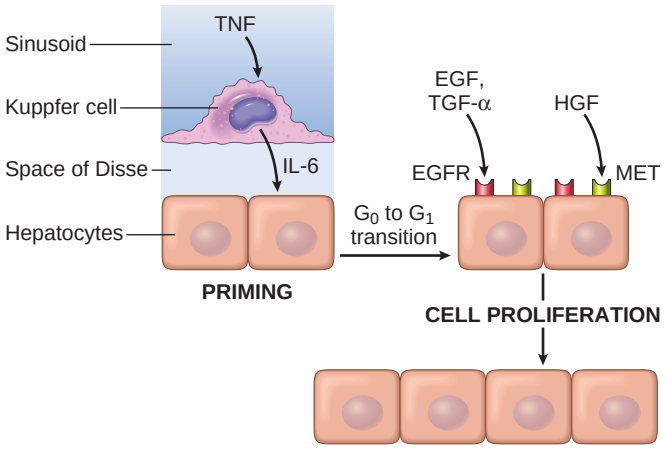

Figure 3-25 Liver regeneration by proliferation of hepatocytes. Following partial hepatectomy, the liver regenerates by proliferation of surviving cells. The process occurs in stages, including priming, followed by growth factor-induced proliferation. The main signals involved in these steps are shown. Once the mass of the liver is restored, the proliferation is terminated (not shown).

- **Liver regeneration from progenitor cells.** In situations where the proliferative capacity of hepatocytes is impaired, such as after chronic liver injury or inflammation, progenitor cells in the liver contribute to repopulation. In rodents, these progenitor cells have been called *oval cells* because of the shape of their nuclei. Some of these progenitor cells reside in specialized niches called *canals of Hering*, where bile canaliculi connect with larger bile ducts. The signals that drive proliferation of progenitor cells and their differentiation into mature hepatocytes are topics of active investigation.

KEY CONCEPTS

Repair by Regeneration

- Tissues are classified as labile, stable, and permanent, according to the proliferative capacity of their cells.
- Continuously dividing tissues (labile tissues) contain stem cells that differentiate to replenish lost cells and maintain tissue homeostasis.
- Cell proliferation is controlled by the cell cycle, and is stimulated by growth factors and interactions of cells with the extracellular matrix.
- Regeneration of the liver is a classic example of repair by regeneration. It is triggered by cytokines and growth factors produced in response to loss of liver mass and inflammation. In different situations, regeneration may occur by proliferation of surviving hepatocytes or repopulation from progenitor cells.

Repair by Connective Tissue Deposition

If repair cannot be accomplished by regeneration alone it occurs by replacement of the injured cells with connective tissue, leading to the formation of a scar, or by a combination of regeneration of some residual cells and scar formation. As discussed earlier, scarring may happen