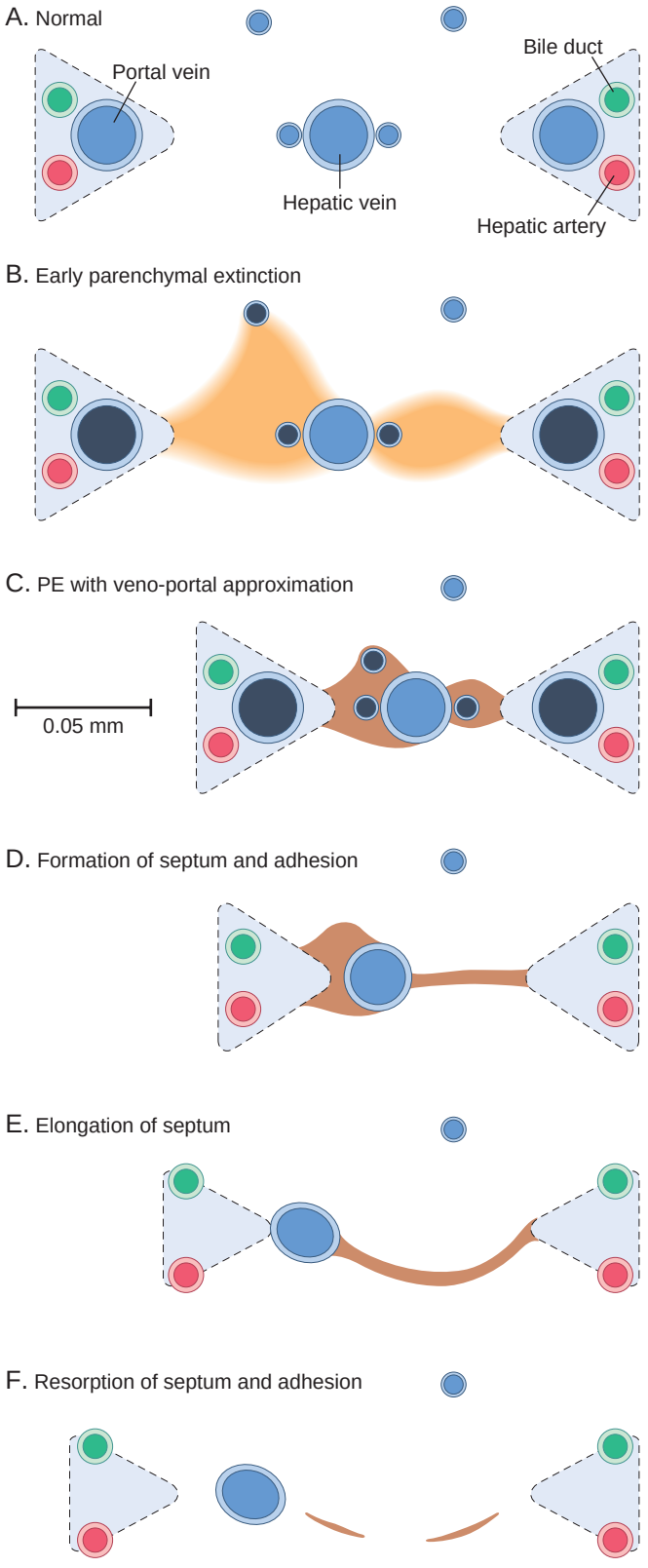

Figure 18-4 Diagrammatic representation of the natural history of small regions of hepatocelleular extinction and the related scarring. **A,** Normal liver with patent portal and hepatic veins (blue). **B,** Extinction occurs when contiguous hepatocytes die, usually after inflammatory injury to their blood supply (ischemic hepatocytes are shown in orange; obstructed veins are black). **C,** Empty parenchyma collapses and begins to scar (brown) and adjacent portal tracts and hepatic veins become approximated. **D,** Scars in regions of extinction contract and condense, becoming fibrous septa. The larger region of extinction (on the left) has formed a short adhesion between the adjacent portal tract and hepatic vein. Obliterated small veins have disappeared. **E,** Septa elongate by the traction caused by hyperplasia of adjacent hepatocytes. Portal tract collagen (light gray) is less than normal as resorption begins. **F,** Septa are resorbed. The resulting tissue has either venoportal fibrous adhesions or hepatic veins that are closely approximated to portal tracts. Portal tracts are remnants, often with no portal vein. (From Wanless IR, et al: Regression of Human Cirrhosis: Morphologic Features and the Genesis of Incomplete Septal Cirrhosis, Arch Pathol Lab Med Vol. 124, page 1606, 2000.)

and tissue inhibitors of metalloproteinases 1 and 2 (TIMP-1 and -2). As they are converted into myofibroblasts, the cells release chemotactic and vasoactive factors, cytokines, and growth factors. Myofibroblasts are contractile cells; their contraction is stimulated by endothelin-1 (ET-1). The stimuli for stellate cell activation may originate from several sources (Fig. 18-5): (1) chronic inflammation, with production of inflammatory cytokines such as tumor necrosis factor (TNF), lymphotoxin, and interleukin-1β (IL-1β), and lipid peroxidation products; (2) cytokine and chemokine production by Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells; (3) in response to disruption of the extracellular matrix (ECM); and (4) direct stimulation of stellate cells by toxins. If injury persists, scar deposition begins, often in the space of Disse. This is particularly important in alcoholic and nonalcoholic fatty liver diseases, but is also a generalized mechanism of scar formation in other forms of chronic liver injury.

Zones of parenchymal loss transform into dense *fibrous septa* through a combination of the collapse of the underlying reticulin where large swaths of hepatocytes have irrevocably disappeared and hepatic stellate cells have been activated. Eventually, these fibrous septa encircle surviving, regenerating hepatocytes in the late stages of chronic liver diseases that give rise to diffuse scarring described as cirrhosis.

Other cells probably contribute significantly to scar deposition in different settings, including portal fibroblasts. Ductular reactions also play a role, both through activation and recruitment of all these fibrogenic cells, but also, perhaps, through *epithelial-mesenchymal transition*. The relative roles played by these other cells and processes are less well understood.

If the chronic injury leading to scar formation is interrupted (e.g. clearance of hepatitis virus infection, cessation of alcohol use), then stellate cell activation ceases, scars condense, becoming more dense and thin, and then, due to metalloproteinases produced by hepatocytes, begin to break apart. In this way, scar formation can be reversed. It should be kept in mind that in any chronic liver disease there are probably areas of both fibrotic progression and regression, but the balance in active disease favors the former and with remission of disease the latter is favored.

Inflammation and Immunity

Innate and adaptive immune systems are, not surprisingly, involved in all manner of liver injury and repair. Antigens in the liver are taken up by antigen presenting cells,