inflammatory reaction. As we discussed, pancreatic enzymes, including trypsin, are synthesized in an inactive proenzyme form. Inappropriate intrapancreatic activation of trypsin can in turn cause the activation of other proenzymes such as prophospholipase and proelastase, which then degrade fat cells and damage the elastic fibers of blood vessels, respectively. Trypsin also converts prekallikrein to its activated form, thus bringing into play the kinin system and, by activation of coagulation factor XII, the clotting and complement systems as well (Chapters 3 and 4). The resulting inflammation and small-vessel thromboses (which may lead to congestion and rupture of already weakened vessels) damage acinar cells, further amplifying intrapancreatic activation of digestive enzymes.

How inappropriate activation of pancreatic enzymes occurs in sporadic forms of acute pancreatitis is not entirely clear, but there is evidence for at least three major initiating events (Fig. 19-2):

- **Pancreatic duct obstruction.** Obstruction is most commonly caused by *gallstones* and biliary sludge, but can also stem from *periampullary neoplasms* (e.g., pancreatic cancer), *choledochoceles* (congenital cystic dilatation of the common bile duct), *parasites* (particularly the *Ascaris lumbricoides* and *Clonorchis sinensis* organisms), and possibly pancreas divisum. Whatever the cause, obstruction raises intrapancreatic ductal pressure and leads to the accumulation of enzyme-rich fluid in the interstitium. Although most pancreatic enzymes are secreted as inactive zymogens, lipase is produced in an active form and has the potential to cause local fat necrosis. The death of adipocytes is hypothesized to produce "danger" signals locally that stimulate periacinar myofibroblasts and leukocytes to release proinflammatory cytokines and other inflammatory mediators that initiate local inflammation and promote the development of interstitial edema through a leaky microvasculature. Edema may further compromise local blood flow, causing vascular insufficiency and ischemic injury to acinar cells.
- **Primary acinar cell injury,** leading to release of digestive enzymes, inflammation, and autodigestion of pancreatic tissues. As described later, acinar cells can be damaged by a variety of endogenous, exogenous, and iatrogenic insults. Oxidative stress may generate free radicals in acinar cells, leading to membrane lipid oxidation and the activation of transcription factors, including AP1 and NF-κB, which in turn induce the expression of chemokines that attract mononuclear

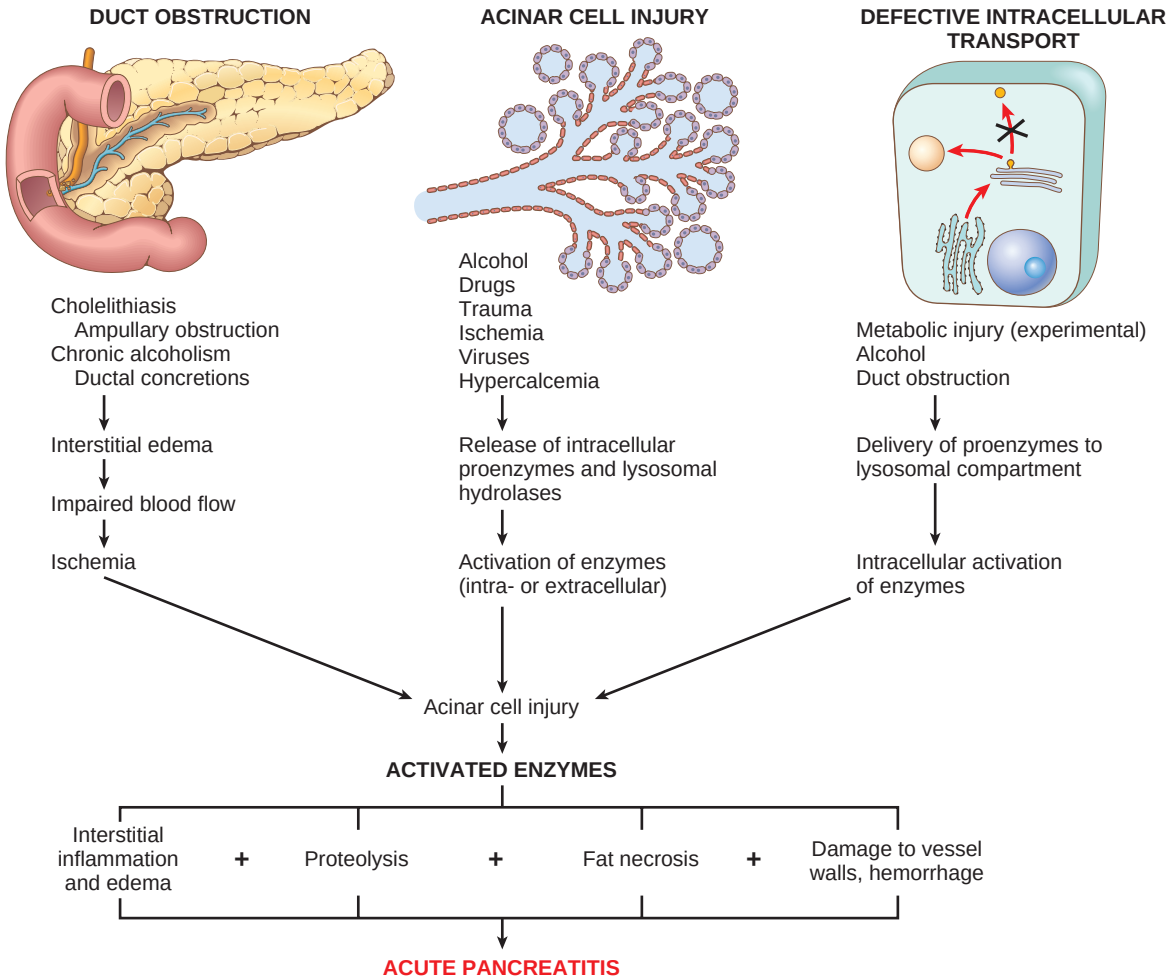

Figure 19-2 Three proposed pathways in the pathogenesis of acute pancreatitis.