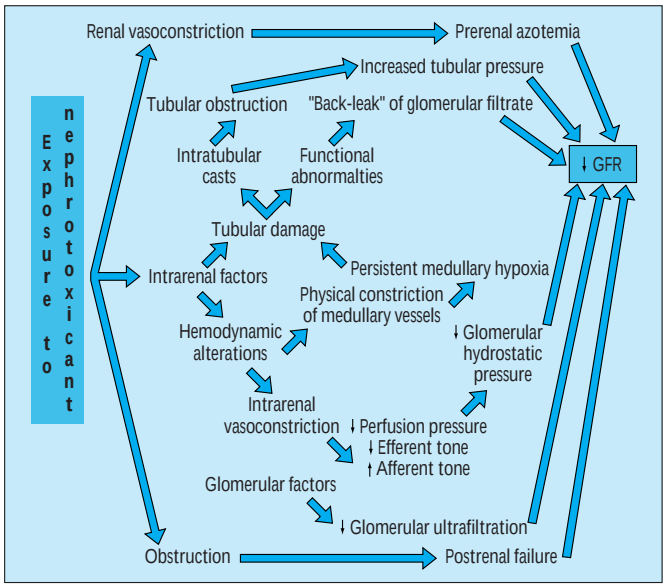

FIGURE 15-6

Mechanisms that contribute to decreased glomerular filtration rate (GFR) in acute renal failure. After exposure to a nephrotoxicant, one or more mechanisms may contribute to a reduction in the GFR. These include renal vasoconstriction resulting in prerenal azotemia (*eg*, cyclosporin A) and obstruction due to precipitation of a drug or endogenous substances within the kidney or collecting ducts (*eg*, methotrexate). Intrarenal factors include direct tubular obstruction and dysfunction resulting in tubular backleak and increased tubular pressure. Alterations in the levels of a variety of vasoactive mediators (*eg*, prostaglandins following treatment with nonsteroidal anti-inflammatory drugs) may result in decreased renal perfusion pressure or efferent arteriolar tone and increased afferent arteriolar tone, resulting in decreased in glomerular hydrostatic pressure. Some nephrotoxicants may decrease glomerular function, leading to proteinuria and decreased renal function.

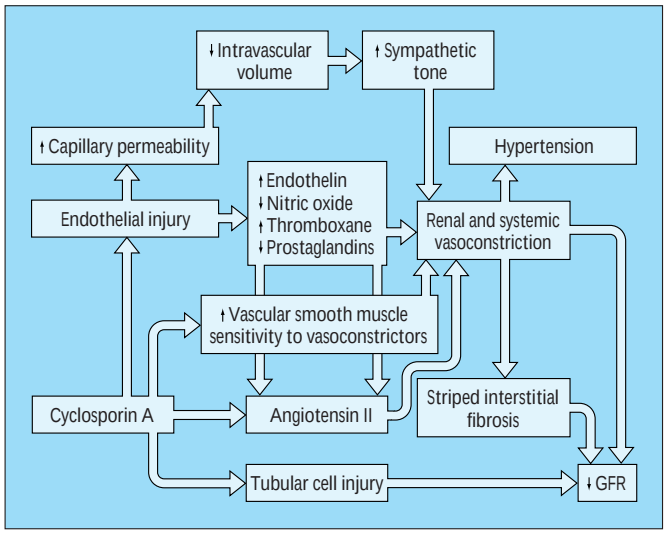

FIGURE 15-7

Renal injury from exposure to cyclosporin A. Cyclosporin A is one example of a toxicant that acts at several sites within the kidney. It can injure both endothelial and tubular cells. Endothelial injury results in increased vascular permeability and hypovolemia, which activates the sympathetic nervous system. Injury to the endothelium also results in increases in endothelin and thromboxane A_2 and decreases in nitric oxide and vasodilatory prostaglandins. Finally, cyclosporin A may increase the sensitivity of the vasculature to vasoconstrictors, activate the renin-angiotensin system, and increase angiotensin II levels. All of these changes lead to vasoconstriction and hypertension. Vasoconstriction in the kidney contributes to the decrease in glomerular filtration rate (GFR), and the histologic changes in the kidney are the result of local ischemia and hypertension.

Renal Cellular Responses to Toxicant Exposures

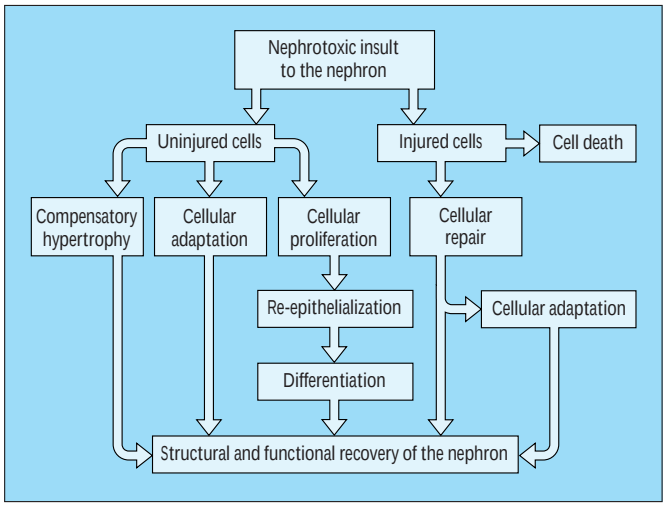

FIGURE 15-8

The nephron's response to a nephrotoxic insult. After a population of cells are exposed to a nephrotoxicant, the cells respond and ultimately the nephron recovers function or, if cell death and loss is extensive, nephron function ceases. Terminally injured cells undergo cell death through oncosis or apoptosis. Cells injured sublethally undergo repair and adaptation (*eg*, stress response) in response to the nephrotoxicant. Cells not injured and adjacent to the injured area may undergo dedifferentiation, proliferation, migration or spreading, and differentiation. Cells that were not injured may also undergo compensatory hypertrophy in response to the cell loss and injury. Finally the uninjured cells may also undergo adaptation in response to nephrotoxicant exposure.

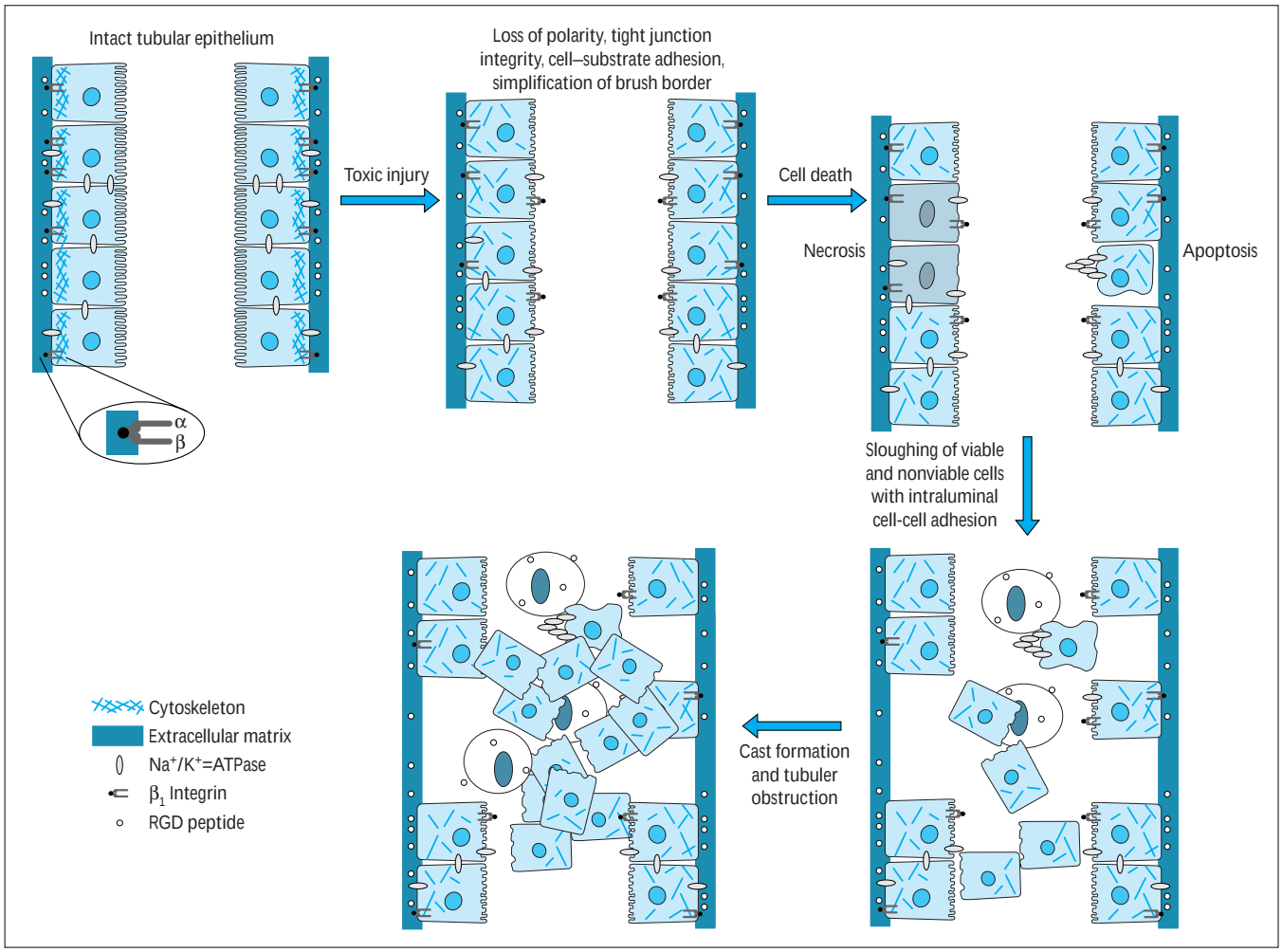

FIGURE 15-9

After injury, alterations can occur in the cytoskeleton and in the normal distribution of membrane proteins such as Na^+, K^+-ATPase and β_1 integrins in sublethally injured renal tubular cells. These changes result in loss of cell polarity, tight junction integrity, and cell-substrate adhesion. Lethally injured cells undergo oncosis or apoptosis, and both dead and viable cells may be sloughed into the tubular lumen. Adhesion of sloughed cells to other sloughed cells and to cells remaining adherent to the basement membrane may result in cast formation, tubular obstruction, and further compromise the glomerular filtration rate. (*Adapted from* Fish and Molitoris [1], and Gailit *et al.* [2]; with permission.)

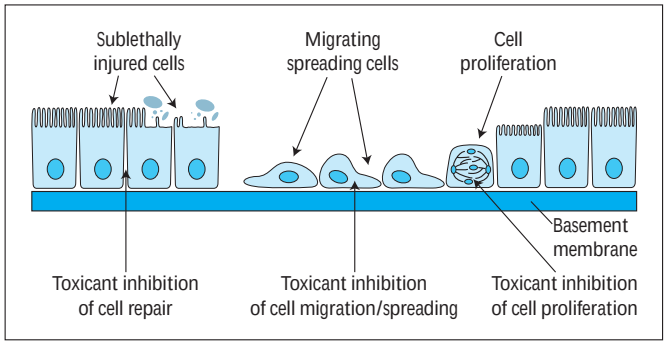

FIGURE 15-10

Potential sites where nephrotoxicants can interfere with the structural and functional recovery of nephrons.

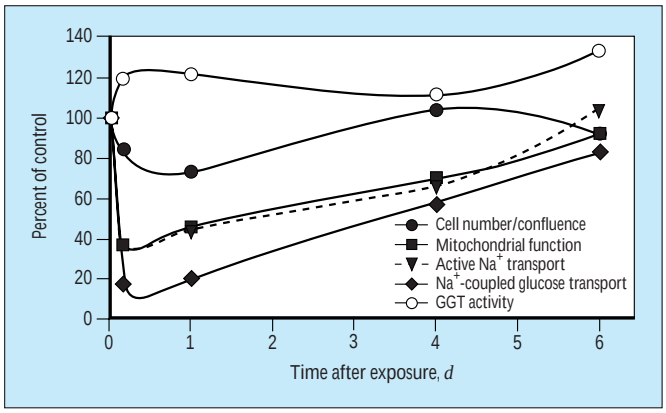

FIGURE 15-11

Inhibition and repair of renal proximal tubule cellular functions after exposure to the model oxidant *t*-butylhydroperoxide. Approximately 25% cell loss and marked inhibition of mitochondrial function active (Na^+) transport and Na^+-coupled glucose transport occurred 24 hours after oxidant exposure. The activity of the brush border membrane enzyme γ-glutamyl transferase (GGT) was not affected by oxidant exposure. Cell proliferation and migration or spreading was complete by day 4, whereas active Na^+ transport and Na^+-coupled glucose transport did not return to control levels until day 6. These data suggest that selective physiologic functions are diminished after oxidant injury and that a hierarchy exists in the repair process: migration or spreading followed by cell proliferation forms a monolayer and antedates the repair of physiologic functions. (*Data from* Nowak *et al.* [3].)

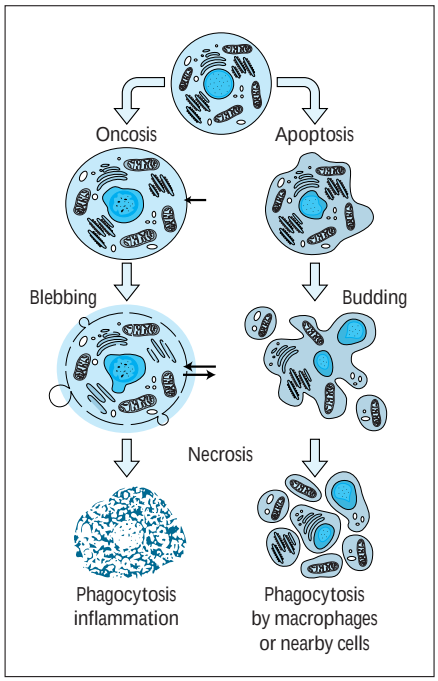

FIGURE 15-12

Apoptosis and oncosis are the two generally recognized forms of cell death. Apoptosis, also known as programmed cell death and cell suicide, is characterized morphologically by cell shrinkage, cell budding forming apoptotic bodies, and phagocytosis by macrophages and nearby cells. In contrast, oncosis, also known as necrosis, necrotic cell death, and cell murder, is characterized morphologically by cell and organelle swelling, plasma membrane blebbing, cell lysis, and inflammation. It has been suggested that cell death characterized by cell swelling and lysis not be called necrosis or necrotic cell death because these terms describe events that occur well after the cell has died and include cell and tissue breakdown and cell debris. (*From* Majno and Joris [4]; with permission.)

Mechanisms of Toxicant-Mediated Cellular Injury

Transport and biotransformation

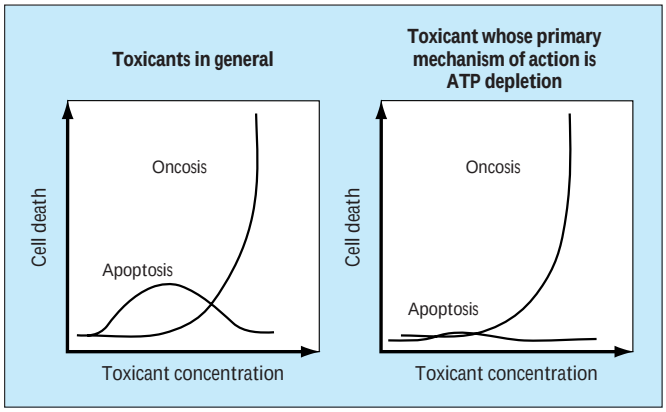

FIGURE 15-13

The general relationship between oncosis and apoptosis after nephrotoxicant exposure. For many toxicants, low concentrations cause primarily apoptosis and oncosis occurs principally at higher concentrations. When the primary mechanism of action of the nephrotoxicant is ATP depletion, oncosis may be the predominant cause of cell death with limited apoptosis occurring.