- *Tubule cell injury:* Tubular epithelial cells are particularly sensitive to ischemia and are also vulnerable to toxins. Several factors predispose the tubules to toxic injury, including an increased surface area for tubular reabsorption, active transport systems for ions and organic acids, a high rate of metabolism and oxygen consumption that is required to perform these transport and reabsorption functions, and the capability for resorption and concentration of toxins.

  Ischemia causes numerous structural and functional alterations in epithelial cells, as discussed in Chapter 2. One early reversible result of ischemia is *loss of cell polarity* due to redistribution of membrane proteins (e.g., the enzyme Na,K^+-ATPase) from the basolateral to the luminal surface of the tubular cells, resulting in abnormal ion transport across the cells and *increased sodium delivery to distal tubules*. The latter incites vasoconstriction via *tubuloglomerular feedback*. In addition, ischemic tubular cells express cytokines and adhesion molecules, thus recruiting leukocytes that appear to participate in the subsequent injury. In time, injured cells detach from the basement membranes and cause *luminal obstruction*, increased intratubular pressure, and decreased GFR. In addition, glomerular filtrate in the lumen of the damaged tubules can leak back into the interstitium, resulting in interstitial edema, increased interstitial pressure, and further damage to the tubule. All these effects, as shown in Figure 20-22, contribute to the decreased GFR.
- *Disturbances in blood flow:* Ischemic renal injury is also characterized by *hemodynamic alterations* that cause reduced GFR. The major one is *intrarenal vasoconstriction*, which results in both reduced glomerular blood flow and reduced oxygen delivery to the functionally important tubules in the outer medulla (thick ascending limb and straight segment of the proximal tubule). Several vasoconstrictor pathways have been implicated, including the renin-angiotensin system, stimulated by increased distal sodium delivery (via *tubuloglomerular feedback*), and *sublethal endothelial injury*, leading to increased release of the vasoconstrictor *endothelin* and decreased production of the vasodilators *nitric oxide* and *prostacyclin* (*prostaglandin* I_2). There is also some evidence of a direct effect of ischemia or toxins on the glomerulus, causing a reduced glomerular ultrafiltration coefficient, possibly due to mesangial contraction.

The patchiness of tubular necrosis and maintenance of the integrity of the basement membrane along many segments allow repair of the injured foci and recovery of function if the precipitating cause is removed. This repair is dependent on the capacity of reversibly injured epithelial cells to proliferate and differentiate. Re-epithelialization is mediated by a variety of growth factors and cytokines produced locally by the tubular cells themselves or by inflammatory cells in the vicinity of necrotic foci.

MORPHOLOGY

ATI is characterized by **focal tubular epithelial necrosis** at multiple points along the nephron, with large skip areas in between, often accompanied by rupture of basement membranes (tubulorrhexis) and **occlusion of tubular lumens by casts** (Figs. 20-23 and 20-24). The distinct patterns of tubular injury in ischemic and toxic ATI are shown in Figure 20-23. The straight portion of the proximal tubule and the ascending thick limb in the renal medulla are especially vulnerable, but focal lesions may also occur in the distal tubule, often in conjunction with casts. It should be noted that the severity

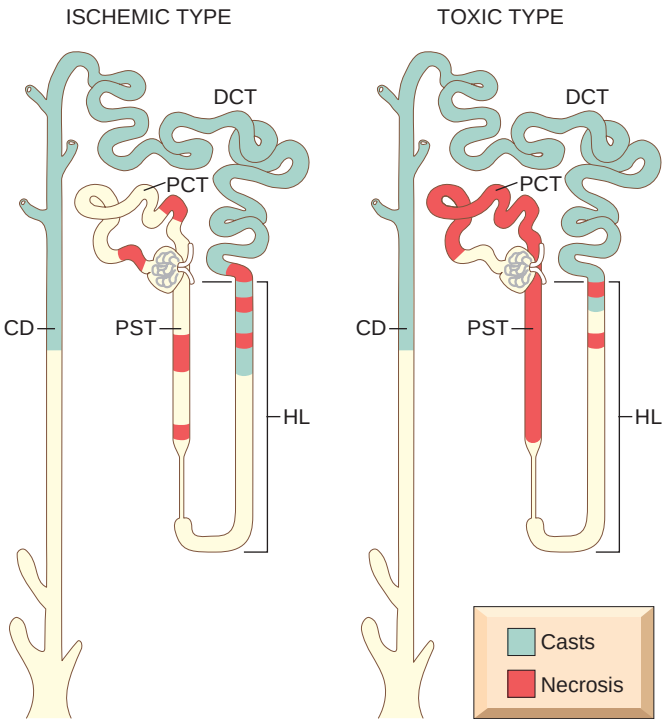

Figure 20-23 Patterns of tubular damage in ischemic and toxic acute tubular injury. In the ischemic type, tubular necrosis is patchy, relatively short lengths of tubules are affected, and straight segments of proximal tubules (PST) and ascending limbs of Henle's loop (HL) are most vulnerable. In toxic acute tubular injury, extensive necrosis is present along the proximal convoluted tubule segments (PCT) with many toxins (e.g., mercury), but necrosis of the distal tubule, particularly ascending HL, also occurs. In both types, lumens of the distal convoluted tubules (DCT) and collecting ducts (CD) contain casts.

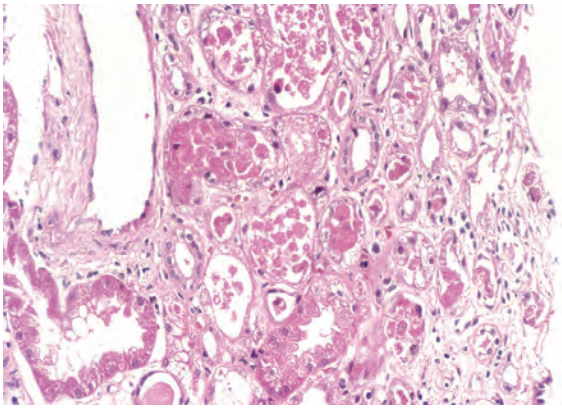

Figure 20-24 Acute tubular injury. Some of the tubular epithelial cells in the tubules are necrotic, and many have become detached (from their basement membranes) and been sloughed into the tubular lumens, whereas others are swollen, vacuolated, and regenerating. (Courtesy Dr. Agnes Fogo, Vanderbilt University, Nashville, Tenn.)