of the morphologic findings often do not correlate well with the severity of the clinical manifestations.

Eosinophilic hyaline casts, as well as pigmented granular casts, are common, particularly in distal tubules and collecting ducts. These casts consist principally of Tamm-Horsfall protein (a urinary glycoprotein normally secreted by the cells of ascending thick limb and distal tubules) in conjunction with other plasma proteins. Other findings in ischemic ATI are interstitial edema and accumulations of leukocytes within dilated vasa recta. There is also evidence of epithelial regeneration in the form of flattened epithelial cells with hyperchromatic nuclei and mitotic figures. In the course of time this regeneration repopulates the tubules so that no residual evidence of damage is seen.

Toxic ATI is manifested by acute tubular injury, most obvious in the proximal convoluted tubules. On histologic examination the tubular necrosis may be nonspecific, but it is somewhat distinctive in poisoning with certain agents. With mercuric chloride, for example, severely injured cells may contain large acidophilic inclusions. Later, these cells become necrotic, are desquamated into the lumen, and may undergo calcification. Carbon tetrachloride poisoning, in contrast, is characterized by the accumulation of neutral lipids in injured cells; again, such fatty change is followed by necrosis. Ethylene glycol produces marked ballooning and hydropic or vacuolar degeneration of proximal convoluted tubules. Calcium oxalate crystals are often also found in the tubular lumens in ethylene glycol poisoning.

Clinical Course. The clinical course of ATI is highly variable, but the classic case may be divided into *three* stages.

- *Initiation phase*, lasting about 36 hours, is dominated by the inciting medical, surgical, or obstetric event. The only indication of renal involvement is a slight decline in urine output with a rise in BUN. At this point, oliguria could be explained by a transient decrease in blood flow and declining GFR.
- *Maintenance phase* is characterized by sustained decreases in urine output to between 40 and 400 mL/day (oliguria), salt and water overload, rising BUN concentrations, hyperkalemia, metabolic acidosis, and other manifestations of uremia. With appropriate management, the patient can overcome this oliguric crisis.
- *Recovery phase* is ushered in by a steady increase in urine volume that may reach up to 3 L/day. The tubules are still damaged, so large amounts of water, sodium, and potassium are lost in the flood of urine. *Hypokalemia, rather than hyperkalemia, becomes a clinical problem.* There is a peculiar increased vulnerability to infection at this stage. Eventually, renal tubular function is restored and concentrating ability improves. At the same time, BUN and creatinine levels begin to return to normal. Subtle tubular functional impairment may persist for months, but most patients who reach this phase eventually recover completely.

The prognosis of ATI depends on the magnitude and duration of injury. Recovery is expected with nephrotoxic ATI when the toxin has not caused serious damage to other organs, such as the liver or heart. With current supportive care, 95% of those who do not succumb to the precipitating cause recover. Conversely, in shock related to sepsis, extensive burns, or other causes of multi-organ failure, the mortality rate can be more than 50%.

KEY CONCEPTS

Acute Tubular Injury

- Acute tubular injury is the most common cause of acute kidney injury and attributed to ischemia and/or toxicity from an endogenous or exogenous substance.
- Tubular epithelial cell injury and altered intrarenal hemodynamics are the primary contributors to acute tubular injury.
- The clinical outcome is determined by the magnitude and duration of acute tubular injury.

Tubulointerstitial Nephritis

This group of renal diseases involves inflammatory injuries of the tubules and interstitium that are often insidious in onset and are principally manifest by azotemia. We have previously seen that chronic tubulointerstitial damage is an important consequence of progression in diseases that primarily affect the glomerulus (Fig. 20-21). *Secondary tubulointerstitial nephritis* is also present in a variety of vascular, cystic (polycystic kidney disease), and metabolic (diabetes) renal disorders, in which it may also contribute to progressive damage. Here we discuss primary causes of tubulointerstitial injury (Table 20-8). Glomerular

Table 20-8 Causes of Tubulointerstitial Nephritis

Infections
Acute bacterial pyelonephritis
Chronic pyelonephritis (including reflux nephropathy)
Other infections (e.g., viruses, parasites)
Toxins
Drugs
Acute-hypersensitivity interstitial nephritis
Analgesics
Heavy metals
Lead, cadmium
Metabolic Diseases
Urate nephropathy
Nephrocalcinosis (hypercalcemic nephropathy)
Acute phosphate nephropathy
Hypokalemic nephropathy
Oxalate nephropathy
Physical Factors
Chronic urinary tract obstruction
Neoplasms
Multiple myeloma (light-chain cast nephropathy)
Immunologic Reactions
Transplant rejection
Sjögren syndrome
Sarcoidosis
Vascular Diseases
Miscellaneous
Balkan nephropathy
Nephronophthisis-medullary cystic disease complex
"Idiopathic" interstitial nephritis