CHAPTER

57 Chronic Tubulointerstitial Nephritis

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Chronic tubulointerstitial nephritis (TIN) encompasses a vast array of chronic kidney diseases that share a primary pathologic process that begins at the level of the tubules and their surrounding interstitial space. In addition, it is now recognized that chronic tubulointerstitial disease is the final common pathway that causes progressive renal functional loss in all chronic kidney disease (CKD), whether it begins in the tubulointerstitium or in other renal compartments. Due to the importance and unique clinicopathologic features of many diseases that cause chronic TIN, many are discussed in greater detail in other chapters. The present chapter provides a general overview and discussion of this entire group of disorders, with an effort to highlight shared and unique features of each. For the purpose of presentation, chronic TIN is divided into subcategories (Table 57.1). One of the most common causes of chronic TIN in developed countries is chronic renal allograft rejection, which is discussed in Chapter 81.

NORMAL TUBULOINTERSTITIAL ARCHITECTURE

Renal tubules constitute the largest component of the renal parenchyma, estimated at 80% to 90%, which explains why disrupted tubular integrity and function plays such an important role in renal functional decline. Most of the tubules in the renal cortex are proximal tubules. The peritubular region is occupied by the vasculature and the interstitial space. The glomerular efferent arterioles branch to form the peritubular capillary network, which serves the vital role of delivering oxygen to support tubular cell metabolic and transport functions. The extravascular peritubular compartment, known as the interstitium, is typically inconspicuous, especially in the renal cortex. However, stromal cells and extracellular matrix proteins residing in the interstitium play a key role during renal development and in polarizing the renal response to injury toward regeneration or chronic sequelae. Residing within the interstitium are two important cell populations. The most abundant are fibroblasts, well recognized for their role of synthesizing extracellular matrix proteins. These proteins (primarily fibronectin; fibrillar; collagens I, III, and VI; and proteoglycans) provide a structural framework for nephrons and the vascular network. The functional heterogeneity of interstitial fibroblasts is increasingly recognized, even within normal kidneys.[1] A subset is specialized to synthesize erythropoietin (Fig. 57.1),[2] whereas others are pericytes closely opposed to peritubular capillaries.[3] Present within the medulla is a unique population of lipid-laden interstitial cells which are thought to be a source of prostaglandins involved in blood pressure control.[4] The second interstitial cell population consists of myeloid cells that are derived from bone marrow cells and are slowly and continuously replenished. This group of cells also has functional heterogeneity. The majority appear to be MCH class II positive dendritic cells, whereas others are scavenger-type macrophages. In normal kidneys the myeloid cells are thought to serve surveillance functions to protect the kidney from noxious materials and foreign invaders. They become actively engaged in renal responses to injury. Interstitial myeloid cells rarely proliferate in situ; the interstitial inflammatory response that characterizes many acute and chronic kidney diseases is dependent upon the recruitment of lymphohematopoietic cells from the circulation.

Ongoing studies are attempting to answer the question of whether a pluripotent stem cell also resides within the renal interstitium.[5] It has been suggested that the renal medulla is a niche for kidney stem cells. These slowing dividing cells can be identified as "label-retaining cells" using detectable thymidine markers. There are conflicting data about the ability of these cells to proliferate and migrate to the site of injury and participate in renal regeneration.[6,7] It has also been proposed that specialized progenitor cells may reside within tubules, but this remains unproven.

HISTOPATHOLOGIC FEATURES OF CHRONIC TIN

The histologic hallmark of chronic TIN is an increase in the fractional volume of the interstitial space caused by an expansion of extracellular matrix proteins—the defining feature

57.1 Chronic Tubulointerstitial Nephritis Classification

PRIMARY TUBULOINTERSTITIAL KIDNEY DISEASES		
Genetic diseases	Familial TIN (MCKD2)	Uromodulin mutations
		Renin mutations
		Unknown mutations
	Nephronophthisis (NPHP)	Isolated kidney disease
		Associated with extrarenal manifestations
	Polycystic kidney diseases (PKD)	Autosomal dominant
		Autosomal recessive
		Syndromic
		Others
	Metabolic disorders	Cystinosis
		Oxalosis
		Mitochondrial cytopathies
		Methylmalonic acidemia
Immunologic diseases	TIN most common kidney manifestation	Sjögren syndrome
		IgG4-related disease
		Sarcoidosis
		TINU
		Renal allograft rejection
		Anti-TBM nephritis
	TIN usually associated with glomerulonephritis	Systemic lupus erythematosus
		ANCA+ vasculitis
		Anti-GBM nephritis
		Cryoglobulinemia
		Membranoproliferative glomerulonephritis
		IgA nephropathy
		Others
Chronic nephrotoxicity	Drugs	Calcineurin inhibitors
		Analgesic nephropathy
		Lithium
	Herbs	Aristolochic acid
		Others
	Heavy metals	Lead
		Cadmium
Chronic metabolic disorders	Hypercalcemia/hypercalciuria	
	Hyperphosphatemia/hyperphosphaturia	
	Hyperuricemia/hyperuricosuria	
	Hypokalemia	
Congenital abnormalities	Dysplasia	
	Obstruction	
CHRONIC KIDNEY DISEASE-ASSOCIATED TIN		
Proteinuria-associated TIN		
Chronic kidney disease universal progression pathway		

(continued)

57.1 Chronic Tubulointerstitial Nephritis Classification (continued)

SEQUELAE TO ACUTE TUBULOINTERSTITIAL INJURY		
Acute kidney injury	Ischemia-reperfusion injury	
Acute interstitial nephritis/ nephrotoxicity	Infections	Bacterial (systemic, pyelonephritis, xanthogranulomatous pyelonephritis)
		Mycobacteria
		Viral
		Fungal
		Parasitic
	Drugs	Proton pump inhibitors
		Chemotherapeutic drugs
		Antimicrobial drugs
		NSAIDs
	Hematologic disorders	Leukemia
		Lymphoma
		Multiple myeloma
		Sickle cell disease

MCKD2, medullary cystic kidney disease type 2, familial juvenile hyperuricemic nephropathy; TINU, tubulointerstitial nephritis with uveitis; anti-TBM, anti-tubular basement membrane; anti-GBM, anti-glomerular basement membrane; NSAIDs, nonsteroidal anti-inflammatory drugs.

of interstitial fibrosis or scarring. This abnormal matrix is comprised of both a greater abundance of normal interstitial matrix proteins and the de novo appearance of additional matrix proteins. Interstitial fibrosis is accompanied by irreversible tubular damage, ranging from abnormally dilated (ectatic) tubules to atrophic tubules surrounded by abnormally thickened and wrinkled tubular membranes to complete tubular drop-out (often leaving behind the signature "atubular" glomeruli). In parallel, peritubular capillaries are also lost. In some diseases such as chronic allograft rejection, an abnormal process of interstitial lymphangiogenesis has been described, but its specificity and functional significance remain unclear.

The other important histopathologic feature that typifies chronic TIN is a significant change in interstitial cellularity. Unlike normal kidneys, the interstitial space becomes populated by transformed fibroblasts that are recognized by their expression of α-smooth muscle actin (α-SMA), a protein typically associated with smooth muscle cells. Known as "myofibroblasts," these cells are considered the primary source of extracellular matrix proteins that generate the fibrotic or scarred interstitium. The second important

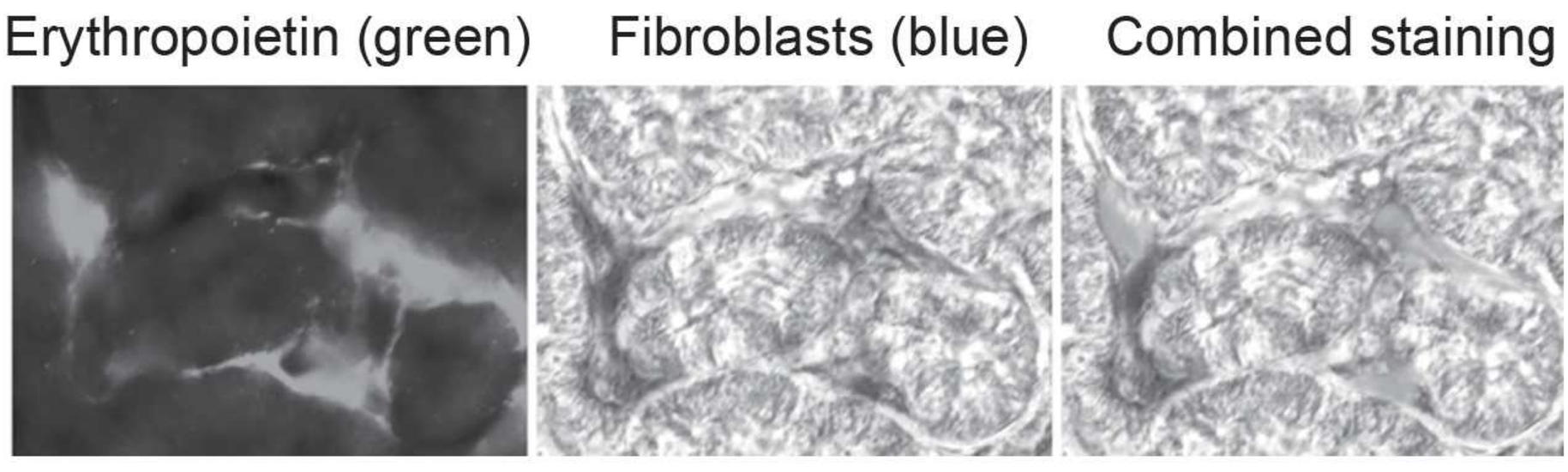

FIGURE 57.1 Peritubular fibroblasts produce erythropoietin. Using a mouse line that was genetically engineered to express green fluorescent protein-labeled erythropoietin, and kidney *Cre*-labeled fibroblasts that are detectable by beta galactosidase staining (blue), peritubular fibroblasts are identified as the source of erythropoietin. Loss of this function explains why anemia may be more severe in patients with chronic kidney disease due to chronic tubulointerstitial nephritis. (From Asada N, Takase M, Nakamura J, et al. Dysfunction of fibroblasts of extrarenal origin underlies renal fibrosis and renal anemia in mice. *J Clin Invest*. 2011;121:3981, with permission.) (See Color Plate.)

57.2 Histopathologic Features of Acute and Chronic Tubulointerstitial Nephritis

Features	Acute	Chronic
Tubules		
Epithelium	Necrosis	Atrophy
Basement membrane	Disrupted	Thickened
Shape	Preserved	Dilated
Interstitium[a]		
Cell infiltrates	Lymphocytes ($CD4^+$ T cell dominant) Eosinophils in early stage	Monocytes and macrophages Lymphocytes
Myofibroblasts	Minimum	Increased
Edema	+++	+
Fibrosis	+	+++ (Collagen and other matrix protein deposits)
Vasculature		
Peritubular capillaries	Preserved	Reduced density De novo lymphatic vessels
Large vessels	Minimum	Varies[b]
Glomeruli	None to minimal change	Periglomerular fibrosis Focal or global glomerulosclerosis

[a]The severity of the changes is given as an estimate with + for minimal to +++ as severe.
[b]Pathologic changes may suggest a primary process such as atherosclerosis, scleroderma, thromboembolic disease, vasculitis, or chronic allograft rejection.

change in interstitial cellularity is the appearance of an infiltrate of mononuclear cells. These cells are primarily of bone marrow origin.

A frequent challenge of a new histopathologic diagnosis of chronic TIN is the lack of clarity of the initiating disease process. For some disease entities, specific diagnoses are made using other criteria: imaging for cystic kidney disease and anatomic genitourinary anomalies, the presence of extrarenal manifestations (autoimmune diseases, metabolic disorders, hematologic diseases, and congenital hepatic fibrosis), a positive family history, or history of exposure to a drug or toxin that is known to cause chronic TIN. In the absence of these diagnostic clues, it may not be possible to determine the primary etiology, as the renal histologic findings of many chronic TINs overlap. When more specific diagnostic criteria are available, they are discussed under the specific disease entities that are reviewed later.

Another potential diagnostic dilemma is the difficulty of differentiating acute and reversible TIN from chronic progressive TIN. Early diagnosis is important for certain disease etiologies, such as an exposure to nephrotoxins or development of treatable autoimmune diseases, for which a delayed diagnosis may be too late for injury reversal. Many of the tubulointerstitial disorders have a variable clinical course that spans the spectrum from acute to chronic and reversible to progressive. The tissue repair process itself may lead to pathologic fibrosis. Frequent regional variations in the TIN process mean that the degree of acute and chronic TIN may vary considerably from one tissue sample to another. The primary histologic findings that are used in an effort to differentiate acute from chronic TIN are summarized in Table 57.2.

CLINICAL MANIFESTATIONS AND LABORATORY ABNORMALITIES

Clinical manifestations of chronic TIN tend to be subtle. Patients with TIN may present with symptoms related to their primary diseases. They often also have nonspecific constitutional symptoms of chronic kidney disease such as fatigue, loss of appetite, nausea, vomiting, and sleep disturbance. In general, tubular dysfunction develops proportionally as glomerular filtration rate (GFR) declines. However, primary TIN diseases may present more prominent tubular dysfunction in the early stage compared to glomerular or vascular diseases. Proximal tubule dysfunction is characterized by inability to reabsorb filtered bicarbonate, glucose, amino acids, and phosphate in varying combinations, resulting in acidosis, glucosuria, phosphaturia, and aminoaciduria, as in

Fanconi syndrome. Low molecular weight proteins such as β_2-microglobulin may not be properly reabsorbed, leading to tubular proteinuria. Distal tubular dysfunction manifests as renal sodium wasting, hyperkalemia, and nonanion gap metabolic acidosis. Collecting duct dysfunction leads to renal concentrating defects including features of diabetes insipidus and countercurrent exchange washout resulting in polyuria. Most TIN affects multiple sites of the nephron simultaneously, but to varying degrees. Hypertension, severe proteinuria, and edema are not usually characteristic of TIN in the early stage, but may develop later as progressing chronic kidney disease (CKD) with glomerular sclerosis. In addition to tubular dysfunction, anemia may be found disproportionally compared to the change in GFR if erythropoietin-producing peritubular cells (Fig. 57.1) are damaged early in the disease. Bone disease may also be prominent, as a result of chronic phosphate wasting caused by proximal tubular dysfunction.

INTERSTITIAL FIBROSIS: THE FINAL COMMON PATHWAY TO CHRONIC KIDNEY DISEASE

In both native and transplanted kidneys, progressive fibrosis of the renal interstitium is the predominant final common pathway of renal destruction, regardless of the etiology of the original kidney disease.[8] Fibrotic injury is not limited to extracellular matrix accumulation, but also results in the subsequent loss of tubules and peritubular capillaries. Histopathologically, interstitial volume and reduced tubular epithelial cell density closely correlate with the loss of renal function and predict long-term outcomes (Fig. 57.2). The pathogenic process leading to fibrosis can be initiated by a variety of insults, including chronic tubular, glomerular, and vascular disease. Chemokines and chemoattractants such as monocyte chemoattractant protein 1 (MCP-1), complement

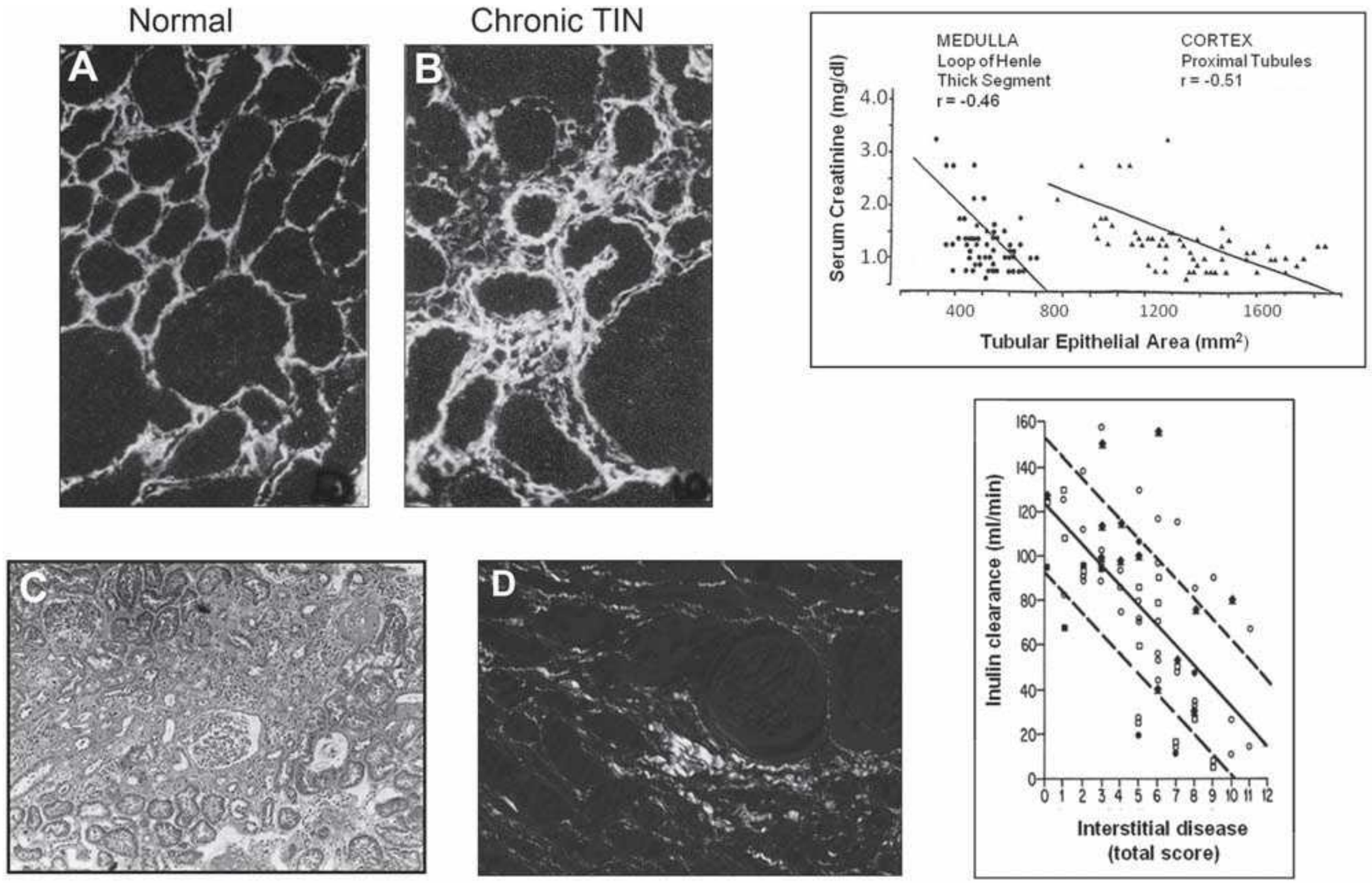

FIGURE 57.2 Interstitial fibrosis: detection and correlation with renal functional loss. The fibrotic or scarred interstitium contains several extracellular matrix proteins, the most abundant being fibrillar collagens such as collagen III **(A,B)**. Routine renal biopsy staining with Masson trichrome reacts with collagen to produce a green-blue color **(C)**. Quantitative pathologic research studies often use picrosirius red staining, which is specific for cross-linked collagen fibrils (polarized image shown in **D**). The key structural change that underlies the loss of renal function in all chronic kidney diseases is tubular atrophy (upper graph) which is closely associated with interstitial fibrosis severity (lower graph). (A and B are from Jones CL, Buch S, Post M, et al. Pathogenesis of interstitial fibrosis in chronic purine aminonucleoside nephrosis. *Kidney Int.* 1991;40:1020. Upper graph is from Mackensen-Haen S, Bohle A, Christensen J, et al. The consequences for renal function of the interstitium and changes in the tubular epithelium of the cortex and medulla in various diseases. *Clin Nephrol.* 1992;37;70. Lower graph is from Schainuck LI, Striker GE, Cutler RE, et al. Structural-functional correlations in renal diseases: Part II: the correlations. *Human Pathol.* 1970;1:631. All are reproduced with permission.) (See Color Plate.)

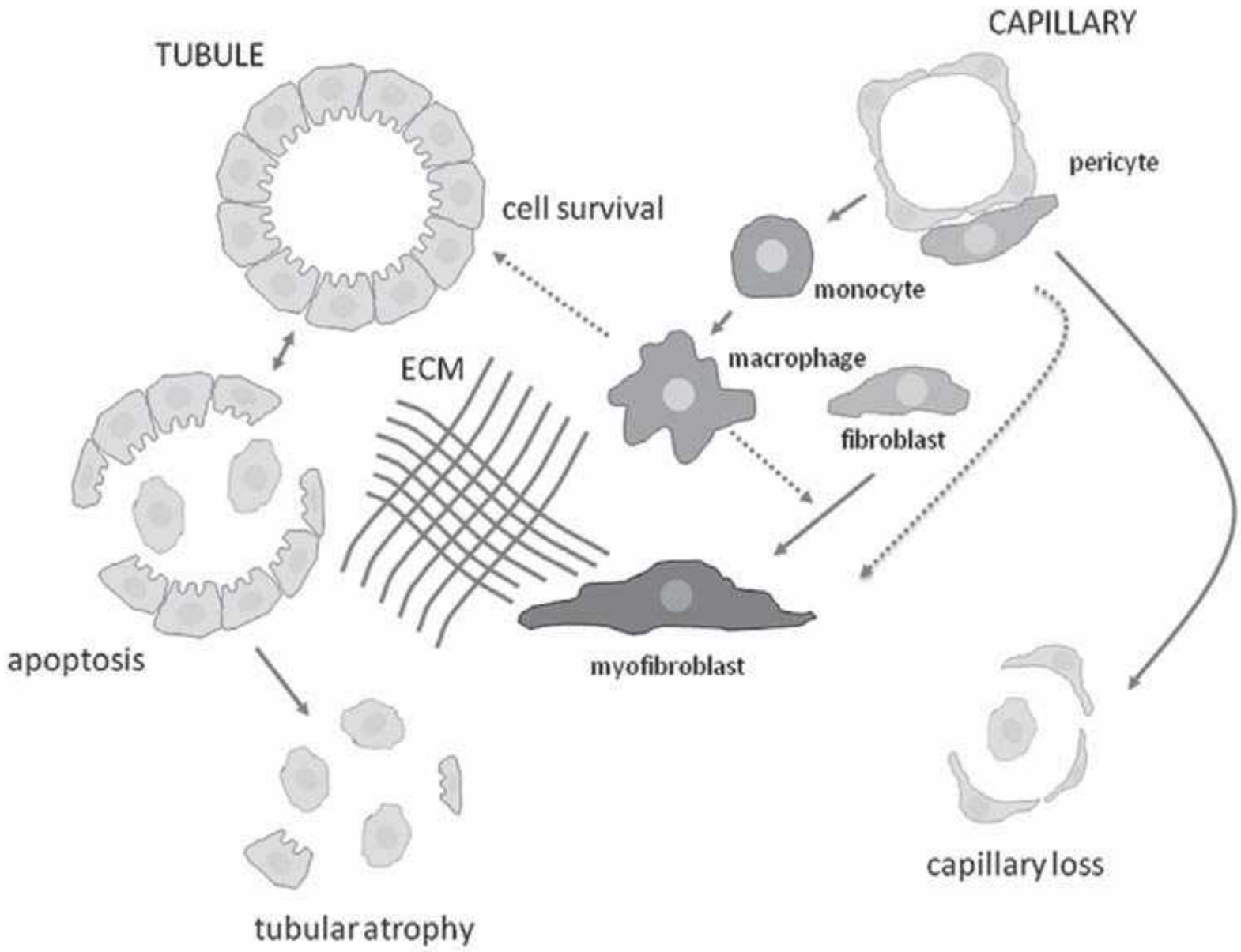

FIGURE 57.3 Schematic summary of the key cellular events contributing to the pathogenesis of chronic tubulointerstitial nephritis. Inflammatory macrophages are primarily recruited from the circulating pool of peripheral blood monocytes, under the direction of chemotactic signals derived from endothelial cells and damaged tubules and facilitated by increased capillary permeability. Functionally distinct macrophage subpopulations either propagate injury or promote tissue repair (including fibrosis) by releasing a variety of cytokines, growth factors, and other soluble products. A population of myofibroblasts appears de novo in the interstitium where they synthesize the majority of the extracellular matrix (ECM) proteins responsible for interstitial scarring. The primary origin of the myofibroblasts is still controversial; resident interstitial fibroblasts and capillary pericytes are considered most likely during active fibrogenesis. Through a variety of mechanisms, including hypoxia and oxidant stress, interstitial capillaries disappear and tubular epithelia undergo apoptotic death in parallel with progressive fibrosis.

component C3, and osteopontin (OPN) activate capillary endothelial cells, leading to increased capillary permeability, recruitment of leukocytes into the interstitium, and activation of myofibroblast precursors. Inflammatory macrophages secrete diverse proinflammatory and profibrotic products that perpetuate injury and promote scarring. This process unleashes a cascade of inflammatory and fibrogenic signals within the interstitium. Some key molecules including fibrinogen, complement components C3a and C5a, tissue plasminogen activator (tPA), and oxidized albumin may arrive by leakage from the plasma, whereas others, such as the major fibrogenic factor transforming growth factor β (TGF-β), connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), tumor necrosis factor α (TNF-α), endothelin-1, angiotensin-II, placental growth factor, and angiopoietin-2, appear to be produced locally. Together, these factors activate fibroblasts, and promote their transformation into α-SMA positive myofibroblasts. The activated myofibroblasts produce collagen I, collagen III, fibronectin, and other matrix proteins, which accumulate in the interstitial space. The fibrotic process culminates in death of tubular cells and peritubular capillaries, leading to ablation of the entire nephron (Fig. 57.3).[9–12]

Key Mechanisms

Tubular Epithelial Cells

The renal tubules account for approximately 80% of the total kidney volume. Tubular epithelial cells may be injured by immunologic, mechanical, chemical, genetic, or ischemic insults, which stimulate synthesis of inflammatory cytokines, cause functional perturbations, and/or lead to necrotic or apoptotic cell death. In acute kidney injury (AKI), tubular epithelial cells proliferate and replace damaged cells, restoring the architecture of the tubules. However, in CKD, complete tubular regeneration fails due to incomplete repair and persistent inflammation, leading to endoplasmic reticulum (ER) stress, loss of cytoskeletal integrity and polarity, and tubular barrier dysfunction, ultimately resulting in irreversible atrophic changes. The failure of tubular restoration is a critical turning point for CKD. Tubular atrophy may leave behind intact, atubular glomeruli, which are nonfunctional nephrons.[13]

Injured tubular epithelial cells often play a direct role in renal inflammation by secreting proinflammatory cytokines and growth factors including TNF-α, MCP-1, TGF-β, and RANTES. The production of growth factors may be cell cycle stage–specific, as it has been shown that acute kidney injury induced by ischemia/reperfusion leads to cell cycle arrest in the G2/M phase, followed by the release of growth factors such as TGFβ-1 and CTGF. These factors activate c-Jun N-terminal kinase (JNK) signaling, which promotes fibrosis.[14]

The fate of tubular epithelial cells is a critical determinant of nephron regeneration, and several mechanisms can direct each cell toward death by necrosis or apoptosis, or toward survival and proliferation. Tubular cell apoptosis is a common feature of CKD, and is known to be triggered by TGF-β1, TNF-α, Fas, p53, caspases, ceramide, and reactive oxygen species. Apoptosis can also be stimulated by the downregulation of survival factors such as epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF). An important step in cell survival following injury is the removal of damaged proteins and organelles by cell-mediated autophagy. In this process, an autophagosome is formed from the ER membrane, engulfs intracellular deposits, and delivers the contents to lysosomes for degradation. There is evidence of enhanced autophagy in obstructed tubules and AKI, which is thought to promote recovery; failure of autophagy may lead to apoptosis and prevent recovery of tubular epithelial cells.[15,16]

When the tubular damage is controlled, the tubules can regenerate. The origin of the new tubular epithelial cells has been a topic of debate. The current prevailing view is that proliferation of surviving tubular cells is sufficient to account for the recovery, without compelling evidence that renal and/or extrarenal progenitor cells are incorporated. However, soluble factors released by bone marrow–derived cells are thought to facilitate the repair process.[7,17,18]

Inflammatory Cells

Infiltration of the interstitium by inflammatory cells is an integral component of the fibrogenic response (Fig. 57.4). One of the most important inflammatory cell types is the macrophage, which primarily originates from circulating monocytes. Resident dendritic cells have limited proliferative capacity. Macrophages are functionally heterogeneous and have the potential to secrete a vast repertoire of soluble mediators, including proinflammatory and profibrotic cytokines. Inflammatory monocytes undergo differentiation in response to cytokines and typically become polarized into one of two distinct phenotypes.[19–21] This polarization process has been extensively investigated in mice, where classically activated "M1" macrophages are generated by exposure to interferon-γ and lipopolysaccharide. The M1 cells produce proinflammatory cytokines that propagate tissue injury. Alternatively activated "M2" macrophages are generated by exposure to interleukin-4 (IL-4) and IL-13. The M2 cells synthesize anti-inflammatory cytokines that promote tissue repair; however, this repair response may also lead to fibrosis. These differential functions have mainly been characterized using in vitro studies. In vivo, macrophage phenotypes are more diverse, and macrophages appear to switch phenotypes in response to different stimuli and microenvironments.[19,21,22] The role of the lymphocytes (which are typically present and may even outnumber interstitial macrophages) and the resident dendritic cells in renal fibrosis is still not clear.[23] It has been hypothesized that chronic

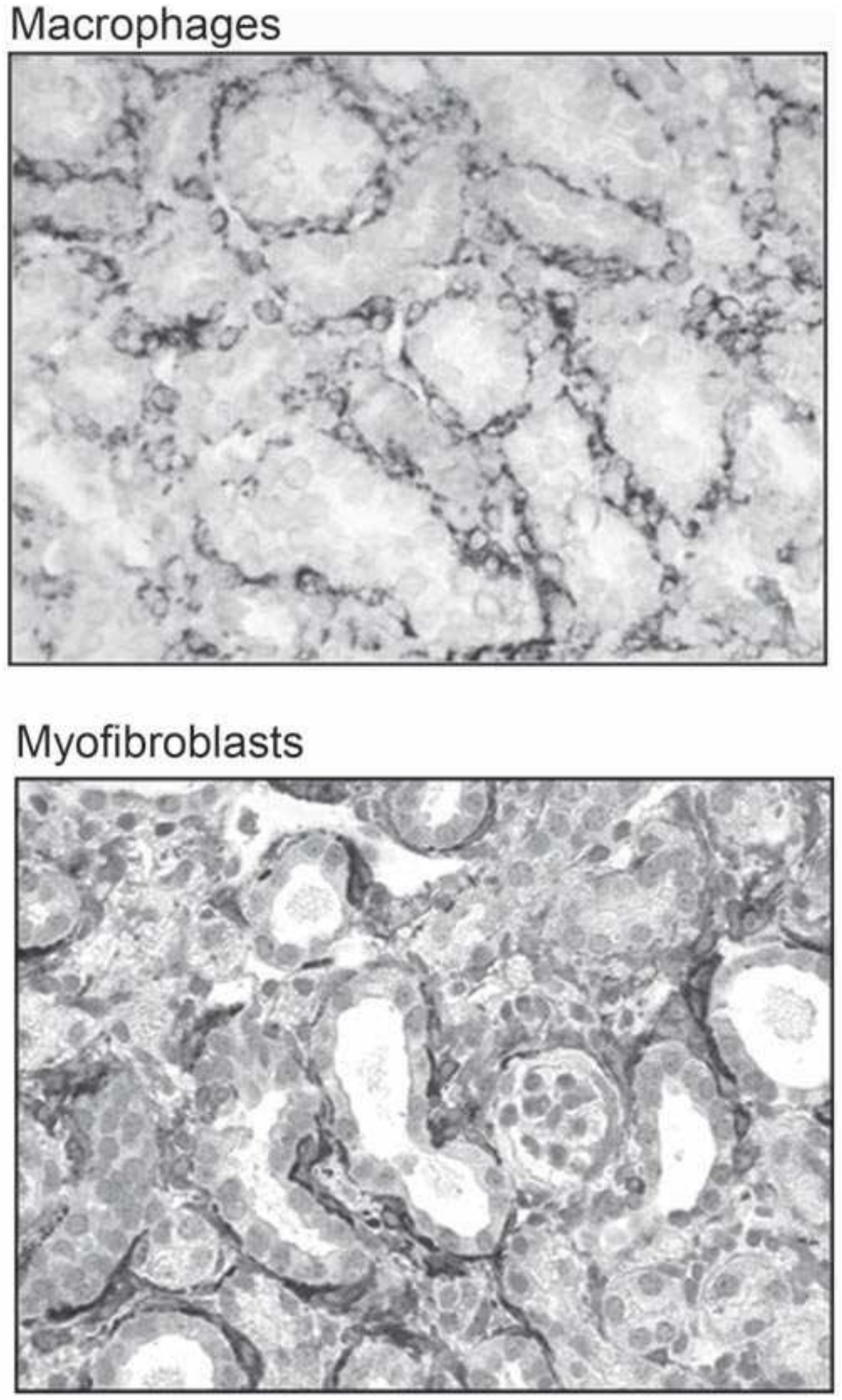

FIGURE 57.4 Interstitial cell mediators of chronic tubulointerstitial nephritis (TIN). Interstitial hypercellularity is a feature of chronic TIN, characterized by the presence of two distinct cell populations: lymphohematopoietic cells, with macrophages in particular (shown by CD68 staining in the upper photomicrograph) known to play an important pathogenic role, and myofibroblasts (shown by alpha smooth muscle actin staining in the lower photomicrograph). Limited human biopsy data show a significant relationship between interstitial myofibroblast density and renal prognosis. (The upper image is from Yamaguchi I, Tchao BN, Burger NL, et al. Vascular endothelial cadherin modulates renal interstitial fibrosis. *Nephron Exp Nephrol.* 2011;120:e20, with permission.)

renal injury may expose neoantigens that trigger a secondary antigen-driven immune response to propagate injury, but this hypothesis has been difficult to test using experimental models. Candidate neoantigens have not been identified, and thus this paradigm remains hypothetical.

Myofibroblasts

Interstitial myofibroblasts serve a pivotal role in renal fibrosis by synthesizing extracellular matrix (ECM) proteins such as collagen I, collagen III, and fibronectin that accumulate within the renal interstitium. Myofibroblasts contain contractile stress fibers and express α-SMA (Fig. 57.4). Myofibroblasts are essential for wound healing and tissue remodeling. During wound healing, they are activated, migrate within the damaged tissue, proliferate, and secrete ECM in response to inflammatory factors such as TGF-β1. Once healing is complete, myofibroblasts disappear by apoptosis. However, in chronic fibrosis myofibroblasts persist and lead to pathologic tissue remodeling, ultimately impairing organ function.[24]

The origin of renal interstitial myofibroblasts is a topic of great interest and some controversy. Myofibroblasts are functionally heterogeneous, depending to some extent on their local environment and perhaps on their origin. Most myofibroblasts appear to be derived from intrarenal cells, which may include resident interstitial fibroblasts, pericytes, or perivascular cells within the adventitia of arterioles and arteries.[3,25] Myofibroblasts might also be derived from epithelial-mesenchymal transition (EMT)[26] and endothelial-mesenchymal transition (EndMT),[27] although both of these events appear to be delayed until the advanced phase of renal fibrosis when basement membranes are destroyed. Other origins could include bone marrow-derived circulating fibroblasts or fibrocytes. Recent cell lineage tracing studies in genetically engineered mice support the view that myofibroblasts are rarely derived from tubular epithelial cells or fibrocytes; rather, they represent transformed interstitial fibroblasts, perivascular progenitor cells, and pericytes.[3] TGF-β and CTGF produced by injured tubular cells and inflammatory interstitial cells not only stimulate fibroblast proliferation and transformation to myofibroblasts, but also induce fibroblast epigenetic changes that influence cell survival. For example, TGFβ-induced hypermethylation of RASAL1, an inhibitor of the Ras oncoprotein, results in prolonged fibroblast activation and kidney fibrosis.[28]

Multiple growth factors such as TGF-β1, PDGF, fibroblast growth factor 2, and CTGF are known to stimulate fibroblast activation and extracellular matrix production, whereas hepatocyte growth factor and bone morphogenetic protein 7 are antifibrogenic. Numerous studies have investigated the downstream signaling cascades leading to fibrogenesis, which are too numerous to describe here.[8,11,12,29,30] Epigenetic mechanisms of regulation such as inhibition of DNA methylation and control of mRNA stability and translation by microRNA are also thought to play important roles in renal fibrosis.[28]

The processes of myofibroblast activation and apoptosis are of considerable interest as potential targets for antifibrotic therapy. TGF-β inhibition would appear to be an ideal strategy, but the complex effects of this multifunctional growth factor have presented challenges. Recent studies have focused on its downstream intracellular signals such as SMAD3, which activates microRNA-21, stimulating matrix production and fibrosis.[31] The renoprotective effects of renin-angiotensin system (RAS) blockade are thought to be mediated at least in part by TGF-β inhibition. Other cell-targeted strategies currently under investigation are aimed at inhibiting the formation of scar-forming myofibroblasts by profibrotic cytokines, promoting myofibroblast apoptosis, and/or inhibiting myofibroblast function (e.g., cell contraction or interactions via specific integrins).[32,33]

Capillary Changes, Hypoxia, and Oxidant Stress

The renal interstitium is perfused by an intricate network of peritubular capillaries that serve the vital role of oxygen delivery to metabolically active tubular epithelial cells. Peritubular capillary endothelial cells (ECs) undergo apoptosis during CKD, leading to capillary loss, and propagation of tissue hypoxia and oxidant stress. Based on several studies in animal models and human chronic kidney diseases, it is known that peritubular capillaries disappear in association with progressive interstitial fibrosis and tubular atrophy (Fig. 57.5).[34–37] Although the sequence of events connecting capillary loss to fibrosis and impaired tubular function is poorly characterized, it has been suggested that interstitial hypoxia caused by arteriolar vasoconstriction and/or peritubular capillary regression is a primary event in CKD.[38]

Under normal conditions, ECs are quiescent and turn over slowly. Vessel stability depends on cell–cell and cell–matrix interactions, normal levels of growth and angiogenic factors, and shear stress from blood flow. However, during kidney injury shear stress is altered, interactions between ECs change, cell–matrix interactions are disrupted, and growth and angiogenic factors are produced, including TGF-β, angiopoietin 2, and in some models VEGF.[39] As a consequence, ECs enter an activated state characterized by hyperpermeability, expression of leukocyte adhesion molecules, release of cytokines and growth factors, and enhanced cell migration and proliferation. EC activation is crucial for host defense and repair but may lead to dysfunctional changes including reduced production of nitric oxide (NO), a chronic proinflammatory state, and apoptotic EC cell death leading to capillary rarefaction.[40,41] Chronic hypoxia is a significant component of the pathogenetic process in interstitial fibrosis, in part because oxygen demand is actually increased above the high basal level during inflammation and tubular epithelial cell regeneration. The distortion and loss of peritubular capillaries establishes a vicious cascade, with worsening hypoxia propagating inflammation and fibrosis, with further nephron loss and renal functional decline.

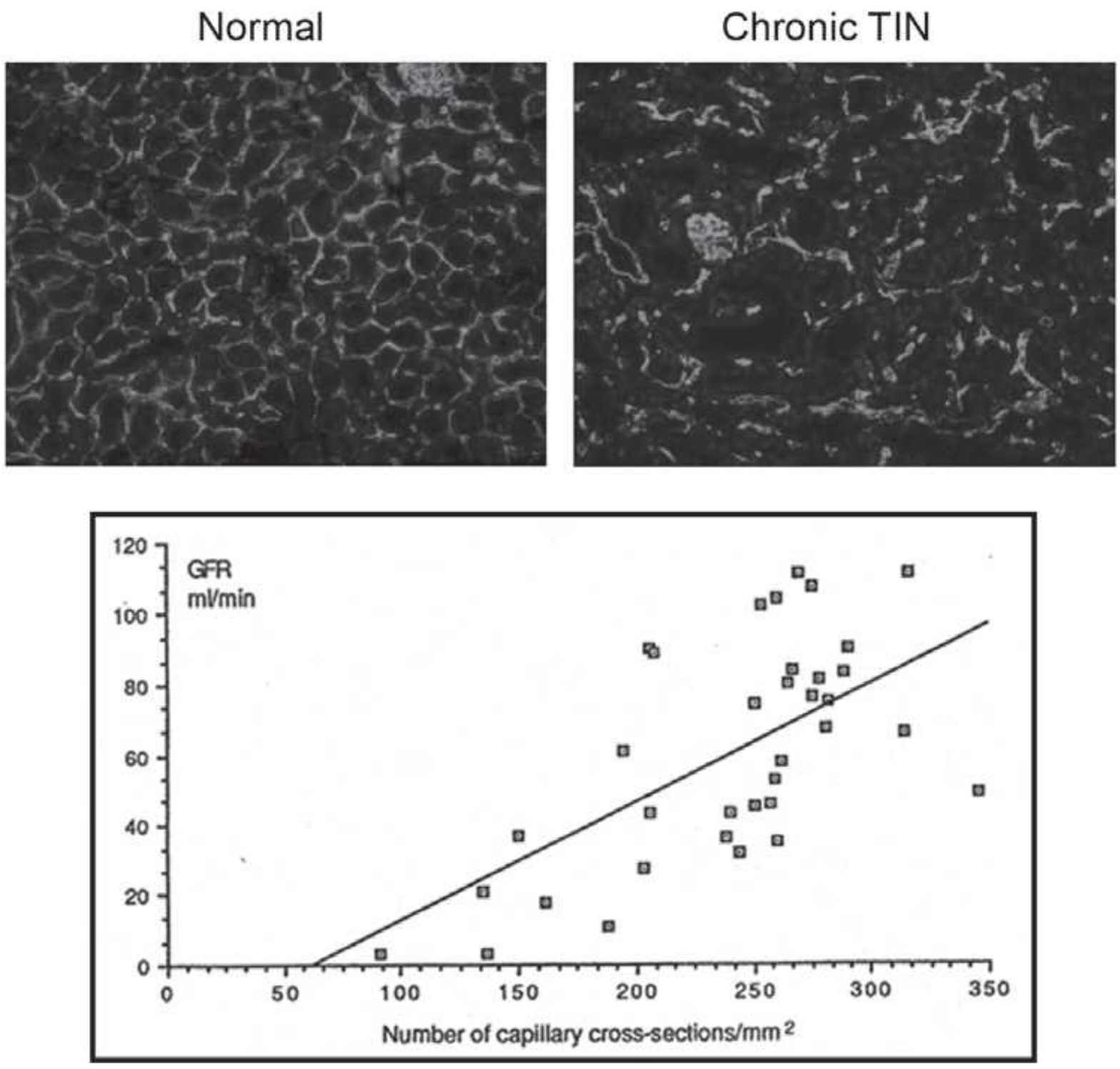

FIGURE 57.5 Interstitial capillary rarefaction is a feature of chronic tubulointerstitial nephritis (TIN). Using CD31 as an endothelial cell marker, the decrease in interstitial capillary cell density in chronic TIN is illustrated by the photomicrographs. In a study of human kidney biopsies, the extent of capillary loss was shown to correlate with the decline in glomerular filtration rate. (The photomicrographs are from Yamaguchi I, Tchao BN, Burger NL, et al. Vascular endothelial cadherin modulates renal interstitial fibrosis. *Nephron Exp Nephrol.* 2011;120:e20 and the graph is from Serón D, Alexopoulos E, Raftery MJ, et al. Number of interstitial capillary cross-sections assessed by monoclonal antibodies: relation to interstitial damage. *Nephrol Dial Transplant.* 1990;5:889, both with copyright permission.)

Matrix Accumulation

During fibrosis, the interstitial space is expanded by the accumulation of native and novel extracellular matrix (ECM) proteins. Expansion of the interstitial matrix appears to be the consequence of both increased matrix protein synthesis by myofibroblasts and decreased degradation by intracellular and extracellular connective tissue proteases. The expanded interstitium may include a gelatinous matrix of glycosaminoglycans (heparan sulfate, dermatan sulfate, chondroitin sulfate) and hyaluronic acid, an early scaffold rich in fibronectin, a fibrillar network of collagens (mainly types I, III and VI), and the presence of a variety of other extracellular matrix proteins (basement membrane collagens IV and V, collagens VII and XV, tenascin), laminin, proteoglycans (aggrecan, versican, decorin, fibromodulin, biglycan, perlecan), and various glycoproteins (thrombospondin, tenascin, hensin, vitronectin, secreted protein acidic and rich in cysteine [SPARC]). In addition to their structural effects, many of these matrix proteins elicit important effects on neighboring cells and molecules. For example, SPARC may inhibit cellular adhesion and proliferation, and also stimulates TGF-β expression and collagen I and fibronectin synthesis. Thrombospondin also activates TGF-β expression.

An unresolved question is the identity of the matrix-degrading proteases that maintain the status quo in normal kidneys despite ongoing collagen synthesis; it is also unclear why these mechanisms are perturbed during fibrogenesis.[42] For example, in normal mouse kidneys, approximately 20% of the kidney collagen is newly synthesized over a 2-week period yet total kidney collagen content does not increase, indicating that a similar rate of collagen degradation is going on at the same time.[43] The metalloproteinases (MMPs) are known to be important for extracellular matrix degradation and were long considered lead candidates for renal matrix homeostasis. MMP-2 and MMP-9 are abundant in the kidney and degrade collagen IV. However, paradoxically, MMP-2 and MMP-9 do not attenuate but accelerate interstitial fibrosis in experimental models. The serine proteases

urokinase-type plasminogen activator (uPA), tPA, and plasmin have been investigated as alternative candidates, but tPA and plasmin were found to promote fibrosis and uPA had no effect, despite the fact that the inhibitor PAI-1 is a potent fibrosis-promoting molecule. The latter effect may best be explained by PAI's ability to enhance macrophage and myofibroblast recruitment in the interstitium. The urokinase receptor (uPAR) attenuates myofibroblast recruitment and fibrosis, and acts in conjunction with its coreceptor LDL receptor-related protein (LRP) to regulate fibroblast proliferation and extracellular signal-regulated kinase (ERK) signaling.[44] Recent studies have focused on the role of an uPAR coreceptor, uPAR-associated protein (uPARAP), also known as the mannose receptor 2 (Mrc2) and Endo180. This receptor is expressed by interstitial macrophages and myofibroblasts and serves as a collagen endocytic receptor that delivers interstitial collagens to lysosomes for degradation by cathepsins.[43] Renal fibrosis is significantly worse in mice with genetic Mrc2 deficiency.

PRIMARY DISEASES ASSOCIATED WITH CHRONIC TIN

Genetic Renal Diseases

Familial Juvenile Hyperuricemic Nephropathy/ Medullary Cystic Disease Type 2

Medullary cystic disease type 2 (MCKD2) is a rare form of autosomal-dominant chronic TIN that is now known to be caused by a mutation on chromosome 16p12 involving the gene that encodes uromodulin (UMOD) (also known as Tamm-Horsfall protein).[45–47] Approximately 60 distinct mutations have been identified. UMOD expression is restricted to the thick ascending limb of the loop of Henle and the early distal convoluted tubule. UMOD is the most abundant normal urinary protein, with levels reported in the range of 50 mg per day. Although its function is still under active investigation, UMOD is known to form a water-impermeable barrier on the surface of these cells. It may also regulate cell membrane function, based on recent evidence that it associates with cilia, lipid rafts, and sodium transporters such as ROMK2.[48] It is also thought to inhibit stone formation. The UMOD mutation results in the production of a misfolded, aberrantly trafficking protein that is trapped in the endoplasmic reticulum (ER), leading to reduced urinary levels (hence the description of MCKD2 as a "UMOD storage disease") (Fig. 57.6). Such accumulation is thought to cause ER stress, which leads to renal tubular cell death. Most patients first seek medical attention with gout symptoms between 15 and 40 years of age, caused by hyperuricemia (present in ~70% of the patients) due to a reduced fractional excretion of uric acid—these patients are found to also have CKD.[47] Some patients have mild urinary concentrating deficits, which may contribute to the genesis of hyperuricemia. The renal biopsy shows nonspecific changes of tubular atrophy, interstitial fibrosis, and mild interstitial inflammation but no unique diagnostic features. Small cysts are detected by renal ultrasound in one third of the patients. Treatment with allopurinol may slow the progression of kidney disease, and RAS blockade may decrease production of the abnormal UMOD protein. Although most patients develop end-stage renal disease (ESRD), the rate of progression is highly variable, with ESRD developing between 30 and 60 years of age.

Familial juvenile hyperuricemic nephropathy type 2 has been reported as a distinct genetic entity (autosomal dominant) caused by a mutation in the REN gene encoding renin.[46,49] The mutations impair translocation of the nascent preprorenin protein into the ER, resulting in reduced or abolished renin biosynthesis and secretion. It has been suggested the mutant preprorenin may be toxic to juxtaglomerular

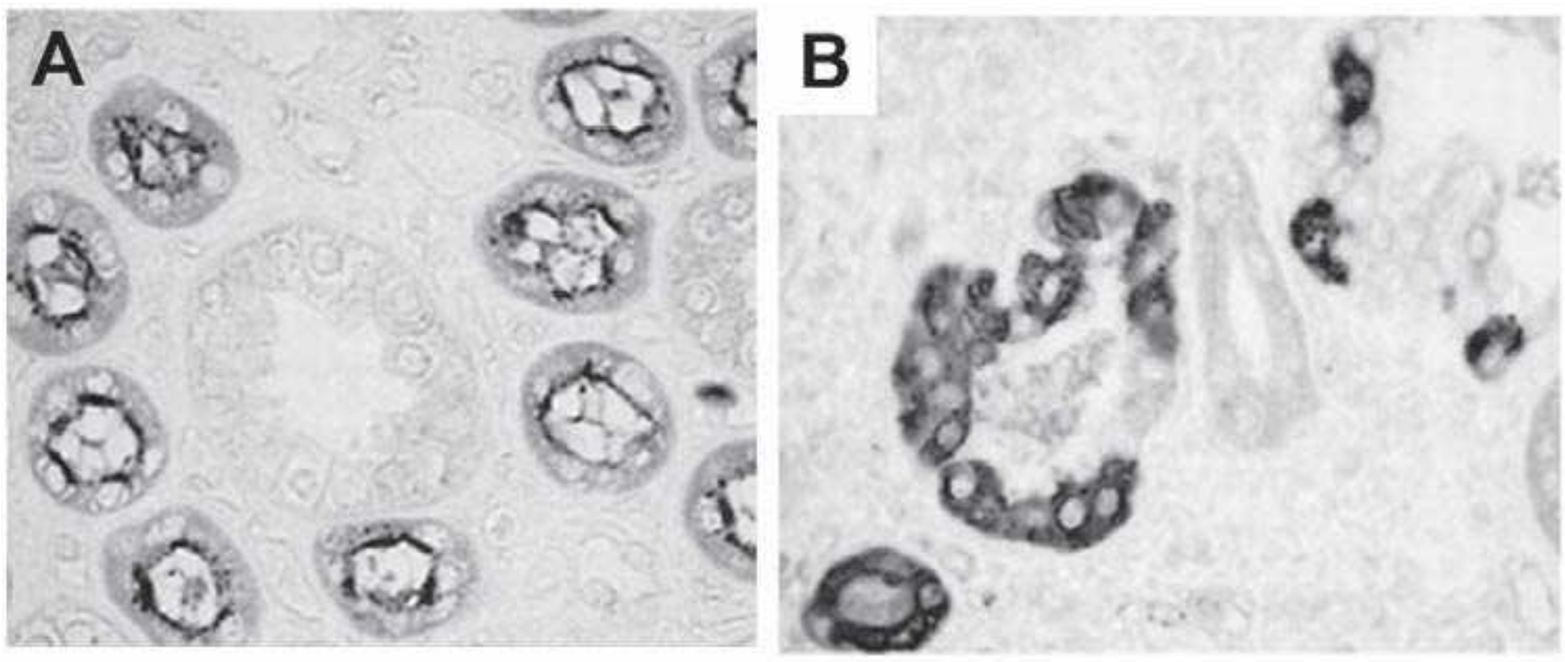

FIGURE 57.6 Familial chronic tubulointerstitial nephritis associated with mutations in the uromodulin (*UMOD*) gene, which encodes a protein normally expressed on the apical membrane of the thick ascending limb of the loop of Henle (shown on left). These mutations result in an abnormal UMOD protein that is trapped within the endoplasmic reticulum (right photograph). (From Dahan K, Devuyst O, Smaers M, et al. A cluster of mutations in the UMOD gene causes familial juvenile hyperuricemic nephropathy with abnormal expression of uromodulin. *J Am Soc Nephrol.* 2003;14:2883, with permission.)

cells, causing additional damage to the RAS and leading to nephron dropout and progressive renal failure. Patients typically present with early-onset anemia due to low erythropoietin production, mild hyperkalemia, and low-normal blood pressure. A history of gout in some affected family members should raise the suspicion of this disorder. Plasma renin, aldosterone, and erythropoietin levels are low; fractional urate excretion is reduced; and kidney biopsies show chronic TIN, although none of these findings alone confirms the diagnosis. Mutational analysis of the REN gene is required. Treatment is supportive. CKD typically develops in the third or fourth decade and progresses slowly.

Nephronophthisis: Associated Ciliopathies

Nephronophthisis (NPHP) is a group of autosomal-recessive disorders that share chronic progressive TIN and genetic mutations in genes encoding proteins that localize to primary tubular cell cilia (reviewed in greater detail in Chapter 15).[50–52] Clinically the patients have been subdivided into four groups based on the presence or absence of extrarenal manifestations and the causative genetic mutation. All patients with renal involvement share a form of chronic tubulointerstitial disease that typically progresses to ESRD before adulthood (median age 13 years). It is estimated that NPHP may account for 5% to 10% of pediatric patients with ESRD. The name nephronophthisis means "disintegration of nephrons" and epitomizes the histologic findings, which include nonspecific tubular atrophy with tubular basement membrane thickening and/or disruption, interstitial inflammation, and fibrosis. Small corticomedullary cysts may be present, especially with more advanced disease. These cysts and small echogenic kidneys may be detected by renal ultrasonography. Clinically, most patients have polyuria, polydipsia, and anemia but are otherwise asymptomatic until manifestations of renal failure develop in the second decade of life. The causative gene has been identified in ~30% of cases, the most common (20%) being a homozygous deletion in nephrocystin 1 (NPHP1), which encodes a protein involved in ciliary function in collecting duct cells. An estimated 10% to 15% of the NPHP patients have extrarenal involvement. The most common is retinitis pigmentosa (Senior-Loken syndrome). Others include cerebellar ataxia (Joubert syndrome) and oculomotor apraxia (Cogan syndrome), as well as several rarer genetic syndromes. Treatment of the kidney disease is symptomatic. The kidney disease does not recur after kidney transplantation.

Polycystic Kidney Diseases

Genetic disorders associated with polycystic kidney disease (PKD) are reviewed in Chapter 16. They are mentioned here to emphasize the importance of interstitial inflammation and fibrosis to disease progression. The progression of CKD is not simply a matter of total cyst volume expanding to mechanically compress adjacent renal parenchyma; the disease is also associated with damage to otherwise normal noncystic nephrons as a consequence of chronic TIN. The degree of renal fibrosis in patients with PKD is closely associated with the rate of progression to ESRD, just as it is in all CKD.[53] Studies by Grantham et al.[54] in the 1990s first suggested a potential pathogenetic link between renal cysts and interstitial inflammation and fibrosis. Many macrophage innate immune response genes are upregulated in cystic mouse kidneys.[55] Polycystin-1-deficient tubular cells have been shown to stimulate macrophage migration and to secrete monocyte chemoattractant protein-1 and the chemokine CXCL16.[56] Inflammatory cytokines are also present in cystic fluid. This inflammatory cell response has been implicated in both cystogenesis and interstitial fibrosis. Anti-inflammatory therapy such as corticosteroids or depletion of monocytes significantly attenuates interstitial inflammation and the rate of renal functional decline in animal cystic kidney disease models (Fig. 57.7).[56,57] Taken together, these data suggest that epithelial cell changes precede and drive the interstitial inflammatory response in patients with PKD.[58] Possible protective tubulointerstitial effects should be taken into consideration as potential beneficial mechanisms when evaluating new drug therapies such as mammalian target of rapamycin inhibitors and vasopressin receptor antagonist.

Genetic Metabolic Disorders

Several severe metabolic disorders that present during infancy and childhood are known to cause CKD via disease processes that primarily involve the tubulointerstitial compartment.

Cystinosis. Cystinosis is an autosomal recessive disorder caused by a mutation in the lysosomal membrane protein cystinosin (CTNS).[59] The estimated incidence is 1 in 100,000 to 200,000 live births. Affected children are normal at birth but develop clinical complications due to renal Fanconi syndrome, which typically brings them to medical attention before 2 years of age with failure to thrive and a history of excessive thirst, polyuria, recurrent vomiting, constipation, and episodes of dehydration. The children may already have evidence of rickets due to renal phosphate wasting. Although this is a systemic disorder, the kidney is the first organ affected and CKD progresses rapidly over the first decade if untreated. In addition to this classical presentation in infancy (nephropathic infantile form), a less aggressive renal disease has been reported but is much less common, accounting for <5% of cases (nephropathic juvenile form). Cystine is a dimeric amino acid formed by the oxidation of two cysteine residues, which become linked by a disulfide bond. Cysteine is a product of normal protein turnover, and the cystine dimer is normally recycled via the lysosomal cystinosin transporter (Fig. 57.8). In its absence, abnormal levels of cystine accumulate within lysosomes, often forming cystine crystals and leading to significant cellular damage. It is thought that the renal proximal tubules are an early target of injury due to their high rate of urinary protein uptake and processing. By 1 year of age, pathognomonic ocular corneal crystals can be detected by slit lamp examination. The

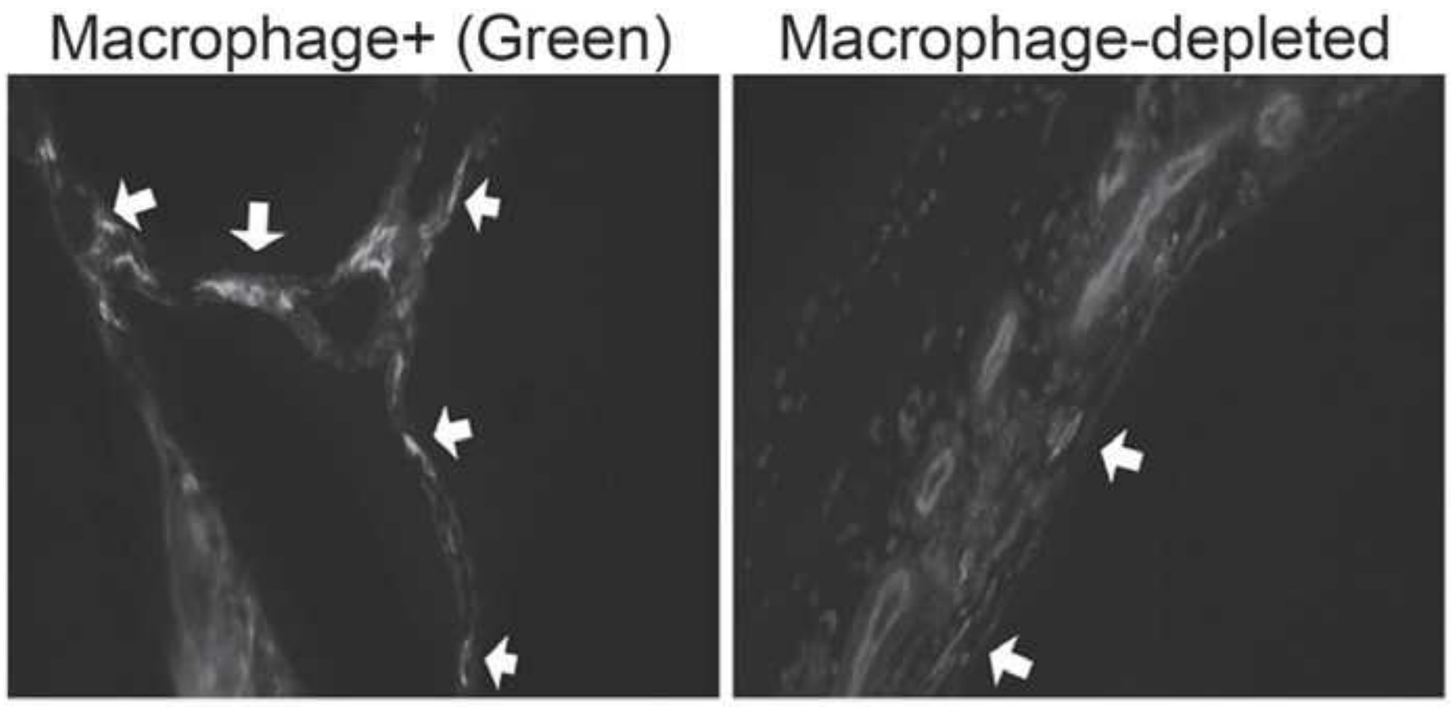

FIGURE 57.7 Interstitial inflammation is a pathogenic feature of polycystic kidney disease. In a mouse model of autosomal dominant polycystic kidney disease, macrophages (green) are seen lining cystic spaces (*upper left*). When macrophages were experimentally depleted (*upper right*), renal parenchyma was better preserved (*lower left*), and kidney function estimated by blood urea nitrogen levels was significantly better in the macrophage depleted (−) mice, shown in the lower right graph. (From Karihaloo A, Koraishy F, Huen SC, et al. Macrophages promote cyst growth in polycystic kidney disease. *J Am Soc Nephrol.* 2011;22:1809, with permission.) (See Color Plate.)

diagnosis is typically confirmed by the presence of elevated cystine levels in peripheral blood leukocytes, measured in a reference laboratory. Since the cystinosis gene (CTNS) was cloned in 1998, over 90 mutations have been reported in the United States and northern Europe—approximately 40% have a homozygous 57 kb deletion.

Human renal pathologic studies and recent studies in a mouse model indicate universal changes in renal tubules. The classical findings of a "swan neck deformity" occur as a consequence of proximal tubular cell atrophy, emphasizing the early and severe involvement of this nephron segment in cystine-associated injury. Progressive CKD is characterized by chronic TIN together with nonspecific chronic glomerular changes. The primary pathogenesis of target organ injury is thought to be due to lysosomal cystine accumulation, which perturbs several cellular functions, leading to altered energy metabolism, oxidant stress, and tubular cell death by apoptosis. However, many aspects of the kidney injury are not completely understood, such as the failure of the early and severe tubular transport defects to improve with cysteamine therapy.[60] In the cystinosin knockout mice, a mild renal phenotype despite high kidney cystine levels and the benefit of bone marrow transplantation suggest that mechanisms beyond renal tubular toxicity are involved.[61]

Medical therapy includes a combination of water, mineral, and electrolyte replacement therapy; nutritional support; and specific therapy with the amino thiol drug cysteamine. Cysteamine lowers lysosomal cystine levels via a disulfide exchange reaction with cystine, generating a cysteine-cysteamine product that can exit via an alternative transport system (Fig. 57.8). If therapy is started at a young age and leukocyte cysteine levels are maintained in the target range, kidney survival can be significantly prolonged; however, most patients still develop ESRD by the second or third decade of life.[62] The disease does not recur in a renal allograft. Most children require a gastrostomy tube in order to maintain fluid and electrolyte balance and to achieve normal growth. A minority of the patients may also require growth hormone therapy. Extrarenal manifestations are universal and may include skin and hair hypopigmentation, hypothyroidism (70% within the first decade), and eye involvement

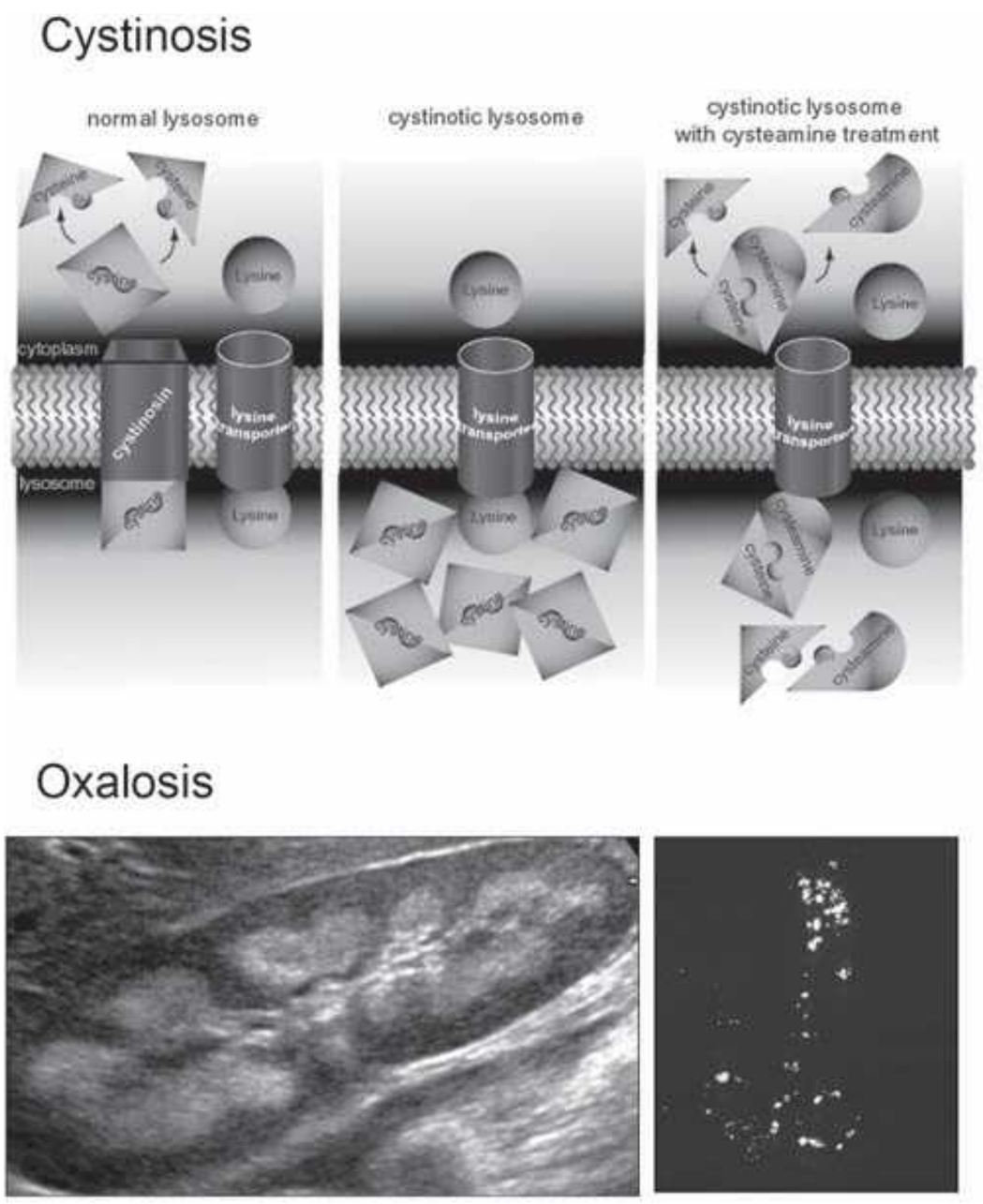

FIGURE 57.8 Inherited metabolic diseases cause chronic tubulointerstitial nephritis. The upper drawing illustrates the abnormal function of the lysosomal membrane in patients with autosomal recessive cystinosis due to a mutation in the *CTNS* gene that encodes the cystine transporter cystinosin. In the absence of cystinosin, cystine accumulates in lysosomes and contributes to some of the associated tissue pathologies. An elevated peripheral blood leukocyte cystine level is diagnostic. The drug cysteamine provides an alternative pathway for cystine exit from lysosomes by forming a cysteine-cysteamine dimer that is transported by an alternative (system c) lysosomal transporter. Though not yet definitively identified, it has been suggested that system c is the lysine transporter. (From Wilmer MJ, Schoeber JP, van den Heuvel P, et al. Cystinosis: practical tools for diagnosis and treatment. *Pediatr Nephrol*. 2011;26:205, with permission.) Primary infantile oxalosis is associated with aggressive chronic tubulointerstitial nephritis due to the deposition of calcium oxalate in renal tubules and the interstitium, which may be detected as nephrocalcinosis on the renal ultrasound (*lower left*) or the actual deposits can be visualized by polarized light microscopic examination of kidney tissue (*lower right*). (See Color Plate.)

with photophobia that requires treatment with topical cysteamine. Neuromuscular involvement and pancreatic insufficiency often develop in the older patients.

Methylmalonic Acidemia. Methylmalonic acidemia (MMA) is an autosomal recessive inborn error of organic acid metabolism.[63,64] Methylmalonic acid, which is normally generated via the metabolism of isoleucine, methionine, threonine, valine, and certain odd-chain fatty acids, accumulates in MMA patients due to a deficiency in its degrading enzyme methylmalonyl-CoA mutase (primarily expressed in the liver). Deficiency of the enzymatic cofactor cobalamin (vitamin B12) can also lead to MMA. The incidence of MMA may be as high as 1:48,000 based on newborn screening data. Although the timing of the clinical diagnosis ranges from the neonatal period to adulthood, the most common form of the disease begins in infancy with clinical manifestations caused by metabolic decompensation: lethargy, vomiting, dehydration, hypotonia, encephalopathy, ketoacidosis, and hyperammonemia. Rarely, infants may present with a hemolytic uremic syndrome. A definitive diagnosis requires measurement of plasma or urine organic acids. Genetic testing is currently available for some of the mutations. In addition to a variety of neurologic complications, many of the patients develop CKD due to TIN.[65] The pathogenesis is unclear but is presumed to result from tubular cell injury due to altered energy metabolism and MMA toxicity.[64] Treatment of the primary metabolic disorder involves dietary control of protein catabolism with a low protein/high carbohydrate diet and cobalamin therapy for patients whose disease is shown to be vitamin B12 responsive. Patients frequently require hospitalization to manage metabolic complications during periods of decompensation. Several patients have undergone successful kidney transplantation, but the primary genetic defect persists due to uncorrected systemic enzyme deficiency. Liver transplantation and combined kidney–liver transplantation have been performed but remain controversial, as liver transplantation only partially corrects the enzyme deficiency due to MMA production by skeletal muscle.[66]

Primary Hyperoxaluria. Hyperoxaluria can be inherited or acquired. The primary diseases are rare autosomal recessive inborn errors of metabolism that are characterized by very high urinary oxalate levels and the development of nephrocalcinosis (Fig. 57.8) and/or recurrent kidney stones leading to progressive renal parenchymal damage.[67] Histopathologically, the kidneys are characterized by the presence of calcium oxalate crystals in tubular lumina, tubular epithelial cells, and interstitial cells (Fig. 57.8), together with interstitial inflammation and fibrosis. Symptoms due to recurrent stone formation typically begin in childhood—approximately 50% progress to ESRD by adulthood. Approximately one quarter of the patients with primary hyperoxaluria present with a severe, life-threatening infantile disease with rapid progression to renal failure. Mutations have been identified in three separate genes encoding enzymes in the pathway that regulates oxalate metabolism. The most common deficit (~80%) is due to a deficiency of the hepatic enzyme pyridoxal phosphate-dependent enzyme alanine glyoxylate aminotransferase (AGT). The second type is caused by a deficiency of glyoxylate reductase/hydroxypyruvate reductase (GRHPR), and the third has been linked to an as yet uncharacterized gene, DHDPSL. The diagnosis of primary hyperoxaluria is suggested by significantly elevated

urinary oxalate levels; elevated urinary glycolate suggests an AGT mutation, whereas elevated urinary L-glyceric acid suggests a GRHPR mutation. A definitive diagnosis requires either molecular genetic studies or documented low enzyme activity in a liver biopsy specimen.

Because the large oxalate burden is primarily excreted by the kidney, treatment is based on strategies to decrease production (~30% of the patients respond to the AGT cofactor pyridoxine) and to decrease urinary oxalate concentration (fluids), together with inhibitors of calcium oxalate crystallization (pyrophosphate, citrate, magnesium). As renal function declines, plasma oxalate levels rise and lead to extrarenal deposits in many tissues—especially bones, heart, vessels, joints, retina, thyroid, and soft tissue. Patients with AGT mutations are most likely to develop ESRD and are now being treated with combined liver–kidney transplants, although variations in this approach are still considered. After transplantation the heavy burden of extrarenal calcium oxalate (especially in bones) is slowly released, leading to persistent hyperoxaluria for a significant period of time posttransplantation.

Mitochondrial Cytopathies. The primary mitochondrial cytopathies are a heterogeneous group of rare genetic disorders caused by mutations in maternally inherited mitochondrial DNA (mtDNA) or nuclear-encoded mitochondrial genes that share common functional defects in the mitochondrial respiratory chain. Multiple organ systems are typically involved, especially in tissues with high metabolic activity. Neurologic and myopathic features are common, although more than 40 clinical syndromes have been reported. Most of the published reports of CKD due to TIN come from children who presented with clinical manifestations before 2 years of age.[68] However, it has been suggested that the prevalence of mitochondrial cytopathies in the adult population with CKD is underestimated.[69,70] From a renal perspective, proximal tubular dysfunction is the most common finding (~50% of the mitochondrial cytopathy patients), often leading to Fanconi syndrome. However, several patients developed chronic TIN in the absence of features of the renal Fanconi syndrome. Other reported renal manifestations include cystic renal disease and glomerulopathies (especially focal segmental glomerulosclerosis in adults). By electron microscopy, a variety of abnormalities have been described in tubular epithelial cell mitochondria, including changes in both morphology and number. Because a detailed analysis of tubular cell mitochondria has only been performed in very few chronic tubulointerstitial diseases, it is unclear whether any of the reported findings are specific to patients with primary mitochondrial cytopathies. Because mitochondria are involved secondarily in many pathways of CKD in association with oxidant stress and apoptosis, acquired morphologic changes might be anticipated. Primary mitochondrial disorders are being recognized with increasing frequency in adults with a variety of clinical manifestations, including chronic TIN. An elevated serum lactate level may be an initial diagnostic clue, but is not universally present in patients with renal mitochondrial cytopathies. Making a definitive diagnosis can be difficult for a variety of reasons, including the lack of a unique clinical phenotype and challenges pertaining to the interpretation of genetic studies. In particular, because spontaneous acquired mutations in the multiple copies of circular mtDNA that are present in each cell (~71,000) are common, it is first necessary to establish the pathogenetic significance of any novel mutations that are detected. Treatment is primarily symptomatic. Coenzyme Q10 therapy is recommended for patients with CoQ10 deficiency, although it is not clear that this treatment improves renal outcomes.

Chronic TIN in Primary Immunologic Disorders

Many of the disorders reviewed in this section are traditionally considered causes of acute TIN, but due to the insidious nature of the clinical manifestations, significant chronic changes are often present by the time that a renal biopsy is performed. TIN is typically one manifestation of a multisystem disorder, and the extrarenal manifestations often attract greater attention initially. From a renal perspective, the disease entities can be arbitrarily divided into two groups: (1) TIN is the primary renal manifestation and (2) TIN occurs in conjunction with glomerulonephritis. It is not clear whether primary humoral mechanisms ever cause TIN as they only target organs involved in the disease process. Studies in the 1990s characterized a circulating antibody in a small number of patients with TIN that bound to a unique 48–54 kd glycoprotein present in tubular basement membranes (especially proximal) and Bowman's capsule but not in the glomerular basement membrane.[71] Some of these patients also had membranous nephropathy. Antitubular basement membrane (TBM) antibodies are most likely to be associated with chronic TIN in patients with antiglomerular basement membrane (GBM) nephritis or Goodpasture syndrome (see Chapter 48). Chronic TIN associated with deposition of immune complexes along the TBM is most likely to occur as a manifestation of systemic lupus erythematosus. However, most TIN that occurs in association with systemic autoimmune disorders is not associated with pathologic evidence of antibody deposition and is presumed to be caused by cell-mediated mechanisms. Although beyond the scope of this chapter, another important immune-mediated cause of chronic TIN is chronic allograft nephropathy (see Chapter 81).

Primary Sjögren Syndrome

Primary Sjögren syndrome (SS) is a systemic autoimmune disease associated with autoantibodies to Ro/SSA and/or La/SSB that principally targets salivary and lacrimal glands. Many patients also have a positive rheumatoid factor, ANA antibodies, and hypergammaglobulinemia. Maripuri et al.[72] recently summarized findings in 24/7,276 patients (0.3%)

with SS and kidney involvement that was confirmed by renal biopsy over a 40-year period. The most common renal finding was TIN (70%), which was chronic in 46%; the severity of chronic TIN identified patients with estimated GFRs of less than 30 mL/min/1.73 m^2. The prevalence of renal involvement in SS is highly variable and likely underrecognized. Because both systemic and renal disease may be effectively controlled with corticosteroids and immunosuppressive therapy, the importance of early diagnosis is evident. Proximal or distal renal tubular acidosis, which is present in ~75% of the TIN patients, often associated with hypokalemia and polyuria, may prove to be a sensitive early indicator of TIN in this patient group.[73] Dysfunctions of the H-ATPase pump and carbonic anhydrase II have been implicated as potential mechanisms. Periodic paralysis due to severe hypokalemia is not uncommon in primary SS patients with severe TIN. Although the inciting antigen and specific pathogenetic mechanisms remain unclear, the TIN is characterized by interstitial infiltrates of lymphohematopoietic cells similar to those in extrarenal target organs. There do not appear to be unique serologic abnormalities that predict the risk of TIN. Tubulointerstitial immune deposits are not typically found by IF or EM. Antibodies to the extractable nuclear antigens Ro and La and perhaps other more recently described antigens (α-fodrin and the muscarinic receptor M3) may ultimately be shown to serve a specific pathogenic role.[74] Treatment is usually guided by the extrarenal manifestations and may include corticosteroids, hydroxychloroquine, and possibly one of the newer anti-TNF or anti-CD20 biologic agents. Patients with primary SS have an increased risk of lymphoma, which should be taken into consideration in the treatment plan. The renal outcome typically depends on the degree of interstitial fibrosis at the time of diagnosis.

IgG4-related Disease

IgG4-related disease was first recognized as a cause of autoimmune pancreatitis in 2001. It is now known to be a cause of TIN (first reported in 2004) as well as a variety of other extrarenal manifestations, including cholangitis, sialadenitis, pneumonitis, pseudotumor, and periarthritis. Although many patients have clinical factors that overlap with SS, serologic findings appear to be unique. In patients with IgG4-related disease, total serum IgG and IgG4 levels are elevated, antibodies to double-stranded DNA, SSA, and SSB are typically negative (although ANA may be positive), and hypocomplementemia is common (~70%). Although SS is a disease of middle-aged women, IgG4-related disease primarily affects older men. Abnormal renal imaging studies suggestive of a mass have been reported in ~30% of patients, manifest as multifocal, low attenuation lesions, or diffuse nephromegaly. On histologic examination, these lesions correspond to areas of TIN. Two recent studies focusing on IgG4-related TIN, from Japan and the United States respectively, reported renal involvement in 20% to 30% of the patients.[75,76] Within this combined cohort, ~50% had documented pancreatic involvement. Histologically, the lesions were characterized by an interstitial infiltrate of plasma cells, many expressing IgG4, together with variable degrees of interstitial fibrosis and tubular atrophy—interstitial eosinophils were also common. Excluding the interstitial inflammatory lesions that were observed in patients with ANCA-associated vasculitis (31% IgG4 positive), only 12% of the patients with other causes of TIN had IgG4+ interstitial cells. Detection of granular TBM immune deposits varied between the two studies: 7% in the first series and 83% in the second. Minor glomerular abnormalities were also observed in a few of the patients. Most patients were treated with corticosteroids with or without immunosuppressive drugs. Short-term outcomes appear to be good—three patients (5%) with renal failure at diagnosis had developed ESRD at last follow-up.

Sarcoidosis

Sarcoidosis is a multisystem disease of unknown etiology that primarily affects the 10- to 40-year age group and is characterized by organ injury associated with noncaseating epithelioid giant cell granulomas.[77] A rare familial form of the disease has been reported to be associated with mutations in nucleotide-binding oligomerization domain 2/caspase activation recruitment domain 15 (NOD2/CARD15), a gene involved in inflammation and apoptosis. In the absence of diagnostic serologic markers, elevated serum angiotensin-converting enzyme (ACE) and lysozyme levels suggest a diagnosis of sarcoidosis.[78] Other characteristic features include hypercalcemia, interstitial lung disease, and hilar adenopathy. Many of the patients (>50%) develop renal insufficiency, which has largely been ascribed to perturbations in calcium metabolism that develop in association with elevated 1,25-dihydroxy vitamin D levels, hypercalcemia, hypercalciuria, and nephrocalcinosis. However, a subset of patients develops a unique form of TIN that is characterized by the presence of interstitial granulomas.[79] Recent studies of granulomatous TIN have identified sarcoidosis as the primary etiology in almost 30% of cases. Like many types of TIN, this lesion is often unrecognized clinically and may be associated with significant chronic TIN when tissue is obtained for histologic analysis typically when patients develop CKD. Autopsy studies have reported granulomatous TIN in ~13% of sarcoidosis patients. Rarely, TIN may be the initial manifestation of the disease. Recurrent disease has been reported in renal allografts. Corticosteroids with or without immunosuppressive therapy are beneficial, although recovery is often incomplete due to the presence of irreversible chronic TIN.

Tubulointerstitial Nephritis with Uveitis Syndrome

The recognition of TIN with uveitis (TINU) syndrome as a distinct clinical entity was first reported in 1995. The syndrome can occur as an isolated entity of unknown etiology or as a manifestation of specific autoimmune disorders (SS, sarcoidosis, systemic lupus erythematosus [SLE], ANCA+

vasculitis, Behçet disease) and certain infectious diseases (tuberculosis, brucellosis, toxoplasmosis, histoplasmosis, Epstein-Barr virus, HIV, chlamydia, mycoplasma). In the absence of a diagnostic serologic marker, the diagnosis of idiopathic TINU is based on the exclusion of other possibilities. The disease is considered an autoimmune disease mediated by a cellular immune response to an antigen that is expressed by renal tubules and the uveal tract of the eye. Modified C-reactive protein has recently been suggested as an antigenic candidate based on the presence of circulating anti-CRP antibodies.[80] Unlike many of the other disorders discussed in this section, idiopathic TINU primarily affects adolescents and young adults and is usually associated with acute systemic manifestations such as fever, weight loss, and general malaise. Flank pain is not uncommon. Although the kidney disease is thought to be self-limited, many patients are treated with corticosteroids with or without immunosuppressive drugs due to severe ocular involvement that may follow a relapsing course and lead to chronic eye disease. The renal disease is typically acute TIN with a good prognosis, but fibrotic sequelae including both ESRD and disease recurrence in a renal allograft have been reported, although these outcomes are considered rare. A recent study of 26 Finnish children with TINU reported that 15% had permanent renal insufficiency and 31% had persistent low molecular weight proteinuria, which suggests that sequelae due to chronic TIN may become evident with longer term follow-up.[81]

TIN ASSOCIATED WITH PRIMARY GLOMERULAR DISEASES

With the exception of steroid-responsive nephrotic syndrome, virtually all glomerular diseases are accompanied by an interstitial inflammatory response, although its severity varies widely. The subsequent progression to interstitial fibrosis and tubular atrophy is an important prognostic indicator, as first shown by the studies of Risdon[82] and Schainuck[83] and their respective colleagues more than 40 years ago. The pathogenetic mechanisms of acute TIN associated with primary glomerular disease have not been clearly elucidated. For immune complex-associated disease such as lupus nephritis, TBM immune deposits may be present and associated with interstitial inflammation, but TIN more commonly occurs in their absence. Occasionally TIN is the primary renal lesion in lupus nephritis. Similarly, anti-TBM antibodies are observed in a subset of patients with anti-GBM nephritis/Goodpasture syndrome, but the tubulointerstitial inflammation is disproportionately severe and its relationship to anti-TBM antibodies is unclear. T-cell mediated immune responses are likely involved, although specific antigens and effector cell pathways remain unknown. For some diseases, such as ANCA-positive vasculitis, interstitial inflammation may be severe and associated with noncaseating granulomas. Crescentic glomerular diseases may be characterized by impressive periglomerular interstitial inflammation, often in association with breaks in Bowman's capsule that allow chemotactic factors, fibrinogen, and other inflammatory mediators to leak directly into the interstitium to trigger TIN. Irrespective of the inciting mechanisms, delayed diagnosis or inadequate therapy means that patients with severe glomerular disease may develop chronic TIN, which has important prognostic implications. This relationship has been well established in patients with lupus nephritis. For example, in a recent study of 313 patients with lupus nephritis, Yu et al.[84] graded the severity of interstitial inflammation, tubular atrophy, and interstitial fibrosis and showed that these changes were a significant predictor of renal survival (Fig. 57.9).

Proteinuria as a Mediator of Progressive Kidney Damage

A series of observations over the last two decades support a pathogenetic connection between severe proteinuria and chronic TIN that underlies progressive functional deterioration, and may explain at least in part why patients with primary glomerular disease develop TIN. The basis of this hypothesis derives from an extensive literature indicating that the degree of proteinuria is one of the strongest predictors of renal outcome (Fig. 57.10),[85,86] coupled with plausible mechanistic paradigms derived from in vitro models, animal models, and careful analytic studies of human kidney tissue. Two distinct (but not mutually exclusive) possibilities have emerged: (1) inflammatory and fibrogenic responses may be triggered by tubular cells reacting to abnormal quantities and/or composition of filtered proteins, and (2) a tubulointerstitial response may be stimulated by a proteinuric glomerular ultrafiltrate that is misdirected to periglomerular and peritubular spaces.

The first hypothesis, summarized in Fig. 57.11, posits that receptors on the apical membrane of proximal tubular cells interact with luminal urinary proteins, triggering responses that lead to basolateral secretion of proinflammatory or fibrosis-promoting factors into the interstitial space.[87] Also plausible are similar effects due to paracellular leakage between tubular epithelial cells directly into interstitial spaces, and the involvement of distal nephron segments, especially if they are distended by obstructing proteinaceous casts. Supporting evidence derives from the observation that animals with "overload" proteinuria develop acute and chronic TIN, and from findings that cultured tubular cells exposed to high concentrations of albumin in particular respond by activating the NF-κB, ERK1/2, and STAT signaling pathways, which stimulate production of a variety of inflammatory mediators (MCP-1, RANTES, IL-6, TNF, fractalkine, complement proteins) and fibrogenic molecules (TGF-β, endothelin-1, extracellular matrix proteins) and activate the RAS.[88]

The identity of the detrimental urinary protein(s) is unclear. Although many of the cell culture studies have used albumin, it is argued that because patients with highly "selective" proteinuria, such as those with steroid-responsive

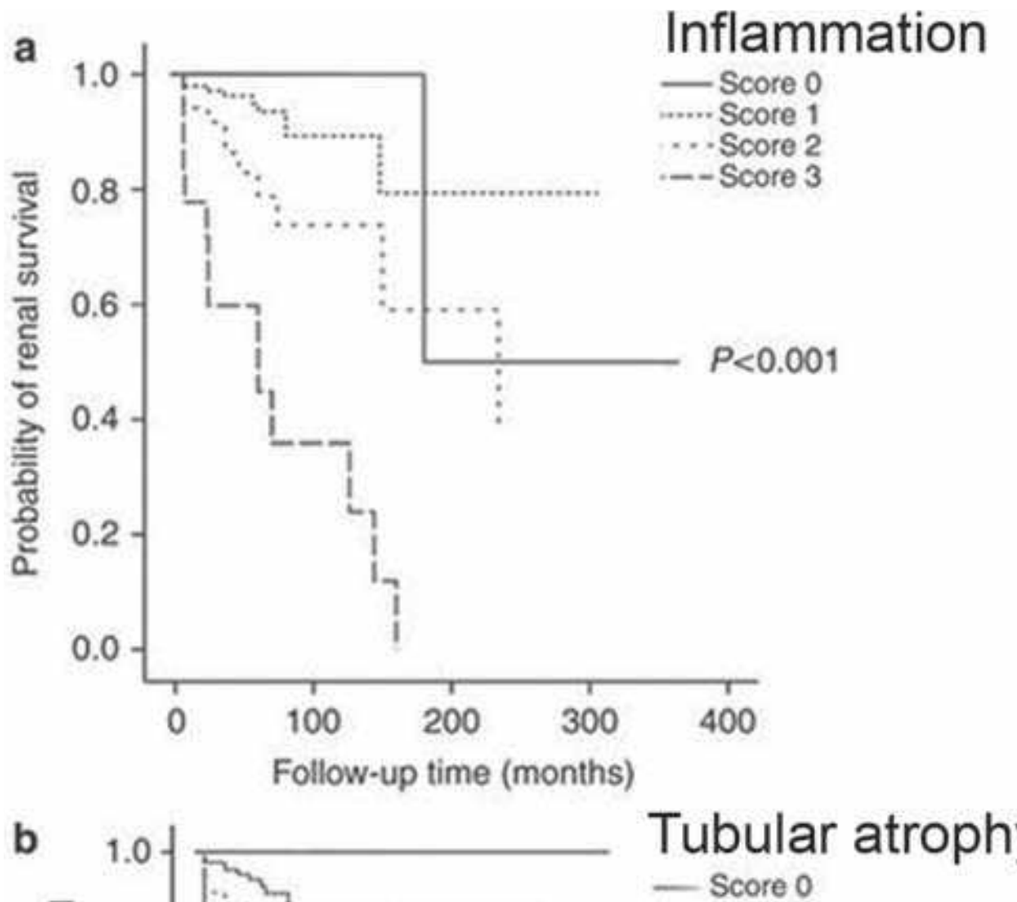

FIGURE 57.9 Severity of chronic tubulointerstitial nephritis predicts renal outcome in primary glomerular diseases. As a representation of several studies, which show similar findings, in this Chinese study of 313 patients with lupus nephritis, the severity of the tubulointerstitial inflammation (a), tubular atrophy (b), and fibrosis (c), graded on a scale from 0 to 3+ based on the area involved, were significant predictors of kidney survival rates. (From Yu F, Wu LH, Tan Y, et al. Tubulointerstitial lesions of patients with lupus nephritis classified by the 2003 International Society of Nephrology and Renal Pathology Society system. *Kidney Int*. 2010;77:820, with permission.)

nephrotic syndrome, do not develop TIN, native albumin is probably not the culprit. However, albumin is known to be a carrier for numerous molecules, making it possible for modified albumin (or its conjugates) to trigger these responses. Alternatively, other urinary proteins may be the primary stimulus—inflammatory cytokines generated within damaged glomeruli, iron-binding proteins such as transferrin and apoferritin, and high molecular weight proteins not normally present in the glomerular ultrafiltrate such as immunoglobulin have been suggested as candidates.

Assuming that the damaging effects of proteinuria are the consequence of a receptor-dependent process, the low affinity albumin receptor megalin has been considered a lead candidate. Expressed on the apical brush border membrane, this scavenger receptor and member of the LDL receptor family internalizes multiple protein ligands by endocytosis and may initiate intracellular signaling after phosphorylation of its cytoplasmic tail. Megalin may engage the nonsignaling receptors cubilin and amnion less in this pathway. Cubilin is also implicated by the finding that a polymorphic variant of the cubilin gene is associated with albuminuria in a large European ancestry cohort.[89] However, a central role for megalin has been challenged by the finding that megalin-deficient mice are not protected from TIN associated with anti-GBM nephritis.[90] The apical membrane of proximal tubules is a rich source of several other receptors that could be activated by abnormal or excessive urinary proteins. Candidates that have already been considered are CD36, complement receptors, Toll-like receptors, chemokine receptors, and growth factor receptors. As genomewide association studies (GWAS), urinary biomarker studies, and genomic and proteomic kidney tissue studies identify new CKD-associated molecules, it is likely that new proteinuria–tubular cell–TIN pathways will emerge. A study by Reich et al.[91] identified 11 genes induced by exposing human tubular cells to albumin, which were also upregulated in the tubulointerstitial compartment of kidney biopsies from human IgA nephropathy patients and correlated with the severity of proteinuria. GWAS studies have identified uromodulin as a pathway of great interest.

To link these early tubular responses to chronic TIN and progressive kidney disease, several plausible pathways have been proposed.[88]

1. Basolateral secretion of proinflammatory mediators may trigger the recruitment and activation of the interstitial fibroblasts that synthesize interstitial collagens and a variety of other extracellular matrix proteins leading to fibrosis, either directly or indirectly as a consequence of inflammatory cell recruitment (Fig. 57.11).
2. Tubular cells may synthesize collagen proteins that directly contribute to the expanding pool of fibrotic interstitial matrix proteins.
3. Tubular cell death, a recognized consequence of interstitial fibrosis, may occur as a consequence of severe proteinuria. Evidence includes a study reporting Fas pathway activation leading to tubular cell apoptosis

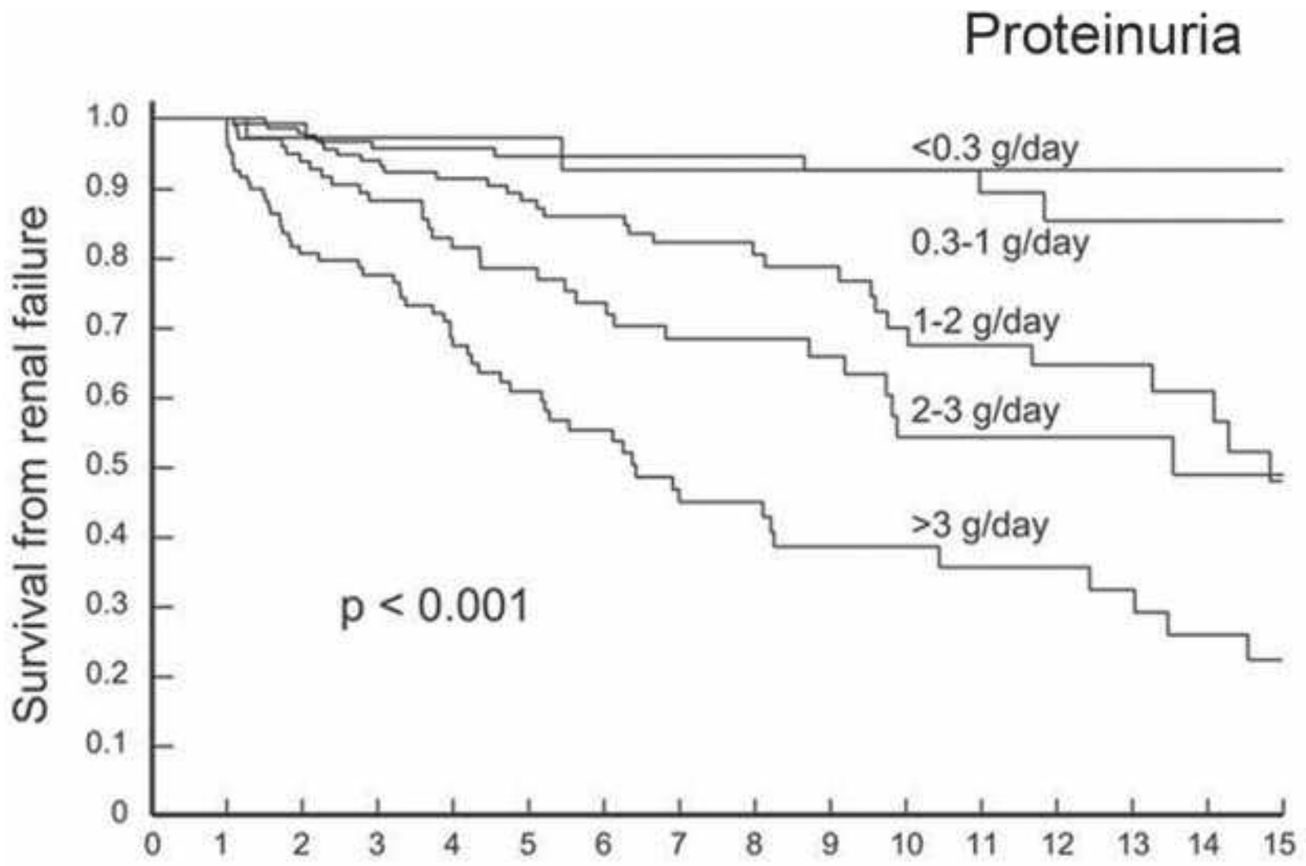

FIGURE 57.10 Proteinuria severity predicts outcomes in chronic kidney disease. An observation that has been made for virtually all chronic glomerular diseases, this representative study of 542 patients with biopsy-proven IgA nephropathy shows that time-averaged 24-hour urinary protein levels predict renal survival rates. Although this association does not establish causality, data from several experimental studies suggest that high levels of proteinuria can trigger tubular injury and the release of several inflammatory mediators. (Data from Reich HN, Troyanov S, Scholey JW, et al. Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol.* 2007;18:3177, with permission.)

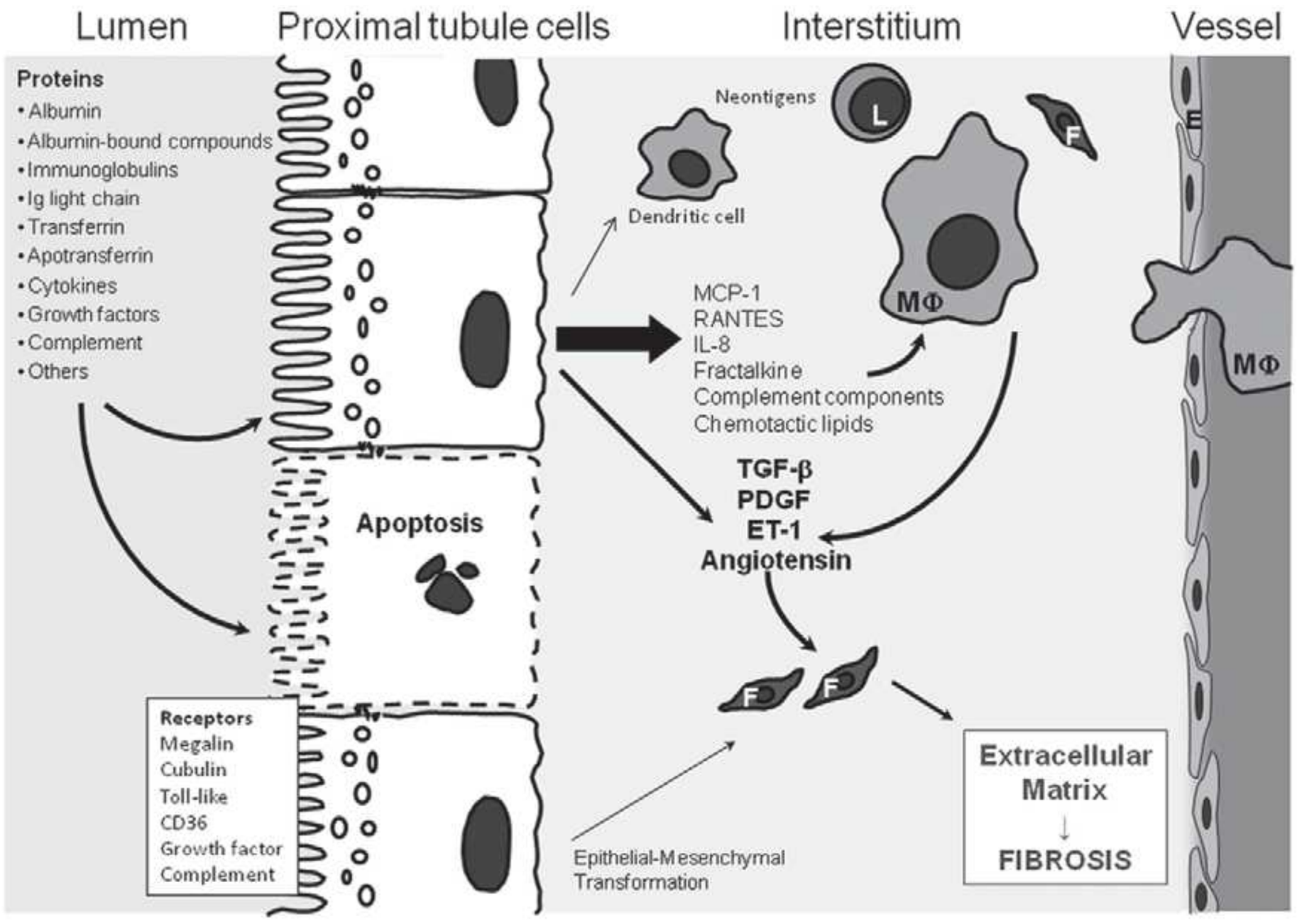

FIGURE 57.11 Schematic summary of the proposed mechanisms of proteinuria-associated tubulointerstitial injury. On the luminal side, a variety of proteins in the glomerular ultrafiltrate may interact with apical receptors on proximal tubular cells. Although megalin has been the receptor of greatest interest, others are likely to be involved. These interactions may trigger the synthesis and release of a variety of proinflammatory and profibrotic molecules across the basolateral membrane, leading to interstitial inflammation and fibrosis. In vitro studies have also reported tubular cell apoptosis and epithelial-mesenchymal transition. A more challenging mechanism to confirm, MCH class II receptors can be upregulated on tubular cells, preparing them to serve as antigen-presenting cells to activate immunologic responses. An important question is the identity of proteinuria-associated neoantigen(s) that might activate such a cascade. (From Zandi-Nejad K, Eddy AA, Glassock RJ, et al. Why is proteinuria an ominous biomarker of progressive kidney disease? *Kidney Int.* 2004;66:S76, with permission.)

following exposure to high albumin concentrations.[92] Oxidant stress triggered by proteinuria may participate in tubular cell death.

4. Following receptor-mediated uptake, urinary proteins are delivered to lysosomes to be recycled as amino acids.[93] It has been proposed that excessive demands on this system may lead to lysosomal rupture and release of cytotoxic contents into the tubular cell cytoplasm, with damaging consequences such as autolysis or autophagy.
5. Proteinuria may trigger the process of epithelial-to-mesenchymal transdifferentiation (EMT), which has been proposed as a mechanism by which tubular cells ultimately become collagen-producing interstitial myofibroblasts after their tight connections with adjacent tubular cells are disassembled and they migrate into the interstitium through breaks in tubular basement membranes.[94]
6. Urinary proteins may be a source of antigenic peptides that are processed by renal dendritic cells to initiate T-cell mediated injury.[95]

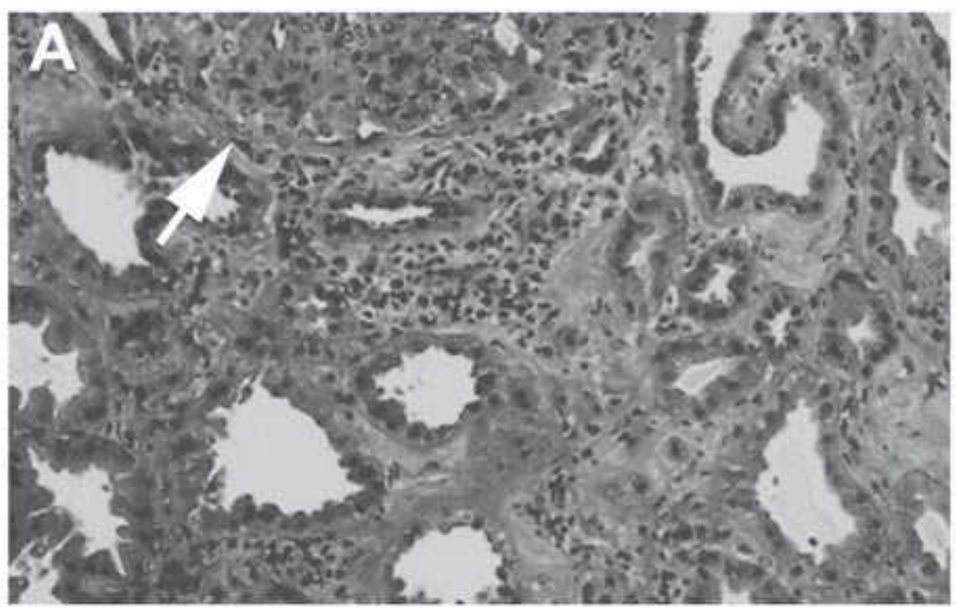

FIGURE 57.12 The misdirected filtration theory of proteinuria-associated chronic tubulointerstitial nephritis (TIN). This paradigm is based on the view that the triggering event is a disruption of the integrity of Bowman's capsule by encroachment of a damaged glomerular tuft (arrow) **(A)**. This change allows some of the glomerular ultrafiltrate to be redirected from the proximal tubule directly into the periglomerular interstitial space. It may also leak out of glomerulotubular junctions at the urinary pole and travel along the outer aspect of tubules. The presence of the ultrafiltrate in these unusual sites triggers chronic TIN. Support for this mechanism is based on the tracer studies that Kriz et al. performed in nephrotic rats. Serial sections of the same nephron illustrate the blue ferritin tracer **(B)** and trichrome-positive fibrosis in the peritubular interstitium **(C)** in an identical distribution pattern. (From Kriz W, Hartmann I, Hosser H, et al. Tracer studies in the rat demonstrate misdirected filtration and peritubular filtrate spreading in nephrons with segmental glomerulosclerosis. *J Am Soc Nephrol.* 2001;12:496, with permission.)

The theory of "misdirected filtration," championed by Kriz and colleagues based on careful histomorphologic studies that were enhanced by tracing the fate of exogenous markers in rat proteinuria models, suggest an alternative mechanistic link between proteinuria and interstitial fibrosis.[96] The theory is based on the premise that proteins derived from the glomerular ultrafiltrate are not delivered to the interstitial space from either tubular lumina or interstitial capillaries. Rather, this theory proposes that damaged podocytes, which are the primary cause of proteinuria, can adhere to Bowman's capsule to create a conduit between parietal epithelial cells through which the glomerular ultrafiltrate leaks into the periglomerular interstitial space (Fig. 57.12). The process then extends to involve the tubules, beginning at the urinary pole of glomeruli, where the ultrafiltrate next appears within the subepithelial peritubular space surrounding proximal tubules. This misdirected glomerular ultrafiltrate is thought to elicit a fibroblast response within the interstitium and cause progressive tubular cell degeneration, beginning with the proximal tubule and extending distally. Ultimately, the affected nephron degenerates, leaving behind a fibrotic interstitial space. Alternatively, the process may obstruct proximal tubules, leading to downstream tubular atrophy and formation of "atubular" glomeruli.

SEQUELAE TO ACUTE TUBULOINTERSTITIAL DISEASES

Acute Kidney Injury

Several recently published studies in adult patients with acute kidney injury (AKI) presumed to be caused by tubular necrosis have reported that surviving patients are at a significantly increased risk of developing advanced CKD. This is true whether patients had normal baseline kidney function or preexisting CKD. A recent meta-analysis of 13 cohort studies reported a pooled adjusted hazard rate of 8.8 for CKD and 3.1 for ESRD compared to a matched patient cohort without AKI (Fig. 57.13).[97] Significant predictors of CKD

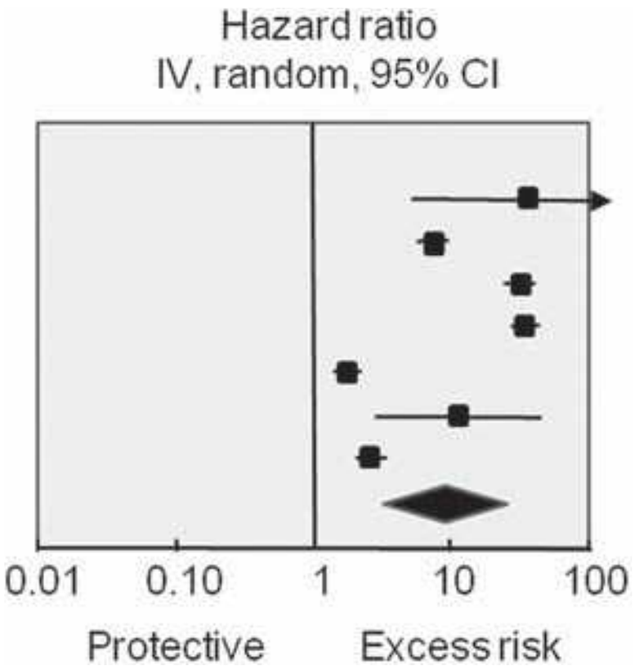

FIGURE 57.13 Severe acute kidney injury (AKI) is a risk factor for chronic tubulointerstitial nephritis. In a review of 13 published cohort studies (>3,000 patients), the pooled adjusted hazard ratio (HR) for chronic kidney disease after AKI was 8.8. *IV*, inverse variance weighted averages of logarithmic HRs. (From Coca SG, Singanamala S, Parikh CR, et al. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int*. 2012;81(5):442–448, with permission.)

risk included the severity of the acute injury (based on need for dialysis or not, mean serum creatinine level), diabetes, and hypoalbuminemia.[98,99] There are few data evaluating renal outcomes in children who survived severe AKI, although relevant studies are now in progress. The best pediatric data come from long-term follow-up of children with diarrhea-positive hemolytic uremic syndrome. A meta-analysis of 49 studies reported combined renal sequelae (CKD, ESRD, proteinuria, hypertension) in 25% of survivors.[100]

Although renal biopsies are rarely performed in this patient group to evaluate findings and potential pathogenetic mechanisms, informative animal models of ischemia-reperfusion injury have been extensively investigated and provide insights that are likely relevant to humans.[101] These data support the view that chronic injury is a consequence of AKI. The acute phase of ischemia-reperfusion injury is characterized by microvascular changes and tubular cell production of a variety of proinflammatory and chemotactic cytokines that recruit lymphohemopoietic cells to the renal interstitium. It is now recognized that specific subsets of interstitial cells (especially neutrophils, macrophages, and B cells) promote kidney injury whereas others (T-regulatory cells, alternatively actuated macrophages) facilitate kidney repair. The studies in animal models have shown that the interstitial inflammation persists for several weeks, even after a single 60-minute ischemic event, and is associated with areas of interstitial capillary rarefaction, tubular atrophy, interstitial fibrosis, and irreversible nephron loss.[102] The specific cellular and molecular mechanisms that are involved in the transition of AKI to chronic TIN are under active investigation. A transformational switch of the interstitial macrophages to an alternatively activated ("M2") phenotype is likely involved.[20] Although M2 cells characterize tissue repair responses, part of the repair response is fibrosis, and when it is "maladaptive," irreversible parenchymal injury ensues. When the rate of replacement of damaged tubular cells by proliferation of surviving tubular cells fails to keep pace with tubular cell death, tubular recovery is incomplete and sets the stage for CKD. To some extent this reparative response could be considered an antecedent event that accelerates normal kidney aging. Glomerular filtration rates decline slowly and progressively with advancing age. It has been reported that the "normal" mean glomerular filtration rates is 60 mL/min/1.73 m^2 in octogenarians (Fig. 57.14).[103] Histopathologically, this decline in renal function is associated with progressive tubular loss and interstitial fibrosis. It is likely that residual damage after severe AKI compromises renal parenchymal reserve, setting that stage for faster aging-associated functional decline.

Acute Interstitial Nephritis

Primary acute interstitial nephritis (see Chapter 35) has multiple etiologies and outcomes. Many of the acute pathogenic immunologic reactions are triggered by exposure to offending

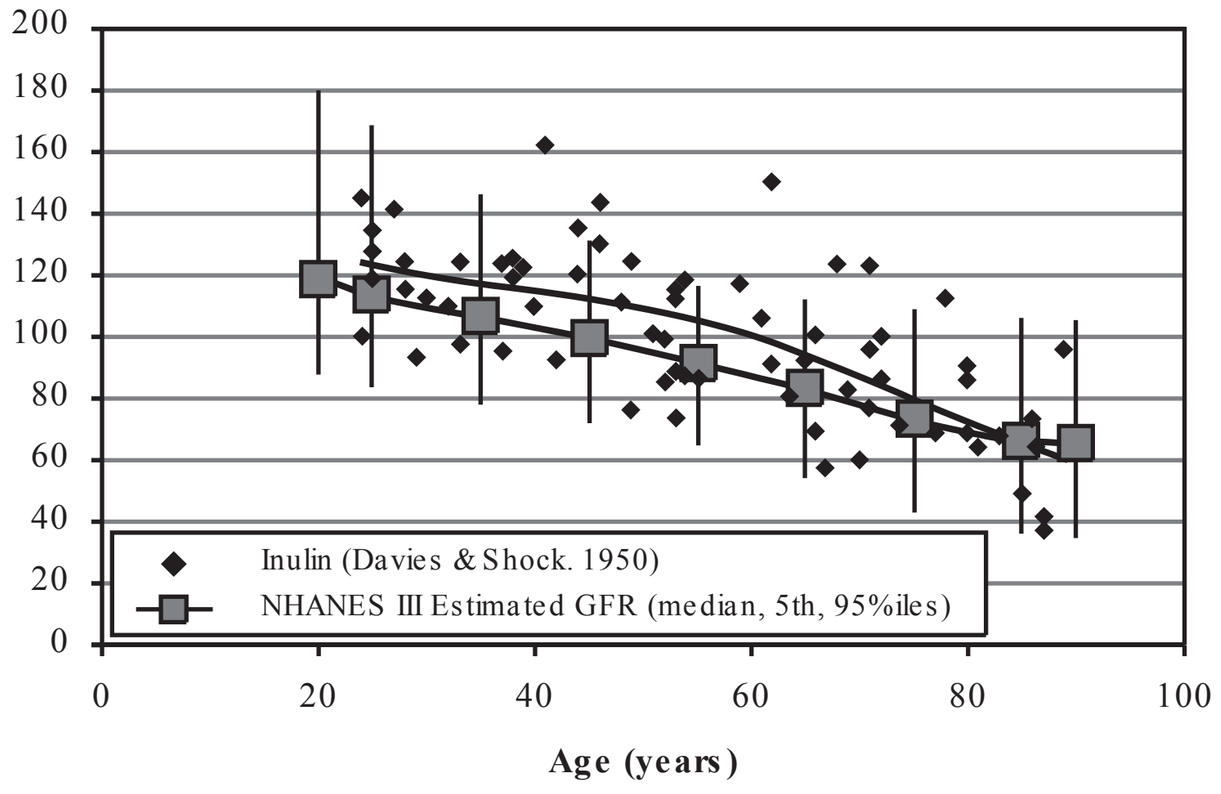

FIGURE 57.14 Decline in estimated glomerular filtration rate with age. Data are derived from the U.S. population using National Health and Nutrition Examination Survey (NHANES) III data and inulin clearances among 70 healthy men. (Abstracted from Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest*. 1950;29:496.) Aging studies in animal models have established aging-related glomerulosclerosis and chronic tubulointerstitial nephritis as the histopathologic correlate of this progressive functional loss. (Figure from Part 4. Definition and classification of stages of chronic kidney disease. *Am J Kidney Dis*. 2002;39:S46, with permission.)

drugs (~70%) or microorganisms (~15%) and subside once the offending agent is identified and eliminated. With normalization of the serum creatinine level and urine sediment, it has traditionally been thought that tubulointerstitial architecture had been restored to normal. Although there are few long-term follow-up data, a study by Rossert et al.[104] reported evidence of renal functional impairment in 40% of patients after drug-induced interstitial nephritis. Additional studies are needed to determine whether patients with reversible kidney injury due to acute interstitial nephritis are predisposed to future CKD and if early steroid therapy can significantly reduce this risk, as suggested by the study of Gonzalez et al.[105]

Bacterial Infection-Associated Chronic TIN

TIN associated with scarlet fever was the first type of interstitial nephritis recognized as a unique clinical entity—dating back to 1860, with Councilman's classic histologic description following in 1898. The incidence of renal parenchymal invasion by bacteria greatly declined after antibodies became available. Indeed, since the 1960s, drugs have become the primary cause of acute TIN. Two mechanisms of bacteria-associated TIN are recognized. In the first, the renal parenchyma is directly invaded and the infected region is characterized by a neutrophil-rich interstitial infiltrate (pyelonephritis).[106] A delay in treatment may lead to abscess formation and/or interstitial scarring. The second pattern is considered an immune-mediated response, characterized by an interstitial infiltrate of mononuclear cells and absence of bacteria within the renal parenchyma.

The association between pyelonephritis and chronic TIN has been most extensively investigated in young children with primary vesicoureteral reflux (VUR). In children less than 5 years of age, serial imaging studies have established a relationship between VUR and renal parenchymal deficits and between febrile urinary tract infection (UTI) and renal scarring. For many years, it was assumed that pyelonephritis caused chronic TIN and that medical interventions designed to reduce UTIs would reduce the risk of new scar formation. This therapeutic approach has been validated for girls less than 5 years of age with high-grade reflux (III-V), but current evidence strongly supports the view that most of the renal parenchymal defects detected in patients with primary VUR predate infections and represent congenital lesions of hypodysplasia (primary renal scarring).[107] Now, with the frequent use of antenatal ultrasound, recent prospective clinical studies have reported low rates of new scar formation after febrile UTIs. In addition, the high prevalence (~50%) of renal parenchymal deficits detected in children with febrile UTIs in the absence of VUR and the presence of renal parenchymal deficits associated with VUR in the absence of infection provide further supporting evidence that many of the renal parenchymal deficits are congenital. This would also explain why the incidence of ESRD due to "reflex nephropathy" has not changed over the past 40 years despite earlier diagnosis and efforts to reduce the frequency of urinary tract infections. It has also become clear that genetic factors play a major role in the risk of VUR even though specific genes have not yet been identified. It is estimated that 30% of the siblings of a child with VUR and 60% of the offspring of parents with VUR also have VUR.[108]

Mycobacterium tuberculosis is an important infectious microorganism that can directly invade the renal parenchyma and cause severe chronic tubulointerstitial destruction and fibrosis when the diagnosis and treatment are delayed. Both caseating and noncaseating interstitial granulomas should always raise suspicion of renal tuberculosis.[109] Despite the fact that the kidney is the extrapulmonary organ most commonly involved in tuberculosis (15% to 20%), there are few data on the role of tuberculosis as a cause of chronic TIN and ESRD, although this outcome has been reported. For example, in a report of 25 patients with chronic granulomatous TIN due to tuberculosis (17 confirmed by biopsy), 20% developed ESRD within 6 months.[110] Although much less common, immune-mediated TIN without direct renal parenchymal invasion by mycobacteria is a well-documented entity.

Several bacterial infections have been reported to cause acute TIN, presumably as a consequence of an immunologic response to a systemic infection. There are few data available on the risk of progression to chronic TIN and CKD, even though recent follow-up data for other causes of AKI suggest that these patients should also be monitored long-term for evidence of CKD. The most commonly implicated microorganisms are Escherichia coli, Enterococcus, Leptospirosis, Mycobacteria, Actinobacteria, Legionella, Streptococci, Campylobacter, Brucella, Staphylococci, Corynebacterium diphtheria, Yersinia, Treponema pallidum, and Mycoplasma.

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis is a unique and uncommon infection-mediated cause of CKD that affects patients of all ages and is typically unilateral.[111] Histopathologically, the disease is chronic TIN with the hallmark feature of numerous interstitial lipid-laden xanthomatous macrophages with variable degrees of chronic tubular damage and interstitial fibrosis (Fig. 57.15). Because of the insidious nature of the clinical presentation, with nonspecific symptoms such as fever, abdominal or flank pain, and weight loss, it is not uncommon for the normal renal parenchyma to be severely damaged and the kidney nonfunctional by the time the diagnosis is made. These changes are often associated with hydronephrosis, renal stones, and an enlarged kidney. Nephrectomy is the usual treatment for patients with advanced disease. The most commonly implicated bacteria are E. coli, Proteus mirabilis, Pseudomonas, Streptococcus faecalis, and Klebsiella. The urine culture is negative ~25% of the time, despite evidence of renal parenchymal infection. The primary pathogenesis of the abnormal immune response that leads to this unusual chronic inflammatory response remains unknown.

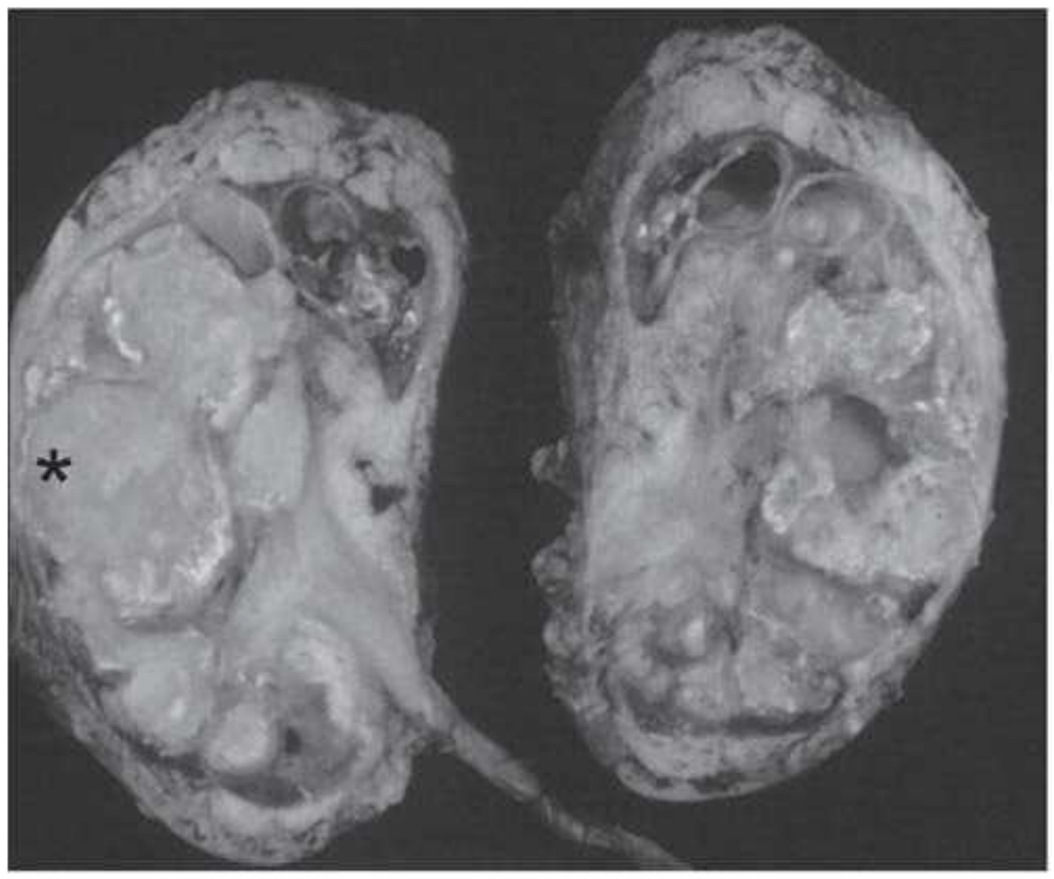

FIGURE 57.15 Xanthogranulomatous pyelonephritis is a bacteria-associated cause of chronic tubulointerstitial nephritis. The nephrectomy specimen shows extensive destruction of the renal parenchyma by cystic cavities, stones, and xanthogranulomas (*). Histopathology shows a plasma cell infiltrate to the right and a dense interstitial foam cell infiltrate which has destroyed the surrounding parenchyma. (From Levy M, Baumal R, Eddy AA, et al. Xanthogranulomatous pyelonephritis in children. Etiology, pathogenesis, clinical and radiologic features and management. *Clin Pediatr*. 1994;33:360, with permission.)

Viral Infections

The recognition of viral infections as a potential cause of chronic TIN is likely to occur with increasing frequency as the use of molecular diagnostics continues to expand. In 1999, Becker et al.[112] provided evidence for the presence of the Epstein-Barr virus genome in the proximal tubules in kidney biopsy specimens from patients with idiopathic chronic TIN and suggested that EBV was involved in disease pathogenesis.

BK polyomavirus is recognized as an important cause of chronic TIN in immunologically compromised individuals, especially renal transplant recipients.[113] Most normal adults have had a prior asymptomatic BK polyomavirus infection and harbor the virus in a latent form in the genitourinary epithelium. Plasma polymerase chain reaction (PCR) surveillance studies suggest that the virus is reactivated in 27% of renal transplant recipients. Without appropriate reduction in immunosuppressive therapy, the virus may invade renal tubular epithelial cells (especially in the medulla) with cytopathic effects that lead to interstitial inflammation and subsequent fibrosis, which is estimated to occur in 5% of renal transplant recipients. In patients with BK virus-associated nephropathy, viral inclusions may be present in tubular epithelia and the presence of the BK virus within nuclei can be confirmed by polyomavirus-specific immunostaining (Fig. 57.16). If renal dysfunction and BK viremia do not improve after a reduction in immunosuppression therapy, other efforts to reduce the viral load are often considered, using intravenous IgG, ciprofloxacin, leflunomide and/or cidofovir, but the efficacy of this therapy remains unclear.[114] Recipients of nonrenal solid organ transplants are also at risk for BK nephropathy, although the incidence is much lower than in kidney transplant recipients. The nephropathy has also been reported in hematopoietic stem cell transplant recipients.[115]

Adenovirus infections are increasingly recognized in kidney transplant recipients, often causing hemorrhagic cystitis.[116] However, granulomatous TIN has also been reported among kidney transplant recipients using in situ hybridization to identify adenoviral DNA within tubular epithelial cells.

Another viral infection that has been shown to infect renal epithelia and trigger chronic interstitial inflammation is HIV-1.[117] Although most patients with HIV-associated nephropathy have significant glomerular pathologic changes, coexistent chronic TIN is more severe than would be anticipated on the basis of the glomerular pathology alone and may be associated with microcystic and/or tubular changes. Although it is often impossible to exclude drugs as a factor contributing to the pathogenesis of TIN in HIV-infected patients, there is experimental evidence that the HIV-1 Vpr gene induces tubular cell apoptosis, suggesting one relevant pathogenetic mechanism of HIV-associated chronic TIN.[118] Similar findings have been reported in patients with hepatitis C virus (HCV)-associated nephropathy. In particular, when patients with membranous nephropathy were matched for the stage of glomerular disease, TIN was more severe in the HVC-positive group and HCV peptide and/or RNA was identified in both tubular and interstitial cells.[119] Several other viruses have also been associated with TIN, including cytomegalovirus, Hantaan, hepatitis B, rubeola, herpes simplex, and mumps viruses. Among this latter group, hemorrhagic fever with renal syndrome (HFRS) caused by Hantavirus is associated with a higher risk of CKD.[120] Humans acquire this infection from infected rodents, primarily in Asia and Europe. A renal biopsy performed during the acute illness shows acute TIN together with widespread tubular necrosis. Patients may also develop hematuria and proteinuria due to glomerular pathology.

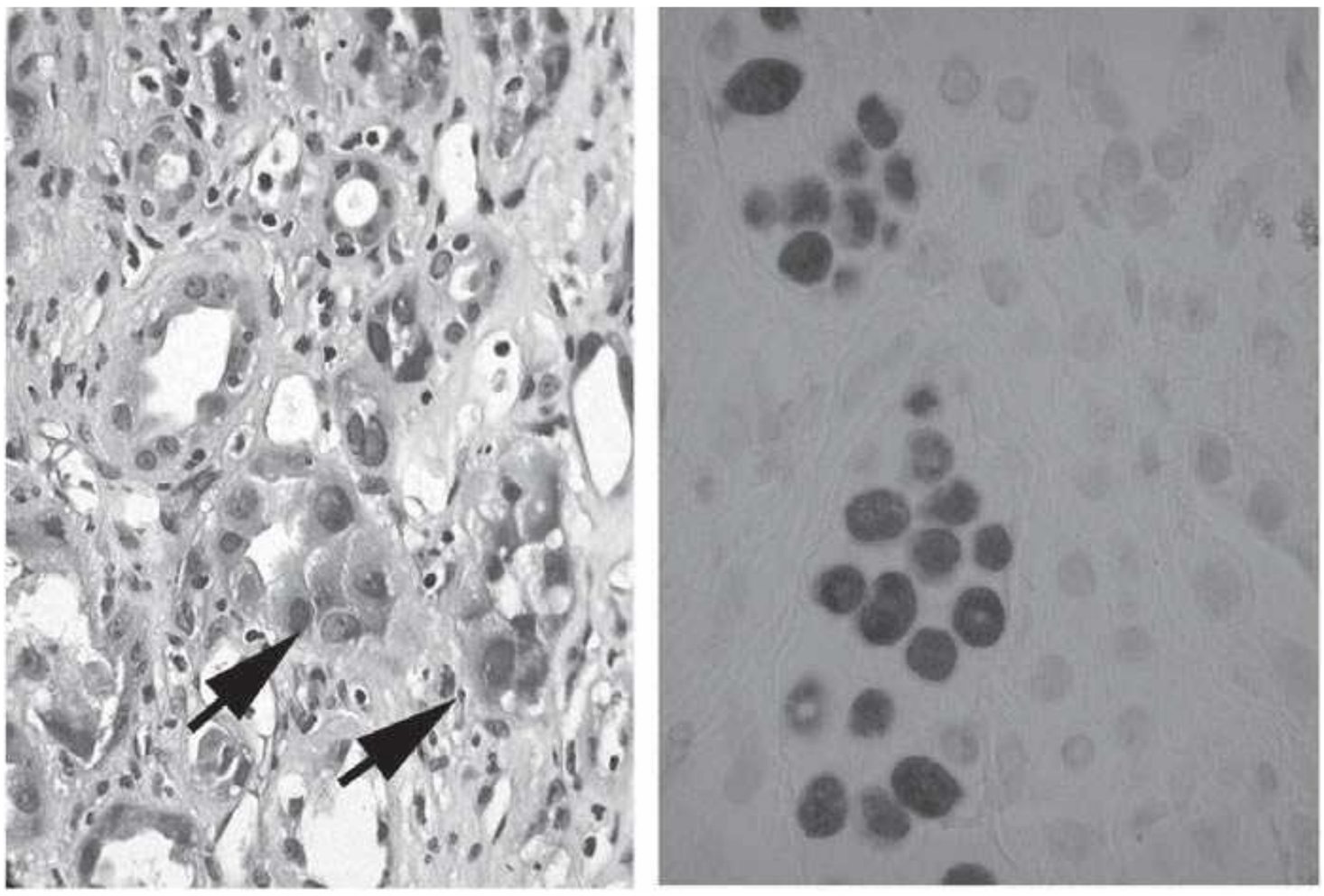

FIGURE 57.16 BK virus nephropathy is a cause of chronic tubulointerstitial nephritis in renal allograft recipients. The presence of intranuclear viral inclusions within tubular epithelial cells (highlighted by *arrows* in left photomicrograph), often more evident in the medulla, should raise suspicion of this diagnosis, which can be confirmed by SV40 T antigen immunostaining (nuclear reaction product in the right photomicrograph). (Photomicrographs were provided by Dr. Laura Finn, University of Washington and Seattle Children's Hospital.)

Other Infections Associated with Chronic TIN

Basically any microbial pathogen known to cause acute TIN has the potential to progress to chronic disease. This list includes certain fungi (histoplasmosis, Candida, and Cryptococcus) and parasites (toxoplasmosis, leishmaniasis, and Rickettsia).

Drugs

Drugs may cause chronic TIN through a variety of mechanisms that can be subdivided into groups.

1. Idiosyncratic immune-mediated TIN. This mechanism is thought to cause most drug-induced acute TIN. There is increasing evidence that chronic TIN may ensue after severe acute injury. Most patients with drug-induced TIN do not present clinically with the classical triad of fever, rash, and eosinophilia that was originally associated with methicillin-induced interstitial nephritis. There are likely many patients who remain asymptomatic without a diagnosis of acute TIN ever being made. Drug exposure then continues for the recommended duration and recovery from TIN may be incomplete, although this concern is impossible to validate. Follow-up studies of patients with an established diagnosis of drug-induced acute TIN have reported that early drug cessation is important for full renal recovery. Both acute and chronic changes may be evident in those with biopsy-confirmed drug-induced TIN. In a case series reported by Schwartz et al.,[121] 31% had permanent loss of renal function. Further studies are needed to determine whether corticosteroid therapy reduces the risk of CKD for those presenting with severe AKI.[105] The spectrum of drugs most likely to cause acute TIN is changing. In particular, protein pump inhibitors have emerged as a leading cause, as shown in a study of biopsy-confirmed cases of TIN between 1995 and 1999, which concluded that 35% were associated with protein pump inhibitor drugs.[122] Given the widespread use of these drugs, often over prolonged time periods without routine kidney function surveillance, there is reason for concern about the risk of unrecognized chronic TIN.
2. Tubular cell nephrotoxicity. Several drugs or their metabolites are known to damage renal tubular cells, often in a dose-dependent fashion. The specific mechanisms are multiple, but they often share in common the generation of oxidant stress and tubular cell death. Depending on the primary cellular target, specific patterns of tubular cell dysfunction may be observed and may be the only manifestation of nephrotoxicity. However, a reduced GFR is not uncommon as a consequence of acute tubular cell death by apoptosis or necrosis and the associated interstitial inflammatory response. Beyond direct tubular cell cytotoxicity, some drugs trigger chemokine and cytokine release that initiates a peritubular inflammatory response that may progress to fibrosis.
3. Tubulointerstitial hypoxia. The primary effect of some nephrotoxins is thought to be mediated by alterations in tubular cell oxygenation due to effects on the vasculature.
4. Crystalline nephropathy. Poorly soluble drugs or their metabolites that are primarily excreted in the urine may precipitate in tubular lumina and cause injury by obstruction, leading to secondary effects on the tubules and interstitial spaces. Such a mechanism has been reported in patients receiving high doses of methotrexate and with antiretroviral drugs.

The classes of drugs most commonly associated with both acute and chronic TIN are summarized in the following text.

Chemotherapeutic Agents

Cisplatinum is the classic chemotherapeutic nephrotoxin.[123] A hydrolyzed intracellular metabolite appears to be the primary mediator of cytotoxicity, which only affects the S3 segment of proximal tubules. Renal magnesium wasting is an early manifestation in more than half of the patients and may be accompanied by salt wasting and features of the renal Fanconi syndrome. Studies in animal models have identified vasoconstriction and interstitial inflammatory responses (neutrophils and T cells in particular) as important pathogenetic features. Long-term follow-up studies of cancer survivors suggest that the nephrotoxic injury persists after treatment is finished.[124]

Ifosfamide, a synthetic analogue of cyclophosphamide, is metabolized to chloroacetaldehyde, which is directly toxic to proximal tubular cells. Energy depletion via mitochondrial damage is thought to be an important pathogenetic mechanism. Disease severity is related to the dose and duration of therapy. Most patients develop tubular transport dysfunction that leads to hypophosphatemia, hypokalemia, metabolic acidosis, and polyuria in addition to reduced GFRs. Limited histologic data highlight tubular cell damage. Long-term follow-up studies have reported variable outcomes depending on the severity of the acute nephrotoxicity. The degree of the tubular dysfunction often improves, but impaired glomerular filtration often persists. Ten-year follow-up studies report a GFR $<$90 mL per minute in 21% and $<$60 mL per minute in 13% of patients.[125]

The nitrosoureas are a class of alkylating agents that have been associated with an insidious form of chronic TIN that develops slowly over 3 to 5 years in patients on long-term therapy. Histologically, the lesion is characterized by tubular atrophy and interstitial fibrosis.

Antimicrobials

Antibiotics are frequently implicated as causes of drug-induced and immunologically mediated TIN, the most common being the beta-lactams, cephalosporins, and sulfonamides. In addition, certain antimicrobials are known to be tubular cell nephrotoxins, especially aminoglycosides and amphotericin B. Gentamicin may cause AKI in as many as 10% to 20% of treated patients, despite drug level monitoring.[126] This high nephrotoxicity rate relates to drug uptake by megalin-mediated endocytosis in the proximal tubules, leading to intracellular levels that may be considerably higher than blood levels. The primary mechanism of injury is tubular cell death due to apoptosis and necrosis. There is histologic evidence from both humans and animal models that interstitial inflammation commonly occurs and is a mechanism of injury propagation.[127] Emerging evidence suggests that single daily dosing in patients with normal renal function may be therapeutically effective and reduce the risk of nephrotoxicity. Although the injury is thought to be reversible, chronic TIN may develop, especially with prolonged use. Long-term follow-up data are not yet available to address the possibility of gentamicin-induced nephrotoxicity as a CKD risk factor.

Amphotericin B reduces GFR in as many as 80% of treated patients. The newer lysosomal preparations are less nephrotoxic for reasons that are not entirely clear—absence of the deoxycholate moiety may be a partial explanation. Renal injury is targeted to distal nephrons within the medullary rays and the outer medulla. In experimental models, tubular injury is associated with evidence of tubulitis, interstitial inflammation, and fibrosis.[128] In addition to directly damaging tubular cells, amphotericin is thought to insert into tubular cell membranes, where it creates pores that may explain renal electrolyte wasting—potassium, magnesium, and bicarbonate in particular. Amphotericin also has direct vascular effects that induce vasoconstriction and hypoxia. In a retrospective review of 494 adults treated with amphotericin, 28% developed renal insufficiency; it was classified as moderate-to-severe (defined as doubling of baseline serum creatinine to $\geq$2.0 mg per dL) in 12%.[129] In the latter group, 70% had a serum creatinine $\geq$0.5 mg per dL above baseline at the time of discharge or death, illustrating the need for long-term follow-up studies to establish the risk of chronic TIN and CKD.

Antiretroviral medications used in combination (highly active antiretroviral therapy or HAART) have been associated with an overall decline in the incidence of CKD in patients with HIV-1 infection.[130] Nonetheless, several of these drugs are nephrotoxic and occasionally cause severe kidney injury. In a retrospective review of 7,378 patients in France, 4.7% had chronic kidney disease (eGFR $\leq$60 mL/min/1.73 m^2); recent exposures to indinavir, tenofovir, and abacavir were associated with an increased CKD risk.[131] Histopathologically, chronic TIN was most common, although different triggering mechanisms may be involved. Indinavir is a protease inhibitor that is known to cause a unique form of TIN associated with intratubular deposition of indinavir crystals, especially when high doses of the medication are used. Formation of renal stones has also been reported. Other protease inhibitors appear to be less nephrotoxic, although there are case reports of TIN and AKI. Now that lower doses are prescribed, protease inhibitor nephrotoxicity is rarely encountered. The nephrotoxic effects of the nucleotide reverse-transcriptase inhibitors, especially tenofovir, are well-established and most common when used in conjunction with protease inhibitor drugs ($\sim$12% incidence). The proximal tubule, where the drug accumulates via the organic anion transporter 1, is the primary target of injury. Evidence of tubular dysfunction (proteinuria, glycosuria, urinary phosphate washing) often precedes measurable changes in GFR. Ultrastructural changes in tubular mitochondria have been highlighted. Evidence of chronic TIN on biopsy and outcome studies suggests that renal injury does not reverse in a significant number of patients ($\sim$25%) after the drug is discontinued.[132]

Nonsteroidal Anti-inflammatory Drugs

The nonsteroidal anti-inflammatory drugs (NSAIDs) have renal effects that can cause chronic TIN by at least three distinct mechanisms. Through effects on prostaglandin metabolism, NSAIDs may alter renal hemodynamics in vulnerable patient groups. These renal effects are generally reversible, but may lead to acute tubular necrosis and its sequelae. Via an idiosyncratic dose-independent mechanism, the NSAIDs may also cause acute interstitial nephritis, typically without fever or rash, but with eosinophilia reported in 40% of cases. A unique feature of NSAID-induced TIN is its frequent association with nephrotic syndrome due to a minimal change-like disease or, rarely, due to membranous nephropathy. This entity has been reported with virtually all of the nonselective NSAIDs, although most commonly with fenoprofen.[133] Schwarz et al.[121]reported that 56% of patients with biopsy-confirmed NSAID-induced TIN had permanent renal functional impairment after the offending agent was discontinued. The third entity, known as analgesic nephropathy, was an important cause of CKD until the disease was recognized and prevention strategies implemented. This slowly progressive kidney disease, characterized by chronic TIN that is often associated with papillary necrosis (25% to 40%), is caused by prolonged daily consumption of combinations of analgesics, usually in conjunction with centrally acting, dependency-inducing substances such as caffeine, codeine, or barbiturates. The damage is most severe in the medulla, often leading to calcification of the medullary pyramids. CT scans have been diagnostically useful in advanced cases, as the small kidneys often have bumpy renal contours and medullary calcifications (Fig. 57.17). It has been suggested that the primary target is capillary endothelial cells that become sclerosed and that the primary offending agent is phenacetin and its metabolites, although

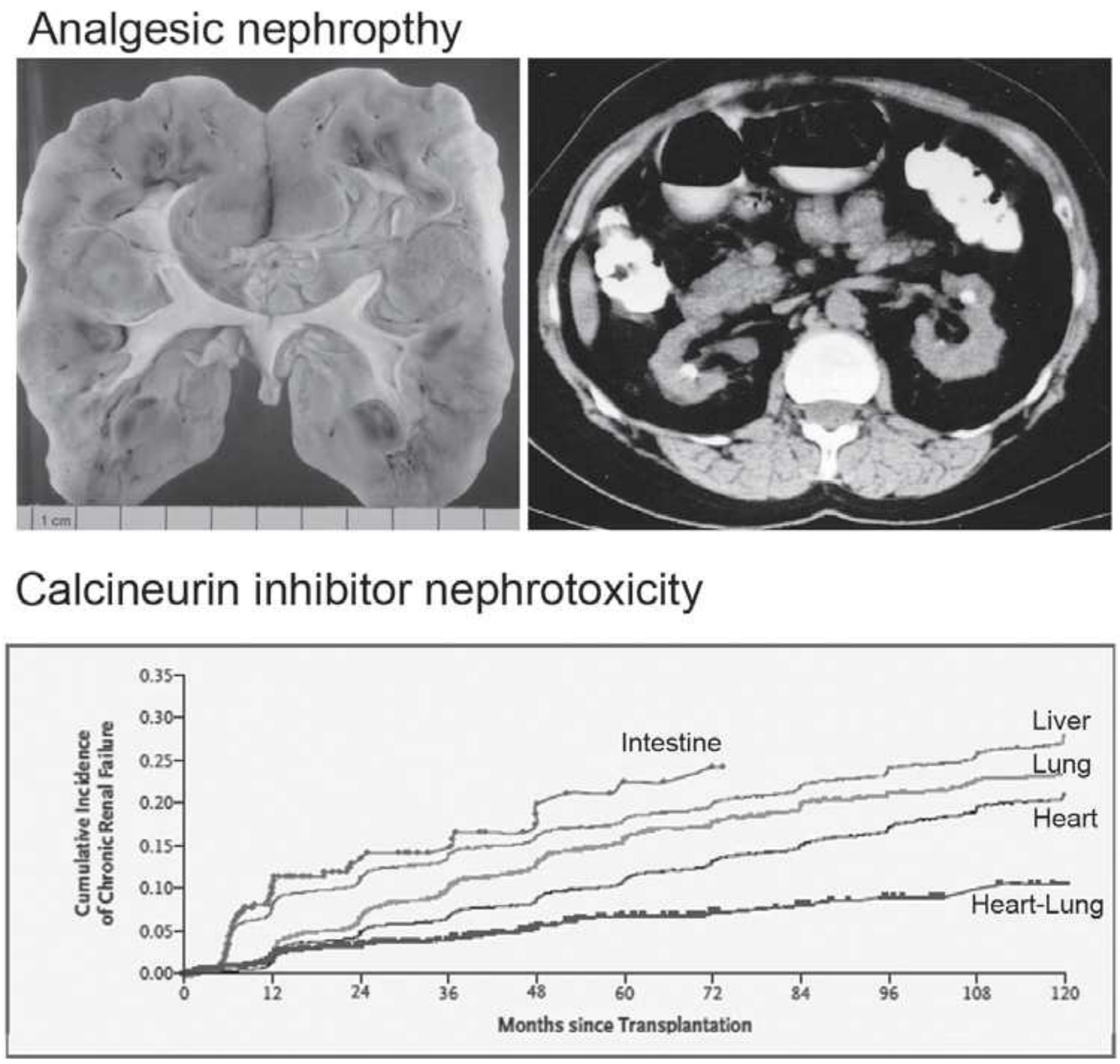

FIGURE 57.17 Drug-induced chronic tubulointerstitial nephritis (TIN). Prolonged ingestion of analgesic combinations may cause analgesic nephropathy. The prototypic disease is characterized by small kidneys with bumpy contours (shown in macroscopic view of an end-stage kidney on the upper left), which is apparent on a computed tomography scan (upper right). (From De Broe ME, Elseviers MM. Over-the-counter analgesic use. *J Am Soc Nephrol.* 2009;20:2103, with permission.) The calcineurin inhibitors have well-recognized dose-related nephrotoxic effects that are characterized by arteriolar vasculopathy and chronic TIN. The high incidence of end-stage renal disease in nonrenal solid organ transplant recipients highlights the potential severity of this nephrotoxicity, even after taking into consideration that multiple factors likely contribute to chronic kidney disease in this complex patient cohort. (From Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med.* 2003;349:931, with permission.)

neither hypothesis has been definitely proven. Once an important cause of ESRD in countries where these combination analgesics products were available, the incidence of analgesic nephropathy has declined since many of the combined analgesics have been discontinued.

Calcineurin Inhibitors

Although cyclosporine and tacrolimus are structurally unrelated, they both inhibit calcineurin as its primary immunosuppressive mechanism, and this effect appears to account for their shared nephrotoxicity.[134,135] Although still a topic of some debate, tacrolimus appears to be slightly less nephrotoxic. The classic histopathologic lesion of chronic calcineurin inhibitor (CNI) nephropathy is chronic TIN that develops in association with a progressive arteriopathy, characterized by nodular hyaline deposits and eventual vascular occlusion. This arteriolar lesion is considered the primary CNI-induced renal lesion, which causes ischemic changes and secondary chronic TIN. However, CNI can directly activate other cellular pathways that likely lead to renal injury, including activation of the RAS, TGF-β production, and tubular cell apoptosis. The risk and severity of chronic TIN are related to drug levels and duration of therapy. Given the overlap between histologic features of CNI nephropathy and other causes of renal allograft dysfunction, including rejection, the undisputed recognition of CNI nephropathy as a distinct entity came from studies of extrarenal transplant recipients and from patients with autoimmune disease. In the early years of CNI therapy, a significant number of nonrenal transplant patients on CNI therapy eventually developed ESRD, highlighting the potent nephrotoxic potential of these drugs (Fig. 57.17).[136] The cornerstone of prevention remains dose optimization to control the primary disease process (such as rejection prevention) with the lowest possible drug doses. It has been reported that kidney CNI drug levels are higher than blood levels, which likely explains the specific vulnerability of this organ to drug toxicity.

The CNI drugs are also known to induce functional renal hemodynamic changes as a result of vasoconstriction of the afferent and efferent arterioles. These effects are considered reversible, but they may lead to significant acute changes in glomerular filtration rates. When this occurs in the face of preexisting renal ischemia and acute tubular necrosis, renal recovery may be delayed, leading to long-term fibrotic TIN sequelae. Calcium channel blockers have been used as a strategy to counteract these vasoconstrictive effects. Evidence of CNI nephrotoxicity may also be suggested by the presence of tubular dysfunction, which leads to hyperkalemia, metabolic acidosis, hyperuricemia, and urinary phosphate and magnesium wasting.

Herbal Medicines

The nephrotoxicity of plant-derived herbal medications is increasingly recognized.[137] The kidney is thought to be particularly vulnerable because it is responsible for excretion of most herbal substances. Chronic TIN has been reported as a complication of long-term use of certain herbal products, the best documented being aristolochic acid (AA). The entity of AA nephropathy was first reported in Belgium in 1991 when women taking AA as part of a weight loss regimen developed CKD. Eventually 300 cases were identified in Belgium, 70% progressing to ESRD within a relatively short time.[138] The histopathology is unique for the intensity of the interstitial fibrotic reaction in the cortex, often with relatively sparse interstitial inflammation. A high proportion of these patients (40% to 45%) also developed urothelial malignancies. AA nephropathy has now been identified worldwide. Despite the fact that AA has been banned in many countries, it is still present in several herbal products. Animal models of AA nephropathy have been developed. Although the disease pathogenesis is not completely understood, arterioles and proximal tubular cells appear to be the primary targets of injury. AA is also considered the leading candidate as the environmental trigger of Balkan endemic nephropathy (BEN). This familial but not inherited type of CKD was first reported in the late 1950s in individuals living in rural communities near branches of the Danube River in Bosnia, Bulgaria, Croatia, Romania, and Serbia.[138,139] By histopathology, BEN is chronic TIN with tubular atrophy and interstitial fibrosis but modest interstitial inflammation that is more severe in the outer cortex. A series of epidemiologic studies support the hypothesis that contamination of the wheat fields in the endemic region by AA is the primary environmental cause of the endemic nephropathy. A unique clinical feature of this group of patients is their high risk of developing urothelial cancer. Many of the identified patients with BEN have developed ESRD.

Lithium

Patients with bipolar disorders who are treated with long-term lithium therapy (10 to 20 years) may develop chronic TIN. The overall incidence is unclear, the onset is insidious, and the rate of disease progression is typically slow, although a small number do develop ESRD.[140] The only predictive factors are duration of therapy and cumulative lithium dose; daily doses and drug levels have not differed between the chronic TIN and unaffected patients. The primary susceptible kidney cell is the principal cell of the collecting duct, where apical sodium channels (ENaC) transport lithium into the cells.[141] Based on this physiology, a hypothetical consideration is the possibility that ENaC inhibition by concomitant use of amiloride might reduce the risk of chronic TIN. Once the disease is well established, discontinuing lithium may not alter the rate of subsequent renal functional decline. Lithium has other effects that may reversibly compromise renal function. Up to 40% of treated patients develop nephrogenic diabetes due to lithium-induced alterations in the expression and trafficking of the vasopressin-regulated water channel aquaporin 2. A significant number of patients (25% to 35%) develop hyperparathyroidism and hypercalcemia that may contribute to chronic TIN.

Heavy Metals

Through a series of unfortunate environmental and occupational exposures, heavy metal-induced kidney disease has been well documented. Because of its ability to reabsorb and store divalent metals, the kidney is typically the primary target organ of toxicity. Lead and cadmium are most commonly implicated as the cause of chronic TIN.[142] Both of these heavy metals primarily target proximal tubular cells, with exposure over many years leading to insidious-onset chronic TIN and renal insufficiency.

Two of the best documented examples of lead nephropathy derive from a cohort of Australian patients with ESRD who shared in common childhood lead poisoning due to exposure to lead-based paints and adults exposed to illegal moonshine whiskey made in lead containers such as radiators. Animal models of lead-induced nephropathy have been developed. Legislation has greatly reduced environmental lead exposure in developed countries by eliminating lead-based paints and lead-containing gasoline, but exposure risk still occurs, especially in poor urban areas, with certain industrial occupations, and in certain unregulated import products. The diagnosis can be inferred by evidence of chronic TIN and an appropriate exposure history. Although the half-life of plasma lead is short (30 days), it extends to 10 to 30 years once lead is deposited in bone. For this reason, plasma levels are not reliable predictors of the total body lead burden. When a definitive diagnosis is desired, the bioavailable pool has been estimated by measuring plasma lead levels after calcium disodium ethylenediaminetetraacetic acid (EDTA) infusion or by bone imaging studies. Although the entity of classic lead nephropathy is now considered rare, recent public health studies have focused on the effects of low-dose lead exposure as an accelerating factor for patients with other causes of CKD.[143] There is ongoing interest in a possible pathologic relationship between lead-related nephrotoxicity, impaired uric acid excretion, and hyperuricemia and its associated complications.

Cadmium occurs naturally in combination with zinc. Following ingestion, it complexes with the low molecular weight protein metallothionein and is efficiently reabsorbed by proximal tubular cells. At this site, metallothionein appears to serve a protective role; when the complex is degraded and cadmium ions are released into the cytosol, tubular cell toxicity ensues. With chronic cadmium exposure, chronic TIN may develop. The urinary cadmium-to-creatinine ratio has been used to estimate the cadmium burden. Numerous household, environmental, and occupational sources of exposure have been identified. One of the best characterized environmental epidemics occurred in Japan as a consequence of soil contamination by an upstream mine, leading to high cadmium levels in rice fields. Affected individuals developed severe bone pain due to associated osteomalacia—"itai-itai-byo" or "ouch-ouch" disease—that was associated with chronic TIN in patients with the most severe disease.

ABNORMALITIES IN MINERAL METABOLISM

Hypercalcemia/Hypercalciuria

In addition to the risk of prerenal azotemia due to afferent arteriolar vasoconstriction, sustained hypercalcemia and/or hypercalciuria can impair renal function due to recurrent nephrolithiasis and nephrocalcinosis. The latter is characterized by calcium phosphate or calcium oxalate deposition in tubular lumina and the renal interstitium in association with parenchymal damage due to chronic TIN. Calcification typically involves the medulla (97%), although cortical nephrocalcinosis has been reported, especially in conjunction with severe cortical diseases, renal allograft rejection, and oxalosis. Hypercalciuria is the primary etiology in most patients. Why some people develop stones and others develop nephrocalcinosis remains unknown—they may occur together. Hypercalcemia may be a predisposing factor, but several renal tubular disorders are associated with nephrocalcinosis in the absence of hypercalcemia. The most common are distal renal tubular acidosis, medullary sponge kidney, premature kidneys, use of loop diuretics, vitamin D therapy, certain inherited tubular disorders, sarcoidosis (less than 50% are hypercalcemic), and conditions associated with increased urinary excretion of phosphate or oxalate. Histopathology may identify calcium deposits within tubular lumina (likely adherent to apical membrane osteopontin or hyaluronan), within tubular epithelial cells, and/or in the interstitium. Interstitial inflammation and fibrosis are usually present and associated with evidence of tubular cell injury and/or atrophy. Clinical manifestations usually relate to the underlying disorder; nephrocalcinosis itself is generally asymptomatic except for polyuria due to impaired urinary concentrating mechanism.[144] The diagnosis of nephrocalcinosis is typically made by renal imaging (Fig. 57.8). The renal prognosis depends on the underlying etiology and the ability to reverse hypercalciuria and the associated conditions that promote renal calcification. For example, in premature infants with nephrocalcinosis, renal ultrasounds are normal in 75% to 90% by age 7.5 years, whereas progressive kidney disease is the rule in children with primary hyperoxaluria.[145] For many, nephrocalcinosis is not reversible but specific medical interventions to reduce further calcification can effectively preserve renal function. ESRD due to nephrocalcinosis-associated chronic TIN is unusual.

Hyperphosphatemia/Hyperphosphaturia

The entity of acute phosphate nephropathy reported in association with the use of oral sodium phosphate bowel purgatives has refocused attention on the importance of hyperphosphaturia as a mediator of acute TIN, which may progress to chronic TIN and irreversible renal functional impairment. Renal histologic data were obtained from a cohort of 21 patients who underwent renal biopsies 2 to 8 months (mean 3.8 months) after a phosphate enema was used as preparation for a colonoscopy and associated with subsequent AKI;

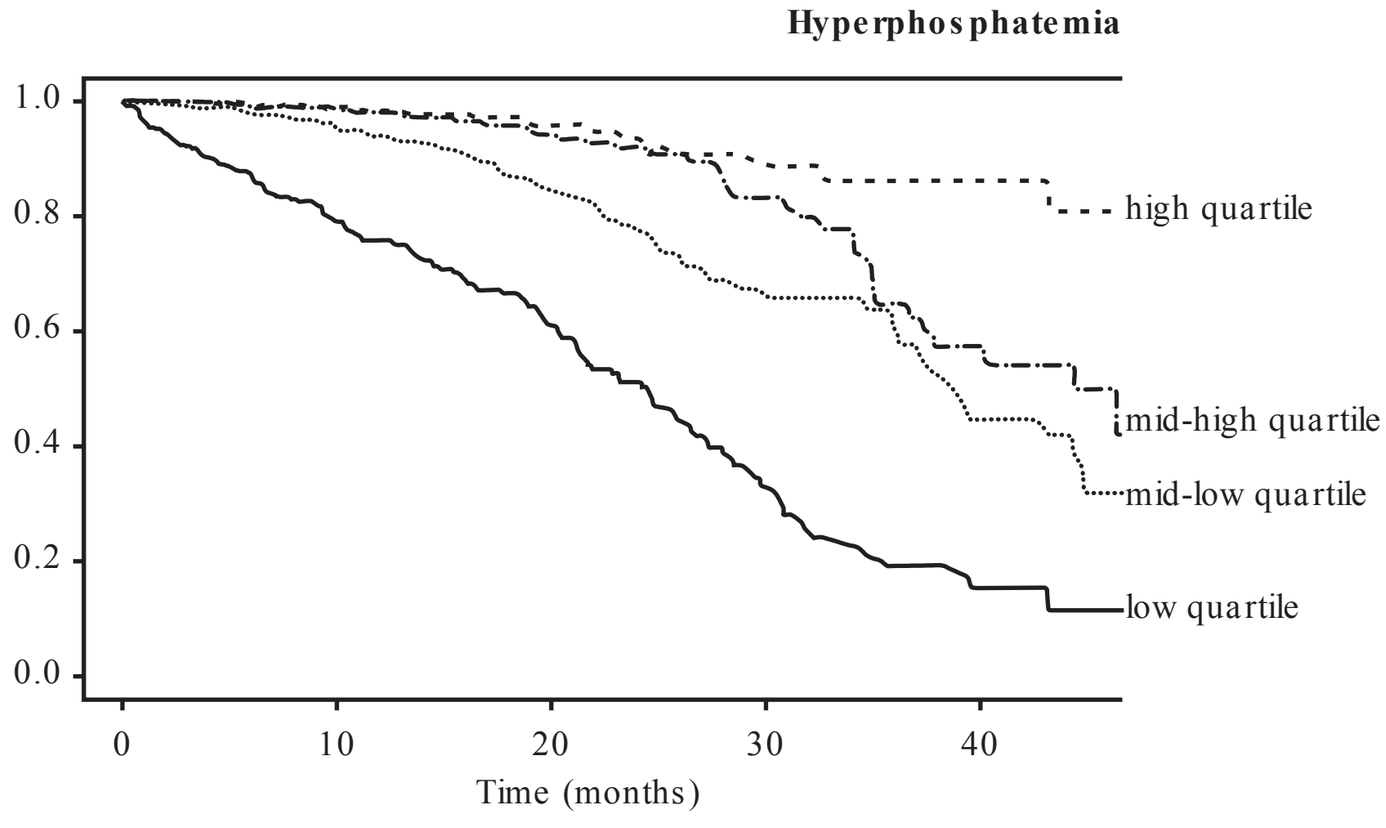

FIGURE 57.18 Hyperphosphatemia as an acquired metabolic cause of chronic tubulointerstitial nephritis (TIN). In addition to the well-known nephrotoxic effects of acute severe hyperphosphatemia, there is a growing body of evidence suggesting that hyperphosphatemia may also play a pathogenetic role in the genesis of the chronic TIN that characterizes all progressive kidney diseases. The graph is from an Italian study of 1,716 patients with chronic kidney disease, which showed a significant relationship between serum phosphorus levels (divided into quartiles) and the rate of progression to end-stage renal disease. (From Bellasi A, Mandreoli M, Baldrati L, et al. Chronic kidney disease progression and outcome according to serum phosphorus in mild-to-moderate kidney dysfunction. *Clin J Am Soc Nephrol.* 2011;6:883, with permission.)

the results showed widespread von Kossa positive calcium phosphate deposits in tubular lamina, tubular epithelial cells, and the peritubular interstitium.[146,147] These changes were associated with evidence of chronic injury—tubular atrophy and interstitial fibrosis. Despite a mean serum creatinine level of 1.0 mg per dL (0.6–1.7 range) pre-colonoscopy, only four patients had a creatinine level less than 2.0 mg per dL at the time of renal biopsy and four patients progressed to ESRD. Although this study is biased to patients with severe AKI following acute oral phosphate loading, it highlights the potential for extreme hyperphosphaturia to cause both acute and chronic TIN. Because the primary pathogenetic mechanisms have not been fully elucidated, it remains possible that hyperphosphatemia also plays a direct role, as suggested by clinical epidemiologic evidence for a significant relationship between the degree of hyperphosphatemia and the rate of CKD progression (Fig. 57.18).[148,149]

Acute, severe hyperphosphatemia caused by the sudden release of endogenous intracellular phosphate can also cause AKI due to calcium phosphate deposition and tubulointerstitial injury. This is a well-recognized complication of acute rhabdomyolysis and tumor lysis syndrome. With the routine use of optimal hydration and rasburicase, the incidence of acute urate nephropathy in patients at risk for tumor lysis has declined substantially, and hyperphosphatemia has become the primary metabolic complication associated with AKI in patients with tumor lysis syndrome. In light of the recent recognition of the risk of chronic TIN following acute phosphate nephropathy, all of these patients deserve long-term follow-up for evidence of CKD.

Hyperuricemia/Hyperuricosuria

In addition to uric acid nephrolithiasis, hyperuricemia may induce tubulointerstitial injury by alternative mechanisms. Best characterized is the entity of acute uric acid nephropathy that frequently developed as a complication of tumor lysis syndrome in the era before effective prevention strategies were employed. Renal failure was associated with acute tubular injury due to the deposition of undissociated uric acid within tubules. A chronic form of TIN is also thought to occur as a result of monosodium urate crystal deposition in medullary tubules, where the crystals induce tubular injury, interstitial inflammation, and fibrosis.[150] However, the prevalence of the entity of chronic crystal–associated uric acid nephropathy has been difficult to establish, due to the frequent presence of potentially confounding variables. For example, many of the earlier studies of chronic urate nephropathy are now thought to represent lead nephrotoxicity. A form of autosomal-dominant chronic TIN associated with hyperuricemia is now known to be caused by a mutation in the gene that encodes the urinary protein uromodulin—the hyperuricemia is no longer believed to serve a primary pathogenetic role. Many of the patients thought to have "gouty nephropathy" also have hypertension and metabolic syndrome but rarely undergo renal biopsy to establish a diagnosis of chronic urate TIN. Perhaps one of the most compelling arguments in support of the existence of chronic urate nephropathy in humans derives from boys with Lesch-Nyhan syndrome, who have been reported to develop increased echogenicity of the medullary pyramids visualized by renal ultrasound.

Rodent models of urate nephropathy have been developed; these models have taken advantage of the fact that hyperuricemia can be induced by inhibiting the uric acid-degrading enzyme uricase.[151] However, the relevance of this model to humans has been questioned, as humans lack uricase and normally have serum uric acid levels that are considerably higher than the rats with nephropathy. Studies based on the rodent models suggest that the primary pathogenic mechanism is not related to crystal-induced injury. Rather, it is proposed that soluble uric acid induces renal microvascular injury and arteriolopathy, with chronic TIN developing as a consequence of hypoxic injury.[152,153] Building on this potential mechanistic paradigm, human epidemiologic studies are now investigating the role of serum uric acid as a pathogenetic factor in patients with hypertension, diabetes-associated vascular disease, and CKD. In several studies of healthy individuals with normal renal function, such as the one reported by Obermayr et al.,[154] the risk for incident kidney disease is higher in those with elevated uric acid levels.

Hypokalemia

Potassium depletion may lead to acute, reversible changes in renal tubular function, especially impaired urinary concentration. Longstanding hypokalemia has been reported to cause chronic, irreversible TIN in both humans and animal models, an entity referred to as "hypokalemia nephropathy."[155] Histopathologically, it is characterized by early renal tubular cell hyperplasia and late tubular atrophy, interstitial inflammation, and fibrosis. The changes are greatest in the outer medulla and may be associated with formation of small cysts. This entity is most commonly reported in patients with severe and prolonged hypokalemia, typically caused by malnutrition or the abuse of laxatives or diuretics in patients with eating disorders. CKD and ESRD have been reported. The early tubular functional changes associated with shorter duration hypokalemia are reversible with potassium repletion. Although the pathogenesis of hypokalemia nephropathy is incompletely understood, studies in animal models have identified renal vasoconstriction, interstitial capillary rarefaction, ammonia-mediated complement activation, and growth factor and cytokine activity as features of this chronic TIN process. In some patients it may be challenging to differentiate between hypokalemia as consequence or a cause of chronic TIN.

CHRONIC TIN IN ONCO-HEMATOLOGIC DISORDERS

AKI is a relatively common complication in patients with malignancies, and a variety of potential mechanisms have been identified.[156,157] Long-term renal sequelae in cancer survivors is a topic of current interest, but very little is known about the specific risk of CKD due to chronic TIN. Efforts to determine this risk are complicated by the fact that many of the patients have comorbidities, including several that could be risk factors for AKI. The most important include exposure to nephrotoxic agents (especially chemotherapeutic agents and antimicrobial drugs), infectious processes, and sepsis syndromes with renal hypoperfusion. Each of these imposes a small potential risk of residual chronic TIN.

Malignant cells may also invade the renal parenchyma (Fig. 57.19). Leukemia and lymphoma are well-established causes of TIN. Autopsy-based studies suggest that such involvement is relatively common, but is typically silent clinically, occurring in as many as one third of patients with Hodgkin lymphoma and 60% with acute leukemia. In a series of adults with acute lymphoblastic leukemia, 10% had enlarged kidneys whereas only 0.4% had clinical evidence of renal disease.[158] Although there are case reports of severe AKI in patients presenting with enlarged kidneys due to leukemic or lymphomatous infiltrates, superimposed tumor lysis syndrome may be a significant contributing factor. Overall, the risk of chronic TIN due to malignant-cell associated acute TIN appears to be low.

The unique malignancy-associated tubulointerstitial disease that carries a risk of progression to chronic TIN occurs in patients with multiple myeloma.[159,160] Almost 50% of newly diagnosed patients have evidence of renal functional impairment, a complication that significantly reduces survival rates (less than 1 year in patients with severe kidney injury). Tubulointerstitial disease is the primary pattern of injury, with a propensity to progress rapidly to chronic TIN. At least four distinct patterns of TIN have been identified, sharing a common primary pathogenetic mechanism pertaining to the plasma cell dyscrasia that leads to the overproduction of free immunoglobulin light chains (kappa or lambda). These light chains appear to owe their nephrotoxic potential to unique physiochemical properties that differ from normal immunoglobulins.

1. Proximal tubular dysfunction. Low molecular weight (~22 kDa) light chains are freely filtered by the glomerulus and reabsorbed in the proximal tubule by megalin-cubilin-dependent endocytosis. Certain abnormal light chains appear to resist intralysosomal degradation and may even form intracellular crystals. These features are thought to be associated with cytotoxic effects, characterized by the production of inflammatory cytokines, TGF-β, interstitial inflammation, tubular cell apoptosis, and interstitial fibrosis.
2. Myeloma cast nephropathy (Fig. 57.19). This classical pattern of tubulointerstitial injury is characterized by the formation of obstructing intratubular casts that contain aggregates of the abnormal light chain together with uromodulin (Tamm-Horsfall protein). Disease risk is correlated with the level of light chain excretion. The severity of the chronic TIN correlates with the degree of renal functional impairment.
3. Interstitial nephritis. A less common pattern of injury, acute TIN may be a consequence of light chain deposition along tubular basement membranes.

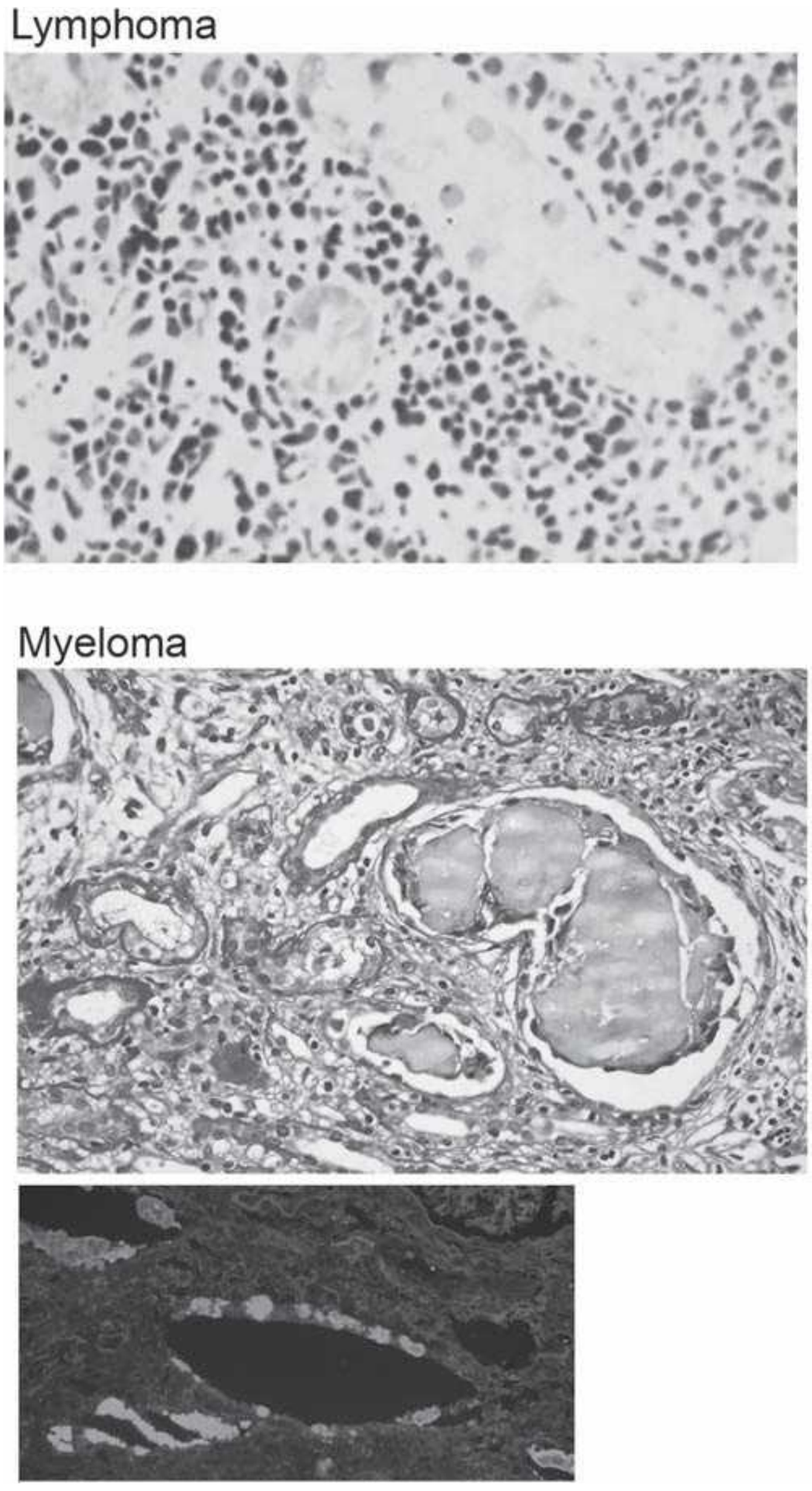

FIGURE 57.19 Hematologic malignancies as a cause of chronic tubulointerstitial nephritis (TIN). The renal interstitium can be directly infiltrated by malignant cells, as shown in the upper photomicrograph of a diagnostic renal biopsy performed on a patient who presented with renal failure and enlarged kidneys of unknown etiology. It revealed a monomorphic interstitial infiltrate of lymphoma cells. The middle photomicrograph shows an example of myeloma cast nephropathy, which is characterized by obstructing tubular casts with a characteristic fractured appearance and evidence of chronic TIN. The lower immunofluorescence photomicrograph illustrates lambda light chains in tubular casts and protein reabsorption droplets. As expected, staining for kappa light chains was negative. (Multiple myeloma photomicrographs were provided by Dr. Agnes Fogo, Department of Pathology, Vanderbilt University.)

4. Plasma cell infiltration. A rare cause of TIN is direct interstitial invasion by the abnormal plasma cells. Other types of myeloma-associated kidney disease involve the glomeruli, associated with variable degrees of chronic TIN depending on disease severity. The latter group of diseases typically cause glomerular proteinuria and include amyloidosis, cryoglobulinemia, and monoclonal immunoglobulin deposition diseases. The specific properties that render myeloma-derived light chains nephrotoxic remain unclear but may be related to their ability to form aggregates, bind to uromodulin, resist lysosomal degradation, and/or mediate tubular cell toxicity. There is considerable variability in the nephrotoxic effects of various free light chains. Early initiation of chemotherapy to eradicate the dysplastic plasma cells and stop free light chain production before severe TIN has developed is the most effective strategy to prevent progressive kidney damage. Although still a debated topic, current data suggest that therapeutic apheresis adds no additional benefit to current immunotherapy.

The classic nonmalignant hematologic disorder known to cause CKD is sickle cell disease, which is reviewed in greater detail in Chapter 62.[161,162] It is estimated that 5% to 18% of patients with sickle cell disease will develop ESRD, typically between 30 and 40 years of age. Proteinuria, an early marker of renal dysfunction, is reported in 40% of patients. In addition to a higher incidence of certain glomerular diseases, a unique renal disorder termed "sickle cell nephropathy" is the most common etiology. Its pathogenesis remains unproven, but the current prevailing view is one of hypoxia-induced chronic tubular damage as a consequence of erythrocyte sickling and sludging in the vasa recta within the hypoxic, acidemic, and hypertonic environment of the renal medulla. During this early phase, deficits in urinary concentration are common. Severe ischemic injury may also lead to papillary necrosis. The unproven but presumed essential secondary step is glomerular hyperperfusion, as a consequence of the production of vasodilating substances such as prostaglandins and nitric oxide. Early glomerular hypertrophy, with a high GFR, progresses to glomerulosclerosis and CKD due to interstitial inflammation and fibrosis. The presence of tubular hemosiderin deposits suggests a potential role for iron-related nephrotoxicity.

SUMMARY

Recent advances in the understanding of the cellular and molecular biology of chronic TIN as the final common pathway of all CKD—whether they start in the glomerular, tubulointerstitial, or vascular compartments—offer new opportunities to identify and treat patients at risk for kidney disease progression. Future genetic studies are likely to identify a series of genetic determinants of kidney fibrosis, and new therapeutics directed at specific molecular targets offer promise

of the ability to attenuate fibrosis severity and enhance renal parenchymal repair and protection. Advances in the field of stem cell and regenerative medicine offer hope that one day we will have the tools to reverse fibrosis and regenerate intact nephrons within regions of renal parenchymal scarring. An increasing number of ongoing research studies are making creative use of human kidney biopsy material to identify distinct molecular and cellular profiles that characterize high-risk patients who would benefit from such therapies.

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