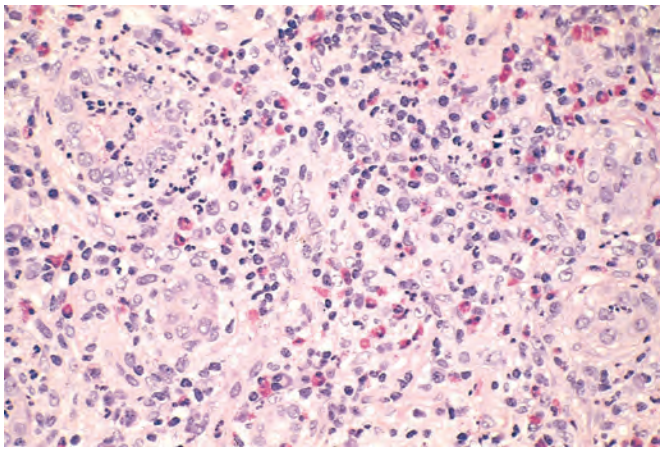

Figure 20-33 Drug-induced interstitial nephritis, with prominent eosinophilic and mononuclear cell infiltrate. (Courtesy Dr. H. Rennke, Brigham and Women's Hospital, Boston, Mass.)

acute recurrent pyelonephritis, such as back pain, fever, pyuria, and bacteriuria. These patients receive medical attention relatively late in their disease course because of the gradual onset of renal insufficiency and hypertension. Reflux nephropathy is often discovered in children when the cause of hypertension is investigated. Loss of tubular function—in particular of concentrating ability—gives rise to polyuria and nocturia. Radiographic studies show asymmetrically contracted kidneys with characteristic coarse scars and blunting and deformity of the calyceal system. Significant bacteriuria may be present, but it is often absent in the late stages.

Although proteinuria is usually mild, some individuals with pyelonephritic scars develop secondary *focal segmental glomerulosclerosis* with significant proteinuria, even in the nephrotic range, usually several years after the scarring has occurred and often in the absence of continued infection or persistent vesicoureteral reflux. The onset of proteinuria and focal segmental glomerulosclerosis is a poor prognostic sign, which may progress to ESRD. The glomerulosclerosis, as discussed, is attributable to the adaptive glomerular alterations secondary to loss of renal mass caused by pyelonephritic scarring (renal ablation nephropathy).

KEY CONCEPTS

Pyelonephritis

- Both acute and chronic pyelonephritis may be caused by infection via the ascending (more common) or hematogenous route. Obstructive lesions of the urinary tract are important predisposing factors.
- Bacteria are the most common infectious agent in acute pyelonephritis and induce a prominent neutrophilic inflammatory response; granulomatous interstitial inflammation is characteristic of fungal or mycobacterial infections.
- Chronic pyelonephritis ensues when anatomic anomalies result in urine reflux or urine outflow obstruction; multiple episodes of this injury leads to irregular scarring of the kidney that is typically more prominent at the upper or lower poles where reflux is more common.

Tubulointerstitial Nephritis Induced by Drugs and Toxins

Drug and toxin-induced tubulointerstitial nephritis is the second most common cause of acute kidney injury (after pyelonephritis). Toxins and drugs can injure kidneys in at least three ways: (1) trigger an interstitial immunologic reaction, exemplified by the acute hypersensitivity nephritis induced by drugs such as methicillin; (2) cause acute tubular injury, as described earlier; and (3) cause subclinical but cumulative injury to tubules that takes years to result in chronic renal insufficiency. The last type of damage is especially worrisome, because it may be unrecognized until irreversible renal damage has occurred.

Acute Drug-Induced Interstitial Nephritis

First reported after the use of sulfonamides, acute tubulointerstitial nephritis most frequently occurs with synthetic penicillins (methicillin, ampicillin), other synthetic antibiotics (rifampin), diuretics (thiazides), NSAIDs, and miscellaneous drugs (allopurinol, cimetidine). The chronic tubulointerstitial nephritis caused by phenacetin-containing analgesics, termed *analgesic nephropathy*, is mostly of historical importance as its incidence has substantially diminished due to the withdrawal or restriction of phenacetin in most countries.

Drug-induced acute interstitial nephritis begins about 15 days (range: 2-40) after drug exposure and is characterized by *fever, eosinophilia* (which may be transient), *a rash* in about 25% of patients, and *renal abnormalities*. The latter takes the form of hematuria, mild proteinuria, and leukocyturia (often including eosinophils). A rising serum creatinine or acute kidney injury with oliguria develops in about 50% of cases, particularly in older patients.

Pathogenesis. Many features of the disease suggest an idiosyncratic immune mechanism that is not dose-related. Clinical evidence of hypersensitivity includes the latent period, the eosinophilia and rash, the fact that the onset of nephropathy is not dose-related, and the recurrence of clinical and pathologic manifestations after re-exposure to the same or a chemically related drug. In some patients, serum IgE levels are increased, and IgE-containing plasma cells and basophils are present in the lesions, suggesting that the *late-phase reaction of an IgE-mediated (type I) hypersensitivity* may be involved in the pathogenesis (Chapter 6). In other cases, a mononuclear or granulomatous reaction, together with positive results of skin tests to drug haptens, suggest a T cell-mediated (type IV) delayed-hypersensitivity reaction.

The most likely sequence of events is that the drugs function as haptens and covalently bind to some plasma membrane or extracellular component of tubular cells. These modified self antigens then become immunogenic. The resultant injury is due to IgE or cell-mediated immune reactions to tubular cells or their basement membranes.

MORPHOLOGY

On histologic examination the interstitium shows variable but frequently pronounced **edema and infiltration by mononuclear cells,** principally lymphocytes and macrophages.