Exposure to Cyclosporine

**FIGURE 10-23**
Toxicity of cyclosporine. Cyclosporine is a neutral fungal hydrophobic 11-amino acid cyclic polypeptide. Cyclosporine is metabolized by hepatic cytochrome P450 to multiple less active and less toxic metabolites. Drugs that inhibit cytochrome P450 enzymes such as ketoconazole, verapamil, diltiazem, and erythromycin increase the concentration of cyclosporine and may thus precipitate renal side effects [20,21].

**FIGURE 10-24**
Cyclosporine and hypertension. Hypertension can develop in 10% to 80% of patients treated with cyclosporine, depending on dosage and length of the exposure. Cyclosporine increases cytosol calcium and, thus, enhances arteriolar smooth muscle responsiveness to vasoconstrictive stimuli. Vasoconstrictive effects of cyclosporine also are mediated by enhanced thromboxane action, sympathetic nerve stimulation, and release of endothelin. Renal vasoconstriction results in salt retention and hypertension. In chronic exposure to cyclosporine, hypertension also is a part of cyclosporine-induced chronic renal failure [22].

**FIGURE 10-25**
Pathogenesis of cyclosporine nephropathy. Chronic administration of cyclosporine may induce sustained renal vasoconstriction. Impairment of renal blood flow leads to tubulointerstitial fibrosis. Cyclosporine increases the recruitment of renin-containing cells along the afferent arteriole. Hyperplasia of the juxtaglomerular apparatus increases angiotensin II levels that, in turn, stimulate tumor growth factor-β (TGF-β) secretion, resulting in interstitial fibrosis [20].
Toxic Nephropathies

FIGURE 10-26
Cyclosporine (CyA) nephrotoxicity in nonrenal diseases. A, Patients treated with cyclosporine (7.5 mg/kg) for psoriasis experienced a median decrease to 84% of the initial values in the glomerular filtration rate after 8 weeks of therapy. B, Of patients treated with cyclosporine (9.3 mg/kg) for autoimmune diseases, 21% showed cyclosporine nephropathy on biopsy, with a decrease to 60% of the initial values in renal function. C, Patients with cardiac transplantation treated with high doses of cyclosporine (10 to 6 mg/kg) developed a reduction to 57% of the initial values in renal function 36 months after transplantation. Patients treated with azathioprine did not show any reduction in renal function. D, Patients receiving cyclosporine (5 mg/kg) for uveitis for 2 years showed a decrease in glomerular filtration rate to 65% of the initial values. (Panel A adapted from Ellis and coworkers [23]; panel B adapted from Feutren and Mihatsch [24]; panel C adapted from Myers and Newton [25]; and panel D adapted from Deray and coworkers [26].)

FIGURE 10-27
Morphology of cyclosporine nephropathy on renal biopsy of a patient with cardiac transplantation. Two different types of lesions are seen in cyclosporine nephropathy. A, Arteriopathy: Hyalin, paucicellular thickening of the intima with focal wall necrosis results in narrowing of the vascular lumen (magnification x 300 periodic acid-Schiff reaction). B, A striped form of interstitial fibrosis characterized by irregularly distributed areas of stripes of interstitial fibrosis and tubular atrophy in the renal cortex. Tubules in other areas were normal (magnification x 100 periodic acid-Schiff reaction).
Exposure to Aminosalicylic Acid

Aminosalicylic acid and chronic tubulointerstitial nephritis. A, A 36-year-old man suffering from Crohn’s disease exhibited severe renal failure after 23 months of treatment with 5-aminosalicylic acid (5-ASA, or Pentasa, Hoechst Marion Roussel, Kansas City, MO). B, The first renal biopsy showing widening and massive cellular infiltration of the interstitium, tubular atrophy, and relative spacing of glomeruli. C, The second renal biopsy 8 months after discontinuation of the drug and moderate improvement of the renal function, again showing important cellular infiltration of the interstitium tubular atrophy, and fibrosis. Several atrophic tubules are surrounded by one or more layers of α-smooth muscle actin positive cells. The patient had normal renal function on beginning treatment with 5-ASA. After 5 years of 5-ASA therapy, the patient demonstrated severe impaired renal function. The association between the use of 5-ASA and development of chronic tubulointerstitial nephritis in patients with inflammatory bowel disease (IBD) has gained recognition in recent years [27,28]. (Courtesy of M E De Broe, M D.)