Cyclosporine

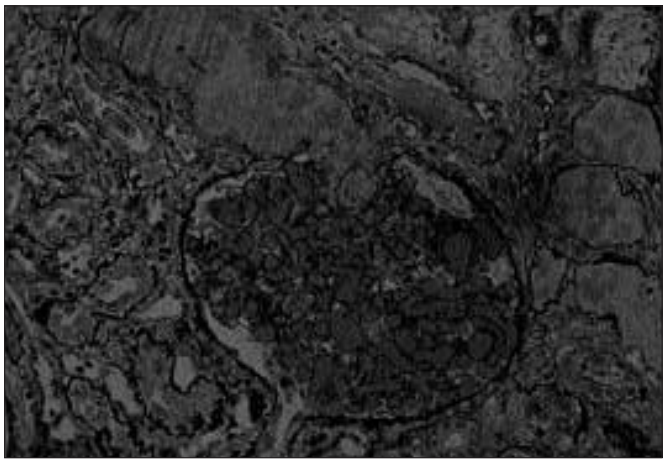

FIGURE 11-13 (see Color Plate)
Intravascular coagulation in a cyclosporine-treated renal transplant recipient. Cyclosporine produces a dose-related decrease in renal function in experimental animals and humans [17] that is attributed to the drug's hemodynamic action to produce vasoconstriction of the afferent arteriole entering the glomerulus. When severe enough, this can decrease glomerular filtration rate. Although the precise pathogenesis of the renal hemodynamic effects of cyclosporine are unclear, endothelin, inhibition of nitric oxide, release of vasoconstrictor prostaglandins such as thromboxane A_2, and activation of the sympathetic nervous system, are among the candidates for cyclosporine-induced vasoconstriction [18].

The diagnosis of cyclosporine-induced acute renal dysfunction is not difficult when the patient has no other reason for reduced renal function (*eg*, psoriasis, rheumatoid arthritis). In renal transplant recipients, however, the situation is completely different. In this clinical setting, the clinician must differentiate between cyclosporine injury and acute rejection. The incidence of this acute cyclosporine renal injury can be enhanced by extended graft preservation, preexisting histologic lesions, donor hypotension, or preoperative complications. The gold standard for this important distinction remains renal biopsy.

In addition, cyclosporine has been associated with hemolytic-uremic syndrome with thrombocytopenia, red blood cell fragmentation, and intravascular (intraglomerular) coagulation. Again, this drug-related intravascular coagulation has to be differentiated from that of acute rejection. The absence of clinical signs and of rejection-related interstitial edema and cellular infiltrates can be helpful.

Vanrenterghem and coworkers [19] found a high incidence of venous thromboembolism shortly after (several of them within days) cadaveric kidney transplantation in patients treated with cyclosporine, in contrast to those treated with azathioprine. Recent studies [20] have shown that impaired fibrinolysis, due mainly to excess plasminogen activator inhibitor (PAI-1), may also contribute to this imbalance in coagulation and anticoagulation during cyclosporine treatment.

Lithium-Induced Acute Renal Failure

SIGNS AND SYMPTOMS OF TOXIC EFFECTS OF LITHIUM

Toxic Effect	Plasma Lithium Level	Signs and Symptoms
Mild	1–1.5 mmol/L	Impaired concentration, lethargy, irritability, muscle weakness, tremor, slurred speech, nausea
Moderate	1.6–2.5 mmol/L	Disorientation, confusion, drowsiness, restlessness, unsteady gait, coarse tremor, dysarthria, muscle fasciculation, vomiting
Severe	>2.5 mmol/L	Impaired consciousness (with progression to coma), delirium, ataxia, generalized fasciculations, extrapyramidal symptoms, convulsions, impaired renal function

FIGURE 11-14
Symptoms and signs of toxic effects of lithium. Lithium can cause acute functional and histologic (usually reversible) renal injury. Within 24 hours of administration of lithium to humans or animals, sodium diuresis occurs and impairment in the renal concentrating capacity becomes apparent. The defective concentrating capacity is caused by vasopressin-resistant (exogenous and endogenous) diabetes insipidus. This is in part related to lithium's inhibition of adenylate cyclase and impairment of vasopressin-induced generation of cyclic adenosine monophosphatase.

Lithium-induced impairment of distal urinary acidification has also been defined.

Acute lithium intoxication in humans and animals can cause acute renal failure. The clinical picture features nonspecific signs of degenerative changes and necrosis of tubule cells [21]. The most distinctive and specific acute lesions lie at the level of the distal tubule [22]. They consist of swelling and vacuolization of the cytoplasm of the distal nephron cells plus periodic acid-Schiff–positive granular material in the cytoplasm (shown to be glycogen) [23]. Most patients receiving lithium have side effects, reflecting the drug's narrow therapeutic index.

DRUG INTERACTIONS WITH LITHIUM

Salt depletion strongly impairs renal elimination of lithium.
Salt loading increases absolute and fractional lithium clearance.

Diuretics	
Acetazolamide	Increased lithium clearance
Thiazides	Increased plasma lithium level due to decreased lithium clearance
Loop diuretics	Acute increased lithium clearance
Amiloride	Usually no change in plasma lithium level; may be used to treat lithium-induced polyuria
Nonsteroidal anti-inflammatory drugs	Increased plasma lithium level due to decreased renal lithium clearance (exceptions are aspirin and sulindac)
Bronchodilators (aminophylline, theophylline)	Decreased plasma lithium level due to increased renal lithium clearance
Angiotensin-converting enzyme inhibitors	May increase plasma lithium level
Cyclosporine	Decreased lithium clearance

FIGURE 11-15

Drug interactions with lithium [24]. Acute renal failure, with or without oliguria, can be associated with lithium treatment, and with severe dehydration. In this case, acute renal failure can be considered a prerenal type; consequently, it resolves rapidly with appropriate fluid therapy. Indeed, the histologic appearance in such cases is remarkable for its lack of significant abnormalities. Conditions that stimulate sodium retention and consequently lithium reabsorption, such as low salt intake and loss of body fluid by way of vomiting, diarrhea, or diuretics, decreasing lithium clearance should be avoided. With any acute illness, particularly one associated with gastrointestinal symptoms such as diarrhea, lithium blood levels should be closely monitored and the dose adjusted when necessary. Indeed, most episodes of acute lithium intoxication are largely predictable, and thus avoidable, provided that precautions are taken [25].

Removing lithium from the body as soon as possible the is the mainstay of treating lithium intoxication. With preserved renal function, excretion can be increased by use of furosemide, up to 40 mg/h, obviously under close monitoring for excessive losses of sodium and water induced by this loop diuretic. When renal function is impaired in association with severe toxicity, extracorporeal extraction is the most efficient way to decrease serum lithium levels. One should, however, remember that lithium leaves the cells slowly and that plasma levels rebound after hemodialysis is stopped, so that longer dialysis treatment or treatment at more frequent intervals is required.

Inhibitors of the Renin-Angiotensin System

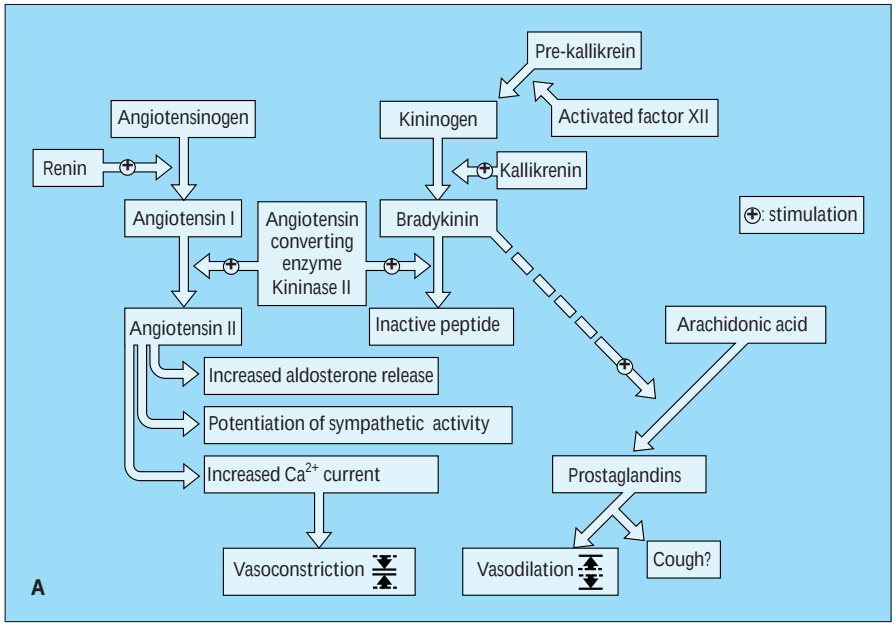

FIGURE 11-16

Soon after the release of this useful class of antihypertensive drugs, the syndrome of functional acute renal insufficiency was described as a class effect. This phenomenon was first observed in patients with renal artery stenosis, particularly when the entire renal mass was affected, as in bilateral renal artery stenosis or in renal transplants with stenosis to a solitary kidney [26]. Acute renal dysfunction appears to be related to loss of postglomerular efferent arteriolar vascular tone and in general is reversible after withdrawing the angiotensin-converting enzyme (ACE) inhibitor [27].

Inhibition of the ACE kinase II results in at least two important effects: depletion of angiotensin II and accumulation of bradykinin [28]. The role of the latter effect on renal perfusion pressure is not clear, **A**.

To understand the angiotensin I converting enzyme inhibitor–induced drop in glomerular filtration rate, it is important to understand the physiologic role of the renin-angiotensin system in the regulation of renal hemodynamics, **B**. When renal perfusion drops, renin is released into the plasma and lymph by the juxtaglomerular cells of the kidneys. Renin cleaves angiotensinogen to form angiotensin I, which is cleaved further by converting enzyme to form angiotensin II, the principal effector molecule in this system. Angiotensin II participates in glomerular filtration rate regulation in a least two ways. First, angiotensin II increases arterial pressure—directly and acutely by causing vasoconstriction and more "chronically" by increasing body fluid volumes through stimulation of renal sodium retention; directly through an effect on the tubules, as well as by stimulating thirst

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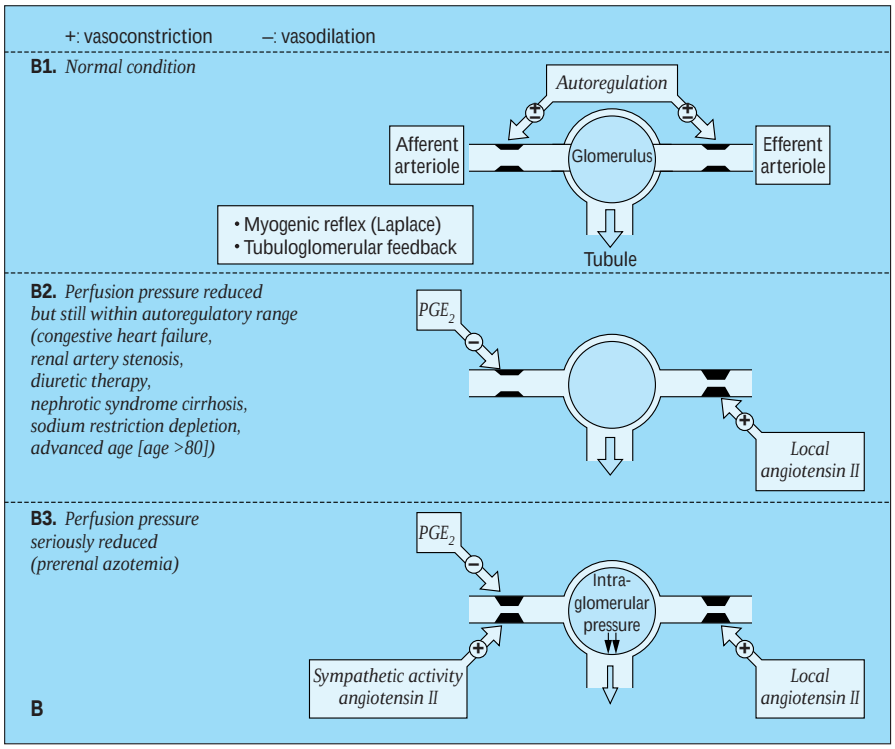

FIGURE 11-16 *(Continued)*

and indirectly via aldosterone. Second, angiotensin II preferentially constricts the efferent arteriole, thus helping to preserve glomerular capillary hydrostatic pressure and, consequently, glomerular filtration rate.

When arterial pressure or body fluid volumes are sensed as subnormal, the renin-angiotensin system is activated and plasma renin activity and angiotensin II levels increase. This may occur in the context of clinical settings such as renal artery stenosis, dietary sodium restriction or sodium depletion as during diuretic therapy, congestive heart failure, cirrhosis, and nephrotic syndrome. When activated, this reninangiotensin system plays an important role in the maintenance of glomerular pressure and filtration through preferential angiotensin II–mediated constriction of the efferent arteriole. Thus, under such conditions the kidney becomes sensitive to the effects of blockade of the renin-angiotensin system by angiotensin I–converting enzyme inhibitor or angiotensin II receptor antagonist.

The highest incidence of renal failure in patients treated with ACE inhibitors was associated with bilateral renovascular disease [27]. In patients with already compromised renal function and congestive heart failure, the incidence of serious changes in serum creatinine during ACE inhibition depends on the severity of the pretreatment heart failure and renal failure.

Volume management, dose reduction, use of relatively short-acting ACE inhibitors, diuretic holiday for some days before initiating treatment, and avoidance of concurrent use of nonsteroidal anti-inflammatory drug (hyperkalemia) are among the appropriate measures for patients at risk.

Acute interstitial nephritis associated with angiotensin I–converting enzyme inhibition has been described [29]. (*Adapted from* Opie [30]; with permission.)

Nonsteroidal Anti-inflammatory Drugs

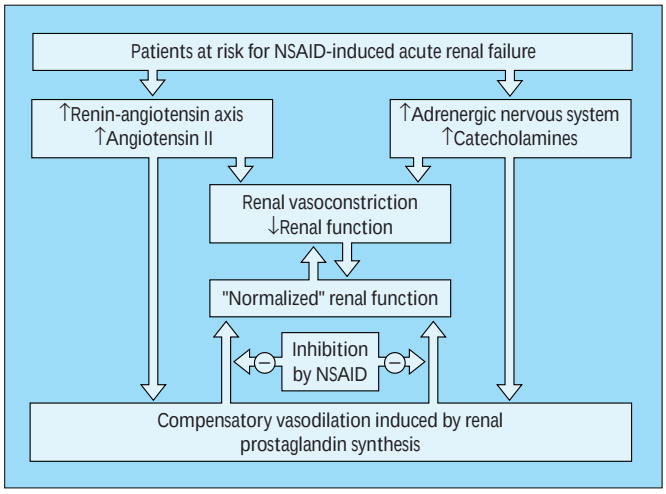

FIGURE 11-17

Mechanism by which nonsteroidal anti-inflammatory drugs (NSAIDs) disrupt the compensatory vasodilatation response of renal prostaglandins to vasoconstrictor hormones in patients with prerenal conditions. Most of the renal abnormalities encountered clinically as a result of NSAIDs can be attributed to the action of these compounds on prostaglandin production in the kidney [31].

Sodium chloride and water retention are the most common side effects of NSAIDs. This should not be considered drug toxicity because it represents a modification of a physiologic control mechanism without the production of a true functional disorder in the kidney.