

# Renal Parenchymal Disease and Hypertension

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**H**ypertension and parenchymal disease of the kidney are closely interrelated. Most primary renal diseases eventually disturb sodium and volume control sufficiently to produce clinical hypertension. Both on theoretical and practical grounds, many authors argue that *any* sustained elevation of blood pressure depends ultimately on disturbed renal sodium excretion, *ie*, altered *pressure natriuresis*. Hence, some investigators argue that a clinical state of hypertension represents *de facto* evidence of disturbed (or “reset”) renal function even before changes in glomerular filtration can be measured.

Many renal insults further induce inappropriate activation of vasoactive systems such as the renin-angiotensin system, adrenergic sympathetic nerve traffic, and endothelin. These mechanisms may both enhance vasoconstriction and act as mediators of additional tissue injury by altering the activity of inflammatory cytokines and promoters of interstitial fibrosis.

Arterial hypertension itself accelerates many forms of renal disease and hastens the progression to advanced renal failure. Recent studies have firmly established the importance of blood pressure reduction as a means to slow the progression of many forms of renal parenchymal injury, particularly those characterized by massive proteinuria. Over the long term, damage to the heart and cardiovascular system resulting from hypertension represents the major causes of morbidity and mortality for patients with end-stage renal disease.

Here are illustrated the roles of renal parenchymal disease in sustaining hypertension and of arterial pressure reduction in slowing the progression of renal injury. As discussed, parenchymal renal disease may refer to either unilateral (uncommon) or bilateral conditions.

CHAPTER

2

### FORMS OF UNILATERAL RENAL PARENCHYMAL DISEASE RELATED TO HYPERTENSION

Renal artery stenosis  
 Atherosclerosis and fibromuscular lesions (Chapter X)  
 Small vessel disease  
 Vasculitis  
 Atheroembolic renal infarction  
 Thrombosis and infarction  
 Traumatic injury  
 Renal fracture  
 Perirenal fibrosis ("Page" kidney)  
 Radiation injury  
 Arteriovenous malformation or fistulas  
 Other diseases  
 Renal carcinoma  
 Enlarging renal cyst  
 Multiple renal cysts  
 Renin-secreting tumors (rare)

**FIGURE 2-1**

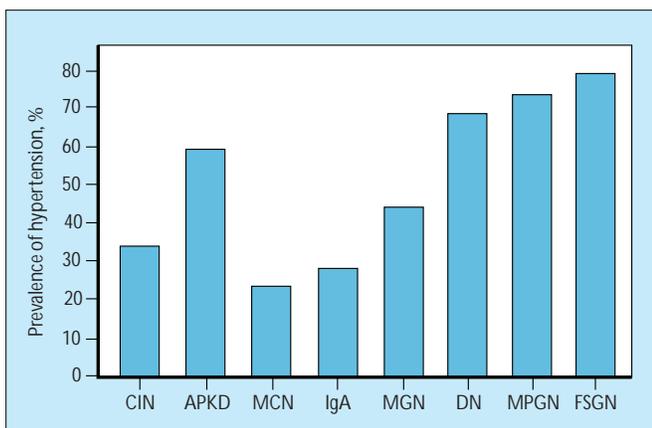
Forms of unilateral renal parenchymal diseases related to hypertension. Many unilateral abnormalities, such as congenital malformations, renal agenesis, reflux nephropathy, and stone disease, do not commonly produce hypertension. However, some unilateral lesions can produce blood pressure elevation. Data for each of these are based primarily on demonstrating unilateral secretion of renin and resolution with unilateral nephrectomy. It should be emphasized that unilateral renal disease does not reduce the overall glomerular filtration rate beyond that expected in patients with a solitary kidney. It follows that additional reductions in the glomerular filtration rate must reflect bilateral renal injury.



**FIGURE 2-2**

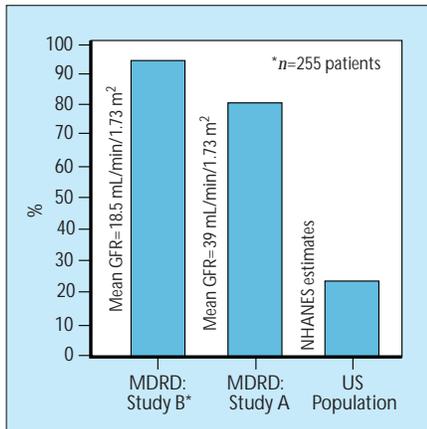
Angiogram and nephrogram of a persistent fractured kidney. The kidney damage shown here produced hypertension in a young woman 2 years after a motor vehicle accident. Measurement of renal vein renins confirmed unilateral production of renin from the affected side. Blood pressure control was achieved with blockade of the renin-angiotensin system using an angiotensin II receptor antagonist (losartan). Many traumatic injuries to the kidney produce temporary hypertension when a border of viable but underperfused renal tissue remains.

## Prevalence of Hypertension in Chronic Renal Disease

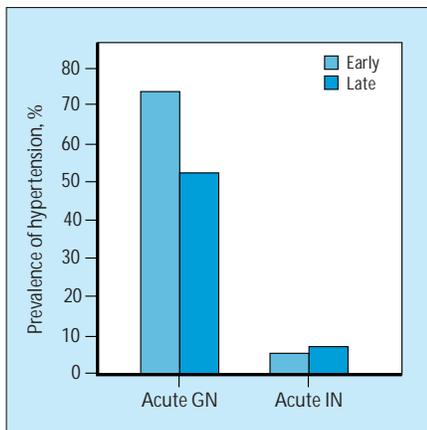


**FIGURE 2-3**

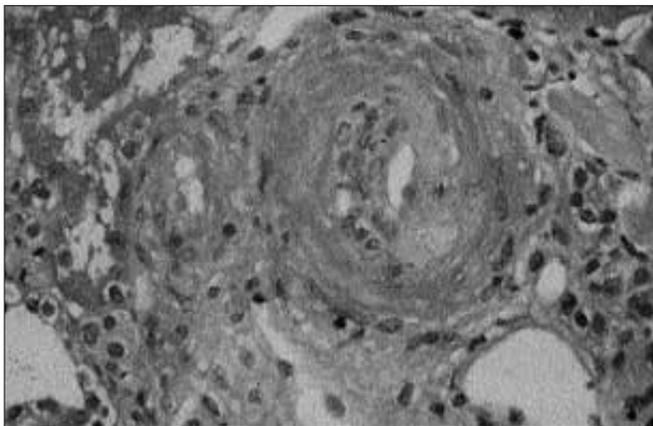
Prevalence of hypertension in chronic renal parenchymal disease. Most forms of renal disease are associated with hypertension. This association is most evident with glomerular diseases, including diabetic nephropathy (DN) and membranoproliferative glomerulonephritis (MPGN), in which 70% to 80% of patients are affected. Minimal change nephropathy (MCN) is a notable exception. Tubulointerstitial disorders such as analgesic nephropathy, medullary cystic diseases, and chronic reflux nephropathies are less commonly affected. APKD—adult-onset polycystic kidney disease; CIN—chronic interstitial nephritis; FSGN—focal segmental glomerulonephritis; MGN—membranous glomerulonephritis. (Data from Smith and Dunn [1].)

**FIGURE 2-4**

Prevalence of hypertension requiring therapy as a function of the degree of chronic renal failure in the Modification of Diet in Renal Disease (MDRD) trial on progressive renal failure. The mean age of these patients was 52 years, with glomerular disease (25%) and polycystic disease (24%) being the most common renal diagnoses in this trial. In Study B, more than 90% of patients were treated with antihypertensive agents, including diuretics, to achieve an overall average blood pressure of 133/81 mm Hg. In general, the more severe the level of renal dysfunction, the more antihypertensive therapy is required to achieve acceptable blood pressures. Patients with glomerular filtration rates (GRFs) below 10 mL/min were hypertensive in 95% of cases. NHANES—National Health and Nutrition Examination Survey. (Data from Klahr and coworkers [2].)

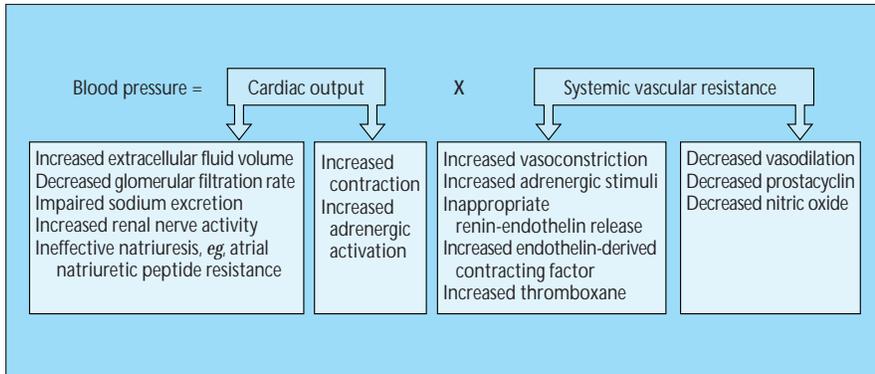
**FIGURE 2-5**

Hypertension in acute renal disease. Acute renal failure is defined as transient increases in serum creatinine above 5.0 mg/dL. During the course of acute renal failure, worsening of preexisting levels or newly detected hypertension (>140/90 mm Hg) is common and almost universally observed in patients with acute glomerulonephritis (GN). Many of these patients have lower pressures as the course of acute renal injury subsides, although residual abnormalities in renal function and sediment may remain. Blood pressure returns to normal in some but not all of these patients. Overall, 39% of patients with acute renal failure develop new hypertension. IN—interstitial nephritis. (Adapted from Rodriguez-Iturbe and coworkers [3]; with permission.)

**FIGURE 2-6 (see Color Plate)**

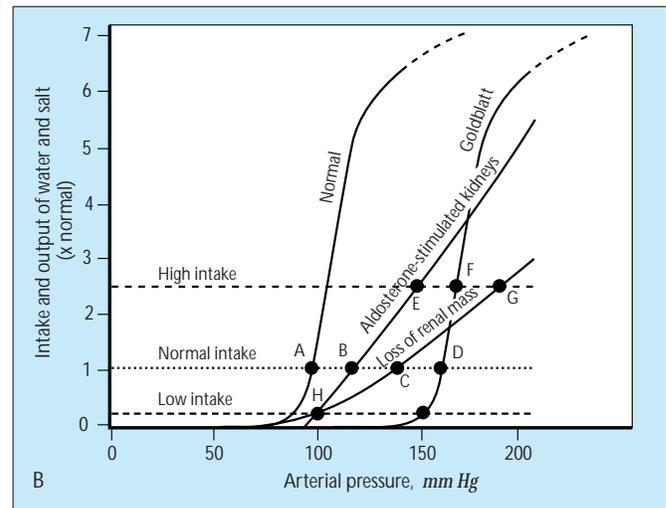
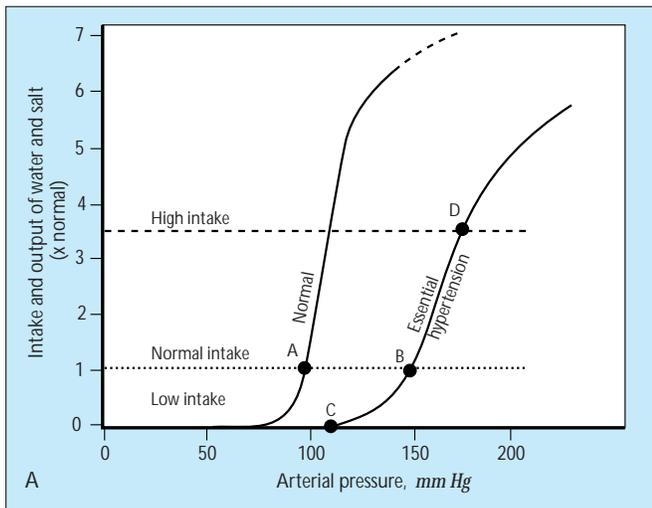
Micrograph of an onion skin lesion from a patient with malignant hypertension.

## Pathophysiology of Hypertension in Renal Disease



**FIGURE 2-7**

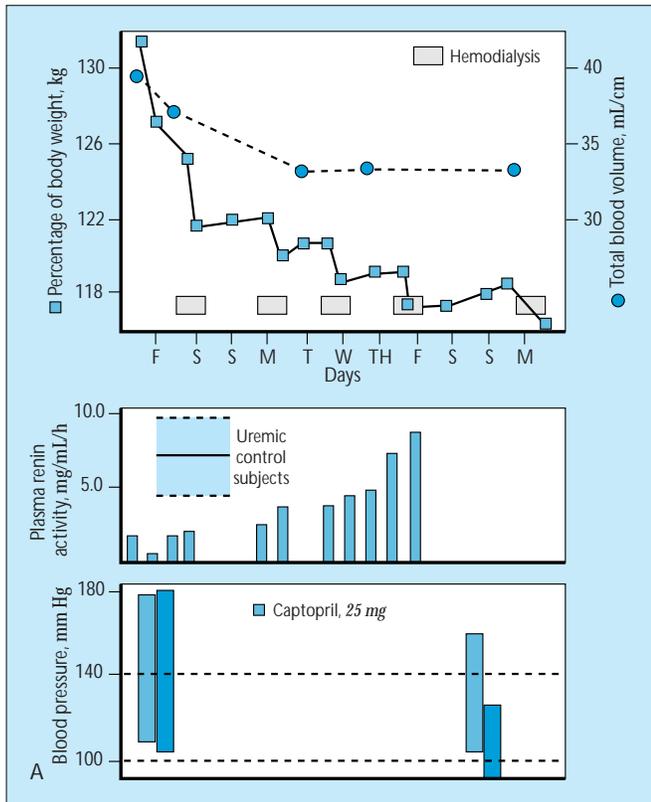
Pathophysiologic mechanisms related to hypertension in parenchymal renal disease: schematic view of candidate mechanisms. The balance between cardiac output and systemic vascular resistance determines blood pressure. Numerous studies suggest that cardiac output is normal or elevated, whereas overall extracellular fluid volume is expanded in most patients with chronic renal failure. Systemic vascular resistance is inappropriately elevated relative to cardiac output, reflecting a net shift in vascular control toward vasoconstricting mechanisms. Several mechanisms affecting vascular tone are disturbed in patients with chronic renal failure, including increased adrenergic tone and activation of the renin-angiotensin system, endothelin, and vasoactive prostaglandins. An additional feature in some disorders appears to depend on reduced vasodilation, such as in impaired production of nitric oxide.



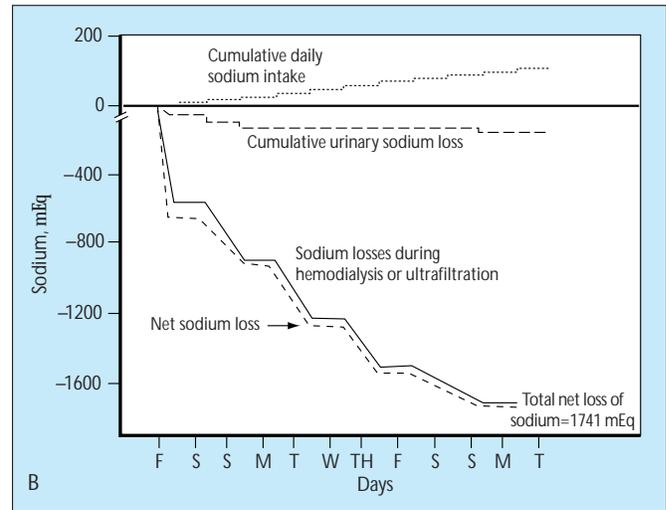
**FIGURE 2-8**

**A.** The relationship between renal artery perfusion pressure and sodium excretion (which defines “pressure natriuresis”) has been the subject of extensive research. Essential hypertension is characterized by higher renal perfusion pressures required to achieve daily sodium balance. **B.** Distortion of this relationship routinely occurs in patients with parenchymal renal disease, illustrated here

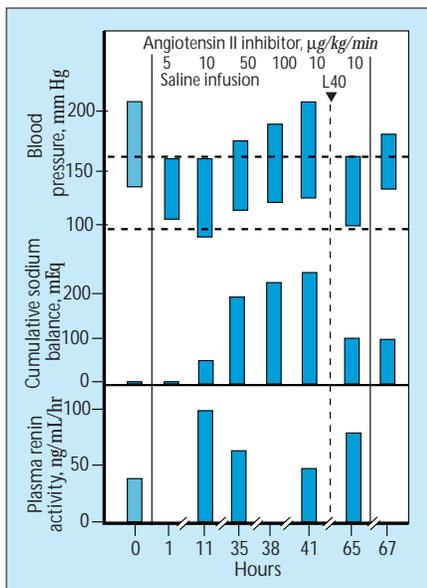
as “loss of renal mass.” Similar effects are observed in conditions with disturbed hormonal effects on sodium excretion (aldosterone-stimulated kidneys) or reduced renal blood flow as a result of an arterial stenosis (“Goldblatt” kidneys). In all of these instances, higher arterial pressures are required to maintain sodium balance.

**FIGURE 2-9**

Sodium expansion in chronic renal failure. The degree of sodium expansion in patients with chronic renal failure can be difficult to ascertain. **A**, Shown are data regarding body weight, plasma renin



activity, and blood pressure (before and after administration of an ACE inhibitor) over 11 days of vigorous fluid ultrafiltration. Sequential steps were undertaken to achieve net negative sodium and volume losses by means of restricting sodium intake (10 mEq/d) and initiating ultrafiltration to achieve several liters of negative balance with each treatment. A negative balance of nearly 1700 mEq was required before evidence of achieving dry weight was observed, specifically a reduction of blood pressure. Measured levels of plasma renin activity gradually increased during sodium removal, and blood pressure became dependent on the renin-angiotensin system, as defined by a reduction in blood pressure after administration of the angiotensin-converting enzyme inhibitor captopril. Achieving adequate reduction of both extracellular fluid volume and sodium is essential to satisfactory control of blood pressure in patients with renal failure. **B**, Daily and cumulative sodium balance.

**FIGURE 2-10**

Interaction between sodium balance and angiotensin-dependence in malignant hypertension. Studies in a patient with renal dysfunction and accelerated hypertension during blockade of the renin-angiotensin system using Sar-1-ala-8-angiotensin II demonstrate the interaction between angiotensin and sodium. Reduction of blood pressure induced by the angiotensin II antagonist was reversed during saline infusion with a positive sodium balance and reduction in circulating plasma renin activity. Administration of a loop diuretic (L40 [furosemide], 40 mg intravenously) induced net sodium losses, restimulated plasma renin activity, and restored sensitivity to the angiotensin II antagonist. Such observations further establish the reciprocal relationship between the sodium status and activation of the renin-angiotensin system [5]. (From Brunner and coworkers [5]; with permission.)

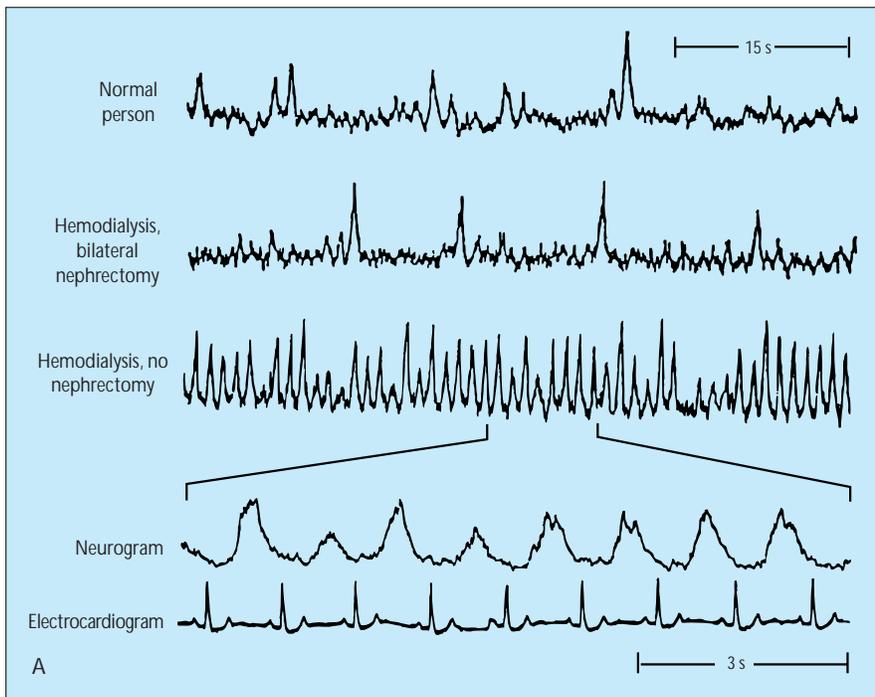
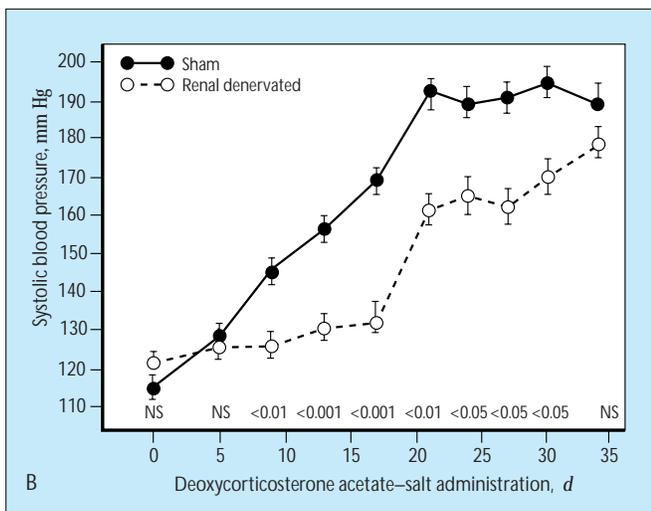


FIGURE 2-11

**A**, Sympathetic neural activation in chronic renal disease. Adrenergic activity is disturbed in chronic renal failure and may participate in the development of hypertension. Microneurographic studies in patients undergoing hemodialysis demonstrate enhanced neural traffic (*panel A*) that relates closely to peripheral vascular tone [6]. Studies in patients in whom native kidneys are removed by nephrectomy demonstrate normal levels of neural traffic, suggesting that afferent stimuli from the kidney modulate central adrenergic outflow. **B**, Delayed onset hypertension in denervated rats. *Panel B* shows evidence from experimental studies in denervated animals subjected to deoxycorticosterone-salt hypertension. The role of the renal nerves in modifying the development of hypertension is supported by studies of renal denervation that show a delayed onset of hypertension, although no alteration in the final level of blood pressure was achieved. NS—not significant. (*Panel A* from Converse and coworkers [6]; with permission. *Panel B* from Katholi and coworkers [7]; with permission.)

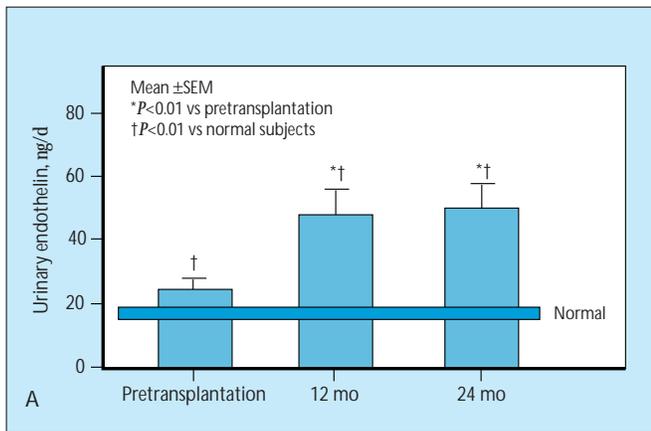


### MAJOR CANDIDATE MECHANISMS THAT MAY ELEVATE PERIPHERAL VASCULAR RESISTANCE IN RENAL PARENCHYMAL DISEASE

Increased vasoconstrictors	Impaired or relatively inadequate vasodilators
Renin-angiotensin system	Nitric oxide: inadequate compensation
Endothelin	Vasodilator prostaglandins: prostacyclin 2
Prostanoids: thromboxane	Natriuretic peptides: atrial natriuretic peptide
Arginine vasopressin	Kallikrein-kinin system
Endogenous digitalis-like substance: ouabain (?)	

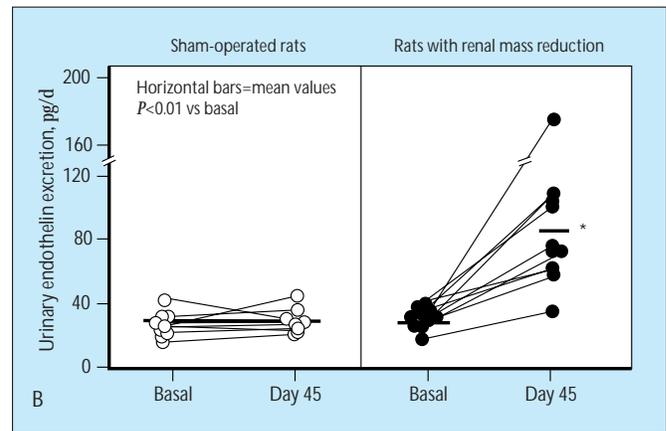
**FIGURE 2-12**

Major candidate mechanisms that may elevate peripheral vascular resistance in renal parenchymal disease. Some data support each of these pathways, although rarely does one mechanism predominate. Experimental studies suggest that endothelin-1 may magnify interstitial fibrosis and contribute to hypertension in some models; however, rarely is the effect major [8,9]. Most levels of vasodilators, including nitric oxide, prostacyclin, and atrial natriuretic peptide, are normal or elevated in patients with renal disease. The vasodilators appear to buffer the vasoconstrictive actions of angiotensin II, which may be increased abruptly if the vasodilator is removed, as occurs with inhibition of cyclo-oxygenase with the use of nonsteroidal anti-inflammatory drugs.

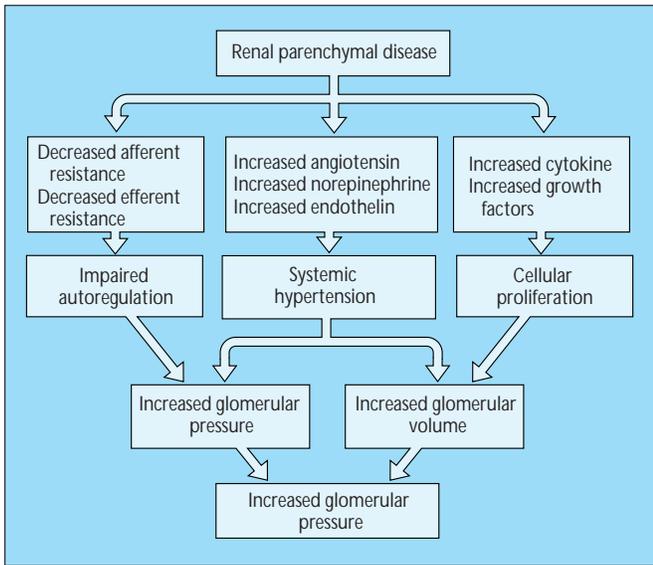


**FIGURE 2-13**

Urinary endothelin in renal disease. **A**, Urinary endothelin levels in patients with cyclosporine-induced renal dysfunction and hypertension before and after liver transplantation. These patients had near-normal kidney function before liver transplantation, after which their glomerular filtration rates decreased from 85 to 55 mL/min, on average. These data underscore the observation that the kidney itself is a rich source of vasoactive materials and that renal excretion of substances such as endothelin is independent of circulating blood levels [10]. Endothelin has properties that both facilitate vasoconstriction and enhance mitogenic and fibrogenic responses, perhaps accelerating interstitial fibrosis in the kidney. Early withdrawal of cyclosporine leads to reversal of a



diminished glomerular filtration rate. With time, however, these changes lose the feature of reversibility [11]. **B**, Renal ablation. Urinary endothelin levels in rats exposed to reduced renal mass achieved by 5/6 nephrectomy. As in humans, plasma levels of endothelin were dissociated from urinary levels, and injected endothelin was not excreted. These results suggest that urinary levels were of renal origin. These studies further support the concept that the diminished nephron number elicits production of potent vasoactive and inflammatory materials that may accelerate irreversible parenchymal injury. (Panel A from Textor and coworkers [10]; with permission. Data in panel B from Benigni and coworkers [12].)



**FIGURE 2-14**

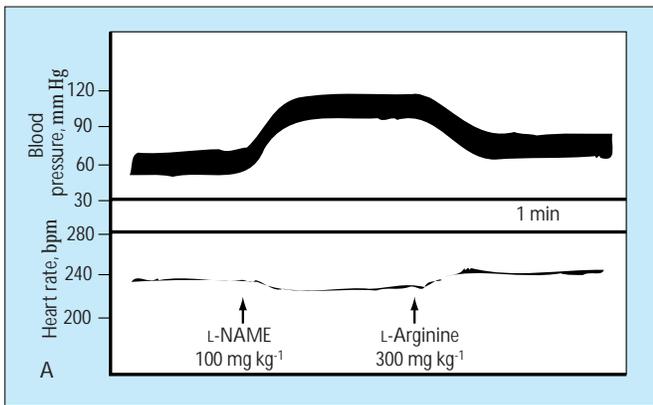
Mechanisms of glomerular injury in hypertension and progressive renal failure. This schematic diagram summarizes the general mechanisms by which disturbances linked to elevated arterial pressure in patients with parenchymal renal disease may lead to further tissue injury. Hemodynamic changes lead to increased glomerular perfusion pressures, whereas local activation of growth factors, angiotensin, and probably several other factors both worsen peripheral resistance and increase tissue fibrotic mechanisms. (From Smith and Dunn [1].)

**PHARMACOLOGIC AGENTS THAT COMMONLY AGGRAVATE OR INDUCE HYPERTENSION IN PARENCHYMAL RENAL DISEASE**

Other agents	
Corticosteroids	Over-the-counter sympathomimetic agents, eg, phenylpropanolamine
Cyclosporine	Supplements containing ephedrine
Erythropoietin	Oral contraceptives (less common with low-dose forms)
Nonsteroidal anti-inflammatory drugs	Amphetamines and stimulants, eg, methylphenidate hydrochloride and cocaine

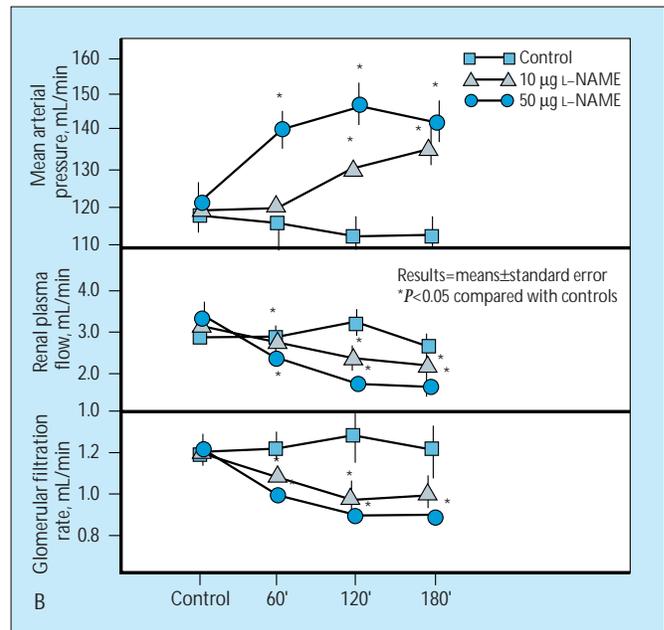
**FIGURE 2-15**

Many pharmacologic agents affect blood pressure levels or the effectiveness of antihypertensive therapy. Shown here are several agents that commonly lead to worsening hypertension and are likely to be administered to patients with renal disease.



**FIGURE 2-16**

Increase in arterial pressure induced by inhibition of nitric oxide. **A**, Intra-arterial pressure in rabbits during *N*-nitro-L-arginine methyl ester (L-NAME) infusion. **B**, Decrease in renal plasma flow and glomerular filtration rate in the blood pressures of rats during nitric oxide inhibition.



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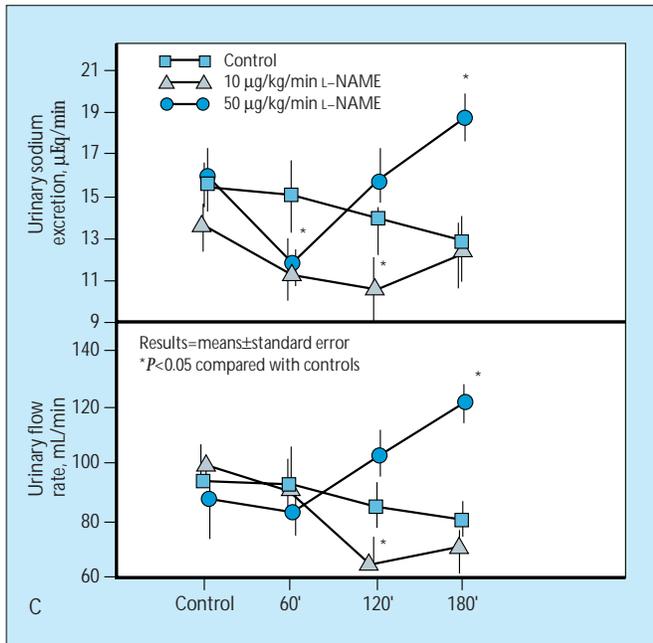


FIGURE 2-16 (Continued)

C, Urine flow rate and urinary sodium excretion over time. Inhibition of nitric oxide synthesis from L-arginine by a competitive substrate such as L-NAME produces dose-dependent and widespread vasoconstriction, leading to an increase in blood pressure [13]. Within specific regional beds such as the kidney, inhibition of nitric oxide produces a decrease in renal plasma flow, diminished glomerular filtration, and sodium retention [14]. The magnitude of these changes in normal animals and humans suggests that tonic nitric oxide production is a major endothelial buffering mechanism preserving vascular tone. The degree to which renal parenchymal disease alters the production of nitric oxide is not known precisely. In some situations, such as nephrotoxicity associated with cyclosporine administration, endothelial production of nitric oxide appears to be substantially impaired [15]. (Panel A from Rees and coworkers [13]; with permission. Panel B from Lahera and coworkers [14]; with permission.)

## Clinical Features of Hypertension in Renal Disease

### A. HYPERTENSION IN PARENCHYMAL RENAL DISEASE: CLINICAL MANIFESTATIONS OF HYPERTENSIVE DISEASE

Cardiovascular disease	Central nervous system	Progressive renal injury
Myocardial infarction	Stroke	End-stage renal disease
Congestive heart failure	Intracerebral hemorrhage	Increased proteinuria
Atherosclerotic vascular disease		
Claudication and limb ischemia		
Aneurysm		

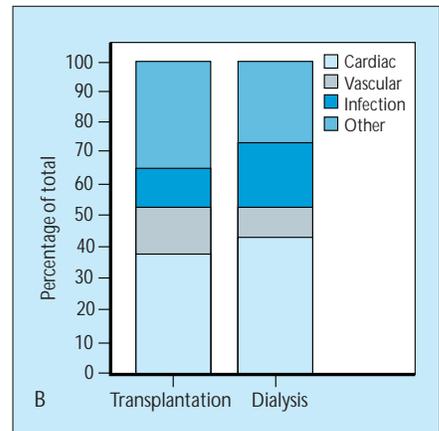
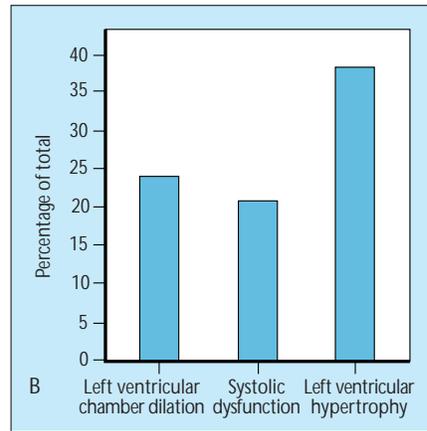
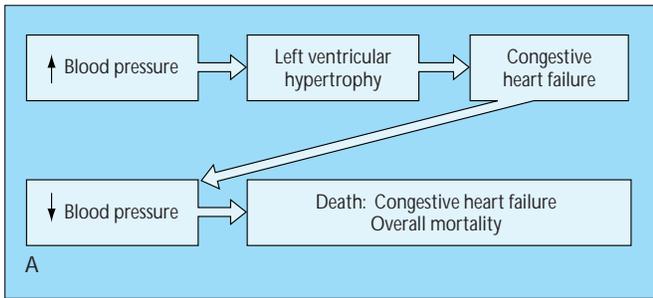


FIGURE 2-17

A and B, Major target organ manifestations of hypertension producing cardiovascular morbidity and mortality in patients with renal disease. More than half of deaths are related to cardiovascular disease in both patients on dialysis and transplantation recipients. These observations underscore the major risk for cardiovascular morbidity and mortality associated with hypertension in the population with chronic renal failure. (From Whitworth [16]; with permission.)

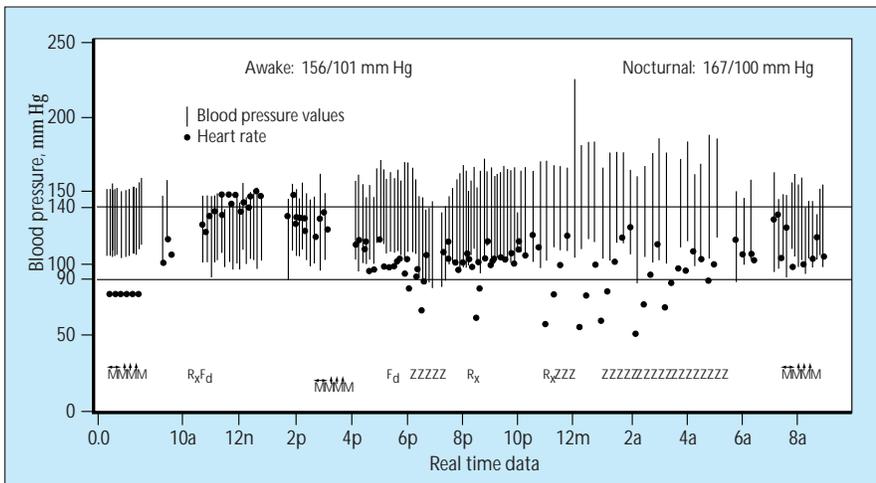
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Hypertension and the Kidney



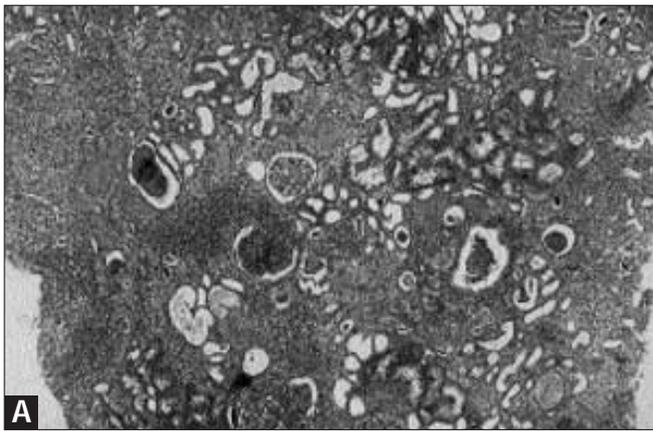
**FIGURE 2-18**

Based on average blood pressure values, a strong direct relationship was found between arterial pressure and left ventricular hypertrophy, left ventricular chamber dilation (by echocardiography), and systolic dysfunction in patients undergoing dialysis for end-stage renal disease. After prolonged follow-up, blood pressures fell with the onset of congestive heart failure and manifest coronary artery disease. With the onset of cardiac failure, there appeared to be an inverse relationship between arterial pressure and mortality. From the outset, the strongest predictor of congestive heart failure was elevated blood pressure. (Adapted from Foley and coworkers [17].)



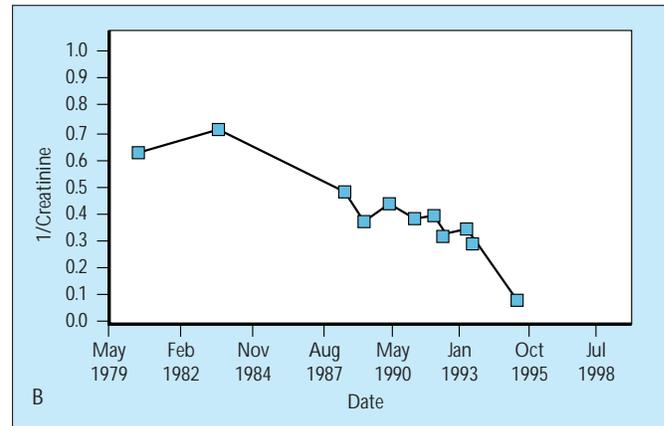
**FIGURE 2-19**

Around-the-clock ambulatory blood pressure monitoring in a patient with renal disease. Loss of diurnal blood pressure patterns have been implicated in increased rates of target organ injury in patients with hypertension. In normal persons with essential hypertension, nocturnal pressures decreased by at least 10% and were associated with a decrease in heart rate. Several conditions have been associated with a loss of the nocturnal decrease in pressure, particularly chronic steroid administration and chronic renal failure. Such a loss in normal circadian rhythm, in particular loss of the nocturnal decrease in blood pressure is more commonly associated with left ventricular hypertrophy and lacunar strokes (manifested as enhanced T-2 signals in magnetic resonance images) and increased rates of microalbuminuria. Data from a single subject with end-stage renal disease studied with are depicted here.

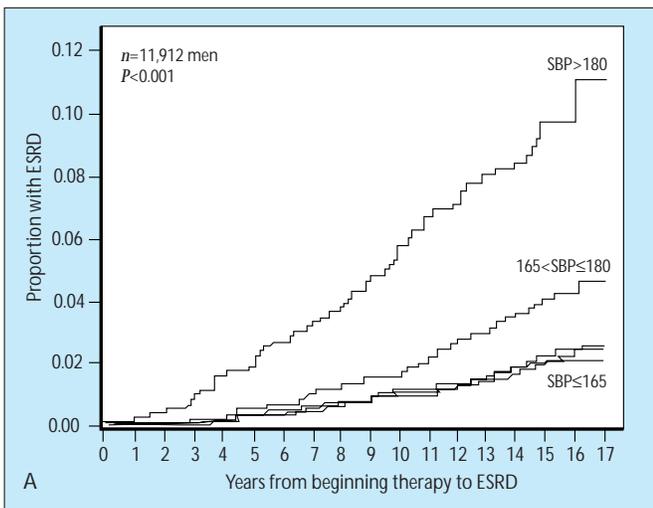


**FIGURE 2-20** (see Color Plate)

Hypertension accelerates the rate of progressive renal failure in patients with parenchymal renal disease. **A**, Photomicrograph of malignant phase hypertension. Regardless of the cause of renal disease, untreated hypertension leads to more rapid loss of remaining nephrons and decline in glomerular filtration rates. A striking example of pressure-related injury may be observed in patients with malignant phase hypertension. This image is an open biopsy specimen obtained from a patient with papilledema, an expanding aortic aneurysm, and

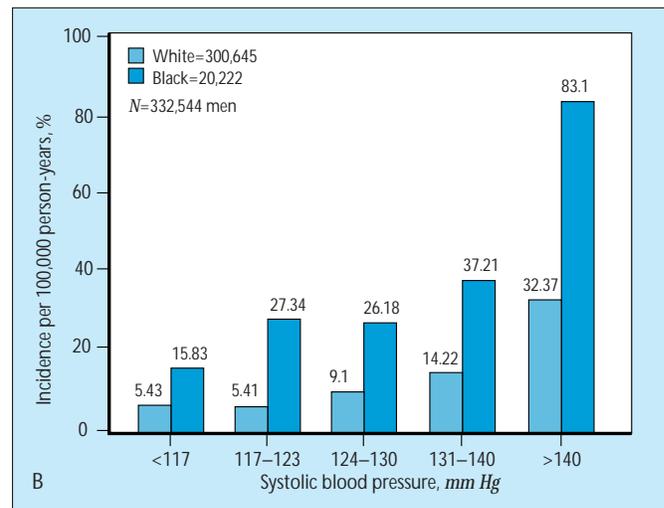


blood pressure level at approximately 240/130 mm Hg. The biopsy specimen shows the following features of malignant nephrosclerosis: these patients develop vascular and glomerular injury, which can progress to irreversible renal failure. Before the introduction of antihypertensive drug therapy, patients with malignant phase hypertension routinely proceeded to uremia. Effective antihypertensive therapy can slow or reverse this trend in some but not all patients. **B**, Progressive renal failure in malignant hypertension over 8 years.



**FIGURE 2-21**

Blood pressure levels and rates of end-stage renal disease (ESRD). **A**, Line graph showing Kaplan-Meier estimates of ESRD rates; 15-year follow-up. **B**, Age-adjusted 16-year incidence of all-cause ESRD in men in the Multiple Risk Factor Intervention Trial (MRFIT). Large-scale epidemiologic studies indicate a progressive increase in the risk for developing ESRD as a function of systolic blood pressure levels. Follow-up of nearly 12,000 male veterans in the United States established that systolic blood pressure above 165 mm Hg at the initial visit was predictive of progressively higher risk of ESRD over a 15-year



follow-up period [18]. Similarly, follow-up studies after 16 years of more than 300,000 men in MRFIT demonstrated a progressive increase in the risk for ESRD, most pronounced in blacks [19]. These data suggest that blood pressure levels predict future renal disease. However, it remains uncertain whether benign essential hypertension itself induces a primary renal lesion (hypertensive renal disease *nephrosclerosis*) or acts as a catalyst in patients with other primary renal disease, otherwise not detected at initial screening. SBP—systolic blood pressure. (Panel A from Perry and coworkers [18]; with permission.)

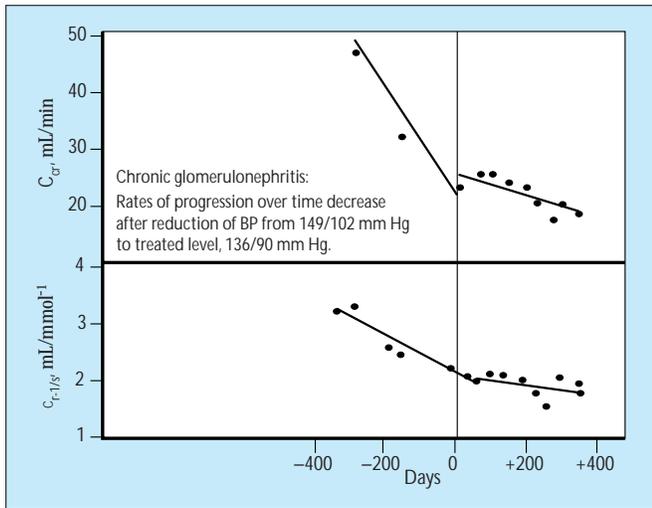


FIGURE 2-22

Rates of progression in glomerulonephritis. The decrease in glomerular filtration rate is illustrated. The rates of decline decreased considerably with administration of antihypertensive drug therapy. Among other mechanisms, the decrease in arterial pressure lowers transcapillary filtration pressures at the level of the glomerulus [20]. This effect is correlated with a reduction in proteinuria and slower development of both glomerulosclerosis and interstitial fibrosis. A distinctive feature of many glomerular diseases is the massive proteinuria and nephron loss associated with high single-nephron glomerular filtration, partially attributable to afferent arteriolar vasodilation. The appearance of worsening proteinuria ( $>3$  g/d) is related to progressive renal injury and development of renal failure. Reduction of arterial pressure can decrease urinary protein excretion and slow the progression of renal injury.  $C_{cr}$ —creatinine clearance rate;  $C_r^{-1/s}$ —reciprocal creatinine, expressed as  $1/\text{creatinine}$ . (From Bergstrom and coworkers [20]; with permission.)

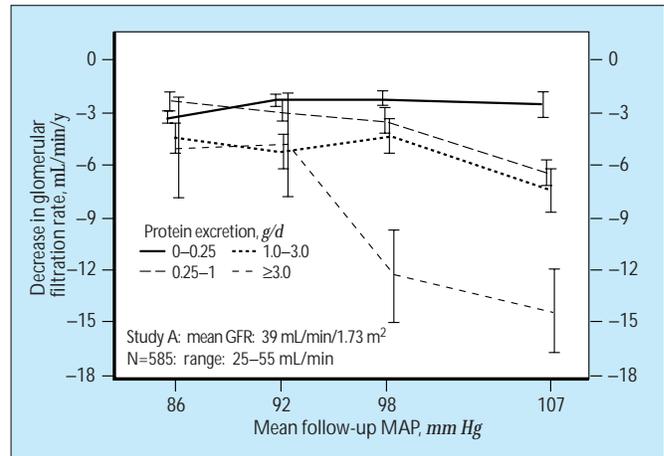


FIGURE 2-23

Blood pressure, proteinuria, and the rate of renal disease progression: results from the Modification of Diet in Renal Disease (MDRD) trial. Shown are rates of decrease of glomerular filtration rate (GFR) for patients enrolled in the MDRD trial, depending on level of achieved treated blood pressure during the trial [21]. A component of this trial included strict versus conventional blood pressure control. The term *strict* was defined as target mean arterial pressure (MAP) of under 92 mm Hg. The term *conventional* was defined as MAP of under 107 mm Hg. The rate of decline in GFR increased at higher levels of achieved MAP in patients with significant proteinuria ( $>3.0$  g/d). No such relationship was evident over the duration of this trial (mean, 2.2 years) for patients with less severe proteinuria. These data emphasize the importance of blood pressure in determining disease progression in patients with proteinuric nondiabetic renal disease. No distinction was made in this study regarding the relative benefits of specific antihypertensive agents. (From Peterson and coworkers [21]; with permission.)

## Effects of Antihypertensive Therapy on Renal Disease Progression

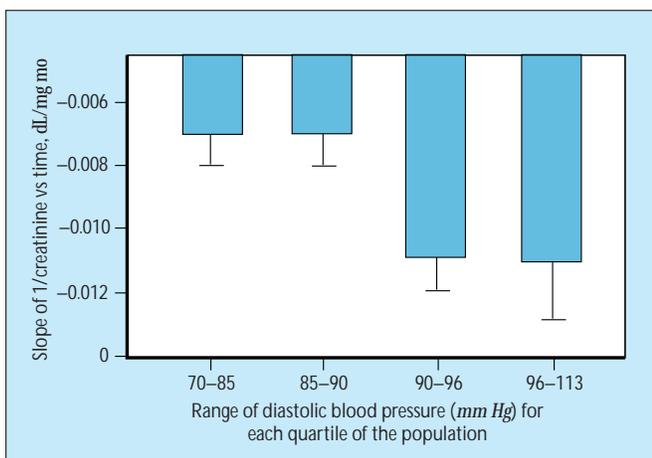


FIGURE 2-24

Blood pressure and rate of progressive renal failure. Rates of disease progression (defined as the slope of  $1/\text{creatinine}$ ) were determined in 86 patients who reached end-stage renal disease and dialytic therapy. The rates of progression were defined between mean creatinine levels of 3.8 mg/dL (start) and 11.4 mg/dL (end) over a mean duration of 33 months [22]. Brazy and coworkers [22] demonstrated that the slope of disease progression appeared to be related to the range of achieved diastolic blood pressure during this interval. Hence, these authors argue that more intensive antihypertensive therapy may delay the need for replacement therapy in patients with end-stage renal disease. As noted in the Modification of Diet in Renal Disease trial, such benefits are most apparent in patients with proteinuria over a shorter follow-up period. (From Brazy and coworkers [22]; with permission.)

### CLASSES OF ANTIHYPERTENSIVE AGENTS USED IN TREATMENT OF CHRONIC RENAL DISEASE

#### Diuretics:

Thiazide class  
Loop diuretics  
Potassium-sparing agents

#### Adrenergic inhibitors

Peripheral agents, *eg*, guanethidine  
Central  $\alpha$ -agonists, *eg*, clonidine, methyldopa, and guanfacine  
 $\alpha$ -Blocking agents, *eg*, doxazosin  
 $\beta$ -Blocking agents  
Combined  $\alpha$ - $\beta$  blocking agents, *eg*, labetalol

#### Vasodilators

Hydralazine  
Minoxidil

#### Classes of calcium-channel blocking agents

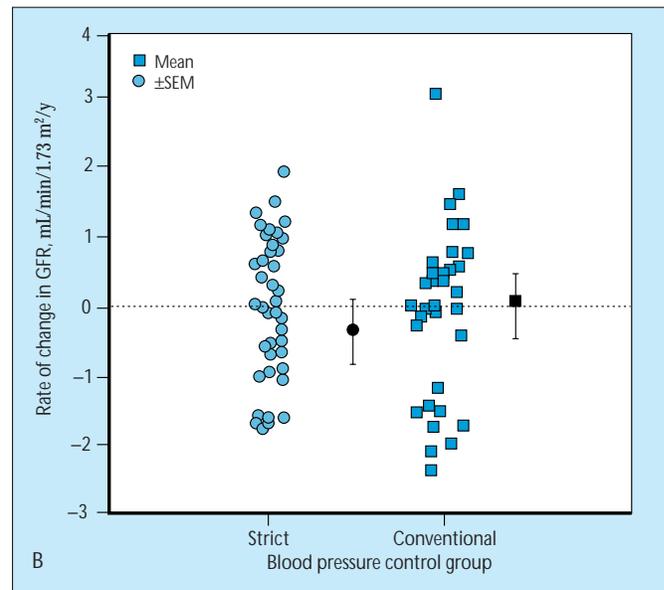
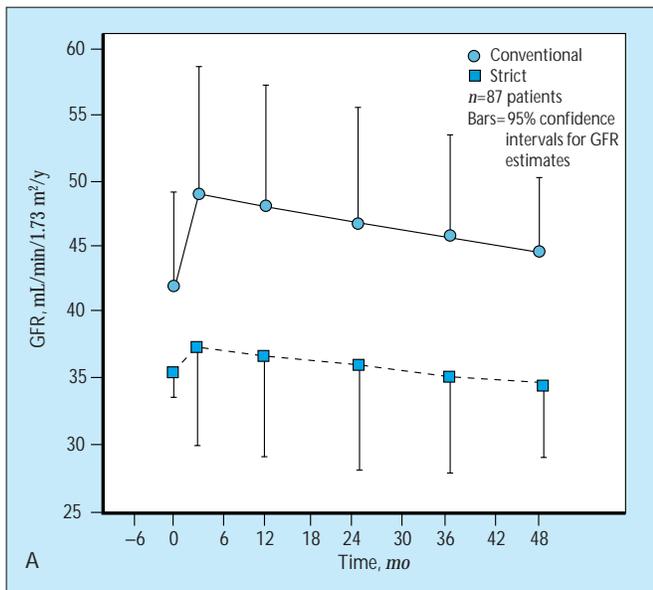
Verapamil  
Diltiazem  
Dihydropyridine

#### Angiotensin-converting enzyme inhibitors

#### Angiotensin receptor blockers

**FIGURE 2-25**

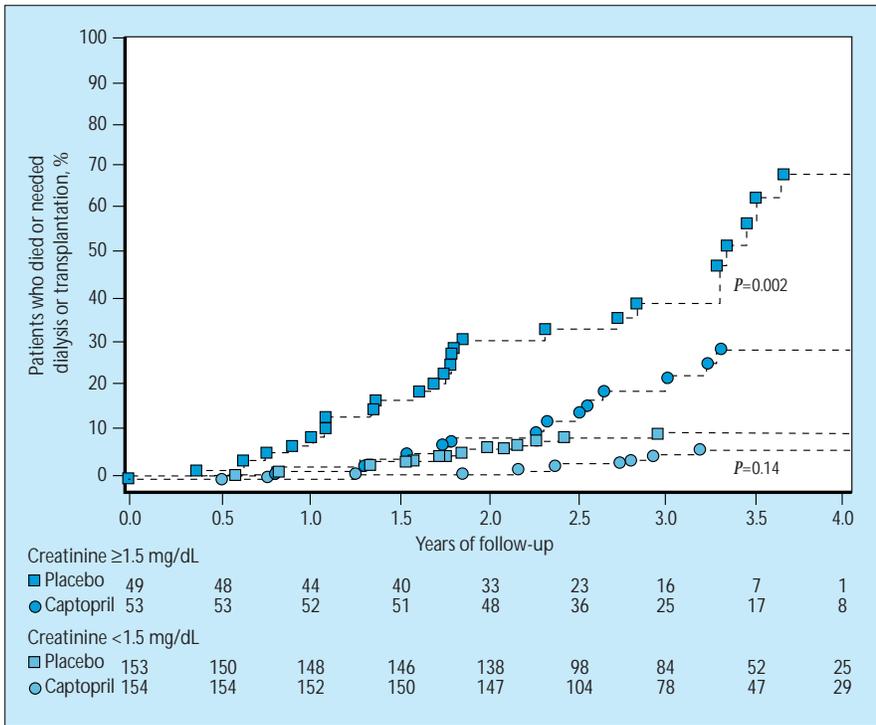
The current classification of agents applied for chronic treatment of hypertension as summarized in the report by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [23]. Attention must be given to drug accumulation and limitations of individual drug efficacy as glomerular filtration rates decrease in chronic renal disease. Potassium levels may increase during administration of potassium-sparing agents and medications that inhibit the renin-angiotensin system, especially in patients with impaired renal function [24].



**FIGURE 2-26**

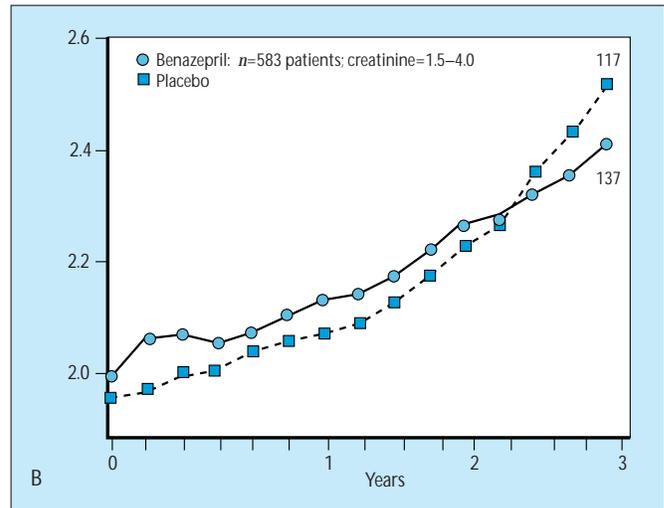
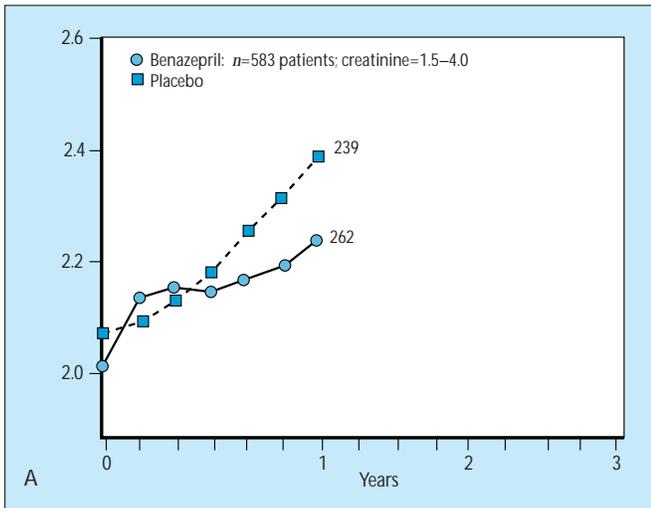
Strict blood pressure control and progression of hypertensive nephrosclerosis. Whether vigorous blood pressure reduction reduces progression of early parenchymal renal disease in blacks with *nephrosclerosis* is not yet certain. **A** and **B**, A randomized prospective trial comparing strict (*panel A*) blood pressure control (defined as diastolic blood pressure [DBP] <80 mm Hg) with conventional (*panel B*) levels of diastolic control between 85 and 95 mm Hg for more than 3 years could not identify a reduction in rates of disease progression [25]. Of patients, 68 of 87 were black. Rates of progression in

these patients were low. It should be emphasized that entry criteria excluded patients with diabetes and massive proteinuria. Initial studies from the African American Study of Kidney Disease trial confirm that biopsy findings in most patients with clinical features of hypertension were considered consistent with primary hypertensive disease [26]. Whether lower than normal levels of blood pressure in these patients will prevent progression to end-stage renal disease over longer time periods remains to be determined. GFR—glomerular filtration rate. (*From Toto and coworkers [25]; with permission.*)



**FIGURE 2-27**

Angiotensin-converting enzyme (ACE) inhibitors and chronic renal disease. Progression of type I diabetic nephropathy to renal failure was reduced in the ACE inhibitor arm of a trial comparing conventional antihypertensive therapy with a regimen containing the ACE inhibitor captopril. All patients in this trial had significant proteinuria (>500 mg/d). The most striking effect of the ACE inhibitor regimen was seen in patients with higher serum creatinine levels (>1.5 mg/dL) as shown in the top two lines. It should be noted that calcium channel blocking drugs were excluded from this trial and the ACE inhibitor arm had somewhat lower arterial pressures during treatment. These data offer support to the concept that ACE inhibition lowers intraglomerular pressures, reduces proteinuria, and delays the progression of diabetic nephropathy by more mechanisms than can be explained by pressure reduction alone. (Data from Lewis and coworkers [27].)



**FIGURE 2-28**

Angiotensin-converting enzyme (ACE) inhibition in nondiabetic renal disease. **A** and **B**. Shown here are serum creatinine levels from the 12-month (*panel A*) and 36-month (*panel B*) cohorts followed in the benazepril trial. In this trial, 583 patients were randomized to therapy with or without benazepril [28]. Slight reductions in the rates of increase in creatinine and of stop points in the ACE inhibitor group occurred; however, these reductions were modest. Whereas these

data support a role for ACE inhibition, the results are considerably less convincing than are those for diabetic nephropathy. These results argue that some groups may not experience major benefit from ACE inhibition over the short term. Preliminary reports from recent studies limited to patients with proteinuria suggest that rates of progression were substantially reduced by treatment with ramipril [29]. (From Maschio and coworkers [28]; with permission.)

### CONCLUSIONS AND RECOMMENDATIONS OF THE SIXTH REPORT OF THE JOINT NATIONAL COMMITTEE ON PREVENTION, DETECTION, EVALUATION AND TREATMENT OF HIGH BLOOD PRESSURE, 1997

1. Hypertension may result from renal disease that reduces functioning nephrons.
2. Evidence shows a clear relationship between high blood pressure and end-stage renal disease.
3. Blood pressure should be controlled to  $\leq 130/85$  mm Hg ( $< 125/75$  mm Hg) in patients with proteinuria in excess of 1 g/24 h.
4. Angiotensin-converting enzyme inhibitors work well to lower blood pressure and slow progression of renal failure.

#### FIGURE 2-29

Conclusions and Recommendations of the Sixth Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation and Treatment of High Blood, 1997 [23]. The JNC Committee has emphasized the importance of vigorous blood pressure control with any agents needed, rather than specific classes of medication. Angiotensin-converting enzyme inhibitors in proteinuric disease are the exception.

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