HYPERTENSION IN KIDNEY DISEASE

DEVELOPMENTS IN NEPHROLOGY

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Hypertension in Kidney Disease

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Preface

Blood pressure control is central to all bodily functions. There are many points in the multifaceted cybernetic system wherein hypertension may be produced.

Hypertension is a 'young' disorder whose existence has been known for less than a century. It is not only extremely prevalent among every population, but also deleterious to the health of mankind. The more we understand about hypertension's harmful effects, the more urgent is the need for its effective control.

The kidney is the central organ that controls vascular tone and body fluid volume; these two factors are dominant in determining arterial blood pressure. Hence, it is not surprising to find in hypertensive disorders that there are abnormalities in the kidneys, functional or anatomical, subtle or overt, that cause or are the consequence of hypertension.

The first suggestion that the kidney could cause hypertension was made in 1836, before arterial pressure could even be measured, by Richard Bright. He observed that cardiac hypertrophy was often present in patients who died of renal disease. It was, however, Goldblatt and his colleagues in 1934 who opened the modern era of experimental and clinical research in renal hypertension. Since then, although far from complete, enthusiastic and intensive research efforts have greatly improved our understanding of the nature of renal hypertension.

The past decade has seen an enormous amount of research devoted to specific approaches in the diagnosis and treatment of various forms of renal hypertension. The major purpose of this book is to update the clinical aspects of these important advances and to establish a rational approach to the management of patients with renal hypertension. The authors of this book are clinical scientists of the highest caliber, who have special expertise in their respective areas and who have made important contributions to those areas. The information contained herein is a result of over a decade of experience with contributions from many who have participated in the

activities of the Rogosin Kidney Center and the Hypertension and Cardiovascular Center of The New York Hospital-Cornell Medical Center. This experience provides the basis for the principles and judgements that we use to treat patients with renal hypertension.

As pioneers in the field of hypertension, however, we are painfully aware that we are still far from the most effective control. With better understanding of intra-renal hemodynamic alterations in renal hypertension, new diagnostic and therapeutic procedures, new antihypertensive drugs that are potent, specific in the mechanisms of action and capable of modulating intra-renal hemodynamics, we are just beginning a new era. We trust this book is not only helpful for those who care for the hypertensive patient, but also for those who do research in and study hypertension.

As with most endeavors, the major impetus behind this book was one person. It was conceived, organized and edited primarily by Dr Jhoong Cheigh. He is uniquely qualified for this task. Fifteen years ago he came to the Rogosin Kidney Center as a Fellow. Following his training he became a permanent member of the staff. For the past 10 years he has been in charge of the inpatient services of the Rogosin Kidney Center, The Ralph Bunche Pavilion. He has had first hand experience dealing with not only the medical problems discussed in this book, but also with the consultants that have rendered opinions on the solution to these problems.

Dr Cheigh's superb clinical judgement demonstrates a holistic approach finely tuned to dealing with the most important of the multiplicity of problems confronting patients with kidney disease. This judgement is clearly demonstrated in his choice of subjects and authors in *Hypertension in Kidney Disease.* As well as the book's having general appeal, it should have special meaning to the nephrologist confronting these problems daily.

January 16, 1986 Albert L. Rubin

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Hypertension in Renovascular Disease
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1. Hypertension in Kidney Disease

JHOONG SHIK CHEIGH, KURT H. STENZEL and
ALBERT L. RUBIN

Renal hypertension

Vascular tone and body fluid volume, the two dominant factors that determine arterial blood pressure, are controlled by the kidneys. Because of this, the kidneys play a central role in the regulation of normal arterial pressure and the development of hypertensive disorders [1–4]. Hypertension in kidney disease may be initiated by either increased cardiac output, increased total peripheral vascular resistance or both, but it is usually sustained by the latter [5–9]. The mechanism of the elevated total peripheral vascular resistance is multifactorial and complex. Although one mechanism, such as hyperreninemia or excessive sodium-fluid volume, may be operational to initiate or maintain hypertension, it is more often that multiple mechanisms, in varying degrees at different stages, contribute to sustain hypertension [1, 3, 10–15] (Table 1).

Table 1. Mechanisms of hypertension in kidney disease

1. Enchanced activities of vasopressor systems:
— Increased renin secretion; absolute or relative
— Increased aldosterone secretion; absolute or relative
— Accentuated sympathetic nerve activities
— Increased catecholamine secretion
— Enhanced vascular response to vasopressor hormones (angiotensin, catecholamines)
2. Increased extracellular fluid volume and sodium content:
— Increased cardiac output
— Activated whole body autoregulatory mechanisms
— Enhanced vascular response to vasopressor hormones (angiotensin, catecholamines)
3. Decreased release of renal vasopressor substances:
— Decreased release of prostaglandins
— Decreased release of kinins
— Decreased release of renal medullary vasodepressor lipids

In most patients with kidney disease, as kidney function progressively declines, hypertension supervenes as a result of the failure of regulatory and compensatory interactions among vasopressor components, vasodepressor components and sodium-fluid overload. Once established, renal hypertension rarely regresses spontaneously, and tends to be more severe and refractory to antihypertensive treatment than essential hypertension. In addition, the presence of both hypertension and renal failure sets off self-perpetuating mechanisms in the progression of renal failure, even if the original pathophysiological mechanism of the kidney disease is no longer operational. Renal hypertension, therefore, is not only a consequence of kidney disease but also the cause of progression and chronicity of the disease [16–20]. As early as 1941, Wilson and Byron [21] advanced the concept that hypertension produces vascular lesions, and these, by reducing the blood flow through the kidney, aggravate kidney function and hypertension. This vicious cycle leads to sustained hypertension and progressive renal destruction.

Hypertension of renal origin, including renovascular disease and obstructive uropathy, consitutes 5 to 10% of all causes of hypertension in the adult population [22–26]. Kidney disease is the most common cause of secondary hypertension. Small vessel diseases (collagen vascular diseases), glomerular diseases (glomerulonephritis, diabetic nephropathy), chronic tubulointerstitial diseases, end-stage kidney disease and kidney transplant are among the kidney diseases frequently (50–80%) associated with hypertension [27–30]. Cystic kidney diseases and acute tubulo-interstitial diseases, however, are rarely associated with hypertension. One notable exception is that polycystic kidney disease is not only frequently associated with hypertension (50–60%) but it also appears in the early stages of the disease [28, 31].

In a review of hypertension secondary to renal parenchymal disease, Johnson and Hunt [32] summarized the histopathological characteristics of hypertensive renal diseases. They stated, that those patients who have a tendency to develop severe hypertension before the appearance of renal failure have histopathologic lesions characterized by vascular narrowing and ischemia on the one hand or glomerular obstruction, scarring or obliteration on the other. Patients who tolerate early and moderate renal insufficiency without hypertension have neither of the above abnormalities to any major degree, and patients who have a tendency to develop hypotension are likely to have lesions which interfere with tubular function and are particularly prone to sodium wasting.

Effects of hypertension on the natural history of kidney disease

Experimental studies

Many studies demonstrate that the superimposition of hypertension in animals with kidney disease, regardless of experimental models (hypertension by DOCA and salt load, two kidney, one clip Goldblatt or spontaneously hypertensive rats; and kidney diseases induced by uninephrectomy, Heymann's nephritis, immune complex nephritis, nephrotoxic serum nephritis) markedly aggravate the progression of glomerular proliferation, glomerular sclerosis, azotemia and proteinuria [33–37]. Hypertension unquestionably affects the kidneys, normal or diseased, adversely in both structure and function. The mechanisms by which hypertension produces the adverse effects on the kidney, however, remain to be elucidated. Recent studies utilizing micropuncture techniques in experimental hypertension seems to unfold underlying mechanisms.

In 1938, Wilson and Pickering [38] were able to produce, in one kidney, one clip Goldblatt hypertensive rabbits, necrotizing and proliferative arterial lesions that were histologically identical with those of malignant hypertension. They suggested that a greatly raised intra-arterial pressure was directly responsible for the development of occlusive arterial lesions. In 1941, Wilson and Byron [21] observed the development of occlusive vascular lesions in the intrarenal arteries of the unclamped kidney in two kidney, one clip Goldblatt hypertension. They proposed the concept of 'vicious cycle in Bright's disease', that is hypertension produces vascular lesions, and these, by reducing blood flow through the kidneys, aggravate hypertension and kidney disease. This vicious cycle leads to sustained hypertension and progressive renal destruction. Since then, it is usually felt that the glomerular changes seen in hypertension are the result of preceeding arterial and arteriolar changes and that the lesions in the glomeruli are the consequence of renal ischemia (ischemic nephropathy) [39, 40]. Renal ischemia in hypertension was thought to be produced by either arteriolar narrowing [39, 40], functional or anatomical, or embolization of materials from damaged vessels supplying the glomeruli [41].

In 1968, in a study of steroid-induced hypertension in uninephrectomized rats, Hill and Heptinstall [42] first suggested that failure of adequate arteriolar constriction, rather than excessive narrowing that would expose 'unprotected' glomeruli to systemic hypertension, was responsible for the hypertensive glomerular lesions. In this experiment they recognized that one of the earliest and most dramatic alterations in intrarenal vasculatures was marked dilatation of the afferent arterioles. This dilatation of the afferent arterioles permits the glomerulus and the postglomerular vasculature to be perfused at increased pressure. The following year, in a study of DOCA-salt

hypertension in the uninephrectomized rats, Still and Dinneson [43] observed endothelial swellings, increase in mesangial matrix, epithelial cell changes and deposition of fibrin in the subendothelial areas of the glomerular capillaries which eventually led to sclerosis of the tufts. These glomerular lesions were present independently from either the presence or absence of arteriolar lesions. They postulated that hypertension affects the glomerular capillaries in the same direct manner that affects other parts of the arterial tree. Glomerular lesions are not necessarily related to ischemia secondary to arteriolar changes. This new concept, afferent arteriolar dilatation and consequent glomerular hypertension and hyperfusion leading to glomerular lesions as the mechanisms of hypertensive nephropathy evolved on the basis of morphologic observations. This hypothesis was subsequently confirmed by single nephron hemodynamic and function studies utilizing micropuncture techniques.

In a study of one kidney, post-salt hypertension in rats, Azar et al. [44] showed glomerular proliferation and sclerosis in association with reduced afferent arteriolar resistance and consequent increases in glomerular transcapillary hydraulic pressure, blood flow and filtration rate. In a subsequent study with two kidney, post-salt hypertension in Dahl's salt sensitive rats that had a genetically reduced number of functioning nephrons, an identical observation was made [45]. These investigators suggested that an adaptive decrease in afferent arteriolar resistance to reduced functioning nephron mass overrode the ability of arterioles to increase their resistance in response to hypertension. On the other hand, in another experiment with spontaneously hypertensive Kyoto rats that had normal kidney function, Azar et al. [46] showed that an increased afferent arteriolar resistance, thus maintaining normal intraglomerular capillary pressure and single nephron GFR, was associated with minimal glomerular changes. Since Kyoto rats' renal hemodynamic response to hypertension resembles that of most essential hypertensive patients, they postulated that relative vasoconstriction of afferent arterioles might help prevent glomerular apparatus from hypertensive damages in benign essential hypertension.

More recently, Dworkin et al. [34] demonstrated that rats made hypertensive by uninephrectomy, combined with DOC and high salt intake exhibited striking structural abnormalities in their glomeruli and increased urinary protein excretion, both in association with augmented glomerular capillary plasma flow rates and transcapillary hydraulic pressure gradients. Interestingly, a low protein diet prevented these increments in glomerular capillary pressures and flows, and protected DOC-salt rats from developing proteinuria and glomerular injuries. These investigators also suggested that glomerular capillary hypertension in the presence of augmented capillary perfusion predisposes glomerular injury in hypertensive rats.

In a subsequent study utilizing identical rat model, Dworkin et al. [47]

examined whether normalization of arterial blood pressure might ameliorate glomerular capillary hypertension and injury. In this experiment, despite normalization of arterial pressure with antihypertensive treatment, intrarenal hypertension persisted, and lower pressure failed to protect glomerular apparatus from hemodynamically mediated injury. This study concurs with the hypothesis that afferent arteriolar dilation as an adaptive response to severely reduced functional renal mass invokes elevations in glomerular pressure and flow that constitutes a general mechanism for eventual glomerular destruction in a wide variety of renal diseases [45, 48, 49]. This study, therefore, suggests that once a functional renal mass is critically reduced, normalization of arterial pressure alone may not be enough to preserve the integrity of the remaining glomeruli unless their hyperperfusion is prevented by concomitant reduction in glomerular solute load (low protein diet) [34].

In summary, hypertension damages the glomerular apparatus directly by increasing glomerular capillary hydraulic pressure, perfusion volume and filtration rate. Renal hemodynamic responses to systemic hypertension include adaptive vasoconstriction of afferent arteriolar resistance, thus preventing glomerular apparatus from hemodynamically mediated injuries. If hypertension is so severe that it overcomes the increased afferent arteriolar resistance or if the afferent arteriolar resistance is reduced as an adaptive response to critical reduction of functional mass, direct transmission of high systemic pressure produces increased glomerular hydraulic pressure, perfusion and filtration rate. These hemodynamic overloads lead to glomerular proliferation, increased mesangial matrix, glomerular sclerosis, azotemia and proteinuria, and that eventually set off self-perpetuating mechanisms in the progression of renal disease. In severe hypertension, such as malignant hypertension, occlusive vascular disease also produces superimposed ischemic nephropathy, in addition to hemodynamically mediated glomerular injuries.

Clinical studies

Hypertension is thought to be one of the most important risk factors that lead to the progression of kidney disease [17, 18]. Despite ample documentation of this notion in experimental studies, there are very few clinical data to support it. In clinical studies showing accelerated progression of kidney disease in patients with hypertension, it is unclear whether severe hypertension is simply a marker of more advanced kidney disease, thus associated with a poor prognosis, or if hypertension is an independent risk factor and perpetuates the progression of kidney disease.

Urakabe et al. [50, 51] reported a considerably faster rate of decline in

kidney function in hypertensives as compared to normotensive patients with chronic glomerulonephritis. They showed that the presence of hypertension was clearly associated with an unfavorable prognosis for the preservation of kidney function at any observation period. Mogensen [52] made a similar observation in diabetic patients with nephropathy in whom the declining rate of GFR (ml/min/month) was proportional to the level of diastolic blood pressure. Mogensen et al. [53], in another study, observed those patients who progressed to overt diabetic nephropathy had higher blood pressure and elevated GFR at the initial examination than did those in whom nephropathy did not develop. They suggested that hypertension, as well as glomerular hyperfiltration, contributes to the development and progression of diabetic nephropathy. In a long-term follow-up study of 79 patients with chronic pyelonephritis, Bengtsson [54] noted that the progression of renal impairment was significantly more rapid in patients who were hypertensive; annual reduction of GFR of those who had severe hypertension (Keith-Wagener's grade 111-1V retinopathy) was 6.2 ml/min/year as compared with 1.4 ml/min/year for those who had either milder hypertension or normotension. In addition to these studies, the association between hypertension and a faster rate of progression to renal failure has been observed in other kidney diseases [20, 55].

On the other hand, there are many studies that show the natural course of a given kidney disease in patients with hypertension is not different from that of normotensives [30, 56–59]. If a difference exists, it is not because of hypertension *per se,* but because hypertension is an independent clinical manifestation of more severe underlying disease that is usually associated with a poor prognosis [30, 57, 58]. For example the incidence and severity of hypertension in lupus nephritis increases progressively from patients with focal glomerular lesions (class I-II; 10%) to those with diffuse glomerular lesions (class III; 30%; class IV; 40%) [57, 58]. In these studies, it appears that hypertension is certainly a consequence of a more diffuse and advanced lupus nephritis, but it is unclear how much hypertension contributes independently to the progression of the disease.

In summary, animal experiments indicate that hypertension probably perpetuates the progression of kidney disease. Clinical studies supporting this notion are, however, too few and equivocal. If long-term, well controlled studies could be performed, it would probably be evident that hypertension is an important risk factor for the progression of any kidney disease.

The effects of treatment of hypertension on the natural history of kidney disease

Since hypertension accelerates the progression of kidney disease, it would be expected that normalization of blood pressure with antihypertensive mea-

sures should deter or prevent deterioration in kidney function. It has been repeatedly demonstrated that reduction of blood pressure in patients with hypertension significantly decreases the incidence of cardiac and cerebrovascular complications [60–65]. However, only a few studies have unequivocally documented that adequate control of hypertension, in either essential or renal types, may help prevent or deter kidney disease from progressive failure. Despite this limited clinical data, some authorities state that control of hypertension is the most important means of preventing chronic renal failure.

Malignant hypertension

The beneficial effects of antihypertensive treatment on the preservation of kidney function has been most adequately studied in malignant hypertension [66–72]. In 1958, in a study of 64 patients with moderate to severe degrees of essential hypertension and azotemia, Moyer et al. [66] first reported that effective reduction of blood pressure arrested the deterioration of kidney function and decreased the mortality rate.

In 1967, in a study of 20 patients with malignant hypertension and azotemia (BUN > 50 mg/dl), Woods and Blythe [67] reported that the reduction of blood pressure in malignant hypertension does not necessarily result in deterioration of renal function and may improve patient survival. In their study, 11 patients (55%) survived beyond a year from the onset, and most of these had either stable or improved kidney function on subsequent follow-up. Mroczek et al. [68] made a similar observation in a study of 25 patients with malignant hypertension and azotemia. They treated these patients with diazoxide and furosemide to maintain diastolic pressure less than 110 mm Hg and urinary output more than 2000 ml/day for 2 weeks. During this period, although cardiovascular status had improved, there was a 19% average increase in BUN and 17% average increase in serum creatinine values. Three months later, however, maintenance of reduced blood pressure was associated with average reduction of 24 mg/dl in BUN and of 2.8 mg/dl in serum creatinine below the control values. Twenty-six months later, in the 16 surviving patients, average concentration of BUN was 22 mg/dl and serum creatinine was 1.8 mg/dl. Luft et al. [72] even reported a sufficient recovery of renal function along with the control of hypertension in three patients who had malignant hypertension and renal failure requiring hemodialysis for a prolonged period of time. Pohl et al. [70] also noted a significant improvement of kidney function in 35 patients with severe essential hypertension when their blood pressure was maintained within normal ranges and their initial creatinine clearance exceeded 8 ml/min.

Before the introduction of potent antihypertensive drugs, malignant hy-

pertension was nearly always a rapidly fatal disease [73, 74]. New clinical studies, however, clearly show that reduction of blood pressure for an extended period of time in patients with malignant hypertension not only increases patient survival rate but also may improve kidney function. Current clinical experience dictates that blood pressure of patients with malignant hypertension, regardless of the level of kidney function at onset and its response to changes in blood pressure, should be reduced and maintained within normal ranges with antihypertensive agents.

The goal of treatment for malignant hypertension should be sustained and stable maintenance of blood pressure within normal ranges. How to reduce blood pressure, with what drugs and by what mechanisms is probably not as important as a prompt and absolute reduction of blood pressure. Since many potent antihypertensive drugs are currently available, bilateral nephrectomy should no longer be considered as an emergency measure to control hypertension [75].

Diabetic nephropathy

The treatment of hypertension in patients with diabetic nephropathy has also been shown to reduce proteinuria and to slow the decline in kidney function [52, 76, 77]. Parving et al. [77] prospectively studied the effects of early aggressive antihypertensive treatment on kidney function in ten insulin dependent diabetic patients. During the mean pretreatment period of 29 months the GFR decreased and the urinary albumin excretion and arterial blood pressure rose significantly. During the subsequent 39-month-period of antihypertensive treatment, urinary albumin excretion decreased from 977 μg/min to 433 μg/min and GFR from 80 to 62 ml/min/1.73 m^2. Although the GFR continued to decrease during the treatment period, the rate of decline in GFR reduced from 0.9 ml/min/month before treatment to 0.3 ml/min/month during treatment. Mogensen [76] also made an identical observation in a small group of patients with diabetic nephropathy; the rate of decline in GFR decreasing from 1.2 ml/min/month before treatment to 0.4 ml/min/month after treatment. These studies suggest that control of hypertension may slow the progression of diabetic nephropathy.

Renovascular hypertension

The merits of any therapy, medical or surgical, in the management of renovascular hypertension are traditionally evaluated by its success rate in reducing blood pressure and its attendant risks. It is only in recent years that attention has been paid to the long-term effects of renovascular disease on renal perfusion and function.

Atherosclerosis, the most common cause of renovascular disease, is a systemic disease and patients with atherosclerotic renovascular disease often have the same process affecting arteries of other vital organs [78]. Adequate control of hypertension with antihypertensive agents may improve the prognosis for patient survival but that may not obviate the progression of ischemic injury to vital organs including the kidneys [78, 79]. Thus, it is evident that therapeutic objectives for patients with renovascular hypertension should include not only cure or improved control of hypertension but also preservation of renal tissue and function. Management of renovascular hypertension with antihypertensive agents alone has not been able to meet these objectives for two main reasons. First, renovascular disease, both atherosclerotic and fibromuscular dysplasia, is progressive and can cause acute [80, 81] or chronic renal failure (ischemic nephropathy) [78, 79, 82]. Second, reduction of blood pressure with antihypertensive agents, by decreasing driving pressure across the stenosis, may further compromise perfusion of kidneys and thus accelerate the progression of ischemic nephropathy [79, 83, 84].

The progressive nature of renovascular disease, with or without antihypertensive treatment has been well documented [78, 79, 82]. Dean and colleagues [79] reported a study of serial renal function and angiographic evaluations on 41 patients with atherosclerotic renovascular disease who had been randomly selected for non-operative treatment. During a mean period of 44 months of follow-up, serum creatinine levels increased more than 25% of controls in 19 patients (46%); GFR decreased more than 25% of controls in 12 patients (29%); kidney length decreased more than 10% (equivalent to more than 30% of kidney mass) of controls in 14 patients (37%); and a significant stenosis progressed to total occlusion in 4 patients (12%). These decreases in kidney mass and function developed despite 88% of the patients having control of hypertension within acceptable ranges. Schreiber et al. [82] in a study of 169 patients with renovascular hypertension who had serial arteriography over a mean period of 35 months, also demonstrated the progressiveness of the disease. This study included 85 patients with atherosclerotic renovascular disease, 75 with fibromuscular dysplasia and 5 with both of them. During the follow-up period, 44% of former, 33% of latter and 55% of the patients with both lesions had progression of the occlusive disease. Wollenweber and colleagues [78] not only observed the worsening of existing lesions but also a development of new lesions in the previously intact renal arteries in 10% of their patients. The progression of the lesions were associated with impairment of renal function and renal mass.

In experimental studies, the significance of stenosis is determined by the area ratio between the stenosed and unstenosed portions of the vessel and the velocity of the flow rate [85]. The higher the flow rate, the less constric-

tion of the vessel is required to be significant. In a lower flow system, however, the fall in flow rate and pressure in the post-stenotic area is more precipitous than that in a high-flow system as long as the degree of stenosis is beyond the critical point. It is not unexpected, therefore, that the reduction of blood pressure with antihypertensive agents, will impair renal function in patients with renovascular hypertension. This is well demonstrated in a clinical study by Textor and colleagues [83]. In a study of 16 patients with either unilateral or bilateral renovascular disease, they measured ERPF and GFR during graded reduction of blood pressure with nitroprusside. They observed a marked decrease in ERPF and GFR in patients with bilateral renal artery stenosis as blood pressure was reduced. A repeated study conducted after the revascularization procedure no longer decreased ERPF and GFR during blood pressure reduction. Thus, it is clear that renal artery stenosis leads to pressure dependent reduction in renal function that is reversible upon restoration of renal perfusion.

In contrast to medical treatment alone, relief of stenosis by either a surgical procedure or percutaneous transluminal angioplasty has not only cured or improved hypertension, but also improved renal function in a substantial number of patients with unilateral, bilateral or transplanted kidney renovascular disease [78, 84, 86–89]. The improvement in both hypertension and renal function has been observed even in patients with acute or chronic total occlusion of renal artery and nonfunctioning kidney [80, 81, 90]. These studies suggest that patients with medically treated renovascular hypertension with inadequate control of blood pressure or evidence of decreasing renal perfusion require renal artery surgery or angioplasty whenever feasible.

In many patients, the presence of refractory hypertension, with or without renal insufficiency, warrants full investigation for renovascular disease, irrespective of the age of the patient or the duration of hypertension. The demonstration of significant renovascular disease should prompt serious consideration of reparative intervention. With the introduction in recent years of innovative diagnostic procedures and therapeutic interventions, such as digital enhanced angiography [91] and percutaneous transluminal angioplasty [92], the disease will be more readily identified and relieved with fewer risks. Even if the lesion is successfully repaired, however, these patients should be monitored indefinitely for the progression of the disease.

Progressive systemic sclerosis (scleroderma)

Scleroderma kidney disease presents with proteinuria, azotemia and hypertension. The onset of these features is generally thought to indicate a poor prognosis. Medsgar et al. [93], in a study of 309 patients with scleroderma,

found that all 16 patients with renal involvement died within several months. Acceleration of hypertension to a malignant phase and progression of renal disease to uremia usually preceeded death within a few months [94]. Bilateral nephrectomy and maintenance hemiodialysis had been recommended to alter the otherwise fatal course of scleroderma kidney disease [94–96].

As in malignant hypertension, the prognosis of patients with scleroderma kidney disease seems to improve with aggressive antihypertensive treatment. There is, however, no data as to how over all prognoses of these patients has improved. There are several anecdotal case reports describing prolonged survival of the patient with improved kidney function as severe hypertension is controlled [97–102]. These reports suggest that scleroderma kidney disease, with uremia and accelerated or malignant phase hypertension, is a reversible process, at least partially, with an appropriate medical treatment.

The general principle of treatment of malignant hypertension can be applied to the management of scleroderma renal crisis. The notion that systemic vascular and renal crises might have been mediated by renin-angiotensin system has not been proven. Antihypertensive measurements that do not block effects of renin-angiotensin system have also reversed the crisis [99]. Since kidney function may improve even many months of severe renal failure, bilateral nephrectomy as a means to control the crisis should be reserved for very unusual circumstances [97].

Other kidney diseases

Chronic glomerulonephritis and tubulo-interstitial nephritis are the two most common kidney diseases, and together they constitute two thirds of all kidney diseases that lead to end-stage renal disease. In addition, they are among the kidney diseases that are most often associated with hypertension. In view of these facts, it is surprising to note that few studies have ever been conducted on the effect of treatment of hypertension on the natural history of the diseases. Cameron [103] stated that we assume that hypertension has adverse effects on the natural history of patients with glomerulonephritis and therefore, we treat all of them for hypertension, but we do not have any data on how the treatment alters the natural history of the disease.

Pohl et al. [70] in a study of eight patients with chronic pyelonephritis and nine with chronic glomerulonephritis, observed the influence of effective blood pressure control upon renal function. During a period of 6 months or more without effective antihypertensive treatment, mean values of creatinine clearance in both groups of patients declined considerably. In the subsequent 6 months, this decrease improved, albeit not statistically significant,

in pyelonephritis patients with effective antihypertensive treatment, while the clearance of patients with glomerulonephritis continued to decline. They concluded that control of hypertension in patients with primary progressive renal disease did not help preserve renal function.

To determine long-term effects of hypertension on kidney function and survival, and the consequence of therapeutic intervention, we studied the clinical course of 132 kidney transplant recipients, whose graft functioned more than 2 years [30]. This study disclosed that hypertensive patients had a significantly lower graft function and graft survival rate than normotensive patients. Hypertensive patients maintaining normal blood pressure with antihypertensive agents, however, did not improve graft function or survival to that of normotensive patients, at least in a mean follow-up period of 68 months. These results concur with that of Pohl et al. [70]. Both studies, however, do not exclude the possibility that the treatment might have deterred the rate of deterioration. Since most primary kidney diseases progress at a slow rate via many independent mechanisms, including hypertension, it seems difficult to discern the beneficial effects of antihypertensive treatment on the preservation of kidney function as long as other injurious mechanisms continue to be operational.

In experimental hypertension produced by nephrotoxic serum nephritis in uninephrectomized rats, treatment of hypertension ameliorated the clinical and histologic manifestations of the nephritis [104]. This effect was attributed to reduced glomerular hydraulic stress. In most experimental hypertension, irrespective of experimental models (spontaneous, one-clip two kidneys, DOC-salt, uninephrectomy, partial renal infarct, immune complex nephritis), control of hypertension with antihypertensive agents has not been shown to preserve either renal function or structure [47, 105–107]. Deterioration of kidney function despite effective control of hypertension might be attributable to glomerular capillary hypertension and hyperperfusion in response to critical reduction of renal tissue. Once the functional renal mass is critically reduced, reduction of glomerular solute load through decreasing protein intake, in addition to concomitant control of hypertension, seems to be a prerequisite in preventing the progression of the disease and preserving the function [34, 108].

More recently, however, Meyer et al. [109] have shown that the use of enlaprril, a converting enzyme inhibitor, in hypertensive rats that have undergone extensive renal ablation, not only controlled hypertension but also normalized the glomerular capillary pressure without reducing the glomerular filtration rate. Maintenance of normal capillary pressure markedly reduced the development of proteinuria and sclerotic lesions in remnant glomeruli. They suggested that antihypertensive therapy directed at reducing the glomerular capillary pressure could retard the progressive loss of renal function in patients with chronic renal failure.

In summary, effective control of hypertension in malignant hypertension, diabetic nephropathy and scleroderma kidney disease clearly helps deter the progression of the disease and preserve function. In renovascular hypertension, however, control of hypertension with antihypertensive therapy alone may not be adequate, and repair of the occlusive lesions should be considered. This approach may not only cure hypertension but also preserve renal function.

There are no clinical data that indicate that control of hypertension favorably alters the natural history of such primary kidney diseases as chronic glomerulonephritis and chronic tubulo-interstitial disease. Experimental studies suggest that once kidney disease is critically advanced, a combined approach with control of hypertension and reduction of glomerular solute load, by low protein intake together might help to deter progression of the disease and preserve renal function. Modulation of intrarenal hemodynamics by the use of new antihypertensive agents, such as enlaprril, to prevent glomerular capillary hypertension, also seems to be a promising approach, but awaits clinical trials.

Irrespective of the nature and progress of the kidney disease, all renal patients with hypertension should be treated with antihypertensive agents to maintain blood pressure within normal ranges, thus preventing extrarenal hypertensive vascular complications. Attention should always be paid to avoid, whenever possible, those antihypertensive agents that adversely effect kidney function [110].

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2. The Kidney in Hypertension: Pathology and Pathogenesis

MYRON SUSIN, JANET MOURADIAN and BARRY WILKES

Introduction

The detrimental effects of high blood pressure were first suggested in the second century B.C., but the important role of the kidney as a mediator of hypertension has only recently been appreciated. The kidneys play many roles in the pathogenesis of hypertensive vascular disease. The kidneys are an important target for end-organ damage resulting from hypertension. This damage can be severe, ultimately resulting in renal dysfunction. In addition, the kidneys may contribute to the pathogenesis of hypertension by playing a central role in modulating hormone systems which regulate blood pressure. The kidney may contribute to blood pressure elevations by either producing an excess of vasoconstrictor substances (i.e., activation of the renin-angiotensin system) or by the underproduction of depressor substances (i.e., prostaglandins).

This chapter reviews the role of the kidney in the pathogenesis of hypertension. The morphologic changes in the kidney in hypertension are described and the contribution of animal models to the understanding of the pathogenesis of hypertension is discussed.

Morphology of the kidney in hypertension in man

Clinical features

There is a wide spectrum of clinical presentations of hypertension. The overwhelming majority of patients with hypertension have a protracted course with mild elevations of blood pressure over a period of decades. The condition has been incorrectly called *benign hypertension* because of the erroneous notion that low levels of blood pressure elevation are not detrimental. At the other end of the spectrum, hypertension may present as a

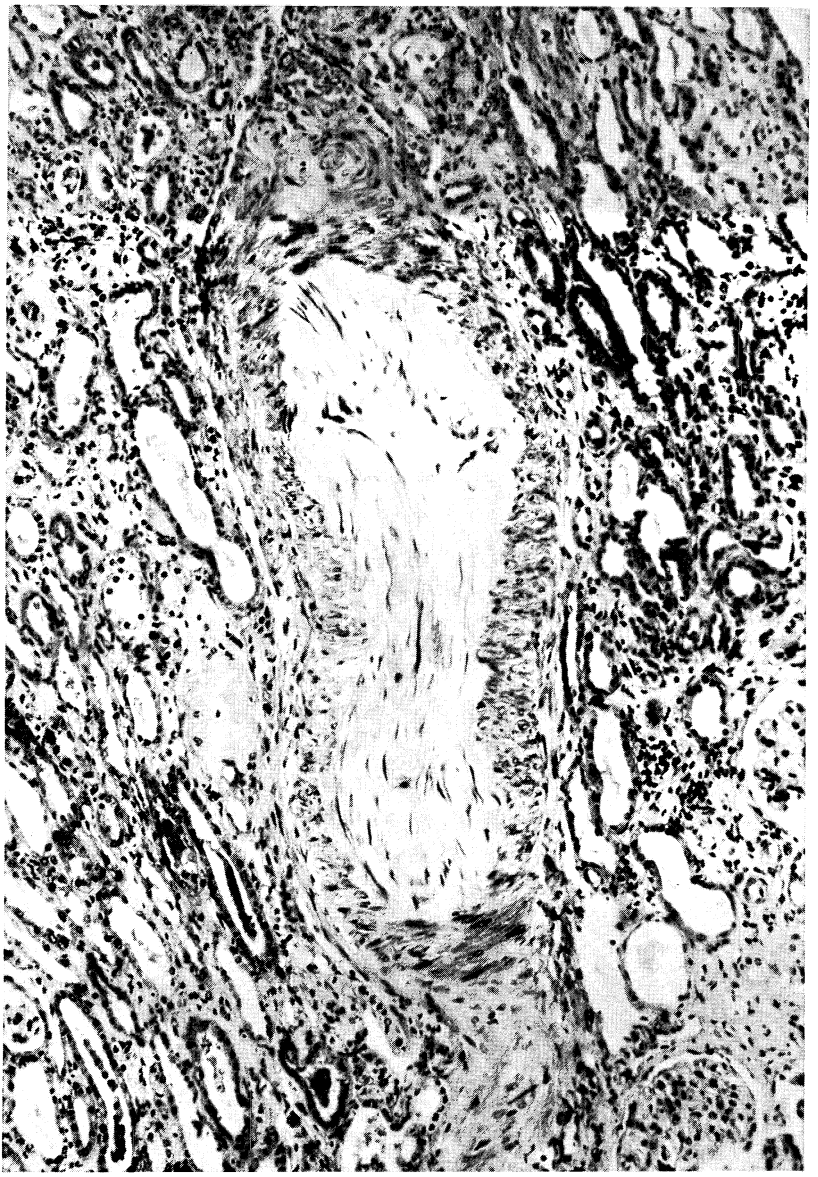


Figure 1. Benign hypertension. The vascular lumen of this small artery is narrowed by fibromuscular intimal thickening. Hematoxylin and eosin ×200.

fulminant crisis with marked elevation of blood pressure, papilledema, retinal hemorrhages and exudates, renal insufficiency and mental changes. This condition, *malignant hypertension,* presents as a dramatic medical crisis requiring immediate intervention to control the elevated blood pressure and its complications. In the following pages, the morphology of benign and malignant hypertension will be reviewed.

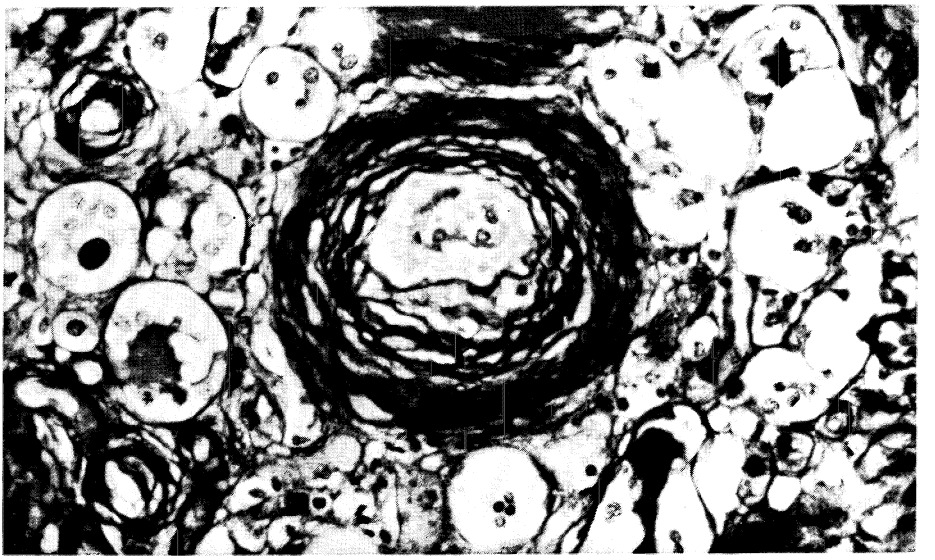


Figure 2. Benign hypertension. Elastosis. Small artery showing reduplication of internal elastic lumina. Elastic Van Gieson × 500.

Benign hypertension

Gross pathologic features

Benign nephrosclerosis is one of the most common forms of renal diseases and is seen at autopsy in the majority of patients over 65 years of age. Grossly, the kidneys usually show only mild to moderate contraction. The subcapsular cortical surface exhibits a fine granulairity.

Histological features

The lumens of arcuate and interlobular arteries display eccentric narrowing by fibromuscular intimal proliferation frequently associated with medial hypertrophy (Figure 1). Special stains may disclose duplication of the internal elastic lamina referred to as elastosis (Figure 2). The lumens of afferent arterioles are narrowed and walls thickened by eosinophilic, homogeneous, and amorphous hyaline deposits. This is a characteristic feature of benign nephrosclerosis and is usually associated with moderate and gradual elevation of blood pressure [1]. These deposits are usually diffuse and occupy the entire wall of the vessel but on occasion may affect only a segment of the arteriole (Figure 3).

By electron microscopy hyaline consists of amorphous granular electron dense material localized to the subintimal space and frequently replacing much of the media as well. It may be admixed with cytoplasmic particles and basement membrane material (Figure 4). The nature and origin of hyal-

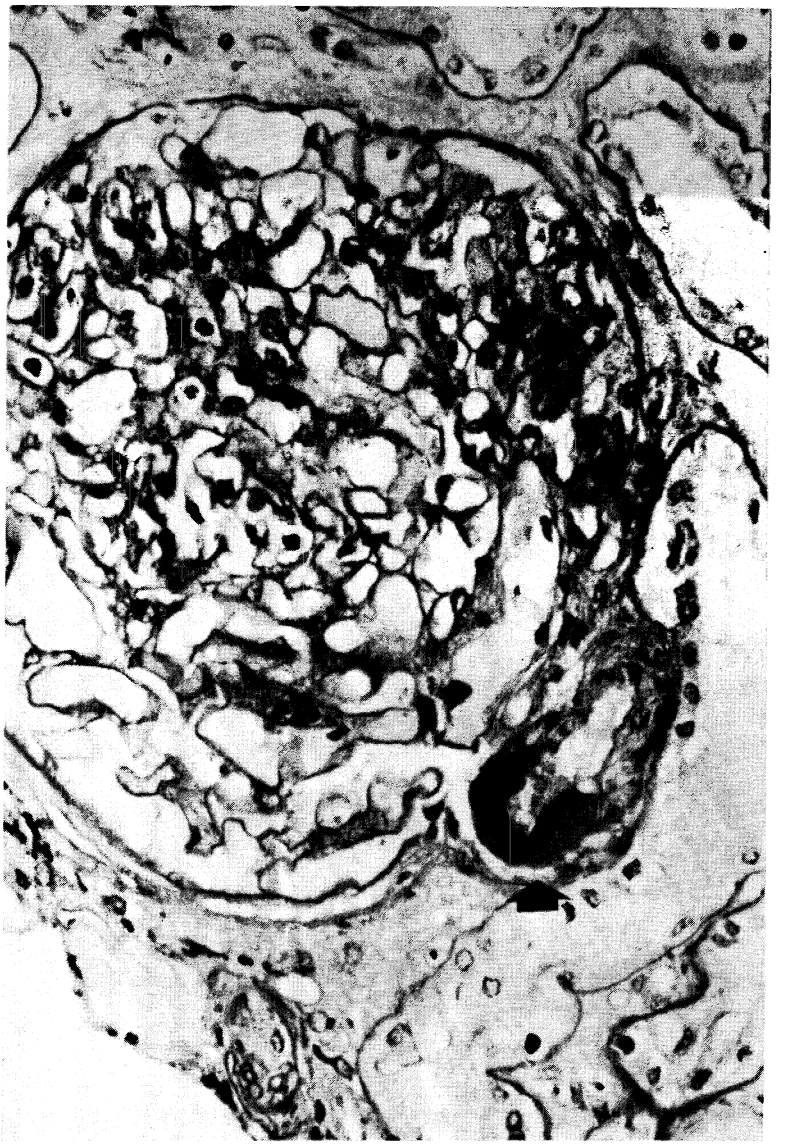


Figure 3. Benign hypertension. Arteriole showing segmental hyaline deposit (arrow). Periodic acid-Schiff × 500.

ine remain undetermined. Some investigators have proposed that this material is derived from plasma proteins [2]. Others believe that these deposits are the result of increased synthesis and coalescence of basement membrane material [1, 3].

Immunofluorescence studies may demonstrate the presence of immunoglobulin and complement components at these sites, probably reflecting the enhanced vascular permeability contributing to these changes [4].

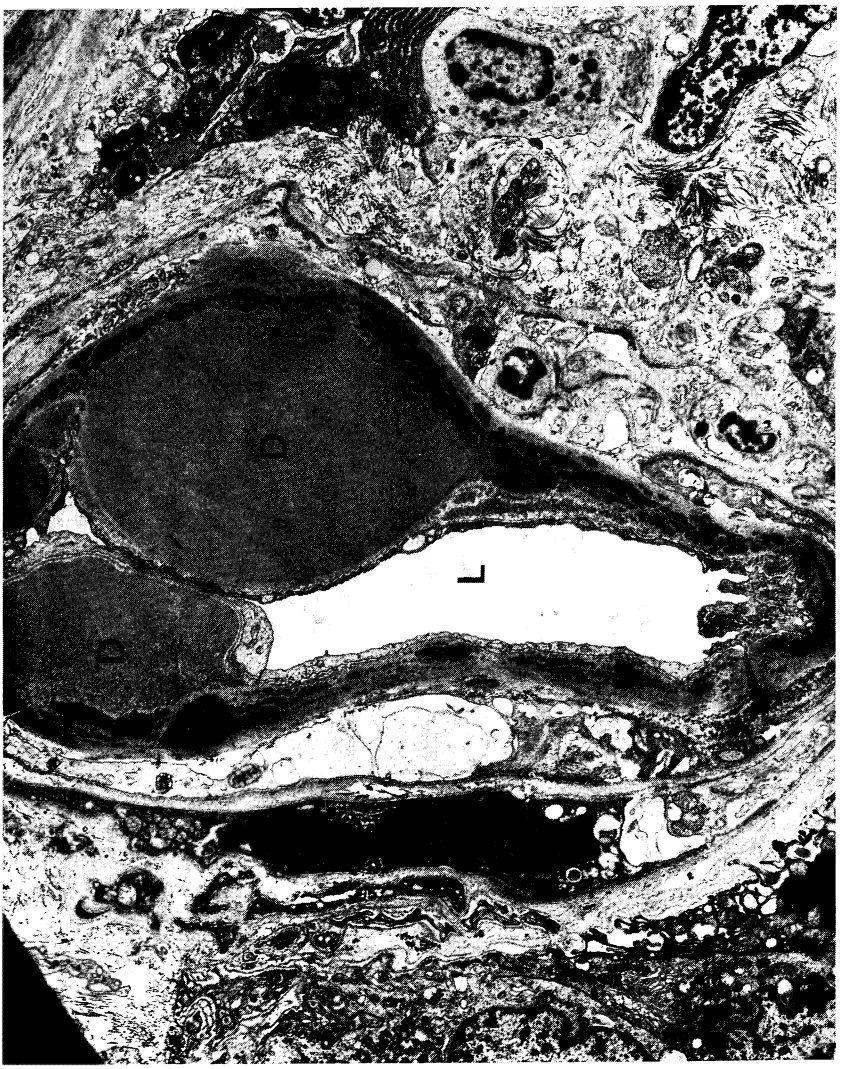


Figure 4. Benign hypertension. Electron micrograph of hyalinzed arteriole showing large amorphous, granular deposits (D) beneath intima and within the media narrowing the lumen (L). Magnification ×4200.

Glomeruli show various ischemic changes which include an increase in mesangial matrix and mesangial cellularity. Glomerular capillary walls are slightly thickened and wrinkled and may be globally or segmentally collapsed, particularly in subcapsular areas. Bowman's capsule is usually irreg-

ularly thickened and Bowman's space may be filled with pale staining collagenous material [5]. The juxtaglomerular apparatus shows no significant changes in contrast to the hypergranularity seen in malignant hypertension.

Interstitial fibrous tissue is focally increased, accompanied by mild tubular atrophy and chronic inflammation with considerable sparing of the intervening parenchyma. Tubules may be focally dilated and filled with proteinaceous material.

Clinical-pathological correlations

On occasion patients with benign hypertension may present with mild to moderate renal insufficiency accompanied by hematuria and proteinuria. Although the morphological features of focal glomerular obsolescence or focal segmental glomerulosclerosis seen in kidney biopsies of such patients are probably due to the effects of hypertension and ischemia, they may resemble healed focal glomerulonephritis. Absence of electron dense granular deposits, immunoglobulin and complement along the glomerular capillary walls and correlation with the clinical setting usually allow the correct diagnosis to be made [6].

Malignant hypertension

Gross pathological features

Kidneys are of variable size in patients with malignant hypertension. They may be normal in weight or moderately contracted, the size related in part to the duration of the hypertension and the presence of the benign phase. This is in contrast to the uniform and marked contraction associated with end stage chronic glomerulonephritis or the asymmetrical contraction of chronic pyelonephritis. The greatest degree of contraction is usually seen in the presence of long standing antecedent renal parenchymal disease. The cortex may be smooth if of recent onset or finely granular and may display petechial hemorrhages.

Histological features

The renal vascular tree is especially sensitive to the effects of accelerated or malignant phase hypertension and the small intrarenal arteries and arterioles tend to be the most severely affected. Several well defined patterns of vascular injury can usually be demonstrated.

Onion skin lesions affecting small arteries are composed of multiple concentric layers of proliferating spindle-shaped cells which produce marked narrowing of the vascular lumens (Figure 5). Fibrin thrombi may complete the obliteration of the vascular lumen correlating with microangiopathic

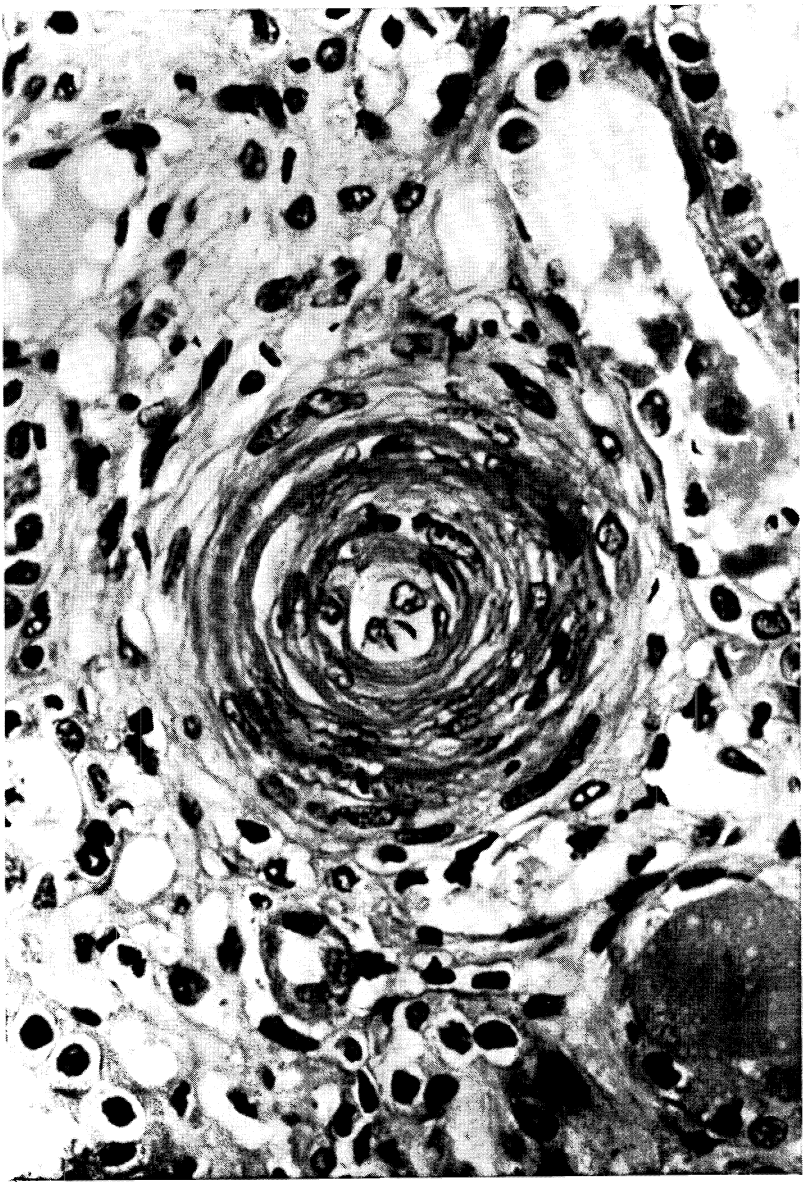


Figure 5. Malignant hypertension. Small artery showing onion skin lesion. Concentric layers of smooth muscle cells have markedly reduced the vascular lumen. Hematoxylin and eosin × 500. From Susin and Mailloux; reproduced with permission of the publisher [34].

hemolytic anemia seen clinically in some of these patients (Figure 6). The media is attenuated and stretched over the expanded intima. As seen by electron microscopy the endothelium may become thin and detached and red blood cell fragments and fibrin can be found in the subintimal space and vessel wall (Figure 7). The migration of proliferating smooth muscle cells

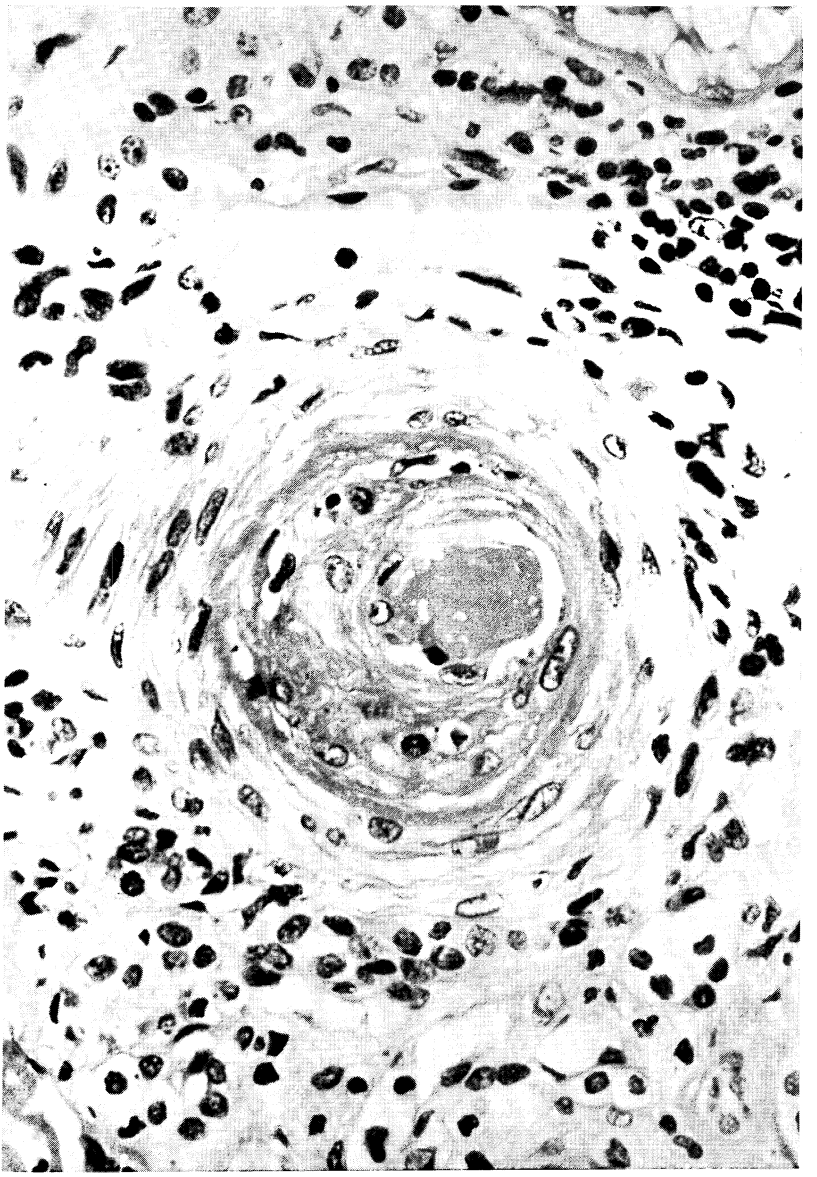


Figure 6. Malignant hypertension. Fibrin thrombus obliterates the lumen of this small artery. Hematoxylin and eosin ×500.

through the disruption in the internal elastic lamina into the subintimal space is thought to represent a fundamental vascular response to acute injury [1].

Mucinous change in small arteries represent an alteration in which sparsely cellular basophilic and amorphous material in subintimal areas narrow the vascular lumen. This material is composed in part of acid mucopolysac-

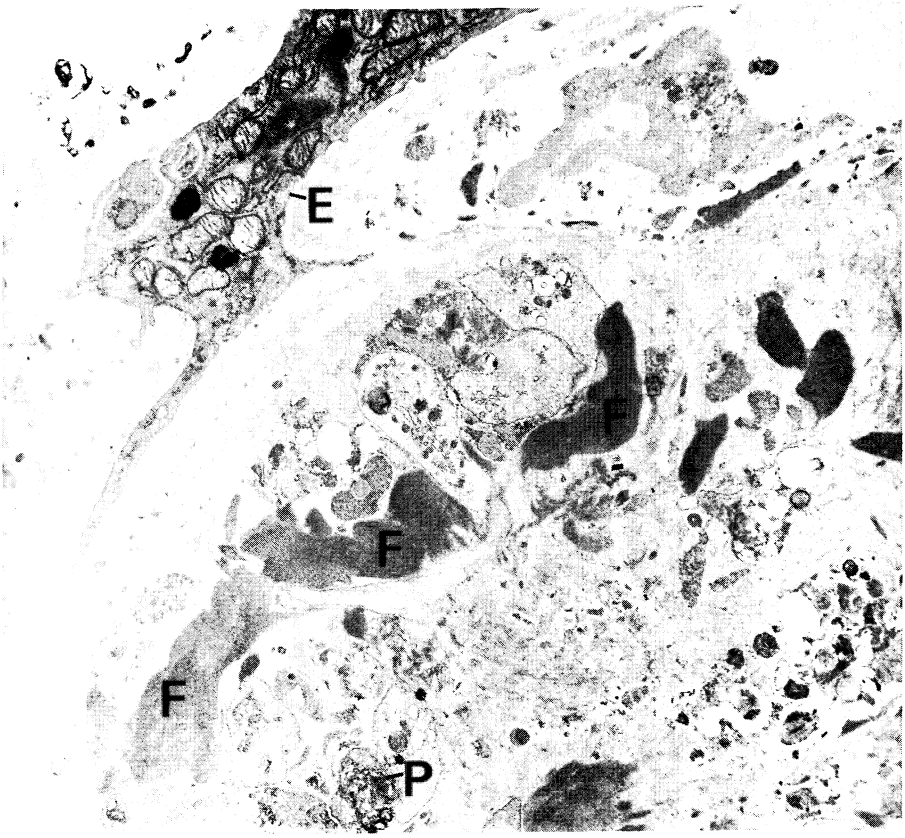


Figure 7. Malignant hypertension. Electron micrograph demonstrating detached endothelial cell (E) apparently lying free in the compressed vascular lumen. Fibrin deposits (F) and platelets (P) have accumulated in the vessel wall. Magnification × 7000. From Mailloux, Mossey, Susin, and Teichberg; reproduced with permission of the publisher [35].

charides and basement membrane material. The vascular lumens of these vessels can be reduced to the diameter of one to two red blood cells or can be totally obliterated (Figure 8).

Fibrinoid change is an alteration which represents the most severe morphological expression of enhanced vascular permeability and has long been considered the hallmark of malignant hypertension. It is usually encountered at the highest level of blood pressure elevation [7]. In practice, how-

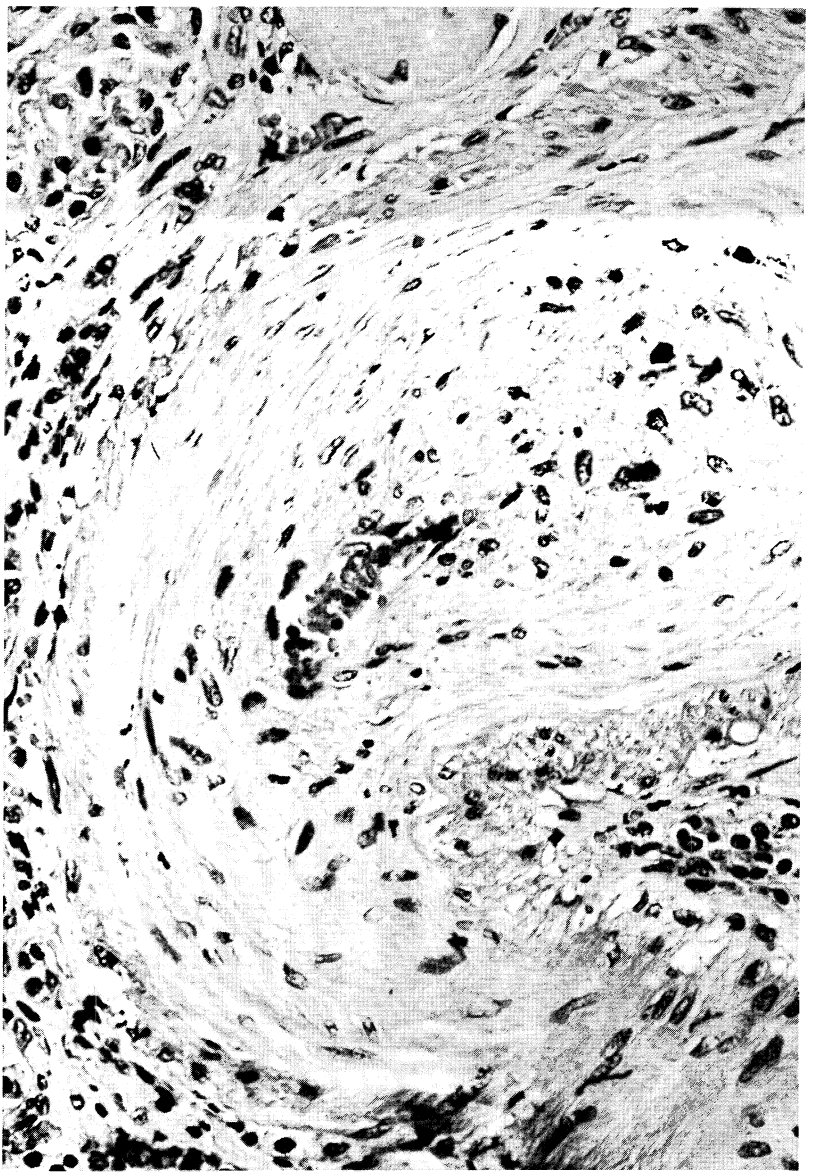


Figure 8. Malignant hypertension. Small artery showing mucinous change. Loose, pale staining, sparsely cellular material narrows the vascular lumen. Hematoxylin and eosin ×500. From Susin and Mailloux; reproduced with permission of the publisher [34].

ever, it is a relatively uncommon finding, especially in patients who have been aggressively treated with antihypertensive medications [8, 9]. Microscopically, the walls of interlobular arteries and afferent arterioles contain intensely staining eosinophilic material which has the tinctorial and histochemical properties of fibrin (Figure 9). Other plasma constituents can also

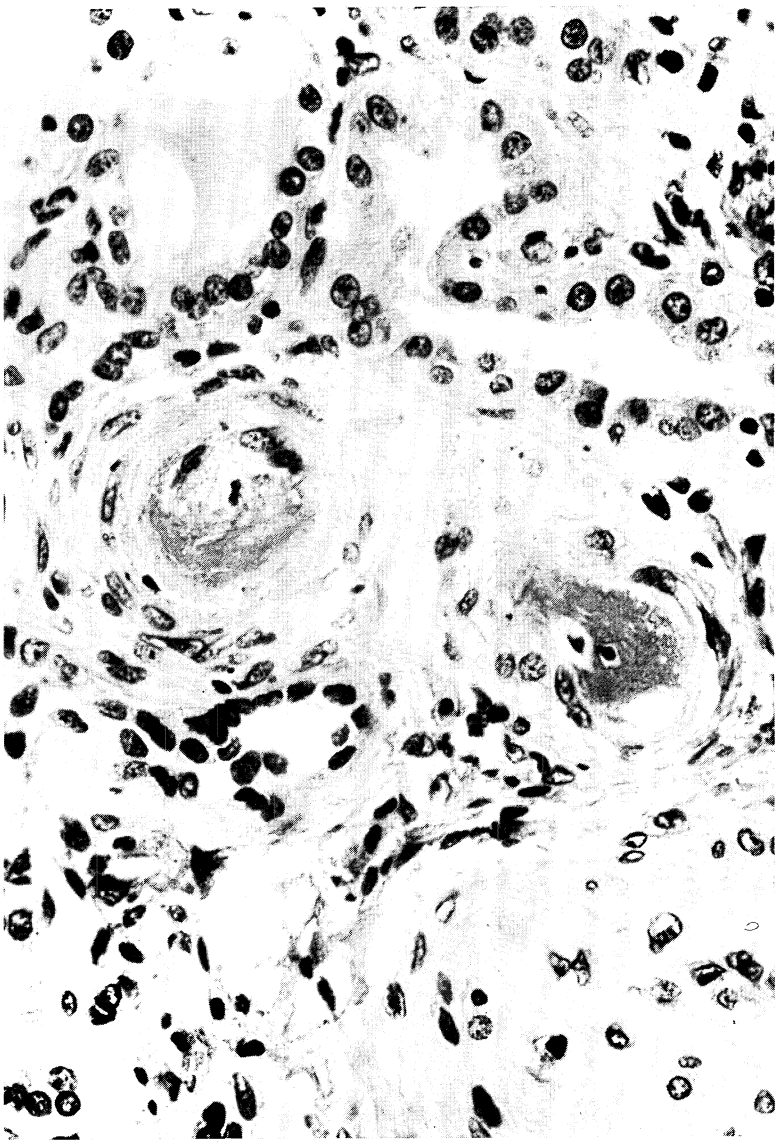
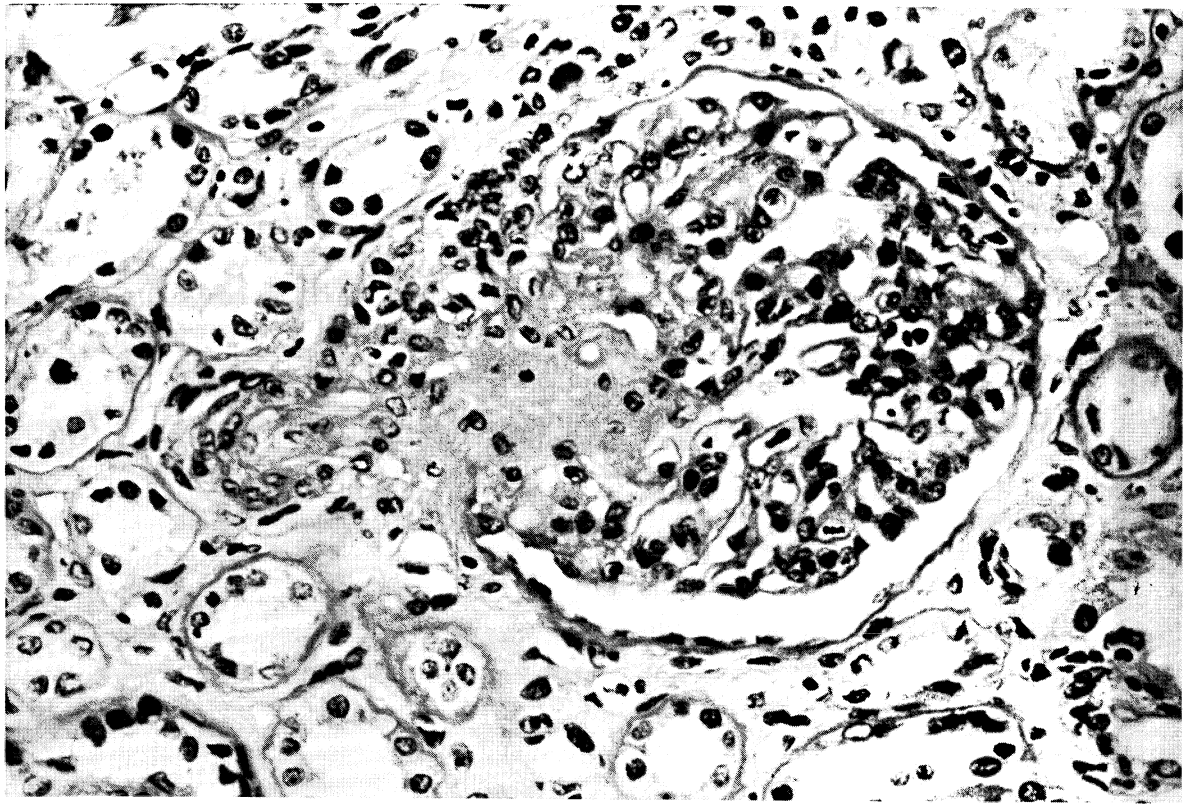


Figure 9. Malignant hypertension. Fibrinoid change. The arterial lumen is occluded and the wall infiltrated by intensely staining, hemogeneous material which has the staining reaction of fibrin. Endothelial cells are detached and smooth muscle nuclei are pyknotic. Hematoxylin and eosin ×500.

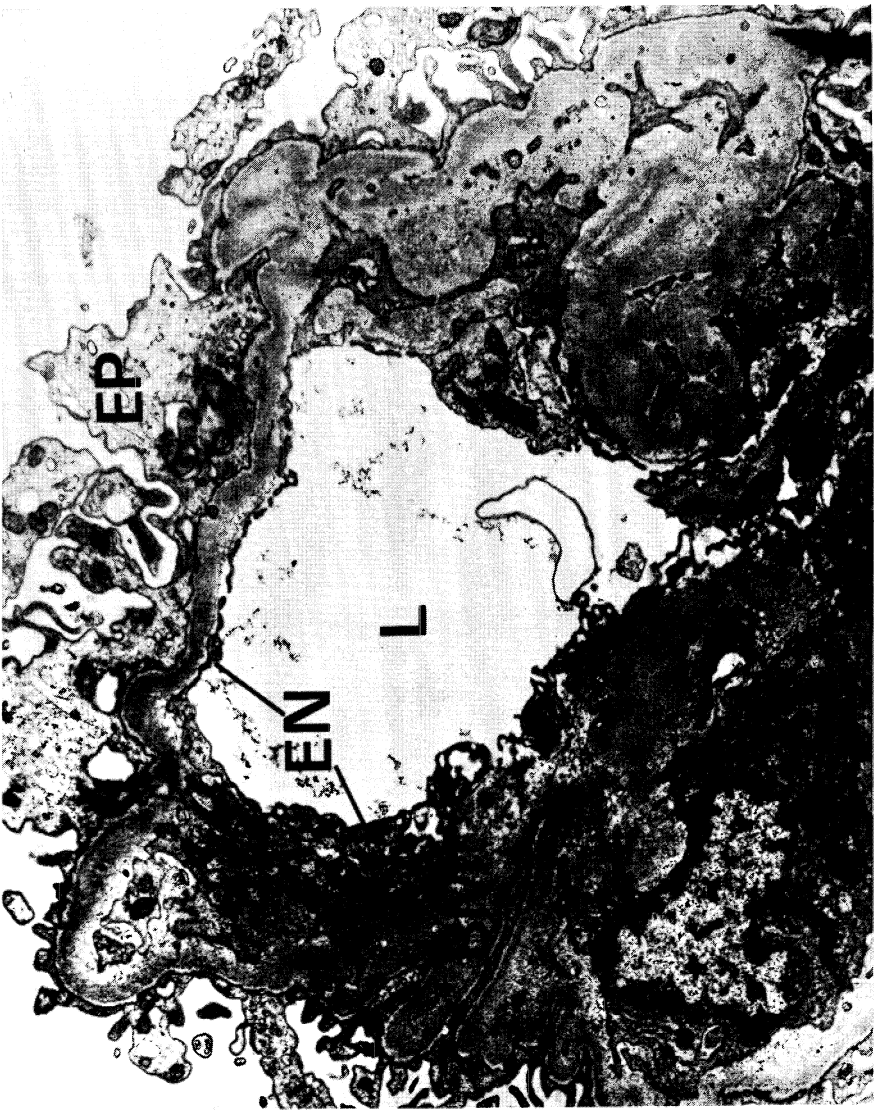
be demonstrated in vessel walls by immunofluorescence techniques including immunoglobulin, complement, and albumin [10].

Actual inflammatory cell infiltration and cellular necrosis are uncommon in these lesions so that the term 'necrotizing arteriolitis' is inappropriate and 'fibrinoid necrosis' is a misnomer. It is probably best to use a more



A

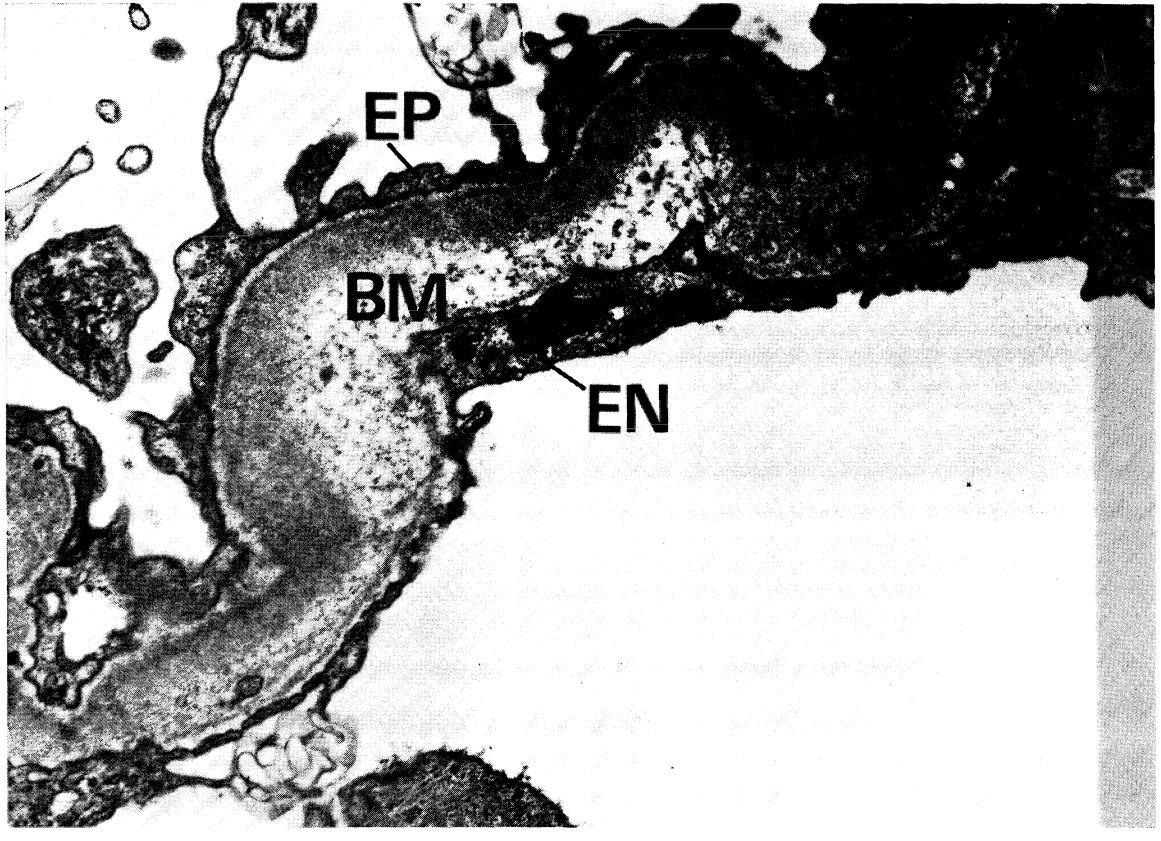
Figure 10. (A) Malignant hypertension. Glomerulus showing segmental sclerosis. Glomerular capillary walls are thickened and wrinkled. Arteriole is markedly sclerotic. Hematoxylin and eosin ×500. (B) Malignant hypertension. Electron micrograph of portion of renal glomerulus showing wrinkling and focal collapse of the glomerular basement membrane (BM) due to ischemia and decreased perfusion through the glomerular tuft. L = capillary lumen; EN = endothelial cell; EP = epithelial cell. Magnification ×7000. From Mailloux, Mossey, Susin and Teichberg; reproduced with permission of the publisher [35].



descriptive term such as 'fibrinoid change' when referring to this lesion [1].

Although these morphological patterns are highly characteristic of malignant hypertension, they are not specific, for they can be seen in such conditions as hemolytic-uremic syndrome, scleroderma, and post partum renal

Figure 11. Malignant hypertension. Electron micrograph of glomerular basement membrane showing expansion of the subendothelial space (BM) by finely granular, electron lucent material resembling plasma. EN = endothelial cell; EP = epithelial cell. Magnification $\times 1500$. From Mailloux, Mossey, Susin, and Teichberg; reproduced with permission of the publisher [35].



failure. Appropriate clinical correlation is necessary in order to properly interpret the morphological findings [9].

Antihypertensive therapy seems to determine the extent of protection against the structural consequences of hypertension. Numerous studies in experimental animals and in human beings have indicated that these vascular lesions are potentially reversible and capable of healing following effective control of the blood pressure [11–16].

Glomerular changes are variable. Small numbers may show segmental necrosis, usually in continuity with necrotic afferent arterioles. These changes may be accompanied by proliferation, exudation, and crescent formation. Less severely injured glomeruli usually demonstrate ischemic changes such as tuft shrinkage, capillary wall thickening and wrinkling with segmental capillary wall collapse and sclerosis and mild mesangial thickening and hypercellularity (Figure 10 A and B). By electron microscopy the subendothelial space of the glomerular basement membrane is expanded by abundant electron lucent material having the appearance of plasma, a change probably related to the intense ischemia affecting these glomeruli (Figure 11) [9]. Numerous glomeruli may be completely sclerotic and obsolescent. The majority, however, will be intact and well preserved in essential malignant hypertension compared with the nearly universal obliteration of glomeruli in chronic glomerulonephritis.

The juxtaglomerular apparatus is markedly hypercellular and hypergranular correlating with the hyperreninemia and severe hypertension seen in these patients [17–20].

Large arteries may show no significant changes or only mild intimal thickening. In those patients on prolonged chronic hemodialysis one may find impressive and extensive intimal thickening [21]. Interstitial fibrosis and tubular atrophy are almost always present and are proportional to the degree of glomerular atrophy and ischemia.

Pathogenesis

A large body of experimental evidence supports the dominant role of elevated blood pressure as the major factor in the pathogenesis of the acute vascular lesions in malignant hypertension [22–27]. In all the animal models acute, sustained and severe elevation of blood pressure induces typical morphological findings. Initially, alternating areas of contraction and dilatation are seen in the small arteries [22, 25, 28]. The constricted areas represent portions of the artery still capable of autoregulation whereas the dilated segments represent damaged portions of the vessel wall in which muscular contraction has been overcome by the mechanical stress of the hypertension.

The acute hemodynamic damage to the endothelial cells in the dilated segments enhance vascular permeability and allows plasma macromolecules to leak into the vessel wall [22–24, 29]. Some workers believe that the leakage of plasma proteins into the dilated vessel walls represents the decisive initial event in the development of the acute hypertensive vascular lesion [22, 24, 26, 27]. The difference between hyaline arteriolar sclerosis and fibrinoid change seems to be related to the tempo and degree of the hypertensive process.

Malignant hypertension triggers an exagerated intravascular coagulative response so that local intravascular thrombi are prominent histological features of the malignant phase. Many of the clinical and pathological features may be related in part to this mechanism [30, 31]. Fibrin deposition in the subintimal space and within the media may be seen histologically as fibrinoid change. Proliferation of smooth muscle cells results in intimal thickening and luminal narrowing. Red blood cells become deformed and fragmented traversing these narrowed and thrombosed vessels contributing further to the fibrin deposition and thereby perpetuating the vascular injury [32].

Decreased blood flow results in ischemic atrophy sustaining the elevated blood pressure. Thus a vicious circle becomes established by which hypertension-induced vascular damage to the renal microvasculature leads to the acceleration and perpetuation of the hypertension and progressive renal destruction [33]. These mechanisms are summarized in Table 1.

Animal models of hypertension

Historical perspective

Since the second century B.C., pathological examination of the kidney at autopsy had suggested a relationship between diseased kidneys and circulatory abnormalities [36]. Richard Bright reported the association between

Table 1. Summary of the events in the pathogenesis of the vascular lesions in malignant hypertension

1. Small arteries and arterioles are exposed to acute and severe elevation in blood pressure.
2. Localized vascular constriction and dilatation occur.
3. Structual damage to the vascular endothelium and smooth muscle cells of the media in the dilated segments is associated with enhanced vascular permeability.
4. Passage of plasma proteins into vessel walls results in fibrin deposition, intimal thickening, thrombosis and red cell fragmentation.
5. Ischemic atrophy in the kidney sustains the hypertension.

hypertrophy of the left ventricle and contracted kidneys and suggested that the link might be increased blood pressure [37]. It was not until 1898, however, that a definitive relationship was established between the kidney and hypertension. In that year, Tigerstedt and Bergman demonstrated that a crude extract from rabbit kidneys when injected into other rabbits produced a rise in blood pressure [38]. They called the extract 'renin'. The earliest demonstration that the ischemic kidney could cause high blood pressure was performed by Goldblatt and colleagues [39] who demonstrated in classic studies that unilateral or bilateral renal artery constriction in the dog leads to high blood pressure. The work was rapidly confirmed and quickly extended to show that a wide variety of manipulations to the kidney could result in hypertension. These included external renal compression by a ligature or cellophane wrapping [40] and unilateral renal infarction [41]. Species differences soon became apparent: unilateral renal artery constriction (two-kidney, one-clip) induced hypertension in rats [42], but bilateral renal artery constriction or unilateral constriction with contralateral nephrectomy was necessary to produce permanent blood pressure elevations in the dog and rabbits [43]. In 1939, Braun-Menendez and Page independently recognized that the pressor peptide, angiotensin, was formed by the action of renin on a substrate [44, 45]. Shortly thereafter, Goormaghtigh described the relationship between the juxtaglomerular apparatus and renin secretion [46]. Advances were rapid over the next two decades. Angiotensin was characterized chemically in 1956 [47, 48] and was synthesized in the following year [49]. With the development of methods to measure renin and angiotensin in the 1950s and 1960s, it soon became clear that elevations in these substances could not account for all forms of hypertension. The 1970s introduced competitive inhibitors of angiotensin, and in the past decade intravenous and then oral angiotensin converting enzyme inhibitors were developed. The availability of these agents has led to a better understanding of the contribution of the renin-angiotensin system to hypertension, and has raised new questions regarding other etiologies of hypertension.

All renal hypertension cannot be explained by excessive activity of the renin-angiotensin system. Two other models of hypertension with important renal components have been described. In one group of models, the combination of subtotal nephrectomy and high sodium intake (renoprival hypertension) results in predictable elevations in blood pressure. A detailed review of renoprival hypertension has recently been published [50]. In another type of model, genetic hypertension has been produced by selective inbreeding rats so that all offspring develop hypertension. Renal cross-transplantation studies have demonstrated that hypertension follows the kidney. When a genetically hypertensive rat is given a kidney from a normotensive donor, blood pressure is lowered. On the other hand, hypertension rapidly develops when a normotensive rat is given a kidney from a genetically

hypertensive donor [51, 52]. Similarly, elevations in blood pressure induced by dietary sodium follows the kidney in cross-transplantation experiments in the Dahl strain [53]. The information derived from animal studies with genetic hypertension points to a role of the kidney in the pathogenesis of several forms of hypertension, but the mechanism of pressure raising has not been fully characterized.

The remainder of the discussion will focus on renovascular hypertension because of the greater understanding of the pathogenesis of this model.

The Renin-Angiotensin System

Inappropriate stimulation of the renin-angiotensin system, or accentuated responses to the hormone may account for elevations in blood pressure in some forms of hypertension. Angiotensin II is the most potent endogenous pressor substance known, and has multiple proposed actions on cell metabolism [54]. Angiotensin II is formed in the blood and in tissues by a series of biochemical reactions. The enzyme, renin, is produced by the juxtaglomerular apparatus of the renal glomerulus and elsewhere catalyzes the breakdown of the hepatic prohormone, angiotensinogen. This results in the formation of the decapeptide, angiotensin I, which is converted by peptidyl dipeptidase (also known as angiotensin converting enzyme) to the active octapeptide, angiotensin II. Renin, angiotensinogen and angiotensin I have no biological activity unless converted to angiotensin II. The further cleavage of the C-terminal amino acid residue results in des-asp-angiotensin II, a heptapeptide, which has both pressor activity, and possibly increased specificity for the adrenal glomerulosa. In pathologic states, including renovascular disease or hemangiopericytoma (a tumor of the juxtaglomerular apparatus), there is increased activity of the renin-angiotensin cascade which may initiate elevations in blood pressure. Increased levels of plasma angiotensin II may be found if any of its precursors or regulatory enzymes are stimulated. For example, in normal pregnancy there is increased synthesis of angiotensinogen by the liver, which results in increased activity of the renin-angiotensin system.

Nomenclature of clip hypertension

Within a few years following the classic description of the effects of partial occlusion of the renal artery by Goldblatt and co-workers [39], it became apparent that differences existed between unilateral and bilateral clamping of the renal artery, and that clip hypertension in the dog was different from that in the rat and rabbit. The confusion which arose from the application

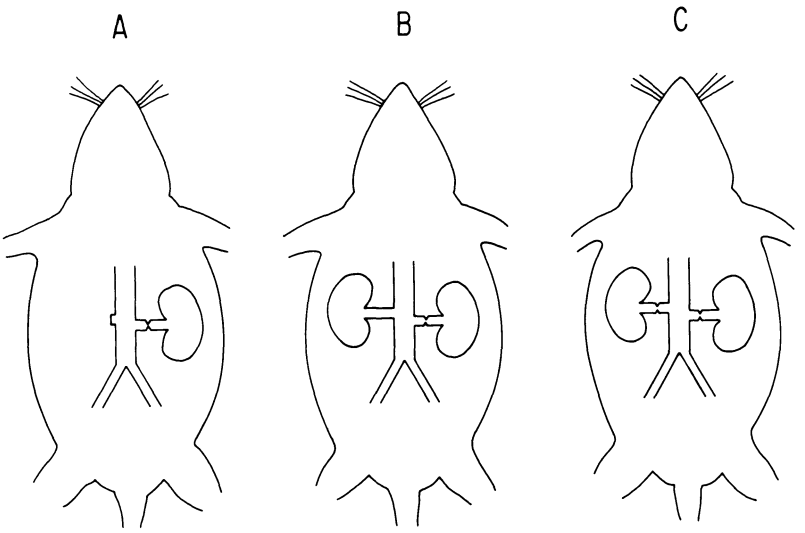


Figure 12. Diagrammatic representation of Goldblatt clip hypertension. (A) One kidney, one clip hypertension (one-kidney removed, the other clipped); (B) two-kidney, one-clip hypertension (both kidneys are in place, but one is clipped); (C) two kidneys, two-clip hypertension (both kidneys are in place, and both are clipped).

of this model in different species, and in different times after clipping, was partially clarified when the Executive Committee of the Council of High Blood Pressure Research introduced standard nomenclature for the various models: One-kidney, one-clip hypertension (one-kidney removed, the other clipped); two-kidney, one-clip hypertension (both kidneys are in place, but one is clipped); and two-kidney, two-clip hypertension [55] (Figure 12).

The renin-angiotensin system in clip hypertension

Dog models

One-kidney, one-clip model. Of the multiple experimental models studied, the clearest picture of renovascular hypertension comes from studies of Goldblatt hypertension in dogs. Using the one-kidney, one-clip model, Bianchi and colleagues [56] devised an experiment to study the renin-angiotensin system and other factors on the development of hypertension in the dog. Their experiments were performed in awake animals that had undergone prior unilateral nephrectomy and placement of the constricting device around the remaining renal artery. These investigators divided the hypertension into the following phases: the first phase lasting hours is associated with a sudden rise in blood pressure, increased peripheral resistance and elevated plasma renin concentration; the second phase, which lasts days, is accompanied by increases in plasma and extracellular fluid volumes and

cardiac output. Peripheral resistance decreases. There is urinary sodium retention and increased water intake. From several days to a few weeks later, varying with the individual animal, there is a third phase during which time peripheral resistance again became the primary factor for maintaining hypertension, while all the other factors returned toward normal [57].

Several additional experimental observations support the important role of heightened activity of the renin-angiotensin system during the first phase of development of hypertension following renal artery constriction. Administration of an angiotensin converting enzyme inhibitor prior to renal artery constriction can prevent the initial rise in blood pressure [58]. Other compelling evidence comes from the similarity between the relationship between changes in blood pressure and plasma concentrations of renin and angiotensin II seen during the first phase of blood pressure elevation following renal artery constriction. These changes are similar to those obtained by intravenous infusion of exogenous renin or angiotensin II. Stimulation of endogenous renin released in unanesthetized dogs produced by inflating a cuff around the renal artery causes both increased renin secretion and systemic blood pressure elevations which follow a similar temporal course [59]. The close temporal relationship between renin release and the elevation of blood pressure suggests that the renin-angiotensin system plays a role in blood pressure elevation during the initial phase of renal artery clamp.

The second phase in the one-clamp model is due largely to sodium and water retention contributing to extracellular fluid expansion, plasma volume expansion, increase in cardiac output and hypertension. There is an increased plasma volume to interstitial fluid volume ratio due to the reduction of compliance of the interstitial space. It has been postulated that a humoral substance which was normally secreted by the kidney was deficient, resulting in the decreased compliance of the interstitial space. It was also postulated that this substance could also act as a depressor material, since at any given extracellular fluid volume it could reduce the intravascular volume [60].

Watkins and co-workers [61] studied the effects of administration of saralasin, a competitive inhibitor of angiotensin II, on the blood pressure rise following renal artery constriction. Although blockage of angiotensin action prevented the rise in blood pressure over the first 4 days following renal artery constriction, blood pressure elevations became apparent by the fifth day and remained elevated thereafter. These experiments suggest that the early rise in blood pressure induced by the renin-angiotensin system may be unnecessary for the second and third phase of unilateral renal artery constriction hypertension.

Two-kidney, one-clip model. Two-kidney, one-clip Goldblatt hypertension

in the unanesthetized dog produces variable amounts of hypertension, both in degree and duration, depending on the technique and extent of renal artery constriction [62–66]. Once again, the rise in blood pressure over the first minutes to hours after constriction appears to be due to elevations in plasma renin and angiotensin, and may be reproduced by exogenous renin infusion. The infusion of various types of inhibitors of the renin-angiotensin system at this time lowers blood pressure to normal. Renin and blood pressure fall after the first day and approach normal by the end of 1 week, although blood pressure still remains above the preconstriction level. The changes in cardiac output and sodium balance are more variable than those observed in the one-kidney, one-clip model.

Rat models

One-kidney, one-clip model. One-kidney, one-clip Goldblatt hypertension in rats is also associated with elevations in plasma renin activity; elevations can be seen the first day after clipping [67–69]. The mechanisms involved during the second and third phase of this model remain controversial. Recently, plasma noradrenalin levels have been shown to be increased [70], and the rise in blood pressure and plasma noradrenalin concentration were prevented by intracisternal administration of 6-hydroxydopamine [71]. These data are compatible with involvement of the sympathetic nervous system in the pathogenesis of Goldblatt hypertension.

Two-kidney, one-clip model. The two-kidney, one-clip Goldblatt model in the rat has been studied extensively. The initial rise in blood pressure in this model is associated with large rises in plasma renin activity [72, 73]. Short infusions of blockers of the renin-angiotensin system lower blood pressure in the acute, but not in the chronic phase in this model [72, 74, 75]. Some, but not all investigators have demonstrated that prolonged infusion of angiotensin inhibitors during the chronic phase may result in lower blood pressure [76, 77]. The reasons for this discrepancy are not clear.

The major difference between two-kidney, one-clip Goldblatt and one-kidney, one-clip Goldblatt hypertension is that there is a greater component of sodium retention in the one-kidney, one-clip model. The one-kidney, one-clip model is a model of both renovascular disease and decreased renal mass and serves as a better model of renovascular hypertension plus chronic renal parenchymal disease. The increase in renal renin production is responsible for the early rise in blood pressure in both models. It is believed that without an unclipped contralateral kidney, angiotensin stimulation of aldosterone biosynthesis and release becomes increasingly important and contributes to the renal sodium retention. This difference in pathogenesis has been demonstrated experimentally [78].

Other factors in clip hypertension

Other hormonal systems are likely to be involved in renovascular hypertension. Increased levels of plasma catecholamines, epinephrine, more than norepinephrine, have been reported [79]. Others have demonstrated increased urinary excretion of catecholamines [80]. Pamnani et al. [81] have shown increased levels of prostaglandin E2 in the contralateral unclipped kidney. Inhibition of prostaglandin synthesis does not appear to significantly alter the development of renovascular hypertension [82]. Others suggested that increased renal prostaglandins may contribute to the increase in sodium and water excretion which follows the initial period of volume expansion [83]. The endocrine, metabolic, and structural causes of irreversible hypertension following release of clamp have not been fully worked out.

Is angiotensin II vasculopathic?

Acute and chronic infusions of angiotensin II have been used by investigators to study the pathogenesis of vascular lesions induced by high blood pressure. Although there have been attempts to describe vascular toxic effects of angiotensin independent of the elevated blood pressure, convincing demonstrations of a vasculopathic action of angiotensin *per se* have not been forthcoming. It has been suggested that angiotensin-mediated vasoconstrictor effects, rather than the level of blood pressure, is the determinant of susceptibility to vascular damage [84]. Experimentally, necrotizing arteriolar lesions have been produced by the injection of kidney extracts [85], semi-purified renin, or synthetic angiotensin II [86], especially in combination with high sodium intake. Compelling arguments against the specific vasculopathic effects of angiotensin II come from data where other vasoconstrictor hormones such as norepinephrebine and epinephrine produce lesions similar to those seen with angiotensin II. Specifically, increased blood pressure and microinfarcts in the myocardium are indistinguishable from those produced by angiotensin infusion [50, 87].

Conclusions

Clinico-pathologic correlation has suggested a strong relationship between hypertension and vascular lesions, a relationship which has been verified unequivocally in several animal models. Furthermore, animal models of renal vascular disease have pointed to the importance of the kidney in the pathogenesis of some forms of hypertension. Advances in our understanding

of the renin-angiotensin system have contributed greatly to our knowledge of a mechanism by which the kidneys may contribute to blood pressure elevation. Although the morphologic changes seen in hypertension reflect both the length and the severity of the blood pressure elevation, the vascular lesions do not imply a particular mechanism by which the blood pressure is raised. Hypertension is the common final pathway of multiple diseases, some yet to be defined, which result in similar end-organ damage. The challenge of the future is to identify the specific entities which comprise 'essential hypertension', and to identify and develop specific preventative measures.

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3. Hypertension in Renal Parenchymal Disease

KWAN EUN KIM

Hypertension is both a cause and a complication of chronic renal disease. In this chapter, hypertension complicating the course of renal parenchymal disease before the initiation of dialysis will be discussed.

Hypertension accelerates the deterioration of renal function. Thus, to provide for the longest possible interval between the onset of renal parenchymal disease and the need for maintenance dialysis or transplantation, hypertension must be controlled.

A precise knowledge of the hemodynamics and pathophysiology of hypertension in renal parenchymal disease coupled with an understanding of the renal and systemic hemodynamic effects of antihypertensive agents is necessary for rational and effective treatment of hypertension.

Hemodynamics

Hemodynamics of hypertension in acute glomerulonephritis

The hemodynamic factors regulating blood pressure may be expressed in the equation $BP = CO \times TPR$, where BP is the mean arterial pressure, CO the cardiac output, and TPR the total peripheral resistance. High blood pressure may result from a high cardiac output or a high total peripheral resistance or a combination of the two. Cardiac output represents the volume of blood propelled into the circulation per unit of time. Total peripheral resistance is a calculated value and is estimated by the ratio of mean arterial pressure over cardiac output, expressed in arbitrary resistance units.

DeFazio and associates reported that the hypertension of acute glomerulonephritis is characterized by a high cardiac output and a normal total peripheral resistance. This is probably due to the marked hypervolemia secondary to salt and water retention [1]. However, Birkenhäger and associates

described a normal cardiac output and a high total peripheral resistance in two patients with acute glomerulonephritis and hypertension. With the improvement of the disease and of the blood pressure, the total peripheral resistance decreased together with a negative cumulative sodium balance [2]. It is, therefore, postulated that the hemodynamic abnormalities may change significantly from the initial phase to recovery.

Hemodynamics of hypertension in chronic renal parenchymal disease

In contrast to essential hypertension and hypertension in end-stage renal disease, information regarding the hemodynamic changes of hypertension in early chronic renal parenchymal disease is limited [3–5].

Frohlich and associates studied 11 patients with early renal parenchymal disease and hypertension, and found that the hypertension was associated with a normal cardiac output and an elevated total peripheral resistance [4].

Brod and associates reported that cardiac output in patients with hypertension secondary to chronic non-uremic, non-anemic renal parenchymal disease was higher than in normotensive patients with renal parenchymal disease [3]. Eleven of the 27 hypertensive patients had high cardiac output, and all 11 patients with high cardiac output had stage I-II hypertension as defined by the World Health Organization. None of the eight patients in stage III had a high cardiac output. There was no difference in the total peripheral resistance between the normotensive renal patients and the hypertensive renal patients with stage I-II hypertension. The total peripheral resistance in hypertensive renal patients with stage III hypertension was higher than that in patients with stage I-II. Therefore, Brod and coworkers postulated that hypertension secondary to renal parenchymal disease may be initiated by a high cardiac output, and at this stage total peripheral resistance is within normal range. The total peripheral resistance starts to increase only with the progress of hypertension to stage III, and this is the reason for the cardiac output decreasing again to its original level.

We have studied 23 patients with chronic renal parenchymal disease without uremia or anemia [5]. There were 15 males and eight females ranging in age from 16 to 55 years, with a mean age of 36 years. Of the 23 patients studied, nine were normotensive and 14 were hypertensive. Patients were excluded from this study if they had a documented family history of essential hypertension or were in the malignant phase of hypertension. Patients with a serum creatinine of 4 mg % or less and a hematocrit of 30% or more were included. Of the nine normotensive patients, five had chronic glomerulonephritis, while polycystic kidney disease, diabetic glomerulosclerosis, chronic interstitial nephritis, and cystic disease in a solitary

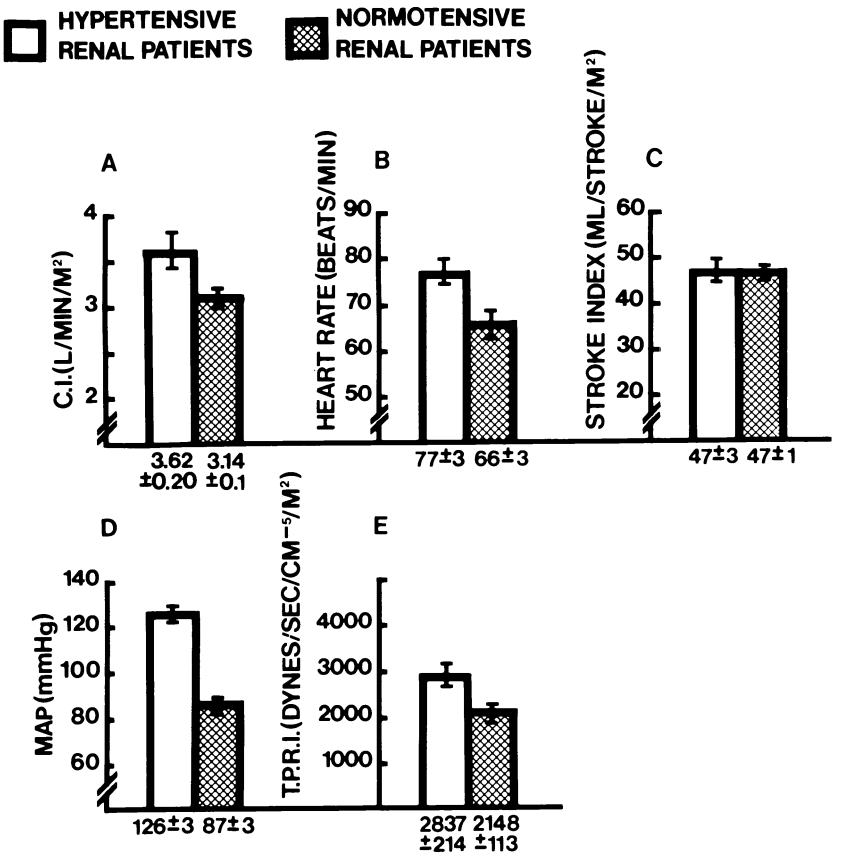

Figure 1. Comparison of (A) cardiac index (CI), (B) heart rate, (C) stroke index, (D) mean arterial pressure (MAP), and (E) total peripheral resistance index (TPRI) of 14 hypertensive and nine normotensive patients with chronic renal parenchymal disease. Hemodynamic values are expressed as mean $\pm$S.E. From Kim et al. [5], with permission.

kidney each occurred in one patient. Of the 14 hypertensive patients, nine had chronic glomerulonephritis, four had diabetic glomerulosclerosis, and one had multiple renal infarcts. The diagnoses were based on kidney biopsy, except for two patients with cystic renal disease where the diagnoses were confirmed by intravenous pyelogram, ultrasound of the kidneys or renal arteriography. The groups of hypertensive patients and normotensive patients were comparable for age, hematocrit, and inulin clearance. The systemic hemodynamics of hypertensive and normotensive patients with chronic renal parenchymal disease are shown in Figure 1. The average mean arterial pressure was 126 ± 3 mm Hg (mean $\pm$ S.E.) in hypertensive patients and 87 ± 3 mm Hg in normotensive patients ($p < 0.0005$) (Figure 1D). The mean cardiac index in the hypertensive patients was 3.62 ± 0.20 l/min/m^2 (mean $\pm$ S.E.), and in normotensive patients the mean cardiac index was

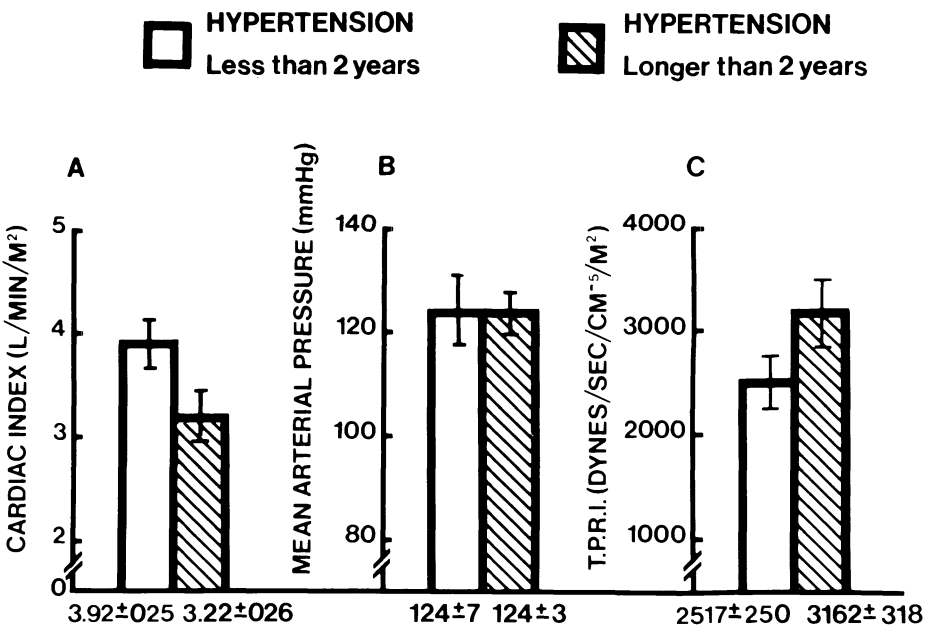

Figure 2. Comparisons of (A) cardiac index, (B) mean arterial pressure, and (C) total peripheral resistance index (TPRI) of seven patients with chronic renal parenchymal disease having hypertension of less than 2 years duration and seven patients with chronic renal parenchymal disease having hypertension of longer than 2 years duration. Hemodynamic values are expressed as mean ±S.E. From Kim et al. [5], with permission.

3.14 ± 0.1 l/min/m^2 ($p < 0.05$) (Figure 1A). The mean heart rate was 77 ± 3 beats/min in hypertensive patients and 66 ± 3 beats/min in normotensive patients ($p < 0.01$) (Figure 1B). The mean stroke index in hypertensive patients was 47 ± 3 ml/stroke/m^2. In normotensive patients the mean stroke index was 47 ± 1 ml/stroke/m^2 (Figure 1C). The mean total peripheral resistance index was 2837 ± 214 dynes/s/cm^{-5}/m^2 in hypertensive patients and 2148 ± 113 dynes/s/cm^{-5}/m^2 in normotensive patients ($p < 0.0125$) (Figure 1E).

The patients with chronic renal parenchymal disease and hypertension were arbitrarily divided into those with hypertension of less than 2 years duration and those with hypertension of more than 2 years duration. The average mean arterial pressure was similar in the two subgroups (Figure 2B). The mean cardiac index was higher in the patients with a more recent onset of hypertension (Figure 2A), while the mean total peripheral resistance index was lower in this group (Figure 2C). This study [5] shows that the overall cardiac index and heart rate of hypertensive patients with chronic renal parenchymal disease were higher than that of normotensive patients with chronic renal parenchymal disease.

When the hypertensive patients were divided into two subgroups accord-

ing to the known duration of hypertension, it appeared that the patients at an early stage of renal hypertension had a higher cardiac output.

These studies [3, 5] suggest that with progression of hypertension the cardiac output may decrease, while total peripheral resistance increases. This hemodynamic natural history is similar to the well documented natural history of essential hypertension [6–8]. However, more extensive studies on hemodynamic changes in early stages of hypertension in chronic renal disease and on their possible evolution are necessary for a definite conclusion.

Pathophysiology

Pathophysiology of hypertension in acute glomerulonephritis

Hypertension in acute glomerulonephritis is associated with fluid overload and subsides with the onset of diuresis that accompanies recovery. The mechanism by which expansion of body fluid increases blood pressure will be discussed in the following section.

Plasma renin levels in hypertensive patients with acute glomerulonephritis have been reported to be low [2, 9, 10]. The absolute renin levels were not elevated, but even a subnormal or low level was interpreted as inappropriately high for such volume expanded patients with acute glomerulonephritis and hypertension [2]. However more recently, it was reported that the suppression of plasma renin levels observed in patients with acute glomerulonephritis and hypertension was comparable to the physiologic response to sodium loading in normal subjects. Therefore, it was suggested that renin did not have a pathogenic role in hypertension associated with acute glomerulonephritis [10].

Pathophysiology of hypertension in chronic renal parenchymal disease

Pathophysiologic studies of hypertension secondary to chronic renal parenchymal disease are limited and conflicting. A variety of factors and abnormal relationships among them have been suggested as contributing to the hypertension.

Volume factors

It has been well demonstrated that in anephric patients and those with end-stage renal disease, salt and water balance plays a major role in the regulation of blood pressure and there is a significant positive correlation between blood pressure and blood volume and between blood pressure and total

exchangeable sodium [11–13]. In the early stages of renal parenchymal disease, not only the role of sodium balance and volume factors remains uncertain and information regarding relationships between blood pressure and body fluid volume is conflicting [14–18].

The importance of sodium balance and volume factors in the pathogenesis of hypertension in chronic renal parenchymal disease is supported by the observation that the prevalence of hypertension is lower in tubulo-interstitial disease than in glomerulonephritis. Tubulo-interstitial disease is associated with renal salt wasting whereas glomerulonephritis is frequently associated with salt retention. Some investigators reported that plasma volume, extracellular fluid volume and total exchangeable sodium in patients with early stage renal disease were high whereas other investigators found plasma volume and exchangeable sodium to be normal [14–18].

Tarazi and associates [14] found plasma volume to be normal but they showed a significant direct correlation between diastolic pressure and plasma volume. Beretta-Piccoli and associates [15] showed blood volume to be normal and they demonstrated no correlation between blood pressure and blood volume. Exchangeable sodium was higher in the hypertensive patients than in the control subjects but was not significantly different in the hypertensive and the normotensive patients. In this study, there was a significant positive correlation between blood pressure and exchangeable sodium [15]. We found no significant difference in blood volume between the hypertensive and normotensive patients with chronic renal parenchymal disease and there was no correlation between mean arterial pressure and blood volume.

The reason for the discrepancies in these studies is not clear. It is possible that body fluid volume may be increased so slightly as to be undetectable by current techniques. The mechanism by which volume expansion of body fluid increases blood pressure remains uncertain.

In 1963, Borst and Borst-De Geus [19] and Ledingham and Cohen [20] introduced the autoregulation theory in the pathogenesis of hypertension. The theory proposed that expansion of body fluid volumes with consequent increase in cardiac output results in perfusion of tissues above their metabolic needs. This in turn elicits myogenic constriction of peripheral vessels, thereby producing an increase in peripheral vessels, thereby producing an increase in total peripheral resistance with a gradual lowering of cardiac output toward the normal level [19, 20]. According to this theory, the initial increase in cardiac output with expansion of body fluid volumes is the cause of hypertension, and the subsequent rise in total peripheral resistance is the result.

Subsequently, Guyton and associates proposed the theory of whole-body autoregulation as the pathogenesis of all forms of hypertension [21, 22].

In dogs with partial nephrectomy subjected to volume expansion, Cole-

man and Guyton described an initial increase in cardiac output followed by an increase in total peripheral resistance [23]. A similar sequence of hemodynamic events has also been reported in anephric patients during volume expansion [24] and in different models of experimental renal hypertension in different species [20, 25–27]. Guyton and associates propose that renal control of body fluid balance is not only one of the important mechanisms for control of arterial pressure but that it overrides all the other long-term pressure control mechanisms [22, 28]. Expansion of body fluid volume in different abnormalities of the kidneys, either pathological or functional, can lead to hypertension through whole-body autoregulation. The subsequent hypertension returns blody fluid volume to a steady state [22, 28].

In contrast, in two-kidney, two wrapped hypertension in rabbits, Fletcher and associates described variable changes in cardiac output at the onset of hypertension, with elevation of total peripheral resistance as the final event [29]. Bravo and associates also found that a sustained rise in blood pressure during administration of metyrapone was associated with three different hemodynamic patterns of response [30]. Terris and associates reported that in six of seven pigs, elevations of blood pressure induced by deoxycorticosterone were entirely the result of increased total peripheral resistance [31]. We performed sequential hemodynamic studies during volume expansion in four anephric patients and six patients with end-stage kidneys. This study results in four different sequential hemodynamic patterns. In all but one patient studied, changes in blood pressure during volume expansion were associated with hemodynamic patterns different from that predicted by the theory of whole-body autoregulation [12, 32]. Therefore, mechanisms other than whole-body autoregulation may play a role in increasing blood pressure during volume expansion. In addition, direct proof of autoregulation as the cause for the observed increases in total peripheral resistance in the intact animal has not yet been obtained [33].

Renin-angiotensin system

The role of the renin-angiotensin system in the pathogenesis of hypertension of chronic renal parenchymal disease is still the subject of considerable controversy. In patients with chronic renal parenchymal disease and hypertension, circulating renin has been found to range from low to high values [15, 16, 18, 34, 35]. Some investigators reported a significant positive correlation between blood pressure and circulating renin or angiotensin II levels in these patients [16, 36], whereas other investigators were unable to demonstrate such a relationship [15, 37]. Wong and associates found a significant correlation between mean arterial pressure and logarithm of plasma renin activity and they described a significant reduction in mean arterial pressure during the infusion of saralasin, a competitive inhibitor of angiotensin II. This reduction in blood pressure was directly proportional to the pre-infu-

sion plasma renin activity. They suggested that hypertension in early renal parenchymal disease might be, at least to some extent, renin-dependent [16]. In contrast, Brod and associates reported that the infusion of saralasin reduced blood pressure in only one of 11 hypertensive patients with chronic renal parenchymal disease. This one patient was found to have a high plasma renin activity and the other ten patients had normal values [38].

Under normal conditions, the circulating levels of renin, angiotensin and aldosterone are closely related to body sodium and water balance. In a person with normal renal function, plasma renin levels can be assessed in relation to dietary salt intake or urinary sodium excretion. A high salt diet or volume expansion decreases plasma renin level whereas a low salt diet or volume depletion increases the level. It has been suggested that plasma renin level, although normal or low, is often inappropriately high for the state of volume expansion in hypertensive patients with chronic renal parenchymal disease. Therefore, the renin-angiotensin system may contribute to the hypertension [15, 18].

The interrelationship between blood pressure, exchangeable sodium, blood volume and plasma renin activity was studied in 40 normal subjects and 40 patients with early stage renal disease by Beretta-Piccoli and associates [15]. Eight patients were normotensive. In the 32 hypertensives, there were significant increases in exchangeable sodium and in the products of the logarithm of plasma renin activity and exchangeable sodium or blood volume. In the 40 patients with renal disease, blood pressure correlated significantly with the blood volume-renin product, but not with blood volume or plasma-renin activity individually. Furthermore, blood pressure showed a closer relationship with sodium-renin product than with exchangeable sodium alone. The authors concluded that hypertension accompanying early stage renal disease might depend on subtle abnormalities in the sodium/volume-renin feedback mechanism.

Vasodepressors

There are few studies available regarding the role of vasodepressors (prostaglandins and kallikrein-kinin system) in the pathogenesis of hypertension in chronic renal parenchymal disease [35, 39–41].

The mean peripheral plasma concentration of prostaglandin A in hypertensive patients with chronic renal parenchymal disease was found to be significantly higher than the mean concentration in normal subjects. Although not statistically significant, the mean value of the hypertensive renal patients was higher than the mean value of normotensive renal patients [39]. It was postulated that this increase in prostaglandin A might be a secondary adaptive mechanism to inhibit pressor substances and to permit excretion of a greater fraction of the filtered sodium and water leading to diuresis and a decrease of blood pressure [39].

The 24-hour urinary kallikrein activity in hypertensive patients with chronic renal parenchymal disease was significantly lower than in normotensive controls [35]. When urinary kallikrein activity was standardized for creatinine clearance, the difference was still significant. There was a significant negative correlation between mean blood pressure and urinary kallikrein activity standardized for creatinine clearance. Therefore, it was suggested that deficiency of the kallikrein-kinin system may play a part in the hypertension of patients with chronic renal parenchymal disease [35].

Sympathetic nervous system

Plasma concentration of norepinephrine is a better index of the sympathetic nervous system activity than total catecholamine concentrations because the latter include between 20 and 37% of plasma epinephrine, presumably of adrenomedullary origin.

Skrabal and associates reported that plasma norepinephrine and epinephrine levels of the hypertensive patients with chronic renal parenchymal disease were not significantly different from those of the normotensive controls [42]. In contrast, Ishii and associates found that plasma concentrations of norepinephrine and epinephrine of the hypertensive patients with early-stage renal parenchymal disease were significantly higher than plasma concentrations of the normotensive renal patients and the normotensive controls [43]. In addition, there was a highly significant positive correlation between plasma concentration of norepinephrine and systolic pressure or diastolic pressure or mean blood pressure in the pooled renal patients.

Plasma concentration of epinephrine also had a significant positive correlation with systolic and mean blood pressure in these patients. The authors suggested that the increased activity of the sympathetic nervous system might participate, in part, in elevating blood pressure in hypertensive renal patients [43].

Prevalence and clinical features of hypertension in primary and secondary renal parenchymal diseases

Almost any primary renal parenchymal disease or systemic disease involving the kidney can cause hypertension. The prevalence of hypertension depends on the etiology of renal disease and the level of renal function. Hypertension is more common in patients with glomerulonephritis than in those with tubulo-interstitial nephritis. Hypertension may develop during any stage of renal disease and hypertension may be the first clinical manifestation of renal parenchymal disease. Blood pressure tends to rise and the prevalence of hypertension increases with decreasing renal function. The prevalence of hypertension reaches 80 to 90% at the end-stage of renal disease just before dialysis is required.

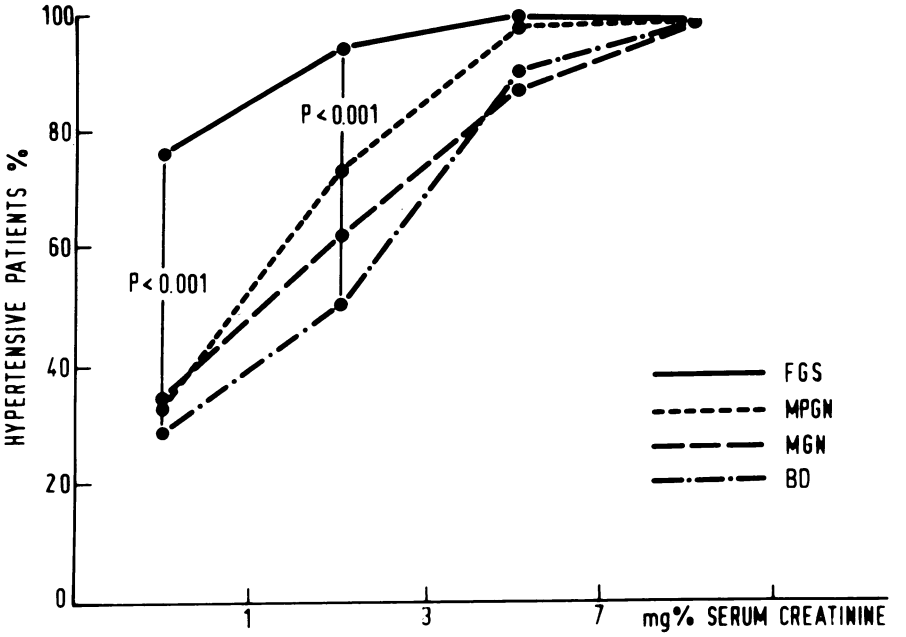

Figure 3. Prevalence of hypertension in 184 patients with different types of primary glomerulonephritis with varying levels of serum creatinine. FGS = focal glomerulosclerosis; MPGN = membranoproliferative glomerulonephritis; MGN = membranous glomerulonephritis; BD = Berger's disease. From Vendemia et al. [44], with permission.

Vendemia and associates reported that when renal function was normal, the prevalence of hypertension was similar in patients with glomerulonephritis and patients with tubulo-interstitial nephritis: 38 and 44% respectively. However, as renal function progressively decreased, the prevalence of hypertension in patients with glomerulonephritis rapidly increased to 64%,

Table 1. Primary and secondary renal parenchymal diseases frequently associated with hypertension

Primary renal parenchymal diseases
Glomerulonephritis
Pyelonephritis
Analgesic nephropathy
Polycystic kidney disease
Radiation nephritis
Secondary renal parenchymal diseases
Diabetic nephropathy
Lupus nephritis
Polyarteritis nodosa
Scleroderma (progressive systemic sclerosis)

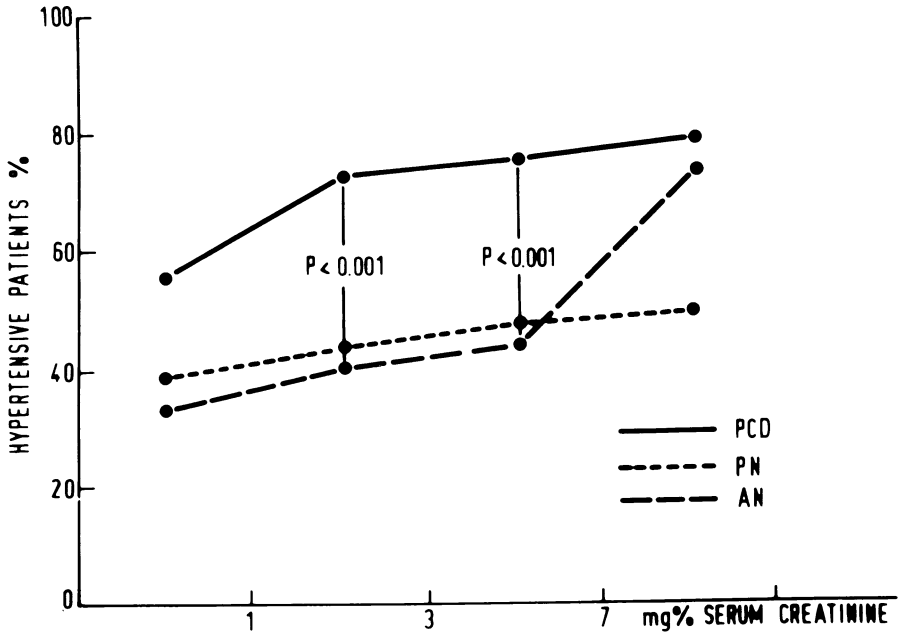

Figure 4. Prevalence of hypertension in 106 patients with different types of chronic tubulo-interstitial nephritis with varying levels of serum creatinine. PCD = polycystic kidney disease; PN = pyelonephritis; AN = analgesic nephropathy. From Vendemia et al. [44], with permission.

95% and 100% (Figure 3), whereas the prevalence of hypertension in patients with tubulo-interstitial nephritis showed a less marked increase: 54%, 62% and 74% (Figure 4). The difference between these two groups was highly significant in the late stages of renal insufficiency (serum creatinine greater than 3.1 mg %) ($p<0.001$) [44].

Primary and secondary renal parenchymal diseases frequently associated with hypertension are listed in Table 1. Unilateral renal diseases associated with hypertension are described in Chapter 4.

Glomerulonephritis

Primary glomerulonephritis is the most common cause of hypertension in patients with renal parenchymal disease. The exact prevalence of hypertension in chronic glomerulonephritis is unknown. Kincaid-Smith found that 56 patients had blood pressure equal to or greater than 140/90 mm Hg in 100 consecutive biopsy cases of idiopathic glomerulonephritis [45]. The prevalence of hypertension depends somewhat on the type of glomerulonephritis and level of renal function. For instance, hypertension is less com-

mon in patients with minimal change disease (lipoid nephrosis) than in patients with focal and segmental glomerulosclerosis.

Figure 3 shows that the overall prevalence of hypertension in 184 patients with different types of glomerulonephritis and normal renal function is 38% and the prevalence of hypertension increases with a progressive decrease in renal function in each type of glomerulonephritis [44]. However, this study is retrospective and many patients were lost to follow-up, therefore, this finding may not be representative. Well designed prospective and longitudinal studies are necessary for a definite conclusion on the prevalence of hypertension in patients with different histologic types of glomerulonephritis during the course of the disease.

Hypertension in chronic glomerulonephritis is usually mild to moderate but malignant hypertension may occur.

Hypertension occurs in 50 to 80% of patients with acute glomerulonephritis. Hypertension in acute glomerulonephritis is associated with body fluid overload. The hypertension is usually mild to moderate but accelerated hypertension associated with encephalopathy may occur.

Pyelonephritis

The prevalence of hypertension in patients with chronic pyelonephritis varies in different series from 10 to 85%, depending on the level of renal function and the criteria used for the diagnosis of chronic pyelonephritis and for hypertension.

In patients with persistent or recurrent urinary tract infection, the presence of hypertension is related to the presence of renal parenchymal scars [46]. Kincaid-Smith and associates reported that 50% of patients with radiographic renal scars due to chronic pyelonephritis had hypertension whereas only 5.9% of patients without scars had hypertension [46].

No causal relationship has been reported between acute pyelonephritis and hypertension.

Analgesic nephropathy

The reported prevalence of hypertension in patients with analgesic nephropathy varies from 15 to 70% [47, 48]. Hypertension is usually moderate. However, severe hypertension associated with salt and water depletion may occur [47]. The mechanism of this physiological paradox is not clear but depletion of renal medullary vasodilator substances and activation of the renin-angiotensin system have been postulated [47].

Polycystic kidney disease

The prevalence of hypertension in patients with polycystic kidney disease has been reported to range from 41 to 82% [49–53]. The differences between the results of these series may be explained by the different criteria for hypertension that have been used and by differences in the severity of the disease. Hypertension may be the first clinical manifestation of polycystic kidney disease. Hypertension often occurs in patients with a normal renal function [53]. As the disease progresses, however, the prevalence of hypertension becomes greater [53]. The presence of hypertension is one of the major determinants of prognosis in polycystic kidney disease [52]. Patients with normal blood pressure at the time of diagnosis live longer than patients with high blood pressure [52].

Radiation nephritis

Hypertension is the most prominent and serious clinical feature of radiation nephritis [54]. Acute radiation nephritis occurs after a latent period of 6 to 12 months following renal radiation in excess of 2,000 rads usually delivered over the course of a few weeks. Chronic radiation nephritis may follow acute radiation nephritis or may develop insidiously after a latent period of 18 months to more than 10 years following radiation exposure. Hypertension frequently accompanies acute or chronic radiation nephritis but may occur as an isolated finding [54]. Luxton reported that 15 of 54 patients (28%) with radiation nephritis developed malignant hypertension. Eight of 20 patients with acute radiation nephritis developed malignant hypertension. Seven patients developed malignant hypertension 18 months to 11 years after radiation [54].

It has also been reported that unilateral nephrectomy cured hypertension in a patient with unilateral radiation nephritis, severe hypertension and high renin activity from the damaged kidney [55].

Diabetic nephropathy

The reported prevalence of hypertension in patients with diabetic nephropathy varies from 52 to 78% [56, 57]. The prevalence of hypertension in patients with juvenile diabetes mellitus closely parallels the prevalence of proteinuria, suggesting that the hypertension is a consequence of diabetic nephropathy [58]. The prevalence of hypertension increases with the progression of renal failure. In one series, 89.7% of patients with end-stage diabetic nephropathy just before commencing dialysis had hypertension [59].

Plasma renin activity and aldosterone are frequently decreased in patients with diabetic nephropathy and hypertension [60]. These patients with hyporeninemic hypoaldosteronism may have hyperkalemia and hyperchloremic metabolic acidosis disproportionately severe for the level of azotemia.

Lupus nephritis

The prevalence of hypertension in patients with lupus nephritis varies depending on the histologic type of nephritis and the level of renal function [61]. Baldwin and associates found that none of the 12 patients with focal proliferative lupus nephritis, two of 12 patients with mesangial lupus nephritis, eight of 24 patients with membran ous lupus nephritis and 24 of 44 patients with diffuse proliferative lupus nephritis, had hypertension at the onset of the disease [61]. Eight of the 44 patients with diffuse proliferative lupus nephritis developed necrotizing renal vasculitis, manifested by severe or accelerated hypertension and rapidly progressive renal failure [61].

Early studies showed that hypertension was a feature of advanced lupus nephritis [62, 63]. In contrast, Budman and Steinberg reported that 22 of 36 patients with diffuse lupus glomerulonephritis had hypertension. Creatinine clearances of the 22 hypertensive patients were significantly lower than those of the 14 normotensive patients. However, two thirds of the hypertensive patients had creatinine clearances of greater than 60 ml/min and there was a considerable overlap in creatinine clearance in the hypertensive and normotensive patients. All other indicators of renal involvement (such as the degree of proteinuria or hematuria, focal necrosis, interstitial inflammation, or crescent formation) were not useful in distinguishing between the hypertensive and normotensive patients. Therefore, the authors concluded that hypertension is not necessarily associated with advanced renal disease and hypertension may occur relatively early in the course of lupus nephritis [64].

Polyarteritis nodosa

Renal involvement occurs in 79 to 87% of patients with polyarteritis nodosa [65, 66]. The prevalence of hypertension in polyarteritis nodosa has been reported to range from 44 to 69% [65, 67, 68]. Hypertension is a prominent feature of polyarteritis nodosa.

Rose and Spencer found that 38 of 86 patients with polyarteritis (44%) had hypertension. Thirteen of the 38 hypertensive patients had malignant

hypertension. In the 38 hypertensive patients, four patients had malignant hypertension at the initial examination and nine others developed malignant hypertension during the follow-up period. A majority of the hypertensive patients had healed arteritic lesions of the kidney and healed glomerular lesions while many of the 48 normotensive patients had active glomerular and arteritic lesions at necropsy [67]. Therefore, hypertension may be caused by renal ischemia which develops during the healing phase.

Severe hypertension associated with hyperreninemia and secondary aldosteronism in patients with polyarteritis nodosa has been reported [69].

Scleroderma (progressive systemic sclerosis)

The reported prevalence of renal involvement in scleroderma is variable and depends on the criteria used for renal involvement and the population of patients under study. Proteinuria occurred in only 109 of 727 patients (15%) scleroderma seen on a dermatology service [70]. Cannon and associates found that 45% of 210 patients with scleroderma had renal involvement, as indicated by the presence of proteinuria or hypertension or a BUN greater than 25 mg% [71]. Kovalchik and associates reported that six of nine patients with scleroderma without clinical evidence of renal disease or hypertension had renal vascular abnormalities on kidney biopsy [72].

The prevalence of hypertension in scleroderma has been reported to range from 24 to 52% [71, 73, 74]. The majority of the hypertensive patients (70%) have proteinuria [71]. Hypertension in scleroderma is usually mild to moderate but malignant hypertension often occurs.

Twenty to 30% of the hypertensive patients present with abrupt onset of malignant hypertension associated with a rapid deterioration of renal function culminating in oliguric renal failure. Cardiac failure and encephalopathy are frequently associated manifestations [71, 73]. Oliver and Cannon found that nine of 11 patients with this syndrome of malignant hypertension (82%) died within 2 months of its onset and the remaining two patients who underwent bilateral nephrectomy survived [73]. Successful treatment with antihypertensive agents in patients with this crisis has been reported [75–78]. In these patients, control of blood pressure with antihypertensive agents was followed by improvement of renal function [75–78]. Therefore, with the advent of new antihypertensive agents such as minoxidil and captopril, it is possible to reverse scleroderma renal crisis with control of blood pressure and to produce subsequent stabilization or even improvement of renal function.

Although this crisis occurs simultaneously with the first clinical diagnosis of diffuse scleroderma in some patients, in the majority it develops months or years after the other manifestations of scleroderma [71].

End-stage renal failure may develop in patients with skin, joint and other visceral evidence of scleroderma without hypertension [74]. These patients without hypertension have the same histological abnormalities in the kidney as patients with scleroderma associated with malignant hypertension and renal failure.

Renal and systemic hemodynamic effects of antihypertensive agents

Diuretics

Although the immediate antihypertensive effect of thiazide derivatives is associated with a decrease in blood volume and cardiac output, prolonged administration of chlorothiazide to hypertensive patients lowers the blood pressure by decreasing total peripheral resistance [79, 80].

It has been reported that acute and chronic administration of chlorothiazide reduced glomerular filtration rate [81, 82]. Recently, Van Brummelen and associates measured glomerular filtration rate, renal blood flow and renal vascular resistance in ten patients with essential hypertension during placebo, and after 1 week, 3, 6 and 9 months of hydrochlorothiazide administration. The authors found a decrease in glomerular filtration rate, although not statistically significant. After the initial decrease, glomerular filtration rate returned gradually to its original value. Renal blood flow was decreased significantly during the first week of the therapy followed by a progressive rise to the control value. Renal vascular resistance increased significantly during the first week and declined thereafter. After 3, 6 and 9 months, renal vascular resistance was significantly lower compared with placebo values [83].

Acute administration of the loop blocking diuretics, furosemide and ethacrynic acid, produces little or no change in both glomerular filtration rate and renal plasma flow, which may be followed by a decrease in glomerular filtration rate and renal plasma flow as a consequence of diuresis and contracted extracellular fluid volume and plasma volume [84, 85]. Acute administration of large doses, however, may induce renal vasodilatation and increase renal blood flow [86]. It has been shown that acute administration of furosemide and ethacrynic acid redistributes renal blood flow; superficial renal cortical blood flow increases whereas outer medullary blood flow and juxtamedullary blood flow decrease [87].

Adrenergic inhibitors

Intravenous administration of guanethidine to patients with essential hypertension reduces blood pressure accompanied by a 30% decrease in cardiac output and no significant change in total peripheral resistance [88]. It also

has been shown that oral administration of guanethidine for 5 to 7 days reduces blood pressure associated with a decrease in cardiac output and no significant change in total peripheral resistance [89]. Intravenous administration of guanethidine decreases glomerular filtration rate and renal plasma flow and increases renal vascular resistance [88]. Short-term oral administration of guanethidine also decreases glomerular filtration rate and renal plasma flow [89].

Methyldopa decreases blood pressure by decreasing total peripheral resistance [90, 91]. Acute intravenous administration of methyldopa decreases glomerular filtration rate and maintains renal blood flow. Renal vascular resistance decreases [90]. Short-term oral administration of methyldopa does not change glomerular filtration rate and renal plasma flow. Renal vascular resistance decreases and the renal fraction of cardiac output increases [91].

Acute administration of clonidine in the supine position reduces blood pressure accompanied by a decrease in cardiac output. In the upright position, the decrease in blood pressure is associated with a decrease in both cardiac output and total peripheral resistance [92]. Long-term administration of clonidine reduces blood pressure associated with a decrease in cardiac output [93]. Glomerular filtration rate and renal plasma flow do not change following acute or prolonged administration of clonidine [92, 94].

It also has been reported that glomerular filtration rate and renal blood flow are not altered after either acute or prolonged administration of reserpine [88].

In hypertensive patients, prazosin decreases blood pressure by decreasing total peripheral resistance with minor effects on cardiac output [95]. Glomerular filtration rate and renal plasma flow are not affected by prazosin therapy [96].

Six β-adrenergic blockers are now marketed in the United States: propranolol, metoprolol, timolol, nadolol, atenolol and pindolol. Intravenous administration of a β-blocker reduces heart rate and cardiac output. Blood pressure does not change and total peripheral resistance increases [97, 98]. During prolonged therapy with a beta-blocker, cardiac output remains depressed and total peripheral resistance decreases toward the pretreatment level as blood pressure decreases [98, 100].

Pindolol has intrinsic sympathomimetic activity and the other five beta-blockers do not have this activity.

Intravenous administration of pindolol does not significantly reduce heart rate or cardiac output nor does it change blood pressure or total peripheral resistance [97, 99]. During long-term treatment with pindolol, cardiac output does not change and the decrease in blood pressure is associated with a significant decrease in total peripheral resistance below the pretreatment level [99, 101, 102].

It has been shown that long-term administration of propranolol reduces glomerular filtration rate and renal plasma flow [103–105]. Rapid deterioration of renal function following treatment of hypertension with propranolol in patients with moderately severe renal failure has been reported [106]. Glomerular filtration rate and renal plasma flow do not change during nadolol administration despite a marked decrease in cardiac output [107, 108].

Glomerular filtration rate and renal plasma flow do not decrease during administration of metoprolol pindolol or atenolol [109–112].

Vasodilators

The antihypertensive effect of hydralazine is associated with an increase in heart rate and cardiac output and a decrease in total peripheral resistance [113, 114]. A single subcutaneous or oral administration of hydralazine produces a significant increase in renal plasma flow and no change in glomerular filtration rate [115, 116]. The increase in renal blood flow following acute administration is lost after prolonged hydralazine treatment [116].

Minoxidil decreased blood pressure by decreasing total peripheral resistance associated with a marked increase in heart rate and cardiac output [117]. Glomerular filtration rate and renal plasma flow are not affected by minoxidil [117].

Angiotensin-converting enzyme inhibitor (captopril)

The antihypertensive effect of captopril is associated with a decrease in total peripheral resistance without a significant change in cardiac output and heart rate [118, 119]. It has been reported that captopril increases renal plasma flow and does not change glomerular filtration rate [120]. More recently, Pessina and associates reported that after 7 weeks of captopril therapy renal plasma flow did not change but glomerular filtration rate decreased [121].

Management of hypertension in renal parenchymal disease

Since the results of several clinical trials on the treatment of mild hypertension have been published [122–128], the issue of whether to treat those patients with a diastolic blood pressure between 90 and 99 mm Hg has been a subject of intense clinical debate [129–132]. Discussion of this issue is beyond the scope of this chapter. It has been our policy to use antihypertensive drugs when diastolic blood pressure is consistently above 90 mm Hg

after a 3- to 6-month trial of appropriate nonpharmacologic treatment. We believe that the long-term prognosis and cardiovascular consequences of even this mild hypertension outweigh the side effects of drugs and the cost of the therapy.

The principle of treatment of hypertension associated with renal parenchymal disease is virtually the same as that of essential hypertension. However, therapy of hypertension in renal parenchymal disease should be guided by knowledge of pathophysiologic changes associated with renal parenchymal disease and hypertension, the pharmacology of antihypertensive agents, and effects of antihypertensive agents on renal and systemic hemodynamics.

In the past, many physicians hesitated to reduce blood pressure in hypertension associated with renal insufficiency because of the fear of decreasing renal function. However, Moyer and associates demonstrated that effective reduction of blood pressure with antihypertensive drugs arrested the further deterioration of renal function in patients with moderately severe, severe and malignant hypertension [133]. Woods and Blythe reported that glomerular filtration rate could be increased or at least maintained by aggressive therapy with antihypertensive drugs in patients with malignant hypertension complicated by renal insufficiency [134]. Mroczek and associates showed that aggressive antihypertensive therapy resulted in a slight worsening of renal function during the first 2 weeks of treatment in patients with the accelerated phase of hypertension with azotemia. Three months later, however, maintenance of reduced blood pressure was associated with improvement of renal function above pretreatment values. Twenty-six months later, renal function was markedly improved in the surviving patients [135].

It also has been reported that reduction of blood pressure in patients with severe hypertension secondary to renal parenchymal disease results in improvement in renal function [136]. Morgensen and associates also showed that control of hypertension retarded the predicted decline of glomerular filtration rate in patients with diabetic nephropathy and severe hypertension [137]. These studies indicate that adequate control of hypertension slows the decline of renal function in hypertensive patients with renal parenchymal disease although the loss of renal function from the primary renal disease continues. Therefore, in patients with renal parenchymal disease and hypertension, control of hypertension is mandatory in order to reduce morbidity and mortality from hypertensive cardiovascular complications and to preserve renal function for the longest possible interval between the onset of disease and occurrence of uremia. The goal of therapy is to maintain the blood pressure below 140/90 mm Hg.

It is well known that dietary restriction of salt significantly reduces blood pressure [138–140]. Moderate salt restriction to 3–5 g of salt a day lowers

blood pressure [141–143]. It is possible to reduce daily salt intake to 5 g daily by avoiding foods known to be rich in sodium such as ham, potato chips, and all processed foods and by not adding salt to food either at the table or during cooking [143]. During severe salt restriction, a person with normal renal function can lower urinary sodium excretion to nearly zero. However, patients with chronic renal disease sometimes have an impaired ability to conserve sodium. In addition, patients with renal insufficiency often cannot excrete a high salt intake. Such patients are vulnerable to salt and water retention and circulatory congestion. On the other hand, severe salt restriction may cause salt depletion, dehydration and further deterioration of renal function. Thus, severe salt restriction should be avoided in patients with chronic renal parenchymal disease and hypertension unless they are fluid overloaded. It is reasonable to prescribe a 3- to 5-g salt diet a day for most hypertensive patients with chronic renal parenchymal disease. This daily salt intake can be adjusted according to the renal capacity to excrete sodium and the responsiveness of antihypertensive agents. Even

Table 2. Guidelines for the use of antihypertensive drugs in patients with chronic renal parenchymal disease

Initial therapy (step 1):	Loop blocking diuretic
	Furosemide
	Ethacrynic acid
Avoid potassium sparing diuretics (triamterene, spironolactone and amiloride)	
First adjunctive therapy (step 2):	Adrenergic blocking agent[a]
	β-adrenergic blocking agent
	Atenolol, metoprolol
	nadolol, pindolol,
	propranolol, timolol
	Clonidine
	Guanabenz
	Methyldopa
	Prazosin[b]
Avoid guanethidine	
Second adjunctive therapy (step 3):	Vasodilator
	Hydralazine
	Minoxidil[c]
	Angiotensin-converting enzyme inhibitor
	Captopril[d]

[a] Listed in alphabetical order.

[b] Prazosin may be used as a step 2 or 3 agent.

[c] Minoxidil may be used in patients resistant to triple-drug therapy.

[d] Captopril may be given alone or with a diuretic or with a diuretic and a β-adrenergic blocking agent in patients resistant to triple-drug therapy.

with the use of diuretics, salt restriction is still required because it has been demonstrated that the antihypertensive efficacy of the oral diuretics may be significantly reduced by the concomittant administration of a high salt diet [144]. Modest salt restriction permits diuretics and other antihypertensive drugs to work more effectively in lowering blood pressure [141, 142, 145].

Table 2 presents guidelines for the use of antihypertensive drugs in patients with chronic renal parenchymal disease.

Thiazide diuretics should be avoided in hypertensive patients with renal insufficiency because these agents decrease glomerular filtration rate and renal plasma flow [81–83]. The diuretic action (and probably antihypertensive action as well) is lost when glomerular filtration rate is reduced below 20 ml/min. Furosemide and ethacrynic acid, however, continue to exhibit natriuretic and diuretic effects, even at low glomerular filtration rates [146, 147]. Therefore, if the patient is not a renal salt waster, furosemide or ethacrynic acid should be the initial therapeutic agent for the treatment of hypertension. Furosemide is preferred to ethacrynic acid because gastrointestinal symptoms and ototoxicity are more frequently observed with the use of ethacrynic acid than with furosemide. The dosage of furosemide varies, depending on the degree of impairment of renal function and the severity of hypertension. Forty milligrams may be given twice daily to patients with mild reduction of renal function and mild to moderate hypertension. Patients with severe reduction of renal function may require 240 mg three times per day or more.

Potassium sparing diuretics, such as spironolactone, triamterene and amiloride are contraindicated when azotemia is present, because of the increased risk of hyperkalemia.

If the desired reduction in blood pressure is not achieved with an oral diuretic, the second drug to be added is an adrenergic blocking agent (a step 2 agent in Table 2). Since all step 2 drugs except for β-adrenergic blockers cause postural hypotension, these agents should be carefully titrated. If side effects of an agent are intolerable, another adrenergic blocking agent may be substituted.

Blood levels of many antihypertensive drugs do not correlate with their hypotensive effects. Therefore, the use of antihypertensive drugs in patients with renal failure, as in patients with normal renal function, should be guided by titration of dosage of the antihypertensive agent against the patient's blood pressure. However, antihypertensive agents primarily eliminated by the kidneys require reduction of dosage.

Although rapid deterioration of renal function following treatment of hypertension with propranolol has been reported, in patients with moderately severe renal failure, this complication seems very rare [106]. Among six β-adrenergic blocking agents available in the United States, propranolol,

metroprolol and timolol are almost exclusively metabolized by the liver. Therefore, normal doses of these three drugs can be used in patients with renal insufficiency. Since approximately 40% of pindolol or atenolol is recovered unchanged in the urine following a single dose, some dosage reduction of these drugs is required in patients with impaired renal function. More than 90% of nadolol is recovered in the urine and feces unchanged. Therefore, the dose should be progressively reduced and dosage intervals should be lengthened in those with renal insufficiency.

Clonidine and methyldopa preserve renal plasma flow and glomerular filtration rate [91, 92]. At least 50% of clonidine is excreted unchanged in the urine. Therefore, a minor reduction of dose is necessary in patients with renal failure. It has been suggested that a plasma concentration of clonidine greater than 2 ng/ml is associated with decreased antihypertensive effect due to peripheral α-adrenoreceptor stimulation [148]. Patients with renal insufficiency are more sensitive to the hypotensive effect of methyldopa at a plasma concentration that is not different than in patients with normal renal function. Therefore, methyldopa should be carefully titrated.

Prazosin, a postsynaptic α-adrenergic blocker with vasodilating effect, may be given either with a diuretic agent (as a step 2 agent) or in combination with a diuretic and an adrenergic blocking agent (as a step 3 agent). Glomerular filtration rate and renal plasma flow are not affected by prazosin therapy [96]. Since about 6% of prazosin is excreted unchanged in the urine, normal dose can be used in patients with renal failure. However, it has been suggested that patients with renal failure exhibit a greater degree of hypotension for a given dose.

Guanethidine should be avoided because this drug frequently causes severe orthostatic hypotension and decreases glomerular filtration rate and renal plasma flow [88, 89]. Reserpine is rarely used because it lacks adequate potency and because of its side effects such as mental depression and nasal congestion.

If the desired reduction of blood pressure is not achieved with a diuretic and an adrenergic blocking agent, hydralazine, a vasodilator, is the third drug to be added. Hydralazine has a favorable renal hemodynamic effect; it increases renal plasma flow and preserves glomerular filtration rate [115, 116].

If adequate control of blood pressure is not achieved with standard therapy (triple-drug therapy), the combination of minoxidil, a β-adrenergic blocker and furosemide may be effective. Minoxidil is the most potent oral vasodilator available. Fluid retention and hirsutism are common side effects of minoxidil. The drug should be administered with a β-adrenergic blocker to prevent reflex tachycardia and with furosemide to prevent fluid retention. Clonidine may be used in those patients who cannot tolerate a β-adrenergic blocker. Minoxidil is effective in the control of resistance hypertension, par-

ticularly associated with renal failure. This drug's propensity to cause hirsutism precludes its use in many women.

Although captopril in small doses has been found to be effective and well tolerated in a trial of patients with mild hypertension [149], the drug is recommended only for patients with hypertension unresponsive to triple-drug therapy with a diuretic, an adrenergic inhibitor, and a vasodilator because of its serious side effects. Captopril preserves glomerular filtration rate and increases renal plasma flow or at least maintains renal plasma flow [120, 121]. A diuretic is often used with captopril, and sometimes a β-adrenergic blocking agent as well in treatment of severe or refractory hypertension. Captopril therapy has been shown to be effective in some patients with refractory hypertension secondary to renal parenchymal disease. Excellent responses have been reported in patients with severe hypertension and hyperreninemia caused by scleroderma or hemolytic uremic syndrome [78, 150]. Because captopril is excreted primarily by the kidneys, the dose should be progressively reduced and the dosage interval should be lengthened in patients with renal failure.

Hypertension associated with acute glomerulonephritis should be treated in a manner similar to hypertension secondary to chronic renal parenchymal disease as described above. Hypertension in acute glomerulonephritis is usually associated with body fluid overload. Therefore, restriction of salt and fluid intake and the use of a diuretic (furosemide) are the most important measures for treatment of the hypertension. Parenteral administration of antihypertensive agents such as diazoxide, hydralazine and sodium nitroprusside is necessary in hypertensive emergencies associated with acute glomerulonephritis.

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4. Hypertension in Renovascular Disease

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Introduction

Among the large population of patients with established hypertension there exists a subgroup with anatomic abnormalities of the kidney or the renal vasculature. However the presence of anatomic disease does not necessarily mean that the demonstrable lesion is the cause of the coexisting hypertension.

The clinical challenge is clear: to identify those patients who would be cured invariably by operative or radiologic intervention to correct or remove the offending renal lesion. Conversely patients with essential hypertension should be spared invasive diagnostic procedures with attending risk and cost. Particularly, patients with renal lesions not of functional significance should not be subjected to surgical intervention and its attendant morbidity and mortality [1].

In this chapter we propose to identify characteristics of renin-dependant renal hypertension on the basis of information gained from the investigation of two experimental models of renal hypertension. We will also show that surgically curable unilateral renovascular hypertension in man shares similar characteristics with the experimental model. Three criteria derived from renin measurements define potentially curable renovascular hypertension with a high degree of accuracy: (1) hypersecretion of renin as reflected by high peripheral plasma renin activity indexed as a function of sodium excretion; (2) unilateral origin of renin secretion with suppression of renin secretion from the opposite kidney, $(V\text{-}A) \sim 0$; and (3) an abnormal increase in renal vein plasma renin activity over that of the artery from the suspect kidney, $(V\text{-}A)/A > 0.50$, which reflects the degree of renal ischemia [2]. Moreover, pharmacologic intervention with antirenin or antiangiotensin II therapy can expose angiotensin II vasoconstriction as a determinant of peripheral resistance and serve as a fourth criterion of surgically curable renovascular hypertension.

Finally, a practical approach to identify renal hypertensions will be outlined which is safe and cost containing and effectively accomplishes the goal of identifying those patients who warrant interventive rather than medical management.

Operation of the renin angiotensin aldosterone system

Whenever there is reduced perfusion pressure in the kidneys, renin is released from the granular stores of specialized cells lining the afferent arterioles (the juxtaglomerular cells). In the blood, renin reacts with a protein substrate, angiotensinogen, to split off the decapeptide angiotensin I. Like renin, this decapeptide is physiologically inert, but in a single passage through the lungs it is converted by pulmonary enzymes to the active octapeptide form, angiotensin II a most potent vasoconstrictor which is then exported to the arterial system.

Angiotensin II raises blood pressure in several ways. It directly and immediately constricts peripheral arterioles by both energizing smooth muscle and by activating sympathetic nervous system hormones. It may also stimulate vasoconstrictive mechanisms by acting in the central nervous system.

On the volume side too, angiotensin raises blood pressure, but this occurs more leisurely and indirectly by its stimulating aldosterone secretion. Aldosterone, in turn over the ensuing 6 to 24 h, induces renal sodium retention with fluid-volume expansion. There is an interesting amplifying crossover effect in that this sodium-volume expansion enhances vascular sensitivity to angiotensin's vasoconstrictive action.

The result is a two-pronged pressor effect: a quick vasoconstrictive one for immediate correction of a perfusion deficit, and a longer, more sustained volume enhancement that works to restore flow. The raised blood pressure so induced then shuts off the initial signal for renin release by acting at the baroreceptor in the renal arterioles – and the cybernetic loop is thereby closed and the system returns to null. The renin system thus functions as a central long-term regulator of blood pressure and of sodium-volume homeostasis.

Pathophysiology of experimental Goldblatt hypertension

It is well established that the renin angiotensin aldosterone system is a central control mechanism for blood pressure, sodium and potassium balance, and peripheral vascular flow and resistance [3]. It would appear logical that renal hypertension would be accompanied by derangements of the system

which might serve as a guide to diagnosis and management. Accordingly after the initial work of Dr Goldblatt [4] it was assumed that excess renin secretion, leading to excess angiotensin II (AII) formation, was the underlying derangement in renovascular hypertension. Unfortunately this possibility was soon challenged when circulating renin levels (PRA) were found to be normal in both animal models and a large number of patients with renovascular hypertension [5, 6].

A search for a clearer understanding of the relationship between the renin system and renovascular hypertension led us to re-evaluate the animal models. The first advancement was the realization that two different models of experimental Goldblatt hypertension can be produced.

In one model, a renal artery is clamped and the opposite kidney is left in place, in the other a renal artery is clamped but the other kidney is removed. Although animals are equally hypertensive in both models, one-kidney one-clip Goldblatt hypertension is characterized by volume expansion and normal or suppressed plasma renin activity [5, 7], whereas in the two-kidney one-clip model, plasma renin activity is increased and renin content is increased in the kidney with the stenosed artery and decreased in the opposite kidney [8, 9]. These changes are summarized in Table 1.

A second advancement in exposing the role of AII in these experimental models was the development of compounds that either block the conversion of angiotensin I to angiotensin II or are specific AII receptor antagonists [10].

Accordingly, these agents have been administered in both hypertensive models at various times in the evolution of the hypertension. In the one-kidney model, the initial rise in plasma renin activity is correlated with the rise in blood pressure and the hypertension can be prevented acutely or reversed either by the administration of an AII antagonist or by inhibition of the AI converting enzyme [11, 12]. Hence, in this model, the initiation of

Table 1. Changes in experimental Goldblatt hypertension

	1-clip, 1-kidney	1-clip, 2-kidney
Human equivalent	Bilateral stenoses	Unilateral stenoses
PRA	Normal	Raised (less in chronic phase)
Plasma volume	Raised	Normal
Exchangeable Na	Raised	Normal
AII antagonist effect on BP	Little change	Falls (less in chronic phase)
Unclipping		
(a) effect on BP	Falls	Falls
(b) on Na excretion	Rises	Falls

the hypertension is mediated by AII-induced vasoconstriction. The renin secretion is quite rapidly suppressed to normal, however, by volume expansion due to salt and water retention [7]. Brunner and co-workers clearly showed that infusion of Sar^1-Ala^8-angiotensin II in the one-kidney Goldblatt rat at 4 weeks failed to lower the blood pressure [13]. The fall in blood pressure that occurs with unclamping of the renal artery is correlated with significant negative sodium and water balance [7]. Hence, in the chronic state, the hypertension is maintained by volume expansion and is not the consequence of elevated AII. The interrelationship between these two hypertensive mechanisms has been shown in the rat by Gavras [14] and in the dog by Ayers [15]. Gavras and co-workers demonstrated that the one-kidney sodium-restricted rat did maintain angiotensin II-dependent hypertension at 4 to 6 weeks, as shown by a marked drop in blood pressure with administration of Sar^1-Ala^8-angiotensin II. In contrast, these same animals failed to show a response to the AII inhibitor after sodium repletion [14]. In the dog, too, Ayers and co-workers showed that the elevated intrarenal resistance characteristic of the chronic model [15] is AII-dependent only when the animal is sodium-depleted.

In contrast to the one-kidney model, Brunner and co-workers showed that the two-kidney Goldblatt rat did remain AII-dependent at four weeks because administration of an angiotensin inhibitor promptly and dramatically lowered the blood pressure [13]. The two-kidney model apparently loses sodium and water through the opposite kidney, allowing renin secretion from the clipped kidney to continue unabated. With time, however, more subtle sodium retention does occur [9], possibly due to contralateral renal damage, and by 14 weeks, overt AII dependency is lost in the rat unless the animal is also sodium-depleted [16].

Implications for human renovascular hypertension

The mechanisms observed in the animal models as the hypertension evolves from a renin-dependent state to a sodium-volume-dependent state do, in fact, occur in patients with renal disease as well. In some patients who appear to have unilateral renal arterial or renal parenchymal disease, PRA is nevertheless normal [2, 17]. This may mean that the contralateral kidney has occult disease and is thus unable to excret sodium normally, which ultimately results in volume expansion and suppression of renin release. The clinical implication is that the blood pressure response to renal revascularization might be limited by the existing disease in the opposite kidney. Improvement or even cure might still be achieved by successful revascularization because restoration of renal blood flow and glomerular filtration to the ischemic kidney could result in enhanced sodium and water excretion

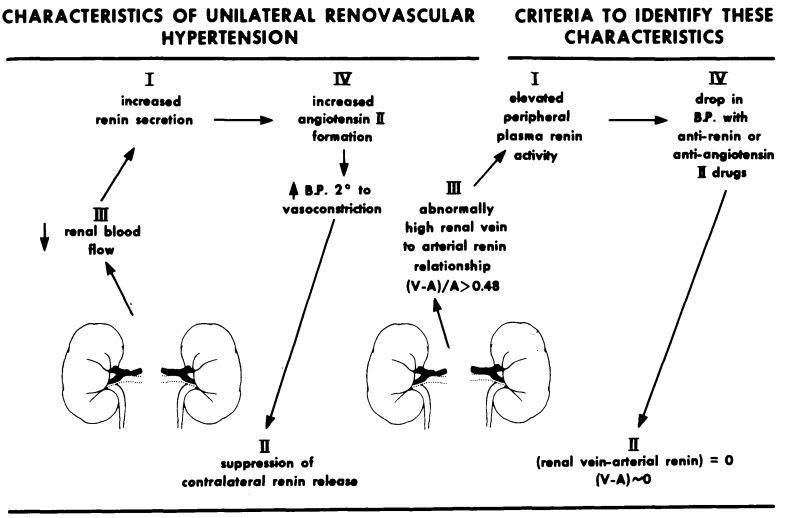

Figure 1. Traits of renin-dependent hypertension found in the two-kidney one-clip rat model (left) and the criteria derived from the animal model which identify the patient with correctable renal hypertension (from Vaughan ED Jr, Cardiovasc Med 1:195, 1976).

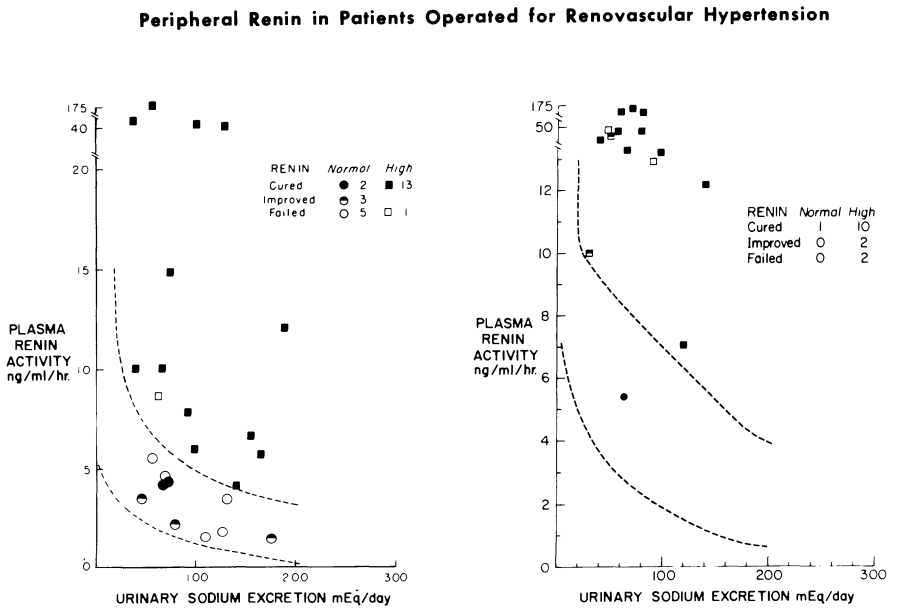

Figure 2. High peripheral plasma renin activity indexed against 24-h sodium excretion as found in 23 of 26 patients with renovascular hypertension cured by corrective surgery. Open symbols represent failures and all open squares represent technical failures (from Vaughan ED Jr, Urol Clin North Am 6:485, 1979).

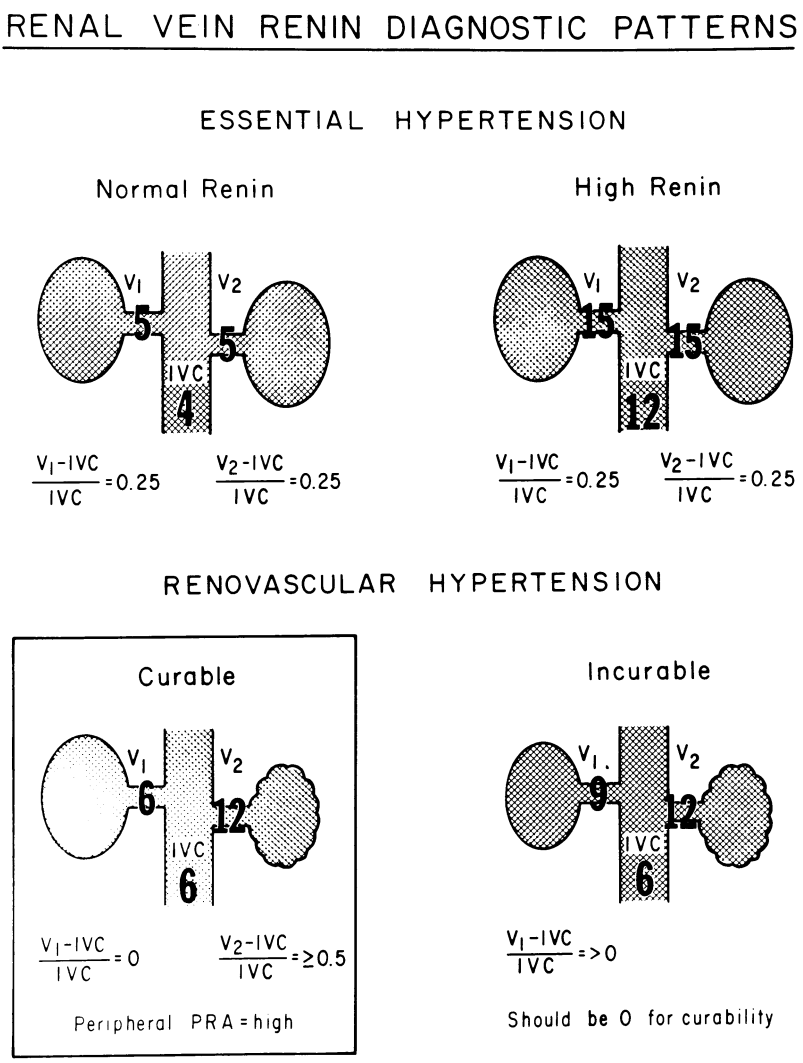

Figure 3. Diagnostic features of renovascular hypertension from renal vein renin measurements. V_1, V_2, and IVC refer to renin activity in renal veins and inferior vena cava. (From Laragh Jh, Sealey JE, Cardiovasc Med 2:1053, 1977)

and a reduction of the volume-dependent component of the hypertension. The overall chance of a cure would be less, however, than if disease were limited to the kidney with arterial stenosis. In these studies, only renal revascularization is indicated; nephrectomy is contraindicated because, obviously, any further reduction of functioning renal mass could prove injudicious.

In the renin-dependent phase, the pure two-kidney model helps identify characteristics of unilateral renovascular hypertension in man (see Figures 1 and 3). Here, the total renin secretion remains elevated, there is no renin

secretion from the normal opposite kidney, blood flow to the kidney with stenosis is reduced, and the resultant hypertension is maintained by AII-induced vasoconstriction. The challenge to the clinician is to identify these characteristics in patients with renal arterial disease.

We now utilize renin measurements to search for three criteria which identify the curable patient with Goldblatt hypertension.

Peripheral plasma renin activity

Unilateral hypersecretion of renin should be the hallmark of potentially curable renovascular hypertension. This hypersecretion should be reflected by an elevated peripheral PRA level as compared with PRA values obtained from normotensive controls and collected and analyzed under exactly the same conditions. In two institutions, we have found that peripheral PRA (determined in blood collected at noon after 4 h of patient ambulation), when indexed against sodium excretion, is an excellent tool in identifying abnormally high renin secretion. This high rate of secretion is present in most patients with proven renovascular hypertension (Figure 2) [2, 18]. The problem is that patient preparation and PRA interpretation must be meticulous. If the pitfalls listed in Table 2 are avoided, the test is extremely useful.

We feel that the peripheral renin level is a true indicator of renal renin secretion. This conviction is based on our study showing that the clearance

Table 2. Pitfalls to avoid in determination of peripheral plasma renin activity (PRA)

1. The 'normal' value for PRA varies from laboratory to laboratory	1. Clearly understand what 'normal' means in your laboratory a. Time of sampling b. State of ambulation (upright posture influences PRA) c. State of sodium intake
2. Blood samples from patients are not collected in a similar fashion as samples used to define the normal range	2. Utilize identical conditions for sampling
3. All antihypertensive and diuretic drugs affect PRA	3. Stop all treatment 2 weeks prior to blood sampling for PRA
4. PRA is inversely related to sodium intake/excretion	4. Collect a 24-h urine for sodium at the time that you collect blood for PRA and use the sodium intake that your laboratory used to define their normal range

Source: E. D. Vaughan Jr, Laboratory tests in the evaluation of renal hypertension. Urol Clin North Am 6(3): 485, 1979.

rate of renin is a constant fraction of the peripheral level of renin in hypertensive patients, irrespective of the absolute level of renin secretion [19].

Differential renal vein renin determinations

Since the work of Judson and Helmer [21], differential renal vein renin determinations have emerged as the most useful tool in identifying correctable renovascular hypertension. The most common approach is to calculate the renal vein renin ratio, stenotic to normal side values (V_S/V_C)*, with some arbitrary 'positive' ratio (usually 1.5:1). Marks and Maxwell have discussed lucidly the value and limitations of this approach with special emphasis on factors responsible for inaccurate results [6]. In addition to technical problems, analysis of the renal vein renin ratio is limited in two important ways. To have predictive value, a 'positive' renal vein renin analysis should signify unilateral hypersecretion of renin from the suspect kidney. However, it is not generally recognized that an abnormal renal vein renin ratio need not indicate either hypersecretion of renin or lateralization of renal disease. For example, renin secretion can be determined only with

Table 3. Renin values for predicting curability of renovascular hypertension

Collection of samples (moderate sodium intake 40–100 mEq/day)	
1. Ambulatory peripheral renin and 24-h urine sodium excretion under steady state conditions (i.e., not on day of arteriography)	
2. Collection of blood for PRA before and after converting enzyme blockade	
3. Collection of supine	
a. Renal vein renin from suspect kidney (V1) and inferior vena cava renin (A1)	
b. Renal vein from contralateral kidney (V2) and inferior vena cava renin (A2)	
4. Enhancement of renin secretion by converting enzyme blockade if initial renin sampling is inconclusive	
Criteria for predicting cure	
High PRA in relation to UNaV	Measurement of hypersecretion of renin
Contralateral kidney: $(V2-A2) = 0$	An indicator of absent renin secretion from the contralateral kidney
Suspect kidney: $(V1-A1)/A1 = 0.50$	An indicator of unilateral renin secretion
$(V1-A1)/A1 > 0.50$	Measurement of reduced renal blood flow
$\frac{(V-A)}{A} + \frac{(V-A)}{A} < 0.50$	
In patients with high PRA	
Means: a. Incorrect sampling	
b. Segmental disease	Repeat with segmental sampling

knowledge of the renal plasma flow and the arterial-to-venous renin difference across the renal bed:

$$RPF\,(RV_{renin} - RA_{renin}) = \text{renin secretion.}$$

Woods and Michelakis [21] clearly demonstrated that both a reduction in renal blood flow and unequal renin secretion contributed to unequal renal vein renin ratios in a group of patients with renal arterial stenosis. In fact, two patients with renal vein renin ratios of 1.9 and 3.4 actually had less renin secretion from the kidney with renal arterial stenosis. Both patients failed to be cured by nephrectomy. In addition a 'positive' renal vein renin ratio does not determine whether or not the opposite kidney is contributing to the total renin secretion. The demonstration of unequal bilateral renin secretion can be determined only by subtracting the arterial renin input from the renal venous renin value ($RV_{renin} - RA_{renin}$)*. If present, bilateral renin secretion is a characteristic of bilateral disease which might limit the blood pressure response to corrective surgery on one side only.

A more rational approach to renin analysis, based on the characteristics of experimental one-clip, two-kidney Goldblatt hypertension, is detailed in Table 3. As previously stated, hypersecretion of renin, as determined by the renin-sodium index, is the first criteria for the diagnosis of renovascular hypertension. However, a high PRA is found in 16% of patients with essential hypertension [22] and 13% of patients with unilateral renal parenchymal disease [17]. Hence, it is necessary to establish the unlaterality of a renin hypersecretory state.

Suppression of renin secretion from the normal kidney can be determined easily by subtracting the arterial plasma renin activity from the renal venous renin activity. Hence, the second criterion of patients with curable renovascular hypertension is an absence of renin secretion from the opposite kidney, $(V - A) \sim 0$, termed contralateral suppression of renin [2, 23].

Contralateral suppression of renin release indicates that the opposite kidney is responding in an appropriate, 'normal' fashion, but does not exclude the possibility of bilateral renal artery stenosis.

The third criterion is based on studies of renal vein and arterial renin relationships in patients with essential hypertension. The mean renal venous renin increment has been determined to be about 25% higher than arterial PRA (Figure 3) [19]. Hence, a total renin increment of approximately 50% is necessary to maintain a given peripheral renin level, $(V - A)/A = 50\%$. However, we have already emphasized that a reduction in renal blood flow also influences the renal venous renin level. In this setting, the renal venous renin concentration is misleadingly high, shifting the renal vein to arterial renin relationship upwards and to the left. Hence, the elevation of the increment above approximately 50% is an index of the severity of the reduction in blood flow subsequent to the vascular lesion [2, 19].

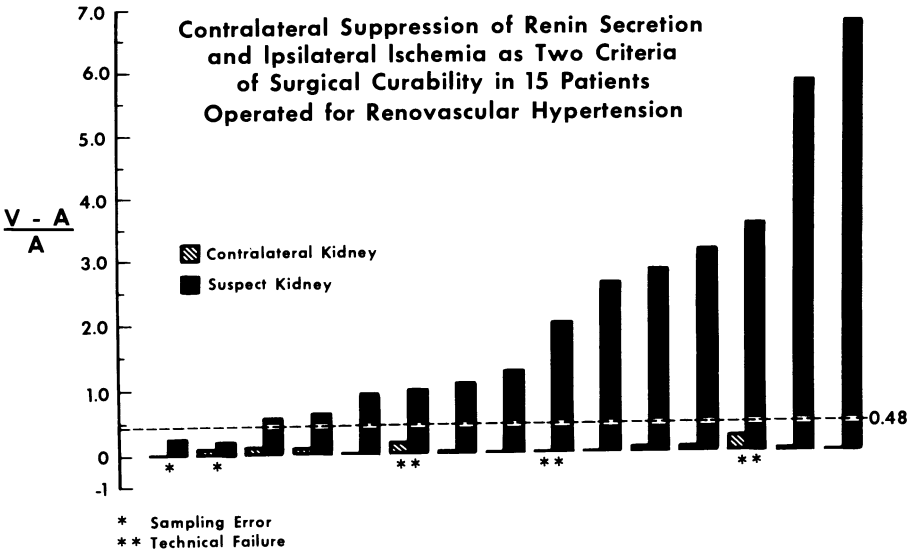

Figure 4. Renal vein renin values in 15 patients operated on for renovascular hypertension.

This physiologic interpretation also explains why the simple renal vein renin ratio analysis (V_s/V_c) has been useful despite the theoretical limitations. If the contralateral ($V_c - A$) is approximately 0, the V_c equals A. Substituting the arterial renin value (A) for the renal venous renin value (V_c) from the opposite or normal kidney, the standard renal vein renin ratio is rewritten (V_s/A). The value indicating a 'positive' ratio (1.5:1) is the same as our physiologically derived equation of $(V-A)/A$ = approximately 50%.

The combination of an abnormal vein-arterial renin relationship from the kidney with the vascular lesion and contralateral renin suppression has been characteristic of curable renovascular hypertension in our experience.

The relationship between the second and third criteria and the results of surgery in 15 patients are shown in Figure 4. Among all patients cured or improved by surgery the contralateral kidney showed little or no renin secretion and the fractional production of renin was greater than 0.50 with two exceptions. The exceptions are important in that the finding of little renin secretion in a patients with a high PRA indicates that either the sampling is improper or that branch or segmental renal disease is present and only renal venous blood from uninvolved renal segments was sampled.

In patients with unilateral renal artery stenosis and hypertension we related renal vein renins to the effects of technically successful angioplasty. Before angioplasty 80% of the patients had high peripheral plasma renin activity, and nearly all showed hypersecretion of renin from the stenosed side coupled with contralateral suppression. Angioplasty was possible in 87% of patients with fibromuscular dysplasia, and 57% with atheroma.

Following successful angioplasty the hypertension was cured or improved in 93% of patients with fibromuscular dysplasia, but in 84% with atheroma.

Most of these patients had renal vein renin values which were diagnostic by the criteria of Vaughan et al. [2]. By these criteria, the sensitivity of abnormal renal vein renin study was 75%, and the specificity 100%. If the renal vein data were analyzed taking only the ratio between the two sides, using 1.5:1 as the upper limit of normal, the sensitivity was 63%, and the specificity 60%. The abnormal renal vein renin patterns returned to normal following angioplasty [24]. Thus, renin-sodium profiling and renal vein renin measurements provide a reliable means for identifying patients who are suitable candidates for renal angioplasty.

Identification of angiotensin II dependency of blood pressure

The fourth characteristic of experimental one-clip, two-kidney Goldblatt hypertension in its early stage is that the hypertension is dependent on AII-induced vasoconstriction. Hence the blood pressure response to a number of pharmacologic probes can provide important information about the degree of renin (AII) dependency of the hypertension in individual patients. Our first hint of these pharmacologic implications followed the observation that beta-adrenergic blocking agents, such as propranolol lower blood pressure largely by lowering renal renin secretion and PRA [25]. Accordingly a good blood pressure response to propranolol indicates renin dependency of the pressure and suggests to the physician that evaluation for underlying renal disease should proceed.

This concept has been strengthened further by development of drugs which more specifically block the renin-angiotensin system. The first drug Sar^1-Ala^8-angiotensin II (saralasin) lowers the blood pressure in patients with renin-dependent hypertension by competing for AII receptor sites [26]. Although a positive (depressor) blood pressure response is valuable information it is now clear that some patients with curable renovascular hypertension will not exhibit a fall in blood pressure [18]. This puzzling lack of blood pressure response is probably because saralasin itself is a partial agonist [27].

Recently, compouns (teprotide, captopril, enalapril) have been developed which block the action of AI converting enzyme and are devoid of agonist activity [28, 29]. Utilizing these compounds almost all patients with high PRA and most with normal PRA lower blood pressure. However, the blood pressure response to the oral agent captopril is not specific enough to differentiate patients with renovascular hypertension and essential hypertension.

In this regard studies by Case and co-workers [30] have demonstrated

that there is another response to angiotensin blocking drugs which has as great or even greater potential in discriminating correctable renovascular hypertension from essential hypertension. Under similar conditions patients with renovascular hypertension have a greater reactive rise in PRA in response to AII blockade than that found in patients with essential hypertension. This 'uncorking' of renin is probably due to a combination of the renin response to a fall in blood pressure and removal of a direct AII feedback suppressing renin release [15].

The observation has two clinical implications. First the reactive rise in PRA can be added to the blood pressure response to angiotensin blockers as indicators of renovascular hypertension [39]. Secondly the 'uncorking' phenomenon may be valuable during renal vein renin sampling. Hence, we and others [30, 31] have found that the increase in renin secretion following administration of captopril issue only from the involved side whereas the renin from the contralateral kidney remains suppressed. Accordingly, the discriminating capability of renal vein renin sampling in identifying unilateral disease is enhanced by the acute administration of captopril. Long term administration of captopril, however, may make renal vein renins uninterpretatable, because the incremental secretion of renin, $(V-A)/A$, from the ischemic kidney is often low [24].

Anatomic confirmation of the four criteria

It should be noted that the entire evaluation of the hypertensive patient can be accomplished without hospitalization. Moreover, not only has screening been accomplished but criteria identified which almost guarantee that the patient has unilateral renal disease of sufficient severity to result in Angiotensin II dependent hypertension which should be reversible by correction of the underlying renal abnormality. Accordingly, only a small number of patients, who are quite likely to be candidates for intervention rather than medical management, are selected for anatomic studies such as renal arteriography, or intravenous urography should the arteriogram exclude renal vascular disease. These anatomic studies serve as a guide to select appropriate surgical or radiological management.

Clinical features of renovascular hypertension

The exact prevalence of renovascular hypertension in the general population is not known, but is often quoted as being around 5% of all hypertensive patients [32]. Since the diagnosis is often missed by conventional screening procedures, this figure may well be an underestimate.

In the overwhelming majority of cases the etiology of the renal artery stenosis is due to atheroma (approximately 2/3) or fibromuscular dysplasia (approximately 1/3), with a small number being due to other causes such as arteritis, post-surgical trauma, or Von Recklinghausen's disease. Renal artery stenosis is not uncommon in patients who have had a renal transplant. Clinical features of renovascular hypertension are given in Table 4. Fibromuscular dysplasia should be suspected in any young non-obese white woman with a recent onset of severe hypertension, but is rare in blacks; atheromatous renal artery stenosis should be suspected in any middle aged hypertensive patient with evidence of the arterial disease such as vascular bruits, or a history of claudication or coronary artery disease. The high incidence of smoking in patients with renovascular hypertension is another diagnostic cue [33].

The prognosis of patients with renovascular hypertension depends on two factors: the etiology of the stenosis and the degree of renal ischemia. Patients with atheromatous stenoses have a high incidence of stroke and myocardial infarction, and may progress to chronic renal failure when the disease is bilateral. Fibromuscular dysplasia is most commonly confined to the renal arteries, but may rarely occur in other vessels as well. The natural history of renovascular hypertension is much more benign when it is due to fibromuscular dysplasia rather than to atheroma, although renal failure may occasionally develop.

Table 4. Clinical characteristics of renovascular hypertension

		Renovascular hypertension	
	Essential hypertension	Atheroma	Fibromuscular dysplasia
Race (black)	29%	7%	10%
Family history	67%	58%	41%
Age at onset			
< 20 years	12%	2%	16%
> 50 years	7%	39%	13%
Duration < 1 year	10%	23%	19%
Obese	38%	17%	11%
Abdominal bruit	7%	41%	57%
High renin profile	15%	80%	80%
Hypokalemia (K < 3.4 mEq/L)	7%	14%	17%
Smoking	42%	88%	71%

Pathology of the renal arteries

The demonstration of a stenosis in a renal artery in a hypertensive patient does not necessarily imply that the stenosis is causing the hypertension, particularly when it is atheromatous. Hypertension from any cause accelerates the development of atheroma, so that in some cases a stenosis in a renal artery may occur secondarily to essential hypertension. To cause renal ischemia and hypertension, a stenosis must occlude at least 75% of the arterial luman, but the correlation between the arteriographic appearance and the degree of ischemia is poor.

Atheromatous plaques occur most commonly in the proximal third of the renal artery, and in many cases plaques in the wall of the aorta may encroach on the ostium of the renal artery. Fibromuscular dysplasia has been divided into a number of subtypes according to their pathological appearance. The commonest variety (65%) is medial fibroplasia with mural aneurysms, which comprises alternate areas of fibromuscular thickening with areas of thinning in the distal renal arteries, and gives a beaded appearance on an angiogram. The next commonest variety is perimedial fibroplasia (25%) where there is proliferation of fibrous tissue in the outer half of the media. Radiographically the appearance is also of beads, but they are not aneurysmal, so that they are of smaller diameter than the arterial lumen. The stenoses are often quite severe. Medial dissection (5%) is characterized by dissection of the internal elastic membrane which produces the appearance of a fusiform enlargement of the renal artery. Medial hyperplasia and internal fibroplasia (5%) are angiographically indistinguishable and may produce a single proximal stenosis which can resemble atheroma.

Diagnosing renovascular hypertension

Many features of the clinical history and examination may suggest the possibility of renovascular hypertension. These include age of onset, abdominal bruits, and unexplained hypokalemia. These features are not always present, however, so that there is a need for a screening test.

For many years the rapid sequence intravenous pyelogram (IVP) has filled this role. Surveys of its usefulness, however, have indicated that the number of hypertensive patients whose treatment is altered as a result of previously unsuspected abnormalities is very small, being 0.9% in one series [34], and 1.3% in another [35]. In the US Cooperative series the criteria for an abnormal IVP were: delayed excretion, a difference in size of 1.5 cm or more between the two kidneys, and differences in dye concentration [36]. It was found that approximately 78% of patients with renovascular hypertension have an abnormal IVP, but there was a false positive rate of 11%. However,

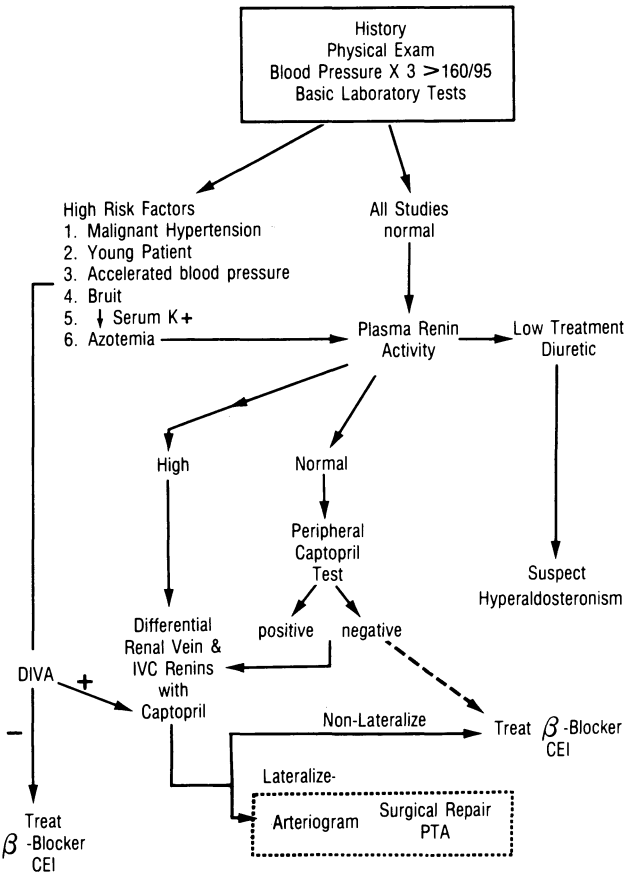

Figure 5. Flow chart for diagnostic evaluation of patients with suspected renovascular hypertension. Note that an IVP is not included, and that arteriography is the last step. (From Sosa RE, Vaughan ED. In: AVA Update Series 2, Lesson 31, 1983)

since the IVP was probably used to make the diagnosis of renovascular hypertension in many of these patients, the true sensitivity of the IVP is probably lower than the reported 78%: many of our patients with renovascular hypertension have had normal IVPs, and we no longer use it as a routine screening procedure.

Renal scans (isotope renograms) have also been used as a screening procedure. These are based on the finding that I^{131} hippuran is selectively taken up by the kidney, and the technique has been used both to measure renal size and blood flow. However, the test has an unacceptably high rate of both false positives and false negatives, and is relatively expensive [37]. Its use as a routine screening procedure is therefore not recommended.

The blood pressure response to infusion of Saralasin, a competitive angiotensin antagonist, has also been advocated by some authors, but it is relatively expensive to perform as a screening tests, not without risk and not very reliable [38].

We believe that renin-sodium profiling is the most cost-effective form of screening procedure presently available for detecting renovascular hypertension, for about 80% of patients have high plasma renin activities [24].

Our own schema for the evaluation of hypertensive patients for renovascular hypertension is shown in Figure 5. We perform renin-sodium profiling after discontinuation of all antihypertensive medications whenever possible. If the patient has complications such as cardiovascular or cerebrovascular disease it may not be possible to do this, in which case the diagnosis can be evaluated by renal sonography, renal vein renins, or digital intravenous angiography. Another very promising diagnostic test is provided by giving the patient a single 25 mg oral dose of captopril and measuring the response of plasma renin activity and blood pressure. Patients with renovascular hypertension show a much bigger rise of renin than in essential hypertension, although the differences in the blood pressure response is less pronounced [20, 39]. For those patients with high renin-sodium profiles or a positive captopril test, we would next proceed to perform renal vein renins, which can be done as an outpatient procedure, preferably while on no medication. These can in some cases be done before and after acute administration of captopril or in conjunction with digital intravenous angiography. If these tests are suggestive of renovascular hypertension the patient is admitted to hospital for arteriography, and if this confirms the diagnosis angioplasty can be performed at the same session.

Tailored therapy for renovascular hypertension

The rationale for identification of patients with renovascular hypertension is that their management will differ from the treatment offered patients with essential hypertension. Indeed, hypertension of renal origin is difficult to manage with conventional antihypertensive drugs. In the randomized study by Hunt in 1973 [40] morbidity and mortality was greater in patients with renal hypertension treated in the medical group as contrasted to the surgical group. Accordingly, for properly selected cases surgical management has been the preferable choice of treatment.

However, with the development of better and more specific antihypertensive drugs such as captopril and beta-blockers it is now possible to treat cases of renovascular hypertension more effectively than ever before. Certainly in our early experience, captopril appears effective in controlling blood pressure in patients who are poor surgical candidates. While more specific medical management is attractive it must be remembered that most renal arterial lesions are progressive, and dramatic reduction of blood pressure can lead to rapid progression and total occlusion. Accordingly, if the physician chooses medical management, both ipsilateral renal function, probably by radionuclide studies, and blood pressure must be monitored.

Surgical management of renovascular hypertension

The is the first operative cure of hypertension followed unilateral nephrectomy [41]. Today the indicators for primary nephrectomy, rather than a procedure to preserve renal function, are limited. Nephrectomy is utilized only (1) if there is poor or absent renal function, (2) in poor risk patients, (3) if there is uncorrectable vascular disease, and (4) following occlusion of an attempted revascularization. Partial nephrectomy can be utilized if there is stenosis of one of multiple renal arteries or of a branch. However, revascularization or angioplasty preferable. Endarterectomy was the first revascularization procedure described as an alternative to nephrectomy, however aorto-renal bypass utilizing saphenous vein or hypogastric artery is now the most commonly utilized surgical technique. In the US Cooperative study the blood pressure response to operative treatment of 502 patients was 51% cured, 15% improved and 34% failed [42]. However, at the time, renin determinations were not available for proper patient selection and postoperative arteriograms were not performed in all patients whose blood pressure failed to respond. Nevertheless, several points are clear. Patients with fibromuscular disease had a favorable blood pressure response (80%) more commonly than patients with atheromatous disease (63%). Moreover, patients with bilateral atheromatous disease had a less favorable response (56%) and a high mortality rate (10%). The overall mortality rate was 6% with a preponderance of deaths in patients with atheromatous (9.3%) disease in contrast to fibromuscular (3.4%) disease [1]. Other significant factors included the presence of atherosclerotic coronary artery disease and serum creatinine levels of greater than 1.4 mg %.

In contrast to the cooperative study, utilizing more rigorous techniques for patient selection, the UCLA group has recently reported an 80% cure, 15% improved, 3% failure and 2% mortality rate in 142 consecutive cases operated upon for renovascular hypertension since 1972 [43]. Moreover, the graft occlusion rate was only 10%. Hence, with improvement of patient selection as previously described, the recent technical advancements surgical management is the treatment of choice if percutaneous transluminal angioplasty is impossible or has failed.

Percutaneous transluminal dilatation (angioplasty)

Dilatation of stenosed renal arteries utilizing angiographic techniques now is gaining acceptance. In 1978, Gruntiz reported successful dilatation of an atherosclerotic renovascular lesion [44]. Subsequently, both fibromuscular and atheromatous lesions have been dilated with success (Figure 6 A and B).

In our own series of 89 patients we found that hypertension was cured or improved in 93% of patients with fibromuscular dysplasia in whom the

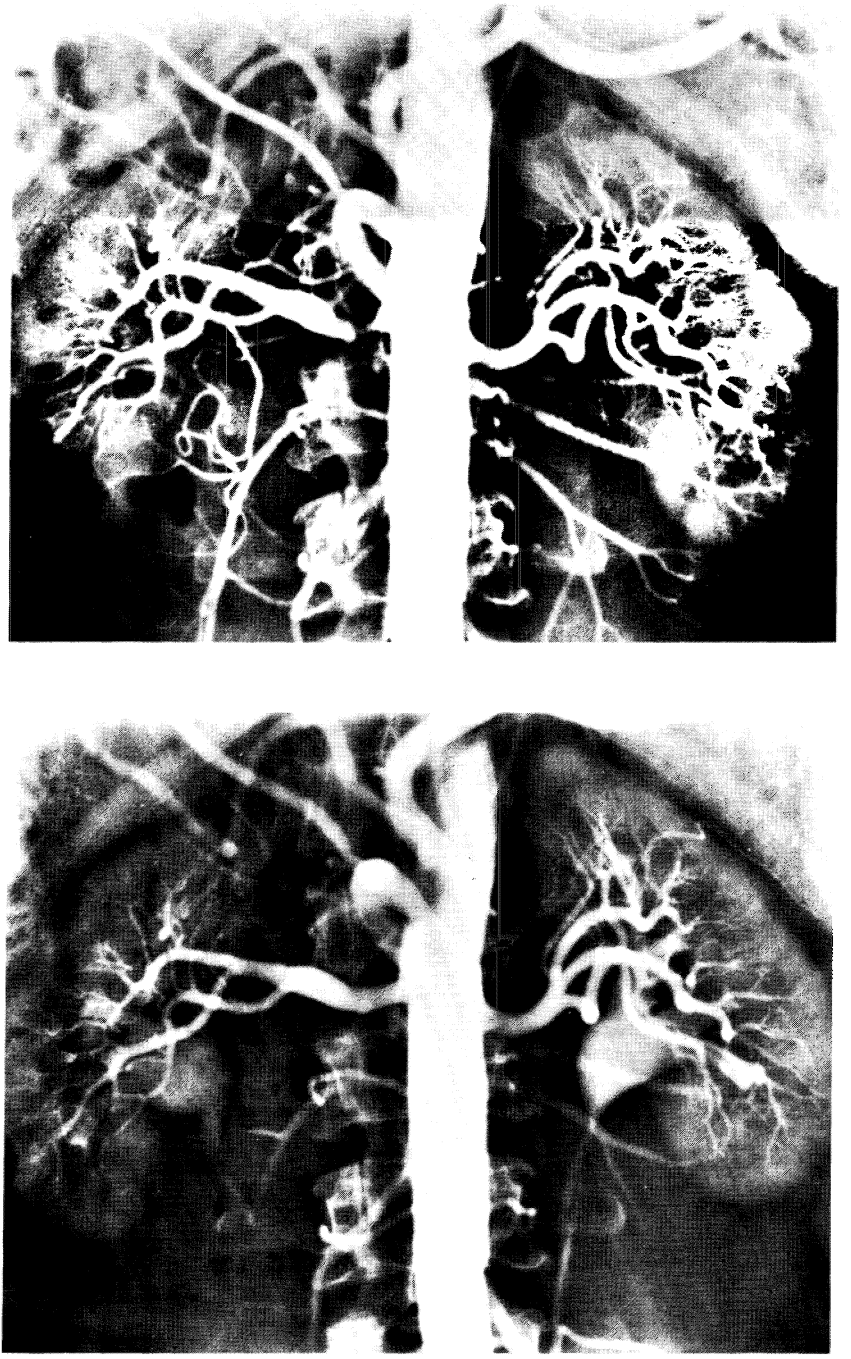

Figure 6. A (upper) and B (lower) arteriogram before and after successful renal angioplasty in a 50-year-old man with atheromatous unilateral artery stenosis. (From Vaughan ED. In: Brenner BM, Stein JM (eds) Hypertension. New York, Churchil Livingstone, (1981).

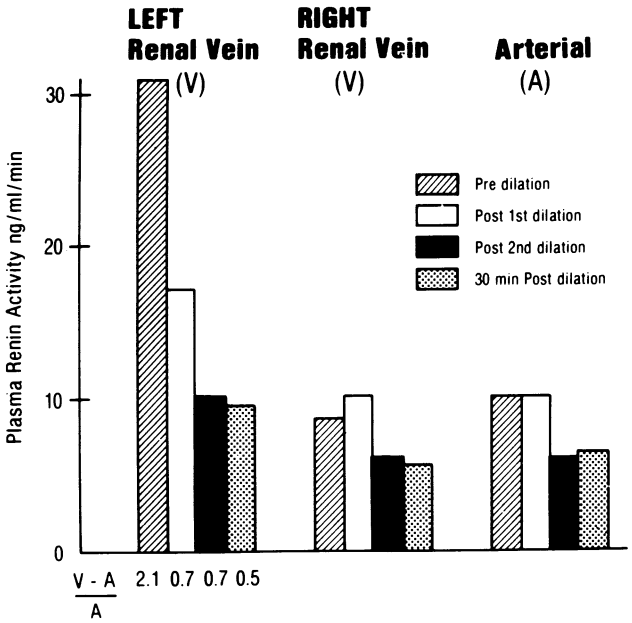

Figure 7. Changes in renal vein renin patterns immediately following successful angioplasty in a patient with left renal artery stenosis. Note rapid restoration of normal patterns.

stenosis could be dilated by angioplasty [45]. Follow-up of these patients for up to 3 years has not shown any significant tendency for the stenosis to recur. In patients with atheromatous renovascular hypertension the situation is different, mainly because in many of them it is not technically possible to pass the catheter across the stenosis or to dilate the stenosis satisfactorily, either because the stenosis is too tight or occluded, or because it is at the ostium of the renal artery as an extension of an atheromatous plaque in the aortic wall. Thus, successful angioplasty could only be achieved in 57% of patients with unilateral atheromatous stenoses, but in these patients the rate of cure or improvement was 84%. In the majority of patients the beneficial effects of angioplasty appear to persist, at any rate of 1 or 2 years; the abnormalities of renal vein renin secretion become normalized, and we observed a 12% increase in the size of previously ischemic kidney over an average follow-up period of 22 months. In some uremic patients renal function may be improved as a result of angioplasty [45]. Successful angioplasty is accompanied by a return of renal vein renins to normal levels (Figure 7).

The major complication of angioplasty is dissection of the intima of the renal artery, which may necessitate surgical repair. This usually can be achieved by revascularization of the kidney, which in most cases would have been done anyway if angioplasty had not been attempted. This occurred in 4% of our patients. In atheromatous patients the prolonged catheter-

ization procedure may result in persistent bleeding at the puncture site, requiring surgical repair, and the volume of dye used during the procedure may cause transient renal failure.

On the basis of these results we believe that renal angioplasty is the treatment of choice for patients with fibromuscular dysplasia, because the therapeutic results are as good as with reconstructive surgery, and with less cost and trauma to the patient. For patients with atheromatous stenoses the situation is less clear cut. When the stenoses is at the ostium of the renal artery angioplasty is rarely beneficial, but such lesions may be bypassed by surgery, which is therefore the preferable form of treatment. For unilateral non-ostial atheromatous stenoses, the results of surgery and angioplasty are comparable, although some groups have reported a high incidence of restenosis following angioplasty [46]. We have not encountered this problem to a major degree, which may be because we dilate the stenosis to a greater extent than some other workers. Since angioplasty can be performed at the same time as arteriography, there is little to be lost by attempting it in such patients.

Laboratory tests following renal revascularization

Inherent in the care of patients with renovascular hypertension is close and continuing post-operative blood pressure recording. In fact, sustained blood pressure response at least one year following surgical correction is mandatory before the diagnosis of renovascular hypertension is validated. In the past, the definition of 'successful' revascularization was often arbitrary especially in terms of the category 'improvement' i.e., 15% decrease in diastolic pressure of 'blood pressure easier to control with antihypertensive medications'.

At present, the definition of a surgical response should be predicated on reversal of the pathophysiologic abnormalities underlying renovascular hypertension. Hence, patients with inadequate blood pressure responses to surgical intervention require repeat PRA determinations and/or anti-angiotensin testing with presence of the criteria for renovascular hypertension (post-operatively) signifying technical failure of renal revascularization [18].

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5. Hypertension in Urological Disease

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Introduction

Renal disease has been recognized in association with hypertension since the early nineteenth century [1]. In 1898 Tigerstadt and Bergman demonstrated that a water soluble extract they named renin, derived from the renal cortex of a healthy rabbit could produce a marked and sustained hypertension when intravenously injected into a second rabbit [2]. They theorized that renin could be indirectly responsible for the cardiac hypertrophy seen in some forms of renal disease. Interest in the relation between renal disease and hypertension did not flourish until Goldblatt's classic experiments in the dog demonstrated that reversible elevation in the systemic blood pressure could be produced by clamping the main renal artery of one of two healthy kidneys [3]. The blood pressure would then return to normal on removal of the kidney or the clamp.

In 1937, Butler reported on a 7-year-old boy with the rapid onset of hypertension in the setting of chronic pyelonephritis and hydronephrosis following relief of obstruction by the removal of a large distal ureteral calculus [4]. Nephrectomy cured the patient of his hypertension and initiated an epidemic of nephrectomies in hypertensive patients who had either small or hydronephrotic kidneys. Smith's careful review of the literature in 1956 exposed a disappointing 26% cure rate for hypertension by nephrectomy [5]. The cure rate was undoubtedly biased as many nephrectomies that failed to correct hypertension were presumably not reported in the literature. Moreover since undoubtedly some of these 'small kidneys' were due to unrecognized renal vascular disease, the cure rate in pure parenchymal disease must have been even lower. It nevertheless became clear that unilateral renal disease coexists with hypertension much more often than is causally related to it. Stricter and more reliable guidelines seemed necessary to justify the removal of a morphologically abnormal kidney in a hypertensive patient.

Widespread use of arteriography in the 1960s shifted the focus of curing hypertension by surgical means to renovascular lesions. By 1975 the cooperative study of renovascular surgery for hypertension revealed a 51% cure rate, a 15% improved rate, a 34% failure rate, with serious morbidity in 13% of cases and a mortality of 5.7% [6]. The success rate clearly was better yet not adequate, demonstrating the need for better diagnostic procedures to help in discriminating functional renal and renovascular anatomic abnormalities from non functional ones, to select patients for potentially curative surgery.

A better understanding of the pathophysiology of renovascular hypertension has come about in the past decade, in large part due to the development of angiotensin II (AII) antagonists (AII A) and converting enzyme inhibitors (CEI). It is recognized that the hypertensive patient with renal artery stenosis or renal parenchymal disease most likely to benefit from surgical or angioplastic intervention is the one whose disease is analogous to the two kidney, one-clip Goldblatt model. This model and patients with potentially curable unilateral renal hypertension exhibit four characteristics: (1) increased renin secretion manifest by an elevated peripheral plasma renin activity (PRA) when indexed against sodium excretion; (2) blood pressure dependency upon a increased circulating AII, demonstrated by a fall in blood pressure with the administration of an AII A or a CEI; (3)

Table 1. Non-vascular renal hypertension in unilateral renal parenchymal disease

I. Diseases where surgery is indicated:
   A. Neoplasia
      1. Renal cell carcinoma
      2. Wilms' tumor
      3. Juxtaglomerular cell tumor
   B. Urinary obstruction
      1. Unilateral obstruction
      2. Bilateral obstruction
   C. Solitary large renal cysts

II. Diseases where the indications for surgery must be demonstrated:
   A. Infectious
      1. Unilateral chronic pyelonephritis
      2. Unilateral renal tuberculosis
      3. Unilateral xanthogranulomatous pyelonephritis
   B. Reflux
      1. Unilateral reflux nephropathy
      2. Congenital segmental hypoplasia
   C. Radiation nephritis
   D. Page kidney
   E. Polycystic kidney disease

absence of renin secretion from the opposite uninvolved kidney, termed contralateral suppression of renin release, as demonstrated on renal venous sampling by equality of renal venous and caval renin (RV – IVC) ≅ 0; (4) an increase in renal venous renin from the involved kidney of 50% or more above the caval renin indicating unilateral renin secretion and usually reduced renal blood flow. For more detail see Chapter 4.

At present, the meticulous assay of PRA, the use of AII A or CEI, taken together with a careful history, physical examination and angiography has led to more reliable identification of those patients whose hypertensive disease will respond to surgical therapy [7, 8].

Renal disease of various forms is the most common cause of secondary hypertension. However, renovascular disease is the most likely form of potentially curable hypertension, accounting for 5–10% of all hypertensive etiologies. In contrast renal, non-vascular causes of hypertension are rare; the exact incidence is not known. In a subgroup of these patients the hypertension is renin mediated, and potentially curable if properly recognized and treated (see Table 1). Renin profiles similar to those that predict surgical curability in renovascular hypertension are found in this subgroup. Awareness of the association of unilateral renal parenchymal diseases with increased renin secretion, the natural history and options for treatment will lead to their more frequent diagnoses and proper management.

Causes of non-vascular renal hypertension

Unilateral chronic pyelonephritis (UCP)

It is of interest that in the 1940s and 1950s unilateral chronic pyelonephritis was the lesion most frequently treated by nephrectomy in hypertensive patients. Today it is rare to find a well documented case of UCP not associated with reflux, where the affected kidney can be proven to be responsible for the pressure elevation [9]. The main reason for this difference is undoubtedly the stricter criteria that are currently utilized to define a pressor kidney, and also stricter criteria for the diagnosis of UCP. Thirty and 40 years ago most small and scarred kidneys were grouped together on morphological grounds under the name of chronic pyelonephritis, regardless of etiology. Renal cortical scarring and thinning may also be due to renal arterial insufficiency with or without infarcts, congenital segmental hypoplasia and reflux refropathy. To ascertain the diagnosis of UCP, a history of recurrent urinary tract infections with occasional associated ipsilateral flank pain and fever is desirable. Differential urine collections for bacterial culture via ureteral catheters will confirm the diagnosis by revealing the affected kidney to be the focus of infection.

Pfau argues that UCP is often associated with excessive salt and water loss, thereby offering the patient protection from pressure elevation [9]. The vast majority of patients with UCP and hypertension will be suffering from essential hypertension requiring medical management.

On the other hand, UCP associated with a history of ureterovesical reflux, appears to have a role in the etiology of hypertension in 10% of these cases [10]. In their study of 16 hypertensive children with reflux, Savage et al. found nine (60%) to have elevated peripheral PRA. Of note, no maneuvers were utilized to enhance renin secretion nor were renal vein renins studied which perhaps would have resulted in the finding of abnormal renin secretions in additional patients. In 100 normotensive children with reflux nephropathy, eight were found to have abnormally elevated peripheral PRA, leading one to wonder if these eight patients will be at greater risk for developing hypertension.

Renal Tuberculosis

The prevalence of hypertension among patients with renal tuberculosis appears to be comparable to that of the general adult population [11]. There are many reports in the literature describing nephrectomies in hypertensive patients with primarily unilateral renal tuberculosis. The results run the spectrum of failure to cure, but the indications for surgery are often less than clear. Stockigt and co-workers reported on a 36-year-old male with rapid onset hypertension and unilateral renal tuberculosis. Despite normal peripheral PRA, renal vein renin assays predicted the surgical cure of hypertension subsequently achieved by nephrectomy [12].

The current emphasis in the management of renal tuberculosis has shifted away from surgery. It is conceivable however, that a very small number of patients with unilateral disease will have suffered sufficient parenchymal and intrarenal vascular damage to produce renin dependent hypertension. Angiographic studies of severely destroyed tuberculous kidneys typically reveal a small but patent main renal artery with marked irregularities and occlusions of the peripheral intrarenal branches that could produce zones of ischemia. If nephrectomy is considered in these patients for blood pressure control, a renin profile that predicts surgical curability should be a *sine qua non.*

Congenital segmental hypoplasia: the Ask-Upmark kidney

The Ask-Upmark kidney represents a rare form of segmental hypoplasia, predominantly affecting girls, and associated with vesicoureteral reflux [13].

Characteristically, there are one or two small kidneys with one or more scarred lobes adjacent to normal tissue. Microscopically, the arteries and arterioles in the hypoplastic areas are tortuous and irregular and glomeruli are difficult to identify. An increased number of juxtaglomerular cells have been identified in the abnormal tissue, appearing in clusters near damaged vascular structures. Amat et al. documented the presence of renin containing cells in these hypoplastic areas utilizing immunofluorescence and peroxidase-antiperoxidase techniques [14]. This finding differs microscopically from UCP where extensive interstitial inflammatory infiltrates and periglomerular fibrosis are found in the affected areas. The immunofluorescence and peroxidase techniques have failed to localize renin containing cells in UCP kidneys [14].

Clinically the Ask-Upmark kidney is accompanied by increased renin secretion, mediating the hypertension in children and young adults. Medical management with β-blockers or CEI or nephrectomy in cases of unilateral involvement are successful options for treatment.

'Page kidney'

Page was able to experimentally produce reversible hypertension by compressing the renal parenchyma using a cellophane wrap placed around the kidney, leaving the main renal artery intact. He found that removal of the compressive force about the kidney, or nephrectomy would normalize the blood pressure [15]. Clinically the 'Page kidney' results when blood or urine is contained under pressure in the subcapsular or peri-renal space, constricting the kidney. This situation may result following blunt trauma, needle biopsy or a bleeding neoplasm. Patients on anticoagulants with other clotting disorders are at higher risk for this problem. Sufrins' review of the literature on this topic revealed a history of blunt trauma in 78% of cases in which 55% of the patients gave no evidence of macroscopic or microscopic hematuria [16]. Hypertension usually became manifest in less than one year, with a range of 24 h to 12 years. At exploration 85% of the patients had hematomas and the remainder had urinomas, all with volumes exceeding 500 ml.

The mechanism of hypertension appears to be a fall in the intrarenal arterial pressure with consequent renal ischemia inducing increased renin release, as a result of renal parenchymal compression by the trapped fluid [17]. However, absence of sustained renin release and blood pressure resistance to AII A in animal models suggests more subtle mechanisms.

The diagnosis may be suspected by the history and physical examination. Radiologic evaluation with IVP and tomography, ultrasound and CTT will further suggest this condition. Arteriography will show a normal main renal

artery with splaying of the intrarenal vessels and displacement of the capsular vessels. Renin assays usually reveal increased ipsilateral levels and elevated peripheral PRA.

The treatment utilized most often has been nephrectomy with an 88% cured or improved rate. Expectant treatment in eight patients resulted in cure or improvement in blood pressure in seven (88%). It seems reasonable to pursue a conservative course early in patients where a stable subcapsular or perirenal collection is radiographically documented. If reabsorption fails to occur after several weeks then evacuation and decortication is recommended. Too long a wait without evidence of fluid reabsorption may result in fibrosis of the perirenal tissue and a protracted course of hypertension. Nephrectomy should be reserved for situations where renin-mediated hypertension persists and renal salvage is not possible due to severe damage to the parenchyma, or in cases that fail more conservative medical treatment.

Renal cysts

Solitary, large renal cysts usually greater than 5 cm in diameter have been reported to compress surrounding renal parenchyma producing hypertension by a similar mechanism as the Page kidney [18]. Renin profiles that include peripheral and renal vein PRA can aid in predicting a response to intervention aimed at decompressing a large cyst for blood pressure control. Medically, CEI or a β-blocker should control pressure as well.

In polycystic kidney disease (PKD), 50–75% of the patients are hypertensive at the time of diagnosis, with a greater than 90% incidence as renal failure occurs. The pressure elevation is thought to be due to sodium retention and volume expansion.

Recently, Nash reported on seven hypertensive patients with PKD who were not in renal failure [19]. Two of these had increased peripheral PRA, with renal vein renins showing a ratio of two. An additional two patients with normal peripheral PRA were found to have lateralization of renin secretion with contralateral suppression. The increased renin activity noted in these patients despite a state of volume expansion is probably due to asymmetric renal perfusion as there is vascular distortion and parenchymal compression caused by the larger cysts.

Therapy for hypertension in this setting is of necessity medical. Knowledge of a high renin activity contributing to the hypertension in these patients dictates the consideration of β-blockers or CEI with or without diuretics for management.

Radiation nephritis

Therapeutic doses of radiation are known to cause renal injury which can progress to renal insufficiency and hypertension [20]. Radiation produces lesions of the glomeruli, renal tubules and vasculature. Extensive thickening, hyalinization and focal fibrinoid change in the media of arterioles and interlobular arteries is found. Lipid containing cells have been noted in the walls of these damaged vessels contributing to further narrowing of the lumina.

Hypertension following radiation injury may occur early but usually takes years to manifest itself. The pathogenesis of the blood pressure elevation includes sodium and fluid retention due to severe renal parenchymal impairment, and increased renin secretion from ischemic areas following intrarenal vascular damage. Patients with unilateral radiation damage, ipsilateral renin hypersecretion, and a normal contralateral kidney, have been rendered normotensive by nephrectomy or β-blockers [21]. In cases where there is bilateral radiation nephritis, or hypertension accompanied by azotemia, surgery is contra-indicated and medical management is advised.

Radiation may produce hypertension by the slow progressive injury it inflicts to large and medium sized arteries that lie within treatment portals. The small and growing arteries in children are especially sensitive to radiation. Their larger arteries become stenotic or hypoplastic while smaller vessels are likely to occlude. It is theorized that injury to the vasovasorum accounts for failure of these vessels to grow normally. In adults, major vessels become stenotic or occluded, apparently from acceleration of atheromatous changes. The result in both groups is the development of renovascular hypertension [22].

Treatment has followed the use of standard renal artery bypass procedures with good short term results. Patients must be carefully selected for these operations, excluding all those with radiation nephritis, whom bypass surgery would not benefit. Unfortunately, even in carefully selected patients, long term results are guarded as the progressive nature of the vascular lesion will result in continuing changes in the affected vessels.

Renal neoplasms

Renal cell carcinoma, juxtaglomerular cell tumors and Wilms' tumor have been associated with high renin hypertension, secondary aldosteronism. Tumor extirpation results in control of the blood pressure and normalization of these factors.

Thirty percent of all patients with renal cell carcinoma are hypertensive at presentation [23]. In two separate studies, patients undergoing evaluation for hypertension were found to have unsuspected renal cell carcinoma at

a rate 15 times higher than expected for aged matched controls [24, 25]. Certainly the association between these two diseases appears to be more than coincidental.

Various mechanisms seem to play a role in the pathogenesis of hypertension in renal carcinoma. Renal tumors have been shown to have endocrine function, secreting renin [26], erythropoietin and a PTH like hormone [27]. The latter produces hypercalcemia which is thought to increase the peripheral vascular resistance thereby elevating the blood pressure. Erythropoietin produces polycythemia increasing the vascular volume, as well as increasing the peripheral vascular resistance by increasing the blood's viscosity. The tumor mass can decrease blood flow to surrounding normal parenchyma by compressing the main renal vessels or by compressing the renal tissue itself, activating the renin axis. Arteriovenous shunts can contribute further to renal ischemia and also act to raise the systolic blood pressure by increasing cardiac output. The only effective treatment for renal cell carcinoma is nephrectomy. The blood pressure can be expected to normalize in one-third of these patients following surgery [28].

Pincoffs and Bradley first recognized the association of hypertension with Wilms' tumor in 1937 [29]. Lattimer et al. reported in 1958 that as many as 60% of patients with this tumor were hypertensive [30]. The blood pressure elevation is characteristically moderate, but severe and malignant elevations are occasionally seen. The mechanisms for hypertension include renin secretion by the tumor itself in the more severe cases [31], as well as compression of normal adjacent parenchyma as described for renal cell carcinoma.

Chemotherapy and radiotherapy that control the tumor also decrease the blood pressure, as does nephrectomy. Return of hypertension has been noted to follow tumor recurrence.

Juxtaglomerular cells in the wall of the afferent arteriole are recognized as the site of marked renal renin synthesis. Tumors originating in these cells are associated with a clinical syndrome that includes an elevated PRA, hypertension, secondary aldosteronism and hypokalemia. The afflicted are typically in their teen years or young adults, although the tumor has been reported in a 7- and a 44-year-old. The hypertension is characteristically marked and sustained. In one case the pressure elevation was paroxysmal, being precipitated by drinking home made wine [32].

The PRA has been elevated in all cases where it was measured, with lateralization to the tumor side and contralateral suppression. Hypokalemia has been reported in all but one case in the literature up to 1979. Catecholamines and steroid levels have not been elevated.

Radiographically, the lesion has been suggested most often by a renal cortical lucency in the nephrogram phase of a renal angiogram. Computerized transaxial tomography has not been evaluated in this rare application

but should prove useful. Intravenous pyelograms and renal scans are not sensitive and fail to show evidence of a lesion in most instances.

The treatment of these tumors has typically been nephrectomy. Connor locally excised a juxtaglomerular cell tumor resulting in normalization of the blood pressure and PRA [33]. At 18 months of follow-up the patient continues normotensive off medications. These tumors appear to be benign as there are no reports of metastases or multicentricity. Segmental resection appears to be a reasonable treatment provided that the diagnosis can be known with reasonable certainty pre- or intraoperatively. Medical treatment with β-blockers has controlled the hypertension in these patients, but due to the presence of a mass lesion in the kidney, it should not be the treatment of choice.

Of interest is the strong association of hypertension, hyperaldosteronism and hypokalemia with a normal IVP in most of these patients. This has led some in the past to the incorrect diagnosis of primary aldosteronism and inappropriate adrenal surgery in those cases where the PRA was not evaluated pre-operatively [34–36]. This error illustrates the importance of assaying the renin activity in the evaluation of hypertension in young patients, where the onset is acute.

Unilateral ureteral obstruction

A causal relation between hypertension and hydronephrosis was first suggested in the mid 19th century [37]. During the 1930s and 1940s several reports of cure of hypertension by removal of a hydronephrotic kidney or by repair of ureteral obstruction appeared. Braasch reviewed 73 cases of hydronephrosis, finding 29 hypertensive patients in this group who were treated surgically [28]. Ten of these were cured of their hypertension (35%), but due to limited pre-operative evaluations one could not reliably ascertain that in all ten of these cases, the hydronephrosis caused the hypertension.

In 1968 Belman [38] demonstrated that a renin profile which would predict surgical curability in a patient with renovascular hypertension was also found in a patient with distal ureteral obstruction that reversed with repair of the ureter. Renin dependent hypertension has since been demonstrated in unilateral ureteral obstruction at all levels, in adults and children [39–42]. However, not all patients with acute unilateral obstruction become hypertensive. Only nine of 30 patients with acute unilateral obstruction were noted to have elevated blood pressure by Schwartz [43].

Hydronephrotic kidneys should be repaired regardless of whether they are associated with hypertension or not, for the sake of maximizing renal function and preventing the other complications of urinary obstruction. Renin studies in this setting are of clinical interest as prognostic indicators of the

reversability of hypertension by surgery. Of greater importance has been the application of known renin physiology to better understand the pathophysiology of ureteral obstruction. Though a full understanding of the mechanisms governing the etiology of hypertension in unilateral ureteral obstruction has not been achieved, some facts have been learned.

Experimentally, mid ureteral obstruction in dogs has shown an ipsilateral increase in renal blood flow (RBF) at 15 min, with eventual decrease to below normal levels at 24 h [44]. Elevated renin secretion does not normalize until approximately 4 weeks later [45].

Schirmer found that unilateral obstruction at the ureteropelvic junction or at the ureterovesical junction in the dog leads to a marked increase in anaerobic glycolysis at the medulla and cortex of the mid portion of the kidney [46]. The renal poles are less affected and a proximal occlusion appears to produce a greater shift to an anaerobic metabolism than does a distal one. The increase in glycolysis suggests tissue anoxia that is most likely secondary to the ischemia suffered by the renal parenchyma following compression by a high pressured renal pelvis in the setting of an already decreased RBF. The role that the prostaglandin thromboxane play to further decrease parenchymal perfusion is not clear, but it is known to be increased in renal obstruction [47].

The ischemic segments of the kidney then secrete renin which leads to the production of AII. Ipsilateral sodium and water retention take place as a direct effect of AII on the tubules and via secondary increase in aldosterone levels [48]. At this early point in the obstruction the hypertension is mediated by the vasoconstrictive properties of the renin angiotensin system and is reversible.

Four weeks following the onset of the ureteral occlusion, the glycolytic process, elevated PRA, and high ureteral pressure return to normal levels. It is speculated that the total peripheral vascular resistance and possible contralateral renal resistance has gradually increased perhaps preventing the compensatory diuresis and natriuresis to maintain the normotensive state. Accordingly, sodium-volume retention now mediate the hypertension. In the chronic hypertensive state, the contralateral kidney which was initially normal, has developed intrarenal vascular disease maintaining the systemic hypertension [48]. Reversal of chronic hypertension by release of the unilateral obstruction is less predictable but has been documented to take place [43].

Bilateral ureteral obstruction

Bilateral hydronephrosis leads to decreased renal function, salt retention and volume expansion that can result in hypertension [49]. Release of the

obstruction is followed by diuresis of excess salt and water; in the absence of other hypertensive diseases, blood pressure normalizes. A similar phenomenon is observed on release of obstruction in a solitary kidney [50]. In both situations, PRA is not elevated. Volume expansion and salt retention mediate the hypertension, analogous to the mechanism it plays in the chronic phase of unilateral ureteral obstruction.

Rarely, the release of a bilateral obstruction will set off a copius urine output that represents the physiologic excretion of retained urea, sodium and water. In a review of 22 patients who experienced urine outputs of 200 ml/h for 12 h or greater following release of bilateral obstruction, 15 patients (77%) were found to be hypertensive at presentation [51]. At the conclusion of the diuresis only two remained hypertensive (12%). This observation suggests that for the other 15 patients, the hypertension was secondary to volume expansion which corrected with return of glomerular filtration rate and renal blood flow towards normal following relief of obstruction.

Mechanisms of hypertension in unilateral renal disease

An increase in the PRA has been experimentally shown to initiate an elevation of the systemic blood pressure in renal artery stenosis, unilateral ureteral occlusion and renal parenchymal compression. Clinically, hyperreninemia has been documented, in these diseases and in a variety of others described in this chapter as the cause of reversible hypertension that responds to appropriate surgical or medical treatment.

In the initial phase, increased PRA mediates the hypertension via the vasoconstrictive properties of AII on the peripheral arterioles. Demonstration of AII mediation of the blood pressure is achieved by demonstrating a fall in blood pressure by administration of AII A or CEI. Sodium retention and volume expansion do not appear to play a role at this time as the contralateral healthy kidney excretes all excess salt and water. Continued blood pressure elevation results in changes in the arterioles producing an increased peripheral vascular resistance with retention of salt and water. Initially, these changes represent a physiologic autoregulation by the viscera and kidneys to increased cardiac output, and are reversible. With chronic elevation of the blood pressure, the arterioles undergo irreversible changes that then may maintain the peripheral vascular resistance at an elevated setting [52]. At this point the blood volume is high for the existing vascular tone, PRA is normal or low, and surgery, CEI or β-blockers alone are not likely to reverse the hypertension. Management with other antihypertensive agents is necessary. The mechanism of this chronic phase of hypertension appears to involve subtle sodium retention acting at either a central (CNS) or peripheral arteriolar level [53].

In the unilateral renal diseases listed in Table 1, it is not uncommon to find normal peripheral PRA, with renal vein renin studies showing ipsilateral renin hypersecretion and contralateral suppression upon review of the literature. This confusing pattern appears to be present more commonly in patients with renoparenchymal disease subsequently cured by nephrectomy than in patients with renovascular hypertension. Whether intermittant normal renin secretion is a characteristic of parenchymal disease or the finding of normal PRA is only methodologic error is unclear. Systematic study of both blood pressure and PRA response to AII or CEI is needed to further understand renin secretion in these patients [54]. Various investigators have succeeded in including hyperreninemia using furosemide or hydralazine in this group [55, 56]. Since the vast majority will not have renin dependent hypertension it would be most impractical to perform renal vein renin studies on all patients with these renal problems who are also hypertensive. At present renal vein renin evaluation should only be pursued in the setting of elevated PRA when indexed to a 24-h urine sodium with the patient off antihypertensive medications, and in those patients with normal PRA who are less than 20 years of age, whose hypertension is of acute onset, or who exhibit a poor response to medical treatment.

The role of the sympathetic nervous system in initiating or sustaining hypertension in unilateral renal parenchymal disease has been studied [57]. With our present methodology no clear contributory role has become evident.

Treatment of non-vascular renal hypertension: medical vs. surgical

Table 1 divides the diseases discussed in this chapter into two groups. In the first group which is comprised of neoplasms and urinary tract obstruction, surgery is the treatment of choice in all cases. Correction of the underlying pathology will correct the hypertension if it was due to renin hypersecretion by the affected kidney. More often in these diseases, the hypertension will be of the essential variety and will remain post-operatively. However, other forms of curable hypertension should always be kept in mind and ruled out. For example, bilateral renal cell carcinomas and pheochromocytomas have been associated with Von Hippel Lindau disease, and removal of the renal tumors will not alleviate the hypertension produced by high levels of catecholamines.

In the second group listed in Table 1 the use of nephrectomy for correction of the hypertension is more controversial and contra-indicated in cases such as PKD where there is known bilateral renal disease. Occult bilateral disease may be present in renal parenchymal diseases thought to be unilateral at the time surgical intervention is being considered [56, 58]. Nephrec-

tomy in this situation often will not benefit the patient. The use of renin assays to prognosticate surgical curability and trial treatment with CEI should be carried out prior to consideration of surgical therapy. If the benefit gained by the removal of a renin source is greater than a deficit created by the loss of functioning nephrons, then nephrectomy can be considered. All other patients will require appropriate medical management.

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6. Hypertension in Kidney Transplant Recipients

JHOONG SHIK CHEIGH

Introduction

Kidney transplantation is a well accepted, therapeutic procedure for patients with end-stage renal disease. Allograft rejection and frequent adverse effects of non-specific immunosuppressive regimens have been the two most important impediments to successful kidney transplantation. Since we now have a greater understanding of transplant immunology, improved clinical management of patients and newer immunosuppressive regimens, renal allograft survival rates have substantially improved in recent years.

At present, renal allograft survival at 2 years is between 60–80% for cadaveric kidney recipients [1] and 80–95% for living related kidney recipients [2]. This improvement in kidney transplant survival has been achieved with significantly lower morbidity and mortality despite the current trend of liberal standards in accepting high risk patients [3–5]. Some centers, such as ours, have reported patient mortality as low as 5% or less at 1 year after either a cadaveric or living related kidney transplantation [4, 5]. The judicious use of immunosuppressive regimens and consequent reduction in infectious complications during the early post-transplant period is the single most important factor for the decrease in morbidity and mortality.

While both patient and graft survival rates have improved, non-infectious complications, such as cardiovascular disease, appear to be increasing and playing an important role in determining the long-term prognosis of kidney transplant recipients [6]. The increased incidence of cardiovascular disease is not unexpected, however, since end-stage renal disease is associated with hypertension, hypercholesterolemia and glucose intolerance. Following transplantation, hypertension may continue to worsen and prednisone treatment may cause overt diabetes mellitus and hypercholesterolemia. Among the risk factors, the deleterious effects of prolonged hypertension undoubtedly play an important role in the increased incidence of lethal cardiovascular disease [7].

Table 1. The incidence of hypertension following kidney transplantation

Authors	Diagnostic criteria	Number of patients	Incidence	Remarks
Hume et al. [128]		52	29%	The incidence in recipients of cadaveric kidney 64%, living related kidney 16%
Cohen [52]	Diastolic pressure ≥ 100 mmHg at 6 months	81	50.6%	The incidence in patients with native kidneys 77.3%, without native kidneys 40.7%
Curtis et al. [55]	Diastolic pressure > 95 mmHg	74 (graft functioned ≧6 months)	24%	All patients received alternate day steroids
Bachy et al. [10]	Average diastolic pressure > 90 mmHg	85 (82 of these received cadaveric kidney; 80 were status post bilateral nephrectomy)	Incidence 82%, prevalence 66%	at 3 months 63% at 1 year 61% at 2 years 56% at 5 years 53% at 7 years 40%
Jacquot et al. [8]	Mean arterial pressure > 110 mmHg at 1 year	50 (graft functioned > 1 year)	20%	Excluded patients with own kidneys, acute or progressive rejection, glomerulonephritis, or transplant renal artery stenosis

Table 1. The incidence of hypertension following kidney transplantation

Authors	Diagnostic criteria	Number of patients	Incidence	Remarks
Rao et al. [11]	Mean arterial pressure ≥ 110 mmHg	164 (graft functioned ≧6 months)	49%	The incidence in those who were hypertensive pre-transplant 60%, normotensive pre-transplant 14%
Whelton et al. [35]	Average diastolic pressure ≥ 90 mmHg	93	40%	The incidence in recipients of cadaveric kidney 57%, living related kidney 21%
McGrath et al. [129]	Diastolic pressure ≥ 110 mmHg	94	Prevalence at 3 months 50%, at 12 months 63%	All received antihypertensive therapy
Chantler et al. [56]		94 (children with the first functioning graft only)	65%	The incidence in those who were on daily steroids 74%, alternate day steroids 43%
Hamilton et al. [53]	Diastolic pressure ≥ 110 mmHg	101	51.2%	The incidence in those who were on cyclosporin only 67%, prednisone & azathioprine 45.5%

Incidence

The incidence of hypertension after kidney transplantation has been reported to vary from as low as 20% to as high as 86%, but usually between 50 and 60% (Table 1). This widely varying incidence can be attributed to differences in the definition of hypertension and in characteristics of subjects studied in these reports. Since the etiological factors for post-transplant hypertension are multiple, the prevalence of hypertension is variable.

The incidence tends to vary with time following kidney transplantation. During the first few months, either an exacerbation of pre-existing hypertension or a transient episode of new hypertension is common [8, 9]. This acute, transient change in arterial pressure is probably related to rejection, volume overload and high doses of steroids. It usually improves as graft function stabilizes and prednisone doses are reduced. In the 85 transplant recipients reported by Bachy et al. [10], the proportion of patients with hypertension rose during the first 3 months, stabilized subsequently around 50–60% for up to 5 years and then tended to decrease to 40%. In addition, over the years, hypertension fluctuated so that one-third of the initially hypertensive patients became normotensive while another one third of the initially normotensive patients became hypertensive. As a result, although never more than 66% of the patients had hypertension at any one time, 82% of all transplanted patients were hypertensive at one time or another during the follow-up period. A similar result has been obtained by Van Ypersele de Strihou et al., who made a longitudinal study of 77 patients whose grafts had functioned for more than 7 years [7]. In this study, the prevalence was 64% in the first year, then it remained stable between 50 to 60% till 11 years after transplant.

The presence of established hypertension prior to transplantation is another important factor determining the incidence of post-transplant hypertension. Of the 164 recipients reported by Rao et al., the incidence of hypertension was 77% (127 patients) prior to transplantation but was significantly reduced to 49% (81 patients) following kidney transplantation [11]. Of the 127 patients who were hypertensive before transplantation, 76 (60%) continued to be hypertensive while 51 (40%) became normotensive after transplantation. On the other hand, of the 37 patients who were normotensive before transplantation, all remained normotensive except five (14%) who became newly hypertensive following transplantation. These data clearly show that established hypertension before transplantation often continues post-transplant despite restoration of normal kidney function.

The presence of either diseased native kidneys, or renal failure (acute or chronic rejection), kidneys from cadaveric donors and higher daily doses of prednisone are all considered risk factors for the development of posttransplant hypertension. The incidence of hypertension in relation to these factors is shown in Table 1.

Mechanisms of hypertension in patients with kidney transplants

Hypertension in kidney transplant recipients appears to be sustained by a high total peripheral resistance [12, 13]. The cause of the elevated total peripheral resistance, however, remains to be elucidated. There are undoubtedly multiple mechanisms and clinicopathological entities causing post-transplant hypertension (Tables 2 and 3). Although one mechanism or another may be operative predominantly to initiate and/or maintain hypertension, it is more often that multiple mechanisms in both vasopressor and vasodepressor systems that interact or regulate abnormally with each other that are conducive to hypertension. Among these mechanisms, as in most cases of renal hypertension [14–17], impaired kidney function and its consequences, inappropriate interactions between vasoconstrictive components and sodi-

Table 2. Mechanisms of post-transplant hypertension

1. Hypertension mediated by the diseased kidneys
Renin-angiotensin aldosterone system
Other mechanisms
2. Hypertension mediated by the transplant kidney
Sodium and fluid retention
Renin-angiotensin aldosterone system
Defective prostaglandin and bradykinin release
3. Other mechanisms
Essential hypertension
Abnormal hormonal, metabolic and neural regulation
Adrenal corticosteroids
Parathyroid hormone
Hypercalcemia
Sympathetic nerve activity

Table 3. Clinicopathological entities causing post-transplant hypertension

1. Persistence of an established pre-transplant hypertension
Essential hypertension
Renal hypertension mediated by the native kidneys
2. Renal hypertension mediated by the transplant kidney
Transplant rejection; acute and chronic
Transplant renal artery stenosis
Recurrence or de novo glomerulonephritis
Obstructive nephropathy; acute or chronic
3. Others
Hyperparathyroidism and hypercalcemia
Immunosuppressive drugs (cyclosporine, corticosteroids)

um-fluid volume overload, appear to be the most important causes of hypertension in these patients.

Renin-angiotensin system and extracellular fluid volume (ECF)

A transplant kidney can respond appropriately with renin secretion and thus aldosterone secretion, to changes in posture and ECF volume [18, 19]. In the first few post-operative months most transplant recipients, particularly with renal failure due to either acute tubular necrosis or acute rejection, have a high peripheral plasma renin activity (PRA) [9, 19, 20]. However, the absolute level of PRA correlates poorly with the level of arterial pressure in individual patients. This suggests that abnormalities in the renin-angiotensin system are not the sole mechanisms for hypertension in the early post-operative period.

Hypertensive transplant patients as a group have PRA either similar to [11, 12, 21–23] or higher [24, 25] than that of normotensive transplant patients. If ECF volume is reduced, however, by either the use of diuretics or restriction of salt intake, renin release of hypertensive patients is considerably different from normotensive patients [14, 25–27]. Bennet et al. [26] observed that 13 hypertensive patients on a low salt diet ($Na < 10$ mEq/day) had a significantly higher PRA ($22.7 + 6.2$ ng/ml/h) in the transplant renal vein than that of normotensive patients on a comparable diet ($4.8 + 1.1$ ng/ml/h). When they were placed on high sodium diets, however, the two groups had an identical PRA level. Linas et al. [27] also made a similar observation but with one important exception. In their study, those hypertensive patients who had multiple kidneys, including a transplant, not only had a higher plasma PRA (13.2 ng/ml/h) but also responded to depressor effects of saralasin when sodium was depleted. Those who had only the transplant kidney had lesser increases in plasma PRA ($6.5 + 2$ ng/ml/h) and had no response to saralasin after sodium depletion. In this study, adequate renal vein samples were obtained from five patients with multiple kidneys. In each patient, PRA was lowest from the transplant kidney. When a ratio of 1.5 (host kidney/transplant kidney) was taken as an index suggestive of lateralization, four of these had lateralized renal vein renin activity to one or both of the host kidneys.

Three to seven percent of kidney transplant recipients have both radiologically significant renal artery stenosis (RAS: more than 50% stenosis of luminal area) and hypertension [11, 28–31]. As in experimental models of one-kidney Goldblatt hypertension, peripheral or transplant renal vein PRA in most of these patients is within normal limits [11, 23, 30, 33, 34]. PRA is increased, however, if RAS is so severe ('tight stenosis'; more than 80% stenosis of luminal area) that expansion of ECF volume cannot compensate

the diminished renal blood flow [23, 30, 32, 34–36], or ECF volume is contracted by either restriction of sodium intake or diuresis [14, 25, 26, 36].

These clinical observations suggest that hypertension in kidney transplant recipients is a clinical analogue of one-kidney Goldblatt hypertension, regardless of whether the pathologic process is confined to a main renal artery, segmental renal arteries or the renal parenchyma. Hypertension is probably initiated by excressive renin secretion by the hypoperfused transplant kidney, but chronic hypertension is probably sustained by excessive ECF volume expansion (volume-dependent). Similar to those patients who have either an underperfused solitary kidney [14] or bilateral parenchymal kidney disease [15, 16, 37], hypoperfused and/or diseased transplant kidney results in hyperreninemia and salt retention. The latter then inhibits renin release but perpetuates the hypertension on a volume rather than a pressor basis. Expanded ECF volume could increase blood pressure not only by raising cardiac output [38] but also by increasing peripheral resistance as it enhances the vascular response to vasopressors, angiotensin II [39, 40] and catecholamines [41, 42], and alter the mechanisms of autoregulation of total blood flow [43]. Some of these patients may not suppress renin release appropriately in response to ECF volume expansion. This relative hyperreninemia may be also of significance in causing renal hypertension. If ECF volume is depleted, however, volume-dependent mechanisms seems to shift into a renin-dependent hypertension. On the contrary, the chronic hypertension in those transplant recipients who have multiple kidneys or 'tight' transplant RAS, appears to be sustained primarily by excess renin secretion (renin-dependent hypertension) regardless of ECF volume status; a mechanism similar to that of hypertension in experimental models of two-kidney Goldblatt hypertension. Sources of hyperreninemia in these patients are either the transplant kidney or one or both of the host kidneys.

Immunosuppressive drugs

Glucocorticoids

Glucocorticoids have a permissive effect on vascular tone and blood pressure; they not only enhance vascular responsiveness to catecholamines and other vasoconstrictors but also suppress the vasodilatory effect of histamine and bradykinin [44]. Glucocorticoids have been proven to be highly potent hypertensive agents in experimental animals. Experimental hypertension produced by glucocorticoids, as opposed to that produced by mineralocorticoids, is not salt-dependent [45], and thus, unresponsive to salt restriction. Since glucocorticoids inhibit the production of prostacycline (PGI2) by vascular endothelium and other cells, it has been suggested that glucocorticoid-induced hypertension is mediated by the decreased prostacycline in the vascular tissue [46].

The incidence of hypertension in patients treated with glucocorticoids has ranged from 4 to 25% and that seems to be directly related to dose, duration of therapy, and the presence of renal disease [47–49]. The rise in blood pressure is not usually noted until 2 weeks of therapy, and the order of magnitude of the increase is about 20 mm Hg [50], although malignant hypertension has also been reported.

Sampson et al. [22] found that aldesterone secretion rates in kidney transplant recipients were approximately four times higher than that of normal controls; that there was a positive correlation between these values and diastolic blood pressure, and that aldosterone secretion in these patients was not under control of the renin angiotensin system. They also showed, in concurrent studies, that adrenalectomized patients were capable of converting the injected C-labeled cortisone acetate into aldosterone or an aldosterone-like metabolite. They suggested that the hypertension seen in transplant recipients was largely due to the conversion of prednisone to a mineralocorticoid. In general, however, the levels of plasma aldosterone do not correlate with the blood pressure in transplant patients [18, 21].

Glucocorticoids may play an important role in the development of hypertension if the administered dose is high, particularly in the early post-operative period [9, 10, 51]. In chronic hypertension and when graft function is stable, however, glucocorticoids do not appear to play an important role [8, 52]. Hamilton et al. [53] reported that the incidence of hypertension is significantly higher (67.6%) among patients who received cyclosporine alone, than among those who received prednisone and azathioprine (45.5%). Similarly a randomized and controlled study [54] could not demonstrate the beneficial effect of alternate day steroid therapy on hypertension, although some uncontrolled, retrospective studies have shown a lower incidence of hypertension among the patients receiving alternate-day steroids [55, 56].

Cyclosporine

Cyclosporine has been used since 1976 as an immunosuppressive drug in patients receiving organ transplants. It is a cyclic peptide of fungal metabolite, and acts primarily by blocking the secretion of interleukin 2 from helper/inducer lymphocytes. Although cyclosporine is not a cytotoxic drug, it has considerable toxic effects on many organs including the kidney.

Patients receiving cyclosporine for heart [57, 58], bone marrow [59] or kidney transplant [53, 60] have been observed to develop hypertension within several weeks of treatment. These patients not only have a higher incidence of hypertension than of a comparable group of patients who were treated with conventional immunosuppressive drugs [53, 57, 60], but the hypertension was more severe and refractory even with combined treatment of more potent antihypertensive drugs [57, 58]. In children, particularly under the age of 15, hypertension may be associated with seizure [59].

The mechanism of hypertension associated with cyclosporine is unknown and may develop irrespective of pretreatment history of hypertension and without clinical evidence of cyclosporine nephrotoxicity [58]. It is associated with slightly elevated peripheral vascular resistance but generally with normal plasma renin activity [58]. In experimental models using spontaneously hypertensive rats and with supratherapeutic doses of cyclosporine, the development of hypertension was associated with increased sympathetic nerve activity, the stimulation of renin-angiotensin aldosterone system and decreased synthesis of renal prostaglandin [61].

Decreased elaboration of renal depressor substances

The kidney elaborates vasodepressor substances including prostaglandins and kinins. The systemic infusion of these hormones produces vasodilatory and natriuretic effects. However, the role of renal vasodepressor substances in regulation of normal blood pressure and pathogenesis of hypertension has remained a topic of debate.

Urinary kallikrein, which is derived from renal tissue and catalyzes the production of kinins from kininogen substrates, has been measured in patients with either essential hypertension or parenchymal kidney disease [62] and in patients with a kidney transplant [63, 64]. These studies have shown that urinary kallikrein excretion was significantly lower in these patients. Some authors suggested that the kallikrein-kinin system might be involved in the pathogenesis of essential hypertension and of the hypertension in patients with parenchymal kidney disease or kidney transplant [62, 63]. However, their studies are limited in that urinary kallikrein is distinct from plasma kallikrein physically, kinetically and immunologically, and the role of endogenous intra-renally formed kinins to systemic hemodynamics is not known [65]. Furthermore, it is unclear as to whether the decreased excretion of urinary kallikrein, which is probably reflecting decreased production of renal kallikrein, is the cause of hypertension or the consequence of hypertension and/or renal failure.

Prostaglandins, PGE in particular, play an important role in maintaining intra-renal homeostasis and preserving renal function in chronic parenchymal kidney disease [66] and renovascular disease [67, 68]. We know little, however, about the synthesis and elaboration of prostaglandins by a transplant kidney, and the response of a transplanted kidney to local or systemic prostaglandins. A transplanted kidney can produce prostaglandins not only by renal tissue *per se,* but probably also by infiltrating cells during acute rejection [69]. An acute transplant rejection is often associated with increased release of thromboxane B2, a stable product of thromboxane A2 [69]. Thus, it is conceivable that the increased release of thromboxane

from the rejected kidney, in addition to increased release of renin as well as salt and water retention, may be a significant factor for the induction of hypertension during the crisis. However, there is no specific information available regarding the significance of either urinary or plasma prostaglandins to hypertension in kidney transplant patients.

Automatic nerve system

The autonomic nerve system plays an important role in most types of hypertension whether these are volume dependent, cardiogenically mediated, or related to stimulation of the renin-angiotensin system [41, 42, 70]. However, the system has been rarely studied in hypertension of kidney transplant recipients.

Smith et al. [13, 71] studied plasma noradrenaline concentration and the response of arterial blood pressure to noradrenaline infusion in 11 hypertensive and 10 normotensive transplant patients. Although there was no difference in resting plasma noradrenaline concentration between the two groups, hypertensive patients had a significantly greater rise in blood pressure in response to noradrenaline infusion (mean arterial blood pressure $153+21$ mm Hg vs. $111+8$ mm Hg, $p<0.005$, at 10 min of noradrenaline 0.05 mcg/kg/min infusion). In the same patient group, they also made the observation that the total exchangeable sodium was significantly greater in hypertensive patients compared to normotensive patients ($44.8+8.4$ mmol/kg vs. $37.6+6.4$ mmol/kg, $p<0.05$). Furthermore, regression analysis showed a significant relationship between the combination of total exchangeable sodium and the rise in mean arterial pressure during noradrenaline infusion with resting mean arterial pressure. Therefore, the authors suggested that extracellular fluid volume expansion associated with increased alpha receptor sensitivity to noradrenaline might cause hypertension in these patients.

Essential hypertension

Patients with essential hypertension and consequent nephrosclerosis comprise approximately 5 to 10% of all patients who have end-stage renal disease and require kidney transplantation [72, 73]. Essential hypertension, by definition has no established cause. Genetic and environmental factors, endocrine, autonomic nerve and renal dysfunction are among the many factors that are thought to be causal or contributory events in the development of essential hypertension.

The concept that the kidney plays a dominant role in the pathogenesis of essential hypertension has been based on clinical studies on predisposed

subjects [74], and experimental and theoretical analyses of the hemodynamics of arterial pressure control [38, 75]. In recent years, this concept has been further supported by studies of blood pressure changes produced by kidney cross transplantation between either salt-sensitive hypertensive rats [76] or spontaneously hypertensive rats [77] and normotensive rats. In each of these rat models, transplantation of kidneys of hypertensive rats into normotensive rats produced hypertension in the recipient rats. Conversely, transplantation of normal kidneys into the hypertensive rats caused normotension. Hypertension still develops in a young normotensive rat after receiving a kidney transplant from a young genetically predisposed rat (spontaneously hypertensive rat) before the onset of hypertension. The animal experiments suggest that blood pressure follows the kidney, and genetically controlled factor(s) operating through the kidney are responsible for the induction of hypertension.

In humans, if renal dysfunction is the primary cause of essential hypertension, a kidney transplantation from a normotensive donor might not only cure uremia, but also essential hypertension in patients with nephrosclerosis. Conversely, if any mechanism other than renal dysfunction is the primary cause, most patients should remain hypertensive even after a successful kidney transplantation.

Curtis et al. [78] specifically examined this question. They reported six patients who received a kidney transplant from normotensive donors for end-stage nephrosclerosis secondary to 'essential hypertension'. After an average follow-up of 4.5 years, all patients were not only normotensive but also had evidence of reversal of hypertensive damage to the heart and retinal vessels. In addition, these patients had comparable levels of plasma renin, plasma aldosterone, plasma epinephrine, urinary sodium excretion and blood pressure changes with that of normal control subjects in response to salt deprivation and salt loading. They also reported 33 additional patients who were said to have 'nephrosclerosis' as their original disease, had a well functioning allograft for at least 1 year and had their native kidneys removed. Of these, eight (24%) still required antihypertensive medications, and the other 25 (76%) were normotensive. Thus, essential hypertension in humans, is shown to be similar to the hypertension seen in spontaneously hypertensive rats in that both can be corrected by transplantation of a kidney from a normotenisve donor.

This observation provides important clinical evidence supporting the view that renal dysfunction is a primary cause of the disease. However, it does not answer the question of how often and how much extrarenal mechanism(s) responsible for essential hypertension continue to play a role, if any, in the pathogenesis of post-transplant hypertension. The observation that 24% of the patients with 'nephrosclerosis' remain hypertensive after transplantation, suggests the possibility that some of these patients may

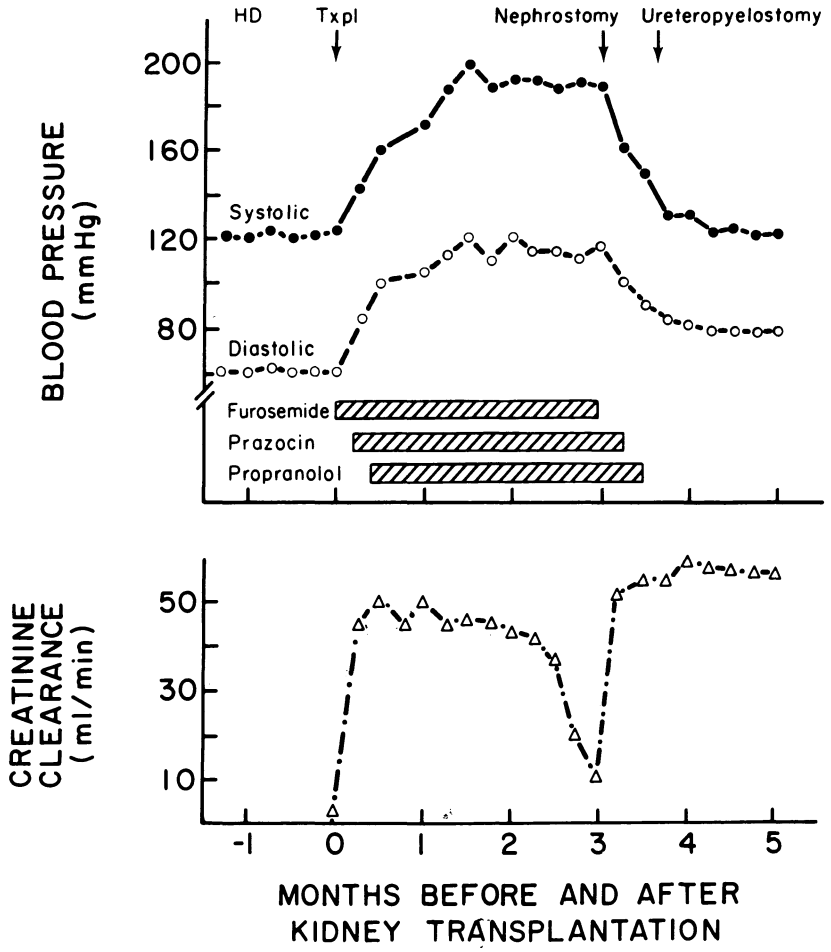

Figure 1. Clinical course of a patient with hypertension and obstructive uropathy. Txpl = kidney transplantation.

continue to have essential hypertension that is mediated by non-renal mechanism(s). Further studies on renal, autonomic nerve and endocrine function of these selected patients will help delineate the significance of extrarenal mechanism(s) of essential hypertension in kidney transplant recipients.

Obstructive uropathy of the transplanted kidney

Both acute and chronic urinary tract obstructions can cause hypertension mediated by either expansion of ECF volume, excessive renin secretion or by neurogenic mechanisms (see Chapter 5). Obstructive uropathy involving either the ureter or the ureterovesical junction is not an uncommon urological complication following kidney transplantation. Urinary tract obstruc-

tion, however, has not been cited as a cause of hypertension in transplant patients. We have seen several patients who have had severe, chronic hypertension that resolved with repair of obstructive lesions in the kidney transplant. The clinical course of such a patient is briefly summarized below and in Figure 1.

A 26-year-old white woman with reflux nephropathy received a cadaveric kidney transplant. The kidney functioned immediately, and 1 week post-operatively her creatinine clearance was 50 ml/min with a serum creatinine of 0.8 mg/100 ml. However, on the second post-operative week, she became hypertensive, with arterial blood pressure of 170/105 mm Hg which was unresponsive to diuretics. Before her transplantation her blood pressure had been normal throughout the course of chronic renal failure including the time she was on hemodialysis treatment. In the following 3 months her blood pressure remained approximately 160–200/100–120 mm Hg despite treatment with propranolol, prazocin and furosemide as much as 320 mg, 16 mg, 120 mg per day, respectively.

During this time, her transplant function also gradually but progressively declined until the end of the third post-operative month when she developed an acute oliguria. Sonograms of the transplanted kidney studied 1 and 6 weeks post-operatively and at the time of oliguria revealed progressive dilatation of the ureter and hydronephrosis consistent with obstruction at the ureterovesical junction. A percutaneous anterograde pyelogram again revealed a severe obstructive lesion at the ureterovesical junction. A percutaneous nephrostomy produced a brisk diuresis with prompt recovery of graft function. At the same time, her blood pressure precipitously returned to normal. Within 2 weeks, she was able to discontinue all antihypertensive medication. Subsequently, she underwent a ureteropyelostomy utilizing her own right terminal ureter anastomosed to the pelvis of the transplant kidney. Since then, she has had a creatinine clearance of 50–60 ml/min and a serum creatinine of 0.8–1.0 mg/100 ml and a blood pressure of 120–125/75–85 mm Hg for the following 3 years.

This patient illustrates a case of severe hypertension associated with an obstructive uropathy of a transplant kidney. Although other factors, such as corticosteroids and rejection episodes may have been contributory to her hypertension, it is interesting to note that her prednisone dose was 20–30 mg/day except for the first 2 weeks, and she did not have any clinically appreciable episodes of rejection. In this patient, circumstantial evidence suggests that the obstructive lesion was primarily responsible for the hypertension.

Hyperparathyroidism and hypercalcemia

Persistent hyperparathyroidism and its attendant hypercalcemia have been observed in one-third of kidney transplant recipients whose creatinine clearance is greater than 30 ml/min [79]. Hyperparathyroidism and the associated hypercalcemia have been implicated as one of the causes of post-transplant hypertension [27, 80].

Chronic, intravenous infusion of parathyroid hormone in normal human subjects produces hypercalcemia and hypertension [81]. Similarly, calcium infusion raises blood pressure in normal rats and a direct correlation between changes in serum calcium and arterial blood pressure [82]. Although calcium infusion alone does not increase blood pressure in parathyroidectomized rats, despite a comparable rise in serum calcium, the administration of both calcium and parathyroid hormone to these rats again raises blood pressure. This experiment suggests that hypertension in hyperparathyroidism requires both hypercalcemia and elevated parathyroid hormone. In patients with primary hyperparathyroidism, however, the mean serum calcium levels in the normotensive and hypertensive patients were similar, ruling against the hypothesis that hypercalcemia is the dominant cause of the hypertension [83].

In a study of kidney transplant patients [84], intravenous calcium infusion produced a significant increase in systolic blood pressure and a decrease in plasma parathyroid hormone. There was an inverse relation between changes in plasma parathyroid hormone levels and systolic blood pressure. However, there was no correlation between the change in blood pressure and either the changes in serum calcium or plasma renin activity. Under the condition of this study, endogenous parathyroid hormone has the characteristics of a vasodepressor hormone. A vasodepressor action of this hormone has been postulated previously based on a relaxing effect of parathyroid hormone on the contractile response of rat aorta [85]. A review of these data suggests that excessive parathyroid hormone and hypercalcemia may play a role in determining arterial blood pressure, but these are unlikely dominant causes of hypertension in most kidney transplant recipients.

Effect of hypertension on the transplanted kidney

In experimental animals, hypertension itself is clearly capable of producing functional and histopathological abnormalities in the kidney. As early as 1941, Wilson and Byron observed that chronic lesions produced in the arteries, glomeruli, tubules and interstitial tissue of the kidney exposed to hypertension resembled those occurring in chronic Bright's disease [86]. They advanced the concept that hypertension produces vascular lesions, and these, by reducing the blood flow through the kidney aggravate impaired

kidney function and hypertension. This vicious cycle leads to sustained hypertension and progressive renal destruction.

Recent studies in experimental glomerulonephritis, diabetic nephropathy, renal infarct and remnant kidney have shown that when systemic hypertension occurs in conjunction with kidney disease, it accentuates the severity of glomerular lesions and accelerates the progress of renal failure [87]. Elevated glomerular pressure and hyperperfusion appear to be the primary mechanisms by which hypertension aggravate glomerular diseases.

Hypertension is thought to be one of the most important factors leading to the progression of a primary kidney disease [88]. Clinical data, however, supporting this notion are sparse [89]. In a long term follow-up study of 79 patients with chronic pyelonephritis [90], the progress of renal impairment was significantly higher in patients who at some time developed hypertension. Annual reduction of GFR of seven patients with severe hypertension (Keith-Wegener's Grade III-IV retinopathy) was 6.2 ml/min/year as compared with 1.3–1.4 ml/min/year for those who had either milder hypertension (Keith-Wegener's Grade I-II) or normotension. Moyer et al. [91] observed in a heterogenous group of patients with hypertension and renal impairment, that the patients with higher arterial pressure had lower RPF and GFR. However, as in many other similar studies, it was unclear whether severe hypertension was a marker of more severe underlying renal disease, and thus, associated with a poor prognosis, or alternatively, whether it was an independent risk factor perpetuating the progression of underlying renal disease.

There is a plethora of studies documenting the improvement of renal function after prolonged control of arterial pressure in patients with malignant hypertension and renal failure. However, few studies have documented whether adequate control of hypertension, associated with primary renal disease, can either favorably alter the natural history of the disease or improve kidney function [92, 93]. Pohl et al. [93] in a group of 83 patients with severe hypertension and renal impairment, observed that the prognosis of these patients was good when blood pressure was adequately maintained and the initial creatinine clearance exceeded 8 ml/min. However, many patients with chronic glomerulonephritis showed a deterioration in renal function despite good blood pressure control.

In a hypertensive kidney transplant patient, the interrelationship between arterial pressure and the transplant kidney function should be similar to that of a hypertensive patient with primary renal disease. Unfortunately, however, we have few data on the effects of hypertension, with or without treatment, on the natural course of transplanted kidneys, and thus, it is difficult to support this supposition.

To determine long-term effects of hypertension on the graft function and survival, we studied the clinical course of 132 kidney transplant recipients

whose grafts functioned more than 2 years [94]. There were 77 males and 55 females; their ages between 5 and 63 years (mean + S.D.; 33.4+11.1) at the time of transplantation; and they were followed for 30–120 months (mean + S.D.; 68.2+32.2). Of the 132 patients, 23 were normotensive (diastolic B.P. <90 mm Hg) throughout the entire observation period, while 109 were hypertensive for most of their clinical course. Among the hypertensive patients, 46 maintained their blood pressure within normal ranges with antihypertensive agents, but 63 were persistently hypertensive despite treatment. Each group's serum creatinine levels (mean + S.D.) and graft survival rates at 2, 5, and 8 years after transplantation are shown in Table 4 and depicted in Figures 2 and 3.

The graft survival rate of normotensive patients was significantly better than that of hypertensive patients ($p<0.005$). However, there was no difference in graft survival rates of hypertensive patients between those whose blood pressure was well controlled with antihypertensive agents and those whose pressure was not. The mean serum creatinine levels in all three groups were stable throughout the observation period. The levels were, however, different among the three groups; normotensive patients (Bo) had the lowest level of serum creatinine, whereas the patients with refractory hypertension (B2) had the highest. The differences were statistically significant ($p<0.005$) at 1 and 2 years post-transplant. These data suggest that hypertensive patients started with a lower graft function and that hypertension *per se,* whether controlled or not, does not appear to adversely affect graft function, at least for a period of several years. The lower graft survival rate in patients with hypertension, therefore, does not appear to be the consequence of hypertension. This study suggested that hypertension and poor graft survival are associated phenomena and may both reflect intrinsic pathological changes in the allografts. Control of hypertension with antihypertensive

Table 4. Graft function and graft survival rates of kidney transplant recipients with and without hypertension

	Graft survival (%)			Serum creatinine (mg/dl)		
	2 Yrs	5 Yrs	8 Yrs	2 Yrs	5 Yrs	8 Yrs
B0	100	96	56	1.4±0.3	2.1±2.1	1.7±1.1
B1	100	70	24	1.9±0.8	2.0±1.1	1.5±0.6
B2	100	63	17	2.3±1.1	2.2±1.3	2.3±1.3

Yrs = years; B0 = patients with normal BP throughout entire observation period; B1 = patients with hypertension but their BP was kept within normal ranges with antihypertensive agents; B2 = patients with persistent hypertension despite treatment. Serum creatinine is expressed in mean ±S.D. The difference in serum creatinine concentrations between B0 and B2 is statistically significant at 2 years ($p < 0.05$).

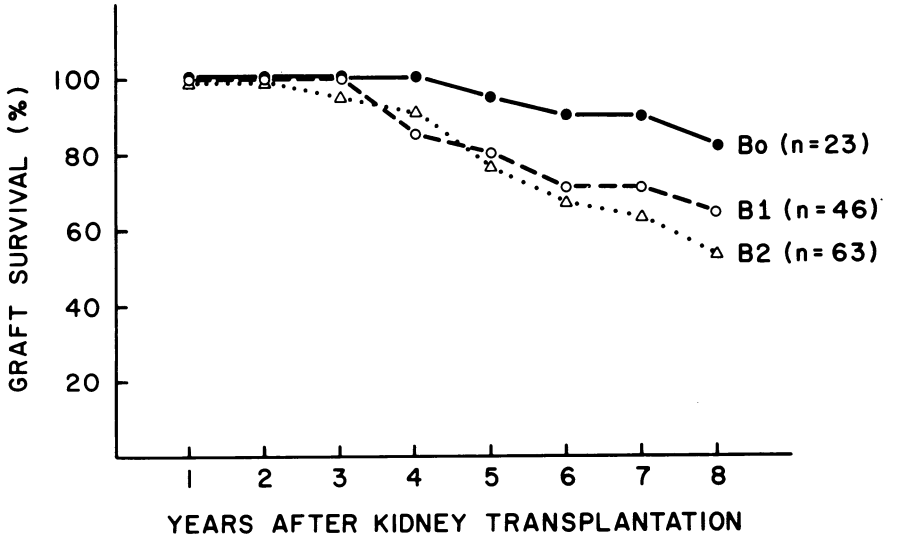

Figure 2. Renal graft survival rates. B0 = normotensive patients; B1 = hypertensive patients but their blood pressure had been maintained within normal ranges with antihypertensive agents; B2 = persistently hypertensive patients despite antihypertensive treatment.

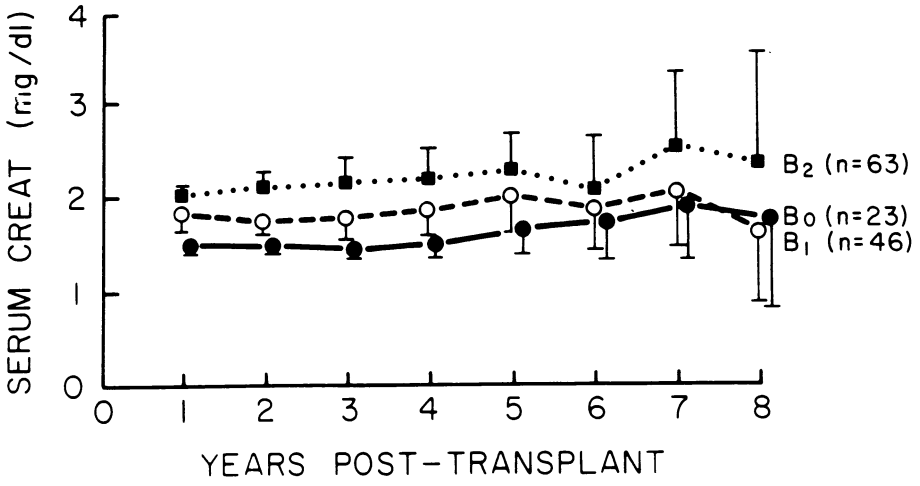

Figure 3. Mean, annual serum creatinine levels in normotensive and hypertensive renal transplant recipients. B0, B1, B2 denote the same groups, respectively, as in Figure 2.

agents does not appear to improve graft survival of these patients to that seen in normotensive patients.

Van Ypersele de Strihou et al. made a longitudinal study of 77 kidney transplant recipients whose graft had functioned for at least 7 years [7]. Among these, 23 patients were consistently normotensive and 32 were consistently hypertensive, whereas 22 oscillated between hypertension and nor-

motension. The authors observed that serum creatinine in the hypertensive group rose progressively over the years. By 84 months, the difference between the normotensive and hypertensive groups was significant. If native kidneys and graft artery stenosis, factors that account for approximately one-third of the cases, are excluded, hypertension in most patients resulted from a functional disturbance of the transplant kidney probably related to slow rejection. No comment was made, however, about whether or not antihypertensive therapy improved graft function and graft prognosis.

Significant transplant renal artery stenosis is often associated with progressive azotemia and worsening hypertension [11, 30, 95]. Restoration of transplant renal perfusion by either surgical renovascular reconstruction [11, 30, 95] or percutaneous transluminal angioplasty [96] helps to resolve hypertension and also helps to preserve graft function.

Curable forms of renal hypertension, such as excessive release of renin from the native kidneys, obstructive uropathy or renal artery stenosis of the renal allograft, should be sought and if found, a repairative procedure should be considered.

In summary, hypertensive patients seem to have a lower graft function and a lower graft survival rate than normotensive patients. Impaired renal function is, however, not the consequence of hypertension, but rather is either the cause of hypertension or an independent process. Maintaining blood pressure within normal ranges with antihypertensive therapy does not seem to improve graft survival to that of normotensive patients. Regardless of how hypertension and its treatment affect transplant kidney function, it is clear, however, that all hypertensive transplant recipients should be treated adequately as they are high risk patients for cardiovascular disease [6, 7]. The treatment may also prevent them from developing malignant hypertension which may precipitate a vicious cycle of renal failure [97]. On the other hand, repairative procedures should be considered in patients with transplant renal artery stenosis and hypertension. This approach may not only cure hypertension, but also may save the graft from progressive failure.

Evaluation and treatment of hypertension

Hypertension in kidney transplant recipients may represent an underlying pathologic process of either the native kidneys, the transplant kidney, other independent disorders or any combination of these (Table 3). Identifying the underlying pathologic process is crucial not only in finding a cure for hypertension but also in attempting to prevent progressive renal failure. All patients with significant hypertension should be treated adequately in order to prevent vascular changes and its attendant complications. In addition, an evaluation of the patient to delineate underlying diseases and/or mecha-

nisms should be pursued. When and how to evaluate hypertension is based on when hypertension developed relative to the time of transplantation, the severity of hypertension and other associated clinical observations, such as changes in graft function and the onset of proteinuria.

Hypertension in the first 6 months of transplantation

The first 6 months is the most unstable period for kidney transplant recipients. During this time the patient receives the highest amount of immunosuppressive drugs, including corticosteroids, and the transplanted kidney is often exposed to varying degrees of immunologic, ischemic, obstructive and nephrotoxic insults. Consequently, many patients continue to have or develop hypertension. However, in many patients hypertension will resolve as graft function stabilizes and the doses of corticosteroids decrease. Therefore, as long as graft function is stable and adequate it is best to avoid invasive diagnostic procedures and treat the hypertension while observing its clinical course. However, minimal non-invasive diagnostic studies such as renal scan, transplant renal sonograms, should be done as part of the transplant evaluation. It cannot be overemphasized that all diagnostic studies and procedures as well as therapeutic approaches should concentrate on the improvement and preservation of graft function rather than on the control of hypertension.

During the early post-operative period, peripheral PRA is often high, particularly in patients with either acute tubular necrosis or acute transplant rejection. Levels of peripheral PRA, therefore, have little diagnostic value. In addition, neither the presence nor the absence of a bruit over the transplant kidney indicates transplant renal artery disease. On the other hand, the observation of a change, either the appearance or disappearance of bruit, does have diagnostic significance. It is important, therefore, for future evaluation, to document the presence or absence of bruit.

Medical treatment of hypertension in transplant recipients is essentially the same as the treatment in patients with parenchymal kidney disease as described in Chapters 3 and 8. The goal of treatment is to bring arterial pressure within normal ranges with the minimum dose of the safest drugs administered in the most practical method.

Fluid balance should be evaluated and managed with the goal of inducing and maintaining a euvolemic state. Most kidney transplant recipients, have sodium and fluid overload as a result of limited graft function and high corticosteroid doses during the first few months after transplantation. Thus, they often require diuretic therapy.

If significant hypertension (>150 mm Hg systolic, >95 mm Hg diastolic) persists despite adequate sodium and fluid balance, hypertension should be

treated with antihypertensive agents. Any or a combination of agents could be used. However, direct vasodilators (hydralazine, calcium channel blockers), alpha receptor blockers (prazosin) and centrally active antihypertensive agents (clonidine, alpha methyldopa) are preferable to beta-adrenergic blockers (except nadalol and pindolol) or renin-angiotensin antagonists (captopril). The latter drugs may reduce renal blood flow and/or glomerular filtration rate [98]. If hypertension is severe and the patient is symptomatic, more potent antihypertensive agents, such as minoxidil, diazoxide or sodium nitroprusside, could be utilized as described in Chapter 8.

Chronic hypertension in kidney transplant recipients

Chronic hypertension in kidney transplant recipients at later postoperative periods is usually a continum of hypertension that existed preoperatively or during the early post-operative period. It may, however, develop *de novo,* at some point after kidney transplantation [11, 33, 99, 100]. In either case, an underlying pathologic process might be one or a combination of those entities listed in Table 3. All patients with chronic established hypertension should have an evaluation to delineate the cause of hypertension, since some of these, such as transplant renal artery stenosis, are correctable. Therapeutic intervention to correct the underlying abnormality, may not only ameliorate hypertension but may also preserve better kidney function. The evaluation of a patient for hypertension should include the following information and data:

1. *A history of hypertension.* The presence of hypertension before transplantation suggests that the patient may have either essential hypertension or renal hypertension secondary to native kidney disease. However, this does not exclude the possibility that either the transplanted kidney or other non-renal mechanisms may also be playing an important role.

2. *Diagnosis of the native kidney disease.* Some kidney diseases, such as focal segmental glomerulosclerosis and membrano-proliferative glomerulonephritis, recur more often than others in a transplant kidney [101, 102]. The recurrence of glomerulonephritis in a transplant kidney usually presents with progressive azotemia, proteinuria and hypertension.

3. *Renal transplant function.* The worse the graft function is, the more likely the transplant is responsible for hypertension. The reverse is not true, however, since patients with renal artery stenosis often have good kidney function.

4. *Proteinuria.* A persistant and significant amount of proteinuria suggests the presence of transplant glomerular disease, such as chronic rejection, recurrent glomerulonephritis or *de novo* glomerulonephritis, that may also be responsible for hypertension [101, 102]. Diagnosis of these processes can be made only by the pathological studies of a transplant kidney biopsy.

5. *Plasma renin activity (PRA).* The measurements of PRA from peripheral blood, renal veins and transplant renal vein provide helpful information in delineating mechanisms of hypertension. If PRA is abnormally high and lateralizes to any one or two of the three kidneys (transplant plus two native kidneys) the finding is extremely informative. A random PRA from peripheral blood, however, is neither sensitive nor specific as a diagnostic index for renal and/or renovascular hypertension in transplant recipients. One of the reasons for this is that the pathophysiology of hypertension secondary to transplant renal artery stenosis often resembles an animal model of one-kidney Goldblatt hypertension (volume-dependent). On the other hand, if one or both of the native kidneys are the source of excessive renin secretion or when the transplant renal artery has a severe stenosis, the pathophysiology of hypertension resembles that of two-kidney Goldblatt hypertension (renin-dependent). On the whole, clinical experience suggests that PRA determination from peripheral venous blood alone or hemodynamic responses to a renin-angiotensin blocker would not in a given patient determine the presence or absence of renovascular hypertension. Likewise, these data could not precisely predict blood pressure results after therapeutic intervention [14, 23, 25, 44] (see Mechanisms of hypertension, in this chapter).

6. *Renal sonogram.* Renal sonography does not depend on renal function for visualization of the kidney and the transplant kidney is close to the body surface, thus enhancing the image. Sonography is an extremely useful procedure in evaluating post-transplant complications. It has a high reliability and sensitivity in disclosing obstructive uropathy as the cause of transplant failure. The degree and the location of obstruction can be readily seen. It should be noted, however, that most transplant kidneys have a mild degree of pelvocaliceal dilatation that has little clinical significance; on the contrary, an acute, complete obstruction in the early post-transplant period may not produce a discernable degree of pelvocaliceal dilatation.

7. *Renal scan.* Renal scan using 99 mTc DTPA (or 99 mTC glucoheptinate) and 131 I hippuran can provide useful information on renal blood flow, and excretory function. Serial studies over time are helpful in evaluating the evolution of renal transplant function. The resolution of images, is, however, neither sensitive nor specific enough to allow an anatomical diagnosis of the transplant kidney disease.

8. *Renal angiogram.* An angiogram is the most crucial diagnostic test in transplant renovascular hypertension. It is useful in confirming the lesion, discerning its nature, location, extent, and evaluating the feasibility of surgical or non-surgical therapeutic intervention. It is important as a diagnostic procedure, and simultaneously can be utilized as a therapeutic intervention (percutaneous transluminal angioplasty) during the procedure. Although it is an invasive procedure and contrast media induced acute renal dysfunction

which can be a considerable risk, the introduction of digital enhancing techniques have minimized these risks. With this technique, a renal angiogram can be obtained with either an intravenous injection of contrast media (digital-enhanced intravenous angiogram) or by injecting an extremely small amount of the media directly into the renal artery.

Transplant renal artery stenosis

Transplant renal artery stenosis (TRAS) may cause severe hypertension and progressive renal failure. An association between renal artery stenosis and hypertension, however, may not always be causal.

In experimental studies, the significance of stenosis is determined by the area ratio between the stenosed and unstenosed portions of the vessel and the velocity of the flow rate [103]. The higher the flow rate, the less constriction of the vessel is required to be significant. In a low flow system, however, the fall in flow rate and pressure in the post-stenotic area is more precipitous than that in a high flow system when the degree of stenosis is beyond a critical point. Clinically, a stenosis that is less than 50% of luminal diameter, corresponding to a patency of more than 25% of cross-sectional area of the vessel, has little hemodynamic significance [104]. A stenosis of more than 50% of arterial luminal diameter is often considered radiologically significant. In order to be hemodynamically significant, however, and result in hypertension or renal dysfunction, it should be at least 65% occlusion [104].

Incidence

The reported incidence of TRAS following a successful renal transplantation varies between 1–12% [11, 28–30, 33, 99, 105]. These figures are, not based on a prospective study but are derived from the number of patients found to have TRAS out of an entire transplant population. Lacombe, with a routine angiographic study of 100 consecutive kidney transplant recipients found TRAS in 23% of the patients, but not all of these were hypertensive [99]. About half of this frequency was noted in another prospective series [104]. The incidence of TRAS among patients who underwent angiographic study because of severe and refractory hypertension was between 37 and 73% [7, 11, 29, 35]. A considerable difference in the reported incidence of TRAS might be due to differences in the diagnostic criteria, the frequency of angiographic study and the inclusion of segmental arterial disease. Suffice to say that TRAS is not an uncommon cause of severe hypertension in kidney transplant recipients.

Pathology

Kidney transplant recipients may develop TRAS any time after the procedure. An acute occlusive disorder of the transplant renal artery in the immediate post-operative period is usually due to either a severe humoral rejection or a faulty surgical technique and often results in graft failure.

A chronic occlusive disorder of the transplant renal artery may develop as early as 1 month and as late as several years after transplantation. Most of these lesions, however, are clinically apparent approximately 3–6 months post-operatively [32, 33, 104, 106]. Although the progression of the narrowing process has been more often observed during repeated examinations [29, 99], a spontaneous regression of the lesion, in both localized and diffuse types, has also been observed [104, 107]. Total remission is, however, unusual.

Lacombe proposed the following morphologic and topographic classifications of TRAS based upon angiographic findings [99].

1. *Stenosis of the recipient's hypogastric artery.* This is usually due to atheromatous plaques in the hypogastric artery. Acute angulation or kinking of this vessel due to a long hypogastric renal artery can be another cause of this lesion.

2. *Stenosis of the suture line.* A faulty suture technique is usually responsible for the stenosis between the recipient's and donor's vessel.

3. *Stenosis of the main or major branches of the transplant artery.* This is the most common type of TRAS. Several mechanisms have been postulated for the development of this lesion, including trauma during pump perfusion or operation [108], atheromatous plaque formation and immunologic responses to the donor tissue. Among these, immunologic damage (rejection) appears to be the most important cause of the lesion. Clinically, two types of lesions, localized and diffuse have been reported:

Localized (segmental) stenosis: This is a short, segmental stenosis that is less than 1 cm in length. This involves either a proximal portion of the renal artery located just beyond the suture line, or a distal portion of the renal artery which is near to the bifurcation or even affecting bifurcation itself or the branches.

Diffuse (tubular) stenosis: This is a tubular narrowing of the entire length of the renal artery. On angiogram, the outline of the stenosed artery may be smooth, but more frequently it is irregular, suggestive of an extensive endothelial proliferation and fibrosis. Histologically, this lesion consists of fibrous endarteritis with severe intimal thickening. A relative stenosis similar to this type of lesion can be seen in adult patients who receive young children's kidneys [109, 110].

4. *Multiple stenoses.* Multiple stenoses consist of two or more stenotic lesions of the same or different varieties as described above.

Diagnosis

A high index of suspicion based on clinical data is most important. In patients with new, severe hypertension or persisting hypertension after kidney transplantation the possibility of TRAS should be considered. In addition to hypertension, a substantial number of patients will have decreased graft function [30, 95, 99, 111] and a bruit over the transplant area on physical examination. Many transplant patients have a bruit without TRAS [112, 113], and not all patients with TRAS have a bruit [30, 33]. Thus, neither the presence of a bruit is diagnostic for, nor does the absence exclude, the possibility of TRAS.

PRA levels, either from peripheral or transplant renal vein, along with native kidney veins, may be helpful in establishing the diagnosis [36, 44]. However, it is elevated in less than half of the patients with significant TRAS [11, 23, 30]. Even if the patient demonstrates a high level of PRA from the transplant renal vein, as well as a hypotensive response to a renin-angiotensin blocking agent, the excessive secretion of renin may not be due to TRAS, but to small vessel disease of allograft rejection [29]. Whenever TRAS is suspected, the confirmation of the lesion, the nature, the location and the extent and feasibility of surgical or non-surgical intervention should be evaluated by angiographic study [99, 104, 106]. A TRAS involving more than 75% of luminal diameter is usually clinically significant but less than 50% is probably not.

Treatment

The goal of therapy in patients with TRAS is the control of hypertension and the preservation of graft function. A reduction of blood pressure obtained by medical therapy without the correction of the stenosis may lead to further deterioration of renal function [29, 99, 114]. The worsening may be due to the progression of the stenosis or to decreased renal perfusion as blood pressure is reduced. In the case of the transplant kidney, the risk of ischemic damage by either one of these mechanisms is even greater because of the lack of collateral circulation. On the other hand, the repair of stenosis by either surgical or non-surgical intervention has not only improved hypertension but graft function as well [29–31, 95, 96, 111]. Therefore, every effort should be made to correct the stenosis.

The conventional approach to repair TRAS has been surgical intervention (see Chapter 10). A patch angioplasty or bypass by the use of saphenous vein has produced fair results in improvement of hypertension and graft function [30, 31, 35, 111]. Surgical correction of TRAS may be difficult and dangerous to the graft due to the fibrous tissue which envelopes the renal hilus. Operative complications, which occur in one-third of the cases, include not only technical failure, but also loss of graft or patient as a direct result of surgical intervention [28–30, 44, 95]. This emphasizes that the sur-

gical procedure is of considerable risk to the patient and should be undertaken only in selected cases. Surgical correction should be considered as the first choice approach for stenosis caused by either angulation, twisting or kinking of the artery.

Percutaneous transluminal angioplasty (PTA) in renal artery stenosis of native kidneys has proved highly efficacious. It presents a lower risk of mortality or other serious complications and it has the added advantages of a shorter hospital stay and less pain [115]. The experience in the use of PTA for a TRAS is limited. Our experience, in addition to others [29, 96], has shown that in appropriately selected cases, the procedure is more effective and safer than the surgical approach to relieve stenosis and improves hypertension and graft function. If stenosis should recur, dilatation of the lesion by PTA can be repeated [96] (see Chapter 9).

If TRAS is not correctable, then the patient is left with conservative treatment with antihypertensive agents. Treatment is essentially the same as for hypertension during the early post-operative period. Drugs should be used with an extra precaution to avoid dehydration and hypotension that will severely compromise graft function. Captopril has been successfully used in transplant patients without significant adverse effects on graft function [116, 117]. However, it is contra-indicated in patients with TRAS. Compromised renal perfusion, as in the case of TRAS, results in increases in angiotensin II which causes increased efferent arteriolar constriction and thus, an augmented filtration fraction and GFR. Captopril, by inhibiting angiotensin II formation, interferes with the kidney's ability to autoregulate the glomerular filtration rate [118, 119]. In patients with bilateral renal artery stenosis or renal artery stenosis of a solitary kidney [114], unilateral renal artery stenosis [120] and TRAS [118], captopril therapy has produced significant, but reversible decreases in GFR. The effects of captopril in patients with small vessel disease of chronic rejection but without TRAS are unknown. Captopril can also produce azotemia and nephrotic syndrome [121].

Hypertension caused by diseased native kidneys

The kidney continues to play an important role as an endocrine organ even when it does not make urine. Nephrectomy results in severe anemia in dialysis patients which is poorly responsive to androgenic hormone therapy [122]. In addition, blood pressure regulation must be accomplished in the absence of a functioning renin-angiotensin system. Consequently, the incidence of symptomatic hypotension during dialysis is much higher in nephrectomized patients than in nephric patients [123]. To avoid severe anemia and symptomatic hypotension during dialysis, nephrectomies are

seldom performed except for specific indications [122]. Therefore, most kidney transplant recipients retain their diseased native kidneys.

Mechanism and incidence

The diseased native kidneys in some patients, regardless of the etiology of the disease, continue to secrete excessive and inappropriate quantities of renin even after successful transplantation, thus, contributing to post-transplant hypertension [7, 16, 23, 27, 124, 125]. Kidney transplant recipients with native kidneys have a 20–30% higher incidence of hypertension than that of those without native kidneys [7, 11, 52]. Van Ypersele de Strihou et al. studied the prevalence of hypertension in 55 patients who he had followed for at least 7 years [7]. Since the prevalence of hypertension averaged 50% and 60% in nephrectomized and non-nephrectomized patients respectively, they estimated that the native kidneys played an etiologic role in 15 of the 65%, that is 23% of non-nephrectomized hypertensive patients.

Evaluation and treatment

Bilateral nephrectomy after a successful kidney transplant has been advocated as a method of curing or improving persistent hypertension [7, 25, 52, 126]. Although lateralization of renin secretion toward native kidneys (host kidney/transplant kidney PRA ratio > 1.5) highly suggests beneficial effects, selective renal vein renin measurements do not consistently predict the outcome of a bilateral nephrectomy [7, 25]. Therefore, these authors recommend bilateral nephrectomy for a successful kidney transplant recipient who has persistent post-transplant hypertension and meets the following criteria:

1. no significant parenchymal kidney disease (chronic rejection, recurrent glomerulonephritis) involving the allograft;
2. no obstructive uropathy or renovascular disease involving the allograft;
3. a well functioning graft (serum creatinine <2.0 mg/dl) for more than 1 year;
4. hypertension cannot be effectively and adequately controlled with antihypertensive agents.

Surgical approaches as treatment of renal hypertension are presented in Chapter 10. Recently, a percutaneous renovascular embolization technique has been used for host kidney ablation [127]. Embolization of the host kidney was performed with selective catheterization of each renal artery and injection of polyvinyl alcohol particles, lyophilized dura mater or ethanol via a balloon occlusion catheter. Although clinical experience utilizing this technique is relatively small, it appears to be an acceptable alternative to surgery in the treatment of hypertension in selected patients.

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7. Hypertension in Pregnancy

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Introduction

The hypertensive pregnant woman presents a challenge both to the obstetrician and the internist. Although the outcome of hypertensive pregnancies is most often favorable, pregnancy induced hypertension represents a major cause of both fetal and maternal morbidity and mortality. The hypertensive disorders of pregnancy are responsible for 1/5 of maternal deaths, and for about 10,000 fetal deaths per year [1].

Any discussion of the hypertensive disorders of pregnancy is complicated by the variability in the criteria for diagnosing these diseases. The diagnosis of hypertension involves what might appear to be an arbitrary separation of normal from abnormal blood pressures. In pregnancy, the usual definition of hypertension is a blood pressure greater than 140/90. However, since there is evidence that perinatal mortality rises with mean arterial pressure (MAP) of 90 or greater [2], it may be more reasonable to consider 130/80 as the upper limit of normal for the first two trimesters. To clarify some of the controversy, the Committee on Terminology of the American College of Obstetrics and Gynecologists has specified the following criteria for the diagnosis of gestational hypertension: (1) a sustained rise of 30 or more mm Hg in the systolic, (2) and/or 15 mm Hg or more in the diastolic pressure, (3) or a sustained blood pressure of $\geq 140/90$ mm Hg or more. Therefore, for women with a blood pressure of 90/60 prior to pregnancy, 120/80 represents an abnormally high blood pressure. This becomes even more important when one considers the fact that woman in the child bearing years are not often aware of 'pre-pregnancy' blood pressures.

Physiology of normal pregnancy

It should be emphasized at this time that studies of hemodynamics in pregnant women are subject to error resulting from the effects of posture on

hemodynamic parameters. When the pregnant women is supine or standing, the enlarged uterus interferes with venous return to the heart, and results in subsequent decreases in cardiac output, renal blood flow, glomerular filtration rate (GFR) and renal sodium excretion [3]. Therefore, ideally all hemodynamic and renal function studies should be performed with the pregnant woman in lateral recumbency.

Hemodynamic changes

There are several striking physiologic adjustments that occur during normal gestation. The cardiac output rises 30–40% relative to the non-pregnant resting state. The increase in cardiac output has been shown to occur as early as the 12th week and is principally the result of an increased stroke volume. The increased stroke volume is believed to be a result of an increase in plasma volume of up to 50%, that occurs beginning in the first trimester and is sustained until term. There is also a modest increase in heart rate that occurs during pregnancy that may contribute to the increased cardiac output. Despite the striking increase in cardiac output, during normal gestation, mean blood pressure decreases early in pregnancy by as much as 15 mm Hg in the second trimester. Blood pressure increases gradually in the third trimester, and often approaches pre-pregnancy levels at term.
Blood pressure is a product of cardiac output and peripheral resistance. Since cardiac output increases, it is obvious that decreased peripheral resistance is responsible for the decreased blood pressure in normal pregnancy.

Renal changes

Most investigators have shown that during normal pregnancy glomerular filtration rate (GFR) and renal plasma flow (RPF) increase 30–50% above pre-pregnancy values and remain elevated until delivery. The increase in GFR is most likely secondary to the increase in RPF, which in turn may be influenced by volume expansion and hormonal changes that occur in pregnancy. One of the consequences of the increased GFR is that the serum creatinine and BUN levels of normal pregnant women are lower than in the non-pregnant state. Therefore, values that are considered normal in non-pregnant women may reflect abnormal renal function in pregnant women. In general, if the creatinine and BUN are higher than 0.8 mg/dl and 13 mg/dl respectively, then one should suspect the presence of abnormal renal function [4].

There are significant adjustments in sodium and volume homeostasis during pregnancy. Total body water increases in pregnancy by 6–8 liters,

4–6 of which are extracellular. There is a cumulative retention of approximately 950 mEq of sodium, about half of which is stored in the extracellular spaces, accounting for the physiologic hypervolemia. The normal pregnant woman, however, will respond appropriately to volume depleting stimuli such as salt restriction or diuretics by increasing sodium reabsorption.

Hormonal changes

Several striking hormonal alterations in pregnancy are in part responsible for the physiologic changes outlined above. The renin-angiotensin aldosterone system is markedly stimulated in normal pregnancy reaching a peak of activity during the third trimester. Wilson et al. studied these hormones throughout gestation and showed that plasma renin activity (PRA) increased 7-fold over non-pregnant levels [5]. About 50% of this increase could be attributed to an increase in plasma-renin substrate which may be in part a consequence of estrogen induced stimulation of renin substrate production. Plasma aldosterone increases 8-fold and urinary aldosterone increases even more. Increases in renal renin activity may be a result of the fall in blood pressure and dilation of the vascular bed. In addition, it has been reported that the uterus is a source of renin in animal species and perhaps in man. The precise role of the increased PRA in maintaining blood pressure is not clear. Angiotensin II (AII) levels are also increased in pregnancy, however, it has been shown that normal gravidas are relatively resistant to the pressor effects of AII.

Recent data have implicated vasodilatory prostaglandins in the maintenance of adequate uteroplacental perfusion. In addition, prostaglandins, particularly PGE and PGI_2 (prostacyclin) are thought to be the mediators of the decreased peripheral resistance that is observed in pregnancy. If so, a deficiency of these substances could be involved in some forms of pregnancy hypertension.

Definitions of hypertensive disorders of pregnancy

Pre-eclampsia and eclampsia

Pre-eclampsia is hypertension with proteinuria (> 0.3 g/24 h) appearing after the 20th week of gestation. Edema may or may not be present. Pre-eclampsia may develop earlier in the presence of trophoblast disease. *Eclampsia* is convulsions in a patient with pre-eclampsia. Severe pre-eclampsia is diagnosed when any of the following conditions are fulfilled:

1. a blood pressure equal to or higher than 160 mm Hg systolic and/or 110 mm Hg diastolic on two occasions at least 6 h apart with the patient at bed rest;
2. proteinuria of at least 5 g/24 h;
3. oliguria, defined as urinary volume of less than 400 ml/24 h;
4. cerebral or visual disturbances;
5. pulmonary edema or cyanosis;
6. epigastric pain.

Pre-eclampsia and eclampsia are also referred to as pregnancy induced hypertension, or hypertension peculiar to pregnancy.

Chronic hypertension of whatever cause

This is diagnosed when hypertension (> 140/90) is present before pregnancy or before the 20th week of gestation, and may be due to essential hypertension or any of the known causes of secondary hypertension such as kidney disease, adrenal tumors, or renovascular hypertension.

Superimposed pre-eclampsia

When a woman with existing chronic hypertension develops a rise of ≥ 30/15 mm Hg in blood pressure, or proteinuria in late pregnancy, she is said to have superimposed pre-eclampsia.

Transient hypertension

This refers to gestational hypertension that occurs late in pregnancy, without proteinuria or edema, and that disappears within 10 days of delivery.

Pre-eclampsia

In prospective studies the incidence of pre-eclampsia is reported to be from 10–22% in primigravidas. The symptoms and signs of pre-eclampsia may occur earlier in the presence of hydatidiform mole. Pre-eclampsia is said to be a disease of first pregnancy, and occurs approximately 15 times more commonly in first than in second pregnancies. Women at extremes of reproductive age (less than 20 years of age and greater than 35) are more frequently affected. When pre-eclampsia occurs in a multiparous woman, one of the following clinical conditions are usually present:

1. large placental mass, in association with multiple gestations;
2. vascular diseases such as chronic essential hypertension, renovascular hypertension, and diabetes mellitus;
3. chronic renal disease.

With regard to the diagnostic criteria for pre-eclampsia, as mentioned above, hypertension in pregnancy is defined as a blood pressure of either 140/90 or a 30/15 mm Hg rise over pre-pregnancy values. These criteria must be present on at least two occasions, 6 or more hours apart to establish a diagnosis of pre-eclampsia.

It should be pointed out that hypertension appearing after 20 weeks does not necessarily imply pre-eclampsia. Many women are unaware of antecedent hypertension, and since blood pressure usually falls in early gestation, an elevated blood pressure after 20 weeks may represent the normal late blood pressure rise of a mild hypertensive.

Proteinuria is defined as the presence of greater than 300 mg or more of protein in a 24-h urine collection, or protein measurement of 2+ or greater in a random urine specimen. It is generally believed that the presence of proteinuria in pregnancy, in association with hypertension, markedly increases the risk of perinatal mortality. Like hypertension, proteinuria is not specific for pre-eclampsia and may not be present when the blood pressure first becomes elevated. The presence of proteinuria is more significant than edema, and all patients with hypertension and significant proteinuria should be assumed to have or be at high risk for pre-eclampsia.

The presence of edema is not crucial to the diagnosis of pre-eclampsia. Edema may be present in 80% of normal pregnant women, and its presence or absence should not make the diagnosis of pre-eclampsia more or less secure. Indeed, Freedman and Neff have found that perinatal mortality for women whose pregnancies were 'complicated' by edema alone was lower than the overall perinatal mortality rate [28].

Pathophysiology of pre-eclampsia

The pathophysiology of pre-eclampsia is incompletely understood at the present time. A multitude of abnormalities have been documented in association with pre-eclampsia, most of which seem to reflect vasospasm, possible endothelial cell damage, localized disseminated intravascular coagulation and compromised utero-placental blood flow.

The initial event leading to the altered physiology of pre-eclampsia is, at the present time unknown. There are, however, several physiological changes that are consistently observed.

Hemodynamics

In contrast to normal pregnant women, women with pre-eclampsia have a decreased or unaltered cardiac output and a contracted plasma volume. The hypertension is characterized by an increased peripheral resistance, and heightened sensitivity to endogenous pressor peptides and amines. In fact, Gant and co-workers have claimed that women destined to develop pre-eclampsia developed increased sensitivity to the pressor effects of AII before they developed clinical signs of increased blood pressure or proteinuria [7].

Several investigators using various techniques have documented decreased plasma volume, low cardiac filling pressures, and decreased colloid osmotic pressure in patients with pre-eclampsia. The contracted intravascular volume seems to be associated with altered capillary permeability, so that patients may be slightly intravascularly volume depleted, but total body salt and water overloaded. Patients with severe pre-eclampsia who have undergone hemodynamic monitoring have been found to have low or normal pulmonary capillary wedge pressures, and high systemic vascular resistance. The cardiac output in such patients has been reported to be both low and high by different investigators.

When pulmonary edema develops in a patient with pre-eclampsia there may be no evidence of left ventricular dysfunction. Rather these patients have been shown to have capillary permeability defects, decreased colloid osmotic pressure, and low pulmonary capillary wedge pressure.

The contracted plasma volume in patients with pre-eclampsia has several consequences, including hemoconcentration and hyperuricemia. Gallery et al. has studied the relationship of plasma volume to birth weight, and found there to be a positive correlation in women with pre-eclampsia [10]. There is additional evidence that the severity of pre-eclampsia is proportional to the degree of volume contraction. It is felt that decreased uric acid clearance, which parallels the decreases in sodium excretion in pre-eclampsia is merely a consequence of relative hypovolemia and reduced renal blood flow. Clinically, physicians have observed for years that uric acid levels in pre-eclampsia correlate with the severity of disease and this seems to be a reflection of the degree of hypovolemia in such individuals.

Renal changes

Patients with pre-eclampsia have a lower GFR and ERPF than normal pregnant women. The decrease in GFR is approximately 25 % in mild cases, so that it still remains above pre-pregnancy values. The decrease in GFR may be secondary to decreased renal perfusion, however, there is a characteristic glomerular lesion in such patients, that undoubtedly has functional significance. The renal lesion of pre-eclampsia is termed glomerular capillary endotheliosis and is thought to be pathognomonic for the condition. The

glomeruli are large and swollen, and on ultrastructural examination there is extensive swelling and vacuolization of the capillary endothelial cells, and on occasion, of the mesangial cells. Currently there is controversy concerning the significance of immunoglobulins and fibrin deposits that are sometimes seen in glomeruli of pre-eclamptic patients. It is argued by some that they are evidence of immunologic injury. In addition to decreased GFR, the renal lesion of pre-eclampsia is probably responsible for the proteinuria that is seen in this disorder. Proteinuria may be minimal or it may be as severe as 25 g/24 h. It is important to realize that the most common cause of the nephrotic syndrome in pregnancy is pre-eclampsia. The proteinuria is non-selective in nature and in severe cases may be associated with hypoalbuminemia.

The issue of renal sodium excretion in pre-eclampsia is still unresolved, even though most investigators have documented an impaired ability to excrete sodium. This tendency for sodium retention may be the result of 'pre-renal factors', such as decreased circulating blood volume, or it may be the result of the renal lesion itself. It must be stressed that the issue of salt handling in hypertensive disorders of pregnancy awaits further clarification, and that at the present time there is no evidence that salt retention causes pre-eclampsia.

Hormonal changes

The activity of the renin-angiotensin aldosterone system in hypertensive pregnancies has been investigated by several laboratories, however, available data is conflicting. As mentioned above, women with pre-eclampsia have increased vascular sensitivity to the pressor effects of AII. This increased sensitivity to AII is not the consequence of alterations in plasma volume or plasma concentrations of renin or AII, but more likely results from a loss of vascular refractoriness to the pressor effects of AII. The significance of this finding in the pathophysiology of pre-eclampsia is not clear at the present time.

Weir et al. reported significantly lower plasma renin concentrations, renin substrate, and angiotensin II levels in pre-eclamptic women compared to normal pregnant women [12]. These findings have been both supported and refuted by others. These differences reported in the literature have been attributed to differences in laboratory technique, the effect of bed rest on plasma renin activity (PPA), and the effect of inadvertent cryoactivation of renin during blood collection. The role of the renin-angiotensin aldosterone system in hypertensive pregnancy is complicated by the possibility that the source of circulating PRA in pregnancy may be both the kidneys and the uteroplacental unit [6]. There are also data suggesting that the placenta may play a role in modifying PRA, perhaps by converting enzyme activity, resulting in increased AII levels. Of interest is the finding by Symonds et al.

that peripheral levels of AII are elevated in pre-eclamptic pregnancies [13]. The role of the observed elevation of AII in the hypertension of preeclampsia is not clear since there are no studies to date on the effects of angiotensin II antagonists or converting enzyme inhibitors in preeclamptic patients. Captopril and enalapril have been given to pregnant rabbits with resulting lowering of blood pressure, however, significant toxicity was observed often resulting in abortion or fetal resorption [14].

As mentioned above, vasodilatory prostaglandins have been implicated in the maintenance of adequate uteroplacental blood flow and decreased peripheral resistance of normal pregnancy. Several authors have reported decreased levels of PGE_2 and prostacyclin (PGI_2) in pre-eclamptic pregnancies. Prostacyclin generation in fetal and maternal blood vessels seems to be reduced or inhibited in pre-eclampsia [15]. In addition, lower PGI_2-like activity has been found in the amniotic fluid of women with pre-eclampsia. Of interest is a recent report in the literature of treatment of a patient with severe pre-eclampsia with prostacyclin infusion [16]. Prostacyclin, not surprisingly, lowered the blood pressure. Furthermore, urinary excretion of PGE_2 has been recently found to be lower in patients with pre-eclampsia. Whether this is a cause or an effect of decreased renal perfusion is not clear at the present time. In any event, there seems to be increasing data in the literature linking altered prostaglandin production and alterations in the renin-angiotensin aldosterone system in the pathophysiology of pre-eclampsia. This is not surprising since prostaglandins are stimulators of renin release by the kidney, and AII in turn has been shown to alter prostaglandin synthesis. Finally, prostaglandin synthetase inhibitors have been shown to reproduce, in otherwise normal pregnant women, heightened vascular sensitivity to AII that is present in pre-eclampsia.

Coagulation

Several other physiologic alterations are present in women with pre-eclampsia. The role of coagulation abnormalities in the etiology of pre-eclampsia is still debated. However, there is no doubt that such patients have varying degrees of hematologic dysfunction. It is believed that with worsening pre-eclampsia there is release of placental thromboplastin into the maternal circulation, and this in turn initiates a consumptive coagulopathy with thrombocytopenia and prolongation of the prothrombin time and partial prothrombin time. Fibrin-fibrinogen deposition is well documented in the placenta, kidney, and liver of patients with pre-eclampsia. Patients with severe pre-eclampsia will occasionally develop hepatic dysfunction with elevations in hepatocellular enzymes and jaundice. Such patients may have evidence of coagulopathy and the hepatic dysfunction may be a manifestation of localized disseminated intravascular coagulation. The consensus at the present

time is that coagulation abnormalities are a consequence rather than a cause of pre-eclampsia.

Etiology

Throughout the years there have been many theories advanced concerning the etiology of pre-eclampsia. There are several clinical features of the disorder that must be explained by any plausable theory. As mentioned, pre-eclampsia is a disease predominantly of first pregnancy, that is known to occur only in humans, and is cured by delivery of the placenta. It occurs in the absence of a fetus with molar pregnancy, and when it appears in second pregnancy, there is usually co-existing chronic vascular disease (essential hypertension, diabetes, or renal disease). There is an increased frequency of pre-eclampsia with large placental mass as in multiple gestations. Finally, it appears that there is a familial predisposition to pre-eclampsia.

These and other observations have led many workers in the field to consider that uteroplacental hypoperfusion is central to the pathogenesis of pre-eclampsia. This may occur as a result of either large placental mass or compromised blood flow. Although direct experimental evidence is often lacking, the manifestations of pre-eclampsia have been explained as consequences of uteroplacental ischemia. For example, with reduced placental perfusion trophoblastic degeneration is thought to occur. This in turn generates thromboplastin resulting in deposition of fibrin and fibrinogin within the renal glomeruli. Imbalances between the renin-angiotensin system and vasodilatory prostaglandins may occur as a result of placental vascular pathology, which may result in altered vascular PGE_2 and PGI_2 production.

The concept of uteroplacental ischemia may explain satisfactorily why a woman with disorders likely to cause generalized vascular pathology such as chronic hypertension or renal disease is more likely to develop pre-eclampsia, but it falls short of explaining why the young primigravida is likely to be affected in the first but not subsequent pregnancies. For several years it has been suggested that pre-eclampsia may have an immunologic etiology. This concept is not new, but it has been difficult to substantiate with currently available experimental techniques. Beer has recently summarized the observations that have been made that support the concept of pre-eclampsia as an immunologic disorder [17]. These observations are: (1) preeclampsia is 15 times more common in first pregnancies than in second pregnancies implying immune protection generated by the first pregnancy. A first pregnancy of any duration confers considerable protection unless the second pregnancy presents the mother with a large trophoblast mass (twins) or a new set of paternal HLA antigens (change in paternity). Marti and Herman

have reported that women who developed pre-eclampsia had less contact with their partner's semen than women who had normal pregnancies [18]. They suggested that exposure to antigens expressed on sperm may be partially responsible for induction of immunologic tolerance. (2) The basement membrane and the epithelial cytoplasm of the trophoblast share antigenic determinants in common with components of the kidney and the brain vasculature. (3) Experimentally induced immunologic injury to the choriodecidual junction in experimental animals produces a disorder indistinguishable from pre-eclampsia. (4) The arterioles of the placental bed in pre-eclampsia are similar in appearance to the vascular changes seen in renal allograft rejection.

In normal pregnancy the fetus is not 'rejected' by the mother. This may be the result of interference with recognition, which might be due to lack of expression of fetal HLA antigens on parts of the trophoblast. On the other hand, this immune 'tolerance' may be the result of active adaptive maternal immune responses. For example, serum factors appear in the blood of normal pregnant women that inhibit the immunologic response of maternal lymphocytes to paternal or fetal lymphocytes in mixed lymphocyte (MCL) reaction. Such blocking factors may be antibodies that 'mask' the antigens on fetal cells and prevent a destructive immune response from occurring. In addition, maternal suppressor cells have been observed in the lymph nodes that drain the uterus of pregnant rats which suppress the development of cytotoxic T cells directed against the fetus. Specific evidence documenting a breakdown of such normal adaptive immunity in pre-eclampsia has only recently begun to emerge. A small study of five primigravid patients with pre-eclampsia has shown that these patients did not demonstrate serum factors that blocked the maternal response to fetal antigens, whereas the control group of normal pregnant women did [19]. Gliecher et al. have found natural killer cell activity to be significantly increased in women with pre-eclampsia [20]. They speculate that this may be due to absence of a specific inhibiting factor in these pregnancies. If insufficient blocking antibodies are produced, in a young nulliparous female then the trophoblast may not be protected against immunologic 'attack' of the mother. The attack would result in infiltration of effector lymphocytes in the cytotrophoblast and arterioles, with destruction or occlusion of placental bed vessels. Since the blood vessels are the source of prostacyclin production, this immune vasculitis may result in decreased prostaglandin production by the placenta, and in turn decreased uterine blood flow. Uteroplacental ischemia then, in the young nulliparous patient may be a result of immunologic injury. With second pregnancy there would be sufficient antigenic exposure as a result of the first pregnancy, enabling the woman to mount an adequate protective immune response, and pre-eclampsia would not occur. In the individual with chronic underlying vascular disease, immunologic injury

need not occur for uteroplacental ischemia to be present and indeed such patients may develop pre-eclampsia after the first pregnancy.

Management of pre-eclampsia

Pre-delivery management

The goal in the management of a women with pre-eclampsia is to deliver a mature, healthy fetus without jeopardizing the health of the mother. This goal is usually easily accomplished when the patient presents close to, or at term. However, when pre-eclampsia develops earlier than the 36th week of gestation the situation becomes more complicated and more hazardous.

Obviously, the first step in management is proper diagnosis. When a woman presents with an elevated blood pressure in the latter part of pregnancy it is necessary to determine whether pre-eclampsia is present, or whether it is more likely the patient has chronic hypertension, or transient hypertension. If the blood pressure is only mildly elevated and there are no signs or symptoms of pre-eclampsia, then it is common for the patient to be followed carefully as an outpatient, and she is instructed to remain at bed rest. When the diagnosis of pre-eclampsia is made, it is standard practice in this country to hospitalize the patient for enforced modified bed rest, and to observe for the development of severe pre-eclampsia or eclampsia.

Severe pre-eclampsia

Severe pre-eclampsia is diagnosed when any of the following is present: the blood pressure is $\geq 160/110$ mm Hg, there is fetal distress, there is proteinuria of at least 5 g/24 h, there is oliguria or azotemia, cerebral or visual disturbances, epigastric pain, hyperreflexia, or pulmonary edema.

One of the most difficult management decisions in obstetrics arises when a woman with an immature fetus develops pre-eclampsia. If the mother's life is clearly in danger, or if there is significant fetal distress, obviously delivery will be accomplished. However, if the mother appears stable and asymptomatic and the only signs of severe pre-eclampsia are high blood pressure and proteinuria, then there are some obstetricians who would try and temporize in order to deliver a more mature infant. Lowering the blood pressure in pre-eclamptic women does not prevent progression of the other features of the syndrome and does not alter the underlying disease process. Furthermore, since placental perfusion is already compromised in pre-eclampsia it is argued by some that prolonged hypotensive therapy is contra-indicated. Although few controlled trials of therapy have been published, there may be some justification for lowering the blood pressure in severe pre-eclampsia in order to avoid imminent delivery. It must be understood that antihypertensive treatment is merely masking one dangerous manifes-

tation of the disorder. The major rationale for antihypertensive therapy in severe preclampsia is to protect the mother from what are considered to be dangerously high blood pressures.

In cases of severe pre-eclampsia, the patient is transferred to or admitted to the delivery floor. Magnesium sulfate is administered parenterally to arrest convulsions of eclampsia and to prevent convulsions in severe pre-eclampsia. Ten grams of magnesium sulfate may be added to 1000 ml of 5% dextrose in water and infused at a rate of 100 ml/h. Hydralazine is administered parenterally (10–50 mg intravenously, as needed) to lower blood pressure when the diastolic blood pressure is 110 mm Hg or higher, and steps are taken to deliver the baby. Magnesium sulfate is the sole agent used in this country for treating central nervous system (CNS) irritability. In sufficient doses it will arrest and prevent convulsions without producing generalized CNS depression. Although not considered to be an antihypertensive agent, several investigators have reported transient decreases in blood pressure in response to magnesium sulfate. Although it is widely used in the United States, magnesium sulfate is not used as much in Europe, where low dose diazepam is commonly administered to treat and prevent convulsions.

Antihypertensive medications. Even if emergent delivery is planned as mentioned above, when the blood pressure reaches levels of 170–180/110–120 mm Hg, emergency therapy is indicated, since these pressures are close to the limit where experimental hypertensive vascular damage begins. Furthermore, even though retinopathy may not be present, there is considerable evidence that the CNS manifestations of eclampsia and pre-eclampsia represent a form of hypertensive encephalopathy [21].

The most commonly used parenteral antihypertensive agent in pregnancy is hydralazine, which is a directly acting vascular smooth muscle relaxant. It may be administered as a bolus or as a continuous infusion, with the goal of therapy to reduce diastolic pressures from 100–110 to 80–90 mm Hg. A potential advantage of hydralazine over other antihypertensive agents is that it may increase rather than compromise uterine blood flow.

Less commonly, agents such as diazoxide and sodium nitroprusside have been used, mainly for intrapartum hypertensive emergencies. Problems with diazoxide are that it may cause a precipitous drop in blood pressure, and it has been shown to reduce uterine perfusion. Furthermore, it will often arrest labor, and result in neonatal hyperglycemia. The reported experience with sodium nitroprusside in obstetric hypertension emergencies is limited. It has been used successfully in isolated cases of severe hypertension and pulmonary edema when hemodynamic monitoring was available. The potential for thiocyanate toxicity in the fetus, and the drug's uncertain effect on placental perfusion have limited its use. Recently there have been reports of newer

agents in the treatment of severe hypertension in pregnancy. There are preliminary reports of the use of labetalol, an α- and β-adrenergic blocking agent, and nifedipine, a calcium antagonist in small numbers of patients, with good results and no adverse affects [33]. Both of these agents represent intriguing possibilities for future investigation, but at the present time there is insufficient data to recommend their use.

Fluid management. It is generally believed that patients with pre-eclampsia have a contracted intravascular volume, and severity of pre-eclampsia correlates with the degree of volume contraction. Nevertheless, patients with severe pre-eclampsia are often grossly edematous and may develop pulmonary edema. The pathophysiology of pulmonary edema occurring with severe pre-eclampsia has not been well documented, but several studies suggest that it is associated with normal or low wedge pressures, and low colloid osmotic pressure.

The fluid management of the severely pre-eclamptic patient is still somewhat controversial. Usually, severe pre-eclamptic patients do not require hemodynamic monitoring unless pulmonary edema or oliguira is present. In general, a conservative approach to fluid administration is the safest. Enough fluid should be given to insure a urine output of 30–50 ml/h which can usually be accomplished with about 125 ml/h. After delivery, however, the underlying pathology will start to correct, and there may be large fluid shifts from the extravascular space to the intravascular space. For this reason it is essential to avoid overhydration during this time. Recently several investigators have reported trials of administering plasma volume expanders such as albumin or dextran, in patients with severe pre-eclampsia [22]. Such therapy has been reported to improve renal function, lower blood pressure, and lower systemic vascular resistance. It is essential that this type of therapy be administered under close surveillance since in certain individuals acute cardiac failure may be precipitated. At the present time we do not feel there is enough data to support widespread use of this therapeutic modality.

Mild pre-eclampsia

Fortunately, most cases of pre-eclampsia are mild, and aggressive therapy is not necessary. The most widely accepted, and most successful approach to such patients is similar to that reported by the group from Parkland Hospital. Essentially, all patients found to have high blood pressures are hospitalized on a high risk Pregnancy Unit and kept on limited activity. In 85% of 347 women studied from this group the blood pressure dropped below 140/90 mm Hg within 5 days. Hypertension recurred before labor in 47% and in another 42% hypertension recurred during labor. Even when the decrease in blood pressure was less dramatic, the pregnancy was allowed to

continue in the absence of other signs and symptoms of severe pre-eclampsia, and in the absence of fetal distress. In addition to limited activity, a regular diet is prescribed. Sodium is not restricted and diuretics are not used. Careful monitoring of protein excretion, weight, renal function, and fetal well-being is undertaken. Hydralazine is used only when the diastolic blood pressure is greater than 110 mm Hg. Delivery occurs when the fetus is mature or when the fetus is immature and there are signs of severe or worsening pre-eclampsia, fetal distress, or fetal growth retardation. With this approach, maternal and fetal outcome has been excellent (maternal mortality of 0 in 154 consecutive cases of eclampsia; perinatal mortality of 3 in 346 nulliparas with pre-eclampsia).

Despite the well documented successful outcome by some institutions using the above approach, it must be emphasized that at the present time our treatment of pre-eclampsia is entirely empiric. The mainstays of our management are close observation, modified bed rest, magnesium sulfate and timely delivery. None of the therapy outlined above is specifically directed at the underlying pathophysiologic abnormalities of the disease. There still remain many unanswered questions about proper therapy. For example, although every obstetrician prescribes bed rest for the patient with pre-eclampsia, there are surprisingly few controlled clinical trials documenting its efficacy, and there is no clear understanding why it should be beneficial. The issue of antihypertensive therapy in pre-eclampsia is also controversial. Most obstetricians will agree to lower the blood pressure with medication when the diastolic pressure reaches 110 mm Hg. Current opinion varies greatly as to whether therapy should be instituted for milder degrees of hypertension. If we confine our remarks here to the patient with an accurate diagnosis of pre-eclampsia and exclude patients with chronic hypertension or renal disease, (which is, in clinical practice, sometimes difficult to do) then there is very little data to support antihypertensive treatment. Perhaps the main objection to antihypertensive therapy is the possibility of reducing an already compromised placental blood flow. Most of the concern is theoretical, since it is very difficult to document directly whether a drug that lowers maternal pressure also compromises placental flow, and if it does, whether the decrease in perfusion is significant enough to be harmful to the fetus. There are data however, to suggest that women with higher blood pressures during pregnancy deliver smaller babies. Whether this applies to women with pre-eclampsia as opposed to chronic hypertension is unclear, and whether it is because of the increased blood pressure or some other deleterious abnormality is also not known. Nevertheless, because of this observation treatment of mild to moderate elevations in blood pressure has become more common.

Post partum management

With the delivery of the fetus and placenta resolution of pre-eclampsia usually promptly occurs. Nevertheless, since eclampsia may develop post partum, close observation and parenteral magnesium sulfate and/or hydralazine are usually continued for 24–48 h, depending on the severity of the patient's condition prior to delivery. In most cases of pre-eclampsia of mild or moderate severity, significant clinical improvement is evident by 48 h after delivery, and often sooner than that. Occasionally, however, a patient with pre-eclampsia will have persistent hypertension, and perhaps proteinuria for a variable course. There are very few published data on the clinical significance of persistent manifestations of pre-eclampsia after delivery. Chesley has reported that persistance of hypertension and proteinuria for 10 or more days after delivery may be predictive of those individuals whose subsequent pregnancies will be complicated by pre-eclampsia [11]. In general, it appears that the greater the severity of the predelivery symptoms, the greater the chance that they will persist for longer than 2 days post partum. Women with severe proteinuria secondary to pre-eclampsia prior to delivery may have persistent mild proteinuria for several weeks post partum. If, however, nephrotic range proteinuria persists for longer than several weeks, then a renal biopsy should be considered.

Occasionally, women who have had moderate hypertension before delivery will become more severely hypertensive post partum. This may be secondary to worsening pre-eclampsia, but we have seen persistence of post partum hypertension while other manifestations of the disease have disappeared. In these cases, administration of intravenous fluid in the peripartum period, in addition to the fluid shifts that occur after delivery may contribute to produce intravascular volume overload and elevated blood pressure, which may be treated with a small dose of a diuretic. Occasionally, pre-eclamptic women with persistent post partum hypertension will require antihypertensive therapy for variable periods of time. If the patient requires antihypertensive therapy for longer than a few weeks, it is likely that chronic underlying hypertension is present. This is the general impression of most obstetricians, however, there are few studies that address the significance of post partum hypertension.

Prophylaxis

The etiology of pre-eclampsia is not known, therefore we do not know how to prevent it. The best we can do at the present time is to detect it early, so that appropriate observation and therapy can be instituted when necessary. Over the years various dietary interventions have been recommended as being useful in the prevention of pre-eclampsia. For many years it was believed that salt played a major role in pre-eclampsia, and there have been many attempts to prove or disprove this theory. Up until the last 10 years

many obstetricians recommended salt restriction and/or diuretics for the prevention and treatment of pre-eclampsia. The preponderance of evidence, however, indicates that neither salt restriction nor diuretics prevents pre-eclampsia. Although it has been shown that sodium restriction returns the pre-eclamptic abnormal vascular responsiveness to AII back to the levels associated with normal pregnancy, the current approach to management of women with pre-eclampsia is to avoid these maneuvers. The reason for this is the recognition that patients with pre-eclampsia have a contracted plasma volume, and the more severe the degree of pre-eclampsia, the greater the degree of intravascular volume depletion. Consequently, it is felt that diuretics or salt restriction would exacerbate the underlying problem. There have been a few clinical trials employing liberal salt diets in patients with pre-eclampsia and these studies have failed to show deleterious effects [23, 24]. There have also been studies that have suggested that pre-eclamptics do not excrete a sodium load normally [25]. Because considerable confusion on this issue still exists, we advocate neither sodium restriction nor 'salt therapy'. There is also some data that diuretics depress placental function, and their usage in pregnancy is associated with higher incidences of maternal and fetal complications. Therefore, the current recommendations are that pregnant women eat an average diet with respect to sodium. Diuretics are relatively contra-indicated in both normal and pre-eclamptic pregnant women, except in cases of overt cardiac failure or renal disease.

If we cannot prevent pre-eclampsia, then we can recommend close observation of women who have predisposing features. As outlined by Chesley these features, in order of importance are: (1) nulliparity, (2) family history or pre-eclampsia, (3) diabetes mellitus, (4) multiple gestation, (5) extremes of age, (6) pre-existing hypertensive vascular or renal disease, and (7) hydatidiform mole.

Prognosis

It has been well established that pre-eclampsia is a disease of first pregnancy, and if the diagnosis is made in a multiparous woman, one should suspect chronic underlying hypertension, renal disease, or diabetes mellitus. If the first pregnancy has been normal, and there has been no change in paternity, and there is no chronic hypertension, renal disease or diabetes mellitus, then pre-eclampsia is quite uncommon in subsequent pregnancies. The woman who has had pre-eclampsia in the first pregnancy, however, will invariably ask what her chances are of developing pre-eclampsia in future pregnancies. This subject has been extensively investigated and reviewed by Chesley [1] and others [26]. Based on follow-up studies of eclamptic nulliparous wo-

men, it appears that approximately 30% of future pregnancies in such individuals will be complicated by hypertensive disorders. In 40% of these there is usually nothing more than a mildly elevated blood pressure, and about 8% of women in this study had either severe pre-eclampsia or eclampsia. This is in contrast to later pregnancies of women having eclampsia as multipares. They often have recurrent severe hypertensive disease (50%) which is most likely because of underlying chronic hypertension. These observations are based on studies of eclamptic women and may or may not be valid in pre-eclamptic patients. The general feeling that a patient with pre-eclampsia in the first pregnancy may have as high as a 25–35% incidence of recurrent hypertension in pregnancy is believed to be true by many obstetricians. If the hypertension does recur, it is usually milder, and occurs later in gestation.

Chronic essential hypertension

When a woman with mild to moderate essential hypertension becomes pregnant, the therapeutic decisions that are made during the pregnancy are primarily directed at the welfare of the fetus, unless superimposed pre-eclampsia has occurred. The issues under considerations during pregnancy, are: (1) what is the optimal mean arterial pressure (MAP) to maximize the chances of delivery of a mature, healthy infant and (2) what are the benefits if any of achieving this optimal mean arterial pressure with antihypertensive therapy.

With regard to the question of optimal maternal blood pressure, the literature is conflicting. There is disagreement over the fetal risk directly associated with chronic hypertension in the absence of other complications. On one hand the data obtained during the British Births Survey in 1970 has been interpreted as showing that in the absence of superimposed pre-eclampsia the perinatal mortality is not increased in hypertension pregnancies [27]. On the other hand, Page and Christiansen report a direct correlation between maternal blood pressure in the mid trimester and retarded fetal growth and stillbirth, which is also corroborated by Freedman and Neff [28]. These data, however, do not distinguish between stable chronic hypertensives and women who develop superimposed pre-eclampsia. It is well established that pre-eclampsia is associated with increased fetal mortality and it is believed that women with chronic hypertension are more likely to develop pre-eclampsia. It is possible then that correlating the level of blood pressure with fetal outcome, without excluding women with pre-eclampsia from the analysis, overestimates the risk.

The main risk to maternal well-being of moderate hypertension during pregnancy is that the likelihood of developing pre-eclampsia is much greater

if there is pre-existing maternal hypertension. The potential long-term cardiovascular sequelae of hypertension are not usually a consideration during pregnancy, and do not warrant treatment at this time.

Antihypertensive therapy in chronic hypertension

To establish that antihypertensive therapy is beneficial in a pregnant women with mild to moderate essential hypertension would ideally be accomplished by demonstrating that such therapy either reduced the incidence of pre-eclampsia or resulted in improved fetal outcome. Leather et al. randomly allocated 100 women to a treatment (methyldopa combined with diuretics) and a non-treatment group [29]. The treated patients who had increased blood pressure prior to 20 weeks of gestation had improved fetal outcome. Redman et al. randomized patients to either treatment (methyldopa) or no treatment groups, and found a higher incidence of mid pregnancy abortion and perinatal death in the patients of untreated group [30]. Birth weights of the infants in the two groups were similar. Of interest, there was no difference in the incidence of superimposed pre-eclampsia (defined as rise in plasma urate in this study) in the two groups, although the treatment group had fewer episodes of severe hypertension.

In deciding whether to institute antihypertensive therapy in a pregnant woman, one must take into consideration that it may be beneficial to the fetus to treat moderate hypertension (diastolic blood pressure of 90–110 mm Hg), although there may not be any clear cut benefit to the mother. If a woman has a diastolic blood pressure of ≥ 110 mm Hg then treatment is indicated. If a patient with essential hypertension is already on medication then it is reasonable to discontinue diuretics, while continuing other medications. The risk of antihypertensive treatment is besides possible adverse effects of the drugs, the theoretical, unproven, reduction in uterine perfusion that may result.

Clearly methyldopa is the most well studied antihypertensive agent that is used in pregnancy. It is free of major problems, and has been well documented to be safe for the fetus. Oral hydralazine may be used in conjunction with methyldopa. Use of hydralazine alone for long periods of time is limited by its tendency to produce tachycardia.

As mentioned above, diuretics are relatively contra-indicated in hypertensive pregnancy. The reason for this is that pre-eclampsia is thought to be associated with volume contraction, and diuretics would make this situation worse. Women with chronic hypertension are advised not to take diuretics for similar reasons, and also because of the observations by several investigators that these agents may reduce uteroplacental blood flow. Some studies have suggested that diuretics may contribute to low birth weight infants, but

this remains controversial. These considerations are not necessarily applicable in pregnant women with advanced renal disease whose hypertension may not be controlled by other agents.

Recently there have been reports in the literature of the use of beta-adrenergic blockers in pregnancy [31, 32]. Although objections to the use of these agents have been voiced because of the concern for the development of neonatal hypoglycemia, fetal respiratory distress, and neonatal brady cardia, the cumulative evidence attests to their safety.

Secondary hypertension

Renal disease

As mentioned earlier, a significant fraction of multiparous woman with gestational hypertension, will, on kidney biopsy, be found to have underlying renal disease. On occasion, a woman with known kidney disease will become pregnant, and current evidence suggests that her subsequent course will be determined by the degree of renal insufficiency that is present before conception, and whether or not she is hypertensive. It seems that if the blood pressure is normal at conception, and if the BUN and creatinine are less than 30 mg/dl and 3 mg/dl, respectively, the pregnancy is likely to be successful. Such individuals, however, are at risk for developing pre-eclampsia in the third trimester, and for this reason they should be closely monitored during gestation.

Pheochromocytoma

Although pheochromocytoma is rare, it may first become clinically apparent during pregnancy. As of 1980, there have been approximately 128 cases of pheochromocytoma reported during pregnancy, and in only 42% of the cases diagnosis was made antepartum. The reported maternal and fetal mortality of this condition may be as high as 50%, therefore, it is critical to make the diagnosis and consider the therapeutic alternatives.

Pheochromocytoma may present with a variety of clinical symptoms including headache, nausea, vomiting, sweating and sustained or paroxysmal hypertension and congestive heart failure. Since the signs and symptoms of pheochromocytoma may mimick those of pre-eclampsia it is reasonable to analyze the urine for VMA, catecholamines, and metanephrines in cases of gestational hypertension which are unusually severe, and where other suggestive symptoms are present [34]. Although the optimum management of this condition in pregnancy has not yet been determined, review

of the recent literature highlights several points. To begin with, it appears that maternal and fetal mortality is greatly reduced when the diagnosis is made antepartum. With the judicious use of alpha-adrenergic blockers at any gestational age fetal and maternal mortality is reduced even further. Based on the available literature most reasonable approach to the management of this condition is as follows: In the first 5 months of pregnancy, the patients should receive alpha-adrenergic blocking agents, and then surgery to remove the tumor [35]. The maternal outcome with such an approach is excellent, although the fetal mortality may still be high. When the diagnosis is made in the third trimester, the best survival seems to occur when the mother is treated with alpha-adrenergic blockers, followed by combined delivery and tumor resection. It is necessary to consider gestational age, fetal maturity and maternal response to alpha-blockade in determining the timing of resection and delivery. Alpha-blockade has been maintained for periods as long as 56 days in third trimester patients.

In conclusion, survival of both mother and fetus is significantly improved if diagnosis of pheochromocytoma in the pregnant woman is made antepartum. Alpha-blockade will reduce fetal mortality even further if instituted as soon as the diagnosis is made. Following alpha-blockade, depending on gestational age, surgical removal of the tumor and delivery can be undertaken.

Renovascular hypertension

When gestational hypertension develops, the most likely diagnosis is either pre-eclampsia or chronic hypertension with or without superimposed pre-eclampsia. Although most of the patients with chronic hypertension have 'essential hypertension', it is important to recognize that women in childbearing years may have underlying renovascular hypertension secondary to fibromuscular dysplasia. Usually, when women with renovascular hypertension become pregnant they are unaware of their condition before conception and their clinical course is variable and difficult to predict. They may have elevated blood pressures throughout pregnancy with or without superimposed pre-eclampsia in the third trimester, or they may be normotensive until the third trimester when they may develop pre-eclampsia. The incidence of renovascular hypertension in women with gestational hypertension is not known, but it is likely that the diagnosis is frequently missed. Landesmen et al. obtained arteriograms postpartum in ten women with gestational hypertension [36]. In two women who had severe pre-eclampsia, renal artery stenosis was seen. Koskela and Kaski performed postpartum renal angiography on 35 patients with gestational hypertension [37]. Thirteen patients with pure pre-eclampsia who became normotensive after delivery

had no renal artery abnormalities. However, two patients out of 16 patients with chronic hypertension and superimposed pre-eclampsia had renal artery abnormalities on angiography. There are only a few additional isolated case reports of renovascular hypertension in pregnancy. Fortunately, screening for renovascular hypertension has become easier in the last several years. It is our belief that all women with moderate to severe pre-eclampsia who remain hypertensive after delivery should be evaluated with a peripheral plasma renin activity determination, and probably with renal vein renin sampling and digital intravenous angiography to rule out renovascular hypertension. The women with chronic hypertension with or without superimposed pre-eclampsia should be considered as any young person with newly diagnosed hypertension. Since the patient is facing a lifetime of antihypertensive medications, potentially correctable forms of hypertension should be searched for, and it is reasonable to pursue the work-up of renovascular hypertension in such individuals as well.

The therapy of renovascular hypertension is discussed in detail elsewhere in this book. Of interest is a recent case report of successful transluminal angioplasty performed in a patient who was 4 weeks pregnant [38]. Whether this therapeutic modality is safe in women of more advanced gestational age is not known at the present time.

Primary aldosteronism

Rarely, a hypertensive pregnant woman will turn out to have primary aldosteronism. There are but a few case reports in the literature. In the first reported case, hypertension was severe, and the pregnancy resulted in a stillbirth. Of considerable interest is the report by Gordon et al. of a pregnant woman with hypertension and severe hypokalemia [39]. A diagnosis of primary hyperaldosteronism was made on the basis of high aldosterone secretion rate and low plasma renin activity. The authors point out that the diagnostic criteria of suppressed plasma renin activity may be as valuable during pregnancy as in the non-pregnant state. Their patient had a left adrenalectomy during pregnancy and did well. Biglieri et al. reported a pregnancy in a woman with a diagnosis of primary aldosteronism. The patient demonstrated increased aldosterone secretion rates, however, during pregnancy on no therapy, her blood pressure and serum potassium remained close to normal until term [40]. The authors speculate that the elevated levels of progesterone in pregnancy may have an aldosterone inhibiting effect.

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8. Medical Treatment of Renal Hypertension

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Introduction

Elsewhere in this text considerable attention has been focused on the complex interrelationship of systemic hypertension with kidney disease. Renal parenchymal and renovascular disease are the two most commonly identified causes of secondary hypertension in the United States [1]. These may account for or contribute to as much as 9% of all hypertension in this country [2]. On the other hand, high blood pressure in turn has been shown to contribute to the development, maintenance and progression of chronic kidney disease, regardless of the initial underlying renal disorder. Among US blacks, hypertensive nephrosclerosis is the most common cause of terminal renal failure [3], and is the major cause of renal failure for nearly 1/5 of all Americans presently receiving dialytic therapy [4]. Furthermore, recent evidence points to a critical role for high blood pressure in the progression of renal disease of non-hypertensive origin [5, 6], perhaps via effects on intraglomerular hemodynamics. With annual expenditures for the US federally-funded End Stage Renal Disease Program now approaching 2 billion dollars [7], the importance of control of hypertension, especially in the setting of shrinking fiscal resources, cannot be overestimated.

The clinical challenge of renal hypertension

Etiologic diagnosis

The obstacles awaiting the clinician as he or she approaches the treatment of hypertension and renal dysfunction are manifold. To start, it is incumbent upon the physician to identify and treat any reversible, underlying causes of renal insufficiency. These may take the form of circulatory (pre-renal), obstructive (post-renal) or renal parenchymal (glomerular, tubular, intersti-

tial) disorders. The potential for reversibility becomes lessened in the presence of chronic renal parenchymal disease. Also, when the disorder has been identified as a chronic intrarenal process, it may be difficult to determine whether hypertension is the underlying cause of the renal dysfunction, or if the converse is true. Features of hypertensive nephrosclerosis are usually not diagnostic; mild to moderate renal insufficiency with subnephrotic range proteinuria (1 to 3 g per day) and an acellular urinary sediment are fairly typical, but not specific findings. There is usually a history of long-standing, poorly controlled, moderate to severe hypertension accompanied by left ventricular hypertrophy and Grade II or III Keith-Wagener hypertensive changes in the retina. In contrast, rapid deterioration in renal function with an active urinary sediment can occur in the setting of malignant hypertension, but is usually easier to distinguish because of its more dramatic presentation (see syndromes of renal hypertension, malignant hypertension, in this chapter).

Table 1. Resistant hypertension and renal insufficiency

1. Inadequate compliance with therapy
   a. Poor communication with patient
   b. Intolerable side effects
   c. Complicated drug regimen
2. Office hypertension
3. Altered pharmacokinetics
   a. Bioavailability
   b. Drug distribution
   c. Drug metabolism
4. Renal site of drug action
   a. Diuretics
   b. Renal vasodilators
5. Drug interactions
   a. Glucocorticoids
   b. Estrogenic hormones
   c. Sympathomimetics
   d. Tricyclic antidepressants
6. Other secondary causes of hypertension
   a. Renovascular disease
   b. Atherosclerotic impairment of aortic compliance
   c. Adrenal disorders
      i. Cushings disease
      ii. Primary hyperaldosteronism
      iii. Pheochromocytoma
   d. Coarctation of the aorta
   e. Thyroid disease
   f. Hyperparathyroidism

Management of resistant hypertension

Another task in the evaluation and treatment of hypertension in the setting of renal insufficiency is the frequent discovery that such patients have hypertension that resists conventional antihypertensive agents. Resistant hypertension is defined here as the failure to control blood pressure despite 'triple-drug' therapy (diuretic plus adrenergic inhibitor and vasodilator). Inadequate compliance (Table 1), perhaps the most frequent cause, may be related to poor doctor-patient communication, intolerable side effects or complicated therapeutic regimens [8]. An additional potential factor in drug resistance is failure to achieve therapeutic levels of the agents used because of renal failure-associated changes in pharmacokinetics. Also, renal disease of any cause impairs the ability to respond to conventional diuretic therapy, especially thiazide-type drugs [9]. Drug resistance may also be created by the concommittant use of agents such as glucocorticoids [10], estrogenic hormones [11], sympathomimetics [12] and tricyclic antidepressants [13], any one of which may blunt the antihypertensive action of an otherwise well-chosen regimen.

Unfortunately, despite meticulous avoidance of these pitfalls, many patients with renal insufficiency will, nevertheless, have elevated blood pressure that is resistant to conventional triple-drug therapy [14]. Perhaps this should not be surprising in view of the highly complex and important role played by the kidneys in blood pressure homeostasis. We are only just beginning to comprehend the full complexity of the many processes by which the kidneys act as the major organs for long term blood pressure regulation. The kidneys control total body sodium and plasma volume as well as acting as producers, regulators and/or target organs of a host of neurohumoral effectors including renin-angiotensin, aldosterone, prostaglandins, kinins, serotonin, natriuretic factors, neutral lipid vasodepressor substances, catecholamines, sympathetic nerve traffic and probably additional as yet undiscovered or unrecognized factors. In light of our limited understanding of these processes and their interactions, it would seem to be unlikely that our present armamentarium of chemotherapeutic agents could be sufficient to easily control blood pressure in all patients with clinically detectable renal dysfunction. Notwithstanding these difficulties, it is now possible, using appropriate combinations of currently available antihypertensive drugs, to control even highly resistant hypertension in the great majority of cases.

Iatrogenic renal impairment

A third issue to be confronted in the treatment of hypertension and renal insufficiency is the potential for further impairment of renal function during

therapy, a phenomenon in direct opposition to one of the major goals of therapy. This may occur through several possible mechanisms. A drug-induced rapid decline in systemic blood pressure may, in the setting of reduced glomerular auto-regulatory function, produce a significant fall in glomerular filtration rate [15]. A growing body of evidence suggests that altered autoregulation is common, and may be universal, in renal parenchymal and renal circulatory disorders [16]. Several recent case reports imply that some antihypertensive drugs may, via an intrarenal effect, reduce glomerular efferent arteriolar tone to a degree that further alters previously impaired glomerular autoregulation [17]. As a result, even clinically subtle changes in systemic hemodynamics may produce a marked decline in renal filtration. Finally, antihypertensive drug therapy may have an adverse effect on renal function by either direct or immunologically-medicated toxic effects on the kidney. Examples include captopril-associated membranous glomerulopathy [18] and diuretic-induced allergic interstitial nephritis [19].

Altered pharmacokinetics in renal disease

Renal insufficiency adds further complexity to the management of hypertension through associated changes in pharmacokinetics [20]. This may take the form of altered bioavailability (drug absorption, first pass metabolism), drug distribution (tissue- and protein-binding, lipid solubility), metabolism and, of course, excretion. The relative importance of these factors varies with each agent and will be considered in depth later in this chapter. A thorough knowledge of the pharmacokinetic properties of each agent used in the treatment of renal hypertension will enable the clinician to achieve drug levels in the therapeutic range while mitigating the chances of renal or extrarenal toxicities.

Adverse effects of therapy may simulate renal or systemic disorders

Still another hurdle in the way of successful treatment of renal hypertension is that side effects of some antihypertensive agents may be confused with clinical manifestations of renal disease. The tendency for edema formation exists in most forms of renal disease, but may also be present as a result of treatment with vasodilating agents or adrenergic inhibiting drugs [21]. Another example is pericardial effusion which can be a manifestation of either minoxidil therapy [22] or uremic toxicity; the specific etiology may not always be easily discernible. Extrarenal clinical features of systemic disorders with associated renal disease and hypertension may also be simulated

by antihypertensive drug therapy. Leukopenia, for example, may be a feature of systemic lupus erythematosis, but has also been attributed to captopril toxicity [23].

Table 2. Antihypertensive drugs reported to induce or activate systemic lupus erythematosus

Definite	Possible
Hydralazine	Reserpine
Methyldopa	Chlorthalidone
Practolol	Atenolol
	Labetalol
	Metoprolol
	Propranolol
	Timolol

Table 3. Summary of current diuretic agents

Generic name	Propriatary name	Dose range (mg/day)	Dose interval (hours)	GFR at which drug effective (ml/min)
Thiazides				
Hydrochlorthiazide	Hydrodiuril, Esidrix, Oretic	25–100	12	> 40
Chlorthiazide	Diuril	500–2000	12	> 40
Hydroflumethiazide	Saluron	25–50	12	> 40
Benzthiazide	Exna	25–50	12	> 40
Quinethazone	Hydromox	50–200	12	> 40
Bendroflumethiazide	Naturetin	2–5	24	> 30
Chlorthalidone	Hygroton	25–100	24	> 30
Polythiazide	Renese	4–8	24	> 30
Trichloromethiazide	Metahydrin, Naqua	4–8	24	> 30
Methylchlorthiazide	Enduron	5–10	24	> 30
Cyclothiazide	Anhydron	1–6	24	> 30
Metolazone	Zaroxylin, Diulo	2.5–15	24	> 30
Loop Diuretics				
Furosemide	Lasix	10–320	8–12	> 5
Ethacrynic Acid	Edecrin	25–200	12	> 5
Bumetanide	Bumex	0.5–10	6–12	> 5
Potassium-sparing				
Spironolactone	Aldactone	50–400	6–12	< 30, contra-indicated
Triamterene	Dyrenium	50–200	12	< 30, contra-indicated
Amiloride	Midamor	5–10	24	< 30, contra-indicated

Therapy with certain antihypertensive drugs (Table 2), such as hydralazine, alpha-methyldopa and propranolol, may result in the development of positive serum antinuclear antibody titers [24–26]. This latter phenomenon is occasionally associated with a lupus-like syndrome including skin rash or serositis (arthalgia, pleurisy, pericarditis). Other features that frequently accompany lupus nephritis such as hemolytic anemia and mental depression must be distinguished from the effects of alpha-methyldopa therapy [27]. In short, the clinician must be thoroughly cognizant of the potential adverse effects of the chosen therapy as well as the potential manifestations and complications of the patients' underlying disorder.

Diuretics

Diuretics are the most commonly used agents in the first-line management of primary hypertension. The reasons for their widespread use include efficacy in the majority of cases, low cost, and manageable side effects. Because sodium retention contributes so importantly to the hypertensive state seen with most forms of renal disease, diuretics often have an indispensable therapeutic role in this setting as well. In addition, diuretics have important synergistic activity in combination with non-diuretic antihypertensives. Because of their different structures and sites of action, these agents can be divided into several categories. These include thiazides, loop-acting diuretics, and the potassium sparing agents (Table 3) [29, 30].

Mechanism of action

The blood pressure lowering action of diuretics is probably more complex than earlier thought. According to early formulations, diuretics worked primarily by lowering plasma volume secondary to the natriuretic action. The reduction in plasma volume lowers venous return and left ventricular filling pressure with a resultant fall in cardiac output. Recent studies [31–33] have demonstrated that during early therapy with diuretics, plasma volume and cardiac output do fall while, interestingly, peripheral resistance actually increases. The latter effect may be a result of stimulation of the renin-angiotensin system [31, 33] or perhaps microcirculatory autoregulation [32]. With chronic therapy, plasma volume and cardiac output return toward pretreatment levels while peripheral resistance drops, thereby preserving the hypotensive effect of diuretics.

There are several possible explanations for the latter attenuation in vascular smooth muscle contractility. Some diuretics have been shown to possess a direct vasodilatory action as well as antagonistic effect on norepineph-

rine and angiotensin II-induced vasoconstriction [34]. Depletion of vascular wall sodium may also play a role [35]. Alternatively, the early reduction in plasma volume may inhibit release of ATPase inhibitor natriuretic substances from the central nervous system or other sites [34–36].

Thiazides

This class of agents cause inhibition of chloride and sodium reabsorption in the terminal portion of the thick, ascending limb of the loop of Henle. All compounds of this group are analogs of benzothiadiazine and are therefore sulfonamides [34].

Effect on renal function

The tubular effects of thiazide diuretics include an increase in the excretion of sodium, potassium, chloride, and magnesium [35]. Urinary excretion of calcium is decreased and may result in hypercalcemia. Release of renin, the proteolytic enzyme that catalyzes the formation of angiotensin II, is stimulated by diuretic-induced volume depletion and inhibition of macula densa sodium transport [37]. Acute administration of thiazide diuretics has resulted in modest (10–20%) reductions in glomerular filtration rate. This has been manifested by corresponding decreases in creatinine clearance and increased levels of blood urea nitrogen [34]. These perturbations may be somewhat more frequent in patients with underlying renal insufficiency. More dramatic impairment in renal function may occur in the setting of diuretic-induced clinically evident volume depletion and hypotension [34, 35]. Allergic interstitial nephritis is another potential cause for thiazide-induced deterioration in renal function [19].

Nonrenal adverse effects

Many of the adverse effects of the thiazides are, for the most part, predictable based on their major site of action in the renal tubular epithelium. These include dehydration, hypokalemia, hyponatremia, hyperuricemia and hypercalcemia [38]. Impairment in carbohydrate metabolism is probably causally related to potassium depletion, since hypokalemia is known to inhibit both pancreatic insulin release and insulin dependent glucose transport [31, 34]. Reactions of an idiosyncratic nature include acute pancreatitis, leukopenia, thrombocytopenia, drug rash and acute allergic interstitial nephritis [19]. Photosensitivity and purpuric skin rash are more likely to occur in individuals with a history of hypersensitivity to sulfonamides [31, 34].

Pharmacokinetics of thiazides

Thiazide diuretics are quickly absorbed from the gastrointestinal tract with most agents showing a diuretic effect within an hour after administration [35]. These drugs are distributed throughout the extracellular space and are excreted unchanged by the kidneys via glomerular filtration and tubular secretion [35]. Long-acting thiazides such as polythiazide, bendroflumethiazide and chlorthalidone have greater lipid solubility and consequently larger volumes of distribution [35]. Chlorthalidone is also preferentially concentrated by renal tissue [34, 35].

Despite the renal route of elimination of thiazide diuretics, their efficacy becomes markedly diminished with renal insufficiency [35]. This may be due to reduced drug-binding by the kidneys. While no specific modification in thiazide dosage is necessary with renal impairment, their effectiveness is lessened and the risk of further renal dysfunction is greater [39, 40].

Metolazone

Metolazone is a quinazolinone derivative of the benzothiadiazines which has actions similar to the parent class. Like the thiazides, metolazone inhibits sodium reabsorption in the cortical diluting segment of the ascending limb of the loop of Henle or in the early distal tubule [41]. It may also inhibit the proximal tubular reabsorption of sodium. There is little effect on carbonic anhydrase inhibition. Used alone, this drug is of intermediate natriuretic potency between thiazide and loop diuretics. Metolazone has been shown to potentiate the diuretic response seen with furosemide [42]. This latter effect may be quite dramatic, resulting in massive fluid losses over the course of several days. The mechanism of metolazone synergism with loop diuretics remains poorly understood.

The side effect profile of metolazone is virtually identical to that of the thiazide diuretics, including hypokalemia, hyperuricemia, glucose intolerance, leukopenia, skin rash, postural hypotension and hyponatremia [43]. The latter two effects are relatively more common and often more severe than seen with either the thiazides or loop diuretics. In the setting of renal insufficiency, the occurrence of metolazone-induced hypotension can be a dangerous insult to the kidneys, resulting in irreversible deterioration of renal function.

In contrast to thiazides, metolazone may maintain remarkable diuretic effectiveness when renal impairment is severe (GFR < 10 ml/min). Thus, the plasma volume component of hypertension seen with progressive renal insufficiency can often be ameliorated with this agent when conventional thiazides have failed. Metolazone is excreted primarily by a renal mechanism; nevertheless, slightly higher than normal doses may be required to

obtain an optimal diuretic effect when renal impairment is present. Metolazone, if properly used, can be a powerful tool for the clinician treating renal hypertension because it remains effective at low levels of renal function, particularly when used in combination with loop-diuretics. At the same time, there is a very substantial risk of sudden, severe fluid and electrolyte depletion that may pose a serious risk to patients and their renal function. Frequent monitoring of standing blood pressure, body weight, serum electrolytes and serum creatinine is essential during therapy with metolazone to avoid these problems [39].

Loop-acting diuretics

Mechanism of action

Drugs of this type include furosemide, a non-thiazide sulfonamide; ethacrynic acid, a phenoxyacetic acid derivative and bumetanide, which is a 3-aminobenzoic acid derivative. Their principal site of action is on the ascending limb of the loop of Henle where they inhibit sodium and chloride reabsorption. This action may be in part due to inhibition of tubular cellular sodium-potassium ATPase [29, 45], causing an impairment in active sodium transport into the intracellular space of this region of the nephron. Bumetanide may have additional natriuretic effects on the proximal tubule [46].

Effects of loop diuretics on renal function

Furosemide, besides its effects on electrolyte excretion, has complex actions within the kidney. Renal blood flow and glomerular filtration rate may decline if systemic blood pressure falls below normal. Frequently, however, total renal blood flow may actually increase in association with furosemide administration. Moreover, there often is a redistribution of intrarenal flow from the medulla to the cortex [47]. This is likely to involve the intrarenal production of vasodilatory prostaglandins, since the cortical shift in blood flow can be blocked or attenuated by indomethacin [48]. Ethacrynic acid has been shown to produce a gradual but significant fall in glomerular filtration rate following intravenous administration and acute diuresis [30, 34, 35, 47, 48]. The effects of these agents on renal hemodynamics and glomerular filtration in the setting of renal insufficiency have not been adequately studied. Until the issue is clarified, it is prudent to frequently monitor blood pressure and renal function in such patients who are receiving these potent diuretic agents.

Adverse effects of loop diuretics

The loop diuretics may cause hypokalemia, hyponatremia, hyperuricemia, dehydration, volume depletion and glucose intolerance [30]. Reversible oto-

toxicity has been seen in patients with chronic renal failure after receiving high dose intravenous furosemide [49]. Other adverse reactions reported to occur during furosemide therapy include pancreatitis, skin rash, interstitial nephritis, leukopenia and thrombocytopenia [34]. Ethacrynic acid, in addition to the side effects seen with the other agents has a relatively high incidence of gastrointestinal side effects [35].

Transient or irreversible ototoxicity has also been reported following oral or intravenous ethacrynic acid [50]. This drug should not be administered to patients with severe renal impairment because its ototoxicity potential is greater than that of furosemide [49, 50]. Adverse reactions with bumetanide include muscle pain and myalgias which may be dose-related [46]. Hematologic reactions attributed to bumetanide include granulocytopenia, leukopenia, and thrombocytopenia [51].

Pharmacokinetics

The loop diuretics are all readily absorbed from the gastro-intestinal tract with a peak diuretic effect in 2 h, they can be used intravenously for a more rapid onset of action of 5 to 30 min. These drugs are highly protein bound with a resultant large volume of distribution. Elimination is primarily via the kidney by glomerular filtration and proximal tubular secretion [52]. Pharmacokinetic parameters of furosemide may be affected differently by different renal diseases. For example, plasma protein binding and the volume of distribution may be increased in the uremic millieu, or decreased when nephrotic syndrome and hypoalbuminemia are present. Generally, the renal clearance of furosemide is similar in magnitude to the creatinine clearance. However, with advanced renal failure, clearance of this drug is reduced to approximately 50% of creatinine clearance [34, 35, 52].

No specific dosage adjustment is necessary for furosemide in renal failure, however, higher than normal doses may be required to achieve a diuretic response. As noted, in the absence of hypoalbuminemia, the volume of distribution of furosemide is increased in end-stage renal disease. No specific dosage adjustment is necessary with ethacrynic acid in patients with mild to moderate renal failure. However, in general, ethacrynic acid is best avoided altogether in severe renal impairment because of serious risk of ototoxicity [39, 50].

With regard to bumetanide, the drug is rapidly cleared from the circulation, even with a creatinine clearance of less than 2 ml/min. Bumetanide clearance has been shown to exceed creatinine clearance, so tubular secretion is probable [35].

These agents have a steep dose response curve and are often effective in patients with impaired renal function. High doses of furosemide (up to 2 g/day) can cause diuresis in patients with GFR as low as 2 ml/min [30, 54]. Intrarenal hemodynamic effects including a shunting of

blood flow to the cortical nephrons may also contribute to the diuretic and antihypertensive effect [48].

Potassium-sparing diuretics

Spironolactone is a synthetic steroid lactone that resembles progesterone. Triamterene, a pteridine derivative, and amiloride, an organic base, block Na^+-K^+ exchange at sites in the distal nephron. This class of agents has weak diuretic efficacy when used alone. However, their effects are additive with those of other diuretics. The most frequent use of these drugs are in combination with the thiazides or loop diuretics, where they can be used to counteract the hypokalemic effect of those more potent, proximally acting diuretics [30].

Mechanisms of action

Spironolactone and its active metabolites competitively antagonize aldosterone and 18-OH-deoxycorticosterone at the mineralocorticoid receptor sites located along the distal tubule [35, 55]. These sites, when normally occupied by aldosterone, act to mediate distal tubular sodium reabsorption in exchange for potassium secretion into the tubular lumen. Triamterene and amiloride inhibit sodium-potassium exchange in the distal tubule, through a process that is independent of mineralocorticoid receptors and probably involves an alteration in basal membrane sodium permeability [30, 35, 55 ,56].

Over 95% of all filtered sodium is reabsorbed prior to the distal tubular portion of the nephron. Thus, the natriuretic effect of these distal-acting, potassium-sparing agents is the least impressive of the major classes of diuretics. The main use of these agents is in combination with thiazide or loop diuretics to ameliorate hypokalemia and potentiate diuresis [30].

Adverse effects

The most common adverse effect of potassium-sparing diuretics is hyperkalemia. Hyperkalemia is especially likely to occur in patients with renal insufficiency. Even moderate degrees of renal impairment pose a significant risk so that at a GFR of less than 30 ml/min, these agents should be used not at all or only with great caution. Other risk factors for hyperkalemia include; diabetes mellitus, hyporeninemic hypoaldosteronism, nonsteroidal anti-inflammatory agents, catabolic states and potassium supplementation [30, 35, 55, 56].

Spironolactone, especially at high doses may produce gynecomastia, breast tenderness and impotence in men, and menstrual irregularities in women. Epigastric discomfort, skin rash, hyperhidrosis, ataxia and alopecia

are also occasionally encountered [56, 57]. Triamterene and amiloride may occasionally produce nausea, vomiting, muscle cramps and dizziness [56, 58, 59]. Depression in glomerular filtration rate and elevation in blood urea nitrogen has occasionally been attributed to each of the three potassium-sparing agents [55, 56]. This effect may be pronounced in patients with underlying renal disease.

Pharmacokinetics

Surprisingly little is known about the metabolism and excretion of spironolactone. It is converted to an active metabolite canrenone which may contribute as much as 75% of the drugs anti-mineralocorticoid activity [30, 55]. Both triamterene and amiloride are rapidly but incompletely absorbed from the gastrointestinal tract. About 60% of absorbed triamterene is bound to plasma proteins, metabolized in the liver, and excreted in the urine via glomerular filtration and tubular secretion. Amiloride is excreted mostly unchanged in the urine [31, 34, 35, 59].

There is no specific recommendation for dose modification of these drugs in renal insufficiency. There is a dichotomy between the natriuretic effect, which becomes weaker, and the potassium-sparing action which is enhanced as renal insufficiency progresses, indicating a lower benefit/risk ratio. With moderate to severe renal impairment, the risks of hyperkalemia will often outweigh any potential benefits of this class of diuretic agents.

Beta-blocking agents

Mechanism of antihypertensive effect

The existence of several distinct types (alpha and beta) of adrenergic receptors was originally hypothesized by Ahlquist in 1948 [60]. This concept

Table 4. Beta-adrenoreceptors

Type	Location	Action
Beta-1	SA node	Sinus tachycardia
	AV conduction system	Increased conduction velocity
	Myocardium	Increase myocardial contractility
	Kidney	Renin release
Beta-2	Vascular smooth muscle	Vasodilation
	Kidney	Renin release
	Lung	Bronchodilation
	Skeletal muscle	Tremor, glycogenolysis
	Pancreas	Insulin release
	Liver	Glycogenolysis, Gluconeogenesis

derived from the finding that the relative potency of sympathomimetic amines varied considerably, depending on the effector organ studied. More recently, beta adrenoreceptors have been further divided into two subgroups [61] (Table 4). Stimulation of beta-1 receptors, existing primarily in the heart, causes cardio-acceleration and enhancement of both A-V conduction and myocardial contractility. These effects together produce an increase in cardiac output. Stimulation of beta-2 adrenoreceptors, located primarily on vascular smooth muscle, results in vasodilation and a corresponding reduction in peripheral resistance. Additional effects of beta-2 receptor activation include bronchodilation, glycogenolysis, and insulin release.

Despite the widespread use of beta-blockers in the treatment of hypertension and the large number of investigations that have been performed, the exact mechanism of the antihypertensive effect of these agents has not been elucidated. Proposed mechanisms are enumerated in Table 5. In this section, these theories are examined and evidence supporting or refuting them is outlined.

A decrease in cardiac output is common to virtually all beta-blockers and has been suggested as the predominant means by which these drugs exert their antihypertensive effect [62]. However, in contrast to the almost immediate decrease of cardiac output that is observed following intravenous administration of beta-blockers, the hypotensive action is not usually apparent until after some delay, often not reaching a maximum effect until several days or even weeks have elapsed. Thus, although reduction of cardiac output may be a prerequisite for a hypotensive effect, a slower onset, more gradual lowering of peripheral resistance must occur before blood pressure reduction becomes evident [63].

Table 5. Hypothetical mechanisms of the antihypertensive action of beta-blockers

A. Decreased cardiac output
   1. Chronotropic effect
   2. Inotropic effect
      a. Antagonism of beta-adrenergic effect on myocardial contractility
      b. Decreased preload via reduction in plasma volume (secondary to inhibition of aldosterone synthesis)

B. Reduction in total peripheral resistance
   1. Suppression of renin release
   2. Central nervous system effects
   3. Resetting of baroreceptors
   4. Pre-synaptic inhibition of norepinephrine release
   5. Inhibition of platelet serotonin release
   6. Autoregulation
   7. Beta-2 adrenoreceptor stimulation (intrinsic sympathomimetic activity, e.g., pindolol)

Almost all beta-blockers inhibit renin release from the kidneys. Since levels of the enzyme renin are rate-limiting in the formation of the powerful vasoconstrictor angiotensin II, there is reason to believe that the renin-lowering effect of beta-blockers may provide an important mechanism by which reduction of peripheral resistance is achieved. Many studies have demonstrated that beta-blockers are preferentially effective in high-renin hypertension [64]. While there is a tendency for patients with low-renin forms of hypertension to respond less well to beta-blocker therapy [65], in some of these patients a paradoxical pressor response has been observed [66]. Results from at least one experimental animal model also support an important role for renin in the blood pressure-lowering mechanism of beta-blockers. Dogs made hypertensive with angiotensin II infusions have undetectable renin levels and fail to respond to either propranolol or captopril. In contrast, the same animals with experimental renal artery constriction and elevated renin levels have a substantial hypotensive response to either captopril or propranolol [67]. In human hypertension, the fact that such a parallelism between hypotensive effects and pretreatment renin status exists with both renin antagonists and beta-blockers has also been cited to favor an important role of renin suppression in the blood pressure reducing effects of these agents. Nevertheless, a considerable body of evidence exists that is not wholly consistent with a renin mechanism in beta-blocker-induced blood pressure reduction. For example, some studies have shown no association between pretreatment renin status and blood pressure response [68]. Furthermore, a correlation between the actual level of decline in plasma renin and the beta-blocker-induced decrement in blood pressure has not been observed [69]. The antirenin concept also fails to explain why plasma renin falls immediately but peripheral resistance and blood pressure drop only after a delay of hours to days after the initial administration of beta-blockers [63]. Furthermore, the doses required to suppress renin are usually much smaller than those needed to lower blood pressure [70]. Finally, and of considerable importance, is the fact that pindolol has little effect on plasma renin activity, yet is an effective antihypertensive agent [71]. Hence, the role of renin suppression in the antihypertensive action of beta-blocking agents is far from clear.

Several neurogenic mechanisms have also been proposed as possible modes of action in the resistance-lowering effects of beta-blockers. Side effects of these drugs include sedation, depression and vivid dreams, all of which may be attributed to effects on the central nervous system [72]. Animal studies have suggested that beta-blockers may have an inhibitory action on noradrenergic neurons of the brain [73]. Against the theory of a centrally-mediated antihypertensive action of beta-blockers is the fact that hydrophilic drugs such as nadolol and atenolol that penetrate the central nervous system poorly are nevertheless effective antihypertensive agents [74]. It is

also possible that beta-blockers may have a resetting action on the afferent limb of the baroreceptor system, although little data exists as of yet to support such a contention. A peripheral neural effect for which there is solid experimental evidence in animals, is that of presynaptic inhibition of norepinephrine release at sympathetic nerve terminals [75]. Such an effect, demonstrated at concentrations of somewhat higher than usual therapeutic levels, may explain the occasionally described beneficial effects of large daily doses of propranolol (i.e., 1–2 g/day).

Conceivably, beta-blockers may produce vascular relaxation via mechanisms that are not directly linked to the adrenergic nervous system. For example, propranolol has been shown to block platelet release of the potent vasoconstrictor amine serotonin [76], an effect that could result in vasodilatation of the microcirculation. Also, by an as yet poorly understood mechanism, arteriolar vascular tone may be affected by local tissue oxygen tension [77]. It is therefore possible that beta-blocker-induced decreased cardiac output and its attendant fall in tissue blood flow may produce an autoregulatory vasodilation, thereby lowering resistance and promoting a return of tissue oxygen delivery to pre-treatment levels.

Pindolol, a beta blocking agent with intrinsic sympathomimetic activity (ISA), may have an additional, unique form of action. Acute studies have shown that this agent produces a relatively small reduction or change in cardiac output while peripheral resistance remains nearly normal [78]. Chronic, oral pindolol administration causes a fall in peripheral resistance to levels well below that normally seen with other beta-blockers [79]. Pindolol, in contrast to conventional beta-blockers, has been demonstrated to have a direct vasodilatory action on vascular smooth muscle [80]. It is probable that this phenomenon is mediated by beta-2 adrenoreceptor stimulation, an effect that differs from beta-blockers that do not possess intrinsic sympathomimetic activity.

These considerations suggest that more than one mechanism may be responsible for the antihypertensive effect of beta-blockers and that the mechanisms involved may be different in different beta-blockers. Pindolol appears to lower the blood pressure primarily by a decrease in systemic vascular resistance rather than by depression of cardiac output which appears to accompany the antihypertensive effect of non-ISA beta-blockers.

Nonselective beta-antagonists

Sites of action

Included in this category are propranolol, nadolol, timolol and pindolol. These agents act as competitive antagonists of both beta-1 and beta-2 adre-

noreceptors (Table 6) which are located in the heart, peripheral vasculature, kidneys and several other major organs. Effects related to beta-1 antagonism include slowing of heart rate, reduced myocardial contractility and inhibition of renal renin release [81]. Blockade of the beta-2 receptors has more complex results which include inhibition of the following: peripheral arteriolar vasodilation, renal renin release, bronchodilation, glycogenolysis, insulin release, gluconeogenesis and muscle tremor [82].

Effects on renal function

Evidence accumulated to date demonstrates that several beta-blockers including propranolol may produce a 10–15% decline in renal blood flow and glomerular filtration rate [83]. This has been attributed to a beta-blocker induced fall in cardiac output. Interestingly, the detrimental renal hemodynamic effects of propranolol may actually be worse in hypertensive patients who do not have a hypotensive response to the drug, perhaps by an unmasking effect on renal vascular alpha-adrenergic tone [84]. Several studies of the renal hemodynamic effects of nadolol and pindolol show that renal blood flow and glomerular filtration rate are relatively well-preserved, even in the face of a decline in cardiac output [85–87]. This has been interpreted to indicate a renal vasodilator action of nadolol, an effect that may be especially advantageous in the treatment of hypertension. The effects of timolol on glomerular filtration and renal hemodynamics have been little studied.

Adverse effects

Many side effects of nonselective beta-blocking drugs can be predicted based on current adrenoreceptor theory. Sinus bradycardia, AV conduction delay and congestive heart failure are the results of blockade of cardiac

Table 6. Clinically important properties of current, US-approved beta-blockers

Generic name	Trade name	B_1 selective	Lipophilic	Daily dose (mg/day)	Dose interval (hours)	Dose reduction with renal failure
Propranolol	Inderal	–	+	20–320	8–12	–
Nadolol	Corgard	–	–	40–320	24	+
Timolol	Blocadren	–	+	20–80	12	–
Pindolol	Visken	–	+	5–40	12*	–
Metoprolol	Lopressor	+	+	50–200	12	–
Atenolol	Tenormin	+	–	50–100	24	+

beta-1 receptors [88]. Bronchospasm, peripheral vascular insufficiency and disturbances in carbohydrate metabolism can be attributed to beta-2 receptor inhibition in bronchial smooth muscle, peripheral arterioles and liver and pancreas respectively [89–91]. Abdominal discomfort and diarrhea may be the result of unopposed parasympathetic activity on the gastrointestinal tract. Adverse reactions that are probably not related to the adrenergic blocking activity of these drugs include skin rash, keratoconjunctivitis and positive antinuclear antibody titer [25]. Psychiatric effects including depression, insomnia, vivid dreams, decreased libido and impotence [72] may be more severe with the use of highly lipid soluble agents (see Table 5).

Pharmacokinetics

All of the nonselective beta-blockers have greater than 90% absorption from the small intestine. Bioavailability differs somewhat depending on the extent of hepatic first-pass metabolism as the drugs enter the portal circulation. This is particularly important for propranolol at low doses in which only 40% of an orally administered dose reaches the systemic circulation [92]. As propranolol doses are increased, a progressively higher proportion becomes available, suggesting the hepatic extraction process is saturable. There are several potentially important consequences of this phenomenon [93]. Firstly, the intravenous dosage is much lower than an equipotent oral dose. Also, there is more likely to be considerable inter-individual variation in the oral dose-response effects of propranolol. Because of the saturable nature of hepatic extraction, the oral dose-response will be nonlinear. Finally, in the case of propranolol, some hepatic metabolites still retain beta-blocking activity.

Propranolol, which is the best-studied of these agents is highly lipid soluble and over 90% bound to plasma proteins resulting in a large volume of distribution [93]. The beta-blockers with greatest lipid solubility are eliminated most quickly from the body via biotransformation (mostly hepatic). These include propranolol and timolol. Nadolol, which is relatively lipid insoluble, is excreted virtually unchanged by the kidneys and has a longer plasma half-life of 14–17 h [94]. Pindolol is intermediate between these with about 40% of the drug excreted unchanged in the urine [95].

The effects of renal insufficiency on the pharmacokinetics of beta-blockers is very complex. Highly water soluble drugs such as nadolol that are excreted entirely unchanged by the kidney, may accumulate to toxic levels when renal impairment is severe. Hence the dose interval of 24 h for this agent should be increased to 36 h for moderate (Ccr 20–50 ml/min) and to 48–60 h for severe (Ccr <10 ml/min) renal insufficiency [94]. A specific recommendation cannot be provided for the other nonselective beta blocking agents. In general no dosage modification is necessary for propranolol, timolol and pindolol in the setting of renal impairment. However, there is

greater than normal inter-individual variation in the bioavailability and metabolism of these substances when renal disease is present. Thus, each agent, when given, should be administered cautiously and in the smallest possible therapeutically effective dose.

Beta-1 selective antagonists

Sites of action

Included in this group are metoprolol and atenolol. These drugs at modest doses competitively block beta-1 adrenoreceptors which are located primarily in the heart. They are sometimes referred to as 'cardioselective'. The major effects of these agents are therefore cardiac, and include slowing of heart rate and lowering myocardial contractility. Renin secretion by the renal juxtaglomerular apparatus is also suppressed [69].

Adverse effects

Side effects of atenolol and metoprolol are primarily cardiac [96, 97] and include bradycardia, AV conduction delay and congestive heart failure. When large doses are administered, these drugs may lose their beta-1 selective effects with consequent development of additional adverse reactions including bronchospasm, Raynaud's phenomenon and abnormalities in carbohydrate metabolism (prolongation of insulin-induced hypoglycemia and inhibition of insulin release). Gastrointestinal disturbances and skin rash, even at low doses, are as frequent as those seen with nonselective agents.

Psychiatric effects are probably not related to beta-receptor selectivity and are probably less common with atenolol because of its poor lipid solubility. What little work has been done to investigate the renal effects of metoprolol and atenolol fails to demonstrate a detrimental effect either on renal blood flow or glomerular filtration rate.

Pharmacokinetics

Metoprolol is virtually completely absorbed from the small intestine. Oral bioavailability is reduced to 40–50% because of extensive first-pass hepatic metabolism [96]. This results in considerable inter-patient variability in dosing requirements. The drug is only slightly (12%) bound to plasma proteins but is highly lipid soluble and readily enters the central nervous system. It is cleared from the body primarily by hepatic oxidative biotransformation to mostly inactive metabolites that are excreted in the urine [98]. Generally, dose reduction is not necessary with even severe renal failure. Nevertheless, greater variation of bioavailibility and accumulation of slightly active metabolites make it necessary to individually adjust the dosage to the patient's requirements when renal disease is present.

Atenolol is also completely absorbed by the oral route. Bioavailability of this drug is 40–50%, virtually all of which is eventually excreted intact by the kidneys [99]. Because of its dependence on a renal route of elimination, the dose of this drug should be modified when renal insufficiency is present. It is recommended that with moderate reduction in renal function, the dosage be lowered by one-half. When renal failure is severe, a reduction in atenolol dosage to one quarter the normal dose is indicated [100].

Clinical use of beta-blockers in renal insufficiency

According to the conventional stepped-care approach to hypertension, adrenergic inhibiting agents such as the beta-blockers are best reserved for second-step therapy. For patients with moderate to severe renal insufficiency this is probably a useful approach. Diuretics are more likely to be successful in such a setting since salt and volume retention are so important in the generation and maintenance of hypertension. With milder forms of renal impairment, beta-antagonists may often be utilized as initial therapy. Factors that may help to sway the clinician in favor of beta-blocker therapy are summarized in Table 7.

Table 7. Indications for beta-blocker use

I. Monotherapy
A. Factors favoring a beneficial response
1. Age <40 years
2. Resting heart rate >80
3. Race – Caucasian
4. Plasma renin activity >2 ng/ml/hour
B. Coincident disorders that may benefit from beta-blockers
1. Angina pectoris
2. Anxiety
3. Intention tremor
4. Hyperthyroidism
5. Migraine headaches
C. Relative contra-indications to diuretic therapy
1. Hyperuricemia
2. Prerenal azotemia
3. Type II diabetes mellitus
4. Hyperlipidemia
5. Allergy to sulfa
D. Intolerable side effects from diuretic therapy
II. Combination therapy
A. Inadequate response to diuretic alone
B. Combination with diuretic and vasodilator therapy

Nevertheless, since some beta-blocker may further impede glomerular filtration, it is important to be especially cautious when utilizing these drugs in renal insufficiency. Other factors that may occasionally limit the use of beta-blockers are listed in Table 8.

Alpha-receptor blockers

Prazosin

Sites of action

Results of animal studies have shown that the antihypertensive effect of prazosin may be due to vasodilation effected by direct vascular smooth muscle relaxation on one hand, and the alpha-adrenergic receptor blockade which interferes with peripheral sympathetic function on the other hand [101]. Some workers have concluded that the dominant component of action is indeed the direct relaxant effect, although such a mechanism of action has not been unequivocally confirmed [101–104].

Stronger evidence exists for the theory that the vasodilatory effects of prazosin are primarily due to peripheral alpha-adrenergic receptor blockade [6]. Recent studies have shown that prazosin causes a functional alpha-adrenoreceptor blockade that differs from a receptor occupancy blockade that has been demonstrated with conventional agents, such as phenoxybenzamine and phentolamine. These agents block both pre- and post-synaptic alpha-receptors, while prazosin has been shown to have an affinity for post-synaptic, alpha-1 receptors. The drug has little affinity for pre-synaptic, alpha-2, adrenergic receptors [102].

It has been postulated that the pre-synaptic alpha-2 receptor mediates a negative feedback mechanism wherein its activation inhibits the release of norepinephrine in response to a given stimulus [105]. Failure of the drug to block the alpha-2 receptor permits norepinephrine to occupy the site and

Table 8. Contraindications to beta-blocker therapy

1. Congestive heart failure
2. AV conduction defects, bradycardia
3. Bronchospasm
4. Insulin-dependent diabetes mellitus
5. Catecholamine excess syndrome
   a. Pheochromocytoma
   b. Clonidine withdrawal
6. Deteriorating renal function

may explain the lack of tachycardia, tolerance, and renin release associated with prazosin.

Effects on renal function

Reports on prazosin use have shown that the drug can either increase or have no effect on glomerular filtration rate and renal plasma flow. In patients with severe renal impairment, the drug has not been shown to adversely affect renal function [106]. In addition, prazosin has been shown not to increase plasma renin activity. In fact, some reports have indicated a decrease in plasma renin activity associated with prazosin therapy. The drug's selective inhibition of post-synaptic alpha-adrenoreceptors is believed to be the reason for this effect [107].

Adverse effects

Overall, prazosin is fairly well tolerated by most patients. The most common adverse effects are postural hypotension, along with associated dizziness and syncope. This problem appears to be largely dose related, with postural hypotension occuring following the initial dose or rapid dose increases. Orthostatic hypotension is also more likely to occur in the elderly or in patients who are receiving diuretics. In the majority of cases, prazosin has been shown not to produce reflex tachycardia as a response to the hypotensive effect. If any changes in heart rate do occur, they are usually mild to moderate. Some effects that have been reported include skin eruptions, dry mouth, diarrhea, nausea, irritability, mental depression, and fluid retention [108].

Pharmacokinetics

Prazosin is well absorbed orally but peak blood level concentrations, as well as time to peak, may vary among patients. The drug is well distributed throughout body tissue and is approximately 97% protein-bound. Prazosin is extensively metabolized in the liver, primarily to the 0-demethylated form. The plasma half-life is approximately 2.5 to 4 h. Since only about 6% of an oral dose is excreted unchanged in the urine and because of the high degree of protein-binding, it is suggested that the dosage need not be markedly altered in patients with renal failure [109].

Therapeutic use in renal insufficiency

Patients with severely compromised renal function appear to be more sensitive to prazosin's effects than those with normal renal function. As such, they may require less drug to achieve desired effects. While no formal dosing guidelines are available, it may be wise for the physician to prescribe lower dosages in these patients while at the same time carefully monitoring response and titrating the drug accordingly [107–109]. A safe starting dose

of prazosin in this setting might be 1 mg twice daily. The first dose of this drug is best administered under supervision because of the potential 'first dose' hypotensive effect that is occasionally observed [103]. Alternatively the patient may take the first dose at home immediately prior to retiring but should be forwarned about potential orthostatic effects. In patients with renal insufficiency prazosin is often added as a 'step-three' drug when the combination of diuretic plus adrenergic inhibitors is not sufficient to achieve normalization of blood pressure. Prazosin may also be used as a second line drug when beta-blockers or central inhibitors are contra-indicated or poorly tolerated. The dose of prazosin can be increased at weekly intervals to a maximum of 40 mg in two or three divided doses daily [107].

Phenoxybenzamine

Sites of action

The effects of phenoxybenzamine are due to alpha-adrenergic blockade. Phenoxybenzamine inhibits both pre- as well as post-synaptic receptors. The drug therefore blocks end-organ response and interferes with feedback inhibition of presynaptic receptor mediated norepinephrine release [105]. The drug also acts at the level of vascular smooth muscle to cause peripheral vasodilation. Because of pre-synaptic alpha-blockade there is an associated reflex tachycardia. A significant effect of the drug is also profound postural hypotension.

Effects on renal function

In hypovolemic patients, phenoxybenzamine has been shown to increase renal blood flow. There are no changes demonstrated in normovolemic patients given the drug. Phenoxybenzamine stimulates renal renin release.

Adverse effects

Adverse effects associated with phenoxybenzamine are due to the degree of alpha-adrenergic blockade. Serious problems are encountered with postural hypotension and reflex tachycardia. With continued therapy these effects may abate somewhat, however, they may recur with exercise or upon ingestion of drugs that cause vasodilation. Phenoxybenzamine-induced tachycardia may be severe enough to aggravate congestive heart failure and angina in patients with compromised myocardial function. The drug should be used with caution in patients with impaired cerebral or coronary blood flow, or renal dysfunction. Fluid replacement may be necessary in patients who experience severe hypotension while on the drug.

Other, less severe, adverse effects include nasal congestion, miosis, sedation, and weakness. Patients may also complain of confusion, headache, dry

mouth, and inhibition of ejaculation. In some cases gastrointestinal upset may occur and can be a limiting factor in therapy.

Pharmacokinetics and therapeutic use

Phenoxybenzamine is variably absorbed from the gastrointestinal tract. The drug has a slow onset of effect and long duration of action. Pharmacologic effects do not appear for several hours upon initial administration, and alpha-adrenergic blockade is cumulative at about 1 week into therapy. The half-life of phenoxybenzamine is approximately 24 h. This pharmacokinetic profile is most likely due to the formation of a fairly stable receptor blockade complex. In addition, the drug is highly lipid soluble, and may accumulate in fat following prolonged use at high dose.

The usual starting dose is 10 mg twice daily and is increased slowly until the pressure is normalized. The patient should be monitored frequently for orthostatic hypotension. The major role of phenoxybenzamine is in blood pressure regulation of patients with pheochromocytoma. It is however a consistently effective drug when used in high enough dosage and could therefore be used in any patient with hypertension resistant to more conventional triple-drug therapy [110].

Phentolamine

Phentolamine is a short-acting adrenergic blocking agent primarily used in the diagnosis of pheochromocytoma and prevention of paroxysmal hypertension prior to, or during, pheochromocytomectomy. The drug has also been investigated in the management of hypertensive crisis caused by sympathomimetic amines or by acute clonidine withdrawal [111]. Phentolamine has also been used to treat increased blood pressure in patients who ingest foods or products containing sympathomimetics or tyramine while being treated with monoamine oxidase inhibitors [111]. The drug is not recommended for use in the treatment of essential hypertension because most of the patients become resistant to the antihypertensive effects with prolonged usage.

Mechanism of action

Phentolamine competitively blocks alpha-adrenergic receptors and as such decreases the response to adrenergic stimuli [112]. The action of the drug is transient, and blockade is incomplete unless large doses are given. Phentolamine has a predominant effect in antagonizing the response to circulating catecholamines rather than directly affecting neurotransmitter release at the level of the nerve ending [113]. The drug also has the capability to cause smooth muscle relaxation in peripheral resistance vessels, thereby inducing

peripheral vasodilation and decreasing total peripheral resistance. Vasodilation is mediated both by direct vascular relaxation and adrenergic blockade. Phentolamine also produces reflex mediated positive inotropic and chronotropic effects in the heart, with resultant increase in cardiac output [112–114]. A hypotensive effect usually occurs in most patients given the drug. The drug also causes a decrease in pulmonary vascular resistance and pulmonary artery pressure at normal doses [114]. Histamine-like actions are also seen with this drug [113].

Effects on renal function

Phentolamine has been shown to decrease glomerular filtration rate and increase plasma renin activity [112]. Fractional excretion of sodium is also decreased by phentolamine [112], but potassium excretion is not affected. Urinary output is reduced by phentolamine administration. It is most likely that these effects are a result of the hemodynamic vasodilatory action of the drug with the consequent effect on renal sodium handling although a direct effect of the alpha-adrenergic blocker on the renal tubular apparatus cannot be excluded.

Adverse effects

Tachycardia, arrythmias, and hypotension have been reported, usually in conjunction with parenterally administered phentolamine [113]. Weakness, dizziness, flushing, and nasal congestion have also been associated with phentolamine therapy. Gastrointestinal toxicity is common and includes nausea, vomiting, diarrhea, and abdominal pain [114]. In some cases, there may be an increase in gastric secretion of both acid and pepsin [113]. It is possible that an exacerbation of peptic ulcer disease may also occur. These gastrointestinal effects have been found to limit the long-term usefulness of phentolamine.

Pharmacokinetics

The pharmacokinetics of phentolamine have been poorly defined, and accurate information is scarce. Phentolamine is poorly absorbed following oral administration. This route of administration is only 20% as effective as the intravenous route. The onset of action is immediate following intravenous administration, and the duration of action is relatively short. Only about 10% of a parenteral dose is eventually recovered in the urine in the active form. The metabolism of the remainder of the drug has not been defined. Neither therapeutic nor toxic blood levels have been defined. No information is available regarding modification in renal failure.

Therapeutic use

As noted, there is little indication for the routine use of phentolamine in

either primary or renal forms of hypertension. Its major indication is in the acute management of hypertensive crises secondary to excessive sympathoadrenergic activity such as pheochromocytoma, clonidine withdrawal or tyramine ingestion with MAO inhibitors. Phentolamine has been utilized by some as a pharmacologic test for pheochromocytoma but has not proven to be specific and may be dangerous. More commonly the drug is administered preoperatively in patients undergoing laparotomy for pheochromocytoma.

The oral form may be administered as 50 mg every 3–6 h but is often poorly tolerated because of gastrointestinal symptoms. Phenoxybenzamine is generally a better tolerated agent. Phentolamine is usually given by the intravenous route starting with a 5 mg bolus [111]. A continuous drip infusion may then be initiated and the dose titrated to the patient's blood pressure response.

Mixed adrenergic blockers

Labetalol

Mechanisms of action

Labetalol is unique among currently used antihypertensive agents in that it competitively blocks both alpha- and beta-receptors. The degree of beta-blockade appears to be much greater than alpha-blockade with a relative potency approaching 7:1 [115]. Beta-blockade appears to involve both beta-1 and beta-2-receptors, while antagonism affects predominantly the post-synaptic alpha-receptors. There is also evidence from clinical and animal studies that labetalol possesses mild intrinsic sympathomimetic activity [116]. It is probable that the antihypertensive action of this agent is related to all three properties, namely beta-blockade, alpha-1 blockade and intrinsic sympathomimetic activity.

Adverse effects

Labetalol is generally well-tolerated. Side effects are usually nonspecific and include light-headedness, headache, gastrointestinal symptoms and a 'tingly' sensation of the scalp [117]. Rare adverse effects of labetalol include postural hypotension, dyspnea, depression and sexual dysfunction, all of which may be related to the drug's beta-antagonism [118]. There have been a few reports of development of antinuclear antibody titers in patients receiving labetalol [27].

Although no reports of significant renal toxicity in association with labetalol therapy have yet surfaced, the renal effects of this agent have not been extensively evaluated. Several studies that have been completed found

no deleterious effects on glomerular filtration rate or renal plasma flow [118].

Clinical use of labetalol

In patients with normal renal function the effective antihypertensive dose range is 300 to 1200 mg/day in two divided doses by mouth. Labetalol may also be administered intravenously in 20 to 80 mg boluses at 10–20-min intervals for a total loading dose of 300 mg [117].

Because labetalol is only weakly lipid soluble, it depends to some extent (20–40%) on the kidneys for elimination [119]. In the setting of renal insufficiency it may prove to be necessary to reduce the dosage of labetalol to avoid hypotension, bradycardia or other adverse effects.

Labetalol has been in widespread use in Western Europe since 1975 and is likely to serve as an important addition to the antihypertensive armamentarium in the US as well. As monotherapy, labetalol may be comparably effective to other beta-blocker-vasodilator combinations such as propranolol-hydralazine. In patients with renal disease it may prove to be most useful when diuretic therapy alone is not adequate for control of blood pressure.

The intravenous and oral forms of the drug have been shown to be effective as monotherapy in the initial control of severe hypertension during hypertensive crises including pheochromocytoma and the clonidine withdrawal syndrome.

Centrally active antihypertensive drugs

Alpha-methyldopa

Sites of action

Among its other actions methyldopa is an aromatic acid decarboxylase inhibitor which thereby inhibits the biosynthesis of the neurotransmitters norepinephrine, dopamine and serotonin. Originally, it was hypothesized that the antihypertensive action of methyldopa was due to decarboxylase inhibition with resultant depletion of intracellular norepinephrine stores [120]. This mechanism has not been found to apply since the inhibition of decarboxylase and the hypotensive effect are not temporally related; also the decarboxylation reaction is not an important rate-limiting step in the formation of catecholamines [121]. A second hypothesis has been that the hypotensive effect of methyldopa is secondary to the formation of a false neurotransmitter, alpha-methylnorepinephrine. This explanation may also be inadequate since alpha-methylnorepinephrine has a vasopressor potency that is not much less than that of norepinephrine [122].

Additional modes of action may include a direct action on vascular tone. This is suggested by animal studies in which alpha-methyldopa has been shown to decrease vascular resistance despite prior surgical or chemical ablation of sympathetic influence [123]. In humans, a direct vascular mechanism is supported by the known hypotensive efficacy of methyldopa in the recumbant position, when sympathetic traffic is minimal.

Inhibition of adrenergic-mediated renin release may further contribute to the blood pressure-lowering effect of methyldopa [124]. Recent investigations favor the view that the predominant mechanism for the hypotensive action of this agent is through stimulation of alpha-2 receptors located in the vasomotor centers of the brain stem by the active metabolite, alpha-methylnorepinephrine [125]. The resultant effect is a reduction in centrally-mediated sympathetic nerve outflow traffic to the peripheral vasculature and a fall in vascular resistance.

Effects on renal function

The hemodynamic effects of methyldopa include a substantial (26–32%) fall in peripheral resistance and a smaller (10%) decrement in cardiac output [126]. A consistent reduction in renal vascular resistance has also been found so that renal blood flow is maintained despite the fall in cardiac output. Accordingly, glomerular filtration rate remains stable or actually increases, even in patients with renal insufficiency. Despite these beneficial effects on renal hemodynamics and function, a large minority (20–50%) of patients will become tolerant to the antihypertensive action of methyldopa due to its mild antinatriuretic effect [127]. This is especially likely to occur in the setting of renal insufficiency; therefore most such patients will require the concomitant use of a diuretic agent.

Adverse effects

Common (15–50%) side effects associated with methyldopa therapy include sedation, dry mouth and orthostatic hypotension [128] (Table 9). These may often improve with continued therapy. Somewhat less common (2–10%) effects include sexual dysfunction, depression, positive direct Coombs' test [27] and positive antinuclear antibody titer [26]. These may be ameliorated by reduction in dose or discontinuation of the drug. Rare or uncommon reactions (less than 2%) include Coombs' positive hemolytic anemia [27], thrombocytopenia, leukopenia, hepatocellular toxicity [129], galactorrhea [130] and hyperpyrexia [128]. All of these require discontinuation of methyldopa therapy. It should be cautioned that, in some patients, abrupt cessation of methyldopa has resulted in rebound hypertension [131].

Pharmacokinetics and therapeutic use

Approximately 40–60% of an oral dose of methyldopa is absorbed from the

Table 9. Summary of central adrenergic inhibitors

Drug	Usual dose	Routes of elimination	Dose reduction with renal impairment	Adverse effects
Alpha-methyldopa	125–1000 mg bid	Renal excretion of methyldopa and conjugated hepatic metabolites (> 50%), metabolites may be pharmacologically active	Double dose interval $C_{cr} < 10$ ml/min	Sedation, xerostomia, orthostatic hypotension, impotence, galactorrhea, hepatitis, drug fever, hemolytic anemia, positive antinuclear antibodies
Clonidine	0.1–1.2 mg bid	Mostly renal (60%), partially metabolized (40%) to inactive products	Dose reduction by 50–75% when $C_{cr} < 10$ ml/min	Sedation, xerostomia, constipation, impotence, hallucinations, rebound hypertension
Guanabenz	4–32 mg bid	Metabolism (99%)	None	Sedation, xerostomia, depression, impotence, rebound hypertension

gastrointestinal tract, although there is considerable intra-individual variation in bioavailability [132]. Peak plasma levels are obtained within about 2 h of oral ingestion. Conjugation of methyldopa to its mono-O-sulfate derivative and other metabolites occurs extensively in liver and intestinal mucosa. Urinary excretion products include the parent compound and its conjugates [133]. Curiously, neither methylnorepinephrine nor its immediate precursor methyldopamine have been found in the urine. The plasma half-life of methyldopa, which is 1.8 h in normal subjects, doubles in the setting of severe renal insufficiency [132]. Hence, the dosage of methyldopa often needs to be decreased in patients with renal or hepatic disease (Table 9). The ordinary dose interval which is 6–12 h, may need to be increased to 12–24 h in the setting of moderate to severe renal dysfunction.

Methyldopa is also available in a parenteral form. This may be administered in the same total daily dose as the oral form in 4 to 6 divided doses by the intravenous route. The onset of action, 1–3 h, is somewhat faster than when the drug is given by mouth. The major indications for parenteral methyldopa is the setting where oral administration and absorption of drugs is not possible (e.g., post-operative state, altered consciousness).

Clonidine

Sites of action

Clonidine is an imidazoline compound with direct alpha-adrenergic action. In a manner probably analogous to that of methyldopa clonidine acts as an agonist of central alpha-2 receptors in the medullary brainstem vasomotor centers [134]. The resultant attenuation of sympathetic nervous outflow produces a reduction in peripheral vascular resistance. The antihypertensive action of clonidine may be amplified by suppression of adrenergically-mediated renin release [131]. Clonidine also has postsynaptic alpha-1 receptor agonism in the peripheral circulation; at high dosage, this may produce a pressor effect [136]. In contrast, at very low doses (0.05 mg orally) a direct vasodilator effect can be seen that may be a function of the drug's binding to presynaptic alpha-2 receptors, thereby producing a negative feedback on neurotransmitter (norepinephrine) release at sympathetic nerve terminals [137].

Effects on renal function

The systemic hemodynamic effects of clonidine result in a moderate fall in total peripheral resistance (especially in the upright position) and a mild decrease in heart rate and cardiac output. Simultaneously, renovascular resistance falls by 15–30%, in parallel with comparable systemic vascular changes [138].

Most studies have shown that renal blood flow and glomerular filtration remain unchanged during acute or chronic oral clonidine therapy [139]. This seems to hold true regardless of the status of pretreatment renal function. There is a tendency among patients taking clonidine, both with and without renal impairment, to show a small degree of salt and water retention and slight weight gain [140]. Clinically obvious edema is uncommon. The mild antinatriuretic effect of clonidine has been attributed to reduced renal perfusion pressure and consequent promotion of proximal tubular reabsorption of sodium. Thus, clonidine does not seem to adversely effect renal function although diuretic therapy may be required for optimal therapeutic effect.

Adverse effects

Side effects commonly associated with clonidine therapy include sedation, dryness of the mouth and eyes, and constipation [141] (Table 9). To some extent these symptoms may be lessened with continued therapy. Disturbance in male sexual potency [142], severe depression, hallucinations [143], and orthostatic hypotension may occur in less than 10% of patients who take clonidine.

There are a number of reported cases of patients who, upon abrupt withdrawal from clonidine, have presented with a clinical syndrome similar to pheochromocytoma [131]. Rebound, accelerated hypertension may be accompanied by anxiety, headache, tachycardia, tremulousness, and insomnia. Urinary catecholamine excretion may be increased. This syndrome of catecholamine excess is best treated by reinstitution of clonidine or by alpha-blockade with phentolamine. The use of beta-blockers in such a setting, although tempting, is probably contra-indicated. Rebound hypertension upon cessation of clonidine may actually be more likely to occur in the presence of concomitant beta-blocker therapy, presumably due to enhancement of 'unopposed' alpha-adrenergic tone.

Pharmacokinetic considerations

Approximately 75% of orally ingested clonidine enters the circulation, mostly within 30 min [144]. This high degree of bioavailability indicates the absence of any major first-pass phenomenon. Bioavailability does not seem to be affected by renal impairment. Clonidine is highly lipid soluble and moderately bound to plasma proteins, resulting in a high volume of distribution (3–6 l/kg) [144].

Metabolism of clonidine involves either cleavage of the imidazoline ring or hydroxylation of the aromatic ring [144]. None of the resultant metabolites have been found to have significant pharmacologic activity. In man, clonidine is eliminated in the urine mostly (50–60%) in the unchanged form. The plasma half-life varies from 6 to 23 h in normal individuals, but

may increase to as much as 48 h in end-stage renal failure [144]. Thus, it is advised that a reduction in dose of up to 50–75% will be necessary when glomerular filtration rate falls below 10 ml/min (Table 9).

It should also be noted that there are several reports in which the antihypertensive effect of clonidine has been antagonized by the concurrent use of tricyclic antidepressants [145] or the H-2 receptor blocker metiomide [146].

Clonidine has been found to be quite effective when administered in combination with diuretics to patients with varying degrees of renal insufficiency [147]. For most patients a significant hypotensive effect will be achieved in the dose range of 0.2 to 0.8 mg per day in two or three divided doses. The maximum recommended dose is 2.4 mg/day for patients with normal renal function. In the presence of moderate to severe renal dysfunction the prolonged clonidine half-life may result in adverse pharmacologic or toxic side effects. Caution should be exercised in such patients at all dose levels of clonidine, but especially at doses exceeding 1.0 mg/day.

Guanabenz

Sites of action

Guanabenz is an aminoguanidine derivative which, like clonidine, has a direct alpha-adrenergic effect. Also like clonidine as well as methyldopa, its predominant mode of action is probably by selective binding to alpha-2 receptors of the vasomotor centers located in the medullary brainstem [148]. The resulting effect is a reduction in centrally-mediated, peripheral sympathetic nerve traffic. When administered parenterally, guanabenz may produce a transient pressor response due to direct peripheral alpha-adrenergic mediated vasoconstriction. This effect has not been seen following oral administration. The antihypertensive action of guanabenz may be contributed to by a modest reduction in renal renin release.

Effects on renal function

Observations following an initial single dose of guanabenz show a 20% parallel reduction in renal plasma flow and glomerular filtration rate coincident with the acute depressor response [149]. This adverse effect is apparently not sustained; several studies have shown that chronic therapy for 1 week or longer is associated with no changes in renal blood flow or filtration rate. While net sodium balance is not measurably altered, a slight (10%) increase in plasma volume has been observed during chronic therapy. Whole animal and *in vitro* studies have suggested that guanabenz may centrally inhibit vasopressin release as well as antagonize its effect at the cellular level in the kidney [150]. The implications, if any, for water metabolism

in man have yet to be elucidated. Moreover, there is little or no information available to allow an assessment of the effects of guanabenz on renal function in the setting of kidney disease.

Adverse effects

Reported side effects [151] of guananbenz are, as expected, similar to those of other centrally active antihypertensive agents, especially clonidine (Table 9). These consist of drowsiness, dry mouth and mild depression. Orthostatic hypotension and sexual dysfunction have been reported but may be less common. The syndrome of catecholamine-excess rebound hypertension has also been associated with abrupt withdrawal of this drug [131]. Guanabenz reportedly produces less salt and fluid retention than either methyldopa or clonidine [146], but this finding needs to be confirmed.

Pharmacokinetics

Guanabenz is almost completely absorbed from the gastrointestinal tract. However, extensive first-pass hepatic metabolism occurs, thereby decreasing bioavailability of this agent [152]. Less than 1% of the drug is excreted in the urine unchanged. The major oxidative metabolites include parahydroxy guanabenz and its glucuronide conjugate [152]. The parent drug is 90% bound to plasma protein and is highly lipid soluble. The onset of the antihypertensive action of guanabenz begins within about 1 h of a single oral dose, reaching a peak effect within 2 to 4 h [153].

The usual dose is 4 to 32 mg orally at 12-h intervals. Since elimination of guanabenz is predominantly through extrarenal metabolism, it is probable that little or no dose adjustment is necessary for patients with renal insufficiency (Table 9). It should be emphasized that the effects of renal impairment on guanabenz pharmacokinetics have not yet been adequately studied. Furthermore, we do not yet know what the effects of guanabenz are on kidney function when renal insufficiency is already present. Thus, in the setting of renal disease, it should be advised that guanabenz be used with particular caution, at least until more information is available.

Neuronal uptake inhibitors

Reserpine

Reserpine is the most commonly utilized derivative of the Rauwolfia alkaloids. This agent has been employed successfully for over three decades for the management of mild to moderate hypertension. However, its use has decreased because of newer agents that are more effective and possess more favorable side effect profiles. In current therapy, the drug is basically a

'step-2' drug, and is most often used concomitantly with other antihypertensives [35].

This synergistic effect is evidenced by the fact that using reserpine with another drug allows an overall dose reduction of both agents thereby maximizing therapy and reducing adverse effects. Reserpine efficacy has been shown to be particularly enhanced when used with a diuretic. In this manner the diuretic will prevent or minimize both sodium and fluid retention, and the resulting tolerance associated with prolonged reserpine administration [35].

Mechanism of action

Reserpine selectively inhibits the sympathetic nervous system by depleting the body's stores of norepinephrine, both peripherally and in the central nervous system. The precise mechinism of action is, as yet, unclear. On a cellular level, the drug probably acts in the area of the catecholamine storage vesicles in adrenergic neurons. Reserpine has been shown to be active on many organ systems, particularly depleting norepinephrine from postganglionic adrenergic neurons, and also serotonin and dopamine in the brain. The mechanism of catecholamine depletion is probably two-fold. Firstly, reserpine inhibits norepinephrine re-uptake at the nerve ending, thereby increasing its exposure to and subsequent metabolism by monoamine oxidase. Secondly, reserpine may also interfere with the synthesis of norepinephine by blocking vesicular uptake of its precursor, dopamine [35, 154].

It is important to note that overall central sympathetic outflow is not significantly reduced. The antihypertensive effect of reserpine is therefore primarily mediated by peripheral rather than central adrenergic blockade. The degree of sympathetic blockade is related to the amount of catecholamine depletion that has occurred at any point in the course of therapy [35].

Upon initiation of treatment with reserpine, particularly with large parenteral doses, there may be a transient sympathomimetic response. With continued use, there is gradual reduction in total peripheral resistance and blood pressure often accompanied by bradycardia. There is also a subsequent reduction in preload and a decrease in cardiac output. Cardiovascular reflexes are only slightly blunted with usual oral dosage regimens. Over long-term therapy, cardiac output returns to pretreatment levels with total peripheral resistance remaining reduced [154].

Effects on renal function

In the early stages of treatment, reserpine has been shown to decrease renal blood flow and glomerular filtration rate. With chronic therapy, these parameters return to pretreatment levels. In addition, the use of reserpine is associated with a suppression in renin release [37].

Adverse effects

The most frequently encountered adverse effects are excessive sedation, bradycardia, nasal congestion, and occasionally impotence and diarrhea. It is important to note that these effects are dose-related and are generally mild in nature. The sedative component is due to norepinephrine, serotonin, and dopamine depletion in the brain. Patients may also complain of nightmares, another result of drug effects on the brain [150, 151].

Bradycardia is due to myocardial catecholomine depletion. In some susceptible patients symptoms of congestive heart failure may be precipitated. This is of particular concern, especially in light of the fluid retaining properties of reserpine. Other reported cardiovascular effects include angina-like symptoms and arrythmias, particularly with concomitant administration of cardiac glycosides, quinidine, or procainamide [35, 154].

Potentially serious adverse effects are mental depression, activation of peptic ulcer, and Parkinsonism. The use of reserpine is contra-indicated in any patient having these as underlying disorders prior to treatment. The occurrence of depression is directly related to drug effects on the brain. This effect may occur in any patient being treated with reserpine, but the incidence is greater if there is a history of mental depression. The symptoms can be serious enough to warrant hospitalization and the patient should be protected against possible suicide attempts. Unfortunately, the symptoms of depression may begin to arise slowly and are sometimes not detected. Onset is variable, with most reactions occurring 2 to 8 months into therapy. This syndrome is cause to discontinue the drug, but symptoms will persist for several months thereafter [154].

Gastrointestinal adverse effects are due to increased parasympathetic activity resulting from adrenergic inhibition. As a result, reserpine can cause excessive secretion of stomach acid and subsequent peptic ulcer disease. This is generally not a significant problem when usual dosages are administered. The situation can become serious, however, at high dosages or in patients with underlying gastrointestinal disease [35, 155].

Extremely large doses of reserpine can also produce a Parkinsonian-like syndrome as well as other extrapyramidal reactions. Should this occur, it may be best to discontinue therapy, at least temporarily, to allow the symptoms to abate [154].

Recently, attention has been focused on reports linking the prolonged use of reserpine with an increased incidence of breast cancer. Those studies have not been confirmed, and current opinion is that a relationship cannot be demonstrated between reserpine use and breast cancer [35, 156].

Pharmacokinetics

Limited information is available about reserpine pharmacokinetics in humans. Oral absorption occurs readily, but is incomplete, with only about

40% bioavailability. The drug appears to have a biphasic distribution profile, with the initial phase lasting about 4 h. This requires further investigation, but the drug does move rapidly from the circulation to distribute into most organ systems [35, 157].

Onset of effects after oral dosing may take a few days to weeks, although peak blood levels are observed within 1 to 3 h. Onset of effect following parenteral administration is 1 to 3 h [157].

The duration of action is 1 to 6 weeks following discontinuation of an oral regimen, and 4 to 12 h following parenteral. Therapeutic and toxic blood level parameters have not been established [30, 157].

Reserpine is extensively metabolized in the liver via hydrolysis and demethylation. Currently, the metabolite profiles are still incomplete. The excretion of drug has been shown to be slowed in patients with impaired renal function. The normal half-life ranges from 50 to 100 h, and increases in those having renal dysfunction. A significant increase in half-life is only seen in cases where there is a creatinine clearance of less than 10 ml/min. Because it is as yet unclear what the ramifications are at the clinical level, there are no formal dosing recommendations in patients with renal failure. Patients should be titrated slowly to clinical effect and observed closely for signs of toxicity [35, 157, 158].

Guanethidine

Guanethidine is primarily used in the treatment of severe hypertension. It is usually reserved for those cases that are resistant to treatment with less potent antihypertensives [159]. Guanethidine is also effective in renal hypertension secondary to pyelonephritis, renal amyloidosis, and renal artery stenosis [159]. Its concomitant use with other agents permits overall dose reductions so that some patients may be able to obtain maximal synergistic effects with tolerable side effect profiles. Guanethidine is most effective when used with a diuretic. This permits the utilization of a lower dosage range, controls sodium and fluid retention, and prevents tolerance from developing [159].

Sites of action

Guanethidine is a postganglionic adrenergic blocking agent that produces a selective block of peripheral sympathetic pathways [160]. The drug is concentrated in the neurosecretory granules of the post-ganglionic sympathetic nerve endings. Guanethidine acts to deplete norepinephrine stores from the granules and also blocks norepinephrine release in response to sympathetic stimulation [160]. The end result is that there is a gradual reduction in blood pressure with an associated bradycardia and decreased pulse pressure.

Guanethidine has also been shown to decrease systolic pressure to a greater extent than diastolic pressure [159]. In most cases, total peripheral resistance is unchanged or only slightly decreased. Vasodilation of the venous bed will cause a decrease in preload with a subsequent decrease in cardiac output [159]. Unfortunately, guanethidine also blunts positional cardiovascular reflexes, which causes problems with postural and post-exercise hypotension.

Effects on renal function

Guanethidine effects on renal function are unclear. Apparently the drug can produce variable effects on renal blood flow and glomerular filtration rate [159]. These functions are either unchanged or decreased slightly, but the overall effect is usually clinically insignificant. Progression to azotemia or oliguria has not been found to occur in the absence of severely compromised renal function prior to therapy. Significant changes, if they do occur, correspond to the acute treatment phase and not with chronic therapy. During the period where there is a marked reduction in blood pressure, the slight reduction in renal vascular resistance that occurs may be insufficient to maintain renal blood flow and glomerular filtration. As such, guanethidine may compromise renal function when renal function is already impaired and should therefore be used with caution. No definitive recommendations are available regarding specific dose modifications.

Plasma renin activity has not been shown to be decreased with guanethidine therapy. In some patients with decreased plasma renin, the drug has actually been shown to increase renin secretion to within the normal range [161]. Guanethidine has been shown to cause sodium and water retention with a subsequent increase in plasma volume [161]. Eventually, a form of tolerance can therefore develop to its antihypertensive effects.

Adverse effects

The adverse effects associated with guanethidine are primarily related to excessive sympathetic blockade or parasympathetic override. The most common side effects include bradycardia, dizziness, weakness, and syncope [159]. Patients may also complain of diarrhea, nasal congestion and sexual dysfunction.

Syncope is a significant problem associated with guanethidine and is related to postural and post-exercise hypotension [159]. A warm environment may aggravate this situation. Patients should be warned against rapid changes in position as well as overexertion. Dosages should be slowly titrated to the patients level of tolerance. Because of increased parasympathetic effect, patients may also experience an increase in the number of bowel movements and incidence of diarrhea [159]. The most likely time of occurrence is frequently after a meal. In some cases, it may be necessary to

give the patient small doses of anticholinergic or gastrointestinal antispasmodics. If the patient complains of severe diarrhea, it may be wise to discontinue the drug.

Sexual dysfunction may occur [160]. The chief complaints are frequently retrograde ejaculation, although some may complain of impotence. This is a significant problem in a large percentage of males taking the drug and is often intolerable.

As with other non-diuretic antihypertensives, sodium and fluid retention are a common problem [161]. The combination of an increased plasma volume as well as possible bradycardia can worsen congestive heart failure in susceptible patients. Some individuals will demonstrate edema, increased weight, as well as dyspnea. As noted, when the plasma volume expands there maybe a gradual tolerance that develops to the effects of guanethidine. It is therefore recommended that the drug be administered with a diuretic. In this manner, the efficacy of guanethidine is enhanced and plasma volume expansion is controlled.

Pharmacokinetics

Guanethidine is incompletely absorbed from the gastrointestinal tract and undergoes a significant first-pass effect [162]. Anywhere from 3 to 50% of an oral dose will eventually appear in the systemic circulation, with a large degree of interpatient variation. Following oral administration, catecholamine depletion occurs very slowly, and blood pressure falls gradually. The degree of overall adrenergic blockade is directly related to plasma concentrations of guanethidine, however accurate therapeutic blood level ranges have not been established. Available information indicates that plasma levels of 8–17 nanograms per ml are associated with effective adrenergic blockade [162]. Maximum effects of the drug occur after 1 to 3 weeks of administration if no loading dose is given; initial response can be detected in as soon as 3 days. It is important to note that differences in dosage responses may be due to patient specific pharmacokinetic variables, in absorption, distribution, metabolism and excretion.

Because of its slow onset of action, attention has been focused on the administration of loading doses in an attempt to decrease blood pressure in a few days time [162]. Smaller maintenance doses would be given to control pressure in the later portion of therapy. If this regimen is utilized, the patient must be monitored closely in the hospital setting for desired clinical as well as adverse effects.

Guanethidine has a half-life of approximately 5 days, and is partially metabolized in the liver [162]. Approximately 50% is excreted unchanged in the urine. A small amount appears in the feces. Both drug and metabolites are excreted by the kidney via glomerular filtration and tubular secretion [162].

Because of the long half-life of the drug, it can be administered once daily [162]. A period of approximately 15 days is required for steady-state to be achieved following any dosage adjustment. Upon discontinuation of guanethidine, the antihypertensive effects persist for 3 to 4 days and then diminish to pre-treatment conditions in 1 to 3 weeks. The therapeutic effect of guanethidine can be antagonized by tricyclic antidepressants and chlorpromazine [160].

Therapeutic use

As noted, because of the high incidence of significant adverse effects, guanethidine is generally held in reserve for patients resistant to almost all other antihypertensive agents. If the drug is to be used, it should be started in small dosage, e.g., 10 mg once daily and gradually increased at 1-week intervals until an adequate level of blood pressure control is achieved. The usual dose required is 20 to 50 mg once daily but may be increased to as much as 100 mg if needed and tolerated [163]. Patients should be checked frequently for orthostatic hypotension. It is prudent to have the patient or a member of the family monitor the blood pressure at home in the sitting and standing position. In most patients a diuretic will prevent or ameliorate any tendency toward tolerance to the antihypertensive effect of guanethidine.

Renin antagonists

Captopril

Mechanisms of action

Captopril (D-3 mercapto-2methylpropanoyl-L-proline) is an orally-active inhibitor of kininase II (angiotensin converting enzyme) [164]. Converting enzyme catalyzes the cleavage of dipeptides from the carboxy-terminal end of small, noncyclic polypeptide molecules. It is responsible for the conversion of the inactive decapeptide angiotensin I to the biologically active octapeptide angiotensin II. Angiotensin II is a potent arteriolar vasoconstrictor and is the major secretagogue for the synthesis and release of aldosterone by the adrenal zona glomerulosa.

The mechanism of the antihypertensive action of captopril is undoubtedly somewhat more complex than originally conceived. Captopril's target enzyme, kininase, derives its name from its role in the degradation of the vasodepressor nonapeptide bradykinin. Thus, an effect of kininase inhibition is to elevate levels of the vasodilator bradykinin, thereby contributing to the antihypertensive action of the drug [165]. Several lines of evidence suggest that elevated levels of the vasodilatory prostaglandin E_2 may also partially mediate the vasodepressor action of captopril [166].

Although the antihypertensive effect of captopril probably involves enhanced production of vasodilators, the weight of evidence favors the concept that the drug's antihypertensive action is primarily the result of inhibition of angiotensin II formation [167]. Angiotensin-induced direct vasoconstriction of the renal and peripheral circulation, central nervous system effects, stimulation of both adrenal medullary release of epinephrine, and adrenal cortical synthesis and release of aldosterone are mechanisms that may all contribute to the generation and maintenance of hypertension [168]. It is likely that the precise mode of blood pressure reduction by captopril in individual patients may depend on the tissue site at which angiotensin II is predominantly acting.

In the absence of heart failure, captopril lowers total peripheral resistance of hypertensives while producing little change in heart rate, cardiac output or pulmonary wedge pressure [169]. The latter two hemodynamic parameters are often improved by captopril when cardiac failure is present [170]. Captopril produces little or no tachycardiac response, which is unusual for a vasodilating drug; this may be a result of venodilation or elevation of bradykinin levels.

Adverse effects (Table 10)

The most common adverse effects of captopril reported to date have been dermatologic reactions [171]. These include morbilliform or maculopapular rashes that have been observed in about 10% of patients. Less common has been the development of angioedema of the face and mucus membranes and, rarely, aphthous stomatitis. Any of these symptoms may be accompanied by fever or eosinophilia. Generally, cutaneous reactions, when they occur, have appeared within the first month of therapy. Occasionally, such reactions have improved in spite of continuation of captopril, although temporary reduction of dosage or discontinuation of the drug is often necessary.

Altered gustatory sensation [167] is a curious effect of captopril that occurs in about 6% of patients. This may take the form of an unusual and persistant 'salty' taste or, more commonly, a reduction or complete loss of all taste sensation. Rarely, ageusia has heralded the onset of severe aphthous stomatitis. Approximately half of all patients who develop taste disturbances will require discontinuation of captopril.

A very uncommon but potentially serious complication of captopril therapy has been the development of neutropenia [23]. This has been reported in less than 0.3% of patients taking the drug, almost always in the first 3 months of treatment. Rarely, agranulocytosis has occurred. There have been several deaths recorded worldwide in patients receiving captopril who had developed severe neutropenia. Almost all of the reported cases of neutropenia have occurred in patients with either renal insufficiency, collagen-vascu-

lar disease or immunosuppressive/cytotoxic therapy. In the absence of one of these conditions, the incidence of captopril-associated neutropenia is quite rare; frequent monitoring of blood counts is usually not necessary.

Renal effects

In essential hypertension captopril acts as a renal vasodilator thereby enhancing renal blood flow. This is especially evident in patients on a salt-restricted diet. Glomerular filtration rate is usually unaffected by captopril but may actually rise somewhat in hypertensive patients with mild renal insufficiency [172].

Table 10. Adverse effects associated with captopril

1. Dermatologic (10%)
   a. Maculopapular rash
   b. Angioedema
   c. Aphthous stomatitis
2. Gustatory (6%)
   a. Loss of taste
   b. Abnormal taste – salty or metallic
3. Gastrointestinal (5%)
   a. Dyspepsia
   b. Diarrhea
4. Renal disturbances (2%)
   a. 'First-dose' effect
   b. Proteinuria/glomerulopathy with chronic therapy
   c. Reversible renal impairment associated with bilateral renovascular disease or renovascular involvement of a sole kidney or allograft
   d. Allergic interstitial nephritis
5. Neutropenia (< 1%)

Table 11. Abrupt hypotensive response to captopril

1. Onset 60–120 min after first dose
2. Predisposing factors
   a. Renin-dependent hypertension
   b. Plasma volume depletion
   c. Diuretic therapy
3. Prevention
   a. Discontinue diuretic at least 1 week before initiating captopril therapy
   b. Appropriate dose reduction for degree of renal impairment (see Table 12)
4. Therapy
   a. Place patient in Trendelenburg position
   b. Intravenous fluids

There are several distinct adverse reactions involving kidney function that may be incurred during captopril therapy (Table 10). The most common of these is acute renal insufficiency that may occur as a result of excessive reduction in systemic blood pressure (Table 11). This 'first-dose effect' is most likely to result when the initial dose of captopril is administered to volume-depleted patients [173]. It can be prevented by avoidance of diuretics during the preceding week and careful blood pressure monitoring of all patients for several hours following the first dose of captopril. Should hypotension ensue, it can be quickly reversed by placement of the patient in Trendelenburg position and institution of intravenous fluid therapy. Renal insufficiency that does occur is generally mild and easily reversible with hydration therapy. Nevertheless, there have been a few patients who, as a result of this first-dose effect in the setting of malignant hypertension, have progressed to severe renal dysfunction necessitating institution of dialytic therapy.

Proteinuria of greater than 1 g per day has been found in approximately 2% of patients taking captopril [174]. Nephrotic range proteinuria (> 3 g per day) occurs in one fourth of these patients. Most cases have occurred between 3 and 12 months of therapy and are more frequent in patients with pre-existing renal disease. Renal histopathologic studies have usually demonstrated the presence of an epimembranous type of glomerulopathy. In some cases, proteinuria has subsided despite continued treatment with captopril; however, cessation of therapy has usually been found necessary. The mechanism of this disorder is unknown, although it closely resembles, clinically and histologically, other drug-induced glomerulopathies such as those caused by penicillamine and gold.

A third renal disorder associated with captopril therapy is that of acute reversible functional deterioration that may occur in the absence of an apparent major reduction in systemic blood pressure. This complication may arise days, weeks or months after initiation of captopril therapy. There are a few cases in which this has taken the form of an acute allergic interstitial nephritis as manifested by fever, skin rash or eosinophilia [175]. Also, as of this writing there have been a number of published cases worldwide of patients without signs of an allergic reaction who have experienced acute delayed-onset deterioration in renal function that reverses or improves upon discontinuation of captopril [176].

All of the reported cases have been in the setting of either bilateral renal artery stenosis, arterial stenosis in a solitary kidney, or vascular stenosis at the anastomotic site of a renal allograft. Patients with two functioning kidneys and unilateral renal vascular disease do not yet appear to be susceptible to this complication. The mechanism is poorly understood, but probably multifactorial. There has been speculation that this syndrome may be a product of captopril-induced systemic and renal hemodynamic changes

occurring in the setting of impairment of glomerular autoregulatory function.

Pharmacokinetics

In the fasting state, approximately 75% of orally administered captopril enters the plasma [177]. This is reduced by 35% if the drug is ingested in the non-fasting state; it is therefore recommended that captopril be taken at least 1 h before or 2 h after meals [167]. The drug is about 30% plasma protein bound and is distributed rapidly in most tissues except the central nervous system.

Slightly more than half of an absorbed dose of captopril is oxidized at the sulphydryl group to form disulfides bound to endogenous thiol compounds [178]. The unmetabolized portion of captopril is excreted rapidly in the urine. The elimination half-life of captopril and its metabolites is markedly increased in patients with moderate-to-severe renal insufficiency. As a result the dosage will usually have to be reduced in the presence of significant renal impairment [179] (Table 12).

Clinical use

Captopril has been shown to be an effective blood pressure reducing agent in almost all forms of clinical hypertension including essential, malignant, renal parenchymal and renovascular hypertension. Because of the relatively high retail price of captopril (approximately 1 cent per milligram) it should usually be reserved for patients in whom the combination of diuretic plus adrenergic-inhibitor is ineffective, contra-indicated or poorly tolerated. In the majority of patients with renal parenchymal disease, a diuretic will need to be administered along with captopril to obtain optimum blood pressure control. Because of the first-dose effect and the possibility of achieving effective monotherapy it is usually advisable to, at least temporarily, discontinue diuretics for at least 1 week prior to initiating captopril treatment.

Table 12. Dosage adjustment of captopril in patients with renal dysfunction

Creatinine clearance (ml/min/1.73 m^2)	Dosage interval [a] (hours)	Total daily dose [b] (mg)
>75	8	75
75–53	12	50
34–20	12–24	25–50
19–8	24–48	12.5–25
<7	48–72	12.5–25

[a] Initial dose 25 mg by mouth.

[b] Increase total daily dosage according to patient response at 2-week intervals.

Each patient should be monitored closely for the first 2 h after initiating therapy with the drug. A common pitfall is the tendency for a too-rapid increase in the dosage of captopril early in therapy. It should be emphasized that the maximum effect of the drug is often not achieved in less than 2 weeks. Laragh and co-workers [180] have carefully documented the existence of a triphasic response in which an initially brisk hypotensive response to captopril is followed by a period of temporary resistance to the drug that may last several days to several weeks. This is followed by the third phase in which there is a return of drug responsiveness. The starting dose of captopril should be chosen along the guidelines in Table 12, and subsequently titrated at biweekly intervals according to the patient's response. It is best to avoid the temptation of increasing the dose any more frequently than once every 2 weeks. This is particularly salient in patients with renal insufficiency, in whom long-term dosage requirements may actually be small while the risk of dose-related toxicities may be greater than normal.

Patients in whom blood pressure control is suboptimal with captopril monotherapy at 150 mg per day will often benefit from the synergistic effect of diuretic therapy. For patients with moderate to severe renal impairment, therapy with a loop-acting diuretic will usually be indicated.

Enalapril

Enalapril (MK-421) is a non-sulphydryl-containing compound with potent converting enzyme inhibitory action. Its structure is that of a carboxymethoxdipeptide (N-(1-S-carbethoxy-3-phenylpropyl)-S-alanyl-S-proline) [181]. Inhibition of converting enzyme produces a lowering of angiotensin II and aldosterone levels, so that patients in whom these factors are pathogenetically important may have a particularly good response to the drug.

Enalapril is orally absorbed and converted by esterases to its active diacid form (MK-422) [182]. Converting enzyme inhibition occurs at relatively lower doses than with captopril. The duration of action is also more prolonged, allowing once or twice daily administration in patients with normal renal function. The effect of renal insufficiency on drug elimination has not yet been adequately evaluated, necessitating caution in its use in this setting. Preliminary results suggest that enalapril is relatively free of side effects such as skin rash, taste disturbance, leukopenia and proteinuria, all of which have been associated with captopril therapy. It is probably too early for a determination of enalopril's potential for nephrotoxicity. Even if the drug is free of glomerulopathic effects, there will likely be some risk of renal functional changes occurring as a result of systemic or intrarenal hemodynamic actions of enalapril.

Preliminary data indicates that the antihypertensive effect of enalapril, like that of captopril, is enhanced by diuretic administration [183]. This is likely to prove to be the case in patients with renal insufficiency, so that concomitant therapy with a loop-acting diuretic will probably be often required for maximum effect of the drug. The dosage requirements for enalopril in patients with renal impairment have not yet been determined.

Saralasin

Saralasin, 1-sarcosine-8-alanine angiotensin II, is an octapeptide that acts as a competitive antagonist of angiotensin II at vascular and adrenal binding sites [184]. Patients with high circulating levels of angiotensin II, as in renin-dependent forms of hypertension will have a depressor response to saralasin. The drug has been developed for use as a diagnostic tool in the detection of renin-dependent (e.g., renovascular) hypertension [185]. The saralasin test is performed by observing the blood pressure response when the drug is administered to patients who have been sodium depleted with furosemide prior to the study. A significant drop in blood pressure aids in the identification of patients in whom angiotensin II is the major cause of hypertension.

There are several drawbacks to the use of this drug as a therapeutic agent. Because saralasin is a peptide it must be given by a parenteral route and is therefore not suitable for outpatient use. Also, saralasin posseses slight agonistic activity at the vascular receptor sites, such that when angiotensin II levels are low a pressor response to the drug may occur [186].

As an intravenous agent, saralasin may prove to be a useful therapeutic agent in the management of malignant hypertension. Patients with this disorder often have a major renin component to their hypertension state, and may not be able to receive oral therapy because of impaired neurologic status. Saralasin may be an effective form of treatment, particularly when nitroprusside is contraindicated or ineffective. As in patients with malignant hypertension who are given captopril, there may be some danger of acute renal insult if the depressor response is too profound.

Saralasin, like angiotensin II, is rapidly metabolized, with a half-life of approximately 6 min [187]. It is best administered by increasing titrated infusion, starting with 0.05 μg/kg/min for the first 10 min. The dosage may be next increased to 5 μg/kg/min and subsequently doubled every 10 min to a maximum of 20 μg/kg/min. At present, the only known limiting factor in continued intravenous infusion is the expense.

Vasodilators

Hydralazine

Mechanism of action

Hydralazine's antihypertensive action is mediated via direct relaxation of arteriolar smooth muscle. In this manner the drug acts to cause vasodilation of arteriolar resistance vessels, with little or no effect on the venous side. The precise cellular mechanism by which this occurs is not clear but may be related to hydralazine's ability to bind with calcium or other trace metals which may be necessary for vascular smooth muscle contraction [188–190].

Hydralazine generally has a greater depressor effect on diastolic than on systolic blood pressure. There is little orthostatic hypotension associated with hydralazine. While the drug has little or no direct effect on the myocardium, there is an accompanying increase in heart rate, cardiac output, and stroke volume. These changes are due to a reflex response to decreased total peripheral resistance, which is mediated by baroreceptor activated adrenergic cardiac stimulus [191]. The increase in cardiac output may blunt the hypotensive effects of hydralazine and is a major component of its side effect profile [190].

Effects on renal function

Glomerular filtration rate, renal tubular function, and urine volume are not predictably affected by hydralazine. While acute administration causes an increase in renal blood flow, this parameter returns to pretreatment status with chronic use. As a result there are no significant alterations in glomerular filtration rate. Hydralazine has been shown to increase plasma renin activity. This effect is probably mediated in part through a reflex sympathetic nervous system mechanism [37].

Hydralazine also causes sodium and fluid retention, with a resultant increase in plasma and extracellular fluid volumes. Tolerance to the effects of the drug may develop with prolonged administration. It is advisable to concomitantly administer a diuretic and a β-blocker with hydralazine in order to maintain therapeutic efficacy [37, 189].

Adverse effects

Most of the adverse effects associated with hydralazine use are due to its vasodilatory properties and reflex cardiovascular responses. Patients will complain of symptoms associated with reflex tachycardia, palpitations, headache, and flushing. In some patients there may be an aggravation of anginal symptoms. These effects are often minimized by the co-administra-

tion of a beta-blocker. Patients are also often distressed by annoyances such as nasal congestion and gastrointestinal disturbances [188–190].

More severe adverse effects that may warrant discontinuation of the drug include drug fever, rash, precipitation of angina or congestive heart failure in patients with underlying myocardial disease [189]. The incidence of hydralazine-induced angina is approximately 7% when the drug is used alone. By increasing cardiac output and heart rate, there is an increase in myocardial oxygen demand. The anginal symptoms can also be associated with EKG changes. The presence of ST segment depression and QRS complex and T wave changes is usually encountered with patients having underlying atherosclerotic heart disease [189, 190].

Hydralazine has also been shown to produce a syndrome similar to systemic lupus erythematosus [24, 26, 192]. While a majority of the cases are related to large dosages of the drug (above 400 mg/day), reports show that the syndrome can occur with patients receiving dosages as low as 75 mg per day. It is generally felt, however, that the incidence of this adverse effect increases with prolonged therapy with large doses over 200 mg per day. Patients who are slow acetylators of the drug are at greater risk than fast acetylators. Symptoms that may arise include polyarthralgias, fever, dermatitis, malaise, and pleuritic chest pain. Additional findings may include splenomegaly, lymphadenopathy, presence of antinuclear antibodies, leukopenia, and LE cells. Hydralazine should be discontinued in patients developing this syndrome unless the potential benefit outweighs the risk [192].

Pharmacokinetics

Hydralazine is rapidly and almost completely absorbed following an oral dose, with the given range being 50–90%. Acetylator phenotype has been shown to be a variable regarding bioavailability with slow acetylators demonstrating greater overall absorption than fast acetylators [193]. Following oral administration peak plasma levels of the drug and metabolites occur within 1 to 2 h. The hypotensive effect occurs within 30 min and has a duration of approximately 2 to 4 h. Following chronic dosing the duration of effect ranges from 30 to 140 h. Onset with intravenous use is within 5 to 15 min with a peak effect occurring in 10 min to 1 h. Plasma levels do correlate directly with hypotensive effect, however, specific therapeutic ranges have not been established [194, 195].

Hydralazine undergoes a significant first-pass effect. The drug is primarily metabolized in the liver via acetylation. This appears to be a capacity-limited saturable kinetic process. In terms of overall metabolic clearance, it appears that the acetylator phenotype has no effect on the pharmacokinetics of hydralazine following intravenous doses. In fact, oral bioavailability may be the major parameter affected by acetylator phenotype and not system clearance [193–195].

Therapeutic use in renal insufficiency

In patients with chronic renal failure, high plasma hydralazine levels have been noted. This accumulation effect may be due to decreased elimination of as yet unidentified metabolites. Current recommendations suggest that in patients with severe renal impairment, the hydralazine dosage interval should be increased to 8 to 16 h for fast acetylators and to 12 to 24 h for slow acetylators. However, it is important to note that there is no conclusive evidence regarding increased hydralazine toxicity in renal failure. Therefore, dosing adjustments may or may not be appropriate [194, 195].

Most commonly, hydralazine is used as a third line drug in combination with a diuretic and beta-blocker. The latter two types of drug are usually required since hydralazine is not very effective when used alone. Furthermore, the drug tends to produce fluid retention and tachycardia which can be nutigated by diuretics and beta-blockers respectively. The usual starting dose is 25 mg three or four times daily and may be advanced to a maximum of 300–400 mg per day.

Minoxidil

Site of action

Minoxidil is a piperidino-pyrimidine deriviative with unusually potent vasodilating properties [196]. The precise mode of action of minoxidil at the level of vascular smooth muscle is not yet well understood. The vasodilating action does not seem to be mediated through antagonism of any known humoral-receptor or neurosympathetic mechanism. The action of minoxidil, like that of diazoxide and hydralazine, is associated with interference with calcium uptake into the cell membrane of vascular smooth muscle [197]. Minoxidil-induced vasodilation is, also analogous to diazoxide and hydralazine, confined to the arteriolar resistance bed. This results in an augmentation of tissue blood flow, a fall in peripheral vascular resistance and a decrease in cardiac left ventricular afterload. The absence of a venodilatory effect results in an increase in cardiac preload. These hemodynamic effects combine to produce an increase in left ventricular stroke volume. Simultaneous stimulation of adrenergically-mediated reflexes produces an increase in heart rate, so that cardiac output is usually markedly enhanced [198].

Adverse effects

Minoxidil is probably the most consistently effective oral antihypertensive agent currently approved for use in the United States. Unfortunately, a number of side effects [199] have limited its use to patients with moderate to severe hypertension refractory to other therapies. Most frequent is that of

sodium and fluid retention. The degree and rapidity of onset of edema may be quite dramatic, with as much as 7 to 10 kg weight gain in less than a week occasionally reported. There does seem to be some correlation between the severity of this effect and dose of minoxidil, as well as the degree of renal impairment. The mechanism of this phenomenon is not well understood; it does not seem to be related to altered renal blood flow. Nor can fluid retention be attributed to renin-mediated hyperaldosteronism since levels of this hormone are usually normal during chronic therapy with minoxidil. It is conceivable that the drug has a direct effect on the renal tubule, or perhaps facilitates angiotensin-mediated redistribution of intrarenal blood flow from the outer cortex to more sodium-avid nephrons of the juxtamedullary cortex. All patients receiving minoxidil require the concomitant administration of loop-acting diuretics such as furosemide or bumetanide. Patients with renal impairment often require extremely high doses of these agents to control fluid retention. Refractoriness to high dose diuretics may, in some cases, be ameliorated with the addition of captopril. In patients with progressive renal insufficiency, dialytic therapy may be indicated for the control of edema. It is curious that even in stable anuric dialysis patients, interdialytic weight gain is often greater than normal in those receiving minoxidil.

Minoxidil produces tachycardia and palpitations due to reflex activation of the adrenergic nervous system [198]. Episodes of angina pectoris and myocardial infarction during treatment with minoxidil have been reported. These effects can be prevented by the simultaneous use of adrenergic inhibing drugs such as beta-blockers or clonidine. Electrocardiographic abnormalities [200] including ST segment depression and T wave flattening, especially in the lateral chest leads, have been seen in many patients receiving minoxidil.

Pericarditis [201], usually with effusion and occasionally with tamponade, has been described in 3–10% of minoxidil-treated patients. Most such patients have had some degree of renal impairment. Interestingly, pericardial effusions are often accompanied by serosal effusions in other sites, resulting in pleural, ascitic and joint effusions. Small to moderate-sized pericardial effusions may improve by reduced dosage or discontinuation of minoxidil, or by an increase in diuretic dosage. All patients receiving minoxidil should be examined regularly for these complications.

Hypertrichosis [202] occurs in the majority of patients treated with minoxidil for more than 6 weeks. This effect is quite distressing to females, since hair growth typically involves the forehead, temples, face, eyebrows, forearms and back. The mechanism is unknown, but does not seem to involve an endocrine imbalance since testosterone and other steroid levels remain normal. Increased cutaneous blood flow may play a role. Patients should be warned of this phenomenon in advance. For cosmetic purposes,

depilatory agents such as calcium thioglycolate may be used on a regular basis. The hypertrichosis is completely reversible within 1 to 2 months after discontinuation of minoxidil.

Effects on renal function

Studies of the effects of minoxidil on total renal blood flow in essential hypertension have given conflicting results [197] with increases, decrements or no change being variously reported. Renal vascular resistance either falls or remains stable. The effect of minoxidil on glomerular filtration rate seems to depend on the pretreatment status. Patients who present with malignant hypertension and azotemic renal insufficiency normally have a poor prognosis when convential medical therapy is employed. Minoxidil therapy has been reported to have a major beneficial effect on GFR in many of these patients resulting in substantial and long-lasting improvement in renal function [195]. The natural history of patients with benign hypertension and mild renal impairment is more difficult to predict. There does not, however, seem to be a clear cut effect of minoxidil on glomerular filtration in these patients in either the short or long-term.

Pharmacokinetics

More than 95% of an orally administered tablet of minoxidil is rapidly absorbed from the gastrointestinal tract [204]. Animal studies have shown extensive tissue binding of the drug by the arterial vasculature, resulting in a large volume of distribution (approximately 250 l). Metabolism of minoxidil to its glucuronide conjugate accounts for 90% of the drug's biotransformation. Subsequent excretion by the kidneys via filtration is responsible for final elimination of the drug [204]. Because the glucuronide derivative has slight antihypertensive activity it may occasionally be necessary to reduce the dosage of the drug in the setting of severe renal insufficiency [204].

Clinical use

Minoxidil is generally reserved for patients with severe, refractory hypertension. Many such patients have varying degrees of renal impairment, yet the drug is often quite effective in this setting. The usual starting dose is 2.5 mg, twice daily, increasing at weekly intervals to a maximum of 40 mg per day. When more rapid control of blood pressure is desired, minoxidil can be administered in progressively higher doses at 4-h intervals. For both acute and chronic therapy it will be necessary to concomitantly administer an adrenergic-inhibiting drug and a loop-acting diuretic for control of heart rate and fluid retention respectively.

Calcium channel blockers – nifedipine

Site of action

Nifedipine is the first of a series of new drugs commonly referred to as calcium channel blockers which are being marketed in the US for use in the treatment of cardiovascular disorders. Of this group of compounds, nifedipine appears to have the most promise as an antihypertensive agent because of its potent vasodilatory effect [205]. The precise mode of action at the cellular level of nifedipine has not yet been completely worked out. Electrophysiologic studies indicate that calcium channel blockers inhibit the transcellular movement of calcium ion thereby interfering with the normal excitation-contraction process [206].

Among the currently approved calcium channel blockers, nifedipine has the least myocardial depressant effect [207]. Its action is predominant in vascular smooth muscle, producing coronary and peripheral arteriolar dilitation. The hemodynamic effects are predictable and include decreases in peripheral resistance, mean arterial blood pressure, and left ventricular end diastolic pressure. Coronary and, presumably, other tissue blood flow is increased along with heart rate (reflex), cardiac output and plasma renin activity [208].

Adverse effects

The known side effects [209] associated with nifedipine administration are those commonly seen with other, less potent vasodilating substances. These include hypotension, headache, flushing and leg edema, all of which seem to occur infrequently. Treatment with nifedipine has been discontinued because of side effects in less than 5% of over 5,000 patients on chronic therapy [208]. Thus this drug appears to be very well tolerated and furthermore has not yet been found to cause alterations in renal, hepatic, pulmonary or hematopoietic function.

Pharmacokinetics

Nifedipine is rapidly and completely absorbed from the buccal and gastrointestinal mucosa. Its onset of action ranges from 3 min when administered sublingually to 20 min by the oral route. Nifedipine is approximately 90% protein bound in plasma. The main metabolic pathway consists of oxidation to a 'free acid', a small fraction of which is converted to a lactone [210]. Approximately 80% of these inactive metabolites are excreted by the kidneys with the balance eliminated by the gastrointestinal tract. At this time no information is available on the effects of renal impairment on nifedipine pharmacokinetics. Since the drug is extensively metabolized to inactive products, it seems likely that even severe renal insufficiency will have little impact on nifedipine dose requirements. Nevertheless, until there is data to

confirm this, the drug should be used cautiously in patients with any degree of renal impairment.

Clinical use

Nifedipine is not yet approved by the US Federal Drug Administration for use in the treatment of hypertension. Nevertheless, this agent is likely to evolve as an important therapeutic tool for the clinician treating patients with resistant hypertension and renal impairment. This is especially likely to be the case if the present safety record of nifedipine is sustained with more extensive clinical experience.

Nifedipine will probably find its niche as a so-called step 2 or 3 drug, to be utilized when diuretic therapy plus an adrenergic inhibitor are unsuccessful or poorly tolerated. Patients with angina may benefit from its coronary vasodilating action. The starting dose of nifedipine is 10 mg by mouth, three times daily. This may be increased to a maximum of 30 mg three times daily. Further increases in dosage are not likely to extend the drug's effect.

Nifedipine may also prove to be useful in hypertensive emergencies in which rapid reduction in blood pressure is thought to be beneficial. The drug may be administered sublingually as 10 mg doses, every 20–30 min until satisfactory improvement in blood pressure occurs [211].

Parenteral agents

Diazoxide

Diazoxide is a benzothiadiazine compound related in chemical structure to chlorthiazide [212]. The drug is a potent vasodilator, but, in contrast to the thiazides, does not have any diuretic effect. Its primary utility is in the management of severe and refractory hypertension, especially in patients with impaired renal function [213].

Mechanism of action

The hypotensive action of diazoxide is due to its vasodilator effect. The drug directly relaxes arteriolar tone, thereby reducing peripheral vascular resistance. This action occurs through a poorly understood inhibition of the vascular contractile mechanism. The vasodilating properties apparently do not involve alpha- or beta-adrenergic-1 receptor blockade [214, 215].

Studies have shown that diazoxide directly competes for calcium receptor sites in vascular smooth muscle. Interfering with calcium's ability to bind its membrane receptor presumably affects contractile-process activation [215].

In addition to receptor blockade, diazoxide may also deplete arterial muscle intracellular calcium or block its release [215].

Other research has suggested that the antihypertensive action of diazoxide may also be due to its effects on cyclic AMP. The drug has been shown to inhibit the activity of phosphodiesterase, the enzyme primarily responsible for degradation of cyclic AMP. Consequently, there are increased intracellular levels of cyclic AMP that may conceivably mediate the vasodilatory action of diazoxide [216].

Effects on renal function

The effects of diazoxide on renal hemodynamics have been studied in man and animals. Both oral and parenteral administration has been shown to decrease urine volume and electrolyte (sodium, potassium, chloride) excretion [217, 218]. The mechanism for the antinatriuretic effect of diazoxide is not clear but may represent a combination of direct action on the renal tubule and systemic or intrarenal hemodynamic alterations. Direct administration of diazoxide into the renal artery in dogs produces different results than those seen with the conventional intravenous and oral routes [217]. In this experimental model the effect is a prompt diuresis with enhanced sodium excretion. There is also evidence of an increase in creatinine clearance and glomerular filtration rate. These actions may also indicate a diazoxide-induced renal vasodilatory effect with consequent alterations in intrarenal hemodynamics [217].

Clinical investigation has shown that, following diazoxide administration, there is a marked reduction in the excretion of water, sodium, potassium, chloride, and bicarbonate. When hypotension is produced, there may be decreases in renal blood flow, glomerular filtration rate, and creatinine clearance [218].

Diazoxide has also been shown to increase plasma renin activity in some patients [219]. The mechanism behind this effect has been shown to be unrelated to changes in plasma volume, extracellular fluid, or sodium excretion. This may be a result of direct renal adrenergic receptor stimulation, or an indirect response to the hypotensive effect and catecholamine release.

Diazoxide with its potent vasodilatory effect produces a marked reduction in renal vascular resistance. Total renal blood flow is usually increased during diazoxide therapy. However, there have been reports of patients who, upon receiving an initial dose of diazoxide, have a profound hypotensive response with subsequent worsening of renal function. This is probably quite uncommon and is most likely to occur in patients who have previously received other antihypertensive therapy including diuretics. In the absence of serious hypotension, glomerular filtration rate is usually unchanged [220].

Diazoxide therapy is associated with a marked tendency toward salt and

fluid retention [220]. This is a frequently encountered effect of all potent vasodilators; it may be due to a combination of redistribution of intrarenal blood flow to deeper, more sodium avid nephrons, stimulation of aldosterone release and, perhaps, a direct tubular effect.

Adverse effects

The major adverse effects of diazoxide are those associated with the cardiovascular system. Because of its action as an arteriolar vasodilator excessive hypotension and reflex sympathetic stimulation can occur. When arteriolar pressure falls, baroreceptor response evokes cardiostimulation, with associated increases in heart rate, stroke volume, and cardiac output. Because of the increase in myocardial oxygen demand, the use of diazoxide can be potentially dangerous in patients with ischemic heart disease or infarction [221]. It has been demonstrated that as many as 50% of the patients receiving the drug in an emergency situation develop ST and T wave changes following diazoxide therapy [221]. Other common side effects with intravenous diazoxide include gastrointestinal discomfort, sodium and water retention, and irritation at the site of infusion. Postural hypotension has also been reported [222].

Diazoxide can also induce significant hyperglycemia. Proposed mechanisms for this effect include reflex increase in catecholamine levels, decreased glucose utilization, and inhibition of insulin release. The latter theory predominates as a significant effect of diazoxide in its ability to inhibit insulin secretion from pancreatic beta-cells [223]. It is important to note that the hyperglycemia is usually transient and rarely requires treatment with oral hypoglycemic agents or insulin. In patients with a history of diabetes, blood glucose levels should be monitored. In this group, it may become necessary to administer hypoglycemic agents to control fluxes in blood glucose. Failure to recognize and treat significant diazoxide-induced hyperglycemia may result in ketoacidosis or hyperglycemic hyperosmolar coma in predisposed individuals [223].

As noted earlier, diazoxide also causes significant sodium and water retention that could be deleterious in patients with hypertension complicated by congestive heart failure and pulmonary edema. Because of this problem, it is often recommended that diazoxide administration be accompanied by diuretic therapy [222] such as intravenous furosemide.

Pharmacokinetic considerations

The serum half-life of diazoxide has been reported to be increased with decreasing renal function. Dose reductions or increased dosage intervals may be required in patients with impaired renal function. Specific guidelines are currently unavailable [224]. Diazoxide's half-life ranges from 20–36 h but does not correlate well with duration of antihypertensive action.

The antihypertensive activity is approximately one-third as long as its half-life [224]. In patients with renal disease the plasma half-life has been reported to range from 20–53 h [224]. Diazoxide is very highly protein bound and it is felt that this is responsible for differences in response after varying rates of drug administration.

After rapid intravenous administration of the usual therapeutic dose of 300 mg, a redistribution phase of 10 min has been reported in patients with normal renal function [224]. In patients with renal failure redistribution phase lasts approximately 3 h. Plateau plasma concentrations at the end of the distribution period are similar for patients with normal and impaired renal function. However, the degree of protein binding has been shown to be significantly depressed in patients with impaired renal function at both low and high plasma drug concentrations. When kidney function is impaired, a greater degree of unbound drug would thereby cause an enhanced antihypertensive effect. As such, the antihypertensive effect of diazoxide following rapid intravenous injection is directly related to the severity of renal failure [224]. Therefore, in patients with severe renal insufficiency it may be prudent to initiate therapy with half the usual dose (150 mg, intravenously) and repeat every 20 min as necessary to achieve a satisfactory therapeutic result. Recently, a method of diazoxide administration by rapid loading followed by continuous infusion has also been shown to be effective [225].

Nitroprusside

Sodium nitroprusside is an effective vasodilator for the management of acute hypertensive emergencies, heart failure, and other vasoconstrictive states. The agent is given parenterally, is very potent, and has the potential for serious adverse effects; its use requires close patient monitoring. It is considered by many to be the agent of choice in the management of hypertensive emergencies [226].

The onset of effect is almost immediate following administration of the drug by intravenous infusion. The antihypertensive effect occurs only as long as the infusion is maintained and rapidly disappears when the drug is stopped [227].

Mechanisms of action

The antihypertensive effect of sodium nitroprusside is due to peripheral vasodilation as a result of direct action on vascular smooth muscle, causing relaxation of both arterial and venous systems. In usual therapeutic doses, the drug has been shown to have a specific affinity for vascular tissue, while having little or no effect on uterine or duodenal smooth muscle [228]. It has been shown to lower esophageal sphincter tone but has no effect on myocardial contractility.

The cellular mechanism of action of nitroprusside is, as yet, still undefined. The drug molecule itself is responsible for the vasodilating properties, with its nitroso group acting on the smooth muscle [228]. Postulated mechanisms include activation of adenylcyclase and inhibition of phosphodiesterase activity in vascular smooth muscle [229]. It has also been proposed that sodium nitroprusside-induced vascular relaxation is mediated via oxidation of specific sulfhydryl groups at smooth muscle receptor sites [230]. It is also possible nitroprusside has an effect on intracellular calcium activation systems, although this hypothesis remains unproven.

Effects on renal function

Sodium nitroprusside has been shown to produce renal vasodilation following administration of usual doses to hypertensive patients [231]. The drug causes little alteration in renal blood flow or glomerular filtration rate. There is evidence of a slight decrease in renal vascular resistance. Accompanying acute reduction in arterial pressure, there is a significant increase in renal venous and systemic venous renin activity. The renal response to reduction in pressure has been found to be more pronounced in patients with renovascular hypertension [232].

Adverse effects

Because of nitroprusside's potency, excessive reduction in blood pressure to frankly hypotensive levels is a major risk. Adverse effects that have been reported include diaphoresis, anxiety, psychosis, headache, palpitations, dizziness, retrosternal discomfort and abdominal pain. These symptoms are often related to a rapid reduction in blood pressure and can be relieved by either decreasing the rate of infusion or discontinuing the drug [233]. If the nitroprusside infusion is stopped, the hypotensive effect will usually disappear within approximately 10 min. It is important that nitroprusside be used only where there is adequate facility for close if not continuous monitoring of blood pressure [233].

The most severe adverse effect associated with prolonged use of sodium nitroprusside is toxicity due to cyanide and thiocyanate (SCN^-) accumulation. A brief review of the chemistry of nitroprusside may help to lend some understanding to this problem. One molecule of nitroprusside has five cyanide groups. Nitroprusside reacts non-enzymatically with hemoglobin to form methemoglobin and an unstable intermediate radical [233]. The intermediate compound eventually dissociates, releasing all five cyanide (CN^-) equivalents. One CN^- equivalent is trapped with methemoglobin to form a cyanomethemoglobin complex. Approximately 10% of the cyanide produced by an infusion of nitroprusside is found in the plasma. The remaining CN^- becomes firmly bound within the erythrocyte. The four remaining CN^- equivalents are converted to thiocyanate (SCN^-) by the hepatic en-

zyme, rhodanase. Thiocyanate is excreted by the kidneys without undergoing further metabolism. Toxic blood levels of nitroprusside have not been established. Therefore during prolonged or higher dose nitroprusside infusions, it is important to monitor for signs of CN^- or SCN^- toxicity, especially in patients with renal or hepatic dysfunction. CN^- levels increase rapidly with nitroprusside infusion. There is evidence that excessive CN^- accumulation is the most likely cause of nitroprusside toxicity, especially in patients with hepatic disease [234]. Cyanide blood levels above 15 mg/dl have been associated with toxicity, however, no rigid interpretation should be made of blood determinations since this is a poor reflection of tissue concentration, which is presumably where the toxicity occurs.

Tachyphylaxis to the hypotensive effect of nitroprusside may be one indication of cyanide accumulation [235]. It has been suggested that CN^- directly antagonizes the effects of nitroprusside. Possible reasons include a direct toxic effect on the smooth muscle in the vessel wall, chemical antagonism, or pharmacologic antagonism at the receptor site [235].

In addition to increasing tolerance to nitroprusside, the patient may begin to develop metabolic acidosis secondary to lactic acid accumulation which can result from cyanide poisoning of the mitochondrial oxidative electron transport system [233]. Tolerance and acidosis may be associated with or followed by dyspnea, headache, vomiting, dizziness, ataxia, and loss of consciousness. Severe toxicity manifests in coma, absent pulse, absent reflexes, dilated pupils, pink skin color, severe hypotension, and shallow respirations [233].

In patients with renal insufficiency there is a relatively greater danger of thiocyanate toxicity. Patients may develop nausea, vomiting, diarrhea, skin eruptions, arthralgia, muscle cramps, irritability, tinnitus, blurred vision, motor aphasia, delerium, psychosis, and depressed thyroid function [236]. Hypothyroidism is related to SCN^- interference of iodine transport by the thyroid gland. In general, when one monitors SCN^-, especially in patients with diminished renal function, levels below 10–15 mg/dl are well tolerated [226]. It should be noted that serum concentrations several fold higher than this range have been reported in which the affected patients had no apparent toxicity [237]. Therefore, a SCN^- serum concentration above 10 mg/dl in an asymptomatic patient should not by itself be considered contra-indication to continuing nitroprusside therapy.

Thus, nitroprusside can produce both cyanide and thiocyanate toxicity. Useful guides to follow include the patients' clinical status as well as venous pH, anion gap and lactate levels. Blood levels of SCN^- and CN^- are less helpful but should be monitored in any patient receiving nitroprusside for longer than 72 h [228]. Cyanide toxicity may be treated by infusions of sodium thiosulfate or hydroxycobalamin, or in severe cases by hemo- or peritoneal dialysis.

Dosage in renal failure

Although no specific dosing recommendations are available, it has been shown that the thiocyanate metabolite accumulates in patients with renal insufficiency [234]. As previously noted, such patients should be monitored closely for signs of thiocyanate toxicity. In addition, patients with hepatic insufficiency should be observed for signs of cyanide toxicity.

Patients undergoing dialytic therapy allow more leeway for the clinician since thiocyanate is dialyzable and may easily be removed by either hemo- or peritoneal dialysis [226]. Indeed, dialysis is an extremely useful method of treating both cyanide and thiocyanate poisoning.

Therapeutic use

The usual starting dose of nitroprusside is 0.5 μg/kg/min; this is titrated against the blood pressure reponse. All patients should have their blood pressure monitored continuously, preferably by means of a pressure transducer connected to an intra-arterial line. The maximum recommended dosage is 10 μg/kg/min; although this may be exceeded somewhat in patients who do not manifest toxicity. Because of its extreme potency, sodium nitroprusside must be prepared in precise concentrations and administered via infusion pump, microdrip regulator, or similar device that will allow accurate flow rate control. It is important to remember that solutions of sodium nitroprusside are extremely sensitive to light-induced decomposition [226]. Therefore, solutions of sodium nitroprusside must be protected from light by wrapping the container in aluminium foil or other opaque material. Even foil-covered administration bottles should be discarded and a fresh solution made up every 6 h.

It is extremely unusual to find a patient who is completely refractory to the antihypertensive effect of nitroprusside when administered at maximum dosage (e.g., 10 μg/kg/min). When this does occur there is often a correctable cause of such resistance. As noted above, nitroprusside solutions that have been exposed to light or are older than 6 h may have deteriorated in potency. This can be prevented by making up a fresh solution every 4–6 h. Another relatively common pitfall in parenteral therapy is the miscalculation of the infusion rate, which itself may be erratic if a freely flowing intravenous post is not available. Secondary salt and fluid retention may produce a form of pseudotolerance after several days of vasodilator therapy and may be treated with conventional diuretic therapy. Rarely, resistance to nitroprusside may occur as a result of cyanide accumulation which would be manifested by lactate accumulation. It would be most prudent in that instance to discontinue nitroprusside and select a different antihypertensive regimen.

Trimethaphan

Mechanism of action

Trimethaphan is a rapidly acting parenteral agent whose onset of action is almost immediate, with peak activity in approximately 5 min [238]. The duration of action is 10–15 min after the end of infusion. Trimethaphan acts by occupying post-synaptic ganglionic acetylcholine receptor sites [239]. By doing so, it stabilizes the post-synaptic membrane and diminishes adrenergic control of resistance and capacitance vessels. The antihypertensive effect is mediated through a reduction in arteriolar and venous smooth muscle tone [240]. The ensuing hemodynamic changes also include a decrease in venous return and cardiac output, as well as a decrease in total peripheral resistance. Blockade of sympathetic nervous reflex activity is unique among parenteral antihypertensives and contributes to its attenuating effect on cardiac output. Trimethaphan may also produce vasodilation via release of histamine from mast cells [240].

Adverse effects

Annoying adverse effects are fairly common and are related to the drug's anticholinergic pharmacology [241]. The usual problems associated with trimethaphan include urinary retention and constipation following prolonged administration. More severe effects on gastrointestinal motility can result in paralytic ileus. This effect may significantly interefere with the ability to convert patients to oral therapy. Visual disturbances may also occur. These include mydriasis and paralysis of visual accommodation.

A more severe reaction that is commonly encountered is marked hypotension [241]. In some cases, blood pressure may be difficult to stabilize. The hypotension may last for 10–15 min after the infusion is stopped. Initial management may necessitate the administration of IV fluids and placement of the patient in Trendelenberg position. In patients where these measures are unsuccessful vasopressers may be needed. It is important to note that the hypotensive effect is most significant when the patient is upright. This maneuver is often utilized to achieve an optimal therapeutic effect. In some patients, trimethaphan may reduce glomerular filtration rate and renal blood flow, and increase renal vascular resistance.

Therapeutic use

Trimethaphan should be used with caution in patients with renal disorders. However, there are no guidelines available regarding dosage modification in these patients. In all patients, the drug is to be titrated to pharmacologic effect with frequent blood pressure determinations. Changes in infusion rate should be made at 3–5 min intervals so the desired endpoint is not exceeded. Continuous monitoring of blood pressure is essential to provide

safe and effective management with this drug. The antihypertensive action of trimethaphan can be accentuated by taking advantage of its blocking effect on sympathetic reflexes. Thus, placing the patient in a head-up, feet-down position will markedly enhance the blood pressure lowering effect of trimethaphan [242]. This maneuver should be performed in every patient prior to advancing to high dosage.

Trimethaphan may find its particular niche in patients with disrupted vascular integrity, as occurs in cerebral hemorrhage or aortic aneurysm [243]. In these settings the cardiodepressant action of this ganglionic blocker may help to protect against further arterial damage and hemorrhagic diathesis.

Areas of investigative drug development

A more sophisticated understanding of the complex factors that are involved in blood pressure homeostasis has provided several new avenues of therapeutic research in hypertensive diseases. It is now becoming increasingly evident that numerous endogenous substances are capable of influencing vascular tone, peripheral resistance and cardiac output. Radioimmunoassay techniques and receptor-binding studies have paved the way for the development of pharmacologic agents that antagonize, simulate or stimulate the action or production of important vasoactive substances. These include vasolidating substances such as prostaglandin E_2 (PGE_2), prostacyclin (PGI_2), bradykinin and dopamine or vasoconstrictors like serotonin, vasopressin and thromboxane.

Prostaglandin analogues

Vasodilatory products of arachidonic acid oxidation primarily include prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) both of which are potent vasodilators. Unfortunately, these substances are extremely rapidly metabolized to inactive products so their therapeutic usefulness in long term blood pressure control has been limited. However, recent developments have occurred in drug delivery systems as well as prostaglandin structure-activity relationships. These have permitted the development of therapeutically useful PGE analogs with potent vasodilatory properties. One such compound now under study is CL 115,347, a derivative of PGE_2 that, when administered transcutaneously, has significant antihypertensive action in animals [244]. Development of this or similar agents may have special relevance to renal hypertension, since deficiency of renal prostaglandin production is one potential mechanism of loss of pressure homeostasis in this condition [245].

Serotonin antagonism

In vitro receptor-binding studies by Peroutka [246] have demonstrated the existence of at least two distinct serotonin receptors. So-called 5-HT_2 (or S_2) receptors have been found to be present on vascular and bronchial smooth muscle and platelets. The effects of serotonin on vascular tone are complex. Depending on the dose, route of administration, and vascular bed studied, serotonin may be vasoconstrictor or vasodilator. In most experimental models the pressor effect of this amine predominates. Currently available antagonists of serotonin such as cyproheptadine of methysergide have either weak, nonselective, or partial agonist activity at serotonin receptor sites.

Ketanserin (R41,468) is a quinazaline derivative that is currently being investigated for its antihypertensive properties [247]. This agent has been shown to competitively block 5-HT_2 receptors located on vascular smooth muscle, and is without activity on the 5-HT_1 receptor. Ketanserin has no agonistic effect on serotonin receptors. It does, however, have some $alpha_1$-blocking activity which may enhance its antihypertensive effect. Preliminary studies suggest that ketanserin is effective as monotherapy in only a minority of patients, but is quite effective in combination with beta-blocking drugs.

Syndromes of renal hypertension

Kidney dysfunction and elevated blood pressure may present in various forms depending on the acuteness and severity of the renal disease and blood pressure disturbance. The underlying pathophysiology, clinical features, therapeutic goals and options differ considerably among these separable clinical entities. In this section we propose to outline an approach to the management of renal hypertension that corresponds to the mode of clinical presentation.

Malignant hypertension

Definitions

Malignant hypertension is a distinct clinical syndrome characterized by severe hypertension (usually greater than 200/125 mm Hg) and manifestations of a systemic necrotizing arteriolitis. Histologic examination [248] has disclosed the presence of subintimal hyperplasia and fibrinoid necrosis of the arteriolar vascular bed, particularly involving vessels of the brain and kidney. The underlying pathophysiology is incompletely understood but may involve a vicious cycle of pressure-induced arteriolar intimal damage and

luminal narrowing leading to impaired organ perfusion [249]. Decreased renal perfusion is a potent stimulus for renal renin-release. Rising levels of angiotensin II produces further vasoconstriction, with resultant acceleration of the hypertensive process [263]. Some components of the renin-angiotensin system may also be directly vasculotoxic [250, 251].

Clinical features

Most patients with malignant hypertension have a history of poorly-controlled underlying essential hypertension [252]. However, patients with sudden development of severe hypertension, who have previously been normotensive, may be especially predisposed to the development of the malignant hypertensive syndrome [253]. Malignant hypertension is most likely to occur in black males in their 4th to 5th decade of life [3].

The most common symptoms [212] reported by patients with malignant hypertension include headache, agitation, malaise, nausea and vomiting, which often begin hours to days prior to medical attention. Physical examination, besides severe hypertension, reveals the presence of advanced hypertensive funduscopic changes including retinal exudates, hemorrhages or papilledema [254, 255]. The retinoscopic findings, which are manifestations of the systemic microvascular nature of this disease, are virtually a *sine quo non* of malignant hypertension. A relatively small number of patients may develop hypertensive encephalopathy with more profound alterations in mental status such as confusion, stupor or come, often accompanied by changing focal neurologic deficits [256]. Cardiovascular examination will often reveal evidence of left ventricular hypertrophy, however frank congestive heart failure is uncommon. Laboratory abnormalities may include proteinuria, hematuria, cellular casts and elevation in serum creatinine and blood urea nitrogen [254]. Some degree of renal insufficiency is usually present at the time such patients come to medical attention. Occasionally, severe acute renal failure may ensue, resulting in the need for dialytic therapy. Hematologic evaluation often indicates the presence of a microangiopathic hemolytic anemia with falling hemoglobin, and elevated reticulocyte count, LDH and schistocytes on peripheral smear [257]. This latter disorder is probably a result of mechanical shearing of erythrocytes during circulation past damaged arteriolar endothelium. Erythrocyte sedimentation rate is frequently elevated during malignant phase hypertension, perhaps as a result of the systemic nature of the necrotizing arteriolitis.

Therapeutic goals

Therapy in malignant hypertension is directed toward reversal or prevention of target organ (especially brain and kidney) damage. This is best accomplished by rapid but well-controlled reduction of blood pressure with parenteral antihypertensive agents. The optimum level of blood pressure

reduction depends in part on the degree of underlying blood pressure control. Patients who were previously normotensive are probably best managed by the prompt return of blood pressure into the normal range. In patients with underlying renal disease or poorly-controlled hypertension there is substantial risk of rapid deterioration in renal function or neurological status if blood pressure is normalized too rapidly. Such patients may be most safely managed by a rapid but only partial (30%) reduction in mean blood pressure followed by a more gradual lowering toward normal over a several day period of time. The presence of hypertensive encephalopathy does however, require a prompt, aggressive approach to blood pressure reduction utilizing rapid acting, closely monitored parenteral therapy.

Management

Treatment of malignant-phase hypertension is most prudently accomplished in an intensive-care unit setting. Most patients require the institution of intra-arterial pressure monitoring as well as continuous observation for signs or symptoms of cardiovascular or central nervous system complications. Renal function should be monitored on a daily basis. It is generally best to avoid diuretics during the initial treatment of malignant hypertension unless clinical evidence of congestive heart failure or marked edema are present. Diuretics are not likely to have a significantly benefical effect since many patients with malignant hypertension are somewhat hypovolemic prior to therapy [258]. Also, diuretic therapy may increase the risk of hypotension from subsequent therapy.

Any of the therapeutic agents listed in Table 13 may be useful in rapid control of blood pressure. The ideal agent would have the following properties: consistency of effect, easily titratable, short onset of action, nontoxic, and little or no monitoring required. Also, there should be a minimal effect of renal impairment on any of these properties. Unfortunately, such an agent has not yet been identified, although sodium nitroprusside may come the closest to possessing such properties. Nitroprusside is metabolized to thiocyanate which itself is excreted by the kidneys and may therefore accumulate when renal failure is present. Manifestation of thiocyanate toxicity include nausea, vomiting, restlessness, agitation, psychotic reactions and seizures. These reactions are most likely to occur when thiocyanate levels exceed 20 mg/ml; any of these require the reduction or discontinuation of nitroprusside therapy.

Diazoxide is an alternative agent which is effective in about 80% of patients with malignant hypertension. This potent direct-acting vasodilator has been shown to be useful in patients with underlying renal disease. Because over 90% of the drug is bound to plasma protein, diazoxide is usually administered as a rapid 300-mg intravenous bolus; this is repeated as necessary to establish and maintain blood pressure control. Patients with

Table 13. Parenteral drugs for treatment of hypertensive emergencies

Drug	Dose range	Advantages	Disadvantages	Contra-indications
Direct vasodilators				
Sodium nitroprusside (Nipride)	0.5–10 μg/kg/min infusion	Almost always works, easily titratable	Requires constant monitoring, variable effects on cardiac output, thiocyanate toxicity	Aortic or cerebral aneurysm (unless) propranolol added), thiocyanate toxicity
Diazoxide (Hyperstat)	Bolus injection: 2.5–5 mg/kg (150–300 mg) Infusion: load 7.5 mg/kg, then 0.75 mg/kg q 6 h	Monitoring may be less intensive after first 30 min, works in 80%, effective and safe in toxemia	Occasional hypotension, tachycardia, chest pain, flushing, hyperglycemia, fluid retention, may slow labor	Stroke, aneurysms, hemorrhage, coronary artery disease
Hydralazine (Apresoline)	10–20 mg q 4–6 h intravenously or intramuscularly	Safe and effective in toxemia of pregnancy, does not require constant monitor	Not consistently effective outside of pregnancy, tachycardia, chest pain	Hemorrhage, aneurysms, coronary insufficiency

Table 13. Parenteral drugs for treatment of hypertensive emergencies

Drug	Dose range	Advantages	Disadvantages	Contra-indications
Sympathetic inhibitors ganglionic blockade				
Trimethaphan	1–15 mg/min	Drug of choice for dissecting aneurysm of aorta, head-up augments effect	Constant monitor, tachyphylaxis at 24–48 h, paresis of bowel and bladder, visual blurring, dry mouth	Post-operative state
Alpha receptor blockade				
Phentolamine	2.5–20 mg IV[a] bolus	Rapid	Short duration of action, hypotension	Use only for catecholamine excess
Central inhibition				
Alpha-methyldopa (Aldomet)	250–500 mg IV[a] q 4–6 h	Smooth, gradual, avoids reflex tachycardia, safe in pregnancy	Somnolence, effect not consistent	CNS depression, hepatic disease, hemolytic anemia

[a] intravenous

severe renal dysfunction should probably receive half the usual starting dose since protein-drug binding may be impaired in uremic patients [259]. Continued use of diazoxide, as well as any other vasodilator, is likely to produce sodium and fluid retention that usually requires potent diuretics.

Among the other drugs listed in Table 13 none are likely to require dosage adjustment for renal impairment. It should however be emphasized that reduction of blood pressure to hypotensive levels with any of these agents can significantly endanger renal function and may precipitate severe acute renal failure.

Acute renal failure and accelerated hypertension

Definition and clinical features

Accelerated hypertension may be best defined by the occurrence of a substantial (15–20 mm Hg) and rapid increase in blood pressure above previous levels. Under most circumstances, accelerated hypertension is not accompanied by the manifestations of acute systemic vascular damage that characterize malignant hypertension, such as advanced retinal changes, central nervous system or hematologic disturbances. Non-malignant, accelerated hypertension in the setting of acute deterioration in kidney function is likely to be secondary to the underlying renal disorder.

Severe hypertension which accompanies acute renal failure may be a helpful clue in the etiologic diagnosis of the disorder. Renovascular occlusion, vasculitis and glomerulonephritis are frequently associated with accelerated hypertension, perhaps through stimulation of the renin-angiotensin or other pressor systems [260]. On the other hand, significant hypertension in the setting of acute renal tubular or interstitial disorders is usually an indication of fluid retention.

Some disorders can closely mimic certain laboratory features of malignant hypertension and may cloud the initial diagnostic process until definitive clinical and laboratory studies can be performed. These would include microvascular disorders such as scleroderma renal crisis, postpartum acute renal failure, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura and acute glomerulonephritis [261].

Management

Therapeutic objectives in the management of severe hypertension associated with acute renal failure differ somewhat depending on the nature of the renal insult. For example, the elevated blood pressure occasionally seen with acute tubular necrosis is usually volume-mediated; this may indicate a significant risk of impending congestive heart failure and pulmonary edema. Treatment should therefore be directed toward prevention of these complications and may be best accomplished with fluid restriction or diuretic

therapy [262]. Vasodilating agents such as hydralazine, prazosin or minoxidil or centrally active agents such as clonidine, methyldopa or guanabenz may be useful adjuncts to diuretic therapy. Beta blockers should probably be avoided because of their cardiodepressant properties.

Severe hypertension associated with acute renovascular or glomerular disorders is more likely to have an overriding vasoconstrictive component [261] and therefore presents the added risk of transformation to a malignant phase. Diuretic therapy or fluid restriction may be less effective in controlling hypertension in these settings. Potent vasodilators including minoxidil, nifedipine, renin antagonists or parenteral agents, as well as potent central inhibitors such as clonidine are usually effective (Table 14). Diuretics may be helpful primarily as adjunctive agents.

Accelerated hypertension with chronic renal disease

Accelerated hypertension may occasionally supervene in patients with chronically impaired but stable renal function. Evaluation of such patients should include a meticulous clinical assessment to obviate the possibility of malignant hypertension or a more subtle preceding renal insult that may underly deranged blood pressure homeostasis. Other possible causes for sudden loss of blood pressure control include renovascular disorders, excessive salt intake and poor compliance with the prescribed medical regimen.

The major therapeutic objective in this setting is the preservation of renal function. Management should be directed first at the identification and amelioration of any of the above potentially responsible entities. Although not a true emergency, it is generally preferable to reestablish control of blood pressure within a few days of initiating therapy. Therefore, oral agents that act relatively promptly are usually of particular benefit such as clonidine, minoxidil, captopril or nifedipine. Diuretics may be cautiously introduced or the dosage increased.

Table 14. Oral therapy for acute reduction of severe hypertension

A. General guidelines
1. Avoid pretreatment with diuretic unless patient is clinically fluid overloaded
2. Monitor closely
3. Continue therapeutic regimen unless clinical status changes
B. Rapidly-acting oral drugs (select one)
1. Clonidine – 0.2 mg plus 0.1 mg every 1–2 h
2. Captopril – adjust dose according to renal function (Table 12)
3. Nifedipine – 10 mg sublingual every 30–60 min
4. Minoxidil – 2.5 mg, double dose as needed every 4 h

Chronic hypertension and mild renal insufficiency

Earlier in this chapter we briefly reviewed some possible mechanisms contributing to loss of blood pressure regulation in patients with chronic renal disease. As noted, most studies have demonstrated the pre-eminent importance of abnormal sodium retention as the initiating event in most patients who develop hypertension secondary to renal parenchymal disease [263]. Hence, successful management usually depends on the prevention or reversal of plasma volume excess.

Moderate sodium restriction (2–3 g/day) is often sufficient to achieve blood pressure control in patients with mild renal insufficiency. It should be recalled that patients with chronic renal disease have a progressively narrowed range of sodium excretory capacity [264]. With severe salt restriction some patients may be unable to conserve sodium and may become volume depleted: this may lead to a worsening of renal function as well as exacerbation of hyperkalemia. Therefore, moderate sodium restriction should be controlled through careful monitoring of the patient's fluid balance and renal status.

For most patients with stable chronic renal disease, diuretics are the mainstay of antihypertensive therapy. Patients with very mild renal impairment will generally respond to thiazide-type diuretics. Thiazides become less effective as the serum creatinine rises above 2.0 mg/dl. High-ceiling diuretics such as metolazone or the loop-acting agents such as furosemide or bumetanide will usually remain effective, albeit at higher than normal dosage, unless the creatinine clearance falls to 10 ml/min or below [265].

Hypokalemia is a relatively less frequent problem in this setting. When it does occur it is generally advisable to avoid overly enthusiastic use of potassium-sparing agents such as spironolactone, triamterene or amiloride [266]. In patients with diabetic nephropathy these drugs should probably be avoided altogether. In most circumstances it is probably safest to treat clinically significant hypokalemia associated with chronic renal disease with cautious oral potassium supplementation.

The goal of antihypertensive therapy is to attain a consistently normal blood pressure; that is, a diastolic presure of 90 mm Hg or below. The long-term objective of such therapy is to prevent or slow down the progression of renal impairment, since virtually all forms of renal disease may be sensitive to the deleterious hemodynamic effects of even mild to moderate chronic elevation in blood pressure [6].

Patients whose diastolic blood pressure remains above 90 mm Hg despite salt restriction and diuretic therapy will often respond to the addition of an adrenergic inhibitor such as alpha-methyldopa or clonidine. Beta-adrenergic blockers are also effective in this setting but should be used cautiously in light of reported adverse effects of propranolol on renal blood flow and

glomerular filtration rate. Whether this caveat applies to all beta-adrenergic blockers remains to be determined. The clinician should also be aware that participation of renal excretory function in the elimination of several of the adrenergic inhibiting agents may result in a further reduction of the therapeutic benefit/toxic ratio when renal disease is present [96, 97].

Hypertension and moderate to severe chronic renal insufficiency

Elevated blood pressure in the setting of moderate to advanced renal failure presents several difficult problems for the clinician. This form of hypertension is often quite resistant to therapy. As a result greater numbers of drugs in higher, potentially more toxic dosage are frequently necessary to establish blood pressure control. While it is clear on one hand that control of hypertension is needed to preserve renal function, there is real danger that too vigorous therapy may, in some instances, worsen renal function. The latter problem is of particular concern since these patients have little renal reserve to sacrifice.

As with mild renal impairment, moderate salt restriction and high-ceiling diuretics and adrenergic inhibitors prove to have important therapeutic roles. Hypertension resistant to these forms of therapy will often respond to a triple-drug regimen including a diuretic, an adrenergic inhibitor and a vasodilating agent. Minor vasodilators such as prazosin or hydralazine are sometimes effective in the latter role and produce little or no risk of nephrotoxicity. Occasionally however, one encounters patients in whom blood pressure remains substantially elevated despite such a triple-drug regimen. Substitution of more potent vasodilating drugs, such as captopril in high renin patients [267], or nifedipine in low renin patients [208] will almost always provide adequate control. There is still a small percentage of patients who prove to be resistant even to this regimen in which case minoxidil will prove to be an effective vasodilator. Resistance to minoxidil in combination with high dose diuretics and adrenergic inhibitor is quite unusual. The limiting factor in minoxidil therapy is often fluid retention which may require either several diuretics in combination such as furosemide and metolazone, or the concomitant use of captopril. The rare patient who fails to respond to such a quadruple or quintuple regimen in maximum tolerating dosages may have one of the following problems: poor drug compliance, another secondary form of hypertension such as renovascular disease or pheochromocytoma, surreptitious use of sympathomimetic agents, or profound end-stage renal failure requiring dialysis or transplantation. Bilateral nephrectomy was, until about 5 years ago, a commonly employed means of establishing blood pressure control in this setting. Fortunately, this procedure is today only very rarely performed for that purpose.

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9. Percutaneous Transluminal Angioplasty in Renovascular Hypertension

THOMAS A. SOS

Introduction

It is estimated that there are approximately 25 million hypertensives in the United States, and of these 5% (or over 1 million) are due to renovascular disease [1]. The incidence, pathophysiology and diagnosis of renovascular hypertension are discussed elsewhere in this volume in greater detail. In this Chapter we shall briefly describe the role of the radiologist in the detection of renovascular hypertension and its treatment by percutaneous transluminal renal angioplasty (PTRA).

Diagnosis of renovascular hypertension

Clinical screening

Hypertensive patients should initially undergo sampling of peripheral blood for determination of plasma renin activity prior to and 60 min following oral administration of 25 mg of captopril. Blood pressure readings should also be obtained before and after administration of captopril. Renin activity should be indexed against urinary sodium measured on a 24-h urine sample collected by the patient [2]. The peripheral plasma renin-captopril 'challenge test' has a sensitivity and specificity of approximately 90% in detecting patients with renovascular hypertension [3].

The roles of selective renal vein renin sampling and digital subtraction angiography

Patients clinically suspected of having renovascular hypertension and supported by the laboratory results above should undergo selective renal vein

and infrarenal vena caval blood sampling for renin activity followed by digital subtraction angiography (DSA) [4]. These two tests are not competitive, but rather complimentary. Since neither of them is absolutely foolproof, one acts as a control upon the other. When there is agreement between these two studies (whether normal or abnormal) the patient can be regarded as having renovascular or essential hypertension with a high degree of certainty. When the two tests disagree, however, further testing or a repetition of one or the other may become necessary. Patients with bilateral renal artery disease may not show lateralization with renal vein renin activity (RVR), however, DSA will often reveal the bilateral stenoses or occlusions. Conversely, patients with peripheral branch renal artery stenoses will be rarely detected by DSA, however, RVR identifies them with greater frequency. For this reason we continue to do both RVR and DSA on our patients with suspected renovascular hypertension on an out-patient basis. Following DSA and RVR, both of which can be done either from the femoral or less conveniently from the brachial percutaneous venous route. Patients stay in the Department from 1 to 2 h after which they can be released home. In several thousand such out-patient procedures we have had only one serious complication, and that occurred due to inadvertent puncture of a small arterial branch.

Arteriography

If patients with suspected renovascular hypertension have lateralizing RVR and a positive DSA they are admitted to the hospital for arteriography to be immediately followed by renal angioplasty or later by surgery. The few patients with renovascular hypertension who are not detected by a combination of the previous tests will often fail medical therapy and an arteriogram will be done to rule out renal artery disease. If an appropriate lesion(s) is detected on the arteriogram these patients also will be considered for angioplasty or surgical therapy. The arteriogram is still the gold standard in the morphologic evaluation of renal artery disease in hypertension.

The rationale for medical vs. invasive (angioplasty or surgery) therapy

While there is universal agreement that severe hypertension requires some form of treatment, the choice of therapy is less clear cut and is often dictated by personal experience and prejudice of the individual physician rather than based on clear cut scientific data. A randomized study to compare the effectiveness of medical therapy, surgery and angioplasty in renovascular hypertension has never been undertaken. In 1974, Hunt [5] published his experience in approximately 200 medically similar patients over a 10-year

period, where half of the patients had been treated medically and half with surgery. In this study the mortality and the incidence of major complications, such as stroke, heart attack, and renal failure, was clearly greater in the medically treated group than in the surgically treated one. Clearly, the data obtained in this study are no longer totally valid, since the introduction of beta-blockers and converting enzyme inhibitors has made antihypertensive therapy of renovascular hypertension far more physiologically specific and clinically successful. In fact, almost all patients with renovascular hypertension can be successfully treated currently with the above medications. At first glance then one would feel justified in treating all patients with renovascular hypertension medically. However, there is clear evidence from our experience and that of others that the natural history of untreated or medically treated patients with severe renal artery stenosis and renovascular hypertension show a significant (approximately 10%) incidence of progression to total renal artery occlusion and a consequent loss of the offending kidney by autonephrectomy [6]. Ironically, the more effectively the hypertension is controlled, the lower the effective perfusion pressure is across the obstructed renal artery, the higher the risk of spontaneous thrombosis of the renal artery. Clearly, losing one of two kidneys, especially in older patients many of whom already have compromised renal function, is not a benign event. Indeed, the incidence of renal artery stenosis or occlusion in patients with renal failure is not known and probably should be looked for more agressively.

The risks of renal artery surgery or angioplasty must be weighed against and compared to this approximately 10% expected loss of kidneys with medical therapy.

The history of angioplasty

Development of the technique

Angioplasty for the treatment of atherosclerotic obstruction of the lower extremities was first reported by Dotter in 1964 [7]. He observed, as had others, that diagnostic arteriographic catheters were sometimes easily advanced across seemingly totally obstructed or severely narrowed arteries. Unlike the others, he had the monumental and ingenious, but fundamentally simple insight that an angiographic technique might be adaptable for dilation of these arteries. Dotter's technique consisted of initially traversing the obstructed artery with a flexible guide wire over which teflon dilators were advanced coaxially (one over the other). This system had several disadvantages: (a) the maximum dilation (10 French) was limited by the fact that the femoral puncture site would have to be dilated equally to the

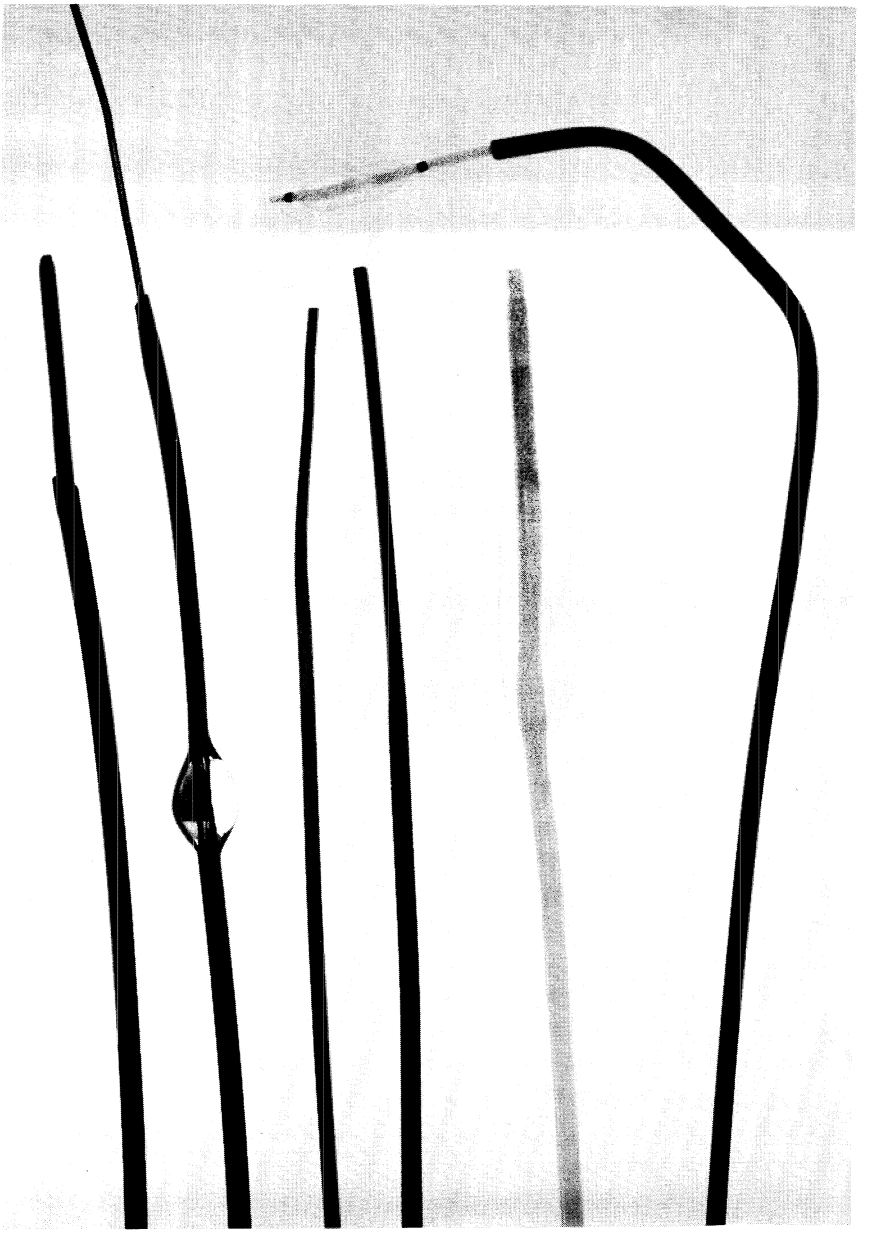


Figure 1. The evolution of angioplasty catheters. (A) Dotter's coaxial catheter system; (B) Porstmann's 'Korsett' latex balloon catheter; (C) and (D) Van Andel's tapered dilators; (E) Grüntzig-type balloon angioplasty catheter; (F) coaxial Grüntzig-type balloon catheter for renal and coronary angioplasty.

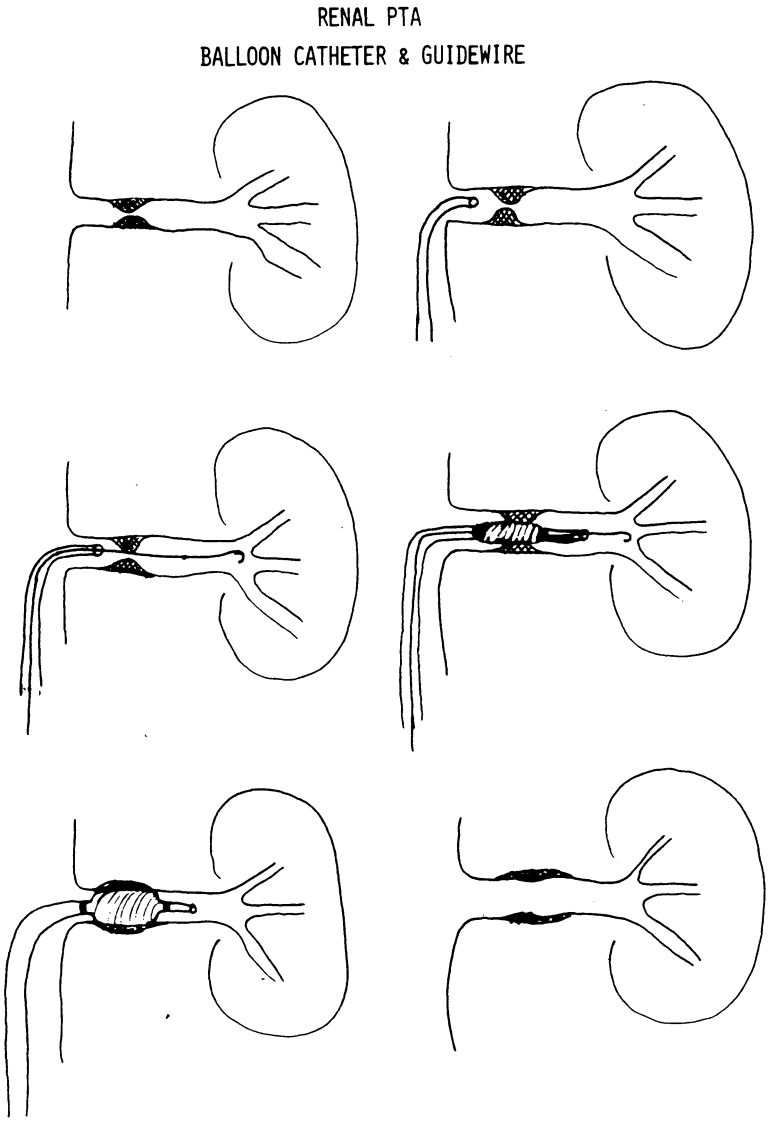


Figure 2. The most frequently used catheter-guide wire technique for renal angioplasty.

lesion; (b) the catheters were relatively untapered and had a great deal of forward shearing in addition to the desired lateral compression which resulted in a relatively high incidence of distal embolization and puncture site problems; (c) the dilators were rigid and had a wide shaft diameter and were thus not suitable for treatment of visceral and coronary arteries.

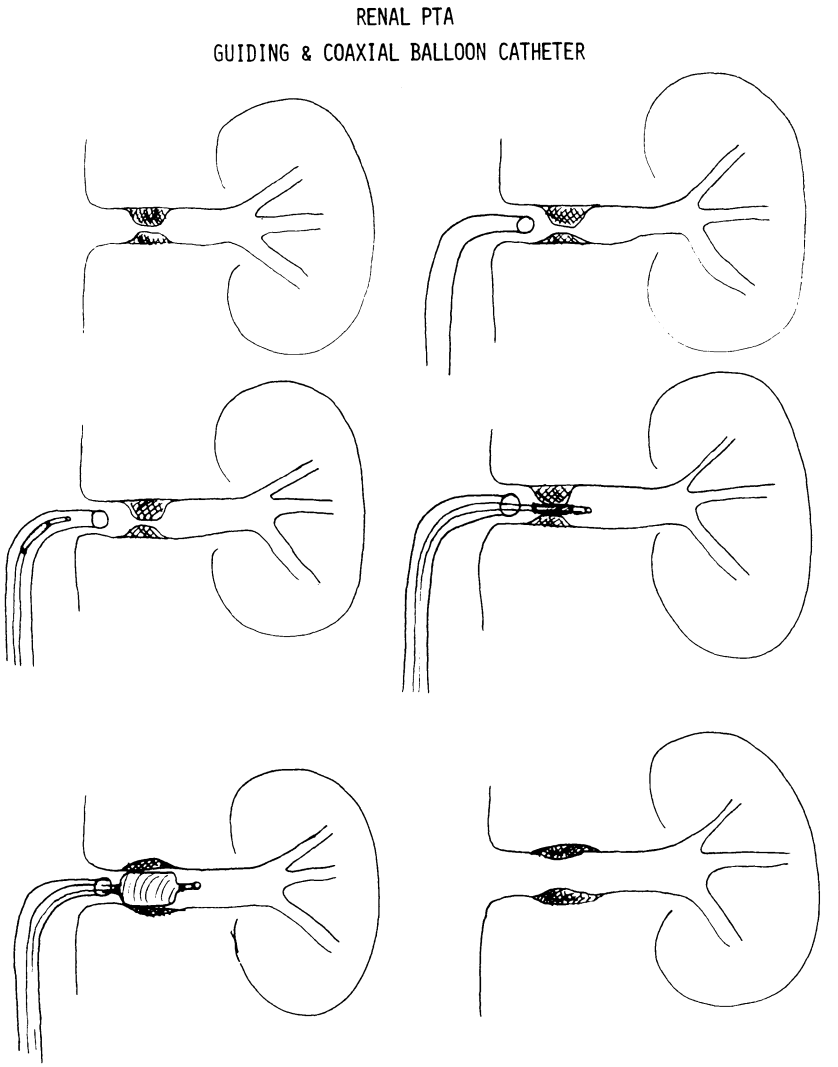


Figure 3. Grüntzig's coaxial guiding catheter and balloon catheter technique for renal angioplasty.

Modifications in catheter designs

In his first paper, Dotter speculated [7] that the ideal angioplasty catheter would have a small shaft diameter where treatment of a local obstruction would be achieved by concentric expansion of only a limited segment of the shaft (i.e., a balloon) in the lesion.

Angioplasty was greeted with a great deal of skepticism in the United States but the Europeans, especially Porstmann [8], Zeitler [9], and Van

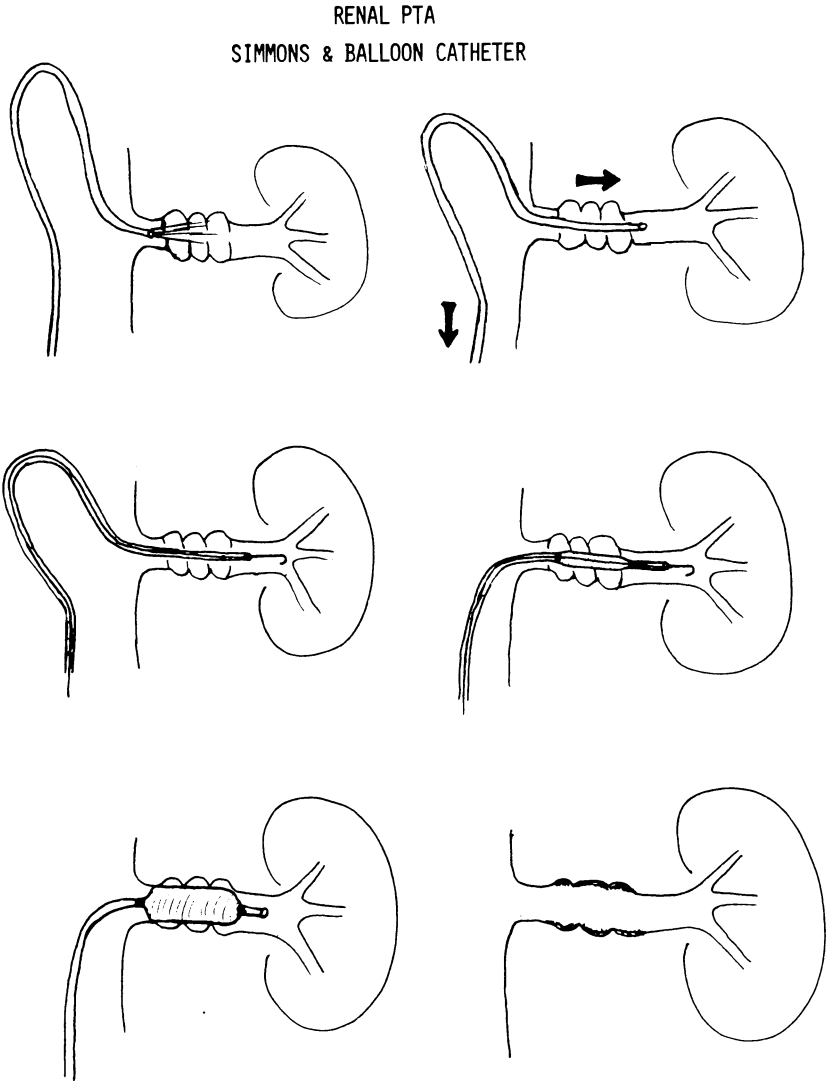


Figure 4. The use of a shepherd's crook shaped catheter for renal angioplasty, which is especially useful in fibromuscular dysplasia.

Andel [10], embraced and improved upon it. Dotter himself [7] and Porstmann [8], experimented with fiberglass and latex balloons, but it was not until 1974 that a clinically effective and reliable balloon catheter was designed and constructed by Grüntzig [11]. These catheters have diameters ranging from 3.5–9 French and have preshaped cylindrical balloons near their tip. The balloons range from 3 to 20 mm in diameter and 1–10 cm in length (Figure 1).

Development of renal angioplasty

In his initial communications, Dotter correctly predicted that his percutaneous method would be suitable for treatment of the coronary and renal arteries [7]. Grüntzig's flexible and small shaft diameter catheter has now permitted fulfillment of Dotter's earlier prediction.

Renal arteries were first dilated by Fry intraoperatively [12] for relief of branch stenoses due to fibromuscular dysplasia. There are anecdotal and often unpublished reports of individual cases of renal artery dilation, but it was Grüntzig who first attempted percutaneous transluminal renal angioplasty experimentally and reported a series of patients [13]. Grüntzig originally used a coaxial system which consisted of a stiff 9 French guiding catheter to engage the renal artery orifice through which a small 3.7 French flexible balloon catheter was advanced into the renal artery and across the stenosis (Figure 2). Most other angiographers use an adaptation of Grüntzig's original technique for femoral dilation, i.e., initially crossing the lesion with a guide wire followed by an appropriate balloon catheter (Figures 3 and 4).

Pathology of renal artery stenosis

Atherosclerosis

The etiology for the renal artery disease in two-thirds to three-quarters of patients with renovascular hypertension is atherosclerosis. Atheromatous involvement generally occurs at bifurcation points and therefore many of the atheromatous lesions occur in the proximal one-third of the renal artery, indeed many are right at the ostium of the artery. Ostial stenoses can also be caused by advanced atherosclerosis of the aorta where the large atheromatous masses impinge upon the origin of the renal artery (Figure 5). Radiation is a rare cause of atheroma, where both fibrosis and premature atherosclerotic changes occur.

Fibromuscular dysplasia

Approximately 25% of patients with renovascular hypertension have fibromuscular dysplasia (FMD) of the renal arteries. The most common type of FMD is medial hyperplasia. In this condition there are alternating dilations and narrowings of the renal artery due to focal hyperplasia of the media and aneurysmal dilation of the vessel in between. The angiographic appearance

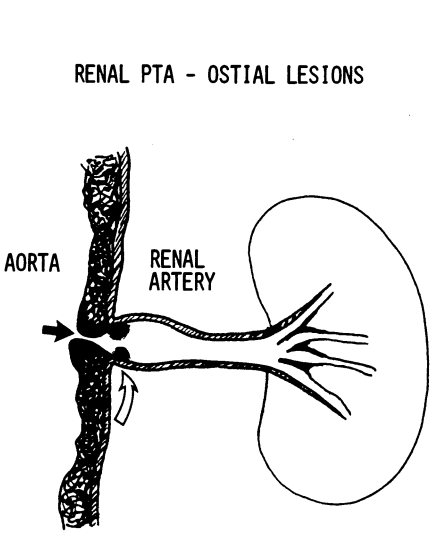


Figure 5. Ostial renal artery stenosis. Angiographically identical apparently ostial stenoses can be due to thickening of the aortic wall which encroaches on the renal artery (black arrow) or to a stenosis within the renal artery but right at its ostium (open arrow).

of these vessels is like a 'string of beads'. Less frequent forms are due to intimal hyperplasia or adventitial fibrosis. Intimal hyperplasia generally produces focal solitary stenoses, whereas adventitial hyperplasia generally produces longer segments of smooth involvement. Spontaneous dissection of the renal artery may occur with any of the forms of fibromuscular dysplasia.

Post-operative stenoses

Post-renal transplantation

The most frequent sites of anastomosis of the transplant artery are to the internal iliac (end-to-end anastomosis) and the external iliac (end-to-side anastomosis). The sites and causes of stenoses may be: (a) pre-anastomotic, which are usually due to atherosclerosis; (b) anastomotic due to faulty suture technique or fibrosis; and finally (c) post-anastomotic which can have multifactorial causes due to immune factors, disturbed hemodynamics, vessel trauma, or kinking.

Graft stenoses

Following aorto-renal or other bypass grafts for renal artery stenosis, stenoses can develop anywhere within the graft. These stenoses can occur at either the proximal or distal anastomotic site, or anywhere within the graft itself due to intimal hyperplasia.

Other non-atheromatous causes

Various forms of arteridites such as Takayasu's arteritis and neurofibromatosis, may lead to renal artery stenosis. The vascular abnormalities range from abnormal fibrous or atheromatous elements to extraluminal neurofibromata compressing the vessel and also producing aneurysms.

Mechanism of action of angioplasty

Atherosclerosis

Dotter and Grüntzig initially thought that the atheromatous material behaved like a 'cold flow' substance and was compressed and remodeled in the dilation process somewhat like freshly fallen snow by a boot [7, 11]. More recent work by Hohn [14], Jester and Sinapius [15], Casteneda-Zuniga and Amplatz [16], and Block [17] has demonstrated however that balloon dilation produces 'controlled injury' to the vessel wall which results in longitudinal fissures in the intima and complete or partial concentric tears and separation between the media and the adventitia. The outer wall of the vessel is somewhat dilated and the atheromatous material is displaced and compressed into it. The lesion in a sense becomes 'turned inside out' and heals in the dilated state. Following even partially successful dilation a striking further improvement in the caliber of the lumen is often seen. It has been speculated that increased flow and pressure produce progressive further distention of the vessel once the restricting atheroma is cracked and that some of the residual thrombotic and atheromatous plaque is spontaneously lysed or 'phagocytized'. It is also well recognized that a relatively minor increase in cross-sectional area of a stenotic vessel can give a dramatic improvement in flow and stenoses of less than 50% diameter (or 75% cross-sectional area).

It is probable that the approximately 20% restenosis rate widely reported in the renal artery [18, 19] is due to under dilation and the resultant incomplete 'cracking' of the atheromatous core and incomplete dilation of the very resistant adventitia. We postulate that stenoses recur for at least two reasons: one is the gradual return of the vessel to its predilated state due to its 'unruptured' elasticity, and the second is the continued progression and build up of atheromatous material at the site of the residual stenosis due to turbulent flow, a recognized contributing factor in the formation of atheromatous stenoses just distal to vascular branching. In renal angioplasty a satisfactory post-dilation lumen (greater than 70% patent) had a higher correlation with the long-term relief of hypertension than did a decrease in the pressure gradient [20]. For these reasons from early on in our experience we

have routinely used balloons one (and recently even two) millimeters greater in diameter than that of the vessel on the angiogram (not attempting to correct for magnification). Restenosis rate for atheromatous renal arteries in our experience is only 10% [20].

Non-atherosclerotic lesions

Non-atherosclerotic stenoses, whether due to fibromuscular dysplasia, radiation, arteritis, or post-surgical stricture are dilated by shearing and rupturing of the obstructing fibrous or muscular tissues [21, 22]. The 'beady' medial form of fibromuscular dysplasia dilates most easily, while post-surgical stenoses and some unifocal (probably intimal) forms of fibromuscular dysplasia and those of Takayasu's arteritis are very resistant and dilate only partially, though they frequently show a marked delayed improvement in caliber [23].

Techniques for percutaneous transluminal angioplasty

Preliminary angiography

The location and nature of the obstructing lesions and the best approach to them must be determined prior to angioplasty with a high quality arteriogram, although in many cases intravenous digital subtraction angiography can give sufficient preliminary diagnostic information. Almost all renal artery lesions can be successfully approached, crossed and dilated via the femoral artery [23]. It is rarely necessary to use the axillary approach. Prior to crossing an obstructing lesion appropriate antispasmodic and anticoagulant medications should be administered, and intravascular pressure measurement obtained prior to and immediately after crossing the lesion [23, 24].

Atherosclerotic and post-surgical stenoses

Most angiographers use an adaptation of Grüntzig's guide wire-catheter technique [11] (Figure 2), though Grüntzig himself prefers a small 4.5 French balloon catheter introduced coaxially through a large and stiff 8 French guiding catheter [13] (Figure 3). A 5 French diagnostic catheter is employed to enter the proximal renal artery and a wire guide with a 5-cm long floppy tipped segment is used for initially crossing the stenosis. The diagnostic and angioplasty catheters are then advanced over the wire. Some atheromatous renal artery stenoses are extremely rigid and require balloons

even 2 mm greater in diameter than the size of the normal artery on the angiogram.

Fibromuscular dysplasia

In patients with fibromuscular dysplasia, especially of the 'beady' medial form, even a very floppy guide wire may become trapped and not be able to cross the stenosis. These lesions can be crossed by using a shepherd's crook shaped catheter without a guide wire while injecting a dilute contrast solution [23] (Figure 4). Most manipulations in the renal artery are easier in cooperative patients, for appropriate inhalation and exhalation change the angle of the renal artery with respect to the aorta.

Renal transplant

Patients with external iliac to transplant artery anastomotic stenoses are best approached from the ipsilateral femoral artery, while stenoses in the hypogastric to transplant artery anastomoses are best approached from the contralateral femoral artery around the aortic bifurcation [22].

Adjunct medical therapy

Antispasmodics

Instrumentation of a vessel can result in severe focal or diffuse spasm [2, 5]. Nifedipine (a calcium channel blocker) is the ideal antispasmodic agent for angioplasty. Ten to 20 mg by mouth or sublingually has a 20-min onset of action and effectively prevents spasm for several hours. Sublingual or paste nitroglycerine are also effective, though their action is shorter and less predictable. Injectable intra-arterial nitroglycerine (100 μg) is very effective to relieve spasm once it has occurred.

Anticoagulation

During attempted dilation, flow across the stenosis is further compromised and the potential for thrombosis at the lesion and proximal or distal to it are increased. In addition, the controlled injury of dilation releases some thrombotic and spasmogenic substances, such as thromboxane from the vessel wall, the atheroma and superimposed thrombus. 3000–5000 units of

heparin administered intravenously or intra-arterially just prior to crossing the stenosis is recommended, especially if working in relatively small vessels with low flow or when the procedure lasts for longer than 1 h. We do not reverse the heparin at the end of the procedure with protamine sulfate.

Restenosis or reocclusion

Following successful angioplasty any remaining normal endothelium will be damaged and at best a rather irregular surface will be left and some thrombogenic and spasmogenic factors will be released from the plaque. Most authorities now feel that heparin (in any mode or dose of administration) is not indicated following angioplasty except in very rare and difficult cases. The effectiveness of long-term anticoagulation with coumadin is uncertain, however there is some evidence that low dose (80 mg q.d.) aspirin therapy may increase the long-term patency.

Complications of renal angioplasty

The use of antispasmodics and anticoagulants as well as meticulous angiographic techniques are most important in the prevention of complications. Death due to PTRA is unusual. In approximately 200 attempted PTRA procedures we have not had a single mortality (up to 30 days following PTRA), in spite of the facts that no patients were excluded based on their medical condition, and that no attempt to search for and correct coexistent cerebrovascular or coronary lesions prior to PTRA was made. We have lost two kidneys, one as a result of an occlusive dissection, and the other following successful dilation where a lower pole branch became occluded by a ruptured balloon. A month later during an attempted lower pole nephrectomy at another institution the entire kidney was removed and the hypertension was cured. Most of the other complications were either self-limited, or could be repaired by surgery. At worst, the surgery is the same as would have been performed if PTRA had not been attempted in the first place, and often it was only an exploration of the groin under local anesthesia.

Results of renal angioplasty (Table 1)

Initial technical results

Patients with fibromuscular disease of the main and/or branch renal arteries are the most suitable candidates for PTRA (Figure 6A–C). Approximately

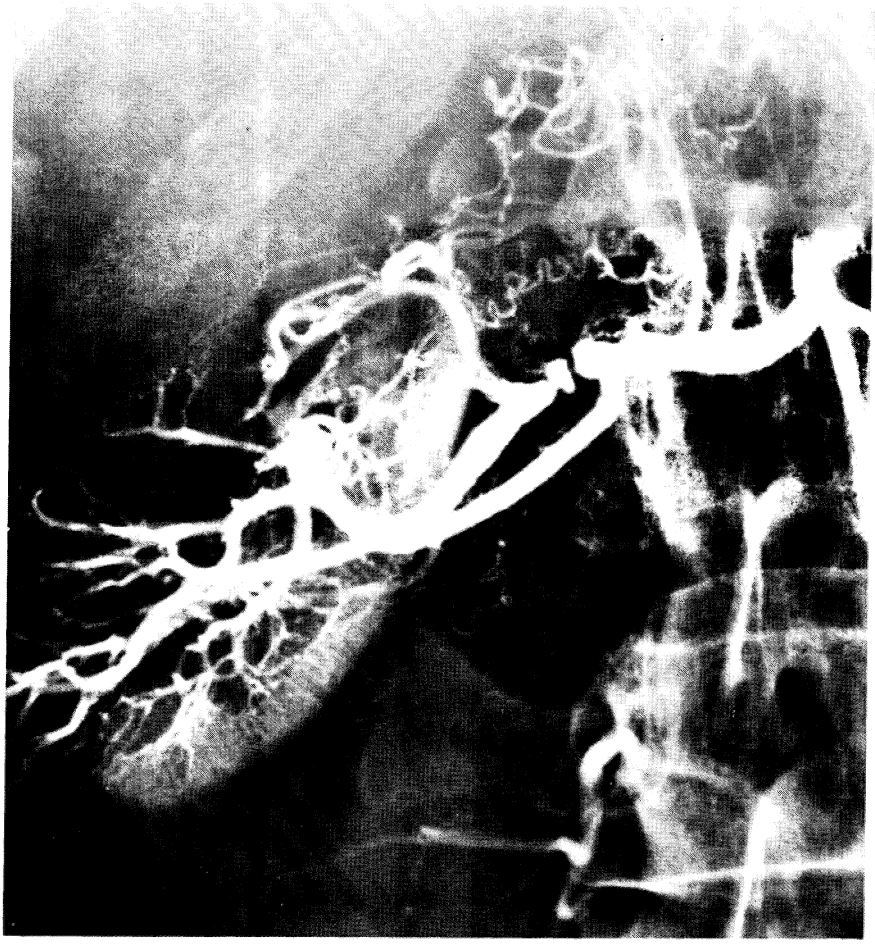


Figure 6. Fibromuscular dysplasia of the renal artery in a 39-year-old hypertensive patient. (A) Before angioplasty; (B) immediately after angioplasty. Note mild residual irregularities in the wall of the artery; (C) Almost 4 years following angioplasty. Note return to absolutely normal appearance of the vessel. The patient was normotensive without medications.

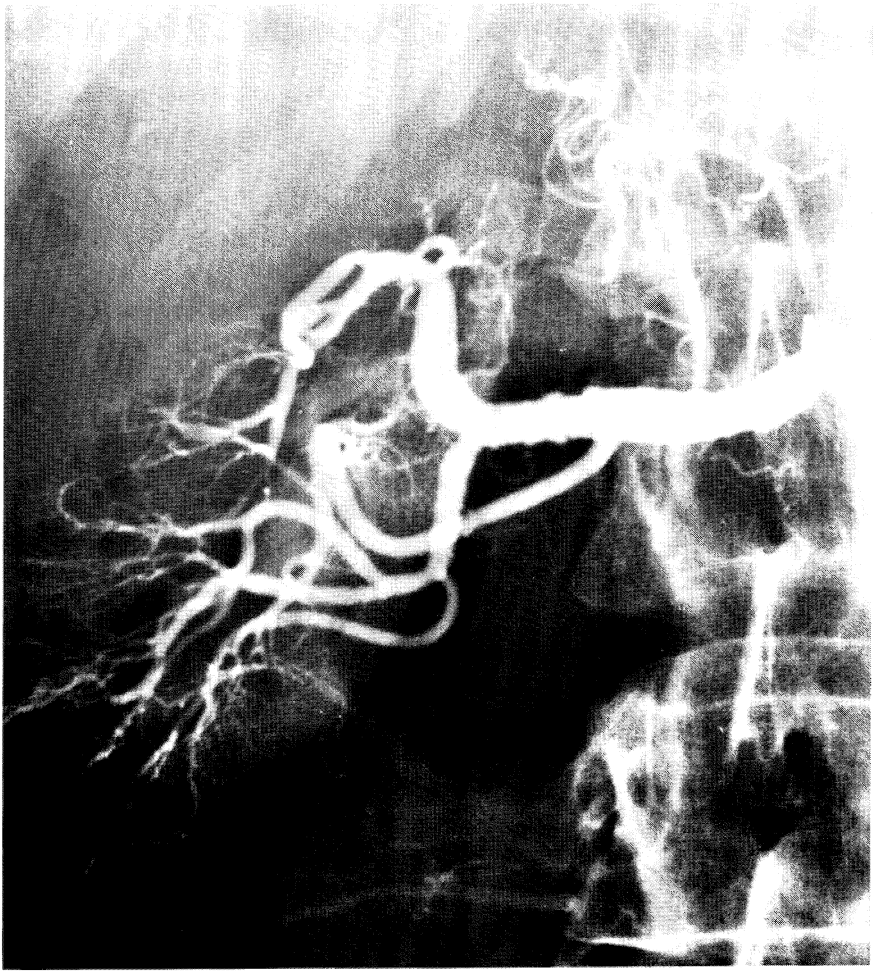


Figure 6 B.

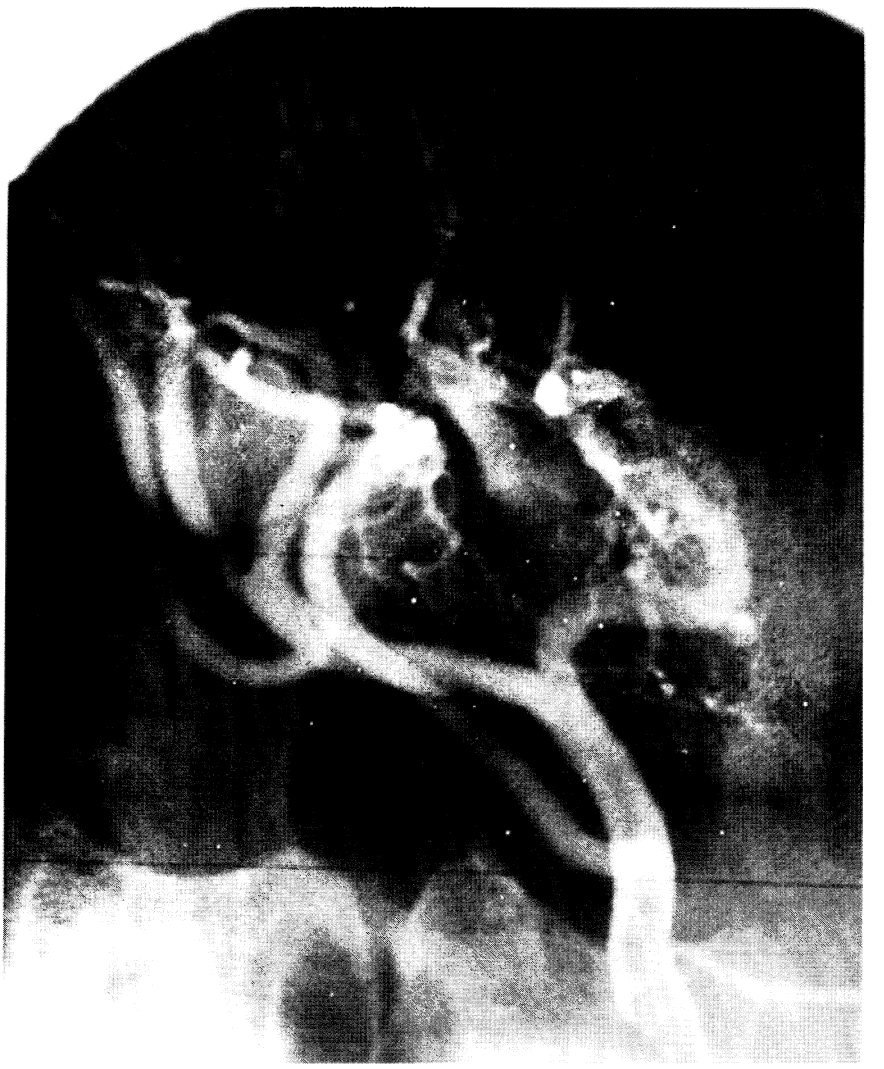


Figure 6 C.

Figure 7. A 61-year-old man with hypertension and a long history of heavy smoking. (A) Aortogram before angioplasty demonstrates complete occlusion of the right renal artery and severe stenoses of the two left lower renal arteries; (B) the right renal artery reconstitutes via collaterals on a delayed film (black arrow); (C) aortogram following successful recanalization and dilation of the previously occluded right renal artery and of the two lower left renal arteries; 1.5 years later the patient was normotensive when he died of bronchogenic carcinoma.

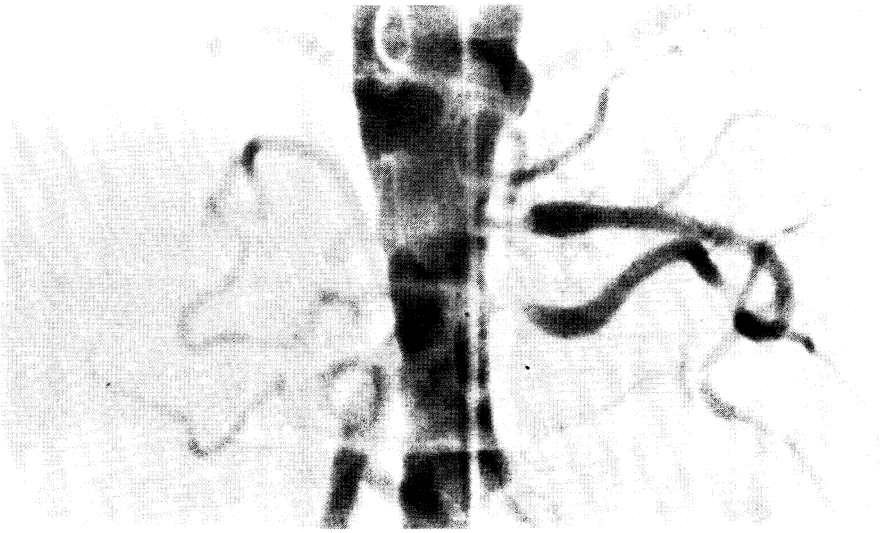
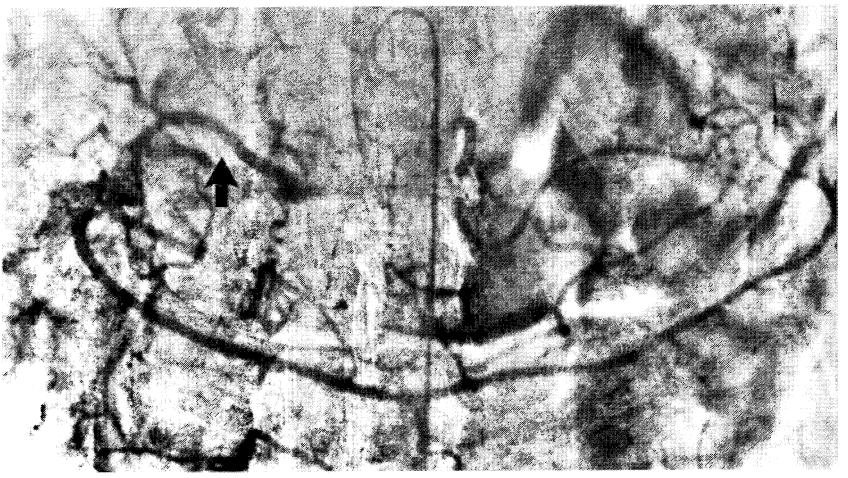


Figure 7 A.



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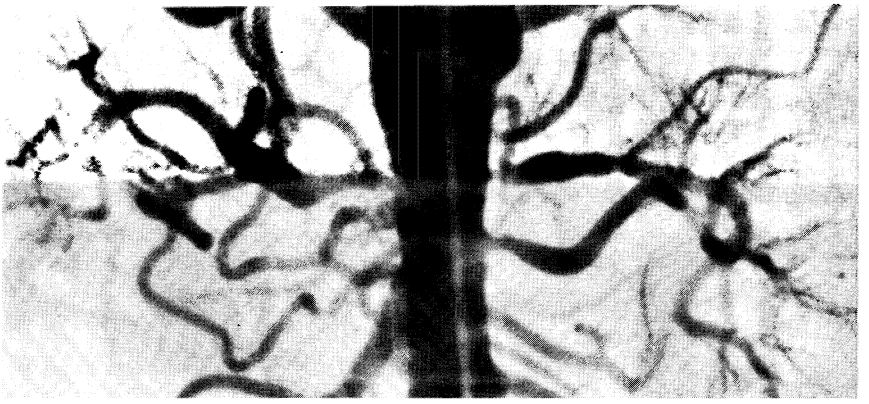

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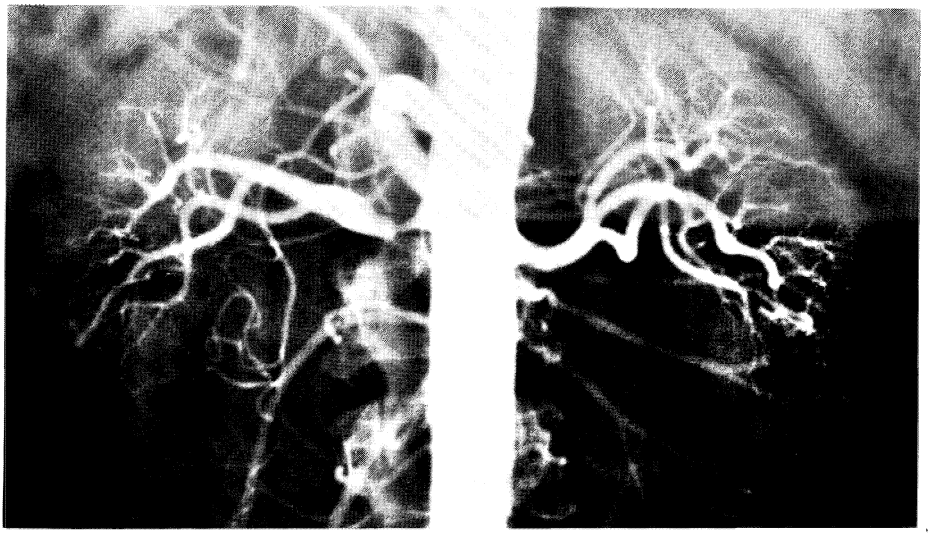
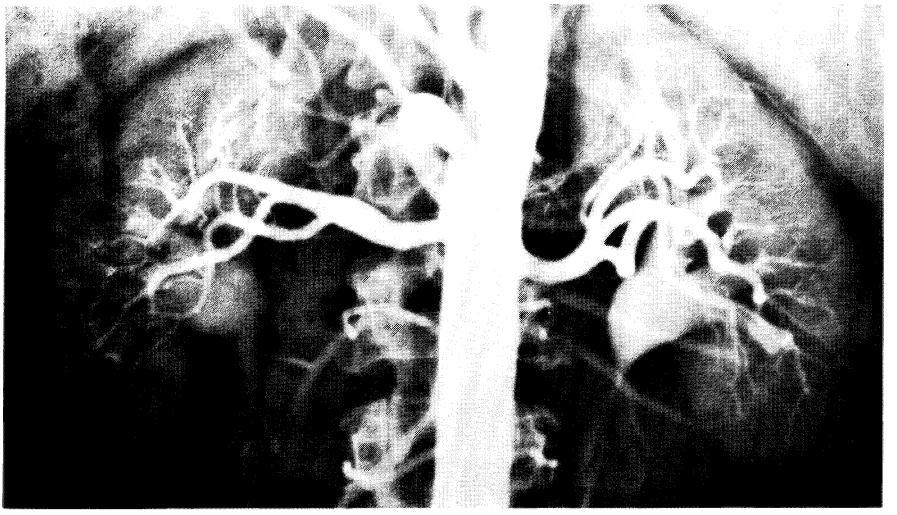


Figure 8. A 51-year-old man with a relatively short known history of severe hypertension. (A) Severe focal atherosclerotic stenosis before angioplasty; (B) successful angioplasty; (C) digital intravenous subtraction angiogram 3.5 years later shows no evidence of restenosis. The patient remained normotensive without medications.



90% of 31 patients in our series with fibromuscular disease had a technically successful renal angioplasty. In 51 patients with atheromatous disease the presence of an occluded renal artery (18 patients) (Figure 7A–C), or a stenosis at the ostium of the renal artery at the aortic wall (15 patients) heralded a low incidence of technical success (approximately 25%), whereas in non-occluded and non-ostial atheromatous lesions we achieved a technical success rate of 75% (Figure 8A–C).

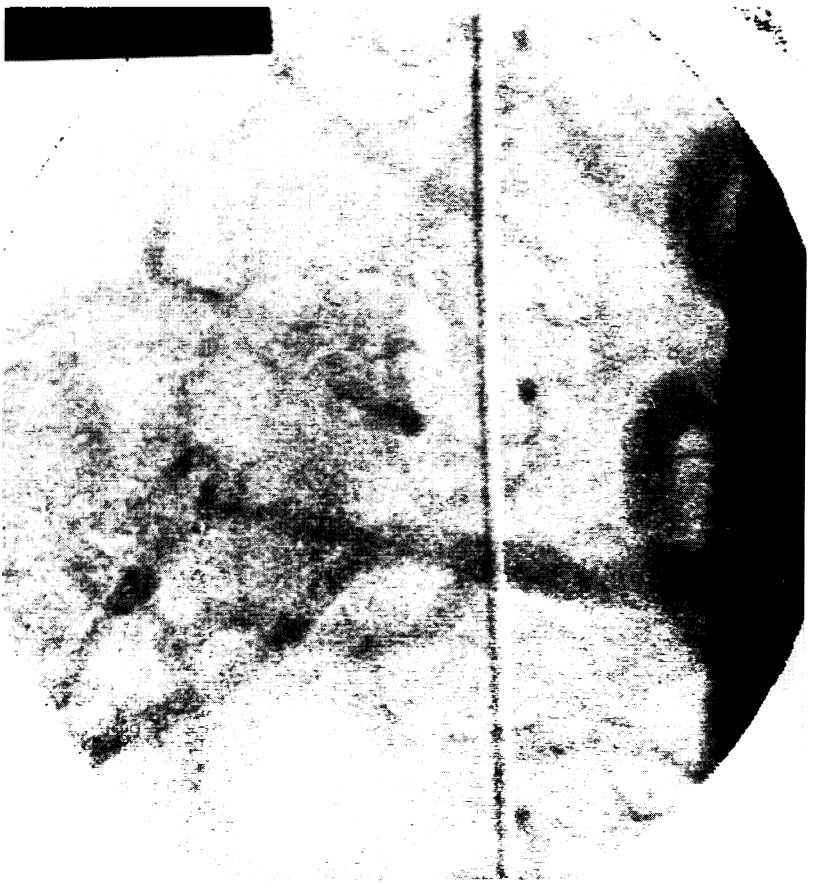


Figure 8 C.

Blood pressure benefit following PTRA

Since 1978 we have attempted PTRA in over 200 renal arteries. We recently reported our 4–40-month (mean 16) follow-up results in the initial 89 patients [20] (Figure 9). The criteria for blood pressure control were similar to those used in the US Cooperative Study for Renovascular Surgery [26]. Patients were classified as cured if their diastolic pressure was less than or equal to 90 mm Hg without antihypertensive medication, improved if there was a 15% decrease though still on medication, and failed if their pressure did not change or it changed less. Following successful PTRA 90% of patients with FMD showed a blood pressure benefit (cured and improved). These results are similar to those reported by other angiographers [27, 30] (Table 1). Following a technically successful angioplasty the blood pressure benefit was 82% in patients with unilateral atheromatous lesions. All of the

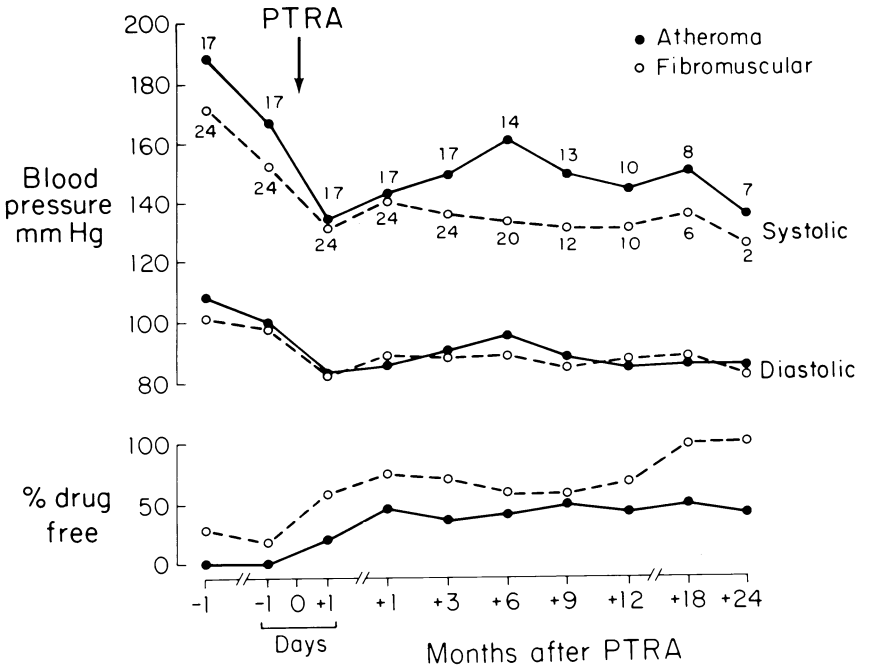


Figure 9. Blood pressure response in patients with atheroma and fibromuscular dysplasia following successful angioplasty. The numbers above each circle indicate the numbers of patients.

Table 1. Results of anglioplasty series for treatment of renovascular hypertension

Author	n	Cured (%)	Improved (%)	Failed (%)	Deaths (%)	Nephrectomy (%)	References
Fibromuscular							
Mahler	6	83	17	0	0	0	28
Kuhlman	13	67	33	0	0	0	27
Geyskes	21	48	48	5	0	0	29
Grim	17	47	35	18	0	6	30
Sos	27	59	33	7	9	3	20
Atheroma							
Mahler	8	13	63	25	0	0	28
Schwarten[a]	52	44	48	8	0	0	31
Kuhlmann	24	35	57	8	9	9	27
Geyskes	44	9	43	48	2	0	29
Grim[b]	25	4	36	60	20	20	30
Sos[c]	20	25	45	30	0	0	20

[a] Includes patients with fibromuscular stenosis.
[b] Results for 4-year follow-up.
[c] Results for complete and partial success in unilateral disease.
n = Number of patients treated.

21 atheromatous patients in whom a physiologically significant renal artery lesion was present bilaterally had severely advanced diffuse vascular disease: two-thirds of them had a total renal artery occlusion and renal atrophy, and half had an ostial stenosis. PTRA has been least successful for treatment of atherosclerotic renal arteries with total occlusion or where the lesions were at the ostium of the renal artery within the aortic wall. Since in bilateral disease only total success in dilating each offending lesion can be expected to successfully alleviate hypertension, it is not surprising that blood pressure benefit was the least in this group.

Kidneys with total renal artery occlusion are often rather shrunken and therefore reconstructive surgery is rarely indicated. Nevertheless, we have successfully recanalized and dilated five of ten such renal arteries [31]. We have also begun to use balloons as much as 3 mm greater in diameter than the involved renal artery and have thus began to achieve successful PTRA in ostial lesions. The incidence of patients with total renal artery occlusions and ostial lesions is higher at our institution than is seen at other centers. For these reasons the technical success rates in PTRA for atheromatous disease reported by many others approaches 90% [27, 29, 31].

Restoration of renal function

Only a few patients in our series had moderate to severe renal failure with creatinines of 4.3 and 3.7 mg/dl prior to angioplasty which fell to 2.5 and 2.9 mg/dl 2 years later. Renal function improved in all patients successfully treated for transplant arterial stenosis (Figures 10A, B).

Restoration of renal size

Renal size is dependent on renal blood flow. The kidneys are sponge-like, they respond to reduced blood flow by shrinking, and immediately upon restoration of normal flow they swell. This has been previously observed immediately following successful revascularization surgery. We have seen the same phenomenon immediately following successful PTRA (Figure 11A–D) and have documented that this increase in renal size is maintained for several years [20]. Fifteen kidneys at a mean follow-up of 20 months following successful PTRA showed a 13% increase in area, which is an approximately 1-cm increase in length. None of the kidneys became smaller and only one remained the same size.

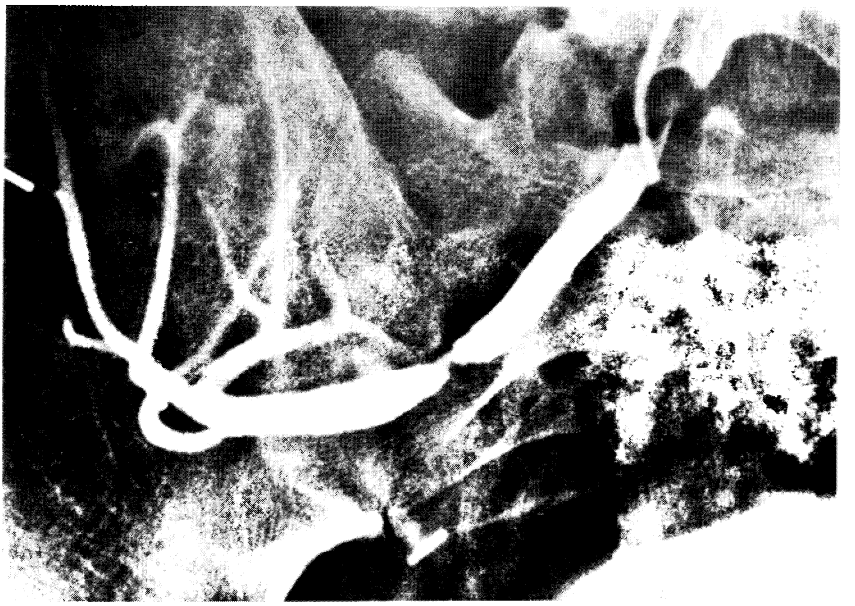


Figure 10. A 21-year-old patient with severe recent onset of hypertension who had renal transplantation 1 year previously. (A) Severe stenosis in the anastomosis between the hypogastric and transplant renal artery; (B) following successful angioplasty the stenosis is eliminated.

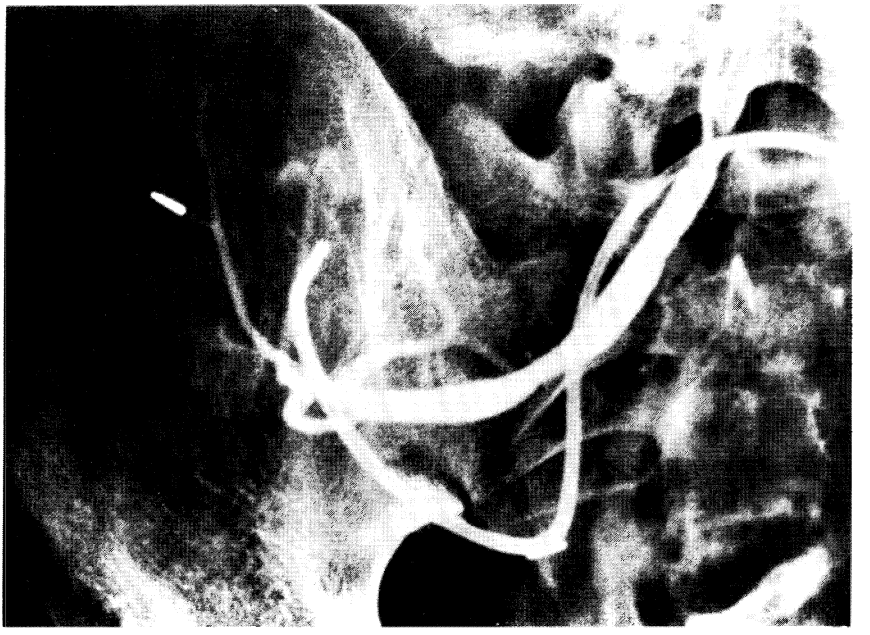


Figure 10 B.

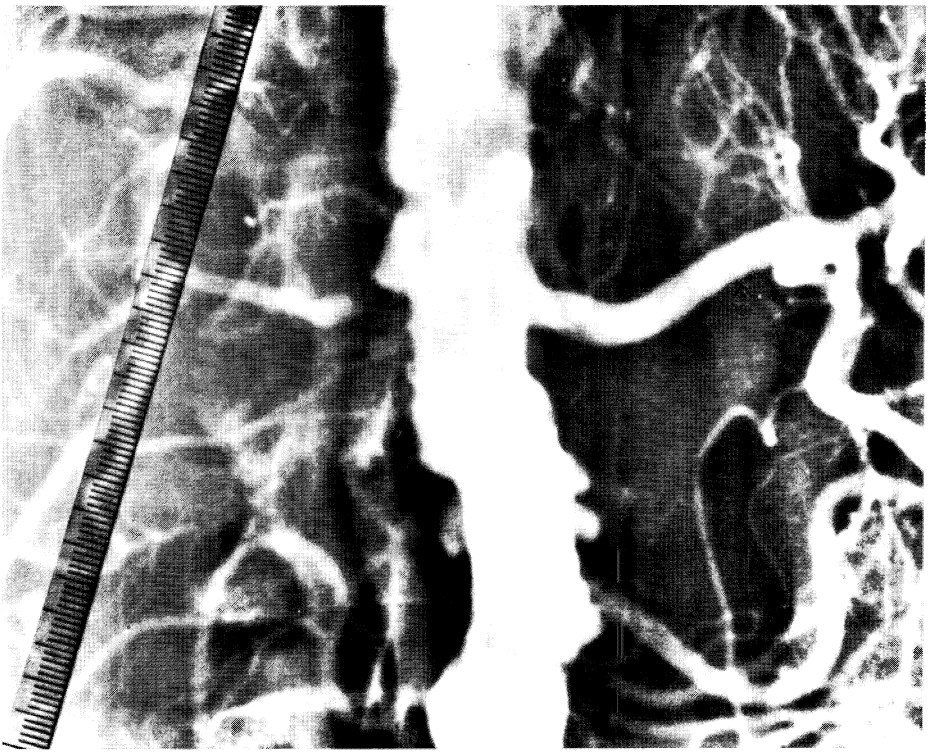


Figure 11. Dramatic change in the caliber of the renal artery and in the size of the kidney immediately following successful renal angioplasty. (A) Severe focal proximal stenosis. Note that the distal renal artery measures only 2.5 mm before angioplasty; (B) following successful angioplasty the increased flow in the renal artery has enlarged it to 5 mm distally; (C) immediately before angioplasty the right kidney was equal in height to the distance of 2.5 vertebral bodies (9.5 cm); (D) immediately following successful angioplasty the right kidney was equal to the height of 3 vertebral bodies (11.5 cm).

Response to PTRA in renal transplantation artery stenosis

Five to 25% [32] of patients develop renal artery stenosis and hypertension following renal transplantation. We recently reported our experience in PTRA for severe transplant artery stenoses [22]. Thirteen of 15 lesions were successfully dilated and ten of these patients had marked improvement in blood pressure and renal function for an average follow-up of 14 months (Figure 10). Restenosis in these patients is more frequent; three of them required redilation at 3–6 months following the initial procedure.

The choice of angioplasty vs. surgery

We have emphasized previously that medical therapy often results in loss of

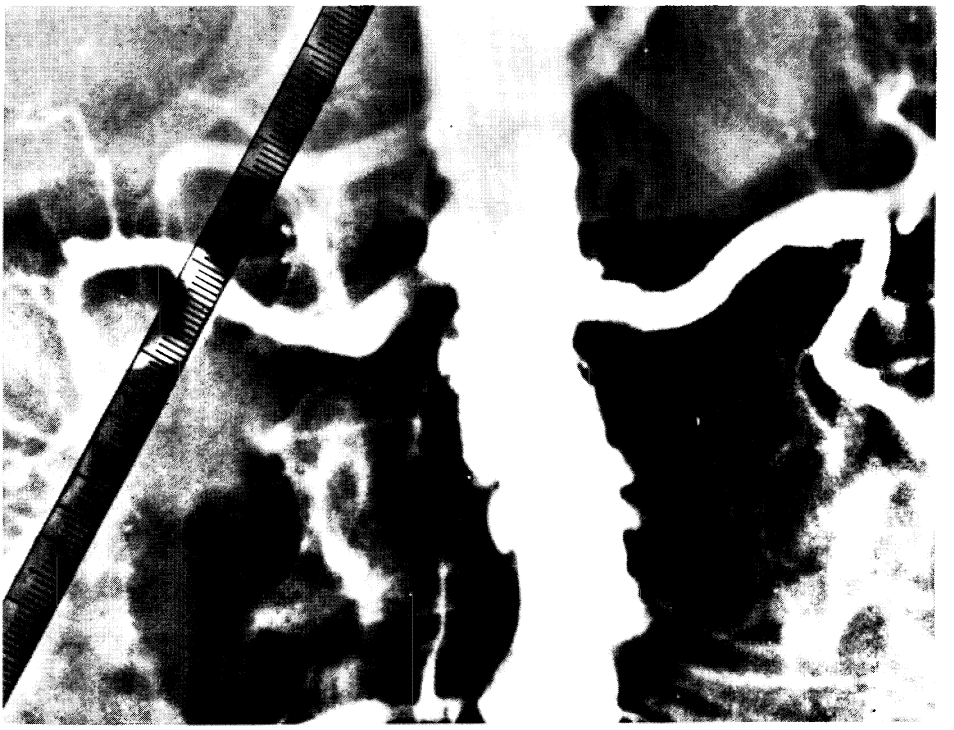


Figure 11 B.

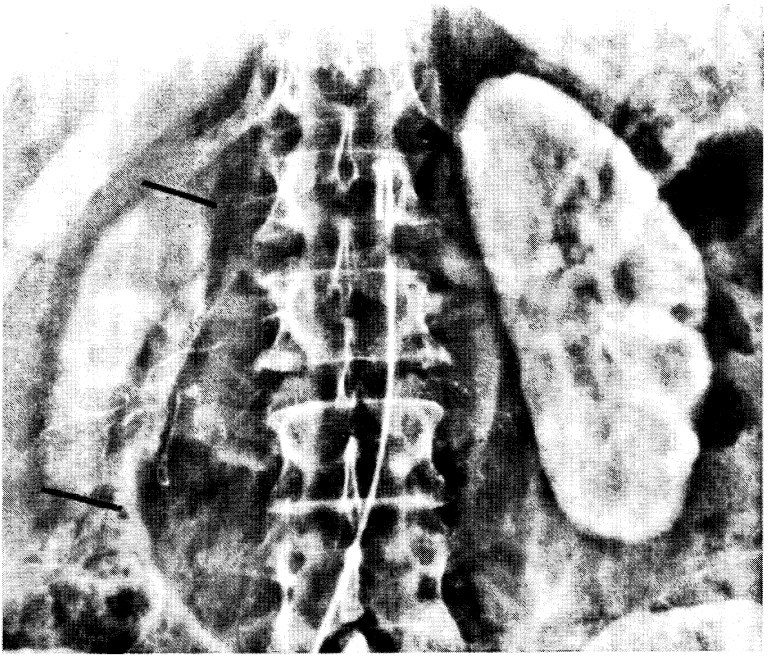


Figure 11 C.

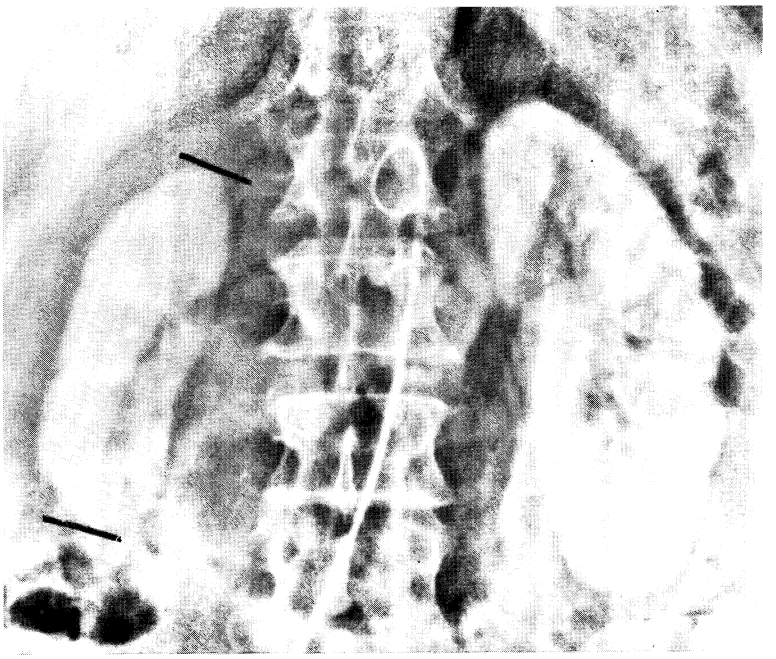


Figure 11 D.

kidneys even if hypertension is well controlled. For this reason, we feel that either angioplasty or surgery should be attempted in all patients who are suitable candidates. Since angioplasty is a 'reconstructive' procedure with a very low mortality and morbidity its failure or a rare recurrence (which can be redilated) usually carries no greater risk than would a prolonged diagnostic arteriographic procedure and therefore reconstructive surgery is almost always still possible. Angioplasty requires only a few days hospitalization and is thereby financially and psychologically advantageous for the patient and society. The mortality and morbidity of surgery is higher and cure is sometimes achieved by nephrectomy rather than by reconstruction. The results of angioplasty in fibromuscular disease are the same as those in surgery although angioplasty has the added advantage that peripheral branch lesions can be treated under direct visualization with fluoroscopy. The results of angioplasty in atheromatous disease are similar to those reported in the US Cooperative Study for Surgery [26], although more recent surgical techniques have produced better results [32–35].

For these reasons we feel that angioplasty should be routinely attempted as the initial treatment in all patients with renal artery stenosis and surgery should be reserved for those in whom angioplasty has failed or has resulted in a significant complication.

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10. Surgical Treatment of Renal and Renovascular Hypertension

M. SEDWITZ and W.T. STUBENBORD

Introduction

The role hypertension plays in the complications of cardiac, cerebral, peripheral vascular and renal disease is well known. Prospective studies have documented that an aggressive approach to the treatment of mild to moderate hypertension decreased morbidity and mortality [1, 2]. Thus, an aggressive approach to correct sustained hypertension medically and surgically is important.

Historical considerations

The concept of a potentially correctable etiology for hypertension had its foundation in the classical studies of Goldblatt. In 1934, he observed that sustained hypertension could be experimentally produced by stenosis of the renal artery in uninephric dogs [3]. This originated the belief that nephrectomy was a potential treatment option in patients with hypertension, who also had a small atrophied kidney and coincidental renal artery stenosis [4]. However, Smith's comprehensive review of 575 nephrectomies dampened enthusiasm when in only 26% of these did patients benefit from the operation [5]. He concluded that nephrectomy should be reserved for those patients with strict urologic criteria and with no regard to hypertension. Subsequently, the advent of renal artery reconstruction failed to generate significant enthusiasm since the mortality appeared excessive and benefited less than half of the candidates. It was obvious that the role of surgery would need to be clarified. However, the evolution of the dynamic hormonal relationships of the renin-angiotensin aldosterone pathway, the increased reliability of renin assays and the improved methods of arteriography have all provided improved patient selection for surgery. Hunt et al. [6] compared prospectively the surgical and medical management of 81 patients

with renal vascular hypertension. Sixty-one percent of the medically treated group died during the 7–14-year follow-up and had a higher complication rate. The surgically treated group had a 29.7% mortality during this period. However, approximately 90% were cured or improved of their hypertension, thus, illustrating the impact surgery has had in the correction of renal vascular hypertension. In general, failure to surgically correct an obstructive renal artery lesion leads to progressive stenosis and occlusion in 36 to 63% of the patients [7, 8]. The natural history of renal artery stenosis is manifested by progressive hypertension with its large number of systemic effects, most importantly deterioration of renal function. Aggressive long-term hypertensive medical management has done little to alter the progression of these lesions and may in fact hasten renal deterioration by lowering the blood pressure necessary to perfuse an ischemic kidney, thus, resulting in kidney atrophy and fibrosis.

Therefore, diagnostic evaluation is generally undertaken in all patients with the recent onset of severe medically uncontrolled hypertension who would be candidates for renovascular reconstruction if a significant and progressive stenosis is found.

Definition of pathologic entities

Renal vascular hypertension is the most common form of correctable hypertension and comprises approximately 5 to 10% of the total hypertensive population. Two major classes of lesions appear to be responsible for renal vascular hypertension. These are atherosclerosis and fibromuscular dysplasia. Rare forms of intrinsic and extrinsic renal disease may also cause renal ischemia and hypertension. Atherosclerosis is the lesion responsible for renal vascular hypertension in 60 to 70% of the cases. It is bilateral in 30% of the patients and has been observed as part of the generalized process of atherosclerosis in every major artery. Typically, the lesions occur within the first 2 cm of the artery or as a result of narrowing of the renal artery secondary to generalized aortic disease.

The other significant cause of renal artery obstruction is fibromuscular dysplasia. This is an idiopathic nonatherosclerotic lesion that comprises 30 to 35% of renal vascular lesions. The cause of this lesion is unknown. It is produced by disruptive and hyperplastic changes within all portions of the artery. Usually it is categorized into the following four subsets: intimal fibroplasia, fibromuscular hyperplasia, medial fibroplasia, and perimedial fibroplasia. Stewart's et al. [9] comprehensive review delineated the incidence and natural history of these lesions.

First, intimal fibroplasia which produces smooth focal stenoses comprises greater than 10% of the group. It is commonly seen in children and young

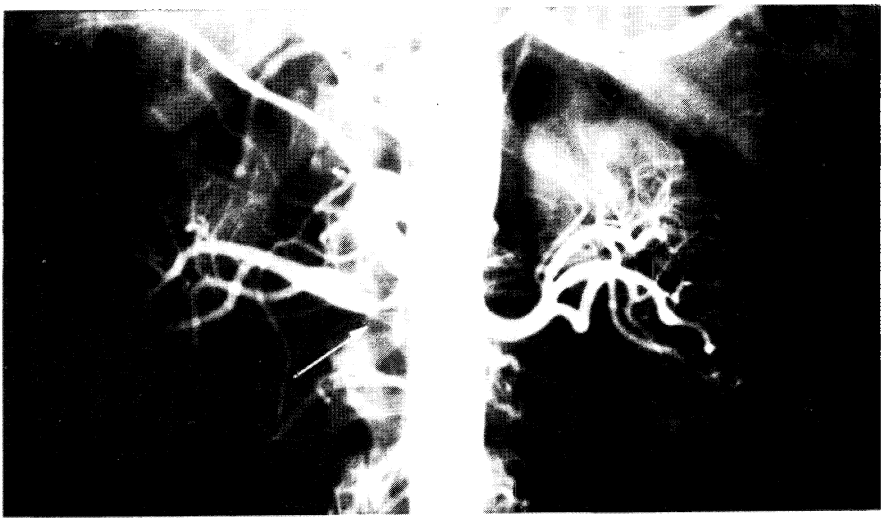

Figure 1. Unilateral renal artery stenosis of the right renal artery due to atherosclerosis.

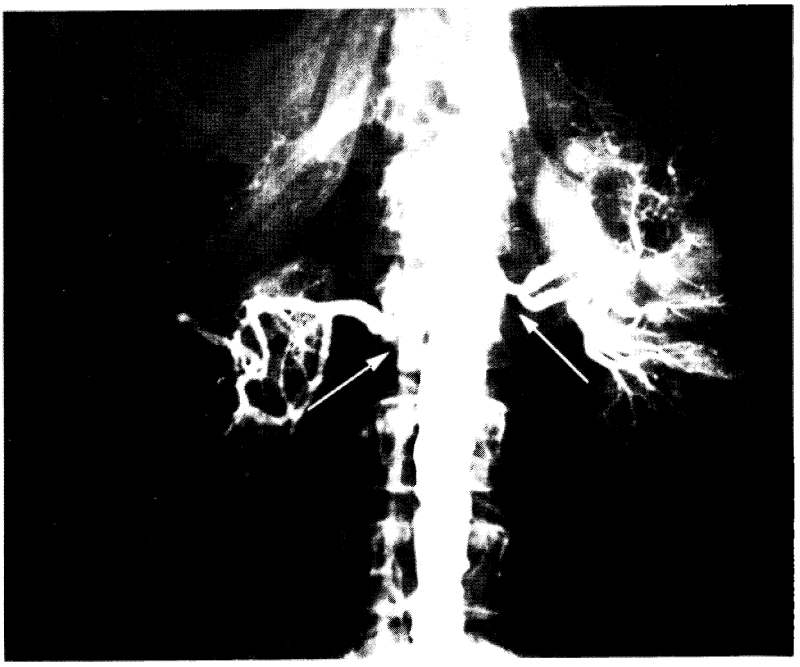

Figure 2. Typical location and appearance of bilateral renal artery stenosis due to atherosclerosis.

adults. This lesion results in progressive obstruction and requires surgery when hypertension is present.

True fibromuscular hyperplasia is rare, difficult to distinguish from intimal fibroplasia and comprises 2–8% of the cases. In young, symptomatic patients surgery is recommended. Medial fibroplasia is the largest subset of

fibromuscular dysplastic lesions. Medial fibroplasia is seen in a younger population (25–50 years of age) and more frequently in women. The right renal artery appears to be more commonly affected and the lesions appear to be bilateral in 25 to 60% of the patients. The most common arteriographic form is a chain of focal stenoses with mural aneurysms that characteristically produce a 'string of beads' appearance. The process appears to begin in the distal main artery and frequently extends into the segmental arterial branches. This lesion often resists dissection, hemorrhage or progression to thrombosis. Thus, in patients with controlled hypertension who are greater than 40 years of age, continued medical management of this lesion may not lead to progressive morbidity. On the other hand, young patients with progressive hypertension should undergo renovascular repair for this lesion.

Finally, perimedial fibroplasia comprises 10–15% of the lesions. It is a progressive disease more commonly seen in women and usually requires surgical intervention when discovered.

The remaining 5% of causes for renal vascular hypertension fall into a miscellaneous category made up of thrombosis, embolus, dissection, trauma, arteritis, extrinsic compression secondary to tumor, cyst or aortic aneurysm, renal artery aneurysm and arteriovenous fistula.

Diagnosis

The diagnostic evaluation is directed at identification of patients with renal vascular hypertension who will benefit from surgery. Rapid sequence intravenous pyelography is an important test in evaluating renal vascular hypertension. Although the accuracy of intravenous pyelography has been higher in the atherosclerotic group (70–90%) it has been less than optimal for fibromuscular disease in both adult (47%) and pediatric (24%) patients [10]. The high false negative rate (17–30%) compromises its usefulness. The intravenous pyelogram accurately depicts size, architecture and presence of kidney pathology. The arteriogram is the most definitive diagnostic test for detecting renal artery lesions. The arteriogram is a low morbidity procedure (1.2%) and has a mortality of 0.11% [11]. The arteriogram delineates the aorta and major, segmental and accessory blood vessels to both kidneys. The arteriogram must demonstrate oblique views of the aorta and renal artery in order to avoid false negative studies. The tortuous course of the left renal artery and the superimposition of one artery upon another may mask a critical stenosis unless oblique views are obtained. Occasionally a false positive renal arteriogram is obtained when spasm is initiated by the tip of the catheter. However, flushing the artery with a vasodilator substance will show disappearance of this false lesion.

Split renal function tests which were popularized by Howard and Stammy have generally been discarded from the diagnostic armamentarium. They have been shown to be time consuming, associated with high morbidity, and more importantly, associated with a high false negative rate (32–58%) [12]. However, split renal function tests may be valuable in determining viability of a severely ischemic kidney. Some centers report that split renal function tests have identified a group of patients with unilateral renal artery stenosis who had nonlateralizing renins but lateralizing split renal function tests who benefited from operative intervention.

The accuracy of renal vein renins, an establishment of renal vein ratios and renal systemic renin indices have shown the greatest accuracy in defining patients who will benefit from surgery [13]. The false positive rate of those modalities is small. However, a problem still exists in the high false negative rate which approaches 50% [14].

In conclusion, it appears that no single diagnostic test is sufficient to predict the role and benefit of surgery. In combination, however, specificity will improve.

Preoperative management

Preoperative assessment of candidates for renal vascular surgery must take into account the accompanying extrarenal manifestations of atherosclerotic vascular disease. The accompanying cardiac, cerebral and peripheral vascular disease significantly affect morbidity and mortality. It is often that this high risk group is relegated to long term medical management and the consequent complications of ongoing hypertension and side effects of antihypertensive drugs. Before renal vascular repair is contemplated, correction of concomitant cardiac or cerebral vascular disease is generally performed. Patients with generalized atherosclerosis have been shown by Stanley [15] to have a significantly greater operative mortality and a 3-time greater failure rate as compared with a group who have a single focal atherosclerotic lesion. When the consequences of hypertension are uncontrolled and renal function is deteriorating, surgery is the only alternative. The key to a successful operation exists in the pre-, peri-, and postoperative management of these high risk patients. The preoperative goal in preparing these patients for surgery is to maximize their cardiac output. Cohn [16] has shown that hypertension increases left ventricular work and decreases cardiac reserve. This is usually in the setting of patients who already have altered cardiac dynamics secondary to congestive heart failure or ischemic cardiac disease. These patients, who have been on chronic antihypertensive therapy often show signs of intravascular fluid depletion which further places them at risk.

As a rule, most antihypertensives, such as diuretics, reserpine or guane-

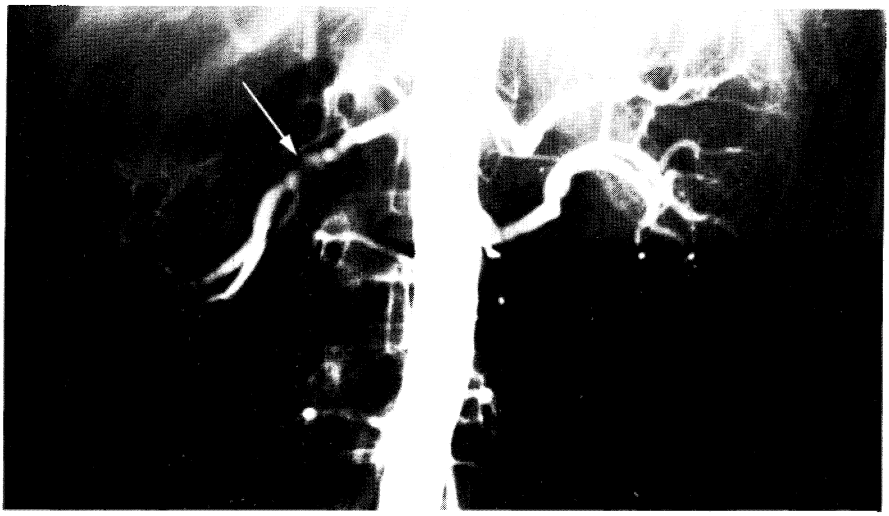

Figure 3. Aortogram showing fibromuscular dysplasia of the right renal artery with the 'string of beads' appearance.

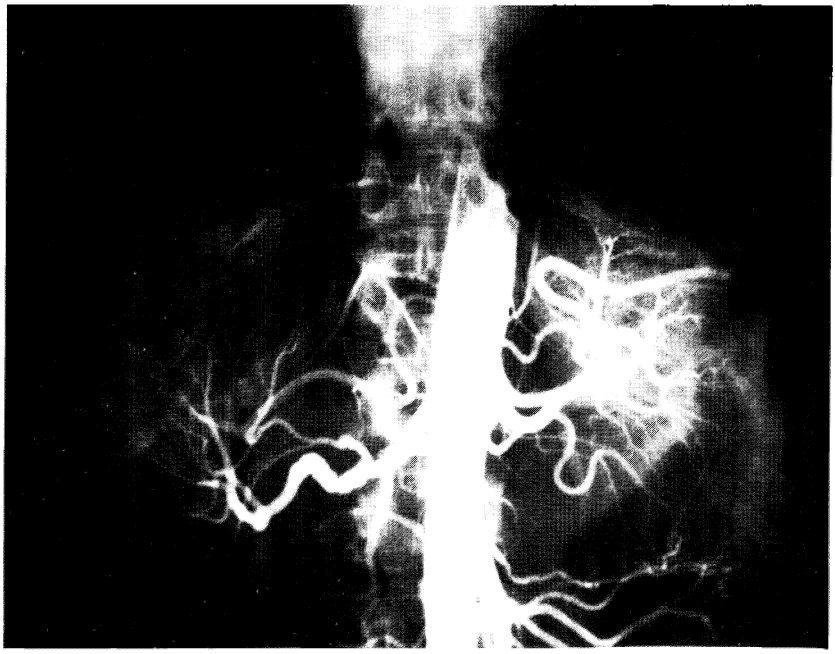

Figure 4. Bilateral renal artery fibromuscular dysplasia including an accessory left renal artery.

thidine should be stopped for approximately two weeks prior to surgery. The patient is then managed with methyldopa since there is little interaction of this drug with anesthetic agents.

The preoperative placement of a Swan-Ganz catheter is one of the most important maneuvers. It permits monitoring of cardiac output and left ven-

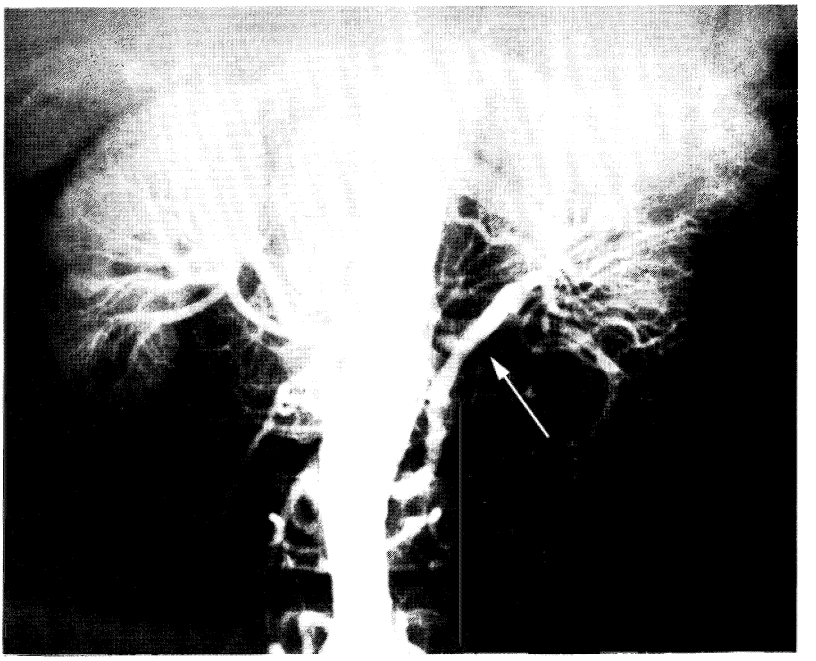

Figure 5. Postoperative aortogram showing a patent side-to-side saphenous vein aortorenal bypass.

tricular pressures. Prior to surgery the patient has baseline measurements of cardiac output and pulmonary capillary wedge pressure. Adequate fluid replacement and afterload reducing agents, such as nitrosprusside and nitroglycerine, can place the patient at the peak of his Starling curve. This will result in improvement in cardiac output, decrease in afterload and decrease in cardiac work. Fry reported in a small series that no deaths occurred in this high risk category [17].

Surgical management

The surgical approach to the problem of renal vascular hypertension has varied between renal artery thromboendarterectomy, bypass surgery and nephrectomy.

Thromboendarterectomy

Thromboendarterectomy has its main advantage in the treatment of atherosclerotic renal vascular hypertension. The advantage of thromboendarterectomy is that it permits access to both major renal arteries, any accessory

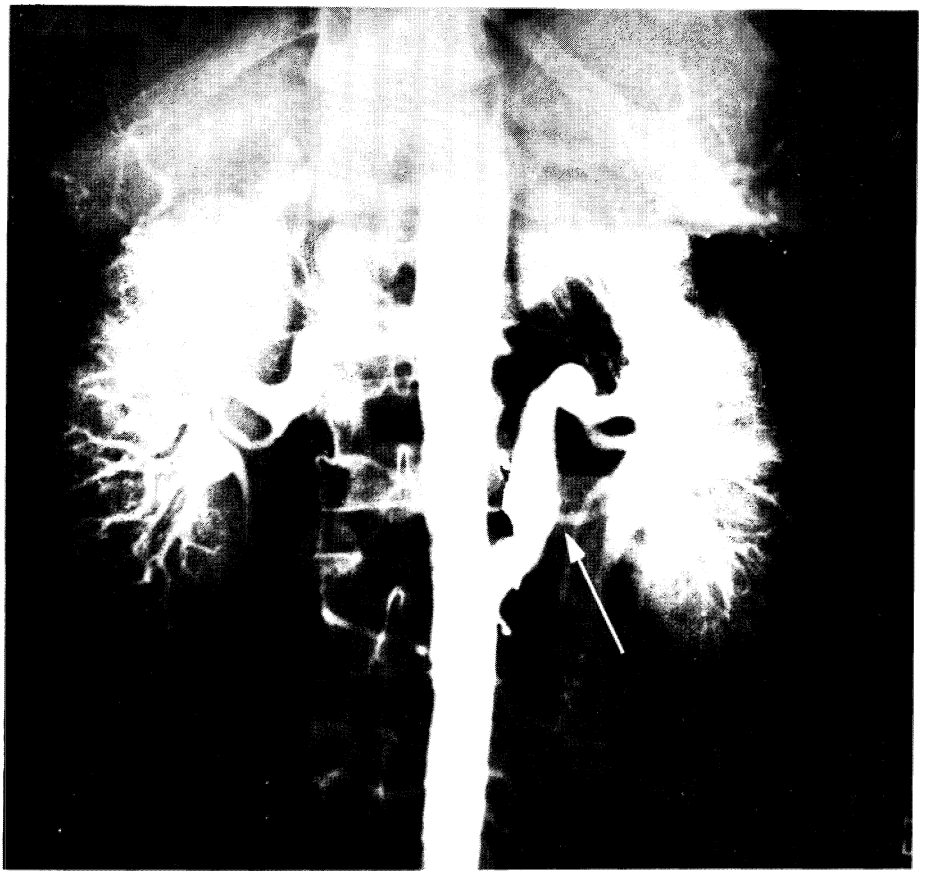

Figure 6. Postoperative aortorenal bypass showing subsequent aneurysmal dilatation of the saphenous vein graft.

renal artery and other generalized pathology within the aorta. The endarterectomy does not require autogenous or prosthetic material. Often the renal orifice is enlarged following endarterectomy. The disadvantages often relate to the time the procedure takes both to skeletonize the aorta and keep the superior aorta clamped. Occasionally, the distal margin of the endarterectomy cannot be properly mobilized obligating an additional transrenal endarterectomy to remove plaque or an arteriotomy to secure an intimal flap. Sometimes, a patch graft angioplasty is necessary to avoid compromise of the lumen of the artery. Availability of arteriography in the operating room to rule out kinking, stenosis, dissection or an obstructing intimal flap is advantageous.

Approximately 76% of patients treated by Wylie and associates [18, 19] were cured or improved by thromboendarterectomy. This has also been the experience at the Cleveland Clinic where 81% of the patients were cured or improved. The postoperative occlusion or restenosis rate was 12% [20].

Bypass grafting

Bypass grafting has been popularized at other major medical centers. Their applicability to both fibromuscular dysplasia and atherosclerotic lesions are well known. The procedures generally consist of end-to-end or end-to-side aortorenal bypasses. Also, selective splenorenal, hepatorenal and iliacrenal bypasses have been performed.

Generally, autogenous vein, artery or prosthetic materials have been utilized. Autogenous vein has been a popular material because of its easy availability and flexibility. Their durability and high performance have been evaluated by Dean et al. [21]. Veins less than 4 mm in diameter have been shown to be fragile and prone to long term dilatation. The vein must be able to withstand flows of 300 to 400 ml of blood/min. Vein graft dilatation has been reported in 20 to 44% of cases. This progresses to aneurysmal dilatation in >50% of cases. Aneurysmal rupture has not been reported, but aneurysms may be a factor in altering blood flow causing thrombosis or as a source of microemboli. Many series have reported excellent results (73–96%) with saphenous vein bypass [22]. Autogenous hypogastric artery and in some cases splenic artery appears to offer other advantages. Their main advantage has been their unmatched durability, particularly in the pediatric age group. Problems arise in the dissection of the artery in the pelvis in determining the significance of the artery to blood flow to the colon and pelvis, and finally in its usability when the artery is affected by atherosclerotic disease. Occasionally, endarterectomy has been required. Wylie and Lye [23] reported a 96% cure rate for renal vascular hypertension without complications at 10 years, using autogenous hypogastric artery. Finally, a prosthetic material may be utilized. It is believed by Kaufman [24] that they have a high chance of patency because of their short length, high flow rate and fixation. Although it is inferior in long term patency and is susceptible to infection it has usually been successful. It is particularly helpful when autogenous tissue is unavailable or of too small a diameter. However, prosthetic grafts less than 6 mm are prone to early thrombosis.

Splenorenal anastomosis has also been utilized. It offers the advantage of using autogenous splenic artery without manipulation of the diseased aorta. Its indications have been for repair of a left renal artery lesion. In bilateral renal vascular hypertension it permits future reconstruction in a virgin field on the right and is an alternative for failed reconstruction on the left.

Hepatorenal bypass using autogenous vein offers the same advantages as previously discussed for splenorenal bypass but only for the right side. An anastomosis end-to-end into the distal renal artery has been performed successfully by Libertino [25].

Ex vivo *repair and autotransplantation*

Evolution of improved vascular techniques and improvement in kidney preservation have provided the foundation for both autotransplantation and *ex vivo* repair. Significant lesions in small segmental arteries, distal renal artery aneurysms and renal artery obstruction in children have been alleviated through *ex vivo* reconstruction. *Ex vivo* reconstruction and autotransplantation are alternatives when *in situ* repair is difficult or when repair is required in vessels less than 3 mm. Belzer [26] reported an 86% cure/improvement rate in 33 patients followed 6 months–10 years with a mortality of 5% using this technique.

Standard temporary nephrectomy is performed. The kidney then is flushed with iced saline solution or continuously pumped with hypothermic perfusate. The defect is corrected utilizing autogenous arterial and/or venous tissue. Management of the ureter is by performing standard ureteroneocystostomy and carries a complication rate of less than 0.5%. It is also possible to perform benchwork surgery with the kidney on a platform while the ureter remains intact and the kidney is continuously perfused. Routinely, all anastomotic leaks should be repaired prior to autotransplantation. However, if arteriography is required it should be performed with dilute 60% megluineiothalamate. Excessive handling and trauma of the kidney may result in vasospasm which leads to postoperative renal complications.

Nephrectomy

Nephrectomy still maintains a role in the treatment of selected cases of renal vascular hypertension. The advances in *ex vivo* reconstruction have reduced the incidence of nephrectomy. Commonly, nephrectomy is reserved for high risk, elderly patients with functioning contralateral kidneys who clinically could not tolerate a prolonged reconstruction. Other indications include patients who have failed a primary reconstruction and who are not candidates for *ex vivo* repair and finally those patients whose kidneys show extensive atrophy and infarction.

In the past, sustained hypertension secondary to total renal artery occlusion has usually been treated by nephrectomy. Those patients having total occlusion secondary to atherosclerosis also benefit from an aggressive approach to revascularization. There seems to be no correlation between the duration of occlusion and renal viability since viability is maintained by the intricate system of collateral periureteric, peripelvic, adrenal, pericapsular and lumbar vessels. These patients show sustained hypertension and elevated renin levels in the setting of a nonfunctioning kidney on intravenous

pyelogram. Often symptoms of impending uremia reflect the renal deterioration of the contralateral kidney in the face of sustained hypertension. It has been amply demonstrated that revascularization in this setting can cure hypertension and reverse the ongoing process of renal failure.

Revascularization is dependent upon intact glomeruli as proven by renal biopsy and patency of the distal renal artery as seen by retrograde flow of the distal renal artery secondary to collateral vessels. Revascularization with bypass or endarterectomy has been shown to effectively treat this type of hypertension and above all improve renal failure.

Results

The success of renal revascularization is well documented by groups from San Francisco, Michigan, Cleveland Clinic and Vanderbilt [15, 18, 19, 21, 28, 29]. Although the success of each procedure varies according to the lesion, extent of disease and other health related variables, it should be emphasized that surgery cures or improves hypertension refractory to medical management and preserves renal function. The mortality for renal revascularization is generally accepted to be less than 2%. It is also accepted that the pediatric age group and adult age group with fibromuscular dysplasia respond better to renal revascularization, and 90 to 95% are cured or improved. The same degree of success (85–91%) has been found in patients with focal atherosclerotic lesions of the renal artery [30]. The operative success usually declines in patients with diffuse atherosclerotic disease. The risk of surgery is higher and the margin for error is less. In this high risk group, 53 to 73% of the patients were improved or cured with atherosclerotic lesions and 85% improved with fibromuscular dysplastic lesions [28]. The success of first correcting the dominant lesion has been demonstrated by Dean [31]. He noted a 21% failure rate when bilateral simultaneous repairs were performed. The significance of the second lesion may be evaluated after the anatomical success of the first operation has been documented.

The mortality in these series ranges from 0 to 21%. In one series there was a group of approximately 6% where an anatomic repair was successful although the hypertension was unchanged. It is believed that although hypertension was not cured, preservation of renal tissue was achieved. It should be noted that secondary procedures, either reexploration or nephrectomy following a previous renal revascularization, have a high yield of success.

Success in pediatric population

Renovascular hypertension in children, secondary to renal artery stenosis, is

the most common form of surgically correctible hypertension second only to thoracic coarctations. Renal artery stenosis in children, is most commonly of the intimal and perimedial fibrodysplastic types. It is usually a single mural or focal lesion distributed anywhere in the course of the artery. There has been a high incidence of neurofibromatosis and abdominal aortic abnormalities accompanying renal artery stenoses. Despite the small calibre of the renal artery and extension of disease into segmental branches, the surgical approach has cured or improved hypertension and preserved renal function. A 97.5% benefit in a review by Stanley et al. [32] of 40 patients has amply demonstrated the successful role of surgery. Repair is usually performed with autogenous vein as an aortorenal bypass graft. It would appear in view of the late complications of vein graft dilatation and aneurysm formation that autogenous internal iliac artery is a superior material [33]. Other approaches to the problem of reconstruction in infants and young children utilize reimplantation of the renal artery into the aorta for a proximal lesion of the renal artery. Dacron has been used in small children whose veins and arteries are too small for bypass without complication. In cases where surgery appears technically impossible, or the infant's condition precludes surgery, temporary medical management appears justified until, at a later time, surgery may be feasible. Lawson et al. [34] reviewed a small group of children with renal revascularization and found that 32% within a 3-month–10-year period developed a contralateral fibromuscular lesion, thus supporting the need for careful follow-up and aggressive surgical intervention at the time the original lesion is discovered. Finally, nephrectomy should be reserved as in adults, for patients with renal atrophy, infarction or severe segmental disease.

Complications

Early problems

Complications of renal revascularization are unique. Complications of renovascular reconstruction include both early and late thrombosis. The early thrombosis rate is approximately 4–8% and is higher when prosthetic materials are used [35]. Continued hypertension and/or hematuria may herald the onset of these early failures in the postoperative period. Technical failures are the most important factor responsible for early thrombosis. These failures are often secondary to intimal flaps, dissections at the distal anastomosis, and kinking of the graft. Careful handling of the vessel and spatulating the ends of the anastomosis in an end-to-end manner will usually decrease some of these early failures. Angiography, heparinization and immediate reexploration are essential if early thrombosis is suspected.

Thromboendarterectomy has its own set of complications. Elevation of the intimal flap may be produced. This is usually the result of failure to identify and remove distal plaque and can be avoided by performing a renal arteriotomy, assessing the distal extent of disease and closing this with a vein patch. Postendarterectomy occlusion also requires prompt reoperation with a subsequent bypass procedure as the operation of choice.

Rare complications are produced as a result of dilators raising intimal flaps for distal fibromuscular dysplasia lesions. The dilators should be greater than 2 mm in diameter to avoid intimal damage and no larger than the diameter of the vessel plus 1 mm. Often these complications result in nephrectomy or the necessity of *ex vivo* repair.

Renal failure is a distressing complication. This may be complicated by an ischemia time greater than 60 min and prolonged intraoperative hypotension. Extensive dissection and interruption of collaterals may further compromise blood flow to the kidney. It is believed that the kidney may be protected by the use of adequate preoperative and intraoperative hydration. The use of hypothermia, mannitol and loop diuretics at the time of renal artery occlusion prolong the available ischemia time.

Long-term problems

Late occlusion or thrombosis is commonly due to dysplastic fibrous tissue at the anastomotic site. Factors responsible for compromise, leading to hemodynamic turbulent flow, include graft malpositioning, perigraft hematoma, which impedes neovascularization of the conduit, as well as initiating a fibroproliferative process, and operative trauma to the graft itself. Stenoses have been reported in approximately 41 % of patients subjected to postoperative angiography [36]. Significant stenoses with hemodynamic alterations have been reported in 8 %. These require prompt reoperation. It is rare to find late stenosis or thrombosis on arteriograms in patients who have undergone thromboendarterectomy or have had autogenous artery used as the graft.

Late stenosis usually manifests itself as recurrent hypertension. Late stenosis must be distinguished from progressive disease in the contralateral kidney. Often it may be treated by transluminal dilatation or other local processes.

Vein graft dilatation in the long term appears to be a significant problem. It appears two times more frequently in the pediatric age group and reflects the fragility of the graft itself.

Finally, renal artery fistulazation has been reported but is rare. Infection of prosthetic grafts is also a rare occurrence. Mortality with infected grafts, however, ranges from 25–75 %. Renal infarction after anatomically success-

ful renal artery repair occurs. Embolic or intraparenchymal thrombosis appears to be responsible. This should be a consideration in the face of sustained hypertension after technical factors during the repair of the artery have been ruled out as a cause. Inadequate systemic heparinization during the time of occlusion of renal blood flow is a potential cause of thrombosis. Since infarcted tissue may produce continued hypertension, surgical intervention may be necessary.

Renal artery aneurysms

Renal artery aneurysms represent an entity that may be responsible for hypertension in selected patients. A relationship appears to exist but proof of a cause and effect is elusive. Hypertension has been reported to be present in patients with renal artery aneurysms (72–79%) [37, 38]. The presence of a stenotic lesion in association with the aneurysm may only be determined during surgery. A mechanism of atheroemboli leading to infarction is also possible. Extension of aneurysmal thrombosis to occlude branch arteries has been suggested. A surgical approach has been aimed at preventing rupture of the aneurysm and to reduce hypertension if the lesion is shown to be contributory. A dissecting aneurysm is an obvious indication for surgery. The approach to prevent rupture is not quite as clear. It is accepted that an aneurysm less than 2 cm may be observed. In a patient who is pregnant or who remains hypertensive, repair is generally indicated even if the aneurysm is smaller than 2 cm. For an aneurysm 2 cm or larger, repair is dictated by the health of the patient and other contributing factors. Treatment thus, should be individualized. Surgery is aimed at preserving renal tissue and function.

Renal arteriovenous fistulas

The incidence of arteriovenous fistulas is very small. It is associated with hypertension approximately 85% of the time [39]. Generally, there are three types of arteriovenous fistulas: congenital, idiopathic and acquired. The largest category is acquired fistulas and is usually the result of renal biopsy or trauma. Although it is reported secondary to neoplasms and infections, these are both very rare. The hypertension is both systolic and diastolic. The latter is a result of the shunting of blood away from the kidney thus rendering parts of the kidney ischemic. Although obtaining meaningful renin levels is difficult, the etiology for the hypertension is believed to be renin-mediated. The symptoms produced by an arteriovenous fistula, congestive heart failure and hypertension, usually resolve spontaneously. Sometimes

closure has been seen approximately 18 months after diagnosis. In rare cases, hypertension persists and surgical intervention will be required. In general, nephrectomy has cured 53 to 60% of patients with hypertension [40, 41]. Alternatives to nephrectomy aim at preserving renal tissue. These procedures consist of *in situ* or *ex vivo* repair, ligation of the branch or feeding vessels and embolization.

Hypertension in the transplant recipient

Hypertension following transplantation may require surgical intervention for two reasons. Some patients whose native kidneys remain in place may require bilateral nephrectomy in an effort to cure their hypertension. The experience of predicting whether or not native kidneys in these patients are producing hypertension by selective renin levels has not been satisfactory. In the presence of no significant transplant renal artery stenosis, bilateral nephrectomy is generally indicated if there is not satisfactory control of hypertension by medication. With the availability of the newer antihypertensive agents, however, bilateral nephrectomy following transplantation has become less common.

Transplant renal artery stenosis occurs in about 5% of transplant recipients. It may take several forms. These include anastomotic scarring or kinking, intimal scarring from cannula damage during kidney perfusion, and finally intimal thickening and scarring beyond the anastomosis which is due to some form of rejection. All of these may produce obstruction to the transplant with the usual pressure gradient and hypertension. Surgical repair of these stenotic lesions is always technically difficult, but yields satisfactory results. The availability of transluminal balloon dilatation has been particularly useful in these patients and is to be recommended generally before surgery, particularly with end-to-end internal iliac to renal artery anastomoses the catheters are easily passed and there is no acute angle to be negotiated. Even repeated dilatations have been quite satisfactory and have largely replaced the surgical approach to this problem [42].

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