KIDNEY DISEASE AND HYPERTENSION

Robert D. Toto, M.D.

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I. INTRODUCTION

End-stage renal disease (ESRD) attributed to primary (essential) hypertension has been increasing at an alarming rate (7.6% per year) over the last decade (1), now accounting for 25% of new cases of ESRD. Moreover, the annual Medicare costs to manage hypertensive renal failure, currently $ 1 billion/year will increase at a rate of $ 40 million/year over the next 10 years (2). New data clearly indicates that in the U.S. it afflicts blacks at a much higher rate than whites. In short, kidney disease due to hypertension is a major public health problem that demands immediate attention. Despite voluminous investigations into the causes of both primary hypertension and renal disease associated with it we still do not know which came first nor do we have a clear understanding of the precise pathogenesis of either one. Thus on the one hand, the question posed by Bright in 1836 remains with us today: Does the kidney disease cause hypertension, or does hypertension cause kidney disease? On the other hand some advances have been made in this field. Recent studies in patients with treated hypertension suggest that hypertension control is effective in at least slowing the rate of renal disease in some patients but is not the only factor leading to progressive renal disease in all patients. Therefore, we now know that persistent elevation of systemic blood pressure is associated with deterioration in renal function in patients with both "malignant" and "benign" forms of primary hypertension and lowering blood pressure effectively slows progression of renal failure in many cases.

The goal of this Grand Rounds is to present some of the new information on and current concepts about the epidemiology, pathology, pathogenesis, pathophysiology, diagnosis and management of kidney disease in hypertension. The role of antihypertensive treatments in the management of patients with kidney disease including: a) specific classes of antihypertensives and b) levels of blood pressure control will be discussed in detail. This discussion will focus on the kidney disease observed in hypertensive patients who do not appear to have other primary renal diseases and whose hypertension appears to be primary. Furthermore, it will focus on "benign" hypertension, therefore "malignant" hypertension while often primary and associated with renal failure, particularly in an acute form will not be discussed at length. From the following discussion I would like the reader to learn four important take home points:

1) The incidence of kidney disease in patients with primary hypertension across all age groups is 4-fold higher in blacks compared to whites.

2) Rigorous control of blood pressure with pharmacologic therapy can preserve renal function in patients with established renal insufficiency due to hypertension.

3) The most efficacious and safest level of blood pressure control in patients with kidney disease and hypertension remains to be established however based on current evidence a level of $< 140/90$ is a reasonable target to aim for.

4) Converting enzyme inhibitors and calcium channel blockers are both effective and safe classes of agents for treatment but proof of superiority over

conventional agent(s) is lacking at present.

5) Future studies are desperately needed to clarify the pathogenesis, identify risk factors, define genetic predisposition, and develop effective preventative strategies for this disease.

II. DEFINITION OF KIDNEY DISEASE AND HYPERTENSION

A. What is hypertensive nephrosclerosis?

Hypertensive nephrosclerosis is a term that has been used loosely. It is used to descibe patints with kidney disease in the setting of hypertension by the clinician and it is used in the laboratory by the pathologist to describe the pathological lesion in the kidney of a patient with hypertension. However, there are problems with both of these terms as applied to patients today. For example, the mere presence of the lesion does not necessarily indicate that clinical renal dysfunction is present nor that it will develop. Furthermore, the pathological changes of hypertensive nephrosclerosis may be seen in kidneys from patients with a variety of disorders (including normal ageing), and there is no (pathognomonic) component that unequivocally distinguishes it from all other renal diseases. Furthermore, even when hypertension is controlled structural and functional deterioration of the kidney may continue to occur apparently unabated in some individuals. Whether these patients have a different disease or simply reach a point of no return in the natural history of renal disease is not known. I will not use this term to refer to patients with renal failure due to hypertension instead the term kidney disease in hypertension will be employed for this purpose.

B. What is "Kidney disease and hypertension" ?

"Kidney disease and hypertension" could be used to describe a wide variety of renal parenchymal or vascular diseases including glomerulonephritides, tubulointerstitial nephritides, polyarteritis, obstructive nephropathy and many others. However, for the purpose of this discussion, and in practical clinical terms, kidney disease and hypertension is defined as the presence of impaired renal function (reduced glomerular filtration rate) with systemic hypertension in the absence of any known renal parenchymal renal disease. It should be noted that by definition azotemia or at least reduced renal clearance is evident moreover, the disease may be progressive. Although this definition implies risk of progression of renal failure it does not mean that an inexorable decline in renal function will ensue particularly if it is identified and treated appropriately. This is an important point since as mentioned above it is still not known whether patients with kidney disease and hypertension have a primary renal disease causing the hypertension. Therefore, in this context one can think of kidney disease and hypertension as a form of primary renal disease independent of glomerulonephritis, tubulointerstitial diseases, etc. This disease is pathologically linked to the findings in the kidney in hypertensive nephrosclerosis which will be described in detail below. Since few patients with kidney disease and hypertension actually undergo kidney biopsy I have chosen to use the phrase kidney disease and

hypertension as a clinical rather than pathological term. Recently, the National Institutes of Health has embraced this terminology and they are actively seeking proposals to study this issue in view of the explosive epidemiological data recently accumulated.

III. EPIDEMIOLOGY OF KIDNEY DISEASE AND HYPERTENSION

A. Mild to Moderate (or "benign") Hypertension as a Risk Factor for Kidney Disease

It is well recognized that few patients with renal insufficiency have a history of malignant hypertension, yet their is a lack of data on the duration of preexisting hypertension in patients with benign hypertension with renal disease.

At present there are no prospective data on the prevalence of prior hypertension in a complete or random sample of patients with renal disease. Nonetheless, as shown below in table 1, three lines of evidence support the view that mild to moderate hypertension is an important risk factor for progressive kidney disease: 1) data from ESRD Network data bases; 2) data from prospective clinical trials of hypertension treatment in the general population; and 3) prospective therapeutic clinical trials in patients with established chronic renal disease.

1. The strongest evidence in support of hypertension as a risk factor comes from analysis of End Stage renal Disease Network databases. Although there are problems with the validity of the database (questionnaires) they are the largest and probably the most representative of information available on the relation between causes of ESRD and patient outcome. These findings indicate a sharp increase in ESRD due to hypertension in the US over the past decade (1). Based on these data it is estimated that approximately 25% of ESRD in the U.S. is due to hypertension, the incidence is rising at a rate of about 8% per year, it is more prevalent in older age groups, more common in men and much more common in blacks (table 2). It is clear that the incidence of hypertension (as well as diabetes mellitus) as a cause has risen steeply since the pre-1974 era in comparison to glomerulonephritides (1,2). Importantly the distribution of ESRD diagnoses are strongly age-related. For example, there is a sharp increase in incidence of ESRD due to hypertension in age ranges 25-54 and the highest incidence occurs

Table 1. Evidence that mild to moderate hypertension is a risk factor for progressive kidney disease.

- **ESRD Network data bases**
- **Prospective clinical trials of hypertension treatment such as the Hypertension Detection and Follow-up Study**
- **Prospective therapeutic clinical trials in patients with**

in the age group ≥ 75. Taken together with the fact that the average age of enrolles in the ESRD program has risen from 55 in 1973 to 60 in 1985, it is likely that ESRD due to hypertension will account for progressively increasing numbers of new ESRD enrolles unless a striking reduction in the incidence of hypertensive ESRD occurs.

Table 2. Epidemiology of Kidney Disease and Hypertension

- **Approximately 25% of cases of ESRD**
- **Incidence has risen 7% per year in the past 10 years**
- **More prevalent in older age groups**
- **More common in men**
- **Much more common in blacks**

2. The prevalence of renal disease due to hypertension has been estimated prospectively in the Hypertension Detection and Follow-up Program (HDFP) (3). In this multi-center, large-scale study which involved nearly 11,000 hypertensive patients and 14 centers throughout the U.S., both morbidity and mortality was assessed over an 8 year period of treatment for hypertension. The patients were randomized into a **"stepped care group"** and a **"referred care group"**. In the former group blood pressure control was performed according to a pre-set protocol and patients were follow-up in a Medical center program while in the latter group there was no pre-set protocol and patients were returned to their referring physician for care. The target BP was the same for both groups. Assessment of renal function by serum creatinine measurement was performed and a value of 1.5 mg% was considered evidence of renal damage. The analysis of renal function in the study, shown below in table 3, revealed several important findings: 1) the incidence of a baseline serum Cr > 1.5 mg% was 5.6%; 2) the occurrence of a serum Cr > 1.5 mg% was 2-fold higher in blacks compared to non-blacks; 3) stepped care of patients with baseline serum Cr of 1.5-1.7 resulted in a significantly slower decline in renal function compared to referred care therapy; and 4) the incidence of decline in renal function was greater in blacks, men, patients aged > 60, and those with higher BP at entry and 5) mortality rate from non-renal cardiovascular disease (stroke and myocardial infarction) was significantly higher in patients with a baseline serum Cr > 1.5 mg%. Patients with the highest baseline serum creatinine were at risk for development of progressive renal disease. These data suggest that an elevated baseline serum creatinine in hypertensive patients is not only a marker for renal disease but also for the development of fatal non-renal cardiovascular complications.

3. It has been clearly established that lowering diastolic blood pressure (DBP) to levels of 95-105 mmHg with antihypertensive drug combinations slows the rate of progression of renal disease in severe or malignant hypertension (4-12). Several

recent studies suggest that lowering blood pressure in patients with mild to moderate hypertension with conventional antihypertensives (e.g., diuretics, β-blockers, central acting α-agonists, and vasodilators) is also of value in slowing renal disease progression (13-16). However, with one exception (14) these studies were not specifically designed to determine the effect of long-term blood pressure control on renal function prospectively. Currently, there are no prospective, large scale, long-term controlled trials which specifically evaluate the effects of blood pressure control on renal function in mild-moderate hypertension (2).

Table 3. Renal Function in the Hypertension Detection and Follow-up Program

- **Incidence of a baseline serum Cr > 1.5 mg% in 5.6%**
- **Occurrence of a serum Cr > 1.5 mg% 2-fold higher in blacks**
- **Stepped care vs referred care resulted in slower decline in renal function.**
- **Incidence of declining renal function greater in blacks, men, patients aged > 60, and higher BP at entry.**

Thus, additional long-term studies are needed to further define the populations at risk for renal failure and to develop improved methods of prevention and treatment of the disease. Of the risk factors elucidated in the Hypertension detection and follow-up program perhaps the most outstanding one is race.

B. Black-White Differences in the incidence of Kidney Disease and Hypertension

Hypertension is more prevalent and the incidence and degree of end organ damage more severe in black than non-black populations (15-17). According to the NHANES II study (18) the age-adjusted prevalence of hypertension in blacks compared to whites in the age group 25-74 were: black men 28% vs white men 21% and for black women 40% vs white women 20%. In addition, both the incidence of renal insufficiency as well as non-renal mortality rates are substantially greater in black compared to non-black hypertensives (13,19-21). Easterling et al (22) first reported that the incidence of ESRD in was higher (3.8-fold) in blacks compared to whites. In a subsequent report Rostand et al (23) reported that the relative ratio of the incidence of referral for ESRD in Jefferson County Alabama was 4.2 times higher in blacks vs whites. The combined analyses from ESRD network databases including Michigan, Georgia, Alabama and Texas have demonstrated not only that the incidence of ESRD in general is higher in blacks compared to whites but also that the incidence of ESRD due to primary hypertension is 3-20 fold higher (depending on the age grouping selected) in blacks compared to non-blacks (22-27). As shown below in Table 4, a number of factors have been cited as possible explanations for the racial difference

in the incidence of ESRD due to primary hypertension. A variety of factors which might be responsible for the observed differences in the rate of ESRD have been cited including increased prevalence of hypertension, higher incidence of severe hypertension, duration of hypertension, access to care, socioeconomic factors, type(s) of antihypertensive therapy, and intrinsic differences in renal hemodynamics.

Table 4. Increased Incidence of ESRD due to Hypertension in Blacks: Possible contributing factors.

- **Increased prevalence of hypertension**
- **Higher incidence of severe hypertension**
- **Duration of hypertension**
- **Access to care**
- **Socioeconomic factors**
- **Type(s) of Antihypertensive therapy**
- **Intrinsic differences in renal hemodynamics**

Although it is not clear what accounts for the increased susceptibility to renal failure in black hypertensives (28-34), it is evident that it is not accounted for exclusively on the basis of higher prevalence of hypertension (18,26,27) or socioeconomic factors (35). Furthermore, there is no evidence that differences in the type of antihypertensives used to treat blacks and whites contributes to these observed differences. Whether intrinsic differences in renal hemodynamics or response to hypertension explain these differences remains to be determined. Whatever the mechanism (s), on the basis of these observations it can be strongly argued that there is a difference in the natural history of hypertension in blacks compared to whites (12). Whether there are key genetic differences that can explain these findings remains to be determined.

There are problems with all of these analyses primarily because of the difficulties encountered in making the diagnosis of renal disease due to hypertension in the absence of known primary renal diseases. This is in part due to the fact that few patients are biopsied and because the nature of the renal disease has not been elucidated. Therefore we need to : 1) better define the phenotype of kidney disease and hypertension and 2) develop precise and accurate methods for making the diagnosis.

IV. DIAGNOSIS OF KIDNEY DISEASE AND HYPERTENSION

As already alluded to the diagnosis of Kidney disease due to primary hypertension is a diagnosis of exclusion. The only way to establish the diagnosis of kidney disease due to hypertension and not other renal diseases is to perform a renal biopsy to exclude other causes of kidney disease associated with hypertension and renal insufficiency. However, at present renal biopsy is not being advocated as a procedure to confirm the diagnosis of kidney disease due to hypertension. The diagnosis is substantiated by evidence of black race, positive family history, onset of hypertension between the ages of 25-45, presence of long-standing or severe hypertension. A history of prolonged hypertension, left ventricular hypertrophy, low-

grade proteinuria (< 1g/d), hypertensive retinopathy, and small contracted kidneys without evidence of primary renal disease are the usual criteria for diagnosing kidney disease and hypertension in uremic patients (2). Some authors believe that even a kidney biopsy is not sufficient to make this diagnosis but offer no alternative method (36). A clinical diagnosis based on the patients age, race, physical examination, routine chemistries and urine analysis is still used to make a presumptive diagnosis. This routine database does not necessarily rule out renovascular hypertension, pheochromocytoma, primary aldosteronism or other secondary causes. However, in by the Hypertension Detection and Follow -Up study this screening data set was adequate in excluding secondary causes in 95% of the cases (37). The presence of proteinuria does not exclude hypertension or other renal diseases and is not helpful per se. The presence of an active urine sediment that includes red blood cells, granular casts with or without hyaline or red cell casts should raise the possibility of glomerulonephritis and serologic studies to look for SLE, postinfectious GN, etc. should be performed. Finally a renal sonogram should be considered to rule out polycystic kidney disease which is the 4th most common cause of ESRD in the U.S. and only 50% of patients give a family history of it.

Mindful of the fact that renal disease is relatively uncommon in patients with hypertension (5.6 % in the HDFP) it would be useful to be able to identify those patients who are at risk for renal disease at an early stage in order to formulate the best approach to prevention and therapy for the future of this disease. There is general agreement that an elevated serum creatinine is an excellent marker of patients at risk for progressive renal disease but it further indicates that renal disease is advanced and is therefore a late marker of renal disease. At the present time no clear early marker of renal dysfunction that portends progressive renal disease. However, some studies have attempted to address this issue as discussed below.

V. CLINICAL MARKERS OF PROGRESSIVE RENAL DISEASE

A. Tubular markers

The studies of Goldring et al (38) called attention the reduced maximal tubular transport activity of patient with primary hypertension as an early sign of renal dysfunction. Reduced renal uric acid clearance has been reported in patients with hypertension (39, 40) and has been correlated with reductions in renal blood flow, increased renal vascular resistance and left ventricular hypertrophy (41). In addition increased urinary excretion rate of N-acetyl-β-glucosaminidase (NAG) has been reported in patients with primary hypertension and renal disease (42-44). Furthermore, effective lowering of blood pressure reduces NAG excretion in such patients (45). These tests have not gained widespread acceptance because of lack of specificity and sensitivity for primary hypertensive renal disease.

B. Glomerular markers

Since decline in renal function can be linked to glomerular damage and loss it makes sense to examine glomerular function early in patients with renal disease.

Proteinuria is a manifestation of abnormal glomerular permselectivity and indicates at least a functional abnormality in the glomerular basement membrane. It is common in patients with hypertension who develop renal vascular lesions and the magnitude varies considerably from patient-to-patient. Parving et al (46) reported increased urinary albumin excretion in patients with primary hypertension in untreated or inadequately treated hypertensives. More recently Morduchowicz et al (47) have reported that proteinuria greater than 1g/day is associated with primary hypertension on renal biopsy and increased risk for progressive renal insufficiency. Several other studies in small numbers of patients have shown a relationship between albuminuria (48-52) as well as overt proteinuria and the presence of hypertension and that blood pressure lowering by enalapril but not nitrendipine (50) reduces albuminuria in some patients. These studies have yet to be confirmed in large numbers of patients. Neither urinary albumin excretion nor overt proteinuria have been carefully studied in untreated or treated patients, therefore the possibility that these may be markers of progressive renal disease needs to be further investigated.

VI. RENAL PATHOLOGY of KIDNEY DISEASE AND HYPERTENSION

A. General comments

The pathology of primary hypertension may be divided into malignant and benign forms on the basis of the severity of hypertension and the vascular lesions. I will focus on the renal lesions of benign hypertension since most cases of end stage renal disease occur in patinas who fit this clinical description of benign hypertension. Table 5 below summarizes the main pathologic findings.

B. Benign Hypertension

1. Hyaline Arteriolosclerosis

This lesion appears as a homogenous amorphous eosinophilic insudation in the walls of small arterioles. Ultrastructural analysis of the lesion reveals atrophy of smooth muscle cells, irregularity of the basement membrane and hyaline deposition. The composition of hyaline is a complex mixture of plasma proteins including complement (53) basement membrane proteins and degenerated components of smooth muscle cells. It is the most commonly observed lesion in patients with primary hypertension and is present in both afferent and to a lesser extent efferent arterioles in 80-100% of patients (54-56). In experimental hypertension, the mesenteric arterioles exhibit increased permeability which has been attributed to endothelial damage (57). In acute angiotensin infusion-induced hypertension similar increased permeability of renal vessels has been observed (58). There is evidence that vasoactive amines induce structural changes within arteriole walls in part by stimulating protein synthesis and alterations in the cytoskeleton of smooth muscle cells. The cells in the wall of the arteriole are responsible for the synthesis of proteins which make up the components of hyalin and therefore play a key role in determining the nature and extent of its deposition in vessel walls. In response to vasoactive amines vessels not only contract but are induced to increase protein synthesis. It is feasible that with short-term

hypertension by vasoconstriction is replaced by long-term hypertension owing to prolonged chemical stimulation of these cells along with ambient growth factors which together may cause wall thickening and fixed increased resistance. The end result can be poorly compliant small vessels with a reduced vascular lumen leading to elevation of peripheral resistance and relative ischemia of the region supplied.

Table 5. Renal Pathology of Primary "Benign" Hypertension.

Arterioles and small arteries
- **Hyalin arteriosclerosis**
- **Myointimal Hyperplasia**

Large Arteries
- **Accelerated atherosclerosis**
- **Renal artery stenosis**

Glomeruli:
Damage due to Ischemia
- **Progressive collapse of glomerular tuft**
- **Global sclerosis**

Damage due to direct hypertensive injury
- **Mesangial expansion**
- **Focal and global sclerosis**

Tubules and interstitium
- **Tubular basement membrane thickening**
- **Collapse of tubules with atrophy**
- **Interstitial fibrosis and chronic inflammation**

2. Myointimal Hyperplasia

Myointimal hyperplasia is a proliferative lesion of small (interlobular) arteries and arterioles that is typically seen in cases of sustained severe hypertension characteristic of malignant hypertension but not uncommon in benign hypertension. This lesion is characterized by proliferation and radial hypertrophy of modified smooth muscle cells which migrate into the intima via fenestration the internal elastic lamina. It has been postulated proliferation results from focal areas of contraction of arterial walls which in turn creates increased permeability in the non-contracted segment and shear forces which damage endothelial cells and release platelet-derived growth factors and vasoactive substances which together stimulate proliferation and migration of myointimal cells (59).

3. Glomerular Pathology

Glomerular damage in hypertension is thought to occur for two major reasons: 1) ischemia; and 2) direct hypertensive hemodynamic injury. The net result is progressive loss of glomerular surface area available for ultrafiltration. The loss of functional glomerular surface are is linked to both progression of renal disease as well as maintenance of a hypertensive state. It is important to emphasize that the glomeruli are not all affected by these changes to an equal degree. In fact there are at least two "populations" of glomeruli in diseased kidneys in hypertension. Those exhibiting atrophic changes of ischemia and those that appear hypertrophic (presumably due to glomerular hypertension).

Ischemia

The glomerular capillary tuft collapses with time presumably as a result of ischemia. As the disease progresses the basement membrane becomes thickened, wrinkled, and condensed simultaneous with the development of global glomerular sclerosis and senescence. Ultrastructural analysis indicates that a gradual increase in mesangial matrix with obliteration of capillary lumina, loss of endothelial cells and increased basement membrane-like material develops.

Direct injury

Direct injury to the glomerular capillaries presumably owing to failure of pre-glomerular vasoconstriction leading to direct transmission of systemic pressure to the capillary loop is associated with glomerular cell proliferation, focal capillary loop necrosis and hyalin changes of glomerular epithelial cells. In the early stage there is thickening of the glomerular basement membrane and an irregular increase in mesangial matrix. As the disease progresses there is increased cellularity, adhesion of glomerular loops to each other and Bowman's capsule and swelling of both endothelial and epithelial cells which proliferate and may form crescentic lesions. These lesions appear more prominently in glomeruli supplied by larger arteries thus they are believed to result from greatly elevated pressure. Experimental animal models of glomerular capillary hypertension support this possibility (60-62)

4. Major Arteries

The larger arteries may also develop pathology in hypertensive individual. It is recognized that atherosclerosis of the renal arteries is accelerated in hypertensive patients (63). This may perpetuate the disease by exacerbating hypertension. Second, these vessels may be the source of atheroemboli which may damage the renal microvasculature further. In addition, there are accompanying changes in the tubules and interstitium in hypertensive renal disease. A chronic tubulointerstitial nephritis with tubular atrophy, focal chronic inflammatory infiltrates and interstitial fibrosis are commonly seen and progress with the progression of vascular disease. The reason for the chronic inflammatory cell infiltrate has not yet been determined.

In summary, although the renal lesions of hypertensive nephrosclerosis are well characterized and seem to preferentially affect the kidney those of benign hypertension are not pathognomonic.

C. Malignant Hypertension

1. General

Both hyalin arteriolosclerosis and myointimal hyperplasia are seen in malignant hypertension. In addition to these changes, there is massive myointimal proliferation leading to "onion skin" appearance of vessel walls with total lumenal occlusion, and proliferative glomerular changes. These include epithelial and endothelial proliferation with endothelial lysis and a bloodless appearance owing to capillary lumen occlusion.

2. Fibrinoid Necrosis

Fibrinoid necrosis or necrotizing arteriolitis is the hallmark of malignant or accelerated

hypertension, the pathoanatomic correlate of the clinical syndrome of severe hypertension with acute end organ damage. The lesion is characterized by obliteration of the normal media by necrosis of the arteriole with fibrin insudation into the wall. In addition, leukocytic infiltration, perivascular hemorrhage and intraluminal thrombosis are sometimes present.

D. Questions concerning pathology and hypertension

1. Is there a pathognomonic renal lesion in hypertension?
All of the lesions describe above can be observed in other conditions. Thus arteriolar nephrosclerosis was observed in about 10% of non-hypertensive subjects examined by Moritz and Oldt (56). The more advanced lesions including fibrinoid necrosis and glomerular proliferative lesions may be seen in various glomerulonephritides. Moreover, arteriolo-and arterio-sclerosis may be seen in patients with diabetic nephropathy. Finally, some patients with chronic hypertension do not have significant vascular lesion on biopsy or at autopsy. Thus, there is no pathognomonic lesion in hypertension. Nevertheless, the lesions described here are observed in chronically hypertensive patients and the severity is roughly correlated with the severity and duration of hypertension leading some authorities to claim that they are distinctive and unique (63).

2. Do the renal vascular lesions cause the hypertension?
Since Johnson reported the association between renal arteriolar wall thickening of Bright's disease with left ventricular hypertrophy (64), the role played by the renal vasculature in the pathogenesis of hypertension has been debated. In the classic studies of Moritz and Oldt (56) based upon the clinical and autopsy examination of 200 consecutive cases of chronic hypertension in whom prolonged hypertension ($\geq$ 150/100 mmHg) was known to be present before death and all cases died of renal failure, cardiac failure, or cerebral hemorrhage. They also compared 100 of these cases with 100 autopsy cases in non-hypertensive patients. Based on their observations they concluded that the only site of arteriolar sclerosis so far as the causation of hypertension is concerned is the kidneys and postulated that renal arteriolosclerosis is the functional analogue of Goldblatt chronic hypertension. (In addition, they noted specifically that the mortality and morbidity of primary hypertension was greater in blacks than in whites and death occurred at an earlier mean age in blacks.) However, reports concerning the correlation between the level of blood pressure and the pathologic findings in the kidney of patients with benign nephrosclerosis are conflicting (65-67). However, the lesions in the kidney tend to correlate better with blood pressure than lesions in the liver, pancreas or adrenal gland (66). Heptinstall (68) studied 50 patients with hypertension undergoing sympathectomy for treatment and observing that more than 30 such biopsies showed only slight vascular changes and concluded that hypertension preceded vascular changes in primary hypertension. Additional studies by Sommers (69), Talbot (70), McGee (71) provided further evidence to support the notion that vascular disease

occurs in response to hypertension. Thus it seems likely based on the functional observations that hypertension precedes the development of the vascular lesions. Therefore, the renal lesions do not cause the hypertension. However, as already mentioned it is likely that vascular wall thickening with luminal encroachment plays a role in increased resistance raising the question of whether the structural lesions correlate with functional impairment of the kidney.

E. Structural-Functional Correlations

There is scanty available data relating renal structure with function in hypertensive renal disease. Bohle and Ratschek (67) have compared the biopsy and serum creatinine data in patients with benign nephrosclerosis in which they specifically looked for hyalinized glomeruli, glomeruli with collapsed capillaries and mesangial sclerosis. They found that patients with evidence of hypertensive glomerulopathy, i.e. increased basement membrane thickness, mesangial expansion and global sclerosis have higher serum creatinine concentrations when compared to patients with equal elevations in blood pressure but without evidence of significant glomerular changes. Interestingly, in their series, 40% of patients with hypertensive glomerulopathy the tentative clinical diagnosis prior to biopsy or autopsy was chronic glomerulonephritis. Talbot et al (71) performed the first studies correlating renal structure with glomerular filtration rate measurements in 20 patients undergoing sympathectomy for treatment of essential hypertension in the early 1940s. They graded the severity of renal lesions on the basis of arteriolar and arterial disease but found that glomerular lesions correlated with the vascular lesions. They also found a strong inverse correlation between the severity of vascular lesions (including glomerular disease) and renal plasma flow (PAH clearance) and a weaker correlation with glomerular filtration rate (inulin clearance). Importantly, there was a positive correlation between severity of vascular lesions and filtration fraction: The greater the vascular disease the higher the filtration fraction. While non-specific, an increase in filtration fraction suggests a relative increase in efferent arteriolar resistance in the more diseased kidneys. Surprisingly, of the 20 patients studied at least 25% of patients did not have alterations in GFR or RPF that corresponded with the severity of vascular disease. Furthermore, Castleman and Smithwick (72) showed that 25% of patients with hypertension had little or no evidence of renal vascular disease. Thus the sensitivity of the pathologic-functional correlation is probably low for the population of hypertensives at large.

VII. RENAL FUNCTION IN PRIMARY HYPERTENSION

A. Renal Hemodynamics

In humans renal hemodynamics are typically measured by performing clearance studies utilizing inulin (or iothalamate) to measure glomerular filtration rate (GFR) and para-aminohippurate to measure renal plasma flow (RPF). Renal hemodynamics

including renal vascular resistance is normal and renal plasma flow (RPF) and glomerular filtration rate GFR) are normal or increased in pre-hypertensive or borderline hypertensive individuals (73-76). In contrast, patients with established hypertension have increased renal vascular resistance, decreased RPF and normal or only slightly reduced GFR hence an increase in filtration fraction (77-80). Isotope and angiographic studies indicate that the major reduction in blood flow is in the cortex of the kidney (81-82).

Goldring et al (38) studied 60 patients with presumed primarily hypertension and concluded that relative renal ischemia was present in the kidney and increased resistance was focused at the efferent arteriole accounting for the increase in filtration fraction. Whether this increase is entirely functional remains uncertain, however in some individuals it was reversible with certain vasodilators suggesting that at least a component of it is functional. Table 6 below outlines the changes in renal function during development and progression of hypertension.

Table 6. Renal Hemodynamics in Primary Hypertension

Hypertension Status	GFR	RPF	FF
Pre	nl or inc	nl or inc	nl
Early	nl	dec	inc
Chronic	dec	dec	inc

Unfortunately there is little data in regard to changes in renal plasma flow and glomerular filtration rate over time in these patients. The longitudinal studies of MacGee et al (83) in 35 patients with treated primary hypertension who underwent serial measurements of GFR and RPF indicate that RPF does not decline significantly after 3-5 years of follow-up whereas GFR does. These patients had a heterogeneous response to treatment and some but not all had demonstrable changes in renal hemodynamics. However it is not clear why certain patients developed progressive renal disease in and others did not whether blood pressure was or was not lowered by antihypertensive therapy. Therefore, the exact meaning of these early changes in renal plasma flow in relation to development of kidney disease and hypertension is unclear. There is no marker for those individuals who will subsequently develop progressive renal disease.

Hollenberg et al (84) have shown that a subgroup of patients with primary hypertension have the inability to modulate renal hemodynamics in response to extremes of dietary salt intake. He has dubbed this group "non-modulators". These patients exhibit a an immutable reduction in renal blood flow and increase in renal vascular resistance in response to salt loading and an exalted vasodilator response to converting enzyme inhibitors in comparison to modulation hypertensives or normal subjects. These data suggest that these patients have an increased sensitivity to

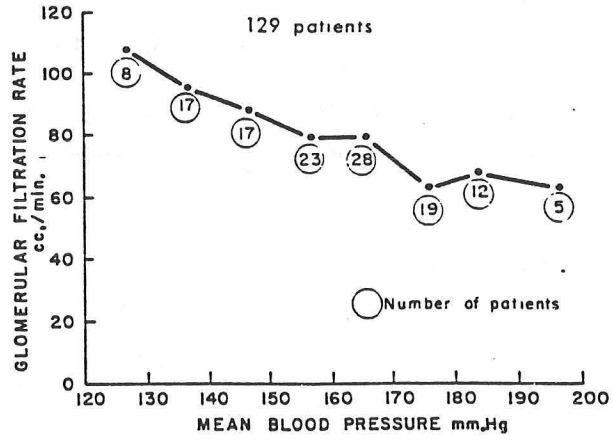
endogenous angiotensin II however this has not yet been proven. Furthermore it is not clear what percentage of primary hypertensives are non-modulators. Nevertheless these observations fit with the hypothesis that angiotensin II may play a role in the renal hemodynamic abnormalities in humans with hypertension.

There is a correlation between the severity of hypertension and the degree of reduction in renal plasma flow and glomerular filtration rate as renal disease progresses. As shown in figure 1 below in hypertensive patients studied by Moyer et al (9) there is an inverse relation between the magnitude of mean arterial pressure and glomerular filtration rate. Similar data for renal blood flow derived from de Leeuw and Birkenhager (85) are shown.

As already noted it seems likely that structural factors contribute to the increased resistance particularly in advanced renal failure when widespread renal arteriolosclerosis and glomerular changes are evident. Further reductions in renal blood flow and glomerular filtration are undoubtedly contributed to by progressive luminal narrowing of afferent arterioles, glomerular ischemia leading to collapse of glomeruli and injury from hyperperfusion of those glomeruli whose afferent arterioles remain patent and fail to prevent transmission of high systemic pressures to them. Thus, as renal failure progresses the increase in filtration fraction persists particularly in these glomeruli.

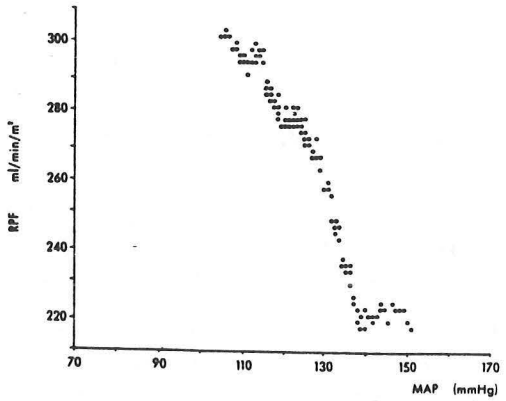
Figure 1.

AVERAGE VALUES FOR GFR COMPARED TO INCREASING SEVERITY OF HYPERTENSION



[Ref: Moyer et al. Am J Med; Feb. 1958, pp 164-176]

RELATION BETWEEN MEAN ARTERIAL PRESSURE (MAP) AND RENAL PLASMA FLOW (RPF)



[Ref: de Leeuw & Birkenhager. In: Hypertension. Pathophysiology, Diagnosis, & Management. Laragh JH & Brenner BM (eds), 1990]

VIII. POSSIBLE MECHANISMS OF RENAL DISEASE IN HUMAN HYPERTENSION

A. General comments

The pathophysiology of hypertensive renal disease in humans is not known. However, new insights provided by experimental animal models have been useful in understanding human disease. However, at present the data from

these models cannot be extrapolated to human disease as Fine has pointed out (86). Three key questions still need to be answered: First, why do some but not all patients with hypertension develop renal disease and how can the susceptible individuals be identified? Second, what factor(s) is responsible for the progression of renal disease in hypertensive patients with established renal disease (i.e. decreased renal function)? Third, does blood pressure lowering prevent progressive renal disease in all patients with normal or impaired renal function? This section will not attempt to discuss the etiology of hypertension. This is a complex issue that is beyond the scope of this discussion. However, taken together the renal pathology, varied clinical course and recent studies in the progression of renal disease and advances in vascular biology allow us to speculate on possible causes of progressive renal disease in hypertension.

B. Do all patients with kidney disease and hypertension progress to end stage renal disease?

Not all patients with kidney disease and hypertension will progress to ESRD. On the one hand, rigorous control of blood pressure in some patients with renal disease can preserve renal function not only in malignant but also in benign hypertension. On the other hand, regardless of rigorous blood pressure control in other patients with renal disease progress to end stage renal disease leaving the clinician perplexed as to how to manage these patients. These disparate results raise the question as to whether the mechanism of renal disease is the same or different in these two patient populations. Of course there may be several reasons why such discrepancies occur including different degrees of renal failure at the time of institution of antihypertensive therapy, genetic differences in tissue response to injury, differences in underlying pathophysiology of the disease process, different phenotypes of the same disease, etc. Proof of these possibilities is often not evident in clinical practice. Several possible reasons why renal disease may not be prevented in patints with Kidney disease and hypertension should be considered and are shown below in table 7. One or more of these may be the explanation in individual patients. Two illustrative cases with divergent results will be presented below to deal with the issue of blood pressure control (see section X). There is good evidence that patients with more advanced renal disease at onset of rigorous blood pressure control have a greater propensity to progress to ESRD (8). Thus advanced renal disease seems itself to be a risk factor for progressive renal failure in some individuals, however because only small numbers of patients with kidney disease and hypertension have been followed specifically corroborating data concerning kidney disease progression per se is not available. Even the Hypertension

TABLE 7. Possible Reasons for Failure to Prevent End-Stage Renal Disease Due to Hypertensive Nephrosclerosis

Patients do not receive therapy
Patients receive therapy too late: Renal vascular damage established
Inadequate control of blood pressure: Target BP too high
Use of drugs that fail to reduce intraglomerular pressure
More patients are protected from cardiovascular mortality
Hypertensive nephrosclerosis is a primary renal disease

None of these reasons is mutually exclusive. BP, blood pressure.

Detection and Follow-up Program was not designed to look at renal failure and could not define clearly who was at risk or who is likely to progress or not progress (3). Prospective long-term clinical trials to determine whether adequate blood pressure control actually preserves renal function and prevents renal failure in patients with normal or impaired renal function have not been performed (2).

C. What causes progressive renal disease in hypertension?

Systemic hypertension is an important (but not the only) risk factor for progressive renal disease in a number of conditions including primary hypertension, diabetes mellitus, various glomerulonephritides, polycystic kidney disease and others. Based on these findings it has been the clinical practice to lower blood pressure with pharmacologic agents in these conditions in an effort to preserve renal function. Unfortunately, while uncontrolled systemic hypertension is a known risk factor for progressive renal disease, careful clinical studies have not been performed to prove that lowering blood pressure per se protects the kidney in hypertension. Recently, we have obtained insights into the relationship between systemic hypertension and glomerular hypertension as an important contributing factor in the pathogenesis of progressive renal failure.

Numerous studies in rat models of renal insufficiency have documented the important role of glomerular hypertension in the pathogenesis of progressive glomerulosclerosis in these animals (87). As shown below in table 8 a variety of experimental rat models with systemic and or glomerular hypertension have been reported. In most of these models failure of pre-glomerular vasoconstriction allows for transmission of high systemic blood pressure into the glomerular capillaries leading to progressive glomerulosclerosis. In the spontaneously hypertensive rat model pre-glomerular constriction is maintained, glomerular capillary pressure is normal and progressive glomerular injury does not occur. When these animals are subjected to uni-nephrectomy the pre-glomerular resistance in the remaining kidney decreases and glomerular sclerosis, proteinuria and renal failure ensue. In all of these models pharmacologic or dietary factors that lower glomerular capillary pressure afford varying degrees of protection of the

Table 8. Experimental models of Systemic/Glomerular Hypertension

1. **Systemic hypertension with glomerular hypertension**
   - Extensive renal ablation
   - Salt-sensitive hypertension
   - Goldblatt hypertension
   - Mineralocorticoid-salt hypertension
   - Nephrotoxic serum nephritis/saline
   - Spontaneously hypertensive rat/glomerulonephritis
   - Spontaneously hypertensive rat/uninephrectomy
   - Spontaneously hypertensive rat/diabetes
2. **Systemic hypertension without glomerular hypertension**
   - Spontaneously hypertensive rat
3. **Glomerular hypertension without systemic hypertension**
   - Adriamycin nephrosis
   - Cholesterol supplementation
   - Dibetes mellitus
   - Passive Heymann nephritis
   - Postpuromycin nephrosis
   - Uninephrectomy

From ref 87

glomerulus and kidney function. Furthermore factors that tend to increase glomerular pressures and flows (e.g. high protein diets) tend to increase injury in these animals tend to aggravate glomerulosclerosis (88). Pathological studies in four different models of systemic hypertension in the rat have furnished data that is consistent with the view that pre-glomerular vasoconstriction protects the glomerulus in hypertension whereas decreased resistance is injurious. (89). In addition to these hemodynamic factors it has recently been shown that glomerular hypertrophy in remnant nephrons also plays a role in the development of structural and functional alterations in the glomerulus of experimental animals (90). If these findings are present in humans with kidney disease due to hypertension then it follows that pre-glomerular resistance must be low and lowering of glomerular capillary pressure should protect the kidney. As already mentioned most patients with established primary hypertension have elevated renal vascular resistance whether GFR is normal or decreased. It has been suggested that in most patients who do not develop renal disease that normal autoregulation of the glomerular microcirculation protects the kidney yet the data of Goldring et al (38) noted earlier suggest that the increase in resistance is in the efferent arteriole in human hypertension. It may be that in patients with kidney disease and hypertension that a failure of afferent vasoconstriction coupled with an increase in efferent vasoconstriction plays an important role in the progression of renal disease particularly in glomeruli that exhibit hypertrophic features (see below). Although this is a possibility in keeping with predictions in the rat model, in human hypertension it is likely that the situation is more complicated and predictably more variable.

The lessons from the animal studies point to at least two potential major mechanisms of renal disease in patients with primary hypertension: reduced global renal perfusion and compensatory renal hypertrophy. These mechanisms probably operate in an interdependently in the animal models and presumably in humans.

1. Reduction in global renal perfusion

It is clear that when global renal perfusion is reduced experimentally by main renal artery clamping (91), by massive renal ablation (87) or by microsphere infusion of the kidneys (92) that hypertension, proteinuria and progressive renal insufficiency result. In these instances one observes that some but not all glomeruli undergo striking atrophy with simplification of the glomerular tuft, capillary closure and sclerosis accompanied by evidence of arteriolar vascular changes all of which are similar to the lesion observed in humans with hypertensive nephrosclerosis. It is clear from pathological specimens in humans with kidney disease and hypertension that considerable heterogeneity of glomerular changes are apparent indicating that similar structural alterations occur in human and experimental animal models.

2. Role of focal glomerular ischemia

Miller et al (92) induced focal glomerular ischemia in rats by injection of microspheres (55 μm) into the renal circulation. In this study the investigators used microspheres of this size to avoid causing large areas of renal infarction. This procedure induced ischemia of about 12% of glomeruli leaving 88% of the glomeruli normal initially thus

generating two populations of glomeruli. After 7 months of follow-up the ischemic glomeruli showed simplification of the glomerular capillaries, narrowed lumina and wrinkling of the basement membranes. As shown below in table 9 systemic hypertension developed in these animals compared to saline-injected normals. However, whole kidney GFR was normal in the micro-sphere-injected animals and single nephron GFR, glomerular plasma flow rate and glomerular capillary pressure were elevated in the non-ischemic (88%) glomeruli of the experimental group. The uninjured glomeruli developed segmental areas of sclerosis after 7 months that were not present at 2 months after microsphere embolization. When one calculates the number of glomeruli by dividing whole kidney GFR by the single nephron GFR (an estimate of the total glomeruli) it is evident that the reduced number of glomeruli cannot be accounted for on the basis of the ischemic glomeruli alone. That is, there is a functional reduction of about 25% of total glomeruli in

Table 9. Renal function and structure in rats with focal glomerular ischemia (Group 1) vs control rats (Group 2)

Renal cortical microcirculation studies.

	AP, mmHg	GFR_{tot} ml/min	SNGFR nl/min	Q_A, nl/min	P_{GC} mmHg
Gp 1	140* ±4	4.69 ±0.16	88* ±4	332* ±22	61* ±1
Gp 2	118 ±2	4.57 ±0.22	63 ±3	238 ±18	55 ±2

AP, mean arterial pressure; GFR; GFR_{total}, total glomerular filtration rate; SNGFR, single-nephron glomerular filtration rate; Q_A, glomerular plasma flow rate; P_{GC}, mean glomerular capillary hydraulic pressure.

Morphological studies.

	Glomeruli (%)			
	Uninjured	Ischemic	Segmental Sclerosis	Volume Uninjured Glomeruli ($10^6 MM^3$)
Gp 1	73.2±1.3*	11.8±1.9	15.0±1.0*	2.33±0.11*
Gp 2	96.6±0.2	0.1±0.1*	3.3±0.2	1.81±0.07

*$p < 0.05$ Adapted from ref 91.

comparison to the 12% lost initially by embolization. This indicates that the focal sclerotic lesions observed in the initially uninjured glomeruli is in part responsible for the apparent loss of glomerular numbers. Glomerular volume of the uninjured glomeruli and kidney weight were significantly increased in the embolized compared to saline-injected animals. Finally, as shown in figure 2, proteinuria was markedly increased in the experimental group. These data indicate that remnant nephrons can maintain GFR within the normal range early in the course of the disease. The contribution of glomerular ischemia to hypertension in humans has not been studied, however ischemic glomeruli have been observed in humans with primary hypertension and it has been proposed that glomerular ischemia may contribute to perpetuates hypertension (69, 93)

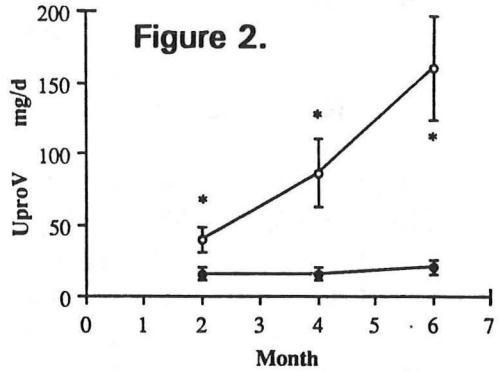


FIG. 3. Twenty-four hour urine protein excretion ($U_{pro}V$) over 6 mo after operation. Proteinuria increased progressively in *group 1* rats (○) subjected to embolization of the kidneys but remained low in *group 2* rats (●) injected with dextrose. * $P < 0.05$ *group 1* vs. *group 2*.

3. Vascular hypertrophy and remodeling

An important component to the renal injury observed in hypertension is hypertrophy of glomeruli and hypertrophy and hyperplasia of the arterioles and arteries which may It has been suggested that decreased luminal area and myointimal hypertrophy may increase vascular reactivity in hypertension. Furthermore, recent studies suggest that autocrine and paracrine vasoactive substances and growth factors modulate vascular structure in hypertension (94). These findings indicate that local and/or systemic growth factors play a role in the genesis of these changes. Moreover several studies suggest that converting enzyme inhibitors may reverse vascular hypertrophy to a greater extent than non-specific vasodilators and β-blockers (95-97). It is not known which or what factors play a central or key role in causing these changes, however several popular candidates have been identified.

Angiotensin II (AII) is a powerful vasoconstrictor and stimulates growth in vascular tissue including vascular smooth muscle, myocardial cells and glomerular mesangial cells (Dzau refs). There are AII receptors throughout the renal vasculature including the glomeruli. If it is increase by local ischemia or other factors locally generated AII could increase vascular and glomerular hypertrophy. AII increases the mRNA abundance and expression of both PDGF and TGF-β in vascular smooth muscle cells. These two factors have opposite effects on cell proliferation such that simultaneous activation of both may lead to cell hypertrophy not hyperplasia which has been described with AII.

Endothelins are a family of vasoconstrictor peptides synthesized by the endothelium. Endothelin is thought to act as an autacoid which like AII is both a potent vasoconstrictor and has mitogenic effects in the renal vasculature (98). It has been shown that serum endothelin-1 levels are elevated in patients with renal disease

and hypertension including patients with primary hypertension. It may have an important role in the genesis of cyclosporin induced hypertension which is thought to result in part from endothelial cell injury (99).

Nitric Oxide is a naturally occurring vasodilator synthesized by the endothelium from L-arginine by the action of nitric oxide synthase. Nitric oxide opposes the actions of AII and endothelin and induces vasodilation by increasing intracellular cyclic GMP. In addition NO has been shown to inhibit vascular smooth muscle and mesangial cell proliferation in response to PDGF (100-101). It is secreted by glomerular endothelial cells in response to calcium mobilizing stimuli (102-104) and may play a role in the regulation of systemic blood pressure and renal hemodynamics in normal rats Furthermore, there is evidence for release of NO in humans with essential hypertension in response to infusion of acetylcholine, a known stimulator of endothelial NO synthesis (105). Nitric oxide has been shown to exert tonic vasodilation in normal animals. Decreased synthesis or activation of the NO receptor could lead to unopposed vasoconstriction and vascular growth in hypertensive kidneys. Furthermore, it has been shown that NO effects reduced in atherosclerotic vessels (106).

Growth factors including epidermal growth factor, platelet-derived growth factor insulin-like growth factor and TGF-β (107, 108) and others may also play a role in the pathogenesis of hypertrophy of the renal vasculature. How these factors induce hypertensive changes in the kidney has not been studied in any animal model. In models of glomerulonephritis Border et al have demonstrated that growth factors play an important role in the pathogenesis of immune-mediated injury associated with systemic and glomerular hypertension. At this time there are more questions than answers concerning the mechanisms and mediators of compensatory and pathological hypertrophy in the kidney in hypertension.

4. Hypothetical mechanism of progressive renal failure in kidney disease and hypertension

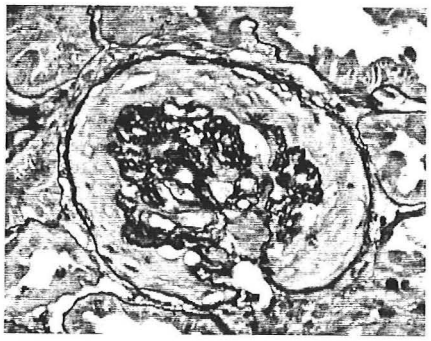
These discussions allow me to propose a possible model for the progression of kidney disease in hypertension. In a patient with systemic hypertension and reduced renal function which may originate from renal ischemia or as a primary event within the kidney, two nephron populations exist as shown below in figure 3: ischemic dying nephrons and compensatory hypertrophied nephrons. The ischemic nephrons are collapsed and have little, if any, functional capacity. In contrast, the other population of nephrons, the hypertrophied group, exhibit relatively low pre-glomerular resistance, they are hypertrophic with some areas of glomerular sclerosis and their functional capacity while high is at its upper limit. It is this population that maintains GFR initially as ischemic nephrons become obsolescent. However, as depicted in figure these hypertrophied nephrons are subject to high systemic pressure owing to pre-glomerular vasodilation and as a result over time develop progressive changes of sclerosis with eventual global sclerosis leading inexorably to end stage renal disease. In the patient with renal insufficiency there may be a critical threshold beyond which lowering glomerular pressure no longer protects the kidney and despite adequate blood

pressure control renal failure progresses.

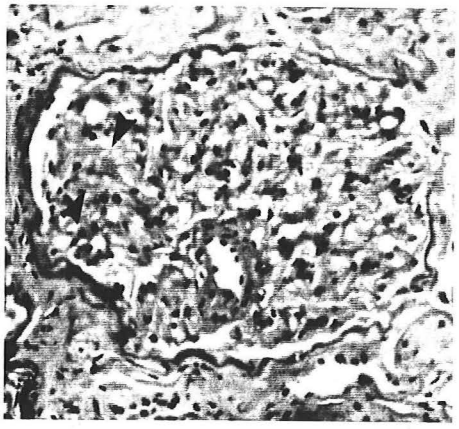
IX. THE NATURAL HISTORY OF RENAL FUNCTION IN UNTREATED HYPERTENSION

The natural history of renal function in untreated hypertension has not been well characterized. The autopsy studies of Bell and Clawson revealed that < 10% of patients with all degrees of hypertension had definite renal failure (55) Perrera (109) followed 500 untreated hypertensive patients of whom 67% were female and 32% were black until death. He observed that 42% had proteinuria and 18% had some degree of azotemia prior to death. The natural history of renal function in these patients was not elaborated. However it is noteworthy that the mean time to death after development of proteinuria was 5 years and for azotemia 1 year. Moyer (9) studied renal function in 64 patients with treated and untreated hypertension over a period of 24-28 months. As shown below in table 10 patients were divided into

Figure 3.



Atrophic, hypoperfused, ischemic glomerulus with capillary collapse and global sclerosis in a patient with kidney disease and hypertension.



Hypertrophied, hyperperfused glomerulus from the same patient with focal segmental sclerosis (arrow).

two groups based upon the diastolic blood pressure. As shown in the right-hand columns untreated patients with diastolic blood pressure > 130 mmHg had significant decline in both renal blood flow and glomerular filtration rate compared to the treated patients. In contrast, untreated patients with diastolic blood pressure < 130 mmHg had only slight decrease in GFR and it was not different than the decline observed in treated patients. In 190 men with diastolic blood pressures ranging from 90-114 mmHg followed in the placebo arm of the VA cooperative study, only 3 developed renal damage compared to 0 in the treated group of 186 (110). In 102 patients in whom renal function was measured by inulin clearance, 42 patients died prior to three years of follow-up and 13 died of renal failure. Eighty-six percent of these 42 patients were black. Twenty six patients were lost to follow-up and 35 patients had sequential renal function studies. There is little additional data on the course of renal function particularly in patients with mild to moderate hypertension.

Table 10. Comparison of Control and Follow-up Renal Function in Treated and Untreated Hypertensive Patients.

Data	Group I (diastolic pressure < 130 mm. Hg)				Group II (diastolic pressure > 130 mm. Hg)			
	Treated		Untreated		Treated		Untreated	
No. of patients	14		8		31		11	
	C	D_1	C	D_1	C	D_1	C	D_1
Blood urea nitrogen (mg. %)	18	19	16	19	27	29	28	91
Glomerular filtration rate (cc./min.)	94	87	98	86	75	72	74	48
Renal blood flow (cc./min.)	899	879	966	755	675	635	648	395
Mean blood pressure (mm. Hg)	152	114	140	141	173	120	183	192
Follow-up	28 mo.		29 mo.		26 mo.		24 mo.	
Improved electrocardiogram (%)	...	50	...	0	...	19	...	0
Improved x-ray (%)	...	20	...	12	...	40	...	0

NOTE: C = control function.
D_1 = Follow-up function.

X. RATE OF PROGRESSION OF RENAL FAILURE IN HYPERTENSIVE NEPHROSCLEROSIS

Further human studies to address the role of blood pressure control in kidney disease need to be conducted. In doing so these studies must address the issue of monitoring renal function in the long-term. The methods for doing so are well established however the interpretation of the rate of progression of renal failure is a problem that by itself must be addressed. Specifically, several problems arise when attempting to measure rate of progression of renal failure. First, it has not been firmly established that treated hypertension is associated with a linear decline in GFR as measured by inulin or iothalamate clearances. In fact, few studies have used repeated measures of GFR as a method of monitoring renal function during careful long-term BP control (14,111-113). Second, limited clearance data on patients with diabetic

nephropathy (112,114-116), polycystic disease (117) and various chronic renal diseases (118,119) indicate substantial degrees of variation of disease progression. Thus if one uses mean slopes to compare groups of patients treated with different regimes, a large number of patients will be required to demonstrate differences. Third, few studies have directly compared the precision of GFR vs. time to 1/Scr vs. time as indices of the rate of progression of renal failure in any renal disease (112,115). Reciprocal of serum creatinine vs. time has been reported as a clinically useful method to monitor renal disease progression in a number of different diseases (14,120-124); however the accuracy of this method has been seriously questioned (125-130).

Two aspects of estimating the rate of progression of renal failure in hypertensive nephrosclerosis must be further delineated. First, it is essential that the intrinsic variability of the GFR measurement be determined. Second, it would be useful to examine the variability and accuracy of ^{125}I-iothalamate clearance as an estimate of GFR in relation to the variability and accuracy of the reciprocal of serum creatinine during long-term follow-up in hypertensive nephrosclerosis. Therefore, more studies are needed in which the following characteristics are incorporated into the study design: 1) patients with a single renal disease; 2) GFR must be assessed serially by more accurate methods; and 3) follow-up is performed for long periods of time.

XI. LONG-TERM BLOOD PRESSURE CONTROL AND RENAL FUNCTION

A. Does long-term blood pressure control prevent the development of renal disease or its progression?

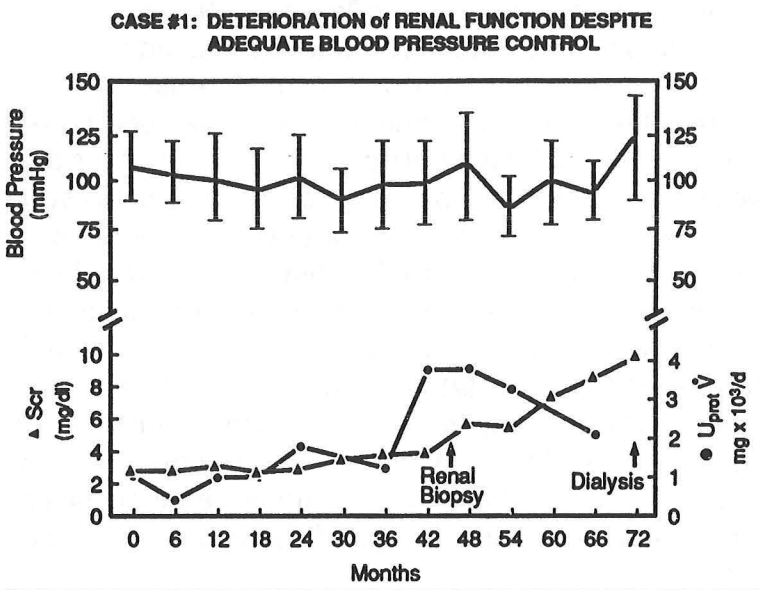
Before discussing the answer to this question it is useful to examine the clinical course of two patients with hypertension of chronic renal disease who were both treated for kidney disease and hypertension in a long-term blood pressure control trial conducted here at Southwestern over the past 7 years (see below for details). Both patients were diagnosed with kidney disease and hypertension and blood pressure was managed similarly yet they had disparate clinical courses over a similar time period.

Case #1 is a 62 year old black male who had a 7 year history of hypertension at entry into the trial. His initial blood pressure was 180/112, serum creatinine 2.4 mg% glomerular filtration rate was 55 ml/min/1.73m^2, and urinary protein excretion rate 1,056 mg/24 hours. After controlling diastolic blood pressure to $<$ 80 mmHg the patients was randomized to diastolic blood pressure control range 65-80 mmHg and he was treated with a combination of hydralazine, hydrochlorothiazide and atenolol. These medications were adjusted every 6 weeks to 3 months to maintain this level of control. His clinical course is displayed below in figure 4. As shown in the figure despite excellent compliance and blood pressure control, the patients renal function deteriorated and he developed nephrotic range proteinuria. A renal biopsy was performed at this time and revealed evidence consistent with hypertensive nephrosclerosis. There was no evidence of any other known renal disease by light, immunofluorescent or electron microscopic study. The patients renal failure

progressed to end stage and he is currently on dialysis.

Case #2 is a 60 yr old black male with a 10 year history of hypertension at entry into the trial. His initial blood pressure was 190/115, serum creatinine 3.1 mg/dl and glomerular filtration rate was 41 ml/min/1.73 m^2 and urinary protein was 564 mg/24 hr. After controlling his diastolic BP to < 80 mmHg he was randomized to a diastolic BP control range of 85-95 mmHg. He was treated with clonidine, atenolol and furosemide to maintain BP in this range and his medications were adjusted as noted above. His clinical course is displayed below in figure 5. As shown in the figure his renal function was maintained throughout the duration of follow-up without significant decline. His BP remains well controlled on this regimen. These two case histories point out the spectrum of response to therapy in this disease. Although the second patient did not have a renal biopsy his clinical data are consistent with kidney disease due to hypertension. It is not clear why these different responses exist. Is it the level of blood pressure control? Does the type of antihypertensive used make a difference?

Figure 4.



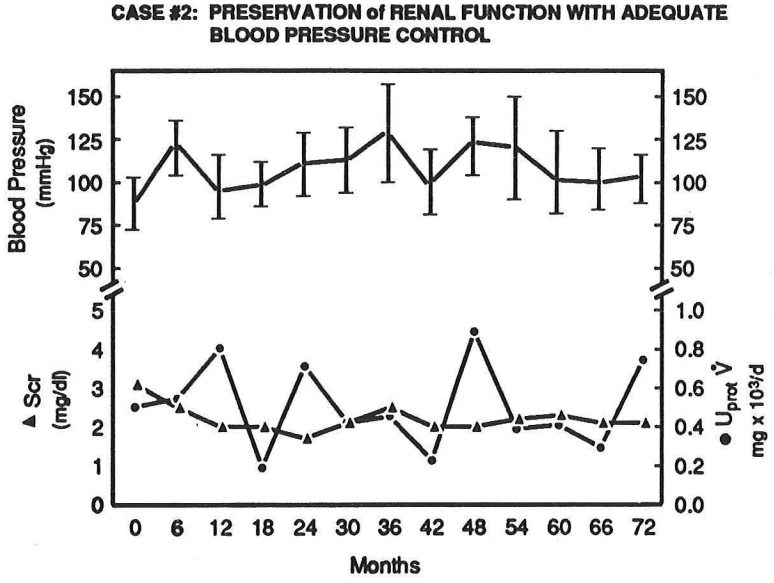
1. Role of antihypertensive therapy

On the one hand both unblinded (4-9, 12-15) and double-blind placebo-controlled trials (131), it has been demonstrated that long-term BP control with conventional antihypertensive medications (including ganglionic blocking agents, reserpine, diuretics, vasodilators and β-blockers) can preserve renal function. On the other hand because of the limited number of patients and renal events some studies do not show any significant difference in renal function between drug-treated and placebo-treated patients over relatively short periods (1 1/2 to 3 years) (110, 131). However, such analyses have been limited for two major reasons: First, large-scale trials were not specifically designed to assess renal function in relation to BP control. Consequently, little or no information on precise measurements of GFR is available from these studies. For example, in the VA cooperative study (83), inulin clearance was measured serially in only 35 placebo-treated or active drug-treated patients: 15 with an initial mean diastolic BP of 117, and 20 with an initial mean diastolic BP of

108 mm Hg. Despite lowering mean diastolic BP to 97 mmHg in the higher diastolic group and continued DBP of 108 mmHg in the lower diastolic group, mean inulin clearance declined in both groups (-15.3 ml/min and -17.1 ml/min respectively) over a 3-5 year period suggesting no renal protective effect of this degree of diastolic BP lowering. Second, patient selection criteria were such that large numbers of patients with normal baseline renal function were followed including in the Hypertension Detection and Follow-up Study (HDFP) (12,19). Therefore, the patient populations are composed of heterogeneous renal function groups making conclusions regarding efficacy of therapy difficult to interpret.

Mitchell, Graham and Pettinger from our institution (8) reported that prospective long-term BP control in patients with refractory hypertension (sustained DBP > 110 mm Hg despite optimal combinations of conventional medications) treated with minoxidil, preserves renal function when diastolic BP is consistently maintained below 100 mm Hg. Despite such control, approximately 50% of patients with benign hypertension have progressive renal disease. IN their study it was clearly shown that those patients with higher initial serum creatinine concentrations were more likely to progress to ESRD and inferentially had more difficult to control blood pressure level. The fact that renal disease progressed in this group is not too surprising given that many renal diseases may progress to ESRD once a critical mass of renal function has been lost (87)

Figure 5



B. Does control of blood pressure prevent progression of renal disease in hypertensives with initially normal renal function?

Rostand et al (12) performed a long-term blood pressure control study in 94 primary hypertensives who had normal renal function at the onset of study. As shown in the upper portion of table 11 despite maintaining average diastolic blood pressure levels of < 90 mmHg throughout the study the serum creatinine increased in every case. It is noteworthy that the two thirds of the patients with progres-sive renal disease were black. These data suggest that renal disease develops in some individuals

despite "adequate therapy". Despite normal creatinine concentrations at onset these patients did not have creatinine clearance or glomerular filtration rate measurements made therefore they may have had abnormal renal function at onset of the study. In addition, without renal biopsy one cannot be sure another renal disease was not present. Of course this criticism can be made of all prospective long-term studies to date.

Table 11. Renal function in treated essential hypertension*

Parameter	Stable function (N=51)	Deterioration in function (N=10)
Blood pressure (mmHg)	**Sys / dia**	**Sys / dia**
Initial	153±19 / 94±12	176±32 / 101±20
Treatment	135±11 / 85±3	145±13 / 85±5
Serum Cr (mg/dl)		
Initial	1.05±0.2	0.96±0.34
Treatment	1.08±0.23	1.63±0.68
Follow-up (mo.)	61.4±38.3	49.3±22.5

*Rostand et al N Engl. J. Med. 320:684-688,1989.

C. Specific antihypertensive medications

1. Experimental animal studies

Data from the animal studies on the protective effects of converting enzyme inhibitors and calcium channel blockers have suggested that two major mechanisms may contribute to progressive renal failure, namely glomerular capillary hypertension and glomerular hypertrophy (132-137). Tolins and Raij (138) have demonstrated that captopril but not the calcium channel blocker TA 3090 reduced proteinuria and glomerulosclerosis in the post-salt hypertensive Dahl salt-sensitive rat with 5/6 nephrectomy. However, Dworkin et al (139) have shown renal protection in rats with 5/6 nephrectomy with both enalapril and nifedipine but the protection is by different mechanisms: enalapril protects by lowering glomerular pressure and nifedipine protects by limiting renal hypertrophy.

2. Human studies

The animal studies have formed a basis for testing the hypothesis in humans that converting enzyme inhibitors (CEIs) and calcium channel blockers (CCBs) may not

only be renal protective in patients with hypertensive nephrosclerosis but may offer a therapeutic advantage over conventional agents (132). Short-term uncontrolled trials utilizing both CEIs alone or in combination with a diuretic in patients with chronic renal disease (140, 141), and one placebo-controlled trial utilizing the CCB nisoldipine (142) have provided evidence that these agents may slow the rate of progression of renal disease and may be more efficacious than conventional agents.

Ruilope et al (140) have reported that captopril treatment in hypertensive patients with various renal diseases slows the rate of progression of renal failure determined by slope of 1/Scr compared to conventional antihypertensive therapy. As can be seen below in figure 6, in these ten patients mean slope of 1/Scr was significantly more negative during conventional therapy compared with captopril therapy. Eliahou (142) has performed a prospective parallel-design placebo controlled trial using the dihydropyridine calcium channel blocker nisoldipine in patients with hypertension and various forms of chronic renal failure. The mean slope of 1/Scr remained constant for placebo treated patients whereas in the nisoldipine treated group, the mean slope became positive. The constancy of slope indicates no change in progression of renal failure while a positive slope suggests improvement in renal function. Taken together, these data suggest that converting enzyme inhibitors and calcium channel blockers may afford an advantage over diuretics and β-blockers in patients with kidney disease and hypertension. Unfortunately, these studies were limited by a) small numbers of patients; b) the use of a retrospectively defined control periods; and c) the lack of a randomized double-blind controlled design. Although both CEIs and CCBs are reported to increase renal blood flow and GFR both acutely and chronically in normal subjects, comparative studies on their effects in patients with renal disease are lacking (143). There are no clinical trials comparing the renal protective effects of BP lowering with CCBs vs. CEIs vs. conventional antihypertensive therapy in patients with hypertensive nephrosclerosis and established renal insufficiency.

Figure 6.

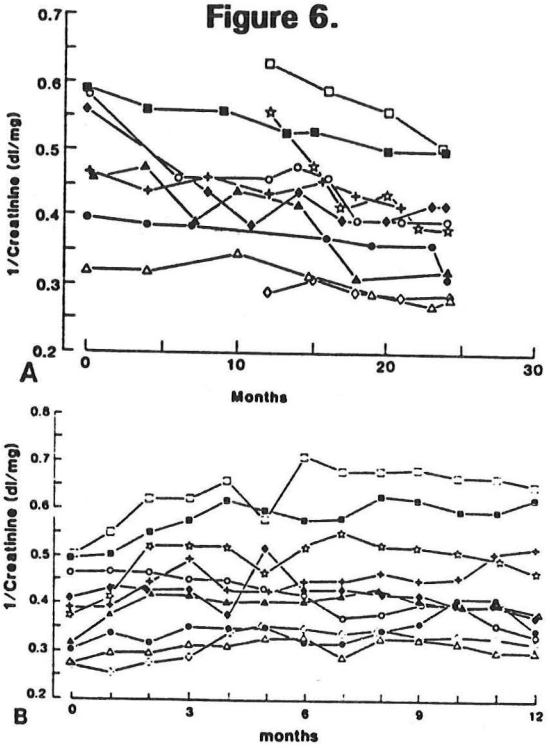


Fig 1. Effect of antihypertensive therapy on progression of chronic renal failure. (A) Individual rates of progression of renal failure of ten patients during the 12 to 24 months preceeding captopril therapy and while receiving propranolol-hydralazine-furosemide, (B) after captopril therapy.

D. The role of BP control level

Magee et al (83) reported that the decline in renal function in treated hypertensives with a mean treated DBP ranging from 97-108 mm Hg was similar during 3-5 years of follow up in the VA cooperative study. Pettinger from this institution (14) recently reported the results of a prospective, randomized, long-term BP control trial designed to determine whether "strict" (DBP < 80 mm Hg) BP control vs. "usual" (DBP 85-95 mm Hg) control preserves renal function in patients with established renal insufficiency (GFR $\leq$ 70 ml/min/1.73m^2) at baseline. Interestingly, this preliminary report described an improvement in mean GFR in 22 patients (89% were black and 79% male), of which 14 were randomized to "strict" BP control and 8 randomized to "usual" control. Mean GFR increased in patients assigned to both BP control groups. These results provided important evidence that renal function can not only be preserved with an intensive, persistent effort to maintain lower BP, but in fact can improve in short-term follow-up. Unfortunately, in this small group significant differences in DBP control were not maintained over the 36 months of follow-up. Thus, with respect to BP control level there were no discernable differences in GFR preservation. Furthermore this is a relatively short time in the spectrum of chronic hypertensive disease.

In a retrospective analysis, Brazy et al (13) reported that the rate of progression of renal failure in treated patients with hypertensive nephrosclerosis correlates positively with the severity of hypertension. Data from their study are shown in figure 7. They studied 16 patients in whom several serum creatinine concentrations were obtained over at least 2 years who while diastolic BP was > 90 mmHg and again over 2 years while diastolic BP was < 90 mmHg. As shown in the figure the slope of the reciprocal of serum creatinine was significantly less negative during the period of time when diastolic blood pressure was maintained below 90 mmHg.

Figure 7.

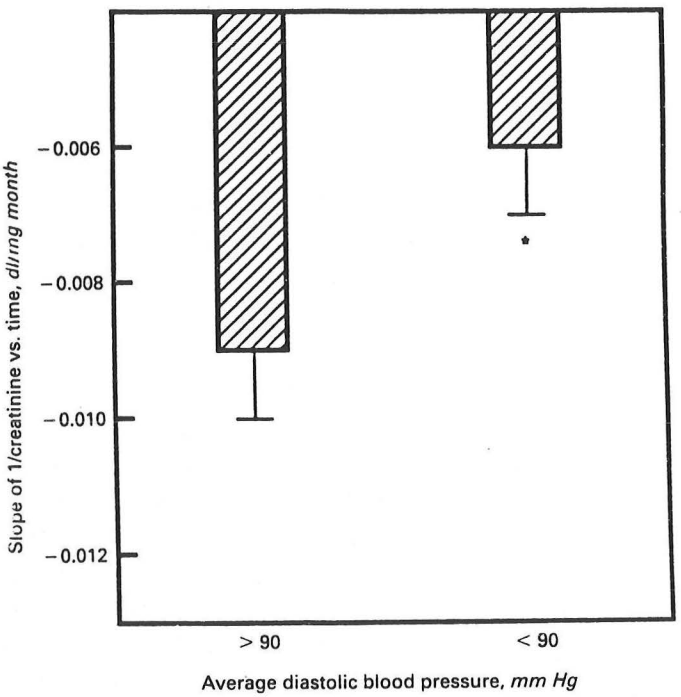


Fig. 2. *Effect of diastolic blood pressure on rates of decline in renal function in individual patients.* Bars represent mean + SE of slope from reciprocal creatinine versus time plot determined at times when their diastolic blood pressure was >90 mm Hg and again when it was <90 mm Hg. *N* equals 19 patients. Statistical comparison between slopes was made using a paired *t*-test and * indicates $P < 0.05$.

E. Clinical Trial of long-term BP control at Southwestern

During the past 7 years we have conducted a clinical trial designed to test the hypothesis that strict BP control defined as supine DBP ranging from 65-80 mm Hg is more effective at slowing the rate of progression of renal failure in patients with kidney disease and hypertension compared to usual BP control defined as supine diastolic BP of 85-95 mm Hg.

1. Methods Patients between the ages of 21-68 with long-standing mild to severe hypertension and chronic renal insufficiency defined as a serum creatinine of > 1.6 mg/dl and a GFR of < 70 ml/min/1.73 m^2 were recruited into the study. Patients with known causes of renal failure other than hypertension were excluded as were patients with a recent history of malignant hypertension, stroke, myocardial infarction, pregnant or lactating women or patients with secondary causes of hypertension.

Patients were managed with conventional antihypertensive medications including minoxidil, hydralazine, β-blockers, clonidine, methyldopa, prazosin, furosemide, triamterene-hydrochlorothiazide and metolazone until 1985, when enalapril or placebo were added as study drugs in a randomized, double-blind fashion to patients in both BP control groups. At the time of addition of enalapril another cohort of patients was recruited into the study without alteration of entry criteria or BP control group definition. BP control medications were initiated and subsequently titrated in a prospectively defined regimen based on the experience of the investigators. Initially an attempt was made to control all patients to the "strict" BP control level in order to exclude patients with severe hypertension who could not be controlled (12). After reducing BP to the "strict" control level, the patients were randomly assigned to "strict" vs."usual" BP control levels; medications were subsequently adjusted to maintain the assigned BP level.

Renal function was evaluated by measuring glomerular filtration rate utilizing ^{125}I-iodothalamate as a marker. The GFR was measured at 6-12 month intervals during follow-up. In addition creatinine clearance, urea clearance and proteinuria were measured periodically.

2. Results The relationship between mean DBP and mean GFR is shown below in Figure 8. At baseline GFR and diastolic blood pressure were similar in both groups as expected. Significant differences in BP control levels separating "strict" from "usual" into two distinct groups was achieved between 3 and 9 months. GFR was maintained relatively constant in the "strict" group from zero to 24 months. Conversely, as the BP was allowed to increase in the "usual" group, there was a tendency for GFR to increase. Thus, mean GFR began to increase in the "usual" group at 3 months and was significantly higher than the "strict" group at 3, 9, 18 and 24 months. Despite persistent differences in BP at 36 and 48 months GFR was not significantly different between groups at these times.

It is clear that there is considerable variability in the rate of progression of renal failure in both groups. Some patients deteriorated and others actually showed improvement in renal function. The mean GFR slope was significantly different from zero in the strict but not the usual control group. Slope of GFR was significantly negative in 3 (range:

-0.33 to 1.13; 2 usual and 1 strict), significantly positive in 5 (range: + 0.18 to + 0.77; 4 strict and 1 usual), and not significantly different from zero in 52 of these 60. The slope of GFR at 48 months was not different from zero in either group and there was no difference in slopes between groups. In this group of 41 patients who are at 48 months, slope was significantly negative in 4 (range: -0.27 to -0.56; 4 usual), positive in 6 (range: 0.15 to +0.43; 5 strict and 1 usual), and not different from zero in 31 patients. However, it is noteworthy that the mean slope in the "strict" group was positive and in the "usual" group it was negative. Mean DBP tended to drift upward in both groups so that the goal supine diastolic BP ranges for both groups were not maintained throughout the study (see below).

Figure 8.

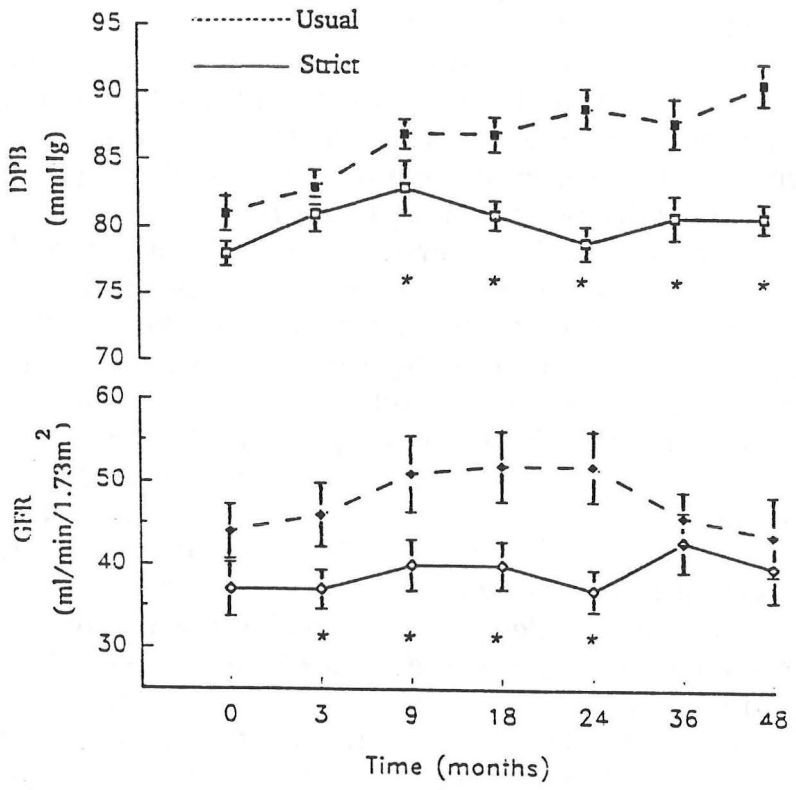


Figure 8. The relationship between mean GFR and mean DBP for "strict" and "usual" BP control groups

Analysis of slope of GFR was after arbitrarily stratifying patients into two groups based on their baseline serum creatinine level at the time of randomization: 1) serum creatinine $\leq$ 2.5 mg/dl and 2) serum creatinine > 2.5 mg/dl revealed that the slope of GFR in the group with Scr $\leq$ 2.5 mg/dl (n=44) was $+0.12 \pm 0.43$ and for the group with Scr > 2.5 (n=16) was -0.06 ± 0.36 ml/min/1.73 m^2. Although the mean slopes were different in direction and magnitude they were not statistically significantly different from each other at 36 months. However, at 48 months of follow-up slope of GFR for Scr $\leq$ 2.5 mg/dl (n=33) was $-0.05 \pm .4$ and for Scr > 2.5 (n=9) was $-0.46 \pm .59$. These slopes were significantly different from each other. These data suggest that progression of renal disease is more rapid in patients with more severe degrees of renal failure. Further follow-up is necessary in these patients to determine whether preservation of

renal function continues or whether renal function eventually deteriorates as it did in case #5 presented above.

A considerable number of patients in this study had severe hypertension thus the average number of medications required to control pressure prior to study was 3.2/patient. We therefore were very concerned about the possibility of cardiovascular complications during the trial in particular in relation to blood pressure control groups. We observed two myocardial infarctions during 2660 patient-months of follow-up, one in a "strict" control patient whose mean SDBP was 74 mm Hg and one in a patient in the "usual" group with a mean SDBP of 84 mm Hg. One patient in the "strict" control group whose mean SDBP was 80 mm Hg suffered a CVA. Therefore, in this group of patients with longstanding hypertension in whom 46% had a variety of cardiovascular complications prior to entry into this study only 3 patients had documented major cardiovascular events during a total period of 6 years.

3. Conclusions:

1) We are able to achieve and maintain two different levels of BP control up to 48 months in this high risk patient population.

2) Overall GFR is remarkably well preserved particularly in patients with baseline glomerular filtration rates in the range of 15-75 ml/min/1.73 m^2 regardless of BP control group assignment for 36-48 months.

3) There is significant inter-patient variability in GFR slope over 3-4 years.

4) the incidence of adverse cardiovascular events in this high-risk population during follow-up was relatively low, 3/60 (5%).

Table 12. Recommendations for Treatment of Hypertension To Protect the Kidney.

- Control blood pressure to <140/90 mm Hg, if practical.*
- Recognize and evaluate early renal insufficiency defined as:

  Renal failure:

  Serum creatinine >1.4 mg/dL (50 percent loss of renal function)
  Serum creatinine >1.3 mg/dL (in patients >60 years of age)
- Reduce daily dietary sodium to approximately 2 grams sodium (5 grams salt NaCl) or <100 mEq sodium.
- Use loop diuretics if serum creatinine is >2 mg/dL.
- Add diuretic to monotherapy if blood pressure is not controlled.
- Measure serum creatinine and electrolytes frequently.
- Assess and manage all cardiovascular disease risk factors.*

* *The Report of the 1988 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure*

C. Summary

Taken together the bulk of the evidence including our own data suggest that control of blood pressure does slow the progression of renal failure in at least some patients with hypertension. Nevertheless as presented earlier it is clear that certain individuals with biopsy proven hypertensive renal disease progress to ESRD even with excellent control of blood pressure. The recommendations of the National High Blood pressure Education Program Working Group Report for Treatment of Hypertension to protect the kidney (2) have recently been published and are shown above in Table 11. I believe these are the best available at the moment given current available knowledge in this field. However, several important questions

remain unanswered. First, if blood pressure control is consistently maintained in the adequate range can end stage renal disease be prevented? If not, can we identify other factors whose prevention and/or treatment will prevent progression to ESRD? Do these patients all have the same renal biochemical and pathological lesion? Is there a critical level of renal function beyond which progression of vascular disease is inevitable despite adequate BP control? Is there a critical level of diastolic BP below which renal function can be preserved indefinitely in most or all patients? Are some BP medications more efficacious in preserving renal function?

XII. CONCLUSIONS AND RECOMMENDATIONS

In conclusion, there is a great deal more that we need to learn about kidney disease and hypertension. The latest information indicates that this disease is increasing in incidence and that it afflicts the American black population at a disproportionate rate. Further studies are needed to improve methods of diagnosis, identify markers that predict the risk of progressive renal disease, define the genetic factors that are responsible for the generation and maintenance of the hypertensive state and the predisposition to renal failure, elaborate more clearly the clinical physiology and the associated structural changes in the kidney of early renal disease, and finally to develop better and more comprehensive prevention strategies. At the present time it seems prudent to follow the recommendations of the National High Blood Pressure Education Program Working Group Report on Hypertension and Chronic Renal Failure.

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