MEDICAL GRAND ROUNDS

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER

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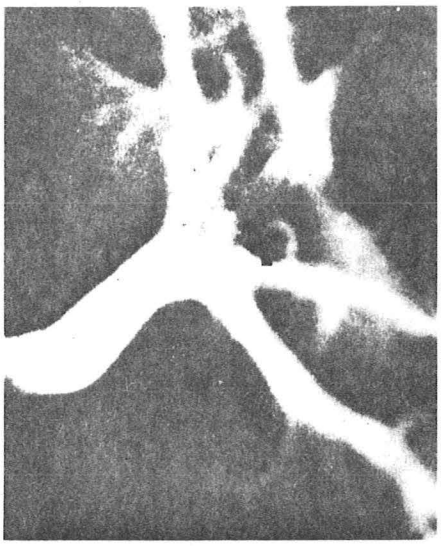
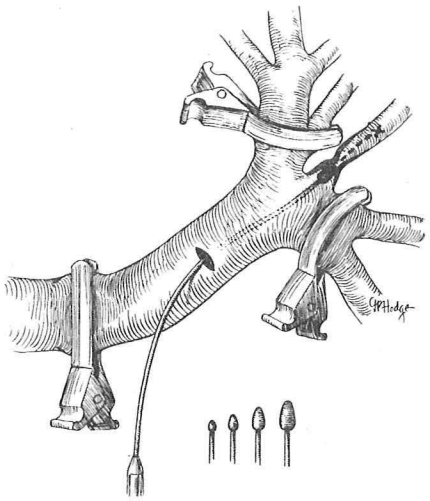
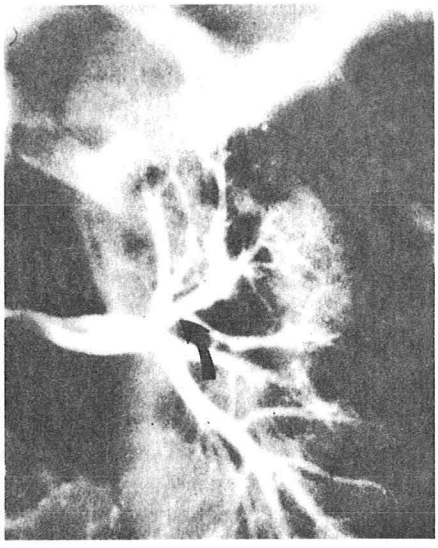
RENOVASCULAR HYPERTENSION

Bryan Holland, M.D.







The role of the kidney in the regulation of arterial pressure was recognized as early as 1898 when two medical students, Tigerstedt and Bergman, demonstrated that a saline extract of the kidney, which they called renin, possessed pressor activity. However, this observation lay dormant until 1934 when Goldblatt discovered that constriction of a renal artery of the dog would lead to the development of hypertension. The search for the humoral mechanism explaining the pathogenesis of this experimental form of hypertension culminated in the discovery of the renin-angiotensin system in 1939--almost simultaneously by Page and Helmer in the United States and by Braun-Menendez *et al* in Argentina. Since the medical therapy of hypertension was abysmal at that time, the possibility of a surgical success was eagerly pursued for those patients with a small kidney. However, in 1956 Smith reviewed 575 cases treated by unilateral nephrectomy and found that only 26% were benefitted. He estimated at this time that no more than 2% of all hypertensive patients had renovascular hypertension which would be benefitted by unilateral nephrectomy. This landmark warning evolved into a second era of renovascular hypertension with the development of vascular surgery and arteriographic techniques in the 1950's. In this second era, patients with hypertension and demonstrable renal artery stenosis were treated by arterial reconstruction or nephrectomy. However, by the early 1960's, it was apparent that less than 50% of such unselected patients so treated were benefitted. Development of methods for study of the function of a kidney with renal artery stenosis led to a third era. This era began with the development in 1957 by Howard *et al* of the split function tests which were subsequently modified by Stamey (1961). The third era also witnessed the development of reliable renin assays to quantitate renin secretion by the involved kidney. In the present, fourth, era considerable experience with these testing procedures and with advances in surgical and arteriographic techniques have led to considerable improvement in the identification and management of those patients with surgically correctable renovascular hypertension. There is hope that with the development of specific angiotensin and converting enzyme antagonists to more clearly identify those patients with renin-mediated hypertension, a fifth era may be close at hand.

Definition and incidence: Renovascular hypertension refers to hypertension caused by renal ischemia. Unfortunately, the arteriographic demonstration of anatomical renal artery stenosis does not provide evidence that renal ischemia is present. Eyler *et al* (1962) noted that 32% of 304 normotensive patients and 67% of 193 hypertensives had some degree of renal artery stenosis by arteriography (Table 1). In those patients over age 60, almost half had some atherosclerotic lesions in their renal vessels. Holley *et al* (1964) noted a similar high frequency of renal artery stenoses at autopsy, and Dustan *et al* (1964) noted that only 50% of 60 patients with marked stenoses seen by arteriography were hypertensive.

Table 1

Incidence of Renal Arterial Lesions in Normotensive and Hypertensive Patients

	Normotensive		Hypertensive	
Age	Normal	Lesion	Normal	Lesion
31–40	7	3	6	10
41–50	26	8	14	22
51–60	99	35	28	50
Over 60	69	56	15	48

From Eyler WR, et al: *Radiology* 78:879, 1962.

The incidence of renovascular hypertension varies considerably (Table 2). However, Tucker and Labarthe (Table 3) have recently reported data from the Mayo Clinic suggesting that the incidence of surgically correctable renovascular hypertension (0.18%) is exceedingly lower than previous estimates. This retrospective study suffers from the fact that a relatively small number of arteriograms were done at the Mayo Clinic during the period of time of the study. However, on the other hand, it would be expected that the patient population coming to the Mayo Clinic would contain a greatly magnified disproportion of patients with renal artery stenosis. Thus, it is unclear whether the reported estimate of 0.18% for surgically correctable renovascular hypertension is an overestimate or underestimate. Nonetheless, it is evident that surgically correctable renovascular hypertension is a rare cause of hypertension in general. Therefore, methods are required to properly identify those patients with renovascular hypertension.

-Reported Frequency of Renovascular Hypertension (a Literature Resume)

Authors, year	Frequency, %	Data base and comments
Hunt & Strong,[2] 1973	5*	214 patients underwent operation
Gifford,[3] 1969	4†	5,000 patients screened in 2 years, 1966 and 1967
Swales,[4] 1976	3	161 patients; 5 operations in 2 years
Bech & Hilden,[5] 1975	1	482 patients; 5 operations in 15 years
Maronde,[6] 1975	<1*	Patients' data base not given
Atkinson & Kellett,[7] 1974	0	985 urograms, 20 arteriograms, no renovascular hypertension found

*Authors' estimate; supporting data not supplied.
†220 cases of renal artery stenosis but only 67 were surgically repaired.

Table 2

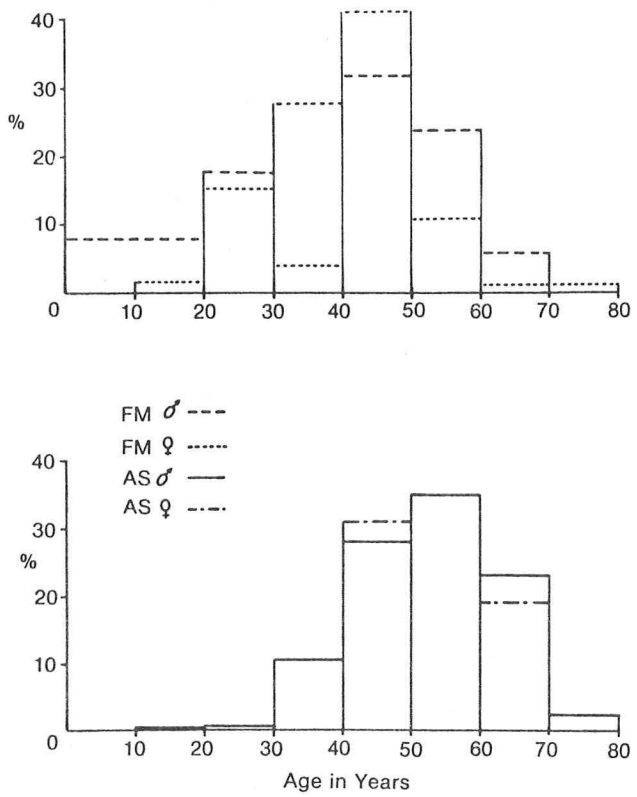
-Average Annual Frequency of Operations for Secondary Hypertension at the Mayo Clinic, 1973, 1974, and 1975

Disorder	No./ year	Hypertensives, expected no.	Hypertensives, per 10,000 No.	Hypertensives, per 10,000 %
Renal artery stenosis	46.7	26,589	18	0.18
Pheochromocytoma removal	10.3	26,589	4	0.04
Aldosterone-producing adenoma excision	2.7	26,589	1	0.01
Total	59.7	26,589	23	0.23

Table 3

Clinical characteristics: The early literature tended to characterize renovascular hypertension as being rather acute and fulminant in character. However, a large cooperative study with 15 collaborating institutions which started in 1960 has painted a different picture. The large number of patients were divided into atherosclerotic (2/3) and fibrodysplastic (1/3) categories and compared with about 1500 patients with essential hypertension as well as with each other. The data obtained agrees fairly well with that from other, smaller studies and, therefore, can probably be accepted as a general experience. The age of occurrence of the atherosclerotic lesions is greater than that for the fibrodysplastic (Figure 1). The distribution of renal artery lesions is presented in Table 4.

In general, there are a relatively small number of clinical characteristics that distinguish patients with renovascular hypertension from those with essential hypertension. Data presented in Table 5 are derived from the entire study; whereas data in Table 6 are derived from a group of 131 patients with renovascular hypertension who were carefully matched to a group with essential hypertension. A striking increase in fibrodysplastic disease in younger white women, particularly those who are slender, is notable. Blacks have a lower incidence of both atherosclerotic and fibrodysplastic disease. However, this contrast is magnified by their increased incidence of essential hypertension in comparison to whites. The presence of an abdominal bruit has been noted to



Right, *Histogram by decade.* AS, *atherosclerosis,* FM, *fibromuscular hyperplasia.*

Figure 1

(Maxwell *et al:* *JAMA* 220:1195, 1972)

DISTRIBUTION OF MAIN RENAL ARTERY LESIONS

ETIOLOGY	UNILATERAL RIGHT	UNILATERAL LEFT	BILATERAL	TOTAL
ATHEROSCLEROSIS	141	199	153	493
FIBROMUSCULAR HYPERPLASIA	143	44	63	250
TOTAL	284	243	216	743

COOPERATIVE STUDY *JAMA* 221:368, 1972

Table 4

CLINICAL CHARACTERISTICS OF ESSENTIAL HYPERTENSION AND RENOVASCULAR HYPERTENSION CURED BY SURGERY

	ESSENTIAL-%	ATHERO-SCLEROTIC-%	FIBROMUSCULAR HYPERPLASIA-%
DURATION OF HYPERTENSION			
<1 YEAR	10	23	19
>10 YEARS	23	12	10
AGE OF ONSET (>50 YR)	7	39	3
SEX (FEMALES)	40	34	81
RACE (BLACK)	29	7	10
FAMILY HISTORY OF HYPERTENSION	67	58	41
BODY HABITUS (THIN)	6	13	30

COOPERATIVE STUDY *JAMA* 220:1209, 1972

Table 5

*Clinical Characteristics of Essential Hypertension and Renovascular Hypertension Cured by Surgery**

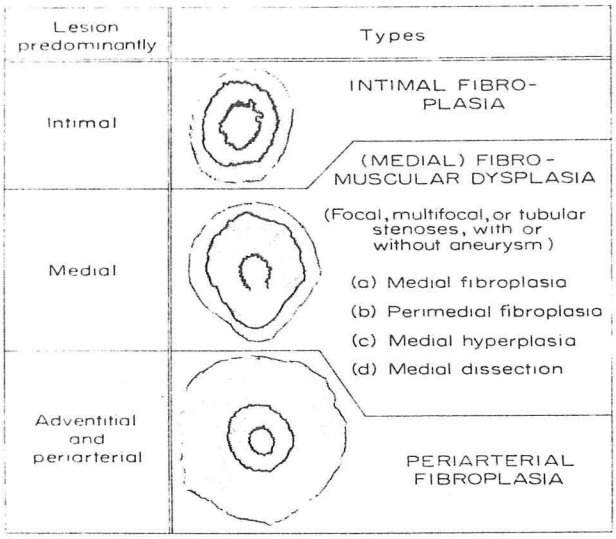
	ESSENTIAL HYPERTENSION (PER CENT)	RENOVASCULAR HYPERTENSION (PER CENT)
Duration of hypertension		
< 1 yr	12	24
> 10 yr	15	6
Age of onset (>50 yr)	9	15
Family history of hypertension	71	46
Fundi (grade 3 or 4)	7	15
Bruit		
Abdomen	6	46
Flank	1	12
Abdomen or flank	7	48
BUN (> 20 mg per 100 ml)	8	15
Serum K (< 3.4 mEq per liter)	8	16
Serum CO_2 (> 30 mEq per liter)	5	17
Urinary casts	9	20
Proteinuria (trace or more)	32	46

*Patients matched by age, sex, race, and diastolic blood pressure (131 matched pairs). All differences included in this table are statistically significant.

Table 6

be the most helpful clinical criteria to distinguish those with renovascular from those with essential hypertension. In the large cooperative study on renovascular hypertension, a bruit was found in 57% of patients with fibrodysplastic disease, 41% of those with atherosclerosis, and 7% of patients with essential hypertension. However, since the incidence of essential hypertension is so much greater than renovascular hypertension, the chance of finding essential hypertension in a given patient with an abdominal bruit is much greater. Greater diagnostic significance is attached to those bruits heard in the flank or those which have a diastolic component. The bruit is most commonly noted in the upper epigastrium. In general, the bruit of renal artery stenosis is frequently higher pitched, of longer duration, and extends out from the midline. This type of bruit is heard much more frequently in renal artery stenosis due to fibrodysplastic disease as opposed to atherosclerotic disease (Eipper *et al*, 1976; McLaughlin *et al*, 1975; Julius and Stewart, 1967). Other clinical characteristics previously noted in some patients with renovascular hypertension were not found by the cooperative study to distinguish these patients from those with essential hypertension.

Types of arterial fibrodysplasias: Considerable difference in terminology exists for this group of disorders. The whole group is sometimes loosely referred to as fibromuscular hyperplasia. In 1971 Harrison and McCormack headed groups of investigators from the Cleveland and Mayo Clinics, respectively, and arrived at a common system of classification of the renal arterial fibrodysplasias. This terminology incorporated slightly different terminologies which had previously been used by the two groups (Figure 2). In 1975 the Michigan group headed by William Fry reviewed their experience with arterial fibrodysplasias and concluded that there were several defects in the Mayo-Cleveland Clinic classification. They, thus, proposed a new system of classification (Stanley *et al*, 1975, Tables 7 & 8).



Types of idiopathic fibrous and fibromuscular stenosis of the renal artery.

Figure 2

The series of Stanley *et al* involved a total of 196 patients (172 females, 24 males) harboring a total of 316 diseased vessels. Renal arterial lesions were documented in 152 adult and 25 pediatric patients. Bilateral renal arterial lesions occurred in 84 patients. Unilateral changes involved the right renal artery of 53 patients and the left renal artery in 15 patients. The mean age of affected women (40.0 years) exceeded that of men (32.2 years). A predilection for females was not evident in 25 pediatric patients (11 girls, 14 boys) ranging from 21 months to 17 years of age. Unilateral renal artery stenoses in these younger patients were evenly distributed (11 right, 11 left). Three children had bilateral disease. Five children had stigmata of neurofibromatosis, an association not observed in adults. Familial renal artery dysplasia was demonstrated in one 44-year-old patient and her 5-year-old daughter. Extracranial cerebrovascular fibrodysplasia affected 17 patients (all women) 21 to 79 years old,

TABLE 7. COMPARISON OF CLASSIFICATION SYSTEMS FOR THE ARTERIAL FIBRODYSPLASIAS

Harrison-McCormack*	Stanley-Fry**
I. Intimal involvement	
A. Intimal fibroplasia	A. Same
II. Medial involvement	
A. Medial fibroplasia	A. Same
B. Perimedial fibroplasia	B. Combine with medial fibroplasia
C. Medial hyperplasia	C. Same, more restrictive pathologic criteria
D. Medial dissection	D. Classified as complication, not type
E. --	E. Perimedial dysplasia
III. Adventitial and periarterial involvement	
A. Periarterial fibroplasia	A. Not considered a primary arteriopathy but considered a secondary process, such as occurs with retroperitoneal fibrosis

**Mayo Clin Proc* 46:161, 1971
***Arch Surg* 110:561, 1975

mean 51.2 years. Of 16 patients who had internal carotid artery disease, 10 had bilateral lesions; 7 of these 16 patients had coexisting vertebral dysplasia including 2 with bilateral disease; 8 patients had associated intracranial aneurysmal disease; and 5 of the 17 had concomitant renal artery lesions. Dysplastic stenoses involving splanchnic vessels were demonstrated in 8 women known to have renal artery fibrodysplasia and were the only abnormal findings in 2 additional patients. Other sites of dysplasia included the celiac artery, the common hepatic artery, the proximal part of the superior mesenteric artery, branches of the superior mesenteric artery, and the external iliac artery. Other investigators have noted involvement of arterial sites other than the renal arteries (Harrington *et al*, 1970; Wylie *et al*, 1966; Stanley *et al*, 1974) with development of subarachnoid hemorrhage, cerebral ischemic symptoms, or visceral ischemic symptoms. This diverse involvement has been confused on occasion with polyarteritis nodosa (Meyers *et al*, 1974). Other familial involvement in three female siblings has been reported (Halpern *et al*, 1965).

The two forms of dysplasia encountered least often, intimal fibroplasia and medial hyperplasia, present problems relating to their pathology quite dissimilar to those encountered in other dysplastic states. Intimal fibroplasia is a common sequel of a variety of arterial injuries including external trauma, arteritis from rubella, and intraluminal insults arising from local alterations in blood flow though the cause of primary intimal fibroplasia

TABLE 8. PATHOLOGICAL CHARACTERISTICS OF ARTERIAL FIBRODYSPLASIAS

Type	Incidence-%	Nature of Stenosis	Pathology
1. Intimal fibroplasia	5	Smooth, focal in older persons; long, irregular tubular in younger persons	Irregular subendothelial cells in a loose matrix of fibrous connective tissue
2. Medial hyperplasia	<1	Focal	Hyperplastic medial smooth muscle without fibrotic changes
3. Medial fibroplasia	85	Continuum--focal to multiple aneurysmal or constricting lesions	Involvement of outer media to entire media; fibrous connective tissue replacing smooth muscle with accumulation of collagen and ground substance; frequent loss of external and internal elastic lamina with aneurysm formation
4. Perimedial dysplasia	10	Usually focal, occasionally multiple; involved midportion of renal artery	Compact collar of relatively acellular tissue near the external elastic lamina

remains an enigma. Medial hyperplasia, like intimal disease, is not associated with an easily identifiable cause to produce isolated hyperplasia of smooth muscle within the circulatory system. This category is extremely rare.

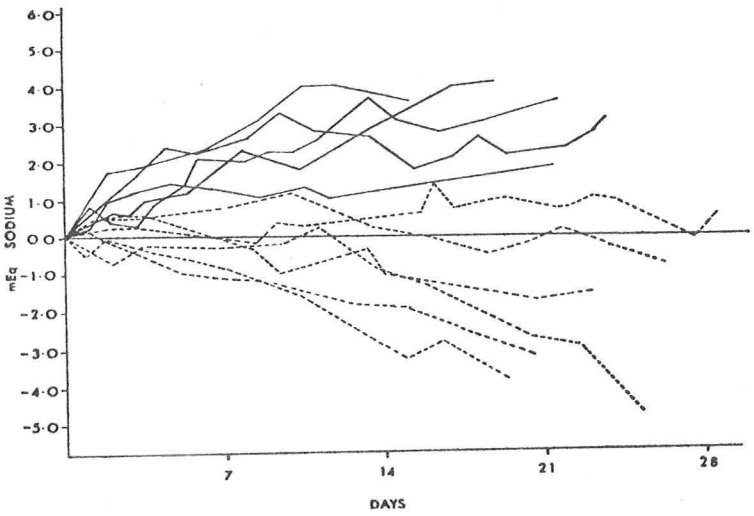
Medial fibroplasia is characterized by an histologic continuum that is demonstrable arteriographically and clinically. The classification of Stanley and Fry lumped what had previously been called subadventitial or perimedial fibroplasia with medial fibroplasia. This appeared to be justified since the peripheral form of medial fibroplasia affects individuals at a younger age than does the diffuse form, and it is likely that initial disease of the outer media progresses to involve the entire media with passage of time. In addition, some patients demonstrated the two histological pictures in different microscopic sections. Further evidence of this evolution is provided by the clinical finding of true macroaneurysms when the entire media becomes diseased later in the course of medial fibroplasia.

Perimedial dysplasia is characterized by the occurrence of the lesion in the mid-renal artery rather than distally. Mechanisms responsible for excessive replication of the elastic tissue must be unique to this form of dysplasia and, perhaps, effects of physical stresses on the arterial wall connective tissue are primarily important in the pathogenesis.

The etiology of arterial fibrodysplasia remains uncertain although the following have been associated with the pathogenesis: (1) Hormonal effects--the unusual predilection for females is noted; (2) Mechanical stresses on vessel walls--Arterial fibroplasia is common to those arteries that undergo the most mechanical stress. The fibrodysplasias are associated with nephroptosis (De Zeeuw *et al*, 1977). Nephroptosis is more common in taller, more slender individuals, and the movement of the kidney is postulated to produce a physical stress on the renal arteries. The greater mobility of the right kidney may explain the preponderance of right sided renal artery lesions. Physical stresses are also produced by stretching of the internal carotid artery over the upper cervical vertebrae on hyperextension of the neck and tension on the superior mesenteric artery from the weight of the attached viscera. (3) Distribution of the vasa vasora--Vasa vasora of muscular arteries invariably originate from branchings of the parent vessels. The renal, extracranial carotid, and external iliac arteries have relatively few branches compared to other vessels of similar caliber and may have a paucity of vasa vasora normally. This may predispose these arteries to vessel wall ischemia. This concept is supported by the frequent involvement of the outermost part of the media where ischemia predictably would be greatest and the lack of fibrodysplasia limited to the inner part of the media. In addition, lesions resembling medial fibroplasia have been produced experimentally in the dog by occlusion of the vasa vasora (Sottiurai, Fry, and Stanley, unpublished data).

Pathophysiology of renovascular hypertension: A massive literature has appeared in the years since Goldblatt first induced hypertension in the dog by partially occluding one artery and removing the opposite kidney. However, a considerable amount of controversy has evolved around the finding that plasma renin activity (PRA), either peripherally or from the renal veins, is not elevated throughout the course of some types of renovascular hypertension (reviewed by Davis, 1977). It appears that this normalization of plasma renin activity results from a setting in which renal ischemia with renin release leads to secondary aldosteronism with resultant sodium retention, volume expansion, and feedback on renin release to produce normal or near-normal levels. However, these levels are inappropriately high for the level of sodium retention. A number of experimental models have been utilized to elucidate this hypothesis. The concept is illustrated by the one-kidney, two-kidney experimental model.

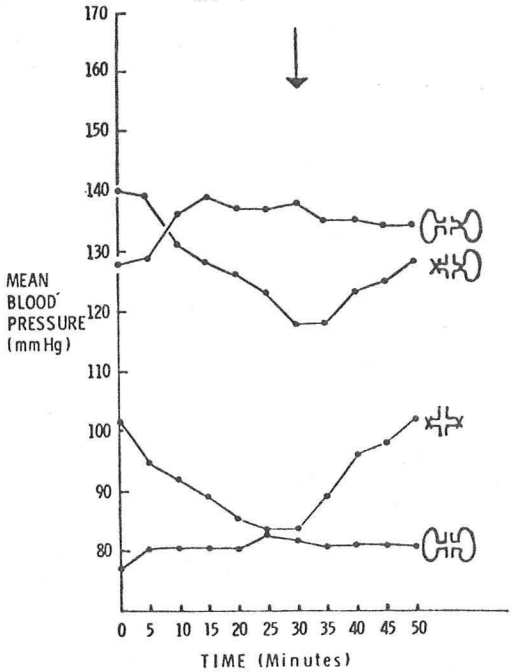
Swales *et al* (1971) are one of several investigative groups who have elucidated this mechanism fairly convincingly (Figures 3 & 4). They noted that those rats with one-kidney hypertension (unilateral clip with contralateral nephrectomy) developed a progressively positive cumulative sodium balance; whereas most two-kidney rats (unilateral clip, contralateral intact kidney) had a decrease in sodium balance. Further, they showed that one-kidney rats, like bilaterally nephrectomized rats, had a fall in blood pressure after removal of sodium and a rise in blood pressure with saline loading. In contrast, the two-kidney rats had a rise in pressure when sodium was removed, suggesting a further increase in renin released from the ischemic kidney.



–Cumulative sodium balance in rats with unilateral renal-artery constriction with (——) and without (- - - -) contralateral nephrectomy.

Mean blood-pressure of contralateral-nephrectomy group rose from 95 mm. Hg preoperatively to 140 mm. Hg at the end of first week, rising to 160 mm. Hg. Clip-only animals remained normotensive for 1–2 weeks and then blood-pressure rose to a mean value of 176 mm. Hg over the next 3 weeks.

Figure 3



–Blood-pressure changes after removal of 1-2 meq. of sodium from rats by peritoneal dialysis.

An approximately equal amount of saline was reinfused after 45 minutes (arrow). Animals had previously undergone unilateral renal artery constriction without or with contralateral nephrectomy, bilateral nephrectomy with saline loading, or sham bilateral nephrectomy.

Figure 4

Further experimental corroboration of this thesis is provided by the demonstration of chronic hyperreninemia in the two-kidney experimental model. Brunner *et al* (1971) infused antiangiotensin II antibody into one-kidney and two-kidney animals (Figure 5). The one-kidney animals had little change in the blood pressure; whereas the two-kidney animals had a distinct fall. When salt depleted, the one-kidney animals became responsive to angiotensin antagonism. Similar results were obtained by the same investigators with a specific angiotensin II antagonist, saralasin, infused intravenously. During renal artery constriction acute elevations in plasma renin activity and plasma angiotensin II concentration concomitant with decreases in renal blood flow and increases in mean arterial pressure have been nicely demonstrated in conscious one-kidney and two-kidney dogs by Caravaggi *et al* (1976). The observed increase in plasma angiotensin II concentration with progressive renal arterial constriction appears to cause entirely the observed blood pressure elevation since

infusion of angiotensin II to attain similar levels of plasma angiotensin II lead to approximately the same changes in blood pressure (Figures 6 & 7).

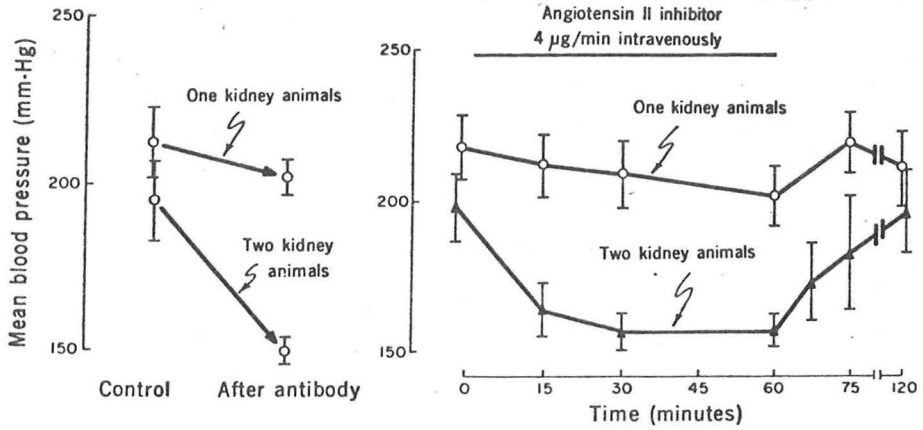
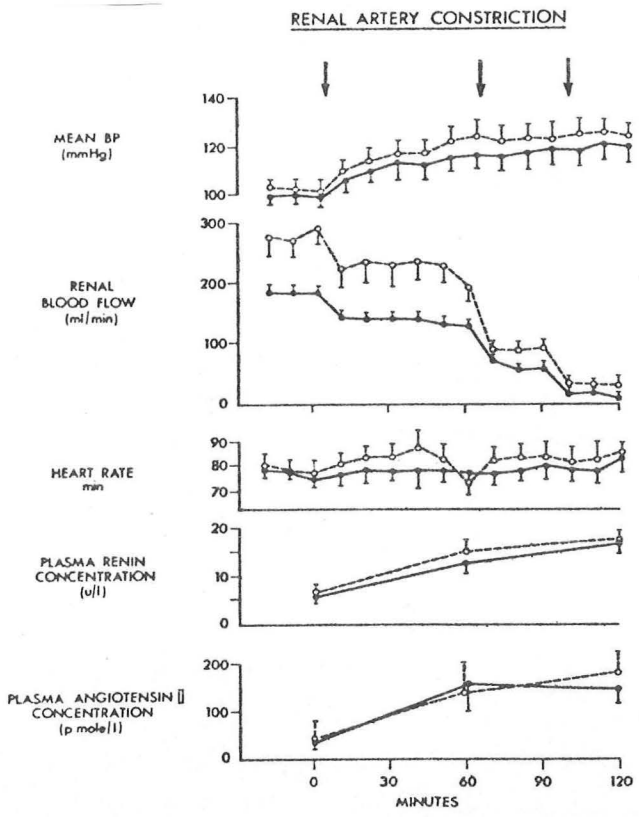


Figure 5

(left). In the two-kidney type of renal hypertension, the administration of 0.6 ml of antibody to angiotensin II induced a fall in mean blood pressure of 41.0 ± 4.0 mm-Hg ($P < .001$), whereas in the one-kidney type of renal hypertension, the blood pressure fell by only 10.0 ± 6.4 mm-Hg. This latter change was not significant ($P > .1$).

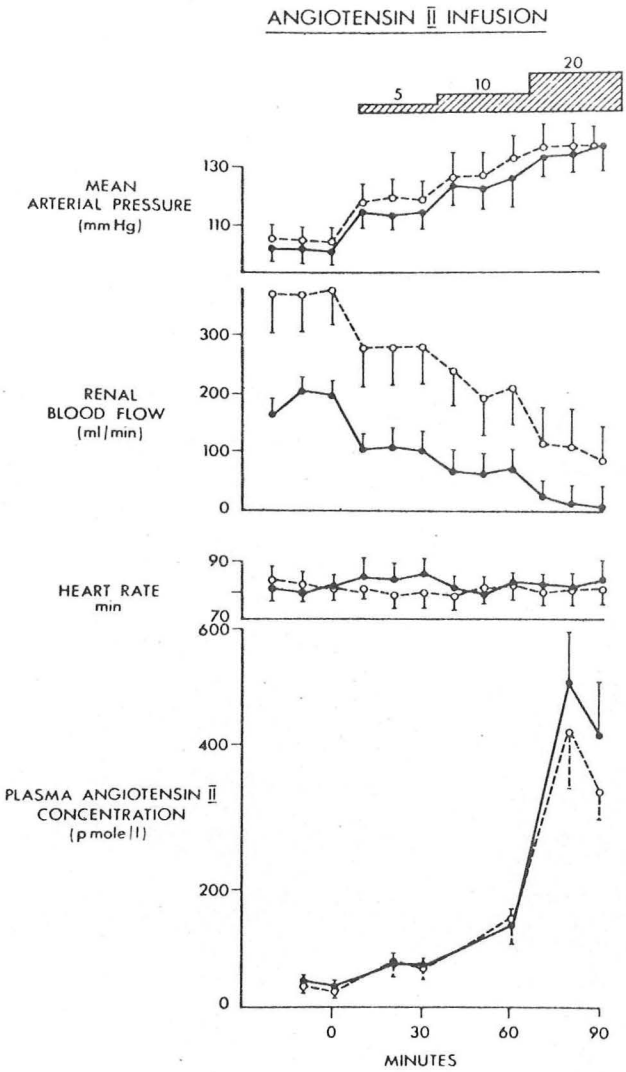
(right). In the two-kidney type of renal hypertension infusion of the angiotensin inhibitor induced an immediate and progressive fall in blood pressure which reached 40.8 ± 4.2 mm-Hg after 60 minutes ($P < .001$). In contrast, the change in blood pressure induced in the one-kidney type of renal hypertension was not significant ($P > .1$).

Figure 7



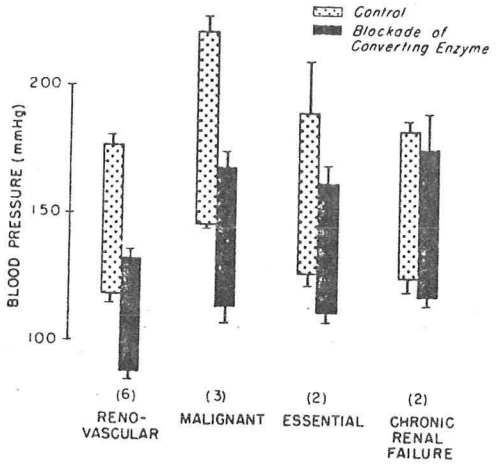
Mean arterial pressure, renal blood flow, heart rate, and plasma renin and angiotensin II concentration in six conscious dogs subjected to progressively increasing constriction of a main renal artery (indicated by arrows). Data obtained before (●—●) and after (O----O) removal of the contralateral kidney. Bars represent 1 standard error of the mean. 1 pmol of [5-isoleucine]angiotensin II per liter is equivalent to 1.046 pg/ml of plasma.

Figure 6



Mean arterial pressure, renal blood flow, heart rate, and plasma angiotensin II concentration in six conscious dogs before and during three periods of angiotensin infusion (5, 10, and 20 ng/kg/min). Experiments were conducted before (●—●) and after (O----O) removal of the contralateral kidney.

The one-kidney, two-kidney model of renovascular hypertension also appears to be applicable to man. In those patients with unilateral renal artery stenosis of recent onset, plasma renin activity is frequently elevated and the blood pressure responds dramatically to several types of angiotensin antagonists (Marks *et al*, 1977; Gavras *et al*, 1974, Figure 8). However, other patients with either bilateral renal artery stenosis or with longstanding unilateral renal artery stenosis and apparent contralateral renal arteriolar nephrosclerosis have normal peripheral and renal vein PRA (Scherer *et al*, 1977). Angiotensin II dependence can only be demonstrated in these patients when a period of sodium depletion before testing is utilized (Marks *et al*, 1977). One factor that remains difficult to assess in this setting is the fact that all hypertensive patients will exhibit a fall in the blood pressure when sufficiently sodium depleted since the renin-angiotensin system assumes a primary effect in maintaining the blood pressure during sodium depletion.



Mean Blood Pressures, Control (Dotted Bars) and during Converting-Enzyme Inhibition (Black Bars) of the Four Groups of Hypertensive Patients.

Brackets represent standard error, and numbers in parentheses the number of patients studied. The blood-pressure reduction induced in the six patients with renovascular hypertension and three with malignant hypertension were statistically significant ($p < 0.01$ and $p < 0.05$ respectively).

Figure 8

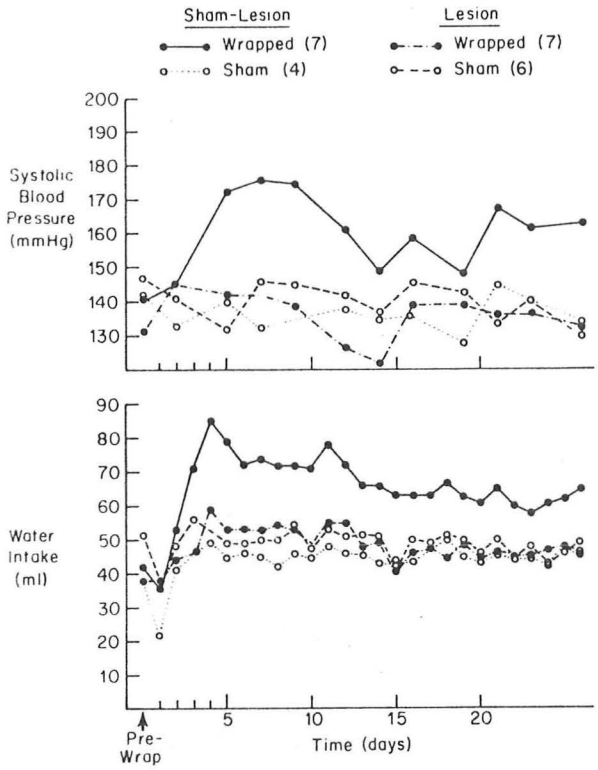
In addition to the known vasoconstrictive properties of angiotensin II and its effect of increasing sodium retention mediated through aldosterone stimulation, it appears that central nervous system mechanisms may be quite important in the pathophysiology of renovascular hypertension.

McCubbin *et al* (1965) noted that chronic infusion of sub-pressor amounts of angiotensin resulted in sustained hypertension in unanesthetized dogs. This hypertension is characterized by an increase in peripheral resistance, and increased pressor responsiveness to tyramine and, therefore, suggests a neural component to chronic renal hypertension.

Buggy *et al* (1977) have identified the anterolateral third ventricle as a site of central angiotensin dipsogenic and pressor mechanisms. Electrolytic lesions of this area in the rat led to an inability to produce renovascular hypertension by the procedure of unilateral nephrectomy and figure of 8 wrapping of the contralateral kidney (Figure 9). Thus, it appears that the central nervous system is important for the expression of renal hypertension.

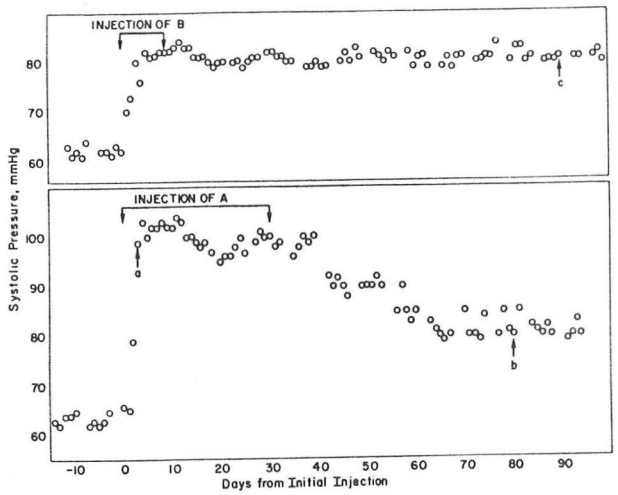
Experimental evidence for other pathogenetic mechanisms in chronic renal hypertension remain. Grollman (1971, 1973) has isolated a factor called nephrotensin which has acute vasoconstrictor activity quite unlike that of angiotensin II. However, the structure of this factor has never been elucidated. In addition, Skeggs (1977) has isolated a new hypertensive substance called renopressin which he believes is important in chronic one-kidney hypertension. This substance produces a delayed slow increase in the blood pressure and, interestingly, after it is administered for a few days, a moderate hypertension which persists indefinitely develops. The response of the blood pressure to renopressin is totally unlike that of renin. The hypertension produced by renopressin cannot be blocked by the administration of angiotensin II antagonists. The blood

pressure of hypertensive rabbits made hypertensive by the injection of renopressin can be lowered to normal by passive immunization with an antibody preparation which has no significant antirenin activity (Figure 10). Further characterization of this substance is required.



Water intake and blood pressure for sham-lesion and AV3V lesion rats before and after renal wrapping or sham-wrapping. After wrapping, sham-lesion rats had sustained increases in blood pressure ($P < 0.01$) and water intake ($P < 0.01$). Lesioned rats failed to increase blood pressure or water intake after wrapping, and did not differ from sham-wrapped controls.

Figure 9



The effect of the injection of rabbit kidney cortex preparations on the blood pressure of normal rabbits. Upper panel: preparation B was given to rabbit 564. Lower panel: preparation A was given to rabbit 568. The daily subcutaneous dose of preparation B contained 3.7 mg of protein and 0.04 Goldblatt units (GU) of renin; the dose of preparation A contained 5.3 mg of protein and 2.6 GU of renin. The elevations of blood pressure in both rabbits were unsuccessfully challenged by blockade of the renin-angiotensin system with [Sar¹,Ile⁸]angiotensin II at the times indicated by a, b, and c.

Figure 10

The hemodynamic changes which have been observed to occur in the development of renovascular hypertension are depicted in Figure 11 (Kaplan, 1973).

Figure 11

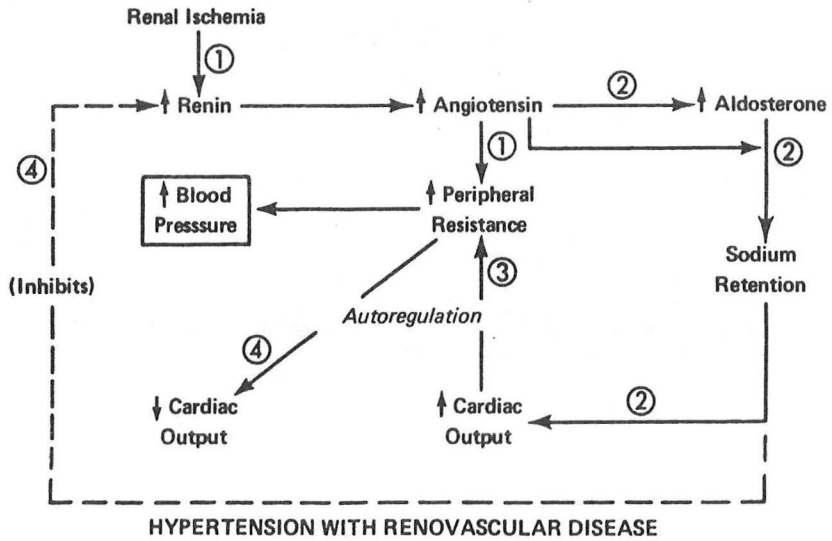


Figure 7-5 Stepwise hemodynamic changes in the development of renovascular hypertension.

Diagnosis of renovascular hypertension: Since clinical criteria other than the presence of an abdominal bruit offer little aid in the diagnosis of renovascular hypertension, other screening tests are required. The most widely used screening test is the hypertensive (rapid sequence) IVP. Disparity in renal length, delayed appearance time, and hyperconcentrations on late films (the three major urographic features) singularly or in combination were found in 78.2% of patients with 50-100% estimated unilateral renal artery stenosis and in 11.4% of patients with essential hypertension in the Cooperative Study (Franklin and Maxwell, 1975, Table 9). The best discriminating

Comparison of Rapid Sequence Urogram and Radioisotope Renogram in Essential Hypertension and Renovascular Disease

Diagnosis	No.	Positive Urogram (per cent)	Positive Renogram (per cent)
Essential hypertension	1051	11.4	24.6
Renovascular disease			
< 50 per cent*	170	22.3	43.5
50 to 80 per cent	148	64.0	68.9
> 80 per cent	133	82.8	77.4
100 per cent	50	95.7	94.0
Total (50 to 100 per cent)	331	78.2	76.1

*Per cent estimated stenosis.

Table 9

abnormality was delayed appearance time, which appeared in 59% of patients with renovascular disease and in only 2% of patients with essential hypertension. In contrast, disparity in renal length (disparity = left-right, >2 cm, <-1.5 cm) was less discriminating--occurring in 38.6% of patients with renovascular disease and 5.6% of patients with essential hypertension. None of the minor urologic features which included ureteral notching, decreased volume of the collecting system, parenchymal atrophy, and renal ptosis correlated better with renovascular disease than simple consideration of differences of renal length. 83.3% of 138 patients who responded favorably to surgery had an abnormal urogram . In the presence of an abnormal urogram, 115 of 148 patients (78%) with unilateral renal artery stenosis responded favorably. Two other large series report a similar favorable experience with the hypertensive IVP (Table 10). However, this favorable experience must be contrasted with the report of Stanley and Fry (1975) in which a positive hypertensive IVP was found in only 24% of pediatric patients and 47% of adults with fibrodysplastic disease.

Diagnostic Accuracy of the Intravenous Pyelogram

Reference	Patients with essential hypertension: No. of cases	Patients with essential hypertension: % Abnormal*	Patients with renovascular hypertension: No. of cases	Patients with renovascular hypertension: % Abnormal*
Cooperative Study: *JAMA* 220:1218, 1972	771	11.4	138	83.0
Maxwell: *New Engl J Med* 270:213, 1964	121	17.0	42	93.0
Wilson: *Arch Intern Med* 112:270, 1963	127	8.0	128	72.0

*Using three variables: differences in renal length, appearance time, and hyperconcentration.
From Bookstein JJ, et al: *JAMA* 220:1218, 1972.

Table 10

Utility of the hypertensive IVP in those patients with bilateral renovascular disease has subsequently been published by the Cooperative Study group (Bookstein *et al*, 1977). Abnormal urographic features were present in 60.7% of 250 patients. The urogram was relatively insensitive in the minority of patients whose lesions were of approximately equivalent severity bilaterally. Of 54 patients with favorable responses to surgery, 83.3% had an abnormal hypertensive IVP--the same percent as those with unilateral disease who responded favorably. As with unilateral renovascular disease, delayed appearance time was the single most frequent abnormality and was present in 43.3% of those with significant stenosis. In patients with bilateral disease, unilateral operation produced favorable results in 80% of patients with an abnormal urogram but in only 18% of those with a normal urogram. Thus, the urogram may play some role in deciding between unilateral and bilateral operations in patients with demonstrated bilateral renovascular disease.

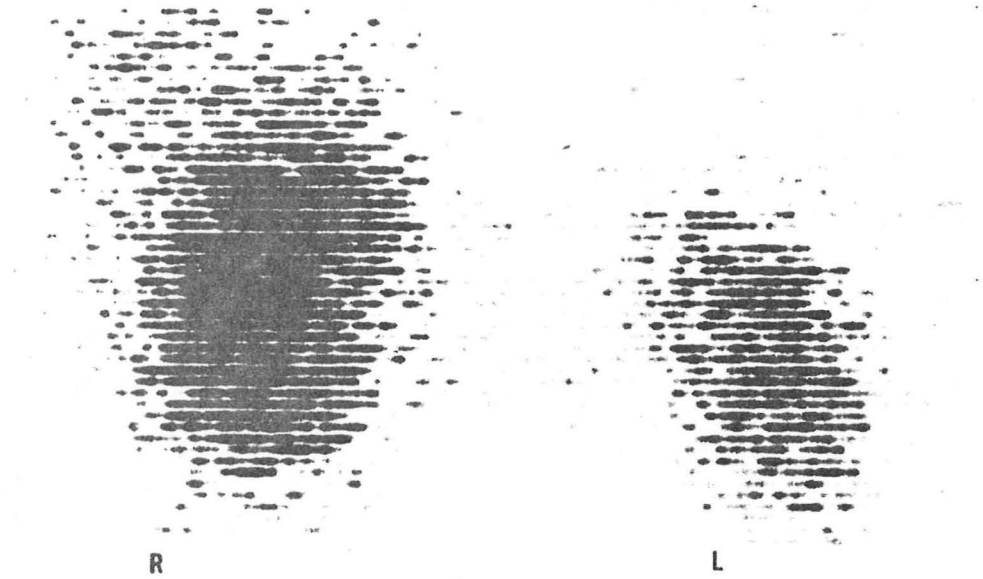
Renography and renal scanning: The radioisotope ^{131}I-Hippuran renogram has been reported to yield a high percentage of positive results in renovascular hypertension, but its specificity has been limited by the high percentage of false positive results in essential hypertension (Table 9). In the Cooperative Study 76.1% of patients with greater than 50% unilateral stenosis by arteriography had an abnormal renogram. However, patients with essential hypertension showed 24.6% abnormal renograms as compared with 11.4% abnormal urograms. The ^{197}Hg-chlormerodrin renogram and renal scan are also commonly done in conjunction with the ^{131}I-Hippuran renogram. Utilizing all three techniques, at least one radioisotope test was found to be positive in 13 of 13 patients with unilateral renal disease (Meier and Beierwaltes). An example of an abnormal renal scan and abnormal ^{131}I-Hippuran and ^{197}Hg-chlormerodrin renograms in a patient with left renal ischemia is seen in Figure 12. Franklin and Maxwell (1975) recommend that an index of functional asymmetry obtained by comparing the ratio of amplitudes of the renogram curve at the time of first kidney peak (T-max) divided by the ratio of amplitudes at the time of one-half its maximal value (T-1/2-max) appears to optimize the discriminatory power of the renogram--especially in limiting the number of false positive studies in essential hypertension. This technique was used on renogram curves from 152 patients with essential hypertension and 164 patients with renovascular disease. Using a critical ratio of 0.8, there were approximately 90% abnormal studies in patients with renovascular disease as compared to 10% abnormal studies in patients with essential hypertension. An additional favorable experience utilizing the traditional ^{131}I-Hippuran renogram in combination with technetium-^{99}m-glucoheptonate renogram and renal scan has recently been reported (McAfee *et al*, 1977). The advantages of the renogram and renal scan are that these procedures can provide clear evidence of renal ischemia, can be done quickly, and with no discomfort to the patient. The major problems are technical and are related to the attention to detail in positioning the probes and to the equipment which is available for testing. Though these testing procedures are not generally as available as the hypertensive IVP, they appear to be of approximately equal value and, certainly, are quite valuable as an additional indirect means of assessing renal ischemia.

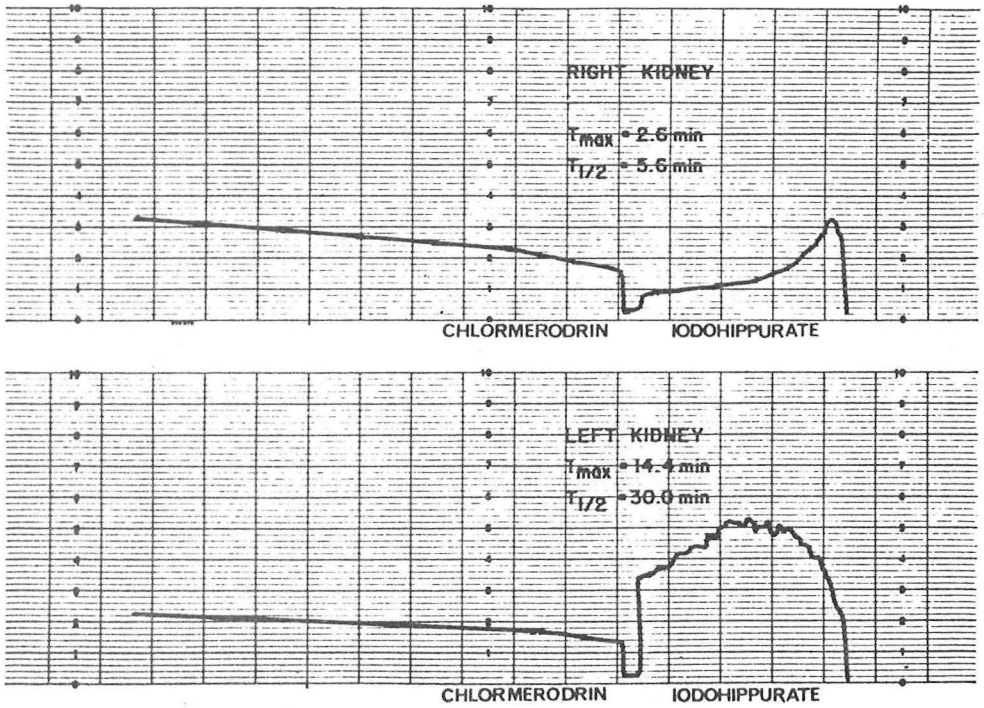
Further comparisons of these diagnostic procedures are given in Table 11.

Table 11

Comparisons of Three Diagnostic Tests for Renovascular Hypertension

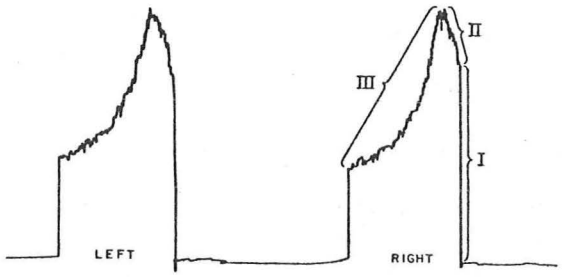
		IVP		Renogram		Split-function	
Reference	No. of Patients	False pos(%)	False neg(%)	False pos(%)	False neg(%)	False pos(%)	False neg(%)
Baker: *New Engl J Med* 267:1325, 1962	26	30	7	20	10	6	17
Wilson: *Arch Intern Med* 112:270, 1963	128	8	28	—	—	—	48
Foster: *Surgery* 60:240, 1966	163	15	27	30	32	6	15
Hunt: *Am J Cardiol* 23:434, 1969	100	—	26	—	29	—	9





Top, Abnormal renal scan in patient with left renal ischemia (case 8). *Bottom*, sodium iodohippurate I 131 and chlormerodrin Hg 197 renograms. Chlormerodrin right slope/left slope = 1.88.

NORMAL RENOGRAM TRACING



I – first segment – "vascular phase"
II – second segment – "functional phase"
III – third segment – "excretory phase"

Figure 12

The results of the Cooperative Study have been analyzed to indicate the possibility of a patient having either essential hypertension or renovascular hypertension on the basis of three screening procedures (Table 12).

Probability of Essential Hypertension or Renovascular Hypertension on the Basis of Screening Procedures

	Essential hypertension (%)	Renovascular hypertension (%)
No abnormality	99	1
Abdominal bruit present	61	39
Abnormal IVP	48	52
Abnormal renogram	74	26
Abnormal IVP and renogram	30	70
Abnormal IVP and renogram, and abdominal bruit present	4	96

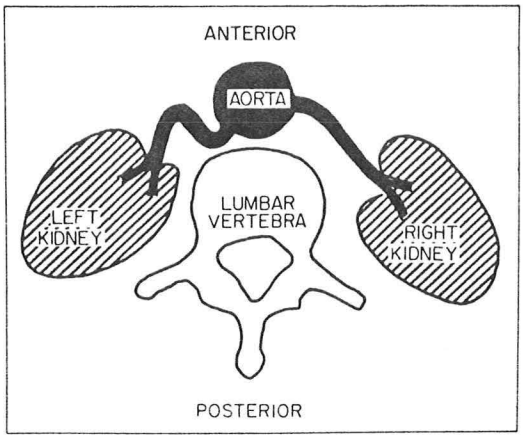
Table 12

Recommendations for obtaining a hypertensive IVP or renogram: McNeil *et al* (1975) have evaluated the costs of these two diagnostic studies for the diagnosis of renovascular hypertension and subsequent identification of those cases who will be surgical cures. They estimate the cost of finding a patient with renovascular disease is about $2,000 and that of a surgical cure is about $20,000. The number of deaths from arteriography and operation is about 15 per 100 surgical cures. These data emphasize the need for careful selection of patients who will be screened for renovascular hypertension. The following recommendations are suggested as reasons to obtain these studies in those patients who are possible surgical candidates and have no other apparent cause for their hypertension.

1. Abdominal or flank bruit
2. Diastolic B.P. >120 mm Hg
3. White women under age 50, particularly those who are slender, with diastolic B.P. >110 mm Hg
4. Onset of hypertension before age 30
5. Evidence of deterioration of renal function
6. Difficulty in blood pressure control

Renal arteriography: The decision to obtain a renal arteriogram to pursue a diagnosis of renovascular hypertension is generally made with considerations about the severity of the hypertension, the difficulty of drug management, and the specific clinical characteristics which suggest secondary hypertension. Almost always, a diagnostic screening test such as rapid sequence urography or radioisotope renography will be done as the initial screening procedure, and the features of these examinations will guide the decision. However, this leaves a very large fraction of hypertensive patients without clear indication for renal arteriography. Clinical criteria which may be utilized to suggest the need for arteriography include the presence or absence of an abdominal bruit, the severity of hypertension, race, sex, age, duration of hypertension, evidence of deterioration in renal function, and response of the blood pressure to medication. Unfortunately, at the present time, there are no clearly documented guidelines to aid in this clinical decision.

At the present time the percutaneous retrograde transfemoral catheterization technique is almost always utilized since it has been demonstrated to be more accurate and safer than the translumbar aortogram. This allows selective visualization of each renal artery and its brnaches. Oblique as well as standard PA views should be utilized (Figure 13). It is also necessary to search carefully for segmental and distal lesions. The Cooperative Study (Bookstein *et al*,



Schematic drawing showing the origins and the course of the renal arteries. Arteriograms made in the straight anteroposterior projection may fail to demonstrate lesions at the orifice of the arteries or in the distal arteries.

Figure 13

—Distribution of Main Renal Artery Lesions (Summary)

Etiology	Unilateral		Bilateral	Total
	Right	Left		
Atherosclerosis	141	199	153	493
Fibromuscular hyperplasia	143	44	63	250
Total	284	243	216	743

Table 13

1972) data about distribution of main renal artery lesions are presented in Table 13. In patients with atherosclerosis, 83% were located at the orifice or proximal third of the renal artery (Table 14). However, with fibrodysplastic disease, the lesion was seen in 54% of cases in the mid and distal third of the renal artery and in segmental branches in 5%. There was no difference in the incidence of single and multiple renal arteries in patients with essential vs renovascular hypertension (Table 15). This Cooperative Study found that 94% of the retrograde femoral procedures were adequate for evaluation of the main renal arteries and 75% were adequate for visualization of segmental arteries as well. Major complications (mainly hemorrhage, thrombosis, and renal injury) were seen in 1.25% of cases (Table 16). Three deaths (0.11%) were noted in 2,719 procedures, in contrast to a previously reported fatality rate of 0.28% of 13,207 translumbar aortographies.

—Location of Maximal Stenosis* in Renal Artery Lesions

Location	A†	FH†	Other
Multiple or entire	25	23	0
Orifice or proximal third	521	100	13
Middle third	27	85	3
Distal third	14	78	4
Segmental	43	15	5
Total	630	301	25

*Only stenoses of more than 25% are included.
†A indicates atherosclerosis; FH, fibromuscular hyperplasia.

Table 14

—Incidence of Supplemental Renal Arteries in EH and OURD*

	Etiology	
	EH	OURD
No. patients	739	333
Single arteries bilaterally	541 (73%)	256 (77%)
One or more supplemental arteries on either side	191 (27%)	77 (23%)

*EH indicates essential hypertension; OURD, operated unilateral renovascular disease.

Table 15

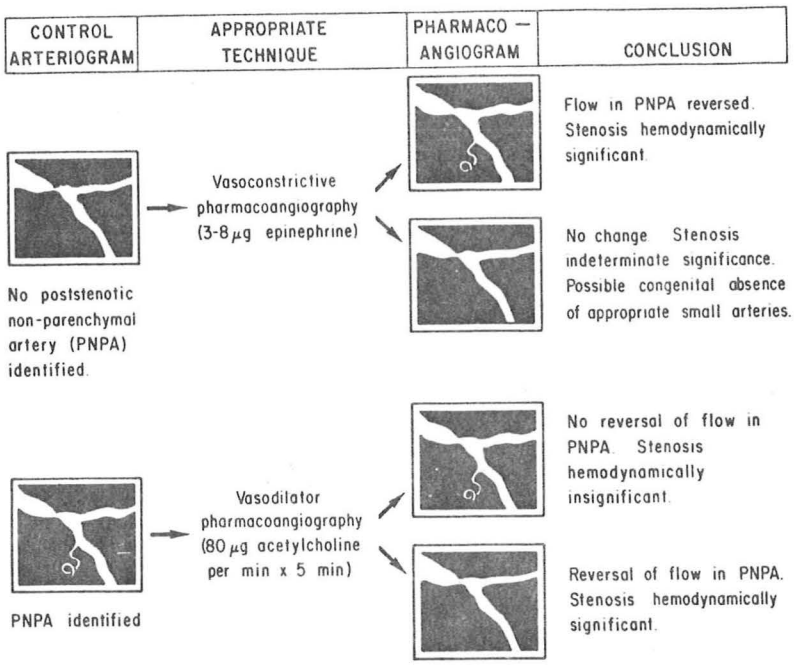
—Major Complications Related to Arteriographic Techniques

Arteriographic Approach	No. of Patients	%	No. of Major Complications	%
Transfemoral catheter	2,089	77	26	1.25
Translumber aortogram	427	16	5	1.2
Transbrachial/ transaxillary catheter	59	2	1	1.7
Transbrachial needle	68	3	2	2.9
Transfemoral needle	46	2	1	2.2
Intravenous	2	...	0	
Incomplete data; technique unknown	27	...	0	
Total	2,719		35	

Table 16

In the Cooperative Study 68% of those patients with atherosclerosis with lesions of greater than 50% reduction in luminal diameter responded to surgery; whereas only 43% of patients with lesions of less than 50% reduction responded. In fibrodysplastic disease, 72% of patients with stenosis of less than 50% had a favorable response; whereas 91% of patients with stenosis greater than 80% had a favorable response. In this series there was no relationship of the surgical response to the presence or absence of collateral circulation or of poststenotic dilatation. Thus, the arteriogram by itself had only limited value in predicting the response to surgery.

Experimentally, it has been noted that a critical degree of stenosis must be present before the distal blood flow and arterial pressures are perceptibly reduced. After this critical stenosis is achieved, relatively small further increases in stenosis caused marked further reductions. This critical stenosis has been estimated by May *et al* (1963) to be 82% for the human renal artery. The length of the stenotic area in the artery is an additional important factor which is difficult to quantitate. Bookstein (1966) noted the reduction of the luminal diameter to less than 1.5 mm was associated with pressure gradient greater than 40 mm Hg. However, cases have been reported with poor correlation between the degree of stenosis as appraised angiographically and the pressure gradients measured during surgery. In addition, determination of the pressure gradients measured at the time of surgery has not proved to be particularly helpful in predicting a therapeutic response. Even though arteriographic evidence of collateral circulation was not found to be of predictive value in the Cooperative Study, further refinement of the evaluation of collateral circulation by the use of pharmacoangiographic manipulation has more recently been reported to be of considerable benefit in assessing the hemodynamic significance of renal artery stenosis and the subsequent surgical response (Bookstein and Ernst, 1973; Bookstein *et al*, 1976, Figure 14). This technique is performed after selective renal arterial infusion of acetylcholine (80 µg for 5 minutes) or after selective renal arterial injection of epinephrine (3-4 µg) depending upon whether or not poststenotic extrarenal arteries were opacified on control arteriography. Reversal of the direction of blood flow in extrarenal arteries by either drug indicates that the stenosis is of hemodynamic significance. If the direction of flow does not reverse, the stenosis is not of



Application and interpretation of pharmacoangiography.

Figure 14

significance. Suitable extrarenal arteries are not present in approximately 4% of patients--in which case the technique is not applicable. Vasoconstrictive angiography was determinant in 18 of 26 (69%) significant stenoses in correctly identifying hemodynamic lesions which responded to surgery. Other angiographic signs of collateral circulation were noted in 7 of the other 8 significant stenoses studied with the vasoconstrictive method. There were no false positive arteriographic diagnoses of significance. Pharmacoangiology provided the only preoperative sign of significance in three stenoses, and directly demonstrated collaterals were the only preoperative sign of significance in a fourth. Renal vein renins were misleading in two of these patients. Vasodilatory pharmacoangiography correctly evaluated each of 9 significant and 11 insignificant lesions and was the only preoperative index of clinical significance in three of these cases. Thus, these techniques appear to add significant advances in predicting surgical response or failure.

Peripheral renin determinations: With the development of reliable bioassays for plasma renin activity, it was initially hoped that accurate prediction of those patients who would respond to surgical correction of renal artery stenosis could be achieved. Unfortunately, it soon became apparent that determinations of peripheral plasma renin activity was of little prognostic value. A recent review of the literature by Marks and Maxwell (1975) reveals an overall predictive rate of only 56% (Table 17). It must be noted that particularly with some of the older studies, adequate attention was not given to standardizing the procedure for determination of peripheral plasma renin activity. This determination is affected by such variables as dietary sodium, time of day of sampling, supine vs upright posture, duration of upright posture before sampling, and influence of various antihypertensive medications which stimulate plasma renin activity (such as diuretics and hydralazine) and medications which suppress plasma renin activity (such as propranolol,

Peripheral Plasma Renin Activity in Representative Verified Cases of Correctable Renal Hypertension

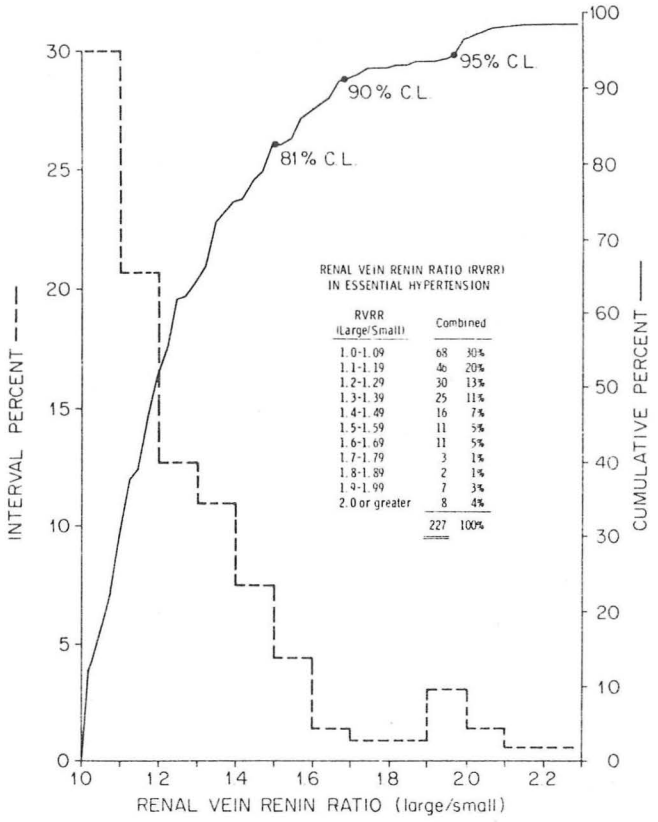
Author	Date Reported	Number with Correctable Renal Hypertension	Number with Elevated Peripheral Plasma Renin Activity
Bath	1968	25	24
Bourgoignie et al.	1970	14	11
Bianchi	1970	27	15
Kaufman et al.	1970	21	10
Strong et al.	1971	25	5
Stockigt et al.	1972	34	20
Hussain et al.	1973	19	6
Poutasse et al.	1973	13	5
Vaughan et al.	1973	18	13
		196	109 (56%)

Table 17

methyldopa, guanethidine, and reserpine). In addition, other medications such as estrogens may result in spurious elevations in plasma renin activity. In addition to these variables which may affect plasma renin activity, there are a number of assay variables which influence the absolute level of measurable PRA in ng/ml/hr. Thus, each laboratory must carefully standardize its renin assay to obtain valid definition of low, normal, and high renin subgroups of hypertensive patients. Nonetheless, it is apparent that even carefully standardized modern assay procedures such as those of Vaughan *et al* (1973, Table 17) do not allow peripheral PRA determinations to identify a large percentage of patients who will respond to corrective surgery.

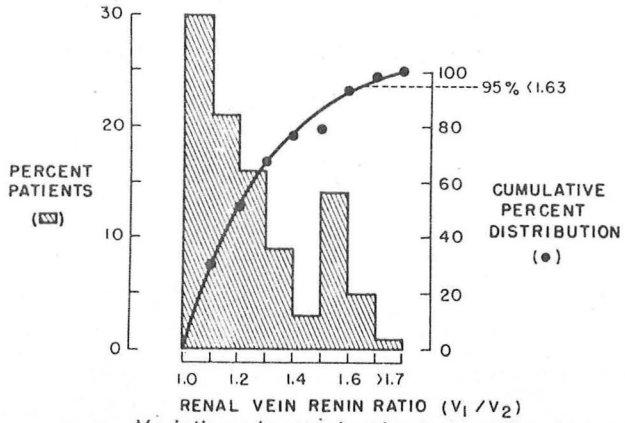
Renal vein renin determinations: Since it quickly became apparent that peripheral PRA would not accurately predict those patients who would respond well to surgery, the technique of bilateral renal vein renin determinations evolved. The first question to be answered was to determine the intrinsic variation in bilateral renal vein renin ratios (RVRR). Maxwell *et al* (1975) have carefully determined renal vein renin ratios in patients with essential hypertension without arteriographic evidence of renal artery stenosis (101 ratios). About half of these patients were on some type of dietary sodium depletion. An additional 126 renal vein renin ratios obtained from the literature were added to their experience to give a total of 227 ratios (Figure 15). The dietary sodium conditions of these patients is unclear. A ratio of 1.5 has commonly been used to separate surgical success from failure. It is notable that 19% of patients with essential hypertension have a ratio of this magnitude. If one is willing to accept the 90% confidence limits to define the critical ratio, the ratio would be 1.68. A renal vein renin ratio greater than 1.96 is necessary to establish the 95% confidence limits. Similar data have also been noted by Sealy *et al* (Figure 16) in patients on normal sodium diet. Thus, these studies in patients with essential hypertension reveal that an appreciable false positive rate with RVRR of 1.5 is to be anticipated.

Soon after RVRR began to be used to predict surgical response, it became apparent that there were many false negative studies. The following factors have been evaluated:



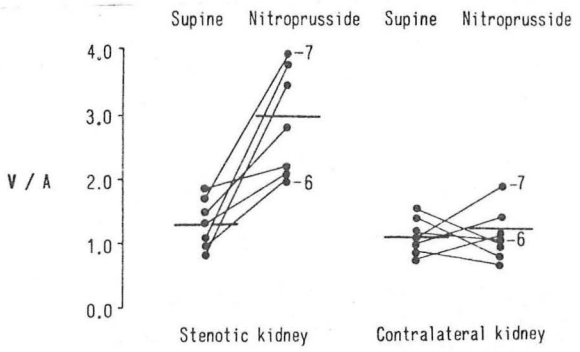
Renal vein renin ratios (RVRR) in patients with essential hypertension. Note that the cumulative curve (*solid line*) approximates one-half of a bell-shaped probability curve. The 95 per cent confidence limits includes ratios as large as 1.96.

Figure 15



Variations in renal vein renin ratios in essential hypertension. The higher value was always divided by the lower value so that a ratio greater than 1.0 was always achieved. The ratio was less than 1.63 in 95 per cent of patients and less than 1.5 in 87 per cent of patients.

Figure 16



Renal-vein-renin studies in seven patients with unilateral renovascular hypertension done when the patient was supine and after nitroprusside-induced normotension.

Results are expressed as venous/arterial ratio of plasma-renin activity on both sides. A factor greater than 1 indicates renin secretion. Plasma-renin activity was measured by the method of Boyd et al.[8] which ensures the exclusive measurement of active renin. Renal arterial renin = peripheral venous renin.[9] Patients 6 and 7 are indicated individually.

Figure 17

1. Sodium depletion: Strong *et al* (1971) and other investigators soon realized that the false negative rate could be lowered by using dietary sodium depletion to accentuate differences between the two sides. In this one series, the correct prediction of the functional significance of the observed stenotic lesion improved from 35% to 90% of 41 patients. Sodium depletion was accomplished with 20 mEq sodium diet for three days accompanied by 1 gm of chlorothiazide daily.

2. Medications: As many medications other than diuretics should be discontinued. In those patients with extremely severe hypertension, the hypertension is best treated with hydralazine (stimulates renin release) in combination with small amounts of other medications such as methyldopa or guanethidine to blunt some of the side effects of hydralazine. Propranolol is best avoided if possible, though it should not be abruptly discontinued to avoid problems with precipitating angina or myocardial infarction. If necessary, however, any of these medications can be given to control the blood pressure, because even renin-suppressing agents such as propranolol have only a modest effect upon basal diuretic-stimulated renin release. However, other stimulation tests performed in this setting will be blunted.

3. Posture: Upright posture has been commonly utilized to stimulate renin release and magnify PRA differences of the stenotic vs nonstenotic kidney. Michelakis *et al* (1969) have emphasized the danger of renal vein blood sampling soon after the patient changes from an upright to a recumbent posture. The half-life of renin is approximately 15 minutes. Therefore, those patients who have been stimulated by upright posture may have a disturbance in their usual renal vein renin to peripheral vein renin ratio for quite some period of time after going from the upright to the supine position. Neilson *et al* have emphasized that renin release from the stenotic kidney may be much more rapid than usual and may become maximal within five to ten minutes after upright posture, in contrast to the normal individual. Therefore, renin determinations are best done 10 minutes and 30 minutes after the assumption of upright posture since, in those patients with renovascular hypertension, a plateau is usually reached at 20-30 minutes; whereas at this time in the normal individual, only a slight to modest increase in peripheral PRA will be apparent.

4. Vasodilator stimulation: Intravenous administration of hydralazine (Mannick *et al*, 1969), nitroprusside (Kaneko *et al*, 1967; Skrabal, 1977), and diazoxide (Stokes *et al*, 1976) have been utilized. It would appear that these agents are potentially quite valuable in minimizing the number of false negative renal vein renin evaluations. Skrabal (1977) in particular has presented data with nitroprusside (Figure 17). However, there are not enough published data to properly evaluate the use of these agents. Adequate renin stimulation in the series by Mannick (1969) and Stokes (1977) appears to have been obtained by dramatic lowering of the blood pressure, sometimes to hypotensive levels. With both hydralazine and diazoxide, these profound changes might result in the precipitation of angina, myocardial infarction, or other side effects. Nitroprusside appears much safer since the fall in blood pressure to a normotensive range can be controlled much more accurately, and problems with increases in cardiac output and myocardial oxygen consumption are not found.

Other problems with renal vein renin determinations: Even though it has recently been claimed that performance of the renal arteriogram shortly before doing the renal vein renin determinations does not invalidate the renin determinations (Whelton *et al*, 1977), the time required for these two procedures usually dictates that they be done on separate days.

Catheter placement is of particular importance since 20-28% of right kidneys and 1-3% of left kidneys may have multiple renal veins (Marks and Maxwell, 1975). In addition, dilutional errors may be caused on the right by admixture of caval blood, since the right renal vein is short, or on the left by gonadal vein blood, which enters the left renal vein (Figure 18).

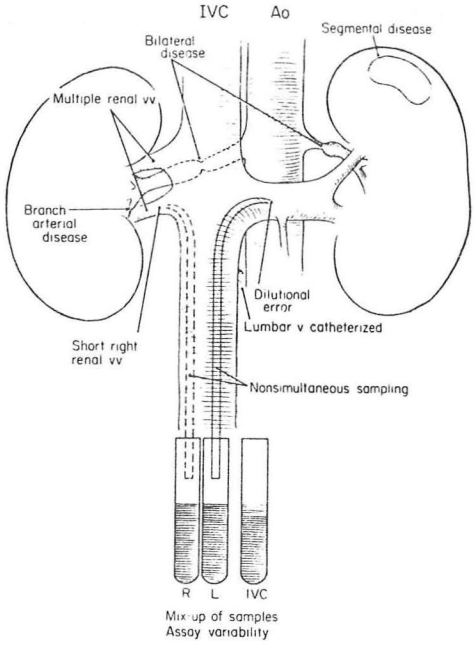


Diagram depicting possible causes of misleading renal vein renin determinations. The primary source of error has been in falsely negative test results.

Figure 18

Simultaneous sampling: To insure greatest accuracy, sampling should be through three separate catheters in the right renal vein, left renal vein, and inferior vena cava, respectively, at the same time. Horvath *et al* (1977) have analyzed the errors found in renal vein sampling (Table 18) and note that the errors can best be minimized by the use of separate catheters and by sampling at three separate times at 5 to 10 minute intervals.

Standard errors in the measurement of PRA in renal vein samples from the group shown in Table 1. All values are for duplicate samples.

Measurement	SEM *ng/ml/3 hr*	SEM *% of mean*
Single determination	2.3	18
Difference between two renal veins sampled simultaneously	3.3	26
Difference between two renal veins sampled nonsimultaneously	4.5	35
Difference between two renal veins sampled simultaneously at three different times	1.8	14

[a] The mean was 12.8 ng/ml/3 hr.

Table 18

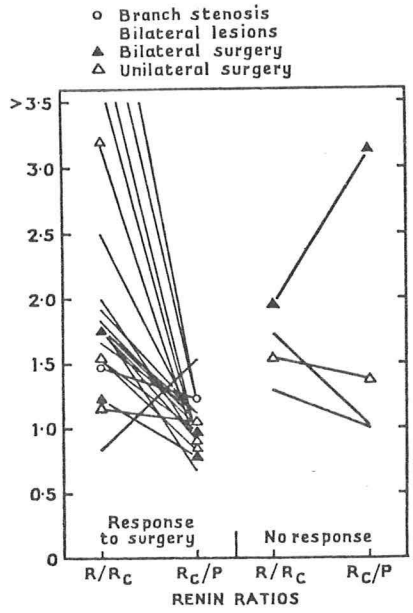
Surgical Predictive Value of the Renal Vein Renin Ratio

Unilateral stenosis: RVRR data from the literature have been extensively reviewed by Marks and Maxwell (1975). The predictive value depends upon whether the lesion(s) are unilateral, bilateral, or segmental. 93.4% of those patients with a lateralizing ratio have benefitted from surgery. Interestingly, however, 50.8% of patients with a non-lateralizing ratio have also benefitted from surgery. Only 6.6% of patients have had falsely positive lateralizing RVRR in spite of the earlier observed percentage of patients with essential hypertension who had lateralizing ratios. This difference appears most likely to have resulted from the use of dietary sodium depletion and upright posture in many of the series to magnify differences in renin release between the stenotic and non-stenotic kidney.

Bilateral renal arterial stenosis: Though about one-third of patients with renal artery stenosis have bilateral disease, the utility of the RVRR in this subgroup has not been as well defined. Strong *et al* (1971) reported 21 patients from the Mayo Clinic with bilateral artery stenosis. All patients in whom renal secretion lateralized to one side were subsequently cured or improved by a unilateral operation (9 patients). However, 6 of the remaining patients whose renin secretion failed to lateralize were also cured or improved by operation, performed on one or both sides. In a more recent study from the Mayo Clinic (Juncos *et al*, 1974), those patients with misleading renal vein renin data often had bilateral disease. Foster *et al* (1973) have noted that in about two-thirds of hypertensive patients with bilateral renal artery stenosis, RVRR will lateralize to one kidney. Six of 8 patients with bilateral disease had lateralizing ratios. However, all were cured or improved after bilateral operations. In contrast, Gittes and McLaughlin (1974) have described that 7 of 8 patients with bilateral disease with lateralizing ratios were improved by unilateral operation of the lateralizing side. Clearly, then, surgery should be initially directed at that side lateralized by the RVRR. However, it is clear that some patients in whom renin secretion fails to lateralize can also be helped by unilateral or bilateral operation performed as two separate procedures.

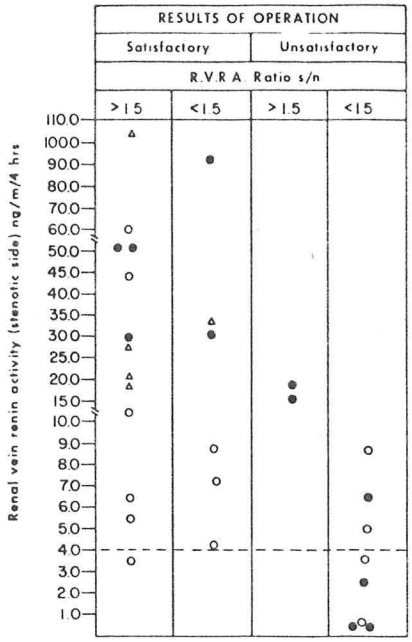
Segmental lesions: A few patients with correctable renal hypertension have disease limited to only a segment of one kidney. These lesions include branch arterial stenosis, focal infarctions, segmental hypoplasia, and small tumors of the juxtaglomerular cells. Schambelan *et al* (1974) have recently demonstrated that when blood is collected directly from a segmental vein draining the involved part of the kidney, a hyperreninemic focus can be identified which may not be detected when main renal venous blood is sampled. In this setting the RVRR should be calculated utilizing the PRA determined in the segmental vein as the numerator.

Contralateral suppression: To increase the predictive value of renal vein renin determinations, the PRA from the renal vein of the nonstenotic kidney is compared to that of peripheral PRA (inferior vena cava). In patients with hypertension from unilateral renal artery stenosis the contralateral kidney adds little, if any, renin to blood perfusing it. Stockigt *et al* (1972) have defined contralateral suppression as a ratio of contralateral renal vein renin to peripheral renin of 1.3 or less (Figure 19). Those patients with R_C/P ratios of >1.3 frequently respond poorly to surgery. These patients have arteriolar nephrosclerosis in the nonstenotic kidney secondary to uncontrolled hypertension which initiates renin release.



Relation between the renal venous renin ratio (R/R_c) and R_c/P in 25 patients with renovascular hypertension, classified according to response to surgery. R_c, nonstenotic or less involved renal vein; P, peripheral blood. (Stockigt JR, et al: *Lancet* 1:1194, 1972.)

Figure 19



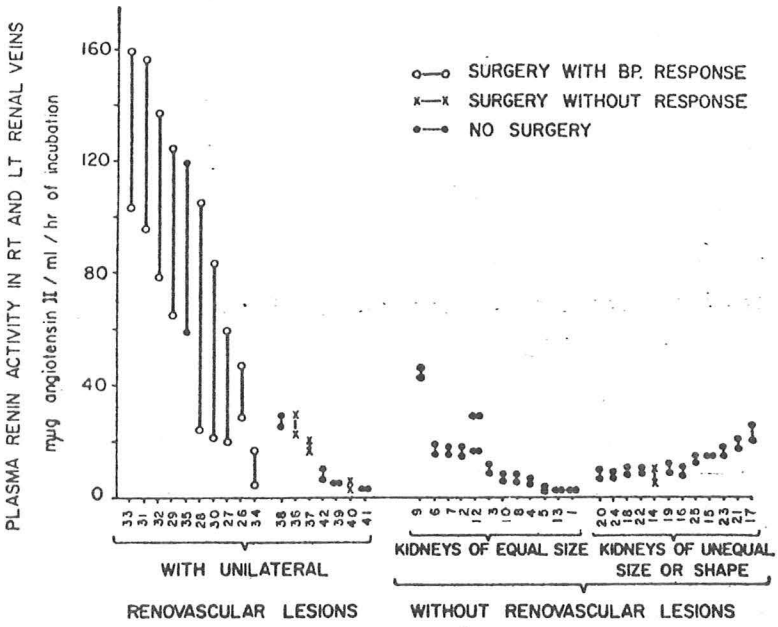
○ Not on antipressor agents
● On antipressor agents during study
△ Stressed (Low sodium and/or diuretics)

Comparison of renal venous renin activity and results of operation in patients with unilateral renal artery disease.

Figure 20

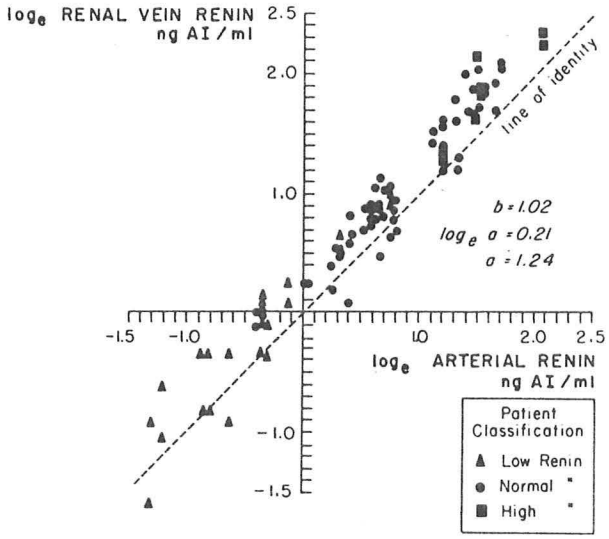
Ipsilateral increase in PRA from the stenotic kidney: Hussein *et al* (1973, Figure 20) noted that an absolute increase in PRA from the stenotic kidney predicted a successful surgical result in 79% of cases of unilateral renal artery disease; whereas the stenotic to nonstenotic renin PRA ratio was accurate 72% of the time. However, the majority of their patients were not sodium depleted at the time renal vein renins were obtained. When both factors were increased, surgical success was found in 86% of patients; whereas when both were normal, a surgical failure was obtained in 5 of 5 patients. When there was a disparity in the two values, the prognostic accuracy was uncertain and the results unpredictable. It must be noted, however, that this method is fraught with all of the difficulties mentioned earlier from numerous factors that may affect a peripheral PRA determination. In addition, contralateral PRA suppression must also be demonstrated. Thus, for the procedure to be valid, it would need to be carefully standardized by each laboratory.

Absolute difference in renal vein renin activity (RVRA): Whelton *et al* (1977) have recently contended that the absolute difference in RVRA should be calculated and utilized in conjunction with the RVRA ratio in order to more accurately predict those patients who will respond to surgery. Their patients were not sodium depleted at the time of study. Winer *et al* (1967) earlier noted significant differences in RVRA in those patients who responded to surgery (Figure 21). The determination of RVRA differences is particularly helpful in those patients who have fairly low PRA determinations since in this setting small changes in the absolute difference which might result from laboratory or sampling errors would be magnified disproportionately in the determination of the ratio. However, this method suffers, again, from the need to have a well-standardized laboratory and testing procedure to appreciate absolute differences in RVRA.



Renin activity in plasma from right and left renal veins in patients with and without angiographic evidence of unilateral renal artery stenosis. Results of surgery are indicated, also observations in patient 12 during periods of high and low sodium intake.

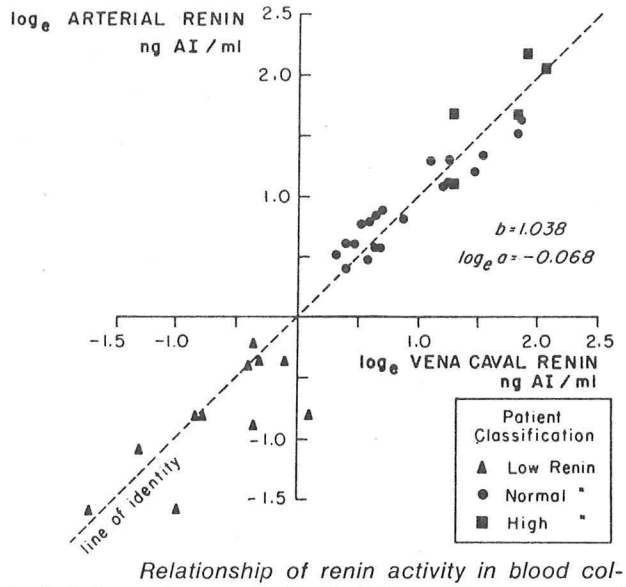
Figure 21



Relationship of renal vein renin to arterial (or venous) renin in patients with essential hypertension. The slope of the line is not different from the line of identity, indicating that the relationship of renal vein renin to arterial renin is constant at all levels of plasma renin activity found in essential hypertension. The intercept of 1.24 indicates that the renal vein renin is 124 per cent of arterial renin.

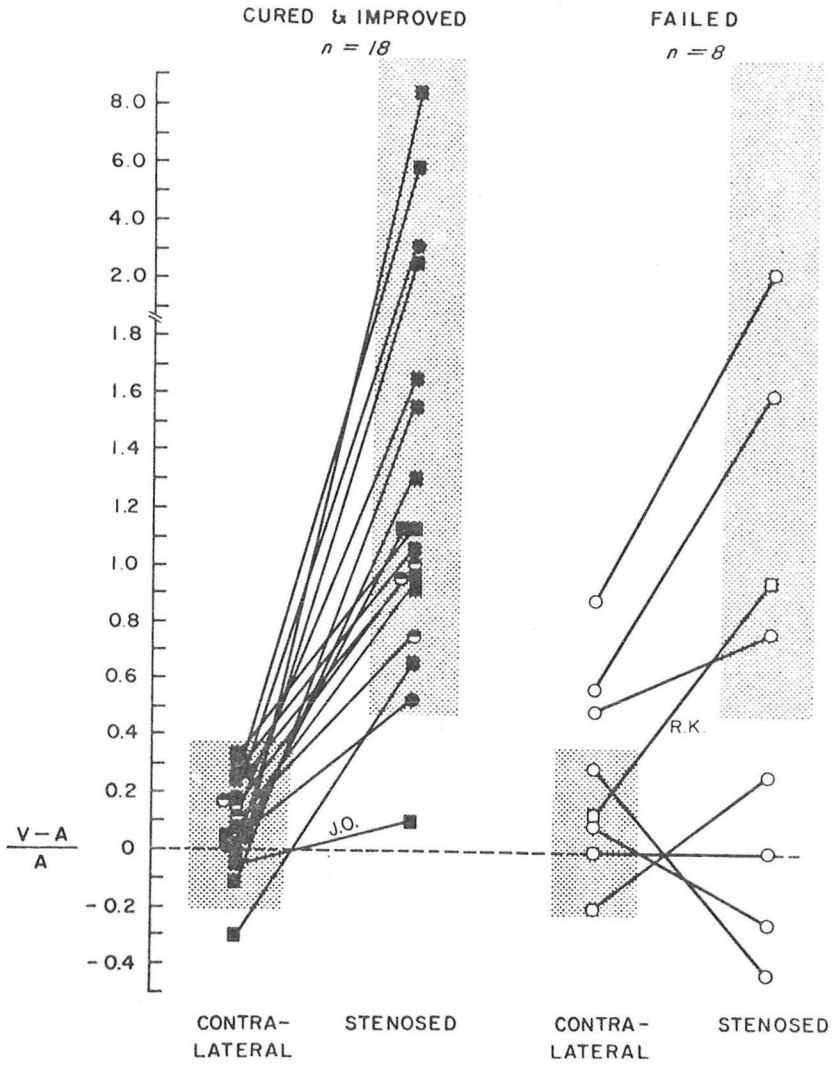
Figure 22

Stenotic to peripheral PRA ratio: Sealy *et al* (1973) demonstrated that normally each kidney contributes 0.24 times the arterial PRA to the renal vein (Figure 22). In the setting of unilateral renal artery stenosis in which there is contralateral suppression, they demonstrated the PRA determined in the renal vein from the stenotic kidney would be greater than 0.48 times the peripheral arterial PRA. Since peripheral arterial PRA and inferior vena cava PRA are equal (Figure 23), the ratio may be determined with the inferior vena cava PRA. This method evolved in response to disenchantment with the use of the stenotic to non-stenotic ratio of greater than 1.5 as an isolated criteria. However, these studies were also done in patients who were not sodium depleted. Vaughan *et al* (1973, Figure 24) have recently proposed a scoring system utilizing: (1) ipsilateral hypersecretion compared with peripheral plasma renin activity, (2) contralateral suppression compared with peripheral plasma renin activity, and (3) peripheral plasma renin activity. When all three criteria were met or when all three were lacking, prognostic accuracy of the scoring system was perfect in 18 operated patients. However,



Relationship of renin activity in blood collected from the aorta to that found in vena caval blood. The two values are not different from each other in patients with essential hypertension.

Figure 23

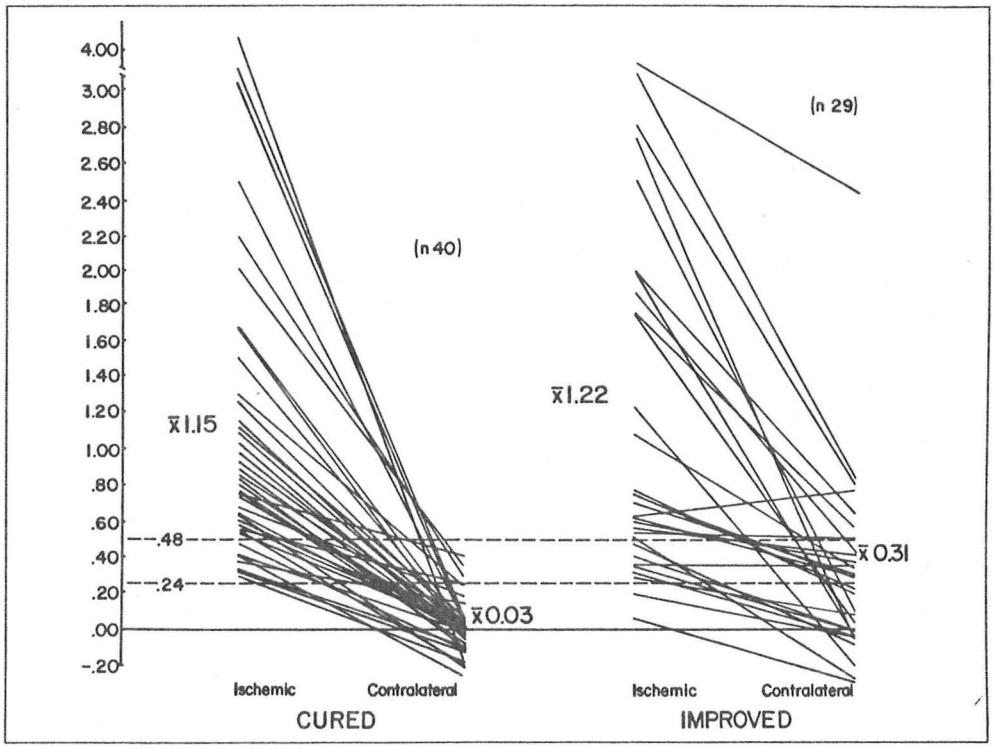


Preoperative stenotic and contralateral renal vein renin levels relative to arterial renin in 28 patients. All cured or improved patients (18) showed contralateral renin suppression (shaded area = 0.08 ± 2 SD) and all but 1 (J.O.), in whom there was a technical error, had an abnormally elevated relationship from the stenotic kidney [shaded area = (V–A)/A > 0.48] indicating renal plasma flow reduction. In contrast, none of the patients who failed to respond to successful surgery (7) met both of these criteria. One patient (R.K.) had a postoperative graft occlusion.

Figure 24

further evaluation of this scoring system is lacking at the present time. It would appear from the data of Stanley and Fry (1977, Figure 25) that the isolated use of the stenotic PRA to peripheral PRA ratio does not offer any advantage over the more commonly used stenotic to non-stenotic ratio. In addition, Maxwell *et al* (1975) have challenged some of the basic mathematical assumptions which led to the derivation by Sealy *et al* of an average renal vein renin of 124% of the peripheral PRA. They note that in individual patients the 95% confidence interval varied from 90 to 170% from the data of Sealy *et al* and from 74 to 236% from their data. The significance of this variation is difficult to assess at the present time.

Split function studies: Split function studies have waned considerably in popularity so that they are only regularly done at a few medical centers--the primary one being at Vanderbilt. It is questionable if their net value is positive except at these few highly specialized referral centers. The interested reader is referred to Stamey (1961), Dahl *et al* (1967), Fair and Stamey (1971), Foster *et al* (1973), and Wilson *et al* (1977).

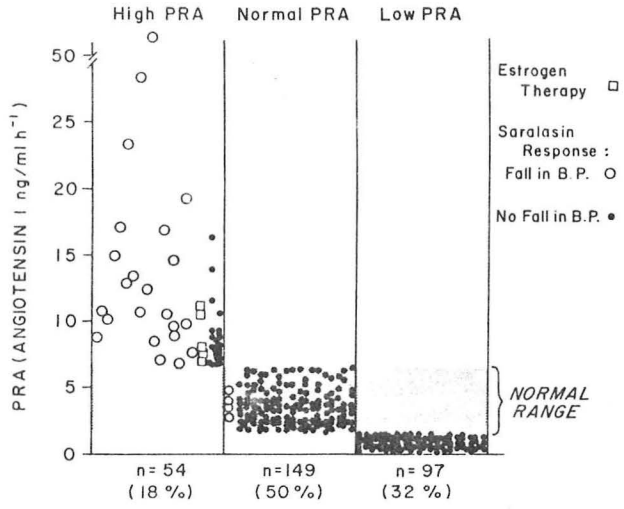


Renal:systemic renin indices comparing individual renal renin activity to systemic renin activity. Mean ischemic kidney hypersecretion in cured vs improved groups (1.15 and 1.22, respectively) did not prove to be statistically different. Contralateral suppression of renin activity was obvious in cured (0.03) group and nonexistent in improved (0.31) group. Differences in degree of suppression proved significant ($P < .01$).

Figure 25

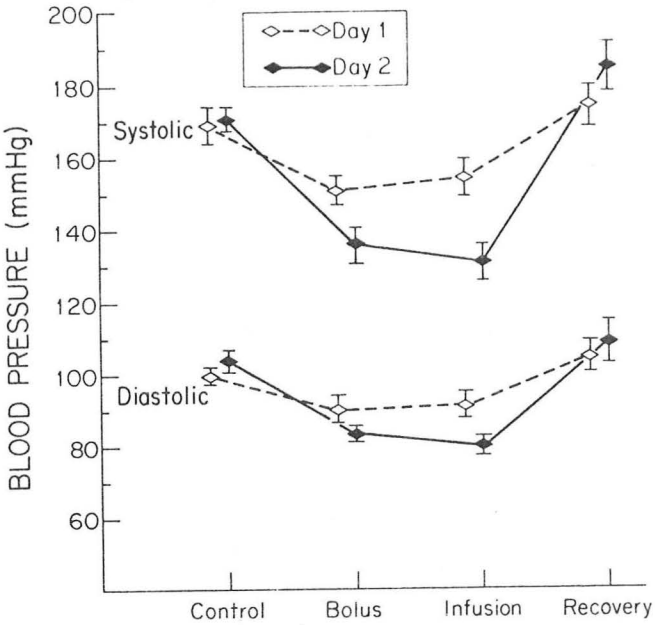
Renal venous output of kinins: Hulthen *et al* (1977) have recently reported that determination of bilateral renal vein kinins in a small number of patients with renal artery stenosis may be of some value. They found a ratio of non-stenotic to stenotic of 2.6 - 6.5, indicating diminished intrarenal kinin generation in the stenotic kidney. This report awaits confirmation by other investigators and further evaluation.

Angiotensin antagonism with saralasin: This selective angiotensin antagonist has recently been utilized to identify patients with angiotensinogenic hypertension. In general there appears to be a good correlation between depressor response with saralasin and PRA status (Figure 26, Streeten *et al*, 1976). It is difficult at present to assess the true benefit of this diagnostic maneuver as a screening test for renovascular hypertension since only a limited number of patients with proven renovascular hypertension have been reported. The largest reported series is that of Marks *et al* (1977, Figure 27). Saralasin was administered to 17 patients with renovascular hypertension before and then 16-18 hours after oral administration of 1 mg/kg furosemide, followed by 10 mEq low sodium diet. Responders were defined as patients whose systolic and diastolic blood pressures decreased after saralasin administration by at least 10 mm/8 mm. On day 1 before sodium depletion only 10 of 17 patients responded to saralasin. However, on day 2 after sodium depletion 16 of 17 patients responded (94%). A net sodium loss of 100-200 mEq was felt to be ideal to maximize the test sensitivity and specificity, though there was considerable overlap in sodium excretion between responders and non-responders (Figure 28).



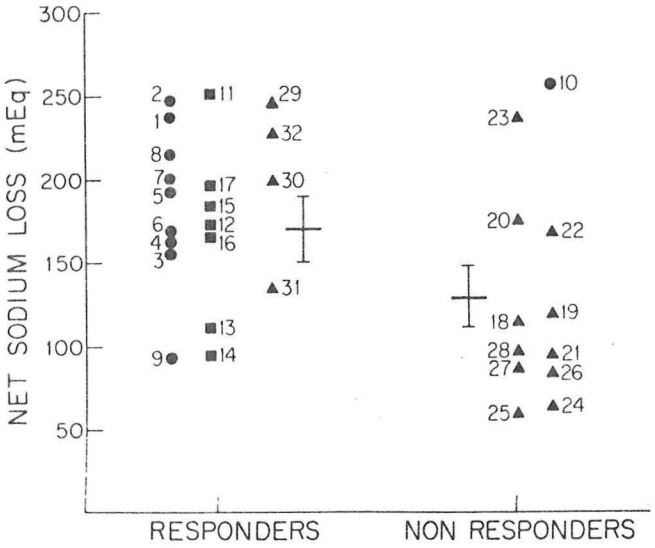
Measurements of plasma renin activity (PRA) in blood from a peripheral vein after the administration of furosemide (40 mg given intravenously 3 hours before) and standing for 2 hours in 300 patients with hypertension. It is evident that only 23 of 54 patients with elevated plasma renin activity levels experienced a fall in blood pressure levels of more than 10/8 mm Hg during saralasin infusion and that four "saralasin responders" had normal plasma renin activity levels. Five patients who were receiving estrogen-progestogen combinations for contraceptive purposes had increased plasma renin activity concentrations but were unresponsive to saralasin.

Figure 26



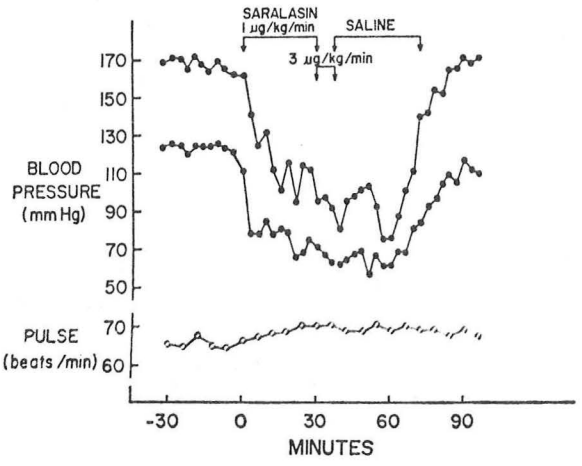
Effects of saralasin on blood pressure (mean ± SEM) in the 20 Patients who showed a vasodepressor response. Note that the vasodepressor responses were more marked after sodium depletion (Day 2) than in the normal sodium state (Day 1).

Figure 27



Net sodium loss after furosemide administration. The average sodium loss of the saralasin responders (170 meq ± 19 SEM) is greater than that of the nonresponders (129 meq ± 19 SEM) ($P < 0.05$), although there is considerable overlap.

Figure 28



-Effect of saralasin infusion on supine systolic and diastolic blood-pressure and heart-rate.

Figure 29

In another series by Wilson *et al* (1977) 100% of patients with proven renovascular hypertension (11 patients with cure or improvement of hypertension after surgery) responded to saralasin. Furosemide (80 mg) was also administered orally 12-18 hours before testing. Saralasin response occurred in 87% (7 of 8) of patients with renal artery stenosis and lateralizing function studies. In contrast, no patients with low renin hypertension and only 20% of patients with normal renal arteriograms demonstrated a saralasin response. However, in this series 23 patients were classed as possible or indeterminant renovascular hypertension (all with arteriographically demonstrable renal artery stenosis). Thirteen of these patients were not saralasin responders, and none demonstrated lateralization of either renal vein renins or split renal function studies. On this basis, none of the patients were operated; and, therefore, it is not possible to determine the predictive value of saralasin in this group of patients.

The Syracuse group headed by Streeten have administered saralasin to a large group of hypertensive patients as a screening procedure for renovascular hypertension. The subjects have been depleted with either 10 mEq low sodium diet or, more commonly, with 40 mg of intravenous furosemide 3½ hours before the initiation of saralasin infusion. A positive response is defined as a fall in blood pressure of more than 10/8 mm Hg during the infusion of saralasin. Out of 700 hypertensive patients (McAfee *et al*, 1977) screened by this procedure, 160 had renal imaging performed with technetium-^{99m} glucoheptonate and iodine-^{131}Hippuran. Scintigraphy was positive in 21 of 24 patients (88%) who eventually had arteriographically demonstrable renal artery stenosis and were judged to have an angiotensinogenic mechanism to their hypertension. 88% of cases of renal artery stenosis were also detected by scintigraphy with technetium-^{99m} glucoheptonate. However, the surgical results of this series of cases were not presented.

Baer *et al* (*Ann Int Med* 86:257, 1977) noted that 11 of 12 patients with a depressor response to saralasin had significant renovascular or renal disease, and that 9 of 10 had renal vein measurements that lateralized to the abnormal kidney. PRA was usually high in responders. Thus, it appears in general that approximately 90% of surgical candidates with renal artery stenosis will be identified by the use of saralasin as a screening diagnostic test if modest sodium depletion is utilized in conjunction. The proper amount of sodium depletion is critical. Pasternak *et al* (1977) demonstrated that normotensive volunteers would predictably have a depressor response to saralasin if urinary sodium loss of greater than 200 mEq was produced. Fagard *et al* (1977) have reported that hypertensive patients will not have a proper depressor response to saralasin when they ingest at least 130 mEq sodium per day. Anderson *et al* (1977) have noted that even low-normal hypertensive patients can be converted to saralasin responders with vigorous diuretic therapy. The fall in blood pressure with saralasin infusion is, thus, directly proportional to the height to which diuretics stimulate plasma renin activity.

It must be recognized that complications of both severe hypotension (Pettinger and Keaton, 1975, Figure 29) and rebound hypertension with encephalopathy (Keim *et al*, 1976) have been recognized. It appears that the severe rebound hypertension is secondary to a loss of the short loop negative feedback mechanism of angiotensin II which inhibits renin release. This reaction can be dissipated by reinstitution of saralasin infusion in combination with propranolol therapy to suppress plasma renin activity.

Converting enzyme inhibition: Two converting enzyme inhibitors--SQ-20,881 which must be administered intravenously and SQ-14,225 which may be administered orally--are presently being investigated as a means of identifying patients with angiotensin-mediated hypertension. Problems with the intrinsic agonist activity possessed by saralasin which limit somewhat its effectiveness as an angiotensin antagonist, are overcome with converting enzyme inhibitors. However, these

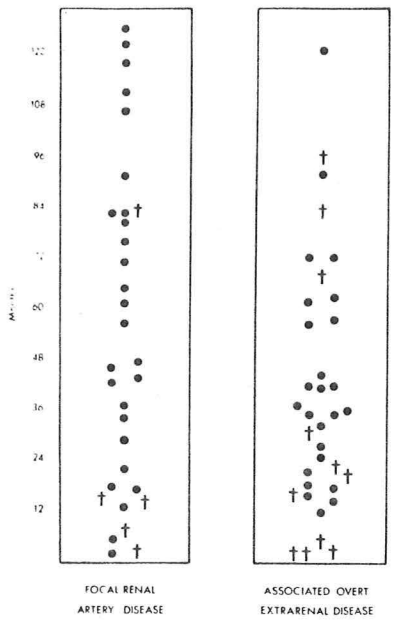
inhibitors suffer another problem--that of inhibiting the breakdown of circulating bradykinin by converting enzyme. Since other kininases are normally present in plasma, the relative significance of the inhibition of this one kininase on plasma bradykinin metabolism has not been assessed. Long term administration of SQ-14,225 may prove to be quite helpful in predicting which patients with renovascular stenosis will respond to surgery. Gavras *et al* (1974) have reported the successful treatment of some patients with renovascular hypertension (Figure 8) with SQ-20,881. Case and Laragh have noted similar depressor responses with SQ-14,225 in patients with renovascular hypertension and feel that measurement of stimulated plasma renin activity during administration of this compound may prove to be predictive of surgical response (personal communication). These exciting agents offer the possibility in the future of considerable improvements in sensitivity and specificity of screening for renovascular hypertension.

Natural History of Renovascular Disease

Atherosclerotic renovascular disease: Renal artery stenosis was noted by Van Velzer *et al* (1961) in 43.7% of patients with both hypertension and abdominal aortic or more distal atherosclerosis; whereas it was present in only 7% of similar patients with normal blood pressure studied angiographically. Eyler *et al* (1962) described the somewhat less striking difference in a similar study. Thus, renovascular hypertension may be a common sequelae of generalized atherosclerosis. Wollenwebber *et al* (1968) followed 109 patients at the Mayo Clinic over a 3-6 year interval with serial renal arteriography performed in 30 patients. Unfortunately, the patients were not divided into those with generalized atherosclerosis and those with more isolated renal artery stenosis for the purpose of comparing their prognosis. Of these 109 patients, 46 had renovascular surgery and the remainder were treated medically. There was no difference in the blood pressure control between the medically treated and surgically treated groups. The estimated 5-year survivorship was 67% compared to 92% in a comparably aged, but normal, population. There was no difference in survival between those treated medically and those treated surgically. Almost 40% of those initially free of symptomatic cardiovascular disease developed this, often despite control of their blood pressure. Among the 30 non-operated patients studied by serial arteriograms, progression of the disease was seen in half. The progressive nature of atherosclerosis was reflected by the impairment of renal function and loss of renal mass.

In another series of 91 patients followed six months to ten years without surgery, 39 had atherosclerotic renovascular disease (Meany *et al*, 1968). Of these 39 the stenosis increased in 10 and thrombosis occurred in 4. Neither the age or sex of the patient nor the appearance of the lesion on the initial examination was useful in predicting the subsequent development of progressive disease. However, Ernst *et al* (1973) have noted that those patients with focal atherosclerotic renal artery stenosis have a much better prognosis than do those with generalized atherosclerosis (Figure 30). Those with focal atherosclerosis had an 87% cure-improvement rate in comparison to 53% for those with generalized disease.

Fibrodysplastic renal artery stenosis: In contrast to the discouraging results which Meany *et al* (1968) found for patients with atherosclerotic renal artery stenosis, 51 patients with arterial fibrodysplasia similarly followed for 6 months to 10 years developed progressive disease in only 4 and new disease in 4 others, all of whom were under 40 years of age at the time of the



Time of postoperative death (†) or of latest follow-up (•) in patients undergoing renal revascularization for arteriosclerotic renovascular hypertension.

Figure 30

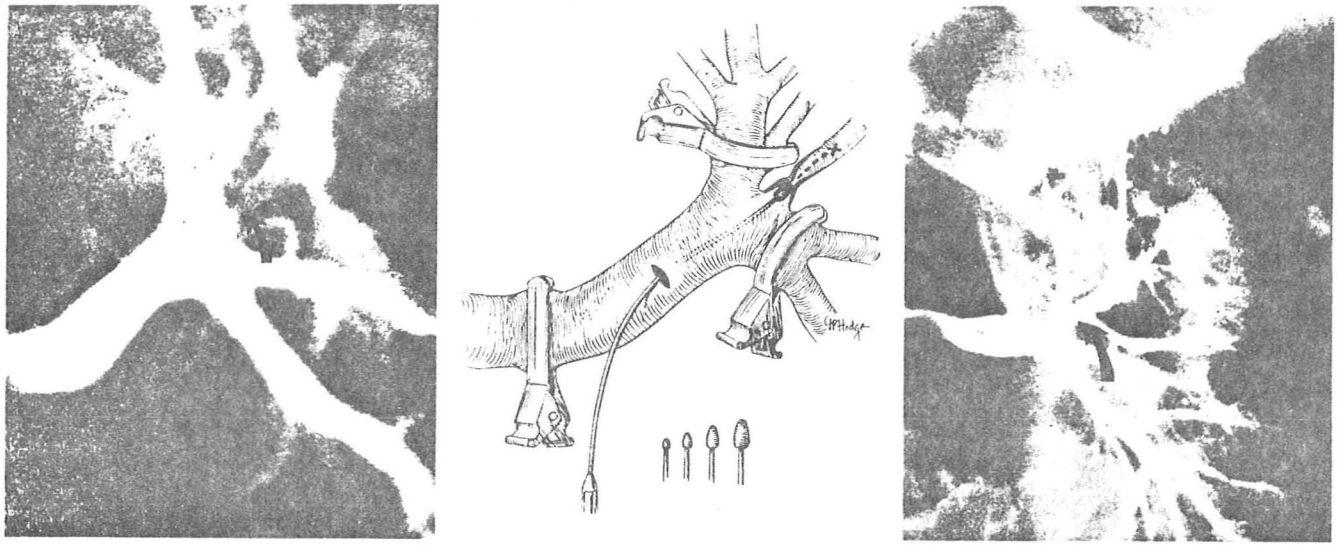
initial examination. Ischemic renal atrophy rarely developed. A less benign overall course in 55 patients was observed at the Mayo Clinic (Shepps *et al*, 1972). During an average follow-up time of 34.3 months during which time 32 of 55 patients were normotensive with medical and surgical management, 19 showed progression (35%). In agreement with the findings of Meany *et al*, progression was less common among patients with medial fibroplasia than in the remainder. However, in contrast to the findings of Meany *et al*, progression occurred in all age groups and appeared to be more common in those over the age of 40. No fibromuscular dysplasia developed in a previously normal-appearing renal artery, although celiac and hepatic artery involvement developed in one patient. No relation was seen between blood pressure control and progression of renal artery stenosis. Diminished renal function was noted in 21 patients and appeared to be secondary to restenosis of grafts as well as to the progression of main renal artery stenosis. Thus, though fibrodysplastic renal artery stenosis has a better long term prognosis, it is clear that the disease is progressive in a significant percentage of patients. This dictates the need for careful follow-up evaluation of renal function and of the renal vessels.

TABLE 19. RARE CAUSES OF RENOVASCULAR HYPERTENSION

I. Intrinsic Lesions
   - A. Aneurysm (Perry: *Arch Surg* 102:216, 1971)
   - B. Emboli (Arakawa: *Arch Int Med* 129:958, 1972)
   - C. Arteritis
     1. Polyarteritis nodosa (Dornfeld: *JAMA* 215:1950, 1971)
     2. Takayasu's (Kirshbaum: *Am Heart J* 80:811, 1970)
   - D. Arteriovenous fistula (Bennett: *Am J Roent Rad Ther Nucl Med* 95:372, 1965)
   - E. Angioma (Farreras-Valenti: *Am J Med* 39:355, 1965)
   - F. Neurofibromatosis (Halpern: *N Eng J Med* 273:248, 1965; Smith: *Arch Int Med* 125:1022, 1970; Hardy: *Br J Urol* 47:137, 1975; Bourke: *Br Med J* 3: 681, 1971)
   - G. Tumor thrombus (Jennings: *Br Med J* 2:1053, 1964)
   - H. Rejection of renal transplant (Gunnels: *N Eng J Med* 274:543, 1966)
   - I. Solitary intrarenal cyst (Babka: *N Eng J Med* 291:343, 1974)

II. Extrinsic Lesions
   - A. Pheochromocytoma (Rosenheim: *Am J Med* 34:735, 1963)
   - B. Congenital fibrous band (Lampe: *Angiology* 16:677, 1965)
   - C. Metastatic tumors (Weidmann: *Am J Med* 47:528, 1969)
   - D. Subcapsular perirenal hematoma (Massumi: *Am J Med* 46:635, 1969)
   - E. Traumatic occlusion (Cornell: *JAMA* 219:1754, 1972)
   - F. Ureteral obstruction (Garrett: *Am J Med* 49:271, 1970; Belman: *N Eng J Med* 278:1133, 1968)
   - G. Stenosis of celiac axis with "steal" of renal blood flow (Alfidi: *Radiology* 102:545, 1972)

Renovascular hypertension in children: Renal artery stenosis is second only to coarctation of the aorta as a cause of surgically remedial hypertension in children, and it is more commonly seen as a form of hypertension than in adults. In contrast to adults, the hypertensive IVP is unreliable as a screening test, as it was found to be abnormal in only 24% of cases with surgically proven renal artery stenosis (Stanley and Fry, 1977). Fry *et al* (1973) have developed delicate techniques of dilating segmental arterial stenoses (Figure 31).



—Left, Preoperative left renal arteriogram showing segmental arterial stenosis (arrow) in a 13-year-old boy. Center, Artist's concept of technique used in dilation of lesion. Right, Postoperative arteriogram two years after dilation of segmental renal arterial stenosis.

Figure 31

Surgical therapy: Considerable advances in surgical techniques have evolved over the past 20 years--in large part due to the effort of the Michigan group which was headed by Dr. William Fry. For a discussion of these techniques, the interested reader is referred to Stanley and Fry (1977), Stanley and Fry (1975), Fry *et al* (1970), Stanley *et al* (1973), Foster *et al* (1973), and to several review articles in a symposium of the management of renovascular hypertension (*Urol Clin N Am*, June, 1975).

A general favorable experience for fibrodysplasias in comparison to atherosclerotic disease is seen. Data from the Cooperative Study are presented in Table 20 (Bookstein *et al*, 1972).

—Etiology of Stenosis and Surgical Results*

	A†	FH†
No.	126	102
Favorable†	83 (66%)	84 (82%)
Unfavorable†	43 (34%)	18 (18%)

*Etiology as determined by arteriography. Data are included only for unilateral stenosis involving main renal artery.
†A indicates atherosclerosis; FH, fibromuscular hyperplasia. Favorable indicates cured or improved; unfavorable, failure.

Table 20

Excellent early results have also been reported by Foster *et al* (1973, Figure 32) for all except those cases of atherosclerosis associated with abdominal aortic lesions (Figure 33). The follow-up results of a 10-year period for this group are presented in Figure 34.

An excellent surgical success rate has also been reported by Stanley and Fry (1977), with over 90% success in all categories except generalized atherosclerosis (Table 21).

Comparison of early results in the operative treatment of atherosclerotic and fibromuscular dysplastic renal artery lesions.

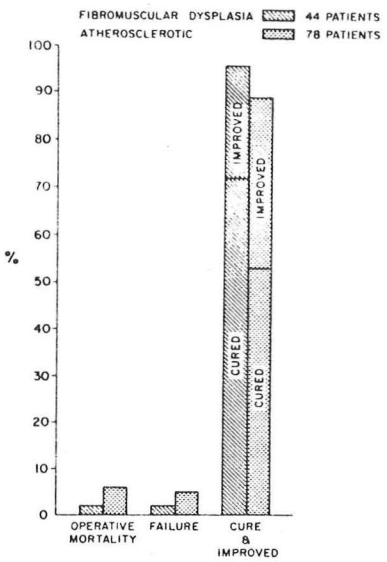


Figure 32

Results in the simultaneous treatment of renovascular and other associated abdominal aortic lesions (16 patients).

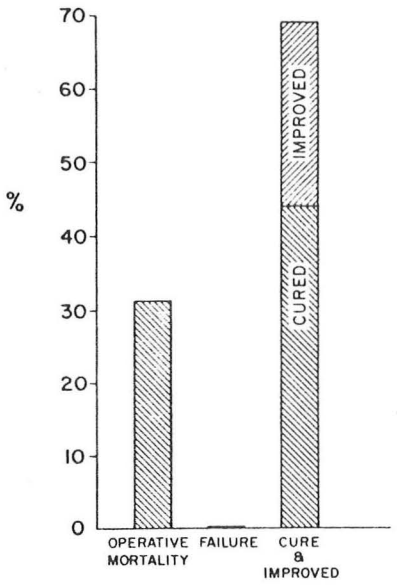
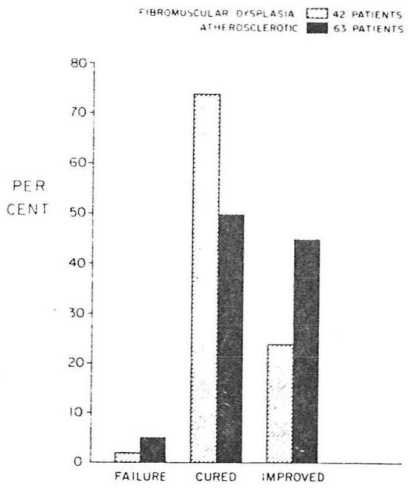


figure 33

Figure 34



Comparison of the late results in the operative treatment of atherosclerotic and fibromuscular dysplastic renal artery lesions.

Results

	Blood Pressure Status			Response to Surgical Treatment	
	Cured	Improved	Failure	Beneficial	Unfavorable
Pediatric	24(89%)	2	1	96%	4%
Adult Fibrodysplasia	76(57%)	51	5	96%	4%
Adult Focal AS	17(31%)	32	5	91%	9%
Adult Generalized AS	13(26%)	24	14*	73%	27%

*3 deaths-only operative mortality among all 264 patients

Overall 94% salutary response to operation

Table 21

Selections of surgical candidates is based on the following:

1. Nature of lesion - atherosclerosis vs fibrodysplasia, focal vs diffuse or multiple, unilateral vs bilateral
2. General medical status
3. History - recent onset has a most favorable prognosis
4. Evidence of lateralization by pyelogram, renogram, renal scan, renal vein renins, and/or split function studies
5. Arteriography including pharmacoangiography
6. Response to saralasin or converting enzyme inhibitors (when available)

Obviously, those patients with multiple criteria in favor of surgical success will be more likely to have a favorable surgical outcome. Unfortunately, many cases, particularly those with atherosclerotic disease, remain very difficult clinical decisions. In general, though, (and particularly at this institution) an enthusiastic approach of favoring surgical over medical therapy is in order. Assuming that the patient has no general surgical contraindications, almost all cases except those with generalized atherosclerosis or those with extensive bilateral disease without lateralization should probably be surgical candidates.

It has become increasingly apparent that those cases without progressive loss of renal function but with significant atherosclerotic lesions can be followed on medical therapy. Several reports have indicated that even if a main renal artery thromboses in this setting, function may still be restored by revascularization procedures for quite some period of time, even when acute renal failure has ensued (Morris *et al*, 1963; Smith *et al*, 1974; May *et al*, 1976; Besarub *et al*, 1976; Glubrandson *et al*, 1977; Zinman and Libertino, 1977).

Medical therapy: The general approach is the same as that for essential hypertension with the following exceptions:

1. Renin-suppressing drugs such as propranolol are favored
2. The danger of severe rebound hypertension with clonidine may be greater (Strauss *et al*, 1977)
3. Diuretics may lead to an elevation in blood pressure in high renin patients (Baer *et al*: *Ann Int Med* 86:257, 1977)

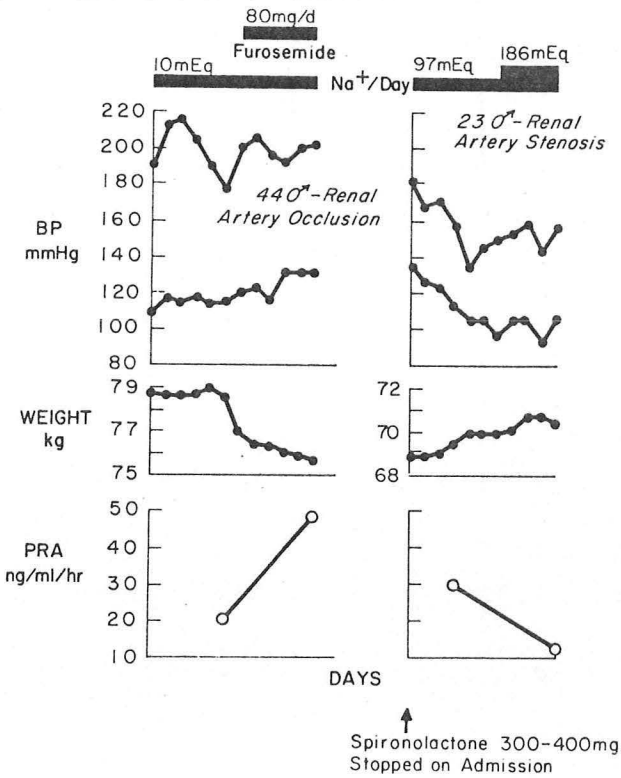


Figure 35

Paradoxical responses to sodium depletion and repletion on blood pressure in renal hypertension. PRA = plasma renin activity; BP = blood pressure.

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19. Cooperative Study of Renovascular Hypertension
See Bookstein 1972a (aims and methods)
Bookstein 1972b (role of urography)
Bookstein 1972c (arteriography)
Bookstein 1977 (bilateral stenosis)
Maxwell 1972 (demographic analysis)
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