THE YALE JOURNAL OF BIOLOGY AND MEDICINE 51 (1978), 635-654

Renovascular Hypertension: Pathophysiology, Diagnosis, and Treatment

HENRY R. BLACK, M.D.,[a] MORTON G. GLICKMAN, M.D.,[b] MARTIN SCHIFF, JR., M.D.,[c] AND ERIK G. PINGOUD, M.D.[b]

[a]*Department of Internal Medicine;* [b]*Department of Diagnostic Radiology;* [c]*Department of Urology, Yale University School of Medicine, New Haven, Connecticut*

Received May 10, 1978

Renovascular hypertension can result from renal artery lesions involving the main renal artery, or its branches. It is generally felt that the elevation of blood pressure results from excessive systemic vasoconstriction secondary to enhanced renin secretion by one or part of one kidney. Renin secretion is enhanced because of constriction of the renal artery and resultant intrarenal ischemia. Clinically patients cannot be distinguished from those with essential hypertension and diagnosis must be made with arteriography although urography and isotope renography may suggest the diagnosis. Surgical cure can be predicted if differential renal vein renin ratios lateralize but a non-lateralizing study does not necessarily mean that surgery will fail. In properly selected patients, surgical results are excellent.

Renovascular hypertension is most commonly recognized in patients with stenosis of a main renal artery, but stenosis or obstruction of renal artery branches, extrinsic masses which compress the kidney, and renal parenchymal lesions that result in ischemia can also cause renovascular hypertension. One or both kidneys may be involved. Since renal artery stenosis may be present in patients without hypertension and since repair of a stenotic renal artery does not always cure hypertension, surgical cure is the only definite criterion for establishing a causal relationship between an anatomic renal abnormality and hypertension [1].

The first surgical cure of hypertension was reported in 1937 [2], shortly after Goldblatt and co-workers demonstrated that dogs could be made hypertensive by constricting one renal artery and removing the contralateral kidney [3]. The concept of surgical therapy for hypertension was appealing, since effective antihypertensive drug therapy was not available. However, a summary in 1956 of results of approximately 2,000 nephrectomy operations in hypertensive patients revealed that only 20 percent were normotensive one year after operation [4]. Since then, much investigative effort has been directed at improving diagnostic procedures to distinguish patients with surgically curable hypertension from those in whom surgery would be futile. During these two decades safe, inexpensive, and effective drug regimens have developed as well, offering an alternative to surgery and making it more important to carefully select patients for operation.

Address reprint requests to: Henry Black, M.D., Department of Internal Medicine, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06515

0044-0086/78/5106-0635 $02.00

PATHOPHYSIOLOGY

Goldblatt first suggested that the direct cause of some forms of hypertension was hypersecretion of a pressor substance released by the kidney in response to ischemia. He implicated renin, an enzyme produced, stored, and secreted by granular cells located in the walls of the afferent arterioles and adjacent to the glomeruli (the juxtaglomerular apparatus). Renin cleaves angiotensin I, a ten amino acid peptide, from renin substrate. Angiotensin I is then metabolized in the lungs and elsewhere by converting enzyme to angiotensin II, an octapeptide which raises blood pressure by two distinct mechanisms: (1) angiotensin II is a potent vasoconstrictor; (2) angiotensin II, both directly and after further metabolism to angiotensin III, stimulates the secretion of aldosterone by the adrenal cortex. Aldosterone, a potent mineralocorticoid, increases sodium reabsorption from the distal tubules resulting in increased blood volume and blood pressure.

The renin-angiotensin system is only one of several mechanisms that regulate blood pressure. It appears to be a critical factor in maintaining blood pressure in the upright position and during hypovolemia [5]. The importance of the renin-angiotensin system in the normovolemic individual is less clear. The precise physiologic stimulus for renin release is unknown; renal perfusion pressure, sodium transport, and the sympathetic nervous system all play some role. Whatever the stimulus, inappropriate renin hypersecretion is associated with some forms of hypertension.

Laragh and co-workers have suggested that hypertension results from abnormalities in either blood volume regulation or the degree of systemic vasoconstriction [6]. Hypertension results from hypervolemia in primary aldosteronism and in hypertension related to decreased renal mass [7]. In these conditions the renin-angiotensin system plays a minor role. Vasoconstriction is probably the primary mechanism in renovascular hypertension. Renin hypersecretion results in excessive systemic levels of angiotensin II leading to generalized vasoconstriction and hypertension. Natriuresis and diuresis are induced in the unaffected kidney, reducing plasma volume and further contributing to systemic vasoconstriction.

The discovery of agents which can interfere with the renin-angiotensin system has lent strong support to the volume-vasoconstriction hypothesis. Saralasin, a competitive inhibitor of angiotensin II, blocks the action of angiotensin II at vascular smooth muscle receptors [8]. In animals, hypertension can be produced with either of two surgical models. In the one-kidney model, the artery supplying one kidney is constricted, and the other kidney is removed. In the two-kidney model, which more closely resembles renovascular hypertension in humans, one renal artery is constricted and the opposite kidney and renal artery are left undisturbed. Saralasin lowers blood pressure in the two-kidney model, suggesting that hypertension in this model is due to vasoconstriction [9]. Saralasin is ineffective in the one-kidney model, suggesting a volume-dependent form of hypertension. Under conditions of salt depletion, blood pressure is reduced by Saralasin in the one-kidney model, but blood pressure in the two-kidney model fails to fall with Saralasin infusion if normal plasma volume is maintained [10].

These studies indicate that both blood volume and vasoconstriction are important variables, and both must be considered in attempting to clarify the nature of any individual case of hypertension. This interrelationship between plasma volume and renin levels makes careful control of plasma volume important during diagnostic evaluation for renal vascular hypertension. Failure to consider the role of plasma

volume changes may have led to some of the incorrect predictions of surgical results in some series.

TYPES OF RENOVASCULAR-RENIN DEPENDENT HYPERTENSION

Atherosclerosis is the most common cause of hemodynamically significant renal artery stenosis. Renovascular hypertension due to atherosclerosis occurs most commonly in men and seldom in patients under 40 years of age, although rare cases have been reported in children. The main renal artery is usually narrowed at or adjacent to its origin. The stenosis is usually eccentric and the luminal surface irregular. Bilateral renal artery stenoses are common.

Angiographic demonstration of renal artery stenosis characteristic of atherosclerosis is not sufficient to diagnose renovascular hypertension. In a series of postmortem arteriograms, moderate to severe atherosclerotic renal artery stenosis was found in as many as 49 percent of individuals who had not been hypertensive. The use of renal vein renin assays to demonstrate renin-dependent hypertension and verify the significance of the arteriographic lesion will be discussed below.

In older patients, renal scarring and atrophy is common. If renal artery branch stenosis, localized scars, or areas of infarction are identified, renal venous samples should be drawn selectively from the involved segmental veins as well as from the main renal veins in order to determine whether renin hypersecretion results from an intrarenal lesion or from stenosis of the main renal artery.

Fibromuscular arteriopathy is the most common cause of renovascular hypertension in patients under 40, but may occur at any age. The disease occurs in women four to five times more frequently than in men in most large series. The right renal artery is involved more commonly than the left, but the lesion is frequently bilateral. Progression of the degree of stenosis and extension of the length of the lesion commonly occurs in patients treated both surgically and non-surgically. Fibromuscular disease may become manifest in the contralateral kidney up to several years after its presentation in the ipsilateral kidney.

The etiology is unknown. The predominance of right sided lesions has led some authors to postulate that the lesions result from renal ptosis or hypermobility [11]. Supporting evidence for this hypothesis is scarce. Pregnancy has been suggested as a contributory pathogenic factor, but the substantial number of men and nulliparous women with fibromuscular arteriopathy cannot be explained by this hypothesis [12]. Histologically identical lesions have been found in numerous arteries other than the renal arteries, which suggests that this may be a generalized systemic arteriopathy [13]. Other suggested etiologies include trauma, embryologic variation, proliferative endarteritis resulting from vascular hyperactivity, and mural ischemia resulting from compromise of vasa vasorum [12,14].

Numerous histologic subclassifications have been proposed, based on the layer of the arterial wall which is most severely affected, and also based on whether the lesion consists of fibrous tissue or hyperplasia of smooth muscle [12,14,15]. Characteristic arteriographic appearances and differences in the natural history of the disease have been described with specific histologic variants, but considerable controversy still exists. Most investigators agree that at least three variants of this disease can be separated: intimal fibroplasia, fibromuscular hyperplasia, and medial fibroplasia.

Intimal fibroplasia consists of circumferential accumulation of collagen within the internal elastic lamina. This variant has been found in five to ten percent of patients with fibromuscular arteriopathy [12,16]. It is most commonly seen in children and

young adults, although similar intimal lesions have been identified in older patients. Intimal fibroplasia is frequently progressive, and dissection and obstruction of the renal artery are common [16]. By arteriography, this lesion characteristically produces long tubular narrowing of the midportion of the renal artery.

True fibromuscular hyperplasia is the least common variant of fibromuscular arteriopathy, comprising only one to five percent of patients in this group [15,16] This variant apparently occurs with similar frequency in men and women. It, too, is frequently progressive and is associated with a high incidence of intramural dissection [15]. The arteriographic appearance of fibromuscular hyperplasia is often indistinguishable from that of intimal fibroplasia. Smooth tubular narrowing is present in the mid and distal thirds of the renal artery, frequently extending into renal artery branches.

Medial fibroplasia consists of circumferential fibrous rings that replace the muscular media of the vessel, alternating with short segments in which the media is thinned or absent and the lumen is dilated. This is the most common variant occurring in 75 to 85 percent of the patients with fibromuscular arteriopathy. It is found in all age groups and predominantly affects women [12,16]. It is also the most easily recognizable variant, as it has a virtually specific angiographic appearance. A long segment of the main renal artery, beginning in the middle third, contains segmental constrictions alternating with aneurysmal dilatations. The dilatations appear to be true aneurysms, since some or all of them are larger in diameter than the uninvolved portions of the renal artery. This appearance can be differentiated from that of another variant, frequently called fibroplasia, which also has a beaded angiographic appearance. In subadventitial fibroplasia, the dilatations are smaller in caliber than the uninvolved portions of the renal artery.

Recognition of medial fibroplasia has clinical importance since this variant seems to progress more slowly than the others. Stewart and co-workers have reported 41 patients with this angiographic appearance who were treated conservatively [16]. The lesion progressed in only two patients, and no progression was observed in any patient over 40 years of age. Other series have documented greater frequency of progression and progression in some patients older than 40, but even in these series the lesion progressed in fewer than 30 percent of patients [15]. The incidence of dissection and other complications also appears lower in this variety than in other forms of fibromuscular arteriopathy.

Hypertension occurs in approximately 10 percent of patients with *neurofibromatosis.* In patients under 18 years old, renal artery stenosis is the usual cause, although many of these patients have abdominal aortic coarctation as well. Pheochromocytoma is also associated with neurofibromatosis and is the most common cause of hypertension in patients with neurofibromatosis whose hypertension begins after the age of eighteen [17].

Renal artery stenosis associated with neurofibromatosis is most commonly located at the origin of the main renal artery. Post-stenotic dilatation is often present [18]. Renal artery stenoses are occasionally bilateral, and in one-fifth of reported cases the aorta adjacent to the renal arteries is also narrowed [19].

In most instance, renal artery stenosis results from intimal fibrous or cellular proliferation, but in some patients neurofibromas within the arterial adventitia have caused stenosis. Although the number of cases reported to date is relatively small and the time of followup is relatively short, surgical revascularization has often been successful [18,20]. Progression of stenosis has seldom been documented, although in

one reported case renal artery stenosis recurred following surgical resection of bilateral stenoses and reimplantation of the renal arteries into the aorta [20].

Renal artery branch stenosis may result from extension of fibromuscular disease of the main renal artery, but occasionally is found in the absence of main renal artery disease. Branch stenosis or obstruction may also result from atherosclerosis, embolization of a mural thrombus from the heart, arteritis, trauma, or vasospastic diseases such as ergotism.

Several *renal parenchymal diseases* have been associated with renin-dependent hypertension. Considerable controversy exists about the etiology and classification of these diseases, such as chronic pyelonephritis and segmental hypoplasia, and many pathologists agree that the classical histologic findings previously considered specific for chronic pyelonephritis secondary to infection may also be the end result of other pathological processes [21]. Considerable evidence suggests that many patients who in the past have been treated with antibiotics in the belief that the disease was caused by repeated infection have instead been suffering from chronic vesico-ureteral reflux. Their deteriorating renal function may have been a result of chronically elevated caliceal pressure rather than infection or even inflammation [22].

Radiologic criteria for the diagnosis of pyelonephritis have consisted of focal or generalized scarring. In view of the clinical and pathological uncertainty of this diagnosis it must be recognized that these urographic findings are non-specific, at least after the age of 25. Scarring following vesico-ureteral reflux, renal infarction, trauma, or other renal insults can produce the same urographic abnormalities [23].

Renin-dependent hypertension has been documented in occasional patients with urographic, clinical, and microscopic findings formerly considered to represent pyelonephritis [24]. Thickening of the walls of blood vessels in areas of involvement is described as part of the characteristic microscopic picture. Renin-dependent hypertension has been demonstrated in patients with renal parenchymal scarring or atrophy that has resulted from trauma, renal tuberculosis, infarction, vesico-ureteral reflux, and hydronephrosis.

Central segmental renal scarring was described by Ask-Upmark and has been considered to result from congenital hypoplasia [25]. This hypothesis is now in doubt, however, since several cases have been described in which histologically identical lesions have appeared in previously normal kidneys following chronic vesico-ureteral reflux [26]. Like "chronic pyelonephritis," "segmental renal hypoplasia" is not a specific diagnosis but a syndrome whose mechanism cannot be inferred from its appearance, unless reflux is demonstrated.

Hypertension is frequently present at the end-stage of many renal parenchymal diseases, and occasionally occurs in patients with scarred kidneys but well-preserved renal function. Goddard and co-workers [27] have called attention to the frequent presence of hypertension in children with Ask-Upmark kidneys, and Meares and Gross have reported adult onset of hypertension associated with this syndrome [28]. Elevated renal vein renin levels and a favorable response to nephrectomy in many of these patients suggests that the mechanism of hypertension, at least in some instances of renal scarring or atrophy, is similar to that in renal artery stenosis. These authors and others have postulated that ischemic zones develop between fibrous tissue and healthy parenchyma and give rise to renin hypersecretion. Hyperplasia of the juxtaglomerular apparatus has been demonstrated microscopically in renal parenchyma adjacent to hypoplastic or scarred segments [27].

Arteriolar nephrosclerosis may result from severe atherosclerosis or from long-

standing hypertension from any cause. In the presence of nephrosclerosis, hypertension may be irreversible even if a localized ischemic zone of parenchyma or an arterial stenosis can be demonstrated and renin hypersecretion verified by renin assay [29]. Arteriographic signs include rapid tapering of intrarenal arteries, diminution in the number of arcuate arteries that are opacified, tortuosity of peripheral arteries, and diminished cortical thickness [30]. Renal artery blood flow rate is reduced from normal. Reduced renal flow rate can be recognized by comparing flow in the renal arteries to that in other abdominal arteries on the aortogram.

Renin-dependent hypertension has been only rarely associated with *expansile renal masses*, and in all reported cases the mass has been a renal cyst [31]. The mechanism appears to be direct compression of intrarenal arteries by the mass, leading to parenchymal ischemia and renin hypersecretion, since renin-dependent hypertension has been reported only in cases with severe distortion of renal parenchyma. Benign cysts are more likely to produce significant parenchymal compression than are abscesses or tumors, since cysts do not infiltrate or destroy renal tissue.

In the presence of an expansile mass in a hypertensive patient, selective magnification arteriograms should be carefully reviewed to exclude other potential causes of renal hypersecretion. Since the source of renin hypersecretion is intrarenal, and renin secretion from distorted segments of the same kidney may be suppressed, blood samples for renin assay should be drawn from segmental veins within the kidneys. Reversal of hypertension may result after removal of the mass, but not always [32]. Renin hypersecretion may be irreversible if parenchymal compression has been sufficiently long-standing.

Renin-dependent hypertension has also been associated with *subcapsular and extracapsular masses* that produce compression of renal parenchyma. In most reported cases the mass was a post-traumatic hematoma. The absence of intrinsic arterial abnormalities, elevation of renin in the venous blood draining the affected kidney compared to the opposite kidney, and reversal of hypertension following surgery verify this mechanism [33]. A similar lesion was produced in several animal species and reported as early as 1939 by Page [34]. He wrapped one kidney in cellophane and subsequently noted a thick perirenal scar that altered intrarenal dynamics and induced hypertension which could be reversed by nephrectomy.

To date, all but one of the reported *renin-secreting tumors* have been benign tumors of renal origin with similar histologic characteristics [35]. The exception was a Wilm's tumor in which autonomous renin secretion was demonstrated [36]. Although the benign renin-secreting tumors contain multiple cellular elements and can therefore be considered hamartomas, the predominant cell types have characteristics that suggest they are derived from the juxtaglomerular apparatus of the kidney. They contain granules whose ultrastructural characteristics are similar to those in the juxtaglomerular apparatus [37]. Other cells appear to be derived from those of renal tubules.

These rare tumors have been reported only in patients below the age of thirty-five. They present with hypertension which is usually severe and uncontrollable pharmacologically. Characteristic laboratory abnormalities include hypokalemia and hyperaldosteronism. Since in at least one of the reported cases aldosterone secretion could not be suppressed by DOCA, the distinction between renin-secreting tumors and primary aldosteronism may be difficult [35]. Renin-secreting tumors are small in size and may be below the limits of resolution of intravenous urography, radionuclide examination, and even aortography, further adding to the diagnostic difficulty.

However, in all previously reported cases plasma renin activity has been elevated, whereas in primary aldosteronism plasma renin activity is characteristically low.

The most sensitive radiographic means of demonstrating small renal masses is selective renal arteriography using magnification techniques. Once the diagnosis is suspected on the basis of elevated plasma renin activity and renal arteriography, it can be confirmed by renin assay of renal vein blood samples from veins draining the tumor. Complete or partial nephrectomy is curative.

Renal ischemia occasionally results from compression of the main renal artery by *extrinsic lesions.* Non-malignant structures that have compressed renal arteries to produce surgically reversible hypertension include congenital fibrous bands and hypertrophied adrenal tissue [38]. Tumors such as lymphosarcoma, renal adenocarcinoma located in the hilum, pheochromocytoma, and metastases from the sigmoid colon and lung have been implicated in the pathogenesis of hypertension [39,40].

True renal artery aneurysms are usually associated with atherosclerosis or fibromuscular disease. Aneurysms are occasionally found in the absence of underlying arterial disease [41,42] These may result from congenital or degenerative factors. False aneurysms result from inflammation or trauma. The majority of renal artery aneurysms are asymptomatic and do not rupture or cause hypertension. The mechanism of hypertension associated with renal artery aneurysm has aroused considerable speculation: embolization of mural thrombi from within the aneurysm to segmental renal arteries, compression of renal artery branches by a high-pressure pulsatile aneurysm, or undetected stenosis proximal or distal to an aneurysm have been proposed.

Renal arteriovenous fistula most commonly results from penetrating trauma, rupture of a renal artery aneurysm, surgery, or renal biopsy [38]. Arteriovenous fistulae may escape detection at surgical exploration or on pathologic examination. Auscultation of a bruit or abrupt onset of hypertension following an injury or biopsy should raise suspicion of a renal arteriovenous fistula. Arteriography is required for definitive diagnosis.

Because of the abrupt pressure drop across an arteriovenous fistula, most of the renal artery flow is diverted through the fistula, and the renal parenchyma distal to the fistula becomes ischemic, resulting in hypertension and renin hypersecretion. If an arteriovenous fistula is identified soon after it develops, the arterial supply may arise primarily from the renal artery, and local resection or partial nephrectomy may be possible. If there is a lag between development of the fistula and surgery, arterial collaterals may enlarge and contribute to the fistula. The presence of collateral circulation considerably increases the technical difficulty of surgical resection, increases the morbidity of resection, and often mandates complete nephrectomy. Angiographic occlusion of the fistula with a balloon catheter is a therapeutic approach that may be useful as an alternative to surgery for intrarenal arteriovenous fistulae.

CLINICAL PRESENTATION

The National Cooperative Study on Renovascular Hypertension in 1972 described the clinical characteristics of 2,442 hypertensive patients, 880 of whom had renovascular hypertension [43,44]. Compared to patients with essential hypertension, those with renovascular hypertension: tended to have hypertension for a shorter period of time; more often had no family history of hypertension; had more severe fundscopic

abnormalities; had bruits in the mid-abdomen six to nine times more frequently; more often had hypokalemia, alkalemia, and azotemia.

However, this study reported no greater frequency of accelerated hypertension or of pharmacologically uncontrollable hypertension in patients with renovascular disease, and no difference was found in the frequency of excessive tension or anxiety between hypertensive groups, contrary to prior reports. Postural hypotension was more common with renovascular hypertension than with essential hypertension but not significantly so, and patients with renovascular hypertension due to atherosclerosis had a higher frequency of peripheral vascular disease, aortic aneurysm, and proteinuria. While renovascular hypertension was more common in patients under 20 and over 50, significant numbers of patients with essential hypertension were younger than 20 or older than 50.

Based on the Cooperative Study data, Maxwell has suggested that patients with an abdominal or flank bruit who also have an abnormal urogram or renogram are very likely to have renovascular hypertension, and conversely patients with no bruits and normal urograms and renograms are virtually certain of having essential hypertension. In the patients studied in the National Cooperative Study only 1.6 percent of those without a bruit and with a normal urogram and renogram had renovascular hypertension [45]. This thesis may only apply to patients whose hypertension is associated with main renal artery stenosis. Many other diseases of unknown frequency have been associated with surgically curable hypertension, so that clinical application of these findings may be premature.

DIAGNOSTIC EVALUATION

Selection of Patients for Evaluation

Renovascular hypertension results from a large variety of conditions. While atherosclerosis and fibromuscular dysplasia are the most common, renin-dependent hypertension may result from tumors, trauma, fibrosis, infections, and arterial aneurysms and arteriovenous malformations. (See above). These patients may be indistinguishable from those with essential hypertension and so the clinician must be familiar with the risks, benefits, and relative usefulness of the many diagnostic procedures available and know which patients should be extensively studied and which should merely be treated once a simple evaluation is completed.

Diagnostic evaluation for renovascular hypertension can be arbitrarily considered to consist of three steps: (1) demonstration of the abnormality, (2) functional evaluation to prove that the abnormality is responsible for the hypertension, and (3) cure or significant improvement after successful surgery. Definitive demonstration of an anatomic abnormality that may be responsible for hypertension requires arteriography. The functional significance of an abnormality demonstrated by arteriography should be verified by renin assay of blood samples obtained selectively from the renal vein, by pharmacoangiography, or both before surgery is considered. Since these procedures are expensive, uncomfortable, and pose a risk to the patient, screening procedures have been proposed to select the proper sub-group of the hypertensive population for these intensive diagnostic procedures. These consist of intravenous urography, radioisotope renography, peripheral plasma renin activity, and Saralasin infusion.

In 1977, a task force from the National Heart, Lung and Blood Institute of the National Institutes of Health recommended no radiologic or physiologic screening

for renovascular hypertension for most patients [46]. Further supporting this approach, MacNeil concluded that from an epidemiological viewpoint that only men who are under 54 and not compliant with therapy should be further investigated for renovascular hypertension [47]. Her projections assumed that ten percent of the hypertensive population had renovascular disease, surely an overestimate. Reevaluation of her data using a smaller estimate of the prevalence of renovascular hypertension may suggest that no hypertensive patients should be screened for renovascular disease, if the cost-effectiveness of such effort is a major goal.

The risks involved in surgery are significant, and the improved results with newer antihypertensive drugs frequently permit clinically adequate control of blood pressure with few side effects. However, the problems of achieving lifelong compliance with medications, and the possibility of progression of arterial stenoses and loss of ability to control the blood pressure remain. The potential long-term effects of antihypertensive therapy are unknown, and may not be as benign as anticipated. Thus the benefits of detection and cure of renovascular hypertension should not be forgotten.

One guideline for patient selection is clear: the patient must be an acceptable surgical risk. Patients with recent myocardial infarction, congestive heart failure, or angina, and patients who have already suffered debilitating cerebrovascular accidents are unacceptable high risks [48]. They need not undergo diagnostic evaluation but should be treated medically. Patients whose hypertension cannot be controlled pharmacologically should be examined for surgically curable disease. Failure to adhere to a pharmacologic regimen puts the patient at risk of significant end organ damage and justifies screening for surgically correctable disease.

Several population groups have a high enough incidence of renovascular hypertension to justify screening. In white women between the ages of 20 and 40, in middle-aged men with recent onset of hypertension, and in all hypertensive children, screening for renovascular hypertension is worthwhile. Patients with an abdominal bruit, especially a diastolic [49] or a systolic-diastolic bruit, should be screened if they are surgical candidates. If the hypertension is difficult to control medically, or if the patient is non-compliant to an effective regimen, intensive screening should be undertaken. The risk of missing a curable lesion and subjecting the patient to uncontrolled hypertension outweighs the expense and the risk of a thorough diagnostic evaluation.

SCREENING PROCEDURES

The ideal screening test for any disease is a simple, safe, inexpensive examination that identifies a sub-group of patients at high risk, so that only that sub-group need be subjected to more definitive but more dangerous diagnostic procedures. In a useful screening test, a moderate percentage of false-positive examinations is acceptable, but significant false-negative results are unacceptable. The problem of screening for renovascular hypertension is particularly complex since no currently available test is without flaws.

Peripheral plasma renin activity (PRA). Since renal vascular hypertension presumably results from renin hypersecretion, demonstrating elevated circulating levels of renin should help to identify those patients whose hypertension can be improved or cured by a surgical revascularization procedure. Plasma renin activity, however, varies not only with physiological parameters such as blood volume and sodium load, but also with age, race, sex, and concurrent diseases such as diabetes mellitus

[50,51,52]. Renin levels decrease with age, and are normally lower in blacks than in whites and in women than in men. No carefully controlled investigation has yet established "normal" levels for each of these groups.

Sealey et al. have attempted to correct for variations in plasma volume in measuring PRA. They assume that twenty-four hours sodium excretion [53] on the day prior to PRA assay accurately estimates volume status. Hypertensive patients were divided into low, normal, and high renin groups by comparison with PRA and sodium excretion levels from a group of normal, non-hypertensive patients. This study and others established that 15 to 20 percent of hypertensive patients have elevated PRA; 33 percent have low or suppressed PRA; and about 55 percent have renin levels similar to those in the control population with similar sodium excretion [54]. In these studies, renovascular hypertension was found most commonly in patients with elevated PRA, often in patients with normal PRA, and rarely in patients with low PRA.

Since PRA varies with age, race, and sex, PRA in hypertensive patients should probably be matched with controls based on these variables as well as plasma volume. PRA should be measured after furosemide administration and after several hours of upright posture. The results should be reproducibly analyzed in a laboratory with broad experience and carefully established normal values. Because of the complex patient preparation, the numerous variables, and the wide range of PRA level in renal vascular hypertension, PRA assay by itself is probably not sufficient for identifying patients with renovascular hypertension [55].

Saralasin. A promising new approach to screening for renovascular hypertension involves the use of specific angiotensin blocking agents, such as Saralasin. In a recent investigation, three hundred hypertensive patients were given intravenous Saralasin infusion [56]. Those whose blood pressure decreased by 10/8 mm Hg or more were selected for urography and arteriography. Renin-dependent hypertension was verified surgically in fourteen of the thirty-one patients with a positive Saralasin test. Results were even better in a similar investigation using Saralasin injected as a bolus rather than by infusion [57]. The false-positive rate was only 9.5 percent. Several false-negative Saralasin tests have subsequently been reported [58]. These patients became normotensive following renal artery revascularization, although Saralasin tests had been negative.

Thus far the best results have been obtained when Saralasin was administered in the volume depleted state. While safer and less complicated than most other screening procedures, Saralasin injection has occasionally resulted in severe hypotensive or severe hypertensive reactions [59].

If further studies confirm these results and refine the testing procedure, Saralasin or a similar agent such as converting enzyme inhibitor may become the primary screening test for identification of renin-dependent hypertensive patients. Those who respond can then be selected for arteriography and renal vein renin assay.

Radionuclide studies currently used in the evaluation of renovascular hypertension assess renal function, arterial perfusion, and morphology of the kidney.

Orthoiodohippurate (OIH) is the most commonly used radionuclide to study renal function (renogram). Most of this tracer is extracted on its first pass through the kidney. Following intravenous injection of OIH, serial scintiphotographs of the kidneys are obtained at rapid intervals for the first twenty minutes. Delayed scintiphotographs are obtained one and two hours after injection.

The data are stored on videotape for later retrieval and generation of renal area

curves. Although interpretation of these curves remains controversial, most investigators believe that the initial slope represents mainly background radioactivity and rapidly accumulating activity in the renal vasculature. The second portion of the curve reflects activity accumulating in the tubules as well as background and renal vascular activity. In the third portion, activity diminishes in the kidney as OIH passes into the ureter.

In the presence of renal artery stenosis, OIH is extracted from the blood less rapidly than usual, resulting in a decrease in the slope of the first and second portion of the curve and a delay in peak activity. The slope of the third portion of the curve is also reduced, most likely because transit of OIH through the tubules is prolonged, due to greater absorption of water and sodium in the hypoperfused kidney. While this pattern is typical of renovascular disease, it is not specific. Similar curves result from dehydration, sodium depletion, renal disease, and obstruction of the renal pelvis or ureter.

Farmelant and Burrows [60] prefer comparison of renogram curves of the two kidneys to comparison with values derived from a selected normal population. In screening for unilateral renovascular disease, these and other authors [61] believe that the descending portion is the most reliable segment of the curve. Farmelant and coworkers considered a difference of 20 percent or more in the fifteen-minute relative retention of radioactivity between the two kidneys (as measured from the time the first kidney reached peak activity) as significant. Farmelant et al. [62] found a false-negative rate of 7 percent (four of fifty-eight patients) and a false-positive rate of 10 percent (four of forty-one patients) in a group of ninety-nine hypertensive patients. Maxwell et al. [63] evaluated the accuracy of multiple renographic studies for renovascular disease and found false-positive rates between 0 and 53 percent, and false-negative rates ranging from 0 to 46 percent. Blaufox et al. [64] state that most centers report false-positive and false-negative rates of about 30 percent similar to the accuracy rate of the rapid sequence intravenous urogram.

Renal morphology is most often studied on scans obtained following 99m Tc-DTPA or 99m Tc-DMSA [65] injection. Kidney size and shape are evaluated in various projections. Since many conditions alter kidney size and shape, the scan is non-specific. Since the kidneys may have normal size and shape in the presence of renovascular hypertension, the scan lacks sensitivity.

Study of renal perfusion is most often performed with technetium pertechnetate [66]; this is an excellent compound to evaluate renal blood flow, since only a fraction is extracted by the kidney.

Following injection, scintiphotographic exposures are obtained every five seconds for two minutes and recorded on videotape for generation of time activity curves. These curves reflect separately the radioactivity in the abdominal aorta and in each kidney. Differential renal blood flow in the two kidneys may be apparent on visual inspection of the scintiphotos and the curves. For quantitative measurements, Adam et al. [67] found the time to peak activity (T_m) to be most sensitive, while Rosenthall found the time to peak activity plus the time to one-half peak activity more reliable.

Koenigsberg et al. [68] evaluated the sensitivity of perfusion scanning in detecting differential renal artery flow rates in dogs. Visual assessment was only reliable in identifying differences in flow rates in the two renal arteries of 40 percent or more. Quantitative analysis permitted detection of differential flow rate if the difference in rate was 25 percent or more.

While this study promises to be useful in screening for renovascular disease, more

statistical data are needed to determine the diagnostic accuracy of this study. Currently it is used as an adjunct to other tests.

The function study (renogram) is currently the most widely used radionuclide study in screening for renovascular hypertension. It is associated with false-negative and false-positive rates of 10 to 20 percent, a diagnostic accuracy comparable to the rapid sequence IVP. Because of the high incidence of false-negative results, its usefulness as a screening procedure has been justifiably questioned.

Intravenous urography is an excellent means of demonstrating diseases of the renal parenchyma and collecting system. Focal or diffuse renal scarring, renal masses, and obstruction of the renal pelvis or ureter are readily demonstrated. The presence of any of these abnormalities may influence therapeutic decisions, whether or not subsequent evaluation verifies a relationship to the patient's hypertension.

In addition, intravenous urography may be helpful in identifying patients with renal ischemia due to renal artery stenosis. The three urographic abnormalities most frequently associated with renovascular hypertension are (1) disparity in renal length, (2) difference between the kidneys in the time of initial opacification of the collecting structures, and (3) difference in the density of contrast medium in the collecting structures of the two kidneys [69].

Renal length is best measured on the initial film, during the time of maximal opacification of the renal parenchyma. Unilateral renal artery stenosis should be suspected if the left kidney is more than two centimeters longer than the right, or if the right kidney is more than 1.5 centimeters longer than the left, assuming the kidneys are normal in shape and the caliceal anatomy is comparable.

Contrast medium injected intravenously is thoroughly mixed with blood during its passage through the heart. Normally, contrast medium should reach the glomeruli on both sides simultaneously. If the two kidneys function symmetrically, glomerular filtration and passage through the renal tubules should be simultaneous. In the presence of unilateral or asymmetrical renal artery stenosis, blood flow rate and the rate of glomerular filtration of contrast medium in the affected kidney are reduced. The most easily observed and measured urographic sign of reduced filtration rate is delayed opacification of the renal calices. If the calices of one otherwise normally functioning kidney become opacified one minute or more before the other, renal artery stenosis should be suspected.

Although the rate of glomerular filtration is decreased in the presence of renal artery stenosis, absorption of water from the renal tubules is increased. Increased water reabsorption results in greater concentration of the contrast medium in the urine produced by the affected kidney. The presence of a visible difference in concentration of contrast medium in the collecting systems of the two kidneys suggests unilateral renal artery stenosis.

In the Cooperative Study, at least two of these urographic studies were present in 45 percent of the patients with significant unilateral renal artery stenosis, whereas the urograms of only 0.5 percent of patients without unilateral renal artery stenosis demonstrated two or more of these abnormalities [69]. The most reliable single urographic abnormality in this study was delayed caliceal appearance time.

In the presence of renal artery stenosis, collateral circulation frequently develops. Collateral circulation via the ureteral artery results in dilatation and tortuosity of this vessel, which accompanies the ureter throughout its length. Occasionally, notching of the ureter due to compression by a tortuous ureteral artery may be visible on the urogram. Although venous tortuosity unrelated to renal artery stenosis may also

produce ureteral notching, the presence of this abnormality in a hypertensive patient supports the suspicion of renal artery stenosis.

Currently screening tests are not accurate enough to constitute an endpoint in a patient's workup. The hypertensive IVP and radionuclide renogram are both associated with false-positive and false-negative rates of ten to twenty percent. This percentage is too high to rely on either of these tests to exclude renovascular hypertension in patients considered to be surgical candidates. The efficacy of the Saralasin infusion test as a routine screening procedure needs to be evaluated further.

However, we perform intravenous urography prior to arteriography, not as a screening procedure for renovascular disease but to provide anatomic information about the kidneys (inflammatory or atrophic disease, masses, malformations). Radioisotope renography may provide similar information but less directly. Whether urography is normal or abnormal, arteriography is performed in all patients in whom diagnostic evaluation for renin-dependent hypertension is justified by clinical criteria.

ARTERIOGRAPHY

Arteriographic evaluation of the hypertensive patient requires careful demonstration of the entire renal arterial tree, from the orifice of the main renal artery to the most peripheral intrarenal branches. Aortography provides safe and accurate evaluation of the number of renal arteries present, and permits visualization of the extrarenal portions of each of the renal arteries without risk of obstructing or dissecting a stenotic orifice with a selectively placed catheter.

Following aortography, selective catheterization and injection of each of the main renal arteries is performed unless contraindicated by stenosis at the renal artery orifice [29]. Selective arteriography is important in evaluating extension of arterial disease into intrarenal artery branches in the presence of stenosis of the main renal artery, and in evaluating parenchymal and intrarenal vascular lesions in the absence of main renal artery stenosis. Selective arteriography of each renal artery is particularly important if the aortogram is normal. If the main renal arteries do not contain stenoses, an intrarenal source of renin hypersecretion must be carefully excluded.

Arteriography provides direct, definitive demonstration of anatomic lesions that may be responsible for renovascular hypertension. In addition to identifying arterial stenoses and providing data which permit estimation of the degree of stenosis, arteriographic findings are often sufficiently specific for diagnosis of the underlying disease.

EVALUATION FOR SURGICAL CURABILITY

As mentioned above, the demonstration of an arteriographic abnormality is not sufficient evidence that the lesion is responsible for the hypertension and that surgical repair will be successful. Biochemical demonstration of renin dependence is considered necessary. Peripheral renin levels are not helpful and Saralasin has not been adequately evaluated as yet. Most centers rely on bilateral renal vein renin (RVR) assays to prove renin dependence and predict cure at surgery. In spite of wide experience with this procedure, the conditions under which the tests should be performed and the ratios most predictive are still controversial. (See below). Many false-positive and false-negative studies continue to be reported. Marks and coworkers reviewed twenty-one published series comprising 412 patients and added their own series of 56 patients, using each author's criterion for a positive examination [70]. They reported successful surgical results in 93 percent of patients who had

abnormal RVR ratios and technically successful operations. However, they also reported a large group of patients in whom RVR studies were considered non-lateralizing. Of these, 57 percent were cured by surgery, indicating a large false-negative rate with RVR ratio estimations. A carefully controlled study on large numbers of patients in whom renal vein samples are obtained under optimal conditions is obviously needed. Until such a study is reported, the incidence of false-positive and false-negative results can be kept at a minimum by ensuring careful preparation of the patients and meticulous catheterization and sampling techniques, by obtaining several samples from each site to serve as internal controls [71], and by judicious selection of sampling sites based on arteriographic results [55].

The difference between the renin levels from the normal and abnormal kidney is greatest under conditions which stimulate renin secretion. Consequently, the following preparatory procedures are recommended.

The patient should receive no more than one gram of sodium per day for at least three days prior to the examination. Furosemide (40 mg) should be administered the night before and again on the morning of the examination. These measures reduce blood volume and stimulate renin. The patient should be recumbent for twelve hours prior to the procedure in order to ensure a relatively steady level of renin secretion. Those antihypertensive medications whose mechanism of action blocks renin release should be stopped at least twenty-four hours before the renal vein samples are collected.

For interpretation of RVR levels, a ratio is constructed comparing the level measured from an abnormal site to the level from a normal site. Most investigators consider a ratio of 1.5 to 1 as the upper limit of normal [55,72,73]. Several reports describe high false-positive rates using this ratio and conclude that ratios of 2 to 1 are necessary to diagnose and localize renin-dependent hypertension [71,73]. However, in these reports some samples were obtained without renin stimulation by low sodium diet and diuretic administration.

In patients with stenosis of the extrarenal portion of one or both renal arteries and no arteriographic abnormality in the intrarenal arteries or renal parenchyma, a set of venous samples for renin assay is drawn from the main renal vein of each kidney. Since levels of renin secretion may change from moment to moment, control samples from a peripheral site are drawn with each set of renal venous samples. A sudden increase in renin secretion due, for example, to anxiety is reflected in the peripheral sample, avoiding misinterpretation of factitious renin levels measured in one or both renal venous samples.

At least two and preferably three sets of samples from each of the renal veins and from a peripheral site are drawn, to ensure that variance of the assay technique and changes in renin secretion affecting any single sample can be identified and discounted [74]. Drawing three sets of blood samples from several sites is technically tedious and expensive, but shortcuts to reduce the number of samples should be avoided. The clinical implications of the RVR levels are major and vagaries of the laboratory assay and of renin secretion are numerous. Although the reported accuracy rates of 85 to 90 percent are impressive, care must be taken to avoid misinterpretation. Verification of the accuracy of renal vein renin results by pharmacoangiography and by drawing a sufficient number of samples to provide internal control are the best available means of documenting the validity of a decision to attempt surgical revascularization or to avoid surgery in individual patients.

In the absence of stenosis of the main renal artery, renal venography for renin

assay should be performed if: (1) stenosis or obstruction is visualized or suspected in the intrarenal arteries on selective renal arteriography; (2) if renal parenchymal abnormalities suggesting infarction, scar, cyst, or tumor are identified by selective arteriography.

Venous samples drawn from the main renal vein often do not identify renin hypersecretion due to localized abnormalities of the arterial tree or parenchyma. Because of streaming within the renal vein or because of duplication of renal vein, samples drawn from the main renal vein may lead to false-negative results. When blood is drawn directly from the vein that drains the affected region, these anatomic sampling errors are avoided [32,74,75].

Arteriography should precede venous sampling so that appropriate sampling sites can be selected. Arterial injection of contrast medium alters renin secretion. Therefore, venous sampling should not be performed on the same day as the arteriogram.

Arteriographic manipulations may also determine the hemodynamic significance of renal artery stenosis. Since collateral circulation does not develop in the absence of a pressure gradient, demonstration of collateral arteries verifies that a stenotic lesion is hemodynamically significant, and a careful search for collaterals should be made in all patients with renal artery stenosis. If they can be identified, the likelihood is high that surgical revascularization will succeed, if technically feasible. But demonstration of collaterals is possible in only a minority of patients with renal vascular hypertension.

Bookstein and co-workers have proposed pharmacoangiographic techniques for increasing the frequency of collateral demonstration and for documentating their hemodynamic significance [76]. These techniques involve selective injections after pharmacologic alteration of the pressure gradient across stenotic renal arteries. Epinephrine induces constriction of peripheral vessels and diminution or obliteration of any pressure gradient that may exist across a stenosis. This results in reduced or reversed flow through collaterals, often permitting opacification of collaterals on selective arteriographic injections. Acetylcholine produces peripheral vasodilatation, augmentation of a pressure gradient if one is present, and increased collateral flow, but reduces the likelihood that collaterals will be opacified in a retrograde direction during selective arteriography.

This method correctly predicted that renal artery stenoses were hemodynamically significant in nine patients, with 100 percent subsequent confirmation [76]. In 11 other cases prediction that stenoses were not hemodynamically significant by pharmacoangiography was also subsequently confirmed.

Although these results represent relatively few cases, they are highly promising. Since the method is without reported complication, it deserves confirmation and perhaps wide application, particularly in patients with bilateral renal artery stenosis and in patients with abdominal aortic coarctation, in whom surgical decisions are most difficult.

Other examinations have been suggested to determine surgical curability once a lesion has been found, including split renal function tests, bilateral renal biopsies, measurement of the pressure gradient across an arterial lesion at surgery, and responsiveness to incremental infusions of angiotensin II. The most useful of these are split renal function tests. Differential renal ischemia can be demonstrated and surgical curability predicted by comparing urine volume and sodium concentration in the urine of the two kidneys. According to Howard [77], the volume of urine flow from an ischemic kidney should be at least 60 percent lower than the volume from a

normal kidney. The volume of urine produced by the kidney depends on the glomerular filtration rate, which is decreased in the presence of renal artery stenosis. The concentration of sodium in the urine depends upon the fractional excretion of sodium and the amount of water reabsorption in the tubules of the kidney. In the presence of renal ischemia, fractional excretion of sodium and water is decreased. Urine osmolality and creatinine concentration are increased. Investigation of volume of urine production and sodium concentration by each kidney requires cystoscopy and bilateral retrograde ureteral catheterization [78,79,80]. The procedure is difficult, unpleasant, and potentially hazardous. Since assay of renal venous blood for renin provides similar information with greater accuracy, and less morbidity, the role of split renal function tests in evaluating patients with renovascular hypertension is minimal.

SURGERY FOR RENOVASCULAR HYPERTENSION

From a successful but relatively unsophisticated beginning, surgical techniques for renovascular hypertension have progressed concomitantly with improvements in diagnostic measures [48]. With proper patient selection, using thorough diagnostic evaluation, sustained improvement in the level of hypertension has been achieved in more than 90 percent of patients following successful surgery [48]. The prime objective or successful renovascular surgery is to preserve renal function while rendering the patient normotensive and eliminating the need for antihypertensive medication. In a number of patients, however, especially those with hypertension of long standing, expectations following successful surgery may need to be tempered with the realization that the patient may still require some smaller amount of medication on a continuing basis.

In most instances, antihypertensive drugs should be continued until the time of surgery, although diuretics should be kept to a minimum to avoid volume depletion. Intravenous fluids are given prior to surgery to insure satisfactory hydration and a urethral catheter is inserted before operation to monitor urinary output and to prevent bladder distention from mannitol-induced diuresis during surgery.

A transperitoneal anterior abdominal incision is used. The renal vessels are usually exposed by colonic reflection together with duodenal mobilization (Kocher's maneuver). In right-sided lesions more extensive dissection and mobilization of the vena cava and right renal vein are necessary to gain access to the origin of the right renal artery.

Autogenous saphenous vein [81,82] or synthetic material, usually dacron [83,84] have been the materials most frequently employed for a bypass graft, although recently the use of autogenous internal iliac artery has been advocated [85]. Saphenous veins are readily available, easy to work with, and usually have a caliber appropriate for an anastomosis to the renal artery. Autogenous veins are less thrombogenic than prosthetic materials and the rate of postoperative occlusion has been reduced to as low as 5 percent [86]. Progressive dilatation of the vein graft after a period of years has been reported in a small number of cases, with some increasing to aneurysmal proportions [87].

Autogenous internal iliac artery bypass is theoretically attractive since the likelihood of subsequent anastomotic stenosis or dilatation is diminished. However, although the internal iliac artery is readily available and may be sacrificed without danger to pelvic organs, obtaining sufficient length may be difficult, and the artery may itself be involved by artherosclerosis. If so, it may be possible to perform

endarterectomy prior to placement of the graft, or to use a piece of external iliac artery, restoring continuity of blood flow to the extremity with a dacron graft [86].

Many vascular surgeons have lost enthusiasm for dacron since a high frequency of thrombosis has been reported with dacron grafts in peripheral arteries. However, dacron grafts may be more effective in the renal artery, since only a short length is needed and since blood flow rate is so much higher than in diseased arteries of the leg. In the presence of a diseased arterial wall, synthetic grafts eliminate the risk of subsequent narrowing of the graft by progression of arterial disease [88].

Severe atherosclerosis or previous surgical procedures occasionally preclude grafting into the aorta. In these cases, the splenic artery [89] for left side lesions or the hepatic artery [90] for right-sided lesions may be used. Hepatic artery bypass requires the juxtaposition of a piece of saphenous vein between the main or right hepatic artery and the right renal artery [90]. Splenic artery bypass of left-sided renal artery stenosis was described as early as 1957 [89].

Endarterectomy of stenoses involving the proximal portion of the renal artery has recently been advocated. Using a transaortic approach, renal artery revascularization can be accomplished with a single maneuver requiring a relatively short period of renal ischemia [85]. Since no autogenous or prosthetic grafts are used, late complications associated with grafts are avoided.

Endarterectomy can also be performed directly through a renal arteriotomy, a technique which avoids cross-clamping the aorta. The renal arteriotomy is frequently closed with a venous patch graft to prevent stenosis at the suture line. This technique may prove difficult when significant disease extends into the aorta, or in elderly patients in whom an extremely thin arterial wall may remain after removal of the plaque.

Localized stenoses in the mid-portion of the renal artery may be resected and closed by end-to-end anastomosis of the renal artery. This technique, which requires careful preparation since the extent of disease may be greater than demonstrated by arteriography, may be facilitated by mobilization of the entire kidney. A variation of this technique is segmental resection and renoaortic re-implantation, used if stenosis is localized at the renal artery origin.

Ex-vivo arterial repair and autotransplantation was described in the early 1960s [91,92]. Widespread application of renal allograft surgery has made generally available the knowledge and experience necessary for renal autotransplantation, but the indications for this procedure in the treatment of renovascular disease are quite limited [93]. With this technique, meticulous microsurgical methods may be used to repair stenoses in vessels too small for repair by more conventional procedures. A prolonged period of renal ischemia is made possible by hypothermia, induced and maintained either by pulsatile perfusion or by simple cold perfusion. Because of hypothermia, the operative field is bloodless, laborious reconstruction can be performed at an appropriate pace, and time is available to check the anatomic results by ex-situ arteriography [94].

Arterial lesions in the upper or lower pole, which are too peripheral for adequate repair, may be treated with partial nephrectomy. After ligation of the diseased segmental artery, the area which it supplies become ischemic and the plane of resection is obviously demarcated. Nephrectomy may be the only possible procedure in the presence of diffused parenchymal disease, fibrous encapsulation of the kidney [95], multiple branch stenoses, or following unsuccessful vascular reconstruction. However, nephrectomy should only be considered as a last resort, since even a totally

occluded renal artery with a completely non-functioning kidney is not necessarily irreparable. Return of renal function following revascularization has been achieved in such cases, provided that the glomerula remain viable, as determined by surgical biopsy and frozen section [93].

The success rates following renovascular surgery depend on multiple factors including the age of the patient, the duration of the hypertension, the presence of bilateral disease, and the technical skill of the surgeon. However, with proper patient selection, sustained improvement in the level of hypertension should be possible in more than 90 percent of patients. Operative mortality rates for this type of surgery range between 3 percent and 8 percent.

REFERENCES

1. Holley KE, Hunt JC, Brown AL, Jr, et al: Renal artery stenosis: A clinical-pathologic study in normotensive and hypertensive patients. Am J Med 37:14–22, 1964
2. Butler A: Chronic pyelonephritis and arterial hypertension. J Clin Invest 16:889–897, 1937
3. Goldblatt H: Studies on experimental hypertension I. The production of persistent systolic blood pressure by means of renal ishemia. J Exp Med 59:347–380, 1934
4. Smith HW: Unilateral nephrectomy in hypertensive disease. J Urol 76:685–701, 1956
5. Sancho J, Re R, Burton J, et al: The role of the renin-angiotensin-aldosterone system in cardiovascular homeostasis in normal human subjects. Circulation 53:400–405, 1976
6. Laragh JH: Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. Am J Med 55:261–274, 1973
7. Dustan HP, Tarazi RC, Bravo EL, et al: Plasma and extracellular fluid volumes in hypertension. Circulation Research supplement 32:1–73, 1973
8. Pals DT, Masucci FD, Denning GS, Jr, et al: Role of pressor action of angiotensin II in experimental hypertension. Circ Res 29:673–681, 1971
9. Brunner HR, Kirshman DJ, Sealey JE, et al: Hypertension of renal origin. Evidence for two different mechanisms. Sci 174:1344–1346, 1971
10. Gavras H, Brunner HR, Vaughan ED, Jr, et al: Angiotensin-sodium interaction in blood pressure maintenance of renal hypertensive and normotensive rats. Sci 180:1341–1369, 1973
11. Garti I, Sirken C, Salinger H: Arterial hypertension and position of the kidneys—an angiographic study. Brit J Radiol 44:682–685, 1971
12. Stanley AC, Gewertz BL, Bove EL, et al: Arterial fibrodysplasia—histopathologic character and current etiologic concepts. Arch Surg 110:561–566, 1975
13. Perry MO: Fibromuscular disease of carotid artery. SG and O 134:57–60, 1972
14. Perry MO: Fibromuscular dysplasia. SG and O 139:97–104, 1974
15. Sheps SG, Kincaid OW, Hunt JC: Serial renal function and angiographic observations in idiopathic fibrous and fibromuscular stenosis of the renal arteries. Am J Card 30:55–60, 1972
16. Stewart BH, Dustin HP, Kiser WS, et al: Correlation of angiography and natural history in evaluation of patients with renal vascular hypertension. J Urol 104:231–238, 1970
17. Tilford DL, Kelch RC: Renal artery stenosis in childhood neurofibromatosis. Am J Dis Child 126:665–668, 1973
18. Mena E, Bookstein JJ, Holt JF, et al: Neurofibromatosis and renal vascular hypertension in children. Am J Roent 118:39–45, 1973
19. Itzchak J, Katznelson D, Borichis H, et al: Angiographic features of arterial lesions in neurofibromatosis. Am J Roent 122:643–647, 1974
20. Schurch W, Messerli FH, Genest J, et al: Arterial hypertension and neurofibromatosis: renal artery stenosis and coarctation of abdominal aorta. Can Med A J 113:879–885, 1975
21. Angell ME, Relman AS, Robbins SL: "Active" chronic pyelonephritis without evidence of bacterial infection. NEJM 278:1303–1308, 1968
22. Hutch JA, Smith DR: Sterile reflux—report of 24 cases. Urol Int 24:460–465, 1969
23. Hodson CJ: The radiological contribution toward the diagnosis of pyelonephritis. Radiology 88:857–871, 1967
24. Castlemam B, Scully RE, McNeely BU: Case records of the Massachusetts General Hospital—case 40—1973. NEJM 289:736–743, 1973
25. Himmelfarb E, Rabinowitz JG, Parvey L, et al: The Ask-Upmark kidney—roentgenographic and pathologic features. Am J Dis Child 129:1440–1444, 1975
26. Johnston JH, Mix LW: The Ask-Upmark kidney: a form of ascending pyelonephritis? Brit J Urol 48:393–398, 1976
27. Goddard C, Vallotton MB, Broyer M: Plasma renin activity in segmental hypoplasia of the kidneys with hypertension. Nephron 11:308–317, 1973

28. Mears EM Jr, Gross DM: Hypertension owing to unilateral renal hypoplasia. J Urol 108:197-200, 1972
29. Bookstein JJ, Walter JF: The role of abdominal radiography in hypertension secondary to renal or adrenal disease. Med Clin N Am 59:169-199, 1975
30. Hollenberg NK, Epstein M, Basch RI: "No-Mans Land" of the renal vascular—an arteriographic and hemodynamic assessment of the interlobar and arcuate arteries in ascentual and excellerated hypertension. Am J Med 47:845-854, 1969
31. Babka JC, Cohen MS, Sode J: Solitary intrarenal cyst causing hypertension. NEJM 291:343-344, 1974
32. Korobkin M, Glickman MG, Schambelan M: Segmental renal vein sampling for renin. Radiology 118:307-313, 1976
33. Marshall WH, Jr, Castellino RA: Hypertension produced by constricting capsular renal lesions ("Page kidneys"). Radiology 111:561-565, 1971
34. Page IH: Production of persistent arterial hypertension by cellophane and perinephritis. JAMA 113:2046-2048, 1939
35. Schambelan M, Howes EL, Jr, Stockigt JR, et al: Role of renin and aldosterone in hypertension due to a renin-secreting tumor. Am J Med 55:86-92, 1973
36. Mitchell JD, Baxter TJ, Blair-West JR, et al: Renin levels in nephroplastoma (Wilm's tumor). Arch Dis Child 45:376-400, 1976
37. Biava CG, West M: Fine structure of normal human juxtaglomerular cells. Am J Path 49:955-961, 1966
38. Lamp WT: Renovascular hypertension: a review of reversible causes due to extrinsic pressure on the renal artery and a report of three unusual cases. Angiology 16:677-689, 1965
39. Blatt E, Page IH: Hypertension and constriction of the renal arteries in man: a report of a case. Ann Int Med 12:690-699, 1939
40. Jennings RC, Shaikh VAR, Allen WMC: Renal ischemia due to thrombosis of renal artery resulting from metastases from primary carcinoma of bronchus. Brit M J 2:1053-1054, 1964
41. Schwartz CJ, White RA: Aneurysms of the renal artery. J Path Bacterial 89:349-356, 1965
42. Stanley JC, Rhodes EL, Gewertz BL, et al: Renal artery aneurysms: significance of macroaneurysms exclusive of the sections and fibrodysplastic mural dilation. Arch Surg 110:1327-1333, 1975
43. Maxwell MH, Bleifer KH, Franklin SS, et al: Demographic analysis of the study. JAMA 220:1195-1204, 1972
44. Simon N, Franklin SS, et al: Clinical characteristics of renovascular hypertension. JAMA 220:1209-1217, 1972
45. Maxwell MH: Cooperative study of renal vascular hypertension. Current Status. Kidney Int 8:153S-160S, 1975
46. Moser M, et al: Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure: A Cooperative Study. JAMA 237:255-261, 1977
47. MacNeil BJ, Vardy PD, Burows BA, et al: Measures of clinical efficacy: Cost effectiveness calculations in the diagnosis and therapy of hypertensive renal vascular disease. NEJM 293:216-221, 1975
48. Franklin SS, Young JD, Jr, Maxwell MH, et al: Operative morbidity and mortality in renal vascular disease. JAMA 231:1148-1153, 1975
49. Eipper DF, Gifford RW, Jr, Stewart BH, et al: Abdominal bruits in renal vascular hypertension. Am J Card 37:48-52, 1976
50. Vander AJ: Control of renin release. Physiol Rev 47:359-382, 1967
51. Davis JO: The control of renal release. Am J Med 55:333-350, 1973
52. Noth RL, Lassman N, Tan SY, et al: Age and the renin-aldosterone system. Arch Int Med 137:1414-1417, 1977
53. Sealey JE, Gerten-Banes J, Laragh JH: The renin system: variations in men measured by radioimmunoassay or bioassay. Kidney Int 1:240-253, 1972
54. Brunner HR, Laragh JH, Baer L, et al: Essential hypertension: renin and aldosterone, heart attack and stroke. NEJM 286:441-449, 1972
55. Stockigt JR, Noakes CA, Collins RD, et al: Renal vein renin in various forms of renal hypertension. Lancet 1:1194-1197, 1972
56. Streeten DHP, Anderson GH, Freibert JM, et al: Use of angiotensin II antagonist (Saralasin) in the recognition of "angiotensin angiotensinogenic" hypertension. NEJM 292:657-662, 1975
57. Marks LS, Maxwell MH, Kaufman JJ: Saralasin bolus test. Lancet 4:784-792, 1975
58. Marks LS, Maxwell MH, Kaufman JJ: Non-renin-mediated renal vascular hypertension: a new syndrome? Lancet 1:615-617, 1977
59. Baer L, Parra-Carrillo JZ, Radichevich I: Detection of renovascular hypertension with angiotensin II blockade. Ann Int Med 86:257-260, 1977
60. Farmelant MH, Burrows BA: The renogram: physiological basis and current clinical use. Sem Nucl Med 4:61-73, 1974
61. Rosenthall L: Radiotechnetium renography and serial radiohippurate imaging for screening renovascular hypertension. Sem Nucl Med 4:97-116, 1974
62. Farmelant MH, Lipetz CA, Bikerman V, et al: Radioisotopic renal function studies and surgical findings in 102 hypertensive patients. Am J Surg 107:1535-1605, 1964

63. Maxwell MH, Hayes M: The renogram in hypertension, Progress in Nuclear Medicine. Edited by MD Blaufox. Vol 2. Baltimore, University Park Press, 1972
64. Blaufox MD, Bell EG: Radiorenography, Diagnostic Nuclear Medicine. Edited by A Gottschalk, EF Potchen. Baltimore, Williams and Wilkins, 1976
65. Arnold RW, Subramanian G, Mcafee GG, et al: Comparison of Tc^{99m}-complexes for renal imaging. J Nucl Med 16:357-367, 1975
66. Rosenthall L: Radiopertechnetate renography with the gamma ray scintillation camera. Can Med A J 105:467-472, 1972
67. Adam WE, Kadatz R, Bitter F, et al: Investigations in kidney perfusion tests with radioactive substances, Radionuclides in Nephrology. Edited by MD Blaufox, JL Funck-brentano. New York, Grune and Stratton, 1972
68. Koenigsberg N, Novich I, Lory N, et al: Detection of asymmetrical renal perfusion by radiopertechnetate angiography. J Nucl Med 15:507, 1974
69. Bookstein JJ, Abrams HL, Buenger RE, et al: Radiologic aspects of renovascular hypertension: II—The role of urography in unilateral renovascular disease. JAMA 220:1225-1230, 1972
70. Marks LS, Maxwell MH, Varidy PD, et al: Renovascular hypertension: does the renal vein renin ratio predict operative results? J Urol 115:365-368, 1976
71. Horvath JS, Baxter CR, Sherbon K, et al: An analysis of errors found in renal vein sampling for plasma renin activity. Kidney Int 11:136-138, 1977
72. Strong CG, Hunt JC, Sheps SG, et al: Renal venous renin activity: enhancement of sensitivity of lateralization by sodium depletion. Am J Card 27:602-611, 1971
73. Maxwell MH, Marks LS, Varady PB, et al: Renal vein renin in essential hypertension. J Lab & Clin Med 86:901-908, 1975
74. Harrington DP, Whelton PK, Russell RP, et al: Renal venous renin sampling: a prospective study of techniques and methods. Presented at the Radiological Society of North America, Chicago, Illinois, 1976
75. Schambelan M, Glickman MG, Stockigt JR, et al: Selective renal vein sampling and hypertensive patients with central renal lesions. NEJM 290:1153-1157, 1974
76. Bookstein JJ, Walter JF, Stanley JC, et al: Pharmacoangiographic manipulation of renal collateral blood flow. Circ 53:328-334, 1976
77. Howard JE, Connor TB: Use of differential renal function studies in the diagnosis of renovascular hypertension. Am J Surg 107:58-66, 1964
78. Rapoport A: Modification of the "Howard Test" for the detection of renal artery obstruction. NEJM 263:159-160, 1960
79. Birchall R, Batson HM, Brannan W: Contribution of differential renal studies to the diagnosis of renal arterial hypertension with emphasis on the values of U sodium—U creatinine. Am J Med 32:164-169, 1962
80. Stamey JA: Renovascular hypertension. Baltimore, Maryland, Williams & Wilkins Co, 1963
81. Ernst CB, Stanley JC, Marshall FF, et al: Autogenous saphenous vein aortorenal grafts. Arch Surg 105:855-864, 1972
82. Straffon R, Siegel DF: Saphenous vein bypass graft in the treatment of renovascular hypertension. Urol Clin N Am 2:337-350, 1975
83. Kaufman JJ: Long term results of aortorenal dacron grafts in the treatment of renal artery stenosis. J Urol 111:298-304, 1974
84. Kaufman JJ, Maxwell MH, Maloney PJ: Synthetic bypass grafts in the treatment of renal artery stenosis. Surg Gynecol & Obnst 126:53-60, 1968
85. Wylie EJ: Endarterectomy and otogenous arterial grafts in the surgical management of stenosing lesions of the renal artery. Urol Clin N Am 2:351-363, 1975
86. Dean RH, Wilson JP, Burko H: Saphenous vein aortorenal bypass grafts: Serial arteriographic study. An Surg 180:469-478, 1974
87. Veith FJ, Yao JST, Dean RH, et al: Treating renovascular hypertension surgically. Cont Surg 9:13, 1976
88. Kaufman JJ: Dacron grafts and spleno-renal bypass in the surgical treatment of stenosing lesions of the renal artery. Urol Clin N Am 2:365-380, 1975
89. DeCamp PT, Snyder CH, Bost RB: Severe hypertension due to congenital stenosis of artery to solitary kidney: Correction by spleno-renal anastomosis. Arch Surg 75:1023-1026, 1957
90. Libertino JA, Zinman L, Breslin DJ, et al: Hepatorenal artery bypass and the management of renovascular hypertension. J Urol 115:369-372, 1976
91. Woodruff MFA, Doig A, Donald KW, et al: Renal autotransplantation. Lancet 1:433, 1966
92. Ota K, Mori S, Awane Y, et al: Ex-situ repair of renal artery for renovascular hypertension. Arch Surg 94:370-373, 1967
93. Lytton B, Stewart B: Extracorporeal surgery. Transplantation Proceedings 9:1263-1266, 1977
94. Sachs SA: Renal autotransplantation and ex-vivo renal surgery. Urol Clin N Am 2:381-400, 1977
95. Grim CE, Mullins MF, Nilson JP, et al: Unilateral "page kidney" hypertension in man: Studies of the renin, angiotensin aldosterone system before and after nephrectomy. JAMA 231:42-46, 1975