Diagnosis and Treatment of Renal Hypertension of Humoral Origin

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THE PARTICIPATION of the kidney in the production of hypertension by the production of a humoral pressor agent was suspected as long ago as the latter part of the nineteenth century.[1] In 1925, Fahr suggested that renal ischemia might be a cause of hypertension in patients with diffuse vascular disease.[2] In 1929, Ask-Upmark [3] reported that a unilateral renal lesion might be associated with hypertension in young children. Goldblatt, in 1934, reported on the production of "Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia." [4] The cure of hypertension by removal of a single damaged kidney emphasized the clinical importance of this concept.[5]

It is the purpose of this paper to summarize current concepts of the pathophysiology, diagnosis and treatment of renal hypertension of humoral origin in man. This will be done by supporting the most likely and currently acceptable view and without referring to the vast amount of work, some of it controversal, interspersed between the classic discovery of Goldblatt and its present relation to the cure of renal hypertension in man.

Some theories of the origin of renal hypertension are summarized in figure 1. At the present time, the evidence is incontrovertible that the ischemic kidney produces a pressor agent which participates in hypertension. The best evidence favors the following hypothesis:

The ultimate source of the pressor substance is in granular cells of the walls of the afferent arteriole of the glomerulus. This cell is known as the juxtaglomerular cell, or *JG cell*. Its position in the wall of the afferent arteriole lends credence to the suggestion that it may actually act as a "stretch receptor." In this connotation, a decrease in pressure (or stretch) within the lumen of the afferent arteriole, would be perceived by the receptor which would respond by secreting a pressor substance in an attempt to correct this situation. The evidence is good that when perfusion pressure is decreased in the kidney by narrowing or clipping one renal artery, the granularity of the JG cells doubles, while perfusion under increased pressure decreases the granularity. Thus, increased granularity should be associated with an increased production of pressor substance. Considerable evidence is available which suggests that production of the precursor of this pressor substance is indeed coincident with the increase in granularity of the juxtaglomerular cells. This substance (renin) was described by Goldblatt. Its present role can be characterized as follows:

Ischemia of the kidney results in increased amounts of renin appearing in renal venous blood. Renin combines with a globulin called angiotensinogen, to produce a material called angiotensin I. Angiotensin I is a decapeptide (containing 10 amino acids). On combination with a second enzyme (converting enzyme) the physiologically potent angiotensin II (an octopepetide) is produced. Angiotensin II is an extremely potent pressor agent whose effect is characterized by direct stimulation of the smooth muscle of the vascular system. Its injection mimics in many ways the physiologic manifestations of human hypertension.

The kidney has also been thought to play a role in preventing hypertension either by metabolizing or by excreting a pressor substance. The ischemic or damaged kidney would be unable to adequately perform this function, and failure to dispose of the pressor substance would result in hypertension. Much of the thinking on this subject has been derived from

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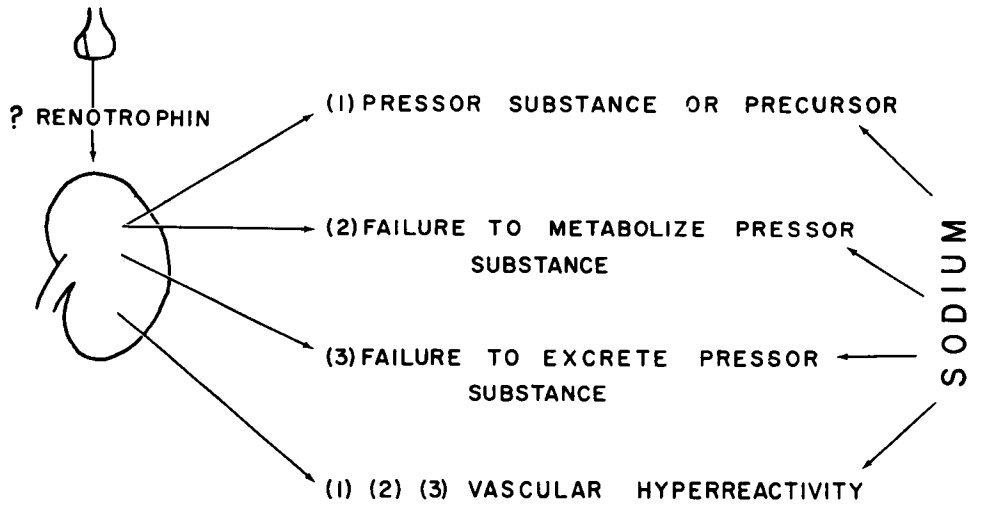

FIG. 1. Role of the kidney in renal hypertension.

animal experiments, but in animal experiments a vast species difference exists. For instance, in the dog, upon constriction of one renal artery, hypertension will result only if the contralateral kidney is removed. Thus the contralateral or normal kidney might be thought to have a depressor role which is eliminated. This is not true in the rat. In the dog, hypertension has been produced by bilateral nephrectomy thereby lending credence to the idea that a depressor regulatory function of the kidney is important. However, these results have been criticized in that changes in the volume of extracellular fluid were not adequately controlled in the nephrectomized animals and that overhydration might have contributed to the results. In man, the evidence is clear that normotensive patients or patients with mild hypertension do not develop severe hypertension when totally deprived of renal tissue, unless they are overhydrated.[6] In a recently observed patient with malignant hypertension, who was maintained by periodic dialyses on the artificial kidney, bilateral nephrectomy produced a slow drop in blood pressure and improvement in vascular disease which was correlated with a negative sodium balance and a decrease in blood volume. There is evidence, also, that the renal role in hypertension may be, at least in part, owing to increased vascular hyper-reactivity to normally occurring pressor substances.[7, 8]

A somewhat different and less precisely investigated hypothesis of the origin of renal hypertension has been presented by Braun-Menendez.[9] Braun-Menendez suggests that under normal conditions the size of the kidney and its functional capacity are regulated by concentration in the blood of a substance "renotrophin" which is probably some by-product of protein metabolism. The rate of production of renotrophin increases under the influence of hormones of the pituitary gland, the thyroid, and the male gonads as well as in animals fed a protein-rich diet. Under normal conditions, an increase in the rate of production of renotrophin causes renal hypertrophy and hyperfunction, a decrease leading to renal atrophy and hypofunction. Unilateral nephrectomy, thus, would cause a transitory rise in the blood level of renotrophin until a new equilibrium was reached, due to the growth in size and function of the contralateral kidney. For some reason, however, when the kidney is unable to respond to renotrophin with an increase in size and function, because its growth is impeded by mechanical or pathologic hinderances (such as a clamp on the renal artery or interstitial fibrosis due to pyelonephritis), hypertension develops. A somewhat similar hypothesis has been proposed [10] suggesting that a given ratio between renal mass and renal blood flow is necessary in order to avoid the production of renin. Thus an in-

crease in this ratio could take place either by decrease in renal flow with unchanged mass or an increase in renal mass without corresponding increase in renal blood flow. Both of these conditions might lead to hypertension. Evidence for this hypothesis is adduced from the fact that five of ten dogs made hypertensive by the application of a Goldblatt clamp to the renal artery became normotensive following removal of approximately one fourth of the constricted kidney; the inference being that the disproportion between decreased renal blood flow (created by the clamp) and normal mass, was corrected by decreasing the normal mass.

Almost universally in experiments supporting the hypotheses listed above, increased sodium intake increases the pressor response and vice versa. This is of considerable importance in view of the evidence that the hormones of the adrenal cortex, particularly the salt-retaining hormones, increase the sensitivity of the vasculature to pressor stimuli. The adrenal cortex and medulla have received their share of attention in the etiology of hypertension in man. We may note the participation of the adrenal medulla in the hypertension caused by pheochromocytoma. Hypertension also occurs in glucocorticoid-secreting adrenal tumors (Cushing's disease). Of extreme importance is the fact that tumors of the adrenal cortex or hyperplasia thereof, resulting in an increased secretion of the mineralocorticoid aldosterone, are also associated with hypertension in man. The inter-relation of the kidney and adrenal in this regard is stressed by animal experiments showing that the presence of adrenal glandular tissue is essential for the development of both renal and reno-prival hypertension,[11] as well as the exciting new developments demonstrating that angiotensin is a potent (if not the only) stimulator of aldosterone secretion.

The foregoing discussion provides a background for proceeding to the discussion of the incidence, diagnosis and treatment of renal hypertension in man. Before doing so, however, previous evidence to the contrary notwithstanding, we should make clear that renal hypertension differs only quantitatively from so-called "essential hypertension." Hypertension of proven renal origin may be mild, may be labile, may decrease with sedation, may be treatable by medical methods, may be nonprogressive, and may not be associated with vascular disease. Indeed, there are a number of writers who believe that all significant elevations of blood pressure may be associated with some degree of renal involvement. This may well be the case.

Clinical Manifestations

For the purposes of the present discussion we will concentrate on renal hypertension which may be surgically remediable. In its most classical form, this situation is represented in man by partial obstruction of one renal artery in an individual with previously normal blood pressure and normal kidneys. As in so many situations in medicine, the classical picture is frequently not present and, indeed, patients with known lesions of the renal vasculature may be normotensive. Typically, however, such individuals would fall in an age group which would not be expected to have "essential hypertension," *i.e.*, below the age of 30 and above the age of 55. The onset may be sudden and may be related to the passage of a stone, to trauma, or to infection. Hypertension is severe with high persistent diastolic pressure, marked symptomatic difficulty and changes in the retinal vasculature. Leukocytosis and polyuria have been mentioned and are occasionally present. Bruits may be heard over the anterior abdomen or the flanks, frequently continuous and with a systolic accentuation. Such bruits are the understandable consequence of narrowing of the lumen of the renal artery or aorta by either intrinsic or extrinsic pressure.[12] However, it should be remembered that of a series of 50 patients with hypertensive disease who had upper abdominal murmurs, only 66 per cent had renal arterial disease established by lumbar aortography and that not every abdominal murmur signifies renal arterial disease.

An occasional patient with elevated blood pressure of renal origin may show a marked drop in pressure in the upright position. Similarly, patients with renal hypertension may show a rise in diastolic blood pressure when ganglionic blocking agents are administered in the supine position. These observations are of more than academic interest since we and

others have demonstrated an increased sensitivity of the vasculature to the pressor effects of epinephrine and norepinephrine in patients with renal hypertension. It has been well known for some time that patients with renal failure may exhibit a "false positive response to Regitine." This false positive test may simply be the unmasking of the vasomotor response to endogenous norepinephrine. Similarly, a rise in blood pressure in the supine position might occur in ganglionic blockade which is known to accentuate the sensitivity of the vasculature to norepinephrine. In the upright position, however, this might not obtain since chronic stimulation of vasopressor nerves might produce a higher threshold for response to such acute changes as assumption of the upright posture.

A number of recent procedures have added to our diagnostic armamentarium. Several of these are based upon an important phenomenon first described by Mueller and his colleagues in 1951 [14] and elaborated by Berliner and Davidson in 1957.[15] Briefly, it has been pointed out that if constriction of a renal artery is accomplished by clamping there occurs with small decreases of filtration rate (and occasionally even in the absence of measurable decrease), a decrease in the volume of urine elaborated from the clamped kidney, an increase in the total concentration (osmolality) and a decrease in the sodium concentration. This may occur even under conditions of a water diuresis and in the total absence of antidiuretic hormone. The hemodynamic factors responsible for this have been described in detail.[15] Thus, impairment in arterial inflow to one kidney frequently results in a decreased volume of urine, an increased osmolality and a decreased sodium concentration on the affected side, when compared with the contralateral organ. Measurements of urine obtained by catheterizing both ureters may thus be compared in these parameters. This test familiarly known as the "Howard test" was described by Howard and his colleagues,[16] later elaborated by Connor and Howard.[17] As they described the test, a 50 per cent reduction in urine volume from one kidney and a 15 per cent or more reduction in sodium concentration constituted a positive result which correlated well with relief of hypertension following surgical procedures on that side. The test has been refined by others [18, 19] who have pointed out that errors in volume measurement due to leakage around the catheters may be minimized by comparing the ratio of sodium concentration to creatinine concentration on the two sides. It should be pointed out that the test should be performed under conditions of adequate hydration and adequate sodium intake to increase the differences in these parameters between the affected and normal side. The infusion of mannitol, an osmotic diuretic, causes increase in sodium concentration and volume and decrease in osmolality of the urine even when constriction of the renal artery is present. Thus, a decrease in the discrepancy between the two kidneys following the infusion of mannitol is further evidence of impairment of arterial inflow on the affected side. Although opinions differ as to the quantitative correlation of this test with the surgical relief of hypertension, when correctly done it appears to be of extreme value. In one series, six of seven patients with surgically proven renal arterial insufficiency showed at least a 75 per cent reduction in $U_{Na}/U_{Creatinine}$.[18] A number of observers have pointed out that the infusion of an intravenous sodium load will actually be excreted with greater facility by the "hypertensive kidney." Since the kidney with renal arterial insufficiency is a hypotensive kidney and its contralateral mate exposed to the effects of systemic hypertension, the hypertensive kidney, it would be expected that the latter would excrete a sodium load with greater facility, thus accentuating the difference between the two.

On the other hand, it is also possible for a pyelonephritic kidney with generalized destruction of renal parenchyma and vascular disease to contribute to the hypertensive process. A kidney generally damaged in this fashion may show an increased concentration of sodium.[20] These differences must be considered in evaluating the "Howard test" and describe in a general way the difference between a kidney contributing to hypertension by reason of renal arterial insufficiency and diffuse pyelonephritis. Involvement of a segmental artery markedly affecting one portion of the kidney and not the other, may result in urinary findings which differ from those of

obstruction of a main branch, in that the former may more closely resemble the results of general decrease in functioning renal parenchyma such as occurs in diffuse pyelonephritis.

Preliminary screening studies, of course, should include an intravenous pyelogram. Here, difference in appearance time of dye, difference in concentration on the two sides, and a difference in size of 1 cm. may be suggestive. It should be remembered, however, that for the same reason that the urine is concentrated on the affected side in the "Howard test," the dye may be more concentrated on the bad side in the intravenous pyelogram, particularly if the patient has not been properly dehydrated for the test.

The normal kidney takes up, concentrates and excretes organic iodides such as Diodrast and Hippuran. By labeling these substances with radioactive material it is possible to place counters over the renal area and quantitate the uptake, concentration and excretion of these substances by the two kidneys, thus comparing their function in this regard. The position of the two kidneys must be determined by roentgen-ray films for accurate placing of the counters. Slow uptake, good concentration and poor secretion on one side compared to these same functions on the other, may suggest renal arterial disease.[21] Poor uptake and concentration may reflect pyelonephritis or decreased amount of functioning parenchyma. The first-named phenomenon may be abolished by the infusion of mannitol even as it is in the "Howard test," thus corroborating renal arterial insufficiency. This test is a valuable adjuvant as a screening test. It has the value, in addition, of being a nontraumatic test.

Direct visualization of the architecture of the renal arterial tree may be accomplished by aortography or selective renal arteriography. Dye may be injected either by the translumbar approach and insertion of a needle into the aorta opposite the mouths of the renal arteries or by passing a catheter to the renal arterial ostia by way of the femoral vessels. This procedure takes a good deal of skill and experience and is not without hazard. In the proper hands, however, it may give direct evidence of renal arterial insufficiency. It must be kept in mind that injections of large amounts of radiopaque dye directly into the renal artery may impair glomerular filtration rate and renal plasma flow for a number of days. Therefore, functional tests should not follow closely upon a renal arteriogram. The most direct evidence of renal arterial insufficiency which may be obtained is, of course, measurement of a pressure drop across an area of suspected constriction. When the evidence is adequate to justify exploration, the pressure gradient on the affected side must be measured. It has been said that a pressure drop of 50 to 60 mm. of mercury should obtain across a suspected obstruction in order for correction of this obstruction to correlate well with improvement of hypertension. Similarly, although such study must necessarily be retrospective, biopsy of the affected kidney with a demonstration of increased "JG" count has been well correlated with relief of hypertension by surgery.[22]

Although it adds considerably to the magnitude of the diagnostic procedures, a good argument can be made for biopsy of the contralateral "normal kidney." It is quite possible that prolonged hypertension may have affected the unobstructed side causing intrarenal vascular disease here. The hypertension, therefore, may now be perpetuated by the kidney without obstruction of the renal artery, and knowledge of the status of the smaller vessels in this kidney would be of value. In the rat, renal hypertension of long duration produced by clamping the right kidney may lead to irreversible changes in the left kidney. Hypertension can only be improved in this animal preparation if the right kidney is unclamped and the left kidney removed. The parallel to the clinical problem in man has been recently clearly demonstrated in a patient in whom hypertension of at least seven years' duration due to coarctation of the right renal artery, was treated by reconstruction of the abnormal artery and restoration of blood flow to the coarcted kidney. Renal biopsies revealed normal microscopic architecture in the right kidney and advanced hypertensive pathology in the opposite kidney. After eight months' observation of persistent moderate hypertension the left kidney was removed with prompt return of blood pressure to normal levels during the subsequent two and one-half years.[23]

TABLE 1. Surgical Treatment of Hypertension Due to Renal Vascular Lesions*

Operations	Number of Patients		
	1950–1959	1960	Total
Nephrectomy	46	6	52
Segmental nephrectomy	7	2	9
Resection of renal artery	11	12	23
Splenorenal anastomosis	11	2	13
Aortic-renal graft	8	3	11
Endarterectomy	3	9	12
Excision aneurysm	2	0	2
Dilation	3	1	4
TOTAL	91	35	126

Data from: Poutasse, E. F.: Diagnosis and treatment of occlusive renal artery disease and hypertension, J. A. M. A. 178:1078, 1961.

Since we have pointed out that renal hypertension is due to a humoral mechanism, it seems obvious that any diagnostic approach should include a search for a humoral pressor substance. Unfortunately, in man it is not possible to demonstrate a pressor substance in the circulating blood in chronic hypertension. Of interest, however, is the recent observation of Hickler [24] that angiotensinase, a substance which causes the destruction of angiotensin, is increased in the peripheral blood of patients with hypertension of renal vascular origin. It might be thought, therefore, that an increased release of angiotensin sets into motion a feedback mechanism by which the angiotensin is destroyed and thus angiotensinase activity increased. This might account both for the finding of lack of angiotensin in the peripheral blood as well as increased angiotensinase activity. Recently it has been demonstrated that if one checks for pressor activity closer to the source of production, (*i.e.*, in the renal vein by way of transfemoral catheterization) that increased pressor activity of serum obtained in this manner is well correlated with renal vascular hypertension. This last technique, as yet incompletely explored, holds great promise.

Six distinct pathologic groups of occlusive lesions have been described.[25] The most common is the atherosclerotic plaque with or without thrombosis. Second is segmental mural fibrosis; third, idiopathic thrombosis; fourth, muscular and fibromuscular hyperplasia, occurring chiefly in young patients and consisting of symmetrical focal constrictions; fifth, intimal sclerosis due to excessive infolding of the internal elastic lamina from a thin layer of fibrosis involving the overlying endothelium; and sixth, dissecting aneurysm. Recently, arteriovenous fistulas of the kidney have been added as a cause for renal hypertension.[26] Multiple renal arteries, alone, apparently do not result in an increased incidence of hypertension.[27] Some idea of the incidence of the relation of unilateral renal disease may be obtained from the study of Barrie.[28] In 5,000 consecutive necropsies there were 106 cases of unilateral renal atrophy. Of the 11 cases in which such atrophy was due to stenosis of the renal artery "malignant hypertension" was present in six and severe essential hypertension in five. Of all the cases of "malignant hypertension" in the 5,000 necropsies, one in six was associated with unilateral renal atrophy. The incidence of hypertension in renal atrophy due to stenosis of main vessels was strikingly higher than that in which the renal atrophy was due to chronic pyelonephritis or obstruction of the urinary tract. This is in keeping with the clinical observations.

In consideration of therapy it must be remembered that not all unilateral renal disease, even renal vascular disease, is associated with hypertension. As has been pointed out initially, even where the affected kidney appears to be directly related to the hypertension, the level of blood pressure and the degree of hypertensive vascular disease may not be severe enough to warrant surgical therapy. Such individuals may respond to medical treatment or may warrant no treatment at all.

Table 1 lists the types of surgical therapy currently used. The type of therapy obviously depends upon the nature of the lesion found preoperatively and intraoperatively. Nephrectomy once was the operation of choice but is now reserved for situations (1) in which repair of the artery is not technically feasible, (2) where the patient's condition does not permit an operation more elaborate than nephrectomy, or (3) when the kidney has undergone advanced atrophy or shows involvement of its arterial branches by sclerosis. Surgical technique has advanced to the point where hypertension due to bilateral stenosis of the renal

arteries has been successfully treated by homografting both renal arteries.[29] Indeed, even when renal arterial stenosis has progressed to azotemia, it is possible to improve renal function by appropriate bypass procedures or grafts.[30]

The results of surgery for reno-vascular hypertension vary from clinic to clinic. A most recent study reports that of 23 hypertensive patients selected on the basis of tests described above, nine patients were classified as cured, six as improved, and six as unimproved. Two patients died after operation.[31] These figures agree with ours and those of other clinics in suggesting that about 65 per cent of patients selected for renal vascular surgery are improved by operative treatment, when the criteria mentioned above are employed in the classification of results. Our experience, like that of Baker and his colleagues,[31] suggests that each of the studies listed above, when properly carried out, is important in the evaluation of patients to be selected for surgery. We agree also that the "Howard test" when properly done is of real value in determining which patients should be operated upon and those most likely to be improved by surgery.

Hypertension of renal etiology can be, and is, controlled by appropriate medical therapy where surgery is not necessary or feasible. It should be remembered also that cases in which only partial improvement has been obtained by surgical procedures appear to be more responsive to medical therapy following operation. Where overall renal function is normal the treatment of renal hypertension does not differ from so-called essential hypertension. Where renal function is impaired, however, the use of ganglionic blocking agents has not been successful. In our hands, a combination of reserpine, dibenzyline and the more recently marketed agent alpha-methyldopa (Aldomet) has been extremely useful in the management of such patients. Some patients appear to respond extremely well to these agents, others poorly. There appears to be little middle ground. Where congestive heart failure and coronary insufficiency are not factors, the use of hydralazine (Apresoline), which increases cardiac output and possibly renal blood flow, may be of value. Salt restriction as a part of the treatment of hypertension in patients with renal failure may be hazardous. Such individuals cannot retain sodium when they are deprived of salt; increasing azotemia may result. Emergency treatment of hypertensive crises due to renal disease should be the intramuscular administration of large doses of reserpine, (2 to 5 mg. every six hours) until an appropriate blood pressure response is obtained. This may be supplemented with intramuscular protoveratrine. Occasionally such patients may respond dramatically to intravenous Regitine (phentolamine). Striking results in hypertensive crises have recently been reported following intravenous infusion of Mutabase. This drug increases cardiac output and decreases peripheral resistance. For reasons as yet unknown, its oral use or long-term use is contraindicated because of the production of diabetes mellitus. This does not appear to be a problem in the acute treatment of acute hypertensive crises.

Summary

Advances in the knowledge of the pathophysiology of renal hypertension have led to improved accuracy in diagnosis. Newer surgical techniques and types of medical therapy have vastly improved the outlook for the patient with renal hypertension. A summary of these advances and their meaning for the patient and physician is outlined above.

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