Hypertension as Related to Renal Ischemia

The George E. Brown Memorial Lecture

By John Eager Howard, M.D.

IT WAS a most unexpected pleasure to receive your invitation to join the distinguished group of men who have previously honored Dr. George E. Brown in this lecture-ship. From a review of Dr. Brown’s extensive bibliography and some of the obituary editorials following his death, it seems clear why Dr. Woodyatt described him as “an unusual man with an unusual story.” Dr. Brown made himself highly expert in what was then known of renal physiology and the heinous effects of high blood pressure. But it was pure chance, as you will see, that led to your speaker’s interest in a curable type of hypertension. In so enigmatic a disorder it behooves us to study with great care those few types that are subject to permanent correction.

At this time and before such an audience, there is no need to belabor the point that ischemia of a kidney can, in man, result in high blood pressure. There are many well-documented instances of such occurrence, with complete and lasting restoration to normotension following nephrectomy or plastic vascular surgery, which is after all the only proof that renal ischemia was causative. But how does one discern with precision the presence of such surgically correctable situations and hence benefit the few without subjecting many to needless and unrewarding operations? How ischemic must a kidney be to result in hypertension? How long can such a kidney remain ischemic and still be susceptible to functional recovery, in the sense that normotension would follow if plastic surgery could reinstitute a normal blood supply? And, lastly, by what mechanisms does an ischemic kidney induce hypertension? These are some of the unresolved questions to which I should like to give attention, sharing with you some observations and speculations directed toward the answers.

Perhaps perspective will be provided for the remarks to follow by a brief historical résumé of the development of our knowledge pertaining to renal ischemia. Though Janeway in 1909 observed that hypertension followed experimental narrowing of the lumen of a renal artery in the dog, credit for the great interest in the subject rightly falls to the classic and exhaustive experiments of Goldblatt. It was not long after Dr. Goldblatt’s first reports that Butler induced his surgical colleagues to remove a pyelonephritic kidney from each of two hypertensive children, with prompt restoration of normotension. There followed a wild flurry of nephrectomies; operations were performed on hypertensive patients who had the slightest evidence of anatomic aberration of one kidney. Even in the carefully controlled groups, less than one third of the patients were benefited by any lowering of their blood pressure. The procedure came into disrepute, to such an extent that a prominent renal physiologist stated flatly that nephrectomy should never be carried out for purposes of benefiting hypertension.

It was about 1950, coincident with the advent of new methods for detection of renal ischemia, that such gloomy dogmatic statements came to be re-evaluated; and surgical attack on ischemic kidneys began to result in a far higher rate of success in alleviating hypertension. These tests included (1) differential renal function studies whereby one deranged kidney may be compared with a presumed normal

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* The term ischemia is meant to denote an arterial blood flow less than optimal for the carrying out of normal metabolic function by renal parenchymal cells.
partner; (2) aortography with visualization of the renal arterial trees; (3) renal scanning with radioisotope-tagged materials for which renal parenchymal cells have especial avidity. Before discussing these procedures, we might revert to how we became convinced that renal ischemia in man and hypertension really are cause-and-effect phenomena.

In 1936, through a series of human errors, a kidney was fortunately removed from a patient, with resulting disappearance of a recently developed malignant hypertension. Following excision of a normal appendix for right-sided abdominal pain, a young man became abruptly hypertensive and his condition proceeded relentlessly to the malignant phase. Perirenal air injection was believed to disclose an adrenal medullary tumor, which proved mythical on exploration. Both sides were explored simultaneously, as was customary in those days. On the other side, a tired intern permitted a retractor to slip; the exposed kidney was removed on the false assumption that a yellowish mass was cancerous. This proved on pathologic examination to be an infarction, and the patient got well.11, 12 Some 15 years later, a physician was seen with so identical a story that his right kidney was removed, despite normal intravenous pyelogram. A similar infarct was found, again with cure of the malignant hypertension.12

Dr. Morgan Berthrong, now of Colorado Springs, pursued the problem of why these two individuals had hypertension when so many infarcted kidneys are found at autopsy with no antecedent history of hypertension. A zone of atrophic but still viable tissue around the necrotic area seemed to distinguish these patients from the nonhypertensive group; such atrophy of renal parenchyma came to be the hallmark in the recognition by the pathologist of renal ischemia causing hypertension.13 Coincidently Priscilla Kincaid-Smith, in an exhaustive autopsy study of patients with pyelonephritis, likewise concluded that atrophic areas of renal parenchyma, indicating ischemic zones, permitted her to predict accurately those patients who in life had hypertension and those who did not.13 I should hurry to say, however, that, as with Goldblatt’s animals, we have, in our own series, kidneys in which the pathologists can find no evidence of ischemic atrophy; and yet there were clear-cut anatomic renal artery stenosis and functional signs of ischemia; the kidneys are out and the patients are well. The conclusion seems justified that though atrophy is indicative of ischemia, there may be reduced arterial flow, producing hypertension, which the histopathologist cannot detect by current methods.

Diagnosis

A discussion of methods and reasoning used to reach the conclusion before operation that a given kidney is responsible for the existing hypertension could easily take the time of several lectures. Let us confine ourselves to a few brief highlights and press on to matters more theoretically interesting and intellectually stimulating.

First, it seems clear from the work of Berthrong on infarctions and Kincaid-Smith on pyelonephritis, that it is reduced arterial flow to renal parenchyma that results in hypertension. Dead kidney tissue does not do this. One sees not infrequently a tiny kidney in a normoten- sive person. Ischemic infarctions, unless surrounded by zones of atrophic (or “physiologically” atrophic) tissue do not cause hypertension. And let me reiterate that before reaching the conclusion that a kidney was responsible in a given case of hypertension, nephrectomy or arterial surgery must result in normotension before that kidney is proved guilty.

Studies of Differential Renal Function

Properly carried out, study of urine derived simultaneously from each kidney yields very precise information when the main renal artery of one kidney is sufficiently stenosed to induce hypertension. The involved kidney produces less urine, and in that urine the concentration of sodium and chloride is lower and the concentration of creatinine (or other substance used as an index of filtration rate) is higher than in urine from the other side.12, 14 In clinical cases we have not seen this rule broken, and the experimental work of White15 (on which the clinical work was based) and that

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of Berliner and Davidson are in complete agreement with this thesis. In our opinion, it is wiser not to use osmotic diuresis during such tests, because this tends to diminish the difference in the urinary pattern from the two sides.\textsuperscript{14} But interpretation of the test becomes more complex when one is dealing with a kidney of which only a segment is ischemic, or with a pyelonephritic kidney (which induces hypertension, we believe, by multiple small focal ischemic areas). Especially is this true in the latter, where so frequently there is bilateral disease. One must recall that a whole kidney may be so ischemic that no urine is produced by it, yet hypertension results; hence a segment of a kidney could be similarly afflicted and induce hypertension. Under such circumstances, one would expect to find urines of identical quality on the two sides, only a lesser quantity from the affected kidney; we have examples of just such instances with cure after heminephrectomy.\textsuperscript{*} There are, however, also two well-documented instances of focal ischemia in which there was identical urine quantitatively and qualitatively from the two sides, and wherein other indications led to nephrectomy with complete cure.\textsuperscript{18} The only plausible explanation offered is that there had been hypertrophy of the uninvolved portion of these segmentally ischemic kidneys. Interpretation of the split function tests must be approached with caution also in the cases with pyelonephritis. The well-known propensity of the pyelonephritic kidney to "waste" sodium and chloride might readily obscure the effect of ischemia to resorb and thus conserve sodium and chloride. It is with kidneys that are ischemic only in part, and in hypertensive patients suffering from pyelonephritis, that we have found the simultaneous catheter studies most difficult to evaluate.\textsuperscript{14, 19} Usually, however, assessment of other factors will lead one to the proper conclusion, though at times it may be the very devil of a job to make up one's mind to advise or not to advise surgery.

But I promised not to belabor minor points in diagnostic methods. Disadvantages of the catheter studies are as follows: unpleasantness to the patient; requirement of a high degree of technical excellence, with consumption of considerable time by an expert urologist; danger of infection; and the interpretative difficulties mentioned above when segmental ischemia or pyelonephritis is the offending lesion. Ever present, too, is the problem that the kidney not under suspicion may also have a vascular lesion of one sort or another. Biopsy will frequently not provide helpful information.

Aortography

Aortography has been an enormous boon. To visualize an exact site of arterial stenosis lends confidence but, more especially, often permits preoperative decision that plastic arterial surgery will be possible, with preservation of the kidney. And it may give warning of previously unsuspected bilateral disease.\textsuperscript{20} Interpretation of renal arteriography can be a tricky business, even among experts. We have observed with amazement findings in arteries by the pathologists that were totally unexpected by our radiologic colleagues. Furthermore, it is obvious that the most perfect radiography can tell us only anatomic facts and nothing of the functional status. There have been frequently disclosed main renal artery stenoses in aortograms performed for Lerich syndrome in normotensive patients. And at times, apparent stenosis has been observed in x-rays (even with post-stenotic dilatation) that have proved to be mythical at the operating

\textsuperscript{*} A most striking example of this phenomenon is the following: A hypertensive patient had surgical correction of the stenotic abdominal aorta for Leriche's syndrome, and during the procedure there was noted hemi-ischemia of the right kidney. A heminephrectomy was carried out with complete cure of her hypertension for a 5-year period. When claudication returned, hypertension was again noted. The simultaneous catheter studies now showed urines of identical quantity and concentrations of sodium and of chloride. The whole kidney was behaving functionally exactly like its halved partner. At a second operation, zonal ischemia of the other kidney was found, with return to normotension after heminephrectomy. After 5 more years the patient remains normotensive.\textsuperscript{17}

\textsuperscript{†} One such patient is reported briefly in reference 18, and the second patient was seen also by my former colleague, Dr. Yendt, whose permission I have to quote the case, as yet unpublished.
Angiotensin

The story of renin and angiotensin is a long one, is not of recent origin, and is by no means finished. An extract of rabbit kidney was shown to be hypertensigenic in 1898 by Tigerstedt and Bergman. After Goldblatt’s demonstration of hypertension by clamping the renal artery, Houssay and Faschiolo proved, by grafting an ischemic kidney to another dog, that the hypertension was induced by a humoral mechanism. It has subsequently been shown that the renal extract, known as renin, is inactive itself, but is an enzyme that acts upon alpha-2 globulin in the serum to produce angiotensin I, which in turn is changed to angiotensin II. Angiotensin II, a potent hypertensigenic agent, is an octapeptide and has been synthesized. Recently, the blood assay of angiotensin II, which hereafter for brevity we shall call angiotensin, has proved an exciting new aid in the diagnosis of renal ischemia causing hypertension. Older methods of angiotensin assay, laborious and time-consuming, carried out for us by Dr. Herbert Langford on renal vein blood obtained at the time of operation, pointed the way by proving to be highly accurate; in four patients who recovered normotension, angiotensin was present; in two whose hypertension was not benefited by nephrectomy, angiotensin was not found. Dr. Russell Morris has devised a much simpler and more rapid method for extraction of angiotensin, which seems to be highly specific, as judged by recovery of 85 per cent angiotensin added to blood and by behavior with the enzyme angiotensinase. Thus far, it is still unfortunately necessary for the assay to be made on the chemically sympathectomized rat; but, with frequent control, the method provides highly reproducible results.

With this semiquantitative technic, results of assays in more than 135 hypertensive patients have been of fascinating interest and, as usual, provided several new avenues of investigation warranting exploration. Arterial blood

* We gratefully acknowledge our indebtedness to Drs. John McAfee, Henry Wagner, and R. C. Reba, who have performed and interpreted all such tests on our patients.

* Methodology is fully described and reasons for belief in its accuracy and specificity are reported in this paper; the reader is referred there for details.

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has been tested for the smallest amount of angiotensin accurately detectable by this method and has been reported either positive or negative. There has not been a single positive test found on arterial blood derived from normotensive patients or those with essential hypertension, chronic glomerular nephritis, aldosterone tumor, Cushing's syndrome, or pheochromocytoma, the total numbering now well over 100. There have also been negative tests in eight patients who have undergone nephrectomy without benefit to their hypertension. The test has been positive on arterial blood from all 26 patients (to whom this test has been applied) whose blood pressure returned to normal after nephrectomy or plastic arterial surgery. Eighteen of these 26 patients had positive angiotensin assay in blood derived from the renal vein of the ischemic kidney, and blood from the opposite kidney was negative. And in two patients with arteriographic evidence of bilateral renal ischemia, angiotensin assay was positive in blood derived from each renal vein. After nephrectomy or arterial surgery, angiotensin has disappeared promptly from the arterial blood. In these patients, now cured of their hypertension, the concentration of angiotensin found in their arterial blood before operation was such as to have elevated the pressure in normal persons to a similar degree, if a like quantity of angiotensin had been intravenously infused.

Among other interesting findings of the studies on angiotensin is its constant absence from peripheral venous blood. A single round of the circulation is enough to dissipate its activity. Since angiotensin acts on the arteriole to constrict it, destruction must take place somewhere between the proximal end of the arteriole and the venous end of the capillary. Angiotensinase, found in the blood cells of many persons, could not possibly act with speed and efficiency to account for this amazing rate of inactivation. Angiotensin infused into one femoral vein at sufficient rate to raise the diastolic blood pressure 30 mm. Hg could not be detected in blood derived from the other femoral vein. Only 10 to 15 per cent is lost during a passage through the lungs, as judged by blood drawn from the right ventricle and compared to arterial blood. In the dog, angiotensin infused into a femoral artery could not be detected in femoral vein blood of the same side until huge quantities of angiotensin were used, life-threatening had they been put into the venous circulation.

Of great interest to us also are several observations on patients whose blood pressure has fallen to normal or only slightly hypertensive levels in hospital at bed rest without medication. At such times angiotensin has not been found in their arterial blood, whereas, when they are up and about their usual activities, the blood pressure was elevated and the angiotensin test was positive. These are persons whose hypertension has at all times been absent following renal surgery.

I wish I had the knowledge or data to tell you where in the kidney the angiotensin is made and what, if anything, aldosterone has to do with the clinical picture as seen in patients with renal ischemia. You will recall the patients of Laidlaw and Yendt and the one of Rosenheim, in whom hypokalemic alkalosis accompanied unilateral renal ischemia with hypertension, promptly disappearing after nephrectomy. None of our patients with unilateral renal ischemia thus far has presented with this syndrome.

By virtue of the clinical results outlined above, it is difficult not to attribute to angiotensin an etiologic role in the hypertension of these patients with renal ischemia. Such a hypothesis has been proposed before, but there have been more objectors than proponents for the suggestion. It takes a minute or more for angiotensin to be formed by interaction between renin and a plasma globulin in the test tube. If a similar time interval is required within the body, several circulations of the blood would have taken place. But once the angiotensin has been made, Scheele, Ransom, and Morris' studies show that it does not survive a single passage from arterial to venous side. Since angiotensin is found in venous blood coming only from the ischemic kidney, it must be formed there faster than it is in vitro.
or the ischemic kidney must store and release it.

When angiotensin is injected intravenously, a prompt rise in blood pressure results from arteriolar constriction and the circulatory dynamics are identical with those observed in patients with essential hypertension. In theory, then, removal of the offending kidney, the source of the angiotensin, should result in immediate fall in blood pressure. Such immediate fall to normotension on the operating table has happened in a few of our patients, and once, in a case reported by Yendt, to shock levels from which the patient died 48 hours after nephrectomy. But the usual sequence has been for the blood pressure to diminish gradually over a period of several weeks until a stable baseline is reached. It is enigmatic why this slow rather than immediate return to normotension takes place; but the same phenomenon occurs frequently after a pheochromocytoma has been removed, and no one doubts that the epinephrine and the norepinephrine secreted by these tumors have been the basic cause of the sustained hypertension. A pattern must have been set in the musculature of the arteriole that is slowly reversible after the initiating factor has been removed. It is just this slow reversibility that provides hope that sooner or later an agent with similar characteristics will be found to be the cause of essential hypertension.

Though perhaps not pertinent to the subject of hypertension per se, it seems not inappropriate to bring to your attention some recent experimental studies concerning angiotensin. Female dogs were used, with ureters so implanted as to permit ready urinary sampling. Intravenous infusion of angiotensin sufficient to raise the diastolic blood pressure approximately 30 mm Hg resulted in prompt changes in renal function. There was a fall in filtration rate and in urinary volume, but coincidently the concentration of sodium and chloride rose, indeed so much that there was actually more sodium excreted than in the control periods prior to infusion of the angiotensin. These renal alterations continued to be reflected in the urine for approximately 3 hours, after which time there was gradual return to pre-angiotensin status. Meanwhile, intravenously administered angiotensin continued to keep the blood pressure elevated and no increase in quantity of angiotensin was required to maintain this over the 6-hour period, even after renal clearances returned to their control status. Some sort of adjustment must occur in the metabolic economy so that the immediate effects of angiotensin on renal physiology are countered, while the hypertensive action continues merrily along.

With use of the same dog preparation, abrupt stenosis of one renal artery was reflected in the opposite kidney by exact mimicry of the angiotensin infusion experiment. There was a sharp fall in filtration rate and urinary volume with a sodium diuresis lasting for several hours and then disappearing. Angiotensin was found in the vein from the ischemic kidney and continued to be found there. That stenosis leads to the production and release of angiotensin, with reflection on the other kidney's function, seems a highly plausible deduction. Furthermore, the dog then had hypertension which was continuous. It is difficult to escape the following conclusions: 1. Angiotensin directly affects the kidney by reducing filtration and effecting a diuresis of sodium and chloride. 2. These effects are transient, and some mechanism supervenes within a few hours to restore to the kidney these parameters of function despite continued administration of angiotensin. 3. Appropriate stenosis of one renal artery mimics exactly the effect of angiotensin on the untouched kidney. Incidentally, the stenosed kidney likewise reflects angiotensive effect—tempered by its reduced over-all capabilities due to the ischemia from the arterial clamp. By the next day the kidneys lost their response to angiotensin and the ischemic kidney behaved as have those in our hypertensive patients, in whom hypertension later disappeared following renal sur-

* The degree of stenosis just sufficient to eliminate pulse had been previously ascertained at operation several days earlier when the screw clamp was put in place.
The case for believing that the ischemic kidney induces hypertension by secreting angiotensin seems to us to be strongly enhanced by these observations.

Comment

I shall revert now to a few more clinical matters before closing. We have found surgically correctable hypertension in patients who have had no more than one fourth of their kidney involved in the ischemic process—stenosis, for one reason or another, of a third branch of a main renal artery.

Patients have reverted to normotension after 10 years of severe hypertension. Our most striking example of recovery after long existence of persistent hypertension is the case of a patient, now 28 years old, seen in consultation with Dr. Katherine Borkovich. At age 16 hypertension had been noted; intravenous pyelograms were normal and renal function was good. After unsuccessful attempts to reduce the pressure by medical means, a subtotal adrenalectomy was performed. With no improvement after this procedure, a total adrenalectomy was carried out 6 months later. For the next 10 years the patient was maintained on substitution doses of adrenal steroids and closely watched, diastolic pressure ranging between 120 and 140. She was without symptoms until she consulted Dr. Borkovich for a minor cerebral accident in the spring of 1960. Overall renal function was good, there was no heart failure, and intravenous pyelograms were again read as normal. Further studies, however, clearly indicted the right kidney as being ischemic and hypertensigenic; and nephrectomy was performed, since plastic surgery was not feasible. Blood pressure gradually fell to normal over a period of 6 months, and the patient's most recent reading 2½ years after operation was 130/90. The lesion proved to be fibromuscular hyperplasia of the renal artery.

The presence of renal insufficiency is not necessarily a contraindication to removal of an ischemic kidney. In 1954 a man of 66 was referred to us, whose severe hypertension was clearly documented as of less than 6 months' duration. There had developed extensive eye-ground changes, heart failure, and renal insufficiency with a nonprotein nitrogen of 50 mg. per 100 ml. of serum. The left kidney was not visualized on intravenous pyelogram, and no urine was secreted on catheter study. After we assured ourselves of the presence of a kidney on this side,* nephrectomy was performed.† In this man, the blood pressure returned to normal within 2 weeks and remained at 130/80 until he died in May 1963, 9 years later, of a ruptured abdominal aneurysm. Over these 9 years, the serum nitrogen remained elevated at approximately the same level, but the eyegrounds cleared, and cardiac competence was maintained. Others have reported surgical correction of unilateral renal ischemia in the presence of renal insufficiency followed by fall of blood urea nitrogen to normal coincident with return to normotension.32

The lesions leading to the renal ischemia have included atheroma, cholesterol emboli (presumably from rupture of an atheromatous plaque), aneurysms of the renal artery, pyelonephritis, polyarteritis nodosa, and carbuncle of the kidney; in younger patients, the commonest lesion has been "fibromuscular hyperplasia" with or without thrombosis of the vessel or vessels involved.

It seems too much to ask that normotension should be restored before calling a renal surgical procedure successful. For example, a man of 65 had been known to be mildly hypertensive for 20 years, diastolic pressure averaging 100 mm. Hg. Suddenly he developed an abrupt rise and proceeded to heart failure and blinding retinopathy. Removal of a right renal artery plaque promptly reduced his pressure to its previous level; his vision returned and his heart became compensated. He continued

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*Congenital absence of one kidney occurs occasionally.
†His kidney showed marked renal parenchymal atrophy presumed to be due to atheroma proximal to where the renal artery was severed. There were a few cholesterol emboli present. The nephrectomy was carried out as rapidly as possible, owing to the critical condition of the patient; and the renal artery, which appeared practically pulseless to the operator, was severed close to its entry into the kidney.
his usual activities in comfort for 2½ years. He then had a stroke and died. In our opinion, and certainly in his, this operation was a highly successful venture.

The practical problem often arises whether or not to remove or to do plastic repair to a kidney that one thinks almost certainly is hypertensigenic, yet the blood pressure is but mildly elevated and can be readily maintained within satisfactory limits by medical management. We are aware of no damage done by an ischemic kidney other than through the production of hypertension. The answer to the question will, therefore, depend upon other factors—the patient’s general condition, age, capacity to withstand operation, etc. In general, there is greater satisfaction in eliminating the cause of a pathologic situation than in counteracting its ill effects.

Sometimes lesions inducing renal ischemia lead to transient hypertension. Whether return to normotension in such cases is due to development of collateral circulation, to further deterioration and total necrosis of the ischemic area, or to some other change is not known. Unless, however, the sudden onset of hypertension follows an unusually rapid, progressive, downhill course, it is probably well to wait 1 or 2 months in the hope that the situation will correct itself.

The material discussed in this lecture pertains solely to hypertension secondary to a gross ischemia of the kidney, and patients with this disorder constitute a very small fraction of the immense hypertensive population. Whether or not clues may be derived from them which bear on the problem of so-called essential hypertension remains to be seen. It is certainly difficult or impossible to distinguish between the two types of hypertension in the office or at the bedside. One only occasionally obtains a strong positive lead by hearing a bruit above the navel to one side or the other, or obtains a history of abrupt development of hypertension after an unexplained abdominal pain, or finds hypertension at an age unusual for “essential” hypertension. Which hypertensive patients should have investigation pursued further, and how, must rest with the judgment of the individual physician. Certain it is that every hypertensive patient cannot be subjected to some of the elaborate procedures we have discussed here. But an instance with cure of a lethal disorder is an immensely satisfying experience to physician and patient alike. The possibility of a situation that can be corrected should at least cross the mind of the doctor whenever he meets a patient with hypertension of significant degree.

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Reports of Medical Cases, with Reference to Morbid Anatomy Preface by Richard Bright—1827

It will form no part of my plan in future volumes, any more than it has done in this, to lay before my readers a succession of striking novelties. Utility is my first object; and the work which I now commence will not, in theory at least, be thoroughly completed, until every disease which influences the natural structure, or originates in its derangements, has been connected with the corresponding organic lesion. Extensive as this undertaking may appear, I do not despair of its completion, to the utmost that the present state of our knowledge will admit.—Original Papers of Richard Bright on Renal Disease. Edited by A. Arnold Osman. London, Oxford University Press, 1937, p. xii.
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