

## THE ASSOCIATION OF UNILATERAL KIDNEY DISEASE WITH HYPERTENSION

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That essential hypertension may be associated with and produced by unilateral renal disease seems now to be an established fact, both experimentally and clinically. Equally certain is the fact that not all cases of essential hypertension are due to unilateral kidney disease and conversely that all patients with unilateral renal disease do not have hypertension. We therefore find ourselves in that confusing stage of clinical investigation where we are attempting to determine which case of hypertension can be attributed to unilateral renal disease.

It has long been known that hypertension may be associated with obstructive lesions of the urinary tract or any other disease which results in severe damage and destruction of renal parenchyma, such as in polycystic kidneys. The conception, however, that unilateral kidney disease might produce hypertension is very recent and a large share of credit for stimulating clinical interest in this phase of hypertension must go to the experimental work of Goldblatt<sup>1</sup>. Working with dogs and monkeys, he showed that when the renal artery on one side was constricted with an especially devised clamp, hypertension resulted which usually tended to return to normal after a period of time, although in some instances of unilateral constriction of the renal artery hypertension has been reported to exist for as long as two years. Removal of this ischemic kidney resulted in prompt return of the blood pressure to normal. Goldblatt also showed that constriction of both renal arteries resulted in a sustained elevation of both the systolic and diastolic pressures of the blood. The same results were obtained with constriction of one artery, followed by removal of the opposite kidney. Hypertension in such experimental animals occurs without detectable diminution in renal function, illustrating the difficulty in detecting these cases clinically with the renal function tests employed at the present.

That the renal ischemia produced is responsible for the elevation in blood pressure is indicated by the following facts:

1. If the ischemic kidney is removed, the blood pressure promptly returns to normal; likewise, if the clamp on the artery is removed, the blood pressure falls.
2. If a kidney is transplanted to the neck or groin, as done by Blalock and Levy<sup>2</sup> and Glenn, Child, and Heuer<sup>3</sup>, and then rendered ischemic by arterial compression, high blood pressure still results.
3. Further confirmatory evidence was reported by Houssay and Fasciolo<sup>4</sup> who transplanted an ischemic kidney into a normal animal with resultant elevation in blood pressure.

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It is thus shown that the ischemic kidney is responsible for the hypertension and must be present for it to occur.

According to Goldblatt, the mechanism of the production of hypertension with renal ischemia can be explained in two possible ways only: (1) nervous reflex affecting the general vasomotor apparatus, or (2) a humoral mechanism which postulates the formation of some pressor substance in the kidney which gets into the circulation. By a variety of experiments, Goldblatt<sup>1</sup>, Page<sup>5</sup>, and others definitely disproved the nervous reflex mechanism by denervation of the kidneys, section of the splanchnic nerve, excision of the entire sympathetic nervous system, etc. None of these procedures prevented the development of hypertension in renal ischemia or relieved it, once produced. The humoral mechanism has been postulated and is indicated by the fact that the removal of the ischemic kidney results in a fall in blood pressure. If the renal vein is obstructed, no elevation of blood pressure results, thus establishing the fact that some substance apparently must get into the general circulation from the kidney. It has been shown that this pressor substance is not excreted in the urine.

An additional method for the experimental production of hypertension is that of Page<sup>5</sup> who showed that wrapping the kidney of experimental animals in cellophane caused an elevation of the blood pressure. At necropsy, the kidneys in these animals were found to be surrounded by a dense hull of tissue 4 to 5 mm. in thickness. Wrapping the kidneys with rubber did not produce such hypertension.

Other important experimental work is that of Hartwich<sup>6</sup>, and Harrison, Mason, Resnik, and Rainey<sup>7</sup>, who produced hypertension by experimental obstruction of the ureter. Blalock and Levy<sup>2</sup> ligated and divided the ureter to one kidney and showed a moderate elevation of the blood pressure which returned to normal following removal of that kidney. Experimental obstruction of the ureter has thus been shown to produce hypertension.

Thus, we have the experimental proof of the renal origin of hypertension and evidence that unilateral renal disease may produce it. The clinical counterpart to this experimental evidence has recently been forthcoming, with the reporting of a number of cases of hypertension associated with unilateral kidney disease. These cases may be divided into two groups: Group I—those which might be termed the typical Goldblatt kidneys, and Group II—those in which the mechanism is not so clear but probably is due to renal ischemia produced in a different manner.

In Group I may be placed the case of Leadbetter and Burkland<sup>8</sup>, in which a rather severe hypertension existed in a child five and a half years of age who had an ectopic pelvic kidney which was removed.

Examination of the specimen showed that the renal artery was partially occluded by a plug of smooth muscle. In the case of Freeman and Hartley<sup>9</sup>, a severe type of hypertension developed in a patient who had a single remaining kidney, the other having been removed by nephrectomy several years previously. At necropsy the lumen of the renal artery was found to be markedly constricted by an atheromatous plaque. Hyman<sup>10</sup> reported a similar case in which marked atherosclerosis constricted the lumen of the renal artery. The blood pressure returned to normal following nephrectomy.

In Group II are placed the cases associated with chronic pyelonephritis, hydronephrosis, calculous disease of the kidney, and trauma. According to Bell and Pederson<sup>11</sup>, no case of hypertension with chronic pyelonephritis had been reported previous to 1930. Since that time a number of reports have appeared. Longcope and Winkenwerder<sup>12</sup> reported hypertension associated with bilateral pyelonephritis. Butler<sup>13</sup> reported fifteen cases of hypertension associated with chronic pyelonephritis in children, six of which were reported in detail. Of these, two had unilateral pyelonephritis, one being associated with ureteral stone. Nephrectomy was followed by a return of the blood pressure to normal. The case of Barker and Walters<sup>14</sup> is of interest in that there was a long antecedent history of kidney trouble with previous operation for the removal of a stone. Hypertension finally developed and was relieved by nephrectomy. Boyd and Lewis<sup>15</sup> reported a case which was found accidentally at the time of bilateral adrenal exploration, the kidney presenting rather marked infarction. Removal of this infarcted, pyelonephritic kidney resulted in a return of the blood pressure to normal levels. McIntyre<sup>16</sup> also reported a case of unilateral pyelonephritis with hypertension in which removal of the kidney resulted in a return of the blood pressure to normal.

Crabtree<sup>17</sup>, in 1938, collected from the literature five cases of unilateral pyelonephritis with hypertension, to which he added one case. In this group, nephrectomy was followed by a return of the blood pressure to normal in four cases. Among these were the two cases previously reported by Butler, and the case of Barker and Walters.

The mechanism of the production of hypertension in these cases is not clear although Crabtree and Prien<sup>18</sup>, in a recent study, showed rather marked vascular changes in cases of chronic pyelonephritis. He studied a surgically removed kidney with a rather acute bacillary pyelonephritis. Definite evidence of vascular injury was seen throughout this kidney and where the inflammation was most severe, he was able to demonstrate actual severance of arteries, surrounded by a zone of hemorrhage. In other areas there was involvement of the smaller arteries with intimal damage, lesions which he felt might later lead to occlusion. He called attention to the fact that since the arteries to the kidney are largely

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terminal, such injury might produce severe renal damage by ischemia. In considering the mechanism, it has been shown that extracts of pyelonephritic kidneys, as well as other kidneys with ischemia or from patients who had hypertension, have a greater pressor effect than extracts of normal kidney.

Some time ago we became interested in this question and through the cooperation of the medical department complete urological investigation was carried out in cases of hypertension. The seventy-three cases reported here constitute the first group studied and include those seen up to January 1, 1940. This group does not include all cases of hypertension seen at the Clinic during the period of this study, but includes cases which were selected to the following extent.

In general, it consisted of the younger patients. With few exceptions, no case with severe renal insufficiency or evidence of congestive heart failure, or those having had cerebral vascular accidents were referred for urologic investigation because of the belief that they constituted the type of patient whose disease had progressed beyond the hope of relief. In other words, investigation was carried out chiefly in those cases with earlier hypertension where there was some hope of finding a remediable cause. There was, however, no selection of cases on the basis of suspected urologic disease. With the exceptions noted above, they were average cases of essential hypertension. Complete urological investigation was carried out, which included cystoscopy, ureteral catheterization, and careful examination and culture of separate kidney urines, differential phenolsulphonphthalein test and bilateral retrograde pyelography. Also, in many cases, intravenous urography was done and most cases had, in addition, a urea clearance test of kidney function. The ages and sex of the seventy-three cases are shown in Table 1.

**TABLE 1**  
AGE AND SEX OF 73 CASES OF HYPERTENSION

<i>Age</i>	
10-19 .....	2
20-29 .....	7
30-39 .....	21
40-49 .....	21
50-59 .....	18
60-69 .....	4
Total .....	73 Cases
<i>Sex</i>	
Men .....	30
Women .....	43
Total .....	73 Cases

Of the seventy-three patients, ten, or 13.7 per cent were found to have outspoken and severe unilateral kidney disease, and they are summarized in Table 2. Nephrectomy was done in seven of these and we were interested in observing what effect this had upon the blood pressure. We found a significant reduction in four cases, and while two of these later experienced some elevation of blood pressures, they did not return to their original levels. In three cases there was no change in the blood pressure following nephrectomy.

TABLE 2  
SUMMARY OF TEN CASES WITH  
SEVERE UNILATERAL KIDNEY DISEASE

Ureteral stone with obstruction and nonfunctioning kidney.....	2
Pronounced hydronephrosis with infection.....	3
Calculous pyonephrosis.....	3
Pyelonephritis.....	2

The ages of the four patients in whom improvement was noted were twenty-two, forty-five, forty-eight, and fifty-four years, three having calculous pyonephrosis and the other having an infected hydronephrosis. The three unimproved cases were forty-three, forty-nine, and seventy-three years of age, infected hydronephrosis being present in two while the third had a chronic pyelonephritis associated with a cortical abscess of the kidney. In addition to these ten patients, there were twenty-four others in whom unilateral kidney disease could not be excluded, either because of a definite history, abnormal findings in the pyelogram, functional studies, or urine examinations. Together, there were thirty-four cases, or 46.5 per cent, in whom unilateral kidney disease may have been a factor in the production of hypertension (Table 3).

TABLE 3  
UROLOGIC INVESTIGATION OF 73 CASES OF HYPERTENSION

Kidneys normal.....	39
Severe unilateral kidney disease.....	10
Positive history of urinary disease.....	11
Duplex kidneys (unilateral).....	5
Chronic pyelonephritis.....	4
Previous operation on one kidney.....	2
Renal trauma (rupture).....	2
	24
Total cases with urologic disease.....	34 (46.5%)

It is granted, of course, that the twenty-four cases referred to may be of doubtful significance, but they were included to record facts which were too outstanding to ignore. For example, there was a definite

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history of urinary disease in eleven cases as shown in Table 4, from which it is seen that four had renal colic with passage of stone, two had periodic hematuria of undetermined origin, two gave a history of recurrent pyelitis or persistent pyuria, two had had transurethral resection for prostatic hypertrophy, and one gave a history of bladder trouble of fifteen years' duration, and was found to have a moderate hydronephrosis of the right kidney.

TABLE 4

### SUMMARY OF 11 CASES WITH POSITIVE HISTORY OF URINARY DISEASE

Renal colic with passage of stone.....	4
Periodic hematuria without demonstrable cause .....	2
Pyelitis, or persistent pyuria.....	2
Previous prostatic operations.....	2
"Bladder trouble" 15 years with mild hydronephritis, right.....	1

There were five patients with a duplex kidney, two of which had complete ureteral reduplication. The significance of these cases cannot be determined at this time, but it seems noteworthy that the incidence of duplex kidney in this group of cases was 7 per cent, which seems unusually high.

Four patients had evidence of chronic pyelonephritis obtained either by positive culture and pus cells in the kidney urine, or by the finding of abnormal pyelograms with fragmented pelves of the type so commonly seen in chronic pyelonephritis. Only one of these cases had an associated antecedent history of pyelitis with pregnancy.

Two patients had had previous operations on one kidney, being pelviolithotomies in both instances. In one patient in whom the pelviolithotomy had been done here, the blood pressure at the time of operation was recorded as normal.

Finally, there were two cases with a history of rupture of the kidney. A recent case which came under our observation was a young man about twenty-six years of age who was admitted with the typical findings of intracapsular rupture of the kidney associated with rather profuse hematuria over a period of eleven days. Conservative management was adopted and no operation was performed. However, during his stay in the hospital, the blood pressure mounted to as high as 160/100, but gradually subsided as the bleeding ceased, and he improved.

The possible relationship between renal trauma and hypertension at least is indicated by these two cases and parallels a case reported by Nesbit and Ratliff<sup>19</sup>, in which hypertension developed some months following rupture of the kidney. Removal of this kidney resulted in a temporary lowering of the blood pressure which, however, ultimately again became elevated although not to the original level.

The importance of these twenty-four patients cannot be assessed, but it is notable that they constituted 33 per cent of the total number of cases studied, which makes them statistically significant. Although no etiological relationship is definitely assigned to this group of cases, future investigations may reveal their true significance.

After considering those patients with hypertension who had associated unilateral kidney disease, it was felt desirable to investigate a similar number of patients who had had nephrectomy for known unilateral kidney disease in order to estimate the incidence of hypertension. Accordingly, the records of seventy-three such cases were studied, which included cases of calculous disease of the kidney or ureter, hydronephrosis with or without infection, pyonephrosis, and a few cases of renal tuberculosis. Of this entire group, only two patients had hypertension, the hypertensive level being arbitrarily placed at 150 mm. of mercury systolic pressure. It thus is apparent that not all cases of unilateral disease have hypertension, and it introduces a problem as to what factors are present to produce hypertension in some cases and not in others. Certainly, from existing evidence, this cannot be answered at this time, but to theorize momentarily, it would seem logical to suppose that the production of hypertension is dependent upon arterial occlusion by inflammation or other pathological processes present in the kidney. Certainly, if one is to accept the Goldblatt principle for all cases, he must believe that the question of whether or not hypertension is present is dependent upon whether or not arterial obstruction is present. Is it not possible, then, that in two groups of patients with similar disease in the kidney one may have arterial occlusion and the other may not?

#### DEDUCTIONS AND CONCLUSIONS

It is thus seen in this study of a group of cases of hypertension that there is a rather high incidence of patients who have evidence of unilateral kidney disease. The percentage of cases seems too high to be coincidental and the etiological relationship at least is suggested.

In the seven cases operated upon, nephrectomy was done primarily because it was indicated on the basis of the existing disease and not because of the hypertension. Even so, there was a definite decrease in blood pressure in four patients, in two of which it returned to normal levels and has remained there.

Finally, *nephrectomy is not being recommended for hypertension*. Nephrectomy must be done *only* when indicated by the existing disease in the kidney and yet bids well to relieve an associated hypertension in a considerable number of patients.

It does seem worthwhile, however, to carry out careful urological investigation in patients with hypertension, for in a certain small pro-

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portion it may be found to be caused by a unilateral renal lesion, removal of which will favorably influence the elevated blood pressure. If we can in this way relieve even a small per cent of patients with hypertension, much will have been accomplished in this otherwise rather hopeless group of cases.

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