Function of the Contralateral Kidney in Renal Hypertension Due to Renal Artery Stenosis

By Alan P. Thal, M.D., Ph.D., Theodor B. Grage, M.D., and Robert L. Vernier, M.D.

The role of the kidney in the control of blood pressure is a complex one. Thus it is now clear from the experiments of Wilson and Byrom that partial constriction of one renal artery in the rat will lead to sustained hypertension and the development of histologic changes in the contralateral kidney that appear to be identical with changes seen in malignant hypertension in man.

These important observations have been amply confirmed and expanded by Floyer. On the basis of his experiments it appears that unilateral constriction of the renal artery initiates hypertension, whereas the maintenance of this state derives from the vascular lesions in the contralateral kidney. Paradoxically the kidney that initiates the hypertension is protected from vascular damage by the damping effect of the artificial coarctation. In the early stages of the experiment the blood pressure may be restored to normal by removing the constriction. After several months, however, removal of the constricting clip results only in partial return to normal. Complete return to normal blood pressure follows removal of the constriction and contralateral nephrectomy.

Whereas a state of renal ischemia initiates and maintains a severe degree of hypertension, a considerable amount of evidence has been presented by Floyer and others that a normal kidney exercises an antihypertensive effect.

The present case history illustrates a precise duplication of the Floyer experiment in the human.

Case Report

A 14-year-old boy was admitted to the University of Minnesota Hospitals on February 2, 1959, for severe hypertension of at least 7 years' duration.

The patient was the youngest boy in a family of six children. There was no history of hypertension in the family. Birth and early childhood were uneventful, and his development appeared to be quite normal. In 1951, following an attack of measles, he complained of a stiff neck, headaches, and pain in the arms and legs. In February 1952, after a grand mal seizure his blood pressure was found to be 185/160 mm. Hg. Subsequent investigation failed to reveal a cause for the hypertension and he was placed on a low-salt diet and a variety of potent hypotensive agents, including hexamethonium bromide, veratrum viride, and potassium sulfocyanate, with little change in the level of his blood pressure. Except for frequent severe frontal headaches he remained relatively asymptomatic for the next few years. By 1956 his blood pressure had risen to 220/185 mm. Hg. One month prior to admission the patient had several episodes of blurring of vision in the right eye and a feeling of numbness over the entire right side of his body.

On admission the boy appeared to be well nourished and well developed. The principal abnormality was hypertension, fluctuating between 190 to 230 mm. Hg systolic and 145 to 170 mm. Hg diastolic. Examination of the ocular fundi revealed severe arteriolar spasm without hemorrhage or exudate. The face suggested mild facial paralysis on the right side, with widening of the palpebral fissure and flattening of the right nasolabial fold.

Laboratory findings on admission included multiple negative urine analyses, blood urea nitrogen 14 mg., serum creatinine 1.1 mg., and normal serum electrolytes. An Addis count of a 12-hour urine specimen was normal. X-ray examination of the chest disclosed minimal cardiac enlargement with prominence of the left ventricle. An electrocardiogram, except for some evidence of left ventricular hypertrophy, was not remarkable.
intravenous pyelogram showed duplication of the renal pelvis and ureter on the right side, with the double ureters extending at least to the pelvic rim. The renal pelvis on the left side was bifid with a single ureter. The right kidney was slightly larger than the left. Multiple studies designed to reveal evidence for epinephrine-producing tumors were negative.

A retrograde aortogram was performed (figs. 1 and 2). The left renal arteries appeared normal, and a dense nephrogram was obtained on that side. On the right side a vessel was seen coming off the aorta for about 0.5 cm., which then narrowed down and fed into a markedly dilated vascular structure, consistent with a coarctation of the right renal artery with poststenotic dilatation. The right kidney received multiple large collateral vessels, probably arising from the lumbar vessels. The nephrogram on the right side was delayed and was considerably weaker than that on the left.

At operation on March 5, 1959, the diagnosis of coarctation of the right renal artery with poststenotic dilatation was confirmed. Blood pressure in the left renal artery measured 210/180 as compared to 55/50 mm. Hg in the right renal artery distal to the coarctation. The stenosed segment of the right renal artery, with an internal diameter of 0.5 mm. at its narrowest portion, was resected and the severed end of the vessel was re-implanted into the lateral side of the aorta (fig. 3). The blood flow through the right renal artery was interrupted for 29 minutes. Systemic blood pressure at the end of the operation was 220/170 mm. Hg.

Immediately after surgery the patient involun-

tarily passed a large volume of urine. After placement of a Foley catheter the urinary flow measured 25 ml. of urine excreted per minute. By that time, approximately 1 hour after surgery and 4 hours after re-establishment of blood flow to the right kidney, the patient had become severely dehydrated as evidenced by a hemoglobin of 22 Gm., a hematoctit value of 62, and a rise in body temperature to 106 F. Electrolyte determination of the urine showed a resemblance to an ultrafiltrate of plasma with 118 mEq./L. of sodium, 8 mEq./L. of potassium, 92 mEq./L. of chloride and 8.6 Gm./L. of protein. Serum electrolytes at that point were sodium 133 mEq./L., potassium 1.5 mEq./L., chloride 92 mEq./L. and a carbon dioxide combining power of 11 mEq./L.

Vigorous replacement of the estimated fluid and electrolyte losses was started immediately. Urine volume and electrolyte concentration of the urine and serum were measured at 2-hour intervals because of the rapid changes taking place (table 1). Repeated doses of “Pitressin” were given, with apparently little improvement in the concentrating ability of the kidney. To decrease the systemic blood pressure and thereby decrease the renal perfusion pressure, an infusion of trimethaphan camphorsulfonate (Arfonad) was started, and the systolic pressure was brought down from 200 mm. Hg to 130 to 140 mm. Hg. Although the urine output continued to be excessive, within 4 hours of surgery it had decreased to about 12 ml. per minute and at 8 hours after surgery it had fallen to 4.7 ml. per minute. Urinary sodium concentration remained between 90 to 140 mEq./L until the
third postoperative day, when it suddenly dropped to 20 mEq./L. with a simultaneous return of the urine flow to more normal levels. Urinary potassium levels began to increase from 8 mEq./L. immediately after surgery to over 50 mEq./L. on the first postoperative day, signifying return of tubular excretory function. The concentration of protein in the urine decreased from an initial value of 8.6 Gm./L. to 0.5 Gm./L. by the end of the day of operation, and on the fifth day after surgery the urine contained only a trace of albumin.

The postoperative course was further complicated by the development of severe uremia. On the second postoperative day blood urea nitrogen was 49 mg. per cent and serum creatinine 3.5 mg. per cent. A clearance study performed on that day revealed an endogenous creatinine clearance of 24 ml per minute and a urea clearance of 18 ml per minute, the latter value representing about 24 per cent of the normal value. On the fourth postoperative day the blood urea nitrogen had risen to 164 mg. per cent and the serum creatinine to 8 mg. per cent. Both values gradually returned to normal over a period of about 14 days. During the period of acute renal impairment the patient was febrile with temperatures ranging as high as 102.8 F. The exact cause of the fever was never determined; however, the patient responded to treatment with antibiotics.

Postoperatively the patient was treated with "Arfonad" for approximately 24 hours and on the first postoperative day was started on reserpine for about 2 days, after which he received apresoline for an additional 3 days. After all hypotensive drugs had been discontinued, his blood pressure ranged from 150-180/90-130 mm. Hg to the time of discharge.

Biopsies of both kidneys and a muscle biopsy were obtained during surgery. Examination of the specimen from the right kidney revealed essentially no abnormality (fig. 4) and the biopsy from the left kidney showed glomerular hyalinization, a moderate degree of arteriolar thickening, and severe intimal fibrous thickening and medial hyperplasia of the smaller arteries (fig. 5). The tubules showed no abnormality, and a scattering of mononuclear cells was seen in the interstitial tissue. The muscle biopsy showed fibrohyaline intimal thickening of the small arteries and arterioles (fig. 6).

The patient was discharged on March 26, 1959, and was re-admitted 3 months later for differential renal function studies. During this interval his blood pressure had remained persistently raised.
to the level of 160-170/110-130 mm Hg. The results of the renal function studies are listed in Table 2.

It appeared that the hypertension, which had persisted since surgery, was due to severe renal insufficiency on the left side. It was decided to observe the patient for 6 months.

During the ensuing 5 months the patient's blood pressure continued to remain elevated and he was re-admitted on November 8, 1959, with a pressure of 170/110 mm Hg. Repeated urine examinations during this time had revealed persistent albuminuria. Repeated renal function studies showed an increase in the inulin clearance to 69 ml. per minute on the right side. Urine collections from the left ureter were unsatisfactory. The para-aminohippuric acid clearance was not determined. An intravenous pyelogram again demonstrated that the right kidney was larger than the left (fig. 7). At this time, however, there was considerably more contrast material excreted on the right side with much earlier appearance of the dye on that side.

In the light of the Floyer experiments and in view of the persistent hypertension and the poor renal function on the left side, a left nephrectomy was done on November 13, 1959. The right kidney was explored and the right renal artery was found to be of about the same size as at the previous operation. It pulsed vigorously into the hilus of the kidney. The postoperative course was uneventful. The blood pressure began to fall rapidly toward normal, beginning on the first postoperative day, and at the time of discharge on November 23, 1959, it measured 130/80 mm Hg.

The removed kidney measured 9.5 by 5 by 4 cm. and weighed 69 Gm. The cortex measured 6 mm. and, grossly, the kidney appeared to have a normal architecture. The surface of the kidney showed fine pitting. Microscopic examination revealed several small foci of atrophic glomeruli and tubules in the cortex. The arterioles showed no marked

### Table 2

<table>
<thead>
<tr>
<th>Renal Function Studies after Initial Operation</th>
<th>Right Kidney</th>
<th>Left Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para-aminohippuric acid clearance</td>
<td>192 ml/min.</td>
<td>54 ml/min.</td>
</tr>
<tr>
<td>Inulin clearance</td>
<td>54 ml/min.</td>
<td>10 ml/min.</td>
</tr>
<tr>
<td>Urine volume</td>
<td>18 ml/10 min.</td>
<td>4 ml/10 min.</td>
</tr>
<tr>
<td>Time of appearance of crystal violet</td>
<td>2 min.</td>
<td>7 min.</td>
</tr>
</tbody>
</table>

*Figure 2*

*Phase III. Retrograde aortogram showing stagnation of dye in dilated poststenotic segment.*

*Figure 3*

*First operation. Surgical division of the renal artery distal to the coarctation with re-implantation into the aorta. The coarcted segment is marked by an arrow and the anastomosis is inferior to this. The vena cava is retracted to the patient's right side.*
changes, but the walls of small and medium-sized arteries were almost uniformly thickened. This thickening was partly fibrous and the intima showed elastic proliferation, with an occasional vessel almost completely occluded. The large arteries and the renal artery were essentially normal. A muscle biopsy, taken at surgery, again showed moderate intimal thickening of the smaller vessels. Pathologic diagnosis of the removed kidney was arteriosclerotic nephrosclerosis in hypertension.

Since surgery, examination of the urine for albumin has been repeatedly negative and the blood pressure has ranged between 120-130/60-85. Clinically the patient is free from symptoms and has been very active.

**Discussion**

The case illustrated here is a pure form of unilateral renal ischemia uncomplicated by generalized atherosclerosis. As such, it bears close comparison with the rat experiments of Floyer.²

The initial response to excision of the co-
artecation was, as one might have predicted, a partial reduction in blood pressure (fig. 8). The contralateral kidney with its severe small-vessel lesions presumably functions as Tobian has suggested, as if microclips had been applied. The extent of the vascular lesion developing in the opposite kidney appears to be a function of time. The time interval needed to produce this state is well known in the rat, but not in the human.

In spite of the severe small-vessel lesions seen on muscle biopsy the blood pressure in this case rapidly returned to normal levels after the second stage. This finding serves to emphasize the occurrence of reversible functional changes in the caliber of vessels, which also demonstrate severe, diffuse, pathologic changes.

The pathogenesis of the massive diuresis following revascularization of the coarcted kidney is puzzling and gives rise to some speculation. In effect, a kidney perfused from birth at a pressure approaching the lower limits of glomerular filtration pressure was suddenly exposed to an arterial pressure of 230/190 mm. Hg. The high urinary flow may have been a function of an elevated glomerular filtration rate in the immediate postoperative period. Thus Leaf et al. were able to demonstrate in the exposed kidney of the dog a direct linear relationship between urinary flow and glomerular filtration rate, when the latter was varied over a wide range by graded compression of the renal artery. Whether this relationship holds true with increasing arterial pressures above normal control values cannot be inferred from these studies. In Selkurt's investigations in dogs, however, an increase in arterial pressure above normal resulted in a proportional increase in urinary volume and sodium excretion, with no apparent change in glomerular filtration rate and renal blood flow as measured by clearance studies. In this patient by the second postoperative day the decrease in the diuresis was associated with a decrease in systemic blood pressure and with a relatively low glomerular filtration rate as measured by creatinine clearance. Unfortunately daily measurements of the glomerular filtration rate were not obtained during this critical period. The experimental studies of Thurau et al. may have some bearing on this problem. These workers demonstrated that in contrast to the renal cortex, the renal medulla lacks autoregulation and that an increase in perfusion of the renal medulla, by increasing renal arterial pressure, produces a pressure diuresis due to excretion of osmotically active substances from the countercurrent system.

Of course, the possibility that this transient and nearly complete failure of tubular function was the result of tubular damage must be considered. This may have been occasioned by the 29-minute period of renal anoxia at the time of repair of the coarcta-

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**Figure 7**

Intravenous pyelogram 4 months after anastomosis of the renal artery. Top. Intravenous pyelogram taken after the first operation showing earlier concentration of contrast material in the right kidney at 2 minutes after injection. Bottom. At 5 minutes intravenous pyelogram shows bilateral function. The pyelograms taken during the first 3 minutes accurately indicated the functional status of the two kidneys.
The absence of a family history of hypertension, the normal urinary findings, and the failure of response to antihypertensive drugs strongly suggest hypertension of unusual cause. The rise in blood pressure in this patient was progressive, and immediately prior to the first operation he experienced a cerebrovascular accident. The possibility must be considered that the child had an early unilateral pyelonephritis in the left kidney to account for the hypertension, yet this seems to us unlikely and in our view the coarctation appears to be of congenital origin and the primary factor initiating the process.

In spite of the extensive anatomic changes in the kidney, the pyelogram showed normal excretory function, and the coarcted kidney, contrary to what is generally expected, was the larger of the two. Biopsy of the two kidneys confirmed the concepts developed initially from the experimental production of hypertension in the rat. Whereas the rat and the human appear to react very similarly to unilateral constriction of the renal artery, in the dog it is almost invariably necessary either to constrict both renal arteries or to constrict one renal artery and remove the other kidney to obtain a sustained hypertension. Furthermore, generalized arterial or arteriolar sclerosis has not been observed in dogs, even after 7 years of persistent hypertension. This species difference may be in part responsible for the lack of agreement among various investigators.

In the available literature the therapeutic approach to treatment of renal hypertension due to renal artery stenosis has frequently been nephrectomy, which all too often has failed to bring about the desired return of the blood pressure to normotensive levels. This case points out the desirability of corrective surgery of the vascular abnormality and the necessity of preserving the kidney that has escaped the deleterious effect of prolonged severe hypertension. The findings in this patient thus confirm in a human case the correctness of the Floyer hypothesis.

**Summary**

Severe hypertension of at least 7 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 8 months’ observation of persistent, moderate hypertension, the left kidney was removed with prompt return of blood pressure to normal levels during the subsequent 2½ years.

These observations demonstrate the precise correlation of hypertension due to renal artery stenosis in the human with the experimental model in rats.

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*Circulation, Volume XXVII, January 1963*
Giovanni Battista Morgagni, the Founder of Pathologic Anatomy

That Morgagni was chiefly concerned with the morbid process as a whole and its evolution, rather than with the static alteration of the organ involved, is illustrated by his anticipation of the role played by the pressure of the blood on the formation of vascular aneurysms. He pointed out that the first noticeable alteration is a degeneration of the inner coat of the artery, followed by the formation of furrows that weaken the middle coat, and, when this occurs, the vessel undergoes dilatation. He realized that these progressive changes are brought about, to a considerable extent, by the pressure of the blood against the arterial wall, and, in support of this concept, he remarked that aortic aneurysms occur most frequently in the arch because of the direct exposure of this portion of vessel to the stream of blood that is projected by the heart. As a logical conclusion, he warned against excess in diet and exercise and mentioned the harmful effect of emotional upsets.

Similarly, in conjunction with his studies of the variations of the pulse, Morgagni visualized, far ahead of his time, that relations exist between the nervous system and the circulatory system. He was cognizant of the fact that circulation may be disturbed by two sets of nervous irritations—one intermediated by the pneumogastric nerves, the other through nerves subservient to the arteries. He gave credit to Valsalva for the discovery that functional disorders in the cardiovascular system follow the division of pneumogastric nerves and he also praised Molinelli for modifying Valsalva's experiment by tying, instead of dividing, these nerves.—C. G. Tedeschi, M.D. Giovanni Battista Morgagni, The Founder of Pathologic Anatomy: A Biographic Sketch On the Occasion of the 200th Anniversary Of The Publication Of His "Decedibus et causis morborum per anatomen indagatis." The Boston Medical Quarterly 12:122, 1961.
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