Our studies on the functional characteristics of renovascular hypertension have been recently published and will be summarized briefly in this paper with particular emphasis on the relationship between renal blood flow and renal hypertension—a relationship which, unhappily, has been depreciated in the last 20 years.

The major problem four years ago was to solve the technical aspects of ureteral catheterization. The difficulties were bladder leakage, inadequate urine flow rates, ureterorenal sympathetic reflexes, postcatheterization morbidity, and a complete lack of criteria for recognizing valid reproducible data. It was clear that, unless these problems were solved first, the functional characterization of a kidney producing human arterial hypertension, as well as the conditions which affected those characteristics, would have to await a different approach. It was equally clear, however, that the normal symmetry of the kidneys in the dog and the human offered an excellent opportunity to examine the function of a kidney responsible for hypertension while the contralateral kidney served as a control.

Methods

The several problems in technique were solved as follows: (a) Bladder leakage was prevented by the use of soft polyethylene catheters. The ratio of the size of the ureteral orifice to the size of the catheter is important. (b) Urine flow rates must be at least 2 ml./min./kidney to avoid artifacts from dead space errors and electrolyte absorption across the ureteral and bladder mucosa. (c) Ureterorenal reflexes which can produce a fall in renal plasma flow (RPF) and an even greater fall in urine flow were demonstrated to be present in the human. These reflexes are avoided by passing the polyethylene catheters only to the mid-ureter or lower, and by waiting 10 to 15 minutes for the reflexes to subside before starting the collection periods. (d) Objective criteria for an adequate study were formulated. These criteria require that the ratio of urine flow rates (the urine flow rate of the diseased kidney/the urine flow rate of the better kidney) agree within 6 per cent in three consecutive 10-minute collection periods. In the average study, the agreement will be closer than 6 per cent. (e) The postoperative morbidity has been reduced to a minimum because the ureteral catheters are removed at urine flow rates approaching 10 ml./min./kidney and the increase in plasma osmolality assures a urine output of several liters following cystoscopy. The exact details of the cystoscopic and infusion technique have been presented in one paper, while the supporting data have been published separately.

The requisite conditions for the study of renal ischemia by ureteral catheterization are: (a) Urea is used as the osmotic diuretic. It was originally chosen because of the experimental observations of Levinsky, Davidson, and Berliner on the effects of urea on urine osmolality in the presence of acute reductions in the glomerular filtration rate (GFR). As will be demonstrated, however, osmolality differences are not the most characteristic functional finding in renal ischemia. (b) The infusion contains a substance which is not reabsorbed with the glomerular filtrate and which serves as a comparative measure of total water reabsorption for each kidney. The concentration of inulin, p-amino-hippurate (PAH) and endogenous creatinine all serve as comparative indices for total water reabsorption. An 8 per cent concentration of urea infused at 10 ml./min. is required for adequate urine flow rates under the conditions of this test. (c) Isotonic saline is the infusate of choice to replace the osmotic loss of salt in the urine. (d) Antidiuretic hormone (ADH) (Pitressin) is given as a loading dose in the
amount of 5 mU./kg. and added to the infusate to deliver 5 mU./kg./hr. ADH is used to place the distal tubules under a maximal stimulus for water reabsorption. This stabilizes the effect of ADH and removes the possibility of a variable endogenous ADH secretion in the patient. (e) The studies are performed under a heavy Nupercaine saddle anesthesia which gives a perineral anesthesia only and prevents pain to the patient.

Material

Twenty-two patients with unilateral main renal artery obstruction, four patients with partial occlusion of a segmental artery to one kidney, and two patients with bilateral main renal artery disease have been studied by this method. Approximately 35 patients with normal blood pressure and unilateral renal disease have served as controls. The functional patterns in these two groups of patients have been distinctly different.

The functional pattern from ureteral catheterization studies on patients with curable renovascular hypertension secondary to occlusive disease of the main renal artery is illustrated by the following patient. V. T. was a slightly obese 18-year-old school girl who, at the age of 16, was found to have a blood pressure of 170/120 mm. Hg during a routine school physical examination. She was an only child. The patient's mother had been a semi-invalid for several years, but did not have high blood pressure. The patient was an attractive, overweight girl who was concerned about her mother's invalidism and the responsibility this placed upon her in an active teenage group of girls and boys. The patient was admitted to a hospital on two occasions, whereupon a fall in blood pressure to nearly normal levels occurred promptly without treatment. Her blood pressure on an out-patient basis varied between 160-180/110-130. She was thought by all observers to have "essential" hypertension. When she was admitted to the hospital in April, 1961, her fundi were not remarkable, the heart was not enlarged, the electrocardiogram and urinalysis were normal, and there were no abdominal bruits. The majority of her blood-pressure determinations were in the range of 140/90, many were 120/70, and an occasional pressure of 170/120 was obtained. The serum urea nitrogen was 11 mg. per cent and the 15-minute phenolsulfonphthalein excretion, 30 per cent. Urine catecholamines were normal. The 10-minute intravenous pyelogram (fig. 1) showed no difference between the two kidneys, except that the calyceal pattern in the left kidney seemed minimally crowded compared to the calyces and infundibulae of the right kidney. The renal cortical outlines could not be visualized. Ureteral catheterization studies were performed on April 26, 1961 (table 1).

On the basis of these studies, the patient was operated upon through a midline incision. The left renal artery was less than 2 mm. in diameter (fig. 2). It was smooth, firm, and cord-like to palpation. The primary branches were similar, but smaller. A thrill was not palpable. Although a 20-gauge needle could be inserted into the renal artery, the diameter of the needle was as large as the lumen of the artery, thereby preventing strain gauge pressure measurements. A nephrectomy was performed. The kidney weighed 90 Gm. and measured 9.7 × 3.5 × 3.2 cm. The lumen of the main renal artery was pinpoint and surrounded by a white ring of tissue. On microscopic section, the intima and media appeared normal, but a thick circular layer of tissue, composed mainly of fibrous connective tissue with some muscle and elastic fibers, surrounded the media. This external fibrous
layer was thicker than the media and ended abruptly as the arteries entered the kidney (we have described this peculiar condition in a previous publication). The renal cortex appeared normal and the juxtaglomerular apparatus was not prominent with the standard H + E sections. The patient’s blood pressure fell immediately to 110/60 and has remained at this level for the seven months since nephrectomy. Her general outlook on life has markedly improved and she seems a much happier individual. Her blood pressure on November 14, 1961, was 112/70.

Functional Characteristics of the Ischemic Nephron

The function studies on this patient (table 1) are representative of the 22 unilateral and two bilateral main renal artery obstructions we have studied. The fundamental characteristics of the ischemic kidney in curable renovascular hypertension are:

1. There is reduced renal blood flow to functioning renal parenchyma. The smallest reduction in renal blood flow has been 23 per cent when the ischemic kidney is compared to the contralateral kidney. The average decrease has been 50 to 60 per cent.

2. The reduction in RPF produces a proportional reduction in GFR—i.e., the filtration fractions are nearly the same in both kidneys. In some patients there is a slight increase in the filtration fraction; in others, as this one, a slight decrease.

3. This reduced volume of glomerular filtrate produces the distinguishing characteristic of this condition: an excessive reabsorption of sodium and water per unit volume of glomerular filtrate. Table 1 indicates that a 50 per cent reduction in GFR is present, but a 5:1 difference in urine flow rates. The difference between the two kidneys in the sodium excretion fractions parallels the difference in urine flow rates, and indicates that the enhanced reabsorption of water parallels the reabsorption of sodium.

4. Inulin crosses the glomeruli of both the ischemic and the normal kidney in equal concentrations. Thus, simultaneous comparision of final inulin concentration differences serves as a comparative index of total water reabsorption in the two kidneys. Since there has been little difference between the filtration fractions in the ischemic and nonischemic kidney, the investigator can compare PAH concentration differences with almost the same validity as inulin for comparing total water reabsorption.

Observe that no other diagnostic index indicates as marked a disparity between the ischemic and nonischemic kidney as do the concentrations of inulin and PAH. These concentration differences are always greater than the sodium concentration differences under the conditions of this study. In our original publication, all patients were studied under oral water diuresis followed by an urea-saline-ADH diuresis. During water diuresis, osmolality is less in the ischemic kidney compared to the contralateral kidney, but with an urea-saline-ADH diuresis, osmolality differences reverse and the pattern observed in table 1 is present. The most striking change when an urea-saline-ADH diuresis is superimposed on a water diuresis is the increase in inulin or PAH concentration differences, and the simultaneous increase in urine flow rate disparity. In other words, a urea-saline-ADH diuresis increases the already excessive
### TABLE 1

**Patient V.T., Eighteen-year-old White Female (69 Kg.) with Left Main Renal Artery Obstruction**

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>Urine flow</th>
<th>PAH concentration</th>
<th>PAH clearance</th>
<th>Urine sodium</th>
<th>Urine osmolality</th>
<th>Inulin clearance</th>
<th>Inulin concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L R</td>
<td>L/R (ml./min.)</td>
<td>L R L/R (mg./100 ml.)</td>
<td>L R L/R (μEq./ml.)</td>
<td>L R L/R (μOsms./Gm. H2O)</td>
<td>L R L/R (ml./min.)</td>
<td>L R L/R (mg./100 ml.)</td>
</tr>
<tr>
<td>-1</td>
<td></td>
<td>Plasma = 140</td>
<td></td>
<td>Plasma = 290</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22 ml. of 10% inulin, 2.4 ml. of 20% PAH, 10 ml./min. to deliver 2.39 mg./ml. % inulin, 1.3 mg./ml. PAH, and 5 ml./kg/hr. of ADH.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>B.P. 170/105 mm. Hg; 1 ml. of 0.25% Heavy Nupercaine (Ciba) injected in the fourth lumbar space for saddle anesthesia.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>No. 8 polyethylene catheters passed easily to mid-ureter of both kidneys.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Bacteriological cultures.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Plasma no. 2 drawn, B.P. 170/105</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62-72</td>
<td>1.75 9.12 0.19</td>
<td>237 91 2.81</td>
<td>187 349 0.54</td>
<td>31.6 89.0 0.58</td>
<td>663 493 1.35</td>
<td>40 80 0.50</td>
<td>650 250 2.61</td>
</tr>
<tr>
<td>72-82</td>
<td>2.05 9.98 0.20</td>
<td>221 81 2.72</td>
<td>189 338 0.56</td>
<td>45.9 89.0 0.52</td>
<td>625 440 1.42</td>
<td>41 76 0.54</td>
<td>579 219 2.65</td>
</tr>
<tr>
<td>82-92</td>
<td>2.32 11.11 0.21</td>
<td>196 74 2.65</td>
<td>191 344 0.56</td>
<td>47.9 87.6 0.55</td>
<td>608 425 1.43</td>
<td>39 79 0.50</td>
<td>485 203 2.39</td>
</tr>
<tr>
<td>95</td>
<td>Plasma no. 3 drawn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma = 144</td>
<td></td>
<td></td>
<td>Plasma = 315</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

920 ml. of 8% urea in saline absorbed. B.P. 175/110.

---

Solute excretion fractions, CEx,*, CIno,*, and filtration fraction (62-92 min.)

<table>
<thead>
<tr>
<th>% Filtered Na</th>
<th>CEx, CIno,*</th>
<th>CEx, CIno,*</th>
<th>Filtration fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>L R L/R</td>
<td>L R L/R</td>
<td>L R L/R</td>
<td>L R L/R</td>
</tr>
<tr>
<td>ml./min.100 ml. GFR</td>
<td>ml./min.100 ml. GFR</td>
<td>ml./min.100 ml. GFR</td>
<td></td>
</tr>
<tr>
<td>1.52 8.05 0.19</td>
<td>10.0 17.9 0.56</td>
<td>-4.85 -5.03 0.96</td>
<td>.213 .227 .94</td>
</tr>
</tbody>
</table>

*A plasma osmolality of 325 was used for CEx, CIno, and filtration fraction calculations.
water reabsorption per unit glomerular filtrate in comparison to the contralateral kidney, and this is reflected by an increasing disparity in urine flow rate and urine inulin or PAH concentration differences.

It is important to recognize that mannitol decreases these disparities and hence tends to obliterate the functional change upon which a diagnosis can be based. The difference in these two solutes is apparent. As more and more of the glomerular filtrate is reabsorbed in the ischemic nephron, urea and mannitol progressively increase their contribution to the total osmotic pressure of the intratubular fluid. Mannitol, a non-reabsorbable solute, inhibits the reabsorption of sodium and water out of the nephron because of its osmotic contribution to the glomerular filtrate. Urea is quite different. The free back-diffusion of urea from the nephron into the plasma eventually adds to the already enhanced water reabsorption. This is shown by the observation that the urea clearance in the ischemic kidney is less in proportion to the Cs of that kidney than the ratio of the urea clearance to the Cs of the contralateral kidney.²

Because the infusion of urea-saline-ADH enhances the already excessive water reabsorption in the ischemic kidney when compared to the contralateral kidney, it might be suggested that the site for this reabsorption is in the counter-current multiplier system of the distal tubule. To the extent that free-water calculations are valid expressions for separating distal tubular reabsorption of water from proximal tubular reabsorption (a concept that is not entirely acceptable), table 1 indicates there is no difference in the amount of solute free water subtracted per 100 ml. of glomerular filtrate (4.85 against 5.03 ml./min.). The osmolar clearances per 100 ml. GFR indicate the marked reabsorption of water from proximal tubular reabsorption (a concept that is not entirely acceptable), table 1 indicates there is no difference in the amount of solute free water subtracted per 100 ml. of glomerular filtrate (4.85 against 5.03 ml./min.). The osmolar clearances per 100 ml. GFR indicate the marked reabsorption of water from proximal tubular reabsorption of water.

Normotensive Unilateral Renal Disease
Thirty-five patients with unilateral renal disease and normal blood pressure have had ureteral catheterization studies. While urine flow rates have been less in the diseased kidney, we have never observed an increase in the concentration of inulin or PAH in the diseased kidney by more than 6 per cent, which is the error of the laboratory method when concentrations are similar. The concentration of inulin and PAH is generally decreased in the diseased kidney secondarily to medullary damage which produces the well-known failure to concentrate urine as well as the medulla of a normal kidney does. We have interpreted these patterns as showing the absence of any effect of reduced blood flow on the volume of glomerular filtrate (there is no excessive water reabsorption), and we conclude that the reduced blood flow in these diseased kidneys is secondary to destroyed nephrons. There is no renal ischemia. On the other hand, when unilateral pyelonephritis is the cause of the patient's hypertension, the characteristic pattern of excessive water reabsorption will be present because of the change in the volume of glomerular filtrate secondary to reduced renal plasma flow.

Bilateral Renal Artery Disease
Bilateral main renal artery occlusions present with a functional pattern of unilateral renal ischemia. This occurs because small differences in renal plasma flow are greatly magnified by marked changes in urine flow. We have studied recently two patients with bilateral main renal artery occlusive disease which appeared reasonably similar on aortography, but the functional patterns showed a 90 and 95 per cent reduction in urine flow rate in...
one kidney, with a 400 and 800 per cent increase in the concentration of PAH. Surgical correction should be directed only at the kidney which shows the relative excessive water reabsorption, not just because it is the most ischemic of the two kidneys, but because the contralateral anatomical lesion may have no physiological significance. Several patients with bilateral main renal artery lesions have now been reported, whose hypertension has been cured by surgical repair of one side only.6-1 The experimental data, showing that a marked occlusion of the renal artery must occur before RPF is reduced to that kidney, explains three important observations: (a) Our finding that, whereas the smallest reduction in RPF to a kidney producing human hypertension has been 23 per cent (when the RPF is compared to the contralateral kidney), the pressure gradients across these main renal artery obstructions have been marked.6,8 (b) The occurrence of renal artery obstructions, i.e., positive aortograms, in normotensive patients. The Baylor University group has reported 18 patients who have renal artery lesions on aortography but who do not have hypertension.9 (c) Patients with bilateral main renal artery lesions whose hypertension is cured by repair of only one artery.5-7 These observations indicate a considerable stenosis must be present in the main renal artery before renal blood flow is reduced, and certainly before hypertension is produced. This particularly indicates the dilemma of those who advocate aortography as the primary diagnostic method: How do you know the functional significance of an anatomical lesion, especially in the older atherosclerotic age group? The functional characteristic of excessive water reabsorption will indicate that renal plasma flow is reduced to functioning renal tissue and that ischemia is present. Because we do not know how much reduction in RPF may be required to turn on the pressor mechanism in the human kidney, it is impossible to say whether excessive water reabsorption will develop simultaneously with the hypertension. For example, if RPF was reduced 10 per cent, would that kidney show this comparative pattern of excessive water reabsorption? We would expect so, but would that degree of reduced RPF produce hypertension? Our data, in a fairly large series, indicate that the smallest reduction in RPF has been 23 per cent, and the average 50 to 60 per cent. We therefore suspect that moderate pressure gradients (20 to 40 mm Hg) and small reductions in RPF may not suffice to produce human hypertension.

Unilateral Main Renal Artery vs. Segmental Occlusive Patterns

With the urea-saline-ADH infusion, the smallest reduction in urine flow rate in unilateral main renal artery or bilateral renal artery disease has been 3:1 in 24 patients. All have had at least a 100 per cent increase in the concentration of inulin except one patient (16 per cent), whose kidney was 80 per cent infarcted from a dissecting aneurysm of the renal artery with active thrombosis at the time of ureteral catheterization.3 Four patients with segmental (branch) arterial occlusion have shown a 2:1 difference in urine flow rate and at least a 16 per cent increase in the concentration of inulin or PAH.

Although we have not had a patient with bilateral segmental disease, this condition, unlike bilateral main renal artery obstruction, could not be detected by function studies unless there was a marked disparity in the size of the segments. However, it is clear that bilateral segmental disease is not amenable to surgery.

Essential Hypertension

Because the essential hypertensive population has a bilateral reduction in RPF10,11,12 it was anticipated that small differences in RPF between the two kidneys would produce a pattern of relative excessive reabsorption of water in the kidney with the slightly greater reduction in RPF. This has proven to be the case, and in fact, the functional pattern in the essential hypertensive population may approach in its greatest disparity the functional pattern in unilateral segmental disease.3 For example, a 5 to 10 per cent greater reduction in RPF to one kidney in a patient with essen-
tial hypertension who has bilateral reduction in RPF may give a pattern of 40 per cent less urine and a 30 per cent increase in the concentration of inulin—very similar to our unilateral segmental artery occlusions with a 50 per cent difference in urine flow rates. Thus, in the atherosclerotic age group of hypertensive patients, this segmental pattern should be confirmed by aortography before considering surgical exploration. Unfortunately, it is in the distal branches of the renal artery where the aortogram is the least useful. However, if the aortogram gave a reasonable visualization of the segmental arteries to the kidney, with 40 per cent decreased urine flow rate and 30 per cent increased inulin concentration, we would feel the patient had "essential" hypertension and was not amenable to surgical care.

The Relation of Renal Blood Flow to Renovascular Hypertension and "Essential" Hypertension

Throughout this presentation the importance of a reduction in renal blood flow as a prerequisite for renovascular hypertension has been emphasized. It may well be that the final step in the mechanism of the pressor substance production is not a decreased delivery of some cellular nutrient as might occur from a flow reduction phenomenon per se. For example, if the juxtaglomerular apparatus is the site of pressor substance production, the final initiating mechanism may be a change in some mechanoreceptor on a stretch or volume basis. But it is clear from these studies that, regardless of what constitutes the final mechanism, renal blood flow must be reduced to functioning renal parenchyma for hypertension to occur; and further, in the human, the reduction in RPF may even have to be reasonably significant (greater than 15 per cent) to initiate the cellular pressor response. The evidence for this can be summarized as follows: (a) The smallest reduction in RPF in 26 patients with unilateral curable renovascular hypertension has been 23 per cent when the RPF of the ischemic kidney is compared with the RPF of the contralateral kidney. The average decrease has been 50 to 60 per cent. (b) The pattern of excessive reabsorption of sodium and water establishes the presence of a reduction in the volume of glomerular filtrate to functioning nephrons. This characteristic pattern has been present in every patient with curable renovascular hypertension. Therefore the reduction in RPF involves functioning renal parenchyma. (c) The failure to find this pattern of excessive water reabsorption in patients with unilateral renal disease and normal blood pressure. (d) The consistent finding at surgery of large pressure gradients across main renal artery obstructions in patients with excessive water reabsorption.

The evidence that "essential" hypertension rests on the same basis of reduced blood flow to functioning renal parenchyma is the following: (a) Numerous independent investigations10, 11, 12 20 years ago established the fact that the essential hypertensive population had reduced RPF in comparison to the normotensive population, and this in spite of the wide variation in normal RPF. Friedman12 was able to correlate the level of the diastolic blood pressure with the degree of reduction in RPF. (b) If reduced RPF to functioning renal tissue occurs in patients with renovascular and essential hypertension, why should the kidneys in patients with essential hypertension with the same reduction in renal blood flow fail to produce a pressor agent? We believe this is the most important evidence. (c) The observation that the functional pattern from ureteral catheterization studies on patients with essential hypertension merges as a continuous spectrum into the pattern of unilateral segmental renal ischemia.2 (d) The fact that the clinical course of essential hypertension is indistinguishable from renovascular hypertension. The patient (V.T.) presented in this paper is a good illustration. Who would have thought that this girl had a 50 per cent reduction in RPF to one kidney—certainly not from her labile hypertension, her anxiety-producing environment, the intravenous pyelogram, the normal estimates
of renal function or the urinalysis. Lastly, if the RPF and GFR had been performed by standard methods of collection from the bladder, the total RPF would have been within the normal range of one standard deviation. The GFR would have been 120 ml./min. Are those patients with essential hypertension in whom RPF is reported to be normal similar to this girl?

In conclusion, we believe that a reduction in renal blood flow is a prerequisite for renal hypertension, that the pattern of excessive reabsorption of sodium and water per unit of glomerular filtrate relative to the contralateral kidney is indicative of reduced RPF to functioning nephrons, that essential hypertension is renal in origin, and that the excessive reabsorption of sodium and water is related to the general salt and water problem of the patient with essential hypertension—perhaps even explaining the increased sodium excretion response to a salt load.

References

FUNCTIONAL CHARACTERISTICS OF RENOVASCULAR HYPERTENSION

Discussion

Dr. Dustan: I think your use of urea infusion will prove very worth while in the study of clinical renal hypertension. I would question your insistence that the functional abnormality in renal arterial stenosis is an enhanced water reabsorption. From the work of Berliner and co-workers, and of Selkurt, it would seem that the primary response to a decrease in intrarenal arterial pressure is an increased sodium reabsorption and that this permits an increased water reabsorption. Another question that I have concerns the functional abnormalities that occur in segmental disease. An occlusive lesion in an arterial branch which supplies as much as half a kidney could produce the functional pattern which you have described. But this is quite a different situation from renal infarction, and I do not understand how renal infarction can cause the disproportionate increase in sodium and water reabsorption that is so characteristic of main renal arterial disease. Lastly, I would like to say that I feel that the functional patterns in renal diseases associated with hypertension are not due to the pressor material released by the kidney, which causes the hypertension, but to the location of the lesions. The determinants of renal function in these situations are decreases in intrarenal pressure and filtration rate as in main renal artery stenosis, and a decrease in total numbers of functioning nephrons as found in renal infarction and pyelonephritis. As you know, Dr. Bricker has shown that unilateral experimental pyelonephritis reduces numbers of nephrons but does not change function within a given nephron.

Dr. Stamey: In answer to your first question, there is no doubt that the excessive water reabsorption is secondary to enhanced sodium reabsorption. Our studies show that the percentage of filtered sodium reabsorbed is always greater than the percentage of filtered water reabsorbed and, in fact, we have used this observation as additional evidence that water reabsorption in the nephron occurs secondarily to active sodium reabsorption. The reason we emphasize water reabsorption rather than sodium reabsorption is a practical one. Most of the water reabsorption occurs in the proximal tubule where sodium reabsorption in the lumen of the nephron remains equimolar with the plasma. Hence the total movement of sodium in the proximal tubule can be determined only by reference to water reabsorption.

In answer to the second question, the functional abnormalities in segmental renal ischemia are qualitatively the same as partial occlusion of the main renal artery, but the changes are quantitatively less, as would be expected. It is true that if the reduction in glomerular filtration rate produced no glomerular filtrate, there would be no urine to identify the characteristic functional change, but in our experience to date these ischemic segments have functioned. Also, I am not sure of what you mean by "renal infarction." The term should be reserved for tissue totally devoid of blood supply, which pathologically presents "ghost cells" with pyknotic nuclei and peripheral hemorrhage. It is true that these segments of complete renal infarction could not be characterized by functional measurements, but then I know of no evidence that they produce hypertension. Lastly, as to your statements concerning the relationship between the functional pattern and the pressor material released by the kidney, we can only say that this specific functional pattern correlates with curable renovascular hypertension. I would like to emphasize that it is important not to avoid the problem of reduced blood flow, regardless of how the final stimulus for the production of renin is elicited.

Dr. Page: The problem as to what the stimulus is to the production of hypertension is still unknown. The problem is more complicated than some suppose. It is true that under some circumstances hypertension occurs when ischemia is produced. The difficulty is that there are many cases, both human and experimental, in which no hypertension is found despite the ischemia. Hypertension can
be produced in dogs by constricting the renal artery by a clamp. True, the constriction can be made sufficient to cause ischemia and hypertension. The trick is to put the clamp on in such a way as to avoid ischemia but still get the hypertension. Dr. Corcoran and I showed many years ago that when cellophane hulls formed in kidneys, hypertension occurred without ischemia and that in a few examples the same was true of the clamp. The cellophane hull forms slowly and I would not suppose it would have a stage where ischemia was produced. In the case of the clamp, it is possible that the initial stimulus was a temporary ischemia which was overcome as the blood pressure rose. I remember often confirming Blalock’s observation, which now is largely forgotten, that the blood vessel wall thins remarkably within the clamp so that much more blood can pass through the clamp and so relieve any ischemia. Lastly, Kohlstaedt and I found that reduction in pulse pressure in the perfused kidney seemed to be the stimulus to renin release, rather than ischemia. There can be no doubt that lesions in the renal artery are usually advanced enough to cause renal ischemia. But this does not entitle me to make the assumption that the ischemia is the cause of the hypertension. So far, the evidence still favors the suggestion that there is no direct relationship between ischemia and the height of the blood pressure. I am sure many people find this just quibbling, but I would like you to note that what we look for in the way of mechanisms responsible for the beginnings of renal hypertension will run head on into this problem. It may be as Dr. Stamey suggests, that it is a reduced blood flow to a reduced amount of renal tissue, though the cellophane perinephritis experiments do not suggest this. So far as I know, this aspect of the problem has not been attacked, if for no other reason than that current methods are not adequate. I am sorry to make this all so complicated but that is the way the world looks to medical men. I'm sure surgeons have much more fun.

Dr. Stamey: Dr. Page, I am delighted you brought this up for two reasons. First, I would agree that reduced blood flow occurs without hypertension. All of our patients with normotensive unilateral renal disease have reduced blood flow, and in some patients renal blood flow is reduced as much as 80 per cent compared to the contralateral kidney. But in these patients there is also 80 per cent less tissue, and therefore we do not see the characteristic pattern of excessive water reabsorption which indicates reduced blood flow to functioning renal tissue. Secondly, it is interesting how many physicians believe that renal function is normal in the hypertensive patient. If the urinalysis, urea clearance, and the phenolsulfophthalein excretion test are within the normal range, they assume that nothing is wrong with renal function, but they have not measured the renal blood flow. The studies of Homer Smith, Meyer Friedman, and others 20 years ago clearly established that renal blood flow, in spite of the wide variation in normal individuals, was reduced in the essential hypertensive population when compared to the normotensive population. It is fair to ask why, with all the evidence of reduced renal blood flow, has this relationship been depreciated in the last 20 years? The most frequently quoted experiments are those on the uninephrectomized dog with a Goldblatt clamp on the renal artery to the remaining kidney. In these experiments, the initial drop in renal blood flow returns to levels approximating the pre-clamp controls, but the hypertension continues. However, a solitary kidney can hypertrophy after renal artery occlusion. Thus there is no certain way to exclude an increase in renal mass during the course of the hypertension. In some recent experiments, Dr. Paul Good and I have produced hypertension using a Goldblatt clamp on one renal artery in the dog and without performing a contralateral nephrectomy. We found that renal blood flow was reduced in the clamped kidney in comparison to the contralateral normal kidney, and that the extraction ratios for PAH in the two kidneys indicated that the comparative reduction in renal blood flow was greater than the standard clearances (without renal vein cor-
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In some dogs, hypertension was produced with a 12 per cent reduction in renal blood flow as determined by standard clearances, which represented a 25 per cent reduction when the disparate extraction ratios were recognized. There is good reason to doubt if consecutive PAH clearances in the uninephrectomized dog are accurate enough to detect a 12 per cent reduction.

Dr. Hawthorne: Some years ago we did publish data which showed that animals with renal hypertension returned to normotension following acute damage to the kidney. Renal blood flow in these animals was reduced, but I think the significant thing is contained in your statement that the ratio of blood flow to the mass of tubular functioning tissue was such that the blood flow to that tissue was reduced. Thus it is true that one has to take into consideration the ratio of the plasma and blood flow to the mass of functioning renal tissue, but I don't see how you could speculate on this with an extraction ratio. You would have to measure the mass of tubular functioning tissue.

Dr. Corcoran: I think the experiments Dr. Stamey was referring to, which would support the view that renal blood flow might persist at normal levels during the course of experimental renal hypertension and which he considers inadequate, are those Dr. Page and I did. As I recall them, a considerable interval elapsed between nephrectomy and clamping of the kidney. Time was allowed for hypertrophy while control observations were done, usually over six weeks or so. I don't recall the number of dogs in which we were able to show that renal blood flow could be reduced and hypertension established. However, a delicate balance was obtained in a few dogs so that renal blood flow was normal three to four days after clamping, yet the animals were hypertensive. From this we concluded that the real determinant of renal hypertension is probably not flow rate, per se.

Parts of this discussion remind me of the first chapter in Pickwick. You remember there was quite a discussion and a Mr. Blotton of Aldgate was referred to by Mr. Pickwick as a humbug, and felt quite incensed. Mr. Pickwick, with his characteristic generosity and graciousness, interpolated that he used the word only in a Pickwickian sense, and Mr. Blotton said that with such a qualification he quite understood and thoroughly appreciated the comment and took it in good part. I suppose we are using the word ischemia in a Pickwickian way. After all, what you have is a drop in pressure, or a drop in filtration rate. If you want to call this ischemia in a Pickwickian way, fine. Otherwise, like Mr. Blotton, I might be incensed—in a Pickwickian way.

Dr. Stanley: Dr. Corcoran, I certainly would not like to incense you. However, these experiments need to be carefully repeated. When we have done this, renal blood flow has been reduced at least 20 to 25 per cent when the clamped kidney is compared to the contralateral kidney. To be sure, collateral blood supply is marked, and may account for as much as 80 per cent or even all of the blood supply reaching the ischemic kidney. This is one reason why experiments in which the Goldblatt clamp is retightened may not show a consistent relationship between levels of renal blood flow and blood pressure.
Functional Characteristics of Renovascular Hypertension with Emphasis on the Relationship of Renal Blood Flow to Hypertension

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