FUNCTIONAL CHARACTERISTICS OF RENOVASCULAR HYPERTENSION*†

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I. INTRODUCTION

In 1953, Howard, Berthrong, Sloan and Yendt (14) reported four patients with malignant hypertension who had demonstrable arterial obstruction to one kidney and who were cured of their hypertension by nephrectomy. This paper clearly documented that serious hypertension could be caused by the kidney and relieved by nephrectomy.

It has not been equally clear how to detect the kidney which is responsible for the hypertension. Since 1953, seven major proposals have appeared on how to recognize the ischemic kidney: (1) the Howard Test (6) (50% reduction in urine flow with at least a 15% reduction in sodium concentration); aortography (21); (3) reduction in urine flow accompanied by an increase in urine osmolality (25); (4) reduction in urine flow with a decrease in the "tubular rejectate fraction" of sodium (2) (a decrease in the percentage of filtered sodium excreted); (5) aortography confirmed at surgery by "demonstration of a significant drop in arterial pressure across the stenotic segment" (9); (6) an index based on tubular-rejection fraction ratios (24) and (7) the radioactive I^{131} renogram (31) (advocated as a screening test).

There have been conflicting reports from the advocates of these different proposals. For example, Poutasse (21, 22), Dustan (10) and Page (19) have repeatedly emphasized the failure of the Howard Test in the presence of segmental or bilateral renal artery obstruction. Schlegel (25), from his studies on a series of hypertensive patients, concluded that urine flow was less, sodium concentrations *equal* but urine osmolality increased in the ischemic kidney of patients

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whose hypertension benefited from nephrectomy. Birchall (2) reported two hypertensive patients with a marked reduction in urine flow on the affected side. One of these had an *increase* in the sodium concentration in the urine of the ischemic kidney compared to the non-ischemic kidney. Because the U/P inulin ratio (the concentration of inulin in the urine/the concentration of inulin in the plasma) was much greater in this kidney, Birchall suggested that an increase in the U/P inulin ratio might be diagnostic. More recently, Brown, et al. (5) also reported that the concentration of inulin and p-aminohippuric acid (PAH) was increased in the urine from the ischemic kidney. Finally, I^{131} scintillation counting has been widely advocated as a screening test (3, 31, 32). In this view, if there is no significant difference in radioactive uptake between the two kidneys, unilateral renal ischemia can be ruled out and the patient saved further diagnostic procedures.

The studies on patients and dogs reported in this paper do not support any of these contentions as a basic approach to the problem of renal ischemia. While each suggested measure may indicate renal ischemia under certain circumstances, they are all open to the serious criticism of giving both false positive and false negative indications for renovascular surgery. Our interest in this problem began when we saw in November, 1956 the patient whose case history is presented below.

This 40 year old pilot was seen in consultation for persistent left flank pain of one week's duration. Repeated urinalyses were negative, and an intravenous pyelogram was normal. A retrograde ureteral catheterization was performed in order to obtain better visualization of the left ureter. This examination revealed a normal ureter, but urine excretion was unexpectedly one-third the volume of the right kidney. The patient's blood pressure was 170/115 mm Hg. He had been treated for hypertension for two years, although his blood pressure was normal prior to 1955. Under Serpasil® therapy his blood pressure had occasionally been 140/90, although the average systolic pressure had been 160 to 170 and the average diastolic 110 to 120 mm Hg. The left flank pain subsided gradually and he returned to work with a blood pressure of 165/120. Three weeks later he developed gross, painless hematuria, and cystoscopy revealed blood effluxing from the left ureteral orifice. His blood pressure remained elevated, the hematuria completely cleared, and he returned to work. Over the next four weeks, his health deteriorated rapidly. He lost ten pounds in weight, and developed severe frontal headaches. Proteinuria appeared for the first time and increased rapidly until it was graded 4 plus. His blood pressure gradually rose to 220/140. Funduscopic examination revealed hemorrhages and exudates. He was hospitalized, ureteral catheters passed to each kidney, and differential urine flow rates, sodium concentration and phenolsulfonphthalein (PSP) excretion studied over a period of 24 hours. Without exception, urine excretion from the left kidney was always one-third of that from the right kidney. Sodium concentration was 138 mEq/L in the urine from the left kidney and 132 mEq/L from the right kidney. The total two hour phenolsulfonphthalein excretion was 53 per cent from the right kidney and 24 per cent from the left kidney.

The left kidney was explored and nephrectomy performed (Figure 1). The upper pole was normal, as was the posterior surface of the kidney in both upper and lower aspects. At the point of the arrow (Figure 1) on the anterior surface there was a sudden change in the thickness of the cortex. A microscopic section through this junction demonstrated the classical pathological picture of segmental renal ischemia bordered by normal renal tissue. The lower pole of the kidney on its anterior surface contained a large yellow infarct encircled by a brown hemorrhagic ring at its outer border. The patient's blood pressure returned to normal over the next eight weeks, and in November, 1958 a thorough examination revealed a normal blood pressure under varying conditions of stress and the recommendation was made that he be returned to flying status.

In November, 1959 he experienced right flank aching and his blood pressure was 162/115. He was treated with 0.25 mg Reserpine® twice daily and 0.5 gm Diuril® once daily. On this regimen his blood pressure varied between 120/90 and 160/100 throughout 1960. On March 2, 1961 inulin and PAH clearances were performed. The glomerular filtration rate (GFR) was 100 ml/min and the renal plasma flow (RPF) 256 ml/min. Funduscopic examination showed slight narrowing of the arterioles. His blood pressure was 140/94. The marked reduction in RPF and the high filtration fraction of 0.39 (GFR/RPF) indicated occlusive arterial disease in the remaining kidney.

With this demonstration that renal ischemia could occur with reduced urine flow and equal sodium concentrations, we felt justified in seeking a characteristic functional pattern other than a reduction in urine flow and sodium concentration.

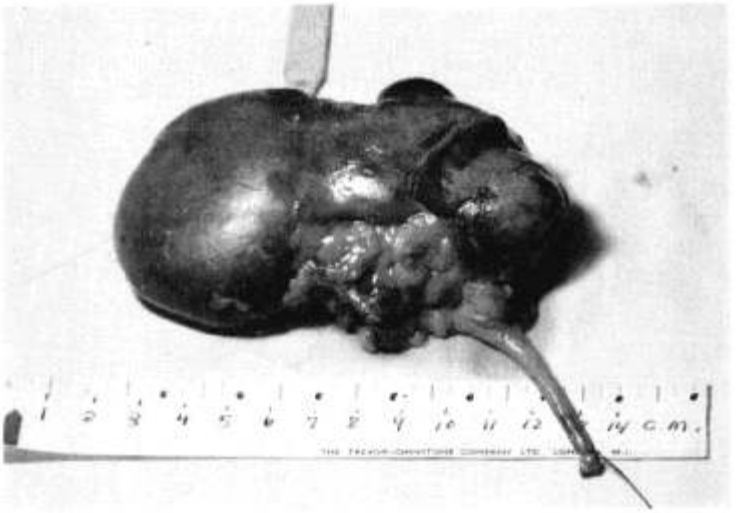


FIG. 1. P.R., 44 year old, W, M. Left kidney, anterior surface. This kidney excreted urine at a rate equal to ⅓ the contralateral kidney, but sodium concentration was increased. The middle ⅓ of the kidney was depressed and pale in color compared to the normal upper pole. The lower pole contained a large yellow infarct surrounded by a brown hemorrhagic ring. The posterior side of this kidney was normal, with the above changes limited to the anterior surface.

It seemed to us that four important considerations in the investigation of renal ischemia had been neglected in previous investigations.

The first, and most important aspect, was the need for data which would define the conditions necessary for repeatable ureteral catheterization studies. Although a wealth of information was available on how to obtain meaningful data when standard renal clearances were collected across the bladder, the problems arising from catheters resting in the ureter or renal pelvis had not been defined. The magnitude of this neglect can be observed in Smith's monumental work on *The Kidney*, published in 1951, in which, out of 2050 references, only 7 were concerned even remotely with data from separate catheterization of both ureters. These publications, including those more recent than 1951, were difficult to interpret because the authors report "the average of the best 10 minute periods", or one 20 minute period. Bladder leakage has been a serious problem. Ureterorenal reflexes resulting in sympathetic vaso-constriction have been described in the dog (13), and ignored in the human. The definition of these problems and the all important matter of technique constitutes Part II of this paper.

The second aspect requiring investigation was the application of recent research on the medullary gradients of urea and sodium and the effects of antidiuretic hormone (ADH) on the reabsorption of water by the distal tubule. Since urine excretion has *always* been less in the ischemic kidney in patients who have had ureteral catheterization studies, the conditions affecting water reabsorption, and, therefore, the *degree* of reduction in urine excretion, are obviously of first importance. In 1957 Berliner and Davidson (1) and in 1959 Levinsky, Davidson and Berliner (16) reduced the renal plasma flow and glomerular filtration rate in one kidney of the unanesthetized dog by inflating a cuff around one renal artery. The contralateral kidney served as a control. In the hydropenic dog on a low protein diet, a fall in RPF and GFR was associated with a *decrease* in the urine osmolality of the ischemic kidney in comparison to the control kidney due largely to a decrease in urea concentration. On the other hand, in osmotic diuresis and particularly with urea infusion there was an increase in urine osmolality in the ischemic kidney even at extreme degrees of reduced RPF and GFR. In other words, an adequate concentration of urea must be presented to the medulla of the kidney for maximal urine concentration. Ischemic kidneys, by virtue of their reduced blood flow, have less urea available for interstitial medullary accumulation than the contralateral kidney. Because constant water reabsorption in the distal tubule is de-

sirable, comparative studies on urine flow should be performed in the presence of maximal antidiuretic hormone. Because urea does not stimulate endogenous ADH production, exogenous ADH should be used in the infusate. Urea, as an osmotic diuretic, causes increased amounts of sodium to be excreted in the urine. For this reason, the urea is infused in isotonic saline. In the studies reported here, changes in plasma sodium concentration have been insignificant. It will also be apparent that urea, although increasing the percent of filtered sodium and water excreted in the urine of *both* kidneys, actually produces a greater *relative* difference between the normal and the ischemic kidney in urine flow rates and sodium excretion fractions than occurs during oral water diuresis. Mannitol, a non-reabsorbable osmotic diuretic, *decreases* the relative difference between the ischemic and non-ischemic kidney in urine flow rates and sodium excretion fractions, and, therefore, tends to mask existing differences. The marked differences between mannitol and urea in the operation of water reabsorption is further demonstrated in stop-flow experiments. Original stop-flow experiments were always performed under mannitol diuresis, and rarely showed more than a ten per cent rise in urine osmolality after release of the obstruction. On the other hand, urea infusion is regularly associated with a hundred per cent increase in urine osmolality in the distal segments after release of the obstruction (29). From these considerations, mannitol, even with ADH, is an extremely poor choice in the study of renal ischemia. Its use may have led to some of the discrepant reports on functional tests for curable unilateral renal ischemia. The approach throughout our research has been to study patients under oral water diuresis followed by an infusion of either four or eight per cent urea in saline containing antidiuretic hormone.

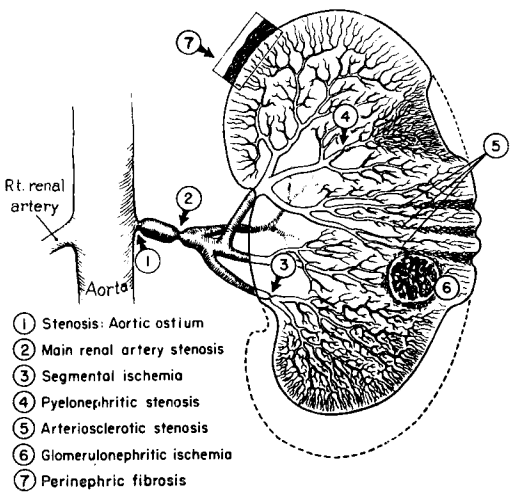


FIG. 2. All of these lesions may reduce renal blood flow to functioning renal parenchyma, and produce the characteristic excessive water reabsorption described in this paper. The hypertension from coarctation of the aorta and hydronephrosis are probably on the same basis.

The third aspect which attracted our attention was the almost complete neglect of the functional characteristics of unilateral renal disease in the *absence* of hypertension. Previous functional studies have been concerned with the difference between patients cured and those not cured by corrective surgery, or by ureteral catheterization studies on patients assumed to have essential hypertension. If there is a functional characteristic of curable unilateral renal hypertension, the definitive measurements must stand out clearly and apart from the functional pattern of unilateral renal disease (or congenitally small kidneys) in normotensive patients. To provide more information about such differences if they exist, controls were selected from normotensive patients who had one kidney smaller than the other, or who had a past history of surgery or disease in one kidney. Even bilateral disease, when more severe in one kidney and occurring in normotensive patients, must not show any functional similarity to unilateral or disparately bilateral renal ischemia. Our investigations have failed to show a single example of overlap in the distinctively different functional patterns of these two groups. The functional characteristics of normotensive unilateral renal disease constitute Part III of this paper.

Lastly, our study of hypertension and renal ischemia has not been limited to disease of the main renal artery or to segmental renal ischemia. Blood flow can be reduced to functioning renal tissue (ischemia) by any lesion from coarctation of the aorta to primary disease of the glomerulus. For definition by ureteral catheterization studies in the method described here, the only requirement is that the pathological process advance at a disparate rate between the two kidneys. Figure 2 illustrates our concept of the kidney and hypertension. Almost all of the

arterial obstructions reported recently in patients with curable renovascular hypertension have involved either the aortic ostium, the main renal artery, or the first major branches of the main renal artery (segmental renal ischemia). Yet, Kincaid-Smith (15) has demonstrated convincingly that the hypertension of pyelonephritis is associated with the same tubular atrophy and compression of glomeruli seen in curable unilateral renal ischemia (Figure 2, No. 4). When pyelonephritis terminates without hypertension, this pathological lesion of vascular ischemia is absent. When these observations are combined with the surprisingly large number of patients with unilateral pyelonephritis and hypertension reported in the classic pathological study of Weiss and Parker (30), a more careful study of this disease is indicated. The functional distinction between pyelonephritis with hypertension and pyelonephritis without hypertension is considered in this paper (Part V).

The question arises as to the frequency with which hypertension may result from bilateral renal ischemia secondary to arterio- and arteriolosclerosis (Figure 2, No. 5). This problem is considered in Part V where the functional studies characteristic of bilateral renal ischemia and essential hypertension are presented in detail.

We have been surprised at the degree of disparity in this pattern of renal ischemia which can exist in hypertension caused by glomerulonephritis (Figure 2, No. 6). The functional patterns from a pair of identical twins with glomerulonephritis, one with severe hypertension and the other normotensive, will be presented in Part V.

Lastly, unilateral hydronephrosis as well as perirenal fibrosis also produce renal hypertension. While the exact mechanism is not known, functional ischemia, in all likelihood, exists from reduced blood flow to viable nephrons caused by chronic compression of the vasculature in both instances.

II. GENERAL CONSIDERATIONS IN THE TECHNIQUE, METHOD AND CONDITIONS FOR REPRODUCIBLE URETERAL CATHETERIZATION STUDIES

The studies reported here were performed under oral water diuresis followed by an infusion of urea, saline and ADH. Whereas the diagnosis of curable renal hypertension is best made using an infusion of urea, saline and ADH, useful information has been obtained by studying the kidney first under oral water diuresis.

1. Method

We prefer that no saluretic be given for at least one week prior to the study. However, the functional pattern of curable unilateral ischemia is readily apparent in the presence of a salt deficit. On the morning of the study, the patient was allowed a liquid breakfast and requested to drink an additional one thousand milliliters of water during the two hours prior to arrival at the cystoscopy room. Upon arrival, the patient assumed a sitting position near the edge of the table. The loading dose of PAH (2 mg/kg of PAH space) and inulin (20 mg/kg of inulin space) was given intravenously after drawing a serum "blank". The infusion of PAH and inulin in 5 per cent D/W was started at a slow rate (1.1 ml/min in these studies) to maintain the desired plasma concentration. The concentration of PAH and inulin in the 5 per cent D/W was calculated from a prestudy estimate of GFR and RPF based on the patient's serum urea nitrogen (SUN), 15 minute PSP and urinalysis.

Once the priming dose and intravenous infusion were established, the lumbar area over the spinous processes was cleaned with a suitable germicide. A lower lumbar interspace was chosen (L-3 to L-5), a cutaneous wheal raised over the area using one per cent Xylocaine®, a standard spinal puncture performed with a #22 gauge needle, and 0.5 to 0.8 ml of a heavy Nupercaine® solution (0.25%) was injected slowly. This entire procedure requires ten minutes. The patient remained in the sitting position for the next fifteen minutes and usually took an additional four to six hundred milliliters of water by mouth. Anaesthesia was limited to the saddle area and was not associated with a fall in blood pressure. A few patients suffered from "post-spinal" headaches, and an occasional male required catheterization several hours later if the Nupercaine® had caused prolonged anaesthesia of the bladder. It was important that these studies be painless to the patient and, at the same time, not produce changes in renal blood flow which would invalidate the functional studies. This method met both requirements.

Fifteen minutes after the Nupercaine® saddle anaesthesia (thirty minutes after the priming dose), the patient was placed in the lithotomy position and the #24 Brown-Buerger cystoscope introduced. The bladder urine was cultured quantitatively and qualitatively. After inspection of the bladder, the catheterizing element containing two

⅛ Fr. polyethylene catheters was placed in the cystoscope.

These catheters contain one hole at the end and two additional side holes at 1 cm intervals from the tip. They have a remarkable capacity for accepting rapid flow rates. Urine will not drain around the catheter into the bladder at flow rates of 20 ml/min/kidney. The important point is to begin catheterization with a ⅛ Fr. and to pass the largest catheter which the ureteral orifice will comfortably accept. If a ⅛ Fr. will not pass the orifice, a ⅞ Fr. is tried, and if that fails, a ⅞ Fr., etc. Approximately one-half of all ureteral orifices will accept a ⅛ Fr. catheter, less than half will require a ⅞ Fr., and a few will need a ⅞ or smaller. The time of each ureteral catheterization should be recorded, especially if there is a delay between catheterization of the two ureters.

The catheters were passed ten to fifteen centimeters (approximately midureter) and stopped. The bladder was emptied, adhesive tape passed from knee to knee to support the cystoscope, both renal urines cultured, and blood drawn for serum from the arm opposite to that which received the infusate. When the one hour requirement for equilibration following the priming dose had passed, consecutive ten minute ureteral collections were started provided the catheters had been in place for approximately fifteen minutes.

Urine was collected directly into graduated flasks, and flow rates accurately recorded at the cystoscopy table. After the initial collections under oral water diuresis had been obtained, the infusion was changed to 8% urea (80 grams of Abbott's Ureaphil®) in 1000 ml of saline containing inulin, PAH and ADH (Pitressin®). The rate of infusion was approximately 10 ml/min. The amount of ADH added to the infusate was calculated to deliver 5 mU/kg/hr. A few minutes after the urea-saline-ADH was started, a loading dose of ADH, 5 mU/kg, was given intravenously. After the last collection period, the final aliquot of blood was drawn for serum.

2. The Requirements for Reproducible Studies

a. Recognition of Uretero-renal Reflexes. In early studies the ureteral catheters were passed to a position estimated to be in the region of the renal pelvis. With more experience it became apparent that if the catheters were not passed to the renal pelvis, the risk of probing a calyx or papilla and causing persistent unilateral vasoconstrictive reflexes was lessened significantly. These latter changes deserve consideration.

In the dog, Hix (13) demonstrated vasoconstrictive uretero-renal reflexes caused by passing a ureteral catheter. In his studies, these reflexes were predominantly unilateral. Our studies in the human established that this reflex was present and must be recognized if ureteral catheterization studies are to have any meaning.

One method of recognizing this reflex was to observe that if ten minute collection periods were begun within three or four minutes of catheterization, the first period practically never corresponded to the repeatable ratio of urine flow rates in the succeeding periods. The error in this first collection period can be analyzed readily by delaying the time between catheterization of the two ureters. Under these circumstances, urine flow ratios usually demonstrate an artificial relative decrease in urine flow, GFR and PAH in the kidney whose ureter was last catheterized in relation to the collection period (Chart I, etc.). This means there is a "settling down" period which varies from patient to patient, but averages ten to fifteen minutes after catheterization of the second ureter. Figure 3 shows the ratio of urine flow rates plotted against the time of ureteral catheterization in studies on several patients. For reasons that will be apparent below, only studies in patients whose urine flow rates were 2 ml/min/kidney or greater are included in this graph. The lapse of time in waiting for this "settling down" period to pass can be practically used by culturing each renal urine, steadying the cystoscope in place, drawing the first specimen of blood for clearance calculations, and testing the dynamics of bladder drainage through the open stopcock of the cystoscope.*

Chart I illustrates a second method of initiating and measuring unilateral ureterorenal vasoconstriction. The patient was a 36 year old, colored female with long standing hypertension and marked renal impairment. When the first "settling down" period is disregarded, the next two consecutive periods (33–43 and 43–53) indicate with perfect agreement that the left kidney excreted less urine by sixteen per cent. The right ureteral catheter was then deliberately advanced into the kidney and immediately with-

* This is done by allowing a few milliliters of cystoscopic irrigating solution to run into the bladder, and observing immediate, complete run-off from the bladder through the open stopcock. This assures the investigator of immediate recognition if leakage occurs around the catheter into the bladder.

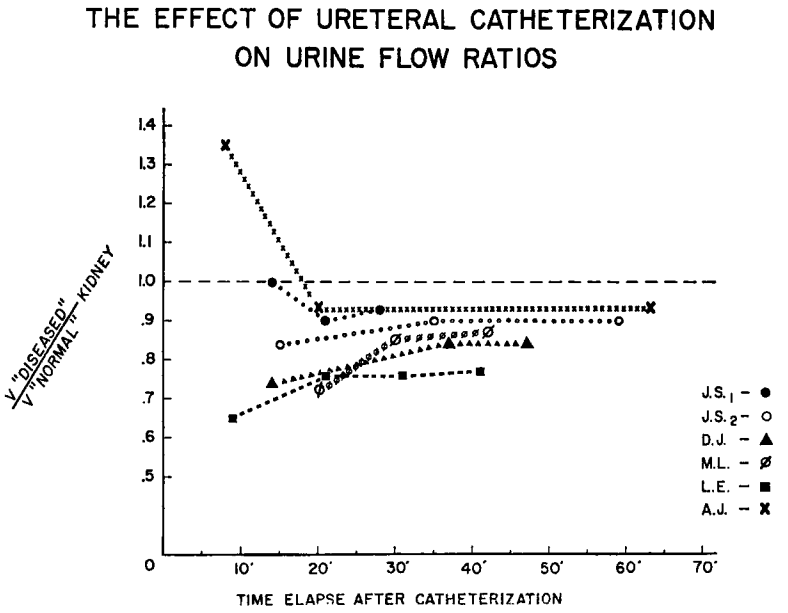


FIG. 3. V equals urine flow rate; each symbol represents a ten minute collection period at urine flow rates greater than 2 ml/min per kidney, thereby avoiding the artifact of inadequate flow rates (Figure 4). There was no bladder leakage.

These data show that the first 10 or 15 minutes following ureteral catheterization rarely represent the true ratio in urine flow rates. Urine should not be collected for functional studies during this period.

CHART I

Severe Cardiovascular Hypertensive Disease

D.J.—36 C, F.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R
min.	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O		
−77	22.4 ml 10% Inulin, 2.45 ml 20% PAH given I.V.; start infusion of 5% D/W at 1.1 ml/min to deliver 13.6 mg/ml Inulin and 7.27 mg/ml PAH.																							
−57	2.5 mg Nupercaine saddle anesthesia.																							
0	#8 polyethylene catheter passed to left renal pelvis with ease.																							
1	#8 polyethylene catheter passed to right renal pelvis with ease.																							
10–20	1.67	2.27	.74	9	12	.75	138	140	.99	24	28	.86	80	69	1.16	14	18	.77	52	49	1.06	106	111	.96
33–43	2.90	3.44	.84	11	13	.85	99	99	1.00	29	32	.91	50	47	1.06	35	34	1.03	42	41	1.02	128	134	.96
43–53	3.03	3.60	.84	11	12	.92	94	89	1.06	30	34	.88	49	47	1.04	37	36	1.03	41	41	1.00	128	126	1.02
57	Right ureteral catheter deliberately advanced into right kidney additional 8–10 cms. without causing pain to the patient, and then withdrawn to previous level.																							
53–60	3.96	3.36	1.18	14	13	1.08	92	99	.93	40	33	1.21	51	49	1.04	40	38	1.05	41	41	1.00	133	131	1.02
60–70	3.30	3.40	.97	14	16	.88	112	119	.94	34	34	1.00	52	50	1.04	40	40	1.00	39	39	1.00	132	135	.98
70–87	2.95	3.04	.97	12	13	.92	107	108	.99	32	31	1.03	54	52	1.04	37	37	1.00	41	41	1.00	128	125	1.02
113	100 mgm. Demerol i.m.																							
113–123	1.90	2.09	.91	11	12	.92	150	153	.98	27	28	.97	79	74	1.07	27	31	.87	58	57	1.01	135	138	.98
124	Infusion changed to 8% urea in saline at 9.2 ml/min to deliver 1.63 mg/ml Inulin, 0.87 mg/ml PAH and 10 mU/kg/hr ADH.																							
138	10 mU ADH/kg given I.V.																							
163–173	2.75	3.32	.83	16	20	.80	151	152	.99	43	51	.84	79	77	1.03	88	92	.97	116	115	1.01	294	302	.97
173–183	3.82	4.36	.88	17	20	.85	113	119	.95	42	48	.88	57	56	1.02	92	92	1.00	105	101	1.04	269	255	1.05
183–193	4.58	4.96	.92	18	20	.90	103	103	1.00	45	48	.94	51	50	1.02	92	92	1.00	98	98	1.00	270	264	1.02
203–213	4.52	5.18	.87	17	20	.85	99	100	.99	44	50	.88	49	49	1.00	92	92	1.00	103	105	.98	273	266	1.03

drawn to its previous site. The patient experienced no discomfort and was unaware of any activity other than the collection of specimens. Urine flow, GFR and RPF became *less* from the right kidney than the left. Perhaps of more importance is the relative persistence of these artificially induced changes for at least sixty minutes. The lesson is clear: Once ureteral catheters are placed in the mid-ureter, they should not be moved again. In the rare instance where this is necessary because of bladder leakage, an appropriate time interval must elapse before definitive collections are again started. With this evidence of physiological reflexes caused by simple catheterization, it would seem that differential renal function studies performed by inflating a balloon in one ureter cannot yield reliable data.

b. Importance of Urine Flow Rates. Once the problem of bladder leakage was solved and catheter artefacts from ureterorenal reflexes recognized, we were in a position to answer the critical question of how fast must the urine flow be in order to yield repeatable data. Without question this is the most important of all problems in carrying out these studies. Our data show categorically that *unless urine flow is at least 2 ml/min/kidney the results have little meaning.* At flow rates less than 2 ml/min/kidney, the error involved can be fifty per cent or greater. Figure 4 represents all collection periods from several patients. Repeatability occurs only when the rate of urine flow is 2 ml/min/kidney or greater. To be sure, some kidneys, ischemic from severe main renal artery stenosis, will not reach this minimum flow rate when the contralateral normal kidney has a flow rate of 10 ml/min or greater. This cannot be avoided, but offers no impediment in diagnosis. However, it does make consecutive agreement in clearance data less likely.

While Figure 4 shows that an occasional ratio of flow rates at low urine flows will represent the true ratio, this is only fortuitous because the clearance calculations are usually meaningless. These large errors result primarily from dead space problems as well as reabsorption of water and electrolytes across the pelvic and ureteral mucosa. For example, in the earlier studies when bladder leakage occurred, we frequently observed that inulin concentration was greater in the bladder urine than in the renal urine. The less the bladder leakage (the slower the flow rate across the ureter), the greater were

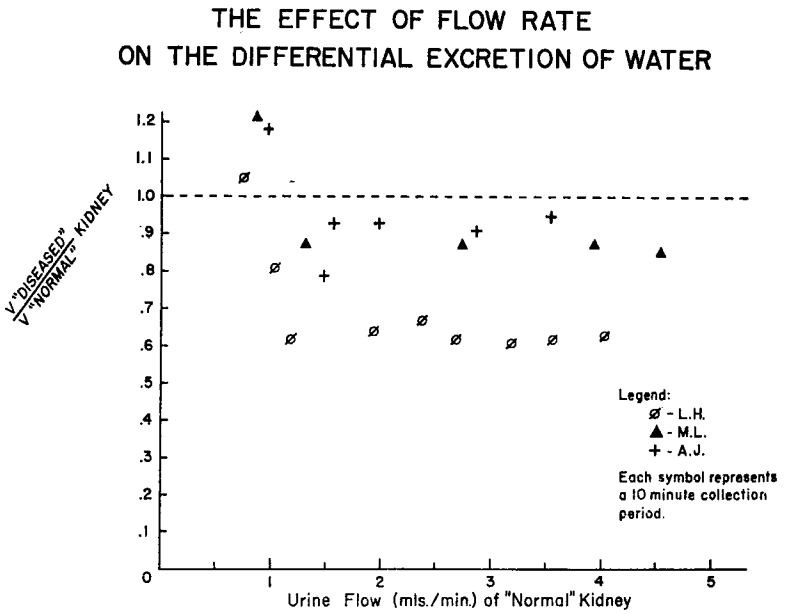


FIG. 4. V equals urine flow rate. The collection periods obtained during the first fifteen minutes of ureteral catheterization are not included. Thus the artifact demonstrated in Figure 3 is excluded. There was no bladder leakage.

These data indicate that unless urine flow rate is 2 ml/min/kidney or greater, the collected urine is not representative of the true urine flow rate.

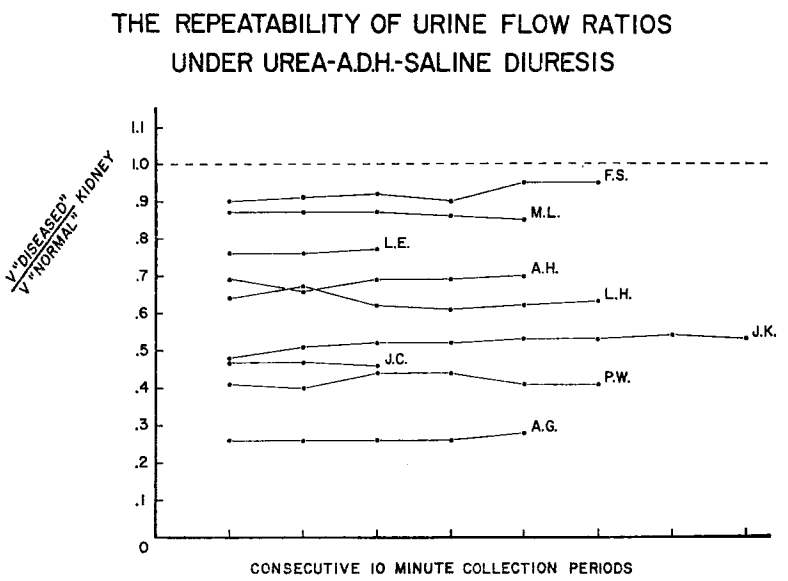


FIG. 5. V equals urine flow rate. The first collection period in each study is excluded as well as any collection which occurred at urine flow rates less than 2 ml/min/kidney. Under these circumstances, the ratio of urine flow rates in consecutive periods should agree within 6%.

these differences in inulin concentration. This was interpreted as water subtraction from the renal urine before reaching the bladder.

In the majority of orally hydrated patients, with initially excellent urine flow rates, it is unusual to obtain more than four ten minute periods before urine flow falls below 2 ml/min/kidney (Chart I, etc.). Certainly ten to twenty per cent of patients, in spite of intensive oral water hydration prior to ureteral catheterization have had negligible urine flows. This is undoubtedly the result of ADH secretion. In some of these patients there was a gradual increase in urine flow to eventually significant rates, but in the majority, there was a minimal increase (still below 2 ml/min) with subsequent fall to even slower rates of urine flow. In practical terms, this means that in a significant number of patients reliable studies cannot be obtained under oral water diuresis.

In the studies reported here, when urine flow rates were less than 2 ml/min/kidney, the urea-saline-ADH was started, followed shortly by a priming dose of ADH.* Almost without exception, within thirty minutes of receiving this urea-saline-ADH infusate, a 70 kg adult will have urine flow rates greater than 2 ml/min/kidney, and within sixty minutes greater than 5 ml/min/kidney. Under these conditions, the ratio of urine flow rates becomes remarkably repeatable. Figure 5 contains the data from a group of patients with varying degrees of unilateral renal damage where *all* consecutive ten minute collection periods were plotted after reaching urine flow rates of 2 ml/min for the normal kidney. Any period occurring within the first fifteen minutes of ureteral catheterization was not included. Repeatability of urine flow ratios within two to four per cent is average for this technique under these conditions. Achievement of this accuracy requires close attention to every detail because, for example, a one milliliter error in a twenty milliliter 10 minute collection period occurring in each kidney and in the opposite direction (1 ml too much in one kidney and 1 ml too little in the other) would result in a ratio error of ten per cent.

* It is generally accepted that the minimal amount of ADH necessary for maximal water reabsorption is between 0.2 and 1.0 mU/kg/Hour. In our early studies we arbitrarily chose ten times this amount. However, at 10 mU/kg/hour of ADH, considerable intestinal cramps and profuse sweating occurred in about thirty per cent of the patients. Accordingly, we reduced the dosage to 5 mU/kg/hour and all side effects disappeared. Recent studies in the dog (18) have established that 1.0 mU/kg/hour may be a conservative estimate, but 5 mU/kg/hour is certainly adequate.

Figure 5 was derived from studies in which the catheter was passed to a point thought to be the renal pelvis. When collections were made from the mid-ureter, the error was slightly greater for the following reason. As diuresis increased, there was no significant increase in the *rate* of ureteral peristalsis. What changed was the *volume* of urine contained in each peristaltic wave. In the dog, for example, increasing urine flow from 0.1 ml/min to 10 ml/min (100 times) did not increase the rate of ureteral peristalsis. There was a minimal increase early in the diuresis, but this soon subsided and increasing urine flow was simply contained in increasing urine volumes of each peristaltic wave. It is apparent then, that when a ten minute period ends sharply at a given second, a significant urine volume (several milliliters) may still be collecting in the renal pelvis awaiting the next peristaltic contraction. Yet this volume of urine has "cleared" the kidney and rightly belongs in the collection vessel. This slight increase in error has been worth the difference in order to avoid artificial ureterorenal reflexes which can persist from thirty to sixty minutes.

c. Prevention of Bladder Leakage. In our earliest studies, we made the mistake of removing the cystoscope. The cytoscope must be left in place in order to detect leakage. Any leakage around the catheters into the bladder will appear immediately at the open stopcock of the cystoscope. There does not seem to be any dead space as the contracted bladder surrounds the cystoscope, and if anything, a positive pressure exists for immediate propulsion of the smallest quantity of urine. In experiments where one ureteral catheter was removed after obtaining repeatable periods with bilateral catheterization, urine appeared at the open stopcock in the same peristaltic fashion as from the ureteral catheter. Further attempts to express more urine by suprapubic bladder compression met with failure. Thus, ureteral urine reaching the bladder presents immediately at the open stopcock. This gives the investigator confidence that bladder leakage has not occurred and immediate recognition of the fact if it does occur. If leakage does occur (about one in forty cases) a simple adjustment of one or both catheters may correct the difficulty.

d. The Use of Urea. We have used 8 per cent urea in patients with all degrees of renal insufficiency and, other than a transient headache and temporary thirst, there have been no side effects. We have not hesitated to infuse the entire 1000 ml of 8 per cent urea (80 grams) at 10 ml/min in an adult. This was usually unnecessary because several repeatable periods at excellent flow rates were obtained long before the infusate was nearing the end. Because the rate of infusion exceeded the urine output in the early stage of the infusion, the rare patient with borderline cardiac failure was fully digitalized before the study. Some patients had a 10 to 15 mm rise in systolic and diastolic blood pressure when they received the entire infusate. The plasma osmolality usually increased fifteen to twenty-five mOsm in the average patient. Serum sodium remained remarkably constant throughout these studies, probably because the saline replaced the osmotic loss in the urine. The serum urea nitrogen rose during the infusion to levels usually between 125 and 250 mg%. There was some elevation of the serum urea nitrogen twenty-four to seventy-two hours later, depending on the degree of renal damage.

The advantages to using urea were as follows: First, urea caused maximal water reabsorption in the ischemic kidney relative to the non-ischemic kidney. Second, urea assured the necessary flow rates for repeatability regardless of ADH secretion in the patient. Without an osmotic diuretic, some ten to twenty per cent of patients were impossible to study. Thirdly, ureteral catheterization studies performed under oral water diuresis were almost invariably terminated with slow urine flow rates and hematuria. This led to blood clots, ureteral colic, and increased chances of acute pyelonephritis. With urea, the study is terminated at flow rates greater than 5 ml/min/kidney, on a rising curve of diuresis, and over the succeeding several hours urine output usually exceeded 1000 ml. To be sure, hematuria was present, but because of the osmotic diuresis post-catheterization complications were reduced to a minimum.

3. Objective Criteria for an Adequate Ureteral Catheterization Study

The studies to be described will demonstrate that the characteristic changes in curable unilateral renovascular hypertension are invariably greater with an infusion of urea, saline and ADH than under oral water diuresis. The con-

ditions for a positive test are those which exhibit the changes to be described in *three consecutive ten minute collection periods, agreeing within 6 per cent of each other in the ratio of their respective urine flow rates.* These criteria can be realized only when flow rates are greater than 2 ml/min/kidney, when bladder leakage is absent, and when any period is discarded which is collected within ten minutes of either the initial catheterization or a later re-adjustment in the position of the ureteral catheter. The single exception of severe main renal artery stenosis, with the attending difficulty of obtaining this flow rate in the ischemic kidney, has already been considered.

4. The Physiological Advantages in Using Bilateral Ureteral Catheterization for the Study of Renal Mechanisms

The collection of urines obtained simultaneously from symmetrically placed ureteral catheters offers an opportunity to examine certain aspects of renal function. Since the composition of glomerular filtrate must be identical in both kidneys, if each segment of the nephron in both the normal and diseased kidney acts on the filtate in exactly the same way, the substances reaching the nephron solely by glomerular filtration should be excreted in the urine in equal concentrations. If the concentrations are different in the presence of unilateral renal disease, this difference may help characterize the functional pattern in that disease. Of the substances measured here, inulin, water and in all probability sodium, meet these requirements of reaching the nephron only by filtration.

Inulin is unique because it is not reabsorbed from the nephron after crossing the glomerulus while 99 per cent of the sodium and water filtered at the glomerulus is reabsorbed. Because the concentration of inulin in the glomerular filtrate is the same as in the plasma, the inulin U/P ratio (the concentration of inulin in the urine/the concentration of inulin in the plasma) is an accurate measure of the *total* water abstracted from the glomerular filtrate between its formation at the glomerulus and the point of collection at the ureteral catheter. If both the diseased and normal kidney reabsorb equal quantities of water, the concentration of inulin in the final urines will be identical. Since the plasma concentrations are the same for both kidneys, reabsorption of water may be compared without reference to the plasma. In the studies to be reported, emphasis is placed on the inulin concentration ratios as a comparative measure of total water reabsorption.

Although the emphasis throughout this research has been to compare total water reabsorption under urea-saline-ADH diuresis, we do not mean to infer that the reabsorption of sodium, together with its attendant anions, is not the active process which determines the reabsorption of water. Indeed, in the patients studied with urea-saline-ADH who had unilateral renal ischemia, sodium excretion fractions (clearance of sodium/clearance of inulin) always show more reabsorption of sodium than reabsorption of water as a comparative ratio between the two kidneys even when the relative reabsorption of water is several times greater in the ischemic kidney. The important point is that a comparison of sodium concentrations does not reflect the magnitude of the basic changes in renal function. This is because differences in sodium concentration reflect only those changes which are secondary to differences in sodium reabsorption in the distal tubule. It will be shown that the quantitatively important change in renal function occurs in the *proximal tubule* where sodium reabsorption proceeds without changes in sodium concentration. Because proximal reabsorption of sodium in both the ischemic and normal kidney can be measured only by reference to water reabsorption (inulin), it is apparent that total water reabsorption is the important consideration.

In these studies, urine osmolality is determined for each kidney and also expressed as a ratio. This information is primarily useful in observing the rates of solute excretion (Uosm $\times$ V) by the two kidneys, and the changes effected when an infusion of urea-saline-ADH is superimposed on a water diuresis. Differences in urine osmolalities between the diseased and normal kidney reflect differences in the distal concentrating mechanism for a given solute load, but do not reflect differences in the total reabsorption of water. If the sodium concentration in the urine is doubled to account for the attendant anions and subtracted from the urine osmolality, the resulting difference should represent an approximation of the osmotic contribution of urea. For this reason, sodium is

expressed in microequivalents per ml (μEq/ml), osmolality in microosmoles per gram of water (μOsm/gm H_2O) and urea, when determined, in micromoles per ml (μM/ml).

Finally, bilateral ureteral catheterization, as a technique for studying renal mechanisms has a distinct advantage in detecting small differences between a diseased and a normal kidney. If one wishes to know only filtration fractions, solute excretion fractions or total water reabsorption (and these are sometimes sufficient for purposes other than the diagnosis of curable renal hypertension) urine flow rates cancel out, removing a large source of error.

Furthermore, since it is the ratio that is important, urines from all collection periods can be analyzed in pairs. In the studies reported here, analysis of the sample from the left kidney was immediately followed by analysis of the sample from the right kidney obtained during the same collection period. Analytic methods were: internal standard flame photometer for Na, cryoscopy for osmolality (4), microdiffusion for urea (8), and colorimetric determinations for inulin (12) and PAH (28).

For certain purposes in this paper, it will be convenient to refer to Chart XV in the appendix. This master chart presents the data from Charts I through XIV in summary form, and was compiled by taking the average of all collection periods which met our criteria for reproducible studies. Brackets to the left of the time columns in Charts I–XIV indicate the exact collection periods used in averaging the data for Chart XV. Data for water and urea diuresis are averaged separately for each patient. The diseased or affected kidney is arbitrarily labeled "X" and always appears first in each column as well as in the numerator of the ratio. Thus, in some patients "X" will be the left kidney and in others, the right kidney. The contralateral normal or less affected kidney is given the symbol "Y" and appears in the denominator of the ratio. It should be noted that the osmolal clearances (C_{osm}) and the free water clearances (C_{H_2O}) are expressed as a percentage of the glomerular filtration rates. This permits a study of these two functions as if nephron populations were equal in each kidney. This not only serves to eliminate original differences in the size of the two kidneys, but, in patients in whom the GFR is reduced by arterial obstruction, the results can be considered as if they occurred in kidneys with equivalent filtration rates.

III. FUNCTIONAL CHARACTERISTICS OF NORMOTENSIVE, UNILATERAL RENAL DISEASE

One is limited to three conditions when considering the common causes of pathological disparity in renal size: (1) Reduction in renal mass from vascular atrophy (ischemia). (2) Reduction in renal mass from destruction of tissue in which we include pyelonephritis, obstruction and calculous disease with and without infection. (3) Reduction caused by failure to develop into symmetrical renal masses. The purpose of this section is to consider the functional characteristics of the latter two conditions.

Although these kidneys resemble those atrophied by ischemia in that they excrete less urine compared to the normal contralateral kidney, it is in the tubular handling of sodium and water that they differ fundamentally.

We studied twenty-five patients who were normotensive despite unilateral reduction in renal mass. Causes for this reduced renal mass were unilateral as well as disparate bilateral pyelonephritis, calculous disease, nephrotomies, unilateral renal tumor, and congenital malformations. Three of these are presented in detail.

P.W. (Chart II) was a 48 year old, colored male who had spent most of his life in a mental institution. An out-patient examiner noted an elevation of blood pressure, and obtained an intravenous pyelogram which disclosed a left pelvic kidney. There was no history of urinary tract symptoms or disease. Admission blood pressures were normal without treatment, and the patient was studied as a control because of a left pelvic kidney.

L.H. (Chart III) was a 31 year old, colored mother of three children. She was admitted with chills, fever and pain in the left lower quadrant. All blood pressures were normal. The urine was infected with E. Coli. After antibiotic therapy had sterilized the urine, her symptoms disappeared. An intravenous pyelogram revealed a left pelvic kidney. Differential renal function studies were performed prior to a retrograde pyelogram.

Because the majority of our normotensive studies have been performed on patients with definite disparity in renal size, one example of a normotensive patient with normal, symmetrical pyelograms is included.

CHART II

Left Pelvic Kidney—No Renal Disease

P.W.—48 C, M.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R
min.	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O		
−72	Start infusion of 5% D/W at 1.1 ml/min to deliver 18 mg/ml Inulin and 10.9 mg/ml PAH.																							
−71	22.4 ml of 10% Inulin and 2.45 ml of 20% PAH I.V.																							
−25	2.5 mg Nupercaine spinal.																							
0	#8 polyethylene catheters passed to each kidney without difficulty.																							
20–28	2.41	5.98	.40	25	62	.40	221	220	1.00	111	282	.39	117	120	.98	38	34	1.12	31	28	1.11	122	118	1.03
28–36	2.34	5.69	.41	28	68	.41	252	251	1.00	123	302	.41	134	135	.99	44	40	1.10	36	32	1.13	135	130	1.04
36–44	2.31	5.69	.41	30	69	.43	213	211	1.00	120	291	.41	132	130	1.02	48	44	1.09	35	33	1.06	140	140	1.00
44–52	2.44	6.23	.39	28	70	.40	241	236	1.02	111	273	.41	116	112	1.03	51	47	1.09	33	32	1.03	142	139	1.02
52–61	2.36	5.72	.41	31	76	.41	275	280	.98	126	293	.43	136	130	1.05	48	44	1.09	38	32	1.18	149	142	1.05
70	Infusion changed to 8% urea in saline at 9.2 ml/min containing 2.17 mg/ml of Inulin, and 1.3 mg/ml of PAH and 9 mU/kg/hr ADH.																							
71–74	Loading dose of 700 mU ADH given I.V.																							
74–82	2.41	6.04	.40	34	85	.40	298	298	1.00	124	305	.41	131	128	1.02	141	139	1.01	79	79	1.00	379	372	1.02
82–90	2.71	6.20	.44	35	84	.42	275	284	.97	124	276	.45	116	113	1.03	141	143	.99	111	111	1.00	397	397	1.00
90–98	2.99	6.86	.44	34	78	.44	239	239	1.00	108	259	.42	92	96	.96	134	130	1.03	116	115	1.01	385	390	.99
112–118	4.10	9.98	.41	37	91	.41	190	192	.99	114	265	.43	71	67	1.06	123	119	1.03	120	127	.94	369	370	1.00
118–130	4.05	9.98	.41	34	82	.41	179	174	1.03	96	228	.42	60	58	1.03	117	117	1.00	133	127	1.04	291	342	.85
	B = .13						B = 212									B = 135								

B = Bladder Leakage.

CHART III

Left Pelvic Kidney—Recurrent Acute Pyelonephritis

L.H.—31 C, F.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R
min.	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O		
−77	1100 ml water given orally.																							
−50	22.4 ml of 10% Inulin and 2.45 ml of 20% PAH given I.V. Start infusion of 5% D/W at 1.1 ml/min containing 13.6 mg/ml Inulin and 7.27 mg/ml PAH.																							
−45	2.0 mg Nupercaine saddle anesthesia.																							
0	#8 polyethylene catheter passed to left kidney without difficulty.																							
7	#8 polyethylene catheter passed to right kidney without difficulty.																							
14–24	2.77	5.46	.51	39	70	.56	246	246	1.00	178	314	.57	100	100	1.00	15	15	1.00	32	32	1.00	71	96	.74
24–34	Bladder leakage noted and right catheter withdrawn 1 cm with cessation of bladder leakage.																							
36–46	0.73	1.18	.62	28	66	.42	648	928	.70	132	283	.47	260	346	.75	72	73	.99	85	112	.76	203	300	.68
48	100 mg Demerol given i.m.																							
46–56	1.32	1.90	.69	52	71	.73	653	624	1.05	239	321	.74	262	248	1.05	47	60	.78	92	96	.96	226	243	.93
56–66	0.78	0.74	1.05	29	31	.94	616	700	.88	132	140	.94	244	273	.89	49	62	.79	87	93	.94	220	258	.85
69	Change infusion to 8% urea in saline at 9.2 ml/min containing 1.63 mg/ml Inulin, .87 mg/ml PAH and 9 mU ADH/kg/hr																							
77	50 mg Demerol given i.m.																							
82–92	0.83	1.03	.81	63	104	.61	1270	1512	.84	384	571	.67	676	802	.84	111	147	.76	264	273	.97	572	661	.87
92–102	1.23	1.93	.64	50	96	.52	674	826	.82	300	535	.56	363	401	.91	81	104	.78	304	330	.92	518	612	.85
102–112	1.60	2.38	.67	46	74	.60	479	517	.93	287	417	.69	259	254	1.02	68	87	.78	325	331	.98	500	555	.90
112–122	1.67	2.68	.62	40	69	.58	399	430	.93	246	391	.63	214	211	1.01	72	79	.91	354	351	1.02	512	553	.93
117–120	9 mU ADH per kg given I.V.																							
124	50 mg Demerol given i.m.																							
143–153	2.20	3.55	.62	37	66	.56	281	308	.91	206	322	.64	135	131	1.03	79	82	.96	338	341	.99	530	551	.96
153–163	2.53	4.02	.63	39	67	.58	255	277	.92	228	354	.64	130	126	1.03	74	83	.89	352	345	1.02	522	542	.96

CHART IV

Interstitial Cystitis—No Renal Disease

A.M.—38 W, F.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L
min.	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O		
−43	20.8 ml 10% Inulin and 2.27 ml 20% PAH given I.V.; start infusion of 8% urea in saline at 9.2 ml/min to deliver 2.39 mg/ml Inulin and 1.3 mg/ml PAH.																							
−38	2.5 mg Nupercaine saddle anesthesia.																							
0	#8 polyethylene catheter passed to left kidney with ease.																							
1	#8 polyethylene catheter passed to right kidney with ease.																							
3–13	1.81	1.99	.91	59	61	.97	723	678	1.07	193	204	.95	279	268	1.04	65	65	1.00	507	507	1.00	680	670	1.01
13–23	2.01	2.05	.98	51	51	1.00	564	550	1.03	175	178	.98	227	227	1.00	70	72	.97	488	486	1.00	670	675	.99
23–43	2.25	2.38	.95	51	47	1.09	469	459	1.02	175	166	1.05	191	192	1.00	78	78	1.00	476	475	1.00	650	655	.99

A.M. (Chart IV) a 38 year old, white female had been previously diagnosed as having interstitial cystitis. Her blood pressure was normal, the urine sterile, and there was no history of renal symptoms. Urea-saline-ADH was started prior to cystoscopy and ureteral catheterization studies performed.

P.W. (Chart II)and A.M. (Chart IV) do not show any differences in the concentration of inulin between the two kidneys. In every case in which there has been a disparity in renal size, without a history of infection or calculous disease, this pattern has been present, indicating that the two kidneys reabsorb water similarly. The glomerular filtration rate, measured by the inulin clearance, is UV/P.* GFR in the left kidney, C_1, equals $U_1 V_1/P$, and in the right kidney, C_2 equals U_2V_2/P. The plasma inulin concentrations are the same. If $U_1 = U_2$, then it follows that $V_1/C_1 = V_2/C_2$, that is, the rate at which urine is excreted per unit GFR is the same in the two kidneys even though GFR may be different. This is apparent in P.W. (Chart II) in whom the ratio of urine flow varied from .40 to .44 and the ratio of the GFR is the same.

When one kidney has been infected the inulin pattern is not the same. The majority of our twenty-five patients with normal blood pressure and a disparity in renal size have acquired their disparity from infection, calculous disease, or renal surgery for correction of these conditions. These studies show a *decrease* in the concentration of inulin in the urine from the diseased kidney when compared with the contralateral kidney. In other words, these diseased kidneys excrete *more* urine per unit GFR than the contralateral normal kidney. In the case of L.H. (Chart III), difficulty occurred with water diuresis, and the data collected prior to 92 min. are not valid. The next five consecutive periods all show more water excreted per unit GFR from the left kidney than from the right kidney. For example, in period 143–153, the ratio of urine flow is .62 while the GFR ratio is .56. The most direct approach to this point is to note that the inulin concentration is persistently reduced in the urine from the left kidney by 7 to 18 per cent. In one sense, we are simply expressing what is already known: in pyelonephritis, active or inactive, renal tubules are less able to concentrate urine, a function which occurs in the medulla. Hereafter, we will refer to this pattern of reduced inulin concentration in the kidney excreting less water as that of a "water-losing nephron". In patient P.W. (Chart II) the U_{In} ratios are close to unity because the pelvic kidney is simply a normal kidney with a smaller mass.

Figure 6 is a plot of the collection periods in a large number of these normotensive patients with varying degrees of renal damage and reduced urine excretion. Each point compares the ratio of urine flows to the ratio of urine inulin concentrations in the two kidneys. Inulin concentration ratios are usually less than 1.00 and never more than 1.06 (which may be 1.00 within the error of the method). We have yet to study a kidney in a normotensive patient which excretes less urine and contains inulin in a concentration

* Plasma clearance of inulin (ml/min)

$$= \frac{\text{U (urine conc. of inulin in mg \%)} \times \text{V (urine flow rate in ml/min)}}{\text{P (plasma conc. of inulin in mg \%)}}$$

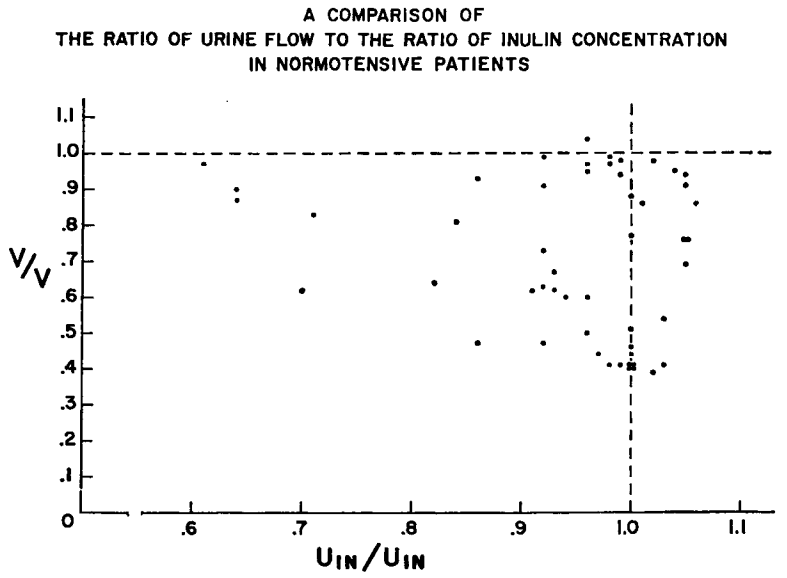


FIG. 6. V equals urine flow rate. U_{In} equals the concentration of inulin in the urine. This figure indicates that regardless of the reduction in renal mass and V in a diseased kidney in normotensive patients, that kidney does not show excessive water reabsorption when compared to the contralateral kidney. When the U_{In}/U_{In} ratio approaches 1.0, total water reabsorption per unit GFR is the same for both the diseased and the normal kidney. 1.06 is within the error of the laboratory method when the concentrations are probably equal.

ratio greater than 1.06 when compared to the contralateral kidney.

Chart XV shows that the sodium excretion fractions as well as the rate at which osmotically active substances are cleared from the plasma per unit GRF are identical for both kidneys in these three patients, and this in spite of marked differences in the size of the kidneys in P.W. and L.H.

In summary, when a disparity in renal size is present in normotensive individuals, the comparative patterns of water reabsorption indicate that either these processes are identical (Figure 7-A) or, in the presence of medullary damage, the diseased kidney *fails* to reabsorb water in comparison to the contralateral kidney (Figure 7-B). In the latter instance, the concentration of inulin is less in the smaller kidney with the lower urine flow rate when compared to the contralateral kidney with the greater urine flow rate.

IV. THE FUNCTIONAL CHARACTERISTIC OF CURABLE, UNILATERAL RENOVASCULAR HYPERTENSION

Four cases of surgically proven main renal artery disease and three cases of segmental artery

	Congenitally Small Kidney	Contralateral Normal Kidney	Diseased/ Normal Kidney
A. Urine Flow	2 ml/min	6 ml/min	.33
Urine Inulin Concentration	200 mg %	200 mg %	1.00
	Pyelonephritis		
B. Urine Flow	2 ml/min	6 ml/min	.33
Urine Inulin Concentration	150 mg %	200 mg %	.75
	Occlusive Main Renal Artery Disease		
C. Urine Flow	2 ml/min	6 ml/min	.33
Urine Inulin Concentration	600 mg %	200 mg %	3.00

FIG. 7. This table illustrates the characteristic pattern of total water reabsorption in three conditions which frequently produce a disparity in the size of the two kidneys.

disease are presented in evidence of the fact that a pathological reabsorption of water should be the criterion for the diagnosis of curable, unilateral renovascular hypertension. In the four main renal artery lesions, a precipitous drop in blood pressure across markedly stenotic obstructions was recorded at surgery. The three segmental lesions all had pathological obstructions in their respective branches. Charts V, VI, VII and VIII represent the ureteral catheterization data on the main renal artery obstructions, while Charts IX, X and XI are studies on the segmental lesions. The pertinent history, physical and laboratory findings on each of these patients can be found in the appendix.

The following conclusions seem warranted from these functional studies:

1. The Functional Lesion

The single, invariable characteristic of renal ischemia is excessive reabsorption of sodium and water. The cause is occlusive disease of the renal arteries which reduces renal plasma flow. The reduction in renal plasma flow decreases the volume of glomerular filtrate, but the renal tubules continue to reabsorb sodium and water as if the volume of filtrate was unchanged. This leads to an excessive reabsorption of sodium and water, predominantly in the proximal tubule where sodium concentration remains equimolar with plasma. Some of the excessive reabsorption of water occurs in the distal tubule, and it is here that a reduction in the concentration of sodium may reflect the characteristic defect.

For example, if vascular stenosis reduces renal blood flow by 20 per cent, and if the filtration fractions are approximately the same, we would expect a 20 per cent reduction in urine excretion compared with the contralateral normal kidney. If the normal kidney excreted 100 ml of urine in a given time period, the ischemic kidney with a 20 per cent reduction in GFR should excrete 80 ml and the inulin concentration would be the same in both renal urines provided reabsorption of water was identical in both kidneys. This does not occur. There is increased reabsorption of water in the ischemic tubule. The ischemic kidney excretes, not 20 per cent, but much less water. The smallest difference in thirteen patients with main renal artery occlusions has been a 67 per cent reduction in urine flow rate when the studies were performed using urea, saline and ADH. This excessive water reabsorption is reflected exactly by a proportional increase in the concentration of inulin. Because the filtration fraction (the fraction of renal plasma flow filtered through glomeruli: GFR/RPF) is nearly the same in the ischemic as in the normal kidney, differences in PAH concentration serve equally as well as inulin. The filtration fractions occasionally show some disparity but the excessive reabsorption of water in the ischemic kidney, at least in the main renal artery obstructions, is so large that small initial differences in the con-

CHART V

Left Main Renal Artery Obstruction

A.C.—50 W, M.

Time	Urine Flow			Inulin Clearance			Inulin Conc.			PAH Clearance			PAH Conc.			Urine Sodium			Urine Urea			Urine Osmolality		
	L	R	R/L	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R
min.	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O		
0	#8 polyethylene catheters passed to each kidney without difficulty. 1000 ml water taken orally 60–120 minutes before catheterization.																							
15–47	.08	.62	.10													51	173	.29	103	157	.66	459	643	.71
47–71	.48	2.88	.17													59	115	.51	153	90	1.70	380	413	.92
73	17 ml of 10% Inulin + 1.9 ml of 20% PAH given I.V.; Infusion of Inulin (12 mg/ml) and PAH (7 mg/ml) in 5% D/W started at 1.9 ml/min																							
84–87	2.43	8.33	.29	63	114	.55	510	269	1.90	204	410	.50	174	102	1.71	15	39	.39	46	33	1.40	105	105	1.00
93–98	2.88	7.14	.40	51	75	.68	350	206	1.70	195	324	.60	140	93	1.51	11	32	.34	34	37	.92	78	90	.86
98–103	2.30	6.86	.34	38	72	.53	319	197	1.62	159	270	.59	143	82	1.75	12	37	.32	59	32	1.84	58	105	.55
105	Infusion changed to 8% Urea, Inulin (2.4 mg/ml), PAH (1.4 mg/ml); ADH (48 mU/hr) in saline at 9.0 ml/min. Also 100 mU ADH injected I.V. within a 3 minute period.																							
119–127	.64	3.12	.20	47	76	.62	1467	437	3.36	274	381	.72	859	244	3.52	113	138	.82	185	167	1.11	710	470	1.51
131–137	1.58	5.20	.30	36	57	.63	451	218	2.07	351	400	.88	444	154	2.88	85	121	.70	316	191	1.65	555	475	1.16
137–143	1.55	7.16	.22	43	72	.60	530	192	2.76	198	334	.59	265	97	2.73	83	106	.78	316	141	2.24	480	363	1.32

CHART VI

Left Main Renal Artery Obstruction

F.W.—49 W, M.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R
min.	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gmH₂O		
−160 to −100	1000 ml water p.o.																							
−65	Blood pressure 160/80–90																							
−65 to −45	Caudal Nupercaine anesthesia. 105 ml 5% D/W given I.V.—then discontinued.																							
−43	24.0 ml of 10% Inulin and 2.6 ml of 20% PAH given I.V.; start infusion of 5% D/W at 1.0 ml/min to deliver 20 mg/ml Inulin and 10.9 mg/ml PAH.																							
−30 to −15	500 ml of water p.o.																							
0	#7 polyethylene catheter easily passed to middle of left ureter.																							
1	#7 polyethylene catheter easily passed to middle of right ureter.																							
3–13	3.10	18.4	0.17	26	77	0.34	172	85	2.03	97	320	0.30	57	31	1.85	7.9	21.1	0.37	23	17	1.35	60	70	0.86
13–23	3.08	18.3	0.17	26	77	0.34	172	85	2.03	95	305	0.31	54	29	1.86	8.6	21.6	0.40	24	17	1.41	60	70	0.86
36–46	1.80	14.5	0.12	21	79	0.27	237	110	2.15	90	297	0.31	88	36	2.45	13.4	31.6	0.42	97	57	1.70	85	95	0.89
46–56	0.46	6.2	0.07	18	69	0.26	798	224	3.56	51	320	0.16	193	91	2.13	20.6	44.0	0.47	152	104	1.46	160	140	1.14
57	Infusion changed to 8% urea in saline at 9.2 ml/min to deliver 2.39 mg/ml of Inulin, 1.3 mg/ml PAH, and 5 mU/kg/hr ADH.																							
58	5 mU/kg ADH given I.V.; Blood pressure 170/90.																							
61–71	0.25	5.7	0.04	20	137	0.15	1645	487	3.38	99	931	0.11	695	286	2.43	67.9	137.8	0.49	208	246	0.84	285	370	0.77
71–81	0.35	6.8	0.05	30	88	0.34	1660	251	6.61	207	506	0.41	1042	130	8.00	78.5	136.0	0.58	278	356	0.78	435	405	1.07
82	Blood pressure 190/98																							
83	35 mg Demerol I.V.																							
84–94	0.59	9.0	0.06	27	81	0.34	935	182	5.14	129	516	0.25	386	101	3.83	61	117	0.52	235	128	1.83	480	365	1.32
96–106	0.75	11.3	0.07	25	90	0.28	661	156	4.24	114	533	0.21	268	83	3.22	56	109	0.51	274	126	2.17	470	355	1.32
107–117	0.80	11.0	0.07	30	85	0.35	759	156	4.87	132	505	0.26	289	81	3.58	56	107	0.52	289	149	1.94	505	370	1.36

CHART VII

Left Main Renal Artery Obstruction

V.M.—24 C, F.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R
min	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H₂O		
−150 to −70	1000 ml H₂O p.o.																							
−68	17.6 ml of 10% Inulin and 1.93 ml of 20% PAH given I.V.; start infusion of 5% D/W at 1.0 ml/min to deliver 20 mg/ml Inulin and 10.9 mg/ml of PAH.																							
−60	2 mg Nupercaine saddle anesthesia. Blood pressure 160/120.																							
−50 to −10	400 ml H₂O p.o.																							
0	#8 polyethylene catheter passed easily to the middle of the left ureter.																							
1–36	#8, #7, #6 polyethylene catheters would not pass up the right ureter. #5 regular woven catheter would pass 4 cm and no further. #4 woven would pass to renal pelvis. Finally decided on #5 woven up 4 cm.																							
43–53	3.21	3.88	0.82	62	55	1.13	351	260	1.35	280	292	0.96	128	110	1.16	7.7	18.2	0.43	46	35	1.31	95	110	.86
53–63	4.16	4.06	1.03	54	58	0.93	239	260	0.92	249	319	0.78	88	115	0.76	6.7	9.6	0.70	30	34	.88	70	90	.78
63	Infusion changed to 8% urea in saline at 9.2 ml/min to deliver 2.39 mg/ml Inulin, 1.3 mg/ml PAH, and 5 mU/kg/hour ADH.																							
63–73	4.63	4.83	0.96	66	73	0.90	262	276	0.95	496	526	0.94	157	160	0.98	9.0	8.1	1.11	29	32	.91	70	80	.87
67	5 mU/kg of ADH given I.V.																							
73–85	1.05	3.78	0.28	56	92	0.61	975	443	2.20	333	750	0.45	465	290	1.60	42.0	57.0	0.73	167	118	1.40	320	265	1.21
85–95	1.63	4.17	0.39	72	83	0.87	805	364	2.21	431	551	0.78	387	194	2.00	59.0	80.0	0.74	347	190	1.83	525	365	1.44
95–105	1.25	4.97	0.25	40	80	0.50	585	294	2.00	231	525	0.44	270	155	1.75	55.0	69.0	0.79	321	182	1.76	480	350	1.37
105	Blood pressure 160/120																							
105–115	1.58	5.49	0.29	56	78	0.72	650	259	2.51	322	470	0.69	299	125	2.39	24.0	62.0	0.39	370	210	1.76	510	350	1.46
115–125	2.14	5.90	0.36	62	81	0.77	526	250	2.11	364	482	0.76	249	120	2.08	28.0	66.0	0.43	363	214	1.70	485	365	1.33
125–135	2.17	5.84	0.37	52	73	0.72	442	229	1.93	285	416	0.69	192	104	1.84	32.0	75.0	0.43	338	210	1.61	490	380	1.29
140	Blood pressure 160/120. No bladder leakage throughout experiment.																							

CHART VIII

Right Main Renal Artery Obstruction

J.B.—12 W, F.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L
min	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O		
−140 to −70	800 ml of water p.o.																							
−67	14.7 ml of 10% Inulin and 1.6 ml of 20% PAH given I.V.; start infusion of 5% D/W at 1.0 ml/min to deliver 13.6 mg/ml Inulin and 7.3 mg/ml of PAH.																							
−60	1.0 mg of heavy Nupercaine saddle anesthesia.																							
−30	400 ml of water p.o.; blood pressure 152/106-110.																							
0	#7 polyethylene catheter passed easily to middle of left ureter.																							
5	#6 polyethylene catheter passed with difficulty 3 cm up right ureter.																							
16–25	0.15	3.34	0.04	26	62	0.42	2665	287	9.30	149	340	0.44	1160	119	9.76	QNS	22.3		101	35	2.89	285	105	2.71
25–35	0.25	3.10	0.08	Urine used for biological studies.																				
35–45	0.20	2.85	0.07	33	58	0.57	2605	315	8.28	286	353	0.81	1172	145	8.10	16.3	26.8	.61	117	42	2.79	325	130	2.50
45–55	0.15	1.62	0.09	24	51	0.47	2500	494	5.06	151	292	0.52	1180	211	5.60	20.3	32.5	.61	122	55	2.22	345	170	2.03
55	25 mg Demerol given I.V.																							
56	Change infusion to 8% urea in saline at 8.6 ml/min to deliver 1.63 mg/ml Inulin, .87 mg/ml PAH, and 5 mU/kg/hour ADH																							
55–66	0.14	1.94	0.07	27	75	0.37	3150	600	5.25	177	596	0.30	1520	359	4.24	28.7	45.9	.63	139	63	2.21	410	215	1.91
71–81	0.4	7.27	0.05	Lab accident												54.5	87.6	.63	291	125	2.33	600	350	1.71
75	Blood pressure 180/110; 5 mU/kg ADH given I.V.																							
82–92	0.52	8.74	0.06	Urine used for biological studies.																				
93–103	0.95	12.17	0.08	29	73	0.40	484	93	5.20	180	476	0.38	221	46	4.83	34.5	80.4	.44	377	124	3.04	510	310	1.65
103–113	1.50	14.17	0.11	32	90	0.36	329	98	3.36	199	391	0.52	155	32	4.80	33.5	74.6	.45	326	124	2.63	430	300	1.43
116	Blood pressure 176/110																							
119–129	1.48	11.09	0.13	Urine used for biological studies.																				
146–156	0.68	6.47	0.11	Urine used for biological studies.																				

CHART IX

Right Segmental Artery Obstruction

J.K.—45 W, M.

Time	Urine Flow			Inulin Clearnace			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L
min	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O		
−210–90	1000 ml water given orally.																							
−60	24.3 ml of 10% Inulin and 2.6 ml of 20% PAH given I.V.; Start infusion of 5% D/W at 1.1 ml/min to deliver 20 mg/ml of Inulin and 10.9 mg/ml of PAH.																							
−50	2.5 mg Nupercaine saddle anesthesia.																							
0	#8 polyethylene catheter passed to left kidney with ease.																							
5	#7 polyethylene catheter passed to right kidney with ease.																							
15–25	0.90	1.55	.58	54	88	.62	1122	1065	1.05	197	304	.65	495	444	1.11	72	68	1.06	85	86	.99	281	287	.98
25–35	1.71	3.14	.54	46	79	.58	508	472	1.08	173	282	.61	229	203	1.12	38	37	1.03	47	42	1.12	146	150	.97
35–45	1.88	3.11	.60	46	73	.63	455	439	1.04	164	262	.63	197	190	1.03	37	37	1.00	38	42	.90	138	142	.97
45–55	2.08	3.56	.58	44	72	.61	395	379	1.04	152	246	.62	165	156	1.05	31	29	1.07	38	35	1.09	111	112	.97
55–65	2.44	4.37	.56	49	77	.64	357	330	1.08	167	281	.59	148	145	1.01	27	26	1.04	30	32	.94	103	97	1.06
65–75	2.05	3.63	.56	46	76	.61	419	390	1.07	157	253	.62	173	158	1.09	30	29	1.03	34	33	1.03	114	111	1.03
81	100 mg Demerol.																							
75–85	1.21	2.24	.54	43	71	.61	671	585	1.14	139	227	.61	261	230	1.13	55	52	1.06	49	49	1.00	192	182	1.05
87	Infusion changed to 8% urea in saline at 9.2 ml/min containing 2.39 mg/ml Inulin, 1.3 mg/ml PAH and 9 mU/kg/hr ADH.																							
102	9 mU/kg ADH given I.V.																							
115–125	2.39	4.67	.51	46	75	.61	360	299	1.20	176	305	.58	166	148	1.12	126	128	.98	189	168	1.13	458	444	1.03
123	50 mg Demerol i.m.																							
135–145	2.87	5.54	.52	42	68	.62	273	230	1.20	162	262	.62	128	107	1.19	111	112	.99	200	180	1.11	430	407	1.05
155–165	2.76	5.24	.53	40	67	.60	272	238	1.14	168	269	.63	137	116	1.18	93	98	.95	250	215	1.16	448	431	1.04
175–185	3.11	5.76	.54	39	66	.59	235	215	1.09	175	284	.62	127	112	1.13	85	90	.94	268	242	1.11	439	430	1.02

CHART X

Right Segmental Artery Obstruction

B.LeV.—25 W, F.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality			Urine Creatinine		
	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L
min	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O			mg/100 ml		
−133	1000 ml of water given orally.																										
−73	12.5 ml of 10% Inulin and 1.4 ml of 20% PAH given I.V.; start infusion of 5% D/W at 1.1 ml/min to deliver 20 mg/ml. Inulin and 10.9 mg/ml PAH.																										
−69	1.6 mg heavy Nupercaine saddle anesthesia. Blood pressure 220/160. Pulse 100.																										
−10	400 ml of water given orally.																										
0	#8 polyethylene catheter passed easily to mid-point of left ureter.																										
1	#8 polyethylene catheter passed easily to mid-point of right ureter.																										
3–13	2.58	4.99	.52	34	47	.72	410	292	1.41	142	181	.78	192	127	1.51	24.4	22.3	1.09	19	14	1.36	85	70	1.21	8.85	6.15	1.44
13–23	2.94	4.90	.60	32	47	.68	337	296	1.14	127	169	.75	152	121	1.26	18.7	20.1	.95	16	13	1.23	65	65	1.00	6.90	6.00	1.15
23–33	3.42	6.05	.57	31	49	.65	285	251	1.14	131	181	.72	134	105	1.28	16.5	17.9	.94	14	14	1.00	60	55	1.09	6.15	5.55	1.11
34	100 mg Demerol i.m.																										
37–47	2.82	5.19	.54	32	49	.65	351	291	1.21	109	163	.67	135	110	1.23	14.4	14.4	1.00	14	13	1.07	55	50	1.10	6.45	5.85	1.10
47–57	4.14	6.77	.61	39	55	.71	290	251	1.16	136	186	.73	115	96	1.20	14.4	12.9	1.08	12	12	1.00	50	45	1.11	5.55	4.65	1.19
60	25 mg Demerol. Pulse 92. Infusion changed to 8% urea in saline at 9.2 ml/min to deliver 2.39 mg/ml Inulin, 1.3 mg/ml. PAH, and 5 mU ADH/kg/hr.																										
65	2 ml of bladder leakage over past 5 min. Left catheter advanced 4 cm leakage ceased.																										
74	5 mU ADH/kg Loading dose.																										
72–82	1.12	2.54	.44	35	64	.55	968	780	1.24	141	288	.49	441	401	1.10	87.6	84.7	1.04	230	210	1.09	465	425	1.09	17.55	13.65	1.29
82–92	1.28	2.30	.56	35	56	.62	838	758	1.11	139	209	.67	387	317	1.22	83.3	86.1	.97	341	332	1.03	560	540	1.04	15.90	14.10	1.13
92–102	1.87	3.19	.59	35	53	.66	580	519	1.12	138	197	.70	259	216	1.20	80.4	83.3	.96	323	315	1.03	510	500	1.02	11.25	9.60	1.17
102–112	2.55	5.26	.48	37	57	.65	450	338	1.33	128	210	.61	176	140	1.26	76.1	81.8	.93	305	264	1.15	465	435	1.07	8.55	6.60	1.30
112–122	3.08	6.46	.48	35	60	.58	351	286	1.23	141	228	.62	160	124	1.30	70.3	77.5	.90	294	263	1.12	450	420	1.07	6.90	6.15	1.12
128	B.P. 208/135. Pulse 86. Patient comfortable. 650 ml 8% urea in saline absorbed (approx.). Plasma osmolality = 265 at start, 295 after infusion.																										

CHART XI

Right Segmental Artery Obstruction

W.G.—19 W, M.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L
min	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O		
0	#7 standard ureteral catheters passed to each kidney—Cultures obtained— 600 ml water, p.o., 60 min before. Nupercaine saddle anesthesia, 2.5 mg.																							
15–26	.36	.53	.68													178	200	.89	197	179	1.10	716	752	.95
	B = .041																							
27	21 ml of 10% Inulin and 2.3 ml of 20% PAH plus 200-300 mU ADH given I.V.; Infusion started at 10 ml/min containing 4% urea, 100 mU ADH/hr, 2 mg Inulin/ml, and 1.4 mg/ml of PAH. (Too much ADH by error.)																							
30	Severe wretching. Profuse sweating and defecation. No fever. B.P. stable.																							
67	Patient quiet and comfortable.																							
72–77	.84	2.92	.29	35	86	.41	611	433	1.41	132	286	.46	284	178	1.60	128	138	.93	164	143	1.15	538	512	1.05
	B = .34		.40	48		.59																		
80–85	1.12	4.22	.27	31	97	.32	409	331	1.24	117	319	.37	188	137	1.37	134	139	.96	193	158	1.22	519	472	1.10
	B = 1.06		.52	60		.62	B = 573																	

"B" is equal to the amount of bladder leakage, and if it is all *assumed* to come from the right kidney, the resulting ratio and higher GFR for the right kidney are indicated. In calculating the adjusted GFR, the inulin concentration of the right kidney urine was used. The PAH clearances for the right kidney do not include this significant bladder leakage. This accounts for the low ratio of C_{PAH} in this chart as well as Chart XV.

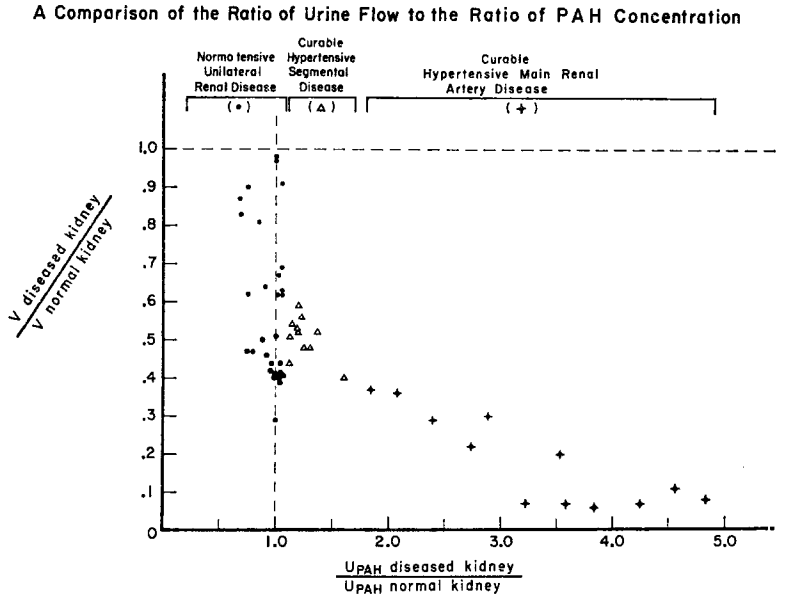


FIG. 8. V equals urine flow rate. U_{PAH} equals the concentration of PAH in the urine. These data show that comparative concentrations of PAH also reflect the characteristic excessive water reabsorption in the ischemic kidney. This is possible because the slight increase in the filtration fraction of the ischemic kidney is insignficant when compared to the excessive water reabsorption along the nephron.

Approximately 3 collection periods per patient are included from the three segmental and four main renal artery occlusions presented in this paper.

centration of PAH in the proximal tubule are not significant. Figure 8 compares the ratio of urine flow rates to the ratio of PAH concentrations (U_{PAH}/U_{PAH}) in patients with normotensive unilateral renal disease and the seven patients presented in this section who had curable renovascular hypertension. Because the determination of PAH is a simple, accurate laboratory method, it offers some advantages over inulin as a measure of the relative increase in water reabsorption secondary to renal ischemia.

Thus, the distinguishing characteristic of the reduced urine flow rate in curable unilateral renal ischemia is not reduction in sodium concentration but a relative increase in the total reabsorption of water. When ischemia involves a small segment of an otherwise normal kidney (Charts IX, X and XI) sodium concentration may be the same or even increased in the urine from the ischemic kidney in comparison with the contralateral kidney, but there still is excessive water reabsorption. Even in the main renal artery lesions the reduction in urine sodium concentration under oral water diuresis does not compare as a differential measurement with the magnitude of increased water reabsorption under urea-saline-ADH diuresis. For example, patient A.C., Figure 9 had a 3 to 1 difference in urine sodium concentrations with water diuresis but a 6 to 1 difference in the concentration of inulin. Patient F.W., Chart VI had a 2.5 to 1 difference in sodium but a 5 to 1 increase in the concentration of inulin. On the other hand, if sodium concentration is divided by the inulin concentration to indicate the comparative sodium excretion fractions (Chart XV),* the relative differences in *total* reabsorption of sodium are always greater than the relative differences in *total* reabsorption of water. This may constitute further evidence that salt reabsorption is the active process by which water is reabsorbed in the renal tubule.

Calculation of the free water clearances shows that the site of this excessive water reabsorption is not limited to the distal tubule. The data in Chart XV indicate that differences between the

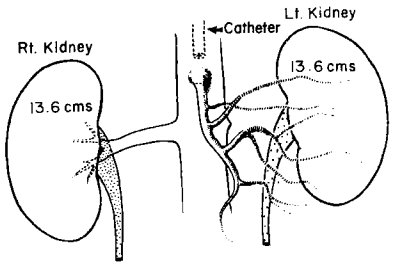
* Comparing sodium excretion fractions by U_{Na}/U_{In} for each kidney applies only for the resulting ratio, X/Y, in Chart XV. The exact percentage of the filtered sodium excreted for each kidney, X and Y, requires the complete calculation of $C_{Na}/C_{In} \times 100$.

ischemic and non-ischemic kidney in the osmotic load per 100 ml of glomerular filtrate ($C_{osm}/C_{In} \times 100$) as well as the "free" water excreted ($+C_{H_2O}$) or reabsorbed ($-C_{H_2O}$) per 100 ml of glomerular filtrate ($C_{H_2O}/C_{In} \times 100$) cannot possibly account for the difference in urine flow rates. Therefore, the distal segment of the nephron, where solute free water is generated by the reabsorption of osmotically active solutes, cannot account for the increase in total water reabsorption characteristic of renal ischemia.

However, the ratio of the sodium excretion fractions (the percent of filtered sodium excreted) corresponds closely to the differences in urine flow rates. It is reasonable that sodium reabsorption is the mechanism by which this excessive reabsorption of water takes place, and that the proximal tubule must play the significant role in the total reabsorption.

The functional lesion in segmental renal ischemia deserves special consideration for several reasons. First, the basic question of how much renal tissue must be ischemic in order to produce symptomatic hypertension can be answered in these patients. Second, these segmental lesions have not been detected in the past by ureteral catheterization studies. The anatomical approach of aortography has obvious disadvantages in detecting the more distal lesions in the cortex. In these segmental or branch lesions, sodium concentration has not been reduced in the urine from the ischemic kidney. In fact, the sodium concentration has often been slightly increased compared to the contralateral normal kidney. The Howard Test (50 per cent or greater reduction in water associated with a 15 per cent or greater reduction in sodium concentration), therefore, is not reliable in the segmentally ischemic kidneys. This is equally true of the segmental lesions reported here. The inulin concentration data in segmental renal ischemia (Charts IX, X and XI) show that these lesions are not non-functioning, as suggested by Connor and Howard (7), but reabsorb water in an abnormal fashion qualitatively similar to that seen in main renal artery obstructions. They do not show the several hundred per cent increase in the concentration of inulin characteristic of main renal artery obstruction because they involve only a portion of one kidney, but they do show a 20 per cent or greater increase in the concentration of inulin, which is significantly greater than the 6 per cent maximal increase (the error of the method) in normotensive patients with a unilateral reduction in renal mass. Furthermore, urine flow rate is decreased in the segmentally ischemic kidney by at least 45 per cent compared to the contralateral kidney.

With the realization that increased relative reabsorption of water and sodium is the characteristic functional pattern rather than reduction in sodium concentration, it is possible to explain why segmental lesions excrete sodium in equal and possibly greater concentration than the contralateral normal kidney. Suppose that the segmental area occupies 25 per cent of one kidney. In the four main renal artery lesions reported here, the ischemic kidney excreted urine at a rate between 1/6th and 1/14th of the normal kidney. If we take the least reduction in urine flow, the maximum contribution of the 25 per cent ischemic segment to the total urine output is only 1/6th of 25 per cent or 4.2 per cent. Suppose the normal kidney excretes in a unit time 100 ml of urine containing 50 mEq/L of sodium. The kidney with segmental renal ischemia excretes 75 ml with 50 mEq/L of sodium from the 75 per cent



	RIGHT	LEFT
COLLECTION PERIOD		
1. CONTROL: Rate (mls/min)	2.65	.15
Na (meq/L)	183	54
2. A.D.H., SALINE & 4% UREA: Rate (mls/min)	10.8	1.1
Osmolality (mosms/L)	417	728
Urea (mgms %)	829	2296
Inulin (mgms %)	220	1288
U/P Ratio	7	41
G F R (mls/min)	77	46
Na Conc. (meq/L)	132	120

FIG. 9. A.C. 50 year old, W, M. Ureteral Catheterization Studies 8/28/59. These studies were performed prior to the unsuccessful splenorenal anastomosis.

normal portion, while the segmental area excretes 4.2 ml of urine containing, for example, 15 mEq/L of sodium (a 70 per cent reduction in sodium—a marked decrease rarely observed). This small amount of urine with 15 mEq/L of sodium dilutes the sodium in the 75 ml of urine from 50 mEq to only 48 mEq/L. On the other hand, if the concentration of inulin was 100 mg per cent in both the normal kidney and the 75 per cent uninvolved section of the ischemic kidney, while being 400 mg per cent in the 4.2 ml from the ischemic segment, this would raise the resulting inulin concentration in the urine of the ischemic kidney to 116 mg per cent or a 16 per cent increase. Whereas this 16 per cent increase in the concentration of inulin is detectable and decidedly different from normotensive unilateral renal disease, there may be more to this problem than looking at the greater differences in water reabsorption than in sodium concentration. For one thing, our differences in water reabsorption in the segmental group have been considerably greater than 16 per cent, usually 20 to 60 per cent. This could be because areas of ischemia with kidneys which we studied were somewhat more than 25 per cent of the kidney. On the other hand, the slightly *increased* sodium concentration is definitely difficult to explain (see Chart IX). The following not only explains these difficulties, but may indicate that even if the 25 per cent ischemic segment were excreting no urine, this lesion might be functionally detected by this measure of water reabsorption. Graves (11) has pointed out that the renal arteries are "end-arteries"; that is, there are no anastomoses of renal arteries between their point of origin at the aorta and the glomeruli. In segmental ischemia, then, reduced blood flow should affect the filtrate volume only in those nephrons whose glomeruli are directly supplied by the segmental artery. This is not true of the post-glomerular circulation where anastomoses occur freely. Here, especially in the crowded renal medulla, one might expect the efferent arterioles of the juxtamedullary ischemic nephrons, by decreasing blood flow in the hair-pin turns of the vasa rectae, to increase the efficiency of the countercurrent system for water reabsorption in adjacent normal nephrons. Therefore, even if urine excretion ceased in an ischemic segment, either from a negligible glomerular filtration or virtually complete reabsorption of the filtrate, the countercurrent effect on this perimeter of normal nephrons could conceivably increase the relative reabsorption of water. Since stop flow experiments have shown that the distal sites for the reabsorption of sodium and "free" water occur at separate points in the distal tubule (29), reabsorption of water in the countercurrent system needs only to be minimally more effective than the reabsorption of sodium to yield a slight increase in the concentration of sodium in the urine from the segmentally ischemic kidney.

2. The Role of Urea in Amplifying Differences in Water Reabsorption

In the four patients with main renal artery obstruction, as well as the patients with segmental arterial obstruction, relatively more water was reabsorbed in the ischemic kidney under urea-saline-ADH infusion than under oral water diuresis. Comparison of urine flow ratios under oral water diuresis with those during urea-saline-ADH infusion shows that the ratio is smaller under the latter circumstances.* That this *relative* decrease in urine excretion in the ischemic kidney is caused by a *relative* increase in water reabsorption is clear from the increase in the ratio of the inulin concentration.

This observation deserves further comment because it is important in the study of renal ischemia. It is true that osmotic diuretics (urea, mannitol, hypertonic NaCl, etc.) increase the per cent of filtered sodium and water excreted in the urine. In these studies this occurred in the ischemic as well as the normal kidney (see Chart XV "% Filtered Sodium Excreted"). However, these studies show that the urine flow rate of the ischemic kidney was relatively less under urea-saline-ADH infusion, and the accompanying increase in the inulin concentration ratio makes it clear that this relative decrease in urine flow was caused by a relative increase in the reabsorption of water. Selkurt (26) first demonstrated in the dog that a graded decrease in GFR in one kid-

* The exception is patient J.B., Chart VIII. This is because the urine flow rate from the right kidney is not only exceedingly low under oral water diuresis, but must also traverse the entire right ureter before collection in the ureteral catheter at the terminal 3 cm of the ureter. Under these conditions additional reabsorptive changes can be quite significant. The marked differences in the free water clearances (Chart XV) between the ischemic right kidney and the normal left kidney are probably due to the additional reabsorption of water in the pelvic and ureteral mucosa.

ney resulted in nearly complete reabsorption of the filtered sodium. In the patients presented here, as sodium reabsorption became more and more complete farther down the tubule of the ischemic kidney, the osmotic diuretic constituted a progressively greater proportion of the total osmotic pressure of the tubular urine. When this osmotic diuretic was urea, back diffusion occurred and additional water was reabsorbed secondary to the urea gradient, thereby *increasing* the relative difference in urine excretion between the two kidneys. Note, however, that when the osmotic diuretic is mannitol, the reverse changes should occur because mannitol is not reabsorbed. As the mannitol forms a progressively greater proportion of the solute in the ischemic nephron, water and sodium reabsorption are retarded and this *decreases* the relative difference between the ischemic nephron and the normal nephron in sodium and water excretion.

The sodium concentration ratios generally show only small changes when urea diuresis is superimposed on water diuresis, and in some cases the relative differences in sodium concentrations are greater under osmotic loading with urea (Charts IX and X). Charts VII, VIII, IX and X indicate that the greater the urea load the greater the sodium concentration differences between the two kidneys, but in general the change will be in the direction of reducing the difference.

The magnitude and direction of the change in sodium concentration differences when an infusion of urea is superimposed on a water diuresis depend on (1) the sodium load under oral water diuresis (the smaller the load the more complete the reabsorption of sodium in the ischemic kidney, and, therefore, the greater the difference) and (2) the degree of reduction in GFR. The urea load will decrease the differences in sodium concentration in those patients whose hypertension is associated with smaller reductions in GFR, but the original sodium differences under oral water diuresis will not be large before the urea infusion. Since the difference in sodium concentration is not the quantitatively important consideration, this change is of little consequence. Chart XV demonstrates that the ratio of sodium excretion fractions remained essentially unchanged.

Chart XII represents the experimental results when a urea load was increased progressively to ten times the amount given in these clinical studies.* The results indicate that the greater the urea load, the greater the difference in the relative reabsorption of filtered water and sodium when the Goldblatt kidney was compared to the control kidney. Sodium concentration differences showed greater disparity under extreme urea loads than with moderate urea loads.

It is apparent then, that not only does urea assure the investigator of adequate urine flow rates for meaningful studies, but further creates the conditions for maximal disparity in studies on differential renal ischemia.

3. The Relation between Hypertension, Renal Plasma Flow, Excessive Water Reabsorption and the Severity of the Main Renal Artery Obstruction as Measured by Pressure Gradients

These relationships have basic practical as well as theoretical implications. Our studies on segmentally ischemic kidneys do not help in defining them because a large percentage of the final urine comes from renal parenchyma with normal blood flow.

Consider the data collected under urea-saline-ADH diuresis on the four patients with main renal artery obstruction: V.M. has a relative decrease in renal plasma flow (RPF) of 37 per cent and a 116 per cent relative increase in the concentration of inulin; A.C. a 40 per cent† decrease in RPF and a 141 per cent increase in the concentration of inulin; J.B. a 55 per cent decrease in RPF and a 328 per cent increase in inulin concentration; and F.W. a 76 per cent decrease in RPF with a 375 per cent increase in the relative concentration of inulin. The excessive water reabsorption in the ischemic kidney is caused undoubtedly by changes in the GFR, but reduction in renal plasma flow must be the primary cause of the fall in GFR. While it is possible that the decrease in the volume of the glomerular fil-

* The average patient receives about 1 gm of urea per kg body weight in two hours. In the experimental studies on the unanesthetized dog (Chart XII) the load of urea exceeds 10 gm/kg in the later collection periods.

† The renal plasma flow averages for A.C. (Chart V), under urea diuresis, show a disproportionate increase in RPF for the left kidney. Therefore, the 40 per cent relative decrease in RPF under water diuresis is probably the true differential, rather than the 12 per cent decrease shown in period 131–137. Also, a 40 per cent relative decrease in GFR was present in the studies prior to the spleno-renal anastomosis (Figure 9).

CHART XII

Experimental Left Renal Artery Obstruction

18 KG FEMALE DOG. All studies performed without anaesthesia. No food or water withheld prior to studies.

Time	Urine Flow			Inulin Clearance			Inulin Conc.			PAH Clearance			PAH concentration			Urine Sodium			Urine Osmolality		
	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R
min	ml/min			ml/min			mg/100 ml			ml/min			mg 100 ml			μEq/ml			μOsm/gm H_2O		
11-1-60	Operation performed to make an exstrophy of the bladder for ureteral catherization studies.																				
11-17-60	Differential renal function studies performed. Results identical to studies on 11/24/60.																				
11-24-60	Experimental studies.																				
−81	Plasma #1 drawn.															Plasma = 143.6			Plasma = 258		
−80	5.71 ml of 10% inulin, 0.61 ml of 20% PAH, and 5 mU/kg ADH given I.V.; start infusion of 8% urea in saline at 5.5 ml/min to deliver 2.73 mg/ml of inulin, .73 mg/ml of PAH and 5 mU/kg/hr of ADH.																				
0	#14 Fr. catheters passed easily to mid-ureter on each side.																				
39	Plasma #2 drawn.															Plasma = 151.2			Plasma = 313		
40 to 50	2.60	2.58	1.01	52.1	48.0	1.10	241	221	1.10	114	102	1.11	45.4	41.1	1.11	96.2	93.4	1.03	780	713	1.10
55 to 65	3.02	2.92	1.03	56.0	47.4	1.17	221	195	1.13	118	114	1.04	41.0	41.0	1.00	98.0	96.2	1.01	700	680	1.03
65 to 75	2.98	2.92	1.02	52.0	47.4	1.08	208	195	1.07	111	102	1.08	39.0	36.3	1.07	95.0	92.0	1.03	715	540	1.32
90	Plasma #3 drawn.															Plasma = 155.0			Plasma = 333		
11-28-60	Goldblatt clamp applied to left renal artery. Thrill produced distal to obstruction.																				
12-8-60	Experimental run.																				
−21	Plasma #1 drawn.															Plasma = 151.2			Plasma = 256		
−20	5.71 ml of 10% inulin, 0.61 ml of 20% PAH, and 5 mU/kg ADH given I.V.; start infusion of 8% urea in saline at 5.5 ml/min to deliver 2.73 mg/ml of inulin, .73 mg/ml of PAH and 5 mU/kg/hr of ADH.																				
0	#14 Fr. catheters passed easily to mid-ureter on each side.																				
31	Plasma #2 drawn.															Plasma #2 = 149.3			Plasma = 300		
32 to 42	2.00	4.30	0.46	26.4	47.4	0.55	336	281	1.20	73	131	0.55	64.4	54.0	1.20	59.0	96.2	0.61	520	575	0.90
42 to 52	2.10	4.80	0.44	27.0	50.0	0.54	326	263	1.24	65	132	0.49	54.1	48.3	1.12	59.0	92.0	0.64	528	563	0.94
56 to 66	2.20	4.90	0.45	27.0	49.4	0.54	312	257	1.21	68	124	0.55	54.1	44.4	1.22	52.0	83.3	0.62	533	560	0.95
67	Plasma #3 drawn.															Plasma = 151.2			Plasma = 315		
68	Infusion changed to 16% urea in saline at 9.2 ml/min to deliver 1.98 mg/ml of inulin, .50 mg/ml of PAH and 5 mU/kg/hr of ADH.																				
86 to 96	4.60	12.7	0.36	31.4	47.3	0.66	174	95	1.83	94	184	0.50	36.0	25.4	1.41	47.4	82.0	0.58	475	450	1.06
103 to 113	2.30	14.7	0.19	26.3	52.0	0.50	239	90	2.66	86	183	0.47	54.1	22.0	2.50	19.0	79.0	0.24	520	475	1.10
133 to 143	5.00	18.0	0.28	28.4	55.0	0.51	145	78	1.90	96	189	0.51	34.0	18.5	1.83	30.2	79.0	0.38	568	495	1.15
165 to 175	6.30	17.7	0.36	33.2	54.5	0.60	134	78	1.71	87	207	0.42	24.2	20.5	1.18	42.0	75.0	0.56	578	540	1.07
178	Plasma #4 drawn.															Plasma = 155.0			Plasma = 493		

trate is the stimulus for renal parenchyma to release renin* and produce hypertension, it is not very likely. It is more reasonable to believe that the reduction in renal blood flow is the primary cause of both the hypertension and the reduction in GFR. If this is true, two important questions arise: (1) Will reduction in the volume of glomerular filtrate with its characteristic excessive reabsorption of water still occur with smaller reductions in renal plasma flow and (2) How much reduction in renal blood flow is required before hypertension is produced?

The experimental evidence in the dog, acute (27) and chronic (17), certainly indicates that the first detectable fall in renal plasma flow (C_{PAH}) is accompanied by a marked reabsorption of sodium and water. The results in our laboratory have followed this same pattern. Therefore, in the comparative technique of bilateral ureteral catheterization described here, small reductions in RPF are readily recognized because they are greatly magnified by excessive reabsorption of sodium and water secondary to changes in the volume of glomerular filtrate.

The second question is more important, because even if small reductions in RPF can be detected readily by this technique, there is good reason to doubt that small reductions in RPF produce curable, unilateral renovascular hypertension. In the seven patients reported here the least reduction in renal plasma flow associated with renovascular hypertension was 37 per cent. Yet, these patients are representative of the general group of patients with curable renovascular hypertension. They include three older patients

* The word "renin" is not meant to imply anything other than what the kidney generates to produce high arterial blood pressure.

(F.W., A.C. and J.K.) where arteriosclerosis was the initiating cause of the renal arterial disease as well as younger patients where fibromuscular hyperplasia was the primary cause (J.B., V.M.). In two patients the hypertension had been present for less than six months (F.W. and J.K.) and in three others the hypertension had been present from six to twelve years (V.M., B.LeV. and W.G.). Thus, it is our belief that renovascular hypertension rests firmly on a basis of reduced renal blood flow, and that in all probability there must be a fairly significant reduction in renal blood flow (at least greater than 10 per cent) to produce hypertension. V.M. (Chart VII) illustrates the fact that reduction in blood flow must be measured as a comparison with the contralateral kidney. While the absolute RPF for the ischemic left kidney is within normal limits, it is 37 per cent less than the contralateral kidney.

All four patients with main renal artery disease had marked arterial obstruction. Arterial pressure gradients between the aorta and a point distal to the site of the obstruction were at least 100 mm Hg in each instance. We have studied recently a 25 year old hypertensive white female with a 23 per cent reduction in the C_{PAH} (the smallest reduction to date in our cases), an 86 per cent fall in urine flow rate, a 424 per cent increase in the concentration of inulin and a main renal artery obstruction. The arterial obstruction exhibited a preoperative bruit, and at surgery a strong thrill was present in the middle of the right renal artery. There was a 70 mm systolic and a 25 mm diastolic drop in blood pressure across the stenotic segment. All this evidence of obstruction was associated with only a 23 per cent relative decrease in the C_{PAH}.*

It is particularly important to emphasize that a marked obstruction in the form of a mechanical blockage to renal blood flow must be present before the renal plasma flow to the kidney, as measured by the C_{PAH}, is affected. The experiments of Selkurt (26, 27) and others have demonstrated amply the autonomic control the kidney exerts over its own blood supply. This control is exercised through the afferent arterioles in such a way that the afferent resistance decreases in the face of a more proximal resistance in the renal arteries. Selkurt's data in the dog demonstrated that mean arterial blood pressure could be reduced from 160 to approximately 100 mm Hg without any change in the C_{PAH} or GFR. There was a progressive decrease in the afferent arteriolar resistance as this drop occurred. At 100 mm Hg of mean arterial pressure the C_{PAH} fell gradually and then precipitously over the next 40 mm Hg. It was particularly interesting that a marked reabsorption of water was the first change at 100 mm Hg since V fell by 50 per cent while GFR remained nearly constant.

The importance of this is at least two-fold. For one thing, a renal artery obstruction can be present without reducing the C_{PAH} and, therefore, without producing hypertension. This is why so many bilateral lesions demonstrated by aortography are now being reported with cure of their hypertension following correction of only one side (23, 33, 34): the anatomical lesion is present on the opposite side without physiological significance to the kidney. This is one of the problems with aortography—it can reveal anatomical lesions without functional importance in relation to reduced renal blood flow or hypertension. Secondly, if surgery is limited to patients who have the characteristic water reabsorbing pattern with reduced blood flow as defined here, the obstructive lesion, if present in the main renal artery, cannot be subtle but must be obvious or apparent with strain gauge manometric measurements. This means that aortography is not required in planning the surgical approach. With good functional studies, aortography should be rarely necessary in the investigation of these patients.

On the basis of these considerations of the functional and pathological changes, together with Selkurt's data, renovascular grafts are not indicated in patients in whom, despite positive aortograms, there are but small drops in pressure across the stenosis (less than 40 mm Hg).

4. Screening Tests for Occlusive Renal Artery Disease

a. Urine Osmolality. These data demonstrate the fallacy in relying on urine osmolality as an indicator of curable, unilateral renal hypertensive disease. F.W., Chart VI, is a classical example. Under oral water diuresis, osmolality is actually less in the ischemic kidney, while under urea-saline-ADH diuresis osmolality is more.

*Again, urea-saline-ADH osmotic loading did not alter significantly the sodium concentration differences which were 60 per cent reduced in the ischemic kidney after 1600 mOsm of intravenous saline and urea.

Even with ADH and urea, differences in urine osmolality (32 per cent increase) are not impressive compared with the relative differences in the concentration of inulin (400 per cent increase). This is true for all of the patients we have studied.

It must be emphasized that the search for a test in which the investigator needs only simultaneous aliquots of urine from each kidney, thereby avoiding the problem of bladder leakage, while admittedly desirable, will not likely be successful. Certainly it cannot be successful in regard to the standard determinations measured in these studies. In addition to the advocates of urine osmolality in this regard, Birchall (2) has suggested the inulin U/P ratios. Rapoport (24) has presented an index based on $U_{Na}/U_{Creatinine}$ ratios. The objection to this approach of using concentration indices lies in the fact that pyelonephritis or calculous medullary damage produces a failure to reabsorb water in the distal nephron. This means the contralateral *normal* kidney will give a higher urine osmolality, or even inulin U/P ratio, which is presumably the characteristic of an ischemic kidney. Therefore, the investigator *must know* urine flow. If the larger urine flow is from the kidney which produces urine with the greater inulin concentration then this is the more nearly normal kidney and the opposite kidney is non-ischemic with medullary failure to reabsorb water. Furthermore, analysis of urine flow ratios offers a criterion for checking repeatability of consecutive collection periods, which cannot be done if only concentration indices are measured. For example, observe the changes in the ratio of urine sodium concentrations which occurred under oral water diuresis in patient B.G., Figure 12 and Chart XIV. Finally, since it is clear that the major defect in renal ischemia is an excessive reabsorption of water which produces *gross* differences in urine flow rates, failure to measure urine flow rates is to miss one of the major characteristics of renal ischemia.

The solute concentrations in these data further demonstrate that urea is not a good indicator for measuring reabsorption of water, probably due to the heavy back diffusion in the nephron. Creatinine is a better measure although at the flow rates necessary for reliable data, endogenous creatinine falls to low concentrations in the urine. In this method of ratio comparisons, small differences at low concentrations yield large comparative differences.

b. The Intravenous Pyelogram. Increased reabsorption of water by the ischemic kidney explains the paradox concerning the intravenous pyelogram. Schlegel (25) and later Peart (20) first called attention to the fact that the kidney excreting the contrast medium with less intensity may actually be the normal kidney. The explanation is readily apparent. The more recent radiographic media are handled predominantly by glomerular filtration. Our studies have demonstrated a 100 to 500 per cent increase in the concentration of inulin which is usually associated with a 30 to 60 per cent reduction in GFR. The ischemic kidney, while filtering 30 per cent less contrast medium (if the GFR is reduced 30 per cent), produces a relative concentration of the contrast medium several times greater than the contralateral normal kidney which more than offsets the reduced GFR. Thus, the contrast medium shows with greater intensity in the ischemic kidney. The most dramatic way to demonstrate this phenomenon is to hydrate a patient with a main renal artery lesion with 1000 ml of water. Thirty minutes later inject 25 ml of Hypaque® and take an x-ray three minutes after injection. The Hypaque will not be visualized in the normal kidney because of the dilution with water, but the water reabsorbing ischemic kidney may give a perfect pyelogram. While this water hydration pyelogram is a simple clinical index of the ischemic kidneys' phenomenal reabsorption of water, this cannot be a screening test. The ischemic kidney may have such marked reduction in blood flow and GFR that too little contrast medium crosses the glomeruli for the subsequent excessive water reabsorption to make any difference. This is exactly the case in patient F.W., Chart VI and Figure 14. The reduction in GFR is too great and the ischemic kidney cannot be visualized even in an intravenous pyelogram performed during dehydration. It is apparent then that the combination of these two opposing forces, one always decreasing the amount of contrast medium and the other always increasing the concentration, may combine to make the ischemic kidney function on intravenous pyelography with more, less or equal intensity when compared to the contralateral normal kidney. It is further apparent that in segmental ischemia, changes in intensity from the ischemic segments will be diluted by urine from the normal cortex.

c. The I^{131} Renogram. There is an urgent need for a simple, harmless and painless method which

will screen patients with hypertension and indicate those who deserve further definitive studies. Whereas such a screening test may indicate understandably a certain percentage of false positives, it must not be guilty of false negatives where potentially curable patients would not be considered candidates for further study.

The studies described here not only suggest the present limitations to I^{131} scanning of the kidney, but may offer the basis for a more adequate screening test. The I^{131} renogram technique has probably, in the best of hands, a 15 to 25 per cent error in estimating renal blood flow. I^{131} labeled diodrast and hippuric acid are indices of renal plasma flow, not the rate of urine flow. The problem with the I^{131} renogram is apparent. To the extent that a given hypertensive population contains patients with curable renovascular hypertension caused by less than a 25 per cent reduction in renal plasma flow to one kidney, the renogram will be ineffective in detecting this asymmetry. Admittedly, the majority of potentially curable patients will have greater than a 25 per cent reduction in renal plasma flow compared with the opposite kidney, but until more patients are studied with accurate PAH clearances, the exact per cent is an unknown quantity. It can be argued that if the accuracy of the I^{131} renogram is increased in the future, the ability to detect smaller disparities in renal plasma flow will serve only to increase the number of patients who fall into the false positive group. There is a point of diminishing return. We believe that as long as the I^{131} renogram is a comparative measure of renal plasma flow it cannot survive as an adequate screening test.

It would be better if the scanning technique compared urine flow rates rather than renal plasma flow. The physician could choose patients for further study who had a 40 per cent or greater reduction in urine flow from one kidney. This would not distinguish between ischemic unilateral renal disease and non-ischemic unilateral renal disease. There would be false positives but no false negatives. The ideal technique would be bilateral scintillation counting which compares the glomerular filtration rate (or RPF) within an error of 5 to 10 per cent, and simultaneously, perhaps from a second pair of probes over the ureters, compares the urine flow rates. The patients most likely to have renal artery obstruction would be those who show the greatest differences in urine flow rates with significantly smaller differences in GFR. However, the most practical screening test, even with the false positives, would be a technique which simply selected those patients with a 40 per cent or greater difference in urine flow rates.

Advocates of the I^{131} renogram should check the accuracy of their predictions by performing ureteral catheterization studies to measure exactly the disparities in renal plasma flow. The I^{131} renogram has been measured too often against the intravenous pyelogram, the 15 minute PSP and total renal clearances collected across the bladder. This is no test of the technique in discriminating between significant degrees of asymmetry. When we have done this, our confidence in the renogram's ability to detect actual differences in renal plasma flow has been shaken. We have been even more disturbed by occasional predictions of severe changes in one kidney only to find less than a 5 per cent difference in RPF, GFR and urine flow.

Finally, it should be pointed out that the technique developed by Burrows and his group (3) in which the rates of *urine outflow* from the kidneys are compared by external scintillation counting offers the best approach for a reliable screening test. It is significant that these authors have observed that mannitol decreases the difference in urine outflow between an ischemic and non-ischemic kidney. Urea should increase the disparity, and thus enhance the reliability of their technique for detecting differences in urine flow.

V. THE DISTAL LESIONS OF RENAL ISCHEMIA

Renal ischemia should not be considered exclusively as a main renal or segmental artery disease (Figure 2). Although arteriolosclerosis, pyelonephritis, and glomerulonephritis commonly occur with a reduction in RPF, hypertension is not always present. The technique described here could determine if there is reduced RPF to functioning renal tissue (from the secondary excessive water reabsorption) in the hypertensive patients, and if this pattern is absent in the normotensive patients. Admittedly, this requires some degree of asymmetry in the reduced RPF. It is possible that progression of the disease may produce increasing asymmetry in this pattern of excessive water reabsorption, or successful arrest of the hypertensive disease could be due to improvement in renal blood flow and, therefore, measurable as a decreasing asymmetry. We have studied a few patients with each of these conditions.

CHART XIII

Essential Hypertension

T.W.—54, C, F.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R	L	R	L/R
min	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O		
0	Two #7 ureteral catheters passed easily to each kidney. 600 ml of water hydration 80 minutes before catheterization.																							
5–15	.50	.85	.59													121	140	.86	75	99	.76	375	444	.84
15–26	.27	.45	.60													152	170	.89	147	168	.88	542	605	.90
30	22.7 ml of 10% Inulin and 2.5 ml of 20% PAH with 100 mU ADH given I.V.; 4% Urea in saline containing 2 mg Inulin/ml, 1.2 mg PAH/ml and 60 mU ADH/hour infused at 10 ml/min.																							
60–66	1.58	1.90	.83	44	46	.96	678	579	1.17	159	192	.83	255	243	1.05	142	132	1.08	162	179	.90	505	502	1.01
66–76	1.93	2.47	.78	42	43	.98	524	425	1.23	202	217	.93	255	217	1.18	133	135	.98	187	178	1.05	575	487	1.18

These studies demonstrate that the functional pattern in the hypertensive patient with segmental renal artery occlusion may be similar to the pattern in chronic renal disease with hypertension. The purpose of presenting these studies is twofold: one, to suggest that the mechanism of hypertension in renal ischemia is probably the same whether this disease is occlusion of the renal artery ostium or glomerulonephritis, and two, that these patterns, by contrast, permit a better understanding of the functional studies in curable, renovascular hypertension.

1. Renal Arteriolosclerosis and "Essential" Hypertension. If a group of patients with essential hypertension show this disparate pattern of excessive water reabsorption associated with a reduced RPF they must have some degree of renovascular hypertension. It has been recognized since 1940 that a reduction in renal plasma flow is the most striking abnormality in renal function in patients with essential hypertension. We have emphasized that a small reduction in renal plasma flow represents a significant compromise in the renal circulation, at least in terms of its ability to compensate further by decreasing the resistance of the afferent arteriolar bed. Therefore, in arteriolosclerosis the degree of the obstruction must be significant in order to produce a fall in renal plasma flow. We have indicated also that small decreases in renal blood flow initiate large relative differences in urine excretion secondary to excessive water reabsorption. It is, therefore, unlikely that bilateral reduction in renal plasma flow can be present in essential hypertension and be completely symmetrical.*

In using this measure of bilateral renal ischemia inulin must be used as an index of relative water reabsorption. In main renal artery obstructions, small differences in filtration fractions are unimportant and differences in PAH concentration serve equally as well as inulin. In bilateral distal renal ischemia small differences in the filtration fraction become significant and could mask the excessive reabsorption of water.

T.W. (Chart XIII) was a 54 year old, colored female with a long history of hypertension. In 1944, at the age of 39 her blood pressure was 150/90. In 1955 she was first seen with a blood pressure of 215/125 mm Hg. On many visits to the Out-Patient Department in 1955, 1956 and 1957 an average blood pressure of 240/130 was found. In 1958 her blood pressure was 260/130 and by 1959 frequent blood pressures were in the range of 300/140. In October of 1959 the average blood pressure was 330–350/130–140. The heart was enlarged on physical examination and chest x-ray. The fundi showed

* It is for this same reason that bilateral main renal artery obstructions in patients with curable renovascular hypertension have always presented as unilateral lesions on functional studies. While the advocates of aortography have written that bilateral main renal artery obstructions make aortography a necessity, the actual case is just the reverse: Bilateral obstructions make a functional measurement mandatory. The investigator must know which is the most ischemic kidney. In bilateral main renal artery lesions, it will be apparent from the studies described here which kidney has the greatest reduction in blood flow and only that kidney should be operated upon. In many instances the repair of the *functionally* ischemic kidney will cure the patient of his hypertension. In these patients, the opposite renal artery obstruction is an anatomical fact without physiological significance in relation to renal blood flow (23, 33, 34). If renal plasma flow is reduced to both kidneys the hypertension may persist—perhaps at a reduced level, but the physician has operated upon the most ischemic kidney and with repeat functional studies the course of action will be apparent.

marked narrowing and tortuosity of the arterioles. The discs were flat. There were a few old exudates and some hemorrhages. The EKG was abnormal with S-T changes, broad P waves and delayed precordial transition. The SUN was 16 mg per cent and the 15 minute PSP 30 per cent. The urine contained no protein or microscopic sediment. Various antihypertensive regimens were ineffective in controlling her hypertension. An intravenous pyelogram showed prompt excretion bilaterally, but a greater intensity of the dye in the cortex of the left kidney. An aortogram showed that the main renal arteries were normal. On October 29, 1959 ureteral catheterization studies were performed (Chart XIII). The first two periods under water diuresis were misleading because they suggested a 40 per cent reduction in urine flow. This was an artifact caused by inadequate urine flow rates, but at the time of this study we were not fully aware of this danger. The 20 per cent reduction in urine flow rate under urea-saline-ADH diuresis was the true differential in urine excretion. Although the GFR was reduced by 2 to 4 per cent in the left kidney, urine flow was decreased by 20 per cent due to excessive water reabsorption. Figure 10 is a bar graph indicating these differences for the last period. A left nephrectomy was performed on 11-27-59. The main artery was injected with barium sulfate and the segmental arteries were patent. The pathological sections revealed moderate arteriolosclerosis. In the 14 months since nephrectomy her blood pressure has been in the range of 190–220/95–110, and her general health has remained unchanged. Repeat renal clearances have shown no change in the GFR or RPF in the remaining right kidney. On February 9, 1961 she was asymptomatic with a blood pressure of 300/130. Urinalysis was negative except for 30 mg per cent protein. This patient had bilateral disease which the ureteral catheterization data indicated. A 20 per cent reduction in urine flow rate is too small a difference for one to consider unilateral renal ischemia. The PAH clearances confirmed the fact that there was a small difference (12%) between the two kidneys in renal plasma flow and furthermore the absolute values for RPF in each kidney were low. Therefore, nephrectomy was ill-advised. Not only were we unaware of the artifact involved in those periods in which there was a 40 per cent reduction in urine flow, but, at that time, we thought, incorrectly, that the effect of urea might be to diminish the relative difference in urine flow rate between an ischemic and non-ischemic kidney. Thus, both the 40 per cent and the 20 per cent reductions in urine flow rate were interpreted incorrectly.

The important point is that this is the pattern of bilateral renal ischemia, and the differences between this disease and curable renovascular hypertension should be clearly

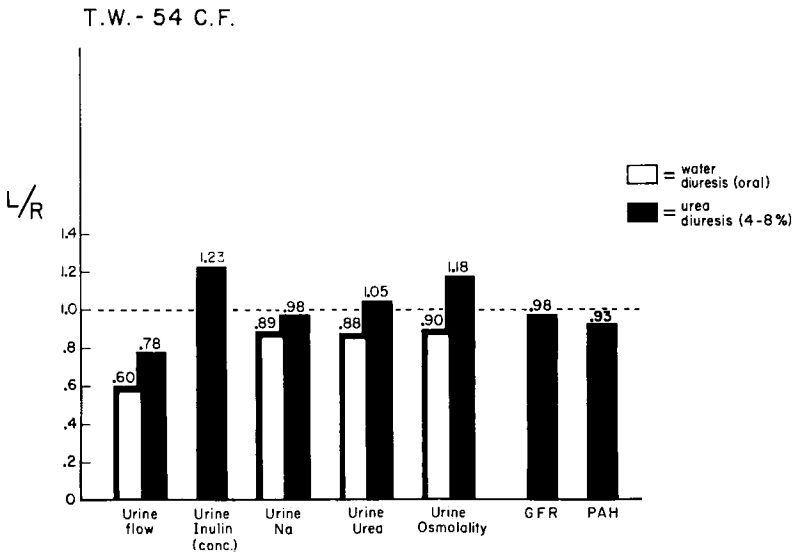


FIG. 10. T.W., 54 year old, C, F. Bar graph illustrating ratio differences in the last collection period Chart XIII. This study with urea diuresis is typical of many patients with essential hypertension. There is excessive water reabsorption in the kidney with the least RPF, (U_{In}/U_{In} = 1.23) but the difference in urine flow is not large enough to indicate curable unilateral or bilateral main renal artery occlusion. However, this pattern, in its greatest disparity, does approach the functional pattern of segmental artery occlusion (Figure 16, Chart IX).

understood. However, the pattern of disparate bilateral renal ischemia secondary to arteriosclerosis will approach in its greatest disparity the pattern of curable, *segmental* renal ischemia. For example, the patient who has a 40 per cent reduction in urine flow rate and a relative increase in the concentration of inulin by 30 per cent could have either disease. If the patient is in the arteriosclerotic age group and if the PAH clearance for the contralateral kidney is depressed beyond doubt, the disease process is probably bilateral arteriosclerosis. This is the one functional pattern where an aortogram may be a distinct help provided an occlusion of a distal branch can be demonstrated. This is unfortunately the area where aortography is the least reliable. Nevertheless, if the aortogram were reasonably normal, and the patient in the older age group, we would not consider surgery for this functional pattern.

2. *Pyelonephritis.* P. Kincaid-Smith (15) has demonstrated convincingly that the wedge-shaped areas of ischemic tubular atrophy are present in the kidneys when patients with bilateral pyelonephritis die with hypertension. When patients with bilateral pyelonephritis die without hypertension, the kidneys show the thyroid areas of non-functioning tubules without ischemic atrophy.

Although the classic studies of Weiss and Parker (30) indicated that unilateral pyelonephritis associated with severe hypertension is not a rare occurrence, we have found it extremely difficult to find such patients. We have studied two patients with hypertension who had active, chronic unilateral pyelonephritis and a contralateral normal kidney. In both patients our ureteral catheterization data indicated that the infected kidney was *not* producing their hypertension. Because we were unable to cure these unilateral infections, a nephroureterectomy was performed on the diseased kidney in both patients. In neither patient has the elevated blood pressure been influenced by the nephrectomy. The pattern of non-ischemic unilateral pyelonephritis is important enough to present one of the two cases. The pattern is essentially that of normotensive unilateral renal disease, that is, the hypertension and the unilateral renal disease are not related in the same way in which hypertension is related to unilateral renal ischemia.

B.G. (Chart XIV) was a 59 year old, white female who was first admitted to the hospital on February 28, 1960 complaining of high blood pressure and fainting spells of one year's duration. She denied all urinary symptoms. Upon admission, her blood pressure was 220/112 mm Hg, the fundi were not remarkable, the heart was enlarged slightly

CHART XIV

Unilateral Pyelonephritis, Right Kidney

B.G.—59 W, F.

Time	Urine Flow			Inulin Clearance			Inulin Concentration			PAH Clearance			PAH Concentration			Urine Sodium			Urine Urea			Urine Osmolality		
	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L
min	ml/min			ml/min			mg/100 ml			ml/min			mg/100 ml			μEq/ml			μM/ml			μOsm/gm H_2O		
−65	19.2 ml of 10% Inulin and 2.1 ml of 20% PAH given I.V.; start infusion of 5% D/W at 1.1 ml/min to deliver 18 mg/ml of Inulin and 10.9 mg/ml PAH.																							
−58	2.5 mg Nupercaine saddle anesthesia.																							
0	#8 polyethylene catheter passed to right kidney with ease; 7 minutes later #8 polyethylene catheter passed to the left kidney with ease.																							
13–26	1.03	2.21	.47	17	63	.27	506	855	.59	73	253	.29	256	415	.62	73	96	.76	42	70	.60	259	370	.70
32–42	.75	1.85	.40	11	41	.27	419	670	.62	42	167	.25	203	327	.62	72	83	.87	36	56	.64	217	282	.77
47–57	1.84	3.79	.49	19	64	.30	316	507	.62	72	274	.26	143	262	.54	50	54	.92	27	43	.63	158	202	.78
50	100 mg Demerol																							
59–69	.34	1.20	.28	4	27	.15	348	666	.52	14	95	.15	147	288	.51	49	49	1.00	27	47	.57	158	196	.80
70	Infusion changed to 8% urea in saline at 9.2 ml/min to deliver 2.17 mg/ml Inulin, 1.13 mg/ml PAH and 9 mU ADH/kg/hr																							
83	600 mU ADH given I.V.																							
93–106	1.26	4.90	.26	18	68	.26	416	415	1.00	70	265	.26	199	196	1.01	96	100	.96	160	175	.91	399	415	.96
120–130	2.45	9.43	.26	13	49	.27	201	194	1.04	53	208	.25	101	103	.98	91	98	.93	145	146	.99	340	346	.98
143–153	3.65	13.16	.28	12	45	.27	144	144	1.00	47	199	.24	69	77	.90	96	96	1.00	138	141	.98	325	338	.96
162	Left Catheter removed.																							
166–172	4.95	14.73	.34	18	57	.32	109	116	.94	72	228	.32	53	59	.90	96	100	.96	131	133	.98	325	343	.94

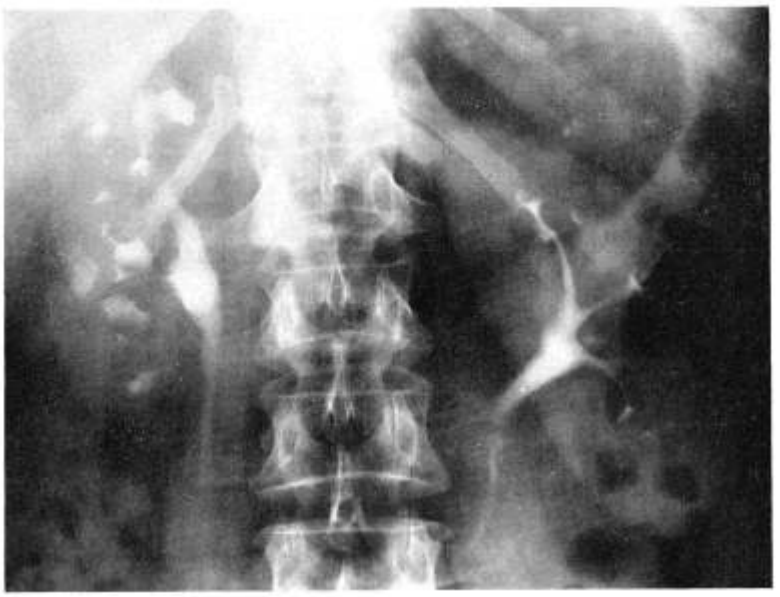


FIG. 11. B.G., 59 year old, W, F. 10 minute intravenous pyelogram. Consecutive cultures were positive for pseudomonas from the right kidney (400 per ml.). The left kidney was sterile.

and her blood pressure remained in the range of 140–200/90–120. She was emotional and anxious with many personal problems. Urinalysis revealed no protein but 20 to 25 WBC/HPF. A urine culture showed 100,000 E. Coli/ml and she was placed on Chloromycetin 500 mg. q.i.d. Figure 11 is an IVP performed on 3/2/60. On March 14, 1960, ureteral catheterization studies were performed (Chart XIV). During the study 6 simultaneous urine cultures were obtained from each kidney. The left kidney was uniformly sterile while the right kidney was infected with Pseudomonas in numbers averaging 400 per ml in each culture. A nephrectomy was performed on March 30, 1960. The patient's blood pressure has not changed from the pre-nephrectomy levels. On February 10, 1961 her blood pressure was 170/95 in the left arm and 160/95 in the right arm. She was receiving antihypertensive medication.

The catheterization data are interesting. Figure 12 is a graph of these ratio changes. The inulin concentration ratios show that the right kidney is a water *losing* kidney (the right kidney excretes a greater fraction of its filtered water than the contralateral kidney)* in contrast to the excessive water reabsorbing pattern characteristic of renal ischemia (Figure 15). It was on the basis of this reduced inulin concentration in the kidney with the smaller urine flow rate that we were able to predict that the patient's hypertension was not caused by this kidney. The reduced blood flow, in the absence of an excessive water reabsorbing pattern was simply a result of reduced renal tissue.

It should be observed that the sodium concentration was reduced enough in the first two periods to constitute a positive Howard Test. The right kidney's relative failure to reabsorb water was more marked than its failure to reabsorb sodium, thus producing a false positive Howard Test. Most of these patients with non-ischemic pyelonephritis have an increase in sodium concentration on the side of the pyelonephritis and not a decrease as occurred in this patient. Even here the right kidney excreted 16 per cent more of its filtered sodium than the left kidney (Chart XV), but the sodium concentration was still less when compared to the normal left kidney. Therefore, there seems to be a stage in pyelonephritis where the failure to reabsorb water is greater than the failure to reabsorb sodium, and the pattern described here is present. We have seen positive Howard Tests in normotensive unilateral renal disease as well.

* The free water clearances in Chart XV illustrate rather striking quantitative differences. When the normal left kidney was subtracting 0.85 ml of solute-free water per 100 ml of glomerular filtrate, the pyelonephritic right kidney was *excreting* 1.0 ml of solute-free water per 100 ml of glomerular filtrate.

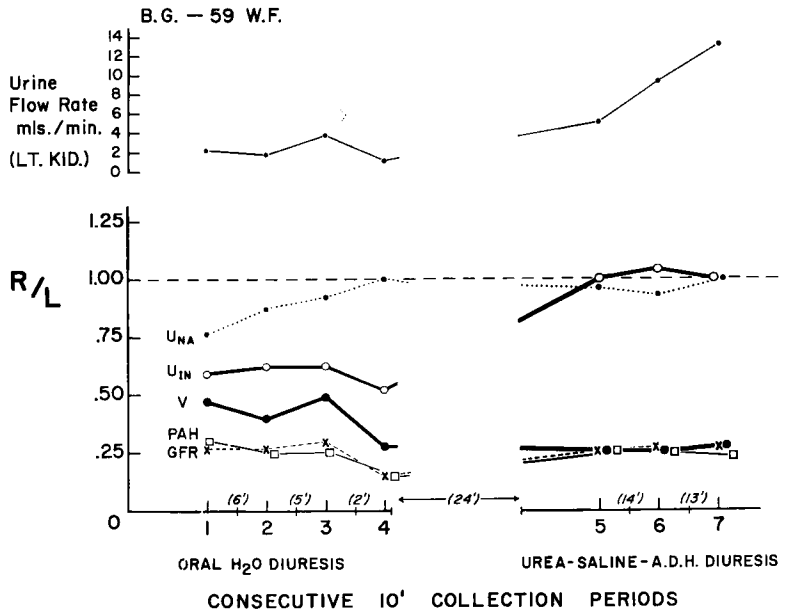


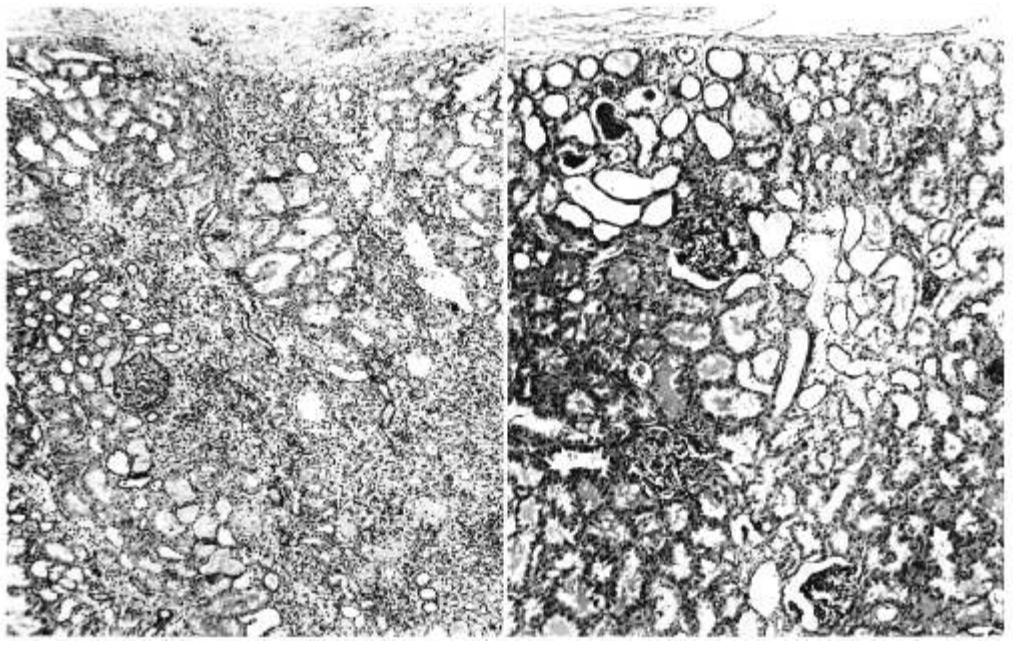
FIG. 12. B.G., 59 year old, W, F. This is the functional pattern of non-ischemic unilateral renal disease with or without hypertension. U_{In} is *reduced* in the diseased kidney—not increased as in renal ischemia. Also note that simultaneous U_{Na} differences show a wide variation, while U_{In} ratios remain constant. This pattern should be compared with Figure 15.

The numbers in (') along the horizontal axis indicate the time elapse in minutes between 10 minute collection periods.

It seems reasonable, although we have not had an opportunity to study such a patient, that when unilateral pyelonephritis produces hypertension, the characteristic ischemic water reabsorbing pattern will be present. We have one word of caution for the future documentation of these cases. Unless the pathological specimen contains unquestionable thyroid-like areas, prenephrectomy recovery of bacteria directly from the renal pelvis will be required to support the diagnosis of pyelonephritis.

3. *Glomerulonephritis.* Glomerulonephritis is the most distal lesion in relation to the nephron which could reduce blood flow to functioning renal tissue. Coarctation of the aorta is the most proximal. In the case of coarctation we would expect renal blood flow to be symmetrically reduced to each kidney and, therefore, not detectable by this method of study. At first thought, glomerulonephritis, like coarctation might be symmetrical.

We have studied two identical twins with glomerulonephritis and their catheterization data are summarized in Chart XV. One twin, Daw. D., was severely hypertensive while the other twin, Dot. D. was normotensive. Both twins had scarlet fever at age 6 and each twin has had proteinuria. In October of 1957, at the age of 17, Daw. D. developed headaches and was found to have severe hypertension. An intravenous pyelogram was normal and a needle biopsy of the right kidney confirmed the diagnosis of glomerulonephritis. In April of 1959, her blood pressure was 250/150, the urine contained numerous fat casts as well as chronic macrophages containing fat particles. The supernatant protein was greater than 200 mg per cent. In May of 1959, a second intravenous pyelogram, as well as an aortogram, were normal and bilateral ureteral catheterization studies were performed for the first time. At urine flow rates greater than 2 ml/min/kidney, three consecutive ten minute collection periods showed that the urine flow rate of the left kidney was decreased by 55 per cent, sodium concentration decreased by 14 per cent and urine urea concentration increased by 55 per cent. The separate urea clearances were, therefore identical. The left kidney was explored on June 19, 1959 with the hope of finding a resectable ischemic segment, but the gross appearance of the cortex was normal. Biopsies were taken from the upper, lower, and middle parts of



(A) (B)

FIG. 13. (A) Open wedge biopsy, glomerulonephritis, with severe hypertension (Daw. D.—Chart XV).

(B) Open wedge biopsy, glomerulonephritis, without hypertension.

The degree of glomerulitis is remarkably similar. However, the tubules in the normotensive patient are not involved, while in the hypertensive patient there is extensive tubular damage.

the kidney and all demonstrated glomerulonephritis with tubular atrophy. Figure 13-A represents a section of this biopsy and it should be compared with Figure 13-B. The latter figure is a section from an open wedge biopsy on a patient of similar age who had glomerulonephritis, the same findings in the urinary sediment but a normal blood pressure. Eleven months later on 13 May 1960 the ureteral catheterization was repeated with complete renal clearances (Chart XV). The values for water and urea diuresis were averaged from three consecutive periods in each instance. The identical decrease in urine flow rate for the left (X) kidney was again noted. The 16 per cent relative increase in the concentration of inulin in the left kidney was similar to studies on the patients with segmental renal ischemia. Severe depression of the GFR and RPF was present. She has remained very hypertensive and difficult to control.

Dot. D., her 20 year old identical twin, had a blood pressure of 110/70, 35 mg per cent of protein on concentrated urine specimens, and concentrated readily to 1.028. On July 28, 1960 differential ureteral catheterization studies were performed. Four consecutive ten minute periods under oral water diuresis and three consecutive periods under urea diuresis were averaged and presented in Chart XV. The total RPF and GFR were reduced slightly and there was a 6–7 per cent reduction in GFR in the right (X) kidney with a 5–7 per cent relative increase in the concentration of inulin. Whether this was excessive water reabsorption or not is difficult to say because the ratios of 1.05 and 1.07 are within the error of the chemical method.

It is surprising that glomerulonephritis can be as disparate as occurred in Daw. D. Two studies, nearly a year apart, confirmed the same degree of asymmetry and yet, the IVP and aortogram indicated symmetrical renal masses.

We have studied only these two patients. It will be important to repeat these studies when and if the normotensive twin develops hypertension. We believe that if these findings are confirmed in a larger series of patients and especially if this pattern of ischemic water reabsorption develops simultaneously with the hy-

CH.
SUMM.

Patient		Urine Flow X	Urine Flow Y	Urine Flow X/Y	Inulin Clearance X	Inulin Clearance Y	Inulin Clearance X/Y	PAH Clearance X	PAH Clearance Y	PAH Clearance X/Y	Inulin Concentration Ratio X/Y	Urine Sodium X	Urine Sodium Y	Urine Sodium X/Y	U V Sodium X	U V Sodium Y	U V Sodium X/
		ml / min			ml / min			ml / min				μEq / ml			μEq / min		
NORMOTENSIVE UNILATERAL RENAL DISEASE																	
A.M.	W	Patient was not studied underwater diuresis.															
Chart IV	U	2.02	2.14	0.94	54.0	53.0	1.02	181	182	0.99	1.04	71.0	72.0	0.99	143	154	0.9
P.W.	W	2.37	5.86	0.40	28.4	69.0	0.41	118	288	0.41	1.00	46.0	42.0	1.09	109	246	0.4
Chart II	U	3.71	8.94	0.42	35.0	83.0	0.42	106	251	0.42	1.01	124.0	122.0	1.02	460	1091	0.4
L.H.		Data from water diuresis are invalid for reasons discussed.															
Chart III		2.00	3.15	0.63	40.5	69.0	0.58	242	371	0.65	0.92	73.2	82.7	0.88	146	261	0.5
MAIN RENAL ARTERY OBSTRUCTION																	
F.W.	W	3.09	18.3	0.17	26.0	77.0	0.34	96	313	0.30	2.03	8.3	21.3	0.38	26	390	0.0
Chart VI	U	0.71	10.4	0.06	27.3	85.3	0.32	125	518	0.24	4.75	57.6	111.0	0.51	41	1154	0.0
A.C.	W	2.59	7.00	0.37	44.0	73.0	0.60	177	297	0.59	1.66	11.5	34.0	0.33	30	238	0.1
Chart V	U	1.56	6.18	0.25	39.5	64.5	0.61	274	367	0.74	2.41	84.0	113.0	0.74	131	698	0.1
J.B.	W	0.20	2.52	0.08	28.0	54.5	0.52	216	323	0.66	8.56	18.3	29.6	0.61	4	75	0.0
Chart VIII	U	1.22	13.17	0.09	30.5	81.5	0.38	190	434	0.45	4.28	34.0	77.5	0.44	42	1021	0.0
V.M.	W	Data from water diuresis invalid because of severe uretero-renal reflex in right kidney.															
Chart VII	U	1.63	5.02	0.32	56.3	81.1	0.69	328	532	0.63	2.16	40.0	68.1	0.60	65	342	0.1
SEGMENTAL RENAL ARTERY OBSTRUCTION																	
J.K.	W	2.03	3.56	0.56	46.2	75.4	0.61	163	265	0.61	1.06	32.6	32.4	1.05	66	115	0.5
Chart IX	U	2.91	5.51	0.53	40.3	67.0	0.60	168	272	0.62	1.16	96.3	100.0	0.96	280	551	0.5
B.L.	W	3.33	5.73	0.58	33.5	50.0	0.67	126	175	0.71	1.16	16.0	16.3	0.99	53	93	0.5
Chart X	U	2.81	5.86	0.48	36.0	58.5	0.61	135	219	0.61	1.26	73.2	80.0	0.92	206	469	0.4
W.G.	W	No valid data because of poor urine flow rates.															
Chart XI	U	0.98	3.57	0.28	33.0	91.5	0.36	125	303	0.41	1.32	131.0	138.5	0.94	128	497	0.2
MISCELLANEOUS — SEE TEXT																	
B.G.	W	1.20	2.61	0.45	16.0	56.0	0.28	62	231	0.27	0.61	65.0	78.0	0.85	78	204	0.
Chart XIV	U	3.00	10.55	0.28	15.0	55.0	0.28	61	225	0.27	0.99	95.0	98.5	0.96	285	1039	0.
D.J.	W	2.96	3.52	0.84	11.0	12.5	0.88	30	33	0.89	1.03	36.0	35.0	1.03	107	123	0.
Chart I	U	3.91	4.45	0.87	17.0	20.0	0.85	44	49	0.88	0.98	91.0	92.0	0.99	356	409	0.
T.W.	W	No valid data because of poor urine flow rates.															
Chart XIII	U	1.75	2.18	0.80	43.0	44.5	0.97	181	205	0.88	1.20	137.5	133.5	1.03	241	291	0
GLOMERULONEPHRITIS — IDENTICAL TWINS																	
Daw.D.	W	1.21	2.53	0.47	11.5	21.0	0.54	41	70	0.58	1.16	120.0	123.0	0.97	145	311	0
20 W.F.	U	2.61	5.37	0.48	13.0	23.3	0.55	49	92	0.53	1.15	105.0	109.0	0.96	274	585	0
Dot.D.	W	4.74	5.26	0.90	36.5	38.8	0.94	116	122	0.95	1.05	19.4	20.1	0.96	92	106	0
20 W.F.	U	4.91	5.65	0.86	41.8	45.0	0.93	154	164	0.93	1.07	110.0	108.7	1.01	540	614	0
TOXEMIA OF PREGNANCY																	
I.J. 12/17/59	W	No valid data because of poor urine flow rates.															
22 C.F.	U	6.90	10.60	0.65	37.0	46.0	0.80	253	306	0.82	1.25	109.0	110.0	0.99	752	1177	0
I.J. 5/11/60	W	4.56	5.14	0.88	49.5	55.0	0.90	220	238	0.92	1.01	14.0	15.0	0.93	64	77	0
22 C.F.	U	2.49	2.89	0.86	46.0	50.0	0.92	232	251	0.92	1.04	71.0	73.0	0.97	177	211	0
EXPERIMENTAL LEFT MAIN RENAL ARTERY OBSTRUCTION																	
8% urea before clamp	U	2.86	2.80	1.02	53.1	47.4	1.11	114	106	1.07	1.09	97.1	93.8	1.03	277	262	1.
8% urea after clamp	U	2.10	4.60	.45	26.7	48.7	0.54	68	129	0.52	1.21	56.5	90.4	0.62	119	416	0.
Change to 16% urea	U	5.30	16.10	0.32	31.0	52.2	0.59	92	193	0.47	1.80	39.7	78.5	0.50	210	1263	0.

Legend:

X = "diseased" kidney.
Y = Normal kidney or less diseased kidney.

% Filtered Na Excreted = $\frac{\text{Clearance of Na}}{\text{Clearance of In}} \times 100$

W = ureteral catheterization data under oral water diuresis.
U = ureteral catheterization data under urea-saline-ADH diuresis.

;V
'RESENTATION

% Filtered Na Excreted			Urine Osmolality			UV osmoles			Plasma Osmolality	$\frac{C_{osm.}}{C_{In}} \times 100$			$\frac{C_{H_2O}}{C_{In}} \times 100$		
X	Y	X/Y	X	Y	X/Y	X	Y	X/Y		X	Y	X/Y	X	Y	X/Y
			μOsm /gm H_2O			μOsm / min			μOsm /gm H_2O	ml / min / 100 ml. GFR			ml / min / 100 ml GFR		
2.10	2.38	0.88	666	666	1.00	1345	1359	0.98	297	8.40	8.62	0.97	-4.64	-4.60	1.01
2.70	2.51	1.07	138	134	1.03	327	785	0.46	263	4.36	4.32	1.01	+3.98	+4.17	0.95
9.19	9.18	1.00	346	367	0.95	1283	3281	0.39	270	13.57	14.63	0.93	-2.97	-3.86	0.77
									260						
2.50	2.60	0.96	516	550	0.93	1032	1733	0.59	265	9.60	9.46	1.01	-4.66	-4.89	0.95
0.70	3.64	0.19	60	70	0.86	185	1281	0.14	275	2.57	0.04	0.42	+9.30	+17.72	0.52
1.07	9.75	0.11	485	363	1.33	344	3775	0.09	283	4.43	15.62	0.28	-1.83	-3.43	0.53
.48	2.32	0.21	68	97	0.70	176	679	0.26	250	1.60	3.72	0.43	+4.30	+5.87	0.73
2.43	7.96	0.30	517	419	1.23	807	2589	0.31	265	7.70	15.14	0.50	-3.74	-5.56	0.67
0.09	0.97	0.09	335	150	2.26	67	378	0.17	270	0.85	2.57	0.33	-0.14	+2.05	---
0.98	9.08	0.10	470	305	1.54	573	4017	0.14	300	6.26	16.41	0.38	-2.26	-.26	---
									260						
0.84	3.08	0.27	468	346	1.34	763	1736	0.43	280	4.83	7.63	0.63	-1.93	-1.44	1.34
1.03	1.11	0.92	122	122	1.00	248	436	0.56	255	2.09	2.25	0.93	+2.29	+2.46	0.93
5.04	5.95	0.84	439	422	1.03	1278	2327	0.54	280	11.31	12.40	0.91	-4.09	-4.17	0.98
1.18	1.39	0.84	58	54	1.07	191	308	0.62	265	2.14	2.32	0.92	+7.79	+9.14	0.85
4.39	6.16	0.71	457	427	1.07	1284	2502	0.51	275	5.13	5.55	0.92	-5.13	-5.53	0.93
									280						
2.59	3.62	0.71	529	492	1.07	518	1756	0.28	300	5.22	6.40	0.81	-2.24	-2.49	0.90
3.00	2.57	1.16	211	284	0.75	253	725	0.34	243	6.50	5.51	1.18	+1.00	-0.85	----
13.86	13.79	1.01	347	360	0.96	1041	3798	0.27	249	27.80	27.69	1.00	-7.80	-8.50	0.91
6.93	7.04	0.98	128	130	0.99	379	458	0.83	262	13.09	13.92	0.94	+13.81	+14.24	0.97
15.18	14.85	1.02	277	272	1.01	1085	1209	0.89	270	23.58	22.35	1.05	-0.58	-0.1	----
									280						
3.91	4.57	0.85	540	495	1.09	945	1078	0.87	282	7.80	8.58	0.90	-3.72	-3.68	1.01
8.79	10.32	0.85	301	308	0.97	364	779	0.46	285	11.10	13.01	0.85	-.005	-.009	0.55
14.68	17.49	0.83	323	326	0.99	843	1751	0.48	310	20.91	24.23	0.86	-.007	-.011	0.63
1.73	1.87	0.92	61	62	0.99	289	326	0.88	250	3.17	3.35	0.94	9.84	10.19	0.96
8.91	9.43	0.94	388	374	1.03	1905	2113	0.90	283	16.12	16.62	0.97	-4.35	-4.03	1.07
									260						
14.51	18.27	0.79	359	333	1.08	2477	3530	0.70	290	23.08	26.45	0.87	-4.32	-3.26	1.32
0.92	1.00	0.92	68	67	1.01	310	344	0.90	268	2.33	2.33	1.00	6.88	7.01	0.98
2.74	3.00	0.91	528	511	1.03	1315	1477	0.89	292	2.73	3.00	0.91	-0.13	-0.18	0.72
3.41	3.61	0.94	731	644	1.13	2090	1803	1.15	323	12.20	11.77	1.03	-6.80	-5.86	1.16
2.96	5.68	0.52	527	566	0.93	1107	2604	0.42	307	13.49	17.39	0.77	-5.61	-7.90	0.71
3.08	15.80	0.19	540	495	1.09	2862	7970	0.35	420	22.00	36.32	0.60	-4.87	-5.49	0.88

pertension, then the hypertension of glomerulonephritis is on the same basis as main renal artery obstruction.

4. *Toxemia of Pregnancy.* The hypertension associated with toxemia of pregnancy resembles curable renovascular hypertension in several aspects. Its sudden onset, the precipitous fall in blood pressure which may occur with delivery, and the diastolic arterial pressure elevation all resemble renovascular hypertension. If the disparate pattern of excessive water reabsorption described here could be demonstrated when the pregnant patient becomes hypertensive, only to disappear when the blood pressure returns to normal, then the hypertension of toxemia is probably renal in origin regardless of the precipitating mechanism.

We have studied one patient. A 22 year old, colored female (I.J., "Toxemia of Pregnancy", Chart XV) delivered her second full term baby on October 10, 1959. She had been hypertensive with her first pregnancy but the details were unknown. She was first seen 8 months along in her second pregnancy without complaints and her blood pressure was 120/90. She appeared on October 10, 1959 in full labor with a blood pressure of 150/90 and had an uneventful delivery of a full term live baby. The pre-delivery catheterized urine showed a 2+ protein and 2 to 5 WBC/HPF. Over the next six days her blood pressure rose to 180/130 and remained in the range of 160–190/110–120 mm Hg. An IVP was normal and the 15 minute PSP was 25 per cent. Over the next two months her blood pressure persisted at a level of 120 diastolic and headaches were a frequent complaint. Ureteral catheterization studies were performed on December 17, 1959. The studies under water diuresis were not valid because of poor flow rates, but two periods under urea-saline-ADH diuresis are averaged in Chart XV under "Toxemia of Pregnancy". The excessive reabsorption of water in the right kidney (X) was similar to the patient with severe essential hypertension (T.W., Chart XIII). During the next six months her blood pressure gradually returned to normal without treatment. Ureteral catheterization studies were again performed on May 11, 1960 and four consecutive ten minute periods under oral water diuresis followed by four under urea diuresis are averaged in Chart XV. The pattern of excessive reabsorption of water in the right (X) kidney was no longer present. Thus, the characteristic functional patter of renal ischemia, *qualitatively* similar to the pattern in curable renovascular hypertension, was present during the hypertension and disappeared when the blood pressure returned to normal.

SUMMARY

(1) A technique of bilateral ureteral catheterization which prevents bladder leakage, recognizes uretero-renal reflexes and defines the requisite urine flow rates for repeatable data is presented in detail. Criteria for a successful ureteral catheterization study are based on consecutive ten minute collection periods which show close agreement (within 6%) in their ratio of urine flow rates.

(2) Patients with normotensive unilateral renal disease and patients with curable unilateral renovascular hypertension were studied under oral water diuresis followed by an infusion of urea, saline and ADH. The functional patterns indicate that the unique characteristic and distinguishing feature of curable renovascular hypertension is a reduction in renal plasma flow to functioning renal tissue which responds with an excessive reabsorption of sodium and water (Figures 7-C and 15). The pattern in normotensive unilateral renal disease is a reduction in renal plasma flow to reduced renal tissue which does not respond by a relative increase in the reabsorption of water (Figures 7-A, B and 12).

(3) The free water clearances indicate that the site of this excessive water reabsorption is primarily in the proximal tubule, where sodium concentration remains equimolar with plasma. Therefore, *total* water reabsorption is the best index of unilateral or bilateral disparate renal ischemia and is measured by comparing the concentration of inulin, PAH or creatinine in the urine from each kidney. These data further show that the infusion of urea, saline and ADH amplifies the difference in total water reabsorption between the ischemic and non or less ischemic kidney.

(4) Patients with main renal artery occlusions, studied with an infusion of urea, saline and ADH have shown at least a 3:1 difference in urine flow with a 100 per cent or more increase in the concentration of inulin. The functional pattern in segmental renal artery disease has been a 2:1 difference in urine flow with a 16 per cent or more increase in the concentration of inulin.

(5) Emphasis is placed on the observation that

renal plasma flow is reduced in curable renovascular hypertension. In this series of patients, the smallest reduction in RPF was 37 per cent in the ischemic kidney when compared to the contralateral kidney. These vascular occlusions were associated with marked gradients in the arterial pressure distal to the stenosis. Because the renal artery in the dog and man may be narrowed by a clamp or atherosclerotic plaque without reducing RPF and without producing hypertension, it is apparent that "positive" aortograms may be present without physiological significance in relation to RPF or hypertension.

(6) A functional definition of renal ischemia is presented based on the asymmetry of excessive water reabsorption. The potentiality of this measure in answering the question of the pressor role of the kidney in essential hypertension, pyelonephritis, glomerulonephritis and toxemia of pregnancy deserves further study.

ADDENDUM

Since submission of this manuscript the authors have performed ureteral catheterization studies on patients F.W. (Chart VI) and J.B. (Chart VIII). The studies were performed on April 21, 1961, nine months after repair of the main renal artery obstructions. Their blood pressures were 135/80 (F.W.) and 130/70 (J.B.). Both were asymptomatic and in excellent health. The averages of several reproducible collection periods were as follows:

	V ml/min			C_{In} ml/min		
	X	*Y*	*X/Y*	X	*Y*	*X/Y*
F.W. (X = L.Kid.)	2.3	2.6	.89	61	68	.89
J.B. (X = R.Kid.)	6.4	6.1	1.05	60	64	.94

	U_{In} Ratio	U_{Na} mEq/L		
		X	*Y*	*X/Y*
F.W. (X = L.Kid.)	1.00	101	72.5	1.39
J.B. (X = R.Kid.)	.91	14.6	8.6	1.70

It is clear that the U_{In} ratios, which were several hundred per cent increased prior to the vascular repair, are now identical (F.W.) or nearly the same (J.B.). The sodium concentration ratios show a marked disparity and do not reflect recovery from the renal ischemia.

APPENDIX

A.C.—Main Renal Artery Obstruction

A.C. (Figure 9 and Chart V) was a 50 year old, white male laborer. He was first admitted to the hospital on 8/5/59 with the complaint of severe occipital headaches of one year's duration. In October of 1958 his blood pressure was recorded as normal by his family physician. There was no family history of hypertension. His blood pressure on admission was 220/130 lying, 170/110 standing. On bed rest, his average blood pressure was 180/110. Funduscopic examination revealed flat discs, no hemorrhages or exudates, but marked narrowing and A-V nicking. The heart was not enlarged. Femoral artery and dorsalis pedis pulses were bilaterally equal. Urinalysis was negative for protein and sugar. The urine sediment contained an occasional RBC. The creatinine clearance was 109 ml/min, the 15 minute PSP excretion 20 per cent, the BUN 16 mg per cent, and the serum creatinine 0.9 mg per cent. The total serum cholesterol was 220 mg per cent.

An intravenous pyelogram was normal. A brachial aortogram demonstrated stenosis at the ostium of the left renal artery. There was no difference between the left and right kidney in the density of the nephrogram phase of the aortogram. The right renal artery was not occluded.

On 8/28/59, differential renal function studies were performed. Two ten minute periods under oral water diuresis were collected and followed by two short periods (two minutes each) under urea-saline-ADH diuresis. There was no bladder leakage and both periods were identical for each set of circumstances. Figure 9 shows the results for one period under each condition. Following the catheterization studies severe left renal colic was experienced with hematuria, temperature elevation to 37.9° centrigrade and the WBC rose to 14,700. An intravenous pyelogram three days after the catheterization studies demonstrated minimal, if any, dye excretion from the left kidney.

Because the functional lesion of excessive water reabsorption in the left kidney prevented the necessary water diuresis to stop the hematuria, exploration was performed on 9/3/60. A palpable thrill was present in the main renal artery of the left kidney. This artery was obstructed from the point of origin in the aorta to the first primary bifurcation into upper and lower segments. There were no gross atherosclerotic plaques visible in the artery. The arterial pressure, recorded by strain gauge manometry, was 220/120 in the aorta and 130/60 in both upper and lower branches of the primary bifurcation. An end to side anastomosis of the splenic artery was made to the upper branch of the main renal artery. Following the

anastomosis there was no difference in arterial pressure between the aorta and either the upper or lower branch of the main renal artery (160/100). Following surgery, the blood pressure initially fell to 150/90 but by the time of discharge on 9/16/59, the blood pressure had returned to 170/110.

During the months of September, October and November the patient continued to experience headaches and his blood pressure varied from 156/104 to 180/116. He was readmitted to the hospital on 12/2/59 and on 12/4/59 differential renal function studies were again performed (Chart V). A nephrectomy was performed on 12/18/59 and by the evening of surgery the blood pressure had fallen to 80/20. Intravenous aramine was required for two days to maintain the blood pressure at 110 systolic.

Pathological sections of the kidney demonstrated scarring and atrophy with crowding of glomeruli in the outer ⅓rd of the renal cortex.

In the year following surgery, the patient's blood pressure has remained in the range of 130/90, the highest blood pressure recorded being 146/92, and the lowest 120/84. He has remained asymptomatic and in excellent health. On January 24, 1961 his blood pressure was 146/96.

F.W.—Main Renal Artery Obstruction

F.W. (Figures 14, 15 and Chart VI), a 49 year old, white male was admitted to the hospital on 6/30/60 complaining of frontal headaches of three month's duration. His blood pressure was normal in February of 1960. Between February of 1960 and July 1960 his blood pressure had been recorded as high as 260/160. On admission to the hospital the blood pressure fell to 160/90 and remained at this level throughout the preoperative studies. Family

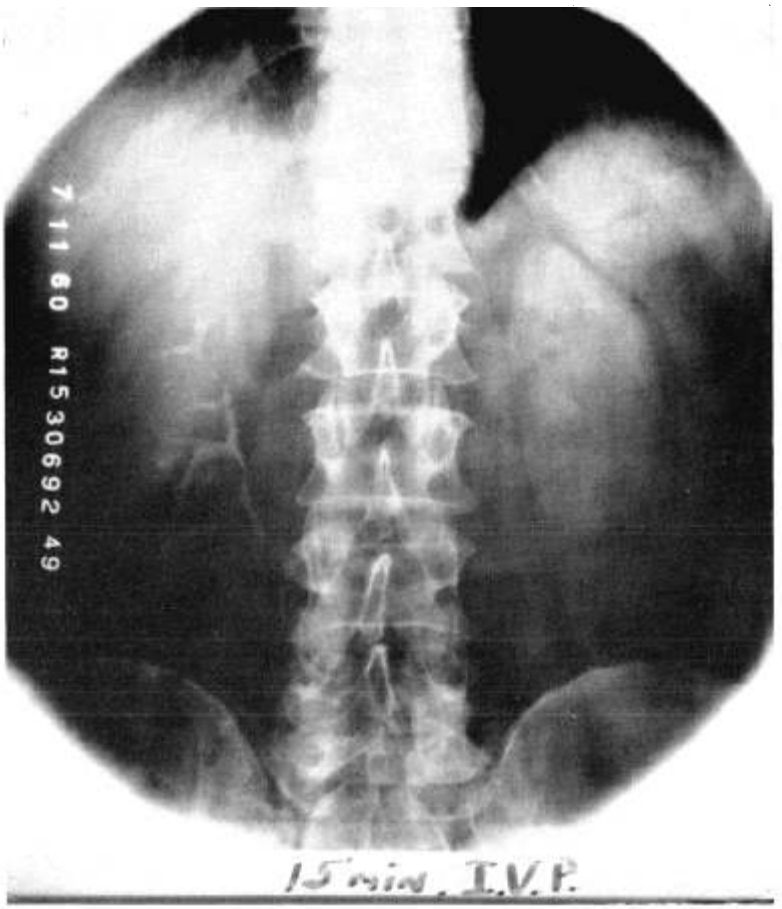


FIG. 14. F.W., 49 year old, W, M. 15 minute intravenous pyelogram showing faint excretion of the contrast medium in the area of the left renal calyces. This kidney, however, excreted 3 ml/min with oral water hydration. The failure to visualize with intravenous pyelography is due to the low GFR.

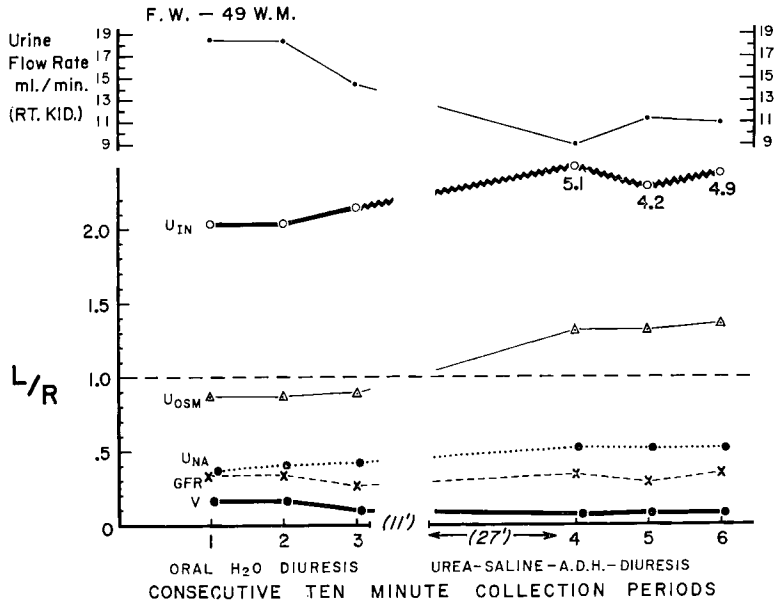


FIG. 15. F.W., 49 year old, W, M. This is the classical functional pattern of curable, unilateral renal ischemia—V is markedly reduced from the left kidney, and U_{In} is twice the concentration of the right kidney. With urea-saline-ADH diuresis, the U_{In} changes from a 100% increase to a 400% increase. Note that no other measurement approaches the diagnostic difference of the U_{In} ratio when the study is performed with urea, saline and ADH.

This pattern should be compared with Figure 12 which represents the functional changes characteristic of non ischemic unilateral renal disease.

history and past history were negative for cardiovascular disease. Funduscopic examination revealed several hemorrhages and exudates. The heart was not enlarged. The ECG was normal. Urinalysis showed no albumin and no significant sediment. A urine culture was sterile. The 15 minute PSP excretion was 27 per cent and the creatinine clearance 125 ml/min.

Figure 14 is an intravenous pyelogram performed on admission. A femoral aortogram demonstrated a severe occlusion in the proximal one-third of the left main renal artery. The right renal artery was not occluded. Ureteral catheterization studies were performed on 7/15/60 (Chart VI). Figure 15 was derived from Chart VI and is the classical functional pattern of total (as opposed to segmental) renal ischemia.

Exploration was performed on 7/26/60. In spite of the appearance on aortography, there was no visible lesion along the renal artery. A very weak pulse was felt in the proximal 1 cm. Arterial pressure in the aorta was 200/132 while only a mean recording of 42 mm Hg was present in the renal artery. An incision was made over the ostium of the renal artery and into the aorta. A large cholesterol plug was easily dissected which exactly blocked the ostium of the renal artery. A dacron patch graft was used to close the defect. At the conclusion of the operation pressure in the aorta was 160/124 and in the renal artery 160/124. By the tenth postoperative day, the blood pressure had fallen gradually from 160/90 to 120/70 and has remained at this level. His headaches have disappeared. On April 21, 1961, his blood pressure was 100/60 mm Hg.

V.L.M.—Main Renal Artery Obstruction

V.L.M. (Chart VII), a 24 year old, colored female was admitted to the hospital on 7/14/60 for evaluation of her hypertension. In 1954, while working as a student nurse, she developed severe frontal headaches and her blood pressure was recorded as 180 systolic. Over the past six years her blood pressure has varied between 180–210/105–120 mm Hg. Because of increasing headaches and difficulty in controlling her blood pressure, the patient was hospitalized in July 1960. An intravenous pyelogram was normal.

A brachial aortogram was suggestive, but not diagnostic of left renal artery obstruction in the distal one-third of the main artery and extending into the first primary branches. The right renal artery was questionably narrowed in the middle one-third.

Her admission blood pressure was 180/105 mm Hg. The distal pulses were equal and strong. The

heart was not enlarged and the electrocardiogram was normal. Funduscopic examination was likewise normal. The 15 minute PSP was 30 per cent, the creatinine clearance 115 ml/min, BUN 10 mg per cent, and the serum creatinine was 0.8 mg per cent. A urinalysis was normal.

Differential ureteral catheterization studies were performed on 7/15/60 (Chart VII).*

On 7/22/60 the left kidney was explored through a mid-line incision. A thrill was faintly palpable near the hilum of the kidney. Arterial pressure in the aorta was 162/135 mm Hg. Pressure in the main renal artery just proximal to the site of bifurcation was recorded as a mean pressure of 60 mm Hg. Pressure in the proximal 1 cm of the renal artery was the same as in the aorta. Accordingly, a dacron patch graft was placed between the normal proximal renal artery and the site of renal artery bifurcation. After completing the patch graft, there was still a difference of 60 mm Hg between the aorta and the branches of the main renal artery. Furthermore, more extensive dissection of these secondary branches revealed a bulbous appearance suggestive of further disease. Accordingly, a nephrectomy was performed. The blood pressure prior to anesthesia had been 170/120. Eight hours later the pressure had fallen to 120/80 and has remained at this level since discharge from the hospital. Pathological studies revealed "fibro-elastosis" of the main renal artery as well as its more distal branches. On January 16, 1961, her blood pressure was 120/90.

J.B.—Main Renal Artery Obstruction

J.B. (Chart VIII), a 12 year old, white female was admitted to the hospital on 6/16/60 for consideration of unilateral renal disease and hypertension. Because of severe occipital headaches in May of 1960, her blood pressure was first found to be elevated in the range of 200/150 mm Hg. On Diuril® and Reserpine® her blood pressure had been controlled to levels of 150/90 mm Hg, although occasionally diastolic pressures reached 120–130 mm Hg. Other than some vague aching in the right flank, there had been no other symptoms. The family history was not remarkable. The heart was normal, as was the ECG. Funduscopic examination revealed blurred discs with a 2 diopter elevation. There was extreme arteriolar narrowing. The 15 minute PSP excretion test was 29%, the creatinine clearance 124 ml/min and the urinalysis was negative.

An intravenous pyelogram was normal. The renal outlines could not be visualized. An aortogram showed multiple arteries to the left kidney, but a gradual tapering in the distal one-third of a single right renal artery. The right kidney was 2 to 3 cm smaller than the left kidney.

Ureteral catheterization studies were performed on July 1, 1960 (Chart VIII).

On 7/19/60, the right kidney was explored. There was gradual narrowing of the right renal artery as it approached the primary bifurcations. Arterial pressure in the proximal renal artery and aorta was 140/120 mm Hg. In the distal main renal artery a mean blood pressure of 42 mm Hg was recorded. A patch graft was placed in the main renal artery. The occlusion time was 22 minutes. After completing the graft, the blood pressure in the proximal renal artery was 150/115, in the primary branch to the upper pole 112/92 and in the lower polar branch 125/105 mm Hg. The kidney was not removed. By the 9th postoperative day the blood pressure had gradually fallen to 120/90 and within one month was 110/80 mm Hg. On April 21, 1961, her blood pressure was 130/70, funduscopic examination was not remarkable, and a urinalysis was negative.

J.K.—Segmental Renal Artery Obstruction

J.K. (Figures 16, 17 and Chart IX), a 45 year old, white male was admitted to the hospital on the 20th of March 1960 complaining of headaches and markedly increased nervousness. In 1952 his blood pressure was normal. In 1955 a routine physical examination revealed a blood pressure of 150/90 and he was placed on Serpasil® for 12 months. At the end of this time he stopped all medication and gave no further thought to his blood pressure. In October of 1959 he experienced upper abdominal pain on the right side at the level of the 11th and 12th ribs. His blood pressure was 130/80, an intravenous pyelogram was normal and he was diagnosed as having "pleuritis" although there were no specific signs. In January of 1960 he first experienced headaches and his blood pressure was found to be 220/130. His blood pressure did not respond to a variety of antihypertensive medications and he was admitted to the hospital for further evaluation. Physical examination on admission revealed

* The remarkable equality of urine flow, GFR and PAH clearances under oral water diuresis (first three collection periods) compared with the sudden disparity after urea-saline-ADH infusion is difficult to understand. There was definitely no bladder leakage. It is possible the thirty-five minutes of difficulty in catheterizing the right ureter caused severe uretero-renal reflexes. This could cause an artificial reduction in inulin and PAH clearances, with a relative increase in urine inulin, PAH and osmolality in the normal right kidney. This is in keeping with the data, especially if the first three periods are compared to the last three. If this interpretation is correct, the sudden appearance of disparity in urine flow rates immediately after the urea-saline-ADH infusion would have to be considered fortuitous.

a blood pressure of 220/130. The electrocardiogram and chest x-ray were normal. Funduscopic examination was not remarkable. The heart was not enlarged.

An intravenous pyelogram demonstrated that the right kidney now contained a depressed area at the junction of the middle and lower poles on the lateral cortical border. The SUN was 9 mg per cent, the 15 minute PSP 45%, the urine contained no protein and there was no significant microscopic sediment. Ureteral catheterization studies were performed on April 1, 1960 (Chart IX). One week later a retrograde femoral arteriogram demonstrated a normal artery to the lower pole of the right kidney but no other arteries were visualized. The left renal artery was faintly visualized and appeared normal. On April 20, 1960 the right kidney was explored. Figure 16 represents the kidney in situ at surgery. The anterior coronal upper two-thirds of the kidney was bluish-grey compared to the normal vascular color of the lower pole as well as the entire posterior coronal plane of the kidney. Figure 17 demonstrates the three vessels which supplied the kidney. The upper vessel, supplying the anterior coronal upper two-thirds of the kidney was blocked by a large thrombus, while the middle vessel supplying the posterior coronal upper two-thirds of the kidney was normal along with the lower polar vessel.

Pathological studies showed the upper vessel was 95 per cent occluded by an arteriosclerotic thrombus, while the middle and lower vessels were normal. The cortex of the ischemic anterior coronal upper two-thirds showed classic ischemic tubular atrophy with crowded glomeruli, while the remainder of the renal cortex was normal.

Following nephrectomy, the patient's blood pressure returned to 120/80. His headaches disappeared and the extreme preoperative restlessness strikingly disappeared immediately following surgery.

Blood pressures have been checked frequently at home by the patient's wife. During the month of December 1960, his blood pressure varied between 126–160/82–110 with an average diastolic of 95. In January of 1961 the average diastolic was 100 mm Hg. The fundi were normal, and the patient was asymptomatic.

B.LeV.—Segmental Renal Artery Obstruction

B.LeV. (Figures 18–21 and Chart X), a 25 year old, white female was first admitted to The Johns Hopkins Hospital on May 10, 1960 complaining of headaches and a recent "stroke". Her history began ten years before in June of 1950, when, at the age of 15, she first developed severe occipital headaches. These were soon followed by nausea, vomiting, dizziness and blurring of vision. She was first examined in December of 1950. Her blood pressure was found to be 240/140 and Grade IV hypertensive retinopathy was present. During the two years prior to 1950 she had experienced substernal pains which were thought by her physician to be angina pectoris. There was an early history of acute rheumatic fever at age 6 treated by bed rest for six to eight months. In January and February of 1951 a subtotal left adrenalectomy and total right adrenalectomy were performed in the Hospital of the University of Pennsylvania. A bilateral sub-diaphragmatic sympathectomy of T-12 through L-2 and a celiac ganglionectomy were performed also. She received cortisone replacement therapy postoperatively. The papilledema, hemorrhages and exudates in the fundi disappeared together with her symptoms. However, the blood pressure remained in the range of 240/140. The cortisone replacement therapy was withdrawn gradually but the blood pressure showed no tendency to change. In September of 1952 she was found to be pregnant and in the first trimester the remaining left adrenal fragment was removed surgically. Her blood pressure remained at approximately the same level and during the 28th week of pregnancy she developed spontaneous labor, giving birth to an 800 gram female child who survived four days. Between the years 1953 and 1960 she was treated with all the antihypertensive drugs, including saluretics, but apparently the blood pressure remained refractory to treatment. No adrenal crisis occurred. During these years she was generally maintained on 37.5 to 50 mg per day of cortisone with intermittent periods of treatment with desoxycorticosterone, 2 mg per day. Since February of 1960 she has received 9 alpha-fluoro-hydrocortisone in a dose of .05 mg per day and 37.5 mg per day of cortisone.

Eight days prior to admission to the hospital on 10 May 1960 she developed a right frontal headache and a staggering gait with a limp favoring her left leg. She began to spill things when using her left hand. Unusual restlessness was present with frequent crying episodes. Upon admission her blood pressure was 196/160, the pulse was 94 and regular. She appeared chronically ill with extreme restlessness but completely oriented. Hyperpigmentation of the lower extremities was present. The heart was not enlarged and funduscopic examination revealed no hemorrhages, exudates or papilledema. The arterioles showed some focal narrowing with mild A-V nicking. Neurological examination disclosed a left-sided motor weakness with some spasticity to the left arm and leg. The deep tendon reflexes were hyperactive. The admission chemistries established a serum sodium of 109 mEq/L and a serum chloride of 82 mEq/L.

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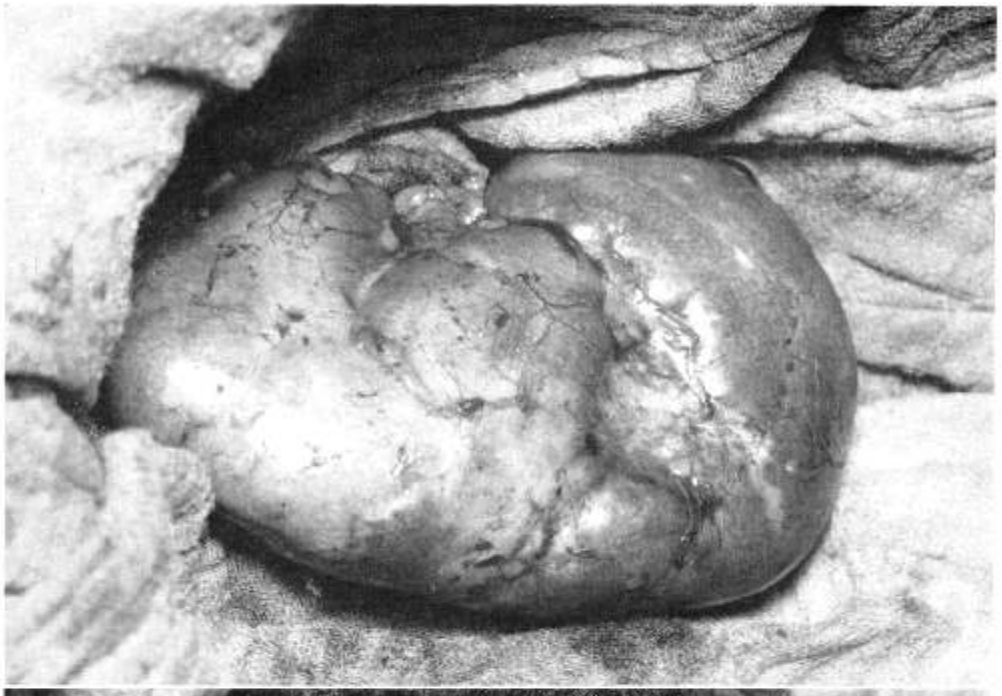

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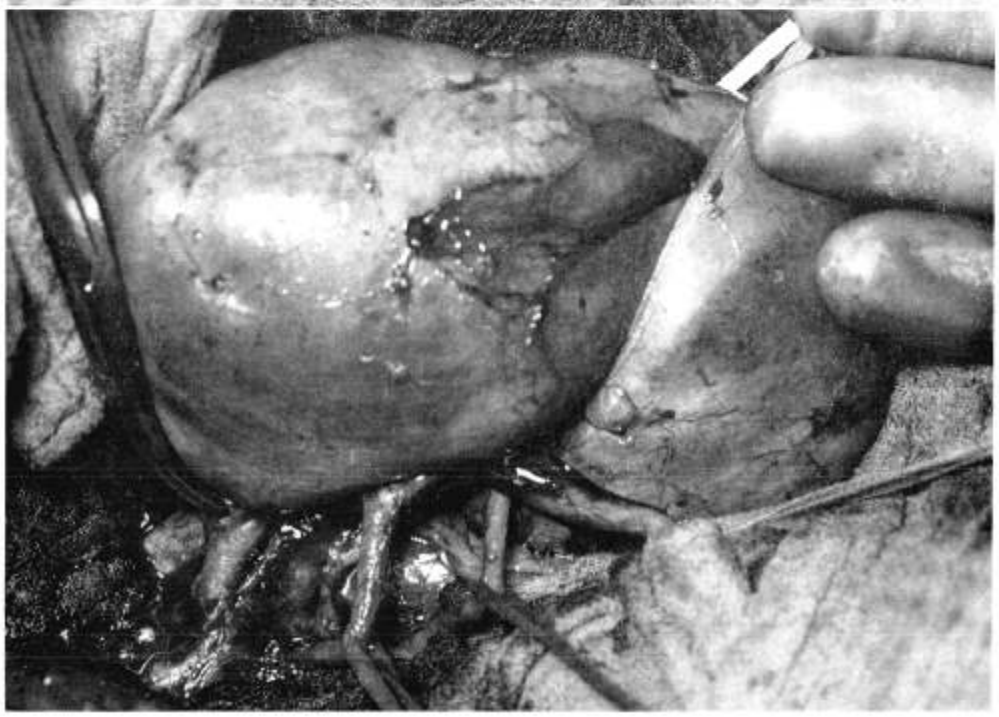


FIG. 16. J.K., 45 year old, W, M. Surgical exposure of the anterior coronal surface, right kidney. The upper pole of the kidney is at the left, and the normal lower pole is to the right. The anterior upper ⅔'s was a pale grey color, and contrasted sharply with the normal color of the remainder of the kidney. The function studies (Chart IX) on this patient are characteristic of segmental renal ischemia. Urine flow was decreased by 50%, but the ischemic area involved only ⅓ of the kidney. Therefore excessive water reabsorption occurred, which was reflected by the U_{In} concentration ratios. Na concentration was *increased,* similar to the segmental lesion in Figure 1.

FIG. 17. J.K., 45 year old, W, M. Surgical exposure posterior surface right kidney demonstrating the three arteries. The arteriosclerotic artery to the anterior coronal upper ⅔ of the kidney is indicated by the clamp. The normal middle artery supplying the posterior coronal upper ⅔ of the kidney is indicated by the adjacent tape. The normal artery to the lower pole is adjacent to the ureter (the lower most tape). The cortex on the posterior surface was normal.

The serum potassium was 4.6 mEq/L, the CO_2 combining power 23.7 mEq/L and the serum urea nitrogen 16 mg per cent. A fasting blood sugar was 70 mg per cent. A clean catch voided urine was clear containing no protein and no sediment. The patient was treated with intravenous saline, oral salt and increased cortisone. By the 10th hospital day her serum sodium was 140 mEq/L. The blood pressure remained in the range of 220/150. A PSP excretion test showed 45% in 15 minutes.

On 5/19/60 an intravenous pyelogram was performed (Figure 18). This demonstrated that the right kidney was smaller than the left and excreted the dye with less intensity than the left kidney.

On 5/26/60 a left ulnar aortogram was performed. This study was unsatisfactory but did show a double left renal artery and a single right renal artery. It further confirmed the fact that the right kidney was smaller than the left—12.5 cm compared to 14.7 cm.

Ureteral catheterization studies were performed under oral water hydration followed by urea-saline-ADH diuresis on 6/2/60 (Chart X).

The dosage of cortisone was increased to 200 mg per day for two days prior to surgery. Exploration was performed on 7/8/60. The right renal artery was fully exposed and found to be normal. Arterial blood pressure in the aorta was 220/140. Arterial pressure at the most distal point of the main renal artery just prior to the bifurcation into the primary branches was also 220/140. With the certain knowledge that functional ischemia was present in the right kidney from the evidence of the ureteral catheterization studies, and having ruled out a main renal artery obstruction, the right kidney was removed. Figure 19 illustrates the gross specimen which weighed 119 grams and measured 10 x 6 x 3 cm. Note that the three branches of the main renal artery appear about the same size in the gross specimen. However, the injection specimen with barium sulfate (Figure 20) indicated a patent posterior artery while the two anterior arteries to the upper and lower poles contained markedly narrowed lumens. As the two anterior branches (the large artery of the three is the posterior branch) approached the renal parenchyma, the internal calibre of the vessels returned to normal. Figure 21 is a section of these arteries immediately after their bifurcation from the main renal artery. The adventitia is replaced by a peculiar, thick, longitudinal fibromuscular layer which surrounds the medial muscle. Especially striking is the observation that as these extra-renal primary branches of the main renal artery approached the parenchyma of the kidney this pathological fibromuscular layer became progressively thinner and completely disappeared upon entering the renal tissue. It is worth emphasizing that the pathological lesion in this patient is clearly different from the fibromuscular hyperplasia described by Wylie and Wellington (33). In this patient the pathological abnormality seemed to be an extra fibromuscular layer superimposed around the normal appearing media.

Within 30 minutes of clamping the renal artery

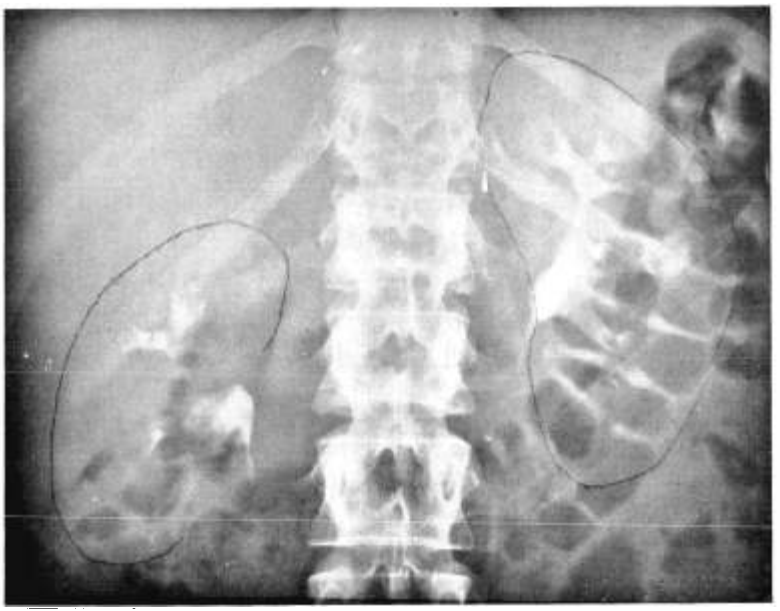
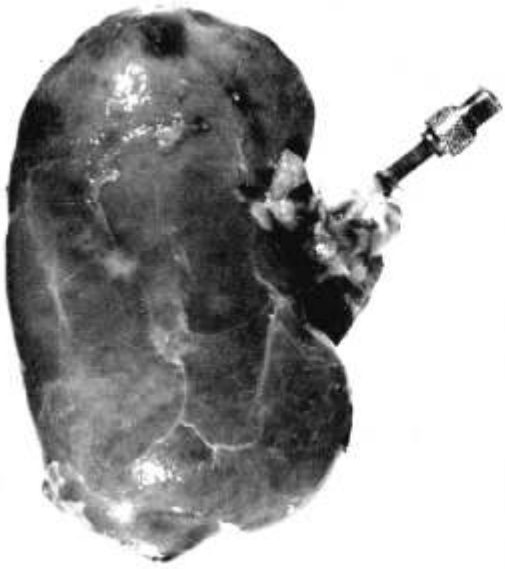


FIG. 18. B.LeV., 25 year old, W, F. 10 minute intravenous pyelogram. Because the patient was thin, there was minimal perirenal fat, and the cortical outlines were difficult to see. This pyelogram was interpreted as "normal" by a number of observers.



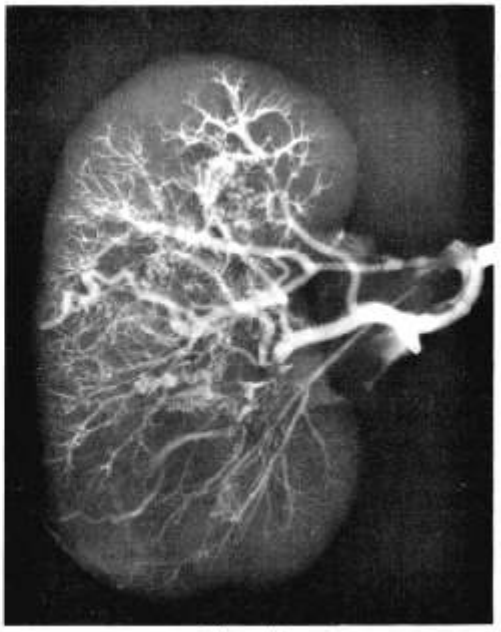


FIG. 19. FIG. 20.

FIG. 19. B.LeV., 25 year old, W, F. Surgical specimen right kidney. The kidney appeared grossly normal. There was no pressure gradient between the aorta and the site indicated by the distal end of the cannula. Note that the three primary branches are nearly the same size. This kidney was removed on the basis of information from functional studies (Chart X).

FIG. 20. B.LeV., 25 year old, W, F. Barium sulfate injection of kidney in Figure 19. Note that one branch is normal, while the other two are narrowed. The diameter of the narrowed vessels increases as they approach the renal cortex.

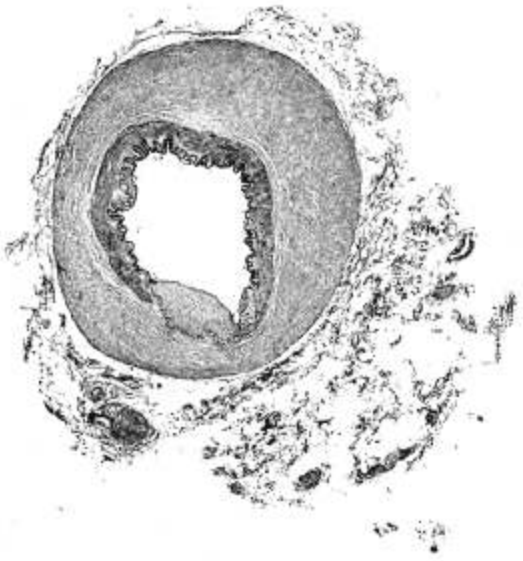


FIG. 21. B.LeV., 25 year old, W, F. Microscopic section (×25) of the anterior branch taken at a point between the bifurcation of the main renal artery and the renal parenchyma. The media is surrounded by a thick longitudional layer of collagen and muscle. This layer gradually disappeared as the artery approached the renal cortex.

the blood pressure fell from 220/140 to 150/100 under anesthesia. Within one hour after surgery her blood pressure was 120/90 and at this level of pressure the remaining left kidney failed to excrete urine. Because of this, an intravenous aramine drip was started and the blood pressure was maintained at 150/100. At this latter level, an adequate urinary output occurred. Each time an attempt was made to stop the aramine drip during the next four days the blood pressure fell to 90/60 and the urinary output ceased. Finally, on 7/12/60 the aramine was discontinued and the blood pressure remained at 140/100. During the two weeks of hospitalization after surgery the blood pressure remained in the range of 160–175/85–110. The most remarkable postoperative effect was the dramatic change in the patient's attitude in her every day life. She felt a new interest in her housework, ceased losing her temper over small incidents and demonstrated an avidity for various activties in life which previously had required too much energy. On discharge from the hospital on 7/21/60 her blood pressure was 160/105. One week later on an outpatient basis the blood pressure was 160/105, sitting and standing. On November 2, 1960 her blood pressure was 150/100. She received cortisone 25 mg daily and Florinef® .05 mg daily. On June 6, 1961 her blood pressure was 140/90 and 130/85.

W.G.—Segmental Renal Artery Obstruction

W.G. (Figures 22–24 and Chart XI) was a 19 year old white male who was admitted to the hospital in November 1959 for exploration of the right kidney. The patient was first seen at the age of 5 years with severe episodic unilateral headaches occasionally followed by vomiting. The patient was treated with phenobarbital and followed in the Epileptic Clinic. His blood pressure was not recorded until three years later when it was found to be 170/110. His blood pressure remained at this level between the ages of 8 and 13. At that time he was transferred to the adult hypertension clinic where his average blood pressure was 165/120 between the ages 13 and 19. Occasional pressures were 180/130. The routine studies including several intravenous pyelograms, concentration tests, PSP's, multiple urinalyses and Regitine Tests were all normal and were repeated many times in the course of a very close follow-up. Urine cultures were always sterile. I^{131} radioactive studies showed no difference in the two kidneys and were performed twice. The patient failed to respond to several antihypertensive medications. An intravenous

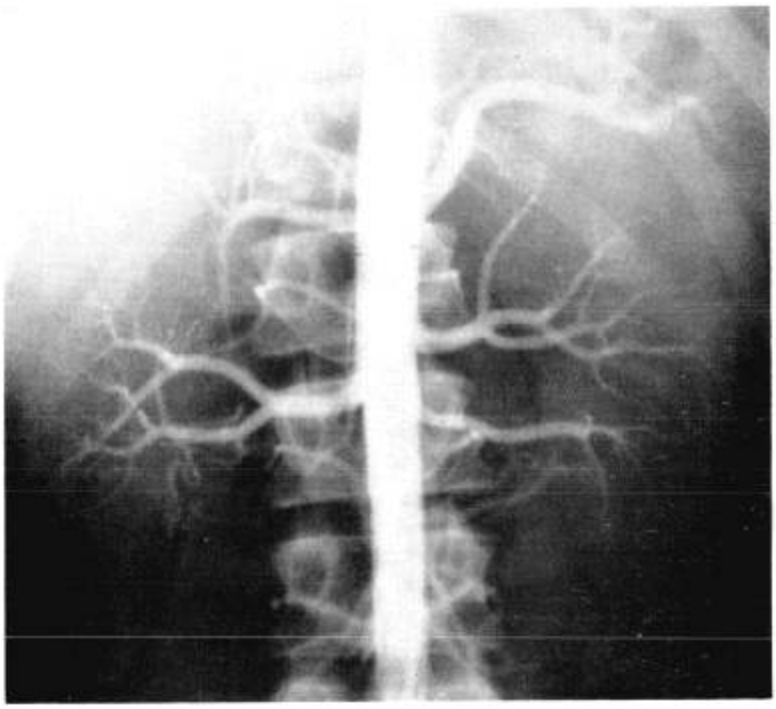


FIG. 22. W.G., 19 year old, W. M. Femoral aortogram. In spite of the excellent contrast filling of the aorta, an artery to the lower pole of the right kidney failed to visualize. The absence of perirenal fat makes the renal outlines difficult to delineate.

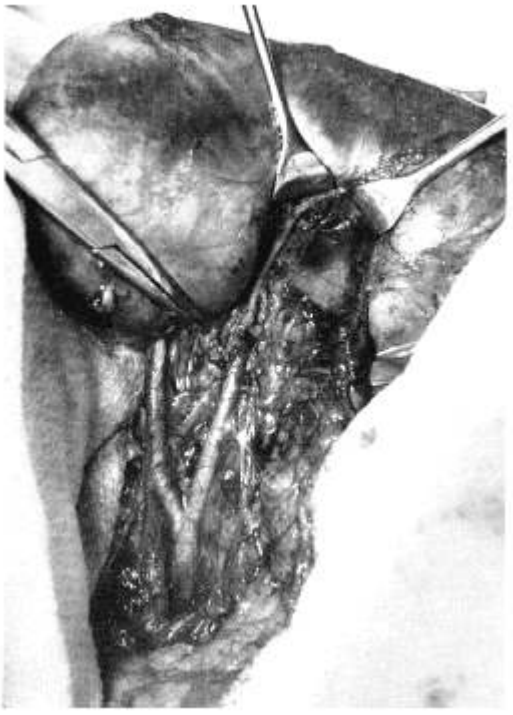


FIG. 23. W.G., 19 year old, W, M. Surgical exposure of the right kidney posterior view. The upper half of the kidney is to the left marked by the clamp. The lower pole is partially obscured by the surgical drape on the right. At surgery, the lower pole was blue when compared to the remainder of the kidney. The change in color began near the vein retractor on the right, but there was no gross change in the thickness or consistency of the cortex.

pyelogram made in October 1959 was normal. An aortogram was performed in September 1959 (Figure 22). Ureteral catheterization studies were performed on October 22, 1959 (Chart XI). Although these studies were performed before we had solved the problem of preventing bladder leakage, the studies under urea-saline-ADH diuresis are significant. On admission to the hospital his average blood pressure was 170/110. The heart and the fundi were normal. The right kidney was explored on November 20, 1959 on the basis of the ureteral catheterization studies. At surgery the lower pole of the kidney was pale and grey compared to the upper two-thirds, but no cortical depression was present at the point of this change in color. On further freeing the kidney from its surrounding tissues the greyish appearance at the lower pole suddenly disappeared. Over the next 60 minutes every radicle of the renal artery present on the aortogram was identified (Figure 23) without finding any pathological changes and without being able to reproduce the ischemic color at the lower pole. We felt this kidney was functionally producing the hypertension on the basis of the ureteral catheterization studies. A decision was made to perform a nephrectomy because we were unable to reproduce the ischemic color at the lower pole of the kidney. After ligating and severing the artery, vein and ureter, a lower polar vessel containing a small aneurysm (Figure 24) was found anterior to the renal pelvis. This aneurysm was bound down by multiple adhesions.

The patient's blood pressure immediately fell to 130/80 and has remained there since surgery. The

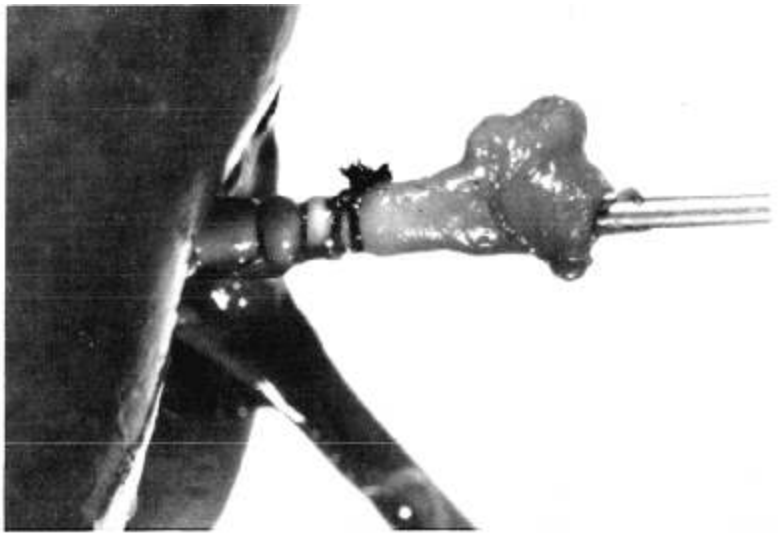


FIG. 24. W.G., 19 year old, W, M. Artery to the lower pole of the right kidney containing a small aneurysm. At surgery, this aneurysm was tightly bound by adhesions. It is of interest that this lower polar artery produced severe hypertension for ten years without changing the renal contour of the lower pole.

kidney was pathologically normal. There was no difference between the upper and lower poles except for some suggestive hypercellularity of the glomeruli in the lower pole. On June 10, 1961, his blood pressure was 125/85 in the sitting position.

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