THE AVAILABILITY of surgical correction of renovascular hypertension without the sacrifice of functional parenchyma has made the detection of unilateral renal disease in hypertensive patients increasingly important. Aortography offers a reasonably accurate means for assessing anatomic abnormalities of the renal vasculature. However, a reliable method for demonstrating the functional significance of such a lesion is desirable. Bilateral ureteral catheterization with comparison of separate kidney function permits accurate evaluation of the functional consequences of renovascular lesions but may be hazardous and technically unsatisfactory. The intravenous pyelogram and radioisotope renogram have therefore been proposed for detecting functional disparity between the separate kidneys. Both of these techniques eliminate the difficulties inherent in performing bilateral ureteral catheterization, but their accuracy in detecting disparity in kidney function remains to be established.

The present study was undertaken in order to determine the reliability of the radioisotope renogram in the detection of unilateral renal disease in hypertensive patients. The protocol for performing this test and the analysis of the renogram contour are based on previous studies in normotensive subjects.1 It was found that urine flow rate and renal tubular transport of hippuran, or a combination of these two factors, were chiefly responsible for the renogram contour. Several arbitrary factors that reflect renal function were derived from the renogram tracing. With their use it has been possible to quantitate the expected disparity between the separate kidney tracings in hypertensive patients without unilateral renal disease. Hypertensive patients with unilateral renal disease could therefore be distinguished from this control group by objective numerical criteria. This approach has demonstrated that the radioisotope renogram can reliably detect significant disparity in kidney function and is therefore of value in the diagnosis of unilateral renal disease in hypertensive patients.

Materials and Methods

I131-hippuran renograms were recorded in 53 hypertensive patients. The systolic blood pressure ranged between 150 and 260 mm. Hg (mean = 195 mm. Hg) and the range of diastolic blood pressure was 95 to 170 mm. Hg (mean = 120 mm. Hg). The absence of severe renal insufficiency was established by measurement of the blood urea nitrogen, which was between 9 and 32 mg. per cent with a mean of 17 mg. per cent.

Patients were divided into two groups as follows: group I, hypertensive patients without unilateral renal disease; group II, hypertensive patients with unilateral renal disease. The diagnosis of unilateral renal disease was established by surgery, bilateral ureteral catheterization with separate kidney function studies, aortography, and intravenous pyelogram. When more than one diagnostic procedure was performed and the results were conflicting, the priority of significance was assigned as follows: surgery; bilateral ureteral catheterization; aortography; intravenous pyelography.

The following criteria were used to designate a
test positive for the presence of unilateral renal disease: surgery—finding of unilateral renal artery stenosis; bilateral ureteral catheterization with separate kidney function studies—unilateral reduction in urine flow rate of at least 50 per cent and reduction of sodium concentration of at least 15 per cent on the same side. A diagnosis of unilateral pyelonephritis was made in one patient in whom the separate kidney function studies revealed a 50-per cent reduction in urine flow rate and an increase in sodium concentration on that side. Aortography—stenosis of a main renal artery on one side or a difference in kidney size of at least 1.5 cm.; intravenous pyelogram—unilateral hyperconcentration, delay in appearance or absence of contrast medium, or a difference in kidney size greater than 1.5 cm.

The instrumentation for recording renograms in this laboratory has been previously described. Following a 12-hour fast an indwelling catheter was inserted into the bladder, and an oral water load of approximately 800 ml. was given to each patient. Twenty microcuries of $^{131}$I hippuran was administered intravenously for the renogram. Only those renograms recorded during a 10-minute period in which urine flow rate ($V$) was between 1.5 and 7.0 ml. per minute were utilized for evaluating the reliability of the renogram. In order to compare the renograms obtained during a urea diuresis to those recorded during a water diuresis a solution of 8 per cent urea with antidiuretic hormone (ADH) was administered intravenously on a separate day to 17 patients.

The following factors were measured: (1) $T_p$—the time of appearance of the peak counting rate; (2) $P:S$—the ratio of the peak counting rate to the counting rate recorded at the end of the first phase (spike); (3) $P_{10}$—the per cent of the peak counting rate remaining 10 minutes after the start of the renogram. Disparities between the separate kidney renograms were calculated for the paired measurements by the formula 100 delta/2 $(R + L)$, where delta equals the difference between the factors of the two sides and $\frac{1}{2}(R + L)$ equals the mean of the two factors.

Based on the renograms obtained in hypertensive patients without unilateral renal disease (group I), control values for the disparity in each renogram factor were determined. A renogram obtained in a hypertensive subject was considered positive for the presence of unilateral renal disease if a disparity of any one of the three factors was greater than the control mean plus 2 standard deviations. When more than one renogram was recorded in any patient and the results were conflicting (five of 33 cases with multiple renograms), the study was considered equivocal.

### Results

#### Group I. Hypertensive Patients Without Unilateral Renal Disease

The absence of unilateral renal disease in 33 hypertensive patients was established by surgery in one, by bilateral ureteral catheterization in seven, and by aortography in the remaining 25 patients (table 1). Intravenous

#### Table 1

Diagnostic Procedures in Patients with Hypertension and No Unilateral Renal Disease ($V = 1.5 - 7.0$ ml./min.)

<table>
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<th>Renogram</th>
<th>Water</th>
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*aUnilateral renal disease not demonstrated at surgery.

+ = positive, unilateral renal disease demonstrated. Each symbol represents one test.

− = negative, unilateral renal disease not demonstrated. Each symbol represents one test.

U = technically unsatisfactory study.

*Circulation, Volume XXXII, July 1965*
pyelography revealed no significant disparity between the kidneys in all 33 cases. The aortogram demonstrated renal artery stenosis in one case proven normal at surgery and in four patients with normal bilateral ureteral catheterization studies.

Fifty-nine renograms recorded when \( V = 1.5 - 7.0 \text{ ml./minute} \) revealed the following disparities for the renogram factors: \( T_p = 20 \) per cent \( \pm 17 \), \( P:S = 11 \) per cent \( \pm 8 \), \( P_{10} = 10 \) per cent \( \pm 7 \). Since a renogram indicating unilateral renal disease must have one factor showing a disparity exceeding the control mean plus 2 standard deviations for that factor, a positive renogram will show at least one of the following: \( T_p \) disparity greater than 54 per cent, \( P:S \) disparity greater than 27 per cent, or \( P_{10} \) disparity greater than 24 per cent. When these criteria were applied to the group-I patients the renogram was found to indicate correctly the absence of unilateral renal disease in 29 of the 33 control patients. The results of the renogram were equivocal in two and falsely positive in two patients.

Group II. Hypertensive Patients With Unilateral Renal Disease

The diagnosis of unilateral renal disease in 20 hypertensive patients was demonstrated at surgery in five and by bilateral ureteral catheterization studies in four patients. Unilateral renal disease was demonstrated by aortography in eight cases and by intravenous pyelogram in three patients (table 2). Bilateral ureteral catheterization studies were negative in 1 patient who was found to have unilateral main renal artery stenosis at surgery.

Table 2

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</table>

+ = positive, unilateral renal disease demonstrated. Each symbol represents one test.

--- = negative, unilateral renal disease not demonstrated. Each symbol represents one test.

U = technically unsatisfactory study.

R. A. = unilateral renal artery disease.

Pyelo. = predominant unilateral pyelonephritis.

N. F. K. = unilateral nonfunctioning kidney.

*Positive factor: \( A = T_p \), \( B = P:S \), \( C = P_{10} \).
Renograms were positive for the presence of unilateral renal disease in 14 of the 20 group-II patients. In three patients the renogram was falsely negative and in three patients the results were equivocal. In two patients with equivocal results, the diagnosis was based solely on aortography, and the intravenous pyelograms were negative. In addition, one patient with a false-negative renogram had a normal intravenous pyelogram and no bilateral ureteral catheterization data were obtained. Hence in three patients categorized as having unilateral renal disease in whom the renogram failed to show positive results, confirmation of the functional significance of the unilateral renal lesion was not available.

The positive renograms, i.e., those showing significant disparity in at least one of the renogram factors, may be divided into three types. In the first type all three factors are increased on the affected side (fig. 1A). This pattern is characteristic of the renogram recorded over a normally functioning kidney when urine flow rate is slow or incomplete ureteral obstruction is present. The second type of renogram contour found in hypertensive patients with unilateral renal disease shows an increase in P10, a decrease in P:S and no alteration in Tp on the diseased side (fig. 1B). This pattern is seen when the tubular transport of I131 hippuran is impaired. The third type of positive renogram represents a combination of unilateral slow urine flow and impaired tubular transport (fig. 1C). In this pattern steps appear in the third phase of the renogram, and P10 and Tp are increased.

The dependence of the type-I renogram upon urine flow rate is illustrated by the series of renograms recorded in patient 37, obtained at various rates of urine flow (fig. 2). When V = 15.3 ml. per minute the renogram was normal (fig. 2A). The renogram recorded when V = 2.7 ml. per minute showed the slow urine flow pattern on the right side (fig. 2B); P10 is elevated producing a significant disparity in this factor. The unilateral slow urine flow pattern is even more apparent in the tracing recorded when V = 1.9 ml. per minute (fig. 2C). In this tracing the disparity of Tp as well as P10 indicates the presence of unilateral renal disease.

The combination of slow urine flow and impaired tubular transport, which produces the type-III renogram, may similarly be obscured by high rates of urine flow. Thus the renogram in patient 36 showed the type-II

![Figure 1](http://circ.ahajournals.org/)

DISPARATE KIDNEY FUNCTION IN HYPERTENSION

pattern when recorded at $V = 11.8$ ml. per minute (fig. 3A). When the renogram was recorded in this patient at $V = 4.3$ ml. per minute, the effect of reduced urine flow became apparent on the diseased side and a type-III renogram was obtained (fig. 3B).

**Urea Diuresis**

A solution of 8 per cent urea with anti-
diuretic hormone was administered intravenously to eight patients from group I and nine patients from group II (tables 1 and 2). In 14 of these patients renograms obtained during both urea and water diuresis at urine flow rates between 1.5 and 7.0 ml per minute were available. In 11 of the 14 patients, renograms recorded during water and urea diuresis were in agreement. In the three remaining patients, all from group II, the renogram obtained during urea infusion showed no increase in diagnostic accuracy compared to those obtained during water diuresis.

Discussion
The factors employed in this laboratory for analysis of the renograms were selected because they seemed best to reflect changes in kidney function. The disparity of the renogram factors found in the control hypertensive patients without unilateral renal disease provided criteria for recognizing hypertensive patients with unilateral renal disease. The renogram confirmed the absence of unilateral renal disease in 29 of 33 patients in the control group (table 1). Among the hypertensive patients with unilateral renal disease the renogram demonstrated a significant disparity in kidney function in 14 of 20 patients. However, in three of the six cases in which the renograms were negative corroborative evidence of the functional significance of the unilateral renal lesion was lacking (table 2). Although the present series is too small to permit a final evaluation of the diagnostic accuracy of the renogram, the role of the renogram in determining disparate kidney function in hypertensive patients has emerged.

Functional interpretation of the renogram and intravenous pyelogram has been based on separate kidney function studies obtained by bilateral ureteral catheterization.2-4 Unilateral main renal artery stenosis characteristically produces a reduction in urine flow rate, urine sodium concentration, and inulin and PAH clearance, but an increase in urine osmolality. Unilateral pyelonephritis also results in a reduction in urine flow rate and inulin and PAH clearance, but sodium concentration is usually increased and osmolality is decreased. In the intravenous pyelogram unilateral renal artery stenosis frequently produces a delay in appearance time and an increase in concentration of contrast medium on the involved side. These findings may be due to the unilateral reduction of urine flow rate and increase in urine concentration. The same functional characteristics of unilateral renal artery stenosis also underlie the slow urine flow, type-I renogram (fig. 1A). On the other hand, the intravenous pyelogram may show reduced concentration of contrast medium on the diseased side. The reduced concentration of contrast medium apparently results from a decrease in glomerular filtration rate or concentrating ability.5 Similarly, impairment of tubular function produces the type-II renogram (fig. 1B). When tubular dysfunction is combined with a reduction of urine flow rate, the type-III renogram is produced (fig. 1C). The counterpart of this renogram pattern in the intravenous pyelogram will show both delayed appearance time and reduced concentration of contrast material on the diseased side.

Unilateral pyelonephritis and renal artery stenosis may produce similar renographic patterns. This similarity results from the fact that both pathologic conditions may cause comparable unilateral reductions in urine flow rate and PAH clearance. The failure of the renogram to distinguish between these different forms of unilateral renal disease has led us to group together all cases of disparate kidney function. The three positive renogram patterns produced by both renal artery stenosis and pyelonephritis are illustrated in figures 1, 2, and 3.

While both the intravenous pyelogram and radioisotope renogram may detect functional changes in the separate kidneys, the renogram is better suited for the appraisal of functional changes. The radioisotope technic permits continuous recording and objective quantitation. Misinterpretation due to artifacts produced by bowel contents does not occur. Moreover, renograms may be repeated safely without significant radiation to the patient. When the intravenous pyelogram is carefully performed,
however, it appears to be a useful adjunct in the diagnosis of the renovascular hyperten-
sion.2, 3

The role of urine flow rate in determining the renographic contour has not been suffi-
ciently emphasized. A number of groups have noted that variations in the renogram may be 
produced by changes in urine flow rate.6-12 However, the influence of urine flow on the 
renogram curve seen in unilateral renal artery stenosis has not been widely recog-
nized. In fact, urine flow rate measurements made during the recording of the renogram 
have not been previously reported. One group has reported renograms under both hydrated 
and hydropenic conditions in each patient, although urine flow rate was not measured.6, 13

These workers employ numerical measures which reflect the effects of urine flow rate 
and tubular transport on the renogram contour and report a high order of reliability in 
detecting unilateral renal artery stenosis. The positive renograms published in their 
series were similar to the three types of positive tracings described above.

If the renogram is to be relied upon for the evaluation of separate kidney function, it is 
essential that the test be performed under optimum conditions. Previous studies in this 
laboratory indicated that the disparity of the separate kidney tracings in normal subjects 
is exaggerated at low rates of urine flow.1

When the urine flow rate from the bladder is less than 1.5 ml. per minute, distortions 
are frequently found in one or both kidney tracings. On the other hand, dependence of 
the renogram contour on the rate of urine flow is lost at urine flow rates above 7.0 ml. 
per minute (figs. 2 and 3). Therefore, maximum reliability for detecting disparity in kid-
ney function occurs when tracings are recorded at a urine flow rate between 1.5 and 
7.0 ml. per minute.

Diuresis induced by a urea infusion when compared to water diuresis has been reported 
to increase the disparity in function between the separate kidneys in patients with uni-
lateral renal artery stenosis.4 In the present study, however, renograms recorded during 
urea diuresis have not demonstrated an increased accuracy in detecting renal artery 
stenosis. Since no advantage in urea infusion could be discerned, we have discontinued its 
use in radioisotope renography.

The Hg208-chloromerodrin renogram has been reported to be superior to the I131-hippuran 
renogram for the detection of unilateral renal disease.14 However, neither objective 
criteria nor optimum urine flow rates were employed by these workers when evaluating 
the I131-hippuran renogram. The tracings obtained with Hg208-chloromerodrin were found 
to be independent of urine flow rate. This observation is supported by autoradiographic 
studies of Hg208-chloromerodrin, which demon-
strate that the renal tissue content of mer-
cury greatly exceeds that found in the urine 
and is independent of the diuresis.15, 16 The 
lack of sensitivity to urine flow rate of the 
Hg208-chloromerodrin renogram reduces the 
value of this technic in detecting one of the 
characteristic functional changes of unilateral 
renal artery stenosis.

These studies suggest that when the I131-
hippuran renogram is performed under appro-
priate conditions it is of considerable value 
in providing objective evidence of disparate 
kidney function. Since a demonstrable anato-
mic lesion need not necessarily produce a 
hemodynamic derangement causing renovas-
cular hypertension,17 it seems vital to establish 
the functional significance of such a lesion. 
Currently available tests of separate renal 
function may not be sensitive enough to detect 
all significant unilateral renal lesions. Despite 
this limitation, a positive renogram offers con-
vincing evidence of the functional signifi-
cance of an anatomic lesion demonstrated by 
aortography. The combination of a positive 
aortogram with an abnormal renogram or 
intravenous pyelogram would therefore seem 
to justify surgical exploration. The more 
dangerous and difficult procedure of bilateral 
ureteral catheterization may thus be avoided 
in the diagnostic study of many hypertensive 
patients. On the other hand, when a renal 
artery abnormality demonstrated by aortog-
raphy does not produce a positive renogram
or intravenous pyelogram, bilateral ureteral catheterization should be performed to establish the functional significance of the arterial lesion.

Summary
The reliability of the radioisotope renogram in detecting functional disparity in the separate kidneys of hypertensive patients with unilateral renal disease was investigated. Renograms recorded in 33 hypertensive patients without unilateral renal disease were employed for establishing control criteria. The physiologic basis for the three types of positive renograms found in the presence of unilateral renal dysfunction has been discussed. The renogram appears to be a valuable method for demonstrating significant disparity in separate kidney function while avoiding the hazards and technical difficulties of bilateral ureteral catheterization.

References

Origin of Knowledge
Nourished by knowledge patiently won, bounded and conditioned by co-ordinate reason, the imagination becomes the prime mover of scientific discovery.—JOHN TYNDAEL.
The Use of the I\textsuperscript{131}-Hippuran Renogram in the Detection of Disparate Kidney Function in Hypertensive Patients

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