Observations on Renal Hypertension
The Role of Renal Biopsy

By Victor Vertes, M.D., and James A. Grauel, M.D.

INTEREST in unilateral renal disease as a possible cause of human hypertension originated with Goldblatt’s classic experiments. In 1937, Butler reported the clinical cure of hypertension following nephrectomy in two cases of unilateral, pyelonephritis with vascular disease in children. In recent years it has been recognized that many cases of human hypertension are on the basis of unilateral renal disease, and unilateral nephrectomy has been performed in many such cases. When ischemia has been found due to stenosis or partial obstruction of a main renal artery, repair of the vascular lesion in various ways (without nephrectomy) has been practiced, with favorable results reported in some cases.

The number of hypertensive patients treated by unilateral nephrectomy or repair of the main renal artery has been mounting precipitously. In a review article it has been stated that “there are upwards of two million subjects with undiagnosed renal artery stenosis in the United States of America.” The implication of this, and of similar statements, is that all of these persons are potential candidates for surgery.

Great interest in the development of technics to detect unilateral renal disease followed the reports of Smith and of Thompson. Smith found that 26 per cent of 535 patients had been cured of hypertension as a result of unilateral nephrectomy, but cautioned that many unsuccessful cases probably had not been reported. However, he eliminated many cases with less than 1 year follow-up, and it is possible also that many successfully treated cases have not been published. It is impossible to determine how many of the treated patients had bilateral renal disease with one kidney being the more severely affected. In such cases the removal of the more diseased kidney would not be expected to result in a cure of the hypertension.

To determine that only one kidney is involved, the major diagnostic procedures, at present, involve either renal aortography, renal split-function studies, or both. The incidence of strictly unilateral renal disease varies greatly in the reports from different clinics.

It is difficult to assess the significance of arteriosclerotic plaques involving the renal arteries, demonstrated by aortography. Eyler and associates implied that probably more than one third of such lesions are not functionally significant.

Renal split-function studies have been of limited value in predicting the outcome after surgical intervention. However, they provide the only currently available guide to the functional significance of stenosis or obstruction of a main renal artery.

It is possible for intrarenal arterial and arteriolar sclerosis to progress more rapidly in one kidney than in the other. This entity is probably more common than the published data would indicate and can give renal split-function results consistent with unilateral renal disease.

Moritz and Oldt demonstrated in 1937 that renal arterial and arteriosclerosis were present bilaterally at autopsy in the majority of cases of hypertension and virtually absent from an equal number of nonhypertensive patients. These authors concluded that their data provided evidence for the "Goldblatt..."
mechanism’’ (unilateral or bilateral renal ischemia) in human essential hypertension.

It is our contention that strictly unilateral renal disease as a cause of hypertension is not so common as present reports would indicate, and that bilateral renal biopsy serves as the best guide for final decision regarding surgical intervention in cases in which the split-function study indicates the probable existence of unilateral renal disease.

Material and Methods

Thirty-six hypertensive patients were admitted to the Metabolic Unit of Mount Sinai Hospital of Cleveland. These patients were unselected admissions from the Hypertension Research Clinic.

Routine laboratory studies were performed. In addition, determination of renal function, intravenous pyelography, and studies to rule out other causes of hypertension were carried out.

Transfemoral aortography was performed by means of the technique of Seldinger.27 Renal split-function studies were performed, with some modification, as described in detail by Stamey et al.21 Inulin and paraaminohippurate (PAH) clearances were determined with a 4-per cent urea diuresis rather than the 8-per cent concentration used by Stamey. This modification of the technic produced an adequate urine flow and decreased the post catheterization morbidity. It was possible in each instance to obtain three consecutive urine volumes that were within 6 per cent of each other when expressed as the ratio $V_1/V_2$.

Results of renal split-function studies were expressed as the ratios $V_1/V_2$ and $U_1/U_2$, as described by Stamey et al.21 $V$ represents the volume of urine in milliliters per minute, and $U$ represents the concentration of inulin in milligrams per cent in the urine. In the ratio $V_1/V_2$, $V_2$ always represents volume in milliliters per minute from the kidney with the greater rate of flow of urine. $U_1/U_2$ is the ratio of the concentration of inulin in the urine specimens that corresponds to the ratio $V_1/V_2$. Thus, in both ratios, the denominator is always the value obtained for the kidney having the greater rate of flow of urine.

Bilateral percutaneous renal biopsy specimens were obtained from all patients. These were interpreted independently by the hospital pathologist and by Dr. Harry Goldblatt. They did not know the indications for biopsy or the clinical history. The specimens were subsequently reviewed and compared again by Dr. Goldblatt without benefit of the clinical data.

Results

Thirty-six aortograms were performed in this group of hypertensive patients. All of these showed evidence of some arterial disease. Eleven (31 per cent) indicated an arteriosclerotic plaque in the region of the renal arteries, or showed some degree of stenosis, with poststenotic dilatation of the renal artery.

Ten of the patients (28 per cent) had renal split-function studies that were consistent with the functional changes characteristic of unilateral renal ischemia.21 A combination of a significantly decreased volume of urine with a significantly increased concentration of inulin in the urine from the affected kidney was considered suggestive of unilateral renal ischemia. A urine volume ratio ($V_1/V_2$) less than 0.80 and an inulin concentration ratio ($U_1/U_2$) greater than 1.12 were considered significant. A combination of these two was necessary for the diagnosis of unilateral renal ischemia. Bilateral renal biopsies were performed in all cases; all the specimens showed bilateral renal disease and most of them exhibited severe arterial and arteriolosclerosis.

The data from 10 patients in whom the renal split-function tests were positive for unilateral renal disease are summarized in table 1. The corresponding bilateral biopsy specimens revealed no significant difference between the two kidneys in the degree of intrarenal vascular disease.

One of these 10 cases deserves special comment because the results of the renal split-function studies unequivocally indicated severe ischemia of one kidney, and the biopsy specimens showed equally severe, bilateral, intrarenal vascular disease. In spite of the latter finding, the decision was made to remove the more diseased of the two kidneys. The history of this patient (L.W.) is reported in more detail below.

Case Report

L.W. is a 54-year-old woman who was first seen in the Out-Patient-Department of Mount Sinai Hospital of Cleveland in 1961. Blood pressure observations during that year ranged from 150 to 210 systolic over 90 to 130 diastolic. In 1962 she was admitted to the Hypertension Research Clinic. Multiple baseline blood pressures were obtained, and the average sitting blood pressure was 199/123. Her past history was nonecontributory and the
family history was essentially negative for hypertension. She was admitted to the hospital and the results of aortography, of split renal-function studies, and of bilateral renal biopsy are recorded in Table 1.

The aortogram revealed no obstructive lesion of the large arteries. Renal split-function studies were unequivocally positive for functionally significant unilateral renal disease. This patient was therefore considered a suitable subject for unilateral nephrectomy according to the criteria in the current literature.3, 6, 8, 10-12, 17, 21, 23, 25, 28-30 However, patient L.W. had evidence, on renal biopsy, of bilateral diffuse intrarenal vascular disease. Despite the renal biopsy findings, patient L.W. was subjected to right nephrectomy in order to study the effects of nephrectomy when bilateral disease is present, more marked in one kidney than the other. The pathologic diagnosis on the nephrectomy specimen was diffuse intrarenal arterial and arteriolosclerosis. The patient tolerated the procedure well and during the postsurgical hospitalization her blood pressure stabilized at 140 to 150 systolic and 90 to 100 diastolic. She was discharged from the hospital and again followed in the clinic where successive blood pressures were obtained at 2-week intervals during a period of 4 months. The average blood pressure after nephrectomy was 190/124, essentially the same as before the operation. The patient is now receiving Ismelin* to control her hypertension.

**Discussion**

In the establishment of the criteria for the diagnosis and the surgical treatment of patients with renovascular hypertension, several pertinent problems arise. The first, and probably the most important one, is the establishment of the existence of hypertension. Most observers are aware of the natural fluctuations of blood pressure that can occur in an individual.14 However, these fluctuations are not ordinarily taken into account.3, 8, 11 Some authorities claim that 50 per cent of males and 60 per cent of females over the age of 40 have hypertension.21 Others assert that 26 per cent of adults in the United States have essential hypertension. Master et al.22 stated that two thirds of females past the sixth decade, and two thirds of males past the seventh decade have hypertension. Therefore, if one were to

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*Ismelin (Guanethidine), Ciba.

**Table 1**

<table>
<thead>
<tr>
<th>Name</th>
<th>Average B.P.</th>
<th>V$<em>{1}$/V$</em>{2}$</th>
<th>U$<em>{1}$/U$</em>{2}$ (Inulin)</th>
<th>Aortogram</th>
<th>Biopsy</th>
</tr>
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<tbody>
<tr>
<td>H.D.</td>
<td>171/117</td>
<td>R/L .577</td>
<td>1.12</td>
<td>Diffusely narrowed bilaterally,</td>
<td>Arteriolosclerosis &amp; pyelonephritis, marked</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>poor nephrogram</td>
<td></td>
</tr>
<tr>
<td>J.B.</td>
<td>215/146</td>
<td>R/L .444</td>
<td>1.78</td>
<td>Right plaque with PSD;*</td>
<td>Arteriolosclerosis &amp; arterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>atherosclerosis</td>
<td>sclerosis &amp; pyelonephritis, moderate</td>
</tr>
<tr>
<td>J.B.</td>
<td>209/111</td>
<td>R/L .728</td>
<td>1.12</td>
<td>Right plaque with PSD</td>
<td>Arteriolosclerosis &amp; arterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>sclerosis &amp; pyelonephritis, moderate</td>
</tr>
<tr>
<td>F.R.</td>
<td>189/107</td>
<td>R/L .646</td>
<td>1.55</td>
<td>Atherosclerosis, nonvascular</td>
<td>Arteriolosclerosis &amp; arterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>masses bilaterally</td>
<td>sclerosis, moderate</td>
</tr>
<tr>
<td>A.B.</td>
<td>220/120</td>
<td>R/L .630</td>
<td>1.14</td>
<td>Atherosclerosis</td>
<td>Arteriolosclerosis &amp; arterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>sclerosis, marked</td>
</tr>
<tr>
<td>D.H.</td>
<td>217/117</td>
<td>L/R .623</td>
<td>1.59</td>
<td>Atherosclerosis</td>
<td>Arteriolosclerosis, severe</td>
</tr>
<tr>
<td>I.T.</td>
<td>215/125</td>
<td>R/L .672</td>
<td>1.39</td>
<td>Left dilated distally, right</td>
<td>Arteriolosclerosis, marked</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>possible narrowing</td>
<td></td>
</tr>
<tr>
<td>K.D.</td>
<td>220/120</td>
<td>L/R .590</td>
<td>1.83</td>
<td>Right narrowed with PSD</td>
<td>Arteriolosclerosis &amp; pyelonephritis, marked</td>
</tr>
<tr>
<td>L.M.</td>
<td>198/113</td>
<td>L/R .767</td>
<td>1.22</td>
<td>Atherosclerosis</td>
<td>Arteriolosclerosis &amp; arterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>sclerosis, slight</td>
</tr>
<tr>
<td>L.W.</td>
<td>199/123</td>
<td>R/L .274</td>
<td>2.19</td>
<td>Atherosclerosis</td>
<td>Arteriolosclerosis &amp; arterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>sclerosis, marked</td>
</tr>
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</table>
RENEAL BISOPI IN RENAL HYPERTENSION

rely solely on blood pressure measurements, using 140/90 as the upper limits of normal, case selection for hypertensive studies could potentially involve one of four young adults and two of three older patients in the United States!

It is well established that radiographic studies of the arterial tree may show evidence of anatomic lesions such as arteriosclerotic plaques, or other vascular irregularities, in patients with or without hypertension. Sutton and associates\textsuperscript{18} found that 10 per cent of 260 patients had evidence of renal artery stenosis on aortography. At the Cleveland Clinic, in 6 years, 617 aortograms were performed; 173 (28 per cent) showed occlusive disease of the main renal artery or its primary branches.\textsuperscript{19} Morris et al.\textsuperscript{17, 28, 29} found that 55 per cent of 642 aortograms showed aortic and large abdominal vessel disease. Therefore, if one were to accept a casual blood pressure determination above 140/90 as evidence of hypertension and would then perform an aortogram, there would be a good chance of demonstrating some sort of anatomic abnormality of the same type that occurs in normotensive individuals. It is generally not possible unequivocally to establish the functional significance of an arterial abnormality demonstrated by aortography.\textsuperscript{8, 22, 25}

The frequency of abnormal aortograms, associated with elevated or normal blood pressure, makes it mandatory to look more critically at this method as a mean of determining the necessity of surgery to cure the hypertension and emphasizes the danger of diagnosing and treating hypertension on the basis of a casual determination of the blood pressure.\textsuperscript{30}

It is the opinion of the authors that renal split-function studies are necessary to help establish the significance of a renal vascular abnormality found by aortography. It is relatively well established that the main functional defect in renovascular hypertension is an increased tubular water resorption due to decreased renal blood flow.\textsuperscript{21} When diffuse intrarenal arterial disease is present, however, the results of renal split-function studies may be equivocal. The same hemodynamic changes that occur with hypertension secondary to main renal artery stenosis can also be produced by diffuse, bilateral, intrarenal, obliterative sclerosis in arteries and arterioles. The development of these lesions may not be symmetrical; therefore, function studies may point to greater involvement in one kidney than in the other. These changes can then be mistaken for unilateral renal artery disease. We believe that our patient, L.W., falls into this category. The dilemma of such a situation can easily be solved. If biopsy of the supposedly “good” kidney shows advanced vascular disease, the basic abnormality is probably diffuse, bilateral, intrarenal, arteriolar disease. However, if the biopsy specimen is normal, or shows only slight vascular disease, the functionally significant lesion is more likely to be in the main renal artery and potentially amenable to surgical intervention.

The results of biopsy in our 36 patients show that in all specimens there was some evidence of intrarenal vascular disease. The group included patients with positive aortograms, as well as abnormal renal split-function tests, and it is our belief that removing active renal tissue from such individuals is contraindicated.

Conclusions

Thirty-six patients with hypertension were studied with aortograms, bilateral percutaneous renal biopsies, and renal split-function tests. It is concluded that hypertension due to unilateral renal ischemia is a disease entity in which anatomic and functional changes point to a lesion in one kidney or in its blood supply; the contralateral kidney is normal or, at worst, has only minimal vascular disease. It is also concluded that when unilateral renal ischemia is suspected, an aortogram should be performed first. If a lesion is evident, a biopsy specimen of the contralateral kidney should then be obtained. If vascular changes are absent, or minimal, a renal function study would then define the importance of the anatomic lesion. If both aortogram and function studies are abnormal on the same side, and the contralateral biopsy specimen

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shows a normal picture or only minimal vascular changes, surgical intervention is indicated. The incidence of such situations is probably much rarer than published studies indicate.  

**Acknowledgment**

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**References**


Art and Science in Medicine

When we compare science and art in medicine we find that, to use a mechanical analogy, the former is enormously the more efficient engine where it is available. Its only necessary fuel is knowledge—given knowledge and the appropriate case, success with a very small margin of error is certain. Medical art on the other hand is as an engine extravagantly inefficient and needs every faculty of the doctor to get it to work at all. This is why it is that he has not only to be taught but to be trained. By teaching I mean the imparting of knowledge, and for that we are dependent on our teachers; by training I mean the cultivation of aptitude, and for that we are dependent on our opportunities and ourselves. It is here that we see most clearly the difference in the requirements of experimental science and of an art. The exactitudes of science call for the elimination of human faculty as far as possible; the lack of exactitude in the practical art calls for the use and expansion of human faculty as far as possible. It would be a poor physiologist who used his eye to estimate the weight of guinea-pigs or his tongue to measure electric currents; but the physician who makes the fundamental observation of medicine and says, “My clinical instinct tells me that man is ill,” though he uses an instrument with an error deplorably great, uses the only instrument capable of making any record at all, and will do well to keep it in repair.—The Collected Papers of Wilfred Trotter, F.R.S. London, Oxford University Press, 1946, p. 96.