Hypertension accompanying renal arterial stenosis is a frequent secondary type of hypertension. Our experience in the past six years has shown the effectiveness of surgical and antihypertensive drug treatments¹,² and has given information concerning recoverability of renal function following revascularization, as well as some indication of the natural history of renal arterial diseases.³

Antihypertensive Effects of Surgical and Drug Treatments

Of 139 patients with renal arterial disease, 102 were treated surgically,² either by nephrectomy or various procedures designed to remove or by-pass obstructing lesions.⁴ Seventy-six of these had had complete operations for periods long enough before review that effectiveness of operation could be evaluated. In 42, arterial pressure became normal postoperatively; two have mild diastolic hypertension occasionally, and three have persistent systolic hypertension. In 12, arterial pressure decreased greatly, although not to normal levels, and in 17, it was unchanged. Reasons for lack of arterial pressure response in the last group are not completely understood, although there were several patients who seemed to have had essential hypertension prior to development of renal artery atherosclerosis and at least one patient with pyelonephritis and renal arterial disease.

At the present time, surgical treatment seems indicated in patients well enough to withstand operation and young enough to achieve long-range benefit. There are, however, patients with renal arterial stenosis for whom surgical therapy is too hazardous because of cerebral and coronary arterial disease, often with associated infarction. Further, there are those with branch arterial lesions and segmental atrophy but with such severe nephrosclerosis in the rest of the kidney tissue that operation would not be helpful. Finally, there are patients with hypertension so mild that surgical treatment seems unwarranted. With the exception of the last group, patients not operated upon will benefit from reduction of arterial pressure. Of 37 patients treated conservatively, 24 were given antihypertensive drugs. In 10 patients, treatment was carefully supervised and its effectiveness judged from analysis of daily home blood pressure measurements. Prior to institution of drug therapy, supine brachial arterial pressure for the group averaged 200/122 mm. Hg; 6 to 30 months later, the group average was 167/89. With the exception of one patient whose supine diastolic blood pressure remains about 105 mm. Hg, nine patients have responded so well to treatment that supine diastolic blood pressure is maintained at normal levels. Thus, in only one patient has treatment been only partially successful, although this patient has responded to guanethidine and maintains a supine diastolic pressure average of 105 mm. Hg—a level considered indicative of good blood pressure control only two years ago.⁵ Eight of these 10 patients received guanethidine; the effectiveness of this drug, which suppresses sympathetic function,⁶ suggests that in patients with renal hypertension arterial pressure is maintained, in part, by neurogenic mechanisms, as has been shown to occur in dogs with chronic renal hypertension.⁷

Recoverability of Renal Function

The present background of experience in the surgical treatment of this type of hypertension seems sufficient to evaluate accomplishments not only in terms of arterial pressure reduction but also of recoverability of renal function following renal revascularization procedures.⁸
Finally, glomerular function can remain at normal levels in spite of apparently extreme arterial narrowing, if the stenoses are bilateral and nonprogressive (see following section on natural history of renal arterial diseases).

These clinical results are reminiscent of those obtained by Omae and Masson, who studied the recoverability of atrophic "endocrine" kidneys. In their experiments in rats, blood flow to the left kidney was reduced sufficiently to produce severe cortical atrophy by constricting the aorta between the origins of the right and left renal arteries. The right kidney showed compensatory hypertrophy. Removal of the aortic clip some weeks later was followed by only slight increases in left kidney weight, for apparently the presence of the right kidney prevented recovery—a type of response found in some patients following repair of unilateral arterial lesions. Recovery was greater if the right kidney and the aortic clip were removed at the same time—a result not unlike unilateral repair in bilateral disease. Atrophy could be prevented if right nephrectomy was performed simultaneously with aortic constriction, and perhaps this is a situation similar to chronic, nonprogressive, bilateral renal arterial stenosis. These clinical and experimental studies suggest that factors in addition to availability of normal blood flow determine recoverability of atrophic kidneys.

Another interesting consequence of arterial repair is its effect on solute and water excretion. In unilateral main renal arterial disease, the affected kidney reabsorbs more sodium and water than the unaffected, and excretes a urine of comparatively lower sodium concentration and higher osmolality. This increase in water reabsorption, presumably stimulated by the increased sodium reabsorption, depresses urine flow out of proportion to the depression of glomerular filtration rate. Following revascularization, sodium excretion is not only greater than it was before but also greater than that of the opposite kidney (fig. 2); as less sodium is reabsorbed, less water is reabsorbed. The result is that urine from the repaired kidney is of lower osmolality than that from the other side. Because of
decreased water reabsorption, urine flow is increased out of proportion to the increase in filtration rate produced by revascularization.

Reasons for these changes in solute and water excretion are not yet known. They may represent spotty ischemic destruction of nephrons with an increased filtration rate in those remaining. Bricker has presented evidence that renal disease reduces the number of nephrons but that those that are left retain functional integrity. 10 He suggests that if glomerular filtration rate per tubule is increased, the resulting increase in filtered sodium load would account for increased sodium excretion by the diseased kidney. Another possible explanation of the saluresis and diuresis found postoperatively is that arterial repair establishes filtration rate through atrophic tubules which are incapable of facultative electrolyte and water reabsorption. If this is the case, these tubules do not recover function quickly because, in our experience, the increased solute and water excretion can persist for as long as two years after successful arterial reconstruction.

**Natural History of Renal Arterial Diseases**

Atherosclerosis is a frequent cause of renal arterial stenosis, is more commonly found in males, and occurs mostly after the age of 40.1 There are other renal arterial diseases 11 which seem unrelated to atherosclerosis. Of these, idiopathic thrombosis and dissecting aneurysm, although rare, can occur without a demonstrable cause. The most frequent nonatherosclerotic lesions are segmental mural fibrosis, intimal sclerosis, and fibromuscular hyperplasia. These are more commonly found in young people.

Information concerning the progression of renal arterial lesions has not previously been available and, because of this, revascularization procedures have sometimes been considered urgent to halt development of renal atrophy. Our recent experience 2, 3 suggests that atherosclerosis may or may not produce progressive narrowing during several months, that segmental mural fibrosis is only slowly progressive, and that intimal sclerosis, once established, may be nonprogressive or so slowly progressive that there has not yet been sufficient time to determine a change.

Concerning the progress of atherosclerosis, we have followed over a 12-month period two patients with lesions of the first portion of one main renal artery. In one patient, function tests of the individual kidneys and renal angiograms gave evidence of increased arterial narrowing during the year, while in the other patient no progress of the lesion was demonstrable. Of about 60 patients presumed to have atherosclerosis, who have been treated surgically, subsequent development of renal arterial lesions in sites other than those operated upon have been demonstrated in five.2

Segmental mural fibrosis seems primarily a disease of young women. 11 This may help account for the fact that 40 per cent of the women with renal arterial disease were less than 40 years of age, while only 25 per cent of males were under 40.1 The possibility that segmental mural fibrosis is only slowly progressive arose from the finding, in the clinical study, that the duration of hypertension prior to diagnosis of renal arterial stenosis was longer in the women than in the men. In support of this possibility are the results of separated renal function studies performed over three to four years following unilateral arte-
In a few patients, information concerning the natural history of renal arterial diseases shows that atherosclerosis need not necessarily cause progressive stenosis over periods as long as one year, and that the nonatherosclerotic lesions, segmental mural fibrosis and intimal sclerosis, once established, can exist without apparent change for as long as three years.

References
Discussion

Dr. Moyer: My comments probably apply more to Dr. Stamey's paper than to Dr. Dustan's, and I will confine my remarks to atherosclerosis as it applies to the renal artery. We know that long-standing hypertension produces diffuse renal damage, yet these investigators used a kidney exposed to the hypertensive process as a control for the kidney with vascular obstruction. This bothers me, especially when the investigators speak in terms of absolute values.

We have done similar studies, but all our patients did not fall into the categories described by Drs. Stamey and Dustan. We did find one group of patients that followed the same pre- and postoperative trend which Dr. Dustan has just described. However, we had a second group that showed no change following corrective surgery, either in the involved kidney or in the opposite kidney. A third group of patients, with severe hypertension of the malignant variety, had almost complete or complete occlusion of the renal artery to one kidney. In the opposite kidney, the glomerular filtration rate was markedly reduced, to as much as 30 to 40 per cent of normal. Following corrective surgery and control of blood pressure, function in the opposite kidney usually increased 80 or 90 to 100 per cent. Our interpretation was that the contralateral renal damage resulted from the hypertensive process, and that renal function improved in the contralateral kidney of the blood pressure.

Dr. Dustan: We have not found situations in which filtration rate does not change. Although these changes may not be large, they have always occurred. We too have seen people with what we assumed to be nephrosclerotic atrophy on one side and the opposite and better kidney supplied by a narrowed renal artery. However, we have seen no change after the affected kidney was removed. Nor have we had this experience after lowering arterial pressure by drugs.

Dr. Moyer: Actually, the blood pressure was controlled medically in some of our patients, while in others it was controlled by surgical therapy.

Dr. Dustan: You mean nephrectomy and decrease in arterial pressure, followed by improvement of renal function?

Dr. Moyer: Yes. For example, in a case of complete occlusion of one renal artery, the glomerular filtration rate in the opposite kidney may be 25 cc./min. After nephrectomy and normalization of blood pressure for a year, the GFR in the remaining kidney may increase to 50 cc./min.

Dr. Dustan: No, we have not had this experience.

Dr. Hollander: In a limited number of cases, our experience has been similar to that of Dr. Moyer. I have three of my own cases who had hypertension due to unilateral atrophic kidney disease, on whom we did split function tests before removal of the diseased kidney. Like Dr. Moyer, we found that both renal plasma flow and glomerular filtration rate increase. I want to emphasize that we removed the kidneys but did not compare the arterial lesions. Hypersecretion of sodium also was found preoperatively in these cases in response to infusion of hypertonic saline. When the diseased kidneys were removed, both blood pressure and sodium excretion returned to normal.

Dr. Dustan: I have no information on these specific points; our emphasis has been on recoverability of the kidney supplied by a narrowed renal artery rather than what happens to the opposite kidney after nephrectomy.

Dr. Stamey: Differences in results may be explained by the use of different methods—whether one occludes a ureter with an inflatable balloon, whether mannitol rather than urea is used as the infusate, etc. However, I am sure that one does not need a "reno-trophic factor" to explain the change in function in the postoperative, vascularized kidney. When previously ischemic and atrophic tubules are suddenly exposed to a large volume of glomerular filtrate, they cannot completely

Circulation Research, Volume XI, July 1968
handle the new volume of filtrate; an analogous situation exists in the diuretic recovery phase of acute tubular necrosis. This explains how the revascularized kidney can have a urine flow rate equal to or even greater than the contralateral kidney while its comparative GFR is markedly reduced. The magnitude of this diuresis depends on the severity of the tubular atrophy at the time of revascularization. In one of our patients with a "non-functioning" kidney, revascularization produced a diuresis of such magnitude that the patient became an electrolyte problem in the immediate postoperative period. I do not understand how you can say that a renal plasma flow of 540 ml./min. to one kidney is necessarily normal. Was that a female patient?

*Dr. Dustan:* No.

*Dr. Stamey:* The normal renal plasma flow for males (both kidneys) is between 500 and 800 ml./min. However, this includes only one standard deviation of the population. It is not impossible then for a rare individual to have a renal plasma flow of 500 ml./min. in one kidney and that kidney to be ischemic—especially since our data indicates that as little as 20 per cent reduction in RPF in one kidney (compared to the other) may be associated with curable renovascular hypertension. There could be another explanation for this admittedly high value for RPF in a single kidney. Whereas it is well recognized that sulfa drugs contribute to the colorimetric reaction for PAH, it is not so universally recognized that chlorothiazides do the same thing. Finally, we too have found that the RPF and GFR in the contralateral kidney may rapidly increase after nephrectomy for unilateral renal ischemia. We think that the rapidity with which the blood pressure returns to normal correlates with the degree of reduced blood flow in the contralateral kidney. When the remaining kidney shows on preoperative studies that the RPF is low, the time required for the blood pressure to return to normal may be weeks or even months. On the other hand, when the RPF is high in the contralateral kidney, the blood pressure will often be normal the evening of the nephrectomy.

*Dr. Dustan:* Concerning your suggestion, Dr. Stamey, that a technical error may be responsible for the high renal plasma flow which can occur in the presence of renal artery narrowing, I would only like to say that I was trained in the laboratory of Dr. Corcoran and Dr. Page and became aware that several substances give a color reaction with reagents used to measure PAH concentration. Accordingly, we always "run a blank"; if the patient is receiving one of the sulfa drugs, we do not feel that we can reliably measure renal plasma flow so we don’t do it. There is one aspect of your discussion, Dr. Stamey, which constrains me to comment because I am confused. On the one hand, you suggest that the kidney supplied by a narrowed artery is "hyperfunctioning" because it so actively reabsorbs sodium and water; yet on the other, you say that the saluresis and diuresis that occurs after arterial repair is simply explained by ischemic tubular atrophy. How do you put those two together?

*Dr. Stamey:* The explanation is not difficult but it is important because it explains what occurs in the ischemic kidney. Prior to revascularization, the excessive sodium and water reabsorption per unit glomerular filtrate does not mean that the renal tubular cells are hyperfunctioning. On the contrary, their total reabsorption is less because of the reduced GFR. But, because the volume of glomerular filtrate is reduced, the ischemic tubular cells have a longer time to act on the intratubular fluid and this allows these cells to reabsorb a disproportionate volume of the filtrate *in spite* of being ischemic. After revascularization, with sudden return of full filtrate volume, the time interval for a tubular cell to act on the filtrate is now short and the volume large. Accordingly, a greater fraction of the filtered water is now passed into the ureter, accounting for the data of equal urine flow rates but reduced GFR in the revascularized kidney.
Some Aspects of Occlusive Renal Arterial Disease in Man
Harriet P. Dustan

Circ Res. 1962;11:221-226
doi: 10.1161/01.RES.11.1.221

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1962 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/11/1/221

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/