BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 30 1960

THE DIAGNOSIS AND TREATMENT OF RENAL-ARTERY STENOSIS

BY

J. J. BROWN, M.B., B.Sc., M.R.C.P.
Lecturer in Medicine

K. OWEN, M.S., F.R.C.S.
Surgeon

W. S. PEART, M.D., F.R.C.P.
Professor of Medicine

J. I. S. ROBERTSON, M.B., B.Sc., M.R.C.P.
Lecturer in Medicine

AND

D. SUTTON, M.D., F.F.R., M.R.C.P., D.M.R.D.
Radiologist

St. Mary's Hospital, London

[WITH SPECIAL PLATE]

The importance of renal-artery stenosis has received emphasis from reports of the alleviation of hypertension by operations which correct a stenosis or remove the affected kidney (Howard *et al.*, 1954; Poutasse, 1956; DeCamp and Birchall, 1958; Owen, 1960; Robertson, 1960). This condition in man parallels experimental hypertension produced in animals by clamping the renal artery (Goldblatt *et al.*, 1934). Renal-artery stenosis is now being recognized with increasing frequency in patients with high blood-pressure, and strict diagnostic criteria must be applied if successful surgical treatment is to be achieved. The diagnosis of renal-artery stenosis based upon inadequate data is likely only to lead to therapeutic failure and to bring the surgical methods employed into disrepute. Certain patients with renal-artery lesions and severe hypertension may be greatly improved by appropriate surgical procedures. It is, however, important that overenthusiastic investigation and treatment shall not result in unnecessary morbidity. We therefore wish to define the diagnostic criteria which, in the light of our experience of this condition, we consider significant. This is an amplification of points made previously (Peart, 1959; Owen, 1959, 1960; Robertson, 1960). The present paper is based on a study of 22 patients in whom renal-artery disease was proved or strongly suspected. Of these, 11 were judged to be likely to benefit from operation (see Table I).

Incidence of Renal-artery Stenosis.—Since 1957 we have routinely performed renal arteriography, usually by the selective method, in patients with severe hypertension. Of 160 cases investigated in this way, a renal artery lesion was demonstrated in 10. In eight of the other cases reported here, renal artery narrowing was revealed at aortography performed for other reasons (usually iliac or aortic stenosis, or abdominal aneurysm). Though these figures give only an approximate indication of the incidence of renal-artery stenosis as a cause of hypertension, they show that it is not rare.

Clinical Features

Aetiology.—The wide variety of disorders which may lead to renal-artery stenosis has been reviewed by

DeCamp and Birchall (1958). The most frequent cause of narrowing, however, is an atheromatous plaque, usually situated close to the origin of the artery. Case 18 of the present series is of particular interest as an example of Takayashu's disease (pulseless syndrome) with renal-artery involvement.

Age Incidence.—There is a tendency for renal-artery stenosis to be seen more commonly in the older age-groups, but the disease is found in younger patients, and DeCamp and Birchall (1958) have reported the case of a 9-months-old baby with stricture of the renal artery and severe hypertension. The ages of the patients of the present series ranged from 17 to 65.

Evidence of Widespread Arterial Disease.—Renal-artery stenosis is to be suspected particularly in those hypertensive patients with evidence of occlusive arterial disease elsewhere. Of the present series, seven patients gave a history of intermittent claudication, five had ischaemic heart disease, and three had suffered strokes. Narrowing of the renal artery was found in 5 out of 32 cases in which aortography was performed to demonstrate a lower aortic occlusion (Starer and Sutton, 1958). The mouth of the renal artery may be involved in an upward extension of an aortic thrombosis (Case 20 of the present series); alternatively, as in Case 6, separate atheromatous renal-artery narrowing may be present in addition to a lower aortic block. Coronary or cerebral arterial occlusion and intermittent claudication are, however, not rare in cases of hypertension in the absence of demonstrable renal-artery stenosis. Conversely, nine cases of the present series (Nos. 1, 3, 4, 9, 10, 11, 17, 19, and 22) had no evidence of arterial disease elsewhere at the time of presentation. Cases 4, 17, and 22 were free of symptoms and were found to have high blood-pressure on routine examination.

Family History.—Only occasionally have we elicited any relevant family history. However, the father of Case 19 and a brother of Case 7 had experienced intermittent claudication, and the father of Case 9 had had both legs amputated "because of gangrene."

Complete Occlusion of Renal Artery.—In this event (Case 19; Adams and Newman, 1958) the patient may

TABLE 1—Case Histories

Bl. urea = Blood urea in mg./100 ml. Chol. = Serum cholesterol in mg./100 ml. Creat. = Creatinine concentration in mg./100 ml. Ex = Exudates. Glom. = Glomeruli. Haem = Haemorrhages. In. = Inulin concentration in mg./100 ml. Na = Sodium concentration in mEq/litre. P.A.H. = P.A.H. concentration in mg./100 ml. Pap. = Bilateral papilloedema. Tub. at. = Tubular atrophy. Ur.Fl. = Urine-flow in ml. per minute. Ur.L.C. = Urine leucocyte excretion rate per hour. Vis.Detn. = Visual deterioration.

Pt.	Diagnosis and Treatment	Clinical Features	I.V.P.	Divided Renal Studies	Aortogram	Pathological Findings	Results
1 Male 47	R. ren. art. sten. Jan. '59, thromboendarterectomy	Vis. Detn.: dyspnoea, B.P. 240/130. Fundi: Pap., Ex. Haem. Pressures: Aorta: 270/110 Before 150/80 After 0	Contrast R. > L.	Ur. Fl. Na Creat. P.A.H. C.P.A.H. 0.17 67 82 752 17 40	Selective Renal: R. stenosis near origin	No proteinuria. Bl. urea = 40. Chol. = 195. Ur.L.C. = 593,000. R. renal biopsy: patchy loss prox. con. tub., Glom. basement memb. thickening. L. renal biopsy: Tubs. normal. Occas. sclerosed glom. Hyalinization of arterioles	May '59, B.P. 150/90, fundi normal, full work. Feb. '60, B.P. 132/82
2 Male 45	L. ren. art. sten. Oct. '58, thromboendarterectomy. May '59, L. nephrectomy	1956, angina, B.P. 140/110. 1958, Vis. Detn.: dyspnoea, B.P. 260/160. Fundi: Pap., Ex., Haem. Abdom. bruit. Pressures: Aorta: 200/150 Before 150/120 After 200/150 165/150	No I.V.P. Pyelogram during aortogram showed equal contrast R. + L.	Ur. Fl. Na Creat. P.A.H. C.P.A.H. 2.1 50 82 180 32 95	Selective Renal: L. stenosis near origin. Lower 1/3 of kidney supplied by separate artery	Proteinuria. Bl. urea = 35. Chol. = 310. Ur.L.C. = 500,000. L. renal biopsy: Upper pole, widespread tub. atrophy; glom. basenent membrane thickening, vessels normal. Lower pole: glom. and tubs normal; vessels, medial hypert.	No fall in B.P. after thromboendarterectomy. No response to drugs. May '59, nephrectomy. Main renal art. thrombosed. July '59, B.P. 150/90. Feb. '60, B.P. 150/90, fundi normal
3 Male 47	L. ren. art. sten. Dec. '59, thromboendarterectomy and spleno-renal anastomosis	Nocturia. Headaches. Vis. Detn. B.P. 230/140. Abdom. bruit. Fundi: Ex., Haem. Pressures: Aorta: 112/82 Before 150/80 After 0	After fluid restriction: Calices on L. narrow. Contrast L. > R. After water load: R. no contrast. L. good contrast: calices wider	Ur. Fl. Na Creat. P.A.H. C.P.A.H. 2.7 10 375 133 38 153	Selective Renal: L. stenosis near origin	Proteinuria. Bl. urea = 44. Chol. = 280. Ur.L.C. = 360,000. L. renal biopsy: normal	Feb. '60, B.P. 140/90. May '60, B.P. 140/90, fundi normal
4 Male 40	R. ren. art. sten. Oct. '59, thromboendarterectomy and side-to-side anastomosis, ren. art. to aorta. Hypotensive drugs	Routine exam. '44, B.P. 120/75. '49, B.P. 145/85. '54, B.P. 180/100. '59, B.P. 240/140. Fundi normal. Abdom. bruit. Pressures: Aorta: 240/150 Before 215/110 After 135/75 190/110	Normal	Ur. Fl. Na Creat. P.A.H. C.P.A.H. 1.0 101 1,982 158 58 165	Selective Renal: R. sten near origin. R. kidney smaller than L.	No proteinuria. Bl. urea = 35. Ur.L.C. = 130,000. R. renal biopsy: few sclerosed glom.; patchy loss of con. tubules. L. renal biopsy: normal except hyalinization of arterioles	No fall in B.P. March '60, divided renal studies: Ur.Fl. Na Creat. P.A.H. 1.8 90 179 182 58 50
5 Male 54	Abdom. aneurysm, L. hydronephrosis, L. ren. art. sten. Oct. '59, aneurysm wired	20 yrs. Claudication, '59, B.P. 180/120. No abdom. bruit. Op. Oct. '59, abdom. aortic aneurysm with adherent L. ureter Pressures: Aorta: 175 Mean 175	L., no contrast. R., normal. Retrograde: L., hydronephrosis. R. normal	Ur. Fl. Na Creat. P.A.H. C.P.A.H. 1.3 38 105 43 14 14	High Aorta Puncture: Aneurysm lower thoracic and abdom. aorta. Stenosis L. renal	No change	No change
6 Male 52	Lower aortic thrombosis. Upper L. ren. art. sten. Feb. '58, L. nephrectomy. Hypotensive drugs	Claudication from childhood. Dyspnoea 1 year. '58, B.P. 300/140. Fem. pulse delayed. Extensive collaterals. Abdom. bruit. Fundi: Haem., Pap.	L., no contrast. R., normal. Retrograde: Small L. kidney	Not performed	Lumbar: Aortic occlusion from inf. mes. to common iliacs. Nephrogram lower 1/3 L. kidney only. L. kidney smaller than R.	No proteinuria. Bl. urea = 39. L. kidney = 62 g. Lower pole artery normal. Small arteries to upper 2/3. Histology: upper 2/3: Marked tub. atrophy. Glom. basement memb. thickening. Art. intimal. Thickening. Lower 1/3: tubules normal. Glom. and vessels as upper 2/3	No fall in B.P. On hypotensive drugs. Gradual rise in bl. urea = 100 (March '60). Fundi normal. B.P. (March '60) = 220/110
7 Male 59	Aorto-iliac stenosis. L. ren. art. sten.	'57, claudication, B.P. 230/120. '59, angina, abdom. bruit, fundi normal	Contrast L. > R. Delayed on L.	Ur. Fl. Na Creat. P.A.H. 0.7 30 393 131 7.0 33 224 62	Lumbar: Irregularity lower abdom. aorta. L. ren. art. sten.	No proteinuria. Bl. urea = 33. Chol. = 235	March '60, unchanged, no treatment, B.P. 150/90
8 Male 65	Ret. art. occlusion. Ischaemic R. kidney. Hypotensive drugs	'58, thrombosis R. cent. ret. art. '59, C.V.A. (dysarthria, ataxia). B.P. 190/120. No abdom. bruit. Fundi: R. optic atrophy L. normal	Contrast R. > L. R. smaller than L.	Ur. Fl. Na Creat. P.A.H. C.P.A.H. 1.2 29 898 280 29 128	High Aortic Puncture: Irreg. dilated aorta. No ren. art. sten.	No proteinuria. Bl. urea = 33. Chol. = 150. Ur.L.C. 23,000	March '60, on hypotensive drugs, B.P. 180/100

TABLE I (Continued)

Pt.	Diagnosis and Treatment	Clinical Features	I.V.P.	Renal Studies			Aortogram	Pathological Findings	Results
				Ur. Fl.	Na	P.A.H.			
9 Female 40	Hypertensive encephalopathy L. ren. art. aneurysm and stenosis lower polar artery. Hypotensive drugs	'50, hypertension during pregnancy. D.C., '59, epileptiform fits, B.P. 230/160, fundi normal. Abdom. bruit. March '60. Opi. L. ren. art. aneurysm. Atheroma main branches. Stenosis lower polar artery. Aneurysm pressures: Aorta 125/105 100/95 Lower polar artery	Normal	Ur. Fl. 2.1 Na 92 In 384 P.A.H. 104	R. 3.8 96 193 83	Bl. 4.6 95 285 75	Selective Renal: Aneurysm left main re- polar artery. Lower polar branch	No proteinuria. Bl. urea = 27. Ur.L.C. = 208,000. Lower pole, gross atrophy prox. con- volutions; glom. basement memb. thickening. Some sclerosed glom. Upper pole. Tubs. normal, some sclerosed glom.	On guanethidine. May '60, B.P. 160/100
10 Female 49	L. ren. art. sten. End-to-end anastomosis, ren. art. to aorta. Hypotensive drugs	'54, B.P. "High," '58, epistaxes, dyspnoea, nocturia. B.P. 260/160 Abdom. bruit. Fundi: Pap. ex., haem. Oct. '58. Opi. end-to-side anastomosis, ren. art. to aorta. No pressure measurements	Contrast equal. R. kidney smaller than L.	Na Creat. Failed to catheterize ureter	R. 99 53	Bl. 70 48	Catheter in Aorta: L. ren. art. sten. near origin. R. ren. art. also narrow	Proteinuria. Bl. urea = 32. L. renal biopsy: Glom.—some sclerosed tubs—focal atrophy, prox. conv. Arterioles-fibrinoid necroses	No fall in B.P. Hypotensive drugs, March '60, fundi normal, B.P. 150/100
11 Female 40	R. ren. art. sten. May '59, R. nephrectomy	'59, headaches, dyspnoea, B.P. 230/130. Fundi: ex. Abdom. bruit. Pressure-drop aorta, ren. art. = 90 mm. Hg	Not available	Na Failed to catheterize ureter	R. 25	Bl. 67	High Aortic Puncture: R. stenosis near origin. R. kidney smaller than L.	No proteinuria. Bl. urea = 45. Cholesterol = 227. R. kidney wt. = 110 g. Histology marked tub. atrophy. Periglom. fibrosis. L. biopsy normal	Nov. '59, B.P. 150/90
12 Male 54	Aneurysm abdom. aorta. L. ren. art. sten. Aug. '59, aneurysm wired	1 yr. attacks L. abdom. pain. B.P. 220/100. E.C.G. old ischaemia. No abdominal bruit. Pressures aorta and distal ren. art. equal	Normal	Not performed	L. 0.5 142 62 910 37 135	R. 1.4 168 35 490 56 199	Catheter in Aorta: Aneurysm lower abdom. aorta. ? stenosis origin. L. ren. art.	Proteinuria. Bl. urea = 36. L. kidney biopsy: mild tub. atrophy; some sclerosed glom.	Nov. '59, unchanged
13 Male 36	? Ischaemic L. kidney. Hypotensive drugs	'56, claudication, dyspnoea, bruit R. fem. No abdom. bruit. B.P. 220/140. Fundi normal	Normal	Ur. Fl. 18 Na 573 Creat. 167 P.A.H. 9 C.P.A.H. 48	L. 0.4 58 573 272 9 48	R. 1.1 89 900 272 45 237	High Aortic Puncture: Two arteries to L. kidney. No stenosis seen	Proteinuria. Bl. urea = 37. Cholesterol = 390. Ur.L.C. = 360,000	April '60, 170/92 B.P.
14 Male 28	Congenital malformation R. kidney and pyelonephritis. Sept. '59, R. nephrectomy	'51, B.P. 155/105. '59, B.P. 200/115. No symptoms. No abdom. bruit. Fundi normal. M.S.U. coliforms. Aorta renal art. pressures equal	R. kidney small. Contrast poor. L. kidney large	Ur. Fl. 18 Na 573 Creat. 167 P.A.H. 9 C.P.A.H. 48	L. 0.4 58 573 272 9 48	R. 1.1 89 900 272 45 237	Selective Renal: R. sten. near origin. Small lobulated R. kidney	Proteinuria. Bl. urea = 38. Cholesterol = 200. R. kidney wt. = 37 g. Histology: congen. malformation and pyelonephritis. L. ren. biopsy normal. Dissection R. ren. art.—no stenosis	Nov. '59, B.P. 150/94
15 Male 60	Aorto-iliac thrombosis. R. ren. art. sten. No treatment	'58, claudication. B.P. 190/100. Bruit R. costovertebral angle. Fundi normal	Contrast R. > L. R. kidney small	Ur. Fl. 42 Na 328 Creat. 151 P.A.H. 151 C.in. 54 C.P.A.H. 186	R. 4.2 42 328 191 91 257	L. 9.4 57 900 272 45 237	High Aortic Puncture: Aortic occlusion just below R. ren. art. Sten. R. ren. art.	Bl. urea = 40. Cholesterol = 220	April '60, B.P. 190/100
16 Male 42	Angina. Gangrene R. foot. L. ren. art. sten. R. lumbar sympathectomy. R. A/K amputation	'54, B.P. 190/100. '58, Angina and gangrene R. foot B.P. 190/100	Contrast L. > R. Calices L. narrower than R.	Ur. Fl. 18 Na 332 Creat. 145 P.A.H. 20 C.in. 111	R. 2.2 18 332 145 20 111	L. 4.0 27 216 100 24 138	High Aortic Puncture: Atheroma abdom. aorta, iliacs, femorals. L. ren. art. sten. near origin	Proteinuria. Bl. urea = 42. Cholesterol = 329. L. renal biopsy = focal cortical scarring. Tub. atrophy. Glom. normal	
17 Female 21	L. ren. art. sten. March '60, spleno-renal anastomosis	No symptoms. B.P. 165/100. Fundi normal. No abdominal bruit	Contrast L. > R. L. kidney smaller than R.	Ur. Fl. 3.0 Na 28 Creat. 315 P.A.H. 111 In more conc. samples Na on L. > R.	R. 3.3 31 237 106	Bl. 4.0 4.0 216 100 24 138	Catheter in Aorta: L. ren. art. stenosis	No proteinuria. Bl. urea = 28. Cholesterol = 180. Renal biopsies: L. many sclerosed glom. tub. atrophy. Foci of lymphocytes. R. normal	April '60, B.P. 130/80. Too early for assessment

TABLE I (Continued)

Pt.	Diagnosis and Treatment	Clinical Features	I.V.P.	Divided	Renal Studies	Aortogram	Pathological Findings	Results
18 Female 17	Pulseless syndrome (Takayasu's disease). Ischaemic R. kidney. Anticoagulants	Greek Cyriot. '53, hemiplegia, blindness. Both car. R. subclavian and axillary pulses absent. Femorals present. No abdom. bruit. B.P. 190/110	Good contrast R. > L. R. smaller than L.	Ur. Fl. Na P.A.H.	R. L. 0.4 0.7 47 95 1,520 745	Thoracic: Occlusion innomin. and both carotids. L. vertebral large. Lower abdom. aorta narrow. R. ren. art. narrow	No proteinuria. Bl. urea = 46. Chol. = 236. W.R. negative	Not known
19 Male 48	Thrombosed aneurysm L. ren. art. Jan. '55. L. nephrectomy. '60, iliac art. stenosis. (Case reported by Adams and Newman, 1958)	June '54, sudden pain L. loin. B.P. 140/90. Fundi normal. Nov. '54, headaches. B.P. 220/140. Fundi: pap., ex., haem. '60, claudication	L. poor contrast. R. normal	Not performed	Not performed	Not performed	Proteinuria. Bl. urea = 34. Chol. = 354. W.R. negative. L. kidney grossly scarred. Thrombosed aneurysm L. ren. art. Some areas complete infarction. Some areas tub. atrophy with intact glom	Oct. '55, B.P. 120/80. Sept. '56, B.P. 120/80. May '60, B.P. 120/80
20 Male 39	Lower aortic occlusion. L. ren. art. sten. 1956. L. nephrectomy and lower aortic graft	'52, Claudication. B.P. 125/60. '55, headaches. B.P. 205/110. Fundi: few haem. Pressure measurements not made	Not performed	Not performed	Not performed	High Aortic Puncture: Complete block abdominal aorta just below renals. Stenosis L. ren. art. L. kidney small	No proteinuria. Bl. urea = 25. Chol. = 200. L. kidney wt. = 145 g. Histology: paucity change with necrosis of many prox. conv. tubs.	March '60, B.P. 130/80. Fundi normal
21 Female 54	R. ren. art. sten. Ischaemic heart dis. Chronic bronchitis. No treatment	1958, chronic bronchitis. B.P. 230/130. Oct. '59, myocardial infarct. Fundi normal. Abdominal bruit	Contrast R. > L. R. calices narrower than L. R. kidney smaller	Ur. Fl. Na In. P.A.H. C.in. C.P.A.H. In more conc. samples Na R. > L.	R. L. 0.1 1.0 90 153 3,100 900 1,590 490 12 37 58 184	Lumbar: R. ren. art. sten. near origin	No proteinuria. Bl. urea = 36. Chol. = 210	March '60, B.P. 130/80
22 Female 28	R. ren. art. sten.	'59, var. vein clinic. B.P. 240/140. No symptoms. Fundi normal. No abdominal bruit	Normal	Ur. Fl. Na In. P.A.H.	R. L. Unreliable 77 123 1,110 324 394 95	Catheter in Aorta: Delay in filling R. ren. art. Probable R. sten.	Proteinuria. Bl. urea = 36. Ur. I.C. = 29,000. R. renal biopsy: atrophy prox. conv. tub. Some sclerotic glom. Periglom. fibrosis. Hyalinization arterioles	Waiting surgical exploration

develop pain in the loin due to partial infarction of the kidney. Fever and neutrophil leucocytosis may occur, and confusion with an attack of pyelonephritis is clearly possible.

Embolism of Renal Artery.—This can lead to severe hypertension reversible by nephrectomy or removal of the clot. The possibility of this occurrence must therefore be borne in mind if a likely source of emboli is known to be present (Prinzmetal *et al.*, 1942; Bourne, 1954).

Arterial Bruits.—Frequently we have found a systolic bruit arising in the stenosed artery. The murmur is usually, but not invariably, audible on clinical examination, and is often best heard near the centre of the abdomen, just above the umbilicus and to one or other side of the midline. Fig. A shows a phonograph record of the abdominal murmur in Case 9. Occasionally the murmur is not heard anteriorly, but is loud in the costovertebral angle (Case 15). In all cases submitted to operation the renal arterial origin of the bruit has been confirmed by direct auscultation. In several instances a palpable thrill has also been found in the affected vessel. The systolic murmur is usually abolished when the patency of the renal artery is restored. In Case 2 thromboendarterectomy was ineffective, and the abdominal murmur persisted after operation, to become inaudible when the artery thrombosed completely. Bruits over other arteries than the renal may, of course, be indicative of more widespread arterial disease.

Appearance of Fundus Oculi.—The hypertension in renal-artery stenosis may be in the benign or malignant phase, and the appearances of the fundus vary accordingly.

Polyuria.—The association of polyuria with narrowing of the renal artery and hypertension figures in five case reports (Øster, 1947; Deming, 1954; Margolin *et al.*, 1957; DeCamp and Birchall, 1958; Dollery *et al.*, 1959). Case 3 of the present series gave a history of nocturnal frequency of micturition in the three years before admission, though the significance of this remains doubtful. In hospital he showed neither frequency nor polyuria.

Potassium Loss and Hypokalaemia.—Dollery *et al.* (1959) reported two cases of renal-artery obstruction with hypertension, hypokalaemia, and urinary potassium loss. Unfortunately, ureteric catheterization studies failed technically. We have not encountered hypokalaemia in the present series; though in many of the cases with renal-artery stenosis we have compared urinary potassium output on the two sides, we have not observed excessive potassium excretion by either kidney.

Proteinuria.—This may or may not be present in renal-artery stenosis, and is usually unhelpful in diagnosis.

FIG. A.—Phonograph record of abdominal murmur in Case 9.

Urinary Cell-excretion Rate (Houghton and Pears, 1957).—Though most of our cases have had a moderately raised leucocyte excretion rate (up to 500,000/hour), this finding is not uncommon in several forms of hypertension, and does not appear to have particular relevance to renal-artery stenosis.

Special Investigations

Ureteric Catheterization Studies

It was shown by Mueller *et al.* (1951) that constriction of one renal artery in the dog resulted in a decrease in the volume and sodium concentration of the urine obtained from the kidney with the narrowed artery, as compared with the normal side. Howard *et al.* (1954) obtained similar results in a patient later shown at operation to have a stenosis of the main renal artery. Further studies of separate renal function in hypertension were reported by Connor *et al.* (1957, 1960). We have routinely carried out divided renal-function studies in patients with suspected renal-artery stenosis.

Method

Sodium pentobarbitone was used for premedication, and in order to ensure adequate flow of urine the patients were given 125–250 ml. of water to drink every 15 minutes during the hour preceding the investigation. Saddle-block spinal anaesthesia was induced by means of intrathecal dibucaine hydrochloride, and olivary-tipped ureteric catheters were passed via a cystoscope. The positions of the catheters were adjusted under radiographic control until the tips were judged to lie in the respective renal pelves. A self-retaining catheter was left in the bladder in order that any leak around the ureteric catheters immediately became apparent. When leakage occurred, the positions of the ureteric catheters were altered until the leak stopped or was reduced to a minimum. The water load was maintained throughout by oral replacement equal to urine volume. After usually two satisfactory urine collection periods had been obtained, 0.9% sodium chloride containing inulin and sodium *para*-amino-hippurate (P.A.H.) was infused at a constant rate into an arm vein. Further periods of urine collection were then taken after equilibration. Blood samples were withdrawn as required from an indwelling venous cannula in the opposite arm. In some patients, endogenous creatinine clearance was measured instead of inulin clearance. A course of nitrofurantoin or sulphonamide was given after the test.

In no case of the present series have we encountered urinary infection after ureteric catheterization, and, apart

from occasional transient discomfort to the patient, the procedure has been free from complications. We would stress the importance of avoiding, if at all possible, any leakage around the ureteric catheters into the bladder. Only in this way can accurate measurements of urine flow and clearances be made. There is evidence (Levinsky and Berliner, 1959; Yendt *et al.*, 1960) that movements of water and electrolytes can take place across the walls of the ureter and bladder, and our experience confirms that calculations of the amount of leakage from either side based upon the relative concentrations of electrolytes in the ureteric samples and in the bladder are unreliable. Investigations where only one ureter is catheterized, the bladder urine being assumed to come entirely from the opposite side, are also open to question.

Ureteric Catheterization Findings in Renal-artery Stenosis

The kidney with the renal-artery stenosis forms a smaller volume of glomerular filtrate than the opposite kidney; further, a higher proportion of the filtered water, sodium, and chloride is reabsorbed on the affected side. Comparing the affected kidney with its fellow, therefore, the characteristic features of renal-artery stenosis on ureteric catheterization studies are, on the side with the lesion, diminished urine flow; lowered clearances of inulin, creatinine, and P.A.H.; increased urinary concentrations of inulin, creatinine, and P.A.H.; and, usually, diminished urinary concentrations of sodium and chloride. As Birchall *et al.* (1958) have pointed out, the final urinary concentration of sodium depends upon two variables, the tubular reabsorption of water and of sodium. It is therefore possible that the proportions of both the filtered water and the sodium reabsorbed on the side with the stenosis could exceed those on the normal side, and yet the final urinary concentration of sodium be higher on the former.

The higher urinary concentration of inulin and creatinine on the affected side in renal-artery stenosis has important implications in relation to intravenous pyelography and is further discussed later.

Findings in the Present Series

The results obtained in three proved cases of renal-artery stenosis (Nos. 1, 3, and 4) are shown in Tables II–IV. In each case the data relating to the affected kidney

TABLE II.—Case 1. Stenosis Right Main Renal Artery

	Period	R	L
Urine volume (ml. min.)	8	0.25	3.7
	9	0.17	4.5
	10	0.15	5.5
Sodium (mEq/l.)	8	45.0	100.0
	9	67.0	135.0
	10	115.0	144.0
Chloride (mEq/l.)	8	19.0	86.0
	9	32.0	123.0
	10	58.0	130.0
Urine P.A.H. concentration (mg./100 ml.)	9	752.0	167.0
	10	2,160.0	173.0
Urine creatinine concentration (mg./100 ml.)	9	81.6	12.4
	10	128.6	11.6
P.A.H. clearance (ml. min.)	9	40.0	234.0
	10	98.0	288.0
Creatinine clearance (ml. min.)	9	17.0	65.0
	10	23.0	70.0

are given first. In these patients, renal-artery stenosis was confirmed at operation, and a distinct pressure-drop across the site of the lesion was measured. In Table V a comparison is made of the normal with the affected kidney in these three cases with regard to urine-flow and the concentrations of sodium, P.A.H., and inulin or creatinine. In each instance the performance of the normal kidney is taken as 100%. In the second part of Table V similar data are presented for nine other cases (Nos. 7, 8, 13, 15, 16, 17, 18, 21, and 22) in which a diagnosis of renal-artery stenosis was regarded as probable, though not proved. For comparison, the findings in nine "control" cases, eight of which had hypertension, are given in the third part of the table.

TABLE III.—Case 3. Stenosis Left Main Renal Artery

	Period	L	R
Urine volume (ml./min.)	11	2.7	9.2
	12	2.0	9.0
	13	2.1	8.0
Sodium (mEq/l.)	11	10.0	30.0
	12	9.0	30.0
	13	6.0	22.5
Chloride (mEq/l.)	11	3.6	27.5
	12	3.5	29.4
	13	0.14	27.5
Urine P.A.H. concentration (mg./100 ml.)	11	133.0	44.0
	12	138.0	39.0
	13	153.0	45.0
Urine inulin concentration (mg./100 ml.)	11	375.0	130.0
	12	586.0	121.0
	13	420.0	134.0
P.A.H. clearance (ml./min.)	11	153.0	172.0
	12	118.0	148.0
	13	137.0	154.0
Inulin clearance (ml./min.)	11	38.0	45.0
	12	40.0	41.0
	13	33.0	40.0

TABLE IV.—Case 4. Stenosis Right Main Renal Artery

	Period	R	L
Urine volume (ml./min.)	14	1.0	3.1
	15	0.8	2.3
Sodium (mEq/l.)	14	101.0	119.0
	15	103.0	127.0
Chloride (mEq/l.)	14	90.0	119.0
	15	93.0	134.0
Urine P.A.H. concentration (mg./100 ml.)	14	392.0	158.0
	15	549.0	212.0
Urine inulin concentration (mg./100 ml.)	14	1,982.0	915.0
	15	1,215.0	1,012.0
P.A.H. clearance (ml./min.)	14	165.0	210.0
	15	196.0	215.0
Inulin clearance (ml./min.)	14	58.0	85.0
	15	36.0	85.0

TABLE V.—Comparison of Normal With Affected Kidney

	Urine Flow		Urinary Sodium		Urinary P.A.H.		Urinary Inulin or Creatinine	
	Range	Mean	Range	Mean	Range	Mean	Range	Mean
Proved renal-artery stenosis (3 cases)	-65 to -97	-80	-15 to -73	-46	+150 to +1,150	+357	+20 to +1,000	+354
Probable renal-artery stenosis (9 cases)	-45 to -96	-66	-45 to +20	-18	+4 to +1,900	+239	+33 to +870	+169
No unilateral renal disease (9 cases)	+24 to -41	-12	-9 to +10	-1	-36 to +50	+5	-37 to +50	0

The figures refer in the cases of renal artery stenosis to percentage variations in the function of the abnormal kidney, the function of the opposite kidney being taken as 100%. In the cases without unilateral renal disease the function of the left kidney has been arbitrarily taken as 100%.

In this last group there was considered to be no evidence of renal-artery stenosis, or any form of unilateral renal disease. In this group differences in urine flow and the urinary concentration of sodium, inulin, and P.A.H. on the two sides were always small, and neither kidney could be taken as the abnormal one. Throughout the group, therefore, the function of the left kidney has been arbitrarily taken as 100%, and the performance of the opposite kidney expressed accordingly. It can be seen from Table V that any differences on the two sides are slight in the "control" group as compared with the cases of renal-artery stenosis. Only very rarely did differences in the function of the two kidneys in the "control" group extend into the range of difference seen in the proved or probable cases of renal-artery stenosis. These occasions were usually isolated collection periods in the patients concerned; for the most part, differences between the two kidneys were well outside the range found in renal-artery stenosis.

More decisive is the pattern of disordered function seen in renal-artery stenosis. In all the probable and proved cases the affected kidney produced less urine, with a higher concentration of P.A.H., inulin, and creatinine, and almost invariably a lower concentration of sodium and chloride than its fellow. This pattern was never seen in the "control" group, where, if one kidney secreted less urine with a lower concentration of sodium than the other, a lower concentration of inulin and P.A.H. was also found on that side.

Variations in Urinary Sodium Concentration on the Two Sides

In none of the fully established cases of renal-artery stenosis in this series have we found, on divided function studies, deviations from the pattern set out above, except where these were associated with a lesion in a segmental artery. In two patients, however (Cases 17 and 21), in whom there was a probable though not finally proved renal-artery stenosis, occasional urine-collection periods showed higher sodium concentrations on the affected than on the unaffected side. In both of these cases the inulin and P.A.H. concentrations were persistently higher on the affected side. In Case 21 calculation showed that a higher proportion of the filtered water and sodium was reabsorbed on the suspect side, even where the final urinary sodium concentration was higher. Similar calculation was not possible in Case 17, since leakage around the ureteric catheters occurred, and the inulin clearance consequently could not be determined.

Birchall *et al.* (1958) reported a proved case of renal-artery stenosis in which ureteric catheterization studies showed persistently higher sodium concentration in the urine from the affected kidney. These workers similarly were able to show that a higher proportion of the filtered sodium and water was reabsorbed on the affected side. Connor *et al.* (1960) have criticized the findings of Birchall and his colleagues, suggesting that the infusion of saline containing inulin and P.A.H. may alter the pattern of electrolyte excretion on the two sides and invalidate the test. We have, as described above, taken samples both before and after starting such infusions, and have never found that the relative urine volumes or sodium concentrations are altered in these circumstances. The total quantity of sodium infused in the course of the test is in fact small, never being more than of the order of 50 mEq. The explanation of Connor *et al.* cannot in any event apply to the two patients in whom we found variations in the relative sodium concentrations

on the two sides, since these variations were found in collection periods taken both before and after the start of the infusion. We were, of course, not able to calculate the tubular reabsorption of sodium and water in the periods before the infusion of inulin, since we had in these no measure of the glomerular filtration rate.

For the present, we prefer to study the wider pattern of disordered function on the suspect side as revealed by the relative urine-flow rates, the inulin and P.A.H. clearances, and the concentrations of sodium, inulin, creatinine, and P.A.H., rather than relying simply on the comparative urine-flow rates and sodium concentrations. To what extent the altered excretory pattern we have described above is specific to renal-artery stenosis is not finally determined.

Cases with No Demonstrable Lesion in the Main Renal Arteries

In two instances (Cases 8 and 13) the divided studies were typical of renal-artery stenosis by our criteria, but arteriography demonstrated no lesion in the major renal arteries. It is possible that intrarenal arterial occlusion had occurred, but no such abnormality was revealed radiologically. These cases have not been subjected to operation, and at present are controlled by hypotensive drugs. They are included as cases of probable but not proved renal-artery stenosis in Table V.

Cases with a Lesion in a Segmental Artery

When the lesion occurs in a segmental artery the amount of renal tissue involved in the ischaemic process may be so small that any difference between the two kidneys as judged by ureteric catheterization studies is masked. This is well seen in Case 9 (Fig. 1, Special Plate; Table VI), in which an aneurysm with an irregular wall was found in the main left renal artery. At operation the pressures in the aorta and in the distal part of the main renal artery were equal at 125/105 mm. Hg; in the attenuated lower polar artery, however, the pressure was only 100/95 mm. Hg. Biopsy of the lower pole of the kidney showed evidence of ischaemia; the upper pole showed minor changes only.

Similar in some respects was Case 2 (Fig. 2, Special Plate; Table VII). This man had an atheromatous plaque at the mouth of the main left renal artery, but the lower pole of the kidney was supplied by a separate artery arising directly from the aorta. It is noteworthy here that, though the greater part of the left kidney was supplied by the affected vessel, the urinary creatinine and P.A.H. concentrations on the left were slightly lower than on the right. Histologically (Fig. 10) tubular damage here was considerable, and this might well have

TABLE VII.—Case 2. *Stenosis Left Main Renal Artery. Aberrant Artery to Lower Pole*

	Period	L	R
Urine volume (ml. min.)	4	2.1	4.1
	5	1.5	2.3
Sodium (mEq/l.)	4	50.0	60.0
	5	66.0	75.0
Chloride (mEq/l.)	4	45.0	52.0
	5	55.0	62.0
Urine P.A.H. concentration (mg./100 ml.)	4	181.0	236.0
	5	334.0	377.0
Urine creatinine concentration (mg./100 ml.)	4	12.0	14.0
	5	19.7	23.6
P.A.H. clearance (ml. min.)	4	94.0	242.0
	5	128.0	219.0
Creatinine clearance (ml. min.)	4	32.0	71.0
	5	41.0	71.0

contributed to the somewhat atypical results. These last two cases have not been included in Table V.

Because of the limitations of divided renal function studies in cases such as those described above, and also in bilateral renal-artery stenosis, some authors have questioned the value of these tests, preferring to rely for diagnosis mainly upon the angiographic appearances (Dustan *et al.*, 1959). Angiography may occasionally be misleading, however, and in such instances ureteric catheterization studies are of great value. Two patients of the present series illustrate this point.

In Case 5 (Fig. 3, Special Plate) aortography showed a lower aortic aneurysm and a narrowing of the left renal artery. Intravenous pyelography failed to demonstrate the left renal tract, and the patient was found to have a left-sided hydronephrosis, the ureter being distorted and obstructed by the aneurysm. Ureteric catheterization studies in this patient (Table VIII) were

TABLE VIII.—Case 5. *Left Hydronephrosis and Possible Left Renal-artery Stenosis*

	Period	L	R
Urine volume (ml./min.)	6	1.3	2.0
	7	2.0	5.0
Sodium (mEq/l.)	6	38.0	76.0
	7	38.0	87.0
Chloride (mEq/l.)	6	32.0	52.0
	7	34.0	60.0
Urine P.A.H. concentration (mg./100 ml.)	6	43.0	484.0
	7	45.0	473.0
Urine inulin concentration (mg./100 ml.)	6	105.0	94.0
	7	116.0	104.0
P.A.H. clearance (ml./min.)	6	14.0	324.0
	7	15.0	290.0
Inulin clearance (ml./min.)	6	4.0	75.0
	7	4.0	69.0

not those typical of renal-artery stenosis, in that, though the urine-flow rate and sodium concentration were lower on the left, there was little or no difference in the inulin concentration on the two sides, and the P.A.H. concentration was distinctly lower on the left. At operation no pressure-drop or alteration in the shape of the pulse wave was found distal to the site of the apparent lesion. In this instance the interpretation of the renal biopsy appearance was complicated by the presence of the hydronephrosis.

Ureteric catheterization studies were not typical of renal-artery stenosis also in Case 14 (Fig. 4, Special Plate; Table IX), where selective arteriography had suggested this diagnosis. Again, the inulin and P.A.H. concentrations were found to be lower on the affected

TABLE VI.—Case 9. *Narrowing of Segmental Artery (Left)*

	Period	L	R	B*
Urine volume (ml. min.)	4	2.1	3.8	4.6
	5	2.2	2.3	5.0
	6	1.9	2.2	4.6
Sodium (mEq/l.)	4	92	96	95
	5	99	98	101
	6	108	106	109
Chloride (mEq/l.)	4	75	78	78
	5	85	86	85
	6	90	92	91
Urine P.A.H. concentration (mg./100 ml.)	4	101	82	75
	5	106	100	
	6	110	97	95
Inulin concentration (mg./100 ml.)	4	384	193	285
	5	343	239	356
	6	425	303	347

* B = bladder.

side. The arteriographic appearance here was later shown to be a radiological artifact (see below).

Lastly, it should be pointed out that the information provided by ureteric catheterization studies is of great value as a measure of the renal reserve, should nephrectomy rather than a reconstructive operation be contemplated.

These tests are tedious for both the patient and the investigator, and it is necessary to interpret the results with care. We have, however, found them to be generally the most reliable index of a renal arterial lesion.

TABLE IX.—Case 14. *Right Pseudostenosis*

	Period	R	L
Urine volume (ml. min.)	5	0.37	1.1
	6	0.37	0.8
Sodium (mEq/l.)	5	58.0	89.0
	6	75.0	111.0
Chloride (mEq/l.)	5	49.0	80.0
	6	67.0	99.0
Urine P.A.H. concentration (mg./100 ml.)	5	117.0	272.0
	6	208.0	333.0
Urine inulin concentration (mg./100 ml.)	5	573.0	900.0
	6	687.0	1,040.0
P.A.H. clearance (ml./min.)	5	48.0	237.0
	6	64.0	216.0
Inulin clearance (ml./min.)	5	9.0	45.0
	6	11.0	36.0

Plain X-ray Films

In many of the cases of renal-artery stenosis the affected kidney was found to be smaller than its fellow, though often the difference was not great enough to be helpful diagnostically. In two instances (Cases 3 and 22) there was no difference in length, and in Cases 4, 7, 15, 17, and 21 the affected kidney was shorter by less than the 1.5 cm. which Hodson (1957) regards as representing a significant difference in kidney size. It should also be borne in mind that in normal persons the right kidney may be appreciably smaller than the left (Moëll, 1956). In no patient of the present series was the unaffected kidney the smaller one. The greatest disparity in size was seen in the girl with Takayasu's disease (Case 18), where the respective lengths of the kidneys were 6.5 and 11.5 cm. Nevertheless, a better pyelogram was seen on the affected side here.

Intravenous Pyelography

This investigation has important implications in relation to renal-artery stenosis. The ureteric catheterization studies showed that renal-artery stenosis typically resulted in higher concentrations of inulin, creatinine, and P.A.H. in the urine from the affected side. The dyes currently employed in excretion urography—sodium acetrizate and sodium diatrizate—are, in the usual doses, excreted mainly by glomerular filtration (Porporis *et al.*, 1954; McChesney and Hoppe, 1957), and the concentrations of radiopaque dye in the urine on the two sides will thus parallel the inulin and creatinine concentrations. It is to be anticipated, therefore, that renal-artery stenosis will be represented on intravenous pyelography by higher contrast and better visualization on the affected side than on the normal, provided that severe structural damage has not occurred in the kidney (Peart, 1959).

Better contrast on the side with the stenosis was, in fact, seen in seven cases of the present series (Nos. 1, 3, 15, 16, 17, 18, and 21) (See Fig. 5, Special Plate). This

may falsely suggest impairment of function in the kidney with the normal renal artery, and there is a very real danger in these cases of the unaffected kidney being removed, with disastrous consequences. This misinterpretation is particularly likely to occur if for some reason dehydration before intravenous pyelography has been inadequate, with the result that the contrast on the side with the normal renal artery is poor. Case 3 affords a striking example of this.

This patient was a man with severe hypertension in whom intravenous pyelography performed at another hospital had shown poor contrast on the right side. It had been suggested, therefore, that there was a lesion of the right kidney, possibly responsible for the hypertension. Ureteric catheterization studies were, however, typical of a stenosis of the left renal artery (Table III), and this was confirmed by selective renal arteriography (Fig. 6, Special Plate). Intravenous pyelography was then repeated with the patient deliberately loaded with 500 ml. of water. This had the effect of obliterating the contrast on the normal side, though the kidney with the renal-artery stenosis was very clearly visualized (Fig. 7, Special Plate).

Several authors have commented on the preservation of the excretion pyelogram of a kidney with a stenosed artery, though the fact that better contrast may often be seen on this side seems to have passed unnoticed (DeCamp and Birchall, 1958; Page *et al.*, 1959; Squire and Schlegel, 1959; Yendt *et al.*, 1960). In consequence, the tendency has been to overstress the limitations of this technique. Several of the illustrations in the paper by Squire and Schlegel, for example, show greater pyelographic density on the side with the lesion, though the pictures are regarded by these authors as showing no abnormality. Intravenous pyelography is often, in fact, a most valuable diagnostic test in renal artery stenosis. Where bilateral renal-artery stenosis is present, particularly good contrast might be expected on excretion urography. The case described by Yendt *et al.* (1960) appears to be an example of this phenomenon.

In many cases an estimation of the rate of urine-flow on the two sides can be made by comparing the degree of filling of the pelvis and calices. Typically, on the side with the stenosis there will be less distension by urine, though contrast will be denser because of the comparatively high concentration of dye present. In some reports the calices have even been described as "spastic" on the affected side.

In those patients with severe renal structural damage (Cases 6 and 19) the pyelogram will, of course, be poor or absent on the side with the lesion, but these are the

LEGENDS TO SPECIAL PLATE

FIG. 1.—Selective renal arteriogram in Case 9, showing aneurysm sac and attenuated lower polar artery.

FIG. 2.—Selective renal arteriogram in Case 2. The artery demonstrated supplied only the upper two-thirds of the kidney.

FIG. 3.—Aortogram in Case 5, showing narrowing at origin of left renal artery.

FIG. 4.—Selective renal arteriogram in Case 14, showing small lobulated kidney and apparent renal-artery stenosis.

FIG. 5.—Intravenous pyelogram in Case 1 15 minutes after injection of the dye, showing better contrast on the side with the renal-artery stenosis.

FIG. 6.—Selective renal arteriogram in Case 3, showing stenosis at origin of left renal artery, with post-stenotic dilatation.

J. J. BROWN *ET AL.*: RENAL-ARTERY STENOSIS

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 6

J. J. BROWN *ET AL.*: RENAL-ARTERY STENOSIS

FIG. 7

FIG. 8

FIG. 9

a

b

c

d

FIG. 11

FIG. 10

exceptions. Even when the affected kidney is distinctly small (Case 18), better contrast may be obtained on that side.

Renal Arteriography

This procedure is of great value in the diagnosis of renal artery stenosis. Three different techniques are available. The first is simple translumbar aortography, the second is aortography by percutaneous transfemoral catheterization using the method of Seldinger (1953), and the third is percutaneous selective renal arteriography using an opaque catheter (Ödman, 1956). Any of these will provide good visualization of the renal arteries. Some workers are strong protagonists of one method as against the others, but all have merits and demerits, and the exact technique used is largely a matter of personal preference. We have used all three procedures during the last seven years. The majority of our patients have, however, been investigated by selective renal arteriography, mainly because this gives the best visualization of the peripheral renal vessels and of the kidney itself, and will, as shown in the illustrations (Figs. 2, 6, and 8, Special Plate), demonstrate renal-artery stenosis very adequately. The two other techniques are less difficult and will usually show a stenosis equally well (Fig. 9, Special Plate, Case 15).

Selective Renal Arteriography: Method

The procedure adopted is a personal modification by one of us (D.S.) of the technique described by Ödman (1956). An opaque catheter, premoulded with an appropriate curve at its tip, is inserted percutaneously from the femoral artery and passed into the mouth of the renal artery under screen control. Ödman uses a different catheter for each side; this involves withdrawing one catheter after use and replacing it by another. We have simplified the procedure by shaping a catheter in such a way that it can be inserted into either renal artery, and both sides can thus be injected with a single catheter. It has been found helpful to have side holes near the catheter tip so that the lumen of the aorta and the proximal part of the renal artery are also shown on the film. One of the alleged difficulties of selective renal arteriography is the presence of double renal arteries. This has not been found to present any particular difficulty in our cases, and we have frequently catheterized both arteries in these instances. A free injection of dye into the aortic lumen may, if necessary, be made before withdrawing. With the selective method

excellent renal arteriograms are regularly achieved, using small doses of diatrizoate (5 ml. of "hypaque" 45% or "urografin" 60%).

We have encountered one patient (Case 14) in whom a diagnosis of renal artery stenosis was suggested wrongly by selective renal arteriography (Fig. 4, Special Plate). In this man the catheter tip virtually occluded the lumen of the artery supplying a small, irregular, and probably pyelonephritic kidney. The film taken at injection also demonstrated an apparent renal-artery stricture. Organic stenosis was not confirmed by ureteric catheterization studies (Table IX), by pressure measurements at operation, or by subsequent examination of the artery after nephrectomy, and it was presumed that the appearance was due to a jet effect as the contrast left the catheter tip. In several other cases where a small artery was virtually occluded, however, no such appearance was produced.

It must be stressed that all these angiographic techniques have their hazards, particularly in the presence of hypertension, with or without impaired renal function. None of them is to be undertaken lightly or by the inexperienced.

Operative Findings and Treatment

Presence of a Bruit in the Affected Renal Artery.—This almost constant finding was mentioned earlier.

Direct Measurement of the Renal-artery Pressure

It is essential to measure, by direct arterial puncture at operation, the pressure in the renal artery distal to the stenosis. Normally, the pressure in the main renal artery is almost identical with the pressure in the adjacent aorta, and, unless a distinct pressure-drop across the site of the supposed obstruction is found, the diagnosis of a truly functional renal-artery stenosis should be strongly queried, whatever the arteriographic appearances suggest. We have seen four patients (Cases 5, 12, 14, and 17) in whom renal artery stenosis was diagnosed on arteriography (Figs. 3 and 4, Special Plate), but in whom there was no pressure-drop or alteration in the pulse wave distal to the site of the supposed narrowing. In two of these (Cases 5 and 14), ureteric catheterization studies had been performed and, as we have described above, had given results which were not typical of renal-artery stenosis.

Case 17 provided several problems. In this patient a left-renal-artery stenosis was suggested by a denser pyelogram on the left, and free aortography demonstrated a stricture near the origin of the left renal artery. Ureteric catheterization studies showed, during the course of the test, urinary sodium and chloride concentrations, which in some periods were higher on the suspect side than on the right. The inulin and P.A.H. concentrations, however, were persistently higher on the left. At operation the renal-artery narrowing was confirmed, though no pressure-drop was found across the stricture. Biopsy of the left kidney showed atrophy of proximal convoluted tubules and sclerosis of a majority of glomeruli, but few vascular changes—appearances typically found distal to a renal artery stenosis. It is possible that in this patient structural damage in the kidney consequent upon main renal-artery obstruction was occluding the renal vascular bed and secondarily maintaining a high pressure in the renal artery distal to the stenosis. DeCamp and Birchall

LEGENDS TO SPECIAL PLATE

FIG. 7.—Intravenous pyelogram with water-loading in Case 3 20 minutes after the injection of the dye. No contrast is seen on the normal side, though the side with the renal-artery stenosis is clearly demonstrated.

FIG. 8.—Selective renal arteriogram in Case 1, showing stenosis at origin of right renal artery, with post-stenotic dilatation.

FIG. 9.—Aortogram in Case 15, showing lower aortic occlusion and right-renal-artery stenosis.

FIG. 10.—Biopsy from upper pole of Case 2 (first operation), showing tubular atrophy.

FIG. 11.—Case 2. (a) Photograph of left fundus before nephrectomy. Papilloedema, haemorrhages, and gross exudate. B.P. 260/160. (b) Photograph of left fundus five months after left nephrectomy. Fundus almost clear. B.P. 150/90. (c) Right fundus before nephrectomy. (d) Right fundus after nephrectomy.

(1958) have recommended that if there is no pressure-drop across the site of the presumed stricture, renal-artery surgery should not be performed. We are not fully convinced that such a finding necessarily excludes significant renal-artery stenosis. Patients of the type discussed above merit further study.

It is, of course, essential to check the pressure in the artery distal to the site of the previous obstruction at the completion of a reconstructive operation. The procedure cannot be regarded as successful unless the pressure in the renal artery has been restored to the level of the adjacent aortic pressure. Figs. B and C show the pressure tracing obtained at operation in Case 3. Before reconstruction, no pressure was recordable in the main renal artery distal to the stenosis. This is probably the result of the lowering of the systemic arterial pressure by anaesthesia to well under the levels normally prevailing (the aortic pressure is around 115/80 in the record; pre-operatively the blood-pressure was of the order of 230/140). Distortion of the renal pedicle by traction might readily collapse the distal renal artery in these circumstances. After thromboendarterectomy and spleno-renal anastomosis, the pressures in the aorta and main renal artery were practically identical (Fig. C). This phenomenon of unrecordable pressure in the renal artery at operation was seen also in Case 1. The point is of some importance, since under operative conditions

the kidney distal to a renal-artery stenosis may be acutely ischaemic for a good deal longer than is represented by the time during which the renal artery is actually clamped. Acute tubular damage may, of course, occur in the operated kidney and persist for several days (Peart, 1959). Undue lowering of the blood-pressure during the operation should therefore be avoided. Further measures designed to protect the kidney, such as whole-body hypothermia or local renal cooling (Birkeland *et al.*, 1959), will probably be more widely employed in future.

Surgical Procedures

Surgical procedures have been described by Poutasse (1956), DeCamp and Birchall (1958), Owen (1959, 1960), and Yendt *et al.* (1960).

In most patients a reconstructive operation is desirable, since the kidney distal to the stenosis is potentially the better of the two, being protected from hypertensive damage by the stenosis. We are still uncertain of the extent of damage which is reversible, and it is important to preserve functioning renal tissue so far as is possible. The basis of conservative procedures is to restore adequate arterial pressure and blood-flow to the kidney with the minimum of acute interference with its blood supply at operation. Interruption of the blood-flow to the opposite kidney is avoided so far as is possible.

Thromboendarterectomy.—The removal of an atheromatous plaque from the renal artery, together with any thickened intima at the origin of the vessel, is a relatively quick procedure, though it may occasionally be difficult to gain access to the origin of the artery on the right side because of the close relationship of the vena cava and renal vein.

Spleno-renal Anastomosis.—The splenic artery is of comparable size to the renal and is usually long enough to be anastomosed to the distal renal artery on the left. It is not always necessary to remove the spleen in this operation, since it may be nourished by the short gastric arteries.

Renal Artery Reimplantation.—The renal artery may be divided and anastomosed to a new site in the aorta. Alternatively, side-to-side anastomosis of the renal artery to the aorta may be performed below the level of the stenosis.

Excision of Stricture.—The usual site of an atheromatous plaque is at the mouth of the renal artery. Occasionally, however, renal-artery stenosis occurs as a result of fibromuscular proliferation of the media, the origin of the artery being spared. In this event the stricture may be excised and end-to-end anastomosis performed.

By-pass Grafting.—A by-pass graft may be inserted from the aorta to the distal renal artery.

Nephrectomy.—This operation is indicated in cases of complete occlusion of the renal artery. Nephrectomy may also be the operation of choice in patients in poor general condition, provided adequate function has been demonstrated in the opposite kidney.

Results of Surgical Treatment

There were no operative deaths in the series. Nephrectomy or reconstructive surgery was performed in six cases (Nos. 1, 2, 3, 4, 11, and 19) in which a diagnosis of renal-artery stenosis was established beyond reasonable doubt. The hypertension was of a severe order in

FIG. B.—Case 3. Pressure tracings obtained at operation, before reconstruction. Upper tracing, aortic pressure; lower tracing, left-renal-artery pressure.

FIG. C.—Case 3. Pressure tracings obtained at operation, after reconstruction. Simultaneous aortic and left-renal-artery pressures.

all six cases, and in three (Nos. 1, 2, and 19) the optic fundi showed bilateral papilloedema, exudates, and haemorrhages. Exudates and haemorrhages, but without papilloedema, were present in Cases 3 and 11. Surgical treatment was followed in all of these patients except one (Case 4) by a fall in the blood-pressure to normal levels, with resolution of the retinal abnormalities (see Fig. 11, Special Plate, and Robertson, 1960). Cardiac size was reduced and there was disappearance of electrocardiographic signs of left ventricular strain. In no instance was there clinical or electrocardiographic evidence of myocardial infarction which might be held responsible for the fall in blood-pressure. This last point is important, since renal-artery stenosis occurs in a group of patients particularly prone to ischaemic heart disease.

Three earlier cases (Nos. 6, 10, and 20) were operated upon after less adequate investigation, the diagnosis of renal-artery stenosis responsible for the hypertension consequently being less surely established. In only one of these three (Case 20) was surgery successful in lowering the blood-pressure.

One further patient (Case 17) had a normal blood-pressure at the time of writing, but this case was operated upon too recently for proper assessment.

Medical Treatment

For various reasons, seven cases of the series have been treated with hypotensive drugs. Cases 8 and 13 were not operated upon, since no lesion was demonstrated radiologically. In Case 9 reconstructive surgery was not possible, and medical treatment was here regarded as preferable to nephrectomy. In Cases 4, 6, and 10 surgical treatment was not followed by a fall in blood-pressure, and these cases have since been controlled medically. In Case 2 thromboendarterectomy was unsuccessful, thrombosis of the renal artery occurring a few days after operation. Subsequent medical treatment was ineffective, and the blood-pressure remained high until nephrectomy was performed.

Though less satisfactory than successful surgical therapy, hypotensive drugs can be useful in the treatment of hypertension due to renal artery stenosis.

Renal Histology

Renal biopsy has been performed routinely at operation, specimens being taken in each case from kidney tissue distal to a stenosis and, wherever possible, either from the opposite kidney or from an unaffected segment of the same kidney. For convenience the biopsies have been taken from the subcapsular region; examination of the whole kidney in those cases where nephrectomy has been performed suggests that the subcapsular zone is the part likely to be most affected by an ischaemic process. The specimens are not, therefore, necessarily representative of the overall renal histology.

Kidney Distal to the Stenosis

Vascular changes have rarely been seen distal to a renal-artery stenosis, suggesting that the lesion protects the vessels from the effects of the raised blood-pressure.

The most constant and most striking change has been tubular damage, though the severity of this has varied widely from case to case. The proximal convoluted tubules have been most severely affected and showed some change in almost every instance. Moderately

severe changes are shown in Fig. 10 (Special Plate), this biopsy being taken from the upper pole of the kidney of Case 2.

The glomeruli have seemed less sensitive to ischaemia, and showed little or no histological abnormality in the cases where tubular damage was slight. In the more severely affected cases, however, various lesions have been found in and around the glomeruli, such as thickening of the capillary basement membrane (Cases 1 and 2), fibrosis of Bowman's capsule (Cases 4 and 9), and more or less widespread glomerular sclerosis (Cases 6, 9, 11, and 17).

In the most severely affected areas of the ischaemic kidney, interstitial fibrosis and lymphocytic infiltration have been found.

In Case 19, with complete occlusion of the renal artery, coarse scarring and fibrosis were present, with numerous infarcts and a few remaining areas of normal tissue.

The histology in the three cases in which no pressure-drop was found across the site of an apparent stenosis is of particular interest. Cases 12 and 17 showed tubular atrophy and glomerular sclerosis, appearances which could well result from ischaemia. Case 5 showed extensive tubular atrophy and some sclerotic glomeruli, but also hyalinization of arterioles and thickening of small arteries. The position here was complicated by the presence of a hydronephrosis.

It is interesting that we have not encountered fibrinoid renal arteriolar necrosis in any proved cases of renal artery stenosis on either side, even where gross hypertensive retinopathy has been present, though in Case 10 fibrinoid necroses were found in the kidney distal to the supposed lesion. In this woman the diagnosis rested solely upon the arteriographic appearances, and we would now regard the case as quite inadequately investigated. The ureteric catheterization studies were unsatisfactory, and renal-artery pressures were not measured at operation. Reconstruction of the renal artery was performed, but the blood-pressure remained high, and has since been controlled with hypotensive drugs. The significance of the renal histology is therefore uncertain.

Opposite Kidney

In contrast to the ischaemic kidney, vascular changes have been prominent on this side. Arteries of all sizes have shown intimal thickening and fibrosis, with elastic hyperplasia and medial hypertrophy. Hyalinization of small arteries and arterioles has been seen frequently. As in the ischaemic kidney, glomerular sclerosis, interstitial fibrosis, and round-cell infiltration have been common. However, the tubules have usually been healthy in appearance on this side, though occasional small areas of tubular atrophy have been found.

The renal histology seen in these cases is in general agreement with the findings in experimental hypertension produced in animals by clamping the renal artery. The closest similarity appears to be with the changes occurring in the kidneys of the rat, this animal most closely resembling man in that severe and persistent hypertension may follow the placing of a clip on one renal artery, the other kidney and renal artery remaining untouched (Wilson and Byrom, 1939). The dog and the rabbit differ from man and the rat in that persistent hypertension is produced usually only if both renal arteries are clamped, or if one renal artery is clamped

and the opposite kidney removed. For the dog, similar changes to those found in man and the rat distal to the renal artery stenosis have been described by Goldblatt *et al.* (1934) and by Child (1938). In the rabbit, in experiments where clips have been applied to both renal arteries, one kidney has usually been found to show extensive tubular atrophy with or without glomerular changes, while the other kidney has shown little or no histological abnormality. Where the rabbit has had one kidney removed and a clip applied to the opposite renal artery, little histological change has been found in the remaining kidney even when severe hypertension has developed (Wilson and Pickering, 1938). There is general agreement for all species that vascular lesions are uncommon distal to a renal-artery clamp.

Discussion

Earlier reports (Poutasse, 1956; Birchall *et al.*, 1958) suggested that the investigation of possible renal-artery lesions might be restricted to certain well-defined groups of patients. Subsequently it has become apparent that renal-artery stenosis is by no means restricted to these groups, and our present experience indicates that renal-artery stenosis should be considered in any patient whose hypertension is otherwise unexplained. As we have pointed out, however, certain historical features may be strongly suggestive of a renal-artery lesion.

There is no short cut to the selection of patients who will be improved by surgery, and, since many aspects of this condition remain obscure, full investigation on the lines indicated here is advisable before an operation is carried out.

No case should be subjected to surgery unless there are definite indications for this. Many of these patients have widespread arterial disease and are unfit to withstand a prolonged operation. Nephrectomy is occasionally advisable, but more often the affected kidney is potentially the better one, and must be preserved if at all possible. A reconstructive operation requires the services of an experienced vascular surgeon, together with measures designed to minimize acute ischaemic changes in the kidney at operation. We are firmly of the opinion that facilities for the measurement of renal-artery pressures at operation are essential to the success of reconstructive procedures.

Renal-artery stenosis as a cause of severe hypertension provides a condition where appropriate surgery may be most rewarding, and there is little doubt that many of these cases have previously passed unrecognized.

The mechanism of the raised blood-pressure in this syndrome remains to be elucidated.

Summary

The presenting symptoms are not necessarily helpful in the diagnosis of renal-artery stenosis.

A systolic bruit over the affected artery is frequently present.

Critical evaluation of the intravenous pyelogram may be of great help. On the side with the stenosis there will often be seen better contrast, but with evidence of reduced urine-flow. The affected kidney may also be smaller than its fellow. In a minority of cases an impaired pyelogram is found on the side with the lesion.

No single investigation permits the diagnosis of renal artery stenosis as a cause of hypertension. Ureteric catheterization studies and renal arteriography are the

most valuable investigations, and must be regarded as complementary rather than rival.

Direct arterial pressure measurement should always be made at operation, and a satisfactory reconstructive result checked by further measurement at the completion of the procedure.

We thank the various physicians and surgeons who have referred cases to us, and particularly Professor C. G. Rob. We are also grateful to Drs. N. Coghill, J. C. L. Adams, and M. J. D. Newman for permission to quote from the early records of Case 19. For the histological interpretations we are indebted to Dr. R. H. Heptinstall. Technical assistance has been given by Messrs. F. Diggins, A. Taylor, P. Harris, and D. Pullen, Misses G. Stean, D. Ross, R. Statham, and M. Tooley, and Mrs. N. N. Mendelson. Dr. Peter Hansell kindly provided the fundus photographs.

REFERENCES

- Adams, J. C. L., and Newman, M. J. D. (1958). *Brit. med. J.*, **1**, 562.
 Birchall, R., Batson, H. M., and Moore, C. B. (1958). *Amer. Heart J.*, **56**, 616.
 Birkeland, S., Vogt, A., Krog, J., and Semb, C. (1959). *J. appl. Physiol.*, **14**, 227.
 Bourne, W. A. (1954). *Brit. med. J.*, **2**, 271.
 Child, C. G. (1938). *J. exp. Med.*, **67**, 521.
 Connor, T. B., Berthrong, M., Thomas, W. C., and Howard, J. E. (1957). *Bull. Johns Hopk. Hosp.*, **100**, 241.
 — Thomas, W. C., Haddock, L., and Howard, J. E. (1960). *Ann. intern. Med.*, **52**, 544.
 DeCamp, P. T., and Birchall, R. (1958). *Surgery*, **43**, 134.
 Deming, Q. B. (1954). *A.M.A. Arch. intern. Med.*, **93**, 197.
 Dollery, C. T., Shackman, R., and Shillingford, J. (1959). *Brit. med. J.*, **2**, 1367.
 Dustan, H. P., Page, I. H., and Poutasse, E. F. (1959). *New Engl. J. Med.*, **261**, 647.
 Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W. (1934). *J. exp. Med.*, **59**, 347.
 Hodson, C. J. (1957). *Proc. roy. Soc. Med.*, **50**, 539.
 Houghton, B. J., and Pears, M. A. (1957). *Brit. med. J.*, **1**, 622.
 Howard, J. E., Berthrong, M., Gould, D. M., and Yendt, E. R. (1954). *Bull. Johns Hopk. Hosp.*, **94**, 51.
 Levinsky, N. G., and Berliner, R. W. (1959). *Amer. J. Physiol.*, **196**, 549.
 McChesney, E. W., and Hoppe, J. O. (1957). *Amer. J. Roentgenol.*, **78**, 137.
 Margolin, E. G., Merrill, J. P., and Harrison, J. H. (1957). *New Engl. J. Med.*, **256**, 581.
 Moëll, H. (1956). *Acta radiol. (Stockh.)*, **46**, 640.
 Mueller, C. B., Surtshin, A., Carlin, M. R., and White, H. L. (1951). *Amer. J. Physiol.*, **165**, 411.
 Ödman, P. (1956). *Acta radiol. (Stockh.)*, **45**, 1.
 Øster, J. (1947). *Acta med. scand.*, **128**, 42.
 Owen, K. (1959). *Postgrad. med. J.*, **35**, 645.
 — (1960). *Proc. roy. Soc. Med.*, **53**, 32.
 Page, I. H., Dustan, H. P., and Poutasse, E. F. (1959). *Ann. intern. Med.*, **51**, 196.
 Peart, W. S. (1959). *Brit. med. J.*, **2**, 1353.
 Porporis, A. A., Elliott, G. V., Fischer, G. L., and Mueller, C. B. (1954). *Amer. J. Roentgenol.*, **72**, 995.
 Poutasse, E. F. (1956). *Circulation*, **13**, 37.
 Prinzmetal, M., Hiatt, N., and Tragerman, L. J. (1942). *J. Amer. med. Ass.*, **118**, 44.
 Robertson, J. I. S. (1960). *Proc. roy. Soc. Med.*, **53**, 375.
 Seldinger, S. I. (1953). *Acta Radiol. (Stockh.)*, **39**, 368.
 Squire, L. F., and Schlegel, J. U. (1959). *Radiology*, **73**, 849.
 Starer, F., and Sutton, D. (1958). *Brit. med. J.*, **1**, 1255.
 Wilson, C., and Byrom, F. B. (1939). *Lancet*, **1**, 136.
 — and Pickering, G. W. (1938). *Clin. Sci.*, **3**, 343.
 Yendt, E. R., Kerr, W. K., Wilson, D. R., and Jaworski, Z. F. (1960). *Amer. J. Med.*, **28**, 169.

The Government is to review the *Antioxidant in Food Regulations, 1958*, and the *Antioxidant in Food (Scotland) Regulations, 1958*, considering in particular the kinds of antioxidants to be permitted, the foods in which they may be used, the maximum allowance for permitted antioxidants, and labelling requirements. Representations on these points should be addressed to the Assistant Secretary, Food Standards Division, Ministry of Agriculture, Fisheries and Food, Great Westminster House, Horseferry Road, London, S.W.1, or to the Secretary, Department of Health for Scotland, St. Andrew's House, Edinburgh, 1, and should arrive by December 31. Details may also be obtained from these two addresses.