G. P. T. BARCLAY *ET AL.*: ABNORMAL HAEMOGLOBINS
IN ZAMBIAJ. N. FERGUS *ET AL.*: KIDNEY FUNCTION AFTER
RENAL ARTERIAL EMBOLISM

FIG. 1.—Haemoglobin H disease (left) in an adult, and an infant's haemolysate with Haemoglobin Bart's (right) in members of the Bemba tribe, Zambia. (Paper electrophoresis at pH 8.9.)

FIG. 2.—Haemoglobin Zambia. Left: control. Right: note that Hb A₂ is decreased. The abnormal α_2 (Zambia) δ_2 runs by this method with Hb A. (Paper electrophoresis at pH 8.9.)

FIG. 3.—“Fingerprint” (peptide chromatogram) of Haemoglobin Zambia. The abnormal peptide stains yellow-brown with ninhydrin, indicating N-terminal glycine. For other details see text.

FIG. 1.—Case 1. Note underfilling of small peripheral branches supplying middle and upper pole of right kidney. Main renal artery appears normal.

FIG. 2.—Case 1. There is a translucent band in subcapsular region of middle and upper pole of right kidney.

FIG. 3.—Case 7. There is adherent thrombus in proximal part of left main renal artery with more recent non-adherent thrombus more distally. Arteries supplying mid-portion of kidney distal to thrombus are diminished and of small size. Ventral branch of main renal artery, though containing some fresh thrombus, is patent. A dorsal branch to upper pole is also patent.

Seven per cent. of the patients with liver metastases had a nonhomogeneous scan pattern similar to that seen in cirrhosis. Hence in noncirrhotic patients suspected of hepatic metastases the presence of even a nonhomogeneous pattern should arouse suspicion of malignancy. Similarly, since metastases to a cirrhotic liver are very rare (only 2% in our necropsy series), the diagnosis of metastasis in patients with known cirrhosis should be made cautiously even when there are focal defects. In rare instances the radioactivity distribution pattern may be entirely normal (10%). Because of the incidence of false-negative and false-positive liver scans, we believe that biopsy should be performed as the next step to the scanning procedure for confirmation of the diagnosis after proper selection of the biopsy site from the scanning image.

In the necropsy group hepatomegaly was present in only 46% of patients with metastatic liver disease, which strongly suggests the possible value of a liver scan in every patient with a known primary cancer, even in the absence of liver enlargement. In 36% of the patients with metastatic lesions larger than 2 cm. in diameter the liver was normal in size. In 45% of the entire 104 patients with liver metastases in the necropsy group metastasis to the liver was not suspected during life. This is consistent with the hypothesis that many cases of metastatic liver disease are missed because suspicion is not aroused in the absence of hepatic enlargement. Fruitless surgery can at times be avoided and the prognosis more accurately assessed if the presence or absence of metastases is established.

The presence of splenomegaly has been reported as a rare occurrence in metastatic liver disease (*New England Journal of Medicine*, 1968). In our necropsy series 29% of patients had an enlarged spleen. The discrepancy, however, regarding the incidence of splenomegaly in patients with liver metastasis in the scan group (7%) and the necropsy group (29%) had two possible explanations. Firstly, it is recognized that even with

an enlarged spleen the anterior view may fail to detect the enlargement, and in these cases the posterior and left lateral views are necessary. Secondly, splenic enlargement may be a late manifestation of metastatic disease of the liver. Fenster and Klatskin (1961) reported a 33% incidence of splenomegaly in patients with hepatic metastases. The mechanism of splenic enlargement is thought to be secondary to portal hypertension or metastasis to the spleen. Splenomegaly without parenchymal metastasis occurred in 26% of our necropsy series. Pancreatic carcinoma most commonly produces splenomegaly by pressure or occlusion of the portal or splenic vein from direct extension of the tumour. In our necropsy series there was enlargement of the spleen in five of nine cases with carcinoma of the pancreas. All were due to splenic congestion. Although metastases to the spleen were found in 19 cases from the necropsy series, in only three could the splenomegaly be attributed to splenic metastases.

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Kidney Function after Renal Arterial Embolism

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[WITH SPECIAL PLATE]

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Summary: Seven patients with atrial fibrillation had acute unilateral renal pain associated with suppression of function in the affected kidney. This was ascribed to renal embolism. Arteriography performed in four patients showed abnormalities in the renal arterial tree in three, though thrombus in a main artery was present in only one.

Considerable function returned spontaneously to the affected kidney in six patients as judged by intravenous pyelography or renography. In two patients the sole functioning kidney was affected, leading to acute oliguric renal failure, but renal function recovered in each case. The routine use of anticoagulants in persistent atrial fibrillation is justified by such cases.

Introduction

Successful renal arterial embolectomy has been reported in patients operated on soon after the embolus had occurred

(Duncan and Dexter, 1962; Brest *et al.*, 1964; Smithwick *et al.*, 1964; Erskine and Blaisdell, 1965; Loomis *et al.*, 1966; Halpern, 1967; Goldsmith *et al.*, 1968). Improvement in renal function after embolectomy delayed for several weeks has also been reported (Perkins *et al.*, 1967; Peterson and McDonald, 1968), but it is generally believed that renal function is unlikely to return after major embolism without early surgical intervention. Thus kidney function returned in only 2 out of 18 cases of renal embolism reported by Goldsmith *et al.* (1968) and in 4 out of 20 cases described by Regan and Crabtree (1948). As renal emboli usually occur in patients with heart disease, in whom surgery is likely to be hazardous, it is particularly desirable that a decision to undertake renal arterial embolectomy should be based on a knowledge of the likely consequences of non-intervention. Yet observations on the course of renal embolism studied after early diagnosis are comparatively few, presumably because correct antemortem diagnosis of renal infarction appears to be rare. Thus the diagnosis had been made in life in only 1 of the 143 cases studied at necropsy by Barney and Mintz (1933) and in only 2 of the 205 cases reported by Hoxie and Coggin (1940).

The present report describes the course of seven cases in which renal embolism was associated with suppression of kidney

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function. Considerable recovery of renal function occurred in six of them.

Case 1

A 61-year-old woman was admitted to hospital after 48 hours of severe abdominal pain, which started centrally but later moved to the right loin and was associated with vomiting and a frequent urge to defaecate. The right loin and subcostal region were tender. Signs of mitral stenosis and incompetence with atrial fibrillation were noted, but there was no evidence of cardiac failure. Proteinuria and microscopical haematuria were present initially but disappeared within two days. The blood urea was 46 mg./100 ml.

Function of the right kidney was grossly impaired as judged both by pyelography and by hippuran renography. Retrograde pyelography showed no abnormality of the right renal tract. Seven days after the onset of symptoms aortography showed no abnormality in the main right renal artery, but filling of the smaller peripheral arteries to the middle and upper pole of the kidney (Special Plate, Fig. 1) was diminished and on the nephrogram phase there was a translucent band in the cortex in the same area (Special Plate, Fig. 2).

The pain went within a few days, but on the 15th day after admission another embolus impacted at the aortic bifurcation, for which embolectomy was successfully performed. On the 23rd hospital day intravenous pyelography (I.V.P.) showed some excretion of the dye by the right kidney, but the length of this organ had decreased from 11 to 9.5 cm. I.V.P. 34 weeks later showed equal dye concentration by the two kidneys with no further contraction of the right kidney. Hippuran renography initially showed gross impairment of function in the right kidney, but considerable function had returned by the 18th day after admission, and a normal renogram was obtained two months later (Fig. 1).

FIG. 1.—Case 1. Hippuran renography: A, on admission; B, two months later.

Case 2

Severe left-sided abdominal pain with vomiting developed suddenly in a 48-year-old woman known to have mitral stenosis and atrial fibrillation. When admitted to hospital 12 hours later the left flank was tender and proteinuria and microscopical haematuria were noted.

I.V.P. showed no evidence of function by the left kidney, which was 10 cm. long. Retrograde pyelography showed a normal left renal tract. Aortography on the second day in hospital showed no abnormality of the left renal artery or its major divisions, but filling of the peripheral arteries was delayed and they were of small size. Hippuran renography on the 14th hospital day revealed severely impaired function by the left kidney.

Anticoagulant therapy was started after the aortogram, and the pain subsided after a few days. Mitral valvotomy was performed four months later. I.V.P.s 18 and 50 weeks after the embolus showed a return of function to the left kidney, but concentration

of the dye by this kidney was not as good as by the right. On the last pyelogram the right and left kidneys measured 10.5 and 7.5 cm. respectively in length. Hippuran renograms 28 and 50 weeks after the embolus showed slight improvement in the function of the left kidney.

Case 3

A woman aged 57 was admitted to hospital with left-sided abdominal pain and vomiting for three days. Five days previously D.C. cardioversion had been performed successfully for atrial fibrillation of unknown cause. One year previously the right kidney had been removed because of multiple calculi.

On admission atrial fibrillation was noted, but there were no other cardiac abnormalities. The left side of the abdomen and loin were tender. A trace of protein was found in the urine but microscopy was normal. The patient was oliguric for four or five days and the blood urea rose to 176 mg./100 ml. on the third hospital day, having varied from 36 to 55 mg./100 ml. over the previous year.

I.V.P. showed no evidence of function by the (solitary) left kidney, the size of which was within normal limits. Hippuran renography showed gross reduction in the function of this kidney, which had given a normal renogram pattern one year previously, before the right nephrectomy.

The pain subsided after three days and renal function improved spontaneously, the blood urea falling to 46 mg./100 ml. within four weeks. Nineteen months later both I.V.P. and renogram showed normal function by the left kidney.

Case 4

A 43-year-old woman with mitral valvular disease was awaiting surgery when she developed severe left loin pain. Atrial fibrillation was present but there were no signs of heart failure. The left loin was very tender and proteinuria and microscopical haematuria were noted. Oliguric renal failure now developed, the patient passing only 65 ml. of urine in the first 24 hours after onset of the pain (Fig. II). Seven years previously I.V.P. had shown no evidence of function by the right kidney, the appearances of which suggested tuberculous disease.

FIG. II.—Case 4. Blood urea and urine volume after renal embolism in the only functioning kidney.

I.V.P. performed within 24 hours of the onset of pain revealed no evidence of function by either kidney, but cystoscopy and left retrograde pyelography showed no abnormality. Arteriography was not performed, as a previous cardiac catheterization had produced a femoral arteriovenous fistula needing surgical correction. Hippuran renograms obtained two and five days after onset of this pain showed grossly impaired function by the left kidney, which did not differ in this respect from the long-diseased right kidney.

Anticoagulant treatment was given and renal function slowly improved (Fig. II). The blood urea rose from 48 mg. to a peak of 209 mg./100 ml., but then fell. Blood urea levels of 69, 52, and 45 mg./100 ml. were recorded 6 weeks, 10 months, and 13 months later respectively. A renogram on the 11th day after onset of the pain showed a slight improvement in the function of the left kidney; improvement was more pronounced three months later, and an entirely normal renogram was obtained from the left kidney 13 months after the embolism.

Case 5

A woman aged 37 was admitted to hospital with a left hemiplegia of sudden onset. This was attributed to a cerebral embolus associated with her long-standing mitral stenosis and atrial fibrillation. Urine examination at that time revealed no abnormality. Four days later she experienced severe left loin pain which persisted for 72 hours and was accompanied by vomiting. Proteinuria and microscopical haematuria were now noted. The blood urea was 33 mg./100 ml.

I.V.P. showed no sign of function by the left kidney, which measured 12 cm. in length; the right kidney was normal. Hippuran renography showed gross impairment of function by the left kidney without any evidence of urinary tract obstruction. These findings in the clinical context were thought sufficient to diagnose renal embolism.

Anticoagulant therapy was given and mitral valvotomy was performed two months later. On a second I.V.P. performed 24 days after the first, some concentration of the dye was seen in the left kidney, which now measured 10 cm. in length. Twelve weeks later I.V.P. showed normal concentration of dye by the left kidney, the length of which had now decreased to 8.5 cm.

Case 6

A woman aged 68 with a long history of idiopathic atrial fibrillation was admitted with acute right loin pain and vomiting. Right loin tenderness, macroscopical haematuria, and proteinuria were noted. I.V.P. within 24 hours of admission showed a normal left kidney but no sign of function by the right kidney. Cystoscopy and right retrograde pyelography were normal. Aortography on the eighth day of the illness showed no abnormality of either the main renal artery or its branches.

The pain and haematuria lasted 36 hours and four days respectively. Three months later I.V.P. showed a normal appearance for both kidneys, which did not differ in length.

Case 7

A 43-year-old man entered hospital with a five-day history of left loin pain and vomiting. Twelve years previously he had undergone mitral valvotomy and now had again the signs of mitral stenosis with atrial fibrillation. The left loin was tender, but repeated examinations of the urine failed to detect haematuria.

I.V.P. showed no evidence of function by the left kidney. Hippuran renography revealed gross impairment of function by the left kidney without evidence of urinary tract obstruction. Selective left renal arteriography (Special Plate, Fig. 3) eight days after the pain started delineated thrombus in the main left renal artery, which was adherent over the first 5 mm. of the vessel and loose more distally. The lumen was not completely occluded. Branches to the middle part of the kidney were largely occluded. The ventral branch to the lower pole was patent though containing recent thrombus. A dorsal branch supplying the upper pole was fully patent. Sufficient detail was obtained in the nephrogram phase to show a very patchy pattern of blood distribution suggestive of multiple small peripheral infarcts. Embolectomy was considered inadvisable in view of the extent and partial adherence of the main embolus and the evidence of multiple microemboli in the kidney. The decision against embolectomy was also influenced by the presence of considerable obstructive airways chest disease and pulmonary oedema. Intravenous streptokinase therapy was started, but within 24 hours severe haemoptysis occurred and bleeding started from the arteriogram puncture site. Streptokinase was therefore discontinued.

Eighteen days after the onset of symptoms renography showed no improvement in the function of the left kidney, but five months later it showed definite improvement. The patient then stopped attending the hospital.

Discussion

Each of these patients had a potential source of emboli in atrial fibrillation, and each had painful unilateral suppression of renal function. Urinary tract obstruction and infection were excluded, but it is difficult to rule out with certainty renal venous thrombosis, though none of the factors known to predispose to this condition in adults were present, and the trivial nature of the proteinuria (see Table I) also argues against this diagnosis. Moreover, two of these patients (Cases 1 and 5) had emboli at extrarenal sites within a few days of the presumed renal embolism, while the clinical features of Case 7, in whom thrombus was found in the renal artery, closely resembled those in the other patients.

TABLE I.—Clinical Features of Seven Patients with Renal Embolism

Case No.	Site of Pain	Vomiting	Temp.		W.B.C.s /cu.mm.	Urine		
			°F.	°C.		Culture	Proteinuria	Haematuria (Microscopic)
1	Central abdominal → R. loin	+	102.0	38.9	9,900	No growth	+	+
2	L. abdomen	+	98.8	37.1	13,000	" "	+	+
3	L. abdomen	+	100.2	37.9	16,500	" "	Trace	0
4	L. loin	0	99.4	37.4	16,000	" "	+	+
5	L. loin	+	99.0	37.2	7,500	" "	Trace	+
6	R. loin	+	98.8	37.1	12,300	" "	+	Macroscopic
7	L. loin	+	100.6	38.1	7,600	" "	+	0

The renal arterial tree showed abnormalities in three of the four patients studied by arteriography, though main vessel thrombus was shown only in Case 7. Possibly this failure to demonstrate large emboli resulted from the delay before aortography, which was performed two to eight days after the onset of symptoms. Several reasons for this delay are discernible: the pain was not at first typically renal in two cases; time was needed to exclude ureteric obstruction; finally, there was reluctance on the part of the medical staff to perform aortography in seriously ill cardiac patients. While therefore agreeing with Halpern (1967) and Goldsmith *et al.* (1968) that greater awareness of the syndrome produced by renal embolism may lead to earlier diagnosis, we suspect that the above factors will continue to delay diagnosis in many patients.

No abnormality was seen in the main renal arteries in three of the four arteriograms at a time when there was no evidence of function by the affected kidney. The suppression of function was thus not due to persistence of mechanical block in large arteries and must be ascribed either to multiple peripheral emboli, as suggested by the arteriograms in Cases 1 and 2, or to some other consequence of ischaemia occurring when the embolus originally occurred. It is of interest that the time course of the renal failure occurring when the sole functioning kidney was involved (Cases 3 and 4) was similar to that in typical cases of acute tubular necrosis resulting from renal hypoperfusion in shock. Possibly a large renal embolus produces intense peripheral renal vasoconstriction and initiates a chain of events similar to that caused by severe hypotension.

Whatever the mechanism of the renal failure in these patients it is clear from their subsequent course that neither absence of function, as judged by pyelography or conventional renography, nor the occurrence of oliguric renal failure when the only kidney is involved precludes spontaneous recovery (Table II). The early removal of demonstrable large thrombi in major renal arteries is desirable in good-risk patients, but the renal potential for recovery shown by our cases should be taken into account in deciding treatment for renal embolism in an ill cardiac patient.

when surgery would be hazardous. Even when a main renal arterial thrombus is present some blood may flow around it, as shown in Case 7 (see also Bellman and Odén, 1960), and the work of Morris *et al.* (1955) has underlined the protective value of perfusion at even subfiltration arterial pressures for the survival of renal tissue.

TABLE II.—*Pyelographic, Arteriographic, and Renographic Findings in Seven Patients with Renal Embolism*

Case No.	I.V.P.		Kidney Length	Retrograde Pyelogram	Aortogram	Hippuran Renogram Function	
	Dye Concentration					Initial	Final
	Initial	Final					
1	0	Normal	↓ 1.5 cm.	Normal	↓ Filling of peripheral arteries	0	Normal
2	0	Reduced	↓ 3 cm.	Normal	" "	0	Reduced
3	0	Normal	No change	—	" "	0	Normal
4	0	—	—	Normal	—	0	Normal
5	0	Normal	↓ 3.5 cm.	—	—	0	—
6	0	Normal	No change	Normal	Normal Thrombus in main renal artery	—	—
7	0	—	—	—		0	Reduced

The incidence of hypertension following renal embolism is unknown, but in the cases we describe the arterial pressure did not rise during the period of observation. This varied from 2 to 19 months after embolism, exceeding six months in four patients.

Finally, it should be noted that despite persistent atrial fibrillation none of these patients were receiving anticoagulant therapy. The occurrence of such an episode is a clear indication for anticoagulants, but more general use of anticoagulant

treatment for persistent atrial fibrillation might have prevented the renal and extrarenal emboli which occurred in these patients.

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Effect of Drugs on Urate Binding to Plasma Proteins

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Summary : The effect of various drugs on urate binding to plasma proteins was investigated in normal subjects. Whereas allopurinol, aspirin, phenylbutazone, probenecid, and sulphipyrazone all significantly reduced plasma urate concentrations, only aspirin, phenylbutazone, and probenecid significantly impaired urate binding. Colchicine and indomethacin in the doses administered had no significant effect on plasma urate concentrations or binding. In the case of aspirin, urate binding was reduced to 25% of normal, and this effect was quickly abolished after cessation of therapy. Phenylbutazone reduced urate binding to 56% and probenecid to 46% of normal ; this impairment was still detected four days after cessation of therapy. Drugs may impair urate binding by competition for plasma protein binding sites, with displacement of bound urate. Impairment of urate binding in vivo by administration of certain drugs may be relevant to the precipitation of acute gouty arthritis, to the formation of gouty tophi, and to the augmentation of uricosuria. Furthermore, the role of drugs must be seriously considered during all studies on urate binding in patients with gout.

Introduction

The ability of human plasma proteins to bind uric acid has been demonstrated by means of several techniques (Shinaberger *et al.*, 1964 ; Alvsaker, 1966 ; Sheikh and Møller, 1968). Although the significance of these observations has not been established they may be pertinent to the mechanisms of both the deposition of urate in tissue and the glomerular clearance of urate.

It has been postulated that urate binding to plasma proteins serves a protective role in the prevention of acute gout by increasing the solubility of urate in hyperuricaemic plasma (Alvsaker, 1966). Impaired binding would then facilitate increased urate deposition, with the consequent development of gouty arthritis and tophus formation (Seegmiller and Howell, 1962). Alvsaker (1966) has postulated the deficiency of a specific urate-binding globulin in some patients having primary gout. During experiments designed to characterize the urate-binding properties of human plasma, however, it was noted that salicylate significantly impaired urate binding (Klinenberg, 1968). Since a variety of drugs are used in the treatment of gout, it becomes necessary to test the effects of the drugs themselves on urate binding before postulating any basic defect of binding in this disease.

Furthermore, it has been assumed that uric acid is completely cleared at the renal glomerulus (Yü and Gutman, 1953) ; but if a proportion of plasma urate is protein-bound then renal clearance might not be complete. A possible mode of action

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