Papers and Originals

Renal Function after Acute Tubular Necrosis

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As a result of a revision in the conservative methods of treatment (Bull *et al.*, 1949) and the availability of haemodialysis and peritoneal dialysis survival can now be expected in a substantial proportion of patients with acute tubular necrosis (Teschner *et al.*, 1960; Kennedy *et al.*, 1963). In the fatal cases death is usually due to the initiating illness, overwhelming infection, or a complication of uraemia such as uncontrolled hyperkalaemia or haemorrhage, and rarely to irreversibility of the renal lesion.

Recently the accuracy of the term "acute tubular necrosis" has been challenged (Sevitt, 1959; Finckh *et al.*, 1962) and alternatives such as acute reversible intrinsic renal failure have been suggested (Luke and Kennedy, 1967). However, in view of the common usage and widespread understanding of the meaning of the term acute tubular necrosis, it will be used in this paper.

Although it is widely accepted that the prognosis in general is good in patients who survive an episode of acute tubular necrosis, there remains some doubt about the exact degree to which glomerular and tubular function will ultimately recover. Lowe (1952), in a preliminary report, found in 14 patients followed for periods varying from 7 to 38 months that renal function tests tended to remain below normal limits, and these findings were largely confirmed by Finkenstaedt and Merrill (1956) in 16 patients followed for 3 to 76 months, though their patients had normal tubular function in spite of a diminished glomerular filtration rate. Edwards (1959), however, reported a return to normal of the rate in 14 out of 15 patients within three months.

The present paper describes the degree of recovery of various aspects of renal function after acute tubular necrosis in 50 patients studied on average at 35 months after the episode of renal failure.

Methods and Material

Fifty patients were studied, 22 male and 28 female, all of whom had a previous well-documented episode of acute tubular necrosis. A total of 138 patients with acute tubular necrosis were admitted to the artificial kidney unit of Glasgow Royal Infirmary during the period February 1960 to June 1965, and the 50 patients in the present study were selected from the 88 survivors. The only method of selection was on the grounds of availability and knowledge of their whereabouts: there is no reason to suspect that these do not form a represen-

tative sample of the patients recovering during this period. The ages of the patients at the time of development of the acute tubular necrosis ranged from 18 to 67 years, with a mean of 38 years. The diagnosis of acute tubular necrosis was made on the grounds of the clinical presentation, course of the illness (Loughbridge *et al.*, 1960), and biochemical investigations: the ratio of urine urea to blood urea fell at some stage in the illness to less than 4:1 in all patients.

The aetiology of the acute tubular necrosis is shown in Table I. The patients were subdivided in the conventional manner into medical, surgical, and obstetric groups. The commonest precipitating factors were abortion, antepartum haemorrhage, surgery, multiple injuries, and ingestion of nephrotoxins, these together accounting for 68% of the entire series.

TABLE I.—*Aetiology of the Acute Tubular Necrosis*

Medical (12)	Surgical (17)	Obstetric (21)
Nephrotoxins (4)	Postoperative (7)	Abortion (11)*
Intravascular haemolysis (2)	Multiple injuries (5)	Antepartum haemorrhage (7)*
Pneumonia	Cholecystitis (2)	Postpartum haemorrhage (3)*
Anticoagulant bleeding	Burns + intravascular haemolysis	
Salmonella enteritis	Intestinal obstruction	
Carbon monoxide poisoning	Perforated duodenal ulcer	
Respiratory failure		
Staphylococcal septicaemia		

* Following pre-eclampsia in 9 out of 10 cases.

Number of patients in each group shown in parentheses.

All grades of severity of renal failure were encountered. This was assessed in two ways—by the duration of oliguria (urine volume of less than 600 ml. per 24 hours) and by the number of dialyses performed. Forty-four of the 50 patients were oliguric for periods ranging from 2 to 40 days, with a mean of 11 days; one patient was not oliguric at any stage of the illness; and in the remaining five patients the duration of oliguria was not known. Haemodialysis was required on at least one occasion in 43 patients. The greatest number of dialyses in any one patient was 15: this patient had a severe degree of renal failure after multiple injuries and was oliguric for 40 days. In the remaining seven patients conservative measures only were used.

Evidence of previous urinary tract disease was present in six patients. Three gave a history of recurrent urinary tract infection, two had symptoms suggestive of prostatic enlargement, and one was a mild maturity-onset diabetic, in whose urine a trace of protein had been noted on several occasions. In addition three patients had significant hypertension (diastolic blood pressure of 100 mm. Hg or higher) and nine had pre-eclampsia at the time of onset of the acute tubular necrosis.

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The interval between the episode of acute tubular necrosis and the follow-up study varied from 4 to 75 months, with a mean and standard deviation of 35 ± 19 months, but in only two patients was it less than one year. A less detailed interim follow-up study was also carried out in 14 of the 50 patients. The mean interval between the acute tubular necrosis and the interim study was nine months and between the interim and formal follow-up studies 37 months.

The formal follow-up study consisted of a clinical assessment plus the following investigations: quantitative urine microscopy and culture (McGeachie and Kennedy, 1963), estimation of proteinuria with the biuret method, blood urea and electrolytes, serum creatinine, and measurement of glomerular filtration rate, concentrating power of the kidney, and ability to excrete an acid load. The glomerular filtration rate was estimated by three methods—endogenous creatinine clearance (49 patients), inulin clearance (41 patients), and the clearance of ^{57}Co -labelled vitamin B_{12} (Nelp *et al.*, 1964) (41 patients). Only the results of the inulin and endogenous creatinine clearances are presented here, as the ^{57}Co -labelled vitamin B_{12} clearance was in fairly close agreement with the inulin clearance (Briggs, 1967). Concentrating power was assessed by measurement of urine specific gravity after 24 hours' dehydration and the ability of the kidney to excrete an acid load by the modified acid load test of Wrong and Davies (1959). In the interim follow-up the following studies were made: urine culture, estimation of proteinuria, blood urea, endogenous creatinine clearance, and pitressin test.

Results

At the time of follow-up all the patients were leading active lives and almost all had returned to their former occupation. Few symptoms which had a possible relation with the acute tubular necrosis were elicited. Three patients complained of excessive tiredness, in two of whom the glomerular filtration rate was moderately reduced. Nocturia was present in nine patients but was as common in those with a normal glomerular filtration rate as in those with a reduced rate. Four of the 17 married women under 40 years had one or more successful pregnancies after the acute tubular necrosis.

Blood pressure.—This was measured a few hours after the patient's admission to hospital while resting in bed. In 36 of the 50 patients the diastolic blood pressure was 90 mm. Hg or less. Eight patients had values between 91 and 100 mm. Hg, while in the remaining six the diastolic blood pressure was greater than 100 mm. Hg. Of this last group, two were known to have had hypertension before the acute tubular necrosis, while the remaining four had pre-eclampsia. Three of the eight patients with levels of 91–100 mm. Hg also had pre-eclampsia and one pre-existing hypertension.

Proteinuria and Urine Microscopy.—The urine was protein-free in 34 patients, and in a further 10 less than 1 g. of protein per 24 hours was recorded. The remaining six had 1 to 3 g. of protein per 24 hours: of these, three had pre-eclampsia before the acute tubular necrosis, one had recurrent pyelonephritis, and one had hypertension with impaired renal function. Urine microscopy revealed pyuria in seven patients, four of whom also had significant bacteriuria.

Urinary Infection.—Significant bacteriuria—that is, more than 100,000 organisms per ml. of urine—was present at the time of follow-up in six patients. This compared with the finding of bacteriuria at some stage of the acute tubular necrosis in 23 patients. Of the six patients with positive urine cultures at follow-up, two gave a history of recurrent urinary tract infection extending back beyond the acute tubular necrosis, one had radiological evidence of pyelonephritis with impaired renal function and was thought in retrospect to have long-standing, occult, chronic pyelonephritis, one had previous

pre-eclampsia but no urinary tract symptoms, and in one the urinary infection followed a prostatectomy.

Blood Urea and Serum Creatinine.—The blood urea and serum creatinine values at the time of the follow-up study are plotted in Fig. 1. Taking 40 mg./100 ml. as the upper limit of normal for blood urea, 24 patients had elevated levels, the highest being 95 mg./100 ml.

FIG. 1.—Blood urea and serum creatinine levels.
*Measured in 48 patients.

Glomerular filtration rate.—The glomerular filtration rates measured by endogenous creatinine and inulin clearances are plotted in Fig. 2. Davies and Shock (1950) have recorded inulin clearances in a large series of normal males related to age, and the inulin clearances in the present study were regarded as normal if they fell within one standard deviation of the mean values of Davies and Shock for each decade. Although a series of comparable size to that of Davies and Shock is not available for females, the data of Homer Smith (1951) show the inulin clearance in females to be approximately

FIG. 2.—Glomerular filtration rate measured by endogenous creatinine and inulin clearance. *Measured in 49 patients. + Measured in 41 patients. ○ Within one standard deviation of. ● More than one standard deviation below, the mean inulin clearance values in normal subjects (Davies and Shock, 1950).

93% of that in males. Normal values for females were therefore arbitrarily taken as being 93% of those quoted for different decades in males by Davies and Shock. Again, the results in the present series were regarded as normal if they fell within one standard deviation of the mean. With the above criteria, 12 of the 41 patients (29%) in whom inulin clearances were performed had normal results.

Concentration Test.—Of the 45 patients in whom the concentration test was carried out, 32 (69%) had a value above

1020 after 24 hours' dehydration. A specific gravity between 1016 and 1020 was obtained in six patients (13%), while in the remaining 8 (18%) the value was below 1016.

Modified Acid Load Test.—An inability of the kidney to reduce the urine pH to less than 5.4 was found in 14 (33%) of the 42 patients in whom this test was performed. Thirteen of these 14 patients had pH values of 5.4 to 5.8 and normal urine titratable acidity and ammonia production. In the remaining patient the urine pH was 6.1 with a very high urine ammonia level (101 μ Eq/min.). The serum electrolytes, however, were normal. The aetiology of this patient's acute tubular necrosis was mercuric chloride poisoning. The normal ranges of urine titratable acidity and ammonia production quoted by Wrong and Davies (1959) were 24 and 33 μ Eq/min. respectively. In 10 patients (24%) the titratable acidity was less than 24 μ Eq/min., in six of whom the ammonia production was below 33 μ Eq/min. Eight of these ten patients had other evidence of generalized renal damage such as lowered glomerular filtration rates, impaired concentration tests, and proteinuria.

Intravenous Pyelogram.—A pyelogram satisfactory for detailed analysis was obtained in 40 patients. The average length of the two kidneys was within normal limits—that is, within one standard deviation of the mean value in relation to body height¹—in 35 patients (87%). In three patients the average kidney length was 1 to 2 cm. below the mean, while in the remaining two it was more than 2 cm. below the mean. There was a significant difference ($P < 0.001$) between the mean glomerular filtration rates of the five patients with small kidneys (54 ml./min.) and that of the 35 patients with kidneys of normal size (91 ml./min.). Calcification of the renal cortex was not observed in any patient, while in one patient with a history of recurrent urinary tract infection before the acute tubular necrosis caliceal clubbing was present.

Interim Follow-up.—In the 14 patients who had both an interim and a formal follow-up study, the mean endogenous creatinine clearances were 87 and 94 ml./min. respectively, the difference not being statistically significant ($P > 0.1$). Similarly, there was no significant difference between the mean blood urea values ($P > 0.1$). In four of the 14 patients there was impairment of concentrating power at the interim follow-up with a return to normal concentrating power at the time of the formal follow-up, but this could be partly due to the more powerful stimulus of dehydration compared with that of pitressin. Table II summarizes the results of the investigations carried out during the formal follow-up study.

TABLE II.—Summary of Follow-up Studies

Type of Test	No. of Patients with Normal Results
Blood pressure	36 (72%)
Urine protein	34 (68%)
Urine culture	43 (86%)
Blood urea	26 (52%)
Serum creatinine	32 (of 48) (67%)
G.F.R. (inulin clearance)	12 (of 41) (29%)
Intravenous pyelogram	35 (of 40) (87%)
Concentration test	31 (of 45) (69%)

Discussion

During this study we were impressed with the fact that normal well-being had been restored in almost all patients with a return to their former occupation. In contrast, analysis of the renal function studies showed that in only 13 of 50 patients were all results within strictly normal limits. It is of course likely that in a small number of patients renal function was impaired before the episode of acute tubular necrosis, in par-

ticular in the one diabetic patient, in the three patients with hypertension, and in the nine with pre-eclampsia. In the majority of patients, however, there were no features suggesting pre-existing renal damage, and the impairment of function noted during this study is therefore likely to be a consequence of the episode of acute tubular necrosis.

A reduction in glomerular filtration rate was the commonest abnormality, this being found in 71% of patients. This finding is in agreement with that of Lowe (1952) and of Finkenstaedt and Merrill (1956), who noted a reduction in glomerular filtration rate in the majority of their patients. However, in only seven patients (17%) in the present series was the glomerular filtration rate, measured by the inulin clearance, severely depressed—that is, below 50 ml./min.

Since the reduction in glomerular filtration rate was in most cases not associated with proteinuria, it is likely that it is due to some nephrons being totally non-functioning rather than urine being formed by some partially damaged nephrons. The pathophysiology of acute tubular necrosis is disputed: there is histological evidence that the primary change occurs in the tubules (Oliver *et al.*, 1951) and also evidence against this view (Finckh *et al.*, 1962). Support for the concept that the lesion is not limited to the tubules is provided by the study of De Luna *et al.* (1964), which showed that the pattern of acid excretion during the recovery phase of acute tubular necrosis—namely, a slightly raised urine pH with very low ammonia excretion—is similar to that seen in generalized renal disease (Wrong and Davies, 1959). The finding by Price and Palmer (1960) that the major histological changes in the kidneys after acute tubular necrosis are in the glomeruli lends support to the theory that the primary abnormality in acute tubular necrosis involves the glomeruli. Studies of animal models have supported the concept that the primary change is a marked drop in glomerular filtration rate (Oken *et al.*, 1966), though subsequent tubular obstruction is also an important factor (Jaenike and Schneeberger, 1966). Direct measurement of renal plasma flow has shown a reduction to about 50% of normal in the early stages of acute tubular necrosis (Reubi *et al.*, 1964; Shaldon *et al.*, 1964). Our findings cannot be taken to support either theory of the pathophysiology of acute tubular necrosis, since nephrons will cease functioning if either the glomerular or tubular damage is severe enough. They do, however, support the concept that there are structural changes at least in some nephrons in acute tubular necrosis, rather than simply a functional lesion (Sevitt, 1959; Finckh *et al.*, 1962).

Bull *et al.* (1950) suggested that after reaching a maximum value a few months after the episode of acute tubular necrosis there followed a steady fall in glomerular filtration rate. Also in animal experiments in mice, Fox (1967) has described progressive deterioration in renal function, accompanied by reduction in renal size and interstitial fibrosis, after recovery from ischaemic acute tubular necrosis. Our data, derived from comparison of the creatinine clearances at the interim and detailed follow-up, suggest, however, that following the slow improvement which takes place over the few months after the acute tubular necrosis renal function remains stable.

Although a prolonged oliguric phase is usually associated with a higher initial mortality, there was no relation in this study between the duration of oliguria and the degree of recovery of renal function in those patients who survived the acute phase. The results in the present series were also examined to see if there was any relation between the aetiology of the acute tubular necrosis and the degree of recovery. It was found that where pre-eclampsia had preceded the acute tubular necrosis there was a higher incidence of hypertension, proteinuria, and reduced kidney size than in the complete series, though the mean glomerular filtration rate in the patients with pre-eclampsia was not significantly lower than the mean of all 50 patients. A poorer prognosis in patients with pre-eclampsia during the course of the acute tubular necrosis has also been

¹ These results were calculated by means of the charts of radiographic kidney size prepared by the Department of X-ray Diagnosis, University College Hospital, London, and printed by Kodak Ltd., London.

demonstrated by Smith *et al.* (1965). They found a higher mortality when acute tubular necrosis occurred in late pregnancy than in early pregnancy and a high incidence of pre-eclampsia in the former group.

Hypertension has been noted in a few patients after recovery from acute tubular necrosis (Lowe, 1952; Edwards, 1959; Price and Palmer, 1960). In the present series, of the six patients with diastolic blood pressures of over 100 mm. Hg at the time of follow-up, four had pre-eclampsia and two had pre-existing hypertension. There is therefore no evidence from this study that acute tubular necrosis leads to the development of hypertension.

A high incidence of urinary tract infection during the course of acute tubular necrosis has been recorded in a previous series (Swann and Merrill, 1953) and is confirmed in the present one, significant bacteriuria having been found in 46% of patients. In only six patients, however, was bacteriuria found at the time of follow-up, and in four of these six there was an adequate explanation for the finding (see Results). There is therefore no evidence that acute tubular necrosis *per se* predisposes to the development of persistent or recurrent urinary tract infection.

The finding that one-third of the patients had urine pH values in the range 5.4–5.8 during a modified acid load test is of dubious significance. The patients with low urine ammonia levels and reduced titratable acidity had in addition proteinuria, low glomerular filtration rates, and impaired concentration tests, and the abnormality of acid excretion therefore probably reflected generalized renal damage. The patient whose urine pH failed to fall below 6 is of special interest. The cause of his acute tubular necrosis was mercuric chloride ingestion. His serum electrolytes, glomerular filtration rate, and concentration test were normal and the urine ammonia high (101 μ Eq/min.). These findings are similar to those described by Wrong and Davies (1959) in their patients with incomplete renal tubular acidosis, and it may be that this patient has suffered specific damage to the hydrogen-ion excretion mechanism of his renal tubules.

In conclusion, this study shows that the long-term prognosis is good in patients who survive an episode of acute tubular necrosis. A normal state of health was almost always regained, though detailed investigation of renal function revealed some abnormality in most patients (74%), most commonly a lowered glomerular filtration rate (71%).

Summary

A detailed examination of renal function has been carried out in 50 patients with a previous well-documented episode of acute tubular necrosis. The time interval between the acute tubular necrosis and follow-up varied from 4 to 75 months, but

was less than one year in only two cases. All patients at the time of follow-up had made a good clinical recovery and were leading active lives. However, investigation of renal function revealed some abnormality in 37 (74%) of the patients, the most common defect being a lowered glomerular filtration rate (71%). Tests of tubular function were found to be abnormal in a much smaller number of patients, the concentration test being impaired in only 31%. No correlation was found between renal function at the time of follow-up and either the severity of the renal failure or the precipitating cause, but patients in whom pre-eclampsia preceded the acute tubular necrosis did have a high incidence of residual renal damage. There was no evidence that the episode of acute tubular necrosis led to hypertension, any alteration in renal size or caliceal changes, or predisposed to urinary tract infection. Serial studies in 14 patients suggested that no subsequent deterioration in renal function followed the initial recovery.

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