RENAL FUNCTION FOLLOWING ACUTE TUBULAR NECROSIS

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Although it is generally recognised that a return to normal health usually occurs in patients who survive an episode of acute tubular necrosis, few detailed studies have been carried out to determine the precise degree to which renal function recovers.

The first long-term follow-up study was carried out by Lowe in 1952 and he showed that while good clinical recovery was the rule, renal function tests tended to remain below normal limits. Finkenstaedt and Merrill (1956) in a series of 16 patients confirmed these findings and they showed that while clearance values of inulin remained low in most patients, tubular function, as assessed by phenolsulphonephthalein excretion and urine specific gravity following dehydration usually returned to normal. Edwards (1959), however, found a return to normal of the glomerular filtration rate in 14 out of 15 patients within 3 months. The present study was undertaken in an attempt to define accurately the degree of recovery of various aspects of renal function in a large series of patients.

METHODS AND MATERIAL

Thirty-six patients were studied, 15 male and 21 female, all of whom had a previous well-documented episode of acute tubular necrosis. The diagnosis of acute tubular necrosis had been made on the basis of clinical findings, course of the disease and biochemical changes in all patients; in addition in one patient renal biopsy was carried out and showed the appearances typical of acute tubular necrosis. Evidence of previous renal disease was present in only one patient, a mild diabetic, in whose urine a trace of protein had been noted on several occasions, although four others gave a history of recurrent urinary infection, and one had features of prostatism for some months prior to the acute renal failure.

The severity of the acute renal failure was variable. Haemodialysis was carried out on at least one occasion in 30 patients while in the remaining 6, conservative measures only were required. The duration of oliguria* varied from 2 to 22 days with a mean of 10 days. The mean age of the patients at the time of development of the acute renal failure was 38 years with a range of 18 to 66 years. The time interval between the episode of acute tubular necrosis and the follow-up study varied from 8 to 72 months, being less than one year in only 2 patients. The aetiology of the acute renal failure is shown in Table I.

Glomerular filtration rate was measured by 3 methods, 24 hour endogenous creatinine clearance, inulin clearance, and clearance of $^{57}$Co labelled B$_{12}$ (Nelp, Wagner and Reba, 1964). The results were adjusted to a body surface area of 1.73 sq. m. The ability of the kidney to concentrate urine was assessed by measurement of urinary specific gravity after 24 hours dehydration and its ability to excrete an acid load by the modified acid load test of Wrong and Davies (1959).

* Twenty-four hour urine volume of less than 600 ml.
TABLE I
Aetiology of the acute tubular necrosis

<table>
<thead>
<tr>
<th>Medical: 10 (28%)</th>
<th>Surgical: 10 (28%)</th>
<th>Obstetric: 16 (44%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxins (4)</td>
<td>Post-operative (5)</td>
<td>Abortion (9)</td>
</tr>
<tr>
<td>Intravascular haemolysis (2)</td>
<td>Multiple injuries (2)</td>
<td>A.P.H. (4)*</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Biliary peritonitis (2)</td>
<td>P.P.H. (3)*</td>
</tr>
<tr>
<td>Anticoagulant bleeding</td>
<td>Burns + intravascular haemolysis</td>
<td></td>
</tr>
<tr>
<td>Salmonella enteritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO poisoning</td>
<td></td>
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</tr>
</tbody>
</table>

* Following P.E.T. in 6 of 7 cases.

RESULTS

At the time of follow-up, all patients were leading active lives, and almost all had returned to their former occupations. Four of the 11 married females under 40 years had one or more successful pregnancies following the acute tubular necrosis.

Blood pressure

A diastolic blood pressure of more than 90 mm Hg was present at follow-up in 14 of the 36 patients*, in 3 of whom it was over 100 mm Hg. Of these 3 patients one was known to have pre-existing hypertension, one had ischaemic heart disease and one pre-eclampsia prior to the renal failure. Of the 11 with diastolic blood pressures of 90-100 mm Hg at follow-up, 4 had pre-eclampsia preceding the renal failure.

Proteinuria and urine microscopy

The urine was protein free at follow-up in 25 patients: in 7, less than 1 g of protein per 24 hours was present and in 4, between 1 and 3 g per 24 hours. Four of the 6 patients in whom pre-eclampsia preceded the acute tubular necrosis had proteinuria as had 3 of the 4 patients in whom a urinary tract infection was present at the time of follow-up. A modified Addis count (McGeachie and Kennedy, 1963) revealed pyuria in 7 patients, 4 of whom also had significant bacteriuria (vide infra).

Urinary infection

Significant bacteriuria (i.e., more than 100,000 organisms per ml of urine) was present in 4 of the 36 patients (11%) at follow-up. This compared with the presence of bacteriuria at some stage of the acute renal failure in 19 of the patients (53%). Of the 4 patients with positive urine cultures at follow-up, 2 had had recurrent urinary infections prior to the renal failure, one had severe renal damage at follow-up with small kidneys and probably had chronic occult pyelonephritis while in the remaining patient the urinary infection followed prostatectomy. There was, therefore, an adequate explanation for the presence of a urinary infection in these 4 patients other than the previous episode of acute tubular necrosis.

Blood urea and serum creatinine

The blood urea and serum creatinine values are plotted in Fig. 1. Taking 40 mg per 100 ml as the upper limit of normal, the blood urea was elevated in 17 patients (47%), the highest value being 62 mg per 100 ml.

* The blood pressure was measured a few hours after admission to hospital.
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![Graph showing blood urea and serum creatinine values in 36 patients.](image)

**Fig. 1.** Blood urea and serum creatinine values in 36 patients.

![Graph showing glomerular filtration rate (inulin clearance) in 31 patients.](image)

**Fig. 2.** Glomerular filtration rate (inulin clearance) in 31 patients.

**Glomerular filtration rate**

An inulin clearance was carried out in 31 of the 36 patients and the results are plotted in Fig. 2.

The lower limit of normal for males was taken as 90 ml per min. and for females as 80 ml per min. Using these criteria, the inulin clearance was normal in 12 patients (38%), moderately reduced in 17 patients (55%) and considerably reduced (i.e., below 40 ml per min.) in 2 patients (7%). Using the same criteria, the endogenous creatinine clearance* was normal in (21 patients (58%), moderately reduced in 14 (39%), and considerably reduced in one (3%) and the $^{57}$Co B$_{12}$ clearance** normal in 8 patients (27%), moderately reduced in 19 (63%) and considerably reduced in 3 (10%). The mean ratio of $^{57}$Co B$_{12}$ clearance to inulin

* Estimated in all 36 patients.

** Estimated in 30 patients.
clearance was 0.9 (±0.14) while that of endogenous creatinine to inulin clearance was 1.2 (±0.34).

**Concentration test**

A urine specific gravity of more than 1.020 was achieved following dehydration in 26 patients (72%). The specific gravity was between 1.016 and 1.020 in 6 patients (17%) and below 1.016 in 4 patients (11%). A correlation was present between impaired concentrating power (specific gravity 1.020 or less) and glomerular filtration rate (inulin clearance), the mean glomerular filtration rate of the patients with normal concentrating power being 91 ml per min. and for those with impaired concentrating power 61 ml per min. (p<0.01).

**Modified acid load test**

This test was carried out in 32 patients. In 10 patients, the urine pH failed to fall below 5.4 (in one of these 10 patients, in whom the acute tubular necrosis followed mercuric chloride ingestion, the pH remained above 6). In 3 patients urine ammonia excretion remained below 30 μEq per min. and in one of these 3 the titratable acidity was also subnormal (less than 20 μEq per min.).

**Intra-venous pyelogram**

A pyelogram satisfactory for detailed analysis was obtained in 28 patients. The average length of the 2 kidneys was within normal limits (i.e., within one standard deviation of the mean value in relation to body height) in 24 of these patients, while in the other 4 there was a reduction in kidney length.* There was a significant difference between the mean glomerular filtration rate of the 4 patients with small kidneys and that of the 24 patients with kidneys of normal size (p<0.05). Calcification of the kidneys was not seen in any of the 28 patients.

The percentages of patients in whom the various renal function tests gave normal results are summarized in Table II.

**TABLE II**

*Summary of results at follow-up*

<table>
<thead>
<tr>
<th>Type of test</th>
<th>No. of patients with normal results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>22 (61%)</td>
</tr>
<tr>
<td>Urine protein</td>
<td>25 (70%)</td>
</tr>
<tr>
<td>Urine culture</td>
<td>32 (89%)</td>
</tr>
<tr>
<td>Blood urea</td>
<td>19 (52%)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>32 (89%)</td>
</tr>
<tr>
<td>G.F.R. (inulin clearance)</td>
<td>12 (of 31) (38%)</td>
</tr>
<tr>
<td>I.V.P.</td>
<td>24 (of 28) (86%)</td>
</tr>
<tr>
<td>Concentration test</td>
<td>26 (72%)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The findings in the present study agree with those of Lowe (1952) and Finkenstaedt and Merrill (1956) in that the glomerular filtration rate at the time of follow-up remained below normal in the majority of patients. Renal damage existing before the episode of acute tubular necrosis cannot be excluded as the explanation for the abnormal results in at least some of the patients.

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

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However, there was no clinical evidence of this with the exception of one patient who was a mild diabetic and possibly the patients with pre-eclampsia. In spite of the fact that in only 28% of the patients were all investigations normal, full clinical recovery almost always occurred with a return to the patients’ former occupation.

There was no relationship between the degree of recovery of renal function and the duration of the oliguric phase of the acute tubular necrosis nor to the aetiology.

Although the diastolic blood pressure at the time of follow-up was greater than 90 mm Hg in 14 patients, hypertension prior to the episode of acute renal failure was present in at least 3, and the hypertension at follow-up in the remaining 11 was mild. There was therefore no evidence that the acute tubular necrosis predisposed to persistent hypertension, this view being in agreement with that of Edwards (1959) and Price and Palmer (1960).

Urinary infection commonly complicates acute renal failure, and the incidence in the present series was 53%. In spite of this, there was no evidence from the present study that urinary infection persists as all 4 patients with active urinary infection at the time of follow-up had reasons for this other than the previous acute renal failure.

It is known that the mortality is higher when acute renal failure occurs in late pregnancy than in early pregnancy and also that pre-eclampsia is often present in the former group (Smith, Browne, Shackman and Wrong, 1965). The present investigation shows that in addition persistence of abnormalities of renal function are more common in patients whose acute tubular necrosis has been preceded by pre-eclampsia. In particular the incidence of hypertension, proteinuria, and reduced kidney length was higher although the mean glomerular filtration rate did not differ significantly from that for the entire series.

Summary

A follow-up study has been carried out of 36 patients who all had a previous well-documented episode of acute tubular necrosis. The time interval between the acute renal failure and follow-up varied from 8 months to 6 years but was less than one year in only 2 cases. At the time of follow-up, all patients had made a full clinical recovery and were leading active lives. However, detailed investigation revealed some deficiency of renal function in 26 of the patients (72%), the most common abnormality being a lowered glomerular filtration rate which was present in 62% of patients. There was no evidence that the episode of acute tubular necrosis led to the development of persistent hypertension or urinary tract infection.

REFERENCES


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DISCUSSION

The CHAIRMAN: Thank you very much. Est-ce que quelqu’un a des commentaires à faire sur la communication du Dr. Briggs?

LEGRAIN (Seine): I would like to ask you if you have performed some kidney biopsies, because our feeling from kidney biopsy done early in the recovery phase of acute renal failure, is that you have a kind of subacute pyelonephritis, and I wonder if the later decrease in renal function could be related to the fact that you have some scars.

Also in the experimental work on ischaemic kidneys, you can see scarring in a high proportion of cases.

BRIGGS (Glasgow): We have not so far carried out renal biopsy in any of these patients, although we intend to do this in a group of them.

FRITZ (Bonn): Last year, we also did functional studies in cases with acute renal failure, in 53 patients.

We had, in nearly 80% of all these cases, normal function at least four months after acute renal failure.

Therefore, I would like to ask you at what time after the acute renal failure you did your functional studies.

In the other 20%, we had a small decrease in function compared with normal.

Naturally, it is always difficult to say if there was previous renal disease, but in most of these cases, we found a chronic pyelonephritis, which we think was connected with their acute renal failure.

I would like to ask you if you had the same results.

It was very interesting for us to see that the first value which became normal was the TM glucose, and then PAH clearance, and finally the insulin clearance.

Did you have the same results?

BRIGGS (Glasgow): To your first question, these studies were carried out between eight months and six years after acute tubular necrosis. In the majority of the patients, it was a greater than two years interval.

To your second question, we had no evidence of any previous renal disease apart from one patient who was a mild diabetic, had pus in the urine and presumably some renal impairment prior to tubular necrosis.

In four patients, there was a history of urinary infection. But again whether this was accompanied by any abnormality of the renal function we do not know, again prior to the acute tubular necrosis.

In the remaining patients, there was no clinical evidence of impaired function before the acute tubular necrosis.

To answer another part of your question, this study agrees with the results of Merrill in 1963 and of Low who found that the majority of patients at follow-up did have impaired glomerular filtration rates.

GOLDSMITH (Liverpool): Is there any evidence that in those cases followed up a long period after the acute episode, renal function was more severely impaired than in those cases followed up, say, within a year?
In other words, is there any evidence that some of the histological damage which may be seen such as periglomerular fibrosis, is perhaps ischaemic in nature rather than infective, and this damage may be progressive.

**Briggs (Glasgow):** In nine of these patients, we carried out a follow-up study on two occasions separated by an interval greater than two years.

The first study in these patients was carried out between six months and sixteen months after the acute tubular necrosis; the second study some years later.

In these nine patients, there was no significant change in renal function over this period of time. So there is no evidence of this.

**The Chairman:** Je pense qu’il nous faut conclure quel’on peut être d’accord pour considérer que dans l’immense majorité des cas l’insuffisance rénale aiguë ne laisse pas de séquelles derrière elle. L’infection urinaire et ses conséquences doivent toutefois faire l’objet d’une surveillance particulièrement vigilante.