Acute tubular insufficiency

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The aerial bombardments during the 1939–45 war led to the re-recognition of acute renal failure complicating trauma. Initially, the interest centred on defining the histological changes in the kidney (Dunn, Gillespie & Niven, 1941; Bywaters & Dible, 1942) followed by animal experimental work attempting to reproduce the lesion.

By 1946 the interest in the subject of acute renal failure created by Bywaters, and the application of physiological thinking to clinical medicine at Hammersmith Hospital under the guidance of the director of the Department of Medicine, Dr John McMichael, set the field for applying new developments in the treatment and study of renal failure. It was the gift of one of the original six rotating-drum artificial kidneys built by Kolff et al. (1943) in Holland to the Medical Department at Hammersmith Hospital, which served as a focal point for attracting patients in renal failure.

The differential diagnosis of acute reversible renal failure from acute irreversible renal damage or the terminal stages of chronic renal disease had almost no factual basis other than presumptive evidence from the history. Our first objective was to keep the oliguric, uremic patient alive as long as possible in the hope that recovery of renal function would take place. The Kolff drum kidney played its part in correcting the biochemical disturbance, but haemodialysis was then a formidable procedure. Although it was claimed that water could be removed from the over-hydrated patient by raising the glucose concentration in the dialysing fluid, this was unpredictable and the variable volume of the vascular compartment (in the cellophane coils) constituted a major danger to those patients in a critical cardiovascular state due to water overload (Bywaters & Joekes, 1948).

It became evident that the commonest immediate cause of death in any uremic patient was water overload, usually iatrogenic, with metabolic causes less common, although hyperkalaemia later became recognized as an important cause of cardiac arrest. Extending Borst's (1948) regime of protein restriction, and control of water intake (Lattimer, 1945), very strict metabolic management of the patients was started, and eventually reduced to an artificial diet consisting of a simple emulsion of arachis oil and glucose in water given by intranasal gastric drip (Bull, Joekes & Lowe, 1949). It was accepted that in an adult the insensible loss of fluid was equivalent to 1 litre in 24 hr and the basic intake was 1 litre of the oil–glucose mixture. Any fluid loss through urine or gastro-intestinal losses was replaced as was the sodium in gastro-intestinal loss. In this way no protein and no additional electrolytes were given and a high calorie intake was maintained. Patients on this regime started recovering renal function and several made a full clinical recovery without recourse to haemodialysis.

As the treatment of the patients with acute recoverable renal failure became more successful, it was possible to study renal function by simple clearance techniques, measuring glomerular filtration by thiosulphate and endogenous creatinine clearance and effective renal plasma flow by para-amino-hippurate (Bull, Joekes & Lowe, 1950). The very low renal blood flow values obtained during oliguric renal failure suggested that a 'by-pass' could be occurring of the blood flow in the kidney, if not in the sense of a 'Truea shunt', at least functionally. Renal vein catheterization made it possible to obtain renal arterio-venous differences at the same time as standard clearances to give renal blood flow by a direct Fick principle, so that total renal plasma flow could be measured by correcting for the lower extraction rate of para-amino-hippurate due to the tubular damage. The results showed falls of the renal blood flow to below 10% of normal. The arterio-venous oxygen saturation difference was also increased at the time of lowered blood flow. The results were interpreted as indicating that there was a true profound fall in renal blood flow without any major intra-renal shunting. These findings were very similar.
to those in three patients with acute renal failure
due to carbon tetrachloride poisoning studied by
Sirota (1949).

By 1950 many patients with acute reversible renal failure due to a wide variety of causes had
been followed through to recovery. Acute tubular
necrosis was suggested as a descriptive term for all such cases irrespective of aetiology—in
retrospect it might have been preferable to have
suggested acute tubular insufficiency. The evolution
of the renal lesion had a predictable course
irrespective of aetiology and was divided into
four phases—onset, oliguric, early diuretic and
late diuretic. It was assumed that the onset phase
was associated with renal ischaemia or direct
toxic damage to the tubular cells. The oliguria
was explained as due to 'leak back' of the greater
part of such filtrates as was formed; the early
diuretic phase (urine volume in excess of 1 litre/
24 hr) represented the restitution of integrity of
the tubular walls, but the, as yet, incomplete
functional recovery of the tubular cells made
control of electrolyte excretion and a high
urinary/plasma ratio of solutes impossible. The
late diuretic phase implied the return of tubular
function with increasing urinary/plasma ratios
of solutes and the ability to control electrolyte
homeostasis; from this time the blood urea and
other blood biochemical abnormalities started to
return to normal.

In patients with uncomplicated acute tubular
necrosis and no infection, tissue damage or
iatrogenic water overload, most commonly seen
in renal failure following abortion, conservative
management could be expected to achieve a
very high percentage of recoveries. With severe
overhydration, hyperkalaemia or a high rate of
catabolism, conservative management was much
less successful. Haemodialysis obviously had a
major part to play in these complicated cases,
but the technical problems were still such that
successful, safe dialysis was never certain.

What have been the developments in this field
since these studies at Hammersmith? Despite
much experimental work and many hypotheses,
a satisfactory explanation of the onset phase is
still lacking. Munck (Brun et al., 1955; Munck,
1958) measured renal blood flow using krypton
and found that neither in a 'shock' state, nor
during the oliguric phase of acute tubular necrosis
was the renal blood flow reduced much
below a third of normal and might be consider-
ably higher. This made it unlikely that ischaemia
per se could explain renal tubular damage, as
had been shown by Deetjen & Kramer (1960,
1961). Using the kidney as a mixing chamber
with the dye indocyanin green dilution, Shalondon
et al. (1963) found very similar values for renal
blood flow in acute tubular necrosis as had
Munck. Recently it has been suggested that en-
dogenous ammonia production during relative
renal ischaemia might play an important role in
tubular cell damage (Wickham & Sharma, 1965).

In a study of renal function during open-
heart surgery (Ghose & Joekes, unpublished),
one patient was observed to go into renal failure;
there was an almost immediate fall in the
urinary urea/creatinine ratio. Such a rapid
change in function might be explicable by the
hypothesis suggested by several workers, that a
redistribution of blood flow in the kidneys occurs.
Only some 5% of the total renal blood flow
passes through the inner medulla—with a higher
flow the counter-current concentrating mecha-
nism could not function. The early onset of
tubular functional impairment could be explained
on a relatively small redistribution of the blood
flow in the kidney.

Jean Oliver's classic studies (Oliver, McDowell
& Tracy, 1951) of the histological lesion demon-
strated the focal disruption of the renal tubules
(tubulorrhesis) differentiating this from the uni-
form nephrotoxic necrosis limited to the proximal
tubule.

As new techniques developed and fixed-capaci-
ty artificial kidneys came into general use,
haemodialysis became routinely used and many
patients with severe trauma or infection have
been saved. Strict metabolic control of the
oliguric and early diuretic phases is still the
mainstay of treatment, but the observations by
Hamburger & Mathé (1952) emphasized the im-
portance of the water of metabolism, equivalent
to about 500 ml/24 hr, so that the basic water
requirement is only 500 ml/24 hr. The necessity
for a high calorie intake is not proven. The
development of safe, efficient peritoneal dialysis
is playing an ever-increasing part in the treat-
ment of acute reversible failure, requiring less
technical experience and equipment, although
complications are certainly higher than with
haemodialysis in experienced hands.

While the theoretical considerations of hae-
modynamic disturbances, pathological changes in
the kidney or renal function during the later
phases have little bearing on the treatment of
patients, this is not so in the 'onset phase'. Even
if recognition of renal functional disturbance
were only to ensure the immediate institution
of correct management, many patients' lives
could be saved. Such recognition centres in most
cases round an observed oliguria and the chemi-
cal composition of the urine. Blood biochemical
changes can never be used for early diagnosis.
Studies of the urinary solute excretion in normal individuals (Joekes, Mowbray & Dormandy, 1957) taking only glucose and water by mouth showed that for the first 3 days there was little change in total solute excretion, always exceeding 0.5 mOsm/min. During the subsequent 3 days, total solute excretion fell progressively to about 0.25 mOsm/min, with very little sodium appearing in the urine and the excretion of potassium and urea being approximately halved. If one accepts 0.5 ml/min as oliguria (720 ml/24 hr), in the first 3 days of glucose and water intake, a urine flow of 0.5 ml/min, or less, the urine solute concentration would be high, as would the urinary specific gravity. During the second 3-day period a urine flow of 0.5 ml/min could have a solute concentration below 500 mOsm/l and a specific gravity in the 1008–1014 range; urinary urea concentration, however, exceeded 1.5 g/l. It was clear that isosthenuria, or ‘fixed specific gravity oliguria’ was not synonymous with renal functional failure. Many observations have emphasized the importance of urinary solute estimation in oliguria.

If at any time urine flow falls below 0.5 ml/min one of the following will be found:

<table>
<thead>
<tr>
<th>Urine</th>
<th>s.g.</th>
<th>mOsm/l</th>
<th>Urea (g/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1020</td>
<td>750</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>1015</td>
<td>600</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>1015</td>
<td>600</td>
<td>1.2</td>
</tr>
</tbody>
</table>

The period of urine collection is not important, but must be accurate. In order to avoid delay and ensure precision the patient must be catheterized and the catheter left in situ so that further accurate observations can be made if necessary.

With the urine characteristics (1) a physiological oliguria is present and renal function is normal. With (2) a physiological oliguria with sodium retention is present; care must be taken to correct ‘pre-renal’ factors, and it is advisable always to measure plasma volume. With (3) a renal functional disturbance is present. Again, plasma volume should be measured before attempting to institute a diuresis. If plasma volume is within normal limits, or has been corrected by infusion of plasma or whole blood, as required, the kidneys should be challenged with the osmotic diuretic mannitol; 200 ml of 20% mannitol is given as rapidly as possible, and the urine flow observed. In some patients the functional disturbance is reversible by mannitol although a water or saline diuresis may never be expected to be effective. An occasional patient, most commonly those with cardiac embarrassment, may not respond with a diuresis until frusemide or ethacrynic acid are given. If a rise of urine flow exceeding 2 ml/min does not occur within 10 min of the mannitol infusion it is advisable to give an immediate intravenous dose of one of the above diuretics. If no diuresis results within 15 min of the challenge with mannitol and a diuretic, strict management of oliguric renal failure must be started.

What then is the explanation of this fascinating reversal of renal function to normal in an oliguric kidney with impaired concentrating ability? Not only does urine flow increase, and is the diuresis maintained with water and adequate electrolyte administration, but there is a rapid recovery of the concentrating power of the tubules. If, on the other hand, no attempt is made to institute a diuresis it is certain that a classical acute tubular necrosis course will be followed. Kramer (1967) has suggested that the effect of mannitol acts through the juxta-glomerular body feedback mechanism. The osmotic diuresis instituted by mannitol leads to a lower sodium concentration in the tubular lumen, the palisade cells of the first part of the distal nephron may be sensitive to sodium concentration changes and instigate an increased renin secretion by the juxta-glomerular cells of its own glomerulus leading to an increased filtration rate by efferent arteriolar constriction or afferent arteriolar dilatation. If this is indeed the correct explanation, it is likely that this glomerular arteriolar tone change could also account for a return to normal of an intra-renal blood flow redistribution, reducing the relative flow through the inner medulla to allow the countercurrent mechanism to become effective again.

**References**


The Epping Jaundice after two years

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The outbreak of liver disease which occurred in Epping and the surrounding district in 1965 has been fully described by Kopelman et al. (1966a) and Kopelman, Scheurer & Williams (1966b) and summarized in a J.A.M.A. Editorial of the same year (Anon., 1966). Briefly, eighty-four persons were known to have been affected after eating bread made from flour contaminated by a chemical hardener 4,4'-diaminodiphenyl methane, spilled from its container while both were in transit. The hepatic lesion so produced was shown by needle liver biopsy to be unique and showed changes in the portal zones of cholangitis early in the disease, but later showed intense centrilobular cholestasis and hepatic-cellular necrosis (Kopelman et al., 1966b). All patients made a good clinical recovery and in one case a liver biopsy taken some 4 months after the onset showed only minor changes from normal.

Subsequent examination of some claimants for compensation revealed a large variety of symptoms ascribed to, or said to have followed, the jaundice. These symptoms included great intolerance to fats, excessive flatulence, constipation, depression and lack of concentration, irritability, general fatigue, intellectual deterioration and, in two cases, visual disturbance. Of fourteen cases examined, ten had symptoms of some severity when seen 7–23 months after the onset of the disease. It was therefore considered that some help in assessing the cause of these symptoms might be obtained by reviewing as many cases as possible after an interval of 2 years from the onset of the disease.

The investigation

Patients known to have had the disease were asked to answer a simple questionnaire by their general practitioner and it was arranged for them to have blood taken for liver function tests. The questionnaire enquired into their general well-being, weight, appetite, food which upset them, bowel function and motions, symptoms of pain, itching, nervous trouble, eye or ear trouble and any other symptom they might have. Liver function tests consisted of estimating plasma proteins, serum bilirubin, the alkaline phosphatase, turbidity tests and serum aspartate transaminase. In addition most patients had a blood count taken. Forty-three patients had their questionnaires completed and returned and liver function tests were done in all but two cases. The forty-three patients included eleven who had previously been examined for insurance purposes.

The results

General fitness

Patients were asked whether they were very well, not quite 100%, or had troublesome symptoms. Of the forty-three replies twenty-eight (63%) said they were very fit, eleven (23%) that they were not quite 100% and only four had troublesome symptoms. One of these four, whose
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