DISTAL TUBULAR AND PROXIMAL TUBULAR NECROSIS IN THE KIDNEYS OF BURNED PATIENTS

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The histological pictures associated with acute renal failure following abortion, incompatible blood transfusion, crush injuries, severe trauma, blackwater fever, sulphonamide intoxication, and many other conditions including burns have been described by various writers (Bratton, 1941; Dunn, Gillespie, and Niven, 1941; Bywaters and Beall, 1941; Bywaters and Dible, 1942; Erb, Morgan, and Farmer, 1943; Shen, Ham, and Fleming, 1943; Lucké, 1946; Goodpastor, Levenson, Dible, 1953). Lucké, whose report included 48 fatally burned subjects, claimed that there was a common morphological picture for acute renal failure caused by a variety of conditions. He coined the term “lower nephron nephrosis” because he considered the essential lesion to be a selective focal degeneration of necrosis of the thick Henle and distal convoluted tubules. This name has been criticized by Oliver and by Dible (Bull and Dible, 1953) because they believe that a widespread tubular necrosis is the essential feature, and they renamed the morphological pattern “acute tubular necrosis.”

The present report is based on a histological analysis of the kidneys of 86 fatally burned patients. Some of these patients had a necrosis of the proximal convoluted tubules whilst others showed a histological picture similar to lower nephron nephrosis. In this paper, the former condition will be termed “acute proximal tubular necrosis” (P.T.N.) and the latter “acute distal tubular necrosis” (D.T.N.).

Proximal and distal tubular necrosis in burned patients are not identical phenomena. Proximal tubular necrosis occurs mainly in elderly subjects who have nephrosclerosis and is usually associated with a severe oliguria. Distal tubular necrosis mainly affects children and younger adults and may or may not be associated with acute renal failure. If the necrosis affects many nephrons and is widespread through the kidneys it is termed “diffuse D.T.N.” and this is associated with anuria or severe oliguria or alternatively with a non-oliguric form of acute uraemia (Sevitt, 1956). If the condition affects few nephrons it is termed “focal D.T.N.” and this is infrequently associated with acute renal failure.

THE PATIENTS

During the six and half years from 1948 to the middle of 1955, 174 burned patients (109 females) died in the Birmingham Accident Hospital and 90 necropsies were performed. For various reasons four are excluded and the present analysis is based on the remaining 86 subjects. Forty-four of these were female. The ages varied from 16 months to 87 years; 21 were less than 5 years old, 16 were between 5 and 15 years, 11 between 15 and 40 years, 14 were between 40 and 60 years, and 24 were older than 60 years (Table I).

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>AGE ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects With</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Distal tubular necrosis ...</td>
<td>13</td>
</tr>
<tr>
<td>Focal ...</td>
<td>9</td>
</tr>
<tr>
<td>Diffuse ...</td>
<td>4</td>
</tr>
<tr>
<td>Proximal tubular necrosis ...</td>
<td>0</td>
</tr>
<tr>
<td>No tubular necrosis ...</td>
<td>8</td>
</tr>
<tr>
<td>Totals ...</td>
<td>21</td>
</tr>
</tbody>
</table>

Most of the patients were extensively burned. In 74 subjects the burns involved 20% to 90% of the body area (20% to 90% burns); 29 patients had 20 to 40% burns, 24 between 40% and 60%, and in 21 patients the burns involved more than 60% of the body surface (Table II). In only
eight patients were the burns less than 10% and seven of them were over 70 years of age.

The survival periods varied from two hours to four and half months; 10 subjects died within 24 hours of burning, 10 within one to two days, 20 within two to five days, 17 within five to 14 days, and 29 lived longer than 14 days.

Seventy-nine of the 86 necropsies were performed within 36 hours of death, 63 within 24 hours, and 30 within 12 hours.

**ROUTINE TREATMENT**

During the first one to three days—the shock stage—80 patients were transfused with plasma: the other six patients were elderly subjects with relatively small burns. Transfusion was begun soon after admission and usually within a few hours of burning. The degree of haemoconcentration on admission and during the course of transfusion was estimated by serial haematocrit observations from which the amount of plasma lost from the circulation was calculated. In recent cases blood volume studies have been carried out by Dr. E. Topley. These tests guided the amount and speed of plasma transfusion through which oligaemia was mainly combated. Some patients were also transfused with blood at this stage but in others blood transfusion was delayed for a week or longer. Other intravenous fluids (dextran 6%, glucose 5%, saline 0.9%) were also given to some patients. During the shock stage, the total volumes of intravenous fluids given were usually between 3 and 10 litres but varied from 700 ml. to 18.6 litres in the different patients according to the age, extent of burn, and other factors. Oral fluids, such as glucose-water, sweetened fruit juice, or sodium lactate, were given when vomiting did not prohibit their use. Two or three days later, feeding by an egg-milk mixture was begun and was continued until an adequate diet could be taken 10–14 days after burning. Skin grafting was usually carried out after two or three weeks and blood transfusion was given during each operation. Some patients were grafted during the first few days.

The burns were first dressed at the end of the shock phase when penicillin cream and/or other local antibiotics were applied to prevent or control wound infection. Systemic therapy with penicillin, aureomycin, polymyxin, or erythromycin, or a combination was introduced when infective complications occurred.

Biochemical analysis of the blood and urine guided the giving of supplementary sodium chloride, potassium salts, etc.

**HISTOLOGICAL METHODS**

One or more blocks from each kidney were examined. Paraffin sections from both kidneys were routinely stained by haematoxylin and eosin and with the pericromallory technique. Sections containing casts were stained by Pickworth's benzidine method and some of these kidneys were also examined unstained. Other staining methods when appropriate included phosphotungstic-acid-haematoxylin, Weigert's fibrin, Prussian blue, periodic-acid-Schiff, and phloxin-tartarazine techniques. Frozen sections were prepared and stained for fat by Sudan IV or oil red O.

**CLASSIFICATION**

On a histological basis the kidneys were classified as follows:

<table>
<thead>
<tr>
<th>Type of Necrosis</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal tubular necrosis</td>
<td>34 (diffuse 16, focal 18)</td>
</tr>
<tr>
<td>Proximal tubular necrosis</td>
<td>17</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>2</td>
</tr>
<tr>
<td>Subacute glomerulonephritis</td>
<td>1</td>
</tr>
<tr>
<td>No significant abnormality</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
</tr>
</tbody>
</table>

In general, distal and proximal tubular necrosis were morphologically distinct but there were a few subjects in whom both conditions were found (two classified as D.T.N. and three or more as P.T.N.). The cases of pyelonephritis and glomerulonephritis will receive no further attention. Those classified as having no significant abnormality showed no evidence of distal or proximal tubular necrosis but included cases with cloudy tubular swelling.

Table I lists the number of patients who had distal tubular necrosis, proximal tubular necrosis, and those without tubular necrosis in the age groups < 5, 5 to 15, 15 to 40, 40 to 60, and > 60 years. Only D.T.N. occurred in children under 15 years (22 cases) and most of those with tubular necrosis who were over 60 years had P.T.N. (11 out of 15 patients). Proximal tubular necrosis did not occur in children and became progressively more frequent with advancing age, whilst the fre-
RENAL TUBULAR NECROSIS AFTER BURNING

quency of diffuse D.T.N. was about the same in all age groups. When the number of cases of D.T.N. and P.T.N. in each age group are added together and the sum is expressed as a percentage of the total number of subjects in the age group, the frequencies of tubular necrosis in the different age groups are about the same. They are 62% (13 out of 21 patients under 5 years), 56% (5 to 15 years), 54% (15 to 40 years), 57% (40 to 60 years), and 62% (over 60 years). In other words, the total incidence of tubular necrosis is the same irrespective of age and about 50% to 60% of all fatally burned subjects at all ages develop one or other form of tubular necrosis. Age, however, may determine which kind of tubular necrosis the patient may suffer. In children this will be a focal or diffuse D.T.N., in adult life either diffuse D.T.N. or proximal tubular necrosis may occur but with advancing age P.T.N. becomes the usual kind. This indicates either that there is some factor in elderly subjects which is not present in younger people and which facilitates the development of P.T.N., or alternatively that younger patients possess some property which facilitates the development of D.T.N. The former appears more likely and renal arteriosclerosis may be the predisposing factor (vide infra).

DISTAL TUBULAR NECROSIS

Distal tubular necrosis is classified into diffuse and focal forms according to whether many or few nephrons are affected. The terms refer to the histological density of lesions, but in both diffuse and focal kinds the individual tubules are commonly affected in a discrete or focal fashion. The histological picture also varies with the period of survival, and early and later stages are recognized. Diffuse D.T.N. was found in the kidneys of 16 patients (nine adults, seven children, 10 females) who died 12 hours to 23 days after burns involving 37% to 80% of the body area. The mean area burned was 67%. Focal D.T.N. was found in 18 patients (10 females), 15 of whom were children. They died 15 hours to 35 days after burns involving 27% to 90% of the body area. The mean area burned was 62%.

Diffuse D.T.N.: Early Stage

This appeared in the kidneys of eight patients who survived 12 hours to two and half days. Severe oliguria rapidly developed in five of them even though transfusion with plasma appeared to be adequate. Their total excretion of urine varied only from 90 to 196 ml. during the 30 hours to two and half days of survival. The urine flow of two others was adequate, but the blood urea of one (age 5 years) was 80 mg.% 12 hours before death which suggested that uraemia might have developed had the patient survived longer. These non-oliguric patients are described elsewhere (Sevitt, 1956). Haemoglobinuria was reported in six patients.

Gross Appearance.—The kidneys of seven patients were moderately or deeply congested and some dripped blood from the cut surfaces. Two were a purplish, cyanosed colour.

Histology.—Histologically the main feature was the presence of numerous haemoglobin and eosinophilic granular casts in many collecting (Fig. 1) and wide Henle tubules (Fig. 2) and often in second convoluted tubules. The casts often distended the tubules and appeared to block them. Many of them were amorphous fused masses of haemoglobin, others were coarsely or finely granular. Occasional groups of red cells were seen within tubules, but these were not a feature. Many of the eosinophilic granular casts which usually stained red or pink in the picromallory preparation were also benzidine positive. Albuminous exudate was frequently mixed with the casts. Early tubulointerstitial necrosis was common in tubules distended by casts, was usually focal and was manifest by nuclear pyknosis and by local thinning and eosinophilic staining of the cytoplasm (Fig. 2). Focal necrosis of Henle tubules which did not contain casts was not common but appeared as a granular cytoplasmic disintegration with nuclear karyolysis. In one patient many focal areas of necrosis affected the proximal convoluted tubules, that is, both distal and proximal tubular necrosis were present. The glomerular capsules generally contained many coarse eosinophilic granules about the size of erythrocytes, also albuminous exudate and occasionally a few red cells. Irregular desquamation of the parietal layer of Bowman’s capsules was frequent. The hyperaemia noted in the gross specimens was histologically confirmed, but irregular small foci of cortical ischaemia were also seen and affected some glomerular tufts and the related peritubular capillary network. In only one case was relative ischaemia a feature. Thrombi in glomerular capillaries were seen in three patients.

Diffuse D.T.N.: Later Stage

A more advanced histological pattern was observed in the kidneys of eight patients. Clinically they are divided into two groups. The first is of four patients who rapidly became severely oliguric or anuric, then uraemia developed and consider-
able azotaemia with hypocalcaemia, hyperpotass-
aemia, hyperphosphataemia, hypochloraemia, and
hyponatraemia were found. They died between
four and five days after burning. For example, a
man of 24 years with 75% burns passed 168 and
20 ml. of urine respectively during the first two
days, failed to pass any more urine and died five
days after burning with a blood urea of 284 mg.
%. Similarly a girl of 9 years with 55% burns
passed 130, 137, 69, 5, and 4 ml. of urine on suc-
cessive days. Her blood urea level rose from 159
mg. % on the third day to 318 mg. % on the fifth
day when she died, her serum potassium and
phosphate values rose to 37 mg. % and 9.2 mg. %
respectively, and her serum sodium and calcium
levels fell to 278 mg. % and 7.7 mg. %. Early
haemoglobinuria was reported in each patient.
These patients represent the classical anuric-
uraemic form of acute renal failure.

The second group consists of three patients who
survived six, 10, and 21 days, and who also had
uraemia with high blood urea levels. However,
their daily urinary output was considered to be
adequate and oliguria did not occur (Sevitt, 1956).
Haemoglobinuria had been reported in two of
them. The eighth patient, a baby of 18 months,
 survived 23 days but neither her urinary output
nor her blood urea levels are known.
The kidneys were swollen and enlarged and the capsules were under tension; the cortices were widened, their outlines were hazy, and sometimes they were pale. In some cases the parenchyma was softer than usual and in four patients minute greyish-white foci were visible, particularly at the bases of the pyramids.

Histologically the characteristic changes are casts and tubular necroses in the distal and collecting tubules, tubulo-epithelial regeneration, tubulo-venous anastomoses and venous thrombi (Fig. 3), interstitial oedema and an inflammatory cellular exudate in the boundary zone, around venules or related to extruded casts or ruptured straight or convoluted distal tubules (Fig. 4).

For example, in one of the patients who died with uraemia and anuria, numerous coarse and finely granular haemoglobin and eosinophilic casts were found mainly in the collecting tubules and ascending limbs of Henle, and some casts also contained desquamated epithelial cells. Some colloid or albuminous casts were also seen. Discrete necroses of straight tubules, particularly in the boundary zone and in the pyramid, were present both at the sites of blockage and elsewhere. Attempts at tubular repair by spreading and regeneration of thin epithelium had begun and had already produced some peculiar tubular forms. Interstitial oedema and collections of lymphocytes and some plasma cells were seen.
around and between many straight and convoluted tubules, particularly those ruptured or blocked by casts. Lymphoid cells were also found around small venules in the boundary zone and elsewhere. Some tubulo-venous anastomoses produced presumably by rupture were seen. The proximal convoluted tubules showed evidence of cloudy swelling and their lumina contained albuminous exudate. Bowman's capsules also contained some exudate. Some glomeruli in this patient and in one other of this group contained capillary thrombi.

In those who survived a longer period epithelial regeneration and the interstitial inflammatory changes were generally more advanced. For example, in one patient who died 10 days after burning, tubular reparative efforts had produced many plicated and bizarre tubular forms. Numerous haemoglobin, cellular and other casts, and focal necroses at the sites of blocked tubules were visible. Numbers of the venules in the boundary zone were thrombosed and parts of the thrombi were surrounded by a single layer of tubular epithelium which had spread from a nearby ruptured and regenerating tubule (Fig. 3). Focal collections mainly of lymphoid and plasma cells, with a few eosinophil leucocytes and oedema of the interstitial tissue, were present. They were seen between and around straight tubules and venules particularly in the boundary zone and were also related to second convoluted tubules (Fig. 4). The parietal layer of many Bowman's capsules had become cubical or even low columnar as if over-vigorous replacement of previously desquamated epithelium had occurred. Some cloudy swelling was found in the proximal tubules; the cortex and medulla were congested and the latter was oedematous.

In one patient haemoglobin casts were not found and haemoglobinuria was not reported; in another case pigmented casts were few. Instead, eosinophil colloid and granular casts which were benzidine-negative were relatively numerous in the distal and collecting tubules but otherwise the histological appearances differed in no way from the other cases.

A common, almost universal feature in the early and later stages of diffuse D.T.N. was the presence of many unusual mononuclear cells within venules, particularly in the pyramids. As Dible (Bull and Dible, 1953) stated, they appeared similar to many bone marrow cells, and he suggested that they arose from the vascular endothelium and were the result of stagnation of the venous blood flow. The appearance was seen both in the oliguric and non-oliguric forms. Indeed, no histological differences between these two clinical varieties of diffuse D.T.N. could be made out.

**Focal D.T.N.: Early Stages**

This was observed in four patients who survived 15 hours to two and half days. Three were known to have had haemoglobinuria. Severe oliguria rapidly developed in one of them; in two others the urinary flow was adequate or even polyuric and in the fourth patient it was not known.

Histologically only a few scattered haemoglobin casts—amorphous and granular eosinophilic forms —were present in a few collecting, ascending Henle (Fig. 5) and second convoluted tubules. The number of casts varied in different parts of the sections but were rarely more than 1 or 2 per low-power field and were often less frequent. The majority of tubules did not contain casts and appeared to be normal. Early discrete tubular necroses (pyknosis) were restricted to some of the blocked tubules, but in one case focal necroses of a few wide Henle tubules which did not contain...
casts were also seen. Extrusion of casts from ruptured tubules was seen in the anuric case. Numbers of glomerular capillary thrombi were found in one patient.

**Focal D.T.N.: Later Changes**

The kidneys of the 14 patients in this group are classified histologically into three subgroups: "active," "healing," and "healed" types. The "active" type numbered six patients, five of whom died two and a quarter to eight and a half days after burning and the other survived 35 days. In this subject the onset of the disorder may have started days or weeks after burning. Oliguria developed after 36 hours in the child who survived only two and a quarter days. In all the others the urinary flow was normal, but one developed uraemia and this was attributed, at least in part, to the severe proximal tubular degeneration which was also present (Table IV). The histologically "healing" and "healed" groups consisted of eight children, none of whom was oliguric. One child died only seven days after burning and the others survived 15 to 26 days.

Altogether eight patients with focal D.T.N. (early and later stages) who were biochemically investigated showed no evidence of azotaemia. Six others were not investigated.

Histologically the "active" form was characterized by the presence of a few haemoglobin and eosinophilic casts in the distal convoluted, ascending Henle (Fig. 5) and collecting tubules in four patients and by colloid casts in a fifth. The epithelium of the distended parts was usually thin, a few localized necrotic epithelial foci were seen and tubular regeneration was in progress particularly in the patient who survived 35 days. Focal collections, mainly of lymphoid cells, were found around some of these tubules (Fig. 6) or around the walls of veins in the boundary zone of the cortex or in both situations. Occasionally these venules were thrombosed and organization of the thrombi was in progress (Fig. 7). Essentially the histological picture was similar to that in the diffuse form except that few tubules were involved.

The sixth patient differed from the others in that multiple haemoglobin casts were present, but few tubules appeared to be blocked and only occasional pykno-necrotic epithelial foci were seen: in other words a diffuse cast state was associated with focal tubular necrosis. Had the patient survived and most of the casts been removed by the adequate urine flow, a characteristic picture of focal D.T.N. would have remained.

The morphological changes which are believed to represent the "healing" stage or the "healed" residue of a recent focal D.T.N. consist of focal collections mainly of lymphoid cells and occasional organizing venous thrombi. The former were located around the walls of small veins, particularly in the boundary zone of the cortex, or were related to second convoluted tubules or were present in both situations. The organizing venous thrombi were also usually seen in the boundary zone and probably represented former tubulo-venous rupture. Direct evidence of tubular necrosis was found in only two subjects, and in three cases a few granular or haemoglobin casts were seen in distal tubules. In four patients parts of an occasional straight Henle tubule showed
Evidence of recent regeneration. The term "healing" is applied when tubular evidence of necrosis or regeneration still persisted: the kidneys of four patients were so classified. The term "healed" is used when there was no tubular evidence of focal tubular necrosis. There were five such cases including one case classified as proximal tubular necrosis. In these the characteristically located lymphoid cell collections, and in one patient an organizing venous thrombus, were accepted as the residue of a focal distal tubular necrosis. The interstitial cellular collections might have led to a diagnosis of interstitial nephritis if the entire histological process was not considered. It may be that some cases diagnosed histologically as interstitial nephritis because of focal collections of lymphoid cells are in reality the healed or healing residue of distal tubular necrosis.

**ACUTE PROXIMAL TUBULAR NECROSIS**

Proximal tubular necrosis was found in 17 patients, excluding the two with distal tubular necrosis in whom severe proximal tubular degeneration was also present. Histologically the condition was characterized by a widespread focal or confluent necrosis particularly of the proximal convoluted tubules, whilst few if any of the tubules in the pyramid were involved.

Unlike those with distal tubular necrosis, all these patients were adults and most of them were elderly (Table I) and had nephrosclerosis. Thirteen of them were 58 to 87 years old and eight were over 70 years. Twelve had moderate or severe nephrosclerosis due to renal arteriosclerosis of senile or other form, and five had renal and cardiac evidence of hypertension. Ten were females.

The extent of burning was usually less than in those with distal tubular necrosis; nine patients had burns between 20% and 40%, four were less extensively burned, and in only four were the burns more extensive (Table II).

The patients are divided into two groups, those who died within five days of burning, the 13 early cases, and those who survived 10 days or longer, the four later cases. This division was made because in at least eight of the early cases acute renal failure had occurred. Seven had anuria or severe oliguria and another (Case 8, Table III) had incipient uraemia without oliguria. His blood urea level rose from 80 to 190 mg. %. Case 2, for example, passed no urine during his 18 hours of survival, Case 3 passed 218 ml. in 1 1/6 days, Case 7 passed 570 and 55 ml., and Case 10 passed 1,115, 170, and 130 ml. respectively on successive days. Four oliguric patients were known to have significant azotaemia with blood urea levels of 70, 85, 110, 140 mg. % respectively (Table III). The acute renal failure was probably related to the burns and to the associated histological picture of proximal tubular necrosis.

On the other hand, none of the later cases developed oliguria and the histological tubular necrosis was not known to be associated with clinical effects. In these patients the necrosis was probably not directly related to the burning but...
TABLE III
PATIENTS WITH ACUTE PROXIMAL TUBULAR NECROSIS

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex, Age, % Area Burned</th>
<th>Survival Period</th>
<th>Neoplastic Lesion</th>
<th>Serum Creatinine</th>
<th>Blood Urea (mg/100 ml)</th>
<th>Haemoglobin</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87 F (80%)</td>
<td>2 hr.</td>
<td>Early Deaths</td>
<td>Coronary and cerebral atheroma</td>
<td>Pulmonary oedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>43 M (60%)</td>
<td>18 +</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>75 M (60%)</td>
<td>14 days</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>87 F (45%)</td>
<td>14 +</td>
<td></td>
<td>Coronary atheroma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>12 M (25%)</td>
<td>14 +</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2 M (15%)</td>
<td>2 +</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>47 M (70%)</td>
<td>2 +</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>20 M (35%)</td>
<td>2 +</td>
<td></td>
<td>&quot;Healed&quot; focal D.T.N. also seen. Acute haemolytic jaundice</td>
<td>Cerebral atheroma. Early broncho-pneumonia</td>
<td>Overtransfusion, oedema ++</td>
<td>Coronary atheroma</td>
</tr>
</tbody>
</table>

was possibly associated with infective complications (bronchopneumonia, septicaemia) in Cases 14 to 16 and with hepatitis and jaundice in Case 17.

The Kidneys

Cortical pallor was present in six early cases but the kidneys of one (Case 8) were very congested. In two subjects a number of pale, more or less circumscribed cortical areas were surrounded by narrow red borders (Fig. 8). These pale zones were restricted to the outer two-thirds or so of the cortex and the deeper cortex and medulla were congested. This appearance suggested a cortical ischaemia and medullary by-pass of the type described by Trueta, Barclay, Daniel, Franklin, and Prichard (1947).

Cortex.—The essential change was a widespread necrosis of the proximal convoluted tubules (Figs. 9 and 11). Their nuclei had either disappeared or stained feebly as if in process of solution. In most patients the tubular epithelial cells were loosened from each other and from the basement membrane. In some places they had lost their tubular arrangement, the lumen had disappeared, and the cells had become more or less jumbled and irregular but were restricted by the peritubular membrane (Fig. 11). In other cases the cells were only slightly loosened and were mostly still arranged around a central lumen (Fig. 9). The fine peritubular membrane was always intact. The extent of proximal tubular necrosis varied but was considerable in each case. In five of the 13 early cases (Cases 1, 2, 6, 12, and 13) necrosis involved most of or all the proximal tubules (+ + + necrosis); in six others (Cases 3, 5, 7, 8, 10, and 11) about half the tubules were obviously necrotic, whilst the remainder appeared viable (+ + necrosis); and in the remaining two (Cases 4 and 9) the necrosis was focal and less extensive (+ necrosis). In Case 3 there was + + necrosis in one kidney and a + + necrosis in the other. In three of the later cases necrosis was + + + but in Case 17 it was + + +.

Necrosis of the second convoluted tubules was also present but was less extensive (Fig. 9). Histologically viable but collapsed spiral tubules with stainable nuclei were often surrounded by necrotic proximal tubules. In the cortex many of the wide straight tubules were necrotic, particularly the proximal descending parts of the first tubules but also many ascending Henle limbs. The narrow descending limbs and collecting tubules usually appeared less affected or even
viable. The glomerular tufts appeared viable in all except three cases. In Case 6 all glomeruli and tubules were obviously necrotic (Fig. 11) and small haemorrhages were present. In Cases 2 and 12 a few of the glomerular tufts were undergoing necrotic changes whilst the majority appeared viable.

Subcapsular Viability.—Subcapsular rims or zones of histologically viable cortex were seen in 13 cases. The rims were usually thin, irregular and often interrupted by foci of necrotic tubules, but in two cases the viable zone extended into the outer quarter or so of the cortex.

Vascular Changes.—In 13 cases there was histological evidence of cortical ischaemia. In three (Cases 6, 12, and 13) most of the peritubular capillary networks were empty of blood, and in the others the ischaemic zones were focal and irregular. A variable number of glomerular tufts were also empty but only in Cases 2 and 3 was this a prominent feature.

Multiple focal haemorrhages were seen in five subjects; in Cases 6, 7, and 13 they were related to dilated cortical veins, in Case 12 they were focal, capillary peritubular haemorrhages, and in Case 4 they occurred in the subcapsular zone.

In Cases 3 and 4 many glomerular capillary thrombi were seen. Arterial thrombosis was found in Case 2 (vide infra).

Pyramid.—In the boundary zone a variable number of Henle tubules were obviously necrotic, but in the pyramids the architecture and nuclear structure of the collecting and Henle tubules were normal (Fig. 10). They were usually collapsed and empty and separated by oedema. In Case 4 there was a hyaline droplet degeneration of the epithelium (in this case there was also considerable exudation into the glomerular spaces). In 10 cases the vasae recti were congested but in five others these vessels were empty.

Casts and Distal Tubular Necrosis.—In 15 cases casts were present. Mostly they were of the kind commonly found in nephrosclerotic kidneys, but in seven cases (Cases 2, 3, 5, 7, 8, 9, and 12) at least some of them contained haemoglobin and they were mostly found within second convoluted
and collecting tubules. Such casts were not numerous, but in Cases 2 and 3 (possibly also Cases 1 and 12) the appearance was suggestive of early distal tubular necrosis.

Other Features.—In Case 8 the presence of focal collections of lymphoid cells around venules particularly in the boundary zone suggested the “healed” residue of a previous focal D.T.N. unrelated to the burning.

Nephrosclerotic atrophy and focal fibrosis of the cortex was seen in 12 cases: in five a hyaline change affected some or many of the afferent glomerular arterioles.

One case merits a fuller description.

Case 2.—A man, aged 43 years, suffered 60% burns from an oxy-acetylene explosion and died 18 hours later. Plasma transfusion was begun one hour after burning and 3.5 litres was given. Haemocencentration was inadequately combated because the haematocrit rose from 45% to 55% on at least two occasions but fell again. His peripheral circulation was poor; he became restless, violent, and irrational and then comatose. No urine was passed and the blood urea level at death was 70 mg.%

Necropsy (22 hours after death) revealed viscid blood, swelling of the brain, and oedema of the tongue, laryngeal opening, and of both lungs. The bladder contained a few millilitres of bloody urine. The kidneys together weighed 13½ oz., were swollen, and their capsules were under tension. When these were stripped the surface of the right kidney was uniformly congested but a number of pale, obviously ischaemic areas were seen on the left cortex (Fig. 8). These varied in shape and size, were 0.5 cm. to several centimetres long, were well demarcated by a narrow (1 mm. diameter) red border and contrasted with the remainder of the cortex, which was congested. Altogether about one-sixth to one-eighth of the cortex was involved in these pallid zones. Longitudinal section showed that the pallor was restricted to the outer two-thirds or three-quarters of the cortex and did not involve the juxtamedullary cortex or the pyramids which were dark red.

Histology.—The pale areas in the left kidney were due to ischaemia of the glomeruli and of the capillary network, whilst the surrounding cortex, much of the juxtamedullary cortex, and the pyramids were hyperaemic. In addition there was an irregular alternation of ischaemic and hyperaemic cortical foci of microscopic size in the other parts of the left kidney.
and throughout the right organ but in the latter ischaemic foci were more numerous. Groups of empty glomerular tufts and peritubular capillaries alternated with hyperaemic groups. The epithelium of most of the proximal and distal convoluted tubules was undergoing obvious necrotic changes or severe degenerative changes approaching a necrosis. This was more extensive in the right kidney and more advanced in some areas than in others. Similar changes involved many of the wide Henle limbs in the boundary zone but the descending limbs were less affected. The lumina of the affected tubules contained albuminous and granular debris, and in parts of the distal tubules much desquamated necrotic epithelium was also present. The peritubular basement membranes were intact. Most of the glomerular tufts appeared viable, but a few also were undergoing necrosis. Under the capsule was a narrow irregular rim of histologically viable tubules. Haemoglobin and other casts were seen in numbers of distal and collecting tubules particularly in the right kidney. Some of them were focally obstructed and necrotic suggesting an early distal tubular necrosis. Otherwise the tubules of the pyramid were collapsed and separated by oedema but appeared histologically normal. Thrombosis of arcuate, interlobar, and some interlobular arteries was seen in the left kidney mainly in relationship to the ischaemic cortical zones. Glomerular capillary thrombosis was not found. Nephrosclerotic changes were slight.

The morbid anatomy and histology suggest that the proximal tubular necrosis was the result of cortical ischaemia. Whilst a part of this may have been in the form of a cortical by-pass mechanism similar to that described by Trueta et al. (1947), most of the ischaemia was not of this kind but was focal, irregular, and widespread and related to many separate groups of afferent arterioles. The thrombosed arteries were more likely the result rather than the cause of the cortical ischaemic zones. This case is similar to that described by Brown and Crane (1943), but their patient survived several days and necrosis had also involved many glomeruli.

**Glomerular Capillary Thrombosis**

This condition was seen in the glomeruli of eight subjects. Histologically the thrombi, which often blocked and distended many of the capillaries of a single tuft, usually appeared as granular eosinophilic elongated masses taking the shape of the capillary lumen. They were stained red in the picromallory preparation and dark blue or black by the phosphotungstic-acid-haematoxylin technique. Sometimes the thrombus or part of it was relatively wide and then it grossly distended part of the capillary loop. Thrombi were not seen in the afferent arterioles. In four patients half the glomeruli or more were involved but in the others fewer tufts contained thrombi.

Five of the eight patients were over 70 years of age, the others were also adults and the condition was not seen in children. Five patients had nephrosclerosis and the thrombosis involved the capillaries of both normal and abnormal glomeruli. The condition was found in five out of 10 patients (50%) who died between 24 and 48 hours after burning and who showed either proximal or distal tubular necrosis. It was seen in only one of the seven subjects who died within 24 hours of burning with distal or proximal tubular necrosis, in only two of the 17 such patients who survived two to five days after burning, and in none of those who survived longer. Thus thrombosis of the glomerular capillaries was particularly found among the elderly people who died with distal or proximal tubular necrosis during the second day after burning. Its aetiology is not clear. The thrombi may be formed locally within glomerular capillaries, the endothelium of which has become temporarily abnormal. Alternatively they may be partly embolic in origin and result from the trapping of fragmented erythrocytes and other microscopic debris within the glomerular capillaries. However they are formed, they appear to be a temporary phenomenon since they are rarely seen in patients who survive more than two days. It is unlikely that they play a significant part in the pathogenesis of tubular necrosis. The condition was known to Wertheim (1867) but has not been described by recent authors.

**DISCUSSION**

By histological analysis the kidneys of 86 burned patients included 34 subjects with distal tubular necrosis and 17 with proximal tubular necrosis. These are histologically distinct although there were a few cases in which there was evidence of both conditions.

Distal tubular necrosis occurred both in a diffuse form when many nephrons were affected (16 cases) and in a focal form when few nephrons were involved (18 cases). Diffuse D.T.N. was similar to the appearance described in burned patients by Pack (1926), Shen et al. (1943), Gibson (1944), and Goodpastor et al. (1946). Essentially it had the same morphological pattern as Lucké's lower nephron necrosis. Histologically it was characterized by the early appearance of haemoglobin casts in many collecting and wide Henle tubules and in distal convoluted tubules. Frequent tubular blockage by casts was often associated with local epithelial necrosis which occurred less frequently in tubules which did not contain casts. Rupture of tubules, dislocation of casts, tubular...
RENAL TUBULAR NECROSIS AFTER BURNING

Table IV

FREQUENCY OF HAEMOGLOBINURIA IN PATIENTS WITH AND WITHOUT TUBULAR NECROSIS AND IN PATIENTS WITH RENAL FAILURE

<table>
<thead>
<tr>
<th>Distal Tubular Necrosis</th>
<th>Proximal Tubular Necrosis</th>
<th>No Tubular Necrosis</th>
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</thead>
<tbody>
<tr>
<td>Diffuse</td>
<td>Focal</td>
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<tr>
<td>All cases</td>
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<tr>
<td>Anuria or severe oliguria</td>
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<tr>
<td>Uraemia without oliguria</td>
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<tr>
<td></td>
<td>12/16</td>
<td>6/18</td>
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<tr>
<td></td>
<td>8/9</td>
<td>1/2</td>
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<tr>
<td></td>
<td>3/4†</td>
<td>0/1§</td>
</tr>
</tbody>
</table>

* Numerals are no. of patients with haemoglobinuria/total no. in the group.
† Excludes four who died more than 10 days after burning (see Table III).
‡ One patient with incipient uraemia.
§ Also severe proximal tubular degeneration.

regeneration, interstitial oedema, peritubular and perivenous infiltration by lymphoid and other cells, tubulo-venous anastomoses, and venous thrombi were found in patients who survived sufficiently long. Clinically the condition was associated with actual renal failure which took one of two courses, oliguric or non-oliguric (Table IV). Nine subjects rapidly developed severe oliguria or anuria and four of them survived sufficiently long to develop uraemia. The urine flow of five others was more or less normal, and if oliguria occurred it was slight and transient: four of these subjects were known to have uraemia in one of whom it was incipient. Thus acute uraemia may occur with or without oliguria. Clinically the non-oliguric form may be overlooked but is important to recognize since recent advances in therapy (high-calorie low-nitrogen feeding) may increase the patient’s chance of survival. Both Shen et al. (1943) and Goodpastor et al. (1946) refer to burned patients with significant azotaemia but without oliguria, the kidneys of whom had changes now referred to as distal tubular necrosis. Acute uraemia without oliguria is not restricted to burned patients. Two severely injured patients studied by Burnett were possibly examples (Smith, 1951), and more recently Teschan et al. (1955) described cases of uraemia without oliguria occurring after battle wounds. One case of post-traumatic uraemia without oliguria in which the histology was that of a diffuse D.T.N. was described by the writer (Sevitt, 1956).

Most of the 18 patients with focal D.T.N. were children (Table I). The urinary excretion of 15 of them was known to be adequate and only two developed severe oliguria (Table IV). The causes of death were unrelated to renal failure and were usually infective conditions like bronchopneumonia or septicaemia. One patient developed uraemia without oliguria, but this may have been the result of a severe proximal tubular degeneration: Eight others were biochemically investigated and showed no evidence of significant azotaemia. Histologically the early phases of the focal condition differed in no qualitative way from the diffuse form; the difference was quantitative. Casts were few, necroses were not numerous, few tubules were involved. The involvement of few nephrons was the essential histological difference from the diffuse form. The diagnosis of the stage of healing or the healed residue was made largely by the finding of characteristically situated cellular foci around venules or between tubules in the boundary zone or at second convoluted tubules: in some cases this was associated with thrombotic evidence of tubulo-venous rupture. In the healing stage there was also residual evidence of tubular necroses or recent regeneration.

The 17 patients who died with extensive proximal tubular necrosis were divided into 13 early cases dying within five days of burning and four later cases surviving 10 days or longer. Eight of the former were known to have acute renal failure which took the form of severe oliguria or anuria in seven and incipient uraemia without oliguria in the other. Most of the patients were elderly and the majority had nephrosclerosis with or without hypertension.

The overall frequency of P.T.N. in the present series was about 20% (17 among 86 subjects). This is probably an underestimation of its true incidence among the 174 fatally burned patients, because necropsies were performed on 55% to 73% of patients in various age groups below 60 years but only in 32% of the 76 patients over the age of 60 years.

The histological appearance was characterized by a widespread focal or confluent necrosis of the proximal convoluted tubules and the condition was restricted to the cortex. Post-mortem autolysis was not responsible for the histological changes, first because the necropsies were not unduly delayed (six were performed within 15 hours of death, 10 within 24 hours, and 16 within 36 hours); secondly, in most patients there was a histologically viable subcapsular rim or area of cortex; and thirdly the pyramid was not necrotic. The histological appearance had many features in common with that described by Dunn and Montgomery (1941) in eight unburned patients under the name acute necrotizing glomerulo-nephritis. Five of their patients were known to have had severe oliguria or anuria and there was a notable rise in the blood urea in the three patients on
whom the test was done. They noted the rapidity of nuclear loss and cytoplasmic changes in the affected epithelium, and this has been observed in the present series.

Pathogenesis

Proximal Tubular Necrosis.—The renal capsule has a separate blood supply and anastomoses with the main renal vessels in the subcapsular cortex. Thus the presence of a viable subcapsular rim of cortex indicated that the tubular necrosis of the cortex was the result of ischaemic changes in the blood supply from the main renal vessels. The histological viability of the tubules in the pyramids could have been the result either of their greater resistance to ischaemic anoxia, or alternatively to an abnormal intrarenal distribution of the blood flow by means of which cortical but not medullary ischaemia is produced. de Wardener (1955) completely occluded the main left renal artery of eight dogs for three to four hours, then released the vessels and killed the dogs a few days later. In each left kidney there was considerable or complete necrosis of the cortex (often including glomeruli) but in several dogs there were thin irregular subcapsular areas of viable cortex. The least affected areas of the cortices in all the necrosed kidneys were in the juxtamedullary zone. On the other hand the tubules of the pyramid were viable in appearance in five dogs and only in three did necrosis occur here. de Wardener's sections have been examined by me and his results confirmed. Thus the distal and collecting tubules of dogs frequently withstand complete ischaemia lasting three or four hours whilst the proximal tubules usually suffer irreversible necrotic changes during this period. In man it is therefore likely that a period of total renal ischaemia sufficiently long to produce proximal tubular necrosis may be insufficient to produce serious changes in the distal or collecting tubules. The viable appearance of the distal and collecting tubules in the present series of patients with cortical tubular necrosis is consistent with this view.

However, an abnormal distribution of the intrarenal blood supply either immediately after burning or after a period of total ischaemia may also have occurred. There was histological evidence of cortical ischaemia in 13 cases, but in most of these the ischaemic zones were focal, multiple, and of irregular distribution. This may have been produced by narrowing of the afferent glomerular arterioles when both the glomeruli and peritubular capillaries were empty of blood, or by narrowing of the efferent arterioles when the former were congested and the latter empty. These processes have been shown to occur in some experimentally burned rabbits, the intrarenal circulation of which has been studied by the injection in vivo of a colloidal gold suspension into the abdominal aorta in a cephalic direction (Sevitt, unpublished observation). In two patients, however, the appearance of cortical, infarct-like areas in the kidneys indicated that ischaemia of these areas was the result of a cortical by-pass mechanism. Trueta et al. (1947) showed that in this by-pass the blood for the distal two-thirds or so of the cortex is diverted through the juxtamedullary glomeruli, the efferent vessels of which loop downwards and drain directly into the tributaries of the renal vein. Moreover they showed that this is likely to happen in nephrosclerotic kidneys because occlusion of the capillaries of the juxtamedullary glomeruli often results in a direct communication between the afferent and efferent arterioles. This has relevance to the present cases most of which were elderly patients with nephrosclerosis.

Studies of the intrarenal blood flow in severely burned animals have been made by Monsaingeon, Tanret, and Daussy (1949) by the injection of various dyes in vivo. They found ischaemia of the outer two-thirds of the cortex in 14 out of 25 burned rabbits, in three out of nine burned guinea-pigs, and in five out of 25 burned rats. Total renal ischaemia was found in four rabbits, four guinea-pigs, and eight rats, and irregular cortical ischaemia was found in seven rabbits and six rats. This frequent and extensive ischaemia was not found by the writer in burned rabbits (unpublished observations), but the animals of Monsaingeon and his colleagues were usually burned more extensively and for longer periods than the writer's.

From a review of the literature of cortical necrosis in unburned patients Dunn and Montgomery came to the conclusion that infections played a part in the genesis of many cases including five of their own. An infective aetiology may account for the changes in three or four of the later cases of the present series but not for the early cases. Renal necrosis in these patients must have been produced by changes set in motion by the burning of the skin which resulted, as has already been indicated, in complete renal ischaemia or by a disturbance of intrarenal circulation or in the latter following a period of complete ischaemia. Case 1, however, may be an exception since she died only two hours after burning and she may already have had proximal tubular necrosis at the time she was burned.

Renal or intrarenal ischaemia is probably produced by vasoconstriction but the mechanism
whereby this occurs is not known with certainty. Renal vasoconstriction, perhaps reflexly produced, may result from the oliguria due to loss of plasma into the burned skin. Oliguria, however, is usually more severe and of more rapid onset in more extensively burned patients, but only four of the subjects with proximal tubular necrosis had burns exceeding 40% of the body area (Table II). This may be compared with an incidence of 30 out of the 34 patients with distal tubular necrosis. Nervous or humoral factors have been incriminated and there is evidence of these in experimentally burned animals. Barac (1946, 1948) found that the anuria in burned dogs was partly determined through excitation of the renal nerves which was both of cerebral and of spinal origin, and Page (1943) showed that the plasma of burned dogs developed vasoconstrictor properties for the vessels of isolated rabbits ears.

Evidently further information is required but the main body of evidence indicates that proximal tubular necrosis after burning is produced by renal ischaemia of vasomotor origin.

**Diffuse D.T.N.**—Three hypotheses have been put forward to explain the severe oliguria and anuria of the classical type of acute renal failure associated with the histological changes now referred to as diffuse D.T.N. These are a shutdown of the renal circulation, obstruction of tubules, and an unselective reabsorption of the glomerular filtrate (Lucké, 1946; Bull et al., 1950). In addition leakage of glomerular filtrate through damaged tubular walls, producing interstitial oedema and a rise of intrarenal pressure, has been postulated to explain the persistence of the oliguria (Oliver et al., 1951; Oliver, 1953; Bull and Dible, 1953). This is unlikely for two related reasons. First, the renal capsules were under tension in both the oliguric and non-oliguric cases of acute uraemia associated with diffuse D.T.N., and, secondly, no difference in the histological degree or extent of the interstitial inflammatory changes including interstitial oedema could be made out between the two clinical forms.

**Haemoglobinuria.**—Among the many nephrotoxic substances which have been incriminated are heme compounds. Intravascular haemolysis commonly occurs after severe burning, and if the plasma haemoglobin level rises above a threshold value (120 to 140 mg. %) haemoglobinuria results. This may be slight and easily overlooked or deep red or reddish-brown and readily recognized; it may be transient, or it may last one or two days or longer. Thus the recording of clinically observed haemoglobinuria is an index of its severity and the incidence of known haemoglobinuria will reflect the frequency of severe haemoglobinuria.

In Table IV the frequency of haemoglobinuria among patients with and without tubular necrosis is set out. On the one hand 12 out of 16 patients (75%) with diffuse D.T.N. had haemoglobinuria; 13 of the total number were known to have developed renal failure (oliguric or non-oliguric), and in 11 of them (84%) haemoglobinuria was known. On the other hand only three out of 24 patients (12.5%) without tubular necrosis had haemoglobinuria. The frequency of haemoglobinuria among patients with focal D.T.N. (six out of 18 or 33%) and early P.T.N. (six out of 13 or 46%) was intermediate. The overall incidence of haemoglobinuria in patients with renal failure was 17 out of 24 (possibly 18 out of 26) or about 70%. Thus haemoglobinuria occurred in most of the patients with acute renal failure, particularly among those who developed diffuse D.T.N. Conversely haemoglobinuria was uncommon both in patients without tubular necrosis and in those who developed focal D.T.N., the great majority of whom did not develop renal failure.

The manner by which haemoglobinuria induces or predisposes to diffuse D.T.N. is not known with certainty, but the histological appearance of many haemoglobin casts which focally block many distal tubules, render them focally necrotic, and induce tubular rupture cannot be disregarded as a pathogenetic factor. Since haemoglobin itself is said to be non-toxic, other factors must also be required before a diffuse D.T.N. occurs. Oliguria producing renal vasoconstriction and ischaemia may be responsible and is under investigation.

**SUMMARY**

A histological analysis of the kidneys of 86 burned patients showed a proximal tubular necrosis in 17 and a distal tubular necrosis in 34 subjects. The combined frequency of both kinds of tubular necrosis is similar in children, adults, and elderly subjects.

Proximal tubular necrosis occurs mainly in elderly subjects who had nephrosclerosis and is commonly associated with severe oliguria. It is characterized by a widespread necrosis of the proximal convoluted tubules, and this probably the result of vasoconstriction of the main renal arteries or of a disturbance of the intrarenal blood flow.

Distal tubular necrosis mainly affects children and younger adults and may or may not be associated with acute renal failure. If the condition
affects many nephrons it is termed diffuse D.T.N. and this corresponds to Lucké's lower nephron nephrosis.

Diffuse D.T.N. was found in 16 patients and was associated with anuria or severe oliguria or alternatively with a non-oliguric form of acute uraemia. No histological differences could be found between the oliguric and non-oliguric forms. Haemoglobinuria was usual and may be of aetiological significance.

Focal D.T.N. which affected few nephrons was found in 18 patients. It usually affected children, was infrequently associated with acute renal failure, and was rarely of clinical importance.

I am indebted to Dr. de Wardener for sending me his sections of dogs' kidneys, to various colleagues for their interest, to my secretary, Mrs. M. Swinden, and to Mr. D. Gibb, A.I.M.L.T., who prepared many of the sections and helped with the photomicrography. The work was carried out in my capacity as a part-time member of the scientific staff of the Medical Research Council.