Virchows Arch [Pathol Anat] (1985) 406:75–89

Virchows Archiv A

Tubular ultrastructure in acute renal failure in man: epithelial necrosis and regeneration

T. Steen Olsen, H. Steen Olsen, and H.E. Hansen
University Institute of Pathology and Department of Medicine C, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark

Summary. It is not clear whether tubular cell necrosis is present or not in acute renal failure (ARF) of ischaemic type ("acute tubular necrosis"). In order to get quantitative data, using precisely defined criteria for tubular cell necrosis, 25 renal biopsies from 24 patients with ARF (11 obtained in the active phase, 14 in the early recovery period) were compared with 12 control biopsies. In all 1959 proximal cells and 1603 distal cells were analysed by electron microscopy. Cellular disintegration was very rare in all groups. Shrinkage necrosis (apoptosis) was not present in the proximal tubules of the controls and was rare in ARF (1.6–2.1%). In the distal tubules of controls 2.7% of all cells showed shrinkage necrosis. The incidence in ARF was not significantly increased. "Non-replacement sites" in distal tubules (probably *loci* where cells have recently been desquamated) were significantly increased in number (5.2%) in the active phase in ARF compared to controls and recovery. The relative number of regenerating cells was not increased.

These data show that there is no widespread necrosis of tubular cells in ARF. The increased incidence in distal tubules of focal, denuded areas of the basement membrane in the active phase of ARF indicates a slightly increased desquamation of cells and/or a failure to cover such sites by adjacent cells. This process is not restricted to the brief induction phase of ARF but continues during the whole active phase.

Key words: Acute renal failure – Renal tubules – Necrosis – Electron microscopy.

Electron microscopic studies of renal biopsies from patients with acute renal failure (ARF) are rare and only a small number of biopsies has been studied using non-systematic methods (Dalgaard and Pedersen 1961; Olsen 1967; Olsen and Skjoldborg 1967; Dunnill and Jerrome 1976). These studies have

Offprint requests to: T. S. Olsen at the above address

not contributed decisively to our understanding of the pathogenesis of ARF in man. A recent report by Jones (1982) (combining transmission electron microscopy (TEM) with scanning electron microscopy (SEM)) has increased our knowledge of renal ultrastructure in ARF but there is still the need for a systematic TEM investigation of a larger series of patients.

The data presented in this paper concern epithelial necrosis and regeneration occurring in the convoluted proximal and distal tubules in a series of patients with (or in early recovery from) ARF of ischaemic type ("shock-kidney", "acute tubular necrosis"). Other articles in this series present a semiquantitative study of cell surface alterations (brush border and basolateral infoldings) and other tubular lesions in ischemic ARF, as well as the ultrastructural pathology of ARF in patients with acute interstitial nephritis (Olsen et al. 1985a–c). A preliminary report of data from these studies has recently been published (Olsen, T.S. and Olsen, H.S. 1984a).

Material and methods

Control biopsies (Group A). Six biopsies were obtained from 6 patients without signs or symptoms of renal disease. Five of these biopsies came from patients at surgery for appendicitis or gall stone and were made with the consent of the patients. Serum creatinine was available at the time of renal biopsy from four patients (133, 53, 88, 88 μmol/l). In 2 of these the creatinine clearance was also determined (135 ml/min, 88 ml/min). One biopsy was obtained just after death from a patient who died from a severe head injury. None of the patients had oliguria, all had a negative test for protein in the urine. On light microscopy (LM) these biopsies were normal.

Six biopsies were from 6 patients with minor change glomerulopathy or glomerulonephritis. Renal function measured by creatinine clearance was normal (90–125 ml/min) in the 4 patients in which it was determined. Two other had serum creatinine values of 80 and 100 μmol/l. All patients had proteinuria. On LM there were normal glomeruli or slight to moderate glomerular mesangial hypercellularity. The vessels, tubules and interstitium were normal on LM.

Patients. Twenty-five biopsies from 24 patients were studied (Table 1). The biopsies were collected during the period 1963–1983. The only criterion for selection was the presence of well-preserved, non-traumatized cortical tubules in the part of the biopsy fixed for electron microscopy (EM) judged from the semithin plastic sections studied by LM before the section of the blocks on the ultramicrotome.

As with other series the biopsies represent only a minor fraction of patients with parenchymatous ARF of non-glomerular origin admitted to the department during the period of collection and the series is not a random sample since (according to usual practice in our own and in other clinical departments) diagnostically uncomplicated ARF were not biopsied. Biopsies from patients with prerenal and postrenal ARF were excluded as were also transplant biopsies.

All patients had, or were in early recovery from, ARF of ischaemic type at the time of biopsy. ARF was defined as a sudden decrease of renal function to a degree not compatible with conservation of normal serum creatinine. Consequently all patients had rapidly increasing serum creatinine necessitating dialysis treatment in 16 patients. Eleven biopsies from 10 patients were taken in the active phase of ARF defined as the period when creatinine clearance was 5 ml/min or lower (Group B). Most of the patients were anuric at the time of biopsy, the rest had oliguria. Thus, no biopsies were from patients in the active phase of non-oliguric ARF. Fourteen biopsies from 14 patients were taken in the early recovery period after ARF (Group C). This group differed from group B not only by the fact that the biopsy had been provided during recovery and not active ARF, but the group also included cases of less severity. Thus 6 patients had suffered from ARF of the non-oliguric type (urine output >500 ml/day at peak of the disease) and had a minimum creatinine clearance at 5–30 ml/min.

On LM, 19 biopsies showed the picture characteristic for ARF (Olsen 1984b): slightly to moderately dilated tubules, presence of scattered casts, often of hem-type and a slight interstitial mononuclear cell infiltration. Two biopsies had prominent doubly refracting crystals in the distal tubules and collecting ducts (FR and NS). Two others had a few focal small interstitial granulomas (BR and IA). Two biopsies had normal structure by LM (PA and PP).

Biopsies with heavy interstitial mononuclear cell infiltration (acute, interstitial nephritis) were not included. An analysis of the ultrastructure of these is reported separately (Olsen et al. 1985c).

Technical procedures. Five renal biopsies from the control group were taken with an Iversen-Roholm needle from the kidney exposed under operation (appendectomy, cholecystectomy). All other biopsies were taken percutaneously with the Iversen-Roholm needle. Tissue for LM was processed according to the routine of our laboratory (Brun and Olsen 1981).

Preparation for electron microscopy. Tissue from each end of the biopsy was put into 2% glutaraldehyde and carefully cut with a pair of razor blades into small one millimeter cubes. They were transferred to a new vial containing 2% glutaraldehyde, fixed for 2 h, postfixed in 1% OsO_4 for one hour, dehydrated and embedded in Vestopal W or Araldite. The specimens were stained *en bloc* with 2% uranyl acetate and at the grid with lead citrate.

Using LM on semithin sections, blocks were selected that were judged to come from the cortical labyrinth due to the presence of glomeruli in the sections. Blocks with signs of mechanical damage were excluded, but no other selection criteria were used. This method permits exclusion of tissue that has been grossly damaged by the biopsy needle or on cutting. It also makes it possible to avoid tissue from the medulla or cortical medullary rays. Since there is variation of the ultrastructure in different segments of the tubules, it is important to be able to identify the tubular section under investigation. Thus the present study concerns contorted proximal and distal tubules.

Electron micrographs covering each tubular profile in one or more pictures were studied at a magnification of 3,525×. These were supplemented by randomly selected series covering 1/3–1/2 of the tubular circumference at a magnification of 11,175×. Only tubular cells with their nucleus represented in the plane of section were counted.

The total number of tubular profiles investigated was 171 proximal and 66 distal in the control groups, 196 proximal and 133 distal in the ARF groups. The number of cells investigated is apparent from Table 2.

Results

Almost all tubular cells only displayed minor deviations (such as increase in the number of lysosomes or vacuoles) from normal structure as described by Ericsson et al. (1965) and Tisher et al. (1966 and 1968). One exception were the alterations of tubular brush border and basolateral infoldings reported in a companion paper (Olsen et al. 1985a). The majority of cells were, therefore, judged as being vital by usual ultrastructural criteria. Three types of necrosis could be distinguished.

1. *Shrinkage necrosis* (cellular dehydration) (Fig. 1). This alteration appeared as condensation and increased electron density of the cell sap with densely packed organelles. Vacuoles and cisterns were distended. Some mitochondria showed cristal distension. The nucleus showed clumping and margination of the chromatin. Its membrane was markedly folded and the nuclear volume appeared decreased. In the present material, this type almost always affected single cells, which contrasted strongly with the adjacent normal epithelium.

Table 1. Clinical and laboratory data of the patients.

Patient Age/sex			Underlying conditions	Anuria Olig. uria	Period of dial. (days)	Minim. cr. clear. ml/min.	Max se. creat. μmol/l	At biopsy				Outcome	
								Cr. clear. ml/min.	Se. creat. μmol/l	Urin. outp. per d. ml	Days after onset	Days to stabil.	Se. creat. μmol/l
Oliguric ARF, active phase													
CJ	71	M	Aortic aneurysm, postop. shock	A	23	<1	715	5	400	400	18	31	195
KF	24	M	Pneumonia, diss. intravasc. coagul.	A	27	<1	920	<1	700	110	18	47	85
JA	49	F	Unknown. Acute haemolytic anemia	A	12	0	1,380	1.5	1,050	520	16	300	105
SN	36	M	Paraquat. intox. Diss. intravasc. coagul.	A	32	0	1,230	0	1,142	24	12	1,825	115
TS	40	F	Post partum haemorrh. shock	A	7	<1	1,520	<1	800	220	8	45	80
BJ	24	F	Post partum haemorrh. Diss. intravas. coagul.	A	5	<1	1,460	<1	1,460	315	6	45	90
EM[1]	50	F	Postoper. shock, sepsis. Metronidazol	A	57	0	–	0	550	0	20	57	anuric died
EM[2]	50	F	Postoper. shock, sepsis. Metronidazol	A	57	0	–	0	800	0	25	57	anuric died
EM	52	M	Unknown cause. Pneumonia?	A	5	<1	960	<1	860	250	2	37	460 died
JN	44	M	Chlorprothixene, alcohol	A	0	<1	1,590	2–3	1,590	670	5	55	9
AN	46	M	Cantharidin poisoning	0	3	<1	–	5	804	550	3	21	100

Early recovery after ARF													
FR	27	M	Leukaemia. Blood uric acid elevated	–	0	11	1,025	15	1,025	3,450	3	12	185
CA	17	M	Diphenhydramine	–	0	20	785	80	114	3,350	9	14	88
NS	31	M	Unknown	–	0	–	1,609	6	1,609	1,550	8	36	135
GJ	31	F	Post partum haemorrh. shock	A	0	2	1,140	13	960	2,750	6	30	100
BR	32	F	Methylene chloride, organic solvents	–	0	12	450	124	65	1,500	30	120	97
PP	26	M	Truxal poison. (=chlorprothixene)	–	0	10	460	35	335	2,475	6	10	105
IA	23	F	Diphenylhydantoin	A	4	<1	–	100	80	1,800	24	22	80
JK	22	M	Chlorprothixene poisoning	–	0	17	860	20	875	2,020	2	6	203
BC	39	M	Diphenhydramine, coffein, (heroin?)	0	5	3	1,000	7	910	1,200	9	22	160
EJ	43	M	Falciparum Malaria, acute haemolysis	0	3	1	627	14	540	2,400	9	35	80
NJ	64	F	Morphine and codeine, chlorpromazine, shock	A	4	<1	1,084	13	725	274	11	20	160
HS	42	M	Pneumonia	A	19	<1	885	22	678	1,500	19	40	70
PA	49	M	Lithium poisoning	0	2	9	485	30	220	2,620	10	20	250
AA	20	F	Mastocytosis – anaphyl. shock.	A	3	<1	603	15	435	2,650	11	14	90

Table 2. Cellular necrosis in biopsies from patients with ischemic ARF. *Cell. disint., Shrink necr., Non-replac.:* Number of cells displaying signs of three forms of necrosis as defined in the section of results. * significantly different from control value ($2p < 0.001$, χ^2 test).

	No biop.	No cells	Cell. disint.	%	Shrink. necr.	%	Non-replac.	%	Regen. cells	%
Proximal tubules										
Control biopsies	12	956	0	0	0	0	0	0	10	1.0
ARF, active phase	11	351	0	0	6	1.6	3	0.8	6	1.6
Recovery after ARF	14	652	1	0.2	14	2.1	6	0.9	6	0.9
Distal tubules										
Control biopsies	12	517	0	0	14	2.7	4	0.7	13	2.5
ARF, active phase	11	344	0	0	4	1.2	18*	5.2*	11	3.2
Recovery after ARF	14	742	2	0.3	21	2.8	5	0.6	30	4.0

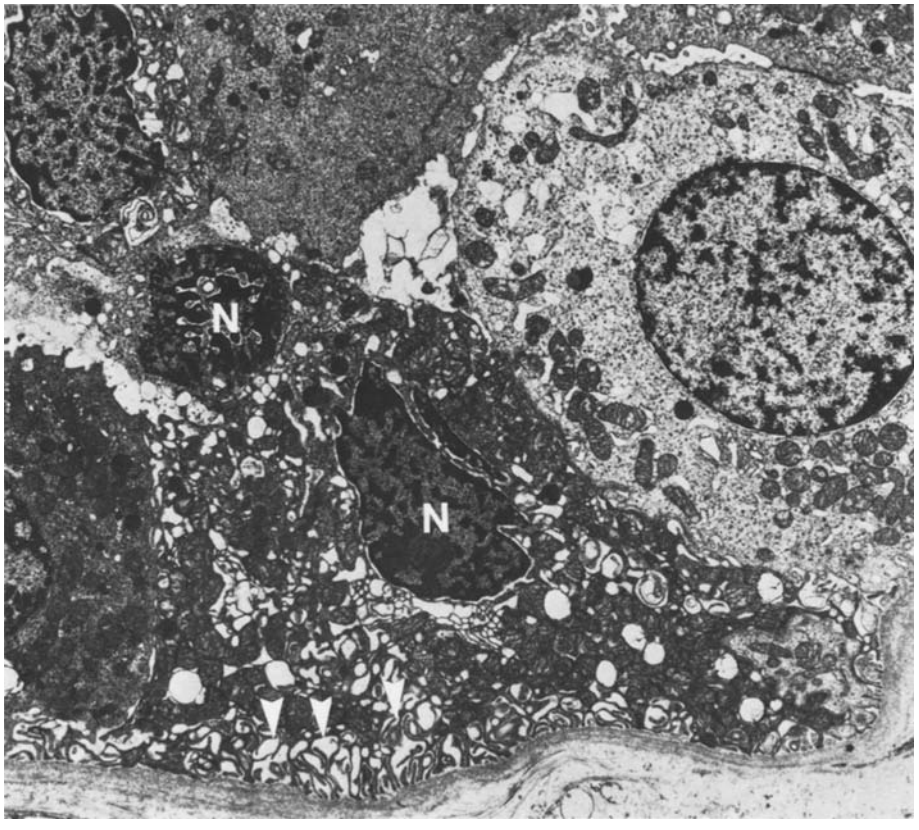


Fig. 1. Shrinkage necrosis of distal tubular cell from a biopsy belonging to the control group. The nucleus (*N*) is angular, heavily shrunken, with clumping of the chromatin. The cell sap is dense, the vacuoles and intercellular spaces distended (*arrows*). The cell to the right is probably in a transition between regeneration and full maturity. There are many polyribosomes, but an appreciable (although not normal) number of mitochondria is a sign of maturity. ×8,100

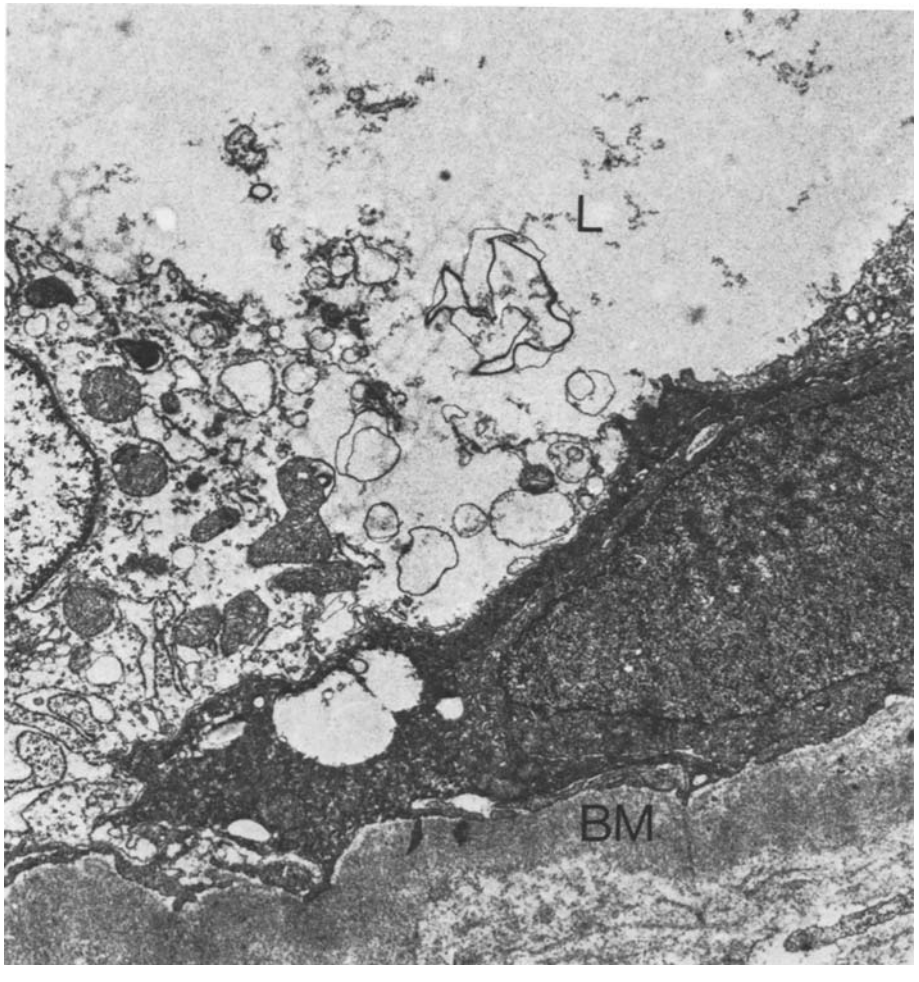
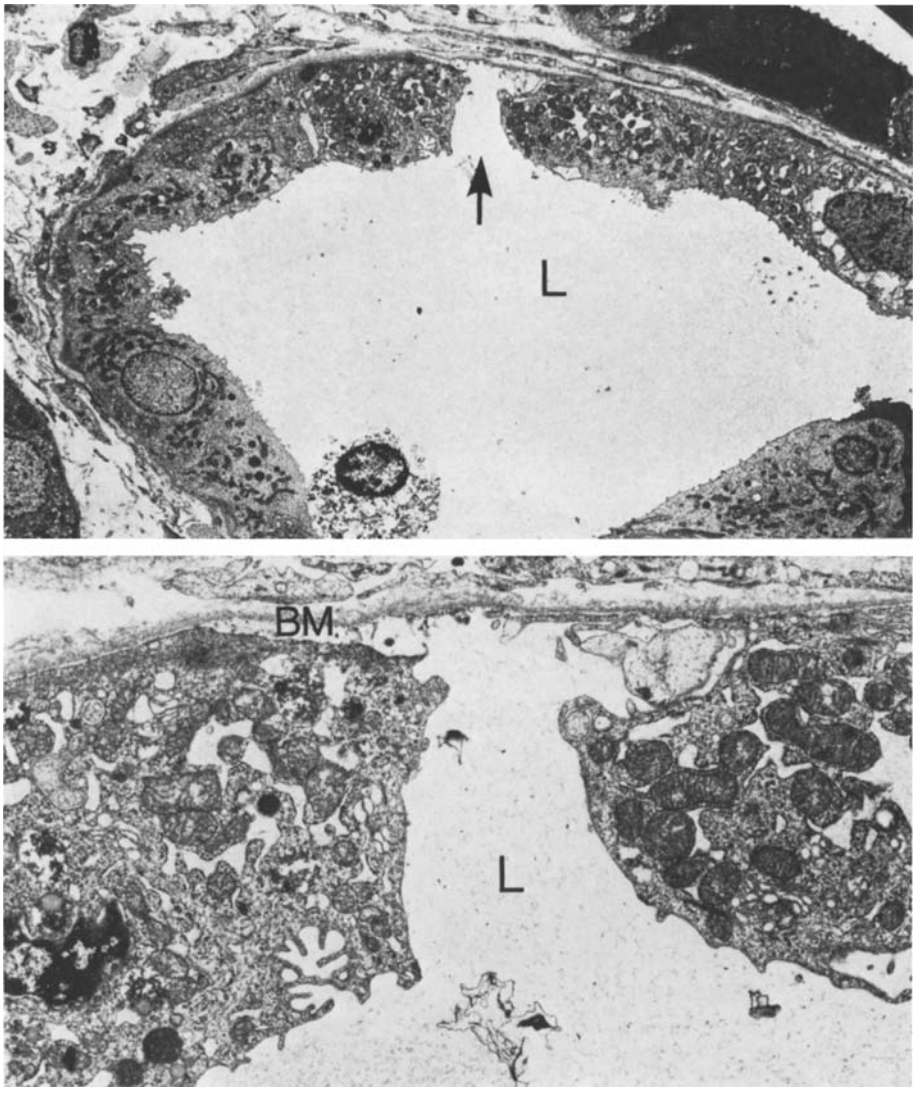


Fig. 2. Part of a tubular cell with disruption of the cell membranes (*left*). To the right a cell with increased density of the cell sap. *BM*: basement membrane; *L*: lumen ×12,500

2. *Cellular disintegration* (Fig. 2). Disintegrated cells usually had a very hydropic cell sap. The plasmalemma as well as the membranes of nuclei and organelles, were disrupted.

3. *"Non-replacement" phenomenon* (Fig. 3). As suggested by Solez et al. (1979) on the LM level, this change is defined as the presence of defects in the epithelial covering of the tubular basement membrane (BM). On EM, denuded BM areas (probably the site of a desquamated cell) were present focally and usually corresponded to no more than the size of one tubular cell. The denuded BM was always intact and breaks did not occur either in any other parts of the tubular profiles studied. The adjacent cells were almost always normal. Rarely a group of epithelial cells was seen in the process of desquamation (Fig. 4).



A

B

Fig. 3A, B. Non-replacement site in a distended distal tubule from a patient with ischaemic ARF. There is a gap in the row of tubular cells (*arrow*). The adjacent cells are vital. *L*: lumen. *BM*: basement membrane. **A** ×2,800; **B** ×11,100

Besides these types, a fourth type of cellular change was noted:

4. *The regenerating cell* (Fig. 5). This cell type was globoid in form, its cell sap was electron lucent, the organelles extremely few, and there was no granular endoplasmic reticulum. A large number of polyribosomes were dispersed over the cytoplasm.

The occurrence of the three categories of cellular damage appears in Table 2.

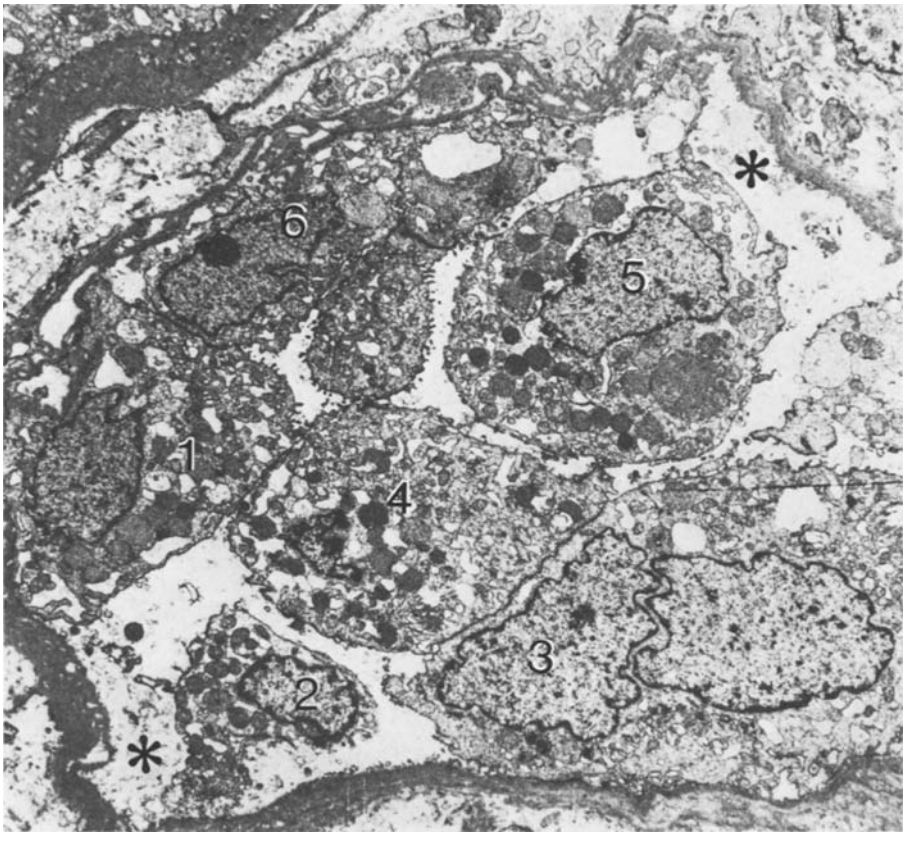


Fig. 4. The cellular desquamation may rarely involve several adjacent tubular cells. Cells number *1, 3* and *6* are still in place although partially loosened from the basement membrane. No. *2* seems to be in the act of desquamation and nos. *4* and *5* are situated free in the lumen (they may, however, have their origin in another part of the nephron). Asterisks at denuded basement membrane. A picture as this suggests that desquamation of cells without morphological evidence of necrosis may take place. From a patient with ischaemic ARF. ×4,500

Cellular disintegration was very rare in this material, occurring in only three cells investigated. Shrinkage necrosis (apoptosis) was not seen in any of the almost 1,000 proximal cells investigated in the control biopsies. It occurred in the proximal tubules of biopsies from patients with ARF or in recovery with very low frequency (1.6–2.1%). In the distal tubules the frequency of this type of necrosis was 2.7% in the controls and in the same level in patients. Non-replacement sites were not observed in normal proximal tubules, and rarely in the patients. In the distal tubules the frequency of these sites was (although rather low) significantly increased in the active phase of ARF compared with the controls and with the recovery period ($2p < 0.001$, χ^2-test). The frequency of regenerating cells was within the range of 0.9%–4.0%. There were no significant differences between patients and controls or between ARF and recovery. Very early biopsies

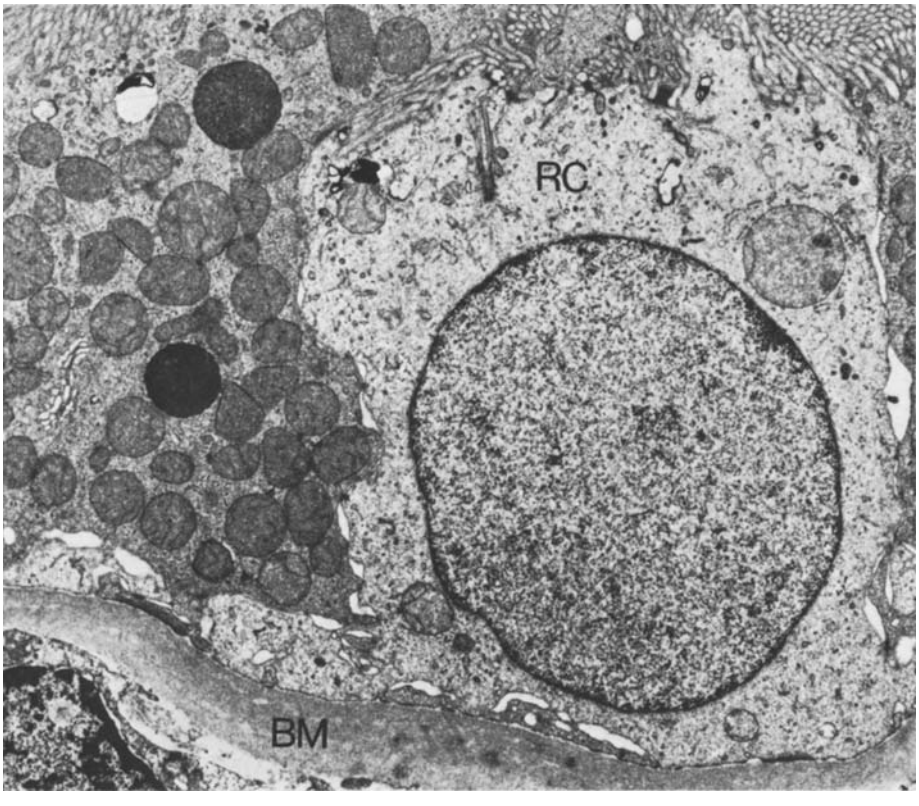


Fig. 5. Regenerative cell (*RC*) in a proximal tubule. There are very few organelles, no granular reticulum but plenty of polyribosomes. The nucleus is globoid with diffusely destributed chromatin. Most or all of the microvilli have probably their origin in the adjacent cells. *BM*: basement membrane. × 11,200

(1–3 days after onset of the ARF) often had low values and the highest value in a single biopsy (17%, distal tubules) occurred in a biopsy taken 11 days after the onset of the disease. Clusters of regenerative cells were seen, indicating that a focal distribution was responsible for the great range (0–17%) of the figures for single biopsies. Only one mitosis was seen in the total of 3562 cells examined.

Discussion

An extensive literature on the ultrastructure of necrosis and degeneration has been published, mainly based upon experimental studies. Papers of particular relevance for the renal tubular epithelium are the careful studies performed by Trump and coworkers (for a review and references see Trump 1982) as well as important contributions by Venkatachalam et al. (1978), Donohoe et al. (1978), Dobyan et al. (1977), Reimer et al. (1972), Davis et al. (1983) and Ormos et al. (1973). Trump and coworkers divided

ischaemic cell injury into a sequence of changes ranging from the normal cellular substructure to the necrotic cell. The initial stages (I–III) are characterized by dilatation of the endoplasmic reticulum (cisternae), surface protrusions and hydropia of the cell sap. The mitochondria appear dense with condensation of the inner compartment and enlargement of the intracristal space as well as the space between the inner and outer membrane. The nucleus shows clumping of the chromatin. The lysosomes are often swollen. In stage IV some of the mitochondria swell, others remain condensed. Some mitochondria contain tiny dense aggregates. These stages are all considered to be potentially reversible.

In stages V and VI, irreversible cell death is heralded. All mitochondria exhibit massive swelling and large flocculent densities appear in the inner compartment. The membrane system begins to dissolve or fragment, including the nuclear membrane and dissolution of the chromatin (karyolysis) takes place. In stage VII, cell degradation is prominent.

The 4 stages of Reimer et al. (1972) correspond rather well to the sequence described by Trump's groups, although a dehydrated cell type is more apparent in their study. This type is possibly identical with the shrinkage necrosis described by Kerr (1971), Kerr et al. (1972) and Searle et al. (1982) under the designation of apoptosis. This latter type of cellular injury, however, is distinct from ordinary necrosis by several traits: apoptosis affects scattered, single cells situated between other cells without signs of degeneration or necrosis. Typical for the apoptotic cell is a rapid condensation of nucleus and cytoplasm followed by nuclear fragmentation. The cell is quickly engulfed by macrophages and even by adjacent epithelial cells and is broken down within hours with formation of large phagolysosomes. Apoptosis occurs under physiological conditions as part of normal cell turnover, and it may be increased by several types of injury (anoxic, chemical, radiation).

The concept of "non-replacement" was introduced on the LM level by Solez et al. (1979). These authors described focal, denuded areas of the tubular BM, probably the site of necrotic and desquamated cells. The scattered denuded BM-areas, seen by EM, correspond to this LM observation. The adjacent cells were usually normal in structure.

Regenerating proximal tubular cells were studied by Ormos et al. (1973) in a rat model of hormone-induced necrosis. Regenerating cells were extremely rich in free ribosomes which were often arranged in rosettes. The early phase of regeneration was characterized by simplified cell structure and no organelles other than polyribosomes. These cells were thin and situated at the BM, beneath necrotic cells. At 48 h the content of polyribosomes reached a maximum and at 72 h the first rough surfaced endoplasmic reticulum began to occur. After one week the ribosome richness had regressed, while other organelles appeared in larger quantity and the brush border began to develop, even between adjacent cells. The basal labyrinth was still missing at this stage. At 2 weeks the regenerated cells had reached normal height with a well developed brush border and apical vesiculation. At 4 weeks the basal labyrinth began to appear in a primitive state and

at 6 weeks it was well developed. Parts of the tubules remained, however, still lined by an epithelium of incomplete maturation. The chromatin in the nuclei of regenerating cells is diffusely distributed (euchromatin) without heterochromatin clumps.

The alterations of epithelial cells seen in the *present material* were similar to some of the forms described above. Alterations pertaining to Trump's stages II–IV occcurred sporadically but not to a severe degree, and without special frequency in any of the patient groups. Since they also occurred in the control biopsies and as it is well known that they may be mimicked by artefacts due to fixation or other technical causes (particularly apt to occur in biopsy material which must be fixed by immersion), they were not regarded as significant. Into this category are included cells with slight to moderate changes in the density of the cell sap which may occur in normal controls as well as biopsies from patients suffering from ARF.

Shrinkage necrosis may resemble fixation artefacts due to hypertonic fixation media (Maunsbach 1973). Since, however, the fixation fluid was isosmotic with cortical tissue, and this cellular alteration invariably involved a whole cell and usually only one, the adjacent cells being normal, fixation artefacts could be ruled out. The fact, that this type of necrosis occur almost always in single cells is characteristic of the apoptosis of Kerr et al. (1972), although nuclear disintegration as seen in the final phase of apoptosis was rare.

In the preliminary analysis of some of the biopsies of the present material (Olsen and Olsen 1984a), ischaemic ARF and acute interstitial nephritis were pooled, and the analysis did not discriminate between different types of cellular damage. The frequency of severe damage was found to be low, and no consistent pattern of difference between controls, ARF and recovery was found. The present definitive analysis of ARF of ischaemic type using the presicely described categories of cellular damage of allegedly irreversible character described above, confirmed the general low frequency of cellular necroses. Only one value was significantly increased against the controls: the slight, but highly significant increase in frequency of non-replacement sites in distal tubules.

The occurrence of apoptotic cells and non-replacement sites in normal distal tubules can be interpreted as stages in normal cell turnover. Since these cell types were not present in proximal tubules from controls, it must be assumed that dying cells in this part of the nephron are desquamated quickly, possibly in advance of manifest morphological changes, and the gap filled almost immediately by adjacent cells.

From the experimental models cited above, it is known that severe ultrastructural damage takes place within a few hours or at most 1–2 days after the responsible insult. If, in human ARF, severely damaged cells are rapidly desquamated, and defects in the row of epithelial cells are quickly covered by the adjacent cells, irreversible injury to a comparatively large part of the cell population might happen at the onset of ARF without an appreciable increase in the number of necrotic cells or non-replacement sites in

biopsies taken days to several weeks after the injury. The fact that the number of regenerating cells was low also in very early biopsies speaks, however, against the occurrence of *extensive* necrosis in the initiating phase. That the main part of the tubular epithelium should be made up of regenerating cells (as suggested by Solez et al. (1983)) is contradicted by the generally mature appearance of the cells together with the fact that differentiation of a regenerating cell demands more than 2 weeks (Ormos et al. 1973). Attention should especially be directed to the observation of these authors that actin bundles were not formed in regenerating cells until about 14 days after the ischaemic injury. Actin bundles are, however, very frequent and hypertrophic in the tubular epithelium from patients with ARF (Olsen et al. 1985b), also in early biopsies.

The former concept of widespread tubular necrosis in ischaemic ARF, reflected by the name still in general use: "acute tubular necrosis" (Bull et al. 1950), was based on investigations of autopsy material, among these also the microdissections of Oliver (1951), where a technique was used which strongly increases the possibility of artificial damage. The concept was challenged by investigators studying renal biopsies by LM (Brun 1954; Brun and Munck 1957) and later by EM (Olsen 1967). These biopsy studies made it clear that no widespread necrosis could be detected in the renal tubules. A recent study by Solez et al. (1979) has revived the possibility of the presence of *focal* necroses. These authors, working with LM demonstrated the presence of scattered denuded areas of the BM, probably the sites of desquamation of necrotic epithelial cells. Indeed this lesion was one of only two out of 10 basic lesions studied, which did not persist in the recovery period, the other being disappearance of the proximal brush border.

Thus, while the occurrence of widespread tubular necroses must be excluded by the present study as argued above, we regard it as possible that an increased cellular desquamation takes place in ARF in the distal tubules or that ARF is associated with a failure or a reduction in the ability of adjacent cells to cover the defects following cell desquamation. Why this is a continuing process and not confined to the brief phase of induction is difficult to explain, but it might conceivably be a consequence of the decreased cortical blood flow characteristic of ARF.

Among the proposed pathogenetic hypotheses of ARF, *back-leak of urine* is still held as a possible cause of anuria or oliguria (Solez 1983) mostly on the basis of experimental data. As mentioned above, extensive tubular necrosis making profuse back-leak possible can be ruled out by the ultrastructural data. There remains, however, the possibility of focal back-leak through the approximately 5% denuded area of BM in the distal tubules found in the present study. Considering the relatively small part of the tubular wall which is deprived of epithelial covering, and since no BM ruptures were seen at all, it is improbable that tubular back-leak through the distal tubules should account for a *substantial* fraction of the reduction of renal function and other factors must be of greater importance. The

severe reduction of tubular cell surface areas, recently detected (Jones (1982); Olsen, T. and Olsen, H. (1984a), Olsen et al. (1985a)) may appear to provide a clue for pathogenesis of ischaemic ARF.

References

Brun C (1954) Acute anuria. Munksgaard, Copenhagen, 1954

Brun C, Munck O (1967) Lesions in the kidney in acute renal failure following shock. Lancet I:603–607

Brun C, Olsen T Steen (1981) Atlas of renal biopsy. Munksgaard, Copenhagen

Bull GM, Joekes AM, Lowe KG (1950) Renal function in acute tubular necrosis. Clin Sci 9:379–404

Dalgaard OZ, Pedersen KJ (1960) Proc Int Congr Nephrol st, p 165

Davis JM, Emslie KR, Sweet RS, Walker LL, Naughton RJ, Skinner SL, Tange JD (1983) Early functional and morphological changes in renal tubular necrosis due to p-aminophenol. Kidney International 24:740–747

Dobyan DC, Nagle RB, Bulger RE (1977) Acute tubular necrosis in the rat kidney following sustained hypotension. Physiologic and morphologic observations. Lab Invest 37:411–422

Donohoe JF, Venkatachalam MA, Bernard DB, Levinsky NG (1978) Tubular leakage and obstruction after renal ischemia: Structural-functional correlations. Kidney Internat 13:208–222

Dunnill MS, Jerrome DW (1976) Renal tubular necrosis due to shock: Light- and electron-microscope observations. J Pathol 118:109–112

Ericsson JLE, Bergstrand A, Andres G, Bucht H, Cinotti G (1965) Morphology of the renal tubular epithelium in young, healthy humans. Acta Pathol Microbiol Scandinav 63:361–384

Jones DB (1982) Ultrastructure of human acute renal failure. Lab Invest 46:254–264

Kerr JFR (1971) Shrinkage necrosis: A distinct mode of cellular death. J Pathol 105:13

Kerr JFR, Wyllie AH, Currie AR (1972) Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26:239

Kreisberg JI, Bulger RE, Trump BF, Nagle RB (1976) Effects of transient hypotension on the structure and function of rat kidney. Virchows Arch [Cell Pathol] 22:121–133

Maunsbach AB (1973) Ultrastructure of the proximal tubule. In: Handbook of Physiology. Renal Physiology. Sect 8. Am Physiol Soc, Washington DC 1973, pp 31–79

Olsen T Steen (1967) Ultrastructure of the renal tubules in acute renal insufficiency. Acta Path Microbiol Scand 71:203–218

Olsen T Steen, Skjoldborg H (1967) The fine structure of the renal glomerulus in acute anuria. Acta Pathol Microbiol Scand 70:205–214

Olsen TS, Olsen HS (1984a) A second look at renal ultrastructure in acute renal failure. In: Solez K, Whelton A (eds) Acute Renal Failure. Marcel Dekker, Inc, New York, Basel

Olsen T Steen (1984b) Pathology of acute renal failure. In: Andreucci VE (ed) Acute renal failure. Martinus Nijhoff Publishing, Boston/The Hague

Olsen TS, Hansen H, Olsen HS (1985a) Tubular ultrastructure in acute renal failure: alterations of cellular surfaces (Brush-border and basolateral infoldings). Virchows Archiv [Pathol Anat] 406:91–104

Olsen TS, Olsen HS, Hansen HE (1985b) Hypertrophy of actin bundles in tubular cells in acute renal failure. Ultrastruc Pathol (in press)

Olsen TS, Wassef N, Olsen HS, Hansen HE (1985c) Renal ultrastructure in acute interstitial nephritis. Virchows Archiv [Pathol Anat] 406 (in press)

Ormos J, Elemér G, Csapó Zs (1973) Ultrastructure of the proximal convoluted tubules during repair following hormonally induced necrosis in rat kidney. Virchows Arch Abt B Zellpath 13:1–13

Reimer KA, Ganote CE, Jennings RB (1972) Alterations in renal cortex following ischemic injury. III. Ultrastructure of proximal tubules after ischemia or autolysis. Lab Invest 26:347–363

Searle J, Kerr JFR, Bishop CJ (1982) Necrosis and apoptosis: distinct modes of cell death with fundamentally different significance. Pathol Annual Part 2:229–259

Solez K, Morel-Maroger L, Sraer JD (1979) The morphology of "acute tubular necrosis" in man: Analysis of 57 renal biopsies and a comparison with the glycerol model. Medicine 58:362–376

Solez K, Racusen LC, Olsen S (1983) The pathology of drug nephrotoxicity. J Clin Pharmacol 23:484–490

Tisher CC, Bulger RE, Trump BF (1966) Human renal ultrastructure. I. Proximal tubule of healthy individuals. Lab Invest 15:1357–1394

Tisher CC, Bulger RE, Trump BF (1968) Human renal ultrastructure. III. The distal tubule in healthy individuals. Lab Invest 18:655–668

Trump BF, Berezesky IK, Dowley RA (1982) The cellular and subcellular characteristics of acute and chronic injury with emphasis on the role of calcium. In: Cowley RA, Trump BE (eds) Pathophysiology of Shock, Anoxia, and Ischemia, Williams & Wilkins, Baltimore, USA, pp 6–46

Venkatachalam MA, Bernard DB, Donohoe JF, Levinsky NG (1978) Ischemic damage and repair in the rat proximal tubule: Differences among the S_1, S_2, and S_3 segments. Kidney Internat 14:31–49

Accepted January 2, 1985