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Tubular ultrastructure in acute renal failure: alterations of cellular surfaces (Brush-border and basolateral infoldings)

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Summary. Using a blind, semiquantitative technique, the degree of reduction of proximal tubular brush border (BB) and proximal and distal basolateral infoldings (BI) were measured in 25 renal biopsies from patients with acute renal failure (ARF) of ischaemic type. For comparison 12 biopsies from patients without ARF were studied, 6 were normal controls, six were from patients with minor change disease and slight glomerulonephritis. The mean scores for reduction of BB as well as proximal and distal BI were strongly increased in ARF compared to controls and the differences were highly significant. Some of the biopsies were taken during recovery and there was a significant negative correlation between the individual scores for reduction of BB and BI and simultaneous renal function. The disappearance of BB microvilli was correlated to tubular dilatation, but it could not be explained exclusively by "stretching" of the luminal surface due to dilatation. There was no correlation between reduction of BI and tubular dilatation.

The data indicate a disturbance of cell membrane turnover in the active phase of ARF, possibly due to decreased synthesis, and they are consistent with a pathogenetic hypothesis implicating a decreased proximal Na^+ resorption and consequently a pre-glomerular vasoconstriction.

Key words: Acute renal failure – Renal tubule – Electron microscopy – Brush border – Basolateral infoldings

The pathogenesis of acute renal failure (ARF) in man is still enigmatic in spite of a great number of studies of human patients and experimental models. One hypothesis, which has gained some support from several lines of evidence, states that reduced renal cortical blood flow in ARF induced by arteriolar vasoconstriction leads to decreased or abolished glomerular filtration. As a possible cause of this arteriolar vasoconstriction, Thurau

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et al. (1976) have proposed that the primary defect is a diminished tubular reabsorption of sodium in the proximal tubules. As a consequence, the Na^+ concentration at the macula densa increases and this leads to release of renin from the juxtaglomerular apparatus.

The transcellular sodium transport through tubular walls is induced by an enzymatic sodium pump located in the greatly folded, and therefore very large, basolateral cell surface of the epithelial cells. Although not directly involved in active sodium transport, the brush-border (BB) of the proximal tubules, which greatly enlarge the luminal cell surface, must be of importance for passive transcellular transport. The appearance of these cell surfaces in ARF is therefore of considerable interest.

Several years ago one of us (Olsen T.S. (1967)) suggested that the basolateral infoldings (BI) might be diminished in ARF. This assumption was, however, based on rather few and unsystematic observations. This report presents a systematic, blind and semiquantitative study of the tubular BB and BI in 25 renal biopsies from 24 patients with ARF of ischaemic type ("acute tubular necrosis"). A preliminary account of this study has been published recently (Olsen T.S. and Olsen H.S. 1984a).

Material and methods

Control biopsies and patients. Six control 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. One biopsy was obtained just after death from a patient who died from a severe head injury.

Six other control biopsies were from 6 patients with minor change glomerulopathy or glomerulonephritis.

Twenty-five biopsies from 24 patients suffering from ARF were studied. 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 at the ultramicrotome.

All patients had, or were in early recovery from, ARF of ischemic 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. 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. The clinical and laboratory data of the patients as well as the controls were given in a companion paper (Olsen et al. 1985).

On LM, 19 biopsies showed the picture characteristic for ischemic ARF (Olsen 1976; 1984a, b): slightly to moderately dilated tubules, presence of scattered casts, often of hem-type and a slight interstitial mononuclear cell infiltration. Two biopsies had prominent double refracting crystals in the distal tubules and collecting duct. Two others had a few focal small interstitial granulomas. Two biopsies had normal structure by LM.

Technical procedures. Renal biopsies from 5 patients in the control group were taken with an Iversen-Roholm needle from the kidney exposed under operation (appendectomy, cholecys-

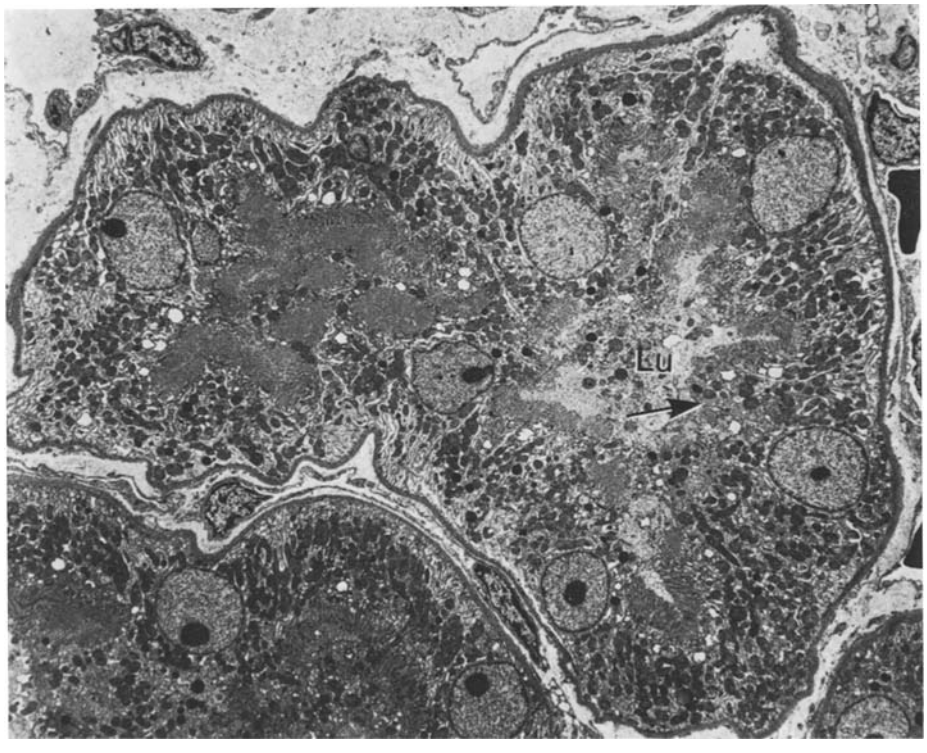

Fig. 1. Proximal tubule from control biopsy. The brush border is preserved. The lumen (*Lu*) is almost closed and blebs are projecting from the cell surfaces (*arrow*), which is normal for immersion fixed tissue. The basal infoldings are extensive. ×3,150

tectomy). 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 has been described in detail in the companion paper (Olsen et al. 1985).

Total tubular cross sections were photographed at a final magnification of 3,125×. Supplementary pictures were taken at a magnification of 11,175× representing a consecutive array of $^1/_2$–$^1/_3$ of all cells in each tubular section. Based on these two sets of pictures each tubular section was given a score (0–3+) for reduction of proximal BB and proximal as well as distal BI.

Semiquantitative scoring. The proximal BB appearing in each total tubular cross section was evaluated and disappearance of microvilli was scored 0–+3. Score 0 was given for the "ideal picture" as revealed in earlier studies of the normal tubular structure in human biopsies (Ericsson et al. 1965; Tisher et al. 1966 and 1968). When judging the normality of tubular cells the effect of fixation and mechanical procedures involved in biopsy taking and cutting for fixation must be taken into consideration (Maunsbach 1973). Thus, the normal tubular structure known from perfusion fixed human tissue (Møller et al. 1982) cannot be used as a paradigm. For instance normal structure in biopsy material is compatible with closed lumina as well as with the presence of large "blebs" from the luminal cell surface, without microvilli (Fig. 1–2). The same applies to distension of the basolateral intercellular spaces.

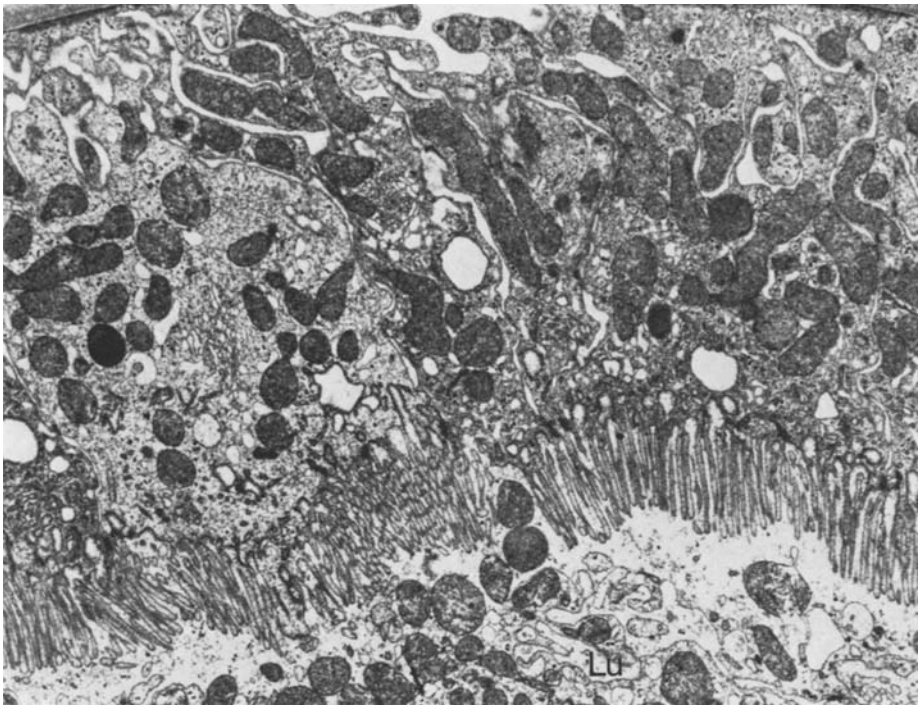

Fig. 2. Proximal tubule from control biopsy. Normal brush border and basolateral infoldings. There is cellular debris in the lumen (*Lu*). ×11,500

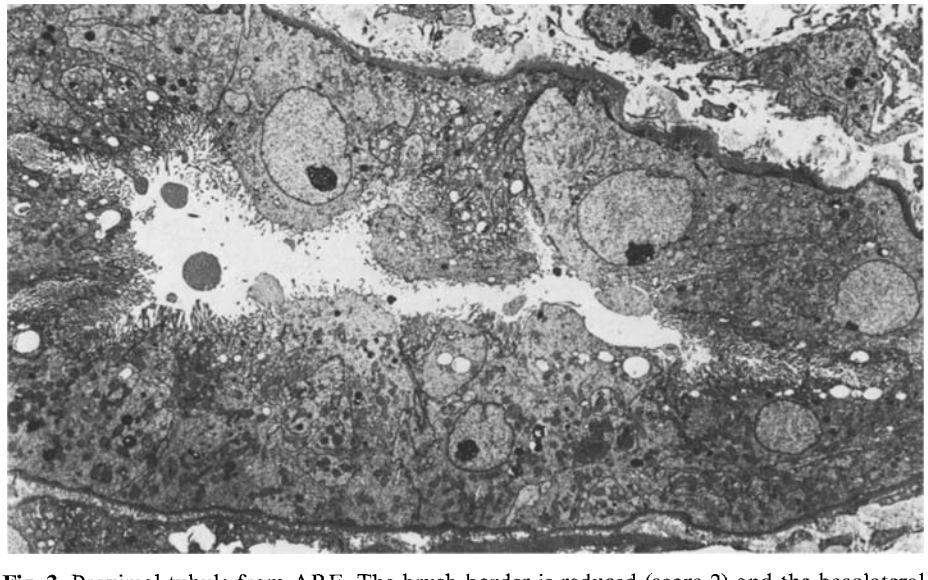

Fig. 3. Proximal tubule from ARF. The brush border is reduced (score 2) and the basolateral infoldings, almost absent. ×3,150

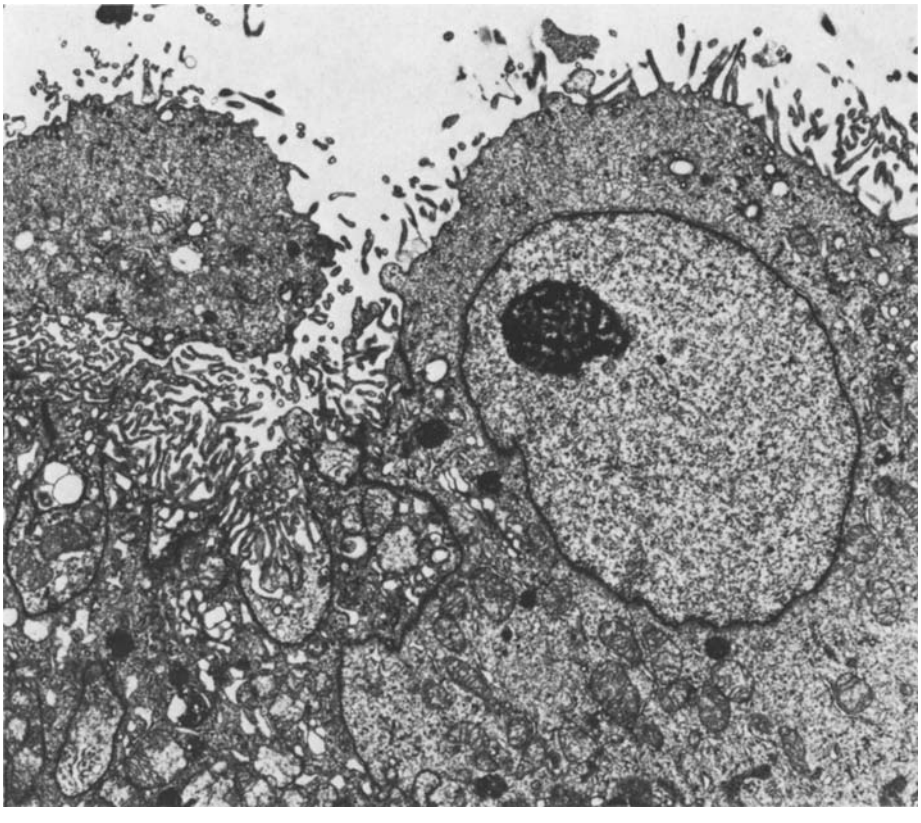

Fig. 4. Luminal part of proximal tubular cells from ARF. The same tubule as Fig. 3. ×11,500

The scores +1 and +2 were used for disappearance of microvilli to a slight or moderate degree (Fig. 3–4). The most severe degree (+3) of BB atrophy was used when only small patches of BB were identified in a total tubular cross section, often only enough to identify it as a proximal tubule[1]. A tubular cross section with total disappearance of BB cannot be identified as such since other ultrastructural details distinguishing proximal tubules are of quantitative character and may be altered by the disease. Reduction of BI was scored 0–+3 on each proximal and distal tubular cross section: 0 representing the ideal normal state, +3 the total or almost total disappearance of infoldings in a cross section (Fig. 5–7).

From the individual tubular scores the mean score of each biopsy was calculated. Although the general quality of the material was good for biopsy material, it nevertheless varied somewhat from place to place, and it was not considered feasible to perform a scoring of each cell. In perfusion fixed material, these cell membranes can be measured quantitatively by morphometry (Møller 1984). For the reasons mentioned above this was not considered possible in the present immersion fixed biopsy material, and the study was therefore performed using a semi-quantitative technique. The scoring was performed blindly, that is without the observer's knowledge of clinical group. Since it sometimes appeared to be possible to identify patients with ARF on ultrastructural features other than those which were under analysis, this blindness was not absolutely effective. Patients belonging to group B could, however, not be distinguished from those in group C. The number of tubular profiles and tubular cells investigated in each group appears from Table 1.

[1] The procedure was slightly different in the preliminary study (Olsen and Olsen 1984, 1)

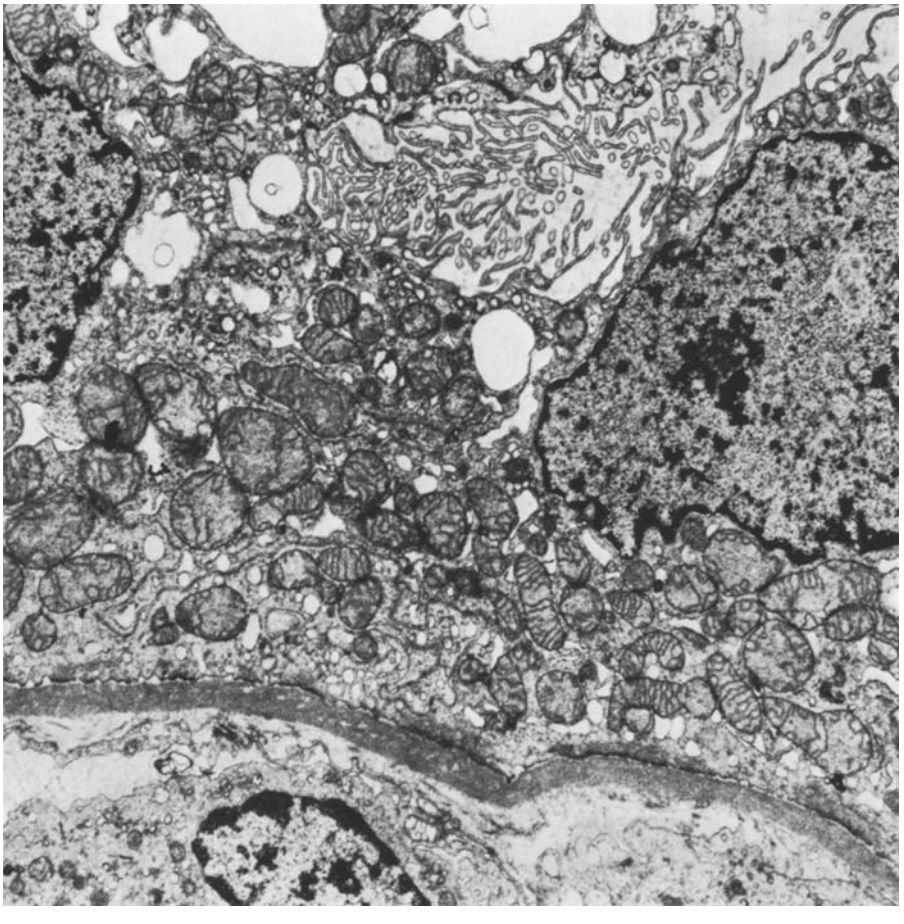

Fig. 5. Proximal tubular cell from ARF with moderate reduction of brush border and reduced basolateral infoldings. ×11,500

Results

The group means of scores for the reduction of proximal BB as well as proximal and distal BI appear in Table 2 and 3. The mean scores of the control group were low, but not 0, which reflects a minor discrepancy between the control material and the ideal picture reported in the literature (Ericsson et al. 1965; Tisher et al. 1966 and 1968). There were no significant differences between the group means of the 6 controls without renal disease and the 6 from patients with minor change disease or slight glomerulonephritis. The values from patients with ischaemic ARF in active phase (group B) were consistently elevated and the difference from controls highly significant, indicating a severe reduction of the luminal as well as the basolateral cell surface of the tubular epithelial cells in this phase. The values were lower in the recovery phase (group C) although still highly significantly

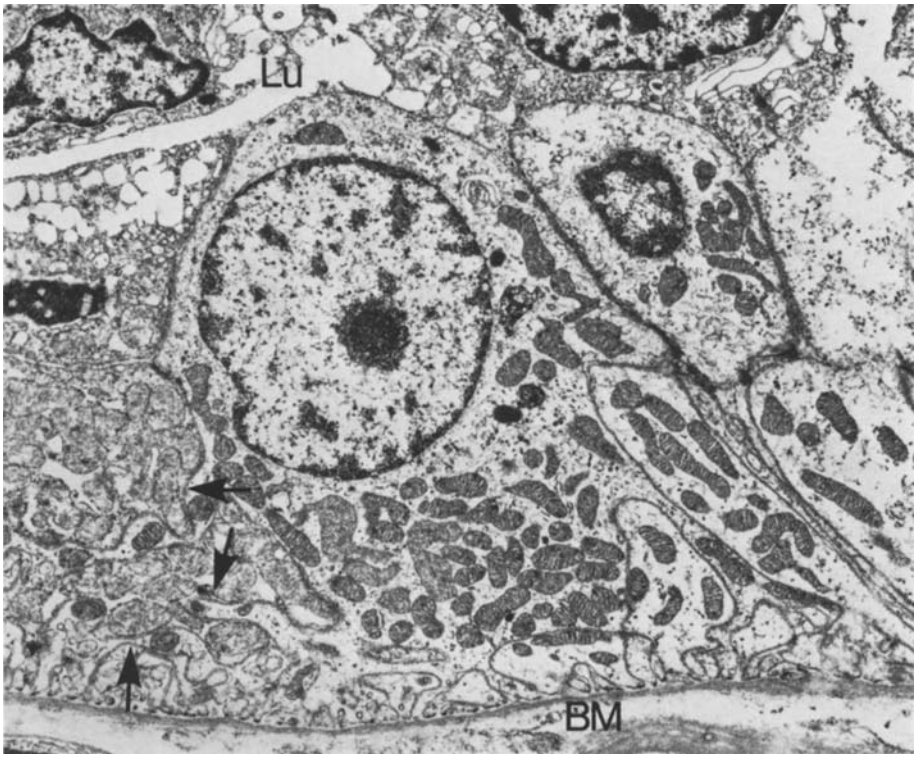

Fig. 6. Distal tubule from control biopsy. Extensive basolateral infoldings (*arrows*) which are less conspicuous below the nucleus. *Lu*: lumen; *BM*: tubular basement membrane. × 5,500

increased compared to the controls. The differences between ARF and recovery were not significant.

Since the patients in the recovery groups had still not regained normal renal function, most of them having a creatinine clearance of 7–30 ml, the lack of significant decrease of the group means of scores in this phase compared to the active phase might be misleading. Therefore it was investigated whether a correlation existed between the means of single biopsies and the creatinine-clearance at the time of renal biopsy. Table 3 shows the r- and p-values for these correlations as well as the equations for the regression lines. Figure 8 illustrates the correlation for proximal BI. Only data from the patient groups (B and C) but not controls were included in this calculation. In order to avoid excessive random variation due to biopsies with few tubular profiles, the scores were weighted according to the number of tubules evaluated in each biopsy (Steel and Torrie, 1960, p. 179). The correlation for BB and renal function was rather weak although significant at the 0.03-level. The correlations between reduction of BI and simultaneous renal function were highly significant.

There was apparently a strong concordance between the individual tubular scores of each biopsy. Statistically this was corroborated by using an

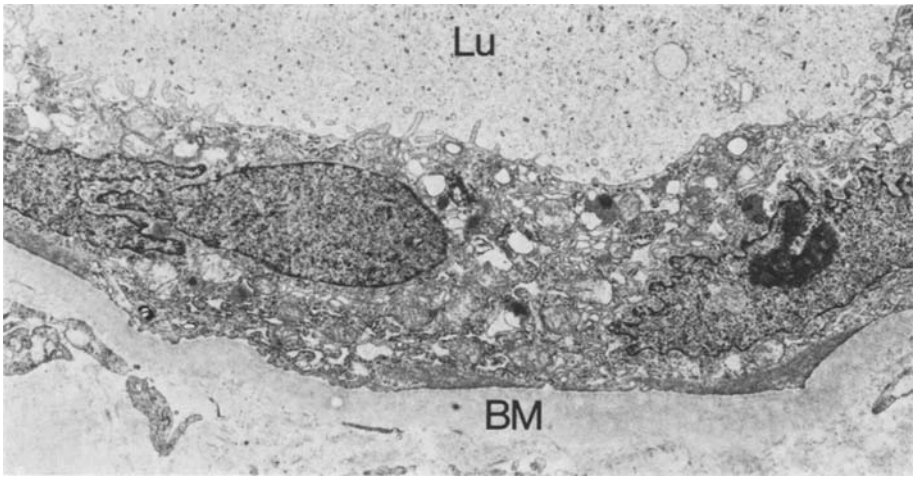

Fig. 7. Distal tubule from ARF. The tubular epithelium is flattened and the basolateral infoldings absent. ×8,500

Table 1. Number of tubular cross sections and tubular epithelial cells investigated

	No. of biopsies	Proximal tubules	Proximal cells	Distal tubules	Distal cells
A. Controls	12	171	956	66	517
B. ARF	11	69	351	37	344
C. Recovery	14	127	652	96	742
	37	367	1,959	199	1,603

ordinary *F*-test which showed a highly significant variation among patients with respect to their average scores (BB: $2p < 0.01$; proximal BI: $2p << 0.01$; distal BI: $2p < 0.01$), i.e. only a small fraction of individual variation in average scores could be explained by score-variation among single tubular prophiles. This concordance was calculated on biopsies with $\geqq 6$ tubular proximal, respectively distal profiles.

Using the non-parametric coefficient of correlation, Kendall's τ, there was a strong correlation between the individual score for BB-reduction for each tubular profile and the degree of dilatation of the same tubule scored from 0–3 + ($\tau = 0.42$; $2p < 0.002$). There was no correlation between the degree of dilatation of the tubule and the scores for reduction of BI. (proximal: $\tau = 0.12$; distal: $\tau = 0.13$).

Discussion

An earlier investigation by transmission electron microscopy (TEM) had given rise to the assumption that the tubular cells in ARF had a simplified

Table 2. Mean Scores of Degree of Reduction of Proximal Brush-border (BB) and Proximal and Distal Basolateral Infoldings (BI). Ischaemic ARF

		Prox. BB	Prox. BI	Dist. BI
	n	$\bar{x}$ s	$\bar{x}$ s	$\bar{x}$ s
A. Controls	12	0.04 ±0.09	0.17 ±0.24	0.14 ±0.23
B. ARF	11	1.24 ±0.88	1.65 ±0.44	2.01 ±0.64
C. Recovery	14	0.89 ±0.82	1.21 ±0.64	1.67 ±0.46

Each tubular cross section was scored 0–+3; n = number of biopsies, $\bar{x}$: mean of the group, s: standard deviation. Controls were different from both ARF and recovery patients with respect to all modalities, $2p \leqq 0.01$, using ordinary non-paired Student's t-test, whereas the differences the two latter groups were insignificant in all cases

Table 3. Correlation between scores for cell surface changes with creatinine clearance. Ischemic ARF
y = mean score of each biopsy.
x = creatinine clearance (ml/min)

Brush border correlated to creatinine clearance
$y = -0.051x + 2.25$ $r = -0.436$ $2p = 0.03$
Proximal infoldings correlated to creatinine clearance
$y = -0.028x + 2.072$ $r = -0.690$ $2p < 0.0002$
Distal infoldings correlated to creatinine clearance
$y = -0.025x + 2.33$ $r = -0.711$ $2p < 0.0001$

basolateral configuration suggesting a reduction of the area of this part of the cell's surface (Olsen 1967) and this assumption was reinforced by a recent study of Jones (1982). Our study from 1967 did not reveal any changes in the proximal BB, probably due to sampling problems with a comparatively small material and to misinterpretation of tubules with strong reduction of BB as distal. That the BB is, however, strongly reduced, was assumed from the appearance of scanning electron micrographs in Jones' study (1982), and from a LM study by Solez et al. (1979). The semiquantitative TEM data given in the present report provide strong evidence of a significant reduction of proximal BB as well as of BI in proximal as well as distal tubules. The group mean of the scores was smaller in the patients in early recovery but not significantly so. This may be due to the fact that renal function in patients in recovery was still considerably reduced compared to normal. In fact, if the scores for each biopsy were correlated with the simultaneous creatinine clearance a strong and significant negative correlation was evident for all three modalities.

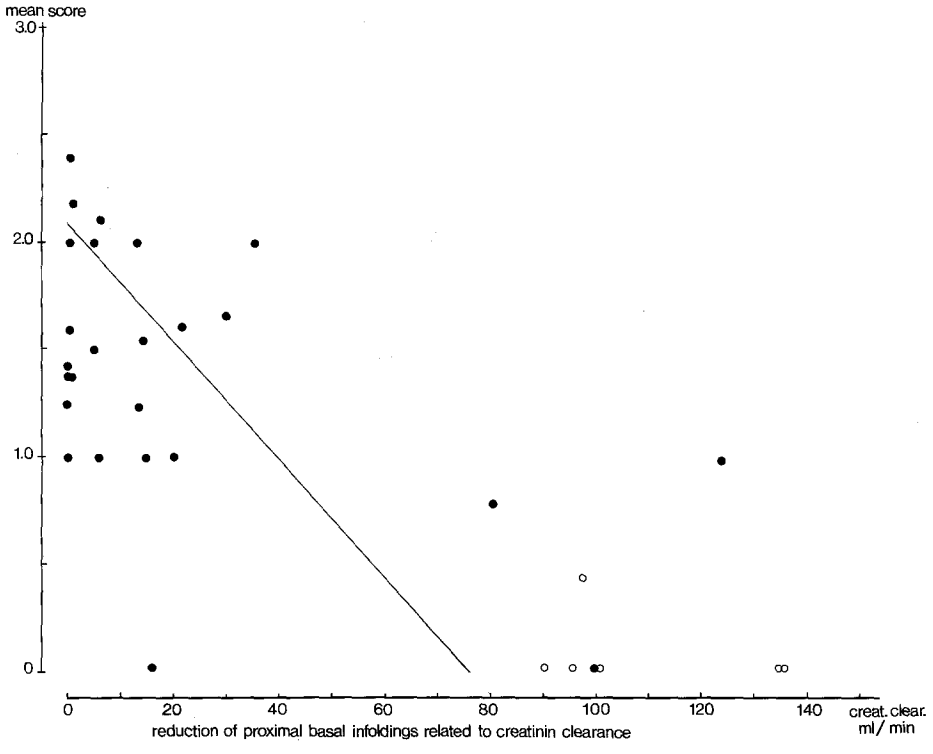

Fig. 8. Diagram showing the correlation between mean score of proximal basolateral infoldings and simultaneous creatinine clearance. The dots show the real, single mean scores but the regression line was calculated by weighting of the data according to the number of tubules scored. Values from 6 controls with known simultaneous creatinine clearance are added (*as open circles*) for comparison. These values were not used for calculation of the regression lines, r or p values ($r=0.69$; $y=-0.028x+2.072$; $2p<<0.001$)

The reduction of the BB was often so marked that the few characteristic microvilli were present in only a small part of the tubular cross section. In fact, it may be assumed that in some tubular profiles BB had totally disappeared, which resulted in a erroneous identification of the tubule as distal. The average ratio between distal and proximal profiles of 0.386 ± 0.096 (SEM) in controls was thus increased to 0.536 ± 0.142 in ARF and to 0.756 ± 0.123 in recovery phase, indicating quite clearly a spurious low fraction of proximal tubules in the two patient groups.

Thus, the present study gives evidence of a strong reduction of luminal as well as basolateral surface area in proximal tubules and of basolateral surface area in distal tubules (distal luminal surface was not estimated). This result raises two main questions: 1) what is the cause of this reduction?, and 2) what is the implication for the pathogenesis of ARF?

The cause of surface membrane reduction. It is well established that tubular lumina are distended in ARF, although the degree depends on fixation

(Olsen 1976; Bohle et al. 1976). The present material also showed dilatation of both proximal and distal tubules, with a considerable focality, groups of distended tubules alternating with normal or almost normal lumina. This raises the question whether disappearance of BB and BI could be a simple consequence of the "stretching" of plasmalemma due to tubular dilatation. The explanation can immediately be discarded concerning BI for which the scores for reduction were not correlated to the degree of tubular dilatation. As concerns the correlation between BB disappearance and tubular dilatation, a simple calculation makes it possible to discard the possibility of a causal connection.

Due to the large number of densely packed microvilli which constitutes the BB of the proximal tubular cells, the luminal cell surface is enlarged approximately 40 times compared to a smooth surface (Maunsbach 1973). Since the area of the inner surface of a cylinder is directly proportional to the radius ($A = 2\pi r \cdot l$), it follows that if a total or almost total disappearance of the BB were caused by dilatation alone, the diameter should be enlarged by a factor 40, which is much more than the measured enlargement of up to 5–8 times the normal which can be seen in renal biopsies from patients with ARF, and then only focally.

The reduction of the cell surfaces indicated by the present semiquantitative analysis must, therefore, be real and reflect an altered cell membrane turnover. Whether this implies a diminished synthesis or an increased breakdown cannot at the moment be determined.

Reduction of BB and BI has been observed in several experimental situations. Thus Davis et al. (1983) found loss of the basal labyrinth in experimental p-aminophenol poisoning (without concomitant loss of BB). The same was earlier found in mercury chloride induced proximal tubular damage by McDowell et al. (1976) and (morphometrically detected) in ischaemia by Phaller (1982). BB disappearance was induced by ischaemia by Glauman et al. (1975), Reimer et al. (1977), Dobyan et al. (1977) and Venkatachalam et al. (1978, 1984). Characteristic for this BB disappearance was that the microvilli were "interiorized" into the cytoplasm, a feature only exceptionally seen in the present study, and that normalization occurred within a few hours. In contrast, the present biopsies showed BB and BI disappearance during the whole active phase of ARF and partially also during recovery, a time span of up to several weeks. This difference between the acute and short-term cell surface alterations in experimental situations and the sustained abnormality in ARF points towards a continuous derangement in cell membrane turnover, which cannot be explained at the moment. It might have something to do with the persistant decrease of cortical blood flow present in ARF (Munck 1958).

Implication for pathogenesis. The renal tubular cells are characterized by an extremely high transcellular transport of water and ions facilitated by one of the most characteristic morphological pecularities of this epithelium; its large, luminal and basolateral surfaces. The simplification of luminal and basal cell surfaces in ARF resulting in a strong reduction of cell mem-

brane area must necessarily reduce the possibility for transport. Reduction of basolateral surface with its enzymatic sodium pump must specifically involve a reduction in Na^+ transport. In accordance with this, the experimental model of Davis et al. (1983) which showed loss of basal labyrinth had also impaired proximal tubular sodium reabsorption (and increased intratubular pressure).

The pathogenetic factors still discussed and regarded as possibly reponsible for ARF are 1) reduced filtration due to a decreased glomerular ultrafiltration coefficient, 2) tubular obstruction, 3) backleak of tubular fluid and 4) arteriolar vasoconstriction mediated by local action of the renin-angiotension system. A defective proximal tubular reabsorption of sodium resulting in an increased sodium concentration at the macula densa has been proposed as a possible stimulus for this pathway (Thurau 1976). Recent discussions of the arguments for and against these hypotheses have been published by Solez (1983 and 1984), Venkatachalam (1980) and Thurau (1984).

It is apparent that the data presented in this article are highly consistent with the fourth hypothesis. It may thus be proposed that the initial damage of the nephron (which may be ischaemic, toxic or other) directly affects mechanisms involved in membrane turnover, for instance by an inhibition of membrane synthesis. The reason why this abnormal membrane turnover is continued, often a long time after the responsible situation has been corrected (i.e. re-established blood pressure or blood volume, clearance of the toxic substance) is not clear. As long as abnormal structural conditions are upheld, however, the sodium reabsorption in the proximal tubule will still be subnormal. Even with a strongly diminished tubular flow, the sodium concentration at the macula which is the signal for local renin action will continue to be increased. The significant negative correlation between the scores for cell membrane simplification and simultaneous renal function provides a strong support for this hypothesis.

Disappearance of BB and BI to the degree seen in ARF, (with the exceptions discussed below) has not been observed by us in other human renal diseases. These lesions are, however, not specific. It has already been mentioned that they may be seen for a brief period in some experimental situations. In man, Jones (1982) has reported on two biopsies from patients with obstructive ARF who also had ultrastructural changes of the tubules resembling those described in ischaemic ARF and we have seen another example of this situation. This does not, however, speak against the hypothesis, since obstructive ARF might involve mechanisms also active in the ischaemic type. What is important in terms of specificity is, however, whether a BI reduction in the proximal tubule to such a severe degree as that found in ARF is present exclusively in conditions with renal failure or whether it may be observed in biopsies from patients with normal renal function. Future investigations should be performed to answer this question.

While the present morphological data are thus consistent with a pathogenesis of ARF involving tubuloglomerular balance, they may also be explained in other ways. The membrane simplification could be a secondary

phenomenon elicited by some abnormal conditions upheld during ARF, i.e. decreased cortical blood flow.

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