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# The distal nephron is preferentially infiltrated by inflammatory cells in acute interstitial nephritis

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**Summary.** In acute interstitial nephritis (AIN), mononuclear cells invade the tubules (tubulitis). The segmental localization of tubulitis is not precisely known. To clarify this question, formalin-fixed kidney biopsy specimens from 13 patients with AIN were studied stereologically by identifying cortical tubules with segment-specific markers. The periodic acid-Schiff reaction, peanut lectin, and antibodies against Tamm-Horsfall protein and epidermal cytokeratins all applied to the same section were used to identify the proximal tubules (PTs), distal convoluted tubules, distal straight tubules, and the cortical collecting system (connecting tubules and cortical collecting ducts), respectively. Morphometrically, an estimate of the relative volume of the inflammatory cell infiltrates within each category of tubular segments was obtained. Inflammatory cells were infrequently found in PTs (1.2%) but were frequently localized in distal tubules and the cortical collecting system (7.6%). There was no difference in the amount of the inflammatory cell infiltrate within these segments. Re-examination of an electron microscopic study of AIN carried out in this laboratory revealed that mononuclear cells were rarely seen in convoluted PTs but were frequently observed in straight PTs and all segments distal to them. The observations indicate that it is the distal nephron which is primarily affected by inflammatory cell infiltration in AIN.

**Key words:** Acute interstitial nephritis – Proximal tubules – Distal nephron – Tubular markers – Tubulitis

## Introduction

Acute interstitial nephritis (AIN) is characterized clinically by sudden unset of renal failure. Most cases are related to the administration of drugs (Neilson 1989). Morphologically, there is interstitial oedema and a focal or diffuse mononuclear cell infiltrate which invades the tubules (Colvin and Fang 1989; Laberke and Bohle 1980). The infiltrating cells are mainly T-lymphocytes and there is enhanced expression of class II major histocompatibility complex molecules on the tubular epithelium (Kelly et al. 1991). It is probable that the inflammatory infiltrate in AIN represents a cellular hypersensitivity reaction towards antigen(s) present in the tubulointerstitium, although little is known about the character, presentation and localization of the alleged antigen(s) (Kelly et al. 1991; Neilson 1989). The term tubulitis (Ooi et al. 1975) refers to the situation in which inflammatory cells localize between the lining epithelial cells, with or without disruption of the tubular basement membrane. The segmental localization of tubulitis is not known precisely. Some authors have concluded that the distal tubules (DTs) appear to be affected more severely by the inflammatory process than the proximal tubules (PTs) (Cogan and Arieff 1978; Hansen and Tauris 1976; Olsen and Asklund 1976; Ooi et al. 1975; Truong et al. 1991), while others have not observed any specific tubular segment preference (Baldwin et al. 1968). Electron microscopically, lymphocytes have been found to be localized in both types of tubules (Olsen et al. 1986). To solve the problem, we have investigated renal biopsy samples from patients with AIN by identifying tubules with immunohistochemical and lectin markers applied to the same section (Iványi and Olsen 1991). The method allows segmental identification of cortical tubules in formalin-fixed, paraffin-embedded material. Using the multiple immunolabelled sections and stereological methods, we have estimated the inflammatory involvement of cortical tubules in each case. A re-investigation of electron micrographs of renal tubules examined previously in our laboratory (Olsen et al. 1986; Olsen and Hansen 1990) was performed in order to identify the segments with presence of intratubular inflammatory cells. The convoluted PTs and DTs, the straight PTs, thin limbs of Henle, straight DTs and collecting ducts (CDs) could be analysed in the ultrastructural part of the study.

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Our results show that the convoluted PTs are resistant to inflammatory infiltration. In contrast, mononuclear cells infiltrate, and eventually destroy, the segments distal to them.

## Materials and methods

The biopsy specimens in AIN were obtained percutaneously from 9 males and 4 females (mean age 48 years, range 13–84 years) with sudden deterioriation of renal function. The onset of AIN was temporally associated with prior administration of one or more drugs in 12 of the patients (Table 1). The cause of AIN was unknown in 1 patient, but may have been due to infection. At the time of biopsy, the mean serum creatinine value was 465 μmol/l (range 125 μmol/l–1100 μmol/l). Originally, all biopsies were examined by light microscopy (formalin fixation, paraffin embedding) and 9 biopsies by the direct immunofluorescence method (frozen sections, FITC-labelled anti-human IgG, IgA, IgM, C3, fibrinogen, kappa and lambda antibodies from Dakopatts A/S, Denmark). Weak reactions for IgG in tubular basement membranes were seen in 2 biopsies. Electron microscopy showed no glomerular deposits in any of the 5 cases examined.

Formalin-fixed, paraffin-embedded kidneys biopsies from 9 patients (5 males, 4 females) were used as controls. Their ages ranged from 17 to 77 years with a mean of 35 years and the diagnoses were minimal change nephropathy or thin basement membrane nephropathy. Serum creatinine values were normal, and no pathological changes were seen in the tubules or interstitium.

The details of the multiple immunolabelling are reported in Iványi and Olsen (1991). In deparaffinized and rehydrated sections the endogenous peroxidase (PO) activity was blocked. This was followed by incubation with fetal calf serum (FCS, Gibco, UK) diluted in 1/10 in TBS (0.05 mol/l TRIS hydrochloride, pH 7.4–7.5, containing 0.15 mol/l sodium chloride and 0.001 mol/l calcium chloride and magnesium chloride, for 20 min. Incubation with PO-labelled peanut agglutinin (Sigma, St. Louis, Mo.; 0.011 μg/ml) was for 1 h, with subsequent aminoethylcarbazole visualization. Then sections were exposed to trypsin (Sigma; dissolved in 0.05 mol/l TRIS hydrochloride, pH 7.8–7.9 containing 0.1% w/v calcium chloride) at 37° C, for 15 min. After treatment with 10% FCS incubation with an anti-Tamm-Horsfall protein antibody (Behring, Marburg, FRG; 1:200) was carried out for 1 h, followed by incubation with PO-labelled swine anti-rabbit immunoglobulins (Dakopatts, 1:50), and aminoethylcarbazole development. Then 10% FCS was applied again, followed by overnight incubation with monoclonal mouse antibodies to human epidermal cytokeratins (clones AE1/AE3, Hybritech, 1:75) and subsequent application of rabbit anti-mouse immunoglobulins and monoclonal mouse APAAP complex (Dakopatts, 1:35, 1:70, respectively). For visualization, fast blue BB and naphtol AS-MX-phosphate substrate was used. Finally, the periodic acid-Schiff (PAS) reaction and counterstain with Mayer's haematoxylin were carried out.

In our stereological investigation the cortex was defined as the area containing glomeruli. It was used as the reference volume for the estimation of the relative volumes of tubules, interstitium and glomeruli in the AIN and control groups. At a magnification of 480× point counting (Gundersen et al. 1988) was used to estimate the volume fractions of PTs, straight DTs, convoluted DTs, cortical collecting system (CCS, connecting tubules and cortical collecting ducts), unidentifiable tubules (UDT), segments belonging to DT+CCS (no subtyping possible), interstitium (IS) and glomeruli. IS was defined as all interstitial tissue including the capillaries. A glomerulus was defined as the Bowman's capsular space including the capsule itself. The tubules included the basement membranes. Since topographic analysis is necessary in the identification of convoluted and straight PTs, a lower magnification (190×) was used to estimate the volume fraction of these segments. All estimations were done using a microscope with a mirror that projected the image onto a table. A motorized stage on the microscope moved the slide in predetermined steps along the length of the biopsy so that the fields for point counting were sampled systematically and all parts of the cortical tissue were investigated. A grid with a double point set with a ratio of 1:9 between larger and smaller points was placed on the table, and larger points hitting the above structures were counted. The smaller points in the grid system were used to estimate the volume fraction of inflammatory cell infiltrates in the different parts of the tubule with the same tubular segment as reference volume. The smaller points were also used to estimate the relative volume of inflammatory cells in the interstitium.

Electron micrographs from two earlier reports of AIN were re-investigated. The patients and the technical procedures are described in Olsen et al. (1986), and Olsen and Hansen (1990). Despite a tendency to reduction of the brush border in AIN (Olsen et al. 1986), PTs could still be identified if remnants of brush border microvilli were present focally in a tubular cross-section. All tubules without remnants of brush border were identified as belonging to the distal system. Tubular sections from the study on cortical ultrastructure in AIN (Olsen et al. 1986) were convoluted PTs and DTs. They had circular contours and were situated close to a glomerulus. Those from the study on medullary tubules (Olsen and Hansen 1990) were straight PTs, the thin limbs of Henle, the

**Table 1.** Clinical data

| Case no. | Age | Sex | Aetiology | Time of biopsy since onset | S-creatinine at biopsy (μmol/l) | Time of follow-up | S-creatinine at follow-up (μmol/l) |
|---|---|---|---|---|---|---|---|
| 1 | 67 | F | Confortid, paracetamol | 4 weeks | 739 | 15 weeks | 295 |
| 2 | 45 | M | Penicillins | 2weeks | 610 | 1 week | 621 |
| 3 | 60 | M | Methicillin sepsis | 2 weeks | 221 | 6 years | 138 |
| 4 | 84 | F | Omeprazol, erythromycin | 5 days | 858 | 2 weeks | 343 |
| 5 | 57 | M | Acinil, erythromycin, methicillin | Few days | 127 | 1 week | 361 |
| 6 | 25 | M | Sulfatrim | Few days | 311 | 1 week | 124 |
| 7 | 38 | M | Methicillin | Few days | 437 | | |
| 8 | 52 | M | Penicillins, streptomycin, cephalothin | Unknown | 349 | 1 week | 186 |
| 9 | 63 | M | Cimetidine | 2 weeks | 460 | 1 week | 231 |
| 10 | 30 | M | Chlorokin | 10 days | 1100 | 1 year | 125 |
| 11 | 13 | F | Probably infection | Several weeks | 125 | 1 year | 79 |
| 12 | 62 | M | Gentamicin | Few days | 407 | 2 years | 154 |
| 13 | 35 | F | Gentamicin, cephalosporin[a] | 5 days | 308 | 1 year | 180 |

[a] Renal allograft, Graft function decreased after treatment with gentamicin and cephalosporin and improved after discontinuation of this treatment without changes in immunosuppressive treatment

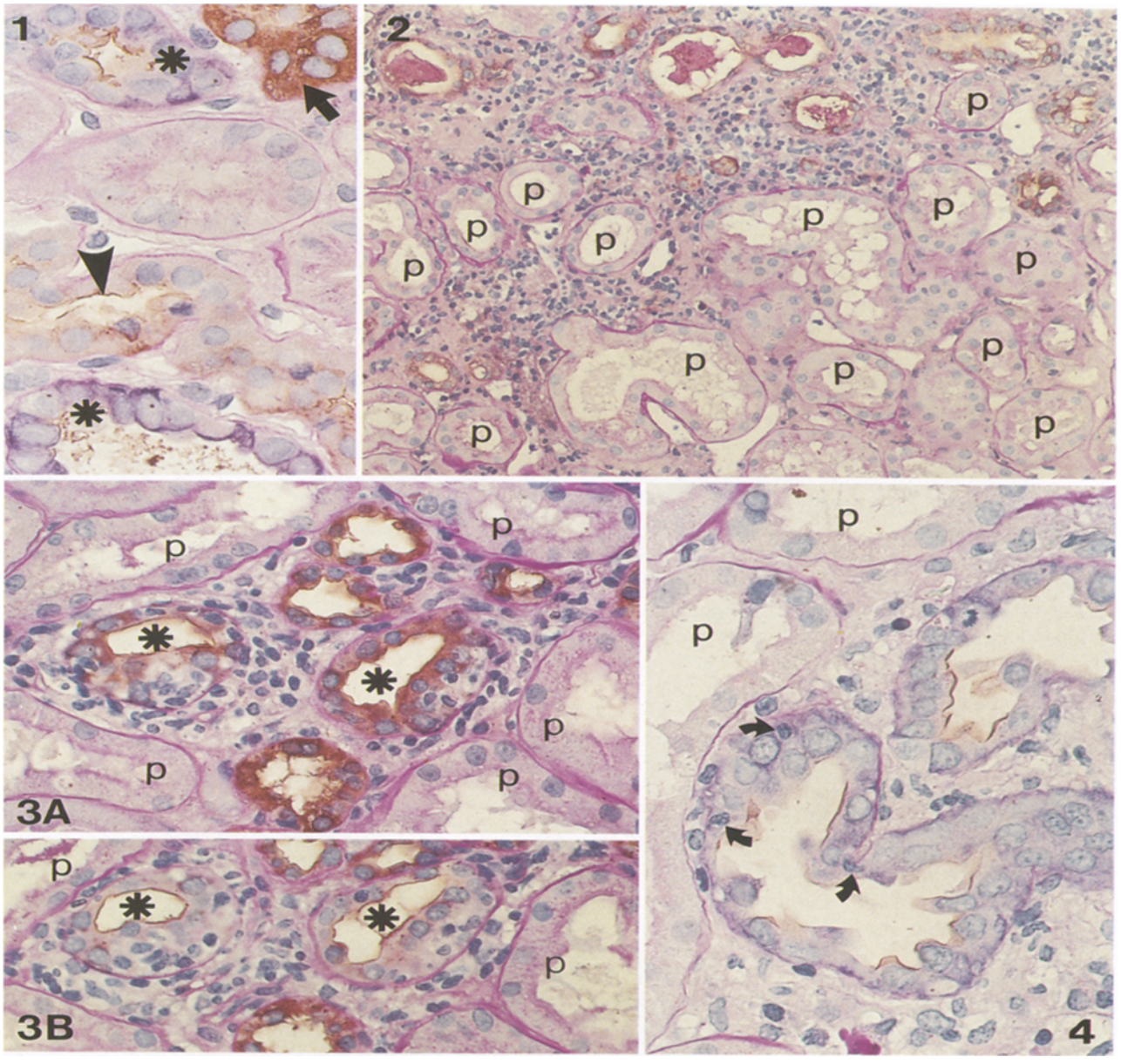


**Fig. 1.** The PAS reaction identifies the proximal tubule (PT) (centre), and the Tamm-Horsfall protein (brown) the straight distal tubule (DT) (*arrow*). The epidermal cytokeratins (*blue*) react with the cortical collecting system (CCS) (*asterisks*). The luminal binding of peanut lectin (*arrowhead*) visualizes the convoluted DT. Control, ×600

**Fig. 2.** The interstitial infiltrates preferentially accumulate around DTs (*brownish*). *p*, Proximal tubule. ×225

**Fig. 3A, B.** Intense lymphocytic infiltration in segments of straight DTs (*asterisks*) from two adjacent sections. Note loss of marker intensity of Tamm-Horsfall protein in **B.** PTs (*p*) are not infiltrated. ×450

**Fig. 4.** The collecting duct is infiltrated by lymphocytes (*arrowheads*). PTs (*p*) are not infiltrated. ×600

straight DTs and the medullary CDs. The criteria for selecting these tubules were that they had a longitudinal, straight and parallel course. It could not be decided with certainty if such tubules were from medullary rays of the cortex or from the outer medulla. The inner medulla could be excluded on the basis of general topography.

Differences between groups were tested using Student's unpaired *t*-test, and differences within the AIN group using Student's paired *t*-test. Statistical significance was accepted at the 5% level. The Fisher's exact test ($P<0.001$) was performed for analysing electron microscopical results.

## Results

The typical light microscopical picture of focal AIN (Colvin and Fang 1989; Laberke and Bohle 1980) was seen. Lymphocytes predominated in the infiltrates. Eosinophils were found in 11 patients. Tubulitis was sometimes accompanied by rupture of the tubular basement membrane and leakage of Tamm-Horsfall protein into the interstitium. Tubular dilatation, swelling of tubular

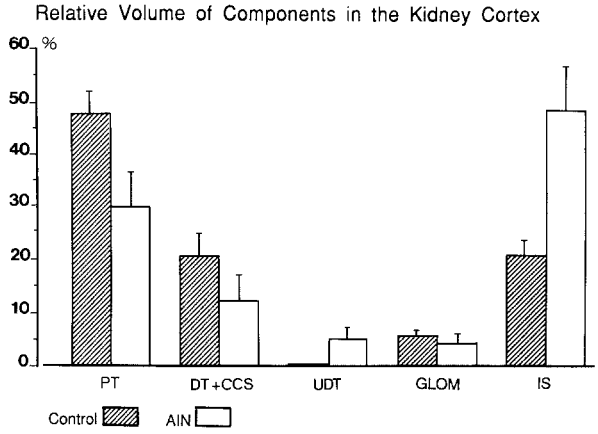


**Fig. 5.** Volume fractions of cortical structures with the cortex as reference volume. *Bars* indicate 1 SD between individuals. $2P < 0.05$, acute interstitial nephritis vs controls

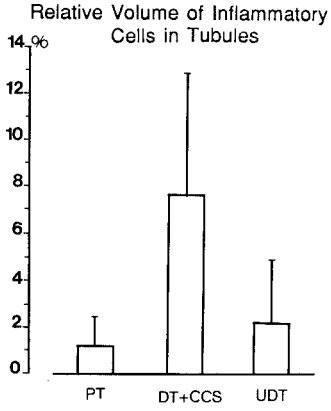


**Fig. 6.** Volume fractions of inflammatory cells in different cortical segments of the nephron. $2P < 0.05$, vs PT

epithelium, and scattered casts of lymphocytes and cellular debris were common findings. PT cells usually exhibited swelling, focal thinning, or partial loss of brush border, and in some cases, necrosis of single cells. Extensive necrosis or cellular desquamation with denudation of the tubular basement membrane membrane were not seen. Glomeruli and vessels appeared normal.

The results of multiple immunolabelling in controls are shown in Fig. 1. In AIN, the infiltrates mainly surrounded segments of DT+CCS and spared areas containing only convoluted PTs (Figs. 2–4). Inflammatory cells were frequently present between the epithelial cells of DTs (straight as well as convoluted parts) and CCS (Fig. 3A, B). In contrast, they were rarely found in PTs. In areas with severe inflammation, the intensity of marker expression of Tamm-Horsfall protein (Fig. 3) or epidermal cytokeratins was markedly decreased. The marker intensity of peanut lectin, however, was preserved, indicating that these injured segments belonged to DT+CCS. In most severely damaged foci, no segmental marker expression could be recognized (UDTs).

The convoluted PTs constituted about 81% of all PTs. The relative volumes of PTs (convoluted as well as straight parts) and DT+CCS were decreased whereas the relative interstitial volume was increased in patients with AIN versus controls (Fig. 5). In the AIN group, the inflammatory cells composed 1.2% of the volume of the PTs. In contrast to this, the relative volume of mononuclear cells in DT+CCS was 7.6% (Fig. 6). In the interstitium the volume fraction of inflammatory cells was 19.8%.

The distribution of mononuclear cells within the tubules in the ultrastructural study is seen in Table 2. Most of the cells were lymphocytes, a few were macrophages. They were typically located basally in the lateral intercellular spaces (Fig. 7) and only rarely in the lumina. Those which were situated in the basal parts of the intercellular spaces were usually separated from the tubular basement membrane by a narrow layer of epithelial cytoplasm (Fig. 7). There was usually no evidence of severe damage or necrosis in the adjacent epithelial cells in spite of a close relationship between lymphocytes and epitheli-

**Table 2.** Occurrence of lymphocytes in electron micrographs of tubules. The index (number of lymphocytes per tubular profile) for convoluted PT-s is significantly lower than for all other tubular segments ($P < 0.001$)

| Segment | N | Tubules with lympho-cytes | Total number of lympho-cytes | Index |
|---|---|---|---|---|
| Convoluted proximal tubule | 38 | 1 | 1 | 0.026 |
| Straight proximal tubule | 18 | 8 | 15 | 0.83 |
| Thin limb of Henle | 20 | 3 | 8 | 0.4 |
| Straight distal tubule | 36 | 13 | 31 | 0.86 |
| Convoluted distal tubule | 52 | 21 | 46 | 0.88 |
| Collecting duct | 10 | 2 | 2 | 0.2 |

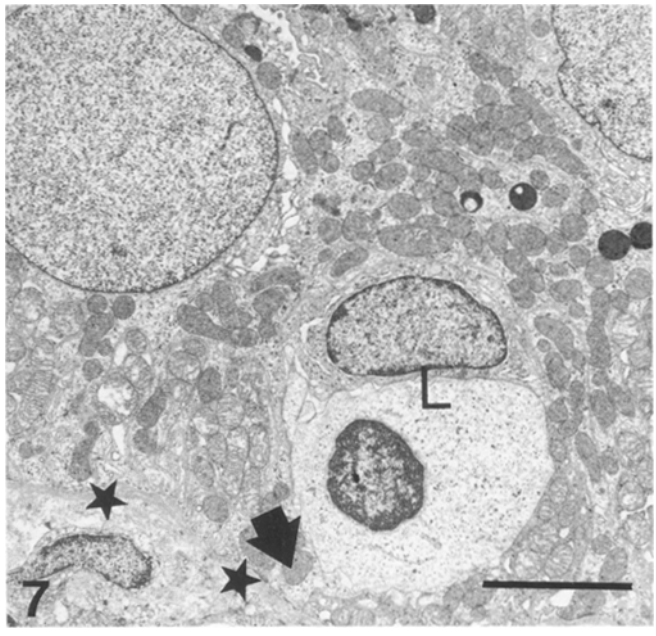


**Fig. 7.** Two lymphocytes (*L*) localize between epithelial cells of a convoluted DT. A narrow layer of epithelial cytoplasm (*arrow*) separates them from the tubular basement membrane (*star*). The length of the bar is 1000 nm

um. However, apoptosis of an adjacent epithelial cell was occasionally observed. Profiles of tubules which were severely damaged often contained several lymphocytes and macrophages, but were not included in the analysis since they had invariably lost structures permitting a precise segmental identification.

## Discussion

In the cortex, tubular segments of the nephron include the convoluted and straight PTs, straight and convoluted DTs, connecting tubules and the cortical CDs. The straight PTs, straight DTs and the cortical CDs mostly localize in medullary rays. The convoluted and straight PTs were identified by the PAS reaction, and the distal segments of the tubular system by the luminal binding pattern of peanut lectin. Peanut lectin has a high affinity for D-galactose (Faraggiana et al. 1982). An anti-Tamm-Horsfall protein antibody marked the entire cytoplasm of cells in the straight DTs (Peach et al. 1988). Connecting tubules and cortical CDs were recognized by the characteristic mosaic staining pattern of epidermal cytokeratins (Bachmann et al. 1983). Using immunoperoxidase-aminoethylcarbazole detection for peanut lectin and Tamm-Horsfall protein, and immunoalkaline-fast blue BB for epidermal cytokeratins, tubules marked solely by the peanut lectin were identified as convoluted DTs (see Fig. 1). Since antibody preparation AE1/AE3 reacts segment-specifically only in the cortex (Rumpelt et al. 1991), tubulitis in the medulla was not investigated in this part of the study. The decrease in intensity of Tamm-Horsfall protein or epidermal cytokeratins in severely affected areas was probably due to partial dedifferentiation of renal epithelium (Bacallo and Fine 1989) in response to toxic injury caused by lymphocytes infiltrating the tubular wall. In contrast, peanut lectin positivity was preserved, allowing identification of the segment as one belonging to DT+CCS. Our experience with the retention of D-galactose epitopes in areas of intense inflammation is consistent with that obtained by Hawkins et al. (1989) in AIN. Similar results with preserved D-galactose epitopes in polycystic kidney disease (Holthöfer et al. 1990) show that glucoconjugate epitopes are more stable cellular markers than epitopes for Tamm-Horsfall protein and epidermal cytokeratins.

The stereological methods used and their application on renal tissue have been described recently (Gundersen et al. 1888; Marcussen and Olsen 1990). The focal distribution of the inflammatory infiltrate could present problems if a rigorous sampling system is not applied. With the method described involving systematic sampling of measuring areas from the whole cortex, an unbiased estimate of tubular infiltration was obtained. The use of biopsies which were randomly obtained from the kidney parenchyma and from several patients reduced the problem of the representativity of the biopsy to one of minor significance.

The segmental identification of tubules by multiple immunolabelling and electron microscopy, and the estimation of the degree of mononuclear cell infiltration within tubular segments has provided, for the first time, the ability to localize the sites of tubulitis in the kidney cortex more precisely. Working with segment-specific markers, Hawkins et al. (1989) have demonstrated involvement of collecting tubules in all their AIN cases. From the morphometric data in the present study, no significant differences were found among inflammatory cell infiltrated segments within DT+CCS. When relative volumes of inflammatory cells in PTs, DT+CCS and UDTs were compared (Fig. 7), PTs proved to be quite resistant to inflammatory infiltration. It cannot be strictly excluded that some of the infiltrated UDTs could have been of proximal origin, but with the morphometric values obtained, this would not change the main conclusion. Since about 81% of PTs were convoluted segments, the resistance of PTs to inflammatory invasion mainly refers to the convoluted PTs. These results are in accordance with those obtained by our electron microscopical analysis, which showed that inflammatory cells spared the convoluted PTs but heavily infiltrated the convoluted DTs. Therefore we conclude that the convoluted PTs in AIN are not the main target of inflammatory infiltration. The electron microscopic data show that tubulitis affects the straight PTs as well as segments distal from these.

The resistance of convoluted PTs to inflammatory infiltration is not easy to explain. The most simple explanation would be that the segmental specificity of inflammatory cell infiltration reflects the location in the kidney of the responsible antigen, which is often a drug or a part of a drug molecule acting as a hapten together with a protein moiety. At the moment no foundations for this assumption can be provided.

In human acute pyelonephritis (Iványi et al. 1988) and renal allografts undergoing acute rejection (Cohen et al. 1984; Nádasdy et al. 1988; Truong et al. 1991), the inflammatory cells invade the distal segments of the tubular system preferentially. This is similar to the situation in AIN, in spite of the fact that these interstitial nephritides have a different aetiological background. It is possible that the Tamm-Horsfall protein (synthesized in straight DTs and localized to DT+CCS) might play a role in mediating segmental inflammatory injury. Although no evidence has been provided from an immune response against Tamm-Horsfall protein in human tubulointerstitial nephritis (Chambers et al. 1986), Tamm-Horsfall protein could interact with lymphokines and thereby mediate enhanced inflammatory infiltration of DT+CCS. As has been shown, the Tamm-Horsfall protein-uromodulin is a specific ligand for interleukin-1 and tumour necrosis factor (Hession et al. 1987; Kumar and Muchmore 1990; Sherblom et al. 1988). Immunohistochemically, interleukin-1 and tumour necrosis factor have been found to localize to straight DTs, and tumour necrosis factor, to a lesser extent, to tubules in close association with straight DTs (Hession et al. 1987). It has also turned out that these lymphokines selectively bind to Tamm-Horsfall protein-uromodulin via carbohydrate domains. Since the binding sites were different from those directed to target cell surface receptors (Hession et al. 1987; Sherblom et al. 1988), it is possible that

the lymphokines might facilitate preferential distal tubular damage during interaction with Tamm-Horsfall protein. Infiltration of the straight PTs could be explained by the location of this tubule very close to the straight DTs where the synthesis of Tamm-Horsfall protein takes place.

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