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Capillarosclerosis of the Lower Urinary Tract in Analgesic (Phenacetin) Abuse

An Electron-Microscopic Study

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Summary. The ultrastructural appearances in capillarosclerosis of the lower urinary tract in analgesic abuse are reported. The capillaries show thickened basement membranes consisting of numerous thin basement membrane lamellae. Between the newly formed basement membrane lamellae, masses of empty vacuoles (fat vacuoles) and a variety of membranous and vesicular structures are present. The pathogenesis of this alteration in the basement membrane is unknown. A common pathogenetic mechanism may be operative in the discoloration of renal papillae and mucous membranes of lower urinary tract on the one hand and capillarosclerosis on the other.

Key words: Analgesic abuse – Microangiopathy – Urinary tract.

Introduction

Analgesic (phenacetin) abuse is a well known cause of chronic nephropathy (Zollinger, 1966; Gloor, 1978) and is associated with malignant tumours of the renal pelvis (Bengtson, 1974).

For epidemiological studies it is of considerable practical importance to know the precise number of analgesic (phenacetin) abusers. An investigation of the validity of recognised morphological characteristics of analgesic (phenacetin) abuse (Mihatsch et al., 1978) demonstrated that only the recently recognised capillarosclerosis, i.e. thickening of the capillary basement membrane in the mucous membranes of the lower urinary tract (Fig. 1) (Torhorst, 1976; Hesse et al., 1976; Gloor, 1978) may be considered as pathognomonic (Mihatsch et al., 1978). Capillarosclerosis is found in about 80% of the cases and it occurs exclusively in this condition (Mihatsch et al., 1978; Gloor, 1978). A brownish discoloration of the mucous membranes (Munck et al., 1970) is usually present in cases of capillarosclerosis, but it is seldom marked enough to be of diagnostic value.

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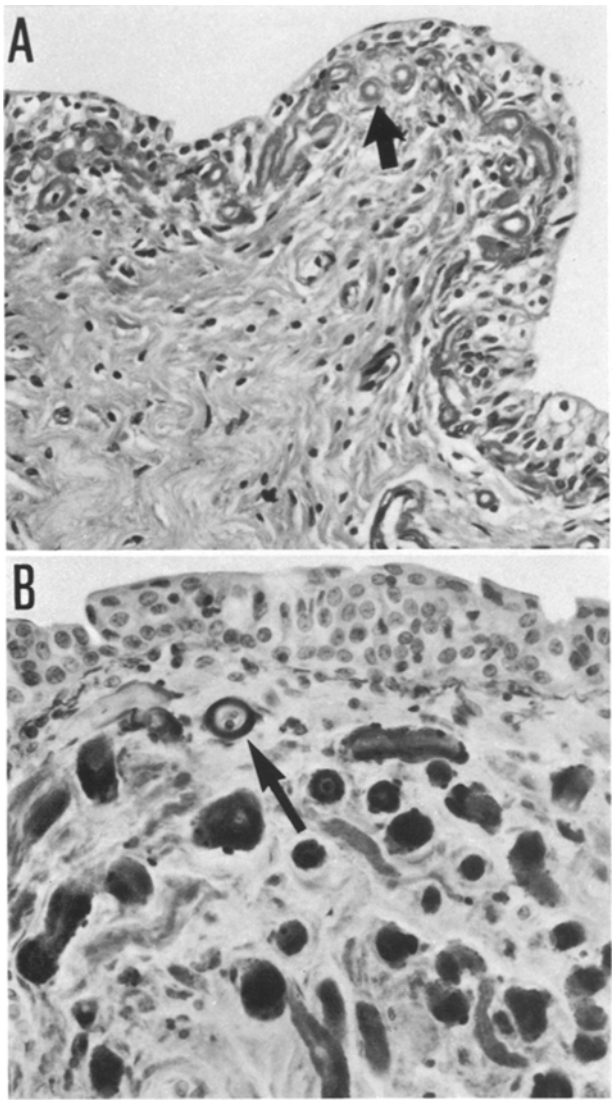

Fig. 1 A and B. Light microscopical picture of capillarosclerosis (→) in PAS-stain (**A**) and Sudan-stain (**B**). (×300)

The present electron microscopic investigation was carried out in order to reveal the nature of basement membrane thickening of capillarosclerosis.

Material and Methods

In 5 abusers of phenacetin-containing analgesics taken in unknown quantities and for unknown durations, capillarosclerosis of the renal pelvis (2 surgical specimens) and of the ureter (3 autopsy specimens, obtained less than 12 h after death) was investigated by electron microscopy. The tissue, initially fixed in 4% formalin, was refixed in 3% glutaraldehyde and embedded in epon. Ultra-thin sections, which were stained with uranylacetate and lead citrate, were examined with a Phillips EM 200.

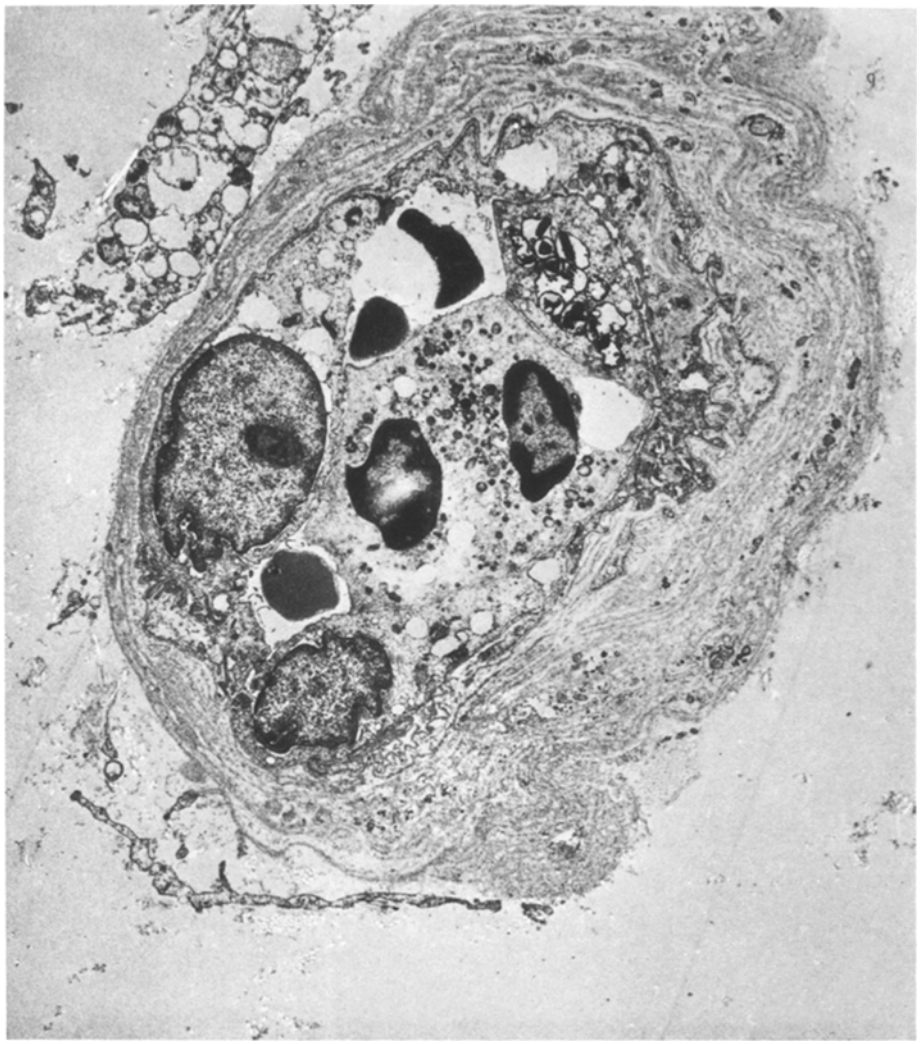

Fig. 2. Capillary surrounded externally by a multilayered ring of thin basement membrane lamellae. The lumen is lined by activated endothelial cells and contains 2 monocytes stuffed with numerous lysosomes. EM ×4,800

Results

The capillaries immediately beneath the urothelium showed three different stages of alteration. Firstly, and in a minority of the capillaries, the basement membranes were of normal thickness. The capillary lumens were lined by endothelial cells which showed a considerable degree of activity and marked lobulation of the nuclei. Secondly, and also only in a minority of capillaries, marked multilayered thickening of the basement membranes (see below) underlying the endothelium and surrounding the pericytes was observed. The endothelial

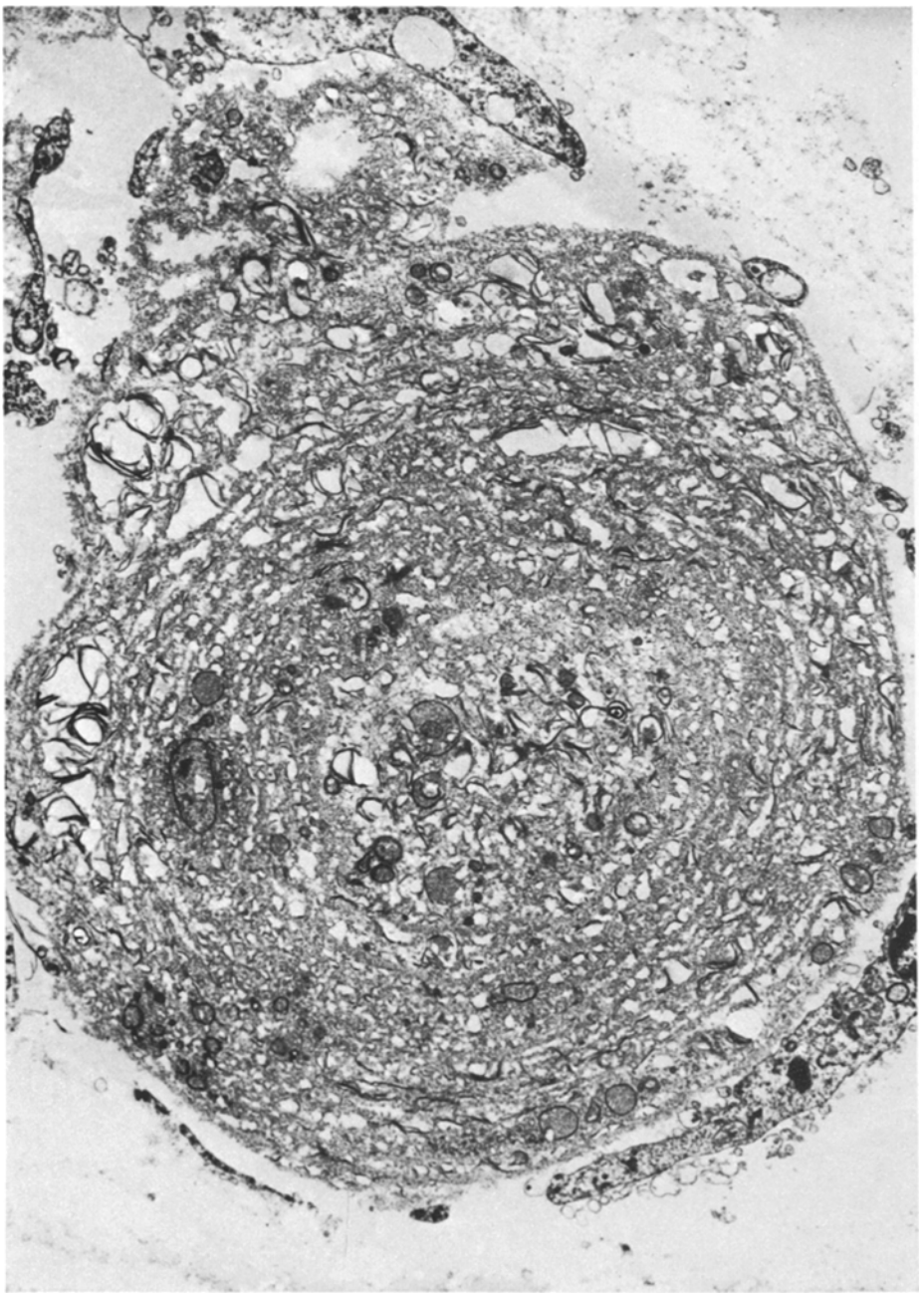

Fig. 3. The capillary lumen is entirely occluded by massive thickening of capillary basement membrane with typical multilayered thin basement membrane lamellae. Between the lamellae masses of vacuoles (fat vacuoles) and vesicular, granular and membranous debris are present. EM ×11,000

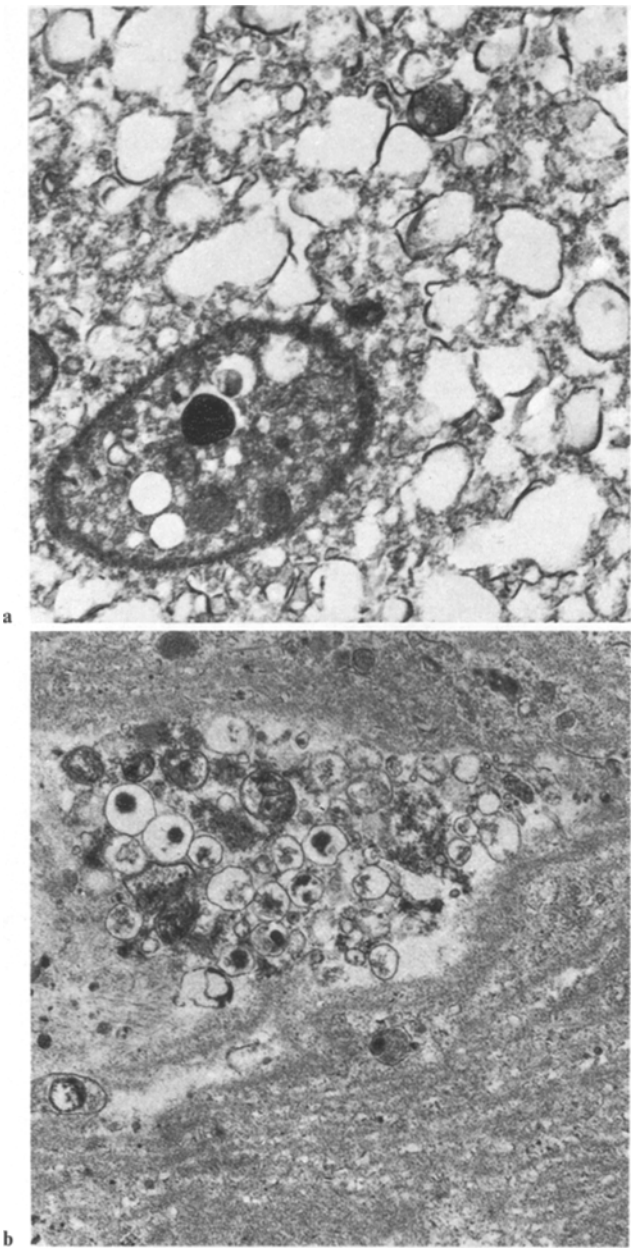

Fig. 4. a Higher magnification of Fig. 3. Empty vacuoles (fat vacuoles) partly surrounded by a highly osmiophilic membrane and a oval structure with heterogeneous content. EM ×32,000. **b** Numerous lysosomes with strong osmiophilic content between basement membrane lamellae. EM ×17,000

cells were activated. The lumens often contained monocytes stuffed with lysosomes (Fig. 2). Thirdly, the majority of capillaries had completely occluded lumens and the endothelial cells were destroyed. They consisted only of concentric annular lamellae of thin basement membranes (Fig. 3). In some cases, pericytes were completely walled-up between the basement membrane lamellae.

A wide variety of vesicular and membraneous structures could be identified between the basement membrane lamellae, amongst which round empty vacuoles (fat vacuoles) lined by a simple, moderately osmiophilic membrane predominated (Fig. 4a). Elsewhere, probably at the sites of completely occluded capillary lumens, there were large accumulations of lysosomes containing strongly osmiophilic material (Fig. 4b). Occasional thread-like structures were present, which had a faint cross striation and sometimes formed rings (Fig. 4a).

Discussion

In analgesic abuse, the electron microscopic appearance of capillarosclerosis with its annular basement membrane lamellae, is unique. Therefore, and because of the high predictive value of capillarosclerosis for analgesic abuse (Mihatsch et al., 1978), we consider capillarosclerosis of the lower urinary tract as pathognomonic.

Basement membrane changes in diabetes mellitus, old age and hypertension are different in that the basement membranes either show protein deposits or a homogeneous thickening (Zollinger and Mihatsch, 1978). The pathogenesis of capillarosclerosis is obscure. It is probable that capillarosclerosis and discoloration of the renal papillae and mucous membranes (Munck et al., 1970) of the lower urinary tract, share the same pathogenetic mechanisms since they usually occur together. The basement membrane in capillarosclerosis is rich in lipids as demonstrated by its strong sudanophilia by light microscopy and by the presence within it of masses of empty lipid vacuoles seen by electron microscopy. The discoloration of mucous membranes in the lower urinary tract, and of cartilage and liver is due to coloured compounds of highly unsaturated neutral lipids which are related to the lipoid fraction of lipofuscin (Berneis and Studer, 1969; Munck et al., 1970; Bianchi et al., 1972).

The morphological appearances of capillarosclerosis may indicate a chronic stimulation of cells capable of basement membrane production, i.e. pericytes and endothelium. This process eventually results in the complete occlusion of capillary lumens. By electron microscopy, the basement membranes of the vasa recta in the renal medulla show identical alterations (Gloor, 1978). Capillarosclerosis in the renal medulla may be the key to the still unknown pathogenesis of the renal papillary necrosis in analgesic nephropathy (Kincaid-Smith et al., 1968).

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