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INVOLVEMENT OF POST-CAPILLARY VENULES IN BEHÇET'S DISEASE: AN ELECTRONMICROSCOPIC STUDY

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Abstract. In Behçet's disease, severe pathological changes are observed in the post-capillary venules, indicating that the venous side of the circulation is generally involved. It is proposed that one of the initial pathological changes is multiplication of the basal lamina surrounding the post-capillary venule.

Key words: Behçet's disease; Oral lesion; Post-capillary venule; Ultrastructure

Morbus Behçet was first described as a clinical entity in 1937 by the Turkish dermatologist Behçet (1889–1948), although it seems likely that it was already known in ancient Greece (15).

The lesions are located as oral and genital ulcerations, and ocular lesions as well (15). However, being a systemic disorder, many other organs may be affected such as the skin, the cardiovascular system, the central nervous system, joints, gastrointestinal tract, and on rare occasions kidneys and lungs (8, 10, 24).

The etiology is as yet unknown, but a viral infection, genetic transmission, and autoimmunity have been proposed (4, 6, 22).

There is strong evidence of a primary vascular disorder, and the underlying pathology seems to be a vasculitis (1, 18). In general the venous side of the circulatory system is involved (9, 15). However, in recent years several reports of arterial involvement have been published (12, 16).

The present electronmicroscopic study of an oral lesion from a patient with Behçet's disease was focused on the post-capillary venules of the submucosa, as these vessels seem to be very sensitive to pathogens and other influences (21).

MATERIAL AND METHODS

The patient is a 37-year-old woman suffering from Behçet's disease for the last 7 years. She presented oral and genital ulcerations, small papulo-pustular elements on the trunk and upper extremities, and signs of a conjunctivitis sicca. She has been treated with prednisolone, 15 mg daily. Following dose reduction, the disease reappeared.

Biopsies were taken from an oral ulceration, about 3 days old, as well as from apparently normal oral mucosa to serve as a control. The specimens were treated according to the procedure previously described (2).

Studies of histocompatibility antigens showed neither HLA-A 11, nor B5.

RESULTS

The mucosal epithelium of the oral lesion was necrotic and had almost disappeared. Therefore, only a description of the underlying submucosa will be presented. In general the ultrastructure of the capillaries and the arterioles was normal, and there were no perivascular leukocytic infiltrations (Fig. 1). The post-capillary venules, however, showed the following pathological changes (Fig. 2): the vessels were dilated, the lumen containing a few erythrocytes and many polymorphonuclear cells, some of which penetrated the dilated intercullular spaces between adjacent endothelial cells. The endothelium showed swelling and occasional mitotic figures, indicating proliferation. The luminal endothelial surface had small plump cytoplasmic projections. A well developed rough endoplasmic reticulum was dispersed throughout their cytoplasm. Occasionally, the cisternae of the reticulum were dilated, and had a finely granulated content. Many ovoid or spherical mitochondria were dilated, showing few cristae. Close to the cellular surface a few micropinocytotic vesicles were found. In the cytoplasm, small membrane-bound granules were occasionally seen as well as multivesicular bodies near the Golgi area. The basal endothelial surface was surrounded by the basal lamina, which showed multiplication (Fig. 3). The perivascular space was dominated by infiltrating polymorphonuclear cells, which displaced the pericytes from

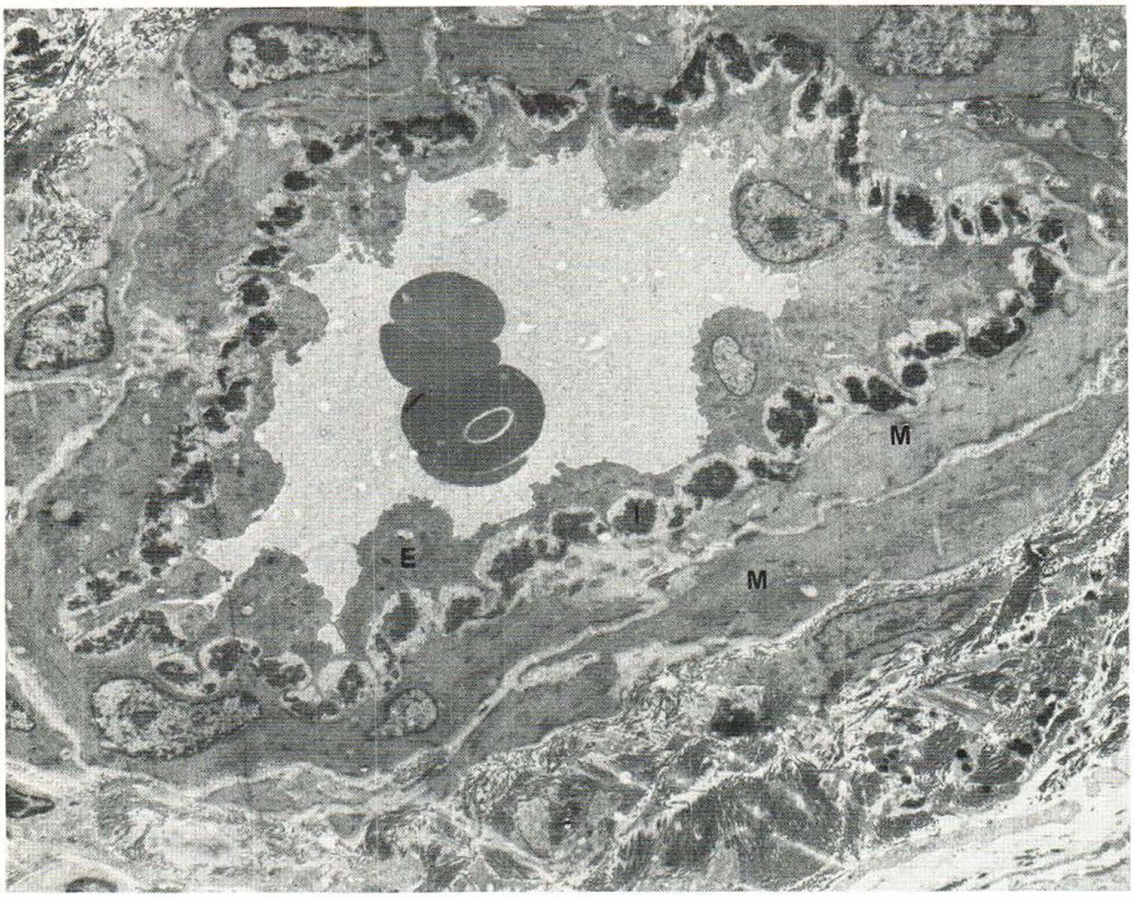

Fig. 1. Arteriole. No perivascular infiltrate is visible. Endothelium (*E*). Internal elastic membrane (*I*). Smooth muscle cell (*M*). ×2600.

the endothelial cells (Fig. 4). Membranous contact between cytoplasmic processes and the endothelium was seen only occasionally. Along the plasma membrane of the pericyte, hemi-desmosomes were located, establishing contact with the adjacent basal lamina. Furthermore, a flocculent material, which was also seen in the lumen of the vessel, was dispersed throughout the perivascular space. The collagen fibrils, which displayed a normal periodicity, were separated because of edema. Hardly any lymphocytes, monocytes or mast cells were observed.

Control biopsy

The endothelium of the post-capillary venules was thin and contiguous. Neighbouring endothelial cells were held together by junctional complexes. In the cytoplasm, many mitochondria showing interdigitating cristae were observed, as well as ovoid or spherical membrane-bound granules. Many micropinocytotic vesicles were present along the luminal and basal plasma-membrane. The basal lamina surrounding the vessel showed multiplication in places, but there was no perivascular leukocytic infiltrate (Fig. 5). Pericytic cytoplasmic processes were lying close to the endothelial cells. A flocculent material was found in the luminal part of the vessel as well as in the perivascular space, although to a much smaller extent as compared with the pathological vessel already described. Normal collagen fibrils lying close together in bundles were present surrounding the perivascular space.

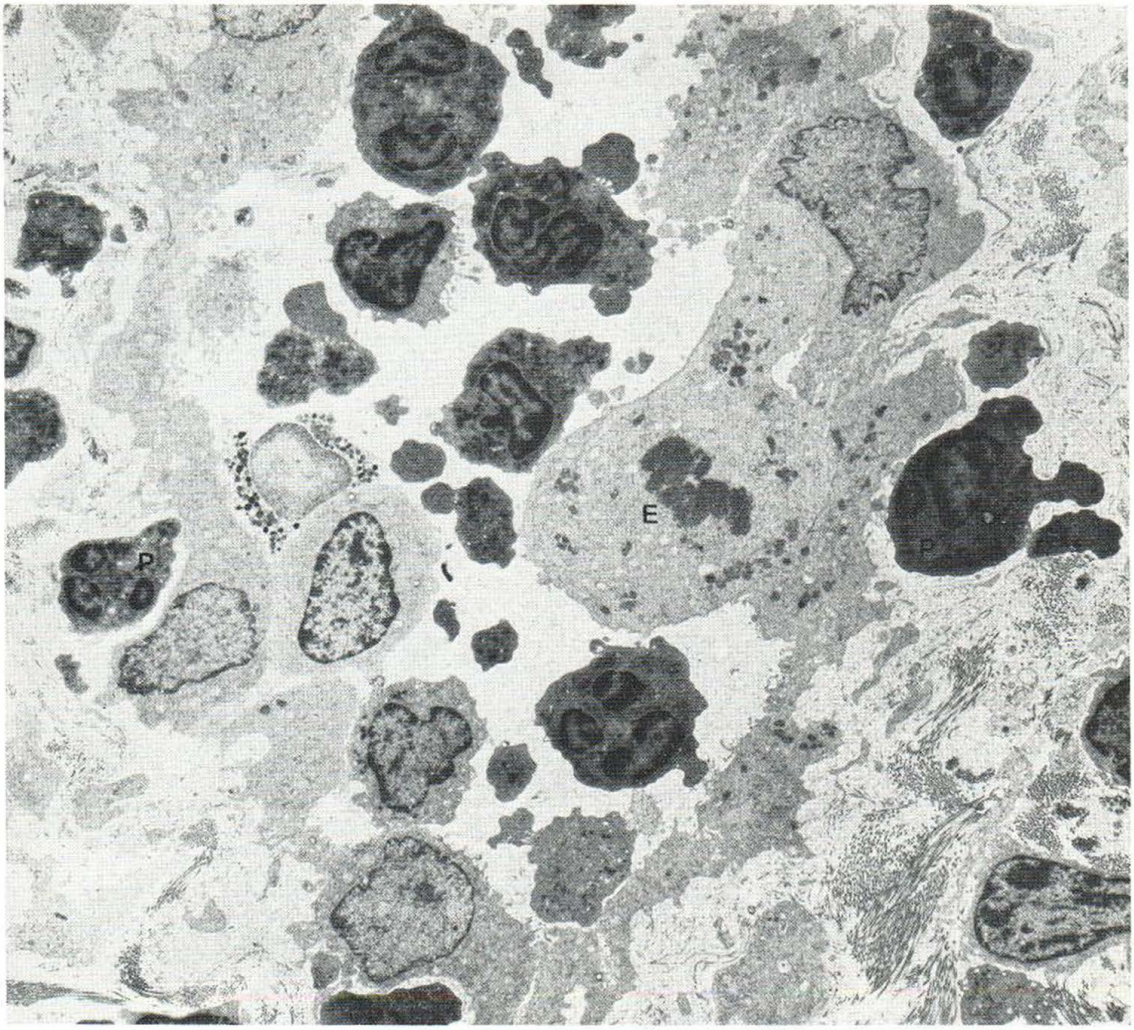

Fig. 2. Post-capillary venule. Perivascular infiltrate of polymorphonuclear cells (*P*). Endothelium showing mitotic figures (*E*). ×2 600.

DISCUSSION

Tissues involved in Behçet's disease show vasculitis, according to light-microscopical studies (8, 18). In small blood vessels, swelling and proliferation of the endothelial cells with partial obliteration of the lumen and occasional fibrinoid necrosis have been reported as well as a perivascular infiltrate consisting mainly of lymphomononuclear cells (1). Thrombophlebitis is frequently found in patients with Behçet's disease, and arterial involvement may lead to the formation of central and peripheral aneurysms (9, 10, 12). Aortic aneurysms, showing destruction of the media, are found on rare occasions in young persons and are extremely prone to rupture (16). Even fetal arterial involvement in Behçet's disease seems to occur. Recently, we have demonstrated severe, pathological changes in the form of scattered smooth muscle cells in the tunica media of a fetal aortic wall. The fetus was removed from the patient by hysterotomy (3).

In contrast to previous light-microscopical studies, as well as the few ultrastructural investigations

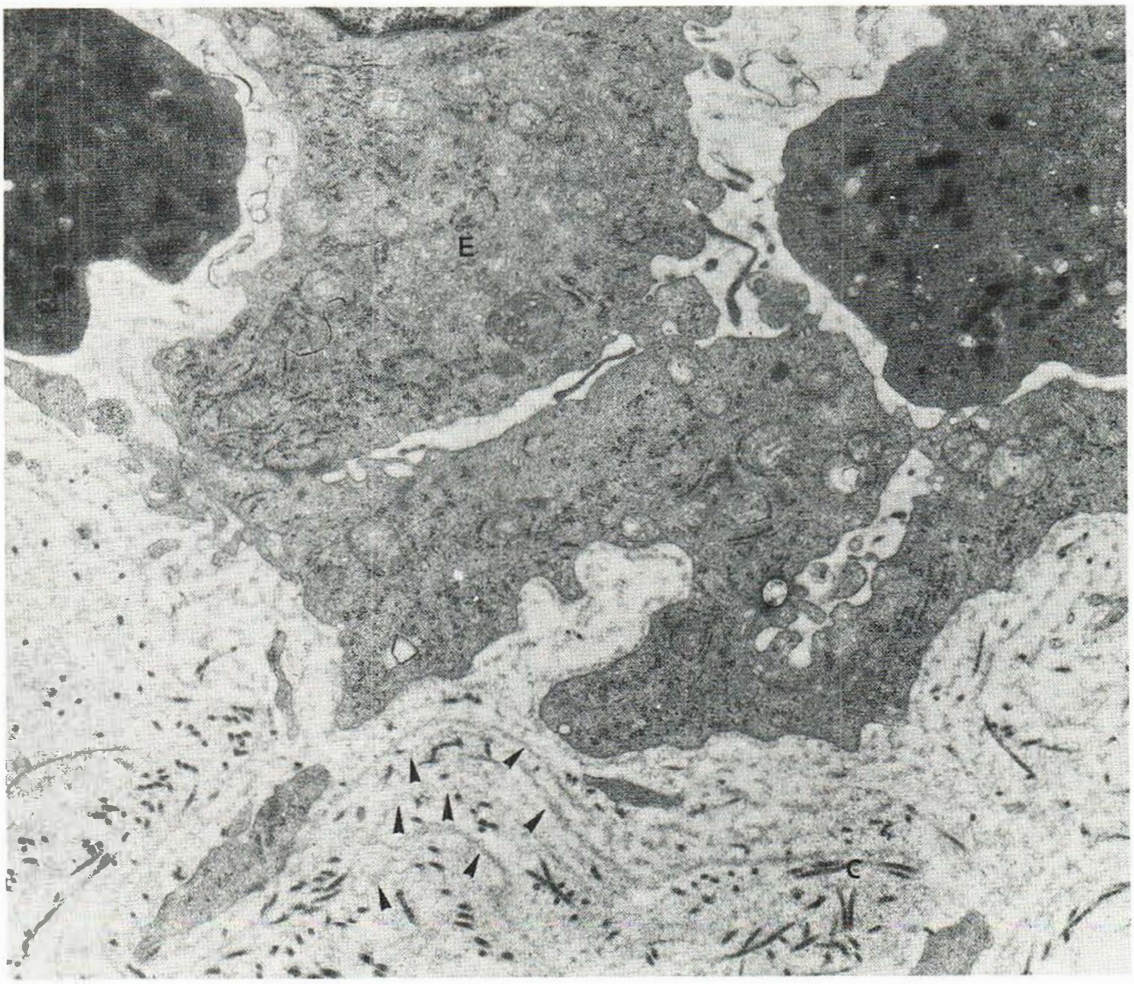

Fig. 3. Post-capillary venule. Multiplication of the basal lamina (*arrowheads*). Collagen fibrils (*C*). Endothelium (*E*). ×13000.

on vascular involvement in Behçet's disease (11, 13, 22), the present report has been focused specifically on the post-capillary venules because they seem to be more easily affected by various influences such as inflammation, allergic reactions, and extreme temperatures, than are true capillaries (20). The post-capillary venules showed pathological changes, resulting in an increase in outward diffusion (edema) and an extravasation of granular leukocytes (19). The reason why only polymorphonuclear cells were found in the perivascular infiltrate is probably that the biopsy was not taken until the oral ulceration was fully developed. In earlier lesions the infiltrate consists mostly of lympho-monocytic cells (7, 13), thus indicating a change in the infiltrate during progression of the lesion. This might suggest an immune-complex-mediated vasculitis (14). Immune-complexes have been found in the serum of patients with Behçet's disease, and by immunofluorescence the presence of immunoglobulins, of complement, and of fibrinogen has been demonstrated in the vascular wall (14). The antigen–antibody complexes have a chemotactic effect on the neutrophil leukocytes infiltrating the perivascular space, thus producing tissue lesions, especially in the vessels (17).

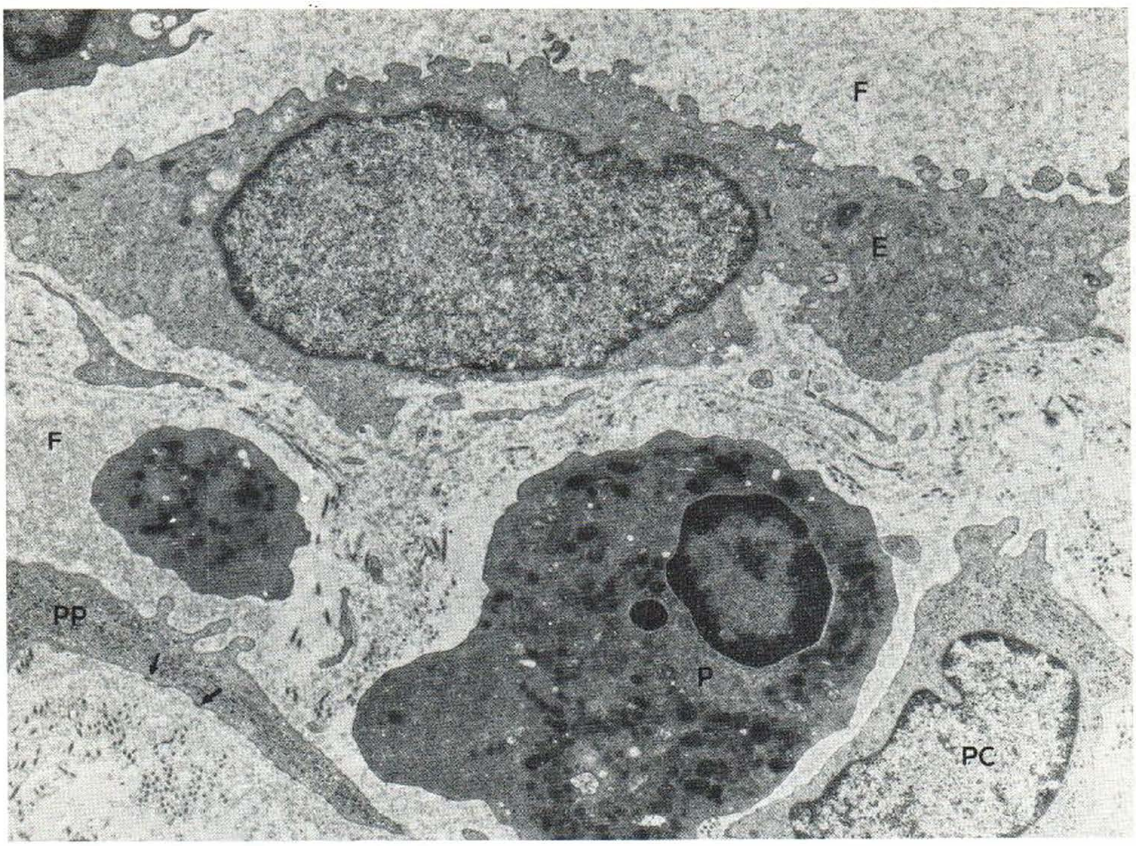

Fig. 4. Post-capillary venule. Endothelium (*E*). Polymorphonuclear cell (*P*) displacing the pericyte (*PC*). Pericytic process (*PP*). Half-desmosome (*arrow*). Flocculent material (*F*). ×6 760.

CONCLUSION

The present report supports the view that the venous side of the circulation is generally involved in Behçet's disease, as reflected by the pathological post-capillary venules. The mitochondrial swelling in the pathological endothelial cells probably indicates a non-specific cellular response to injury. Based on the ultrastructural findings from apparently normal submucosa it is proposed that one of the initial pathological changes in the post-capillary venule might be multiplication of the basal lamina.

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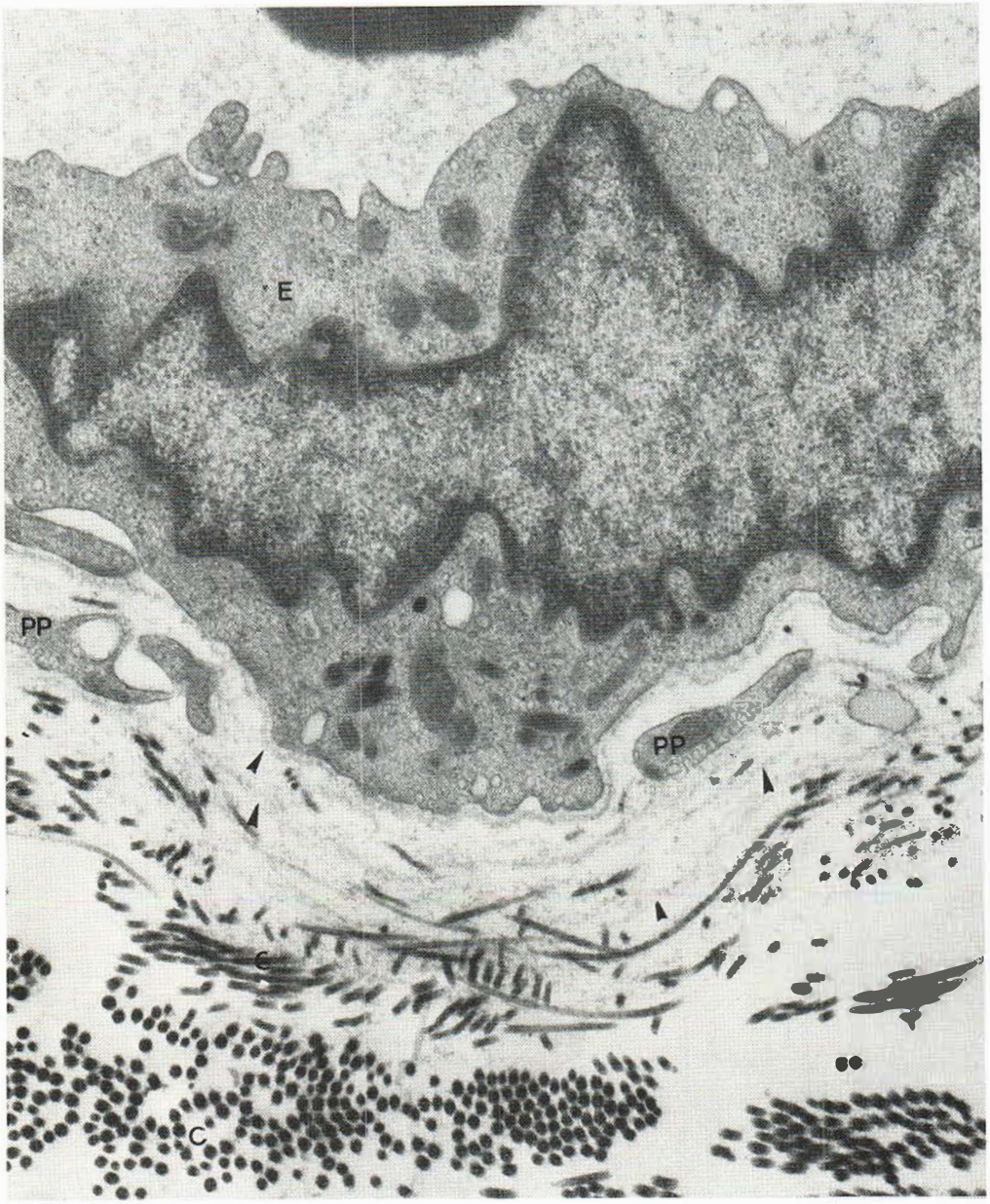

Fig. 5. Control biopsy. Post-capillary venule. Endothelium (*E*). Pericytic process (*PP*). Multiplication of the basal lamina (*arrowheads*). Collagen fibrils (*C*). ×26 000.

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