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Capillaries in the lamina propria of human seminiferous tubules are partly fenestrated

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Abstract. The three capillary parts of the microvasculature of the human testis, namely the arterial side inter-Leydig cell capillaries, the intramural capillaries, and the venous side inter-Leydig cell capillaries, were studied in detail by dual detection of alkaline phosphatase enzyme activity and endothelial marker immunoreactivity, and by means of light- and transmission-electron microscopy. Alkaline phosphatase enzyme activity was seen in intertubular arterioles, capillaries, and venules, and in intramural capillaries of the human testis, whereas the lamina propria of human seminiferous tubules showed no staining. Alkaline phosphatase enzyme activity and the endothelial marker detected by the Qbend 30 antibody co-existed within the endothelial cells of the microvasculature. Electron-microscopically, the endothelial cells of the arterial and venous side inter-Leydig cell capillaries, and of the intertubular capillaries free of Leydig cells were of the continuous type without fenestrations (A-1-α type). The intramural capillaries consisted of non-fenestrated (A-1-α type) and fenestrated sections (A-2-α type). The fenestrations faced the germinal epithelium. Capillaries with a continuous non-fenestrated endothelium contained a large number of transcytotic vesicles and channels. These were numerous in the endothelial cells of the inter-Leydig cell capillaries and the non-fenestrated part of the intramural capillaries. Capillaries partly ran in between the layers of the lamina propria and therefore represented the capillarization of the seminiferous tubules. Thus the multilayered lamina propria probably requires its own capillary supply to allow rapid exchange between the microvasculature and the epithelium of the human seminiferous tubules.

Key words: Microvasculature – Fenestrated capillaries – Lamina propria – Testis – Human

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Introduction

The microvasculature of an organ represents the part of the vascular system that is responsible for the exchange of gases, nutritional substances, and hormones. For a long time, this functional role of the microvasculature in the human testis was neglected. During the past decade, the testicular microvasculature has attracted attention because of its assumed modulation by endocrine and paracrine mechanisms that are important for the regulation of spermatogenesis (Bergh et al. 1988; Damber et al. 1987, 1989; Sharpe 1990; Setchell 1990; Bergh and Damber 1992). This is supported by the detection of androgen receptors on the arterial side of the microvasculature and of estrogen receptors in the vasculature of the human testis (Ergün and Ungefroren 1995).

The results concerning the organization of the microvasculature of the human testis are to some extent controversial (Hundeiker 1971; Kormano and Suoranta 1971a, b; Suzuki and Nagano 1986). Earlier studies have shown a “rope-ladder-like” organization of the capillaries of rat or mouse testis (Müller 1956; Hundeiker and Keller 1963; Hundeiker and Mullert 1966; Kormano 1967a). Similar results have been reported for the capillary bed of the human testis by Kormano and Suoranta (1971a) and Hundeiker (1971). However, Suzuki and Nagano (1986) have found no evidence for the existence of such a “rope-ladder-like” capillary organization in the human testis. By using serial sections and computer-aided three-dimensional (3-D) reconstructions, we have described the detailed capillary organization of the human testis (Ergün et al. 1994) and have, for the first time, provided evidence that capillaries connect Leydig cell clusters with adjacent seminiferous tubules in a serial manner. Moreover, we have divided the microvasculature of the human testis into three parts, namely inter-Leydig cell capillaries on the arterial and venous side and intramural capillaries, which are localized within the lamina propria of the seminiferous tubules.

The literature concerning the ultrastructural features of testicular capillaries is very limited. Hundeiker (1971)

has found that, in contrast to other endocrine organs, the endothelium of the capillaries in the human testis is not fenestrated, shows a low degree of transcytosis, and belongs to the A-1-α type capillaries (classification according to Bennet et al. 1959), similar to those found in muscle (Fawcett et al. 1969). There is also evidence that, in the testis of some laboratory animals, the intertubular and peritubular capillaries are non-fenestrated (Wolf and Merker 1966; Fawcett et al. 1970; Meyerhoffer et al. 1989; Meyerhoffer and Bartke 1990). The present paper reports the results of a detailed study of the ultrastructural and histochemical features of the different parts of the microvasculature of the human testis.

Materials and methods

Tissue

Tissue samples were obtained from the testes of 20 patients who had been orchiectomized because of carcinoma of the prostate.

Light and electron microscopy

Eight testes were perfused through the testicular artery with 5.5% phosphate-buffered glutaraldehyde under manual pressure after rinsing with 0.15 M phosphate-buffered saline (PBS). Small blocks of these testes were excised and immersed for 8 h in the same fixative, followed by fixation in 1% OsO4 for 2 h. The blocks were then embedded in Epon 812. Serial semithin sections (1 μm thick) were stained with toluidine blue/pyronin (Holstein and Wulfhekel 1971). For electron microscopy, ultrathin sections (about 80 nm thick) of perfused testicular tissue were cut with a Porter MT2B ultramicrotome, contrasted with uranyl acetate and lead citrate, and observed in a Philips EM 300.

Computer-aided 3-D reconstructions

For light-microscopic examination, serial sections (1 μm thick) from the perfused testes of 10 patients were stained with toluidine blue/pyronin. For the computer-aided 3-D reconstructions, the stained serial sections were digitalized with the aid of a Sony 3-chip camera connected to an Intel 486 personal computer via an integrated screen-machine-card and saved as TIFF-graphic files. From these files, 3-D reconstructions were generated in the Institute for Information and Mathematical Sciences in Medicine, University Hospital Eppendorf.

Immunocytochemistry

Small blocks of fresh testes from 6 men were frozen with liquid nitrogen. Cryostat sections (6–8-μm thick) were mounted on chrome-gelatine-precoated slides and air-dried. The sections were fixed for 15 min with 4% paraformaldehyde. After being washed with PBS, the sections were further processed for the visualization of the corresponding antigens by the use of four monoclonal antibodies directed against the endothelial cell markers Qbend 10, 20, 30, and 40.

For the visualization of the antigens under study, an amplification combination of the peroxidase anti-peroxidase (PAP) and the avidin-biotin-peroxidase complex (ABC) techniques according to Davidoff and Schulze (1990) was applied. Briefly, the sections were treated with 2% normal rabbit serum to block non-specific binding sites and incubated for 48 h in a humid chamber with the primary antibodies against Qbend 10, 20, 30, and 40 (Serotec, France) at an optimal dilution of 1:10. After being rinsed with PBS, the sections were incubated with a biotinylated anti-mouse IgG (DAKO, Denmark; 1:250), with mouse PAP (1:100), and in the fourth step of the staining, with an Elite avidin-biotin-peroxidase complex (Vector, USA; 1:250). The peroxidase activity was developed with diaminobenzidine and hydrogen peroxide (Davidoff and Schulze 1990). The sections were dehydrated and covered with DePeX (Serva).

Alkaline phosphatase activity was visualized histochemically on cryostat sections fixed with formol (1:9)-$CaCl_2$ (1%) according to the technique of Burstone (1962), by using naphthol AS-MX phosphate as the substrate and Fast blue BB as the coupler. In some cases, a double sequential visualization of the immunoreactivity for the endothelial cell marker (Qbend 30) and the enzyme activity of alkaline phosphatase was performed, with the aim of establishing which cellular components of the capillary wall (endothelial cells, pericytes, or perivascular cells) possessed alkaline phophatase activity.

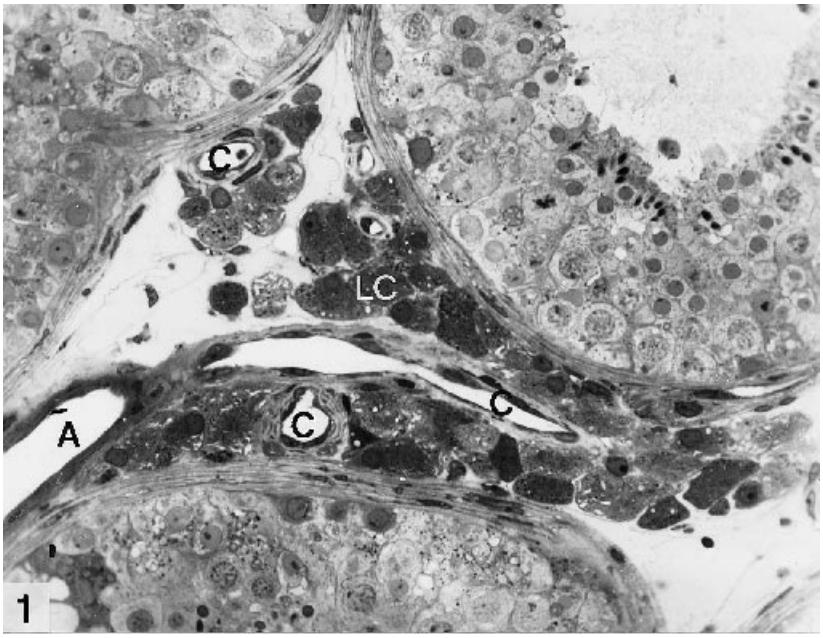
Results

Light microscopy

The light-microscopic investigation of semi-thin sections of the human testis shows that interstitial capillaries, which arise from arterioles in the interstitium (Fig. 1), branch repeatedly into multiple capillaries mostly situated among Leydig cells (Fig. 2). Subsequently, these capillaries run toward the adjacent seminiferous tubules and penetrate their lamina propria (Fig. 2). After a distance of variable length within the lamina propria, the capillaries leave the wall of the tubules. During their further course, they are again surrounded by interstitial Leydig cells before they terminate in interstitial venules or intralobular small veins. The relationship between the testicular capillaries, Leydig cells, and seminiferous tubules can be visualized by means of the computer-aided 3-D reconstruction (Fig. 3), which shows the branching of an interstitial capillary within a Leydig cell cluster and its penetration into the lamina propria of a seminiferous tubule.

The vascular organization in the human testis is graphically displayed in Fig. 4, which summarizes the current results regarding the fundamental subdivision of the capillary pathway, connecting Leydig cells and seminiferous tubules, into inter-Leydig cell capillaries on the arterial side, intramural capillaries (within the lamina propria), and inter-Leydig-cell capillaries on the venous side. Thus, the Leydig cells and seminiferous tubules in the human testis are connected serially, viz., Leydig cells – seminiferous tubules – Leydig cells, by the blood stream via the microvasculature.

Following visualization of alkaline phosphatase enzyme activity, a strong staining intensity was observed in the microvasculature consisting of arterioles, capillaries, and venules (Fig. 5). In contrast, large vessels, such as intralobular arteries and veins, showed no activity (Fig. 6). Alkaline phosphatase activity was found in all interstitial sections of the capillaries, whether they were



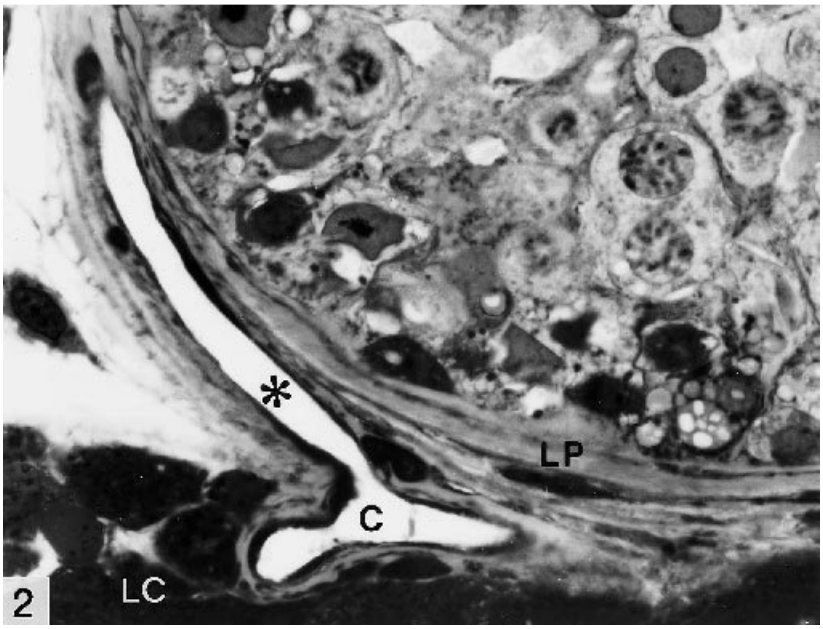


Fig. 1. Intertubular arteriole (*A*) and numerous capillary sections (*C*) among Leydig cells (*LC*). ×255

Fig. 2. A bifurcating capillary (*C*) among interstitial Leydig cells (*LC*). One of these capillaries (*) penetrates into the lamina propria (*LP*) of the seminiferous tubule. ×850

surrounded or not by Leydig cells, and in the intramural capillaries. The staining intensity of all the capillary regions of the human testis was similar. The peritubular cells of the lamina propria were devoid of alkaline phosphatase activity, whereas intratubular spermatogonia and Sertoli cells were positive.

The immunocytochemical visualization of the four endothelial markers demonstrated that only the Qbend 30 antibody selectively stained the endothelial cells of all blood vessels of the human testis (Fig. 7), revealing a dense capillarization of the testicular parenchyma. After dual subsequential histochemical staining, the endothelial cell marker Qbend 30 and alkaline phosphatase enzyme activity were observed to be co-localized in the endothelial cells of the testicular capillaries (Fig. 8).

Electron microscopy

The electron-microscopic examination of the testicular capillaries showed that the individual sections of these vessels had different endothelial structures.

Arterial side inter-Leydig cell capillaries

These capillary sections were located within a Leydig cell cluster and were surrounded by Leydig cells and fi-

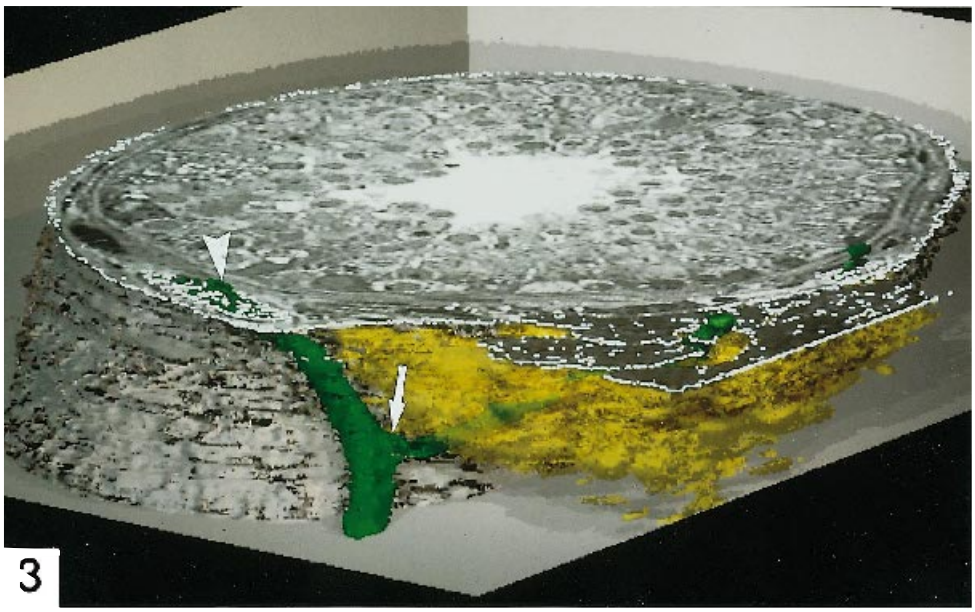


Fig. 3. Computer-aided 3-D reconstruction showing the organization of the testicular capillaries (*green*) in relation to a Leydig cell cluster (*yellow*) and the seminiferous tubule (*grey*). Note that, after the bifurcation within the Leydig cell cluster (*arrow*), one capillary penetrates into the lamina propria (*arrowhead*) of a seminiferous tubule

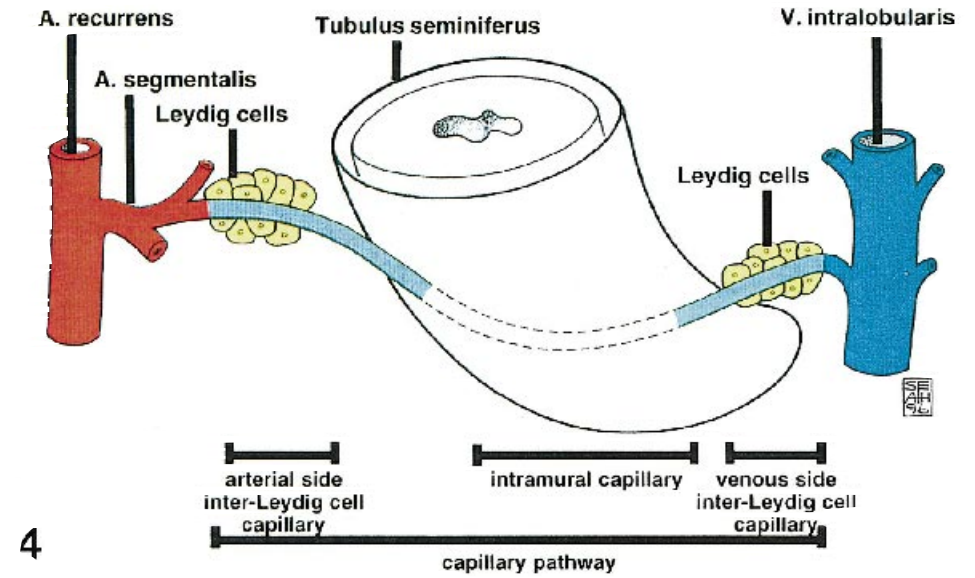
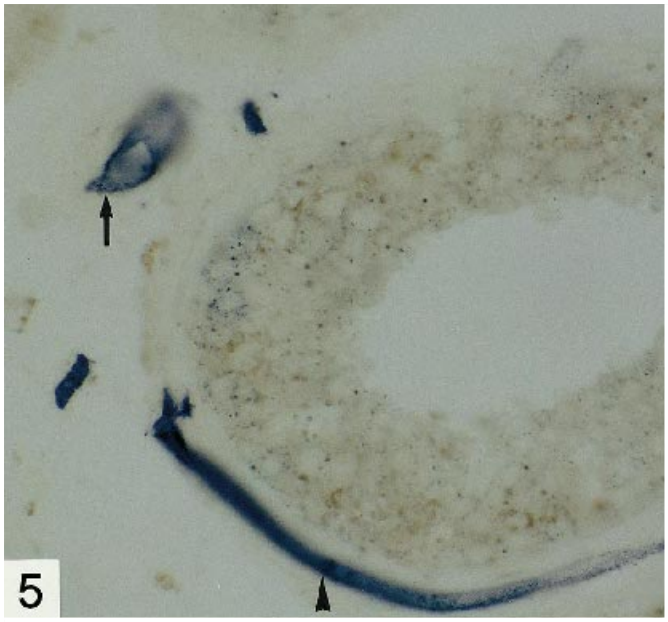


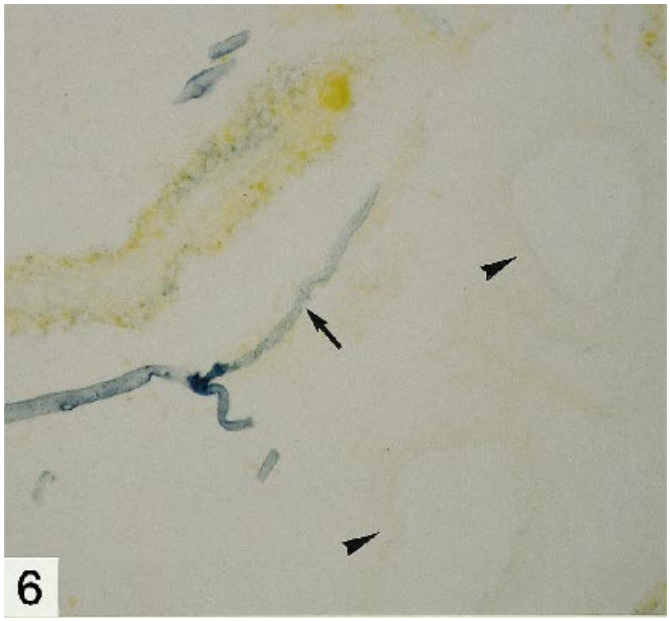
Fig. 4. Graphical demonstration of the subdivision of the capillary pathway of the human testis in relation to the Leydig cells and seminiferous tubules. Arterial side inter-Leydig cell capillaries pass through Leydig cell clusters on the arterial side of the testicular microvasculature. Intramural capillaries are localized within the lamina propria of seminiferous tubules. Venous side inter-Leydig cell capillaries are surrounded by Leydig cells on the venous side of the testicular microvasculature

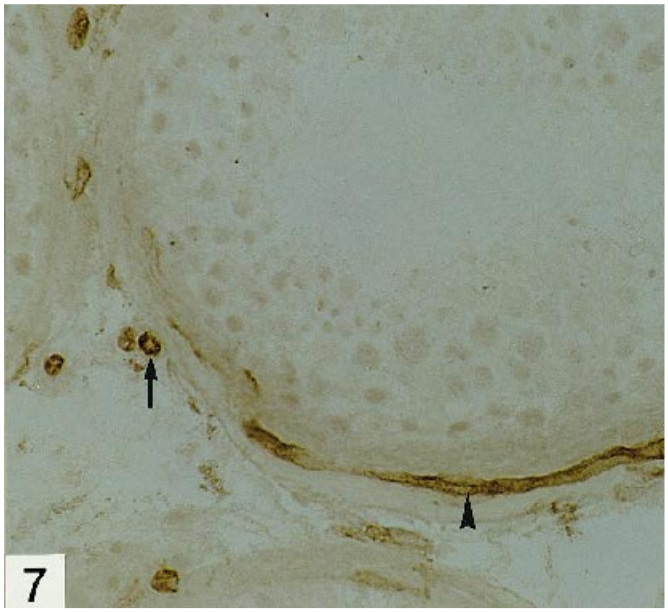
brocyte processes (Fig. 9). They exihibited a continuous endothelial lining and a continuous basal lamina in which pericytes were included (Fig. 10) and belonged to the A-1-α type of capillaries. Electron-microscopic examination demonstrated numerous endocytotic vesicles of variable size located on both sides of the endothelium, directed to the capillary lumen and to the basal lamina (Fig. 11). In some endothelial cells, fusion of these vesicles with each other into larger intracytoplasmic channels could been observed. Some vesicles were surrounded by a double membrane (Fig. 12). A smaller number of endocytotic vesicles was observed in endothelial cells of interstitial capillaries that were not surrounded by Leydig cells. Distinct tight junctions were seen in the contact zones between two endothelial cells in these capillaries (Fig. 12).

Intramural capillaries

These capillaries ran within the lamina propria and were surrounded by processes of the myofibroblasts (Fig. 13). They comprised capillary segments characterized by marked differences in endothelial ultrastructure. Each capillary within the lamina propria had a continuous non-fenestrated endothelium and continuous basal lamina (Fig. 13). Accordingly, this segment of the intramural capillaries resembled the A-1-α type. The endothelial cells of this segment of the intramural capillaries contained a large number of intracytoplasmic vesicles and intracytoplasmic channels (Fig. 14). A section of an intramural capillary that contains two different endothelial segments, viz., fenestrated and non-fenestrated, is shown in Fig. 15. The fenestrated endothelial segment possess-







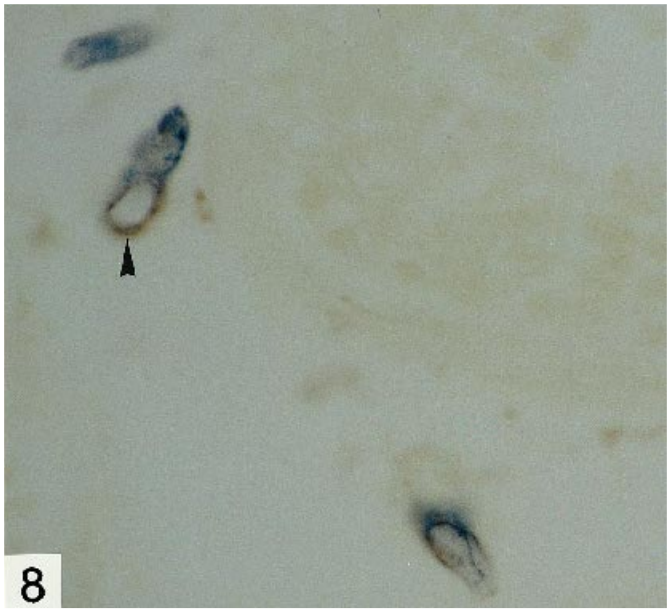


Fig. 5. Alkaline phosphatase enzyme activity of interstitial (*arrow*) and intramural capillaries (*arrowhead*). ×400

Fig. 6. Alkaline phosphatase activity of inter-Leydig cell capillaries (*arrow*). Note that the large interstitial blood vessels (*arrowheads*) are negative. ×200

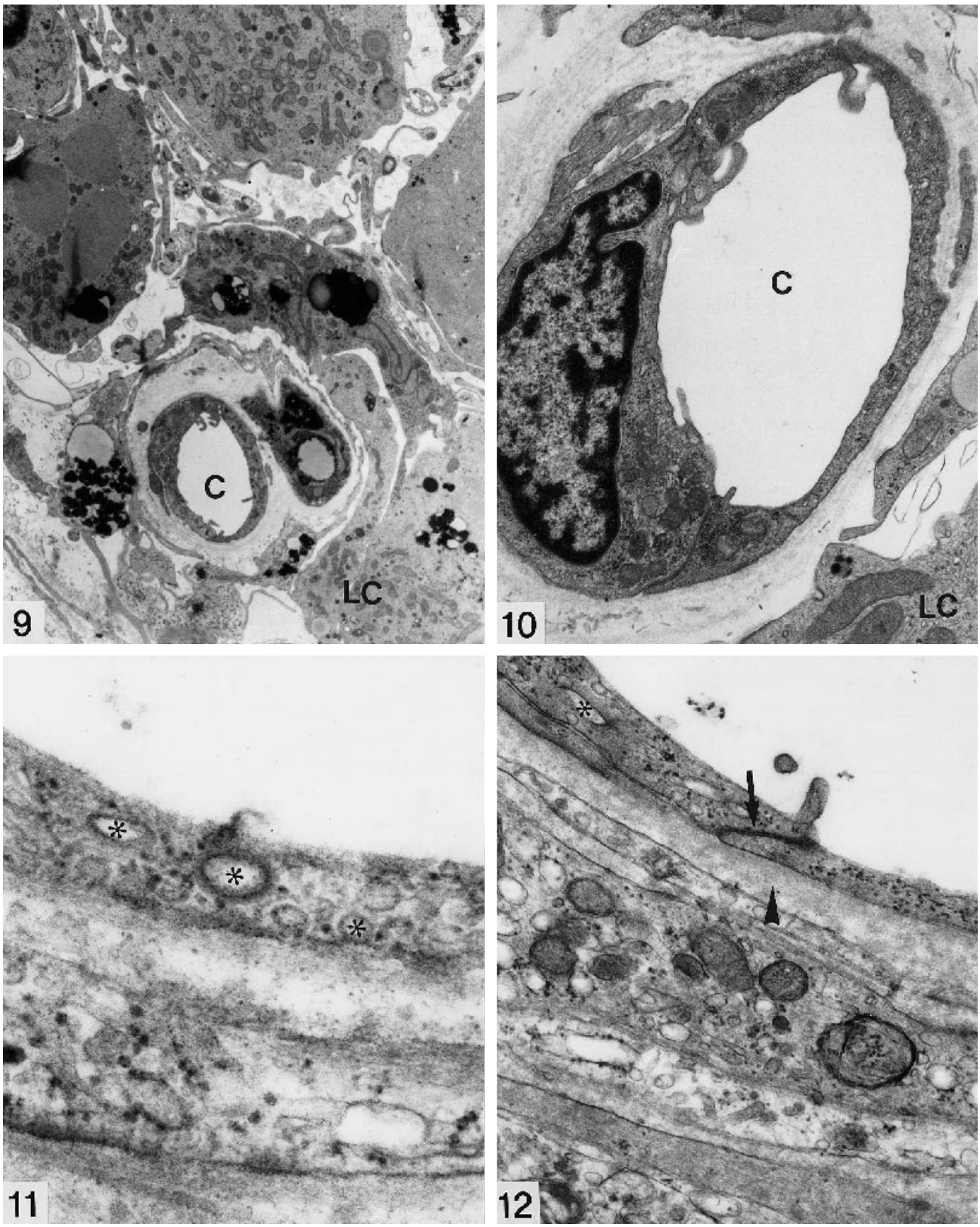
Fig. 7. Qbend-40 immunoreactivity of endothelial cells of an interstitial (*arrow*) and an intramural capillary (*arrowhead*). ×400

Fig. 8. Co-localization of alkaline phosphatase activity and Qbend-40 in the endothelial cells of the human testicular microvasculature (*arrowhead*). ×630

es a continuous basal lamina in which pericytes are included (A-2-α type). The fenestrated side of the endothelium is generally oriented toward the germinal epithelium (Fig. 15). Higher electron-microscopic magnification of this capillary shows that the fenestrations are closed by typical diaphragms (Fig. 16). In this fenestrated capillary section, only a few intracytoplasmic vesicles can be observed in the opposite non-fenestrated segment of the endothelium. Tight junctions can often be observed at the contact zones between the endothelial cells within the intramural segment.

Venous side inter-Leydig cell capillaries

In all investigated cases, capillaries of this section possessed a continuous non-fenestrated endothelium with a continuous basal lamina (A-1-α type; Fig. 17). In com-



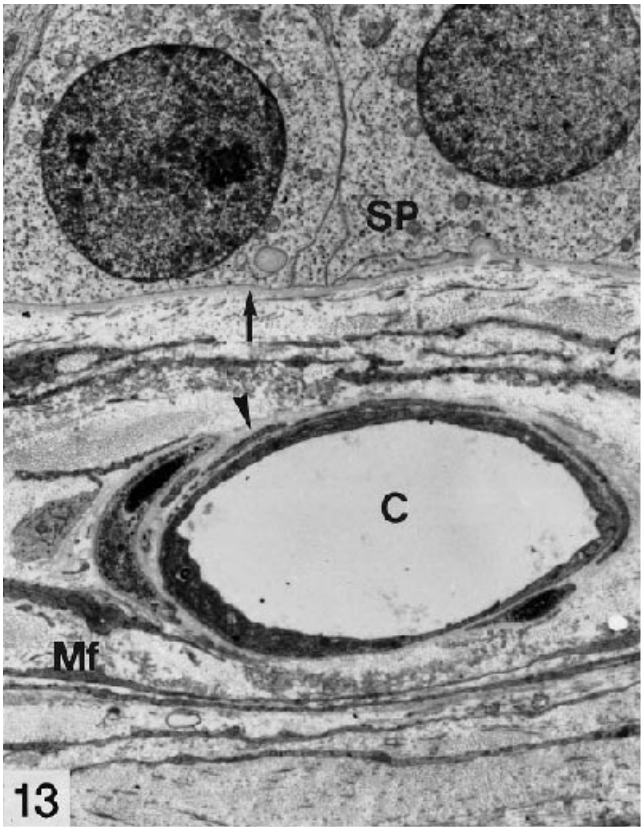
Figs. 9–12. Electron-microscopic structure of arterial side inter-Leydig cell capillaries

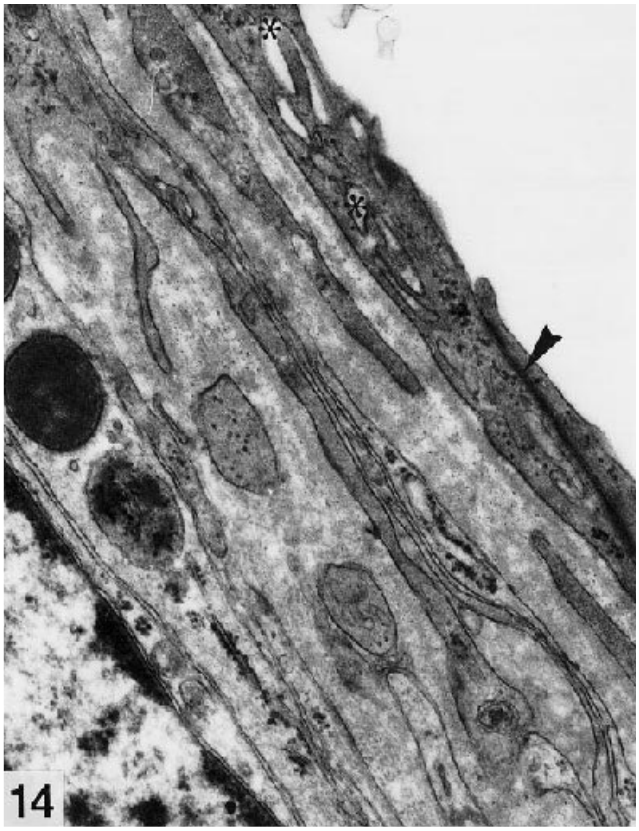
Fig. 9. Cross-section of a capillary (*C*) surrounded by Leydig cells (*LC*). ×2560

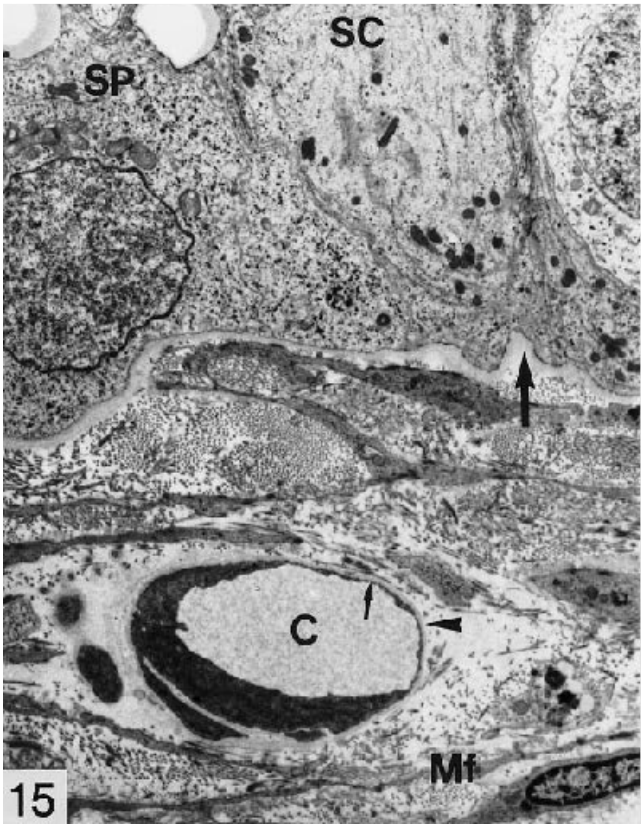
Fig. 10. Arterial side inter-Leydig cell capillary (*C*) with continuous non-fenestrated endothelium (A-1-α type). Leydig cell processes (*LC*) surrounding this capillary. ×6500

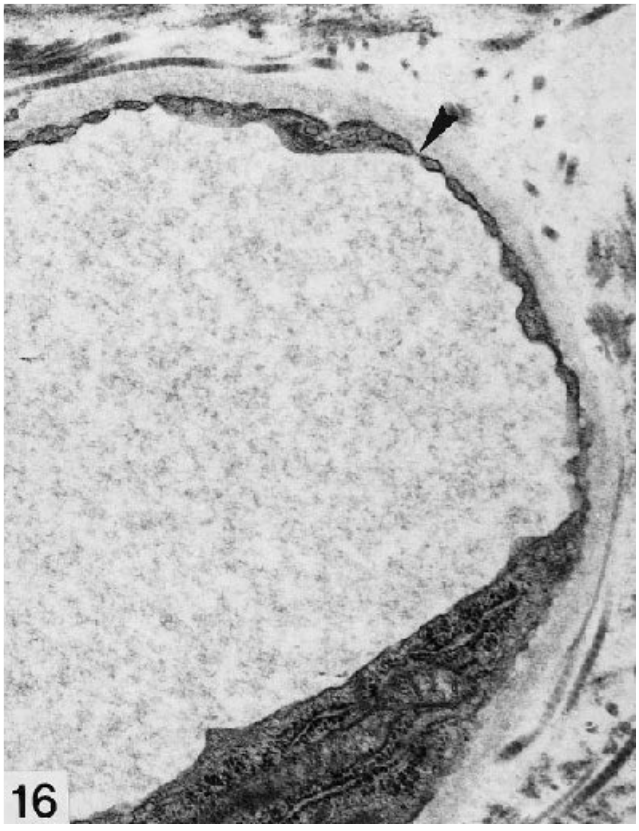
Fig. 11. Numerous trancytotic vesicles (*) in the endothelium can be seen at higher magnification. ×16 400

Fig. 12. Tight junction between two endothelial cells of an arterial side inter-Leydig cell capillary (*arrow*). Transcytotic vesicles in the endothelium (*). *Arrowhead,* Basal lamina of the capillary wall. ×16 400









Figs. 13–17. Electron-microscopic structure of intramural capillaries

Fig. 13. This segment of an intramural capillary (*C*) possesses a continuous non-fenestrated endothelial lining (A-1-α type). *Arrowhead*, Basal lamina of the capillary wall; *Mf*, processes of myofibroblasts; *arrow*, basal lamina of seminiferous tubule; *SP*, spermatogonium. ×4800

Fig. 14. Higher magnification. Transcytotic channels within the endothelium (*) and a tight junction (*arrowhead*) in the contact zone between two endothelial cells. ×16 400

Fig. 15. Segment of an intramural capillary (*C*) containing both continuous and fenestrated endothelial linings (A-2-α type). The fenestrations (*small arrow*) are directed toward the germinal epithelium. *Arrowhead*, Basal lamina of capillary wall; *large arrow*, basal lamina of seminiferous tubule; *Mf*, processes of myofibroblasts; *SC*, basal part of a Sertoli cell; *SP*, spermatogonia. ×4800

Fig. 16. Higher magnification of the fenestrated capillary from Fig. 15. Note that the fenestrations are closed by diaphragms (*arrowhead*). ×24 000

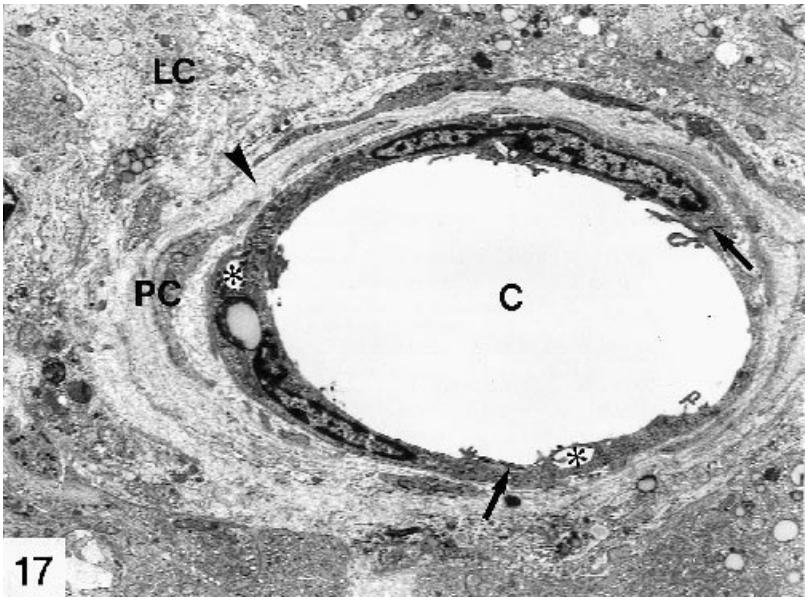


Fig. 17. Cross-section of a venous side inter-Leydig cell capillary with a continuous non-fenestrated endothelial lining. Transcytotic channels (*) through the endothelium and tight junctions in the contact zone between neighboring endothelial cells (*arrow*). *Arrowhead* Microvilli of endothelial cells, basal lamina of the capillary wall; *PC,* processes of pericytes; *LC,* Leydig cells. ×4080

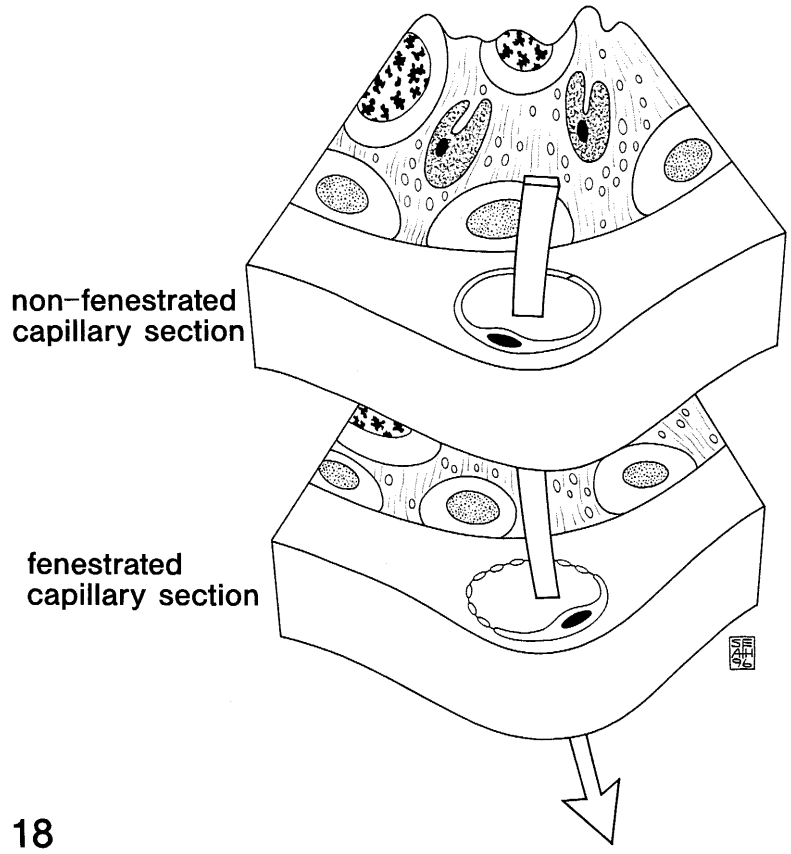


Fig. 18. The diagram illustrates both non-fenestrated and fenestrated parts along an intramural capillary. The fenestrations, which are closed by diaphragms, face the germinal epithelium. *Arrow,* Blood flow direction within the intramural capillary

parison with the arterial side, the diameter of the capillaries in this section was larger and their endothelium appeared thinner. Numerous large intracytoplasmic vesicles that were partly surrounded by a double membrane were seen.

The results obtained in the present study are summarized in Fig. 18, which shows the course of non-fenestrated and fenestrated parts of a testicular capillary in relation to the lamina propria of the seminiferous tubules.

Discussion

The present investigation provides the first evidence for ultrastructural differences between the previously defined three general subdivisions of the microvasculature of human testis, namely the arterial inter-Leydig cell capillaries, intramural capillaries, and venous inter-Leydig cell capillaries (Ergün et al. 1994), in relation to the features of the endothelial cells and the degree of transcytosis.

The observed ultrastrutural features allow the classification of the arterial inter-Leydig cell and the venous inter-Leydig cell capillaries as the A-1-α type, whereas the intramural capillaries, which contain two segments, are A-1-α and A-2-α types (classification according to Bennet et al. 1959). One of the most intriguing results is the observation that long segments with both fenestrated and non-fenestrated endothelial cells exist within the intramural capillaries. Moreover, the fenestrated endothelial cells are located on the capillary side facing the germinal epithelium, whereas the non-fenestrated endothelial cells face the interstitium. There is no evidence in the literature for similarly organized capillary sections in the testis of other species (Hundeiker 1971; Setchell 1994). Setchell has (1994) pointed out that, unlike all other endocrine tissues, which typically posesses fenestrated capillaries, the testicular capillaries are non-fenestrated and belong to the A-1-α type. Concerning this type of capillary, there is evidence that transcytotic and transitory openings of the interendothelial contacts play a crucial role in the permeability of various solutions and specific substances (Schnittler et al. 1990).

In this respect, the human testis shows a unique structural feature. The functional significance of these different types of capillaries in the human testis is not known. The observation that the fenestrated segments of the intramural capillaries face the germinal epithelium suggests that they are responsible for an enhanced selective exchange of substances. This selectivity of exchange may depend on the proteoglycan composition of the diaphragms of the endothelial fenestrations (Simionescu and Simionescu 1988). Presumably, the fenestrated segments of the intramural capillaries fulfil special functions regarding the exchange of metabolites and hormones between the seminiferous tubules and the blood circulation. Thus, the fenestrated segments of the intramural capillaries differ significantly from the organization of the remaining segments of the microvasculature of human testis. A closed endothelial lining is present in the arterial inter-Leydig cell capillaries and in the venous inter-Leydig cell capillaries.

The endothelial cells of the capillary sections that are surrounded by Leydig cells at the arterial and the venous side contain many more transcytotic vesicles and channels than the remaining interstitial capillary segments which are free of Leydig cells. The endothelial cells of these various capillary segments show different transcytotic activity. The numerous transcytotic channels in these capillary segments reflect receptor-mediated transport of proteins (Simionescu and Simionescu 1987). Concerning transcytotic activity, the non-fenestrated intramural capillary segments resemble the intra-Leydig cell segments. The numerous transcytotic structures in the endothelial cells of the testicular capillaries reflect an active exchange between the interstitial Leydig cells, the periphery of the seminiferous tubules, and the blood circulation.

The functional significance of the Leydig cells that surround the capillary walls is not fully known. In addition to the release of testosterone, the Leydig cells may be important for the regulation of blood transport within the testicular vasculature. It has recently been suggested that Leydig cells and endothelial cells influence the contractility of the smooth muscle cells and pericytes of the vessel walls by nitric oxide (Davidoff et al. 1995). In addition, preliminary results show that the endothelial cells and pericytes of the arterial intra-Leydig capillaries and intramural capillaries, but not venous intra-Leydig cell capillaries, exhibit androgen-receptor immunoreactivity (Ergün and Ungefroren 1995), providing evidence for close interrelationships between the Leydig cells and the endothelial cells. A modulatory activity of testosterone on the vasomotion (rhythmical variations in the capillary blood flow) and permeability of the testicular vessels has previously been established in other species (Damber and Bergh 1992).

The experiments with sequential staining have shown that the endothelial cell marker (Qbend 30) and alkaline phosphatase activity are co-localized in the endothelial cells of the testicular microvasculature. Qbend 30 is an antibody against a cell-surface-associated antigen of human endothelial cells. It has been reported that alkaline phosphatase enzyme activity is localized in structures for which active transport processes are typical events (Lojda et al. 1976). However, alkaline phosphatase enzyme activity has been observed only within endothelial cells of arterioles and all capillary segments. This localization of alkaline phosphatase activity corresponds only in part to the localization described earlier for rat testis (Kormano 1967). For this species, a positive reaction is seen not only in the capillaries, but also in components of the lamina propria. These differences between the rat and human probably reflect the more complicated construction of the human lamina propria (DeKretser et al. 1975; Davidoff et al. 1990) and variations in the organization of the capillary and lymphatic vessels of both species (Holstein et al. 1979). The multilayered human lamina propria represents a less diffusible barrier for agents released by the seminiferous tubules or the interstitium. In the rat, the one-layered lamina propria allows for easier diffusion of substances from the peritubular capillaries and the well-developed peritubular network of lymphatic vessels toward the seminiferous tubules and vice versa. In the human testis, the lymphatic vessels are preferentially located within the septula testis, whereas in the interstitium, they are rare (Holstein et al. 1979). The multilayered construction and the lower permeability rate are presumably the reason for the human lamina propria being capillarized in contrast to the lamina propria of laboratory animals (rat, mouse). In addition, the interstitium of the human testis contains a poorly developed lymphatic network and no alkaline phosphatase activity in the structures of the lamina propria. Therefore, unlike in rat or mouse, the distribution and transport of hormones and other substances in the human testis may be regulated predominantly by the microvasculature.

The interstitium of human testis shows a different spatial organization, concerning the Leydig cells, the lamina propria, and the seminiferous tubules, from that of well-investigated laboratory animals. The distances between the above mentioned compartments in humans are much larger, and substances have to move over

greater distances by diffusion. To overcome these hinderances in the human testis, the transport path toward and from the germinal epithelium is shortened by the intramural segments of the capillaries. Indeed, the transport of hormones and nutritional substances from the interstitium to the seminiferous tubules may occur via the afferent part of the microvasculature. The exchange of hormones, nutritional substances, and gases between the germinal cells and the blood circulation may be conducted via the intramural segment of the microvasculature, whereas the transport of these substances from the seminiferous tubules to the interstitium and the Leydig cells at the venous side may be accomplished via the efferent part of the microvasculature. Our results therefore provide new perspectives for the understanding of the organization of the microvasculature and its functional significance in the performance of complicated regulatory processes in human spermatogenesis.

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