HISTOLOGY of the HUMAN EYE

An Atlas and Textbook

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branch more often and form extensive intercommunications. The fibrils are not so uniformly spaced as they are in the cornea and there is less ground substance. Posteriorly the fibrils assume dimensions more like those in the sclera, their diameter being between 700 and 1000 A. The fibroblasts of the limbal stroma are like those of the cornea and sclera. Only occasional macrophages and leukocytes are seen here.

Most of the vessels encountered in the limbal stroma are the veins of the deep and intrascleral plexuses. Small arterial channels are found throughout the stroma and a net of small arteries appears in the region of Schlemm's canal, but those vessels do not communicate directly with the lumen of the canal.

Myelinated and unmyelinated nerves are seen throughout the limbal stroma, most of them being branches of the ciliary nerves which are destined for the cornea.

Aqueous Outflow Apparatus (Figs. 4-16 and 4-17)

The limbus contains structures which are specially developed for the removal of aqueous humor. The elements involved in removal of the aqueous humor are mostly found in the internal scleral sulcus. The outflow apparatus is composed of tissue derived from the cornea, sclera, iris, and ciliary body and will be described as follows:

1. Schlemm's canal and collector channels
   a. Schlemm's canal
   b. External collector channels
   c. Internal collector channels
2. Trabecular meshwork
   a. Corneoscleral meshwork
   b. Uveal meshwork
   c. Pectinate fibers or iris processes
3. Scleral spur
4. Deep corneolimbus
5. Innervation

Figure 4-16. Drawing of the aqueous outflow apparatus and adjacent tissues. Schlemm's canal (a) is divided into two portions. An internal collector channel (Sondermann) (b) opens into the posterior part of the canal. The sheets of the corneoscleral meshwork (c) extend from the corneolimbus (e) anteriorly to the scleral spur (d). The rope-like components of the uveal meshwork (f) occupy the inner portion of the trabecular meshwork; they arise in the ciliary body (CB) near the angle recess and end just posterior to the termination of Descemet's membrane (g). An iris process (h) extends from the root of the iris to merge with the uveal meshwork at about the level of the anterior part of the scleral spur. The longitudinal ciliary muscle (i) is attached to the scleral spur but has a portion which joins the corneoscleral meshwork (arrows). Descemet's membrane terminates within the deep corneolimbus. The corneal endothelium becomes continuous with the trabecular endothelium at (j). A broad transition zone (double-headed arrows) begins near the termination of Descemet's membrane and ends where the uveal meshwork joins the deep corneolimbus.

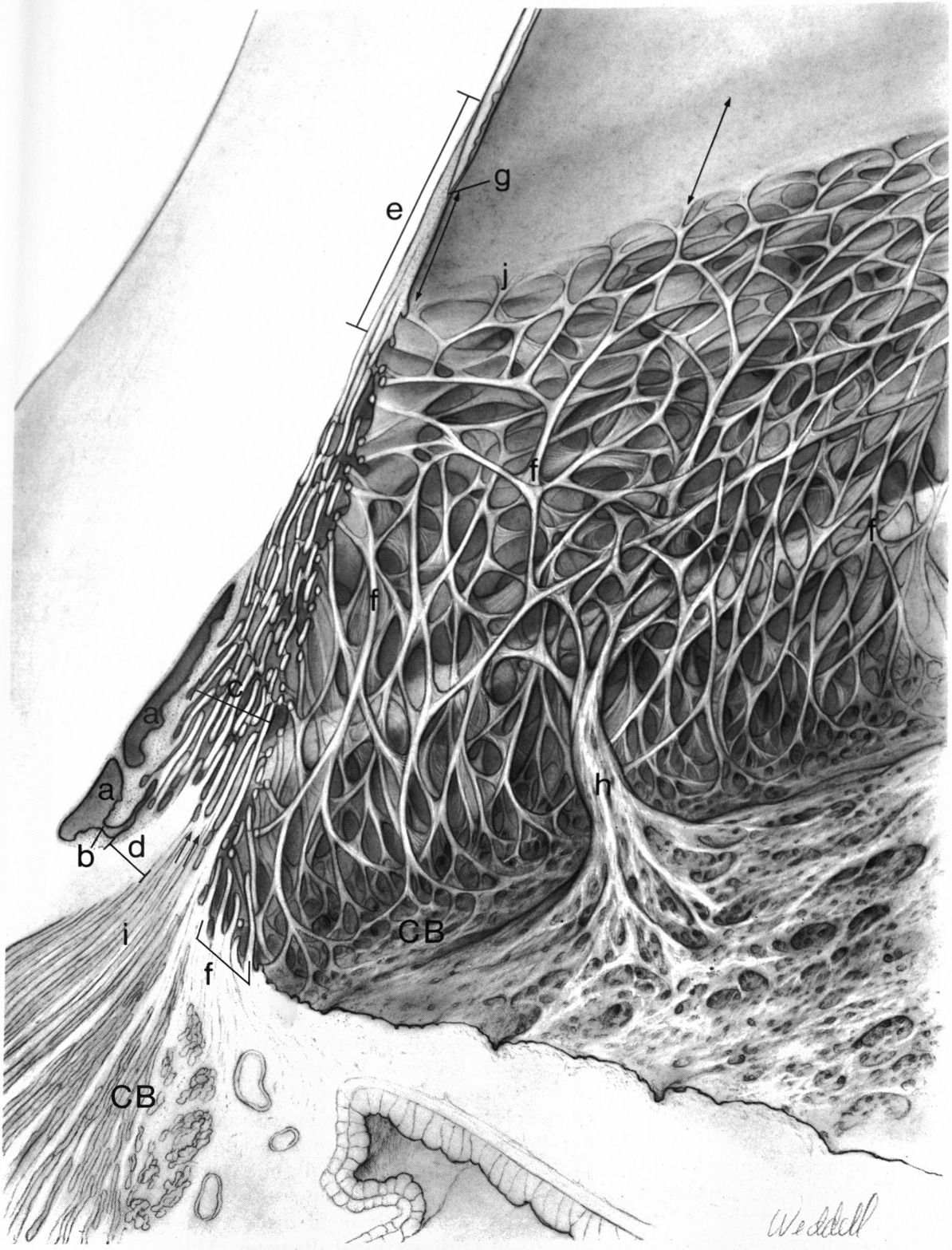

Figure 4–16. *See legend on opposite page.*

Figure 4-17. Light micrograph of the aqueous outflow apparatus. Schlemm's canal (a) is split into two portions. The external wall of the canal is relatively smooth in comparison with the inner wall. The inner canal wall is identified by single arrows. The scleral spur (b) with its denser collagenous tissue is seen posteriorly. The empty intertrabecular spaces (double arrows) are formed by the sheets of the corneoscleral meshwork. The thin cords of the uveal meshwork are adjacent to the anterior chamber; one cord (c) is shown. (× 310.)

Schlemm's Canal and the Collector Channels

Schlemm's Canal (Figs. 4-18 to 4-29). This circular venous channel lies in the outer portion of the internal scleral sulcus. The external wall of the canal is located quite close to the limbal stroma but is separated from it by the thin layers of connective tissue that form the canal wall. The internal wall of the canal of Schlemm is adjacent to the deepest part of the corneoscleral meshwork. The deep sclera is close to the posterior boundary of Schlemm's canal, and on its anterior side are the sheets of the corneoscleral meshwork.

The ring formed by the canal measures 36 mm. in circumference (McEwen, 1965), and it has a flattened elliptical cross-section. Its meridional width varies between 350 and 500 μm. in adults, being somewhat smaller in children, and the lumen frequently becomes very narrow or even splits into branches which enclose islands of tissue. Salzmann (1912) likened this configuration to that of a river that is subdivided by islands along its course. The surface of the canal is varicose, the varicosities having cross-sectional shapes from round to oval, or even triangular (Ashton, 1951). When the shape is triangular, the base is posterior and measures 50 μm. in width, while the anterior apex narrows to 5 or 10 μm.

A thin connective tissue wall surrounds the endothelial lining of Schlemm's canal. On the external side the wall is 5 to 10 μm. in thickness and can be differentiated easily from the adjacent limbal stroma by its cellularity and large deposits of finely fibrillar material. The greater part of this layer is composed of fibroblasts having numerous arrays of rough-surfaced endoplasmic reticulum, a well developed Golgi apparatus and many mitochondria. It is likely that the fine granular material present near these fibroblasts is synthesized by the cells. If this material is tropocollagen, it will undergo further polymerization to form the mature collagen fibrils. The collagen fibrils in the external adventitia resemble those of the corneal stroma, measuring approximately 300 A. in cross-sectional diameter. The fibrils are irregularly dispersed in an abundant matrix composed of a slightly osmiophilic, amorphous ground substance.

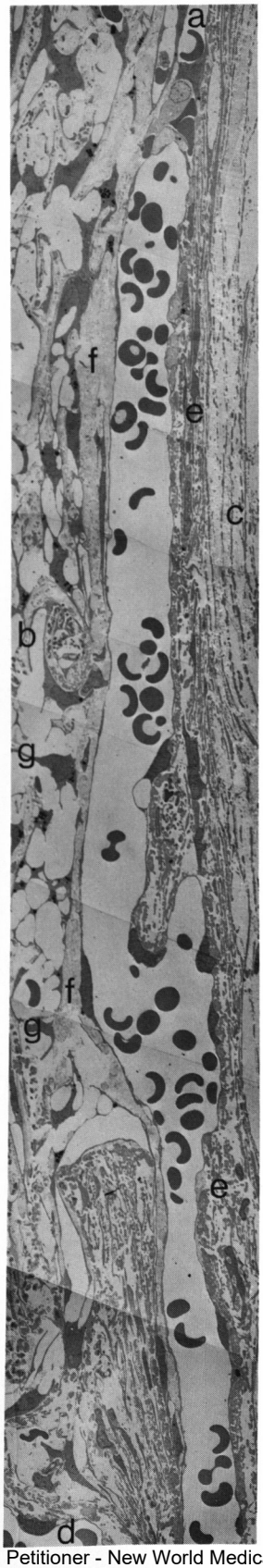

Figure 4-18. Composite electron micrograph of Schlemm's canal. The anterior canal is near (a), the inner side is at (b) and the limbal stroma is at (c). The canal has a length of 500 μm. and an average width of 40 μm. Numerous red blood cells occupy the lumen of the canal, probably as a result of backflow into the canal at surgery. An internal collector channel (d) or canal of Sondermann is seen at the bottom of the photograph near the posterior canal. The external wall of the canal is at (e) and the internal wall is at (f). In this photograph the inner wall of the canal shows no giant vacuoles in the endothelium. The bridging of the intertrabecular spaces by endothelial cells and subdivisions of the trabecular sheets is evident at (g). (× 760.)

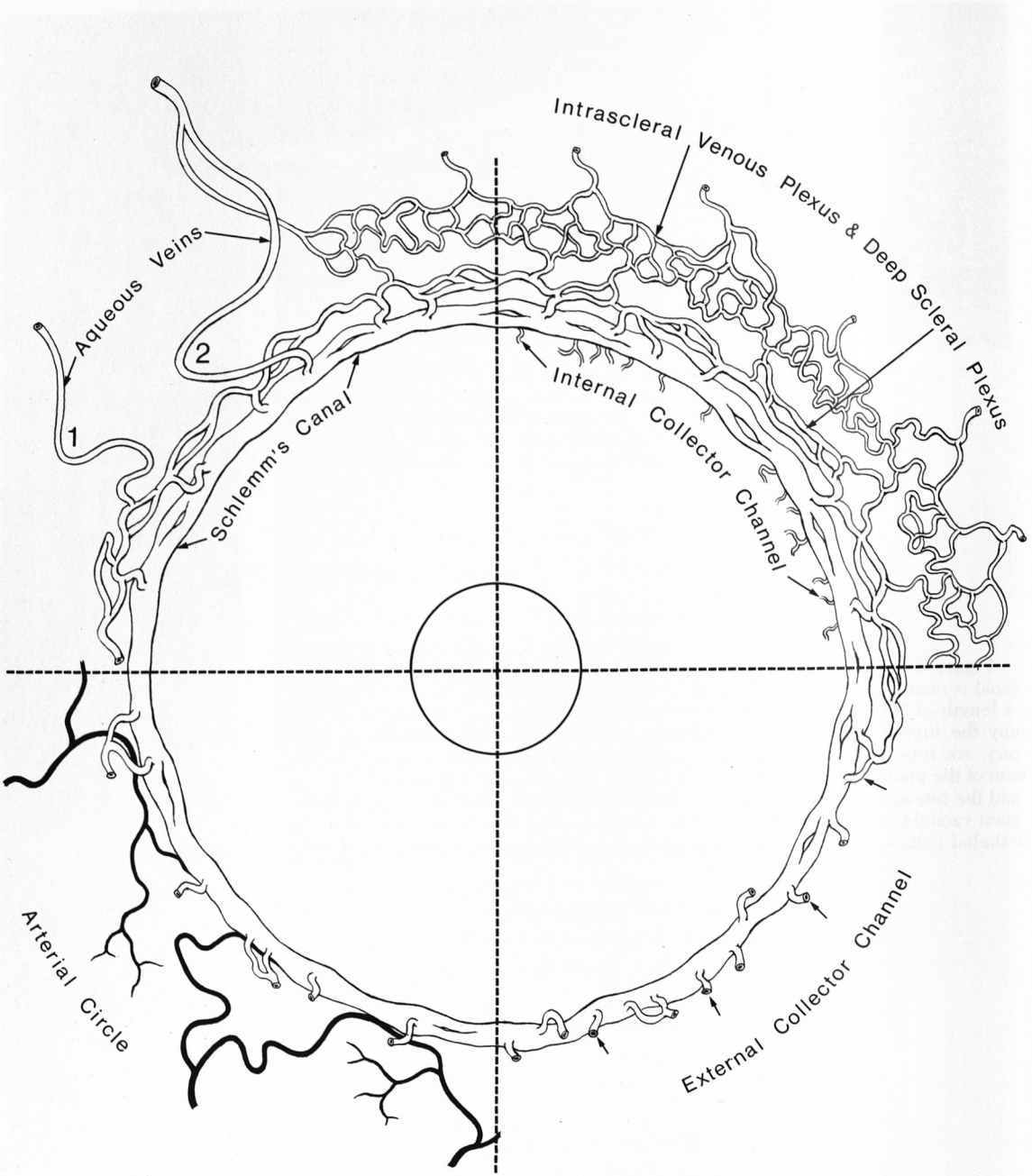

Figure 4-19. Schematic drawing showing the circular course and related vessels of the canal of Schlemm. The canal divides into two or more portions intermittently. The drawing is divided into four portions by the dotted lines. The internal collector channels of Sondermann are labeled in the upper right sector as they extend into the trabecular meshwork. The external collector channels are seen in the upper and lower right sectors, arising from the canal and uniting with the deep intrascleral plexus or extending directly to the episcleral veins. The deep and intrascleral venous plexuses are external to the canal.

In the upper left sector an aqueous vein (1) arises from the deep scleral plexus and another (2) arises from Schlemm's canal and runs directly to the episcleral venous plexus. External collector veins are seen to arise from the canal and join the deep scleral plexus.

In the lower left sector the arteries of the deep sclera are seen to be in close relation to the canal of Schlemm.

Polymorphonuclear leukocytes, macrophages and mast cells are seen occasionally in this narrow cellular connective tissue layer. It is surrounded by a transition zone measuring 20 to 30 μm. in thickness and composed of 8 to 10 lamellae of collagenous tissue. These collagenous lamellae run in all directions and are separated from each other by long fibroblasts. The collagen fibrils of the lamellae gradually increase in cross-sectional diameter from 300 A. to 800 to 1000 A. in diameter so that they come to resemble scleral collagen.

The cell wall internal to Schlemm's canal continues posteriorly around the wall of the canal and joins the external wall. This internal wall has been studied for many years by light microscopists, who noted the presence of many cells and a complete absence of trabecular spaces in the zone adjacent to the canal. It has been called the pore tissue by Flocks (1956), the cribriform area by Rohen (1961, 1963, 1964), and the juxtacanalicular connective tissue by Fine (1966). If a title has to be applied, juxtacanalicular tissue is most satisfactory, but we prefer to consider it as the inner wall of Schlemm's canal.

The structure and thickness of this canal wall vary in different sections along its sinuous outline. Many areas are seen in the wall where the ground substance has been extracted during the processing of the tissue, causing further changes in its character. Extracted areas of this type have been mistaken in the past for trabecular spaces, introducing an additional error in estimation of the actual thickness of the canal wall. In general, this layer measures between 10 to 20 μm. in thickness between the "basement membrane" of the endothelium and the nearest intertrabecular space. In well fixed specimens a complete endothelial layer is generally demonstrable at the junction of the outermost trabecular space with the canal wall.

The relationship between the trabecular spaces, the cell wall and the canal of Schlemm is as follows: (1) a layer of endothelium lines the outermost trabecular space; (2) next to this is found connective tissue of the canal wall which is composed of the same cells, collagen, tropocollagen and amorphous ground substance as we have described in the external canal wall; and (3) the endothelium of Schlemm's canal and its basement membrane. However, even in well fixed specimens there may be a few areas where the first and second components are lacking, and in such regions only the endothelium of the inner canal wall and its basement membrane separate the canal of Schlemm from the nearest intertrabecular space.

The lumen of Schlemm's canal is lined by an endothelium which has a rather smooth luminal surface everywhere except for its sinuous inner side. Most of the endothelial cells are small, having an average diameter of 10 μm. and a thickness of 0.2 μm. (Holmberg, 1965). Those along the inner wall, however, have a diameter of 20 to 50 μm. An endothelial basement membrane has been described, especially at the inner wall of the canal (Garron et al., 1958). This membrane is quite different from basement membranes found in other tissues, such as those of the corneal epithelium and of capillary endothelium. It is poorly defined, inconstant, frequently interrupted and of variable thickness; it is often separated from the endothelium by an irregular space. The lateral walls of the endothelial cells are joined by tight junctions, mainly zonulae occludentes, near their luminal surfaces. The points of membrane fusion are unusually small, measuring between 100 and 200 A., and occasionally the intercellular space is not closed by a tight junction.

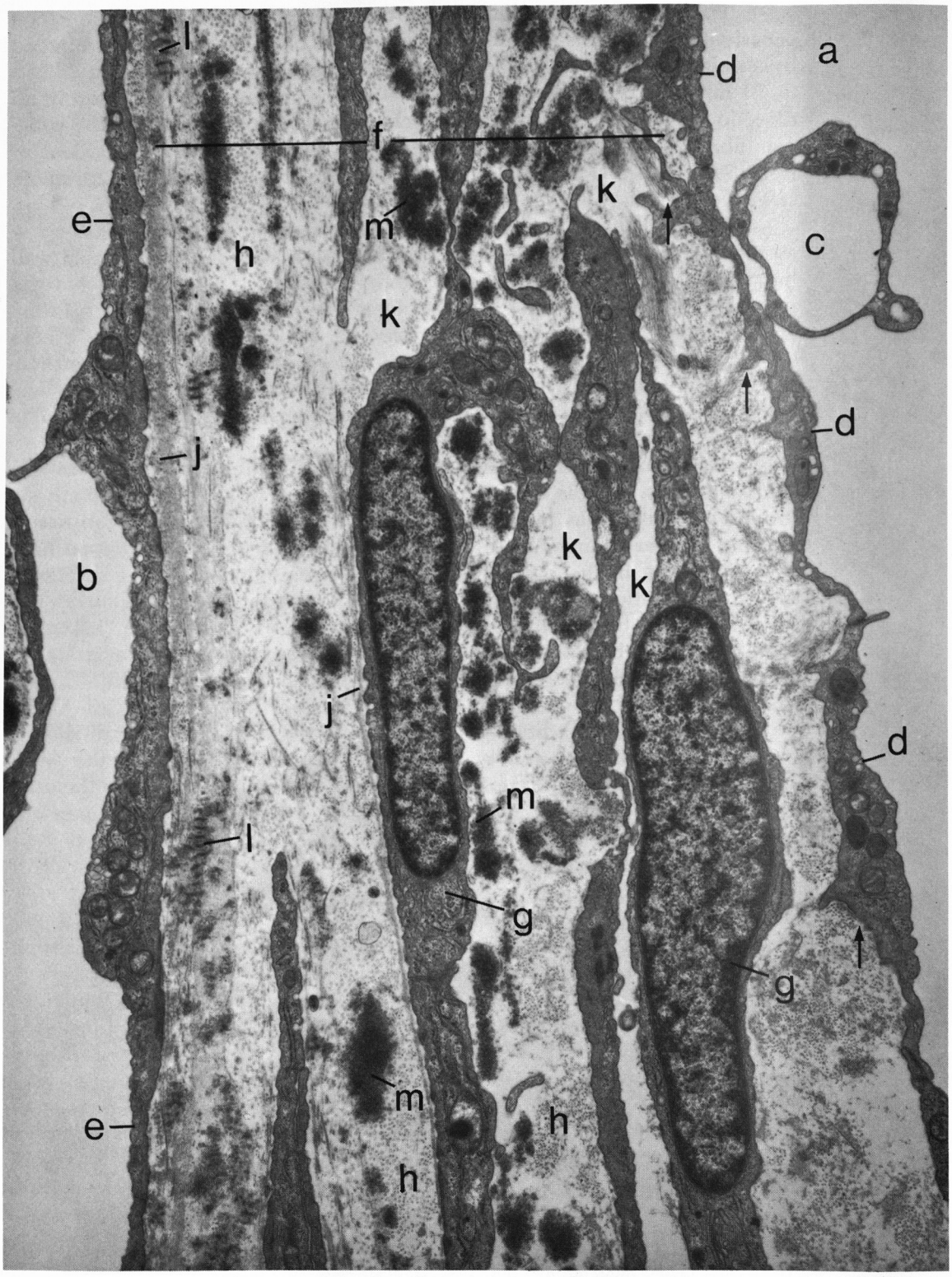

Figure 4-20. Schlemm's canal, internal wall. The lumen of the canal is at (a) and the nearest trabecular space is at (b). One endothelial cell lining the canal contains a giant vacuole (c) which measures 2.5 μm. in diameter and protrudes into the lumen of the canal. Four endothelial cells (d) line the inner canal wall. The trabecular space (b) is lined by portions of

The cytoplasm of these endothelial cells is mainly characterized by its content of filaments and free ribosomes. The mitochondria are very small, and the Golgi apparatus and profiles of rough-surfaced endoplasmic reticulum are seen only occasionally. Numerous pinocytotic vesicles, similar in size and distribution to those seen in the endothelium of capillaries, are found along the cell membranes of this endothelium.

Many of the cells along the internal canal wall possess cytoplasmic vesicles or vacuoles of extraordinary dimensions and of specific distribution. These have come to be known as giant vacuoles and are found only in the cells of the inner wall of Schlemm's canal. The vacuoles are outlined by a single membrane, with the largest vacuole measuring up to 14 μm. in length by 5 μm. in width. Holmberg (1965) made serial sections of 10 μm. portions of canal wall and found an average of 0.5 vacuoles per 10 μm. The range for six eyes was from 0.3 to 0.9 vacuoles for 10 μm. These giant vacuoles have been the subject of numerous studies, but their role and importance in aqueous humor transport into the lumen of Schlemm's canal is not entirely clear. In some early studies the vacuoles were shown to have an opening into the lumen of Schlemm's canal measuring about 0.3 to 2.0 μm. in diameter. A number of investigators (Speakman, 1960; Rohen, 1961; Holmberg, 1959, 1965) have also seen openings from these vacuoles into the nearest trabecular spaces. It has been suggested that the vacuoles might provide a direct pathway for the movement of aqueous humor from the innermost trabecular space into the canal of Schlemm (Garron et al., 1958; Garron and Feeney, 1959; Holmberg, 1959, 1965; Leeson and Speakman, 1961; Spelsberg and Chapman, 1962; Iwamoto, 1967a; Kayes, 1967; Vegge, 1963, 1967; and Tripathi [Rhesus], 1968).

The presence of the canal wall as a practically continuous layer between the endothelial lining of the canal and the nearest trabecular space makes it difficult to believe that the vacuoles can provide a constant pathway for the flow of aqueous humor. The vacuoles may actually open into the connective tissue, but in recent studies they have not been observed to open into the nearest trabecular space. Feeney and Wissig (1966), using an electron-opaque tracer (ferritin), showed that the vacuoles are not constantly open. When tracer material was perfused into the anterior chamber it accumulated in high concentration within some vacuoles, while it was entirely absent in others. It seemed to these investigators that the vacuoles must

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Figure 4–20. *Continued.*
two endothelial cells (e). One cell branch almost crosses the intertrabecular space to join the endothelial cell of a trabecular sheet. The cells lining the spaces of the trabecular meshwork are thicker and more extensive than those lining Schlemm's canal.

The inner wall of the canal (f) includes all the tissue between the endothelium (d) of the canal and the endothelium (e) of the nearest trabecular space (b). The canal wall contains numerous fibroblasts (g) and thin collagen fibrils (h). The collagen fibrils measure 300 A. in diameter and most often are seen in cross-section when the sections are meridional. Adjacent to the canal some collagen fibrils are in close contact with its endothelium (arrows). This arrangement is similar to that found in lymphatic channels. The endothelial cells lack a basement membrane in this portion of the canal for 20 μm. At (j) a fibroblast appears to have what has been described as a "basement membrane." The abundant ground substance of the canal wall has been extracted during preparation of the tissues, leaving numerous empty spaces (k) which were formerly misinterpreted as trabecular spaces. Wide-spacing fibers (l) are found near the trabecular space, and dense clumps of very fine filaments (m), possibly tropocollagen, are scattered throughout the wall. (× 12,400.)

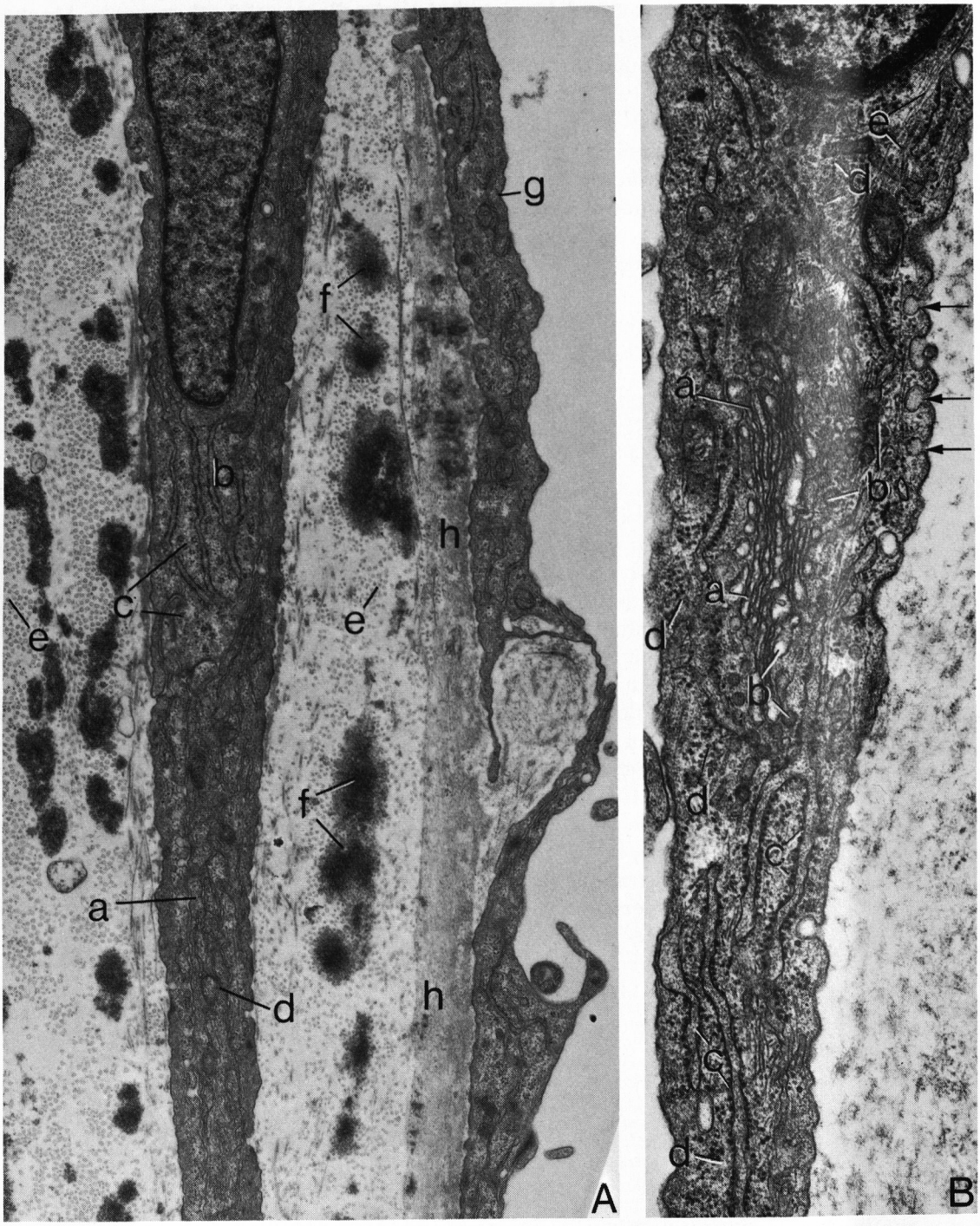

Figure 4-21. The inner wall of Schlemm's canal. *A*, The fibroblasts (a) resemble those of the cornea in their thickness and length. Long interconnecting cisternae of the rough-surfaced endoplasmic reticulum (b) and free ribosomes (c) are indicated. The mitochondria are small (d) and relatively sparse, and the nuclear chromatin is dispersed. The collagen fibrils (e) seen here measure less than 300 A. in diameter and are cut mostly in cross-section. Some of these fibrils are associated with masses of an electron-dense material (f). The endothelium of a trabecular space (g) is seen on the right. There is a layer of fibrillar material which varies in thickness adjacent to the endothelium, but it does not clearly represent a basement membrane. It contains clumps of wide-spacing fibers. (× 13,000.)

open and close intermittently, emptying their contents into the canal. The main function of the vacuoles would appear to to be in the active transport of large molecules such as proteins across the endothelium in order to circumvent the barrier presented to these molecules by closure of the intercellular space by the zonulae occludentes. The smaller pinocytotic vesicles also found in the endothelium of Schlemm's canal probably work in conjunction with the large vacuoles in the active transport of substances.

It is not clear whether a barrier to aqueous outflow is presented by the endothelium of the trabecular space nearest the juxtacanalicular tissue. Since this endothelium is not always continuous, aqueous humor may freely enter the connective tissue of the canal wall and then be incorporated into those vacuoles which are open. Finally, it should be emphasized that the greatest volume of aqueous humor diffuses passively through the wall of Schlemm's canal and that active transport may be needed only for large macromolecules and electrolytes.

The External Collector Channels (Fig. 4-28). Twenty-five to 35 veins emerge from the external wall of the canal of Schlemm and either join the deep scleral plexus directly or pass to the surface of the eye as aqueous veins. They are the principal route for the flow of aqueous humor from the canal of Schlemm into the episcleral veins. The channels are unevenly distributed around the circumference of the canal, being more numerous nasally than temporally, and are often connected to it in groups (Theobald, 1934). Theobald showed in serial sections of human eyes that these channels connect with each other and with the deep scleral plexus of veins, but not with arterial channels. Ashton (1951), using neoprene injections, verified the existence of these channels in human eyes and verified their origin from the canal of Schlemm. In addition to those veins which arise from the canal of Schlemm and pass directly to the episcleral plexus, he found others that joined the deep scleral plexus of veins; from this plexus, collector channels then joined the episcleral vessels. Ashton also confirmed the absence of arterial connections to these veins even though the arteries were located close to, or even embedded in, the wall of Schlemm's canal. His preparations also showed the presence of veins connecting the ciliary venous plexus with the deep scleral plexus.

When studied with the electron microscope, the external collector vessels are seen to be lined by an endothelium similar to that along the outer wall of Schlemm's canal. The connective tissue of the wall of Schlemm's canal continues outward along the external collector channels as a very simple layer which may show an occasional muscle cell. The adventitia disappears from the walls of those vessels which join the deep scleral plexus.

Internal Collector Channels (Fig. 4-29). Sondermann (1933) was the first to indicate that endothelial-lined canaliculi might connect the anterior

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Figure 4-21. *Continued.*

B, Area similar to *A* to show the details of another fibroblast. The Golgi complex with its flattened cisternae (a) and associated vesicles (b) is prominent in the cytoplasm. Branching cisternae of rough-surfaced endoplasmic reticulum (c) also are prominent. Several vesicles are also observed, with an opened end toward the extracellular region (arrows). Free ribosomes (d) and cytoplasmic filaments (e) are indicated. (× 31,000.)

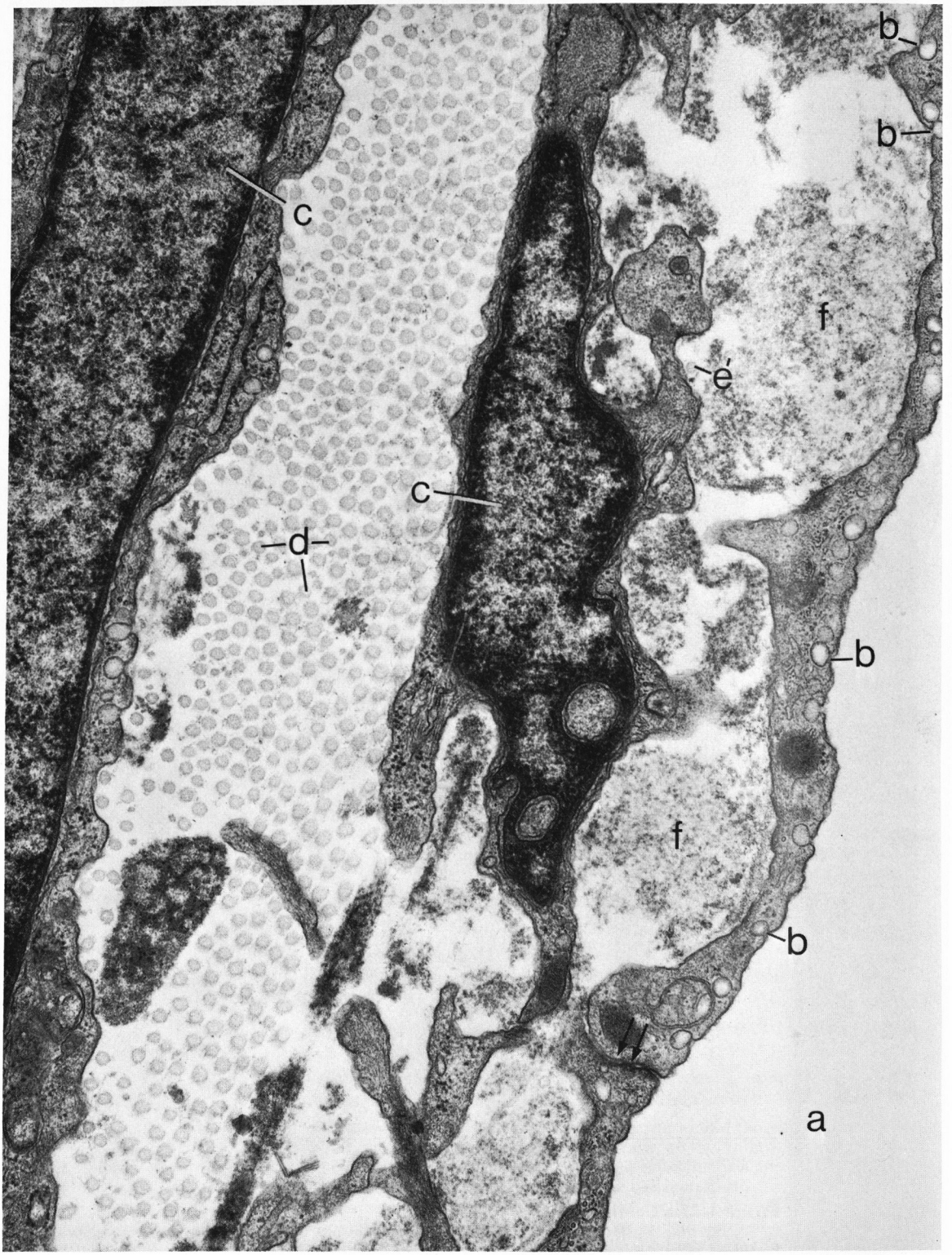

Figure 4–22. *See legend on opposite page.*

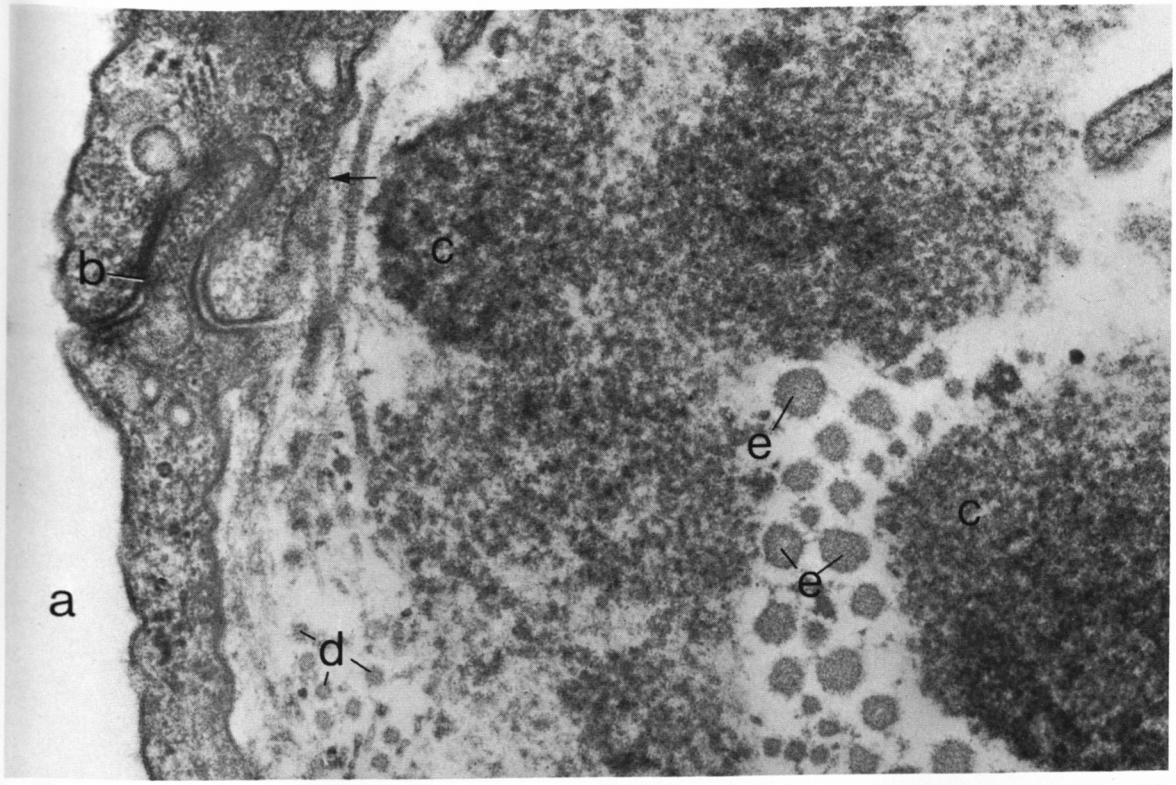

Figure 4-23. Schlemm's canal, external wall. The lumen of Schlemm's canal is at (a), while the junction of two endothelial cells is seen at (b). The granular, particulate nature of the material (c) is quite evident. Mature collagen fibrils are seen in cross-section (d,e), measuring 1000 A. and 2000 A., respectively. A collagen fibril (arrow) is in contact with the endothelium, a relationship often seen in lymphatics. (× 67,500.)

chamber to Schlemm's canal. Such channels were also described by Theobald (1934); Thomassen and Bakken (1951); François and associates (1955); Ashton (1956); Unger and Rohen (1959) and Iwamoto (1967 a, b). Other observers have denied their existence, including Fortin (1942); Flocks (1956); Garron and Feeney (1959); Feeney and Wissig (1966); and Vegge (1967). Sondermann demonstrated at least five internal collector channels per external collector channel through serial sections and reconstructions of this region in a number of human eyes. Theobald observed that these channels are easy to overlook unless serial sections are made, since they are not evenly distributed around the eye.

Routine histologic sections of human eyes often show small endothelial-

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Figure 4-22. Schlemm's canal, external wall. The lumen of the canal is at (a). Pinocytotic vesicles (b) lie adjacent to both the outer and inner endothelial cell membrane. Two tight junctions or areas of membrane fusion are identified between two endothelial cells (arrows). The nuclei of two adjacent fibroblasts are shown at (c). Most of the mature collagen fibrils (d) are found a short distance from the canal wall; the cross-sectional diameter of the largest of these fibrils is approximately 600 A. A few collagen fibrils (e) appear within the fine particulate material (f) adjacent to the canal wall. This granular particulate material appears to be the ground substance of the canal wall. It is probably produced by both the fibroblasts and endothelial cells. (× 31,000.)

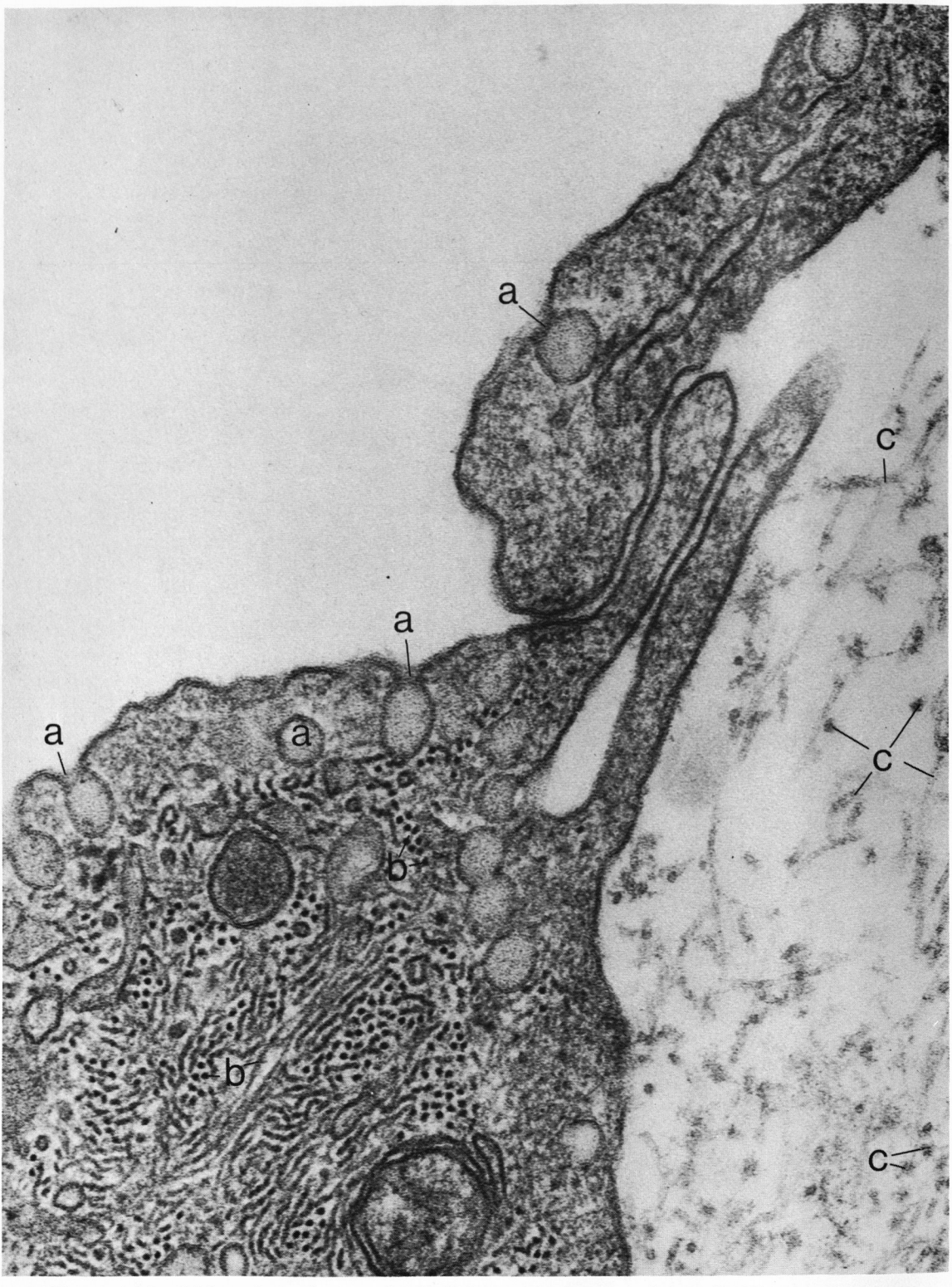

Figure 4-24. Schlemm's canal, internal endothelium at the junction of two cells. There are numerous pincoytotic vesicles (a) which are filled with a finely granular material. These cells contain a large number of cytoplasmic fibrils (b). The intercellular space measures 200 A. except for a small area of contact. Small collagen fibrils (c) measuring approximately 200 A. are seen in longitudinal and cross-section. (× 88,000.)

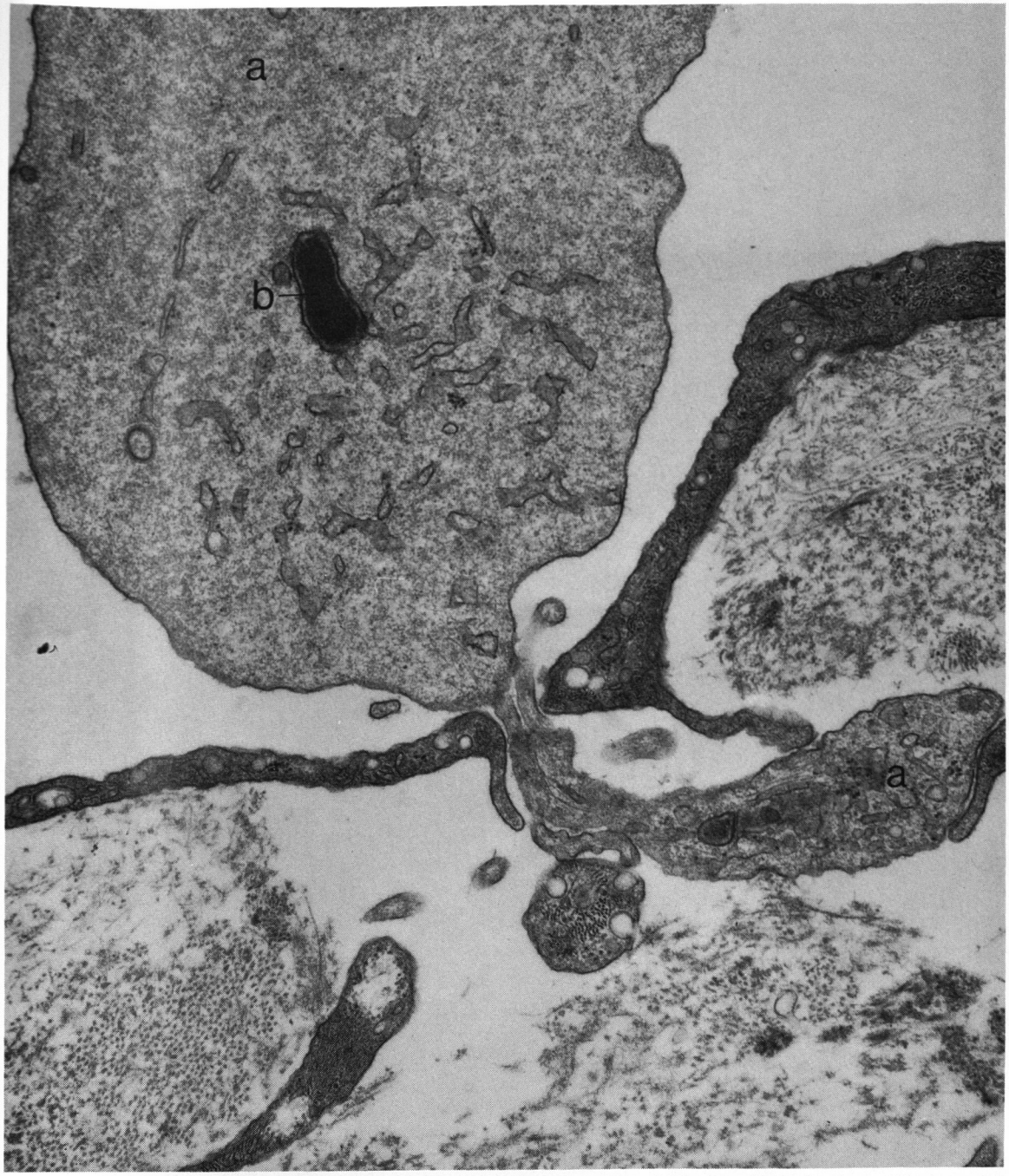

Figure 4-25. Schlemm's canal, inner wall. Red blood cells and other cells are seen occasionally "in transit" between contiguous endothelial cells. A leukocyte (a) containing a bacterium (b) is mostly within the lumen of Schlemm's canal, but a small portion is in the canal wall. (× 32,000.)

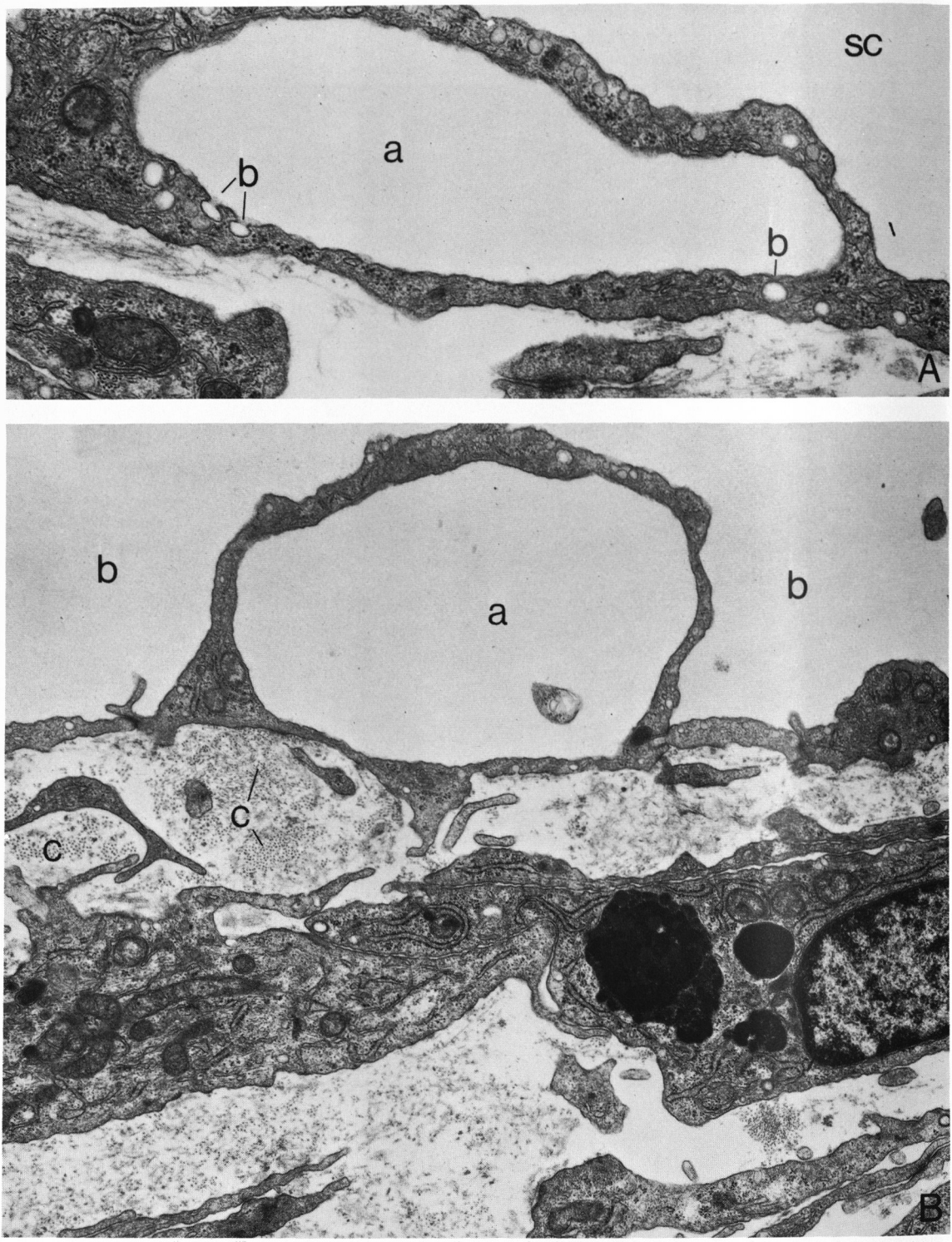

Figure 4-26. *A*, Inner wall of Schlemm's canal (SC) showing a large endothelial vacuole. Large vacuoles are found only in the inner wall of the canal. The giant vacuole (a) or vesicle measures 5 μm. by 1.5 μm; its endothelial lining has several pinocytotic vesicles (b) opening into the lumen. (× 25,000.)

B, Inner wall of Schlemm's canal. A giant vacuole (a) protrudes into the lumen of the canal (b). This vacuole measures 3 by 5 μm. The internal canal wall has a number of fine collagen fibrils (c) measuring around 200 A. in diameter. Some fibroblasts are seen at the bottom of the figure. (× 14,000.)

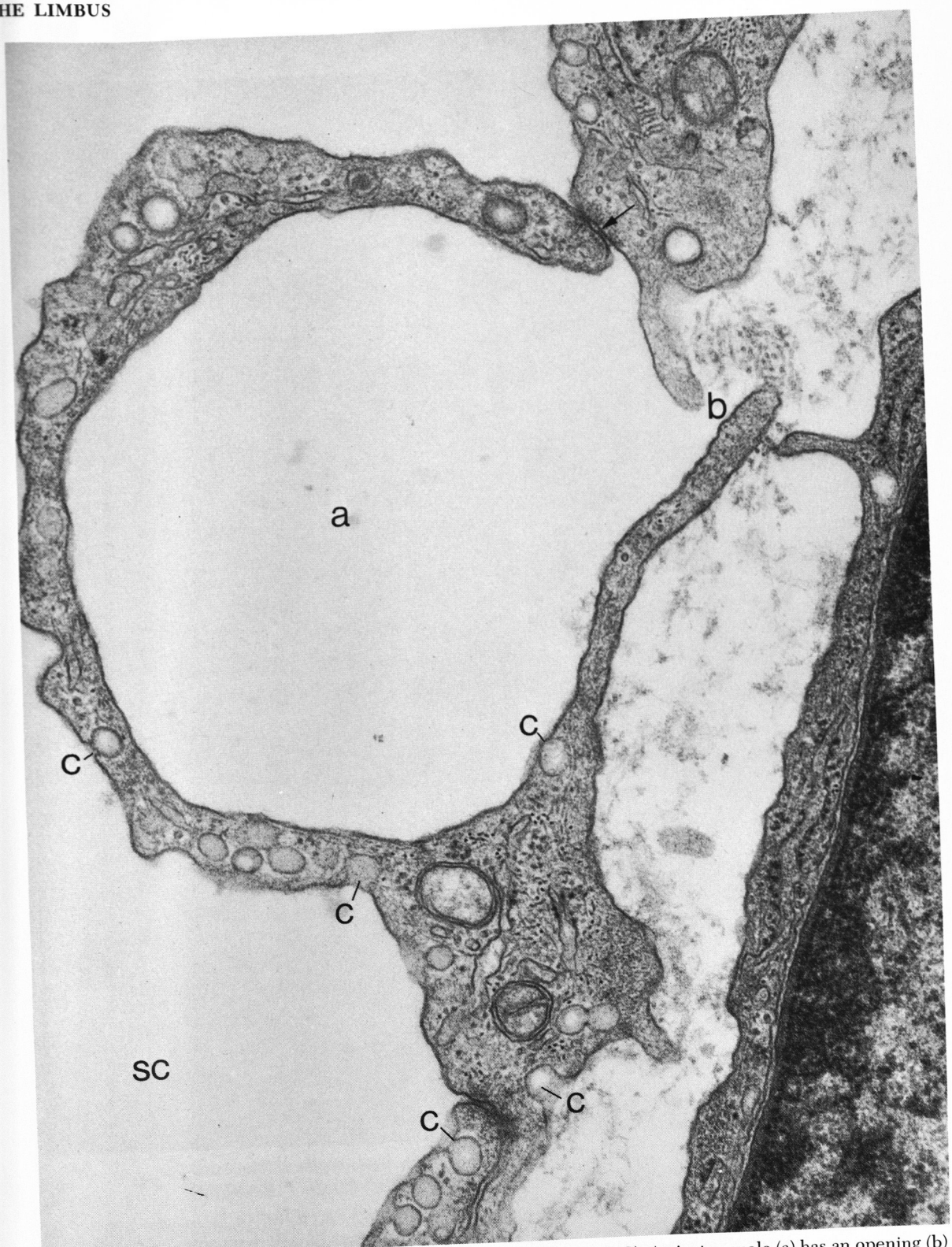

Figure 4–27. Inner wall of Schlemm's canal (SC). A giant vacuole (a) has an opening (b) which provides a clear passageway into the canal wall. Pinocytotic vesicles (c) are abundant. The arrow points to a tight junction between two endothelial cells. Pictures such as this suggest that some "vacuoles" may be formed by large marginal folds. When such large folds appear, however, they rarely extend freely into the canal lumen. (× 46,500)

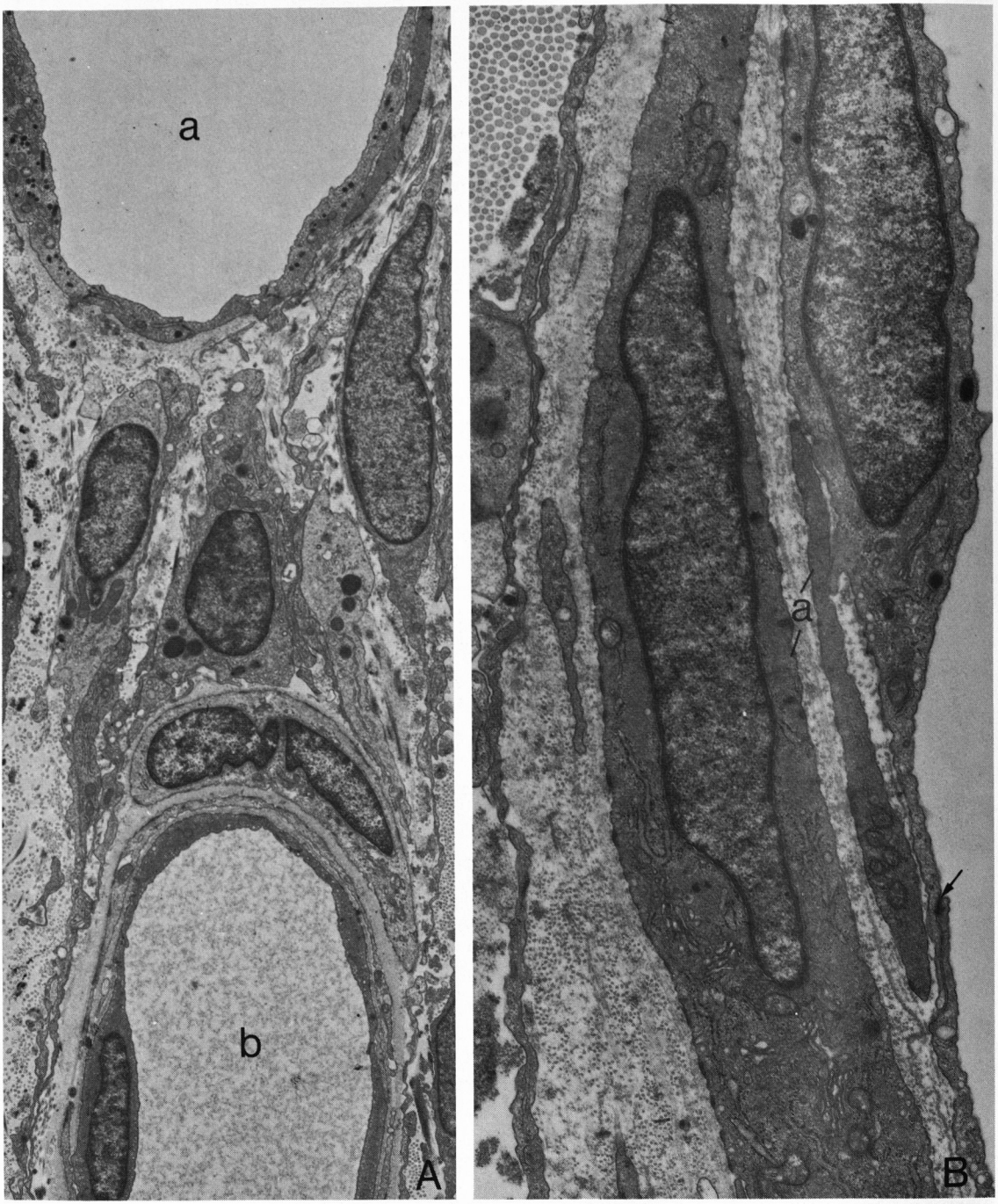

Figure 4-28. External collector channels and the deep scleral venous plexus. The external collector channels may join the deep scleral venous plexus or extend directly to the surface of the eye, where they join the episcleral venous plexus.

A, An aqueous vein (a) can be differentiated from a deep scleral vein (b) by the absence of plasma in its lumen. The wall of the aqueous vein is thinner and less developed. (× 6200.)

B, Higher magnification view of the wall of an aqueous vein. The endothelial cells are like those in other vessels and they are joined to each other by a zonula occludens (arrow). Occasional smooth muscle cells (a) may be seen in the wall of the aqueous vein. (× 13,000.)

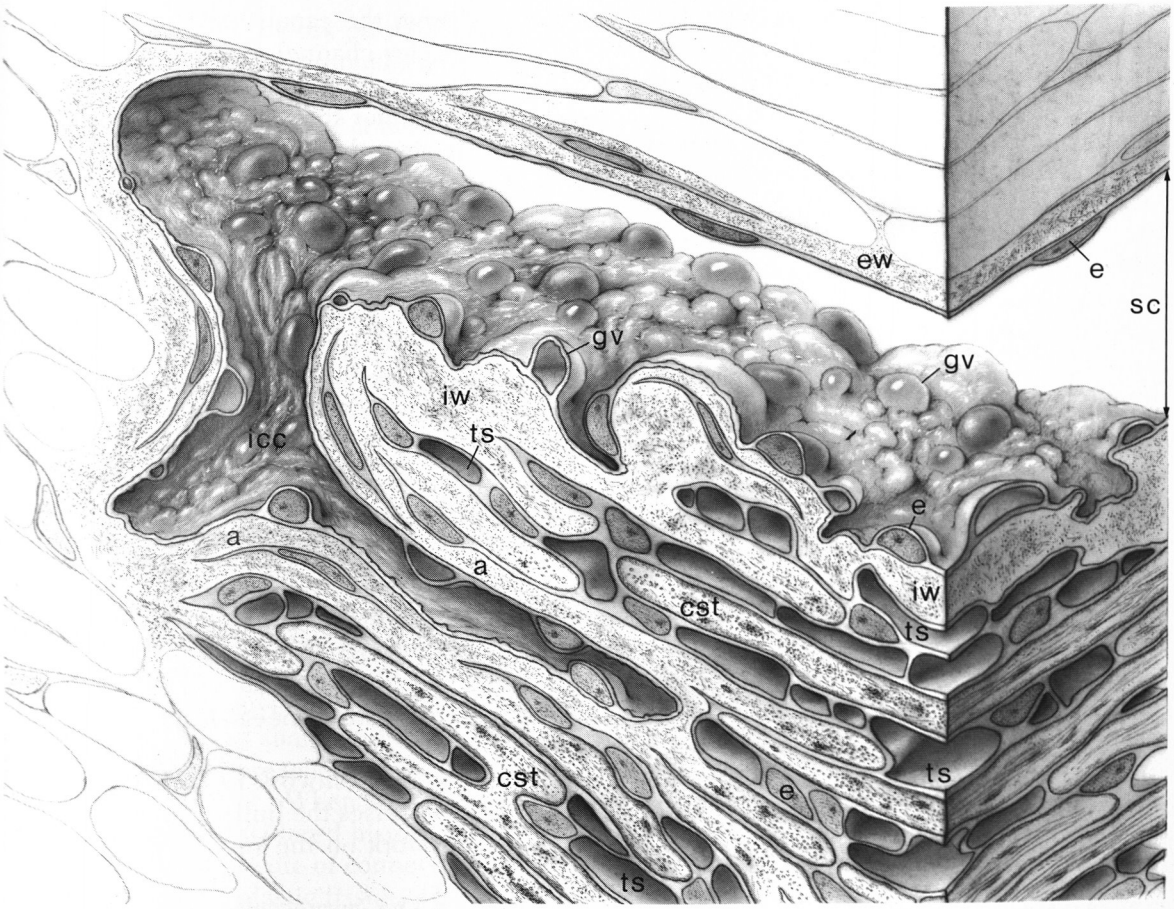

Figure 4–29. Drawing of the canal of Schlemm, an internal collector channel and adjacent tissues. The lumen of the canal (SC) is lined by endothelium (e). The endothelium of the inner wall is quite irregular, with many folds and outpouchings. Giant vacuoles (gv) are seen in the endothelial cells along the inner wall. The external wall of the canal (ew) is shown. The internal wall (iw) lies between the endothelium and the nearest trabecular space (ts). An internal collector channel (icc) arises near the posterior canal wall and extends into the trabecular meshwork, where it is lost. Like Schlemm's canal, it also is surrounded by a wall (a) which separates its lumen from the adjacent trabecular spaces. The corneoscleral trabecular sheets (cst) branch frequently, and their endothelial cells often form bridges between adjacent sheets.

lined channels arising near the posterior part of Schlemm's canal and curving forward into the trabecular meshwork. Some of these channels can be traced for a fairly long distance into the meshwork, but they almost always terminate in the inner trabecular meshwork. They have not been shown to traverse the entire corneoscleral meshwork into the anterior chamber.

Iwamoto (1967a, b) employed light and electron microscopy to study these collectors and did find endothelial-lined channels that opened into Schlemm's canal from the deep intertrabecular spaces in both human adult and infant eyes. He followed some of these channels a considerable distance toward the anterior chamber; he failed, however, to demonstrate that they are uninterrupted channels from Schlemm's canal to the anterior chamber.

We have studied these channels carefully in a number of eyes. The internal collector channels most often commence near the posterior part of Schlemm's canal as right-angle branches which are lined by endothelium

and surrounded by adventitia. Shortly after emerging from the canal they turn to become parallel with it. The width of the collector channel at its opening into Schlemm's canal may be as large as 12 to 15 μm. The diameter diminishes rapidly and soon is the caliber of the intertrabecular spaces. The internal collector channels are tortuous and branch frequently. We have been unable to establish a clear direct connection of the lumen of the collector with an intertrabecular space. We feel that the internal collectors are simply diverticulae of Schlemm's canal that serve to increase the total surface area of the inner wall. They are always surrounded by a wall which separates their endothelium from the nearest trabecular space. Those opposed to the theory of the existence of through-and-through channels from the anterior chamber to the canal of Schlemm argue that the size and number of Sondermann's canals are too great to be consistent with known facts about the bulk flow of aqueous humor.

Trabecular Meshwork (Fig. 4–16).

The trabecular meshwork occupies most of the internal scleral sulcus. It has a somewhat triangular shape, its apex being near the end of Descemet's membrane and its base at the scleral spur. The anterior meshwork contains three to five layers and the posterior meshwork 15 to 20 layers. The larger number of posterior sheets is due to formation of new sheets from the wall of the internal scleral sulcus, and also from branching of pre-existing sheets as they extend posteriorly.

Virchow (1910) was the first to divide the trabecular meshwork into scleral or corneoscleral and uveal portions. The former comprises the bulk of the meshwork, the latter forming only a thin, loose network on the inner surface of the corneoscleral meshwork.

Corneoscleral Meshwork (Figs. 4–30 to 4–37). The corneoscleral meshwork extends from the region of the end of Descemet's membrane and deep cornea to the sclera, scleral spur and ciliary body. Most of the meshwork inserts into the sclera. Two to three sheets of the corneoscleral

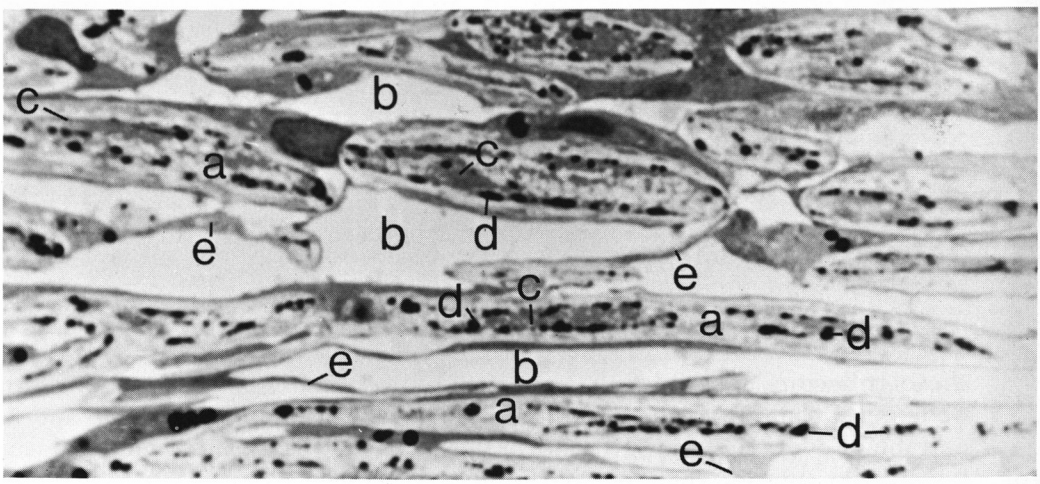

Figure 4–30. Corneoscleral meshwork, light micrograph. The sheets (a) and intertrabecular spaces (b) of the trabecular meshwork form an irregular mesh. The sheets show clumps and strands of pale material (c) and prominent clumps of dense material (d). The corneoscleral trabecular sheets vary in size, thickness and shape. Each sheet is surrounded by a continuous endothelium, and the sheets branch and merge with other sheets, causing the intertrabecular spaces to vary considerably in size and shape. Endothelial cells also branch and cross the intertrabecular spaces (e). (× 688.)