THE DEMONSTRATION OF A BLOOD-OCULAR BARRIER IN THE ALBINO RAT BY MEANS OF THE INTRAVITAM DEPOSITION OF SILVER*

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Plates 130 to 133

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Silver nitrate administered to rats in their drinking water from 6 months to a year or more, results in generalized argyria (1). In the central nervous system, the intravitam deposition of the silver, as revealed by histological and electron microscopical examinations (Wislocki and Leduc, (2); Dempsey and Wislocki, (3)), approximates the pattern of the hematoencephalic barrier.

In the further course of examining silver-treated albino rats, we have noticed that silver accumulates mainly in two regions of the eyes, namely, in the basement membranes of the ciliary processes and in Bruch's basal membrane between the retinal epithelium and the choriocapillary layer of the chorioid membrane. Silver also accumulates in traces, visible only with the electron microscope, in the basement membranes of the retinal capillaries. We regard the deposition of silver in these sites as manifestations of a blood-ocular barrier.

The purpose of this paper is to describe the deposition of silver in the several regions of the blood-ocular barrier of the albino rat, as revealed by histological examination and by the electron microscope. In the discussion, the blood-ocular barrier will be compared with the hematoencephalic barrier.

Materials and Methods

The eyes of 4 male albino rats of the Sprague-Dawley strain, which had received 0.15 per cent silver nitrate in their drinking water for 10 and 13 months and had been maintained on a standard purina chow diet, formed the subjects of this investigation. At autopsy the eyes were excised and cut open in the equatorial plane and the lenses were removed. For histological study the anterior and posterior halves of the eyes were placed in Orth's fixative. The specimens were dehydrated, embedded in paraffin, and 5μ sections were cut. The deparaffinized sections were stained by the periodic acid–Schiff method and some were counterstained with Ehrlich's hematoxylin. Some of the sections were exposed to saliva for 1 hour before staining them, to eliminate glycogen.

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For electron microscopy parts of the retina attached to the chorioid membrane, and the ciliary body were excised and cut into appropriately small pieces with a razor blade. The tissues were immediately fixed for 2 hours in buffered osmic acid (4) or buffered osmic-chromate mixture (5), washed in distilled water for 30 minutes, and dehydrated in 60 per cent and 80 per cent ethanol for 1 hour in each. They were left overnight in two changes of 95 per cent ethanol. The next morning, they were placed in each of the following for 1 hour: absolute alcohol, equal parts of absolute alcohol and *n*-butyl methacrylate, and 2 changes of pure *n*-butyl methacrylate. The tissues were embedded in gelatin capsules containing *n*-butyl methacrylate to which the catalyst 2,4-dichlorobenzoyl peroxide was added, and polymerization was carried out overnight in an oven at 45°.

Ultrathin sections, cut with a glass knife on a Servall microtome, were floated on a 20 per cent acetone solution, picked up on collodion-covered copper grids, and examined in an RCA electron microscope, EMU-2C, without removing the methacrylate.

Electron micrographs of the tissue sections were taken at original magnifications of approximately 1000 to 10,000 times and enlarged photographically as desired.

The eyes of normal albino rats which were not given any silver nitrate were used as controls. Sections of these were prepared and examined by the same means as the eyes of the rats which received silver nitrate.

We wish to express our appreciation to Mr. Arthur J. Mitchell for his invaluable help in preparing the excellent sections for electron microscopy.

RESULTS

Histological Observations.—The intravitam deposition of silver in the rat's eye, as observed with the light microscope, is confined to the ciliary processes and the choriocapillary layer and basal membrane of the chorioid. The longer silver nitrate is administered, the more heavily it accumulates. Its appearance in the ciliary processes in the light microscope is illustrated in Figs. 1 and 2. It is located primarily interstitially in a basement membrane upon which the ciliary epithelium rests. Some is also present in the cytoplasm of macrophages which are fairly abundant around the larger vessels in the stroma of the ciliary processes. None has been seen in the ciliary epithelial cells.

In the entire extent of the choriocapillary layer of the chorioid underlying the retina, silver is deposited heavily in Bruch's basal membrane between the choriocapillaris and the retinal epithelium and in the walls of the capillaries themselves, as illustrated in Figs. 3 to 6. With the light microscope, silver does not appear to be present in the retinal epithelium or in the photoreceptor cells. Silver is not detected in the walls of the retinal blood vessels which supply the inner layers of the retina.

In the choriocapillary layer silver is deposited heavily in the lamina basalis (Bruch's membrane) which appears as a dense black line (Figs. 4 and 5). It is also deposited in the basement membranes surrounding the capillary net of the choriocapillaris, accumulating especially on the sides of the capillaries which face the lamina basalis. None is visible in the outer layers of the chorioid. The visible deposition of silver ceases at the ora serrata, none being apparent in the orbicular ring, the broad posterior zone of the ciliary body between the ciliary processes and the retina.

Electron Microscopy.—In the ciliary body, observed with the electron microscope, the epithelium of the ciliary processes rests upon well vascularized stroma. The outer portion of the stroma abutting the ciliary epithelium consists of a broad homogeneous basement membrane bounded on one side by the basal plasma membranes of the epithelial cells and on the opposite side by the loose textured, collagenous connective tissue enclosing the blood vessels. In this broad basement membrane silver has been deposited in a great number of small masses or granules of uneven size. The silver granules are located mainly in the middle of the membrane (Figs. 6, 7, and 8), whereas the inner zone contiguous to the ciliary epithelium is free of silver particles (Fig. 8). Sheets of the basement membrane, heavily laden with silver, extend inward between the sides of neighboring epithelial cells (Figs. 7 and 8) for a distance of about a quarter of the height of the cells. Silver granules are also occasionally present in the loose collagenous tissue surrounding the blood vessels. Here, also especially in the stroma around larger blood vessels, macrophages are encountered with their cytoplasm densely filled with silver (not illustrated). The endothelial cells lining the blood vessels do not contain silver.

The ciliary epithelial cells appear to be devoid of silver but they show several noteworthy cytological features with the electron microscope. The plasma membrane at the base of each cell is elaborately infolded (Figs. 6, 7, and 8). The folds enclose narrow clefts which are bounded by an osmiophilic plasma membrane. The clefts contain a substance which is continuous at the bases and sides of the cells with the broad basement membrane upon which the epithelium rests (Figs. 7 and 8). Despite this continuity, silver particles do not become deposited in the clefts between the infolded plasma membranes (Figs. 7 and 8). In the extreme depth of some of the clefts, bits of the infolded plasma membranes appear to become pinched off and to give rise to small vesicles, or profiles within the cytoplasm of the basal parts of the cells (Fig. 8, arrow). In the cell cytoplasm distal to the basal infoldings, numerous large mitochondria are present.

Granular masses of silver are also visible in great abundance with the electron microscope in Bruch's basal membrane and the choriocapillary layer of the chorioid. The masses are most conspicuous and heavy in Bruch's basal membrane (Figs. 9 and 13). Silver is also somewhat less abundantly present in the collagenous stroma and basement membranes surrounding the capillary net of the choriocapillaris (Fig. 9). It is more heavily deposited in the perivascular basement membrane and stroma facing Bruch's membrane than on the side of the capillaries facing the supracapillary layer. Here also, as in the ciliary body, the endothelium of the capillaries does not contain any silver. The heavy, uneven-sized masses of silver occur throughout the entire thickness of Bruch's basal membrane (Figs. 9 and 13), differing in this respect from the basement membrane of the ciliary processes in which silver is not deposited in the portion of the membrane contiguous to the epithelium (Fig. 8). In

Bruch's membrane, granular masses of silver are directly in contact with the basal plasma membranes of the retinal epithelial cells.

The plasma membrane of the basal surfaces of the retinal epithelium is infolded (Figs. 9 and 13), although to a lesser degree than the basal plasma membranes of the ciliary epithelial cells. Very occasionally a granule of silver is observed in the base of one of the clefts (Fig. 9, arrows), but none are encountered deeper in. The epithelial cells contain very large, oval, elongated mitochondria located mainly in the basal halves of the cells. Quite occasionally, one of the mitochondria appears to contain some silver in its interior (Fig. 10). In addition to mitochondria, the cytoplasm contains numerous clear vesicles with beaded contours which resemble ergastoplasm (Fig. 9 *E*). In the apical region of the cells there are numerous, larger spherical or ovoid objects containing rather evenly dispersed, stippled, osmiophilic material (Fig. 12). The contours of these objects are smooth but a definite membrane enclosing them is not distinguishable. A few of them appear to contain dense, irregular, eccentrically placed masses which resemble silver (Fig. 9). The possibility that these masses are silver should be dismissed, however, because similar electron-dense bodies are encountered in the apices of retinal epithelial cells of normal rats. What these electron dense inclusions or material actually represent has not been further investigated. The apical cytoplasm of the epithelial cells also contains osmiophilic, stellate masses which are interpreted as representing lipide droplets (Fig. 9, *F*). The surface cytoplasm forms a complex series of slender, branched, cytoplasmic protuberances with electron-dense contours. These surround the distal, strongly osmiophilic rod outer segments and appear as though they were fairly firmly attached to the surfaces of the rods (Fig. 12).

Silver is not apparent in the photoreceptor and other neural elements of the retina. Extremely minute granules of silver are sparsely scattered in an osmiophilic, and presumably proteinaceous, ground-substance which occupies a narrow perivascular space, equivalent to Virchow-Robin's space surrounding the capillaries of the inner retinal layers (Fig. 11, arrows). Contrary to the large amounts of silver in Bruch's membrane and the ciliary processes observed with both the daylight and electron microscopes, these minute granules are only barely perceptible with the electron microscope.

DISCUSSION

The epithelium covering the ciliary processes is generally believed to give rise to the aqueous humor (Walls, (6)) and the processes have been equated on both morphological and physiological grounds with the chorioid plexuses of the cerebral ventricles (Wegefarth and Weed, (7)). The chorioid plexuses are regarded as forming the blood-cerebrospinal fluid barrier which normally restrains vital dyes, foreign particulate substances, and various metabolites from

entering the cerebrospinal fluid (*cf.* Schaltenbrandt, (8)). The ciliary processes have been assigned a similar role with respect to the restraint of passage of substances into the aqueous humor (Wegefarth and Weed, (7)). The observed deposition of intravitally administered silver in the stroma of the ciliary processes and in the basement membrane of the ciliary epithelium is quite analogous to the accumulation of intravitally administered silver seen in the chorioid plexuses (Wislocki and Leduc, (2); Dempsey and Wislocki, (3); van Breemen and Clemente, (9)).

The accumulation of silver in the ciliary processes and in Bruch's basal membrane can be most readily demonstrated in the eyes of albino animals, such as the white rat. This probably accounts for the fact that in the pigmented human eye the deposition of silver has not been recorded in generalized argyria (*cf.* Hill and Pillsbury, (10)). The accumulation of a vital dye, pyrrhol blue, has been reported within macrophages which are abundant in the ciliary processes of albino rabbits (Schnaudigel, (11)), a result which one of the present investigators confirmed at one time using trypan blue. Macrophages are not abundant enough in the stroma of the choriocapillary layer of the eye to resemble the storage of vital dyes by macrophages in the ciliary processes. Neither the ciliary nor retinal epithelia store vital dyes, differing in this respect from the epithelial cells of the chorioid plexuses which become heavily laden with trypan blue (*cf.* Wislocki and Leduc, (2)).

The heavy deposit of silver in Bruch's membrane and in the walls of the choriocapillary net bespeaks, in our estimation, the presence there of an important blood-ocular barrier which protects the retina and screens the photoreceptor elements from exposure to various substances. The capillaries of the chorioid coat are believed to be the principal source of nourishment of the vertebrate retina (Walls, (6)). The deposition of silver preponderates in Bruch's membrane, although some metal is also present in the stroma and basement membranes around the flattened capillaries. Silver granules are more numerous in the capillary basement membranes facing Bruch's membrane than in the outer surfaces of the capillary net facing the supracapillary layer of the chorioid coat. This difference in the amount of silver deposited on the inner and outer sides of the flattened capillary net, suggests that there is a greater transfer of silver towards Bruch's membrane and the retina than outward into the chorioid membrane. These differences in the amounts of deposited silver are consonant with the assumption that transfer is oriented mainly from the capillary layer of the chorioid coat towards the adjacent retinal epithelium.

Compared to the brain, the nearest analogy of the choriocapillary-retinal barrier would appear to be the chorioid plexuses. The single-layered retinal epithelium which faces the cavity of the embryonic optic vesicles rests upon richly vascularized mesenchyma, namely the choriocapillaris. These relation-

ships are practically identical with those of the chorioid plexuses, where the single-layered ependyma lining parts of the embryonic ventricles differentiates into the chorioidal epithelium, which becomes associated with richly vascularized periaxial mesenchymal tissue. Thus it would appear justifiable to consider these ocular structures as representing a blood-retinal barrier similar in structure to the chorioid plexus barrier.

The presence of silver in a few mitochondria of the retinal epithelium is comparable to silver encountered by Dempsey and Wislocki (3) in occasional mitochondria in the chorioidal epithelium of the brain. We attribute the accumulation of silver in mitochondria to a leakage of the barrier upon long administration of the metal. A similar and more abundant overflow of silver into the parenchymal cells has been observed in the liver, kidney, and pancreas (Dempsey and Wislocki, (12)).

Walls assigns a subsidiary or supplemental nutritive role to the retinal capillaries of the central artery of the vertebrate eye which variously vascularize the inner retinal layers. These vessels, as is visible with the electron microscope but not in ordinary histological preparations, contain small amounts of silver in an osmiophilic substance of moderate electron density which occupies a narrow, but well defined perivascular space (Fig. 11, arrows). In this respect they correspond to the capillaries of the brain in general, which, in rats that have received silver for as long as a year, also store very fine particles which are visible solely with the electron microscope and are located in an interstitial substance or basement membrane which occupies Virchow-Robin's pericapillary space. Although minute in both cases, the particles of silver in the perivascular substance of the cerebral capillaries are somewhat larger and more numerous than those in the perivascular space of the retinal capillaries.

The present observations on the perivascular structures of the retinal and cerebral capillaries are novel. They dispose not so much of Virchow-Robin's perivascular spaces as they indicate that these spaces are filled, not with interstitial or intercellular fluid as is generally supposed (*cf.* Tschirgi, (13)), but with an osmiophilic, presumably proteinaceous, ground-substance. The observations also indicate that the blood-brain and blood-retinal barriers, in so far as the transfer of silver by the cerebral and retinal capillaries is concerned, are not located in the capillary endothelium or in the "glial" membrane, but in the ground-substance filling the Virchow-Robin spaces. Contrary to accepted belief, the behavior of the silver illustrates, as Wislocki and Leduc (2) have pointed out, that the hematoencephalic barrier is composed of a succession of thresholds, different levels of which variously inhibit the passage of different substances.

From the study of trypan blue administered either intravenously or into the aqueous humor, Palm (14) observed that the retina is not stained after the first procedure, but that it is penetrated by the dye after the latter pro-

cedure. These phenomena, which are analogous to the behavior of vital dyes with respect to the brain, led him to conclude that there is a barrier in the retinal blood vessels similar in nature to the blood-brain barrier in the cerebral capillaries. These differences in retinal staining, dependent on the way in which the trypan blue is administered, are clarified by observations of Tschirgi (13) upon vital staining of the brain. The latter observed that if trypan blue is dissolved in saline solution and then injected intrathecally, the dye readily penetrates the brain, but, if it is first dissolved in blood plasma in which it conjugates with protein, and then injected, it will no longer penetrate the brain.

The present observations, based on the intravitam deposition of silver, suggest the presence of a blood-ocular barrier divisible into three parts: (*a*) a blood-aqueous humor barrier located in the basement membrane of the ciliary processes, which is related to the formation of the aqueous humor; (*b*) a blood-retinal barrier located in Bruch's membrane and the choriocapillary layer, which is related to the functional activity of the retinal photoreceptor elements; and (*c*) a blood-retinal barrier located in the ground-substance surrounding the retinal capillaries, which is related to the activities of the inner retinal layers (the ganglion cells and the bipolar neurons). It is not our intention to speculate as to why the blood-retinal barriers in the ciliary body and Bruch's membrane accumulate large amounts of silver and the barrier surrounding the retinal capillaries stores relatively little in the same period of time. It must suffice at present to point out merely that a parallelism with the brain exists with respect to these phenomena. Thus the first two retinal barriers, in which there is a dense accumulation of silver, are analogous to the blood-cerebrospinal fluid barrier of the chorioid plexuses of the brain, whereas the third barrier, located in the retinal capillaries, appears to be equivalent to the blood-brain barrier of the general cerebral vascular bed.

Another point, namely the way in which the silver reaches its destinations in the brain and the form in which it is deposited there, will be dealt with briefly. In a previous paper, Wislocki and Leduc (2) suggested that the silver nitrate given by mouth was probably carried in the blood stream, conjugated with a protein, possibly albumin, as has been postulated for the transport of trypan blue. Dempsey and Wislocki (3, 12) have pointed out that the silver, which is probably transported in the blood in a protein complex, is probably reduced in a variety of basement membranes by a carbohydrate possessed of adequate reducing activity. Moreover, since the silver obeys the principle of the hematoencephalic barrier, it is probably conveyed as a proteinate carrying a negative charge. Nevertheless, whether the dense granules represent reduced metallic silver or a silver complex cannot be positively stated. To the present writers, it seems possible that the silver which, unlike trypan blue, carries a positive charge, may be conjugated with globulin rather than albu-

min. Also, unlike thorium and protargol which are metallic proteinates representing neutral foreign bodies which are phagocytized by the reticuloendothelial system, the silver proteinate is probably an unstable compound which is readily dissociated and reduced. In any event, the terms "silver granules" or "particles" are used in the present paper in the sense that they indicate the presence of silver without any categorical decision as to its physical or chemical state.

Still another point of interest concerns the infoldings of the basal cytoplasm of the ciliary epithelial cells and the retinal epithelium. It would be tempting to postulate that these infoldings facilitated the elaboration of the aqueous humor and the transfer of fluid and nutrient substances to the photoreceptor elements of the retina. However, in the chorioid plexuses of the brain, which are believed to be analogous to the ciliary processes in that they are thought to secrete the ventricular fluid, no such infoldings of the basal plasma membranes are apparent (unpublished observations). Thus, in two types of cells which are believed to possess essentially similar functions, one kind possesses infoldings and the other one none.

SUMMARY

When silver nitrate is administered to rats in their drinking water for many months, they develop a generalized argyria. In the central nervous system, the deposition of silver follows the pattern of the so called hematoencephalic barrier (Wislocki and Leduc, (2); Dempsey and Wislocki, (3)). The present observations concern the deposition of silver in the rat's eye, investigated by both light microscopy and the electron microscope. In the eye, silver is not detected in the specific neural elements of the retina. Instead, it is heavily deposited in the basement membrane of the epithelium of the ciliary processes and in Bruch's basal membrane between the choriocapillary layer and the retinal epithelium. Traces of silver are visible in the basement membranes of the retinal capillaries with the electron microscope, but cannot be identified with the light microscope. In all of these respects, the pattern of the silver resembles the mode of its deposition in the brain. The heavy accumulation of metal in Bruch's membrane and the ciliary processes is analogous to that observed in the chorioid plexuses, and the traces encountered in the walls of the retinal capillaries correspond to traces observed in the basement membranes of the cerebral capillaries. Hence, with respect to silver, the eye possesses a blood-ocular barrier similar to the hematoencephalic barrier. Silver appears to be restrained from entering the aqueous humor by a barrier in the basement membrane of the ciliary processes, from reaching the photoreceptor elements of the retina by Bruch's basal membrane, and from penetrating the inner layers of the retina by a barrier in the basement membrane surrounding the retinal capillaries.

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EXPLANATION OF PLATES

PLATE 130

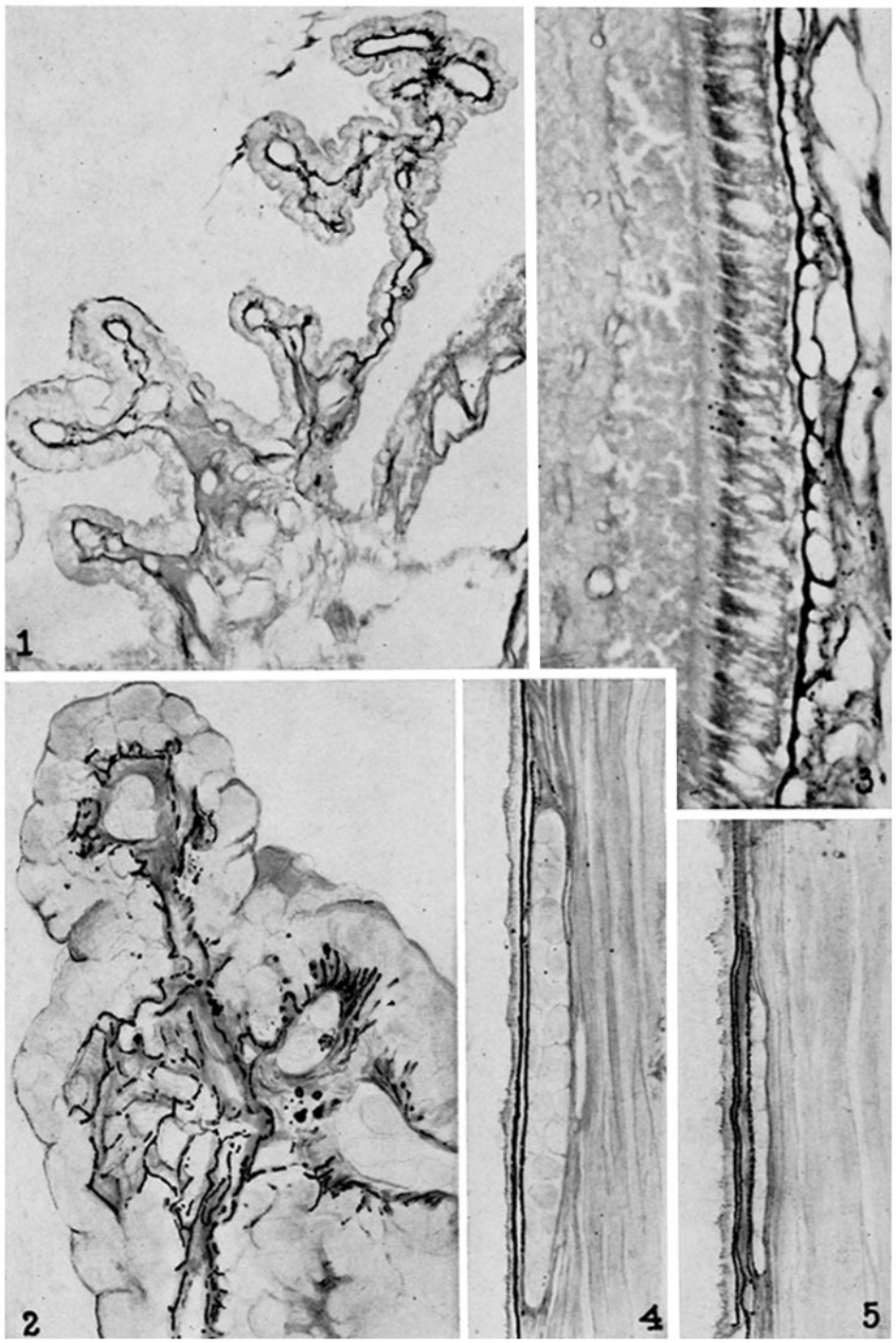
All of the tissues illustrated in this plate were fixed in Orth's fluid and stained by the periodic acid–Schiff method.

FIG. 1. The ciliary body of an albino rat, illustrating the deposition of silver in the stroma of the ciliary processes, following administration of silver nitrate to the animal in its drinking water for 13 months. × 230.

FIG. 2. A drawing of a single ciliary process at higher magnification. × 450.

FIG. 3. The retina of an albino rat, illustrating the deposition of silver in the choriocapillaris and Bruch's membrane following administration of silver nitrate for 13 months. × 375.

FIGS. 4 and 5. Drawings of portions of the choriocapillaris and Bruch's membrane illustrating the relationship of the deposited silver to the blood vessels. × 450.



(Wislocki and Ladman: Demonstration of blood-ocular barrier)

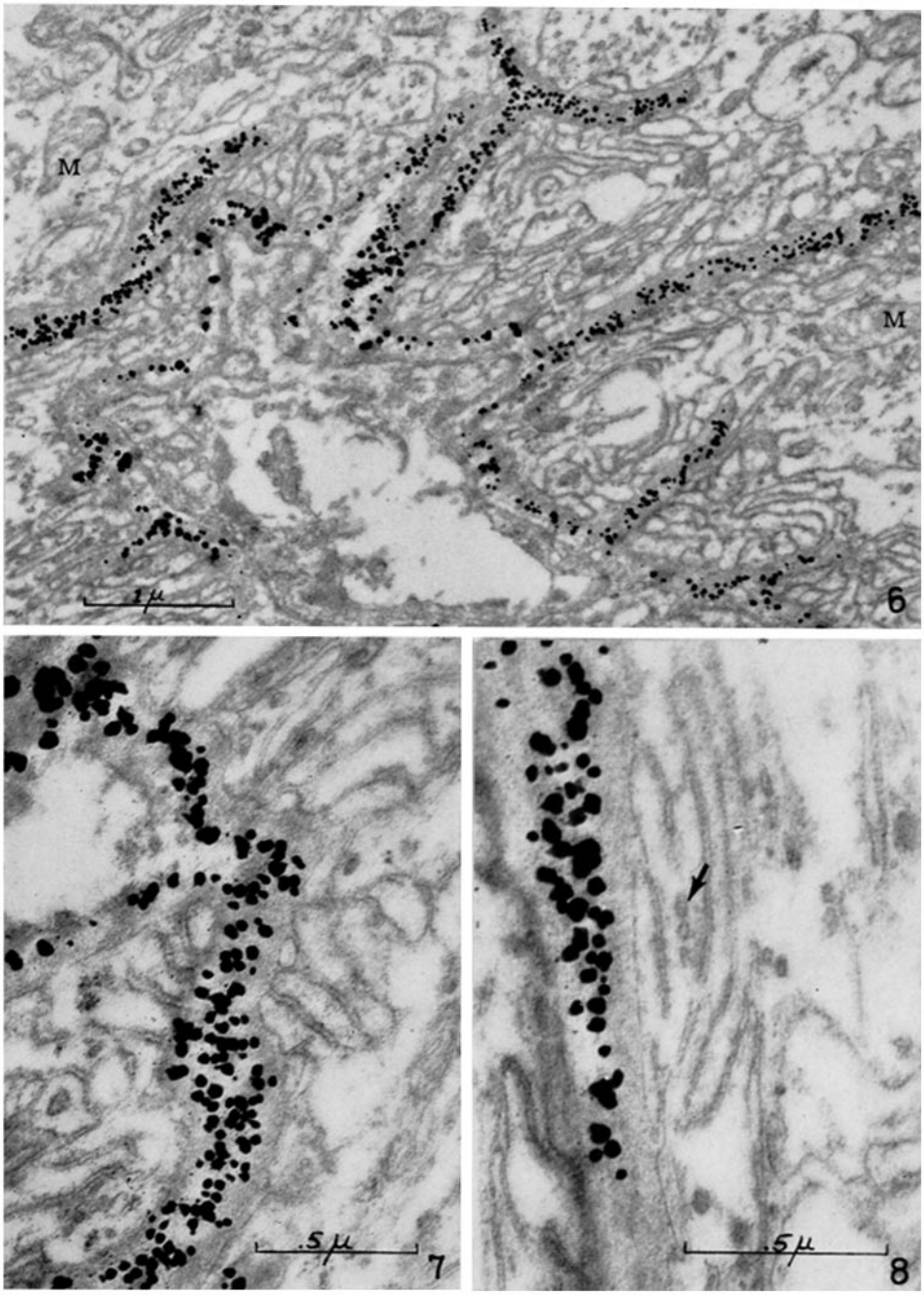
PLATE 131

The tissues illustrated in this plate were fixed in buffered osmium-chromate mixture (5).

FIG. 6. Electron micrograph of a typical bit of a ciliary process showing the basement membrane, laden with silver, situated beneath and among several ciliary epithelial cells. Observe the complex infoldings of the plasma membranes in the bases and sides of the cells. Compare with Fig. 2. *M*: mitochondria. × 20,350.

FIG. 7. A detail of the basement membranes between two ciliary epithelial cells, illustrating the infoldings of the plasma membranes and their relations to the basement membrane. × 44,200.

FIG. 8. Another detail of the basement membrane between two cells, illustrating the seeming pinching-off of small vesicles from the depths of folds (arrow) and a silver-free inner zone of the basement membrane contiguous to the ciliary epithelium. × 55,525.



(Wislocki and Ladman: Demonstration of blood-ocular barrier)

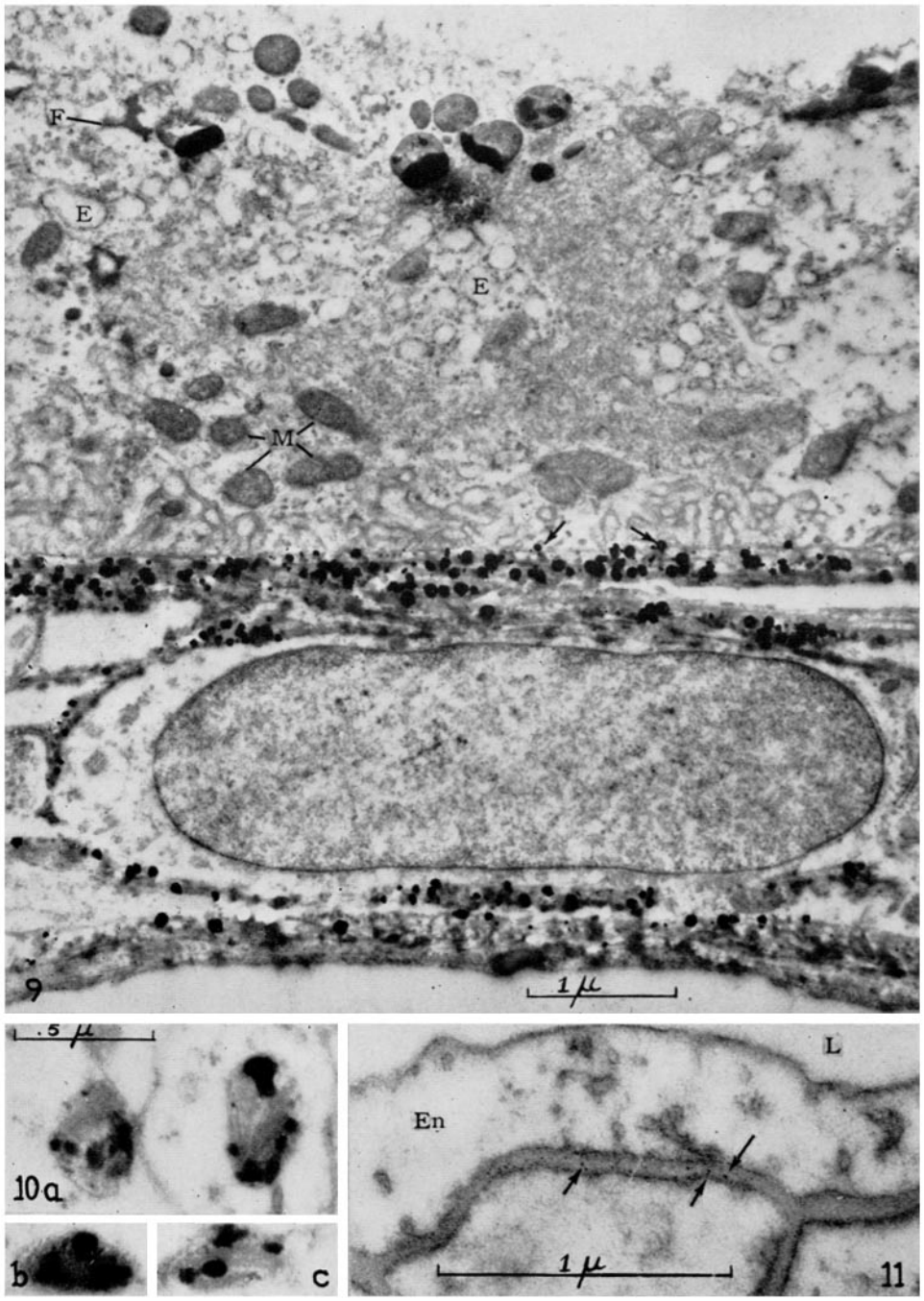
PLATE 132

The tissues illustrated in this plate were fixed in buffered osmic acid (4).

FIG. 9. The cytoplasm of a retinal epithelial cell is visible, resting upon Bruch's membrane which is heavily laden with granules of silver. Beneath Bruch's membrane is the silver-laden stroma of the choriocapillary layer, containing a fibroblast with a large ovoid nucleus surrounded by cytoplasm. The retinal epithelial cell reveals small basal infoldings of its plasma membrane with an occasional granule of silver in the lumen of one of the infoldings (arrows); large, dark mitochondria (*M*) in its basal cytoplasm; clear, beaded vesicles interpreted as ergastoplasm (*E*) in the central region, and spherical, osmiophilic bodies in its distal cytoplasm. Note the presence of a lipide droplet (*F*). Compare this cell with the basal and distal ends of other epithelial cells shown at a higher enlargement in Figs. 12 and 13. For further details and discussion of the micrograph, consult the text. × 20,650.

FIG. 10. *a*, *b*, and *c*. Examples of occasional mitochondria which contain silver, encountered in the retinal epithelium. × 38,400.

FIG. 11. Much enlarged portion of a bit of the wall of a retinal capillary to illustrate the basement membrane containing particles of silver which are barely perceptible (arrows). *En:* endothelial cell. *L:* lumen of capillary. × 40,150.



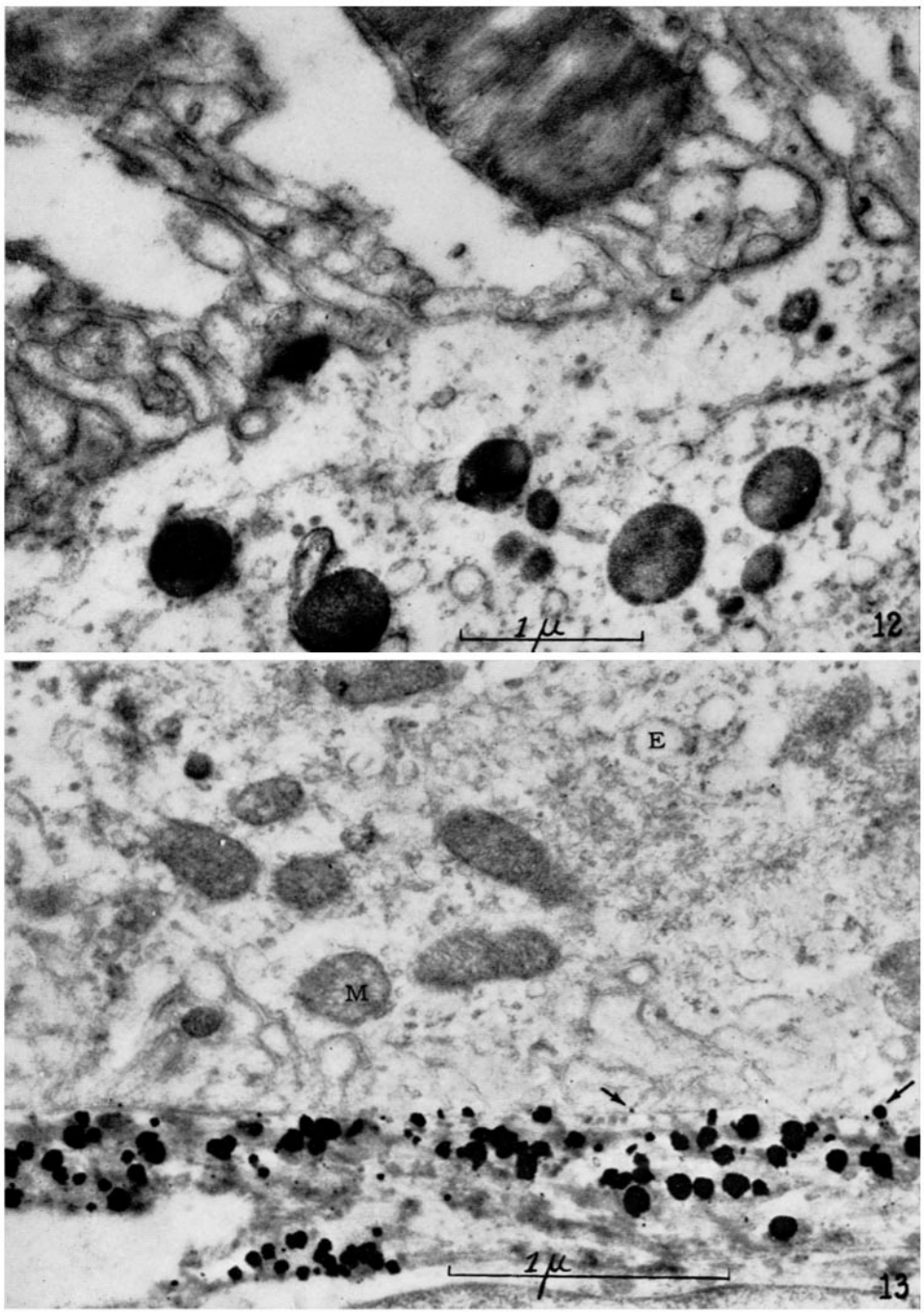
(Wislocki and Ladman: Demonstration of blood-ocular barrier)

PLATE 133

The tissues illustrated in this plate were fixed in buffered osmic acid (4).

FIG. 12. The distal surface of an epithelial cell sends out processes which appear to surround the ends of the rod outer segments, one of which is visible at the top of the photograph. The distal cytoplasm of the epithelial cell contains a number of strongly osmiophilic spherical bodies. × 24,875.

FIG. 13. The basal portion of an epithelial cell rests upon Bruch's membrane which is laden with silver granules. The plasma membrane is somewhat infolded into the basal cytoplasm. The arrows indicate where two silver granules, one large and one small, appear to be located in the interstitial clefts at the entrances of such infoldings. A number of sizable mitochondria (*M*) and several vesicles with somewhat beaded contours interpreted as ergastoplasm (*E*) are visible in the cell cytoplasm. × 38,550.



(Wislocki and Ladman: Demonstration of blood-ocular barrier)