

# AN ELECTRON MICROSCOPIC STUDY OF THE PASSAGE OF COLLOIDAL PARTICLES FROM THE BLOOD VESSELS OF THE CILIARY PROCESSES AND CHOROID PLEXUS OF THE RABBIT

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## ABSTRACT

The thinnest areas of the capillaries of the choroid plexus and ciliary processes in the eye of the rabbit are characterized by the presence of fenestrae. When various colloidal particles opaque to the electron beam (thorotrast, gold sol, and saccharated iron oxide) were injected into the blood stream, none were found in fenestrae or in areas that might suggest their having passed through fenestrae. The passage of marker particles from the lumen to the surrounding connective tissue does take place on occasion in the areas of thicker walls in the capillaries and venules rather than in the attenuated and fenestrated endothelial walls. The pathway taken by these markers may be either through the cytoplasm of the endothelial cells *via* membrane-bounded vesicles and vacuoles or through the intercellular spaces of the vessels. An altered aqueous humor (cloudy and plasmoid) was produced by endotoxin injection or by making a draining fistula in rabbit cornea. Both methods gave rise to the same changes in the blood vessels of the ciliary processes. Under such conditions of inflammation the passage of colloidal particles through the thicker walls of the capillaries and venules was greatly increased and occurred primarily as an intercellular passage between the endothelial cells. The attenuated and fenestrated areas of the endothelium of the small capillaries remained unchanged with no particles passing through them. These results on the altered vessels of the ciliary processes parallel those of Majno and Palade (26) on the rat cremaster muscle.

## INTRODUCTION

In certain areas known for fluid transport, such as the renal tubule (1), intestinal villi (2, 3), ciliary body of the eye (4) and the choroid plexus (5, 6), the capillaries tend to have a similar appearance. They possess a very attenuated endothelium with fenestrae ranging in diameter from 300 to 500 Å.

The renal glomerular endothelium conforms to this general pattern, although the pores are larger, more numerous and are regularly arranged. The

transendothelial passage of opaque markers to the basement membrane of the kidney glomerulus *via* these fenestrae or pores has been described (7, 8).

Both the ciliary processes of the eye and the choroid plexus are normally engaged in secretion, the ciliary processes in aqueous humor formation and the choroid plexus in the formation of cerebrospinal fluid (9). The fine structure of the capillaries of the ciliary processes and choroid

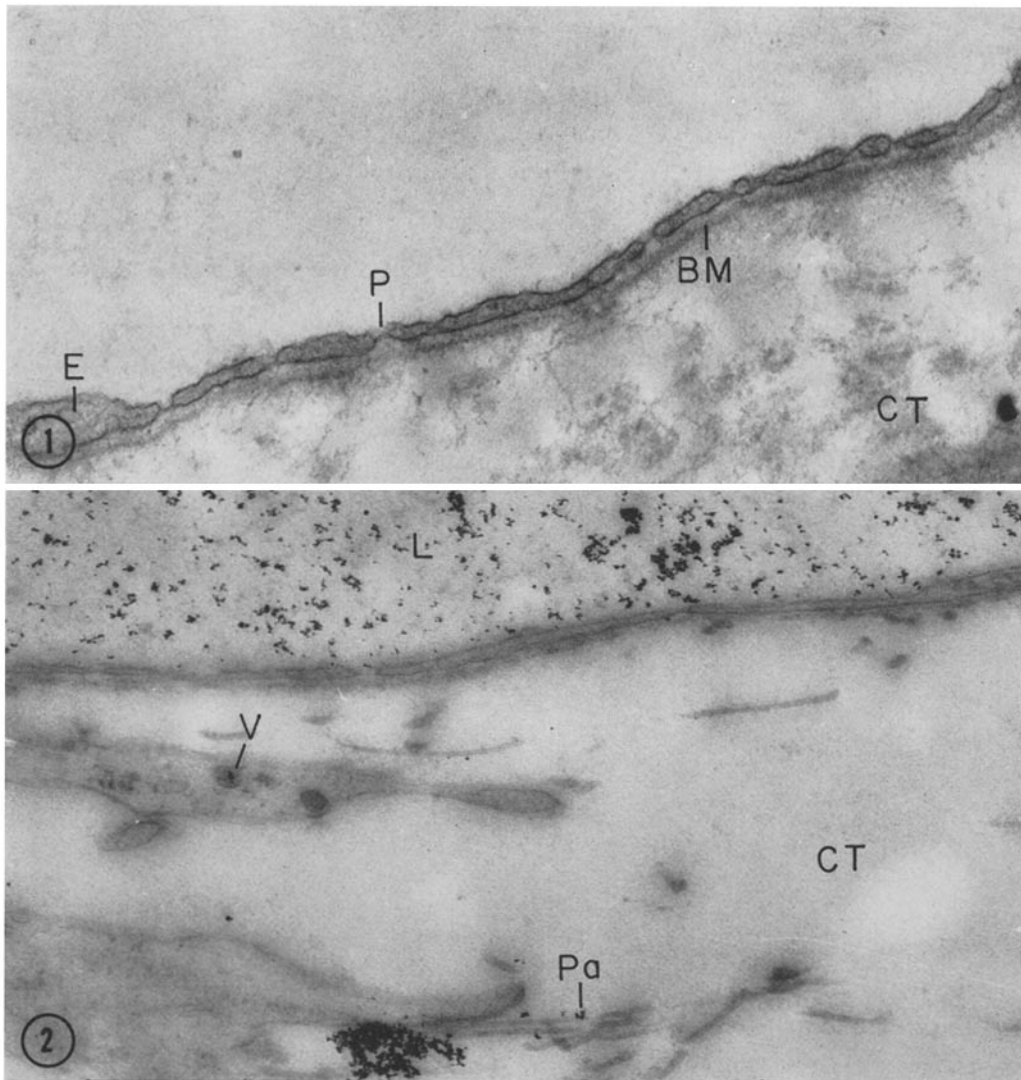


FIGURE 1

Electron micrograph of a portion of a capillary in the ciliary processes of an adult albino rabbit. The endothelial cell (*E*) is about 300 Å thick at the most attenuated area. Fenestrations or pores (*P*), about 400 Å wide, are irregularly scattered along the attenuated endothelium. The pore space is traversed by a diaphragm which is less dense and thinner than the endothelial cell membrane. The basement membrane (*BM*) is continuous and has a more condensed fibrous structure about 250 Å from the surface of the endothelial cell facing the connective tissue (*CT*). × 35,000.

FIGURE 2

Electron micrograph of a thin walled portion of a capillary of the ciliary body. Thorotrast was injected intravenously 30 minutes before the tissue was fixed. Particles (*Pa*) of  $\text{ThO}_2$  have left the blood and have entered the connective tissue (*CT*). A small portion of a connective tissue cell in this section contains vacuoles (*V*) containing  $\text{ThO}_2$  particles. Marker particles are found in great abundance in the lumen (*L*) of the capillary. However, few if any particles have been found in transit through these fenestrated and very thin areas of endothelium. Marker particles have been found apparently passing through thick walled blood vessels (see Figs. 4 to 6). × 42,000.

plexus has been described previously (4, 10, 5, 6). In contrast to the situation described in the renal glomeruli, the endothelial fenestrae of these capillaries are less numerous, are smaller (300 Å) and are irregularly disposed along the attenuated endothelial cell wall. In order to determine the effect of the thickness of the endothelium and the patency of these capillary fenestrae on transport activity, various colloidal particles opaque to the electron beam (thorotrast, gold sol, and saccharated iron oxide) were injected into the blood stream and subsequently were observed in the electron microscope.

When normal aqueous humor secretion is altered so that the "blood-aqueous barrier" is no longer maintained, a cloudy and plasmoid aqueous results. In this study such an altered aqueous humor was brought about by endotoxin injection (11) or by making a draining fistula in the cornea of rabbits (4, 12). In order to determine the changes from the normal pathway in vascular transport of colloidal particles, the blood vessels of the ciliary processes of these animals were studied.

#### MATERIALS AND METHODS

Tissue was taken from immature and adult rabbits, of Dutch and albino strains. Colloidal particles were injected into an ear vein 20 minutes to 2 hours before the ciliary processes and choroid plexus were fixed. In the newborn rabbits, the injection was given intracardially. Thorotrast (Testagar & Co., Detroit, Michigan), a suspension of 25 per cent ThO<sub>2</sub> stabilized with dextran, was used in a concentration of 1 ml per 250 gm body weight. A 40 per cent concentration of saccharated iron oxide (Amend & Co., New York City) was made up in distilled H<sub>2</sub>O and one ml per 250 gm body weight was used. Lange's colloidal gold solution (Mager Chemicals, Inc., Cornwall Landing, N. Y.) was concentrated about five times by evaporation and 1 ml/250 gm body weight was subsequently used.

*Shigella* endotoxin, kindly supplied by Professor Seymour Halbert of the Department of Ophthalmology, was suspended in water and 1 microgram/250 gm body weight was injected into the ear vein. Slit-lamp examination showed that aqueous humor in the anterior chamber became cloudy between 2 and 3 hours after endotoxin injection, indicating that a plasmoid aqueous was being formed.

A fistula was cut into the cornea and kept patent by removing the clotted plasmoid aqueous every few minutes with fine forceps.

A 1 per cent OsO<sub>4</sub> solution buffered with Veronal acetate at pH 7.4 was used as a fixative for the choroid plexus. The fixative was injected directly into the third ventricle so that fixation started *in situ* prior to

removal (6). Total fixation time was 1 to 1½ hours at 4°C. The ciliary processes were also fixed *in situ*, *i.e.*, the fixative was injected directly into the eyeball (13). Subsequently, the processes were removed and placed in cold fixative (4°C) for 1 to 1½ hours. The 1 per cent OsO<sub>4</sub> solution used to fix the ciliary processes was buffered at pH 8.2 and CaCl<sub>2</sub> was added (0.01 per cent) to the solution just before it was used. Both tissues were dehydrated in cold ethanol and embedded either in a methacrylate mixture (80 per cent butyl and 20 per cent methyl methacrylate) or Epon 812.

Sections were cut on a Porter-Blum microtome and examined in an RCA EMU 3-C or 3-F electron microscope.

#### OBSERVATIONS

The walls of the finest capillaries in the choroid plexus and the ciliary processes have some areas that are extremely thin. These areas are composed of single, narrow cytoplasmic sheets (250 to 300 Å)

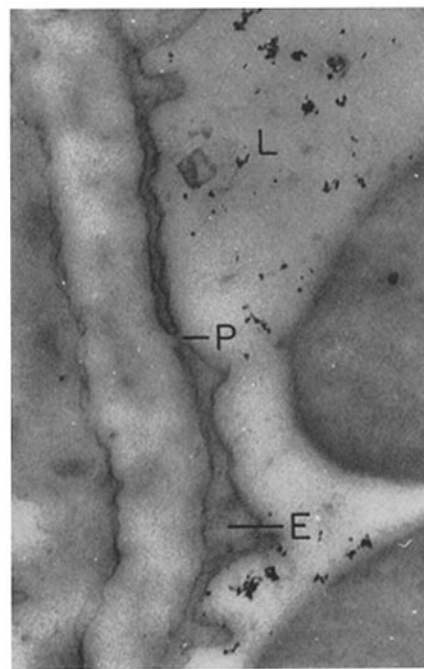


FIGURE 3

A portion of a capillary of the choroid plexus of a newborn rabbit fixed 30 minutes after the injection of thorotrast. Particles of ThO<sub>2</sub> can be found in the lumen (L) but, as in the case of similar attenuated areas of capillaries in the ciliary body (Fig. 2), no markers can be found in transit through the endothelium (E) or through the pores (P). Marker particles have been found apparently passing through the thicker walled blood vessels (see Figs. 4 to 6). × 42,000.

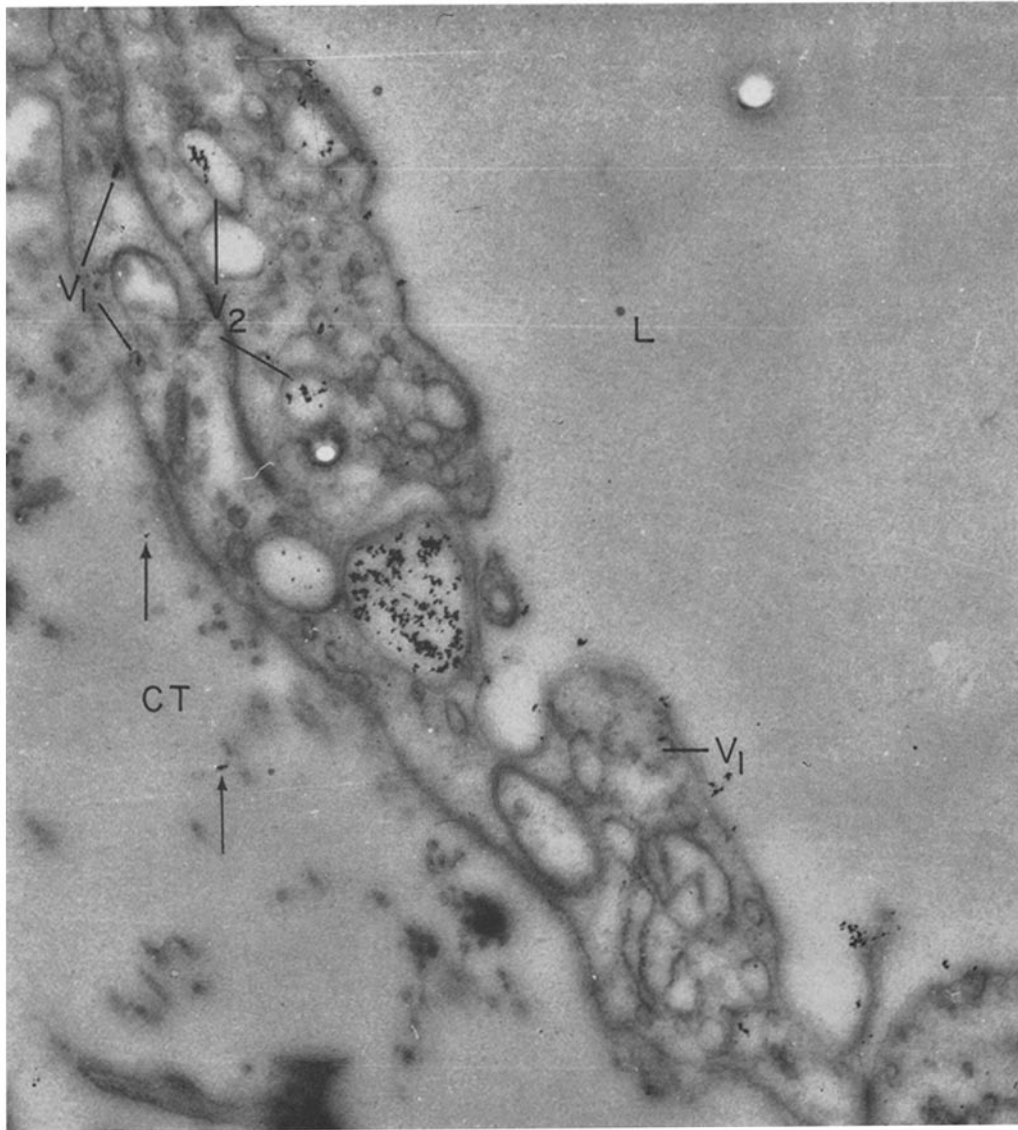
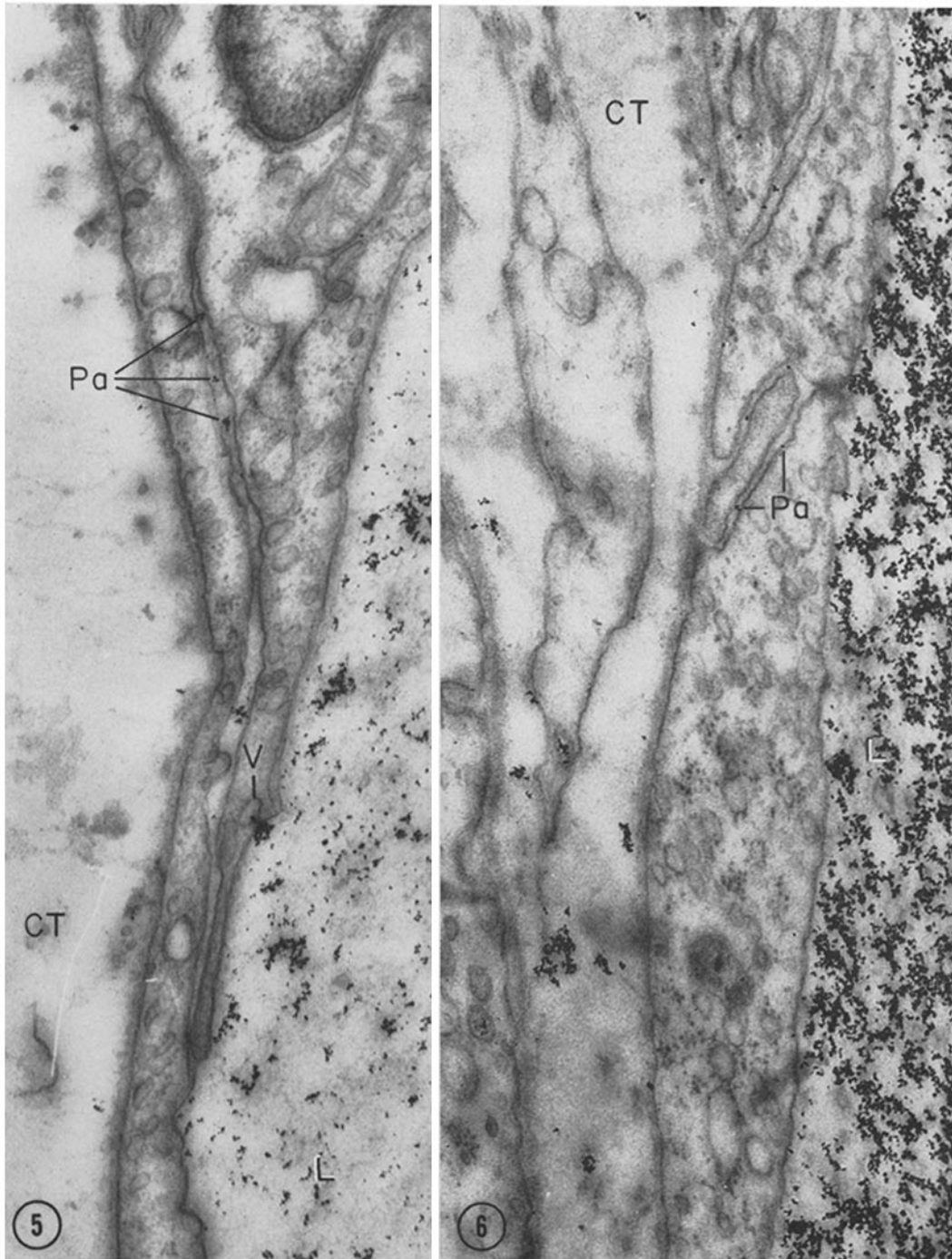


FIGURE 4

Electron micrograph of a blood vessel in the choroid plexus. This vessel has a thicker wall than that shown in Fig. 3. This tissue of a newborn rabbit was fixed  $1\frac{3}{4}$  hours after the intracardial injection of thorotrast. Particles of  $\text{ThO}_2$  are found adhering to the endothelial cell membrane in the lumen (L). Apparently the particles (at arrows) reach the connective tissue (CT) by traversing the endothelial cell apparently by means of vesicles ( $V_1$ ) and larger vacuoles ( $V_2$ ). Such intracytoplasmic passage of marker particles is sometimes found in these thicker walled vessels and not in the thinner fenestrated vessels.  $\times 40,000$ .

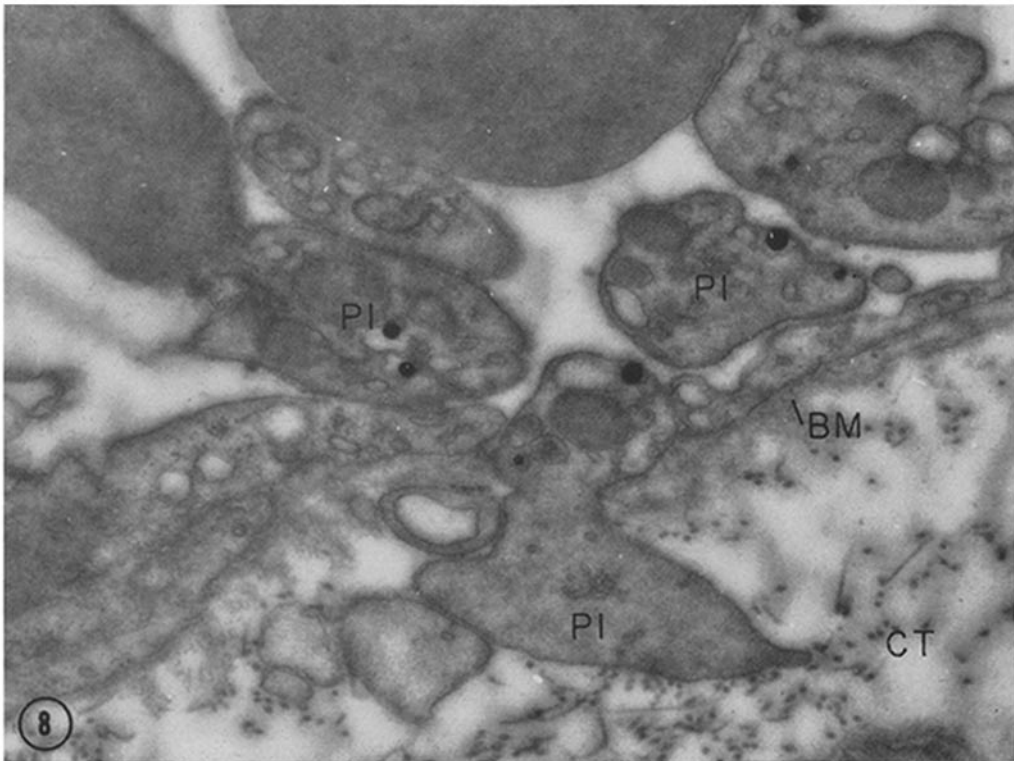
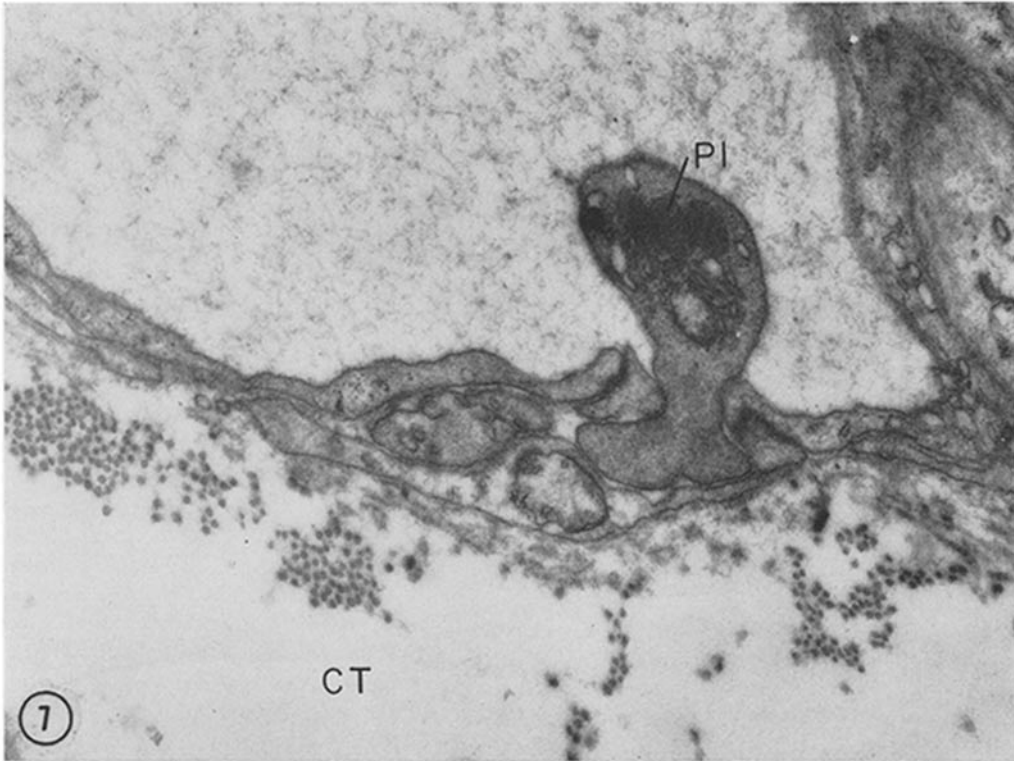
which contain local discontinuities or fenestrae which are 300 to 400 A in diameter (Figs. 1 and 2). The margin of the fenestrae is formed by the cell membrane which passes (or is reflected) from

the luminal surface and connective tissue surface of the endothelial cell. The pore space is covered by a diaphragm similar to that present in the fenestrae of endocrine capillaries (14, 15). The



FIGURES 5 AND 6

Electron micrographs of endothelial cell junctions of vessels in the choroid plexus of rabbit. Thorotrast was injected intravenously 30 min. before fixation. Occasionally some particles ( $P_a$ ) of  $\text{ThO}_2$  can be found in the intercellular margin between adjacent endothelial cells. The terminal bar area is present and the width of the intercellular space appears normal. Thus, an intracellular (Fig. 4) and an extracellular (Figs. 5 and 6) pathway may exist for the passage of marker particles from the lumen (L) to the connective tissue stroma (CT). (In Fig. 5, a clump of  $\text{ThO}_2$  particles is lodged in the "neck" of a vesicle (V) apparently forming on the luminal surface of the endothelium cell.)  $\times 40,000$ .



diaphragm is in contact with the endothelial cell membrane. This line or diaphragm is less dense and thinner than the cell membrane. On the outer endothelial cell surface facing the connective tissue, a basement membrane envelops the entire vessel. The basement membrane is continuous and has a condensed fibrous structure about 250 Å from the outer endothelial surface (Fig. 1).

Twenty minutes to 2 hours after an intravenous injection of thorium dioxide, saccharated iron oxide, or gold sol, particles can be found in the surrounding connective tissue (Fig. 2), having passed through a blood vessel wall. The markers have not been found directly in the pores or in areas which might suggest their having passed through pores (Figs. 2 and 3), nor have markers been found in transit in the attenuated endothelial cytoplasm.

The passage of marker particles from the lumen to the connective tissue apparently takes place in the thicker walled areas in the capillaries and venules. Occasionally, particle-laden vesicles and vacuoles are present in endothelial cells, indicating a transcytoplasmic passage. In Fig. 4, particles of thorium dioxide can be seen adhering to the luminal surface of the endothelial cells. Particles are also present as inclusions of various sizes ( $V_1$  and  $V_2$ ) in the endothelium. Particles are also present in the nearby connective tissue (at arrows).

Under normal conditions, marker particles are sometimes found between apposing endothelial cell margins (Figs. 5 and 6). This may indicate the existence of an extracellular pathway. There is no increase in the intercellular space, and the terminal bars or desmosomes between apposing endothelial cell membranes on the luminal surface are present in these sections.

Blood vessels of the ciliary processes of the eye under conditions of altered permeability have also been studied with the electron microscope. Intravenously injected endotoxin or a corneal lesion such as a draining fistula produces a cloudy

and plasmoid aqueous (4, 11, 12). Under these inflammatory conditions, blood cells and platelets can be seen in the process of migrating from the lumen to the connective tissue stroma. The cells and platelets appear to wedge themselves into and enlarge the intercellular space between endothelial cell boundaries (Fig. 7). Subsequently, they penetrate through the basement membrane and enter the connective tissue (Fig. 8).

Enlarged spaces or gaps between endothelial cell junctions may also occur when a plasmoid aqueous is produced by a corneal lesion (Figs. 9 and 10) or by endotoxin injection (Fig. 11). When gold sol is injected intravenously 20 minutes before fixing the ciliary processes, particles of gold are found in such gaps (Fig. 9). Apparently the basement membrane (not very clear in Fig. 9) has blocked their exit into the connective tissue. However, in Fig. 10, the gold particles have passed through the basement membrane. In this micrograph, portions of two erythrocytes have migrated into the enlarged intercellular space. When saccharated iron oxide is injected, iron particles also accumulate in the enlarged gaps and then infiltrate through the basement membrane to the surrounding connective tissue (Fig. 11).

Not all of the sections of the small blood vessels show enlarged gaps between the endothelial cell margins (Fig. 12). The thickened apposing membranes forming the terminal bars may appear unchanged. An accumulation of marker particles is found distal to the luminal side of the terminal bar. One or two particles can be found in the intercellular space near the terminal bar area in Fig. 12. Particles are also found in the surrounding connective tissue.

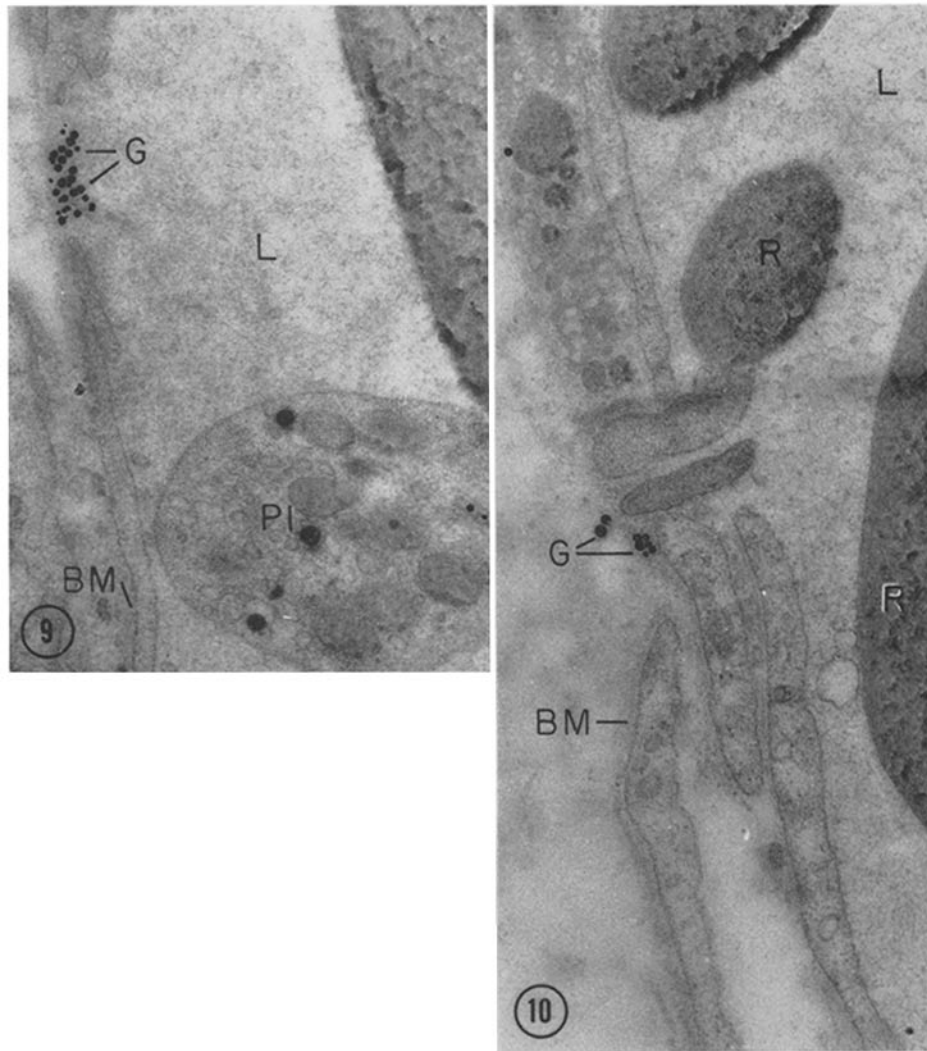
## DISCUSSION

Direct light microscopic observations on the passage of dyes or carbon particles through the blood vessel walls (16, 17) have formed the basis of our knowledge of the morphological events of

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### FIGURES 7 AND 8

Electron micrographs of portions of blood vessels of the ciliary body fixed 20 minutes after making a draining fistula in the cornea, causing the aqueous humor to become plasmoid. Platelets (*Pl*) appear to wedge themselves into and enlarge the intercellular space between endothelial cell boundaries. The platelet, *Pl*, in Fig. 8 has penetrated through the basement membrane (*BM*) and has partially entered the connective tissue (*CT*). Most platelets in these two figures contain, in membrane-bounded vacuoles, gold particles that were previously injected into the blood stream.  $\times 32,000$ .



FIGURES 9 AND 10

Electron micrographs of portions of blood vessels of the ciliary body fixed 20 minutes after a draining fistula in the cornea has brought about a plasmoid aqueous. Enlarged gaps between endothelial cell junctions occur and gold particles (*G*) may be found in such gaps 20 minutes after intravenous injection (Fig. 9). Apparently the basement membrane (*BM*) has blocked their exit into the connective tissue. In Fig. 10, however, gold particles (*G*) as well as processes of two red blood cells (*R*) have passed through the basement membrane (*BM*). Red blood cells (*R*) and platelets (*Pl*) are found in the lumen (*L*) of these vessels.  $\times 35,000$ .

capillary permeability. Electron micrographs reveal to us that capillaries of the choroid plexus and of the ciliary processes are characterized by areas of attenuated endothelium which contain fenestrae (Figs. 1 to 3). We have not been able to demonstrate marker particles in the process of transit through such fenestrae. The presence of a

diaphragm across the pores can be demonstrated in thin sections of well preserved tissue (Figs. 1 and 3). In the rat kidney glomerulus, however, Farquhar (7) and Farquhar *et al.* (8) have demonstrated that marker particles (ferritin and gold) do pass through the more numerous pores of the endothelial cells and accumulate in the surround-



ing basement membrane. The pores of the glomerular endothelial cells, however, differ in that they appear patent in the electron microscope. On the other hand, Rhodin (18) believes that in the mouse kidney the fenestrae of the endothelial cells, including those of the glomerulus, are closed by diaphragms. The presence of a diaphragm across the pores of the endothelial cells in the ciliary processes and choroid plexus does not necessarily rule out the patency of the fenestrae to substances other than the colloidal particles employed in these studies. Rhodin has suggested that such diaphragms may both serve as a barrier to large molecules and also be effective in allowing a rapid diffusion of smaller molecules (18).

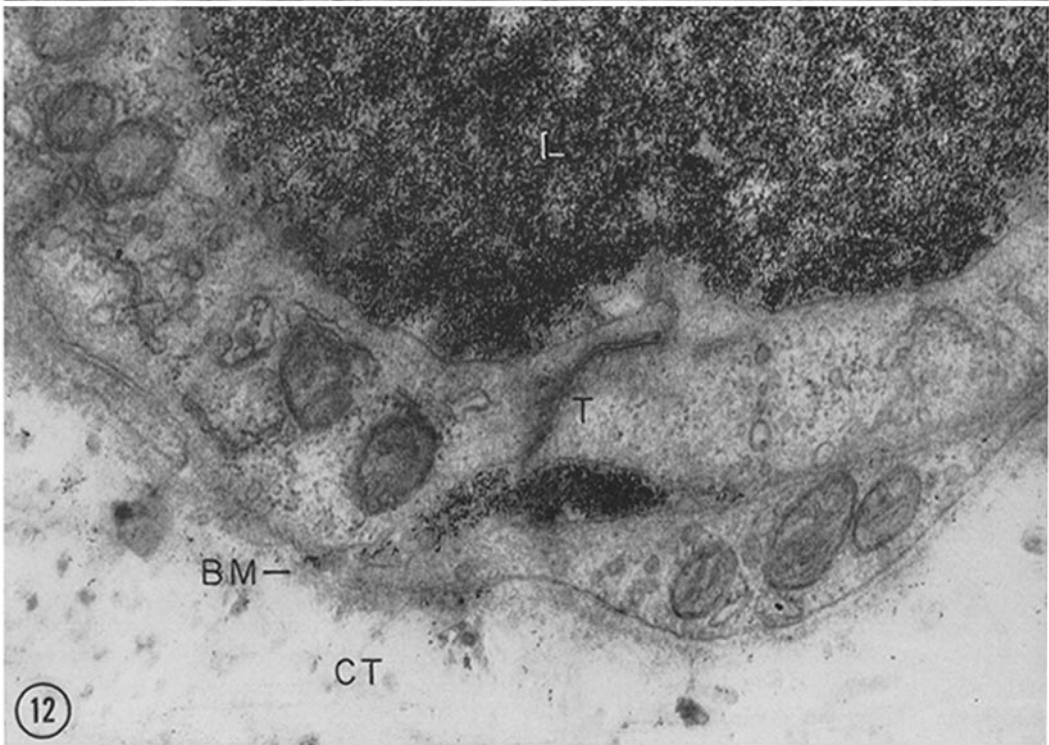
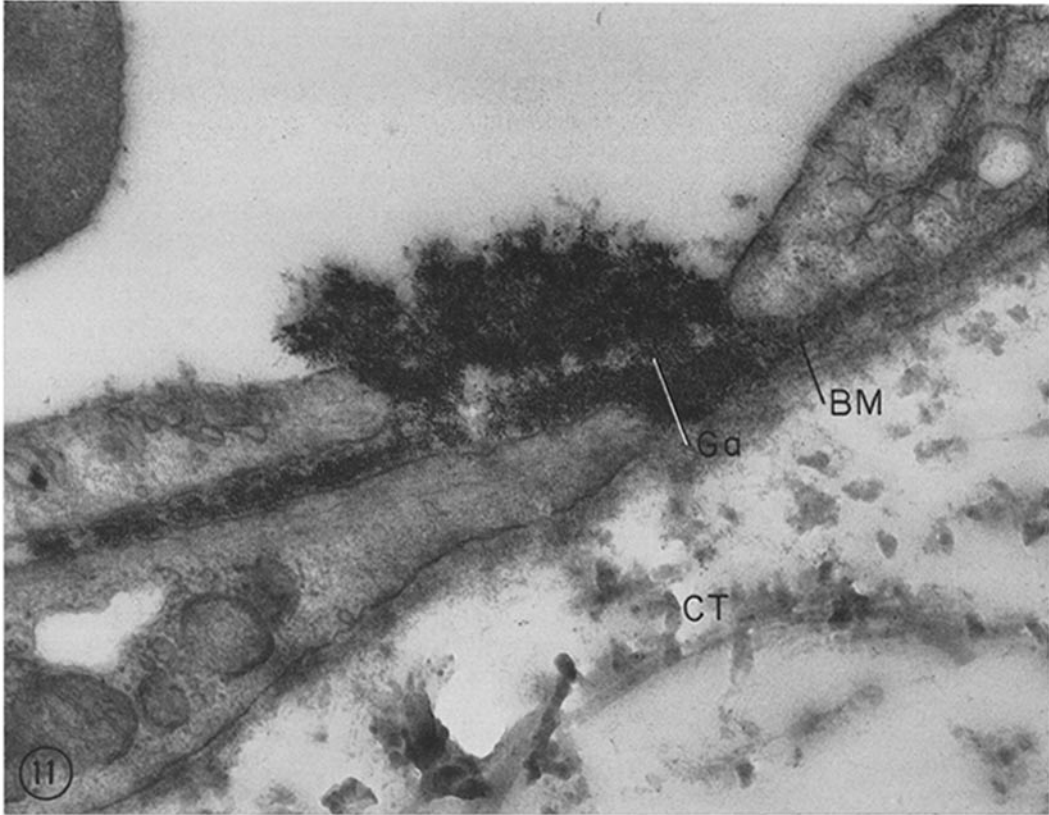
It is interesting to note that the blood vessel wall of the ciliary processes of the rabbit is not greatly attenuated and does not contain fenestrae before the blood-aqueous barrier is established (4). Similarly the wall of the capillaries in the cerebral cortex, although continuous, becomes thinner as the animal progresses to the adult stage (19). In recent studies (20, 21) marker particles were found to traverse the corneal endothelium (Descemet's mesothelium) by an intercellular pathway. In this area, the particles appear to be streaming out of the intercellular space where they fan out into Descemet's membrane. Such an outflow of fluids may not be taking place through the attenuated and fenestrated capillaries of the ciliary processes and choroid plexus. Furthermore, we have not been able to determine the functional significance of the greatly attenuated endothelial cells with the use of colloidal particles. According to Krogh (pp. 328-329, reference 16) the failure of marker substance to pass through capillary walls "does not necessarily mean that the capillary wall is impermeable to the substance but may be due to an insufficient filtration of water." Landis (17), in his work on microinjection into single capillaries in the frog's mesentery, determined that the passage of the dye solution through the capillary depends primarily on capillary pressure. A greater inflow pressure brings about a greater outflow of the dye through the capillary wall. In the present study, however, no attempt was made to determine the pressure in the blood vessels.

The passage of marker particles from the lumen to the surrounding connective tissue in the ciliary processes and choroid plexus does take place occasionally in the areas of thicker endothelium in the capillaries and venules rather than in the

attenuated and fenestrated endothelial walls. The colloidal particles which were injected intravenously 20 minutes to 2 hours prior to fixation were sometimes found in membrane-bounded vesicles and vacuoles which vary in diameter from 500 to 1200 A (Fig. 4). Palade (22) postulated that the more uniformly sized vesicles found in the endothelial cells of muscle capillaries might, through the process of pinocytosis, be the vehicles of transport for materials through the capillary wall. Later, Palade (23, 24) demonstrated that marker particles (gold sol and ferritin) entered some of the vesicles which were at the luminal surface and were then transported from the lumen to the connective tissue stroma by these small vesicles. The attenuated and fenestrated type of endothelium, frequently no thicker than 300 A, does not contain pinocytotic vesicles (Fig. 1, 2, 3). The areas of thicker walls in the capillaries and collecting venules of the ciliary processes and choroid plexus contain vesicles and vacuoles of varying sizes, in contrast to muscle where the vesicles are of more uniform size (24, 25).

Occasionally, particles of thorium dioxide can be found at the junction between the thicker endothelial cells of the larger capillaries of the choroid plexus (Figs. 5, 6). These observations suggest that under normal conditions some extracellular as well as intracellular transit of these marker particles may occur at these sites. Majno and Palade (26), in a study on vascular permeability, using colloidal mercuric sulfide as a tracer, noted that leakage of these particles between the endothelial cells of the larger capillaries and venules of muscle does occur on occasion. They suggested that the vascular injection of this tracer material may liberate endogenous histamine, which would expand the junction between endothelial cells. However, such enlarged spaces or gaps are not apparent after injections of thorotrast, saccharated iron oxide, or gold sol. The intercellular space of the vessels in the choroid plexus of the rabbit is unchanged (Figs. 5 and 6). The terminal bars appear to be intact, despite the fact that particles are present in this area.

Florey and his coworkers (27, 28) have studied the pathway of  $\text{ThO}_2$  and iron oxide particles through the mesothelium and the lymphatic vessels after intraperitoneal injections. They demonstrated the passage of particles through a predominantly extracellular pathway between mesothelial cells and between the endothelial



cells of the lymphatic vessels. Vacuoles containing particles were also found to a lesser degree in the cytoplasm of the mesothelial cells.

Kaye and Pappas (20) have demonstrated in the corneal endothelial cell layer (Descemet's mesothelium) that particles entering the cornea from the aqueous humor travel primarily between the endothelial cells. The tracer particles, however, by-pass the terminal bar *via* pinocytosis and subsequent fusion of the pinocytotic vesicles with the lateral cell membranes of the endothelial cells. Evidence of such a detour occurring in the blood vessels of the ciliary processes and choroid plexus is scant. A single possible example of this may be found (*V*) in Fig. 5.

Vascular changes were studied when normal aqueous humor secretion was altered so that a cloudy product was formed by the ciliary processes. A draining fistula in the cornea brought about plasmoid aqueous formation in a few minutes, whereas systemic injection of endotoxin produced similar inflammatory effects in 2 to 3 hours. Both methods gave rise to the same changes in the blood vessels. Intracellular passage of colloidal particles in the thicker walls of capillaries and venules was not nearly so prevalent as the extracellular passage. The attenuated and fenestrated areas of the endothelium of the small capillaries remained unchanged, with no markers passing through them.

Alksne (29) suggested that an increased intracellular passage of marker particles occurs during

inflammation. On the contrary, we have found that the process of transport of colloidal particles in inflammation is a predominantly extracellular passage or flow between the endothelial cells of the blood vessel wall. Similarly, the processes of emigration of blood cells and platelets (diapedesis) through vessels *via* the intercellular junctions (Figs. 7, 8, 10) has been noted previously in electron microscopic studies of inflammation of different origins (30-32, 26).

Our findings on the altered vessels of the ciliary processes parallel the more extensive studies of Majno and Palade (26) and Majno *et al.* (33) which are based on the blood vessels in rat cremaster muscle. Palade (24) has suggested that the transport of colloidal particles occurs normally *via* pinocytosis in the small capillaries as well as in the larger vessels of muscle, but that in inflammation the "leakage" occurs principally in the venous capillaries and venules. We have found, however, that passage of colloidal particles in the ciliary processes under normal and inflammatory conditions occurs in the same site, *i.e.*, in the areas of thicker walls in the capillaries and venules.

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#### FIGURE 11

Electron micrograph of a portion of a blood vessel of the ciliary body of a rabbit treated with endotoxin so that a cloudy aqueous was present in the anterior chamber of the eye at the time of fixation. Thirty minutes before fixation, saccharated iron oxide was injected intravenously. A large accumulation of the iron particles is present in the enlarged gap (*Ga*) between endothelial cells. Marker particles have also infiltrated into the basement membrane (*BM*) and into the surrounding connective tissue (*CT*).  $\times 55,000$ .

#### FIGURE 12

A portion of a blood vessel from the ciliary processes of an endotoxin-treated rabbit which was subsequently injected with saccharated iron oxide. The iron particles fill the lumen (*L*) of the vessel. In this section the thickened apposing endothelial cell membranes forming the terminal bar area (*T*) appear normal. An accumulation of marker particles is found distal to the luminal side of the terminal bar and enters the basement membrane area (*BM*). Some particles are also found in the surrounding connective tissue area (*CT*). One or two particles are present near or in the intercellular space of the terminal bar area.  $\times 44,000$ .

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