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Electron Microscopic Studies on the Choroid Plexus of the Experimental Head Injury

by

YOUSUKE ARAI

From the Department of the 2nd Surgery, Juntendo University School of Medicine
(Director : Prof. Dr. KENJI TANAKA)

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INTRODUCTION

Since the experiments of DANDY¹⁸⁾¹⁹⁾ or other investigators, it has been common concept that the cerebrospinal fluid is mostly produced by choroid plexus. In recent years, electron microscopic observations have been made on the choroid plexus epithelium of several animals by DEMPSY²¹⁾²²⁾, WISLOCKI²³⁾ and other workers²⁴⁾²⁵⁾²⁶⁾²⁷⁾²⁸⁾²⁹⁾³⁰⁾³¹⁾³²⁾³³⁾³⁴⁾³⁵⁾. The silver nitrates were used as a tracer for their studies by DEMPSY and WISLOCKI, van Breemen and Cremonte, and it was concluded that the choroid plexus had the function of a blood-cerebrospinal fluid barrier.

On the other hand, brain edema has been studied for long times on the head injuries, experimentally¹⁾³⁾⁵⁾ or clinically²⁾. Especially, electron microscopic studies of the brain edema¹⁾⁶⁾⁷⁾⁸⁾⁹⁾¹⁰⁾¹¹⁾¹²⁾¹³⁾¹⁴⁾¹⁵⁾¹⁶⁾¹⁷⁾ are interesting in concern to a blood-brain barrier.

However, we have not found any investigations that reported ultrastructural findings of choroid plexus after head injuries, particularly relation of brain edema and blood-cerebrospinal fluid barrier.

This report was restricted to the study of ultrastructural findings of the choroid plexus epithelium after head injuries.

MATERIALS AND METHODS

A) Experimental Study

Mongrel adult dogs weighing 7 to 18 kg were used.

1. The choroid plexus of the 4th ventricle were removed as the specimens for the electron microscopy by following methods under intravenous pentobarbital anesthesia. Brain was exposed by removal of the vault of the skull, and ice cold 2 % osmium tetroxide, buffered with phosphate in the manner of Millonig³⁸⁾, was poured by pipetté to the subarachnoid space and the 4th ventricle through the cerebellum prior to brain removal. The specimens were removed as soon as possible after brain removal, cut in to small pieces, and fixed in above fixative³⁸⁾³⁹⁾ for about 2 hours, and then they were dehydrated

with a graded series of ethanol, and embedded in a n-butyl-methyl methacrylate¹⁴⁾³⁷⁾ or the epon 812⁴⁰⁾ (according to the method of Luft).

The thin sections were cut on a Porter-Blum microtome, and were stained with lead hydroxide by Millonig method⁴¹⁾ for only the epon 812 embedded, and examined in a H-S 7 or H-U 11A electron microscope.

2. For histological observations of the head injuries, brain was fixed by 10% formalin solution and cut in 3 mm thickness by frontal section, and examined by ordinary histological procedures, (H. E. or Klüver-Barrera staining), light microscopically.

Animals were sacrificed by following procedures :

1. Ten dogs were sacrificed without head injury, and examined as control for the head injuries.

2. Experimental head injuries

Head injuries were made on the animals by the following several methods.

a) Injury by accelerated pendulum (Group A).

Rowbotham¹⁾ or Langfit⁵⁾ have made on animals head injury by this method. This principles were used in our studies and head injuries were made on anesthetised dogs fixed on a rack which was able to driven every direction with 4 wheels, by means of a specially constructed pendulum (Fig. 1).

The energy in this blow was calculated at 8.4×10^7 erg.. Most of the animals were kept in rest for one of 2 days after head injury, and a few dogs were observed with several symptoms, for example, vomiting, respiratory disturbance, and epistaxis, all of which recovered gradually.

Forty six dogs were included in this group, and they were sacrificed from one hour to 5 weeks after injury.

b) Cerebral compression by balloon inserted into the extradural space (Group B).

Brain edema has been studied in this method experimentally by many investigators⁵⁾¹¹⁾¹⁶⁾. We applied in this manner to examine whether the morphological changes of the choroid plexus in brain edema or not.

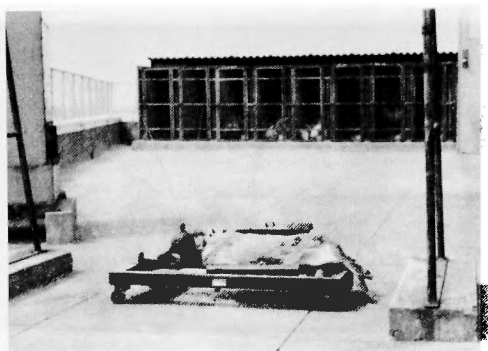
A small rectangular trephine (1 × 2 cm) was made on the left parieto-temporal region of the animals under the pentobarbital anesthesia. A small rubber balloon which had been attached a rubber tube on a tip, was carefully inserted into the extradural space, and bone defect was repaired by resin plate. The animals were recovered from this operation, thereafter the balloon was inflated very slowly by injecting 2.0 or 3.0 cc sterile water through the tube.

Sixteen dogs were dissected as this group. Specimens were taken 24, 48, 72, hours and one or 15 weeks after balloon inflation, and were examined by light and electron microscope.

c) Experimental cerebral contusion on

Table 1. Macroscopical findings on the brain following experimental head injury.

Macroscopical findings	Group A.	Group B.	Group C.
No remarkable change	25	7	0
Intracranial bleeding			
Subdural bleeding	4	0	10
Intracerebral hemorrhage	8	2	2
Ventricular bleeding	13	3	0
Unilateral ventricular enlargement	3	0	0
Cerebral laceration	0	0	10
Softening of the brain	1	0	0



When the iron ball hanging from C is lifted up to B, and then, it left B, it start a movement of pendulum toward A.

If v is iron ball speed at A, m is it's weight. l is the length of wire between C and B, and θ is the angle of A C B, iron ball speed at A is shown

$$v^2 = 2gl(1 - \cos \theta).$$

and kinetic energy at A is shown following equation,

$$\frac{1}{2}mv^2 = mgl(1 - \cos \theta)$$

then, if m is 4000 grams, l is 160cm., θ is 60° . the kinetic energy at A is calculated 8.4×10^7 erg..

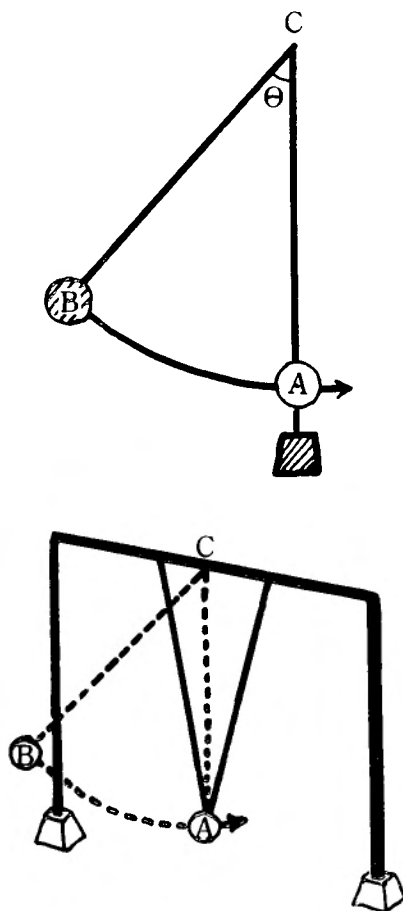


Fig. 1 The apparatus producing head injury by accelerated pendulum on dog.

the bilateral frontal lobe (Group C).

The material in this group comprised 10 dogs. Two small burr holes were placed on the frontoparietal region symmetrically far 2 cm lateral from midline. The dural incision was made, and glass bar was inserted into brain tissue about 3 cm through the burr hole, and experimental cerebral contusion was made on the bilateral frontal lobe. (Fig. 2) The specimens were taken in 24, 48, hours and one or 3 weeks after injury.

B) Histological study on the brain of the autopsy cases.

In order to compare with these experimental studies, the histological changes of the injured human brain obtained from head injury autopsy cases in the Tokyo examiner office, were researched light-microscopically. Eight cases were contained in this object, and the age, sex, survival period, and the principal pathological findings were shown respectively in table 3. The head injury of these cases were caused by traffic accident.

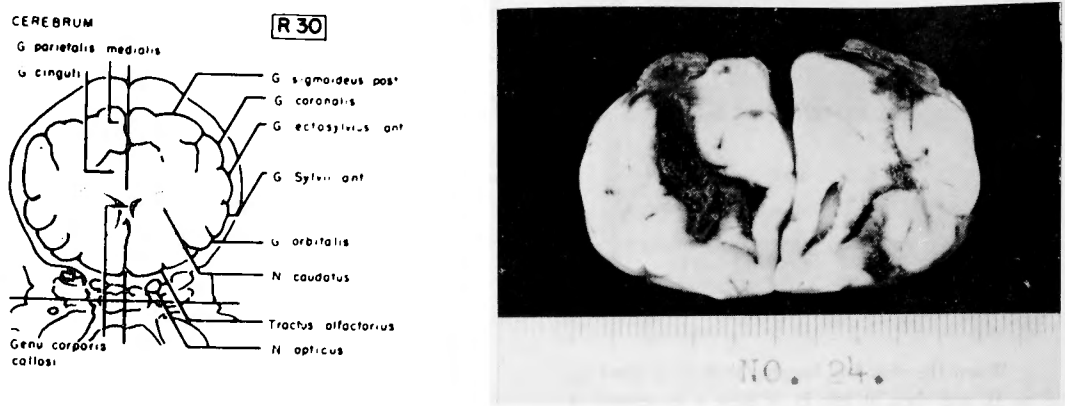


Fig. 2 The photograph of experimental contusion on the bilateral frontal lobe.

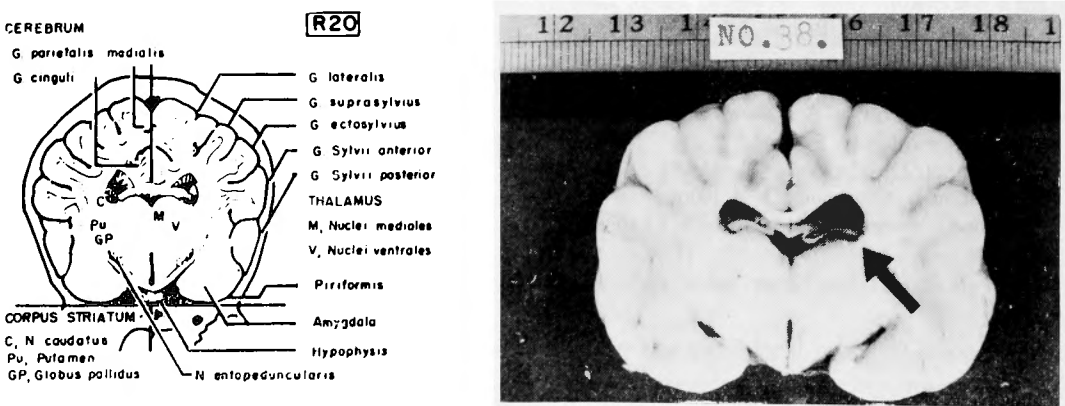


Fig. 3 This photograph shows the left side lateral ventricular enlargement following experimental head injury.

Table 2. Electron microscopical findings on the choroid plexus and the capillary endothelial cells following experimental head injury

Electron microscopical findings	1-12 (hours)	12-24 (hours)	24-48 (hours)	48-72 (hours)	4-7 (days)	7-14 (days)	2 (weeks)
Choroid plexus epithelium							
Expansion of the polypoid border	+	+	##	+	+	+	-
Increase of the apical vacuoles	+	+	##	-	+	+	-
Plasma membrane							
Winding of the lateral p.m.	-	-	##	##	##	##	+ ~ -
Increase of the pinocytotic vesicles on the basal p.m.	+	+	+	+	-	-	-
Mitochondria							
Swelling	##	##	##	##	##	+	+ ~ -
Continuous disorder of the cristae.	##	##	##	##	+	+	+ ~ -
Dense mitochondria	+	##	##	+	-	+	-

Rough surfaced endoplasmic reticulum. (rEr)							
Increase of the small rEr.	++	##	##	++	++	—	—
Enlargement of the rEr.	+	++	##	##	++	+	±
Development of the Golgi complex	+	+	##	+	—	+	±
Nucleus							
Disorder of the nuclear membr.	+	+	+	++	++	+	+
Capillary endothelial cell.							
Increase of the pinocytotic vesicles.	+	##	++	+	—	—	—

Table 3. Pathological findings on the brain and choroid plexus in the head injury autopsy cases

Case No.	Age	Sex	Survival period	Pathological findings on the brain	Pathological findings on the ependymal cells	Schema of the injured brain
1.	31	♂	8 mont.	1. Disseminated brain softening in the left frontal, right parietal lobe and anterior wall of the 4th ventricle. 2. Diffuse cerebral white matter degeneration. 3. Nerve cell swelling. 4. Neuronophagy.	1. Ependymal cell swelling. 2. Edema of the choroid plexus stroma.	
2.	4	♂	4 days	1. Bleeding in the basal ganglia (caud. Nc. and Putamen) (coagulation necrosis and ring bleeding of the ganglia cells). 2. Brain edema.	1. Degeneration of the ependymal cells. 2. Pyknosis of the choroid plexus epithelium.	
3.	64	♀	15 hours	1. Epidural hematoma in the left temporal region. 2. Rupture of the left middle meningeal artery. 3. Nerve cell swelling. 4. Hydropic degeneration of the glial cells.	1. Cloud swelling of the ependymal cells.	
4.	55	♂	7 days	1. Contusion in the left frontal lobe (coup) and right occipital lobe (contre coup) and bilateral parietal lobe. 2. Subarachnoid hemorrhage. 3. Nerve cell swelling and incomplete necrosis. 4. Gliosis in the perivascular region.	1. Degeneration and pigmentation of the ependymal cells.	
5.	38	♀	11 days	1. Contusion in the right occipital lobe. 2. Petechial bleeding in the corpus callosum and gyrus hippocampus. 3. Nerve cell swelling and incomplete necrosis. 4. Swelling of the macroglia.	1. Swelling of the ependymal cells.	

6.	44	♂	27 days	1. Petechial bleeding in the corpus callosum. 2. Brain edema. 3. Perivascular hemorrhage and neuronophagy in the cortex. 4. Diffuse incomplete necrosis of the white matter.	1. Degeneration of the ependymal cells.	
7.	51	♂	3 days	1. Contusion and bleeding in the left temporal lobe. 2. Nerve cell swelling. 3. Petechial and ring bleeding in the white matter. 4. Hydropic degeneration of the glial cells.	1. Degeneration of the ependymal cells. 2. Coagulation necrosis of the subependymal cells.	
8.	66	♂	8 days	1. Extensive petechial bleeding in the white matter of the brain stem, internal capsule and bilateral lobe. 2. Brain edema. 3. Hydropic degeneration of the glial cells.	1. Ependymal cell swelling.	

OBSERVATIONS

I) Macroscopic findings of the brain.

Macroscopic findings of the brain after injuries were shown on table 1. In the several materials of the group A, a small clot was noticed in the lateral ventricle, and other remarkable findings were subcortical bleeding or slightly enlargement of the lateral ventricle on the injury side.

II) Light microscopical findings of the choroid plexus after injury.

The histological structures of a normal choroid plexus was reported by many authors and the structural change in the choroid plexus after head injury was written on the human specimens by Rand³⁶⁾.

In our experimental study, the pathological findings after head injury were as follows. In general, the free epithelial margin of normal choroid plexus was shown only slightly irregular, but the margin of the individual cells was given a remarkably irregular or serrated appearance in places. The cytoplasmic process was inflated directly to the ventricular space (Fig. 4). In places, numerous small vacuoles were seen in the upper part of cytoplasm (Fig. 5), cellular stain was decreased, and inter-cellular spaces between the epithelial basement membrane and the underlying blood vessels were enlarged. These findings could be seen most remarkably on the choroid plexus from which 24 to 48 hours after injury. These changes were decreased thereafter.

On the other hand, the structural changes in the human specimens were similar in animals specimens. It was only noticed that the choroid plexus and ependymal cells of the case 1 (in which survival period after injury was long), were almost kept normal in their structure (Fig. 6), but on the case 2 (selective bleeding in the basal ganglia) they were swollen remarkably, and their nucleus were degenerated (Fig. 7).

III) Electron microscopical observation.

A) Normal structure of the choroid plexus

The ultrastructural findings of normal choroid plexus were reported on rats^{2) 24) 25)}

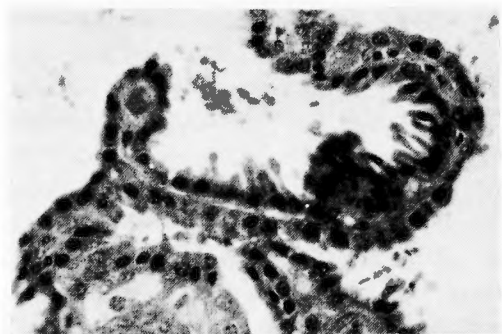


Fig. 4 The photograph of choroid plexus by light microscope. (H. E. staining, Group A. 24 hours after injury.) The cytoplasm of the epithelium is projected on the free margin toward the ventricular space.

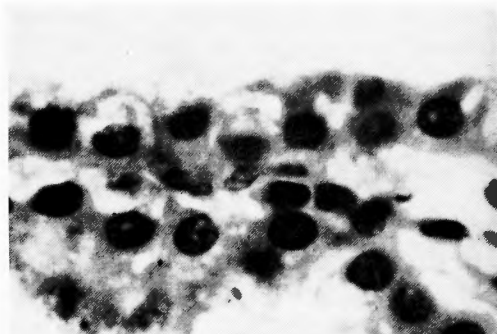


Fig. 5 Many large vacuoles are shown in the epithelial cells. (H. E. staining, Group A. 24 hours after injury.)



Fig. 6 The choroid plexus epithelium of the autopsy cases (Case 1, white matter degeneration) in the light microscopic examination. (H. E. staining)

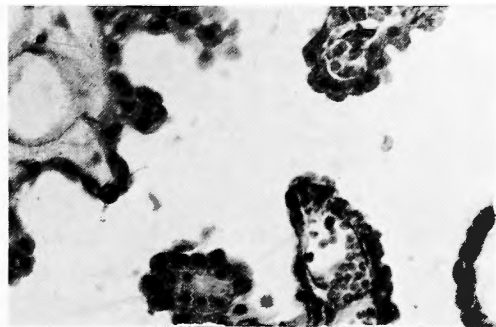


Fig. 7 (Case 2, selective basal nuclear bleeding.)

rabbits²⁶⁾, monkeys²⁷⁾, and other animals^{27) 29) 30) 33) 34)}, especially, were reported on dogs by WISLOCKI²⁷⁾ or SHRYOCK²⁸⁾. We described our observations on the normal findings for the purpose to compare with those after injuries.

1) Choroid plexus epithelium

The epithelial cells of the choroid plexus were columnar in shape, having free distal edge toward the ventricular space and lying on the basement membrane. The oval or round nucleus that consisted of DNP granules and nuclear membrane occupied the central portion of the cell. Nuclear membrane consisted of three layers, inner was dense, intermediate was less dense, and outer was dense layer. In this nucleus, one or two nucleoli consisting of RNA granules were observed.

The free margin of the cells toward the ventricular space showed numerous microvilli which appeared to consist of extensions of the cytoplasm bound by the dense plasma membrane. This microvilli were called polypoid border (polypoid process). The height of the polypoid border was measured 600 m μ -900 m μ .

The cilia was not found in our materials.

The plasma membrane of polypoid border on its root was infolded into the cytoplasm between the adjacent polypoid border (apical caveolae) (Fig. 8). The lateral surface of the plasma membrane was formed terminal bar near the apical portion between adjacent cells to one another, and its upper parts could be seen with tight junction structures, but lower parts were proceeding away from terminal bar toward the basal part.

The inter cellular space of adjacent cells was generally of almost constant width about 300 Å under the junctional complex, and ran nearly straight except the one or two inter-digitations on the way of it. On the basal part of the cell, this space was few in the mediate part of the basal plasma membrane, although it was abandoned in the lateral part on account of irregularly encroached plasma membrane toward the cytoplasm (Fig. 9).

Numerous mitochondria were distributed almost equally in the cell cytoplasm. Each mitochondrion had a small rod shape, and was shown round outline in cross section or oval profiles in longitudinal sections. In these oval profiles, the average diameter was about 400-800 m μ in length. The mitochondria was surrounded by a double membrane, inner membrane projected many process which was called cristae mitochondriales.

It was written by Wislocki and Ladman that when sections were cut through the long axis of a crista, a slightly electron dense, homogenous material can be discerned within its oval contours, and a mitochondrial matrix was greater electron opacity, but in our observation, a mitochondrial matrix was little electron dense in bold contrast to the greater density of the cristae and surrounded membrane.

Golgi apparatus (Golgi complex) was confined supranuclear or perinuclear cytoplasm, and consisted of three fundamental elements.

- (1) Golgi flattened sacs, which were piles of long rod shapes formed by a smooth surfaced double membrane.
- (2) Golgi vacuoles, which were surrounded by its double membrane.
- (3) Small vesicles, which were made from aggregation of numerous small vesicles.

Golgi complex was comparatively developed in the choroid plexus epithelium. The endoplasmic reticulum was distributed in the cytoplasm everywhere, that was shown large or small vesicles, and rough surfaced endoplasmic reticulum was much of all. Rough surfaced endoplasmic reticulum was formed by surrounded double membrane having irregularly with small dense RNP granules. Although it was noticed in some investigation that they had some relation in distribution of mitochondria and endoplasmic reticulum, in our observation, such relation was not found between both organellae.

The small vesicles were seen in the cytoplasm near the apical caveolae, which were surrounded by a smooth surfaced membrane and their diameter were about 1000 Å (apical vacuoles).

Pinocytotic vesicles were observed in the cytoplasm near the basal plasma membrane. Many free ribosomes were spread in the cytoplasm in all.

As the other cytoplasmic constituent, a few small body was found in the cytoplasm of some epithelial cells, which consisted of a limited double membrane and was packed with dense numerous fine granules (granule diameter was about 100-400 Å) in it. These bodies were oval in shape, and average dimension of these profiles was about 600 m μ in length and 500 m μ in width. These bodies were called dense body in this paper provisionally.

The less dense layer was adjacent to the basal plasma membrane and ran parallel to it. This layer was of almost constant width of $400 \text{ \AA}$ except for the portion of basal membrane infolding as described above, and continues into the intercellular space between the epithelial cells.

Basement membrane was laid down outside of this less dense layer, was homogenous, osmophil, and was about 500 to $1000 \text{ \AA}$ in thickness.

2) Capillary.

The capillaries were situated below these epithelial cells beyond the extracellular spaces. The capillary wall was formed by a single layer of endothelial cells, less dense layer and homogenous osmophil basement membrane (about $500 \text{ \AA}$ in thickness) around of it. The cytoplasm of the endothelial cells was enlarged around the nucleus. A few mitochondria, small vesicles, and a little pinocytotic vesicles were observed in this portion. But other portion of the cytoplasm was very thin and covered the capillary internal cavity.

At places in the endothelial cytoplasm, the interruption of it could be seen (endothelial pore or fenestration). These pores were amounted 400 to $900 \text{ \AA}$ in width, and were presented several in number on one section.

3) Extracellular space.

The extracellular space between the basement membrane of the epithelium and the capillary was various in width, for example, in case of most narrow space, both basement membrane attached as if being one layer.

In this space, connective tissues were observed e.g. collagen fibers, reticular fibers, and fibroblasts.

B) Electron microscopical changes in the choroid plexus following head injury.

1) Epithelial cells.

Many changes affecting practically all constitutive of the choroid plexus were present after head injury, these changes were written this paper correspondingly with the preceding description, In general, the epithelial cell could not be seen marked change in size and shape.

Polypoid border

Most remarkable changes in polypoid border of choroid plexus epithelium following trauma were elongated in its height and enlarged in its distal portion (Fig. 11). These findings were designated as expansion of polypoid border. The polypoid borders were very difficult to estimated in their heights because many of them were presented in confusion one another, but the average dimation of these expansive polypoid borders which were able to measure, was calculated about 2μ in height (Fig. 10).

On the group A, a few cases showed these expansion of polypoid border in the 3 hours after injury, but most cases did not showed these dispositions. From 24 to 48 hours after injury, a number of cases was shown these expansive polypoid borders, and their expansion was very remarkable. In company with these findings, apical vacuoles were increased in the cytoplasm. However, these findings were reduced gradually, and never observed in cases of 3 weeks or more after injury.

On the group B these findings were remarkable in most cases of 48 to 72 hours after injury, and were observed in a few cases of 10 weeks after injury.

On the group C, these findings were observed in a period like group B, but expansive

degree was slight as compared with group B.

Terminal bar

Any changes were not shown on the terminal bar of every group and every time. In this fact, the terminal bar or tight junction was firm connection with adjacent cell as well as other epithelial cells (Fig. 12).

Plasma membrane

The lateral surface of the plasma membrane running in parallel with adjacent cells was wound and torn of its way, but basal membrane infolding and basal plasma membrane had not marked changes.

On the group A, this change was observed for the first time in the case of 24 hours after injury (Fig. 13), and then observed in 1/3 cases of all thereafter. This membrane winding was observed in a half of the group B and C on 24 to 48 hours after injury, there after, the process of the group B was seen like that of group A, but on the group C, this finding could not be seen 1 week or more after injury.

While, the pinocytotic vesicles were increased in the cytoplasm near the lateral surface of the plasma membrane. This increase was noticed at first in 1 or 3 hours after injury in the group A, and its maximum was from 12 to 24 hours, and then restored gradually within 1 week. In the group B and C, its maximum change was 24 to 48 hours (Fig. 14). Especially, the restoration period of group B was prolonged as compared with group A.

Basal membrane infolding had not remarkable changed in every group.

Mitochondria

The findings of mitochondria showed most remarkable change. This change was divided two types. The one, the density of mitochondrial matrix was increased, and in consequence, the cristae mitochondriales were not observed apparently (Fig. 20). The another, the density of mitochondrial matrix was decreased, the size of it was enlarged (the average dimension of these mitochondria was about 1000 m μ to 1400 m μ in the long axis.), and much of all were round of oval in shape. These mitochondria were regarded as swollen ones, and sometimes the continuous disorder of the cristae or circumference double membrane was observed (Fig. 15).

Dense mitochondria were observed at first in 7 hours after injury in group A. After 12 to 24 hours, this mitochondrion was increased, and was decreased more after, and then, in 72 hours, this mitochondrion was not observed. This mitochondrion was distributed all over the cytoplasm through every process of head injury. In cases of group B and C, this mitochondrion was scarcely observed.

The swollen mitochondria were observed in 5 hours at first in group A, and increased gradually to 12 hours, and got to peak in 12 to 48 hours, and was decreased more after, restored after 2 weeks. In group B, this mitochondrion was observed in 24 hours at first, and convalescent period was prolonged. In group C, the progress was like in group B, but restoration was very soon. In general, this mitochondrion was distributed equally in cytoplasm, but occasionally, was concentrated in the cytoplasm near the free margin (Fig. 16).

Rough surfaced endoplasmic reticulum

The findings of the endoplasmic reticulum consisted from two principal changes.

1. small round shape endoplasmic reticulum (diameter was about 700-800 Å) was increased in number.

2. inner cavity of the endoplasmic reticulum was spread, and was elliptic, or irregular in shape.

In the cases of group A, the small endoplasmic reticulum was increased in the basal part of the cytoplasm in 1 or 3 hours. It is particularly interesting that this finding was accompanied with the increase of pinocytotic vesicles as mentioned above (Fig. 15). In addition to this finding, the spread endoplasmic reticulum was distributed in the cytoplasm of upper or lower part of nucleus. In 12 hours, inner cavity was more spread, and in 12 to 24 hours, the small endoplasmic reticulum was increased in every cytoplasm, and the spread one was distributed among there. In 48 hours, the large endoplasmic reticulum was more shown in the cytoplasm of the upper part than the lower part of nucleus (Fig. 12). In 3 to 7 days, the increment of the small endoplasmic reticulum was reduced, and after 2 weeks, this increment was not seen. while the spread was observed after 4 weeks in few cases (Fig. 17).

In the cases of group B, the progress of the structural changes in endoplasmic reticulum was similar to that of group A until 7 days, but the increment of small one was continued more after.

In the cases group C, the structural changes of endoplasmic reticulum were maximum in 48 hours, and after 1 week, these changes were not seen.

Free ribosome

The findings for free ribosomes were undefined.

Golgi complex

Hypertrophic Golgi complex was observed in the cytoplasm under the nucleus 1 or 3 hours after head injury in the cases of group A. In 12 to 24 hours, Golgi complex was more developed around the nucleus, small vesicles and flattened sacs were increased in number, and Golgi vacuoles were enlarged (Fig. 18, 19). In 24 to 48 hours, these changes reached to maximum, and were reduced gradually thereafter, and then, were restored after 7 days. In the cases of group B, hypertrophic Golgi complex was seen on some occasions in 24 hours, but except for this, peculiar findings were not obtained.

Dense body

The dense bodies were often, but not always, characteristically assembled in the cytoplasm near the basal plasma membrane, but this finding had not evident inclination.

Nucleus

The nuclei of the epithelial cells had not showed marked changes in 48 hours after injury. After 48 hours, the nuclear membrane, which was double, was disordered in layers, and it run rough in some cases, but it was restored in due time, and 2 weeks later this finding was not observed.

Basement membrane

The basement membrane was thickened about 1200 Å in some cases of after 48 hours on group A (Fig. 21), but this thickning was not always, and thickness of basement membrane was difference in sections on no head injury group. Therefore, we cannot resolved this finding in relation to head injury.

2) Capillaries

Several findings were noticed for the structure of the capillaries in some cases of group A, but not always.

1. The endothelial pore (fenestration) which was recognized in the layer of endothelial cells, was spread in the case of 24 hours and 48 hours (Fig. 22).

2. The numerous pinocytotic vesicles arranged on the plasma membrane toward the cytoplasm were observed in the case of 24 to 48 hours (Fig. 23), and after 72 hours, these findings were reduced as time passes.

3. Golgi complex was developed in the cytoplasm near the nucleus, in the case of 48 hours (Fig. 24).

3) Extracellular space

The remarkable changes were not seen in extracellular spaces.

DISCUSSION

When DANDAY¹⁸⁾ had been produced the obstructive hydrocephalus experimentally, he recognized that the cerebrospinal fluid were produced by choroid plexus. Following his experiment, the study of the experimental obstructive hydrocephalus has done by many other workers⁴²⁾⁴³⁾⁴⁴⁾, and cerebrospinal fluid production or absorption²⁰⁾ were discussed for many long time⁴⁵⁾⁴⁶⁾⁴⁷⁾⁴⁸⁾.

GREENBERG⁴⁹⁾ reported that cerebrospinal production from the choroid plexus was not only ultrafiltration but secretion.

There have been many more papers written on the formation or absorption of cerebrospinal fluid by choroid plexus. The secretion theory was described by WEED⁵⁰⁾ for his histological study. Electric barrier was discussed by STIEHLER⁵¹⁾ between epithelium and stroma of the choroid plexus, the enzyme activity of the epithelium was measured by FIEDENWALD⁵²⁾ and FISHER⁵³⁾. The content of electrolyte in the fresh liquor producing from choroid plexus was measured by ROUGEMONT⁵⁴⁾. Ten % fluorescein was used as indicator for discharge from the choroid plexus (SCHALTENBRAND⁵⁷⁾. SWEET⁵⁸⁾ and others⁵⁵⁾⁵⁶⁾⁵⁹⁾⁶⁰⁾ studied on the function of choroid plexus by using isotope. Electron microscopical studies on the choroid plexus were done by Dempsey and Wislocki and other investigators.

If the choroid plexus epithelium should produce the cerebrospinal fluid, the ultrastructural change of the epithelium following head injury might be concerned with the alteration of intracranial pressure. Van Breemen and Clemente²⁴⁾ described that the cerebrospinal fluid might be produced as the bleb formation of the polypoid border, MAXWELL and PEASE²⁶⁾ supported this opinion, SCHLTENBRAND⁵⁷⁾ mentioned that a protrusion of protoplasm through the brush border was thought as definite proof of secretion.

KUROSUMI⁶¹⁾ classified the secretory cells into five types for the reason of his electron microscopical observations concerned with the excretory mechanism on them, and he referred that to the secretory mechanism in the polypoid border of the choroid plexus (mentioned by MAXWELL and PEASE) comparable to III type (microapocrine mechanism) of his classification. We observed the finding on the polypoid border which supported these interpretation (Fig. 11).

Therefore, if the cerebrospinal fluid production of the choroid plexus was taken by the microapocrine secretion mechanism, it was possible to consider that the extension of

the polypoid border and the increment of the apical vacuoles following head injury (which were observed in our study) were implied increase of the water transport from cytoplasm toward the free surface of the cell.

The basal membrane infolding has been discussed in connection with water transport on the epithelial cells⁶³⁾. SJÖSTRAND and RHODIN⁶²⁾ described on the tubular epithelial cell of the kidney. MAXWELL and PEASE²⁵⁾ mentioned on the choroid plexus epithelium. WISLOCKI and LADMAN²⁷⁾ reported on the choroid plexus epithelium and ciliary process or choroid plexus of the eye. The basal membrane infolding on the choroid plexus was not remarkable change following trauma in our experiment, so that the change of polypoid border and apical vacuoles may be the finding of epithelial edema.

The polypoid border of the choroid plexus were differentiated from the microvilli of the small intestinal villus^{64) 65)} on their structures, and therefore, polypoid border were considered as relation to secretory rather than absorptive function.

The cilia have been seen on the many animals^{25) 26) 27) 29) 30)}, but we have no opinion to discuss for this.

Junctional complex between adjacent cells were observed characteristic tripartite as described by FARQUHAR and PALADE⁶⁶⁾, and after head injury, these complex were not remarkable changes. They mentioned that the epithelial permeability were influenced by these junctional complex. If this theory was true, pathological water transport was scarcely possible through the intracellular space of the choroid plexus epithelium following head injury.

The winding and tearing of the lateral plasma membrane was considered as the incidence of the intracellular changes rather than intercellular.

The pinocytotic vesicles were increased along the lateral or basal plasma membrane of the epithelium and capillary endothelial plasma membrane in 24 to 48 hours after injury. PALADE⁶⁷⁾ was observed pinocytotic vesicles on the capillary endothelial cell of the heart and skeletal muscles, he depicted these vesicles as a transporter from blood to cellular tissue, and testified this theory by using tracer⁶⁸⁾. KUROSUMI have been similar observations on the human sweat gland. If this theory was adequate, the increase of these pinocytotic vesicles may be increase of transportation from blood through the epithelial cell to ventricular space.

In this period, small rounded rough surfaced endoplasmic reticulum were increased in the cytoplasm of the basal part of the cell, then increased in all cytoplasm, and large rough surfaced endoplasmic reticulum was noticed in the upper part cytoplasm. Golgi complex also developed in this period, especially, flattened sacs were grown. Development of these organella is interpretable as the increment of the water transport together with the pinocytotic vesicles increase. This opinion relation to the rough surfaced endoplasmic reticulum was reported by PORTER⁶⁹⁾ or WATANABE⁷⁰⁾. It was emphasized that the brisk cell in function was remarkable in formation of small vesicles⁷¹⁾. Golgi complex was closely related to production of the secretion since Palade mentioned^{61) 72) 73) 74) 75)}, and he interpreted that the protein particles of the secretion were produced by the endoplasmic reticulum for the reason of his observation of the pancreas cell⁷⁶⁾.

KUROSUMI⁶¹⁾ said that if the high molecular compounds of the secretion were stored in the endoplasmic reticulum as the dilute solution, these endoplasmic reticulum changed

their form and swelled, and then, the solution in the endoplasmic reticulum was transported to the Golgi complex, and this solution was concentrated. The change of the endoplasmic reticulum and Golgi complex which we were observed, was identical with his opinion. The increment of the flattened sacs was interpreted as the increment of the reserved membrane. He explained that basalm embrane infolding⁷⁷⁾ was closely connected with the active transport of the water, but we could not observed remarkable change in this part.

The swollen mitochondria was observed on the nerve and glial cells in experimental brain edema by LUSE⁹⁾, STRUCK¹³⁾, LAZORTHES¹⁴⁾, TANI¹⁷⁾, ISHII¹¹⁾, and many other workers¹⁵⁾¹⁶⁾. It was observed on the Purkinje cell of the cerebellum in experimental head injury by MAKITA¹²⁾, and he was observed dense mitochondria was not degenerative, but new created one.

Recently, histochemical study of the mitochondria was performed, and several enzyme activity was measured for the membrane fraction of the mitochondria. CLELAND and SLATER⁷⁸⁾ isolated mitochondria from heart muscles of cat, rat, rabbit, and guinea pig. They measured on succinoxidase, cytochrome oxidase activity in thier insoluble fraction.

WATSON and SIEKEVITS⁷⁹⁾ measured succinoxidase, and cytochrome oxidase activity in the mitochondrial membrane fraction of the rat liver.

GREEN et al reported⁸⁰⁾ that the enzyme of citric acid cycle was existed in the mitochondrial matrix, the granules of electron transport system with oxidative phosphorylation were existed in the cristae mitochondriales, and the granules of electron transport system without oxidative phosphorylation were existed in the single membrane by means of the experimental heart muscle mitochondria isolation.

FUNABASHI⁸¹⁾ described that if thyroxine was given for the mice, the oxidative phosphorylation uncoupler of the mitochondrial inner membrane and cristae of the liver was inhibited selectively, ATP production was suppressed, and mitochondria was swollen. Therefore, he thought the suppression of the ATP production and increment of the dehydrogenesis activity as the mechanism of the mitonhondrial swelling, and that the dense matrix of the mitochondria was suggested vigorous rotation of the Krebs cycle.

Another swollen mitochondrion was found on the apocrine sweat glands by KUROSUMI, and he was noticed some granules and vacuoles which may vary in size, in large mitochondrion of the adrenal cortex, corpus luteum cell and interstitial cell of testis. He recognized that the lipid droplets were closely connected with mitochondria.

It is considered to us that swollen mitochondria and dense mitochondrial matrix in our observation, being related with Golgy complex and endoplasmic reticulum, probably should have important function on the relation of cerebrospinal fluid production.

For the dense body, WISLOCKI and LADMAN observed on the choroid plexus epithelium of the dog and rabbit. They regarded the granules in this dense body as the hemosiderin that was reported by FLATHER. CASE⁸²⁾ also considered this granules as hemosiderin for his histochemical study. It seems to us this body like a some lysosome, but we have not any histochemical study for this body, so that it was not decided.

We could not observed remarkable changes on the epithelial and capillary endothelial basement membrane.

BREEMEN and CLEMENT²⁴⁾, DEMPSY and WISLOCKI²³⁾, studied on the choroid plexus,

of rats by electron microscope by administration of silver nitrate in drinking water. They considered that the basement membrane had some mechanism as a blood cerebrospinal fluid barrier for the reason of the silver deposition was found perivascular space along the basement membrane.

PAPPAS and TENYSON⁸³⁾ also have same opinion by thier study which were observed the passage of colloidal particles from the blood vessels to the cilliary processes and choroid plexus of the rabbit eye.

PALADE^{87) 88) 84)} reported that the basement membrane of the capillary endothelium of the kidney or heart muscle do not pass the colloidal particles.

The other hand, the observations of the ultra-structural changes on the brain edema following head injury was reported by many investigators mentioned above, and these changes were presented almost reversible. The changes of the choroid plexus of our observations were almost reversible, and they were not observed with lapse of time.

In these changes, the swollen mitochondria, the increment of pinocytotic vesicles and nuclear membrane winding, were mentioned on the nerve and glial cells of the experimental brain edema by investigators. Therefore, these changes were regard as the finding of tissue edema.

JOHN L. FOX⁸⁶⁾ was emphasized that, the recent experiments indicate that normally most of the diffusion of ions into the brain may be via the cerebrospinal fluid and not through the blood-brain barrier. There most likely was a relative blood-cerebrospinal fluid barrier presented by the layer of ependymal cells, there was interstitial space in the choroid plexus and which may have secretory functions as well as allowing diffusion.

From these reports, brain edema produced not only destruction of the bloodbrain barrier, but change of the brain-cerebrospinal fluid or blood-cerebrospinal fluid barrier, especially the letter two having most important function in concern with the transfer of the electrolyte and water. The choroid plexus was situated as these barrier.

CONCLUSION

The choroid plexus of the mongrel dogs in the experimental head injury has been studied with the light and electron microscope. The animals were sacrificed between 1 hour and 3 months after head injury.

On the one hand, the histological observation has investigated on the brain and choroid plexus of the several autopsy cases of head injury by ordinary histological procedures.

The results obtained were summarized as follows.

1. The microvilli, exist as polypoid border on the free margin of the epithelial cells toward the ventricular spaces, were elongated in their height and enlarged in thier extreme portion in 3 hours after injury. In company with these findings, apical vacuoles were increased in the cytoplasm. These findings were very remarkable in 24 to 48 hours, and then, after 72 hours, reduced gradually.

2. The lateral surface of the plasma membrane was wound and torn of it's way 24 to 48 hours. This change was observed till 2 weeks after injury.

3. Pinocytotic vesicles were increased in the cytoplasm near the basal plasma membrane and the basal part of the lateral plasma membrane following head injury. These increment got to maximum in 24 to 48 hours, and were decreased gradually from

after 72 hours.

4. Mitochondria were swollen remarkably from 12 to 72 hours after injury, and more after, much of all were restored. In some other cases, the density of the mitochondrial matrix was increased remarkably.

5. Rough surfaced endoplasmic reticulum was increased in number in the cytoplasm near the basal plasma membrane in 1 or 3 hours, and in 12 or 24 hours this increase was extended to every cytoplasm. Dilated endoplasmic reticulum were observed in the cytoplasm near the upper part of nucleus. These changes were not shown after 1 week.

6. Golgi complex was developed in 12 to 24 hours.

7. Nuclear membranes became irregular after 2 or 7 days.

8. Pinocytotic vesicles were increased in the cytoplasm of the capillary endothelial cells.

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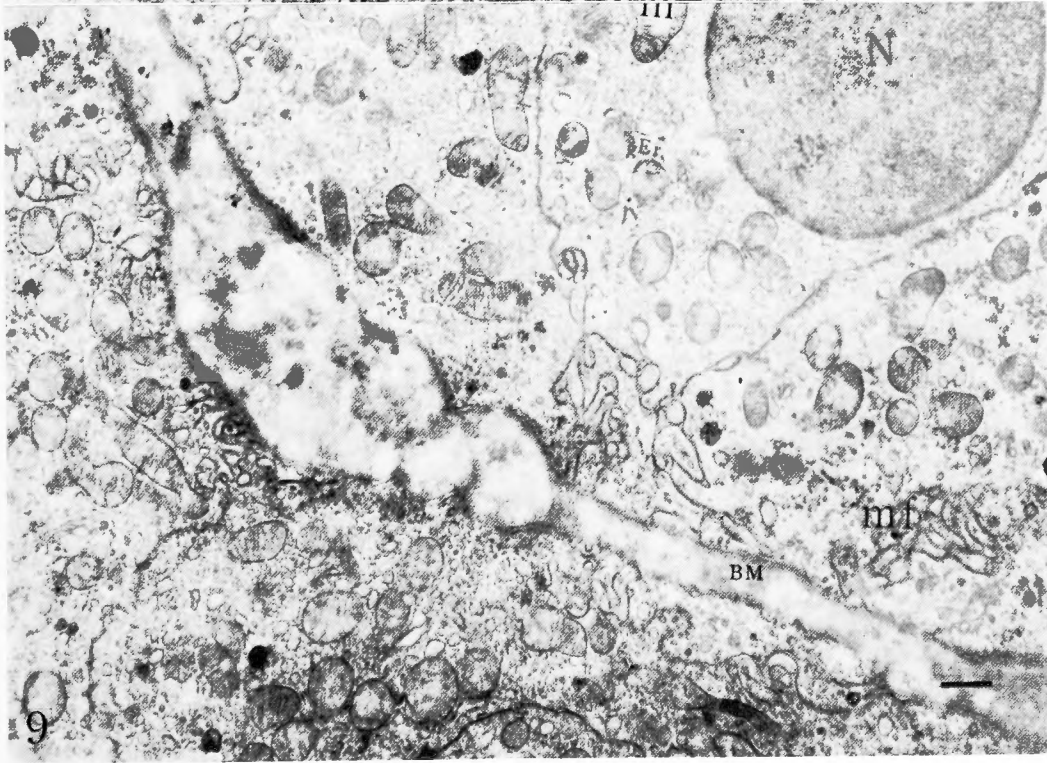
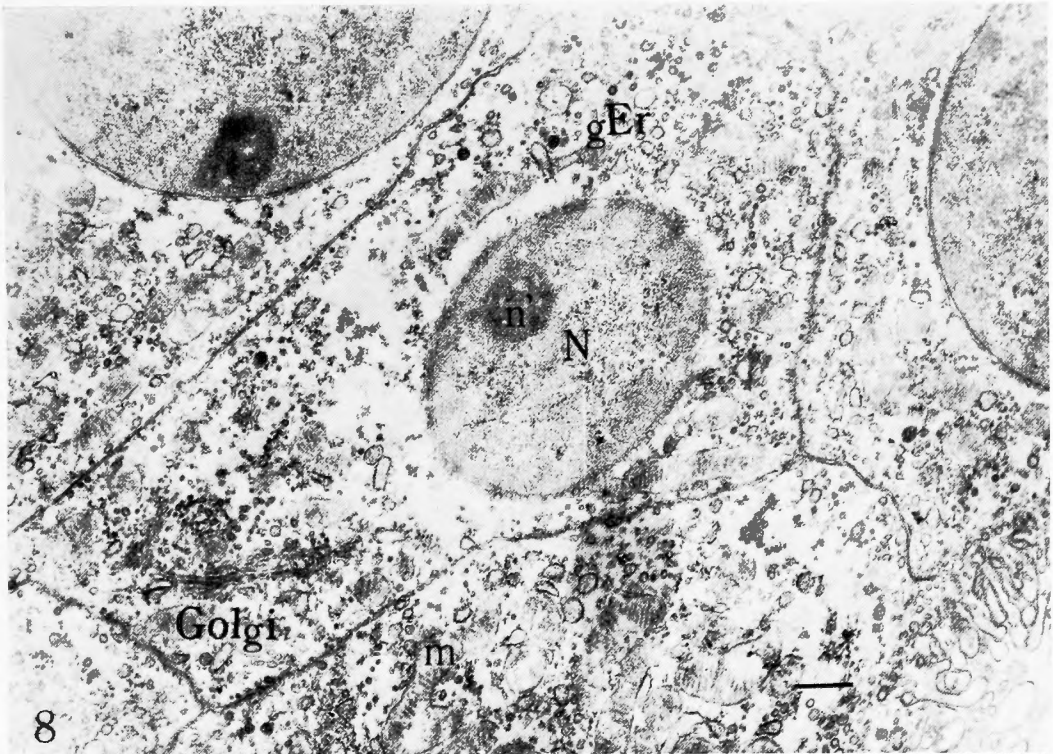
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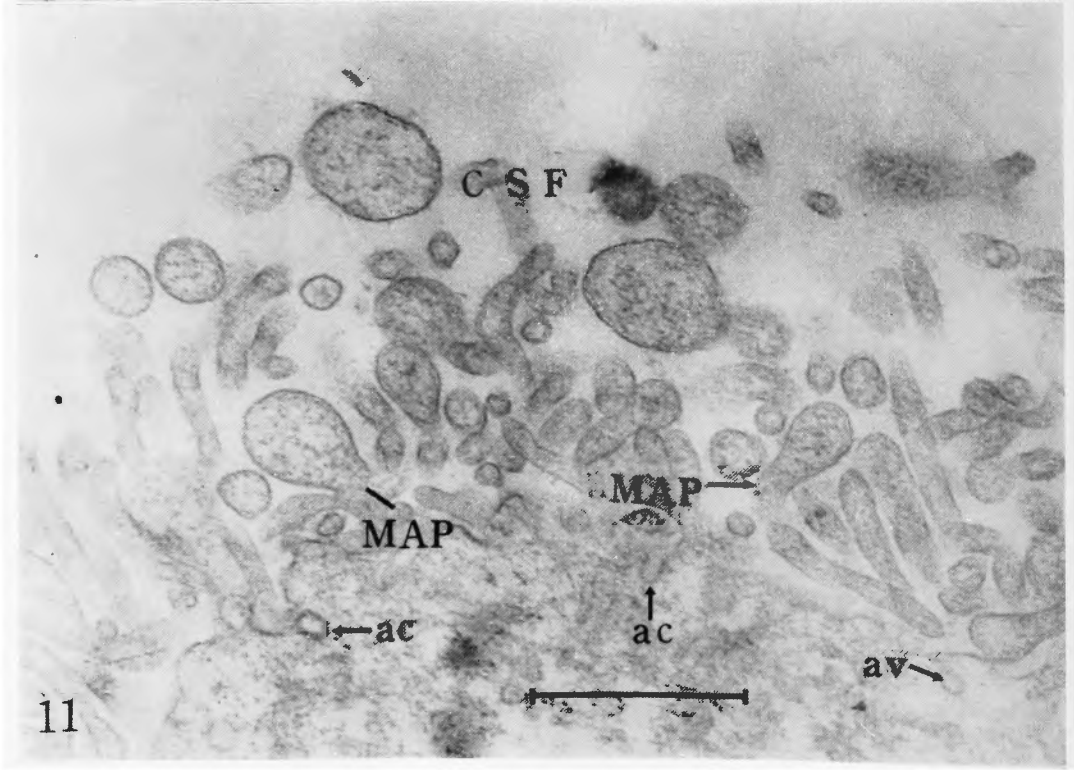
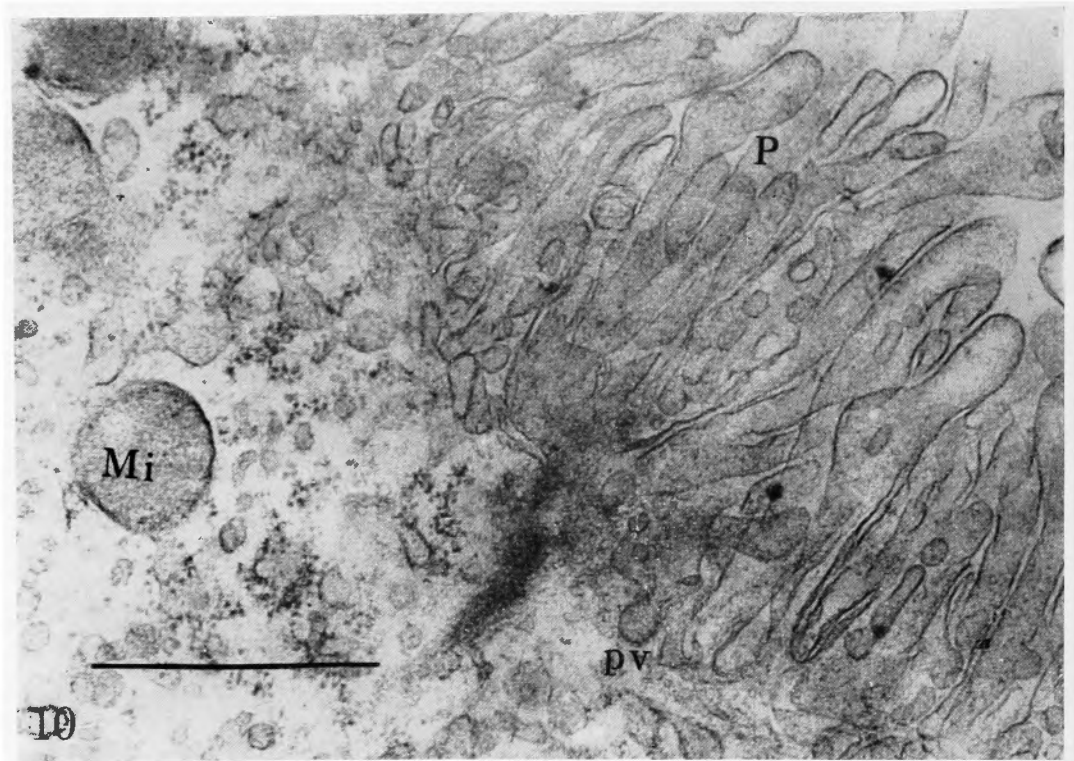
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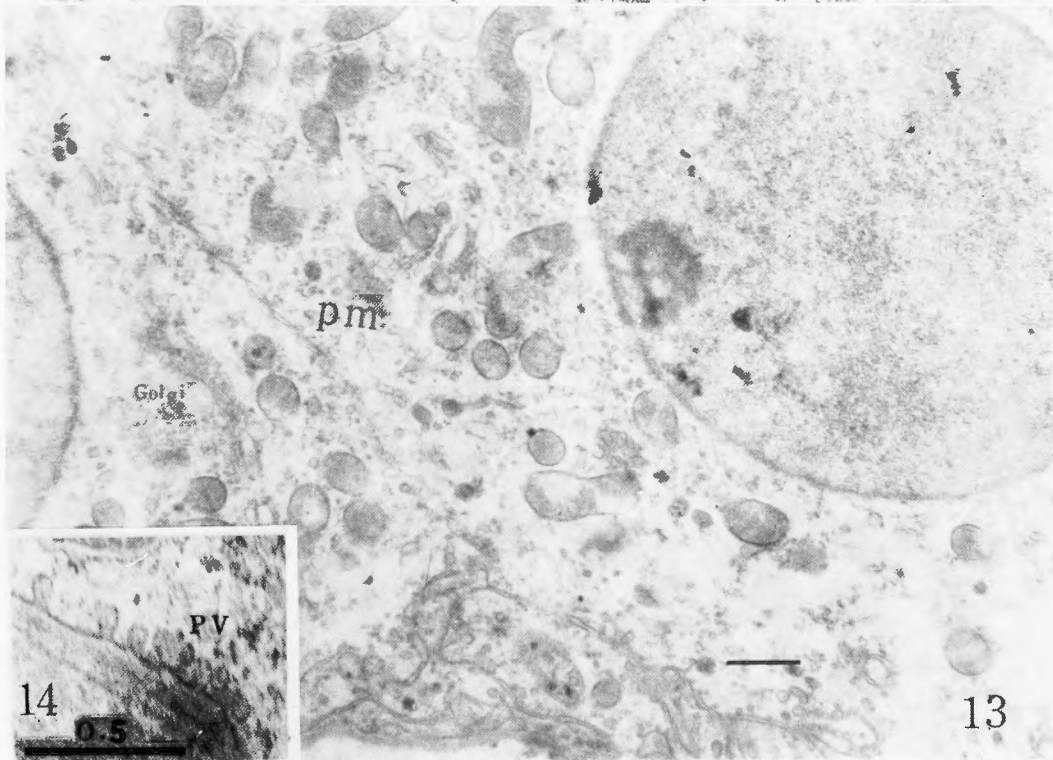
Explanation of electron micrograph

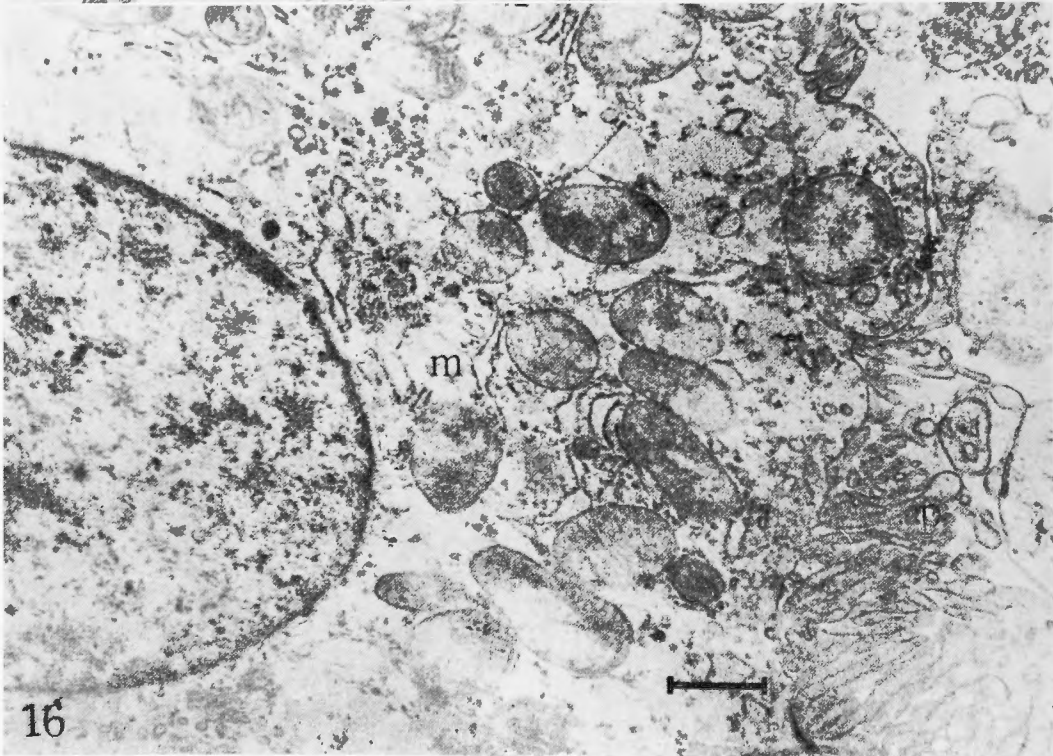
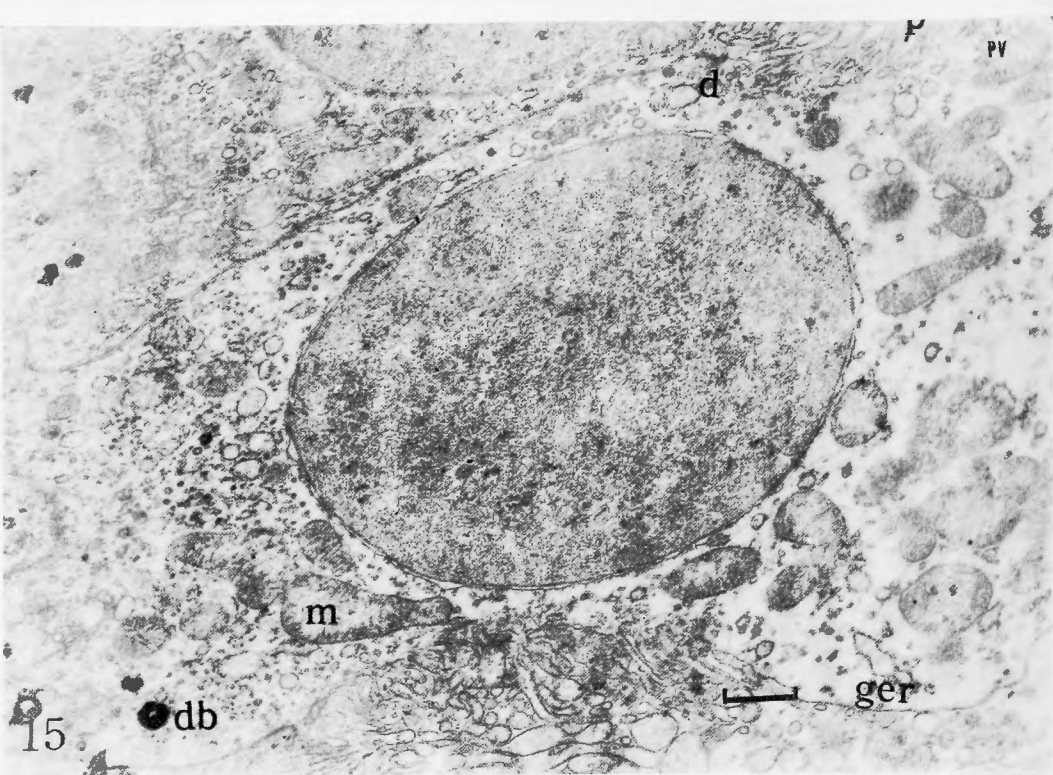
- Fig. 8** Electron micrograph of the normal choroid plexus epithelium of the dog. The nucleus of the epithelium (N) is in the center and upper portion of the field, the basal part of the cell is in the lower left. Rough surfaced endoplasmic reticulum (gEr) is shown in the cytoplasm, and polypoid border is in the right under of the field.
- Fig. 9** Electron micrograph of a basal part of the normal choroid plexus epithelium. The nucleus (N) is at the right upper part of the field. The membrane infolding (mf) is observed in the center and right lower part of the field. Basement membrane (BM) is run from the left upper to the right lower part, along the basal part of the epithelium. Mitochondria (m) are observed in the cytoplasm every where. Collagen fibers (CF) is noticed in the extracellular space.
- Fig. 10** This polypoid border (P) is elongated in the length and enlarged at the apex in the upper part of the field. This specimen was picked from Group A, 24 hours after injury.
- Fig. 11** The extreme portion of the polypoid border is enlarged toward the cerebrospinal fluid space (CSF), as if microapocline secretion was done in this portion (MAP). Apical caveolae (AC) and apical vacuoles are noticed in the upper part of the cytoplasm. This material was taken from Group A, 24 hours after injury.
- Fig. 12** This photograph shows that many spread rough surfaced endoplasmic reticulum was distributed in the cytoplasm near the lateral plasma membrane, and swelled mitochondria (M) was in the right upper of the field. (This specimen was obtained from Group A, 48 hours after).
- Fig. 13** The lateral surface of the plasma membrane (Pm) running with adjacent cell is wound and torn of its way. Golgi complex (Golgi) is in the left lower in the field, Gogi vesicles are developed. (Group A, 24 hours after).
- Fig. 14** Pinocytotic vesicles (PV) are increased along the basal plasma membrane. A line shows 500 m μ . This specimen was obtained from dog of group B, 48 hourr after injury.
- Fig. 15** This picture shows that mitochondria (m) was swelled, small round endoplasmic reticulum was increased in number and the outer layer of the nuclear membrane was disordered slightly. (This specimen was removed 6 hours after injury, from group A.)
- Fig. 16** Swelld mitochondria (m) was disordered at continuous of the cristae and circumference double membrane was ruptured. (Group B, 43 hours after.)
- Fig. 17** This specimen was removed group A, 1 month after head injury, but yet, many spread rough surfaced endoplasmic reticulum are observed in the cytoplasm near the free surface.
- Fig. 18** Hypertrophic Golgi complex is shown in the left of this picture, especially flattened sacs development are noticed. Dence body (DB) is observed near the side. Some mitochondria shows disorder of cristae mitochondriales. (Group A, 12 hours after.)
- Fig. 19** Small vesicles of the Golgi complex (Golgi) are developed in the upper portion cytoplasm of the nucleus. (Group A, 12 hours after.)
- Fig. 20** The density of mitochondrial matrix (M) is increased. A large vacuole is observed in the upper portion cytoplasm near the nucleus, nuclear membrane is disordered on small portion. (Group A, 7 hours after.)

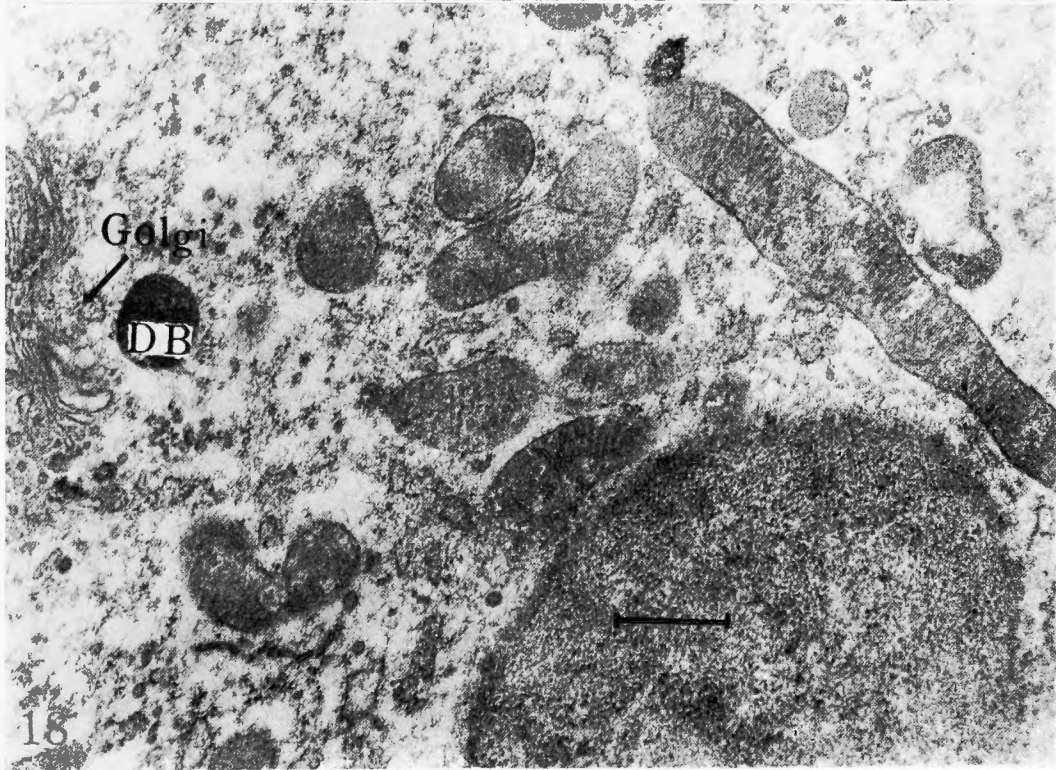
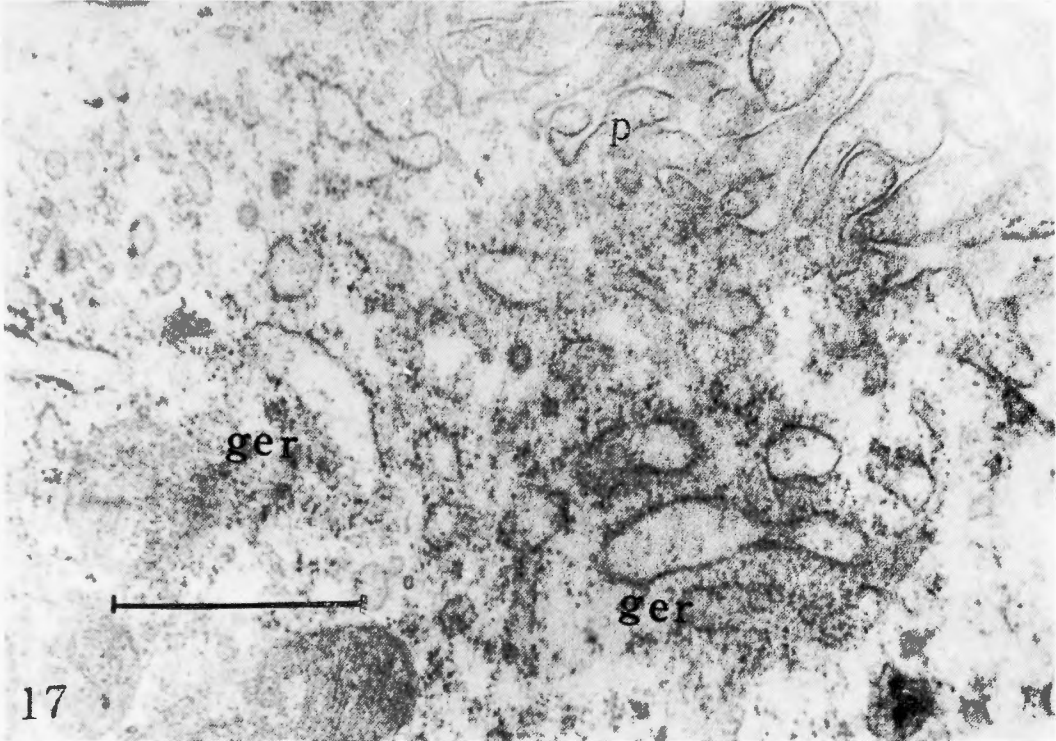
- Fig. 21** This photograph shows the basal part of the epithelial cell (left side in the field) extracellular space, (center in the field) and capillary lying under the epithelium (right side in the field). Basement membrane of the epithelial cell (bm) and collagen fibers are observed.
(Group A, 48 hours after.)
- Fig. 22** This picture is the basal part of epithelial cell. Epithelial cell is in the right upper and capillary is in the left lower part of the field. Enlargement of endothelial pores or fenestratin (F) are seen in the left lower portion which is shown by arrow.
(Group A, 48 hours after.)
- Fig. 23** Upper part of this picture is choroid plexus epithelium and lower part is adjoining capillary wall. Pinocytotic vesicles (PV) are increased on the basal plasma membrane of epithelium and endothelial wall.
(Group A, 27 hours after.)
- Fig. 24** This electron micrograph is the perinuclear portion of the adjoining capillary endothelial cell. Endothelial nucleus (END) is in the center, developed Golgi complex (Golgi) is in the left upper portion of the field.
(Group A, 48 hours after.)

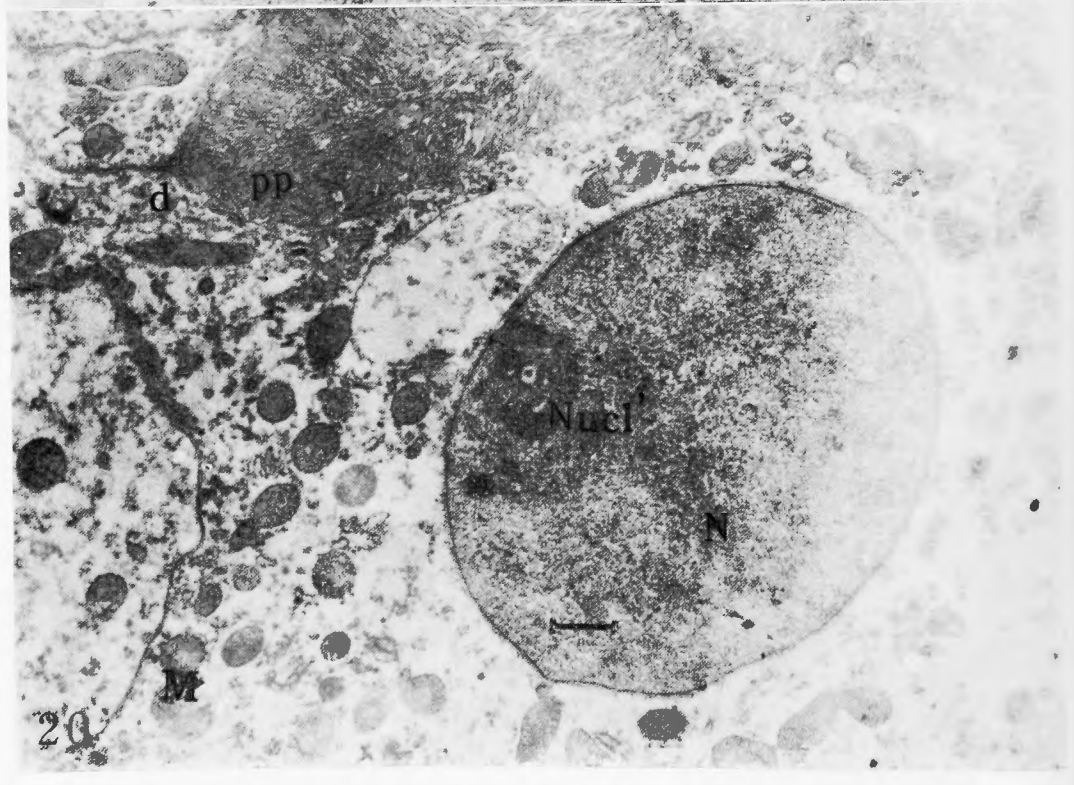
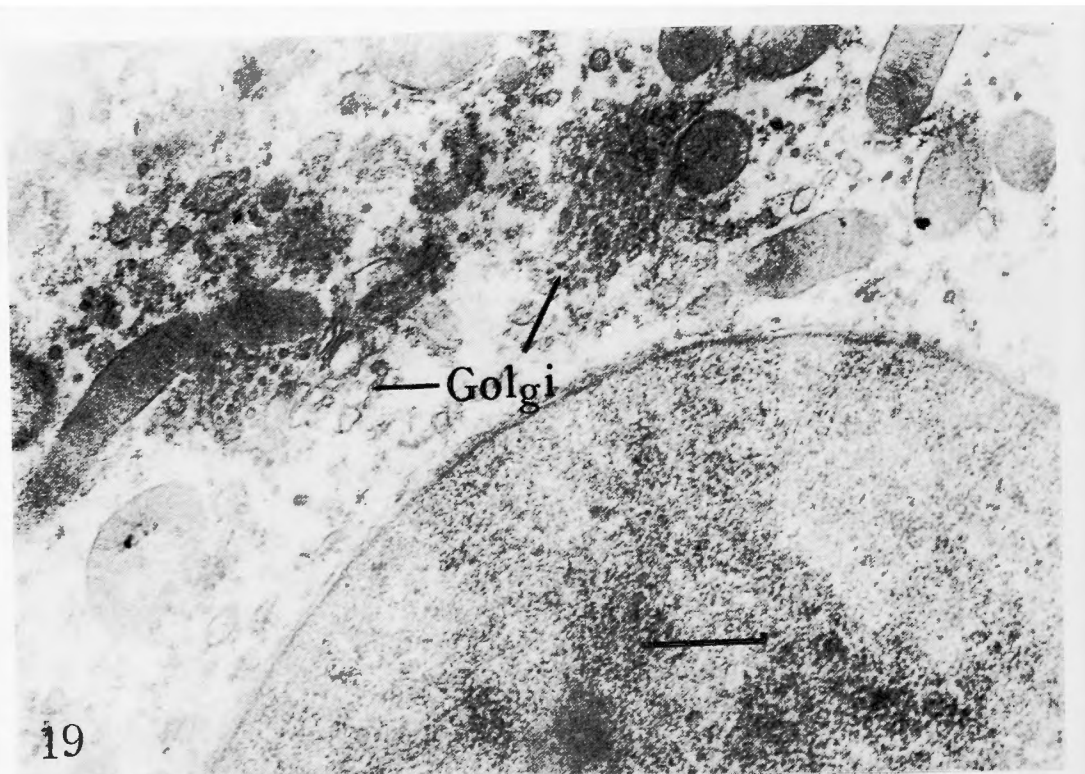


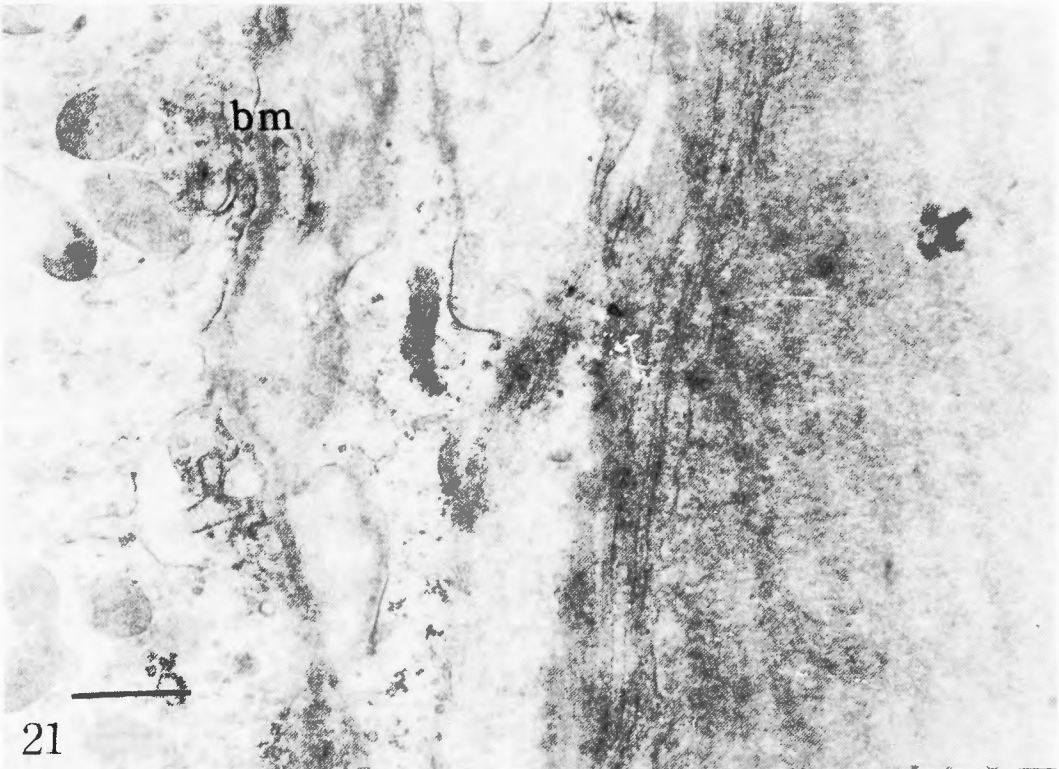


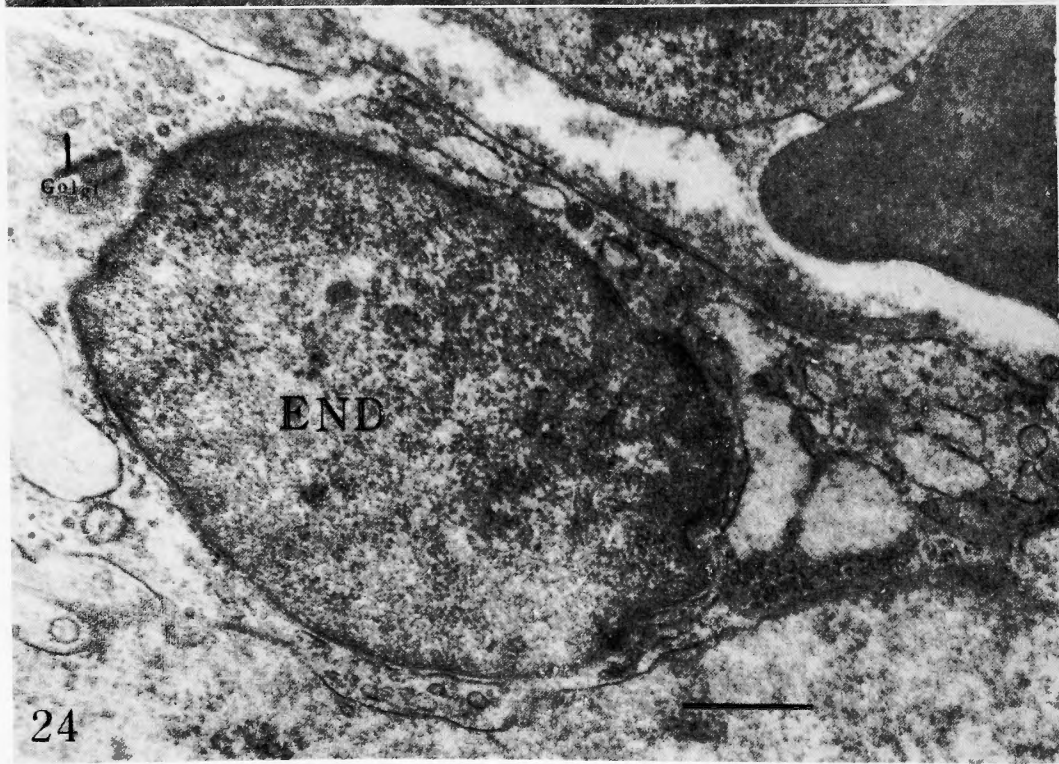
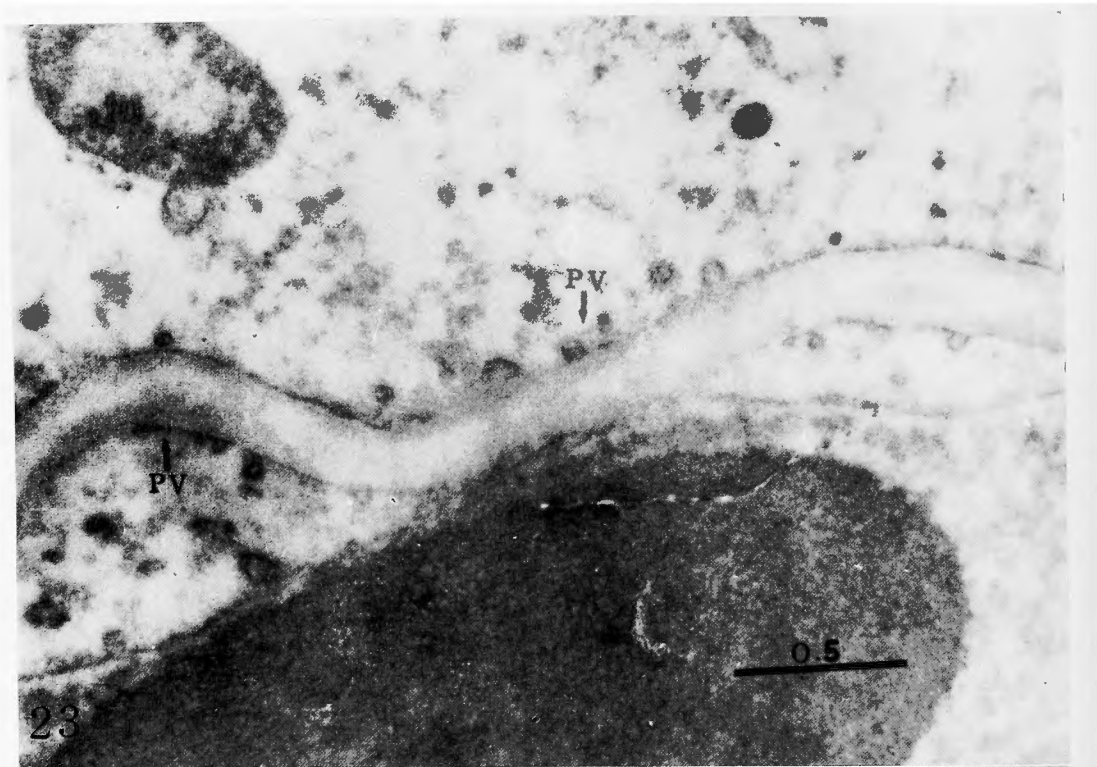












和 文 抄 録

実験的頭部外傷時における脳室脈絡叢の電子顕微鏡的研究

順天堂大学医学部第2外科学教室(指導:田中憲二教授)

新 井 洋 右

雑種成犬, 72頭を用いて3種の方法(A群:一定の加速度を持った振子により頭部を打撃したもの, B群:硬膜外 Balloon 挿入圧迫法によるもの, C群:両側前頭部に骨孔をあけて前頭葉に挫傷を作成したもの)により, 実験的頭部外傷を作成し, 脳及び脳室脈絡叢を光学顕微鏡にて観察すると共に, 第4脳室脈絡叢を電子顕微鏡を用いて観察した。

一方, 東京都監察医務院にて行なわれた頭部外傷剖検例, 8例の脳を光学顕微鏡にて観察し, 脳における病変の広がり及び脳室脈絡叢の変化を検討した結果, 下記の如き所見を得た。

実験的頭部外傷犬の脳室脈絡叢における微細構造の変化では,

(1) 上皮細胞自由面の polypoid border は肥大傾向を示し, A群では外傷後3時間頃からこの所見がみられ始め, 24~48時間で最も顕著となり, 72時間以後は漸次正常に復する。之に伴つて, Apical vacuoles も増加を示し, ほぼ同様の経過をたどつた。B群, C群では肥大傾向出現時期がやや遅れ48~72時間で最も顕著となり, 正常像への復帰も幾分遅れた。

(2) 上皮細胞側壁部限界膜の走行の乱れを観察した。A群では24時間頃からこの傾向が現われ始め, 約2週間持続する。B群, C群ではこの傾向を示す例が更に多くみられた。然しC群では長期に亘つてこの傾向を示したものはなかつた。

(3) 上皮細胞基底部並びに側壁部限界膜の基底部附近に, pinocytotic vesicles の増加傾向を認めた。これはA群で1~3時間頃より増加を示し始め, 72時間以後は次第にその増加傾向は失なわれて行つた。B群, C群もほぼ同様の経過をたどつたが特にB群ではその傾向を示す例がA群よりも多く, 又, 外傷後6週の長期例でも猶この傾向を示すことがあつた。

(4) 上皮細胞内 mitochondria は膨化を示し, 時には脳室側自由縁近くの cytoplasm 内に集積している所見を示すこともあつた。A群では12~72時間に亘つて著しい膨化を示し, 1週以後は正常に復するものが多かつた。之に比べてB群では膨化の現われ始める時

期がやや遅れ, 回復の時期もA群に比べて遅くなり, 長期に亘つて膨化を示す傾向があつた。C群の膨化出現時期はB群とほぼ同じであるが, 回復は早く1週以後膨化を示したものはなかつた。これら膨化した mitochondria を示すものとは別の例で, 外傷初期に matrix の density が高くなつている mitochondria を認めることもあつた。

(5) 上皮細胞内粗面小胞体は, 外傷初期に於て基底膜附近の cytoplasm 内にて増加を示し始め, 次第に cytoplasm 全域に及び, 時間の経過と共に内腔の拡大した大型の小胞体が核上部の cytoplasm 内に散見された。A群でこの小型粗面小胞体の増加は1~3時間頃から始まり, 12時間頃より大型のものが目立ち始め, 24~48時間では拡大した粗面小胞体が原形質のほぼ全域に散見され, 1週以後は之等の所見は次第に失われた。B群における粗面小胞体の変化もほぼA群と同様であつたが小型粗面小胞体の数の増加がA群よりやや長期に亘つた。

(6) Golgi 装置の発達も外傷初期より認められた所見で, A群では1~3時間頃より核下部の cytoplasm 内にて発達を示し始め, 24~48時間頃最も顕著となり(然しこの時期では細胞内の部位的特徴は認められない), 1週に至る迄漸次発達傾向は減弱していつた。

B群, C群では Golgi 装置についての著しい変化は認められなかつた。

(7) 上皮細胞基底面近くにある毛細血管内被細胞の cytoplasm 内に pinocytotic vesicles の増加を認めたが, それはA群で上皮細胞基底膜にみられた pinocytotic vesicles の増加とほぼ一致した経過をたどつた。

頭部外傷剖検例に於ては, 一般に脈絡叢並びに ependymal cell の腫脹, 濁濁を認めたが, 撰択的基底核出血などの例では脈絡叢の変性も可成り高度で脳室周囲の血管障害が推察された。

本稿要旨は第22回及び第24回日本脳神経外科学会及び第64回日本外科学会総会にて発表した。