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# Electron Microscopic Study of Experimental Acute Hypertensive Encephalopathy*

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*Summary.* Electron microscopic examinations were carried out in the brains of cats with acute arterial hypertension produced by intermittent compression of the descending aorta.

The ultrastructural changes included swelling of the astrocytic processes, dilatation of the endoplasmic reticulum, and slight enlargement of the extracellular space of the white matter. Swelling of the mitochondria with disruption of the cristae was sometimes observed. The extracellular space of the gray matter showed no expansion.

The changes in the ultrastructure of the central nervous system in hypertensive and ischemic encephalopathy were found to be very similar. This finding is discussed with special regard to the pathogenesis of acute hypertensive encephalopathy.

*Zusammenfassung.* Es wurden elektronenmikroskopische Untersuchungen am Gehirn von Katzen bei akuter Hypertonie, die durch wechselnde Kompression der absteigenden Aorta erzeugt wurde, ausgeführt.

Die ultrastrukturellen Veränderungen umfaßten Schwellung der Astrocytenausläufer, Erweiterung des endoplasmatischen Reticulums, und geringe Erweiterung des Extracellulärraumes des Gehirnmarks. Manchmal wurde auch Schwellung der Mitochondrien mit Zerstörung der Cristae beobachtet. Der Extracellulärraum der Gehirnrinde zeigte keine Erweiterung.

Die Veränderungen in der Ultrastruktur des Zentralnervensystems werden im Hinblick auf die Pathogenese der hypertonischen Encephalopathie diskutiert.

**Key-Words:** Hypertensive encephalopathy—Ischemic-anoxic encephalopathy—Edema anoxic—Electron microscopy—Astrocytic swelling.

OPPENHEIMER and FISHBERG in 1928 introduced the term "hypertensive encephalopathy" to describe the functional and histological changes in the brain associated with arterial hypertension. Post mortem examination of the brains of hypertensive patients and results of animal experiments have shown that the severity of clinical manifestation of hypertension is directly related to an abnormal increase of water in the brain (OPPENHEIMER and FISHBERG; ALAJOUANINE; THUREL). However, no general agreement has been reached with regard to the edema formation and the pathogenesis of hypertensive encephalopathy. In the past, morphological distinction was made between extracellular brain edema and intracellular brain swelling, but in light of modern investigations, such a distinction is no longer valid (BAKAY and LEE, 1965). It is, however, generally accepted that cerebral edema varies a great deal as far as the location and chemical composition of the excess fluid is concerned. In most cerebral edemas the increase in

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brain water and solutes is associated with an increase in the permeability of the blood-brain barrier. The few data available on barrier permeability in hypertensive encephalopathy resulted in controversial conclusions. Some investigators believe that high arterial pressure damages the vascular wall; this results in the exudation of plasma into the surrounding brain tissue (MOYER *et al.*, 1952; FEIGIN and POPOFF; HARA). Others maintain that the muscular layer of the arterioles reacts to the increased intraluminal pressure by constriction or spasm and that hypertensive encephalopathy is a consequence of ischemia (BAYLISS; FLOREY; FOG; MEYER *et al.*; BYROM; RODDA and DENNY-BROWN). Since light microscopy is inadequate to detect the subtle changes in membrane permeability and tissue hydration, and since the pathogenesis of hypertensive encephalopathy cannot be elucidated in the complicated chronic cases of hypertension, the present investigations were carried out to study the ultrastructural changes in the brain of cats rendered acutely hypertensive and to correlate these changes with alterations possibly promoted by ischemia.

## Material and Methods

Adult cats of 2.9—3.6 kg body weight were used. Under Nembutal anesthesia, tracheostomy was performed, and the animal was placed on artificial respirator. The respiratory rate was regulated at 14—16 per minute with an air pressure of 14—18 Hg mm. The right common carotid artery was exposed, and a cannula was inserted in the direction of heart. The blood pressure was continuously monitored by a Sanborn electro-manometer after the artery was ligated distal to the cannula. Acute hypertension was achieved through intermittent interruptions of the blood flow by compressing the descending thoracic aorta as described by LEE and OLSZEWSKI. Upon opening the chest, a loop of suture silk was passed around the aorta close to the diaphragm. The two limbs of the loop were threaded through a glass tube. When these limbs were pulled, the aorta was drawn up by the loop firmly against the lower end of the tube, and thus, the blood flow was interrupted, This maneuver was carried out for 10—15 sec at 5-min intervals. The duration of the experiments ranged from $1^1/_2$—3 hours. Toward the end of the experiment, perfusion-fixation with glutaraldehyde was carried out as described previously (LEE and BAKAY, 1965). The sections were stained with lead citrate and covered by carbon film. As our experiments were designed to produce acute arterial hypertension in the left hemisphere and ischemia in the right, the following tissues obtained from both sides were processed for studies with a JEM-T6S electron microscope: frontal cortex and white matter, head of caudate nucleus, thalamus, cerebellar cortex and white matter, and area postrema.

## Observations

The average initial arterial pressure was 60/50 Hg mm. The systolic pressure rose to a maximum of 200 Hg mm, following the compression of the aorta, and returned to normal upon release of the vessel. However, after a few repeated compressions, the resting pressure became higher; it was usually maintained at a level of 100—125 Hg mm systolic pressure (Fig. 1).

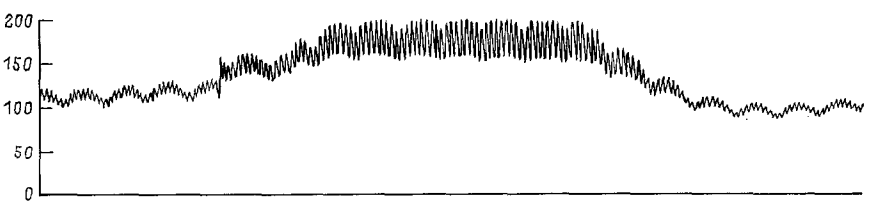


Fig. 1. A sample of recorded blood pressure (Hg mm) of right carotid artery obtained before, during, and after compressing the descending thoracic aorta for 10—15 sec at 5-min intervals

The gross appearance of the perfused brains was not remarkable. They were firm and pale with no overt sign of swelling.

Ultrastructural changes were observed in both the hypertensive and the supposedly ischemic sides involving all selected areas. Surprisingly enough, the changes were similar in the two hemispheres. The capillary wall appeared intact without any enlargement of the space between the endothelial cells. However, the pinocytotic activity seemed to be increased as evidenced by the formation of numerous large vesicles in the endothelial cytoplasm (Fig. 2). The basement membrane was

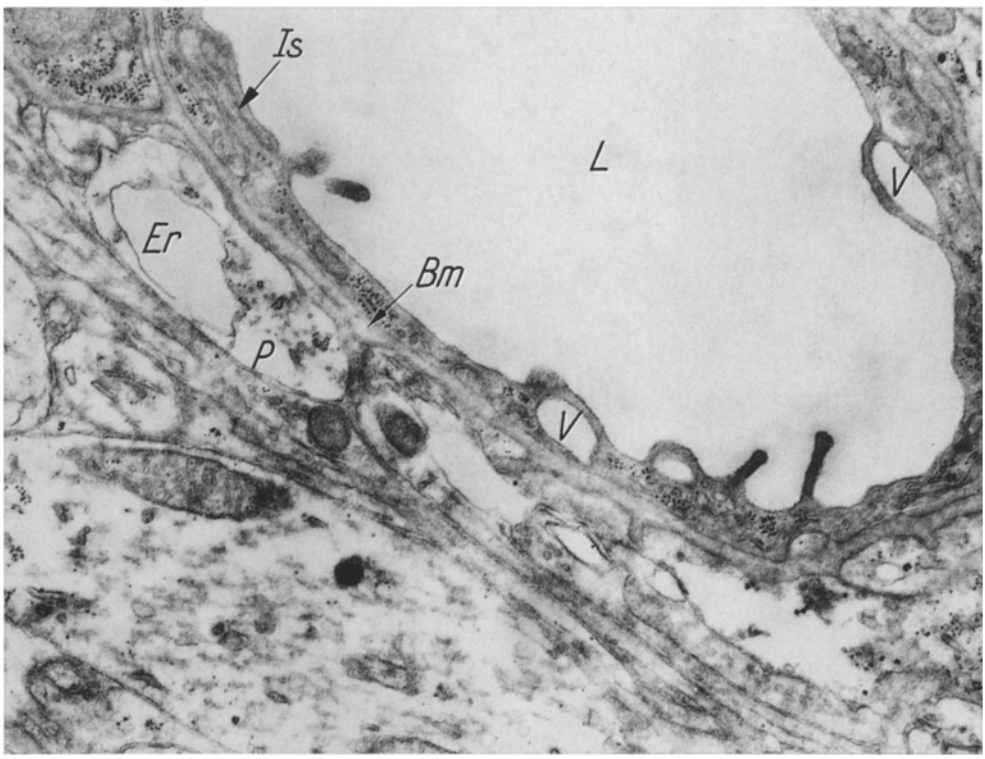


Fig. 2. Caudate nucleus. The intercellular space (*Is*) between the endothelial cells of a blood capillary is intact, but there are many large pinocytotic vesicles (*V*) inside the endothelial cells. The basement membrane (*Bm*) is slightly widened, and its electron density is reduced. The perivascular astrocytic processes (*P*) are swollen with distended ER; however, the intercellular space between the processes is not enlarged. *L* lumen of artery (×11,100)

widened, and its electron density was reduced (Figs. 2 and 3). The perivascular astrocytic processes were swollen to a varying degree, but their endoplasmic reticulum (ER) was definitely distended (Figs. 2 and 3). The plasma membrane of these processes was intact, and the intercellular space remained in the 150—200 Å range. The swollen astrocytic processes with distended ER were also found in the neuropil and among the myelinated nerve fibers of the white matter (Fig. 4). In the neuropil of the thalamus or caudate nucleus, some dendrites were swollen (Fig. 5). Here the ER was also distended. Changes in mitochondria were sometimes seen;

these consisted of swelling and disruption of cristae (Fig. 6). The mitochondrial changes occurred predominantly in the myelinated axons and the oligodendroglial processes of the white matter (Figs. 6 and 7). In the white matter, slight enlargement of the intercellular space was observed (Figs. 3 and 6). This was never seen in the gray matter (Figs. 2 and 4). The nerve cells did not show any abnormality.

## Discussion

Both acute and chronic hypertension, with or without functional changes, was found to be associated with cerebral edema (Alajouanine; Thurel). Moyer *et al.*

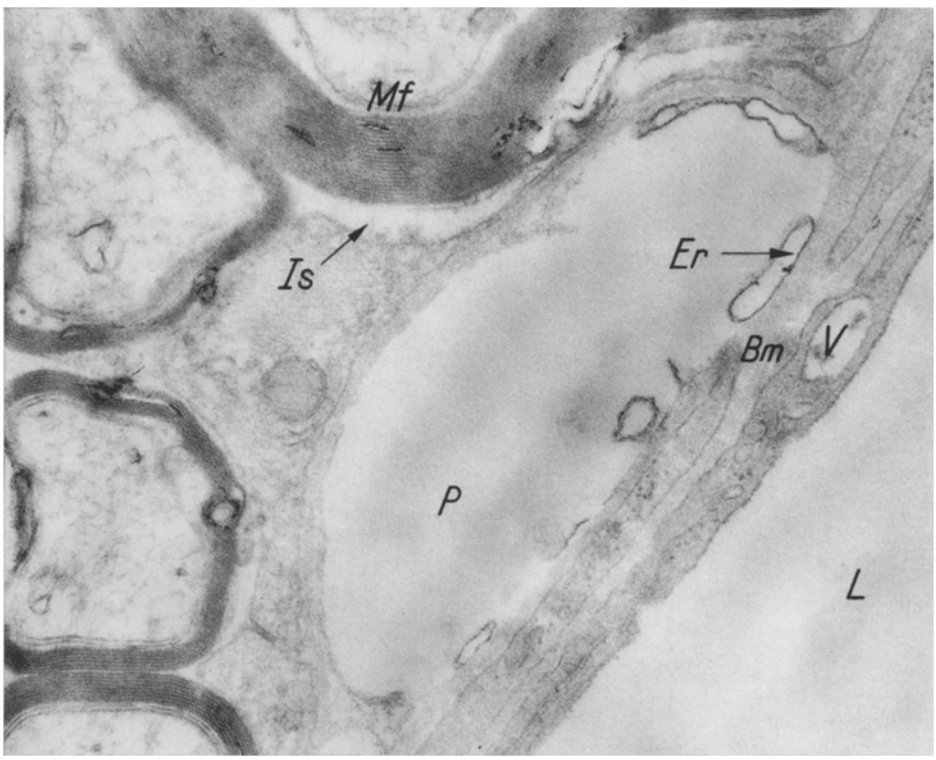


Fig. 3. Cerebellar white matter. The widened basement membrane (*Bm*) is in close contact with a hydrated astrocytic process (*P*). The ER is moderately distended and is pushed against the basement membrane. The intercellular space (*Is*) is slightly enlarged in the vicinity of myelinated fibers (*Mf*). *L* lumen of capillary (×18,000)

(1952) postulated that hypertensive encephalopathy is caused by a relative relaxation of the muscle tone of the vascular wall in the presence of increased arterial pressure. The diminished vascular tone allows transmission of pressure to the capillary bed with subsequent transudation of fluid into the surrounding brain tissue. Feigin and Popoff found PAS-positive material, similar to plasma constituents, in the perivascular space of hypertensive brains. Hara observed by means of light and electron microscopy that hypertensive cerebral edema is extracellular, resulting from destruction of the vascular wall. These studies suggest that the edematous

changes of hypertensive encephalopathy are due to exudation of plasma from the intravascular lumen into the extravascular space because of a breakdown of the blood-brain barrier or a gross destruction of the vascular wall. However, most of these observations were made in longstanding, chronic arterial hypertension that furnishes no information about the initial changes in tissue hydration.

We found that although the astrocytic processes are swollen, their limiting membrane is intact, and the intercellular space in the neuropil remains 150—200 Å (Figs. 2 and 4). The appearance of the hydrated cytoplasm is clear. The capillaries do not change except for the numerical increase of pinocytotic vesicles. It appears

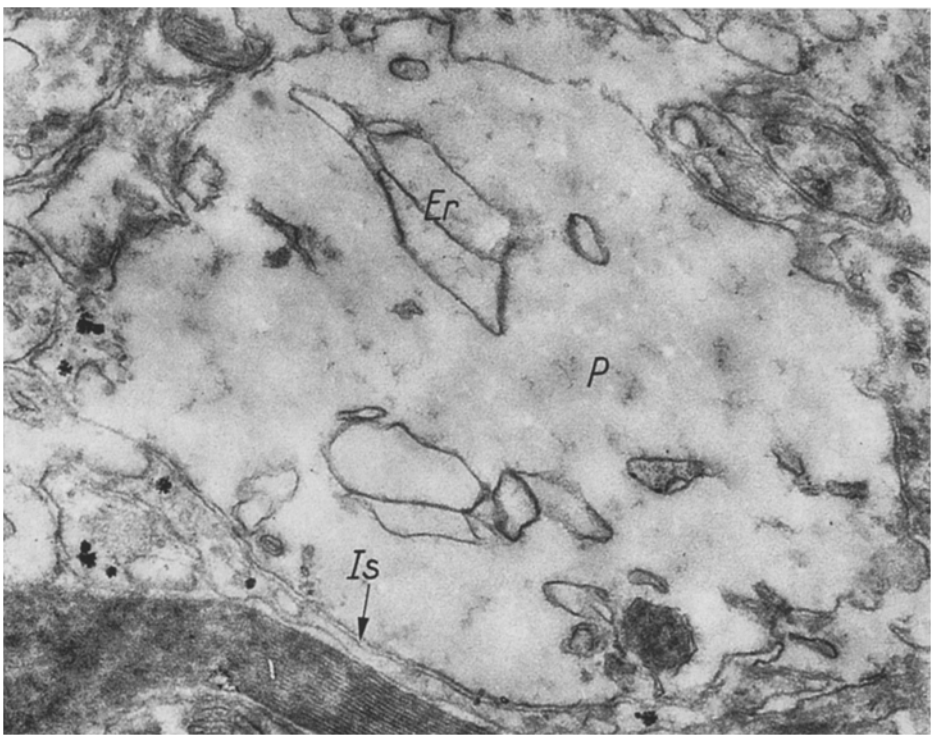


Fig. 4. Cerebellar cortex. A swollen astrocytic process (*P*) contains distended ER. The intercellular space (*Is*) is not enlarged (×16,000)

that the swelling in the neuropil is intracellular rather than extracellular, at least at the early stages of acute hypertension. Slight enlargement of the intercellular space has been observed only in the white matter (Figs. 3 and 6). The changes in hypertensive encephalopathy are comparable to, but less pronounced than, those secondary to cold injury and electric coagulation (Torack *et al.*; Lee and Bakay, 1966; Bakay and Lee, 1966). The PAS-positive substances found in the perivascular space (Feigin and Popoff) are not necessarily proof of extravasation of the blood plasma, since such substances are present in the cytoplasm of normal glia cells (Lumsden). Our observation that the initial phase of the cerebral swelling in hypertension takes place in the astrocytes is suggestive of an increased perme-

ability of the blood-brain barrier and of the astrocytic plasmalemma to water and electrolytes, but not necessarily to large molecules such as plasma proteins.

It is interesting to note that our findings show a similarity of ultrastructural changes between the left cerebral hemisphere rendered hypertensive and the right hemisphere which is supposedly ischemic from the ligation of the right common carotid artery. It can be argued that the hypertensive side is also ischemic or that the ischemic side is actually hypertensive through collateral circulation. Since the circle of WILLIS is known to be a poor pressure equalizer in acute ischemia of one

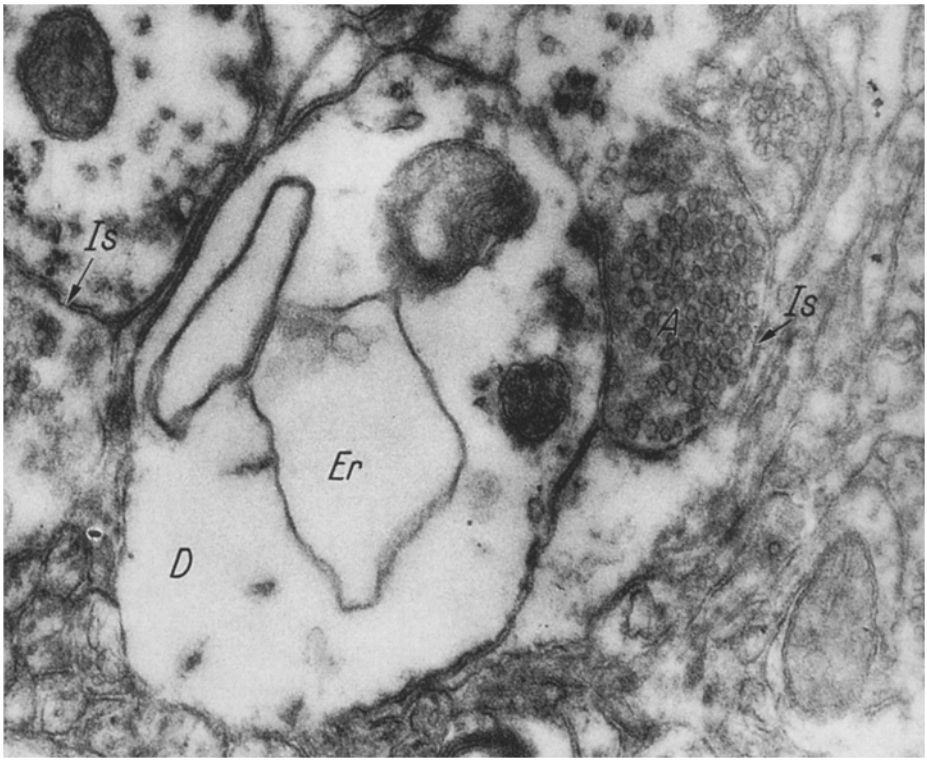


Fig. 5. Thalamus. A swollen dendrite (*D*) is in synaptic relation with an axon terminal (*A*). Note distended ER in the dendrite. The intercellular space (*Is*) of the neuropil is not enlarged (×21,700)

hemisphere (DICKINSON, 1961b), it is unlikely that the relatively ischemic hemisphere on the side of the ligated carotid artery would be supplied by the same amount of blood from the other side. It is much more likely that the identical changes seen in both hemispheres are caused by ischemia.

Ischemia as a sequel to hypertensive encephalopathy has been reported by many investigators. This could be explained by the assumption that the muscular layer of the arterioles reacts to increased intraluminal pressure by contraction, although the Bayliss effect is still a matter of controversy as far as the cerebral vasculature is concerned. Both FLOREY and FOG observed tonic changes of the pial arteries in response to an increased arterial pressure. MEYER *et al.* demonstrated

a similar constriction of small cerebral arteries. According to BYROM, and RODDA and DENNY-BROWN, the constriction may be accompanied by spasm. All these reports indicate that the muscular contraction and subsequent narrowing of the vascular lumen with an increase of the peripheral resistance are common to most cases of hypertension. Based on the principles of physics, reduction of the arterial lumen to half of its normal diameter would diminish the volume of blood flow through the artery to $^1/_{16}$ of its previous level (CORDAY *et al.*). Therefore, even the slight constriction of the vascular wall of hypertensive patients would significantly

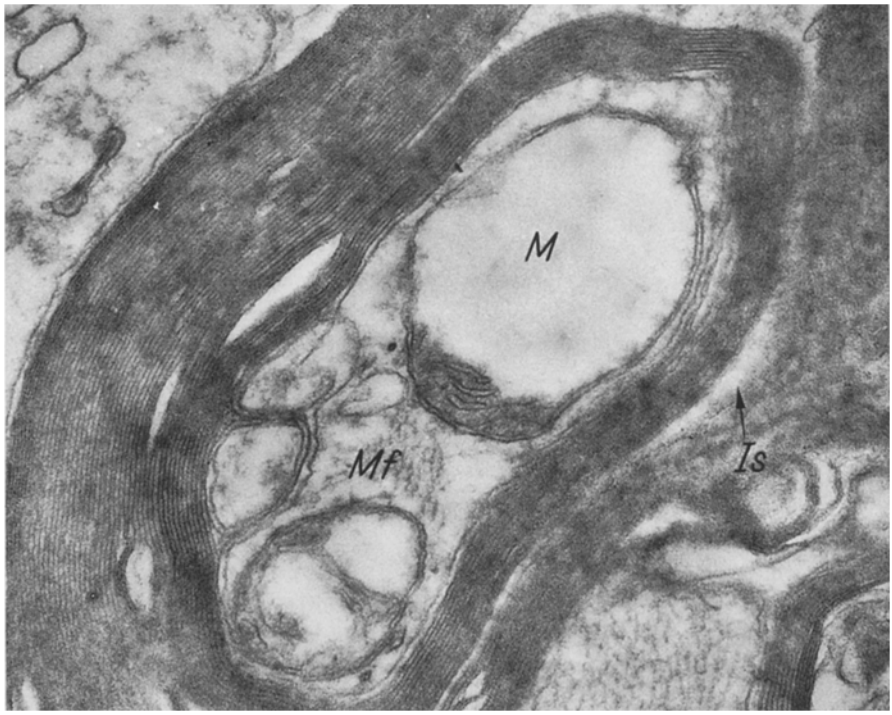


Fig. 6. Cerebellar white matter. A swollen mitochondrion (*M*) with disrupted cristae is located inside a myelinated axon (*Mf*). The intercellular space (*Is*) is moderately enlarged (×30,800)

reduce the volume of blood flow to the brain tissue and result in cerebral ischemia. That hypertension, in itself, is related to the production of cerebral ischemia has been emphasized by RONNOV-JESSEN, and MARSHALL, Furthermore, REINMUTH and EDMUNDO measured the cerebral blood flow of relatively young patients with hypertension and infarction of brain and observed a 50% reduction. A higher rate of reduction was expected in older patients. DICKINSON (1961a) found that the decrease of blood flow through the medullary vessels was proportionate to the degree of hypertension. The relationship between arterial hypertension, reduction of blood flow, and cerebral ischemia seems, therefore, to be well estabished. Our observation of similar ultrastructural changes suggest a correlation between arterial hypertension and cerebral ischemia, although the exact degree of vascular constriction and ischemia in the two hemispheres could not be ascertained on account of the unavoidable perfusion-fixation procedure.

With regard to the effect of ischemia, it is uncertain whether or not anoxia is solely responsible for the edematous changes. Although it is possible that histological changes of hypertensive encephalopathy are the result of ischemic anoxia, final conclusions cannot be reached until the relative importance of anoxia, hypercapnia, and other concomitant changes is properly evaluated at the electron microscopic level. Our present findings suggest that anoxic edema of the type seen in hypertensive encephalopathy can be induced only by the combination of oxygen deprivation and $CO_2$ accumulation.

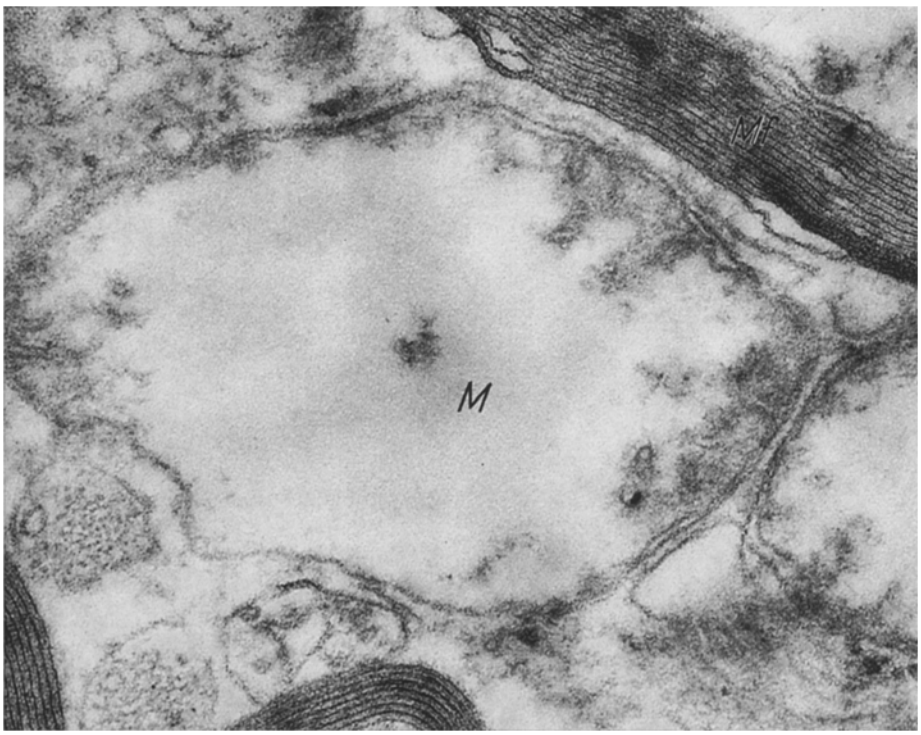


Fig. 7. Cerebellar white matter. A swollen mitochondrion (*M*) with disrupted cristae is seen in an oligodendroglial process. *Mf* myelin sheath (×35,000)

In our experiments, swollen mitochondria were found with disruption of the cristae (Figs. 6 and 7). This may indicate changes in the oxidative enzyme system. Mitochondrial abnormalities have been observed in ischemic-anoxic encephalopathy (BECKER), in conjunction with a decrease in the oxygen and glucose uptake and loss of some oxidative enzymes (MACDONALD and SPECTOR; ATKINSON). It is, therefore, interesting to note that a reduction of glucose utilization and oxygen uptake has also been found in patients with hypertensive encephalopathy (REINMUTH *et al.*; MOYER *et al.*, 1953). It seems that in this respect, a similarity exists between ischemic-anoxic encephalopathy and hypertensive encephalopathy.

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