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Ultrastructure of Capillary Plaque-Like Degeneration in Senile Dementia

Mechanism of Amyloid Production

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Summary. By electron microscopy cerebral cortex taken post portem from a case of senile dementia was examined especially with regard to „Drüsige Entartung der Hirnarterien" (Scholz, 1938).

The basement mebrane of capillaries was irregularly enlarged, and had produced numerous amyloid fibrils and collagen. In the cytoplasm of the endothelial cells amyloid fibrils were also observed. Amyloid fibrils of the core of senile plaques would seem to be produced by the basement membrane of the blood vessels.

Key words: Senile Plaque — Amyloid Fibril — Blood Vessel.

Introduction

Primary brain atrophy of senile dementia and presenile dementia, such as Alzheimer's disease and Pick's disease have been studied and the senile plaque is the most important finding of the senile changes (Braunmühl, 1957).

Electron microscopic observations of the senile plaque have been reported by Kidd (1963, 1964), Terry *et al.* (1963, 1964), Schlote (1965), Suzuki *et al.* (1967) and Wiśniewski *et al.* (1970).

In the present study, we found that amyloid fibrils were made by the blood vessels.

Report of a Case

K. H., a man of 68 became forgetful and burst into a passion for a trivial matter when aged 61. The symptoms progressed and he became disorientated and unable to care for himself. Aged 67, he became incontinent of feces and urine. On admission physical examination was not contributory. He was euphoric, lacked control and was remarkably excited. He lost his memory and revealed the Korsakow's syndrome. Aged 68 he was demented and died of emaciation. He did not have hypertention nor any other previous illness. There was no hereditary disease in his family history.

Material and Methods

Parts of the cerebral cortex were immersed post mortem in 4% formaldehyde solution: they were cut into small pieces and washed in phosphate buffer pH 7.4 for 10 min, then immersed for 2 hrs in 2% osmium tetroxide in phosphate buffer of pH 7.4. The tissues were dehydrated in alcohol and embedded in epon. Thick sections were stained with toluidine blue for light microscopy. Thin sections 300—500 Å were stained with uranyl acetate and lead acetate solutions, examined with a Hitachi 11 A electron microscope. Routine examination by light microscopy of facts of the brain was carried out.

Results

The brain weighed 1060 g. The basal and medial arteries showed slight atheroma. The diencephalon was remarkably atrophic and ventricles dilated.

The cerebral cortex showed diffuse loss of the nerve cells: some remaining nerve cells were atrophied. Abundant senile plaques were demonstrated in the temporal, frontal and parietal cortex and especially in Ammon's horn. Alzheimer's neurofibrillary changes were demonstrated in same areas. Granulo-vacuolar degeneration was found in the pyramidal cells of Ammon's horn. The findings were those of senile dementia. The main finding was that the capillaries usually run through the senile plaques or the boundary of the senile plaques. In toluidine blue preparations, amorphous material had accumulated in the perivascular spaces, especially in Ammon's horn. The senile plaques were less intensely stained than the surrounding tissue.

Alzheimer's neurofibrillary tangles were observed by the electron microscope in the cytoplasm of the nerve cells and consisted of many closely packed fibrils (Fig.1).

The core of the senile plaques consisted of amyloid fibrils surrounded by the cellular perikarya, axons and dendrites filled with neurofibrils and dense bodies (Fig.2).

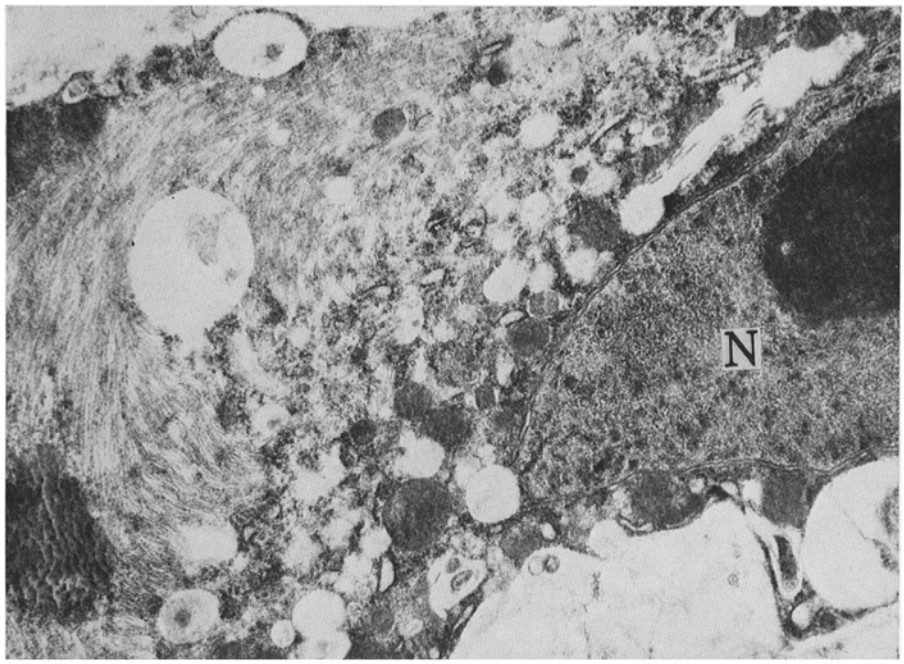
The capillaries near or within the plaques had a thick, tortuous basement membrane. Amyloid fibrils occurred in the basement membrane, and extended from it radially into the parenchyma and also into the endothelial cytoplasm. In some vessels, the lumen was narrowed and occluded (Fig.3). The basement membrane contained many collagen and amyloid fibrils which extended externally (Fig.4). All the basement membrane which produced amyloid fibrils was irregularly thickened or interrupted. The process of amyloid production was confirmed by finding amyloid fibrils in the basement membrane and extending from it into the parenchyma and the endothelial cell cytoplasm (Fig.5). Thickened basement membranes which were separated from blood vessels produced numerous amyloid fibrils (Fig.6) and thick amyloid fibrils were randomely interwoven into stellate formations (Fig.7). Individual fibrils were approximately about 100 Å in diameter.

Discussion

The clinical and histopathological findings of this case were consistent with those of senile dementia: the senile plaque is the most consistent histopathological senile change. However, how is the senile plaque produced ? Various theories, such as the neuron theory, glia theory, blood vessel theory and amyloid deposit theory have been proposed.

Luse *et al.* (1964) examined plaques by electron microscopy in a biopsy of the frontal cortex of a patient with Alzheimer's disease. They upheld the neuron theory; the senile plaques are composed of a twisted mass of varicose neuronal process that contain numerous small dense abnormal mitochondria, dense bodies and microvesicles. Gonatas *et al.* (1967) also supposed the neuron theory.

Scholz (1938) reported the plaque-like degeneration of arteries and capillaries (drüsige Entartung der Hirnarterien). He concluded that the core of senile plaque consisted of material which permeated from the blood vessels. The reports



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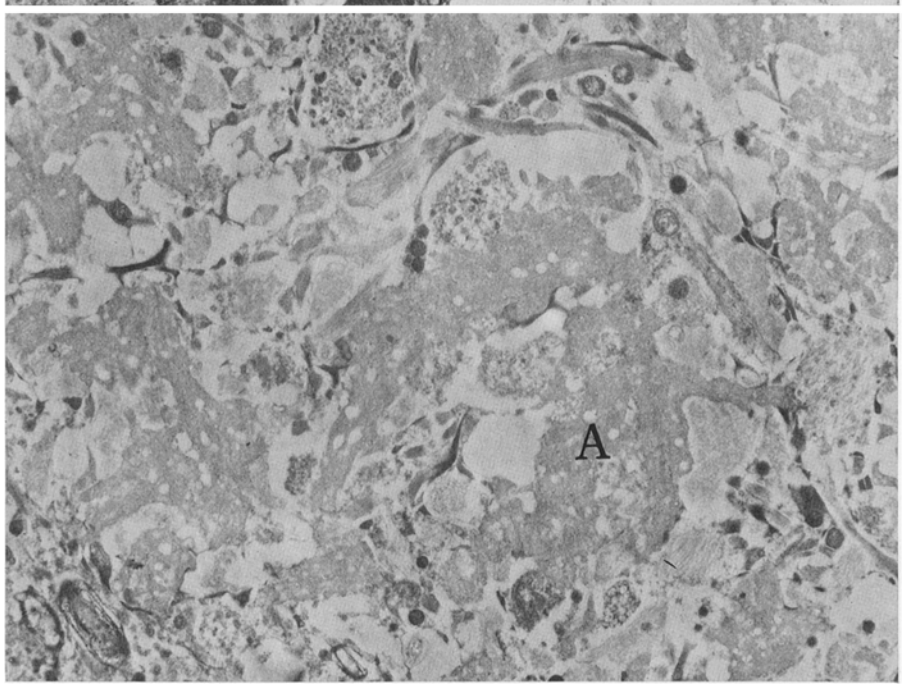

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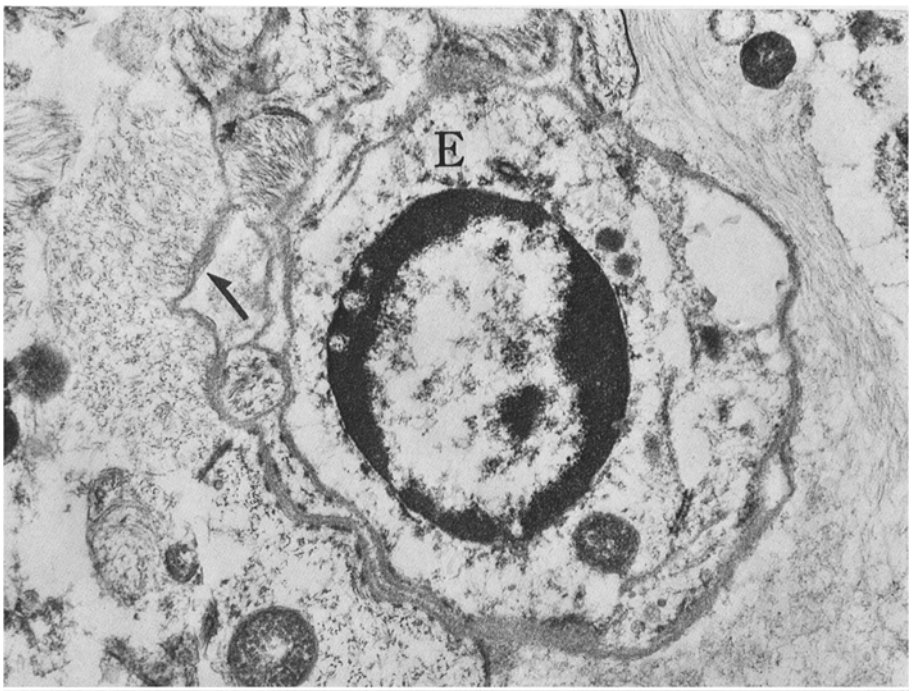
Fig. 1. Pyramidal nerve cell of the hippocampus. The Alzheimer's neurofibrillary tangle consisted of fibrils about 200 Å thick. (*N*) nucleus. ×13000

Fig. 2. Senile plaque in the hippocampus. The core consists of amyloid (*A*). The cellular perikarya, axons and dendrites filled with neurofibrils and dense bodies surround the core. ×4000



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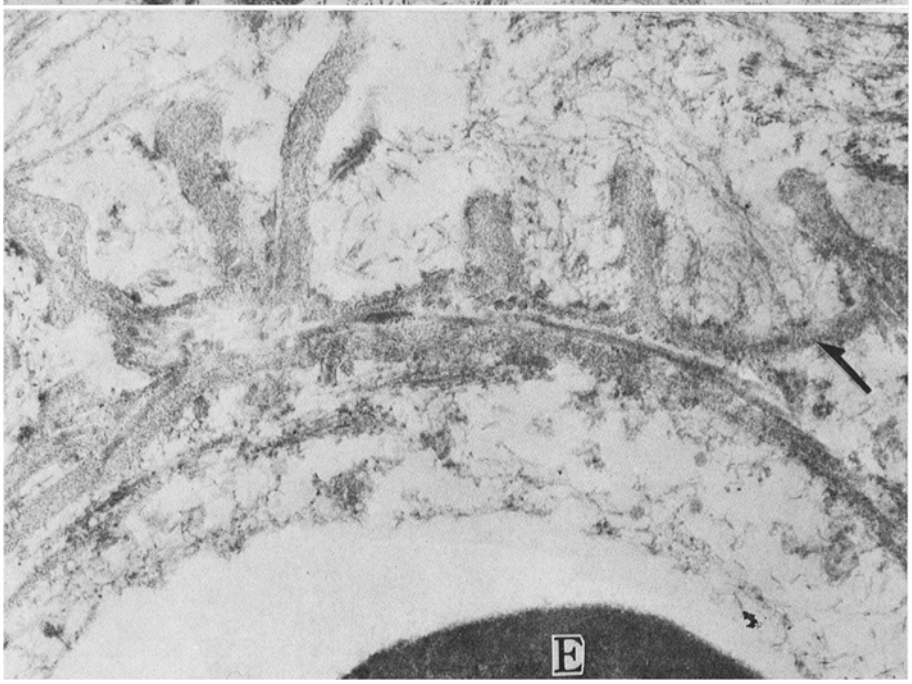

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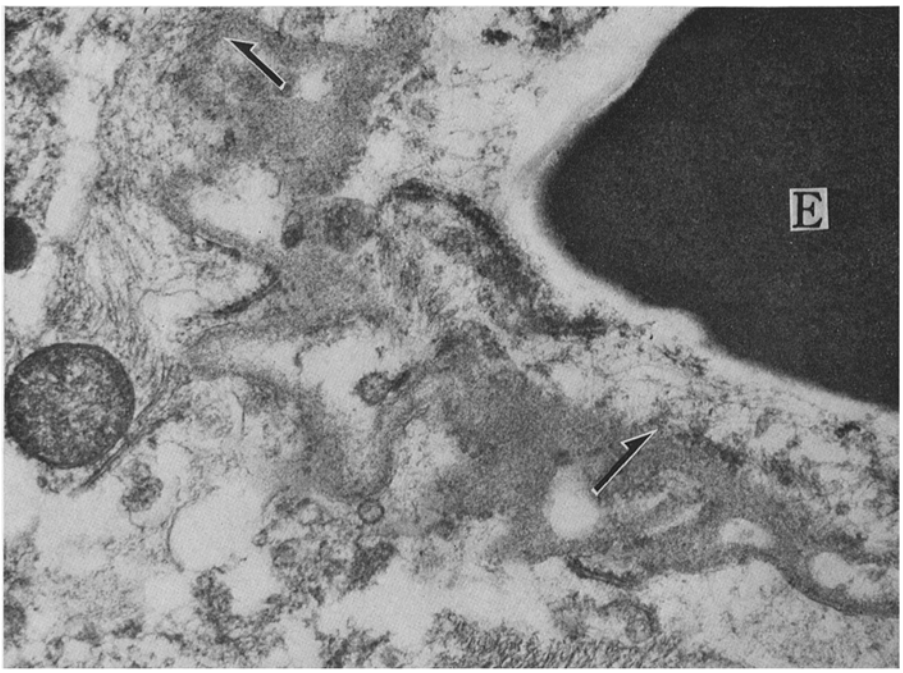
Fig. 3. Capillary. The basement membrane is thickened and tortuous and contains amyloid fibrils which extend into the parenchyma (arrow). The endothelial cell (*E*) is hypertrophied and the lumen narrowed and obstructed. ×23000

Fig. 4. Capillary. The basement membrane projects externally, produces amyloid fibrils (arrow). Collagen is also observed in the basement membrane. (*E*) erythrocyte. ×35000



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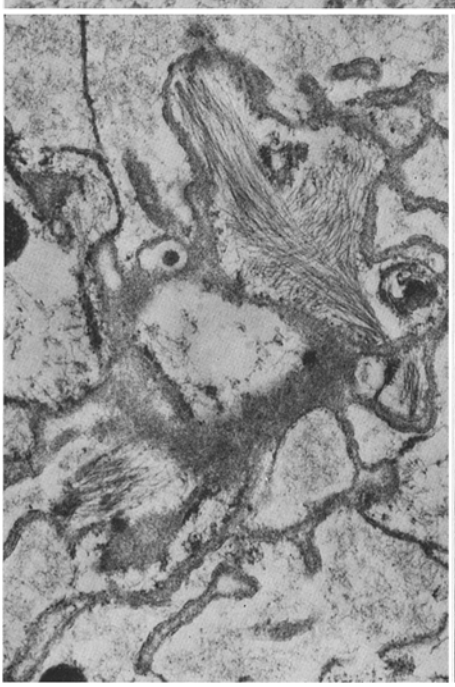

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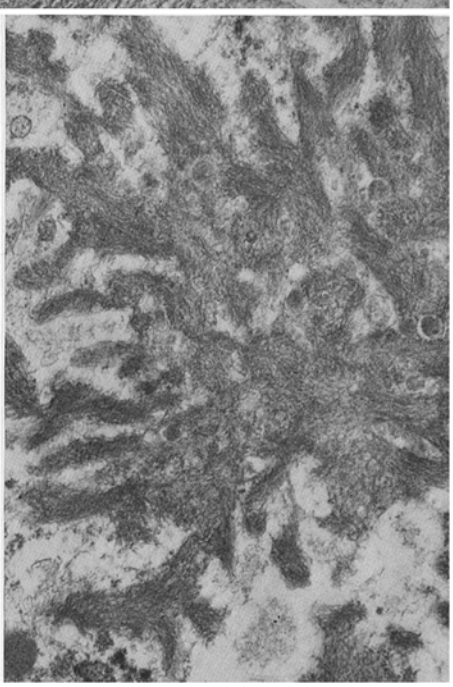

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Fig. 5. Capillary. Amyloid fibrils occur in the irregularly thickend basement membrane and extend externally (arrow: upper left) and into the endothelial cytoplasm (arrow: lower right). (*E*) erythrocyte. ×38500

Fig. 6. Increase of the basement membranes which are separated from the blood vessel. Numerous amyloid fibrils occur in the basement membrane. ×24000

Fig. 7. A mass of amyloid fibrils in a stellate formation. ×22000

of Corsellis *et al.* (1954) and Yokoi *et al.* (1958) described amyloid in the plaque-like degeneration of arteries and capillaries. Ishii (1958, 1969) emphasized the blood vessel theory and that the senile plaques were related to the blood vessels and capillaries both spatially and chemically, and that the blood vessels played an important part in the production of senile plaques. Morel *et al.* (1952) reported that the aged had paraproteinemia and this influenced the capillaries to produce senile plaques. According to the histochemical examination of senile plaques, amyloid deposition has been said to be most characteristic (Ishii, 1958; Margolis, 1959).

Terry *et al.* (1964) examined the Alzheimer's presenile dementia and described that the senile plaque of Alzheimer's disease as seen with the electron microscope, had 4 major components: a) a central fibrillar core; b) cellular perikarya; c) axons and dendrites filled with an excess of neurofibrils; d) cell processes with dense bodies. They supposed the amyloid deposit theory, however, their views on the origin of amyloid fibrils coincided with that of Suzuki *et al.* (1967) who insisted that the amyloid deposit was a secondary reaction following primary degeneration of the nerves. However Kidd (1963, 1964) insisted that the amyloid deposit was primary.

In our examination, the cores of senile plaques were made up of amyloid fibrils much or less and we do not doubt that the amyloid play the most important part in producing the senile plaques.

Schlote (1965) examined the "drüsige" degeneration of the arteries of the cerebral cortex in old age by polarization and electron microscope in a case of a 65 year old patient who died with symptoms of senile dementia, and observed amyloid fibrils in the vascular wall. The common character is the fascicular, parallel or radial formation of filaments of the amyloid in the striped layers of the vascular walls and in the centers of the senile plaques, which is not related to a local structure and seems comparable to a peculiar crystaline-like precipitation. Wiśniewski *et al.* (1970) examined senile plaques and cerebral amyloidosis in aged dogs. In this, they described that the amyloid deposits were generally confined to the vessel wall but occasionally infiltrated beyond the outer basement membrane into the surrounding parenchyma. The small parenchymal vessels and capillaries displayed two patterns of amyloid deposits. The first was focal and radiated deep into the parenchyma. In the second type of amyloid deposition, the amyloid extended around the whole circumference of the vessel. Radiating spikes of amyloid penetrated the basement membrane, but projected only a short distance into the surrounding tissue. In the surrounding neuropil, the widespread distribution and deep penetration of perivascular amyloid was not associated with type of degenerating neurites seen in plaques. Although the amyloid per se seemed not to be the primary cause of the neuritic changes, there remains the possibility that the large perivascular deposits caused a local compression of adjacent neurities, thereby interfering with axoplasmic flow and producing subsequent dying back or Wallerian degeneration of the terminals.

However, it is still unsolved how the amyloid fibrils are produced. Till now no proof of amyloid producing mechanism have been done.

Firstly, we observed the senile plaques were related to the capillaries as had been pointed out by Ishii (1958, 1969). Amyloid fibrils were observed in the base-

ment membrane and the cytoplasm of endothelial cells, and many amyloid fibrils are made in the basement membrane of capillaries and emigrate thence to the parenchyma. These findings could be observed only in serial sections. The findings suggest that amyloid fibrils are made by capillaries and play an important part in plaque formation.

Heefner *et al.* (1962) reported light and electron microscopic findings of experimental amyloidosis induced by injections of casein for periods up to 3 months and they found that the majority of amyloid fibrils lay extracellulary. In many instances, however, fibrils were found within or contiguous with the cytoplasm of reticuloendothelial cells. These findings might be due to some unexplained reaction of the blood vessels. Furthermore, we speculate that the antigen antibody reaction between the blood and the vessels may play an important role in the production of amyloid in senile dementia.

Terry *et al.* (1964) stated that the source of amyloid was uncertain, but it seems probable that it is a local cellular product, rather than a secretion from the blood. The cytoplasm of cells in the senile plaque also contains amyloid fibrils. The microglial cell in the central nervous system is the counterpart of the reticuloendotherial cell, and is a very likely source of amyloid material in the senile plaque. Certainly, we observed the glial cells which contained amyloid fibrils in their cytoplasm. However, there was no remarkable increase of glial cells. Considering the function of microglial cell it may be appropriate that the amyloid fibrils in the cytoplasm of glial cells were ingested by them.

Regarding the thickened tortuous basement membrane, similar changes have been reported by Kidd (1964) in Alzheimer's disease and by Wiśniewski *et al.* (1972) in Pick's disease. In experimental hypertension (Wiener *et al.*, 1965) and in subacute dementia (Torak, 1969) similar changes have also been observed.

In the present case, the basement membrane was thickened and tortuous and produced a great deal of amyloid fibrils and collagen and much basement membrane extended into the parenchyma. These findings have not previously been reported. The chemical constituents of collagen are very similar to those of basement membrane and some pathological mechanism in the formation of collagen may result in the production of amyloid fibrils.

Future research in the chemistry of amyloid production will play an important part in elucidating the etiology of senile dementia.

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