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The Relationship Between Senile Plaques and Cerebral Blood Vessels in Alzheimer's Disease and Senile Dementia

Morphological Mechanism of Senile Plaque Production

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Summary. Several kinds of senile plaque found in 6 brains (4 from patients with Alzheimer's disease and 2 from patients with senile dementia) were examined in serial sections by light electron microscopy. The results obtained were as follows.

All the senile plaques contained at least some amyloid fibrils, and these seemed to be produced at the basement membranes of capillary endothelial cells and projected into the surrounding parenchyma.

Even when the senile plaques themselves appeared to lack amyloid fibrils by light microscopy, at least one degenerable capillary containing amyloid fibrils was demonstrabled when serial sections were examined ultrastructurally.

The findings described above suggest that the amyloid fibrils which form the cores of the several kinds of senile plaque, seem to be produced at the basement membrane of the endothelial cell. It is speculated that the capillary degeneration with the formation of amyloid fibrils may be primary change in the genesis of senile plaques.

Key words: Senile plaque – Amyloid fibril – Capillary degeneration with amyloid angiopathy

Introduction

It is well known that the senile plaque is one of the most important findings in primary brain atrophy occurring in senile and presenile dementia (Braunmühl 1957). Although there have been many reports describing senile plaques, the mechanisms whereby they are formed have not yet been clearly resolved.

In the present study several kinds of senile plaque have been examined morphologically in detail using serial sections for both light and electron

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Table 1.

Case No.	Clinical diagnosis	Sex	Age (year)	Onset (year)	Clinical course of disease	Histopathological findings
1	Alzheimer's disease	male	56	48	8 years	Alzheimer's disease
2	Alzheimer's disease	female	52	49	3 years	Alzheimer's disease
3	Alzheimer's disease	male	63	56	7 years	Alzheimer's disease
4	Senile dementia	male	84	73	11 years	Senile dementia
5	Senile dementia	male	78	70	8 years	Senile dementia
6	Alzheimer's disease	male	65	60	10 years	Alzheimer's disease

microscopy, in order to observe the relationship between senile plaques and capillary blood vessels.

Materials and Methods

The material used consisted of 4 cases of typical Alzheimer's disease and 2 cases of typical senile dementia. The clinical and histopathological findings were entirely consistent with the diagnoses given (Table 1).

Parts of the cerebral cortex were removed from the 6 brains immediately after death, cut into small pieces and immersed in 3% glutaraldehyde in phosphate buffer (pH 7.4) for 2 h. They were washed in phosphate buffer (pH 7.4) for 10 min, then immersed for 2 h in 2.5% osmium tetroxide in phosphate buffer (pH 7.4). The tissues were dehydrated in alcohol and embedded in epon. Five blocks were selected from each brain and serial sections were stained with toluidine blue for light microscopy. Then, 200 sheet meshes of serial thin sections (300–500 Å) were taken from each block of all cases examined. They were stained with uranyl acetate and lead acetate solutions or alkali bismuth solution, and examined with a Hitachi 12 A electron microscope. Ninety senile plaques were examined completely in the serial sections. In addition, 300 serial sections, 5 μm thick, were cut from the paraffin blocks in each case and stained with PAS and silver solution for examination by light microscopy.

Results

Light Microscopical Findings

The silver stain proved the best method for observing senile plaques. In the silver-stained sections, an abundance of senile plaques of various sizes were seen in the cerebral cortex in all the cases examined. Some of them contained capillaries, while in others capillaries appeared to be lacking. For observing both the senile plaques and the blood vessels, the PAS-stained preparations proved convenient. In these sections, almost all the senile plaques or amyloid deposits had a close relationship with the capillaries.

Electron Microscopical Findings

In some serial sections, amyloid fibrils were found near capillaries with amyloid angiopathy, but they did not, however, seem to have any relation to the capillaries themselves (Fig. 1 a). On the other hand, in adjacent serial sections, the amyloid fibrils bore a close relation to the capillaries with

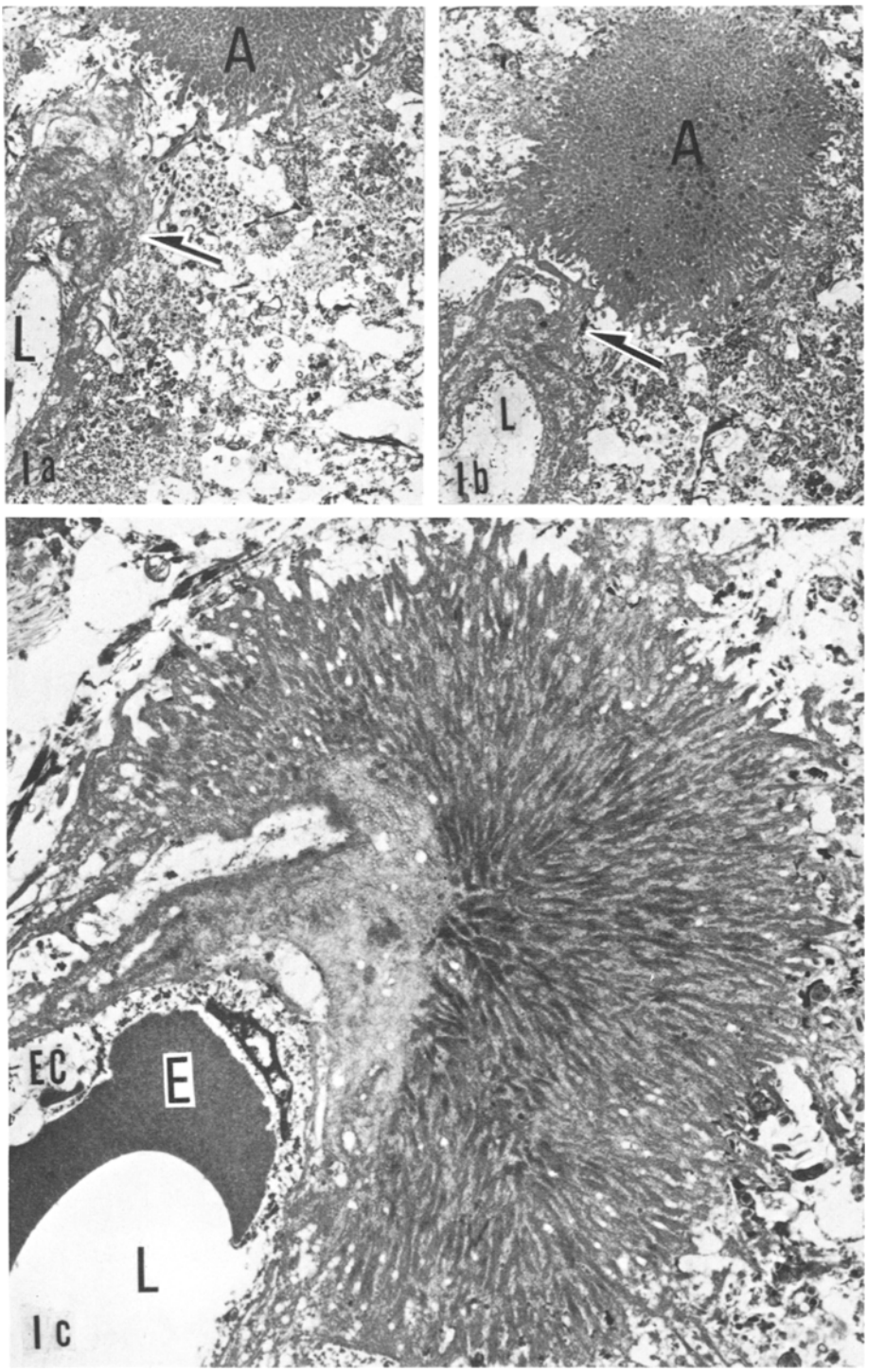

Fig. 1a–c. Serial sections of a capillary (Case 1). **a** Amyloid mass (*A*) separates from a degenerate capillary with amyloid angiopathy (*arrow*). (*L*) lumen of a capillary. ×2,100. **b** Certain parts of the amyloid mass (*A*) consisting of amyloid fibrils connected with a degenerate capillary with amyloid angiopathy (*arrow*). (*L*) lumen of a capillary. ×2,230. **c** Amyloid mass consisting of amyloid fibrils directly attached to a degenerate capillary with amyloid angiopathy. This shows that numerous amyloid fibrils project into the surrounding parenchyma from the capillary. (*E*) erythrocyte (*L*) lumen of a capillary (*EC*) endothelial cell. ×3,500

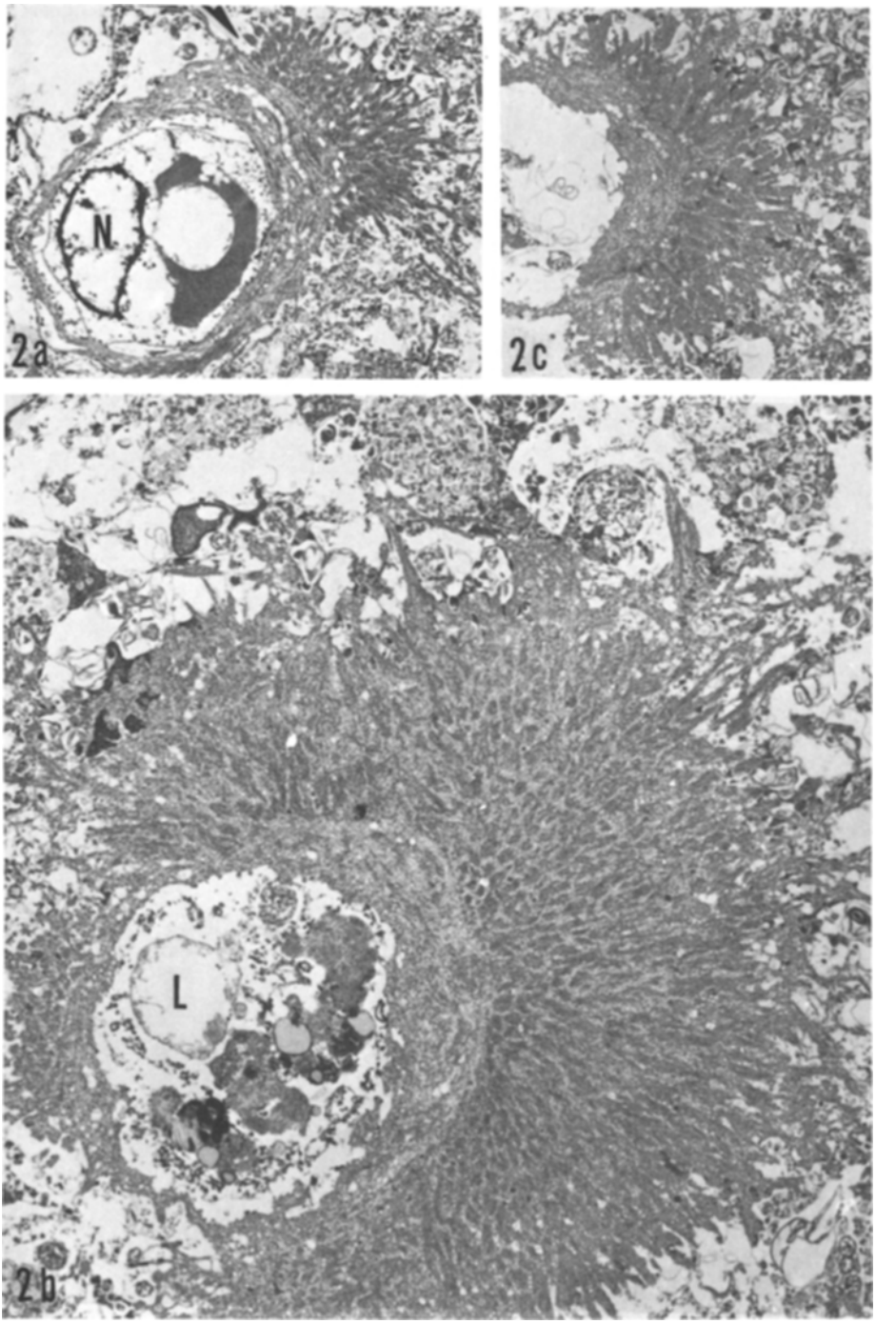

Fig. 2a–c. Serial sections of a capillary (Case 6). **a** Amyloid fibrils (*arrow*) project directly from the area of the basement membrane of a capillary with amyloid angiopathy. (*N*) nucleus of endothelial cell. ×3,580. **b** Amyloid mass, forming the central core of a senile plaque, surrounds a degenerate endothelial cell which contains many lysosome-like bodies. The lumen of the capillary is very narrow. (*L*) lumen of a capillary. ×5,800. **c** Only the amyloid mass consisting of amyloid fibrils is observed. ×4,200

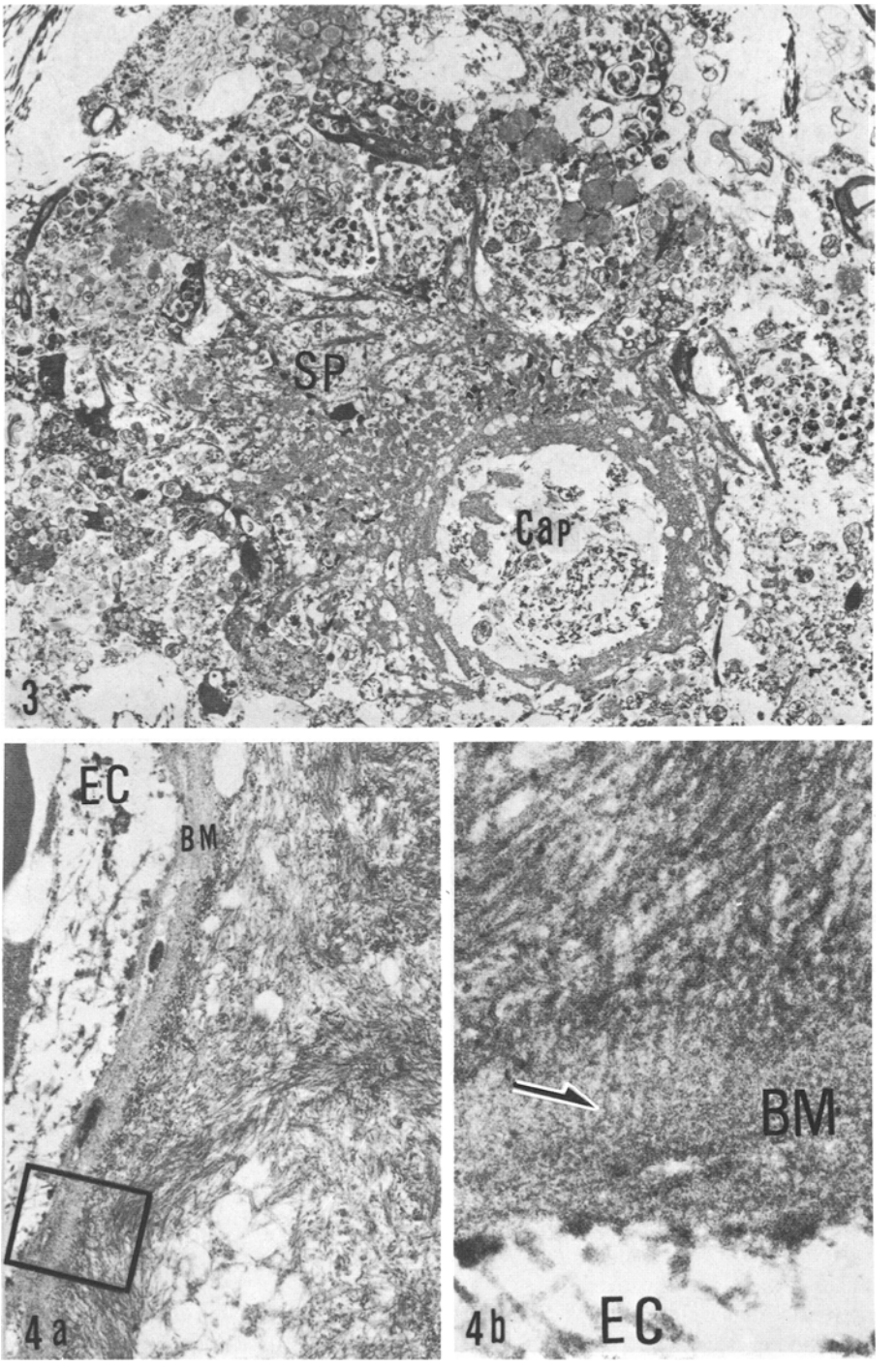

Fig. 3. Senile plaque (Case 5). Transverse section of a degenerate capillary. The lumen of the capillary (*Cap*) is filled with debris from destroyed endothelial cells. Many amyloid fibrils project from the capillary and extend into a senile plaque (*SP*). ×4,100

Fig. 4. **a** A capillary with amyloid angiopathy (Case 2). (*BM*) basement membrane (*EC*) endothelial cell. ×17,200. **b** Magnification of square shown in **a**. Amyloid fibrils apparently appear in the basement membrane (*arrow*). (*BM*) basement membrane (*EC*) endothelial cell. ×82,000

amyloid angiopathy and some connecting amyloid fibrils were observed (Fig. 1 b). In subsequent serial sections, numerous amyloid fibrils projected directly from the capillaries with amyloid angiopathy into the surrounding parenchyma (Fig. 1 c).

In some capillaries, amyloid fibrils projected from the basement membrane area (Fig. 2 a) and at other points these same capillaries exhibited changes of amyloid angiopathy. In these areas numerous amyloid fibrils projected into the surrounding parenchyma and formed the cores of typical senile plaques. The endothelial cells were swollen and undergoing destruction (Fig. 2 b). In subsequent sections, the capillaries were completely destroyed and only amyloid fibrils could be seen (Fig. 2 c).

Even when senile plaques seemed to have no relation to the capillaries under the light microscope, electron microscopy invariably demonstrated at least one degenerate or destroyed capillary with amyloid angiopathy (Fig. 3). However, it was only by the use of serial sections that the capillaries could be identified as such, since as they underwent destructions, their lumina became filled with debris formed from destroyed endothelial cells.

Examining the amyloid fibrils projecting from capillaries (Fig. 4 a), the fibrils seemed to be produced at the capillary basement membranes (Fig. 4 b).

On the other hand, in small arteries with amyloid angiopathy, amyloid fibrils were found only in the walls of the blood vessels, and not related to senile plaques.

Discussion

In 1892, Blocq and Marinesco found senile plaques in the brains of patients with epilepsy and Alzheimer (1907) observed abundant senile plaques in the brains of patients with Alzheimer's disease and senile dementia. Since then, senile plaques have been considered as characteristic findings in Alzheimer's disease and senile dementia. Senile plaques are also observed in physiological aged brain, but in much less number than in the diseases described above (Simchowicz 1911).

Regarding the mechanism of senile plaque production, many morphological examinations have been reported to date. In these studies, Terry et al. (1964) examined senile plaques in Alzheimer's presenile dementia by electron microscopy and reported that they consisted of four components: a) a central fibrillar core b) a cellular perikarya c) axons and dendrites filled with an excess of neurofibrils d) cell processes with dense bodies. These authors regarded amyloid deposition as a secondary reaction following a primary degeneration of the nerves. The source of the amyloid was uncertain, but it seemed probable that it was a local cellular product, rather than a secretion from the blood. Luse and Smith (1964) and Gonatas et al. (1967) also agreed with this opinion.

According to Wiśniewski and Terry (1973), the neurite plaques were composed of degenerating neuronal terminals, amyloid and reactive microglial cells, macrophages and astrocytes. The arrangements and relative pro-

portions of these components determined the appearance of the plaque as primitive, classic, or compact in type. Since amyloid may be found in various situations in the brain without degenerating neurites, although large clusters of these neurites are always accompanied by amyloid, they were led to the conclusion that the origin of the classic plaque lies in the degeneration of neurites which precedes the deposition of amyloid, Vessels are only occasionally related to plaques when viewed in serial 1 μm sections. On the other hand, Kidd (1964) reported that the amyloid deposit was a primary change of the senile plaque. Scholz (1938) reported plaque-like degeneration of arteries and capillaries (drusige Entartung der Hirnarterien) and concluded that the core of senile plaque consisted of material which permeated from the blood vessels, and other authors (Morel and Wildi 1952; Pantelakis 1954; Corsellis and Brierlery 1954; Yokoi and Ishii 1958) have described similar findings. Ishii (1958 and 1969) emphasized that senile plaques were related to blood vessels and capillaries, and considered that blood vessels played an important part in the production of senile plaques. In 1961, Surbeck reported "dyshoric angiopathy" and showed that plaque-like angiopathy follows senile plaques. Mandybur (1967) reported that there was correlation between the presence of amyloid-rich plaques and cerebral amyloid angiopathy (especially the plaque-like angiopathy) but no correlation with "amyloid poor" senile plaques or Alzheimer's neurofibrillary degeneration. Schlote (1965) reported that plaque-like angiopathy results from the infiltration of vessels by certain plasma proteins and electron micrographs of affected vessels exhibits amyloid fibrils arranged in the form of "brush-like structures" on the adventitial surface, a situation that could be taken to indicate a transmural flow of "precursor" substances through the vessel to the cerebral parenchyma. The filamentous metamorphosis of basement membranes, the medial degeneration that follows amyloid deposition, and the formation of thick amyloid accumulation on the inner aspect of the adventitia all suggest a role of blood plasma factors in the genesis of cerebral amyloid, and these studies support the concepts of Scholz (1938) and Morel and Wildi (1952).

Glenner (1979) reported that in a large proportion of cases of Alzheimer's presenile dementia, the major causual mechanism was an alteration of the blood-brain barrier resulting from the deposition of Congo red-positive material in the walls of small blood vessels occurring in a relatively young age group. He concluded that a partially-digested, filamentous protein (filarin) is further cleaved enzymatically by microglia cells to produce the amyloid core of the neurite plaque.

However, Teilum's suggestion (1964) that generalized amyloid fibril deposition may be from reticular cells led some researchers to believe that amyloid fibrils in the brain may be produced by glial cells.

Recently, Wiśniewski et al. (1981) considered the pathogenesis of amyloid fibril and senile plaque production. In this paper, they reported that amyloid deposits in all areas were closely associated with rod-shaped or oval cells rich in free and membrane-bond ribosomes and containing a distended endoplasmic reticulum. These amyloid-associated cells appeared by both light and electron microscopy to be reactive microglial cells.

From our detailed examination of serial sections by light and electron microscopy, all of the amyloid fibrils in senile plaques seemed to be produced at the basement membranes of endothelial cells.

Regarding the amyloid deposits themselves our findings coincide with those of Wiśniewski et al. (1970). However, we differ from Wiśniewski et al. regarding the origin of the amyloid fibrils in senile plaques. After examining in detail serial sections with an electron microscope, destroyed capillaries with amyloid fibrils could be found in all plaques. Amyloid fibrils forming the cores of all senile plaques seemed to have intimate relationship with capillaries and the fibrils appeared to form at the capillary basement membranes. These findings appear to support the concepts of Scholz (1938); Morel and Wildi (1952); Schlote (1965).

We also observed glial cells containing some amyloid fibrils in their cytoplasm. We could not deny the possibility that microglial cells produce amyloid fibrils, but considering the function of these cells, it seems likely that the amyloid fibrils were ingested by them. An important finding was the difficulty in recognizing severely damaged capillaries as such unless serial sections were examined in the electron microscope. Unless this is done, the impression might be formed that many senile plaques bear no relationship with capillaries.

In a previous report (Miyakawa et al. 1974), we noted the presence of capillary plaque-like degeneration by electron microscopy and pointed out that the senile plaque had an extremely close relation to the capillary when with examined the scanning electron microscope (Miyakawa and Uehara 1979). In this paper, we suggest that all the amyloid fibrils forming the core of senile plaques have an intimate relationship to the capillary and that several kinds of senile plaque seem to be the result of a primary change in the capillary involving the formation of amyloid fibrils.

Histochemically, Katenkamp et al. (1970) reported that amyloid in the brain was of the γ-globulin type and Zucker-Franklin and Franklin (1978) suggested that amyloid might be synthesized through the surface-associated enzyme system of blood monocyte. Ishii et al. (1975) pointed out the presence of components or fragments of immunoglobulins in senile plaques, and suggested that immunological factors are involved in their pathogenesis and probably also in that of senile dementia and Alzheimer's disease. Recently, Powers and Spicer (1977) concluded from their histochemical studies that the amyloid found in senile plaques is of the apudamyloid type originating from neuronal sources. Further work is necessary to clarify these points.

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