Critical Review.

THE NATURE AND SIGNIFICANCE OF SENILE PLAQUES.*

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FEW problems in neuropathology have aroused more discussion than the question of origin and development of so-called miliary or senile plaques. Although more than thirty years have passed since the first adequate description, the histological nature of these bodies is still a matter of controversy. An even greater uncertainty surrounds the exact clinical significance of the plaques, and their importance in the pathology of the senile psychoses.

The first reference to the existence of senile plaques is contained in a paper by Blocq and Marinesco in 1892, on the pathology of epilepsy. In the brain of an aged epileptic they found small circular masses, measuring about 60μ in diameter, scattered throughout the cortex. These bodies were conspicuous on account of their deeper colouration. A vague stippling of the interior suggested to the authors the possibility of their being "nodules of neuroglial sclerosis."

There appeared in 1898 the first important record of these nodular masses in a paper by Redlich who described them in the brains of two senile epileptics. Redlich spoke of them as "miliary scleroses." Other contributions followed, notably those of Perusini, Alzheimer, Oppenheim and others. Miyake described them as "glial rosettes," Léri as "sclérose névroglique miliaire." The term "senile plaque" was first proposed by Simchowicz. Fischer's contributions in 1907, 1908 and 1910 were the next important landmark in the study of the plaques; this author proposed the word "Drusen" or "drusigen Nekrosen," and also—from their resemblance to the lesions of actinomycosis—"Sphärotrichien." Later writers have usually employed the term "senile" or "miliary plaques," though in Germany one still speaks of "Drusen," "sphærotrichea cerebri multiplex" or "Redlich-Fischer plaques."

More recently, valuable contributions to the problem have been made by Rizzo and Bolsi in Italy, Uyematsu in the United States, Marinesco in Roumania, Hechst in Hungary, Divry in Belgium and Bouman in Holland.

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HISTOGENESIS.

In the broadest terms, senile plaques may be described as small, circular areas of densification, scattered throughout the cerebral cortex. They stain intensely with silver-impregnation methods, such as those of Bielschowsky or Levaditi. Special tinctorial methods, as those of Hortega, demonstrate the presence of microglial elements, while other stains, such as Cajal's silver method, may reveal neurofibrillary structures. Histochemical tests may also give evidence of amorphous lardaceous bodies or aggregations of lipid.

FIG. 1. Cortex of a senile dement, aged 91, showing numerous plaques of various sizes. (Levaditi stain).

Minute study of the plaques demonstrates a remarkable variation in the finer structure, but numerous *form-constants* can be recognised, including rings, radial figures, star-shaped bodies, and circular homogeneous areas. It is doubtful whether these different forms represent distinct types or merely transition stages.

Following with some modification, the classifications of Uyematsu, Marinesco and others, one may speak of three main varieties :—

1. A diffuse or homogeneous form.

2. A spheroidal or ring-like form containing a central cellular body.
3. A spheroidal or ring-like form containing in the centre an amorphous non-cellular body.

Uyematsu also adds to these a perivascular variety.

1. The first type is made up of circular areas measuring from 10μ to 150μ in diameter. Their structure consists of a mass of fine, interlacing fibrils, entangled together to form a meshwork. At times, a few nuclei are

FIG. 2. High-power representation of same specimen as Fig. 1.

visible in the interstices. The fibrils are strongly argentophil in their staining reactions. In some of the plaques of this type the interior is relatively less dense than the peripheral part.

2. In the second variety, one recognises an outer ring of variable thickness, made up of a fibrillary network with occasional cells. Alzheimer called this zone the "Hof" in contradistinction to the central "Kern." Sometimes cells lying immediately outside the plaque send in fine processes which pierce

the peripheral ring. Bounded by the outer ring is a narrow, clear zone surrounding a central, nuclear-like mass. In this particular type of plaque, this consists of a cellular body with a circular or oval light-staining nucleus. This structure is also argentophil but varies in its power of taking up stains. Thus, in some cases, the external ring stains deeper than the interior, while in others the reverse is true. With appropriate technique, granules of lipoid may be seen within the cytoplasm. In a number of instances the fibrils of the peripheral area tend to assume a radial arrangement, constituting the so-called 'morning-star' appearance.

3. The third type resembles the second except for the character of the central mass, which is amorphous, acellular, and usually of irregular outline.

FIG. 3. Still higher magnification, showing the detailed structure of three plaques (x 500).

This portion differs from the periphery in its lack of affinity for silver stains. Divry has demonstrated the bi-refractile property of these bodies.

More detailed histochemical study of the plaques, particularly since the use of the Hortega methods, has brought to light several important points in the structure :—

- (a) The plaque as a whole is essentially argentophil.
- (b) There may be a very narrow acellular zone surrounding the periphery of the plaque (=the "zona x" of Tumbelaka).
- (c) The acellular central masses have the histochemical and physical properties of amyloid or of some analogous substance (Divry *et al.*).
- (d) The plaques do not react to neuroglia stains although in the older varieties large neuroglial spider-cells may be seen in the vicinity.

- (e) Appropriate staining methods reveal the presence of lipid within the central portion as well as inside the fibrillary zone of the plaque.
- (f) Hortega methods reveal an important participation of microglia cells. In the plaques belonging to the first type they may be entirely absent, but are particularly frequent in the other forms. Microglia cells occur both in the peripheral and in the central zones. In the former case they may become swollen and their processes may hypertrophy. Within the innermost portion one or two microglia cells may be visible. Their processes spread out in a radial fashion and tend to swell as they traverse the peripheral zone. At a later stage, they undergo regressive changes; they distend, lose their processes and become amoeboid. Intracellular granules of lipid material may be visible.
- (g) Oligodendroglia apparently does not participate in the structure of the plaques.
- (h) In the older plaques neurofibrils may be demonstrable by Cajal's silver stain ("neurotisation"). Occasionally, myelinated axis-cylinders may be seen.

Although Fischer and Oppenheim both emphasized the frequent close relationship of the plaques to the blood-vessels and capillaries, it seems that such an association is far from constant. Indeed, the majority of plaques appear to have no intimate connection with the vessels. On the other hand, a proportion of the plaques are obviously intimately related to and seem actually to grow in the wall of a vessel, which may be either healthy or diseased. Uyematsu, indeed, describes a fourth or perivascular variety of plaque. Bouman has given an interesting study of the development of this type of plaque from its earliest stages. According to his account the following processes may be noted (see illustration):—

- (a) A bean-shaped homogeneous clump, of argentophil material, attached to one side of a blood vessel.
- (b) The mass now surrounds the vessel in an asymmetrical fashion (the 'signet-ring'). The edge farthest away from the vessel wall stains darkest with silver.
- (c) The outer wall of the clump now shows a ray-like formation resembling a brush.
- (d) The rays become thicker and stain more intensely.
- (e) The rays increase still further and become irregular. They grow out to a peripheral limiting horny ring in a radial or spoke-like manner (=the 'morning-star').
- (f) The blood-vessel atrophies and the central clump shrinks.

Uncertainty exists as to the significance of the various types of plaque. On the one hand, they may represent entirely distinct varieties, differing essentially in histological structure. Alternatively, they may represent different stages in the development of an adult form; thus, type 1 might be regarded

as a relatively younger type, although Urechia and Elekes consider them as the older varieties. There is, however, a third possible explanation of the different appearances; the plaques may be regarded as spheroidal masses consisting of an external shell of fibrillary meshwork or felting, surrounding a core of a cellular or hyaline nature. Transection through the equator of such spherical masses will show them as annular areas with a central nuclear mass. Sections which do not pass through the diameter but merely 'top' the plaque appear as circular areas of homogeneous fibrillary structure, with or without a relatively less dense interior.

FIG. 4. Schematic representation of the development of the perivascular type of plaque. 1-6. (see text). 2: "the signet-ring." 5: "the morning-star." (After Bouman).

TOPOGRAPHY.

Senile plaques are practically confined to the cerebral cortex. Here, the frontal lobe, the cornu Ammonis, and the island of Reil show the maximum change. Plaques have also been described in the cerebellar cortex and in the medulla; they are never seen in the spinal cord. In the great majority of cases no plaques are to be found in the basal ganglia; Bouman and Bok, however, have recorded nine cases in which the putamen, claustrum and caudate were markedly infiltrated by plaques. They point out that their technique of

fixation may be of importance, and that since the routine employment of their new method plaques have been discovered in the basal ganglia "almost regularly." The general experience, however, is to confirm the rarity and diminutive size of plaques within the corpus striatum. It is perhaps worth emphasizing that in Bielschowsky preparations small bundles of nerve fibres, cut transversely, may give an appearance which superficially resembles that of the homogeneous variety of plaque.

Within the cerebral cortex the plaques appear chiefly in the deeper (pyramidal cell) layers. When very numerous the more superficial laminae as well as the immediately subjacent white matter may contain a few; in such cases the larger plaques are situated in the deeper strata. When the cerebellum is the seat of plaque formation the molecular layer is the most usual site, although at times plaques may be seen near the Purkinje cell laminae.

OTHER ASSOCIATED PATHOLOGICAL APPEARANCES.

The intrinsic nature of the anatomical circumstances under which senile plaques are found makes it probable that other pathological changes will co-exist. Chief among the associated lesions are those which belong to the pathology of the senium. These include neuronal atrophy, neuroglial changes both proliferative and regressive type, and intracellular pigmentary depositions. Of special importance are the intracellular fibrillary changes of Alzheimer's disease; this lesion particularly often coexists with senile plaques (Bielschowsky, Uyematsu, Stief, Bolsi), although in Fuller's cases Alzheimer's fibrils were rare.

Lesions of an arteriosclerotic nature may be present in brains rich in senile plaques (Fuller, 62 per cent.; Uyematsu, 27 per cent.). There is a general agreement, however, with Fuller's statement that arteriosclerosis alone has but little direct causative relationship with the formation of plaques. Bleuler, indeed, stated that arteriosclerosis seems to give a certain amount of immunity against the development of senile plaques.

Sigg drew attention to the constancy with which sclerosis of the basal arteries occurred in his series of plaque-containing brains, and he tentatively regarded his cases as lying midway between senile brains with soft blood vessels and those of arteriosclerosis with intensely hard arteries.

In his study of the glia in chronic vascular disease of the brain Globus has noted circumscribed, rosette-like aggregations of microglia. Such bodies need to be distinguished from senile plaques in histological studies.

Laignel-Lavastine and Tinel have described in the cortex of senile brains irregular "fern-leaf" precipitates of argentophil material. These deposits are larger than the ordinary senile plaques and produce no reactionary change in the nerve cells of neuroglia. They are only exceptionally associated with the ordinary senile plaques. On account of their physical properties and staining reactions Tinel concluded that they were fatty in nature. The authors regarded these bodies as representing a variety of miliary plaque, of more rapid development; they were never found except in brains of senile demented and usually

in those whose clinical history had been short. Tinel looked upon the classical senile plaque as a "vestigial, cicatricial, and dystrophic relic" left by the re-absorption of his type of fatty plaque. In support of this view, he demonstrated in three cases structures which he regarded as transition-forms between the fatty or acute plaque and the more chronic senile plaque of Redlich and Fischer. Rizzo, however, believes that the fatty plaques of Laignel-Lavastine and Fischer are artefacts due to the methods of fixation, and he denies the existence of transition types.

THE NATURE OF SENILE PLAQUES.

Fischer's original hypothesis regarded plaques as the expression of a specific infection due to a streptothrix-like micro-organism. This view, however, never gained popularity.

Prior to the employment of the Hortega methods in the study of miliary plaques much uncertainty existed as to their exact nature. Some regarded them as originating from decayed nerve-cells (Redlich, Bonfiglio, Perusini, Bickel) with or without secondary neuroglial infiltration. It was pointed out, however, that the occasional finding of plaques in the molecular layers of the cortex and in the white matter is evidence against their neuronie origin.

Theories as to the primary glial nature of the plaques were held by Miyake, Léri, Ziehen and others, although it was found that the plaques fail to react to pure glial stains.

The researches of Ley and Timmer demonstrated for the first time the importance of microglia in plaque formation. Both healthy and pathological Hortega cells in the peripheral and central zones have already been mentioned as occurring in a large proportion, though not all, of the plaques. It has furthermore been shown that oligodendroglia does not participate in the structure of the senile plaques.

Lastly, the histochemical work of Divry showed that according to the optical properties, the staining reactions and the solubility in various solvents, the plaques are composed of amyloid, and he regards them as the expression of a disseminated hyalo-amylosis affecting the cortex.

The modern conception of the plaque is that of a reactionary change directed against a specific metabolic process of toxic nature. The probable successive steps in the development may be stated as follows: there is primarily an involutional alteration in the chemistry of the fundamental ground-substance wherein the elements of the nervous tissue live. (Both Timmer and Ley regarded the original metabolic change as being disintegrated microglia). In this way lipid (or possibly amyloid) substances are precipitated which are strongly argentophil. These bodies provoke a microglial reaction; Hortega cells become incorporated and insinuate themselves into the innermost part; here they themselves undergo degeneration. Marinesco believes that necrosis of the microglia is the cause of the central depositions of amyloid material:

in this way plaques of type 3 would be of later development than those of type 2. Microglial cells also appear in the periphery ; later they hypertrophy and then break down and finally disintegrate.

Although macroglia plays no essential part in the histogenesis, at a later stage hypertrophied astrocytes may be seen collected in the vicinity so as to form a ring round the plaque.

Nerve cells and fibres may also become involved during the final stages according to Marinesco there may be an actual new-formation of nerve fibres, some of which attempt to penetrate the plaque. Here, however, the environment is unsuitable and the fibre-growth becomes arrested.

Why the cerebral cortex should almost exclusively be the seat of plaque formation has never been satisfactorily explained. Löwenberg suggested two possible hypotheses ; first, there might be some peculiarity in the cortical reticulum favouring plaque-formation. On the other hand the predilection might depend upon the presence of capillary fibrosis in the senile cortex.

THE CLINICAL SIGNIFICANCE OF MILIARY PLAQUES.

Most interest, and at the same time the greatest controversy, centre round the possible clinical significance of the senile plaques. As their name implies they are chiefly encountered in the brains of the aged and particularly in cases of senile psychosis. The main problems are, therefore, whether plaque formation is essentially an involutional process, or whether it is associated more intimately with psychotic states. Lastly, the possible specificity of the plaques in any particular clinical type of mental or physical change needs consideration.

It was believed by the earliest investigators that there might be a causal relationship between the presence of plaques and the clinical expression of epilepsy (either senile or idiopathic). Thus it will be recalled that the original cases examined by Blocq and Marinesco and by Redlich were of aged epileptics. Léri, in his thesis on the senile brain, refers to the occasional presence of plaques (miliary sclerosis) which, as he says, " would seem to be associated with attacks of senile epilepsy, or possibly with dementia." In Fischer's series, fits occurred in five out of the 58 cases in which plaques were demonstrable ; in his control series of 53 plaque-negative brains, epilepsy occurred four times.

Later work clearly indicated that there was little or no direct association between plaques and epileptic attacks, and interest centred upon their occurrence in the senile or presenile psychoses. Thus, in 1906, Alzheimer referred to their presence in the malady which now bears his name, and three years later Perusini described three similar cases. The contributions of Fischer, however, appearing over the years 1907-1910, drew attention to the occurrence of plaques in cases diagnosed clinically as senile dementia, and in particular to their presence in that variety known as presbyophrenia. Thus out of his series of 110 brains of patients dying with various psychoses, plaques were found in 56 : of these 42 had been diagnosed as presbyophrenics, while the

other 14 were patients with paranoid, catatonic or manic-depressive states. In a later contribution Fischer expressed the opinion that the plaque-positive cases represented a definite clinical entity which he termed "presbyophrenic dementia"; in cases of simple senile dementia no plaques occurred.

Oppenheim (1909) demonstrated plaques in six out of 11 senile brains; of these, six were from patients with senile dementia with presbyophrenic trends and three were from cases of dementia senilis simplex with arteriosclerosis. Sigg, too, associated plaque-containing brains with the clinical picture of agitated states, and plaque-free cases with torpidity.

In the same year, Schönfeld demonstrated plaques in 22 brains from patients older than 50; the maximum incidence was in the ninth decade. The clinical diagnoses in the 22 cases were as follows: presbyophrenia 8; presbyophrenic trends 5; dementia senilis simplex 2; chorea with psychosis 2; undiagnosed cases 3; no mental change 2. Schönfeld concluded that plaques were constantly present in cases of presbyophrenia but that they were not pathognomonic of that condition.

Latterly, the correlation between senile plaques and presbyophrenia has been less insisted upon, and there has been a greater tendency to associate them with simple senile dementia or even the normal senium. Thus Uyematsu criticizes Fischer's conception of presbyophrenia as being unlike Wernicke's original description, and resembling rather the definition of ordinary senile dementia as formulated by the American Psychological Association.

How far one can speak of a 'normal' or 'healthy' old age is, of course, debatable, but it is noteworthy that plaques have often been demonstrated in brains of senile patients who had shown no obvious mental symptoms. Thus Fischer found plaques in two out of 35 brains of normal aged subjects; Oppenheim found them in two cases of healthy old age. In the brain of a normal old man who died at the age of 105, Costantini found plaques, but only in very small number. I have had the opportunity of studying the brains of two aged subjects aged 99 and 102 respectively. In both cases only a very few scattered plaques were found, particularly in the precentral gyri.

Simchowicz's contributions are of particular interest; he regards plaques as typical of the normal senium but believes that they increase with advancing years. He points out that it is not sufficient merely to record the presence of plaques, but that their number, size and arrangement must also be considered. He therefore suggested that a so-called 'senile index' should be taken; the maximum number of plaques in a microscopic field (Leitz obj. 3, eyepiece 3, magnification 80) is noted. Examinations are made of different cortical regions, taking sections cut at a thickness of 20μ , and stained by the methods of Bielschowsky or Mann-Alzheimer. The actual number of plaques in each piece is taken as a 'senile index' and tabulated as follows:—

Index of frontal lobe	—	—	—	—	I.F.
„ temporal lobe	—	—	—	—	I.T.

Index of cornu Ammonis	-	-	-	I.A.
„ parietal lobe	-	-	-	I.P.
„ motor cortex	-	-	-	I.M.
„ occipital lobe	-	-	-	I.Occ.

The 'senile formula' is then recorded thus :—

$$\text{I.F. : I.A. : I.T. : I.P. : I.M. : I.Occ.} = 52 : 26 : 26 : 17 : 8 : 5$$

(in a case of senile dementia).

In a normal old man of 104, the formula was :—

$$\text{I.F. : I.A. : I.T. : I.M. : I.Occ.} = 8 : 5 : 3 : 0 : 0.$$

In Alzheimer's disease, the maximum plaque incidence was found to be in the visual cortex, thus :—

$$\text{I.F. : I.A. : I.T. : I.P. : I.M. : I.Occ.} = 45 : 42 : 44 : 62 : 30 : 74.$$

The ratio I.F./I.Occ. is, therefore, important, in Simchowicz's opinion, in differentiating Alzheimer's psychosis from senile dementia on pathological grounds. According to this author's results, the differences between healthy old age and senile dementia are purely quantitative, and depend entirely on the actual number of plaques.

In cases of Alzheimer's disease, senile plaques are present in the cortex but always in conjunction with the characteristic intracellular fibrillar alterations.

The present conception of the significance of the senile plaques is to regard their presence in large numbers as indicative of senile dementia, though not pathognomonic. As Fuller says, plaques occur with greater frequency in senile dementia than in any other form of insanity. Uyematsu's conclusions are particularly worthy of quotation : "All cases of senile dementia should show miliary plaques, and in those cases failing to do so ; a diagnosis of senile dementia is doubtful. . . . Miliary plaques do not necessarily indicate the diagnosis of senile dementia although their presence proves to be highly suggestive. By the absence of plaques a diagnosis of senile dementia can be ruled out. . . . The miliary plaques are characteristic of senile dementia and not for any special form of the disease." Much further clinico-pathological research is obviously necessary before Uyematsu's last statement can be accepted unhesitatingly. Thus it will be necessary to investigate more fully the clinical aspect of the plaque-free cases of senile dementia ; to enquire whether the size, number or arrangement of the plaques can be correlated with any distinct clinical variety of dementia senilis. In this connection the question of senile plaques in the corpus striatum would repay further investigation ; indeed there is some evidence to suggest that the clinical course of such cases may be outside the usual picture. Stief indeed has associated the presence of miliary plaques in the striopallidum with the picture of senile rigidity (the *senile Muskelstarre* or *Vorsteifung* of Jakob).

More study is also due to those rare cases in which senile plaques have been encountered in the brains of relatively younger individuals. Thus plaques

were present in the cortex of one of Simchowicz's patients dying from Korsakow's syndrome at the age of 71. One of Marinesco's patients, a female of 45, also showed clinically a polyneuritis with Korsakow's psychosis. A patient of Tiffany's dying at the age of 31 from tabes without mental change also showed numerous miliary plaques.

It is noteworthy that miliary plaques are characteristically absent from one very important variety of senile psychosis, viz., circumscribed cortical atrophy or Pick-Spielmeyer's disease. With the exception of the examples recorded by Kufs and by Altmann, and the fourth and distinctly atypical case of v. Braunmuhl, no instance is on record of the presence of senile plaques in Pick's disease, and in the cases reported by the two first mentioned observers the plaques were extremely small and infrequent.

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