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The laminar distribution of neuritic plaques in the fascia dentata of patients with Alzheimer's disease*

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Summary. Neuritic plaques are prominent in the fascia dentata of the hippocampus and are often linearly oriented in stratum moleculare. Since the afferents to this region are also organized in a laminar pattern, the present study focused on the relative number and laminar distribution of plaques in this region to shed light on the genesis of the neuritic plaques. Examination of 19 brains from patients with Alzheimer's disease showed approximately the same number of plaques in the stratum moleculare of the fascia dentata and in CA1 (Sommer's sector) of the hippocampus, even though the area of the latter is much greater. Laminar analysis of plaque location showed that the plaques were centered on a band between 26% and 40% of the way between the border of stratum granulosum and the outer edge of stratum moleculare. The mean location was 35% of the way through the layer at the intersection of the inner and middle thirds. Plaques appear in approximately the same location, but in lesser numbers, in non-demented patients. The significance of this localization is discussed in terms of the normal anatomy of the fascia dentata and its possible reorganization in Alzheimer's disease. The predictability of plaque formation in this region could be useful in defining the pathogenesis of the neuritic plaque.

Key words: Alzheimer's disease – Neuritic plaques – Fascia dentata – Hippocampal formation

Alzheimer's disease affects selected neuronal populations throughout the brain, including those of the hippocampal formation. This regional vulnerability has led to the term "hippocampal dementia" as a description of Alzheimer's disease [6], a description substantiated by the observation that the major inputs and outputs of the hippocampus are severely damaged in this disorder [24, 25]. Within the hippocampal formation, quantitative studies of the relative distributions of neurofibrillary tangles, granulovacuolar degeneration, and neuritic plaques have emphasized the selective vulnerability of the subiculum and CA1 [5, 22, 23, 50, 52]. In contrast, little attention has been paid to the fascia dentata, which contains few or no neurofibrillary tangles or cells displaying granulovacuolar degeneration. However, plaques are prominent in this region [44] and are often linearly oriented within stratum moleculare [25]. Since the afferents to the fascia dentata are also organized in a laminar pattern [2, 34], the present study was designed to determine the relative number and laminar distribution of plaques in the fascia dentata. The location of the plaques may be an important determinant of hippocampal function in patients with Alzheimer's disease and may also provide clues about the pathogenesis of the plaque.

Materials and methods

Nineteen brains from patients with Alzheimer's disease were examined. These were received consecutively at the Joseph and Kathleen Bryan Brain Bank of the Alzheimer's Disease Research Center at Duke University between April, 1985 and May, 1986. The diagnosis of Alzheimer's disease was based on a clinical history of dementia and the presence of numerous neuritic plaques, tangles, and cells with granulovacuolar degeneration in hippocampal formation, and numerous plaques, with or without prominent tangles, in the neocortex. The mean age of the patients was 73 years (range: 56 to 92 years). There were 8 males and 11 females.

Forty-one additional brains from patients without a history of dementia were also examined. These cases were selected from the general autopsy service at Duke University Medical Center on the basis of the patient's age at death. The following age groups were represented: 29–40 years ($n = 4$), 41–50 ($n = 9$), 51–60 ($n = 7$), 61–70 ($n = 10$), 71–80 ($n = 7$), 81–90 ($n = 4$). These were 19 males and 22 females. Although plaques were numerous in some of these cases, granulovacuolar degeneration

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was absent and tangle formation was limited to rare cells in the entorhinal cortex.

After at least 2 to 4 weeks of fixation in 20% formalin, one block was taken through the hippocampal formation at the level of the lateral geniculate nucleus. The tissue was embedded in paraffin. One section from each block was stained with the microwave King technique for neuritic plaques and neurofibrillary tangles [32]. An adjacent section was stained with hematoxylin and eosin and counterstained with Luxol fast blue (H&E/LFB).

Each plaque was identified and localized to CA1, CA2, CA3–CA4, or fascia dentata (Fig. 1). For each plaque in the stratum moleculare, the distances were measured from the border of stratum moleculare and stratum granulosum to the center of the plaque (distance to center) and from the border of stratum moleculare and stratum granulosum to either the pial surface or the obliterated hippocampal fissure (total distance). The location of each plaque was then expressed as a percentage: $100 \times$ (distance to center)/(total distance). When the location of the hippocampal fissure could not be precisely determined, that plaque was included in the total count but eliminated from the laminar analysis.

Results

Regional distribution of plaques within hippocampal formation

CA1 was the largest subdivision of the hippocampal formation and was identified by its widely spaced pyramidal neurons, roughly divided into two layers, and by the presence of a relatively cell-free stratum radiatum [9, 33]. CA2 had a narrow layer of tightly packed pyramidal cells, many of which contained prominent pigment depositions readily visualized in silver-stained preparations. CA3–CA4 included all the area within the hilus of the fascia dentata and extended to the CA2 border. In this study, fascia dentata included just the granule cell layer (stratum granulosum) and the molecular layer (stratum moleculare); the deeper layer of polymorph cells was included with CA3–CA4 (Fig. 1).

As reported in previous studies, plaques were most numerous in CA1, where there were 942 plaques in 19 cases of Alzheimer's disease. The number of plaques per case ranged from 0 to 290, with a median of 29. (The case lacking plaques in CA1 had numerous plaques in other areas of hippocampal formation and neocortex and numerous CA1 cells contained tangles and showed granulovacuolar degeneration.) More plaques were present in CA1a (adjacent to subiculum) than in CA1b (adjacent to CA2). Although plaques were present in all layers, there was often a distinct line of plaques at the junction between stratum lacunosum-moleculare and stratum radiatum. CA3–CA4 also had numerous plaques, with a total of 432 counted. The number of plaques per case ranged from 0 to 64, with a median of 22. CA2, the smallest of the areas, had disproportionately few plaques, 0 to 8 per case, with a median of 0 and a total of 18 counted. For comparison, a total of 882 plaques was counted in the fascia dentata of 19 cases. The numer of plaques per case varied from 5 to 102, with a median of 41. Thus, the fascia dentata contains approximately the same total number of plaques as CA1, even though the total area of the former is much smaller than that of the latter. All the plaques were in stratum moleculare; none were seen in the highly cellular stratum granulosum.

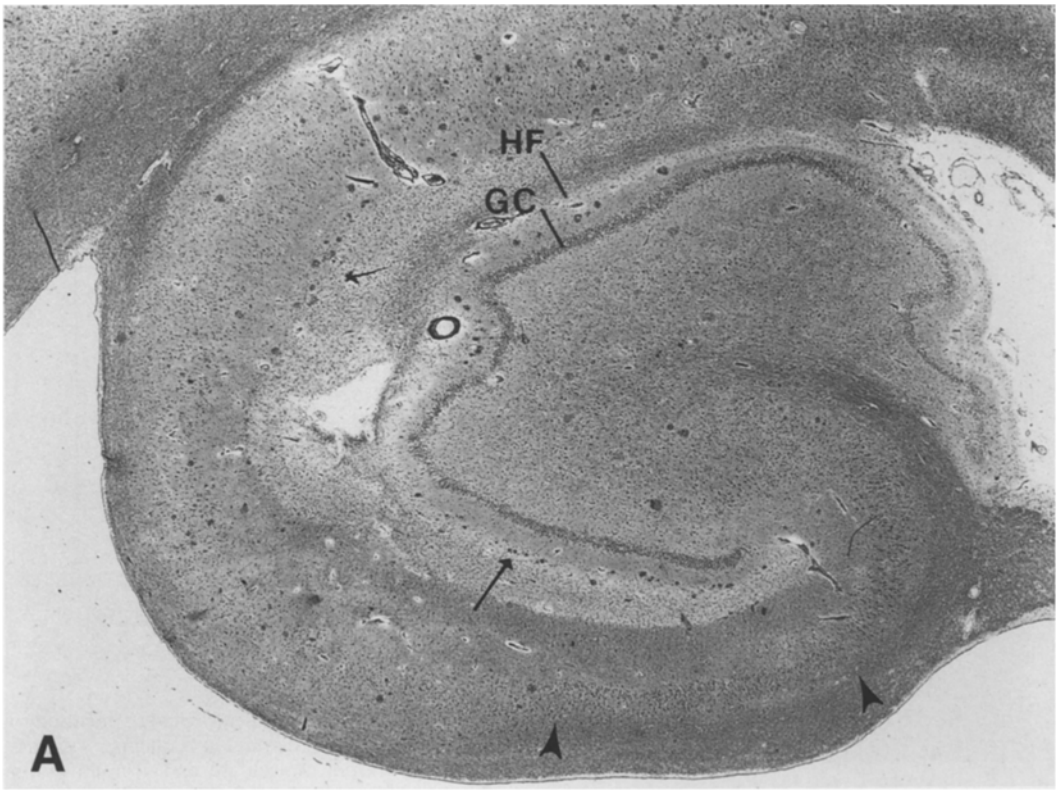
Laminar distribution of plaques in fascia dentata in Alzheimer's disease

A striking laminar distribution within the inner half of stratum moleculare was seen in all cases with Alzheimer's disease (Figs. 1, 2). In 11 of 19 cases, the sections were oriented such that the borders of stratum moleculare were clearly identifiable throughout most, if not all, of the fascia dentata (Fig. 1). Thus, the laminar distribution of the plaques in these cases was readily quantified. In the remaining 8 cases, a qualitatively similar laminar distribution of plaques was also apparent, but the exact location of the hippocampal fissure could not be determined.

The location of each of 340 plaques (out of a total of 517 in 11 cases) was expressed as a percentage: $100 \times$ (distance to center of plaque)/(total distance). The relative distribution of the plaques is illustrated in Fig. 3. The plaques were centered on a band between 26% and 40% of the way between the border of stratum granulosum and the outer edge of stratum moleculare. Forty-nine percent of all plaques fell in this range, and 67% of all measured plaques were located between 21% and 45%. Only 7% of the plaques were located 55%–100% of the way through the layer. The mean location of plaques pooled from all 11 cases was 35%. This value varied from 25% to 42% in different patients. Our subjective impression was that the distribution of plaques which could not be measured was similar. However, the possibility that a subpopulation of plaques with a somewhat different laminar distribution was systematically eliminated from the analysis cannot be completely ruled out.

Laminar distribution of plaques in fascia dentata in non-demented patients

Eight of 41 non-demented patients (ages 52–85 years) had plaques in stratum moleculare of the fascia dentata as well as in other hippocampal and neocortical regions, but none met our histological criteria for Alzheimer's disease. The laminar distribution was similar to that seen in the cases with Alzheimer's disease.



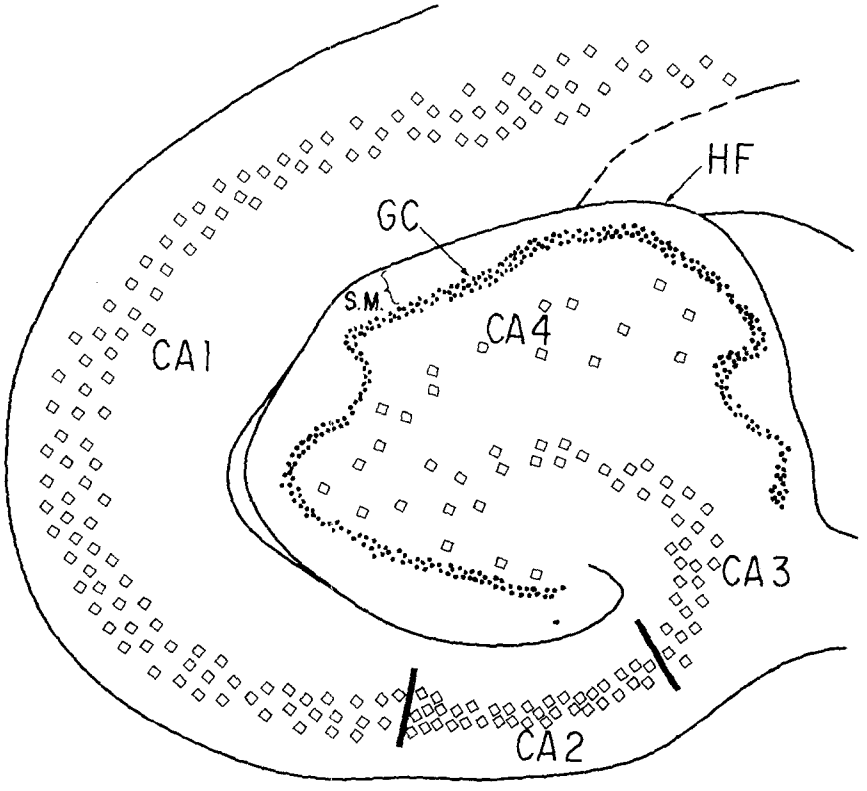


Fig. 1. A The distribution of neuritic plaques in the hippocampus in Alzheimer's disease. Neuritic plaques (*arrow*) are darkly stained by the microwave-King silver stain [32] and are oriented in a row parallel to the granule cells (*GC*). The hippocampal fissure (*HF*) is indicated. The CA1–CA2 and CA2–CA3 borders are indicated by *arrowheads*. **B** A drawing of the same section emphasizes the borders of CA1, CA2, CA3, and CA4. The granule cells (*GC*) in stratum granulosum are labeled. Stratum moleculare (*SM*) and the hippocampal fissure (*HF*) are also indicated. ×14

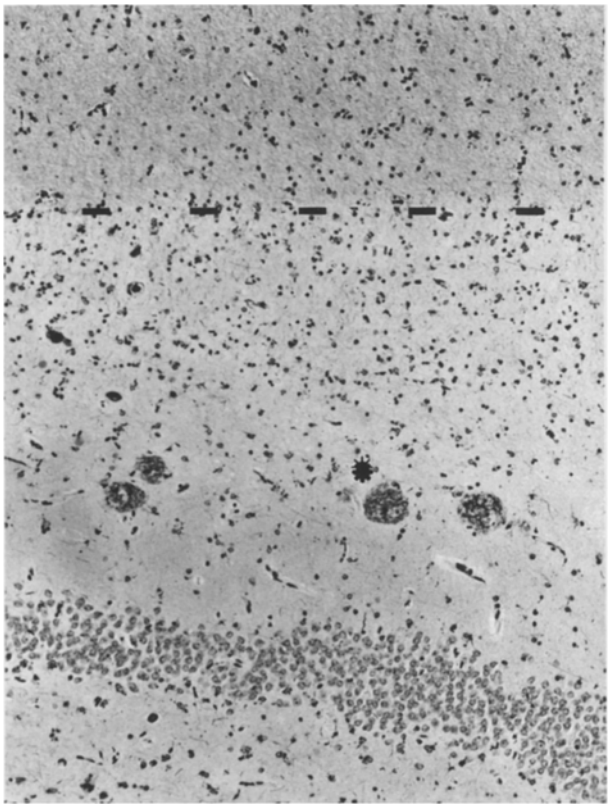


Fig. 2. Neuritic plaques (*asterisk*) stained by the microwave-King silver stain [32] are present in a row parallel to the granule cells. The hippocampal fissure is represented by the *dashed line*. ×94

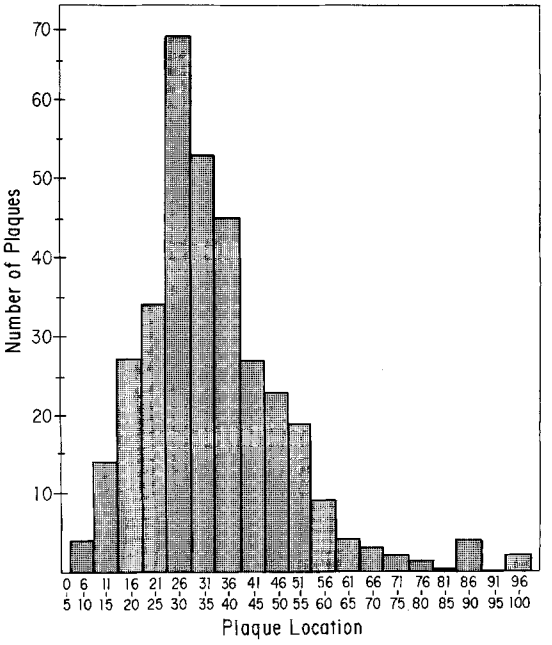


Fig. 3. Quantitative analysis of neuritic plaque location in stratum moleculare of the fascia dentata in Alzheimer's disease. The border between stratum moleculare and stratum granulosum corresponds to "0", while the pial surface or hippocampal fissure corresponds to "100"

Discussion

The selective vulnerability of certain neuronal populations to Alzheimer's neurofibrillary change and granulovacuolar degeneration is well known, but there is less insight into the regional vulnerability to the formation of neuritic plaques. Since fibers containing a variety of putative neurotransmitters may participate in plaque formation, recent studies in neocortex have shifted away from an emphasis on specific neurotransmitter systems and towards an emphasis on the intrinsic cytoarchitecture and circuitry of the cortex [16, 25, 47]. A similar approach has been taken in the present study of neuritic plaques, where neuritic plaques are strikingly centered about a zone 25% – 40% of the way between stratum granulosum and the surface of the fascia dentata. Theoretically, the localization of neuritic plaques might represent either the localization of cell bodies affected by Alzheimer's disease or the localization of abnormal axons or dendrites. Evaluation of these possibilities is facilitated in the fascia dentata, where the normal laminar organization has been well characterized in rodents and subhuman primates [2, 33, 34].

The tightly packed somata of the dentate granule cells extend their dendrites out through the neuropil of stratum moleculare to the surface of the fascia dentata, whereas their axons descend in the opposite direction into the hilus and thence to the pyramidal cells of the ipsilateral CA3 region. The granule cell bodies appear largely resistant to Alzheimer's disease. Thus, the distribution of neuritic plaques in the fascia dentata does not correlate with the locations of affected neuronal cell bodies.

Afferents to stratum moleculare normally show a well-defined laminar distribution [12]. Thus, the laminar distribution of plaques in Alzheimer's disease might correlate with the distribution of one or more inputs to this layer. These inputs include the entorhinal cortex, the commissural-associational projection, the cholinergic septal projection and noradrenergic and serotonergic fibers.

By far the largest source of axon terminals in this zone is the entorhinal cortex, which accounts for 86% of the synapses in the outer two thirds of stratum moleculare in the rat [37] and is severely affected by Alzheimer's disease [39]. In some advanced cases, nearly all the neurons in entorhinal cortex in layer two and the superficial part of layer three either contain neurofibrillary tangles or disappear [24 – 26]. Tangles and neuronal loss are found in layer four as well. Thus, as might be expected, the perforant path from entorhinal cortex to the fascia dentata is demyelinated

in Alzheimer's disease [24]. As previously pointed out [24, 25], neuritic plaques are numerous in the middle third of stratum moleculare, which is part of the entorhinal cortical termination zone. However, they are extremely rare in the outer third, where entorhinal cortical terminals are also numerous, and are quite common in the inner third, where entorhinal cortical terminals are absent (Fig. 3). Thus, the distribution of neuritic plaques cannot be completely explained by a pathological process in the entorhinal projection.

The next largest input into stratum moleculare is the commissural-associational projection from the CA4 pyramidal cells of both sides of the brain to the inner third, or slightly less, of stratum moleculare [34, 35, 53]. As previously noted, many of the multipolar nerve cells in CA4 show tangles or granulovacuolar degeneration, although these changes are much milder than in CA1 [6, 50]. A simple co-localization of plaques and commissural-associational terminals would not explain the numerous plaques in the middle third of stratum moleculare.

The distribution of neuritic plaques also fails to correspond to the cholinergic, noradrenergic, and serotonergic afferents to stratum moleculare.

The medial septum (along with the nucleus of the diagonal band of Broca) is the largest extrinsic source of cholinergic input to fascia dentata [27, 38, 41], although this pathway is not exclusively cholinergic [1, 27]. Unlike the neuritic plaques, cholinergic axon terminals in the projection are found in very thin zones just above and just below stratum granulosum; fibers and terminals are also present in the outer two-thirds of stratum moleculare [2, 17, 18, 41]. A variable, often marked, loss of cholinergic neurons from the septum, nucleus basalis of Meynert and other related deep forebrain nuclei has been well documented in tissue from Alzheimer's disease patients [13, 15, 36], as have corresponding decreases in levels of choline acetyltransferase and acetylcholinesterase [15]. However, these changes are not associated with losses in postsynaptic muscarinic or nicotinic receptors [21]. Finally, relatively sparse projections from the noradrenergic locus ceruleus and the serotonergic raphe nuclei synapse primarily in the dentate hilus. A few diffuse terminals are also present in stratum moleculare [2, 12].

In addition to the above anatomically defined afferents, a number of minor immunocytochemically defined fiber systems in the fascia dentata have also been described and reviewed elsewhere [2]. Enkephalin-immunoreactive (-IR) fibers are located in the outer third of stratum moleculare in rats [19] though not always in humans [8]. Occasional adrenergic axons containing dopamine-beta-hydroxylase-IR run perpendicular to stratum granulosum [49]. Somatostatin-IR and glutamic acid decarboxylase-IR fibers are present in the outer half to two-thirds of stratum moleculare and arise from cells in the hilus [3, 4]. Neuropeptide Y-IR fibers are found in the outer one third in the rat [28] and throughout the layer in the human [10]. Glutamic acid decarboxylase-IR boutons are also most numerous in the outer third or half of stratum moleculare [7]. None of these laminar patterns corresponds to the laminar distribution of neuritic plaques illustrated in Fig. 2.

Receptors for various neurotransmitters and other substances have also been localized within stratum moleculare. Mu opioid receptors are preferentially localized in the outer third of the layer in the suprapyramidal portion of the dentate [14, 40, 43, 51]. However, muscarinic cholinergic [29, 30, 44], delta opioid [14], GABA [48] benzodiazepine [48], alpha-1-adrenergic [45], and beta-adrenergic [45] receptors all appear uniformly distributed throughout stratum moleculare. Glutamate receptors also appear throughout stratum moleculare. Although some subpopulations of these binding sites have laminar distributions within stratum moleculare, none corresponds to the distribution of plaques [42]. Finally, the autoradiographic location of binding sites for the calcium channel antagonist nitrendipine also fails to correspond to the laminar distribution of plaques [46].

To summarize the above descriptions, the distribution of neuritic plaques in stratum moleculare in Alzheimer's disease does not seem to correspond to any single known normal afferent system. Rather, in the cases selected for the present morphometric study, the plaques are centered about a zone 25% – 40% of the way between stratum granulosum and the surface of the fascia dentata, or roughly at the intersection of the inner and middle thirds of the layer. The principal afferents to these two areas are the commissural-associational system and the entorhinal cortex, respectively. The cells of origin of the commissural-associational system (pyramidal cells in CA3, CA4) are moderately affected by Alzheimer's disease and the layer two neurons in entorhinal cortex are severely affected [25]. Thus, the pathogenesis of the plaques could be related to abnormal axon terminals emanating from these two populations of affected neurons. The distribution of plaques might correlate either with a unimodal process centered on the intersection of these two pathways and their interactions during Alzheimer's disease or on a bimodal process with overlap between two sets of plaques associated with independent alterations in the middle and inner thirds, respectively. If the distribution of plaques is principally correlated with a portion of the entorhinal cortical projection as suggested by Hyman et al. [24–26], the relative absence of plaques in the outer third

of the layer, where entorhinal cortical terminals are also found, must somehow be explained.

Attempts to correlate the distribution of neuritic plaques with the normal laminar distribution of afferents to stratum moleculare must consider that many pathways have been analyzed only in rodents and also that the normal lamination apparently changes in humans with Alzheimer's disease as some pathways are lost and other expand in response. Specifically, Geddes et al. [20] have reported that the commissural-associational system, as defined by kainic acid receptor autoradiography, expands in patients with Alzheimer's disease. Rather than being limited to the inner one-third of stratum moleculare, it expands to occupy the inner half of the zone. In addition, Alzheimer's patients without a severe loss of cholinergic input to the hippocampus show increased acetylcholinesterase activity, a marker of the septal cholinergic pathway, in the outer part of the stratum moleculare, and decreased acetylcholinesterase activity on the inner part of the layer [20, 26]. Different patients may show different patterns of acetylcholinesterase activity depending on whether the septum is also damaged by Alzheimer's disease [26]. These examples of neuronal plasticity in the human correspond with the changes in neuronal circuitry seen in rats after entorhinal cortical lesions [31, 35, 53] or entorhinal cortical lesions plus septal lesions [11]. Thus, the laminar distribution of plaques in Alzheimer's disease may correspond to a reorganized layer, rather than one normally present. Indeed, the broader zone of plaque formation, with 85% of plaques located 16%–55% of the way through the stratum moleculare, may correspond to the new, broader distribution of commissural-association fibers in the inner half of the layer. In this case, plaque formation might be related to a chronic loss of some commissural-associational and entorhinal cortical terminals and their replacement by other commissural-associational, septal, or other terminals.

Since different patients may show different patterns of damage due to Alzheimer's disease, a more definitive correlation of plaque location with the laminar neuroanatomical organization would require labeling plaques and pathways in the same or an immediately adjacent hippocampal section. Careful quantitative studies of cell loss in regions such as the entorhinal cortex and the septum would also be necessary. Even if correlations between plaque location and the laminar organization of stratum moleculare eventually prove to be fortuitous, such data on normal human anatomy and on synaptic rearrangements due to disease processes would be valuable. At the very least, the results of the present study suggest that within stratum moleculare of the fascia dentata there is a layer in which neuritic plaques routinely and predictably occur in Alzheimer's disease and normal aging and an immediately adjacent layer where such plaques are virtually absent. In light of the predictability of plaque location in this area, the study of this small and well-defined anatomic region could be useful for identifying the early ultrastructural or chemical changes associated with plaque formation and thereby defining the pathogenesis of the neuritic plaque.

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