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The Limbic System in Alzheimer's Disease

A Neuropathologic Investigation

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The morphologic alterations of Alzheimer's disease, presenile and senile dementia, have conventionally been associated with the cerebral cortex; however, it is clear that other areas of the brain, notably the hippocampus and amygdala, are involved as well. These structures, together with others such as the fornix, cingulate gyrus, septal nuclei, and mamillary bodies, constitute the limbic system, which has been recognized as the anatomic substrate of memory, emotion, and learning. Disturbances in these modalities are central to the clinical expression of Alzheimer's disease; therefore, the limbic system was studied in its entirety in 9 patients with Alzheimer's disease and in 3 elderly individuals with Down's syndrome, in whom identical morphologic lesions were present. The findings disclose that the limbic system is regularly involved in Alzheimer's disease, to a severe degree and in a distinctively patterned distribution. (Am J Pathol 85:1–20, 1976)

IT HAS BEEN INCREASINGLY APPARENT in recent years that a pathologic process in the brain characterized by senile plaques, neurofibrillary tangles, and granulovacuolar degeneration is a major cause of infirmity and mortality. It has been estimated that life expectancy is diminished by half a decade in patients who develop these lesions and become symptomatic by age 74.[1] Conventionally, the term *Alzheimer's disease* has been applied when these morphologic changes occur before age 65 years, and confusingly, the term *senile dementia* has been employed to designate the same pathologic process in an older age group. In this paper, the term *Alzheimer's disease* will be used inclusively for all age groups, in accord with a recent editorial.[1]

Although it is generally supposed that the intellectual impairment

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which is a hallmark of this disease relates to structural alterations in the neocortex, the symptomatology of Alzheimer's disease has not been well correlated with the anatomic distribution of the pathologic lesions. The study of Blessed *et al.*[2] indicates that the degree of intellectual deterioration is quantitatively associated with senile plaque formation in the cerebral cortex. However, there have been only limited attempts to define whether or not other aspects of the symptomatology of Alzheimer's disease correlate with lesions in other anatomic locations.

The clinical expression of Alzheimer's disease is well characterized.[3,4] The compromise of intellectual or cognitive facility is but one of the many expressions of this complex disorder. The severe debility is as closely related to loss of memory and orientation, and to curtailment of emotional stability and drive, as it is to impairment of cognitive function. The modalities of memory, emotion, and learning have been associated not with the cerebral cortex but rather with the limbic system.

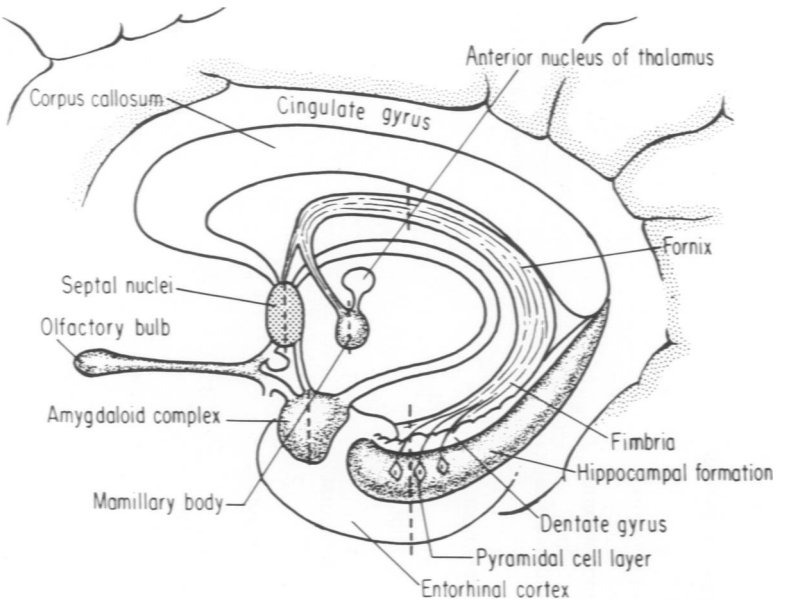
Since the time of Papez it has been recognized that the limbic system consists of nuclei and fiber tracts that have an integral function in the "mechanism of emotion, memory, learning and the organization of behavior." [5] Although the exact role of this system remains unsettled, it has been conceptualized as the critical interface between the diencephalon and the neocortex; thus it would appear to be the integrating system for the modulation of memory and emotions.[6]

It is well established that the elderly patient with Down's syndrome regularly and precociously develops the full morphologic expressions of Alzheimer's disease.[8-12] Again in this setting the manifestations of the lesions compromise memory, orientation, and the performance of routine tasks.[11,13]

The idea that the limbic system may be involved in the neuropathologic changes of Alzheimer's disease is not new; however, examinations to date have generally been restricted to one or several of the following nuclear groups: the amygdala, the hippocampus, the mamillary bodies, and the cingulate cortex.[7] The present studies were designed to evaluate the limbic system in its entirely, recognizing that it is complex both in function and structure (Figure 1 and Text-figure 1). To lend breadth to these studies, the examinations concerned demented patients of divergent ages and also individuals with Down's syndrome.

Materials and Methods

The brains of 9 patients with Alzheimer's disease and 3 patients with Down's syndrome were examined in detail by light microscopy. Those of 2 aged, nondemented patients served as controls. The diagnosis of Alzheimer's disease was made clinically and confirmed by the demonstration of the pathognomic histologic changes in the absence of other



TEXT-FIGURE 1—A schematic diagram of the limbic system. The *dotted lines* outline regions sampled for histologic study.

significant findings. The diagnosis of Down's syndrome was made by the association of mental retardation and the characteristic phenotypic appearance.

Gross examination took note of the presence of cortical atrophy, atherosclerosis, and other specific abnormalities. In each case, histologic sections were prepared from each of the following structures: the frontal, temporal, and cingulate cortex; the hippocampus and entorhinal cortex; the amygdala; the septal nuclei; the mamillary bodies; and the fornices. In addition, sections were examined from any area that showed gross abnormality. Sections of the brainstem, hypothalamus, and anterior thalamic nuclei were prepared in selected cases.

Histologic preparations from each region were processed as follows: a) frozen sections were prepared by the Lester King silver method, and b) paraffin-embedded sections were stained by hematoxylin and eosin/Luxol-fast blue, and c) selected slides were stained by the periodic acid-Schiff, alcian blue, Congo red, or Holmes methods.

Each slide was carefully examined for the presence of senile plaques, neurofibrillary tangles, and granulovacuolar degeneration, as well as for other abnormalities of neurons, glia, blood vessels, and myelin. In each anatomic area, lesions were quantitated at a magnification of 100 × by averaging the number of senile plaques or neurofibrillary tangles found in five or more fields. These figures were recorded as follows: 1+ = 1 to 20 plaques or tangles per 100 × field, 2+ = 21 to 30 per field, 3+ = 41 to 60 per field, 4+ = 60 and greater per field. Granulovacuolar degeneration was classified as 1+ = mild, 2+ = moderate, and 3+ = severe. The diameters of the fornices and mamillary bodies were noted by using a micrometer disc.

Results

The findings in the 12 diseased patients and the 2 controls are given in Tables 1 and 2. Table 1 chronicles the age, sex, brief summarization of the

Table 1—Gross Pathologic Findings in Alzheimer's Disease and Down's Syndrome

Case No.	Age (yrs)	Race & sex	Clinical diagnosis	Gross pathologic findings				
				Brain weight (g)	Cortical atrophy	Ventricular dilatation	Cerebral atherosclerosis	Other features
1	84	BF	Senile dementia, arteriosclerotic cardiovascular disease	870	4+ Temporal, insular*	4+	±	
2	67	WF	Organic brain syndrome with pyschosis, chronic pyelonephritis, *pneumonia*	850	4+ Temporal, parietal	4+	±	
3	71	BF	Senile dementia, diabetes mellitus, ASCVD	970	4+ Frontotemporal	4+	±	Hyalinized cerebral arterioles
4	88	WF	Senile dementia, blindness, OD, acute laryngotracheal obstruction	1010	2+ Frontotemporal	2+	±	Right optic nerve atrophy
5	84	WM	Alzheimer's disease 10 years, cerebrovascular accident with rapid intellectual decline, ASCVD	1100	3+ Frontotemporal	3+	±	Vascular disease in cerebral cortex septum, amygdala
6	89	WM	Severe chronic brain syndrome, malnutrition, pneumonitis, decubitus ulcers, ASCVD	1040	3+ Frontotemporal	2+	±	
7	72	WM	Organic brain syndrome with psychosis, emaciation, ASCVD, pneumonitis	1100	2+ Frontotemporal	2+	±	
8	72	BF	Chronic brain syndrome, congestive heart failure, atrial fibrillation mitral insufficiency	1020	4+ Frontotemporal	4+	3+	
9	79	WF	Senile dementia, ASCVD, pneumonia, extreme emaciation, congestive heart failure	1080	2+ Frontotemporal	2+	±	
10	55	WF	*Down's syndrome,* aspiration pneumonia, chronic pyelonephritis, malnutrition	900	4+ Parietofronto-temporal	3+	0	
11	53	WM	*Down's syndrome,* seizure disorder, septic shock, renal failure, Dilantin many years	880	4+ Frontotemporal	2+	0	Old cerebral contusions, cerebellar atrophy
12	54	WM	*Down's syndrome,* diabetes mellitus 10 years, diabetic coma	1160	3+ Frontotemporal	2+	±	Small cerebellum
Control	95	BM	Status posttransurethral fulgeration, acute sigmoid colon volvulus	1180	1+ Frontal	1+	1+	Parietal lobe infarct
Control	60	WM	Severe atherosclerotic cardiovascular disease, acute myocardial infarction	1480	–	–	2+	

ASCVD = arteriosclerotic cardiovascular disease.

* See Figure 2.

Table 2—Microscopic findings in Alzheimer's Disease and Down's Syndrome

	Frontal cortex		Temporal cortex		Cingulate cortex		Hippocampal formation			Entorhinal cortex		Amygdaloid complex			Septal area		Mamillary body area	Fornix area
Case No.	SP	NFT	SP	NFT	SP	NFT	SP	NFT	GVD	SP	NFT	SP	NFT	GVD	SP	NFT	(sq mm)	(sq mm)
1	4+	1+	4+	1+	2+	1+	1+	4+	1+	4+	1+	4+	0	1+	2+	0	6.9	10.2
2	3+	0	4+	1+	4+	1+	1+	1+	1+	4+	0	4+	0	1+	3+	0	6.7	6.0
3	2+	3+	4+	4+	2+	3+	2+	4+	3+	4+	4+	4+	4+	3+	2+	3+	11.1	5.5
4	4+	1+	3+	1+	2+	1+	2+	4+	3+	1+	4+	3+	4+	2+	3+	4+	16.4	6.1
5	3+	1+	4+	0	2+	1+	2+	3+	3+	4+	3+	4+	4+	2+	2+	1+	14.5	4.8
6	4+	1+	3+	0	2+	1+	2+	4+	2+	2+	4+	2+	3+	0	1+	0	8.2	12.4
7	4+	1+	2+	1+	2+	2+	1+	4+	3+	2+	3+	2+	3+	2+	2+	3+	12.4	6.7
8	3+	1+	4+	1+	2+	1+	4+	2+	2+	2+	2+	2+	3+	2+	2+	1+	18.5	4.8
9	3+	1+	4+	1+	3+	2+	2+	4+	3+	2+	4+	3+	2+	1+	2+	1+	11.1	6.9
10	3+	1+	4+	4+	1+	0	3+	3+	3+	3+	3+	2+	4+	2+	2+	1+	—	4.6
11	3+	1+	4+	0	2+	0	2+	1+	2+	3+	0	4+	2+	2+	2+	1+	—	5.2
12	2+	0	4+	0	2+	0	2+	0	0	3+	0	2+	0	0	3+	0	9.8	4.8
Control	1+	0	1+	0	0	1+	1+	1+	0	1+	0	0	0	0	0	0	15.4	11.6
Control	1+	0	1+	0	0	0	1+	1+	0	0	1+	0	0	0	0	0	13.8	10.8

SP = senile plaques, NFT = neurofibrillary tangle, GVD = granulovacuolar degeneration.

clinical data, and gross brain characterization. Table 2 quantitatively estimates the involvement by lesions of Alzheimer's disease in specific anatomic regions.

Gross Observations

As recorded in Table 1, the 9 patients with Alzheimer's disease did not differ markedly from one another in their terminal clinical illness or in the gross appearance of their brains. The ages of the 6 female patients and the 3 male patients at the time of death ranged from 67 to 89. The 3 patients with Down's syndrome, though classed as elderly, were all in their mid-fifties. They will be discussed separately. The weights of the brains of patients with Alzheimer's disease ranged from 850 to 1100 g, notably less than normal, while the weights of the brains of 2 control cases were 1180 and 1480 g. Regularly in Alzheimer's disease, there were cortical atrophy and ventricular dilatation of a moderate to severe degree, and the atrophy was predominantly in a frontotemporal distribution.

Case 1 presented a marked degree of atrophy. The most severe tissue loss was along the inferomedial surfaces of the temporal lobes and about the Sylvian fissures, within the insular cortices (Figure 2). The temporal horns of the lateral ventricles were disproportionately dilated, and the hippocampus and amygdala were greatly reduced in size. (Figure 3). The atrophy in the other cases of Alzheimer's disease was more uniformly distributed over the frontal and temporal lobes. In approximately half of the cases, the mamillary bodies were notably diminished in size; the fornix and anterior commissure in most cases were significantly shrunken and demyelinated. The hippocampus was visibly shrunken in Cases 1, 2, 3, 4, 8, and 9. Cerebral atherosclerosis was marked in only 1 case (Case 8) and in general bore no apparent relation to either systemic atherosclerosis or to the degree of cortical atrophy.

Microscopic Observations

Cortex

Microscopic changes in the cortex were the classic ones of Alzheimer's disease. Cortical regions stained with hematoxylin and eosin/Luxol-fast blue showed neuronal depopulation, astrogliosis, and occasionally swelling and increase in the number of endothelial cells. No Pick bodies were noted in the brains. Lester King stains revealed large numbers of senile plaques in all cases—from 20 to 100 per 100 × field. These lesions were focal, spherical collections of extracellular argyrophilic material and were visible in all cortical layers, both underlying the sulci and within the gyral apices. Congo red staining of selected cases demonstrated the typical core

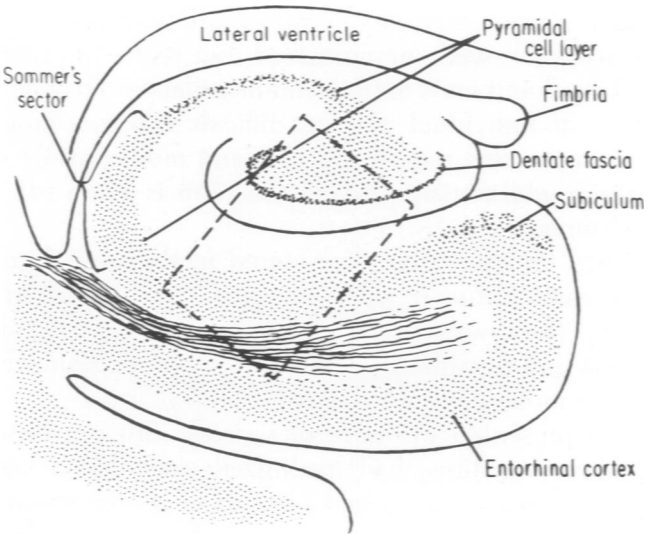
of amyloid. In cases where plaques were most numerous, especially in Case 1, they were not well circumscribed, but tended to blend together and become a confluent mass of dark-staining filamentous material, which made counting of individual plaques difficult and inaccurate. In most cases these changes were more numerous and more distinct in temporal cortex than the frontal or cingulate regions. This is noteworthy in light of subsequent observations.

Neurofibrillary tangles were encountered in the frontal and temporal cortex of most cases but were not present in the same abundance as the senile plaques. They were readily identified as argyrophilic bundles within the soma and proximal processes of neurons. Again, the temporal cortex was often more heavily involved.

Several cases presented evidence of vascular disease. Case 3, with a history of diabetes mellitus, had hyalinized small blood vessels in the cortex and other regions. Case 5 had a history of cerebrovascular accident 3 months before death, and there were subcortical areas containing macrophages and reactive astrocytes, as well as small areas of vascular disease in the septal regions and amygdala. Case 8 had marked atherosclerosis of the large cerebral vessels and thickened blood vessels in cortical areas. In general, however, alterations in blood vessels were not a prominent or an apparently significant component of the pathologic change in the brain. Even in the enumerated cases, senile plaques and neurofibrillary tangles were present in large numbers and did not appear anatomically related to the vascular changes.

Hippocampus

The hippocampi of all brains were markedly affected by the changes of Alzheimer's disease; these often exceeded the severity of involvement elsewhere. In tissues stained with hematoxylin and eosin/Luxol-fast blue, the most conspicuous features were decreased widths of all layers, pale fimbria, and severe depopulation within the pyramidal cell layer (Text-figure 2 and Figures 4–6). Neuronal loss was usually prominent and rarely, if ever, were the remaining neurons normal. Pyramidal cells frequently appeared shrunken and pyknotic or were distended by materials such as lipofuscin. Granulovacuolar degeneration, a neuronal change peculiar to Alzheimer's disease, consisted of large clear cytoplasmic vacuoles enclosing basophilic granules (Figure 7). This lesion was a prominent feature in most of the hippocampi, particularly in Cases 3, 4, 5, and 7. Neurons showing granulovacuolar degeneration were most commonly found in the outer portion of the hippocampal coil, the area known as Sommer's sector (Text-figure 2). This finding is in accord with other studies.[14,7]



TEXT-FIGURE 2—A schematic diagram of the hippocampus in a coronal plane. The *dotted lines* enclosed the region illustrated in Figures 4–6.

King staining made the senile plaques and neurofibrillary tangles of the hippocampus more readily visible (Figure 10). In most cases a large percentage of the pyramidal neurons contained the dark material that is characteristic of this alteration; in Cases 1 and 2 there were few residual neurons, thus a low density of cells to exhibit neurofibrillary change. The configurations of the pyramidal cells were distinctive; the neurofibrils were arranged in parallel bundles, as if painted with a stiff bristle brush (Figure 9). The involvement was generally severe and usually exceeded 60 altered cells per 100 × field. Senile plaques were very large, prominent, and common in this region; usually between 20 and 30 were found in the pyramidal layer per 100 × field. Although they were typically less numerous in the hippocampus than in the neocortex, the cortical plaques were seldom as well defined or darkly stained as those in the hippocampus. The dentate fascia was intact in all instances except Cases 1 and 2, where disruption of its architecture was striking. In no case were plaques or tangles visible within it.

Entorhinal Cortex

The entorhinal cortex and parasubicular and presubicular cortices (Text-figure 2 and Figure 10) were uniformly atrophic, pale, and contained many glial cells but few intact neurons. These changes were so severe in Case 1 that neurons were no longer identifiable in this region. In all other

cases, neurons that were altered by neurofibrillary tangles had unusually dark argyrophilic cell processes that imparted spider-like configurations (Figure 10). Characteristically these cells clustered near the surface or deep within the cortex. The tangles were distinctly different from those found in the nearby pyramidal cells; they appeared as ropy coils rather than stiff brushwork. Senile plaques were conspicuous and tended to laminate between the clumps of neurofibrillary tangles. The prosubiculum was confluently involved like the hippocampus. The better preserved subiculum was sandwiched between it and the altered presubiculum.

Amygdala

The amygdala was grossly atrophied in Cases 1 and 2, and regularly it was the site of very interesting neuronal changes. The neurons contained a variety of intracytoplasmic inclusions that were visible with hematoxylin and eosin stains; these included pigment accumulations, lipofuscin, eosinophilic material, vacuoles, and granuovacular degeneration. In Cases 2 and 3, astrogliosis and neuronal loss were prominent, and in Case 5 a small infarct was present. Without exception the Lester King stain revealed the most distinctive alteration, notably, sharp demarcation between areas of dense senile plaque formation and regions free from involvement (Figure 11). The corticomedial portion of the amygdaloid complex was particularly affected, as has been noted.[7] Speculation has suggested that this has its base in embryonic development, since the corticomedial nuclei appear phylogenetically before the basolateral and might, therefore, be more susceptible to lesions.[7] The anterior commissure, the interhemispheric conduit for amygdalofugal projections, was atrophic in most cases.

Fornix

The fornix was uniformly altered (Table 2). The calculated cross-sectional areas contain, however, a considerable margin of error. In some instances, the fornices were notably smaller than the controls, but in several, they were larger. In the latter instances, the increased size was attributed to disruption and splitting of bundles of axons, for there was consistent demyelination and loss of axis cylinders (Figures 12–15). This finding is noteworthy since the fornix receives a large contribution of axons from the pyramidal cell of the hippocampus. Thus the changes in this pathway principally reflect the degree of structural damage that has occurred in the hippocampus.

Mamillary Bodies

The mamillary bodies receive a sizeable projection of fibers from the hippocampus via the fornix. The size of this nuclear area was highly variable and did not correlate directly with the degree of Alzheimer's change elsewhere. A moderate number of senile plaques, generally less

than 20 per 100 × field, was present in most cases, but neurons did not show neurofibrillary change. This is in agreement with the findings of others.[7]

Septal Nuclei

The septal nuclei are a major target of projections from the fornix and other limbic structures. Generally these nuclei contained few plaques, and these were indistinct and difficult to quantitate. Similarly, neurofibrillary change was present but not striking. In Case 5 there was an old infarct in this area. Most cases showed only a mild neuronal loss and a slight degree of astrogliosis. Generally, plaques and tangles were more striking and numerous in the adjacent subcallosal and septal cortex.

Down's Syndrome Patients

The brains of 3 elderly patients with Down's syndrome (Cases 10, 11, and 12) were examined in the same manner as those with Alzheimer's disease. Table 1 shows the brain weights to be from 880 to 1160 g. The gross appearances of the brains were similar to those of Alzheimer's disease, that is, they showed cortical atrophy in a frontotemporal distribution. In addition, there were other abnormalities: Case 11 had severe old contusions with softening and discoloration of the subfrontal region and tips of the temporal lobes; the cerebellar hemispheres in this case and in Case 12 were extremely small and atrophic. In Case 11 there was a long standing history of seizures and Dilantin therapy.[15] Atherosclerosis was notably absent, even in Case 12, where diabetes had been present for 10 years and the cause of death was considered to be diabetic coma.

The distribution and characteristics of the neuropathologic findings in these brains were indistinguishable from those in the cases of Alzheimer's disease. Senile plaques were regularly found in large numbers in the cortex, and the changes in the limbic structures were marked, especially in Cases 10 and 11. As in the cases of Alzheimer's disease, the temporal lobes were the major site of pathologic change. Senile plaques were generally far more common than neurofibrillary tangles. It is curious that in Case 12, although senile plaques were numerous in the conventional areas, no neurofibrillary tangles were found. This has been observed in other studies; it has been suggested that in patients with Down's syndrome senile plaques develop earlier and persist as a more prominent feature than neurofibrillary tangles.[8]

Discussion

This study demonstrates that the temporal lobes and, in particular, the limbic structures that are contained within this region—notably the hip-

pocampus and amygdala—are severely and routinely affected in Alzheimer's disease. In addition, this study broadens the base of identity between the lesions of Alzheimer's disease and those in elderly patients with the phenotypic picture of Down's syndrome. Although it is difficult to establish close correlation between clinical deficits and anatomic lesions relative to diencephalic functions, these observations support the concept of "limbic dementia" in these two groups of patients.

Other disease processes that are similarly confined to the temporal lobes and limbic system serve to reinforce this concept. Notable among these are: herpes simplex encephalitis,[16] "carcinomatous encephalitis,"[17] and certain cases of vascular disease with infarctions.[18,19] Neurosurgical bilateral ablations of the hippocampi have caused profound and selective loss of memory, especially for recent events.[20] Other procedures that involve larger portions of the temporal lobes may produce more varied symptomatology, including a syndrome resembling that originally induced in monkeys by Klüver and Bucy.[21] In all these situations, the most outstanding symptoms are related to memory, orientation, and affect, the same symptoms which are so prominent in Alzheimer's disease.

The constant involvement of the hippocampus and related structures by the changes of Alzheimer's disease is significant and deserves special comment. Tomlinson and his colleagues, in their study of nondemented elderly persons, found that senile plaques, granulovacuolar degeneration, and neurofibrillary tangles could be seen in the hippocampus long before similar lesions were noted in the neocortex.[22] They commented upon the peculiar susceptibility of the hippocampus to these changes, noting an association between the presence of the lesions and the age of the patients. That the early appearance of lesions in this location could be related to the benign form of forgetfulness frequently encountered in elderly people has been discussed by Roth, Tomlinson's co-worker, in the Ciba Symposium on Alzheimer's disease.[7]

The difference between "benign forgetfulness" and the frank memory loss of Alzheimer's disease appears to be closely related to the quantity of neuropathologic lesions. In a subsequent study of brains of demented elderly persons,[23] these authors found that the same pathologic features seen in nondemented patients were present in patients with a clear-cut history of dementia. After vascular disease had been excluded as an etiologic factor, the distinguishing feature between these two groups was purely quantitative; the demented patients had a much greater degree of plaque and tangle formation than did the nondemented patients. The hippocampal damage in the former was always notably more severe than that in the latter.

Several lines of evidence indicate that in Down's syndrome, too, the hippocampus and temporal lobe structures are predictably and very precociously involved by the changes of Alzheimer's disease. On clinical grounds, a recent study of the performance of patients with Down's syndrome on a battery of psychologic tests suggests that recent memory is the earliest faculty to become impaired with age.[13] The older patients with Down's syndrome performed significantly worse in delayed-matching-to-sample testing than either younger patients with the syndrome or mentally retarded subjects of a comparable age who do not have Down's syndrome. Since the test is considered to be especially useful for assessing temporal lobe functions, attention is directed to the underlying pathologic alterations in this region. A study of the brains of Down's syndrome patients of varying ages suggests that the hippocampus is indeed involved very early by the lesions of Alzheimer's disease, and that these changes progress notably with age.[8]

Alzheimer's disease has been traditionally interpreted as a cortical disease with the manifestations of cortical dysfunction. The mental changes associated with aging in Down's syndrome have been frequently ignored because of the difficulty in evaluating them in the presence of already limited cognitive skills. Yet in both Alzheimer's disease and the elderly patient with Down's syndrome, there are neuropathologic lesions whose distribution is not strictly cortical. Rather the senile plaques, neurofibrillary tangles, and granulovacuolar degeneration in both of these instances have a particular predilection for the temporal lobes and limbic structures, as well as for the cortex. The pattern of these lesions may well impart a special character to the dementia, giving credence to the term *limbic dementia*.

References

1. Katzman R: The prevalence and malignancy of Alzheimer disease: A major killer. Arch Neurol 33:217–218, 1976
2. Blessed G, Tomlinson BE, Roth M: The association between quantitative measures of dementia and of senile changes in the cerebral gray matter of elderly subjects. Br J Psychiat 114:797–811, 1968
3. Wells CE: The symptoms and behavioral manifestations of dementia. Dementia. Edited by CE Wells. Philadelphia, F. A. Davis & Co, 1971, pp 2–11
4. Katzman R, Karasu TB: Differential diagnosis of dementia. Neurological and Sensory Disorders in the Elderly. Edited by W Fields. New York, Stratton Intercontinental Medical Book Corp., 1975, pp 103–134
5. Smythies JR: Brain Mechanisms and Behavior. New York, Academic Press, 1970
6. Powell EW, Hines G: The limbic system: An interface. Behav Biol 12:149–164, 1974
7. Corsellis JAN: The limbic system in Alzheimer's disease and in other conditions associated with dementia. Alzheimer's Disease: A Ciba Foundation Symposium. Edited by GEW Wolstenholme. London, J. & A. Churchill, 1970, pp 37–50

8. Burger PC, Vogel FS: The development of the pathologic changes of Alzheimer's disease and senile dementia in patients with Down's syndrome. Am J Pathol 73:457–476, 1973
9. Crapper DR, Dalton AJ, Skopitz M, Scott JW, Hachinski VC: Alzheimer degeneration in Down syndrome: Electrophysiologic alterations and histopathologic findings. Arch Neurol 32:618–623, 1975
10. Ellis WG, McCulloch JR, Corley CL: Presenile dementia in Down's syndrome: Ultrastructural identity with Alzheimer's disease. Neurology 24:101–106, 1974
11. Olson MI, Shaw CM: Presenile dementia and Alzheimer's disease in mongolism. Brain 92:147–156, 1969
12. Jervis GA: Early senile dementia in mongoloid idiocy. Am J Psychiatr 105:102–106, 1948
13. Dalton AJ, Crapper DR, Schlotterer GR: Alzheimer's disease in Down's syndrome: Visual retention deficits. Cortex 10:366–377, 1974
14. Woodard JS: Clinicopathologic significance of granulovacuolar degeneration in Alzheimer's disease. J Neuropathol Exp Neurol 21:85–91, 1962
15. Utterback RA: Parenchymatous cerebellar degeneration complicating diphenylhydantoin (Dilantin) therapy. Arch Neurol Psychiatr 80:180–181, 1958 (Abstr)
16. Gascon GG, Gilles F: Limbic dementia. J Neurol Neurosurg Psychiatr 36:421–430, 1973
17. Corsellis JAN, Goldberg GJ, Norton AR: "Limbic encephalitis" and its association with carcinoma. Brain 91:481–496, 1968
18. Glees P, Griffith HB: Bilateral destruction of the hippocampus (cornu ammonis) in a case of dementia. Monatsschr Psychiatr Neurol 123:193–204, 1952
19. DeJong RN, Itabashi HH, Olson JR: Memory loss due to hippocampal lesions: Report of a case. Arch Neurol 20:339–349, 1969
20. Scoville WB, Milner B: Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatr 20:11–21, 1957
21. Terzian H, Ore GD: Syndrome of Klüver and Bucy: Reproduced in man by bilateral removal of the temporal lobes. Neurology 5:373–380, 1955
22. Tomlinson BE, Blessed G, Roth M: Observations on the brains of non-demented old people. J Neurol Sci 7:331–356, 1968
23. Tomlinson BE, Blessed G, Roth M: Observations on the brains of demented old people. J Neurol Sci 11:205–242, 1970

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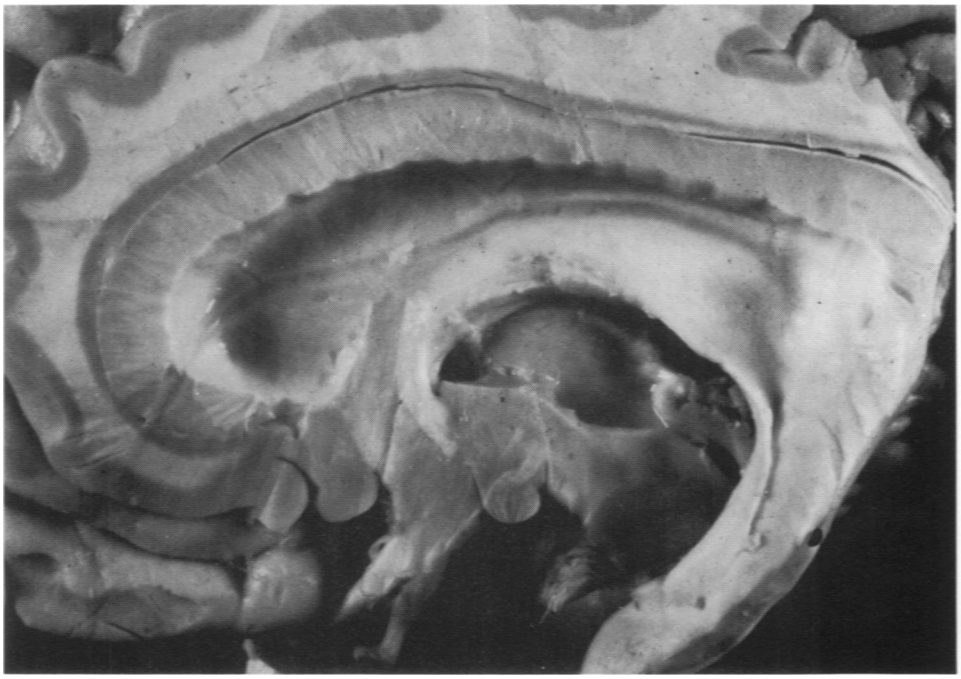
[*Illustrations follow*]



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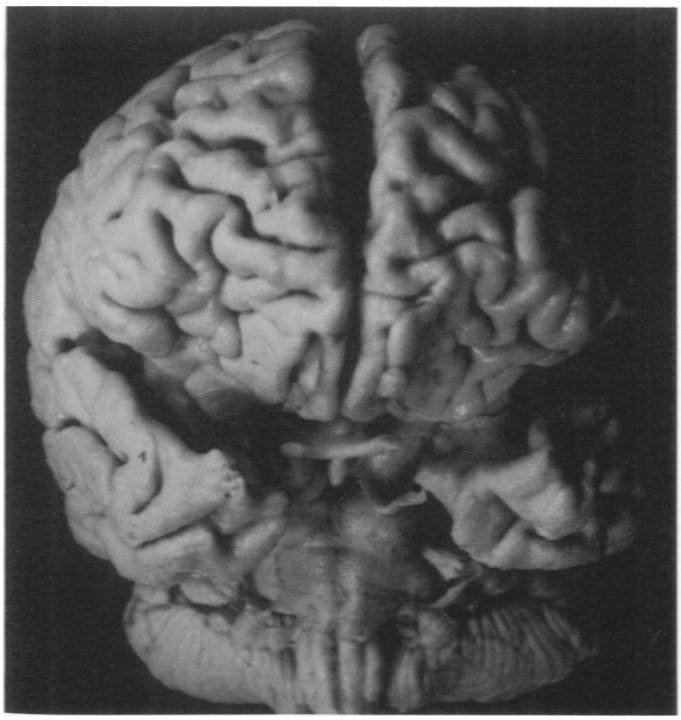

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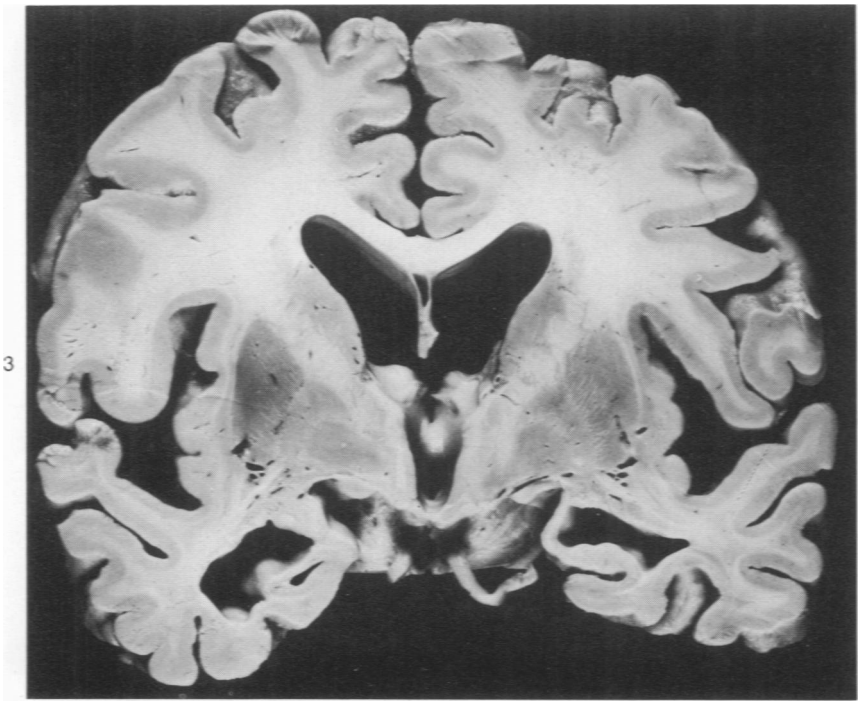
Figure 1—The limbic system of the normal human brain, viewed in the sagittal plane. The hippocampus (*lower right*) gives rise to the fibers of the fornix (*center*), which arch superiorly, then anteriorly and inferiorly to the mamillary bodies and septal nuclei. The amygdala, which lies anterior to the hippocampus, is not shown. **Figure 2**—A frontal view of Case 1 shows an unusually severe degree of atrophy of the temporal lobes. Due to marked atrophy of the hippocampus, amygdala, and entorhinal and insular cortex, there is a wide separation between the temporal lobes and subfrontal region.



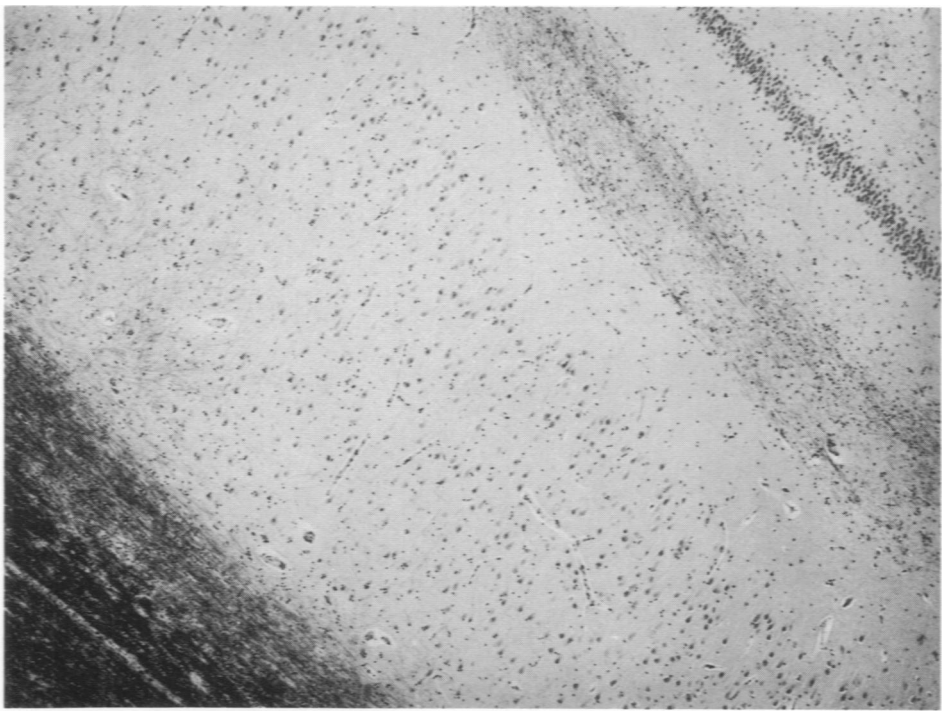
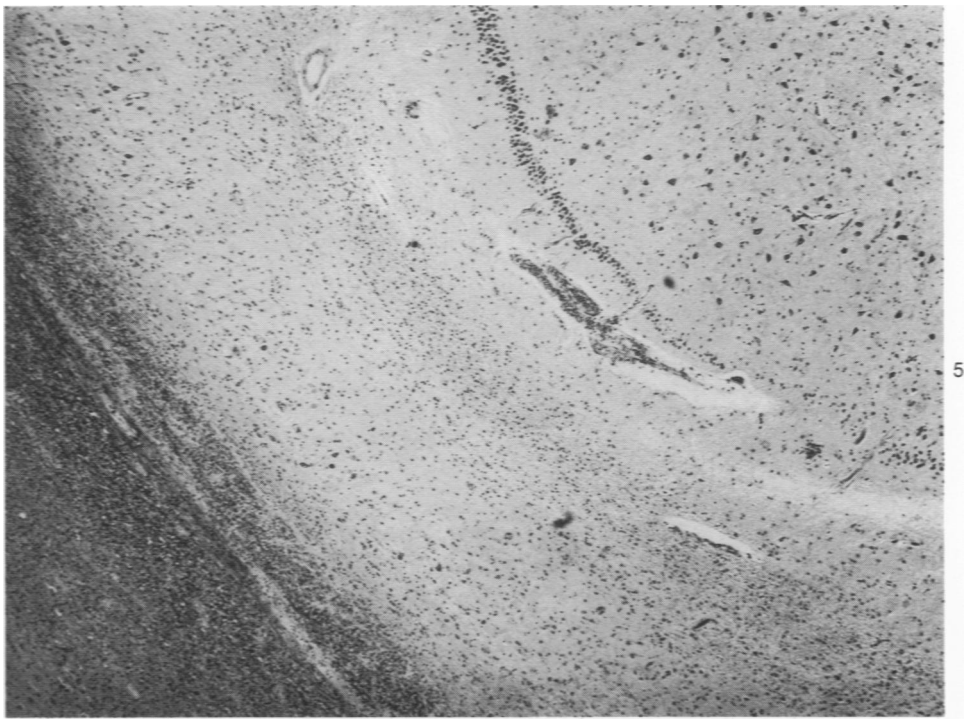


Figure 3—A coronal section of Case 1 at the level of the mamillary bodies shows severe atrophy of the temporal lobes and insular cortex. The hippocampi are greatly reduced in size bilaterally, and the temporal horns of the lateral ventricles are disproportionately dilated. The mamillary bodies are shrunken, while the third ventricle is enlarged. **Figure 4**—The hippocampus of the control, a 95-year-old man without signs of dementia, shows a well-defined dentate fascia (dark band at *upper right*), a wide band of well-formed pyramidal cells (*center*), and darkly staining myelinated fibers (*lower left*). (H&E/Luxol-fast blue, × 40)



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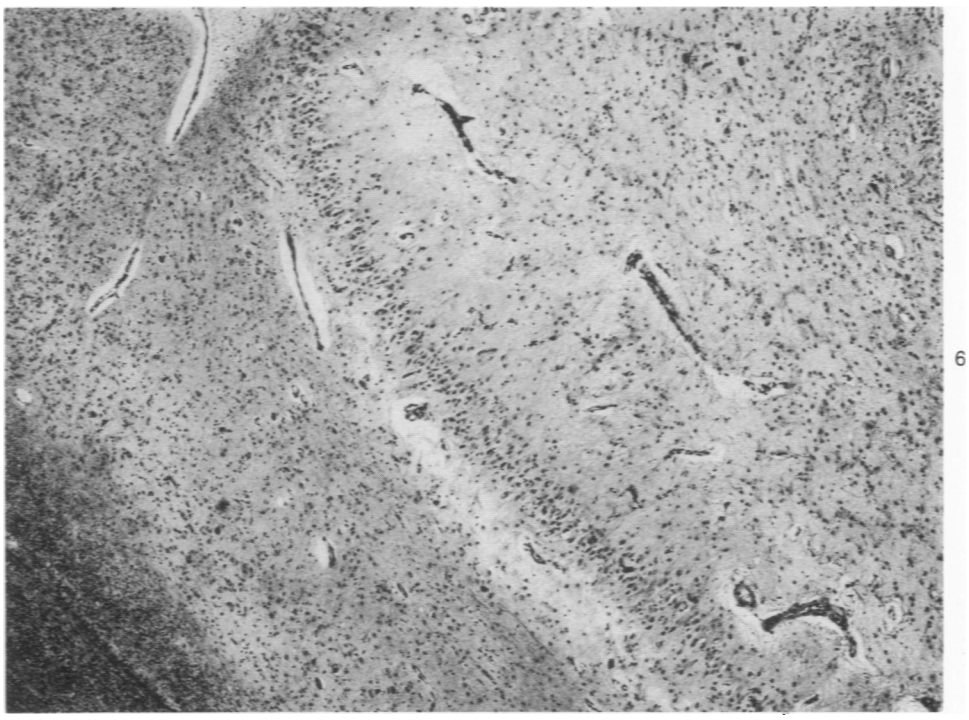

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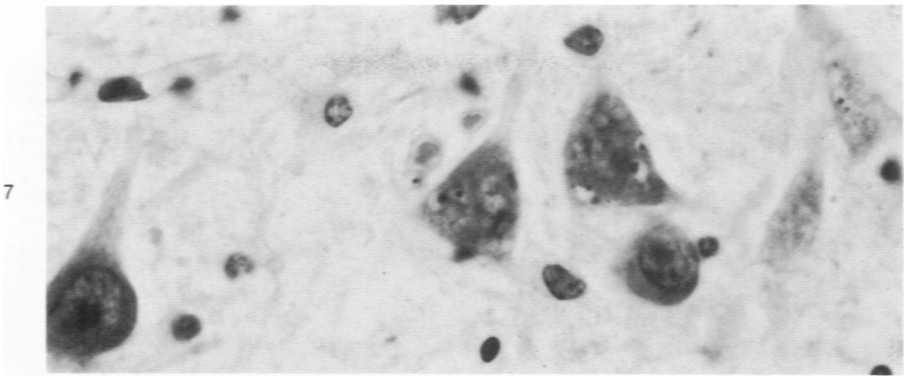
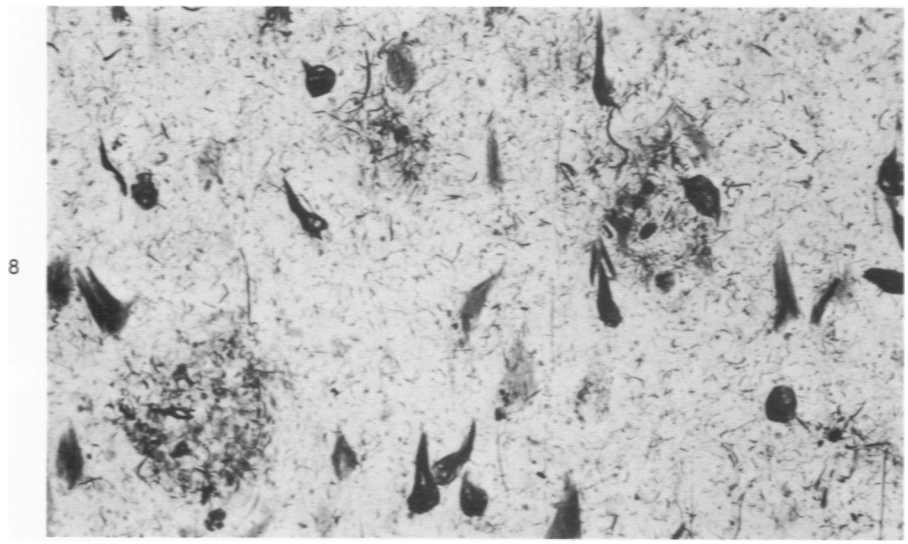
Figure 5—A section of the hippocampus of an 84-year-old woman with senile dementia (Case 1). The dentate fascia is severely disrupted; the pyramidal cell layer is greatly reduced in size; and the underlying white matter is pale and demyelinated. (H&E/Luxol-fast blue, × 40) **Figure 6**—The hippocampus of a 67-year-old female with a long history of organic brain syndrome with psychosis (Case 2) shows similar changes. There is marked loss of pyramidal neurons, and the remaining cells are altered, many containing granulovacuolar degeneration. Senile plaques and neurofibrillary tangles are poorly visualized with this stain. (H&E/Luxol-fast blue, × 40)





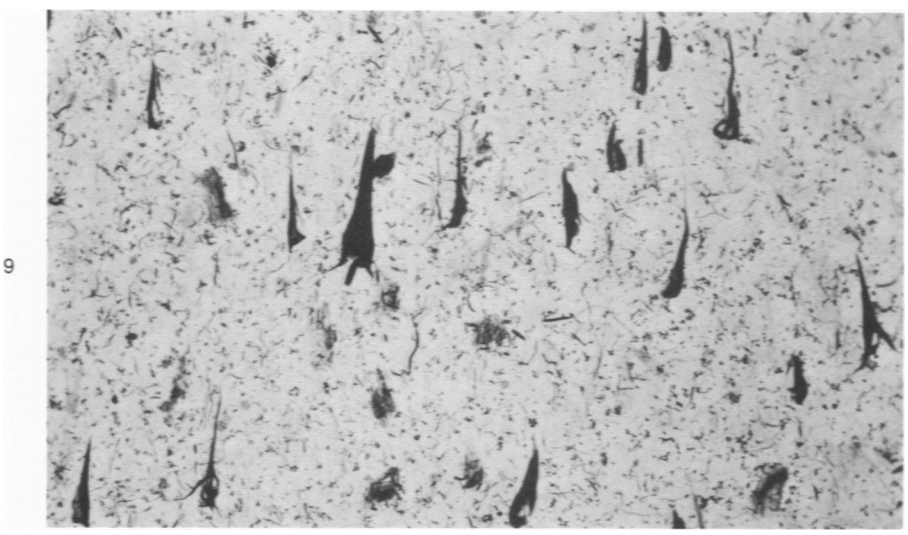
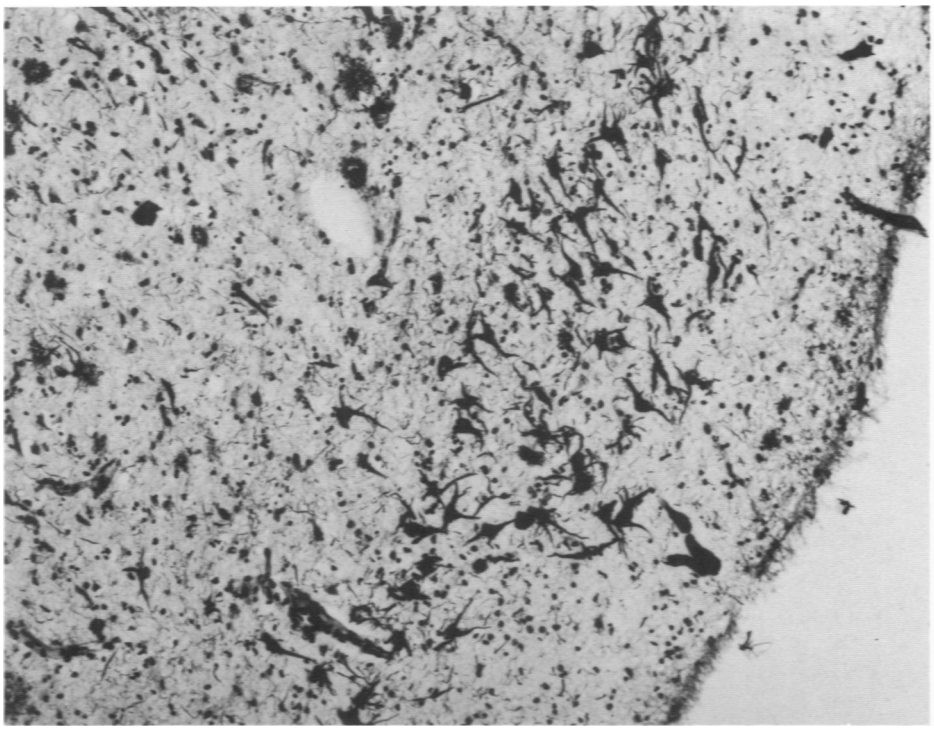


Figure 7—Granulovacuolar degeneration, as seen in the pyramidal neurons of the hippocampus of Case 2, is characterized by large cytoplasmic vacuoles enclosing basophilic granules. An unaffected neuron is visible (*far left*). (H&E/Luxol fast blue, × 480) **Figure 8**—Senile plaques and neurofibrillary tangles are prominent in the pyramidal cell layer as visualized with the Lester King silver stain. The plaques are loose clusters of argyrophilic neurites, while the tangles are argyrophilic bundles within the perikaryon of neurons. (King silver stain, × 100) **Figure 9**—Neurofibrillary change in the pyramidal layer. Distinctive of this region is the ensheathed, stiff appearance of the neurons, as if the staining feature had been applied with a stiff bristled brush (King silver stain, × 100)



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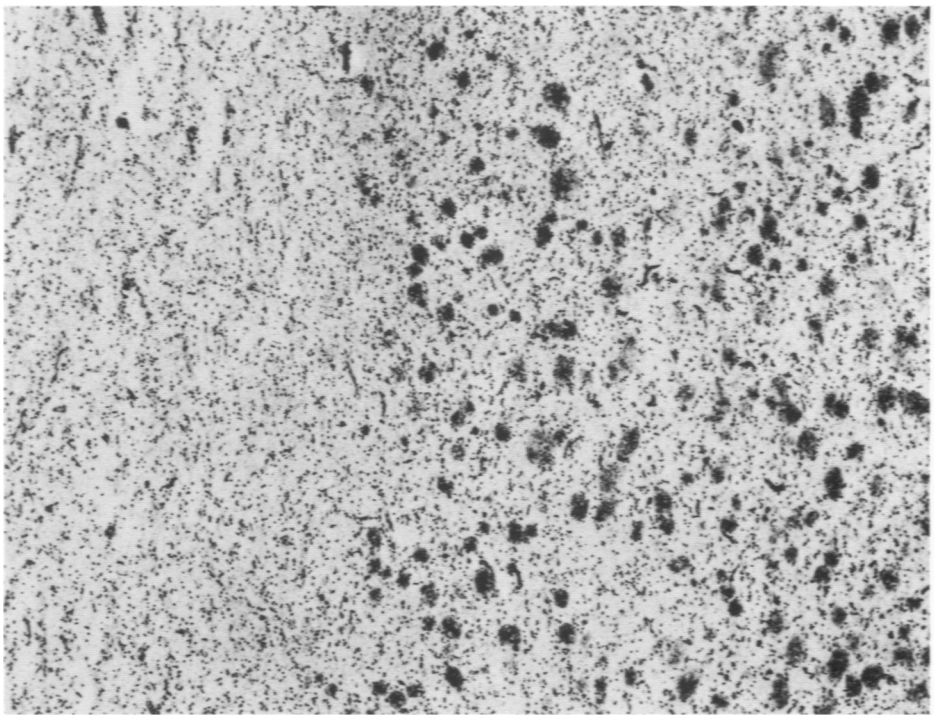

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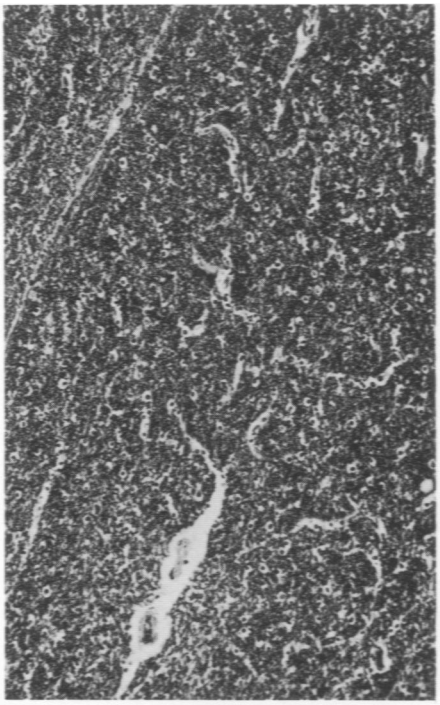
Figure 10—In the entorhinal cortex, adjacent to the hippocampus, the neurofibrillary tangles are typically stellate or spider-like, while the characteristic plaques are numerous and situated deeper within the cortex (King silver stain, × 100). **Figure 11**—Typically in the amygdala, large numbers of senile plaques (*right*) are juxtaposed to regions of gray matter free of involvement (King silver stain, × 40).



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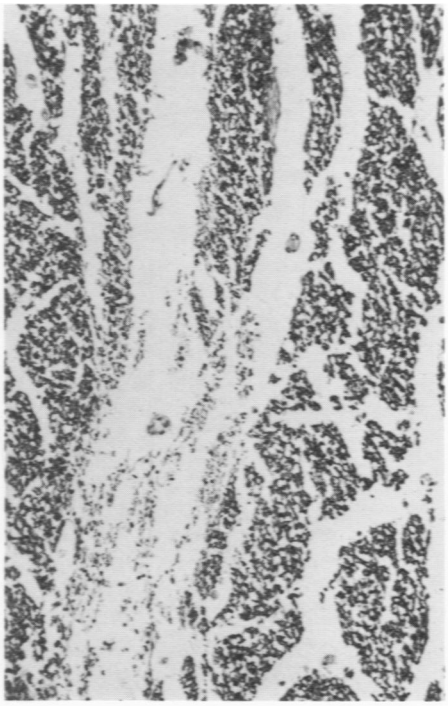

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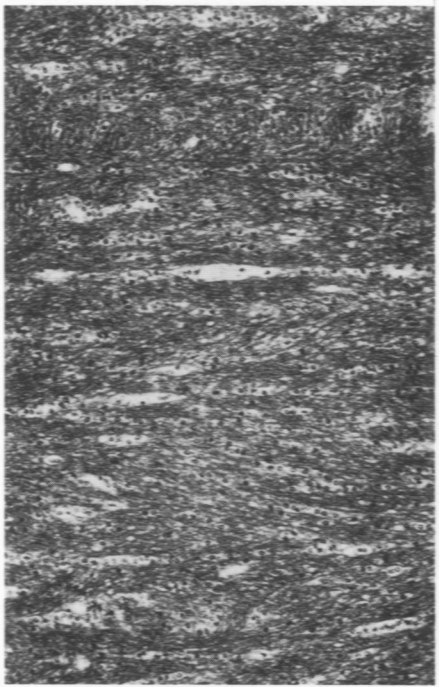

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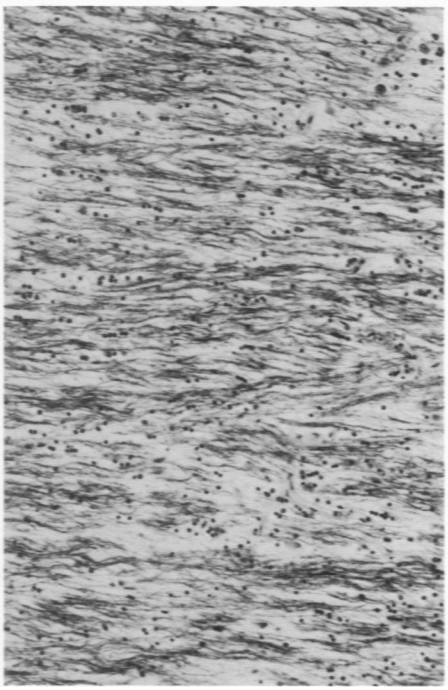

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Figures 12–15—The normal fornix in cross-section is compact and densely myelinated (**12**). By contrast, the fornix from a patient with Alzheimer's disease (Case 1) is loosely structured and markedly deficient in myelin (**13**). These features are also readily apparent in longitudinal sections (**14** and **15**).