ALZHEIMER'S DISEASE IN LATE ADULT LIFE

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A long-standing problem in the morphologic classification of brain disease is the question of the identity of or a distinction between Alzheimer's disease and senile dementia. Most pathologists dealing directly with this problem tend to consider the two entities as basically identical, although the morphologic changes are of relatively mild severity in senile dementia as compared to the presenile form of Alzheimer's disease.[1,2] Assuming identity of these entities, the incidence of Alzheimer's disease has been reported as high as 10 per cent among necropsies at mental hospitals.[3] Yet in much of the modern literature, as well as often in practice, a "presenile" age of onset of dementia is considered mandatory for the diagnosis of Alzheimer's disease and the onset of senium, admittedly arbitrarily, is set at age 60 or 65 years. With such restricted definition, the incidence of Alzheimer's disease among individuals necropsied at mental hospitals has been reported as low as 1 per cent.[4] Senile dementia, on the other hand, is often considered a nondescript entity without clear-cut clinicopathologic correlation, and possible interrelationships with arteriosclerosis and other conditions associated with aging are often overemphasized.

In the middle years of the human life-span in which Alzheimer's disease is an unquestioned clinical and pathologic entity, it is known that the disease increases in incidence with each decade of age. It is probable that exclusion of all cases beyond age 60 is causing increasingly serious underestimation of the importance of the disorder in our aging population. Assessment of the role of Alzheimer's disease in the general problem of senile dementia is demanded by the rising geriatric patient population in state mental hospitals.

The chief cause for confusion in the classification of Alzheimer's disease in late adult years is an inadequacy of commonly used morphologic criteria. Senile plaque formation and neurofibrillary changes have a

This study was supported by Department of Health, Education and Welfare, Public Health Service National Institutes of Health Grant No. MH 08603, sponsored by Camarillo State Hospital, Camarillo, Calif.

Accepted for publication, June 15, 1966.

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very good correlation with gross cerebral atrophy and a history of dementia during mid-adult years, but this correlation is lost in the later years. Gellerstedt,[5] for instance, found senile plaques in 84 per cent of brains in cases with death at age 65 years without history of dementia. Most clinical concepts in the area of senile dementia are based on pathologic studies which are notably lacking in control material. Detailed discussion of histologic criteria and a review of literature pertinent to Alzheimer's disease and senile dementia up to 1958 have recently been presented in scholarly manner by McMenemey.[6]

It is the intent of the present study to determine the incidence of Alzheimer's disease in a state mental hospital. It is of particular importance to ascertain by controlled observation the clinical significance of the morphologic criteria related to Alzheimer's disease in cases having the onset of dementia beyond age 60. Necropsy material from cases without psychiatric disorders is included in the study as a means of control of pathologic observations and also in an effort to establish some approximation of the prevalence of Alzheimer's disease in the general population in later adult years.

Material and Methods

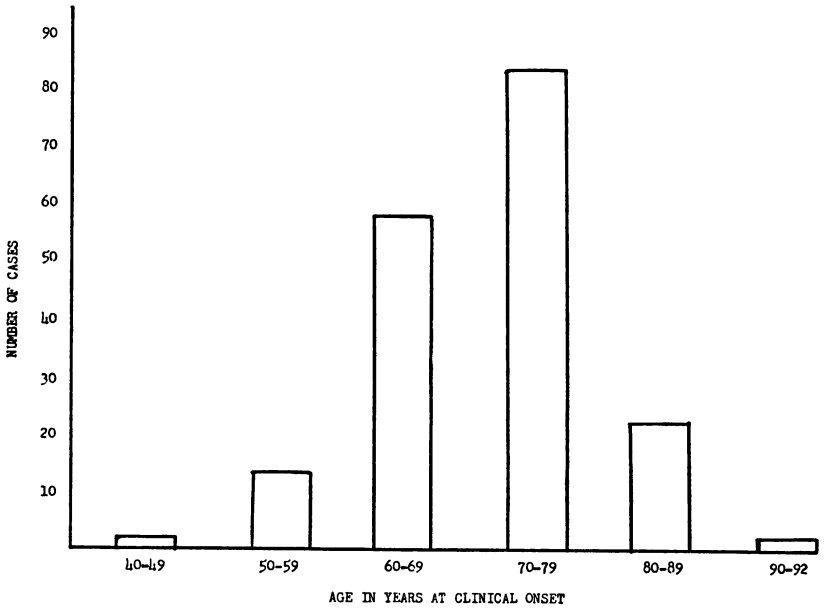
The study is based on an analysis of 1,000 necropsy cases from 3 state mental hospitals in southern California. Seven hundred cases representing consecutive unselected necropsies were performed at Camarillo State Hospital, a large mental institution having an average patient population of 5,879 during the period of the study. Essentially all deaths at this hospital were cases of psychosis acquired in adult years and during the period of study complete necropsies were performed in 50 per cent of deaths. Included also are 300 consecutive necropsy cases from Pacific State Hospital and Fairview State Hospital, these institutions serving only mentally deficient individuals. For control purposes 100 additional necropsy cases were studied from local nonpsychiatric sources including chiefly the St. Joseph's hospital in Burbank, California, the City of Hope Medical Center in Duarte, California, and from regional county coroners. Only patients over 60 years of age at death were included in the latter group but they were otherwise unselected.

After fixation by immersion in 10 per cent formalin each brain used in the study received uniform gross and histologic examination. A minimum of 20 brain tissue blocks were examined in the first 700 cases including samples of hippocampus and ventral temporal neocortex from both sides. Additional samples of neocortex were regularly taken from the frontal, occipital and insular areas of the right cerebral hemisphere. On the basis of data obtained from this material it was determined that equivalent information could be obtained from fewer carefully selected samples and on this basis the remaining cases in the series had a minimum of 10 preselected samples. The latter samples included the original representation of hippocampal formation and areas of cerebral neocortex from the right cerebral hemisphere as given above, a mid-level of the lentiform nucleus, the diencephalon at the level of the mammillary body, a full thickness section of the cerebellar hemisphere on one side and 3 transverse levels of brainstem. Hematoxylin and eosin staining was used regularly. In addition, the hippocampus and ventral temporal neocortex from one side was stained by the Bielschowsky method and counterstained lightly with

Harris' hematoxylin in the first 500 cases in the series but was then discontinued as having little diagnostic value. In addition all gross lesions encountered were also examined histologically using hematoxylin and eosin, the Kluver-Barrera method (luxol blue and cresyl violet) for myelin and Nissl substance, the Bielschowsky silver method for neurofibrils and the periodic acid-Schiff method for polysaccharides. Frozen sections were stained with Sudan III for demonstration of free fat and the Cajal silver chloride method was applied for astrocytes.

OBSERVATIONS

Among the 700 unselected consecutive necropsies at the mental hospital serving adults with psychosis, 190 cases (27 per cent) had all of the clinical and morphologic features essential to the diagnosis of Alzheimer's disease. These cases had a mean survival following the date of admission of 3.6 years. Distribution of the cases with respect to age at onset of dementia is illustrated graphically in Text-figure 1.



TEXT-FIG. 1. Distribution of the cases of Alzheimer's disease according to age of onset of the dementia.

For the purpose of this study the diagnosis of Alzheimer's disease was based on the clinical features of progressive dementia having its onset in middle or late adult life and the microscopic features of granulovacuolar neuronal degeneration, senile plaque formation and neurofibrillary degeneration. Granulovacular degeneration, first described in 1911 by Simchowicz,[7] consists of cytoplasmic accumulation in hippocampal pyramidal neurons of small vacuoles measuring up to 5 μ in diameter, each containing a small basophilic granule. In neurofibrillary degenera-

tion, described by Alzheimer [8] in 1907, there is argentophilia, thickening and contortion of the fibrils within the neuronal cytoplasm producing conspicuous "tangles" in Bielschowsky stain preparations. The senile plaques are masses of argyrophilic particles with variable patterns of organization; these are present in the cerebral cortex of most brains beyond age 65. A detailed discussion of the essential microscopic stigmas (Figs. 1 and 2) has been presented by McMenemey.[6] The granulovacuolar degeneration was subjected to some quantitation, this being considered consistent with Alzheimer's disease only when involving 9 per cent or more of the pyramidal neurons in the ventrolateral quadrant of the hippocampal formation.[9]

Alzheimer's disease is generally known to be associated with diffuse cerebral atrophy and it is well recognized that the atrophy tends to be most severe in cases with earlier onset of dementia (Fig. 3). The present study, however, has revealed the age factor to have more than a simple quantitative effect on gross features. In cases with more advanced age at clinical onset, the atrophy was noted to be relatively restricted to the hippocampal formations and occasionally the adjacent neocortical convolutions, these being selectively and severely involved with rare exception even in the most aged individuals (Fig. 4). With less regularity there was some tendency for selective atrophy of the medial occipital convolutions in the older patients and also some minimal diffuse atrophy of cerebellar folia.

Of the microscopic features, only granulovacuolar degeneration of the hippocampal neurons remained specific; the other features of Alzheimer's disease, such as senile plaque formation and neurofibrillary changes tended to become a function of age beyond the age of 60 years. While the more commonly used criteria were often encountered among the older institutionalized patients with psychosis in cases of schizophrenia and in many cases of thoroughly documented organic psychosis such as general paresis, granulovacuolar degeneration in significant abundance was not encountered in a single case lacking clinical features at least consistent with Alzheimer's disease. Remarkable bilateral symmetry was present in the distribution of granulovacuolar degeneration in the hippocampal formations; selective gross atrophy was equally symmetrical in all cases. Many other histologic features were noted to be characteristic, i.e., capillary fibrosis, focal thickening of the pial glial membrane and mild loss of Purkinje neurons. These, however, did not occur with sufficient regularity to be of diagnostic value. Of special interest was the appearance of concentric hyaline cytoplasmic inclusion bodies in the pigmented nuclei of the brainstem in 14 cases among the older patients with Alzheimer's disease from the mental hospital.

Among the older patients with Alzheimer's disease, 6 showed superimposed brain disease of such type and magnitude as to challenge the causative role of Alzheimer's disease in the production of mental symptoms. The superimposed disease was usually cerebrovascular in character, although in 1 case there was clinically unrecognized nonsuppurative meningoencephalitis. The lesions in the 5 cases with more extensive cerebrovascular disease were similar to those seen in association with arterial hypertension; the smaller arteries were affected. Indeed, these cases were unusual within the Alzheimer group in having clinical records of hypertension and notations of cardiomegaly as a necropsy finding. In 3 additional cases a few small areas of infarction were noted in basal brain structures apparently related to atherosclerotic changes in the basilar arteries. A more common cerebral ischemic alteration was specifically associated with Alzheimer's disease and was encountered in 14 per cent of the cases. This had no relationship to hypertension or demonstrable cerebral arterial diseases and consisted of segments of ischemic cerebro-cortical necrosis lacking the usual sparing of the subpial zone and encroaching slightly upon the subcortical white matter. These lesions often showed selectivity for the border zones of the vascular supply (Fig. 5). Microscopically there was often regional intensification of capillary fibrosis and pial thickening. Taking into consideration the overall group of cases of Alzheimer's disease, no consistent relationship between the clinically significant brain parenchymal degeneration and any gross or histologic alteration in the cerebral arteries could be detected. Instances of severe atherosclerosis in the basilar arteries were unusual.

A notable exception to the usual age dependency of the disease was observed among the cases with mental retardation. Among 34 cases of mongolism, 4 met the morphologic requirements of Alzheimer's disease; these represented all of the older patients with ages at death ranging from 52 to 65 years. Even with a relatively young onset of Alzheimer's disease among the mongols, gross atrophy and microscopic alterations were greatly restricted to the hippocampal regions, features otherwise observed only in the "senile" group. The hippocampal formations usually showed severe selective atrophy and microscopically there was granulovacuolar degeneration as well as neurofibrillary sclerosis and senile plaque formation in abundance.[10] Other than in mongolism Alzheimer's disease was encountered in only 2 cases of mental deficiency. These were patients in whom during the mid-adult period manifestations of progressive dementia and extrapyramidal disorders became superimposed upon a lifelong state of moderate mental retardation. In these cases the hippocampal features of Alzheimer's disease and an obscure

adult form of neuron storage disorder were observed.[11] The combination of mental retardation, superimposed neuron storage disease in adult life and the morphologic features of Alzheimer's disease was reported in a single case by Hallervorden[12] in 1938.

The control brains procured from nonpsychiatric sources, while limited in number, confirmed the specificity of the criteria used for the recognition of Alzheimer's disease. Among these 100 patients who died beyond the age of 60 years, 6 showed the gross and microscopic features of Alzheimer's disease. These formed a unique group in having well documented histories of progressive dementia even though they were not in institutional confinement at the time of death. Such a successful clinicopathologic correlation was achieved only by virtue of the degree of quantitation afforded by granulovacuolar degeneration in the hippocampus.[9] A much larger group of cases without documented dementia exhibited granulovacuolar degeneration with an incidence of 1 to 7 per cent in ventrolateral quadrant hippocampal pyramidal neurons; in individuals manifesting dementia this incidence ranged from 15 to 50 per cent.

Unfortunately clinical records seldom included a sufficiently complete mental examination to establish a relation between minor degrees of intellectual degradation and slight manifestations of Alzheimer's disease, with granulovacuolar degeneration in 7 per cent or less. It is noteworthy that among the patients without psychiatric disorders none showed the segmental cortical necrosis seen in 14 per cent of the institutionalized cases with Alzheimer's disease. Concentric hyaline inclusion-body formation in the control cases was restricted to one with Alzheimer's disease.

Discussion

Senile plaque formation and neurofibrillary changes are constantly present in Alzheimer's disease at any age but lose their clinicopathologic significance after age 60. Granulovacuolar degeneration of hippocampal neurons is the only morphologic criterion that maintains its significance throughout the life-span, perhaps partly because it lends itself to rough quantitation. As the age of clinical onset increases, gross atrophy as well as the histologic features of Alzheimer's disease tend to become relatively restricted to the hippocampal formations and adjacent neocortical convolutions.

Loss of specificity of the more commonly used microscopic criteria explaining clinical manifestations beyond age 60 is largely responsible for serious underestimation of the importance of Alzheimer's disease in the older age group. No doubt the incidence of Alzheimer's disease increases with each decade of the life-span and the vast majority of cases

have the onset of dementia beyond age 60. The controlled criteria used in this study place the incidence of the disease as high as 27 per cent among necropsies at a large state mental hospital. Since Alzheimer's disease is inevitably a clinically progressive dementia, it follows that no significant number of cases requiring commitment would be removed from this status before death and the death rate should be essentially identical to the admission rate. From the necropsy incidence of 152 cases each year and considering the 50 per cent representation of deaths in the necropsy studies, it can therefore be determined that approximately 100 new cases of Alzheimer's disease appear yearly at Camarillo State Hospital. In view of the average survival of 3.6 years it can be estimated that 422 living patients, 7 per cent of the hospital's patient population, have the disease. These considerations clearly take the entity of Alzheimer's disease out of the category of rare conditions and establish it as one of the most prevalent forms of disabling brain disease. While the broad clinical classification of senile dementia no doubt includes other morphologic entities, notably cerebrovascular disease, the majority of cases fall into the category of Alzheimer's disease.

The control necropsy material obtained from nonpsychiatric sources confirms the validity of the histologic criteria used in this study. Only 6 cases exhibited the pathologic criteria required for the identification of Alzheimer's disease and all these had well documented clinical records of progressive intellectual deterioration; there were no other long-standing neuropathologic alterations of significance. The number of cases is relatively small. The occurrence of 6 instances in 100 unselected necropsy cases among nonpsychiatric patients dying after the age of 60 years, however, would suggest that dementia on the basis of Alzheimer's disease is present in approximately 6 per cent of the general population in this age group not committed to mental hospitals.

The occurrence of the microscopic features of Alzheimer's disease in older individuals with mongolism was noted by Jervis.[13] The present study suggests that the disease is readily identifiable in the majority of patients with mongolism where there is survival beyond the age of 50 years; the disorder may also complicate certain other forms of genetically determined mental retardation. It is further worthy of note that even younger individuals with Alzheimer's disease superimposed on mental retardation exhibit morphologic features which are not characteristic of the presenile form of the disease. Rather the lesions are similar to those seen in the older age group in the general population having a predilection for the hippocampus. The appearance of Alzheimer's disease among the mentally retarded is an important demonstration of the etiologic complexity of the disorder and indicates that under certain

circumstances a genetic abnormality, such as trisomy 21, may be an important contributing factor.

The observation that 3 per cent of the cases of Alzheimer's disease exhibited a superimposed neuropathologic alteration of another type which might itself provide a basis for dementia is to be anticipated; cerebrovascular disease has a high general incidence in the older adult age range. Overlapping of diseases cannot be construed as necessarily indicating any essential interrelationship between the distinct entities. On the other hand, segmented foci of complete cortical necrosis restricted to borders of major vascular supply zones and exhibiting such microscopic features as capillary fibrosis, occurring in 14 per cent of the cases of Alzheimer's disease, are best considered to be part of Alzheimer's disease since they are rarely seen in its absence.

Concentric hyaline inclusion-body formation in pigmented brainstem nuclei appeared with an incidence of 8 per cent in Alzheimer's disease. This may represent a superimposed feature of special significance possibly implicating a relationship between Alzheimer's disease and idiopathic Parkinson's disease. The inclusions, occasionally referred to as Lewy bodies, have long been known to be a characteristic feature of Parkinsonism. Among necropsy cases of mental disease with the onset of symptoms after the age of 50, these inclusions have been found in 27 per cent of cases not otherwise permitting classification in well established brain disease categories.[14] With the notable exception of Alzheimer's disease, inclusion-body formation occurs in a remarkably discrete group of patients with late adult psychoses. The 100 necropsies performed upon older adults without psychiatric disorders have reestablished the relationship of inclusion bodies to mental disease; the abnormality was found in only 1 case, this being 1 of the 6 individuals with Alzheimer's disease.

Summary

The commonly used morphologic diagnostic features of Alzheimer's disease lose clinicopathologic significance after the age of 60 years. Thus, most, if not all, cases in late adult years are excluded from this category despite the fact that the incidence of the disease in general is a function of age. Judging from necropsies in a state mental hospital serving patients with acquired psychosis the incidence of Alzheimer's disease has been estimated to be 27 per cent among patients dying and 7 per cent among those living in the institution. In an additional 300 cases from hospitals serving patients with mental deficiency, Alzheimer's disease was recognized at necropsy in only 6 patients with genetically determined mental retardation (i.e., mongolism) with relatively long

survival. Among 100 unselected necropsied patients from nonpsychiatric sources with ages at death of 60 years or more, 6 cases presented the clinical and morphologic features of Alzheimer's disease. This suggests that approximately 6 per cent of the older general population of adults eventually become demented on this basis. There is no doubt a higher incidence of intellectual impairment short of documentable dementia in the general population resulting from the same pathologic process.

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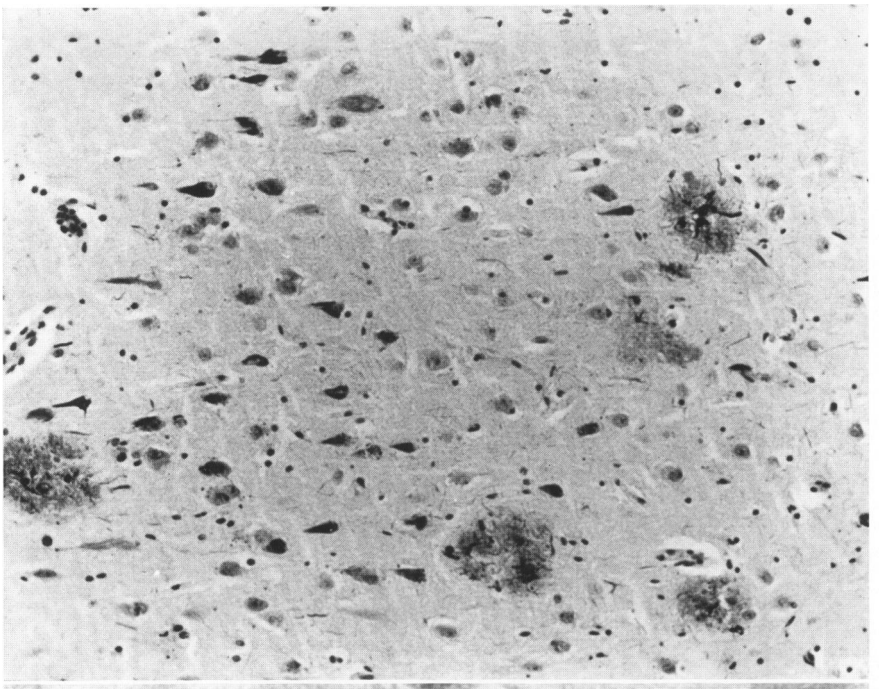
[*Illustrations follow*]

Legends for Figures

FIG. 1. Hippocampal cortex in Alzheimer's disease. Apparent are senile plaques and an abundance of neurons with neurofibrillary sclerosis. Bielschowsky stain. × 75.

FIG. 2. The hippocampal neurons in Alzheimer's disease exhibit granulovacuolar degeneration. Bielschowsky stain. × 380.



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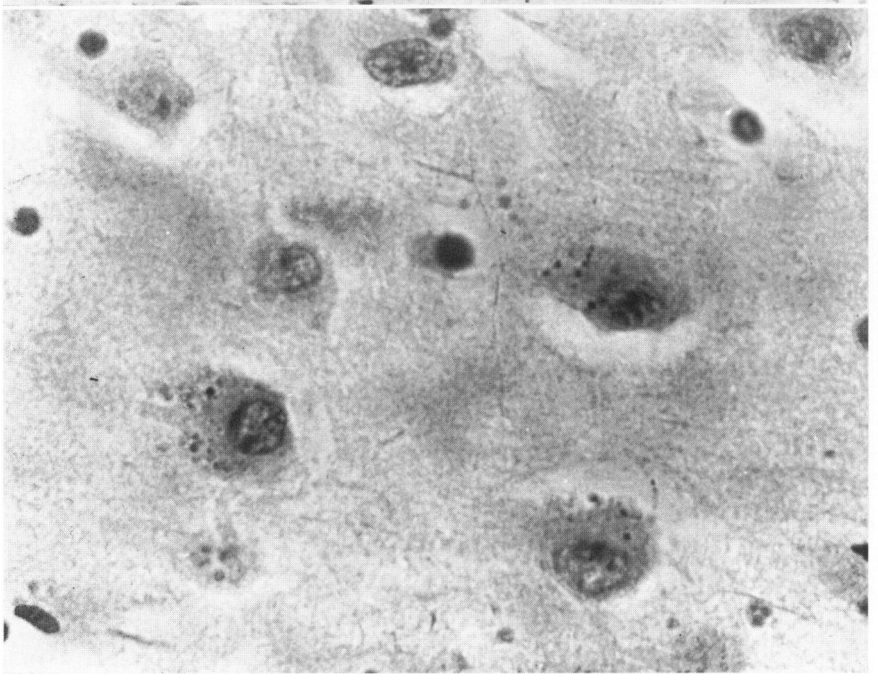

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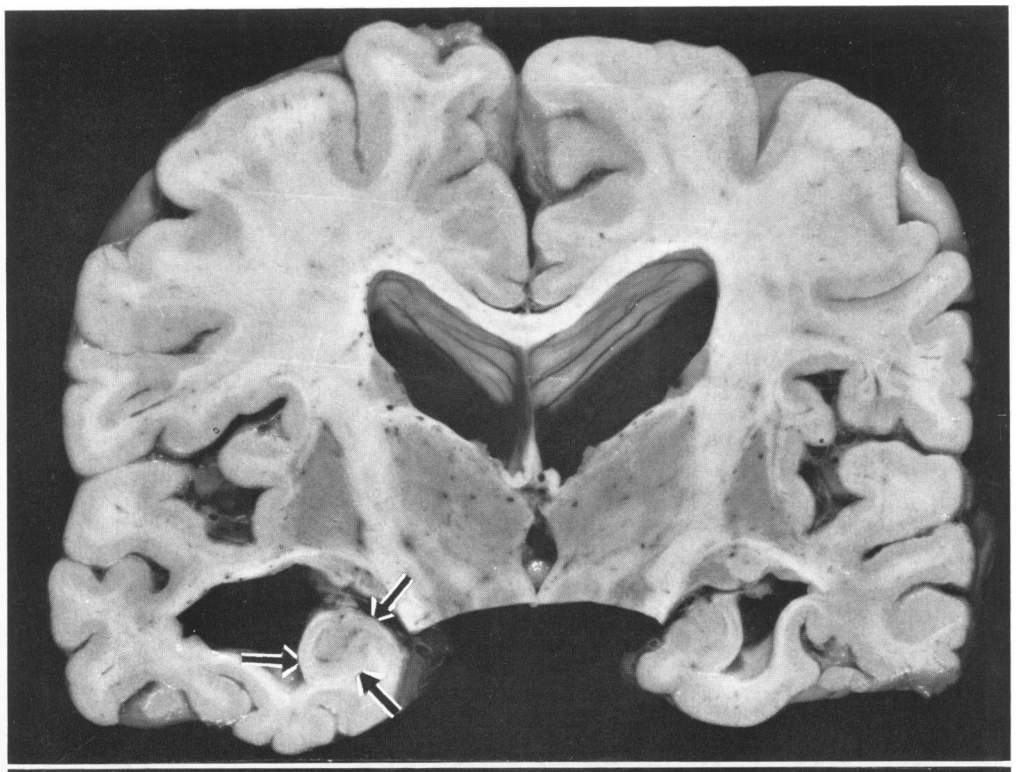

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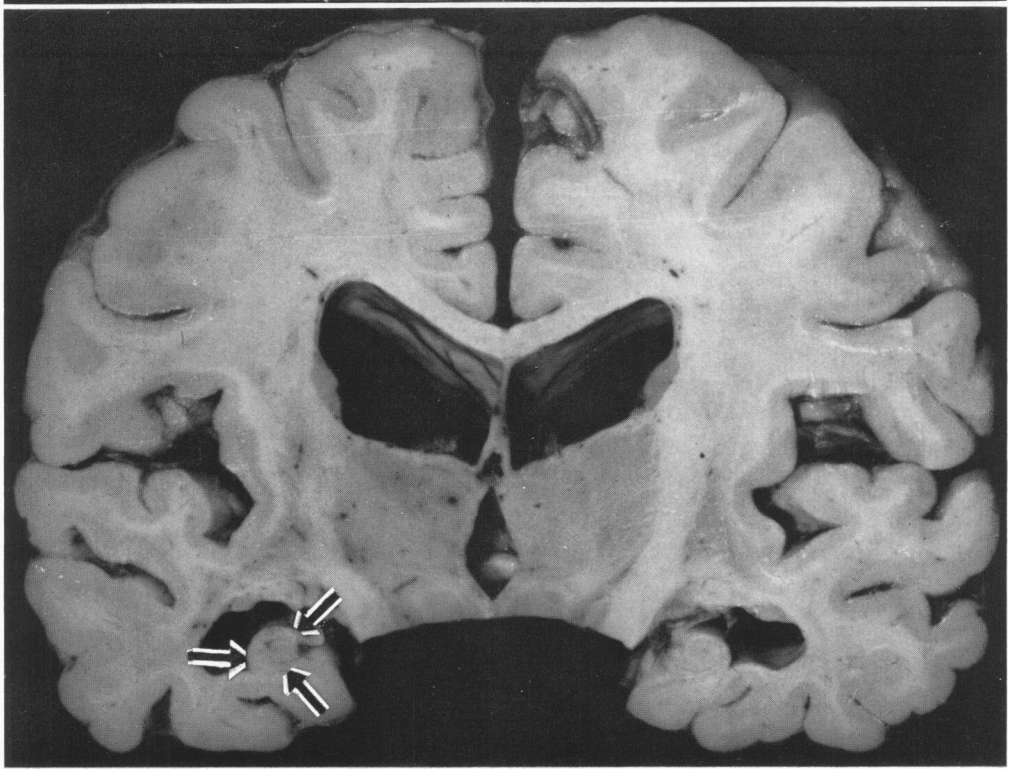

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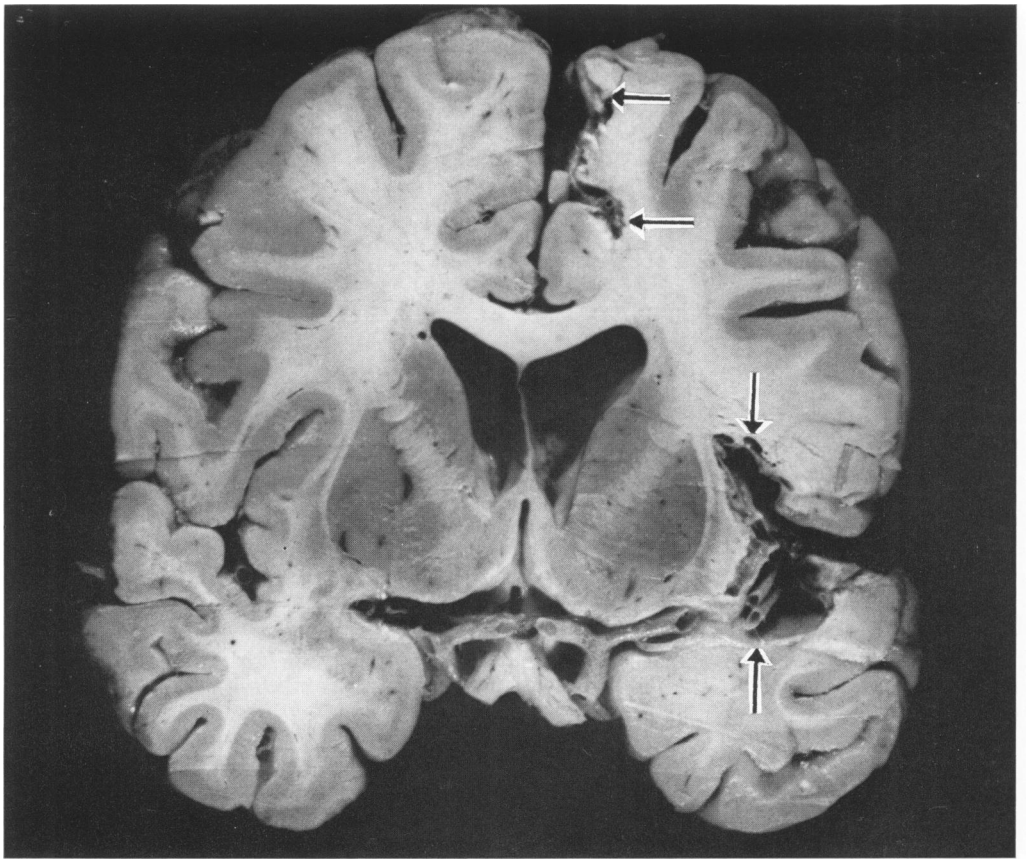

FIG. 3. A case of presenile Alzheimer's disease with clinical onset at age 49 years. Diffuse cerebral atrophy is shown. The hippocampal formations (arrows) exhibit no selective atrophy.

FIG. 4. Selective hippocampal atrophy (arrows) is apparent in a case of Alzheimer's disease with age of onset at 75 years.

FIG. 5. A case of Alzheimer's disease in an old adult. Segmental ischemic cavitation appears in the border zones of vascular supply (arrows).