ALZHEIMER'S DISEASE AND RELATED CONDITIONS

A Ciba Foundation Symposium

Edited by
G. E. W. WOLSTENHOLME
and
MAEVE O'CONNOR

J. & A. CHURCHILL
104 GLOUCESTER PLACE, LONDON
1970

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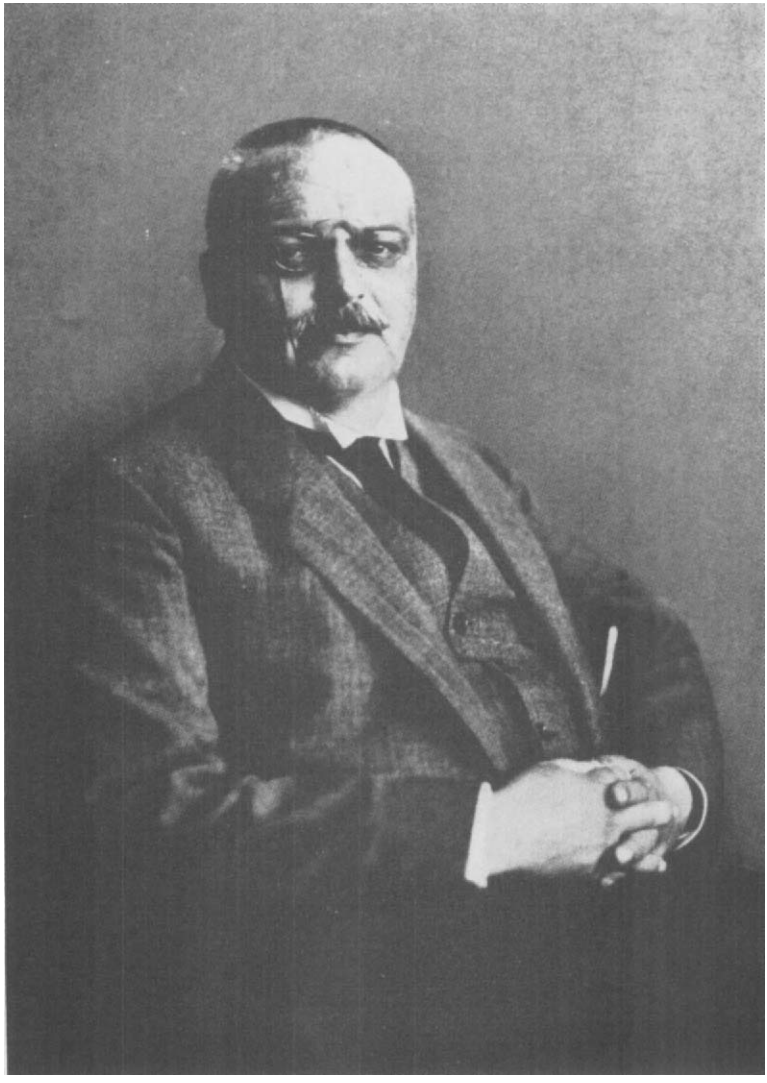

Alois Alzheimer, 1864–1915

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The Ciba Foundation

The Ciba Foundation was opened in 1949 to promote international cooperation in medical and chemical research. It owes its existence to the generosity of CIBA Ltd, Basle, who, recognizing the obstacles to scientific communication created by war, man's natural secretiveness, disciplinary divisions, academic prejudices, distance, and differences of language, decided to set up a philanthropic institution whose aim would be to overcome such barriers. London was chosen as its site for reasons dictated by the special advantages of English charitable trust law (ensuring the independence of its actions), as well as those of language and geography.

The Foundation's house at 41 Portland Place, London, has become well known to workers in many fields of science. Every year the Foundation organizes six to ten three-day symposia and three to four shorter study groups, all of which are published in book form. Many other scientific meetings are held, organized either by the Foundation or by other groups in need of a meeting place. Accommodation is also provided for scientists visiting London, whether or not they are attending a meeting in the house.

The Foundation's many activities are controlled by a small group of distinguished trustees. Within the general framework of biological science, interpreted in its broadest sense, these activities are well summed up by the motto of the Ciba Foundation: *Consocient Gentes*—let the peoples come together.

Preface

THIS symposium, held at the suggestion of Professor W. H. McMenemey, brought together neurologists, pathologists, psychiatrists, biophysicists and others. In spite of illness, Professor McMenemey gave much time and thought both to the organization of the meeting and later to the preparation of the material for publication. The Foundation is deeply grateful to him for his initiative, continuing interest, advice and help.

We are also much indebted to Professor M. Roth for taking the chair at a meeting where such different disciplines were represented. His sympathetic direction of the proceedings enabled clinicians and laboratory scientists to communicate effectively and to appreciate each other's work.

Finally, the editors wish to thank all the participants, who by their work before, during and after the meeting have made this book a record which we hope will be of wide interest.

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The frontispiece is reproduced from *Grosse Nervenärzte*, vol. 2, ed. K. Kolle, 1959, by kind permission of Georg Thieme Verlag, Stuttgart.

CHAIRMAN'S OPENING REMARKS

PROFESSOR M. ROTH

I should like to welcome you all to this meeting and to express both my pleasure and my misgivings in having been asked to act as your Chairman. Research in this as in every other field of neuropsychiatry has become a highly professional, specialized activity and the task of a Chairman is a difficult one. In this context I recall with a certain sympathy the comment of Dr Johnson when he was listening with evident apathy to the performance of a certain violin player. His host tried to encourage him and said: "Dr Johnson, you know this piece is very difficult." "Difficult do you call it, Sir? I wish it were impossible." However, the interest of the subject and the work of the international group of scientists invited by the Ciba Foundation more than compensates for the challenge.

I should like to make certain general points about the groups of disorders we shall be discussing, in an attempt to construct a conceptual framework for our discussions here. There is evidence to suggest that Alzheimer's disease is partly determined by heredity. However, the genetic factor in question does not appear to be of the classical, major, all-or-none Mendelian kind. We are in that very difficult ill-charted territory of genes with additive effects. The second point follows from the first and is a paradoxical one. If we deal with additive genes, we should normally expect the disease in question to have the features of a quantitative variant of the norm. Alzheimer's disease does not conform to this expectation, the clinical findings being in far better accord with an all-or-none phenomenon. Yet the pathological changes have been demonstrated to occur in a less pronounced form in normal elderly subjects, as Gellerstedt (1933) and others have shown. The third point again follows naturally and relates to the specificity of the pathological changes. Are they the common end-result of a number of distinct forms of neuronal degeneration and destruction, or is it possible that the modern ultrastructural and histochemical techniques that have taught us so much in recent years would reveal a

diversity beneath the apparent uniformity of the light microscope appearances in Alzheimer's disease, normal senescence, senile dementia, amyotrophic lateral sclerosis and other disorders? It would, I believe, be generally agreed that these changes are in some measure to be found in a variety of disorders.

Fourthly, the phenomenon appears to be linked in some as yet undisclosed manner, as are so many of the problems of modern medicine—arterial hypertension, cancer, cerebrovascular and cardiovascular disease—with the degenerative processes of middle and late life. What is this relationship? Are we dealing with a caricature of the ageing process, or are the clinical and morphological similarities to Alzheimer's disease deceptive and misleading? One finding which enhances the general biological interest of the subject is the markedly increased mortality in Alzheimer's disease and related disorders.

Fifthly, this is a disease in which the primary, most conspicuous and specific changes are in the brain and the brain has a fixed population of post-mitotic cells. Such organs are particularly prone to exhibit adverse changes in the course of senescence. Sixthly, memory disturbance is invariable and generally among the earliest manifestations of the condition. In this memory disturbance we are looking at failure of one of the basic processes of the cerebrum—its capacity for forming a short-term or a lasting record of experience. How fundamental is this change and what is its pathological correlate? Is there a generalized change at synapses or some specific localized lesion in the hippocampus or limbic system which has aroused such wide-ranging neurobiological interest in recent years?

We embark on this symposium as a collection of experts with different special interests. At the end of Ciba Foundation symposia, as far as my experience goes, the participants form a more closely aggregated group and have often achieved a useful consensus about a number of problems. I hope that we shall succeed in sustaining the Foundation's splendid record. Lewis Carroll may have dimly foreseen a predicament similar to our own when he wrote, in *Through the Looking Glass*, "All the time the guard was looking at her, first through a telescope, then through a microscope, and then through an opera glass. At last he said, 'You are travelling the wrong way!'." We have been set the task of evaluating what has been achieved in Alzheimer's disease with the aid of different methods of investigation applied at different organizational levels. We may be fortunate enough to achieve fresh insights. But a wide range of long-established and novel approaches

are represented here and some of us may have to arrive at the more modest, though not less useful, conclusion that we are travelling the wrong way.

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ALOIS ALZHEIMER AND HIS DISEASE

W. H. McMENEMEY

Department of Pathology, National Hospitals for Nervous Diseases, Maida Vale Hospital, London

THE trail we are to follow during these three valuable days was laid in Tübingen in the first week of November 1906, at a meeting of the South West German Society of Alienists. Alois Alzheimer recounted his clinical and neuropathological findings in a 51-year-old woman whose symptoms began with loss of memory and disorientation; later came depression and hallucinations, and in under five years profound dementia and death. The brain was found to be atrophied and the cerebral cortex contained miliary lesions (*Herdchen*), presumably of the type which Blocq and Marinesco described in 1892 and which were at that time being studied by Fischer. But Alzheimer also noted, thanks to the use of Bielschowsky's method of silver impregnation, a curious clumping and distortion of the cortical neurofibrils which we now associate with his name.

His presentation was noted by title only in the *Neurologische Zentralblatt* in 1906 and the report, without illustrations, is to be found in the *Allgemeine Zeitschrift für Psychiatrie* in the following year. There was no discussion after his presentation. He seems to have been impressed not only with the severity of the pathological process and especially the changes in the neurons but also with the early age of onset of a clinical condition which in an older person he would have regarded as senile dementia.

In 1908 Bonfiglio described a neurosyphilitic male with the disease but Perusini's four cases published in 1910 were more straightforward. He believed the condition to be independent of senility and therefore a disease *sui generis*. This was also the view of Kraepelin who in the same year proposed that it be named after his observant neuropathologist, Alzheimer. Italian writers have understandably called it the Alzheimer-Perusini disease.

Alzheimer was 42 years old when he read his historic paper and he could boast of having received part of his training in Würzburg under von Kölliker, the histologist and one-time colleague of Virchow. His fruitful association with Franz Nissl, a brilliant technician and his senior by four years, began in 1889 in Frankfurt-am-Main and lasted for six years. Later

their times in Kraepelin's department in Heidelberg overlapped for a year until Alzheimer accompanied Kraepelin to Munich in 1903. As a man of private means, Alzheimer could afford to combine his histological studies with clinical work, an association of pursuits which although unpopular in some quarters today continues to produce important results and deserves every encouragement.

It is fitting that in our tribute to the memory of Alzheimer we should feel it necessary to review both the clinical and pathological aspects of the disease, and I would ask those who decry the use of eponymic terms in medicine what alternative name workers in the second decade of this century could have used? We must ask ourselves whether we are ready to change this designation to another which succinctly conveys our present-day notions on its aetiology and pathogenesis.

An eponym in medicine raises the question of how far we are justified in departing from the criteria originally laid down by the person or persons who first described the malady. Many believe that when a disease has a firm basis in pathology, pathological rather than clinical findings constitute the more important criterion for acceptance of diagnosis. In Alzheimer's disease, therefore, the association of more or less generalized cortical atrophy with the presence of many argyrophilic plaques and neurons afflicted with changes in the neurofibrils ("tangles") constitutes the essence of the pathology. Granulovacuolar degeneration of the pyramidal cells of the hippocampus is clearly acceptable but it was only described in 1911 by Simchowicz and the same can be said of two further landmarks in our knowledge of the disease, namely, the recognition of amyloid by Divry (1934), of which we shall hear more later, and the interesting electron microscopic features of this disease. Pathological findings unknown to Alzheimer and Perusini can surely be accepted provided they are constant and the case histories are typical.

The symptomatology in Alzheimer's disease has also been widened since the year 1910 and these additions are presumably acceptable provided the pathological findings are typical. The disease has been found in persons, particularly those with heredofamilial histories, who have not reached an age when they could be regarded as in any way presenile. The age range therefore has been widened.

But the so-called "senile plaques", one of the two hallmarks of Alzheimer's disease, are to be found in a variety of other conditions, as well as in the elderly, and the same is true of that other hallmark, the curious neurofibrillary change: only in well-established cases of Alzheimer's disease, however, does one find them so constantly together and in such

numbers. Some may say "what about in senile dementia?" and the answer to this could be "if this brain came from a person aged 86, then pathologically speaking she was a senile case of Alzheimer's disease", which is of course the reverse of what Alzheimer apparently thought in 1906 in his presenile case of presumed senile dementia! Fischer (1907) would have called these late examples of Alzheimer's pathological syndrome "presbyophrenic dementia", and there is perhaps a case for resuscitating this term as a pathological diagnosis if plaques and (especially) altered neurons are more scantily and locally distributed in the brains of many elderly dements—and they are practically all women—than in a classical instance of Alzheimer's disease. There are cases too of elderly dements whose brains lack the classical pathological features of Alzheimer's disease although there is a conspicuous increase in the lipochrome content of the surviving cortical neurons.

Dr Wolstenholme has entitled this symposium "Alzheimer's disease and related conditions". He knew well, I think, that the confines of an eponymic disease are liable to be indefinite. I am sure it would help if we could pronounce on the legitimate boundaries of Alzheimer's disease. There have been those who argue that there are differences in symptomatology between it and "senile dementia" which cannot be accounted for by diminished ability on the part of an old person to react to a cerebral disorder with its train of disturbing symptoms. If therefore we are prepared to accept or reject a demarcation between Alzheimer's disease and presbyophrenic dementia—let us call it—or Fischer's disease, it would be useful. The paper by Dr Sourander which follows will, I am sure, help us to make up our minds because the author comes from a country noted for its intensive genetic and clinical studies as well as for careful neuropathology.

What other "related conditions", then, are relevant to our symposium? Pick's disease springs to mind, not because it can be difficult to distinguish on clinical grounds, but because of the occasional reports of classical histological features of Alzheimer's disease confined to the atrophied parts of the brain, the curious association of the two diseases as reported by Berlin (1949) and, as we shall hear today, the greater involvement of one lobe or side in some cases of Alzheimer's disease, just as in Pick's disease and in Lissauer's dementia. Finally that orphan of neuropathology—or perhaps family of orphans—Creutzfeldt-Jakob disease, is unlikely to be far from our thoughts.

The pathologist and the electron microscopist—in spite of the undoubted value of biopsy and the advances in cytochemistry—see only the debris of the battlefield and it is left to the clinician, the neurophysiologist and the

chemist to deduce what actually happens in the struggle between the healthy brain and the disturbance which affects it. As neurons seem to be selectively and extensively picked out in Alzheimer's disease can a dormant virus or slow virus be considered in part or wholly responsible? Can geneticists explain why one uniovular twin in Edinburgh died after 19 years with this form of dementia while her sister in Australia was in good health four years after her death? It is worth remembering that the afflicted twin experienced a period of febrile delirium during the 1918–19 epidemic of influenza but she also had acne rosacea, for which reason Davidson and Robertson (1955) suggested that somatic mutation might account for the double discordance.

The term "abiotrophy" was coined by Gowers (1902), although the idea of localized diminished vitality was advanced by Aristotle. Is the word still respectable or, in the wider group of diseases under discussion—occasionally heredofamilial though usually sporadic—shall we soon be able to implicate a particular gene or group of genes as being wholly or partly responsible?

The Ciba Foundation has to its credit a series of five colloquia on the subject of ageing, and the spirited discussion which followed Dr Kallmann's paper (1957) on twin data was mostly concerned with the relationship of the presenile dementias to ageing. That debate could well be regarded as the prelude to this symposium, but would we be justified in attributing Alzheimer's disease to ageing any more than to, say, diabetes mellitus or cancer? The Alzheimer cell change has been found in many conditions unrelated to senility. However we shall know more about this when we have heard of the recent work on the spatial arrangement and chemistry of neurofilaments and neurotubules and on the pathology of synapses: by then we may be nearer to understanding the basic lesions of Alzheimer's disease and important aspects of protein metabolism in the brain.

Fortunately, in this gathering we have many types of specialists who can help to solve our problems and we are of varied ages: those recently qualified are proficient in the use of new techniques and see the problems with sharp eyes and fresh minds; the older of us have the benefit of experience and longer memories which should serve us well, provided that our strata glomerulosa are functioning properly and are not already encumbered by bloated neurofibrils.

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THE CONCEPT OF ALZHEIMER'S DISEASE AND ITS CLINICAL IMPLICATIONS*

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"Nomina si nescis, perit et cognitio rerum" (Linnaeus, in *Philosophia Botanica*, 1751)

IN order to determine the place of Alzheimer's disease in the spectrum of neuropsychiatric disorders the clinical and morphological characteristics of the condition must be described, and the borderlines between this disease and related conditions must be defined by using suitable structural and functional parameters.

GENERAL FEATURES OF ALZHEIMER'S DISEASE

Light microscopic and clinical characteristics

The disease first described by Alzheimer (1907, 1911), for which Kraepelin (1910) coined the eponym Alzheimer's disease, is a primary degenerative polioencephalopathy of unknown aetiology and pathogenesis. Morphologically it appears as cortical atrophy with many neurofibrillary tangles and so-called "senile" plaques, best shown in light microscopy by silver stains, birefringence after Congo red staining (Divry, 1934) and fluorescence after treatment with thioflavine (Schwartz, 1965). These changes occur in the isocortex and allocortex of both cerebral hemispheres and are sometimes seen also in the subcortical grey matter and occasionally in the brain stem. Neuronal loss, accumulation of lipofuscin and astrogliosis are subsidiary features without relevance for the differential diagnosis.

The clinical symptoms and course of Alzheimer's disease have been regarded by many investigators as fairly well defined (Rothschild and Kasanin, 1936; Sjögren, 1950, 1952, 1956; Delay, Brion and Garcia Badarocco, 1955). In our material (68 cases) the onset was between 45 and

* The investigation was supported by grants from the Swedish Medical Research Council, Project 21X-618-01, A-B, and from the United Life Group Insurance Co., Stockholm.

59 years of age in 50 per cent, between 60 and 64 years in 30 per cent and between 65 and 69 years in 20 per cent.

The course is progressive, without remissions. Sjögren (1950, 1951, 1952) distinguished three stages in the development of the disease. The initial stage, lasting two to four years, is characterized by mnestic disturbances, spatial disorientation and in most cases a pronounced lack of spontaneity. In the second stage progressive organic dementia and focal symptoms appear, particularly agnosia, aphasia and apraxia. Certain motor disturbances of a hypertonic-akinetic character are also frequently observed. The terminal stage is characterized by complete dementia, often accompanied by cerebral seizures and in most cases by a Klüver-Bucy-like syndrome (described separately later on). In a previous investigation (Sjögren, Sjögren and Lindgren, 1952) many of the symptoms in Alzheimer's disease were attributed to damage to the frontal and parietal lobes. In this presentation the importance of temporal lobe damage for the symptomatology will be particularly stressed.

Sjögren (1956) reported observations on a number of patients showing a symptomatology which in some respects resembled Alzheimer's disease, but which on the other hand was not typical of this disease. The characteristic features were: (1) much later onset than in Alzheimer's disease proper; (2) none of the lack of spontaneity characteristic of Alzheimer's presenile dementia; (3) absence of extrapyramidal features; (4) absence of cerebral seizures; (5) progressive dementia with agnosia, aphasia and apraxia as in Alzheimer's disease in younger individuals. The degree and distribution of cerebral atrophy was the same as in Alzheimer's disease but plaques and particularly fibrillary tangles were much less frequent than in classical Alzheimer cases.

This condition, which was called "atrophia senilis cerebri", differed markedly from cases of dementia senilis simplex and presbyophrenia. In the latter conditions focal neurological symptoms were absent, brain atrophy was rather slight and tangles in the isocortex were rare. There is a close clinical and morphological resemblance between "atrophia senilis cerebri" and the "démence sénile alzheimerisée" of the Geneva school of psychiatry (cf. Arab, 1954). The cases covered by the eponym possibly represent late manifestations of Alzheimer's disease. At least some of the so-called "juvenile" cases reported in the literature may represent early manifestations, although the clinical deviations from the classical type of Alzheimer's disease appear even more marked in these cases than in senile "alzheimerized" dementia.

A considerable number of familial cases of Alzheimer's disease have been

reported (Lowenberg and Waggoner, 1934; McMenemey *et al.*, 1939; Essen-Möller, 1946; Lauter, 1961; Bucci, 1963; Nahman and Rabinowicz, 1963; Heston and Loventhal, 1966). Some of these were cases with an early onset (van Bogaert, Maere and de Smedt, 1940). In the familial cases the genetic transmission has usually been described as autosomal and dominant. For the sporadic cases T. Sjögren assumed there was a cumulative polygenic action (Larsson, Sjögren and Jacobson, 1963).

Histochemical, ultrastructural and biochemical findings

Numerous papers have been written on the histochemistry of "senile" plaques and Alzheimer's neurofibrillary tangles. The main interest has been focused on the amyloid-like properties of a substance accumulating in the core of the plaques, in the tangles and in the walls of cortical vessels (cf. Hechst, 1929; Divry, 1934, 1935, 1939; Scholz, 1938; Missmahl and Hartwig, 1954; Margolis, 1959; Diezel and Vogel, 1965). In biopsy material Friede (1962, 1965) demonstrated increased enzyme activity in cortical zones corresponding to the early stage of plaque formation. The oxidative enzymes were increased at the periphery of the plaques, whereas acid phosphatase activity was increased throughout the fully developed plaques, particularly in the central deposits of granular material and in invading microglia. The marked increase in oxidative enzymes was interpreted as indicating that plaque formation may be induced by activation of metabolic processes in the neuropil. The considerable size and central degeneration of mature plaques were explained on the basis of inadequate capillarization.

Electron microscopic studies by Terry (1963) on cortical biopsies in Alzheimer's disease showed a neuropil structurally normal save for moderate gliosis. The ultrastructural localization of the acid phosphatase activity within the plaques in Alzheimer's disease was studied by Suzuki and Terry (1967). Dense bodies, probably of lysosomal character, were seen in distended axons and dendrites within the plaques. By analogy with changes occurring in early Wallerian degeneration, Suzuki and Terry hypothesized that formation of the plaques was "secondary to a proximal degeneration in neuronal perikaryon, possibly related to the neurofibrillary tangle of Alzheimer". Gonatas, Anderson and Evangelista (1967) identified some of the neuronal processes within the plaques as being presynaptic terminals. According to Terry (1968), the ultrastructural studies of brain biopsies in Alzheimer's disease suggest that "the clinical symptoms may be due to intraneuronal neurofibrillary lesions and to loss of cortical neurons".

For the highly characteristic neurofibrillary tangles originating in the cytoplasm of neurons the eponym Alzheimer's neuronopathy may be suggested. It has been known since the time of Cajal that changes resembling Alzheimer's neuronopathy may occur spontaneously, e.g. during hibernation, or may be induced by various methods, e.g. cold combined with inanition (cf. Jackson, 1925) or dehydration (Alexander, 1934; Stern and Elliott, 1949). Recently aluminium phosphate injected intracranially into rabbits has provided an interesting experimental model for both the acute and the chronic stages of Alzheimer's neuronopathy (Klatzo, Wiśniewski and Streicher, 1965; Terry and Peña, 1965; Terry, 1968; Wiśniewski, 1968). The use of quantitative cytochemical and histochemical techniques with this model indicated that the synthesis of proteins of a neurofibrillary type increased in the neurons showing tangles (Embree, Hamberger and Sjöstrand, 1967). This observation is of considerable interest since the electron microscopic studies by Kidd (1964, 1965) on cortical biopsies in Alzheimer's disease have shown that the filaments in this disease are not identical with normally occurring smooth neuronal filaments but appear to have periodically arranged expansions suggestive of the formation of an abnormal protein. Further discussion of the experimental models falls outside the scope of this presentation.

Since plaques, tangles and amyloid-like changes of the cortical vessels (congophilic angiopathy) are not specific for Alzheimer's disease, their histochemical characterization does not provide a reliable basis for delineation of the concept of Alzheimer's disease.

Only a few biochemical studies have been made in Alzheimer's disease. The content of non-haemin iron in various cortical fields in this disease and in normal senile involution showed (Hallgren and Sourander, 1960) no increase corresponding to the histologically detectable cortical iron deposits which Goodman (1953) assumed to be due to a primary disturbance of iron metabolism in Alzheimer's disease. The cortical accumulation of stainable iron, particularly in glial cells, may be secondary to a redistribution of iron caused by altered binding of the iron in the severely degenerated cortical tissue. Studies by Svennerholm on brain lipids from ten individuals in our series of Alzheimer cases did not provide evidence of any primary disturbance of lipid metabolism, and the normal figures for non-lipid hexosamine made a primary disturbance of the glycosaminoglycan metabolism less likely (Sjögren, Sourander and Svennerholm, 1966). Suzuki, Katzman and Korey (1965) found an increase in total acid polysaccharides in the cerebral cortex and this was assumed to reflect the presence of amyloid in the core of the plaques.

In recent years disturbances in monoamine metabolism, particularly in Parkinson's disease, have received much attention. Low values for homovanillic acid (HVA), the *o*-methylated acid metabolite of dopamine, were shown in autopsy specimens from the neostriatum in individuals with senile dementia (Gottfries, Gottfries and Roos, 1969) and Alzheimer's disease (Roos, personal communication). It was suggested that these conditions may be associated with a disturbance of monoamine metabolism which is reflected in a reduction of HVA in the neostriatum. A statistically significant relation was found between a low HVA concentration and a high degree of dementia, but since the clinical diagnosis of Alzheimer's disease seems not to have been neuropathologically verified no definite conclusion can yet be drawn about the monoamine metabolism in this malady.

COMPARATIVE STUDIES ON ALZHEIMER'S DISEASE AND RELATED CONDITIONS

The results presented here are essentially based on a joint clinical (Sjögren) and morphological (Sourander) investigation. All cases derive from the same source: Clinic I, Women's Department, Lillhagen Mental Hospital.

Brain atrophy

The weight of the brain was determined in 400 cases (Sjögren, 1965). The age at death of 318 patients is shown in Fig. 1. Fig. 2 shows the marked differences in distribution of brain weights in the three main diagnostic groups, i.e. the "nuclear" group consisting of patients afflicted with progressive organic presenile or senile dementia, the cerebrovascular group, and patients with other psychiatric disorders principally of the geriatric functional type. This third group includes disorders of mainly psychogenic origin, such as paraphrenic, melancholic and psychoneurotic states, without obvious structural changes in the brain. Brain atrophy is most pronounced in the nuclear group and Fig. 3 shows the distribution of brain weights and the degree of atrophy in this group. The reduction in brain weight is much more pronounced in most cases of Alzheimer's disease than in senile dementia (dementia senilis simplex and presbyophrenia). In the clinically somewhat different but morphologically related cases of Alzheimer-like senile dementia, the severity of brain atrophy is comparable to that seen in Alzheimer's disease, and its location is the same. In both conditions there is marked atrophy of the temporal-limbic structures.

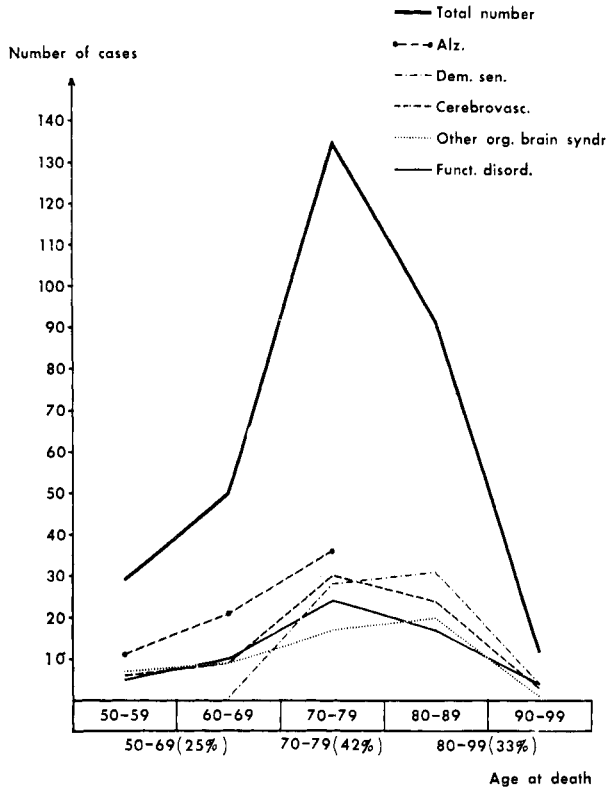

FIG. 1. Age at death of 318 patients.

Argyrophilic plaques and neurofibrillary tangles

The presence and intensity of plaques and tangles were studied in 318 cases. The clinical classification of the material is presented in Table I. It is well known that plaques and tangles are not specific for Alzheimer's disease but may occur in many different disorders. Gellerstedt (1933) in a meticulous study showed that they may also appear in so-called normal brains of mentally and neurologically presumably healthy individuals over 65 years of age. Since no detailed neuropsychiatric and psychological examinations had been performed on this material, the significance of these high figures for the so-called senile changes obtained in some cases is questionable. Corsellis (1962) showed that plaques and tangles were absent in the brains of most psychiatric patients belonging to the cerebrovascular group and the functional division. We carried out the same type of semiquantitative screening on our material and, as Fig. 4 shows, the two sets of results agree remarkably well.