ALZHEIMER’S DISEASE

A REPORT OF SIX CASES

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The present paper concerns six examples of Alzheimer’s disease met with in a series of 487 consecutive necropsies performed in two mental hospitals, giving an incidence of 1.23 per cent. in those of their population submitted to post-mortem examination. Four of these occurred in a sequence of 48 necropsies, showing the fallacy of estimating frequency on the basis of small numbers. Yet, although the precise incidence of Alzheimer’s disease is difficult to assess, it would appear from the experience of several workers that the disease, contrary to what was formerly believed, is not uncommon. For instance, Rothschild and Kasanin (1936) found a 4 per cent. incidence in a series of 234 necropsies performed at the Foxborough State Hospital. The view is further borne out by Mayer-Gross (1938), who reports that seven examples were sent to the Maudsley Hospital for histological examination in 18 months, representing only a fraction of the L.C.C. Mental Hospital material, and also by Newton (1939), who found three instances in a year in a total of about 100 necropsies at Napsbury Hospital where others are under observation in the wards.

In this paper it is proposed, after giving a succinct account of the clinical and pathological findings of these cases, to discuss certain features of their symptomatology and histology, which are of interest in the elucidation of the aetiology of this disease. In the subsequent analysis of the histological factors common to these six cases, particulars will be added of a further instance, described elsewhere (McMenemey, Worster-Drought, Flynd, and Williams, 1939), occurring in a family afflicted with presenile dementia.

In presenting an account of these six cases, it is realized that the anamnesis and examinations, both clinical and histological, were incomplete, yet it is felt that the material is of value in arriving at certain conclusions, the more so, as Jervis (1937) has recently recalled the need for further clinical and pathological reports.

It should be added that in our conception of Alzheimer’s disease we are including all those examples of subacute or chronic organic dementia characterized at autopsy by findings of widespread atrophy of the cortical neurones, alterations in the neurofibrils and the presence of plaques, which, by reason of
the subjects' age or on account of severity of pathological lesions, are not suitable for inclusion in the category of senile dementia. After the presentation of these cases an attempt will be made to justify this wider outlook in the definition of Alzheimer's disease and to differentiate this malady from senile dementia.

Case histories and autopsy findings

Case 1.

A married woman, aged 56 when first admitted to hospital: symptoms consisted of gradually oncoming mental confusion with periods of restlessness which, after a few weeks, necessitated removal to hospital.

On admission, she was confused and unable to give any account of herself. She was of sparse build, emotional, restless, and anxious, sitting up in bed and staring about her in a vacant way, mistaking identities, and pulling continuously at the bed-clothes. She was described as "tremulous" with a gait of the senile type, although all reflexes were normal. The heart was enlarged with a systolic bruit at the apex conducted into the axilla; at the aortic base there was a localized systolic bruit and a sharp metallic ring to the second sound.

She became more and more demented, at no time showing any insight into her condition: the loss of memory was great and rational conversation was impossible. Contractures of the hamstrings developed gradually and she became mute, resistive, and helpless. She died in an emaciated state at the age of 62, the illness having lasted 6 years.

Autopsy: The brain was small and weighed 1,012 grammes, all convolutions with the exception of the precentral and postcentral gyri being noticeably smaller and perhaps a little firmer than normal. The atrophy was symmetrically distributed. The leptomeninges were thickened and more opaque than normal, but the Pacchionian bodies were scanty in number. The vessels at the base of the brain were singularly free of arteriosclerosis, in contrast to the findings elsewhere in the body. On cutting the brain, after fixation, the grey matter of the cerebral cortex, and more particularly of the frontal lobes, was noticeably thinned: the ventricular system was slightly dilated. The histological findings were characteristic of an old-standing case of Alzheimer's disease with some thickening of the small vessels. A feature of note was the relative immunity of certain parts of the occipital cortex when adjacent areas appeared to be severely affected; for instance, in some sulci the one convolution was only slightly atrophied and plaques were infrequent, whereas the contiguous gyrus was architecturally disorganized with abundant plaque formation.

The other findings included some coronary atheroma with thickening of the media and proliferation of the intima, and an aneurysmal dilatation of the ascending part of the aorta with scattered plaques of calcification in the arch and descending portion, the disease being active in many parts with some proliferation of the intima and organizing thrombus adherent to it: the elastic laminae were intact, but there was considerable swelling of the subintimal region with much cholesterol debris and a periadventitial round cell infiltration with commencing fibrosis, without, however, any evidence of mesaortitis. The kidneys were decidedly senile in type, with a thick, fairly adherent capsule, thickened arterioles, a diminution of cortex, and an increase of intramedullary fat. Histologically, there was an early and active interstitial change with very little involvement of the glomeruli and tubules, the capsules were thickened, and there was some proliferation and thickening of the vessels.

Commentary.—The interesting factors are the arteriosclerosis of the aorta, coronary arteries, renal arterioles, and, to some extent, of the vessels of the brain. The thickening of the leptomeninges, together with an aneurysmal dilatation of the first part of the aorta, at once suggests the possibility of syphilis, but histological investigations do
not support this view; in fact, the aortitis is characteristically atheromatous, for the media is little altered. The renal changes, however, suggest that widespread functional and organic alterations in the arterioles and precapillaries may be a contributory factor in the pathogenesis of the brain disease, greater than at first appears likely from a histological study of the cortical vessels.

This case, therefore, although clinically typical and histologically characteristic of Alzheimer's disease, is complicated by the presence of a somatic disorder, which, even if not in an organic form, may have preceded the mental illness as a preliminary disturbance of function. As physical signs of the aortitis were present at the first examination, when the mental illness was thought to have lasted only for a few weeks, it is most likely that the generalized arteriopathy antedated the cerebral changes of Alzheimer's disease. A record of the blood pressures would have been instructive. Krapf (1931) has suggested that arterial hypertension, rather than arteriosclerosis, requires consideration in Alzheimer's disease, especially as a factor in the etiology of epileptiform symptoms.

In this instance the leptomeningeal thickening is greater than in most cases of Alzheimer's disease, but is much less than is usual in neurosyphilis; it is interesting to postulate what would have been the findings had the cerebrospinal fluid been examined on several occasions. An increased cell count would not be unexpected at some stage in the disease. The atrophy of the brain was greater in this case than in any of the series, and this, in itself, might have been sufficient to determine the degree of meningeal thickening. Some degree of atrophy is usual even when, with a short history, the brain weight is not appreciably reduced, as in case VI. Fuller (1911) in a study of senile brains made the observation that 87·5 per cent. of cases with plaques had naked-eye evidence of atrophy.

Case 2.

A widow, aged 60 when first seen, whose history was not possible because of the absence of relatives, but it was certain that she had been under certificate for 2 years and 7 months in other hospitals. The reception order referred to her as an irresponsible woman who was unable to give any clear account of herself and who presented several delusions, imagining, for instance, that the hospital spoons and forks were her own property.

On admission, the pupils were sluggish in their reactions to light; otherwise, the central nervous system appeared normal. The heart was not enlarged, but there was accentuation of the aortic second sound. There was complete apathy and an absence of emotional response; she was quite out of touch with her environment and the passage of time. On the rare occasions when she would reply to a question it was always with the same answer—"Yes." At times she was very agitated, constantly fumbling with her clothing and wandering aimlessly about the ward. The blood Wassermann reaction was negative.

The dementia became gradually more and more profound, but the agitation persisted. Epileptic fits developed and death occurred at the age of 62 in a stage of emaciation some 6 years after the commencement of the illness.

Autopsy revealed a brain weighing 1,000 grammes, atrophied as a whole, but especially in the frontal lobes, atheroma of aorta, and red hepatization of the right lower lobe of the lung.

Histologically the changes were characteristic of Alzheimer's disease.

Commentary.—The course is similar to the preceding case, occupying 6 years in all, but it was terminated by an acute illness; had the patient survived the pneumonia, the extended lease of life might have led to more extreme changes in the brain.

The patient was one of two of this series who developed epileptiform convulsions. When one considers how universal is the neuropathy in this disease and how widespread the intercellular alterations which accompany it, it is surprising that the
incidence of epileptiform convulsions is not higher. Although well recognized as a symptom of Alzheimer’s disease, convulsions are probably to be attributed to an inherent tendency to epileptic escape phenomena in the presence of brain disease rather than to a specific attack of the pathological process on the cortical cells controlling a particular group of movements. Krapf (1931) maintains that the chronicity and involutional nature of Alzheimer’s disease is not likely to give rise to epileptiform attacks without a considerable measure of the epileptic disposition, and that if the underlying diathesis is as strong as this, other precipitating factors met with in the life of the patient will have, in all probability, “brought it out” before the advent of a presenile dementia. Whilst subscribing to the general principle of epileptic diathesis one finds it difficult to accept the contention of Krapf that the pathological process underlying Alzheimer’s disease is unlikely per se to give rise to epileptiform phenomena without a strong inborn disposition. The decortication can be considerable and the disease is by no means always chronic; in fact, it is often subacute and quite as devastating as general paralysis, so that epileptiform phenomena might be expected in a like proportion of cases were these diseases to be compared in the same age groups. There is, however, a point of pathological importance in this connection: the motor area in Alzheimer’s disease enjoys a greater measure of freedom from organic destruction relative to other parts of the cortex, and the Betz cells, in particular, are little damaged. Slight pathological changes were encountered in the Betz cells of both cases showing epilepsy, but similar alterations were also present in others; in case VI, for instance, the changes were not inconsiderable. But it must be emphasized again that histological appearances are no guide in the study of epilepsy, which may be sometimes the result of disturbance of function. The second part of Krapf’s contention, namely, that other precipitating factors met with in the life of the patient will have, in all probability, “brought it out” the epileptiform phenomena before the advent of a presenile dementia, is offset by the absence, in our experience, of any records of cases giving a previous history of epileptiform attacks, the more so, as the epileptic disposition tends to get less as age advances. It would be interesting to know if the incidence of epileptiform seizures is higher in Alzheimer’s disease than in the more chronic and less widespread disorder of senile dementia; we believe this to be the case, although vascular disease, even if unaccompanied by a change in structure, is a likely concomitant over the age of 60, which would tend to make a statistical enquiry both difficult and unreliable. Finally, it must be emphasized that in a greatly demented patient, objective epilepsy only can be recognized: as such patients will, in all probability, be unable to appreciate or describe sensory phenomena, we can have no idea of the true incidence of epilepsy proper in this disease.

The emaciation which characterizes the majority of these cases has several possible explanations, a diminished assimilation of food, either due to anorexia, dementia, or impaired digestion and absorption, to interference with the nutritional centres by the disease, or as part of a generalized disease of metabolism of which the nerve cells are only a part. It is probable that the emaciation is due to many different factors acting at the same time. It may be found in any acute psychosis.

In this connection, however, one recalls the important case of Schob and Guntz (1932); the patient was a woman of 64 who for two and a half years before death had lost weight, becoming progressively weaker and more demented, with loss of hair and teeth. At death her weight was 4 stones 8 lb. The brain, which weighed 960 gm., gave the naked-eye and histological features of Alzheimer’s disease, whilst examination of the hypophysis revealed degeneration of the anterior lobe with only a little surviving parenchyma, the rest consisting of connective tissue. The authors describe it as an association of Alzheimer’s disease with Simmond’s disease, and, while admitting the possibility that the syndrome is coincidental, they suggest that the one disease may cause the other or that both may be attributed to some common factor at present unknown. While it might, perhaps, be said that the evidence for the diagnosis of Simmond’s disease, in this case, is inconclusive, especially in view of the known wasting
in Alzheimer's disease, the importance lies rather in the recognition of the possibility of underlying endocrinopathies, especially of the hypophysis, in the presenile dementias. It illustrates the need for a wider approach to the study of these diseases for, from a histological point of view, an examination cannot be regarded as complete which does not include representative sections from the somatic tissues. The possibility of an extracerebral origin for disease of the brain has been emphasized by Globus (1932), MacNamara and Dickson (1932), Ferraro (1933) and by Meyer and Tennent (1936) in Schilder's disease and the same likelihood must be admitted in many other conditions.

Case 3.

A widow, whose symptoms began insidiously at the age of 57 with mental confusion, loss of memory, and expansive delusions. Dementia followed gradually, certification taking place 3 months later, and death ensued 3½ years after the commencement of the illness at the age of 60 in a state of profound dementia and emaciation (weight 5 stone).

Autopsy showed a brain of 1,180 gm., particularly wasted in the frontal lobes, but also in the superior and, to a lesser extent, the inferior parietal lobules, myocardial degeneration, and patchy consolidation of the lungs, with an area of grey hepatization going on to abscess formation.

The histological features of the brain were consistent with the diagnosis of Alzheimer's disease (Figs. 1 and 2). The general appearance of the frontal cortex, for instance, was one of extreme neuronal atrophy with an abundance of plaques and a reactive gliosis. Neurofibrillary alterations were numerous. In spite of this cortical atrophy, however, there were many areas where the nerve cells appeared quite normal, although a few plaques were scattered amongst them; these minute islets of apparently healthy neurones were scattered irregularly throughout the frontal cortex and their distribution did not appear to be explicable on the basis of a vascular pattern. Oligodendroglia were numerous in the deeper layers of the cortex being aggregated around...
nerve cells (satellitosis) and vessels. In the gyrus hippocampus and neighbouring gyri it was noticed that there was much gliosis of the zona molecularis and that many plaques were present in this layer. Altogether, the appearances in this case suggested chronicity, the astrocytes being abundant and hypertrophied around the plaques.

A noteworthy feature was the presence in the cornu Ammonis of granular argyrophil deposits of various sizes and shapes in the cytoplasm of the pyramidal cells. The vessels showed only a minimum of fibrosis.

The general architecture of the cerebellum was well preserved except for the Purkinje cells, which were evidently undergoing a process of degeneration; many cells had, in fact, already disappeared and some showed round them a reaction of small glial cells. There were no plaques in the cerebellum, but some were to be seen in the corpus striatum, especially in the putamen, where there was also a moderate degree of nerve-cell atrophy.

Commentary.—The clinical and histological features of the case are characteristic of Alzheimer's disease. Death was attributed to lobar pneumonia.

An interesting feature is the presence of a degeneration in the Purkinje cells of the cerebellum and, also, in the cells of the nucleus dentatus. Simchovicz (1910) recognized and Grünthal (1930) agreed that the Purkinje cells are sometimes diminished in number in senile dementia. Rothschild (1934) describes, in case 1 of his Alzheimer series, great reduction in the number of Purkinje cells with shrinkage of those remaining; the patient, in common with the others, had plaques in the cerebellum, but, in addition, there were a few cerebellar signs. Uyematsu (1923) referred to degenerative changes in the Purkinje cells of some of his senile psychotics as well as the presence of plaques; no relationship was found between them. Critchley (1931) in his Goulstonian lectures recalled the work of Ellis (1918, 1920) on the quantitative reduction of these cells with advancing age. According to this worker the anterior lobe shows the greatest deficiency of Purkinje cells in both subnormal and senescent cerebella.
The argentophil granulations in the pyramidal cells of the cornu ammonis are mentioned by Urechia (1930) as being an infrequent finding in Alzheimer's disease and of a different order from the neurofibrillary alterations; it is presumably the same as the granulovacuolar degeneration of Alzheimer (1911) and Simchovicz (1914).

The vacuolation of the Betz cells would appear to be an unusual finding.

CASE 4.

A married woman, the mother of four children, was admitted to hospital at the age of 59 on account of a sudden nervous breakdown. She was well until 3 weeks before admission when she became confused, depressed, and disorientated. It was thought, however, by her relatives that she "had not been herself" and that her memory had been failing "for some time."

On admission she did not appear older than her years. She was dull, retarded,

![Figure 3](image)

**Fig. 3.—Case IV: Occipital Cortex.** Plaques can be seen in the white matter limiting the spindle cell layer of the cortex. (Hortega's silver carbonate.)

and, at times, confused and disorientated both in time and place. She could answer only the simplest of questions and that only after much delay. She chattered incessantly, sometimes accusing the nurses of injuring the patients. At times she was restless, wandering aimlessly about throughout the whole day. Her memory for past as well as for recent events was impaired. Her previous and families' histories were negative, as was also the blood Wassermann. The urine contained a trace of albumen, pus cells, and a few hyaline casts.

The dementia progressed rapidly, death taking place about 8 months after the initial breakdown.

Autopsy revealed a brain weighing 1,170 gm. with slight wasting of the frontal lobes, more especially of the anterior ends of the middle and inferior frontal gyri. Different portions of the frontal cortex varied so much in the extent of the disease when examined histologically that it was hard to believe that these samples were from the same case. Nevertheless, the cellular and neurofibrillary alterations were, as a whole, only moderate in severity. Plaques were smaller and more granular than usual,
tending to lack the cellular elements in the centre. The vessels as a whole were healthy, but a few were sclerotic (Fig. 4). Plaques were found in the grey matter which comprised the third nerve nucleus adjoining the aqueduct and ventral and cephalic to the fourth ventricle and also some in the tegmentum. In the cerebellum there was a partial degeneration of the Purkinje cells and also, to a lesser extent, of the molecular layer. The nuclei of the Purkinje cells were pyknotic and many of them gave an irregular contour. There was little in the way of microglial activity and the changes were presumably early.

The other findings included chronic pyelonephritis and brown induration of the myocardium. The kidneys were small and contracted, the capsules being thickened and stripping with slight difficulty; the cortex was diminished and the pelvis thickened and chronically inflamed.

Commentary.—The clinical history is that of a rapidly progressing dementia associated with pyelonephritis. Death took place 8 months after the initial breakdown.

Histologically all the features of Alzheimer's disease are present, but the severity is only moderate, as indeed one would expect with so short a history. The changes are most intense in the occipital cortex, and it is interesting to speculate whether or not the disease had been active here for some time before the frontal cortex became involved. It is of interest, too, to note that the postcentral gyrus shows more changes than the precentral convolution. A feature of note is the patchy nature of the changes in the frontal cortex, some areas being destroyed almost completely, whilst the change is early in others. Also noteworthy is the presence of plaques in the corpus striatum and pons, together with the changes in the Purkinje cells suggesting that the disease is widespread.

Plaques have been noted in the white matter by several authors. Fuller (1911) and Uyematso (1923) mention that they occur not only in the subcortical white matter but also in the "very centre of the marrow stalk."
ALZHEIMER'S DISEASE

The clinical picture is, therefore, one of acute toxic psychosis and progressive dementia associated with pyelonephritis, and the histological changes show that this psychosis is the result of Alzheimer's disease. Whether the brain changes had antedated the mental illness by long, that is to say, whether in fact the pathological lesions of Alzheimer's disease had for some time been present without symptoms, is speculative, but the possibility cannot be excluded. The renal disease was old-standing, so that it may have induced the specific changes in the brain.

In view of the profound dementia in a person of 59 and the characteristic histology of the brain, even with so short a history, it is difficult to get away from the diagnosis of Alzheimer's disease.

It might of course be said that in this case three points, namely, the late age of onset, the absence of focal signs, the relative paucity of neurofibrillary alterations and the short course, are more reminiscent of senile dementia; but there are certain features which make the alternative diagnosis more likely, namely, the mental illness began acutely, the disease was of short duration and yet alterations were relatively considerable and the symptomatology included the characteristic restlessness and reactive features: the fact that neurofibrillary alterations were not more in evidence is to be attributed to the short course of the illness. Nevertheless, this case does illustrate the frequent difficulty of differential diagnosis, for it lies almost in the no-man's-land between these two diseases.

Case 5.

A female was admitted to hospital at the age of 58 on account of mental confusion, incoherence, and fits. Little appears to be known of her history previous to admission, except that she was a married woman whose memory had been failing for some time.

She was an undernourished woman showing signs of recent loss of weight. Confused, rambling, and incoherent, she frequently talked to imaginary voices. She could answer only the simplest of questions and she was quite unable to give any account of herself. Her memory was much impaired and she had no trace of insight into her condition. Restlessness and resistiveness were considerable at times. She was faulty in habits. Apart from much dental sepsis there was no evidence of somatic disease. The blood Wassermann and Meinicke reactions were negative. The cerebrospinal fluid was negative in all respects.

During the week following admission she had three major epileptic fits. An exacerbation of the restlessness and mental confusion coincided with a short attack of fever of uncertain nature. The blood pressure during this time was 115/90. Following one of the fits there were choreiform movements of the limbs of both sides. She gradually became more emaciated and demented, taking little notice of questions, but speaking occasionally, towards the end, in a whisper and smiling vaguely when spoken to. Death occurred 5 months after coming under observation.

At autopsy the body weighed only 4 stone 2 lb. There were neither pigmentation nor contractures. The heart was small, the muscle of the left ventricle being firm, indurated, and brown, while the right ventricle was collapsed and the wall swollen and jelly-like. The aorta contained several patches of atheroma, but no calcified areas.

The brain weighed 1,050 gm. and, as a whole, was wasted except for the orbital surface of the frontal lobes and the precentral and postcentral gyri in their upper halves. The atrophy was only moderate in degree and there was no appreciable thickening of the leptomeninges. On section, there was slight internal hydrocephalus. Histologically all the features of Alzheimer's disease were present. The outer part of the sensory cortex showed a fair amount of capillary fibrosis. Here also there were several plaques which appeared to arise in the superficial parts of the white matter, but they were probably associated with the sixth cortical lamina, because they were most frequent in those sections which had been cut rather tangentially. In the cornu Ammonis the glial response was considerable and the impression given was one of
chronicity. Plaques were present, with slight cell atrophy, in the claustrum. There were also plaques in the putamen and a few in the optic thalamus (Fig. 6), but none in the globus pallidus, where, however, there were a few minute calcareous deposits. An advanced alteration in the neurofibrils could be seen in the grey matter adjacent to the median raphe in the pons and there were a few scattered plaques. Sclerosis of the vessels was considerable in some parts, although patchy in distribution. In the medulla the astrocytes showed some clasmatodendrosis in the grey matter and there were a few plaques around the cranial nerve nuclei. With the usual silver impregnation techniques there was a fine granular deposit which appeared to run in palisades both traversely and horizontally in the basket cell layer of the cerebellum; under the high power the appearance was finely fibrillary, but under the low power their occurrence in aggregates suggested "young plaques" (Fig. 5). These changes, except in a few instances did not correspond with the vascular pattern. As they were not present in all preparations they were possibly artefacts. The changes in the Purkinje cells and their fibres, consisting of argentophil granulations in the nuclei of the former and irregularity of staining of the latter, could not be regarded as strictly pathological because they might represent only an agonal or even post-mortem change. The cells of the nucleus dentatus were partly atrophic.

Commentary.—Unfortunately the patient was under observation only for 5 months

Fig. 5.—Case V: Cerebellum. Finely fibrillar argentophilic areas are present in the molecular layer; they are mostly acellular and without glial reaction. Some of the Purkinje cells of this case are atrophic. (Hortega's double impregnation.)
before death, and it was not possible to say how long she had been ill before certification. It seems unlikely that she could have avoided certification for long with a disease so extensive as this, so the chances are that the clinical course was short, probably not more than 1 year.

On the histological side the findings are characteristic of Alzheimer's disease and again there are plaques in the putamen, as well as in the optic thalamus, pons, and medulla.

A point of interest is the appearance of plaquelike argentophil deposits in the molecular layer of the cerebellum. They are, however, indefinite and in their staining reactions capricious: they are granular and without cellular elements (Marinesco's type I). They are possibly identical with the structures mentioned by Creutzfeldt and Metz (1926) under the name "Filzwerke" in the molecular layer of the cerebellum in a case of Alzheimer's disease and in another case of presenile dementia.

Rothschild (1934) found plaques constantly in the cerebellum in his series of cases of Alzheimer's disease and they have been recorded also by Barrett (1913) and Hannah (1936). Fuller (1911) did not find plaques in the cerebellum of any of his series of 93 elderly brains, neither did Tiffany (1914), but Uyematsu (1923) noted them in a few of his series of 100 senile psychotics, whilst Gellerstedt (1933) found them in two of his series of 50 brains of old age: in one case they were in the molecular layer, in the other in the Purkinje cell layer; they are both illustrated as typical plaques and not resembling those met with in this present case.

The accompanying somatic diseases, which may have played some part in the conduct of the mental disorder, were extreme dental sepsis and a severe degree of degeneration of the myocardium.
Case 6.

A female was admitted to hospital at the age of 61 on account of excitement and restlessness. She was quite well until 3 months before admission, when, on account of a lifelong history of dyspepsia, which had become worse during the last 3 years, she was persuaded to go into hospital for an operation on her gall bladder. This was undertaken soon after entering hospital and the gall bladder was removed together with stones and the patient made a good recovery, leaving hospital some four weeks later. Her husband noticed a change in her soon after this, for he remarked that she had become quarrelsome and cantankerous, and he attributed these symptoms to her recent operation. Later she became noisy, restless, and confused and it was necessary to send her to hospital. She had three children, all of whom were well.

On admission she was confused and unable to answer questions or give any account of herself, wandering away when spoken to and muttering to herself. Her facies betrayed anxiety and she kept asking if she could "go to the party." She was noisy and destructive and at times resented any attention or interference. Physical examination revealed little apart from signs of myocardial degeneration. The blood Wassermann and Meinicke reactions were negative.

Throughout her stay in hospital the most noticeable features of her illness were the restlessness and confusion. Her appetite was poor and it was with great difficulty that she could be persuaded to take her food. The restlessness became extreme and was accompanied by cough, dyspnæa, and swelling of the ankles, and death occurred suddenly, the mental illness having lasted in all about 8 months.

At autopsy, the heart was small and showed brown induration of the myocardium, the right chambers being a little dilated; the valves were healthy, but the coronary arteries were decidedly thickened, although far from being occluded. The aorta showed only slight patchy atheroma. The liver was chronically congested and fatty, the gall bladder was absent, and in the common bile duct there was the head end of a rubber catheter draining into the duodenum; there were no post-operative adhesions nor signs of inflammation.

The brain weighed 1,300 gm., but in spite of this there was atrophy of the frontal poles and inferior parietal lobules, the leptomeninges being slightly but distinctly thickened. The vessels of the base were free from naked-eye evidence of arteriosclerosis. On section, the lateral ventricles were moderately dilated and the choroid plexuses were cystic. Histologically the findings were those of Alzheimer's disease. The Betz cells had not escaped destruction in this case and there were plaques, too, in the lamina molecularis, but they were of the "granular" type and not typical. There were a few plaques to be seen in the claustrum, putamen, globus pallidus, and optic thalamus. The changes in the globus pallidus exceeded those in the putamen, the cells being partly atrophic. The astrocytes had undergone a fibrous transformation and many of them had an argentophil material adherent to the processes. There was some calcification of the vessels in the globus pallidus.

Commentary.—The facts of interest in this case are the relatively late onset at 61, the rapid history of only 8 months, characterized by restlessness and confusion ensuing a month after cholecystectomy, and the sudden death. This last feature has been noted by Rothschild (1934), who suggests that it may be due to disease in the basal ganglia or vegetative centres. In the present case plaques were found in the globus pallidus and optic thalamus, as well as in the putamen, and there was, in addition, a sclerosis and calcification of the vessels of the globus pallidus. Rothschild and Kasanin (1936) have commented on the relative invulnerability of the globus pallidus, but Gellerstedt (1933) described plaques in the pallidum of four out of his 50 cases of senile brains.

Other points of interest are the low weight of the patient on admission, 5 stones 11 lb. falling to 4 stones 6 lb. at death, and the findings of coronary artery sclerosis and terminal capillary bronchitis.
Again the histological findings are characteristic of Alzheimer's disease and the clinical symptomatology is atypical only in its short course. One wonders if the foreign body could have, in any way, contributed to or influenced the course of the illness.

**Histological analysis of six cases**

Some authors have found it convenient to enumerate the senile plaques. Simchovicz (1910), for instance, has elaborated a method of counting so many per field under standard optical conditions. The labour can hardly be justified, however, in view of the fact that so many brains tend to shrink, with resulting condensation of plaques; for not only will the “packing” of the cellular elements depend upon the age of the brain, the pathological process, and its duration, but also upon the mode of death, the agonal fluid changes, delay before and mode of fixation, rate of freezing and alterations caused by impregnating reagents and mounting; moreover, the count depends upon the resultant of these changes as they affect three dimensions.

Partly for these reasons, but more because the distribution of the lesions in these cases was so often patchy, especially in those with the shorter clinical course, it was decided that a less accurate method would suffice. Accordingly, a rough estimate of the changes was made in several areas of cortex and the six cases were compared at the same examination and the results set down alongside each other. This method of assessment is, of course, open to many objections; it is not always possible, for instance, to compare the identical portion of cortex in two brains or even to obtain a section cut absolutely at right angles to the surface; the patchy nature of the changes in some of them makes it difficult to give more than an average for the whole of that particular area of cortex; but, having in mind these shortcomings, the markings given under the headings of cell atrophy, neurofibrillary alterations and atrophy, and plaques represented the impression gained when the six cases were compared side by side.

The following conclusions were drawn:

1. The atrophy may involve most of the neurones of the cortex, and other highly organized cells such as the Purkinje cells may be affected. The Betz cells seem to escape destruction, but are sometimes altered (case VI, for instance).

2. In general, the intensity of the three types of change runs parallel; that is to say, plaques are most abundant where cell atrophy is greatest, and atrophy of the neurofibrils, together with the more spectacular and characteristic “tangles” and “loops,” when present, runs parallel with both; there are exceptions to this, as, for instance, in the outer and, to a less extent, the inner granular layers, where sometimes plaques are scanty, although cell atrophy is extreme. Rothschild (1934) commented on the correspondence between the intensity of the three components of the characteristic histology, viz. non-specific cell alteration, plaque formation, and neurofibrillary change. Perusini (1910) and later Grünthal (1930, 1936) remarked on the parallelism between neurofibrillary
alterations and plaques. Barrett (1913) noted a maximum incidence of plaques in the cerebellum in those places where atrophy of the nervous elements of the molecular layer and alteration of Purkinje cells were most marked.

3. The changes are most extreme, as a rule, in the outer three layers. Plaques were numerous and atrophy extensive in the internal granular layer of the sensory cortex of case II. In case IV, however, this layer was well preserved in the occipital cortex whilst the spindle-cell layer contained more plaques than in any of the others examined: moreover, quite a few could be seen in the white matter immediately deep to the cortex (Fig. 3). In this case the second and third layers were also severely affected in the occipital cortex. Plaques were also noted in case III in the white matter deep to the motor cortex.

4. When the frontal and occipital cortices are compared, the changes in the former are slightly in excess of the latter in cases III, VI, and VII, while the reverse holds in cases IV and V. Comparing the six brains together, the frontal and occipital cortices are almost identically afflicted as regards severity of the process. Simchovicz (1924) maintained that plaques were most abundant in the occipital cortex in Alzheimer's disease and in the frontal lobe in senile dementia. Jervis (1937) was unable to confirm this observation, concluding that the differential diagnosis between these diseases was not possible on the basis of the numerical distribution of the plaques. Our experience agrees with the latter author.

5. The most altered part examined is the insula of case V (the history and course of which were short); the next most diseased area is the frontal cortex of case II. In general, however, the most intense changes correspond with the longest clinical course, but there are exceptions. The frontal cortex reveals more extensive lesions in the chronic cases II, III, and VII, than in those with the short histories, i.e. cases IV, V, and VI. Our experience agrees with that of Rothschild (1934), who maintains that there is no direct relationship between the severity of the illness and the number of plaques. On the other hand, it would seem as if the case with a short clinical course is associated with a smaller, more granular, and less cellular plaque than is met with in instances of the disease which have survived many years. Case IV was an example of this.

6. In general, the motor and sensory regions are damaged less than the frontal and occipital cortices; an exception is case VI where the changes in the pre- and postcentral convolutions exceed those in both frontal and occipital areas; it is noteworthy that this case was of short duration only and epileptiform phenomena were not evident.

7. The changes in the gyrus hippocampus are similar in extent to those in the frontal cortex, but, in general, they are not so severe. The distribution of lesions in the cornu ammonis, however, is erratic; most changes are found in case I, whilst there are few only in cases III (chronic) and VI (acute); in two the fascia dentata is extensively affected; in three it is intact.

8. Characteristic lesions in the corpus striatum, especially putamen, are usual, whereas the globus pallidus and optic thalamus are less often affected; Urechia and Danetz (1924) noted that plaques are more frequent in the striatum than in the pallidum. The frequency of changes in the corpus striatum is
worthy of note and it is probably to be accounted for by reason of the known embryological unity of this ganglion with the cerebral cortex (prosencephalon).

9. The choroid plexus does not show changes other than those usual for the age of the patients. This confirms the observation of Rothchild and Kasanin (1936). It will be recalled that in the juvenile case of Malamud and Lowenberg (1929) the alterations in the choroid plexus were extensive, amounting to degenerative changes in the vessels of the villi. For this reason the choroid plexus deserves careful consideration in any histological study of this disease.

Current theories as to the nature of senile plaques and the significance of the histological changes in Alzheimer's disease

Blocq and Marinesco (1892) are usually credited with having been the first to describe the senile plaques. In the brain of an epileptic they spoke of "petits amas ronds du diamètre de 60μ environ." They called them "plaques sclereuses de nevrogie" and the term "plaques seniles" was first given to them by Simchovicz in 1911, who believed that their absence was against the diagnosis of senile dementia.

The nature of senile plaques has been well dealt with by many authors and it would serve no useful purpose to give more than an outline of the recent theories advanced, both as to their origin and life-history; the subject is rendered difficult to some extent by reason of a confusion of terminology, especially in regard to the essential origin of the plaque. Amongst early papers of importance are those of Redlich (1898), Alzheimer (1907), Fischer (1910), Perusini (1910), and Fuller (1911). The most valuable post-war accounts are given by Uyematsu (1923), Critchley (1929), Ferraro (1931), Braüniuhl (1931, 1932), Marchand (1932), and Bouman (1934). Uyematsu classified plaques into four types: (1) a spheric form with a nuclear-like central mass; (2) a spheric form without a nucleus, found abundantly in severe cases; (3) a perivascular variety; and (4) a diffuse spheric type with a globule-like centre found especially in the region of the large pyramidal cells of Ammon's horn. Marinesco (1928) grouped them into three stages of development: (1) argentophil granular deposits of irregular contours and without cellular components; (2) a plaque through the centre of which pass the swollen processes of microglia; and (3) a type consisting of an argentophil filamentous wreath containing a clear space and in the middle one or many microglial cells with pyknotic nuclei and swollen processes. In referring to the anatomy of the plaque and its essential origin, Uyematsu (1923) says: "The structure common to all (plaques) is the court (Hof) which consists of dark-stained fibrils of indefinite characters. This part represents, in all probability, a destructive process of the ground tissue following the primary thickening of the neuroglial reticulum. The primary thickening of the reticulum is considered to be a reaction to the various degenerative processes of the ectodermal and mesodermal elements such as ganglion cells, neurofibrils, glia cells, glia fibres, blood vessels, and products of pathological metabolism. So far as the nature of the pathological metabolism is concerned the writer has no definite conception, although the ganglion cell origin is suspected. The
abnormal reaction of the reticulum . . . may be attributed to primary exhaustion of nutritive energy or a secondary characteristic caused by specific exogenous agencies." Creutzfeld and Metz (1926) conclude: "The nerve cells and their branches, the glial cells and their ramifications are embedded in a ground substance (Grundsubstanz) whose nature and structure we do not know exactly. The feltwork (Filzwerk), the network of filaments (Fadchengeflechte), and the plaque nuclei are either particular alterations of the ground substance or pathologicalstorings in them."

The origin of plaques has been variously accredited to disease of the nerve cells, axis cylinders, all types of glial cells and their processes, and even to the deposition of abnormal products of metabolism; there is perhaps something to be said for all of them. Ferraro (1931) concluded a careful analysis of the literature and a personal study with the opinion that plaques could originate from either altered microglia (the commonest) or oligodendroglia and sometimes from nerve cells. He laid emphasis on his impression that the microglia and oligodendroglia seem to possess insufficient vitality to elaborate fat, supporting this contention with the well-known fact that gitter cells are rarely found outside the plaques, suggesting that there is an absence of migration of the fat-laden cells. He postulated a particular type of degeneration for these glial elements, the nature of which is not yet known, and he maintained that these degenerated cells may constitute a small plaque or the origin of a larger one.

Most authors, however, now believe that the role of the microglia and oligodendroglia is secondary. Perusini (1910), for instance, advocated that the plaques had their origin in a disease of the nervous tissue giving rise to a densification of the glial reticulum in which afterwards pathological products of metabolism became encrusted. The most generally accepted view on the causation of plaques is based upon the studies of Marinesco. In 1911 he wrote "on pourrait admettre que l'élément primordial de la plaque est constitué par des principes chimiques qui se déposent dans différentes régions de l'écorce à la suite d'un trouble dans l'équilibre colloidal." This view was endorsed by the same author in 1928. The exegesis of the senile plaque was carried a stage further by von Braunmühl (1931), who identified its origin with the process of "protoplasmahysterese" advanced by Růžička (1922, 1924); hysteresis or condensation of living substance being, according to this author, the third biological process, the other two being assimilation and dissimilation. Experiments were made to show that the morphology of plaques (primitive plaques) is in keeping with the growth of a chemical substance rather than a cellular organism. His intention was to find out not so much what plaques are, but what they are not and from what they do not arise! Their origin on the basis of "Fällungsvorganges" is stressed and nervous and glial structures are accredited with no part in their birth. In the following year, von Braunmühl summarized the existing views concerning the condensation of the glial reticulum, namely that a primary destruction of nervous tissue precedes the densification of the glial reticulum (Simchovicz, 1911) or else that a densification of tissue comes first and is followed by the deposition of plaque substances (this view was held by Bielchowsky in 1911). He concludes that the vast majority are examples of
condensation of ground substance ("Grundgewebsverdichtunges")—or, in other words, plaques have the appearance of a secondary phenomenon and that the material giving rise to plaques ("Plaque formende Stoff") was originally contained in colloid solution. Marchand (1932) expresses the origin of the plaques as follows: ". . . elles sont constituées par une alteration très localisée du réseau fibrillaire compris entre les différents éléments cellulaires du cortex."

Rothschild (1934) supports the view that the plaques are formed in the intercellular ground substance, but draws attention to the fact that they are most abundant in areas rich in unmyelinated nerve fibres—as, for example, the third cortical lamina and the outer molecular layer of the gyrus dentatus. With regard to the essential origin of the plaques he adds that as they are secondary manifestations only, they are not necessarily an accurate measure of the severity of the primary colloidal change.

A recent development in the study of the plaques is the attempt made by Jervis and Soltz (1936) and Jervis (1937) to differentiate senile dementia from Alzheimer's disease by the intensity of the microglial reaction. They find that there are two types of reaction: the one in senile dementia where the microglia is healthy, and the other in which the microglia show severe degenerative changes; this latter type they believe to be characteristic of Alzheimer's disease. A few years previously, Verhaart (1929) had commented on the role of the microglia, stating that in old age the plaque runs a more favourable course, the Hortega glia "gaining the victory," whereas in pathological states the microglia show evidence of toxic degeneration, and as early as 1911 Fuller, in a study of 93 elderly brains, had remarked that the glial attempts at elimination of deposited products of pathological metabolism and their replacement did not appear successful. Ferraro (1931) commented on the apparent lack of vitality of the microglia and their inability to continue the work which they have begun, adding that "gitter" cells are rarely found leaving the plaque. Hannah (1936) noted absence of microglial reaction in his case of Alzheimer's disease.

A view on the origin and growth of the plaque which is in keeping with the known phagocytic activity of the microglia is that of Hortega (1939). According to this worker there are three stages in the formation of the plaques. First, there is a focal mortification of the tissue ("tejido"); by this word Hortega implies all the elements of the brain, including cells, nerve, and glial; usually the plaque begins in an area which is composed of nerve and glial fibres and in this early phase it is possible to recognize abnormalities in the cylinder axis, such as thickenings in parts with fusiform nodules every now and then. Next, there is the stage of microglial mobilization; these mesodermal cells, in doing this, are fulfilling their normal function of scavenging; they are attracted chemotactically to the necrobiotic focus as to an area of softening and accumulate around it in the shape of a rosette. At the same time, the centre of the plaque becomes more granular, with filaments radiating from it reminiscent of a spherocrystal. This centre sometimes gives histochemical reactions similar to amyloid (cf. Hechst, 1929). The microglia are admittedly altered as other authors have shown, but this change is physiological and has to do with their phagocytic activities. The typical appearances of the mobilized "microglia"
are a reduction in the number and ramifications of their processes, an increase of their somatic protoplasm with the assumption of a more spherical form (Fig. 7c) and a more amœboid career. They are almost constantly present in this stage and in number they vary from one to twenty; quite often there is one in the centre in the cytoplasm of which fat inclusions are to be seen. This second phase is, therefore, one of microglial intervention and it has been regarded by some workers as a pathological change in the microglia. These phagocytic activities of the microglia are the same in both Alzheimer's disease and senile dementia, the only difference being one of degree; in the former, the disease is more acute and extensive, whereas in the latter the process is gradual and less severe; in the one case the microglia is very active; in the other it is only slightly so. In the third period, there is a characteristic reaction on the part of the astroglia. These cells undergo an alteration consisting of some degree of cellular hypertrophy with fibrous transformation of the protoplasmic fibrils and the apparent formation of new fibres by dissociation of already existing processes. These large glial cells surround the young plaque in the form of a marginal ring, and their fibrous feet penetrate into the centre of the necrotic area in the same way as in a cicatrice. The cells themselves remain at some
distance from the centre of the plaque so that sclerosis of the whole area is seldom compact; the centre, however, is contracted and sometimes a vessel may be detected there. The microglia usually remain in or near the centre of the plaque, (Fig. 7d) for it is the exception to see laden phagocytes retiring from the scene of necrobiosis; after many months it is possible that the microglia undergoes a process of degeneration, but there is no evidence in favour of this view. Thus it is that, although nerve and glial processes are usually the first to be involved in a senile plaque, sometimes a vessel is caught up, occasionally a nerve cell, an oligodendrogliaocyte, or an astrocyte, and perhaps rarely a microgliocyte.

We believe that this conception of the life-history of the plaque best fits in with our knowledge of the morphological variations found in Alzheimer's disease, senile dementia, and in other conditions.

The origin of the plaque, however, is still a matter for conjecture, although the Růžička-Grünthal hypothesis seems the most likely explanation. The reason for the alteration of the axis cylinders is not known. Bouman (1934) explains these changes, and, indeed, most of the alterations we associate with Alzheimer's disease and senile dementia, on the basis of hyperdifferentiation or "an attempt of the nervous system to differentiate in the direction of a specific neuron, an attempt which may advance beyond the normal." He bases his view on the morphological identity of these changes to those taking place after injury. According to this view, the Alzheimer neurofibrillary changes result when hyperdifferentiation occurs in a ganglion cell, a "torpedo" if in a neurite and a dendritic swelling in a dendrite. If hyperdifferentiation takes place in a neurite which is involved in a plaque there results the eyes, buds, knots, and argentophil fibres, and if it occurs in the nondifferentiated protoplasmic ground reticulum a senile plaque is born.

Apart from the presence of plaques, Alzheimer's disease and, to a less extent, senile dementia, are associated with characteristic changes in the neurofibrils and widespread degeneration of the nerve cells. The first of these changes, which Critchley (1930) regards as constituting the outstanding feature in Alzheimer's disease and which has been explained by Bouman on the same hypothesis of hyperdifferentiation, is associated with the name of Alzheimer (1907), who first described them in his classical case of the disease in a woman of 51 years; he believed that these neurofibrillary alterations in the nerve-cells played a big part in the disease. They consist of an irregular thickening and alteration in the alignment of the nerve fibrils with the formation of loops, tangles, kinks, and often bizarre patterns. The nerve-cell change which is usually associated with the neurofibrillary alteration is readily visible unless the cell has already completely atrophied and disappeared, only the abnormal neurofibrils remaining. If the neurofibrillary alteration is an attempt at hyperdifferentiation, as Bouman (1934) suggests, we must surely imagine that the attempt has failed and the distorted neurofibrils remain as a permanent tombstone to mark the site of the deceased cell. Simchovicz (1910) explained the change in the neurofibrils as a peculiar degeneration attributable to some abnormal product of deposition. Satellitosis and neuronophagia are frequently seen around degenerating nerve
cells, and when the oligodendroglia are for this reason very abundant a characteristic appearance is produced.

Neurofibrillary alterations have been absent in some cases; Fuller and Klopp (1912) could find none in the 300 sections examined from theirs, neither were any present in the second of Lowenberg and Rothschild's (1931) series. It is probably coincidental, but yet worthy of note, that both these examples were associated with toxæmia; the one was of 7 months' duration only in a person with a streptococcal infection of the throat and rheumatism, while the other was the important case with an 8-year remission between the two attacks of toxic psychosis, the first of which developed late in pregnancy, producing a permanent defect. Possibly the absence of neurofibrillary change is attributable to the short course of the illness in these cases, in the same way that their relative infrequency in senile dementia can be put down to the shorter average duration of the illness as compared with the presenile disease. Schnitzler's case (1911) had neurofibrillary changes, but no plaques; this patient is said to have had myxædema with a gradually oncoming dementia; symptoms began at the age of 31 and death occurred at 36. Urechia (1930) is inclined to regard this case as an example of Pick's disease.

A paper by Alexander (1934) deals with the artificial production of alterations in the neurofibrils. In the absence of other histological features of Alzheimer's disease, neurofibrillary alterations, according to this author, should be interpreted with care. Alexander concludes that in Bielschowsky preparations argentophilia of the nuclei serves as an indicator for the neurofibrillary change produced artificially (by soaking).

Not all neurones, however, which atrophy are associated with neurofibrillary changes. The atrophy of nerve cells, which in this disease may be considerable, is also consequent upon a variety of changes in the morphology of the cell, which are seen to a lesser degree in the brain of many old people; perhaps the commonest of them is a fatty degeneration of the cytoplasm, well exemplified in case III of this series, especially in the frontal cortex. Another variety of alteration is characterized by the presence of argentophil granules of irregular size and shape in the cytoplasm; this was well seen in the cornu Ammonis of case III. This change is the granulovacular degeneration of Alzheimer (1911) and Simchovicz (1914). In addition to these findings, shrinkage of the whole cell with pyknosis of the nucleus and an irregular cell outline, pigment deposits in and vacuolation of the cytoplasm, with eccentricity of the nucleus, are common. Sometimes cells are seen which are pale and swollen. None of these changes, some of which may at times be post-mortem in origin, is specific for Alzheimer's disease, and it is not always possible to say how much of the cell atrophy is to be attributed to them and how much is consequent upon degeneration of the neurofibrils; in all probability the latter contributes the most.

The activities of the glia around the plaque and the satellitosis of oligodendroglia have been mentioned already; in addition there is sometimes a tendency for astrocytes to congregate in clusters in the grey matter; we have noticed them not uncommonly in the molecular layer of the cerebral cortex (Chaslin's gliosis,
1891), where the fibrous processes are numerous whilst the cell nuclei are infrequent. The cortical astrocytes nearly all exhibit a fibrous transformation. Clasmatodendrosis was sometimes observed. Curious comet-shaped astrocytes ("cometaria") were noted, particularly in the occipital cortex of case III (Fig. 2).

In general, the cortical vessels in Alzheimer's disease have been accepted as blameless. Such changes as are present are usually compatible with the age of the patient, if we accept the view that senescence is entitled to a certain amount of vascular change; and if in excess of "normal" it might be said that the alterations are secondary to degenerative changes, the vessels becoming modified by reason of the presence of abnormal products of metabolism. Although the vessels are generally absolved from blame in this disease, a word of caution is necessary in respect of accepting a normal histological picture as evidence of normal function of the tissues; preceding structural alterations in the smaller vessels there are disturbances of function which we are not always able to detect. Marchand (1932) held that the small blood vessels are always diseased in Alzheimer's presenile psychosis. Case I of this series showed more vascular changes than most, but the histology of the great vessels revealed no suggestion of syphilis. The others of this series exhibited only patchy sclerosis of the cortical vessels: in cases II and III it was noted in the frontal cortex, the former giving the appearance of capillary proliferation whilst the latter revealed an aggregation of oligodendroglia around certain of the precapillary vessels. There was sclerosis of the vessels of the occipital cortex in case IV (Fig. 4) and V, of the pons in instances V and VI, and in the globus pallidus of case VI.

Criteria of diagnosis and the relationship of Alzheimer's disease to senile dementia and certain forms of toxic-infective psychosis

Within recent years, in America especially, much attention has been paid to Alzheimer's disease, and valuable papers have appeared which, in addition to presenting further case reports and important deductions on aetiology, serve also to summarize the knowledge available up to date. Amongst the more important of these are the writings of Malamud and Lowenberg (1929), Lowenberg and Rothschild (1931), Rothschild (1934), Rothschild and Kasanin (1936), Jervis and Soltz (1936), Hannah (1936) and Jervis (1937).

The earlier view that Alzheimer's disease amounted only to a senium praecox (Fuller, 1912) was questioned by Barrett (1913) after a study of a case dying at the age of 37. Grünthal (1926) also doubted if the disease could in any way be related to senility. In spite of the present tendency to regard Alzheimer's disease and senile dementia as separate disorders there has been a general disinclination to break away from the custom of associating them as manifestations of the involution of the brain. Rothschild and Kasanin (1936), for instance, believe Alzheimer's disease to be something more than a variant of senile dementia, but the similarity of the lesions suggests to them that like factors may operate, a view in which Jervis and Soltz (1936) concur. Jervis (1937) goes so
far as to assert that in this relationship to senility one may find the only clue in the aetiological interpretation of Alzheimer's disease. These latter authors believe, however, with Grünthal, that histological examination cannot differentiate Alzheimer's disease from senile dementia and they support Kraepelin in the view that the clinical symptomatology is a solid unit and, as such, must play an important role in final diagnosis. They doubt if the disease can be related to senility in view of its known occurrence in the second and third decade. Rothschild (1934) says "the possibility cannot be excluded that Alzheimer's disease may, in most instances, be caused by some underlying factors that lead to senile dementia, but a close relationship between the two is perhaps less frequent than has hitherto been supposed."

Rothschild and Kasanin (1936) describe two cases of rapid clinical course, with a symptomatology of acute toxic psychosis, and, although the histological changes in one of them (case 6) are consistent with the diagnosis of Alzheimer's disease, they are unwilling to accept it as such, because they maintain that to include cases of clear-cut toxic psychosis in the group destroys the concept of Alzheimer's disease as a clinical entity. They remark that Alzheimer's disease is not known in a latent phase and that such an occurrence is improbable in a statistical sense.

That the pathological changes in this disease are not specific is generally agreed. Gellerstedt (1933) in a careful study of the histological changes of the brain in elderly persons found plaques in 84 per cent. of 50 cases when the impregnation method of von Braunmühl was employed. The maximum number was found in the frontal cortex and in three cases the figure exceeded 100 per field. Marinesco (1911), on the other hand, found them only occasionally in his series and Critchley (1931) noted them in only a few of his cases and in two subjects, aged 99 and 102, only a very few were found, particularly in the precentral gyri (1929). Apart from "healthy" senescence and senile dementia, plaques have been found, although in small numbers, in some half-dozen different diseases, mostly neurological, and neurofibrillary alterations of the type seen in Alzheimer's disease are known in conditions as far apart as disseminated sclerosis and hibernation in animals. Nevertheless, the presence of abundant plaques and neurofibrillary alterations together with extensive atrophy of the neurones is found only in Alzheimer's disease and senile dementia. In the former, the changes are, in the main, both more severe and widespread, although it cannot but be expected that cases dying early in the course of the illness, perhaps by reason of an intercurrent infection, will show fewer of the characteristic lesions. In senile dementia, on the other hand, plaques are usually less plentiful and neurofibrillary alterations are infrequent and may be absent. To this there are, of course, exceptions, and Grünthal (1930) maintains that the alterations in senile dementia are frequently as pronounced as in Alzheimer's disease. The neurofibrillary alterations, for instance, which Critchley (1930) regards as being as characteristic of Alzheimer's disease as plaques are of senile dementia, were found in 85 per cent. of cases of senile dementia by Grünthal (1930) and in 92 per cent. by Rizzo (1924). Both Rothschild (1937) and Lowenberg (1937), however, hold the opinion that senile dementia can occur in
the absence of plaques, although Uyematsu (1923) and Grünthal (1936) maintain that this diagnosis can be ruled out if plaques are wanting.

In general, therefore, it holds that the changes in Alzheimer's disease are of a greater degree of severity than in senile dementia, a view which makes it difficult to believe that the former is only a presenile "senile dementia"; for one would expect a disease associated with, if not attributable to, senility to show its maximum changes in the senior decades and not in the presenium or earlier. On the other hand, if the view that senility is the prime cause of the histological changes be discredited, then the greater amount of tissue damage in Alzheimer's disease can be satisfactorily explained on the assumption that to cause dissolution of a patient with organic dementia requires a greater amount of noxa in the presenile than in the senile age group. To put this in another way, one might say that the young and healthy tissue will tolerate a more severe organic insult than will the tissue whose metabolism is impaired by reason of age. Grünthal (1930), in fact, explained the greater number of plaques in Alzheimer's disease as due to the fact that the process is affecting younger subjects and has, therefore, longer to run. The same argument might, of course, be advanced to account for the essential difference in symptomatology between those diseases so well epitomized by Hannah (1936) who, while recognizing overlapping, described Alzheimer's disease as being characterized by energy misdirected, especially in the early stages, whereas senile dementia is typical of exhaustion of the whole organism from the start; the argument would be that the younger person will resist the oncoming psychosis with a greater reserve of physical and mental energy and will be able to make a determined "attempt at rejuvenescence" (to quote the apt words of Rothschild and Kasanin (1936)), whereas the older person is less able to do so. Stertz (1921) stated this in another way when he talked of senile dementia as part of a general ageing of the constitution, whereas Alzheimer's disease is tantamount to ageing of part of the brain only.

There are other considerations which make it inexpedient to regard the changes in Alzheimer's disease as but a premature senile dementia. The suggestive case described by Malamud and Lowenberg (1929) commencing at the age of 7, after an attack of scarlet fever and proving fatal at the age of 23, is hard to fit into the category of senile disease, especially when there was no suggestion of dissolution of the pars anterior of the hypophysis. Moreover, there are three well-established cases (Perusini, 1910; Urechia and Danetz, 1924; and Lowenberg and Waggoner, 1934) commencing under the age of forty, the last of these being hereditary. Two other cases might be added to these, the first, case 7 of Schottky's series (1932), whose symptoms commenced at the age of 41, but with a suspicion that earlier alterations of the whole personality dated from soon after a premature menopause at the age of 37, and the second, a female described by Barrett in 1913, whose illness began at the age of 35, death occurring two years later. The symptomatology of the latter was unusual, but there seems to be no reason for not including it in the category of Alzheimer's disease. Finally, mention should be made of Struwe's case (1929) of a mongoloid woman of 37 with numerous senile plaques in the cortex. These cases all lend support to the view that the disease is not necessarily
associated with an ageing process, although something might be said on the
other side for Schottky’s case with the premature cessation of menstruation.
Lowenberg and Rothschild (1931), on the other hand, report an instance of a
woman who gave birth to a healthy child several years after the commence-
ment of the mental illness, a phenomenon incompatible with senility of the
somatic organs at any rate.

There is, however, a case to be made out for the abiotrophic view of
Alzheimer’s disease. It can be said that the histological changes in this malady
are of the same order as those of the most characteristic psychosis of old age,
namely, senile dementia, and that each represents a pathological parody of
those found in extreme old age. The severer changes of the presenile psychosis
can be attributed to younger and, therefore, more resistant cerebral tissues, a
longer lease of life for the disease, and possibly a more severe form of the
disease; moreover, abiotrophy implies a devitalization and premature ageing of
the affected tissue, so that senescence of the body as a whole does not have time
to take place. A strong point in favour of the abiotrophic view is the occurrence
of certain familial examples of Alzheimer’s disease.

These conflicting views lead us to agree with the conclusions expressed by
Malamud and Lowenberg, and upheld by Jervis and Soltz, namely, that
Alzheimer’s disease may be caused by a variety of factors. Accepting the
Růžička (1922, 1924) conception of “protoplasmahysterese” as expounded
by von Braúnnmuhl (1931, 1932) it is easy to imagine with Rothschild (1934)
that the process as far as the ætiology of the plaques is concerned may be a
manifestation of ageing in some instances and of exogenous processes in
others. After all, we have in pathology many examples of similar histology
being caused by different ætiological factors.

A recent paper by Rothschild (1937) has expressed well the ætiological
plurality of the senile plaques. He says “with advancing age, the brain shows
an increasing tendency to the formation of plaques, but there may be other
factors concerned in their origin and these factors, although still unknown, are
largely independent of age and may well differ from case to case. This is in
line with the theory that senile plaques may be a manifestation of the ageing
process on the one hand, and may represent a general type of tissue reaction on
the other.” It is not necessary, therefore, to regard Alzheimer’s disease as an
ageing process; in fact, to approach the ætiology of this disease in an unbiassed
way, one should, perhaps, dissociate it in one’s mind from senility.

In the same paper by Rothschild there is the important suggestion that the
ability of individuals to compensate for brain damage varies considerably and
that this difference in reserve power of the brain will account for the fact that
some elderly persons afflicted with organic disease of the brain develop senile
dementia and others do not. Assuming that this theory is correct and it is in
keeping with the recognized views on the importance, in psychiatry, of the pre-
psychotic personality, we can understand why some senile dments have fewer
organic changes than do persons of the same age who have experienced no
disturbance of the mind. A natural development of this theory is to postulate
the possibility of latent senile dementia; that is to say, one can imagine that the
senile decorticating process has already begun and the patient awaits only an emotional shock or an attack of influenza to precipitate the onset of symptoms. Depending upon the mental reserve power of the patient the precipitating factor, in order to produce the clinical picture, may need to be considerable or only slight. This view of difference of reserve power in the brain is not confined to the senile age group, for it is well recognized that depending upon the personality make-up and reserve power of the brain, symptoms of dementia syphilitica will be apparent early in some, yet latent and masked in others. Individual differences in susceptibility of the higher cortical centres to the action of excitants and depressants and the rapid deterioration which occurs in a number of general paretics at the outset of malariatherapy are instances of the ready unmasking of latent tendencies.

Similarly, there may exist a "preclinical" stage of Alzheimer's disease, but because of the rapidity of the spread of the pathological process the likeliness of encountering it at its inception is less than in the more leisurely progressing senile dementia. Such potential patients would not be found in mental hospital populations, but elsewhere, and the changes in the brain would indeed be slight in the absence of mental symptoms. Much might be learnt from a study of this disease in its earliest stages; such observations as are available are drawn from biopsies. Flügel (1929), for instance, has reported the characteristic changes of the disease revealed by a biopsy on an early case of organic psychosis; the patient was a 54-year-old man with a 3 weeks' history of dementia. The possibility, therefore, of finding preclinical Alzheimer's disease at autopsy outside a mental hospital is remote. That, as Rothschild and Kasanin (1936) observed, a latent form has not been reported, affords no reason to deny its existence, especially since the total number of cases of Alzheimer's disease reported does not much exceed one hundred.

If, then, one recognizes the possibility of symptoms developing after the commencement of the pathological process then cases previously ascribed to toxic and infective factors such as case 7 of Rothschild and Kasanin's series (1936) might be explained as examples of this process. We would suggest that in deciding whether a case is or is not to be labelled Alzheimer's disease we should be guided by the pathological findings rather than by the clinical history. This is not to belittle the importance of a clinical classification, nor to deny the fact that there is a well-defined symptomatology; neither is it to shut our eyes to the fact that the microscope reveals only a picture of the battlefield when the war is over; but until more is known of this disease, the pathological anatomy is the only rational basis for its definition. In this way, atypical clinical cases, which we believe to be not uncommon, are not likely to be missed. The modern conception of disease has been largely built up on morbid anatomy, and in a subject such as psychiatry, which has apparently little to show in the way of anatomical charges, it is undesirable to neglect any opportunity of correlating morbid symptoms with morbid structures. The clinical conception of general paralysis would not be possible were it not for the histological picture, which has helped in distinguishing its several varieties. The fact, that the ætiology of Alzheimer's disease is not yet determined should not deter us from accepting its
histological picture as evidence of its presence or as forming part of the basis of its classification. The aetiology of many of the diseases of the reticulo-endothelial system is little understood, but this has not prevented the adoption of a classification based on histological rather than clinical features.

There has been a tendency in the literature to regard 2 years’ duration as a minimum for the course of this disease, and almost a reluctance to accept anything under this as certain. There is, however, no reason why the course should not be acute; it may, as happened in some of the present series, be cut short by an intercurrent fatal infection before it has had time to advance far enough for the histological features to become marked; or the process may, as we have suggested here, be latent for some time before some precipitating factor serves to make it apparent. Rothschild (1934) speaks of exogenous factors accelerating the progress of the disease in two of his cases; one of them (case III) was clinically at a standstill for 2 years. Case II of Lowenberg and Rothschild (1931) was instructive in that there was a relative remission for 18 years in the course of the illness, during which time a healthy child was born. The two acute phases presented the features of a toxæmia, but the symptoms of restlessness, confusion, and impairment of memory and the findings of abundant plaques serve to establish the diagnosis of Alzheimer’s disease. Neurofibrillary alterations were not present. Whatever induced the first attack caused permanent damage, so that it is tempting to think that organic changes were already present after the first attack and that they did not progress materially until the relapse several years later.

The diagnosis of Alzheimer’s disease is only certain by biopsy (for which there is sometimes justification) or at necropsy—although clinical and radiological (Guttmann, 1936) evidence can often be convincing. The clinician can differentiate from senile dementia, the separate entities of a widespread ("multifocal") presenile dementia, and a toxic psychosis of the presenile age group which is associated with dementia; these will constitute the majority of the cases of Alzheimer’s disease, but they have to be distinguished from presenile toxic psychosis without dementia and from the host of other dementias, especially arteriopathic, which may occur in the presenium.

We have seen that Alzheimer’s disease is not necessarily confined to the presenile age group (40–60). Is it possible, then, to have examples occurring after the sixtieth year? Several authors have published cases over this age which they were convinced were examples of Alzheimer’s disease, and they have been criticized on the grounds that the patients were no longer presenile. Hannah (1936), for example, is not in favour of accepting any case after the "middle fifties" as belonging to this disease. Grünthal (1936), on the other hand, gives 50–60 as the usual age of onset, but states that the disease may begin later even until the senium is well advanced. It seems unreasonable, however, to fix a particular age limit for disease, especially in view of the known differences in ageing of families, individuals, and even tissues. We believe, therefore, that each case for consideration as an example of Alzheimer’s disease must be judged on its own merits. We have seen that many authors believe that there are differences between this malady and senile dementia, but we must be prepared to
**ALZHEIMER'S DISEASE**

meet with cases on the borderline between the two. Grünthal (1930), for instance, states that alterations in senile dementia may be as advanced as in Alzheimer's disease, and that the only difference is a tendency in the latter malady towards more local symptoms. Until more of these have been described it would seem best to reserve judgment on the question of the upper age limit of Alzheimer's disease.

Our plea, therefore, is to build up our ideas of this disease on the assumption that all cases at any age showing an abundance of senile plaques, neurofibrillary changes, and cell atrophy, which cannot be regarded as senile dementia, belong to the Alzheimer category.

**The aetiology of Alzheimer's disease and its classification**

After perusal of the literature it is clear that in the past there has been much latitude in defining the clinicopathological entity of Alzheimer's disease and confusion has naturally resulted by reason of the similarity of the organic lesions to those met with in senile dementia. We have suggested the desirability of including in the conception of Alzheimer's disease all examples of subacute or chronic dementia attributable to widespread atrophy of the cortical nerve cells, alterations in the neurofibrils and the presence of numerous plaques, which by reason of their younger age and more severe nature are not suitable for inclusion in the category of senile dementia; we have asked, in other words that, at any rate until more is known about this disease, the histological picture rather than the symptomatology should be the ultimate proof of diagnosis and should serve in arriving at any scheme of classification: in this way we believe that the net will be cast wider so as to include juvenile cases and those examples of subacute toxic psychosis with characteristic histology which are at present tending to be excluded from the confines of this malady.

It is possible to hold the view that the disease is purely constitutional; that is to say that there is some defect in the germ plasm by which ageing processes in the brain may occur before their time (abiotrophy), or one may feel that many extraneous factors can determine a tissue reaction amounting to a series of changes of the kind found in pathological senility along the lines of protoplasmahysteresis. Rüzička and Vejnarova (1924), for instance, have shown the importance of inflammatory states in determining protoplasmahysteresis: Malamud and Lowenberg (1929) have published cases of Alzheimer's disease complicated by chronic inflammatory conditions. A case described by Neubürger and von Braunmühl (1930) is of importance in a teleological study of senile plaques in association with dementia; the patient was a man of 56 years who had a traumatic dementia dating back 34 years. At autopsy, numerous senile plaques were found in the cortex with a nerve cell degeneration in the immediate vicinity of the old traumatic focus. It would be interesting to know at what age the plaques appeared.

It seems difficult to get away from the idea that constitutional factors play some part in the aetiology: the occurrence of familial cases of this malady would seem to favour this view; apart from those examples recorded by Schottky
(1932); von Braunmühl (1932), Lowenberg and Waggoner (1934), McMenemey, Worster-Drought, Flynd and Williams (1939), there are possibly others. Rothschild’s (1934) case 5, for instance, with a course of 26 years commencing at the age of 44, gave a history suggesting that the patient’s mother had had a similar mental illness which also proved fatal. Henderson (1933) believes the process may be dependent on inherited factors. A point of interest is the reference by (Lowenberg (1937) to an example of senile dementia in a father and Alzheimer’s disease in the son. There is nothing concrete concerning heredity in senile dementia according to Grünthal (1936), although Meggendorfer and Weinberger are quoted as believing that heredity does play some part.

On the other hand the importance of toxic factors cannot be minimized in certain cases, especially those with a symptomatology of subacute toxic psychosis with dementia.

Boyd (1936) has suggested a subdivision into three groups (a) presenile, (b) intermediary (hereditary), and (c) juvenile. If a classification is sought we prefer emphasis to be laid on the fact whether or not constitutional or exogenous factors are most obvious. For, on the one hand, we have the purely familial examples in which exogenous factors are minimal (Garrod, (1927) says: “in the abiotrophies the tissue defects are the most potent causative factors and the influence of external exciting causes is minimal”), and at the other extreme we have the syndrome of subacute toxic psychosis with dementia and the characteristic histological findings. Between these two we may expect all gradations. The majority of the cases recorded to date appear to lack obvious exogenous factors. It is possible that when the scope of this disease becomes better known more examples of the subacute toxic variety will be brought to light: many present themselves as a confusional psychosis and the dementia is often masked for this reason; moreover, the course of the illness is often short and the brain may be macroscopically normal and therefore not submitted to histological examination. It is quite likely that the disease as we have outlined it will eventually be subdivided into types, for there appear to be at least two clinical varieties.

Summary

Six cases of Alzheimer’s disease are recorded with pathological findings.

A plea is made for a wider conception of this disease at any rate until such time as more is known about it, and that this conception should be founded on the pathological histology.

It is suggested that two factors may be involved in any given case; the one endogenous or constitutional and the other exogenous. The former is represented by familial cases; the latter by those examples of subacute toxic-infective psychosis with dementia which present the characteristic histology of Alzheimer’s disease. Between these two all gradations may be expected, but most cases and especially the classical type which presents a fairly typical clinical picture, approximate to the endogenous variety.

The importance is stressed for the need for more complete histological
examinations of the other organs of the body. The possibility of extracerebral factor must ever be in mind.

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