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Distribution of Cerebral Degeneration in Alzheimer's Disease

A Clinico-Pathological Study*

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Summary. Seven cases of Alzheimer's disease were studied in detail from a clinical and neuropathological point of view. The degenerative process was mapped with regard to regional variations in the intensity, extent and consistency of focal accentuations.

The degeneration was regularly found to be most pronounced in certain areas: maximal cortical degeneration occurred in the medial temporal (limbic) area and, in the lateral hemisphere, consistently within a field expanding from the posterior inferior temporal areas to the adjoining portions of the parieto-occipital lobes. In addition, the posterior cingulate gyrus was severely involved. On the other hand certain areas were notably and consistently spared or less involved, mainly the anterior cingulate gyrus and the calcarine and central sensory motor areas (primary projection areas). The frontal lobes occupied an intermediate position, being less severely involved than is usually reported.

The clinical symptoms correlated well with this pattern of degeneration. Thus groups of symptoms such as memory dysfunction, emotional and personality alterations, and some symptoms of the Klüver-Bucy syndrome, were referable to the limbic lesions.

The cortical lesions of the temporo-parieto-occipital association cortex correlated with the symptoms of agnosia, aphasia and apraxia, which were recorded in all cases.

The relative sparing of the primary projection areas correspond well to findings of retained motility and perception even in later stages of the disease. The relative sparing of the frontal lobes and the anterior cingulate gyrus was related to the preservation of habitual personality traits.

The pattern described may be related to ontogenetic features, and the tendency to focalization to the age of disease onset. The role of genetic factors and of other diseases is discussed.

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Key words: Alzheimer's Disease – Distribution of Degeneration – Focal Cortical Preservation – Limbic Degeneration – Clinico-Pathological Correlation – Klüver-Bucy syndrome.

Zusammenfassung. Sieben Fälle von *Morbus Alzheimer* wurden klinisch und neuropathologisch gründlich untersucht. Der degenerative Prozeß wurde auf seine *regionalen Unterschiede* der Intensität, Ausdehnung und Konstanz seiner fokalen Akzentuierung analysiert.

Die Degeneration war regelmäßig in bestimmten Arealen besonders betont. Im limbischen System des Allocortex vorwiegend *medial temporal* im Ammonshorn und hinteren Gyrus cinguli, in der lateralen Hemisphäre, im hinteren temporo-parieto-occipitalen Isocortex. Andererseits waren manche Regionen konstant ausgespart oder weniger betroffen, vor allem der anteriore Gyrus cinguli, die Calcarina und zentrale Teile des sensomotorischen Cortex. Die Degeneration des meist weniger stark betroffenen Frontallappens nahm eine Mittelstellung ein.

Die Krankheitssymptome korrelieren gut mit diesem Degenerationsmuster. Die vorwiegend limbischen Läsionen sind Korrelate von Gedächtnisstörungen, emotionalen und Persönlichkeitsveränderungen und Teilsymptomen eines Klüver-Bucy-Syndroms. Die Läsionen im temporo-parieto-occipitalen Assoziationscortex entsprechen bei allen Fällen den Symptomen von Agnosie, Aphasie und Apraxie.

Die relative Aussparung der primären Projektionsareale korreliert mit den geringen oder fehlenden motorisch-sensiblen Störungen sogar in späten Krankheitsstadien. Das relativ geringe Betroffensein der Frontallappen und des vorderen Gyrus cinguli entspricht wahrscheinlich dem relativen Erhaltenbleiben von Habitus, Verhaltensweisen und Persönlichkeitszügen.

Ontogenetische Faktoren der beschriebenen regionalen Degenerationsmuster, Korrelationen mit dem Alter des Krankheitsbeginns und die Bedeutung genetischer Faktoren werden diskutiert.

Schlüsselwörter: Alzheimersche Krankheit – Regionale Degeneration – Erhaltene Rindenfelder – Limbische Degeneration – Klinisch-pathologische Korrelationen – Klüver-Bucy-Syndrom.

Introduction

The atrophic cerebral process in Alzheimer's disease is mostly considered diffuse although regionally more marked degeneration has been described and regarded as particularly important for the clinical picture. The literature, however, presents divergent opinions regarding the tendency to local accentuation of atrophy (McMenemy, 1963; Tariska, 1970). McMenemy (1963) in his review stressed the marked involvement of frontal, temporal and occipital lobes. The most widely acknowledged focalization is the medial temporal (limbic) atrophy (Sourander and Sjögren, 1970; Corsellis, 1970) with the addition of a parietal "focus" as pointed out by some authors (i.e. Delay and Brion, 1962; Brion, 1966). In order to

further expand the basis for symptom correlations the extent and intensity of cerebral lesions, especially their regional variations, were looked for in victims of Alzheimer's disease, in an attempt to delineate areas more or less affected by the degeneration. The purpose was to relate the pattern of degenerative changes to symptoms, age characteristics and factors possibly bearing on the etiology of Alzheimer's disease.

Material and Methods

The material consisted of seven cases diagnosed as Alzheimer's disease, clinically as well as neuropathologically. They represent a consecutive series of deceased cases with this diagnosis confirmed at autopsy from a long-term study of patients with presenile dementia. The analysis of clinical and neurophysiological findings in the total material has been published (Ingvar and Gustafson, 1970; Gustafson and Risberg, 1974; Gustafson, 1975; Gustafson and Hagberg, 1975; Hagberg and Ingvar, 1976). The patients had previously had no psychiatric and only minor somatic disorders. They had not abused alcohol or drugs, nor had severe head injuries or apoplexy with gross neurological symptoms. When the patients entered the study the somatic investigation did not reveal any dysfunctions of heart, liver, kidneys or thyroid glands and the mean blood pressure of the patients was 104 ± 9 mm. The age characteristics of the patients are presented in Table 1.

For the pathoanatomical study the brain was sectioned frontally and studied in 5—8 μ whole hemisphere paraffin sections every other centimeter with supplementary, smaller pieces of tissue in between, stained with H & E, van Gieson, Luxol blue, Naoumenko and Holmes silver methods, congo red, and Sudan black B.

The degree of cortical degeneration, especially the nerve cell degeneration and gliosis, was graded and termed "none" (—), when there was no descernible alteration though there may be a mild nerve cell loss as well as scattered senile plaques and tangles; slight (+) when encompassing up to 25% of the cortical width; moderate (++) equalling 25—50%, and severe degeneration (+++) when involving 50—75%. The degeneration rarely advanced further than that except for certain limbic structures in which it reached levels between 75 and 100% of the tissue and was termed total (++++).

The psychiatric investigation of all patients was performed according to a formalized rating scale for symptoms (Gustafson, 1975) describing various aspects of mental dysfunctions, emotional reactions and behaviour changes in dementia. Information was also collected from members of the patient's family, hospital journals and national registers regarding previous and present health of the patient and his relatives. The patients were followed up at regular intervals by

Table 1. Age characteristics (in years) of seven patients with Alzheimer's disease

Case No.	Sex	Age at onset	Age at death	Duration
1	M	56	69	13
2	M	59	66	7
3	M	50	60	10
4	F	65	74	9
5	F	50	58	8
6	F	59	66	7
7	F	59	67	8
Mean values		56.9 ± 5.4	65.7 ± 5.4	8.9 ± 2.1

psychiatric investigations and psychometric tests and their families and nursing staff were questioned regarding symptoms during the disease. At the first investigation the patients underwent neurological tests, including pneumoencephalographic (PEG), neurophysiological (EEG and regional cerebral blood flow measurements, Ingvar and Gustafson, 1970; Gustafson and Risberg, 1974; Gustafson and Hagberg, 1975; Hagberg and Ingvar, 1976) and somatic investigations.

Results

Clinical Findings

The dementing disorders of our seven cases showed several common clinical characteristics. Thus the disease started insidiously and progressed slowly. During its first years the patients showed memory failure, lack of concentration and initiative and often failed in complex tasks or situations. The most prominent symptoms of dementia—aphasia, apraxia and agnosia—were clearly manifested during the first 3 or 4 years. There was an increase of muscular tension in all cases and their gait became shuffling with small steps. Three cases also had coarse tremor of the hands, while cogwheel phenomena were observed only late in the course. Depressive reactions and emotional lability were seen early in the course, while later on emotional shallowness and lack of insight were dominating. In the terminal stage the patients were aspontaneous with few adequate reactions to the environment. They uttered few understandable words except for short outbursts of emotional speech.

Case Reports in Brief

Table 2. The distribution of principal clinical symptoms and signs in seven cases of Alzheimer's disease

Case	1	2	3	4	5	6	7
Sex	M	M	M	F	F	F	F
Confabulation	–	+	–	++	+	+	–
Euphoria	–	–	–	++	+	–	–
Aggressiveness	+	–	+	(+)	+	++	–
Hyperorality	++	–	++	+	–	+	–
Echolalia	+	–	–	–	–	–	+
Logoclonia	++	–	–	++	–	–	++
Logorrhea	–	–	–	++	–	–	–
Tremor	++	–	+	–	–	–	++
Cogwheel rigidity	–	–	+	+	+	+	++
Hallucinosis	++	–	++	–	++	–	–
Generalized epileptic seizures	++	+	++	–	–	++	–
Myoclonic twitchings	–	+	+	–	–	++	–
Dysarthria	+	+	(+)	+	(+)	+	++
Unsteady gailt	–	–	–	+	–	++	++

Symbols: (+) = slight, + = moderate, ++ = strong, evident manifestation of the symptom

Table 3. Degree of degeneration in various regions of the brain in seven patients with Alzheimer's disease

Anatomical structure	Case No						
	1	2	3	4	5	6	7
Cingulate gyrus, anterior	0–+	0	0–+	0–+	+	+	+
Cingulate gyrus, posterior	+++	++	++–+++	+++	++–+++	+++	++
Hippocampus	+++	++	+++	+++	++–+++	+++	++
Subicular and entorhinal cortex	+++	++	+++	++++	++–+++	+++	+++
Uncus and amygdala	+++	+++	+++	+++	++–+++	++–+++	+++
Insula	+–++	+–++	0–+	+	+–++	+	++
Broca's area	0–+	+	0–+	0–+	++	+	++
Frontal gyrus	+	0–+	0–+	++–+++	++	+	+–++
Motor cortex	0–+	0–+	+	0–+	+–++	0–+	0–++
Superior + median temporal gyrus	+	+	+	0–+	+–++	+	++
Inferior temporal + fusiform gyrus	++	+++	+++	++–+++	+++	++–+++	++
Parietal gyrus	+++	+++	+++	++–+++	+++	+++	++–+++
Occipital gyrus	+++	+++	+++	++–+++	+++	+++	+–++
Calcarine cortex	0	0	0	0–+	0–+	0	0–+
Mamillary bodies	0–+	0–+	0–+	+++	0	+	+
Basal ganglia	0–+	0	0–+	0–+	0–+	+	+–++
Cerebellum	0–+	0	+	+	0–+	+	+
Brain stem	0–+	0–+	0–+	0–+	0–+	+	+
Substantia nigra	0–+	0	0–+	0	0–+	+	0–+

Symbols: 0 = none, + = slight, ++ = moderate, –++ = severe, ++++ = severe-total degeneration.

The seven cases are presented as short case reports, which in addition include pathological findings. The distribution of certain principal clinical findings is shown in Table 2 and the neuropathological results in Table 3. The extent of the cerebral lesions appear in Figure 1 and 2.

Case 1. Male, factory worker. Age at onset 56 years, at first examination 60 years old. In two sisters senile psychosis was diagnosed at 70 years of age. They developed memory failure, personality changes and delirious states with hallucinosis. At autopsy both sisters had general arteriosclerosis, also involving brain arteries with small softenings of brain tissue.

Case 1 was previously of good mental and somatic health. The intellectual deterioration showed during the first years intermittent accentuations and during the fourth year a rapid progress with apraxiá, agraphia, visual agnosia and disorientation as to time and space. He also developed echolalia, logoclonia and global aphasia, and showed during his last 2 years aggressive spells, hyperorality, generalized epilectic seizures and persistent hallucinosis. He died at 69 years of age.

At the first examination he had a slow staggering gait and a coarse manual tremor. Blood pressure: 160/100. PEG: slight ventricular dilatation.

Autopsy showed bilateral bronchopneumonia, femoral vein trombosis with pulmonary emboli and infarctions. There was also a pyelo-cystitis, arteriosclerosis and benign nephrosclerosis.

The brain, which weighed 1260 g, showed in general a moderate atrophy, most obvious in temporo-parietal areas and the ventricular system was only slightly widened. The circle of Willis was only slightly arteriosclerotic.

Microscopic examination showed changes compatible with Alzheimer's disease in the cerebral cortex with the severity and distribution shown in Table 3 and Figure 1. The mamillary bodies, basal ganglia, cerebellum and brain stem, including the substantia nigra, showed only

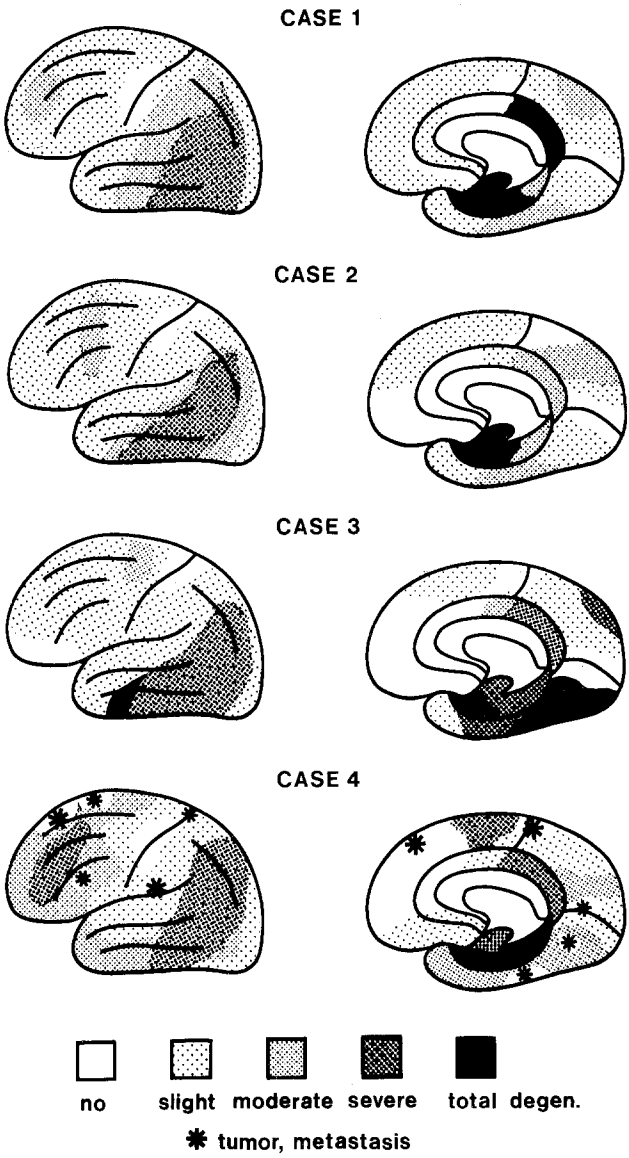

Fig. 1. Distribution and degree of cortical degeneration in cases of Alzheimer's disease

slight changes, such as dropout of occasional nerve cells, a few plaques and tangles and a slight gliosis.

Case 2. Male, civil servant. Age at onset 59 years, at first examination 65 years. His mother died aged 92 years with the diagnosis of senility. He had previously been in good health. His dementia was in its early stage dominated by memory failure. He developed persecutory delusions and had at a later state epileptic fits and myoclonic twitchings. A transitory attack of one-sided facial weakness was recorded a few days before death. He died at 66 years of age.

On first examination a normal neurological status was found and the blood pressure was 160/80.

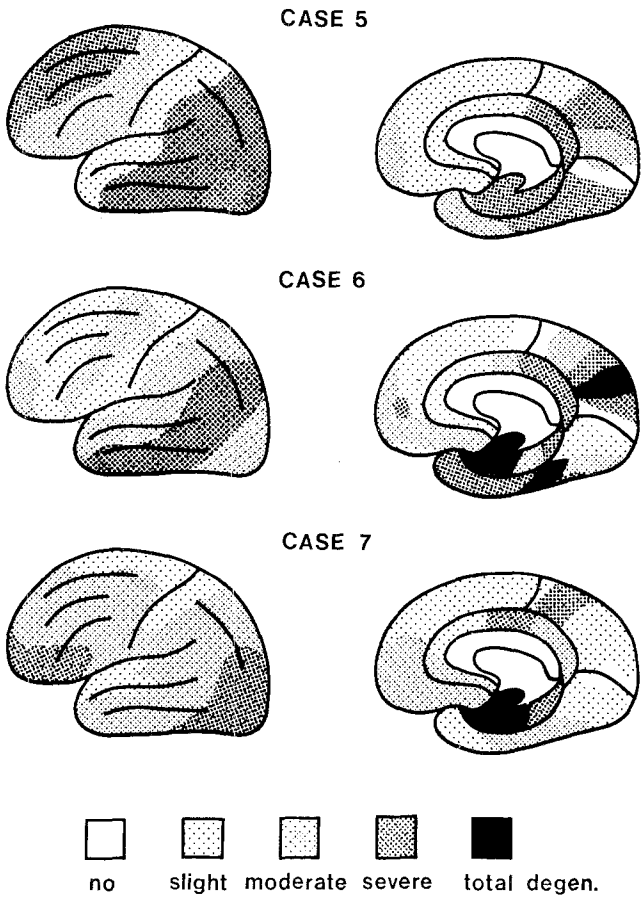

Fig. 2. Distribution and degree of cortical degeneration in cases of Alzheimer's disease

Autopsy showed haemorrhagic bronchopneumoniae, pancreatitis and myocardial fibrosis. The brain weighed 1150 g and revealed a diffuse atrophy with a temporo-parietal accentuation. A slight widening of the ventricular system was noted. The vessels of the circle of Willis were only moderately arteriosclerotic.

Histological examination revealed degenerative cortical changes of the type seen in Alzheimer's disease (see Table 3 and Fig. 1). The white matter showed gliosis which was most marked within the temporo-parietal areas. Of the areas not shown in the tables and other illustrations the mamillary bodies and the brain stem had only slight degenerative changes whereas the basal ganglia, the cerebellar cortex and the substantia nigra appeared virtually normal.

Case 3. Male, farm worker. Age at onset 50 years, at first examination 53 years old. Both parents were mentally well preserved in old age. His mother died of a stroke aged 88 years.

Case 3 early in his dementia manifested apraxia, agraphia and acalculia. During the fourth year of the disease he had a rapid loss of weight, polydipsia and his gait became slow and stumbling. At the first examination a slight increase of tendon reflexes in the right arm was observed. He had tremor of his hands, small frequent facial twitchings and an easily elicited startle response. PEG showed ventricular dilatation. Blood pressure: 160/80.

Case 3 had a few syncopal attacks with transient muscular weakness which were interpreted as ischemia of the brain stem. In the terminal stage he had a low, labile blood pressure and grand mal. He died aged 60 years.

Autopsy revealed extensive bronchopneumonia and bronchitis. There was also advanced coronary arteriosclerosis, myocardial fibrosis and pulmonary oedema. The brain, which weighed 1000 g, showed a rather pronounced atrophy which was accentuated in the temporo-parietal areas. A certain sclerosis of the cerebellar cortex was also noticeable. The ventricular system was widened, particularly the temporal horns. The left thalamus showed a smaller cavity.

Histological examination of the cerebral cortex revealed the changes of Alzheimer's disease (Table 3 and Fig. 1). Changes in the mamillary bodies, basal ganglia, and brain stem, including the substantia nigra, were slight with only occasional senile plaques and tangles. In the thalamus the small cavity mentioned above corresponded to a small old infarction. The cerebellar cortex showed in places a rather extensive dropout of Purkinje cells with replacement gliosis.

Case 4. Female, university educated. Age at onset 65 years, at first examination 70 years. Her mother, who had migraine, died at 61 years of "arteriosclerosis," which possibly indicates intellectual deterioration. A sister had severe attacks of vertigo, nausea and encopresis, which first appeared at about age 30. Since the same age, case 4 suffered from fainting spells, lasting a couple of minutes. An attack followed by a short-lasting (about 10 min) delirious state, was observed at an early stage of her dementia. She became euphoric, fancifully confabulating with a voluble, partly neologistic speech, which at later stage ended in semi-mutism. At the first examination a small malignant melanoma on the right shoulder was diagnosed and removed. Neurological examination showed no abnormalities and blood pressure was 155/95. PEG and gammacisternography revealed a ventricular dilatation and a slow resorption of cerebral spinal fluid. A therapeutic attempt with a ventriculoatrial shunt was without effect on her mental symptoms.

Autopsy Findings. The cause of death was bilateral pulmonary emboli from femoral vein thrombi. Signs of terminal cardiac failure with pulmonary oedema. Chronic pyelonephritis. Multiple metastases of malignant melanoma within abdominal organs, lungs and heart.

The *brain*, which weighed 1290 g, also showed multiple metastases of malignant melanoma, mainly in the cortex, but also a few within the basal ganglia. These metastases were mostly pea-sized with little or no surrounding oedema. The brain was generally only moderately atrophic with slightly withened sulci without obvious lobar preference. Slight fibrosis of meninges. The vessels of the circle of Willis showed only slight arteriosclerosis. The anterior communicating artery was wide and patent, with a small aneurysm measuring about 3 mm, in diameter. The ventricular system was slightly widened. No gross changes in the brain stem.

Histological examination confirmed the gross diagnosis of multiple metastases of malignant melanoma within the cortex and basal ganglia. There were also histological changes of Alzheimer's disease in the cortex of a rather diffuse extent and uniform severity, though with some accentuation within the frontal and temporo-parietal areas as appears from Table 3 and Figure 1. Small areas of the cortex could not be judged with respect to the Alzheimer process due to the tumour changes. These areas are left white on the brain charts (Fig. 1). The mamillary bodies showed a rather severe involvement, with numerous senile plaques and tangles within retained neurons. The basal ganglia, brain stem and substantia nigra showed only slight changes whereas the cerebellar cortex revealed dropout of Purkinje cells within rather large areas and with a replacement gliosis.

Case 5. Female, charwoman. Age at onset 50 years, at first examination 55 years. A brother died from a brain tumor at 27 years of age. Her mother died aged 87 from polyarteritis nodosa. Following smallpox vaccination at age 25 years, case 5 had a long period of fatigability and severe headache. During the early stage of the dementia, periods of inadequate elation were observed. At first investigation an old left-sided paresis of the sixth nerve was recorded. PEG showed general cerebral atrophy. Blood pressure was 140/65. In the terminal stage she had hallucinosis, spells of crying and aggressive behaviour. She died aged 58.

At *autopsy* the cause of death was found to be extensive pulmonary embolism. There also were bilateral bronchopneumoniae and coronary arteriosclerosis with slight myocardial fibrosis.

The *brain*, weighing 900 g, showed a marked, diffuse atrophy and widening of the ventricular system. On microscopic examination of the cortex the changes were found to be due to an Alzheimer's disease which was widespread though with regional variations as listed in Table 3 and Figure 2. The mamillary bodies, basal ganglia, cerebellar cortex and brain stem, including the substantia nigra, showed only slight to no changes.

Case 6. Female, housewife. Age at onset 59 years, at first examination 61 years. Her father died severely deteriorated aged 82. Her daughter developed myxoedema following a thyroiditis and a sister had a thyreotoxicosis. Case 6 many years ago had a period of thyroid dysfunction for which she had taken medicine. Early in the dementia she complained of headache and dizziness and she had periods of confusion and aggressiveness. Her gait became unsecure and staggering, and she had a positive Romberg test at first examination. Blood pressure: 140/80. PEG showed general cerebral atrophy. In the terminal stage case 6 had a general muscular rigidity, generalized epileptic seizures and long periods of solitary and generalized myoclonic twitchings. The blood pressure was than low and labile. She died aged 66.

Autopsy showed widespread bronchopneumoniae and urinary tract infection.

The *brain*, which weighed 935 g, showed on the convexities of the hemisphere, a diffuse, marked atrophy, most marked in the temporo-parietal areas. The medial temporal lobe, including the uncus, showed a severe atrophy. The brain stem and cerebellum also appeared somewhat reduced and sclerotic. There was little or no arteriosclerosis in the basal vessels. On frontal sectioning the ventricular system was widened with atteunation of the callosal body. There were no infarctions or haemhorrhages.

On *microscopical examination* there was a severe cortical degeneration of the Alzheimer type. This process was diffuse but most marked in the temporo-parietal areas and in the medial portions of the temporal lobes. The mamillary bodies, basal ganglia, brain stem and substantia nigra showed slight to moderate changes with senile plaques and tangles, and the cerebellar cortex had lost Purkinje cells over wide areas with replacement gliosis. The extent and severity of changes appear in Table 3 and Figure 2.

Case 7. Female, factory worker. Age at onset 59 years, at first examination 61 years. Her mother died severely demented. One sister died at 59 years of age from SLE and a brother at 50 from chronic nephritis. Another brother at 60 years of age suffered from Parkinson's disease with memory failure and PEG showed a slight brain atrophy. Case 7 had since age 31 a high sedimentation rate and obtained the diagnosis of SLE. She was treated with corticosteroids for many years, also during the course of the dementia. Disorientation as to time, and dysgraphia appeared as early signs of dementia. She also had headache, dizziness and a slow staggering gait. At the first examination she had a coarse tremor of the left hand, rigidity of the left arm and bilateral dysdiadochokinesia. PEG showed ventricular dilatation, most pronounced in the right hemisphere. Blood pressure: 130/90. She developed dysarthria, echolalia and a marked logoclonia. She also had perioral tremor, bilateral cogwheel rigidity and easily elicited mass discharges of muscular twitchings.

Autopsy was limited to a brain examination. The *brain* weighed 1130 g and showed a diffuse atrophy of moderate intensity, with a slight accentuation within the temporo-parietal area. The medial and basal temporal areas were severely involved. Little or no arteriosclerosis of the basal vessels. A slight sclerosis of the cerebellar hemispheres was noted. On frontal sectioning the ventricular system was found to be widened, particularly within the temporal areas.

Microscopic examination showed widespread cortical changes of the Alzheimer type, the intensity and the distribution of which appear in Table 3 and Figure 2. The motor cortex was partly preserved, partly involved in the degenerative process. Mamillary bodies, brain stem, and substantia nigra showed slight to moderate changes and the basal ganglia more pronounced degenerative alterations. The cerebellar cortex revealed a rather widespread loss of Purkinje cells and replacement gliosis. There was also a slight loss of myelin within the pyramidal trats with mild gliosis. The Broca area showed a moderately severe degeneration.

Summary of Neuropathological Findings

Most of the cortex of the hemisphere showed some involvement with a degenerative process of the type seen in Alzheimer's disease. This consisted of degeneration and dropout of neurons, appearance of senile plaques, neurofibrillar changes, gliosis and lipofuscin accumulation within retained neurons. In the hippocampus there was in addition a granulo-vacuolar neuronal degeneration. The degenerative changes were diffusely and roughly symmetrically distributed within the two hemispheres, though with focal accentuation in certain areas. The following account refers to the left, dominant hemisphere (Table 3 and Figures 1 and 2).

The *Limbic areas* showed the severest and most consistent lesions. The cingulate gyrus was in all cases severely involved in its posterior portion, anterior to and including the isthmus segment. In its anterior two-thirds it was well preserved or showed only slight alterations, except in case 7 where there was also a severe degeneration of its middle third. The amygdala, hippocampus, uncus, presubicular-subicular and entorhinal areas in all cases showed extensive degeneration, by and large the worst observed. The medial portions of the amygdala were worse off than the lateral portions. The island of Reil showed only slight changes, mainly in its posterior portion (cases 3, 4 and 6), though somewhat more pronounced changes were found in some patients (cases 1, 2, 5 and 7).

Of other areas on the *medial aspects of the hemisphere* the inferior temporal and fusiforme gyri and the occipital medial cortex were moderately to severely involved. The calcarine cortex, however, was in four cases well preserved and showed only slight degeneration in the remaining three (cases 4, 5 and 7). The medial frontal cortex showed slight to moderate degeneration.

The *lateral aspect of the hemisphere* showed in all but one case (case 1) moderate to severe involvement of the temporal lobe within a field including the inferior and medial temporal gyri and extending posteriorly into the parietal and occipital lobes. The superior temporal gyrus showed slight involvement in four cases (1, 2, 3 and 4) and slight to moderate in three (cases 5, 6 and 7), but never severe degeneration.

In the *frontal lobes* the lesions were in general slight, but areas of moderate severity were seen in three cases (cases 4, 5 and 7). The Broca area was only slightly involved in four cases, but cases 5 and 7 here showed somewhat more pronounced dropout of neurons and gliosis.

The *central area,* including the pre- and postcentral gyri, showed only none to slight degeneration in five of the seven cases and more advanced widespread lesions only in two cases (cases 5 and 7).

The *mamillary bodies* revealed severe changes only in one case (case 4) and the basal ganglia likewise only in one (case 7).

In the *brain stem* there were changes in all cases, but of a relatively subtle nature with slight gliosis and occasional plaques, but never to a degree comparable to that of the cortex. These changes were most marked in cases 6 and 7. The substantia nigra showed in its lateral parts some cell loss and depigmentation most marked in case 1.

The *cerebellar cortex* was the site of Purkinje cell and granular neuron dropout beyond amounts regarded as normal for age in four cases (cases 3, 4, 6

and 7) and an accompaning reduction of neurons was found in the inferior olives in some of these cases.

Discussion

The atrophic process, mainly, judged by nerve cell dropout and gliosis, thus was found to vary in distribution and regional severity according to a rather uniform pattern. The most severe and consistent involvement was found in the limbic structures, the basal parts of the temporal lobe and the adjoining temporo-parieto-occipital (TPO) cortex. Other areas such as the pre- and postcentral gyri, calcarine cortex and the anterior third of the cingulate gyrus stood out as comparatively spared from the degenerative process.

The predilection for *limbic structures* in Alzheimer's disease, in particular the amygdaloid nucleus, hippocampus and entorhinal-presubicular cortex, is recognized by other authors (Sjögren et al., 1952; Sjögren and Sourander, 1962; Sourander and Sjögren, 1970; McMenemy, 1963; Jamada and Mehraein, 1968 b; Corsellis, 1970). Focalized involvement of the cingulate gyrus, however, appears to be a rare observation in non-retarded victims of Alzheimer's disease and is mentioned in one case of an afflicted patient with Down's syndrome (Olson and Shaw, 1969). It is even reported as not particularly vulnerable (Corsellis, 1970). Jamada and Mehraein (1968 b) report on changes in the intermediate portion, which in all cases of ours had a slight to moderate involvement. The consistently more severe involvement of the posterior cingulate gyrus and sparing of the anterior in all seven cases reported here is a pattern not pointed out before. It is an interesting finding which presumably is not accidental. The island of Reil, which might be included in the limbic lobe by the wider definition (Grossman, 1967; Akert and Hummel, 1968), however, escaped the severe degeneration shared by other parts of this lobe. A slight to moderate involvement was noted only in the posterior insula.

Next to the limbic lobe the basal parts of the *temporal lobe* and adjoining areas of the *parieto-occipital lobes* showed the most severe degeneration. Temporal engagement in Alzheimer's disease is often reported and occipital involvement is stressed by several authors (Simchowicz, 1919; Sjögren et al., 1952; McMenemy, 1963). However, the consistency of the distribution of lesions within an area extending from the base of the temporal lobe towards the vertex of the occipital and parietal lobes has been stressed only by some authors (e.g., Delay and Brion, 1962; Brion, 1966). This distribution was, however, a constant finding in the seven cases presented here, usually as an area of focally accentuated degeneration against the background of a diffuse and milder involvement. The degeneration was not of the circumscribed type found in Pick's disease (Sjögren et al., 1952; Mansvelt, 1954; McMenemy, 1963).

Other areas of the telencephalon were clearly less severely involved. The frontal lobe is usually ranked among the worst damaged parts of the brain, followed by the temporal, especially its medial portions, and then the occipital lobes (McMenemy, 1963; Corsellis, 1969; Jervis, 1971). In our material the

frontal lobes showed a diffuse, mild degeneration with severe lesions only in three cases (4, 5 and 7) and then of a limited extent. To the areas with conspiciously slight involvement belonged the areas of Broca, the anterior cingulate gyrus, the central gyri (especially the motor strip), and in particular the calcarine cortex. Relative sparing of these latter two areas has been described in atrophic brains of old patients (Arendt, 1972). The calcarine cortex showed virtually no changes in four of our cases. The relative sparing of primary sensory projection areas and motor cortex, which is a consistent finding in our Alzheimer patients, has only occasionally been commented upon by previous authors (Delay and Brion, 1962; Tariska, 1970).

Two important questions arise from the present neuropathological findings, namely: to what extent might the clinical symptom pattern be related to these neuropathological findings and what factor or factors lie behind this distribution of degenerative changes?

When analysing the relationship between clinical symptoms and brain lesions it is desirable to differentiate between elementary neurological symptoms on one side and disturbances of complex symbolic functions on the other (Luria, 1964). Elementary neurological symptoms, such as disturbances of perception, movement, muscular tension and so on, have a stronger local significance, while failure of complex functions, such as aphasia, agnosia and apraxia, in which larger or more widespread cerebral regions are involved, cannot be used in the same way to identify focal brain lesions.

The clinical pictures of our cases were in good agreement with previous descriptions of Alzheimer's disease (Sjögren et al., 1952; Jervis, 1956; Brion, 1966; Lauter, 1968, 1970) with a common pattern of mental dysfunctions: amnesia aphasia, apraxia, spatial dysfunction and agnosia. It seems justified to relate most of this symptom pattern to the consistent degeneration of the association cortex of the temporo-parieto-occipital (TPO) region of the brain (Critchley, 1953; Luria, 1966, 1973). These symptoms thus suggest a specific localization of the degeneration. The fact that they appeared relatively early in the disease, furthermore, indicates the significance of the TPO lesions and this "focalized" symptom pattern in Alzheimer's disease as well as in dementia in general (Gustafson and Risberg, 1974).

The clinical importance of limbic lesions in organic dementia is well documented. Dementia has been reported in various types of hippocampal degeneration (Glees and Griffith, 1952; Corsellis et al., 1968; Corsellis, 1969). Corsellis (1970) describes limbic degeneration in Alzheimer's disease and Gascon and Gilles (1973) describe cases of "limbic dementia" caused by a rather selective destruction of limbic areas. The limbic system is in general considered functionally involved in memory functions and emotions (Papez, 1937; McLean, 1949; Brierly, 1961) and the effect of mamillary body, hippocampal and temporal lobe lesions on memory functions is well documented (Victor et al., 1961; Milner, 1959; Delay and Brion, 1969). The memory disturbances in our cases may possibly be related to the pronounced degeneration of the limbic structures of the temporal lobes. The fact that confabulation was most marked in case 4 might be explained by the degeneration of mamillary bodies and/or the frontal lobe involvement in this case (Ule, 1958; Brierly, 1961; Luria, 1973).

The clinical implications of lesions in the cingulate gyrus also has to be considered. Destructions of its anterior portions, which has its closest connections with the frontal lobes (Russell, 1961) has been reported to have severe effects on emotional and social life and to a lesser extent affect cognition (Ward, 1948; Girgis, 1971). Although personality alterations were reported in all our cases, most of them, even at an advanced stage, could give a non-verbal emotional contact. This amiability and cautiousness which has beeen considered rather typical for Alzheimer's disease might be due to the relative sparing of the frontal lobe cortex and the anterior cingulate gyrus. It might be noted that euphoria and disinhibition, symptoms associated with a frontal lobe syndrome (Rylander, 1949; Petrie, 1949; Luria, 1966) were recorded only in case 4 and case 5, which also had the most pronounced frontal degeneration. The posterior cingulate gyrus is more closely connected with the temporo-parietal region (Russell, 1961) and thereby to cognitive functions (Girgis, 1971). Therefore the consistent degeneration of the posterior cingulate gyrus might contribute to agnostic and amnestic disturbances.

In contrast to the profound intellectual deterioration there was, as long as a reliable neurological examination could be performed, no or only slight sensory impairment including sight and hearing capacities. Moreover, simple motor functions were retained, manifesting an improductive hyperactivity until the terminal stage of akinesia and severe postural disturbances. These clinical findings are in good agreement with our observation that primary projection (sensory and motor) areas are relatively spared although secondary and tertiary cortical areas (Luria, 1966, 1973) are severely involved.

All patients developed severe expressive as well as receptive aphasia. Case 4 also had a voluble paraphasic, partly neologistic, jargon. In agreement with previous studies (Nielsen, 1947; Schiller, 1947; Luria, 1958; Gustafson and Risberg, 1974) this speech disturbance might be explained by the postcentral (TPO) degeneration (impaired sensory mechanism) in combination with frontal lobe degeneration (loss of speech-regulating functions) in this patient. In contrast to the severe and relatively early manifestation of aphasia, the dysarthria was mostly slight (except case 7). This is in agreement with the finding of only slight degenerative changes in Broca's region, except in case 5 and 7. The semi-mutistic behaviour of the terminal stage can hardly be attributed to a severe degeneration of the cortical speech centre, but rather looked upon as part of a general inertia associated with widespread limbic and fronto-temporal, especially anterior-temporal degeneration (Schiller, 1947; Conrad, 1954; Robertson et al., 1958; Bay, 1962; Luria, 1966, 1970, 1973; May, 1968), which was present in all cases. Logoclonia observed in three of our cases has by some authors been considered pathonogmonic for Alzheimer's disease. It has been related to extrapyramidal lesions, especially in the caudate nuclei (Sjögren, 1952). Since only case 7 had a marked degeneration of this type, other lesions are possibly involved in the production of logoclonia.

The Klüver-Bucy syndrome (Klüver-Bucy, 1938, 1939) and its neuropathological basis in Alzheimer's disease has been discussed by Pilleri (1966) and Sourander and Sjögren (1970). Our seven cases showed some symptoms of the syndrome, such as visual agnosia, severe amnesia, apathy and hyperorality, while

the other characteristics were found inconsistently. Abnormal sexual behaviour, bulemia and so called hypermetamorphosis were uncommon and as to emotional behaviour the alterations often went in the direction of increased aggressiveness. Regarding the connection between the Klüver-Bucy-like syndrome and the localization of brain degeneration in Alzheimer's disease our results seem to confirm the importance of temporal-limbic lesions (Sourander and Sjögren, 1970). Severe temporal-limbic degeneration was present in all our cases, while the Klüver-Bucy syndrome was present only partly. This finding indicates the importance of other brain structures for this symptom pattern as suggested by Pilleri (1966). Thus visual agnosia although strongly influenced by disturbance of attention and memory is possibly linked to degeneration of secondary and tertiary visual zones of the TPO cortex. Furthermore, hypersexuality and bulemia, which might be considered signs of disinhibition, were less prominent in our cases, possibly due to their less marked frontal lobe involvement.

Paroxysmal motor phenomena are reported as common in Alzheimer's disease (Sourander and Sjögren, 1970; Jacob, 1970). Four cases (1, 2, 3 and 6) had generalized epileptic seizures and the fainting spells of case 4 might also be of epileptic nature. These symptoms have mostly been related to the degeneration of temporal limbic structures. However, the bilateral synchroneous episodes in the EEG in all cases but one (case 5) might indicate the significance of subcortical lesions for these phenomena (Ingvar and Gustafson, 1970; Johannesson et al., 1977). The none or slight degeneration of motor cortex makes this area a less plausible focus for grand mal as well as for myoclonic twitchings. Myoclonia was observed in three cases. Two of these cases also had cerebellar degenerative changes which is in agreement with the idea of a connection between myoclonia and cerebellar atrophy (Haltia et al., 1969): Our seven Alzheimer cases had a change of motility of the *akinetic-hypertonic character* described by Sjögren et al. (1952). These motor disturbances might, in combination with poverty of facial movements, give an impression of parkinsonism. These symptoms in Alzheimer's disease have been ascribed to involvement of basal ganglia (Rotschild and Kasanin, 1936), to a frontal lobe degeneration (Sjögren et al., 1952) or to "a supranuclear type of extrapyramidal disorder" (Pearcy, 1974). Our finding that the only patient (case 2) without tremor as well as cogwheel rigidity also had preserved basal ganglia, strongly supports the importance of basal ganglia lesions for these changes of motility. By contrast, the slight frontal lobe degeneration is possibly indicative of the unimportance of precentral structures for these symptoms. However, it cannot be excluded that the gait disturbance, especially the shuffling unsteady character and the postural unsecurity are related to cerebellar lesions. Actually, in our cases the unsteady gait was strongly associated to degenerative changes of the cerebellar cortex and nuclei.

Thus there appears to exist a specific relationship between the various symptoms and the degree and localization of cerebral degeneration in Alzheimer's disease.

The conceivable factors behind the distribution of cerebral degeneration in our Alzheimer cases remains to be discussed. Certain symptoms detailed in the clinical account as well as the distribution of lesions might arouse a suspicion of an *ischemic* brain disorder. The lesions coincide to some extent with predilection

areas for anoxic-ischemic lesions, mainly those in the parieto-occipital areas, which is partly a circulatory border zone, the hippocampus and the cerebellum. The findings of a disturbance of cerebral glycolytic metabolism in Alzheimer' disease might also indicate a hypoxic state (Gottfries et al., 1974). Histologically, however, there was nothing to substantiate this opinion in terms of scarring with vascular proliferation, macrophage reactions, reactive type of gliosis, cavity formation or laminar necroses in the cortex. Furthermore, there was no dropout of Sommer sector neurons in the hippocampus and only the dropout of Purkinje cells in the cerebellar cortex might be taken as an indication of anoxia-ischemia. In addition, other predilection areas for ischemia, including other border zones, do not show changes indicative of anoxic-ischemic insults, and, in agreement with other studies (Sjögren et al., 1952; Sjögren and Sourander, 1962; Jamada and Mehraein, 1968a), the cerebral vessels showed only slight or at best average arteriosclerotic changes. The reduction of regional cerebral blood flow (rCBF) found in Alzheimer's disease has been shown to correspond to the degree of cortical degeneration (Brun et al., 1975; Gustafson et al., 1976). This is in agreement with the generally accepted opinion that rCBF values reflect the local functional activity in the brain (Ingvar and Lassen, 1975). The reduction is not the primary cause of, but mirrors the degree of structural degeneration. The observed diffuse loss of neurons may thus mainly be caused by the Alzheimer process, though hypoxic-ischemic factors may contribute. In addition, the distribution of the cerebral degeneration is not likely to be explained by a vascular or ischemic factor.

The pattern of degeneration may be related to *ontogenetic* and *functional* aspects of the various brain areas. The cortical areas spared are mainly primary projection areas which pursue a developmental course with an early completion, whereas the reverse is true for many of the more severely damaged areas. This ontogenetic aspect, holds true even for adjacent areas of the same lobe, such as the calcarine cortex, which stands out undamaged amidst neighbouring, more severely degenerated medial parts of the occipital lobe. It also concerns the cingulate gyrus which in its anterior, undamaged part belongs to the area with an early development, whereas the vulnerable posterior portion is clearly behind in development aspects (Brun, 1965).

The *functional* aspects focus upon the importance of the activating systems of the brain. The activity of the secondary and tertiary cortical areas, which are the most degenerated regions, are strongly influenced by the nonspecific activating system of the brain, in contrast to the relatively spared primary projection areas, which are more dependent on the specific projection systems. Thus the pattern of degeneration might indicate an association to dysfunction of the unspecific activating system. Subnormal function of the associaton cortex as well as the physiological pattern of cortical activation has been reported in Alzheimer's disease (Ingvar et al., 1975).

The pattern of degeneration might also be connected to an *age-dependent susceptibility* of different brain regions to Alzheimer's disease. This idea is supported by the reported tendency to decreasing clinical *Fokalisierungstendenz* with increasing age of onset of Alzheimer's disease (Lauter, 1968, 1970) which agrees with the decreasing focalization of the atrophic process with increasing age of

debut. In accordance herewith case 4, who had the latest onset of the illness (65 years), showed the least focalized cortical atrophy. The pattern described also conforms with that for the degeneration reported in brain atrophy with age (Arendt, 1972).

Genetic studies of Alzheimer's disease have shown a familial aggregation (Essen-Möller, 1946; Feldmann et al., 1963; Lauter, 1968), but also discordancy even in monocygotic twins (Davidson and Robertson, 1955; Hunter et al., 1972) as well as a connection between Alzheimer's disease and senile dementia (Sjögren et al., 1952; Larsen et al., 1963). Many authors consider Alzheimer's disease and senile dementia as one disease entity (Albert, 1964; Lauter and Meyer, 1968), perhaps with a polygenetic inheritance for a shared predisposition (Pratt, 1970). This opinion is contested by Sourander and Sjögren (1970). The present results with positive family histories of presenile dementia (cases 4 and 7) and senile dementia (cases 1, 2, 6 and 7) may support the first opinion, but indicates also the possible significance of other hereditary somatic disorders (e.g., collagenosis, vascular dysfunction, migraine and thyroid disorders) in the family.

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