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Limbic Lobe Involvement in Presenile Dementia

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Summary. Limbic lobe involvement in presenile dementia was studied from a neuropathological and neuropsychiatric viewpoint. The material consisted of seven cases of Alzheimer's disease, four cases of Pick's disease, and four cases of Jacob-Creutzfeldt's disease. These three groups showed different patterns of distribution of the degeneration characteristic for each group, in particular for the first two. Among the groups, these patterns differed with regard to involvement both of nonlimbic and limbic areas. Thus the Alzheimer group had a mainly temporoparieto-occipital and posterior cingulate gyrus involvement. The Pick group in many respects showed an inverse distribution with frontotemporal and anterior cingulate gyrus accentuation of the damage. Basal temporal limbic areas were involved in both groups. The Jacob-Creutzfeldt group had a less schematic lesion pattern, without involvement of limbic areas. From a neuropsychiatric aspect, these differences were reflected in symptoms that could be referred both to areas spared and those more pronouncedly destroyed by the degenerative process. Thus the Alzheimer group long retained emotional qualities that were lost early in the Pick group. The possible relationship between neurotransmitters and regional accentuation of the degeneration is discussed.

Key words: Presenile dementias – Alzheimer's disease – Limbic lobe – Pick's disease – Jacob-Creutzfeldt's disease – Neurotransmitters.

Introduction

Limbic lobe involvement in organic dementia has been the subject of many investigations, though most often limited to one disease entity, such as Alzheimer's disease (A. D.) and the closely related senile dementia (S. D.) (Corsellis,

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1969, 1970; Sourander and Sjögren, 1970; Hooper and Vogel, 1976). Most reports regarding connections between clinical symptoms and limbic degenerative changes have dealt with the mamillary bodies and the temporal limbic system, mainly the hippocampus and amygdala (Milner, 1959; Victor et al., 1971; Brierley, 1961; Pilleri, 1966; Delay and Brion, 1969; Sourander and Sjögren, 1970). Hippocampal degeneration has been reported to lead to dementia with severe amnesia (Glees and Griffith, 1952; Corsellis et al., 1968; Corsellis, 1969, 1970) sometimes described as limbic dementia (Gascon and Gilles, 1973). There are few studies on the importance of lesions of the cingulate gyrus in dementia (Corsellis, 1970; Brun and Gustafson, 1976).

Most previous studies on organic dementia have been performed on selected smaller areas of the brain, and therefore the entire picture, including both distribution and relative severity of the cerebral process, could not be taken into account. This, as pointed out by Corsellis (1970), is necessary for an appraisal of the relative clinical importance of the dysfunction of various regions due to the dementing process. A further pitfall inherent in limited areal sampling is the regional variation in severity of the degenerative disease, e. g., in Alzheimer's disease (Brun and Gustafson, 1976). Generalizations based on the findings in small samples may lead to over- or underestimation of the degree of involvement in larger areas of the different lobes. The only safe method is serial whole brain sectioning, something that is impractical in most laboratories except in a limited number of specimens. The present study, employing whole brain gap sections, would seem to overcome some, if not all, of these obstacles.

With this technique the present material of various types of presenile organic dementia was investigated with the aim of studying the occurrence and distribution of limbic lobe involvement in various disorders and the reflection of the degenerative pattern on the clinical picture, also taking into account nonlimbic lesions.

Materials and Methods

The material consisted of 15, eight male and seven female, patients, representing a consecutive series of deceased patients, previously presented from a neuropsychiatric, psychometric, neurophysiological, and neuropathological aspect (Ingvar and Gustafson, 1970; Gustafson and Risberg, 1974; Hagberg and Ingvar, 1976; Brun et al., 1975; Gustafson et al., 1977; Johannesson et al., 1977). The patients had previously no psychiatric and only minor somatic disorders. They had neither abused alcohol or drugs, nor had severe head injuries or stroke with gross neurological symptoms. The dementia of the 15 patients started between 45—60 years of age (mean 53.9 ± 6.6 years) and mean age of death was 62.7 ± 6.8 years (range 51—74) with a mean duration of the disease of 8.7 ± 4.1 years (2—17 years).

The neuropathological study included the entire brain, using multiple whole brain 5—8μ thick paraffin gap sections, from planes roughly one centimeter apart, covering all lobes as well as brain stem and cerebellum. The stainings used were hematoxylin-eosin, van Gieson, luxol fast blue, Naoumenko, Congo red, and Sudan black B.

From the whole brain sections were prepared camera lucida drawings on which were indicated the location and extent of the degeneration. This information from the various planes of sectioning was then gathered on the brain templates used in the figures to show the distribution and severity of the lesions.

The severity of the degeneration was judged mainly on the basis of neuronal dropout, estimated under standardized magnification in 8-μ thick Nissl stained sections. Rough counts were made of the remaining neurons exhibiting a nucleolus and the number related to the normal neuronal density of the area under consideration. The accompanying shrinkage, loss of architecture, and gliosis were also taken into account. With advancing severity of the degeneration, these changes extended from superficial layers toward the deeper cortical strata. These parameters were supplemented by density of senile plaques and neurofibrillar tangles occurring in all layers, viewed in silver impregnations on sections parallel to the Nissl-stained slides.

The severity of the degeneration was on this basis graded from none to slight, moderate, severe, and 'total', according to Table 1 and Figure 1a—i.

The psychiatric investigation of the patients was performed according to a formalized rating scale for symptoms (Gustafson, 1975) describing various aspects of the mental dysfunction, personality alterations, and emotional reactions in dementia. Patients were followed up at regular intervals by psychiatric investigations and psychometric testing. The patients underwent neurological tests including pneumoencephalography (PEG), EEG, and regional cerebral blood flow (rCBF), as well as somatic investigations.

Results

Neuropathological Study

The 15 patients were separated into three groups (A, B, and C) according to the neuropathological findings, mainly the localization of focalized severe grey matter involvement of the degenerative process. Group A contains seven cases

Table 1. Degree of degeneration in brain areas not shown in Figure 1a—i in 15 patients with presenile dementia

Case		Insula	Mam. bodies	Striate body	Thalamus	Brain stem	Subst. nigra	Cere-bellum
A	1	+(+)	(+)	(+)	0	(+)	(+)	(+)
	2	+(+)	(+)	0	0	(+)	0	0
	3	(+)	(+)	(+)	0	(+)	(+)	+
	4	+	+++	(+)	0	(+)	0	+
	5	+(+)	0	(+)	0	(+)	(+)	(+)
	6	+	0	+	(+)	+	+	+
	7	++	(+)	+(+)	(+)	+	(+)	+
B	8	++	(+)	+	0	(+)	0	0
	9	++(+)	(+)	+	0	0	0	0
	10	+++	+	+	0	0	(+)	0
	11	+(+)	0	+++	0	+++	++	++
C	12	+(+)	–	(+)	0	(+)	+	(+)
	13	(+)	–	(+)	0	+	0	0
	14	0	–	0	0	+(+)	++	+
	15	+(+)	+	+	0	+(+)	++	(+)

Symbols: 0 = none, (+) = slight, + = moderate, ++ = strong, +++ = severe—total degeneration

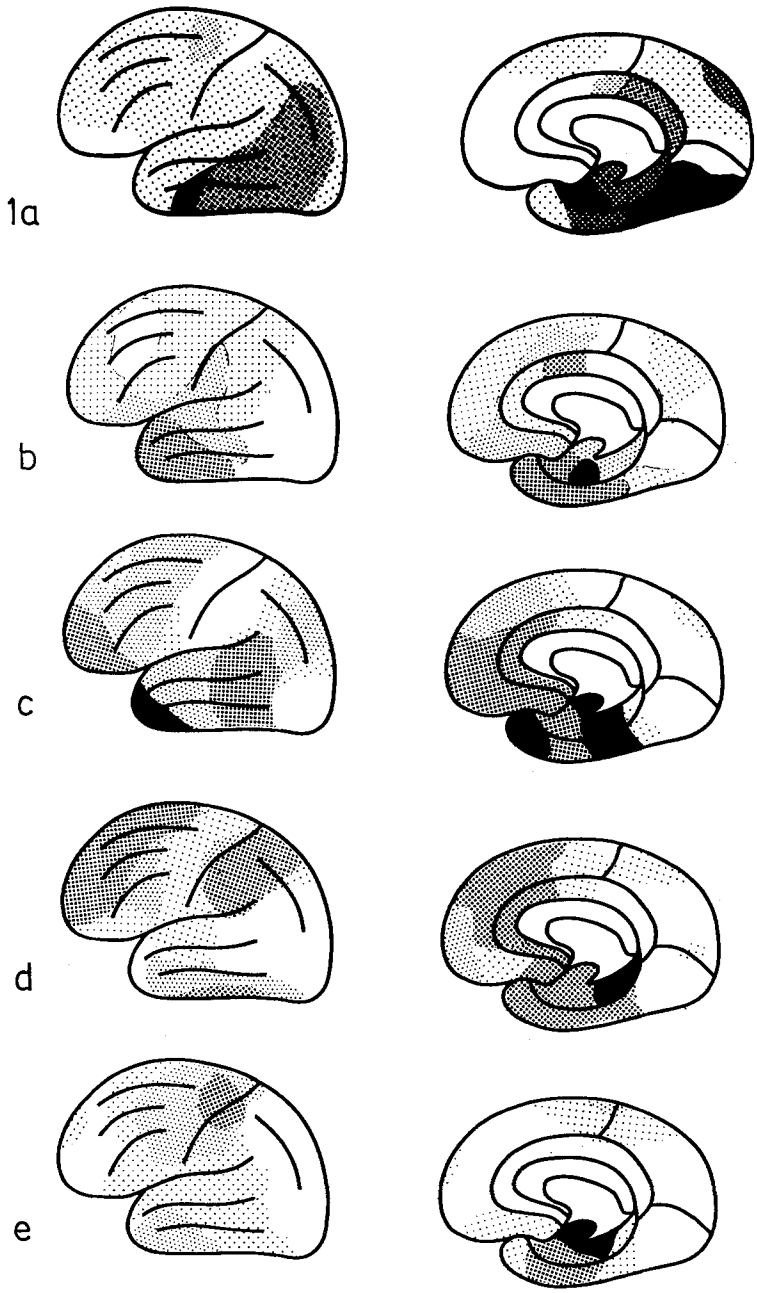

Fig. 1a—i. Distribution and degree of cortical degeneration in cases with presenile dementia. Mapping of grey matter degeneration on lateral and medial aspect of the brain. **a**: Representative case of Alzheimer's disease (case 3) from group A. **b—e**: Cases 8—11 from group **B**. **f—i**: Cases 12—15 from group C. Severity of degeneration is graded from no □, to slight ▨, moderate ▩, severe ▩, or 'total' ■

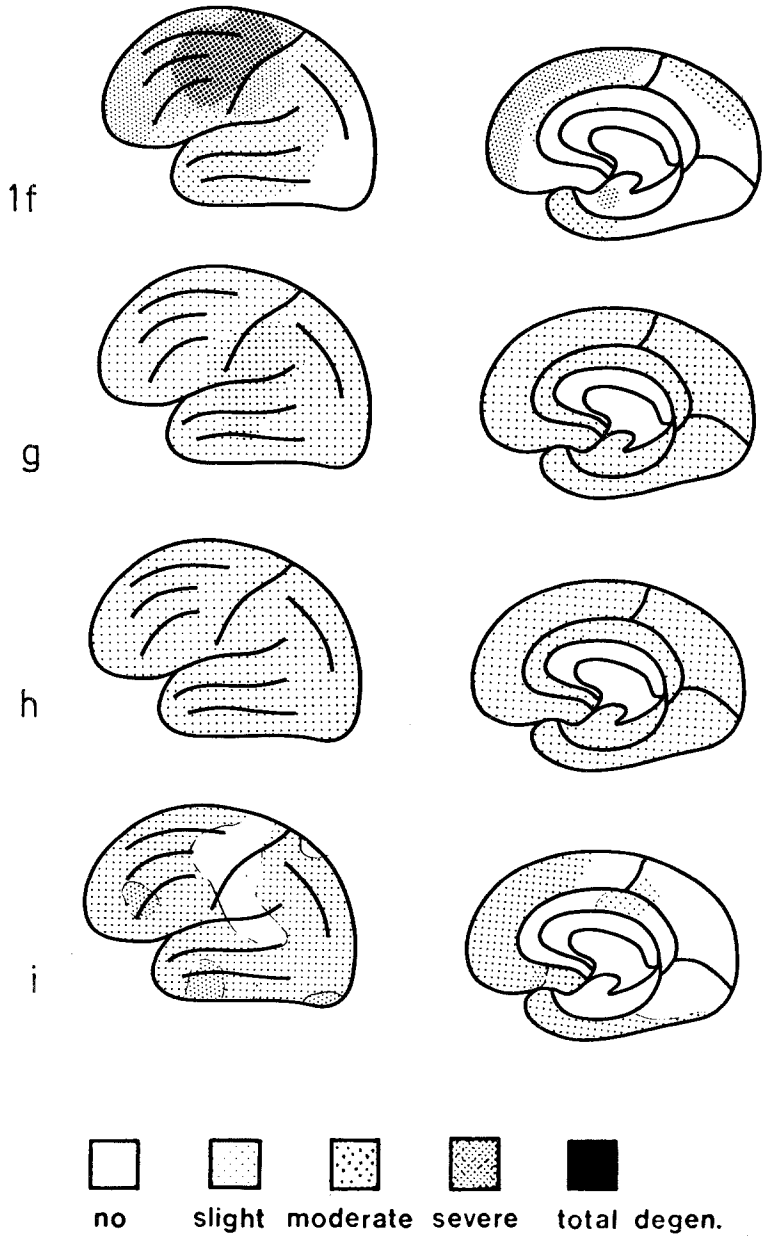

Fig. 1.

with mainly temporoparietal cortical and limbic degeneration, group B contains four cases with frontotemporal cortical and limbic involvement, and group C contains four cases with milder and less focalized cortical and no limbic damage.

Group A (cases 1—7) showed grey matter degeneration characterized by neuronal loss, gliosis, senile plaques, neurofibrillar tangles, and granulovacuolar degeneration, compatible with the diagnosis of *Alzheimer's disease.* The vessels had little or no arteriosclerotic changes but prominent amyloid depositions. There were no infarctions or hemorrhages. The distribution of the degenerative process was diffuse with temporoparieto-occipital (TPO) accentuation and involvement of temporal limbic areas and the posterior cingulate gyrus, whereas the anterior cingulate cortex, the sensorimotor, and calcarine areas were wholly or largely spared. The distribution and severity of these changes appear in Table 1 and Figure 1a, in the latter shown by a representative illustration based on the patients in group A. A full neuropathological description and individual mapping of the degeneration in these cases is given elsewhere (Brun and Gustafson, 1976).

Group B (cases 8—11) also had diffuse cortical degeneration, though dominating frontotemporally, in the temporal limbic structures as well as in the anterior half of the cingulate gyrus. The posterior half of the cingulate gyrus was notably spared. The degeneration was least pronounced in the occipital lobes, which in areas escaped apparently unharmed. The changes consisted of neuronal shrinkage, degeneration, or disappearance, with reactive astrocytic gliosis. Only occasional inflated cells of the Pick type were seen in cases 8—10, but the distribution and type of degeneration corresponds to Pick's disease. Case 11 had less severe frontal and no cingulate gyrus involvement but, apart from that, had the same telencephalic distribution of lesions. This case also had degeneration of the brain stem and the cerebellum as in a Shy-Drager syndrome. The distribution of changes are shown in Table 1 and Figure 1b—e.

Group C (cases 12—15) also showed a diffuse cortical degeneration, though less pronounced than in groups A and B and without a consistent pattern of focalization. There was practically no limbic involvement, including no cingulate gyrus degeneration. Cases 14 and 15 also had brain stem lesions of moderate severity. The cortical degeneration consisted of dropout of neurons, mild spongiosis, and slight gliosis. There were no signs of Alzheimer's neuronopathy. The picture was taken to indicate *Jacob-Creutzfeldt's disease,* though with reservations particularly with regard to case 15, mainly due to the discreteness of the process in many places. The brain stem lesions in cases 14 and 15 were of the same nature as those in the cortex, and included also a degeneration of the substantia nigra. The lesions are shown in Table 1 and Figure 1f—i.

Clinical Findings

All patients showed progressive dementia, starting in the presenile period. The symptom pattern and the clinical diagnoses differed in many respects in the three patient groups, which are constituted on the basis of the neuropathological findings.

Table 2. The distribution of principal clinical symptoms and signs in 15 cases of presenile dementia

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Sex	m	m	m	f	f	f	f	m	f	f	m	f	m	m	m
Euphoria	–	–	–	++	+	–	–	–	(+)	+	+	(+)	–	–	–
Aff. bluntness	–	–	–	+	–	–	–	+	++	+	–	–	(+)	–	+
Aff. lability	–	–	–	–	+	–	+	+	++	+	+	++	+(+)	++	(+)
Amimia	–	–	–	–	(+)	–	+	(+)	+	+	+	+	(+)	–	+
Hyperorality	++	–	++	+	–	+	–	–	+	–	–	+	–	–	+
Aggressiveness	+	–	+	(+)	+	++	–	+	+	–	(+)	–	–	+	+
Amnesia	++	++	++	++	++	++	++	++	++	++	+(+)	+	+	+	+
Confabulation	–	+	–	++	+	+	–	+	++	++	–	–	–	–	–
Desorient. temporal	+	+	+	+	+	+	+	(+)	+	–	–	+	–	+	–
Expr. aphasia	+	+	+	+	+	+	+	(+)	+	+	+	+	–	–	+
Stereotypy of speech	–	–	–	(+)	–	–	–	+	+	+	–	–	–	–	+
Logorrhea	–	–	–	+	–	–	–	–	+	+	–	–	–	–	–
Recept. aphasia	+	+	++	+	++	++	++	–	+	–	–	(+)	–	(+)	–
Dysarthria	+	+	(+)	+	(+)	+	++	+	(+)	+	+	+	–	–	–
Anarthria mutism	–	–	+	(+)	–	+	+	–	+	+	+	+	–	–	+
Apraxia	+	+	+	+	+	+	+	–	–	(+)	–	(+)	–	+	–
Agnosia	+	+	+	+	+	+	+	–	+	–	–	–	–	–	–
Restless	+	+	–	+	–	+	–	+	+	–	–	–	+	+	+
Hallucinosis	++	–	++	–	++	–	–	–	–	–	–	++	++	++	–
Delirious states	+	–	–	–	–	–	–	+	–	–	–	+	+	+	–
Increased need of sleep	+	–	–	+	–	–	–	+	+	–	+	+	+	+	+
Gen. epil. seizures	++	+	++	–	–	++	–	–	–	+	–	–	–	–	–
Tremor	+	–	+	–	–	–	+	–	–	–	–	+	+	+	–
Rigidity	–	–	+	+	+	+	++	–	–	+	+	+	–	+	(+)

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

All seven cases in group A were diagnosed as Alzheimer's disease and case reports have been presented elsewhere (Brun and Gustafson, 1976). These patients had progressive mental deterioration, mostly starting insidiously. They showed memory failure and lack of concentration, and became anxious and restless. Symptoms of aphasia, agnosia, and apraxia appeared during the first three or four years of the disease. The patients often had an increased muscular tension with the 'akinetic hypertonic character,' described in Alzheimer's disease (Sjögren et al., 1952). They became emotionally shallow and in the terminal stage aspontaneous with few adequate reactions to stimuli. Even at an advanced stage, however, most patients were capable of a nonverbal emotional contact. Individual symptoms of the seven Alzheimer cases are given in Table 2.

In group B, i.e., patients with frontotemporal and limbic involvement, the symptom pattern was in certain respects different from that of group A. Emotional deterioration and alterations of the personality dominated as well as progressive expressive dynamic aphasia, which developed into anarthria mutism. These cases became emotionally shallow and blunt with stereotyped disinhibited, sometimes even antisocial, behavior. At the terminal stage of dementia, they lacked emotional and mimical contact with other people, even their close relatives, while spatial orientation and certain practical abilities were relatively spared. Case 11 had in addition a Shy-Drager syndrome (Shy and Drager, 1960) with severe postural hypotension, impotence, and parkinsonism.

In group C with diffuse cortical degeneration and no limbic involvement, the clinical picture was dominated by amnesia, emotional lability, anxiety, and restlessness. Cases 12—14 showed fluctuations with periodically delirious, paranoic hallucinatory states. Case 14 showed some similarity to the A.D. cases of group A and, as already mentioned, case 15 clinically rather belonged to group B. The shortest duration of the disease, 2 and 3 years, was observed in two cases of group C (cases 12 and 13). Individual symptoms are presented in Table 2.

Discussion

The important question to be discussed is to what extent the different patterns of degenerative cortical and in particular the limbic changes can be related to the neuropsychiatric symptoms. The exact degree of tissue damage necessary for the production of symptoms is not known, but we know from previous studies that differences in neuronal dropout roughly estimated at 25% is clearly reflected in a decrease of cortical functional activity as measured with the regional cerebral blood flow method (Brun et al., 1975; Gustafson et al., 1977). Such differences also appear to be responsible for neuropsychiatric symptoms (Brun and Gustafson, 1976), though it may be presumed that considerably less damage is required. What we describe here is not naked eye atrophy, but accentuated degeneration on a microscopic level, not necessarily expressed as visible collapse of tissue areas. Any distinction between such grades is irrelevant to a clinicopathological correlation, since function is impeded long before structural integrity is lost to the point of grossly visible atrophy.

The regional differences recorded here are therefore thought to be of clinical relevance and appear to be reflected in the symptom pattern differences between the groups. The regional differences could neither be explained by cerebrovascular disease, nor by abuse, which is in accordance with the clinical criteria for selection of patients for the study.

The neuropathological criteria for the grouping of the cases was the distribution of lesions. On this basis group A turned out to be composed purely of cases with Alzheimer's disease. Group B was entirely dominated by a degeneration pattern tallying with Pick's disease. Group C contained cases with degeneration most likely of the Jacob-Creutzfeldt type, though the diagnosis was deemed insecure in at least one of the cases (case 15).

The differences in distribution of lesions between the groups would seem to form a good basis for an evaluation of the clinical weight of the regional lesions.

The symptoms and signs that were observed during the course of dementia are presented in Table 2. The evaluation of type and degree of certain symptoms, such as aphasia, agnosia, and apraxia, reflects the state when there was still some reliable communication with the patient, and not the terminal stage. The pattern of lesions and its clinical implications in the group of Alzheimer cases have been pointed out in a recent publication (Brun and Gustafson, 1976). The consistent finding in the Alzheimer patients was marked cortical degeneration in the posterior cingulate gyrus, the medial temporal limbic area, and the temporoparieto-occipital (TPO) cortical area (Fig. 1a). Here, thus, the anterior portion of the cingulate gyrus was spared, as were the anterior lateral areas of the hemisphere. This concordance of regional sparing and degeneration was regarded as not coincidental. This assumption appears to be strengthened by the findings in group B, where the pattern was, in several respects, the reverse. Here, thus, the frontotemporal accentuation was coupled with an anterior cingulate involvement and sparing of posterior areas of the cingulate and the postcentral lateral hemispheric cortex. This may point to a direct connection between areas of the frontal lobe and the anterior cingulate cortex, as well as between the posterior cingulate gyrus and the TPO areas. These connections may rather be of a structural functional nature than an expression of a common susceptibility to an etiologic pathogenetic agent, since they occurred in two different diseases. In support of the former theory, the posterior cingulate gyrus is closely connected with the temporoparietal region (Russell, 1961) and thereby to cognitive functions (Girgis, 1971). Moreover, the anterior cingulate gyrus belongs to the frontolimbic system (Nauta, 1973; Kelly, 1973) and has important fiber connections with, e.g., frontal areas 6, 8, 9, 10, 11, 12, and 13. These cortical areas, which include the prefrontal cortex, cover the major part of the lateral and the basal surface of the frontal lobes. In addition, the anterior cingulum receives main afferents from the anterior thalamic nuclei and thereby indirectly from the mamillary bodies (Crosby, 1962; Divac, 1972; Nauta, 1973).

The involvement of temporal limbic structures shared by the Alzheimer and Pick groups might be relevant to the amnesic syndrome observed in both groups. Although slight confabulation of the momentary type was observed in both groups, only four cases (cases 4, 8, 9, and 10) manifested productive confabulation of the fantastic type (Berlyne, 1972) usually connected with the early stages

of Korsakoff's syndrome. Most previous studies on confabulation have presented ample evidence connecting it with lesions in the hypothalamic-diencephalic structures, especially in mamillary bodies (Ule, 1958; Brierley, 1961; Luria, 1973; Mehraein and Rothemund, 1976) and the dorsomedial thalamic nuclei (Peters, 1967; Victor et al., 1971). In agreement with this, involvement of the mamillary bodies was found in cases 4, 8, 9, and 10. This type of degeneration was, however, also found in cases without confabulation. This might indicate a prerequisite of some further pathological change to produce this behavior. In addition to the mamillary degeneration, the four cases accordingly showed a consistent involvement of the prefrontal cortex, which has important connections with the dorsomedial thalamic nucleus (Divac, 1972), and to the anterior cingulum (cases 8—10). These findings indicate that there must be a more disseminative dysfunction of frontolimbic as well as of hypothalamic-diencephalic structures to produce confabulation.

The mamillary bodies were in both groups A and B on the whole only mildly or not affected. This is in accordance with the findings of other authors, particularly with the regard to A.D. (Jamada and Mehraein, 1968; Corsellis, 1970; Hooper and Vogel, 1976). In group C, relevant material for study was not available in all cases, but with reference to the known distribution of lesions in Jacob-Creutzfeldt's disease, lesions here would not be expected. This is in good agreement with the less pronounced memory failure of these patients.

There were some differences in affective and personality changes in the three groups. The Alzheimer cases were characterized by lack of concentration, restlessness, and emotional shallowness. However, even late in the course they reacted with amiability and cautiousness, and retained fragments of the premorbid personality. Spontaneously or when frustrated, the patients could react with aggressive spells. These symptoms as well as some symptoms of the Klüver-Bucy syndrome can possibly be referable to the limbic lesions (Brun and Gustafson, 1976).

The four cases of group B as also case 15 in group C showed a different type of personality alteration. This was dominated by emotional bluntness, lack of concern, and inadequate control of behavior. The mood changed to an euphoric, dysphoric tone with affective lability, and later developed into total emotional indifference, lack of facial movements (amimia), and mutism. These defects might be related to the more pronounced frontotemporal cortical and anterior cingulate involvement of these cases. Lesions of the prefrontal, anterior temporal, and anterior cingulate cortex have been associated with changes of 'tone, inclination and emotion' (Luria, 1973), disturbances of social consciousness, and to failure to control behavior. It affects less gnostic and practical abilities (Ward, 1948; Tow and Whitty, 1953; Brown and Lighthill, 1968; Girgis, 1971; Meyer, 1960; Luria, 1973). In our cases, emotional deterioration seems to be related to the degeneration of the frontotemporal and anterior cingulate cortical areas.

The cases of group C showed a less consistent symptom pattern and also a greater variability of topography of lesions. They showed less memory failure and no confabulation, which is in good agreement with the lack of involvement of limbic structures. Cases 12—14 showed affective lability, sometimes even spells of crying and marked fluctuations of the clinical course. They had delirious periods

with disorientation, agitation, hallucinosis, and paranoid delusions. In between these states, cases 12—14 appeared rather well preserved, though anxiously depressed and with some insight even regarding their hallucinosis. The neuropathological diagnosis of these three cases was Jacob-Creutzfeldt's disease and the symptom pattern described is consistent with this clinical diagnosis (May, 1968; Kirschbaum, 1968). The fluctuating course, hallucinosis, increased need of sleep, and the extrapyramidal signs might be related to the degenerative involvement of brain stem and extrapyramidal nuclei.

Thus, our series of patients with presenile dementia could be separated into three main groups with respect to the distribution of lesions in the brain. The differences in degeneration might be related to ontogenetic and functional aspects of the various brain areas. In the Alzheimer cases, the degeneration regularly involved the postcentral secondary and tertiary cortical areas and consistently spared primary projection areas and the anterior cingulate gyrus. These different areas pursue a different developmental course, earlier completed in the anterior part of the cingulate gyrus and the primary projection areas (Brun, 1965). The symptoms of amnesia, agnosia, aphasia, and apraxia correlated well with the lesions of the temporoparieto-occipital association cortex and the temporal limbic degeneration. The level of activity in the association cortex and in the hippocampal formation is possibly strongly dependent on the nonspecific activating system. This diffuse arousal system is thought to be mainly cholinergic (Lewis and Shute, 1967; De Feudis, 1974). There is considerable evidence that cholinergic pathways are involved not only in arousal but also in associative and memory functions (Drachman and Leavitt, 1974; De Feudis, 1974; Weiss et al., 1976; Drachman, 1977). Thus the most severely damaged brain areas in Alzheimer's disease seem to be strongly influenced by cholinergic projection systems. Our findings might support biochemical studies indicating a cerebral cholinergic defect in dementia of the Alzheimer type (Davies and Maloney, 1976; Bowen et al., 1976; Spillane et al., 1977; Perry et al., 1977). The cholinergic system of the parietal cortex was severely affected according to Perry et al. (1977). This is in good agreement with the marked degeneration of TPO cortex and the symptom pattern in A.D. (Brun and Gustafson, 1976).

The Pick group (group B) showed in certain respects an inverse distribution of degeneration that dominated frontotemporally and in three out of four cases also involved the anterior cingulate gyrus. The distribution of cortical degeneration is similar to that described in a Pick family by Schenk (1940). The cases described by Schenk also showed a preponderance for the anterior cingulate areas, though not as consistently as in our cases. This may be so for two reasons. Firstly, our cases have an atypical form of this disease in terms of lack of so-called Pick cells. Secondly, the family described by Schenk may for genetic reasons be expected to have a form of the disease with certain peculiarities. The familial form in question showed a sparing of sensorimotor and calcarine cortex.

This pattern recalls the consistent preservation of the same cortical fields in our Alzheimer cases. These areas, and especially the calcarine area, are also often spared in senile dementia and may thus be appointed particularly resistant.

The region involved in our Pick cases belongs to the so-called limbic forebrain area (Kelly, 1973; Nauta, 1973) with important connections with the ascending

monoaminergic neuron systems (Björklund, 1977). A dysfunction of certain transmitters might be crucial for the frontotemporal distribution of the cortical degeneration as well as for the clinical picture in group B. The possibility of a neurotransmitter failure might be supported by the fact that one patient (case 11) also had a Shy-Drager syndrome, in which disease transmitter abnormalities have been demonstrated (Bannister et al., 1977).

The less consistent symptom pattern of the patients of group C was in good agreement with the hazardous distribution of areas of degeneration, varying from case to case in our material. A consistent pattern of cortical degeneration has only been reported in Jacob-Creutzfeldt's disease of the Heidenhain type (Meyer et al., 1954). The pattern of degeneration in our cases did not show any obvious correlation to ontogenetic or functional aspects of the different cortical regions. A previous study has shown impairment of the monoamine metabolism in Jacob-Creutzfeldt's disease (Brun et al., 1971), probably related to the slow-virus infection generally presumed to underlie this disorder (Gibbs and Gajdusek, 1972).

Thus the different clinical pictures and different patterns of degeneration in the two classical forms of presenile dementia, Alzheimer's disease and Pick's disease, might be related to involvement of different functional and/or neurotransmitter systems in the brain. This has been shown in other degenerative brain disorders such as Parkinson's disease, Huntington's disease (Bird and Iversen, 1974; Enna et al., 1976; McGeer and McGeer, 1976), and in senile dementia of the Alzheimer type (Bowen et al., 1976; Davies and Maloney, 1976; Spillane et al., 1977; Perry et al., 1977). If certain types of presenile dementia are caused by neurotransmitter failure, they might be accessible to pharmacological treatment. Oral cholinergic therapy has been tried in senile dementia of the Alzheimer type with no cognitive improvement (Boyd et al., 1977). For this type of treatment, however, an earlier identification of the different types or presenile dementias is necessary. This is possible using a combination of clinical (neurological, psychiatric, and psychometric), radiological, and neurophysiological (rCBF and EEG) investigations (Ingvar and Gustafson, 1970; Gustafson et al., 1977; Johannesson et al., 1977). Using the ^{133}xenon inhalation technique, (Risberg et al., 1975; Obrist et al., 1975) thus rCBF can easily be studied repeatedly in demented patients, e.g., during drug treatment (Nilsson et al., 1977; Gustafson et al., 1978).

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