INVESTIGATION AND DIAGNOSIS OF PRIMARY CEREBRAL ATROPHY USING SINGLE PHOTON EMISSION TOMOGRAPHY AND QUALITATIVE PSYCHOLOGICAL ASSESSMENT

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UNIVERSITY OF EDINBURGH

1990

DECLARATION

This thesis has been composed by myself. The work is my own apart from that referred to in the acknowledgements. None of the material has been submitted for other degrees or professional qualifications.

ACKNOWLEDGEMENTS

Though I personally examined almost all the patients who are presented in this thesis and performed and analysed their single photon emission tomograms, the studies contained herein would not have been possible without the help of many people, in particular staff from the departments of neurology, nuclear medicine and medical physics at Manchester Royal Infirmary. I would like to thank them all at this point.

Both Dr D. Neary and Dr H.J. Testa, Consultants in Neurology and Nuclear Medicine, provided valuable guidance throughout my period of study. Many of the ideas presented in this thesis were initially theirs. Research performed in both departments prior to my appointment provided a useful framework upon which to build my studies.

I am indebted to the two neuropsychologists with whom I worked, Dr. J.S. Snowden and Mrs B. Northen. Several medical physicists, in particular, Mr. A.W.I. Burjan, Dr. R. Lawson and Dr. R. Smith, gave invaluable instruction on the mechanics of emission tomography, the computerised analysis of acquired data and methods of displaying and photographing tomographic images. Mr. A.W.I. Burjan and Dr. R. Lawson wrote the computer program for the semi-automatic method of quantification presented in Chapter Five.

Dr. D. Mann performed the autopsies on the three patients with dementia and motor neurone disease and discussed the implications of his findings. He also kindly provided the pathological illustrations.

Statistical advice was given by Mrs L. Hunt with additional help from Dr. R. Smith, Mrs B. Northen and Dr. J.S. Snowden.

I was funded for a three year period by the North West Regional Health Authority. They also provided additional financial support which allowed me to present material at several national scientific meetings.

Lastly, I would like to thank the patients who were subjects of this thesis and particularly their carers who, despite knowing that they themselves had little to gain in terms of 'treatment', travelled often considerable distances to attend our research clinics. Hopefully, more accurate diagnosis and a better understanding of the natural history of types of primary cerebral atrophy will make definitive treatment more likely in the future.

DEDICATION

This thesis is dedicated to my wife, Gail, who provided much needed support and encouragement during its composition.

ABSTRACT

Recent biopsy and necropsy studies have demonstrated that a significant proportion of patients with dementia due to primary cerebral atrophy do not have Alzheimer's disease. However, these patients are rarely identified during life despite the fact that different forms of primary cerebral atrophy may be characterised by specific patterns of impairment on neuropsychological assessment. This is because independent assessments of cerebral function have not been available. Single photon emission tomography, using brain seeking radiopharmaceuticals, such as 99mTc-HMPAO, has recently provided such a tool. An earlier preliminary study has shown single photon emission tomography to be successful in helping to distinguish between Alzheimer's disease and Dementia of Frontal Lobe Type. A close relationship was demonstrated between visually reported areas of reduced tracer uptake and the profile of neuropsychological breakdown determined clinically. Uptake was reduced in the posterior hemispheres of Alzheimer patients, whilst patients with Dementia of Frontal Lobe Type showed a selective anterior hemisphere abnormality. The appearances on single photon emission tomography allowed further patients with Dementia of Frontal Lobe Type to be identified with greater precision.

In this study 23 patients, showing selective anterior hemisphere abnormalities, are compared with a group of 45 patients with clinically suspected Alzheimer's disease, in whom scans demonstrated the presence of posterior hemisphere defects. Differences were demonstrated at the level of historical presentation, the findings on physical examination, the profile of neuropsychological breakdown, the results of electroencephalography and demographic data. Necropsy examination of the

brains of similar patients to those studied has excluded Alzheimer's disease and revealed neuronal loss, spongiform change and gliosis, predominantly affecting the frontotemporal lobes of the brain.

In a further study, four patients with the clinical manifestations of Dementia of Frontal Lobe Type who later developed features of motor neurone disease are described. Single photon emission tomography revealed prominent anterior hemisphere abnormalities. Three of the patients subsequently died and at autopsy the histological characteristics of both Dementia of Frontal Lobe Type and the amyotrophic form of motor neurone disease were detected in all three brains and spinal cords, indicating an association between the two disorders.

A further patient with presumed non-Alzheimer cerebral atrophy is described, who developed over five years, a progressive aphasic syndrome without other features of intellectual impairment. However, right sided pyramidal and extrapyramidal signs also emerged. Single photon emission tomography showed selective reduced tracer uptake in the left hemiphere and left subcortical grey matter, indicative of lobar atrophy. Since the histological changes of other documented cases of progressive aphasia are similar to those of Dementia of Frontal Lobe Type then both disorders may represent different lobar forms of a common and perhaps related pathological change.

Visual assessment of single photon emission tomograms has been shown to be a useful qualitative tool in determining the anatomical distribution of pathology in primary cerebral atrophy. However the technique suffers the relative disadvantage of being non-quantitative. Accordingly, a new semi-automatic method of quantifying uptake of

99mTc-HMPAO has been developed. The technique has shown promise as an aid to qualitative reporting of images. It is simple and rapidly performed and is capable of distinguishing patients with Alzheimer's disease and those with Dementia of Frontal Lobe Type from normal controls. Moreover, assessment of two year follow-up images in both diseases showed significant measureable decreases in tracer uptake over time.

The studies presented in this thesis indicate that single photon emission tomography is a valuable imaging technique in the investigation and diagnosis of dementia due to primary cerebral atrophy. The areas of reduced tracer uptake indicate the regions of impaired cerebral function that underly the distinct clinical neuropsychological syndromes which characterise different forms of cerebral atrophy.

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CHAPTER ONE BACKGROUND

1.1. DIAGNOSIS OF DEMENTIA DUE TO PRIMARY CEREBRAL ATROPHY

It is often assumed that almost all patients with dementia due to primary cerebral atrophy will have Alzheimer's diease. However, histological examination of the brains of such patients at necropsy (Sulkava et al, 1983) or by cerebral biopsy (Neary et al, 1986) has demonstated this assumption to be incorrect, as the pathological hallmarks of Alzheimer's disease are absent in a significant minority. These patients are rarely identified during life despite the fact that different forms of primary cerebral atrophy may be characterised by specific patterns of impairment on neuropsychological assessment (Neary et al, 1986). This appears to relate to the lack of an independent, non-clinical assessment of the nature and distribution of impaired cerebral function.

1.2. IMAGING OF BRAIN FUNCTION IN DEMENTIA DUE TO PRIMARY CEREBRAL ATROPHY

The site of pathological change in primary degenerative dementia should be identified by techniques which demonstrate some localised aspect of cerebral function. Activity of physiological systems has traditionally been assessed by use of radiopharmaceuticals in the specialty of nuclear medicine. However, until recently, apart from radioactive gases such as 133-Xenon, radiopharmaceuticals used to image the brain were restricted to water soluble agents, such as Technetium-99-pertechnetate. These tracers can only enter brain cells following damage to the blood brain barrier. This is an anatomical structure which leads to relative exclusion

of many substances from the central nervous system. It is made up of capillary endothelium, capillary basement membrane and adventitia, and the foot processes of astrocytes (Adams & Victor, 1985). In primary degenerative dementia the blood brain barrier is normal, preventing cerebral uptake of such water soluble tracers.

Recently however, there have been a number of exciting developments in the field of nuclear medicine. Firstly, several lipid soluble radiopharmaceuticals have been synthesised which can pass across the intact blood brain barrier, and secondly two techniques, namely positron emission tomography and single photon emission tomography, have evolved which allow the cerebral distribution of these compounds to be accurately detected. Positron emission tomography utilises positron emitting isotopes of brain metabolised compounds and is used to measure regional cerebral metabolism and regional cerebral blood flow. In contrast, single photon emission tomography employs gamma emitting radiopharmaceuticals, which are typically taken up and trapped by brain cells, and provides images which are thought to reflect regional cerebral perfusion.

Both techniques have been used to study patients with dementia due to primary cerebral atrophy. Positron emission tomography has demonstrated reduced metabolic activity in the posterior hemispheres of patients with clinically presumed Alzheimer's disease (Frackowiak et al, 1981; Foster et al, 1984), in keeping with the predominant distribution of pathological changes found at necropsy (Brun & Englund, 1981). However, due to the cost of a cyclotron, necessary for the production of positron emitting radiopharmaceuticals, positron emission tomography is unlikely to become freely available.

In contrast, the use of single photon emission tomography with a rotating gamma camera is already widespread. This technique is employed by many nuclear medicine departments to investigate diseases affecting other areas of the body as well as those of the nervous system. For some years, the most promising radiopharmaceuticals for demonstration of regional cerebral perfusion were 123-Iodine labelled derivatives of amphetamine (Winchell et al, 1980). One such compound, 123-I-isopropylamphetamine (123I-IMP) was found to indicate reduced perfusion in the parieto-occipital regions in patients with presumed Alzheimer's disease (Gemmell et al, 1984). However, 123-Iodine is not an ideal radionuclide. It is cyclotron produced and has a half-life of 13.3 hours. It is therefore expensive and has limited availability.

Much research effort was therefore directed towards the development of a 99m-Technetium labelled radiopharmaceutical because this radionuclide is more freely available being generator produced and having a widespread application throughout nuclear medicine. Such an agent, 99mTc-propyleneamine oxime (99mTc-PnAO) was first developed in 1984 by Volkert et al. However, despite lipid solubility and high initial brain uptake, the redistribution of this compound was too rapid for tomographic brain imaging using a rotating gamma camera. Many related compounds were synthesised in an attempt to overcome this problem, the most suitable to date being the d,l, diasterioisomer of 99mTc-hexamethyl propyleneamine oxime (99mTc-HMPAO). Studies in rats (Nowotnik et al, 1985) and human volunteers (Burjan, 1986; Costa et al, 1986; Sharp et al, 1986b; Shields et al, 1986) showed both rapid cerebral uptake and minimal washout.

1.3. PATTERN OF UPTAKE OF 99mTc-HMPAO IN NORMAL SUBJECTS

This new brain seeking radiopharmaceutical became available in Manchester in 1985 and biodistribution studies were performed in eight normal volunteers (Shields et al, 1986 and Burjan, 1986). Intravenous injection of 99mTc-HMPAO was followed by measurement of initial brain uptake, 24 hour blood and urine sampling, whole body imaging and rotaing gamma camera tomography using an International General Electrics 400 A/T rotating gamma camera (Figure 1.1) interfaced with a Medical Data Systems A-cubed computer.

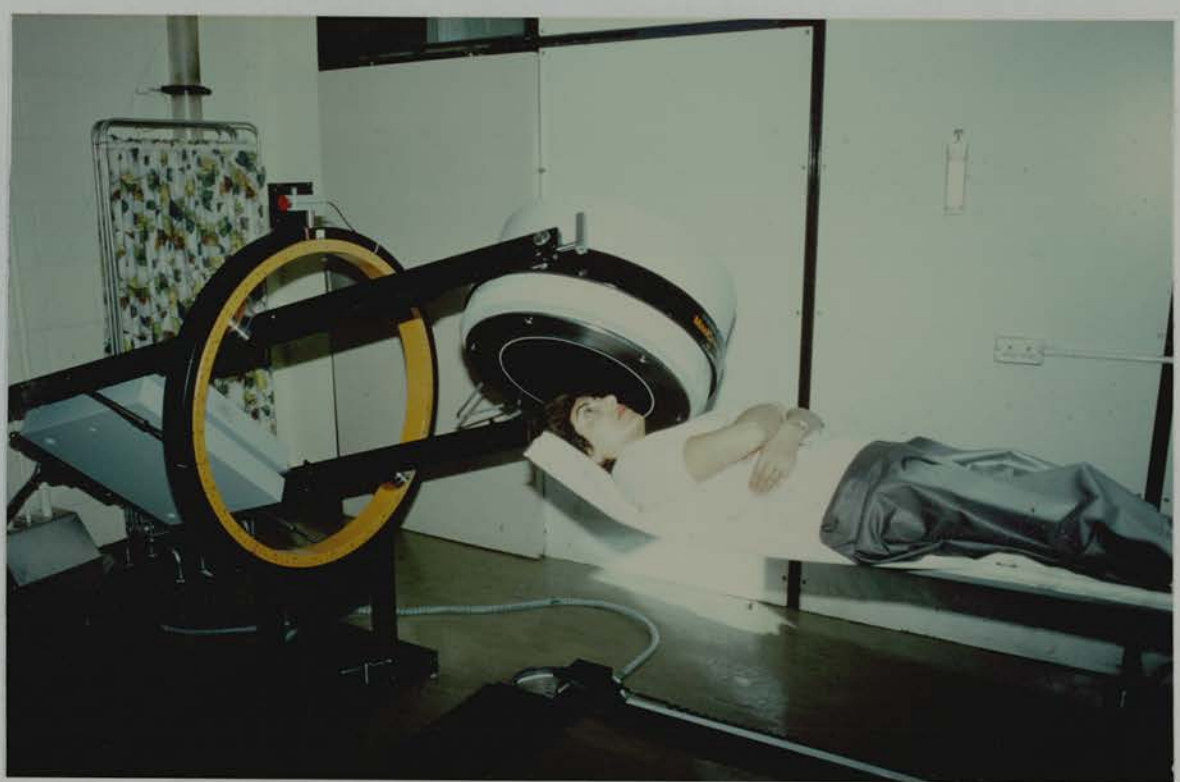
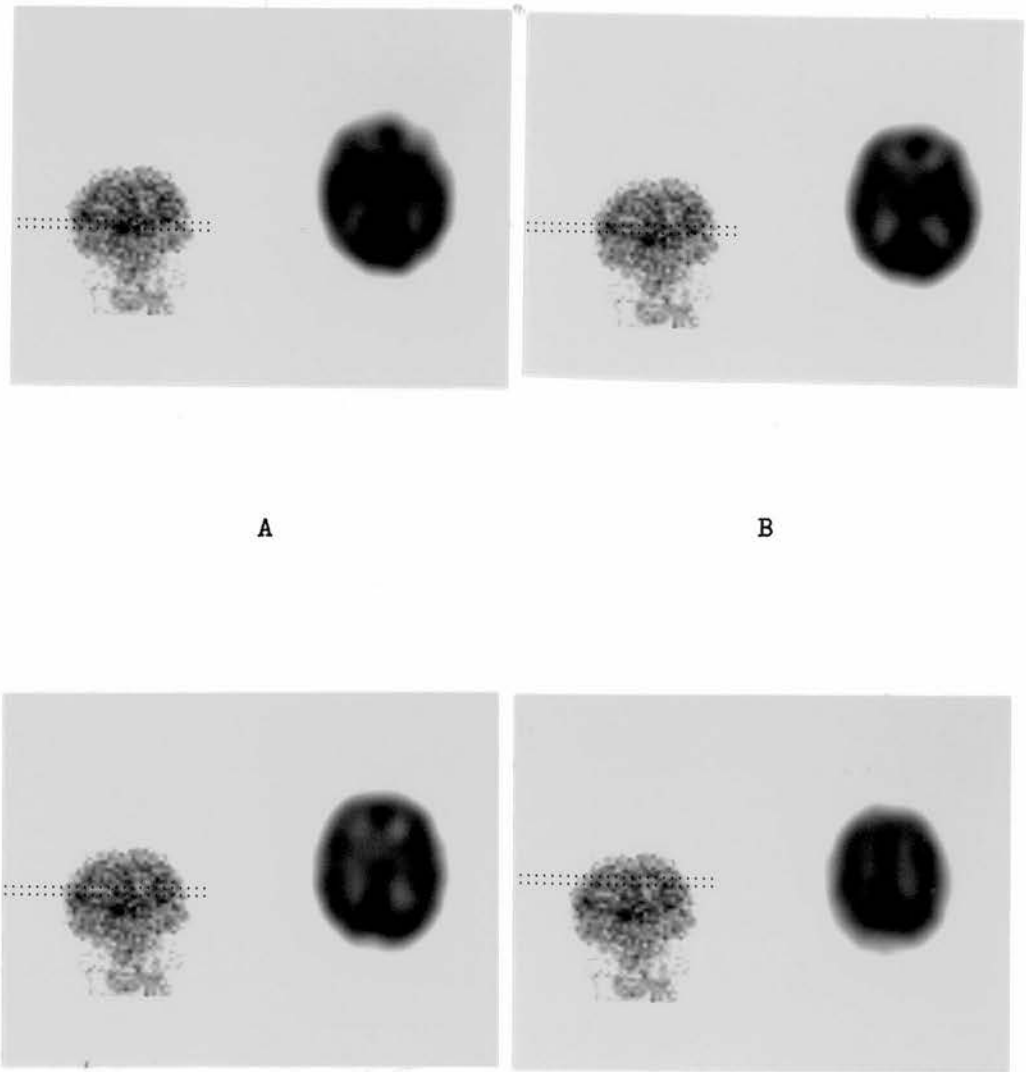


Figure 1.1.

The IGE 400 A/T rotating gamma camera.

There were no adverse reactions to 99mTc-HMPAO. Mean brain uptake was 4.4% of the injected dose, ten minutes after injection and remained effectively constant for six hours. The tracer was shown to be excreted by both the liver and the kidney. The estimated dose equivalent, a measure of radioactive risk, was calculated to be 7.8 mSv for females and 6.7 mSv for males, using a dose of 550 MBq. These vaues were similar to that of 6 mSv, the equivalent value for a conventional Technetium-99m-pertechnetate brain scan, using a standard 600MBq dose.

The tomographic brain images suggested that 99mTc-HMPAO is distributed with respect to regional cerebral perfusion and a typical set of four transaxial sections is shown in Figure 1.2. Each image is displayed adjacent to an anterior planar view in order to indicate the level of the section. There is high uptake of tracer, fairly uniformly distributed throughout most of the cortical grey matter, with increased uptake in the occipital region reflecting the more active visual cortex. Uptake is relatively low in the white matter and ventricles, whilst the subcortical grey matter is seen as regions of high activity in the centre of the lower sections. Single photon emission tomography using 99mTc-HMPAO and a rotating gamma camera therefore appeared to be ideally suited for study of regional cerebral perfusion in patients with dementia due to primary cerebral atrophy.



A B

C D

Figure 1.1.

Four transaxial sections parallel to the orbito-meatal line from a normal volunteer. Image A is the lowest section and image D is the highest section. Anterior is superior and the right hemisphere is on the left. I am grateful to Mr. AWI Burjan for permission to use these images.

1.4. PREVIOUS STUDY OF SINGLE PHOTON EMISSION TOMOGRAPHY IN THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA DUE TO PRIMARY CEREBRAL ATROPHY (NEARY ET AL, 1987)

Patients with clinically presumed and biopsy proven Alzheimer's disease (n = 23), non-Alzheimer Dementia of Frontal Lobe Type (n = 9) and Progressive Supranuclear Palsy (n = 9) were examined using 99mTc-HMPAO and single photon emission tomography in order to assess the diagnostic potential of single photon emission tomography in primary cerebral atrophy. The three groups did not differ significantly in terms of age or length of illness at the time of scanning. In all patients Hachinski Ischaemic Scores (Hachinski et al, 1975) were less than four and X-ray computed tomography revealed cerebral atrophy in the absence of vascular lesions. The eight normal volunteers who had participated in the earlier biodistribution studies, described above, served as a reference group.

Images were produced following the intravenous administration of 550 MBq of 99mTc-HMPAO, using the method described by Shields et al, 1986 and Burjan, 1986 (Appendix 1). Transaxial sections were photographed and reported in a blind fashion by two independent observers with respect to areas of reduced tracer uptake.

Characteristic abnormalities were reported in each patient group. Reduced tracer uptake in the posterior hemispheres was significantly more common in patients with Alzheimer's disease (Figure 1.3) than in the other two patient groups, whereas selective anterior hemisphere abnormalities were significantly more common in both Dementia of Frontal Lobe Type and in Progressive Supranuclear Palsy than in Alzheimer's disease. Scans were reported as normal in a small number of patients with mild Alzheimer's disease. Patients with Progressive Supranuclear

Palsy could be distinguished from those with Dementia of Frontal lobe type by the appearance of the frontal lobe abnormality. In patients with Progressive Supranuclear Palsy a rim of frontal cortical uptake was typically preserved (Figure 1.4) whilst frontal cortical uptake was characteristically absent in Dementia of Frontal Lobe Type (Figure 1.5).

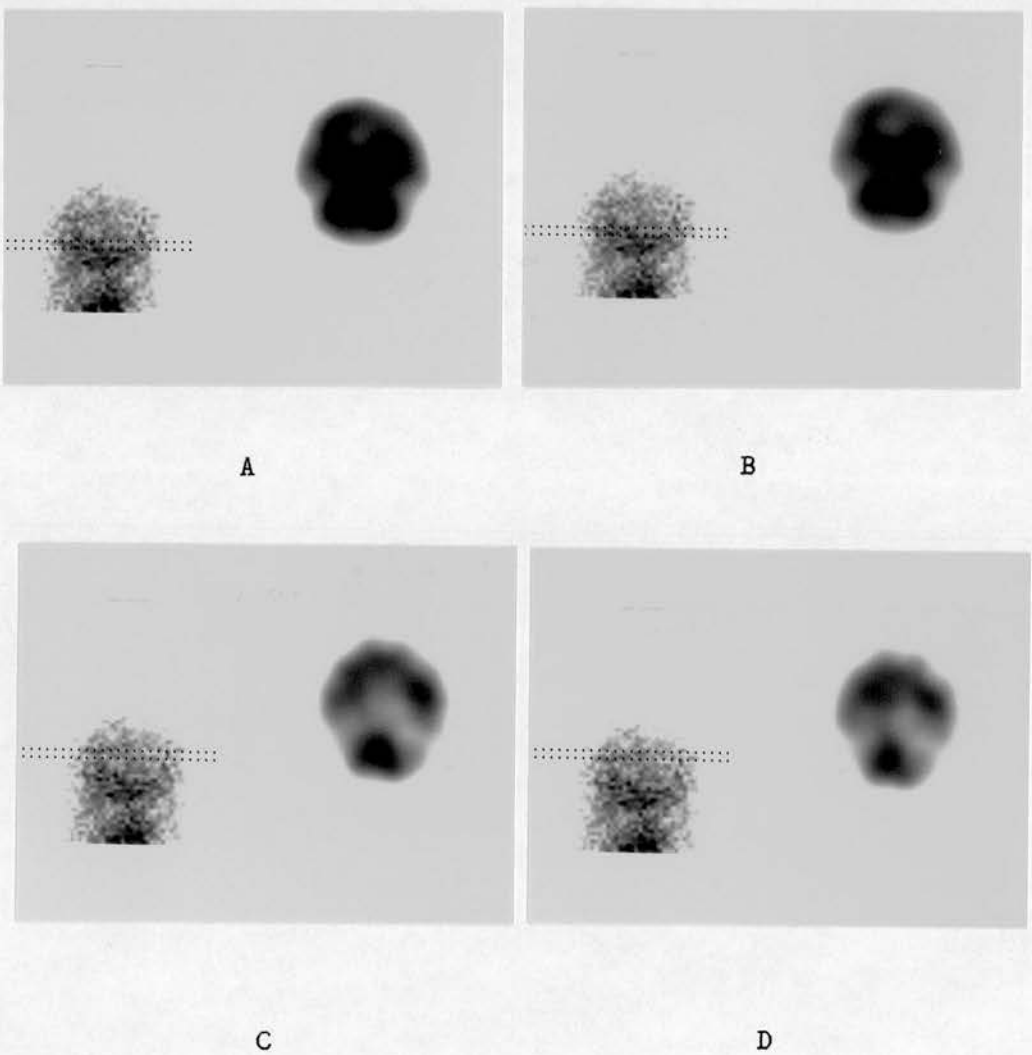
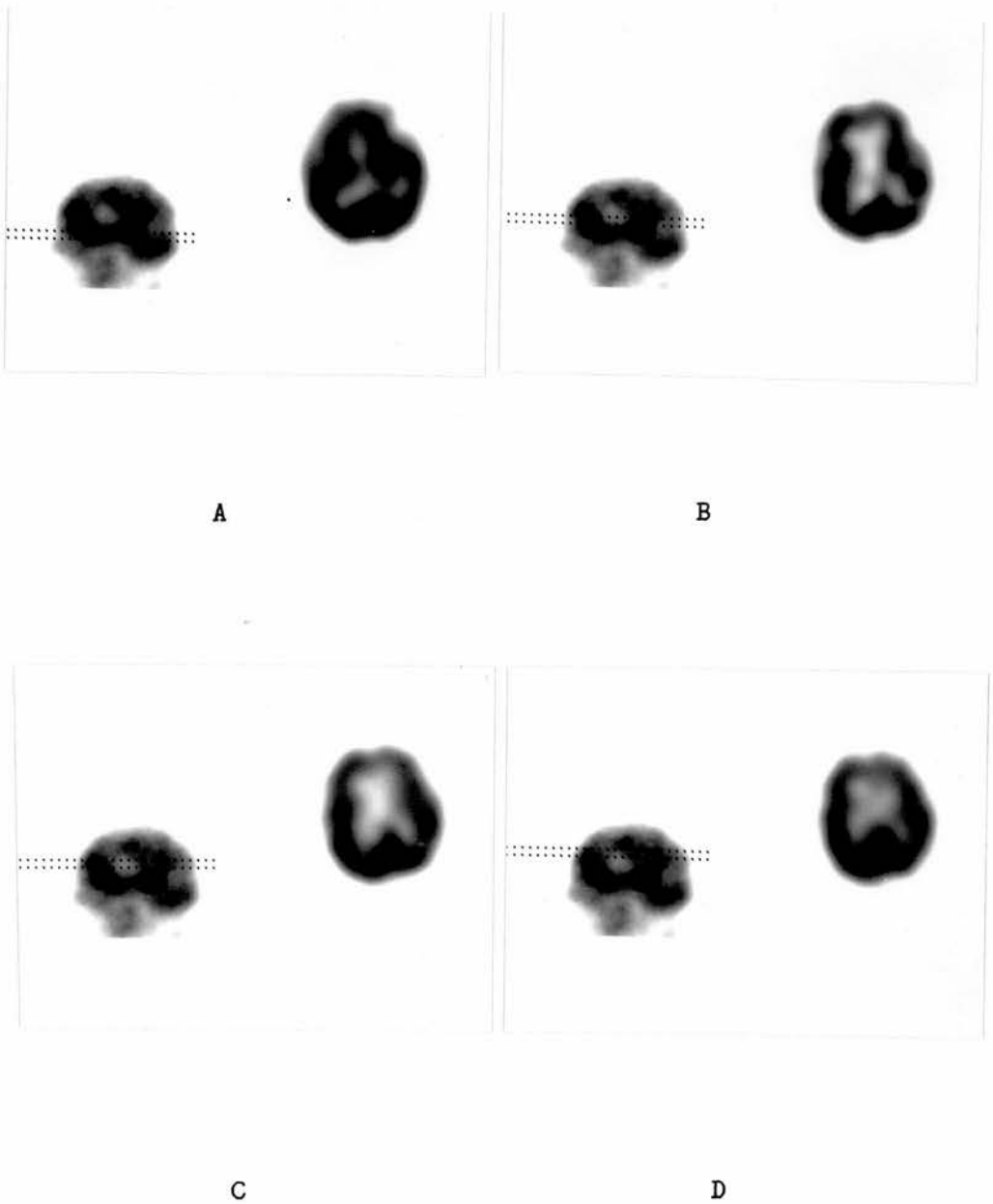


Figure 1.3.

Alzheimer's disease. There is a clear reduction of uptake of 99mTc-HMPAO in both posterior regions.



A B

C D

Figure 1.4

Progressive supranuclear pasy. There is a marked perfusion defect in the anterior regions but a preserved rim of frontal cortical uptake.

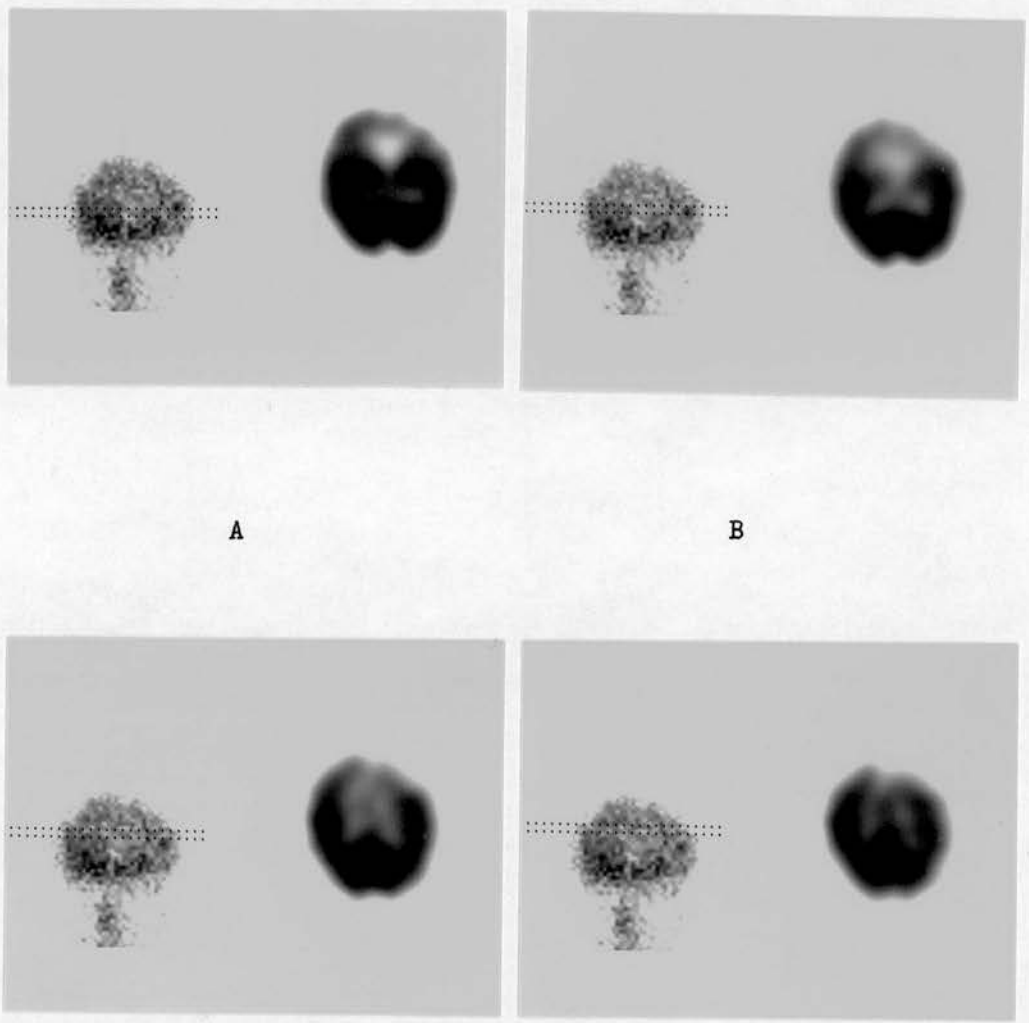


Figure 1.5.

Non-Alzheimer Dementia of Frontal Lobe Type. There is a clear reduction of uptake of 99mTc-HMPAO in both frontal regions, rather more pronounced on the left and extending through the cortical rim. I am grateful to Dr D. Neary for permission to illustrate the above three scans.

The distribution of tracer abnormality appeared to reflect the topographical distribution of impaired cerebral function in the three patient groups. Disturbed visuospatial abilities, reflecting parietal lobe dysfunction were a feature in all Alzheimer patients showing posterior hemisphere abnormalities, whilst Alzheimer patients with preserved visuospatial skills typically had normal scans. The anterior hemisphere abnormality seen in Dementia of Frontal Lobe Type and in Progressive Supranuclear Palsy was in keeping with the disorder in regulation of behaviour present in both diseases. The preserved rim of frontal cortical uptake in Progressive Supranuclear Palsy appeared to reflect the known subcortical distribution of pathology in this disease, whilst the absent frontal cortical uptake suggested that Dementia of Frontal Lobe Type was predominantly a disorder of the anterior cerebral cortex.

This study appeared to indicate that single photon emission tomography, using 99mTc-HMPAO and a rotating gamma camera, had potential value in the differential diagnosis of dementia due to primary cerebral atrophy.

1.5. PURPOSE OF THE PRESENT STUDY

Since this preliminary study suggested that the dementia associated with anterior cerebral reductions in tracer uptake is a form of cerebral atrophy distinct from Alzheimer's disease, it was proposed to:-

1). Collect a larger group of patients with primary cerebral atrophy showing selective anterior cerebral hemisphere abnormalities, thought to have Dementia of Frontal Lobe Type, and compare it with a group of patients with bilateral posterior hemisphere abnormalities who were clinically presumed cases of Alzheimer's disease

2). Compare the two groups to determine whether valid distinctions could be demonstrated in terms of:-

a). Historical presentation.

b). Profile of neuropsychological breakdown.

c). Appearance on electroencephalography.

d). Demographic data.

e). Pathological appearance when necropsy was carried out

3). Evaluate single photon emission tomography in patients with other neuropsychological syndromes due to primary cerebral atrophy.

4). Develop a technique for quantifying regional tracer uptake in order to measure the relative tracer uptake in particular cortical regions in forms of primary cerebral atrophy and to determine whether changes in relative tracer uptake developed in patients who were re-examined over a period of time.

CHAPTER TWO COMPARISON OF DEMENTIA OF FRONTAL LOBE TYPE WITH ALZHEIMER'S DISEASE

2.1. INTRODUCTION

Since a previous study, described in Chapter One, had suggested that Dementia of Frontal Lobe Type was a form of primary cerebral atrophy distinct from Alzheimer's disease and that patients could be distinguished by pattern of tracer uptake on single photon emission tomography, two larger groups of patients were studied in order to characterise Dementia of Frontal Lobe Type. The two groups were compared in terms of historical presentation, pattern of neuropsychological impairment, appearance on electroencephalography, demography and pathology.

2.2. PATIENTS

The entire study group consisted of 68 patients, referred to a neurology department, fulfilling the criteria detailed below. There were 29 males and 39 females. All patients had presented with progressive intellectual deterioration and decreased social independence and had a history of illness of at least one year's duration. Criteria for inclusion in the study were: 1). absence of a history of vascular disease, alcohol abuse and major head trauma; 2). absence on examination of clinical evidence of cerebrovascular or systemic disease; 3). X-ray computed tomography appearance limited to cerebral atrophy; 4). Hachinski ischaemic score (Hachinski et al, 1975) of less than four.

On the basis of a previous study (Neary et al, 1987) in which neuropsychological data were correlated with the appearance of tracer

uptake on single photon emission tomography, the patients were divided into two groups - presumed Dementia of Frontal Lobe Type and presumed Alzheimer's disease.

GROUP A). Presumed Dementia of Frontal Lobe Type

In these patients single photon emission tomography (Appendix One) had shown a selective anterior hemisphere reduction of tracer uptake. The area of reduced tracer uptake typically extended through the anterior cortical rim (see Figure 1.4.).

GROUP B). Presumed Alzheimer's disease

In these patients single photon emission tomography had demonstrated reduced tracer uptake affecting the posterior cerebral hemispheres (see Figure 1.2.).

2.3. METHODS

A). CLINICAL ASSESSMENT

i). History

Information was obtained from interviews with patients and their relatives, from hospital notes and from patients' general practitioners. Nursing staff were often able to supply detailed descriptions of the behaviour of the patients resident on long stay wards.

ii). Physical Examination

General and neurological examinations were carried out.

iii). Mental Examination

a). Qualitative assessment.

Patients underwent qualitative mental testing (Neary et al, 1986) in order to determine their 'neuropsychological profile'. The tests used are described in Appendix Two.

b). Quantitative assessment.

Provided a patient's mental disability was not severe, further tests were performed. These tests are thought to tap particular aspects of mental function, have been standardised using normal individuals and give rise to a numerical score. The following tests and the predominant aspect of mental function which they are thought to examine were used.

Language	- Shortened Token Test (De Renzi & Faglioni, 1978).
	- Boston Naming Test (Kaplan et al, 1983).
Perceptuo-spatial	- Dot counting.
	- Money Road Map (Money et al, 1965).
Memory	- Recognition Memory Test (Warrington, 1984).
	- Paired associate Test of Learning.
Regulation/	- Weigl's Blocks (De Renzi et al, 1966).
Frontal Lobe	- Wisconsin Card Sorting Test (Nelson, 1976).
	- Design Fluency (Jones-Gotman & Milner, 1977).
	-'20 Question Test' (Becker et al, 1986).

Where possible patients were also tested using the WAIS (Wechsler, 1944).

B). NEUROLOGICAL INVESTIGATIONS

i). Electroencephalography

A standard examination was performed on all patients.

ii). X-ray computed tomography

Patients were examined using a General Electric 8800 CT scanner.

2.4. RESULTS

Twenty-three patients fulfilled criteria for Group A (Dementia of Frontal Lobe Type), having scans showing a selective anterior hemisphere abnormality whereas 45 patients fulfilled criteria for Group B (Alzheimer's disease) having scans revealing the presence of posterior hemisphere abnormalities.

In section A, the 23 patients with Dementia of Frontal Lobe Type are compared with the 45 Alzheimer patients. In section B, the differential characteristics of Dementia of Frontal Lobe Type and Alzheimer's disease are exemplified by case studies of seven and five patients respectively who were representative clinically and demographically of groups A and B as a whole.

SECTION A COMPARISON BETWEEN DEMENTIA OF FRONTAL LOBE TYPE AND ALZHEIMER'S DISEASE)

Table 2.1. summarises the principal distinctions between the two groups.

TABLE 2.1. CHARACTERISTICS OF DFT AND AD

	DFT	AD
HISTORY	Early personality change and social breakdown	Early amnesia, spatial and language disorder
PHYSICAL SIGNS	Primitive reflexes	Rigidity, akinesia, myoclonus
CONDUCT AND AFFECT	Apathy, unconcern	Anxiety
	Inappropriate jocularity	
	Disinhibition, distractibility	
	Loss of social awareness	Preserved social awareness
	Loss of emotional empathy	
	Obsessionality, gluttony	
LANGUAGE	Economical output	Impaired verbal expression
	Verbal stereotypes	Comprehension, repetition and naming disorder
	Concrete	
	Mutism in late stages	Palilalia in late stages
SPATIAL ABILITIES	Preserved	Early spatial disorder
MEMORY	Variable memory loss	Consistent amnesia
EEG	Normal	Abnormal

DFT = Dementia of Frontal Lobe Type.

AD = Alzheimer's disease.

HISTORY

In Dementia of Frontal Lobe Type early features were characterised by social breakdown and personality change with inappropriate affect and lack of concern. Initiative was reduced, patients neglected hygiene and personal responsibilities, their behaviour became rigid, inflexible and socially inappropriate. Their affect was bland or fatuous and they exhibited a callous loss of sympathy for others. Hypochondriacal, obsessional and paranoid symptoms and a tendency towards gluttony were common. Insight was lost. Restlessness and distractibility were frequently observed. Memory disturbance was reported as variable and idiosyncratic. Speech abnormalities were not prominent early symptoms, although gradual reduction in speech output was sometimes noticed as the disease progressed. Symptoms of visuospatial disorientation were notably absent even in advanced disease.

Presenting features in Alzheimer patients, in contrast, were of cognitive rather than social breakdown. Social graces were remarkably well preserved in the early stages. Anxiety, distress and querulousness were common. The earliest symptom in most patients was of a failing memory. Symptoms suggestive of visuospatial disorder occurred early in the disease and were sometimes the presenting symptom. Difficulty in verbal expression and in word finding, and in reading and writing were common symptoms, particularly as the disease progressed.

PHYSICAL SIGNS

Patients with Dementia of Frontal Lobe Type were remarkably free from neurological signs, even in the presence of gross behavioural and cognitive change. Signs were generally limited to the emergence of

'frontal' reflexes as the disease progressed. Akinesia, rigidity and myoclonus which became notable in the later stages of Alzheimer's disease were absent in patients with Dementia of Frontal Lobe Type.

MENTAL EXAMINATION

a). Conduct

In patients with Dementia of Frontal Lobe Type, economy of mental effort and unconcern regarding accuracy of responses characterised test performance. Responses were impulsive and tasks were readily abandoned. Yet, correct answers could often be elicited by cajoling and encouragement. Alzheimer patients, in contrast, applied themselves diligently to tasks, expressing concern regarding the accuracy of their responses.

b). Language

Spontaneous conversation was often reduced in Dementia of Frontal Lobe Type, resposes being brief and unelaborated. In some patients, there was a press of speech, responses being inappropriately constrained by the question. Stereotyped remarks were common and echoing of questions or reiteration of phrases occurred. Thinking was concrete, verbal paraphasias occurred and generic terms replaced precise substantives. Failure to grasp instructions and irrelevant responses to questions gave the impression of comprehension impairment, although variability in performance together with demonstrated preserved understanding of complex syntactic sentences and low frequency substantives suggested that the disorder may not be primarily linguistic. Hypophonia and dysprosody were observed in a minority of patients.

In Alzheimer patients reliance on social platitudes with disease progression suggested a decrease in information available to the patient. Speech was fluent, although utterances begun could often not be completed owing to loss of train of thought. Comprehension was impaired, particularly where a question involved substantial memory load or functional words expressing a spatial relationship. The idiosyncratic word usage and literal thinking noted in patients with Dementia of Frontal Lobe Type were not a feature of Alzheimer patients. Palilalia, absent in patients with Dementia of Frontal Lobe Type, was a common feature in Alzheimer patients as the disease progressed.

c). Visuospatial abilities and praxis

Patients with Dementia of Frontal Lobe Type could manipulate objects normally and in dressing showed no difficulty in spatial orientation of clothing. They could localise objects in space and did not become lost in their environment. Drawings and block constructions revealed preservation of spatial configuration and the relationship between elements. However, in carrying out constructional tasks patients showed little concerted strategy or persistence despite awareness of error. Errors were interpreted therefore as secondary to failures of attention and effective strategy, rather than to visuospatial disorientation or apraxia. Spatial disability was notably absent even in patients with advanced disease.

In Alzheimer patients spatial disorientation and apraxia were common. Patients had difficulty localising objects in front of them, they became lost in familiar environments, including their own homes and in dressing they failed to orientate their clothes correctly. Drawings and block

constructions revealed striking loss of spatial configuration and relationship between elements.

d). Memory

Patients with Dementia of Frontal Lobe Type were typically well-orientated in place and time and could provide information regarding day to day events. Yet they preformed poorly on formal tests of memory. This discrepancy between the the clinical impression of well preserved memory and the demonstrated impairment on formal tests suggested that these patients' 'amnesia' resulted from a strategic failure to use their memory efficiently, rather than an inability to acquire and retain new information per se. Relatives' reports of variable and eccentric memory in these patients would seem consistent with this interpretation.

In Alzheimer patients impaired memory was consistent and pervasive. Temporal and spatial disorientation were common and recall of day to day events was severely limited. Impaired performance on formal memory tests was compatible with and corroborated the clinical impression of amnesia.

ELECTROENCEPHALOGRAPHY

In all patients with Dementia of Frontal Lobe Type electroencephalography was normal. In all but five Alzheimer patients moderate slowing of wave forms was present.

DEMOGRAPHIC FEATURES

Details of sex, presence of family history of dementia in a first degree relative, age at first symptom and length of history of illness at the time of scanning in the two groups are summarised in Table 2.2.

TABLE 2.2. DEMOGRAPHIC FEATURES

	NUMBER	FEMALES:MALES	FAMILY HISTORY	AGE AT FIRST SYMPTOM (YEARS) MEAN	RANGE	LENGTH OF HISTORY (YEARS) MEAN	RANGE
DFT	23	11:12	11	55	46-65	6	1-17
AD	45	28:17	6	59	45-74	4	1-14

a). Age

The mean age of onset of symptoms in the Dementia of Frontal Lobe Type group was 55 years (SD 5.5 years), range 46-65. In the Alzheimer patients the mean age of onset was 59 years (SD 5.6 years), range 45-74. The difference between the two groups with respect to age of onset of disease was statistically significant (Students unpaired t test $T = -2.6$, $p < 0.05$ two tailed test). Referral bias would account for the overall youthfulness of the two populations but not for the the relative youth

of the Dementia of Frontal Lobe Type group compared to the Alzheimer group. The data suggest that Dementia of Frontal Lobe Type is a disease predominantly of the presenium, contrasting with Alzheimer's disease, which becomes more prevalent with increasing age.

b). Sex

Of Dementia of Frontal Lobe Type patients there were 11 females and 12 males. This contrasts with 28 female and 17 male Alzheimer patients. The higher incidence of Alzheimer's disease in females compared with males is well-known (Lishman, 1987). While the relatively small numbers of Dementia of Frontal Lobe Type patients preclude precise inferences regarding sex incidence, the figures suggest that Dementia of Frontal Lobe Type is much less predominantly a disease of females than is Alzheimer's disease.

c). Family History

A history of dementia in a first degree relative was recorded in 48% of 23 patients with Dementia of Frontal Lobe Type. By contrast, amongst the population of 45 patients with Alzheimer's disease a positive family history of dementia could be established only in 13%. These findings are consistent with previous reports of a higher familial incidence in non-Alzheimer forms of dementia (Sim et al, 1966; Sulkava et al, 1983).

PATHOLOGY

Prior to the commencement of the study right frontal cortical biopsy in two Dementia of Frontal Lobe Type patients (Neary et al, 1986) had shown non-specific changes, the absence of senile plaques and

neurofibrillary tangles and revealed no evidence of reduction in choline acetyltransferase or in acetylcholine synthesis. Although none of the studied patients have as yet come to necropsy, three clinically similar patients, one a first cousin of a studied patient have died and pathological examination has been carried out. None of the three had been examined using single photon emission tomography.

Macroscopically there was gross atrophy of the frontal and temporal lobes. In the frontal lobes, the inferior and middle frontal gyri and the cingulate gyrus were particularly affected, whereas superior frontal as well as parietal and occipital cortices were less severely atrophied. The superior, middle and inferior temporal gyri were all affected more severely at the anterior pole. The brain stem and cerebellum appeared grossly normal. The lateral venticles were grossly dilated with marked atrophy of the caudate nucleus and putamen. The thalamus and globus pallidus appeared normal. The amygdala and hippocampus were moderately atrophied. The substantia nigra was well pigmented. The major cerebral arteries and those of the circle of Willis were free from atheroma and no infarction of the brain was observed.

On microscopic examination, the frontal, anterior temporal, insular and parietal regions revealed severe cortical atrophy characterised histologically by shrinkage and loss of pyramidal neurones particularly at layer III and to a lesser extent at layer V. There was pronounced accompanying status spongiosus and mild astrocytosis in layers I-III, with prominent astrocytosis at the grey/white boundary. There was considerable loss of myelin from the underlying white matter. Within the temporal cortex the inferior and middle temporal gyri were most severely affected, the superior temporal gyrus being only mildly involved. The

occipital (calcarine) gyrus was unaffected. The claustrum and caudate nucleus showed similar neuronal atrophy, spongiform change and gliosis. The hippocampus (Ammon's horn and subicular areas) appeared histologically normal as did the amygdala, although adjacent areas of temporal cortex showed the same histological appearance as anterior temporal regions. There was severe loss of cells from the nucleus of Meynert. The globus pallidus, cerebellum and dentate nucleus appeared normal.

Senile plaques and neurofibrillary tangles were completely absent from the brain and there was no evidence of intraneuronal inclusions of the type associated with Pick's disease. In no areas of the brain were there any abnormalities of the larger extraparenchymal or the smaller intraparenchymal arteries.

Right temporal cortical biopsy (Neary et al, 1986) had been carried out prior to the study on a three of the patients with Alzheimer's disease. All three biopsies had shown senile plaques and neurofibrillary tangles, and reduction of choline acetyltransferase activity and acetylcholine synthesis in cortical synaptosomes. Two of the studied Alzheimer patients, including one in whom a cerebral biopsy had been carried out, have since died and necropsy has been carried out. In both brains macroscopic examination revealed generalised cerebral atrophy with enlargement of the ventricles and cortical sulci. Microscopy showed neuronal cell loss with senile plaques and neurofibrillary tangles affecting the limbic system, neocortex, nucleus of Meynert and locus caeruleus. The pathological findings are described in more detail in section B of this chapter.

SECTION B CASE REPORTS

DEMENTIA OF FRONTAL LOBE TYPE

The following descriptions of patients exemplify the syndrome of Dementia of Frontal Lobe Type and encompass the nature of the progress of the disorder. All patients were right handed.

PATIENT ONE

A 55 year old female presented with a two year history of mental slowing, increasing apathy and neglect of personal hygiene and household chores. Occasional urinary incontinence led to no distress, embarrassment nor appropriate explanation. Her mood was reported to be abnormal and variable; sometimes she was irritable, negativistic and uncooperative, and on other occasions jovial and amenable. She denied any change in personality or in mental or physical health. She drove her car with less care but without getting lost. She spoke less and more quietly.

There was no previous personal of family history illness of psychiatric illness.

Physical Examination

The general examination was normal. Neurological examination revealed extensor plantar responses, a positive jaw jerk and a prominent snout reflex.

Mental examination

She was inert, with a bland affect. She lacked persistence in carrying out mental tasks, although satisfactory performance could often be obtained by by coaxing and encouragement.

She did not volunteer conversation and her answers to questions were economical and unelaborated. There was mild hypophonia and dysprosody. She could designate left and right correctly and comprehension of sentences involving complex syntax was intact. Confrontation naming was normal. She could read and spell, although writing yielded perseveration: when asked write about her job, she wrote "I mind about the weather"

eight times in succession despite repeated encouragement to write something different. In calculating she responded impusively, making errors. When encouraged to check her responses she could generally make appropriate corrections.

Elementary perceptual and spatial abilities were intact. She could identify line drawings of objects and faces of celebrities, and was able to localise correctly cities on a map of Great Britain and reproduce non-representational hand movements accurately. Drawings were normal and she could represent the three dimensional aspect of a cube. She was able to reproduce simple Koh's block figures. She could carry out whole body, limb and buccofacial gestures and reproduce motor sequences.

She was fully orientated for time and place. Her digit span was six forwards and two backwards. She could repeat a seven item name and address and recalled four of seven items after a two minute delay. Her retention of a short story was accurate over an interval of an hour, although repeated probing was necessary to elicit the required information. On the Warrington recognition test she scored 32/50 on the word test and 39/50 on the face test, results being below the 5th percentile and at the 25th percentile for her age.

She performed poorly on tests sensitive to frontal lobe dysfunction. On the Nelson modification of the Wisconsin card sorting test she achieved two sorting categories only. Nineteen percent of errors were perseverative. On a verbal fluency test she could produce only six animal names and four words beginning with the letter F, each in one minute. Design fluency revealed striking perseveration: she produced two pages of virtually identical rectangles, despite constant repetition of the instructions to produce different non-representational designs.

WAIS testing yielded a verbal IQ of 86, performance IQ of 76 and full scale IQ of 81.

Investigations

Electroencephalography showed a minor excess of theta rhythm in the right temporal region, thought to be normal for her age. Bifrontal cerebral atrophy worse on the left side was reported on X-ray computed tomography. Single photon emission tomography showed a selective

anterior hemisphere abnormality, involving the cortical rim and worse on the left. The images are illustrated in Figure 1.5.

Progression

Deterioration in her mental status was observed over a one year follow-up period. She became increasingly apathetic, maintained a fatuous expression and giggled inanely when spoken to. Her test performance was characterised by increasing economy of mental effort, although there was no convincing evidence of specific linguistic or perceptuospatial difficulties. On repeat administration of the Nelson card sorting test she achieved one catagory only and 56% of errors were perseverative. She remained physically well with no increase in neurological signs.

PATIENT TWO

A 61 year old female presented with a five year history of progressive change in personality and social conduct. Formerly, she had taken pride in her personal appearance, her home and her job. She had begun to neglect personal hygiene, ceased to carry out domestic tasks, and would spend her days wandering aimlessly. She tended to misconstrue events, and expressed suspicion and irritability against her family. She had outbursts of rage which were socially embarrassing. She was forgetful, disclaimed previous events, and made false claims for non-existent happenings. She was hypochondriacally obsessed with a pain in the perineum, which had been extensively investigated, but she denied mental symptoms.

There was no personal history of psychiatric illness. Her mother had died aged 65 years of a similar illness, and was noted to have wandered in the street at night in night attire. Eccentric behaviour had been observed also in other family members. In no case had necropsy been undertaken.

Physical Examination

The tendon jerks were mildly accentuated and the jaw jerk was brisk.

Mental Examination

She was restless, impatient and disinhibited. She responded impulsively, launching into tasks without listening fully to the instructions.

She displayed a press of speech, which was frequently off the point, and contained stereotyped phrases and play-on-words, which amused her. Her thinking was literal and concrete. In following verbal instructions she had difficulty grasping what was required, although formal assessment of comprehension of syntax did not reveal specific abnormalities. There was some word finding difficulty, and she made occasional verbal paraphasic errors. She could read, and produce a well formed script which was grammatically correct, and could carry out simple written sums, although she made errors on mental subtractions.

Elementary perceptual and spatial abilities were intact. Drawings showed preserved spatial configuration, but omission of detail. She could produce Koh's block figures, although manipulated blocks in an arbitrary fashion until the correct solution was achieved, apparently with no concerted strategy for carrying out the task. Whilst manual dexterity and manipulative abilities were intact, executive tasks involving production of a sequence of motor actions presented difficulty. She failed to reproduce simple motor rhythms, and a sequence of three hand postures, immediately after these were demonstrated.

She was orientated for time and place. She had a normal digit span of six digits forwards and three backwards. She recalled only four of seven items from a name and address immediately after hearing it, and no items after a two minute delay. She could not abstract the gist of a paragraph read to her. Performance was at chance level on both the word and face sections of the Recognition Memory Test.

Performance was impaired on 'frontal lobe tasks'. On the card sorting test she achieved three categories, from a possible eight, and 49% of errors were perseverative. In a verbal fluency task she produced only eight animal words and seven words beginning with F in one minute. In a design fluency test she violated constantly the two rules that designs should be non-representational and be constructed from four lines only, despite constant reiteration of these instructions.

On the WAIS she achieved a verbal IQ of 73, performance IQ of 77 and full scale IQ of 75.

Investigations

Electroencephalography was normal and X-ray computed tomography revealed mild generalised cerebral atrophy. A selective reduction of tracer uptake affecting the anterior hemispheres and extending through the frontal cortical rim was demonstrated on single photon emission tomography.

PATIENT THREE

A 49 year old housewife had progressively altered in her personality and behaviour over three years. Previously an out-going, pleasantly mannered and hard working person, she became stubborn, lacking in motivation, neglectful of self-care, personal hygiene and domestic responsibilities. Her behaviour became socially embarrassing, inappropriate and disinhibited. She adhered fixedly to a rigid and obsessional daily routine, while spending much of the day pacing restlessly, laughing and chattering inanely. She fabricated tales, often expressing paranoid ideas and gave distorted accounts of real events. However, she appeared to be able to retain information of emotional significance to her. Her speech, sight and ability to find her way around were thought to be normal. The patient denied mental symptoms and interpreted her hospital admission as rejection by her husband.

There was no history of previous psychiatric illness. Her eldest brother and a cousin had suffered from a similar illness, both dying when middle aged. Necropsy had been performed on the cousin and demonstrated a non-Alzheimer fronto-temporal cerebral atrophy. The findings are described in section A.

Physical Examination

At presentation both general and neurological examination was normal.

Mental Examination

She was unconcerned, mildly disinhibited and distractible. Responses were produced impulsively, without thought, resulting in errors. Her immediate response to a question was often " I don't know", even though with encouragement she could produce the correct answer.

Utterances were grammatically correct, although content was not always to the point. She tended to substitute generic terms such as "thing" for the correct noun, indicating word finding difficulty. Verbal paraphasias were elicited by confrontation naming testing (for example "bisexuals" for lens of spectacles). She could read, write and spell, although with sporadic errors which suggested failure of attention rather than a primary linguistic disorder. She made errors in calculating, although again some variability in her performance was noted.

There was no evidence of visual agnosia, spatial disorientation or apraxia. She could identify line drawings and faces of celebrities, showed intact geographical orientation and could reproduce non-representational hand postures accurately. Gesture and pantomime and reproduction of drawings and Koh's block figures were all carried out normally. Explanation of pictorial scenes was limited by her unwillingness to apply herself to the task and tendency to say "I don't know".

She was fully orientated and gave a good account of personal day to day events. However, she failed to provide information regarding current news events. Her digit span was six digits forwards and three backwards. She repeated a seven item name and address correctly but denied memory of it after a two minute delay. Abstraction of the gist of a short paragraph read to her was severely limited immediately after presentation and she showed no recall after a one hour delay. Her performance on both the word and face versions of the Warrington recognition memory test lay below the fifth percentile for her age group.

On the Nelson card sorting test performance was highly abnormal. She achieved one category only, 100% of errors being perseverative. She made no attempt to change her method of sorting despite appreciation that her responses were incorrect. On a verbal fluency test she produced only six animal names and nine F words, each in a minute. On a design fluency

test she demonstrated perseveration of a single idea and violated the rule that designs should be confined to four lines.

On the WAIS she achieved a verbal IQ score of 89, performance IQ of 92 and a full scale IQ of 90.

Investigations

Electroencephalography was normal and x-ray computed tomography showed generalised cerebral atrophy. Single photon emission tomography revealed selective reduction of uptake in the anterior hemispheres which extended through the frontal cortical rim.

Progression

Six months later extensor plantar responses and a positive sucking reflex were elicited and after a further six months a grasp reflex was present. Her family were aware of a deterioration in her behaviour; she had become increasingly restless, inattentive and socially disinhibited and would eat and drink greedily and to excess. She would wander the streets for miles, although without becoming lost. On mental examination she was restless and distractable. Her verbal output was more restricted than formerly: she did not initiate conversation and answered questions monosyllabically or with maximum economy of effort. Speech was increasingly repetitive, with liberal use of expletives and stereotyped phrases. She tended to echo questions put to her in place of constructing a novel response. However, she remained fully orientated and there was no evidence of perceptuospatial disorder.

PATIENT FOUR

At the age of 57 years a previously efficient and independent business woman became progressively more disorganised and irrational, neglecting both her business and domestic responsibilities. She became apathetic and lacking in motivation, although she denied feelings of depression or anxiety, and appeared to be unaware of ill-health. Her speech and sight were thought to be normal.

The patient's father had suffered a similar change in his personality and behaviour in his middle years, and spent his last years in a mental

hospital. His symptoms at the time had been attributed to heavy alcohol intake. No necropsy had been carried out.

Physical Examination

On initial examination, six years after onset of symptoms, there were no physical signs.

Mental Examination

Behaviour oscillated between facile and giggling compliance and sullen uncooperativeness. She carried out tasks impulsively without checking, expending minimal mental effort. She was unconcerned by failures.

She did not initiate conversation, and responses to questions were brief and unelaborated. Her utterances were linguistically correct and without paraphasic error, although content indicated some concreteness of thought, and some word finding difficulty. She could read, write and spell normally.

Elementary visual perception, spatial orientation and praxis were normal. However, she failed to interpret thematic pictorial scenes, itemising elements of the picture while making no attempt to integrate elements meaningfully. Drawings and block constructions showed intact spatial configuration, but some omission of detail and poor organisation.

She was fully orientated, her digit span was seven digits forwards and three backwards, and immediate recall of a seven item name and address was error-free. However, she failed to recall any information from the name and address after a two minute delay, even with the aid of multiple choice alternatives. Recognition memory performance for both verbal and non-verbal material was at chance level.

Impaired performance was demonstrated on 'frontal lobe tasks'. She could complete only one sorting category on the Nelson card sorting test, and 82% of errors were perseverative. Her verbal fluency performance was limited to only six animals and five F words in one minute.

WAIS testing yielded a verbal IQ of 59, performance IQ of 60 and full scale IQ of 57.

Investigations

Her electroencephalogram showed a minor excess of slow wave activity, thought to be normal for her age and X-ray computed tomography revealed fronto-temporal atrophy, particularly affecting the left hemisphere.

Progression

Her condition worsened considerably over the ensuing two years, necessitating her institutional care. She remained restless and would pace the ward, aligning objects obsessionally. When seated she exhibited stereotyped rocking trunkal movements, and constant hand clapping, and because of injuries incurred her hands had to be padded. She had become totally dependent, making no attempt to dress or wash herself. She would eat voraciously, although did not mouth inedible objects. She was virtually mute, although occasional echolalia or use of the word "yes" occurred.

Physical examination revealed the presence of a snout reflex and palmomental responses. She failed to respond to verbal commands, but could negotiate her way around her environment without difficulty, suggesting preserved perceptuospatial appreciation.

Single photon emission tomography was carried out at this time and revealed a striking selective reduction of tracer uptake affecting the anterior hemispheres and extending through the frontal cortical rim.

PATIENT FIVE

A 64 year old male had received psychiatric treatment for an unverifiable illness in his mid-twenties. In his late forties, he began to neglect his appearance, became less affectionate and showed no interest in activities beyond his work. At age 61 he became irritable and intolerant, and then increasingly withdrawn and restless, with poor appetite and insomnia. A diagnosis of agitated depression was made and his condition improved slightly with electroconvulsive therepy. However, he remained apathetic and inactive. His family noted that he displayed virtually no emotion or motivation. Although he was not inclined to converse, his actual speech was thought to be normal, and he had no difficulty finding his way about.

Both his parents died in their fifties though the cause of their terminal illness was not known.

Physical Examination

General examination was normal. Neurological examination revealed bilateral extensor plantar resonses, a prominent snout reflex and mildly positive palmomental reflexes. His speech was hypophonic and dysprosodic.

Mental Examination

He was alert, with a bland affect. Motor activity was generally slow, although paradoxically impulsive responses also occurred. He was cooperative, although made no attempt to respond to tasks of a mentally demanding nature.

He did not initiate conversation and his responses were brief, often elicited only by continual encouragement. Yet there was no evidence of linguistic disorder and no paraphasias or word finding difficulty were noted. Comprehension was intact, although interpretation of metaphor and proverb was concrete. He could read, write and spell, but had difficulty calculating, particularly in carrying out mental subtractions.

There was no evidence of agnosia, spatial disorientation or apraxia. He could identify line drawings of objects and faces of celebrities, reproduce non-representational hand postures and use gesture and pantomime accurately. His drawings and block constructions showed preserved spatial configuration, although he showed some lack of persistence, abandoning tasks without checking the accuracy of his attempts.

He was fully orientated, had a normal digit span of seven digits forwards and five digits backwards and could repeat a seven item name and address accurately. After a two minutes delay his recall was 5/7. He could provide the gist of a short story read to him and showed no loss of information over an hour. On the Recognition Memory test, he scored 43/50 on the word task, which is within normal limits and 26/50 on the face task which is at chance level.

Performance on the Nelson card sorting test was highly abnormal: he achieved one category only, 93% of errors being perseverative. Verbal

fluency was reduced: he produced seven animal names and seven F words, each in a minute. Design fluency was grossly abnormal: he produced 61 designs in a ten minute period, 59 of which were perseverative.

Assessment on the WAIS yielded a verbal IQ of 73, performance IQ of 80 and full scale IQ of 74.

Investigations

His electroencephalogram was normal and the X-ray computed tomogram showed cerebral atrophy, predominantly affecting the frontal lobes. Single photon emission tomogram demonstrated a selective reduction of uptake in the anterior hemispheres but with preservation of a rim of frontal cortical uptake. The scan is illustrated in Figure 2.1.

Progression

His clinical picture changed little over a two year follow-up period. He remained inert, although with increasing somnolence. He did not initiate conversation nor purposeful activity. Despite paucity of verbal output there was no evidence of aphasia. He could demonstrate retention of day-to-day events and showed no perceptual or spatial disturbance.

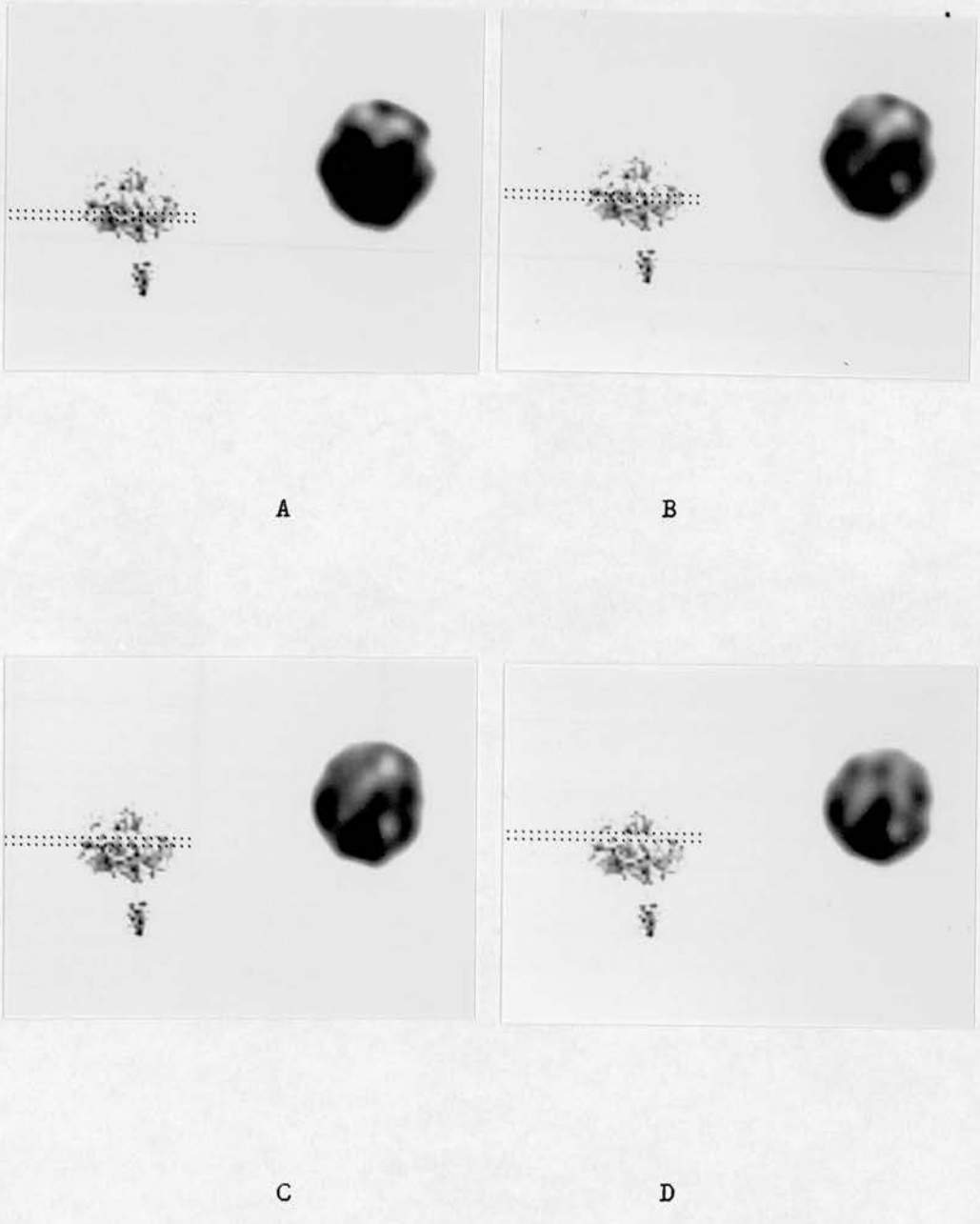


Figure 2.1.

Single photon emission tomogram from Patient Five. There is a selective reduction of tracer uptake affecting the anterior hemispheres but with preservation of a rim of frontal cortical uptake.

PATIENT SIX

Over the previous two years a 50 year old shop manager suffered a gradually progressive change in his personality. He became outspoken, rude and callous, lacking in initiative, self-care and responsibility towards his family. His mood would fluctuate between facetiousness and jocularity and negativism and irritability, with verbal and physical aggression. This was thought to be totally out of character. He was inattentive and forgetful but no change in his speech or navigational skills had been noticed.

His mother died aged 82 years in a psychiatric hospital, having become demented in her middle fifties. Prior to death she was mute and had remained in an essentially vegetative state for the previous ten years. No necropsy was undertaken.

Physical Examination

General examination was normal and he was free from neurological signs.

Mental Examination

He was generally courteous, although mildly disinhibited, talking excessively loudly and giving frequent and inappropriate guffaws of laughter. In carrying out tasks he was impulsive and unconcerned, failing to check his responses. He showed no insight.

His speech was normal. There was no evidence of impaired comprehension. He was left/right orientated and no word finging difficulty was evident. Repetition tasks led to perseveration of previous responses. He could read and write although spelling was poor. He showed substantial difficulty in calculating, failing to carry out the simplest mental subtractions.

He had no difficulty in the perceptual identification of line drawings of objects and the faces of celebrities. He could locate objects in the environment, match fingers on the corresponding hands, reproduce non-representational hand movements and locate towns on to a map of Great Britain. He could pantomime actions and use gesture normally. Block constructions were produced slowly but were accurate copies of the original. Drawings were crude and slapdash, with omission of detail,

although the spatial relations between elements were preserved. Perseverative pencil strokes were apparent.

He was fully orientated and displayed preserved memory for day-to-day events. He recalled six of seven items of a seven figure name and address immediately and after a two minute delay. He could not summarise a short story immediately after reading it aloud, although his ability to provide accurate answers to specific questions about the story indicated that the information was available to him. His delayed recall after an hour revealed no loss of information over time. Performance on the word version of the Warrington recognition test was normal (48/50) but on the face version was at chance level (26/50).

He failed to cooperate sufficiently to carry out the Nelson card sorting test. On a verbal fluency test he produced 16 animals and one F word, each in one minute. On a design fluency test his responses depicted concrete objects rather than non-representational figures and perseveration of a single idea was common.

WAIS testing yielded a verbal IQ of 92, performance IQ of 82 and full scale IQ of 87.

Investigations

His X-ray computed tomogram was normal and his electroencephalogram showed patchy theta activity, thought to be within normal limits.

Progression

Over a four year follow-up period his behaviour became increasingly rigid and inflexible, and violent outbursts were more common. He was inert and lacked initiative. Stereotyped mannerisms were increasingly evident. His cognitive performance remained qualitatively similar, although increasing impulsivity, carelessness and lack of attention to the task resulted in reduced performance accuracy.

Single photon emission tomography was performed six years after the onset of symptoms and showed reduced tracer uptake in the anterior hemispheres extending through the cortical rim.

PATIENT SEVEN

A male electrician was suspended from work at the age of 55 years because of increasingly clownish behaviour, and a reduction in his level of personal and social responsibility. Following a psychiatric referral he resumed work in a more menial capacity, for which he showed no concern. His behaviour became progressively more puerile, fatuous and disinhibited, resulting in his retirement and forcing his wife to assume responsibilty for all household and financial affairs. His wife had noted a memory loss although thought this to be selective in his own favour. The patient denied symptoms, and regarded himself as competent to carry out his job.

There was no history of previous psychiatric illness and no known family history of mental illness or dementia.

Physical Examination

Examination two years after onset of symptoms was limited to exaggerated tendon jerks and a right extensor plantar response.

Mental Examination

He was distractible and restless, with poor engagement and persistence in mental tasks. Behaviour was disinhibited, impulsive and inappropriate, with an exaggerated and melodramatic emotional display. He would break into song or relate rhymes without prompting. In his verbal remarks he showed a callous unconcern for the feelings of others.

His speech was linguistically correct, without paraphasias. However, utterances, produced rapidly, were frequently off the point, and there was a tendency to produce puns and stereotyped phrases. He did not show formal difficulty in comprehension, although his literal interpretation of metaphors and proverbs indicated concreteness of thinking. There was some word finding difficulty for low frequency words. He could read and write although spelling was erratic. He had difficulty carrying out mental calculations.

Perceptual and spatial abilities were intact, as measured by his ability to identify objects, line drawings and faces of celebrities, to trace the Money road map, to copy non-representational hand postures, to locate towns on a map of Great Britain, and to reproduce Koh's block designs. His copies of drawings of objects and abstract designs showed accurate

overall configuration and spatial relationships between elements. Manual tasks were all carried out normally; he could use gesture and pantomime, reproduce sequences of hand positions, and motor rhythms.

He was fully orientated for time and place, and could give an accurate account of day-to-day events. He reproduced a seven item name and address immediately after hearing it but failed to recall any items after a two minute delay.

On a verbal fluency test he produced only nine animal words and six F words in a minute. However, performance on the Nelson card sorting test was intact; he achieved six complete categories, and 38% of errors were perseverative.

Performance on the WAIS at this time yielded a verbal IQ of 93, performance IQ of 106 and full scale IQ of 99.

Investigations

Electroencephalography was within normal limits and X-ray computed tomography showed generalised cerebral atrophy.

Progression

His behaviour was monitored over the following six years, during which time progression was slow but clinically evident. He remained disinhibited, distractible and overactive, constantly making puerile remarks intended as jokes. His press of speech increased so that his utterances, although grammatically correct were barely intelligible. While his speech content was superficially informative, it was only loosely constrained by the question posed. Moreover, he appeared to have an increasingly restricted repertoire of phrases, sentences and anecdotes, which, when 'triggered', were reiterated on each occasion with virtually identical wording. He reproduced the reply "I don't speak German" to all but the simplest verbal commands. He had word finding difficulty, and made verbal but not literal paraphasic errors.

During the six years of follow-up he retained a digit span of five or six digits forwards and four backwards. He could read, and write with a well formed script, although spelling was poor. Perceptual and spatial abilities continued to be well preserved. He remained fully orientated in time and place, and capable of some new learning, as evidenced by his

ability to recite anecdotes about recent autobiographical episodes. However, his memory appeared patchy and idiosyncratic. He displayed no knowledge of current news events. Word and face recognition memory was at chance level. On the Nelson card sorting test performance was now grossly abnormal, he achieved only one complete catagory and 95% of errors were perseverative. Motor skills were excellent; he had normal manual dexterity, and could carry out alternating hand movements without difficulty. He remained physically well and agile, with the emergence of a snout reflex and bilateral grasping reflexes as the only additional neurological signs.

Single photon emission tomography was carried out seven years after first symptom and showed selective reduction of tracer uptake in the anterior hemispheres extending through the frontal cortical rim.

ALZHEIMER'S DISEASE

The following case histories exemplify the neurological syndromes associated with Alzheimer's disease. The descriptions depict the longitudinal progression of the disease. Patients were right handed except where stated.

PATIENT EIGHT

Over a three year period, a 57 year old housewife had developed progressive deterioration of her memory, particularly for recent events. Despite being able to identify small objects she had become disorientated in her own home. She had difficulty dressing and tended to put her clothes on back to front. She had developed problems finding the correct word when speaking, lost track of the narrative when reading and could no longer sign her name. She had lost consciousness twice and had become confused for several hours afterwards on both occasions. She had remained physically well apart from mild slowness of gait.

Past medical history was unremarkable and both parents had lived into old age without mental impairment.

Physical Examination

General examination was normal. She had an expressionless face and symmetrically brisk tendon jerks. Visual acuity was normal.

Mental Examination

She was pleasant, well groomed, anxious, and appropriately concerned regarding the accuracy of her performance.

There was evidence of language impairment. She made occasional literal paraphasic errors during spontaneous speech and when repeating a series of words. Comprehension of spatial terms was impaired. Although she could point to specified objects in front of her she could not say whether objects were on her left or her right. She could interpret correctly metaphor and proverb. Her digit span was decreased to four digits forwards and none backwards. Spelling was impaired. Reading, although slow, was essentially normal. When writing, letters were poorly constructed and she made spelling errors. Calculation was severely impaired. She could not add pairs of single digits.

Elementary visual perception was intact. She could recognise common objects and the faces of celebrities. In contrast, spatial abilities were impaired. She had difficulty locating objects in front of her and could not correctly orientate clothes when dressing. She failed to trace around the Money road map and could not copy non-representational hand movements with either hand. Her drawing was severely abnormal, with disintegration of spatial relationships. When copying she tended to draw on top of the original. She had similar problems with block constuctional tasks, she could not complete the simplest design and again tended to build on the original.

There was rapid loss of information from memory. She could recall only four items from a seven item name and address immediately after hearing and no items after a two minute delay, even with the aid of multiple choice cues. She remembered only one item from a short story on immediate recall and had no recollection of the story after a five minute delay. She had no knowledge of current events and was disorientated in time.

Investigations

Electroencephalography showed generalised slowing of the background rhythms without epileptiform activity and X-ray computed tomography revealed generalised cerebral atrophy.

Progression

She was next examined three years later and considerable deterioration had occurred, necessitating the institution of day care. She continued to have occasional generalised seizures. Physical examination revealed moderate rigidity of the limbs, loss of arm swinging, with a flexed posture and occasional multifocal myoclonic jerks.

Mentally, she remained cooperative, with preserved social behaviour. However, there had been marked progression of her language disorder. Literal paraphasias were more frequent in her spontaneous speech. She could no longer follow simple instructions and had difficulty naming common objects. When reading sentences, she sometimes omitted words, having difficulty tracking along a line. She could still identify line drawings of objects but had difficulty identifying famous faces. The latter appeared to represent a loss of knowledge in some cases and a naming difficulty in others. When drawing she could only produce single perseverative strokes.

Single photon emission tomography was carried out at this time and revealed a striking reduction of tracer uptake in the posterior regions of both hemispheres, most marked on the right.

Six months later, her utterances contained phrases of severe palilalia and after a further six months she failed to recognise common objects, possibly because of a failure to fixate on objects presented to her. One year later she had no speech and no apparent understanding. She appeared cortically blind. She had a flexed posture, with marked rigidity of all four limbs, and frequent multifocal myoclonus. Single photon emission tomography was repeated and revealed small bilateral frontal as well as more striking bilateral posterior hemisphere abnormalities.

PATIENT NINE

A 64 year old printer presented with a five year history of increasing forgetfulness and a tendency to mislay objects. His wife had noticed that on occasions he appeared confused as to his whereabouts, and at night he might go into the wrong bedroom after rising to urinate.

Twenty years previously he had received a head injury which had left him unconscious for three days. He had made an uneventful recovery. One year previously he had suffered an incomplete left sided optic nerve infarct. There was no family of dementia.

Physical Examination

The left optic disc was pale. Visual acuity was preserved, but colour vision was impaired in the left eye. There was a left sided upper temporal field defect. Examination was otherwise normal.

Mental Examination

He was pleasant and cooperative and applied himself diligently to the tests. He had insight into his mental difficulties.

His language was normal. His utterances were grammatically correct and his comprehension of the spoken and written word were normal. He could interpret metaphor and proverb. He had a normal forward span of six digits but could only reverse three digits. Reading, writing and calculation were normal.

Perceptual and spatial abilities were intact. He could recognise line drawings of objects and the faces of celebrities and could identify objects from the their component parts. He could track aroung the Money road map and interpret both absurd and complex picrtures. Drawings and block constructions were carried out normally.

Memory testing showed a rapid loss of information with an inability to learn. He could repeat all seven components of a seven item name and address immediately after hearing but could recall none after a two minute delay. Immediate recall of a short story was limited to one fact and he had no knowledge of the story after a further two minutes. He had some knowledge of contemporary personalities but was completely disorientated and had little information about recent news events.

Investigations

X-ray computed tomography revealed mild cerebral atrophy with prominence of the sylvian fissures especially on the left. Electroencephalography showed slow waves in the frontotemporal regions most marked on the left. Right temporal lobe biopsy showed senile plaques and neurofibrillary tangles, and reduced acetylcholine synthesis was demonstrated on neurochemical analysis.

Progression

Three years later, although his predominant problems remained in the area of memory he had now developed mild spatial impairment. He had difficulty orientating clothes when dressing and in locating and matching objects in space. His copies of designs were poorly executed and he was slow to perform block constructions and had a tendency to build on the original. His language remained normal apart from mild difficulty understanding relational terms. He had substantial difficulty carrying out conceptually demanding tasks such as picture sequencing and block sorting. His spatial abnormality and amnesia appeared to account for his poor performance to some extent.

Two years later there was loss of facial expression, decreased arm swing when walking and mild rigidity of the limbs. The tendon jerks were brisk and there was a positive snout reflex. His behaviour remained sociable and cooperative and he retained some insight into his difficulties. Language impairment had emerged. His utterances were somewhat hesitant and conveyed little information. He made occasional literal paraphasic errors when repeating words. Comprehension was noticeably impaired and he could not grasp simple instuctions. He was significantly anomic and was unable to write his own name. He had mild difficulty identifying line drawings of objects. His drawings now showed loss of spatial configuration and he could no longer reproduce the simplest of Koh's block figures. 'Frontal lobe tests' could not be performed because of poor comprehension, spatial impairment and rapid loss of information.

Single photon emission tomography was carried out and revealed reduced uptake in both posterior hemispheres with a smaller abnormality in the left frontal region.

Mental and physical deterioration continued necessitating institutional care. He died from bronchopneumonia two years later, the total length of his illness spanning twelve years. Necropsy was carried out.

Pathological Findings

The major cerebral arteries and those of the circle of Willis were free from atheroma. The brain was generally atrophic, with a defect in the right middle temporal gyrus caused by the previous biopsy. The brainstem and cerebellum appeared macroscopically normal. On slicing the lateral ventricles were markedly dilated, especially within the temporal horn. The substantia nigra appeared well pigmented and the locus caeruleus noticeably underpigmented.

On microscopic examination there was widespread, frontal, temporal cingulate, insular and parietal cortical amyloid (A4) protein deposition, mainly occurring in cortical layers I-III. Only a few cortical plaques were seen on silver staining. Only mild cell loss and mild astrocytosis were seen throughout the cerebral neocortex. There were a moderate number of silver staining plaques in the hippocampus, with mild associated astrocytosis. There was mild cell loss from the CA1 area and the subiculum with complete loss of the large neurones. Many silver staining plaques were seen in the amygdala and granular deposits of A4 protein were demonstrated within the caudate nucleus, putamen, nucleus accumbens, periaqueductal grey matter and hypothalamus. The nucleus basilis showed a mild loss of cells and the locus caeruleus a severe loss of cells. The substantia nigra appeared normal. There were numerous neurofibrillary tangles in the hippocampus and amygdala. A moderate number of tangles were seen in the temporal, insular and cingulate cortex and in the nucleus basalis and dorsal raphe, whilst only a few tangles were seen in the frontal and occipital cortex. Many pial and intraparenchymal vessels showed amyloidosis.

PATIENT TEN

Since becoming lost on holiday in Blackpool three years previously a 61 year old housewife had developed progressive deterioration in her navigational skills, her memory and her powers of communication. She had

difficulty finding her way around her own home and would lose her way if she went out alone. She had problems orientating her clothes when dressing and had lost the ability to tell the time. Although she had been previously keen on current affairs and politics, her husband had noticed that she had only the most superficial knowledge of the news and was often unaware of the day or date. Her letter writing skills had deteriorated. Her words ran into each other and she made spelling errors. Her husband believed her personality to be unchanged and indicated that she tried to cover up her mental difficulties by using social pleasantries.

She had been previously well and there was no family history of dementia.

Physical Examination

General examination was normal. Neurological examination revealed a brisk jaw jerk and a pouting reflex with symmetrically brisk tendon jerks.

Mental Examination

She was a pleasant well-dressed lady. She provided an excellent social facade, belying her cognitive impairment. She was fully cooperative and appeared not to appreciate the extent of her difficulties.

There was a mild language disorder. Her utterances were linguistically correct, although information content was reduced and she relied largely on social platitudes. She could point to objects about the room but could not retain a sequence of objects. She also failed to understand questions involving relational terms, such as "touch your left ear with your right hand". In contrast, her ability to explain metaphor and proverb showed a normal level of abstraction. She had a normal forward span of six digits but a reduced backward span of only two digits. Naming was slow but otherwise normal. She could read aloud although with some hesitancy. Writing showed omissions of some letters and repetitions of others, suggesting a failure to keep track of performance

Elementary perceptual abilities were intact contrasting with her impaired spatial skills. She could identify objects, line drawings of objects and the faces of celebrities. However, she was unable to track the

Money road map, being distracted by irrelevant solid lines and had difficulty locating objects in front of her. She was unable to copy drawings or constructions, merely tracing or building on parts of the original.

She was profoundly amnesic. She was disorientated in time and place and had an impaired knowledge of current news events. When a short story was read to her she was unable to recall any relevant details immediately or after a delay. She showed only minimal benefit from multiple choice cues.

Investigations

Electroencephalography showed mild slowing of the background rhythms and X-ray computed tomography revealed generalised cerebral atrophy. Single photon emission tomography showed a moderate reduction of tracer uptake in both posterior hemispheres with normal uptake anteriorly.

PATIENT ELEVEN

A 67 year old retired engineer presented with a two year history of progressive decline in memory and naming skills. He had begun to forget day to day incidents and had trouble remembering the names of his friends. In conversation, occasional word finding difficulty had been noticed. His wife believed his personality to be unchanged.

Past medical history was unremarkable and there was no family history of dementia.

Physical Examination

General and neurological examination was normal save for symmetrically brisk tendon jerks.

Mental Examination

He was a pleasant rather apologetic man who had a smart appearance. He engaged in all tasks conscientiously and performance was generally slow and effortful. He commented on his difficulties and demonstrated retention of insight.

He was a left handed man whose language was impaired. His utterances were hesitant, although paraphasic errors were not present. He could point to single objects when described in simple terms but failed when objects were described using low frequency words such as "transparent" or "illumination". He could not retain a sequence of objects. He had difficulty understanding syntactic utterances such as "Does it snow in summer?" and made errors when given commands involving relational terms. He had a normal forward digit span of six but a reduced backward span of three. He had difficulty naming objects to confrontation and from description. His errors were largely omissions, although he made occasional verbal paraphasic errors, such as pencil for pen. Spelling, reading and writing were normal. Calculation was impaired, particularly when the carrying over of a figure from one column to the next was required.

Primary perceptual and spatial abilities were intact. He could identify line drawings of objects and famous faces but had substantial difficulty finding their names. He could identify framented figures and give appropriate interpretations of absurd and complex visual scenes. He could trace around the Money road map although performance was slow. His drawings and constructions showed preserved spatial relationships although with the latter he had to be reminded of the instructions. His use of communicative gesture was somewhat inaccurate and he tended to use body part as object when pantomiming the use of objects. Errors appeared in keeping with his linguistic impairment.

Memory performance was characterised by a rapid loss of information but with some ability to lay down new memories. He could recall immediately four items of a seven item name and address but had no recollection of any items, even with multiple choice cues after two minutes. He had no recall of a short story immediately after it was read for him and had no recollection of the drawings he had copied earlier. However, he was orientated for time and had some knowledge of day to day events.

He had difficulty performing 'frontal lobe tasks' because of his inability to remember the instructions. However, despite this disability, he showed normal powers of abstraction on a picture sequencing task. He

ordered the cards slowly but logically and checked the positioning of the cards in a normal manner.

Investigations

Electroencephalography showed slowing of background rhythms more marked on the left and X-ray computed tomography revealed generalised cerebral atrophy.

Progression

Further deterioration occurred over the next two years and he was admitted to a nursing home. Examination at this time revealed restricted upgaze and impaired convergence, with mild rigidity of the limbs and mild bradykinesia. Occasional myoclonic jerks of the upper limbs were also present.

The striking abnormality on mental testing remained a marked anomia, such that he was unable to name any objects to confrontation or from description. Occasional literal paraphasias were present in his spontaneous speech and when repeating words. He now had difficulty following simple instructions and was unable to write his name. Mild spatial impairment had emerged. He occasionally omitted lines when copying designs and although he could still complete constructions using Koh's blocks, he tended to build on the original. Immediate and delayed recall remained poor, although this appeared to be to some extent secondary to his anomia. He was able to give an adequate account of day to day events, suggesting that he was not densely amnesic. Perceptual abilities and social behaviour remained intact. Single photon emission tomography was performed at this time and showed reduced tracer uptake in both posterior hemispheres more marked on the left.

One year later he had developed a pouting refex and rigidity in the limbs was more marked. He walked with a flexed posture and had lost 7Kg in weight. His speech had become palilalic. He was markedly apraxic and this appeared more pronounced than his spatial disability. Despite being unable to copy hand movements, he could still locate objects in front of him and copy drawings in a space separate from the original. He died six months later after an illness spanning six years and necropsy was performed.

Pathological Findings

The major cerebral arteries and those of the circle of Willis were free from atheroma. The brain showed moderate atrophy of the inferior and middle temporal gyri and lesser atrophy of the frontal and parietal cortex. The brainstem and cerebellum appeared normal. On slicing, the lateral ventricles were moderately enlarged. The amygdala and hippocampus were not atrophied. The basal ganglia appeared normal but the substantia nigra seemed slightly underpigmented.

Microscopy revealed numerous senile plaques and neurofibrillary tangles within the amygdala, uncus and hippocampus (CA1 and subiculum) with associated loss of neurones and fibrous astrocytosis. There were moderate numbers of plaques and tangles within the association areas of the frontal, temporal, insular and parietal cortex and a few plaques but no tangles in the occipital cortex. There was a moderate loss of nerve cells from cortical layer III and mild reactive astrocytosis in neocortical areas. The nucleus basalis showed severe cell loss, mild astrocytosis and the presence of neurofibrillary tangles. Occasional pial vessels appeared amyloidogenic.

PATIENT TWELVE

A 63 year old civil servant presented with a four year history of progressive decline in his memory and intellect. His wife had noticed that when speaking he would often become lost for words and lose the thread of the conversation. He could not remember the plot of a novel when reading and his writing had deteriorated markedly, such that he could barely sign his name. He had become disorientated in space, misaligned cutlery when setting the table and had difficulty orientating clothes when dressing. Despite his intellectual impairment, his wife believed his basic personality to be unaltered.

He had been previously well and there was no family history of dementia.

Physical Examination

General and neurological examination was normal.

Mental Examination

He was pleasant and cooperative and had insight into his mental difficulties becoming distressed and anxious when he could not complete tasks.

His language was impaired. His utterances were hesitant and contained occasional literal paraphasias. He tended to lose track of the topic of conversation. He could point to objects described using low frequency words but had difficulty understanding prepositions, such as "under" or "next to". Both forward and backward digit spans were reduced at five and three digits respectively. Reading was normal. He could not spell to dictation and omitted letters when attempting to write his name. He could add pairs of single digits but failed to perform calculations involving the carrying over of numerals.

Perception was intact. He could identify objects, line drawings of objects and the faces of celebrities. In contrast spatial abilities were markedly impaired. He could not place a cup onto a saucer and had difficulty locating objects in front of him. When asked to locate the city of Manchester onto a map of Great Britain he placed it in the Irish Sea. His drawings showed loss of spatial awareness. His representation of a bicycle featured only two wheels and a pair of handlebars, the latter drawn unattached and incorrectly orientated. He could not copy drawings or constructions, merely tracing or building on top of the original. He was also apraxic. His use of gesture was somewhat crude and he tended to use body part as object when pantomiming the use of objects.

Memory testing revealed rapid loss of information with some preservation of knowledge for recent events. His could recall only two items of a seven item name and address immediately after hearing and had no recall after two minutes. His immediate recall of a short story read to him was limited to one fact and he denied any knowledge of the story after two minutes. He had no recollection of any of the drawings he had previously executed. He knew the month, although was otherwise disorientated in time and place.

'Frontal lobe tests' could not be attempted because he either failed to understand or rapidly forgot the instructions and because of spatial impairment.

Investigations

Electroencephalography was normal and X-ray computed tomography revealed generalised cerebral atrophy. Single photon emission tomography showed reduced tracer uptake in both posterior hemispheres in the absence of anterior hemisphere abnormalities.

Progression

Continued mental deterioration with the emergence of mild rigidity of the limbs was observed over a two year follow-up period. He had begun to attend hospital day care and the nursing staff had described him as 'a real gentleman' and always polite and cooperative. He has remained painfully aware of his mental difficulties and has indicated to his wife that he wishes he were dead.

Mental examination at this time was dominated by his limited memory capacity and his tendency to lose track rapidly. This essentially prevented him from carrying out any task since he was unable to maintain continuity over more than a few seconds. His spontaneous speech was hesitant with frequent literal paraphasias and neologisms and some palilalia. He was still able to point to objects described simply. Naming was severely impaired. He could read single short words but not phrases or sentences. He could not copy his own name. Perception remained largely preserved. He could still identify objects and line drawings of objects. His severe spatial disorder had progressed, so that he had difficulty seating himself on a chair or climbing on to a bed and was completely unable to dress himself.

Single photon emission tomography was repeated and continued to show bilateral posterior hemisphere abnormalities but with the emergence of a smaller area of reduced tracer uptake in the left anterior region.

2.5. DISCUSSION

Comparison of patients with selective anterior hemisphere abnormalities on single photon emission tomography (Dementia of Frontal Lobe Type) with those showing posterior hemisphere reductions of uptake

of 99mTc-HMPAO (probable Alzheimer's disease) revealed major differences between the two groups. In Dementia of Frontal Lobe Type social breakdown and personality change are prominent. Cognitive impairment appears to be in the realms predominantly of regulation of behaviour: in directing and maintaining attention to a task, implementing effective strategies for achieving a solution and checking of responses. Such an interpretation which suggests a disorder predominantly of frontal lobe function is supported by patients' poor performance on tests known to be sensitive to frontal lobe dysfunction, which place demands on powers of abstraction and mental flexibility. In contrast, Alzheimer patients exhibit a picture of amnesia, aphasia and spatial disorientation with relative preservation of social behaviour, a neuropsychological profile which points to a disorder of the posterior association cortex and the limbic system. Dissociations in clinical findings of Dementia of Frontal Lobe Type and Alzheimer patients indicate that purported distinctions are not merely an artifact of disease severity. Indeed, differences between Dementia of Frontal Lobe Type and Alzheimer's disease persist across a broad spectrum of dimensions: demography, history, neurological signs, psychological features and electroencephalography.

Dementia of Frontal Lobe Type has also been shown to be pathologically distinct from Alzheimer's disease. Although none of the group studied has as yet come to necropsy, examination of three clinically similar patients has shown fronto-temporal atrophy associated with cell loss, gliosis and spongiform change affecting predominantly cortical layer III with loss of myelin from the underlying white matter. Similar pathological findings have recently been reported by an independent group of investigators from the University of Lund, Sweden

(Brun, 1987; Gustafson, 1987; Risberg, 1987; Englund & Brun, 1987). In their prospective study of 158 patients with "organic dementia", 20 were found at necropsy to have a non-Alzheimer frontal lobe atrophy. Four showed the neuronal swellings and inclusions characteristic of Pick's disease. These changes were absent in the remaining 16, who were labelled "frontal lobe degeneration of non-Alzheimer type". Histological changes in these patients consisted of neuronal cell loss, slight gliosis and spongiosus affecting layers 1-III of the frontal, anterior temporal, anterior cingulate and anterior insular cortex. There was a mild accompanying white matter gliosis. In contrast, minimal change was seen in the sensori-motor, parietal and occipital cortex. The basal ganglia and brain stem were larely normal apart from mild loss of nigral neurones. The nucleus basalis of Meynert was normal.

The clinical features (Gustafson, 1987) and regional cerebral blood flow findings (Risberg, 1987) of all 20 Swedish patients with non-Alzheimer frontal lobe atrophy were reported in detail and closely resemble the studied patients and single photon emission tomograms in Dementia of Frontal Lobe Type. No qualitative differences were reported between patients with Pick cells and inclusions and those labelled frontal lobe degeneration of non-Alzheimer type, although degree of disinhibition, dietary overactivity, echolalia and frontal blood flow abnormality appeared more severe in the former.

The pathological findings reported to date in Dementia of Frontal Lobe Type therefore suggest a range of non-Alzheimer histological change affecting predominantly the anterior cerebral hemispheres. The relationship to Pick's disease is debatable because there is not uniform agreement on what constitutes the pathological criteria for this form of

cerebral atrophy. Some authorities demand the presence of neuronal swellings and inclusions (Alexander & Geshwind, 1984; Adams & Victor, 1985; Brun, 1987), whilst others recognise Pick's disease without these neuronal alterations (Tissot et al, 1985). Until these controversies are settled the descriptive term 'Dementia of Frontal Lobe Type', suggesting a major area of cerebral dysfunction rather than specific pathological findings seems more appropriate. Future necropsy studies ought to determine whether there are fundamental differences between frontal lobe atrophy with or without neuronal swellings and inclusions.

Within the current patients with Dementia of Frontal Lobe Type two broad spectrums of behaviour could be identified: one of slowness, apathy, inertia and aspontaneity, the other of restlessness, overactivity, distractibility and disinhibition. These behaviour patterns cannot be regarded as mutually exclusive, since features of both may occur in the same patient. Nevertheless, patients do tend to fall predominantly into one or other category; amongst the case studies described patients one and five epitomise the first group and patients two, three, four and seven the second. The picture of slowness and inertia is associated with such features as perseveration at the level of single actions and hypophonia. The disinhibited, overactive picture is associated with more evident word finding difficulty and the presence of verbal paraphasias. Such dissociations in symptomatology suggest that Dementia of Frontal Lobe Type is not entirely uniform and raises the possibility of distinct sub-types.

Pathological reports of Pick's disease have recognised distinct sub-groups. In one report (Munoz-Garcia & Ludwin, 1984), a distinction was made between a form of disease with almost exclusive fronto-temporal

cortical pathology and a second form involving also subcortical structures. In another report (Tissot et al, 1985), the authors contrasted forms of disease involving respectively predominantly frontal and predominantly temporal pathology. Fronto-temporal subcortical pathology also predominates in the non-Alzheimer, progressive subcortical gliosis (Neumann & Cohn, 1967; Verity & Wechsler, 1987). The suggestion within the present patient series of some clinical heterogeneity would be consistent with such purported regional differences in prominence of pathological change. For example, patients presenting a picture of slowness and inertia may correspond to the picture of subcortical pathology. Conversely, the picture of overactive and disinhibited behaviour with striking anomia might be anticipated to be associated with the presence of cortical pathology. Patterns of anterior hemisphere abnormality on single photon emission tomography lend some support this hypothesis. The majority of scans showed absent frontal cortical uptake, in keeping with clinical features suggesting disordered frontal cortical function. However, scans from three of the 23 patients (including patient five) showed preservation of a rim of frontal cortical uptake. In all three slowness and inertia were dominant clinical features, and suggested a predominant subcortical distribution of pathology.

Electroencephalography was a useful investigation for distinguishing patients with Dementia of Frontal Lobe Type from those with Alzheiemer's disease. Background rhythms were normal in all Dementia of Frontal Lobe Type patients but were significantly slowed in all but a small minority of patients with Alzheimer's disease. Comparable findings have been reported by others (Johannesson et al, 1979).

Clinical studies of dementia frequently assume that almost all patients with primary degenerative dementia associated with cortical atrophy will have Alzheimer's disease. In view of this assumption, the ratio of Dementia of Frontal Lobe Type to Alzheimer's disease in the present series (greater than 1:2) is highly significant. Referral bias, pattern of follow-up and regional variations in the prevalence of a strongly familial disorder may have influenced these figures. However, it may also be that the incidence of Dementia of Frontal Lobe Type has generally been underestimated. Traditional reliance on exclusion criteria for diagnosis rather than positive diagnostic criteria would serve to submerge distinct forms of dementia.

In the present study inferences regarding the nature of performance breakdown are drawn largely from a qualitative analysis of patients' performance and the nature of errors. That inferred distinctions are valid is borne out by their strong correlation with independent findings on single photon emission tomography. Diagnostic distinctions between groups appear to lie less in which tasks patients fail than how they fail. A neuropsychological evaluation which relies on the interpretation of numerical scores alone is likely to obscure rather than highlight group differences. Scores on the WAIS, for example, taken in isolation would give rise in patients with Dementia of Frontal Lobe Type, as in Alzheimer patients, to the interpretation of 'generalised intellectual impairment' and would fail reliably to distinguish the two groups. That patients with impaired function of the 'anterior' and 'posterior' cerebral hemispheres may achieve comparable scores yet perform qualitatively differently on a standard psychological test has been demonstrated also by others (Johanson et al, 1986). Traditional emphasis of psychological

assessment on quantitative measurement of performance may have contributed to an underestimate of the incidence of Dementia of Frontal Lobe Type. Furthermore, prior to the development of emission computed tomography cerebral imaging was unable to identify regional differences in cerebral function amongst the cerebral atrophies. The finding of generalised cerebral atrophy on X-ray computed tomography may have served to reinforce the concept of generalised intellectual impairment in patients with cerebral atrophy. Moreover, reliance on accepted psychiatric criteria for the diagnosis of possible and probable Alzheimer's disease (American Psychiatric Association, 1980; McKhann et al, 1984) would have subsumed both Dementia of Frontal Lobe Type and Alzheimer's disease as 'probable Alzheimer's Disease'.

Although Dementia of Frontal Lobe Type accounts for only a minority of patients with presenile dementia, the incidence appears sufficiently great to suggest that Alzheimer's disease should not be regarded as the inevitable diagnosis in patients meeting the clinical criteria for primary degenerative dementia. The advent of the distinction between cortical and subcortical dementia (Albert et al, 1974; Cummings & Benson, 1984) represents an initial step in the clinical distinction between forms of dementia. A further distinction appears warranted: that between the relatively common 'posterior' cortical dementia of Alzheimer's disease and the 'anterior' cortical dementia described in this chapter.

2.6. CONCLUSIONS

Single photon emission tomography when combined with neuropsychological evaluation and electroencephalography has successfully delineated a group of patients with disease of the anterior

cerebral hemispheres (Dementia of Frontal Lobe Type) and distinguished it from the more common disease of Alzheimer's disease in which the posterior cerebral hemispheres are principally affected.

Dementia of Frontal Lobe Type is a distinct type of primary cerebral atrophy. Patients present in the presenium, with clinical features of a frontal lobe syndrome. There are minimal physical signs and mental examination reveals a disorder of regulation, with preserved spatial abilities. The electroencephalogram is normal. There is cerebral atrophy on X-ray computed tomography and a selective anterior hemisphere abnormality on single photon emissionn tomography.

Comparison of Dementia of Frontal Lobe Type with Alzheimer's disease reveals qualitative differences in clinical presentation, physical signs, pattern of psychological impairment, electroencephalography, single photon emission tomography and demography.

The histological changes in the brains of three patients with a similar clinical picture, one a first cousin of a studied patient, have revealed fronto-temporal atrophy with loss of large cortical neurones, spongiosus and mild gliosis. The histological hallmarks of Alzheimer's disease have been absent.

CHAPTER THREE DEMENTIA OF FRONTAL TYPE AND MOTOR NEURONE DISEASE.

3.1. INTRODUCTION

During the course of the previous study, four patients presented with a degenerative disorder of the nervous system, which appeared to resemble closely Dementia of Frontal Lobe Type but which was associated with the later development of motor neurone disease. Although the association appears to be rare (Brownell et al, 1970; Poloni, et al, 1986), the combination of dementia and motor neurone disease has been increasingly recognised in recent years (Hudson, 1981). Formerly identified as part of the Dementia-Parkinsonism complex, occurring commonly on the Pacific island of Guam (Hirano et al, 1961a; 1961b), there have since been several reports of the association from Japan (Mitzuyama, 1984; Morita et al, 1987) and from Western countries (Allen et al, 1971; Finlayson et al, 1973; Pinsky et al, 1975; Hudson, 1981; Salazar et al, 1983; Horoupian et al, 1984; Clark et al, 1986). However, the pattern of mental change in these patients has not been clearly defined. A variety of conclusions has been drawn from the results of clinical assessment. The dementia has been variously reported, to resemble Alzheimer's or Pick's disease (Hudson, 1981), to have features of a global intellectual impairment (Allen et al, 1971), or to indicate an unclassified presenile dementia, not typical of Alzheimer's or Pick's disease (Horoupian et al, 1984; Mitsuyama, 1984; Morita et al, 1987).

This chapter presents the results of investigation of four patients with dementia and motor neurone disease. The pattern of mental impairment was studied by psychological assessment and was compared with the regions of reduced tracer uptake on single photon emission

tomography (For Methods see Appendices One and Two). The brains of three patients were studied at necropsy, permitting an examination of clinico-pathological relationships.

3.2. CASE STUDIES

In none of the four patients was there any previous medical or psychiatric history. There had been no occupational exposure to chemicals or heavy metals. They had never suffered a major head injury and did not abuse alcohol. There was a family history of dementia in patient two only. Biochemical, haematological and serological investigations were normal in all four patients. All four patients were right handed.

PATIENT ONE

A 52 year old male security officer presented with a 12 month history of personality change and deterioration in his behaviour and intellect. Formerly equable and conscientious, he became progressively more withdrawn and unmotivated, his sole interest being in food. He spoke little with an impoverished vocabulary. He was rude and verbally aggressive. His speech had become slurred. He continued to carry out activities of daily living independently. He had not become lost in his environment. He did not complain of physical symptoms including weakness.

Physical Examination

General examination was normal. Neurological examination revealed slight weakness of the right side of his face, dysarthria, weak cough and gag reflex, wasting and fibrillation of the tongue. The jaw jerk was exaggerated. Muscular power was normal but there was a mild spastic increase in tone in the lower limbs. There was fasciculation of the muscles of the shoulder girdle and the biceps. Tendon jerks were brisk, the plantar responses flexor and abdominal reflexes present. Sensation, coordination and gait were normal.

Mental Examination

His affect was bland and he showed no concern or insight into his predicament. His behaviour was mildly disinhibited. He cooperated fully and showed normal application to tasks.

His speech was dysarthric and mildly circumlocutary but otherwise linguistically correct and without paraphasias. He could understand complex sentences, recite overlearnt series such as the months of the year and had a normal digit span of six forward and four backwards. He could read and write without linguistic error. However there was evidence of concrete thinking: he gave literal interpretations of metaphors and proverbs and for questions requiring a 'generalised' answer he substituted specific personal anecdotes. On the shortened Token test, he scored 32/36. On the Boston naming test, he named 51/60 items correctly. For the nine pictures which he failed to name, in eight cases he substituted a description of the object's function and in one case he made a semantic category error.

There was no evidence of perceptual, spatial or praxic disorder. He identified line drawings of objects and faces of celebrities. He could locate objects in the room, track the Money road map and reproduce non-representational hand postures. His spontaneous drawing of a house and copies of a cube and abstract figures were normal, with preserved spatial configuration and relationship between elements. He could reproduce Koh's blocks figures. He had no dressing difficulty. He could demonstrate actions by gesture and pantomime.

He was fully orientated for time and place and could give a good account of day to day events. He could summarise short stories after reading them aloud and recalled them to a comparable level of proficiency after a one hour delay. On the Warrington word and face recognition tests, he scored respectively 40/50 and 39/50, lying at the tenth centile for his age group. On a paired associate task he failed to learn six pairs of unrelated words over six learning trials. However, when provided with a visual image strategy for learning he could learn a matched set of unrelated word pairs on the first trial.

He performed poorly on tasks sensitive to frontal lobe dysfunction. On the Nelson card sorting test, he achieved two categories only. Despite frequent reiteration of the instructions he persistently placed cards

with respect to those previously placed rather than to the four stimulus cards. On the Weigl's block test, he achieved one method of grouping only. When blocks were grouped by the examiner he could identify the underlying sorting criterion in one case only, on subsequent trials displaying perseveration of this original sorting rule. On a task based on the '20 questions principle', performance was concrete and lacking in strategy. he pointed to individual pictures at random and made no attempt to generate questions that would eliminate effectively the greatest number of alternatives.

Investigations

Electroencephalography was normal. X-ray computed tomography did not show evidence of cerebral atrophy. Single photon emission tomography revealed reduced uptake of tracer in the left frontal region of the brain with preservation of uptake in the posterior cerebral hemispheres.

Neurophysiological studies demonstrated normal motor nerve conduction velocities and sensory nerve action potentials. Electromyography of muscles of the upper and lower limbs revealed abundant multifocal fasciculation, motor unit potentials as great as 10 mvolts and reduced interference pattern, compatible with motor neurone disease.

Progression

His condition deteriorated dramatically over the ensuing six months. However, for geographical reasons re-examination was not possible.

PATIENT TWO

A previously conscienscious 45 year old heavy goods vehicle driver lost his job through loss of punctuality in delivering goods. His wife noticed him to be increasingly apathetic and he abandoned his former interests in gardening, amateur dramatics and music. He ceased to demonstrate any affection towards his family and was prone to aggressive outbursts, which were totally out of character. He had difficulty in calculating, no longer read and would wander off on his own, although without becoming lost. His mental state deteriorated dramatically over the ensuing 18 months, culminating in his referral to

a neurological centre. He would spend the day pacing the room. He made no spontaneous attempt to dress, wash or toilet himself. His speech output had become progressively reduced so that he would rarely say anything other than "no, no, no". He had taken to laughing spontaneously and rubbing his hands together with glee. He had lost three stones in weight during a period of two months. There was no history of physical symptoms including weakness.

Physical Examination

The general examination was normal. On neurological examination the cranial nerves were intact, though the jaw jerk was brisk. Power and tone of the muscles was normal but there was evident wasting of the muscles of the shoulder girdle, upper arms and small muscles of the hands. Widespread fasciculation was present in the trunk and upper and lower limbs. Tendon jerks were brisk, the plantar responses were flexor and the abdominal reflexes present. It was possible to elicit pouting, sucking and grasping reflexes. Sensation, coordination and gait were normal.

Mental Examination

He maintained a fatuous grin and on making eye contact with the examiner he grinned and rubbed his hands together childishly. Assessment was restricted by his restlessness and repeated attempts to leave the room. He did not initiate speech spontaneously. In response to questions he answered monosyllabically or not at all. Responses were idiosyncratic and irrelevant. Perseverative iteration of a single word was common. Because of the paucity of his verbal output his level of comprehension was difficult to ascertain. However, when his wife was asked whether he smoked he took out a cigarette packet from his pocket and lit a cigarette. When she was asked whether a blood sample could be taken he removed his jacket and rolled up his sleeve. Such behaviour suggested some comprehension of at least nominal terms. He had a forward digit span of four digits. Occasionally he named objects to confrontation. More frequently he made verbal paraphasias or perseverated previous responses, or else failed to respond at all. Writing was markedly perseverative. He failed to comply with

constructional tasks. However, features of his behaviour suggested relative preservation of spatial abilities. He placed his home town correctly on a map of Great Britain; he displayed no difficulty in locating objects in space and could negotiate his environment without becoming lost; when an article of clothing was presented to him inside out he had no difficulty rectifying this and could orientate the article correctly in order to put it on. His impoverished powers of communication prevented evaluation of his memory.

Investigations

Electroencephalography showed moderate theta activity which was thought to be within normal limits. X-ray computed tomography revealed cerebral atrophy which was most marked in the frontal lobes. Single photon emission tomography showed marked defects in tracer uptake, most prominent in the frontal lobes.

Neurophysiological investigations revealed normal motor nerve conduction velocities and sensory nerve action potentials. Electromyography of the muscles of the upper and lower limbs showed multifocal fasciculation and fibrillation. Lack of cooperation prevented further evaluation but the findings were in keeping with anterior horn cell disease.

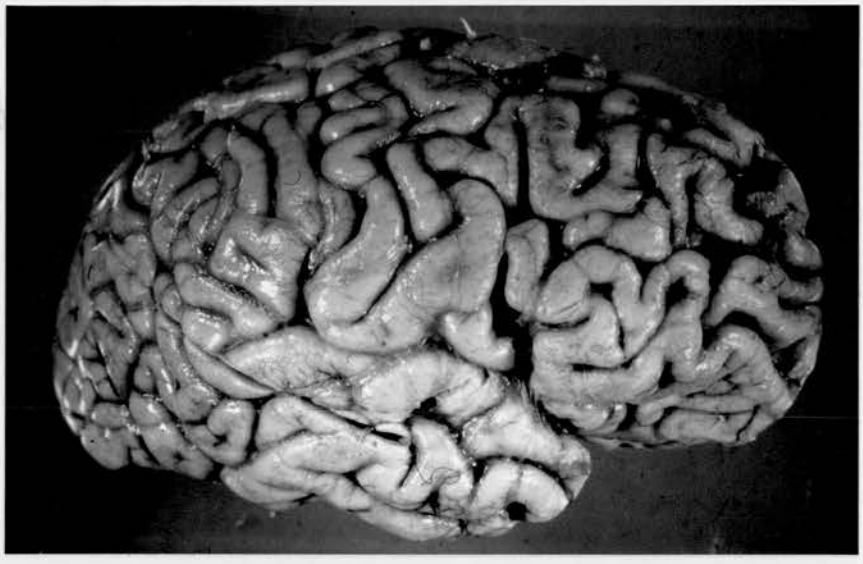
Progression

He continued to deteriorate rapidly and died six months later, having a total duration of illness of two years. The brain and spinal cord were removed for examination.

Pathological Findings

The major cerebral arteries and those of the circle of Willis were free from atheroma. Superficially, the brain showed focal cortical atrophy, localised to the frontal lobe, particularly the middle and superior frontal gyri (Figures 3.1a and 3.1b). The remaining areas of the cerebral cortex, brain stem, cerebellum and spinal cord were unremarkable. On slicing, both lateral ventricles, third and fourth ventricles were all moderately dilated. There was widening of the

sylvian fissure but all areas of the cerebral cortex, basal ganglia, brain stem, cerebellum and spinal cord appeared macroscopically normal.



A

B

Figure 3.1.

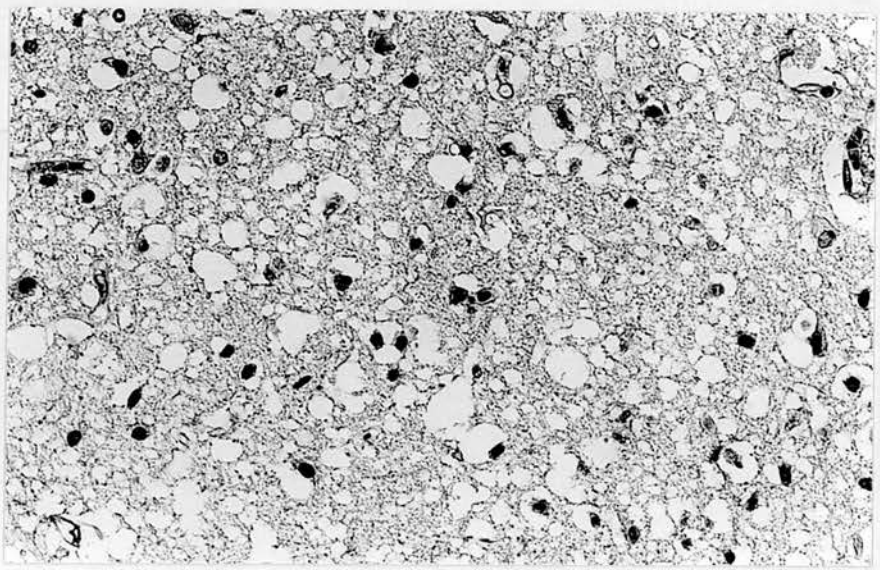
The right cerebral hemisphere from Patient Two viewed laterally (A) and anteriorly (B). Atrophy is evident within superior and middle frontal gyri; other cortical gyri appear normal.

On microscopic examination the middle and superior frontal gyri showed a moderate spongiform change affecting layer II principally (Figure 3.2A). There was loss of pyramidal cells from layer III particularly and also from layer V. There was fibrous gliosis, mild in layers I-V but dense in layer VI (Figure 3.2B). The deep white matter showed only a slight demyelination but no gliosis. These changes were seen to a lesser extent in the inferior frontal gyrus, cingulate gyrus and anterior temporal pole but were absent from other cortical areas. In the hippocampus, the subiculum and end-folium were gliosed but without apparent cell loss; CA regions appeared normal. The basolateral nuclei of the amygdala also showed gliosis, but cortical nuclei and uncus appeared normal. Although a slight gliosis was present within the caudate nucleus, the putamen, thalamus and globus pallidus all appeared histologically normal. The nucleus accumbens however was moderately gliosed. The nucleus basalis, locus caeruleus and raphe nuclei all appeared histologically normal. The cerebellum appeared normal.

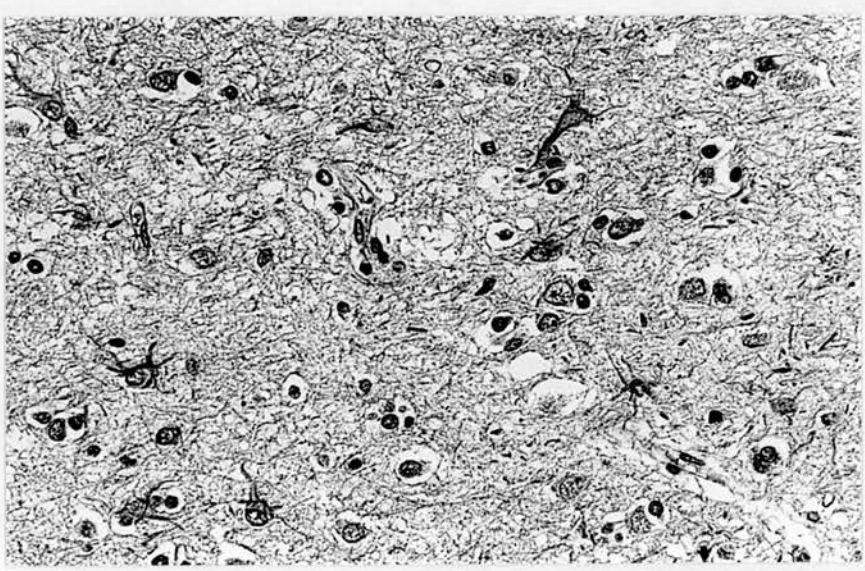
In the brain stem, the substantia nigra showed a severe loss of nerve cells; clumps of melanin pigment within the neuropil were prominent (Figure 3.3A) and a heavy reactive fibrous astrocytosis was present (Figure 3.3B). No Lewy bodies were seen in surviving cells. The hypoglossal nucleus showed atrophy and loss of neurones; trigeminal and facial nuclei appeared normal.

In the motor system, the Betz cells of the precentral gyrus were shrunken though not obviously reduced in number. The cerebral peduncles and corticospinal tracts in pons and medulla showed no demyelination, though there was slight loss of myelin from lateral columns of the spinal cord at all levels. Within the anterior horns there was gross loss of neurones at all levels, though in lumbar and sacral segments such cell loss was more severe medially (Figure 3.4A) than laterally (Figure 3.5B). Many surviving cells contained large pale inclusions within the cytoplasm (Figures 3.4A and 3.4B).

No senile plaques or neurofibrillary tangles were present on silver staining or antibody staining and no Pick or Lewy type inclusions were present in cortical or subcortical neurones.



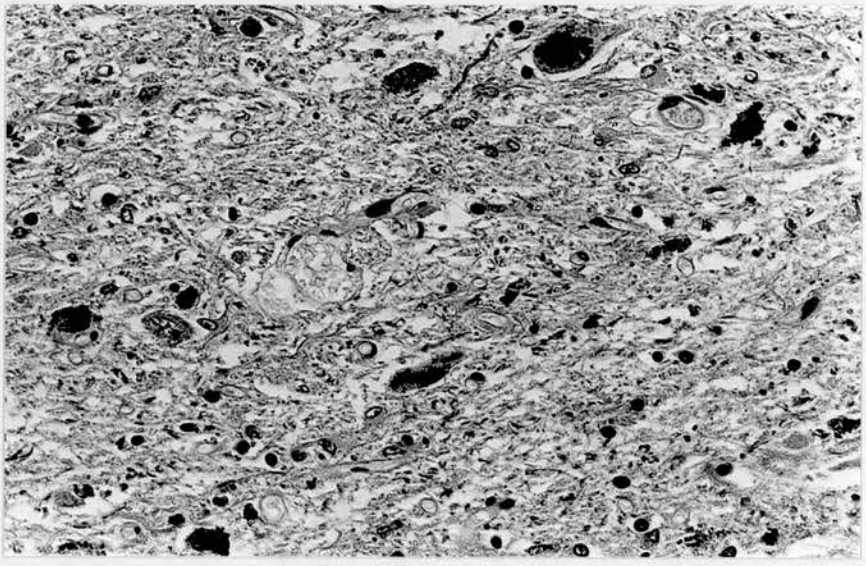
A



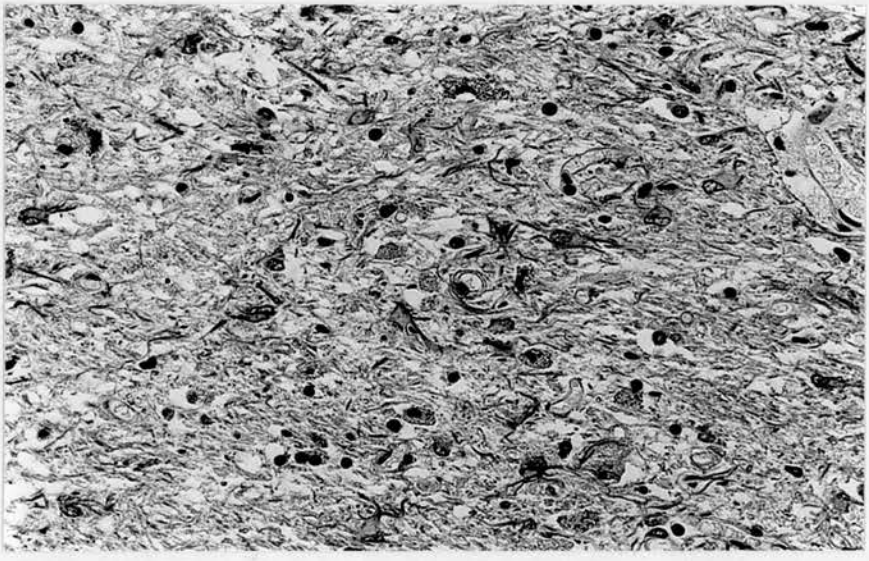
B

Figure 3.2.

Microscopic changes within the cerebral cortex of Patient Two. Layer II of the superior frontal cortex shows a pronounced spongiform change (A) whereas within layers V and VI there is marked fibrous astrocytosis (B).



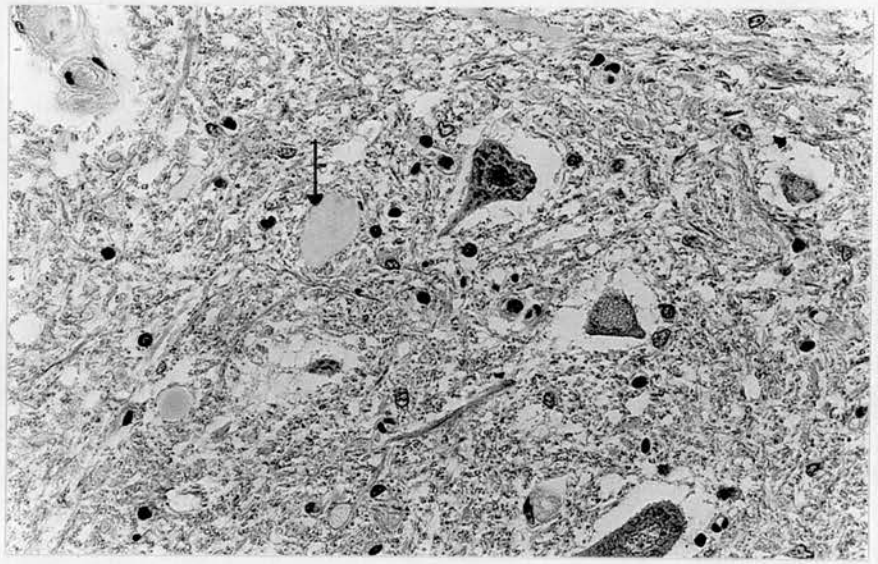
A



B

Figure 3.3.

Microscopic changes in the brainstem of patient Two. There is severe loss of pigmented nerve cells in the substantia nigra (A) and a heavy reactive astrocytosis (B).



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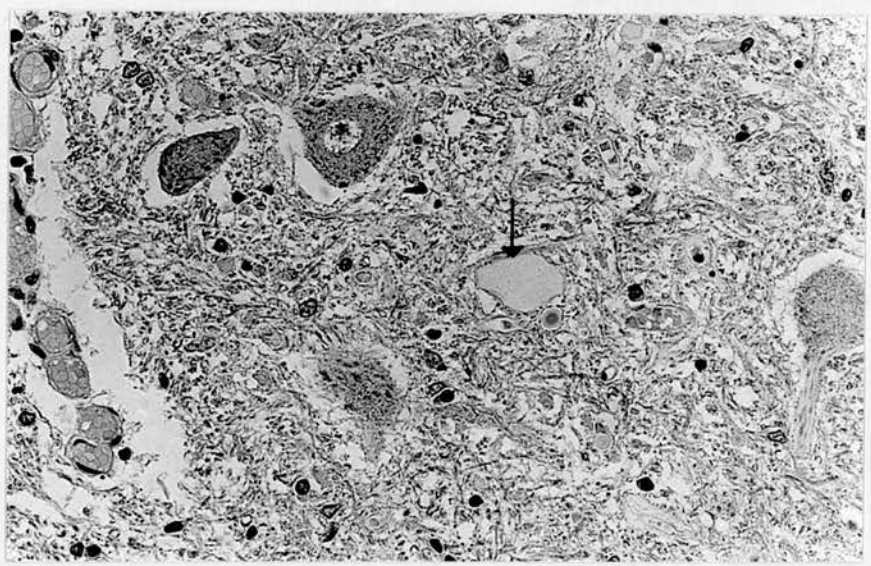


B

Figure 3.4.

Microscopic changes in the spinal cord of patient Two. There is atrophy and loss of medial anterior horn cells at all levels (A), whereas at lumbar levels many anterior horn cells appear preserved (B). At all levels of cord, anterior horn cells containing large eosinophilic inclusions (arrowed) are present (A and B).

PATIENT THREE

A 44 year old warehouse manager presented with an 18 month history of progressive deterioration in behaviour, intellect and memory. Formerly a conscientious man, he neglected domestic and occupational responsibilities and when sacked from work showed no concern. He became self centred and callous and emotional empathy with his family was lost. His behaviour and thinking were rigid: having adopted an idea this would become fixed in his mind and could not be shifted. He would become aggressive if his own wishes were thwarted. His behaviour was unpredictable, impulsive and dangerous: he attempted for example, to remove the battery from his car whilst the engine was running. He became increasingly restless, and would wander the local streets, always keeping to the same route. Although superficially active he lacked persistence in tasks, so that his activities were essentially unconstructive. Previously an excellent handyman he was no longer manually capable. He became increasingly gluttonous, raiding the food cupboard surreptitiously and invariably spending 'pocket-money' on sweets voraciously eaten. He lost interest in sexual relations.

Increasing difficulty had been noted in his speech and his conversation had become reduced. He had difficulty finding words and would substitute semantically related alternatives, for example, "windows" for "curtains". His comprehension appeared impaired, although his contrary behaviour suggested wilfulness. He was 'forgetful' and could not carry out simple shopping errands. He could wash, dress and shave himself without difficulty and could negotiate his environment without becoming lost. There had been no episodes of incontinence. He complained of no physical symptoms including weakness.

Physical Examination

General examination was normal. Neurological examination revealed fibrillation of the tongue and a positive jaw jerk. Power and tone were preserved but there was wasting of the small muscles of the hands and widespread fasciculation in the muscles of the upper limbs and shoulder girdle. Snout, suck and grasp reflexes were elicitable and the tendon jerks were very brisk. The plantar responses were flexor and the abdominal reflexes were present. Sensation and coordination were normal.

Mental Examination

His affect was bland and he had a fatuous grin. He denied mental symptoms and showed no concern or curiosity regarding his predicament. While superficially cooperative he lacked persistence in tasks and was restless, frequently leaving the room. He responded rapidly and impulsively, without checking the accuracy or relevance of his responses. He demonstrated a marked economy of mental effort.

Speech output was reduced. He rarely initiated conversation. Answers to questions, when appropriate, were economical and unelaborated. Often responses were irrelevant and had a telegrammatic quality: "Used to be a warehouse manager. Earned 15 grand. Got the sack. I can drive a tank. I can drive a fork lift truck. One of them things!". Stereotyped reiteration of words and phrases was common. Speech was dysprosodic but articulation was normal. No literal paraphasic erors were detected.

He could understand simple nominal terms but not complex syntax. On the shortened Token test he scored 11/36. He had a forward digit span of five digits but in a reversed digit task he failed to understand what was required. He failed to repeat sequences of four words in the correct order. He showed some word finding difficulty to confrontation and from description and perseveration of previous responses occurred. Performance on the Boston naming test was impaired (30/60 correct), the predominant error type being semantic category substitutions, for example, "zebra" for camel. His reading performance was variable: omissions or misreading of words occurred sporadically, unrelated to the linguistic difficulty of the material and suggested inattention to the task. In writing to dictation omissions and perseverations of words occurred. He failed to carry out the simplest mental and written calculations.

Perceptual and spatial abilities appeared largely intact. He had no difficulty locating objects and could find his way around the environment. He could identify line drawings of objects, traced the path through the Money road map with ease and could localise towns on a map of Great Britain. He could copy non-representational hand postures and his drawings and constructions revealed preserved spatial configuration. Evaluation was however complicated by his perfunctory performance. He failed to name faces of contemporary celebrities, although comments

suggested awareness of their identity. He could manipulate objects dextrously and could use gesture and pantomime accurately. However, he had sequencing difficulties in copying a series of hand postures and he could not copy simple motor rhythms.

Performance on formal tests of memory was invariably impaired. Scores on the word and face recognition test were at chance level. Nevertheless, he was orientated in time and place and could recall personal day to day events.

He performed grossly abnormally on all tests sensitive to frontal lobe dysfunction. On the Nelson card sorting test, he achieved one sorting dimension only, 98% of errors being perseverative. On the Weigl's block test he grouped blocks arbitrarily. When they were grouped for him he could not identify the underlying sorting rule. On a verbal fluency task he produced in one minute, only seven animal names and one word beginning with the letter F. Design fluency performance was perseverative, concrete and not constrained by the four line rule imposed by the task: he produced a series of circles, triangles and squares.

Investigations

Electroencephalography was normal. X-ray computed tomography revealed generalised cerebral atrophy. Single photon emission tomography demonstrated marked decrease in uptake of tracer, most prominent in the frontal regions.

Neurophysiological investigations showed normal motor nerve conduction velocities and sensory nerve action potentials. Electromyography of muscles of the upper and lower limbs revealed abundant multifocal fasciculation and some giant motor unit potentials. The results were in keeping with anterior horn cell disease.

Progression

His condition deteriorated rapidly, necessitating his institutional care. Review six months after initial assessment revealed evident wasting of the muscles of the shoulder girdle in addition to the small muscles of the hands. Fasciculation was now visible in the lower limbs.

Plantar responses were flexor and the abdominal reflexes present. Sensation and coordination remained normal.

He had a fatuous staring expression and grinned inanely. He rushed about purposelessly, retaining a surprising physical agility. He had acquired a seemingly stereotyped behaviour pattern of undressing at intervals throughout the day and getting into bed, getting up and dressing again only minutes later. He remained able to feed, dress and wash himself without difficulty.

Formal mental testing was no longer possible. He could not be persuaded to remain in one place for more than a few minutes. He volunteered no conversation and responses were monosyllabic or stereotyped phrases, often perseverative and inappropriate. Echolalia occurred, particularly of the final noun in a question. No literal paraphasias were evident. Speech was both dysprosodic and dysarthric. Assessment of comprehension was complicated by the paucity of his responses. He obeyed simple commands requiring whole body and limb movements and he could understand simple nominal terms and name some common objects on confrontation. It is likely, nevertheless, that his powers of comprehension were severely restricted. Repetition was limited to one word only, usually the last one given. When overlearned series such as the days of the week were initiated for him, he could produce the next item in the sequence but could not be induced to continue with the series. His writing and drawing showed marked perseveration. His continuing ability to dress, locate objects and negotiate his environment indicated the continued absence of spatial disorder.

He died aged 45 years, approximately 28 months after disease onset and necropsy was undertaken.

Pathological findings

The brain weight was 1260g. The major cerebral arteries and those of the circle of Willis were free of atheroma. Macroscopically, the cerebral hemispheres showed a well demarcated area of atrophy within the frontal lobes, affecting particularly the medial and superior aspects. The remaining cerebral cortex, brainstem and cerebellum appeared superficially normal. The spinal cord was thin at all levels but particularly so within the cervical region. Spinal ganglia appeared

normal. On slicing, apart from slight enlargement of the lateral ventricles the cerebral cortex, basal ganglia, brainstem and cerebellum appeared normal. Substantia nigra and locus caeruleus were well pigmented.

On microscopic examination, the frontal cortex, in particular the middle and superior frontal gyri, showed a moderate spongiform change affecting mainly layer II. There was some loss of pyramidal cells from layers III and V. There was also a mild gliosis in layers II-VI inclusive. This was particularly heavy in layer VI and extended into the adjacent white matter. The white matter itself showed no demyelination or obvious loss of axons. Similar histological changes were seen, although to a lesser extent, within the inferior gyri of the frontal cortex, the cingulate gyrus and the anterior pole of the temporal lobe. In the hippocampus the subiculum and end folium were severely gliosed, but the Ammons's horn areas appeared normal. The basolateral nuclei of the amygdala also showed heavy gliosis but this was slight in hippocampal cortical nuclei and in the uncus. In no region of the hippocampus or amygdala was nerve cell loss seen. No abnormalities were seen in the cerebellum or basal ganglia. The nucleus basalis of Meynert, locus caeruleus, dorsal and median raphe all appeared histologically normal.

In the brain stem, the substantia nigra showed a moderate to severe loss of nerve cells but no Lewy bodies were present in surviving cells. The hypoglossal nucleus showed atrophic neurones though those of the facial and trigeminal nuclei appeared normal.

In the motor system, the Betz cells of the precentral gyrus were largely preserved in number though many were grossly shrunken. There was no obvious demyelination within the corticospinal tracts, in pons, medulla or spinal cord. Within the anterior horns there was a gross loss of neurones at all cervical and thoracic levels, though in lumbar and sacral segments loss of anterior horn cells was confined to medial areas.

On silver staining, no senile plaques nor neurofibrillay tangles were observed in any region of the brain. Using antiamyloid staining, only a single fine deposit of amyloid protein was seen within the end-folium of

the hippocampus. No tangles were demonstrated with anti-PHF staining. No Lewy bodies or Pick-type inclusions were observed.

PATIENT FOUR

A 58 year old labourer presented with an 18 month history of personality change and disordered conduct. Formerly sociable and considerate he became thoughtless and callous. He was restless and impatient and could no longer apply himself contructively to tasks. Previously an occasional Bingo player he became obsessed with the game. Yet, he would miss the numbers called because of poor concentration. He lost his former meticulous table manners and would cram food into his mouth and eat noisily. He had developed an abnormal fondness for chocolates. He was noted to feel the cold more than before. One year after the onset of his symptoms his behaviour was more overtly disinhibited: he would shout and swear in public and appeared oblivious to social mores. Although previously little interested in sexual relations he became obsessed with sex and would proposition females indiscriminately, including an 80 year old aunt.

Approximately nine months after the onset of his mental symptoms he was noted to develop weakness of the arms and six months later of the legs. In the two months prior to investigation he had developed slurring of speech and difficulty swallowing.

The patient denied mental or physical difficulties and despite his weakness persisted in driving his car, professing himself competent to do so.

The patient's mother had undergone a similar change in personality and conduct aged 60 years. She had neglected personal hygiene and self care and refused to eat. When her family stocked her larder for her she posted the food through neighbours' letterboxes. She too had become obsessed with Bingo. She had begun to drink heavily, resulting in falls. She had been admitted to an elderly persons home where she had become aggressive and disinhibited, tending to sing bawdy pub songs throughout the day. She had wandered incessantly. In contrast to her mental difficulties she had remained physically well and there was no report of

weakness, slurred speech or difficulty swallowing, even in advanced disease. She had died aged 74 years. No necropsy was undertaken.

Physical Examination

General examination was normal. Neurological examination revealed tongue wasting and fibrillation. Profuse fasciculation was noted in the trunk and all four limbs, with marked wasting and weakness particularly in the upper limbs. Tone was normal. Reflexes were symmetrically brisk and the plantars extensor. Pout and grasp reflexes were elicited, the latter more marked on the right. Sensation and coordination were normal.

Mental Examination

He had an unconcerned demeanour, was inattentive and restless during the examination and performance was perfunctory.

Speech ouput was reduced. He rarely initiated conversation and answers to questions were often monosyllabic without elaboration. Mild word finding difficulty was noted and he made occasional verbal paraphasic errors. Speech was both dysarthric and dysprosodic. He could follow simple verbal instructions, could designate left and right correctly and understood syntactically complex sentences. However, he demonstrated concreteness of thought in the interpretation of metaphor and proverb. He had a normal immediate forward span of seven digits but reduced backward span of only two digits. He could repeat polysyllabic words without paraphasic error. Naming to confrontation and from description revealed a mild anomia. On the Boston naming test, he named correctly only 32 of 60 items, the predominant error type being the substitution of an object's function for its name. There was some perseveration of previous responses. He could read aloud and write his name and address without spelling error. He could carry out two and three digit mental and written additions and subtractions accurately.

There was no evidence of perceptual or spatial disorder. He could identify line drawings of objects and the faces of celebrities. He could locate objects in the environment and when dressing could orientate clothes normally. He could track around the Money road map. Performance on visuoconstructional tasks was compromised by his physical disorder. Nevertheless, he succeeded in completing simple Koh's block designs. In

reproducing rhythms tapped on the table, he displayed motor perseveration.

He was well orientated for time and place and could give an accurate autobiographical account of day to day events. However, performance on formal memory tests was poor. He scored only 27/50 on the word section and 30/50 on the face section of the Warrington recognition memory test. Moreover, he failed to generate information about current news events.

Performance on tests sensitive to frontal lobe dysfunction was impaired. On the Nelson card sorting test he achieved one sorting category only, 100% of errors being perseverative. On the Weigl's block test, he failed to achieve any correct groupings. He showed concreteness of thought, placing the blocks together to form pleasing designs rather than according to a common dimension. He failed to identify the sorting dimension when the blocks were sorted for him. On the 20 questions task, he exhibited concreteness of thought and adopted no concerted strategy for efficient identification of the target item. On a verbal fluency test he produced only nine animal names and six words beginning with the letter F in one minute. On a picture sequencing task he placed cards arbitrarily, describing the contents of each whilst making no attempt to integrate information into a logical sequence.

Investigations

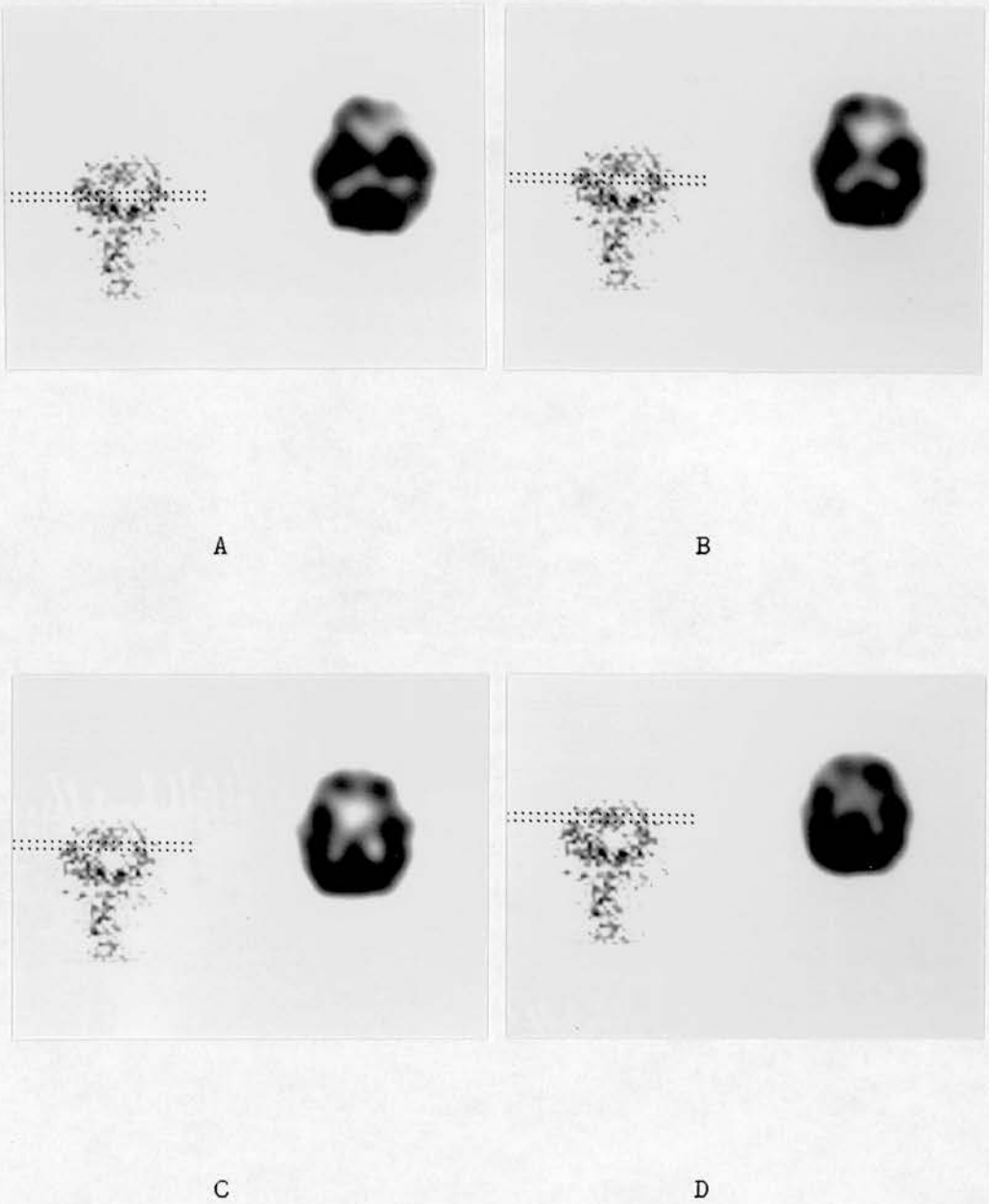
Electroencephalography was normal. X-ray computed tomography revealed cerebral atrophy with fronto-temporal predominance. Single photon emission tomography demonstrated reduced uptake of tracer in both frontal lobes more marked in the left hemisphere (Figure 3.5).

Neurophysiological examination revealed normal motor nerve conduction velocity and sensory nerve action potentials. Electromyography demonstrated profuse, widespread fasciculation and fibrillation, compatible with motor neurone disease.

PROGRESSION

He continued to deteriorate rapidly, both physically and mentally and died from bronchopneumonia seven months after examination. The total duration of his illness was approximately twenty-five months. Necropsy

was undertaken and the brain and spinal cord were removed for neuropathological examination.



A B

C D

Figure 3.5.

99mTc-HMPAO scan from Patient Four. There is reduced uptake of tracer in the anterior regions of both hemispheres, which is most marked on the left.

Pathological findings

The major cerebral blood vessels were free from atheroma. Moderate cortical atrophy was present within the superior and middle gyri of the frontal cortex and within the temporal pole. The remainder of the cerebral cortex, the brainstem and cerebellum appeared macroscopically normal. On slicing, a mild enlargement of the lateral ventricles was seen, and the corpus callosum was somewhat thinned, especially at the level of the optic chiasma. The substantia nigra appeared totally depigmented. No other abnormality was observed. The spinal cord appeared superficially normal.

On microscopic examination, there was mild spongiform change within layer II of the frontal and anterior temporal cortex, but no gliosis nor obvious pyramidal cell loss was seen. Occasional vessels within temporal white matter showed hyalinazation and tortuosity, with focal loss of myelin. A mild gliosis was seen in layers V and VI of the entorhinal cortex and within the amygdala. In the hippocampus, a local region of neuronal loss was present within the CA1 and subiculum, associated with some gliosis. The posterior temporal, parietal and occipital lobes were macroscopically normal.

In the brainstem, the substantia nigra showed a virtually complete loss of cells but there was no accompanying gliosis. The locus caeruleus appeared normal. Occasional blood vessels within the basal ganglia (caudate/putamen and thalamus) showed hyaline change but no microinfarction was present. The cerebellum appeared normal. No senile plaques, amyloid deposits or neurofibrillary tangles were seen in any region of the brain.

In the motor system, the Betz cells of the precentral gyrus appeared normal, morphologically and in number. There was no pyramidal tract demyelination. However, again occasional vessels in the medulla and pons showed hyalinization and tortuosity. The hypoglossal nucleus showed atrophy and loss of neurones. In the cervical spinal cord there was gross loss of anterior horn cells especially medially, but without accompanying gliosis. Within the grey matter there were numerous 'knots' of tortuous hyalinized blood vessels, including arterioles, capillaries and venules. Similar vascular changes were seen within the lateral and dorsal columns, however, without accompanying demyelination. The

anterior spinal artery and vein appeared normal. The spinal roots and ganglia were unremarkable and no long tract demyelination or gliosis were seen. Similar pathological changes were seen in the lumbar cord, though here the degree of vascular hyalinization and anterior horn cell loss was less severe. Some surviving cells in the lateral parts of the anterior horns contained large eosinophilic inclusions.

3.3. DISCUSSION

The findings on history taking, physical examination, mental assessment and single photon emission tomography in these four patients with dementia and motor neurone disease indicated impaired function of the frontal lobes. Results were in keeping with the subsequent demonstration of predominant anterior hemisphere distribution of pathology in patients Two, Three and Four. Historically, there was progressive personality change and conduct disorder, characterised by disinhibition, impulsivity, apathy and unconcern. Changes in eating habits and sexual behaviour also occurred. Physical examination revealed frontal lobe release phenomena. Psychological assessment indicated a progressive disorder of frontal lobe function, being characterised by an early impairment of use of strategy and abstraction and an increasing tendency to perseveration and stereotypy. The pattern of language impairment also suggested predominant anterior hemisphere dysfunction. Spontaneous speech was impaired to a greater degree than comprehension, which became increasingly concrete with disease progression. Perceptual, spatial and executive abilities were relatively preserved and memory disturbance indicated an impaired strategic use of memory as opposed to the pervasive failure of retention associated with a limbic system disorder.

Other reports of patients with dementia and motor neurone disease, although not explicitly stated, also suggest an anterior hemisphere disorder, which usually became apparent prior to evidence of physical impairment (Salazar et al, 1983; Mitsuyama, 1984). Behavioural disorder is commonly described. One patient falsely insisted he could speak several foreign languages (Allen et al, 1971), another wandered the street inappropriately dressed (Sherratt, 1974) and a further patient developed altered eating habits (Dickson et al, 1986). Reduction in spontaneous speech has been reported to be a common feature in Japanese patients with dementia and motor neurone disease, in whom an absence of apraxia and agnosia has also been noted (Mitsuyama, 1984).

The pattern of psychological breakdown, suggestive of anterior hemisphere dysfunction in patients with dementia and motor neurone disease is distinct from the posterior hemisphere disturbance shown by patients with Alzheimer's disease in whom social graces are preserved until late in the disease (Cummings & Benson, 1983; Neary et al, 1986). In contrast, psychological findings closely resemble those demonstrated by patients with Dementia of Frontal Lobe Type (Gustafson, 1987; Neary et al, 1988; Chapter Two). Electroencephalography is also characteristically normal in this disorder (Neary et al, 1988; Chapter Two). The observation, reported in an independent clinical study of dementia of frontal lobe type (Gustafson, 1987), of fasciculation in two of 20 patients, emphasises the clinical association between this disease and dementia and motor neurone disease.

The appearance of single photon emission tomograms of patients with dementia and motor neurone disease also closely resembles those of patients with Dementia of Frontal Lobe Type (Risberg, 1987; Neary et al,

1988; Chapter Two). Scans from both groups of patients show reduced uptake of tracer in the anterior hemispheres, which contrast with the posterior hemisphere defects characteristic in Alzheimer's disease (Cohen et al, 1986; Sharp et al, 1986; Neary et al, 1987; Johnson et al, 1988).

A putative distinction from Dementia of Frontal Lobe Type is the rate of disease progression. In the four patients described a dramatic deterioration occurred over a 12 month period. Indeed, the total duration of illness was only two years in the three patients who came to necropsy. In a review of 34 Japanese cases the average duration of illness was three years (Morita et al, 1987). This relatively rapid course contrasts with the mean duration of eight years reported in patients with frontal lobe degeneration without motor neurone disease (Gustafson, 1987) and is more akin to the time course in classical motor neurone disease (Hudson, 1981). It is worthy of note however that the mother of patient three died after a dementing illness of 14 years duration. The pattern of her mental change strongly suggests a diagnosis of Dementia of Frontal Lobe Type, but unlike her son she exhibited no signs of motor neurone disease.

The pathological changes were similar in the three patients examined. Macroscopic examination revealed fronto-temporal atophy, particularly affecting the middle and superior gyri of the frontal cortex, whilst dominant features on microscopic examination were of spongiform change (cortical layer II), pyramidal cell loss (cortical layers III and V) and gliosis (cortical layer VI) affecting the fronto-temporal cortex; cell loss and depigmentation of the substantia nigra; and loss of cells from the hypoglossal nuclei and anterior horns of the spinal cord with little pyramidal tract demyelination or gliosis. The pathology is unlikely to

have been caused by ischaemia as the cerebral blood vessels were normal in patients Two and Three and only minimal changes were present in the small vessels of the brain and spinal cord in patient Four. The patients in the present study closely resemble those described in the review of 34 Japanese cases with dementia and motor neurone disease (Morita et al, 1987). In those cases cortical abnormalities were confined to the frontal and anterior temporal gyri. There was spongy change in cortical layers I-III, loss of pyramidal cells and gliosis in cortical layer VI. Degeneration of the substantia nigra was present in 18 patients. As in the current patients, senile plaques, neurofibrillary tangles, Pick cells, Pick bodies and Lewy bodies were absent.

Guamanian patients with dementia, parkinsonism and motor neurone disease (Hirano et al, 1961b) show some pathological similarities with the current three cases but also notable differences. Similar findings include the confinement of cortical atrophy to the frontal and temporal lobes and the presence of severe cell loss, gliosis and depigmentation in the substantia nigra. Notable differences comprise the presence in Guamanian patients of numerous neurofibrillary tangles and granulovacular inclusions in the neurones of the limbic system, hypothalamus and brainstem and severe depigmentation of the locus caeruleus. A further difference between the two groups is that Guamanian patients show predominant parietal lobe abnormalities on positron emission tomography (Peppard et al, 1989), contrasting with the reduced frontal lobe uptake on single photon emission tomography characteristic in the studied patients. The dementia, parkinsonism, motor neurone disease complex found on Guam therefore appears to represent a clinico-pathological syndrome distinct from the studied cases.

Pathological changes in the present cases do however overlap with those described in Dementia of Frontal Lobe Type, (Brun, 1987; Chapter Two) and progressive subcortical gliosis (Verity & Weschler, 1987). Pathological findings reported in Dementia of Frontal Lobe Type (Brun, 1987; Chapter Two) have emphasised the presence of frontal lobe atrophy, characterized by spongiform change, neuronal loss and gliosis of cortical layers I-III, with additional astrocytosis at the grey-white matter boundary in some patients. Anterior parts of temporal, cingulate and insular gyri were similarly affected, although to a lesser degree. The hippocampus and amygdala either showed mild atrophy or were spared. No nigral depigmentation or gliosis was reported. In only one case was there a slight loss of anterior horn cells but no pyramidal tract degeneration.

In a report of two cases of progressive subcortical gliosis (Verity & Weschler, 1987) the frontal and anterior temporal cortex was affected by a variable cortical neuronal loss with extensive gliosis in cortical layer VI and in the associated white matter. There was also some superficial spongiosus. Gliosis was also present within the subiculum of the hippocampus. The substantia nigra showed minimal neuronal loss in one case but no gliosis. The spinal cord was essentially normal.

Thus, the pathological changes in the frontal lobes in the present three cases mirror closely those of Japanese patients with dementia and motor neurone disease (Morita et al, 1987). The changes in addition share features of Dementia of Frontal Lobe Type with respect to cortical layers I-III (Brun, 1987; Chapter Two), although the deeper cortical gliosis would be more in keeping with progressive subcortical gliosis (Verity & Weschler, 1987). However, in neither Dementia of Frontal Lobe

Type nor in progressive subcortical gliosis does nigral cell loss and gliosis appear prominent, nor are those conditions associated with significant spinal cord pathology as in the three patients described. The difference in topographical distribution and severity of pathology may reflect the more rapid course of disease to death in patients with dementia with motor neurone disease.

It is of interest that despite the severe nigral changes patients did not exhibit notable extrapyramidal signs. It is possible that the early death of patients preempted the emergence of such signs. However, the severe gliosis seen in the nigra also occurred within the frontal cortex, nucleus accumbens, subiculum and amygdala. These changes may therefore represent degeneration within mesocortical and mesolimbic pathways, contributing to the mental changes as opposed to nigro-striatal degeneration leading to extrapyramidal signs. It is worthy of note that unlike in Alzheimer's disease the nucleus basalis, the locus caeruleus and dorsal raphe were all well preserved.

There is much controversy concerning the nosological status of cases of dementia and motor neurone disease. As Jakob, in 1921, described this association in one of three patients (Jakob, 1977), the syndrome of dementia and motor neurone disease was for many years considered a subgroup, the amyotrophic variant, of Jakob-Creutzfeldt disease. A number of patients have been and still are classified in this way (Allen et al, 1974; Sherratt, 1974; Neumann & Cohn, 1987). However, other authors have suggested that the association with Jakob-Creutzfeldt disease may be inappropriate because of the absence of the typical intracellular spongiform change and failure to transmit the condition to primates (Salazar et al, 1983). More recently, however positive transmission has

been reported in a single case (Connolly et al, 1988). In the four patients described in the present study the normal electroencephalogram, absence of myoclonus and circumscribed 'frontal lobe' clinical picture contrast sharply with the strikingly abnormal electroencephalogram, conspicuous myoclonus and widespread cognitive impairment characteristic of classical Jakob-Creutzfeldt disease (Mathews, 1985). Moreover, the superficial extracellular spongiosus and striking degeneration of the substantia nigra found in this and another study (Morita et al, 1987) have not been reported in patients with transmissible subacute spongiform encephalopathy (Salazar et al, 1983).

Whereas some authors suggest that the condition represents a new distinct entity (Mitsuyama, 1984; Morita et al, 1987), there is agreement amongst others that it is a variant of motor neurone disease (Hudson, 1981; Salazar et al, 1983). The pathological changes of the three patients described within the spinal cord, hypoglossal nuclei and motor cortex are indeed consistent with motor neurone disease. However, the severity of pyramidal changes is mild and less than would be expected at necropsy. The relative mildness of the changes may reflect the short span of physical symptoms exhibited by the patients. The presence of large eosinophilic inclusions within surviving anterior horn cells in patients Two and Four is similar to that described by others in motor neurone disease without dementia (Leigh et al, 1988). The relative brunt of disease on the anterior horn cells as opposed to the motor cortex and descending motor pathways is also described in the Japenese studies (Mitsuyama, 1984; Morita et al, 1987).

An association with motor neurone disease is supported clinically by the finding in patients with classical motor neurone disease who have no

mental symptoms, of specific mental difficulties in carrying out cognitive tasks sensitive to frontal lobe dysfunction (David & Gillam, 1986). Other authors have suggested an association with Pick's disease (Brion et al, 1973; Dickson et al, 1986), although in neither the present cases nor in the large series of Japanese cases (Morita, 1987) have the ballooned cells and inclusions pathognomonic of Pick's disease been demonstrated. The clinical and pathological findings in this study point to an association between dementia with motor neurone disease and Dementia of Frontal Lobe Type, suggesting that genetic factors may be important in the pathogenesis and expression of the disease. Dementia of Frontal Lobe Type is known to be a strongly familial disorder, with the incidence of dementia in a first degree relative being reported as 50% and 46% in two independent studies (Gustafson, 1987; Neary et al, 1988).

Whilst neurological and electrophysiological findings in patients with dementia and motor neurone disease appear similar to those of classical motor neurone disease, the pattern of dementia and nature of pathological change resemble those of Dementia of Frontal Lobe Type. The condition may be considered to represent an interface between non-Alzheimer frontal lobe dementia and motor neurone disease. Electrophysiological studies of patients with Dementia of Frontal Lobe Type and the psychological assessment and brain imaging of patients with motor neurone disease might identify subclinical or presymptomatic changes which would help to clarify the nature of the association between the two conditions.

3.4. CONCLUSIONS

In each of four patients with dementia and motor neurone disease the pattern of mental impairment, findings on physical examination and regions of reduced tracer uptake on single photon emission tomography indicated a disorder of the anterior cerebral hemispheres. Subsequent pathological examination in three patients confirmed that cerebral cortical abnormalities were confined to the frontal and anterior temporal lobes. Histological findings were of large cell loss, spongiosus and gliosis in the fronto-temporal cortex, depigmentation, cell loss and gliosis in the substantia nigra and loss of anterior horn cells with relative preservation of the pyramidal tract in the motor system.

The pattern of mental impairment, appearance on single photon emission tomography and necropsy findings in patients with dementia and motor neurone disease closely resemble those in Dementia of Frontal Lobe Type but are distinct from those found in Alzheimer's disease. Findings suggest a relationship between motor neurone disease and Dementia of Frontal Lobe Type.

CHAPTER FOUR PROGRESSIVE APHASIA WITH RIGHT-SIDED EXTRAPYRAMIDAL SIGNS

4.1. INTRODUCTION

In 1982, Mesulam described six patients with primary cerebral atrophy who developed progressive linguistic disturbance without generalised intellectual impairment over a seven year period. He labelled the syndrome 'slowly progressive aphasia without generalised dementia' and suggested that it may represent a localised degeneration of the left perisylvian region. Since this description a number of similar patients have been identified (Wechsler et al, 1982; Heath et al, 1983; Kirshner et al, 1984; Holland et al, 1985; Taboada et al, 1986; Kirshner et al, 1987). Indeed, it has been suggested that the composer, Maurice Ravel, was affected (Henson, 1988). Focal hypometabolism has been demonstrated in the left perisylvian region with positron emission tomography (Chawluk et al, 1986) and pathological examination has shown non-Alzheimer histological change, which predominantly affects this locus (Wechsler et al, 1982; Holland et al, 1985; Taboada et al, 1986; Kirshner et al, 1987), thus confirming Mesulam's original hypothesis.

During the course of the present study, a patient presented with a similar progressive disorder of language without apparent involvement of other intellectual abilities. Interestingly, he had in addition developed right-sided tremor and rigidity. This combination of clinical features has not been previously reported and appears to represent another mode of presentation of this localised cerebral atrophy. The results of investigation of this patient are presented in this chapter (For Methodology see Chapter Two and Appendices One and Two).

4.2. CASE REPORT

A 64 year old right handed male presented with an 18 month history of insidiously progressive deterioration in his language together with a tremor of the right hand. He had been previously well and there was no history of vascular disease or head injury. His mother, who died at the age of 83, was said to have had Parkinson's disease and became 'confused and wandering' late in life.

Physical Examination

He was normotensive and general examination revealed no evidence of vascular disease. Visual fields were intact. Eye movements were abnormal with reduced voluntary upward gaze and impaired convergence. He had an expressionless facies and slight right sided facial asymmetry. Tone was minimally increased on the right and there was a resting tremor of the right hand. Reflexes were symmetrically brisk and plantar responses flexor. Sensory testing, dexterity and gait were normal.

Mental Examination

Assessment revealed a selective language disorder. His spontaneous speech was non-fluent, stuttering and effortful with word finding difficulty and the occasional intrusion of literal and verbal paraphasias. Comprehension was mildly impaired. Repetition of non-words and complex sentences was defective. Confrontation naming was within normal limits. He could read aloud and understand single words, but misread complete phrases and sentences. His writing although conveying the sense adequately, contained spelling errors and was telegrammatic in style. He could perform written three-digit additions and two-digit subtractions.

In contrast to his impaired linguistic ability, praxis, perception, spatial abilities, and non-verbal memory were preserved. His personality was unchanged and his social conduct was appropriate. He could communicate by gesture and pantomime. He identified line drawings, fragmented pictures and photographs of celebrities and correctly interpreted pictorial scenes. Logical reasoning was intact as measured by his ability to order pictures appropriately to illustrate a story. He drew a bicycle and a clock face normally and copied line drawings

accurately. He could manipulate objects and trace a maze. He was not clinically amnesic. He could recall day to day and current news events. Whilst his score on a word recognition test was at chance level, performance on a picture recognition test was error free.

Investigations

X-ray computed tomography revealed widening of the left sylvian fissure and prominence of the left lateral ventricle. Otherwise, investigations including electroencephalography and carotid angiography were normal.

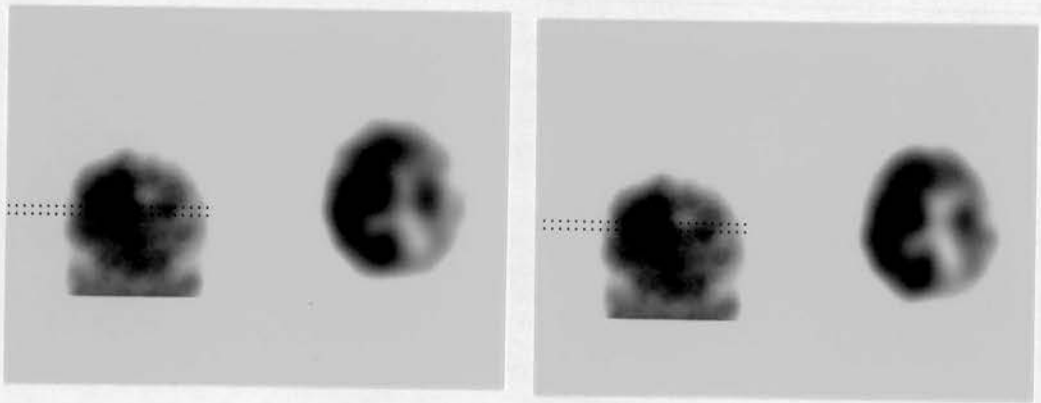
Progression

Two years later he had deteriorated both physically and in his powers of communication. He retained insight into his language problems and became easily upset.

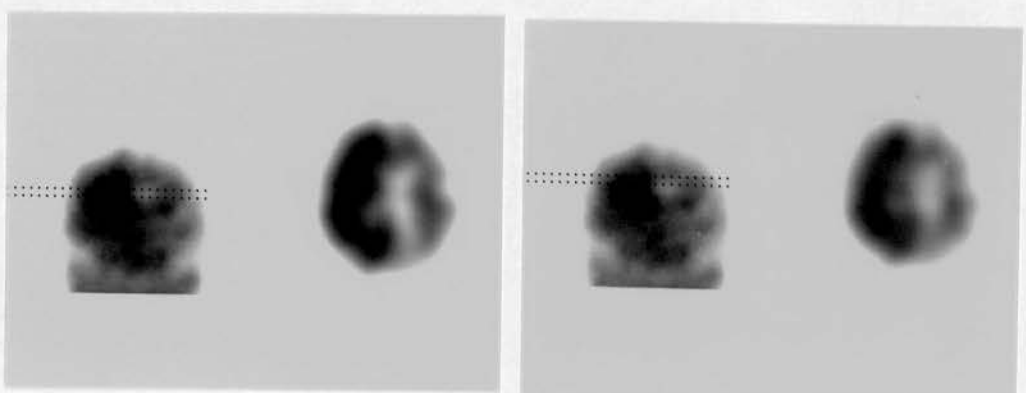
Neurological examination revealed emotional lability, increase in tremor of his right hand, moderate right-sided hypertonia and bradykinesia. He dragged his right leg when walking.

His spontaneous speech was by now limited to "yes", "no" and infrequent stereotyped phrases. Occasional neologisms occurred. Comprehension had deteriorated although he could follow elementary commands. Repetition was limited to two words. He was severely anomic. He could no longer sign his name. He had difficulty communicating by gesture or pantomime. Perceptual and spatial abilities remained well preserved. He could still recognise line drawings of objects and photographs of celebrities, invariably selecting the correct name from alternatives. He located towns on a map and interpreted absurdities in pictures by pointing to irrelevant parts. He could copy non-representational hand postures and his drawings showed preserved spatial relationships. Although memory could not be formally tested his wife believed that he could recall day to day events.

Single photon emission tomography performed at that time demonstrated a striking reduction in uptake in the left frontal, temporal and parietal regions and in the left subcortical grey matter, whilst right hemisphere uptake was normal (Figure 4.1).



A B



C D

Figure 4.1.

99mTc-HMPAO scan from patient with progressive aphasia. There is striking reduction of tracer uptake involving the left cerebral cortex, apart from the occipital region, and the left subcortical grey matter.

A year later, five years after onset of symptoms, a mild right-sided pyramidal weakness had developed in addition to the extrapyramidal signs. Tendon jerks on the right were brisk and the right plantar response equivocal. He had a right-sided grasp reflex, with pout and sucking reflexes.

Speech was limited to arbitrary production of "yes" and "no" and comprehension to following midline commands. Perception and spatial abilities again appeared preserved in that he negotiated his environment without becoming lost, and recognised objects, oriented and used them appropriately. He was still able to arrange pictures in sequence. Performance was normal on a forced choice recognition test suggesting at least some preservation of visual memory. His personality was unchanged and he continued to show initiative in daily activities.

X-ray computed tomography was repeated and demonstrated increased cerebral atrophy and ventricular dilatation on the left, with the addition of mild right sided involutional changes (Figure 4.2).

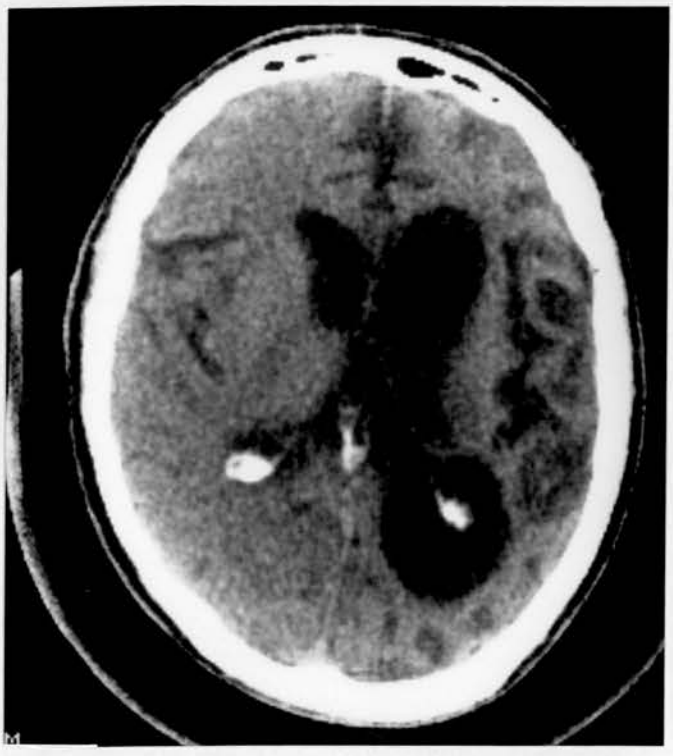


Figure 4.2.
X-ray computed tomogram. The left hemisphere is on the right.

4.3. DISCUSSION

The patient exhibits a fascinating clinical disorder, in which a progressive disorder of language together with right sided tremor, rigidity and bradykinesia is associated with selective left hemisphere abnormality on single photon emission tomography. There are strong grounds for assuming that the patient has a form of primary cerebral atrophy. There has been a slow progressive development of neurological signs in the complete absence of stroke-like episodes and without risk factors for vascular disease. Cerebral angiography has excluded large vessel disease and the possibility that emboli from the heart or small vessel disease would produce such a striking, predominant involvement of the left cerebral hemisphere is unlikely. Computed tomography showed no low density lesions to suggest cerebral infarction. The electroencephalogram was normal whereas in vascular dementia focal slowing is usual (Roberts et al, 1978).

It is unlikely that this patient suffers from Alzheimer's disease. The presence of progressive and selective language disorder in the absence of other cognitive deficits is distinct from the characteristic picture of Alzheimer dementia, in which language disorder is combined with profound amnesia and perceptuospatial impairment ((Neary et al, 1986). Whilst Alzheimer's disease may present with language disorder (Pogacar & Williams, 1984), other cognitive deficits emerge. Moreover, the normal electroencephalogram and strikingly asymmetric X-ray computed tomogram contrast with the significant slowing of wave forms on electroencephalography (Johannesson et al, 1979) and the either normal or generalised atrophic scan appearances (McGeer, 1986), reported in Alzheimer's disease. Reduced tracer uptake in the temporo-parietal

regions in Alzheimer's disease has been consistently demonstrated by positron emission tomography (Foster et al, 1984; Duara et al, 1986) and single photon emission tomography (Neary et al, 1987; Johnson et al, 1988; Chapter Two). Whilst the left hemisphere may be predominantly affected in patients with disproportionate language disorder (Foster et al, 1983), abnormalities are not exclusively unilateral. In the present case, abnormalities appear to involve virtually the entire left hemisphere, with the exception of the occipital areas, whilst right hemisphere uptake is normal.

This patient closely resembles cases of slowly progressive aphasia without generalised dementia (Mesulum, 1982, Chawluk et al, 1986), one of whom also developed a right hemiparesis (Taboada, et al, 1986). Left temporal and parietal hypometabolism found by positron emission tomography (Chawluk et al, 1986) is consistent with the reduced left hemisphere tracer uptake demonstrated by single photon emission tomography in the present case. Although an association has been reported between progressive aphasia and extrapyramidal features (Morris et al, 1984), unlike the present case, this was in the context of more widespread cognitive changes, indicating bilateral affection. Occasionally extrapyramidal disorder has occurred in combination with fronto-temporal atrophy (Tissot et al, 1985), but more commonly with additional clinical features of motor neurone disease (Hudson, 1981; Salazar et al, 1983).

A spectrum of pathological change has been demonstrated in slowly progressive aphasia without generalised dementia. Common to all patients has been cell loss and gliosis, predominantly affecting the left perisylvian cortex, and gliosis of the adjacent white matter (Wechsler et

al, 1982; Holland et al, 1985; Taboada et al, 1986; Kirshner et al, 1987). Some authors have commented on additional cortical spongiform change (Wechsler et al, 1982; Kirshner et al, 1987), whilst others have identified swollen cells and argyrophilic inclusions, characteristic of Pick's disease (Wechsler et al, 1982; Holland et al, 1985). Degenerative change in subcortical structures has been indicated in two reports. One described cell loss and gliosis in the caudate nucleus and substantia nigra (Taboada et al, 1986) and the other the presence of Pick bodies in the thalamus and substantia nigra (Holland et al, 1985).

The pathological changes described in slowly progressive aphasia without generalised dementia are similar to those reported in other localised cerebral atrophies. Focal cortical cell loss, gliosis and spongiform change have been described in patients with Dementia of Frontal Lobe Type (Brun, 1987; Chapter Two) and in those with progressive subcortical gliosis (Verity & Wechsler, 1987). In cases of frontal lobe dementia with extrapyramidal signs and/or clinical features of motor neurone disease there has been additional involvement of the corpus striatum, substantia nigra and/or anterior horn cells and corticospinal tracts (Hudson, 1981; Salazar et al, 1983; Morita, 1987; Chapter Three).

These findings suggest that types of localised cerebral atrophy may possibly be related and that the spectrum of clinical manifestations may be determined by the topographical distribution of pathological change. The possible relationship between localised frontal lobe atrophy and motor neurone disease has already been discussed in the previous chapter of this thesis. One case of progressive aphasia without generalised dementia who in addition developed signs of motor neurone disease has

also been reported (Kirshner et al, 1987). The case described in this chapter is an example of a predominantly left hemisphere degeneration presumably involving primarily the perisylvian regions and subcortex.

4.4. CONCLUSION

It is suggested that the clinical syndrome in this patient, of progressive aphasia with right-sided extrapyramidal signs, represents one of a spectrum of possible manifestations of localised cerebral atrophy all of which may share a similar pathological basis, the anatomical distribution of which determines the clinical presentation.

CHAPTER FIVE QUANTIFICATION OF DATA AND INITIAL FOLLOW-UP STUDIES

5.1. INTRODUCTION

The previous studies in this thesis have shown that single photon emission tomography using a rotating gamma is a useful tool in the investigation and diagnosis of patients with dementia due to primary cerebral atrophy. In Alzheimer's disease, Dementia of Frontal Lobe Type, dementia with motor neurone disease and progressive aphasia without dementia there was a strong correlation between visually apparent areas of reduced tracer uptake on single photon emission tomography and regions of impaired cerebral function predicted by psychological assessment. Reported areas of reduced uptake were also in keeping with the distribution of pathology reported in each disease (Brun & Englund, 1981: Brun, 1987; Morita et al, 1987; Kirshner et al, 1987). Despite the proven value of qualitative visual assessment in diagnosis, this technique is less useful in the measurement of change in tracer uptake when patients are rescanned over a period of years. Such information may be valuable for the study of rate of deterioration of regional cerebral perfusion in types of dementia due to primary cerebral atrophy and in the assessment of its possible improvement related to therapeutic intervention.

A method of quantifying tracer uptake is likely to be more suitable for this purpose. Calculation of an absolute value for regional tracer uptake is fraught with difficulty because of both limited knowledge concerning the mode of uptake of 99mTc-HMPAO and the large amount of data processing necessary during filtering, back-projection and attenuation correction (Britton, 1982). Relative quantification is

however widely used. Uptake in an area of interest is compared with that in a reference region considered to be normal. Several techniques have been used, including a number of computerised, relatively operator independent methods (Burjan et al, 1988; Spreafico et al, 1988) which appear to have the potential for both speed and reproducibility.

This chapter describes the preliminary assessment of a new, semi-automatic method of quantification. In order to determine the sensitivity of the technique, it was initially used to measure regional cerebral uptake of 99mTc-HMPAO on previously visually reported single photon emission tomograms of normal controls, and patients with three types of dementia due to primary cerebral atrophy. In the second part of the study the suitability of the technique for detecting change in tracer uptake over time was assessed by comparing initial and repeat scans which were carried out on patients followed up over a period of at least one year.

5.2. PATIENTS

The study group consisted of consecutive referrals satisfying inclusion criteria for Alzheimer's disease, Dementia of Frontal Lobe Type and dementia with motor neurone disease (Chapters Two and Three). Five volunteers in whom there was no complaint of mental impairment acted as controls. The age and sex of patients and controls and the length of history of illness in each patient group are shown in table 5.1. There was no significant difference between the ages of patients and controls (unpaired t-tests). The relatively short length of history in patients with dementia and motor neurone disease reflects the rapid progression of disease in these patients (Chapter Three).

TABLE 5.1 DESCRIPTION OF SUBJECTS

	M:F	MEAN AGE (RANGE) (YEARS)		MEAN LENGTH OF HISTORY (YEARS)	(RANGE)
CONTROLS	1:4	54	44-60		
AD	4:10	62	58-70	5	1-10
DFT	8:6	60	48-74	4	1-7
D-MND	4:0	51	45-58	2	1-2

AD = Alzheimer's disease; DFT = Dementia of Frontal Lobe Type;
D-MND = dementia with motor neurone disease.

Five patients with Alzheimer's disease and four with Dementia of Frontal Lobe Type had repeat scans after a mean interval of 22 months (range 16-31).

5.3. METHODS

Single photon emission tomography was performed as previously described (Appendix Two). Two contiguous midventricular transaxial sections were examined from each subject, because experience gained from a previous study (Neary et al, 1987) had suggested that these sections were particularly useful for distinguishing patients with Alzheimer's disease from those with Dementia of Frontal Lobe Type. The operator

dependent part of the analysis was confined to the definition, by means of a joystick manoeuvred cross, of anterior, posterior and both lateral margins of the cortical rim (Figure 5.1).

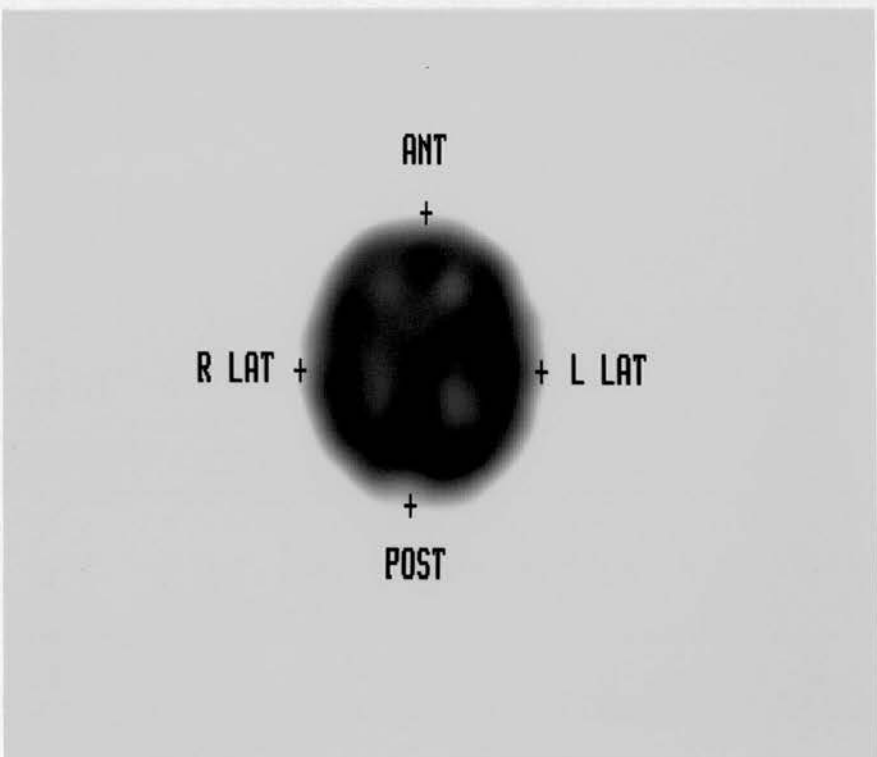


Figure 5.1.

The anterior, posterior and both lateral margins of the cortical rim are defined by means of a joystick manoeuvred cross.

The remainder of the analysis was carried out by the computer according to a predefined sequence. The four margins of the cortical rim were joined together so as to form an ellipse and pixels within the ellipse were described in polar coordinates. The data were then transformed by splitting the transaxial section from the centre to the posterior cortical margin and unfolding the image to form a rectangular array with the cortex uppermost and the centre of the image stretched along the base (Figure 5.2).

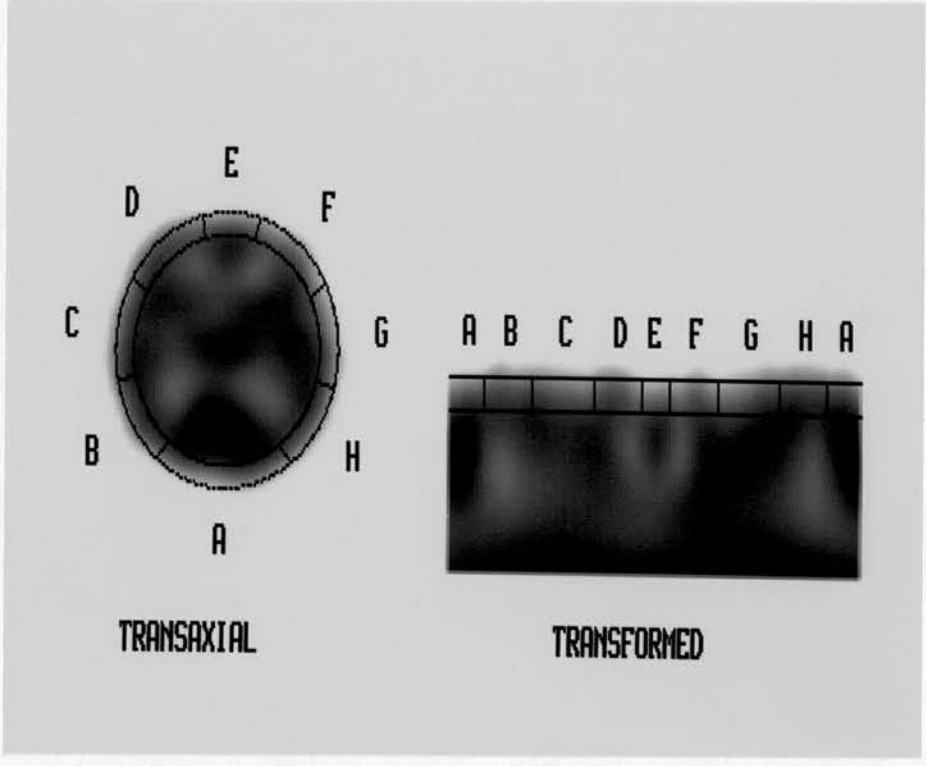


Figure 5.2

Transformation of transaxial section and position of predefined cortical areas of interest. Region A is occipital and the right hemisphere is on the left. For key to regions see table 5.2.

Eight contiguous cortical regions of interest (A-H) were then automatically defined, with respect to predetermined angular dimensions measured from the centre of the ellipse. The angular size of the occipital region (A) was such that it enclosed the area of high occipital uptake seen on the images of controls. A small middle anterior region (E) was included to assess uptake in the area where the two medial frontal cortices are closely opposed. The left and right anterior (F and D) and posterior (H and B) cortical regions were of equal, angular size and the left and right middle cortical regions (G and C) slightly larger. The depth of each region was set at one fifth of the distance between the margin and the centre of the ellipse as this appeared to correlate with the thickness of the rim of cortical uptake seen on the images of normal controls. This depth was of at least five pixels thickness (equivalent to 21 millimetres). Counts per pixel in each region were normalised to those in the occipital region (A). The analysis was repeated by each of three operators.

Statistical analysis was performed as follows. Differences between the transaxial sections, operators and patient groups for each region of interest were assessed by a three way analysis of variance. Differences in regional uptake between normals and each type of degenerative dementia were calculated by unpaired t-tests. Initial and two year follow up images were compared using paired t-tests.

5.4. RESULTS

i). Anaysis of patient groups

Although the identification of the margins of the cortical rim required meticulous care, the overall time required for the analysis was short, taking less than five minutes for each transaxial section.

There was no significant difference between the two transaxial sections with respect to measurements of relative regional uptake. The median variation between each region made up only 5% (range 0.2-22%) of the total variation. In spite of the attempt to restrict operator dependent steps to a minimum, a consistent interoperator variation was detected. This was significant for all cortical regions ($p < 0.05$).

The mean uptake for each cortical region relative to the occipital cortex for normal controls and for each of the three types of degenerative dementia is shown in table 5.2.

TABLE 5.2. NORMALISED REGIONAL UPTAKE OF TRACER

REGION	CONTROLS (n=5)		AD (n=14)		DFT (n=14)		D-MND (n=4)	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
B RIGHT POSTERIOR	94	9	86*	9	93	7	96	8
C RIGHT MIDDLE	92	8	93	10	85	10	84	11
D RIGHT ANTERIOR	94	14	94	11	79*	10	76*	18
E MID-ANTERIOR	97	15	97	12	73*	13	75*	18
F LEFT ANTERIOR	90	11	96	10	74*	11	74*	17
G LEFT MIDDLE	92	7	96	9	85*	8	84*	8
H LEFT POSTERIOR	96	8	89*	11	94	9	95	7

Region A OCCIPITAL = 100.

Data for single operator. * significant $p < 0.05$

In the normal subjects, uptake in all other cortical regions was less than that in the occipital region (A), reflecting high activity in the visual cortex. Uptake in both posterior cortical regions (B and H), although not in other regions was significantly lower in patients with Alzheimer's disease than in normal subjects ($p < 0.05$). In contrast, in both patients with Dementia of Frontal Lobe Type and those with dementia with motor neurone disease uptake was significantly lower ($p <$

0.05) than in normal subjects in all anterior cortical regions (D to F) and the left middle cortical region (G) but not in the right middle (C) or both posterior regions (B and H). This pattern of results was reproducible across different operators provided that the same operator analysed the images from both patients and controls. In the absence of the same operator, interoperator variation took effect and the only consistent areas of reduced uptake, at the 5% level of significance, were the right posterior region (B) in patients with Alzheimer's disease and the mid-anterior region (E) in patients with Dementia of Frontal Lobe Type.

As can be seen from Table 5.2, level of uptake in a particular cortical region did not completely separate patients from controls. There was some overlap in measurements even in those regions where relative uptake in patient groups was calculated to be significantly reduced.

ii Follow up studies

Mean regional uptake in initial and follow-up images, and respective paired t-values for patients with Alzheimer's disease and Dementia of Frontal Lobe Type are shown in Table 5.3. In Alzheimer patients, uptake had decreased over time in all cortical regions apart from the right posterior region (B) and was significantly lower ($p < 0.01$) in the mid-anterior, left anterior and left posterior regions (E, F and H). In patients with Dementia of Frontal Lobe Type, uptake had decreased in all regions apart from the right anterior region (D) and had reduced significantly ($p < 0.01$) in the left middle, left posterior and right posterior regions (B, G and H). The aforementioned areas of reduced uptake were identified by all three operators in patients with

Alzheimer's disease ($p < 0.05$) and by two of three operators in patients with Dementia of Frontal Lobe Type ($p < 0.05$), provided that the same operator analysed both initial and repeat scans. However, if different operators analysed the pairs of images non-significant results were often a feature.

TABLE 5.3 FOLLOW-UP STUDIES

REGION	AD (n=5) INITIAL MEAN	AD (n=5) FOLLOW-UP MEAN	AD (n=5) PAIRED T-VALUE	DFT (n=4) INITIAL MEAN	DFT (n=4) FOLLOW-UP MEAN	DFT (n=4) PAIRED T-VALUE
B RIGHT POSTERIOR	84.5	85.3	0.52	91.3	87.6	4.16#
C RIGHT MIDDLE	90.2	89.1	0.67	81.9	80.6	0.86
D RIGHT ANTERIOR	91.8	89.2	1.43	75.6	76.5	0.88
E MID-ANTERIOR	94.0	88.4	3.03*	77.4	74.5	2.28
F LEFT ANTERIOR	90.1	81.5	5.32#	79.1	77.3	1.52
G LEFT MIDDLE	89.3	86.0	2.08	86.7	80.8	3.63*
H LEFT POSTERIOR	89.6	80.4	4.06#	97.3	89.8	4.74#

* significant $p < 0.01$. # significant $p < 0.001$.

Although anterior cortical uptake had decreased significantly over time in patients with Alzheimer's disease, comparison of follow-up images with scans from normal subjects showed that significant ($p < 0.05$) areas of reduced uptake remained confined to the posterior cortical regions (regions B and H). A similar comparison in patients with Dementia of Frontal Lobe Type showed that uptake in all cortical regions had become significantly reduced ($p < 0.01$) compared with control subjects although severity of reduced uptake remained greatest in the anterior regions.

5.5. DISCUSSION

The method of quantification used in this study identified areas of reduced uptake which distinguished the images of patients with three types of dementia due to primary cerebral atrophy from those of normal controls. The specific areas of reduced uptake identified by quantification were identical to those previously reported by qualitative visual analysis in each disease (Chapters Two and Three). These findings suggest that the quantitative technique is sensitive and a valid measure of reduced uptake. The overlap in relative uptake observed between patients and controls reflects the spectrum of disease severity in each of the three groups of demented patients and is in keeping with the finding that mildly affected individuals with Alzheimer's disease may have scans which are qualitatively normal (Neary et al, 1987). A possible disadvantage of the current technique is that it fails to sample medial temporal structures which may show tracer abnormalities in early Alzheimer's disease (Burns et al, 1989).

The results from follow-up studies suggest that the technique may be of use in monitoring progression of disease in types of primary degenerative dementia. Comparison of original and follow-up images revealed that uptake had decreased significantly in the mid-anterior, left anterior and left posterior cortical regions in patients with Alzheimer's disease and in the left middle, left posterior and right posterior cortical regions in those with Dementia of Frontal Lobe Type. Although the numbers of patients are as yet small these results are in keeping with the natural history of each disease. In Alzheimer's disease, both severity of frontal cortical hypometabolism and of frontal lobe degenerative change increase with disease progression, whereas temporoparietal changes characterize early disease (Frackowiak et al, 1981; Brun & Englund, 1981). In Dementia of Frontal Lobe Type, abnormalities of language commonly emerge with disease progression (Gustafson, 1987; Neary et al, 1988; Chapter Two), suggesting that the degenerative process may extend predominantly into the left hemisphere in the later stages.

The technique permits quantification to be simply and rapidly performed. After careful identification of the margins of the cortical rim the remainder of the analysis is carried out automatically, adding little extra time to that necessary for reconstruction and photography of transaxial tomographic sections. In contrast, traditional manual construction and placement of multiple regions of interest (Sharp et al, 1986; Jagust et al, 1987; Johnson et al, 1987; 1988), is dependent on several manoeuvres being performed by the operator and takes considerably longer, possibly precluding its use as a routine method of analysis.

A series of cortical areas of interest were used in the current study because in all three types of dementia examined the pattern of mental change suggests impaired function of the cerebral cortex as opposed to the subcortex (Cummings & Benson, 1983). Furthermore, pathology has been shown to affect predominantly particular cortical regions in each disease, the temporo-parietal cortex in Alzheimer's disease (Brun & Englund, 1981) and the frontal and anterior temporal cortex in Dementia of Frontal Lobe Type and dementia with motor neurone disease (Brun, 1987; Morita et al, 1987). A number of other studies of primary degenerative dementia have also used cortical regions of interest (Johnson et al, 1987; Jagust et al, 1987; Risberg, 1987; Johnson, 1988), although others have examined regions of interest which included data from the subcortex and ventricles as well as from the cerebral cortex (Sharp et al, 1986; Spreafico et al, 1988), possibly diminishing the likelihood of detection of abnormalities in regional cortical uptake.

The occipital region was used as the reference area; first, because the occipital cortex is relatively spared in the three diseases studied (Brun & Englund, 1981; Brun, 1987; Morita et al, 1987) and second, because this area of the brain was represented in each of the two midventricular sections studied, obviating the need to examine additional sections. Other authorities have used different reference areas. These have included the whole transaxial slice (Jagust et al, 1987) and the cerebellum (Johnson et al, 1987; 1988). Both appear to have disadvantages. The whole transaxial slice must include data from potentially abnormal areas of cerebral cortex and therefore appears inherently unsuitable as a normal reference area. Although the cerebellum is pathologically spared in the three diseases studied, uptake is

unlikely to be normal as cerebellar function is highly dependent on that in the opposite cerebral hemisphere, due to the phenomenon of crossed cerebellar diaschisis. Indeed, uptake in a cerebellar hemisphere has been shown to fall by as much as 15% during anaesthesia of the opposite cerebral hemisphere (Biersack et al, 1987).

The current method of analysis appears to have little potential for observer bias. The regions of interest are created automatically following identification of the margins of the cortical rim. Furthermore, as the regions are contiguous the whole of the cerebral cortex in a particular transaxial section is sampled. Manual placement of areas of interest appears to be less objective. Such areas are likely to be placed over visually apparent areas of reduced tracer uptake rather than on standardised brain regions. Moreover, previous studies have not arranged regions of interest so as to examine cortical uptake throughout the whole transaxial section.

The overall results, with regard to patients versus controls and to initial versus follow-up investigations, were reproducible across different operators, provided that the same operator analysed the images under comparison. However, if studies were analysed by different operators many results became non-significant, indicating a degree of operator variation. This occurred despite the attempt to keep operator dependent steps to a minimum. Variation appeared to be largely due to the sensitivity of the technique to the position of the occipital region of interest. As this region was used as the reference area, slight misplacement of the occipital margin of the cortical rim, gave rise not only to errors of measurement in the occipital region but also in other regions. However, as this error affected all regions to a similar degree,

relationships between regions were relatively undisturbed. Modification of the current technique by use of thresholding to identify more precisely the cortical rim may reduce inconsistencies in the position of the occipital region of interest. The presence of interoperator variation in this semi-automatic technique emphasises the need for methods of quantification to be standardised. Traditional forms of analysis which are highly operator dependent are likely to be subject to still higher degrees of operator variability.

The present technique was subject to a degree of inaccuracy due to the partial volume effect. This is the phenomenon by which contrast is lost when imaging objects (volumes of reduced uptake) smaller than the resolution of the system. For optimal accuracy of quantification it is necessary to use volumes of side length greater than twice the resolution at FWHM (Todd-Pokropek & Jarritt, 1982). This would correspond to at least seven pixels with the current system. The depth of the cortical regions of interest were often less than this optimal side length because of the desire to confine regions to the observed thickness of cerebral cortical uptake. Errors also may have occurred in the vertical plane because despite the study of two contiguous transaxial sections total thickness was only four pixels.

5.6. CONCLUSION

This preliminary assessment suggests that the method of quantification described may be a useful adjunct to qualitative visual assessment of single photon emission tomographs of patients with dementia due to primary cerebral atrophy. Modification of the method by which the margins of the cortical rim are identified may reduce the

variability of measurements observed between operators. Analysis of follow-up images from a larger number of patients is necessary.

CHAPTER SIX CONCLUSIONS

The application of single photon emission tomography to the diagnostic assessment of cerebral atrophy has led to a number of interesting and original findings. The syndrome of Dementia of Frontal Lobe Type has been defined and its association with motor neurone disease observed. Dementia of Frontal Lobe Type has been shown to differ from Alzheimer's disease across a range of clinical, demographic and investigative parameters. Lobar atrophy of the dominant hemisphere and adjacent subcortical grey matter has been depicted as the cause of progressive aphasia with unilateral extrapyramidal signs in one patient. The primary qualitative information gleaned from single photon emission tomography has been enlarged upon by the development of a semi-automatic method of quantification.

The findings of the studies presented in this thesis have important implications for the understanding of the concept of dementia. It has been shown in both Dementia of Frontal Lobe Type and in Alzheimer's disease that patients manifest distinct patterns of abnormality on single photon emission tomography which correlate closely with the areas of impaired cerebral function predicted by psychological assessment. Both have been shown to relate to the characteristic distribution of pathology in patients coming to necropsy. It can therefore be seen, as has been suggested elsewhere (Sagar & Sullivan, 1988), that the manifestations of 'dementia' are peculiar to the topography of brain disease and that terms such as 'global dementia' (Lishman, 1987) and definitions of dementia based on arbitrary

combinations of symptoms and signs (American Psychiatric Association, 1980; Cummings et al, 1980) can be dismissed.

How then should single photon emission tomography be used in the investigation of patients with dementia due to primary cerebral atrophy? Its major application would appear to be as an aid to diagnosis and classification. It provides information about the distribution of impaired cerebral function which is independent but often complementary to that obtained by clinical assessment. Thus Alzheimer's disease can be distinguished from forms of lobar atrophy, in paticular from Dementia of Frontal Lobe Type. Precise diagnosis of cerebral atrophy is a prerequisite for clinical management, prognosis of disease, genetic counselling and the selection of patients for theraputic trials. Unfortunately, at present, DSM III (American Psychiatric Association, 1980) and other standard diagnostic criteria for Alzheimer's disease (McKhann et al, 1984) are largely based on the exclusion of forms of secondary dementia and do not distinguish other cortical degenerations, including Dementia of Frontal Lobe Type. Thus a significant proportion of 'Alzheimer study groups' are likely to include patients with other forms of cerebral atrophy. The present study suggests that strict inclusion criteria for type of cerebral atrophy, encompassing both areas of reduced uptake on single photon emission tomography and pattern of mental impairment will be necessary to increase the likelihood that patients conform to a single diagnosis.

The preliminary assessment of a new, semi-automatic method of quantification of relative tracer uptake (Chapter Five) suggests that with certain modifications the technique may be of use as a measure of

the rate of deterioration in both Alzheimer's disease and Dementia of Frontal Lobe Type. Such a measure would be a valuable addition to clinical examination in trials designed to assess the efficacy of types of treatment in these two diseases. Follow-up scans on a larger number of patients and comparisons between emerging areas of reduced uptake and neuropsychological deficits are necessary to confirm the usefulness of the technique.

The high incidence of affected first degree relatives in patients with Dementia of Frontal Lobe Type strongly suggests that in many families the disorder has an autosomal dominant inheritance. Thus, the possibility exists for the identification of a genetic marker for the disease. Such a finding may allow predictive testing for Dementia of Frontal Lobe Type as has recently been possible in Huntington's chorea (Harper, 1986). Unfortunately, genetic studies in Dementia of Frontal Lobe Type are likely to be more difficult because of the relatively late age of patients at disease onset. Patients may die of unrelated illnesses prior to development of the symptoms of Dementia of Frontal Lobe Type, making it unlikely that many individuals from the same family will be available for examination. Nevertheless, potentially informative families of the current patients are presently being investigated.

There were few problems with the current method for performing single photon emission tomography. The tracer, being Technetium labelled, was freely available, allowing scanning to be carried out electively. No side effects were detected. The procedure was well tolerated by patients with a range of psychological problems, which included restlessness, distractibility, amnesia, aphasia and visuospatial impairment. Sedation

was required in only a minority of overactive patients. Compliance with the technique compares favourably with demented patients' ability to tolerate other forms of imaging.

There has been much speculation about the relationship between uptake of 99mTc-HMPAO and cerebral blood flow (Lassen et al, 1988; Matsuda et al, 1988). However, with present technology measurements of both can only be an approximation. Errors relate both to the poor spatial resolution of current gamma cameras, especially the rotating system used in the current study, and to scatter of radiation. Furthermore, significant changes of cerebral blood flow occur with minor alterations of respiration, blood pressure and sensory stimulation (Harper, 1989). Nonetheless, despite these limitations, the current technique was able to demonstrate abnormalities which reflected both the distribution of impaired cerebral function predicted by psychological assessment and the eventual pathological topography in forms of primary cerebral atrophy.

Whilst the main value of X-ray computed tomography and magnetic resonance imaging in dementia is in the identification of structural brain lesions, these imaging modalities may occasionally be of use in the diagnosis of type of primary degenerative dementia. Widening of the left sylvian fissue is sometimes a feature of progressive aphasia without generalised dementia (Mesulam, 1982; Kirshner et al, 1987) and predominant frontal lobe atrophy is occasionally seen in Dementia of Frontal Lobe Type (Chapter Two). Unfortunately however, in the vast majority of patients with primary cerebral atrophy, whatever the aetiology, scans would appear to show generalised cerebral atrophy and are unhelpful in differential diagnosis. Furthermore, although cerebral

atrophy is detected in a substantially greater proportion of patients with primary degenerative dementia than in age matched normals, there is much overlap such that this radiological finding is not diagnostic of dementia in the individual case (McGeer, 1986). The finding of generalised cerebral atrophy on X-ray computed tomograms of patients with primary degenerative dementia has perhaps done much to perpetuate the myth that the primary cerebral atrophies are a single disease, characterised by global intellectual impairment.

How might the current technique for performing single photon emission tomography be improved in the future? One minor problem was associated with relative instability of the tracer. Immediately after reconstitution, lipid soluble 99mTc-HMPAO begins to convert to a water soluble secondary complex such that a dose made up for injection is unsuitable for use after 30 minutes (Ceretec data sheet). Such instability is overcome by use of a new technetium labelled radiopharmaceutical, 99mTc-ECD (N,N'-1,2-ethylenedialbis-L-cysteine, diethylester), which otherwise appears to share all the favourable properties of HMPAO (Ell et al, 1988). Plans have been made to compare the utility of the two tracers.

The diagnostic value of the current technique is likely to be further improved by the use of a gamma camera dedicated to brain imaging (Keyes, 1982; Cullum, 1987). Such an instrument has two principal advantages over the rotating gamma camera used in the current studies. Firstly, a dedicated head scanning gamma camera can be much more closely opposed to the head and thus permit spatial resolution as good as six millimetres FWHM, which compares favourably with the present resolution of 15 millimetres. Improved resolution would allow cerebral

structures to be identified more accurately, especially those deep in the brain such as the medial temporal lobes and the basal ganglia. Secondly, cameras dedicated to cerebral imaging can acquire data from several brain regions simultaneously and thus dramatically reduce scanning time. Artifacts caused by movement would be less likely if scanning time could be reduced.

Rapid scanning time, together with the use of a radiopharmaceutical with a rapid brain washout permits repeated examination of the same patient at a single sitting. Xenon-133 has traditionally been used for such studies, although the rapidly redistributed injectable compound 99mTc-PnAO may possibly be of value in the future. Such dynamic brain imaging would give an added dimension to the study of primary cerebral atrophy. For example, patients could be examined before and during performance of psychological tests designed to tap specific areas of cognition. Such activation techniques have been used to study frontal lobe activity in schizophrenia (Weinberger et al, 1986a), Parkinson's disease ((Weinberger et al, 1986b) amd Huntington's chorea (Weinberger et al, 1988). Moreover, therapeutic manoeuvres, such as the immediate effects of the administration of certain neurotransmitters would be capable of assessment.

Refinements in techniques for single photon emission tomography ought to lead to greater precision in the imaging of cerebral pathologies. The interpretation of images in conjunction with neuropsychological analysis should shed further light on the cerebral atrophies and other diseases which lead to dementia.

APPENDIX ONE TECHNIQUE FOR PERFORMING ROTATING GAMMA TOMOGRAPHY OF THE BRAIN USING 99mTc-HMPAO

The technique was developed by the departments of medical physics and nuclear medicine at Manchester Royal Infirmary and has been previously described by Burjan, 1986 and Shields et al, 1986.

i). Administration of radiopharmaceutical

Freeze dried hexamethyl propyleneamine oxime (HMPAO) was reconstituted with freshly eluated 99mTc-pertechnetate to produce 99mTc-HMPAO. A dose of 550 MBq was then prepared for intravenous administration to the patient. 99mTc-HMPAO slowly converts to a secondary, water soluble compound which is not suitable for brain imaging. To ensure administration of an optimal concentration of 99mTc-HMPAO patients were injected within 30 minutes of tracer preparation and chromatography was performed to ascertain that the dose administered contained at least 80% lipophilic 99mTc-HMPAO. Patients were injected via an anterior cubital vein, whilst sitting in a quiet room with their eyes open.

ii). Data aquisition

This was performed between five minutes and four hours after injection of tracer. Patients were scanned supine on a cantilevered tomography table with the head positioned in a low attenuation carbon fibre head rest such that the orbitomeatal line was vertical. Data were acquired using an International General Electric 400 A/T rotating gamma camera fitted with a low energy general purpose collimater (Figure 1.1) and a Medical Data Systems A3 computer. A computerised table motion (the programmable body contour option) allowed elliptical acquisition and thus

patient/camera distance to be kept to a minimum during a full 360 degrees of rotation about the long axis of the patient. The set comprised 64 images, each of 20 seconds duration, typically yielding four million counts per acquisition. Data were stored on a 64 x 64 matrix with a zoom factor of 1.48. Each pixel thus represented 4.2 millimetres.

iii). Image processing

Prior to reconstruction each image was corrected for non-uniformity of the camera and spatially smoothed using an 11 point, two dimensional spatial filter. Transaxial tomographic sections of two pixel thickness were then reconstructed by filtered back projection, using a Butterworth filter of order four with a cut-off of 0.76 cycles per centimetre. Attenuation correction was performed based on Sorenson's method, 1974. Sections from the orbitomeatal line to the vertex were displayed with a cut-off of 20% of maximum counts and photographed. Transaxial slices were shown alongside an anterior planar view to indicate the level of the section. The resolution of the system has been calculated to be 15 millimetres Full Width Half Maximum in the plane of the reconstructed tranverse section.

iv). Reporting

To avoid bias images were reported by a nuclear medicine consultant who had no knowledge of the clinical findings nor contact with the patients. He was asked to compare scans with those from control subjects and comment on areas of reduced tracer uptake.

Ethical approval for examining patients with primary cerebral atrophy using single photon emission tomography was obtained from the Manchester Central District Ethical Committee, and use of 99mTc-HMPAO was approved by the Administration of Radioactive Substances Advisory Comittee of the Department of Health and Social Security. The nature of the investigation and its purpose was explained to patients and their relatives and written consent for single photon emission tomography was obtained from the next of kin.

APPENDIX TWO QUALITATIVE MENTAL ASSESSMENT

The 'neuropsychological profile' has been previously described (Neary et al, 1986). It consists of a number of short tests designed to provide qualitative information about different aspects of mental function, tasks being sufficiently easy to avoid floor level performance in demented patients. The tests are summarised below and divided for convenience into five main groups. However, since failure may arise for multiple reasons, interpretation of disability was based on quality of performance and not rigidly according to the task's allocated catagory.

i). Language

Spontaneous speech: social conversation with the examiner.

Series speech: production of overlearned sequences, such as the days of the week.

Comprehension: of word meaning and grammatical relations, interpretation of metaphor and proverb.

Repetition: digit span, repetition of spoken phrases and word lists.

Word finding: naming objects and body parts to confrontation and description.

Verbal fluency: production of words conforming to specified catagory.

Spelling: oral spelling of specified words and aural identification of spelt words.

Reading: reading aloud and comprehension of spelt material.

Writing: reproduction of letters, words and phrases to dictation and composition of sentence to command.

Calculation: mental and written additions and subtractions.

ii). Perceptual and spatial

Identification: of objects, line drawings, famous faces and jig-saw figures.

Location: of objects and body parts, and points on a map, matching fingers on the two hands.

Integration: interpretation of complex visual scenes.

Visual tracking: tracking a dotted line.

iii). Praxis and visuo-constuctional

Symbolic motor actions: use of gesture and pantomime.

Non-representational: copying hand configurations.

Motor sequences: production of motor rhythms, sequences of hand movements, and alternating taps.

Constructional: drawing to command and from copy, reproduction of block constuctions.

iv). Memory

Verbal memory: immediate and delayed recall and recognition of name and address and short story.

Visual memory: reproduction of drawings from memory, recognition of pictures.

General Knowledge: identification of contemporary and past celebrities.

v). Regulation: planning and conceptual functions

Picture sequencing: ordering pictures to tell a story.

APPENDIX THREE PUBLICATIONS ASSOCIATED WITH THIS THESIS

PAPERS

Neary D, Snowden JS, Northen B, Goulding P.
Dementia of frontal-lobe type.
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Goulding P, Burjan A, Smith R, Lawson R, Snowden J, Northen B, Neary D, Testa H.
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Goulding PJ, Northen B, Snowden JS, MacDermott N, Neary D.
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Dementia of frontal lobe type and motor neurone disease.
Journal of Neurology, Neurosurgery and Psychiatry 1990;53:in press.

APPENDIX FOUR ORAL PRESENTATIONS ASSOCIATED WITH THIS THESIS

PRESENTATIONS TO LEARNED SOCIETIES

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Dementia of frontal-lobe type.
Association of British Neurologists. St Bartholomew's hospital, London. November 1987.

Goulding PJ, Burjan AWI, Neary D, Testa HJ.
SPET imaging with 99mTc-HMPAO in slowly progressive aphasia without generalised dementia.
British Nuclear Medicine Society. Imperial college, London. April 1988.

Burjan AWI, Goulding PJ, Shields RA, Neary D, Testa HJ.
Tomographic elliptical annular profiles on transaxial sections (teapots).
British Nuclear Medicine Society. Imperial college, London. April 1988.

Goulding PJ.
The differential diagnosis of dementia using SPET and HMPAO.
Norwegian Nuclear Medicine Society. Ulleval Hospital, Oslo. October 1988.

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Goulding PJ, Burjan AWI, Smith RJ, Lawson RS, Snowden JS, Northen B, Neary D, Testa HJ.
Semi-automatic quantification of regional cerebral perfusion in dementia using 99mTc-HMPAO and single photon emission tomography.
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Goulding PJ, Neary D, Mann DMA, Snowden JS, Northen B, MacDermott N.
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Dementia of frontal lobe type and motor neurone disease.

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