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Review Article

Dementia and Parkinson's Disease

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Recent research into the dementia of Parkinson's disease has exposed a complex area in which it has not always been possible to match clinical and pathological observations. Certain neuropsychological deficits result from a disruption of basal ganglia and frontal lobe interactions. These are unrelated to a global dementia, the prevalence of which exceeds twice that in the normal population. The associated pathological lesions comprise cortical pathology, either Alzheimer's disease or Lewy bodies, in combination with moderate degeneration of the subcortical, cholinergic, basal nucleus of Meynert.

James Parkinson's observations of six patients with the 'Shaking Palsy', published in 1817, led him to believe in "the absence of any injury to the senses and to the intellect" (Gardner-Thorpe, 1987). Consequently he suggested "that the morbid state does not extend to the encephalon", and supposed that the medulla was the site of pathology. By the second half of the 19th century, neuropsychiatric manifestations of Parkinson's disease (PD) were described (Ball, 1882), and in 1923 Lewy's monograph on PD recorded various mental derangements and dementia in as many as three-quarters of patients (Lewy, 1923). By the 1960s, dementia had become quite widely accepted as a frequent complication of later stages of the disorder (Mjönes, 1949; Loranger *et al*, 1972).

The prevalence of dementia in PD is now believed to be greater than in the general population (Mayeux, 1982), but there is still a considerable diversity of opinion on the approximate frequency of cognitive change (Taylor *et al*, 1986*a*). Widely differing estimations of prevalence are quoted, some ranging as high as 90% (Hoehn & Yahr, 1967). The last decade has seen research in this field expanding, as has other research in PD, but this flourishing interest has also been ascribed to the realisation that L-dopa fails to correct progressive cognitive impairment, despite alleviating motor disability. The discovery of the morphological and biochemical alterations associated with Alzheimer's disease (AD), particularly the depletion of cortical choline acetyl transferase (ChAT), has also encouraged the search for similar abnormalities in PD. Progress in clinical, histopathological, and biochemical areas has amassed considerable data. While uncertainties persist in a number of areas, some definite conclusions can be made. Lately there has been support for James Parkinson's view that the intellect remains intact.

The purpose of this review is to answer two questions. Firstly, how frequently does dementia occur in PD, and does it occur more often than in the general population? Secondly, is the dementia caused by AD, and if not, what is the mechanism for it? Answers to these questions necessitate an attempt to define dementia in PD, an interpretation of various cognitive changes reported in PD, and a thorough review of pathological processes. The management of dementia will not be addressed.

The diagnosis of dementia in Parkinson's disease

Interviewing patients with PD is often frustrating because of their difficulties with verbal communication, due to slowness, apparent diffidence, and disordered speech production. A slight hesitation, difficulty in finding words, and perseveration are common, so that cognitive difficulties can be suggested when these do not exist. Non-verbal communication also contributes to first impressions and in PD suggests disturbances of mood, personality, and intellect (Pentland *et al*, 1987). Silent video-recordings of four medicated patients with PD (two were stage 2 and two were stage 3 on the Hoehn and Yahr scale) and four with ischaemic heart disease were assessed using visual analogue scales concerned with aspects of personality. None of the patients showed disturbance of affect, personality, or intelligence by standard psychological tests, but remedial therapists rated the patients with PD as appearing more anxious, tense, hostile, unhappy, introverted, sensitive, passive, and less intelligent. In addition, patients may fail to appreciate the patterns of intonation and facial expression of others (Scott *et al*, 1984). Another study found that smiling in response to cartoons was reduced in patients with PD, and that this reduction correlated with higher depression scores (Katsikitis & Pilowsky, 1988). Patients with PD tend to have normal verbal content and memory, and their indifferent facial expressions seem to mask characteristically precise and analytical minds, and sometimes a dry sense of humour. Formal assessment of intellectual function is necessary

before making ill informed and false assumptions about cognitive state.

There are two principal endeavours in the diagnosis of dementia in PD for the purpose of clinical and pathological studies. First is the identification of sufficient cognitive decline. The diagnosis of dementia is made difficult by the nature of its usually slow and indefinite onset. Second is the use of a robust definition sufficient for the comparison of PD and control populations. Parkinsonian motor deficits tend to impinge on diagnostic criteria for dementia by limiting activities or increasing dependency. Diagnostic criteria, as laid out in DSM-III-R (American Psychiatric Association, 1987), state that there is impairment of "short- and long-term memory, associated with impairment in abstract thinking, impaired judgement, other disturbances of higher cortical function, or personality change":

(a) Evidence of short- and long-term memory impairment
(b) At least one of the following
  (i) impaired abstract thinking
  (ii) impaired judgement
  (iii) aphasia, apraxia, agnosia, and 'constructional difficulty'
  (iv) personality change
(c) (a) and (b) must interfere with work, social activity or personal relationships
(d) these deficits must occur without delirium
(e) either: (i) evidence of a specific organic factor related aetiologically or (ii) absence of non-organic mental disorder, such as depression.

Grades: mild - capacity for independent living exists, despite (c)
moderate - supervision is necessary
severe - continual supervision and personal care are required.

The important distinction made from 'benign senile forgetfulness' is an impairment of social or occupational functioning. Limitation of activity and increased dependency are thus features of dementia, as well as of PD.

One unavoidable drawback in any definition of dementia is that the criteria are partly subjective, so that the number of persons included in a category of mild disease is likely to vary between observers and on successive assessments. In addition, the DSM-III criteria (American Psychiatric Association, 1980) include both reversible and irreversible states. In the case of a degenerative disease, it is mostly progressive dementia that is of interest, so it is necessary to clarify whether deficits can be partly or completely reversed. For example, adjusting medication may alleviate confusion. Other drug side-effects, age, fatigue, depression, and complicating illnesses influence cognitive state (Brown & Marsden, 1987). The precise threshold for dementia remains difficult to define, but the DSM-III criteria have encouraged accuracy and provide the most reliable guide available. Accuracy might be improved by addressing only those with moderate and severe DSM-III-R dementia.

Cognitive deficits in Parkinson's disease

Quantitative assessments of cognitive state help in the evaluation of dementia and provide information such as would contribute to criteria (a) and (b) of the DSM-III-R diagnosis. In PD these quantitative assessments are confounded by two main difficulties. Firstly, some neuropsychological tests do not distinguish between motor and mental impairments, thereby allowing poor motor performance to intrude in the results. For example, in PD the performance part of the Weschler Adult Intelligence Scale (WAIS) frequently results in a lower score (mean 95.3) than the verbal part (mean 115.6; Loranger *et al*, 1972), a discrepancy which is likely to reflect motor impairment. Consequently a decline in performance IQ might not reflect dementia. Secondly, multiple mild cognitive deficits of uncertain nature, some of which may not be purely artefacts of motor tasks, have been identified in areas of memory, language, problem-solving, perceptual motor, and visuospatial skills (Reitan & Boll, 1971; Portin & Rinne, 1980; Pirozzolo *et al*, 1982).

In general, the abnormalities detected seem to be independent of a more pervasive cognitive decline, but as in the case of visuospatial disorder, they might reflect abnormality of higher cortical (parietal) function, or result from some other motor and cognitive disorder. This subject is complicated by the complexity and variation of many of the tasks that have been employed (Brown & Marsden, 1987), some of which are impaired, and some of which are not. An adequate classification of functions tested in visuospatial tasks does not exist, although Boller *et al* (1984) proposed three general categories of spatial function, namely the appreciation of the relative position of stimulus objects in space; the integration of these objects into a coherent spatial framework; and mental operations involving spatial concepts. Factors that might influence the outcome on these tasks in PD include their motor requirements, the switching of mental perspectives in spatial tasks, and the theoretical possibility of verbal rather than spatial strategies for solving tasks (Brown & Marsden, 1986).

In the case of visuospatial or perceptual motor function, some performance of constructional tasks, orientation, tracing or tracking of lines, and sequencing simultaneous movements are impaired (Schwab *et al*, 1954; Proctor *et al*, 1964; Flowers, 1978*a*,*b*; Stern *et al*, 1983). Similar deficits could be reflected in lower scores on the performance subtests of the WAIS, such as the Digit Symbol, Block Design, and Object Assembly components, compared with verbal subtests, although motor impediments may not be directly responsible. Stern *et al* (1983) studied 16 medicated patients with PD and nine controls, none of whom had dementia. Their performance on two tracing tasks was assessed by measuring both tracing velocity and accuracy. One test required the tracing of a straight line between two points and the other involved tracing a sawtooth line. Tracing accuracy was assessed by measuring the area encompassed by the deviation from the correct course. As expected, tracing velocity was impaired in the patients with PD, and was related to motor symptom severity. In addition, tracing accuracy was impaired, and performance was even less good on the sawtooth pattern, suggesting an additional perceptual disorder unrelated to that attributable to motor impairment. Flowers (1978*b*), who had found a similar tracking deficit, postulated that the inaccuracy of movement was due to a lack of predictive ability in some higher-order system. Indeed, similar deficits in tracking have been reported in animals with caudate lesions (Bowen, 1969).

Boller *et al* (1984) employed a battery of spatial tests requiring visual and motor input, but varying in the complexity of the motor response. He included tests of dementia, an information score and the Hamilton Rating Scale for Depression. He concluded that even the visuoperceptual tests requiring rather less motor response were impaired, although there was no simple relationship between the severity of PD and the visuoperceptual dysfunction. Nevertheless, some tests predominantly involved with spatial testing were normal. Della Salla *et al* (1986) used a task similar to that of Stern *et al* (1983), but as a point of difference excluded a motor component. Mildly disabled patients showed no difference compared with controls on the spatial ability requiring prediction of the point of geometrical intersection by one straight but incomplete line, and one rebounding but incomplete line. Psychometric assessment of general cognitive competence showed similar results in the two groups. Such a task does not therefore reveal an underlying visuospatial disorder, but taken with the previous study suggests that organisation of information in a strategy for movement, or the employment of movement strategies, may be defective.

In recent studies of visuospatial function, Brown & Marsden (1986) employed tests discriminating between left and right, and the mental manipulations of these right–left concepts. Independent assessments of intellectual and motor function were made. The patients did not show loss of accuracy compared with controls, or for that matter prolongation of choice reaction times, or difficulty with reversal of mental concepts (see later). Taylor *et al* (1986*a*, 1987), using a series of five visuospatial tests including object discrimination and naming, mental rotation, and right–left orientation, showed normal accuracy, but the speed of block counting was reduced. This task might be unrelated to visuospatial function, and indeed the authors pointed out that the slowness of their patients, in the presence of preserved attention, suggests bradyphrenia.

These studies of visuospatial and perceptual motor function do not therefore point to a generalised visuospatial disorder, and do not suggest a disturbance of parietal lobe function.

Among the other cognitive deficits suggested above is a defect of memory, which may be related to cholinergic deficiency (see later), but other mechanisms have recently been discussed (Sagar *et al*, 1988). Language disorder in PD generally concerns motor speech production (dysprosody, dysarthria), rather than the language deficits of AD (Cummings *et al*, 1988). Problem-solving deficits may relate to frontal lobe dysfunction in PD (see later).

Prevalence of dementia in Parkinson's disease

Comparing studies concerned with the prevalence of dementia is often impossible because of imprecise and inconsistent diagnostic criteria. Study designs and methods of assessment vary widely. In general, difficulties lie in the quantitative evaluation of dementia (as above) and the qualitative evaluation of the Parkinsonian disorder: is the disorder actually PD?

Most hospital-based surveys suggest prevalence rates for dementia of 30–40% (Brown & Marsden, 1984), but diagnostic criteria have not always been as strict as those of DSM–III (Lees, 1985). Such figures have also been challenged because of the inclusion of patients with reversible confusional states and other bradykinetic-rigid syndromes related to PD (Brown & Marsden, 1984). Reversible dementias or confusional states are frequently drug-related, but may be due to chest infections or subdural haematoma (Harding, 1984). Any one of

the anti-Parkinsonian drugs may aggravate mental problems, although anticholinergics are particularly prone to do so. An example of these diagnostic difficulties is the large study of Lieberman *et al* (1979), in which 32% (168) of the patients were considered to have moderate or marked dementia, whereas only 3.4% of similarly aged spouses did. However, the criteria for those with moderate dementia were not as stringent as in DSM–III, and anticholinergics and amantadine may have been responsible for poor performances on tests of memory and intellectual function.

Pathological data suggest that there is considerable error in the average diagnosis of PD, with other Parkinsonian disorders creating confusion. For example, Forno & Alvord (1971) found that only 29 (43%) of 67 patients with undiagnosed Parkinsonian disorders showed Lewy bodies in the substantia nigra, which are the pathological hallmark of PD. In clinical studies attempting to exclude alternative, mostly non-Lewy-body Parkinsonian disorders (Gibb & Lees, 1989), diagnostic accuracy varies from 70% (Forno, 1966) to 95% (Jellinger & Riederer, 1984). Clinical diagnosis is even more uncertain in the presence of dementia, especially when this occurs early in the course of the illness. This interferes with an assessement of the effect of L-dopa, and restricts the value of observing disease progression over time. In addition to Steele–Richardson–Olszewski syndrome, other Parkinsonian disorders associated with mild to severe dementia include Alzheimer's disease with a shuffling gait or essential tremor, corticobasal degeneration, and gait apraxias due to bilateral subcortical vascular disease, communicating hydrocephalus, or trauma. Rare causes are Hallevorden–Spatz disease, Wilson's disease, repeated head trauma, and frontal lobe tumours.

Adjusting the 30–40% prevalence rate for these potential inaccuracies in the diagnosis of PD and dementia has suggested a figure of about 20% as a better estimate of irreversible, unequivocal dementia (Brown & Marsden, 1984). However, there are still doubts (Lees, 1985) that a 20% prevalence rate for dementia in PD compares with one of 5–7% for moderately and severely demented patients with AD over 65 years of age in the general population (Henderson & Kay, 1984). Lees (1985) used DSM–III criteria to diagnose dementia from the mental state examinations on 48 elderly PD patients, of mean age 74 years, and mean disease duration of 18 years. Most of the patients were severely disabled, but only seven (15%) were demented. Taylor *et al* (1986*a*) found that eight patients of unstated age among 100 (8%) referrals to the Toronto Western Movement Disorder Clinic with mild and moderate PD had clear evidence of dementia, and an additional seven had cognitive changes while on medication, four of whom improved when medication was changed. Another study quoted a figure of 7% among 36 patients, but an additional 31 patients in the original cohort either died or were lost to follow-up (Oyebode *et al*, 1986). One argument that might explain recent discrepancies is that neurologists tend to see younger patients in whom dementia is rare, whereas general physicians see an older population which is subject to an age-related rise in the prevalence of dementia; although this point is not reflected by the study of Lees (1985). It might also be argued that some figures are not generally applicable to the PD population as a whole, because general physicians and neurologists receive referrals biased towards dementing Parkinsonian patients with management problems, although these studies mostly refer to cases of dementia emerging during follow-up.

The question of age, dementia, and PD has recently been examined in young patients, because most existing surveys have been concerned with the prevalence of dementia in the over-50 age group. All patients developing PD at a young age are likely to be referred to a neurologist, and are likely to survive for a sufficient length of time to determine whether dementia is a common or invariable complication of long survival.

Quinn *et al* (1987) collected 56 patients with disease onset between age 21 and 39 years, with a median age of 35 years. None of these patients developed dementia, despite a median disease duration of 15 years, and a range of 1–35 years. The authors pointed out that only four had reached the age of 65 years. Dementia was also absent in a group of 21 patients whose disease started before the age of 39, and whose mean disease duration was 19 years (Lima *et al*, 1987). Lastly, in a study of 46 patients with disease onset before 46 years, a median age of onset of 38 years, and median disease duration of 12 years, only one patient had dementia of moderate severity (Gibb & Lees, 1988). Five patients were over 65 years. These three studies contain 123 patients with disease onset before 46 years and only one (0.8%) patient had dementia.

Another study of this kind included 49 patients with PD whose disease began before the age of 60, only one of whom (2%) was demented according to DSM–III criteria, whereas 13 of 59 (25%) with disease starting after 60 were demented (Hietanen & Teräväinen, 1988). Another recent study, consistent with these findings, showed that 8.5% of patients with PD starting before 70 years developed dementia, compared with 20.9% of patients with

disease onset after 70 years (Mayeux *et al*, 1988). The prevalence of dementia was assessed by retrospective examination of patient records, according to adapted DSM-III criteria, and amounted to 10.9% in the total of 339 patients.

In contrast to suggestions that the PD process differs in young and old patients, our experience of both clinical and pathological characteristics is of a remarkably uniform disease process, particularly with regard to its cerebral distribution and rate of progression (Gibb & Lees, 1988). The rarity of dementia in young-onset patients suggests that the pathology of PD (Lewy bodies and nerve cell loss), in the absence of age-related factors, is insufficient to cause dementia. Dementia therefore appears to be more closely related to age than disease, although age cannot be the only factor because of the higher frequency of dementia in PD compared with the normal ageing population. On taking account of these various prevalence estimates for dementia, the lifetime risk of moderate and severe DSM-III dementia over 65 years is probably 10–20%, or just over twice that of the general population.

Subtypes of dementia

The concept of two types of dementia, cortical and subcortical, is one that evolved in the 1970s; it implies the predominant sites of pathology in two qualitatively different processes. Recently this distinction has been questioned on clinical and pathological grounds. It has even been argued that the dementia of 'subcortical' disorders such as PD and Huntington's disease might not be sufficiently distinct from that of AD to continue employing the term (Whitehouse, 1986). Slowed mental processing has proved difficult to validate, and depression might contribute to the subcortical disturbance. Lastly, pathology is present in subcortical regions in AD, and cortical regions in PD.

Cortical or temporo-parietal dementia

This is most commonly associated with AD and is characterised by severe disruption of memory and thought processes, associated with aphasia, apraxia, agnosia, and spatial disorientation. Mental alertness and motor function are preserved until late in the course of the disease. The amnesia and cortical deficits are believed to result from hippocampal and neocortical pathology, comprising nerve cell loss with accumulations of neurofibrillary tangles and senile plaques. Pathological changes also occur in the nucleus basalis of Meynert, locus coeruleus, raphé nucleus and substantia nigra.

Parkinsonian features have been observed in the later stages of AD, but these are mostly non-specific signs, such as muscular stiffness and slowness of movement. Rest tremor, which is more specific evidence for PD, is reported in only 4% (Sulkava, 1982) and 10% of patients (Mölsä *et al*, 1984). This agrees with pathological data which show that nigral pathology is common in AD, but is usually mild (Gibb *et al*, 1989*a*). The prevalence of PD pathology (Lewy bodies in the substantia nigra) complicating AD is similar to that in the general population (Gibb *et al*, 1989*c*). Other cortical dementias may be accompanied by Parkinsonian features, including cortical Lewy body dementia, corticobasal degeneration (Gibb *et al*, 1989*d*), multi-infarct dementia, rare cases of Pick's disease, and Creutzfeldt–Jakob disease. Parkinsonian disorders with dementia lacking cortical features include Steele–Richardson–Olszewski syndrome, Hallervorden–Spatz disease, communicating hydrocephalus, glial dystrophy, Parkinsonism–dementia complex of Guam, and motor neuron disease. Moderate or severe dementia in PD is not thought to be explained purely by subcortical dementia.

A parallel consideration in idiopathic dementia is the possibility of predicting the neuropathological lesion according to the clinical features. Recent cortical biopsy or autopsy-based studies of patients with idiopathic degenerative dementia found AD in 71–82% (Sulkava *et al*, 1983; Mölsä *et al*, 1985; Neary *et al*, 1986). Other diagnoses were vascular disease, PD, no diagnostic pathology, subcortical gliosis, and normal-pressure hydrocephalus. A recent cortical biopsy study in clinically diagnosed AD has been more optimistic (Martin *et al*, 1987). In the case of dementia complicating PD, the chance of cortical Lewy body dementia is high, and the clinical distinction between cortical Lewy body dementia and AD difficult or impossible.

Subcortical or frontolimbic dementia

Neuropsychological definition of subcortical dementia

Mental slowing in Parkinsonian states has been recognised for many years, one of the first descriptions being that of Naville (1922), who coined the term 'bradyphrenia' to describe the state following encephalitis lethargica. Terms such as 'persistent somnolent psychosis', 'psychic torpor', 'bradypsyche', and 'psychic akinesia' were later used to describe the same phenomenon (see Rogers, 1986; Lees, 1989). Albert *et al* (1974), without reference to this extensive literature, proposed the term 'subcortical dementia'

to describe a number of neurobehavioural changes observed in the Steele–Richardson–Olszewski syndrome. This syndrome comprised slowing and inflexibility of thought processes (mental inertia), impaired concentration, and loss of initiative and drive (apathy), associated with impaired ability to manipulate acquired knowledge, lack of imagination, mild forgetfulness, emotional dullness, and a tendency to repetition. As in previous literature, a striking resemblance to the dementia following frontal lobe lesions was noted (Drewe, 1974; Nelson, 1976). The term 'subcortical dementia' was then used to describe the cognitive changes present in other disorders with predominantly subcortical pathology, for example PD (Albert, 1978) and Huntington's chorea (McHugh & Folstein, 1975).

Bradyphrenia is now subsumed under the title of subcortical dementia, where the emphasis lies on mild memory disturbance, mildly disordered thought processes, slow and poorly articulated, quiet speech, apathy, and depression (Benson, 1984). Generally this leads to rather mild intellectual impairments as assessed on a modified mini mental state examination when compared with AD patients at an equivalent functional stage of disability (Mayeux *et al*, 1983). This is similar to the relatively mild nature of the subcortical dementia in Steele–Richardson–Olszewski syndrome (Duvoisin *et al*, 1987). However, qualitative differences in neuropsychological impairments compared with AD cannot be detected using the mini mental state examination (Mayeux *et al*, 1983). AD and PD patients with comparable performances on verbal, visuospatial, and global memory tests show more severe verbal memory disorder in AD, and impaired performance on tests sensitive to frontal lobe dysfunction in PD (Pillon *et al*, 1986; Huber *et al*, 1986; Freedman & Oscar-Berman, 1986).

Bradyphrenia, or subcortical dementia, is recognised clinically by an undue delay in the production of appropriate verbal responses in a co-operative individual without other communication difficulty. The term implies that slowness of verbal responses is due to slowed mental, as distinct from motor, processes. In addition to slowed mental processes, it has been suggested that the neuropyschological deficits underlying bradyphrenia include difficulty in changing mental concepts, and defective attention and motivation (Lees, 1989). However, it has not been possible to show a convincing and consistent reduction in some tests dependent on the speed of mentation. Wilson *et al* (1980) found that high-speed scanning of short-term memory was prolonged in PD, although only in older patients.

Hansch *et al* (1982) examined the long-latency P3 component of the event-related potential in an auditory discrimination task, which is believed to reflect the speed of information processing. The latency of this response in 20 patients with PD was significantly increased compared with controls, and was significantly correlated in a negative fashion with scores on a symbol-digit test. This was interpreted as evidence for bradyphrenia in view of correlation between a test of mental function and the latency of the response. In a study of auditory-evoked potentials in dementia, the N2 and P3 components of the cerebral responses were prolonged in AD and demented patients with PD meeting DSM–III criteria (Goodin & Aminoff, 1986), but not in non-demented patients with PD (Goodin & Aminoff, 1987), so that in the absence of serious cognitive impairment there appears to be no abnormality. The authors pointed out that the P3 response was clearly not specific for bradyphrenia, and could be prolonged in a number of causes of dementia. They noted that the delay in N2 and P3 responses was greater in the demented Parkinsonian patients, and that an additional abnormality was a delay in the N1 component compared with AD.

Evarts *et al* (1981) examined visual and kinaesthetic simple and choice reaction times, and compared these with movement times. There was some correlation between reaction and movement times, but a wide scatter in reaction times, such that they appeared to be independent in some patients. No selective prolongation of choice reaction times was found. In a computer-controlled task, a warning signal was followed by a signal consisting of a light or a high-pitched tone. In the simple reaction-time task, the response (lifting a finger) was made with the dominant hand, and in the choice reaction-time task, the dominant hand was used to respond to the light and the non-dominant hand to the tone (Stern *et al*, 1984). Both simple and choice reaction times were delayed in 39 PD patients. Brown & Marsden (1986) using a left–right discrimination task, both with and without a spatial component, showed no differential impairment of choice reaction time over simple reaction time. Perhaps one of the simplest explanations for the failure of these tests to reveal mental slowing is that they are of the wrong kind, the thought processes being directly driven by the stimulus.

The second neuropsychological defect proposed to underlie bradyphrenia is difficulty in changing mental concepts or sets, a 'set' being defined as "a state of brain activity which predisposes a subject to respond in one way when several alternatives are available" (Flowers & Robertson, 1985). Put another way it is "the ability to reorganize behaviour according to the requirements of a task" (Cools

et al, 1984). Cools *et al* (1984) described the inability to reorganise behaviour in PD as a "diminished shifting aptitude", which could be either frontally or basal-ganglia mediated. The Wisconsin Card Sorting Test (WCST) and the Benton Word Fluency Test in early, untreated PD have identified difficulty changing conceptual sets and perseverative errors (Bowen *et al*, 1975; Lees & Smith, 1983). In established PD, Taylor *et al* (1986*a*), also found abnormalities in similar frontal tasks, especially the WCST and Bead-Tapper test (simultaneous manual tasks) and later reported that the WCST, the Rey Auditory Verbal Learning and Bead-Tapper tests were also impaired in nine untreated and 20 treated patients (Taylor *et al*, 1987). Flowers & Robertson (1985) used an odd-man-out discrimination task, and found that Parkinsonian patients had difficulty alternating between two rules on successive trials. The pattern of errors suggested an instability of cognitive set, and not of reasoning ability, perseveration, or distractibility. Taylor *et al* (1987) found that mental processing time on the Trail-Making Test, which tests mental set alternation and excludes motor speed variation, was prolonged in a group (called the poor-response group) showing a declining response to L-dopa (pathological diagnoses in this group are not known), but not in other PD groups. Depression ratings were excluded, but there were no differences in tests of attention and concentration.

Lastly, a number of studies have investigated attention and motivation in patients swinging 'on' and 'off' as a result of L-dopa therapy. An arousal effect of L-dopa has been suggested as the cause of improved mental performance with L-dopa (Loranger *et al*, 1972), and this might be associated with increased speed of thought and absence of perseveration. One of these studies employed the modified Alice Heim test, which incorporates tests of reasoning ability for verbal, numerical, and spatial material (Brown *et al*, 1984). There was no correlation between changes in mental and motor performance; in fact, changes in mental impairment were relatively mild and present only in a proportion of individuals. If one factor was associated with functional impairment, the only real choice was a subjective disturbance of mood and alertness measured during 'off' periods. However, self-rating analogue scales, as used to assess mood and motivation, have been criticised on account of perseveration by the patients (Lees, 1989). These findings are consistent with those of Delis *et al* (1982) and Taylor *et al* (1987), who failed to show alteration in cognitive state dependent on physical state, although importantly the tasks evaluated different functions. Finally, attention and motivation may be an important consideration in six patients with an MPTP-induced Parkinsonian state who showed worse general intellectual function, constructional ability, category naming, and frontal lobe function (Stroop Word-Color test, Part C) compared with eight controls (Stern & Langston, 1985). The two women in the group were depressed.

Other factors of possible relevance to bradyphrenia include the relationship between dopamine and effort in memory processing (Newman *et al*, 1984), 'state-dependent' impairment of memory (Huber *et al*, 1987), and defective planning of movement (Flowers, 1978*b*).

Mechanisms of subcortical dementia

Searches for the pathological substrate of subcortical dementia have included the nucleus basalis, ventral tegmental area, thalamus, and substantia nigra. Neuropsychological deficits now point to a considerable disturbance of frontal lobe function, but how might this arise? Rafal *et al* (1984) postulated that if bradyphrenia resulted from the same dopaminergic imbalance as bradykinesia, then these phenomena should fluctuate in parallel. This question was investigated in six patients with end-of-dose akinesia, who were asssessed with simple measurements of the rate of memory scanning, of shifting attention in the visual field, and the time required for the preparation of a movement. Overall reaction times increased when patients were in the akinetic 'off' state, but without analogous slowing of the cognitive components of these tasks, implying that bradykinesia and bradyphrenia do not result from the same dopaminergic abnormality of the basal ganglia. The absence of slowed mentation accords with the results of other tests of cognitive speed (see above), which unfortunately may not be the most appropriate for evaluating bradyphrenia.

With the benefit of an excellent historical review, Rogers (1986) has outlined the close relationship between bradyphrenia, motor impairment, and depression. Reactive depression as a response to motor disability in the form of apathy and depression is commonly, but not invariably, recognised in those patients with bradyphrenia (Albert *et al*, 1974). Psychological deficits similar to bradyphrenia have also been recognised in depression (Caine, 1981). To what extent is depression related to bradyphrenia in PD? In a study of 30 newly diagnosed patients with PD, not receiving dopaminergic agonists, and 30 patients with primary depressive illness, there was an equivalent slowing of manual responses to a computerised digit symbol substitution test compared with controls (Rogers *et al*, 1987). Rating of motor

impairment by the Webster scale and affective impairment by the Hamilton Rating Scale for Depression showed significant differences between each of the PD, depression, and control groups. Matching time, which was a measure of cognitive processing and visual scanning speeds on the tests, was significantly prolonged compared with controls in the nine PD patients with structural disorder on CT scan (cerebral atrophy or infarct). Matching times in the whole PD group were significantly associated with the Hamilton rating. The 18 patients with a normal computerised tomography scan (three did not have a scan) did not even show slowing of the response time (which includes motor speed). Similarly, the 15 more severely depressed patients had a significantly prolonged matching time, and these patients generally had a high Webster score of motor impairment. In both groups some patients were retested after treatment with a dopaminergic agonist or antidepressants, and there seemed to be a relationship between improvement in depression rating and speed of response. The relationship between affect and speed of cognitive processing appeared to be so closely linked that the authors concluded that overlap exists between PD and depressive illness, with the suggestion that the mesocorticolimbic dopaminergic system may be impaired in both states. Evidence was cited for reduced dopamine turnover, assessed by concentration of homovanillic acid in the cerebrospinal fluid, in depressed patients with retardation.

However, some difficulty in identifying damage to the mesocorticolimbic system is apparent from neurochemical data in Steele–Richardson–Olszewski syndrome. In this disorder, frontal lobe deficits are more severe than in PD (Maher *et al*, 1985; Pillon *et al*, 1986), and frontal cortex hypometabolism detected by positron emission tomography is considerable (D'Antona *et al*, 1985). However, dopamine levels in the nucleus accumbens and frontal cortex are not reduced (Ruberg *et al*, 1985; Kish *et al*, 1985), although dopamine receptors are. This contrasts with reductions of frontal cortex dopamine in PD (Scatton *et al*, 1982). In contrast to PD, caudate nucleus dopamine levels are reduced by an equal or greater amount than putamen values. Taylor *et al* (1968*a*) have proposed that frontal lobe dysfunction in PD results primarily from disturbance in caudate outflow as part of the 'complex' loop, comprising a cortico–caudato–nigro–thalamo–cortical circuit (DeLong *et al*, 1983). In PD it is suggested that the defect in the mesocortical system adds an additional non-essential insult to the pre-frontal component of the 'complex' loop.

Depression

The possible relation between depression and bradyphrenia has been discussed. Mild depression occurs as a prodromal feature of PD in as many as a quarter of patients, but occurs at some time during the course of the disease in 30–40% (Mayeux, 1982). This level of depression may be no higher than in other chronic illnesses. For example, Gotham *et al* (1986) found a frequency of 46%, which was similar to that in chronic arthritis. In most cases the depression is believed to be reactive, for example in response to the fear of a progressive degenerative disease. Some, but not all, studies have found correlation with severity of illness and functional disability (Gotham *et al*, 1986). Patients show pessimism, hopelessness, decreased motivation and drive, increased concern over health, and emotional lability. Impaired short-term memory, a feature of primary endogenous depression, is absent (Taylor *et al*, 1986*b*). There is less self-blame, guilt, worthlessness, and self-destructive feeling compared with endogenous depression (Gotham *et al*, 1986; Taylor *et al*, 1986*b*). Endogenous mechanisms seem likely in the few patients who have substantial depression in the prodromal phase or depression associated with psychotic features.

Basic pathology of Parkinson's disease

The hallmark of PD was first described by Friederich Lewy in 1912 as an eosinophilic neuronal inclusion in the nucleus basalis and dorsal vagal nucleus. Tretiakoff (1919) described a similar inclusion body in the substantia nigra, and suggested that it was relatively specific for PD. This has remained a matter of doubt until recently, when the Lewy body has been demonstrated in a proportion of remaining pigmented neurons of the substantia nigra in every case of PD (Gibbs & Lees, 1989). Pathological diagnostic criteria for PD can now be proposed, the first of which is the invariable presence of the Lewy body in two unilateral sections of substantia nigra. The second is a greater than 60% loss of nigral neurons. The third is the exclusion of striatonigral degeneration, Steele–Richardson–Olszewski syndrome, and other Parkinsonian disorders associated with neuronal loss in the substantia nigra. Lewy bodies also occur in the substantia nigra in as many as 10% of elderly healthy controls (incidental Lewy body disease), believed to have pre-clinical PD, and may thus be an incidental finding in other Parkinsonian disorders. In addition, they are an inconsistent feature in a variety of uncommon disorders (Gibb, 1986).

The Lewy body lies within the cytoplasm of nerve cells, in nerve cell processes, or is occasionally free

in neuropil; it is recognised by its characteristic eosinophilic staining and surrounding halo. Ultrastructurally, a large part of it comprises filamentous material, roughly similar to neurofilament. Other cytoskeletal components have also been identified immunocytochemically (Dickson *et al*, 1985), and still other components, principally those of the dense and variable 'core', have not been identified. Lewy bodies have a specific and consistent distribution in the nervous system, their other principal locations being the locus coeruleus, raphé nuclei, thalamus, nucleus basalis, cerebral cortex, and the entire autonomic nervous system, including the hypothalamus, dorsal vagal nucleus, intermediolateral columns, sympathetic ganglia, and parasympathetic myenteric plexi. Lewy bodies are not found in these different parts of the nervous system without also being present in the substantia nigra and locus coeruleus, although their occurrence in anterior horn cells, which is restricted to rare cases of motor neuron disease (Hirano *et al*, 1984), is the single exception to this rule.

In PD, Lewy bodies are almost invariably found in the nucleus basalis, dorsal vagal nucleus, autonomic ganglia, and hypothalamus, and in a third of cases in the cerebral cortex (Gibb & Lees, 1987). Neuronal loss has been demonstrated for most of the locations in which Lewy bodies are found. Additionally, neuronal loss in PD does not occur without Lewy bodies, so they are considered an early marker of neuronal cell degeneration, when neuronal loss is not apparent (Langston & Forno, 1978). The generalised but specific distribution of Lewy bodies in PD, the identical distribution of Lewy bodies in patients presenting with autonomic failure or dementia, and the occurrence of Lewy bodies in a population with insufficient nigral neuronal loss to cause symptoms, suggests a single disease entity with varying manifestations, prompting the inclusive term 'idiopathic Lewy body disease' (Gibb & Lees, 1988*b*).

In the context of the present discussion, the comparatively large size of the pre-clinical PD population, the prevalence of which rose from approximately 2% in the 1950s to 10% in the '80s, emphasises three points (Gibb & Lees, 1988*b*). First, there is a critical threshold for symptoms, which depends on the degree of nigral neuronal loss (estimated at 60%), striatal dopamine loss (estimated at 80%), and compensatory post-synaptic dopaminergic hypersensitivity. Second, the degree of nigral neuronal loss at death is always moderate at 75–80%, and never extreme. Third, the much lower prevalence of symptomatic compared with pre-symptomatic PD suggests a long pre-clinical period, and a slow rate of nigral destruction. This moderate neuronal loss is also seen in the ventral tegmental area (estimated at 40–64%, Bogerts *et al*, 1983), the locus coeruleus (estimated at 75–80%, Mann *et al*, 1983), and the nucleus basalis (estimated at 20–80%, Ezrin-Waters & Resch, 1986), emphasising that critical thresholds are likely to determine whether symptoms will result from damage at other sites.

The pathology of dementia in Parkinson's disease

Neuropathological and biochemical research into the cause of dementia in PD can be divided into three main phases: firstly, the identification of Alzheimer-type neocortical pathology; secondly, the discovery of cell loss in the nucleus basalis; and thirdly, the recognition of Lewy bodies in the cerebral cortex. Each of these lesions has received support as a principal cause of dementia, but there is no clear consensus as to their relative contributions. Initially, the direction of research was influenced by the abnormalities found in AD.

Alzheimer's disease and Alzheimer pathology

The principal lesions associated with the dementia of AD comprise senile neuritic plaques, neurofibrillary tangles, neuronal loss, and granulovacuolar degeneration, predominantly in hippocampal pyramidal cells and neocortex. These changes are also found in elderly persons who are not demented (Quinn *et al*, 1986), and in other disorders such as pugilistic encephalopathy, Parkinsonism–dementia complex of Guam, and Hallervorden–Spatz disease. Nevertheless, they are more severe in AD compared with the elderly, non-demented population, and their distribution especially involves the neocortex rather than the hippocampal region alone.

In the 1960s it was proposed that the number of plaques and tangles correlated approximately with the severity of dementia (Corsellis, 1962; Roth *et al*, 1966). Blessed *et al* (1968) found a mean plaque count of 20.8 in 60 fields (1.3 mm in diameter, 25 μm section thickness) from 12 cortical areas, compared with a count of 5.1 in controls. Tomlinson *et al* (1968, 1970) stated that large numbers of evenly distributed plaques (more than 18 per 'low-power field'), neurofibrillary tangles throughout the cortex, or numerous hippocampal pyramidal cells showing granulovacuolar degeneration occurred only in demented elderly persons, and not in normal elderly persons.

Concern that the correlation between dementia scores and plaques was imperfect (Blessed *et al*, 1968; Tomlinson *et al*, 1970; Wilcock & Esiri, 1982) turned attention to the possibility that tangles serve as

a more accurate histological arbiter of disease severity. Ball (1977) derived an adjusted tangle index and, like previous authors (Tomlinson *et al*, 1970; Dayan, 1970), found greater numbers of tangles in the hippocampus of demented subjects compared with a control population. Wilcock & Esiri (1982) examined the relationship of plaques and tangles in different lobes of the brain and found that tangles, but not plaques, were significantly correlated with dementia, especially in superior and middle temporal gyri. Tangles were also more easily quantified, as they are smaller and of more uniform size.

Despite these developments, the most appropriate histological parameter of AD is still disputed. Ball *et al* (1985) found that in every case diagnosed clinically as uncomplicated AD, the hippocampus contained (a) at least 20 tangle-bearing neurons per mm^3 (the adjusted tangle index), and/or (b) at least 55 nucleolated neurons per mm^3 showing granulovacuolar degeneration, and/or (c) a population of less than 5600 nucleolated nerve cells per mm^3. In contrast, most investigators consider that the extent of neocortical pathology most efficiently distinguishes between normal ageing and dementia, but precise neuropathological criteria for the diagnosis of dementia (e.g. number of tangles in temporal cortex) are difficult to establish, partly because of the effect of age on counts of neocortical plaques and tangles (Mann *et al*, 1984). Older compared with younger patients with AD show fewer tangles and plaques (Rossor *et al*, 1984).

Minimum criteria for histological diagnosis have been suggested (Khachaturian, 1985). The minimum number of areas to be sampled include three regions of neocortex, the amygdala, and the hippocampus. Other causes of dementia are excluded. In any microscopic field in the neocortex encompassing 1 mm^2 (magnification $\times 200$) there should be more than two to five plaques and tangles in patients younger than 50 years, more than eight plaques between ages 50–65, more than ten plaques between ages 66 and 75, and more than 15 plaques over age 75 years. Tangles are often present, but may be absent over 75 years.

Additional pathological findings in AD include loss of cortical neurons and reduced brain weights. Cell loss is restricted to a small subpopulation of large neurons, which are reduced by 40–50% in frontal and temporal cortex (Terry *et al*, 1981; Mountjoy *et al*, 1983). Reduction of brain weight is usually slight, but younger patients show atrophy, particularly in the anterior temporal lobes and other cortical association areas. Lastly, granulovacuolar degeneration usually affects more than 9% of hippocampal pyramidal cells (Tomlinson *et al*, 1970; Ball, 1977, 1978).

The level of ChAT, the biosynthetic enzyme for acetylcholine, is decreased in the cortex (Davies & Maloney, 1976; Perry *et al*, 1977*a*,*b*; White *et al*, 1977) broadly in line with the severity of dementia and the number of plaques (Perry *et al*, 1978) and tangles (Wilcock *et al*, 1982). ChAT is also reduced in the nucleus basalis (Davies, 1979; Reisine *et al*, 1977; Rossor *et al*, 1982; Candy *et al*, 1983*a*), a finding of particular interest, as this structure contains cholinergic neurons projecting to the cortex. In addition Whitehouse *et al* (1981, 1982*a*,*b*) demonstrated that nucleus basalis cell numbers were reduced by a mean of 79%. Most other investigators found less impressive reductions of 35–76%, which approximately match the cortical cholinergic deficit (Arendt *et al*, 1983; Tagliavini & Pilleri, 1983; Wilcock *et al*, 1983; Candy *et al*, 1983*a*), although not in all studies (Perry *et al*, 1983*a*). This finding is now fundamental to the cholinergic hypothesis of dementia.

The primary site of neuronal damage is unknown, although ChAT activity seems to be reduced by over 90% in the nucleus basalis, whereas the loss of cholinergic perikarya is only 35%, suggesting a primary degeneration of axons projecting to the cortex, with secondary loss of perikarya (Candy *et al*, 1983*b*). Cortical abnormalities may induce retrograde degeneration of projections from the nucleus basalis, as well as other areas, such as the locus coeruleus and raphé nuclei (Perry, 1985; Mann *et al*, 1985).

A recent study of early-onset AD showed that acetylcholine synthesis in temporal cortex biopsy specimens correlated with cognitive impairment, suggesting that a deficit in the pre-synaptic cholinergic system occurs relatively early in the disease, and that post-synaptic changes in cortical neurons might be a secondary effect not so closely linked to the defect (Francis *et al*, 1985).

In addition to cell loss in the nucleus basalis, some of the remaining neurons contain tangles. Other subcortical nuclei showing cell loss and tangles, particularly in young-onset cases, are the locus coeruleus (Mann *et al*, 1983), raphé nuclei (Yamamoto & Hirano, 1985), and to a lesser extent the ventral tegmental area (Mann *et al*, 1987) and substantia nigra (Tabaton *et al*, 1985; Rinne *et al*, 1986; Gibb *et al*, 1989*a*). There are consequent reductions of noradrenaline and serotonin in the cortex, and of dopamine in the caudate nucleus and putamen.

Alzheimer's disease and Parkinson's disease

The discovery of correlations between plaques and tangles and the dementia of AD led to the description

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of cell loss, plaques, and tangles in the neocortex, and granulovacuolar degeneration in the hippocampus of patients with PD and dementia (Alvord *et al*, 1974; Hakim & Mathieson, 1979; Boller *et al*, 1980; Ditter & Mirra, 1987; Leverenz & Sumi, 1986). This carried the implication that an increased prevalence of AD explained the dementia of PD. However, such changes received limited quantification, and formal psychological evaluations were not arranged prospectively, the mental status being estimated from information obtained from clinical records. Nevertheless some authors have continued to support the view that dementia is caused by coexistent AD (Cummings *et al*, 1980; Boller, 1980), while others were critical of the methodology in these early studies, and believed they overestimated the severity of the neocortical changes (Mann & Yates, 1983; Ball, 1984; Perry *et al*, 1985).

Cortical atrophy has been described in typical (Selby, 1968) and 'atypical' cases (Sroka *et al*, 1981) of PD, the degree of which has been linked to age and disease duration (Jellinger & Riederer, 1984). However, in most cases brain weights are within the normal range. A study of computerised tomography scans found that ventricular enlargement, but not cortical atrophy, correlated with mental change (Portin *et al*, 1984).

Some early studies in which mental function was not examined failed to find significant depletions of cortical ChAT (Lloyd *et al*, 1975; Reisine *et al*, 1977). Later Ruberg *et al* (1982) found a fall in ChAT levels in frontal cortex of about 50%, and a rise in muscarinic cholinergic receptor density that correlated with the degree of dementia assessed retrospectively. Parallel observations were made by Perry *et al* (1983*a*). It was also suggested that a fall in ChAT concentration preceding the onset of dementia might explain the tendency for many patients to suffer reversible confusional states, especially when prescribed cholinergic antagonists (DeSmet *et al*, 1982; Dubois *et al*, 1983). Anticholinergic drugs were known to have adverse effects on memory in PD (Sadeh *et al*, 1982), but the more specific proposal of Dubois *et al* (1983) was that subthreshold doses of an anticholinergic, which would have no effect on controls, would have deleterious effects on intellectually normal Parkinsonian patients already depleted of cortical acetylcholine.

This was tested in 32 Parkinsonian patients and 32 controls matched in groups for age, education, and intellectual state (Dubois *et al*, 1987). In a double-blind, single-cross-over study, the patients were given scopolamine (0.25 mg) or placebo on day 1, followed by the second of the medications on day 2. In control subjects the anticholinergic had no effect on five tests of memory, but the patients failed on two of the tests that required that meaningless drawings were recognised, results ascribed to possible frontal lobe dysfunction.

Whitehouse *et al* (1983) identified nucleus basalis cell loss in PD, with the greatest depletion occurring in patients with dementia. In another small series, cell loss ranged from 30% to 68%, but could not be related to mental state (Tagliavini *et al*, 1984). Other investigators recorded depletions of 58–77% in patients with dementia (Arendt *et al*, 1983; Rogers *et al*, 1985). Whitehouse *et al* (1983) also reported that in PD, neuronal loss occurred throughout the magnocellular basal forebrain system, the nucleus basalis, medial septal nucleus, and nucleus of the diagonal band of Broca, but in the latter two sites neurons were intact in non-demented patients. A limited statistical analysis showed 74% loss in nucleus basalis in demented cases compared with non-Parkinsonian controls. Taken with the publications on Alzheimer pathology, this would imply that dementia might be due to tangles and plaques in the cortex and neuronal degeneration in the nucleus basalis, either alone or in combination. The strength of evidence favouring the cholinergic hypothesis of dementia and the finding of cortical ChAT depletion in AD and PD encouraged the view that the cause of these dementias was identical.

First suspicions that the analogy with AD (nucleus basalis neuronal loss and cortical Alzheimer pathology) might not be so close came from Gaspar & Gray (1984). They confirmed significantly greater (60%) nucleus basalis cell loss in demented patients compared with that in non-demented patients (32% loss), where mental status was examined retrospectively. The 46% mean loss was lower than obtained in previous studies. ChAT activities were severely reduced in five patients and appeared to correlate with dementia, but could not be linked to cortical tangles and plaques, suggesting that in some patients degeneration of the main ascending cortical input from the nucleus basalis occurred without cortical Alzheimer pathology.

In another study, of 11 patients whose mental state was not examined, eight had 60% depletion of nucleus basalis neurons, but without significant AD lesions (Nakano & Hirano, 1984). A study of 14 PD cases included three that had pathological features sufficient for a diagnosis of AD (Perry *et al*, 1985). In the remainder, tangles were absent from the cortex, and senile plaques lay within the previously established normal range of 0–14/1.3 mm^3. Seven of these 11 patients were mentally impaired, and their ChAT levels were reduced by 66–78%, in all four cortical lobes, with less severely reduced acetyl-

cholinesterase. The ChAT activities correlated with mental impairment, assessed by tests of memory and information, and also with neuronal loss in the nucleus basalis, which amounted to 72% in the mentally impaired subgroup. It did not correlate with neocortical tangle or plaque formation.

Ball (1984) reviewed the data presented by Hakim & Mathieson (1979) concerning the high frequency of Alzheimer pathology in PD, and noted that although Alzheimer pathology was more common in PD there was no statement concerning a possible correlation between the severity of the pathological change and mental state. Reworking of the data using Student's *t*-test showed no significant difference between the number of tangles in 19 subjects with dementia when compared with the 15 without dementia.

Overemphasis and incorrect interpretation of Alzheimer pathology has probably been a factor encouraging many studies to propose that AD and PD are in some way associated. While AD and PD must occasionally coexist, there are virtually no studies which discount a specific association. On occasions Alzheimer pathology and Lewy body neuronal degeneration are clearly dissociated, and can be separately linked with dementia. In AD, neurofibrillary tangle/neuronal degeneration in the nucleus basalis, cortical Alzheimer pathology, and cortical ChAT depletion are associated with dementia; in PD Lewy-body/neuronal degeneration in the nucleus basalis is associated with cortical ChAT depletion, cortical Lewy bodies and dementia. It is therefore a statistical question whether AD and PD coexist more often than chance would allow. In this regard, purely clinical studies are meaningless, because of the inaccuracies inherent in the clinical diagnosis of AD and PD, as reviewed above. Most pathological studies have quantified cortical tangle and plaque pathology in patients with PD, but this approach is also of dubious accuracy in the absence of well defined quantitative thresholds for the pathological diagnosis of AD. An alternative strategy is to study the number of patients with pre-symptomatic PD among a population with AD, and to compare this with controls.

Jellinger & Riederer (1984) reported 128 cases of senile dementia of Alzheimer type and 68 cases of AD, with mean ages of 80.7 years and 65.4 years respectively. The combined mean age was 75.4 years, which compared with a mean of 74.3 years in 180 control patients. Examination of locus coeruleus and substantia nigra showed Lewy bodies in 15–22% of the AD cases and in 10–16% of controls, figures which are not significantly different. In another study, 12 (7.8%) of 273 controls dying over 60 years showed nigral Lewy bodies compared with 14 (14.0%) of 100 cases of AD, with mild nigral cell loss (Gibb *et al*, 1989*c*). The patients with AD and nigral Lewy bodies showed fewer cortical tangles and plaques, but the same cortical ChAT activities, suggesting that Lewy body degeneration in the nucleus basalis contributed to the cholinergic depletion and therefore to the dementia, but not to the cortical Alzheimer pathology. A slightly higher prevalence of Lewy bodies in the patients with AD was probably due to selection into the study of pre-symptomatic or borderline cases of AD, in which dementia was precipitated by coexistent Lewy body pathology.

Lastly, Down's syndrome, which is frequently complicated by premature AD (Godridge *et al*, 1987), is not associated with Lewy body pathology. In general, there does not therefore appear to be evidence for a link between the fundamental pathological processes underlying AD and PD, although one or two exceptions are discussed below. Dementia in PD appears to be commonly associated with Alzheimer pathology because of the dual insult, principally to the innominato-cortical system and cerebral cortex.

At this point we can conclude that dementia in PD is associated with Lewy-body/neuronal degeneration in the nucleus basalis, with or without AD pathology, of a degree that is either pre-symptomatic or symptomatic for dementia. What other pathological lesions are associated with dementia?

Cortical Lewy bodies

Forno (1969) found Lewy bodies in the cerebral cortex in six out of 50 persons (12%) with incidental nigral Lewy bodies (pre-clinical PD), and they can be found in the parahippocampus or temporal cortex in about one third of patients with PD (Gibb & Lees, 1987). Multiple cortical Lewy bodies associated with dementia were first described in Hallervorden–Spatz disease (Helfand, 1935), and later in patients with idiopathic PD (Okazaki *et al*, 1961). Of 23 'idiopathic' cases reported by Japanese neuropathologists, the mean age at onset was 56.7 years (range 26–72 years) (Gibb *et al*, 1987). It was 59.7 years (range 27–74 years) in 17 additional cases (Sima *et al*, 1986; Clark *et al*, 1986; Dickson *et al*, 1987; Gibb *et al*, 1987), although Lewy bodies were restricted to the hippocampus in some (Dickson *et al*, 1987, cases 1, 3, and 5). Paranoid delusions, visual hallucinations, aphasia, apraxia, agnosia, and spatial disorientation were common. Twelve of the series of 23 had considerable cortical Alzheimer pathology, possibly of sufficient severity for AD, although in some other

cases it was mild or absent (Gibb *et al*, 1987). It was described as mild or absent in seven of the 17 patients (41%) reported more recently (Sima *et al*, 1986; Clark *et al*, 1986; Dickson *et al*, 1987; Gibb *et al*, 1987).

The occurrence of substantial Alzheimer pathology in 19 of 40 reported cases (48%) argues in favour of Alzheimer pathology contributing to the dementia in some patients. While the expected prevalence of AD would be well below 10%, around a mean age of 58 years, the frequency of Alzheimer pathology in the hippocampus is 40.0% in the 50–59-year age group, 50.0% at 60–69 years, and 57.1% at 70–79 years, figures collated by combining data from seven studies (Gibb, 1987). If the severity of Alzheimer pathology is not formally quantified, there is probably considerable scope for implying a diagnosis of AD based on a subjective assessment of tangle and plaque numbers. Enthusiastic assessment of pathology relevant to the aetiology of dementia is likely to influence this subjective and poorly defined diagnostic threshold. Despite these arguments, it is clear that dementia in PD can be associated with cortical Lewy bodies alone, or with additional Alzheimer pathology, so that Alzheimer changes are not an obligatory factor. Indeed, the general rule in cases of Hallervorden–Spatz disease with Lewy bodies is that Alzheimer pathology is absent.

I have implied that all patients with cortical Lewy body dementia have PD, but this is not the case. The inclusive pathological term 'idiopathic Lewy body disease' describes the characteristic distribution of Lewy bodies and neuronal degeneration in the nervous system. In some cases the process causing dementia progresses more rapidly and causes symptoms at a time when nigral cell loss is equivalent to the pre-symptomatic stage of PD (less than 60%). Parkinsonian features may or may not emerge during the course of the dementia; if they do not, the condition remains indistinguishable from AD (Gibb *et al*, 1989*b*). Cortical Lewy bodies are not usually associated with obvious cell loss, but a degree of neuronal degeneration would be consistent with their effects elsewhere in the nervous system.

The term 'diffuse Lewy body disease' was introduced to describe patients with cortical Lewy bodies and dementia (Kono *et al*, 1976; Yoshimura *et al*, 1980), but this term is inappropriate because the distribution of the disease is no more widespread than usual, and Lewy bodies do not occur 'diffusely' in the nervous system. It is the emphasis and severity of the Lewy body disease in different parts of the nervous system that varies. Lewy bodies in the cortex are found only in certain neurons located mostly in the deeper laminae, and they do not occur in the hippocampus. They have a consistent propensity to occur in the temporal and frontal cortex, insular cortex, and cingulate gyrus.

Occasional cortical Lewy bodies are often found in non-demented Parkinsonian patients, moderate numbers are found in a few patients, approximately 5–7% (Yoshimura, 1983), and numerous Lewy bodies in fewer than 2%. Despite the high frequency of cortical Lewy bodies in PD, our experience would suggest that not more than 5% of patients with idiopathic Lewy body disease develop dementia, with or without Parkinsonian features, wholly or partly related to cortical Lewy bodies. There is a spectrum of cortical disease, and there are no convincing reasons for considering cortical Lewy body disease/dementia pathologically distinct from PD. Factors that may account for the relatively recent recognition of cortical Lewy bodies include the subcortical location of most pathology in PD, the pursuit of Alzheimer changes in early studies of dementia, and the less conspicuous histological nature of cortical Lewy bodies. In addition, numerous other cortical neurons lacking Lewy bodies often show less well defined, non-staining, pale inclusions (Gibb *et al*, 1987). Recognition of cortical Lewy bodies might have led to alternative interpretations in some recent studies (Heilig *et al*, 1985; Chui *et al*, 1986; Leverenz & Sumi, 1986; Ditter & Mirra, 1987).

The functional consequence of cortical Lewy bodies is unknown. In AD there is a consistent reduction in cortical somatostatin (Davies *et al*, 1980), which may result from degeneration of intrinsic somatostatin neurons (Beal *et al*, 1986). Demented Parkinsonian patients also show reduced cortical somatostatin (Epelbaum *et al*, 1983) and cerebrospinal fluid somatostatin-like immunoreactivity (Jolkkonen *et al*, 1986). Some cortical Lewy bodies develop in somatostatin-containing neurons.

Having attempted to discount a specific pathological association between AD and PD, there are eight patients recorded in whom Lewy bodies and AD pathology coexisted at such a young age, less than 60 years, that their association is difficult to dismiss as one of chance. They were aged 22–47 years at onset of their Parkinsonian disorder or dementia, and aged 28–56 years at the time of death (Kosaka *et al*, 1973; Kayano *et al*, 1980; Okeda *et al*, 1982; Gibb *et al*, 1987, case 2; Popovitch *et al*, 1987; Delisle *et al*, 1987; Gibb *et al*, 1989*c*, two cases). Five of these cases had fairly florid cerebral involvement with both Lewy body and Alzheimer pathology. The case of Popovitch *et al* (1987) was a 28-year-old mentally retarded man who developed dementia from age 22 years, followed by muscular rigidity and

a quadriparetic flexion posture before death. A twin brother was healthy, but "both maternal parents had histories of mental illness". A CT scan at 27 years showed "ventricular dilatation associated with cerebral atrophy" and autopsy showed many cortical and subcortical tangles, an unstated number of cortical Lewy bodies, and brainstem Lewy bodies also. A patient aged 49 years, described by Delisle *et al* (1987), developed motor neuron disease at the age of 36, followed by extrapyramidal rigidity and dementia a few months before death. There were moderate numbers of cortical Lewy bodies, with mild Alzheimer pathology, and loss of anterior horn motor neurons, and Lewy bodies in the spinal cord, although not in surviving motor neurons. These few cases should not detract from the weight of evidence that argues against a specific association between Lewy body disease and Alzheimer pathology in the majority of patients.

The locus coeruleus and dementia

Other nuclear groups that have been investigated in relation to dementia include the locus coeruleus, where neuronal loss is reportedly greater in patients with dementia (Gaspar & Gray, 1984), as are the reductions in noradrenaline (Cash *et al*, 1987). However, cortical noradrenaline levels show equivalent reductions in demented and non-demented patients, or significant reductions in demented patients, that do not correlate with the severity of the dementia (Francis *et al*, 1985). When interpreting the effects of neuronal degeneration in the locus coeruleus, the possibility of coexistent Alzheimer pathology, as for the nucleus basalis, needs to be considered.

The substantia nigra and dementia

Rising prevalence rates of dementia with increasing disease duration aroused suspicion that dementia might be closely linked to progressive motor impairment, or even to long-term L-dopa therapy (Sweet *et al*, 1976; Rajput *et al*, 1984). It was suggested that loss of nigrostriatal activity, the cause of increasing motor disability, might contribute to dementia (Ball, 1984). It is also true that improvement in some cognitive functions often follows the start of L-dopa therapy (Portin *et al*, 1984), although this has been attributed to its awakening effect. One careful examination of the relationship between intellectual performance and motor function involved a group of patients experiencing severe and rapid fluctuations in motor disability between phases of extreme immobility and mobility (Brown *et al*, 1984). There were no significant alterations in intellectual performance assessed using the modified Alice Heim test, but minor fluctuations were thought to be due to alterations in mood and alertness. Lastly, histological studies have not been able to correlate the degree of nigral neuronal loss with dementia (Gaspar & Gray, 1984). Any apparent ill-effect of L-dopa is thus likely to be related to age and the duration of the disease, which are related to the prevalence of dementia.

Ventral tegmental area and dementia

Impaired function of the ascending dopaminergic mesocorticolimbic projection is widely believed to contribute to the frontal lobe dysfunctions contributing to dementia (but see above), but is not thought to be important in severe dementia.

Summary

In this review I have identified the following main points.

(a) Neuropsychological deficits described in PD do not signify widespread cortical pathology, but frontal lobe deficits imply disruption of caudate nucleus outflow.
(b) The prevalence of dementia is approximately 10–20%, which is twice that in the general population.
(c) Dementia is rare in young-onset PD, despite long survival, and is therefore more closely related to age than to PD.
(d) Important characteristics of Lewy body disease are slow rates and modest degrees of neuronal loss. There are thresholds of neurochemical depletion corresponding to the onset of symptoms, which are functionally important and most readily appreciated in the substantia nigra.
(e) The three major pathologies associated with dementia are AD, Lewy body neuronal degeneration in the nucleus basalis, and cortical Lewy bodies.
(f) There is no concrete evidence favouring a greater than chance association between AD and PD.

What then is the pathological substratum for dementia? Of the three pathologies cited, only AD is more closely related to age than to disease. One other possible factor is an age-related reduction in numbers or function of nucleus basalis neurons (McGeer *et al*, 1984), although this is not well

substantiated. There is no evidence that Lewy body disease shows a different spectrum at different ages. Lewy-body/neuronal degeneration in the nucleus basalis or cortex is no more severe in older-onset patients. Tagliavini *et al* (1984) observed in PD that nucleus basalis depletion does not vary with age; and the mean age of patients presenting with cortical Lewy body dementia is similar to the mean presenting age for PD. The threshold level at which symptoms arise as a result of nucleus basalis damage is unknown, but nerve cell depletions between 20% and 50% are quoted for non-demented patients, and between 40% and 80% for demented patients (Ezrin-Waters & Resch, 1986). The isolated cholinergic depletion that results may cause amnesia, but is probably an insufficient cause for dementia. Additional cortical pathology is presumably mandatory.

The rare occurrence of dementia in young-onset PD indicates that nucleus basalis degeneration, with or without cortical Lewy bodies, is not usually severe enough to cause dementia. Cortical Lewy body pathology is probably sufficiently severe to precipitate dementia in very few patients, for example less than 2%, which is the prevalence figure for dementia in young-onset PD. In an additional 5–7% of patients over 65 years, dementia is provoked by moderate to severe AD, as in the general population.

An additional 3–13% prevalence is required to tally with the 10–20% prevalence of dementia in PD. This might be derived from: (a) about 7% of patients with pre-symptomatic Alzheimer pathology and Lewy-body/neuronal degeneration in the nucleus basalis; (b) about 3% of patients with pre-symptomatic cortical Lewy body disease and Lewy-body/neuronal degeneration in the nucleus basalis; and (c) up to 5% of patients in whom dementia is associated with a combination of cortical Alzheimer pathology, nucleus basalis depletion, and cortical Lewy body disease. However, in the latter situation cortical Lewy bodies are mostly of little significance in view of their usually small numbers, and their presence should not be interpreted as a culpable factor for the dementia.

There are a number of areas of interest in the further elucidation of dementia in PD. Sadly the scope for specific therapy is limited. More information is required on the spectrum of nucleus basalis damage in PD, at different ages of onset, and different disease durations. Accurate data on the chemical and neuronal depletions in the nucleus basalis are required when additional pathologies, such as AD, are present. Greater knowledge of the neurochemical consequences of cortical Lewy bodies and AD could conceivably reveal specific therapeutic approaches. Identification of more young patients with Alzheimer and Lewy body pathology, especially if familial, may unravel pathogenetic mechanisms. Ideally the material to answer such questions should be selected from the countless individuals with dementia or Parkinsonian disorders, who should be prospectively evaluated clinically, as well as pathologically.

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