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Dementia with Lewy Bodies. A Distinct Non-Alzheimer Dementia Syndrome?

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Lewy body formation is central to the pathological phenotype of a spectrum of disorders. The most familiar of these is the extrapyramidal syndrome of idiopathic Lewy-body Parkinson's disease (PD). Studies of dementia in the elderly suggest that another manifestation of Lewy body pathology is equally or more common than Parkinson's disease. This syndrome of Dementia with Lewy bodies (DLB) has been given a number of diagnostic labels and is characterised by dementia, relatively mild parkinsonism, visual hallucinations, and fluctuations in conscious level. Although many of these features can arise in Parkinson's disease, the patients with DLB tend to have early neuropsychiatric features which predominate the clinical picture, and the diagnosis of the syndrome in practice is more concerned with the differential diagnosis of Alzheimer's disease (AD). Distinction from AD has clinical importance because of potentially differing therapeutic implications. Diagnostic guidelines for the clinical diagnosis and pathological evaluation of DLB are reviewed. Research into the disorder has centered around characterising the clinical, neuropsychological, pathological, neurochemical and genetic relationships with Alzheimer's disease on the one hand, and Parkinson's disease on the other. Many cases of DLB have prominent pathological features of AD and there are some shared genetic risk factors. Differences from the pathology of PD are predominantly quantitative rather than qualitative and evidence is discussed which suggests that DLB represents a clinicopathological syndrome within the spectrum of Lewy body disorders. The possibility that the syndrome represents a chance association of PD and AD is not supported by published studies.

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Introduction

Lewy bodies are found as coincidental pathology in a wide range of conditions (Table 1) but are characteristically associated with idiopathic Parkinson's disease (79, 152). Dementia associated with Parkinson's disease is increasingly recognised to be a frequent component of the disease in clinical practice (172). The range of clinical disorders in which Lewy bodies form a characteristic and necessary part of the pathological substrate includes extrapyramidal movement disorders, cognitive impairment, autonomic failure and dysphagia (Table 2). These observations have given rise to the concept of a spectrum of Lewy body disorders among which Parkinson's disease is the best recognised (132, 276). The work of Kosaka and colleagues has provided a framework of pathological observations behind these differing clinical syndromes based on the concept that the clinical manifestation of Lewy body pathology depends on the severity and anatomical distribution of Lewy body involvement in the CNS and PNS (133, 137). A key part of this work was the recognition that a cortical form of Lewy body is frequently encountered in Parkinson's disease, especially in cases complicated by cognitive impairment (100).

Pathological studies over many years have also drawn attention to the overlap, and common concurrence of the pathologies of Parkinson's disease and Alzheimer's disease (18, 28, 56, 66, 75, 85, 121). In the late 1980's several groups in the USA and Europe began

Disorder	Ref
Ataxia telangiectsia	(47, 184)
Corticobasal degeneration	(200,98, 268)
Down's syndrome	(223, 17)
Familial early-onset Alzheimer's disease	(147)
Hallervorden-Spatz disease	(94,46,58, 123,76, 268)
Motor Neuron disease	(93, 272)
Multiple system atrophy	(186,78, 243)
Neuraxonal dystrophy	(264, 273, 256)
Progressive supranuclear palsy	(78, 185)
Subacute sclerosing panencephalitis	(80)

Table 1. Disorders in which LB are reported as a coincidental feature.

Disorder	Severity of neuroanatomical involvement					ref.
	Cortex	SN/LC	Vagus nucleus	Myenteric plexus	Autonomic ganglia	
Dementia with Lewy Bodies:						
'Common form' or 'Lewy Body Variant'	+ → +++	+ → ++	+	?	?	(88, 132, 212)
'Pure form' or 'Diffuse Lewy Body Disease'	+ → +++	++ → +++	+	?	?	(132, 212)
Parkinson's disease	+ → ++	+++	+	+	+	(65, 269, 276)
LB dysphagia	- → +	+	+ → ++	++ → +++	?	(117)
Pure autonomic failure	-	- → +	-	?	++ → +++	(84)

- = not involved; +, ++, +++ = increasing frequency of LB formation; ? = insufficiently characterised/unknown

Table 2. Disorders primarily characterised by Lewy body pathology.

Country	Centre	ref.
Austria	Vienna	(119)
Canada	Toronto	(16)
	Winnipeg	(244)
Germany	Frankfurt am Main	(59)
Holland	Enschede	(45)
Japan	Yokohama	(138)
	Tokyo	(142)
Norway	Oslo	(106)
UK	Newcastle upon Tyne	(212)
	Nottingham	(30)
	London	(68)
USA	San Diego	(87)
	New York	(52)

Table 3. Geographical location of Centres reporting significant cohorts of DLB cases.

to draw attention to a group of elderly demented patients with clinical features that were atypical for Alzheimer's disease (30, 52, 88, 137, 212)(Table 3). These patients showed variable Alzheimer-type pathology, but had significant numbers of Lewy bodies in both cortical and subcortical regions. Retrospective review revealed a characteristic clinical profile including a number of features which differ significantly from Alzheimer's disease (30, 212). Chief among these were fluctuation in cognitive performance and conscious level, visual hallucinations, and extrapyramidal motor features of variable severity. Often such cases were found to have neocortical senile plaque formation at densities equivalent to that found in Alzheimer's disease in the elderly, but neocortical neurofibrillary tangles were infrequent (52, 88, 87, 138, 212). A smaller group of these patients had only minimal plaque pathology. These findings sparked a heated debate over terminology regarding the relationship of this syndrome to Alzheimer's disease. Additional problems of pathological interpretation arose from the perspectives of the varied clinical background and orientation of these groups in neurology and psychogeriatrics. Among clinicians a different debate arose regarding the relationship between this atypical dementia syndrome and dementia occurring as part of Parkinson's disease.

These two controversies are still unresolved and the subject of debate:

1. What are the clinical, pathological, and etiological relationships among the spectrum of Lewy body disorders?
2. How does atypical dementia with Lewy bodies relate to Alzheimer's disease?

The terminological confusion (outlined in Table 4) reflects the differing emphasis put on various aspects of the problem. An attempt at rationalisation was made at the 1st International Workshop on Dementia with Lewy Bodies in 1995. Consensus guidelines on clinical diagnosis and pathological evaluation were adopted to allow research in the field to proceed in a comparable way in different centres (177). In order to use and understand these guidelines it is necessary to appreciate the following:

1. The term Dementia with Lewy bodies was adopted because it is encompassing and non-specific. It does not prejudge the significance of Lewy bodies as a pathological substrate for dementia. As such these are primarily research-based guidelines and there is still a place in rou-

tine clinical practice for a more specific diagnostic label. The DLB Workshop Consortium explicitly left it open for individual clinicians and pathologists to use their favoured terminology (as in Table 4) in the context of routine clinical practice. Currently in the literature the most frequently used of these terms are 'Diffuse Lewy body Disease (DLBD)', the 'Lewy Body Variant of Alzheimer's Disease (LBV)' and 'Senile Dementia of the Lewy Body Type (SDLT)'. For many practical purposes these terms are interchangeable.

2. The pathological guidelines were designed to allow unbiased evaluation of the pathological features. A scheme was devised to allocate any case with Lewy bodies into three categories - 'neocortical', 'limbic (transitional)', and 'brainstem predominant'. There is no direct evidence that Lewy body pathology follows a hierarchic pattern of progression analogous to that proposed in 'Braak staging' of Alzheimer's disease (21) and the extent to which cases evolve from one category to another is uncertain. The DLB Consortium shared an expectation that dementia would tend to be most frequent when cases were in neocortical or limbic categories, but it is not necessary for cases to be in any particular pathological category to be regarded as 'Dementia with Lewy bodies'. Equally a diagnosis of DLB can only be made on the basis of a clinical history of dementia. Finally a diagnosis of Dementia with Lewy bodies (or one of the more specific terms) does not preclude other diagnoses. Alzheimer-type pathology especially should be assessed, according to established criteria (CERAD (183, 182) or NIA-Reagan Institute (193)), and an opinion given as to whether there is sufficient pathology to warrant that diagnosis.

Clinical Phenotype

Within the spectrum of Lewy body disorders there is a group of elderly demented people who have a consistent pattern of clinical features. This group comprises the second most frequent diagnostic category in many hospital-based autopsy series of elderly demented patients (212). The clinical syndrome is distinct from Alzheimer's disease although there is some inevitable overlap which is particularly apparent if broad diagnostic criteria for Alzheimer's disease are adopted such as NINCDS-ARDRA (127). DLB shows a similar age range and insidious onset of dementia as AD and the terminal severity of cognitive impairment is comparable (87, 212). Survival in published series is shorter than for AD, and DLB patients are especially vulnerable to neuroleptic medication which further accelerates mortality (174). The features which have been most consistently described as differentiating this group from Alzheimer's disease are extrapyramidal signs, and psychiatric/behavioural symptoms (3, 83, 177). These now form the basis of the core features in the Consensus criteria for the clinical diagnosis of DLB (Table 5).

Cortical Lewy body disease
Diffuse Lewy body disease
Senile Dementia of the Lewy Body Type
Parkinson's disease dementia
Parkinson's disease plus Alzheimer's disease
Alzheimer's disease with incidental Lewy bodies
Lewy body dementia
Lewy body Variant of Alzheimer's disease

Table 4. Nomenclature used to classify DLB cases.

Extrapyramidal signs in DLB and AD. Parkinsonian signs are not infrequent in AD and may be present in up to 50% in the later stages (72) even in the absence of neuroleptic medication. LBs are present in up to 25-30% of 'AD' patients at most, and therefore parkinsonism must be multifactorial. In DLB parkinsonian features can often be an early feature and may be present at initial presentation. They are usually less severe than in Parkinson's disease (71, 155) and often fail to fulfil PD diagnostic criteria; in particular resting tremor is uncommon in DLB. Other subtle differences in the clinical features suggest differences in the underlying pathological and neurochemical substrate of the movement disorders in PD and DLB (208). The temporal relationship between onset of PD and dementia is not resolved in the DLB consensus guidelines; a cut-off of one year has been proposed for the onset of dementia following a definite diagnosis of PD (177).

Psychiatric and Behavioural symptoms. Two prominent features in DLB are visual hallucinations and fluctuation in cognitive performance. The visual hallucinations are characteristically recurrent, well formed and detailed and in the earlier stages may be associated with insight into their nature (29, 129, 178, 180, 212). Descriptions of these hallucinations show similarity to those experienced during systemic metabolic disturbances or anticholinergic toxicity and differ from those induced by other hallucinogens. Data from several

1. The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.

2. Two of the following core features are essential for a diagnosis of probable DLB, and one is essential for possible DLB:
   a. Fluctuating cognition with pronounced variations in attention and alertness
   b. Recurrent visual hallucinations that are typically well formed and detailed
   c. Spontaneous motor features of parkinsonism

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3. Features supportive of the diagnosis are:
   c. Repeated falls
   d. Syncope
   e. Transient loss of consciousness
   f. Neuroleptic sensitivity
   g. Systematised delusions
   h. Hallucinations in other modalities

4. A diagnosis of DLB is less likely in the presence of:
   d. Stroke disease, evident as focal neurologic signs or on brain imaging
   e. Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

from: (177)

Table 5. Consensus criteria for the clinical diagnosis of probable and possible Dementia with Lewy Bodies.

groups suggest that hallucinations involving other sensory modalities are considerably less frequent, and may be no more frequent than encountered in AD patients.
Another major feature of DLB in the elderly is fluctuation in the cognitive state and/or consciousness which occur over periods ranging from a few hours to weeks or longer (177). They are sometimes associated with intercurrent illness but can also be quite spontaneous. They are independent of normal diurnal variation in performance. However this symptomatology remains controversial, not least because of difficulties in defining fluctuation, and in its quantification.

A number of other clinical features have been included as supportive in the diagnosis (Table 5). Falls, syncopal episodes, and loss of consciousness may represent the effects of Lewy body pathology in the peripheral, especially autonomic, nervous system. The other features (neuroleptic sensitivity, systematised delusions and hallucinations in other modalities) are presumed to arise on the basis of other, as yet incompletely characterised, neurochemical abnormalities.

Exclusion criteria include any other known disorder which could account for the symptoms. This restriction on the clinical diagnosis needs to be interpreted with circumspection given the frequent occurrence of comorbidity in elderly patients (120, 188). For example it is not yet known whether DLB patients have the excess of cerebrovascular pathology similar to that described in AD.

Validation of clinical diagnostic criteria. Studies of the sensitivity and specificity of clinical diagnostic criteria for DLB show values similar to comparable studies of Alzheimer's disease. Most of these studies are retrospective or the patients were diagnosed by using one of two protocols which preceded the DLB Consensus guidelines (29, 178). On average the sensitivity and specificity of the diagnostic criteria reported in these studies is around 80% (175, 176, 181). A preliminary report of the performance of the Consensus Guidelines in a prospective cohort shows sensitivity of 83% and specificity of 92% compared with comparable values of 78% and 87% for a diagnosis of 'probable AD' (NINCDS-ARDRA criteria) in the same study (105).

Neuropsychological profiles in AD and DLB. This area has received considerable attention from many groups using a wide range of psychological assessment instruments. Detailed analysis of the field is beyond the scope of the present review but some broad conclusions have been drawn. Many studies have identifed significant deficits in attention, fluency and visuospatial processing in DLB compared to AD (87). It is also apparent that 'pure DLB' cases (with minimal Alzheimer'-type pathology) show a combination of deficits that can be classified as 'cortical' (impaired memory, language, executive functions, visuospatial abilities) and 'subcortical/nigrostriatal' (impaired learning, attention, visuoconstructive abilities, psychomotor speed) (74, 226-228, 230).

Pathological Phenotype

Spectrum of Lewy body disorders. Consideration of the neuropathology of DLB must take into account the spectrum of conditions in which Lewy body pathology is regarded as a primary component of the disorder. These conditions can be readily interpreted on the basis of the neuroanatomical burden of the degenerative process (Table 2). The motor features of Lewy body disorders thus predominantly manifest as an extrapyramidal syndrome (e.g. Parkinson's disease with a 'paucity of movement'), but in some occasional cases may be associated with dystonia (e.g. Meig's syndrome with an 'excess of movement')(164). Such differences in clinical phenotype reflect underlying complex neurochemical imbalances in affected brain regions and are not a specific consequence of Lewy body degeneration.

Rare cases of atypical dementia with parkinsonism and cortical Lewy bodies were first described by Okazaki et al. (198) and the concept of a spectrum of Lewy body diseases was originally proposed by Kosaka and colleagues (133, 135). The peripheral and central areas of the nervous system involved by LB in Parkinson's disease include hypothalamic nuclei, nucleus basalis of Meynert, dorsal raphe, locus ceruleus, substantia nigra, dorsal vagus nucleus, and intermediolateral nucleus (48). In addition a 'neuritic' form of Lewy body was described in the dorsal vagus nucleus, sympathetic ganglia, and in intramural autonomic ganglia of the gastrointestinal tract . Kosaka and colleagues later demonstrated cases with extensive cortical and basal ganglia involvement (131, 136). Thus a spectrum of Lewy body disease was proposed and classified into three types: brainstem, transitional and diffuse. This concept is now the basis for the categories defined by the Consensus Guidelines on the evaluation of DLB (177). More recently Kosaka proposed a 'cerebral' subtype of Lewy body disease in patient with progressive dementia and no detectable parkinsonian features (134). Pathologically this individual showed widespread neocortical and limbic LB involvement. The pigmented brainstem nuclei only showed rare LB with no neuronal loss and the patient had no significant Alzheimer-type pathology. The significance of these observations relates especially to the evolution and spread of LB pathology. In Alzheimer's disease there is evidence that the disease in most patients follows a hierarchic evolution from medial temporal lobe regions to other 'limbic' areas and then to temporal, parietal, frontal and occipital neocortex (8, 21). Within the spectrum of Lewy body diseases there is no evidence for such hierarchic spread:

1. **Essential** for the diagnosis of DLB	
Lewy bodies	
2. **Associated** with DLB but not essential	
Lewy Neurites	
Alzheimer-type pathology	Senile plaques Neurofibrillary tangles
Regional neuronal loss	especially affecting substantia nigra, locus ceruleus, and nucleus basalis of Meynert
Microvacuolation	
Synapse loss	
Neurochemical abnormalities/neurotransmitter deficits	

From: (177)

Table 6. Pathological features associated with DLB.

Cases may present with brainstem LB, clinically manifesting as PD, who live for many years but show very few cortical LB at autopsy. In contrast DLB patients (including the 'cerebral Lewy body disease' patient described above) may get severe cortical involvement as an early feature with minimal brainstem disease. In addition patients may develop predominant involvement of the peripheral nervous system (e.g. Lewy body dysphagia and Primary Autonomic Failure) with minimal central involvement. Very few cases of DLB can be explained by progression of PD pathology from the midbrain and brainstem to the cerebrum.

Therefore the role of the Pathologist, when confronted by a case with an appropriate clinical history, is to address two questions:

1. Is this disorder associated with Lewy body pathology?
2. What is the anatomical distribution of LB and what is the regional severity of involvement?

In relation to the second question the Pathology section of the Consensus Guidelines for the Evaluation of cortical LB were offered as a means of standardising assessment of LB pathology in cortical regions (177). They were designed to be equally applicable, in addition to a survey of LB pathology in other relevant CNS and PNS regions, in cases with or without dementia.

Pathology of DLB

The pathological lesions encountered in DLB are given in Table 6.

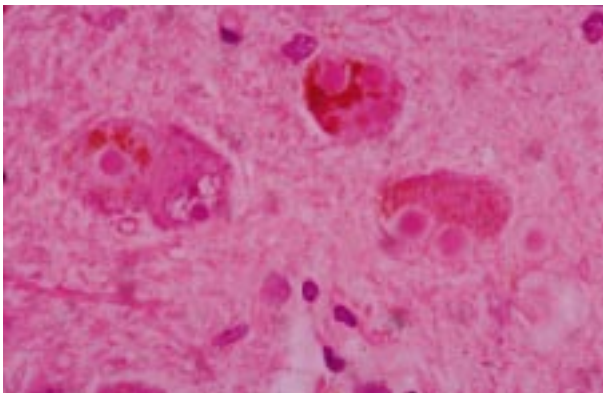

Figure 1. At least seven Lewy bodies are present in relation to three neurons in the substantia Nigra.

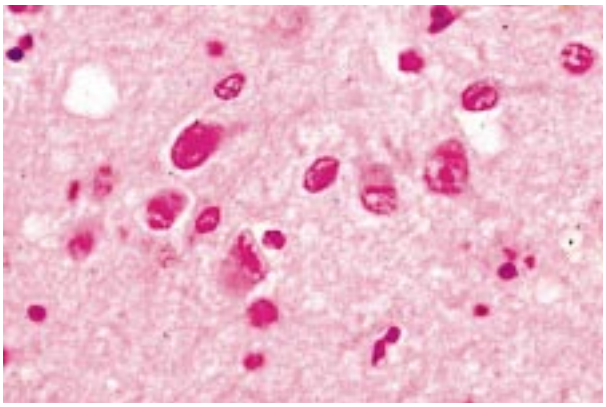

Figure 2. Cortical Lewy bodies in neurons from layer 5/6 of the temporal lobe cortex. Searching for these structures requires assessment at a reasonably high magnification.

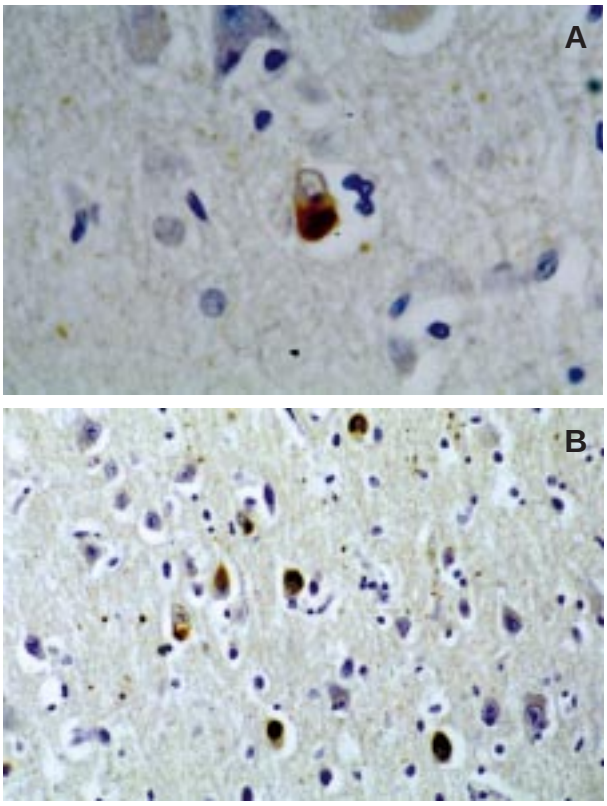

Figure 3. Anti-ubiquitin immunostaining is a sensitive marker for cortical Lewy bodies (**a**) and makes detection of cortical Lewy bodies relatively easy even at relatively low magnification (**b**). Higher magnification is required to discriminate between cortical Lewy bodies and small spherical tangles which can also stain with anti-ubiquitin.

Lewy bodies. Lewy bodies are encountered in both subcortical nuclei (as in Parkinson's disease) and also in cerebral cortical regions. In the pigmented brainstem nuclei the Lewy bodies show a classical morphology comprising an eosinophilic core and peripheral halo (Figure 1). In the cortex they are much less distinct in conventional stains, which probably accounts for their being overlooked by many previous workers, appearing as a diffusely granular eosinophilic spheroid with no halo (Figure 2). In routine practice most laboratories now use ubiquitin immunocytochemistry to demonstrate cortical LB, and H/E for brainstem lesions (Figure 3). In one report it was shown that ubiquitin ICC was 2.4x more sensitive on average in the detection of cortical Lewy bodies (151), but others have shown either no difference between these methods or higher counts with H/E (Perry RH; personal communication). The factors contributing to these tinctorial and antigenic variations are unknown but may reflect differences in fixation and processing schedules. At present there does not appear to be a single 'ideal' marker of cortical LB although recent findings suggest that α-synuclein may be useful in this regard (253). The only silver staining method which can reliably demonstrate cortical LB is Campbell-Switzer (22), although fixation is an equally important variable in the efficacy of all silver impregnation methods, and other ICC methods are less reliable than ubiquitin. A single report of optimal LB staining using an antibody to MAP5 has not been generally accepted in routine practice (70). The most important practical problem in the evaluation of cortical Lewy bodies is the distinction from small globular tangles in those cases with combined Alzheimer-type and LB pathologies. Since LB are usually unstained by antibodies to PHF-tau it has been suggested that LB should only be confirmed, in cases with cortical NFT, if they are negative for a reliable anti-tau antibody.

In the brainstem the frequency of LB in pigmented

nuclear groups may be low, and frequently is not associated with loss of substantia nigra neurons of a severity comparable with PD patients. Taken as a group DLB patients show SN neuron counts which are intermediate between PD and AD (106, 212). However cases vary, and there may be SN neuron loss in the PD range so that individuals may show variable expression of parkinsonian symptoms. Another brainstem nucleus regularly affected in PD is the cholinergic pedunculopontine tegmental nucleus which may also be preferentially affected in DLB. Similarly individual patients will vary in the involvement of serotonergic nuclei although no quantitative studies in DLB are published. The locus ceruleus tends to be very severely affected by neuronal loss and LB in both PD and DLB patients (212, 278).

Some degree of cortical LB involvement has now been described as a feature of PD whether or not the patient has dementia (100). A recent study found cortical LB in 75% of 37 PD cases and a tendency for dementia to be associated with neocortical LB (257). Thus the difference between PD and DLB in terms of cortical LB pathology is likely to be quantitative not qualitative. This is a particularly problematic area since no published work has compared a substantial series of elderly PD patients (including groups both with and without dementia) with DLB using adequately defined diagnostic criteria. In both DLB and PD the distribution of LB in the cortex is most frequent in limbic areas and the Consensus Guidelines include evaluation of the transentorhinal cortex and the anterior cingulate (177). Quantitative studies have shown that cingulate involvement is more marked in Brodmann area 24 compared to 23 (212). The amygdaloid complex, insula, entorhinal and transentorhinal cortices have also been shown to be sites of predilection for LB formation (23, 109, 138, 225, 239) but they are not found in the hippocampal formation. Neocortical involvement is usually most severe in the temporal lobe and follows the gradient: temporal>parietal=frontal>occipital (138, 212). The Consensus Guidelines do not include the occipital region where Lewy bodies are infrequent, even in the most severely involved cases of DLB, and where their presence does not contribute to a significant distinction between pathological categories (212).

Most groups report that cortical LB are most frequent in deeper layers (especially cortical layers 4, 5 and 6) in all affected regions. (138) The population of affected neurons has yet to be adequately characterised. On morphological grounds they occur in small and medium sized neurons (52, 138). Recent studies confirm that these are pyramidal neurons on the basis of immunoreactivity to SMI32 (a marker of non-phosphorlylated neurofilament medium and heavy subunits) and the absence of parvalbumin (a marker of gaba-ergic interneurons). (249, 265) The total number of SMI32 positive neurons was reduced by 70% in DLB in this study suggesting that LB formation is associated with severe neuronal dysfunction or death. (265) However there was also a 40% reduction in parvalbumin immunoreactive neurons suggesting that there is only relatively selective vulnerability of pyramidal neurons. Some groups report that cortical LB frequency is positively correlated with the intensity of dementia (233) although this finding remains controversial. Thus the extent to which LB are themselves the substrate for dementia in DLB or PD is doubtful. Even in the most severely affected cases of DLB the frequency of cortical LB is at least 10^3x less than would be the case for neurofibrillary tangles in AD patients with a similar level of cognitive deficit (212). It is likely that the substrate of cognitive deficits in 'pure' DLB cases will eventually be explained on the basis of a complex interaction of pathological lesions (cortical and subcortical), diffuse molecular pathological changes, and neurochemical alterations in both cortical and subcortical neurotransmission.

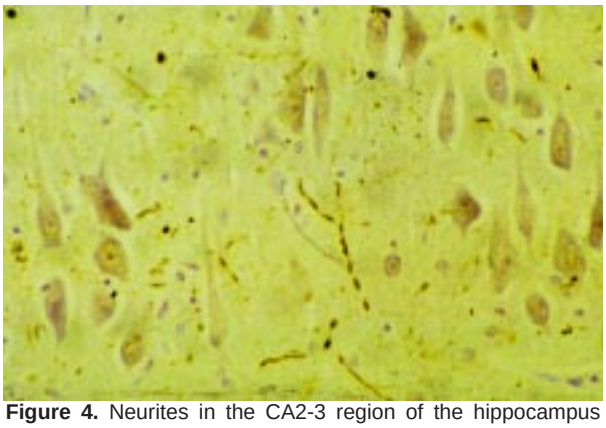

Figure 4. Neurites in the CA2-3 region of the hippocampus detected by anti-ubiquitin immunostaining appear as beaded and corkscrew-shaped structures.

Lewy neurites (Lewy-related neurites). Attention was first drawn to the occurrence of distinctive ubiquitin-immunoreactive neuritic processes in the CA2 sector of the hippocampus in DLB (Figure 4)(53, 54). These lesions were originally proposed as a means of distinguishing hippocampal pathology in AD and DLB where Alzheimer-type pathology can be significant (see below). While this concept remains valid, further reports have shown that these neurites are also a consistent fea-

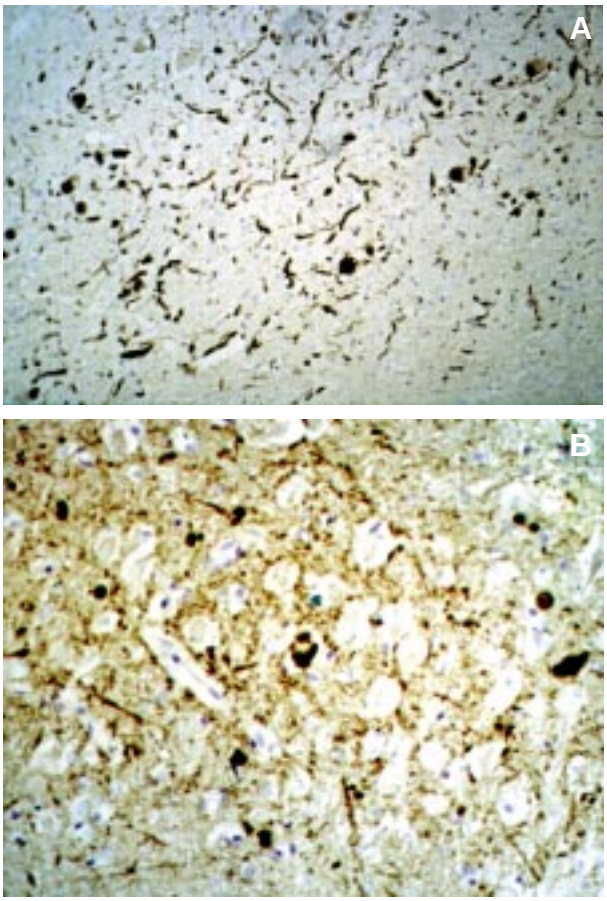

Figure 5. Neurites and Lewy bodies show immunoreactivity for α synuclein shown here in substantia nigra (**a**) and hippocampal regions (**b**) of the brain (Pictures courtesy of Dr. M. Spillantini).

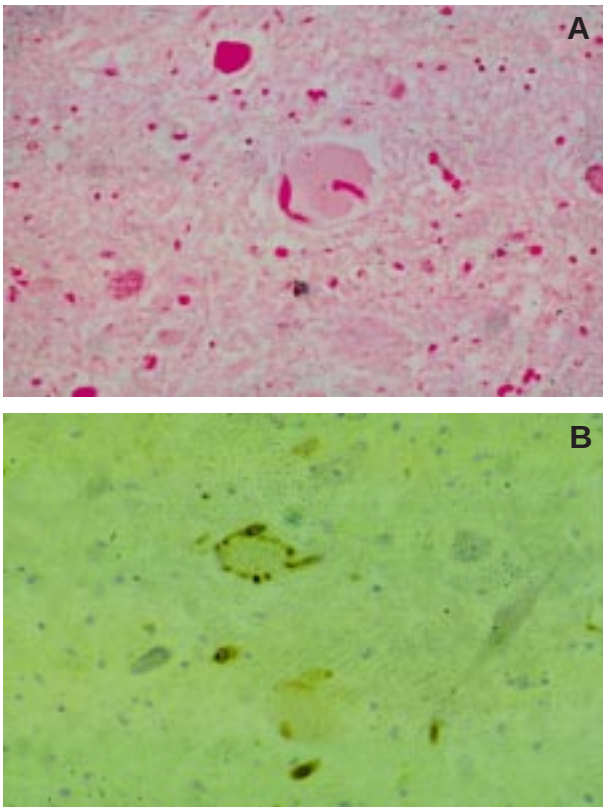

Figure 6. Neurites can be seen in the dorsal vagal nucleus in DLB and PD appearing as bright hyaline structures on H&E staining (**a**) and showing strong ubiquitin immunoreactivity (**b**).

ture of PD and are independent of dementia (45). Neurites are also immunoreactive for neurofilament epitopes (especially phosphorylated epitopes) and also α-synuclein (Figure 5). Immunoreactivity to Alz50 andTau-2 have also been reported but not to NFT specific tau isoforms (54). Electron microscopy confirms the major component of intermediate filaments within these structures. They are also described in the amygdala (23) basal forebrain, substantia nigra, pedunculopontine nucleus, raphe nuclei, dorsal vagal nucleus (Figure 6) and neocortex (69, 201). In all of these sites neurites can be present in very high density but they are not co-localised with immunoreactivity to tyrosine hydroxylase, suggesting that they do not arise in the distal projections from the substantia nigra. Lewy bodies and neurites co-exist (128), and in one study the intensity of CA2 neurites and cortical LB formation were shown to be correlated (219). Neuritic pathology resembling that seen in PD has also been described in Huntington's disease (HD) (31, 116) and in one subtype of frontotemporal dementia (118, 258). In both these instances the distribution of neurites differed from that seen in PD and DLB.

The significance of Lewy-neurites in DLB is uncertain both in terms of their pathogenesis and their role in neuronal dysfunction or clinical phenotype. In HD the evidence suggests that neuritic pathology alone may be the only cytological marker of neurodegeneration: In patients with late-onset HD these ubiquitin-immunoreactive and huntingtin-immunoreactive neurites are prominent pathological features in the cerebral cortex, while in young-onset patients (correlating with large CAG repeat expansion of the huntingtin gene) nuclear inclusions are the most characteristic finding (55, 237). It is likely that Lewy neurites, in common with other disorders involving abnormal neuritic degeneration (including AD), will be explained by the sequestration of an abnormal protein, complexed with ubiquitin, within nerve cell processes. In this respect the functional significance of α-synuclein accumulation in these structures is of great interest.

Alzheimer-type Pathology. Many cases of DLB have features of the pathology of Alzheimer's disease. The present paper is biased towards the view that DLB should be regarded as a syndrome that is distinct from AD. Others have put forward a differing viewpoint which cannot be disregarded (87). Two areas of pathological observation can be used to support the distinction of DLB from AD: Firstly the occurrence of cases in whom there is no significant Alzheimer-type pathology, and secondly quantitative and qualitative analysis of the Alzheimer-type pathology that is found in DLB.

Several of the published series of autopsy cases, which first drew attention to DLB as a distinct dementing syndrome in the elderly, included a minority of cases with virtually no ATP (52, 138, 212), including an absence of senile plaques of any type. These cases were shown to be clinically indistinct from other DLB cases, and the burden of ATP was less than in many age-matched individuals who were cognitively intact at the time of death (154). These cases correspond to the category of 'pure DLBD' described by Kosaka (132) to distinguish them from those cases with ATP who comprise the 'common form of DLBD'.

The relationship between AD and Lewy body diseases is problematic. Various observations have been reported in the literature which predate the emergence of DLB as a distinct entity. Such observations include:

1. More frequent Alzheimer-type pathology in PD cases than in age-matched control (18, 66, 78, 85, 100)
2. An increased frequency of LB in AD including familial cases related to APP gene mutations (56, 86, 121, 147)

Since these studies also predate a widespread awareness of the frequency of cortical Lewy bodies, and the use of sensitive methods to detect them, they are very difficult to interpret in the context of more recent concepts. It is likely that DLB represents an undiagnosed group within many of these older reported cohorts and the syndrome may account for much of the clinicopathological overlap described between AD and PD. Review in Newcastle of cases reported by Professor B. Tomlinson prior to 1982 include a proportion of demented cases which correspond to the entity 'Senile Dementia of the Lewy Body Type' (R.H. Perry personal communication). This is certainly the case with respect to the category 'plaque-only Alzheimer's disease': Re-examination of the original cohort, from whom this diagnostic category was formulated, showed that most patients could be re-interpreted as DLB (89).

In the neocortex quantitative studies showed that the burden of senile plaques is similar in many DLB cases and age-matched AD patients, even in cohorts among whom the DLB patients died more rapidly after onset of dementia (87, 212). In image analysis studies of DLB and AD cohorts, matched for age and degree of dementia, the area occupied by βA4 immunoreactive deposits was reported to be equal and there was no difference in the ratio of different morphological categories of plaque type (77, 179). Qualitatively this reflects the burden of βA4 amyloidosis, and not the cytoskeletal pathology of AD. The major difference between the senile plaques of AD and those in DLB is the paucity of a neuritic component that is immunoreactive for PHF tau. This is not to say that DLB plaques of 'classical' appearance with neuritic involvement are not frequent, but rather that these neurites do not contain Alzheimer disease-related tau (51, 232). It is exactly this spectrum of changes which characterise the previously mentioned sub-group of 'plaque-only' AD (89). It is also reported that neuritic plaques in DLB have a higher expression of GAP-43 (168), suggesting increased aberrant neuronal sprouting compared with AD, in which GAP-43 expression is down-regulated (43). The extent to which DLB cases have neocortical neurofibrillary tangles is very variable. In most series published these lesions are infrequent and largely confined to the temporal lobe (87). Some cases undoubtedly do have a burden of neocortical neurofibrillary tangles comparable with AD cases but they are a minority (87, 106). This distinction is one of the key features which discriminates AD from DLB. The possibility that AD-related PHF tau changes occur in DLB without the formation of neurofibrillary tangles has been explored in two studies based on the characterisation of extracted cortical proteins by ELISA. There is no evidence for a global alteration in tau isoforms towards the insoluble PHF-related species (92, 255) which characterise AD. It is now clear that the cortical dysfunction associated with DLB is not explicable on the basis of neurofibrillary pathology.

DLB cases have an excess of hippocampal ATP when compared with age-matched controls and with both demented and undemented PD patients (104). The burden of amyloidosis in the entorhinal cortex may be equal to that found in AD in DLB cases corresponding to the 'common form' (or 'Lewy Body Variant AD'), but cases of 'pure' DLB have much lower densities of senile plaques in this region (7). Neurofibrillary tangles and granulovacuolar degeneration showed intermediate densities with considerable inter-case variation (104). Morphological markers of the integrity of the perforant

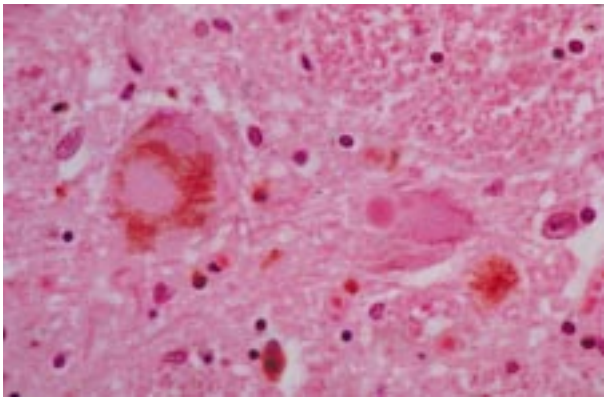

Figure 7. A pale body surrounded by neuromelanin in a nigral neuron. A classical Lewy body is present in an adjecent neuron for comparison.

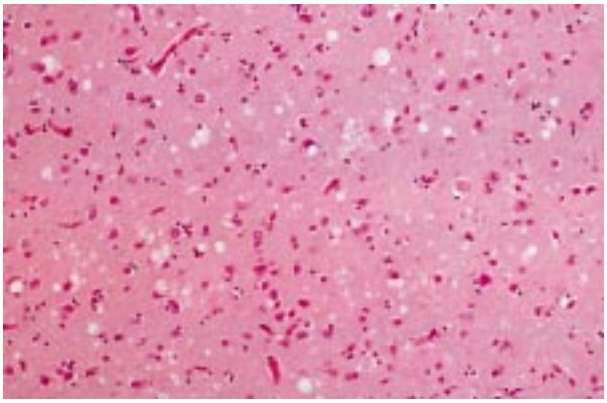

Figure 8. Cortical microvacuolation in the mesial temporal lobe structures associeted with cortical Lewy bodies.

pathway also show intermediate changes in DLB of lesser severity than in AD (153, 266). Whilst these changes may contribute to neuropsychological features such as defective short-term memory they do not account for much of the clinical picture of DLB.

The above discussion encapsulates the problem of defining the relationship between AD and DLB and the confusion of nomenclature in the literature. The issue centres around the criteria used to define AD. In the US literature these criteria have evolved from a scheme in which only the numerical burden of neocortical senile plaques was evaluated (127), through the CERAD criteria (182, 183) and its revisions which rely on neuritic plaques, to the latest NIA-Reagan Foundation guidelines which include evaluation of both plaques and neocortical tangles (193). This represents a convergence towards the view published by Tomlinson (259) which also required both neocortical plaques and tangles. Thus the extent to which DLB cases represent a variant of AD is entirely dependent on the diagnostic criteria used (90). If a plaque-based method is used then many DLB patients can be interpreted to have AD, depending on the molecular pathological qualification of plaque type. If a requirement for neocortical tangles, or PHF tau-immunoreactive plaque neurites, is adopted then most DLB patients fall short of AD.

Pathologists should also be aware that political considerations have clouded these issues. Some groups involved in DLB research operate in a funding climate in which dementia research is predominantly available to study AD, and not the more 'obscure' dementia syndromes.

Regional neuronal loss. A characteristic of the core clinical syndrome of DLB is the presence of parkinsonian signs which often fall short of the full diagnostic criteria for PD. In contrast to the cognitive features of DLB the pathological and neurochemical substrate for this motor component is well characterised. DLB patients on average have substantia nigra degeneration which is intermediate between that seen in PD and normal control individuals of the same age (212). Macroscopically the degree of de-pigmentation of the SN is at often only moderate, and the microscopic evidence of neurone loss and incontinence of pigment is usually less than in PD. The mechanism of neuronal loss associated with LB diseases is not known although evidence is reported to support the possibility of apoptosis (260). The cellular pathology in the SN is identical in PD and DLB and includes both classical LB and pale bodies (Figure 7). The latter are regarded as a precursor lesion and may be more frequent than LB (41). In contrast AD patients do not usually have significant nigral degeneration, although some cases have SN neurofibrillary tangles and a small proportion may develop frank parkinsonism (4), sufficient to warrant a clinical diagnosis of Parkinson's disease, on the basis of tangle pathology. Atypical AD patients may attract an erroneous clinical diagnosis of DLB due to the prominence of parkinsonian signs (105). Erroneous diagnoses of DLB may also arise in the context of other atypical variants of tau-related neurodegenerative disorders including progressive supranuclear palsy and corticobasal degeneration (34, 63). Some cases of DLB have fully developed Parkinson's disease and in these cases the nigral cell loss will exceed the commonly cited threshold for the development of PD (>70% of SN counts in age matched controls). Occasional cases are encountered where there is marked SN neuron loss but no overt parkinsonism. In these cases it is postulated that additional pathology in

the striatum produces a compensatory effect with no overall loss in the balance of neurotransmitter activity (see below).

The locus ceruleus is routinely more severely affected than the SN and is often totally de-pigmented to the naked eye. LB are usually frequent in the surviving neurones. Some cases with additional significant Alzheimer-type pathology may show tangle formation in SN neurons in addition to LB.

Other brainstem and midbrain nuclei which project into the cerebrum contain LB, including the serotonergic raphe subdivisions and the pedunculopontine nucleus. No quantitative studies are published comparing these nuclei in DLB, AD, PD and controls but neuronal loss would be expected to occur.

Neuronal loss in the cholinergic nucleus basalis of Meynert has been reported (119). In PD, DLB and AD the degree of cell loss is approximately 70% of age-matched controls. In DLB cases with significant AD pathology this neuronal population may contain both LB and NFT.

Microvacuolation. Early reports of DLB emphasised the presence of cortical spongiform changes in the temporal cortex (88) (Figure 8). The appearance of this pathology was said to closely resemble prion disease although the anatomical distribution was distinctive. The possible involvement of prion disease was excluded on the basis of failed animal transmission experiments and lack immunocytochemical staining for prion protein (162, 250). There is no clear relationship between spongiosis and the distribution or severity of cortical LB pathology in individual cases. However affected areas have been shown to be related to the presence of 'ubiquitin-positive granular structures' (UPGS) (108). Spongiform degeneration is also encountered in otherwise typical cases of AD but there is a reduction in the frequency of UPGS (110).

Synaptic loss. Analysis of synaptic density in tissue sections using a combination of immunocytochemistry for synaptic proteins followed by densitometric measurement of the intensity of staining is now an established technique (169). It is more readily applied to cohorts of patients than previous electron microscopic methods for measuring synaptic density. Reduced synaptic densities of up to 50% have been reported in patients dying of Alzheimer's disease (170,35). It was hypothesised that this abnormality was a major substrate for the reduced cognitive performance of Alzheimer patients compared to controls. Similar data have been reported for other diseases including vascular dementia (277) and AIDS (167). Data relating to DLB are less easy to interpret. Reported synaptic loss in the neocortex and entorhinal cortex of DLB patients were equivalent to those of patients with Alzheimer's disease (168, 267). However these patients were all from the 'Lewy body variant' subgroup in whom there was significant concomitant Alzheimer-type pathology especially in the entorhinal region. Thus the synaptic loss measured may be due to the Alzheimer-type pathology and not LB pathology. In a more recent study these authors have used a dot-blot assay for cortical synaptophysin to compare LBV patients with 'pure DLBD'. This study concluded that a significant synaptic loss of 20% was present in LBV patients whereas the pure DLBD group showed only a non-significant decrease of 10% (231). In our own material we could not demonstrate synaptic loss in 'pure DLB' cases using densitometry of immunocytochemical preparations. In contrast AD patients showed an average reduction of staining density of 15% compared to aged control individuals (P.G. Ince; unpublished observations). Such data underline the current lack of a clear consensus on the pathological and neurochemical substrates which underlie cognitive failure in those DLB cases which lack significant Alzheimer-type pathology.

Neurotransmitters and Neurochemistry in DLB

The neurochemical profile of the brain in DLB in comparison to AD and PD has been studied from three perspectives: i) correlation with the clinical features; ii) correlation with the severity and distribution of pathological lesions; iii) the identification of rational therapeutic targets. Drugs currently used to treat psychotic features, depression , anxiety and cognitive impairment act on specific neurotransmitter systems (dopamine, 5-HT, GABA and acetylcholine). In degenerative conditions such as AD such therapies are considered to be symptomatic or palliative at best but evidence of neurotrophic consequences of neurotransmitter signalling, mediated at the level of alterations in gene trancription, indicate that chronic manipulation of neurotransmitter function can have either neurotoxic or neuroprotective effects. In DLB the major clinical features, particularly psychotic, can occur in the absence of cortical Alzheimer type pathology or synaptic loss and may be at least partly functional. The fluctuating course of the disease also supports this idea. Such observations raise the possibility that neurotransmitter targeted therapies may be of particular benefit in DLB compared with AD.

Neuronal loss occurs in specific subcortical nuclei in

		References
1. Proteins regarded as major constituents related to LB formation		
Neurofilaments (NF):	Light, Medium and Heavy chains	(67,73,82,217,219)
	NF phosphorylation and truncation	(9,96,240)
	NF cross-linking	(218,219)
α-synuclein		(253)
2. Ubiquitin and cell stress or ubiquitination-related proteins		
Ubiquitin		(156)
Ubiqutin C-terminal hydrolase		(133, 157)
Polyubiquitin chains		(115)
26S proteasome		(64, 103)
αB crystallin		(158)
multicatalytic protease		(143, 166)
Cu/Zn superoxide dismutase		(195)
3. Other molecules		
Amyloid precursor protein		(5)
Ca2+/calmodulin-dependent protein kinase II		(114)
Synaptophysin		(194)
Chromogranin A		(194)
MAP 5		(70)
cyclin-dependent kinase 5		(26)
p35nck5a		(190)
chondroitin sulphate proteoglycan		(50)

Table 7. Cellular constituents found in LB.

DLB as it does in AD and PD (see above). The systems which have received the most neurochemical attention in DLB, because of consistently observed abnormalities and likely clinical correlates, are the cholinergic (relating to cognitive and psychotic symptoms) and the dopaminergic (relating to parkinsonism). The role of noradrenergic or 5-HT systems in depression or delusions, as has been suggested in AD, has not yet been explored in DLB, nor the significance of neuropeptide changes eg somatostatin or CRF which are evident in DLB (52, 149).

Cholinergic Systems. Cortical cholinergic abnormalities and degeneration of basal forebrain nuclei are considered to contribute to cognitive impairments including memory loss in AD. In PD, cortical cholinergic activities and nucleus basalis neuron counts, are lower in demented compared with nondemented individuals. In DLB neocortical choline acetyltransferase (ChAT) is lower than in AD and similar to that in demented PD (52, 146, 205). Cognitive impairment can be less severe in DLB than AD, and the clinical correlate of this neocortical cholinergic deficit may not be cognitive but neuropsychiatric, specifically visual hallucinations. Cholinergic activity is lower in hallucinating compared with non-hallucinating DLB cases while 5-HT activity is relatively preserved (206). This observation may be linked to the tendency of antimuscarinic agents such as atropine and scopolamine to induce visual hallucinations of a type similar to those experienced by patients with DLB (210). Such drugs interact with muscarinic M1, M3 and M4 receptor subtypes which predominate in the cortex, thalamus and striatum.

Loss of striatal ChAT in DLB (146), which reflects pathology of intrinsic local circuit neurons, may account for the reduced severity of extrapyramidal clinical symptoms in some DLB patients who have equivalent loss of dopaminergic substantia nigra neurons as PD patients (212). Loss of ChAT activity in the thalamic reticular nuclei has also been reported in DLB (203). The reticular nucleus receives joint innervation from basal forebrain and brainstem pedunculopontine cholinergic nuclei. Disturbances in its function may lead to disruption of sensory processing and affect attentional or perceptive processses, possibly contributing to visual hallucinations.

In DLB the muscarinic M1 subtype is elevated in the cortex, as it is in PD (211), reflecting upregulation of postsynaptic receptors in response to cholinergic denervation. Together with a normal extent of receptor coupling via G proteins this suggests that cholinoceptive neurons are intact in DLB (204). In contrast there is no up-regulation if the M1 subtype in AD, at least in advanced cases, and receptor uncoupling is widely reported. These differences reflect the more 'destructive' cortical pathology, including neurofibrillary tangle formation, in AD. Other muscarinic receptor subtypes remains to be examined in DLB.

The nicotinic receptor which binds nicotine with high affinity (considered to consist primarily of a4b2 subunits) is equally reduced in the cortex in DLB compared to AD and PD (211). In the substantia nigra, where nicotine binding is concentrated in the pars compacta in association with the pigmented dopaminergic neurons, receptor binding is as depleted in DLB as it is in PD, despite the greater loss of neurons in PD (209). This suggests that loss or down-regulation of the receptor may precede neurodegeneration. Nicotinic agonists upregulate the receptor and possible protective effects of nicotine may involve reversal of age or disease-related loss of the receptor. Another nicotinic receptor subtype, comprising α7 subunits, binds α-bungarotoxin and is not affected in the cortex in DLB or AD. In the thalamus this receptor is concentrated in the reticular nucleus and is reduced in both disorders (203) although a clinical correlate of this additional thalamic cholinergic abnormality is not established.

The therapeutic implications of the cholinergic neurochemical pathology so far identified in DLB can be summarised as follows:

i) since cortical cholinergic abnormalities exist in most cases in the absence of typical Alzheimer

pathology (especially tangles), and muscarinic receptors are functionally intact, cholinergic replacement therapy (anticholinesterases ,muscarinic or nicotinic agonists) is likely to be more effective than in AD;

ii) since the cortical cholinergic deficits in DLB relate more to psychiatric than cognitive symptoms, therapy may be more effective in alleviating the former.

There is already some support for the second of these propositions. In AD patients the anticholinesterase tacrine has been reported to be more effective in alleviating psychotic features such as hallucinations, delusions and than in improving cognition (39). In a small series of patients with PD and dementia, hallucinations have been reported to be reduced or abolished in all cases treated with tacrine (101). Paradoxically, given that extrapyramidal movement disorder is relieved by muscarinic antagonists, parkinsonian features were not excacerbated but actually alleviated. One explanation of this effect of tacrine may be that elevating acetylcholine in the striatum leads to nicotinic as well as muscarinic stimulation resulting in greater release of nigral dopamine. Stimulation of nicotinic receptors as a therapeutic strategy in DLB may be of particular relevance because both mental and motor symptoms should be relieved. The possibility that nicotinic stimulation may also be neuroprotective has been raised by epidemiological studies of smoking in PD and AD (38).

Dopaminergic systems. The loss of pigmented substantia nigra neurons and clinical evidence of parkinsonian symptoms in DLB indicate disruption of the dopaminergic input to the striatum. Reduced dopamine or the metabolite (homovanillic acid):dopamine ratio have been reported in autopsy tissue in DLB (146, 207). While a correlation between nigral neuron loss and striatal dopamine loss has been reported (208), interpretation is complicated by selection of patients (e.g. via neurology or psychogeriatric clinics, with less emphasis on extrapyramidal symptoms in the latter), and by treatment with neuroleptic drugs (which block D2 receptors and also reduce dopamine metabolism).

The dopamine transporter molecule is affected in both PD and DLB. SPET imaging shows that the striatal/cerebellar ratio is significantly lower in DLB compared to AD (2.1 versus 5.5) (57). Loss of mazindol binding, which also marks the transporter, distinguishes DLB from AD (204). Compared with the striatum, there is much less dopamine in the cortex and in autopsy tissue no marked changes have been observed in those cortical areas that have been examined (208). Although L-dopa may induce hallucinations in PD no dopaminergic parameters distinguish between patients with and without hallucinations.

The status of dopaminergic receptors in DLB is less clear. Autopsy findings suggest no alteration in D1, D2 or D3 subtypes in un-medicated patients (204)(Piggott, M. et al, in prep). The absence of any D2 up-regulation, such as occurs in the course of PD in response to diminishing dopaminergic input, is surprising and suggests that basal ganglia pathology may be distinct between the two diseases. There is also clinical evidence to support this possibility. In a retrospective survey of cases, rest tremor and response to L-dopa were significantly less prevalent and myoclonus significantly more prevalent in DLB compared to PD (155) and DLB patients are unusually sensitive to typical neuroleptic D2 antagonists (174). This neuroleptic sensitivity may be related to a dysregulation in D2 receptors: receptor numbers were up-regulated in patients tolerant of the drugs but not in the drug-sensitive group (213). In vivo SPET imaging shows a reduced caudate:putamen ratio in DLB compared to AD and may have diagnostic value (270).
The limited neurochemical studies so far conducted in DLB show some features similar to PD (cortical cholinergic and striatal dopaminergic deficits), and others to similar AD (striatal cholinergic deficits). D2-receptor dysregulation and changes in cortical 5-HT and turnover levels may differ in DLB compared to both AD or PD (208). The Consensus Guidelines for clinical diagnosis of DLB (177) raise the possibility that DLB patients will be distinguished by their therapeutic response to cholinergic, and dopaminergic therapies.

Pathogenesis of DLB

Molecular pathology of LB. The biogenesis of LB remains incompletely understood and has previously been reviewed (219). In terms of disease processes it is clear that there is a group of disorders in which the formation of LB is a characteristic and invariable component of the pathogenetic cascade (Table 2). This is clearly of no help in understanding the pathogenesis of LB since these disorders are defined by the presence of LB and not the underlying disease process. In addition there is a large group of conditions in which LB, as defined by modern immunocytochemical concepts, are sometimes associated (Table 1). At present there are no animal or cell models of neuronal Lewy body formation, and the mechanisms of LB formation are not yet amenable to

direct experimentation. As a consequence current concepts of Lewy body pathogenesis are predominantly based on immunocytochemical observations at light microscopic and EM levels.

Neurofilaments. By analogy with other conditions (e.g. hepatic Mallory body formation) the LB has come to be regarded as an intermediate filament inclusion, a view which is supported by immunoelectron microscopic studies which indicate that the core filamentous component is derived from neurofilaments (219). Since the formation of another intermediate filament inclusion, the Mallory body, can be studied in murine models of hepatocellular toxicity (49) this approach is now being used to gain insight into LB formation (220). There is no evidence for an underlying alteration in neurofilament expression in LB formation (15) although the mechanism of their formation may involve primary damage to neurofilaments. However, the possibility remains that the primary pathogenetic insult may be directed at other intracellular targets which are crucial to the regulation and maintenance of neurofilament assembly, transport or disassembly. In this alternative model the subsequent phosphorylation and truncation of aggregated neurofilaments occurs as a secondary process (159).

Candidate enzymes involved in the phosphorylation of neurofilaments incorported into LB have been sought. Cyclin-dependent kinase 5 has been proposed as a likely candidate on the basis of immunolocalisation, in both cortical and subcortical LB (26), together with its regulatory subunit p35nck5a (190). Such studies do not overcome the problem of whether phosphorylation of neurofilaments preceedes or follows LB formation.

Ubiquitin. Much interest has focused on the role of the ubiquitin pathway in LB formation and the concept has developed of LB as a cellular protective mechanism (159). Cortical LB purified from DLB brains reacted predominantly to an antibody recognising polyubiquitin chains rather than free ubiquitin or monoubiquitinated forms (115). The possibility was raised that incomplete activation of ubiquitin-mediated proteolytic pathways may contribute to the pathogenesis of LB degeneration. The dynamic nature of LB formation in comparison to some other inclusion bodies in neurodegeneration has been suggested (157, 158). Recent findings of differences in the expression of both ubiquitin and the 26S proteasome in LB compared to neurofibrillary tangles have been described which support this concept (103)

A large diversity of other peptide constituents have been detected in LB by immunocytochemical methods (Table 7) but the significance of many of these should be interpreted with caution because of their normal widespread cytosolic distribution.

Clinical Genetics of AD, DLB and PD

There are marked similarities between the clinical and pathological manifestations of DLB and both AD and PD. It is likely that genes which appear to confer risk of AD and PD will also be of relevance to DLB. Studies of the genetics of neurodegeneration have drawn attention to many such risk factors, predominantly in relation to AD. This approach therefore has major potential in illuminating the basis for the overlapping clinical and pathological features of AD, DLB and PD. The following account must necessarily be preliminary since relatively few of the recently described risk factors have been studied in DLB cohorts of adequate size. This field is likely to be an area of continuing rapid advance in the next few years as many more genetic risk factors are discovered.

Alzheimer's disease genes and DLB. There is evidence to suggest both genetic and non-genetic influences on the development of AD, the major influence being genetic. Twin studies have shown that there is double the risk of developing AD in monozygotic compared to dizygotic twins. (14) suggesting that genetic factors account for up to 80% of the variance of AD. Although similar studies have not been applied in DLB it is conceivable that there is also a strong genetic influence underlying the aetiology of DLB. Pathologically confirmed DLB in monozygotic twins, and families with more than one DLB case in a generation, have been identified (111)(I.G. McKeith and R.H. Perry; personal communication). This contrasts with PD where concordance rates for PD and familial aggregation are lower than in AD. (44)

The role of genes in the development of AD includes both mutations associated with early onset autosomal dominant AD and genetic polymorphisms which constitute risk factors in the 'sporadic' population of AD cases. Mutations in the APP gene have been shown to cause familial AD in which the pathology includes LB degeneration (86, 147). LB may also complicate the AD pathology found in most elderly cases of Down's syndrome (17, 223). Such findings clearly indicate that LB degeneration can occur via genetically driven pathways leading to Alzheimer's disease.

One of the major genetic influences on AD is the $\epsilon 4$ allele of the Apolipoprotein E (APO E) gene located on chromosome 19. (36, 216, 235) APO E $\epsilon 4$ has been

shown to reduce the age at onset of developing AD. ϵ4 homozygotes develop AD at approximately 70 years, ϵ4 heterozygotes at 75 years, and individuals lacking the ϵ4 allele at 80 years (187). Because of the association of the ϵ4 allele with AD, and the presence of b-amyloid in DLB, several groups have reported genotyping studies in DLB. The e4 allele frequency is elevated in a manner analogous to that found in AD(12, 91, 125, 126, 199). In Parkinson's disease (12, 130, 163) no association is observed with APO E ϵ4 so that DLB is more similar to AD than PD in terms of this genetic risk factor. There are however subtle differences in the APO E allele frequencies between AD and DLB in that the latter shows a higher ϵ2 allele frequency and a reduced incidence of the ϵ4/4 genotype. (144)

Differences in the APO E frequencies may account for some clinicopathological differences between DLB and AD but they are unlikely to be the sole genetic determinant accounting for these differences. Several groups have investigated the possibility that the influence of the APOE ϵ4 allele in AD is reflected in an increased burden of the conventional neuropathological markers of the disease, βA4 amyloidosis and neurofibrillary tangles. These investigations are largely driven by the desire of proponents of the amyloid cascade hypothesis to show data relating increased risk to increased amyloidosis. Apo E interacts with the βA4 component of senile plaques and induces the formation of monofibrils (33, 234, 254), and Apo E4 shows the highest affinity for βA4 (161). It has been hypothesised that Apo E4 acts as the most efficient pathological chaperone and induces the formation of senile plaques by promoting the accumulation of βA4. Evidence of a dose dependent increase in βA4 deposition associated with this allele has been reported (197, 224, 238) which may support this model of amyloidogenesis. The results of studies using quantitation of senile plaque density in AD cortex have been controversial and unresolved. Some groups report an ϵ4 allele dose-related increase in senile plaque density with no effect on frequency of neurofibrillary tangles (91, 102, 224, 238). Others report that both plaques and tangles are increased with increasing APO ϵ4 allele dose (189, 197, 221). Yet other groups report no effect of allele dose on either plaques or tangles (145, 187, 252). Similar confusion is reported for lesion density in DLB. Some groups report no relationship between plaques or tangles and allele dose (13, 187). Other groups have reported that there is a relationship between allele dose and senile plaque density in 'common' DLB (i.e. cases with significant Alzheimer-type pathology) but not in 'pure' DLB (125, 165, 199). Thus it appears that the role of Apo E4 in DLB relates to the extent of associated Alzheimer-type pathology and not the LB degeneration.

Unlike dominantly inherited forms of AD the APO E e4 allele only specifies a risk for AD. Thus interactions with other genes and environmental factors must affect the disease. (62) Some individuals who are homozygous for ϵ4 survive beyond the ninth decade without showing symptoms of AD (251), and there are numerous individuals who develop AD but do not carry the ϵ4 allele. (187) Estimates suggest that the APO E locus accounts for 50% of AD cases at most and there are a potential four other major loci for AD alone, including regions on chromosomes 4, 6 (40), 12 and 20 (202).

The HLA-DR locus on chromosome 6 was recently shown to be significantly associated with the risk of developing AD in those cases lacking the APO E ϵ4 allele. (40) HLA-DR 3 appears to specify risk for developing AD and HLA-DR 6 appears to protect against AD. This study suggests that up to 40% of AD cases can be attributable to the HLA-DR locus. Work is currently under way to determine the influence of the HLA-DR locus in DLB.

It is suggested that the butyrylcholinesterase gene K variant (BCHE K) is also a risk factor for AD development in conjunction with APO E ϵ4 and increases the risk of AD 18-fold compared to the APO E ϵ4 allele alone. (150) This locus is being studied in both DLB and in AD and some interesting preliminary findings are apparent (Singleton et al, in preparation). Approximately 10% of the DLB population appear to be homozygous at the BCHE K locus compared to only 1 or 2% in the AD group, so that this genetic risk factor seems to distinguish the two diseases. This finding may be relevant to the hypothesis that DLB cases are more likely to respond to cholinergic therapy than AD. If DLB cases have reduced cholinesterase activity due to the BCHE K variant (BCHE K has only 30% of the activity of the normal enzyme), then application of cholinesterase inhibitors would be expected to have more effect in BCHE K homozygotes than in heterozygotes or normal individuals. Screening at the BCHE locus for mutations with reduced activity could therefore be used to identify individuals who are likely to have a good response.

Other genetic associations with AD have been reported including polymorphisms in the genes for Presenilin 1 (274), Presenilin 2 (27), and alpha-1 anti-chymotrypsin (124). Other attempts to verify these findings in AD (144, 242, 245, 247) showed no associations, nor with DLB (246), and it is likely that these genes do not have a major effect on disease development for either

AD or DLB.

There is also a body of evidence that suggests that non-genetic factors influence the development of AD. Twin studies show that there is discordance in monozygotic twins for AD, with co-twins remaining unaffected for over a decade. (24) Prior history of major head trauma (173), and of cigarette smoking (95) have been shown to modify the risk of developing AD. Prior non-steroidal anti-inflammatory use has been shown to protect against the development of AD (25). This effect may be related to the finding that the risk of AD is altered by the major histocompatability locus class II antigen HLA-DR on chromosome 6, which is commonly associated with rheumatoid arthritis (40). The influence of all these factors in DLB remains to be investigated.

Parkinson's disease. The influence of genetics on the development of PD does not appear to be as strong as that found in AD. On the basis of some twin studies it was suggested that the concordance rates for PD in twins was low, but this interpretation is now thought to be overly cautious (60, 122, 263). Several studies have shown that PD cases may show familial aggregation patterns indicating a strong genetic influence on the disease (60,81). More recently the identification of several pedigrees with pathologically confirmed autosomal dominant PD suggest that genetics may be a key component of the pathogenesis of PD (262).

Because of the assumption that the majority of PD is sporadic most genetic studies of PD have focused on a candidate gene approach in disease association studies. Mutations in the cytochrome P450 gene CYP2D6 (debrisoquine 4-hydroxylase) and related enzymes have been extensively studied following the hypothesis that the disease may be due to an environmental toxin interacting with a specific gene. Elevated frequencies of the common CYP2D6 mutant allele, CYP2D6B, have been found among PD patients compared to controls, with an approximate doubling of risk for subjects homozygous or heterozygous for this allele (6, 214, 248). Whilst some studies have substantiated these early findings (2, 139, 141, 271) other studies have not (20, 160). Studies of the CYP2D6 gene in DLB has been equally inconclusive; one report suggesting an increased frequency of the B allele findings similar to PD (229), and one study showing no association (19). Our own studies do not support a role for the CYP2D6 B locus in DLB in that similar frequencies were found in controls, DLB and Alzheimer's populations, though an increased frequency of the B allele was seen in PD (Atkinson et al, unpublished). The results of CYP2D6 genotyping from our studies tend to place DLB with AD rather than PD in relation to the contribution of this genetic influence.

Candidate gene approach to genetic influences in PD have also centred upon the dopaminergic system. Several genetic markers have been variably associated with PD such as monoamine oxidase A (99, 191) monoamine oxidase B (37, 140), dopamine receptors and transporters (148, 192, 215), and catechol-O-methyl transferase (97). It would be of interest to ascertain the status of these genes in DLB given that dopaminergic dysfunction and pathology are also a central part of the disorder. An association of the N-acetyl transferase 2 gene locus has been reported in familial PD (11). This gene is involved in xenobiotic metabolism and suggests a role for these enzymes in detoxifying dopamine metabolites.

A similar approach has been applied following the finding of defects in oxidative phosphorylation in PD (236). Several point mutations in the mitochondrial genome have been reported in PD together with evidence of heteroplasmy (variable copy numbers of mutant mitochondrial DNA) in the PD brain (10,61, 112, 139, 241,). Similar associations with mitochondrial mutations are also reported in AD (42,61) suggesting that they are not disease specific. Mitochondrial mutations are found in DLB at similar levels to those found in AD and PD (Neil et al, in preparation) and the possibility remains that they are may be an acquired function of neurodegeneration, although they may still be capable of accelerating the disease process.

Whilst families with autosomal dominant PD are rare (171), the identification of such families has recently provided a possible genetic link between PD, DLB and AD (196). Polymeropoulos and colleagues have reported the identification of a large PD kindred showing linkage to, and the presence of a missense mutation in, the α-synuclein gene on chromosome 4 (222). Non-amyloid component precursor NACP, now identified as α-synuclein, has been described as a major component of neuritic plaques in AD (261, 113, 107) but to date no mutations or associated polymorphisms have been linked to AD (32, 275). The identification of mutations in the α-synuclein gene, and the presence of the protein in LB (253) will no doubt provide an impetus to search both for other mutations in PD and also for associations with DLB in which LB are similarly immunoreactive for α-synuclein, and in which familial disease is recognised. In the first report of PD associated with the α-synuclein gene there was a point mutation giving rise to an

ala53thr substitution. Very recently another study has reported a family with PD in whom the gene shows an ala30pro substitution (Kruger R. et al. (Feb 1998) Nature Genetics 18: 106-108). The mechanism of neurodegeneration in these PD cases associated with α-synuclein gene mutations is not clear. Studies of the function of synucleins, which are synaptic proteins, are still awaited that will provide a link between the normal role of α-synuclein, neurofilaments and LB pathology.

Summary

The relationship between DLB,PD and AD is complex and incompletely understood. Within the spectrum of Lewy body disorders there is a neuropsychiatric syndrome, with associated parkinsonism, in the elderly which is sufficiently distinct in terms of its clinical, pathological and neurochemical profile to warrant recognition as a distinct condition. The syndrome can be reliably diagnosed by the Consensus Guidelines and has particular therapeutic and other management implications compared to PD or AD. The pathology of the disorder should be considered from two perspectives: The Lewy body pathology is qualitatively similar to PD but with a different anatomical distribution of the major burden of lesions; The Alzheimer-type pathology which frequently, but not invariably, complicates the pathological picture may change the clinical and neurochemical features so that they more closely resemble AD. Genetic studies indicate that DLB cases tend to share many risk factors for AD.

Many elderly demented patients with Lewy body pathology will have autopsy findings compatible with a diagnosis of DLB. Others may be interpreted as 'AD with incidental Lewy bodies' or 'Dementia in Parkinson's disease' but these cases appear to be a minority. Clarification of the relationship between patients within these, and other, diagnostic categories will depend on an accumulation of pathological, genetic and neurochemical data in order to understand pathogenesis. Pending resolution of this debate the use of the diagnostic category 'DLB', as described in the Consensus Guidelines for clinical diagnosis of DLB, is recommended in both research and routine practice.

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