Neuropathology in movement disorders

W R G GIBB

From the Parkinson's Disease Society Brain Bank, Institute of Neurology, London, UK

SUMMARY This review concentrates on the definition and classification of degenerative movement disorders in which Parkinsonian symptoms are often prominent. The pathological spectrum and clinical manifestations of Lewy body disease are described, and associations with Alzheimer's disease and motor neuron disease are explored. A classification of pallidonigral degenerations is based on clinical features, distribution of pathology, and morphological abnormalities; some of these patients have mild nigral degeneration and no Parkinsonian features. Many other juvenile and familial Parkinsonian cases are not included among the pallidonigral degenerations. Most of these latter syndromes have been organised into preliminary groups, in particular, autosomal dominant dystonia-Parkinson syndrome, juvenile Parkinsonian disorder and autosomal dominant Lewy body disease.

Degenerative and secondary Parkinsonian disorders (for example from carbon monoxide) are all associated with major structural pathology within or directly affecting the basal ganglia. Drug-induced states are the exception; but here elderly patients are often indistinguishable from Parkinson's disease, and some are likely to be vulnerable to neuroleptics because of mild Lewy body neuronal degeneration in the substantia nigra.^{1,2} Consequently drug-induced Parkinsonian states probably show nigral Lewy bodies more frequently than the normal population. In contrast, some forms of dystonia³ and chorea⁴ have not been linked to a particular pathological abnormality. In drug-related dyskinesia non-specific nigral degeneration might contribute to susceptibility.⁵ In other cases of idiopathic and drug-related tardive dyskinesia degenerative changes in one or more of the following locations have been reported; caudate nucleus, putamen, pallidum, substantia nigra and inferior olive;⁶ but these findings are not consistent or necessarily excessive for age-related effects. Four cases of drug-induced dyskinesia apparently showed abnormally inflated neurons in the dentate nucleus.⁶

(IDIOPATHIC) LEWY BODY DISEASE

In 1969 Forno introduced the phrase "incidental Lewy body cases" when describing 50 brains from persons dying without Parkinson's disease, but in which Lewy bodies were present in the locus coeruleus, substantia

nigra, and in other locations characteristic of Parkinson's disease.⁷ Consequently she proposed that they represented early or preclinical cases rather than a manifestation of normal ageing.⁷ The term "Lewy body disease" was then introduced to describe the common pathological substrate of incidental cases and Parkinson's disease.⁸ The word "diffuse"⁹ was added, giving "diffuse Lewy body disease", to describe patients in whom the degenerative process with Lewy bodies appeared to spread with unusual severity into limbic areas and cerebral cortex, associated with dementia with or without Parkinson's disease.¹⁰ A number of terms have thus emerged but do these refer to the same basic disorder or not? Diffuse Lewy body disease intentionally suggests a distinct disease entity, but is this justified?^{10,11} The following discussion will attempt to clarify this area by describing the spectrum of Lewy body disease.

Parkinson's disease: diagnosis and definition

Encephalitis lethargica was unhelpful to the progress of neuropathology because in years subsequent to the epidemic it proved impossible to distinguish consistently the lesions of post-encephalitic and idiopathic Parkinsonian states by clinical and pathological study. Encephalitis lethargica pointed to the substantia nigra as a major site of damage in Parkinsonian states, but this was not generally acknowledged until 1938.¹² In the 1950s Lewy bodies in the substantia nigra were linked to idiopathic cases, and neurofibrillary tangles with post-encephalitic patients, but it is well-known that many patients without a history of encephalitis lethargica, some of whom had subclinical disease, and some labelled "idiopathic" encephalitis, do not

Address for reprint requests: Dr W R G Gibb, Department of Neurology, Guy's Hospital, London Bridge SE1 9RT, UK.

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invariably show Lewy bodies. In the 1960s three degenerative Parkinsonian disorders were described, which to a greater or lesser extent resembled Parkinson's disease clinically: striatonigral degeneration,¹³ Steele-Richardson-Olszewski syndrome¹⁴ and corticobasal degeneration.¹⁵ Despite this clarification there were other disorders resembling Parkinson's disease, but without Lewy bodies; they were designated as idiopathic Alzheimer tangle disease or extranigral cases,⁸ thus raising persistent doubt over the relevance of the Lewy body to Parkinson's disease. However, recently Lewy bodies have been found in the substantia nigra in the majority of patients believed to have established Parkinson's disease.¹⁶ Where they cannot be identified there is always other structural pathology outside the substantia nigra, usually conforming to striatonigral degeneration or Steele-Richardson-Olszewski syndrome, assuming that drug-induced cases have been excluded.¹⁶

In Parkinson's disease Lewy bodies are always sufficiently numerous to be found within surviving nigral neurons in two 7 μ m-thick, unilateral, midbrain sections. This is due to their relative frequency and also to the substantial number of neurons (approximately 25% of normal) that remain. Unlike post-encephalitic Parkinsonian syndrome and some examples of striatonigral degeneration and Steele-Richardson-Olszewski syndrome the neuronal loss is never complete despite durations of clinical disease in excess of 20 years. The power of the Lewy body is to exclude Parkinson's disease if absent in two nigral sections, 330 pigmented nigral nerve cells, or 150 pigmented nerve cells in the locus coeruleus.¹⁶ Lewy bodies also exist as in Forno's incidental cases, or coincidentally with an alternative pathology responsible for the Parkinsonian state, or in corticobasal degeneration and Hallervorden-Spatz disease, more or less often than once every 330 nigral nerve cells. These situations not infrequently lead to misdiagnosis. Consequently, a diagnosis of Parkinson's disease also depends on depletion of nerve cells in the substantia nigra by 60%, and the exclusion of other Parkinsonian disorders.

Lewy bodies are also found in specific extranigral sites in Parkinson's disease, mostly in medium to large monoaminergic and cholinergic neurons, and throughout the autonomic nervous system (table 1). They are present in many smaller nuclear groups, for example in the midbrain region, the intracapsular nucleus of the ventral tegmentum and pedunculo-pontine neurons are included. It is sometimes erroneously stated that in Lewy body disease they occur in the striatum, pallidum, subthalamic nucleus, motor cranial nerve nuclei (hypoglossal), and pontine nuclei. The only other cells hosting Lewy bodies are cranial nerve and spinal lower motor neurons in some

sporadic and familial cases of motor neuron disease (see below). These somatic motor neurons contrast with the visceral and autonomic neurons affected in Parkinson's disease. In Parkinson's disease this distinction is appreciated by noting involvement of the Edinger-Westphal nucleus, and sparing of adjacent neurons of the oculomotor nucleus proper.¹⁷ Adrenal bodies described in the adrenal medulla in a proportion of cases of Parkinson's disease are unrelated to Lewy bodies. They are not specific to the disease and are seen just as frequently in controls.¹⁸ Indeed, the adrenal gland is histologically normal for age in Parkinson's disease; and the finding of decreased catecholamines in the adrenal medulla in Parkinson's disease,¹⁹ has not been confirmed. Failure of adrenal autografts in Parkinson's disease cannot therefore be attributed to degenerative disease in the adrenals.

Lewy bodies always signify neuronal injury which is usually apparent in pigmented nuclei in terms of fragmented neurons and extraneuronal melanin, with or without neuronal loss, in excess of that acceptable for age alone. Indeed, neuronal loss is documented for most regions containing Lewy bodies.²⁰ Our present understanding is that Lewy bodies are an essential part of all neuronal degeneration in Parkinson's disease. However, rare and complex cases of Lewy body Parkinson's disease with motor neuron disease are unaccompanied by Lewy bodies in anterior horn cells.^{21 22} One region of interest in relation to levodopa therapy, and its reduced effect with time, is the striatum. In 1938 Hassler¹² largely resolved a long-standing dispute about the existence of striatal and pallidal gliosis and nerve cell loss. He re-examined ten cases of Parkinson's disease previously examined by the Vogt's, and with an additional nine cases, identified lesions of the substantia nigra, but could not substantiate the pallidal abnormalities that were previously reported.²³ Cell counts in the pallidum were not reduced in Parkinson's disease compared with controls, but cytoplasmic and nucleolar RNA were reduced and nucleoli were significantly larger.²⁴ Large cells of the caudate nucleus were reduced to a greater extent than small cells, but counts were not repeated or done blind to the diagnosis.²⁵ If a very few striatal cells are unexpectedly lost in late Parkinson's disease this will be difficult to show convincingly in view of morphometric difficulties. Medium spiny neurons, which represent the target population for nigrostriatal neurons, show simplified dendritic arrangements and fewer dendritic spines.²⁶

Concept of (idiopathic) Lewy body disease

Neuropathologists in addition to Forno⁷ reported finding Lewy bodies in the substantia nigra or locus coeruleus in persons dying without established Parkinson's disease. Prevalence estimates range from

6.8%²⁷ to 20.9%²⁸ for persons aged over 60 years. A recent series found that the age-specific prevalence rises from 3.8% in the sixth decade to 12.8% in the ninth decade.²⁹ There is considerable evidence indicating that all such persons have presymptomatic Parkinson's disease, the most important of which is the identical nature and distribution of the pathology, and histological evidence indicating a rate of neuronal loss in the substantia nigra exceeding that of ageing alone. If pathological observation is correct that all nigral Lewy body disease progresses at a similar rate, then by implication there is a long presymptomatic period of approximately 30 years.²⁹

What are the consequences of neuronal loss in the other specific regions in Lewy body disease? Cell loss in the nucleus basalis is not dependent on the degree of damage to the substantia nigra, and wide ranging estimates of neuronal loss are reported. In Parkinson's disease losses range from 20 to 40% in patients without dementia to 40 to 80% for those with dementia,³⁰ and these reductions correlate with activities of cortical choline acetyltransferase. Such a lesion may predominantly cause amnesia, and dementia attributed to nucleus basalis damage has never presented before Parkinson's disease. In part this relates to the usually moderate, subthreshold damage, but also the need for coexistent cortical pathology, usually Lewy bodies and/or Alzheimer pathology.

"Moderate to large" numbers of Lewy bodies in the parahippocampus, other limbic regions and neocortex have been found in patients dying with dementia alone (comprising 20% of such reports), presenting with dementia followed by Parkinsonian features (30% of reports) or Parkinson's disease followed by dementia (18% of reports).^{11,31-34} In other cases (32%) dementia and Parkinson's disease have developed concurrently. These patients exhibit dysphasia, dyspraxia, dyscalculia, visual and auditory hallucinations, paranoid delusions and fluctuating confusion. Visual hallucinations and delusions are more common than in Alzheimer's disease. It seems surprising that Lewy bodies restricted mostly to deeper cortical layers and not associated with the degree of nerve cell loss seen in Alzheimer's disease could be responsible for dementia. However, parts of the limbic system are predominantly involved, many nerve cells without Lewy bodies show structural changes including cytoplasmic swelling or deposits of filamentous material likely to indicate functional compromise, and there is always contributory disorder in the nucleus basalis, caudate nucleus and so on. Often there is Alzheimer pathology, at least a degree of which is found in 50% of controls aged 60 to 69 years.²⁰ Furthermore, cortical Lewy bodies are seen in at least 30% of patients with Parkinson's disease,^{35,36} but probably occur as a major contribution to dementia in only 5 to 7%, and as the

principal pathological feature in 2%.³⁷ Relative to the prevalence of Parkinson's disease only a small number of patients have cortical Lewy body disease presenting with dementia, in the absence of Alzheimer pathology. In addition to Parkinson's disease and dementia the third major manifestation of Lewy body disease is autonomic failure, but this is also uncommon in relation to the population affected.³⁸ Understandably, most other locations of Lewy bodies and neuronal loss have been linked to some clinical manifestation, but these associations are difficult to substantiate. Frontal lobe deficits are explicable in terms of compromised caudate nucleus outflow.³⁹

The same Lewy body disease is thus responsible for incidental or presymptomatic cases (the majority), Parkinson's disease as the commonest clinical presentation, and dementia or autonomic failure, depending on the regional emphasis of damage. The term diffuse Lewy body disease, describing patients with dementia and multiple cortical Lewy bodies, is misleading. These patients are not otherwise known to be different from the rest of the population with Lewy body disease. There is no association with severe Lewy body disease in other regions, and Lewy bodies do not occur "diffusely" in any part of the nervous system. The most accurate descriptive information in (idiopathic) Lewy body disease is provided by the terms (brain-stem) Lewy body Parkinson's disease, cortical Lewy body dementia and Lewy body autonomic failure.

Lewy body disease and Alzheimer's disease

There are no convincing reports showing a pathological association between Lewy body disease and Alzheimer's disease, although there are numerous published instances when the two diseases have occurred together in patients over age 60 years, presumably by chance. The problem lies with the high prevalence of these pathological lesions in the population and the difficulty providing age-related pathological data for the diagnosis of Alzheimer's disease. Joachim *et al*³⁶ found that 18% of 131 patients with Alzheimer's disease had nigral Lewy bodies, some of whom had Parkinson's disease, and erroneously compared this with figures of "3 to 7% for large series of normal subjects." Interestingly, many of the Alzheimer's disease patients with nigral Lewy bodies had less cortical Alzheimer pathology than Alzheimer's disease patients without Lewy bodies. We have found nigral Lewy bodies in 7.8% of controls and 14% of Alzheimer's disease cases over age 60 years. However, cortical Alzheimer pathology was much reduced in the cases of "Alzheimer's disease" with Lewy bodies compared to those without, although cortical choline acetyltransferase activities were similar.⁴⁰ Lewy body neuronal degeneration in the nucleus basalis may thus contribute to the lowering of

cholinergic activity, and to the dementia, but not to the cortical Alzheimer pathology. Such data strongly argue against a greater than chance association between Alzheimer's disease and Parkinson's disease. However, the chance of Lewy body and Alzheimer's disease pathologies coexisting in patients dying before 60 years is small, and this occurrence suggests an association in the individuals concerned. Eight such patients are reported dying between ages 28 and 56 years;^{21 34} Case 2 40, two cases 41–44 and there are probably a variety of reasons for the association. Another area of doubt is cortical Lewy body dementia in which substantial Alzheimer pathology has been reported.³⁷

However, a lack of quantification and the anecdotal nature of many reports are major criticisms. A very large pathological study would be required to clarify the link between these processes, the most important element of which would be establishing age-related control data for Alzheimer pathology. If a mild excess of Alzheimer pathology was discovered its significance would remain obscure. Some authorities believe that any Alzheimer pathology signifies the early stages of Alzheimer's disease; but a wide variety of disease processes are secondarily associated with Alzheimer pathology.⁴⁵ While Lewy body disease might also precipitate Alzheimer pathology, many advanced cases are never associated with plaques or tangles.

Table 1 *Extranigral locations of Lewy bodies in Parkinson's disease (PD)*

Location	Frequency of involvement in PD (%)
Locus coeruleus	100
Nucleus basalis	? 100
Raphé nuclei	?
Thalamus	? 100
Cerebral cortex	> 30
Autonomic nervous system:	
Hypothalamus, Edinger-Westphal, salivatory and dorsal vagal nuclei	} 100
Intermediolateral columns, sympathetic and parasympathetic ganglia	
	? 90

Lewy bodies and motor neuron diseases

Anterior horn motor neurons have the ability to host a wide variety of neuronal inclusions in different forms of motor neuron disease. Lewy bodies are described in sporadic^{46–48} and familial motor neuron disease^{49–52} and they also occur in motor cranial nerve nuclei.⁵² Despite definite Parkinsonian features in some patients⁴⁶ Lewy bodies do not seem to occur in the substantia nigra or in other regions affected in Lewy body disease. Furthermore rare patients with Lewy body Parkinson's disease and motor neuron disease do not have Lewy bodies in motor neurons, although they are, of course, present in other regions (table 1).^{21 22} Idiopathic

Table 2 *Pallidonigral degenerations: classification and possible variants*

Hallervorden-Spatz disease ⁵⁵
Rigidity, dystonia, pyramidal signs, dementia, + / - retinitis pigmentosa—most reported are young-onset—autosomal recessive and sporadic. Variants: mentally retarded—adult-onset—sporadic—with neurofibrillary pathology ⁵⁶
Adult-onset—autosomal dominant ⁵⁷
Dentatorubropallidolusian degeneration ⁵⁸
Ataxia, chorea, dementia, dystonia, gaze palsy—wide age range of onset—autosomal dominant and sporadic
Variants: ataxia, chorea, dysarthria—onset in 2nd and 3rd decades—autosomal dominant with extended pathology ⁵⁹
Solitary case, age 41, dementia, somnolence, ataxia, rigidity, gaze palsy, death at 43—degeneration extending to substantia nigra and dorsomedial nucleus of thalamus, with eosinophilic bodies in striatum, thalamus and cerebral cortex ⁶⁰
Pallidonigrolusian atrophy ^{61 63}
Akinesia, rigidity—adult-onset—sporadic
Variants: akinesia, cervical rigidity, upgaze palsy—sporadic—with degeneration of the centrum medianum ⁶⁴
Solitary case—akinesia, cervical and limb rigidity, upgaze palsy—multiple corpora amylacea in pallidum, nigra, cerebral and cerebellar white matter ⁶⁵
Akinesia, generalised rigidity and motor neurone disease ^{66 67}
Pallidonigral degeneration with spinal muscular atrophy ⁶⁸
Solitary case, age 54, proximal weakness and wasting, rest tremor, rigidity, akinesia, death at 65. Mild neuronal loss and gliosis in internal pallidum, degeneration of nigra and anterior horn cells
Hereditary (holotopistic) striatal degeneration ⁶⁹
Psychomotor retardation, apathy, rigidity and chorea—mostly infants and young children—autosomal dominant and recessive
Variant: two siblings aged 20 months with stiff legs or hemiparesis and ataxia, died aged 2 and 3—also had idiopathic hypersplenism and sickle cell trait—pallidal necrosis ⁷⁰
Idiopathic calcification of the basal ganglia ⁷¹
Spasticity, rigidity, bradykinesia, tremor, dystonia, chorea, dementia—onset in first decade and middle age—autosomal dominant and recessive. Variant: with familial ataxia and pigmentary macular degeneration ⁷²
Pallidal polyglucosan bodies in cerebral palsy ⁷³
Cerebral palsy, chorea, dystonia—sporadic cases

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Lewy body disease and motor neuron disease with anterior horn cell Lewy bodies appear to be mutually exclusive pathological processes.

Young and old-onset Parkinson's disease

Bernheimer *et al*⁵³ identified Lewy body Parkinson's disease in patients with first symptoms between age 20 and 87 years, but apart from longer survival and greater nigral cell loss in young onset cases there are probably no real differences in Lewy body disease at these extremes of age.⁵⁴ The prevalence of dementia increases with age but this can be attributed to coincident Alzheimer pathology. The mean age of onset in 44 patients with cortical Lewy body dementia was 59.1 years, range 26–75 years.^{11 31–34} Lewy body autonomic failure also occurs at various ages. The emphasis of Lewy body disease in extranigral sites therefore seems unrelated to age.

PALLIDONIGRAL DISEASE (table 2)

At the present time a classification of pallidal and pallidonigral degenerations is approximate, because they are all rare, and it is not known how many separate disorders exist. Previous attempts at classification have suffered by their unjustified complexity. Possible variants have also been tabulated (table 2) but not all are described below. Secondary pallidal lesions resulting from external insults, for example, manganese, carbon monoxide, carbon disulphide and cyanide intoxication, are not included. Many more degenerations show mild or less consistent pallidal disease, usually associated with more important pathological lesions elsewhere. These include infantile neuroaxonal dystrophy, striatonigral degeneration, Steele-Richardson-Olszewski syndrome, Huntington's chorea, neuroacanthocytosis, Pick's disease, motor neuron disease, Creutzfeldt-Jacob disease and Guam-parkinsonism dementia complex. There is some disagreement in the literature about the consequences of pallidal lesions in experimental animals, but Mettler found that large bilateral lesions in monkeys cause bradykinesia.⁷⁴

Distal axonal spheroids are a universal feature in the nucleus gracilis in middle-aged and elderly persons. They are also numerous in the nucleus cuneatus and are occasionally seen in the spinal cord, medial segment of the globus pallidus and substantia nigra, although their frequency in the latter sites has probably been overestimated.⁷⁵ Occasionally, mild neuronal degeneration in the medial pallidum and focal damage in the substantia nigra zona compacta, accompanied by spheroids and concretions of melanin, are found in healthy persons. The significance of this process is unclear, but it is distinct from the moderately diffuse and mild loss of nigral pigmented neurons normally starting about the age of 40 years. Axonal spheroids

are present in a variety of diseases and can be induced experimentally, so their existence is not exclusive to Hallervorden-Spatz disease.

Hallervorden-Spatz disease

The neuroaxonal dystrophies, which include Hallervorden-Spatz disease, refer to numerous spheroids and substantial neuronal degeneration, usually dispersed outside regions affected by ageing, in the absence of an alternative aetiology. The spheroids occur throughout nerve cell processes, and some elements may be found in neuronal perikarya, but they are more often sited in distal axons. Ultrastructurally their content varies little and consists of various organelles, normal and swollen mitochondria, vesicles, dense granules, neurofilaments, microtubules and tubulomembranous structures. Mature spheroids with dense cores contain electron dense homogeneous matter. In Hallervorden-Spatz disease spheroids, lipofuscin or melanin pigment deposits (ranging from granules to concretions), and other calcium and iron positive concretions fill the pallidum, especially the medial segment, and much of the substantia nigra (figs 1 and 2).^{55 76} Spheroids are also found in other parts of the nervous system. The severity of damage to the substantia nigra zona compacta is often understated and the iron deposition overstated.

The majority of cases show onset in the first and second decades and manifest rigidity, dystonia, chorea, tremor, pyramidal signs, epilepsy, dementia and retinitis pigmentosa. Autosomal recessive inheritance is often apparent, and in some 15% of solitary cases there is parental consanguinity. Combinations of a Parkinsonian syndrome, dystonia and dementia are presenting features in adults.^{77 78} Relative restriction of pathology to the pallidum is occasionally seen,⁷⁶ and tangles have been described as a prominent pathological feature.⁵⁶ A metabolic defect leading to cysteine accumulation has been proposed.⁷⁹ Lewy bodies in perikarya and proximal nerve cell processes are reported in 15% of cases,²⁰ which raises intriguing comparisons between the nature of spheroids and Lewy bodies. CT and MRI are likely to show the pallidal lesion,⁸⁰ but this may not be specific to Hallervorden-Spatz disease.

Dentatorubropallidolusian degeneration

The clinical and pathological spectrum of this disorder shows considerable variation and further clarification is required.^{58 81} In 37 recorded cases onset was between age 5 and 68 years, 57% starting before age 30 years, with a duration of between 2 and 30 years. Autosomal dominant inheritance has often been reported. Ataxia, then chorea (ataxo-choreoathetoid type) or chorea and dementia (pseudo-Huntington type)⁸¹ may be prominent but dysarthria, dystonia, rigidity, supra-

nuclear gaze palsies, muscle fasciculations and atrophy, and possibly myoclonic epilepsy occur. Dentate and red nuclei, lateral pallidum and subthalamic nuclei often show neuronal loss and gliosis, but the most consistent changes are recorded in the dentate nucleus and brainstem tegmentum. There is also atrophy with demyelination of superior cerebellar peduncles, medial longitudinal fasciculi, medial lemnisci, central tegmental tracts, pallidal efferents, spinocerebellar tracts and posterior columns. Anterior horn cells may be depleted and pathology extends into other regions,^{81, Case 4} but there is little or no damage to the substantia nigra and locus coeruleus. The pallidal degeneration varies in severity, is most severe in the lateral segment, and may be associated with scattered pigment deposition.

Variants have been described: an autosomal dominant pattern of dysarthria, ataxia and chorea with onset in second and third decades.⁵⁹ In addition to dentatorubropallidoluysian atrophy the one necropsied case apparently showed degeneration of the substantia

nigra, the centromedian thalamic nucleus, optic tracts, parts of the spinal cord, anterior horn cells and other less substantial locations.⁵⁹ The internal pallidum showed gliosis but little neuronal loss.

Pallidonigroluysian atrophy

Contamin *et al*⁶¹ described a man with akinesia and "hypertonia" showing moderate neuronal loss and gliosis apparently in the pallidum, substantia nigra, and subthalamic nucleus. Severe akinesia, a Parkinsonian gait, cervical rigidity and upgaze palsy, resembled Steele-Richardson-Olszewski syndrome, and were seen in two unrelated persons aged 61 and 64 years at onset, with durations of 5 and 7 years.⁶⁴ The pallidum and substantia nigra zona compacta showed degeneration with deposition of pigment and spheroids, and there was gliosis and neuronal loss in the centrum medianum, periaqueductal grey area and superior colliculus. The spheroid ultrastructure was oddly different from neuroaxonal spheroids and consisted of filaments and dense collections of granules.

Fig 1 Pigment in the pallidal nuclei in Hallervorden-Spatz disease. Taken from Kessler *et al* 1984⁷⁶ with permission.

Kosaka *et al*⁶⁵ described an almost identical man dying aged 67, additionally with severe limb muscle rigidity. Levodopa had a transient effect on akinesia and rigidity. There was a little gliosis in the lateral part of the ventrolateral nucleus of the thalamus, with a few spheroids and many corpora amylacea in the substantia nigra and pallidum, in addition to their usual sites.

Gray *et al*^{66,67} described two unrelated patients with identical pathological lesions. The first developed an unsteady gait, chorea and torticollis from age 29 years, followed by proximal limb weakness, muscle wasting and fasciculation, and a course of six years.⁶⁶ The maternal grandmother died at age 30 years with a Parkinsonian disorder. The second case had rigidity, bradykinesia, postural imbalance, and motor neuron disease with onset at age 32 and a duration of two years.⁶⁷ A maternal uncle developed a Parkinsonian syndrome at age 45. Neuronal loss and gliosis were most severe in the subthalamic nuclei, followed by the pallidum, and lastly the substantia nigra where the changes were not as severe. There was neuronal loss affecting the hypoglossal nuclei and anterior horn cells

with demyelination of corticospinal tracts. The striatum, thalamus and locus coeruleus were free of lesions.

In these patients, described as pallidonigrolusian atrophies the pallidum has been diffusely involved with emphasis on either the internal⁶⁵ or external⁶³ segment.

Pallidonigral degeneration

This category is very small, and may not constitute a separate disorder. The case of Serratrice *et al*⁶⁸ was said to show normal subthalamic nuclei, and shows some overlap with motor neuron disease. The two pathological reports of van Bogaert⁸² and Davison⁸³ have often been cited as examples of pallidonigral degeneration, but pallidal changes were mild, and it is not possible to classify the cases. In one of the patients, symptoms of rigidity, tremor and postural instability started at age 7, and she lived to early adult life.⁸² In the second case right arm tremor started at age 10 years, followed by progressive rigidity, akinesia and rest tremor from age 27 years, and death at 65 years.⁸³

Fig 2 (a) Loss of myelin staining in the external pallidum (arrow); (b) degeneration with spheroids in the pallidum ($\times 86$); (c) degeneration with concretions in the pallidum ($\times 57$); (d) degeneration with neuronal loss, gliosis and deposits, Kluver-Barrera stain ($\times 57$). Taken from Kessler *et al* 1984⁷⁶ with permission.

Pallidal degeneration

It is doubtful that pallidal degeneration exists as a separate entity. Lange and Poppe⁸⁴ described six siblings, in whom they made a clinical diagnosis of pallidal atrophy. They confirmed their diagnosis at necropsy in one of the siblings, but the pallidal changes were mild.⁸⁵ Case 1 of Jellinger^{86,87} developed dystonia at age 13 years and died at 36 years. Classification is uncertain. Case 2 had pallidonigroluysian atrophy (figs 3 and 4).⁸⁷

Hereditary (holotopistic) striatal degeneration

Symptoms usually appear at 3 to 4 months of age, but children up to the age of 6 years are recorded; and even isolated adults.⁶⁹ Inheritance is autosomal dominant, and possibly recessive. In children psychomotor retardation and apathy occur, with dysarthria, rigidity and chorea in older individuals. Striatal degeneration is moderately severe with volume loss, neuronal depletion and gliosis. Pallidal involvement is variable, reportedly varying from absent⁸⁸ to mild.^{89,90}

Idiopathic calcification of the basal ganglia

The family described by Fritzsche⁹¹ is probably similar to others,⁹²⁻⁹⁴ although mental retardation was prominent.

Pallidal polyglucosan bodies in cerebral palsy

At least nine patients dying aged 15 to 90 years are recorded with chorea and dystonia, with or without other non-progressive intellectual and motor deficits, associated in most cases with a documented hypoxic perinatal insult.^{73,95-97} Numerous polyglucosan bodies are found in neuronal cytoplasm, nerve cell processes and neuropil of the lateral pallidum, with occasional bodies in the putamen, and sometimes the substantia nigra and brainstem tegmentum. Patchy neuronal loss and gliosis in the putamen and thalamus are present in some, but not all cases. The polyglucosan bodies show an electron dense core and a fibrillary outer zone interspersed with rough endoplasmic reticulum and ribosomes.

JUVENILE PARKINSONIAN SYNDROMES

Reports of juvenile Parkinsonian syndromes extend back to that of Siehr in 1899. The term is used here to refer to Parkinsonian syndromes of unknown cause presenting in the first two decades of life. Rarely the pallidonigral degenerations might be responsible for isolated Parkinsonian deficit (table 2). These patients are difficult to distinguish from older Parkinson's disease patients, but a high familial incidence has been reported ("paralysis agitans juvenilis familiaris").⁹⁸

Fig 3 Case 2⁸⁷. Atrophy and pigmentation of pallidal nuclei in pallidal degeneration. (a) Heidenhain stain, (b) Kanzler-Arendt stain. Taken from Jellinger, 1968⁸⁷ with permission.

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More recently assorted patients have been described with Parkinsonian disorders starting before age 40 years^{99 100} in which there is a high familial incidence, and high levodopa response rate. Juvenile cases are of great interest because very few pathological studies have been done, and there may be lessons to learn for Parkinson's disease. The age definition of juvenile cases is somewhat arbitrary, but partly depends on the observation that Lewy body Parkinson's disease is not documented before the age of 20, and is unlikely to occur before the latter part of the second decade. Patients presenting with Parkinson's disease between ages 20 and 40 years are indistinguishable from Parkinson's disease in older age groups and do not generally have a higher familial incidence.^{54 101 102}

One well-defined juvenile group is autosomal dominant dystonia-Parkinson syndrome which tends to follow a stereotyped clinical picture commencing with dystonia, and only later showing prominent Parkinsonian manifestations.¹⁰³ Onset is with dystonic foot inversion in the first decade of life, progressing at a slow, even imperceptible pace, to more generalised dystonia with Parkinsonian features. Levodopa

provides substantial improvement, without losing its effect with time, and life expectancy can be normal or nearly so. A single patient showing many of these features, but accidentally dying at 39 years, showed selective neuronal degeneration confined to the substantia nigra and locus coeruleus, associated with Lewy bodies.¹⁰⁴ May be the pathology of other cases is the same.

Hunt¹⁰⁵ is traditionally referenced in papers concerning juvenile Parkinson's disease or pallidal degeneration of assorted kinds. He described four patients with onset of a Parkinsonian disorder at ages 15, 13, 26 and 30 years. Parents of the second case were consanguineous and the diagnosis is unknown. There can be little doubt that the third and fourth cases had young-onset Parkinson's disease. The first patient developed rest tremor of the left foot spreading to the hand, with weakness and muscle rigidity. Symptoms spread to the right limbs, and were associated with a Parkinsonian gait. The patient died aged 40 and Hunt's pathological report describes loss of large cells from the pallidum, putamen, caudate nucleus and nucleus basalis. Because examination of the brainstem was not re-

Fig 4 Case 2⁸⁷. Neuronal loss and gliosis in pallidum. Cresyl violet, $\times 80$. Taken from Jellinger, 1968⁸⁷ with permission.

ported it is not possible to make conclusions about the diagnosis. This case, however, may be one of a substantial group of patients recorded in the literature showing an identical clinical picture comprising akinesia, rigidity and rest tremor with or without a postural component; and referred to here as juvenile Parkinsonian disorder. Some have mild dystonic features,¹⁰⁶ as in young onset Parkinson's disease, and all show a substantial initial response to levodopa within days of starting it. Long term follow-up is not reported in such cases. Occasional patients should be excluded from the group; for example, a child aged 5 years who suffered a severe encephalopathy six months before developing symptoms.¹⁰⁷ The remainder consist of two siblings with onset aged 7 and 8 years,¹⁰⁸ two siblings with onset aged 10 and 19 years¹⁰⁹ and another two siblings with onset aged 9 years and 10 years.¹⁰⁷ Two other patients were described aged 8 years¹⁰⁶ and 11 years at onset¹¹⁰ without affected siblings, although the second of these later developed a cerebellar syndrome, with amyotrophic and peripheral neuropathy. Two of these patients developed levodopa chorea¹⁰⁹ and two had extensor plantar responses and were consequently called pallidopyramidal syndrome,¹⁰⁸ but there is no evidence for believing that any of these patients have pallidal disease.

Although the pathological changes in this apparently well-defined group are unknown, two reports describe similar patients with the same pathological change of isolated nigral degeneration. The first of these reports describe three siblings with a slowly progressive Parkinsonian disorder manifesting bradykinesia, rigidity, and rest tremor from ages 12, 13 and 20 years.¹¹² The first two siblings were akinetic, rigid and virtually bedbound in 1954, when aged 36 and 45 years respectively. The third sibling died at 49 years with leukaemia. The substantia nigra was depigmented with moderately severe neuronal loss without additional features, and there were no unequivocal changes reported in the striatum, pallidum or locus coeruleus. The second report, in abstract, describes a 24 year old woman with onset of dystonia and Parkinsonian features at age 11, who was found to have moderate to severe nigral cell depletion, little or no pathology in the locus coeruleus and no Lewy bodies.¹¹² Clearly more pathological study is required to determine whether non-specific nigral degeneration is the only abnormality in juvenile Parkinsonian disorder.

Other juvenile Parkinsonian cases comprise one with onset at age 15, with an affected sister, whose age was not stated.¹¹³ Quinn *et al*¹⁰¹ reported four patients with disease onset at ages 17, 17, 19 and 20, each having at least one first degree relative with a Parkinsonian disorder, with a total of seven affected relatives between them, all of whom developed a Parkinsonian

state before age 40 years. Lastly, some members of the family described by Muentner *et al*¹¹⁴ presented in the second decade.

FAMILIAL PARKINSONIAN SYNDROMES

For the purpose of this review the category covers the few existing clinical and pathological studies on familial Parkinsonian syndromes, mostly with disease onset over age 20 years. Only pure Parkinsonian disorders are covered, with the exception of dementia in a few. Disorders showing additional features such as motor neuron disease or peripheral neuropathy are excluded. The age distinction is also arbitrary and there is overlap with juvenile cases, but it is based on the assumption that familial cases at this age are unlikely to have Parkinson's disease. However, some families have two, and rarely more, members with an adult-onset syndrome likely to be Parkinson's disease.

One of the early reports on familial Parkinsonian disorders was that of Bury,¹¹⁵ who described a brother and sister, with disease starting at ages 35 and 18 years, and responding to hyoscine. He was unable to confirm that two sisters died of the disorder aged 16 and 26 years. Spellman¹¹⁶ described a family with eight affected members in three generations, with onset between ages 26 and 45 years and death 2 to 12 years later. Davison⁸³ described four individuals all with extensor plantar responses. One occurred sporadically with onset at 24 years. In another, parents were consanguineous, onset was at 24 years and a sister probably had the same disease starting at 22 years. The third and fourth cases were siblings, aged 17 and 18 years at onset, of consanguineous parents. Yamamura *et al*¹¹⁷ described 15 cases, aged 13 to 28 at onset (four younger than age 20 at onset), from eight families. Two families, each with two affected siblings, showed parental consanguinity. Remaining families had two to four affected siblings. The affected offspring of consanguineous marriages^{83 105 117} presumably reflect autosomal recessive inheritance. Although ages of onset are generally higher, this disease might be identical to juvenile Parkinsonian disorder.

Muentner *et al*¹¹⁴ described a family of 12 individuals spanning four generations (similar to Spellman's¹¹⁶) that suffered a Parkinsonian disorder, followed by dementia, starting in the second or third decades and lasting 4 to 11 years. Neuropathological findings showed Lewy bodies in the usual specific areas, including limbic regions. Golbe *et al* (abstract) reported a large Italian family with many members afflicted with a Parkinsonian disorder, but no dementia, starting between 32 and 68 years with an approximate survival of 6.5 years. Lewy bodies were present in pigmented brainstem nuclei. These two families indicate an autosomal dominant Lewy body disease.

Two additional families do not accord with this

classification. Mayer *et al*¹¹⁸ described a man aged 19 with a levodopa responsive Parkinsonian syndrome associated with areflexia and retinal degeneration. He died at age 56 from pancreatic cancer. His brother had an identical illness from age 24 and died at 81 years, and the father had late onset Parkinson's disease. Autosomal dominant inheritance was suggested. Pathology showed atrophy of the midbrain, pons and spinal cord with depigmentation of the substantia nigra. There was gliosis in the pallidum, to a lesser extent the thalamus and substantia nigra, and mild atrophy of the dentate. In the substantia nigra there was moderate loss of pigmented cells of the zona compacta without Lewy bodies or tangles. There was degeneration of the dorsal columns of the spinal cord. The second family¹¹⁹ consisted of three siblings with a Parkinsonian disorder, dementia and possible pyramidal signs starting at ages 25, 23 and in the early twenties. They were unresponsive to levodopa. The third patient died at 31 years and the cerebral pathology was similar to that in Guam-parkinsonism dementia complex, except for sparing of the pallidum.

Further rational classification of these juvenile and familial syndromes depends on pathological study. The possibility of identifying pathogenetic mechanisms in these disorders, and in Lewy body disease, depends on the pathological findings.

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