for willed movements only, but subsequently also for following movements and the upward movement of the eyeballs which occurs on closing the lids. At a later stage, lateral conjugate gaze is also affected, the loss again first involving voluntary movements and at a later stage reflexly induced or following movements.

Tremor is not a feature of this condition, which is unlikely to be missed if ocular movements are tested routinely in every case of "Parkinsonism."

CREUTZFELDT-JAKOB DISEASE

This disease, which may occasionally show striatal features, broadens our vista of pathogenetic agents capable of causing Parkinsonism. It is the second chronic degenerative disease of the human nervous system (after kuru) to have been transmitted to chimpanzees[86] and is probably due to a "slow virus."

For a long time the disease was thought to be a slowly progressive disorder characterized by Parkinsonism, dementia with pyramidal signs, and sometimes wasting of the hands and feet.[25] The clinical spectrum covered by the name Creutzfeldt-Jakob disease has been broadened considerably in recent years[86-88] and now includes patients presenting with more rapidly progressive dementia, mutism, and myoclonus—or even cerebellar ataxia.[89] The symptoms in all these patients have been found to arise on a similar pathological substratum. Patients previously described as suffering from "spongiform encephalopathy"[90] are now thought to have Creutzfeldt-Jakob disease.

Creutzfeldt-Jakob disease should be suspected when Parkinsonian features are seen in the context of a progressive and widespread neurological disorder, involving any of the forementioned symptoms or signs. The presence of associated cerebral arteriosclerosis may, for a while, delay recognition.

OLIVOPONTOCEREBELLAR ATROPHY

Occasional patients with olivopontocerebellar atrophy, which usually presents as a progressive cerebellar ataxia, may exhibit generalized rigidity, expressionless facies, tremor at rest (in addition to intention tremor), drooling of saliva, and dementia.[91] A dominant mode of inheritance has been recorded in the affected kinships. The positive family history and associated dementia and cerebellar signs help differentiate this rare condition from more common forms of Parkinsonism.

PROGRESSIVE PALLIDAL ATROPHY

In the absence of encephalitis or of the administration of drugs, Parkinsonism in a child is extremely rare. Progressive pallidal atrophy is occasionally the pathological substratum of cases of juvenile Parkinsonism, [92] [93] though "pure" pallidal atrophy more often results in choreo-athetotic disorders or torsion dystonia.[94]

Parkinsonism—Neuropathology

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Experimental studies, often of great value in elucidating disorders of central nervous function, have been of limited use in studying Parkinsonism. The full Parkinsonian syndrome cannot be reproduced in animals, though if the midbrain of monkeys is damaged bilaterally to cause loss of cells in the substantia nigra, tremor and hypokinesia may appear.[95] [96] The relation of the deep grey masses of the cerebrum to involuntary movement is well known, and the importance of the substantia nigra in this respect is suggested by the many anatomical studies in various species revealing its connexion with the corpus striatum. Nigrostriatal fibres have been shown by conventional histological means,[97-99] and a nigrostriatal pathway has been convincingly demonstrated by formalin-induced fluorescence. This technique can be used to show the localization of dopamine in microscope sections, and reveals high concentrations of this catecholamine both in nigral cell bodies and in striatal nerve endings.[100] Since experimental lesions of the brainstem which produce loss of cells in the substantia nigra reduce the concentration of dopamine in the corpus striatum,[101] it is not unreasonable to infer that the striatal depletion of dopamine in Parkinsonism[102] is the result of nigral damage. That lesions of the nigrostriatal pathway are responsible for Parkinsonism is indeed borne out by the neuropathological findings.

Until the end of the last century lack of neurophysiological knowledge and clinicopathological correlations allowed only guesses at the nature of Parkinsonism. James Parkinson himself thought that it originated in a damaged cervical spinal cord and lower brainstem, while preservation of intellectual function suggested to him that the cerebral hemispheres were spared.[37] In contrast, William Gowers, noting—ten years before the concept of an extrapyramidal pathway had been formulated—that Parkinsonism was a purely motor disorder, believed it to arise from a disturbance of the cerebral cortex.[39]

The midbrain and substantia nigra were first implicated in 1893.[103] Blocq and Marinesco's case, a man of 38 with left-sided Parkinsonian signs, was shown at necropsy to have a circumscribed lesion 2·5 cm in diameter replacing the right half of the substantia nigra and adjacent structures. The suggestion that lesions of the nigra might be responsible for idiopathic Parkinsonism was made soon afterwards,[104] but neuropathologists, concentrating their efforts on the basal ganglia, seem to have ignored this region for more than twenty years. In 1919 Tretiakoff examined the brains of nine patients with Parkinsonism and observed a variety of degenerative features and reduction of

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numbers in the pigmented cells of the substantia nigra.[105] Besides some non-specific neuronal changes, he found peculiar concentric inclusions in the cytoplasm of these cells. These have become known as Lewy bodies, after the author who first reported them,[106] in neurons of the dorsal vagal nucleus and the nucleus substantiae innominatae in idiopathic Parkinsonism. With the paper of Foix and Nicolesco[107] knowledge of the morbid anatomy of the disease was more or less complete by 1925.

Idiopathic Parkinsonism

In the brain of patients with idiopathic Parkinsonism the only naked-eye abnormality is loss of pigmentation of the substantia nigra and locus caeruleus pontis. Under the microscope the substantia nigra shows a decrease in the number of pigmented neurons, shrinkage and vacuolation often being visible, and the presence in macrophages of neuromelanin granules, presumably derived from dead nerve cells. As well as Lewy bodies, other types of intraneuronal inclusion may be recognizable. These differ in not being concentric; some are ill-defined, while some resemble the corpora amylacea so frequently seen in normal brains. Gliosis is present in proportion to the loss of neurons. Similarly affected brainstem structures include the locus caeruleus, reticular formation, and dorsal vagal nucleus. Non-pigmented as well as pigmented cells are reduced in number in this nucleus.[71] The hypoglossal nucleus also shows neuronal loss, in association with cytoplasmic inclusions that are well stained by aniline blue, though similar inclusions are a common incidental necropsy finding.[108]

With emphasis now being placed on nigral damage as the primary abnormality in Parkinsonism, discussion of the pathology of the globus pallidus takes second place. Changes in the globus pallidus and putamen are less constant and usually less severe than those in the substantia nigra, and it has been suggested that they are merely the result of loss of nigral neurons and come about through trans-synaptic degeneration.[109] They include patchy atrophy, with disappearance of some neurons and accumulation of lipofuscin (normally an ageing phenomenon) in others, reactive gliosis, and loss of myelinated fibres. While the lentiform nucleus is sometimes affected by severe, bilaterally symmetrical degeneration, the lesions are generally minor.

Abnormalities of the cerebral cortex in Parkinsonism are non-specific and mild, but perhaps worthy of note in view of the increasing recognition of dementia in this condition. Some reports describe cortical atrophy, loss of neurons in the frontal region, and the parenchymatous changes of advanced age; in the absence of convincing control data, they cannot be fully accepted, and further quantitative studies are needed.

More should be said at this stage about Lewy bodies.

They measure 20μ or more in diameter, and are usually solitary (but sometimes more than one is present in a cell), hyaline and concentrically ringed, with a pale halo and a darker core. They may fill the neuronal body, compressing the nucleus into a peripheral crescent. They are eosinophilic and well shown by trichrome stains like Lendrum's Martius-Scarlet-Blue, which gives a deep red core and light blue halo. Those that are free-lying are believed to be the remnants of dead neurons. While Lewy bodies are said to occur in the brains of a few old people without apparent neurological disorder[110] it must be remembered that Parkinsonism is very common after 60 and may be overlooked clinically. Lewy bodies can be found in at least 90% of cases of idiopathic Parkinsonism, and only rarely, if ever, in cases diagnosed as postencephalitic.[111 112] Taking into account errors of diagnosis, there is some reason to believe that they are peculiar to the idiopathic form of Parkinsonism.

Den Hartog Jager and Bethlem[113] have shown that Lewy bodies may be very widely distributed throughout the nervous system, confirming earlier observations. They may be found in neurons of many diencephalic and brainstem nuclei, lateral and posterior horns of the spinal cord, ganglia of the sympathetic chain, and coeliac ganglion. Thus they are far from being specifically related to pigmented nerve cells, though whether they occur in catecholamine-synthesizing neurons generally remains to be seen. Their nature is uncertain. Chemical analysis has not contributed significantly. Histochemical studies[114] have been interpreted as showing the presence of sphingomyelin. Electron microscopy[115 116] appears to show two varieties of intracytoplasmic inclusion. One is presumably the typical concentric Lewy body and is composed of granular and fibrillary material, with more densely packed granules in the core and radiating fibres peripherally in the halo. The other is more clearly marginated, lacks a core, and contains coarse fibrillary material and scattered large dense granules. This type closely resembles corpora amylacea. It has been suggested that Lewy bodies are formed from degenerate neurofilaments, though how they are formed is quite unknown.

So far morphological and chemical analysis has failed to give a clue to the nature of the disease process that produces idiopathic Parkinsonism; and it is hard to see how further studies by conventional means of Lewy bodies—however characteristic they may be—will advance understanding of this condition. All that can be said at the present time is that the pathological findings show a constant pattern of neuronal degeneration, which links the disease perhaps to the vast group of "abiotrophies,"[117] neurological disorders without known cause but presumably with an as yet undetermined enzymic defect. As many as 16% of cases have a family history of Parkinsonism,[4] which suggests that the possible underlying metabolic disorder may be genetically determined. Only in some ways has knowledge of the cause of the disease been advanced by the pathologist since James Parkinson wrote[27] "not having had the advantage, in a single case, of that light which anatomical examination yields, opinions and not facts can only be offered."

Postencephalitic Parkinsonism

Another neuronal alteration sometimes found in idiopathic Parkinsonism should be mentioned here. This is neurofibrillary degeneration, in which the nerve-cell cytoplasm becomes filled with bands and skeins of argyrophilic material. In idiopathic Parkinsonism it may occur together with neuronal loss in the substantia nigra, and it may affect various brainstem nuclei to a minor extent, though a comparable degree of involvement has been found in aged brains examined routinely. Cases of postencephalitic Parkinsonism, in contrast, often show widespread and severe neurofibrillary degeneration, affecting not only substantia nigra and locus caeruleus but also the putamen, thalamus, hypothalamus, and sometimes oculomotor nuclei. In these cases the pigmented regions of the brainstem may lose all their neuromelanin, and very few intact neurons may remain. Fibrous gliosis in the substantia nigra is marked.

Neurofibrillary degeneration, which is such a prominent finding in postencephalitic Parkinsonism, is commonly seen in Alzheimer's disease and in senile brains, and it is also seen—often in younger age groups—in many other neurological states, including various forms of encephalitis.[118] There are topographical differences in the degenerative process in these different conditions, but its histological and ultrastructural appearances are uniform. Neurofibrillary degeneration is thus a general tissue response to a host of unknown factors and its occurrence in postencephalitic Parkinsonism cannot be interpreted either as a sign of premature ageing or of persistent viral infection. Evidence of viral encephalitis in the form of an inflammatory infiltrate or inclusions is totally lacking. This is perhaps not surprising since most patients die many years after their original encephalitic illness. It should be remembered that the earliest observations emphasized perivascular lymphocytic infiltration in the pons, midbrain, and diencephalon, and complete destruction of the nigra could occur very rapidly. Thus the lesions seen nowadays in the postencephalitic brain could well represent the end-stage of a long-completed process.

TABLE I—*A Comparison of Pathological Findings in two Types of Parkinsonism*

	Idiopathic	Postencephalitic
Main changes in neurons of substantia nigra and pigmented brainstem nuclei	Reduced numbers of neurons; Lewy bodies and other inclusions	Reduced numbers of neurons; neurofibrillary degeneration
Main changes in neurons outside substantia nigra and pigmented brainstem nuclei	Lewy bodies and other inclusions	Neurofibrillary degeneration

TABLE II—*A Comparison of the Major Neuronal Alterations in two Types of Parkinsonism*

Alterations	Idiopathic	Postencephalitic
Lewy bodies	Almost always found	Not found
Neurofibrillary degeneration	May occur; mild	Always found; severe

Other Forms of Parkinsonism

Arteriosclerotic Parkinsonism has no firm pathological basis. Though occasional patients are reported as having multiple vascular lesions in the corpus striatum and brainstem and an apparently normal substantia nigra, possibly the changes of idiopathic Parkinsonism have been overlooked and the striatal softening are an incidental finding. There is little factual evidence to support an arteriosclerotic aetiology for Parkinsonism, and the case for its existence must be regarded as unproved pathologically.

A rather better characterized but small group of cases has striatonigral degeneration, first described in 1961 by Adams, van Bogaert, and van der Eeken.[119] Though pathologically there is some heterogeneity, these patients have in common neuronal degeneration of the corpus striatum (notably the putamen) as well as the substantia nigra. The putamen is usually atrophic, with loss of neurons and myelinated fibres, densely gliotic, and contains abnormal pigment. The substantia nigra and locus caeruleus are depigmented and depleted of neurons. In some cases neuronal loss has been observed in the cerebral cortex, hypothalamic and subthalamic nuclei, and dentate nucleus, while one of the original cases resembled olivopontocerebellar atrophy. Lewy bodies are absent.

Clinically, these patients have a disorder that is indistinguishable from idiopathic Parkinsonism: detailed neuropathology, on the other hand, has shown them to have a distinctive condition. Pathology has also been of value in defining certain other chronic neurological syndromes which share some features with Parkinsonism and may occasionally have been so diagnosed. These include progressive supranuclear palsy,[84] in which neuronal depletion and neurofibrillary and granulovacuolar degeneration are found in the deep cerebral and cerebellar grey structures and the brainstem; and the Shy-Drager syndrome.[80] In this condition both olivopontocerebellar atrophy and Lewy body-like inclusions have been described.[120 121] These dissimilar pathological states coincide in a few patients,[122 124] suggesting that the syndrome may have an aetiological unity and may possibly be related to idiopathic Parkinsonism. Olivopontocerebellar atrophy itself often has extrapyramidal features, and some patients may be frankly Parkinsonian.[124] In these cases the condition is inherited as a dominant trait, and at necropsy obvious loss of cells from the substantia nigra is found as well as the characteristic neuronal depletion and gliosis in olives, dentate nuclei, cerebellar cortex, and pons. Progressive pallidal atrophy is another rare disease which may sometimes cause Parkinsonism.[93] Cases of "juvenile Parkinsonism," investigated in life and found to have normal copper metabolism, are occasionally seen. Some of these may show reduced numbers of large neurons in the globus pallidus and putamen, with a normal substantia nigra. More frequently this pathological picture is associated with torsion dystonia and contractures.[95]

DRUG-INDUCED PARKINSONISM

The pathology of drug-induced Parkinsonism is poorly understood, partly because the situation is often reversible. Thus, though a Parkinsonian picture is often seen in patients treated with the phenothiazine drugs, very little information about its neuropathology is available. Nevertheless, patients with phenothiazine-induced oral dyskinesia almost always show reduced numbers of cells in the substantia nigra and gliosis of the midbrain,[125] and minor changes of this type could well account for the Parkinsonian syndrome. Manganese poisoning produces a complex neurological disorder with prominent features of Parkinsonism. The very few neuropathological reports describe a diffuse loss of nerve cells with glial scarring in the basal ganglia and cerebral cortex. Experimental manganese intoxication in monkeys causes diffuse cerebellar damage but fails to produce a consistent pattern of lesions in the corpus striatum or substantia nigra.[126] Another toxic cause of Parkinsonism is carbon monoxide poisoning. Though this is uncommon, its pathology is well documented, and anoxic damage of the globus pallidus and substantia nigra is implicated.

This is not the place to describe the detailed morbid anatomy of Huntington's chorea, Wilson's disease, and Creutzfeldt-Jakob disease, the pathology of which is beyond the scope of this article. Nevertheless, in each of these disorders Parkinsonian signs can be related to lesions of the corpus striatum. Thus in the first two there is severe atrophy of the caudate nucleus and putamen, with only mild and inconstant nerve cell loss and scarring in the globus pallidus and substantia nigra. Creutzfeldt-Jakob disease shows neuronal loss, astrocytic proliferation, and status spongiosus affecting to a varying degree the cerebral cortex, corpus striatum, thalamus, cerebellar grey matter, and motor pathways. Corticostriatal and corticostriatospinal forms are among the clinicopathological variants that have been described.[87]

Batten's disease (neuronal ceroid-lipofuscinosis) is another rare disorder with Parkinsonian features, severe rigidity, and bradykinesia sometimes accompanying the prominent visual and intellectual symptoms. A clinical onset in the third decade has been described. Atrophy of cortical and central grey matter occurs, with neuronal loss and lipofuscin deposition in the survivors. The neurons of the substantia nigra are filled with large, protein-containing inclusions.[127]

The brains of punch-drunk boxers, whether or not there is clinical evidence of Parkinsonism, always show loss of cells throughout the substantia nigra. There are no Lewy bodies. Other evidence of neuronal damage is presented in the form of neurofibrillary degeneration, mainly in the temporal cortex, without senile plaque formation. The overall neuropathological picture seems to be specific.[128]

Finally, a word about the Parkinsonian picture seen occasionally with cerebral tumours: pathological data are scanty,[129] and the suggestion that midbrain compression is responsible is hard to accept since with tumours brainstem compression is very common, and Parkinsonism very rare.