INTRODUCTION
Although the clinical syndrome of parkinsonism (rigidity, bradykinesia, and tremor) is most often owing to idiopathic Parkinson’s disease (PD), it may also be associated with a variety of other underlying pathologies (Table 1). Each of these other pathological conditions tends to have a characteristic clinical phenotype, however atypical cases are increasingly recognized. Moreover, some patients with PD have additional clinical features such as dementia, autonomic dysfunction, or gastrointestinal dysmotility. As a result, the accurate diagnosis of a patient with parkinsonism, and especially those with atypical or additional clinical features, ultimately depends on neuropathological examination. This chapter will review the pathological changes that characterize those conditions that may present with or have parkinsonism as a major feature, either in isolation or combined with other clinical manifestations. Although the focus of this text and chapter are the atypical causes of parkinsonism, a description of the pathological features of typical PD is included for comparison.

IDIOPATHIC PARKINSON’S DISEASE
Although there is some controversy as to the most appropriate use of the term, Parkinson’s disease is most often used to denote idiopathic parkinsonism associated with the pathological finding of neuronal loss and Lewy bodies in the substantia nigra. External examination of the brain is generally unremarkable, although PD patients who develop dementia may have mild to moderate cerebral atrophy. On cut sections, there is usually loss of pigment from the substantia nigra and locus ceruleus (Fig. 1A). The caudate, putamen, globus pallidus, thalamus, and other brainstem structures appear normal. The histopathological hallmark of PD is the loss of dopaminergic neurons from the substantia nigra associated with the presence of intraneuronal inclusions called Lewy bodies (LBs). Cell loss in the substantia nigra occurs in a region-specific manner, with the lateral ventral tier of the pars compacta being most affected. It is estimated that at least 50% of the nigral neurons must degenerate...
to produce symptoms and, at autopsy, most cases show more than 80% reduction (15). Significant neuronal loss also occurs in the locus ceruleus, dorsal motor nucleus of the vagus, raphe nuclei, and nucleus basalis. LBs may be found in all of these locations as well as numerous other subcortical structures. Neurodegeneration is accompanied by reactive changes including astrogliosis and microglial cell activation. In pigmented nuclei, neuromelanin is released from dying neurons and may lie free within the neuropil or be taken up by macrophages.

In 1912, Frederich H. Lewy first described intraneuronal inclusions in the substantia innominata and dorsal motor nucleus of the vagus, in patients with paralysis agitans (16). Seven years later, Tretiakoff recognized similar inclusions in the substantia nigra and called them corps de Lewy (17). Since then, LBs have been considered the pathological hallmark of idiopathic PD and most

Table 1
Causes of Parkinsonism

<table>
<thead>
<tr>
<th>1. Neurodegenerative disease: synucleinopathies</th>
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<tbody>
<tr>
<td>• Lewy body disorders</td>
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<tr>
<td>• idiopathic Parkinson’s disease</td>
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<tr>
<td>• dementia with Lewy bodies</td>
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<tr>
<td>• multiple system atrophy</td>
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<tr>
<td>• Hallervorden–Spatz syndrome</td>
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<tr>
<td>tauopathies</td>
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<tr>
<td>• corticobasal degeneration</td>
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<tr>
<td>• progressive supranuclear palsy</td>
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<tr>
<td>• FTDP-17</td>
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<tr>
<td>• parkinsonism/dementia complex of Guam</td>
</tr>
<tr>
<td>other:</td>
</tr>
<tr>
<td>• Alzheimer’s disease</td>
</tr>
<tr>
<td>• motor neuron disease and frontotemporal dementia with MND-type inclusions</td>
</tr>
<tr>
<td>• Huntington’s disease</td>
</tr>
<tr>
<td>• spinocerebellar ataxia</td>
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<tr>
<td>2. Infectious disease:</td>
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<tr>
<td>• postencephalitic parkinsonism</td>
</tr>
<tr>
<td>• HIV</td>
</tr>
<tr>
<td>• other (bacteria, viruses, parasites, fungi)</td>
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<tr>
<td>3. Vascular disease</td>
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<tr>
<td>4. Trauma</td>
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<td>5. Toxins:</td>
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<tr>
<td>• MPTP</td>
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<tr>
<td>• others</td>
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<tr>
<td>6. Drugs:</td>
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<tr>
<td>• neuroleptics (phenothiazines)</td>
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<tr>
<td>7. Metabolic disease:</td>
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<tr>
<td>• Wilson’s disease</td>
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<tr>
<td>• aceruloplasminemia</td>
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<tr>
<td>8. Space-occupying lesions</td>
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<tr>
<td>9. Hydrocephalus</td>
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Note: It has recently become popular to classify some neurodegenerative diseases based on the protein abnormality (molecular pathology) that is believed to be central to the pathogenesis. This interpretation is often supported by genetic analysis of familial cases. Although this type of classification may help to organize discussion of the comparative pathology and biochemistry between conditions, it may be an oversimplification, which will require revision in the future. For instance, it is increasingly recognized that many of the “tauopathies” often have some accumulation of α-synuclein and vice versa.
Neuropathologists are reluctant to make the diagnosis in their absence. Classical LBs are spherical intracytoplasmic neuronal inclusions, measuring 8–30 µm in diameter, with an eosinophilic hyaline core and a pale-staining peripheral halo (Fig. 1B). They occasionally have a more complex, multilobar shape and more than one LBs may occur in a single cell. Following neuronal death, LBs may remain as an extracellular deposit in the neuropil. Ultrastructurally they are composed of radially arranged 7- to 20-nm filaments associated with granular electron-dense material.

An additional finding in most cases of PD is the presence of pale bodies: ill-defined rounded areas of granular pale-staining eosinophilic material that also occur in pigmented neurons of the substantia nigra and locus ceruleus (Fig. 1C). Although they are distinguished from LBs histologically, their similar immunocytochemical profile suggests they likely represent precursors to LBs (18,19).

LBs are difficult to isolate and purify and so most of our understanding of their chemical composition is based on immunohistochemical studies. Until recently, the two main components were α-synuclein immunoreactive and tau-immunoreactive.

Table 2
Comparative Neuropathology of Major Causes of Parkinsonism

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<tr>
<th>Disease</th>
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<th>Other Characteristic Pathology</th>
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<tr>
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<td>subcortical LBsα</td>
<td>cortical LBsα, pale bodiesα,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lewy neuritesα</td>
</tr>
<tr>
<td>dementia with Lewy bodies</td>
<td>cortical LBsβ</td>
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</tr>
<tr>
<td>multiple system atrophy</td>
<td>glial cytoplasmic inclusionsγ</td>
<td>glial intranuclear inclusionsγ, neuronal cytoplasmic and intranuclear inclusionsγ</td>
</tr>
<tr>
<td>corticobasal degeneration</td>
<td>achromatic neurons</td>
<td>cortical neuronal cytoplasmic inclusionsδ, corticobasal bodiesδ, thorn-shaped astrocytesδ, coiled bodiesδ, threadsδ, granule degeneration</td>
</tr>
<tr>
<td>progressive supranuclear palsy</td>
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<td>cortical NFTsδ, thorn-shaped astrocytesδ, coiled bodiesδ, threadsδ</td>
</tr>
<tr>
<td>FTDP-17T</td>
<td>various neuronal cytoplasmic inclusionsα, various glial cytoplasmic inclusionsβ</td>
<td>achromatic neurons</td>
</tr>
<tr>
<td>ALS/parkinsonism/dementia of Guam</td>
<td>cortical and subcortical NFTsδ</td>
<td>glial cytoplasmic inclusionδ</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>cortical SPs</td>
<td>subcortical SPs (subcortical NFTsδ)</td>
</tr>
<tr>
<td>postencephalitic parkinsonism</td>
<td>cortical and subcortical NFTsδ</td>
<td>glial cytoplasmic inclusionδ</td>
</tr>
<tr>
<td>vascular parkinsonism</td>
<td>cerebral infarcts</td>
<td></td>
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<tr>
<td>posttraumatic parkinsonism</td>
<td>NFTsγ</td>
<td>SPs</td>
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LB, Lewy body; NFT, neurofibrillary tangle
α-synuclein immunoreactive

Neuropathology of Atypical Parkinsonian Disorders

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thought to be neurofilament proteins and ubiquitin, although many other protein and non-proteinaceous elements are also recognized (20–22). The biochemistry of LBs was clarified following the discovery of mutations in the gene for α-synuclein in some families with autosomal dominant PD (23). α-Synuclein is a presynaptic nerve terminal protein and immunohistochemistry of normal brain tissue shows punctate staining around neuronal perikarya. Direct involvement of α-synuclein in the pathogenesis of all LB disorders (sporadic as well as familial PD and dementia with LB) is supported by immunohistochemical studies confirming α-synuclein as a major component of both brainstem and cortical LB, as well as pale bodies and Lewy-related neurites (19, 24). In addition to these neuronal pathologies, recent reports have described the presence of argyrophilic, α-synuclein-positive cytoplasmic inclusions in both astrocytes and oligodendrocytes in PD (Fig. 1D) (25, 26). The consistency and significance of this glial pathology awaits clarification.

DEMENTIA WITH LEWY BODIES

Although it has long been recognized that a significant proportion of PD patients develop dementia (12), the pathological substrate for this cognitive dysfunction remained uncertain. In 1961, Okazaki reported finding LBs in the cerebral cortex of two patients with PD and atypical dementia (27).
Although subsequent cases of diffuse Lewy body disease (DLBD) were published, the condition was initially considered rare. In the late 1980s, with greater awareness of cortical LBs and the development of more sensitive staining methods, several groups reported finding cortical LBs in 15–25% of elderly demented patients, both with and without parkinsonism (28,29). It has recently been proposed that dementia associated with Lewy bodies (DLB) represents a recognizable clinicopathological syndrome that may be distinguishable during life from other causes of dementia (30). The proposed diagnostic criteria are purely clinical however, and recommendations as to how to quantitate LBs are only designed to assess the hypothesis that dementia is more likely to occur when LBs are numerous and widespread (i.e., DLB = DLBD) (30). Although numerous cortical LBs are most characteristic of DLB, smaller numbers are found in most (if not all) patients with idiopathic PD, even in the absence of dementia (31). As a result, the clinical and pathological relationship between PD and DLB and the appropriate terminology remains an ongoing source of controversy.

Some cases of DLB show microvacuolation of the superficial neocortex, particularly in the temporal lobe. Cortical LBs occur primarily in small and medium-size pyramidal neurons of the deeper cortical layers and are most abundant in the transentorhinal and cingulate cortex, less numerous in neocortex, and generally spare the hippocampus. They tend to be less well defined and are more difficult to recognize than classical brainstem LBs, using conventional staining methods (Fig. 2A). It is largely the advent of more sensitive immunohistochemical methods of detection (especially for ubiquitin and α-synuclein) that has allowed the extent of cortical LB pathology to be fully appreciated (Fig. 2B).

A distinctive neuritic degeneration was first reported in cases of DLB (32) but has subsequently been found in many cases of PD, as well (33). These abnormally swollen neuronal processes are not seen using hematoxylin and eosin (H&E) or conventional silver stains but are well demonstrated using ubiquitin and α-synuclein immunohistochemistry (Fig. 2C) (19). Often referred to as Lewy neurites, they are most concentrated in the CA2/3 region of the hippocampus but are also found in the amygdala, nucleus basalis, and various brainstem nuclei. In addition to accumulating in neuronal cell bodies and processes, α-synuclein-positive glial inclusions have also been reported in DLB (25,34).

Most, but not all, cases of DLB have some degree of Alzheimer’s disease (AD)-like pathology (28,35). Senile plaques (SPs) are the most common finding with the majority being of the “diffuse” type. When neuritic plaques are present, most contain only tau-negative, ubiquitin-positive neurites. Neurofibrillary tangles (NFTs) and neuropil threads, containing paired helical filaments, may be found in the limbic structures and mesial temporal lobe but are uncommon in the neocortex. This pattern of pathology may be sufficient to fulfil pathological criteria for AD that are based on SP numbers (such as CERAD) (36) but not those that stress the importance of NFTs (such as Braak staging) (37). This overlap between DLB and AD pathology, combined with the lack of universally accepted pathological diagnostic criteria for either disorder, has resulted in confusion over the relationship between the conditions and the appropriate terminology. It also raises questions as to the pathological substrate for dementia in DLB patients. Although some studies have shown a correlation between the numbers of cortical LBs and cognitive dysfunction (38–41), others have not (29). This suggests that coexisting AD pathology, Lewy neurites, and/or degeneration of specific neuronal populations could all contribute to dementia, possibly in an additive fashion (42,43).

THE SPECTRUM OF LB DISORDERS

There is striking clinical and pathological overlap between PD and DLB. Up to one-third of patients with a clinical diagnosis of PD will develop dementia (9,12,42) and most (but not all) patients with DLB display some degree of parkinsonism (30). LBs are the defining histopathological feature of both conditions. In PD, LBs are most numerous in subcortical nuclei and it is the associated loss of dopaminergic neurons that is largely responsible for the characteristic extrapyramidal features. However, small numbers of cortical LBs may be found in virtually all cases of PD, even in the absence of dementia (31). In DLB, cortical LBs are usually more numerous and some studies have shown a
Fig. 2. Dementia with Lewy bodies. (A) Cortical Lewy body (LB) (H&E stain). (B) Three neurons in deep layers of neocortex containing LBs (α-synuclein immunohistochemistry). (C) Lewy neurites in CA2 region of hippocampus (ubiquitin immunohistochemistry).
correlation between their number and the degree of dementia (38–41). Even in the absence of parkinsonism, however, the vast majority of DLB cases display some brainstem LB. Recognition of this overlap has led to the concept of a spectrum of LB disorders with different clinical features, depending on the severity and anatomic distribution of LB involvement (44–46). Other less common clinical manifestations may be associated with involvement of other neuroanatomic regions, autonomic dysfunction with involvement of sympathetic ganglia, dysphagia when the dorsal motor nucleus of the vagus is damaged, and gastrointestinal dysmotility with LBs in enteric plexi (10,11). Each condition may occur in isolation or in various combinations. Although this concept is attractive, at least one recent study failed to demonstrate the degree of clinical-anatomic correlation predicted (38).

FAMILIAL PARKINSON’S DISEASE

At the time this manuscript was being prepared, at least 11 different genetic loci had been linked to familial PD, including mutations in four specific genes (47,48). The pattern of inheritance includes both autosomal dominant and recessive and the clinical phenotypes vary from typical PD to families with juvenile or early onset and others with atypical clinical features. For most of these, information about the pathological findings is not yet available. Families with autosomal dominant PD and mutation of the gene for α-synuclein have changes similar to sporadic PD, with nigral degeneration and LBs (23). Cases of autosomal recessive, juvenile-onset PD and parkin mutations have neuronal loss in the substantia nigra and locus ceruleus, but only one report has described finding LBs (49). A single family has been identified with a mutation in the gene for ubiquitin C-terminal hydrolase L1 (UCH-L1) (50). No pathological information is available from this family but mice with intrinsic deletion of this gene develop axonal degeneration (51).

MULTIPLE SYSTEM ATROPHY

Although the term multiple system atrophy (MSA) has been used rather indiscriminately in the past, recent advances in our understanding of the genetic, biochemical, and pathological basis of a number of neurodegenerative diseases has resulted in some reclassification and refinement of the definition. On the basis of a common pathological substrate, the diagnosis of MSA is currently restricted to include cases formerly designated as striatonigral degeneration (SND), olivopontocerebellar atrophy (OPCA), and some (but not all) cases of Shy–Drager syndrome. Because of the high degree of clinical and pathological overlap between these conditions, a recent Consensus Conference recommended using the terms MSA-P for cases with prominent parkinsonism and MSA-C for those with mainly cerebellar features (52). A review of 100 cases of the clinical course of MSA found that almost all eventually developed parkinsonism and autonomic dysfunction whereas cerebellar features occurred in less than half (53).

Several excellent reviews of the neuropathology of MSA have recently been published (54,55). Macroscopically, there is atrophy of specific cortical and subcortical regions, which reflects the anatomic distribution of degenerative change. In cases previously designated as SND (most probably corresponding to MSA-P), there tends to be severe atrophy and discoloration of the putamen and loss of pigmentation of the substantia nigra and locus ceruleus (Fig. 3A), whereas in OPCA (MSA-C) the cerebellum, middle cerebellar peduncles, and basis pontis are most affected (Fig. 3B). Microscopically, the involved gray matter structures show neuronal loss and reactive gliosis whereas associated white matter tracts demonstrate loss of myelin. The degree and pattern of degeneration vary from case to case but the putamen, substantia nigra, locus ceruleus, inferior olives, pontine nuclei, Purkinje cell layer, and intermediolateral columns are most often affected in some combination (56). Nerve biopsy may show a reduction in the number of unmyelinated fibres (57).

The specific histopathological changes that characterize MSA, and which are now considered mandatory for the diagnosis (58), were first described in a series of articles by Papp and Lantos (59–61). The most characteristic change is the presence of small flame or sickle-shaped structures in the...
Fig. 3. Multiple system atrophy. (A) Gross photographs of a case of striatonigral degeneration showing atrophy and discoloration of the putamen (arrows) and loss of pigmentation of the substantia nigra (inset). (B) Gross photograph showing atrophy of the pons in a case of olivopontocerebellar atrophy (OPCA) compared with normal control (C). (C,D) Numerous glial cytoplasmic inclusions (GCIs) in oligodendrocytes (Gallyas silver stain). (E) GCIs immunoreactive for α-synuclein.
cytoplasm of oligodendrocytes, referred to as glial cytoplasmic inclusions (GCIs). They are difficult to detect in routine H&E-stained sections but are well demonstrated with a variety of silver stains, particularly the Gallyas method (Fig. 3C,D). Although GCIs show variable immunoreactivity for a variety of proteins including tau, ubiquitin, tubulins, and B-crystallin (59,62–64), they are most strongly immunoreactive for α-synuclein (Fig. 3E) (65,66). The ultrastructural composition includes tubules and straight and twisted filaments associated with granular material (59,60,62–65). GCIs tend to be widely distributed throughout the brain, beyond the areas showing obvious degeneration. They are found in motor cortex, putamen, globus pallidus, subthalamic nucleus, pontine nuclei, various cranial nerve nuclei, and several white matter tracts in the cerebrum, brainstem, and spinal cord. In addition to GCI, argyrophilic, ubiquitin-, and α-synuclein immunoreactive fibrillar or filamentous inclusions are also found in the cytoplasm of neurons and the nuclei of both neurons and glia in MSA (60,63,67). These other types of inclusions tend to be less numerous and have a more restricted anatomical distribution, found primarily in the putamen and basis pontis, and their presence is not required for diagnosis.

CORTICOBASAL DEGENERATION

This clinicopathological entity was first described under the name corticodentognal degeneration with neuronal achromasia (68) and early reports stressed the characteristic movement abnormalities, which often include akinetic rigidity (69). More recently, however, a number of postmortem studies have found abnormalities of higher mental function, such as language disturbance and dementia, to be a common and sometimes predominant feature in patients with corticobasal degeneration (CBD) pathology (6,8,70–74).

Cortical atrophy is often focal and asymmetric with parasagittal, peri-Rolandic, or peri-Sylvian regions most often involved (Fig. 4A). Macroscopic degeneration of subcortical structures is variable with depigmentation of the substantia nigra being most consistent. Microscopically, degenerative changes are more widespread but the severity and anatomical distribution vary between cases. In addition to neuronal loss and gliosis, the affected cortical regions may show superficial laminar or transcortical microvacuolation. Of subcortical structures, the substantia nigra tends to be the most severely and consistently affected whereas involvement of globus pallidus, striatum, subthalamic, thalamic nuclei, and brainstem regions is more variable.

The original description identified numerous swollen achromatic neurons (ANs) as the characteristic histopathological feature of CBD (68). ANs are most numerous in limbic cortex and amygdala in CBD, however this finding is not disease specific (75,76). Of greater diagnostic significance is the presence of neocortical ANs, which are most common in layers III, V, and VI of posterior frontal and parietal lobes. They may also be present in small numbers in subcortical regions. ANs resemble cells undergoing central chromatolysis; the perikaryon is swollen and often rounded, the Nissl substance is inconspicuous, and the nucleus is often in an eccentric position (Fig. 4B). They occasionally show cytoplasmic vacuolation. Although easy to recognize with standard H&E stain, ANs are best demonstrated by their strong cytoplasmic immunoreactivity for phosphorylated neurofilament and αB-crystallin (Fig. 4C) (75,77). Argyrophilia, tau-, and ubiquitin-immunoreactivity are more variable (72,78). The other change visible with H&E stain is the presence of ill-defined faintly basophilic filamentous cytoplasmic inclusions in surviving neurons of the substantia nigra and some other subcortical structures (Fig. 4D). These were originally termed corticobasal bodies (79) but appear to have the same immunophenotype and ultrastructure as the NFTs found in broader distribution in progressive supranuclear palsy (PSP) (80,81).

The major recent advance in understanding the pathology of CBD has been the demonstration of widespread accumulation of abnormal phosphorylated tau protein in both glia and neurons (72,80,82–84). Tau is a microtubule-associated protein (MAP) whose primary function is to promote the assembly and stabilization of microtubules. It is constitutively expressed and is normally found in axons
and mature neurons. Most of the tau-positive inclusions of CBD are also well demonstrated with silver stains such as Gallyas method but tend to react poorly with antibodies against ubiquitin protein. Neurons in the cerebral cortex may show diffuse granular cytoplasmic staining or contain denser inclusions, resembling either Pick’s bodies or small NFTs (Fig. 4E,F) (72,80,85). Filamentous or fibrillar cytoplasmic inclusions are also found in some subcortical neurons, especially in the substantia nigra, where they correspond to the corticobasal bodies (80,81).

Several types of tau-immunoreactive, argyrophilic inclusions are found in the cytoplasm of glial cells. The most specific is the astrocytic plaque, which consists of a circular arrangement of short cell processes in the cortical or subcortical gray matter (Fig. 4G) (72,82,83,86,87). Although vaguely resembling the neuritic plaques of AD, these structures are not associated with extracellular amyloid and double-immunolabeling has confirmed they represent tau accumulation in the most distal portion of astrocytic processes (72). More numerous but less disease specific are thorn-shaped astrocytes and coiled bodies (83,88,89). Thorn-shaped astrocytes result from the accumulation of tau in the cell body and most proximal portion of astrocytic processes, producing short, sharp processes (Fig. 4H).
These are seen in cortical and subcortical gray matter and white matter. Coiled bodies occur in oligodendrocytes and appear as delicate bundles of fibrils that wrap around the nucleus and extend into the proximal cell process (Fig. 4l). They are located primarily in the subcortical white matter. One of the most striking changes in CBD is the presence of numerous tau-immunoreactive, silver-positive threadlike processes in affected gray and white matter (Fig. 4j) (72,80,82,83,85,90). In contrast with the neuropil threads of AD, which are exclusively neuronal in origin, the threads of CBD are primarily glial (72,90). Although similar threads are found in some other conditions such as PSP, their extreme number in CBD is diagnostically helpful.

PROGRESSIVE SUPRANUCLEAR PALSY

In the original description of this disease entity, patients with supranuclear ophthalmoplegia, pseudobulbar palsy, dysarthria, rigidity, and mild cognitive deficits were found to have abundant NFTs in subcortical nuclei (91). The clinical phenotype is now recognized to be much more variable and includes both pure parkinsonism and frontotemporal dementia with no movement abnormality (1,2,4,5,71).

The macroscopic changes are quite variable. The cerebral cortex often appears normal but may show significant frontotemporal atrophy that may be quite circumscribed (Fig. 5A). The midbrain and pontine tegmentum are often atrophic whereas the globus pallidus is the most commonly affected part of the basal ganglia (Fig. 5B). Microscopic degeneration with neuronal loss and gliosis also tends to be more widespread and severe in PSP than CBD, with substantia nigra, locus ceruleus, globus pallidus, subthalamic nucleus, midbrain dentate nucleus, and pontine nuclei usually involved.

As with CBD, the histopathology of PSP is characterized by the abnormal accumulation of tau protein, in both neurons and glia, which can be demonstrated with immunohistochemistry or silver methods such as Gallyas (82,83,86,88,90,92). The most characteristic feature is widespread NFT formation (Fig. 5C) (91). Current diagnostic criteria require the presence of numerous NFTs in at least three of the following sites: pallidum, subthalamic nucleus, substantia nigra, or pons, and at least some tangles in three of striatum, oculomotor nucleus, medulla, or dentate (93,94). The tangles in these subcortical regions often have a rounded or globule shape (Fig. 5D) and ultrastructural studies show they are composed predominantly of 12–20 nm straight filaments. NFTs may also be found in cerebral cortex where their morphology more closely resemble those seen in AD, being flame-shaped and composed of paired helical filaments (95–97). Although the number and distribution of cortical NFTs in PSP is usually more restricted than in AD, some studies have shown a correlation with cognitive dysfunction (98). ANs (more characteristic of CBD) may be found in some cases of PSP but tend to be limited to limbic cortex (76).

Several types of argyrophilic, tau-positive glial inclusions occur consistently in PSP. Many of these, such as thorn-shaped astrocytes, coiled bodies, and threadlike lesions, are nonspecific, also being seen in other tauopathies such as CBD and Pick’s disease (82,83,88,90). The most diagnostic glial pathology in PSP is the presence of tufted astrocytes, which are most numerous in striatum but that are also found in other subcortical regions and frontal cortex (86,88). Although immunoreactive for tau, the morphology is best appreciated with Gallyas silver method, which shows the filamentous inclusion material surrounding the astrocyte nucleus and extending into a complex collection of long delicate processes, producing a shrublike appearance (Fig. 5E). This is different from thorn-shaped astrocytes where the inclusion material is restricted to more proximal processes (Fig. 4G) and astrocytic plaques in which only the most distal parts of processes are involved (Fig. 4F).

Finally, a unique pathology, which may be seen in the cerebellar dentate nucleus in PSP, is grumose degeneration in which granular eosinophilic material surrounds neurons, some of which are achromatic (Fig. 5F). Ultrastructural studies have shown the granular material to be degenerating axon terminals of Purkinje cells (99).
Fig. 5. Progressive supranuclear palsy. Gross photographs showing (A) lobar frontal atrophy and (B) atrophy and discoloration of basal ganglia. (C) Multiple neurofibrillary tangles (NFTs) and pretangles in midbrain (tau-immunohistochemistry). (D) Globose NFT (H&E stain). (E) Tufted-astrocyte (Gallyas silver stain). (F) Grumose degeneration (arrows) of neurons in cerebellar dentate nucleus (H&E stain).
FTDP-17T

The term frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) was recommended at a consensus conference in 1997 to denote a growing number of families recognized, in which frontotemporal dementia (FTD), behavioral disturbances, language abnormalities, and/or parkinsonism are inherited in an autosomal dominant fashion and genetic analysis shows linkage to chromosome 17 (100). The following year, a number of reports were published, describing mutations in the tau gene in some of these families (101–104). It is now common for a “T” to be added to the end of the acronym to distinguish these cases from other chromosome 17-linked FTD in which the tau gene is normal and there is no tau accumulation in the brain (105,106). At the present time, more than 80 FTDP-17T kindreds have been identified, with more than 30 different tau mutations (107). The types of genetic abnormality include missense, deletion, and silent transition mutations in the coding region of the tau gene and intronic mutations near the splice site of the intron following exon 10 (108). Sufficient material is now becoming available to allow for detailed examination of how different genetic abnormalities correlate with the clinical and pathological phenotypes (108,109).

FTDP-17T shows significant heterogeneity in both the clinical manifestations and the underlying neuropathology (100,108–110). In some families, FTD predominates and parkinsonism is variable, mild, or of late onset, whereas other pedigrees have parkinsonism as the major feature. A limited amount of postmortem information is available on FTDP-17T families. Most cases show frontotemporal atrophy with varying degeneration of subcortical nuclei and tracts (100,110). Loss of pigmentation of the substantia nigra is common. The histopathology of all cases described to date is characterized by the accumulation of abnormal hyperphosphorylated tau in neurons and/or glial cells (108,110). Neuronal changes may include ballooned neurons, pretangles, NFTs, Pick’s-like bodies, and/or neuritil threads. A variety of tau-positive inclusions may be seen in both astrocytes and oligodendrocytes. In some cases, the pattern of pathology closely resembles one of the sporadic tauopathies such as AD (111), CBD (112,113), PSP (114), or Pick’s disease (115,116), whereas others show some novel combination of findings (117). Although a detailed description of each of the different patterns of pathology in FTDP-17T is not possible in this review, two specific conditions are worth mentioning because of the prominence of parkinsonism and availability of detailed neuropathology.

Parkinsonism is the dominant feature of several families with the N279K mutation in the alternatively spliced exon 10; this includes the American kindred designated as having pallido-ponto-nigral degeneration (PPND), for which there is detailed pathological information (118). Most patients show mild frontotemporal atrophy with grossly obvious degeneration of the globus pallidus and substantia nigra. The histopathologic and immunohistochemical findings include ballooned neocortical neurons, pretangles, NFTs, Pick’s-like bodies, and tau-positive subcortical threadlike structures, globose NFTs (corticobasal bodies), and oligoden-droglial inclusions resembling coiled bodies. Astrocytic inclusions are uncommon and tufted astrocytes and astrocytic plaques are not a feature. Although these findings most closely resemble sporadic CBD, the anatomic distribution is more similar to that seen in PSP.

Parkinsonism is also a major feature in the Irish-American kindred with disinhibition-dementia-parkinsonism-amytrophy-complex (DDPAC). This was the first family to be linked to chromosome 17 and has subsequently been shown to be owing to an intronic mutation of the exon 10 5’ slice site (119). There is gross atrophy of temporal lobes, prefrontal cortex, cingulum, basal ganglia, and substantia nigra (120). Affected cortical regions show gliosis, occasional ballooned neurons, and tau-positive NFTs and spheroids. The hippocampus is relatively spared. Subcortical regions affected include the amygdala, substantia nigra, globus pallidus, striatum, midbrain tegmentum, and hypothalamus. In these areas, neuronal loss and gliosis are accompanied by small numbers of ballooned neurons, argyrophilic neuronal inclusions, and spheroids. Some neuronal inclusions resembled AD-type NFTs and are immunoreactive for tau whereas other have a more spiculated appearance and are positive for neurofilament and ubiquitin but are tau negative. Argyrophilic, tau-positive tanglelike inclusions are also present in oligodendrocytes in various white matter tracts.
ALS/PARKINSONISM DEMENTIA COMPLEX OF GUAM

A high incidence of neurodegenerative disease is found within the Chamorro population of the Western Pacific island of Guam, and includes parkinsonism, dementia, and amyotrophic lateral sclerosis (ALS), each of which may occur in isolation but are more commonly combined (121). The cause is unknown but a toxic or viral etiology has been postulated (122–124). The histopathology is dominated by the presence of numerous NFTs (125,126), with similar immunohistochemical, biochemical, and ultrastructural features as those seen in AD (127,128), but usually in the absence of SP (Fig. 6A,B). The anatomical distribution of NFTs is different from AD (129) and more similar to that seen in PSP and postencephalitic parkinsonism (PEP) (130,131). Chronic degenerative changes including neuronal loss and gliosis are found in regions where NFTs are numerous, including the frontotemporal neocortex, hippocampus, entorhinal cortex, nucleus basalis, basal ganglia, thalamus, subthalamus, substantia nigra, locus ceruleus, and periaqueductal gray (125,126,129). Glial pathology has recently been described and includes argyrophilic, tau-positive coiled bodies in oligodendroglia and granular inclusions in astrocytes (132). There tends to be large numbers of Hirano bodies and abundant granulovacuolar degeneration in the hippocampus (133). Cases with clinical features of ALS have pathologic changes in the pyramidal motor system, similar to sporadic ALS (134).

OTHER NEURODEGENERATIVE CONDITIONS

Many other common idiopathic neurodegenerative conditions have parkinsonism as an inconsistent or minor clinical feature. Extrapyramidal symptoms are very common in AD and may take the form of true parkinsonism (135–137). Many patients with a clinical diagnosis of AD and parkinsonism are found to have coexisting LB pathology at autopsy, either restricted to subcortical structures or also involving the cerebral cortex (138). The correct terminology for these cases is uncertain, because of the lack of universally accepted neuropathological diagnostic criteria for both AD and DLB (see subheading Dementia with Lewy Bodies). Interpretation is further complicated by recent reports of LBs as a common incidental finding in AD patients, even in the absence of extrapyramidal features (139). However, parkinsonism also occurs in some AD patients who have only SP and NFT pathology (136,138,140). SPs are a consistent finding in the striatum and are occasionally seen in the substantia nigra in AD, however most are the diffuse type of SP, which lack amyloid and are thought not to be injurious to neurons (137,141,142). Numerous NFTs in the substantia nigra is also a consistent feature of AD (137,141–143). Whereas some studies have reported loss of pigmented neurons in the nigra in AD (143), others have found the difference not to be significantly different from age-matched controls (144). It is not clear which, if any, of these changes is the substrate for parkinsonism in AD. Though several studies have found that extrapyramidal features in AD correlate with pathology in the substantia nigra (and not the striatum), there is disagreement as to whether the association is a result of neuronal loss or the number of NFTs (140,144).

Motor neuron disease (MND) may be complicated by dementia and/or akineti-rigidity (145). In addition to the characteristic changes in the pyramidal motor system, cases of MND with dementia have a unique pathology in the extramotor cortex; ubiquitin-immunoreactive neuronal cytoplasmic inclusions and dystrophic neurites are present in the neocortex and the hippocampal dentate granule layer (146). Degeneration of various subcortical structures, including substantia nigra and basal ganglia, is well recognized in MND (145). Recently, several studies have described various types of ubiquitin-positive neuronal inclusions and dystrophic neurites in a wide range of these subcortical locations (Fig. 7A,B) (147–149). Although detailed clinicopathological correlation is still lacking, we have recently reported that MND-dementia patients with extrapyramidal features have a greater burden of ubiquitin pathology in the substantia nigra and striatum (Fig. 6) (150).

Although the movement abnormality in most cases of Huntington’s disease (HD) is chorea, juvenile or early-onset cases may have akineti-rigidity. The most characteristic pathological feature of HD is severe atrophy of the caudate nucleus and putamen, with neuronal loss and gliosis (Fig. 8A).
Fig. 6. ALS/parkinsonism/dementia complex of Guam. (A,B) Numerous neurofibrillary tangles in CA1 region of hippocampus (A, tau-immunohistochemistry) and temporal neocortex (B, Bielschowsky silver stain). Photographs courtesy of C. Schwab.
Fig. 7. Case of motor neuron disease with dementia and parkinsonism. (A) Dystrophic neurites and neuronal cytoplasmic inclusions (arrow) in striatum (ubiquitin-immunohistochemistry). (B) Filamentous skein-like cytoplasmic inclusion in substantia nigra neuron (ubiquitin-immunohistochemistry).

The globus pallidus, thalamus, and cerebral cortex may also be affected and loss of pigmented neurons has been reported in the substantia nigra (151). A recent finding in HD is the presence of intranuclear neuronal inclusions and dystrophic neurites that are immunoreactive for huntingtin, ubiquitin, and polyglutamine repeats, in the striatum, allocortex, and neocortex (Fig. 8B) (152,153).

Parkinsonism may be a presenting or prominent feature in some types of autosomal dominant spinocerebellar ataxia (SCA) (154), particularly those caused by trinucleotide repeat expansions. Degenerative changes are most severe in the cerebellum and its connections but are also found in the substantia nigra and basal ganglia (155,156). Many of these conditions have neuronal intranuclear inclusions that are immunoreactive for ubiquitin, polyglutamine repeats, and/or the disease-specific mutant protein (157,158).

Hallervorden–Spatz disease (HSD), recently renamed neurodegeneration with brain iron accumulation type I (NBIA-1), is a rare neurodegenerative disorder in which various abnormalities of movement are associated with cognitive decline. Some cases are familial, usually with an autosomal
recessive inheritance pattern. Extrapyramidal features are more often a presenting feature in adult-onset cases (159). The neuropathology is characterized by axonal dystrophy (spheroids) and the intra- and extracellular accumulation of iron in the globus pallidus, substantia nigra, and other locations (Fig. 9A,B). It has been recognized for some time that some cases of HSD have LBs (166). Recent reports of α-synuclein immunoreactivity in LBs, axonal spheroids, and neuronal and glial inclusions (161–163) has resulted in HSD being classified as a synucleinopathy, along with more classical LB disorders (PD and DLB).
POSTENCEPHALITIC PARKINSONISM

Following the pandemic of encephalitis lethargica (von Economo’s disease), in the early part of the 20th century, a large proportion of individuals who survived the acute encephalitic phase developed parkinsonism, after a latency of several years or decades. PEP was therefore common in the 1940s and 1950s but is now rarely encountered. Although a viral etiology (possibly influenza A) has long been suspected, this remains to be proven (164,165).

Most detailed accounts of the neuropathology of PEP were published several decades ago (166,167). There may be mild cerebral atrophy and the substantia nigra and locus ceruleus show loss
of pigmentation (Fig. 10A). There is severe chronic degeneration of substantia nigra with neuronal loss and gliosis. The histopathology is characterized by the presence of numerous NFTs (Fig. 10B). The tangles may be either flame-shaped or globose (164) and have the same immunohistochemical and ultrastructural features as those seen in AD (168,169). NFTs are most numerous in the substantia nigra, locus ceruleus, hippocampus, and nucleus basalis, but are also found in many other cortical and subcortical regions (130). This distribution is different from that seen in AD (170) and more similar to other causes of parkinsonism with numerous NFTs, such as PSP and parkinsonism-dementia complex of Guam (94,130,131). Tau-positive glial inclusions include tufted astrocytes, thorn-shaped astrocytes, and astrocytic plaques (164,171,172).

VASCULAR PARKINSONISM

Patients with cerebrovascular disease may develop features of parkinsonism (173–175) and a small but significant fraction of those with a clinical diagnosis of idiopathic PD will turn out to have vascular lesions demonstrated by neuroimaging or at autopsy (2,176). This “vascular pseudoparkinsonism” is most often seen in patients with cerebral arteriolosclerosis and multiple small lacunar infarcts affecting the basal ganglia or deep cerebral white matter (173–177) but has also been reported with isolated lesions of the substantia nigra (178,179).

POSTTRAUMATIC PARKINSONISM

Parkinsonism immediately following a single episode of acute head injury is rare (180) but has been reported with direct penetrating lesions of the midbrain (181) and with subdural hematoma (182). Epidemiologic studies have shown a history of remote head trauma to be a risk factor for PD, however the mechanism is unclear (183–184). Repeated head injury may result in a syndrome that includes psychiatric symptoms, memory loss, and/or parkinsonism (dementia pugilistica, punch-drunk syndrome). This most often occurs in professional and amateur boxers, with the onset of symptoms occurring several years after the end of their athletic career. Pathological studies have shown loss of pigmented neurons in the substantia nigra and the presence of widespread AD-like pathology, with numerous tau-immunoreactive NFTs and amyloid β (Aβ) containing SPs (185,186). A direct link between these pathological changes and preceding trauma is supported by studies showing Aβ deposits in the brains of individuals dying a few weeks following severe head injury (187) and evidence that both Aβ and phosphorylated tau accumulate following brain injury in experimental animals (188,189). Anatomical-pathologic correlation for movement disorder in some of these patients is supported by in vivo neuroimaging, showing damage or dysfunction of the nigrostriatal system (190–192).

MPTP INTOXICATION

Some intravenous drug addicts who use a synthetic heroin-like drug (meperidine) develop chronic parkinsonism as a result of contamination by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (193). MPTP is metabolized in the brain to 1-methyl-4-phenylpyridinium (MPP+) (194) and is selectively transported into dopaminergic cells, which it kills by inhibiting mitochondrial function (195). Human postmortem studies reveal severe depletion of pigmented neurons in the substantia nigra without LBs (196). The presence of active gliosis and microglial activity has been interpreted as indicating ongoing neurodegeneration, years after the initial exposure. MPTP-induced parkinsonism in experimental nonhuman primates has become a valuable model for studying idiopathic PD (197). In addition to nerve cell degeneration in both the substantia nigra and the locus ceruleus, these animals develop eosinophilic neuronal inclusions that show both similarities and differences compared with LBs in human disease (198).
Fig. 10. Postencephalitic parkinsonism (PEP). (A) Gross photograph showing atrophy of the midbrain with degeneration of the substantia nigra in PEP compared with normal control (C). (B) Globose neurofibrillary tangle (H&E stain).
Wilson’s disease is an autosomal recessively inherited disorder of copper metabolism in which the metal deposits in a number of organs including brain. Neurologic findings vary but often include extrapyramidal features. The neuropathology also varies depending on the rate of disease progression. There is degeneration of the basal ganglia, which may appear shrunken or even cavitated and often has a brown discoloration (Fig. 11A). The putamen tends to be more severely affected than the caudate, globus pallidus, and substantia nigra. Other areas that may be involved include the pons, thalamus, cerebellum, and subcortical white matter. There is neuronal loss, extensive fibrillary gliosis, and macrophages containing lipid and hemosiderin pigment. There may be visible accumulation of copper around capillaries. A number of more disease-specific cellular changes may be present. Alzheimer type II astrocytes are commonly seen in cases of chronic hepatic failure with neurological dysfunction and are numerous in most cases of Wilson’s disease. They have swollen pale nuclei with little chromatin, prominent nucleoli, and sometimes contain small dots of glycogen (Fig. 11B). Large multinucleate Alzheimer type I cells are rare and not seen in every case (199). Most disease specific is the presence of cells with small nuclei, abundant granular or foamy cytoplasm, and no obvious processes (200). These “Opalski” cells are of uncertain origin, possible derived from astrocytes, macrophages, or degenerating neurons (Fig. 11C). They are most numerous in the thalamus, globus pallidus, and substantia nigra and rare in the striatum.

CONCLUSION
Parkinsonism may be associated with a wide range of underlying pathologies, in which the common feature is damage to the striatonigral system. In addition to the diseases discussed, virtually any pathological process that affects the striatonigral system has the potential to produce Parkinsonism; these include various toxins (201–206), infections (207–212), mass lesions (213), and other conditions. As a result, neuropathological examination is essential for accurate diagnosis in an individual with clinical Parkinsonism.

FUTURE RESEARCH
It was the recognition of a unique pattern of histopathology that originally allowed most of the conditions described in this chapter to be designated as specific disease entities. Over the past few decades, greater understanding of the biochemical and genetic basis of these conditions has helped to clarify the disease pathogenesis and has shed light on the relationship between diseases (e.g., tauopathies, synucleinopathies, etc.). Although it is anticipated that future advances will occur primarily in the field of molecular genetics, the role of tissue pathology should not be overlooked. Defining the cellular localization and anatomical distribution of abnormal protein accumulations in postmortem tissue will continue to illuminate mechanisms of disease and help to confirm the relevance of new molecular findings. It will be the combination of genetic, biochemical, and histopathological research, matched with appropriate clinical correlative studies, that will further our understanding of these fascinating conditions.

MAJOR POINTS
• Parkinsonism may be associated with a variety of underlying pathologies.
• Most of the conditions that cause parkinsonism have damage of the striatonigral system as the anatomicopathological substrate.
• The most common causes of parkinsonism are neurodegenerative diseases, each of which has a defining pattern of neuropathology, often characterized by the abnormal accumulation of protein in the form of a cellular inclusion.
• For many of these conditions, recent molecular genetic findings have helped to define disease pathogenesis and have clarified the relationship between disease entities.
Fig. 11. Wilson’s disease. (A) Gross photograph showing cystic degeneration of putamen. (B) Alzheimer type II astrocytes with swollen pale nuclei (H&E stain). (C) Opalski cell (H&E stain).
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