function with toxic effects may contribute to the phenotype observed in these patients.

- A third genetic form of FTLD-TDP is the result of mutations in the gene encoding progranulin. In contrast to TDP-43 and C9orf72 mutations, these have not been linked to ALS. Progranulin mutations cause loss of function and the disease mechanism is believed to stem from deficient progranulin activity. Progranulin is a secreted protein expressed in glia and neurons that is cleaved into multiple small peptides. These peptides have been implicated in regulation of inflammation in the brain, but the link between this activity and the accumulation of TDP-43 containing inclusions in FTLD is currently obscure.

MORPHOLOGY

The gross appearance is similar to the other forms of FLTD, with atrophy of frontal and temporal lobes of variable extent and severity. This is accompanied by varying degrees of neuronal loss and gliosis. Normally, TDP-43 is found diffusely in the nucleus; with disease, there is loss of this staining and formation of inclusions (Fig. 28-39*C*). These may be found in the cell body (neuronal cytoplasmic inclusions or NCI), in the nucleus (neuronal intranuclear inclusions or NII), or in neurites. In the inclusions, TDP-43 is phosphorylated and ubiquitinated. Inclusions are most abundant in the frontal and temporal cortex, in the striatum and in the dentate gyrus of the hippocampus. There is an extremely strong correlation between the presence of needle-like NII's and progranulin mutations (Fig. 28-39*D*).

There are forms of FTLD in which there are neither tau- nor TDP-containing inclusions. While these are infrequent, the underlying genetic causes show overlap with the pathways identified as contributors to pathogenesis of FTLD-TPD. Mutations in the *FUS* (fused in sarcoma) gene may cause either FTLD or ALS, and FUS is another RNA-binding protein that may be involved in formation of stress granules.

Parkinson Disease (PD)

PD is a neurodegenerative disease marked by a prominent hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the substantia nigra. The clinical syndrome of *parkinsonism* combines diminished facial expression (often termed *masked facies*), stooped posture, slowing of voluntary movement, festinating gait (progressively shortened, accelerated steps), rigidity, and a "pill-rolling" tremor. **This type of motor disturbance is seen in a number of conditions that have in common damage to the nigrostriatal dopaminergic system**. Several neurodegenerative diseases include symptoms of parkinsonism. In addition, similar symptoms may be pharmacologically induced by dopaminergic antagonists or by toxins that selectively damage the dopaminergic system. The principal degenerative disease that involves the nigrostriatal system is PD. Also discussed later are other rare diseases that have parkinsonism as part of the clinical presentation.

The presumptive diagnosis of PD can be based on the presence of the central triad of parkinsonism—tremor, rigidity, and bradykinesia—in the absence of a toxic or other known underlying etiology. This impression is confirmed by symptomatic response to L-DOPA replacement therapy. Although the diagnosis of PD is based in large part on the presence of the motor symptoms, which reflect the decreased dopaminergic innervation of the striatum, there is clear evidence that the disease is not restricted to dopaminergic neurons or to the basal ganglia; in fact, there is evidence from pathologic investigations that the degeneration of the substantia nigra (which results in the motor symptoms) represents a mid-stage in a progressive disease that begins lower in the brainstem and can eventually progress to involve the cerebral cortex, leading to cognitive impairment (see Dementia with Lewy Bodies, later).

The dopaminergic neurons of the substantia nigra project to the striatum, and their degeneration in PD is associated with a reduction in the striatal dopamine content. The severity of the motor syndrome is proportional to the dopamine deficiency, which can, at least in part, be corrected by replacement therapy with L-DOPA (the immediate precursor of dopamine). Treatment does not, however, reverse the morphologic changes or arrest the progress of the disease; moreover, with progression, drug therapy tends to become less effective and symptoms become more difficult to manage. Deep brain stimulation has emerged over the past decade as a therapy for the motor symptoms of PD. In addition, the well-characterized neural and biochemical deficits in PD have also provided a rationale for early therapeutic trials of neural transplantation and gene therapy.

An acute parkinsonian syndrome and destruction of neurons in the substantia nigra follows exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), discovered as a contaminant in illicitly synthesized batches of the opioid meperidine. This toxin has been used to generate animal models of PD that are being exploited to test new therapies. Epidemiologic evidence has also suggested that pesticide exposure is a risk factor for PD, while caffeine and nicotine may be protective.

Molecular Genetics and Pathogenesis. **PD is associated with protein accumulation and aggregation, mitochondrial abnormalities, and neuronal loss in the substantia nigra and elsewhere in the brain.** While most PD is sporadic, a series of genetic causes have been identified that shed light on its pathogenesis.

- The first gene to be identified as a cause of autosomal dominant PD encodes α-*synuclein*, an abundant lipid-binding protein normally associated with synapses. This protein was then demonstrated to be a major component of the Lewy body, which is the diagnostic hallmark of PD. Mutations in α-synuclein are rare; they take the form of point mutations and amplifications of the region of chromosome 4q21 that contains the gene. The occurrence of disease caused by changes in gene copy number implies a gene dosage effect, and suggests that polymorphisms in the α-synuclein promoter that alter its expression may influence the risk of PD. Like Aβ in Alzheimer disease, α-synuclein has been demonstrated to form aggregates; of these, small oligomers appear to be the most toxic to neurons. There is also evidence that