aggregates can be released from one neuron and taken up by another, suggesting a capacity for a prion-like pattern of spread within the brain. Consistent with this idea, α-synuclein containing aggregates (in the form of Lewy bodies and Lewy neurites) first appear in the medulla and then in contiguous areas of the brain, ascending through the brainstem and extending into limbic structures and finally the neocortex.

- *Mitochondrial dysfunction* has been implicated as a contributing factor for PD based on autosomal recessive forms of PD that are caused by mutations in genes that encode the proteins DJ-1, PINK1, and parkin. DJ-1 has multiple cellular roles, including acting as a transcriptional regulator, but in settings of oxidative stress it can relocate to the mitochondria and have cytoprotective effects. PINK1 is a kinase that is degraded in the mitochondria under normal circumstances; with mitochondrial dysfunction, it recruits parkin, which is an E3 ubiquitin ligase. Under normal circumstances, the combination of PINK1 and parkin results in clearance of dysfunctional mitochondria through mitophagy. Intriguingly, levels of mitochondrial complex I, a component of the oxidative phosphorylation cascade, are reduced in the brains of patients with sporadic PD.
- Mutations in the gene encoding *LRRK2* (leucine-rich repeat kinase 2) are a more common cause of autosomal dominant PD and are found in some sporadic cases of the disease. LRRK2 is a cytoplasmic kinase. Several of the pathogenic mutations increase the kinase activity of LRRK2, suggesting that gains in LRRK2 function—either hyperphosphorylation of normal targets or emergence of novel targets—might contribute to the development of PD.

MORPHOLOGY

A characteristic finding in PD is **pallor of the substantia nigra** (compare Fig. 28-40*A* and *B*) and locus ceruleus, which is due to loss of the pigmented, catecholaminergic neurons in these regions. Lewy bodies (Fig. 28-40*C*) may be found in some of the remaining neurons. These are single or multiple cytoplasmic, eosinophilic, round to elongated inclusions that often have a dense core surrounded by a pale halo. Ultrastructurally, Lewy bodies are composed of fine filaments, densely packed in the core but loose at the rim; these filaments are composed of α-synuclein. Lewy bodies may also be found in the cholinergic cells of the basal nucleus of Meynert, which is depleted of neurons (particularly in patients with abnormal cognitive function), as well as in other brainstem nuclei including the locus ceruleus and the dorsal motor nucleus of the vagus. Areas of neuronal loss also typically show gliosis. Lewy neurites are dystrophic processes that contain aggregated α-synuclein.

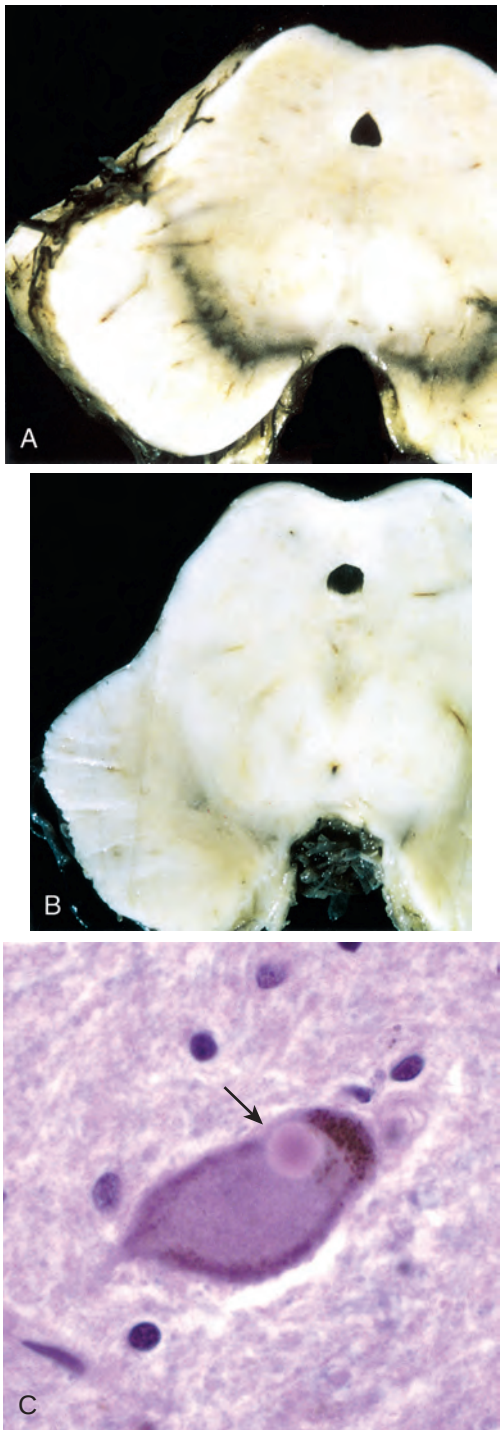

Figure 28-40 Parkinson disease. **A,** Normal substantia nigra. **B,** Depigmented substantia nigra in idiopathic Parkinson disease. **C,** Lewy body in a substantia nigra neuron, staining bright pink *(arrow)*.

Dementia with Lewy Bodies

About 10% to 15% of individuals with PD develop dementia, particularly with advancing age. Characteristic features of this disorder include a fluctuating course, hallucinations, and prominent frontal signs. While some affected individuals have pathologic evidence of Alzheimer disease (or, less frequently, other degenerative diseases associated with cognitive changes) in combination with PD, in others the most prominent histologic correlate is the presence of widespread Lewy bodies in neurons in the cortex and brainstem. As already mentioned, dementia with Lewy bodies may represent an advanced stage of PD in which protein aggregates appear to have "spread", possibly through propagation of misfolded proteins, to neurons in the cerebral cortex.

Cortical Lewy bodies are less distinct than those observed in the brainstem but are also composed