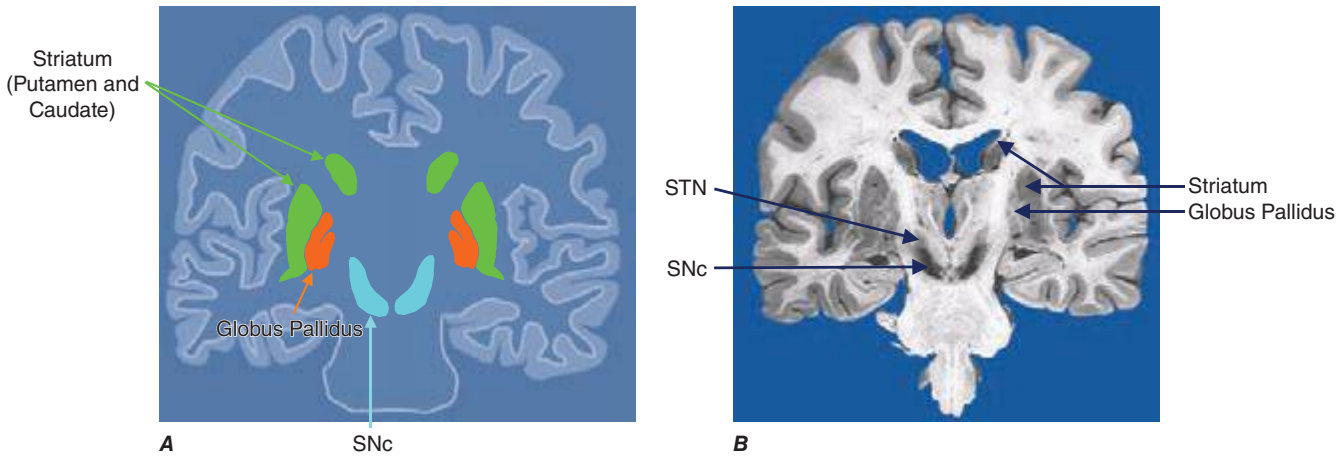

FIGURE 449-2 Basal ganglia nuclei. Schematic (***A***) and postmortem (***B***) coronal sections illustrating the various components of the basal ganglia. SNc, substantia nigra pars compacta; STN, subthalamic nucleus.

PSP is characterized by degeneration of the SNc, striatum, subthalamic nucleus, midline thalamic nuclei, and pallidum along with neurofibrillary tangles and inclusions that stain for the tau protein.

Corticobasal ganglionic degeneration is less common and is usually manifest by asymmetric dystonic contractions and clumsiness of one hand coupled with cortical sensory disturbances manifest as apraxia, agnosia, focal limb myoclonus, or alien limb phenomenon (where the limb assumes a position in space without the patient being aware of it). Dementia may occur at any stage of the disease. Both cortical and basal ganglia features are required to make this diagnosis. MRI frequently shows asymmetric cortical atrophy. Pathologic findings include achromatic neuronal degeneration with tau deposits. Because other disorders such as PSP can present with a similar clinical picture, the term corticobasal ganglia syndrome should be used until a precise diagnosis can be confirmed pathologically.

Secondary parkinsonism can occur as a result of drugs, stroke, tumor, infection, or exposure to toxins such as carbon monoxide or manganese. Dopamine-blocking agents such as the neuroleptics are the commonest cause of secondary parkinsonism. These drugs are most widely used in psychiatry, *but physicians should be aware that drugs such as metoclopramide and chlorpromazine, which are primarily used to treat gastrointestinal problems, are also neuroleptic agents* and common causes of secondary parkinsonism (as well as acute and tardive dyskinesias; see below). Other drugs that can cause secondary parkinsonism include tetrabenazine, calcium channel blockers (flunarizine, cinnarizine), amiodarone, and lithium.

Finally, parkinsonism can be seen as a feature of other degenerative disorders such as Wilson's disease, Huntington's disease (especially the juvenile form known as the Westphal variant), dopa-responsive dystonia, and neurodegenerative disorders with brain iron accumulation such as pantothenate kinase (PANK)–associated neurodegeneration (formerly known as Hallervorden-Spatz disease).

Some features that suggest parkinsonism might be due to a condition other than PD are shown in Table 449-3.

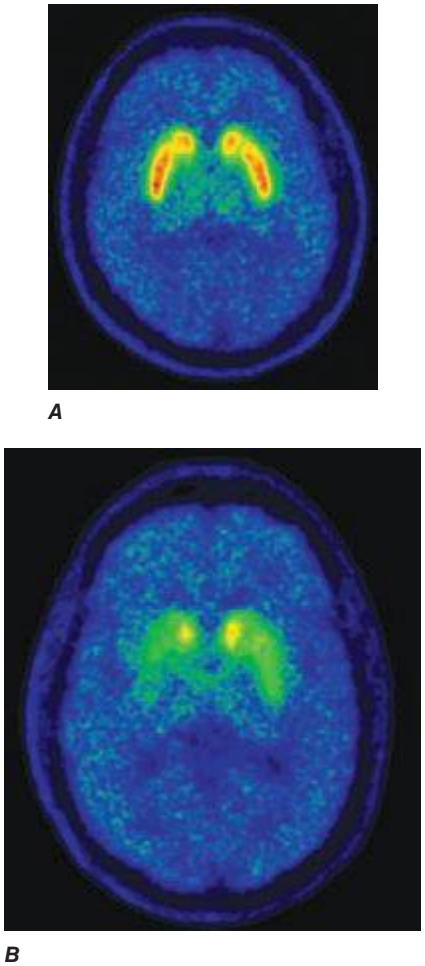

FIGURE 449-3 [^{11}C]Dihydrotetrabenazine positron emission tomography (a marker of VMAT2) in healthy control (*A*) and Parkinson's disease (*B*) patient. Note the reduced striatal uptake of tracer, which is most pronounced in the posterior putamen and tends to be asymmetric. *(Courtesy of Dr. Jon Stoessl.)*

ETIOLOGY AND PATHOGENESIS

Most PD cases occur sporadically (~85–90%) and are of unknown cause. Twin studies suggest that environmental factors likely play an important role in patients older than 50 years, with genetic factors being more important in younger patients. Epidemiologic studies also suggest increased risk with exposure to pesticides, rural living, and drinking well water and reduced risk with cigarette smoking and caffeine. However, no environmental factor has yet been proven to cause typical PD. The environmental hypothesis received support with the demonstration in the 1980s that MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), a byproduct of the illicit manufacture of a heroin-like drug, caused a PD-like syndrome in addicts in northern California. MPTP is transported to the central nervous system, where it is oxidized to form MPP^+, a mitochondrial toxin that is selectively taken up by, and damages, dopamine neurons. However, MPTP or MPTP-like compounds have not been linked to sporadic PD.

About 10–15% of cases are familial in origin, and multiple specific mutations and gene associations have been identified (Table 449-4). Genetic factors have also been linked to sporadic cases, with several typical PD cases found to carry the *LRRK2* mutation, and genome-wide association studies (GWAS) implicating alpha synuclein, tau, and