

## Disorders of the Basal Ganglia (Dr. Merchut)

### 1. Pathophysiology of the basal ganglia

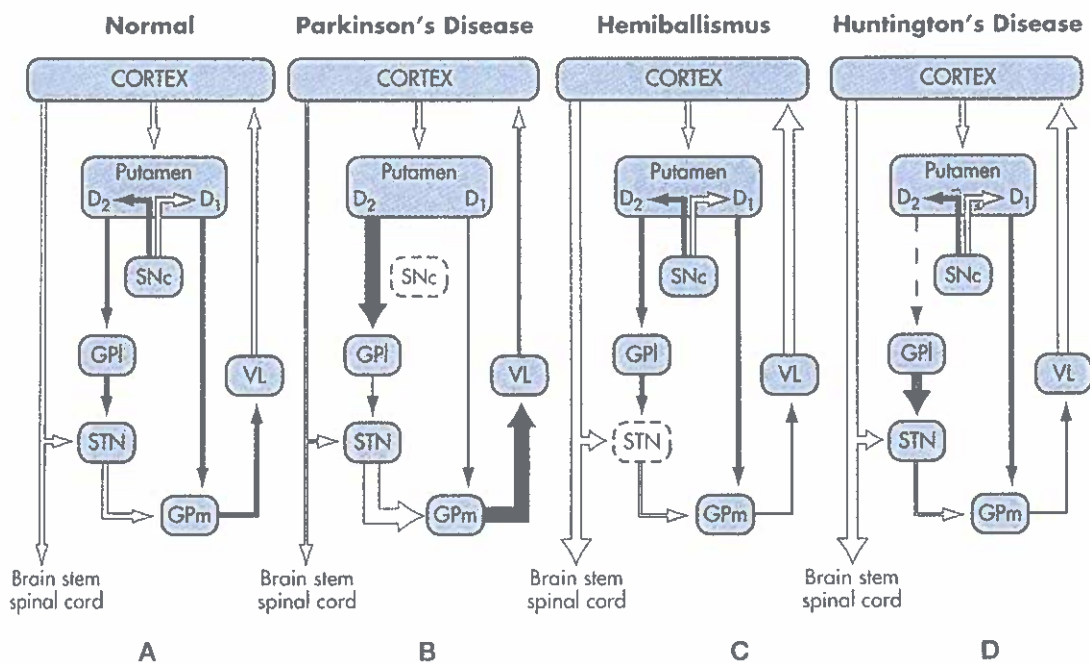
The basal ganglia consists of the striatum (caudate and putamen), globus pallidus, substantia nigra, and subthalamic nucleus, and is also called the “extrapyramidal system” since it has significant influence on motor function, but is a network “outside” or anatomically distinct from the pyramidal system (corticospinal and corticobulbar tracts). Lesions in different parts of the basal ganglia may cause strikingly different clinical symptoms. **Hypokinesia** is found in Parkinson’s disease, where motor activity is reduced or slowed, except for the resting tremor. **Hyperkinesia**, such as choreoathetosis or hemiballismus, consists of excessive, involuntary movements from other lesions in this network.

In **Parkinson’s disease**, progressive loss of dopaminergic neurons in the substantia nigra causes less “direct pathway” inhibition and more “indirect pathway” stimulation of the medial globus pallidus (GPM) (Fig. 1B). This **net increased inhibitory output of the GPM** to the ventrolateral (VL) thalamic motor nuclei reduces stimulation of the motor cortex, leading to slow or absent movements clinically.

In certain **hyperkinetic disorders of the basal ganglia, there is a net decrease of medial globus pallidus (GPM) output**, so the reduced inhibition of the ventrolateral (VL) thalamic motor nuclei leads to greater stimulation of motor cortex, and excessive motor activity. In hemiballismus, destruction of the subthalamic nucleus (STN) lessens stimulation of the GPM, and thus lowers GPM output (Fig. 1C). In Huntington’s disease, loss of “indirect pathway” putaminal neurons to the lateral globus pallidus (GPI) increases inhibition of the subthalamic nucleus (STN), which lessens stimulation of the GPM, and lowers GPM output (Fig. 1D), which causes choreoathetosis. It is thus understandable with this simplified scheme how net decreases in GPM activity lead to hyperkinesias in general, while other unique effects serve to distinguish the movements of hemiballismus from those of choreoathetosis.

These lesions within the basal ganglia may be caused by several processes. An ischemic infarction, hemorrhage, or tumor in the striatum or subthalamic nucleus could cause contralateral choreoathetosis or hemiballismus. Degenerative disorders involve selective, progressive destruction of certain neuronal groups or types, presumably from metabolic dysfunction related to hereditary or environmental factors, or both. The choreoathetosis of Huntington’s disease and hypokinesia of Parkinson’s disease are features of such neurodegenerative disorders. Medications with effects on dopamine receptors may also cause motor side effects. In treating Parkinson’s disease, increased doses of dopamine agonist drugs may cause hyperkinesias such as choreoathetosis or dystonia, which improve with dose reduction. The older neuroleptic drugs used to treat schizophrenia have dopamine antagonist effects, and at higher doses cause symptoms of parkinsonism, relieved by lowering the dose.

It should be remembered that not all hyperkinetic disorders are related to lesions of the basal ganglia. Essential tremor, which is often familial, dystonia, and tics have unknown anatomical lesions, while myoclonus and asterixis are seen with diffuse metabolic or structural lesions of the brain.



**Fig. 1**

Basal ganglia function in normal state (A), Parkinson's disease (B), hemiballismus (C), and Huntington's disease (D). Excitatory projections are shown by open arrows, GABA-ergic inhibitory pathways by solid arrows. Narrowing or widening of arrows represent decreased or increased pathway activity, respectively. Putaminal neurons with D<sub>1</sub> dopamine receptors are the "direct pathway" to the medial globus pallidus (GPm), and putaminal neurons with D<sub>2</sub> dopamine receptors are the "indirect pathway" to the GPm. Lesions are outlined by broken lines. (See text for details on each disorder.) *GPI*, Lateral globus pallidus (globus pallidus externa); *GPm*, medial globus pallidus (globus pallidus interna); *SNc*, substantia nigra pars compacta; *STN*, subthalamic nucleus; *VL*, ventrolateral nuclei of thalamus. (Modified from Bergman H, Wichmann T, DeLong MR: Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* 249(4975):1436, 1990.)

## 2. Parkinson's Disease

The generic term "parkinsonism" (without the capital "P"), may be used initially to describe the characteristic signs and symptoms discussed below. Etiologies of parkinsonism include use of dopamine antagonist medication, toxic exposure to manganese or carbon dioxide, or multiple ischemic infarctions of the basal ganglia. Survivors of the encephalitis lethargica epidemic of 1917-1928 also developed parkinsonism. (The British neurologist Oliver Sacks successfully treated these patients in 1969 with the new drug levodopa. His story, "Awakenings," was later made into a movie in 1990, and starred Robin Williams and Robert De Niro.) **The most common cause of**

**parkinsonism is Parkinson's disease** (with a capital "P"), a **progressive, degenerative disorder of unknown cause**. It occurs in older adults with varying symptom severity and rate of progression.

**The primary clinical signs of Parkinson's disease (PD) include resting tremor, rigidity, bradykinesia, and impaired postural reflexes.** The **resting tremor** is prominent when the patient is sitting or reclining, **most often involving the distal upper limbs asymmetrically**, and sometimes the chin or lower limbs. It is exacerbated by stress, and may accompany volitional movements such as walking. The supinating-pronating tremor of the hand resembles the rolling of a pill or cigarette between the index finger and thumb and is thus described as **"pill-rolling."** The resting tremor and rigidity begin on one side of the body and predominate there even as the symptoms spread to the other side. **Rigidity** may be reported as stiffness or weakness, and is felt as a constant resistance or increased tone when passively moving the affected limb. A rigid arm may not naturally swing as the patient walks. **"Cogwheeling"** refers to the ratchety or jerky feeling created by tremor when the rigid limb is moved, similar to the mechanism of a clock or watch movement. Rigidity may also be felt when passively rotating or turning the patient's trunk. **Bradykinesia** is the slowness or lack of movement. A patient may rock several times to rise off a chair, and then slowly shuffle across the room, with stooped posture, needing to take multiple small steps to turn around. As the disease progresses, the patient may periodically "freeze" the feet to the floor. Manual tasks are also slowed and clumsy. "Automatic" movements like eye blinking occur at slower rates, and the unconscious swallowing of secretions is inadequate, causing drooling. The **impairment of postural reflexes** refers to balance instability while standing or walking, often out of proportion to the degree of rigidity or bradykinesia. If lightly bumped, or when a minor irregularity in the floor is encountered, the patient may be unable to maintain their footing and fall. This clinical feature often is least responsive to dopaminergic medication.

Other secondary signs often found in patients with PD include masked facies, an emotionless "poker face," due to the lack of subtle facial movements. The typical hypophonic speech of PD is hoarse, soft, and difficult to understand. Micrographia refers to the tendency of handwriting to get smaller. Involvement of the autonomic nervous system manifests as severe constipation, bladder dysfunction, or orthostatic hypotension. Some patients develop REM behavior sleep disorder.

The **diagnosis of Parkinson's disease is primarily a clinical one**. Other causes of parkinsonism must be eliminated, at least 2 of the 4 primary clinical signs should be present, and atypical features should be absent. Virtually all patients with PD show some improvement when first treated with dopaminergic medication. Unresponsiveness to levodopa or an atypical clinical finding suggests that parkinsonism may be due to other rarer degenerative diseases like progressive supranuclear palsy or multiple system atrophy. While most cases of PD are sporadic in onset, some are hereditary.

Historically, the pathological hallmark of PD has been **loss of the pigmented dopaminergic neurons in the substantia nigra**, many of which have  $\alpha$ -synuclein-positive, eosinophilic, cytoplasmic inclusions called **Lewy bodies** (Fig. 2). Grossly the substantia nigra and locus ceruleus appear pale from the loss of these pigmented (neuromelanin-containing) neurons. The precise trigger of this disease remains unclear. Along with Lewy body dementia and multiple system atrophy, Parkinson's disease is

considered a synucleinopathy, where accumulation of the protein  $\alpha$ -synuclein appears to play a central role in the degenerative process.

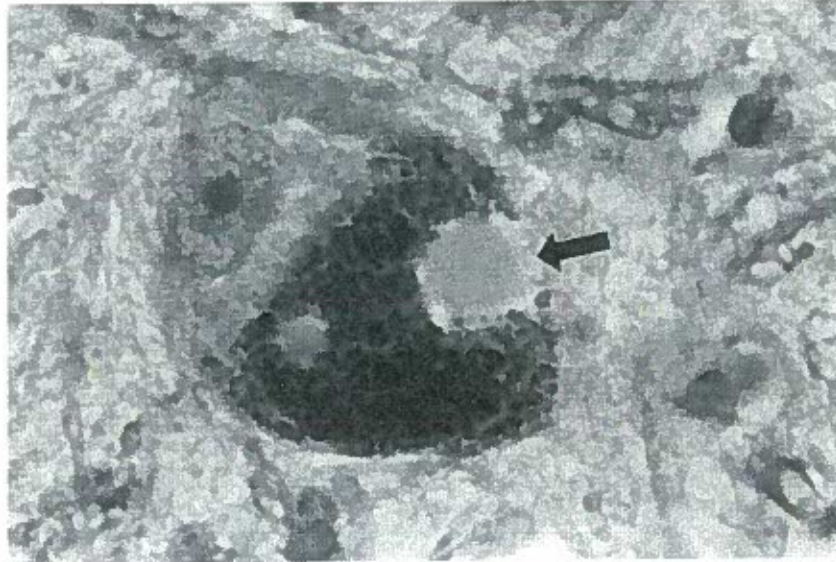


Fig. 2

Pigmented neurons from substantia nigra showing intracytoplasmic Lewy body (*arrow*) from a patient with Parkinson's disease. (Photograph courtesy Dr. John M. Lee.)

The treatment of PD depends on the symptomatic impairment of the patient. Tremor and rigidity in one arm may be tolerable for an inactive retiree who remains ambulatory, but could be career-ending for a younger architect if untreated. No curative therapy yet exists. **Levodopa (L-dopa)**, the precursor of dopamine, is **the most effective medicine for Parkinson's disease**. Levodopa is combined with **carbidopa**, a decarboxylase inhibitor, which limits the peripheral catabolism of levodopa before it enters the brain. Hallucinations or psychosis may be troublesome side effects of levodopa in older patients. Unfortunately, as the disease progresses, each levodopa dose provides less asymptomatic "on" time and more "off" time with bradykinesia and rigidity, sometimes alternating with excessive movements (dyskinesia) resembling choreoathetosis or dystonia. Plasma levodopa levels can be further increased by taking a **catechol O-methyltransferase (COMT) inhibitor** like entacapone, which smoothes out some of the undesirable motor fluctuations. The beneficial motor effects of dopamine itself can be extended if its catabolism is reduced by a **monoamine oxidase (MAO) type B inhibitor** like selegiline, which probably exerts other effects as well. Prior to the advent of levodopa, **anticholinergic drugs** like trihexyphenidyl were tried to "balance" the unopposed cholinergic system in Parkinson's disease with little success, although they do provide some control of the resting tremor. **Dopamine agonists** (ropinirole, pramipexole) improve parkinsonism to a lesser degree than levodopa, yet when used



initially as monotherapy, may reduce the longer term side effects of dyskinesia. In advanced Parkinson's disease, patients refractory to medication may benefit from surgical therapy. With modern brain imaging and computer-guided techniques, a stereotactic surgical lesion (pallidotomy) could be accurately placed in the medial globus pallidus (GPM), thereby counteracting its increased inhibition of the ventrolateral (VL) thalamic motor nuclei (Fig. 1B). A safer means of achieving the same effect on the GPM is to insert an electrode into the **subthalamic nucleus (STN), inhibiting it by means of repetitive electrical stimulations** from a programmable pacemaker-like device. This technique has been loosely called "**deep brain stimulation.**"

### 3. Huntington's Disease

Another disorder of the basal ganglia is Huntington's disease, which clinically consists of **choreoathetosis, dementia, and behavioral syndromes** such as depression, anxiety, moodiness, and agitation. It is an autosomal dominant degenerative disease, usually manifest around 35 to 40 years of age with early motor symptoms. The clinical diagnosis is confirmed with a blood test demonstrating **multiple trinucleotide repeats in the huntingtin gene** on chromosome 4. Early on, there is preferential loss of putaminal GABA-ergic neurons projecting to the lateral globus pallidus (GPI) as the "indirect pathway" (Fig. 1D) This deficit increases GPI inhibition of the subthalamic nucleus (STN), subsequently lowering activity of the GPM, and enhancing VL excitation of motor cortex to produce choreoathetosis. Later in the disease, cholinergic neurons are also lost. Grossly there is atrophy of the caudate nuclei, with less severe atrophy of cerebral cortex. The caudate atrophy in advanced Huntington's disease is readily detected on MRI or CT scans of the brain, where the frontal horns of the lateral ventricles appear relatively enlarged.

Dopamine antagonist drugs help lessen the choreoathetosis by blocking the inhibitory D2 receptors on the GABA-ergic neurons of the "indirect pathway" which helps restore some inhibitory output of the GPM to the VL. Dopamine antagonist drugs also help control some of the psychiatric symptoms. Tetrabenazine, a catecholamine depleter, also helps reduce the choreoathetosis. Antidepressant treatment is also crucial where indicated, since there is a high rate of suicide in Huntington's disease. Sadly there is no curative treatment at the present time.