CHAPTER 19
Motor Systems II: Basal Ganglia and Movement Disorders

I.ANATOMICAL BACKGROUND (Fig. 19-1, 19-2)

The term "basal ganglia" originally included the deep telencephalic nuclei: the caudate, putamen, globus pallidus, the claustrum, and nucleus accumbens. The globus pallidus and putamen are lens shaped and are called lenticular nuclei. Collectively the putamen and caudate are called the corpus striatum. Additional structures now included within this group are the substantia nigra, the subthalamic nuclei, the ventral tegmental area and the ventral pallidum. The caudate and putamen have the same structure and are continuous anteriorly. The globus pallidus has two sectors: a medial or inner and a lateral or outer. The substantia nigra has two components: a ventral pars reticularis which is identical in structure and function to the medial sector of the globus pallidus and a dorsal darkly staining component the pars compacta which contains large dopamine

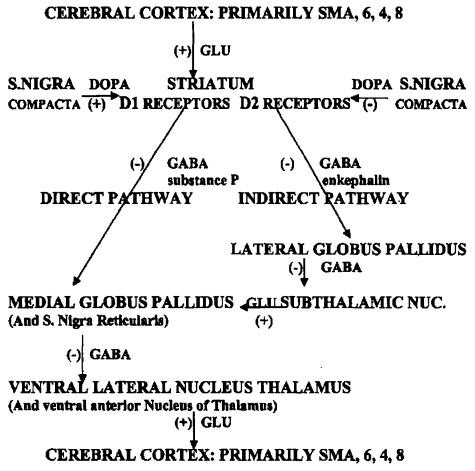

Figure 19-1.Diagram of the connections of the basal ganglia with transmitters and major transmitter action (+) excitatory or (-) inhibitory. GABA = gamma aminobutyric acid (-); GLU = Glutamate (+); Dopamine = Dopa (+). The action of acetylcholine within the striatum has been omitted. See text for details.

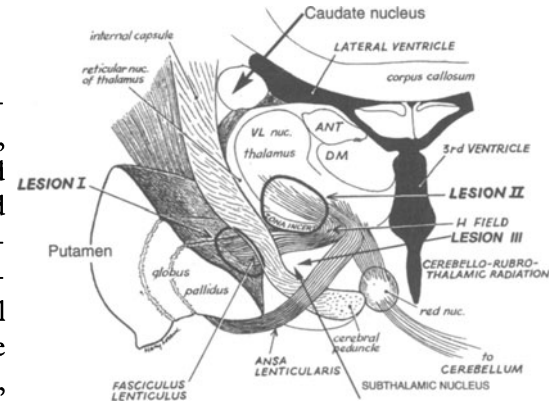

Figure 19-2 Major connections of the basal ganglia with sites for surgical lesions or implantation of stimulators in Parkinson's disease. Lesion I-globus pallidus. Lesion II-Ventral lateral nucleus of the thalamus (the sector of VL involvement is termed VIM= nuc. ventral inferior medial). Lesion III- subthalamic nucleus, (Modified from Lin, F.H., Okumura, S., and Cooper, I.S.: Electroenceph. Clin. Neurophysiol. 13:633, 1961)

and melanin containing neurons.

The nuclei of the basal ganglia may be categorized as (1) input nuclei (caudate, putamen and accumbens), (2) intrinsic nuclei (lateral segment of the globus pallidus, subthalamic nucleus, pars compacta of the substantia nigra and the ventral tegmental area) and (3) output nuclei (medial segment of the globus pallidus ,pars reticularis of the substantia nigra and the ventral pallium. The consideration of the chemical and pharmacological anatomy of transmitters and circuits within the system will provide an understanding of function and dysfunction within this system.

It should be noted that the nuclei of the basal ganglia, the circuits involving the basal ganglia, the cortical areas projecting to the basal ganglia, the cerebellar nuclei relating to the basal ganglia, and the reticular formation (which has connections with both the cortex and the basal ganglia) were once grouped

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together as an "extrapyramidal system". The term "extrapyramidal disorders" - was used to refer to the effects of lesions within the basal ganglia system. However, the term "extrapyramidal" was also utilized to refer to the descending pathways: corticorubral spinal and cortical-reticulospinal that were alternative descending systems to the pyramidal system. The term extrapyramidal then becomes very non-specific and confusing and had best not be utilized. It is important to note, moreover that the cortical areas giving rise to this extrapyramidal system are also, in part, the same areas giving rise to the pyramidal system.

Additional discussions of the gross anatomy will be found in chapter 1, and in Noback, et al (1991); Alexander, et al (1986); Young and Penney (1988).

The connections and transmitters within this system are presented in the diagram of Figure 19-1 and are summarized below.

The essential pathways are the following: cerebral cortex (+) to striatum (caudate / putamen) (-) to globus Pallidus (-) to ventrolateral thalamus (+) to cerebral cortex. Additional circuits involve subthalamus and s. nigra.

TABLE 19- 1 ANATOMICAL DIVISIONS OF CORPUS STRIATUM

Basal Ganglia – Telencephalic Nuclei	Function
NEOSTRIATUM	
Dorsal-Caudate /putamen	Input nuclei-neocortical and s. Nigra .Nigra compacta
Ventral-Nucleus accumbens	Input nucleus limbic system
PALEOSTRIATUM (Globus pallidus)	
-Dorsal portion:	-Intrinsic nucleus
-Lateralsegment	-Output nucleus
-Medial segment	-Output nucleus
Ventral portion	
Ventral pallidum	
Basal Ganglia – Associated Nuclei	**Function**
Subthalamic nucleus of diencephalon	Intrinsic nucleus
Substantia Nigra of Midbrain	
- dorsal -pars compacta (dopaminergic)	-Intrinsic nucleus
- ventral- pars reticularis	-Output nucleus

Adding greater detail to the outline indicates the following sequence:

1. The major input into the basal ganglia is from the cerebral cortex to the striatum (caudate nucleus/putamen/accumbens). This input is excitatory - utilizing the transmitter glutamate and arises primarily from the supplementary motor premotor and motor cortices (areas 8, 6, and 4). However, the projection from the neocortex occurs from many other areas. In general, frontal and parietal, lateral temporal and occipital areas project to the caudate nucleus, supplementary motor, premotor and primary motor cortex and primary somatosensory cortex project to the putamen. The hippocampal areas, medial and lateral temporal project to the nucleus accumbens. Alexander, Delong and Strick (1986) have distinguished the following segregated basal ganglia - thalamocortical circuits based on the origin of the initial cortical input: 1. Motor 2. Oculomotor 3. Prefrontal 4. Orbital frontal 5. Cingulate-limbic. These are outlined in Table 19-2

2. There are local circuits within the striatum, which involve the excitatory transmitter acetylcholine.

3. The striatum also receives a major dopaminergic input from the substantia nigra compacta. Based on the type of receptor, this input may be either excitatory (D1) or inhibitory (D2). Dopamine receptors have been classified based on the dopamine mediated effects on the enzyme adenylate cyclase (which is involved in the ATP to cyclic AMP transformation). D2 receptors are involved in the inhibition of the enzyme; D1 receptors in stimulation of the enzyme. Note that 5 dopamine receptors have now been identified The complex and still evolving topic has been reviewed by Cooper et al, 1991, Guttman, 1992, Gerfen and Engber, 1992.

4. Because of this differential input two pathways have been identified: the direct and the indirect

5. The major direct outflow pathway arises

TABLE 19-2 CEREBRAL CORTEX TO BASAL GANGLIA TO THALAMUS TO CEREBRAL CORTEX CIRCUITS MODIFIED FROM ALEXANDER ET AL,)

LOOP SEQUENCE	MOTOR	OCULOMOTOR	PREFRONTAL	ORBITAL	LIMBIC
1A. Major cortical input	Area 6/ SMA	Frontal eye field/ Area 8	Dorsolateral Prefrontal	Lateral orbital frontal	Anterior cingulate (area 24)
1B. Additional Cortical inputs	Areas 4, 6/PMA, 1,2,3, (post central)	Dorsolateral prefrontal, Posterior parietal	Posterior parietal, arcuate/frontal, PMA	Limbic / Anterior cingulate See limbic	Hippocampus, parahippocampal amygdala entorhinal, temporal neocortical
2. Striatum	Putamen	Caudate (body)	Caudate (head)	Caudate(head)	N. accumbans
3. Pallidum/ S. Nigra reticularis	Globus Pallidus/ S.Nigra/ reticularis	Globus pallidus (caudal) dorsomedial), S. Nigra reticularis	Globus pallidus (lat.dorsalmedial). / S. Nigra reticularis	Globus Pallidus (dorsomedial)/ S. Nigra reticularis	Ventral pallidum, , globus pallidus, (rostral lat.) S.N.reticularis
4. Thalamic nuclei	Ventro- Lateral (pars oralis/ medialis)	Ventral anterior (magnocellularis) Medial dorsal (parvocellularis)	Medial dorsal (parvocellularis), Ventral anterior (parvo Cellularis)	Medial dorsal (magnocellularis) Ventral Anterior (parvo Cellularis)	Medial dorsal (postmedial)
5. Projection to Cortical Area	6/SMA	Frontal eye field/ 8	Dorsolateral prefrontal	Lateral orbital	Anterior Cingulate

from those striatal neurons receiving excitatory dopaminergic input (D1) and passes to the medial globus pallidus - mediated by the inhibitory transmitter gamma aminobutyric acid (GABA). Substance P is also involved as a transmitter or modulator in this pathway. The major outflow is to the inner (medial) segment of the globus pallidus. There is a lesser outflow of fibers from the striatum to the substantia nigra reticularis, which has the same microscopic structure as the globus pallidus. The outflow of the neurons of these structures is to the ventral lateral and ventral anterior thalamic nuclei, mediated again by the inhibitory transmitter GABA This outflow passes via two fiber systems: the fasciculus lenticularis and the ansa lenticularis. The fasciculus lenticularis penetrates through the posterior limb of the internal capsule; the ansa lenticularis loops around the undersurface of the most inferior part of the internal capsule and then passes upward to join the fasciculus lenticularis. These two fiber systems join at a point known as the Field H2 of Forel, then curve back towards the thalamus in the Field Hl of Forel where they are known as the thalamic fasciculus. This fasciculus then enters the ventrolateral and ventral ant-erior nuclei of the thalamus. The outflow of these thalamic nuclei is excitatory to the motor areas of the cerebral cortex predominantly to the premotor and supplementary motor areas.

6. The indirect outflow pathway arises from those striatal neurons receiving inhibitory dopaminergic input (D2) and passes to the lateral (or external) sector of the globus pallidus mediated by the inhibitory transmitter GABA. Enkephalin is also involved as a transmitter or modulator in this pathway. The neurons of the lateral globus pallidus give rise to inhibitory fibers again utilizing GABA which connect to the subthalamic nucleus. This nucleus gives rise to excitatory fibers utilizing glutamate which provide additional input to medial (inner) sector of the globus pallidus and the substantia

nigra reticularis. As in the direct pathway the subsequent connection of these structures is inhibitory to the ventral lateral and ventral anterior nuclei of the thalamus. The subsequent step in the sequence as in the direct pathway is excitatory to the motor areas of the cerebral cortex utilizing the transmitter glutamate. In the case of both the direct and the indirect pathways a loop has been completed: cerebral cortex to striatum to globus pallidus to ventrolateral and ventral anterior thalamus back to cortical motor areas

7. In terms of final effect of this system on the thalamus, if one starts the analysis at the striatum, the end result of the direct system on the thalamus is excitatory. Inhibition of inhibitory drive is referred to as disinhibition In contrast following through the sequences of the indirect system; one finds that the end result is inhibitory

If one begins at the substantia nigra compacta and follows through the direct and indirect circuits, it is evident that both have the same end result as regards the final effect at the thalamic and the cortical level.

8. It is then possible to analyze the eventual thalamic and cortical effects of a decrease in dopaminergic input at the level of the striatum: the thalamus and cortex will receive less excitation. The results are the same whether the direct or indirect pathway is considered. Movement then will be decreased or slowed down. The terms akinesia or bradykinesia are employed.

On the other hand, if there is increased dopaminergic activity, the end results at the thalamic or cortical level will be an increase in motor activity irrespective of whether the direct or indirect pathway are considered. The terms hyperkinesia or dyskinesia are employed

The ultimate effect of dopamine then is to facilitate movement. (Cote &Crutcher, 1991 and Bergman, et al, 1990).

The striatum also has GABA mediated inhibitory outflow to S.nigra compacta. Specific sites in the striatum project to the S.nigra compacta (and receive afferent input from the S.nigra compacta)[1].

Now let us consider the more complex nature of the microanatomy of the striatum.

1. From a histochemical and histological standpoint, distinct areas may be noted, referred to as patches within the larger background matrix. The patch areas have a high density of neurons; matrix areas are less dense. Patch zones contain little acetylcholine esterase; matrix areas are rich in acetylcholine esterase. Patch areas are associated with bundles of dopamine fibers early in development. Later in development there are less dense dopaminergic inputs to the matrix. (Graybiel & Ragsdale, 1978). Neurons within the striatum may be additionally categorized on the basis of size and morphology of the dendrite and size as (a) medium-sized, spiny neurons (b) large or small aspiny neurons. The different properties of these regions and neuron types are presented in table 19-3.

There is considerable evidence that the dopamine-containing terminals and their related synapses and the cholinergic synapses in the striatum have essentially antagonistic actions. Normally, however, they remain in a particular balance. We will discuss the problem of an imbalance when we come to discuss Parkinson's disease (Duvoisin, 1967; Hornykiewicz, 1970). As discussed above both tend to be found in specific sites in striatum (striasomes). These sites exist in a larger matrix of the striatum.

Several additional loops and circuits must now be considered:

1. In addition to its major input from the cerebral cortex, the caudate-putamen also receives a lesser afferent input from the nucleus centrum medianum (C.M.) (excitatory transmitter presumed to be glutamate or aspartate). It should be noted that the C.M. represents a major interlaminar nucleus of the thalamus and is the main thalamic extension of the

[1] *A more detailed examination of the striatum in terms of microscopic neuroanatomy and neuropharmacology suggests a much more complex story (Wexler et al, 1991, Albin et al, 1989, Martin and Gusella 1986).*

reticular formation. The centrum medianum, however, also receives fibers from the globus pallidus (inhibitory transmitter: GABA). This again completes an additional loop; relating the basal ganglia to the reticular formation.

2. It should also be noted that some fibers leave the ansa lenticularis and, rather than passing into the thalamus, descend to the pedunculopontine nucleus within the tegmentum of the mesencephalon. This nucleus then projects back to the globus pallidus.

3. There is also evidence for a direct excitatory input from motor and premotor areas to the subthalamic nucleus providing an additional circuit for modulating motor activity.

Overview of the dopaminergic systems: In addition to the dopaminergic nigral- striatal pathways, which are of major concern in our discussion of motor function, there are other major dopaminergic pathways. These other pathways, however, are of importance when one begins to utilize L-Dopa (the precursor of Dopamine) in therapy of Parkinson's disease. In addition, these pathways are of importance when agents (such as neuroleptics employed in the treatment of psychoses or other psychiatric syndromes) are used to block the dopamine receptor or to prevent the storage of dopamine In addition, the overall disease state in Parkinson's disease may also involve these pathways.

(a) The mesolimbic system - originating in the ventral tegmental area - medial and superior to the S. nigra and projecting to the nucleus accumbens (ventral striatum); the stria terminalis septal nuclei; the amygdala, hippocampus; mesal frontal, anterior cingulate, and entorhinal cortex. A major role in emotion, memory and perception is postulated for this system. Hallucinations are a side effect of a high dose of L-Dopa in the Parkinsonian patient.

(b) The mesocortical system- originating in the ventral tegmental area and projecting to neocortex particularly dorsal prefrontal cortex with a role in motivation, attention, & organization of behavior.

TABLE 19-3: THE COMPLEX NATURE OF THE MICROANATOMY OF THE STRIATUM

MATRIX REGIONS	PATCH REGIONS
1. Matrix areas form large background regions with a low density of neurons	1. The patch areas are smaller and have a high density of neurons.
2. Receive afferent input from superficial cortical layers and multiple sites (motor, sensory, motor, premotor, frontal, parietal and occipital) and intralaminar thalamic sites Young and Penney 1988).	2.Patch neurons receive input from deeper cortical layers in prefrontal and limbic cortex.
3. Matrix areas are rich in acetylcholine esterase	3.Patch zones contain little acetylcholine esterase. Patch neurons contain GABA and substance P and project to the S. nigra compacta. Patch neurons receive a dense dopaminergic input from the substantia nigra compacta.
SPINY NEURONS	**ASPINY NEURONS**
Spiny neurons in general project outside the striatum and account for 90% of striatal neurons.	Aspiny neurons in general are interneurons, form 10% of the neurons and are intrinsic to the striatum.
Spiny neurons contain a transmitter and a neuropeptide modulator Types of Spiny Neurons: **a.** Spiny matrix neurons containing GABA and the neuropeptide substance P and projecting to medial globus pallidus and substantia nigra pars reticularis. **b.** Spiny,matrix neurons, containing GABA and another neuropeptide: dynorphin projecting to the medial globus pallidus and substantia nigra pars reticularis. **c.** Spiny Matrix neurons containing GABA and the neuropeptide enkephalin and projecting to thelateral globus pallidus. **d.** Patch neurons containing GABA and substance P and projecting to the S. nigra compacta.	Large aspiny interneurons within the matrix contain the transmitter acetylcholine Small aspiny interneurons within the matrix contain the neuropeptides Somatostatin and Y.

(c) Hypothalamic (arcuate nucleus) to infundibular stalk of pituitary involved in hypothalamic inhibition of prolactin release.

Overlap with the cerebellar system. It is also important to remember that the major outflow from the cerebellum (via the superior cerebellar peduncle) terminates in relation to the same ventrolateral and ventral anterior nuclei of the thalamus[2]. This thalamic nucleus receives a projection from both the cerebellum (predominantly the dentate nucleus) and the globus pallidus. However, the information from the cerebellum is projected in a more limited manner primarily via ventrolateral to the motor areas of cerebral cortex, predominantly the pre-motor and motor cortices. The basal ganglia differ from the cerebellum in several important respects. In contrast to the more limited relationship of cerebellum to ventral lateral nucleus of thalamus (projection to motor areas of cortex - and projections from motor areas of cortex via pontine nuclei to the cerebellum), the basal ganglia have widespread inputs from the cerebral cortex and via several thalamic nuclei back to multiple cortical areas. These cortical basal ganglia relationships are not diffuse or overlapping but instead, are organized in parallel systems.

It should be very clear then that patients with disease of the basal ganglia may have significant manifestations not only of motor function but also of cognitive and emotional function (Cooper, et al [1991] and Starkstein, et al (1989) in relationship to Parkinson's Disease and Laplane, et al [1989] with regard to obsessive compulsive behavior change.

There is considerable overlap with frontal lobe, premotor and supplementary motor dysfunction as one might predict, based on the anatomical connections discussed above. An understanding of the basic anatomical interrelationships will aid in an understanding of the effects of the various medical and surgical modalities of treatment in Parkinson's disease. Thus, when dysfunction develops in the circuit, lesions at specific critical points, such as ventrolateral thalamic entry area or the subthalamic nucleus may allow restoration of considerable function. The usual location of surgical lesions for the relief of the tremor and rigidity of Parkinson's disease are shown in *Fig. 19-2.* It should be evident that the lesion in the ventral lateral nucleus of the thalamus would also be extremely effective in eliminating tremor originating in the cerebellum since such a lesion would prevent a disordered cerebellum from acting on the circuits passing through this nucleus and this disordered cerebellum would no longer influence motor activities originating at a cortical level.

We must consider the circuits through the basal ganglia modulators of cortical function, particularly as regards movement. For voluntary movement, these circuits clearly provide complex modulation acting on the supplementary motor cortex. This modulation represents a focused equilibrium of opposing influences. When one of these influences acts to a disproportionate degree, dysfunction in the main circuit from the cortical motor cortex to the anterior horn cells and to the reticular formation will result.

CLINICAL SYMPTOMS AND SIGNS OF DYSFUNCTION

General - overview Based on the anatomical circuits considered above a variety of symptoms and signs may occur.

(1) A lack of movement, an inability to initiate movement or a slowness of movement because of excessive inhibition (a lack of excitation) so that the excitatory effect of ventral lateral nucleus - of thalamus on supplementary motor neurons fails to occur due to a decrease in dopamine. This lack of movement and slowness of movement is defined as akinesia and bradykinesia as discussed above.

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[2] *It should be noted that the dentate nucleus of the cerebellum also has some outflow (via the superior cerebellar peduncle) to the red nucleus. After synapsing at the red nucleus, fibers are also conveyed to the ventrolateral nucleus of the thalamus. The major outflow, however, apparently is directly to these thalamic nuclei from the dentate and, to a lesser degree, from the emboliform nucleus of the cerebellum.*

(2) Elimination of inhibition at a critical point in the system may result in a release of disordered movement. The disordered movements are defined as dyskinesia and tremor.

(3) The relationship of muscle tone in antagonists and agonists may be altered so that excessive tone is present, defined as rigidity. Tremor superimpose on this rigidity produces cogwheel rigidity.

(4) A specific extreme of posture may be maintained defined as dystonia.

(5) Problems in the sequencing of movements as in walking or of posture as in standing may occur.

(6) Disorganization of those higher level-righting reflexes discussed in the previous Chapter 18 may occur.

Not all of these symptoms and signs occur in a given disease or case. Some of these symptoms and signs occur with disease at other sites. As already discussed, akinesia or bradykinesia is frequently seen in patients with disease of frontal - premotor and supplementary motor areas. Refer to Delwaide&Gance (1988) for additional discussion of correlation of symptoms and signs with anatomy/physiology).

It should also be very clear then that patients with disease of the basal ganglia might have significant manifestations not only of motor function but also of cognitive and emotional function. (see Cooper, et al, 1991 and Starkstein, et al, 1989 in relationship to Parkinson's Disease and Laplane, et al (1989) with regard to obsessive compulsive behavior change.

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SPECIFIC SYNDROMES

PARKINSON'S DISEASE AND THE PARKINSONIAN SYNDROME (Recent reviews are provided by Dunnett & Bjorklund, 1999, Lang&Lozano, 1998,Olanow &Tanner, 1999, Quinn, 1995,Riley&Lang, 2000)

The most common disease involving the basal ganglia is Parkinson's disease, first described by James Parkinson in 1817[3]. Parkinson's disease after Alzheimer's disease is the most common degenerative disorder of the central nervous system affecting approximately 1 million individuals in the United States. The basic pathology is the progressive loss of dopamine producing neurons in the pars compacta of the substantia nigra. A certain mixture

[3] *As we will discuss below, other disease entities may overlap with many of the same symptoms and signs and it is appropriate to refer to the larger group as the Parkinsonian Syndrome. The term "Parkinsonism" has also been employed for this larger group.*

of symptoms then develops each of which may vary in severity. The essential (cardinal) signs and symptoms consist of: tremor, rigidity, akinesia and defects in postural and righting reflexes. Charcot essentially described this total picture and he named the disease after Parkinson (Goetz, 1986). The cardinal signs and symptoms are summarized in table 19-4.

TABLE 19-4:CLINCAL SIGNS IN PARKINSON'S DISEASE

Clinical Signs	Clinical Appearance
Rhythmic tremor at rest: Alternating type, initially fine, 4-5 Hz, and then, as the disease progresses, often Coarse. The tremor disappears on movement, but may re-emerge when a posture is maintained	The tremor affects not only the extremities, but also the eyelids, the tongue and voice. The alternate movements of thumb against opposing index finger are often referred to as "pill rolling".
Clinical rigidity which must be differentiated from decerebrate rigidity which is primarily spasticity with the jack-knife quality of spasticity (a sudden resistance is encountered, which, as additional force is applied, suddenly gives way).	Comparable to the resistance of a lead pipe bending under force in which the resistance is relatively constant throughout the range of motion. As with spasticity, rigidity may reflect increased activity of the gamma system.
Akinesia- lack of spontaneous movement and difficulty in initiating movement. A corollary term is bradykinesia which refers to a slowness of spontaneous movement.	Seen in the fixed facies of the Parkinsonian patient, lack of spontaneous blinking and movement, loss of associated movements (the swing of the arms in walking). Correlated as discussed above with the reduction in dopaminergic input.
Defects in posture righting reflexes are best noted as the patient stands, walks and attempts to turn.	Normally, as an individual turns, the eyes move initially in the direction of the turn, his head moves, then shoulders and arms, and the body then follows. The patient with Parkinson's disease, however, turns "en bloc", In walking at times, develops forward propulsion, seems to tilt forward and develop increasing speed – producing loss of balance with falls and injuries, and instability when turning.

Some cases, throughout their course may continue to manifest primarily tremor as the major symptom and such cases tend to have a more favorable prognosis. Several types of Parkinson's disease and syndromes may be specified. The most common variety is the idiopathic or primary Parkinson's disease, a degenerative disease arising insidiously in the patient of age 40, 50 or 60. In a series of 1644 patients with Parkinsonism, evaluated by Jankovic (1989) at a movement disorder clinic, 82% were found to have idiopathic Parkinson's disease. At times, there is a family history of the same disease.

1. Pathology of Parkinsonian Lesions. The basic pathology involves a progressive loss of the pigmented neuromelanin containing neurons of the pars compacta of the substantia nigra *(Fig.19-3)*. (The pigmented neurons of the locus ceruleus are also affected.)[4] (The student will recall that both melanin and dopamine are steps in the metabolic pathway involving phenylalanine.) A long pre-clinical period estimated at 5 years occurs in this progressive disease. Various estimates suggest that when symptoms first occur, 70-80% of striatal

[4] *Whether the Dopamine-nigral-striatal-(mesostriatal) system involvement is the entire story in Parkinson's disease is unclear. The mesolimbic cortical Dopaminergic system is also affected (50-60% decrease). Noradrenergic and serotoninergic and cholinergic systems are also affected; e.g., 50-60% decrease in nor-adrenalin concentrations in cerebral cortex, locus ceruleus, limbic system, hypothalamus and cerebellum; 58% loss of serotonin in dorsal raphe nucleus. There is also cholinergic nerve cell loss of 32-87% in nucleus basalis of Meynert. In general, none of these systems show the degree of degeneration found in the nigral-striatal-dopaminergic system (Estimated as 80-90% depletion of striatal dopamine and 60-70% degeneration of S. Nigral neurons when symptoms first emerge). For extensive reviews and discussions, see Agid et al, 1987, 1989.*

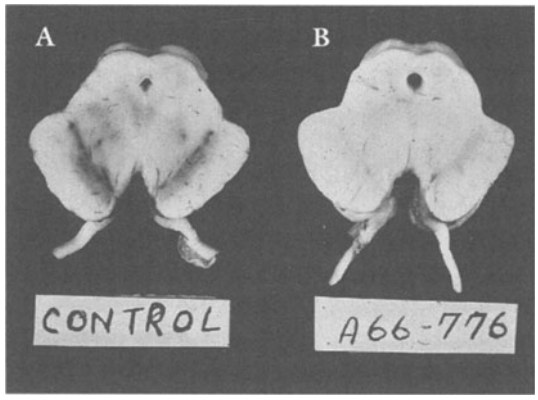

FIGURE 19-3. Parkinson's Disease. The substantia nigra in Parkinson's disease. A, Normal substantia nigra. B, Similar region in case of idiopathic Parkinson's disease. A marked loss of pigmentation is evident. (Courtesy Dr. Thomas Smith. Neuropathology University of Massachusetts)

dopamine is depleted. In terms of neurons in the pars compacta of the substantia nigra 50% (compared to age matched controls) to 70% (compared to young individuals) are already lost. Normally the rate of cell loss in the nigra during normal aging is 5% per decade. In patients with Parkinson's disease the rate of cell death is subsequently 45% per decade.

On histologic examination *(Fig. 19-4)*, there is a characteristic, specific finding of Lewy bodies: round, eosinophilic bodies surrounded by a clear halo within the cytoplasm of surviving neurons of the substantia nigra. In many cases, these Lewy bodies are found in other neurons, e.g., cerebral cortex. Immunocytochemistry has demonstrated that a small protein a-synuclein is a major component of the Lewy body *(Fig.19-5)*. Under normal circumstances this protein is located in presynaptic nerve terminals. It is therefore likely that the Lewy body represents degenerated and aggregated neurofilaments. The Lewy body may also be found diffusely in cerebral cortex in Lewy body dementia.

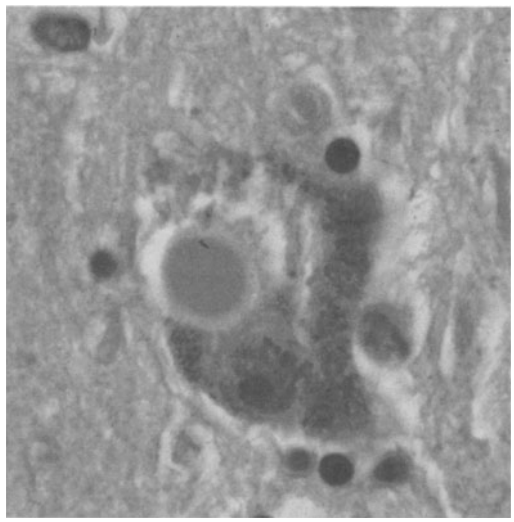

Figure 19-4. Lewy body in a pigmented neuron of the substantia Nigra. H&E stain, original at 125X. (Courtesy of DR. Thomas Smith).

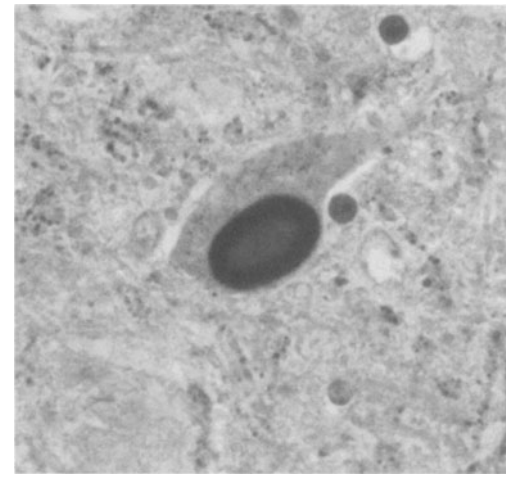

Figure 19-5. Lewy body. Slide stained for alpha synuclein.100X. (Courtesy of Dr. Thomas Smith).

2. Etiology of Parkinson Disease. Why do the neurons degenerate? The majority of cases with L-DOPA responsive Parkinson' s disease do not have a clear-cut genetic basis. However mutations in the alpha synuclein gene have been found in several families of Italian or Greek origin with early onset autosomal dominant Parkinson's disease mapping to locus 4Q21-25 (Goedert et al, 1998 and Duvoisin, 1998). Other families with autosomal recessive juvenile onset disease have implicated the parkin gene at locus 6q25.2-27.Other gene loci are discussed by Dunnett & Bjorklund, 1999.

The major etiologic factors have involved a genetic predisposition and possible toxic exposures.

Neuroleptic agents: The use of neuroleptic agents may unmask an underlying genetic

predisposition to Parkinson's disease. A significant percentage (15-60% depending on age), of patients who receive neuroleptic tranquilizers also will develop symptoms of Parkinsonism. These agents include pheno thiazides such as chlorpromazine, and haloperidol and reserpine. Reserpine interferes with the storage of dopamine within the nerve cells and, thus, depletes the brain of this neurotransmitter. Pheno thiazides and related compounds, on the other hand, block the post-synaptic receptors at dopaminergic synapses. In general, of the symptoms produced by these agents, the akinesia, rigidity and tremor will disappear when the agent has been cleared from the body. However, in some cases, the Parkinsonian features appear to remain as a permanent deficit. In such patients, one may find evidence in the family history of other cases of Parkinson's disease (Schmidt and Jarcho, 1966). As discussed by Koller (1992), there is then a clear indication that neuroleptic induced Parkinsonism represents early or latent Parkinson's disease made evident by anti-dopaminergic medications.

Toxic Agents. The major impetus for the study of possible toxic exposure has come from the study of cases of Parkinson's disease developing in miners exposed to manganese and more recently in cases exposed to the agent MPTP.

Manganese Poisoning. A relatively rare cause of a Parkinsonian syndrome is manganese poisoning. Manganese apparently accumulates in the melanin containing neurons of the substantia nigra and interferes with the enzyme systems involved in the production of dopamine (Mena et al, 1970),

MPTP Toxicity. Another form of Parkinson's disease induced by the drug MPTP, has provided major insights in the possible etiology of the degeneration of the dopamine containing neurons in the substantia nigra. (MPTP is the abbreviated term for 1-Methyl- 4 phenyl-1, 2,3,6, tetrahydropyridine). This agent is a by-product of the chemical process for the production of a reverse ester of meperidine (demerol): 1-methyl-4 propionoxypiperidine (MPPP). Meperidine is a controlled narcotic; MPPP is not controlled, has narcotic action, and can be produced in clandestine labora-tories. MPTP had been recognized shortly after its legitimate synthesis in 1947 to produce a severe rigid - akinetic state in monkeys. However, it was not until the summer of 1982, when MPPP was produced on a large scale in Northern California, for illicit mass distribution, that significant numbers of young drug abusers began appearing at emergency rooms with an acute Parkinsonian syndrome. The investigation of these cases has been presented in a series of papers by (Langston et al, 1983; 1992; and Ballard et al, 1985). Essentially, the compound MPTP has selective toxicity on the dopaminergic neurons of the pars compacta of the s. Nigra, not only in human but also in subhuman primates, such as the Rhesus monkey, Macaca mulatta, and the squirrel monkey. Both in the human and the monkey, MPTP reproduces the clinical disease, the pathological findings and the effects of pharmacological therapy of Parkinson's disease to a relatively complete degree, including in older animals, the presence of Lewy bodies. With such an animal model, experimental medical and surgical therapy can be studied with a clear-cut correlation with the human disease (for example, see Aziz et al, 1991; Langston, et al, 1984,Kopin 1988). Moreover, since there were many patients exposed to the agent but not all exposed patients and not all acute cases developed the chronic Parkinsonian state, prospective studies can be performed as to the natural history and factors influencing the onset of the disease (Stone, 1992). In part because of MPTP, increased attention has been focused on other environmental exposures that may be involved in producing neurotoxic effects culminating in Parkinson's disease (Tanner&Langston, 1990,Olanow &Tatton, 1999).

Other pathological processes These disorders also will produce some of the symptoms of Parkinson's disease without the presence of Lewy bodies (Gibbs, 1988).

1. Bilateral necrosis of the globus pallidus

may produce akinesia. Such a necrosis could occur in carbon monoxide poisoning, or anoxia, or in relation to infarction. Rigidity in flexion may also follow bilateral necrosis of the putamen or the globus pallidus.

2. A tremor at rest may occur with destructive lesions involving the ventro-medial tegmentum of the midbrain. Such lesions, apparently, interrupt the pathway from the substantia nigra to the striatum. A degeneration of neurons in the substantia nigra and a decrease in dopamine in the corpus striatum occurs.

3. "Arteriosclerotic or vascular (multi infarct)" variety in which bilateral infarcts occur in the putamen Usually this is the accompaniment of a lacunar state in which multiple small infarcts occur in the basal ganglia and internal capsule. The resultant syndrome of rigidity and akinesia affects the lower half of the body and thus can be clearly distinguished from the classical idiopathic l-dopa responsive Parkinson's disease.

4. Von Economo's Encephalitis. A certain proportion of cases may be termed post-encephalitic. These cases had a clear onset in relation to the epidemic of Von Economo's encephalitis lethargica in the years 1916-1926. Approximately 50% of the survivors of this devastating disease developed a Parkinson's syndrome due to severe loss of neurons in the substantia nigra. In such cases, Lewy bodies are not found but neurofibrillary tangles are present in surviving cells (see Alzheimer's disease in Chapter 30 for a discussion of neurofibrillary tangles). In addition to the aforementioned Parkinsonian symptoms and signs, these patients presented other evidence of involvement of the central nervous system, including oculogyric crises (tonic vertical gaze), chorea, dystonia and sleep disorders. The symptoms and signs indicated the involvement not only of the substantia nigra, but also of multiple other sites including the midbrain, hypothalamus and hippocampus (see Gibb, 1988). The essential distribution of the pathology was in the periventricular areas about the aqueduct and third ventricle A dramatic example of post encephalitic Parkinsonism and its treatment is presented in the movie "Awakenings", based on the book by Oliver Sacks.

Management (Refer to Lang & Lozano, 1998 and Riley &Lang, 2000).

When one considers that the basic pathology in Parkinson's disease represents a marked loss of Dopamine containing neurons in the S.Nigra and a marked decrease in Dopamine concen-tration in the striatum whereas, other transmitters and neurons are affected to a much lesser degree (e.g., cholinergic system within corpus striatum now has a relatively unopposed action) then the possible types of treatment are very evident.

1. *Early medical treatment:* For many years, the standard treatment involved the use of anticholinergic compounds such as belladonna and atropine or of synthetic analogues. Trihexyphenidyl (Artane) and benztropine (Cogentin) are examples of such agents. The anticholinergic compounds affect primarily the tremor and to some extent the rigidity of Parkinson's disease and in many cases may produce limited improvement.

2. *Early approaches to surgical intervention.* Various surgical procedures were attempted in the 1940s and 1950s, involving limited ablations of area 4 or area 6 or section of the cerebral peduncle. In 1952, while attempting to section the cerebral peduncle, Cooper accidentally occluded, the anterior choroidal artery, and the Parkinsonian patient showed a significant improvement in contralateral symptoms, presumably as a result of infarction of the inner section of the globus pallidus. Cooper soon came to employ stereotaxic techniques for the direct production of lesions in the globus pallidus (Fig. 19-2 lesion 1). The procedure produced a significant reduction in contralateral tremor and to a lesser extent, a decrease in the contralateral rigidity. Cooper was able to demonstrate later that lesions in the ventrolateral thalamus were much more effective (Fig.19-2, lesion 2). Initially, the stereotaxic lesions were produced by the injection of alcohol or coagulation. In later procedures, a freezing cannula was employed.

3. *Transmitter replacement:* With the increasing knowledge of the neurotransmitters involved in the substantia nigra and corpus striatum and with reports of deficits of dopamine in these structures in patients with Parkinson's disease, the use of replacement therapy with L-Dopa (dihydroxyphenylalanine) subsequently developed (Cotzias et al, 1967, 1969). As we have indicated, the anticholinergic drugs had a limited effect primarily on the tremor and rigidity; surgery affected primarily the tremor; the use of L-Dopa, which was more a physiological technique, improved the severe akinesia in addition to decreasing the tremor and rigidity. The use of L-Dopa required large amounts of medication since much of the administered dosage was decarboxylated to dopamine at peripheral systemic sites and never crossed the blood brain barrier to be converted to dopamine (note that L-Dopa-crosses the blood brain barrier; dopamine does not). There were significant side effects due to the peripheral actions of the drug. By combining L-Dopa with a peripheral Dopa decarboxylase inhibitor, Carbidopa (in the form of Sinemet) a much lower dosage of L-Dopa was required with fewer gastrointestinal and blood pressure side effects. Central side effects continued to occur, e.g., peak dose related dyskinesias such as chorea and myoclonus. The short duration of action also continued to provide problems in terms of wearing off of dose. Other sudden on-off effects with sudden arrests of movement that were not entirely related to time of dose also occurred as the disease progressed. Individual titration of dosage, specific to the particular patient is often required. The basic problem is that Parkinson's disease is progressive. Once the neurons in the s. Nigra have all died off or have become dysfunctional, there is no capability to convert L dopa to dopamine.

4. *Other therapeutic maneuvers* have been developed for such patients. Various dopamine agonists have been developed to bypass the problem of conversion of L-dopa to dopamine. Additional surgical procedures involving the implantation of stimulators in deep brain structures such as the globus pallidus, thalamus and subthalamic nucleus have also been developed. Transplantation of fetal mesencephalic cells into the striatum has benefit in younger patients but may increase dyskinesias. The problems of management are reviewed in the following patient who was followed for 19 years.

Case 19-1: This 48-year-old married left-handed white male schoolteacher and administrator, 3 months prior to evaluation in 1982 developed a sense of fatigue, stiffness and lack of control in the left arm. After a period of prolonged writing, he would have to make a conscious effort to continue writing Approximately one month prior to the evaluation; he first noted a slowing down in movements of the left leg. "I have to remember to lift it."

Neurological examination: *Cranial Nerves:* He had a tremor of the closed eyelids and a positive glabellar sign (he was unable to suppress eyelid blinking on tap of forehead). *Motor System:* In walking there was a tendency to turn en bloc and a decreased swing of the left arm. There was a slight increase in resistance to passive motion at the left elbow, wrist and knee (rigidity without definite cogwheel component). Although the patient was left-handed, there was a slowness of alternating finger movements of the left hand. No tremor was present. Handwriting was intact with no evidence of micrographia.

Clinical diagnosis: Early Parkinson's disease, predominantly unilateral.

Laboratory data: All studies were normal including CT Scan of the brain, and thyroid studies.

Subsequent course: The patient did not

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[6] This is a combination of 10 mg. of carbidopa (Dopa decarboxylase inhibitor) and 100 mg. of L-Dopa. Higher dosage combinations are a) 25 mg. of carbidopa with 100 mg L-Dopa, and b) 25 mg. carbidopa with 250 mg. L-Dopa. A sustained release form is also available (50 mg. of carbidopa with 200 mg. of L-Dopa), and is marketed as Sinemet CR.

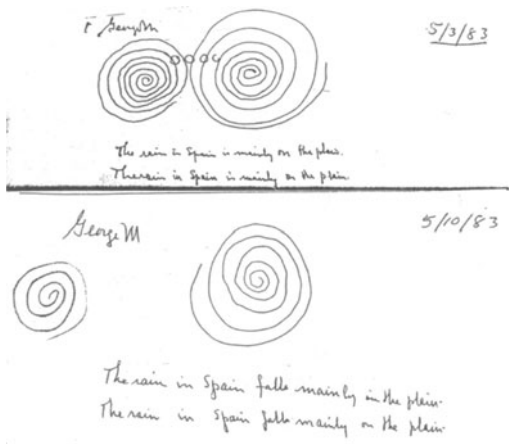

Figure 19-6. Parkinson's disease. Case 19-1. See text. Handwring sample: on 05/03/83 before therapy with L-dopa/Carbidopa and 05/10/83-one week after starting therapy. In each example, the larger circles have been drawn by the examiner.

wish to begin any treatment at that point in time. Re-evaluation at 3 months indicated progression. One year after onset of symptoms there was significant micrographia *(Fig. 19-6A)* and cogwheel rigidity at left shoulder, elbow and wrist. Therapy with Sinemet (10-100 mg, 3 times per day.)[6] was begun. Re-evaluation one week later demonstrated a marked improvement in handwriting *(Fig.19-6B)* and decreased cogwheel rigidity.

As the dose of Sinemet was increased to (10/100) mg 5x/day over the next week, occasional choreiform movements of the fingers of the left hand and occasional backward flinging (hemi ballistic) movements of the left arm occurred at 60-90minutes after later doses of Sinemet. As the dose reached 10-100 mg. 6x/day, the patient reported that his handwriting now was back to normal. Examination confirmed the significant improvement in all findings. The patient did experience 90 minutes after a Sinemet dose - a tremor of the left shoulder and an exaggerated grasp of the left foot toes on lifting the leg (possible form of dyskinetic or dystonic reaction). He was aware that some symptoms of his underlying disease would emerge 3-4 hours after a dose of Sinemet. Five years after onset of symptoms, despite a higher dosage of Sinemet of 25/100 mg. tablets, 7 or 8 x/day, more resting pill-rolling tremor of the left hand had emerged. (In actuality 75-100mg of carbidopa is probably sufficient to saturate the peripheral dopa decarboxylase system). Moreover, choreiform -movements of the left arm occurred 60 to 90 minutes after each dose of Sinemet. The choreiform movements disappeared when the dosage of Sinemet was reduced to 25/100mg 6/day. The increased rigidity and tremor responded to the addition of a DOPA agonist Bromocriptine (Parlodel). Over the subsequent years other agents were employed but the disease continued to progress with all of the problems in management discussed above. Eventually, in 1997 he underwent mesencephalic fetal cell transplantation. Evaluation 3 years after the transplant demonstrated a little improvement but a marked increase in the dyskinesias. Some improvement in dyskinesias occurred after dopaminergic medications again were reduced.

DIFFERENTIAL DIAGNOSIS OF PARKINSON'S DISEASE:

1. *In considering the akinesia and bradykinesia of Parkinson's disease, the major differential diagnosis in the older population are the syndromes of gait apraxia related to frontal lobe,* as discussed in Chapter 18. These may be outlined as follows:

a. Normal pressure hydrocephalus

b. Other types of hydrocephalus: late decompensation of aqueductal stenosis

c. Multiple lacunar infarcts (the lacunar state)

d. Leukoariosis - or Binswanger's Disease involving the periventricular white matter and seen in elderly hypertensive patients

e. Alzheimer's disease: Note, however that Mayeux et al, 1985, found that 34% of patients with Alzheimer's disease had some extrapyramidal signs. To confound the picture, 44% of patients with Parkinson's disease have dementia, with 29% found to have Alzheimer's disease and 10 % Lewy body dementia.

f. Frontal lobe tumors, e.g., subfrontal or parasagittal meningiomas.

g. Myxedema with hypothyroid state.

h. General paresis of neurosyphilis, now uncommon but refer to case 30-5.

In general, frontal lobe syndromes do not have a prominent tremor (unless a coincident essential or senile tremor is present). Rigidity may be present but this variable rigidity is of the frontal lobe type referred to as gegenhalten. A cogwheel component (to this frontal lobe rigidity) is usually not present unless there is a superimposed tremor of other cause. The rigidity and akinesia predominantly affect the lower extremities.

2. *In considering the tremor of Parkinson's disease - the major differential diagnosis is essential (or senile or familial tremor.)* In general, this is a tremor of the outstretched hand with some increase as termination of movement or when a sustained posture is maintained. The tremor is not present at rest and there is no pill rolling quality. Rigidity is not present, and gait is normal with a good swing of the arm. The tremor is usually long-standing without major disability. Note that there is a small group of Parkinson's disease patients with favorable outcome who have a resting tremor as a predominant symptom over many years. They will, however, have to a minor degree, on careful examination, many of the other cardinal symptoms of Parkinson's disease.

3. *Secondary Parkinsonism: Neuroleptic, toxic or vascular induced.* In the series of Jankovic (1989), and Siemer and Reddy (1991), these cases accounted for 10% of all cases of Parkinsonism.

4. *Parkinsonism plus syndromes.* (Table 19-5) In the same series these cases accounted for 10% of all cases of Parkinsonism. These latter patients all share the following characteristics:

a. A progressive disorder is present.

b. From a clinical and pathological standpoint, the pathology of primary neuronal degeneration is much more widespread than in idiopathic Parkinson's disease. The term multisystem atrophy is often applied to some of these cases.[7]

c. Lewy bodies are not found.

d. In general, the patients are all poorly responsive to Levodopa. (Since the pathology extends far beyond the Dopaminergic producing neurons of the S. Nigra.)

e. Some of the patients have a familial disorder.

The more frequent types may be briefly noted (excellent, more detailed discussions are found in Jankovic, 1989, Riley &Lang, 2000).
5. Other neurological syndromes with rigidity and akinesia:

a) Early onset Huntington's Disease and Wilson's disease (see below).

b) Hallervorden Spatz Disease: A rare familial (autosomal recessive disorder with linkage to chromosome 20P) in which prominent iron deposits and neuronal degeneration in globus pallidus and substantia nigra are associated with childhood onset of Parkinsonian syndrome, dementia, spasticity, dystonia and chorea.

c) Parkinsonism - dementia - ALS complex found in the Chamorros of Guam (and several other Pacific groups)- a probable toxic disease involving an excitatory amino-acid (beta N methyl-amino L - alanine) - derived from the cycad seed once used in the production of floor.

d) Creutzfeldt -Jakob Disease: See discussion of dementia (chapter 30)

CHOREA, HEMICHOREA AND HEMIBALLISMUS:

Chorea[8] may be defined (Committee 1981) as "excessive spontaneous movements irregularly repeated randomly distributed and abrupt in character". These movements,

[7] *Many patients with Parkinson's Disease have some symptoms, usually minor, that suggest some degree of involvement beyond the S.Nigra and beyond the Dopaminergic nigral - striatal system, e.g., orthostatic hypotension which is present in the untreated patient. Idiopathic Parkinson's patients also may have some minor degree of upward gaze impairment.*

[8] *At times the adjective choreiform is used to describe the movement rather than employing the noun: chorea*

TABLE 19-5 PARKINSONISM PLUS SYNDROMES

Name	Abbreviation	Pathology-type	Location	Clinical syndrome
1. Progressive supranuclear palsy (the most common)	PSP	Neuron loss and abnormal tau protein in neurofibrillary tangles in neurons and glia Cortex and subcortex	Midbrain tegmentum and ectum, substantia nigra, globus pallidus, subthalamic nuc. basal nuc., cortex	Parkinsonism plus supranuclear impairment of gaze particularly in vertical plane Imaging=atrophy of midbrain
2. Corticobasal degeneration	CBD	Ballooned and achromatic neurons plus abnormal neurofibrillary tangles with tau protein. Linked to chromosome 17 in familial cases	Asymmetrical involvement of frontal –parietal cortex (superior frontal), S. nigra, caudate, thalamus	Akinetic-rigid Parkinsonism plus, dementia plus lateralized apraxia, useless hand, and lateralized myoclonus Overlap with Pick's, Frontal dementia and PSP. Imaging= focal atrophy of frontal- parietal cortex.
3. Multiple system atrophy Incorporates 3 previously separate disorders a. striatal nigral degeneration b. olivopontocerebellar atrophy c. Shy-Drager Syndrome	MSA	Neuronal loss, gliosis, and inclusions in oligodendroglia neuronal cytoplasm, nuclei and glia containing filaments derived from cytoskeletal proteins: tau, ubiquitin and alpha synnuclein	S.nigra, striatum, olivopontocerebellar-lar pathways plus intermediolateral cell column of spinal cord	Akinetic –rigid Parkinsonism (predominates in 80%) plus cerebellar ataxia (predominates in 20%) plus dysautonomia (with neurogenic orthostatic hypotension) Imaging = atrophy of striatum or pons/cerebellum depending on predominant symptoms

although involuntary, consist of fragments or sequences of normal, coordinated movements. Face, mouth, head, proximal or distal limbs may be involved.

Two types of processes must be distinguished – (1) lateralized hemichorea and (2) generalized chorea. The lateralized hemichorea merges into a remarkable disorder hemiballismus characterized by sudden flinging or ballistic movements at the proximal joints such as. throwing or sudden swinging movements at the shoulder joint. Patients may start with hemichorea and evolve into hemiballismus. In discussing this topic, we will deal first with the focal problem and then with the generalized type. We will see in both varieties abnormalities of the anatomic sequences discussed earlier in this chapter.

HEMICHOREA AND HEMIBALLISM:

Initial clinical and experimental studies, correlated these disorders with lesions of the contralateral subthalamic nucleus (see Carpenter, et al, 1950; Whittier and Meller, 1947; Whittier, et al, 1949). It was recognized that the underlying lesion could be a small infarct due to posterior cerebral penetrating branch involvement, often on a lacunar basis, in a patient with hypertension or diabetes mellitus. At times, the adjacent thalamic areas were involved, as well, e.g., the ventral posterior lateral or ventral lateral nucleus. At times, the responsible lesion was a small hemorrhage in the subthalamic nucleus *(Fig.19-10)* and, rarely, a small metastatic tumor.

As regards the explanation for such contralateral excessive movement, hemichorea or hemiballismus, one needs only to consult Figure 19-1. Decreasing the excitatory drive from the subthalamic nucleus actingoin the medial globus pallidus and the substantia nigra reticularis would decrease the inhibitory drive from those structures acting in the thalamus.

Therefore the thalamic/premotor-SMA circuit would be more active and more movement would result.

There were other clinical studies that did suggest other possible localization in the striatum (Cooper, 1969; Goldblatt, et al, 1974; Martin, 1957; Meyers, 1947; Schwarz and Barrows, 1949). In experimental studies Crossman, et al, 1988 demonstrated that local injection of a GABA antagonist into the border of the lateral segment of the globus pallidus and the adjacent medial segment of the putamen would produce hemichorea in the monkey. Such lesions interrupt the inhibitory afferent input to the lateral globus pallidus from the putamen. The lateral globus pallidus would then have greater inhibitory drive on the subthalamic nucleus. The overall effect then would be equivalent to producing a lesion of the subthalamic nucleus; hemichorea or hemiballismus would result. (See Mitchell et al, 1989).

The responsible lesion in these cases would be in the territory of the lenticulo striate penetrating branches of the middle cerebral artery.

Another factor to be considered in chorea and other induced dyskinesias is the possible unopposed action of the nigral striatal Dopaminergic circuits as discussed earlier in this chapter. L-Dopa will exacerbate choreiform disorders[9]. Agents that block dopamine receptors, e.g., the butyrophenones (such as haloperidol) are often very effective in alleviating hemichorea, hemiballismus and chorea (see Crossman, 1990; Klawans, et al, Albin Young and Penney, 1989) for additional discussion.

Hemichorea: Case history 19-2 presented below provides an example of hemichorea with MRI correlation of lesion location in the striatum (caudate/putamen) following a hemorrhage into those structures.

Case 19-2: This 88-year-old, right-handed, widowed white female with a past medical history of profound hearing impairment, adult onset diabetes, euthyroid goiter, coronary artery disease, and hypertension, 5 days prior to admission, developed the insidious onset of involuntary rotary movement in the left foot which increased in intensity and progressed to involve the left shoulder. The movements were constantly present, even during sleep and with progression; her ability to ambulate with a walker was impaired. She also had a dull headache greater on the left side than on the right during the last few days.

Neurological examination: *Cranial Nerves:* Intact except: for left eye blindness (cataracts), and gross impairment of hearing such that shouting was necessary to communicate. *Motor System:* There was minimal weakness in the left upper extremity (5-/5). There was a persistent hemichorea: involuntary twisting movements of her left foot and upward and rotary movements of her left shoulder. The movement was exacerbated by motor-- tasks but did dissipate with sleep. Gait was slightly unsteady due to hesitant placement of the left foot. She did quite well with minimal assistance. *Reflexes:* Deep tendon reflexes were symmetrical, and physiologic except for decreased Achilles secondary to diabetes. the left plantar response was extensor. *Sensation:* Symmetrically diminished vibration sense in toes..

Clinical diagnosis: hemichorea

Laboratory data: *MRI scan* 3 days after admission, revealed mild cortical atrophy and a hyperdense area the right basal ganglia (particularly the head of caudate and putamen) and external capsule consistent with subacute hemorrhage *(Fig.19-7).*

Hospital course: The patient was begun on haloperidol 0.5 mg by mouth every morning and advanced to 1 mg., by mouth three times per day with improvement in the hemichorea, particularly in the upper extremity over the next two weeks

Hemiballism: As we have previously indi-

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[9] *L-Dopa induced dyskinesias are not observed in intact monkeys and humans who have normal dopaminergic and normal basal ganglia function. Parkinsonian patients, monkeys with MPTP lesions and patients with a predisposition to Huntington disease will develop dyskinesias after receiving L-Dopa (see discussion below and Luquin et al, 1992).*

cated, the movements of hemi-chorea may evolve or merge into more violent, uncoordinated, rotatory, flinging movements at the shoulder joint and other proximal joints; termed hemi ballistic. The responsible lesion was located in the subthalamic nucleus *(Fig. 19-8)* or in the putamen or at the border of lateral pallidum - putamen, as discussed above.

The following case history illustrates this movement disorder in a patient seen prior to the era of CT and MRI scans in which the localization is relatively clear.

Case 19-3: This 79-year-old, right-handed, white housewife had the abrupt onset in the early morning hours, 2 days prior to admission, of almost constant flinging movements of the right arm over which she had no control. At the same time, she noted that her right arm felt numb and heavy. Over the next 2 days, the movements decreased markedly and she regained more control of the arm.

Past history: The patient had been a known diabetic for 21 years, receiving insulin - most recently, lente insulin, 25 units each morning.

Neurological examination: *Motor system:* Minimal weakness was present in the right upper extremity at the elbow, wrist and fingers. Alternating movements and finger-to-nose testing in the right hand were markedly impaired. Occasional involuntary flinging movements occurred at the right shoulder. *Sensory System:* Pain, touch, vibration and position sense were all absent in the right upper extremity to the elbow and decreased in this extremity above the elbow.

Clinical diagnosis: hemiballismus due to a lesion of penetrating branches of the posterior cerebral artery, which involved the subthalamic nucleus and ventral posterior lateral nucleus of thalamus.

Laboratory data: Chest and skull X-rays EEG, and cerebrospinal fluid studies were all normal.

Subsequent course: The flinging movements of the right arm subsided spontaneously, shortly after admission. Position sense returned and pain sensation showed a mild improvement. The ataxia on finger--to-nose testing disappeared.

GENERALIZED CHOREA: Bilateral generalized chorea may occur under the following circumstances:

(1). *Acute onset with an immunological basis* (a) one aspect of rheumatic fever (plus or minus carditis and arthritis). (b) In relationship to various autoimmune disease such as lupus erythematosus.

(2). *As an acute complication of L-dopa therapy* in patients with compromise of the dopaminergic system or with disease of the basal ganglia - as discussed above.

(3). *As an acute or chronic complication of various metabolic disorders:* hepatic, renal, hypocalcemia, etc. rarely occurring in pregnancy. In acute hepatic encephalopathy, a number of toxic substances that would normally be removed from the portal venous system on passage through the liver are not removed. Instead, in patients with liver disease, portal hypertension may develop, portal - systemic shunting develops and toxic substances such as ammonia may accumulate in blood and brain. In addition to depression of consciousness (hepatic coma), a hepatic "flap" or "asterixis" may develop. With the arms outstretched, extended at the elbows, and the hands extended at wrist, an irregular flexion extension movement will develop at the wrists and at the metacarpal - phalangeal joints. A similar "asterixis" may also be noted in other metabolic diseases such as uremia and pulmonary disease with $C0^2$ retention. In all of these disorders: ataxia, dysarthria and action tremor of hands may also occur. With uremia and hypocalcemia, myoclonus (sudden jerks of the extremities) or generalized convulsions may occur.

With repeated episodes or prolonged periods of hepatic encephalopathy, more profound and lasting changes in neurological function occur producing a syndrome characterized by chorea and athetosis, ataxia, dysarthria, tremor and dementia. Neuro pathological examination of the brain demonstrates cavities within the basal ganglia, cerebellum, and cerebral cortex. Swollen astrocytes are found, particularly

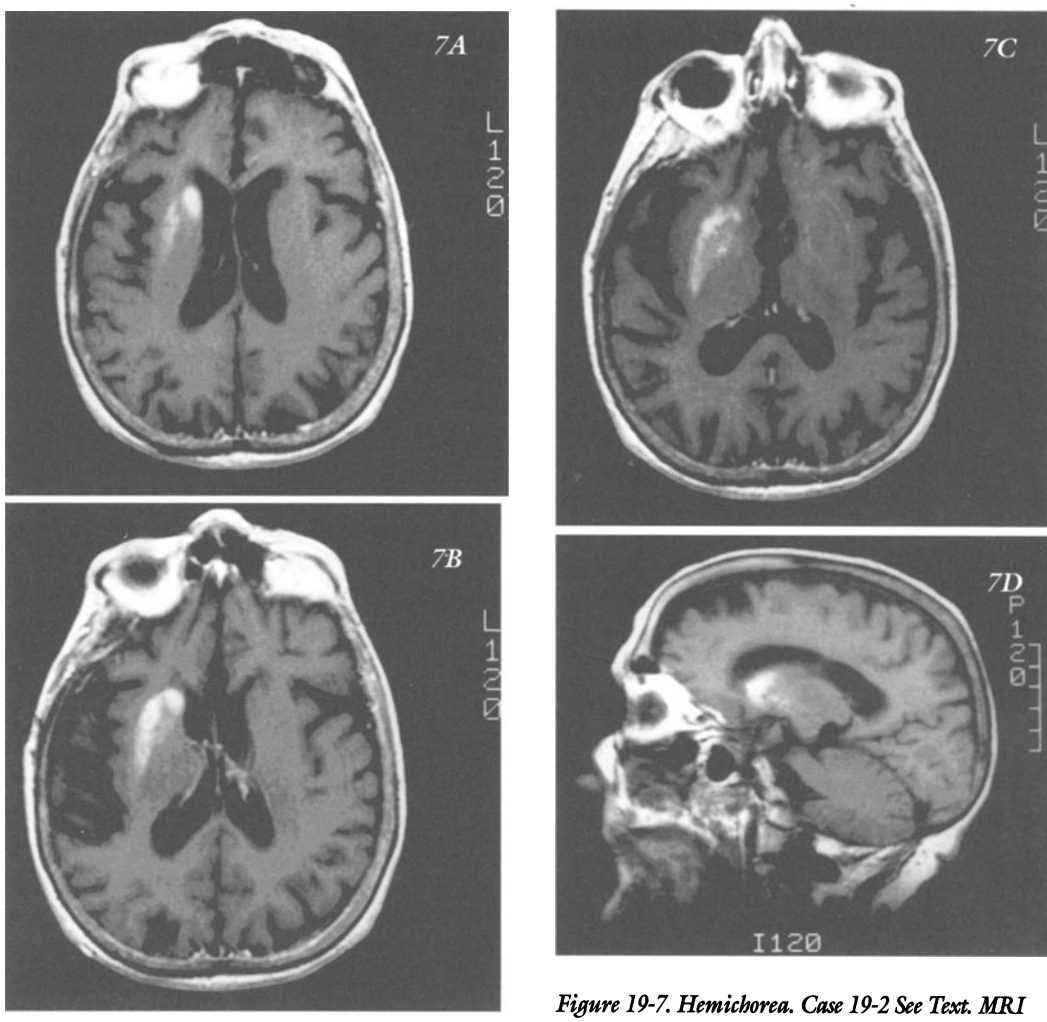

Figure 19-7. Hemichorea. Case 19-2 See Text. MRI demonstrates a hyperdense area of the head of the right caudate, adjacent putamen and external capsule - consistent with a hemorrhage. A, B, C - sequential horizontal sections at 5 mm. intervals - Tl; weighted D - Sagittal section 12.5 mm to right of midline.

within basal ganglia. This chronic irreversible syndrome was initially described as the acquired non-Wilsonian type of hepatocerebral degeneration. (Victor et al, 1965).

(4) *As a chronic progressive disorder - indicating a degenerative disease - affecting the striatum and other sectors of basal ganglia and cerebral cortex.*

The most frequent disease in this category is Huntington's disease. Huntington's disease is of importance beyond its frequency in the population of 5-10/100,000. The disease was originally described in 1872 by George Huntington, based on clinical observations made by his grandfather, his father and himself of an apparent autosomal dominant syndrome of high penetrance that occurred in families living on Long Island in New York state. The syndrome was characterized by the development in mid life of a progressive psychological change (depression, paranoia, psychoses), dementia and involuntary choreiform movements. The disease often affected multiple members of a family over a number of generations. Genetic studies have confirmed that the pattern of inheritance follows an autosomal dominant pattern with extremely high penetrance. In large series, 50% of offspring will manifest the disease that is all who carry the affected gene will manifest the trait. The

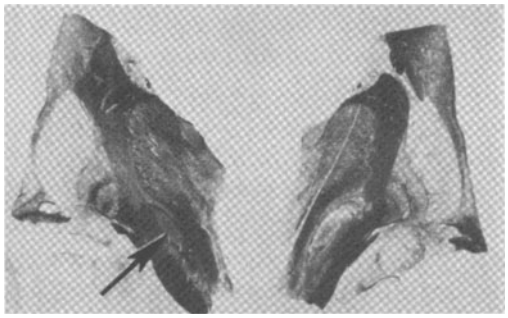

Figure 19-8. Hemiballismus. Myelin stain of basal ganglia demonstrating a discrete hemorrhage into the right subthalamic nucleus. The arrow points to the subthalamic nucleus of the normal left hemisphere. (From Luhan, J.A.: Neurology, Baltimore, Williams & Wilkins, 1968, p.334).

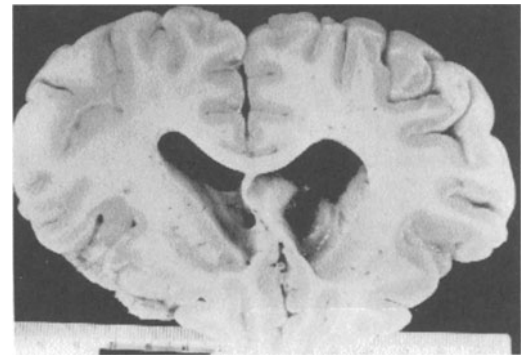

Figure 19-9. Huntington's disease. Marked atrophy of the caudate and putamen with secondary dilatation of the lateral ventricles is evident. Cortical atrophy was less prominent in this case. (Courtesy of Doctor Emanuel Ross, Chicago.)

expression of the gene may vary. Mean age of onset in a large sample as defined by choreiform movements was 42 years. However, behavioral changes, including depression and suicide attempts may precede the movement disorder by ten years or more. Earlier onset of disease is associated with a more rapid course and with the earlier development of features of rigidity. Such patients, for unknown reasons, are more likely to have inherited the gene from the father. Late onset cases (onset between 50 and 70 years of life) have a much more prolonged course and choreiform movements are often the predominant feature (see Sax and Vonsattel, 1992). At times the term senile chorea has been utilized for these late onset cases, which are more likely to have involved cases in the maternal line.

Modern genetic analysis using recombinant DNA techniques and studying families with large numbers of affected individuals or large numbers at risk have allowed the localization of the marker site for the gene on the short arm of chromosome 4. (See Gusella et al, 1983; Martin and Gusella, 1986; Penny and Young, 1988; Roberts, 1990; Wexler, et al, 1991). The specific mutation has now been identified as an unstable trinucleotide repeat in the CAG series coding for poly glutamine tracts at the 4p16.3 locus on this chromosome. Normal individuals have 6-34 repeats; patients with Huntington's disease have 36-121, (Zoghi &Orr, 2000)[10]. The gene product is huntingtin. Patients with onset at an early age or with a more severe form of the disease have a greater number of repeats. As we have already discussed in chapter 9 on the spinal cord, similar mutations involving an excessive number of CAG repeats have also been found in a number of other neurological disorders including several of the spinocerebellar degenerations and spinobulbar muscular atrophy. Other disorders such as myotonic dystrophy and Friedreich's ataxia have an excessive number of repeats in other trinucleotide sequences. Presymptomatic detection is possible but this should be done under circumstances where a full gamut of genetic counseling is available. The underlying gross pathology has been well established *(Fig.19-9)*. Marked atrophy of caudate nucleus and putamen are the pathologic and neuroimaging hallmarks. This gross pathological feature allows for diagnosis and subsequent monitoring of progression by means of CT scan and MRI scan (Fig.19-9) (Vonsattel et al, 1985; and Myers et al, 1985). In addition significant cortical atrophy also occurs as the dis-

[10] *The Huntington Disease Working Group1996 however has set the affected range as greater than 38 repeats*

[11] *These neurons are located in the matrix. Matrix neurons that appear late in development are the earliest affected, it is not until very late in the disease that patch neurons are affected.*

ease progresses. The gene product huntingtin is expressed widely throughout the brain. There are high levels in large striatal interneurons and medium spiny neurons, as well as cortical pyramidal cells and cerebellar Purkinje cells.

Additional analysis has indicated that not all cells and transmitters in the caudate and putamen are involved in the process of degeneration. The extensive studies have been reviewed' by Albin et al, 1990; Martin and Gusella, 1986; Penney and Young, 1988; Young et al 1988; and Wexler et al, 1991. The cells affected are classified as medium sized, spiny neurons that project to sites outside the striatum and which constitute approximately 90% of all striatal neurons. All contain the transmitter GABA[11]. However, different subtypes are distinguished based on the specific associated neuropeptide that they contain e.g., enkephalin, substance P. and/or dynorphin and based on the projection destinations. On the other hand other cells with interneuron functions are not affected: (a) The large, spiny acetylcholine containing interneurons and (b) the small aspiny interneurons containing the neuropeptides somatostatin and substance Y. Refer to Table 2 above.

Early in the course of the disease there is a loss of those spiny neurons which contain the GABA and enkephalin transmitters and which project to the lateral globus pallidus. At this point in the disease, the loss of these striatal inhibitory inputs to the lateral globus pallidus results in increased activity (inhibitory) of the lateral globus pallidus neurons. Since the lateral globus pallidus is the main input to the subthalamic nucleus and this input is inhibitory, an increased inhibition of the subthalamic nucleus results. As a result, the excitatory output from the subthalamic nucleus to the medial globus pallidus (MGP) and S. nigra reticularis (SNR) is reduced. The output of neurons in MGP and SNR is reduced. This output is inhibitory and destined for ventrolateral thalamus. The output of ventrolateral thalamus is no longer inhibited - and increased activity occurs in the ventrolateral to supplementary motor cortex circuit. Abnormal excessive movements due to increased activity of SMA then results as discussed above under hemichorea

The following case history provides an example of Huntington's disease.

Case 19-4: This 54-year-old right-handed white female was referred for evaluation of a movement disorder. The patient lived alone and it was difficult to obtain much of any history from the patient. She denied any neurological or psychiatric disorders except for a problem with memory during the last year. She did indicate that she had worked for 10 years as a secretary/computer operator but had been fired 10 years ago because "she did not work fast enough". She had a past history of hypertension but had not been reliable in taking her prescribed medication. The patient's son was aware that changes in emotion, personality, speech, gait and a movement disorder had been present for at least 3 years.

Family history: The patient denied any neurological family history except for a maternal uncle who had the "shakes" (actually a maternal aunt with essential tremor), additional investigation revealed that her father clearly had Huntington's disease with onset of choreiform movements at age 30, and of irritability, paranoia and gait disturbance in his early 50s. The patient's eldest daughter age 34 had been depressed for 5 years and had problems with speech and walking for a number of years.

Neurological examination: *Mental status:* the patient often avoided eye contact. Affect was usually inappropriate with laughter as the response to many questions. The overall mini-mental status score was 27/30.The only deficit related to delayed recall portion of the test 0/3 objects. *Cranial nerves:* the patient had a hyperactive jaw jerk. She had frequent facial grimacing. *Motor system:* the patient had decreased tone at wrists and elbows. As she sat she had frequent restless and at times choreiform movements of hands and feet. Gait was often "bizarre" in terms of occasional sudden movements of a leg as moved down the hall and came to a stop. These same movements occurred, as she remained standing. In addi-

tion in standing or walking, there were intermittent dystonic postures of either left or right arm. *Reflexes:* Deep tendon stretch reflexes were everywhere hyperactive but plantar responses were flexor.

Clinical diagnosis: Huntington's disease.

Laboratory data: *MRI scans of head (Fig.19-10)*: The heads of the caudate nuclei were very atrophic. Cortical sulci were wide consistent with cortical atrophy. The lateral and third ventricles were secondarily dilated. PCR testing for the CAG trinucleotide repeats of the huntingtin gene indicated one allele normal at 17; and the second excessive at 42 repeats.

Subsequent course: The patient refused any treatment for the movement disorder. According to the son, the patient's neurological status worsened to a moderate degree over the subsequent 3 years as regards speech, unsteadiness of gait, and mood swings.

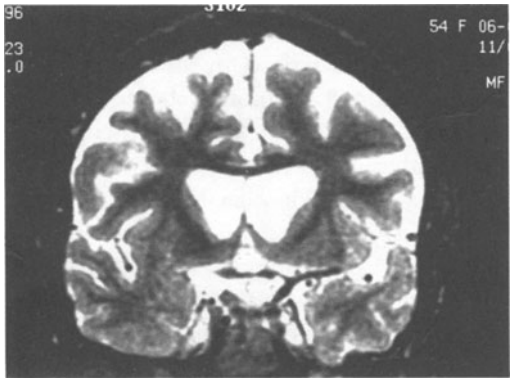

Figure19-10. Huntington's disease. Case 19-4. MRI. (T2) Refer to text. Marked atrophy of cerebral cortex and of caudate nucleus is evident in this patient with a familial history of the disorder and a significant increase in the CAG trinucleotide repeats.

Case 19-5 presented on CD ROM provides an example of a patient with Huntington's disease followed over a longer period of time. Onset occurred at age 32 with definite diagnosis of the disorder in both the father and paternal grandfather.

OTHER MOVEMENT DISORDERS ASSOCIATED WITH DISEASES OF THE BASAL GANGLIA:

1. **Double Athetosis:** Athetosis may be described as instability of posture, a relatively continuous alternation or swing between two positions. For example, in the hand, this would involve a swing from hyperextension of the fingers and thumb with pronation at the wrist to full flexion of the fingers with flexion and supination of the wrist. In a sense, there is an alternation between grasp and avoidance. Occasionally, following cerebral infarction at various age's athetosis may occur as a unilateral phenomenon admixed with hemichorea. In general athetosis occurs as a bilateral congenital phenomenon with involvement not only of the upper extremities but also of the lips, tongue and lower extremities. Double athetosis is one of the varieties of cerebral palsy discussed in chapter 18. The pathology of double athetosis is found in the putamen that may have a marbled or mottled appearance as a result of the presence of excessive numbers of abnormally situated myelin sheaths. To a lesser degree, the thalamus may also be involved. The etiology is not certain: anoxia at birth or other perinatal or prenatal pathology is considered the likely cause. Some of the cases can be related to kernicterus. A rise in bilirubin has occured in the perinatal period owing to hemolysis of red blood cells when an Rh factor or other incompatibility of blood type has been present.

2. **Hepatolenticular Degeneration (Wilson's Disease):** This is a familial disorder (recessive inheritance), which affects, to a variable degree, the liver and the central nervous system and in many cases, the kidney and bones. In the central nervous system, the most severe involvement occurs in the basal ganglia: the putamen and globus pallidus (cavitation, loss of neurons and an increased number of swollen astrocytes). To a lesser extent, the cerebellum and cerebral cortex are involved.

The basic etiology has now been clearly established as a metabolic defect. There is a deficient plasma level of the circulating copper-binding globulin, ceruloplasmin[12]. As a result, there is an excessive serum level of unbound copper. Normally, the binding of copper to ceruloplasmin prevents the passage of copper

out of the serum. In Wilson's disease, however, the increased amount of unbound copper results in passage of this metal into the brain[13], liver, and kidney (The total combined level of both bound and unbound serum copper is less than normal). In some cases, usually of early onset, the symptoms of liver involvement predominate. Wilson's disease should always be suspected when hepatocellular disease develops in a child or adolescent. In other cases, the central nervous symptoms predominate and hepatic disease may be only minor. Deposition of copper also occurs in the cornea at the scleral junction. The resultant greenish brown pigmentation is referred to as the Kaiser-Fleischer ring. This ring is almost always present when central nervous system involvement is present. Overall, 54% of cases present with neurological onset, 31% with hepatic dysfunction, 14% with psychiatric symptoms, 2% with eye symptoms, 1 to 2% with hemolytic anemia and 1% with heart disease (see Patten, 1988). In patients with hypersplenism as a complication of the hepatic disease, thrombocytopenia may develop.

The actual symptoms referable to the neurological involvement depend on the age of the patient. In early onset cases (late childhood and early adolescence) rigidity predominates. When cases begin in early adult life, movement disorders predominate (tremor and choreoathetosis). The tremor is coarse and best described as sustained postural. The term "wing beating" is often used. The copper also produces damage to the renal tubules, resulting in glycosuria and aminoaciduria. Diagnosis can be based on the clinical findings, ceruloplasmin levels, (normal levels are 200to400 mg/liter), serum copper (normal total levels are 11 to 24 umol/liter versus 3 to 10 in Wilson's disease). The most definitive study involves analysis of copper content in a liver biopsy. The CT scan and MRI may demonstrate the lesions in the putamen and globus pallidus.

The treatment of Wilson's disease is dependent on a reduction of copper in the diet or the administration of an agent that will bind copper. Penicillamine (B.B-dimethyl- cysteine) is an effective chelator of copper. It is well absorbed on oral administration and promotes the urinary excretion of copper, resulting in a decreased level of copper in the serum, central nervous system, and liver.

The following **Case 19-6** presented on CD ROM illustrates the clinical problem of hepatolenticular degeneration in a 21 year old female who developed progressive neurologic syndrome characterized by mood swings, a wing beating tremor, choreoathetosis, dysarthria, ataxia and a Kayser Fleischer ring. Her brother had died at age 16 with hepatic disease, a Kayser Fleischer ring and choreoathetosis. The patient had serum elevation of free copper and a decrease in protein bound copper and an abnormal liver biopsy. She was successfully treated with penicillamine.

3. Dystonia:

Dystonia is a hyperkinetic disorder dominated by sustained muscle contractions frequently causing twisting and repetitive movements or abnormal postures. (Jankovic & Fahn, 1988) Dystonia may be focal (43%), segmental (30%), generalized (22%)or unilateral (5%). Focal dystonias are more common than the relatively rare generalized form.

Focal and segmental idiopathic dystonias: Focal dystonia affect predominantly a single body part primarily cranial and cervical muscles. Involvement of limbs is less common. Segmental refers to dystonia involving multiple segments usually cranial and cervical. Included within this category of cervical dystonia is the relatively common entity of spasmodic torticol-

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[12] *In a few cases, ceruloplasmin levels are just within normal limits, but biliary excretion of copper is low. Absorption of copper is normal in all cases.*

[13] *The distribution of copper in the normal brain corresponds in general to the distribution of catecholamine containing neurons. Dopamine B hydroxylase is a copper containing enzyme with considerable localization to the basal ganglia. However, copper is also found in cytochrome C-oxidase that is found throughout the brain.*

lis in which sudden movements of the head to one side occur. The movement may be intermittent or sustained. Focal or segmental dystonia involving the cranial nerves is termed Meige's syndrome.

The most frequent of the cranial dystonias is blepharospasm in which there is forced eye closure. Other aspects of cranial dystonia may involve the tongue and jaw termed lingual and oromandibular. Other overlapping variants may involve the larynx-spasmodic dysphonia, or the pharynx with the latter producing difficulty in swallowing. Other focal dystonias known as occupational dystonias involve the more specific muscles of the hand and arm utilized in specific actions: writers, typists, violinists and pianists. The underlying neuropathology has never been clearly established in idiopathic cases. However, blepharospasm, or dystonia of the foot does occur in Parkinson's disease; retrocollis and oculogyric crises occur in post encephalitis Parkinson's disease. L-dopa and neuroleptic agents may both induce focal dystonias. The most effective treatment of focal /segmental dystonia is botulinum toxin injections that must be repeated every 3-4 months.

Generalized dystonia: The terms "primary generalized idiopathic dystonia" and "idiopathic torsion dystonia" have replaced the older term "Dystonia musculorum deformans". Most cases begin in childhood or adolescence and are familial. Autosomal dominant inheritance is now considered predominant in both Ashkenazi Jewish and non-Jewish families. A mutation in a gene on chromosome 9 that codes for a protein torsin A has been identified for the majority of cases of juvenile limb onset cases. Other cases which predominantly involve the cervical and cranial muscles have a different genetic background. No specific structural neuropathological abnormality has been found. However neurochemical analysis of the brain does suggest abnormalities. Anticholinergic drugs at high dosage levels may improve the symptoms of generalized dystonia in some patients. Approximately 10% of juvenile onset cases beginning in the lower extremities described by Segawa have a remarkable response to low dosage of L-Dopa (termed the L Dopa responsive variant .of progressive generalized dystonia). This is an autosomal dominant disorder coding to chromosome 14 and involving guanosine triphosphate cyclohydrolase It has therefore been recommended that all juvenile onset cases receive a trial of the L-Dopa/carbidopa combination.

Hemidystonia: Approximately 75% of patients in this group do have the history, findings or CT or MRI evidence of a contralateral neuropathology involving the striatum, usually the putamen or striato-pallido-thalamic pathway. The corticospinal pathways are not usually involved. There is then presumably an excessive input into premotor/ supplementary motor cortex resulting in the excessive contralateral movement.

4. Movement Disorders Induced By Dopamine Blocking Agents (Sethi, 2001) has provided a comprehensive review of this topic).

These agents produce frequent acute and chronic complications in psychiatric patients

1) *Acute dystonic reactions*-which occur in 2-5% of patients within hours or days after onset of therapy. Note that this complication occurs not only in psychiatric patients but also in patients receiving agents of this class as antiemetics.

2) *Acute akathisia:* acute restlessness and an inability to sit still, occurs in 20% of patients receiving dopamine-blocking agents

3) *Acute drug induced Parkinsonian syndrome* discussed above. Although symptoms may appear in any patient given sufficient amount of dopamine blocking agents to block 80% of receptors, there does appear to be a predisposition to develop symptoms at lower more therapeutic range in patients with a family history of Parkinsonism.

4). *Tardive dyskinesia and other tardive reactions.* In this context, tardive has been defined as 3 months of exposure to the agent (1 month for patients over the age of 60 years).

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[14] *In younger individuals, the limbs and trunk are more often involved.*

There may be a genetic predisposition

Tardive dyskinesias are hyperkinetic choreiform movements. Usually these are seen in the older patient involving the mouth. tongue, lips and face[14]: (oral buccolingual facial masticatory syndrome). Symptoms usually develop after 6-24 months of drug therapy and in many patients the symptoms decrease after drug withdrawal.

In another group of patients, symptoms develop only after neuroleptic drugs have been withdrawn or dosage has been reduced again after prolonged use. In one series, such withdrawal or dose reduction resulted in tardive dyskinesia in 40% of patients receiving chronic neuroleptic therapy. The presumed pathophysiology is not entirely clear,

5. **Tics:** Motor tics are sudden, brief involuntary movements resembling jerks or gestures. The patient may experience a poorly defined sensation of an irresistible urge to move prior to the movement. These movements may be simple: an eye blink, a head jerk, or a facial grimace. In some cases, the movement is more complex and patterned. resembling a compulsive act. In some cases (syndrome of Gilles de la Tourette which has autosomal dominant transmission), multiple tics occur accompanied by vocalizations. The vocalization may consist of a simple sound or may involve the use of obscene 4 letter words referring to defecation, genitalia, or sexual acts (coprolalia). In contrast to other movement disorders, voluntary effort accompanied by anxiety may serve to inhibit the occurrence of the tic or tics. Then a flurry of tics may occur after the suppression. Tics may continue to occur in sleep.

The usual idiopathic tics are common in children and may persist into adult life. Lees and Tolosa (1988), indicate one of 10 schoolboys will have idiopathic tics. Males are affected three times as often as females both in idiopathic tics and in Tourette's syndrome. No specific neuropathology has been established. Use of dopaminergic receptor blocking agents such as haloperidol or pimozide or fluphenazine may often produce a significant decrease in the clinical symptoms. In contrast, dopaminergic agents (L-dopa. bromocriptine) and amphetamines may produce an exacerbation of symptoms (Jankovic, 1987, Singer, 2000).

6: **Familial Paroxysmal Dyskinesias:** These disorders although not common are of significance because they undoubtedly occur on the basis of channelopathies. The specific genetic mutation has not yet been identified. In this regard, they are similar to the episodic ataxias discussed in chapter 20, periodic paralysis, and familial hemiplegic migraine in which the specific ion channel mutation has been identified. (See Bhatia, 2001 and Bhatia etal, 2000). In all of the syndromes, the neurological examination is normal between attacks. In the majority autosomal dominance occurs and males predominate. Two major entities may be identified (1) paroxysmal kinesigenic choreoathetosis/dyskinesias (PKC/PKD) and (2) paroxysmal dystonic choreoathetosis/ nonkinesigenic dyskinesias (PDC/PNKD). The first type (PKC/PKD) is the most common. Attacks lasting less than 5 minutes begin in childhood with multiple attacks per day induced by movement of chorea, dystonia, and ballism. The attacks are significantly reduced by the administration of low doses of the anticonvulsant, carbamazepine that has action on the sodium/potassium channel. Several families have mapped to the peri centromeric region of chromosome 16, where a group of ion channel genes are present. The second type (PDC/PNKD) begins in infancy or childhood with infrequent attacks that last from 10 minutes to 6 hours and are predominantly dystonic. The attacks are induced by stress, fatigue, alcohol and caffein. In a number of families (Jarman, etal, 1997) the genetic defect has been mapped to chromosome locus 2q33-q35, an area where a number of ion channel genes are located. Paroxysmal exercise induced dyskinesia (PED) is a third less common variety.