Movement Disorders
Part I

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Introduction

- **The term "movement disorders"** refers to a group of neurological conditions that cause abnormal movements.
- **Tow Major categories:**

1. Hypokinetic movement disorders, and
2. Hyperkinetic movement disorders

- **Anatomy:** basal ganglia and related nuclei

Historical Background

Extra-pyramidal system and extra-pyramidal syndrome.

- These terms were frequently used in the past to refer to the pathological basis of movement disorders in an attempt to make a clear distinction from the pyramidal system.

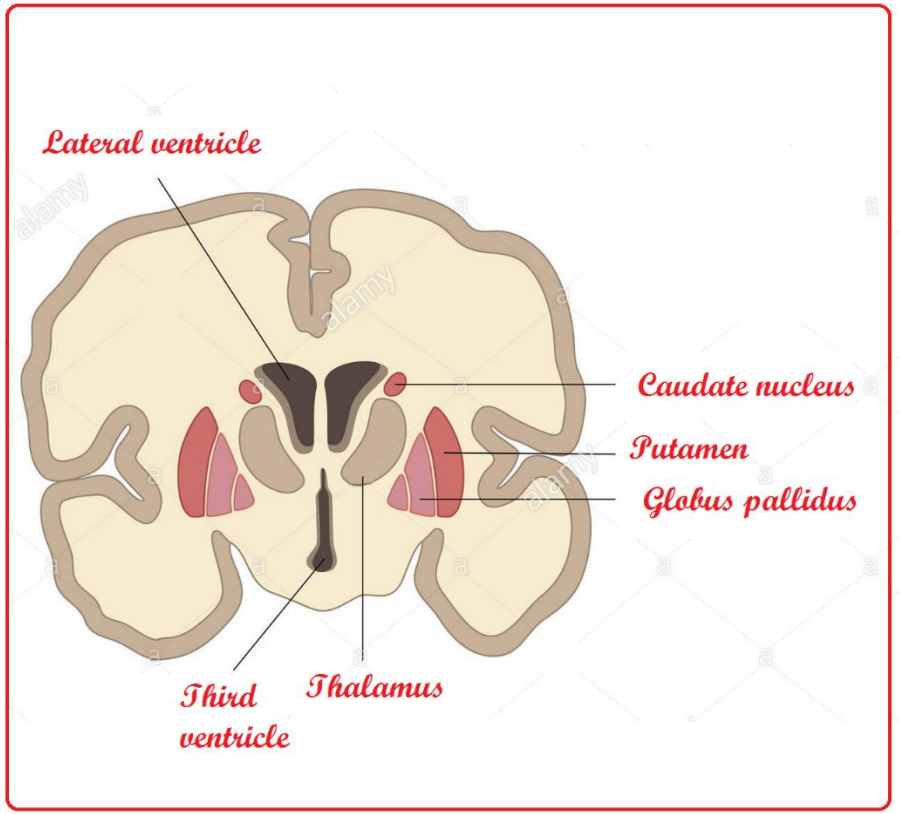
These terminologies are not absolutely accurate.

- Extrapyramidal is more a functional concept than a purely anatomical one.
- There are many other motor pathways that are anatomically extrapyramidal and yet not necessarily related to the basal ganglia, including cerebellar, reticulospinal, and vestibulospinal pathways.

At present, these terms are seen as obsolete and misleading by many authors.

Basal Ganglia

- **The term basal ganglia typically refers to nuclei embedded deep in the brain hemispheres:**
  - **Caudate nucleus,**
  - **Putamen and**
  - **Globus pallidus**.
- **Whereas related nuclei consist of structures located in the:**
  - Diencephalon (**subthalamic nucleus**),
  - Midbrain (**substantia nigra**), and
  - Others.



N.B. Lentiform nucleus = Putamen + Globus pallidus

Striatum = caudate nucleus + putamen

Connections of the Basal Ganglia

The basal ganglia and related nuclei can be broadly categorized as:

1) **Input Nuclei:**

– Are those structures receiving incoming information from different sources, mainly cortical, thalamic, and nigral in origin. The caudate nucleus and the putamen are considered input nuclei.

2) **Output Nuclei:**

– Are those structures that send basal ganglia information to the thalamus and consist of the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulate (SNr).

3) **Intrinsic Nuclei:**

– Are those located between the input and output nuclei in the relay of information. Such as the external segment of the globus pallidus (GPe), the subthalamic nucleus and the substantia nigra pars compacta (SNc).

Neurotransmitters in Basal Ganglia

- **Although neurotransmitters** relate to all neuroanatomical discussions, they are of particular interest in relation to the **basal ganglia** and their function.
- **Much of the basic understanding of neurotransmitters** came from studies of human basal gangliar disorders.
- **Neurotransmitters in Basal Ganglia are:**
  - Dopamine.
  - Acetylcholine.
  - Gamma-Aminobutyric Acid (GABA).
  - Glutamate.
  - Norepinephrine.
  - Serotonin (5-hydroxytryptamine [5-HT])

The Function of Basal Ganglia

I. **Motor Control:** The basal nuclei use proprioceptive input from the periphery to equate the movement patterns produced by the cerebral cortex with the actual movement, allowing a continuous refinement of the movement.

II. **Muscle tone.**

III. **Cognitive functions.**

Definitions

- **Tremor:** To-and-fro oscillation around a joint
- **Chorea:** Involuntary rapid and irregular movements
- **Dystonia:** Twisting, sustained posture
- **Athetosis:** Twisting contorsion, a form of dystonia, usually associated with birth injury or cerebrovascular accidents
- **Ballismus:** Violent chorea, involving large muscle groups
- **Myoclonus:** Shocklike jerks, focal or generalized
- **Stereotypy:** Repetitive movement, simple or complex
- **Tics:** Stereotypy that typically involves face, neck, and vocal apparatus more than other body parts

CLASSIFICATION OF MOVEMENT DISORDERS

Classification of Movement Disorders

I. Hypokinesias

- Primary Parkinsonism (Parkinson Disease).
- Secondary Parkinsonism.
- Parkinsonism plus syndromes.

II. Hyperkinesias

- Chorea.
- Dystonias.
- Athetosis.
- Hemiballismus.
- Tics.
- Myoclonus.

Parkinson Disease

Parkinson disease (PD)

- **Parkinson disease (PD)** is one of the most prevalent neurologic diseases, affecting about 1% of people over the age of 60 and resulting in worsening impairment that can be delayed but not stopped by treatment.
- **The lack of pigmented dopaminergic neurons** in the substantia nigra pars compacta, as well as the presence of **Lewy bodies and Lewy neurites**, are the two most frequent neuropathologic findings in Parkinson's disease.
- **The incidence and prevalence of Parkinson disease** increase with age, and the average age of onset is approximately 60 years.
- **Onset in persons younger than 40 years** is relatively uncommon.
- Parkinson disease is about **1.5 times more common in men** than in women.

ETIOLOGY of Parkinson Disease (PD)

Although the etiology of Parkinson disease is still unclear, most cases are hypothesized to be due to a combination of genetic and environmental factors.

1. Environmental risk factors.

Environmental risk factors commonly associated with the development of Parkinson disease include use of pesticides, living in a rural environment, consumption of well water, and exposure to herbicides..

2. Interference with mitochondrial function.

Several individuals were identified who developed parkinsonism (over several weeks) after self-injection of **1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).** The metabolite of MPTP accumulates in mitochondria and interferes with its function. A chemical resemblance between MPTP and some herbicides and pesticides suggested that an MPTP-like environmental toxin might be a cause of Parkinson disease.

3. Oxidative stress.

The oxidation hypothesis suggests that free radical damage plays a role in the development or progression of Parkinson disease.

4. Genetic factors

Genetic factors in Parkinson disease appear to be very important when the disease begins at or before age 50 years.

PATHOLOGY of Parkinson Disease

Pathological findings of Parkinson's disease (PD) include:

- **Depigmentation and neuronal loss in the substantia nigra (SN).**

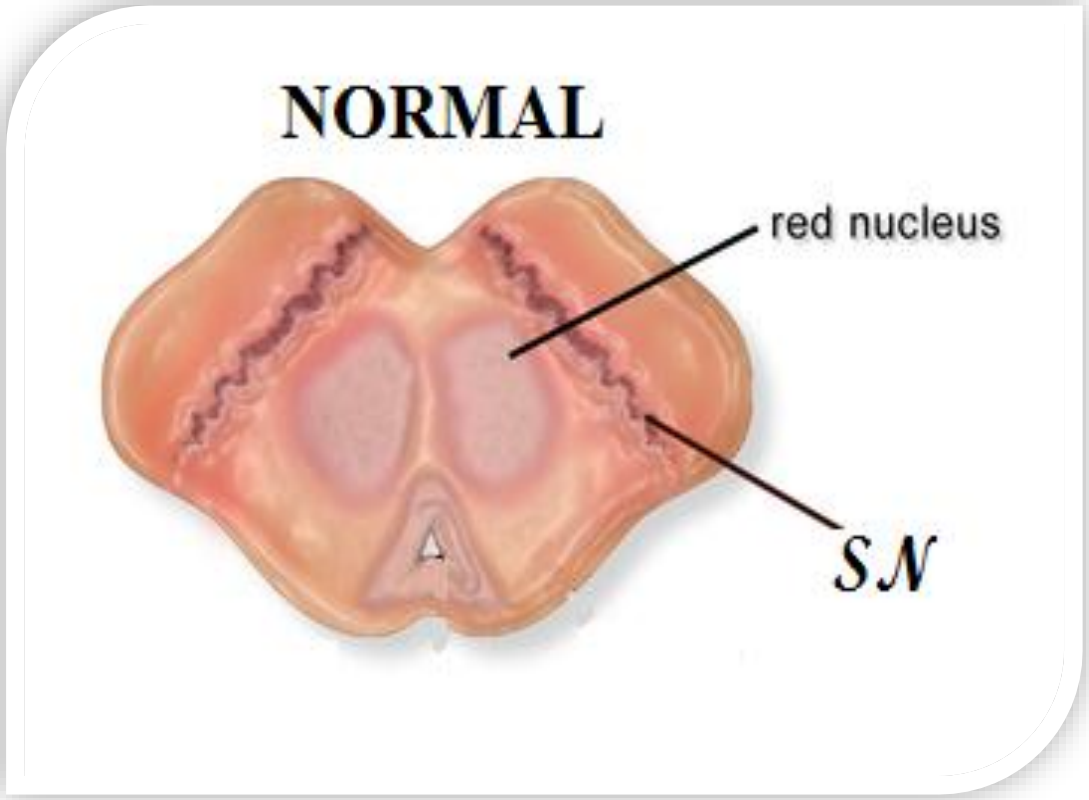
  Because the degenerating cells in the SN normally synthesize the neurochemical dopamine, the pathophysiological hallmark of PD is dopaminergic underactivity at the site of these cells' axonal projection—that is, the striatum (caudate nucleus and putamen)

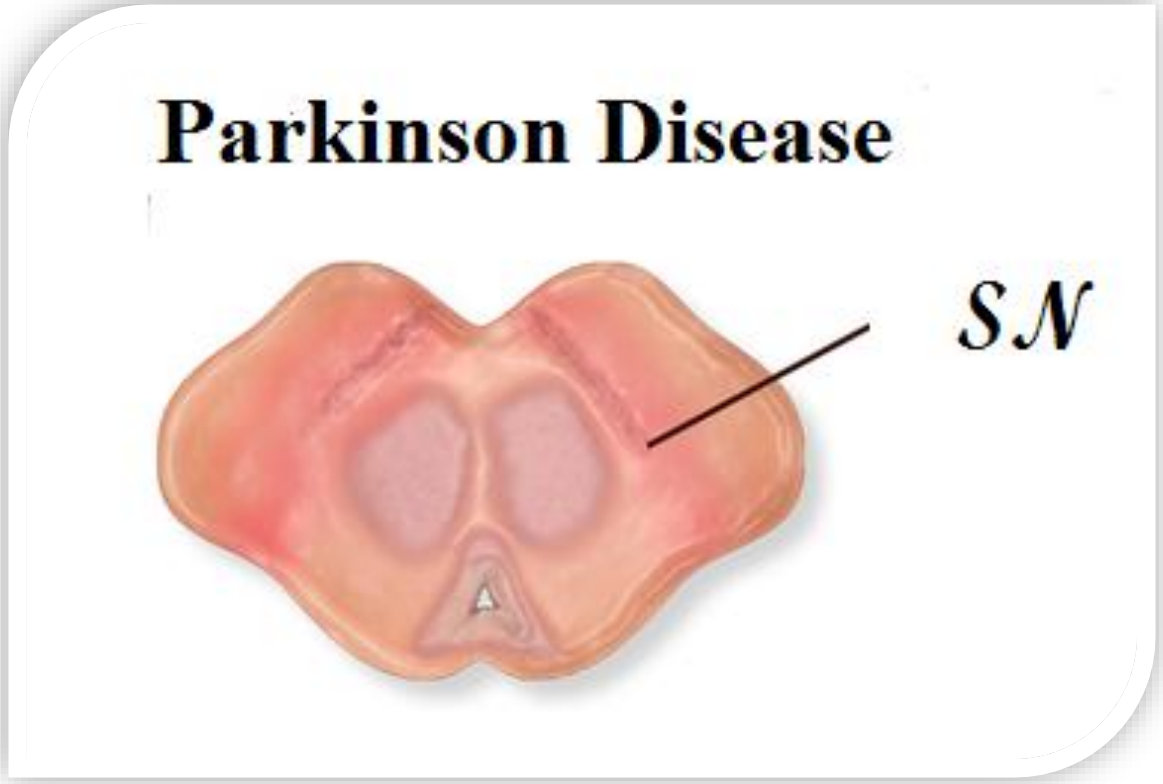
- **The presence of Lewy bodies.**

  Lewy bodies are eosinophilic inclusions. The mechanism of Lewy body formation and cell death in PD is not known, but the degenerative process is highly localized at the beginning of the illness (SN). Besides the SN they are also present in the basal ganglia, cortex, brain stem, and spinal cord. Although characteristic of PD, Lewy bodies are also seen in Alzheimer's disease and ataxia-telangiectasia.

- **It is estimated that 60% to 85% of nigral neurons and striatal dopamine** is lost prior to the development of PD symptoms.

PATHOLOGY of Parkinson Disease





CLINICAL PRESENTATION of Parkinson Disease

- **The cardinal features of PD include:**
  1) Bradykinesia
  2) Rigidity
  3) Rest tremor
  4) Postural instability.
- **In addition to:**
  - A good response to levodopa or dopamine agonists.
  - Asymmetrical presentation.

Bradykinesia

- **Bradykinesia (slowness of movement) or hypokinesia (poverty of movement)** is manifested by slowing of activities of daily living, such as dressing, feeding, brushing teeth, and bathing.
- **Other features of bradykinesia or hypokinesia include:**
  - Masked facies,
  - Hypokinetic dysarthria (soft slow monotonous speech),
  - Drooling, and
  - Slow and small handwriting (micrographia).
- **On examination,** rapid alternating movements are performed slowly and with decreasing amplitude.
- **In more advanced stages, frequent arrests of movement, called "freezing" or "motor blocks,"** may be seen. These are manifested by start hesitation such as an inability to initiate gait or other movements, and freezing when turning or walking through narrow passages

Rigidity

- **Rigidity refers to** an increase in resistance to passive movement about a joint.
- **The resistance can be either** smooth (lead pipe) or oscillating (cogwheel).
- **Some patients may describe stiffness in the limbs**, but this may reflect bradykinesia more than rigidity.
- **Rigidity is usually tested by** flexing and extending the patient's relaxed wrist and can be made more obvious by having the patient perform voluntary movements, such as tapping, with the contralateral limb.

Tremor

- **The rest tremor usually consists** of an oscillatory movement of 4 to 7 Hz frequency that involves the limbs, jaw, face, and tongue but almost never involves the head.
- **The tremor of the forearm** is often pronating and supinating, whereas the hand tremor has been described as “pill-rolling”.
- **Early in the course of the disease,** the tremors and other signs are usually asymmetrical but eventually become bilateral.
- **Most patients also have a postural tremor,** which is evident with the hands extended or in action. This postural tremor probably represents re-emergence of rest tremor or coexistent essential tremor.
- **Head tremor, however, is rare in parkinsonism,** and its presence should suggest the diagnosis of essential tremor.

Postural Instability

- **Postural instability** often occurs in the more advanced stages of the disease.
- **Impairment of the postural reflexes** is responsible for the falls that are frequently experienced by parkinsonian patients.
- **Parkinsonian Gait often reflects** a combination of bradykinesia, rigidity, and postural instability.
- **Festinating Gait:** a gait in which the patient involuntarily moves with short, accelerating steps, with the trunk flexed forward and the legs flexed stiffly at the hips and knees.

Non-motor symptoms of PD

- **Before motor symptoms appear and the diagnosis is made**, patients may have a variety of pre-motor symptoms. These may start as early as 10 or more years before the diagnosis.
- **These symptoms are:**
  - **Depression and anxiety.**
  - **Dementia.**
  - **Psychosis.**
  - **Orthostatic hypotension.**
  - **Sexual dysfunction.**
  - **Gastrointestinal dysfunction.**
  - **Sialorrhea.**
  - **Sweating**
  - **Sleep fragmentation and insomnia**

DIFFERENTIAL DIAGNOSES of Parkinson Disease

1) Essential Tremor.
2) Secondary (acquired, symptomatic) parkinsonism
   - Infectious: postencephalitic.
   - Drugs: dopamine receptor–blocking drugs (antipsychotic, antiemetic drugs)
   - Toxins: MPTP, CO, Manganese, Hg, cyanide
   - Vascular: multi-infarct, Binswanger's disease
   - Trauma
3) Parkinsonism-plus Syndromes
   - Progressive supranuclear palsy (PSP)
   - Multiple system atrophy (MSA)
   - Cortical-basal ganglionic degeneration (CBGD)
4) Other of parkinsonism. e.g.
   - Huntington's disease (HD)
   - Wilson's disease (WD)

EVALUATION of Parkinson Disease

- **When all four cardinal characteristic signs are present,** and the patient shows a good response to dopaminergic therapy, the diagnosis is straightforward.
- **Part of the workup usually includes a magnetic resonance imaging (MRI)** scan searching for evidence of alternate diagnoses such as stroke, intoxications, or other degenerative disorders.

Treatment of Parkinson Disease

- **Unfortunately, no effective neuroprotective treatment** for PD is available today.
- Several decades after levodopa came in widespread clinical use for PD, this drug is still a cornerstone in our treatment of motor symptoms in PD.
- **It is important to treat each patient** individually.
- **Focus should be put on which symptoms**—motor as well as non-motor—that are most bothersome to the patient in each stage of the disease.

Treatment of Parkinson Disease

A. Pharmacological Therapy.

1. **Dopaminergic drugs.**
    1. **Levodopa**. carbidopa-levodopa combination (25/100, 25/250, or 10/100).
    2. **Dopamine agonist.** Bromocriptine, Pergolide and Pramipexole.
2. **Anticholinergics.** Trihexyphenidyl and Biperidine
3. **MAO-B (monoamine oxidase B) inhibitors.** Selegiline and Rasagiline.
4. **COMT (Catechol-O-methyltransferase) inhibitors.** Entacapone.
5. **Amantadine.**

B. Non- Pharmacological Therapy.

- **Deep Brain Stimulation (DBS)**

Pharmacological Therapy.

- **Levodopa** is the most effective treatment for the symptoms of PD, but the chronic use of levodopa is complicated by the development of two motor problems, namely, fluctuations and dyskinesias in approximately half the patients.
- **Dopamine agonists (agents that stimulate dopamine receptors):,** when introduced in early stages of PD, dopamine agonists provide adequate symptomatic benefit and delay the need for levodopa, thus minimizing the risk of levodopa related dyskinesias and motor fluctuations.
- **Anticholinergic agents** can be used for tremor not adequately controlled with dopaminergic medication, but these are not first-line drugs, because of their limited efficacy and the possibility of neuropsychiatric side effects.
- **MAO-B inhibitors** plays an important role in dopamine metabolism in the brain. It can be used as monotherapy in early stage or in combination with levodopa.
- **Catechol-O-methyltransferase (COMT) inhibitors:** By limiting dopamine metabolism, they increase levodopa bioavailability, reduce motor fluctuations, and allow a reduction in daily levodopa dosage.
- **Amantadine** is an antiviral agent that has antiparkinsonian activity. Its mechanism of action is not fully understood, but amantadine appears to potentiate CNS dopaminergic responses.

Treatment strategies

- **For Patients with No Clinically Significant Disability**
  - Consider MAO-B (monoamine oxidase B) inhibitors.
- **For Patients with Clinically Significant Disability**
  - Young and tremor-predominant disease: anticholinergic drugs, amantadine, MAO-B inhibitors.
  - Older patients: amantadine, dopamine agonists
  - Elderly patients or cognitively impaired: levodopa
- **Above Patients with Progressive Disability**
  - Add levodopa (if not added).
  - Once on levodopa, if prolongation of effect is needed, add MAO-B inhibitors if patient is not currently taking it or, COMT inhibitors.

- **Patients with Specific Complications**
  - Patients on levodopa who develop motor fluctuations:
    - More frequent, small doses of levodopa.
    - MAO-B inhibitors or COMT inhibitors.
    - Consider deep brain stimulation.
  - Patients with unremitting tremor
    - Deep brain stimulation
  - Patients with hallucinations
    - Reduce medications. Stop all drugs except levodopa.
    - Consider (atypical antipsychotics) Clozapine or Quetiapine,

Secondary
(Acquired, Symptomatic)
Parkinsonism

Secondary (Acquired, Symptomatic) Parkinsonism

- Post-encephalitic Parkinsonism.
- Drug-induced Parkinsonism.
- Toxin-induced Parkinsonism
- Vascular Parkinsonism
- Trauma

Post-encephalitic Parkinsonism

- **Post-encephalitic parkinsonism (PEP)** is believed to be caused by a viral illness which causes degeneration of the nerve cells in the substantia nigra, resulting in clinical parkinsonism.
- **Although common during the period of the First World War**, PEP has become a rare entity today. PEP was recognized globally for the first time during the epidemic of encephalitis lethargica (EL) in Europe and other countries between 1915 and 1930.
- **EL was an acute illness, which was characterized by** fever, somnolence and ophthalmoplegia and sometimes other focal signs such as hemiplegia or aphasia.

Drug-induced Parkinsonism

- **Drug-induced parkinsonism (DIP)** is defined as the appearance of parkinsonism on treatment with pharmaceutical agents. Most of those drugs impair dopamine function.
- **Initially, it was considered to be an exclusive side effec**t of first-generation neuroleptics that block D2 receptors.
- **Other agents,** such as calcium channel blockers, gastrointestinal prokinetics (e.g. antiemetics), antiarrhythmics, and antidepressants, have also been implicated in DIP.

Toxin-induced Parkinsonism

- **MPTP.**
- **Carbon Monoxide (CO)**
- **Manganese**
  - Manganese is a basal ganglia toxin associated with Parkinsonism. Manganese exposure can occur in working with steel, battery manufacturing, intravenous synthetic drug use, and long-term parental nutrition. Does not consistently respond to L-dopa therapy.
- **Cyanide**
- **Organophosphates**

Vascular Parkinsonism

- **Parkinsonism occurring in patients with cerebrovascular,** mainly lacunar, disease has been clearly documented in cases without autopsy evidence of Lewy bodies.
- **Clinical patterns taking 3 forms are described:**
  1) **Gait difficulty, symmetrical rigidity and absent tremor**, mainly in patients with history of hypertension, often referred to as **Lower Body Parkinsonism**, which may be the most common form;
  2) **A more insidious onset of parkinsonism** with reasonable similarity to idiopathic PD, and some indication of a dopaminergic therapy response, and
  3) **Acute-onset parkinsonism**, due to vascular lesions in the basal ganglia, which is relatively rare.

Parkinsonism-Plus Syndromes

Parkinsonism-Plus Syndromes

1. **Progressive Supranuclear Palsy (PSP).**
   - PSP shares some clinical features with PD, such as bradykinesia, rigidity, dysarthria, and dementia. However, PSP patients rarely exhibit tremor and usually have much more profound postural instability.
2. **Multiple System Atrophy (MSA).**
   - The hallmark features of MSA are parkinsonism that is poorly responsive to levodopa therapy and varying degrees of autonomic, cerebellar, and pyramidal dysfunction.
3. **Corticobasal Degeneration (CBD).**
   - Cortical signs, asymmetrical rigidity, bradykinesia, postural and action tremor, and marked dystonia, usually predominantly in one upper extremity

Tremor

Tremor

- **Tremor** is an involuntary, rhythmic, oscillatory movement of a body part.
- **It is the most common movement disorder** encountered in primary care.
- **The diagnosis of tremor is based on** clinical information obtained from the history and physical examination.
- **The most common tremors** are enhanced physiologic tremor, essential tremor, and parkinsonian tremor.

Classification of Tremors

Tremor type	Description
Resting	**Occurs in a body part that is relaxed and completely supported against gravity.**
Action	**Occurs with voluntary contraction of muscle.**
Postural	Occurs when the body part is voluntarily maintained against gravity.
Isometric	Occurs as a result of muscle contraction against a rigid stationary object
Kinetic	Occurs with any form of voluntary movement.
Intention	Subtype of kinetic tremor amplified as the target is reached.

Etiological Categories Of Tremor

- **Enhanced Physiologic Tremor**
- **Essential Tremor**
- Parkinsonism
- Cerebellar Tremor
- Dystonic Tremor
- Orthostatic Tremor
- Primary Writer’s Tremor
- Asterixis

Enhanced Physiologic Tremor

- **All persons have** an asymptomatic physiologic tremor.
- **It is a low-amplitude, high-frequency** tremor at rest and during action.
- **This tremor can be enhanced by several factors, e.g.:**
  1) Stress, fatigue, anxiety, emotion
  2) Endocrine: hypoglycemia, thyrotoxicosis, pheochromocytoma, adrenocorticosteroids
  3) Drugs and toxins: b-agonists, amphetamines, lithium, tricyclic antidepressants, neuroleptics, theophylline, caffeine, valproic acid, alcohol withdrawal, mercury, lead, arsenic, others
- **Patients with a tremor that comes and goes** with anxiety, medication use, caffeine intake, or fatigue do not need further testing.

Essential Tremor (ET)

- **ET is the most common** pathologic tremor.
- **It is an action tremor.**
- **ET** has been described as postural, kinetic, and even as a sporadic resting tremor.
- **ET** is most obvious in the wrists and hands when patients hold their arms in front of them; however, it can also affect the head, lower extremities, and voice.
- **It is generally bilateral**, present with different tasks, and interferes with activities of daily living.
- **ET diminishes with** rest, ethanol, b-noradrenergic blockers (usual dose, propranolol 80 to 240 mg/day), primidone (25 to 750 mg/day), and benzodiazepines.
- **In addition, some patients** may benefit from gabapentin, and topiramate.

تمت بحمد الله

Thank you