Parkinson Disease

History of Presenting Illness
- Will typically be ONE –SIDED
- Will eventually spread to other limbs and trunk

ASK ABOUT:
- Stiffness and slowed movements: Cogwheel rigidity
- Tremor or shaking at rest ( ! PILL-ROLLING TREMOR ! )
- Difficulty getting out of a chair or rolling over in bed
- Frequent falls or tripping
- Difficulty walking
- Memory loss
- Posture shifts forward into stoop
- Speech changes (eg, whispering, rapid speech)
- Slower handwriting
- Drooling (“sialorrhoea”)
- Ask: when did they stop driving? (a good indicator of progression)

CLASSIC TRIAD:  
- TREMOR
- RIGIDITY
- BRADYKINESIA

Findings on Examination
1. Look at the GAIT:
   - Shuffling.
   - Festinating (staggering forward)
   - No arm movement
   - Difficulty stopping
   - Posture is stooped forward

2. Kinesia Paradoxaica:
   - Fast movements are OK
   - Slow movements are absent

3. Tremor:
   - Characteristic pill-rolling 5 hertz movement, usually assymmetrical
   - Disappears with voluntary movement (i.e a resting tremor)

4. Tone
   - Cogwheel Rigidity: especially when distracted
   - Reflexes are NORMAL !

5. Face
   - Mask-like face
   - Absence of blinking, the glassy “parkinsonian stare”
   - Seborrhea (feel the oily forehead)
   - Weakness of upward gaze is CHARACTERISTIC of Parky’s

6. Speech
   - Monotonous, Rapid and whispering,
   - “Palilalia” (repetition of last syllable)

7. Autonomic features:
   - Orthostatic Hypotension will be present.
   - Slowed enteric motility and constipation
   - Urinary retention and incontinence

8. Dysphagia
**Differential Diagnoses**

- Progressive supranuclear palsy
- Multisystem atrophy
- Shy-Drager syndrome
- Olivopontocerebellar atrophy
- Wilson disease
- Drug-induced Parkinsonism (neuroleptics, metoclopramide, reserpine)
- Toxin-induced Parkinsonism (methyl-phenyl-tetrahydropyridine [MPTP], manganese, carbon monoxide, carbon disulfide, cyanide)
- Metabolic causes (anoxic, hypothyroidism, hypoparathyroidism)
- Multiple strokes
- Subdural hematoma
- Basal ganglia tumour
- Normal pressure hydrocephalus
- Postencephalitic PD
- Vascular PD (lesions of the caudate, putamen, globus pallidus, or brain stem)
- Creutzfeldt-Jakob disease
- Structural PD (brain tumor compromising or invading the basal ganglia)

**Tests and Investigations**

Diagnosis of PD is based almost entirely on results of the HISTORY and PHYSICAL EXAM. !!! SHOULD BE ABLE TO DIAGNOSE IT FROM THE WAITING ROOM !!!

In atypical cases, lab investigations may be performed to exclude other causes of Parkinsonism.

- **Plasma ceruloplasmin and copper** to exclude Wilson disease
- **Thyroid-stimulating hormone** (TSH) levels if hypothyroidism is suggested
- **Toxin screening** if clinically indicated by a history of possible exposure

**MRI may suggest the following:**

- Normal pressure hydrocephalus (large ventricles)
- Subdural hematoma
- Tumor
- Multiple infarcts
- Multisystem atrophy (eg, decreased T2 signal in the striatum)
- Progressive supranuclear palsy (eg, midbrain atrophy)

**Disease Definition**

*Parkinson's disease is a chronic, progressive extrapyramidal disorder, which results from the destruction of neurones in the striata nigra pars compacta.*

**Management:**

**SOFT, FLUFFY MANAGEMENT:**

- **Physiotherapy**
  - includes measures to decrease rigidity and increase range of motion (eg, stretching)
  - to improve postural control, endurance, mobility, and gait, eg. marching to the beat of a metronome
  - ambulation aids (eg, walkers, canes)
  - how to fall safely and get up from the floor

- **Occupational Therapy:**
  - exercises to improve upper extremity fine motor skills and dexterity
  - , functional training in self-care and ADL,
  - dressing aids (eg, reachers, sock aid), railings, grab bars, etc.

- **Speech Therapy:**
  - to improve the quality of voice in patients with hypokinetic dysarthria.
  - better breath and rate control, as well as improved articulation and better volume.
  - Beneficial effects of the therapy do not seem to persist after it has been discontinued.

**Dysphagia** tends to occur later in the disease process and can lead to drooling, aspiration, malnutrition, and inability to ingest medications. Speech therapy interventions can include

- positioning the neck in flexion,
- teaching a double swallow technique,
- using smaller amounts of food,
- modifying the patient's diet and incorporating thickened liquids.
SURGICAL INTERVENTION:

Destructive therapy

- **Ventral intermediate nucleus thalamotomy**
  - Only for drug-resistant PD; and usually only fixes the tremor
- **Pallidotomy**
  - used for advanced PD; especially those who have L-dopa therapy complications
  - idea is to kill the globus pallidus to disinhibit the motor thalamus and cortical motor areas
- **Chronic deep brain stimulation**
  - In the ventral lateral thalamic nuclei (performed to decrease tremor with a good response in 80-85% of patients),
  - In the globus pallidus (for bradykinesia, gait, speech, drug-induced dyskinesias),
  - in the subthalamic nucleus (for bradykinesia, rigidity, tremor, gait/posture).
  
  **Downside:** a 12 hour operation in a stereotactic frame.

PHARMACOLOGICAL INTERVENTION:

NEUROTRANSMITTER REPLACEMENT THERAPY

**GOAL:** to enhance dopaminergic neurotransmission as nigrostriatal fibres degenerate.

**BUT:** more dope in the Nigrostriatal pathway means MORE DOPE EVERYWHERE ELSE thus overexcitation of other brain areas; THUS \( \Rightarrow \) characteristic side effects; (eg. the mesocortical and tuberinfundibular dopaminergic systems)

**i. Levodopa**

- the metabolic precursor of dopamine
- DOPA decarboxylase converts L-DOPA into dopamine
- Oral L- DOPA can cross the blood brain barrier via aromatic amino acid transporters

**BUT:** ORAL ADMIN = ONLY 1% penetrates into the brain !! PISS POOR !!

WHY? DOPA decarboxylase @ periphery metabolises all of it USELESSLY into peripheral dopamine.

**THUS:** give together with a DECARBOXYLASE INHIBITOR (which doesn’t cross the BBB)

This way there is no L-dopa metabolism outside the CNS, and in the CNS the decarboxylation is uninhibited.

Examples are benzerazide or carbidopa.

**effectiveness and duration of action of l-DOPA diminishes in parallel with neurodegeneration.**

**ii. Inhibitors of dopamine breakdown**

- **Monoamine oxidases** convert dopamine into inactive metabolites.
  - MAOB is the predominant form of MAO in the brain And it is concentrated in the vicinity of dopaminergic nerves.
  - Selegiline (deprenyl) inhibits MAOB and improves the therapeutic efficacy of L-DOPA.
  - Although controversial and unproven, it has been hypothesised that selegiline might slow the progression of dopaminergic degeneration in Parkinson's disease possibly due to inhibition of formation of toxic metabolites by MAOB.
  - Catechol-O-methyl transferase (COMT) is also involved in breakdown of extrasynaptic dopamine.
  - COMT inhibitors are currently being investigated in clinical trials for use in Parkinson’s disease.

**iii. Direct dopamine receptor agonists**

- THESE DRUGS MIMIC DOPAMINE ACTION AT POSTSYNAPTIC RECEPTORS!
  - can be of benefit in combination with L-DOPA.
  - These include Bromocriptine, Pergolide and Apomorphine

**iv. Amantadine**

Although the mechanism underlying the therapeutic benefits of this antiviral drug in Parkinson's disease is not clearly established, it seems likely that it enhances release of dopamine from nerve terminals.

**v. Dopaminergic neuron replacement.**

Dopaminergic neurones from human fetal brain have been transplanted into patients with some success. \( \Rightarrow \) DOES NOT ALWAYS WORK! New neurones sure are dopaminergic, …but THEY ARENT UNDER ANYBODY’S CONTROL
Prognosis: Disease Is PROGRESSIVE

L-DOPA does NOT halt the degenerative process; in fact it may accelerate it. Generally, progression is slowest if the dominant symptom is unilateral tremor. Progression is FASTEST if the presenting symptom is gait or posture disturbance. ALSO the disease progresses more quickly in older patients.

Epidemiology

Signs of an extrapyramidal disorder found in 15% of people 65-75, and 50% of over-85s. Incidence of Parkinson Disease = 10-20 cases per 100,000 population per year. Prevalence = 100-200 cases per 100,000 population.
- MEAN AGE OF ONSET = 61 years
- 1 in 10 over-85s has PD

Mortality/Morbidity: Prior to introduction of levodopa,
- PD caused severe disability or death in 25% of patients within 5 years of onset,
- in 65% in the next 5 years,
- in 89% of those who survived 15 years
- With introduction of levodopa, mortality rate has dropped approximately 50%, and longevity has been extended by several years

Race: including South African and Nigerian blacks have lower incidence...However, blacks living in Mississippi seem to be affected to the same degree as the white population. Lower incidence also has been reported in Asian populations, but not in Asian Americans

Sex: The male-to-female ratio in PD is 3:2.

Prevalence of PD increases with age.

Genetics

!! increased incidence in the monozygotic twins of PD sufferers
- First-degree relatives of patients are twice as likely to develop the disease as controls.
- Approximately 5% of parkinsonian patients have a familial form of the disorder.

Three genes for the parkinsonian phenotype have recently been identified:
- Two types of Alpha-synuclein mutation:
  normally a vesicle-forming protein that releases dopamine
- Deletions of the parkin = autosomal recessive parkinsonism;
  (parkin is a protein expressed in the substantia nigra.)
- missense mutation of the ubiquitin carboxy-terminal hydrolase L1 gene

Drug-Induced Movement Disorders: Michael J. Fox Syndromes

drug-induced movement disorders (DIMD) are most commonly associated with antipsychotic drugs, but can also be caused by antidepressant drugs, stimulants, alcohol and mood stabilising drugs. In neurology, dopamine agonists and anticonvulsants are commonly implicated.

Tricyclic antidepressants are often a cause of hand tremor and myoclonic jerks.

Occasional anecdotes of dyskinesia and dystonia have been reported with these drugs.

serotonin-specific reuptake inhibitors (SSRI) are associated with peripheral tremor, which is usually a mild action tremor, but becomes coarse when toxic levels are reached. Lithium produces myoclonus less often, and is also known to exacerbate the parkinsonian side effects of neuroleptics.

Stimulants are associated with stereotypies, dyskinesia, tremor, dystonia and myoclonus.

Anticonvulsants (e.g. phenytoin, carbamazepine, etc.) are associated with dyskinesia, tremor and tics, in toxic doses will produce nystagmus, ataxia and dystarthis.

Anticholinergics can exacerbate dyskinesias.

Dopamine agonists (L-dopa, bromocriptine, pergolide) are commonly associated with chorea, dystonia and myoclonus, especially in the late stages of Parkinson's disease.

Calcium channel antagonists cause mild extrapyramidal effects.

Cigarette smoking appears to be a protective factor against Parkinson Disease!
Motor control, planning and execution

NEEDS CONTINUED FEEDBACK FROM SENSES to make INFLIGHT CORRECTIONS; i.e a “sensorimotor” system

WHY? : Most minor movements change the centre of gravity, thus whole body must respond.
- Eg. posture, walking, gross movement

BUT: many movements are too rapid to rely on feedback regulation, eg. returning a tennis serve.

THUS: regulation of “Ballistic” movements needs FEED-FORWARD regulation, improved by motor learning
- Eg. speech, musical performance, riding a bike

THERE ARE HIERARCHICAL LEVELS OF CONTROL:

**Lowermost:** SPINAL AND BRAINSTEM MOTOR NEURONS
- mediate movement execution.
- ALSO at this level are the interneuronal pools which mediate simple and complex reflexes,
  - e.g., withdrawal, locomotion, lateral and vertical gaze.
- THESE REFLEX ARC INTERNEURONS ARE UNDER CONTROL FROM ABOVE

**Intermediate level:** BRAINSTEM CORTEX AND CEREBELLUM
- (primary motor cortex, red nucleus, cells of reticulo spinal and vestibulospinal pathways)  
  - TWO FUNCTIONS:
    - movement tactics, the trajectory of your limbs and the sequence of muscle contractions
    - motor learning, critical for the feed-forward regulation of ballistic movements that occur too rapidly to be regulated by feedback.

**Highest level:** PREMOTOR, PREFRONTAL, Post. PARIETAL and BASAL GANGLIA
- These forebrain regions organise the goals of the voluntary movement, and the movement strategy to achieve best those goals, in the context of a “mental image” of the body and its relationship to its environment.

**emotional motor system** = major impact on sensorimotor functions at each of the levels described above

UPPER and LOWER MOTOR DISTINCTION

Two other brain regions involved in the control of movement are the cerebellum and the basal ganglia.

"lower" motor neurons are at the spinal cord: form synaptic contacts directly with the skeletal muscle.
- in the brain stem they form two distinct columns of nuclei,
  - general somatic efferent (GSE)
  - special visceral efferent (SVE)
- in the spinal cord organized as longitudinal columns @ ventral horn
  - medial columns innervate axial musculature and proximal muscles of the limbs,
  - lateral columns innervate distal limb muscles

"upper" motor neurons are at cerebral cortex/brain stem . control the lower motor neurons by:
- Descending cortical pathways (corticospinal and corticobulbar tracts)
- Descending brainstem pathways (rubrospinal tract, tectospinal tract, and reticulospinal tracts)
- VENTROMEDIAL: control balance and posture (antigravity, extensor tone).
- LATERAL: control distal limb muscles.

HIGHER ORDER MOTOR CONTROL:
- Primary Motor,
- Premotor,
- Supplementary Motor.
- ALL project CONTRALATERALLY except Supplementary M.A. which projects BILATERALLY

Basal ganglia : consists of

**DIRECT PATHWAY:** !!! EXCITATORY !!!
- neostriatum (putamen and caudate nucleus),
  - receives input from wide areas of cortex
  - projects back to globus pallidus and substantia nigra
- globus pallidus,
  - receives input from neostriatum
  - projects to cortex via thalamus

**Substantia Nigra (pars COMPACTA) balances the two pathways**
- This is done via DOPAMINE which can act as an excitatory and an inhibitory neurotransmitter, depending on which receptor it binds
  - (D1= excitatory, D2= inhibitory)

The CEREBELLUM:
- Vestibulocerebellum (archicerebellum; flocculonodular lobe) receives direct vestibular input and influences the spinal cord and brain stem via vestibular nuclei.
- Spinocerebellum (paleocerebellum; anterior lobe and paravermal areas) receives proprioceptive input from the spinal cord and the brain stem. It influences motor cortical areas and brain stem "upper" motor neurons.
- Neocerebellum, (lateral lobes of the cerebellar cortex) receives input from the cerebral cortex via pontine nuclei. It influences motor cortical areas via the thalamus. An important role of the neocerebellum may be the learning and automation of complex movements.

**INDIRECT PATHWAY: >> INHIBITORY <<**
- Adds a loop via the subthalamic nucleus
  - Which excites an inhibitory neurone in the globus pallidus
Drugs that specifically modify the actions of different neurotransmitters can do so by changing the availability of neurotransmitters within synapses at any of the steps mentioned below, or by directly acting on neurotransmitter receptors.

**SYNTHESIS**

ENZYMES at the nerve terminal either
- **SYNTHESISE** small molecule transmitters
- **CLEASE** neuropeptides from large precursor proteins; eg. dopamine synthesis below.

THESE PATHWAYS CAN BE INFLUENCED:
To INCREASE the levels of the transmitter, one must supplement the substrate
BEYOND THE RATE LIMITING STEP;
To DECREASE it one must inhibit the rate limiting step enzyme

**STORAGE**
STORED IN HIGH CONCENTRATION IN VESICLES AT THE NERVE TERMINAL
- Disrupt storage by mimicking the storage process. Thus: inactive chemical released from vesicles
e.g. guanethidine is stored and released from noradrenergic nerves but does not activate adrenoceptors
- Or block transport into vesicles. Thus: empty vesicles release nothing;
e.g. tetrabenazine depletes catecholamines

**RELEASE + DIFFUSION**
calcium dependent exocytosis of vesicular stores.
- Depolarisation wave travels to synapse
- Calcium concentration rises (via voltage-gated Ca++ channels)
- Increase in calcium triggers neurotransmitter release
- Neurotransmitter is detected by presynaptic autoreceptors
- The autoreceptors give NEGATIVE FEEDBACK: inhibit release of neurotransmitter after the synaptic concentration has reached the point of saturation.

**ACTION ON RECEPTORS**
- **two major kinds of receptor;**
  - ligand gated ion channels : FAST TRANSMISSION (milliseconds)
    - why so fast? Well, the receptor is also the channel, so the response is immediate.
  - second messenger coupled receptors: SLOW TRANSMISSION (100 milliseconds to many seconds)
    - MODULATES the responsiveness of postsynaptic membranes and presynaptic terminals.
    - Both small, e.g. dopamine and glutamate, and large neuropeptides mediate slow neurotransmission.
    - WHY SO SLOW? Receptor is generally G-protein coupled; the G-protein then kicks off a cascade of enzyme events that result ultimately in some sort of metabolic change

Each neurotransmitter acts on a variety of specific receptors which are differentially expressed in different tissues and different locations in the synapse, e.g. there are five distinct genes encoding dopamine receptors. Some receptors (e.g. D2 and D4) can also form multiple mRNA alternate splice variants. D1-like receptors (D1, D5) are coupled to generally excitatory second messengers and D2-like receptors (D2, D3, D4) are generally inhibitory, e.g. inhibition of exocytosis from dopaminergic nerve terminals. Drugs can act as agonists (mimic neurotransmitter) or antagonists (block) with distinct selectivities for receptor types.

**TERMINATION OF ACTION**
EVENTUALLY the neurotransmitter will diffuse away; BUT NOT FAST ENOUGH- this would limit the bit-rate of the CNS.
THUS: Small molecule transmitters are **inactivated by enzymes**
e.g. catechol-O-methyl transferase [COMT] and monoamine oxidase [MAO] inactivate dopamine,
and/or "re-uptake" transporters which effectively **pump the transmitter back into the terminal**.
Re-uptake is the principal mechanism for inactivation of the actions of dopamine in the synapse.
Drugs that inhibit these enzymes (e.g. selegiline for MAOB see LT 7.5) or re-uptake (e.g. doxepin and cocaine block dopamine re-uptake) increase the concentration or **dwell time** of transmitters in the synapse.
ANATOMY OF THE FOREBRAIN STRUCTURES

- Thalamus is the SCENIC GATEWAY to the CORTEX:
  - gets inputs from everywhere; sends outputs to cortex

**Thalamic Nuclei**

- Midline (ML)
  - BRF, basal ganglia, all cortex
    - (arousal, pain, autonomic)

- Intralaminar (IL)
  - BRF, basal ganglia, cerebellum, all cortex
    - (arousal, pain, autonomic)

- Medial Dorsal (MD)
  - Prefrontal cortex
    - (personality, pain, memory, emotion)

- Pulvinar (Pul)
  - Visual/parietal cortex
    - (attention, multisensory)

- Medial Geniculate (MG)
  - Cochlear, auditory cortex
    - (audition)

- Lateral Geniculate (LG)
  - Retina, visual cortex
    - (vision)

- Anterior (Ant)
  - Mamillary body, cingulate cortex
    - (emotion, memory)

- Lateral Posterior (LP)
  - Parietal cortex
    - (attention, multisensory)

- Ventral Lateral (VL)
  - Basal ganglia, cerebellum, motor cortex
    - (motor)

- Ventral Posterior (VP)
  - Dorsal column, trigeminal, somatosensory cortex
    - (tactile, proprioception, pain)

**HORIZONTAL SECTION OF INTERNAL CAPSULE:**

- is a TWO-WAY HIGHWAY: here is the direction of fibres

**Anterior limb:**
- From cortex to pons
- From cortex to all brainstem cranial nerve nuclei

**Genu:**
- From cortex to Cranial nerve nuclei of Medulla

**Posterior Limb:**
- Corticospinal tracts

**THALAMUS projects throughout the capsule**
Slice A is slightly inferior to slice B
The Dungeons of the Brain:

**caudate:**
- serpent-like shape
- follows the contours of the lateral ventricle.
- inputs from frontal cortex;
- outputs to globus pallidus.

**putamen:**
- forms lateral 2/3 of lentiform nucleus
- (other 1/3 formed by globus pallidus).
- the caudate and putamen are continuous.
- separated from globus pallidus by thin lateral medullary lamina.
- Connections of putamen are similar to caudate:
  - inputs from frontal cortex;
  - outputs to globus pallidus.

**globus pallidus:**
- forms medial 1/3 of the lentiform nucleus
- (lies immediately medial to putamen).
- Has many GABAergic cells: all the better to inhibit you with, my dear subthalamus.
- Has 2 segments:
  - GPi (internal)
  - GPe (external).
- GP connects to thalamus via the ansa lenticularis,
  a.k.a. the pallido-thalamic pathway.
- inputs are from caudate/putamen/subthalamus;
- outputs are to thalamus via ansa lenticularis

**substantia nigra:**
- lies in the midbrain:
  - just above the white matter of the cerebral peduncle
  - just below the red nucleus.
- It has two major divisions:
  (i) **Pars compacta (SNc):**
    - dorsal black zone, the inner core
    - Cells are rich in dopamine and melanin (hence black).
    - Has many projections to the caudate and putamen.
  (ii) **Pars reticulata (SNr):**
    - ventral reticular zone, outer rim
    - adjacent to cerebral peduncle.
    - Cells lack pigment but are rich in iron;
    - no dopamine here.
    - is considered extension of globus pallidus, since its cells and connections are same.

**subthalamus:**
- @ medial border of internal capsule
- ventral to thalamus (best seen in coronal sections).
- Subthalamus has many glutamatergic cells.
- rich connections with the globus pallidus.
- Very highly excitatory
STILL MORE BASAL GANGLIA: summary of projections

Gross Anatomy of the hated GANGLIA:

- Corpus callosum
- Septum pellucidunt
- Lateral ventricle
- Body of caudate
- Choroid plexus of lat. ventricle
- Stria Terminalis
- Superior thalamostriate vein
- Body of fornix
- Internal cerebral vein
- Tela choroidea of 3rd ventricle
- Choroid plexus of 3rd ventricle
- Thalamus
- Putamen
- Globus pallidus
- Internal capsule
- 3rd ventricle and interthalamic adhesion
- hypothalamus
- tail of caudate
- optic tract
- choroid plexus of lat ventricle
- temporal horn of lat. ventricle
- fimbria of hippocampus
- hippocampus
- dentate gyrus
- parahippocampal gyrus

Coronal section of brain: posterior view
Anatomy of the Cerebellum

Coordination and Timing of motor activity:
(And lots of other activity, eg. autonomic, higher function etc)
As a rule:
- The cerebellar cortex receives
- The deep nuclei send

Cortex:
- 3 layers, same thickness and density throughout
- Major input is from mossy cells (500 signals per second) (This is 99.9% of all input)
- Other input is from the climbing fibres (Responsible for complex learning of motor tasks)
- Output is via Purkinje cells

Cortical Localisation @ Cerebellum:

Cerebro:
- Plans movement, smooths fine motor activity, tones muscles.
- Lesion: intention tremor, hypotonia, explosive dysarthria, overshooting of limbs, Poor distance judgment.

Spino:
- Smoothness of gait: lesion = ataxia, no timing to movements. Think ether

Vestibulo:
- Maintains balance and equilibrium, coordinates eye movements with head movements.
- Lesion: ataxic wide-base stance and nystagmus (see opposite)

Rules of Thumb:
- You will stagger to the side of the lesion
- Each cerebellum portion has its own nucleus
- If you are able to fix gaze despite nystagmus, it's not a cerebellar lesion (i.e. it's in the brainstem)

Deep nuclei:
- Sit in the white matter, deep inside the cerebellum
- Produce the major output of the cerebellum
- Dentate: looks just like the inferior olive; nucleus of cerebrocerebellum
  Big tract sends motor corrections to VL thalamus (dentatothalamic tract)
- Globus & emboliform: middle nuclei of spinocerebellum
  Send fibres to red nucleus
- Fastigial: in midline, the roof of 4th ventricle; nucleus of vestibulocerebellum
  Balance and vestibular; sends fibres to vestibular nuclei

Peduncles:
- Superior: strictly output; to midbrain
  Mainly motor adjustments, coordination etc
  Thalamus + red nucleus
- Middle: strictly input; from pons
  Conduct from pontine nuclei to the post. cerebellar cortex
- Inferior: some input and output; from medulla
  Spinocerebellar tract (posture, balance, etc) → ant. cerebellar cortex
  Inferior olive → all over the cerebellar r cortex; complex learning of motor tasks
  Fastigial nucleus output to the vestibular nuclei

Cerebellum makes up 10% of brain volume, but 50% of the total cell number!!

Modified from Aanonsen & al (1983)
Neuronal degenerations = progressive disorders of the nervous system that affect related systems of neurons.

Cell biology of the CEREBELLUM

CELL TYPES:
- STELLATE, BASKET, GOLGI: GABA-ergic cells
  → predominantly interneurons
- MOSSY CELLS:
  Major input cell: 99% of input is in this form
  Simple signalling; always firing - 500 hits/second
  Hand signal over to granular cells:
- GRANULE CELLS
  = are tiny GLUTAMATE cells; very easily excited
  = send a bifurcated axon up to molecular layer:
  thus, connect lots of purkinje cells together
  thus one mossy cell can activate up to 500 purkinjes
- PURKINJE cells
  → form a monolayer;
  → these are really extremely large.
  LINED UP: one dendrite sent up to yhe molecular layer
to receive signals from granule cells:
the AXON extends DOWN THROUGH THE CORTEX
into the DEEP NUCLEI and thus
out of the cerebellum
- CLIMBING CELLS:
  Weird specialised ANTISOCIAL cells:
  ONLY COME FROM INF.OLIVE OF MEDULLA!
  ONLY TALK TO ONE PURKINJE CELL AT A TIME!
  …Monogamous!
  Fire only twice a second; but when they do-
  the purkinjes go BERSERK (this happens ONLY
  while you’re learning a new motor activity: once its
  learnt, the mossy cells take over and the climbing fibres
  fall silent.

NEURODEGENERATION

For example, a motor degeneration can affect the linked upper and lower motor neurons, but leave closely adjacent neurons intact.

Common examples of nervous system degenerations are
- Alzheimer's disease,
- Parkinson's disease,
- Huntington's disease,
- and motor neuron disease.

The abnormal gene or genes for some degenerations, for example Huntington's disease and familial motor neuron disease, have been found, and the list of known abnormal genes grows every year.

Many researchers think an "abnormal gene + environmental toxin" combination causes some of the more common disorders, and that oxygen free radicals play a part in the destruction of cells. Increased synthesis and release of excitatory neurotransmitters is also thought to play a part in some neurodegenerations. (EXCITOTOXICITY)

A neuron is not an independent entity, but depends on the neurons synapsing with it both upstream and downstream for its continued survival. Therefore if one neuron dies, the directly synapsing neurons often suffer as well. Hence "chains" of neurons can die in neuronal degenerations.

Neurodegenerations resulting in movement disorders are common, the most common being Parkinson's disease. This affects the neurons of the nigro-striatal pathways, with the lack of their neurotransmitters (in particular dopamine) causing abnormal body movements. Loss of pigmented neurons in the midbrain and a particular intraneuronal inclusion, the Lewy body, are the pathological hallmarks of Parkinson's disease.

Iron-induced oxidative stress has been implicated in the pathogenesis of Parkinson's disease, since the nuclei affected contain large amounts of iron, and iron in tissues can promote free radical formation.
POSSIBLE MECHANISM of PATHOGENESIS:

- **MPTP**
  - MAO-B
  - MPP+ = Inhibits complex-1
- **Faulty complex 1**
  - of the electron transport chain
- **Point mutation** in mitochondrial DNA
  - Naturally occurring striatonigral IRON
    - = creates free radicals (OH-)
- **Faulty Alpha-Synuclein**
  - (normally a vesicle-forming protein involved in the release of dopamine)
  - Free Dopamine: without alpha-synuclein to make vesicles, it makes reactive O2 species
  - Lewy bodies

**MITOCHONDRIAL DAMAGE**
- Awful for the energy-intensive basal ganglia!
- **Energy Loss**
  - (no more ATP!)
- **Increased [Free Radicals]**

**APOPTOSIS**
- Of the Striata Nigra pars Compacta
  - at least 80% must be lost

**OVERACTIVE SUBTHALAMUS**
- Normally kept on a leash by SN dopaminergic neurons; but no longer!

**Calbindin** protein
- (a calcium binding protein) protects some dopaminergic neurons from destruction in PD

**LIPID PEROXIDATION**
- + DNA damage,
  - + more free radicals are generated

**OVERINHIBITION of Pedunculo-pontine area:**
- THUS: No glutamate sent to the Ventral Horn of S.C.
- THUS: SELDOM IS A MOVEMENT INITIATED

- **BRADYKINESIA**
  - No ventral control over stretch receptors; thus spinal reflex arcs go wild!
  - **COGWHEEL RIGIDITY**

**OVERINHIBITION of G.P. THALAMUS:**
- THUS: UNOPPOSED STIMULATION BY CEREBELLUM

**Normal movements**
- Abnormal movement
  - Proprioceptive feedback to the cerebellum
  - Cerebellum excited; initiates a corrective movement
  - Corrective movement is not opposed by g.p. inhibition; thus, you move abnormally

- **TREMOR!**
PARKINSONS DRUGS WILL NOT BE EFFECTIVE IN THESE CONDITIONS!!

## Related Conditions: Parkinsonism and...

### Wilson's Disease:
- LOTS of abnormal movements besides tremor
- There is family history,
- age of onset is VERY EARLY
- you get associated Kayser-Fleischer rings,
- serum copper is LOW
- test for ceruloplasmin

### Huntington's Disease
- strong family history
- accompanied by dementia
- confirmed by genetic studies.

### Shy-Drager Syndrome
- impaired autonomic function, eg.
  - postural hypotension
  - abnormal thermoregulatory sweating
  - disturbances of bladder and bowel control
  - impotence
  - gastroparesis
- widespread neurologic involvement
  (pyramidal, cerebellar, or lower motor neuron signs).

### Striatonigral Degeneration
- bradykinesia and rigidity, but not tremor
- Antiparkinsonian drugs are generally ineffective.

### Progressive Supranuclear Palsy
- abnormalities of vertical gaze
- dementia,
- pseudobulbar palsy,
- axial dystonia
- no response to antiparkinsonian drugs.

### Cortical-Basal Ganglionic Degeneration
- intellectual decline
- aphasia
- apraxia
- sensory neglect

### Diffuse Lewy Body Disease
- parkinsonism + conspicuous dementia
- evidence of more widespread neurologic involvement.

### Creutzfeldt-Jakob Disease
- parkinsonian features are overshadowed by the rapidly progressive dementia;
- myoclonus
- ataxia
- visual disturbances
- electroencephalographic findings are often characteristic

### Alzheimer's Disease
- Parkinsonian features much less obvious than raging dementia