

PATHOPHYSIOLOGY- NERVOUS SYSTEM- DEGENERATIVE DISEASES



By

Mr Mahesh Bhanudas Narkhede

Asst Prof

Department of Pharmacology,

Dr Rajendra Gode College of Pharmacy, Malkapur

www.drgcop.co.in

www.mbnpharmacologist.wordpress.com

Learning Objectives



Upon completion of this topic learner should be able to learn :

Parkinson's Disease (PD)

Alzheimer's disease

Topic outline



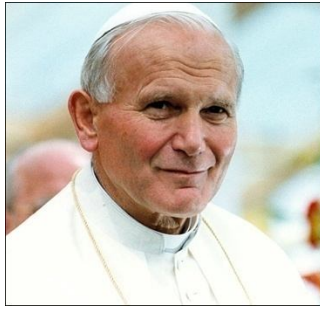
Includes :

- Introduction
- Etiology
- Pathogenesis
- Sign and symptoms

Degenerative Diseases of the Nervous System



- Chronic neurological conditions associated with progressive loss of neurons.
 - No evidence of inflammation.
 - No evidence of cellular necrosis.
- Examples:
 - Alzheimer's disease.
 - Parkinson's disease.
 - Motor neuron disease (ALS).



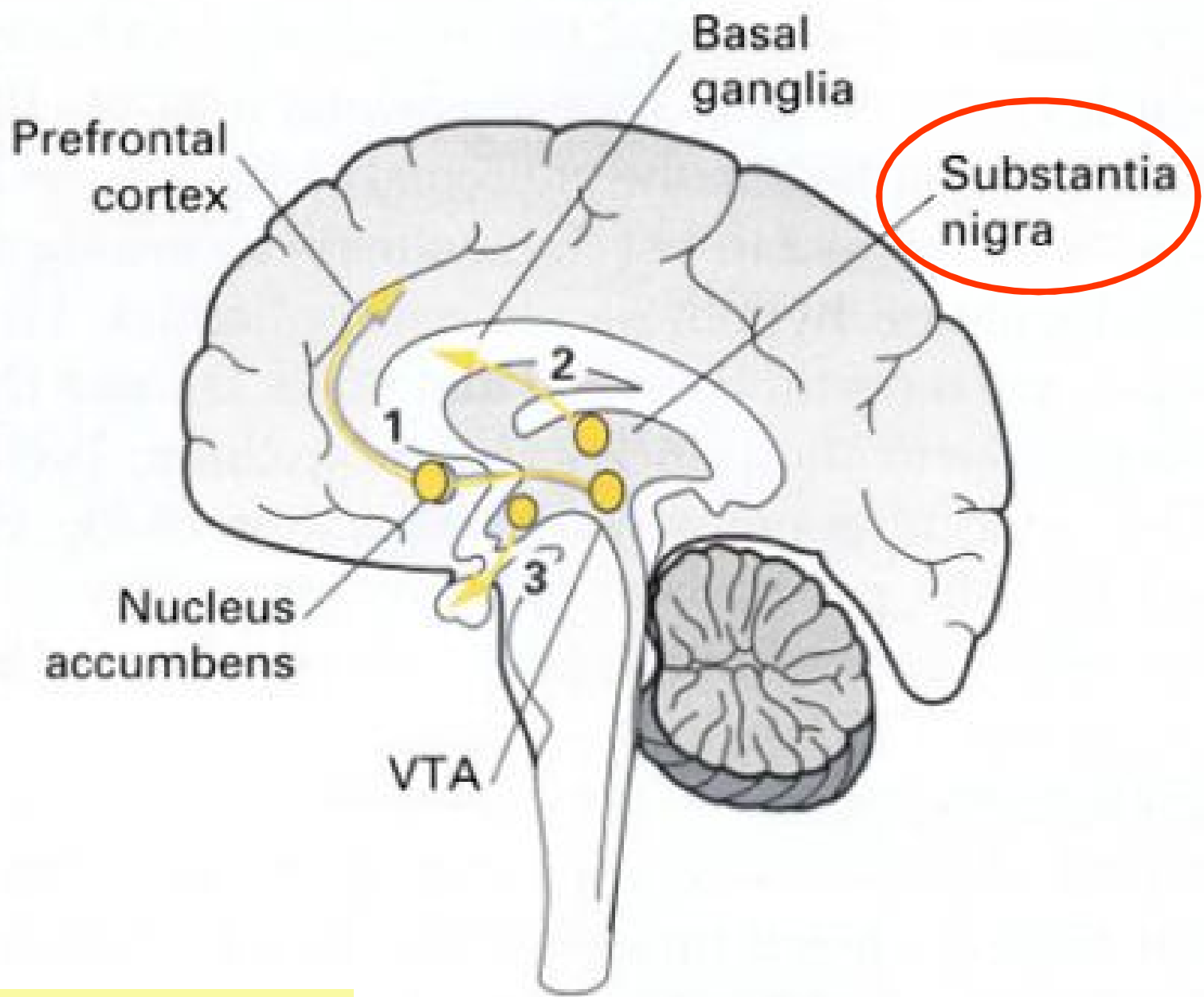
Parkinson's disease (PD) is a progressive neurodegenerative disorder.

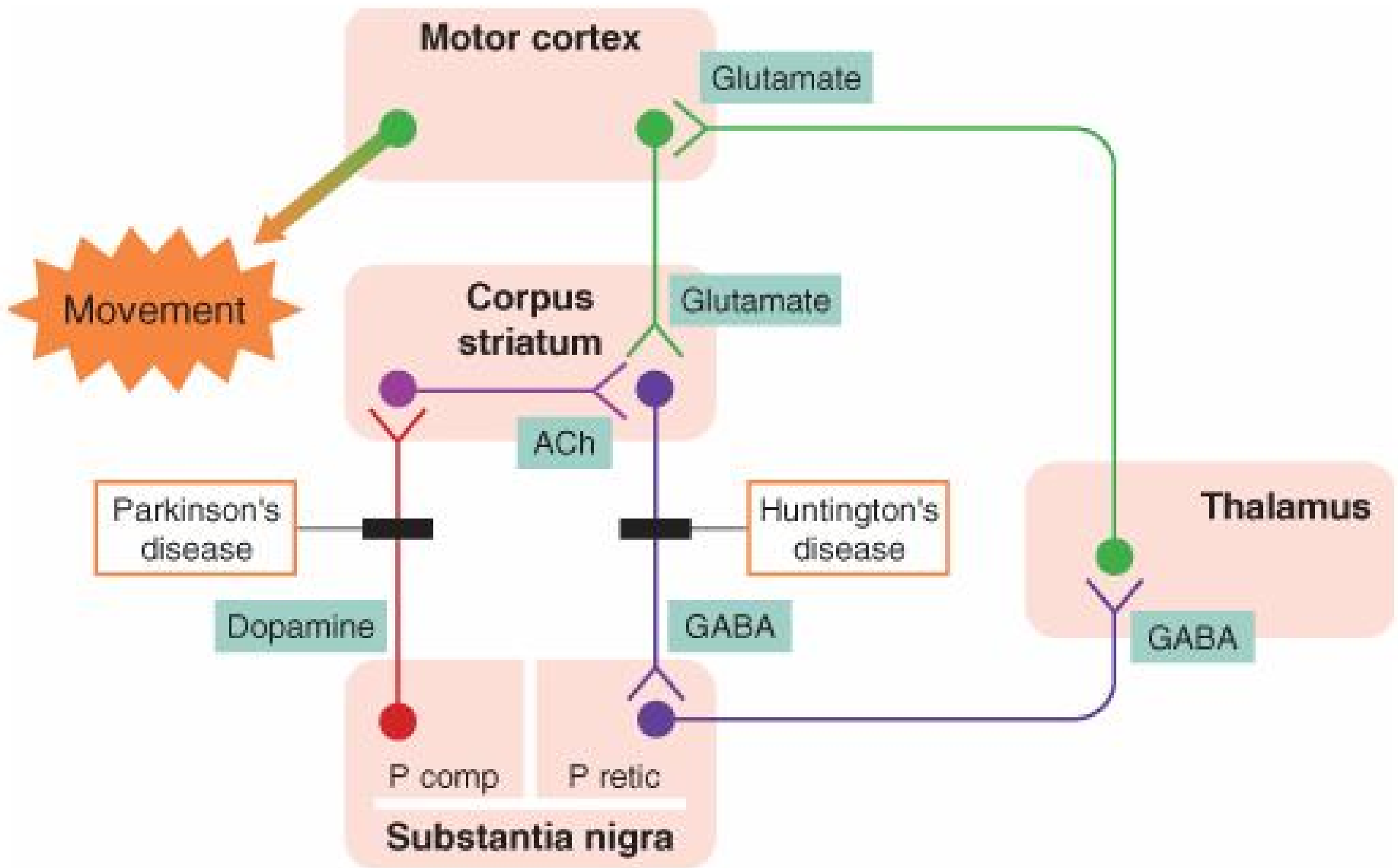
It is caused by ***degeneration of substantia nigra in the midbrain***, and consequent loss of DA-containing neurons in the nigrostrial pathway.

Two balanced systems are important in the extrapyramidal control of motor activity at the level of the corpus striatum and substantia nigra; in the first the neurotransmitter is ACh, in the second – DA.



Q) PD- 1st describe by James paracelsus
in 1817.

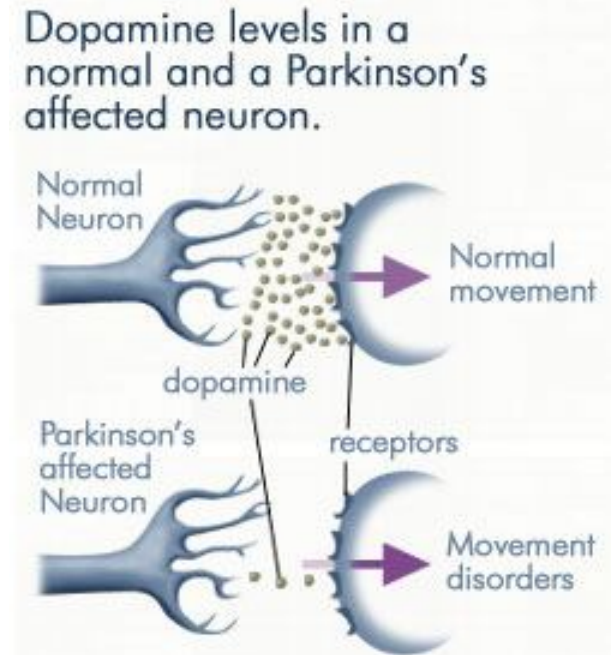


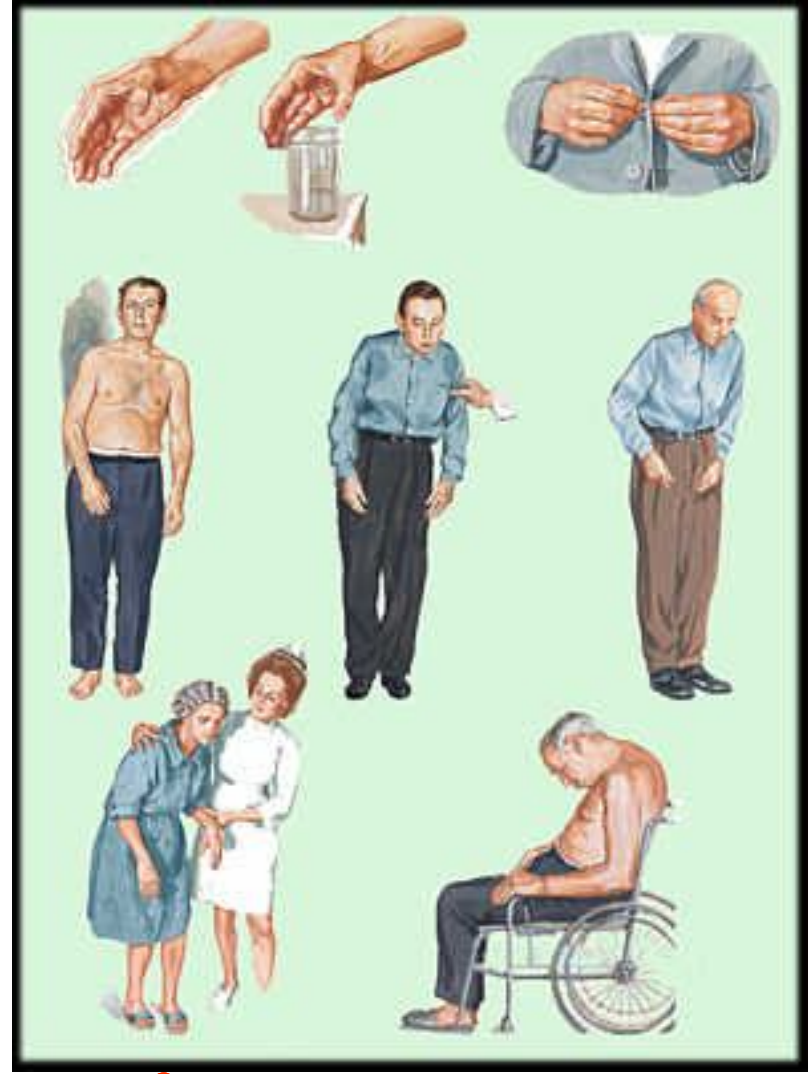
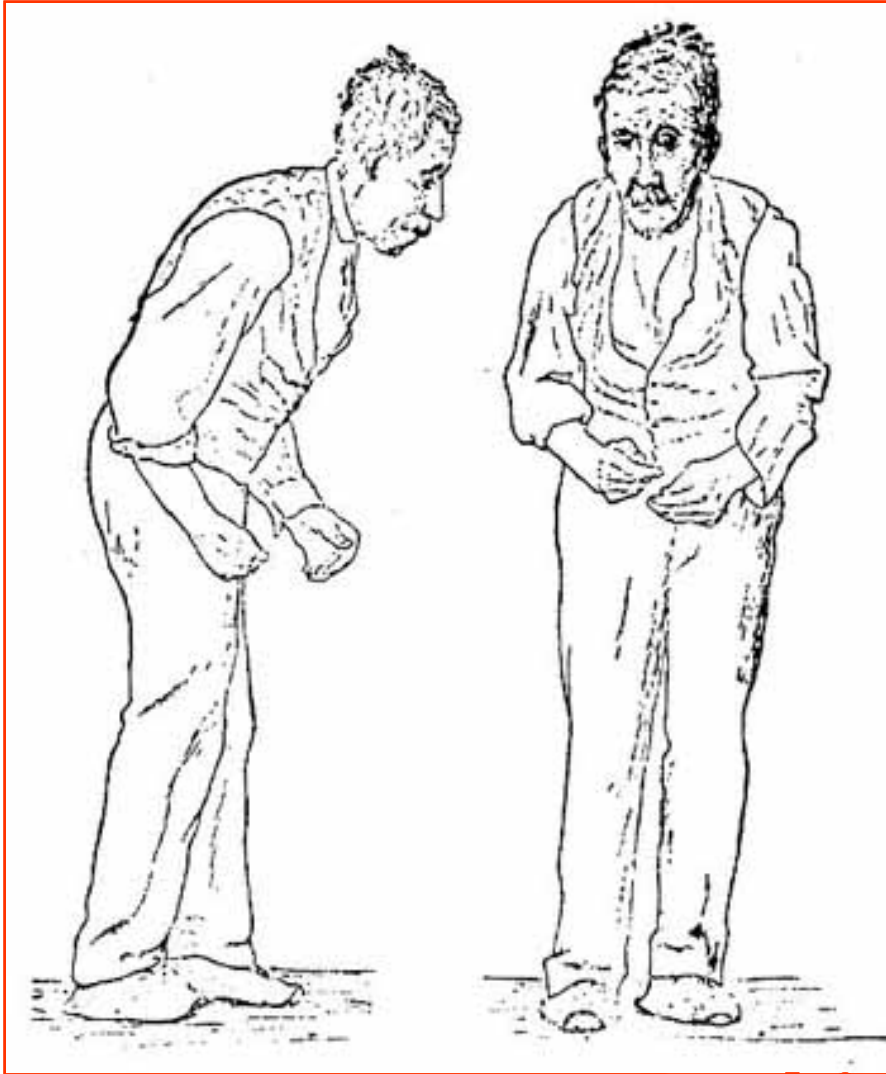


Rang et al. Pharmacology – 5th Ed. (2003)

Symptoms

- caused by insufficient dopamine.
- 3 main symptoms:
 - Tremors
 - Rigidity
 - Slowed motion (Bradykinesia)
- Other symptoms include:
 - Dementia, sleep disturbances, depression, etc.



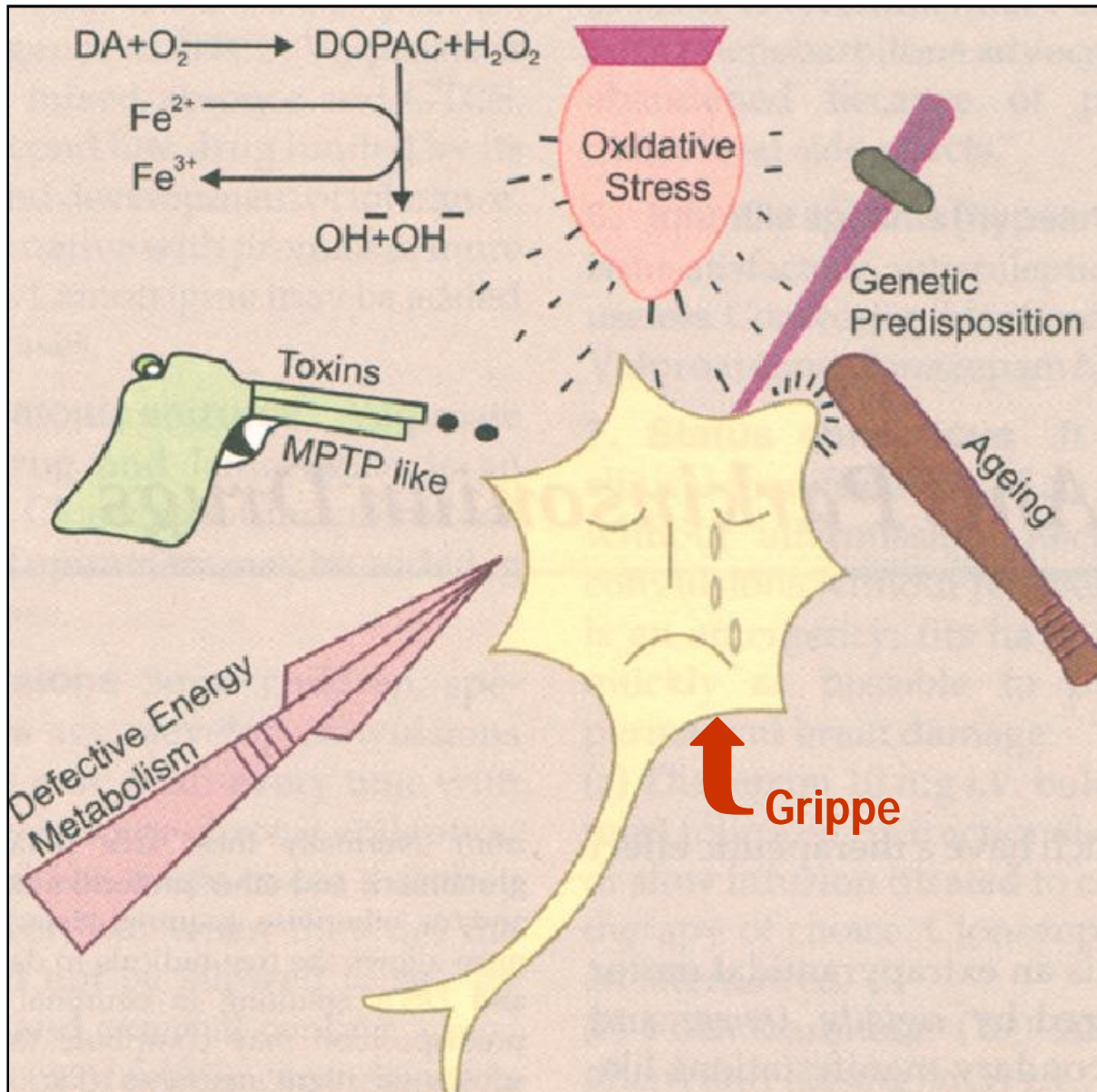


Parkinsonism

Etiology



- Heredity
- Antipsychotic drugs /Neuroleptic agent
- Anteriosclerosis
- Neurotoxins such as cyanide, manganese & carbon monoxide



Essential of Medical Pharmacology – 5st Ed. (2003)

Factors contributing to degeneration of nigrostriatal DA-ergic neurones causing PD

① Genetics -

- Single genetic mutation.
- The mutated gene is passed from generation to generation resulting in PD.
- mutation of $LRRK_2$ gene

② Environmental Factors - \rightarrow MPTP like chemical present in environment used in farming (toxins)

- Pesticides, herbicides
- Traffic or industrial pollution

All above factors responsible of aging & generation of free radicals \rightarrow resp. for PD

③ Free radicals -

Oxidation of Dopamine by MAO-B and aldehyde dehydrogenase generate hydroxyl free radicals ($\cdot OH$) in presence of ferrous ion free radical damage lipid membrane and DNA resulting in neuronal degeneration.

④ Ageing →

Ageing induces defect in mitochondrial electron transport chain. Environmental toxins / ~~or genetic factors~~ impaired energy metabolism in Dopamine neuron.

⑤ MPTP → N-methyl-4-phenyl-tetrahydropyridine.

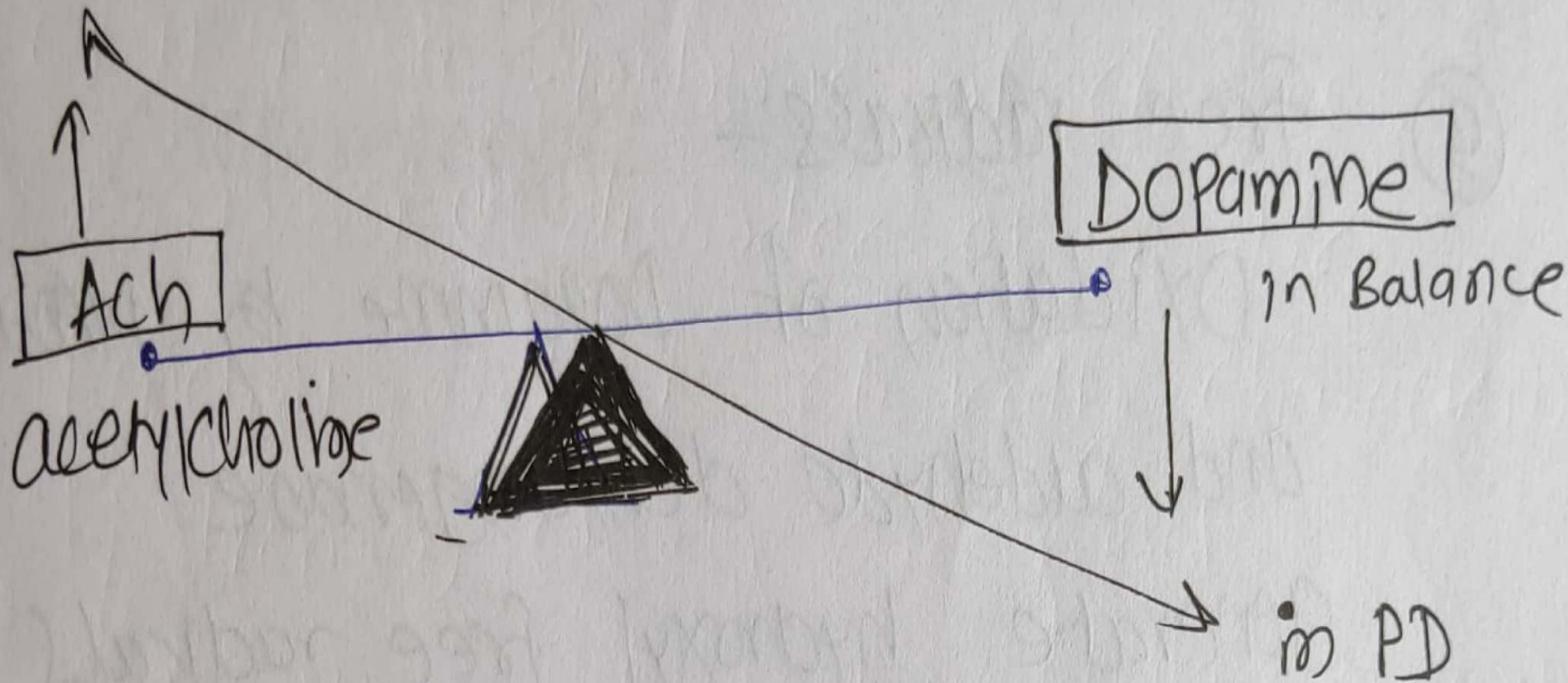
Chemical produce nigrostriatal degeneration

⑥ Drugs induced PD.

Neuroleptics, metoclopramide (dopamine receptor blockers)

Pathogenesis of PD

- ② PD is degenerative nervous disease
- ① In PD degeneration of neurons occurs in substantia nigra pars compacta and the nigrostriatal dopaminergic tract.
- ② This results in loss of dopamine in striatum which controls muscle tone and coordinated movement
- ③ An imbalance between DA & ACh inhibitory and excitatory systems occurs give rise to motor defect.



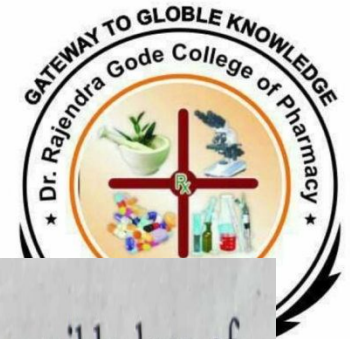
Imbalance of neurotransmitters
in PD

Pharmacological Treatment of Parkinson's Disease



- Goals:
 - Primary = restore dopamine receptor function.
 - Secondary = inhibition of muscarinic cholinergic receptors.

Alzheimer's disease



Alzheimer's disease is a progressive neurologic disease of the brain leading to the irreversible loss of neurons and the loss of intellectual abilities, including memory and reasoning, which become severe enough to impede social or occupational functioning. During the course of the disease plaques and tangles develop within the structure of the brain. This causes brain cells to die. Patients with Alzheimer's also have a deficiency in the levels of some vital brain chemicals which are involved with the transmission of messages in the brain - neurotransmitters. AD usually occurs in old age, and is marked by a decline in cognitive functions such as remembering, reasoning, and planning.



Alzheimer's disease (AD) is the most common form of dementia, a neurologic disease characterized by loss of mental ability severe enough to interfere with normal activities of daily living, lasting at least six months, and not present from birth. **OR**

ETIOLOGY



- **Advancing age:** After the age of 65 the risk of developing Alzheimer's doubles every five years.
- **Family history:** People who have a close family member who developed Alzheimer's have a slightly higher risk of developing it themselves - just a slightly higher risk, not a significantly higher risk.
- **Whiplash and head injuries:** Some studies have identified a link between whiplash and head injuries and a higher risk of developing Alzheimer's.
- **Aluminum:** Aluminum exists in the plaques and tangles in the brains of Alzheimer's patients. Some have suggested that aluminum absorption by humans could increase the risk.
- **Down's syndrome:**

People with Down's syndrome have an extra copy of chromosome 21, which contains a protein that exists in the brain of people with Alzheimer's. As people with Down's syndrome have a larger amount of this protein than others, their risk of developing the disease is greater.
- APOE 4 genotype, Obesity, Insulin resistance, Vascular factors
- Dyslipidemia, Hypertension, Inflammatory markers, Traumatic brain injury

In addition, epidemiologic studies have suggested some possible risk factors (eg. previous depression) and some protective factors (eg, long-term use of nonsteroidal anti-inflammatory drugs).

Genetic causes

SYMPTOMS



- 1) Memory loss that disrupts daily life. One of the most common signs of Alzheimer's, especially in the early stages, is forgetting recently learned information.
- 2) Challenges in planning or solving problems. Some people may experience changes in their ability to develop and follow a plan or work with numbers.
- 3) Difficulty completing familiar tasks at home, at work or at leisure. People with Alzheimer's often find it hard to complete daily tasks. Sometimes, people may have trouble driving to a familiar location, managing a budget at work or remembering the rules of a favorite game.
- 4) Confusion with time or place. People with Alzheimer's can lose track of dates, seasons and the passage of time.
- 5) Trouble understanding visual images and spatial relationships. For some people, having vision problems is a sign of Alzheimer's. They may have difficulty reading, judging distance and determining color or contrast.
- 6) New problems with words in speaking or writing. People with Alzheimer's may have trouble following or joining a conversation.
- 7) Misplacing things and losing the ability to retrace steps. A person with Alzheimer's disease may put things in unusual places. They may lose things and be unable to go back over their steps to find them again.
- 8) Decreased or poor judgment. People with Alzheimer's may experience changes in judgment or decision making.
- 9) Withdrawal from work or social activities. A person with Alzheimer's may start to remove themselves from hobbies, social activities, work projects or sports.
- 10) Changes in mood and personality. The mood and personalities of people with Alzheimer's can change. They can become confused, suspicious, depressed, fearful or anxious.



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