

# CHHATRAPATI SHAHU JI MAHARAJ UNIVERSITY

**DRUGS FOR NEURODEGENERATIVE DISEASE**

**{ PARKINSONISM }**

**PHARMACOLOGY & TOXICOLOGICAL SCREENING METHODS – 1<sup>ST</sup>**

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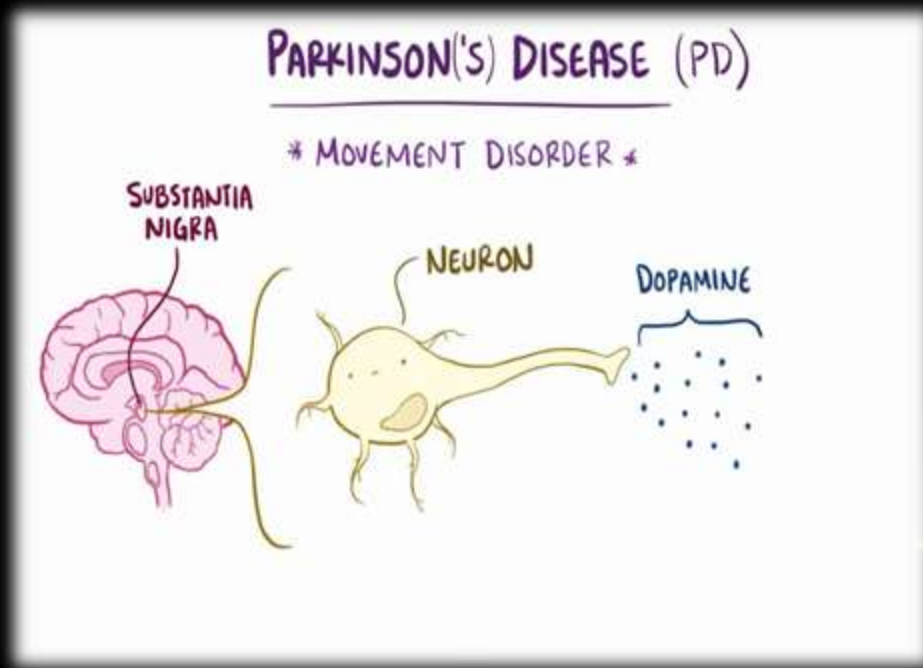
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# INTRODUCTION

- ❖ Parkinson's disease (PD) , which is the second most common neurodegenerative disorder after Alzheimer's disease , is firstly defined after James Parkinson.
- ❖ It is a movement disorder & combination of tremor. (shaking movement)
- ❖ Parkinson's disease was first medically described as a neurological syndrome by **James Parkinson** in **1817**.
- ❖ Parkinson's is a long - term neurodegenerative disease disorder of the central nervous system that mainly affect the motor system.
- ❖ The symptoms appear slowly & as the disease worsens , non motor symptoms become more common.

- ❖ In Parkinson's disease , certain nerve cells (neurons) in the brain gradually break down or die.
- ❖ In parkinsonism is disease neuron from substantia nigra to corpus striatum of basal ganglia are lost.
- ❖ This result in reduced dopamine activity in basal ganglia causing movement problems like hypokinesia , rigidity and tremors.
- ❖ Many of symptoms are due to a loss of neurons that produce a chemical messenger in your brain called dopamine.



# SYMPTOMS

- ❖ Parkinson's disease (PD) is typically characterized by ...
- ❖ When dopamine levels decrease , it causes to impaired movement

❑ Motor (movement ) symptoms. These symptoms include : other symptoms of Parkinson's disease.

- ❖ Tremor at rest , such as a slight tremor in hand or feet.
- ❖ Rigidity (stiffness) of limbs, neck, or shoulder .
- ❖ Difficulty balancing ( postural instability).
- ❖ Slowness of movement or gradual loss of spontaneous movement (bradykinesia).

# CAUSES

❖ The cause of Parkinson's disease is unknown, but several factors appear to play a role, including :

❖ **Genes** : Certain gene variations appear to increase the risk of Parkinson's disease.

❖ **Environmental triggers** : Exposure to certain toxins or environmental factors may increase the risk of later Parkinson's disease, but the risk is small.

## ❖ Risk factors

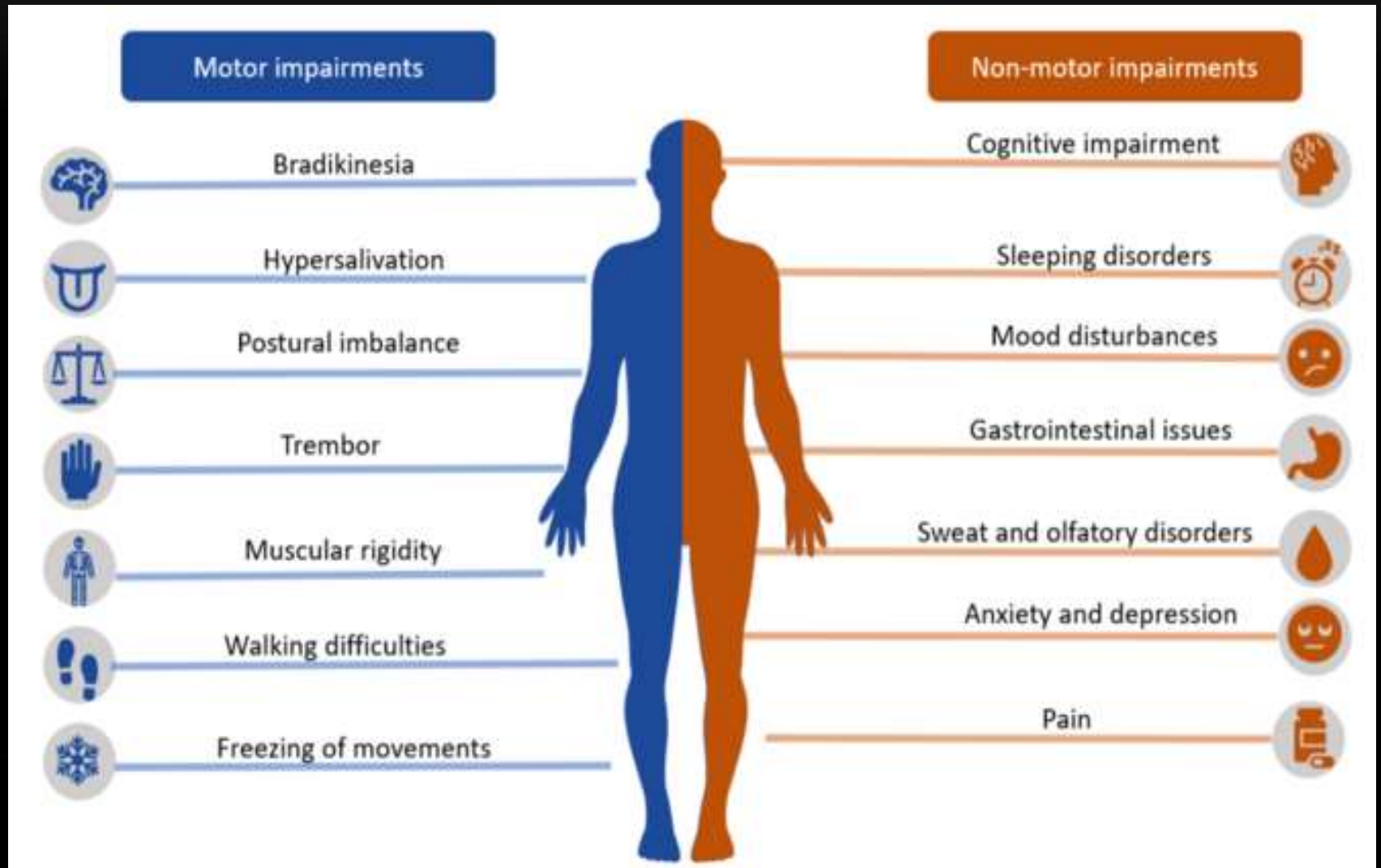
Risk factors for Parkinson's disease include :

➤ **Age** : Young adults rarely experience Parkinson's disease. It ordinarily begins in middle or late life, & the risk increases with age. People usually develop the disease around age 60 or older.

## ❑ NON – MOTOR SYMPTOMS :

- ❖ Symptoms may also differ in severity among different people. Some possible non-motor symptoms include:
- ❖ Reduced sense of smell (Hyposmia).
- ❖ Gastrointestinal issues , such as constipation.
- ❖ Urinary issues, like a frequent & urgent need to urinate.
- ❖ A drop in blood pressure that occurs when standing (orthostatic hypotension)
- ❖ Excessive sweating.
- ❖ Problem with sleep & wakefulness, including excessive daytime sleeping, tiredness.
- ❖ Behavioral problem may also occurs with depression, anxiety, & apathy occurring in many people with PD.

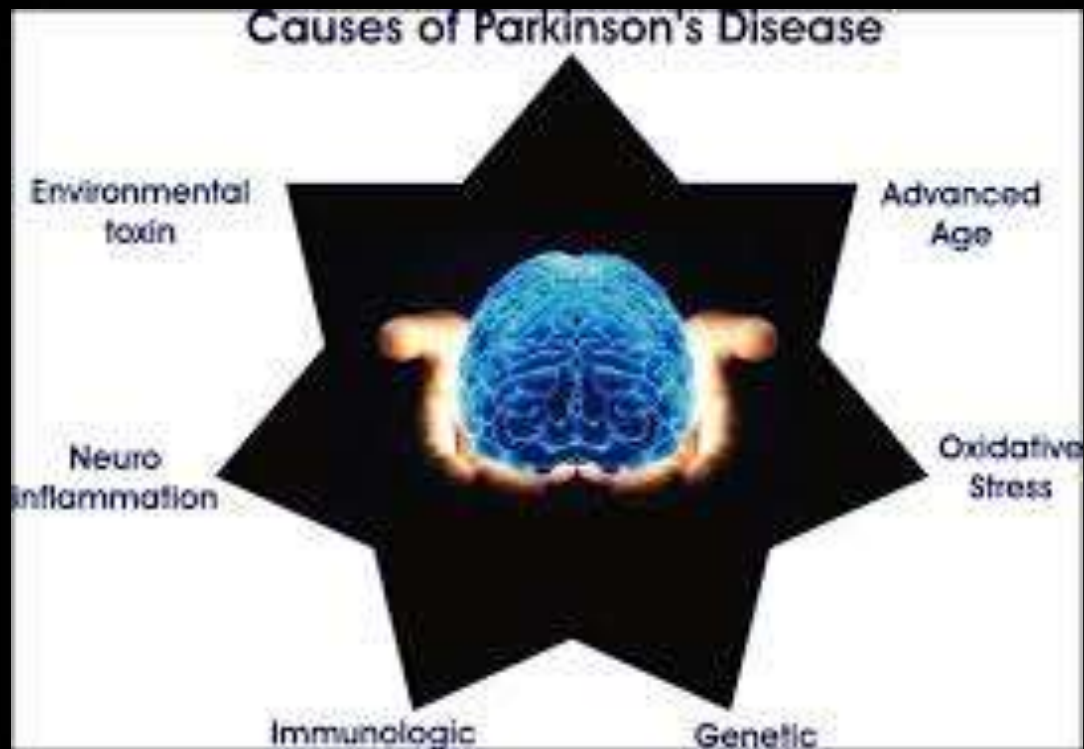
- THE MOST OBVIOUS EARLY SYMPTOMS ARE TREMOR , RIGIDITY, SLOWNESS, OF MOVEMENT & DIFFICULTY WITH WALKING





➤ **Sex** : Men are more likely to develop Parkinson's disease than women.

➤ **Heredity** : Having a close relative with Parkinson's disease increases the chances that you'll develop the disease.



# PREVENTION

- ❖ Because the cause of Parkinson's is unknown , there are no proven ways to prevent the disease.
- ❖ Regular aerobic exercise might reduce the risk of Parkinson's disease.
- ❖ Some other research has shown that people who consume caffeine – which is found in coffee , tea & cola – get Parkinson's disease less often than those who don't drink it .



# PATHOPHYSIOLOGY :

ETIOLOGICAL FACTOR  
ENVIRONMENTAL FACTOR  
GENE MUTATION

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graph TD; A["ETIOLOGICAL FACTOR  
ENVIRONMENTAL FACTOR  
GENE MUTATION"] --> B["DEGENERATIVE DISEASE DESTRUCTION OF  
DOPAMINERGIC NEURONAL CELLS IN THE SUBSTANTIA  
NIGRA IN THE BASAL GANGLIA."]; B --> C["NEURONAL CELLS LOSS"];
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DEGENERATIVE DISEASE DESTRUCTION OF  
DOPAMINERGIC NEURONAL CELLS IN THE SUBSTANTIA  
NIGRA IN THE BASAL GANGLIA.

NEURONAL CELLS LOSS

DEGENERATION OF DOPAMINERGIC ACTIVITY  
PARTICULARLY IN THE NIGRO – STRIATAL PATHWAY



DEPLETION OF DOPAMINE STORE IMBALANCE B/W  
EXCITATORY (ACETYLCHOLINE) & INHIBITING (DOPAMINE )  
NEUROTRANSMITTER IN THE CORPUS STRIATION.



IMPAIRMENT OF EXTRAPYRAMIDAL TRACT CONTROLLING  
COMPLEX BODY MOVEMENT



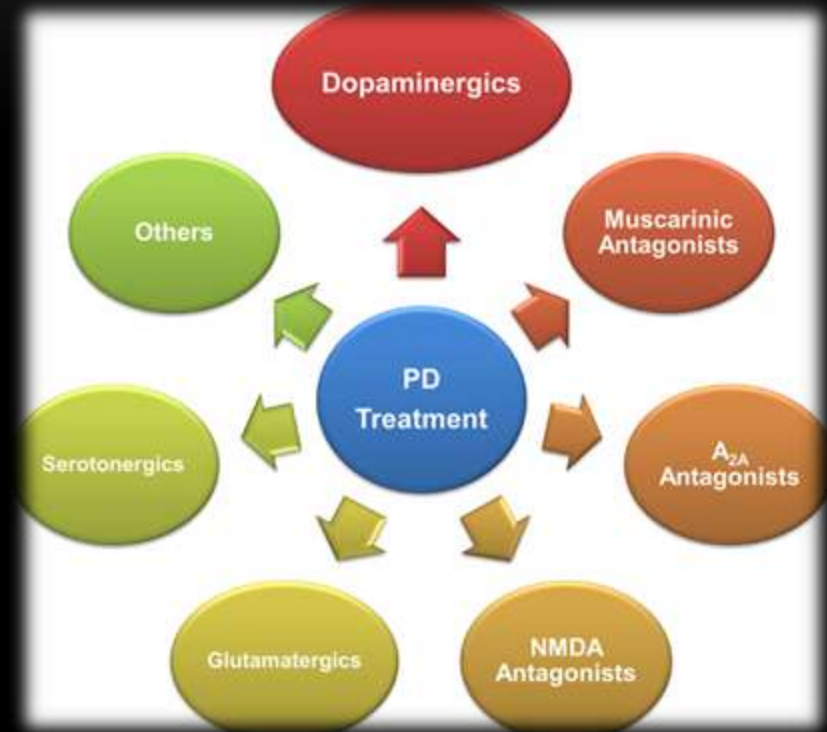
Tremor

RIGIDITY

POSTURAL  
INSTABILITY  
& ETC

# TREATMENT

- ❖ DOPAMINE PROMOTER
- ❖ ANTIDEPRESSANT
- ❖ COGNITION – ENHANCING  
MEDICATION
- ❖ ANTI-TREMOR
- ❖ EXERCISE



# SCREENING MODELS FOR PARKINSON'S DISEASE

- ❖ Tremorine and oxotremorine antagonism
  - ❖ MPTP model in monkeys
  - ❖ Reserpine antagonism model
  - ❖ 6 – OHDA induced model
  - ❖ Pesticide induced model
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# TREMORINE & OXOTREMORINE ANTAGONISM

- ANIMAL : Mole NMRI mice ( 18 – 22 gm)
- STANDARD DRUG : 5 mg / kg (Benzotropine mesilate )
- INDUCER : 0.5 mg / kg ( oxotremorine ) by S.C route

## ❖ PROCEDURE :

Groups of 6 – 10 male NMRI mice weighing 18 -22 g are used



They are dosed orally with the test compound or the standard (5 mg / kg benzatropine mesilate) 1 hour prior the administration of 0.5 mg / kg oxotremorine  
S.C.



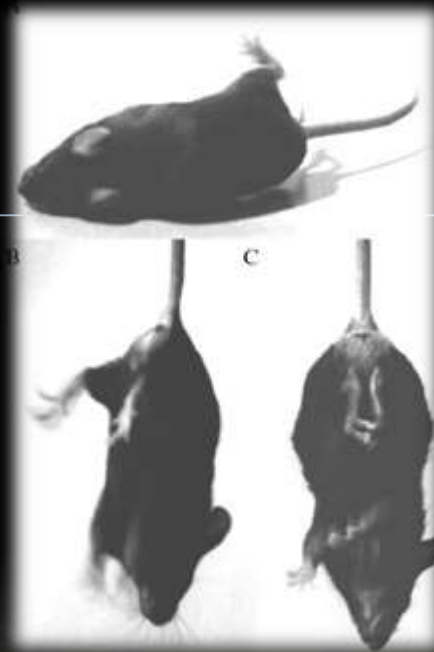


Rectal temperature is measured before administration of the compound (basal value) & 1, 2 & 3 h after oxotremorine injection.



Tremor is scored after oxotremorine dosage in 10 sec. Observation periods every 15 min for 1 hour.

Tremor	score
Absent	0
Slight	1
Medium	2
Severe	3



❖ Salivation & lacrimation are scored 15 & 30 min after oxotremorine injection.

❖ Absent 0

❖ Slight 1

❖ Medium 2

❖ Severe 3

## □ Evaluation

### ➤ Hypothermia :

❖ The differences of body temperature after 1, 2 & 3 h versus basal values are summarized for each animal in the control group & the test groups.

❖ The average values are compared statistically .

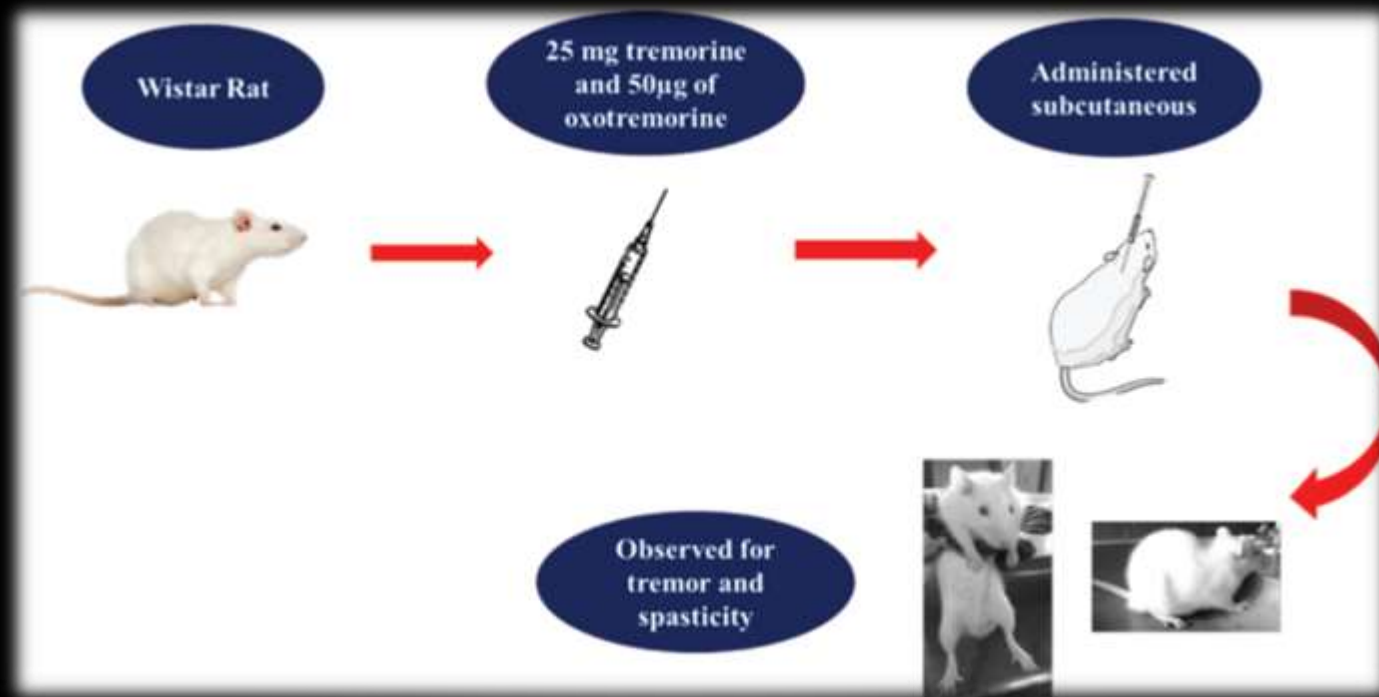
### ➤ Tremor :

❖ the scores for all animals in each group at the 3 observation periods are summarized.

❖ The numbers in the treated groups are expressed as percentage of the number of the control groups.

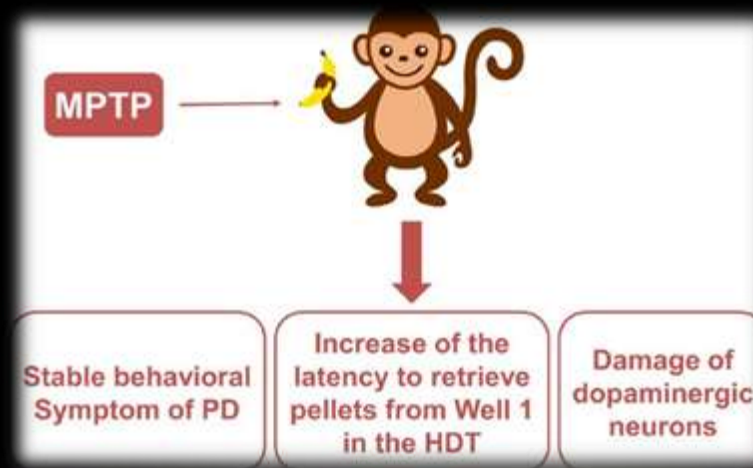
## ➤ Salivation and lacrimation :

- ❖ The scores for both symptoms for all animals in each group are summarized at the 2 observation periods.
- ❖ The numbers in the treated groups are expressed as percentage of the number of the control group.



# MPTP MODEL IN MONKEYS

- PURPOSE AND RATIONALE :
- ❖ N – MPTP ( N – methyl -4- phenyl – 1,2,3,6- tetrahydropyridine ) has been shown to cause symptoms of Parkinson's disease in exposed individuals.
- ❖ When administration to primates this compound causes a partial destruction of basal ganglia and a syndrome that resembles Parkinson's disease.



# PROCEDURE :

- Burns et al. (1983) treated 8 adult rhesus monkeys weighing 5–8 kg over a period of 5–8 days with cumulative intravenous doses of *N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine* (N-MPTP) up to 10–18 mg/kg.
- These animals showed a parkinsonism like disorder (akinesia, rigidity, postural tremor, flexed posture, eyelid closure, drooling)
- Which was reversed by the administration of L-dopa.
- The pathological and biochemical changes produced by N-MPTP are similar to the well established changes in patients with Parkinsonism.

# EVALUATION : THE SEVERITY OF PARKINSONISM SYMPTOMS IS RATED BY TRAINED OBSERVERS

- movement (0: normal; 1: reduced; 2: sleepy)
- checking movements (0: present; 1: reduced; 2: absent)
- attention and blinking (0: normal; 1: abnormal)
- posture (0: normal; 1: abnormal trunk; 2: abnormal trunk and tail; 3: abnormal trunk, tail, and limbs; 4: flexed posture)
- balance and coordination (0: normal; 1: impaired; 2: unstable; 4: falls)
- reactions (0: normal; 1: reduced; 2: slow; 3: absent)
- vocalizations (0: normal; 1: reduced; 2: absent).



# RESERPINE ANTAGONISM

## ➤ Purpose and rationale

- Reserpine induces depletion of central catecholamine stores.
- The sedative effect can be observed in mice shortly after injection, followed by signs of eyelid ptosis, hypokinesia, rigidity, catatonia, and immobility.
- These phenomena can be antagonized by dopamine agonists.