

# *PARKINSON'S DISEASE –AN OVERVIEW TEN STEP APPROACH*

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## *PROF C.D. MARSDEN- A GENIUS IN MOVEMENT DISORDERS*

- ♦ PARKINSONS DISEASE and PSYCOGNIC
- ♦ RIGID STATES (AKINETIC)
- ♦ OTHER DEGENERATIVE PARKINSONISM
- ♦ FIBRILLATION AND FASCICULATION
- ♦ CHOREA INCLUDING HEMIBALISM
- ♦ DYSTONIA
- ♦ MYOCLONUS, MYOKYMIA, MYRHYTHMIA
- ♦ ATAXIA, AKATHESIA, ATHETOSIS, ABD. DYSKINESIAS
- ♦ RESTLESS LEG SYNDROME
- ♦ STEREOTYPY, SPASM (HEMI FACIAL), JUMPY STUMPS
- ♦ DYSKINESIAS (PAROXYSMAL)
- ♦ ESSENTIAL TREMOR INCLUDING ALL TREMORS, EPILEPSIA (HYPER)
- ♦ NEUROLEPTIC INDUCED – TARDIVE DYSKINESIAS AND NMS.

# ***SIX - SENSES***

- ◆ **Perceptual Sense** - **Observation**
- ◆ **Word Sense** - **Recording**
- ◆ **Clinical Sense** - **Insight / Idea**
- ◆ **Statistical Sense** - **Methodology**
- ◆ **Research Sense** - **Application**
- ◆ **Common Sense** -- **Thinking**

# *JAMES PARKINSON'S 250<sup>TH</sup>* *BIRTHDAY*

- 1 INTRODUCTION AND UNRESOLVED CLINICAL ISSUES.
- 2 DIFFERENTIAL DIAGNOSIS.
- 3 INVESTIGATIONS.
- 4 PROGNOSTIC FACTORS-PROGRESSION FOR PD.
- 5 MEDICAL TREATMENT .  
MOTOR AND NON MOTOR

**Success is a prize to be won. Action is the road to it.**

**Chance is what may lurk in the shadows at the road side.**

**- O. Henry**

- 6 SURGICAL TREATMENT.
- 7 INVESTIGATIONAL PHARMACOLOGICAL TREATMENT.
- 8 INVESTIGATIONAL SURGICAL TREATMENT.
- 9 ALTERNATIVE TREATMENT.
- 10 FUTURE DIRECTIONS.

*Discipline Weighs Ounces  
Regret Weighs Tons*

*STEP ONE:*

◆ INTRODUCTION  
& UNRESOLVED  
ISSUES:

## IN ASIA:

- ♦ **Parkinson's Disease in Southern Asia (Extrapolated Statistics)** Afghanistan 104,829, Bangladesh 519,634 Bhutan 8,035 India 3,915,700 Pakistan 585,280 Sri Lanka 73,180.
- ♦ Prevalence in Parsi community is 328.3/1000 population (Bharucha.N.E).

*Do not fear to be eccentric in opinion for every opinion now accepted was once eccentric-bertrand russel*

# PARKINSON'S DISEASE

## Classical Clinical Features

- Resting Tremor
- Cogwheel Rigidity
- Bradykinesia
- Postural Instability

*"There is dignity in suffering; nobility in pain;  
but failure is a salted wound, that burns and burns again!"*



# PARKINSON'S DISEASE

## MOTOR MANIFESTATIONS:

- Micrographia
- Hypophonia
- Hypomimia
- Shuffling gait / festination
- Drooling
- Dysphagia

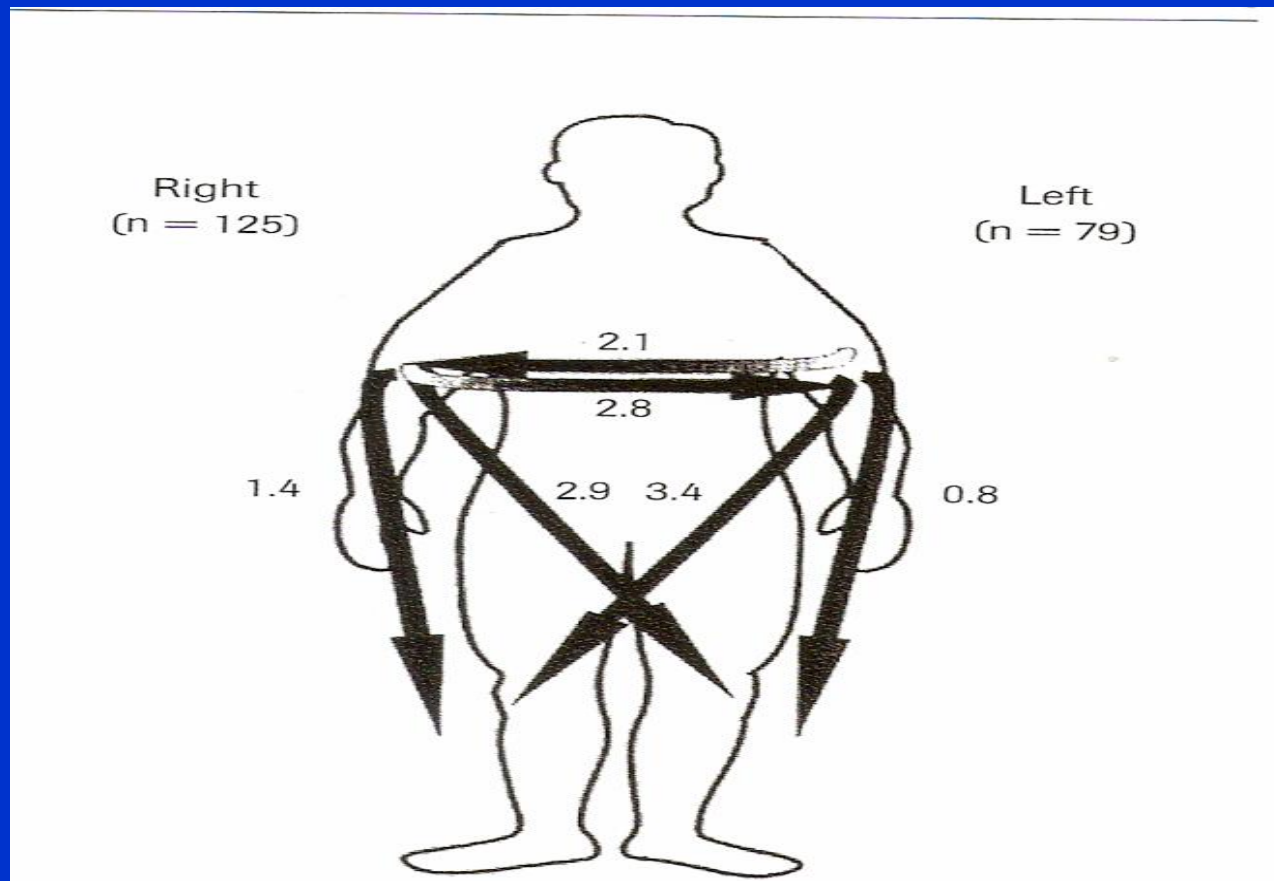
*The power to believe in yourself, is the power to change fate*

# *NON MOTOR SYMPTOMS OF PD:*

- ◆ COGNITIVE PROBLEMS-  
APATHY,DEPRESSION  
ANXIETY,HALLUCINATIONS,FATIGUE.
- ◆ GAIT AND BALANCE  
DISTURBANCE,HYPOPHONIA,SLEEP  
DISORDERS AND SEXUAL DYSFUNCTIONS.
- ◆ BOWEL PROBLEMS,DRENCHING  
SWEATS,SIALORRHOEA AND PAIN

*Memory, the daughter of attention ,  
is the teeming mother of knowledge - Martin  
Tupper*

# *UNRESLOVED ISSUES- SOMOTOPTOPIC PROGRESSION OF PARKINSON'S DISEASE:*



# *STAGES OF PD*

- ♦ EARLY
  - no functional impairment
- ♦ MILD
  - honeymoon period
- ♦ MODERATE
  - multiple drugs, occupational and social activities affected.
- ♦ SEVERE
  - side effects from drugs, resistant to therapy, reduced quality of life.
- ♦ LATE
  - dependent in ADL, wheelchair or bed bound

*Eugene C. Lai, M.D., Ph.D.*

*We do not know one millionth of one percent about anything –*

*Thomas Edison*

# *CLINICAL CLUES:*

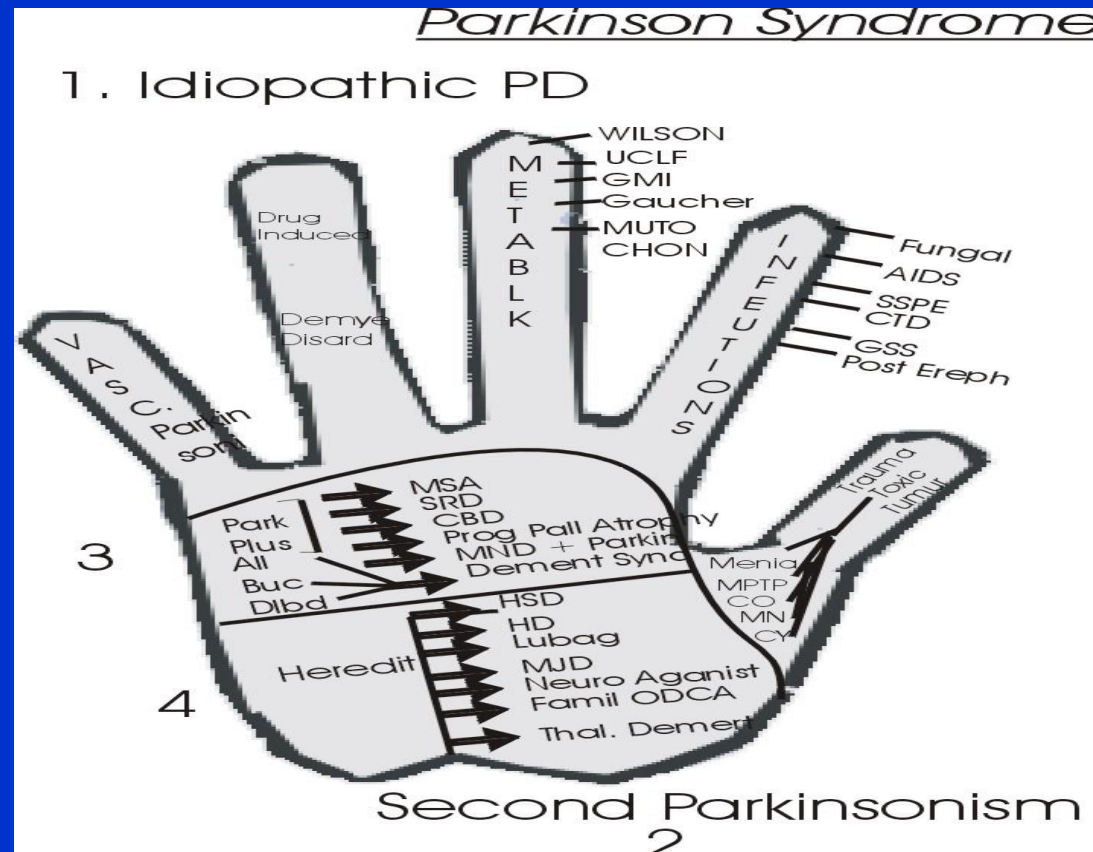
- ♦ YOUNG ONSET-WD,HSD,DRUG.
- ♦ ABSENT TREMOR-PSP,VAS-PARKIN.
- ♦ ATYPICAL TREMOR-CBD,MSA.
- ♦ GAZE PARESIS-PSP.OPCA,CBD,DLBD,PSG.
- ♦ HALLUCINATIONS,DEMENTIA-DLBD.
- ♦ DYSAUTONOMIA-MSA.
- ♦ MYOCLONUS-CBD,CJD,MSA.
- ♦ AMYOTROPHY-MSA GUAM'S DEMENTIA.

**Marriage and Private Practice are the two extinguishers of science**

*STEP TWO:*

DIFFERENTIAL  
DIAGNOSIS:

# DIFFERENTIAL DIAGNOSIS:



*“Many Ideas grow better when transplanted into another mind than in the one where they sprang up”*

*– O.W. Holmes*

*STEP THREE:*

◆ INVESTIGATIONS:



# *IMAGING NEUROTRANSMITTER FLUXES*

- ◆ SPECT & PET – study synaptic Neurotransmitter fluxes.
- ◆  $^{11}\text{C}$ -raclopride-PET
- ◆  $^{11}\text{C}$ -raclopride binds d2 receptors only.
- ◆ %Reduction of Striatal(and Not that Of Frontal reduction) endogenous DA leads to Problems with Executive Tasks

# *Brain Imaging-Newer Developments:*

- ♦ 1)Trans Cranial Sonography
- ♦ 2)Diffusion Weighted Imaging-MRI
- ♦ 3)Diffusion Tensor Imaging
- ♦ 4)Imaging of Neurotransmitter Fluxes
- ♦ 5)Imaging of Microglial activation
- ♦ 6)Blood Brain Barrier Imaging
- ♦ 7)Future Research.

*The world is full of willing people some willing to work the rest willing to let them-R.,Frost*

## *STEP FOUR:*

- ◆ PROGNOSTIC  
INDICATORS AND  
PROGRESSION OF PD:

# *PROGNOSTIC INDICATORS*

- ♦ LONGER DISEASE DURATION OF DISEASE.
- ♦ DEMENTIA.
- ♦ SE<70,PIGD SCORE.
- ♦ BRADYKINESIA.
- ♦ SYMMETRICAL DISEASE AT BASELINE.
- ♦ SEX AND DEPRESSION.

*The great aim of education is not knowledge but action-henry spencer.*

*STEP FIVE:*

◆ MEDICAL  
TREATMENT FOR  
PD:

# **MEDICAL TREATMENT:**

## **THE EVOLUTION:**

- ♦ 1800 - Anti Cholinergics (Bell. Alkaloids)
- ♦ 1950 - Synthetic
- ♦ 1960 - L Dopa
- ♦ 1970 - L Dopa / C Dopa
- ♦ 1976 - Dopa Recep.agonists, BCP pergolide
- ♦ 1987 - LD / CD – SR
- ♦ 1989 - M.A.O. b Inhibitor selegiline

***Expert is one who think to his  
chosen mode of ignorance***

# *Newer drugs*

Mid 1997 - Pramipexole

a) DRA Late 1997 - Ropinirole

b) Comt Inhib. Early 1998 - Tolcapone

c) Apomorphin Inj. 2001 -  
(1951)

d) LDME, LDEE

Levodopa patches and nasal spray –  
Research

settings

*“By Nature All Men/ Women are alike but  
by Education widely different”*

# *Symptomatic therapy*

- *EARLY SYMPTOMS*

- Anti Cholinergics
  - Amantidine
- Young Tremu. Pts.
  - Mild Bradykinesia
  - Mild Rigid
  - Mild Gait Disturb.

*Material Gains Soul Losses*



# LONG STANDING POLEMIC – EARLY OR LATE

## ♦ Early:

Mortality is less  
loss of Efficacy and  
side effect Increase

Dyskin. increase in younger  
onset PD (Cederbium and  
kosnc 1991)

(Diamond 1987, Scigil 1990)

- Empirical clin. observation to cellu. biochemist
- Murer 1998 – No Study – Detrim. to human Nigral cells

## ♦ Sign of Independence Decreased – Start

*“Back pain – prize human beings pay  
for their UPRIGHT POSTURE”*

## • 4 DRUGS

- 10 mgm BCP– 1mgm Perg. – 1 mgm Prami. - 3 mgm. Ropir
- (Goeth 1999)
- All are D<sub>2</sub> Agonists, each has unique profile to D<sub>1</sub>, Noradr, Serto, Activit
- High Dose BCR – 50 mgm / Day – Comp. To L Dopa (Moutastrier 1989 – 3 years)
- Other drugs not studied
- Reduction of Motor Fluctuations

❖ 300 – 600  Agonist is Added

L Dopa      Disability More

Side Effects: Hypotension, Dyskinesia, Halln

- Pramipexo: 45 mgm; Ropinirole 24 mgm /Days
- ❖ Cabergoline – Once daily 1997; 1998. Rinne.
- ❖ Seligi can be added to L Dopa; Olanow 1998

*A true commitment is a heart felt promise to yourself  
from which you will not back down – D. McNally*

♦ Catecholamine – O – Methyl Transferase inhibited ‘ COMT Inhib.’

- Entacapone

Tolcapone

ACTS

- Prim. Extracerebrally      Extra and intra cerebrals  
Inhi. Meta. of Dopam.  
in brain (NUTT 98)  
- Hepatic Toxicity

*“Woman needs society demands”*

## ♦ *ADVANCED PARK. DISEASE*

- Tremor, Bradykinesia, Motor Fluctuations
- Dyskinesias, Freezing, Dysphagia
- Dysautonomia, Beha., Psychia Symptoms
- Diff. Approach → Free Interact → May  
limit Therapy

*“Healthy Mind and Healthy expression of Emotion  
Go hand in Hand”*

- Fluctuations (Motor) – Short, Medium, Long

- On

Peak Dose -  
Square Wave } Mobile Choro –Dystonic

- Interface      Diphasic  
                         Diphasic

- Off              Off Period  
                     Early Morning

} Fixed Dystonic

Untreated/Drug Holiday

*Starving Emotion* – *Humor Less; Rigid;*

*Stereotype*

*Repressing Emotion* – *Literal; Holier than thou*

*Encouraging Emotion* – *Performs in Life*

*Discourage Emotion* – *Poison Life*

*Juseph Colins. 1868*

***Table Symptoms unresponsive to levodopa therapy***

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**Motor**

- Postural instability
- Freezing of gait
- Speech abnormalities
- Dysphagia

**Mental Changes**

- Dementia
- Depression
- Apathy

**Autonomic nervous system dysfunction**

- Constipation
- Sexual dysfunction
- Urinary problems
- Sweating

**Sensory phenomena**

- Pain
- Dysesthesias

**Sleep disturbances**

- Sleep fragmentation
  - Sleep apnea
  - REM behavioral disorder
  - Restless leg syndrome
-

- ***DYSARTHRIA / HYPOPHONIA***
  - Speak Slowly
  - Aug. Comm. Devices
  - Using Writt. Notes
  - Rule out Imp hearing
- ***DYSPHAGIA***
  - Diff. to treat
  - Coughing after swallow – Early ASPN
  - Weight - Gastrostomy
- ***IMBALANCE AND FREEZING***
  - Diff. to treat
  - Wheelchair – Walker

*“He who cannot forgive others destroys the bridge over which*

*he himself must pass” — Anon*

- **URINARY SYMPTOMS**

- Incontinence never occurs but urgency / Ppt. can
- Obst. Sympt. Poor pharmacology
- Off period anuria
- High incidence of post surg. Incontinence

- **CONSTIPATION**

- Mild - Exercise/Fluid/Fiber/Fresh leaves/Stool softener
- Bowel stimulant Bisacodyl; Senna casenca

- **IMPOTENCE**

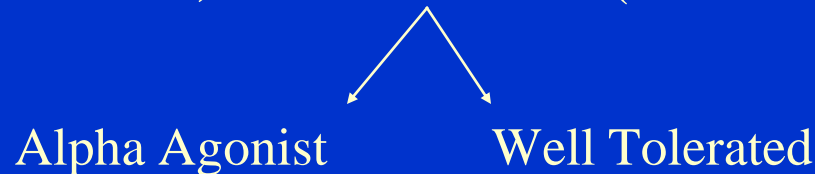
- Devices and Drugs : Sildenafil

*The Truth is fear and immorality are two of the greatest inhibitors of Performance too progress*



# ORTHOSTATIC HYPOTENSION

- Avoid Hypnotics and anti depress.; increase hypotension
- Avoid Deprenyl – Worsen L Dopa Hypotension
- Take Sometime to resolve
- High Sodium diet; pressure stockings;
- Fludrocortisone; MIDODRINE (Low 1997)



- NSAIDS; CLONIDINE; EDHEDRINE; DOMPERIDONE  
PROPANALOL

*“Men of Genius Admired: Men of Wealth envied:  
women of power feared: But only women of character are  
trusted”*

*-A- Friedman*

# ***COGNITIVE AND BEHAVIOUR PROBLEMS***

- Fecal impaction – Worsens Behaviour
- Hypersexual; Visu. Hallu; Paranoid Ideation; Reversal of sleep wake cycle decrease NREM - Dopa agonist
- Confusion can be produced by digoxin; propranolol oxybutynin or Diphenhydramine
- Haloper/Thioridazine - Paranoid ideation; or agitation  
clozapine is ideal (PSG – 1999) – Agranulocytosis
- Risperidone / Olanzapine - Do not tolerate
- **Quetiapine – Promising**

*“ Maintaining the right attitude is easier than regaining the right mental attitude ”*

# *Non dopaminergic therapies*

- Estrogen - Women (Dementia less motor disab. less)
- VIT D-Elderly people Mards 98 Saunders 95



Hip #s (SATO 1999)

*Many Ideas grow better when transplanted into  
another mind than in the one where they sprang UP*  
*O.W. Holmes*

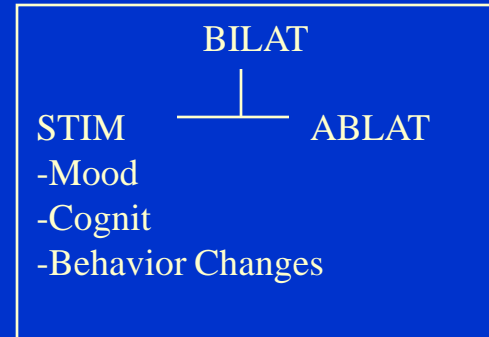
*STEP SIX:*

◆ SURGICAL  
TREATMENT:

## ♦ *SURGERY*

- Asymmetrical Tremor- Thalamus
- Asym. Dyskinesia - GB(I)
- Both - STN

(Bler 1999)



## ♦ *IMPLANT OF EMBRY. DOPA TISSUE*

- Fahn 1995
  - Benefits under 60
- (40 Pts)
  - No improv. in Dyskinesias/Motor Fluctuations
  - Improve in off symptoms
- Genetically engineered cells. Pre clinical Develop

*“Peace Rules the day where reason Rules the mind”*  
– Colling

# *INVESTIGATIONAL MEDICAL TREATMENT-CONTD.,*

- ♦ MAO INHIBITORS:  
**SAFINAMIDE, BRASOFENSINE.**
- ♦ AGENTS WITH NOVEL MECHANISMS OF ACTION:  
ADENOSINE RECEPTOR ANTAGONISM:  
Istradefylline, BIIB14/ V2006, E2007, SIB1508 Y.
- ♦ CEP-1347(KINASE FAMILY)
- ♦ E2007(AMPA RECEPTOR ANTAGONIST) .
- ♦ SIBI 1508 Y(NICOTINIC ACH RECEPTOR AGONIST).
- ♦ GDNF
- ♦ GP1-1485(NEUROIMMUNOPHILIN RECEPTOR PROTEINS)
- ♦ **CREATINE, MINOCYCLINE, COENZYME Q 10.**

# *DBS Conclusion*

Symptoms	STN	GPI	VIM
Tremor	+++	++	+++
Akinesia	+++	+	0
Rigidity	+++	++	+
Gait	+++	++	0
Dyskinesia	Short	+++	+
Off Period Dystonia	+++	++	0

*Experience can be defined as yesterday's answer to today's problems*

## *STEP SEVEN*

# ◆ INVESTIGATIONAL MEDICAL TREATMENT:



# *NEWER DRUGS FOR DYSKINESIA:*

- ♦ SARIZOTAN –affinity for 5HT1A,D2,3&4 receptors.
- ♦ LEVITARECETAM,SV2A receptor binder.
- ♦ ACP103 -5HT 2A/C antagonist.
- ♦ FIPAMEZOLE-alpha-2adrenergic antagonist (similar to yohimbine and idazoxan).

*The last enemy that shall be destroyed is death-corinthians.*

*STEP EIGHT:*

◆ INVESTIGATIONAL  
SURGICAL  
TREATMENT :

- ◆ NOVEL STIMULATION APPROACHES:  
PPN,MOTOR CORTEX STIM,EARLY DBS.
- ◆ INTRACEREBRAL DRUG INFUSION:  
GDNF,NEURTURIN
- ◆ FETAL TRANSPLANTATION.
- ◆ STEM CELL THERAPY:  
EMBRYONIC NEURONAL & NON NEURONAL
- ◆ GENE THERAPY:  
DOPAMINE SYNTHESIS, TO ALTER  
BASAL GANGLIA PHYSIOLOGY, PARKIN  
GENE THERAPY & IV GENE THERAPY.

*It does not matter how slowly you go as long as you don't stop-Confucius*

# *Gene Therapy for PD*

- DA Replacement by delivering NT Synthesizing gene
- Donor cell or genetically engineered cells as alternate to fetal cells
- To provide L-dopa into brain by introducing Tyrosine Hydroxylase (TH) gene
- Initial studies - Cell line Rat fibroblast, NIH 3 T3 cells, Endocrine cell line, Primary cell, Neuro Precursor cells

*Being ignorant is not so much a shame as being unwilling to learn*

*STEP NINE:*

◆ ALTERNATE  
THERAPY:

# *ALTERNATIVE THERAPY:*

- ♦ NON WESTERN MEDICAL SYSTEMS:  
TRADITIONAL CHINESE  
MEDICINE, AYURVEDICA MEDICINE.
- ♦ NATUROPATHY.
- ♦ HOMEOPATHY.
- ♦ CHIROPRACTIC.
- ♦ COMPLEMENTARY THERAPY.

*Education is a progressive discovery of our own  
ignorance. W. Durant.*

*STEP TEN:*

◆ FUTURE  
DIRECTIONS:

- ***RESEARCH***

- Trans Magnetic Stimulation
- 10 Hz - Akinesia / Rigidity
- 0.5 Hz - Post and Gait Distur.
- Transdermal Nicotine patch
- Flumazenil
- Lazabemide
- GM1 Ganglioside
- Viagra
- Trophic effect of L Dopa

*“Give us the **GRACE** to accept with serenity the things that cannot  
be changed;*

*The **COURAGE** to change the things that should be changed and;  
The **WISDOM** to know the difference”*









*Dedicated to my family  
for making everything worthwhile*



READ *not to contradict or confute*  
*Nor to Believe and Take for Granted*  
*but* TO WEIGH AND CONSIDER

THANK YOU

**My sincere thanks to**  
**BANGLADESH SOCIETY OF MEDICINE**  
**DHAKA-09/12/17**

**Former Faculty in Institute of Neurology,**  
**Madras Medical CollegeChennai-03**