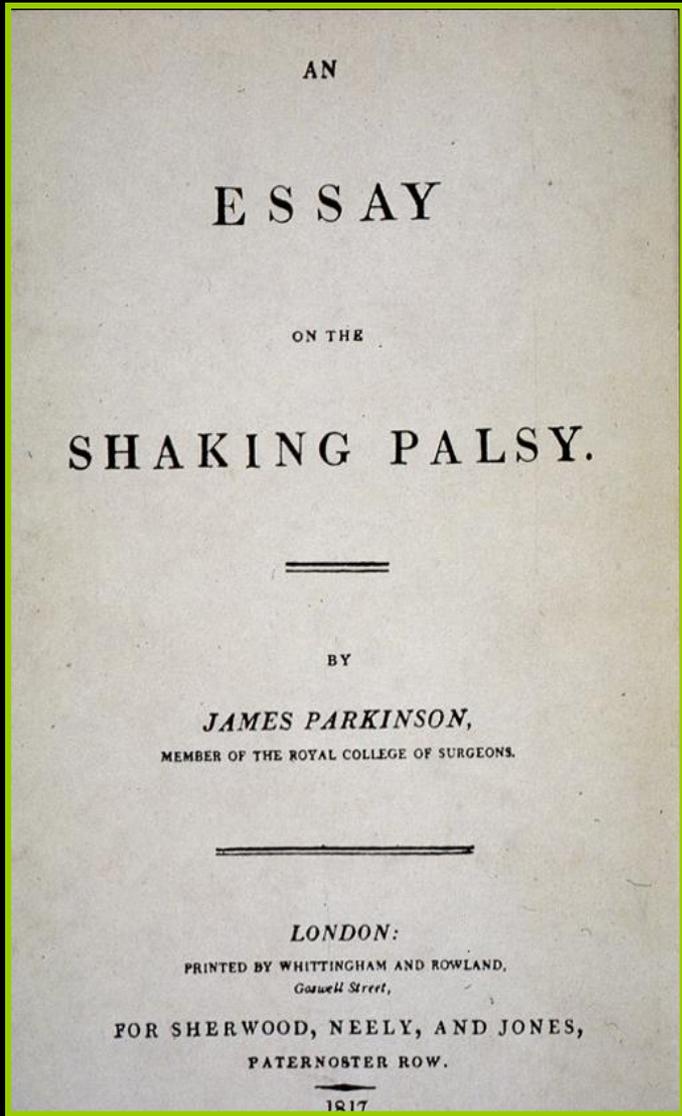


ABCs of Parkinson's Disease

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Parkinson's Disease (PD) Background



- First described as “shaking palsy” by James Parkinson in 1817
- Approximately 1 million patients in the United States
- 60,000 new cases each year
- Average age at onset: 55 to 60 years old
- Increased number of patients with age (3% of everyone >65 years old)

PD Biology

- PD is one of several “neurodegenerative diseases” with no clear cause in most cases: including Alzheimer’s Disease and Lou Gehrig's Disease.
- Neurodegenerative diseases show premature dysfunction and death of specific groups of nerve cells (neurons) which are not replaced.
- In PD, a severely affected group of neurons contain the neurotransmitter dopamine in a brain region called the substantia nigra. Their loss is the basis for the most movement related symptoms of PD and improvement with L-dopa



Brain of Normal Patient

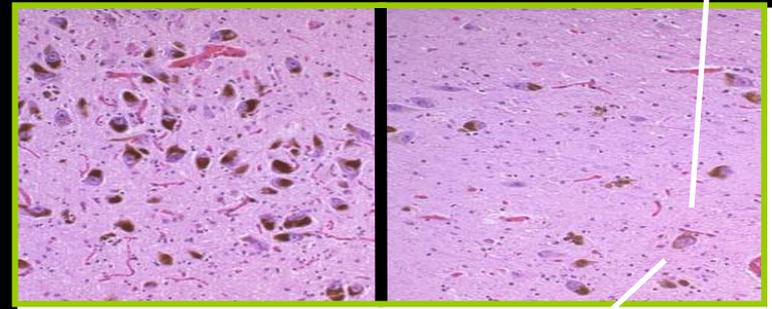


**Brain of Patient with
Parkinson's Disease**



Cell Changes in PD - Lewy Bodies

- Lewy bodies are the microscopic feature of Parkinson's disease
- Dense protein aggregates inside surviving brain cells.
- The major protein component of **ALL** Lewy bodies is α -synuclein where mutations are the first known cause of inherited PD (1996)
- α -synuclein is a major target for therapy for PD



Onset of Parkinson's Disease

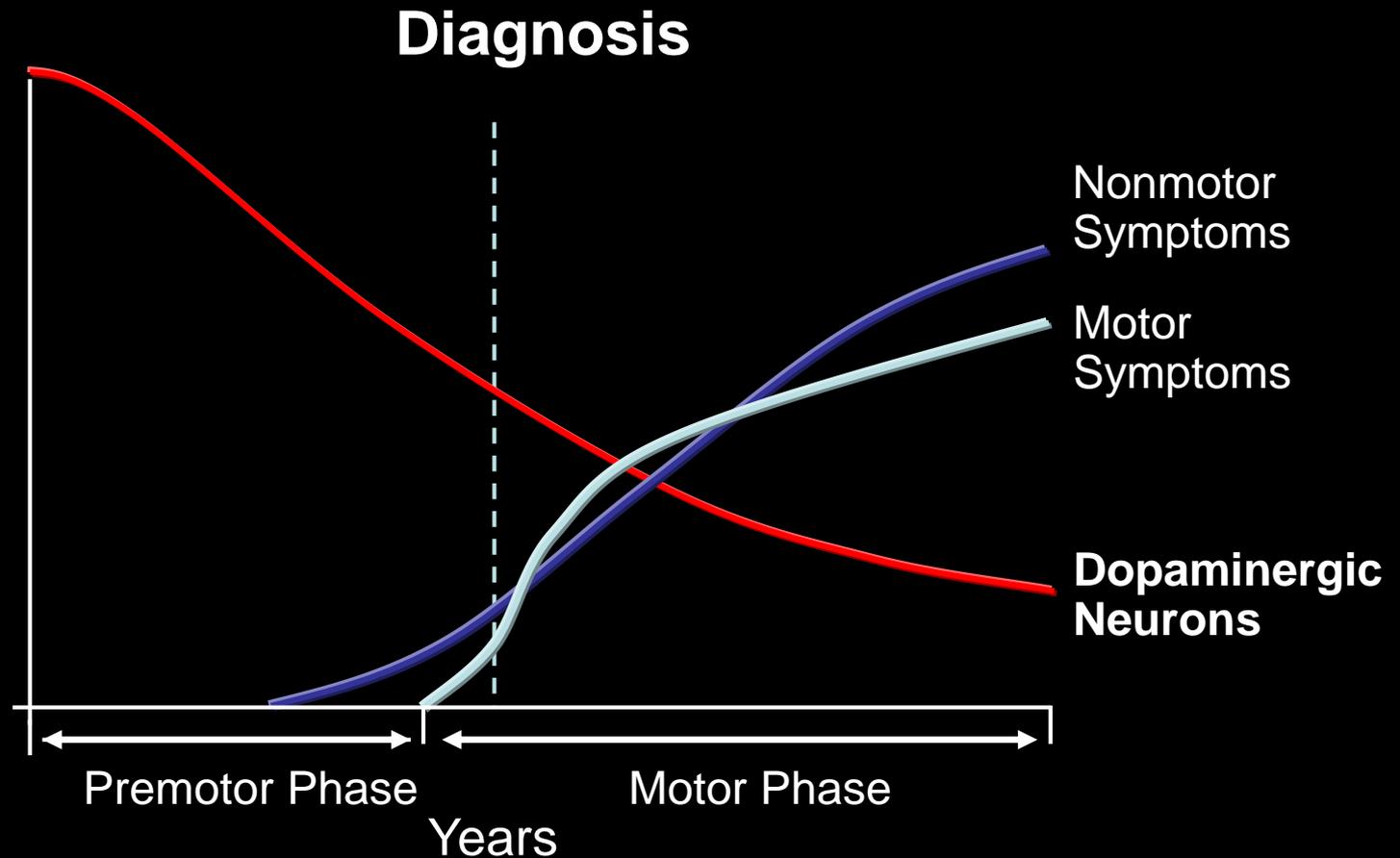
“So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow is its progress, that it rarely happens, that the patient can form any recollection of the precise period of its commencement.”

James Parkinson 1817

Early PD Symptoms

- Voice changes
- Handwriting changes
- Difficulty with buttoning buttons
- Holding an arm against your side
- Walking more slowly
- Hand shaking

Brain Changes Happen Years Before First Movement Related Symptoms of PD



A Dopamine Based Brain Scan (DaT) Is Reduced in PD Even Before Motor Signs

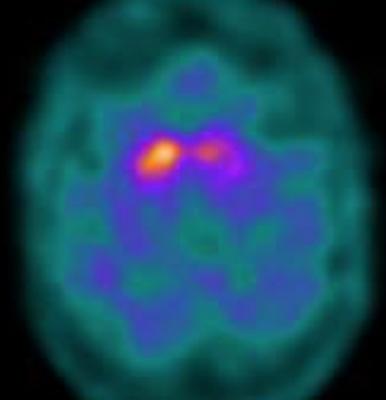
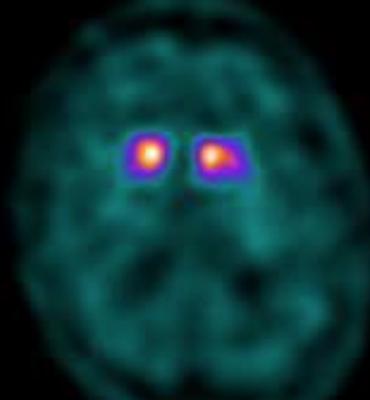
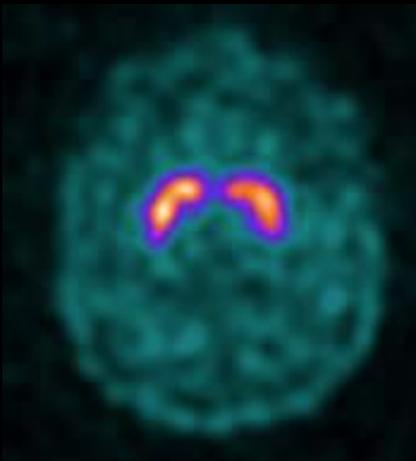
Normal
Dopamine
Uptake

Reduced Dopamine Uptake Gets Worse as PD
Worsens

At Dx

5 years later

10 years later



Non-motor Symptoms Can Occur First in PD

- Loss of sense of smell
- Sleep disorder (RBD)
- Constipation
- Depression

PD: Motor Signs

- Resting tremor
- Bradykinesia (slowness of movement)
- Rigidity (stiffness of the limbs)
- Postural instability (balance difficulty)

PD and “Parkinsonism”

- The accuracy of initial diagnosis of PD is only 80% even by experts when compared to brains donated by patients after death.
- Why?
 - 1) Other related Neurodegenerative Diseases
 - 2) Symptoms due to other causes such as stroke, certain medications and rarely infections

This may explain why about 20% of Parkinsonism is usually L-Dopa unresponsive.

Other Conditions Can Mimic PD

Distinguishing Features

Misdiagnoses

Tremor only



Essential tremor (ET)

Early falling, abnormal eye movements



Progressive supranuclear palsy (PSP)

Abnormal BP control, imbalance



Multiple system atrophy (MSA)

Awkward limb with abnormal touch



Corticobasal degeneration (CBD)

Early dementia, visual hallucinations



Dementia with Lewy Bodies (DLB)

Treatment Goals in Parkinson's Disease

- Relieve symptoms and minimize interference with function
- Avoid, delay, or reduce complications/side effects of treatment
- Slow or halt progression (**NO CURRENT PROVEN TREATMENT**)

Stages of Parkinson's Disease

Early

Moderate

Advanced



- Mild symptoms, no disability

- Moderate symptoms, some disability,
- Increasing medication

- Worsening symptoms
- Fluctuating response to therapy

- Increasing disability despite therapy

Management Options in Early PD

- Physiotherapy and exercise (of Proven Benefit)
- Medications – They all work at this point
- Complementary and alternative therapies
(No Consistent Benefit in Clinical Studies)

Carbidopa/L-dopa

- After 50 years still the most effective and widely used therapy, usually with the fewest side effects (nausea, dizziness)

Why not use just C/L on everybody with PD?

DOSE FLUCTUATIONS

Problems with L-dopa: *Wearing Off*

- L-dopa only lasts briefly in the blood (90 minutes)
- In mild PD it lasts much longer.
- After years of use, L- dopa acts like a short acting medication needing frequent dosing.

Problems with L-dopa: *Dyskinesias*

- Years of use of L- dopa leads to involuntary movements called dyskinesias
- Dyskinesias occur usually at high blood levels of L-dopa
- Patients tolerate mild forms of dyskinesias
- Severe dyskinesia can interfere with normal movements

Narrowing “Therapeutic Window”

- The therapeutic window of levodopa therapy narrows with years



- The Goal: Be “ON” as much of the day as possible with dyskinesia. But How?

Extend the Time that L-Dopa Works

- Block the breakdown of L-dopa (carbidopa, selegiline, rasagiline, tolcapone, entacapone)
- Long acting forms of carbidopa/l-dopa (CR, SR, SA, LA, Rytary)
- Adjustable pump of L-dopa into the gut (Duopa)



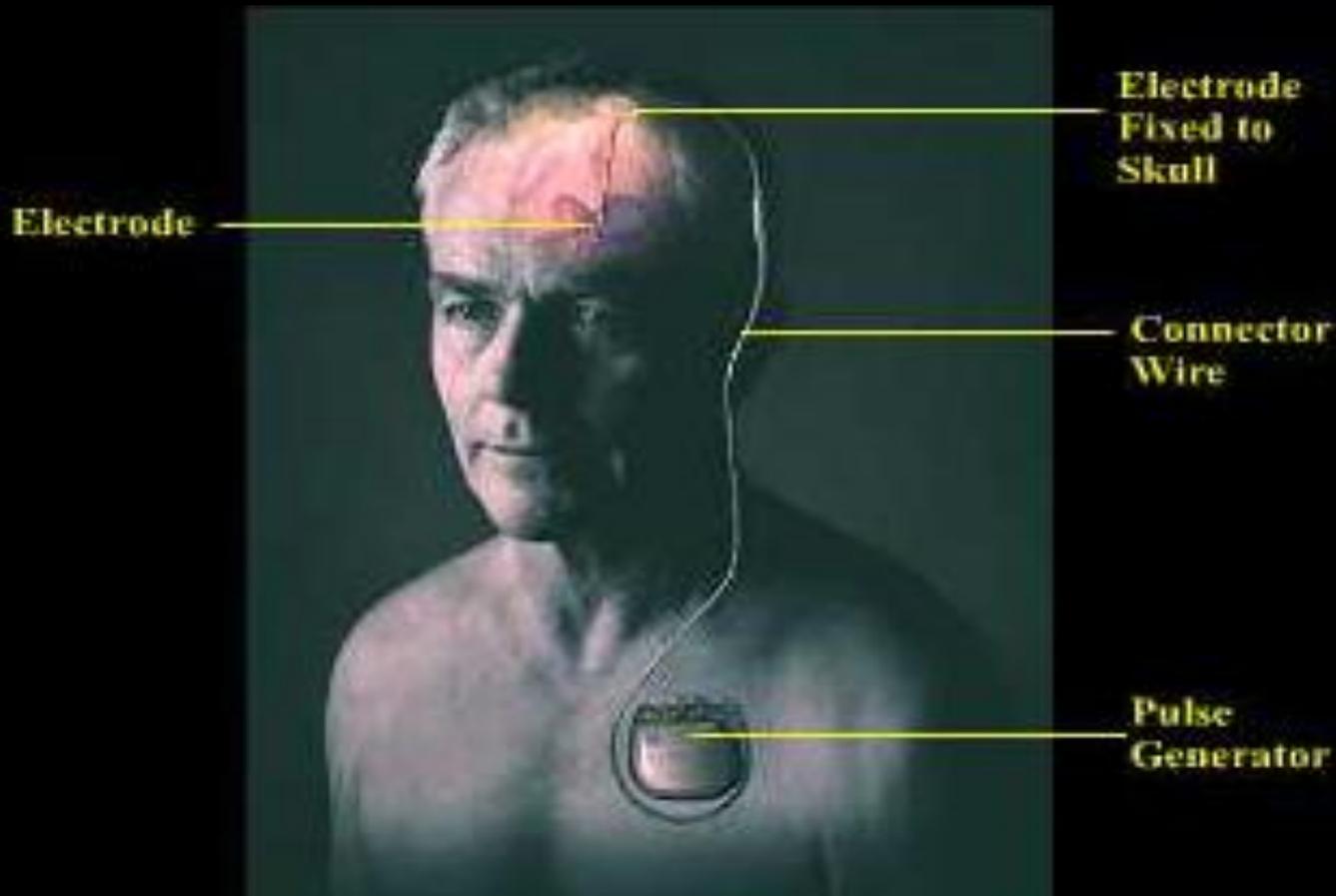
Longer Acting Meds for PD: Dopamine Agonists

- Pramipexole, Ropinirole, Rotigatine
 - Longer acting with less frequent dosing
 - Used alone in mild PD, and along with levodopa
 - Lower risk of developing dyskinesias
- BUT
 - More psychiatric side effects. Impulse control disorder
 - Less robust anti-PD effects compared with levodopa

Deep Brain Stimulation (DBS):

- An implantable pacemaker like device that interacts with brain activity to improve motor symptoms
- Symptoms improved by surgery **are also those** best improved with medication
- Motor fluctuations can be substantially improved, allowing a patient to be “ON” without dyskinesias

DBS – The Basics



The electrode is implanted in brain, fixed to skull by a cap and runs underneath the skin to the pacemaker like pulse generator implanted in the chest

Symptoms Not Improved by Surgery

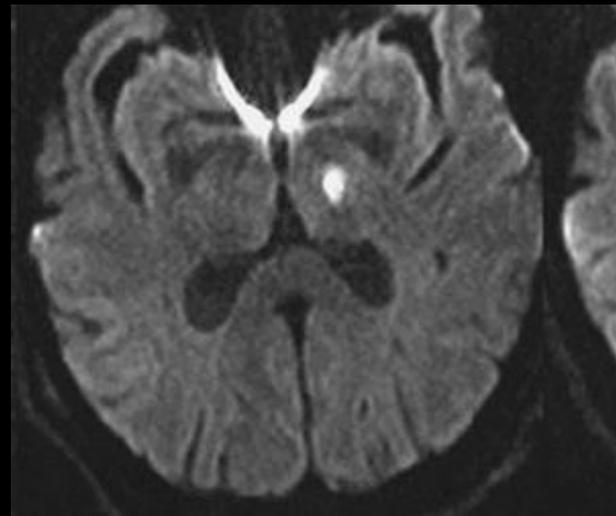
- Cognitive and Psychiatric Symptoms
- Swallowing Difficulties
- Poor Balance

Risks of Surgery

- Bleeding into the brain 2-3%
- Infection 1-3%
- Hardware Problems 1-5%
- Short Term Changes in Thinking and Behavior (5%)

Non-Invasive Brain “Surgery”. What’s All the FUS About?

- Pre-DBS – Destruction of overactive brain centers by surgical placement of a microwave heat probe
- Now Experimental – Destruction of overactive brain centers by MRI guided **focused ultrasound (FUS)** without surgery



Advanced PD

Symptoms Unresponsive to Dopamine Therapy

- Loss of Balance
- Freezing
- Loss of thinking capacity

Symptoms Worsened by Dopamine Therapy

- Blood pressure regulation with position
- Dementia
- Psychosis



Psychosis and Dementia

- All PD medications can worsen psychosis (hallucinations and delusions).
- Most anti-psychotic meds can worsen motor symptoms of PD
- Anti-Alzheimer's drugs (AChE Inhibitors) may also be helpful in PD for both dementia and psychosis

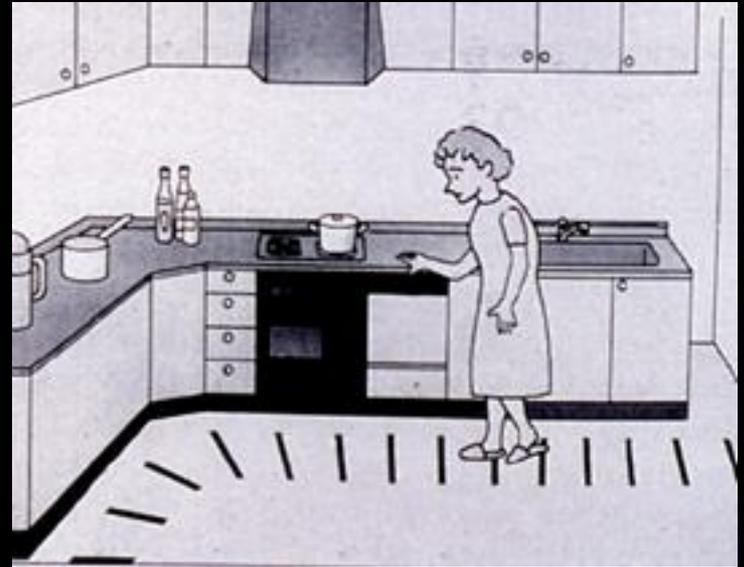
Falling

Many medications will worsen balance (sedatives)

In severe PD, medications usually do not help balance

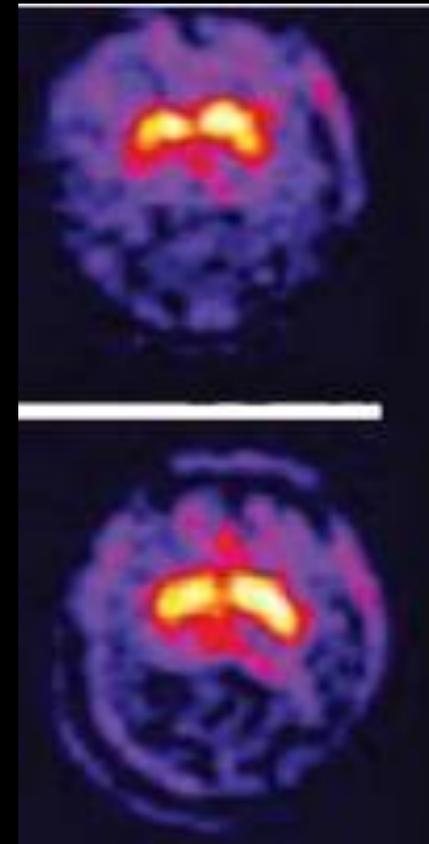
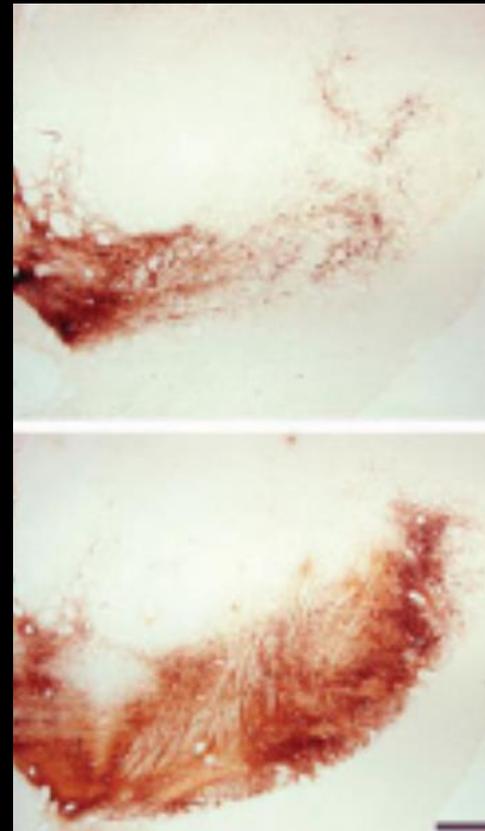
Falls can be prevented with

- Gait and Safety Training (PT)
- Appropriate Device



Experimental Restorative PD Therapies

- ❑ Drugs to block the toxicity of synuclein or accelerate its clearance
- ❑ Growth Factor Infusion
- ❑ Gene Infusion
- ❑ Stem Cell Transplantation



Maintaining a Balance of Hopeful Optimism and Healthy Skepticism

“Ah but a man’s reach should exceed his
grasp, Or what’s a heaven for?”

Robert Browning

“For every complex problem there’s an
answer that is clear, simple, and.....
wrong”

H. L. Mencken