Parkinsonism or Parkinson’s Disease

I. Symptoms: Main disorder of movement.

Named after ________________, an English physician who described the then known ________________, in 1817.

Four (4) hallmark clinical signs:
1) Tremor: ________________________________
   (Note - tremors are often earliest signs of disease (early stage)).

2) Rigidity: ______________________________

3) Bradykinesia: ______________________________
   (Note - these are the symptoms occurring in the later stages).

4) Akinesia: ______________________________

Other clinical signs associated with Parkinsonism: expressionless features (mask like expression), feeling of weakness, flattening (monotone) and weakness of voice, small writing, excessive salivation, difficulty in focusing eyes, sleep disturbances.

- in some cases, especially in advanced stages, symptoms overlap with depression and Alzheimer’s disease.
Parkinsonism is a disease of the “extrapyramidal motor system”.

Question: What is pyramidal motor pathway?

II. Etiology (causes)
Natural causes of Parkinson’s disease are not known - but some clues about its etiology are:
- it’s onset usually occurs later in life - first symptoms appear in approximately _____ of individuals between the ages of ________.

- approximately 1% of people over 60 have Parkinson’s disease.

- it is a __________ illness - usually begins with benign symptoms (tremors) before it produces serious motor dysfunctions.

- many observed ____________________ in the presentation of initial symptoms, progression of disease, and response to pharmacological treatment.

- in 1997, a group of scientist at NIH claimed the discovery of an abnormal gene that is linked to the development of Parkinson’s disease, but _______________________________.

- some observed links with environmental (chemical) pollution - but incidence has not really changed since beginning of industrial revolution, when human-made harmful chemicals were in low abundance.

Note: the syndrome can be caused by certain drug treatment (MPTP), (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine).
III. Underlying mechanisms
Basic studies of movement have identified 3 systems involved in motor control:

1) __________________________
2) __________________________
3) __________________________

Parkinsonism imply a disorder of the ________________________.

Components and function of extrapyramidal motor system:

The extrapyramidal circuit _________ the final motor program from motor cortex (provided by the pyramidal system) to muscles.

Anatomical components:

**Basal Ganglia:**

a. __________
b. ______
c. __________
d. ________________________________
e. __________

Input to basal ganglia: ________________________________

Output of basal ganglia: ________________________________

_______________________________________________.
Connections of basal ganglia:

Important facts to remember about basal ganglia:
- inputs to caudate and putamen are excitatory (______________
  __________________________________________________________________________).
- Caudate and putamen neurons (_______________________________) are
  normally quiet and project to Globus pallidus.
- Globus pallidus neurons (_______________________________) are normally
  _______ - project to, and inhibit, ventral lateral nucleus of thalamus.
- neurons in ventral lateral nucleus of thalamus are __________
  (_________) and project to premotor and supplementary motor areas
  of the frontal lobe.
- there is a _____ pathway going through the internal Globus pallidus.
- there is an ________ pathway going through the external Globus
  pallidus via the subthalamic nucleus.
- activation of both direct or indirect pathways lead to _______ of the
  internal Globus pallidus and ______________ of thalamic nucleus.
because the basal ganglia receives inputs from multiple cortical areas, it is believed that the system helps mediate higher order cognitive aspects of motor control - ex. fine tuning, initiation, and termination of muscle sequences.
Specific neural defects associated with Parkinson’s disease:

Determined by a series of important findings:
1. Animal studies by Swedish scientists in the 1950’s
   a. large concentration of ___________ in striatum.
   b. treatment of laboratory animals with _________ (a tranquilizer) depletes brain DA and produces _______________ similar to those of Parkinson’s patients.
   c. ________could normalize (even reverse) the deficits in reserpine-treated animals.

2. Post-mortem studies on human brains in 1960
   a. large decrease in DA content of brain of Parkinson’s patients compared to ____________________.
   b. high correlation between the _____________________ and the magnitude of DA depletion.
   c. accumulation of ___________ (aggregates of cytoskeletal proteins) within the cytoplasm of substantia nigra neurons (dying cells??).
   d. _____________________________________ - these cells are the source of DA and their destruction results in decreased DA release at their target (striatum).
3. Human clinical studies, first report in 1967
   - L-DOPA treatment produced dramatic improvement in the symptoms of Parkinson’s patients.

   **This was the first discovery that a neurological disorder could be the result of a specific neurotransmitter disorder.**

**Review of Dopamine synaptic transmission**

A. Synthesis of neurotransmitter:
   1. Facilitated transport of precursor (amino acid tyrosine) into cell.
   2. Conversion of precursor molecule into DA (produced by a series of enzyme-mediated chemical reaction).

B. Package DA molecule into vesicles
   1. Facilitated transport of DA into vesicle.

C. Release (exocytosis) of DA into synapse
   1. Action potential invades presynaptic terminal.
   2. Opening of voltage-dependent Ca++ channels.
   3. Influx of Ca++ into presynaptic terminal.
   4. Ca++ mediated fusion of synaptic vesicle with presynaptic membrane.
   5. DA exocytosis.

D. Neurotransmitter action
   1. DA binds to postsynaptic receptors; or
   2. DA binds to presynaptic receptors

E. Inactivation of DA
   1. Re-uptake of DA into presynaptic neurons (transporter protein):
      a. recycling of DA into vesicles; or
      b. degradation of DA in neuron (monoamine oxidase-B)
Drugs and molecules that modulate DA transmission

1) **phenylalanine**: amino acid that can be converted to tyrosine by enzyme phenylalanine hydroxylase.
2) **alpha-methyl-p-tyrosine**: blocks tyrosine hydroxylase.
3) **carbidopa**: ________________________________.
4) **reserpine**: ________________________________.
5) **conotoxin**: voltage-gated Ca$^{++}$ channel blocker.
6) **bromocriptine, pergolide**: ________________________________.
7) **haloperidol**: D$_2$ dopamine receptor antagonist.
8) **amphetamine, cocaine, methylphenidate**: block reuptake of DA into presynaptic terminal (also facilitate release from synaptic vesicles).
9) **deprenyl**: inhibitor of monoamine oxidase type B.

Draw a synapse, with all components involved in DA transmission.
Treatment of Parkinson’s disease

Specific defect is: ________________________________.

Treatments: Overall strategy is: ________________________________.

A. Specific drug therapies, effectiveness, and short-comings:

1. *Give dopamine (DA):* not effective - _____________________________
   
2. *Give DA precursor (L-DOPA):* effective in improving and even relieving symptoms.
   - ________________________________
   - produces some ________________________ (nausea, confusion, involuntary movements).

3. *Give L-DOPA and carbidopa:* can be more effective than L-DOPA alone in relieving symptoms.
   - has similar side-effects as with L-DOPA alone.

4. *Give D_2 receptor agonist with L-DOPA:* can have increased effectiveness compared to L-DOPA alone, especially in the more advanced stages of the disease.
   - can produce ____________________________________________________________

5. *Give DA re-uptake blocker:* may be effective initially, but will lose effectiveness at more advanced stages of disease when too many substantia nigra neurons are dead.
   - because it increases overall dopamine activity at all dopaminergic synapses, these produce a range of side-effects.

6. *Give a drug that blocks DA degradation:* effectiveness and side-effects similar to DA re-uptake blockers.
Treatment of Parkinson’s disease (continued)

B. ________________________: lesions of the internal globus pallidus (pallidotomy) have been attempted to remove the “inhibition” and improve the symptoms of tremor and rigidity. 
- proved to be moderately effective, but did not usually improve the bradykinesia.

C. ________________________________________________: a relatively recent FDA approved treatment (1997) for Parkinson’s disease is the implantation of stimulating electrodes in the subthalamic nucleus, which can be turned on by the patient (thoracic implant).
- shown to improve slowness of movement (akinesia, bradykinesia).

D. ________________________: involves implanting directly into the striatum (caudate or putamen or both) undifferentiated cells from adrenal chromaffin cells or mesencephalic substantia nigra neurons.
- has provided extremely limited relief of symptoms, and has been shown to have a high rate of perisurgical complications.
- implants from adrenal chromaaffin cells usually do not survive and provide no DA to the striatum.
- slightly more promising for mesencephalic tissue implant (some DA cells shown to survive, but patients remained symptomatic).