Development Disorders

- Inherited metabolic disorders: deficiency in the production of an enzyme.
  Genetic bases
- PKU (Phenylketonuria): deficit in phenylalanine → tyrosine conversion
  - Lack of myelination
  - Mental retardation if untreated
  - Detectable by birth. Preventable by appropriate diet (low protein)
- Lack of vitamin B6: damage to thalamus and cerebellum
- Lack of (mile) glucose metabolism (Galactosemia): damage to cerebellum and cortex
- Tay-Sachs disease: inability to breakdown cellular ate products. Accumulation of waste, brain swelling, death. Eastern European Jewish population. There is a retinal diagnosis
- Down Syndrome: Congenital (‘born with it’)
  - 1/700 children. 350,000 people in the US
  - Extra chromosome 21 in mother’s ovum. Over-expression of genes. Can be detected before birth
  - 10% less brain. Less neurons in frontal lobe and Sup. Temp. Gyrus (Wernicke’s area)
  - Mild to severe mental retardation. Can learn to have almost normal lives. No curve
  - Research: Focused on avoiding associated diseases (heart condition, epilepsy, hearing/vision deficits…). Determine gene over-expression pattern

Degenerative Disorders

- Transmissible Spongiform Encephalopathy (aka mad cow disease)
  - E.g.: Bovine Spongiform Encephalopathy (BSE= mad cow disease), Creutzfeldt-Jakob disease, scrapie (animals only)
  - Sporadic: can be infectious or genetic
  - Caused by ‘protein infectious agents’ (prions). Found in neural membrane, important for synaptic function and myelin. Normal aminoacid composition, but misfolding
  - Symptoms similar to Alzheimer’s but faster and deadlier
  - No known treatments in human. Genetic manipulations in mice

- Scrapie can be treated by late onset destruction of (normal) Prions. Prions are useful for development. Treatment involves a prion-destructive protein produced after 12 weeks (mice)
● Possible genetic therapies: Selective activation of cell death in infected cells only. Use Caspases: Enzyme that triggers cell death (aka apoptosis)
● **Parkinson’s Disease**: classified as movement disorder
  ○ Symptoms
    ▪ Rigidity, slow movement, absence of reflexes, tremors at rest (but not during sleep or voluntary movements), posture and walking abnormalities, bradykinesia, and akinesia
    ▪ Initially, little intellectual impairments. As it progresses: speech impairments, decreased Short Term Memory, slower problem-solving and slower visual spatial skills
    ▪ Mood changes, including depression. Anxiety also common
    ▪ In general not hereditary. Sporadic. Affects 0.5% of adult population, slow progression (about 20 years).
    ▪ No single causes (genetic, strokes, tumors, infections…) No cure

**Degenerative of the Basal Ganglia**
● Neural structures affected
  ○ Degeneration of Pars Compacta region of Sub. Nigra → Basal Ganglia
  ○ Caused by cell death of dopamine neurons
  ○ Decreased activity of 4 areas that receive inputs from the basal ganglia
    ▪ Motor cortex
    ▪ Oculomotor and associative areas
    ▪ Limbic system
    ▪ Orbitofrontal cortex

**Physiological Mechanism of PD**
● Lack of Dopamine
  ○ Nigro-striatal dopaminergic neurons almost gone
● Lewy bodies: protein ‘growth’ within dopamine cells
● Possibly due to a defect on Chromosome 4: the protein produced is misfolded
● Toxic gain of function: production of a toxic protein by a faulty gene
● Mutation on chromosome 6: Parkin gene
● Ubiquitin tags faulty/misfolded protein
● Tagged proteins are destroyed by proteasomes
● Parkin gene helps in ubiquitin tagging
● Mutation → Loss of Parkin function
● Not only genetic: other possible mechanism included decreased mitochondrial activity and iron build-up
● Ubiquitin +misfolded protein → ‘tagged’ misfolded protein→ proteasomes→ amino acids

**Parkinson’s Disease**
● Treatments
MAO inhibitors (e.g. deprenyl): prevents the destruction of monoamines. Slows down progression of PD

L-Dopa: promote the production of dopamine. Side effects (hallucinations). Effects are temporary. Eventual complete destruction of dopamine neurons

Direct fetal dopamine cell transplantation in Basal Ganglia. Side effects (involuntary movements)

Pallidotomy: precise lesions of the Globus Pallidus

Deep brain inhibitory stimulation of subthalamic nucleus (STN)

**Current Research on PD**

- Gene Therapy: modified virus that inhibits STN → Increase activity in Supplemental Motor Area → Decrease PD symptoms
- Neuroprotective agents- chemical that protects brain. Control alpha-synuclein
- Stem cells- increase dopamine secretion

**Degenerative Disorders**

- **Huntington’s Disease**
  - Symptoms
    - Incontrollable and excessive movements. Uncoordinated activation of motor programs
    - Rare, associated with dementia. Syndrome appear after 35 years old, death after 15 years from onset
    - Terminal disease. Hereditary (dominate gene, C4) *Misfolded* protein (Huntington) accumulation. Toxic gain of function
    - 1630’s Witches of Bures (UK)
  - Neural substrate: degeneration of caudate and putamen: affect GABA and Ach cells in the Basal Ganglia. Enlarged ventricles
  - Treatment
    - No treatment. 1/10,000 people. Management therapies
    - Gene is identified, and tests exits to determine whether it is present
    - Research focuses on Gene therapy

- **Alzheimer’s Disease**
  - Symptoms
    - Affects 10% of the > 65 year old population, 50% if > 85 year old
    - Not entirely hereditary
    - Progressive: Depression, loss of memory and mental function (dementia). Resemble anterograde amnesia of declarative memory
    - Down syndrome develops sometimes into Alzheimer’s
    - Terminal disease
  - Neural substrate
    - Degeneration of Ach center (nuc. Basalis)
- Degeneration of the hippocampus, frontal and temporal cortices, raphe nucleus and locus coeruleus
- Development of:
  - Beta Amyloid plaques: Accumulation of Beta Amyloid... cell death
  - Neurofibrillary tangles. Dead microtubules. Also in Down syndrome
  - Treatment
    - No cure. Causes unclear. Gene mutation on chromosome 21 (amyloid gene)

- **Amyotrophic Lateral Sclerosis** (Lou Gehrig’s disease)
  - Symptoms
    - Stiffness of movement, exaggerated reflexes, muscular atrophy, paralysis, terminal disease (5-10 after onset). No dementia
  - Mostly sporadic cases (1/20,00)
  - In some cases, related to chromosome 21 (misfolding of protein, toxic gain of function)
  - Neural substrate: degeneration of spinal cord motor neurons and cranial nerves. Excitotoxicity
  - Treatment: no cure. Drug that decrease glutamate release, improves symptoms. Gene therapy

- **Multiple Sclerosis**
  - Symptoms
  - Neural substrate: autoimmune disease. Degeneration of myelin and formation of selective plaques
  - Treatment: Genetic component (Gypsues and Asians are low risk), environmental component (childhood in cool climates are high risk). Influencing the immune system. No cure. Partial recovery

**Infectious Diseases**
- **Encephalitis and Meningitis**
  - Symptoms
    - Fever, irritability, nausea → convulsion, delirium
    - 10% is terminal, 20% results in permanent brain damage. Deafness
  - Neural substrate
    - Viral infections (mosquitoes or sexually transmissible diseases), bacteria, fungi
    - Encephalitis: affect the whole brain
    - Meningitis: affects the meninges
  - **Encephalitis**
Treatment: none in general

- Herpes Simplex: cold sores. Virus that lives in spinal ganglion and ‘breaks-out’ periodically along sensory nerves. Encephalitis results from breakout to the brain (rare), frontal and temporal lobes. Treatable (acyclovir), but no cure
- Polio: damage to all motor neurons (brain + spinal cord) Vaccine (Jonas Salk)
- Rabies: Fever, headaches → convulsions, seizures, death within a week. Affects cerebellum and hippocampus. Vaccine
- AIDS (not HIV): brain damage in 75% of cases (if untreated). Due to excess of Ca2+ through NMDA receptors (excitotoxicity). Hippocampus and cortex
- Meningitis: headache, stiff neck → convulsion, death. Infection of meninges, damage resulting in impaired blood/CSF circulation. Cranial nerve damage. Treatable by antibiotics. Vaccine