I. Metabolic Disorders

A. Lysosomal disorders
- Lysosomal enzyme deficiency resulting in accumulation of material in secondary lysosomes
- Includes glycogenosis type II, sphingolipidoses, mucopolysaccharidoses, mucolipidoses, and gangliosidoses
- Combined prevalence of 11–14/100,000
- Mechanisms of lysosomal enzyme deficiency
  - Mutations of lysosomal enzyme genes (most common cause)
  - Failure of addition of mannose-6-phosphate marker
  - Absence of cofactors
  - Errors in posttranslational modification of enzyme protein
  - Defects in lysosomal transport
  - Drug-induced dysfunction

B. Tay-Sachs disease
- GM₂ gangliosidosis
- Autosomal recessive
- Ashkenazi Jewish population
- Hexosaminidase A deficiency (lack of synthesis of α subunit of enzyme)—type B
- Hexosaminidase A and B deficiency (Sandhoff)—type O, infantile onset
- Activator protein deficiency, hexosaminidase levels generally normal—type AB, infantile onset
- Accumulation of GM₂ ganglioside
- Normal at birth, psychomotor retardation starts after 5–6 months
- Later hypotonia and spasticity develop, seizures
- Brain weight normal or decreased/increased
- Balloon neurons with cytoplasmic vacuoles
- Visceral organs generally do not show much evidence of ganglionic accumulation
- Electron microscopy: whorled membranes or zebra bodies
- Cherry red spot in macula, blindness
- Death age 2–3 years
- Late infantile form (onset after 18 months) and rare adult forms exist

C. GM₁ gangliosidosis
- Autosomal recessive
- Infantile form (type I)—failure to thrive, hepatosplenomegaly, facial dysmorphisms, cardiomyopathy, psychomotor retardation, seizures, and cherry red spots
- Late infantile/juvenile (type II)—progressive mental retardation and motor retardation, seizures, death ages 3–10 years, organs normal size
- Rare adult form (type III)
- 50% with cherry red spot
- Defect in β-galactosidase (chromosome 3p21)
- Stored material—GM₁ ganglioside, keratin sulfate, glycoprotein
- Brains generally appear grossly normal or atrophic (initially may be enlarged)
- Balloon neuronal cytoplasm with foamy quality and megalneurites and white matter gliosis

D. Niemann-Pick disease
- Autosomal recessive, chromosome 11p
- Mutations common in Ashkenazi Jewish (type A) population
- Sphingomyelinase deficiency—types A and B, a subset of patients do not have a sphingomyelinase deficiency
- Accumulation of sphingomyelin and cholesterol
- Five phenotypes (A–E)
  - Type A—75–80% of cases (severe infantile neurovisceral form)
  - Type B—visceral disease only, normal central nervous system (CNS function, survive into adulthood
  - Types C and D caused by defect in intracellular cholesterol circulation
♦ Electron microscopy: membranous cytoplasmic bodies, zebra bodies
♦ Brain decreased weight, balloon neurons, and glial cells
♦ Multiorgan involvement with type A including hepatosplenomegaly, cherry red spots of macula, and lung infiltrates
♦ May see ballooned ganglion cells in the gastrointestinal tract (Auerbach and Meissner plexuses)
♦ Niemann-Pick cell—foamy phagocyte storage cell seen in extra-CNS organs (sea blue histiocytes)
♦ Death age 2–3 years for type A

A. Gaucher’s disease
♦ Autosomal recessive
♦ Frequency 1/50,000; most common lysosomal storage disease
♦ Glucocerebrosidase deficiency, chromosome 1q21
♦ Accumulation of glucocerebroside in reticuloendothelial cells and neurons
♦ Three clinical phenotypes
  − Type 1—most common, high prevalence among Ashkenazi Jews; develops in childhood and young adults; hepatosplenomegaly, bone lesions, anemia, and thrombocytopenia, no CNS involvement
  − Type 2—acute neuronopathic, symptoms before age 2 years, death by age 2–4 years; stridor, strabismus, swallowing difficulty, opisthotonus, spasticity, and hepatosplenomegaly
  − Type 3—subacute neuronopathic, common in northern Sweden, symptoms similar to type 2 but more slowly progressive with survival into young adulthood
♦ Brain gross appearance generally normal
♦ Gaucher cells (reticuloendothelial cells) rarely vacuolated, fibrillary cytoplasm, “crumpled tissue paper”; cells often perivascular in distribution in the CNS
♦ Neurons shriveled and destroyed, especially cortical layers III and V, Purkinje cells, and dentate nucleus
♦ Electron microscopy: distended, elongated lysosomes with stacks of lipid bilayers

B. Ceroid-lipofuscinoses (Batten disease)
♦ Most autosomal recessive
♦ Prevalence of 1/12,500–25,000; infantile type is most common in Finland
♦ Eight genes involved
♦ Five main clinical types
  − Infantile type—psychomotor regression starting at about 8 months, visual loss, hypotonia, ataxia, microcephaly, death age 3–10 years; chromosome 1p32 (CLN1 gene)
  − Late infantile type—seizures start between 18 months and 4 years, death 4–10 years; chromosome 11p15 (CLN2 gene)
  − Juvenile type—retinopathy presentation at 4–9 years, seizures, gait disturbance, hallucinations, death late teens; chromosome 16p12 (CLN3 gene)
  − Adult type (Kufs disease)—onset around age 30 years with myoclonic epilepsy, dementia, and ataxia
♦ Accumulation of autofluorescent lipopigments in neurons
♦ Brain usually atrophic, skull thickened
♦ Neuronal ballooning and loss, gliosis, loss of myelin including subcortical fibers
♦ Electron microscopy: granular, curvilinear, fingerprint patterns
♦ Biopsy: skin, rectum, or brain to diagnose; can evaluate lymphocytes in some cases

C. Mucopolysaccharidoses
♦ Classification
  − Type I—Hurler/Scheie; α-L-iduronidase deficiency; chromosome 4p16.3
  − Type II—Hunter; iduronate sulfatase deficiency; chromosome Xq28
  − Type III—Sanfilippo; heparan-N-sulfatase, α-N-acetyl glucosaminidase, acetyl-CoA: α-glucosaminide acetyltransferase deficiency and N-acetylgalcosamine-6-sulfatase; subset with chromosome 12q and 17q abnormalities
  − Type IV—Morquio; β-galactosidase deficiency; chromosomes 16q24 and 3p21
  − Type VI—Maroteaux-Lamy; arylsulfatase B, chromosome 5q13-q14
  − Type VII—Sly; β-glucuronidase deficiency; chromosome 7q21
  − Type IX—hyaluronidase deficiency; chromosome 3p21
♦ Accumulation of dermatan sulfate or heparan sulfates
♦ Storage of mucopolysaccharides in lysosomes in multiple organ systems
♦ Hurler’s syndrome—psychomotor retardation, coarse facial features, protuberant abdomen, short stature, corneal clouding, heart disease, hepatosplenomegaly, and dysostosis multiplex