Biochem Block IV Diseases

- Vitamins
  - Beriberi
    - Vitamin B1 (Thiamin) deficiency
    - Peripheral neuropathy, cardiomyopathy
  - Wernicke-Korsakoff
    - Vitamin B1 (Thiamin) deficiency
    - Often seen in alcoholics
    - Confusion, ataxia
    - Intravenous infusion of glucose-containing fluid may precipitate acute thiamine deficiency in alcoholics (depleted by pyruvate dehydrogenase reaction)
  - Pellagra
    - Niacin deficiency
    - Diarrhea, dermatitis, dementia
  - Rickets/Osteomalacia
    - Vitamin D deficiency in children/adults
    - Rickets affects cartilage→bowlegged
    - Osteomalacia only affects developed bone
    - Hypercalcemia, renal calculi
- Glucose and Pyruvate Metabolism
  - Pyruvate Kinase Deficiency
    - Most common enzyme deficiency in glycolytic pathway
    - Somewhat offset by an increase in 2,3 BPG
    - Damaged RBC's subject to macrophage destruction in the spleen→increase in unconjugated bilirubin (hemolytic jaundice)
  - Pyruvate Dehydrogenase Deficiency
    - Increase in pyruvate→increase in lactic acid and alanine (via transamination)
    - Decrease in Acetyl-Coa→decrease in ATP production
    - Lactic acidosis, neurological defects, myopathy; usually fatal at early age
- Galactose Metabolism
  - Galactokinase Deficiency
    - Increase in galactose and galactitol (sugar alcohol)
    - Cataracts
  - Galactosemia
    - Deficiency of GALT (galactose-1-phosphase uridyltransferase: UDP-glucose + galactose-1-phosphate → UDP-galactose + glucose1-phosphate)
    - Increase in galactose (blood, urine), galactose-1-phosphate (very toxic), and galactitol (sugar alcohol)

        - Cirrhosis, mental retardation, cataracts, galactosuria
- Fructose Metabolism
    - Frutosuria
        - Fruktokinase deficiency
        - Fructosuria
        - Benign
    - Hereditary Fructose Intolerance
        - Aldolase B deficiency
        - Increase in fructose and fructose-1-phosphate (toxic)
        - Toxic liver damage, renal disease
        - Excess fructose traps phosphorous in cells→hypophosphatemia→decrease in ATP→increase in AMP
        - Severe fasting hypoglycemia
        - Increased uric acid level (metabolism of AMP)
- PPP
    - Glucose-6-Phosphate dehydrogenase deficiency
        - Inadequate NADPH production (pyruvate not shuttled into PPP)→reduction in antioxidant activity of glutathione in mature RBCs→hemolytic anemia often induced by infections, oxidant drugs, and fava beans
        - Most common cause of hemolytic anemia
- Glycogen Storage
    - Von Gierke's
        - Glucose-6-phosphatase deficiency→can't export glucose into blood
        - Liver and kidney
        - Severe fasting hypoglycemia, ketosis, hyperlipidemia, lactic acidosis, enlarged liver and kidneys
    - Pompe's
        - α1,4-glucosidase deficiency in lysosomes→can't break down glycogen
        - Infant form: mental retardation, hypotonia, cardiomegaly leading to death by age 2
    - Cori's
        - Debranching enzyme (amylo-α-1,6-glucosidase) deficiency→can't break down glycogen effectively
        - Muscle and liver
        - Leads to abnormal glycogen→many short-branched chains (α-limit dextrins)
        - Mild hypoglycemia, hepatomegaly
    - Andersen's
        - Branching enzyme (glucosyl 4,6 transferase) deficiency
        - Liver and spleen

        - Very long glycogen chains with very few branches
        - Hepatosplenomegaly, cirrhosis, liver failure leading to death by age 2
    - McArdle's
        - Muscle glycogen phosphorylase
        - Muscle cramping, fatigue, and myoglobinuria with strenuous exercise
        - NO increase in lactic acid after exercise
    - Hers's
        - Liver glycogen phosphorylase
        - Similar symptoms to Von Gierke's disease, but less severe
    - Tarui's
        - Muscle PFK-1 deficiency→ Can't perform glycolysis
        - Cramps, pain, myoglobin in urine, hemolytic anemia
    - Fanconi/Bickel
        - GLUT-2 deficiency in liver
        - Failure to thrive, enlarged liver, rickets, kidney dysfunction
- Sphingolipidoses: Lysosomal Storage Diseases
    - Nieman-Pick Disease (Type A & B)
        - Sphingomyelinase deficiency→can't cleave sphingomyelin to phosphatidylcholin + ceremide
        - Accumulation of sphingomyelin
        - Hepatosplenomegaly; mental retardation; fatal early in life
        - Type C→inability to transport sphingomyelin out of lysosome
- Degredation of AA's
    - Classic PKU
        - Phenylalanine hydroxylase deficiency (Phe→Tyr)
        - Increased Phe and decreased Tyr
        - Mental retardation, mousy odor
    - Malignant PKU
        - BH_2 reductase deficiency (Reduces BH_2 back to BH_4)→BH_4 required cofactor for phenylalanine hydroxylase
        - Increased Phe and decreased Tyr and BH_4
        - Similar symptoms to classic PKU
        - Neurologic problems occur regardless of restricting Phe intake
        - Inability to metabolize tryptophan or tyrosine (require BH_4)→decreases synthesis of neurotransmitters serotonin and dopamine, respectively
    - Alkaptonuria
        - Homogentisate oxidase deficiency (homogentisate→maleylacetoacetate)
        - Involved in breakdown of tyrosine to fumarate