Interconversions Involving Nucleotide Sugars

- Reactions of UDP-Glucose
  - Activated sugar nucleotide; precursor of glycogen and lactose, UDP-glucuronate and glucuronides, and the carbohydrate chains in proteoglycans, glycoproteins, and glycolipids (Figure 30.1)
  - UDP-Glucuronate: A Source of Negative Charges
    - Precursor of other sugars and of glucuronides (Figure 30.3)
    - Formed by the oxidation of the alcohol glucose to an acid by NAD+-dependent dehydrogenase
    - Adds negative charges to increase solubility of compounds
    - Present in the diet
    - Can also be formed from degradation of inositol (sugar alcohol that forms inositol trisphosphate[IP3]), an intracellular second messenger for many hormones
- Formation of Glucuronides
  - Heme -> degraded to bilirubin (unconjugated, only slightly soluble) in reticuloendothelial system -> transported to liver bound to albumin -> in liver, UDP-glucuronate transfers glucuronate residues -> bilirubin monoglucuronide -> bilirubin diglucuronide (conjugated, more soluble) -> transported into bile for excretion
  - Similar process for xenobiotics, drugs, steroids, etc; occurs in endoplasmic reticulum and cytoplasm of liver and kidney (Table 30.1)
  - Glucuronate reenters pathway of glucose metabolism by conversion to D-xylulose 5-phosphate (from pentose phosphate pathway)
- Synthesis of UDP-Galactose and Lactose from Glucose
  - Lactose synthesized from UDP-galactose and glucose
  - Galactose not required in diet b/c it can be synthesized: UDP-glucose forms UDP-galactose via epimerization
  - Lactose Synthesis
    - Lactose synthase (made of galactosyltransferase and α-lactalbumin) in ER of lactating mammary gland catalyzes transfer of galactose from UDP-galactose to glucose
    - α-lactalbumin is protein modified synthesized after childbirth in response to prolactin
    - In absence of α-lactalbumin, galactosyltransferase transfers galactosyl units to glycoproteins
    - Ingestion of lactose is not required for lactation
      - UDP-galactose in the mammary gland is derived principally from the epimerization of glucose
      - Dairy products are a major dietary source of Ca2+, so need increased Ca2+ from another source
- Formation of Sugars for Glycolipid and Glycoprotein Synthesis
  - Reason for the large variety of sugars attached to proteins and lipids is that they have specific and different functions, such as targeting a protein toward a membrane; providing recognition sites on the cell surface for other cells, hormones, or viruses as acting as lubricants or molecular sieves
  - The pathways for use and formation of many of these sugars are summarized in Figure 30.8; many of the steps are reversible, so that glucose and other dietary sugars enter a common pool from which the diverse sugars can be formed
Amino sugars are all derived from glucosamine 6-phosphate
- N-acetyltransferases in ER and cytosol provide another means of chemically modifying sugars, metabolites, drugs, and xenobiotic compounds
- Individuals may vary greatly in their capacity for acetylation reactions
- Mannose is found in the diet in small amounts and is an epimer of glucose

**Glycoproteins**

- **Structure and Function**
  - Contain short carbohydrate chains covalently linked to either serine/threonine or asparagine residues
  - Most proteins in the blood are glycoproteins; also serve as hormones, antibodies, enzymes (including those of the blood clotting cascade), secretions of mucus-producing cells, and as structural components of the extracellular matrix
  - Most glycoproteins are secreted from cells, some are segregated in lysosomes, where they serve as the lyosomal enzymes
  - In receptors (for hormones), transport proteins and cell-recognition/attachment sites, hydrophobic regions of the protein remain attached to the cell membrane, and the carbohydrate portion extends into the extracellular; bacteria and viruses also bind to these sites

- **Synthesis**
  - Protein portion of glycoproteins is synthesized on the ER
Clinical Correlates

Glycolipids
- Structure and Function
  - Derivatives of lipid phingosine; includes cerebrosides and gangliosides
  - Contain ceramide with carbohydrate moieties attached
  - Involved in intercellular communication
  - Identical oligosaccharides are present on both glycolipids and glycoproteins associated with the cell membrane; serve as cell recognition factors
- Synthesis
  - Cerebrosides made from ceramide and UDP-glucose or UDP-galactose; contain a single sugar
  - Gangliosides contain oligosaccharides made from UDP-sugars and CMP-NANA
  - Defects in the degradation of sphingolipids cause sphingolipidoses (AKA gangliosidoses) (Table 30.3)
  - Sphingolipids are produced in Golgi complex
  - Lipid component becomes part of membrane of secretory vesicle that buds from Golgi and fuses to become part of outer layer of cell membrane
  - Carbohydrate component extends into extracellular space; sometimes used as recognition signal for foreign particles (Cholera toxin binds to carbohydrate portion of the GM1 ganglioside to allow active subunit to enter cell)

Clinical Correlates
- Blood Transfusions
  - Blood antigenic determinants are located in the oligosaccharides of the glycoproteins and glycolipids of the cell membranes
  - The most important blood group in humans is the ABO group, which comprises two antigens: A and B (Table 30.4)
    - Type A: produce N-acetylgalactosamine transferase that attaches N-acetylglactosamine to the galactose residue of the H substance.
    - Type B: produce galactosyltransferase that links galactose to the galactose residue of the H substance.
    - Type AB: produce both transferases
    - Type O: produce a defective transferase and do not attach either N-acetylglactosamine or galactose to the H substance; only have the H substance
- Tay-Sachs Disease
  - Autosomal recessive disorder that is rare in the general population (1 in 300,000 births), prevalence in Jews of Eastern European extraction is 1 in 3,600 births
  - One in 28 Ashkenazi Jews carries this defective gene
  - Dx: measure the tissue level of the protein produced by the gene (hexosaminidase A) or by recombinant DNA techniques; skin fibroblasts of concerned couples planning a family are frequently used for these tests
  - Carriers have a reduced but functional level of this enzyme that normally hydrolyzes a specific bond between an N-acetyl-D-galactosamine and a D-galactose residue in the polar head of the ganglioside
  - Tx: no effective therapy is available; enzyme replacement has met with little success because of the difficulties in getting the enzyme across the blood–brain barrier
  - Children with Tay-Sachs disease accumulate ganglioside GM2, but not globoside
  - Mutation of the HexB gene leads to inactivation of both hexosaminidase A and B activity -> leads to Sandhoff disease; similar clinical course to Tay-Sachs but with an accelerated timetable because of the initial accumulation of both GM2 and globoside in the lysosomes
  - Children identified with Tay-Sachs symptoms, but normal hexosaminidase A and B activity -> Sandhoff activator
- Because the lipid cannot be degraded, it accumulates and causes degeneration of the affected tissues, with progressive malfunction such as the psychomotor deficits that occur as a result of the central nervous system involvement seen in most of these storage diseases.

- Sphingolipidoses are caused by a mutation in a protein that is needed to activate hexosaminidase A activity. In the absence of the activator, hexosaminidase A activity is minimal, and GM2 initially accumulates in lysosomes; has no effect on hexosaminidase B activity.
- Sphingolipidoses affect mainly the brain, the skin, and the reticuloendothelial system (e.g., liver and spleen).
- Complex lipids accumulate, each contains a ceramide as part of its structure.
- Rate at which the lipid is synthesized is normal, but lysosomal enzyme required to degrade it is not very active, because:
  - It is made in deficient quantities as a result of a mutation in a gene that specifically codes for the enzyme.
  - A critical protein required to activate the enzyme is deficient.
- Because the lipid cannot be degraded, it accumulates and causes degeneration of the affected tissues, with progressive malfunction such as the psychomotor deficits that occur as a result of the central nervous system involvement seen in most of these storage diseases.