Chapter 26: Lipids. Hydrophobic (non-polar, soluble in organic solvent), typically of low molecular compound or organic origin

- fatty acids and waxes
- essential oils
- many vitamins
- hormones (non-peptide)
- components of cell membranes (non-peptide)

Share a common biosynthesis that ultimately derives their carbon source from glucose (glycolysis)

Glucose → pyruvate → lactate

26.1: Acetyl Coenzyme A. AcSCoA is a thioester.

R= H, CoASH
R= acetyl, AcSCoA

Pyrurate dehydrogenase: Multi-enzyme complex that converts pyruvate to AcSCoA.
Acetyl CoA is a thioester. Thioesters are more reactive toward nucleophilic acyl substitution than esters, but considerably less reactive than acid chlorides and anhydrides.

\[
\text{S-CoA} + \text{Nu-H} \rightarrow \text{Nu} + \text{CoASH}
\]

Thioester enolize more readily than esters. The enol can react with electrophile to afford \(\alpha\)-substitution products

\[
\text{S-CoA} \rightarrow \text{E} \rightarrow \text{E-CoA}
\]

\[
\text{S-CoA} + \text{HCO}_3^- \rightarrow \ln \text{CoA}
\]

26.2: Fats, Oils, and Fatty Acids. Fatty acids: refers to long, straight-chain saturated and unsaturated acids, typically from \(\text{C}_{12} - \text{C}_{20}\) (Table 26.1, p. 1069).

saturated fatty acids:

- \(\text{CH}_3(\text{CH}_2)_n\text{CO}_2\text{H}\)
  - \(n=10\), lauric acid (\(\text{C}_{12}\))
  - \(n=12\), myristic acid (\(\text{C}_{14}\))
  - \(n=14\), palmitic acid (\(\text{C}_{16}\))
  - \(n=16\), steric acid (\(\text{C}_{18}\))

unsaturated fatty acid

\[
\text{C}_{18}, \text{oleic acid}
\]

polyunsaturated fatty acids (PUFA)

- \(\text{C}_{18}, \text{linolenic acid} \ (18:3)\)
- \(\text{C}_{18}, \text{linoleic acid} \ (18:4)\)
- \(\text{C}_{20}, \text{arachidonic acid} \ (20:4)\)
**Fats and Oils: Triglycerides** (triacylglycerols) are tri-esters of glycerol (1,2,3-trihydroxypropane) and fatty acids.

The R groups can be saturated or unsaturated, the same or different.

Soaps: sodium & potassium salts of fatty acid produced from the saponification (base hydrolysis) of animal fats (glycerides)

Soaps have a hydrophilic, polar “head group” (carboxylate salt) and a hydrophobic, non-polar “tail.”

Fatty acid amides (FAA):

- Anandamide: an ethanolamine amide of arachidonic Acid (C20)
- Tetrahydrocannabinol
26.3: Fatty Acid Biosynthesis. Fatty acid biosynthesis is performed by a cluster of discrete enzymes in bacteria, and a very large multi-protein assembly in animals (fatty acid synthase, FAS). The fatty acid is attached to an acyl carrier protein (ACP), while other proteins perform an iterative two-carbon chain extension reaction that will yield the fatty acid.
Ketoreductase: NADPH (nicotinamide adenine diphosphate phosphate) is a nucleophilic hydride (H–) donor (reducing agent)

Dehydratase (DH):

Enoyl Reductase (ER)

Iterative two-carbon chain extension
Thioesterase

26.4 Phospholipids.

Glycerophospholipids are important components of cell membranes. Nonpolar tails aggregate in the center of a bilayer ionic head is exposed to solvent Cell membranes are ~5 nm thick

Phosphatidylcholine (lechtins)

26.6: Waxes. esters of long chain fatty acids (C_{16} - C_{36}) with long chain alcohols (C_{24} - C_{36})

\[ CH_3(CH_2)_n CO_2-(CH_2)_n CH_3 \]
26.6: Prostaglandins. (eicosanoids) C\textsubscript{20} compounds derived from arachidonic acid and related fatty acids

*hormone*: (Greek, *horman*, to set in motion) chemical messengers from one cell to another, that acts as a signal for a biochemical event.

Prostaglandin biosynthesis
COX-1 is a constitutive enzyme that is expressed in virtually all mammalian cells.
COX-2 is an inducible enzyme that is expressed as a result of a biochemical response; expressed in phagocytes (macrophages) as part of an inflammation response.

NSAIDs: non-steroidal anti-inflammatory drugs
Aspirin, ibuprofen, and naproxen are non-selective inhibitors of COX.

Celebrex, vioxx, and brextra are selective inhibitors of COX-2 (coxibs).

**Thromboxanes:** named for their role in thrombosis, the formation of a clot inside a blood vessel

Leukotrienes

**Arachidonic acid**

Lipoxigenase

Heme, O2

Leukotriene A4

Leukotriene D4

Thromboxane A2

Thromboxane B2
26.7: Terpenes: The Isoprene Rule. Isoprenoids- C\textsubscript{10} (terpenes), C\textsubscript{15} (sesquiterpenes) and C\textsubscript{20} (diterpenes) plant; essential oils

Ruzicka isoprene rule: terpenoids are derived from “isoprene units” (C\textsubscript{5})

The precursor to C\textsubscript{10} terpenoids (monoterpenes) is geraniol diphosphate (diphosphate), which consists of two C\textsubscript{5} “isoprene units” that are joined “head-to-tail”

C\textsubscript{15} sesquiterpenoids are derived from farnesyl diphosphate, which consists of three C\textsubscript{5} “isoprene units” that are joined “head-to-tail”

C\textsubscript{20} diterpenoids are derived from geranylgeranyl diphosphate, which consists of four C\textsubscript{5} “isoprene units” that are joined “head-to-tail”
$C_{25}$ sesterpenoids are derived from geranylfarnesyl diphosphate, which consists of five $C_5$ “isoprene units” that are joined “head-to-tail”

$C_{30}$ triterpenoids and steroids are derived from squalene, which consists of two $C_{15}$ farnesyl units” that are joined “tail-to-tail”

$C_{40}$ tetraterpenoids are derived from phytocene, which consists of two $C_{20}$ geranylgeranyl units” that are joined “tail-to-tail”
26.8: Isopentyl Diphosphate: The Biological Isoprene Unit.
Mevalonic acid is the biosynthetic precursor to the actual C₅ "isoprene units," which are isopentyl diphosphate (IPP, tail) and dimethylallyl diphosphate (DMAPP, head)

26.10: The Pathway from Acetate to Isopentenyl Diphosphate.
Mevalonate Pathway

Conversion of mevalonic acid to IPP and DMAPP

26.9: Carbon-Carbon Bond Formation in Terpene Biosynthesis.
Conversion of IPP and DMAPP to geraniol-PP and farnesyl-PP
Conversion of genanyl-PP to monoterpenes
*Limonene & α-Terpineol*

- **Geranyl diphosphate**
- **Neryl diphosphate**
  
  C=C bond acts as a nucleophile

**α-terpineol**

26.11: Steroids.

**Cholesterol biosynthesis** (mechanism 26.3, p. 1089)

part a: the cyclization
Cholesterol biosynthesis, part b: the 1,2-shifts

26.12: Vitamin D. (please read)

26.13: Bile Acids. (please read)

26.14: Corticosteroids. (please read)
26.15: **Sex hormones.** (please read)
androgens (male)

- Testosterone
- Androsterone
- Androstenedione
- dianabol

estrogens (female)

- Estrone
- Estradiol
- Progesterone
- Ethynylestradiol

26.16: **Carotenoids.** (please read) derived from phytocene (C_{40})

- Lycopene
- β-carotene