ANSC/NUTR 618
LIPIDS & LIPID METABOLISM
Fatty Acid Elongation and Desaturation

I. Fatty acid elongation

A. *General*

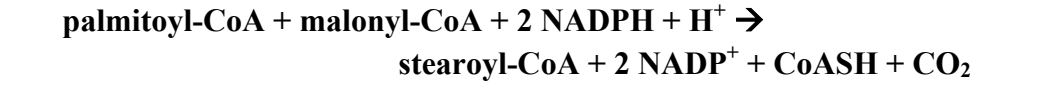
1. At least 60% of fatty acids in triacylglycerols are C18.
2. Free palmitic acid (16:0) synthesized in cytoplasm is elongated to stearic acid (18:0) by the addition of a C2 unit at the *carboxyl* terminal.
3. Virtually all cells contain one or more elongase isoenzymes.

B. *Mitochondrial system*

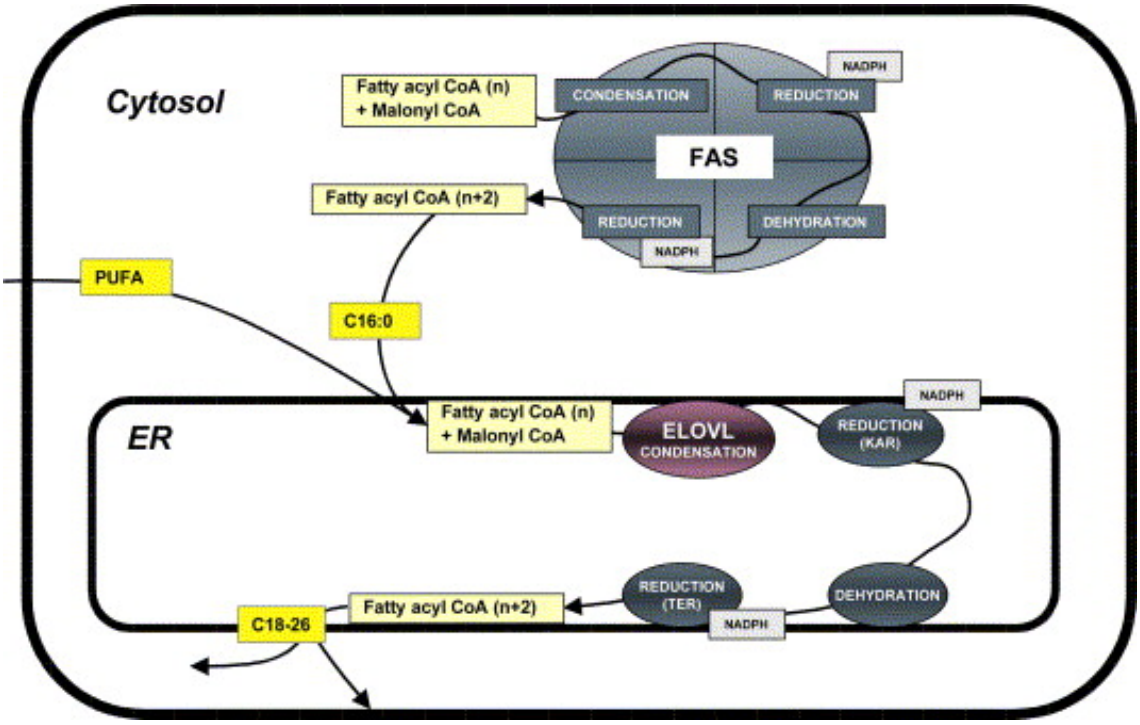
1. Palmitic acid is activated to palmitoyl-CoA in the cytoplasm (*acyl-CoA synthase*).
2. Palmitoyl-CoA is transferred into the mitochondria via the carnitine acyltransferase system.
3. A C2 unit is added by what appears to be a reversal of ß-oxidation.
   a. Uses acetyl-CoA as carbon source.
   b. Uses NADH as source of reducing equivalents.
   c. FAD-dehydrogenase in the first step of ß-oxidation is replaced by an NAD^+-reductase.
4. Involved primarily in production of fatty acids for mitochondrial membranes; prefers unsaturated fatty acids as substrates.

C. *Microsomal system*

1. Palmitate is activated to palmitoyl-CoA in the cytoplasm.
2. Elongase enzymes are located in endoplasmic reticulum (microsomes) (*not cytoplasm*).
3. A C2 unit is added essentially as in the fatty acid biosynthetic pathway.
   a. Uses acyl-CoA (not acyl-ACP).
   b. Requires MalCoA (not AcCoA) as substrate.
   c. Can use NADH or NADPH as source of reducing equivalents.
   d. Pathway:



   e. *Virtually all fatty acids can be elongated (saturated, monounsaturated, and polyunsaturated).*



C. ***Elongase isozymes***

1. Saturated and monounsaturated fatty acids – ELOVL1, 3, and 6
   (ELOVL = Elongation of Very Long Chain Fatty Acids)
2. Polyunsaturated fatty acids – ELOVL2, 4, and 5

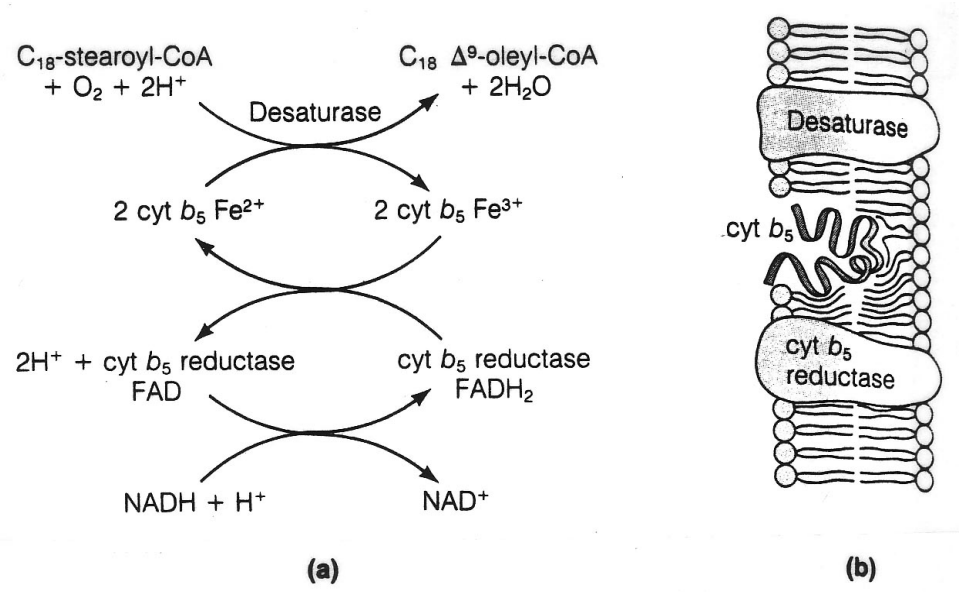
II. Fatty acid desaturation

A. ***General***

1. Usually alternates with fatty acid elongation.
2. Only three desaturases are present (Δ^9-, Δ^6-, and Δ^5-desaturases). There may be two independent Δ^6-desaturases.
3. If substrate fully saturated or is a trans-fatty acid, then first double bond is at C9 (e.g., stearic acid 18:0 to oleic acid 18:1Δ^9)
4. If substrate already unsaturated, then double bonds are inserted between the carboxyl group and the double bond nearest to the carboxyl group. (e.g., linoleic acid 18:2$\Delta^{9,12}$ to γ-linolenic acid 18: $\Delta^{6,9,12}$).
5. Desaturation maintains 1,4-diene composition of fatty acid.
6. Desaturation produces *cis*-double bonds.

B. ***Stearoyl-Coenzyme A desaturase (SCD)***

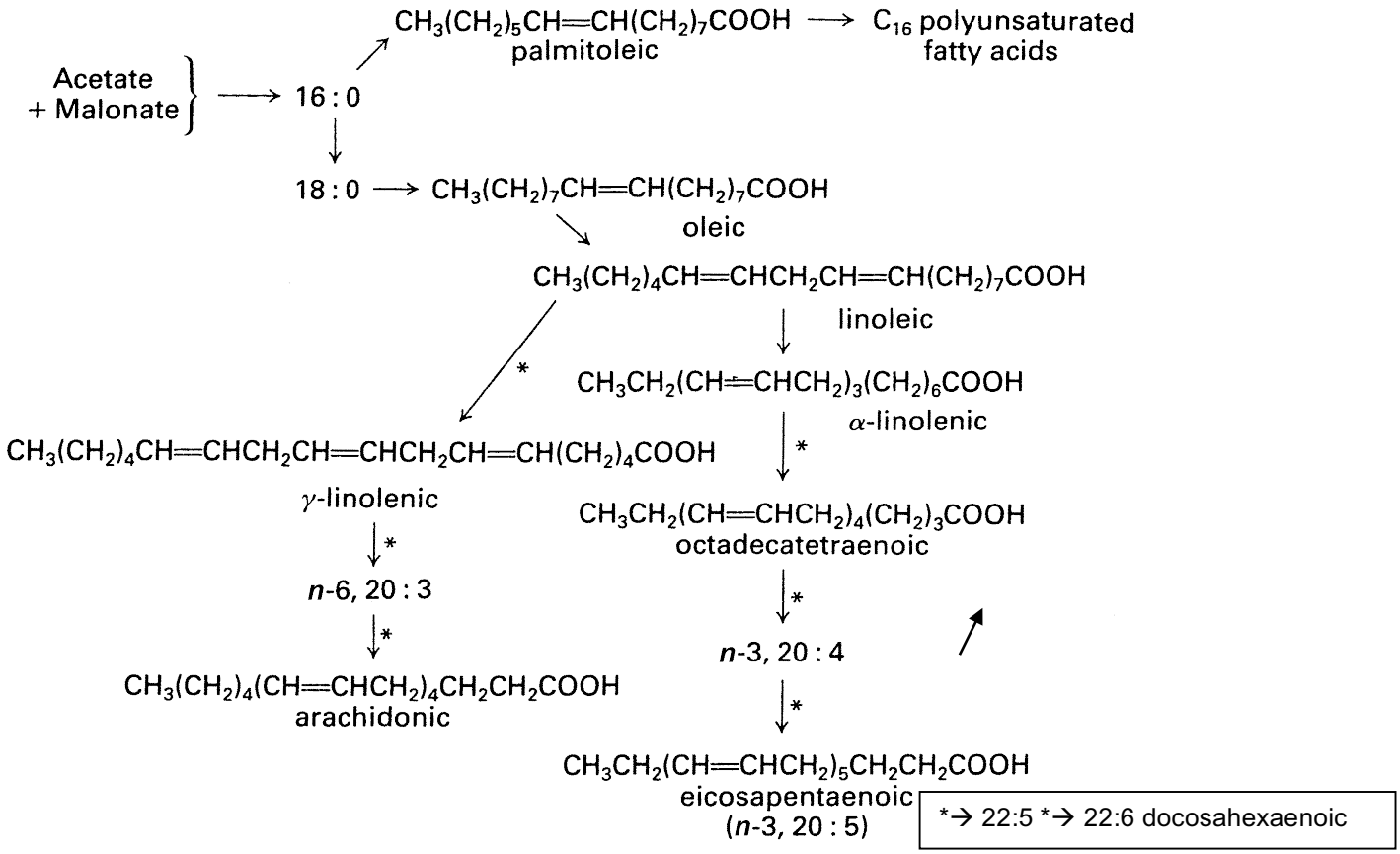
1. SCD is located on the endoplasmic reticulum (microsomes).
   a. SCD1 – liver
   b. SCD2 – adipose tissue
   c. As many as 5 SCD genes in mice and humans
2. SCD contains flavoprotein and cytochrome b_5 or cytochrome P-450.
3. Molecular oxygen is partially reduced by the NADH to produce an enzyme-bound superoxide radical, which oxidizes stearoyl-CoA.
4. *SCD can desaturate any saturated fatty acid and many trans-fatty acids.*



Overall reaction of stearoyl-CoA desaturase

C. ***Other desaturases***

1. ***Plants***
   a. Starts with the *cis*-9 fatty acid (oleic acid) as substrate.
   b. Oleic acid must be incorporated into phospholipids of plant membranes.
   c. Desaturation is toward the ω-carbon.
   d. There is no Δ^6 desaturase activity in most plants.
      1) Arachidonic acid (20:4n-6) does not occur in most plants.
      2) Fatty acid carbon is conserved for the production of α-linolenic acid (18:3n-3).
   e. Most plants cannot elongate α-linolenic acid.
   f. Most plants do not have a Δ^{15} desaturase.
      1) Many terrestrial plants are enriched with α-linolenic acid.
      2) Marine algae are the only organisms that can make large amounts of docosahexanoic acid.



Major pathways for polyunsaturated fatty acid synthesis in plants and algae. *Indicates a pathway found in high levels in marine algae and mosses, but less commonly in other algae or plants. **This pathway is now known to be active in some lower fishes.**

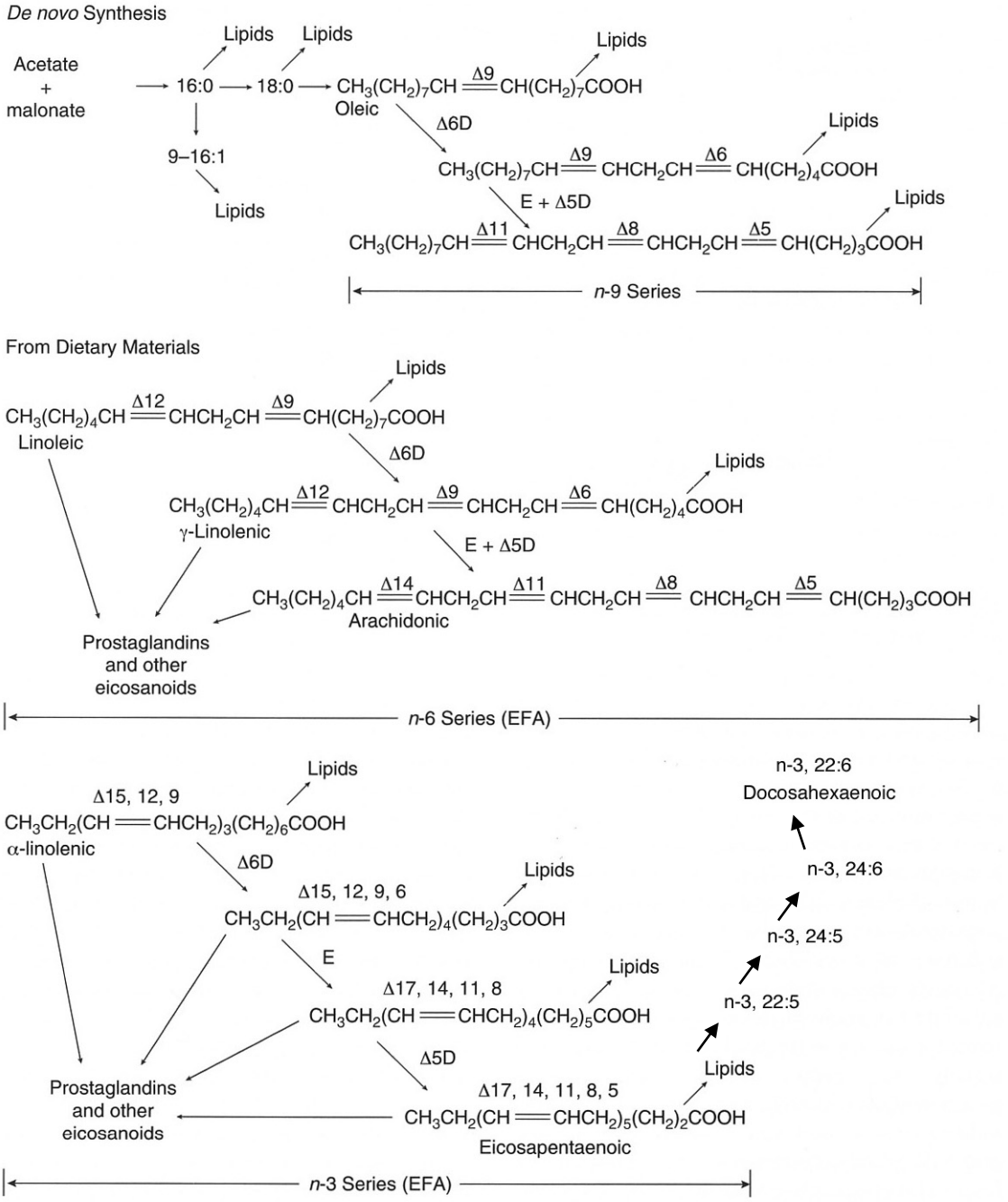
2. ***Animals***

a. Starts with a saturated fatty acid as substrate.

b. The fatty acid must be activated to its acyl-CoA thioester.

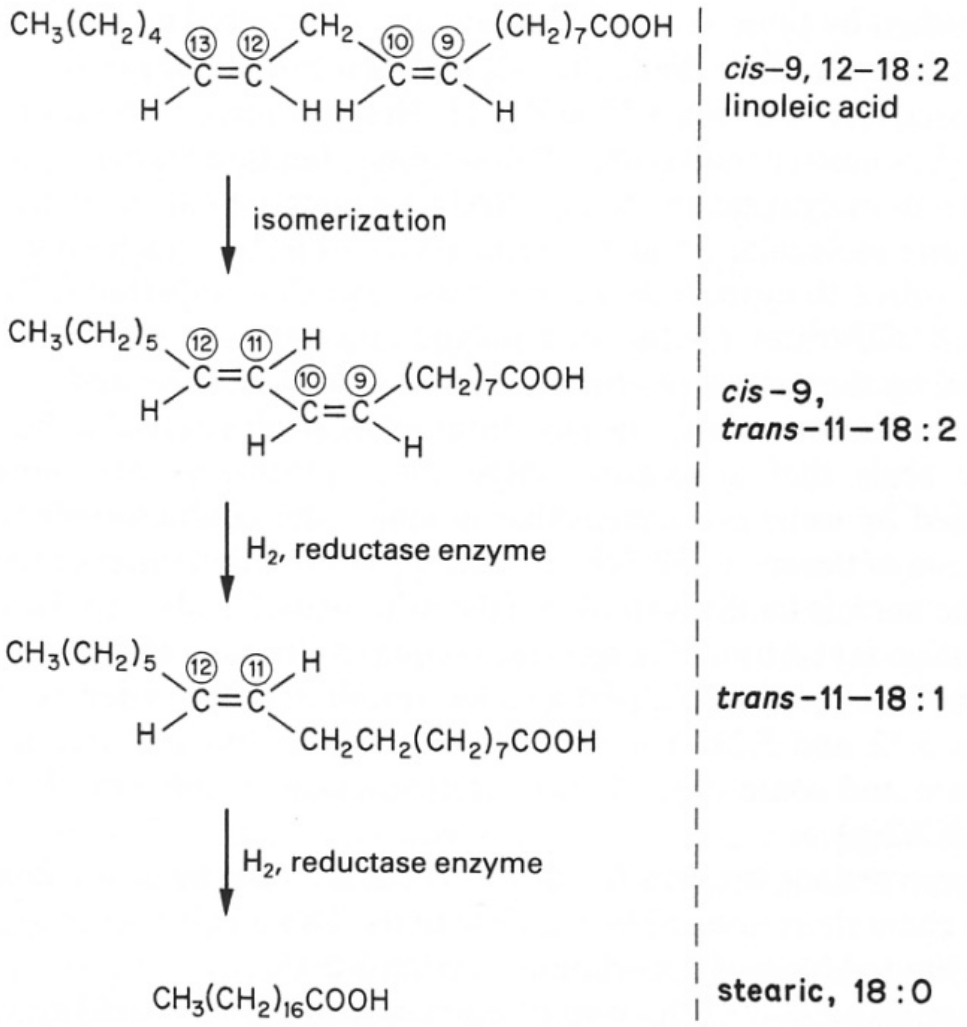
c. The first double bond is always at the Δ^9 position.

c. Desaturation is always toward the carboxyl-carbon.



Important pathways for unsaturated fatty acid formation in mammals. E = elongase; D = desaturase (positional specificity indicated).

3. ***Fatty acid biohydrogenation***
   a. The double bond toward the methyl carbon is isomerized to a *trans*-double bond.
   b. The double bond nearest the #1 carbon is reduced (***hydrogenated***).
   c. The *trans*-double bond is reduced, usually producing stearic acid (18:0).
   d. Each reaction is carried out by a different microorganism.



Biohydrogenation.