FATTY ACID SYNTHESIS FUNCTION

To synthesize fatty acids from acetyl-CoA (Fig. 13-1)

FATTY ACID SYNTHESIS LOCATION

Liver and adipose cytoplasm

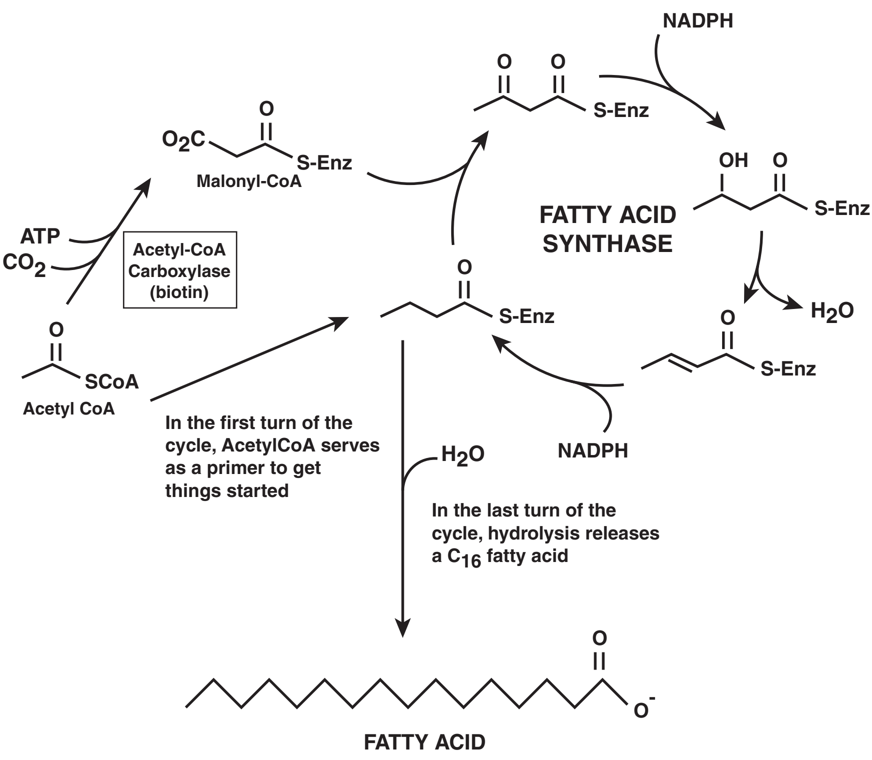

Figure 13-1 Fatty Acid Synthesis
The first formation of a carbon–carbon bond occurs between malonyl and acetyl units bound to fatty acid synthase. After reduction, dehydration, and further reduction, the acyl enzyme is condensed with more malonyl-CoA and the cycle is repeated until the acyl chain grows to C_{16}. When the growing fatty acid reaches a chain length of 16 carbons, the acyl group is hydrolyzed to give the free fatty acid.

FATTY ACID SYNTHESIS CONNECTIONS

From *TCA* and mitochondria through *citrate* to *C_{16} fatty acid*
Through C_{16}-acyl-CoA to *elongation* and *desaturation* pathways
Through C_{16}-acyl-CoA to *triglycerides*

FATTY ACID SYNTHESIS REGULATION

Primary signals:	*Insulin* turns *on*.
	Glucagon turns *off*.
	Epinephrine turns *off*.
	Phosphorylation turns *off*.
Secondary signals:	*Citrate* activates (acetyl-CoA carboxylase).

The major control point for fatty acid synthesis is acetyl-CoA carboxylase. The enzyme is inactivated by phosphorylation and activated by high concentrations of citrate.

FATTY ACID SYNTHESIS ATP COSTS (FOR C_{16})

8 acetyl-CoA_{mito} $\longrightarrow$ 8 acetyl-CoA_{cyto}	−16 ATP
7 acetyl-CoA $\longrightarrow$ 7 malonyl-CoA	−7 ATP
14NADPH $\longrightarrow$ 14$NADP^+$	−42 ATP
Total cost:	−65 ATP

Calculating energy costs for the synthesis of a C_{16} fatty acid from acetyl-CoA is not as simple as you might first think. The major complication is that acetyl-CoA is made in the mitochondria, but fatty acid synthesis occurs in the cytosol—acetyl-CoA can't cross the mitochondrial membrane. Acetyl-CoA gets out of the mitochondria disguised as citrate. The acetyl-CoA is condensed with oxaloacetate to give citrate, and the citrate leaves the mitochondria. In the cytosol, the citrate is cleaved by an ATP-dependent citrate lyase into acetyl-CoA and oxaloacetate:

$$\text{Citrate} + \text{ATP} + \text{CoA} \longrightarrow \text{acetyl-CoA} + \text{ADP} + P_i + \text{oxaloacetate}$$

This reaction and the reactions required to get oxaloacetate back into the mitochondria set up the cycle shown in Fig. 13-2.

Another point that you should appreciate is that in cycles like this, writing a balanced equation for the reaction is terribly easy. You just write the stuff that goes into the cycle on the left and the stuff that comes out on the right. It's not necessary to write down all the individual reactions that make up the cycle itself. The compounds that are members of the cycle itself (such as oxaloacetate or citrate shown earlier) will not show up in the final balanced equation. The balanced equation for Fig. 13-2 is

$$\text{Acyl-CoA}_{\text{mito}} + 2\text{ATP} + \text{CoA} + \text{NADH} + \text{NADP}^+ + \text{CO}_2 \longrightarrow \text{CoA} + \text{acyl-CoA}_{\text{cyt}} + 2\text{ADP} + 2\text{P}_\text{i} + \text{NAD}^+ + \text{NADPH} + \text{CO}_2$$

If we cancel the things that appear on both the left and right, we have

$$\text{Acyl-CoA}_{\text{mito}} + 2\text{ATP} + \text{NADH} + \text{NADP}^+ \longrightarrow \text{acyl-CoA}_{\text{cyt}} + 2\text{ADP} + 2\text{P}_\text{i} + \text{NAD}^+ + \text{NADPH}$$

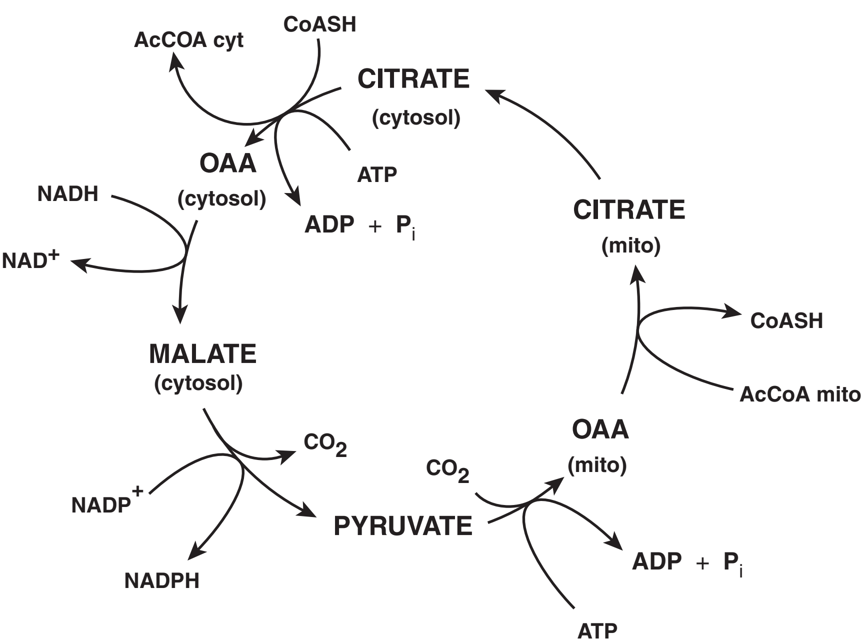

Figure 13-2
Getting **ACETYL-CoA OUT OF THE MITOCHONDRIA** and into the cytosol for fat synthesis.

In addition to moving acetyl-CoA from the mitochondria to the cytoplasm, this cycle also converts an NADH to an NADPH. If we assume that the amount of ATP that we could get from NADH and NADPH oxidation is the same, making NADPH from NADH and $NADP^+$ doesn't cost any energy. So we can conclude that the cost of just moving the acetyl-CoA out of the mitochondria is 2 ATPs per acetyl-CoA.

The synthesis of C_{16} fatty acid from acetyl-CoA requires 1 acetyl-CoA and 7 malonyl-CoA. The synthesis of each malonyl-CoA requires an ATP (and the cofactor biotin).

$$\text{Acetyl-CoA} + CO_2 + \text{ATP} \longrightarrow \text{malonyl-CoA} + \text{ADP} + P_i$$

From here it's just the reaction catalyzed by fatty acid synthase.

$$\text{Acetyl-CoA} + 7\ \text{malonyl-CoA} + 14\text{NADPH} \longrightarrow C_{16}\ \text{fat} + 14\text{NADP} + 7CO_2 + 8\text{CoA}$$

If we count the NADPH (cytosol) as 3 ATP equivalents, which could have been oxidized by the TCA cycle if they hadn't been used for fatty acid synthesis, then the synthesis of C_{16} fat requires

8 $\text{acyl-CoA}_{mito} \longrightarrow$ 8 acyl-CoA_{cyto}	−16 ATP
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14NADPH $\longrightarrow$ $14NADP^+$	−42 ATP
Total cost:	−65 ATP

This is not the kind of number you want to remember, but if you're into ATP counting (and who isn't these days), you might want to understand how to go about figuring it out if you need to.

FATTY ACID SYNTHESIS EQUATION

$$\text{Acetyl-CoA} + 7\ \text{Malonyl-CoA} + 14\text{NADPH} + 14H^+ \longrightarrow C_{16}\ \text{fatty acid} + 14NADP^+ + 7CO_2 + 8\text{CoA}$$

Requires a phosphopantetheine cofactor

The reactions of fatty acid synthesis all occur on one enzyme—fatty acid synthase.[1] This enzyme has multiple catalytic activities on one polypeptide chain. The intermediates of the reaction are not released until

[1] A *synthase* is an enzyme that makes something but doesn't directly require the hydrolysis of ATP to do it. A *synthetase* requires the hydrolysis of ATP to make the reaction go.

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Once fatty acids have been made 16 carbons long, they can be lengthened by adding 2 carbon atoms at a time with malonyl-CoA in a reaction that looks a lot like the first step of fatty acid synthesis. However, the elongation reaction is carried out on the fatty acyl-CoA and by an enzyme that is different from fatty acid synthase.[4]

The inability of animals to put in double bonds at positions farther than 9 carbons from the carboxylate carbon atom (it's numbered 1) makes for obvious exam questions about whether a given unsaturated fatty acid comes from a plant or animal source. Animals can still elongate fatty acids even after they have been desaturated, so you can't just look at the number of the position of the double bond and decide whether or not animals could have made it. For example, if we take a C_{18} fatty acid with a double bond at C-9 (the first carbon of the double bond that you encounter when walking from the carboxylate end is at C-9), it can be elongated by adding 2 carbons to the carboxylate end. This changes the number of the double bond from C-9 to C-11. Each elongation step increases the number of each double bond by 2. However, if we count the number of carbons from the CH_3 end of the fatty acid, you'll notice the number isn't changed by elongating the fatty acid.

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CO_2$

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

$C_{16:0}\omega0$ or $\Delta^0C_{16:0}$

Desaturation ↓

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

$CH_3CH_2CH_2CH_2CH_2CH_2CH{=}CHCH_2CH_2CH_2CH_2CH_2CH_2CH_2CO_2$

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

$C_{16:1}\omega7$ or $\Delta^9C_{16:1}$

Elongation ↓

18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2{=}CHCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CO_2$

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

$C_{18:1}\omega7$ or $\Delta^{11}C_{18:1}$

[4] Notice that fatty acid synthesis makes the fatty acid rather than the fatty acyl-CoA as a product. It would be a chemically simple task to take the fatty acid off the fatty acid synthase by a reaction with CoA. In fact, *Escherichia coli* does it this way and makes fatty acyl-CoA as a product. Most reactions that use the fatty acid (such as desaturation, elongation, or triglyceride synthesis) require the fatty acyl-CoA, so we have to turn right around and spend some ATP to make it when we could have just made it in the first place without spending any ATP. This strategy was obviously designed by a government committee.

Notice that elongation doesn't change the number of carbon atoms between the double bond and the CH_3 group at the left end. If a double bond is closer than 7 carbon atoms to the CH_3 group (numbering the CH_3 as 1, the first double bond you bump into would start at carbon 7), a plant must have made it.

Two nomenclature camps have grown up around the naming of unsaturated fatty acids. The first camp calls C-1 the carboxyl group and numbers the double bonds from this end. This is the delta (Δ) nomenclature. The number of carbons is given, followed by the number of double bonds. The positions of the double bonds from the carboxylate carbon are indicated as a superscript to the delta. The other camp, the omega (ω) system, numbers the chain from the CH_3 end. The position of the first double bond is indicated after the ω. Often in the ω system, the other double bonds are not specified except in the $C_{22:3}$ part. For example, $C_{22:3}\omega 6$ would mean a C_{22} fatty acid with three double bonds, the first of which was 6 carbons from the CH_3 end. The other two double bonds would each be 3 carbons farther away from the CH_3 group (at 9 and 12 carbons from the CH_3 end). The ω nomenclature has the advantage that the position numbers of the double bonds do not change with elongation since the new carbons are added to the carboxylate end. In the Δ nomenclature, the $C_{22:3}\omega 6$ would be called $\Delta^{10,13,16}$ $C_{22:3}$.

ω 1 2 3 4 5 6═7 8 9═10 11 12═13 14 15 16 17 18 19 20 21 22

Δ 22 21 20 19 18 17═16 15 14═13 12 11═10 9 8 7 6 5 4 3 2 1

If you ever have to interconvert between these two nomenclatures, it may be easier for you to write down a representation of the structure rather than to try to figure out the relationships between the length, number of double bonds, and how you add and subtract what to get whatever.

TRIGLYCERIDE AND PHOSPHOLIPID SYNTHESIS

Glycerol phosphate comes from glycerol (*not in adipose*) or from dihydroxyacetone phosphate (in *liver* and *adipose*).
Nitrogen-containing phospholipids are made from diglyceride. Other phospholipids are made from phosphatidic acid.

(See Fig. 13-3.)

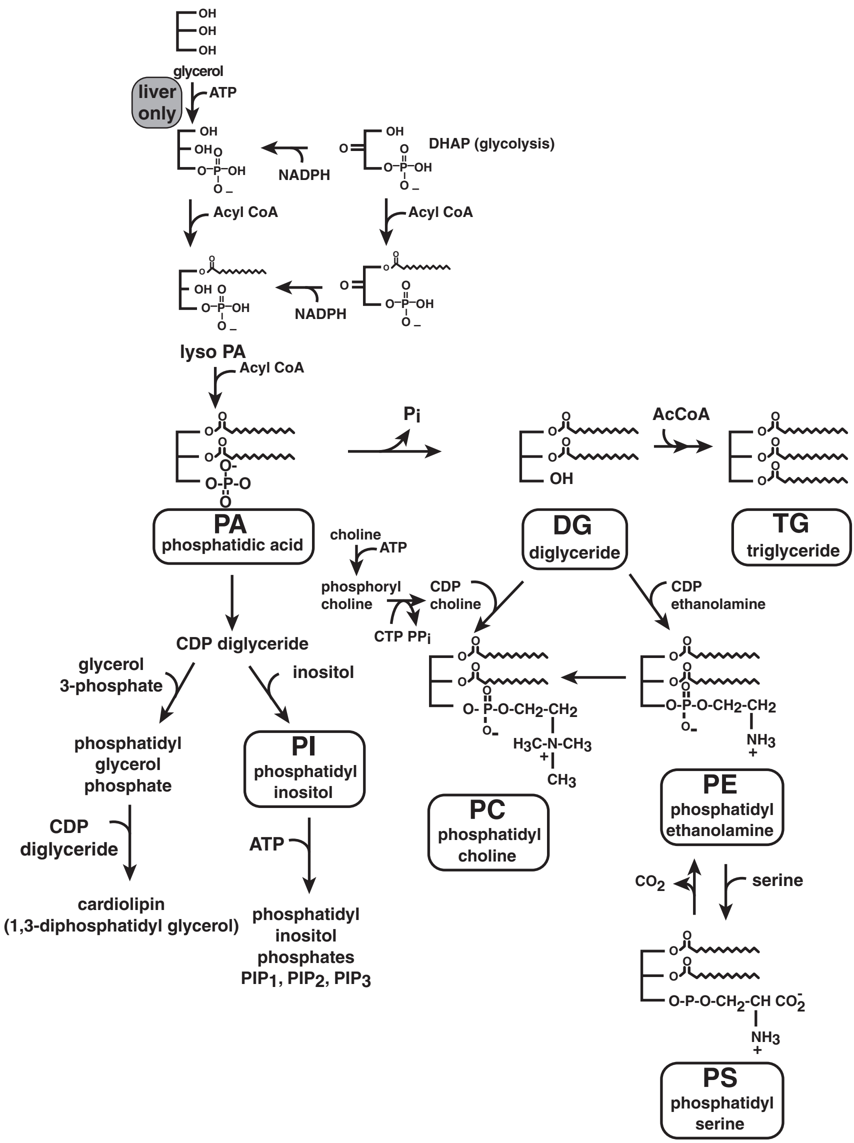

Figure 13-3 Synthesis of Phospholipids and Triglycerides
Glycerol utilization depends on the tissue. Adipose tissue can't use glycerol. Nitrogen-containing phospholipids are made from diglycerides, while other phospholipids are made from phosphatidic acid (PA). PI = phosphatidylinositol; PC = phosphatidylcholine; PE = phosphatidylethanolamine; PS = phosphatidylserine.