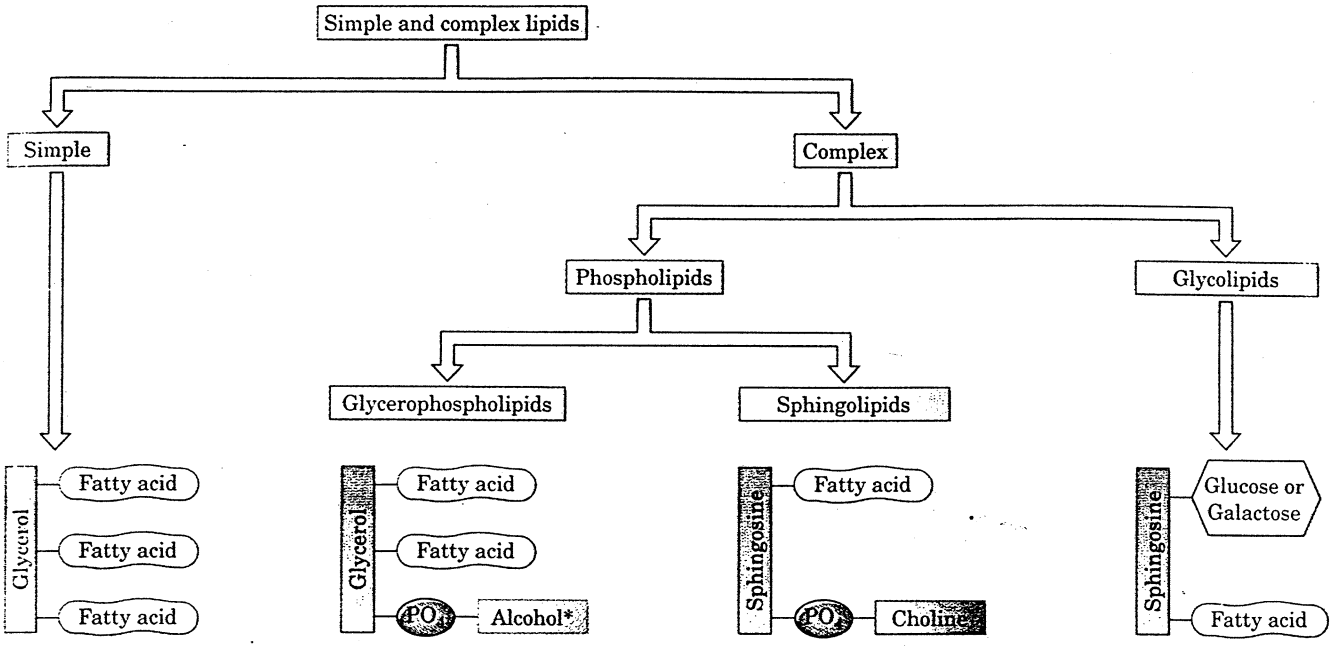
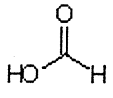


FIGURE 11.1 Schematic diagram of simple and complex lipids.
* The alcohol can be choline, serine, ethanolamine, inositol, or certain others.

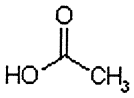
Fatty acids

Formic acid (1:0)



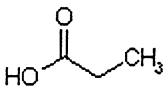
C00058

Acetic acid (2:0)



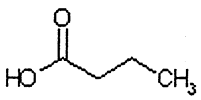
C00033

Propionic acid (3:0)



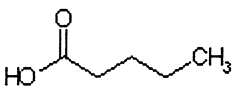
C00163

Butyric acid (4:0)



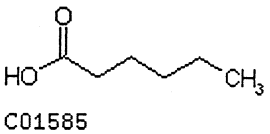
C00246

Valerianic acid (5:0)



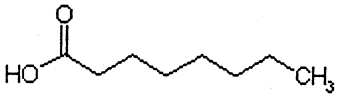
C00803

Caproic acid (6:0)



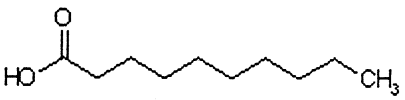
C01585

Caprylic acid (8:0)



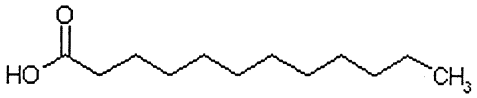
C06423

Capric acid (10:0)



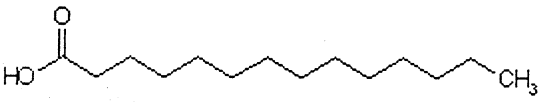
C01571

Lauric acid (12:0)



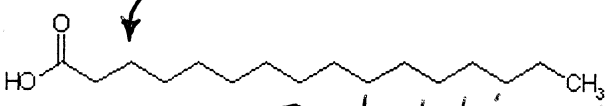
C02679

Myristic acid (14:0)

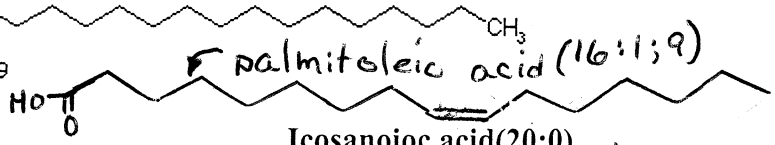


C06424

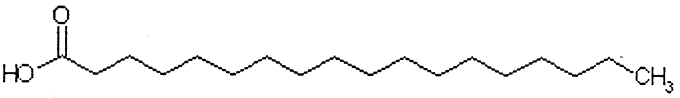
Palmitic acid (16:0)



C00249

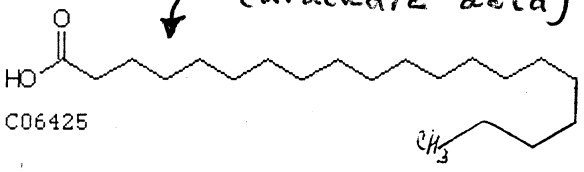


Stearic acid (18:0)



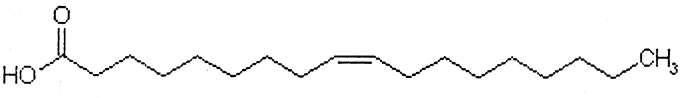
C01530

Icosanoioc acid(20:0)
(araeadic acid)



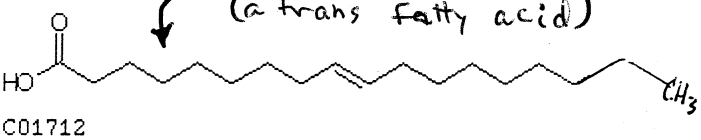
C06425

Oleic acid (18:1;9)



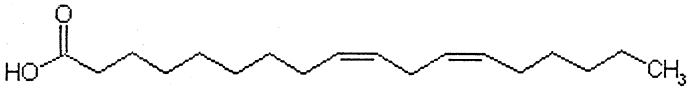
C00712

Elaidic acid (18:1;9)
(a trans fatty acid)



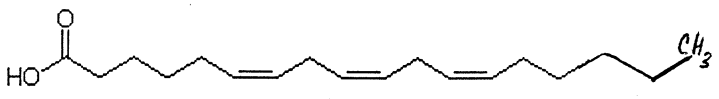
C01712

Linoleic acid (18:2;9,12)



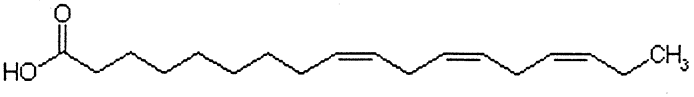
C01595

gamma-Linolenic LinolenicLinolenic a (18:3;6,9,12)



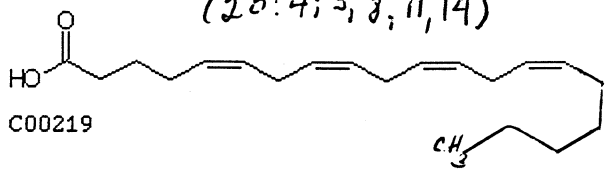
C06426

alpha-Linolenic acid (18:3;9,12,15)



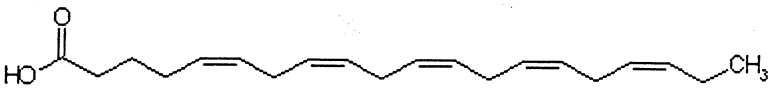
C06427

Arachidonic acid(20:4;5,8,11,1
(20:4;5,8,11,14)



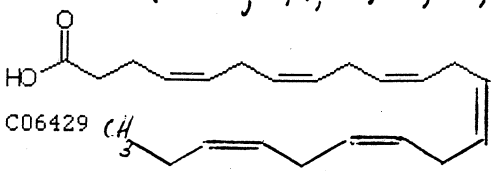
C00219

Eicosapentaenoic acid (20:5;5,8,11,14.17)



C06428

Docosahexaenoic acid (22:6;4
(22:6;4,7,10,13,16,19)



C06429

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Wild King Salmon

SFChronicle
Sunday Oct 7, 2001

By Ulysses Torassa
CHRONICLE MEDICAL WRITER

Rich in omega-3 fatty acids, the oils found in fish, walnuts and flaxseed have well-documented benefits to the heart and vascular systems, earning them endorsements from mainstream medicine, including the American Heart Association.

But an increasing amount of research and attention is now being paid to the effects that omega-3s have on the brain – both in the development of healthy neurons in infants and their possible use in treating mental illnesses such as depression and bipolar disorder, commonly known as manic depression. Some advocates are raising the possibility that omega-3 deficiency could play a role in schizophrenia, attention deficit hyperactivity disorder and even Alzheimer's disease and autism.

Leading the charge is Dr. Andrew L. Stoll, a Harvard psychiatrist at McLean Hospital outside of Boston, who is the author of "The Omega-3 Connection," and is now selling fish-oil supplements on the Internet.

Omega-3s are one of several essential fatty acids that play a key role in the body and are one of the major building blocks of membranes that protect every cell. Although it is not known for certain, researchers believe their effect on the membranes surrounding neurons may account for their beneficial effects on the brain.

Impressive results from Stoll's study of 30 bipolar patients treated with fish oil supplements reported in the Archives of Psychiatry in 1999 kicked off much of the present interest in the psychiatric benefits of the supplement. He has a $1.5 million grant from the National Institutes of Health to conduct a longer and larger study to validate his earlier results.

Other studies looking at fish oils in attention deficit hyperactivity disorder and postpartum depression are going on in Arizona, Indiana and Texas. At Stanford, researchers are recruiting bipolar patients who are considering pregnancy for a study using omega-3s instead of traditional drugs, which carry a small risk of birth defects.

Still, much of the the evidence supporting the use of omega-3 supplements in psychiatric disorders comes from small studies and reports of a single case.

A researcher at the NIH has published studies showing a correlation between fish consumption in various countries and lower rates of depression and, especially, postpartum depression in new mothers.

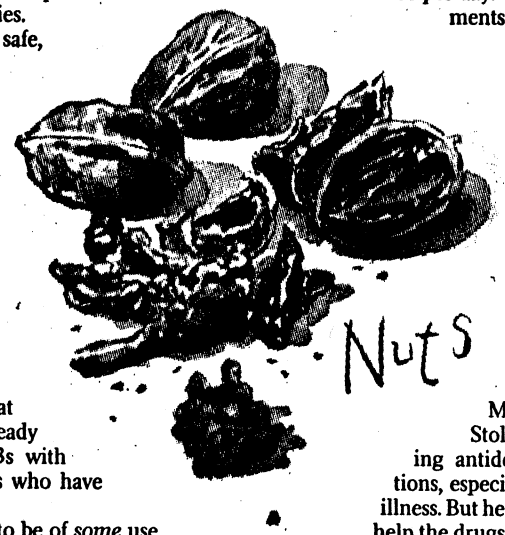
Fish consumption and lower rates of dementia have also been found in studies in Europe, giving rise to theories that the anti-inflammatory effects of omega-3s could help in diseases such as Alzheimer's.

In other studies, researchers have detected lower levels of some essential fatty acids in the bloodstream of schizophrenics, boys with attention deficit disorder and some with autism.

"The correlational data is very interesting, but it doesn't tell you what's going on," said Dr. Philip R. Muskin, professor of clinical psychiatry at Columbia College of Physicians and Surgeons and author of last year's "Complementary and Alternative Medicine in Psychiatry."

Muskin – who takes fish oil supplements himself (for his heart) and frequently recommends them to patients – said there could be many reasons for the correlation, including genetics and exercise patterns in fish-eating countries.

Still, fish oils are safe, perhaps even beneficial for other parts of the body, and the small studies like Stoll's provide tantalizing evidence to Muskin that it may help some psychiatric patients.



Dr. Terence Ketter, associate professor of psychiatry at Stanford, has already been using omega-3s with many of his patients who have bipolar disorder.

"I've found them to be of *some* use, although they're not fantastic," Ketter said. "It's been most helpful with people who have mild depressive symptoms. For people who have very bad depression, it doesn't cut it."

Ketter is involved in the study of pregnant bipolar women. While he doesn't study other psychiatric disorders, he said he can see the usefulness of omega-3s in all kinds of brain diseases. And he said their safety profile makes them worth considering for many people.

"If people have the idea that it makes the membranes of nerve cells function better, it could help all kinds of brain functions," he said.

"If people have some mild symptoms but not a major problem, and you take the general health benefits with the potential benefits for mood, I think it would be a reasonable thing to" try the supplements, Ketter said.

Stoll became an omega-3 enthusiast after conducting his double-blind study with fish oil capsules and a placebo on patients who had failed other treatments.

"Usually you can't tell who is on placebo and who is on the real stuff, but this time the patients said they could swear they were on the real thing because they said they felt better," Stoll said. "It was pretty striking."

However, there are downsides. In Stoll's study, patients were given a whopping 9 grams of omega-3s per day. To get that much from supplements commonly available on the market, you'd have to take 30 pills a day, Ketter said. The most he's been able to get his patients to take is 15 a day – five pills three times a day with meals.

The pills are large, can leave people with "fishy" breath and are expensive.

"It could be $3 a day if you're taking many pills," Muskin said.

Stoll said he doesn't endorse tossing antidepressants or bipolar medications, especially for people with significant illness. But he thinks omega-3s may be able to help the drugs act more effectively.

Some of the most recent evidence is coming from brain scans of people who took omega-3 supplements. Stoll said that the membranes surrounding brain cells were more fluid (think oil versus butter), and that may help cells communicate better.

Meanwhile, many infant formulas will soon be fortified with essential fatty acids, including omega-3s. The Food and Drug Administration this summer cleared the way for companies to add the nutrients, which are found naturally in human breast milk and have been shown to improve IQ scores.

The supplements are especially important for babies born prematurely who may miss out on getting them from their mothers during the final trimester of pregnancy, when significant brain development occurs.

E-mail Ulysses Torassa at utorassa@sfchronicle.com.

Following omega-3 chain of command

Not all omega-3s are created equal, and Dr. Andrew L. Stoll has some specific ideas about what kinds are best.

First, there are long-chain and short-chain versions of Omega-3s. The shorter-chains are contained in vegetable and plant sources such as walnuts and flaxseed oil and leafy green vegetables. Most people convert at least some of these to the longer chains, but Stoll said not everyone is able to do so at the same rate.

That's why he recommends fish oil supplements, which contain the long-chain omega-3s that are needed by animals, including humans.

There are two main components to omega-3s, docosahexonoic acid (DHA) and eicosapentanoic acid (EPA). Stoll believes that it is EPA, which has anti-inflammatory properties, is more relevant to regulating mood than DHA and recommends supplements with a higher EPA-to-DHA ratio. DHA, however, is also key for healthy cells and is found in high concentrations in the brain, retina and sperm, and is especially crucial for pregnant and nursing women and infants.

For most people, Stoll believes 1 to 2 grams per day (about 3 ounces of wild salmon, one of the best sources of omega-3s) is adequate. Those using it to treat the symptoms of a mood disorder should use 2 to 5 grams.

Omega-3s are a mild blood thinner, so anyone who is already taking medication to thin the blood should be wary. And Stoll strongly suggests coordinating fish oil supplementation with your doctor.

– Ullysses Torrassa

These membranes are made of **lipid bilayers** (Figure 11.2). In a lipid bilayer, there are two rows (layers) of complex lipid molecules arranged tail to tail. The hydrophobic tails point toward each other because that

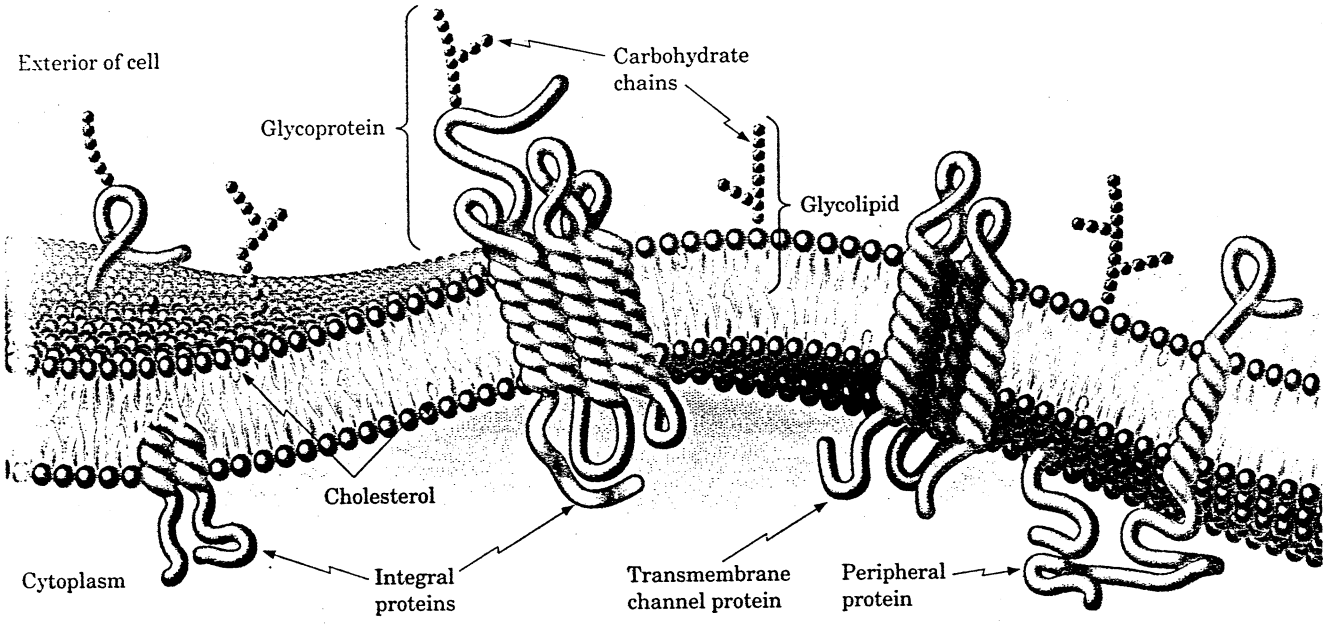
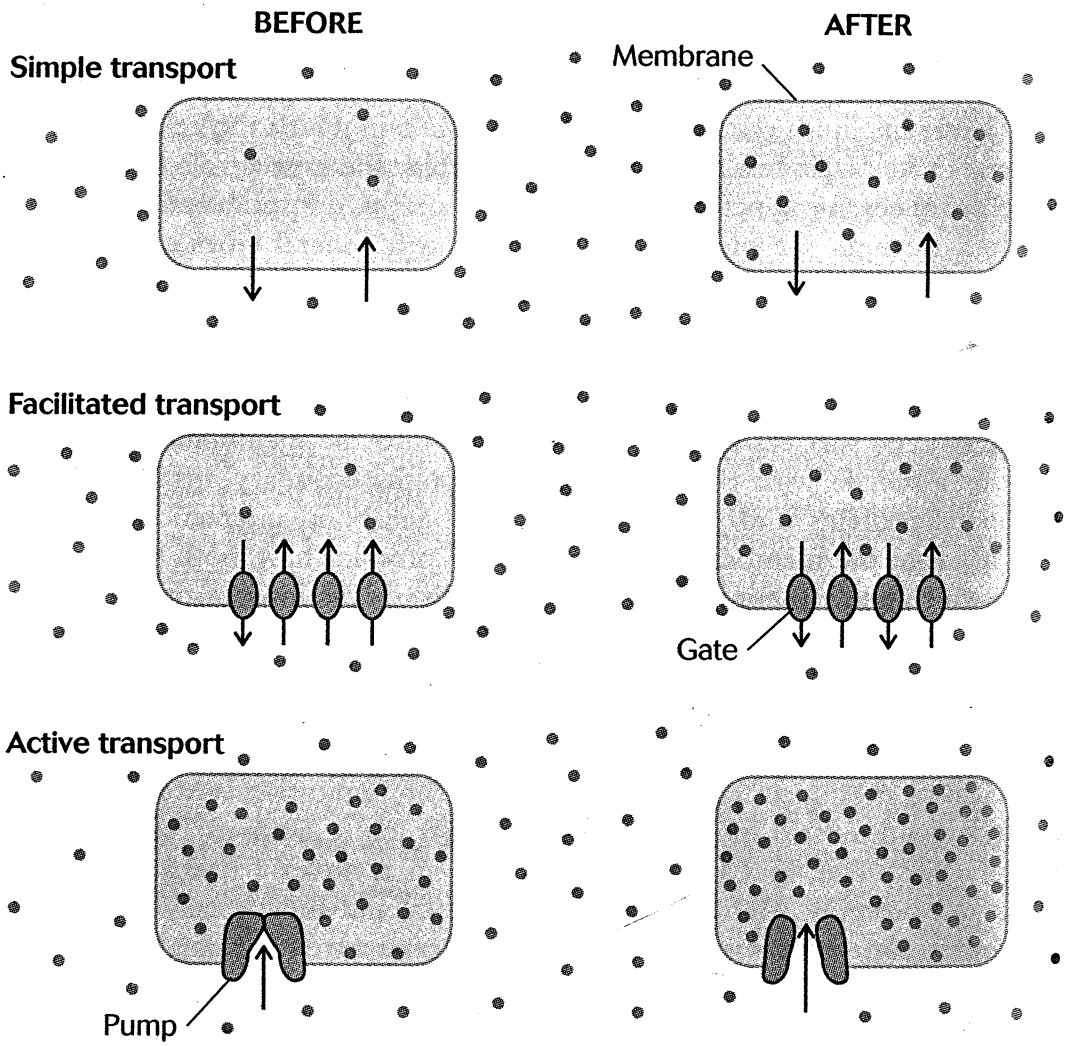
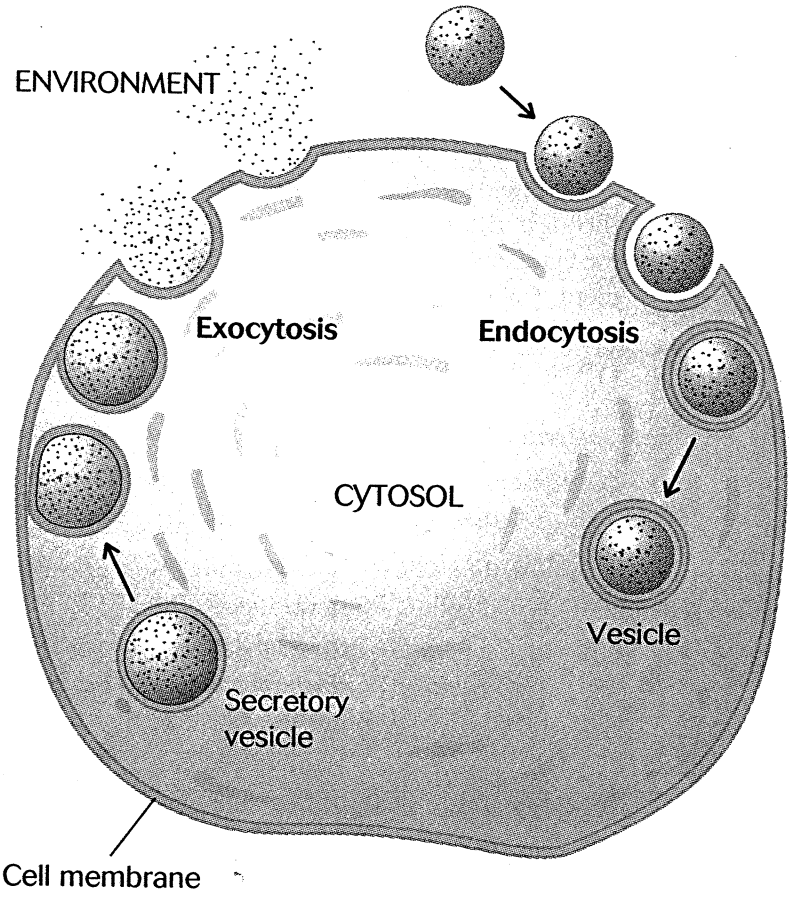


FIGURE 11.2 The fluid mosaic model of membranes. Note that proteins are embedded in the lipid matrix.


BEFORE
AFTER
Simple transport
Membrane
Facilitated transport
Gate
Active transport
Pump


ENVIRONMENT
Exocytosis
Endocytosis
CYTOSOL
Vesicle
Secretory vesicle
Cell membrane

BOX 11D

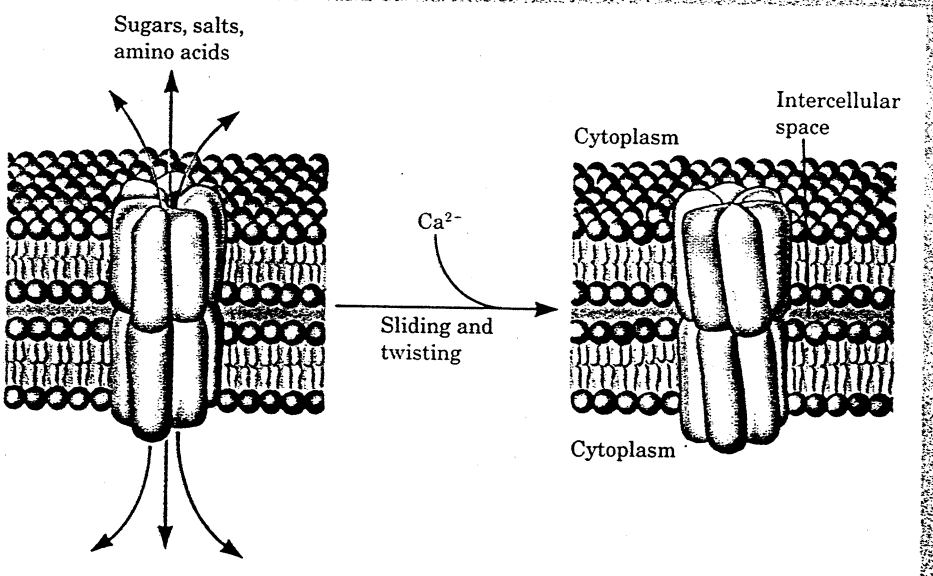
Transport Across Cell Membranes

Membranes are not just random assemblies of complex lipids to provide a nondescript barrier. For example, in human red blood cells, the outer part of the bilayer is made largely of phosphatidylcholine and sphingomyelin, while the inner part is made mostly of phosphatidylethanolamine and phosphatidyl serine. In another example, in the membrane called sarcoplasmic reticulum in the heart muscles, phosphatidylethanolamine is found in the outer part of the membrane, phosphatidylserine is found in the inner part, and the phosphatidyl choline is equally distributed in the two layers of the membrane. Membranes are not static structures either. In many processes, membranes fuse with one another; in others they disintegrate, and their building blocks are used elsewhere. When membranes fuse, for example, in vacuole fusions inside of cells, certain restrictions prevent incompatible membranes from intermixing.

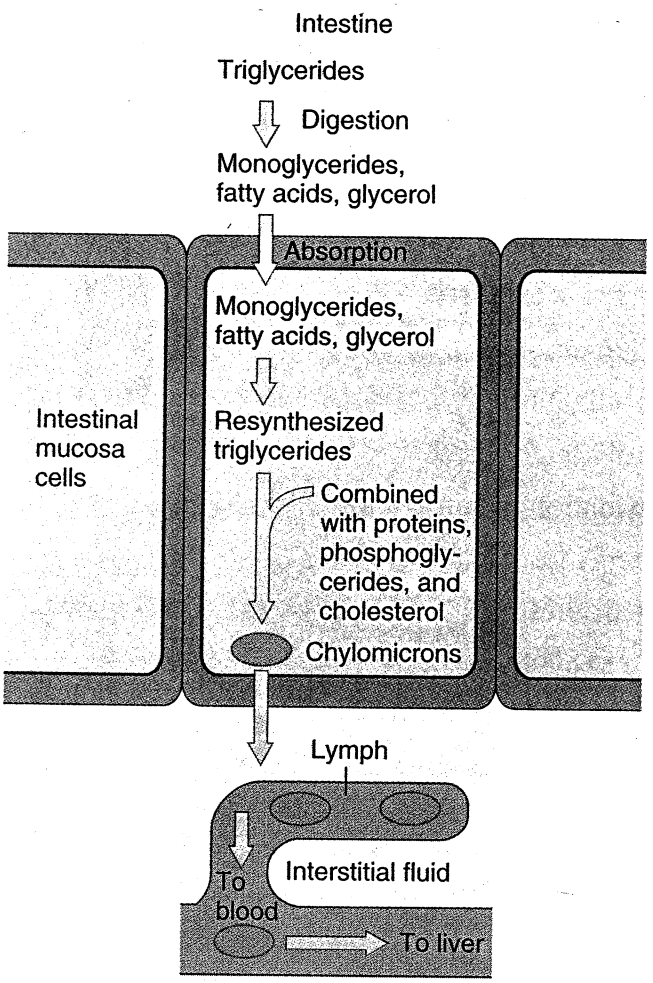
The protein molecules are not dispersed randomly in the bilayer. Sometimes they cluster in patches, but they also appear in regular geometric patterns. An example of the latter are **gap junctions,** channels made of six proteins that create a central pore (Figure 11D). This allows neighboring cells to communicate. Gap junctions are an example of **passive transport.** Small polar molecules, which include such essential nutrients as inorganic ions, sugars, amino acids, and nucleotides, can readily pass through gap junctions. Large molecules such as proteins, polysaccharides, and nucleic acid cannot.

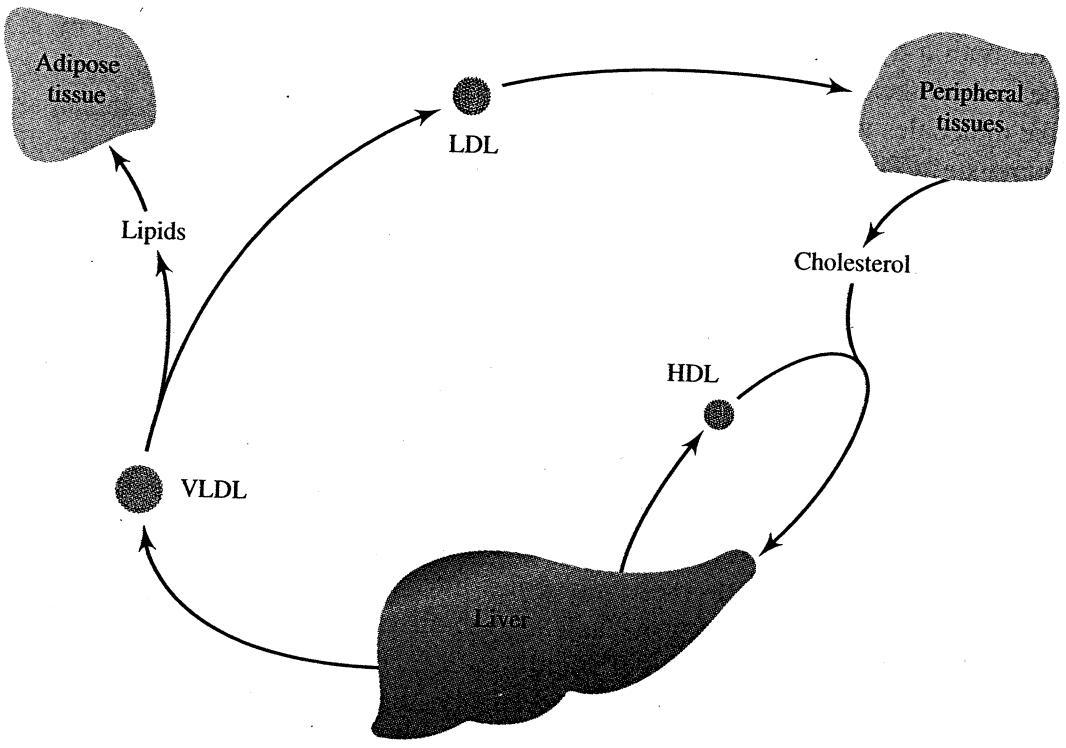
In the **facilitated transport** there is a specific interaction between the transporter and the transported molecule. An example is the **anion transporter** of the red blood cells through which chloride and bicarbonate ions are exchanged in a one-for-one ratio. The transporter is a protein with 14 helical structures that span the membrane. One side of the helices contains the hydrophobic parts of the protein. These can interact with the lipid membrane. The other side of the helices forms a channel. The channel contains the hydrophilic portions of the protein, which can interact with the hydrated ions. In this manner, the anion passes through the erythrocyte membrane.

Active transport involves the passage of ions against concentration gradient. For example, the K^+ has a higher concentration inside the cells than outside in the surrounding environment. Still, potassium ion can be transported from the outside into a cell, but at the expense of energy. The transporter, a membrane protein called Na^+, K^+ ATPase, uses the energy from the hydrolysis of ATP molecule to change the conformation of the transporter which brings in K^+ and exports Na^+.



■ *FIGURE 11D* Gap junctions are made of six cylindrical protein subunits. They are lined up in two plasma membranes parallel to each other forming a pore. The pores of gap junctions are closed by a sliding and twisting motion of the cylindrical subunits.





◀ **FIGURE 29.8**
Schematic representation of t lipid distribution system throu the bloodstream.

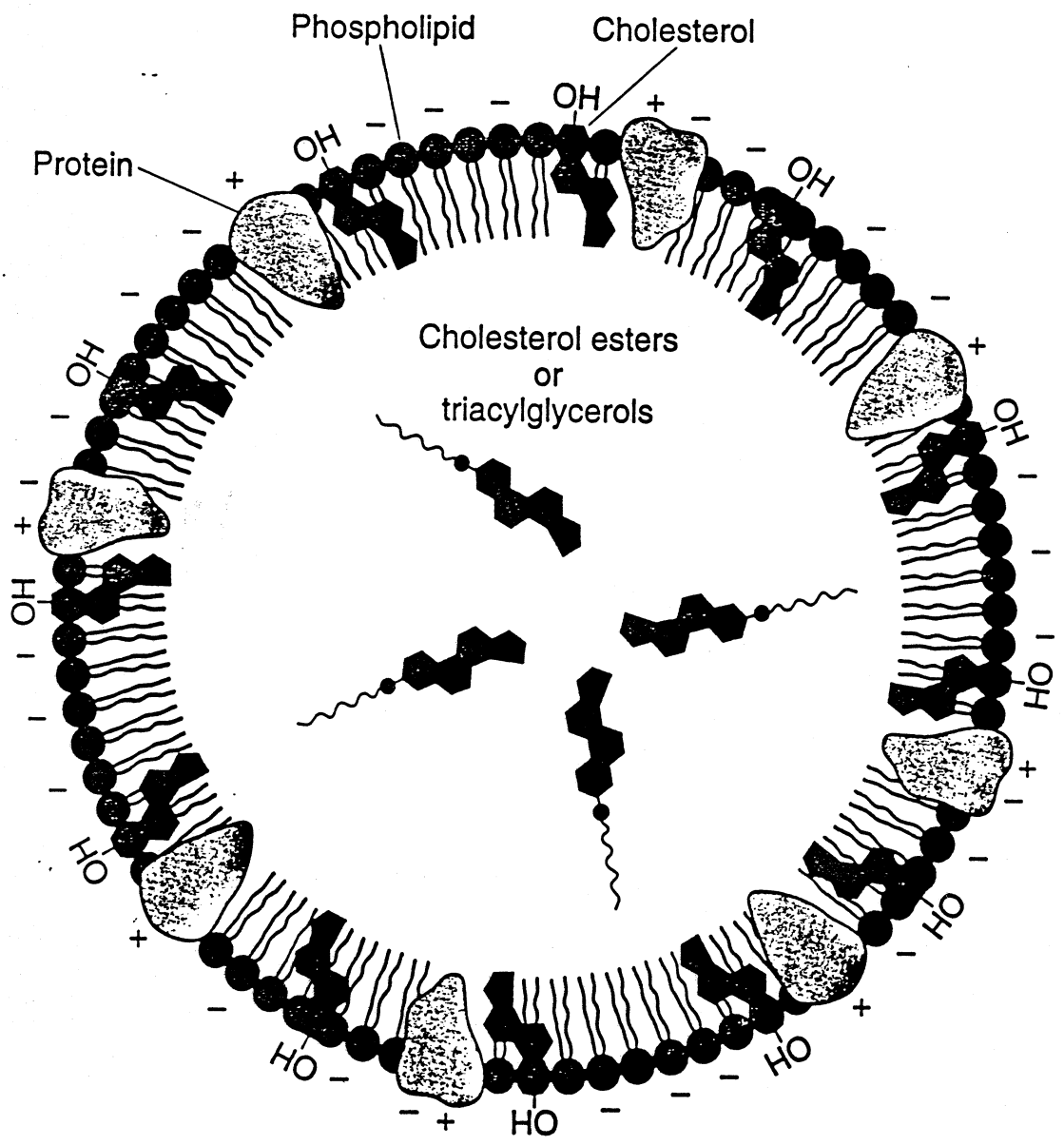
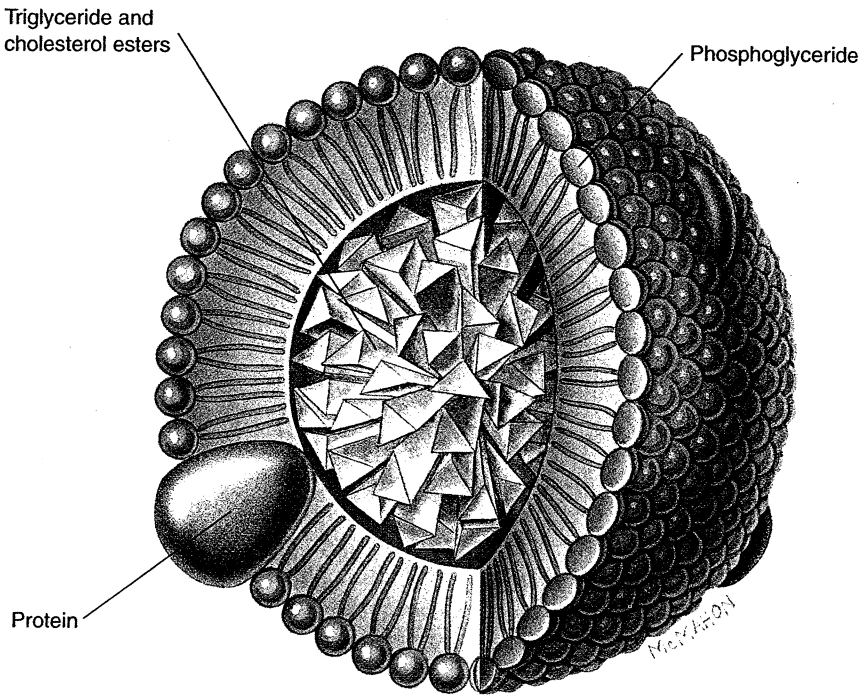


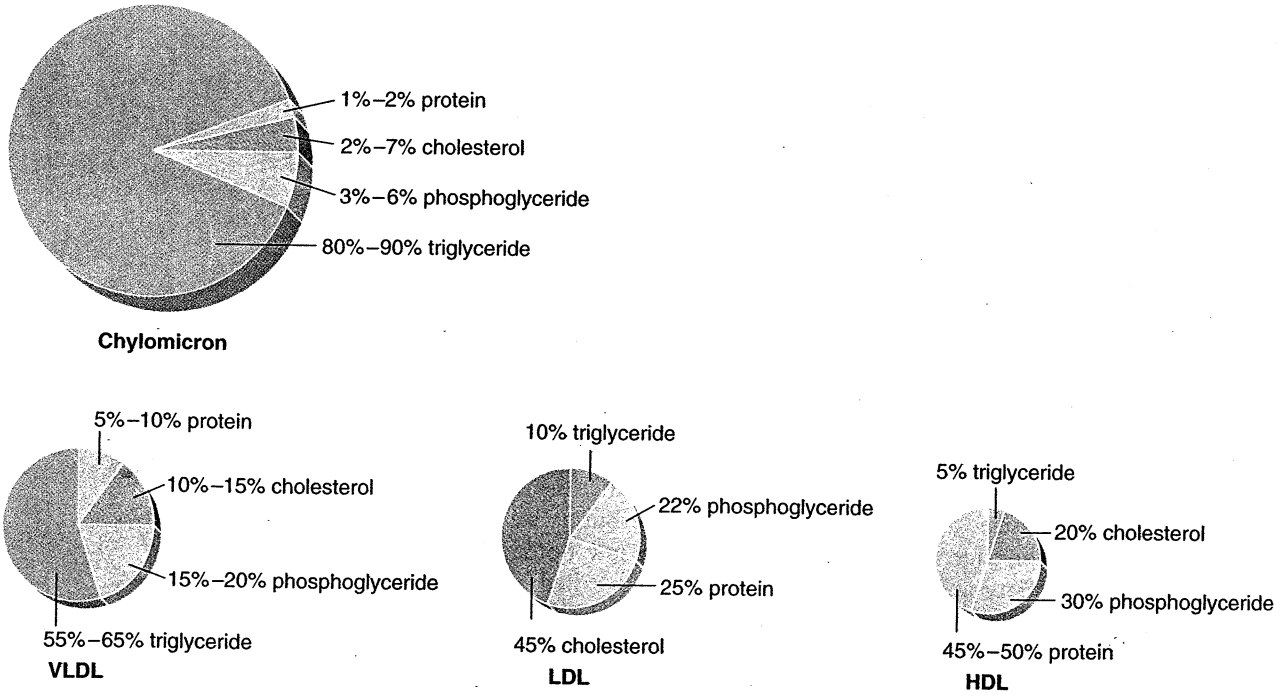
FIGURE 9.9
A model for the structure of a plasma lipoprotein. The various lipoproteins are composed of a shell of protein, cholesterol, and phospholipids surrounding more hydrophobic molecules such as triglycerides or cholesterol esters (cholesterol esterified to fatty acids).



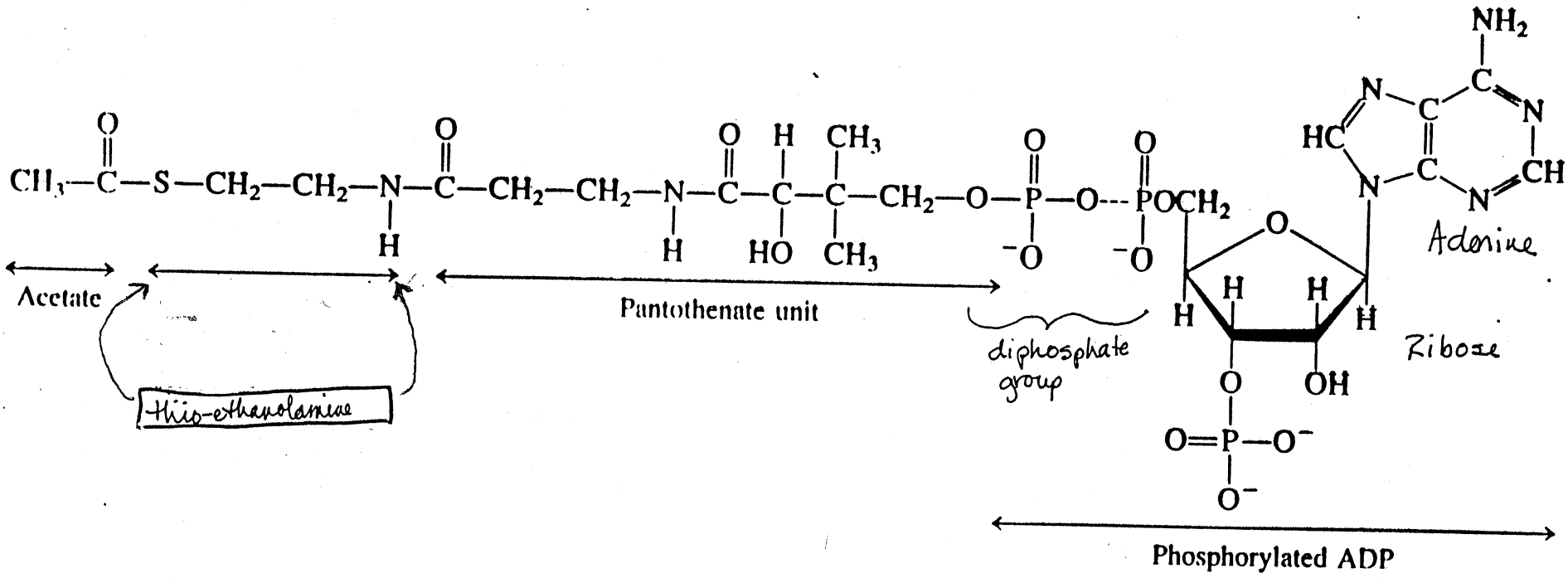
➤ **FIGURE 14.3** A schematic model of low-density lipoprotein (LDL).

Brain cells are bathed in cerebrospinal fluid and do not obtain nutrients directly from the blood (the blood-brain barrier). Glucose and many other substances can cross the barrier into the cerebrospinal fluid, but fatty acids cannot.

When body cells need fatty acids for energy, the endocrine system is stimulated to produce several hormones, including epinephrine, which interact



➤ **FIGURE 14.4** Relative amounts of cholesterol, protein, triglyceride, and phosphoglyceride in the four classes of lipoproteins.



Acetyl coenzyme A
(acetyl CoA)

Fatty Acid Oxidation