contents) unless cholesterol is added to the culture fluid. The added cholesterol is incorporated into the plasma membrane, thereby enabling the cells to survive.

The precise fluidity of the plasma membrane must be biologically important, since bacteria, yeast, and other poikilothermic organisms, whose temperatures fluctuate with that of their environment, change the fatty acid composition of their plasma membrane so as to maintain a relatively constant fluidity. As the temperature falls, for example, fatty acids with more *cis*-double bonds are synthesized, so that the decrease in bilayer fluidity that would otherwise result from the drop in temperature is avoided. Certain membrane transport processes and enzyme activities can be shown to cease when the bilayer viscosity increases beyond a threshold level.

## The Lipid Bilayer Serves as a Solvent for Membrane Proteins[5]

The lipid compositions of several biological membranes are compared in Table 6–1. Note that bacterial plasma membranes are often composed of one main type of phospholipid and contain no cholesterol; in the absence of cholesterol, mechanical stability is provided by the overlying cell wall (see Figure 6–54, p. 312). The plasma membranes of most eucaryotic cells, however, contain not only large amounts of cholesterol but also a variety of phospholipids. The plasma membrane of many mammalian cells, for example, contains four major phospholipids—*phosphatidylcholine, sphingomyelin, phosphatidylserine,* and *phosphatidylethanolamine.* The structures of these molecules are shown in Figure 6–9. Note that only phosphatidylserine carries a net negative charge; the other three are electrically neutral at physiological pH, carrying one positive and one negative charge. Together these four phospholipids constitute more than half the mass of lipid in most membranes (Table 6–1). Other phospholipids, such as the *inositol phospholipids* (see p. 702), are functionally important but present in relatively small quantities. The crucial role of the inositol phospholipids in cell signaling is discussed in Chapter 12.

One may wonder why the eucaryotic plasma membrane contains such a variety of phospholipids, with head groups that differ in size, shape, and charge. In seeking an answer it may be helpful to think of the membrane lipids as constituting a two-dimensional solvent for the proteins in the membrane, just as water constitutes a three-dimensional solvent for proteins in an aqueous solution. It may be that some membrane proteins can function only in the presence of specific phospholipid head groups, just as many enzymes in aqueous solution require a

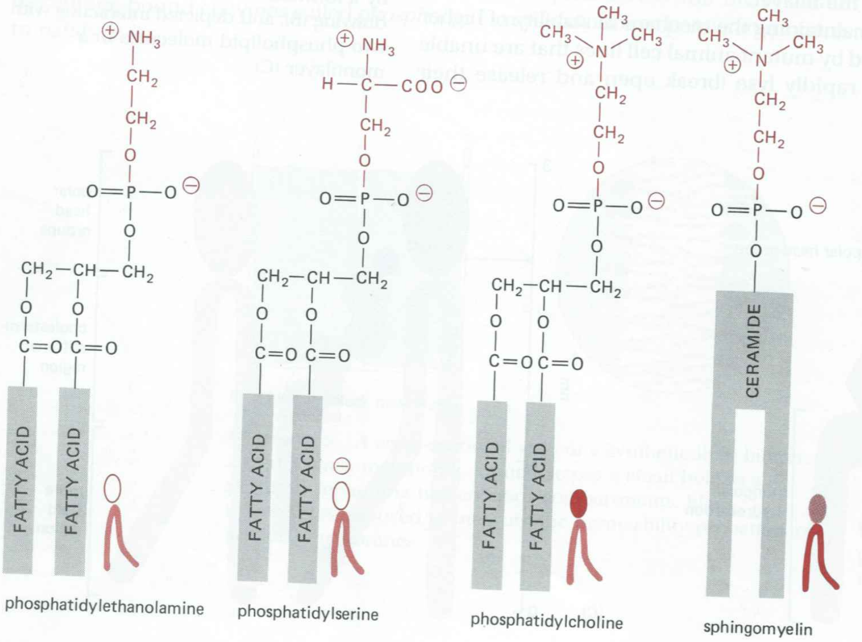

**Figure 6–9** Formulas and symbols of four major phospholipids in mammalian plasma membranes. Note that different head groups are represented by different symbols in this figure and the next. All of the molecules shown are derived from glycerol except for sphingomyelin, which is derived from serine. The structure and formation of ceramide are shown in Figure 6–11.

**Table 6–1** Approximate Lipid Compositions of Different Cell Membranes

|  | Percentage of Total Lipid by Weight |  |  |  |  |  |
|---|---|---|---|---|---|---|
| Lipid | *Liver Plasma Membrane* | *Erythrocyte Plasma Membrane* | *Myelin* | *Mitochondrion (inner and outer membranes)* | *Endoplasmic Reticulum* | *E. coli* |
| Cholesterol | 17 | 23 | 22 | 3 | 6 | 0 |
| Phosphatidylethanolamine | 7 | 18 | 15 | 35 | 17 | 70 |
| Phosphatidylserine | 4 | 7 | 9 | 2 | 5 | trace |
| Phosphatidylcholine | 24 | 17 | 10 | 39 | 40 | 0 |
| Sphingomyelin | 19 | 18 | 8 | 0 | 5 | 0 |
| Glycolipids | 7 | 3 | 28 | trace | trace | 0 |
| Others | 22 | 13 | 8 | 21 | 27 | 30 |

particular ion for activity. Consistent with this view is the finding that some membrane proteins, when inserted into a synthetic lipid bilayer, will function optimally only if the bilayer contains certain specific phospholipids.

## The Lipid Bilayer Is Asymmetrical[6]

The lipid compositions of the two halves of the lipid bilayer in those membranes that have been analyzed are strikingly different. In the human red blood cell membrane, for example, almost all of the lipid molecules that have choline—$(CH_3)_3N^+CH_2CH_2OH$—in their head group (that is, phosphatidylcholine and sphingomyelin) are in the outer half of the lipid bilayer, while almost all of the phospholipid molecules that contain a terminal primary amino group (phosphatidylethanolamine and phosphatidylserine) are in the inner half (Figure 6–10). The fatty acid tails of phosphatidylcholine and sphingomyelin are more saturated than those of phosphatidylethanolamine and phosphatidylserine; therefore, the asymmetry in the distribution of the head groups is accompanied by an asymmetry in the distribution of hydrocarbon tails that may make the inner monolayer somewhat more fluid than the outer monolayer. In addition, because the negatively charged phosphatidylserine is located in the inner monolayer, there is a significant difference in charge between the two halves of the bilayer.

Most of the membranes in a eucaryotic cell, including the plasma membrane, are synthesized in the endoplasmic reticulum (ER), and it is here that the phospholipid asymmetry is generated by the phospholipid translocators in the ER that move specific phospholipid molecules from one monolayer to the other (see p. 449). Although the function of the lipid asymmetry is largely unknown, there are membrane-bound enzymes that make use of it: when *protein kinase C* is activated, for example, it is bound to the cytoplasmic face of the plasma membrane, where phosphatidylserine is concentrated, and it requires this negatively

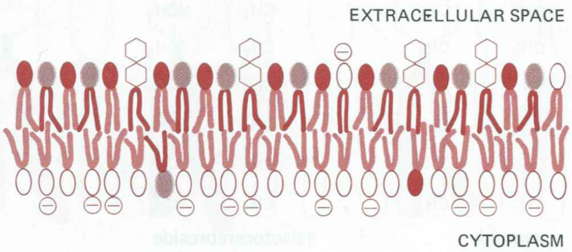

**Figure 6–10** The asymmetrical distribution of phospholipids and glycolipids in the lipid bilayer of human red blood cells. The symbols used for the phospholipids are those introduced in Figure 6–9. Glycolipids are drawn with hexagonal polar head groups. Cholesterol (not shown) is thought to be distributed about equally in both monolayers.

charged phospholipid in order to act (see p. 704). The importance of having specific inositol phospholipids concentrated in the cytoplasmic leaflet of the plasma membrane lipid bilayer, where they can be used to generate intracellular mediators in response to extracellular signals, is discussed in Chapter 12 (see p. 702).

## Glycolipids Are Found on the Surface of All Plasma Membranes, but Their Function Is Unknown[7]

The lipid molecules that show the most striking and consistent asymmetry in distribution in the plasma membranes of animal cells are the oligosaccharide-containing lipid molecules called **glycolipids.** These intriguing molecules are found only in the outer half of the bilayer, and their sugar groups are exposed at the cell surface (see Figure 6–10), suggesting some role in interactions of the cell with its surroundings. The asymmetric distribution of glycolipids in the bilayer derives from the addition of sugar groups to the lipid molecules in the lumen of the Golgi apparatus, which is topologically equivalent to the exterior of the cell (see p. 408).

Glycolipids probably occur in all animal cell plasma membranes, and they generally constitute about 5% of the lipid molecules in the outer monolayer. They differ remarkably from one animal species to another and even among tissues in the same species. In bacteria and plants almost all glycolipids are derived from glycerol-based lipids, as is the common phospholipid phosphatidylcholine. In animal cells, however, they are almost always produced from *ceramide,* as is the phospholipid sphingomyelin (see Figure 6–9). These *glycosphingolipids* have a general structure that is similar to that of the glycerol-based lipids, having a polar head group and two hydrophobic fatty acid chains. However, one of the fatty acid chains is initially coupled to serine to form the amino alcohol *sphingosine,* to which the second fatty acid chain is then linked to form ceramide (Figure 6–11).

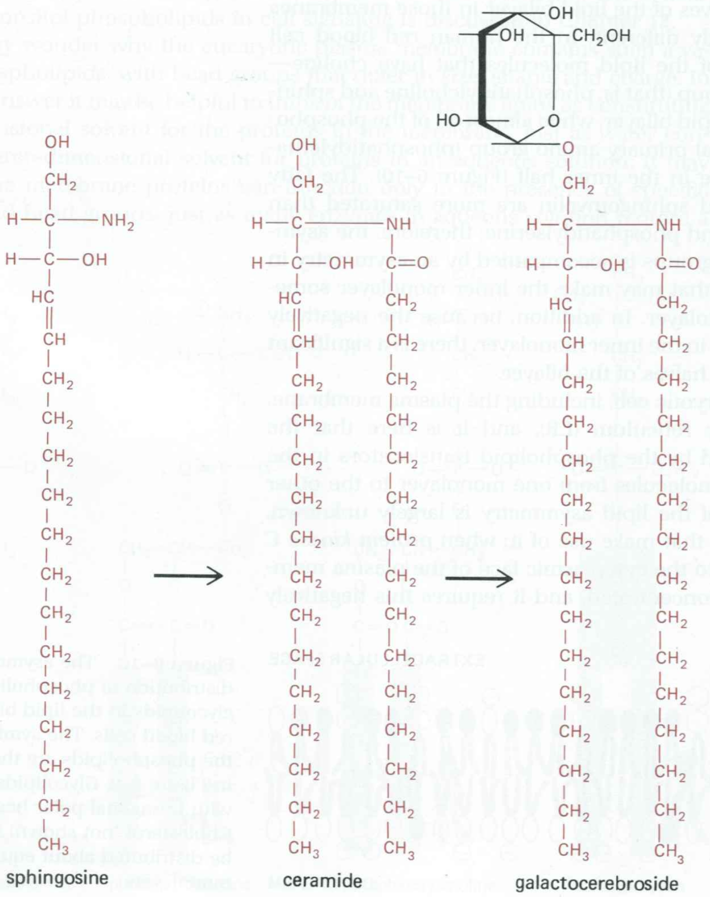

**Figure 6–11** Final steps in the synthesis of the simple glycosphingolipid galactocerebroside. Sphingosine is formed by condensing the amino acid serine with one fatty acid; a second fatty acid is then added to form ceramide, as shown. Ceramide is made in the endoplasmic reticulum and the carbohydrate is added in the Golgi apparatus (see p. 449). Ceramide is also used to form the major phospholipid sphingomyelin (see Figure 6–9).

Glycolipids are distinguished from one another by their polar head group, which consists of one or more sugar residues. Among the most widely distributed glycolipids in the plasma membranes of both eucaryotic and procaryotic cells are the **neutral glycolipids,** whose polar head groups consist of anywhere from 1 to 15 or more neutral (uncharged) sugars, depending on the organism and cell type. One example is *galactocerebroside,* one of the simplest glycolipids, which has only galactose as its polar head group (see Figure 6–11). It is the main glycolipid in myelin, which consists of many concentric layers of plasma membrane wound around a nerve cell process (an axon) by a specialized myelinating cell (see p. 1073). The myelinating cells can be distinguished by the large amount of galactocerebroside in their plasma membrane, where it constitutes almost 40% of the outer monolayer. Galactocerebroside is largely absent from the membranes of most other cells, and it is thought to play an important part in the specific interaction between the myelinating cell and the axon.

The most complex of the glycolipids, the **gangliosides,** contain one or more sialic acid residues (also known as *N*-acetylneuraminic acid, or NANA), which gives them a net negative charge (Figure 6–12). Gangliosides are most abundant in the plasma membrane of nerve cells, where they constitute 5–10% of the total lipid mass, although they are found in much smaller quantities in most cell types. So far more than 40 different gangliosides have been identified. Some common examples are shown in Figure 6–13, where the nomenclature used to describe them is also introduced.

There are only hints as to what the functions of glycolipids might be. For example, the ganglioside $G_{M1}$ (Figure 6–13) acts as a cell-surface receptor for the bacterial toxin that causes the debilitating diarrhea of cholera; cholera toxin binds to and enters only those cells with $G_{M1}$ on their surface, including intestinal epithelial cells. The entry of cholera toxin into the cell leads to a prolonged increase in the concentration of intracellular cyclic AMP, which in turn causes a large efflux of $Na^+$ and water into the intestine (see p. 697). Although binding bacterial toxins cannot be the *normal* function of gangliosides, such observations suggest that these glycolipids may also serve as receptors for normal signaling between cells.

## Summary

*Biological membranes consist of a continuous double layer of lipid molecules in which various membrane proteins are embedded. This lipid bilayer is fluid, with individual lipid molecules able to diffuse rapidly within their own monolayer. However, most types of lipid molecules very rarely flip-flop spontaneously from one*

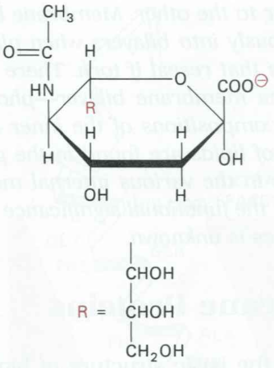

**Figure 6–12** The structure of sialic acid (*N*-acetylneuraminic acid, or NANA). In cells this acid exists in its ionized form (—COO⁻), as shown.

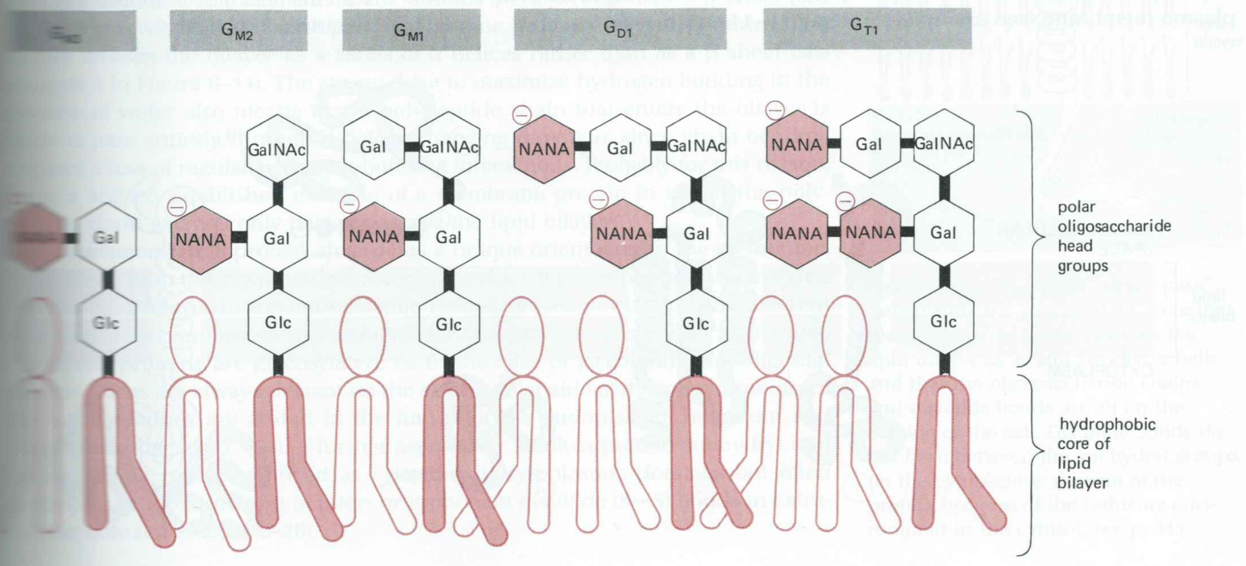

**Figure 6–13** Some representative gangliosides with their standard designations. In $G_{M1}$, $G_{M2}$, $G_{M3}$, $G_{D1}$, and $G_{T1}$, the letters M, D, and T refer to the number of sialic acid residues (mono, di, and tri, respectively), while the number that follows the letter is determined by subtracting the number of uncharged sugar residues from 5. NANA = *N*-acetylneuraminic (sialic) acid; Gal = galactose; Glc = glucose; GalNAc = *N*-acetylgalactosamine. Gal, Glc, and GalNAc are all uncharged, whereas NANA carries a negative charge (see Figure 6–12).

*monolayer to the other. Membrane lipid molecules are amphipathic and assemble spontaneously into bilayers when placed in water; the bilayers form sealed compartments that reseal if torn. There are three major classes of lipid molecules in the plasma membrane bilayer—phospholipids, cholesterol, and glycolipids—and the lipid compositions of the inner and outer monolayers are different. Different mixtures of lipids are found in the plasma membranes of cells of different types, as well as in the various internal membranes of a single eucaryotic cell. For the most part the functional significance of the different lipid compositions of different membranes is unknown.*

## Membrane Proteins

Although the basic structure of biological membranes is provided by the lipid bilayer, most of the specific functions are carried out by proteins. Accordingly, the amounts and types of proteins in a membrane are highly variable: in the myelin membrane, which serves mainly to insulate nerve cell axons, less than 25% of the membrane mass is protein, whereas in the membranes involved in energy transduction (such as the internal membranes of mitochondria and chloroplasts), approximately 75% is protein; the usual plasma membrane is somewhere in between, with about 50% of the mass being protein. Because lipid molecules are small in comparison to protein molecules, there are always many more lipid molecules than protein molecules in membranes—about 50 lipid molecules for each protein molecule in a membrane that is 50% protein by mass.

### 6-10 6-11 The Polypeptide Chain of Many Membrane Proteins Crosses the Lipid Bilayer One or More Times[8]

Many membrane proteins extend across the lipid bilayer (examples 1 and 2 in Figure 6–14). Like their lipid neighbors, these so-called **transmembrane proteins** are amphipathic: they have hydrophobic regions that pass through the membrane and interact with the hydrophobic tails of the lipid molecules in the interior of the bilayer and hydrophilic regions that are exposed to water on both sides of the membrane. The hydrophobicity of some of these membrane proteins is increased by the covalent attachment of a fatty acid chain that is inserted in the cytoplasmic leaflet of the bilayer (see example 1 in Figure 6–14). Some intracellular membrane proteins are associated with the bilayer only by means of such a fatty acid chain (see example 3 in Figure 6–14 and p. 417), while some cell-surface proteins are attached to the bilayer only by a covalent linkage (via a specific oligosaccharide) to phosphatidylinositol, a minor phospholipid, in the outer lipid monolayer of the plasma membrane (see example 4 in Figure 6–14 and p. 448).

**Figure 6–14** Five ways in which membrane proteins can be associated with the lipid bilayer. Transmembrane proteins extend across the bilayer as a single α helix (1) or as multiple α helices (2); some of these "single-pass" and "multipass" proteins have a covalently attached fatty acid chain inserted in the cytoplasmic monolayer (1). Other membrane proteins are attached to the bilayer solely by a covalently attached lipid—either a fatty acid chain in the cytoplasmic monolayer (3) or, less often, via an oligosaccharide, to a minor phospholipid, phosphatidylinositol, in the noncytoplasmic monolayer (4). Finally, many proteins are attached to the membrane only by noncovalent interactions with other membrane proteins (5). The details of how membrane proteins become associated with the lipid bilayer in these ways are discussed in Chapter 8.