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Chapter 16

Phospholipid Metabolism

This chapter quizzes the reader on the biological roles of phospholipids, sphingolipids, and glycosaminoglycans. Diseases relating to these large molecules will be the focus of this chapter.

QUESTIONS

Select the single best answer.

1 A patient presents with rapidly progressive weakness of the lower extremities, loss of deep tendon reflexes, respiratory distress, and autonomic dysfunction following a flulike illness. This disease is an autoimmune inflammatory reaction to tissue made up chiefly of which of the following chemical structures?
(A) High-density lipoproteins
(B) Elastin
(C) Sphingolipids
(D) Glycoproteins
(E) Glycogen

2 The above patient is in the recovery phase of her illness. She wants to "naturally" help her body recover using dietary methods. Which of the following foods is best in providing the chemicals needed to regrow the affected tissues?
(A) Soybeans
(B) Calves' liver
(C) Pork kidney
(D) Green leafy vegetables
(E) Potatoes

3 A newborn infant had trouble breathing at birth. The infant was 3 months premature. The physicians treated the infant with a solution, which was directly injected into the lungs. Within seconds, the infant responded with much improved breathing. A major component of this solution is which one of the following?
(A) Dipalmitoyl phosphatidylcholine
(B) Palmitate containing ceramide
(C) Sphingosine
(D) Sphingomyelin
(E) Diacylglycerol

4 Considering the case in the previous question, the major function of the suspension utilized to improve breathing is which of the following?
(A) To allow oxygen exchange with red blood cells
(B) To facilitate carbon dioxide extraction from red blood cells
(C) To reduce surface tension at the air–water interface
(D) To stabilize the structure of lung cells
(E) To facilitate blood flow through the lung

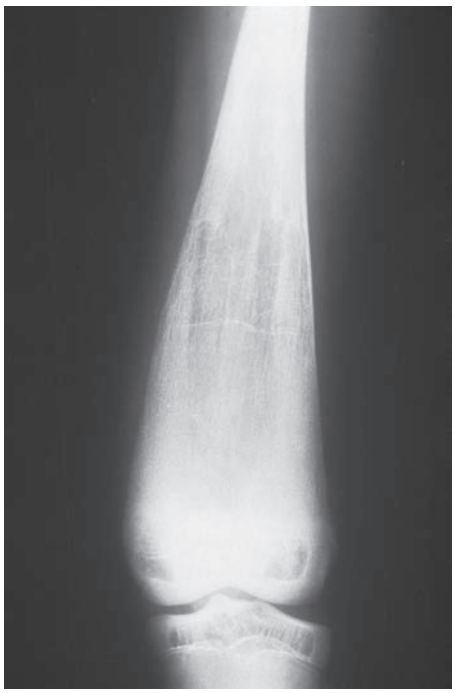
5 A 9-month-old child is taken to the pediatrician for lethargy and poor feeding. The physician notes a cherry-red spot in the child's retina. The baby seemed fine for the first three to six months, then began to have problems swallowing, overreacted to loud sounds, seemed to have problems with her vision, and began losing muscle mass and strength. Measurements of which two metabolites is critical to correctly diagnose this disorder?
(A) GM2 and globoside
(B) GM2 and GM3
(C) GM1 and globoside
(D) GM1 and GM2
(E) Globoside and sphingomyelin

6 Considering the child described in the previous question, a diagnosis of Sandhoff disease was made. This results in a loss of which of the following enzymatic activities?
(A) Hexosaminidase A and Hexosaminidase C
(B) Hexosaminidase B and Hexosaminidase C
(C) Hexosaminidase A and Hexosaminidase B
(D) Hexosaminidase A and sphingomyelinase
(E) Hexosaminidase B and sphingomyelinase

7 Considering the child described in the last two questions, multiple enzymatic activities are lost. This is due to which of the following?
(A) A common operon for the two genes contains a mutation in the promoter region
(B) An inactivating mutation in an activator for the lost enzymatic activities
(C) A transcriptional activator is inactivated
(D) A common mutated subunit is present in the multiple activities
(E) A transcriptional repressor is activated

8 A 4-month-old infant is brought to the pediatrician for a variety of problems. The child is frequently irritable, small for age, vomits frequently, and displays hypotonia, as well as hyperesthesia (auditory, tactile, and visual). Liver and spleen size are normal. As the child ages, his condition worsens, with rapid psychomotor deterioration, seizures, and blindness. This disorder is caused by an accumulation of which of the following in neuronal lysosomes?
(A) Galactosylceramide
(B) Sulfatide
(C) Glucosylceramide
(D) Sphingomyelin
(E) Ceramide

9 A 6-month-old boy is brought to the pediatrician due to a large stomach. The doctor noticed splenomegaly, with no pain. The boy was always tired and had anemia. The boy also has thrombocytopenia and bruises easily. X-rays show a deformity of the distal femur, as shown below. This disorder is caused by an accumulation of which of the following in macrophage lysosomes?



(A) Galactosylceramide
(B) Sulfatide
(C) Glucosylceramide
(D) Sphingomyelin
(E) Ceramide

10 The sphingolipidoses, as a class, are most similar to which one of the following disorders?
(A) Glucose-6-phosphate dehydrogenase deficiency
(B) von Gierke disease
(C) Zellweger syndrome
(D) MELAS
(E) I-cell disease

11 A child has been diagnosed with Tay–Sachs disease, in which a particular lipid accumulates within the lysosomes. The component of this lipid which cannot be removed in the lysosome is which of the following?
(A) Ceramide
(B) Sphingosine
(C) Fatty acid
(D) Glucose
(E) *N*-acetylgalactosamine

12 A depressed patient is prescribed lithium by his psychiatrist. The effect of lithium is to block the generation of which of the following?
(A) Diacylglycerol
(B) Inositol trisphosphate
(C) Inositol bisphosphate
(D) Inositol phosphate
(E) Inositol

13 An alcoholic patient with advanced cirrhosis presents with spur cell anemia. For virtually all cell types and organelles, the phospholipid composition of the inner and outer leaflets of the membrane is different. The spur cell anemia is the result of the loss of one potential benefit of such phospholipid asymmetry. Which of the following best explains this benefit?
(A) To vary the melting temperature of the membrane
(B) To represent all phospholipids species within the membrane
(C) To mark cells for recognition by outside systems
(D) To distinguish between intracellular organelles
(E) To prevent fusion of intracellular organelles

14 Phosphatidylinositol contributes to phospholipid bilayer asymmetry by being in the inner leaflet of membranes, facing the cytoplasm of the cell. This is most likely due to which of the following?

(A) The hydrophobic nature of inositol is unstable facing the cellular exterior
(B) Inositol is very similar in structure to glucose and could compete with glucose for binding of ligands to the extracellular surface
(C) Phosphatidylinositol acts as a substrate for intracellular processes
(D) Phosphatidylinositol binds to phosphatidylserine, another inner leaflet specific phospholipid
(E) Inositol interacts with intracellular actin, linking the inner leaflet to a cell's cytoskeleton

15 The use of proteoglycans in synovial fluid of joints is advantageous due to the ability of the proteoglycans to form which type of interactions with other components of the fluid?
(A) Disulfide and ionic bonds
(B) Hydrogen and ionic bonds
(C) Covalent and ionic bonds
(D) Covalent and hydrogen bonds
(E) Disulfide and hydrogen bonds

16 Your 52-year-old male patient, an avid soccer player in his youth, who had several knee injuries, has been complaining of knee pain for the past 6 months. The knees are tender, stiff, and feel warm when touched. He wants long-term relief, not just short-term relief. You suggest that the patient take which of the following to try and reduce the knee pain, for the long term?
(A) Aspirin
(B) Acetaminophen
(C) Sphingomyelin
(D) Glucosamine
(E) Inositol

17 Children with either I-cell disease or Hurler syndrome show very similar clinical features. One method to distinguish between the two is to find which of the following elevated in the blood?
(A) Heparan sulfate
(B) Short-chain dicarboxylic acids
(C) Lysosomal hydrolases
(D) Dermatan sulfate
(E) Cytochrome *c*

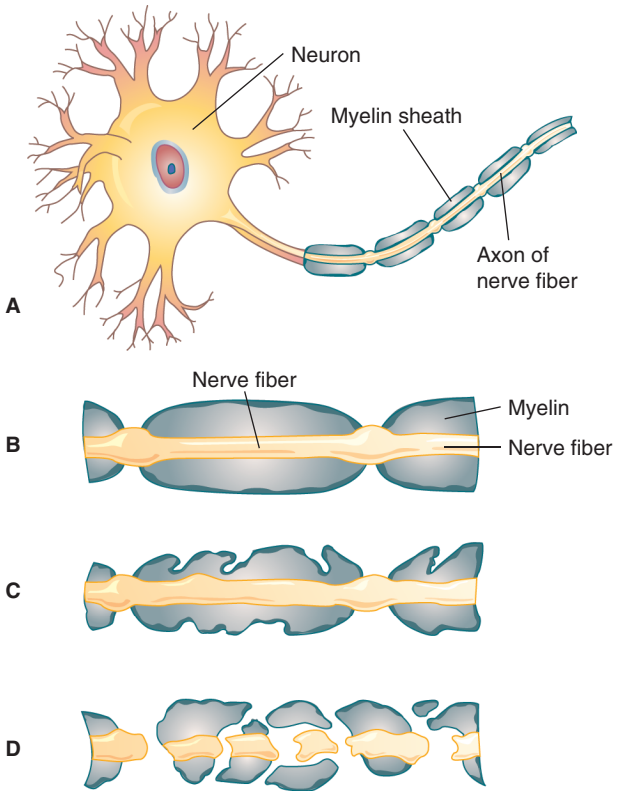
18 A 27-year-old woman sees her physician due to weakness and tiredness. She has tingling and numbness in her fingers and toes, loss of balance and falling, and blurry vision, sometimes double vision. Her ophthalmologist has diagnosed optic neuritis in her. An MRI of the brain shows "skip lesions." The component that is primarily defective in this patient is composed of which of the following?
(A) Phospholipids and proteins
(B) Triacylglycerol and protein
(C) Phospholipids and triacylglycerol
(D) Gangliosides and protein
(E) Triacylglycerol and gangliosides

19 A woman has a history of premature miscarriages (three), thrombocytopenia, and several episodes of deep vein thrombosis. She has a positive lupus anticoagulant but does not have systemic lupus erythematosus (SLE). Examination of the proteins in her blood should find antibodies directed against which of the following?
(A) Cytochrome *c*
(B) Phospholipids
(C) DNA
(D) RNA splicing proteins
(E) Ribosomes

20 An athlete presents to the ER with sudden pain in his calf after hearing a "popping noise," and inability to push off with his toes when he tries to run. He gives a history of having a "cortisol shot" in his heel area for Achilles tendonitis and he just finished a course of ciprofloxacin for chronic prostatitis. Physical exam reveals a mass in the superior posterior lower leg and an inability to plantar flex his foot. Biopsy of the Achilles tendon would be expected to reveal fibrotic areas, neovascularization, and an increase of which of the following in the extracellular matrix?
(A) Cholesterol
(B) Glycosaminoglycans
(C) Triglyceride
(D) Sphingosine
(E) High Density Lipoprotein (HDL)

ANSWERS

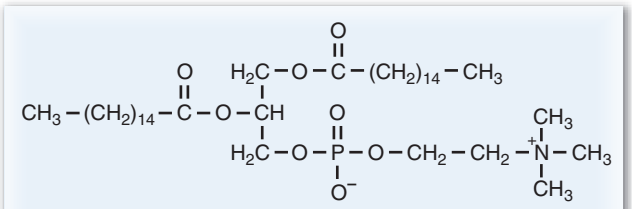
1 **The answer is C: Sphingolipids.** This patient has the classic symptoms of Guillain–Barré syndrome which is an inflammatory autoimmune neuritis wherein T-cells formed in response to a viral illness mistakenly attack the myelin sheath of peripheral nerves. The myelin sheaths are composed primarily of sphingolipids and phospholipids and do not contain high-density lipoproteins, elastin, glycogen, or a significant level of glycoprotein. A view of demyelination is shown below.



An overview of demyelination. **Panels A** and **B** depict normal conditions, whereas **panels C** and **D** show the slow disintegration of myelin, resulting in demyelination and a loss of axonal function.

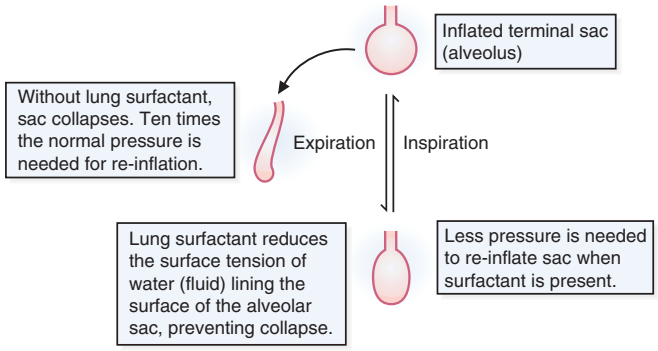
2 **The answer is A: Soybeans.** Foods considered the highest sources of sphingolipids include dairy and soy products. Foods highest in phospholipids include those high in lecithin, such as eggs, soy, and wheat. Sphingolipids and phospholipids are found mostly in neural tissue. Other organs and muscle do not contain as high a quantity of these lipids as do neural tissues.

3 **The answer is A: Dipalmitoyl phosphatidylcholine.** The patient was treated with an artificial preparation of lung surfactant, which reduces surface tension within the lung at the air–water interface. In premature newborns, the type II cells within the lung have not yet begun synthesizing surfactant, so the application of surfactant to the baby will allow this compound to be present until the type II cells begin their synthesis of this complex. The major phospholipid in surfactant is dipalmitoyl phosphatidylcholine (DPPC), and it is complexed with a number of small proteins (surfactant proteins A, B, and C). While small amounts of sphingomyelin may be present in surfactant, DPPC is the major component. The structure of DPPC is shown below.



Dipalmitoyl phosphatidylcholine, the major component of lung surfactant

4 **The answer is C: To reduce surface tension at the air–water interface.** The phospholipid–protein mixture of surfactant interacts at the surface of lung cells, allowing expansion and contraction due to reducing surface tension at the air–water interface (see the figure below). Surfactant does not affect oxygen exchange with the red blood cells, nor does it allow carbon dioxide removal from such cells. Surfactant does not stabilize lung cell structure (although it is essential for the function of the lung cell), nor does it facilitate blood flow through the lung.

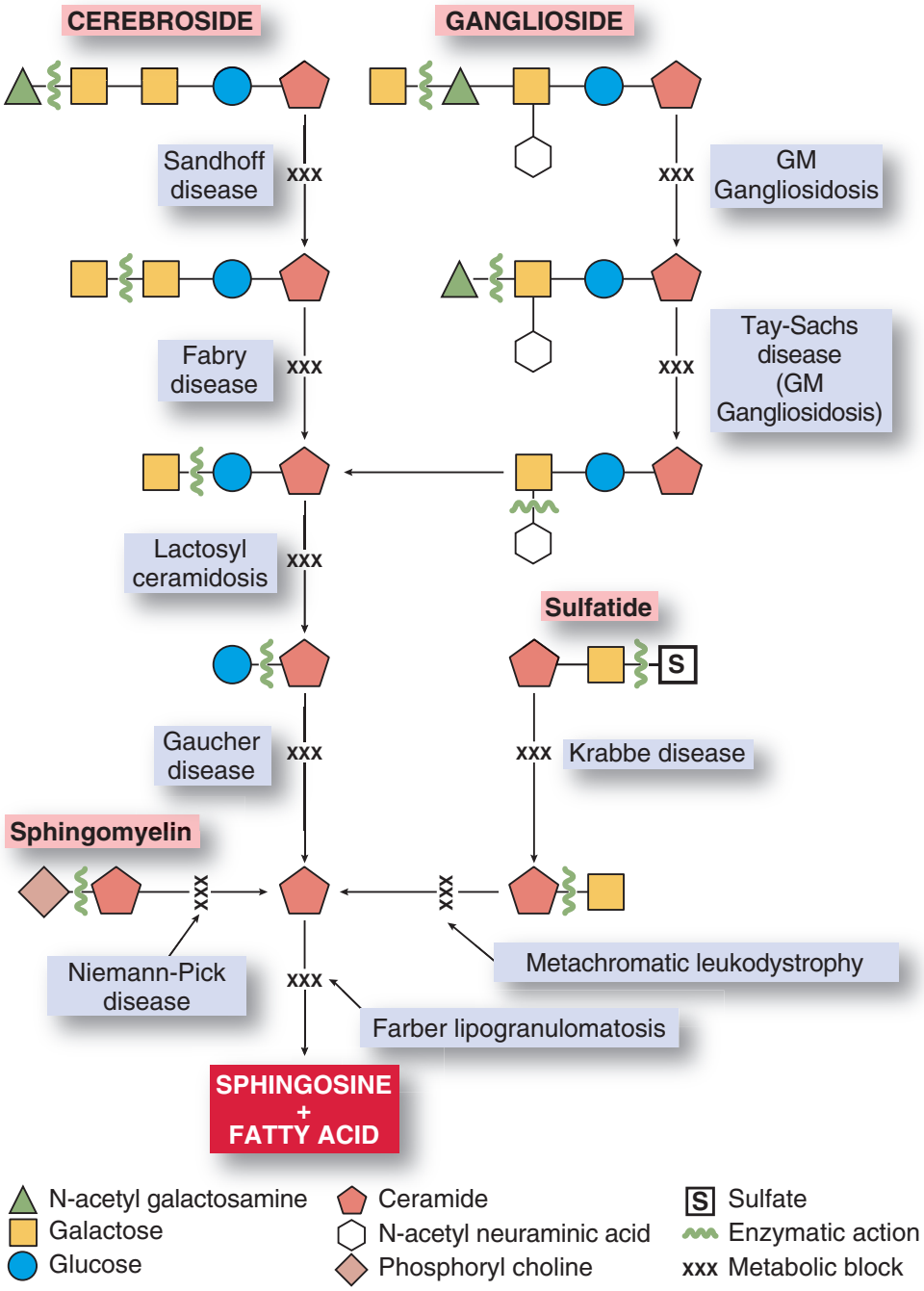


The effect of lung surfactant

5 **The answer is A: GM2 and globoside.** The cherry-red spot is indicative of either Tay–Sachs disease (an autosomal recessive disorder leading to a loss of hexosaminidase A [hex A] activity) or Sandhoff disease (an autosomal recessive disorder leading to a loss of both hexosaminidase A and B [hex B] activity). With just a

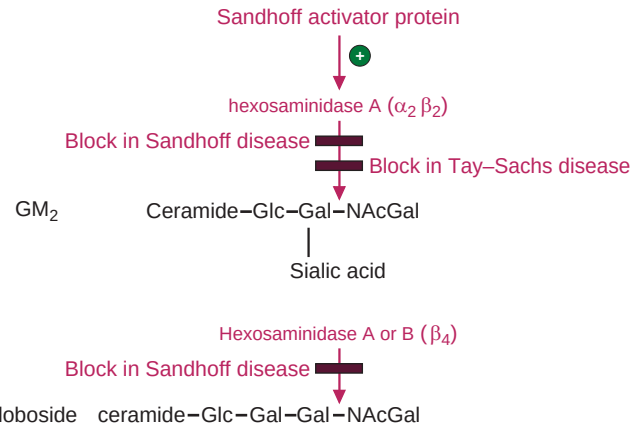
loss of hex A activity, GM2 would accumulate. With a loss of hex B activity, globoside and GM2 would accumulate. Thus, by measuring the levels of GM2 and globoside, one can distinguish between Tay–Sachs and Sandhoff disease. A loss of either hex A or hex B would not affect GM1 or GM3 degradation.

6 **The answer is C: Hexosaminidase A and Hexosaminidase B.** In Sandhoff disease, both hex A and hex B activities are lost. The mutation in Sandhoff disease does not affect sphingomyelinase activity, and there is no hexosaminidase C activity. Sandhoff disease is one of many which affect sphingolipid metabolism. An overview of the sphingolipidoses is shown in the figure below.



Answer 6: A summary of the sphingolipidoses in diagrammatic form.

7 **The answer is D: A common mutated subunit is present in the multiple activities.** The hexosaminidase A gene encodes the hex A protein, and the hexosaminidase B gene encodes the hex B protein. Hexosaminidase A activity requires a complex of hex A and hex B proteins; hexosaminidase B activity only requires a complex of hex B proteins. Tay–Sachs disease is a defect in the hex A protein, affecting only hex A activity. Sandhoff disease is a defect in the hex B protein, which affects both hex A and hex B activity, due to the sharing of a common subunit between the two proteins. hex A and hex B are not in an operon (which is only operative in bacteria); in fact, the genes are on different chromosomes. There is an activating protein for hex A activity, but not hex B activity (a loss of the activating protein is known as Sandhoff activator disease, with symptoms very similar to Tay–Sachs disease). There are no mutations in transcriptional control proteins (either an activator or inhibitor) in Tay–Sachs or Sandhoff disease. The interactions of the hex A and hex B proteins are shown in the figure below.



Substrate specificities of hexosaminidase A and B, and the function of the activator protein. Defects in the β-subunit inactivate both hex A and hex B activities, leading to GM2 and globoside accumulation. A defect in Sandhoff activator protein also leads to GM2 accumulation, as hex A activity is reduced. Defects in the α-subunit only inactivate hex A activity, such that hex B activity toward globoside is unaffected. Glc, glucose; Gal, galactose; NAcGal, *N*-acetylgalactosamine.

8 **The answer is A: Galactosylceramide.** The child has Krabbe disease, a mutation in a galactosidase, which cannot remove galactose from galactose cerebroside (an inability to break the bond between galactose and ceramide). The buildup of galactose–ceramide leads to the neuronal and muscle damage seen in the child. An inability to degrade a sulfatide would lead to metachromatic leukodystropy, which has very different symptoms than Krabbe disease. An inability to degrade glucosylceramide leads to Gaucher disease, again, with a very different disease progression than that seen with Krabbe disease. A defect in the degradation of sphingomyelin leads to Niemann–Pick disease, with a different set of symptoms than that seen with Krabbe disease. A defect in degrading ceramide leads to Farber disease, a defect in ceramidase. Farber disease is similar to Krabbe disease, but often presents with hepatomegaly and splenomegaly. See Table 16.1 in the next answer for a summary of all the sphingolipidoses and the material that accumulates within the lysosomes. Additionally, the figure associated with the answer to question 6 of this chapter depicts the metabolic blocks of the sphingolipidoses.

9 **The answer is C: Glucosylceramide.** The child has a form of Gaucher disease, which is a defect in a glucosidase which removes glucose from glucosylceramide. The accumulation of glucosylcerebroside in the lysosomes leads to the observed symptoms. Defects in degrading galactosylceramide lead to Krabbe disease, which does not result in hepatomegaly and splenomegaly. A defect in degrading sulfatide leads to metachromatic leukodystrophy, which has different symptoms than what the child is experiencing. A defect in the degradation of sphingomyelin leads to Niemann–Pick disease, with a different set of symptoms than that seen with Gaucher disease. A defect in degrading ceramide leads to Farber disease, a defect in ceramidase, with more severe symptoms than those observed in Gaucher disease. Table 16-1 summarizes the sphingolipidoses, the enzyme defect, and the material that accumulates. Utilize this table with the figure associated with the answer to question 6 of this chapter for a thorough understanding of the consequences of the sphingolipidoses.

10 **The answer is E: I-cell disease.** The sphingolipidoses and I-cell disease are both lysosomal storage diseases, whereas the other disorders listed do not involve lysosomal dysfunction. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) is a mitochondrial disorder, and Zellweger's is a disorder of peroxisomal biogenesis. G6PDH (glucose-6-phosphate dehydrogenase) deficiency and von Gierke disease are single gene mutations which do not alter lysosomal function (although type II glycogen storage disease, Pompe disease, is a lysosomal storage disease).

11 **The answer is E: *N*-acetylgalactosamine.** Tay–Sachs is a defect in hexosaminidase A, which removes the terminal *N*-acetylgalactosamine residue from ganglioside GM2, producing the free sugar and GM3. Hexosaminidase A does not cleave glucose, ceramide, sphingosine, or the fatty acyl component of ceramide from GM2; it is specific for *N*-acetylgalactosamine.

12 **The answer is E: Inositol.** Lithium primarily inhibits the phosphatase which converts inositol phosphate to free inositol, thereby disrupting the phosphatidylinositol cycle, leading to increased levels of the intermediates of the cycle, which are often signaling molecules. Lithium does not affect the generation of diacylglycerol, inositol trisphosphate (IP_3), inositol bisphosphate (IP_2), or

Table 16-1. Defective enzymes in the gangliosidoses

Disease	Enzyme Deficiency	Accumulated Lipid
Fucosidosis	α-Fucosidase	Cer–Glc–Gal–GalNAc–Gal:Fuc H-isoantigen
Generalized gangliosidosis	G_{M1}-β-galactosidase	Cer–Glc–Gal(NeuAc)–GalNAc:Gal GM1 ganglioside
Tay–Sachs disease	Hexosaminidase A	Cer–Glc–Gal(NeuAc):GalNAc GM2 ganglioside
Tay–Sachs variant or Sandhoff disease	Hexosaminidase A and B	Cer–Glc–Gal–Gal:GalNAc Globoside plus GM2 ganglioside
Fabry disease	α-Galactosidase	Cer–Glc–Gal:Gal Globotriaosylceramide
Ceramide lactoside lipidosis	Ceramide lactosidase (β-galactosidase)	Cer–Glc:Gal Ceramide lactoside
Metachromatic leukodystrophy	Arylsulfatase A	Cer–Gal:OSO_3 3-Sulfogalactosylceramide
Krabbe disease	β-Galactosidase	Cer:Gal Galactosylceramide
Gaucher disease	β-Glucosidase	Cer:Glc Glucosylceramide
Niemann–Pick disease	Sphingomyelinase	Cer:P–choline Sphingomyelin
Farber disease	Ceramidase	Acyl: sphingosine Ceramide

NeuAc, *N*-acetylneuraminic acid; *Cer*, ceramide; *Glc*, glucose; *Gal*, galactose; *Fuc*, fucose: site of deficient enzyme reaction.

inositol phosphate (IP); it affects just the conversion of IP to free inositol and a phosphate.

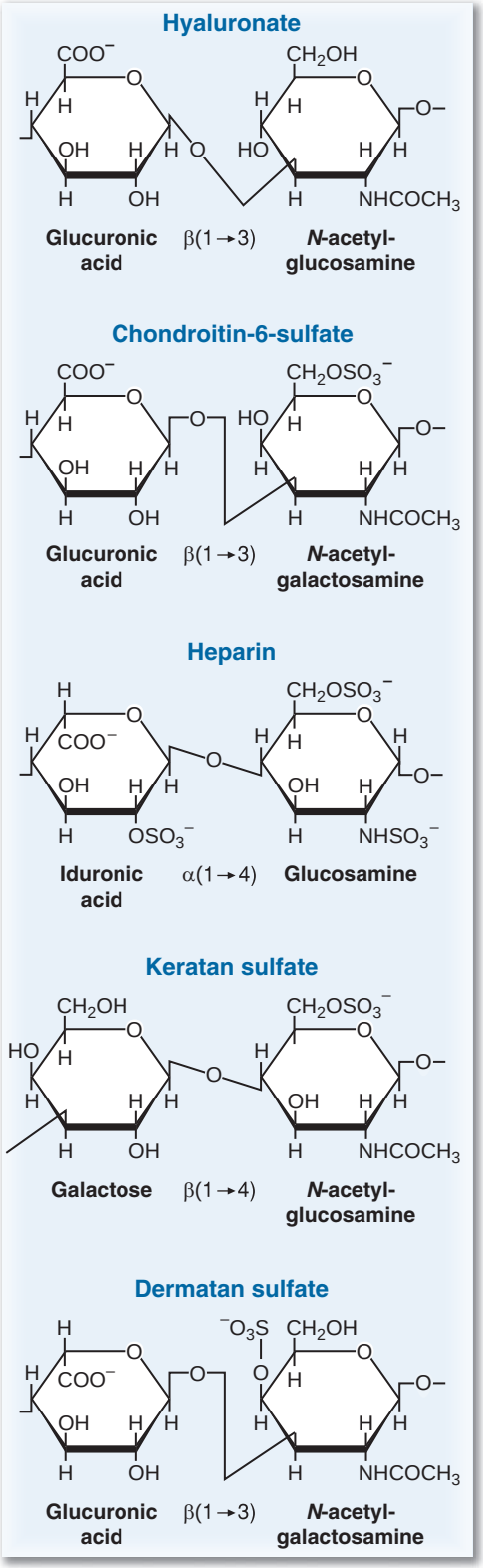
13 **The answer is C: To mark cells for recognition by outside systems.** By having different phospholipid compositions of the inner and outer leaflets of membranes, one can utilize phospholipid head groups (which face the aqueous phase of their leaflet) as markers for "inside" and "outside" the membrane structure. For example, the exposure of phosphatidyl serine on the "outside" of red blood cells as is seen in spur cell anemia is a signal for the removal of the cells from circulation by the spleen, as the serine residue should be facing the "inside" of the red blood cell. Spur cells are large red blood cells covered with spikelike projections from preferential overexpansion of outer membrane components, leading to a spurlike shape. Movement of the phospholipid is a signal of cell aging. The melting temperature of the membrane is better determined by the fatty acid composition of the phospholipids, not the head group composition. Not all phospholipids are represented in all membranes (for example, cardiolipin is found almost exclusively in the mitochondria). Assymetric phospholipid compositions do not distinguish one organelle from another (that is primarily due to protein content), and assymetry in phospholipid composition may promote fusion (vesicles need to bud from and fuse with other membranes, particularly in the Golgi apparatus).

14 **The answer is C: Phosphatidylinositol acts as a substrate for intracellular processes.** Phosphatidylinositol is used as the substrate to provide signaling molecules in response to the appropriate stimuli (the phosphatidylinositol cycle). As such, it must face the cytoplasm of the cell such that when the inositol phosphate derivatives are produced, such as IP_3, they can move to their target receptors to elicit a cellular response. Inositol contains six hydroxyl groups and is a very hydrophilic molecule. Inositol's structure is quite different from glucose (there is no carbonyl group in inositol), so it is unlikely that glucose and inositol would compete for binding to the same receptors. Phosphatidylinositol does not bind to phosphatidylserine in the inner leaflet of membranes. Inositol also does not interact with the actin cytoskeleton.

15 **The answer is B: Hydrogen and ionic bonds.** The high concentration of negative charges provided by the proteoglycans attracts cations that create a high osmotic pressure within cartilage, drawing water into this specialized connective tissue and placing the collagen network under tension. The water remains due to hydrogen bond formation with the proteoglycans. At equilibrium, the resulting tension balances the swelling pressure caused by the proteoglycans. Cartilage can thus withstand the compressive load of weight bearing and then re-expand to it previous dimensions when that load is relieved. Disulfide bonds and covalent bonds do not play a role in proteoglycan stabilization of joints.

16 **The answer is D: Glucosamine.** While aspirin and acetaminophen may provide short-term relief, the use of glucosamine may help to rebuild the proteoglycan layer in the knees, reducing the osteoarthritis (although medical studies are controversial concerning the use of glucosamine and glucosamine

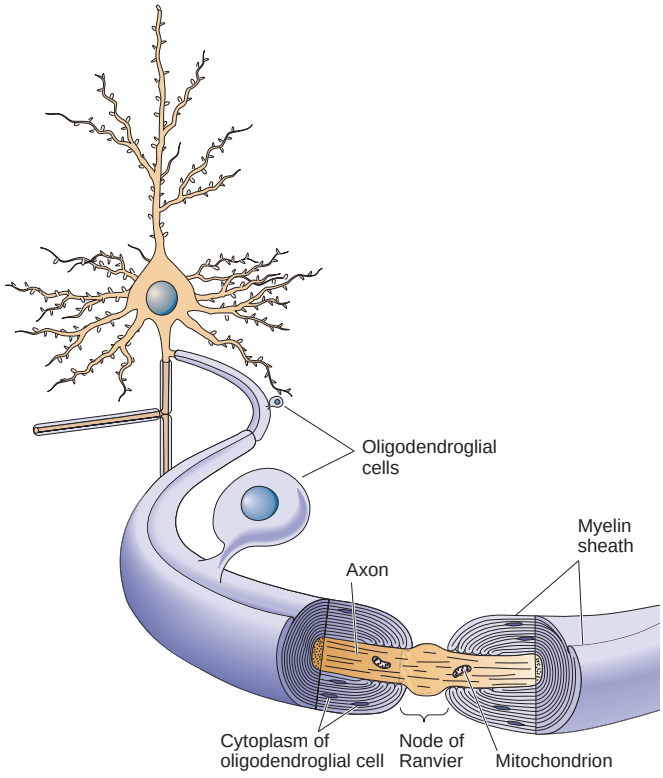
sulfate, in terms of providing relief from joint pain). Sphingomyelin and inositol are not important components of the cartilage in joints. Proteoglycans contain long carbohydrate chains, which consist of repeating disaccharide units (see the figure below). Note the inclusion of glucosamine derivatives in three of the five repeating disaccharide units.



Repeating disaccharide units found in glycosaminoglycans.

17 **The answer is C: Lysosomal hydrolases.** In I-cell disease, the lysosomal hydrolases are mistargeted and are excreted from cells into the circulation. As the pH of the blood is above 7 and the pH optimum of these enzymes is around 5, there is no activity of the hydrolases in blood. In Hurler syndrome, a defect in the degradation of mucopolysaccharides, there is an accumulation of dermatan and heparan sulfate in the urine, but not in the blood. Short-chain dicarboxylic acids are produced with a defect in medium chain acyl-CoA dehydrogenase, and cytochrome *c* release into the cytoplasm of cells from mitochondria is the signal to initiate apoptosis.

18 **The answer is A: Phospholipids and proteins.** The woman is experiencing the symptoms of multiple sclerosis, a demyelinating disease. In this disorder, the myelin sheath around nerves degenerates, eventually interfering with nerve conduction due to a lack of insulation (see the figure below for a schematic representation of the myelin sheath in the central nervous system). The myelin sheath is composed primarily of phospholipids and proteins. Triacylglycerol and gangliosides are not found in the sheath.



The oligodendroglial cells synthesize the myelin sheath found surrounding the neurons in the central nervous system.

19 **The answer is B: Phospholipids.** The woman has primary antiphospholipid syndrome (Hughes syndrome), in which the body produces antibodies against its own phospholipids and protein/phospholipid complexes (the major one being an anticardiolipin antibody). These antibodies will bind to proteins involved in coagulation and increase the risk of blood clots. Antibodies directed against cytochrome *c*, DNA, RNA splicing proteins (which occurs in SLE), or ribosomes are not observed in this disorder.

20 **The answer is B: Glycosaminoglycans.** Fluoroquinolones have been associated with spontaneous tendon rupture yielding the classic histopathologic findings as described in the case. Other risk factors for Achilles tendon rupture include steroid injections into the tendon, gout, rheumatoid arthritis, and renal transplantation. During tendon degeneration, glycosaminoglycan synthesis is increased in the extracellular matrix material of the tendon. Cholesterol, HDL, and triglyceride have no function in the tendon rupture. In addition, sphingosine is also not found in the extracellular matrix of the tendon.