Question 1: What are brain ventricles, and what functions have been ascribed to them over the ages?

Answer: Brain ventricles are hollow, fluid filled spaces within the brain. The Greek physician and writer Galen (A.D. 130–200) suggested that the body functioned according to a balance of four vital fluids or humors. Sensations were registered and movements were initiated by the movement of humors to or from the brain ventricles via the nerves. He thought that the brain ventricles helped the brain register sensations and control the limb movements. In the early seventeenth century, French inventors supported the fluid-mechanical theory of brain function. This theory stated that the fluid forced out of the ventricles through the nerves cause the movement of the limbs by inflating the muscles. The chief advocate of this theory was the French mathematician and philosopher Rene Descartes.

Question 2: What experiment did Bell perform to show that the nerves of the body contain a mixture of sensory and motor fibers?

Answer: Bell tested the possibility that the two spinal roots, which are formed by the division of spinal nerves just before they join the spinal cord, carry information in opposite directions. The dorsal root enters toward the back of the spinal cord while the ventral root enters toward the front. He cut each root separately and observed the consequences in experimental animals. He found that cutting only the ventral roots caused muscular paralysis. Later, Magendie was able to show that the dorsal roots carry sensory information into the spinal cord. Bell and Magendie concluded that each spinal nerve contains a mixture of many wires, some of which bring information into the spinal cord and others that send information out to the muscles.

Question 3: What did Flourens' experiments suggest about the functions of the cerebrum and the cerebellum?

Answer: Flourens used the *experimental ablation method* in a variety of animals and birds to test the functions of the cerebrum and cerebellum. In this approach, parts of the brain are systematically destroyed to determine their function. He showed that the function of the cerebellum is coordination of movements and the function of the cerebrum is sensation.

Question 4: What is the meaning of the term animal model?

Answer: Many neuroscientists use *animal models* to examine the process that they wish to study in humans. Animal models can be experimented upon for the purpose of relating experimental results to humans. The theory that the nervous systems of different species evolved from common ancestors and utilize many common mechanisms is the rationale for relating the results of animal experiments to humans. For example, rats show clear signs of addiction if they are given the chance to self-administer cocaine repeatedly. Consequently, rats are a valuable animal model for research focused on understanding how psychoactive drugs exert their effects on the nervous system.

Question 5: A region of the cerebrum is now called Broca's area. What function do you think this region performs and why?

Answer: Broca's area is a portion of the left frontal lobe of the human cerebrum. Paul Broca is the person credited with tilting the scales of scientific opinion firmly toward localization of function in the cerebrum, specifically, language. Broca was presented with a patient who could understand language but could not speak. Following the man's death in 1861, Broca examined the brain and found a circumscribed lesion in the left frontal lobe. Based on this

case and several others like it, Broca concluded that this region of the human cerebrum was specifically responsible for the production of speech.

Question 6: What are the different levels of analysis in neuroscience research? What types of questions do researchers ask at each level?

Answer: In ascending order of complexity, the levels of analysis in neuroscience research are molecular, cellular, systems, behavioral, and cognitive. The questions asked at each level are:

i) Molecular science level

(1) Identify the molecules that are crucial for brain function and act as:

(a) Messengers that allow neurons to communicate with one another

(b) Sentries that control what materials can enter or leave neurons

(c) Conductors that orchestrate growth

(d) Archivists of past experiences

ii) Cellular neuroscience level

(1) How many different types of neurons are there?

(2) How do the different types of neuron differ in their functions?

(3) How do neurons influence other neurons?

(4) How do neurons become “wired together” during fetal development?

(5) How do neurons perform computations?

iii) Systems neuroscience level

(1) How do different neural circuits analyze sensory information?

(2) How do they form perceptions of the external world, make decisions, and execute movements?

iv) Behavioral neuroscience level

(1) How do neural systems work together to produce integrated behaviors?

(2) How are different forms of memory accounted for by different systems?

(3) Where in the brain do "mind-altering" drugs act?

(4) What is the normal contribution of these systems to the regulation of mood and behavior?

(5) What neural systems account for gender-specific behaviors?

(6) Where in the brain do dreams come from?

v) Cognitive neuroscience level

(1) Identify the neural mechanisms that are responsible for the higher levels of human mental activity such as:

(a) Self-awareness

(b) Mental imagery

(c) Language

Question 7: What are the steps in the scientific process? Describe each one of them.

Answer: The steps in the scientific process are observation, replication, interpretation, and definition.

i) **Observation –** The first step in the scientific process is observation. Observations are typically made during experiments designed to test a particular hypothesis. Observations can also be made by carefully watching the world around us, from introspection, or from human clinical cases.

ii) **Replication –** The second step is replication. Experimental or clinical observation needs to be replicated before it can be accepted by scientists as fact. Replication simply means repeating the experiment on different subjects or making similar observations in different subjects, as many times as necessary to rule out the possibility that the observation occurred by chance.

iii) **Interpretation –** The third step is interpretation. After the scientist believes the observation is correct, he or she makes an interpretation. Interpretations depend on the state of knowledge (or ignorance) at the time the observation was made and on the preconceived notions (the "mind set") of the scientist who made it and do not always withstand the test of time.

iv) **Verification -** The final step in the scientific process is verification. Verification means that the observation is sufficiently robust and can be reproduced by any competent scientist who precisely follows the protocols of the original observer. Therefore, the process of verification, if affirmative, establishes new scientific facts.

Question 1: State the neuron doctrine in a single sentence. To whom is this insight credited?

Answer: The neuron doctrine is the idea that the neurons are not continuous with one another but are discrete cells that communicate by contact and not by continuity. This insight is credited to Santiago Ramón y Cajal.

Question 2: Which parts of a neuron are shown by a Golgi stain and are not shown by a Nissl stain?

Answer: The Golgi stain shows the neuronal cell body with the dendrites and the axon. The Nissl stain shows only the cell body.

Question 3: What are the three physical characteristics that distinguish axons from dendrites?

Answer: The three physical characteristics that distinguish axons from dendrites are:

i) The cell body usually gives rise to a single axon while many dendrites extend from the cell body.

ii) The axon is of uniform diameter throughout its length while dendrites rarely extend more than 2 mm in length.

iii) The branches of an axon generally extend at right angles while dendrites generally taper to a fine point.

Question 4: Among the following structures, state those which are unique to neurons and the ones that are not: nucleus, mitochondria, rough ER, synaptic vesicle, and Golgi apparatus.

Answer: The synaptic vesicle is unique to neurons whereas the nucleus, the mitochondria, the rough ER, and Golgi apparatus are not unique to neurons.

Question 5: What are the steps by which the information in the DNA of the nucleus directs the synthesis of a membrane-associated protein molecule?

Answer: Protein synthesis, the assembly of protein molecules, occurs in the cytoplasm. The DNA never leaves the nucleus. The intermediary that carries the genetic message to the sites of protein synthesis in the cytoplasm is a long molecule called messenger ribonucleic acid, mRNA. The process of assembling a piece of mRNA that contains the information of a gene is called transcription and the resulting mRNA is called the transcript. Messenger RNA transcripts emerge from the nucleus through pores in the nuclear envelope and travel to ribosomes, the sites of protein synthesis in the cytoplasm. At these sites, protein molecules are assembled by linking individual amino acids into a chain. Amino acids of 20 different kinds are the building blocks for protein. Amino acids are brought to the ribosome by transfer RNA (tRNA). The assembling of proteins from amino acids under the direction of the mRNA is called translation.

Question 6: Colchicine is a drug that causes microtubules to break apart or depolymerize. What effect would this drug have on anterograde transport? What would happen in the axon terminal?

Answer: Vesicles containing molecules needed at the axon terminal "walk down" the microtubules within the axon on "legs" provided by a protein called kinesin. The process is fueled by ATP. Kinesin moves material only from the soma to the terminal. Movement in this direction is called anterograde transport. The application of colchicines causes microtubules to disintegrate and when applied to the axon disrupts the path for anterograde transport. As a result, all movement of material from the soma to the terminal (anterograde transport) ceases. If the colchicines application does not

kill the whole cell, then the material to be transported will accumulate on the side of the axon closest to the soma.

Question 7: Classify the cortical pyramidal cell based on (a) the number of neurites, (b) the presence or absence of dendritic spines, (c) connections, and (d) axon length.

Answer: Classification of the cortical pyramidal cell is as follows:

(a) Cortical pyramidal cells have three or more neurites and are multipolar.

(b) Cortical pyramidal cells have dendritic spines.

(c) Axons of cortical pyramidal cells project to other cortical areas and also to several subcortical areas as well.

(d) In the cerebral cortex, pyramidal cells usually have long axons that extend to other parts of the brain and are therefore Golgi type I neurons.

Question 8: What is myelin and what does it do? Which cells provide myelin to the central nervous system?

Answer: Myelin refers to layers of glial membrane that insulate axons. Myelin speeds the propagation of nerve impulses down the axon. The oligodendroglial cells provide myelin in the central nervous system.

Question 1: What are the two functions that the proteins perform in the neuronal membrane to establish and maintain the resting membrane potential?

Answer: Proteins in the neuronal membrane:

1) Provide channels that control the movement of specific ions across the neuronal membrane and

2) Pump sodium and potassium ions across the membrane against their concentration gradient to maintain the resting membrane potential.

Question 2: On which side of the neuronal membrane are Na^+ ions more abundant?

Answer: The neuronal membrane potential depends on the ionic concentrations on either side of the membrane. K^+ is more concentrated on the inside of the neuronal membrane, whereas Na+ and Ca2+ are more concentrated on the outside.

Question 3: When the membrane is at the potassium equilibrium potential, in which direction (in or out) is there a net movement of potassium ions?

Answer: The potassium equilibrium potential represents a balance between the chemical and electrical forces driving potassium across the membrane through potassium channels. There is no net movement of potassium ions at potassium's equilibrium potential, which is –80mV.

Question 4: There is a much greater potassium K^+ concentration inside the cell than outside. Why, then, is the resting membrane potential negative?

Answer: The resting membrane potential is negative because the neuron is filled with negatively charged molecules, such as proteins, that do not traverse the cell membrane through channels the way ions do.

Question 5: When the brain is deprived of oxygen, the mitochondria within the neurons cease to produce ATP. What effect would this have on the membrane potential and why?

Answer: The neuronal membrane potential depends on different concentrations of sodium and potassium on either side of the membrane. Ionic concentration gradients are established by the action of the sodium-potassium ion pump, an enzyme that requires ATP. Without ATP, the pump will not function. As a result, the resting membrane potential will not exist and the brain will not function.

Question 1: Define membrane potential (V_m) and sodium equilibrium potential (E_{Na}). Which of these, if any, changes during the course of action potential?

Answer: The membrane potential (V_m) is the voltage across the neuronal membrane at any moment in time. The potential of the resting membrane is –75 mV. The sodium equilibrium potential (E_{Na}) is the steady equilibrium potential achieved when the membrane is permeable only to sodium ions. The value of E_{Na} is 62 mV. However, in its resting state, the membrane is not permeable to sodium. During the application of action potential, sodium channels open and sodium rushes into the cell. The large sodium current takes the membrane potential from its negative resting state toward E_{Na}. Sodium channels are deactivated after 1 msec, and the membrane repolarizes due to potassium efflux, which takes the membrane potential back toward the equilibrium potential of potassium.

Question 2: Which ions carry the early inward and late outward currents during the action potential?

Answer: During the early part of the action potential, the influx of sodium ions across the membrane briefly depolarizes the membrane. The brief inward sodium current is a consequence of opening the voltage-gated sodium channels for only 1 msec. Membrane repolarization is the result of potassium efflux, which is the outward potassium current because of opening voltage-gated potassium channels after a delay of 1 msec.

Question 3: Why is the action potential referred to as “all-or-none”?

Answer: Action potential is termed “all-or-none” because no partial action potentials exist. A physical or electrical event opens sodium permeable channels, but the resulting influx of sodium ions and the resulting depolarization – called a generator potential — must reach a

critical level before the axon generates an action potential. The critical level is called a threshold. After achieving threshold depolarization, the cell fires an action potential.

Question 4: Some voltage-gated K^+ channels are known as delayed rectifiers because of the timing of their opening during an action potential. What would happen if these channels took much longer than normal to open?

Answer: Voltage-gated potassium channels open 1 msec after membrane depolarization. The resulting potassium conductance rectifies, or resets, the membrane potential. This conductance is called the delayed rectifier because of the 1 msec delay in rectifying the membrane potential. If these channels took longer than normal to open, the action potential would be wider, which means that it would take longer to restore the resting membrane potential.

Question 5: Imagine you have labeled tetrodotoxin (TTX) to be able to see it with a microscope. If we wash the TTX on to a neuron, what parts of the cell would you expect labeled? What would be the consequence of applying TTX to the neuron?

Answer: TTX is a natural toxin that interferes with the function of voltage-gated sodium channels. TTX blocks the sodium permeable pore by binding tightly to a specific part outside the channel and blocking all the sodium-dependent action potentials. Applying TTX to a neuron would block all impulses in that nerve, preventing it from firing any action potential, regardless of input. Labeled TXX could be visualized on the cell's axon, where voltage-gated sodium channels are concentrated.

Question 6: How does the conduction velocity of action potential vary with axonal diameter? Why?

Answer: The speed of action potential depends on how far depolarization spreads ahead of action potential. This, in turn, depends on the physical characteristics of axons. The two paths that a positive charge can take are inside an axon and across the axonal membrane. When the axon is narrow with many open pores, more of the current flows across the axonal membrane and is lost. When the axon is wide with a few open pores, the current flows inside the axon. The farther down the axon the current flows, the farther ahead of the action potential the membrane will be depolarized and the faster the action potential will propagate. As a result, the conduction velocity of axons increases with the diameter of axons.

Question 1: What is meant by quantal release of neurotransmitter?

Answer: The elementary unit of a neurotransmitter release is the content of one synaptic vesicle. Each vesicle contains several thousand transmitter molecules. The total amount of transmitter released at a synapse is a multiple of this number, depending on how many vesicles release their contents into the synaptic cleft. The amplitude of postsynaptic EPSP is a multiple of the response to the contents of one vesicle. It reflects the number of transmitter molecules in one synaptic vesicle and the number of postsynaptic receptors available at the synapse.

Question 2: You apply ACh and activate nicotinic receptors on a muscle cell. Which way will current flow through the receptor channels when V_m = –60 mV? When V_m = 0 mV? When V_m = 60 mV? Why?

Answer: Nicotonic ACh receptors are permeable to both sodium and potassium. When V_m = –60 mV, net current flow through ACh-gated ion channels is inward, toward the equilibrium potential of sodium, causing depolarization. At V_m = 60 mV, the direction of net current flow through the ACh-gated ion channels is outward, toward the equilibrium potential of potassium, causing the membrane potential to become less positive. The critical value of membrane potential at which the direction of current flow reverses is called the reversal potential. In this case, the reversal potential is 0 mV because this is the value between the equilibrium potentials of sodium and potassium. At 0 mV, no current flows.

Question 3: In this chapter, we discussed a GABA-gated ion channel that is permeable to Cl^-. GABA also activates a G-protein-coupled receptor called the $GABA_B$ receptor, which causes potassium-selective channels to open. What effect would $GABA_B$ receptor activation have on the membrane potential?

Answer: Activated GABA-gated Cl^- ion channels bring the membrane toward the equilibrium potential for Cl^-, which is –65 mV. If the membrane potential was less negative than –65 mV when the transmitter was released, activation would cause hyperpolarization. The activation of $GABA_B$ receptors causes potassium-selective channels to open. As a result, $GABA_B$ activation brings membrane potential toward the equilibrium potential of potassium, which is –80 mV. If the membrane potential was less negative than –80 mV when the transmitter was released, activation would also cause hyperpolarization. This channel might also impact the neuron by shunting inhibition, allowing a depolarizing current from an excitatory synapse to leak out. This, in turn, decreases the likelihood of action potential. The action of a G-protein-coupled receptor is, however, slower than that of the GABA-gated Cl^- ion channel or a typical excitatory synapse. Therefore, its effects would be slower to occur and would last longer.

Question 4: You think you have discovered a new neurotransmitter, and you are studying its effect on a neuron. The reversal potential for the response caused by the new chemical is –60 mV. Is this substance excitatory or inhibitory? Why?

Answer: If the new chemical has a reversal potential of –60 mV, the substance is likely to be inhibitory. The reversal potential reflects the types of ions the membrane is permeable to after the application of the neurotransmitter. A reversal potential of –60 mV suggests that the neurotransmitter activates ion channels that make the membrane more negative. If a neurotransmitter causes the membrane to move toward a value that is more negative than the action potential threshold, the neuron becomes less likely to fire an action potential, which means it is inhibited.

Question 5: A drug called strychnine, isolated from the seeds of a tree native in India and commonly used as rat poison, blocks the effects of glycine. Is strychnine an agonist or an antagonist of the glycine receptor?

Answer: Strychnine is an antagonist of glycine at its receptor. Mild strychnine poisoning enhances the startle and other reflexes and resembles hyperekplexia. High doses can eliminate glycine-mediated inhibition in circuits of the spinal cord and the brain stem. This leads to uncontrollable seizures and unchecked muscular contractions, spasms, and paralysis of respiratory muscles. It might ultimately result in painful, agonizing death from asphyxiation.

Question 6: How does nerve gas cause respiratory paralysis?

Answer: Nerve gases interfere with synaptic transmission at the neuromuscular junction by inhibiting AChE. Uninterrupted exposure to high concentrations of ACh for several seconds leads to a process called *desensitization*. In this process, transmitter-gated channels close despite the continued presence of ACh. Normally, the rapid destruction of ACh by AChE prevents desensitization. However, if AChE is inhibited by nerve gas, ACh receptors will be desensitized and neuromuscular transmission will fail, causing respiratory paralysis.

Question 7: Why is an excitatory synapse on the soma more effective in evoking action potentials in the postsynaptic neuron than an excitatory synapse on the tip of a dendrite?

Answer: A current entering the sites of synaptic contact must spread to the spike-initiation zone and this zone must be depolarized beyond its threshold to generate an action potential. In addition, depolarization decreases as a function of distance along a dendrite. As a result, the effectiveness of an excitatory synapse for triggering an action potential depends on how far

the synapse is from the spike-initiation zone. Because the soma is closer to the spike-initiation zone, an excitatory synapse on the soma is more effective for evoking action potentials than an excitatory synapse on the tip of a dendrite.

Question 8: What are the steps that lead to increased excitability in a neuron when NE is released presynaptically?

Answer: The steps that increase the excitability of a neuron when NE is released presynaptically are:

1. The NE receptor bound to a β receptor activates G-protein in the membrane.

2. G-protein activates the adenylyl cyclase enzyme.

3. Adenylyl cyclase converts ATP into the second messenger cAMP.

4. cAMP activates a protein, kinase.

5. Kinase causes a potassium channel to close by attaching a phosphate group to it.

This produces little change in membrane potential but increases the membrane resistance and increases the length constant of dendrites. This enhances the response that a weak or a distant excitatory synapse produces. This effect can last longer than that of the presence of the transmitter.

Question 1: If you could place microelectrodes into both a presynaptic and a postsynaptic neuron, how would you determine whether the synapse between them was chemically or electrically mediated?

Answer: A microelectrode placed in the presynaptic and postsynaptic neuron would show different results for electrical and chemical transmission. For electrical transmission, the two electrodes would show identical or similar changes in electrical activity, *i.e.*, the action potential in the presynaptic membrane would produce an action potential in the postsynaptic membrane. Chemically mediated synapses operate differently. An action potential in the presynaptic membrane causes neurotransmitter release in the synaptic cleft, and the postsynaptic membrane might respond to the neurotransmitter with changes in conduction, but not an action potential. An action potential is generated in the postsynaptic neuron of a chemically mediated synapse only if the whole neuron is sufficiently depolarized. This action potential would not be evident in a postsynaptic dendrite or cell body (typical synaptic sites); you would have to record for the axon of the postsynaptic neuron.

Question 2: List the criteria that are used to determine whether a chemical serves as a neurotransmitter. What are the various experimental strategies you could use to show that ACh fulfills the criteria of a neurotransmitter at the neuromuscular junction?

Answer: Three certain criteria must be met for a molecule to be considered a neurotransmitter.

1) The molecule must be synthesized and stored in the presynaptic neuron.

2) The molecule must be released by the presynaptic axon terminal upon stimulation.

3) The molecule, when experimentally applied, must produce a response in the postsynaptic cell that mimics the response produced by the release of the neurotransmitter from the presynaptic

neuron. Immunohistochemistry shows where specific molecules are localized, and *in situ* hybridization shows where specific mRNA transcripts for specific proteins are located. These methods could be used to demonstrate the presence of ACh in the presynaptic terminal at the neuromuscular junction. It would be useful to show that the synthesizing enzyme is present as well.

Question 3: What are three methods that could be used to show that a neurotransmitter receptor is synthesized or localized in a particular neuron?

Answer: Three methods are used to study the receptors of various neurotransmitters: neuropharmacological analysis of synaptic transmission, ligand-binding methods, and molecular analysis of receptor proteins. Neuropharmacological analysis studies the actions of different drugs. Ligand-binding methods can be used to identify the location of receptors by labeling ligands that bind to them, such as specific agonists, antagonists, or chemical neurotransmitters. Molecular analysis studies the protein molecules and the subunits that form the neurotransmitter receptors, such as transmitter-gated ion channels and G-protein-coupled receptors. This method may also be used to examine the genes that encode these proteins and the consequences of altering the genes or the gene products.

Question 4: Compare and contrast the properties of (a) AMPA and NMDA receptors, and (b) $GABA_A$ and $GABA_B$ receptors.

Answer: (a) AMPA and NMDA are glutamate receptor subtypes; both are activated by glutamate, but the drug AMPA acts only on the AMPA receptor and the drug NMDA acts only on the NMDA receptor. AMPA and NMDA are chemical agonists used to differentiate the glutamate receptor subtypes. Their antagonists can also distinguish receptor subtypes, for

example, the antagonist for AMPA is CNQX and the antagonist for NMDA is AP5. The differences in the receptors are related to slight differences in the protein. An important property of the NMDA receptor is that it is only active in the presence of glutamate *and* sufficient depolarization in the postsynaptic neuron.

(b) $GABA_A$ and $GABA_B$ are GABA receptor subtypes; both respond to GABA but muscimol is the agonist for the $GABA_A$ receptor, and the agonist for $GABA_B$ is baclofen. The antagonist for $GABA_A$ is bicuculline whereas the antagonist for $GABA_B$ is phaclofen.

Question 5: Synaptic inhibition is an important feature of the circuitry in the cerebral cortex. How would you determine whether GABA or Gly, or both, or neither, is the inhibitory neurotransmitter of the cortex?

Answer: Synaptic inhibition is represented by inhibitory postsynaptic potentials in the postsynaptic neuron of an inhibitory synapse. To determine whether GABA or Gly or both are inhibitory neurotransmitters, you could record IPSPs in response to GABA or Gly application in an *in vitro* preparation. You might also examine the nature of the postsynaptic receptors. Both GABA and Gly receptors gate a chloride channel, which when opened, would help hyperpolarize the postsynaptic cell and make that neuron less likely to fire an action potential.

Question 6: Glutamate activates a number of different metabotropic receptors. The consequence of activating one subtype is the *inhibition* of cAMP formation. A consequence of activating a second subtype is *activation* of protein kinase C. Propose mechanisms for these different effects.

Answer: The subtype of glutamate metabotropic receptor that inhibits cAMP formation may activate G_i. This is the mechanism used by the NE receptor subtype called α_2, which inhibits adenylyl cyclase and, consequently, inhibits cAMP formation. The other subtype of glutamate metabotropic receptor might activate a G-protein that stimulates the enzyme phospholipase C (PLC). PLC splits the membrane phospholipids PIP_2 into two parts: DAG and IP_3. DAG stays in the plane of the membrane and activates the downstream enzyme protein kinase C (PKC). (IP_3, on the other hand, diffuses away and causes organelles to discharge their calcium stores.)

Question 7: Do convergence and divergence of neurotransmitter effects occur in single neurons?

Answer: Diverging neurotransmitter effects are represented by the multitude of consequences a single neurotransmitter may have because it affects many different receptor subtypes in postsynaptic neurons. This effect may occur in a single neuron that possesses G-protein-coupled receptors with two or more intracellular functions or, potentially, single neurons that elaborate different types of receptors in different parts of the neuron. Convergence occurs when several transmitters affect a single effector system. This can occur in a single cell at the level of the G-protein, the second messenger cascade, or the type of ion channel. Neurons integrate divergent and convergent signaling systems, resulting in a complex map of chemical effects.

Question 8: Ca^{2+} ions are considered to be second messengers. Why?

Answer: Ca^{2+} ions are considered to be second messengers because elevations of Ca^{2+} ions in the cytosol can have widespread and long-lasting effects on the neuron. An example of this is

Ca^{2+} activation of the enzyme calcium-calmodulin-dependent protein kinase (CaMK), which is important in molecular mechanisms of memory.

Question 1: Are the dorsal root ganglia in the central or peripheral nervous system?

Answer: The somatic sensory neurons collect information from the skin, muscles, and joints, and enter the spinal cord through the dorsal roots to synapse on dorsal root and ventral root neurons. The cell bodies of these neurons lie outside the spinal cord in clusters called dorsal root ganglia. The dorsal root ganglia are in the peripheral nervous system because they are situated outside the spinal cord. Furthermore, they are derived from the neural crest cells during embryologic development, as are all parts of the peripheral nervous system. Neurons of the central nervous system are derived from the neural tube.

Question 2: Is the myelin sheath of optic nerve axons provided by Schwann cells or oligodendroglia? Why?

Answer: The retina and optic nerve are part of the central nervous system, as they are derived from the neural tube. We know that oligodendroglia provide myelin for the central nervous system and Schwann cells provide myelin for the peripheral nervous system. Therefore, oliogodendroglial cells must provide the myelin for the optic nerve.

Question 3: Imagine that you are a neurosurgeon, about to remove a tumor lodged deep inside the brain. The top of the skull has been removed. What now lies between you and the brain? Which layer(s) must be cut before you reach the CSF?

Answer: Three layers lie between the surgeon and the brain: first the tough, white, avascular dura, then the spider-like arachnoid, and finally the pial membrane. The dura mater forms a tough, inelastic bag that surrounds the brain and the spinal cord and must be retracted to get a good view of the brain. The arachnoid membrane lies just under the dura, separated from the pia mater by a space filled with salty clear liquid called cerebrospinal fluid (CSF).

Question 4: What is the fate of tissue derived from the embryonic neural tube? Neural crest?

Answer: The entire central nervous system (CNS) develops from the walls of the neural tube, which is initially only a thin sheet of ectoderm that deepens to form a neural groove with folds that fuse to form the neural tube. On either side of the neural tube are pockets of neuronal precursors called neural crest cells. The entire PNS develops from these neural crest cells.

Question 5: Name the three main parts of the hindbrain. Which of these is also part of the brain stem?

Answer: The three main parts of the hindbrain are the cerebellum, the pons, and the medulla oblongata. The cerebellum and pons develop from the rostral half of the hindbrain and the medulla develops from the caudal half.

Question 6: Where is CSF produced? What path does it take before it is absorbed into the bloodstream? Name the parts of the CNS it will pass through in its voyage from brain to blood.

Answer: The choroid plexus in the lateral ventricles of the cerebral hemispheres produces CSF. CSF flows from the paired lateral ventricles through a series of unpaired ventricles in the thalamus, midbrain, and brain stem as well as the spinal canal. CSF also surrounds the outside of the brain. CSF exits the ventricular system via the subarachnoid space through small apertures near the base of the cerebellum. In the subarachnoid space, CSF is absorbed into the blood by the blood vessels called arachnoid villi.

Question 7: What are three features that characterize the structure of cerebral cortex?

Answer: Cerebral cortex in the brain of all vertebrate animals has three features. First, the cell bodies of cortical neurons are always arranged in layers or sheets that lie parallel to the surface of the brain. Second, the layer of neurons closest to the surface or the most superficial cell layer is separated from the pia mater by a zone that lacks neurons. This zone is called the molecular layer or *layer I*. Third, at least one cell layer contains pyramidal cells that emit large dendrites called *apical dendrites* extending up toward layer I where they form multiple branches. This characteristic cytoarchitecture distinguishes cerebral cortex from the nuclei of the basal telencephalon and the thalamus.

Question 1: Most tastes are some combination of the five basic tastes. What other sensory factors can help define the specific perceptions associated with a particular food?

Answer: The taste of each food is made unique by triggering different combinations of the five basic tastes and smell is an important contributor to taste. In addition, taste depends on several qualities of the way food feels, including texture, temperature, and pain.

Question 2: The transduction of saltiness is accomplished, in part, by a Na^+-permeable channel. Why would a sugar-permeable membrane channel be a poor mechanism for the transduction of sweetness?

Answer: The taste of salt is mostly the taste of the cation Na^+ so a Na^+-permeable channel is an efficient way to detect it. The taste of sugar, on the other hand, arises from many different sweet tastants with different chemistries, some natural and some artificial. It would be necessary to devise many different sugar-permeable membrane channels to accomplish what is done very efficiently by two members of the T1R family, T1R2 and T1R3. Many different chemicals can stimulate these receptors to result in the sensation of sweetness.

Question 3: Chemicals that have sweet, bitter, and umami tastes all activate precisely the same intracellular signaling molecules. Given this fact, can you explain how the nervous system can distinguish the tastes of sugar, alkaloids, and amino acids?

Answer: The sweet, bitter, and umami tastes comprise G-protein coupled receptors and that are exactly the same second messenger pathways that transfer signals to the afferent axons. But these three basic taste receptors are expressed in different taste cells. Each taste cell expresses only one class of taste receptor proteins and is connected to different gustatory axons receiving information for only one type of taste cell. The gustatory axons deliver

messages of umami, sweetness, or bitterness to the brain separately. The activity of different gustatory axons reflects only the chemical sensitivities of the taste cells that drive them. The nervous system distinguishes the tastes of sugar, alkaloids, and amino acids because separate transmission lines carry information for each taste.

Question 4: Why would the size of an animal's olfactory epithelium (and consequently the number of receptor cells) be related to its olfactory acuity?

Answer: The olfactory epithelium is a thin sheet of cells high up in the nasal cavity. Sniffing brings air through the nasal passages and a small percentage of that air passes over the olfactory epithelium, triggering the sense of smell. The surface area of the olfactory epithelium is larger in some animals than others. For example, the surface area of the olfactory epithelium of dogs is over 170 cm^2 but only $10cm^2$ in humans. Moreover, dogs have about a hundred times more receptors in one square centimeter than humans. The increased area and receptor density of the dog olfactory epithelium makes it possible for dogs to detect (and recognize) a few molecules left by someone who has passed by hours before. A much higher concentration of molecules is necessary for humans to detect most odorants.

Question 5: Receptor cells of the gustatory and olfactory systems undergo a constant cycle of growth, death, and maturation. Therefore, the connections they make with the brain must be continually renewed as well. Can you propose a set of mechanisms that would allow the connections to be remade in a specific way, again and again, over the course of an entire lifetime?

Answer: The new connections might follow a chemical trail left by the processes of the dying cells. In addition, connections might follow a chemical gradient set up by substances

diffusing from the target structures. Different chemicals might specify different targets. Neuronal firing patterns could also have an influence on growing pathways, so new axons would target structures that have similar patterns of electrical activity.

Question 6: If the olfactory system does use some kind of spatial mapping to encode specific odors, how might the rest of the brain read the map?

Answer: The rest of the brain would not be looking for spatial patterns of olfactory stimuli because olfactory localization is relatively crude, but the brain might use neural odor maps to distinguish between chemicals. Alternatively, spatial maps may simply be a mechanism for forming appropriate connections between related sets of neurons, and have no other functional importance.

Question 1: What physical property of light is most closely related to the perception of color?

Answer: Light is electromagnetic radiation, which has three properties: wavelength, frequency, and amplitude. Wavelength is closely related to the perception of color because wavelengths of 400-700 nm are visible to the naked human eye. Within this visible spectrum, different wavelengths appear as different colors.

Question 2: Name eight structures in the eye that light passes through before it strikes the photoreceptors.

Answer: The eight structures of the eye through which light passes before striking the photoreceptors are the cornea, the aqueous humor, the lens, the vitreous humor, the ganglion cell layer, the inner plexiform layer, the inner nuclear layer, and the outer plexiform layer.

Question 3: Why is a scuba mask necessary for clear vision under water?

Answer: The refractive power of the cornea depends on the slowing down of light at the air-cornea interface. Replacing air with a medium, such as water, which allows light to pass at about the same speed as the eye eliminates the refractive power of the cornea. When you open your eyes under water, the water-cornea interface has very little focusing power and things look blurred. A scuba mask restores the air-cornea interface, and consequently, the refractive power of the cornea.

Question 4: What is myopia, and how is it corrected?

Answer: Myopia, or nearsightedness, occurs when the eyeball is too long. Parallel rays from a distant light source, which are bent by the cornea and the lens, normally converge at exactly the same plane as the retina. When the eyeball is too long, the rays of light converge and cross before the retina. As a result, the image on the retina is a blurred circle rather than a

point. This occurs because the amount of refraction that the cornea and the lens provide is too large to focus distant objects on the retina. To see distant points clearly, nearsighted people must use artificial concave lenses that help focus the image on the retina.

Question 5: Give three reasons explaining why visual acuity is best when images fall on the fovea.

Answer: Visual acuity is best when images fall on the fovea for three reasons: 1) Visual acuity improves as the ratio of photoreceptors to ganglion cells decreases. Relatively few photoreceptors feed each ganglion cell in the fovea, resulting in a low ratio, which maximizes visual acuity. 2) The fovea sits in a pit that the lateral displacement of the ganglion and bipolar cells creates above the photoreceptors. This allows light to strike the photoreceptors without passing through the other layers of retinal cells, minimizing light scatter that can blur the image. 3) Visual space is not mapped to the targets of visual input uniformly. The central few degrees of the retina are over-represented in "neural space." Signals from individual cones in the fovea are represented in a larger volume of brain tissue than input from photoreceptors in peripheral regions of the retina. This specialization contributes to high acuity in central vision.

Question 6: How does the membrane potential change in response to a spot of light in the receptive field center of a photoreceptor? Of an ON bipolar cell? Of an OFF-center ganglion cell? Why?

Answer: Photoreceptors hyperpolarize in response to light. As a result, they release less neurotransmitters at the photoreceptor/bipolar cell synapse. ON-center bipolar cells depolarize in response to light in the receptive field center. This is their response to less

glutamate release at the photoreceptor/bipolar cell synapse. ON-center ganglion cells depolarize in response to light in the receptive field center. These ganglion cells receive direct input from ON-center bipolar cells.

Question 7: What happens in the retina when you "get used to the dark"? Why can't you see color at night?

Answer: Getting used to the dark is called dark adaptation. This capability is a consequence of a duplex retina, in which cones function best at high levels of illumination and rods function best at low levels of illumination. When moving from high to low levels of illumination, the retina must be adapted to the dark before the rods are maximally sensitive. Dark adaptation is a biochemical process in which rhodopsin, the rod photopigment, regenerates after being bleached in the light. The functional circuitry of the retina also readjusts as rhodopsin regenerates. Consequently, information from more rods is available to ganglion cells. The regeneration of unbleached rhodopsin and the resulting changes in functional circuitry take about 20-25 minutes. At night, it is difficult to detect colors because the cones, which have three photopigments with different spectral sensitivities, are inactive. Only cones are capable of color vision. At low levels of illumination, only rods are active and they contain only one photopigment. Rhodopsin's peak sensitivity is 500 nm.

Question 8: In what way is retinal output *not* a faithful reproduction of the visual image falling on the retina?

Answer: The eye functions like a camera, but the retina does not function like the film. The retina is a part of the brain. The physical arrangement of photoreceptors and the interconnections among all the retinal neurons represent the beginning of visual information

processing. In other words, information about light falling on the retina is already being processed at the level of the retina, and retinal output is a result of the processing.

Question 9: In retinitis pigmentosa, early symptoms include the loss of peripheral vision and night vision. The loss of what type of cells could lead to such symptoms?

Answer: Rods are responsible for night vision. The degeneration of rod photoreceptors can lead to early symptoms, such as loss of peripheral and night vision. The density of rod photoreceptors increases in the peripheral retina.

Question 1: How is the conduction of sound to the cochlea facilitated by the ossicles of the middle ear?

Answer: Sound waves traveling through air move the tympanic membrane, which, in turn, moves the ossicles. These transfer the movement of the tympanic membrane to the oval window, and the movement at the oval window vibrates the fluid in the cochlea. However, the fluid in the inner ear resists movement more than air does, so greater pressure is needed to vibrate the fluid. The ossicles amplify the pressure. The surface area of the oval window is smaller than that of the tympanic membrane, and the force is greater at the oval window than at the tympanic membrane because the ossicles act as levers. Because of these two mechanisms, the pressure at the oval window is about 20 times greater than the pressure at the tympanic membrane. This increase in pressure is sufficient to move the fluid in the inner ear. The movement of fluid in the cochlea causes a response in sensory neurons.

Question 2: Why is the round window crucial for the function of the cochlea? What would happen to hearing if it suddenly didn't exist?

Answer: The round window is a membrane located at the base of the cochlea. When the ossicles move the membrane that covers the oval window, the inward movement at the oval window pushes the perilymph into the scala vestibuli. This increases the fluid pressure on the oval window, pushing the membrane at the round window outward. A complementary motion at the round window accompanies any motion at the oval window. This movement is crucial because the cochlea is filled with incompressible fluid held in a solid bony container. If it were absent, the fluid in the cochlea would not move in response to pressure at the oval window and the auditory receptors would not be stimulated.

Question 3: Why is it impossible to predict the frequency of a sound wave simply by looking at which portion of the basilar membrane is the most deformed?

Answer: Frequency must be coded in some way other than the site of maximal activation in tonotopic maps for two reasons. First, tonotopic maps in the central auditory pathways do not contain neurons with low characteristic frequencies — below 200 Hz — so there must be some other way to distinguish them. Second, something other than tonotopy is needed because the region of the basilar membrane maximally displaced by sound depends on its intensity and frequency. At a fixed frequency, a more intense sound produces maximal deformation at a point further up the basilar membrane than a less intense sound does.

Question 4: Why would the transduction process in hair cells fail if the stereocilia as well as the hair cell bodies were surrounded by perilymph?

Answer: Endolymph, which is similar to intracellular fluid, surrounds stereocilia and hair cell bodies. It has a high K^+ concentration and a low Na^+ concentration. The high K^+ concentration is responsible for a K^+ equilibrium potential of 0 mV. As a result, when K^+ channels open, hair cells depolarize, moving toward the equilibrium potential of K^+, which is 0 mV. In contrast, neurons, which have a K^+ equilibrium potential of –80 mV, hyperpolarize when K^+ channels open. Perilymph has an ionic concentration similar to CSF, which is low K^+ and high Na^+. If perilymph surrounds the stereocilia and hair cell bodies, hair cells will not depolarize when K^+ channels open.

Question 5: If inner hair cells are primarily responsible for hearing, what is the function of outer hair cells?

Answer: Outer hair cells amplify the movement of the basilar membrane during low-intensity sound stimuli. They are cochlear amplifiers. The key to this function is the action of motor proteins in the membranes of outer hair cells. The motor proteins change the lengths of the outer hair cells. This changes the physical relationship between cochlear membranes, which causes the stereocilia on the inner hair cells to bend more, increasing the transduction process and producing a greater response in the auditory nerve. This mechanism causes about a 100-fold increase in the peak movement of the basilar membrane.

Question 6: Why doesn't unilateral damage to the inferior colliculus or MGN lead to deafness in the ear?

Answer: Each auditory nerve projects to the dorsal and ventral cochlear nuclei on the ipsilateral side, so cochlear neurons listen to only one ear. On the other hand, cells in the ventral cochlear nucleus project to the superior olive on both sides of the brain stem. As a result, olivary neurons hear from both ears. The first binaural neurons in the auditory pathway are found at the level of the superior olive. This is in contrast to the visual system, where the first binocular neurons are found in the visual cortex of the occipital lobe. Binaural olivary neurons project to the inferior colliculus, which projects to the medial geniculate, so each structure hears from both ears. Because of the early convergence of input from both ears, only the destruction of cochlear nuclei can cause unilateral deafness.

Question 7: What mechanisms function to localize sound in the horizontal and vertical planes?

Answer: Horizontal sound localization results from two mechanisms: interaural time delay and interaural intensity difference. For example, if the sound source is on the right, sound reaches the right ear sooner than it reaches the left ear. Specialized neurons in the brain stem detect

this interaural delay. Comparing continuous tones localizes them when the same phase of the sound wave reaches each ear. The second mechanism, interaural intensity difference, localizes high, continuous frequencies of 2,000-20,000 Hz. The head casts a sound shadow that alters the intensity of sound in each ear, depending on its origin. The resulting difference in sound intensity localizes sound. Neurons in the superior olive are sensitive to interaural delays. Vertical localization depends on the sweeping curves of the outer ear, which are essential for assessing the elevation of a source of sound. Bumps and ridges produce reflections of entering sound, and the delays between the direct path and the reflected path change as a sound source moves vertically. The combination of direct and reflected sound is different for different elevations. High-frequency sounds also enter the auditory canal more effectively when they come from an elevated source.

Question 8: What symptoms would you expect to see in a person who had recently had a stroke affecting A1 unilaterally? How does the severity of these symptoms compare with the effects of a unilateral stroke involving V1?

Answer: Lesions of the auditory cortex are less severe than lesions of the visual cortex. The main symptom of a stroke affecting the A1 unilaterally is the inability to localize the source of a sound. It is possible to detect the side from which the sound is coming but not its precise location. In contrast, a unilateral lesion of the visual cortex produces complete blindness in the part of the visual field corresponding to the site of the lesion.

Question 9: What is the difference between nerve deafness and conduction deafness?

Answer: Nerve deafness is caused by the loss of neurons in the auditory nerve or the loss of hair cells in the cochlea. Tumors affecting the inner ear and specific drugs, such as quinine and

some antibiotics, may cause nerve deafness. Explosions and loud music can also cause nerve deafness. A disturbance of sound from the outer ear to the cochlea causes conduction deafness. This deficit may be due to simple problems, such as excessive wax in the ear, or serious problems, such as rupture of the tympanic membrane or pathology of the ossicles.

Question 10: Each macula contains hair cells with kinocilia arranged in all directions. What is the advantage of this as compared to an arrangement with all cells in the same direction?

Answer: Each macula contains enough hair cells to cover a full range of directions. The direction preferences of hair cells vary in a systematic way. When the head moves, the mirror image orientation of the saccule and utricle on either side of the head excites some hair cells, inhibits others, and has no effect on the rest. The central nervous system can clearly interpret all possible linear movement. If the arrangement of hair cells is in the same direction, a slight movement of the head may excite all hair cells.

Question 11: Imagine a semicircular canal rotating in two different ways, around its axis — like a rolling coin, or end-over-end — like a flipped coin. How well would its hair cells respond in each case, and why?

Answer: When the semicircular canal rotates around its axis, the wall of the semicircular canal and the cupula begins to spin but the endolymph remains behind because of inertia. The endolymph exerts force on the cupula. The cupula bows, which bends the cilia. This bending either excites or inhibits the release of neurotransmitters from the hair cells on to the vestibular nerve axons, depending on the direction of rotation. When the semicircular canal is flipped end-over-end, the hair cells do not bend right or left and do not respond as a result.

However, this type of motion corresponds to rotation around the axis of another semicircular canal, which would register the movement for the vestibular system.

Question 12: How would you expect the functions of otolith organs and semicircular canals to change in the weightless environment of space?

Answer: Otolith organs detect the force of gravity and the tilt of the head. Semicircular canals are sensitive to the rotation of the head. In the weightless environment of space, the lack of gravity might hinder the functioning of the otolith organs that help detect the force of gravity.

Question 1: Imagine rubbing your finger across a pane of smooth glass and then across a brick. What kinds of skin receptors help you distinguish the two surfaces? As far as your somatic sensory system is concerned, what is different about the two surfaces?

Answer: Smooth glass might produce a stimulus with no vibrations and no changes in pressure. To detect this surface, mechanoreceptors, such as Merkel's disks or Meissner's corpuscles, should be close to the surface of the skin. To be detected, the stimulus that glass creates would have to excite slowly adapting mechanoreceptors because its surface does not change. Merkel's disks are slowly adapting and have small receptive fields. A brick might produce a stimulus with vibrations and changes in pressure related to the raised parts of its surface. This is a good stimulus for the Pacinian corpuscles and Ruffini's ending. To detect the successive peaks and valleys on the surface of the brick, a rapidly adapting receptor might best detect the stimulus. This requirement might make a Pacinian corpuscle the ideal receptor for this stimulus because Pacinian corpuscles are rapidly adapting, whereas Ruffini's endings are slowly adapting.

Question 2: What purpose is served by the encapsulations around some sensory nerve endings in the skin?

Answer: Encapsulations around Pacinian corpuscles provide a mechanism that makes the Pacinian corpuscles rapidly adapting, which is a property that makes them sensitive to vibrating high-frequency stimuli. If the encapsulations are stripped away, as done by Loewenstein and colleagues in the 1960s, the naked nerve terminals become less sensitive to vibrating stimuli and more sensitive to steady pressure.

Question 3: If someone tossed you a hot potato and you caught it, which information would reach your CNS first — news that the potato was hot or that it was relatively smooth? Why?

Answer: If someone tossed you a hot potato and you caught it, news about the smooth surface would reach your CNS faster than news about the temperature of the potato. In the CNS, C fibers mediate the pain and temperature sensations. They are the slowest axons, conducting at about 0.5-2 m/sec. C fibers are slow because they are the smallest axons, with diameters of less than 1 μm, and they do not contain myelin. On the other hand, cutaneous mechanoreceptors mediate touch sensations. The relatively large Aβ axons, which can conduct at up to 75 m/sec, convey these sensations. As a result, the sensation of the smooth surface reaches the CNS faster than the sensation of temperature.

Question 4: At what levels of the nervous system are *all* types of somatic sensory information represented on the contralateral side: the spinal cord, the medulla, the pons, the midbrain, the thalamus, the cortex?

Answer: Information from the dorsal columns crosses at the level of the medulla after synapsing in the dorsal column nuclei, so dorsal column information is contralateral as it courses through the medial lemniscus to synapse in the thalamus and then in the cortex. The trigeminal touch pathway crosses at the level of the pons to synapse contralaterally in the VP nucleus of the thalamus. Information in the spinothalamic tract crosses early, at the level of the spinal cord, so all its information is contralateral by the time the afferents reach their targets in the thalamus. As a result, all types of somatic sensory information are represented on the contralateral side at the level of the thalamus.

Question 5: What lobe of the cortex contains the main somatic sensory areas? Where are these areas relative to the main visual and auditory areas?

Answer: Most of the cortex concerned with the somatic sensory system is located in the parietal lobe. These include Broadman's area 3b, which is the primary somatosensory cortex, and areas 3a, 1, and 2, which are all in the postcentral gyrus. Additional somatosensory areas include areas 5 and 7 in the adjacent posterior parietal cortex. In contrast, the main visual areas are in the occipital lobe at the back of the brain, and the main visual areas are in the superior temporal gyrus of the temporal lobe on the lateral surface of the brain.

Question 6: Where can pain be modulated in the body, and what causes its modulation?

Answer: Pain is modulated at many places. It can be modulated at the level of pain receptors by simultaneous activity in low-threshold mechanoreceptors; this is why it feels good to rub the skin around a bruise. Strong emotions via activity in the periventricular and periaqueductal gray (PAG) matter of the midbrain also modulate pain. For example, electrical stimulation of the PAG can produce analgesia. In addition, the nervous system produces endogenous opiates or endorphins. Endorphins and their receptors are widely distributed in the CNS and are particularly concentrated in the PAG, the raphe nuclei, and the dorsal horn of the spinal cord. Endorphins and their receptors at these sites may prevent the passage of nociceptive signals into higher levels of the brain where pain perception takes place.

Question 7: Where in the CNS do information about touch, shape, temperature, and pain converge?

Answer: The posterior parietal cortex is the area where segregated streams of somatosensory information converge to generate complex neural representations. Neurons in this cortical

area have large receptive fields with stimulus preferences that are a challenge to characterize because they are so elaborate. This area is also concerned with visual stimuli and movement planning. Lesions in this area can result in agnosia, the inability to recognize objects even though simple sensory skills are normal. The posterior parietal cortex is essential for the perception and interpretation of spatial relationships, accurate body image, and the learning of tasks involving coordination of the body in space, all of which involve input from the visual system.

Question 8: Imagine this experiment. Fill two buckets with water, one relatively cold and one hot. Fill a third bucket with water of an intermediate, lukewarm temperature. Put your left hand into the hot water, your right hand into the cold, and wait one minute. Now quickly plunge both hands into the lukewarm water. Predict what sensation of temperature you will feel in each hand. Will they be the same?

Answer: No, they will not feel the same. The hand previously placed in hot water will feel much cooler in lukewarm water than the hand previously placed in cold water. The lukewarm water will feel relatively warm to the hand previously placed in cold water. These differences, however, will be transient.

Question 1: What did Sherrington call the "final common pathway," and why?

Answer: Sherrington called the lower motor neurons of the spinal cord the "final common pathway" that controls behavior. These motor neurons, also called the somatic motor neurons, directly command muscle contraction. They are the output of the motor system. Inputs to lower motor neurons include the sensory afferents entering the dorsal horn (providing information about muscle length), the upper motor neurons in the motor cortex, and the interneurons within the spinal cord that participate in spinal motor programs. Regardless of the source of the input, the output is the lower motor neurons, the final common path.

Question 2: Define, in one sentence, motor unit. How does it differ from motor neuron pool?

Answer: A motor unit consists of one alpha motor neuron and all the muscle fibers that the alpha motor neuron innervates. This is the elementary component of motor control. A motor neuron pool consists of all the alpha motor neurons that innervate a single muscle.

Question 3: Which is recruited first, a fast motor unit or a slow motor unit? Why?

Answer: Most muscles have a range of motor unit sizes. These motor units are recruited in order of size–the smallest being recruited first and the largest last. This explains why finer control is possible when muscles are under light loads than when they are under greater loads. Small motor units have small alpha motor neurons and large motor units have large alpha motor neurons. Small neurons are more easily excited by signals descending from the brain.

Question 4: When and why does rigor mortis occur?

Answer: The stiffening of muscles after death is a condition known as rigor mortis. Muscle contraction occurs because of the interaction between myosin, the major thick filament

protein, and actin, the major thin filament protein, during excitation contraction coupling. The heads of myosin filaments bind to actin filaments and undergo a conformational change. This causes the thick filament to move with respect to the thin filament, shortening the muscle fiber during muscle contraction. ATP is required to release the myosin heads from the actin filament. When no ATP is available because the tissue is dead, the attachment between the thick and thin filaments becomes permanent.

Question 5: Your doctor taps the tendon beneath your kneecap and your leg extends. What is the neural basis of this reflex? What is it called?

Answer: When your doctor taps the tendon beneath your kneecap, the tendon attached to the quadriceps muscle of your thigh is stretched. When this muscle is stretched, the muscle spindle afferents deliver sensory feedback about the muscle length. This causes the muscle to contract and your leg to extend. This is a monosynaptic reflex arc involving the spindle afferents that enter the dorsal horn and the motor neurons that control the muscle. The knee-jerk reflex tests the intactness of the nerves and muscles in this reflex arc.

Question 6: What is the function of gamma motor neurons?

Answer: Alpha motor neurons innervate extrafusal muscle fibers, causing muscle contraction. On the other hand, gamma motor neurons innervate the intrafusal muscle fiber at the two ends of the muscle spindle. The activation of these fibers causes a contraction of the two poles of the muscle spindle, pulling the noncontractile equatorial region and keeping the Ia axons active. The gamma motor activity keeps the muscle spindle during muscle contraction under control. Otherwise, during muscle contraction, the muscle spindles would become slack and insensitive to muscle length.

Question 7: Lenny, a character in Steinbeck's classic book *Of Mice and Men*, loved rabbits, but when he hugged them, they were crushed to death. Which type of proprioceptive input might Lenny have been lacking?

Answer: Lenny might have been lacking the proprioceptive input of reverse myotactic reflex. The normal function of the reflex arc is to regulate muscle tension within an optimal range. In extreme circumstances, the reflex arc protects the muscle from being overloaded. This type of proprioceptive input is particularly important for the proper execution of fine motor acts, such as the manipulation of fragile objects with hands, which requires a steady, but not too powerful, grip.

Question 1: List the components of the lateral and ventromedial descending spinal pathways. Which type of movement does each path control?

Answer: The components of the lateral descending spinal pathways are the corticospinal tract and the rubrospinal tract. The components of the ventromedial descending spinal pathways are the vestibulospinal tract, the tectospinal tract, the pontine reticulospinal tract, and the medullary reticulospinal tract. The lateral pathways are involved in the voluntary movement of the distal musculature. The lateral pathways control the fine movements of arms and fingers. The ventromedial pathways control the posture of the head and neck.

Question 2: You are a neurologist presented with a patient who has the following symptom: an inability to independently wiggle the toes on the left foot, but with all other movements (walking, independent finger movement) apparently intact. You suspect a lesion in the spinal cord. Where?

Answer: Lesions in the descending motor tracts, which originate in the upper motor system, can cause an abnormal Babinski sign. This was described by French neurologist Joseph Babinski in 1896. Scratching the sole of the foot from the heel toward the toes causes reflexive upward flexion of the big toe and an outward fanning of other toes. The normal response to this stimulus for anyone older than 2 years is to curl the toes downward.

Question 3: PET scans can be used to measure blood flow in the cerebral cortex. What parts of the cortex show increased blood flow when a subject is asked to think about moving her right finger?

Answer: When subjects are asked to mentally rehearse finger movements without actually moving the fingers, area 6 is active but area 4 is not. The portion of area 6 called SMA sends

axons that innervate distal motor units. Therefore, this area is likely to be active when rehearsing finger movements rather than PMA, which innervates proximal motor units. When subjects actually move their fingers after rehearsing the movement mentally, area 4 of the cortex registers increased blood flow. This is because area 4 is involved in executing movements.

Question 4: Why is dopa used to treat Parkinson's disease? How does it act to alleviate the symptoms?

Answer: The organic basis of Parkinson's disease is a gradual degeneration of dopaminergic (DA) neurons in the substantia nigra that project to the striatum. DA normally facilitates the direct motor loop by activating cells in the putamen, which releases VLo from globus pallidus–induced inhibition. The depletion of dopamine in Parkinson's disease closes the funnel that feeds activity to SMA through the basal ganglia and VLo. Dopa is used to treat the depletion of dopaminergic input to the basal ganglia caused by Parkinson's disease. Dopa crosses the blood-brain barrier and boosts DA synthesis in the dopaminergic neurons that remain in the substantia nigra. While this treatment alleviates some of the symptoms, eventually many neurons are lost and dopa treatment is no longer effective. Dopa also has some troublesome side effects.

Question 5: Individual Betz cells fire during a fairly broad range of movement directions. How might they work together to command a precise movement?

Answer: Upper motor neurons are located in cortical layer V of M1. Layer V has a population of large pyramidal neurons called *Betz cells.* Betz cells were first described as a separate class

of cells by Russian anatomist Vladimir Betz in 1874. Single unit recordings in M1 by Georgopoulos and colleagues showed the following:

i) Most of the motor cortex is active during every movement.

ii) The activity of each cell represents a single "vote" for a particular direction of movement.

iii) The direction of movement is determined by a tally of the votes registered by each cell in the population.

iv) Although the population-coding scheme is hypothetical, experiments on the superior colliculus conclude that a population code is used by this structure to command precisely directed eye movements.

Question 6: Sketch the motor loop through the cerebellum. What movement disorders result from damage to the cerebellum?

Answer: Axons arising from layer V pyramidal cells in the sensorimotor cortex—frontal areas 4 and 6, somatosensory areas on the postcentral gyrus, and the posterior parietal areas—form a massive projection to clusters of cells in the pons, the pontine nuclei, which in turn feed the cerebellum. The lateral cerebellum projects back to the motor cortex through a relay in the ventral lateral nucleus of the thalamus. This completes the motor loop through the cerebellum. Damage to the cerebellum results in ataxia, dysynergia, and dysmetria. Ataxia is a condition in which movements become uncoordinated and inaccurate. Dysynergia is characterized by the decomposition of synergistic multijoint movements. Dysmetria is characterized by clumsiness similar to that which accompanies ethanol intoxication.

Question 1: Battlefield trauma victims who have lost large volumes of blood often express a craving to drink water. Why?

Answer: Under conditions of lowered blood volume or pressure, kidneys secrete renin into the bloodstream. Renin in the blood promotes the synthesis of the peptide angiotensin II, which excites the neurons in the subfornical organ. The subfornical neurons stimulate the cells in the lateral area of the hypothalamus, causing an increase in vasopressin (ADH) production and an overwhelming feeling of thirst. So, to a limited extent, the kidneys control the brain. This is why battlefield trauma victims who have lost large volumes of blood crave water.

Question 2: You've stayed up all night trying to meet a term paper deadline. You now are typing frantically, keeping one eye on the paper and the other on the clock. How has the periventricular zone of the hypothalamus orchestrated your body's physiological response to this stressful situation? Describe in detail.

Answer: Under conditions of physiological stress, the periventricular hypothalamus secretes corticotropin-releasing hormone (CRH) into the hypothalamo-pituitary portal circulation. This triggers the release of adrenocorticotropic hormone (ACTH) into the general circulation. ACTH stimulates the release of cortisol from the adrenal cortex. Cortisol is a steroid with a significant effect on neuronal activity. It acts by mobilizing energy reserves and suppressing the immune system. In the brain, cortisol interacts with specific receptors that inhibit CRH release, ensuring that circulating cortisol levels do not increase drastically.

Question 3: Why is the adrenal medulla often referred to as a modified sympathetic ganglion? Why isn't the adrenal cortex included in this description?

Answer: The adrenal medulla receives preganglionic sympathetic innervation and secretes epinephrine into the bloodstream when activated. The release of adrenaline from the adrenal medulla into the blood ensures that all the cells of the body are exposed to sympathetic stimulation even if no postganglionic neurons reach them directly. For this reason, the adrenal medulla is referred to as a modified sympathetic ganglion. The adrenal cortex, which produces the steroid hormone cortisol, is under the control of pituitary hormones rather than the sympathetic division of the autonomic nervous system.

Question 4: A number of famous athletes and entertainers have accidentally killed themselves by taking large quantities of cocaine. Usually the cause of death is heart failure. How would you explain the peripheral action of cocaine?

Answer: *Cocaine* is a powerful CNS stimulant that exerts its effects at the synapses made by the dopaminergic and noradrenergic systems. Cocaine gives its users a feeling of increased alertness and self-confidence, a sense of exhilaration and euphoria, and a decreased appetite. It is sympathomimetic, which causes peripheral effects that mimic the activation of the sympathetic division of the ANS. Some peripheral effects are increased heart rate and blood pressure and dilation of the pupils. Large increases in heart rate and blood pressure when consuming sizeable quantities of cocaine can trigger heart failure.

Question 5: How do the diffuse modulatory and point-to-point synaptic communication systems in the brain differ? List four ways.

Answer: 1) Point-to-point communication in the sensory and motor systems requires anatomical precision. In contrast, diffuse modulatory systems form widely divergent axonal connections over a broad expanse of the brain, which communicate with several thousands of other cells.

2) Point-to-point communication requires mechanisms that restrict synaptic communication to the cleft between the axon terminal and its target. On the other hand, diffuse modulatory neurons release their neurotransmitters into extracellular fluid rather than into the synaptic cleft, and their transmitter molecules diffuse to many neurons rather than being confined to the vicinity of the synaptic cleft. 3) Point-to-point communication is brief. Only minute quantities of neurotransmitters are released with each impulse, and these molecules are quickly destroyed enzymatically or taken up by neighboring cells. In contrast, diffuse modulatory systems tend to act relatively slowly — the time ranges from seconds to minutes — and the molecules linger for long periods. Because of their broad, protracted action, diffuse systems can orchestrate entire behaviors. 4) Point-to-point connections originate with discrete sensory and motor systems, such as visual, auditory, and somatosensory. Neurons of the diffuse system that projects to each system arise from a common source at the central core of the brain and mostly originate from the brain stem.

Question 6: Under what behavioral conditions are the noradrenergic neurons of the locus coeruleus active? The noradrenergic neurons of the ANS?

Answer: Recordings from awake, behaving rats and monkeys show that locus coeruleus neurons are most activated by new, unexpected, nonpainful sensory stimuli in the animal's environment. They are least active when the animals are not vigilant and are sitting around quietly, digesting a meal. The locus coeruleus may participate in general arousal of the brain during interesting events in the outside world. Because NE can make neurons of the cerebral cortex more responsive to salient sensory stimuli, the locus coeruleus may function to increase brain responsiveness, speed up information processing by the point-to-point sensory

and motor systems, and make them more efficient. The noradrenergic neurons of the ANS, or the sympathetic division, are activated by crises, frenetically mobilizing the body for short-term emergencies, such as fight, flight, and fright. This system also participates in the final stages of coitus.

Question 1: A surgical approach to reducing excessive body fat is liposuction: the removal of adipose tissue. Over time, however, body adiposity typically returns to precisely the same value as before surgery. Why does liposuction not work? Contrast this with the effect of gastric surgery to treat obesity.

Answer: After undergoing liposuction, the person typically overeats until the original level of body fat is attained. This is because of the inherent need of the body to maintain energy homeostasis. The brain monitors the amount of body fat and acts to "defend" this energy store against perturbations. This theory is called the lipostatic hypothesis. Therefore, the body tries to rectify any alteration made to adipose tissue. Gastric surgery involves removal of ghrelin-secreting cells of the stomach. This causes a loss of appetite and is therefore a more effective treatment of obesity.

Question 2: Bilateral lesions of the lateral hypothalamus lead to reduced feeding behavior. Name three types of neuron, distinguished by their neurotransmitter molecules that contribute to this syndrome.

Answer: Bilateral lesions of the lateral hypothalamus cause anorexia (reduced feeding behavior). This is referred to as lateral hypothalamic syndrome. 1) A group of neurons in the lateral hypothalamus (LH) receiving direct input from the leptin-sensitive cells of the arcuate nucleus synthesize melanin-concentrating hormone (MCH). Injections of MCH into the brain stimulate feeding behavior. These lateral hypothalamic neurons have widespread connections with cortex, and are thus in a perfect position to inform the cortex of leptin levels in the blood and contribute to motivating the search for food. 2) A second group of LH neurons with widespread cortical connections contain another peptide called orexin; orexin injections

also stimulate feeding behavior. These cells also receive direct input from the arcuate nucleus and are thus informed of blood leptin levels. 3) Finally, LH neurons sensitive to NPY and AgPR inputs from the arcuate nucleus also stimulate feeding behavior.

Question 3: What neurotransmitter agonists and antagonists would you design to treat obesity? Consider drugs that could act on the neurons of the brain, as well as drugs that could act on the PNS.

Answer: There are four known orexigenic peptides. Two are made by neurons in the arcuate nucleus, neuropeptide Y and agouti-related peptide (AgRP), which projects to the lateral hypothalamus. Two other orexigenic peptides are made by neurons in the lateral hypothalamic area: melanin-concentrating hormone and orexin. These neurons project to widespread areas of cortex. Because these peptides stimulate feeding behavior, synthetic antagonists may decrease feeding behavior. In addition, two anorectic peptides made in the arcuate nucleus, alpha-melanocyte-stimulating hormone (alpha MSH) and cocaine-and-amphetamine-regulated transcript, inhibit feeding behavior. Synthetic agonists to these peptides may help decrease feeding behavior. A natural example of this type of treatment is provided by AgRP and alpha MSH, which are antagonistic peptides that compete for MC4 receptors on neurons in the lateral hypothalamus. Activating the MC4 receptors inhibits feeding, and blocking the receptor stimulates feeding. Alpha MSH is the receptor agonist and AgRP is a natural antagonist that blocks the stimulation of alpha MSH.

Question 4: Name one way the axons of the vagus nerve might stimulate feeding behavior and one way they inhibit it.

Answer: The vagus nerve carries most of the mechanosensory afferents from the stomach wall to the brain, which are stimulated when the stomach is full. The vagal sensory axons activate neurons in the nucleus of the solitary tract in the medulla. These signals inhibit feeding behavior. Cholecystokinin (CCK) is a peptide present in some of the cells that line the intestines that inhibits meal frequency. The major action of CCK as a satiety peptide is exerted on the vagal sensory axons. CCK acts synergistically with gastric distension to inhibit feeding behavior. The nucleus of the solitary tract receives visceral sensory input from the vagus nerve. This nucleus serves as an important integration center in the control of feeding. Because the gustatory nucleus is a division of this nucleus, satiety induced by a full stomach may be delayed while eating tasty food. Therefore, the vagus nerve may also participate in feeding behavior.

Question 5: What does it mean, in neural terms, to be addicted to chocolate? How could chocolate elevate mood?

Answer: Serotonin plays a crucial role in linking food and mood. Measurements of serotonin in the hypothalamus reveal that levels are low during the postabsorptive period, they rise in anticipation of food, and spike during a meal. Serotonin, derived from the dietary amino acid tryptophan, and tryptophan levels in the blood vary with the amount of carbohydrate in the diet. Chocolate may elevate mood by increasing in blood tryptophan and brain serotonin.

Question 6: Compare and contrast the functions of these three regions of the hypothalamus: the arcuate nucleus, the subfornical organ, and the vascular organ of the lamina terminalis.

Answer: The arcuate nucleus of the hypothalamus lies near the base of the third ventricle and is activated by a rise in blood leptin levels. Arcuate neurons are characterized by a

distinctive mix of peptide neurotransmitter molecules. 1) The arcuate nucleus comprises neurons that play an important role in inhibiting and stimulating feeding behavior. 2) The neurons of the subfornical organ are sensitive to circulating angiotensin II. Angiotension II levels rise in response to reduced blood flow to the kidneys, which occurs with low blood volume during dehydration. Neurons of the subfornical organ directly stimulate the magnocellular neurosecretory cells of the hypothalamus to release vasopressin and stimulate volumetric thirst. Circulating vasopressin causes the kidneys to conserve body water by reducing urine output. In this way, the subfornical organ helps regulate water balance in response to volumetric signals with both behavioral and humoral mechanisms. 3) The vascular organ of the lamina terminalis (OVLT) is a specialized region of the telencephalon lacking a blood-brain barrier. It is involved in osmometric thirst, the motivation to drink water when the blood is hypertonic. Neurons in this brain region sense blood hypertonicity associated with low blood volume. The OVLT neurons directly excite the magnocellular neurosecretory cells that secrete vasopressin and stimulate osmometric thirst. Lesions of the OVLT completely prevent the behavioral and humoral responses to dehydration but not the responses to loss of blood volume.

Question 1: Suppose you have just been captured by aliens who have landed on Earth to learn about humans. The aliens are all one gender, and they are curious about the two human genders. To earn your freedom, all you must do is tell them how to reliably distinguish males from females. What biological or behavioral tests do you tell them to conduct? Be sure to describe any exceptions that might violate your gender tests—you don't want the aliens to get angry!

Answer: There are many biological characteristics and qualities that distinguish between males and females, including the sex chromosomes, the anatomy of the reproductive organs, and secondary sex characteristics, such as hair distribution and mammary glands. The most reliable test of gender is to examine the chromosomes. Females have two X chromosomes whereas males have an X chromosome from the mother and a Y chromosome from the father. In rare cases, there are too few or too many sex chromosomes but gender is always determined by the presence or absence of the Y chromosome. Another important exception is androgen insensitivity syndrome. A genetic male has the phenotypic appearance of a female because his androgen receptors are insensitive to this masculinizing hormone and his body follows the default pathway, which is to develop female secondary sexual characteristics and gender identity.

Question 2: Trace the chain of events that might link psychological stress and reduced male sperm production and potency.

Answer: Neural activity in the hypothalamus is influenced by numerous psychological and environmental factors, which can cause changes in the release of gonadotropin-releasing hormone (GnRH). GnRH controls the release of LH and FSH from the pituitary gland. LH

and FSH are particularly important for normal sexual development and function in both males and females. LH and FSH play vital roles in male fertility. LH stimulates the testes to produce testosterone, and FSH is involved in the maturation of sperm cells within the testes. Stress may alter male potency by influencing the neural activity of the hypothalamus and the release of GnRH.

Question 3: Figure 17.14 shows an interesting but unexplained observation: In the brain of a mother rat during periods of lactation, the size of the somatosensory cortex representing the skin around the nipples expands. Speculate about a likely mechanism for this phenomenon. Suggest a reason why such brain plasticity might be advantageous.

Answer: Sexually dimorphic changes in the brain are sometimes transient or cyclical, coinciding with the sexual behavior to which they are related. In female rats, the somatosensory cortex contains a sensory representation of the ventral skin surrounding the nipples. This representation expands dramatically but temporarily across the cortex when the mother rat nurses her young. This is an example of somatosensory map plasticity. The cortical region in a lactating rat is enlarged compared with that of a nonlactating rat. Regions of somatosensory cortex subserving other regions of the body are not affected by the lactating state. Experiments reveal that topographic maps in somatosensory cortex are dynamic, and adjust depending on the amount of sensory experience. The relative size of cortex devoted to each body part is correlated with the *density* of sensory input received from that part. Size on the map is also related to the *importance* of the sensory input from that part of the body. Perhaps the observed plasticity in the lactating rat's somatosensory cortex is mediated by changes in the receptor density in the nipple area related to lactation, and the sensory input related to

suckling pups. Hormones related to lactation, such as oxytocin, may enhance cortical plasticity in lactating rats.

Question 4: Estradiol is typically described as a female sex hormone, but it also plays a critical role in the early development of the male brain. Explain how this happens, and why the female brain is not similarly affected by estradiol.

Answer: The testes produce androgens, which trigger the masculinization of the nervous system by regulating the expression of a variety of sex-related genes. In the absence of androgens, the brain is feminized through a different pattern of gene expression. But it is not testosterone that causes the changes in gene expression; it is estrogen that triggers masculinization of the developing nervous system. Testosterone is converted within the neuronal cytoplasm into estradiol in a single chemical step catalyzed by the enzyme aromatase. Because female gonads do not produce an estrogen surge in early stages of development, female brains normally escape this steroid-triggered transformation.

Question 5: Where and how can steroid hormones influence neurons in the brain, at the cellular level?

Answer: There are several examples of the cellular effects of steroid hormones. 1) Neurite outgrowth increases in the hypothalamic neurons of newborn mice treated with estradiol, and estradiol increases cell viability and spine density. 2) A particularly fascinating example is the estradiol-related increase in dendritic spines on hippocampal neurons in female rats. Dendritic spine numbers fluctuate dramatically during the 5-day estrous cycle, increasing with estradiol levels. This effect is mediated by inhibitory interneurons with estradiol receptors. Increases in estrogen decrease GABA production so the hippocampus has less

inhibition. Decreased inhibition leads to an overall increase in neural activity and an increase in spines and excitatory synapses on the pyramidal cells. 3) Estradiol also has a protective effect on neurons. Cells in culture that are exposed to extradiol are more likely to survive hypoxia, oxidative stress, and exposure to various neurotoxic agents. These protective effects are not well understood but probably involve multiple cellular mechanisms.

Question 6: Suppose a research team has just claimed that a small and obscure nucleus in the brain stem, nucleus X, is sexually dimorphic and essential for certain "uniquely male" sexual behaviors. Discuss the kinds of evidence you would need to accept these claims about (a) the existence of a dimorphism, (b) the definitions of uniquely male behaviors, and (c) the involvement of nucleus X in these sexual behaviors.

Answer: a) Evidence of sexual dimorphism in neural structures requires quantitative analysis of tissue from the brains of male and female animals that are the same age and from the same type of environment. The tissue also needs to be handled in exactly the same ways for histological preparation. Because the quantitative differences are likely to be small, large numbers of brains should be examined. It would be best to show sexual dimorphism in more than one species if possible and to look at the development of the dimorphism pre- and postnatally. b) Uniquely male behaviors associated with copulation are easy to observe and quantify. Other "uniquely" male behaviors related to aggression are also observable but need good operational definitions. c) Demonstrating the link between the dimorphic structure and uniquely male behavior may include lesion studies where obliterating the structure obliterates the sexual behavior. Demonstrating the male behavior in androgenized females who also show masculinization of the sexually dimorphic brain structure is also a powerful

demonstration of the link between the structure and the behavior. You may also try blocking the androgen receptors as a way to reverse the sexual dimorphism in male animals.

Question 1: According to the James-Lange and Cannon-Bard theories of emotion, what is the relationship between the anxiety you would feel after oversleeping for an exam and your physical responses to the situation?

Answer: According to the James-Lange theory of emotion, we experience emotion in response to physiological changes in our body, such as increased heart rate, inhibited digestion, and increased sweating. As a result of the body's response to the situation, the person becomes afraid. According to the Cannon-Bard theory, emotional experience is independent of emotional expression. The threatening stimulus first causes a feeling of fear and the physiological reaction follows.

Question 2: How has the definition of the limbic system and thoughts about its function changed since the time of Broca?

Answer: French neurologist Paul Broca named the collection of cortical areas that form a ring around the brain stem limbic lobe (cingulated gyrus, medial temporal lobe, including the hippocampus). There was no mention of emotion; the structures were primarily thought to be involved in olfaction. By the 1930s, evidence suggested that a number of limbic structures were involved in emotion. American neurologist James Papez proposed an "emotion system" on the medial wall of the brain, which linked the cortex with the hypothalamus (cingulated cortex, hippocampus, hypothalamus, anterior nuclei of the thalamus). Papez believed that damage to certain cortical areas caused profound changes in emotional expression with little change in perception or intelligence. Papez proposed that activity in the cingulated cortex adds emotional coloring. The term limbic system was popularized in 1952 by American physiologist Paul MacLean. According to MacLean, the evolution of a limbic system enabled

animals to experience and express emotions. It freed animals from the stereotypical behavior dictated by their brain stem. Some of the components of the Papez circuit are no longer thought to be important for the expression of emotion, such as the hippocampus. In addition, some structures involved in emotion are also involved in other functions, and some researchers question the utility of trying to define a single, discrete emotion system.

Question 3: What procedures will produce an abnormal rage reaction in an experimental animal? How do we know that the animals *feel* angry?

Answer: The removal of the cerebral hemispheres produces abnormal rage reactions in experimental animals. Experiments performed in the 1920s showed a remarkable behavioral transformation in cats or dogs when this procedure was performed. Animals that were not easy to provoke prior to the surgery flew into a state of violent rage with the least provocation after the surgery. Sham rage is observed if the anterior hypothalamus is destroyed along with the cortex, but it is not seen if the lesion is extended to include the posterior half of the hypothalamus. Therefore, the posterior hypothalamus is particularly important for the expression of anger and aggression in animals and is normally inhibited by the telencephalon. We do not know whether or not the animals feel angry, because feelings are subjective experiences that can be reported verbally by humans but not by rats.

Question 4: What changes in emotion were observed following temporal lobectomy by Klüver and Bucy? Of the numerous anatomical structures they removed, which is thought to be closely related to changes in temperament?

Answer: Neuroscientists Heinrich Klüver and Paul Bucy found that the bilateral removal of temporal lobes, also called temporal *lobectomy*, in rhesus monkeys had a dramatic effect on

the animals' fear and aggression, which were decreased. The animals were placid in the presence of humans and other animals that they normally fear, such as snakes. The animals showed a decrease in vocalizations and facial expressions typically associated with fear. It appeared that both the normal experience and normal expression of fear and aggression were severely decreased. Amygdala appears to be a critical element in the brain circuitry that processes fear and aggression. It is thought to be closely associated with changes in temperament. The removal of amygdala reduces fear and aggression in experimental animals.

Question 5: Why might performing bilateral amygdalectomy on a dominant monkey in a colony result in that monkey's becoming a subordinate?

Answer: Evidence indicates that amygdala is involved in aggressive behavior. Lesions of the amygdala may result in the flattening of emotion and other behavioral abnormalities. Bilateral amygdalectomy in animals can profoundly reduce fear and aggression. Therefore, bilateral amygdalectomy on a dominant monkey will make the monkey placid and less difficult to challenge. As a result, the second monkey in the hierarchy will push the dominant monkey to a subordinate position. Electrical stimulation of the amygdala may produce a state of agitation or affection aggression.

Question 6: What assumptions about limbic structures underlie the surgical treatment of emotional disorders?

Answer: The assumption that the limbic system controls emotion led to the conclusion that people with emotional problems can be helped by altering the system surgically. In the 1930s, John Fulton and Carlyle Jacobsen of the Yale University reported that frontal lobe lesions had a calming effect in chimpanzees. It has been suggested that frontal lesions have

this effect because of the destruction of limbic structures, particularly in connection with frontal and cingulate cortex. (This surgery is also associated with blunted emotions, inappropriate behavior, difficulty in planning and working toward goals, and difficulty in concentrating.) In addition, reduced aggression in amygdalectomized animals led some neurosurgeons to use this method in humans. Clinical reports claim considerable success in reducing aggressive asocial behavior, increasing the ability to concentrate, decreasing hyperactivity, and reducing seizures with this type of brain surgery.

Question 7: The drug known as Prozac is a serotonin-selective reuptake inhibitor. How does this drug affect a person's level of anxiety and aggression?

Answer: The neurotransmitter serotonin is involved in regulating aggression; decreased serotonin is associated with an increase in aggression, and increased serotonin is associated with decreased aggression. The link between aggression and anxiety is not perfectly clear, but it is known that serotonin antagonists increase aggressiveness and agonists of the 5-HT1B and 5-HT1B serotonin receptors decrease anxiety and aggressiveness in mice. It is also known from experimental work in animals that anxiety and aggression increase and decrease together. Prozac is a selective serotonin reuptake inhibitor (SSRI) that effectively increases the amount of serotonin in the synaptic cleft by preventing its reuptake into the presynaptic element. This increase in serotonin availability is associated with decreased anxiety, so in addition to its use as an antidepressant, Prozac and other SSRIs are used as antianxiety agents.

Question 1: Why do EEGs with relatively fast frequencies tend to have smaller amplitudes than EEGs with slower frequencies?

Answer: The amplitude of the EEG signal depends on the synchronization of the activity of the underlying neurons. If a group of cells are excited simultaneously, the tiny signals sum to generate one large surface signal. However, when each cell receives the same amount of excitation, but spread out in time, the summed signals are meager and irregular. In this case, the *number* of activated cells and the *total amount of excitation* has not changed; however, the timing of the activity has changed. Therefore, EEGs with relatively fast frequencies tend to have smaller amplitudes than EEGs with slower frequencies.

Question 2: The human cerebral cortex is very large and must be folded extensively to fit within the skull. What do the foldings of the cortical surface do to the brain signals that are recorded by an EEG electrode at the scalp?

Answer: For the most part, an EEG measures voltages generated by the currents that flow during synaptic excitation of the dendrites of many pyramidal neurons in the cerebral cortex. The signal must penetrate several layers of non-neural tissue, including the meninges, fluid, bones of the skull, and skin, to reach the electrodes. The population of cells deep within the folds of the cortical surface contributes very little to the recorded EEG, which measures activity only in the superficial layers of cortex close to the skull.

Question 3: Sleep seems to be a behavior of every species of mammal, bird, and reptile. Does this mean that sleep performs a function essential for the life of these higher vertebrates? If you do not think so, what might be an explanation for the abundance of sleep?

Answer: No single theory of the function of sleep is widely accepted, but the most reasonable ideas fall into two categories: theories of restoration and theories of adaptation. The theory of restoration states that we sleep in order to rest and recover, and to prepare to be awake again. The theory of adaptation states that we sleep to keep out of trouble, to hide from predators when we are most vulnerable or from other harmful features of the environment, or to conserve energy. Even animals that never rest, such as dolphins, give each hemisphere a nap: about 2 hours asleep on one side, then 1 hour awake on both sides, 2 hours asleep on the other side, and so on for 12 hours every night. Similarly, the blind Indus River dolphin uses microsleeps of 4-6 seconds in duration, adding up to 7 hours in a 24-hour day to rest its brain. This reinforces the importance of sleep but the reason for its importance remains unknown. And it is possible that sleep is simply a byproduct of some other vital process. Nonethless, rats deprived of sleep lose weight in spite of increased food intake, become weak, accumulate stomach ulcers and internal hemorrhages, and in severe cases even die. They are unable to regulate body temperature and metabolic needs.

Question 4: An EEG during REM sleep is very similar to an EEG when awake. How do the brain and body in REM sleep *differ* from the brain and body when awake?

Answer: Rapid eye movement sleep, or REM sleep, is a state where the whole body (except for the eye and respiratory muscles) is immobilized, and vivid, detailed illusions called dreams are conjured up. The oxygen consumption of the brain is higher in REM sleep than when the brain is awake and concentrating on difficult mathematical problems. Some areas, including primary visual cortex, are equally active in the two states. However, extrastriate cortical areas and portions of the limbic system are significantly more active during REM sleep.

Conversely, regions of the frontal lobes are noticeably less active during REM. Most of the body is incapable of moving during REM sleep, whereas the body can be moved normally when awake. The paralysis that occurs during REM sleep is almost a total loss of skeletal muscle tone. The muscles controlling eye movement, the tiny muscles of the inner ear, and the muscles of respiration are the exceptions, as these are strikingly active. During REM sleep, the same core brain systems that control the sleep processes of the forebrain actively inhibit the spinal motor neurons, preventing the descending motor activity from expressing itself as actual movement.

Question 5: What is a likely explanation for the brain's relative insensitivity to sensory input during REM sleep, compared to the waking state?

Answer: The control of REM sleep, as with the other functional brain states, derives from diffuse modulatory systems in the core of the brain stem, particularly the pons. The diffuse modulatory systems control the rhythmic behaviors of the thalamus, which in turn controls many EEG rhythms of the cerebral cortex; slow, sleep-related rhythms of the thalamus apparently block the flow of sensory information up into the cortex.

Question 6: The SCN receives direct input from the retina via the retinohypothalamic tract, and this is how light-dark cycles can entrain circadian rhythms. If the retinal axons were somehow disrupted, what would be the likely effect on a person's circadian rhythms of sleeping and waking?

Answer: Input from the retina to the suprachiasmatic nucleus (SCN) of the hypothalamus is essential and sufficient to entrain sleeping and waking cycles to night and day. When retinal axons are disrupted, and this essential input to the SCN is absent, the sleep-wake cycles

cannot be entrained by light. Such an individual would be subject to a free-running clock, which would drift out of phase with the typical light or dark cycle because a free-running clock runs on a longer day than normal (25 hours in the short-term, 30-36 hours in the long-term). Such an individual would become sleepy during the day and wakeful at night, until the cycle drifted back into phase with the normal light or dark cycle.

Question 7: What differences would there be in the behavioral consequences of a free-running circadian clock versus no clock at all?

Answer: A free-running circadian clock still has certain alternating phases of sleep and wakefulness, and other behavioral and physiological cycles, such as body temperature, continue to alternate, although they may become desynchronized so that sleep-wake and body temperature cycle at their own pace, uncoupled. On the other hand, when the SCN is lesioned, circadian rhythms are abolished—the periodicity is lost. For example, squirrels and monkeys with no SCN have persistent high-frequency rhythms of both brain activity and temperature with no evidence of regular cycling.

Question 1: How is it possible for a split-brain person to speak intelligibly if the left hemisphere controls speech? Isn't this inconsistent with the fact that the left hemisphere must direct motor cortex in both hemispheres to coordinate movements of the mouth?

Answer: Some midline features are represented in both sides of the brain, such as the fovea, which is represented in both right and left hemispheres. Motor control of the mouth and larynx may be similarly represented on both sides of the brain. In addition, the motor system works according to the population code rather than a strict one-to-one correspondence between neural activity and neural output. This may "loosen" the topographic relationships between motor cortex and motor output. Finally, the two hemispheres can communicate via the anterior commisure in split-brain individuals because this subcortical fiber tract remains intact when the corpus callosum is severed.

Question 2: What can you conclude about the normal function of Broca's area from the observation that there are usually some comprehension deficits in Broca's aphasia? Must Broca's area itself be directly involved in comprehension?

Answer: Functional localization is an appealing and important concept that helps us understand how the nervous system processes sensory information and commands motor output. But it is important not to lose sight of the interconnectedness of various brain structures. The predominant function of Broca's area is language expression, and this function is diminished when Broca's area is lesioned. But the entire circuitry of language processing must also be disrupted in the absence of this structure, affecting the functioning of the circuit as a whole, including Wernicke's area, which appears to mediate language comprehension. In addition, Broca's area does not have easily discernable boundaries, and strokes rarely involve discrete

regions of cortex. Such lesions may involve other brain structures beyond Broca's area. Finally, it is quite possible that Broca's area participates in language comprehension even though its main function is language expression.

Question 3: Pigeons can be trained to press one button when they want food and other buttons when they see particular visual stimuli. This means the bird can "name" things it sees. How would you determine whether or not the pigeon is using a new language—"button-ese"?

Answer: Human language is creative—new word combinations and sentences are constantly being made, and the combinations have clear meaning according to the meaning of the individual words plus the rules for arranging them. Animals use symbols to identify known objects, but creative use of symbols appears to be limited. A good way to determine whether an animal is capable of language is to see whether the animal can use the symbols it has learned in novel combinations, *i.e.*, combinations that have not been taught, to signify novel stimuli.

Question 4: What does the Wernicke-Geschwind language-processing model explain? What data are inconsistent with this model?

Answer: The Wernicke-Geschwind language processing model offers simple explanations for key elements of Broca's and Wernicke's aphasias. A lesion in Broca's area seriously interferes with speech production because the proper output signals for speech execution can no longer be sent to motor cortex. On the other hand, comprehension is relatively intact because Wernicke's area is undisturbed. A lesion in Wernicke's area produces serious comprehension problems because this is the site where sounds are transformed into words.

The ability to speak is usually unaffected because Broca's area is able to drive the muscles required for speech. The following data is inconsistent with the Wernicke-Geschwind model:

i) Words do not have to be transformed into a pseudoauditory response in Wernicke's area. Visual information can reach Broca's area from visual cortex without making a stop at the angular gyrus.

ii) The severity of Broca's and Wernicke's aphasias depends on how much cortex is damaged beyond the limits of Broca's and Wernicke's areas. In addition, aphasia is influenced by damage to subcortical structures, such as the thalamus and caudate nucleus, which are not in the model. When parts of cortex are surgically removed, the resulting language deficits are usually milder than the deficits resulting from stroke, which affects both cortical and subcortical structures.

iii) There is significant recovery of language function after a stroke. Other cortical areas apparently compensate for what is lost.

iv) Most aphasias involve both comprehension and speech deficits.

Question 5: In what ways is the left hemisphere usually language dominant? What does the right hemisphere contribute?

Answer: Hemispheric dominance for language is best illustrated by the responses of people with a severed corpus callosum when visual input is restricted to only one hemisphere. Numbers, words, and pictures visually presented in the right visual field (and thus the left hemisphere of the brain) can be repeated or described with no difficulty because the left hemisphere is usually dominant for language. In addition, objects manipulated by the right hand (but out of view of both eyes) can be described. However, such simple verbal descriptions of sensory

inputs are not possible for the right hemisphere. If an image is shown only in the left visual field or an object is felt only by the left hand (and thus the right hemisphere), a split-brain subject is unable to describe it. This absence of response by the right hemisphere is a consequence and demonstration of the left hemisphere being language dominant. The right hemisphere has language comprehension and can read and understand numbers, letters, and short words as long as the required response is nonverbal.

Question 6: What evidence is there that Broca's area is not simply a premotor area for speech?

Answer: Several lines of evidence indicate that Broca's area is not simply a premotor area for speech.

i) The difference in the aphasic's ability to use content words and function words suggests that Broca's area and nearby cortex may be particularly involved in making grammatical sentences out of words.

ii) Wernicke suggested that the area damaged in Broca's aphasia contains memories for the fine series of motor commands required for articulating word sounds, and this theory is upheld by some people.

iii) Comprehension is good with Broca's aphasia but comprehension deficits can be demonstrated by tricky questions.

iv) In addition, patients sometimes have considerable anomia, suggesting that they have problems "finding" words as well as making the appropriate sounds.

Question 1: What differences are there between the conscious states of a person with neglect syndrome and a split-brain individual who can only describe things in the right visual field?

Answer: In neglect syndrome, a person appears to ignore objects, people, and sometimes his own body to one side of the midline. In severe cases, the patient behaves as if half the universe no longer exists (*e.g.*, draws half a clock face, eats food from only one side of his plate). Most cases occur from lesions in the posterior parietal cortex in the right hemisphere. In split-brain individuals, both the hemispheres work like independent brains without acknowledging the contribution of the other side. Split-brain individuals can only describe things in the right visual field because the left hemisphere is dominant for language. They do not neglect the left visual field; they are unable to identify works and objects verbally because the right hemisphere has no verbal output. For example, embarrassing images shown to the left visual field can evoke blushing and laughter even if the subject says he sees nothing, indicating that the image has been perceived.

Question 2: In what ways is unilateral spatial neglect different from blindness in half of the visual field?

Answer: In the case of unilateral spatial neglect, the patient behaves as if half the universe no longer exists. He may shave only one side of his face, brush the teeth on only one side of his mouth, dress only one side of his body, and eat food from only one side of his plate. It is known to be more common following the right hemispheric damage. The patient acts as if there has been shrinkage in the left half, leading to a problem in space perception. However, he can see objects in the neglected half, but simply ignores them. In blindness, a person is unable to perceive anything in the blind visual field, yet he or she still attends to objects in

the blind half of the visual field by using other senses. In blindness, a person has no difficulties viewing objects in the intact half of the visual field and has no problems of space perception. Finally, people with neglect syndrome often recover, at least partially, whereas blindness caused by a loss of visual cortex is permanent.

Question 3: How would you use fMRI or PET imaging to look for brain areas involved in directing selective attention in humans?

Answer: The fMRI technique has been used to visualize how brain activity changes when the location of the visual sector being attended to changes. (Subjects always kept their gaze fixed at the center of the bull's-eye stimulus.) Depending on what part of the visual field is being attended to, the pattern of brain activity shifts retinotopically. This indicates that selective changes in brain activity are typically associated with spatial shifts in attention in a pattern that follows the retinotopic organization of visual cortex. The technique of PET imaging was used when humans performed a same-different discrimination task—the images were identical, but subjects attended to different features, such as color, direction of movement, and so on. Brain activity shifted to different visual areas depending on what features were attended to, *e.g.*, there was more activity in V4 when the subjects were attending to color. These effects of attention to different features are roughly consistent with the tuning properties of neurons in extrastriate visual areas. Similar experiments could be conducted for the other sensory systems. It is interesting to examine subcortical structures such as the pulvinar.

Question 4: What neural mechanism(s) could be responsible for the receptive field changes observed in area V4 in response to shifts in attention?

Answer: Robert Desimone and his colleagues at the National Institute of Mental Health have revealed specific effects of attention on the response properties of neurons in visual cortical area V4. Two sets of stimuli are presented within a neuron's receptive field, but one set is effective in producing action potentials and the other is ineffective. When the subject attends to the effective stimuli the neuron fires action potentials. When the subject attends to the ineffective stimuli the neuron fires much less, although the effective stimuli are still present on the other side of the receptive field. It's as though selective attention enabled the neuron to ignore the effective stimuli in the unattended side of the receptive field. Perhaps inhibitory interneurons help prevent the cell from firing when attending to ineffective stimuli. Such neurons need to be governed by attentional mechanisms. Alternatively, attentional mechanisms may be able to shrink the area of the receptive field to which the neuron is sensitive by enhancing sensitivity in the attended side rather than dampening sensitivity in the unattended side.

Question 5: How are shifts in attention and eye movements related?

Answer: There appears to be a close association between eye movements and attention. Recent experiments suggest that the brain circuitry responsible for directing the eyes to objects of interest might also play a critical role in guiding attention. Two sets of experiments are relevant here. First, Robert Wurtz and colleagues showed that the response of neurons in the posterior parietal cortex of awake, behaving monkeys is enhanced *before* the animal makes a saccade to a specific target within the neuron's receptive field (the receptive fields are quite large here). This increased neuronal activity prior to the saccade is thought to be a consequence of shifting attention as preparation for shifting eye position. Second, Moore and

colleagues examined the frontal eye fields (FEF) in awake, behaving monkeys. Neurons in the FEF have motor fields—small areas in the visual field—and when a sufficient electrical current is passed into the FEF, the eyes rapidly make a saccade to the motor field of the stimulated neuron. The researchers also showed that passing a small amount of current through neurons in FEF lowered the threshold needed for that neuron to detect dimming in the target stimulus, *i.e.*, the researchers artificially enhanced the responsiveness of the neuron by stimulating the FEF neuron, simulating what happens when the animal attends to the stimulus.

Question 6: How might feedback from the frontal eye fields modulate the responses of neurons in visual cortex?

Answer: FEF neurons make direct connections with numerous areas known to be influenced by attention, including areas V2, V3, V4, MT, and parietal cortex. Moore and colleagues also showed that stimulating neurons in FEF can enhance the sensitivity of neurons in distant visual areas such as V4. The feedback from FEF neurons apparently primes the visual cortical neurons in other parts of cortex so they are more likely to fire an action potential when an effective stimulus is presented. The nature of this input is not known, but FEF neurons may depolarize the neurons in distant cortical areas sufficiently to change their threshold for firing an action potential.

Question 7: How would a system for guiding attention to features differ from a system directing attention to different locations?

Answer: A system for guiding attention to features will require the observers to pay attention to either a single feature or all features and base their judgment on changes in features

regardless of locations. This will involve individual visual cortical areas specialized for different stimulus features, such as V4, which is specialized for color, area IT, and other visual cortical areas in the temporal lobe. A system for guiding attention to location will always require the observers to make use of their retinotopic maps, which are represented in several visual cortical areas in the occipital lobe.

Question 1: Why and where do benzodiazepines reduce anxiety?

Answer: The proper action of GABAergic interneurons is critical to the proper functioning of the brain. $GABA_A$ receptors are GABA-gated chloride channels that mediate fast IPSPs. In addition to its GABA binding site, the $GABA_A$ receptor contains sites where chemicals can act to powerfully modulate its chloride ion channel function. Benzodiazepines bind to one of these sites and act to make GABA highly effective in opening the channel and producing inhibition. A study of patients with panic disorder using PET imaging demonstrated a reduced number of benzodiazepine binding in regions of frontal cortex that show hyperactive responsiveness during anxiety. Therefore, the calming actions of benzodiazepines may be due to the suppression of activity in the brain circuits used in the stress response.

Question 2: Depression is often accompanied by bulimia nervosa, which is characterized by frequent eating binges followed by purging. Where does the regulation of mood and appetite converge in the brain?

Answer: In severely depressed patients, the HPA axis is hyperactive. Blood cortisol levels are elevated as is the concentration of CRH in the CSF. The activation of the hippocampal glucocorticoid receptors by cortisol leads to feedback inhibition of the HPA axis. In depressed patients, this feedback is disrupted, explaining why HPA function is hyperactive. In addition, the regulation of mood and appetite converge at the hypothalamic-pituitary-adrenal (HPA) axis. Therefore, hyperactivity of the HPA axis may also be responsible for the disruption in feeding behavior termed as bulimia nervosa.

Question 3: Snuggling with your mom as a baby might help you cope with stress better as an adult. Why?

Answer: Tactile stimulation activates the ascending serotonergic inputs to the hippocampus, and the serotonin triggers a long-lasting increase in the expression of the glucocorticoid receptor gene. More glucocorticoid receptors equip the organism to respond to stressors as adults. The beneficial effect of tactile stimulation is limited to a critical period of early postnatal life. Stimulation in adults does not have the same effect.

Question 4: What three types of drugs are used to treat depression? What do they have in common?

Answer: The most popular antidepressant drugs include:

(1) Tricyclic compounds, such as imipramine, which block the reuptake of both norepinephrine and serotonin by transporters.

(2) SSRIs, such as fluoxetine, which act only on serotonin terminals.

(3) NE-selective reuptake inhibitors, such as reboxetine, and

(4) MAO inhibitors, such as phenelzine, which reduce the enzymatic degradation of serotonin and norepinephrine.

All of these drugs elevate the levels of monoamine neurotransmitters in the brain, but their therapeutic actions take weeks to develop.

Question 5: Psychiatrists often refer to the dopamine theory of schizophrenia. Why do they believe dopamine is linked to schizophrenia? Why must we be cautious in accepting a simple correlation between schizophrenia and too much dopamine?

Answer: According to the dopamine hypothesis of schizophrenia, psychotic episodes in schizophrenia are triggered specifically by the activation of dopamine receptors. A link between the mesocorticolimbic dopamine system and schizophrenia has been made on the basis of two main observations. The first relates to the effects of amphetamine in otherwise healthy people. Amphetamine enhances neurotransmission at catecholamine-utilizing synapses and causes the release of dopamine. An overdose may lead to a psychotic episode with positive symptoms that are virtually indistinguishable from those of schizophrenia. The second reason to associate dopamine with schizophrenia relates to the CNS effects of drugs that are effective in reducing the positive symptoms of the disorder. The neuroleptic dosages effective in controlling schizophrenia correlate well with the binding affinities of the drugs for D2 receptors. Therefore, we must be cautious in accepting a simple correlation between schizophrenia and too much dopamine. There seems to be more to the disorder than an overactive dopamine system. One indication is that newly developed antipsychotic drugs, like clozapine, have little effect on D2 receptors. Another indication is that there is more to schizophrenia than dopamine comes from the behavioral effects of phencyclidine (PCP). PCP intoxication is typically accompanied by many symptoms of schizophrenia, both positive and negative. However, PCP has no effect on dopaminergic transmission.

Question 1: What do we mean by saying that the cortex develops “inside-out”?

Answer: The first cells to be generated in the neocortex arrive in the cortical plate and become layer VI neurons, followed by the layer V cells, layer IV cells, and so on. This process repeats until all layers of the cortex have differentiated. It is because of this arrangement, where the later generated cells should migrate past the earlier generated cells to reach their destinations in more superficial layers of the cortex, that cortical development is said to be inside-out.

Question 2: Describe the three phases of pathway formation. In which phase (or phases) does neural activity play a role?

Answer: The three phases of pathway formation are pathway selection, target selection, and address selection. The growing retinal axon makes several “decisions” to find its correct target. During pathway selection, the axon chooses the correct path. During target selection, the axon chooses the correct structure to innervate. During address selection, the axon chooses the correct cells to synapse with in the target structure. Synaptic rearrangement is the final step in the process of address selection. Synaptic rearrangement occurs as a result of neural activity and synaptic transmission. Therefore, neural activity plays a role in the phase of address selection.

Question 3: What are three ways that Ca^{2+} is thought to contribute to the processes of synapse formation and rearrangement?

Answer: According to the model of synapse formation provided by the neuromuscular junction, interaction between growing axon and target occurs in both directions; induction of a presynaptic terminal involves proteins in the basal lamina. Basal lamina factors provided by

the target cell evidently stimulate Ca^{2+} entry into the growth cone, which triggers neurotransmitter release. Besides mobilizing transmitter and Ca^{2+} entry into the axon, Ca^{2+} also triggers changes in the cytoskeleton that cause it to assume the appearance of a presynaptic terminal and to adhere tightly to its postsynaptic partner. Ca^{2+} may also play a role during synapse rearrangement. A specific type of glutamate receptor, known as NMDA receptor, can only be activated when glutamate is released by the presynaptic element and the postsynaptic membrane is sufficiently depolarized to dislodge an Mg ion from the NMDA receptor. The NMDA receptor conducts Ca^{2+} ions. It is the magnitude of the Ca^{2+} flux passing through the NMDA receptor channel that specifically signals the level of pre- and postsynaptic coactivation. This occurs only when there is highly correlated activity—the necessary condition for synaptic enhancement during development.

Question 4: How are the elimination of polyneuronal innervation of a muscle fiber and the segregation of retinal terminals in the LGN similar? How do these processes differ?

Answer: The similarities are that in the process of polyneuronal innervation of a muscle fiber, eventually each muscle fiber receives synaptic input from a single alpha motor neuron. In the process of segregating retinal inputs from the two eyes, axons from the two eyes intermingle in the LGN layers at first and then segregate into the eye-specific layers characteristic of the adult nucleus. In both the neuromuscular junction and the LGN, synaptic segregation is a consequence of neural activity and synaptic transmission. Silencing neural activity disrupts segregation. On the other hand, the synapses at the neuromuscular junction and LGN use different neurotransmitters. In addition, the innervation of muscle by alpha motor neurons in the peripheral nervous system may regenerate after injury but damaged retinogeniculate

connections in the central nervous system that are established during development are permanent, and cannot regenerate.

Question 5: Not long ago, when a child was born with strabismus, the defect was usually not corrected until after adolescence. Today, surgical correction is always attempted during early childhood. Why? How does strabismus affect the connections in the brain, and how does it affect vision?

Answer: Strabismus is a common visual disorder in humans in which the eyes are not perfectly aligned. As a result, the fovea in each eye is not focused on the same point in the visual field. Ocular misalignment must be corrected in early childhood, as soon as surgically feasible, to avoid permanent visual disability. This is because strabismus prevents corresponding binocular input to cortical neurons (input from both the right and left eye to cortical neurons representing the same point in space). This noncorrespondence prevents the development of binocular cortical neurons, which are essential for stereopsis, the ability to discriminate fine differences in three-dimensional spaces. In addition, people with strabismus often favor one eye over the other. The nonprefered eye is at a disadvantage during the critical period of visual cortical development when the process of binocular competition determines which eye wins synaptic space in visual cortex. The preferred eye establishes more than its share of synaptic contacts in visual cortex, and after the critical period ends, the unequal distribution becomes permanent. Corrective surgery for strabismus during adolescence may realign the eyes, but the cortical connections will not change. Establishing the correct cortical circuitry requires that corrective surgery be done early, before the critical period for cortical development ends.

Question 6: Children are often able to learn several languages apparently without effort, while most adults must struggle to master a second language. From what you know about brain development, why would this be true?

Answer: There are critical periods for language development just as there are critical periods for sensory system development. Early in life, the brain tissue subserving language shows the same sorts of plastic changes that occur in the visual cortex, *e.g.*, changes in synaptic capacity, activity-dependent synaptic rearrangement, synaptic segregation, and synaptic competition. It is easy to imagine how these plastic mechanisms can enhance the ability to acquire language during childhood, particularly in early childhood (toddler, preschool) when children of all cultures acquire their native language. Later in life, when plasticity decreases and the critical period of language acquisition passes, language learning would rely on other mechanisms typical of learning in adults.

Question 7: Neurons that fire out of sync lose their link. Why?

Answer: In most locations in the CNS, including the visual cortex, a single synapse has little influence on the firing rate of the postsynaptic neuron. To be "heard," the activity of the synapse should be correlated with the activity of many other inputs converging on the same postsynaptic neuron. When synaptic activity consistently fails to correlate with a strong postsynaptic response, the synapse is weakened and eliminated. Synapses are weakened when the presynaptic axon is active, whereas the postsynaptic neuron is weakly activated by other inputs. This is long-term synaptic depression (LTD). The mechanism for LTD is lower levels of NMDA receptor activation and less Ca^{2+} influx. One consequence of LTD is the eventual loss of AMPA receptors from the synapse. With fewer AMPA receptors, these

synapses lose influence over responses of cortical neurons. LTD may also result in synapse elimination. Therefore, neurons that fire out of sync lose their link.

Question 1: If you try to recall how many windows there are in your house by mentally walking from room to room, are you using declarative memory, procedural memory, or both?

Answer: In trying to recall the number of windows in your house by mentally walking from room to room, you are using your declarative memory. In this case, the memory is a conscious effort pertaining to a fact. These features are typically associated with declarative memories.

Question 2: What evidence is there that declarative and nondeclarative memory use distinct circuits?

Answer: Studies support the idea that declarative and nondeclarative memories use distinct circuits. Most of these are lesion studies. For example, animals with lesions of the hippocampus or temporal lobe are unable to form declarative memories, but procedural memory is intact. Animals with lesions of the striatum are unable to form procedural memories, but declarative memory is intact. A very dramatic example of the disassociation between structures subserving the two types of memory is the renowned case of amnesia resulting from temporal lobe damage in the subject H.M. At the age of 27, H.M. had an operation in which an 8-cm length of medial temporal lobe was bilaterally excised to control seizures, including cortex, the underlying amygdala, and the anterior two-thirds of the hippocampus. The surgery controlled his seizures, but left him unable to form new declarative memories (he has remained hospitalized for over 40 years), yet his procedural memory is intact.

Question 3: What abilities and disabilities do you think a person completely lacking working memory would have?

Answer: Working memory is a temporary form of information storage that is limited in capacity and requires rehearsal. It is information held in the mind—keeping a memory alive through repetition is a hallmark of working memory—like remembering a phone number until you dial it. Working memory is commonly tested by measuring digit span. If a person lacks working memory, his inability to retain recently acquired information may cause him to duplicate the same actions over and over again. If a person is searching for some document in a set of files, the lack of working memory may cause him to keep checking the same files again and again because he cannot remember where he has already looked, and he may not be able to remember what he is looking for while he is searching the files.

Question 4: Why did Lashley conclude that all cortical areas contribute equally to learning and memory? Why was this conclusion later called into question?

Answer: American psychologist Karl Lashley conducted experiments to study the effects of brain lesions on learning in rats. He trained rats to run through a maze from start to finish without entering blind alleys. He then systematically lesioned larger and larger areas of cortex and looked at its effect on learning. He found that greater areas of cortical destruction were associated with more errors made while the rats learned to run the maze. The rats with larger lesions had difficulty remembering which arms of the maze were blind alleys. Based on these findings, he speculated that all cortical areas contribute equally to learning and memory because no single area caused a specific deficit. This conclusion was later questioned because the lesions were so large that they each damaged several cortical areas involved in learning the maze task. Another problem was that the rats may solve the maze in several different ways—by sight, feel, and smell—and the loss of one memory may be

compensated for by another. Subsequent research in this area had proven Lashley's conclusions to be incorrect.

Question 5: What evidence indicates that long-term memories are stored in neocortex?

Answer: Short-term memories are initially held in a particularly fragile form. For example, when we try to remember a phone number, an interruption can make us forget. However, long-term memory is much more robust. It can survive interruption, anesthesia, and the normal bumps and traumas that life involves. Because of this robustness, it is believed that memories are ultimately stored in structural changes in neocortex. Hebb suggested that the brain can use cortical areas for both the processing of sensory information and the storage of memories. This notion is supported by single unit recordings in area IT where neuronal responses to the presentation of monkey faces changes with repeated presentations. In addition, people with expertise distinguishing birds or cars show extrastriate visual areas that are significantly more activated by stimuli that match their expertise, as if the visual cortex is used not only to decode the information but also to store the long-term memories essential for developing expertise.

Question 6: If you were using a microelectrode to record from the brain and you suspected that a neuron you encountered was involved in storing long-term memories, how would you test that hypothesis?

Answer: If you were recording from an awake, behaving monkey, you could test the animal in a long-term memory paradigm and correlate his behavior with the output of the neuron. You could also remove the brain area and test the animal's ability to form long-term memories after the surgery. It might also be useful to apply a molecule that temporarily disabled the

neuron. The animal could be tested while the neuron was disabled and again when the molecule's effects were reversed. The behavior could then be correlated with the two conditions to determine the contribution of the neuron of interest.

Question 7: If a neuron in visual cortex responds to faces, how could you determine whether it is involved in perception or storing memories for faces?

Answer: One way to distinguish perception from memory is to watch the response pattern of the neuron after repeated presentations of the faces. If the neuron's responses are always the same, regardless of how often the stimuli are presented, it is likely to be only involved in perception. However, if the response properties of the neuron change with repeated presentations, perception cannot be its only function. If the changes are systematic, you may discover a pattern that is consistent with the formation of memories. For example, a single neuron in area IT was recorded while a subject monkey was presented with pictures of other monkeys. At first all the faces produced the same level of neuronal activity, but over time, the cell became selectively active only for certain faces. This dynamic aspect of responses in area IT supports the view that the brain can use cortical areas for both the processing of sensory information and the storage of memories. Therefore, if a neuron in visual cortex responds to faces, it may be involved in both perception and storing memories for faces.

Question 8: What are place cells, and where are they found? In what ways are the response characteristics of place cells different from the receptive fields of sensory neurons?

Answer: Place cells are found in the hippocampus. They fire maximally when an animal is in a specific location in the environment, such as the northwest corner of a box, but not when the animal is elsewhere in the box. This is the cell's place field. Other hippocampal neurons fire

maximally when the animal is elsewhere. Place cells are unlike receptive fields of sensory neurons because they fire when the animal returns to the place field even if the visual cues are absent. In addition, place cells are dynamic; that is, they change in ways to suit the current environment.

Question 9: What role does the hippocampus play in spatial memory, working memory, and relational memory?

Answer: Spatial memory is the ability to create a spatial map of the environment. Recordings from hippocampal place cells suggest a role for the hippocampus in spatial memory as these neurons fire maximally when the animal is in a specific location in his environment (northeast corner of the box). Working memory is the ability to retain recently acquired information, such as the arms of a radial arm maze in which a food reward has already been retrieved, and to use it for efficient navigation (never go down the same arm twice). The notion of relational memory tries to integrate these two processes by suggesting that highly processed sensory information comes into the hippocampus and nearby cortex, and memories are formed in a manner that links all the things happening at the time. In relational memory, neurons encode information about place as a series of simple associations between nearby objects and concurrent sounds and smells. Such memories can provide an understanding of the layout of the environment without having a complete organized map of space in the hippocampus. Eichenbaum and colleagues did odor discrimination experiments to study relational memory in rats and showed that the response of the hippocampal neurons related the specific odors, their spatial locations, and the fact that they were presented separately or together.

Question 10: What is working memory, and in what brain areas have neural correlates of working memory been observed?

Answer: Working memory is a temporary form of information storage that is limited in capacity and requires rehearsal. It is often referred to as information held "in mind." Different digit spans in different modalities suggest the presence of multiple temporary storage areas in the brain (probably cerebral cortex)—depending on the sensory system. Hippocampal lesions cause a deficit in working memory (as tested in the radial arm maze) and so do lesions of the prefrontal cortex (as tested in the Wisconsin card-sorting test). Six areas in the frontal lobe showed activity during the delay period in an fMRI study of working memory. The active areas could be separated into three groups: those active during the facial identity task alone, those active during both the facial identity and spatial memory tasks, and those active during the spatial memory task alone.

Question 1: Outline the steps involved in the presynaptic release of neurotransmitter. Why would the closure of a potassium channel in the presynaptic axon terminal change the amount of Ca^{2+} entering and change the amount of neurotransmitter released?

Answer: The membrane voltage changes during an action potential. The opening of voltage-gated sodium channels causes the rising phase, and closing of the sodium channels and the opening of the potassium channels cause the falling phase. In the axon terminal, voltage-gated calcium channels stay open as long as the membrane voltage exceeds a threshold value. The resulting entry of Ca^{2+} stimulates the release of neurotransmitter. The closure of potassium channels in the axon terminal prolongs the presynaptic action potential, widening the falling phase of the action potential. As a result, the voltage gated Ca^{2+} channels stay open longer, admitting more Ca^{2+} into the terminal, resulting in the release of more quanta of neurotransmitter. This is the molecular basis for sensitization, intensifying the response to all stimuli, even ones that previously evoked little or no reaction.

Question 2: Rabbits can be classically conditioned to blink in response to a tone. This is accomplished by repeatedly pairing the tone with an air puff to the eye. Richard Thompson and his colleagues at Stanford University have made the following observations: Learning fails to occur, and the memory is wiped out, if the cerebellum is surgically removed; the air puff activates cells in the inferior olive; the tone activates cerebellar mossy fibers. Using your knowledge of synaptic plasticity in the cerebellum, propose a mechanism for classical conditioning in the rabbit.

Answer: Classical conditioning involves associating a stimulus that evokes a measurable response with a second stimulus that normally does not evoke this response. We know that in

the cerebellum, learning occurs at the Purkinje cell dendrite, where inputs from the parallel fibers and the climbing fibers converge. This is the Marr-Albus theory of motor learning. This circuitry can also mediate classical conditioning of the eye blink response to a tone paired with a puff of air. If we know that the air puff activates cells in the inferior olive, we know that the climbing fiber input to the Purkinje cells will be carrying this information. If we know that tone activates cerebellar mossy fibers, we know that the parallel fibers will be carrying this information, because mossy fibers synapse on granule cells in the cerebellum, which give rise to parallel fibers that synapse on the Purkinje cells. If these two inputs are paired repeatedly, the air puff (stimulating the climbing fibers) and the tone (stimulating the parallel fibers) will cause long-term potentiation at the Purkinje cell dendrite where the inputs converge. LTP results when synaptic stimulation coincides with strong postsynaptic depolarization. The air puff will cause strong postsynaptic depolarization that will potentiate the input from the parallel fibers representing the tone. As a result, input from the parallel fibers alone will be sufficient to cause the response (eye blink), even though the tone previously did not elicit the eye blink.

Question 3: In Figure 25.16, the mechanisms of classical conditioning in *Aplysia* and LTD in the cerebellar cortex are compared. Expand this comparison to include LTP in the hippocampus. What would events 1 and 2 be? How do these signals converge to affect a common intracellular process? How is the synaptic change expressed?

Answer: LTP results when synaptic stimulation coincides with strong postsynaptic depolarization. In the hippocampus, event 1 would have strong stimulation to a bundle of Shaffer collaterals that synapse on a CA1 neuron. Event 2 would be postsynaptic

depolarization of the CA1 neurons, which occurs as a consequence of *many* excitatory synapses active at the same time (unlike the climbing fiber input to the cerebellum). The intracellular process responsible for LTP in the hippocampus is related to the postsynaptic NDMA receptors on the CA1 neurons (which are not present in the cerebellum). NMDA receptors conduct Ca^{2+} when only glutamate binds and the postsynaptic membrane is depolarized enough to displace Mg^{2+} ions that normally clog the channel. Ca^{2+} entry via the NDMA receptor specifically signals when the presynaptic and postsynaptic elements are active at the same time. The synaptic change is usually expressed as a change in the magnitude of the CA1 neuron's EPSP.

Question 4: What property of the NMDA receptor makes it well suited to detect coincident presynaptic and postsynaptic activity? How could Ca^{2+} entering through the NMDA receptor possibly trigger both LTP and LTD in CA1 and neocortex?

Answer: NMDA receptors have a very high affinity for glutamate, so the transmitter remains bound to the receptor for many tens of milliseconds. Both LTD and LTP are triggered by postsynaptic Ca^{2+}entry through the NMDA receptor. The key difference lies in the level of NMDA receptor activation. When the postsynaptic neuron is only weakly depolarized, the partial blocking of the NMDA receptor channels by Mg^{2+} prevents all but a trickle of Ca^{2+} into the postsynaptic neuron. On the other hand, when the postsynaptic neuron is strongly depolarized, the Mg^{2+} block is displaced entirely, and Ca^{2+} floods into the postsynaptic neuron. These different types of Ca^{2+} response selectively activate different types of enzymes. Instead of the kinases that are activated by high $[Ca^{2+}]_i$, modest and prolonged elevations in $[Ca^{2+}]_i$ activate protein phosphatases, enzymes that pluck phosphate groups off

proteins. Therefore, LTP adds phosphate groups, and LTD takes them off. High-frequency stimulation or multiply active excitatory inputs cause LTP by inducing a large elevation of $[Ca^{2+}]$. Low-frequency stimulation and minimal postsynaptic depolarization causes LTD by producing only a small elevation of $[Ca^{2+}]$.

Question 5: In H.M and R.B. (see Chapter 24), destruction of the hippocampus appears to have impaired the mechanism that "fixes" new memories in the neocortex. Propose a mechanism involving CREB explaining why this might be true.

Answer: R.B. had bilateral hippocampal damage as a result of oxygen deprivation during surgery. H.M. had most of his temporal lobes removed in an effort to control his seizures. Both instances resulted in severe anterograde amnesia. One transcription factor that regulates the process of gene expression required for memory consolidation is called the cyclic AMP response element binding protein (CREB). CREB is a protein that binds to specific DNA segments called cyclic AMP response elements (CREs). It regulates the transcription of neighboring genes. CREB-2 represses gene expression when it binds to CRE. CREB-1 activates transcription, but only when it is phosphorylated by protein kinase A. Memory consolidation can be manipulated by manipulating the availability of CREB-1 and -2. A mechanism involving CREB that blocks memory consolidation in patients such as H.M. and R.B. would require a link between the hippocampus and either an increase in CREB-2 or a decrease in CREB-1, or a decrease in CREB-1 phosphorylation. Perhaps CREB-1 phosphorylation depends on activity in the hippocampus. Phosphorylation is an intracellular process that can be initiated by second messengers in response to neurotransmission at G-

protein-coupled receptors. We can hypothesize that hippocampal activity is necessary for CREB-1 phosphorylation and thus, memory consolidation.