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.