

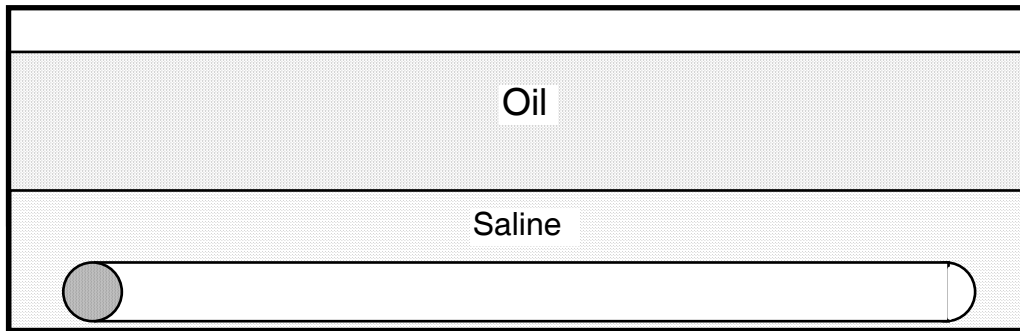
**MEDICAL & GRADUATE STUDENTS ONLY**

**Neuroscience Course Conference – 2005**

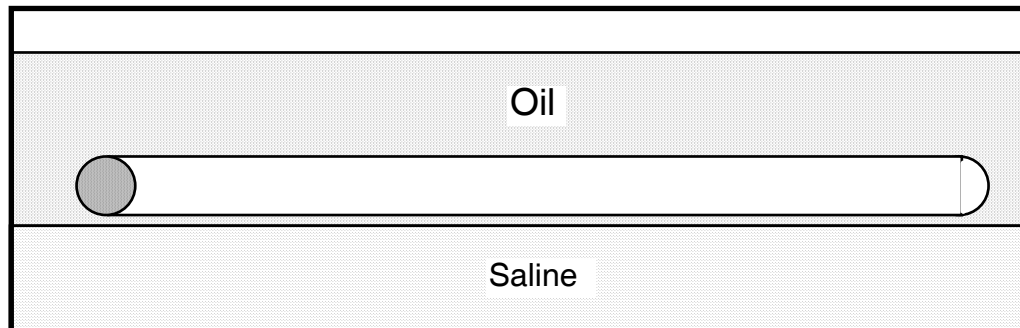
Please read these questions and think about them before the conference on "Cellular Neurophysiology". *Do not get frustrated* if you cannot answer some of the questions. They are meant to serve as discussion points that will lead you to a better understanding of the material. Thus some of them are purposefully a bit open-ended.

1. When an isolated (non-myelinated) axon was placed in bath of saline and stimulated, it conducted action potentials at 90 m/sec (A). When the same nerve was then placed in mineral oil (B), only a thin film of saline clung to the hydrophilic sheath of

**A**



**B**



connective tissue surrounding the nerve. Under these conditions, conduction velocity was reduced to 50 m/sec.

- a. What might have caused this slowing?

- b. The passive spread of current that propagates the action potential flows not only ahead of the action potential, but also behind it. Why doesn't it re-excite the axon and trigger repetitive firing?
2. In demyelinating syndromes such as multiple sclerosis, an action potential propagating into a demyelinated zone from a normally myelinated zone may fail.
  - a. What could cause this failure?
  - b. What type of drug might you try to overcome this conduction failure?
  - c. What might be the side effects of such a drug?
3. Although  $g_{Na}$  increases as a graded function of membrane depolarization (Fig. 9-6 of textbook), the action potential has a discrete voltage threshold. Why?
4. During epileptic seizures, massive synchronous bursts of activity in cortical neurons cause changes in the extracellular concentrations of  $K^+$ .
  - a. Why is the  $[K^+]_o$  concentration more likely to change significantly than the concentrations of  $[Na^+]_o$  and  $[Cl^-]_o$ .
  - b. What effects might changes in  $[K^+]_o$  concentration have on the excitability of cortical neurons?
5. The M-type voltage-gated  $K^+$ -permeant channel is a heteromeric tetramer. This channel, which is activated by depolarizations near resting potential, plays an important role in controlling spike-train encoding by neurons in the central and peripheral nervous systems. There is a clinical syndrome involving the CNS that is caused by mutations in the genes that encode the M-type  $K^+$  channels. The result of these mutations is a decrease in amplitude of the  $K^+$  current through these channels when the cell is depolarized. What might be the consequences of such a mutation for membrane excitability? What type of neurological disease might be caused by such a mutation? What type of drug might you give to try to ameliorate the symptoms?
6. Severing or damaging a peripheral nerve can sometimes lead to a chronic pain syndrome that involves the sensory field innervated by the afferent portion of that nerve. The chronic pain sensations result from an excessive excitability of the nociceptive sensory pathways activated by the damaged nerve. Recent studies using animal models have shown that nerve damage leads to increased excitation of the dorsal horn projection neurons that receive synaptic excitation from the primary nociceptive afferents and synaptic inhibition from spinal

interneurons. The chronic pain sensation results because the competition between synaptic excitation and inhibition impinging on the relay neurons is biased toward excitation, so there is an increased probability that pain signals may ascend to higher levels of the CNS where perception occurs. What cellular changes in which neurons might cause this increase in excitability? What type of drug might one try to reduce the pain?

7. You examined a patient who exhibited neuromuscular weakness. A small sample of intercostal muscle with the attached nerve trunk was removed for biopsy. You found that the end-plate potentials were sub-normal in amplitude but the miniature end-plate potentials were normal in amplitude.
  - a. Do you think the primary defect in neuromuscular transmission has a presynaptic or a postsynaptic locus?
  - b. What physiological or biochemical tests would you perform to determine the precise cause of the deficit in transmission?
  - c. What general type of pharmacological agent might you try to generate symptomatic relief of this syndrome? Why?
  - d. How would you expect the electromyogram (EMG) of such a person to behave in response to tetanic stimulation of a motor nerve? (The EMG is an extracellular recording of the entire population of individual muscle fiber action potentials.)
  
8. A dominant mutation in the gene that encodes the  $\alpha$ -subunit of the voltage gated  $\text{Na}^+$  channel in skeletal muscle has been shown to cause the mutant channels to have defective inactivation gates. In a heterozygote, approximately half of the channels are normal and the other half are in the mutant form. The mutant channels are normal, except that at any given time about 6% of them will not inactivate as quickly as they should. As a result, they will stay open longer during and following an action potential. Although only 3% of all the voltage-gated sodium channels (mutant plus wild type) are defective in gating, people expressing the mutant genes may have severe clinical symptoms. How can such a tiny minority of channels have such a large effect?
  
9. Skeletal muscle myotonia caused by  $\text{Cl}^-$  channel mutations generally has more severe symptoms in recessively-inherited homozygotes than in dominantly-inherited heterozygotes. Can you speculate as to why that might be so?

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<http://www.neuro.wustl.edu/neuromuscular/>