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Third Edition

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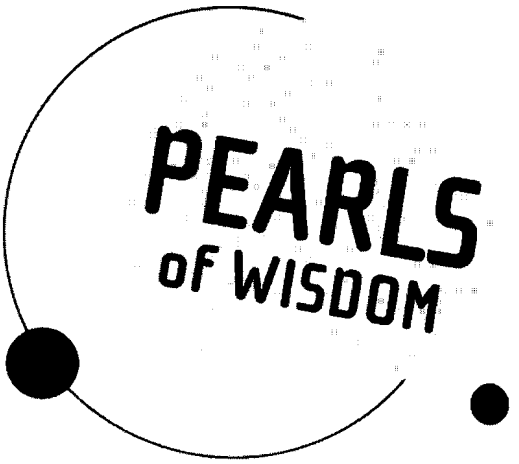
Michael Labanowski • Nicholas Lorenzo



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DEDICATION

To my wife and children, Cathy, Alex, Sawyer and Harrison,
whose love and understanding made this possible.

And to my mentors, Drs. Elliott Frank, Paul Dyken, Christian Guilleminault
and Joe Bicknell, who inspired and guided me in the pursuit of knowledge.

Michael Labanowski

To my wife, Anne, whose undying love and support I am thankful for everyday.
To my son, Adam, from whom I have learned and shared many of life's great lessons.

To my two sisters, Donna and Connie, and my many nieces/nephews from whom I derive great pleasure.
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INTRODUCTION

Congratulations! *Neurology Board Review: Pearls of Wisdom* will help you improve your knowledge base. Originally designed as a study aid to improve performance on the Neurology Boards and In-service Exams, this book is full of useful information. A few words are appropriate in discussing intent, format, limitations and use.

Since *Neurology Board Review* is primarily intended as a study aid, the text is written in a rapid-fire question/answer format. This way, readers receive immediate gratification. Moreover, misleading or confusing "foils" are not provided. This eliminates the risk of erroneously assimilating an incorrect piece of information that makes a big impression. Questions themselves often contain a "pearl" intended to reinforce the answer. Additional "hooks" may be attached to the answer in various forms, including mnemonics, visual imagery, repetition, and humor. Additional information, not requested in the question, may be included in the answer. Emphasis has been placed on distilling trivia and key facts that are easily overlooked, quickly forgotten, and somehow seem to be needed on board examinations.

Many questions have answers without explanations. This enhances ease of reading and rate of learning. Explanations often occur in a later question/answer. Upon reading an answer, the reader may think, "Hm, why is that?" or "Are you sure?" If this happens to you, go check! Truly assimilating these disparate facts into a framework of knowledge absolutely requires further reading of the surrounding concepts. Information learned in response to seeking an answer to a particular question is retained much better than information that is passively observed. Take advantage of this! Use this book with your preferred texts handy and open.

Neurology Board Review has limitations. We have found many conflicts between sources of information. We have tried to verify in several references the most accurate information. Some texts have internal discrepancies further confounding clarification.

Neurology Board Review risks accuracy by aggressively pruning complex concepts down to the simplest kernel—the dynamic knowledge base and clinical practice of medicine is not like that! Furthermore, new research and practice occasionally deviates from that which likely represents the right answer for test purposes. This text is designed to maximize your score on a test. Refer to your most current sources of information and mentors for direction for practice.

Neurology Board Review is designed to be used, not just read. It is an interactive text. Use a 3 x 5 card and cover the answers; attempt all questions. A study method I recommend is oral, group study, preferably over an extended meal or pitchers. The mechanics of this method are simple and no one ever appears stupid. One person holds this book with answers covered and reads the question. Each person, including the reader, says "Check!" when he or she has an answer in mind. After everyone has "checked" in, someone states his/her answer. If this answer is correct, on to the next one; if not, another person says their answer or the answer can be read. Usually the person who "checks" in first receives the first shot at stating the answer. If this person is being a smarty-pants answer-hog, then others can take turns. Try it, it's almost fun!

Neurology Board Review is also designed to be re-used several times to allow, dare we use the word, memorization. A hollow bullet is provided for any scheme of keeping track of questions answered correctly or incorrectly.We welcome your comments, suggestions and criticism. Great effort has been made to verify these questions and answers. Some answers may not be the answer you would prefer. Most often this is attributable to variance between original sources. Please make us aware of any errors you find. We hope to make continuous improvements and would greatly appreciate any input with regard to format, organization, content, presentation or about specific questions. We also are interested in recruiting new contributing authors and publishing new textbooks. We look forward to hearing from you!

Study hard and good luck!

M.L. & N.L.

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BASIC NEUROPHYSIOLOGY AND NEUROTRANSMISSION

L. John Greenfield, Jr., M.D., Ph.D.

❍ How are the components of a membrane like an electric circuit?

The cell membrane isolates the cytoplasm from the rest of the world. It also keeps certain charged ions inside and others outside. Membranes contain ion channels that can be opened by a voltage signal or a neurotransmitter. Since ion channels are selective conductors of ionic currents, they act like resistors. Ionic currents, like electrical currents, always flow in complete circuits. The membrane lipid bilayer acts like a capacitor because it is thin and good at separating charged particles. The distribution of ions across the membrane creates a transmembrane potential that acts like a battery, creating a driving force for ions to flow.

❍ How are ions distributed across a membrane?

Ions are distributed according to their electrical and chemical gradients. They move down the chemical gradient from areas of higher to lower concentration until the accumulation of electrical charges, which tend to repel each other, causes a transmembrane voltage gradient that balances the chemical gradient in the other direction. The point is the equilibrium potential.

❍ What determines the equilibrium potential for an ion?

Equilibrium potential is determined by the amount of that ion found on the inside and outside of the membrane, and can be calculated using the Nernst equation:

Eion = RT/ZF * log ([Ion]out / [Ion]in) = -58 mV * log ([Ion]out / [Ion]in), where Eion is the equilibrium potential, RT/F are a bunch of constants, and Z is the charge of the ion.
The equilibrium potential for potassium is very negative (about -80 mV in neurons, -90 mV in muscle cells) because there is a lot more potassium in the cell than outside. Conversely, it is very positive for sodium and calcium, for which the outside concentrations are much higher than inside. The Nernst equation predicts a 58 mV change in membrane potential for a tenfold change in potassium concentration.

❍ What determines the resting membrane potential of a cell?

Membrane potential is determined by the relative permeability (conductance) to specific ions. Most neurons and muscle cells have a high resting permeability to potassium and chloride and a low conductance to sodium and calcium ions. Thus, many neurons and muscle cells have resting membrane potentials near -70 mV. Active Na+/K+ transporters (requiring ATP) contribute minimally to the resting membrane potential, but maintain the ionic distribution of sodium and potassium. Cells with membrane potentials more negative are said to be hyperpolarized; those with less negative or positive membrane potentials are depolarized.

❍ What is Ohm's law?

Ohm's law states that V = IR (voltage equals current times resistance). Or, since conductance (g) is the inverse of resistance, V = I/g. Currents are defined as the flow of positive ions, thus, both the flow of Na+ ions into a cell and the flow of Cl- ions out of a cell would be considered inward currents.

❍ What does Ohm's law have to do with neurons?

A lot. Ohm's law helps you figure out what will happen when an ion channel opens. When voltage- or neurotransmitter-gated ion channels open, the current passing through those channels (I) is the product of the conductance of the opened channels and the driving force for that ion. The driving force is the difference between membrane potential (Em) and the equilibrium potential for the ion, Eion: I = gion * (Em - Eion).

❍ What happens to currents as it moves along a membrane?

The resistive and capacitative components (ion channels and lipid bilayer) of the membrane form an RC circuit. An RC circuit acts like a filter and attenuates current amplitude exponentially. This limits the spread of electrotonic (passively) conducted currents to short distances. Passively conducted potentials are variable in amplitude.

❍ What is an action potential?

An action potential is a self-sustaining depolarization that propagates along an axon or muscle cell resulting from the activation of voltage-gated ion channels. When a neuron or muscle cell is depolarized past a threshold, a sufficient number of channels open that the inward flow of positive ions depolarizes the adjacent areas of membrane, resulting in propagation of the potential. They are "all-or-nothing;" once past threshold, the size of the action potential does not change as it moves along the membrane.

❍ What are the ionic components of action potentials?

The inward current of most action potentials is usually carried by sodium ions, which depolarize the cell close to the sodium equilibrium potential, about +50 mV. Sodium channels open only for a few milliseconds before closing (inactivating), giving the action potential its spiky appearance. The membrane depolarization also opens voltage-gated potassium channels that remain open as long as the membrane is depolarized; potassium ions flow outward and repolarize the cell. Potassium currents persist after the closure of sodium channels, resulting in an afterhyperpolarization (since the equilibrium potential for potassium is slightly more negative than the resting membrane potential). The inward current component is sometimes carried by calcium instead of sodium ions (especially in muscle cells and dendrites). Calcium channels do not inactivate as quickly as sodium channels, so calcium action potentials are much longer lasting than sodium action potentials, up to hundreds of milliseconds.

❍ What drugs affect action potentials?

Drugs acting on sodium channels affect action potentials. Sodium channels are the target of antiepileptic drugs (phenytoin, carbamazepine, valproic acid, lamotrigine, topiramate), cardiac antiarrhythmics and local anesthetics (lidocaine). These agents block repetitive action potentials in depolarized cells. Toxic effects of these agents include diplopia (double vision), ataxia (poor coordination), and lethargy. Tetrodotoxin, from the pufferfish, and saxitoxin, a dinoflagellate toxin, also poison sodium channels and can lead to paralysis and death.

❍ What are the major classes of calcium channels?

Calcium channels include high voltage activated (L, N, P/Q, etc.) and low voltage activated (T-type) channels. These types are distinguished by their biophysical properties and toxin sensitivities. Drugs acting at calcium channels include the dihydropyridine antihypertensives nifedipine, verapamil and diltiazem. Nimodipine is a calcium channel blocker used to prevent cerebrovascular vasospasm after subarachnoid hemorrhage. Ethosuximide, an anticonvulsant used in generalized absence epilepsy, inhibits low-voltage activated (T-type) calcium channels.

❍ What diseases are caused by mutations in voltage-gated channels?

Mutations in Na+ channels are responsible for hyperkalemic periodic paralysis, paramyotonia congenita and potassium-aggravated myotonia. In the latter two, the mutations result in incomplete inactivation, leading to muscle stiffness or involuntary contraction. Hypokalemic periodic paralysis may result from mutations causing enhanced inactivation in skeletal muscle voltage-gated Ca++ channels. Mutations in potassium channels are responsible for a rare syndrome of episodic ataxia with myokymia, and a mutation in the delayed rectifier K+ channel in heart muscle is one of the causes of long QT syndrome, a cardiac conduction defect. Myotonia congenita (Thomsen's disease) may be caused by mutations in the ClC-1 chloride channel that reduce background chloride conductance.

❍ How is conduction speed of an axon related to axon diameter?

The largest diameter fibers have the fastest conduction rate (this follows from cable conduction theory). Type IA myelinated sensory afferents fibers are about 20 mm diameter and have a maximal conduction velocity of 120 m/s, while unmyelinated type IV (C-fibers) that carry pain information are about 1 micron in diameter and conduct at only 2 m/s. (That's why it takes a full second between stubbing your toe and screaming in pain!). An average value for a large myelinated nerve is about 50 m/s.

❍ What is the role of myelin in nerve conduction?

Myelin is formed from specialized glia (oligodendrocytes in CNS, Schwann cells in PNS) that wrap tightly around axons. They act as "insulation," decreasing the membrane capacitance (its ability to store electrical charge). Gaps between myelin sheaths are called nodes of Ranvier. Voltage gated Na+ and K+ channels are clustered mainly at nodes, with few channels at the "internodes" (areas covered by myelin sheaths). Myelination increases the speed of action potential propagation by making current flow jump from node to node; this is called saltatory conduction.

❍ Name some disorders of myelination in the CNS.

1. Multiple sclerosis is an autoimmune disorder of central myelin.
2. Pelizaeus-Merzbacher is a hereditary CNS demyelinating disorder caused by a mutation in myelin proteolipid protein.
3. Metabolic demyelinating diseases include metachromatic leukodystrophy (deficiency of arylsulfatase A), adrenoleukodystrophy (faulty metabolism of very long chain fatty acids) and Krabbe's globoid cell leukodystrophy.
4. Central pontine myelinolysis, a catastrophic disruption of corticospinal pathways in the brainstem resulting in a "locked-in" syndrome, occurs with overrapid correction of hypo- or hypernatremia.
5. Progressive multifocal leukoencephalopathy (PML) is a viral patchy white matter encephalopathy (due to JC virus, but associated with HIV infection).

❍ Name some disorders of peripheral nervous system myelin.

1. Guillain Barré Syndrome (GBS, a.k.a. acute inflammatory demyelinating polyradiculoneuropathy, AIDP) is an autoimmune attack on peripheral myelin, often after a viral or bacterial illness, resulting in sudden rapidly progressive weakness and areflexia. EMG shows slowing of nerve conduction and conduction block. Prognosis is worse if Campylobacter jejuni is involved. Treatment options include plasma exchanges or intravenous IgG.
2. CIDP (chronic immune demyelinating polyradiculoneuropathy) is a chronic or relapsing form of GBS. CIDP responds to steroids; GBS doesn't.
3. Charcot-Marie-Tooth is an autosomal recessive (usually) or X-linked (rarely) distal peripheral neuropathy; mutations in myelin membrane binding proteins (Po) or connexin gap junction proteins result in progressive demyelination, distal weakness and atrophy with foot drop and a "stork-like" gait. There is also an axonal form (HSMN2).

❍ How do neurons communicate?

Neurons communicate by three basic mechanisms. The most common is chemical neurotransmission at a synapse, a specialized asymmetric contact between two neurons (or a neuron and a muscle cell) in which one cell secretes a neurotransmitter and the other has postsynaptic receptors for that transmitter. Neurons can communicate via direct coupling through electrical synapses (gap junctions) that allow passage of electrical signals and small molecules without synaptic delay. Finally, a more indirect neurohumoral or endocrine form of communication occurs in which neurons secrete substances (e.g., vasopressin, oxytocin) that are more broadly distributed, often by the circulation.

❍ **Describe the mechanisms involved in chemical synaptic transmission.**

Synaptic boutons at the ends of axons contain synaptic vesicles, cytoskeletal support proteins, mitochondria, and enzymes for transmitter synthesis, transport, and degradation. When an action potential invades the bouton, voltage-gated calcium channels open, allowing calcium to enter the terminal. This promotes vesicle membrane fusion at active zones and secretion of neurotransmitters. Transmitters cross the synaptic cleft by diffusion and bind to postsynaptic receptors, which either activate ion channels or alter levels of second messengers in the post-synaptic cell. Spontaneous release of single vesicles (quanta) of transmitter result in miniature post-synaptic potentials. These "minis" can be excitatory or inhibitory, depending on the neurotransmitter and the postsynaptic receptor or channel. Action-potential-evoked release of many vesicles results in excitatory (EPSPs) or inhibitory (IPSPs) post-synaptic potentials. EPSPs and IPSPs summate over space and time in the postsynaptic cell; if the result is a depolarization past threshold, the postsynaptic cell will fire an action potential.

❍ **What happens at the neuromuscular junction?**

Acetylcholine (ACh) released from presynaptic vesicles binds to nicotinic acetylcholine receptors (nAChRs) at the postsynaptic motor end plate, opening channels permeable to both Na+ and K+ resulting in muscle depolarization. Spontaneous release of a single vesicle results in a miniature end plate potential; the summation of a large number of vesicles released by a motor nerve action potential can evoke a muscle action potential. When ACh is unbound from the receptor, it is degraded by acetylcholinesterase (AChE) at the edge of the postsynaptic cleft into choline and acetate. The choline is taken up by the presynaptic terminal where it is resynthesized into ACh by choline acetyl transferase (CAT). The extra membrane from insertion of synaptic vesicles is also taken up into clathrin-coated pits and recycled into new vesicles.

❍ **What happens when the presynaptic terminal is stimulated repeatedly?**

Repetitive stimulation can cause facilitation (increased release) due to accumulation of presynaptic Ca++, which makes vesicles more likely to be released, or depression (decreased release) when the "releasable pool" of vesicles is depleted. Which event occurs depends on the frequency of stimulation, and the type and health of the synapse.

❍ **Describe some presynaptic disorders of neuromuscular transmission.**

1. Botulism is caused by a toxin made by Clostridium botulinum, found in improperly canned foods. Botulinum toxin (Botox) impairs release of acetylcholine at neuromuscular junctions resulting in oculomotor weakness, dysphagia, and ultimately respiratory paralysis and death. Infantile botulism often comes from ingestion of spores in raw honey and represents C. botulinum infection, resulting in weak feeding, weak cries and flaccid paralysis. Botox is used in small amounts for focal dystonias.
2. Black widow spider venom promotes presynaptic release of acetylcholine, resulting in depletion of neurotransmitter, muscle spasm followed by weakness.
3. Lambert Eaton Myasthenic Syndrome is a paraneoplastic disorder usually related to small cell carcinoma of the lung (>90%) resulting in proximal muscle weakness. Antibodies against presynaptic N or L-type calcium channels block calcium entry into the presynaptic bouton, inhibiting release. Repetitive stimulation or exercise causes accumulation of presynaptic calcium, facilitation of release and transiently improved strength/reflexes. Treatment involves blockade of presynaptic K+ channels, which prolongs the presynaptic depolarization and allows more calcium to enter.
4. Tetanus toxin blocks release of inhibitory neurotransmitters at the spinal level, resulting in persistent activation of antagonist muscle groups, muscle spasms and rigidity, especially of the masseter muscles (trismus) and lip retraction (risus sardonicus).