LECTURE 17

NEUROPATHOPHYSIOLOGY

The true pathophysiological conditions that occur with the nervous system are numerous. However, for purposes of this introductory course, neuropathophysiological disruptions can be conveniently grouped into several generalized categories with each one including disorders that share basic mechanisms or etiologies. For this lecture, text readings will be included with each disorder as it is discussed.

SYNAPTIC FAILURES

Recalling the basic anatomy of chemical synapses is essential to understanding how synapses can fail and produce pathophysiological disorders. A chemical synapse requires a **presynaptic neuron** with neurotransmitter vesicles contained in and released from the axon terminal. Released neurotransmitter diffuses across the **synaptic cleft** to combine with receptors on the dendrite or cell body of the **postsynaptic cell**, which may be either another neuron or a muscle or gland cell. Neurotransmitter is then removed from the cleft by enzyme action (cholinesterase with acetylcholine) or uptake by adjacent cells. If a synapse is to fail, it is most likely to occur with the pre- or postsynaptic cell in some way.

Myasthenia Gravis

Read text pages 1087-1089 before proceeding.

Myasthenia gravis is a progressive motor disorder that may have an autoimmune origin since thymic involvement can often be demonstrated. With myasthenia the failure comes from loss of acetylcholine receptors on the postsynaptic skeletal muscle cells. It is first evident by unusually rapid fatigue of high activity muscles, such as those that control eyelid opening, speech and swallowing. It may progress to involve muscles of the extremities as well. Since it is a receptor defect, the acetylcholine that is normally released at the neuromuscular junction is inadequate to activate the few remaining receptors. The disease responds to cholinesterase inhibitors since their action allows more acetylcholine to accumulate in the synapse insuring that the limited receptors will be activated.

Muscular Dystrophy (Duchenne's)

Read text pages 843-844 before proceeding.

With this type of muscular dystrophy, the condition is genetic and is inherited as a sex-linked recessive carried on the X chromosome. Unfortunately, the condition often appears too late (around puberty) for a family to know their carrier status sufficiently early to avoid having additional children who may be similarly afflicted. The actual cause of M. D. is not completely known. Experiments have shown that the nerves supplying affected muscles are normal, ruling out any presynaptic dysfunction. Autotransplants of normal muscle into affected ones does restore function, confirming the normalcy of presynaptic neurons. The problem is apparently with the postsynaptic muscle cells. The recessive gene fails to direct the production of the muscle protein, dystrophin, which is thought to be essential for muscle contraction. Loss of muscle activity eventually leads to atrophy of the muscle with loss of muscle cells and their replacement with adipose and other connective tissues. There is no cure and the long-term prognosis is very poor.

Since the myelin sheath is essential for action potential conduction in white matter, any disruption of the myelin can interfere with the normal conduction across myelinated neurons. The most common cause of demyelination disorders is an autoimmune response.

Multiple Sclerosis (M. S.)

Read text pages 1090-1091 before proceeding.

Multiple sclerosis is thought to be an autoimmune disease resulting in disruption of conduction along myelinated neural tracts. As a result of immunological dysfunction, a type of plaque develops on the myelin sheaths of nerve tracts. The presence of the plaque interferes with action potential conduction along the affected tract. The disease is characterized by periods of remission followed by exacerbations, each with unpredictable intervals of duration and severity. Over time, the damaged tracts fail to recover completely and the deficits become permanent. The signs and symptoms of M.S. can be quite varied depending upon the tracts affected. In fact, the disease can be fatal if physiologically important pathways, such as those supplying respiratory muscles, are involved.

Guillian-Barre'

Read text pages 1089-1090 before proceeding.

Guillian-Barre' (acute inflammatory demyelinating polyneuropathy) is another immunological anomaly, probably a hypersensitivity reaction similar to an allergy. It is

not uncommon for signs and symptoms to appear after an infection, vaccination or surgical procedure. Hypersensitized lymphocytes attack and destroy the myelin of peripheral nerves particularly of the cord and facial nerve (Cranial Nerve VII). Since both anterior and posterior nerve roots can be affected, both sensory and motor deficits can occur. Deterioration usually begins low in the cord and affects the lower extremities first. As the disease progresses, it moves bilaterally up the cord toward the cranial nerves and can impair respiratory movements requiring ventilation. Autonomic nerves are not exempt and can result in serious arhythmias of the heart when involved. The prognosis is generally good with 85% of clients recovering completely in 4-6 weeks. However, in some cases death can result from respiratory impairment or emboli resulting from immobilization of lower extremities.

HYPERACTIVITY DISORDERS (SEIZURES)

Hyperactivity disorders are just as their name implies, areas of the brain of varying sizes within which neurons display bouts of hyperactivity resulting in seizures. Seizures, as well as their classification schemes, can be quite varied ranging from mild, transient "loss of attention" to the convulsions of Grand Mal epilepsy. For purposes of this course, three classes of seizure behavior will be distinguished. Post-event amnesia is not uncommon, leaving the victim with no memory of the seizure.

Read text pages 1000-1004 before proceeding.

PARTIAL seizures are the least serious of the three types. In a partial seizure, the hyperactivity is unilateral in the brain and focused in a localized area. Since different areas of the brain can be involved, the signs and symptoms can vary from a transient loss of attention to mild sensory and/or motor deficits in various parts of the body depending upon the brain region involved. Recovery is usually rapid and complete making diagnosis difficult without electroencephalographic (EEG) testing.

GENERALIZED seizures are more severe and are bilateral involving both hemispheres and greater brain areas. Behavior is often described as convulsive, but can still vary from mild to severe. These are the seizures commonly referred to as epileptic. Mild epileptic seizures are described as Petit Mal while the more severe ones are termed Grand Mal.

SECONDARY seizures are, as their name implies, secondary to some primary metabolic disturbance. The most commonly encountered secondary seizures are those resulting from electrolyte imbalances, drug withdrawal, or lesions of brain tissue from trauma or cerebral blood supply disruption as with strokes.

COMA AND DIFFUSE AXONAL INJURY (D.A.I)

Coma, or loss of consciousness, results with changes in arousal level of the brain. Arousal is a level of consciousness involving the cerebral cortex. In fact, arousal levels

can vary normally from sleep to high anxiety levels in the course of a normal day's activity. These arousal levels are controlled by brain structures deep within the cerebral hemispheres and brain stem which send action potentials to the cerebral cortex where consciousness is centered. Such activity arouses one from sleep and controls the "consciousness levels" characteristic of daily activity. These cerebral regions and their white matter tracts to the cerebral cortex are collectively termed the **Reticular Activating System (RAS)**. Injury to any part of the RAS can result in coma, the severity of which is determined by brain area involved. Some coma states resemble sleep without the characteristic REM eye movements characteristic of sleep cycling. Some situations can involve motor impairments with sensory abilities intact. With these clients, awareness of surroundings is good but they are unable to react to any stimulation. Consequently, care should be exercised as to conversational topics in casual conversation around comatose clients.

Read text pages 1024-1029 before proceeding.

Supratentorial coma results from damage to the white matter tracts leading from the tentorium of the midbrain to the cortex, Diffuse Axonal Injury, and can yield decorticate posturing. Depending upon the extent of white matter disruption, the prognosis would vary accordingly. Mild disruptions can (no guarantee) regenerate enough function for recovery while severe damage can result in a prolonged or permanent comatose states. Unfortunately, recovery is difficult to predict.

Infratentorial coma results from damage to the brain stem areas below the tentorium of the midbrain and can yield decerebrate posturing and disturbances in respiratory patterns. Since the lower brainstem is involved in Infratentorial coma, the prognosis is worse and, depending upon the cause and extent of injury, complete recovery is less likely.

ISCHEMIC DISORDERS

Again, as the title suggests, ischemic disorders result when a portion of the nervous system, particularly the brain, is deprived of its blood supply. If the deprivation is extreme or prolonged, death (**necrosis**) of brain tissue results in permanent deficits in the area affected. Since ischemic disorders of the heart are referred to as "heart attacks", the same event in the brain is now being referred to as a "brain attack" or stroke. Since strokes are cardiovascular in origin, they are often referred to as **cerebrovascular accidents (CVA's)** and can vary in both origin and severity. Mild ischemic events are termed **Transient Ischemic Attacks (TIA's)** and usually result from small blood clots lodging in small arteries of the brain. These events usually lead to complete recovery with no major deficits. However, their occurrence should be a warning that clots are forming somewhere upstream in systemic circulation and could lead to a major stroke eventually.

Read text pages 990-995 before proceeding.

HEMORRHAGIC ORIGIN involves a ruptured blood vessel with bleeding into the surrounding tissue. Such bleeding deprives tissue downstream from the broken blood vessel of its blood supply and results in its death. This stroke origin is simple to understand but difficult to manage since the bleeding must be stopped quickly to avoid more extensive damage and increased intracranial pressure.

THROMBOEMBOLIC ORIGIN requires the formation of a blood clot somewhere in the superior systemic circulation (from the left atrium to the carotid arteries). Once formed, the thrombus breaks loose (**embolus**) and migrates into cerebral arterial blood vessels until it lodges and occludes smaller branches. The occlusion stops blood supply to tissues downstream causing their subsequent deaths. The extent of damage depends upon the size of the vessel affected. The larger the artery, the greater the damage. **Atrial Fibrillation** can lead to clot formation and the potential of a major thromboembolic stroke. Additionally, **atheromatous plaque** in the carotid arteries can serve as another site for clot origin.

Regardless of whether the origin of the stroke is hemorrhagic or thromboembolic, the sequele of events that follows is important. Observing a stroke victim shows that the damage appears to worsen for several hours after the initial event. This spread of damage is termed the "**Penumbral Effect**" and involves the release of the neurotransmitter **glutamate** from dying nerve cells. Cells that die from the initial event release glutamate, which spreads to adjacent normal cells. When reaching a normal cell, the glutamate stimulates calcium channels to open allowing an influx of calcium ions into the healthy cells. Too much intracellular calcium kills these cells and they too release more glutamate causing the penumbral effect to spread like a domino effect. The prompt administration of glutamate receptor blockers or calcium channel blockers is being explored as a means to minimize this unfortunate aftereffect of strokes.

PAIN

No neuropathophysiological discourse would be complete without giving some attention to pain. Unfortunately, pain has both physiological and psychological aspects which makes its severity extremely unpredictable. Some people endure painful situations with minimal complaints while others have difficulty coping with comparatively mild pain stimuli. These differences may be perceptual and have a psychological basis or there may be physiological differences in pain thresholds. Regardless, the pain, to the individual experiencing it, is likely real and should not be taken lightly.

Read text pages 1007-1012 before proceeding.

The neurological transmission of pain begins with stimulation of specialized pain receptors, the **nociceptors**. These receptors respond to the breakdown products of injured tissue and to the chemical, thermal and/or mechanical stimuli that cause tissue damage. So, when pain is felt, tissue is being damaged. Thus, the pain sensation evolved to get individuals away from noxious stimuli that can damage tissue.

Action potentials generated by active pain receptors travel into the spinal cord along the sensory portions of peripheral nerves. Once in the cord, the nerve tracts cross over and ascend the cord contralaterally in the **anterolateral spinothalamic tracts** to the appropriate area of the postcentral gryrus corresponding to the affected body region. Since pain information travels a spinothalamic tract, it should be slow and difficult to localize. This is true for some pain, but not for all. In fact, sharp pain is well localized while dull aches appear typical of spinothalamic transmissions by being diffuse and difficult to localize. These two pain sensations can be separated into distinctly different pathways leading from nociceptors to the anterolateral spinothalamic tracts. **A-delta** fibers are small, well myelinated fibers that carry sharp, easily localized pain sensations of thermal or mechanical origins. A second fiber tract, the **C fibers**, are unmyelinated. They carry the more diffuse, aching pain sensations resulting from chemical stimulation by tissue breakdown products and some thermal sensations.

The human nervous system has a built-in system for modulating pain intensity. As the pain pathways enter the cord and/or brainstem, they can be affected by specialized neurons that release enkephalins or endorphins. These materials are naturally occurring "opiate-like" molecules that work like other opiates (e.g.- morphine) to block pain transmission pathways producing a natural analgesic effect.

REVIEW QUESTIONS:

1. Compare and contrast the pain mechanisms for a toothache and a paper cut.

2. Contrast the etiologies of myasthenia gravis and multiple sclerosis.

3. Compare and contrast localized and generalized seizures.

DISCUSSION QUESTIONS: (Post answers to the "Patho Discussion Group")

1. Compare and contrast hemorrhagic and thromboembolic strokes.

2. A comatose patient with decerebrate posturing most likely has lesions where in the central nervous system? Discuss the prognosis.