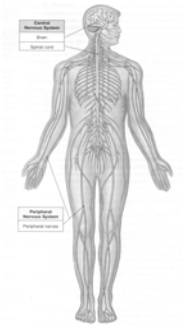
NERVOUS SYSTEM TOXICOLOGY

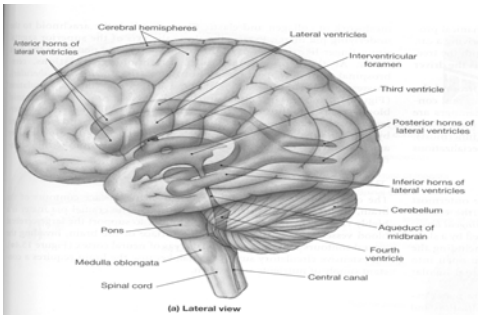
OUTLINE

- Nervous system development
- Nervous system anatomy and physiology
- Manifestations of neurotoxicity
  - Neuronopathies
  - Axonopathies
  - Myelinopathies
  - Neurotransmission-associated anomalities
- Prototypical toxicological agents
  - Methylmercury
  - Carbon disulfide
  - Lead
  - Nicotine
  - Organochlorine insectides
  - Organophosphorous insectides
  - Venoms

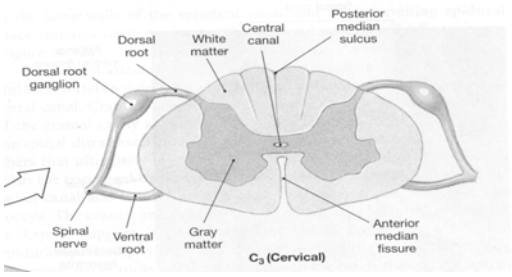
NERVOUS SYSTEM



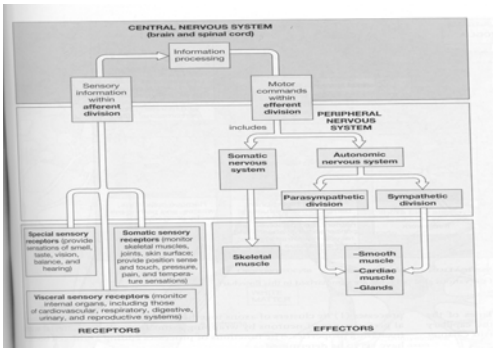
NERVOUS SYSTEM
BRAIN



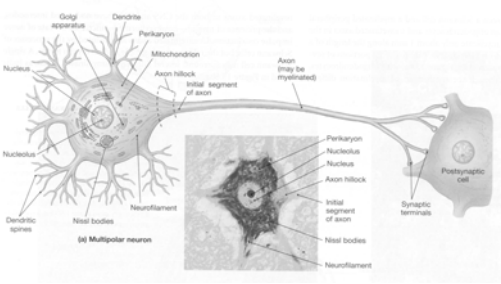
NERVOUS SYSTEM
SPINAL CORD



NERVOUS SYSTEM



NERVOUS SYSTEM ANATOMY



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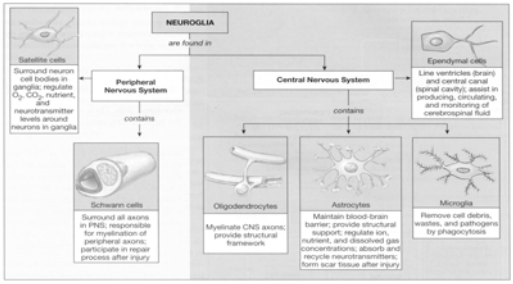

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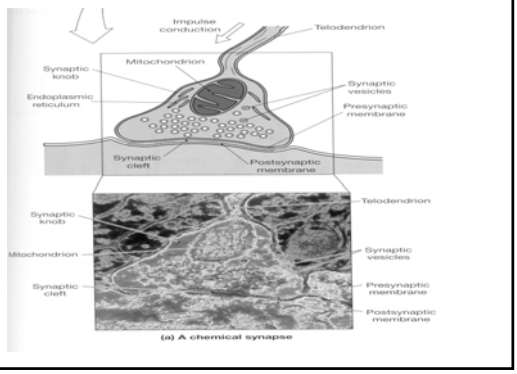
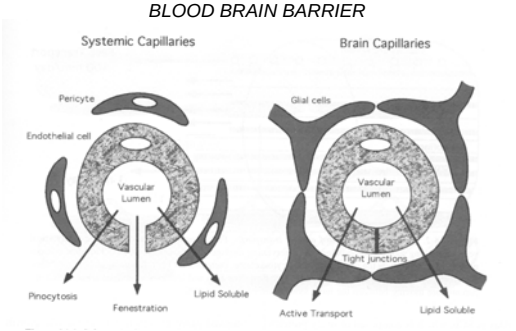


NERVOUS SYSTEM ANATOMY

BLOOD BRAIN BARRIER



MANIFESTATIONS OF NEUROTOXICITY

MANIFESTATIONS OF NEUROTOXICITY

- Neuronopathies
- Axonopathies
- Myelinopathies
- Neurotransmission-associated anomalities

MANIFESTATIONS OF NEUROTOXICITY

NEURONOPATHIES

- Injury or death to neurons
- Irreversible loss
- Initial injury followed by apoptosis or necrosis
- Caused by CO, ethanol, carbon tetrachloride, methyl mercury, lead

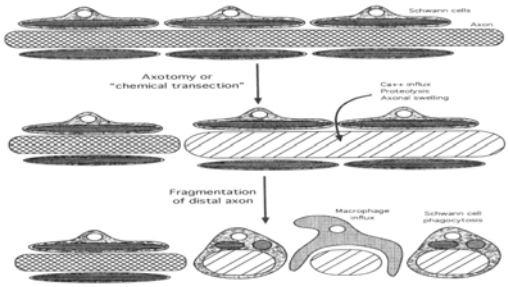
MANIFESTATIONS OF NEUROTOXICITY

AXONOPATHIES

- Primary site of toxicity is axon
- Degeneration of axon, surrounding myelin, but cell body remains intact
- Irreversible in CNS, but reversible in PNS
- Caused by CS_2, acrylamide, gold, organophosphorous esters

MANIFESTATIONS OF NEUROTOXICITY

AXONOPATHIES



MANIFESTATIONS OF NEUROTOXICITY

MYELINOPATHIES

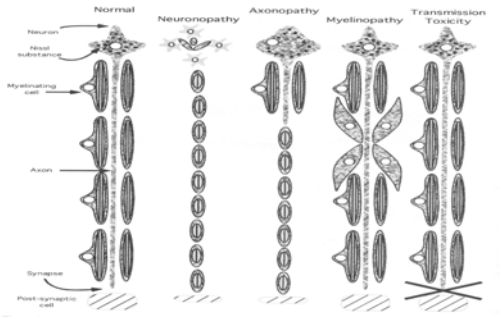
- Intramyelinic edema
- Demyelination
- Remyelination in CNS occurs to a limited extent
- Remyelination in PNS done by Schwann cells
- Caused by amiodarone, disulfiram,Pb

MANIFESTATIONS OF NEUROTOXICITY

NEUROTRANSMISSION-ASSOCIATED ANOMALITIES

- Interruption of impulse transmission
- Blockade of transsynaptic communication
- Inhibition of neurotransmitter uptake
- Interference with second-messenger systems
- Caused by nicotine, amphetamines, cocaine

MANIFESTATIONS OF NEUROTOXICITY



MERCURY

- Vapor from degassing in earth's crust
- Methylated by microorganisms to CH_3Hg
  - CH_3Hg is most significant form of Hg in terms of toxicity from environmental exposure
  - Bioconcentration in aquatic food chain
  - 90 to 95% absorption in GIT
  - Crosses placenta

MERCURY

METHYL MERCURY

- Neurotoxic effects lead to,
  - Paresthesia
  - Ataxia
  - Neurasthenia
  - Vision and hearing loss
  - Coma and death
- Neurotoxic effects due to focal necrosis of neurons

MERCURY

METHYL MERCURY

- The critical or lowest level of observed adverse health effect in adults is paresthesia
- The average long-term intake associated with paresthesia calculated to be 300 µg/day for an adult
- Poisoning therapy utilizes chelators such as cysteine, penicillamine, thiol resins

CARBON DISULFIDE

- Used in the production of viscose rayon, cellophane, pesticides, as a solubilizer for waxes and oils
- Exposure is predominantly occupational
- OSHA has established a PEL of 20 ppm as an 8-h TWA

CARBON DISULFIDE

- Direct interaction with free amine and sulfhydryl groups
- Microsomal activation to reactive sulfur intermediates that bind macromolecules
- Produce neuronal degeneration in CNS; in PNS produce myelin swelling and fragmentation

LEAD

- Ubiquitous toxic metal
- Primary route of exposure is by ingestion
- Source is from lead-based paint, contaminated drinking water, lead-glazed pottery
- Encephalopathy occurs at blood lead levels of 80-100 µg/dL

LEAD

- Symptoms of encephalopathy include lethargy, vomiting, irritability, loss of appetite, and dizziness
  - Progression of symptoms lead to ataxia, reduced level of consciousness, which may progress to coma and death
  - Recovery is often associated with life-long epilepsy, mental retardation, optic neuropathy, blindness

LEAD

- Chronic toxicity affects PNS; Schwann cell degeneration
- Mechanisms of toxicity include,
  - Impairment of cell-cell connections
  - Alterations in neurotransmitter levels
  - Disrupts calcium metabolism

NICOTINE

- Exposure from smoking
- Binds to nicotinic cholinergic receptors
  - Increase in HR
  - Elevated BP
- Acute overdose leads to excessive stimulation of nicotinic receptors leading to ganglionic paralysis

ORGANOCHLORINE INSECTICIDES

- DDT, lindane, dieldrin
- High lipid solubility, low degradation rate
- Persistence in environment, bioconcentration and biomagnification in food chains
- Produce disturbances in ion transport across axon leading to increased excitability and seizures

ORGANOPHOSPHOROUS PESTICIDES

- Malathion, parathion, “nerve gases”
- Inhibits acetylcholinesterase (AChE) leading to continuous stimulation
- Neurobehavioral, cognitive, neuromuscular disturbances
- Intermediate syndrome
- Death from respiratory distress

VENOMS

ARACHNIDA

- Scorpions, spiders
- Contain low molecular weight proteins that affect ion transport along axon
  - Impairs action potential
- Symptoms include tachycardia, respiratory distress