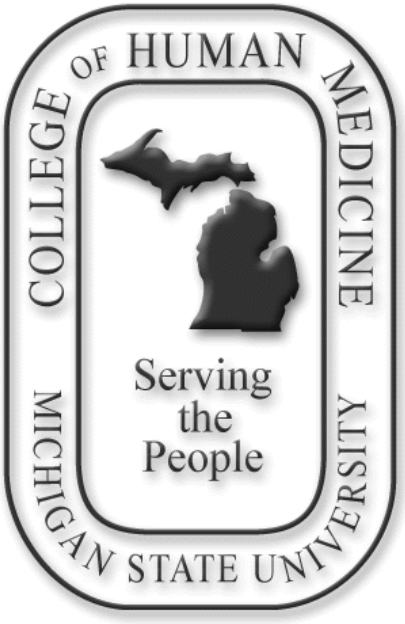
# TOXIC AND NUTRITIONAL DISORDER MODULE



**Objectives:**

For each of the following entities the student should be able to:

1. Describe the etiology/pathogenesis and/or pathophysiology, gross and microscopic morphology and distribution of the lesions whenever possible;

2. List clinical signs and symptoms

- Lead poisoning
- Carbon monoxide toxicity
- Methanol toxicity
- Wernicke's encephalopathy & Korsakoff's syndrome (thiamine/vitamin B1 deficiency)
- Subacute combined degeneration (B12 deficiency)
- Kernicterus (bilirubin toxicity)
- Hepatic encephalopathy

## I. Toxic Disorders

### A. General Concepts

Toxins include: heavy metals, certain poisons, organic compounds, drugs (of addiction and/or therapy) and anesthetics. Occasionally, the mechanism of action is clear, as in the anoxic poisons, carbon monoxide and cyanide. More often the relationship of biochemical and morphological lesions is obscure. Alcohol, for example, is a depressant drug which may cause nervous system and muscle pathology directly or through metabolites or through association with nutritional deficits.

### B. Heavy Metals

Heavy metals such as lead and mercury cause damage to the nervous system which is differently manifested in children and adults. Other toxins, both endogenous and exogenous, usually affect the nervous system with no age dependence. An important source of exposure to heavy metals is through occupational or environmental exposure.

#### 1. Lead Poisoning

Infants and children are especially vulnerable to lead toxicity. Lead exposure begins in utero because lead readily crosses the placental barrier. The developing nervous system is extremely susceptible to lead toxicity. It is estimated that over 10% of preschool children have lead levels high enough to cause intellectual impairment, behavioral abnormalities, and learning deficits. A major source of lead for children is paint chips or paint dust in homes.

##### a. Central Nervous System Effects

- Age dependence: children are more likely to show CNS effects of lead poisoning
- Locations: cerebral and cerebellar cortex
- Pathological changes: edema, white matter necrosis, vascular proliferation, glial proliferation, neuronal damage
- Clinical signs of lead encephalopathy: signs of increased intracranial pressure, seizures, ataxia, may progress to coma (acute cases); seizures, attention deficits, loss of motor skills, mental deficits, weakness, anemia (chronic cases).

##### b. Peripheral Nervous System Effects

- Location: specifically affects motor nerves
- Pathological changes: segmental demyelination early; degeneration of axons and myelin later
- Clinical signs: weakness in the distribution of affected nerves; usually distal, e.g. wrist-drop; slowed nerve conduction

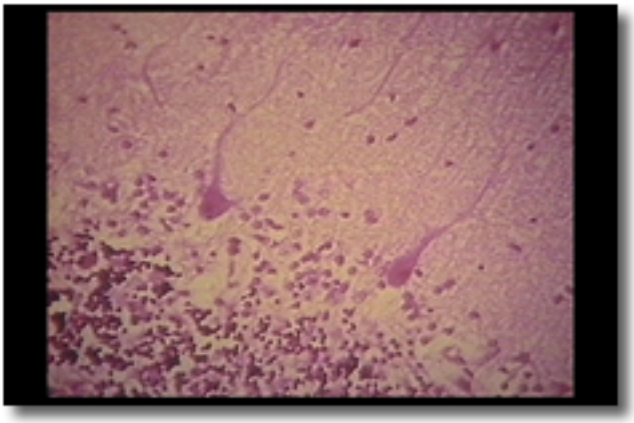
2. Other Heavy Metals

Chronic arsenic poisoning causes primarily sensory neuropathy.

Mercury has a variety of effects, including extra-pyramidal and cerebellar signs, mental fatigue, polyneuropathy

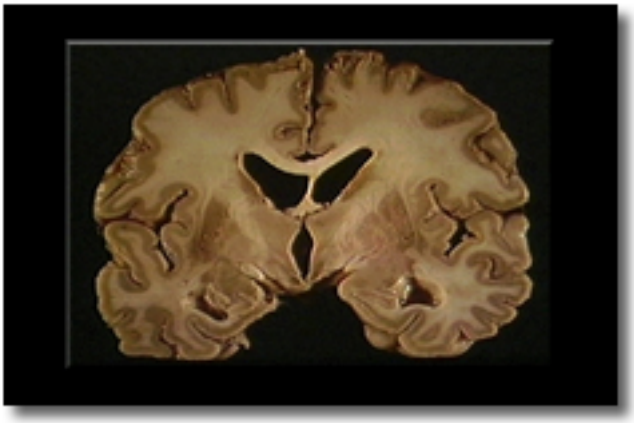
C. Carbon Monoxide

Many of the pathological changes caused by acute carbon monoxide exposure are due to hypoxia. Changes may include neuronal necrosis in cerebral cortex (laminar necrosis), hippocampus, and cerebellum (Purkinje cell death). Necrosis of globus pallidus neurons may also occur, and is more common in carbon monoxide-induced hypoxia than in hypoxia from other causes.



**TRN 01**

**Acute hypoxia typically causes eosinophilic changes and necrosis in selective populiations of neurons, including Purkinje cells in the cerebellum (shown here), pyramidal neurons in the cerebral cortex, and pyramidal neurons in the hippocampus**.



**TRN 02**

**This coronal section from a patient with hypoxia shows chronic changes due to necrosis of cerebral cortex and basal ganglia nuclei.**

D. Methanol

The pathological consequences of methanol toxicity most often occur in the retina, where degeneration of retinal ganglion cells ma cause blindness. Selective CNS changes may also occur in severe cases.

E. Ethanol

The “toxic” effects of chronic ethanol intake may be either due to direct effects of ethanol or secondary nutritional deficits. The nutritional deficits in chronic alcoholics are described below. The effects of acute ethanol intoxication are reversible.

## II. Vitamin Deficiencies

A. General Concepts

Malnutrition in general impairs both the developing and developed nervous system. A number of vitamin deficiency states, especially B vitamins, cause specific nervous system pathology. Examples of B1 and B12 deficiency states are described below. The B1 (thiamine) deficiency conditions are often associated with alcoholism and may be complicated by general malnutrition, but are ameliorated or reversed by B1.

B. Thiamine (vitamin B1) Deficiency

1. Alcoholic Polyneuropathy

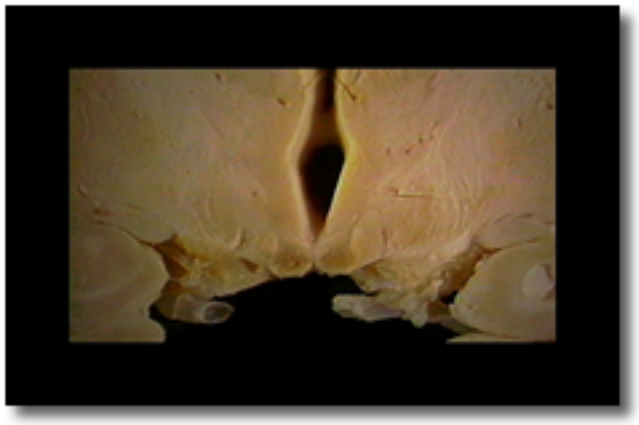
a. Clinical Signs : numbness, paresthesias, weakness; distribution depends on the specific nerves involved; both motor and sensory nerves affected, distal regions affected first

b. Pathology: degeneration of both myelin and axons with axonal reaction in anterior horn cells; posterior root degeneration with secondary degeneration of posterior columns

2. Wernicke's Encephalopathy & Korsakoff's Psychosis (Wernicke-Korsakoff syndrome)

a. Clinical Signs: Wernicke's encephalopathy: confusion, ophthalmoplegia, ataxia (classic triad of symptoms). In late stages, severe memory defects and confabulation may appear, producing Korsakoff's psychosis; the combination is referred to as Wernicke-Korsakoff syndrome.

b. Location of Lesions: hypothalamus; mammillary bodies; periaqueductal gray matter including third nerve nuclei and medial longitudinal fasciculus; floor of fourth ventricle including vestibular nuclei



**TRN 03**

**This coronal section close-up shows the mammillary bodies (bottom of picture below the third ventricle) with petechial hemorrhages in a case of Wernicke-Korsakoff syndrome.**

c. Pathological Characteristics: vascular changes, including capillary tortuosity, prominence, endothelial swelling and petechial hemorrhages; neuronal damage; macrophage response and gliosis

C. Vitamin B12 (cobalamin) Deficiency - Subacute combined degeneration

Vitamin B12 deficiency causes a typical pattern of degeneration of the white matter in the CNS that can be manifested clinically as encephalopathy, myelopathy (subacute combined degeneration of the spinal cord), peripheral neuropathy and optic neuropathy. The mechanism of action is unclear. This disorder is often associated with pernicious anemia, but administration of folic acid can mask the megaloblastic anemia caused by vitamin B12 deficiency. The primary lesion appears to be in myelin.

1. Clinical Signs: loss of position sense and other sensory deficits; lower extremity weakness, spasticity, increased deep tendon reflexes, Babinski signs

2. Location of Lesions: symmetrical degeneration of

- posterior columns of spinal cord (affected first)
- lateral columns of spinal cord

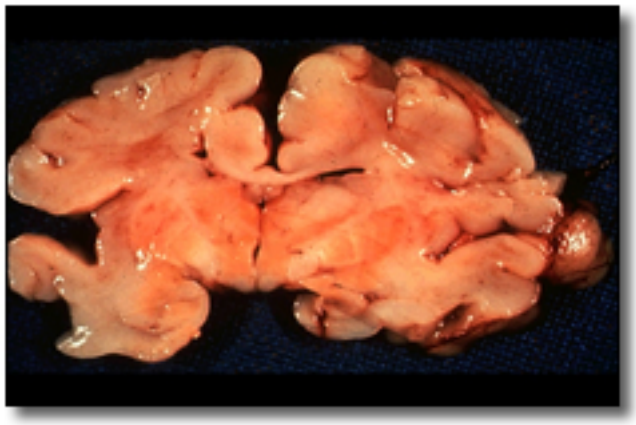
3. Pathological Characteristics: diffuse, spongy degeneration of white matter; myelin and axonal degeneration; macrophage response and gliosis

Effects involving the cerebral hemispheres may include cognitive decline and neuropsychiatric dysfunction. Pathological changes may involve white matter of brainstem, optic nerves, or cerebrum.

## III. Neurologic Sequelae of Metabolic Disturbances

A. Bilirubin Toxicity (Kernicterus)

This disorder involves yellow staining of selected grey matter structures by unconjugated bilirubin. Kernicterus is the major problem which exemplifies the toxic disorders of the newborn. A number of factors operate to produce devastation of the nervous system of the immature infant. The main source of increased bilirubin levels is hemolytic disease, but sepsis is also a cause. In the premature infant, relatively low levels of bilirubin can damage the nervous system, especially if the infant has very low albumin levels. Besides the presence of hypoalbuminemia, other insults can contribute to toxicity of low levels of bilirubin, e.g. drugs which may compete with albumin binding sites, anoxia (which increases the permeability of the blood brain barrier and leads to acidosis), and acidosis (which impairs bilirubin conjugation in the liver)



**TRN 04**

**This coronal section from a newborn with kernicterus shows the yellow staining of subcortical gray matter structures.**

B. Hypoglycemia

The cellular effects of diminished glucose are similar to those of hypoxia.

C. Hyperglycemia

Hyperglycemia is most often found in patients with inadequately controlled diabetes mellitus and can be associated with ketoacidosis or hyperosmolar coma.

D. Hepatic Encephalopathy

Hepatic encephalopathy appears to be associated with elevated blood ammonia levels, which impair neuronal function and promote generalized brain edema. Clinical manifestations include disturbances in consciousness and motor abnormalities. The cellular response in the CNS is predominantly glial.