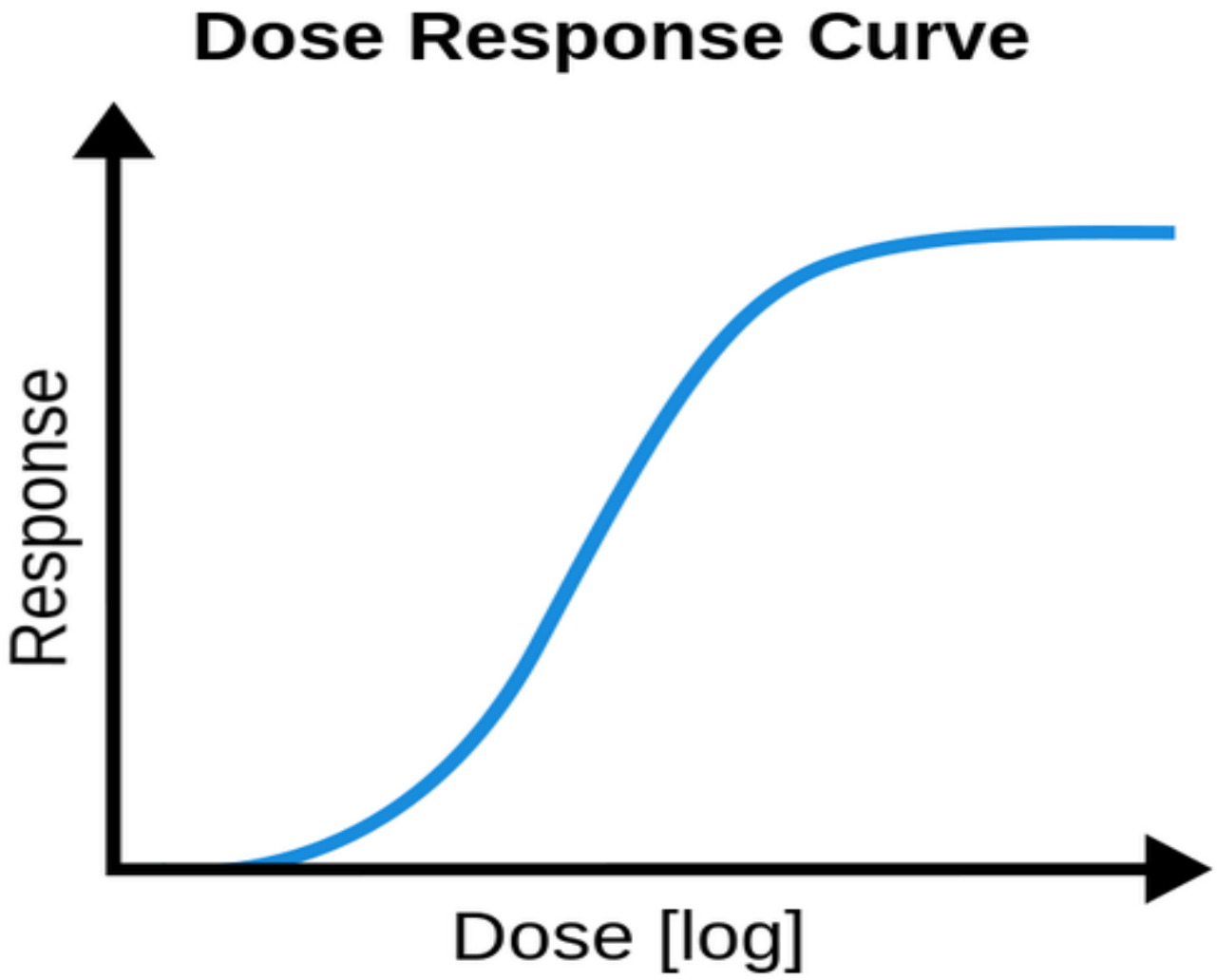
Neurotoxicology

present by: Nazanin Izadi

Associate Professor of TUMS

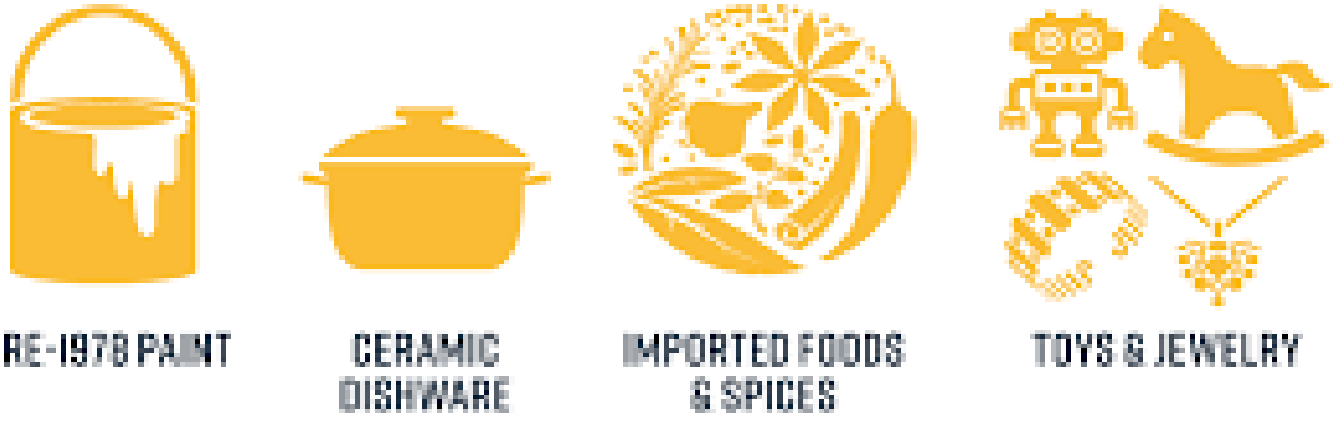
General principles:

- A dose-toxicity relationship exists in the majority of neurotoxic exposures.
- Typically :nonfocal,symmetric neurologic syndrome.
- There is strong temporal relationship between exposure and the onset of symptoms.
- In most cases recovery is possible.
- Some toxins present with a pathognomonic neurologic syndrome.


Dose Response Curve
Response
Dose [log]

Neurotoxins

lead exposure



Lead

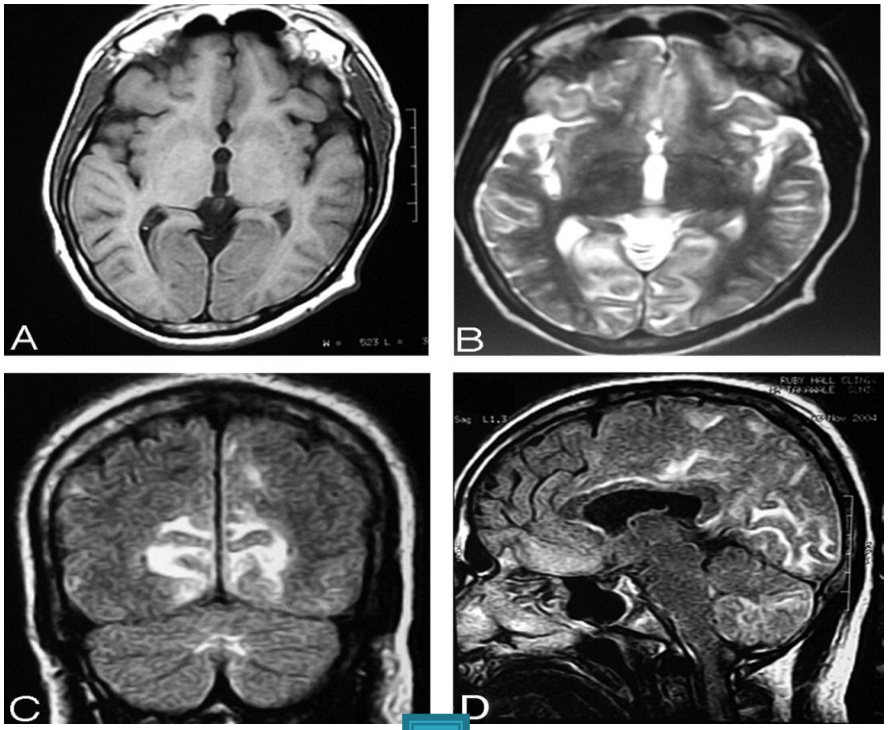
1. ***Acute high level:***

Headache, tremor, apathy, lethargy

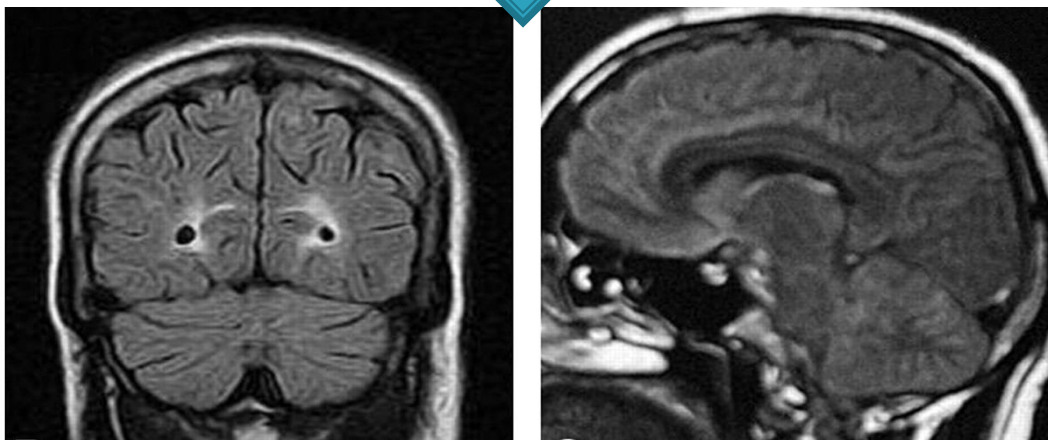
- Massive intoxication:

Lead encephalopathy: lead blood levels of> 50-70 μg/dl

convulsions ; Stupor ; cerebral edema ; coma



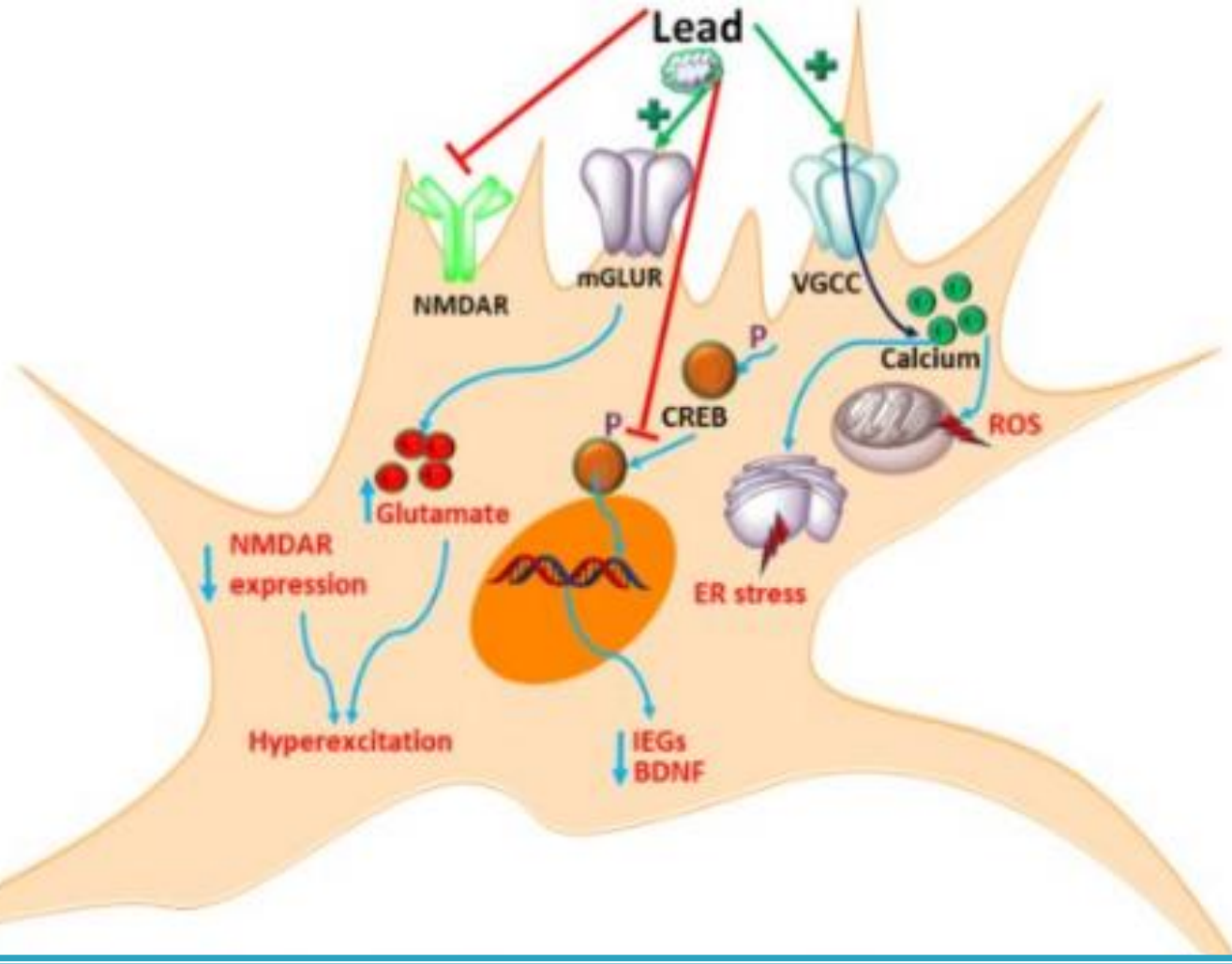
After chelation therapy



Lead

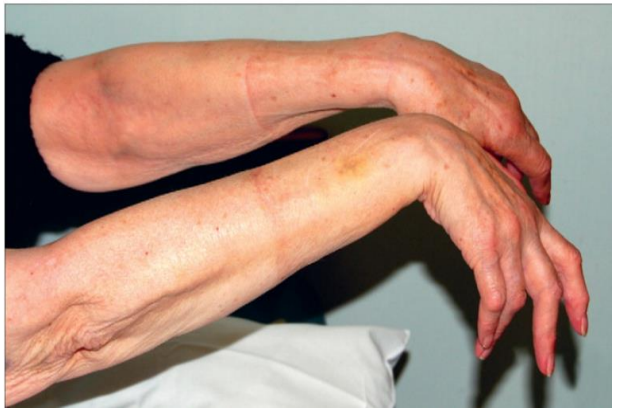
2. *Chronic low-level exposure* :

- Impaired intellectual development in children
- Decrease IQ
- Behavior disturbance,….



Neuronal stress, inflammation, apoptosis, hyper excitability and cognitive dysfunction

Lead



- Classic description:
- bilateral wrist-drop and foot-drop.

(we can also see asymmetry here)

- The best known clinical syndrome is a predominantly motor neuropathy with little if any sensory symptoms.
- Toxicity also may manifest as a generalized proximal & distal weakness and loss of DTR.
- lead level $>$ 40 μg/dl: ***Asymptomatic &*** NCV abnormalities.

Mercury

- amalgam makers, dentists
- Barometer, thermometer makers
- battery makers
- chemical laboratory workers
- chlor-alkali petrochemical workers
- fluorescent lamp makers
- gold and silver extractors
- insecticide makers

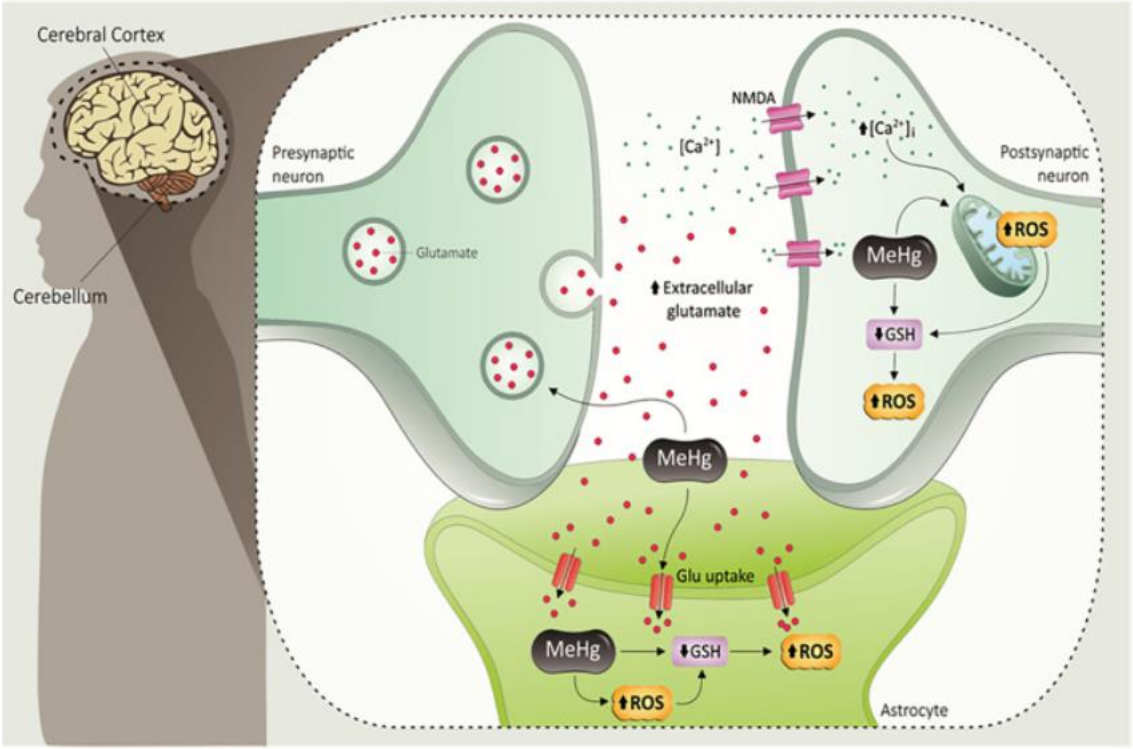
Mercury

- Mercury poisoning causes a diffuse encephalopathy:
- (euphoria,irritability,anxiety,emotional lability
- confusion, altered level of consciousness)

- *Inorganic mercury*: PNS ,Neuropathy
  Acute = Guillain-Barre syndrome
  Subacute and chronic = ALS

Organic mercury :CNS disturbances

(tremor, cerebellar ataxia, hearing Loss, visual field constriction, hyperreflexia and Babinski sign)



Arsenic

Wood preservatives, Semiconductor industry, agriculture.

- The most common manifestation of neurotoxicity(acute or chronic) : *Peripheral neuropathy*.

- Acute exp:
  acute polyneuropathy(1-3 weeks) = Guillain-Barre syn.

- Chronic exp:
  Symmetrical sensorimotor polyneuropathy
  (distal weakness>>>>proximal weakness)

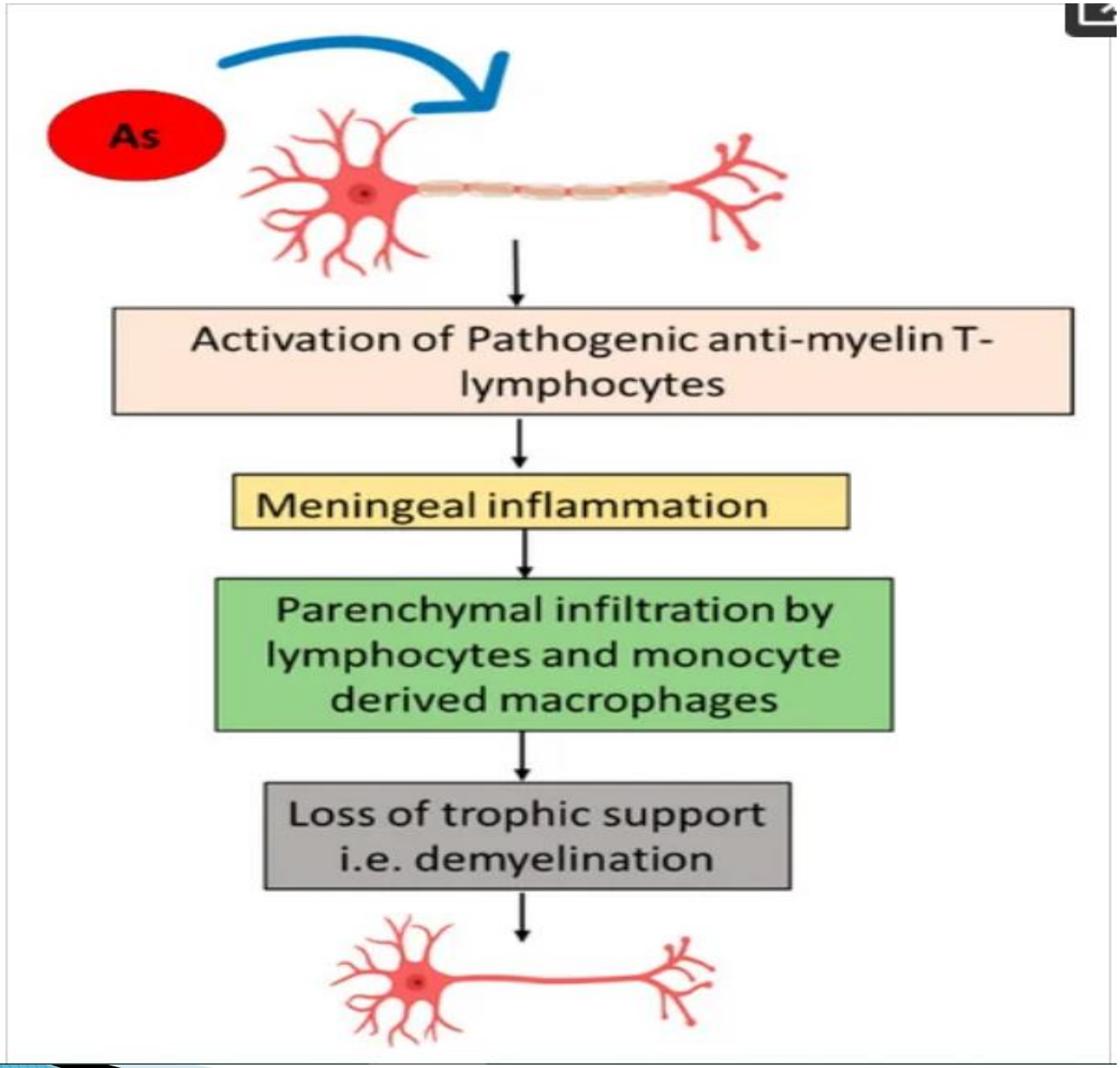
Arsenic:

- Chronic low level exposure:

-impaired memory and concentration

-lower verbal performance in child

-hearing impairment in child


As
Activation of Pathogenic anti-myelin T-lymphocytes
Meningeal inflammation
Parenchymal infiltration by lymphocytes and monocyte derived macrophages
Loss of trophic support i.e. demyelination

Manganese

- The classic syndrome: extrapyramidal disorder (idiopathic Parkinson disease)
- Compared to idiopathic Parkinson disease:

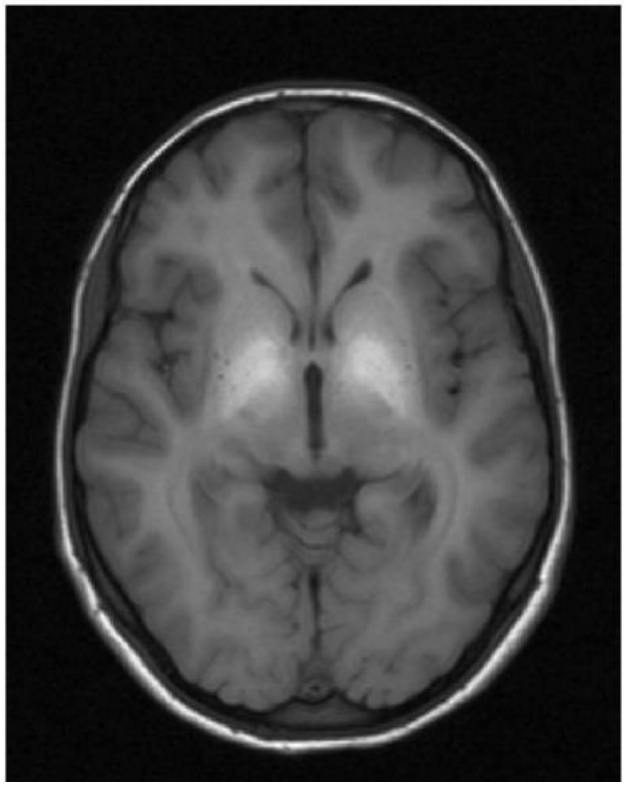
- the extrapyramidal symptoms of manganism are less responsive to dopaminergic therapy.

-neurologic deficits often continue to progress for many years after cessation of exposure.

-Brain MRI :+/_increase signal on T1 in manganese toxicity.

-In manganese toxicity psychiatric sign are before extrapyramidal sign .

T1-weighted axial MRIs of the brain showing an increased signal in the globus pallidus



Carbon Monoxide

- 0.01–0.02%: headache and mild confusion.
- 0.1–0.2%: somnolence or stupor
- 1% more than 30 minutes can be fatal.

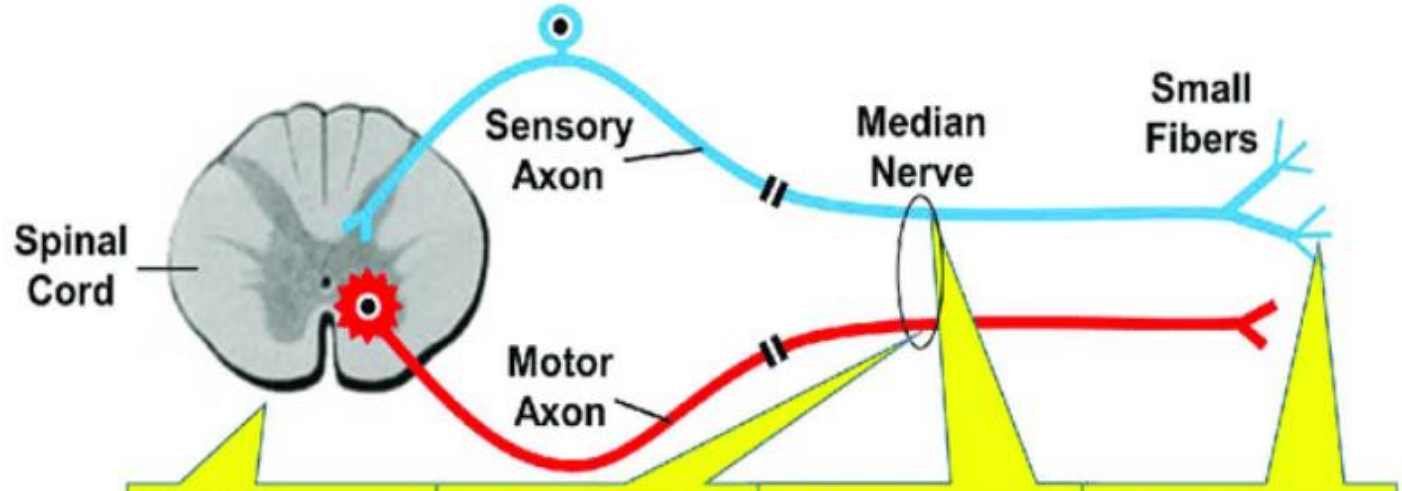
- More prolonged or severe hypoxia is accompanied by a varying combination of tremor, chorea, spasticity, dystonia, rigidity, and bradykinesia.

- PH/E may show release signs of frontal lobe and extrapyramidal dysfunction.
- Recovery in acute exposure is often 1-6 weeks later.
- Some residual memory deficits and parkinsonism are common.
- The effect of long term exposure to low levels is unclear.

Nitrous Oxide(N2O)

- *Myeloneuropathy* = *V*itamin B_{12} deficiency.
- Paresthesias in the hands and feet, Gait ataxia, sensory loss, Romberg sign.
- DTR :diminished or lost (peripheral neuropathy)
- pathologically brisk (spinal cord involvement)

- Serum vitamin B_{12} & Schilling test are often normal.
- serum homocysteine level may be elevated.
- Repeated exposures are necessary to cause symptoms.
- A brief exposure to nitrous oxide(anesthesia) is sufficient to precipitate symptoms in patients with presymptomatic B_{12} defciency.



	A. MRI T2 Hyperintensity	B. Motor Axon Dysfunction	C. Sensory Axon Dysfunction	D. Abnormal Thermal QST
N_2O Abuse	More Prevalent	More Prominent	Less Prominent	Similarly Affected
Vitamin B12 Deficiency	Less Prevalent	Less Prominent	More Prominent	Similarly Affected

Hexacarbons (n-Hexane and Methyl n-Butyl Ketone)

solvents and adhesives

- ***acute encephalopathy***
  euphoria, hallucination, and confusion.

- *Nonspecific symptoms:*
- insomnia and irritability, may be present.

Sensory loss and weakness are readily demonstrable on examination.

Achilles stretch reflexes are lost early in the disease.

The most well-known syndrome:

glue-sniffer's neuropathy

(*distal symmetric sensorimotor polyneuropathy)*

- Early symptoms are paresthesia and sensory loss. Weakness involves distal muscles initially.

- Proximal musculatures are affected in more severe cases.

- Optic neuropathy and facial numbness may present.

Organophosphates

Pesticides and herbicides

- *acute neurologic effect* :
- muscarinic and nicotinic overactivity(hours)
- abdominal pain, miosis, blurred vision, muscle fasciculations, convulsion, muscle paralysis, coma.

- *Intermediate syndrome :*
- is result of excessive cholinergic stimulation and block of neuromuscular junction(12-96h)
- weakness of proximal muscle, neck flexor, cranial muscle.

- *Delayed syndrome(*1-4W):
- paresthesia, cramping pain, spasticity.

Syndrome	Neuroanatomy	Symptoms and Signs	Examples
Acute encephalopathy	Diffuse; cerebral hemispheres	headache, irritability, disorientation, convulsions, amnesia, psychosis, lethargy, stupor and coma	Acute exposure to many **toxins** at sufficient doses
Chronic encephalopathy	Diffuse; cerebral hemispheres	Cognitive and psychiatric dis-turbances	Chronic or low-dose exposure to many **toxins**
Parkinsonism	Basal ganglia & other extra-pyramidal motor pathways	Tremor, rigidity, bradykinesia, gait instability	**Mn, CO, Methanol**
Motor neuron disease	Spinal cord motor neurons	Muscle atrophy, weakness	**Lead, manganese**
Myeloneuropathy (myelopathy & polyneuropathy)	Spinal cord & peripheral nerves	Paresthesias, sensory loss, hyperreflexia, Babinski sign,	**NO, organophosphates, n-hexane**
Polyneuropathy	Peripheral sensory, motor & autonomic nerve fibers	Paresthesias, numbness, weakness, loss of DTR, autonomic failure	Many **toxins** at sufficient doses

Toxic polyneuropathies

Mostly sensory or sensorimotor polyneuropathy
(little or no weakness)

- Acrylamide
- Carbon disulfide
- Ethylene oxide
- Metals: arsenic, lead, mercury, thallium
- Methyl bromide

- *Predominantly motor polyneuropathy or sensori-motor polyneuropathy with significant weakness:*

- Hexacarbons: n-hexane, methyl n-butyl ketone
- Metals: lead, arsenic, mercury
- Organophosphates

Cranial neuropathy:

- Thallium
- Trichloroethylene (trigeminal neuropathy)

Purely sensory neuropathy (disabling sensory loss with no weakness):

- Cis-platinum
- Pyridoxine abuse

Prominent autonomic dysfunction:

- Acrylamide
- n-Hexane (glue-sniffer)
- Thallium

THE END
Thank you