




# Neurotoxicology: Toxins in the CNS

Charles J. Vella, PhD

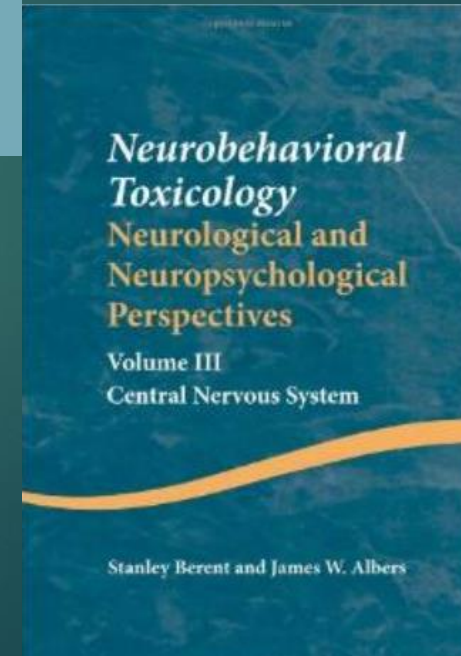
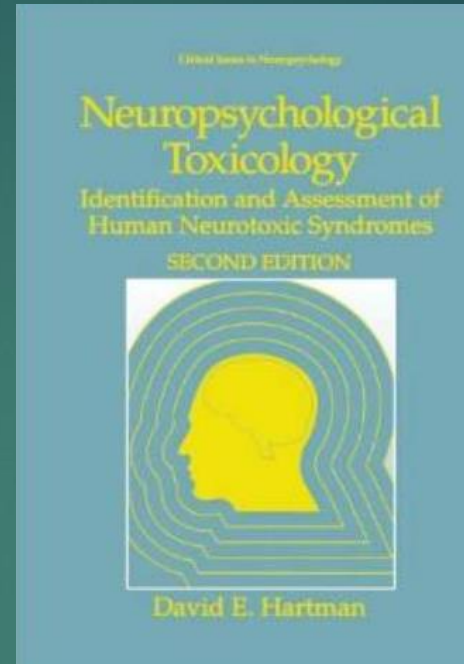
June 7, 2017

Thanks to David Hartman,  
Steven G. Gilbert, R. Singer, Lisa Morrow, et. al.



# References

- ▶ Neuropsychological Toxicology – David Hartman
- ▶ Neurobehavioral Toxicology – Stanley Berent & James Albers
- ▶ Neurotoxicity - Raymond Singer  
chapter in Little Black Book of NP
- ▶ <http://www.beyondpesticides.org/health>



# Paracelsus

- ▶ All substances are poisons;
- ▶ There are none which is not a poison.
- ▶ The dose differentiates a poison from a remedy.
  
- ▶ Example: Rat Poison = Warfarin; Digitalis/foxglove

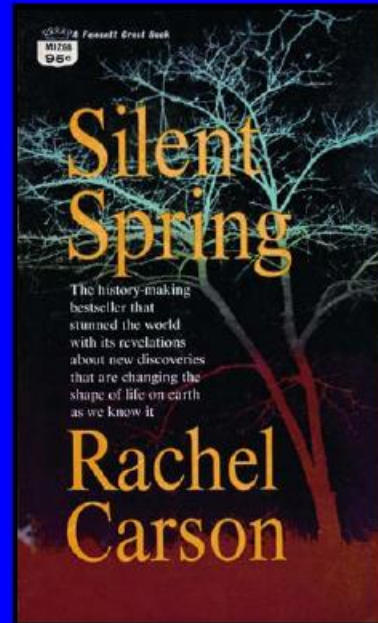
## 1930's – Ginger-Jake Syndrome

- During prohibition, an alcohol beverage was contaminated with TOCP (triorthocresyl phosphate) causing paralysis in 5,000 with 20,000 to 100,000 affected.

## 1950's – Mercury poisoning

- Methylmercury in fish cause death and severe nervous system damage in infants and adults.

# Rachel Carson, 1962: Beginning of Environmental Movement



In the lower Mississippi, fish have been dying from a cause as yet undetermined. In Oklahoma, quail are not hatching their full clutches of eggs... In Washington, representatives of a chemical company that makes endrin have testified that no "substantial" amounts of the poison enter the Mississippi from the company's plant, but, as Miss Carson pointed out in her last book, no one can yet say what a "substantial" amount of a modern poison really is.

E.B. White, The New Yorker

# Environmental Toxicants

## Environmental Toxicants

- Most recognized toxicants were discovered only as a result of an environmental disaster
- Increasing evidence linking toxicants with cognitive deficits and behavioral problems at levels previously thought to be innocuous or safe
- Increasing evidence linking toxicants with child and adolescent psychopathology
- Need to revise regulations and reduce exposures to environmental chemicals and toxicants



# Current Awareness

- ▶ “The upsurge of interest in recent years in academia, industry, and government on the effects of toxic chemicals on the nervous system has created a new discipline of neurotoxicology.”
  - ▶ Peter S. Spencer & Herbert H. Schaumborg, in Experimental and Clinical Neurotoxicology, 1980

# Neurotoxicity

“Neurotoxicity refers to the capability of inducing adverse effects in the central nervous system, peripheral nerves or sensory organs. A chemical is considered to be neurotoxic if it is capable of inducing a consistent pattern of neural dysfunction or change in the chemistry or structure of the nervous system.”



# What is Neurotoxicity?

- An adverse change in the chemistry, structure or function of the nervous system during development or at maturity, following exposure to a chemical or physical agent.
- Exposure to neurotoxic substances results in a wide range of changes in neuropsychological status due to alteration of brain function.

# Sperm Count decline

- 2017 meta-analysis of 185 studies: Developed countries (n North America, Europe, Australia and New Zealand) show evidence of a 50% reduction in male sperm count (sperm concentrations below 40 million/ml); but not in South America, Asia and Africa. A sperm concentration below this threshold is associated with a "decreased monthly probability of conception."
- A 52% decline in sperm concentration and a 59% decline in total sperm count over a nearly 40-year period ending in 2011
- Likely culprit: exposure in utero to endocrine disrupting chemicals (i.e. phthalates in plastics) can harm male reproductive system development and fertility potential. (Commonly used chemicals, including pesticides, lead and fire retardants, esp.); prenatal chemical exposure, adult pesticide exposure, smoking, stress, obesity, increasing temperature.

Hagai Levine, et al., 2017

# Manufactured Chemicals in Human Body

- ▶ Bill Moyers: 84 chemicals; Various other individuals: 105-210 chemicals: evidence of hazardous chemicals in common use – as well as compounds banned for more than a quarter century – and others so obscure that almost no public information
- ▶ In Moyers: Dioxins (meat, dairy), PCBs, Phthalates (plastics), organochlorine (DDT) & organophosphate pesticides (food crops, bug sprays), volatile organic solvents (Xylene: varnish, paint thinner)
- ▶ The majority of the synthetic chemicals used in US manufacturing today were only developed in the second half of the twentieth century.

# Seeds and Pesticides

- ▶ The world's six largest agrochemical (pesticide) manufacturers are also the largest seed industry giants.
- ▶ The "Big 6" pesticide and GMO corporations are BASF, Bayer, Dupont, Dow Chemical Company, Monsanto, and Syngenta. They are so called because they dominate the agricultural input market -- that is, they own both the world's seed and the pesticides used on the latter.
- ▶ GMO seeds often escape into the environment
- ▶ Farmers must sign agreement not to use a 2<sup>nd</sup> generation of seeds; can only use bought seeds once; Monsanto sues farmers who save seeds
- ▶ Processed foods contain 80% GMO food
- ▶ "Pesticide treadmill": need new pesticide to protect vs plant resistance to old pesticide

# US Chemical Companies: Psychopaths

- ▶ Over the last two decades, chemical companies have spent millions of dollars to thwart the implementation of the Toxic Substances Control Act (TSCA) and the EPA agency it established to regulate toxic chemicals.
- ▶ Of the 80,000 man-made chemicals that have been registered with the EPA for possible manufacturing use, some 15,000 are actually produced each year in major quantities.
- ▶ Only about 43 percent of these have ever been tested for their effects on humans.
- ▶ Nearly 25 years after TSCA was enacted, only five types of chemicals have been banned by law.

# EPA

- ▶ The Trump administration has proposed cut the EPA's budget by 31% and the NIH by 18%.
- ▶ These are the leading programs to safeguard us against toxic chemicals.



# One Big Legal Obstacle Keeps Trump from Undoing Greenhouse Gas Regulation

- ▶ But Trump officials face a major roadblock in their efforts, legal scholars say.
- ▶ It is the U.S. Environmental Protection Agency's 2009 formal "endangerment finding," which states carbon dioxide and five other greenhouse gases emitted from smokestacks and other man-made sources "threaten the public health and welfare of current and future generations."
- ▶ This agency rule, supported by two Supreme Court decisions, legally compels the government to do exactly what its new leaders want to avoid: regulate greenhouse gases.

# EPA cuts

- ▶ There are two main science advisory boards at EPA, both of which can hold significant sway over policy and regulation. The Trump administration has proposed a major weakening of both.
- ▶ "The role that science has played in the agency in the past, this step is a significant step in a different direction," he said today. "Anecdotally, based on what we know about the administrator, I think it will be science that will appear to be friendlier to industry, the fossil fuel industry, the chemical industry, and I think it will be science that marginalizes climate change science."
- ▶ A spokesman for the E.P.A. administrator, Scott Pruitt, said he would consider replacing the academic scientists with representatives from industries whose pollution the agency is supposed to regulate, as part of the wide net it plans to cast.

# Climate Change effects

- ▶ Every one of the past 40 years has been warmer than the 20th century average. 2016 was the hottest year on record. The 12 warmest years on record have all occurred since 1998. Increased CO<sub>2</sub> is the primary driver of global warming. The cause is our burning coal, natural gas, and oil
- ▶ Global warming is already having significant and harmful effects on our communities, our health, and our climate.
  - ▶ Sea level rise is accelerating; coastal flooding.
  - ▶ The number of large wildfires is growing.
  - ▶ Dangerous heat waves are becoming more common: heat waves creates serious health risks, and can lead to heat exhaustion, heat stroke, and aggravate existing medical conditions.
  - ▶ Extreme storm/hurricane events are increasing in many areas.
  - ▶ More severe droughts are occurring in others; lower groundwater supplies.
  - ▶ increased air pollution and a longer and more intense allergy season.

# Climate change

- ▶ Roll back major Obama-era regulations on climate change and clean water protection.
- ▶ In recent weeks, the agency has removed some scientific data on climate change from its websites, and Mr. Pruitt has publicly questioned the established science of human-caused climate change.
- ▶ In his first outings as E.P.A. administrator, Mr. Pruitt has made a point of visiting coal mines and pledging that his agency will seek to restore that industry, even though many members of both of the E.P.A.'s scientific advisory boards have historically recommended stringent constraints on coal pollution to combat climate change.

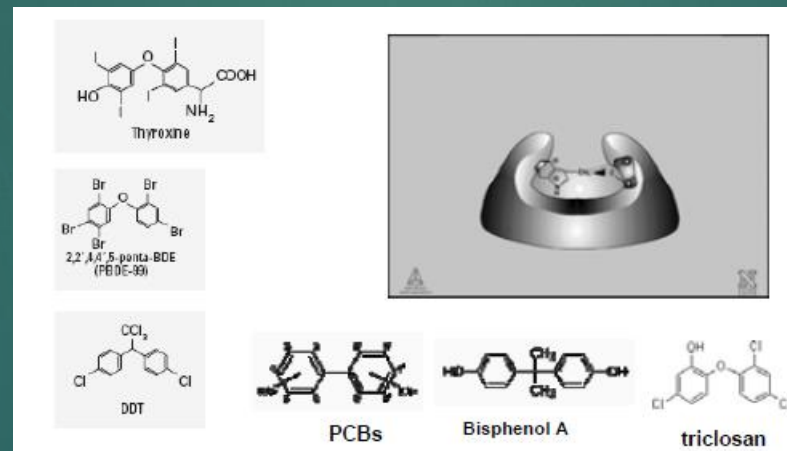
# Chemical Body Burden

- ▶ Each of us has some load of industrial chemicals stored in or passing through our bodies. These chemical residues – termed the "chemical body burden" – can be detected in blood, urine and breast milk. Most people are unaware that they carry chemical compounds in their bodies.

The health effects of chronic exposure to low levels of chemicals are only beginning to be studied.

- ▶ In addition, scientists have never assessed the effects of exposures to the endless combinations of chemicals found in people.
- ▶ All animals on earth are contaminated.

# Chemicals that look like a hormone may fit in it's receptors: Estrogen like chemicals



Went to a movie this week. Theater had Bisphenol A warning about canned soda drinks.



# BPA (Bisphenol A) = weak estrogen

## CDC finds BPA in 92% of Americans children > adults



Over 50% of canned goods on US market shelves are lined with BPA resin. It is not possible to identify the BPA lining via visual inspection.



- BPA acts as a weak estrogen in animals and probably does so in humans as well.
- It has chemical properties similar to estradiol and can impact biological systems in very low dose.
- In animals, prenatal exposures lead to changes in behavior including hyperactivity, increased aggression, impaired learning



Can contain Bisphenol A

BPA is the starting material for making polycarbonate plastics. Any leftover BPA that is not consumed in the reaction used to make a plastic container can leach into its contents.

# BPA: Don't handle thermal paper

- ▶ BPA (bisphenol-A) is a potentially toxic estrogen-mimicking compound used in plastic production that has been linked to breast & prostate cancer, early puberty, infertility, ADHD and other maladies. Banned in baby bottles in Europe, Canada, China—but not in the U.S. FDA refuses to ban it
- ▶ 95 per cent of Canadians have measurable levels of BPA in their blood or urine, with the highest levels found in children.
- ▶ Plastic baby and water bottles; DVDs
- ▶ 50% of all food can liners (soda, coconut milk, soup, meat, vegetables, meals, juice, fish, beans, meal-replacement drinks, and fruit )

# BPA 2

- ▶ Plastic food storage containers (for leftover food)
- ▶ Retail outlet print sales receipts (thermal paper); Hand Sanitizer Speeds Absorption of BPA From Receipts; All Cash if you keep receipts in wallet
- ▶ Only way to avoid: eat only fresh food, drink tap water (or glass/steel cup), avoid anything canned, don't use plastic coffee makers, don't eat off of plastic, keep plastic out of the freezer, microwave and dishwasher (BPA leaches if hot or cold)

# BPA level & Meningiomas

- ▶ Those with the highest urine BPA levels were about 1.6 times more likely to be diagnosed with meningioma compared to those with lower concentrations.

- ▶ Duan, B, X Hu, H Zhao, J Qin and J Luo. 2012. **The relationship between urinary bisphenol A levels and meningioma in Chinese adults.** *International Journal of Clinical Oncology* <http://dx.doi.org/10.1007/s10147-012-0408-6>.

# BPA-S

- ▶ Replacement for BPA-A, BPA-S is equally bad in relation to estrogen mimicry
- ▶ Chemical mimics estrogen and could harm brain and reproductive development in fetuses, infants and children
- ▶ Nearly 81 percent of Americans have detectable levels of BPS in their urine.
- ▶ Currently, no federal agency tests the toxicity of new materials before they are allowed on the market.
- ▶ Almost all of the 455 commercially available plastics that were tested leached estrogenic chemicals.

# Children's Environmental Health Center (CEHC) at Mt Sinai School of Medicine

- ▶ A large number of the chemicals in widest use have not undergone even minimal assessment of potential toxicity. Knowledge of environmental causes of neurodevelopmental disorders is critically important because they are potentially preventable.
- ▶
- ▶ CEHC developed the list of ten chemicals found in consumer products that are suspected to contribute to autism and learning disabilities to guide a research strategy to discover potentially preventable environmental causes.
- ▶ The top ten chemicals are:
  - ▶ 1. Lead
  - ▶ 2. Methylmercury
  - ▶ 3. PCBs
  - ▶ 4. Organophosphate pesticides
  - ▶ 5. Organochlorine pesticides
  - ▶ 6. Endocrine disruptors i.e. PBA
  - ▶ 7. Automotive exhaust
  - ▶ 8. Polycyclic aromatic hydrocarbons
  - ▶ 9. Brominated flame retardants
  - ▶ 10. Perfluorinated compounds



# Historical Sources

- ▶ Drug-induced neurotoxicity
- ▶ Occupational toxins
- ▶ Environmental toxins
- ▶ > 100 000 chemicals in use, 2000 new chemicals / year; yet minority tested for neurotoxicity (+/- 800 recognized neurotoxins)
- ▶ 850 chemicals identified as capable of producing neurobehavioral disorders: solvents, metals, pesticides, carbon monoxide, mold

# Nervous System is Vulnerable

- ▶ Large surface area with high lipid content
  - Chemical exposures are intensified and prolonged
- ▶ High metabolic demand
  - Low reserve for oxidative stress
- ▶ Limited capacity for regeneration
  - Severe damage can be irreversible

# History of discovery of neurotoxins

- ▶ Agni and Hera
  - Carbon monoxide
- ▶ Natural neurotoxins used since antiquity
  - Ethanol, datura, curare (arrow poison)
- ▶ Metals were the first industrial neurotoxins
  - Lead, mercury, arsenic
- ▶ First organic neurotoxicants from alchemic studies
  - Coal tar pitch derivatives: CS<sub>2</sub>, benzene
- ▶ World War II
  - Organophosphate pesticides and nerve gases
- ▶ Iatrogenic neurotoxicity
  - Pharmaceuticals

# What causes neurotoxicity?

Wide ranged of agents  
– chemical and physical

Fetal Nervous System

Developing Nervous System

Mature Nervous System

Aging Nervous System

# Occupational Neurotoxicity

- ▶ Over 70,000 registered industrial chemicals
- ▶ Millions of workers are exposed each year
- ▶ Exposure limits often set by neurotoxicity
- ▶ Neurotoxicity is not always evaluated



# Big Four

- ▶ Solvents – Alcohols, n-Hexane, TCE, CS<sub>2</sub>
- ▶ Metals – Lead, Mercury, Arsenic, Manganese, Copper
- ▶ Pesticides – Organophosphates, Carbamates, Pyrethroids (RAID), Nicotinics
- ▶ Mold
- ▶ Each can have multiple neurotoxic effects

# Neurotoxicity Exposure Routes

- Inhalation (e.g. solvents, nicotine)
- Ingestions (e.g. lead, alcohol)
- Skin (e.g. pesticides, nicotine)
- Physical (e.g. load noise)

# Acute Toxidrome

- ▶ A toxidrome is a syndrome made of symptoms and signs consistent with specific groups of drugs and chemicals.
- ▶ Anti-cholinergic      Tricyclics
- ▶ Pro-cholinergic      Organophosphates
- ▶ Sympathomimetic      Amphetamines
- ▶ Serotonergic      SSRIs
- ▶ Anti-dopaminergic      Antipsychotics
- ▶ GABAergic      Benzos, Barbs
- ▶ Opioid      Methadone, heroin

# Common Symptoms

## Central Nervous System

Cognitive change

Seizure

Movement disorder

Ataxia, incoordination

## Peripheral Nervous System

Weakness

Sensory abnormality

Pain

## Autonomic Nervous System

Blurred vision

Sweating

Nausea

# Neuropsychological Results

- ▶ Following exposure, impairment on NP tests is typically diffuse
- ▶ Alterations in memory, learning, attention, VS ability, motor speed, executive functions.
- ▶ Psychological: anxieties, depression, mood swings, irritability, delirium or delusions

# Manifestations of Neurotoxicity



# Manifestations of Neurotoxicity

- ▶ • Neuronopathies
- ▶ • Axonopathies
- ▶ • Myelinopathies
- ▶ • Neurotransmission-associated anomalies

# Neuronopathies

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

# Axonopathies

- ▶ Primary site of toxicity is axon
- ▶ Degeneration of axon, surrounding myelin, but cell body remains intact
- ▶ Irreversible effects in CNS, but reversible in PNS
- ▶ Caused by CS<sub>2</sub>, acrylamide, gold, organophosphorous esters, Hexane, Acrylamide

# Myelinopathies

- ▶ Intramyelinic edema
- ▶ Demyelination (Damage to myelin (e.g. Schwann cells))
- ▶ Remyelination in CNS occurs to a limited extent
- ▶ Remyelination in PNS done by Schwann cells
- ▶ Caused by amiodarone, disulfiram, lead, hexachlorophene

# Neurotransmission-Associated Abnormalities

- ▶ Interruption of neurotransmission
- ▶ Blockade of transsynaptic communication
- ▶ Inhibition of neurotransmitter uptake
- ▶ Interference with second-messenger systems
- ▶ Caused by nicotine, amphetamines, cocaine, organophosphate pesticides, DDT

# Examples of Neurotoxicology

## Diseases

Parkinson's, Alzheimer's, MS, ALS

## Environmental

Lead, Methylmercury, PCBs

## Occupational

Solvents, Pesticides

## Drugs - Clinical

Vincristine, cisplatin

## Drugs - Social

Alcohol, cocaine, nicotine



# Neurotoxic Effects

## Cognitive Effects

- memory, learning, confusion

## Motor Effects

- weakness, convulsion, paralysis

## Sensory Effects

- vision, auditory, touch, balance

## Mood and Personality Effects

- sleep, depression, irritability, excitability

## General Effects

- loss of appetite, fatigue

# Classification of neurotoxicants by mechanism of action

## Temporary inhibition of nerve function

- Agents which alter membrane function
- Agents which interfere with synaptic transmission

# Neuronal Physiological Sensitivity

- Dependence on oxygen
  - Little anaerobic capacity
  - CO – less available oxygen
  - Cyanide – inability to use oxygen
- Dependence on glucose
  - Sole energy source
- High metabolic rate

# Reversibility of Damage

Neurons CANNOT divide and replace themselves

Neurons CAN repair limited axonal damage

Most Recovery

- Redundancy of Function
- Plasticity of Organization

# Classification of neurotoxicants by mechanism of action

## Permanent inhibition of nerve function

- Agents which cause Anoxia
  - Anoxic anoxia
  - Ischemic anoxia
  - Cytotoxic anoxia
- Agents which damage myelin formation
  - Oligodendroglia (CNS)
  - Schwann cells (PNS)
- Agents which damage peripheral axons
- Agents which damage nerve cell body
- Agents which cause localized CNS lesions

# Neurological and Behavioral Effects of Exposure to Toxic Substances

**Motor Effects** - Convulsions, weakness, tremor, twitching, lack of coordination, unsteadiness, paralysis, reflex abnormalities, activity changes

**Sensory Effects** - Equilibrium changes, vision disorders, pain disorders, tactile disorders, auditory disorders

**Cognitive Effects** - Memory problems, confusion, speech impairment, learning impairment

**Mood and personality effects** - Sleep disturbances, excitability, depression, irritability, restlessness, nervousness, tension, delirium, hallucinations

**General effects** - Loss of appetite, depression of neuronal activity, narcosis stupor, fatigue, nerve damage



# Neurotoxicity Outcomes

## Neurotoxicity Outcomes

reported for >25 chemicals out of 750  
(Anger and Johnson, 1985)

| <u>Motor</u>     | <u>Sensory</u>    | <u>Cognitive</u> | <u>General</u> | <u>Affect/<br/>Personality</u> |
|------------------|-------------------|------------------|----------------|--------------------------------|
| Activity changes | Auditory          | Confusion        | Anorexia       | Apathy                         |
| Ataxia           | Equilibrium       | Memory           | Autonomic      | Delirium                       |
| Convulsions      | Olfactory         | Speech           | ChE inhibition | Depression                     |
| Incoordination   | Pain disorders    |                  | CNS Depression | Excitability                   |
| Paralysis        | Pain, feelings of |                  | Fatigue        | Hallucinations                 |
| Pupil size       | Tactile           |                  | Narcosis       | Irritability                   |
| Reflex abnormal  | Vision            |                  | Neuropathy     | Nervousness                    |
| Tremor           |                   |                  |                | Restlessness                   |
| Weakness         |                   |                  |                | Sleep disturbed                |

# Effects of Neurotoxicants

## Epidemiological Research findings: Some Effects of neurotoxicants

- Lower IQs
- Hyperactivity/ effects on attentional behaviours
- Less able to self-quiet (newborns)
- More startles and altered reflexes (newborns)
- Smaller head circumference (newborns)
- Lower scores on tests of learning and attention
- Lower scores on tests of visual memory, verbal abilities
- Less cooperative/ play
- Inability to catch a ball/ draw a person
- motor coordination and balance
- More aggressive
- Heightened responses to stress or disappointments
- Effects on motivation (experimental research)

# Neurotoxicity Syndrome

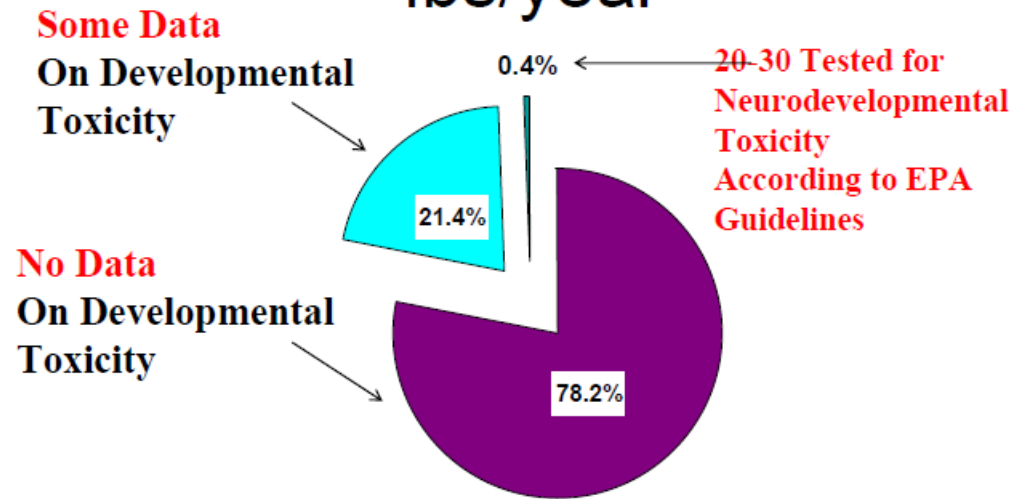
- ▶ Attention/concentration deficit: more distractibility
- ▶ Learning/memory deficit: acquisition difficulty
- ▶ Cognitive and psychomotor speed slowing: “brain fog”
- ▶ Language: word finding, effortful speech
- ▶ Executive dysfunction

# Neurotoxicity Syndrome 2

- ▶ Emotional: irritability, depression, anxiety, social withdrawal
- ▶ Neurological: HA, chronic fatigue, temperature dysregulation, motor dysfunction, photophobia, sleep disturbance
- ▶ Peripheral neuropathy
- ▶ *Neurotoxicity Screening Survey* (Singer 1990)

# Developmental Toxicity Testing: Little to None

## Developmental Testing of 2,863 Chemicals Produced > 1 million lbs/year



# Neurotoxicity

- ▶ 5000 new chemicals/year
- ▶ EPA estimate: 25% neurotoxic
- ▶ High vulnerability of the developing brain
- ▶ >200 chemicals known to cause neurotoxic effects in adults



# Neurodevelopmental toxicants

## Known neurodevelopmental toxicants- prenatal or early-life exposure

Includes certain :

- Classes of NT Pesticides – e.g. ACH is a target enzyme of major classes of pesticides– also regulates CNS neuronal growth, differentiation, and plasticity
- Solvents (eg trichlorethylene , styrene, acetone, xylene, phenols)
- Dioxins and PCBs
- Metals (lead, methylmercury, cadmium, manganese, aluminum)
- Alcohol; toluene; arsenic
- Nicotine (e.g. smoking in pregnancy/passive smoke)
- X-irradiation
- Drugs of abuse – e.g. cocaine, methamphetamine
- Drugs (e.g. phenytoin (Dilantin) ; isotretinoin (Accutane)

# Chemicals of Concern

## Additional Chemicals of Concern

- Food additives (MSG, ASP, food dyes and additives)  
17 of 23 studies positive for neurobehavioural effects)
- Fluoride; 2,4- D; pyrethroids, carbamates, etc.
- Trichlorethylene
- PBDEs (brominated fire-retardants)
- Chemicals that interfere with hormones e.g. have anti-thyroid actions, or affect sex hormones and sex differentiation in the brain
- 200-300 industrial chemicals known to cause clinical toxic effects in adults (Lancet article 2006)
- Perfluorinated chemicals (water and grease repellants)

## Ancient Awareness

“Lead Makes the Mind Give  
Way”

Dioscorides – Greece, 2 BC

Once lead enters the body, very little one can do.

# Clean water crisis

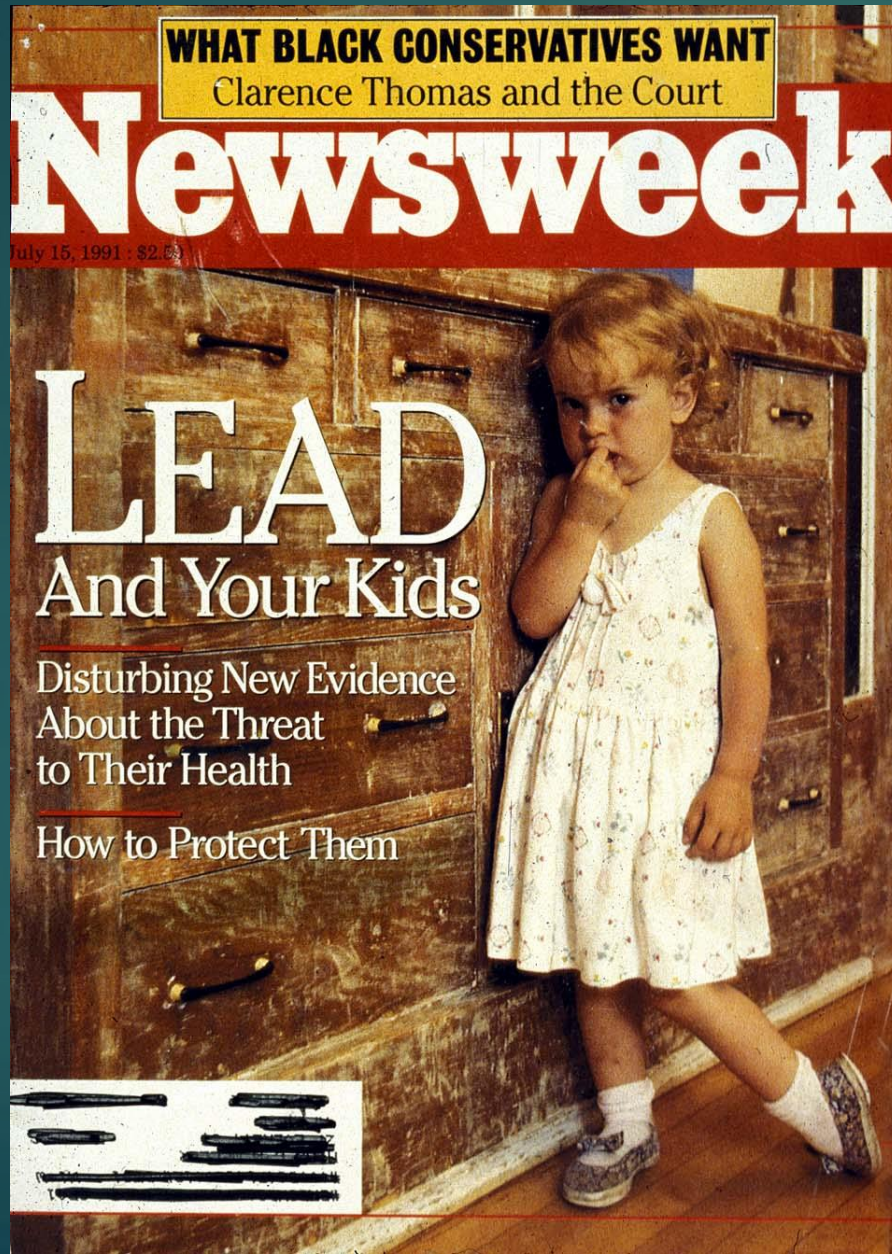
- ▶ CDC in 2004 said water with lead was safe for children to drink; in DC, 40,000 children were exposed
- ▶ Flint MI water in lead pipes crisis (140 ppb): same in dozens of other cities; Flint drank poisoned water for 3 years before public notification; sx's of fatigue, hair loss, rashes, etc.
- ▶ Congress banned lead water pipes 30 years ago, yet between 3 to 10 million older ones remain. More than 40 million U.S. residents use water "that can contain lead in excess of 15 ppb"
- ▶ EPA clean water office being decimated by Trump
- ▶ Pruitt, head of EPA, denies problems and is anti EPA.
- ▶ Some homes: 1 sample 13000 ppb, 5000 ppb considered hazardous waste
- ▶ Flint official testings required flushing water for 5 minutes (diluted lead)

## Lead & Gas companies

- ▶ *Poisoner's Handbook*: New York coroner's office and Dr. Gettner (& American Experience episode)
- ▶ In 1920s concluded lead was neurotoxin.
- ▶ Gas industries got federal government to undo state prohibitions vs leaded gas.
- ▶ Leaded gas supported by Alfred P. Sloan and Charles Kettering of General Motors; remembered today for having founded the prestigious Sloan-Kettering Cancer Center.



# Lead In Homes



2 Books: *Deceit and Denial & Lead Wars* by  
Gerald Markowitz & David Rosner

Industry attacks researchers and to  
undermine government regulation  
i.e. lead, asbestos, furniture flame  
retardants, PCB

Corporate greed & war on science

John Hopkins Study, 1990s: Kids  
as guinea pigs  
(AA single mothers, put in 7  
houses with different levels of lead  
removal; consent forms did not  
mention lead (funded by lead  
abatement companies))

# Lead process in body

- ▶ Lead hides as calcium in bones and brain
- ▶ Calcium in synapse replaced by lead; disrupts synaptic communication
- ▶ IQ of 86 not 100
- ▶ Volume loss, larger ventricles; mostly in frontal lobe
- ▶ Removes calcium from fetus to use in mother if lead present

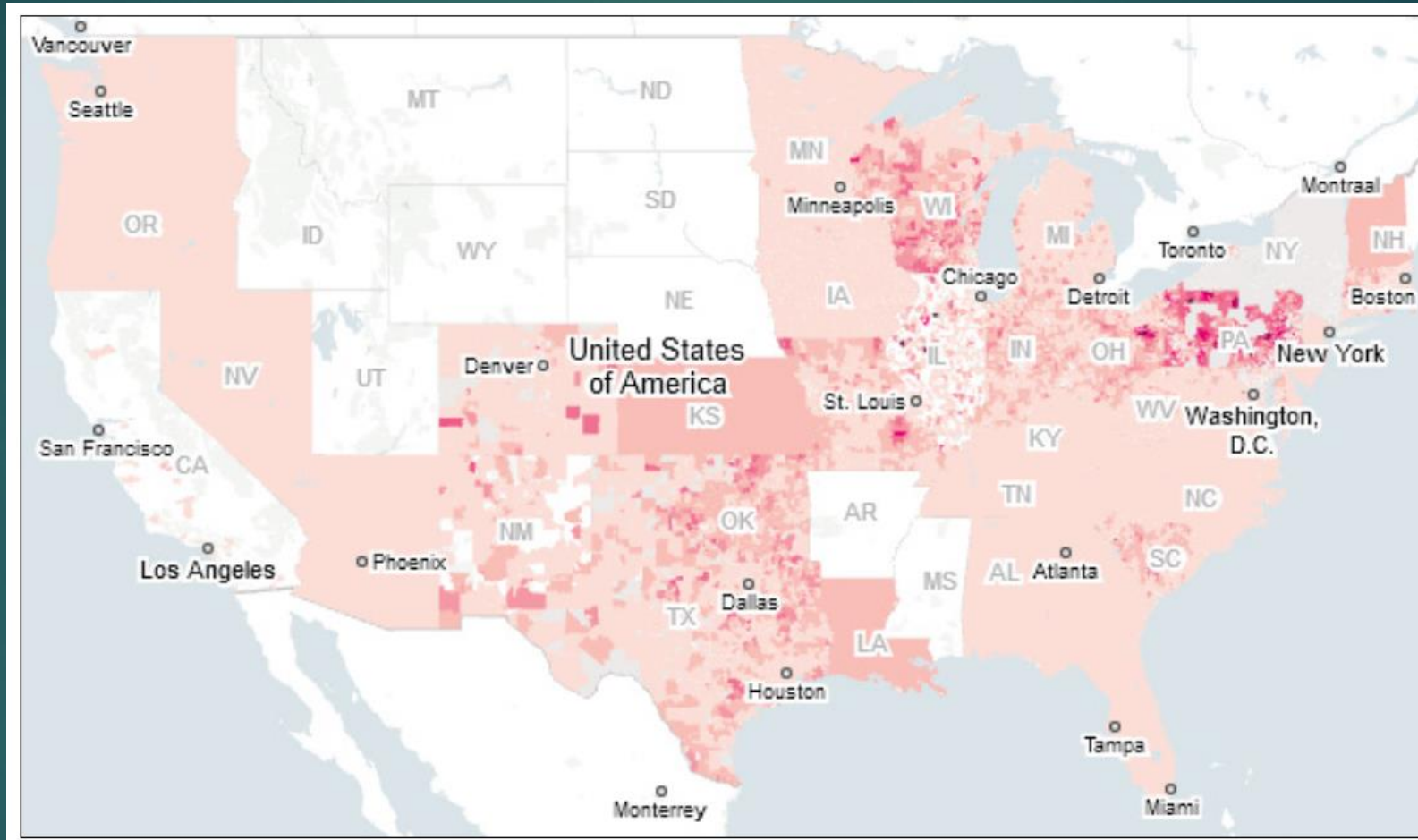


# Poisoned by Policy:

## Flint, Michigan: 5% of children have lead poisoning

- ▶ Flint, MI: EPA under Obama did nothing for long time. 40% of homes; 8000 children exposed
- ▶ 2016 analysis of childhood lead testing results across the country. Reuters found nearly 3,000 areas with recently recorded lead poisoning rates at least double those in Flint, MI; more than 1,100 of these communities had a rate of elevated blood tests at least four times higher
- ▶ Cleveland, Baltimore, PA, TX, St. Joseph, MO, etc.
- ▶ Since the heavy metal was phased out from paint and gasoline in the late 1970s, children's average blood lead levels have dropped by more than 90 percent. Children in at least 4 million U.S. households are exposed to high levels of lead. Many of these localities are plagued by legacy lead: crumbling paint, plumbing, or industrial waste (mines) left behind.

# Lead Sites in USA



It would cost tens of billions of dollars to clean up all the old lead, which is mostly a problem in poor communities populated by people of color.

# Lead Pipes

- ▶ Mostly from pipes, brass fitting, lead solder; protective scale on pipes are protective
- ▶ Federal law requires corrosion control (inhibitor) for lead lines in water system. Attack scale on pipes, then more lead in water.

# Lead Poisoning

- ▶ In children up to age 6, the CDC threshold for an elevated blood lead level is 5 micrograms per deciliter. Any child who tests high warrants a public health response; even a slight elevation can reduce IQ and stunt development (ADHD (20% of cases due to lead), behavioral impulsivity, seizures)
- ▶ Nationwide, the CDC estimates that 2.5 percent of small children have elevated levels. Poverty is a potent predictor of lead poisoning, but all levels have it.
- ▶ Congress recently directed \$170 million in aid to Flint. That's 10 times the CDC's budget for assisting states with lead poisoning this year.

# Lead at age 5-6 is more predictive

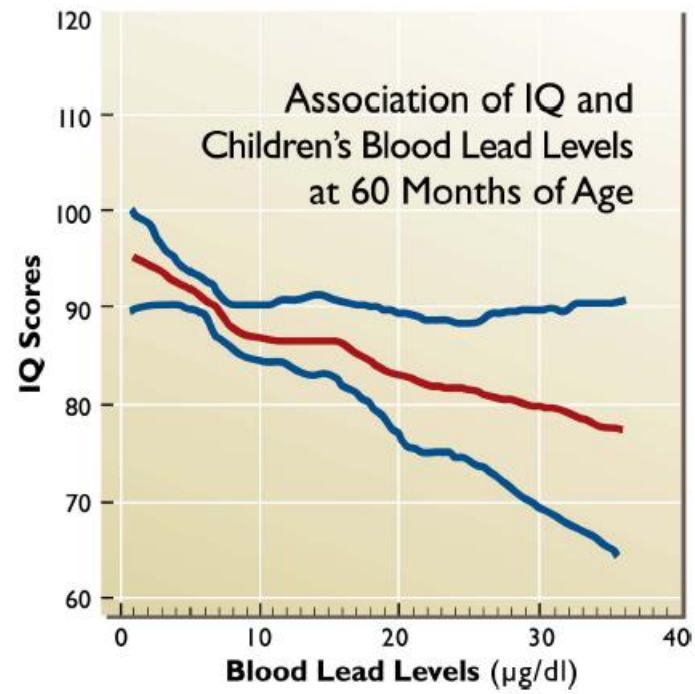


From the brains of 157 now-adult Cincinnati study participants. Red and yellow areas show regions that sustained a lead-related reduction in tissue volume, based on blood data collected when each individual was 5 years old.

- Many studies have linked elevated lead exposures in 2-year-olds with a diminished IQ at school age — even when peaks never exceeded the federal action level, 10 micrograms of lead per deciliter of blood.
- Analyzed data on lead levels and IQ from 462 children.
- Higher ratios at early ages showed a much smaller impact on IQ than elevated ratios at ages 5 and 6 lead ratios at ages 5 and 6 were most predictive of IQ losses,
- Later childhood exposures correlate more strongly than earlier ones with an exaggerated risk of incurring future criminal arrests for violent behavior.

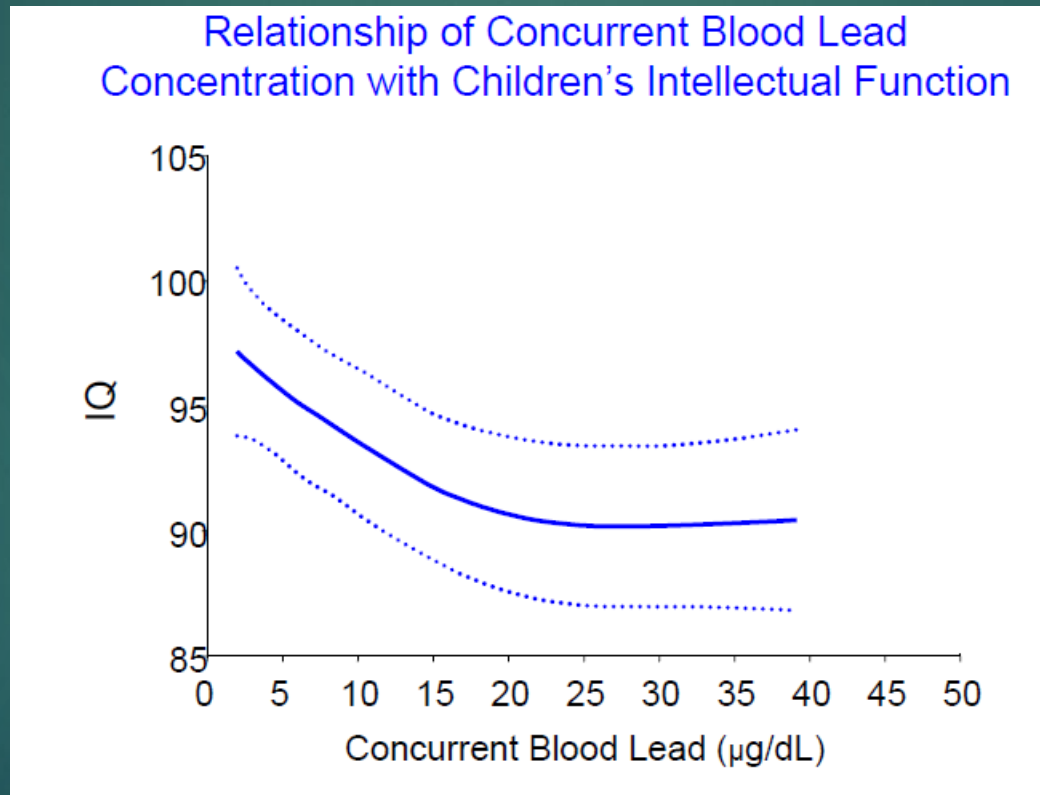


# IQ and Lead



Canfield R, et al. NEJM 2003;348:1517-1526.

# Lead and IQ





# Lead



Illustration 12: Dr. A.J. Turner, President of the International Branch of the World Medical Association, 1909



“Prevention is easy. Paint containing lead should never be employed ... where children, especially young children, are accustomed to play”

A.J. Turner, 1909

# Lead Exposed Child

## **“Draw a Person” — 4.5 y.o.**

Guillette et al, 1998

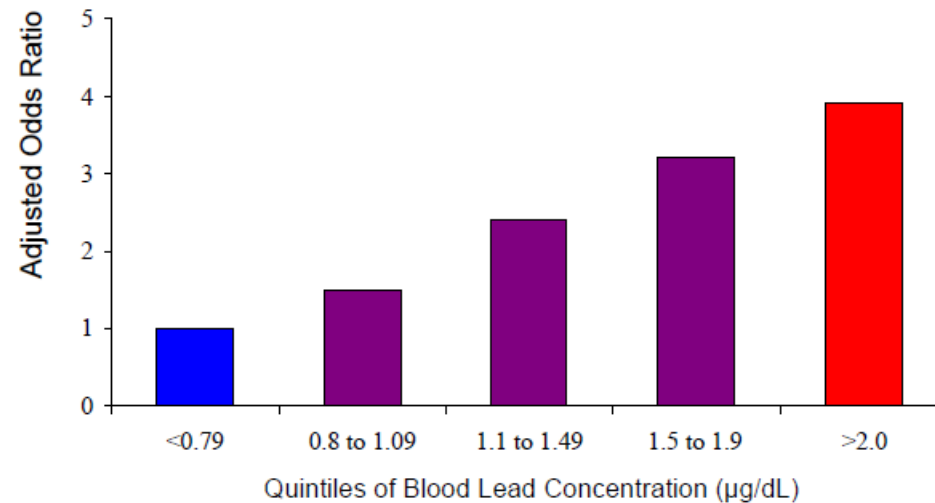


**Non-Exposed**

**Exposed**

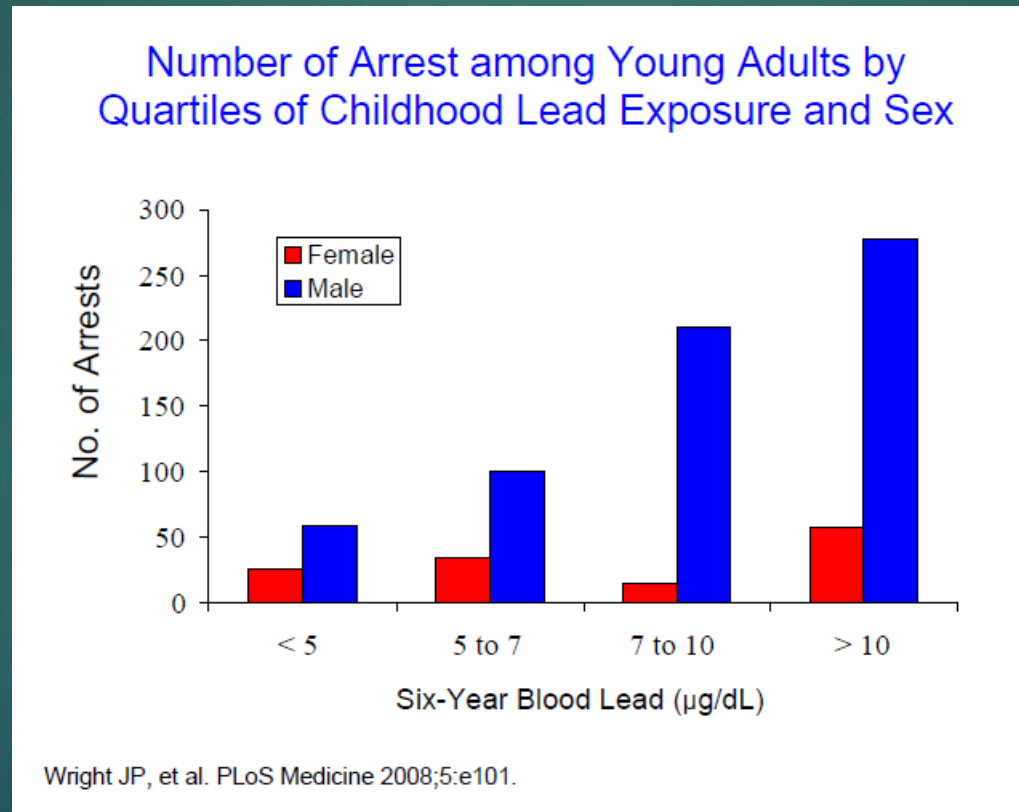
# Lead and ADHD risk

Risk of ADHD by Blood Lead Levels in US Children,  
4 to 15 years, NHANES 1999-2002



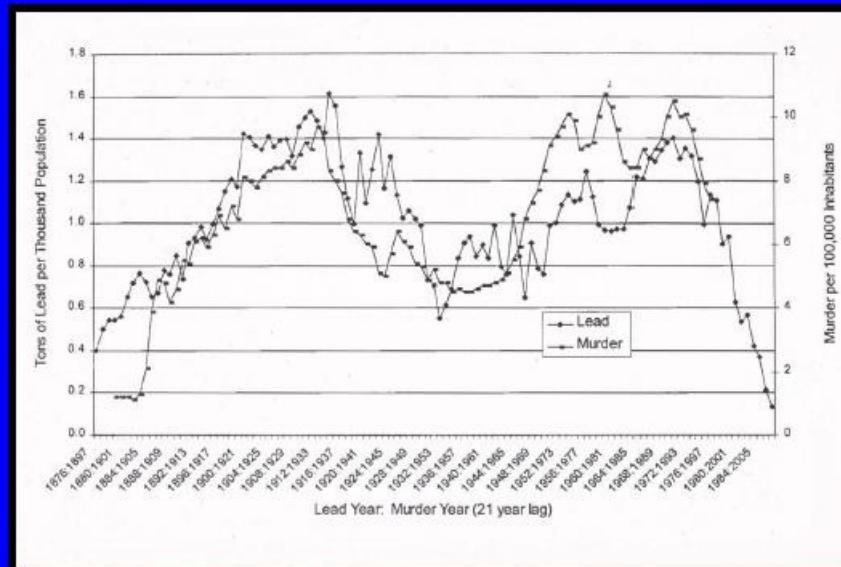
Adjusted for child's age, sex, race and ethnicity, preschool attendance, prenatal tobacco exposure, serum ferritin, poverty, and health insurance status. Braun J, et al. EHP 2006;117:500-505

# # of Arrests & Lead Exposure



# Murders & Lead

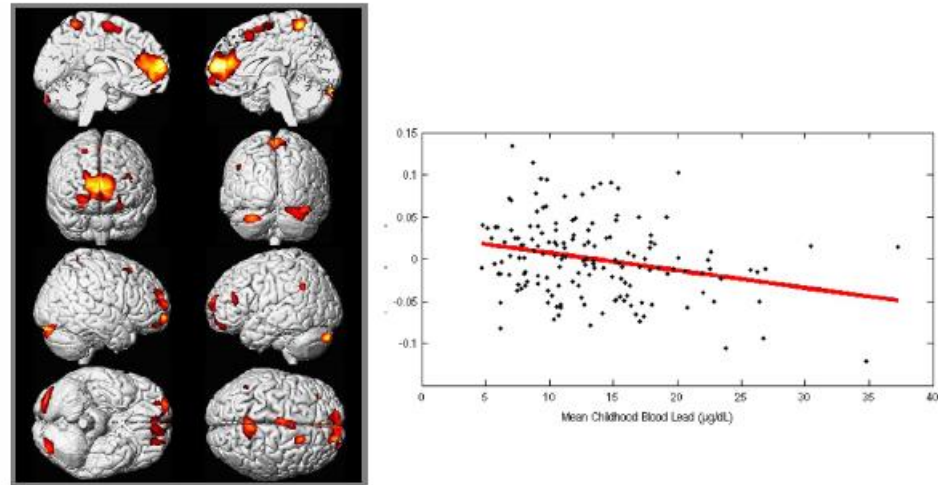
## Relationship of Lead Exposure and Murder Rate (/100,000) in the United States



Nevin R. Environmental Research 2000:83;1-22

# Neuron loss & Lead Exposure

## Gray Matter Loss by Childhood Lead Exposure (n=157)



Adjusted for child's age, birth weight. Sex, gestational age, IQ, prenatal tobacco, prenatal alcohol, prenatal marijuana, total intracranial volume, SES and HOME Inventory did not alter results (Cecil K, PLoS Med 2008;5:e112).

# Lead neurotoxic exposure symptoms

- ▶ Deficits in fine motor skills (esp. in kids)
- ▶ Deficits in attention/concentration
- ▶ Deficits in learning and visual memory
- ▶ Cognitive inflexibility/executive dysfunction
- ▶ Lower IQ



# Mercury

- ▶ • Ubiquitous toxic metal
- ▶ • Primary route of exposure is by ingestion
- ▶ • Source is from lead-based paint, contaminated drinking water, lead glazed pottery, Chinese produced toys
- ▶ • Encephalopathy occurs at blood lead levels of 80-100  $\mu\text{g/dL}$

# Mercury

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

# Mercury

- ▶ 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

# Mercury

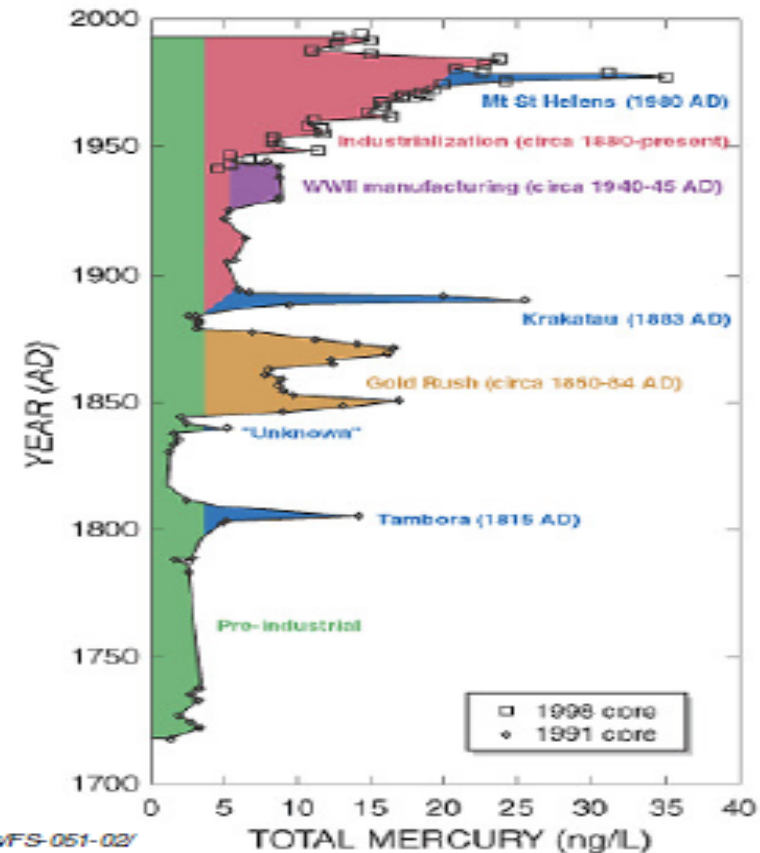
## Mercury

**A man made problem**

**Major atmospheric releases detected in the ice core**

- Natural background
- Volcanic
- Gold rush
- World War II
- Industrialization

**Hg released in the last 100 years: 70% from human activities**



<http://toxics.usgs.gov/pubs/FS-051-02/>

# Mercury sources

- ▶ 1. Coal-burning power plants: produce 50% of electricity; largest human-caused source of mercury emissions to the air in the United States, accounting for over 50 percent of all domestic human-caused mercury emissions (Koch brothers & climate denial)
  - ▶ Pruitt at EPA has systematically been decimating coal power regulations.
- ▶ 2. Cement kilns
- ▶ 3. Chlor-alkali plants (chlorine gas for PVCs (chloride beach))
- ▶ 4. Trash incinerators
- ▶ 5. Gold Mining (San Jose mine into Bay)

# METHYL MERCURY

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

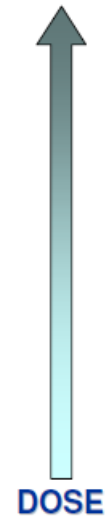
# METHYL MERCURY

- ▶ 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



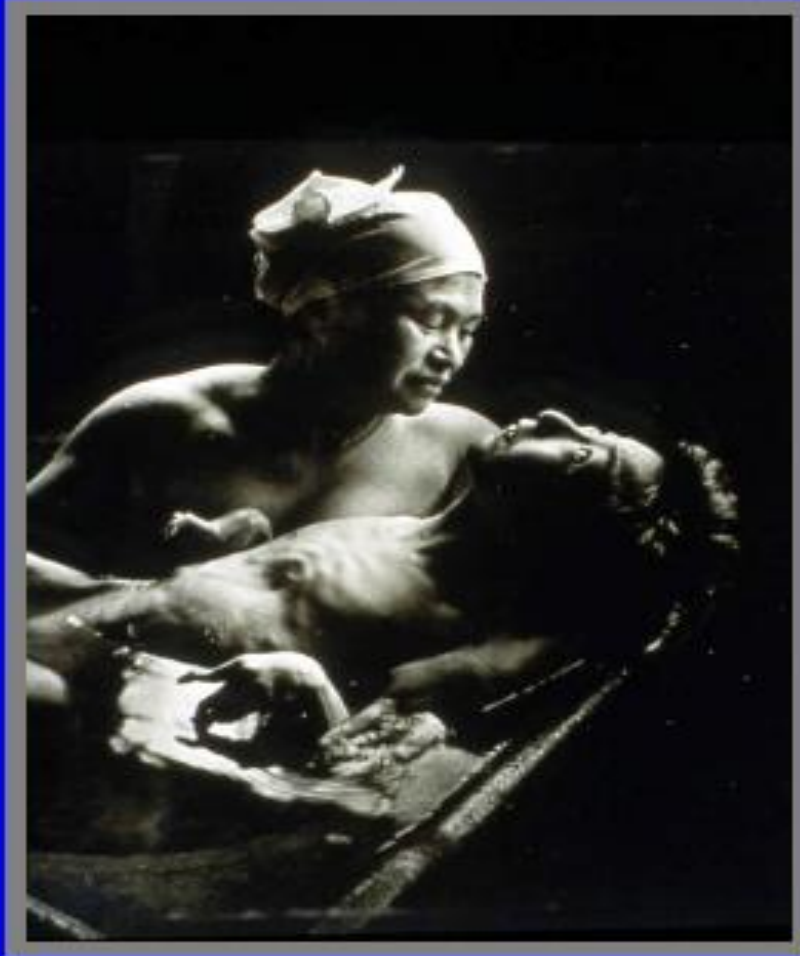
# Prenatal Exposure

- ❖ Mental retardation
- ❖ Ataxia & cerebral palsy
- ❖ Seizures
- ❖ Vision & hearing loss
- ❖ Delayed developmental milestones
- ❖ Language disorders
- ❖ Deficits in fine motor function
- ❖ Visual spatial disabilities
- ❖ Memory problems
- ❖ Low cardiac rate variability
- ❖ ? Blood pressure



DOSE

# Minamata Disease: Methylmercury exposure in pregnancy



Symptoms include ataxia, numbness in the hands and feet, general muscle weakness, narrowing of the field of vision and damage to hearing and speech. In extreme cases, insanity, paralysis, coma and death follow within weeks of the onset of symptoms.

Minamata , Japan, in 1956. It was caused by the release of methylmercury in the industrial wastewater from the Chisso Corporation's chemical factory, which continued from 1932 to 1968.

## ANOTHER ORGANIC MERCURY: THIOMERSAL

- ▶ Mercury preservative used in
  - ▶ Eye drops, antiseptics, other pharmaceuticals
  - ▶ Multidose vaccinations
- ▶ 49.6% ethylmercury
  - ▶ T<sub>1/2</sub> ~7 days in babies
  - ▶ Crosses blood-brain barrier

# Flame retardants in Furniture

- ▶ Children's low IQ is linked to antifire chemicals
- ▶ Increased exposure among pregnant women to flame retardants in old furniture is linked to lower IQs in their children
- ▶ For every tenfold increase in women's exposure during pregnancy to polybrominated diphenyl ethers or PBDEs was associated with a 3.7 point decrease in child's IQ. PBDEs were banned in 2004.
- ▶ Also found a relationship of PBDEs exposure and ADHD.
- ▶ Furniture with foam labeled California TB117 likely contain flame retardants; use furniture filled with polyester, down, wool, or cotton
- ▶ Prevent children from mouthing cell phones and remote controls

# EXPOSURE TO THIOMERSAL IN IMMUNIZATIONS

- ▶ Vaccine practices in the 1990s raised the body burden of mercury for small and preterm babies\*
- ▶ Thiomersal-free vaccinations for newborns \*\*
- ▶ In the US, all infant vaccinations are thiomersal-free since March 2001, except some influenza
- ▶ Still used to prevent microbial contamination of multidose vials in some countries
- ▶ No clear cut evidence of deficits in neuropsychological functioning in children from thiomersal in vaccines \*\*\*

*\* Stajich 2000, \*\* Ball 2001, \*\*\* Heron 2004, Thompson 2007*

# Invalid science

- ▶ Myths: vaccines cause autism (Andrew Wakefield research retracted; banned from practicing medicine)



# Pepto Bismol: rare bismuth toxicity

- ▶ Bismuth subsalicylate (Pepto-Bismol®) and other bismuth-containing compounds have been used for many years to treat gastroenterological complaints.
- ▶ Although safe in the majority of patients, bismuth can cause a well-described toxic state marked by progressive neurological decline. Features of bismuth toxicity include confusion, postural instability, myoclonus, and problems with language.
- ▶ In this case study, we present a patient who was using bismuth salicylate in toxic quantities to help control diarrhea. On initial presentation, several diagnoses were entertained before bismuth levels were obtained.
- ▶ This case study highlights the fact that bismuth toxicity, while rare, should be considered in a patient with progressive neurological decline..



# Fish Consumption Guidelines

## For women and young children (USA)

1. Do not eat Shark, Swordfish, King Mackerel, or Tilefish
2. Eat up to 12 ounces (340 g) or two average meals per week of a variety of fish and shellfish that are lower in mercury
  - Shrimp, canned light tuna, salmon, pollock, and catfish are examples
  - Albacore ("white") tuna has more mercury than canned light tuna, you may eat up to 6 ounces (170 g) or one average meal per week.
3. Check local advisories. If no advice is available, eat up to 6 ounces (170 g) or one average meal per week of fish you catch, but don't consume any other fish during that week.

...to your young child, serve smaller portions!

From US EPA/FDA

# Childhood Exposure to 2<sup>nd</sup> Hand Tobacco Smoke

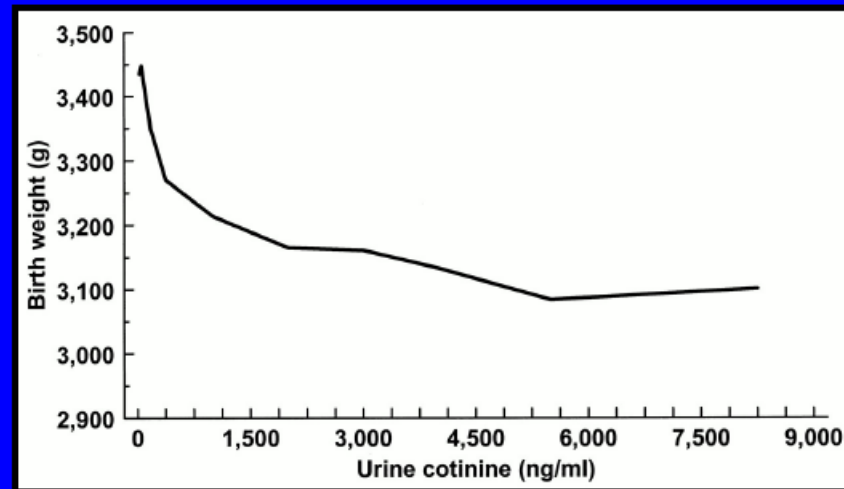


# Nicotine

- ▶ 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
- ▶ New e-cigs just as bad

# Birth Weight & tobacco exposure

Mean Adjusted Birth Weight by Third-trimester Urine Cotinine Concentration (n = 2,481)

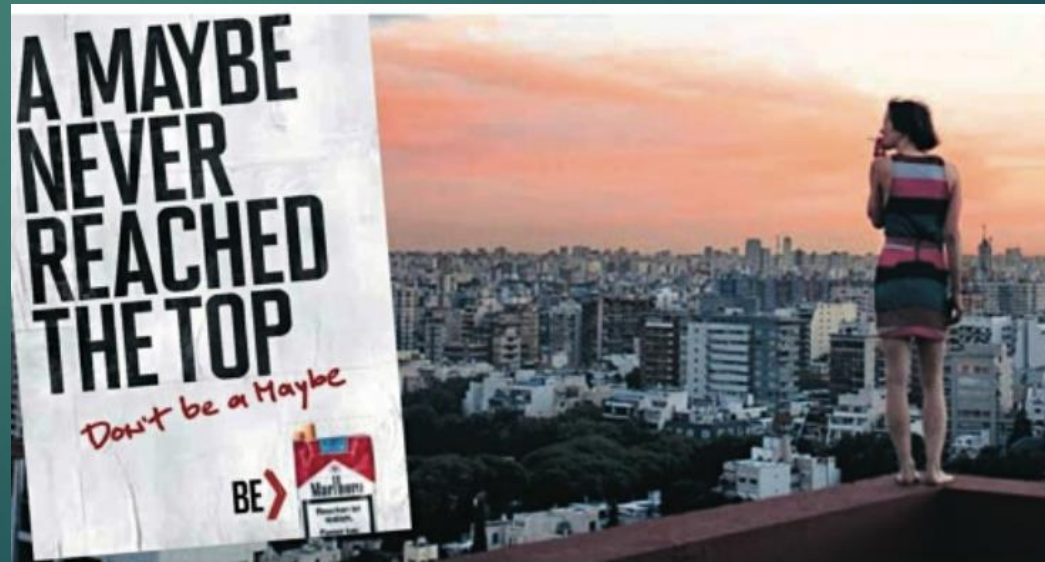


England L J, et al. Am J Epidemiol 2001;153:954-960; doi:10.1093/aje/153.10.954

# Philip Morris & International Tobacco: Be Marlboro

- ▶ Philip Morris (Marlboro) lost in USA, but goes legally after every country (Australia, Uruguay, Togo, Brazil, Colombia and Switzerland, etc.) that attempts to reduce smoking by public health laws
- ▶ They have an ad campaign “Don’t be a Maybe” pushing the Marlboro “values” of “truth, bold, etc.”; banned in many countries.

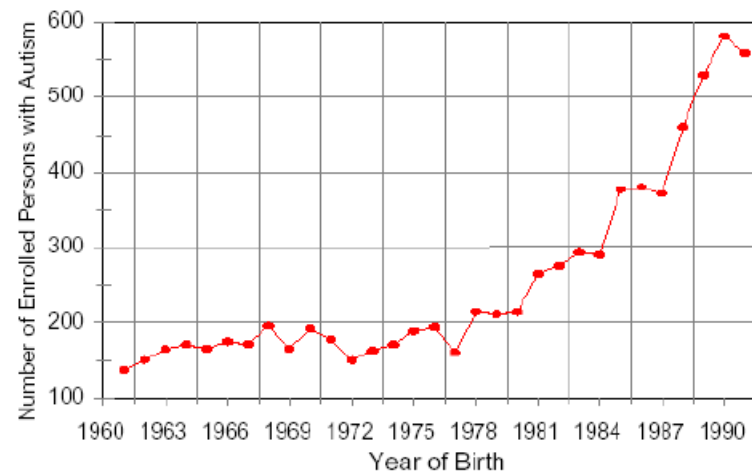
All 5 Marlboro cowboys in  
commercials  
died of lung cancer





# Autism Increasing

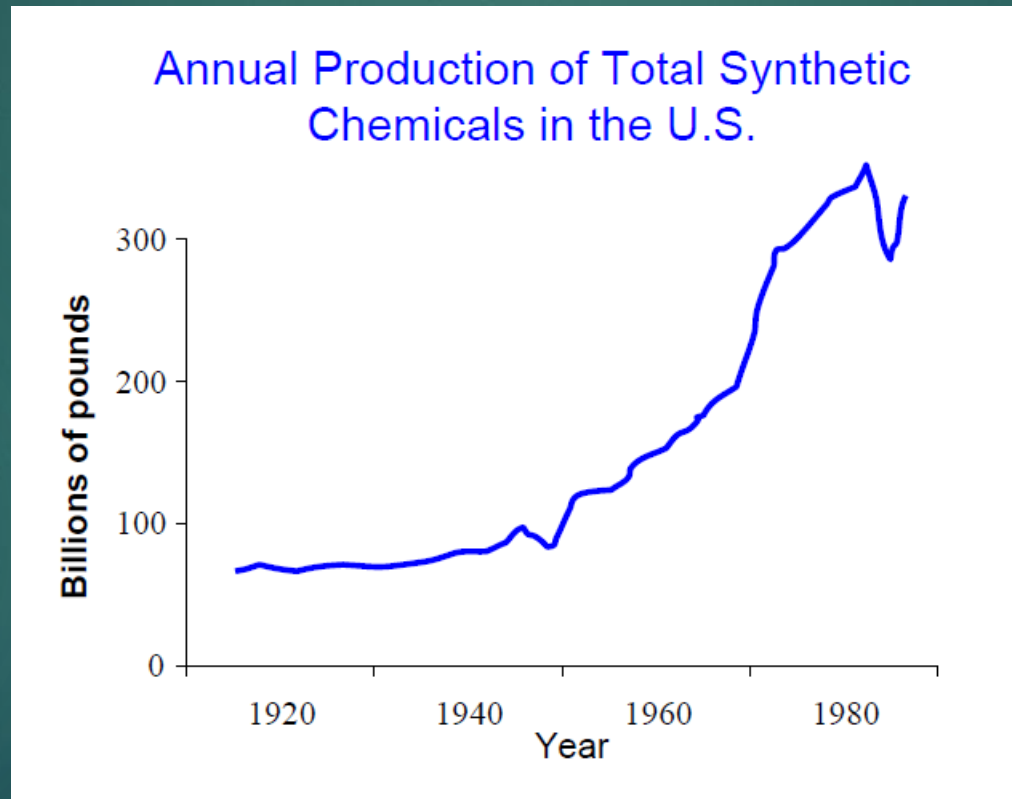
Number of Persons with Autism  
in California, 1960 to 1990



Byrd RS, et al. Report to the California State Legislature, 1999.

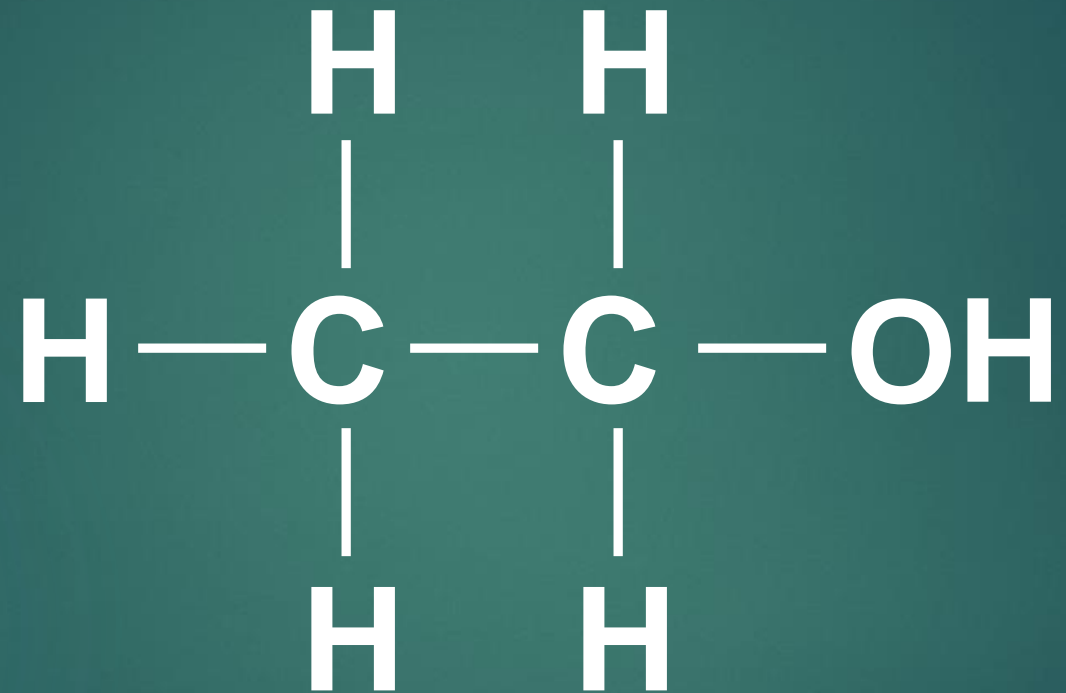
Although genetics predominate

# Chemicals in US





## Alcohol (ethanol)



Ethyl Alcohol

# Alcohol

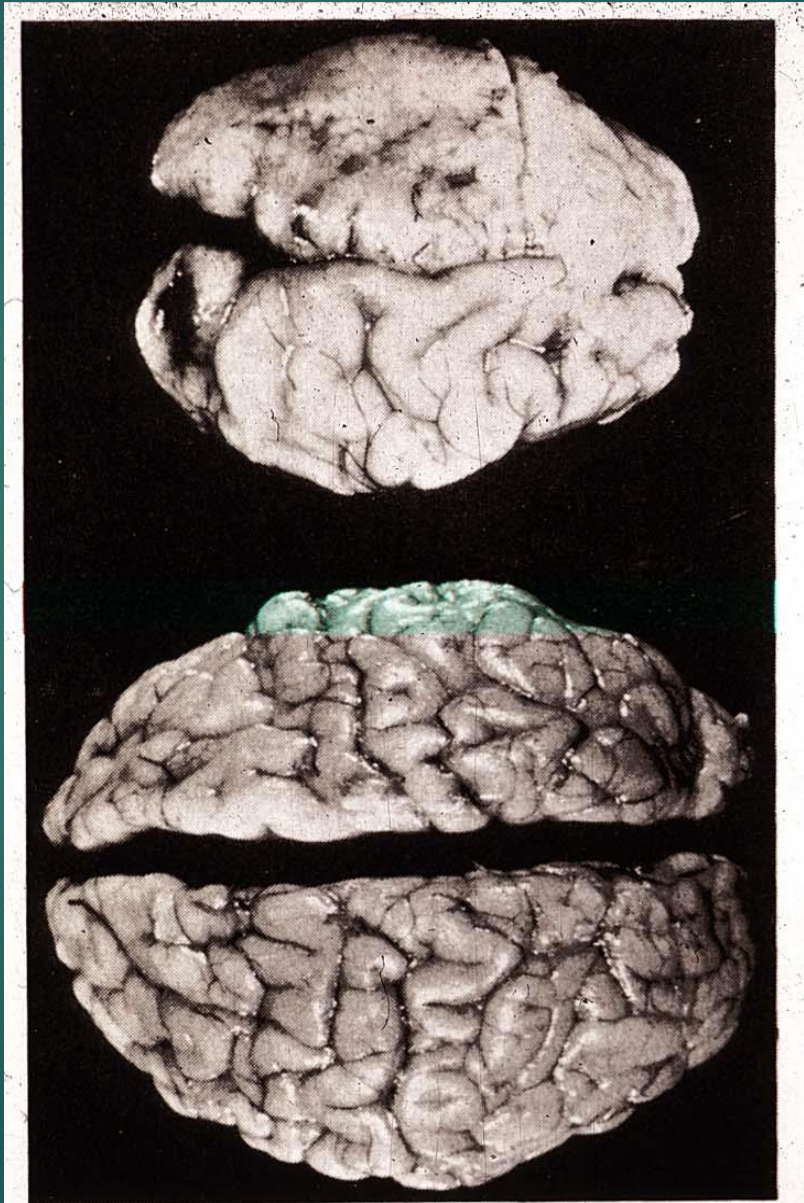
Vulnerability of Developing  
Nervous System

FAS – Fetal Alcohol Syndrome

FAE – Fetal Alcohol Effects

What is a safe level of  
consumption during pregnancy?

# Effects of Prenatal Alcohol





THE PREVENTABLE TRAGEDY

# FETAL ALCOHOL SYNDROME

Text and photographs by GEORGE STEINMETZ



**MPTP**



**1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine**

# MPTP Effects

- 1980s – Designer Drug
- Similar to Organophosphates
- Caused parkinsonian motor disorder due to damage to substantia nigra that secrete dopamine
- Resulted in advance in understanding etiology of Parkinsonism

# Manganese, Welders, and Parkinsonism

- In welders, Parkinsonism is caused by exposure to manganese.
- Welders exposed to manganese-laden fumes develop a form of Parkinsonism
- Has been documented since the mid-1800s, when miners inhaled particulates of the heavy metal
- There is an accumulation of heavy metals in the basal ganglia and reduced dopaminergic signaling in the caudate nuclei of welders, and also revealed that more than 15 percent of welders exhibit symptoms of parkinsonism



# General Anesthesia

"Anesthesia and Developing Brains -- Implications of the FDA Warning.", D. Andropoulos & Michael F. Greene, 2016

- For more than 15 years, the potential for lasting neurotoxic effects of agents used to induce general anesthesia and sedation when administered to young children -- and indirectly through pregnant women to fetuses with developing brains -- has been a subject of concern and considerable research interest.
- On December 14, 2016, the FDA issued a "Drug Safety Communication" ([www.fda.gov/Drugs/DrugSafety/ucm532356.htm](http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm)) warning that general anesthesia and sedation drugs used in children less than 3 years of age or in pregnant women in their third trimester who were undergoing anesthesia for more than 3 hours or repeated use of anesthetics "may affect the development of children's brains."
- This warning will result in a labeling change for 11 common general anesthetics and sedative agents that bind to GABA or NMDA receptors, including all anesthetic gases such as sevoflurane, and the intravenous agents propofol, ketamine, barbiturates, and benzodiazepines.

# FDA and drug approval

- The Food and Drug Administration is under pressure from the Trump administration to approve drugs faster, but researchers at the Yale School of Medicine found that nearly a third of those approved from 2001 through 2010 had major safety issues years after they were widely available to patients.
- Seventy-one of the 222 drugs approved in the first decade of the millennium were withdrawn, required a “black box” warning on side effects or warranted a safety announcement about new risks
- FDA approves drugs faster than its counterpart agency in Europe, and that the majority of pivotal trials in drug approvals involved fewer than 1,000 patients and lasted six months or less.
- It took a median time period of 4.2 years after the drugs were approved for these safety concerns to come to light, and issues were more common among psychiatric drugs, biologic drugs, drugs that were granted “accelerated approval” and drugs that were approved near the regulatory deadline for approval.

# FDA and drug approval

- Drugs ushered through the FDA's accelerated approval process were among those that had higher rates of safety interventions. These approvals typically rely on surrogate endpoints, meaning that researchers measured something other than survival, such as tumor size, to determine whether the drugs worked.
- The study included market withdrawals of three drugs: the anti-inflammatory drug Bextra, a drug called Zelnorm that treats irritable bowel syndrome and the psoriasis drug Raptiva. Bextra and Zelnorm were withdrawn over cardiovascular risk, and Raptiva was withdrawn because of increased risk of a rare and fatal infection that damages material in the brain.

# Chemotherapy & Chemobrain

- ▶ Chemotherapy, one of the hallmark treatments for cancer, may also be doing long-term damage to the brain
- ▶ More than 80 percent of people who receive chemotherapy for cancer report annoying memory and concentration problems that linger for months
- ▶ Lingering problems with impaired memory and an inability to concentrate or multi-task and a spaced-out feeling, during and after chemotherapy -- known as "chemobrain" among cancer patients.
- ▶ May effect neurogenesis in hippocampus
- ▶ Chemotherapy or cancer effects?

# Organophosphorous Pesticides

- ▶ Organophosphate pesticides are versions of wartime nerve agents.
- ▶ Malathion, parathion
- ▶ Inhibits acetylcholinesterase (AChE) leading to continuous stimulation
- ▶ Neurobehavioral, cognitive, neuromuscular disturbances
- ▶ Death from respiratory distress
- ▶ Dursban (on the market since 1965 and contained in some Raid and Black Flag brand sprays) can damage the brain.



# 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

## Neurobehavioral sx's of organophosphate neurotoxicity

- ▶ Impaired attention and vigilance
- ▶ Impaired executive functioning
- ▶ Slow information processing and psychomotor speed (bradyphrenia/bradykinesia)
- ▶ Verbal fluency deficit
- ▶ Psychiatric sx's (depression, anxiety, irritability)



# Trump's EPA Just Greenlighted a Pesticide Known to Damage Kids' Brains

- ▶ EPA director Scott Pruitt signed an order denying the agency's own proposal to ban chlorpyrifos, made by Dow AgroSciences.
- ▶ It's a organophosphate and an endocrine disrupter
- ▶ Strong evidence that low doses of chlorpyrifos inhibits kids' brain development, including when exposure occurs in the womb, with effects ranging from lower IQ to higher rates of autism. Several studies have found it in the urine of kids who live near treated fields. In 2000, the EPA banned most home uses of the chemical, citing risks to children.
- ▶ [Trump admin proposing a 31 percent cut in the EPA's budget.](#)

# Chlorpyrifos: Wash your food

- ▶ The common insecticide known as chlorpyrifos can still be found in the brains of young children now approaching puberty; children exposed to chlorpyrifos in the womb had persistent changes in their brains throughout childhood. There were measurable volumetric changes in the cerebral cortex
- ▶ Commonly used indoors in bug sprays prior to the indoor ban
- ▶ The children in this study were exposed to lower levels of chlorpyrifos than found in a random sampling from a Cincinnati blood bank (which showed levels twice as high as those in the affected children); lower in organic food
- ▶ Wash your vegetables and fruit!!

## Some chemicals to watch out for

- ▶ Toluene (a common degreaser and solvent, linked to fetal toxicity)
- ▶ Carbon disulfide (used to make synthetic fibers, linked to fetal toxicity)
- ▶ Benzene (used in manufacturing and in gasoline, linked to developmental delays).
- ▶ <http://householdproducts.nlm.nih.gov/>

# Mold

- ▶ Mold, mycotoxins, bacteria (repeated water intrusions)
- ▶ Neurotoxicity syndrome, incl. anorexia, lassitude & nausea
- ▶ Indoor environment: *Aspergillus* fumigates results in air quality issues (ergot alkaloids)
- ▶ LSD: ergot mycotoxin from rye fungus

# Environmental Pollution

- ▶ Environmental releases of only 1 percent of about 80,000 chemicals in business are required to be reported to the Toxic Release Inventory from select industries
- ▶ The National Academy of Sciences has estimated that 25 percent of developmental and neurological problems in children could be caused by environmental pollution combined with genetic factors.
- ▶ It cites the increase in low birth weight births, premature births, atrial septal defects, genito-urinary defects, attention deficit hyperactivity disorder and autism.

# Car Exhaust Toxins: Don't live by freeways

- ▶ Breathing street-level fumes for just 30 minutes can intensify electrical activity in brain regions responsible for behavior, personality and decision-making, changes that are suggestive of stress
- ▶ Breathing normal city air with high levels of traffic exhaust for 90 days can change the way that genes turn on or off among the elderly; it can also leave a molecular mark on the genome of a newborn for life
- ▶ Children in areas affected by high levels of emissions, on average, scored more poorly on intelligence tests and were more prone to depression, anxiety and attention problems than children growing up in cleaner air, separate research teams in New York, Boston, Beijing, and Krakow, Poland, found.
- ▶



# Car exhaust toxins 2

- ▶ Older men and women long exposed to higher levels of traffic-related particles and ozone had memory and reasoning problems that effectively added five years to their mental age
- ▶ Exposure to air pollutants, especially traffic-related pollutants, may increase the risk of type 2 diabetes and possibly of hypertension.
- ▶ The emissions may also heighten the risk of Alzheimer's disease and speed the effects of Parkinson's disease.





# Butter Flavoring

- ▶ The Butter Flavorant, Diacetyl, Exacerbates  $\beta$ -Amyloid Cytotoxicity
- ▶ Buttery flavor and aroma of microwave popcorn, margarines, snack foods, candy, baked goods, pet foods and other products.
- ▶ The flavorant, diacetyl, already is linked to lung damage in people who work in microwave popcorn factories. This led many microwave popcorn makers to stop using diacetyl in their products
- ▶ Evidence that the ingredient, diacetyl (DA), intensifies the damaging effects of an abnormal brain protein linked to Alzheimer's disease.

# Perchlorate in Water Widespread & in Breast Milk



Adversely affects human health by interfering with iodine uptake into the thyroid gland.

# Sugar = Toxic

- ▶ Sugar leads to Cancer, obesity, HTN, CV, DM2
- ▶ High fructose corn syrup; 10 t in can soda
- ▶ Increases insulin
- ▶ Sugar is addictive: dopamine increase; more exposure, less reward, more addictive
- ▶ Recommend: 150 calories (9 t) for men/100 for women (can of Coke = 240 Calories)
- ▶ Robert Lustig: Sugar, bitter truth on YouTube

# Contamination

- ▶ About 1.6 million women in the US of childbearing age eat sufficient amounts of mercury-contaminated fish to risk damaging the brain development of their children.
- ▶ Prenatal exposure to PCBs at current environmental levels can potentially affect brain development.
- ▶ One million children in the US have more lead in their blood than the currently accepted level to affect behavior and learning.
- ▶ Breakdown products of chlorpyrifos, recently banned, are in the urine of 90 percent of children tested recently in a Minnesota study.

# Strawberries in California

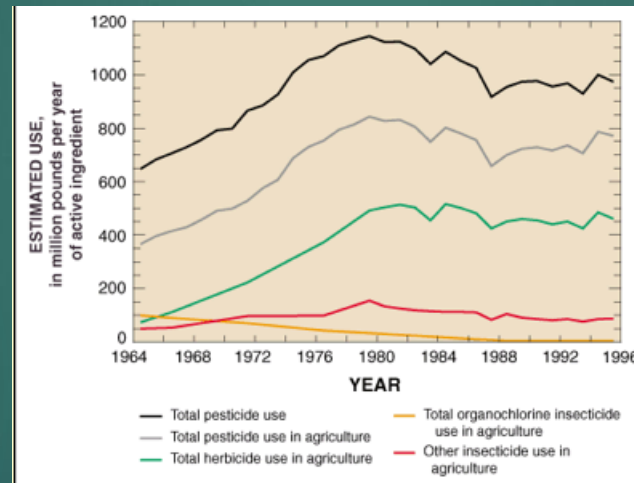
- ▶ Methy iodide: toxic pesticide
- ▶ In April, DPR announced an exposure limit of 96 ppb
- ▶ California will allow 120 times greater than its own panel recommended.

# Testing for developmental neurotoxicity

- ▶ Testing for developmental neurotoxicity is not routinely required to register pesticides, and nearly 78 percent of the 3,000 chemicals produced in the greatest quantity have no screening information on their neurological and developmental effects on children.



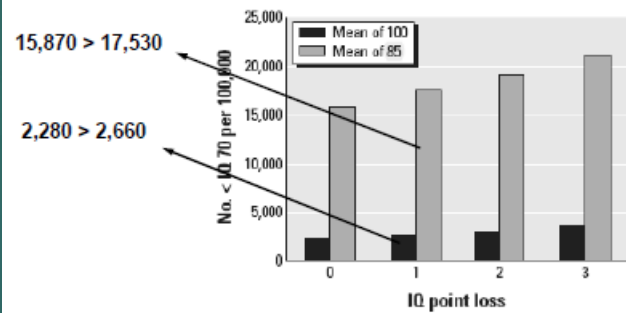
# Pesticide use in USA



Pesticide use in the United States. Source: U.S. Geological Survey

# Neurotoxins greater in Disadvantaged Communities

Neurotoxic chemicals:  
impact much greater in disadvantaged communities



Weiss and Bellinger, 2006 EHP

# Organic Solvents in Workplace

- ▶ Organic solvents
  - ▶ hydrocarbon-based non-aqueous solvents derived by distillation of petroleum
  - ▶ comprised of the lighter more volatile petroleum fractions
    - ▶ *VOCs - volatile organic compounds*
- ▶ 2 major classes of components
  - ▶ aliphatics -- short-chain hydrocarbons, alcohols, ethers, ketones
    - ▶ may include n-hexane, MBK, MEK, etc. i.e. WD40
  - ▶ aromatics -- benzene ring derivatives
    - ▶ includes toluene, xylene, styrene, benzene, ethylbenzene, etc.

# Organic Solvents in Workplace 2

- ▶ Solvent mixtures
  - ▶ commercial solvent mixtures
    - ▶ varsol, white-spirit, mineral spirits, petroleum distillates, etc.
  - ▶ 'industrial-grade' solvents
    - ▶ specific solvent chemical (95% purified) e.g. 95% xylene
  - ▶ petrochemical fuels (gasoline, diesel fuel, jet fuels)
    - ▶ complex mixture of aliphatic and aromatic hydrocarbons

# Diesel Trucks

- ▶ Diesel truck produces 63 x the pollutants as 1 car
- ▶ 4 million children are in schools next to major thoroughfares
- ▶ Significant predictor of asthma in children

# Occupational exposures and hazards of solvents

- ▶ 50 million tons of solvents produced annually (U.S.)
  - ▶ 10 million U.S. workers potentially exposed to solvents
  - ▶ mainly poorly-defined solvent mixtures
- ▶ Some (not all) solvents are potentially hazardous to health
  - ▶ more highly *volatile* (higher air concentrations)
  - ▶ more highly *lipophilic* (more readily absorbed, penetrate blood-brain barrier)
  - ▶ slower excretion from body (e.g. 12-24 hour biological half-life)
  - ▶ involves formation of toxic metabolites in body



# Occupational exposures and hazards of solvents 2

- ▶ Many solvents have an affinity for nervous system targets
  - ▶ aliphatics tend to affect mainly PNS (e.g. n-hexane)
  - ▶ aromatics tend to affect mainly CNS (e.g. toluene)
- ▶ Acute sensorimotor impairment
  - ▶ drowsiness, euphoria, clumsiness
  - ▶ reversible upon discontinued exposure

# Symptoms of workers with Chronic Solvent Encephalopathy

**Acute symptoms:** dizziness, headache, nausea, feelings of intoxication

**Common chronic symptoms:**

- forgetfulness
- memory does not tolerate intervening factors
- difficulties in learning new things
- irritability, depressive mood, mood swings
- feeling tired, problems in maintaining wakefulness
- sleep problems
- difficulties getting things started, difficulties in planning
- slowness
- withdrawal from social relations
- headache, impotence

# Neuropsychological findings in CSE

## What is impaired?

- Attention (shifting, dividing) \*\*
- Ability to learn new material (visual, verbal)
- Retrieval process (slow and ineffective)
- Information processing speed
- Performance speed (speech, eye and hand co-ordination, visuomotor functions)

## What is intact?

- Basic verbal or visual functions
- Academic skills (if not developmental handicap!)
- No more forgetting than normally
- Recognition memory

# Questionnaire Results

## The most often reported symptoms:

- ▣ 90% report memory & concentration symptoms
- ▣ objects fall from hands, powerless hands/feet, difficulties controlling hand movements, hand tremor
- ▣ dizziness, balance
- ▣ difficulties beginning to work, slowness in daily activities
- ▣ irritability, impatience, lack of enthusiasm

# Toluene leukoencephalopathy

- ▶ Toluene (methylbenzene)

- ▶ very common aromatic solvent in industry and commerce (also gasoline)
  - ▶ paint, rubber, printing inks, dyes, hairspray, stain remover, nail polish, glues ...

- ▶ Solvent abuse (estimated 10-15% teen usage rate in U.S.)

- ▶ intentional inhalation of very high toluene concentrations (>1000 ppm)
  - ▶ narcosis and euphoria (addictive)
- ▶ toluene is a highly lipophilic CNS toxicant

# Toluene leukoencephalopathy 2

- ▶ Toluene leukoencephalopathy
  - ▶ repeated high-dose exposure leads to gradual chronic neuropsychiatric syndrome
    - ▶ *leuko* = myelinated 'white matter' in brain tissues
    - ▶ *encephalopathy* = brain damage (encephalon = brain)
- ▶ Symptoms of CNS damage related to selective white-matter damage: subcortical
  - ▶ motor dysfunction -- tremors, ataxia
  - ▶ cognitive dysfunction -- mild confusion, impaired memory --> dementia
  - ▶ emotional disturbance -- hard to distinguish from psychiatric disease



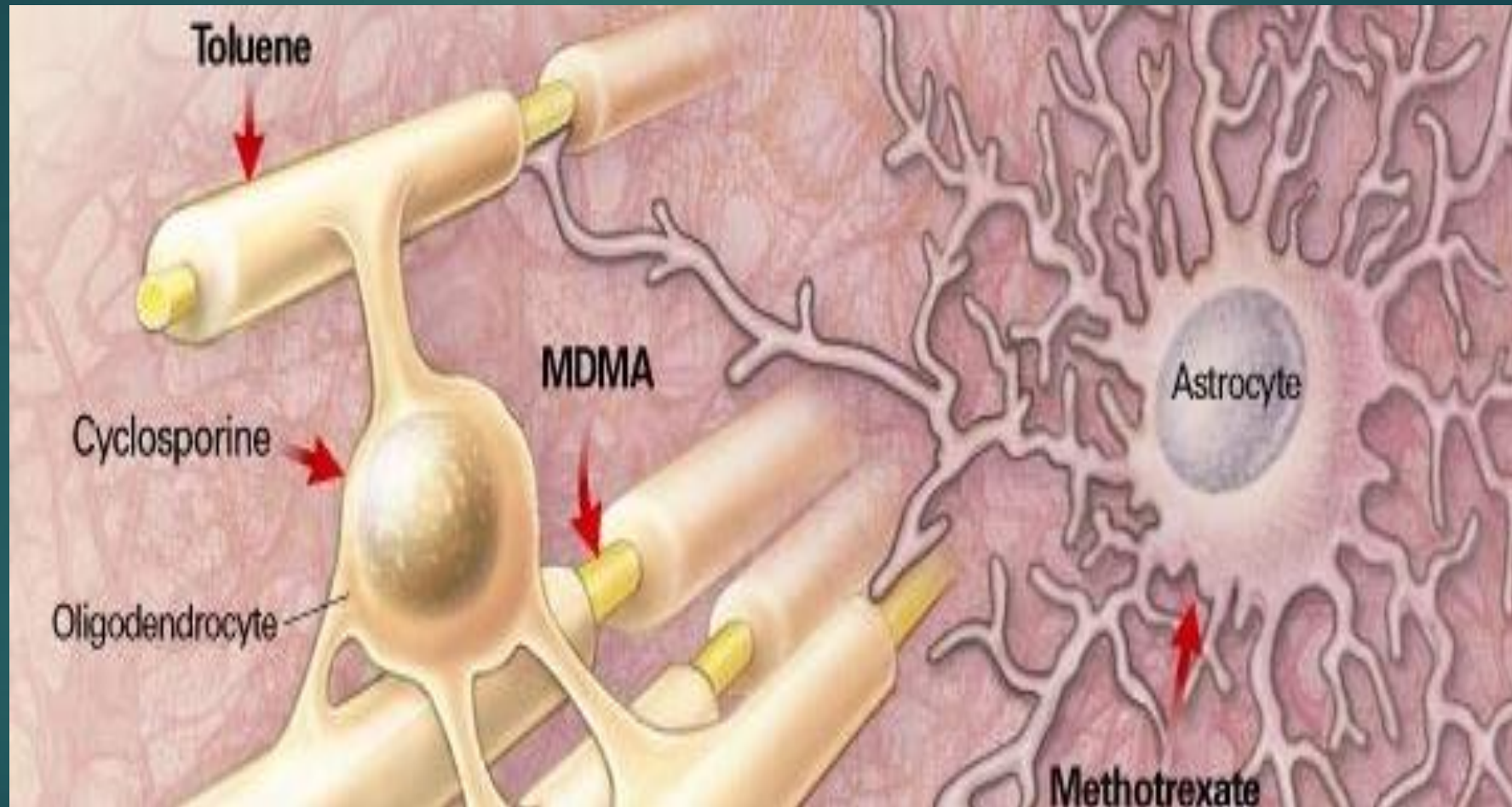
# Neuronal pathologies - *demyelination disorders*

- ▶ myelin sheath
  - ▶ lipid-rich cellular sheath surrounding many (not all) axons
    - ▶ voluntary motor axons in PNS
    - ▶ some sensory neurons in PNS
    - ▶ 'white matter' neurons in CNS
  - ▶ comprised on cell membrane of Schwann cells
- ▶ myelin functions
  - ▶ speeds nerve velocity for long sensorimotor axons
  - ▶ insulates against axonal 'short circuits' in axon bundles

# Toluene solvent CNS pathogenesis

- ▶ Toluene is selectively concentrated in CNS tissues (lipophilic)
- ▶ demyelination of CNS neurons
  - ▶ toluene selectively damages myelin sheath in white-matter of brain
  - ▶ *primary* demyelination process -- not secondary to axonopathy
  - ▶ myelin fragments scavenged by phagocytic brain astrocytes
- ▶ visible structural changes in MRI scans
  - ▶ widespread white-matter abnormalities
- ▶ dose-dependent damage
  - ▶ neurotoxicity damage only seen at higher dose levels (>100 ppm)

## Sites of cellular damage from various CNS toxicants



# Chelation therapy

- ▶ Chelation therapy: binds to heavy metals (including mercury) from the blood
- ▶ Valuable for treating poisoning, to decrease lethality, provide symptomatic relief
- ▶ Chelation therapy does not reverse cognitive impairment in exposed children
- ▶ Emphasis is on prevention of neurotoxicity exposure

# The Problem

- ▶ The problem lies in the lack of industry regulation.
- ▶ Currently, no federal agency tests the toxicity of new materials before they are allowed on the market.



# Failure of Toxicity Testing

## Failure of Toxicity Testing

- Of the nearly 3,000 high production volume chemicals, 75% lack even the most basic toxicity tests. <sup>1</sup>
- Of the 140 registered pesticides EPA considers to be neurotoxic, the majority have not been tested for developmental neurotoxicity. <sup>1</sup>
- Animal testing may not be sensitive enough to protect humans. <sup>2</sup>

1. Claudio L. Toxicol Appl Pharm 2000;164:1-14.

2. Rice D. Env Health Persp 1996;104:205-215.



# Rachel Carson



It's all of a piece. Thalidomide and pesticides - they represent our willingness to rush ahead and use something new without knowing what the results are going to be.

Rachel Carson

# Conclusions

- Increasing evidence linking toxicants with learning and behavioral problems in children at levels of exposure previously thought to be safe
- Subtle effects observed in childhood often progress to more serious disease or disabilities
- Childhood exposures to toxicants are associated with life-long effects on brain function and behavior

# Implications

- Require developmental neurotoxicity testing for all high-production volume chemicals
- Ban, replace or control recognized or suspected environmental toxicants
- Observational studies of low-level exposure to persistent toxicants using biomarkers

# Toxicology resource: Toxnet.nlm.nih.gov

|  |  |
|--|--|
| <b>BREASTFEEDING &amp; DRUGS</b>           | <a href="#">LactMed</a><br>Drugs and Lactation Database. Drugs and other chemicals to which breastfeeding mothers may be exposed   |
| <b>DEVELOPMENTAL TOXICOLOGY LITERATURE</b> | <a href="#">DART</a><br>Developmental and Reproductive Toxicology Database. References to developmental and reproductive toxicology literature   |
| <b>CHEMICAL RELEASES &amp; MAPPING</b>     | <a href="#">TOXMAP</a><br>TOXMAP: Environmental Health Maps provides searchable, interactive maps of EPA TRI and Superfund data, plus US Census and NCI health data<br><br><a href="#">TRI</a><br>Toxics Release Inventory. Annual environmental releases of over 600 toxic chemicals by U.S. facilities |
| <b>GENOMICS</b>                            | <a href="#">CTD</a><br>Comparative Toxicogenomics Database. Access to scientific data describing relationships between chemicals, genes and human diseases   |
| <b>HOUSEHOLD PRODUCT SAFETY</b>            | <a href="#">Household Products Database</a><br>Potential health effects of chemicals in more than 10,000 common household products   |
| <b>OCCUPATIONAL EXPOSURE TO CHEMICALS</b>  | <a href="#">Haz-Map</a><br>Links jobs and hazardous tasks with occupational diseases and their   |

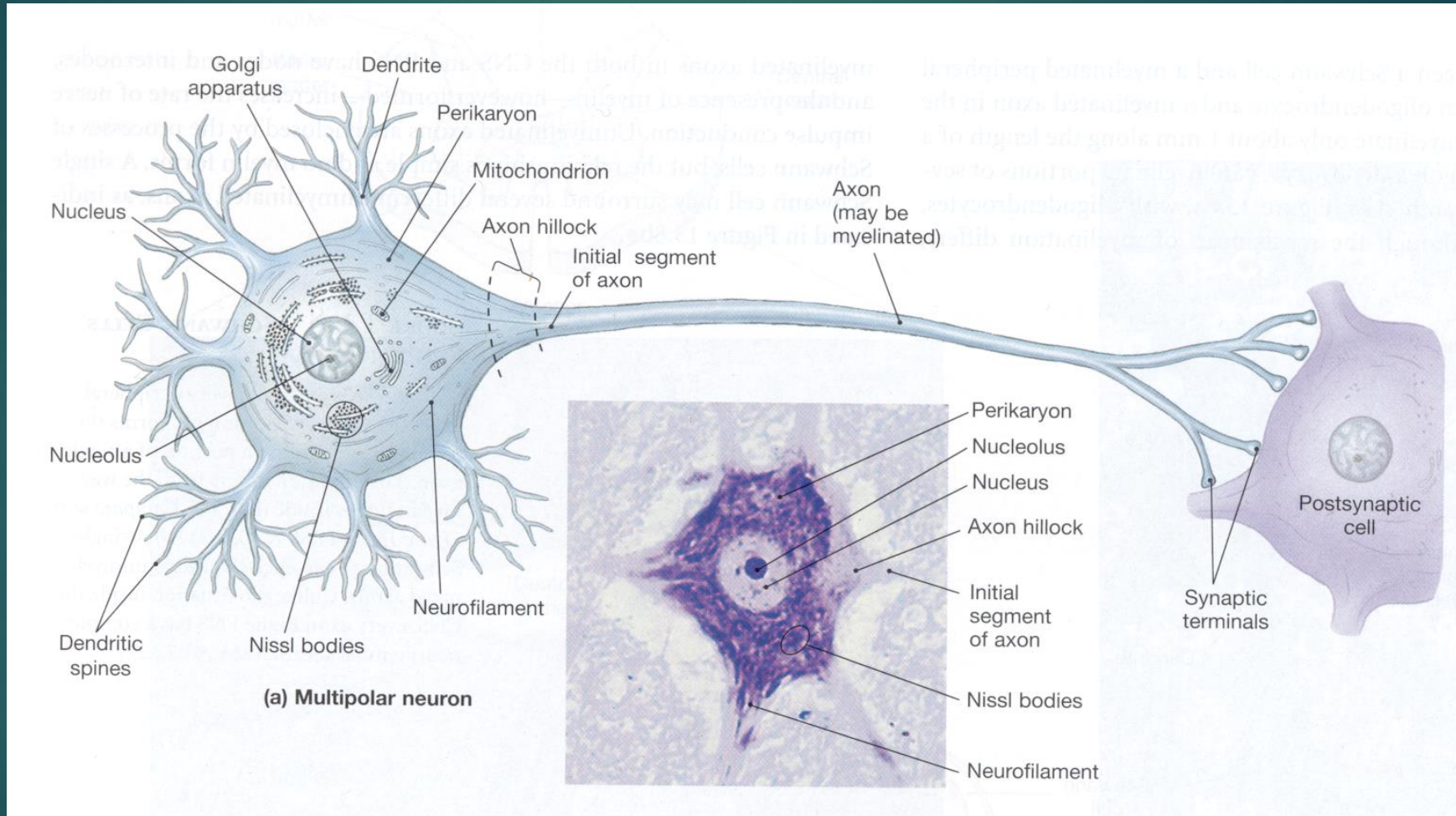
# NERVOUS SYSTEM TOXICOLOGY

# OUTLINE

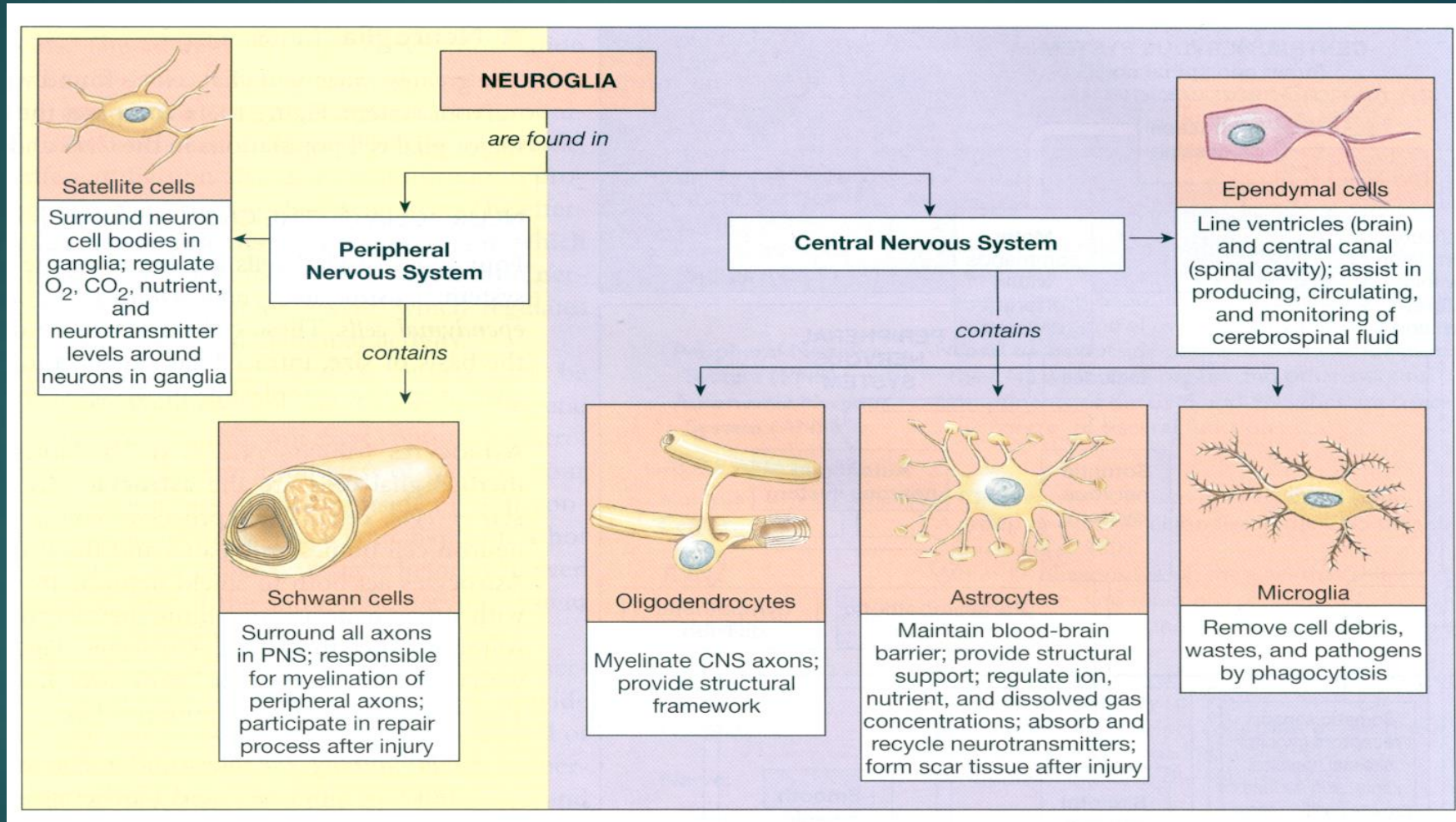
- ▶ Nervous system development
- ▶ Nervous system anatomy and physiology
- ▶ Manifestations of neurotoxicity
  - ▶ Neuronopathies
  - ▶ Axonopathies
  - ▶ Myelinopathies
  - ▶ Neurotransmission-associated anomalies
- ▶ Prototypical toxicological agents
  - ▶ Methylmercury
  - ▶ Carbon disulfide
  - ▶ Lead
  - ▶ Nicotine
  - ▶ Organochlorine insecticides
  - ▶ Organophosphorus insecticides
  - ▶ Venoms



# NERVOUS SYSTEM ANATOMY



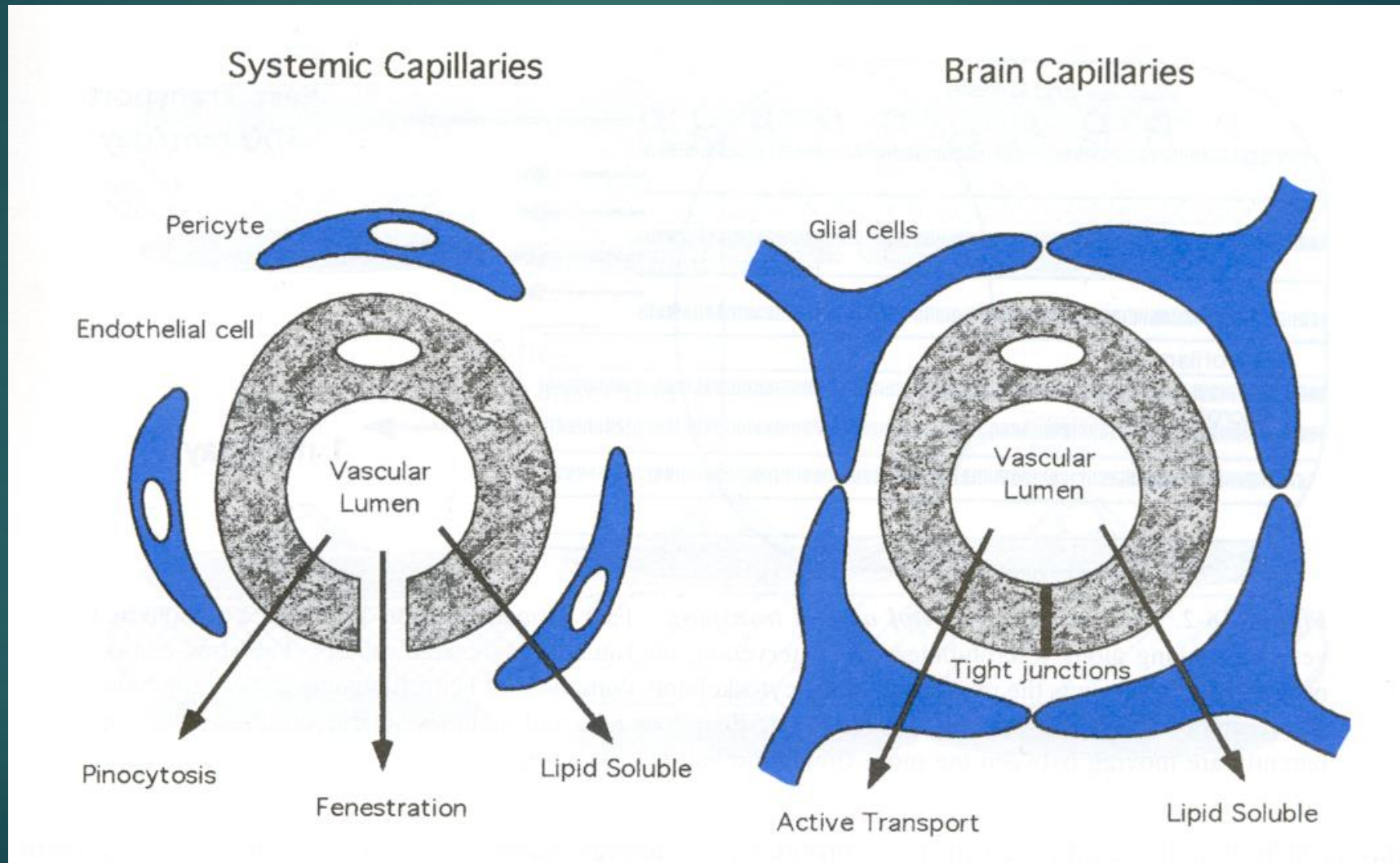
# NERVOUS SYSTEM ANATOMY





# NERVOUS SYSTEM ANATOMY

## *BLOOD BRAIN BARRIER*



# MANIFESTATIONS OF NEUROTOXICITY

# MANIFESTATIONS OF NEUROTOXICITY

- ▶ Neuronopathies
- ▶ Axonopathies
- ▶ Myelinopathies
- ▶ Neurotransmission-associated anomalies

# 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



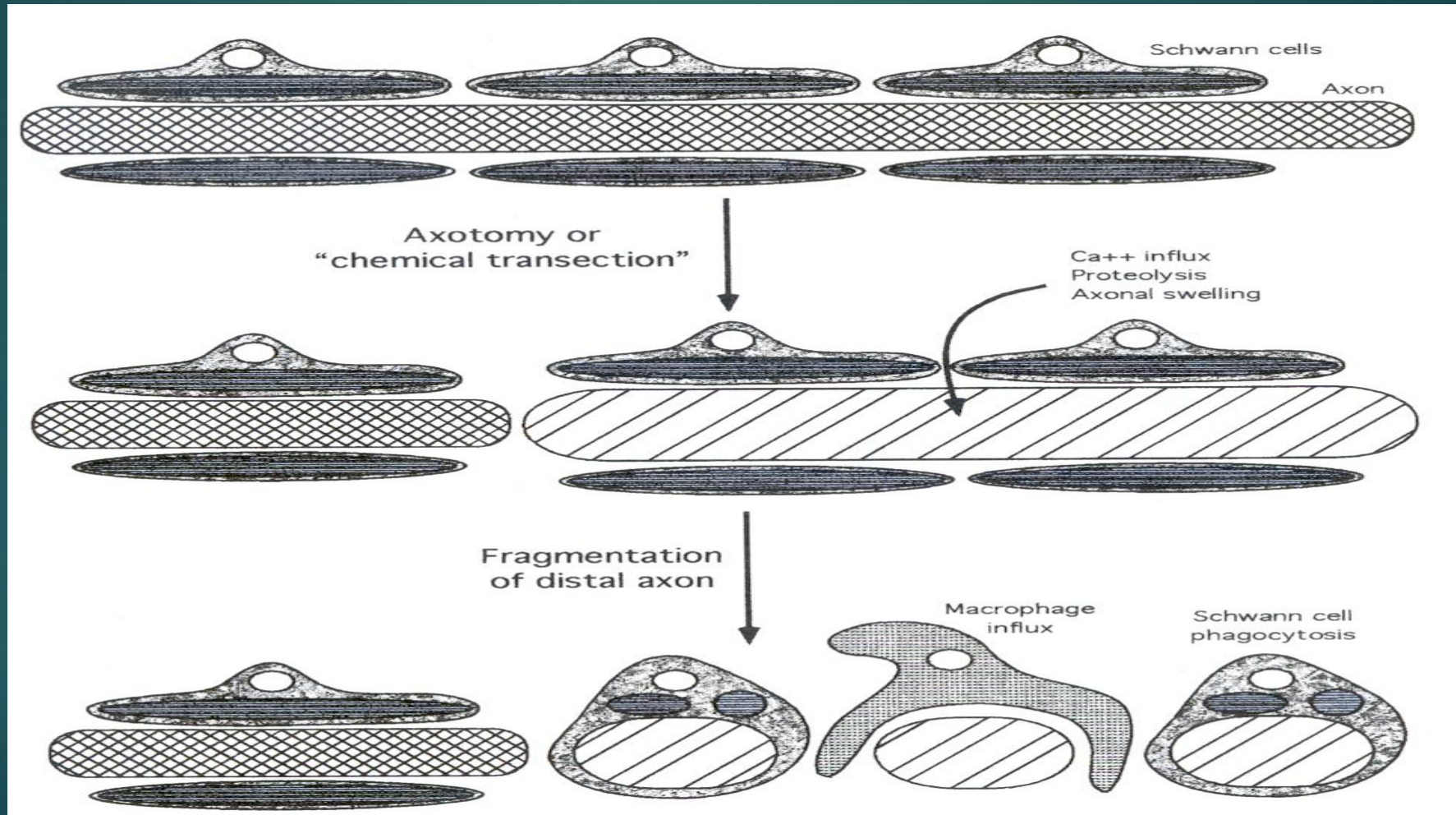
# MANIFESTATIONS OF NEUROTOXICITY

## *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<sub>2</sub>, acrylamide, gold, organophosphorus 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

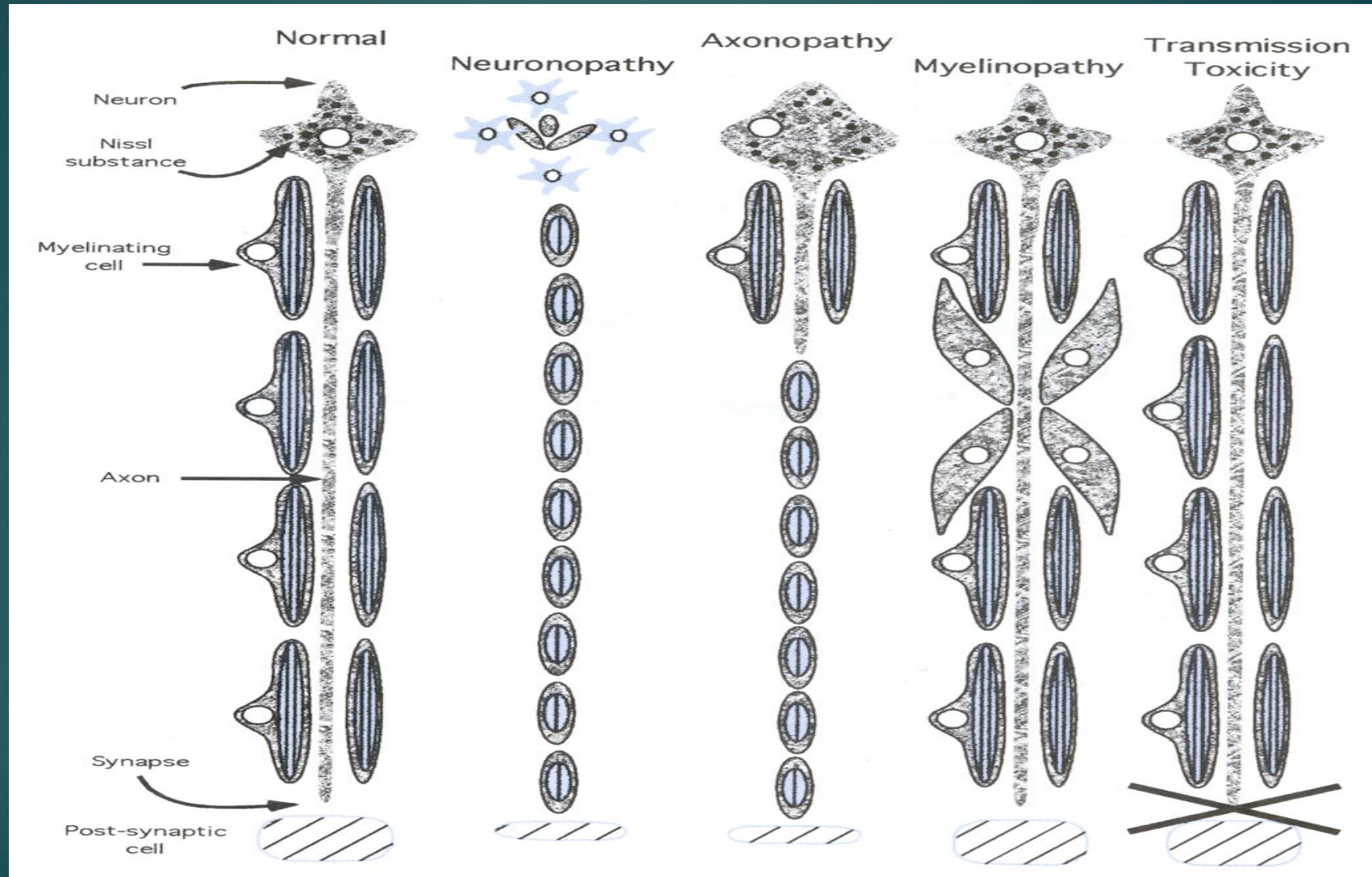
# MANIFESTATIONS OF NEUROTOXICITY

## *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  $\text{CH}_3\text{Hg}$ 
  - ▶  $\text{CH}_3\text{Hg}$  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



# DISORDERS OF THE NERVOUS SYSTEM

DR. A. MORTAZAVI MD

OCCUPATIONAL MEDICINE  
SPECIALIST

# clinical manifestations

## *central nervous system*

- ▶ headache,
- ▶ cognitive and psychiatric disturbances,
- ▶ visual changes,
- ▶ seizures,
- ▶ ataxia,
- ▶ tremors,
- ▶ rigidity,
- ▶ weakness, and sensory loss

## *peripheral nervous system*

- ▶ pain,
- ▶ weakness,
- ▶ parasthesias, and numbness
- ▶ autonomic disturbances.

## *Occupational injuries result in:*

- ▶ Generalized poly neuropathy (*Neurotoxins*)
- ▶ Focal compressive mononeuropathies (*Nerve trauma*  
*,Nerve entrapment*)
- ▶ Impaired neuromuscular transmission
- ▶ Myopathy

# Neurotoxicology: GENERAL PRINCIPLES

- ▶ A dose-toxicity relationship
- ▶ nonfocal or symmetric neurologic syndrome
- ▶ strong temporal relationship
- ▶ a limited capability to regenerate
- ▶ Multiple neurologic syndromes are possible from a single toxin
- ▶ Few toxins present with a pathognomonic neurologic syndrome

## phenomenon of *coasting*

► the continuing deterioration sometimes seen for up to a **few weeks** after discontinuation of toxic exposure.

1. pyridoxine (vitamin B<sub>6</sub>) abuse,
2. n-hexane toxicity,
3. vincristine chemotherapy.

▪

# APPROACH TO PATIENTS

- ▶ Sufficiently intense or prolonged exposure to the toxin
- ▶ Appropriate neurologic syndrome
- ▶ Evolution of symptoms and signs over a compatible temporal course
- ▶ Exclusion of other neurologic disorders that may account for a similar syndrome.
- ▶ mode of exposure
- ▶ confounding factors such as alcoholism, psychosocial issues, and possibility of secondary gains



## temporal course of the disease

Symptoms may appear

- ✓ acutely (minutes or days)
  - ✓ subacutely (weeks or months)
  - ✓ chronically (years).
- 
- ▶ **Fluctuating symptoms** may suggest recurrent exposures or unrelated superimposed factors.
  - ▶ **Recovery** after discontinuation of exposure helps to implicate the exposure

# Central Nervous System

***Encephalopathy*** (a common syndrome):  
diffuse dysfunction of cortical or subcortical  
structures.

- ▶ **Acutely**, the encephalopathy may be associated with alteration in the level of consciousness.
- ▶ **Chronically**, the primary symptoms may be cognitive and psychiatric

# Central Nervous System

Relatively *selective injury*:

- ▶ **vestibular system or the cerebellum**: resulting in disequilibrium, vertigo, and gait or limb ataxia.
- ▶ **Basal ganglia**: lead to an extrapyramidal syndrome of bradykinesia, tremors, and rigidity. (same as idiopathic Parkinson disease)

| Syndrome  | Neuroanatomy  | Symptoms and Signs  | Examples  |
|---|---|---|---|
| Acute encephalopathy                            | Diffuse; cerebral hemispheres                         | Varying combination of 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 disturbances  | Chronic or low-dose exposure to many toxins       |
| Parkinsonism                                    | Basal ganglia and other extrapyramidal motor pathways | Tremor, rigidity, bradykinesia, gait instability  | Manganese, carbon monoxide, methanol              |
| Motor neuron disease                            | Spinal cord motor neurons                             | Muscle atrophy, weakness  | Lead, manganese                                   |
| Myeloneuropathy (myelopathy and polyneuropathy) | Spinal cord and peripheral nerves                     | Paresthesias, sensory loss, hyperreflexia, Babinski sign, gait ataxia   | Nitrous oxide, organophosphates, <i>n</i> -hexane |
| Polyneuropathy                                  | Peripheral sensory, motor and autonomic nerve fibers  | Paresthesias, numbness, weakness, loss of deep tendon reflexes, more rarely, autonomic failure                            | Many toxins at sufficient doses (see Table 27–2)  |

## Evaluation

- ❖ cognitive complaints : at least a mini-mental stat examination.
- ❖ gait unsteadiness, dizziness, or vertigo :  
examined for cranial nerve or cerebellar deficits.  
(testing of gait, tandem walk, and Romberg sign)
- ❖ presence or absence of nystagmus, hearing deficits, limb ataxia, and sensory deficits.
- ❖ Tremors : at rest, and with the hands outstretched or performing pointing maneuver (the finger-to-nose test)
- ❖ Muscle tone should be tested for rigidity

# Laboratory tests

- ▶ often are needed to evaluate:
- ▶ physiology function of the central nervous system
- ▶ detect unrelated neurologic diseases that mimic neurotoxic disorders
  
- ▶ brain or spinal cord imaging studies (e.g., MRI),
- ▶ lumbar puncture,
- ▶ electroencephalogram (EEG),
- ▶ evoked potentials,
- ▶ *However, in many clinical settings and especially in the mildly affected patients, these studies may not show any abnormality*



# Peripheral Nervous System

- ▶ *sensory disturbances and weakness*
- ▶ *impairment of the deep tendon reflexes*
- ▶ ***polyneuropathy*** : symmetric peripheral neuropathy.
- ▶ **mononeuropathy** : the result of local mechanical injury
- ▶ **myopathy** (alcoholism and medical use of the statins, toxic myopathy is uncommon)

## polyneuropathies

- ▶ *The hallmark*: distal distribution of the clinical symptoms and signs.
- ▶ The most common syndrome:
- ▶ subacute onset of tingling or numbness experienced in a symmetric *stocking-and-glove distribution*.
- ▶ Neuropathic pain: burning, deep aching, lancinating, *hyperpathia* or *allodynia*.

# polyneuropathies

- ▶ **Motor nerve fibers involvement**: muscle atrophy and weakness. (at first in the distal-most muscles i.e., the intrinsic foot and hand muscles).
- ▶ **More severe cases** : involve muscles of the lower legs and forearms, leading to bilateral foot drop or wrist drop
- ▶ **Physical examination** : muscle strength, sensation, and tendon reflexes of all four extremities.
- ▶ (The longest axons are the most vulnerable, **SO** neurologic deficits severity in **feet > hands**)
- ▶ diminished or absent stretch reflexes of the Achill tendons and demonstrable sensory impairment in the toes

# DDx

- ❑ most nonspecific syndrome :  
distal symmetric sensorimotor polyneuropathy.  
( alcoholism, uremia, diabetes mellitus, and vitamin B<sub>12</sub> deficiency)
- ❑ Some toxins, such as lead, cause a neuropathy with prominent weakness.  
Hereditary and immunologic neuropathies (Charcot-Marie-Tooth )
- ❑ Approximately one-half to two-thirds of all polyneuropathies remain **undiagnosed** despite thorough investigation

Mostly sensory or sensorimotor polyneuropathy (little or no weakness)

Acrylamide

Carbon disulfide

Ethylene oxide

Metals: arsenic, lead, mercury, thallium

Methyl bromide

Polychlorinated biphenyls (PCBs)

Thallium

Predominantly motor polyneuropathy or sensorimotor polyneuropathy with significant weakness

Hexacarbons: n-hexane, methyl n-butyl ketone

Metals: lead, arsenic, mercury

Organophosphates

“Purely” sensory neuropathy (disabling sensory loss with no weakness)

cis-Platinum

Pyridoxine abuse

Cranial neuropathy

Thallium

Trichloroethylene (trigeminal neuropathy)

Prominent autonomic dysfunction

Acrylamide

n-Hexane (glue-sniffer)

Thallium

Vacor (PNU)

Possible association with neuropathies (mostly anecdotal)

Benzene

Carbon monoxide

Dioxin

Methyl methacrylate

Pyrethrins



# laboratory evaluation

- ▶ NCV

- ▶ EMG

(painful and uncomfortable)

- ▶ Nerve biopsy

- ▶ Ultrasonography (visualization of the nerve at sites of entrapment):carpal tunnel and the ulnar groove

- ▶ MRI & CT

Asymptomatic but radiologically significant  
spondylitis disease:

*frequently in the normal population.*

MRI or CT abnormalities:

more than **50% of asymptomatic** subjects older  
than **50** years of age

approximately **20%** of those younger than **50** years  
of age.

*Thus imaging studies should never replace a  
careful clinical evaluation*

CAUSED BY SPECIFIC TOXINS

# Acrylamide

- ▶ Workers who handle monomeric acrylamide in the production of polyacrylamides and those exposed to monomeric acrylamide used in grouting.
- ▶ Intoxication occurs by **inhalation** or **skin absorption**.
- ▶ Acute exposure:
- ▶ confessional state, disorientation, memory loss, and gait ataxia (*largely reversible, irreversible in very intense exposure*)

# Acrylamide

Chronic lower-dose exposure :

- ▶ dizziness, increased irritability, emotional changes, and sleep disturbances.
- ▶ The primary site of action: the peripheral nerve.
- ▶ Both sensory and motor nerves are affected (sensory loss, weakness, ataxia, and **generalized loss of tendon reflexes**)
- ▶ Autonomic involvement, such as hyperhidrosis and urinary retention, is common.

# Acrylamide

- ▶ abnormal accumulation of neurofilaments in axons (similar :organic solvents, notably the hexacarbons)
- ▶ Unlike hexacarbons, secondary demyelination does not occur.
- ▶ Nerve-conduction studies:
- ▶ little or no slowing of nerve-conduction velocities (axonal degeneration)



# Arsenic

- ▶ arsenic compounds are used as **wood preservatives**, as gallium arsenide in the semiconductor industry, and as **defoliant** and **desiccant** in agriculture.
- ▶ leaching of arsenic byproducts in smelting or heavy agricultural use of arsenicals:
- ▶ *Contamination of well water*

## Arsenic (acute exposure)

- ▶ Intense exposure: mental confusion, psychosis, anxiety, seizure, or coma. nausea, vomiting, abdominal pain, and diarrhea.
- ▶ Dermatologic lesions: hyperkeratosis, skin pigmentation, skin exfoliation
- ▶ Mees lines, occur in many patients 1-6 W after onset of disease.
- ▶ most common neurologic manifestation (acute or chronic exposure) : Peripheral neuropathy

## Arsenic (acute exposure)

- ▶ After a **single massive dose**:
- ▶ acute polyneuropathy (within 1-3 W)
- ▶ mimics **Guillain-Barre syndrome** (respiratory failure may occur rarely)
- ▶ Symmetric parasthesias, pain may occur (+/- distal weakness)
- ▶ ***With progression of neuropathy***, sensory and motor deficits spread proximally. Shoulder and pelvic girdle weakness, as well as gait ataxia, are common in severe cases.

## Arsenic

### (Chronic low-level exposure)

- ▶ subtle impairment of memory and concentration.
- ▶ In exposed children: lower verbal performance and hearing impairment.
- ▶ EMG and NCV: nonspecific axonal neuropathy.
- ▶ Arsenic is detectable in **blood** and **urine** during ongoing exposure, and may persist in **urine** for several weeks after *a single massive exposure*

- ▶ low-level exposure:
- ▶ **Blood arsenic level** returns to normal in about 12-24 hours
- ▶ **Urine arsenic** clears within 48-72 hours after exposure.
- ▶ Arsenic remains detectable in *hair and nails* for months after exposure.
- ▶ false-positive results !
- ▶ Pubic hair is preferable

# Carbon Disulfide

- ▶ as a solvent in perfume production and varnishes, in soil fumigants and insecticides, and in industrial manufacturing



## CS2 (acute exposure)

- ▶ brief inhalation exposure to a toxic level (300 ppm or above) : dizziness and headache, followed by delirium, mania, or mental dulling.
- ▶ Concentrations above 400 ppm have a narcotizing effect and may lead to convulsion, coma, and respiratory failure.

## CS2 (chronic exposure)

- ▶ **PNS**: parasthesias and pain in the distal legs, loss of Achilles reflexes, and evidence of involvement of sensory and motor axons on NCV
- ▶ **CNS**: nonspecific syndrome of fatigue, headache, and sleep disturbances
- ▶ On MRI of the brain, some exposed patients have *scattered abnormal foci in the subcortical white matter*.
- ▶ resembles :patients with small-vessel disease and multiple subcortical strokes, although pathologic confirmation is not available.

# Carbon Monoxide

- ▶ Inhaling low concentrations (0.01-0.02%):
- ▶ headache and mild confusion.
- ▶ A higher concentration (0.1-0.2%):
- ▶ somnolence or stupor
- ▶ inhalation of 1% for more than 30 minutes :
- ▶ fatal , **Early symptoms**: headache, dizziness, and disorientation.
- ▶ **More prolonged or severe hypoxia** : combination of tremor, chorea, spasticity, dystonia, rigidity, and bradykinesia.

## CO (acute exposure)

- ▶ Recovery from the hypoxia : **incomplete**
- ▶ take one or more years
- ▶ Residual dementia, spasticity, cortical blindness, and Parkinson

## CO (acute exposure)

- ▶ Neurologic examination:
- ▶ **encephalopathy** with prominent signs of **frontal lobe** and **extrapyramidal** dysfunction.
- ▶ (bradykinesia, spasticity, and limb rigidity)
  
- ▶ Risk factors for developing encephalopathy :
- ▶ significant period of unconsciousness and an advanced age.

## CO (acute exposure)

- ▶ CT or MRI :
- ▶ abnormalities in bilateral subcortical white matter
- ▶ involvement of the basal ganglia, especially the globus pallidus and the thalamus.



## CO (chronic exposure)

The effect of long-term exposure to low levels of carbon monoxide is **unclear**.

Nonspecific symptoms:

- ▶ anorexia, headache, personality changes, and memory disturbances

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

- ▶ volatile organic compounds in homes and industries as **solvents** and **adhesives**
- ▶ Human disease is a result of a toxic intermediary metabolite  $\gamma$ -diketone 2,5-hexanedione
- ▶ Toxic exposure : *inhalation* (especially in poorly ventilated spaces) or excessive *skin contact*.
- ▶ Another solvent used in paints and adhesives, methyl ethyl ketone, may potentiate the neurotoxicity

## Acute exposure

- ▶ Acute encephalopathy: euphoria, hallucination, and confusion.
- ▶ The acute euphoric : abuse as a recreational drug
- ▶ **Glue-sniffer's neuropathy:**
- ▶ acute euphoric effect, distal symmetric sensorimotor polyneuropathy (parasthesias and sensory loss and weakness of distal muscle initially)
- ▶ Proximal musculatures involvement (in more severe cases)

- ▶ Optic neuropathy and facial numbness
- ▶ Autonomic symptoms (uncommon - in very severe cases)
- ▶ Nonspecific (CNS) symptoms : insomnia and irritability
- ▶ On examination, sensory loss and weakness are readily demonstrable
- ▶ No Achilles stretch reflexes (early in the disease)
- ▶ **Recovery**: begins after a few months of abstinence –incomplete

# n-Hexane

- ▶ *distinctive neuropathology.*
- ▶ Multiple foci of neurofilament accumulations form inside the nerve axons.
- ▶ Secondary demyelination.
- ▶ Because of this demyelination, slowing of motor nerve-conduction velocities.
- ▶ Cerebrospinal fluid (*CSF*) *protein* content is typically *normal*, in contrast to most *other demyelinating neuropathies*, which are associated with *elevated CSF protein*

## Chronic exposure

- ▶ The clinical features are essentially **similar**, although the syndrome evolves **more slowly** and results in **less severe deficits**



# Lead

## Industrial sources

paint,  
batteries,  
pipes,  
solder,  
ammunition,  
cables.

## Nonindustrial sources

pottery,  
bullet fragments,  
traditional folk remedies

## Lead (Acute high-level exposure )

- ▶ Accidental ingestion
- ▶ Inhalation
- ▶ Industrial exposure

## Lead (Acute high-level exposure )

- ▶ **Syndrome** of abdominal colic and intermittent vomiting, accompanied by neurologic symptoms such as headache, tremor, apathy, and lethargy.
- ▶ **Massive intoxication** : convulsions, cerebral edema, stupor, or coma and eventually to transtentorial herniation
- ▶ acute lead-induced encephalopathy, brain CT or MRI may show focal areas of edema, most commonly in bilateral thalami and basal ganglia

# Lead

- ❑ Lead encephalopathy typically appears in adults at blood levels of 50–70 mg/dL or higher.
- ❑ Behavioral disturbances and neuropsychologic impairment may be present at blood levels as low as 10 mg/dL
- ❑ Children are more vulnerable than adults (immaturity of the blood-brain barrier)
- ❑ Chronic low-level exposure to lead is responsible for impaired intellectual development in children.

- ▶ adults with past industrial exposure may have a faster rate of cognitive decline than that expected from normal aging
- ▶ These subjects typically have normal blood lead levels

but elevated lead levels in bone, as measured by x-ray fluorescence

- ▶ The lead storage in bone potentially can be mobilized throughout life, particularly with **bony fractures**

# Lead (Chronic low-level exposure)

- ▶ Peripheral neuropathy
- ▶ Predominantly motor neuropathy (little or not sensory symptoms)
- ▶ Mimics motor neuron diseases (ALS)
- ▶ Bilateral wrist drop and foot drop.
- ▶ Generalized proximal and distal weakness and loss of the tendon reflexes.
- ▶ chronic lead toxicity: intracranial calcification



# Manganese

- ▶ manufacture of steel, alloys, and welding , alkaline batteries and various fungicides
- ▶ Poisoning:
- ▶ mining, smelting, milling, and battery-manufacturing industries.
- ▶ methylcyclopentadienyl manganese tricarbonyl (MMT):  
an additive used in gasoline

# Manganese

- ▶ manganese poisoning, or manganism:  
extrapyramidal disorder(idiopathic Parkinson disease)
- ▶ Tremor, rigidity, masked facies, and bradykinesias develop slowly.
- ▶ Compared with idiopathic Parkinson disease
  - 1- Dystonia  
(an uncommon finding in idiopathic Parkinson)
  - 2- manganism are less responsive to dopaminergic therapy.

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

# Manganese

- ▶ selectively damages neurons in globus pallidus and the striatum.
- ▶ brain MRI:
- ▶ increased signal in the globus pallidus  
(not seen in Parkinson disease and other forms of parkinsonism)

- ▶ clearance of dietary manganese : liver
- ▶ chronic liver failure:
  - parkinsonism, cognitive impairment, and gait ataxia
  - abnormal T1 signal in the globus pallidus
  - mildly elevated blood manganese level.

# Mercury

- ▶ Mercury poisoning by exposure to :
  - ✓ Methyl mercury (alkylmercury compounds)
  - ✓ Elemental mercury (mercury vapor)
  - ✓ Inorganic mercuric salts.

# Mercury

batteries, fungicides, electronics, and other industries.

- ▶ Mercury in sludge and waterways is methylated by microbes into methyl mercury that is readily absorbed by humans.
- ▶
- ▶ Several large endemics :Minamata Bay (Japan), in Iraq



## Mercury (acute exposure)

- ▶ Diffuse encephalopathy: (euphoria, irritability, anxiety, and emotional lability.)
- ▶ In More severe exposure: Confusion and an altered level of consciousness .
- ▶ Tremor and Cerebellar ataxia, Hearing loss, visual field constriction, hyperreflexia, and Babinski sign
- ▶ (organic mercury, metallic mercury, mercury vapor, or inorganic salts)

## Mercury (acute exposure)

- ▶ **Organic mercury poisoning** : prominent CNS disturbances, with little or no peripheral nervous system involvement.
- ▶ **Inorganic mercury poisoning**: Neuropathy is prominent.
- ▶ metallic mercury or mercury vapor exposure :
- ▶ subacute predominantly motor neuropathy,
  - acute syndrome resembles Guillain-Barre syndrome,
  - subacute syndrome may mimic ALS.

# Methanol

- ▶ neurotoxicity of methanol:
  - ▶ formaldehyde and formate
- ▶ Most cases result from **accidental ingestion** or **occupational exposure**
- ▶ Neurologic symptoms usually appear after a latent period of 12–24 hours
- ▶ headache, nausea, vomiting, and abdominal pain. Tachypnea(significant metabolic acidosis)

# Methanol

- ▶ *Visual symptoms* appear early and range from blurring to complete blindness.
- ▶ *encephalopathy*, from mild disorientation to convulsion, stupor, or coma.
- ▶ In severely affected individuals,
- ▶ *bilateral upper motor neuron signs* such as hyperreflexia, weakness, and Babinski
- ▶ Brain CT or MRI :
- ▶ infarction or hemorrhage:
- ▶ in bilateral putamina or subcortical white matter.

# Methanol

- ▶ Treatment of acute poisoning :
  - sodium bicarbonate,
  - fomepizole or ethanol :  
(competitive inhibition of the conversion of methanol to formaldehyde )
  - gastric lavage or hemodialysis.
- ▶ The neurologic effect of chronic low-level methanol is less clear.

# Methyl Bromide (MeBr):

- ▶ Organic bromides are more toxic than inorganic ones
- ▶ used in greenhouses and fields for control of nematodes, fungi, and weeds.
- ▶ acute central nervous system toxicity
- ▶ with longer exposures peripheral neuropathy and neuropsychiatric dysfunction.

# Methyl Iodide

- ▶ various pharmaceutical and pesticide synthesis processes.
- ▶ Narcotic
- ▶ case reports :  
parkinsonism, cerebellar, and latent  
neuropsychological sequela similar to MeBr.



# Nitrous Oxide

- ▶ substance abuse
- ▶ myeloneuropathy indistinguishable from vitamin B12 (cobalamin) deficiency
- ▶ parasthesias in the hands and feet. Gait ataxia, sensory loss, Romberg sign, and leg weakness
- ▶ Tendon reflexes:  
diminished or lost (peripheral neuropathy)

# Nitrous Oxide

inactivates vitamin B12 and interferes with B12-dependent conversion of homocysteine to methionine.

- ▶ Serum vitamin B12 and the Schilling test often are normal, whereas the serum homocysteine level may be elevated
- ▶ symptoms in normal individuals with Repeated exposures .
- ▶ brief exposure to nitrous oxide, for example during anesthesia, precipitate symptoms in patients with asymptomatic B12 deficiency.

# Organic Solvents

- ▶ industrial contact or volitional abuse.
- ▶ Most organic solvents possess acute narcotizing properties.
- ▶ Brief exposure at high concentrations: reversible encephalopathy.
- ▶ Coma, respiratory depression, and death occur after extremely high exposures.
- ▶ Chronic exposure to moderate or high levels of solvent :  
dementing syndrome, personality changes, memory disturbances, and other nonspecific neuropsychiatric symptoms. A sensorimotor polyneuropathy.

- ▶ chronic low-level exposure:
- ▶ *painters' syndrome, chronic solvent encephalopathy, and psycho-organic solvent syndrome*
- ▶ Nonspecific symptoms:
- ▶ headache, dizziness, asthenia, mood and personality changes, inattentiveness, forgetfulness, and depression, cerebral atrophy in chronically exposed subjects

# Organophosphates

- ▶ Organophosphates (OPs) are used:
  - ✓ commonly as pesticides and herbicides
  - ✓ to a lesser extent, as petroleum additives, antioxidants, and flame retardants.
- ▶ They are highly lipid soluble
- ▶ absorbed through skin contact or through mucous membranes via inhalation and ingestion
- ▶ Inhibiting the enzyme acetylcholinesterase

## acute neurologic effects

- ▶ Muscarinic and Nicotinic overactivity.
- ▶ Symptoms : (within hours of exposure) abdominal cramps, diarrhea, increased salivation, sweating, miosis, blurred vision, and muscle fasciculation's.
- ▶ **Severe intoxication**: Convulsions, coma, muscle paralysis, and respiratory arrest
- ▶ **Recovery** : complete and within 1 week
- ▶ Acetylcholinesterase activity level: restored only partially.

## intermediate syndrome

- ▶ occurs within 12-96 hours of exposure
- ▶ result of excessive cholinergic stimulation of nicotinic receptors in skeletal muscles. (blockage of neuromuscular junction transmission)
- ▶ Weakness of proximal muscles, neck flexors, cranial muscles, and even respiratory muscles
- ▶ Sensory function is spared



# delayed syndrome

- ▶ Peripheral neuropathy occurs 1-4 W after acute exposure.
- ▶ OPs inhibit neuropathy target esterase (NTE), forming an OP-NTE complex. (irreversible OP-NTE complex - known as *aging*)

Resulting in the delayed polyneuropathy:

- ▶ parasthesias and cramping pain in the legs
- ▶ Sensory loss is usually mild on physical examination.
- ▶ Weakness (distal to proximal muscles)
- ▶ Spasticity and other upper motor neuron signs
- ▶ Recovery is slow and incomplete

| Toxins            | Acute Exposure   | Chronic Exposure  |
|-------------------|--|---|
| Carbamates        | Cholinergic overactivity (similar to organophosphates)         | Encephalopathy, tremor, polyneuropathy  |
| Ethylene oxide    | Encephalopathy   | Sensorimotor polyneuropathy   |
| Manganese         | None (symptoms take weeks or months to develop)                | Parkinsonism (tremor, rigidity, gait disturbances), encephalopathy, possible motor neuron disease |
| Organotin         | Encephalopathy, visual disturbances                            | Encephalopathy, visual disturbances, hearing loss, vertigo  |
| Thallium          | Subacute polyneuropathy after massive exposure, encephalopathy | Sensorimotor polyneuropathy   |
| Toluene           | Euphoria or narcosis, encephalopathy                           | Cerebellar ataxia, tremor, encephalopathy   |
| Trichloroethylene | Euphoria or narcosis, encephalopathy, trigeminal neuropathy    | Trigeminal neuropathy, encephalopathy   |

# Zinc

- ▶ Myeloneuropathy: similarly to a nitrous oxide myelopathy
- ▶ Various common foods and in some denture creams.
- ▶ Inhaled in occupational hazard:
  - ▶ welding, construction, or the automotive industry.
- ▶ Excessive zinc ingestion antagonizes copper absorption, (hypocupremia, a condition associated with myelopathy and neuropathy)
- ▶ diagnosis : presence of elevated zinc and depressed copper levels in the serum