

## Target Organ Toxicology

Principles of Environmental Toxicology  
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 University of Idaho

## Learning Objectives

- Define target organ toxicity.
- Explain the basis for specificity of organ toxicity.
- Contrast the toxicity mechanisms for:
  - Hemotoxicity.
  - Hepatotoxicity.
  - Nephrotoxicity.
  - Neurotoxicity.
  - Dermotoxicity.
  - Pulmonotoxicity.

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## Learning Objectives, 2

- Describe examples of target organ toxicity.
- Discuss the characteristic evaluative procedures for determining toxicity in target organs.
- Explain the concept of oxidative stress and demonstrate an understanding of the action of antioxidant enzymes and redox cycling compounds.
- Examine the molecular pathways of cholinesterase inhibition.

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## Target Organ Toxicity

- Adverse effects or disease states manifested in specific organs in the body.
- High cardiac output = higher exposure.
- Organs each have specialized tissues and specialized cells.
- Differentiated cellular processes and receptors.
- Toxicants and metabolites may have specific reactive pathways.

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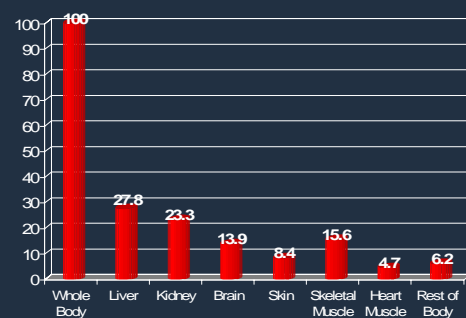
## Target Organ Toxicity, 2

- Toxicants do not affect all organs to the same extent.
- A toxicant may have several sites of action and target organs.
- Multi-toxicant exposure may target the same organ.
- The target organ may not be the site for storage.
- Toxicokinetic processes determine concentrations in target organs.

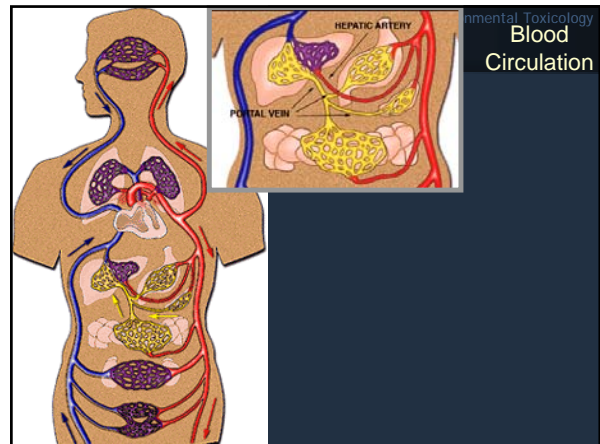
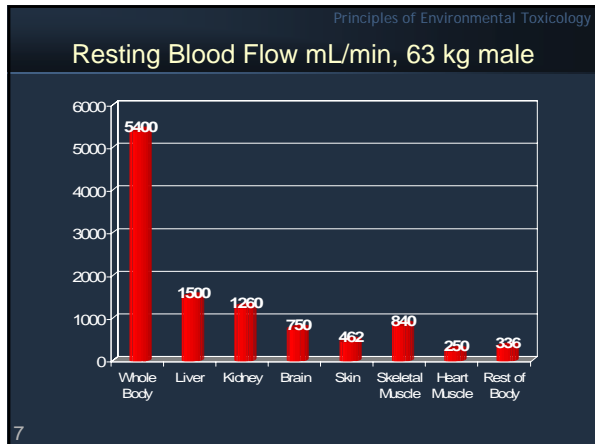
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## Resting Cardiac Output %, 63 kg male



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### Hemotoxicity

- Blood cell components: erythrocytes, leukocytes, thrombocytes.
- Hemotoxicity occurs when the number or function of blood cells is toxicant impaired.
  - Function:  $\text{NO}_3^-$ ,  $\text{CN}^-$ ,  $\text{CO}$ ,  $\text{H}_2\text{S}$ ,  $\text{Zn}^{2+}$ .
  - Number: anemia, leukemia, thrombocytopenia, agranulocytopenia.
- Evaluation.
  - CBC, ABG, toxicant/metab.

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### Case Study: Methemoglobinemia Following Unintentional Ingestion of Sodium Nitrite, NY 2002

- On May 16, 2002, Yonkers, New York, emergency personnel were called to a household in which five adults of Middle Eastern descent (three men aged 40, 43, and 44 years and two women aged 60 and 29 years) reported symptoms of dizziness, lightheadedness, and cyanosis almost immediately after sharing a meal. Two of the men also reported vomiting. A sixth person, a man aged 21 years, who did not eat the meal, was asymptomatic.
- On arrival, the first responders found the younger woman unresponsive; all others were awake and alert. En route to the hospital, both women had progressive respiratory distress and loss of consciousness and were intubated; the older woman began having seizures.

10 MMWR (2002) 51(29):639-642

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### Case Study: Methemoglobinemia Following Unintentional Ingestion of Sodium Nitrite, NY 2002

- On arrival at the emergency department (ED), the five persons were markedly cyanotic and had oxygen saturation levels by pulse oximetry of 72%--96% (normal:  $\geq 92\%$ ). Blood drawn for routine testing was described as "black colored."
- Empiric therapy with methylene blue was initiated for suspected methemoglobinemia after consultation with a poison control center. Subsequently, the patients were found to have extremely high methemoglobin levels (range: 21.1%--87.0%) (normal: 1%--3%).

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### Case Study: Methemoglobinemia Following Unintentional Ingestion of Sodium Nitrite, NY 2002

- Within 10--15 minutes after administration of methylene blue, cyanosis resolved and oxygenation improved. After therapy, the three men became asymptomatic, and the two women continued to require ventilatory support; the younger woman did not regain consciousness immediately.
- After overnight observation, the three men were discharged. The older woman was extubated on May 18, and the younger woman was extubated on May 20; all patients recovered completely.
- Follow-up investigation suggests that sodium nitrite used for meat curing by an acquaintance was put into a bag marked "Iodized Table Salt" in English and Arabic. This nitrite salt was added during cooking.

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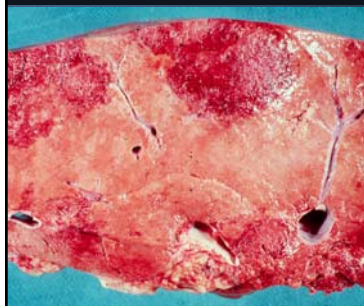
## Hepatotoxicity

- Functionally important organ for life processes.
  - Biosynthesis, nutrient metabolism.
- Most important organ in detoxication and biotransformation.
  - Site for toxication by metabolism.
- High cardiac output and first pass effects.
- Enterohepatic recirculation.
  - Potential for re-exposure.



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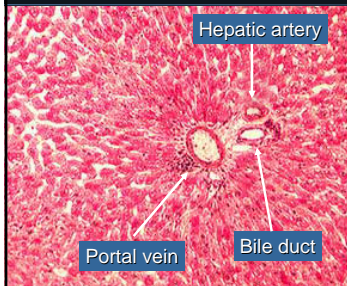
## Liver



Infarction, necrosis, hemorrhage (bovine)

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## Liver Histology



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## Hepatotoxicity

- Cytotoxic.
  - Lipid peroxidation (oxidative stress).
  - Necrosis.
  - Cirrhosis, fibrosis.
  - Fatty liver.
- Cholestatic.
  - Flow of bile interrupted.
- Liver function indicators.
  - Liver enzymes.
  - Gross tissue effects.

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## Focus Area: Oxidative Stress

- All aerobes generate free radicals in normal respiratory function.
  - Superoxide,  $O_2^*$ .
- Normal antioxidant enzyme system detoxifies the radicals.
- Antioxidant enzymes are inducible.
  - Catalase.
  - Superoxide dismutase.
    - SOD.
  - Glutathione peroxidase.
    - GSH-px.

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## Redox Cycling Compounds

- Some xenobiotic compounds are readily oxidized and sequentially reduced by normal biochemical processes.
  - Radical formation.
  - Rechargeable cycle.
- Toxic endpoints.
  - Lipid peroxidation.
  - DNA strand breaks.

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## Redox Cycling Compounds, 2

- Typical compounds are highly polar.
- Able to be oxidized by  $O_2$ .
- Able to be reduced by flavin enzyme (FAD).
  - Paraquat.
  - Nitro aromatics.
  - Chelated metals ( $Zn^{2+}$ ).

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## ROS, RNS Examples

Halliwell, 1996

- Reactive oxygen species.
  - Superoxide.
    - $O_2^-$
  - Hydroxyl.
    - $OH^*$
  - Peroxyl, alkoxy.
    - $RO_2^*$ ,  $RO^*$
- Reactive nitrogen species.
  - Oxides of nitrogen.
    - $NO^*$ ,  $NO_2^*$

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## Reactive Radical Species

- Where do they come from?
  - Breathing oxygen
  - UV radiation
  - Infection
  - Oxidants, and redox cycling compounds found in diet and environmental exposure.



## Free Radicals

- Highly reactive.
- Can initiate chain reactions - find electron rich molecules.
- Damage to cells, DNA.
- Factor in degenerative disease.
- Antioxidants are radical scavengers.
  - Vitamin C and  $\beta$ -Carotene quench reactive oxygen.
  - Vitamin E and  $\beta$ -Carotene break chain reactions.
  - Se-GSH-px quenches peroxide.

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## Beneficial Oxidative Processes

- Chemotaxis of cells with immunological functions.
- Phagocytosis.
- Triggering of clotting mechanisms.
- Apoptosis.

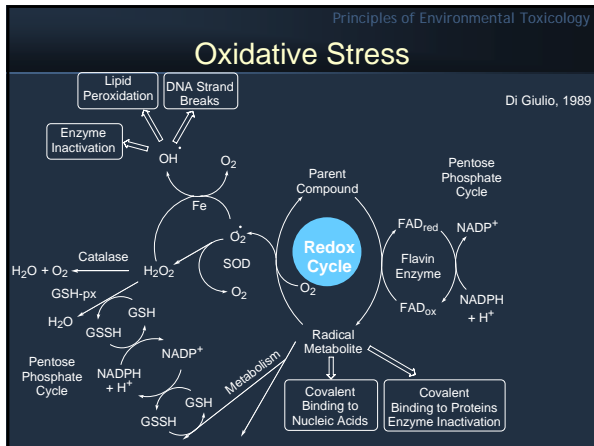
Bury, 1995  
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## Antioxidants

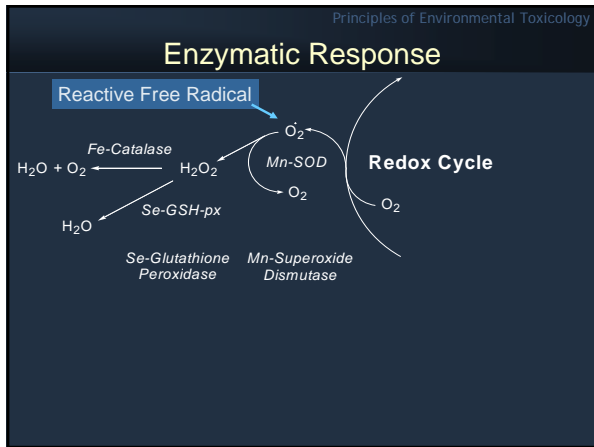
### Mechanism of Action


- Decreasing ROS, RNS formation.
- Binding redox cycling metal ions.
- Scavenging ROS, RNS and precursors.
- Adaptive antioxidant enzyme response.
- Repairing oxidative damage to biomolecules.
- Enhancing repair enzymes.

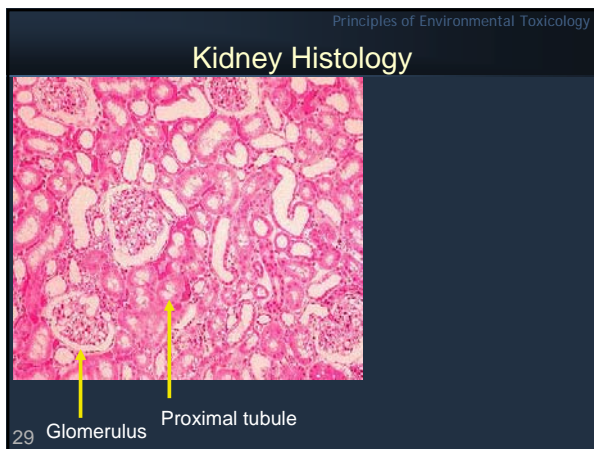
NAS, IOM 2000  
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- ## Endpoints of Oxidative Stress
- Lipid peroxidation.
  - DNA strand breaks.
  - Enzyme inactivation.
  - Covalent binding to nucleic acids.
  - Covalent binding to proteins.
- 
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- ## Nephrotoxicity
- Processes of the kidney.
    - Glomerular filtration.
    - Tubular re-absorption.
    - Tubular secretion.
  - Toxic effects.
    - Porosity, osmotic changes.
    - Modification of tubular re-absorption.
      - Water, electrolyte, nutrient loss.
    - Active transport loss.
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- ## Nephrotoxicity, 2
- Nephrotic syndrome.
    - Glomerular filtration injury.
    - Proteinuria.
      - Lead toxicosis.
  - Nephritic syndrome.
    - Glomerular filtration injury.
    - Hematuria.
  - Acute tubular necrosis (ATN).
    - Acute renal failure.
  - Tubular re-absorption effects.
  - Obstructive uropathies.
    - Kidney stones.
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## Toxic Acute Tubular Necrosis

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## Kidney Function Indicators

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- Glomerular filtration rate (GFR).
- Active tubular secretion of PAH.
- Removal of serum waste products.
  - Blood urea nitrogen (BUN).
    - Catabolism of protein.
  - Creatinine.
    - Muscle metabolism product.

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## Pulmonotoxicity

- Gas exchange function critical to life.
- Rapid exchange, high surface area and sensitivity of mucosal tissues make the respiratory system susceptible to damage.
- Chemical irritants, carcinogens, allergens, mineral dusts, cytotoxic chemicals.
- Endpoints: Inflammation, edema, necrosis, fibrosis, carcinoma.
  - ARDS, asthma, lung cancer, infarcts, emphysema.



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## Asbestos

Asbestos fiber  
in lung tissue

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## Dermatotoxicity

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- Irritant contact dermatitis.
- Allergic contact dermatitis.
- Phototoxicity.
  - UV and a phototoxic compound.
- Integumentary cellular effects.
  - Chloracne.

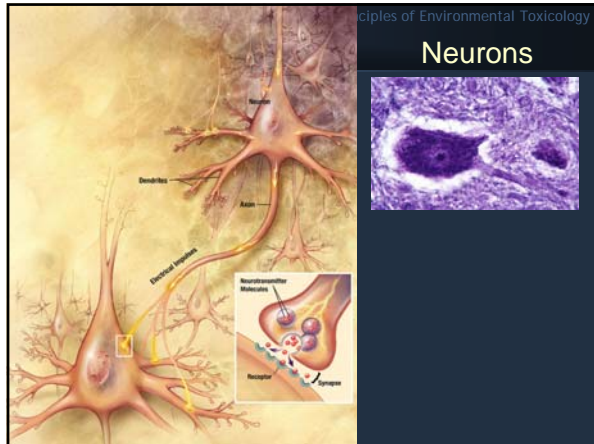
Phytophotodermatitis  
from Oil of Bergamot  
(found in citrus)

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## Neurotoxicity

- Central nervous system (CNS).
  - Brain and spinal cord.
- Peripheral nervous system (PNS).
  - Sensory and motor control.
- Neurons.
  - Cell body, dendrites, axon.
- Glial cells; structure.
  - Astrocytes, nutrient transport.
  - Oligodendrites/Schwann, myelin
  - Microglia, immune function.

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## Neurotoxicity, 2

- Active transport of Na<sup>+</sup> (out) and K<sup>+</sup> (in) creates an electrical potential across axonal membrane.
- Passive reverse transport initiates cascading depolarization.
- At the synapse, neurotransmitters are released to chemically transmit a depolarization to the next neuron.
- Neurotransmitters cross the synaptic cleft to receptors.

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## Neurotoxins

- Can impact Na<sup>+</sup>/K<sup>+</sup> channels.
  - Inhibition; stimulation.
- Bind neurotransmitter receptor sites.
- Inhibit enzymes responsible for neurotransmitter catabolism.
- Damage myelin sheath.
- Morphological (membrane) damage.
- Necrosis.

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## Case Study: Equine and Yellow Star Thistle

Nigropallidal encephalomalacia

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## Cholinesterase Inhibition

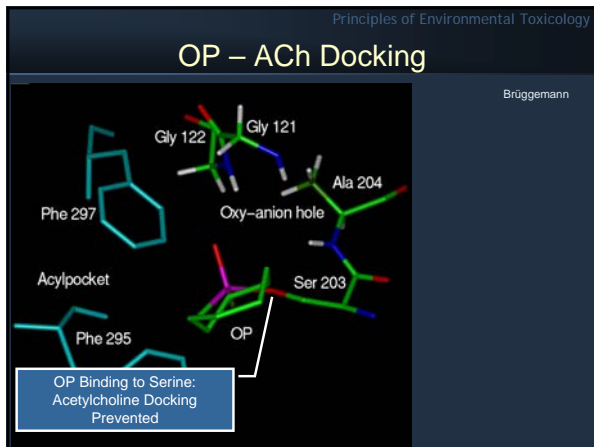
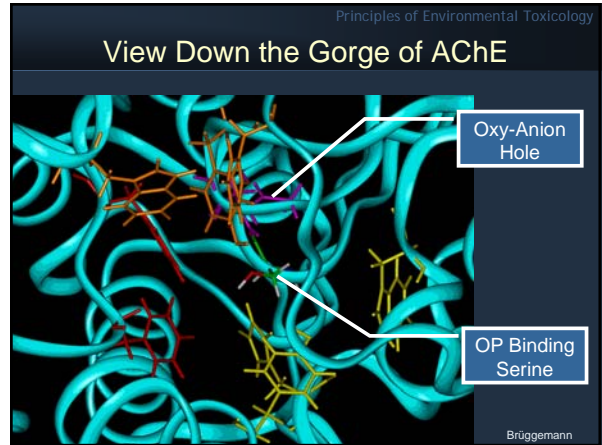
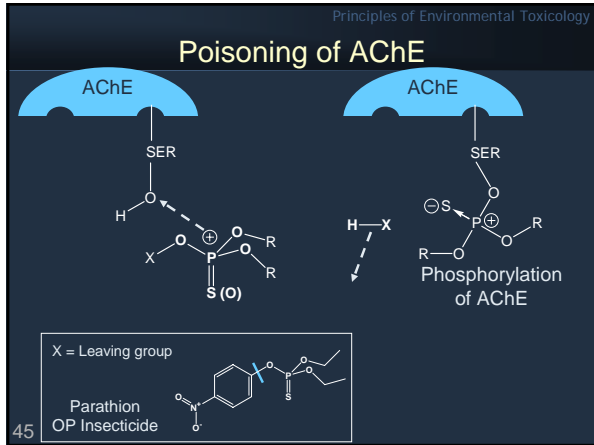
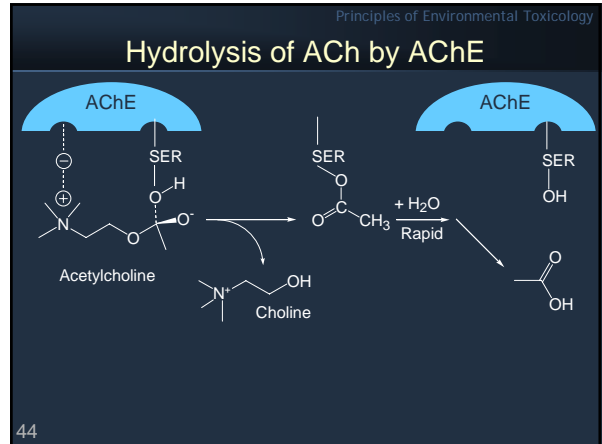
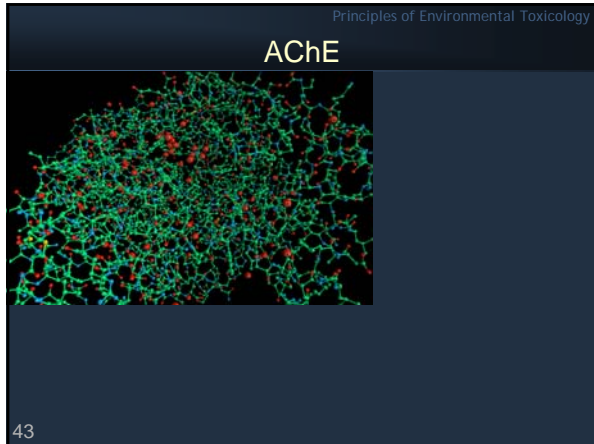
- Acetylcholine is the chemical mediator responsible for physiological transmission of nerve impulses across the synapse.

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## Acetylcholinesterase

- The function of acetylcholinesterase is to hydrolyze acetylcholine.
- The active site of AChE contains two sub-sites, the esteratic and the anionic.
- Nerve impulses release ACh which is rapidly destroyed by AChE; allows normal propagated impulse.
- Interferences of AChE activity leads to accumulation of the neurohormone ACh.

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### 2-PAM Antidote

- 2-PAM chloride cleaves the neurotoxic agent from the cholinesterase enzyme and restores the enzyme's activity.

Pyridine aldoxime methochloride  
(Protopam® Chloride,  
2-PAM, 2-PAM Chloride)

- Most noticeable at tissues with nicotinic receptors vs. atropine which is effective at peripheral muscarinic sites.
- Immediate therapy or "aging" occurs.

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## Case Study: Anticholinergic Poisoning from Herbal Tea, New York City, 1994

- During March 1994, the New York City Department of Health investigated seven cases of anticholinergic poisoning in members of three families; three of the seven ill persons required emergency treatment for characteristic manifestations.
- For all cases, manifestations occurred within 2 hrs after drinking tea made from leaves purchased commercially and labeled as Paraguay tea -- an herbal tea derived from the plant *Ilex paraguariensis*, which is native to South America.

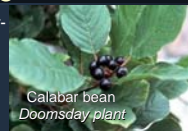


49 MMWR (1995) 44(11):193-195

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## Anticholinergic Poisoning: Patient

- On March 20, a 39-year-old man and his 38-year-old wife shared a pot of Paraguay tea. Within 30 minutes after drinking the tea, both developed acute symptoms (including agitation and flushed skin).
- They were transported by ambulance to a local hospital. In the emergency department, the man was disoriented and agitated. Findings on examination included fever (101.2 F {38.4 C}), dilated and nonreactive pupils, and dry skin and oral mucous membranes; bowel sounds were absent.
- Anticholinergic poisoning was diagnosed based on clinical findings. After treatment with two doses of intravenous physostigmine (reversible cholinesterase inhibitor obtained from the Calabar bean), signs and symptoms completely resolved.



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