An Overview of Chemical Terrorism Agents

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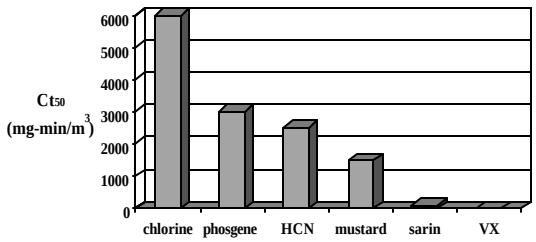
Chemicals Used as Weapons

- **Lung-damaging agents**
  - **Chlorine, phosgene**
- **Blood agents**
  - **Cyanide, cyanogen chloride**
- **Blister agents (vesicants)**
  - **Sulfur mustard, lewisite**
- **Nerve agents**
  - **Sarin, Tabun, VX**

Comparative Toxicity of Chemical Weapons Agents (lethal dose)

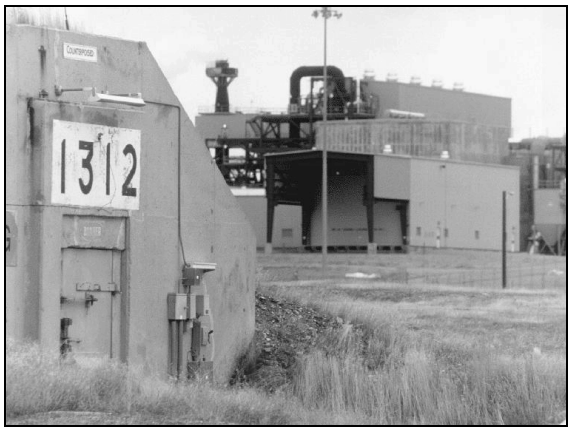


Biological/Chemical agents that may be used as used as weapons

- **Ricin (Castor bean plant)**
- **Botulinum toxin (*Clostridium botulinum*)**

Chemical Weapons Convention

- **143 countries (including US) have ratified (2001)**
- **Countries must destroy stockpiles by 2007**
- **Non-signatories: Egypt, Iraq, Israel, Libya, Syria, North Korea**



Respiratory Agents

Respiratory Toxicants

- **Chlorine**
- **Phosgene**
- **Diphosgene**
- **Zinc Oxide**
- **Titanium Tetrachloride**

Chlorine – Physical Properties

- **Gas at STP (bp = -34° C)**
- **2.5 times heavier than air**
- **Green-yellow color**
- **Acrid, pungent odor**

Chemical Warfare

- **WW I – April 22, 1915**
- **Ypres, Belgium**
- **Germans released 150 tons of chlorine from 6,000 cylinders**
- **2,500 – 3,000 incapacitated, 800 dead**

Chlorine - High volume industrial chemical

- **US production (14 million tons– 1998)**
- **Industrial uses**
  - **bleach* (paper, cloth)**
  - **synthetic rubber**
  - **plastics**
  - **chlorinated solvents**
- **Water disinfection**
- **Transportation accidents**

Chlorine reactions in respiratory tract

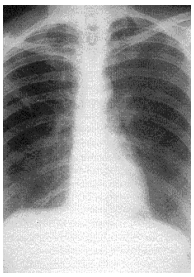
Generation of HCl and HOCl

$Cl_2 + H_2O \; ? \quad HOCl + HCl$

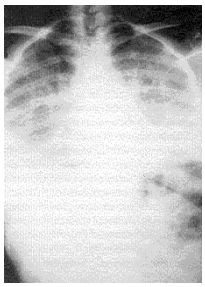
Generation of oxygen free radicals

$Cl_2 + H_2O \; ? \quad 2HCl + O^{\cdot}$

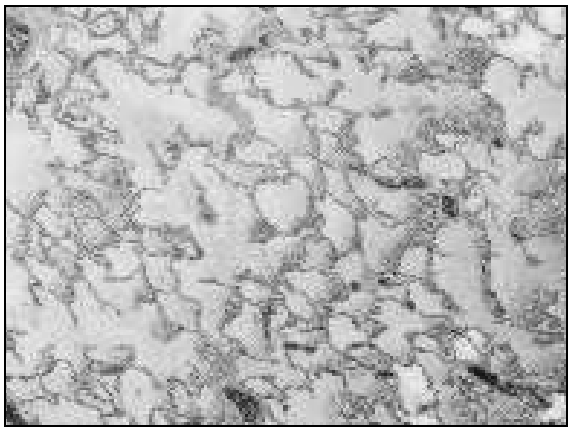
$HOCl \; ? \quad HCl + O^{\cdot}$



- **Normal CXR**



- **Severe edema**



Treatment for Chlorine Exposure

- **Administer aerosolized bronchodilators for bronchospasm**
- **Secure airways with endotracheal tube**
- **Treat hypoxemic respiratory failure with positive-pressure ventilation**
- **Treat bacterial infection (3-5 days post-exposure)**

Blood Agents

"Blood" Toxicants (Cytotoxic Poisons)

- **Cyanide**
- **Cyanogen chloride**

Hydrogen Cyanide – Physical Properties

- **Colorless gas/liquid (bp = 78° F)**
- **Gas density: 0.94**
- **Completely soluble in water and organic solvents**
- **Scent of bitter almonds? (~25% anosmic)**

Chemical Warfare

- **Used by France in WW I**
- **Used by Iraq against Iran and against Iraqi Kurds**

Cyanide – High volume industrial chemical

- **US production: 0.73 million tons in 1997**
- **Industrial uses**
  - **Electroplating**
  - **Chemical synthesis**
  - **Gold and silver extraction**
- **Fumigation**

Cyanide related deaths

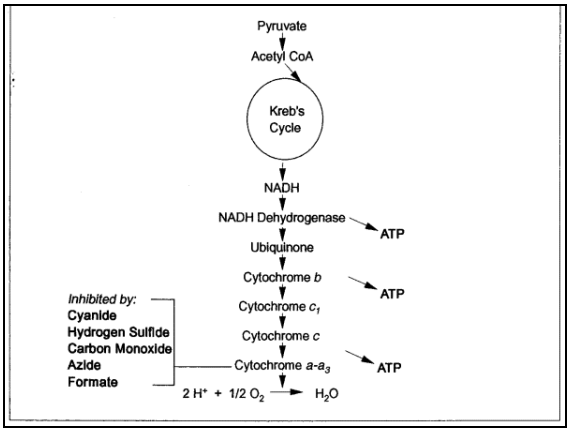
- **WW II – Nazi concentration camps**
- **1982 – Seven deaths from cyanide adulterated Tylenol**
- **Executions in US prisons**
- **1998 - 359 cases of cyanide poisoning reported to Poison Control Centers**
  - **301 accidental, 33 intentional, 25 not reported**
  - **10 fatalities**

Most bizarre case of cyanide poisoning

- **1978 – mass suicide of 913 followers of Rev. Jim Jones in Jonestown, Guyana**

Cyanide: Toxicological mode of action

- **Blocks electron transport in mitochondria**
  - **binds to Fe in cytochrome oxidase**
  - **prevents electron transfer to oxygen**
- **Shift to anaerobic metabolism (glycolysis)**
- **Oxygen-dependent tissues most affected (CNS, heart)**



Hydrogen Cyanide (High dose inhalation exposures)

- **Transient hyperpnea (stimulation of respiratory chemoreceptors)**
- **Brain seizures**
- **Respiratory arrest**
- **Cardiac arrest (6-8 minutes post exposure)**

Treatment for cyanide toxicity

- **Stop further exposure**
- **Institute supportive therapy**
  - **Assisted ventilation**
  - **i.v. sodium bicarbonate for metabolic acidosis**
  - **Control seizures with anticonvulsants (diazepam)**
- **Administer antidotes (if unconscious)**

Antidotes for cyanide toxicity

Pasadena (Formerly Lilly) Cyanide Antidote Kit

(1) Amyl nitrite and sodium nitrite

(2) Sodium thiosulfate

Antidotes for cyanide toxicity

Administer amyl nitrite (inhalation) or sodium nitrite* (iv)

- **Oxidizes hemoglobin to methemoglobin (Fe+2 ? Fe+3)**
- **Cyanide binds to methemoglobin rather than to cytochrome oxidase**

Antidotes for cyanide toxicity (cont.)

Administer sodium thiosulfate (iv)

- **Rhodanese catalyzes conversion of cyanide to thiocyanate (requires sulfur)**
- **Other metabolic pathways may also detoxify cyanide**

Ricin

Castor bean plant

- **Cultivated in India, China, Brazil for oil**
- **Grown as ornamental in U.S.**
- **Grows as weed in southwest U.S.**
- **Ricin - Natural toxin extracted from castor beans**

Ricin toxicity

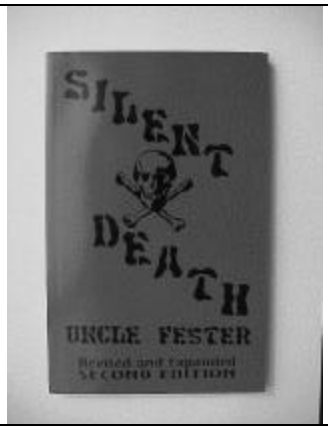
- **> 750 cases of human intoxication reported from ingesting castor beans (14 deaths)**
- **Circa WW II, U.S. and Britain tested ricin bomb – no further development**
- **Terrorist agent**
  - **Included in Al-Qa`ida training manuals**

Terrorist use of ricin – cont.

- 1995 – Minnesota Patriots Council
  - plotted to kill Federal marshal with ricin
  - 4 members convicted under U.S. Biological Weapons Anti-Terrorism Act
- Jan 2003 – police raid a London apartment
  - find castor beans and equipment
  - arrest 6 suspected Islamic militants

Ricin

- Extracted from castor beans (1-5% by weight)
- 2 chain protein – linked by a disulfide bond
- MW = 66,000
- Water soluble



Toxicological mode of action

- **B chain binds to cell membrane**
- **A chain – endonuclease**
- **Cleaves a specific adenosine from 28s subunit of ribosomal RNA**
  - **Inhibiting intracellular protein synthesis**

Clinical effects

- **Depends on route of administration**
- **More toxic by inhalation than by ingestion**
- **Symptoms appear 2-3 hours after exposure**
- **Death $\geq$ 3 days**

Clinical Effects (Oral)

- **Gastroenteritis and fluid depletion: nausea, vomiting, bloody diarrhea, severe dehydration, vascular collapse, shock**
- **Treatment: Supportive**

  Activated carbon gavage, intravenous fluids, electrolyte replacement

Clinical Effects (Inhalation)

- **Progressive respiratory failure:**

  cough, weakness, respiratory distress, necrotizing pneumonia of airways, alveolar inflammation and edema
- **Treatment: Supportive**

  assisted ventilation, supplemental oxygen, anti-inflammatory agents

Nerve Agents

Nerve Agents

- **Tabun (GA)**
- **Sarin (GB)**
- **Soman (GD)**
- **VX**

History

- **Germany (WW II) developed nerve agent munitions – but did not use!**
- **Used by Iraq in Iran-Iraq war and against Kurds**
- **US stockpiles remain**

Terrorist use of Sarin

- **Aum Shinrikyo cult (Japan)**
- **Matsumoto, 1994**
  - **~200 casualties**
  - **7 deaths**
- **Tokyo, 1995**
  - **~5,000 casualties**
  - **12 deaths**

Toyko Sarin Attack

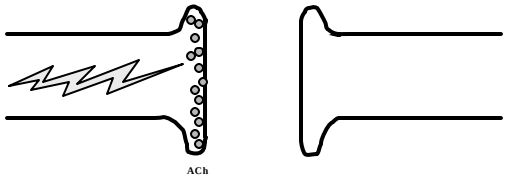
Physical Properties

- **Liquid at room temperature**
  - **"nerve gas" is misnomer**
- **Soluble in fat and water**
  - **Absorbed through eyes, respiratory tract, skin**
- **Persistency in soil**
  - **hours (Sarin)**
  - **days (VX)**

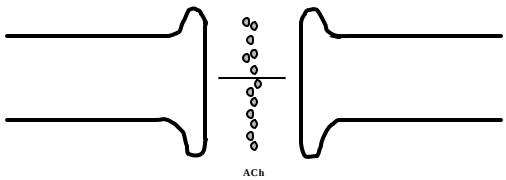
Toxicity

Agent	LCt_{50} (mg-min/m^3)
Tabun (GA)	400
Sarin (GB)	100
Soman (GD)	70
Cyclohexyl Sarin (GF)	50
VX	10

Nerve Transmission: Nerve to Nerve



Nerve Transmission: Nerve to Nerve



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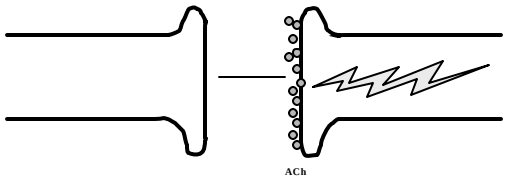
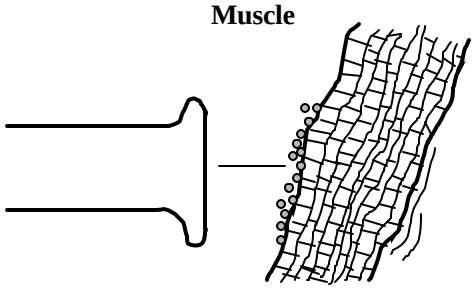
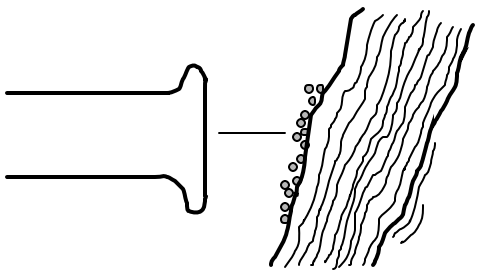


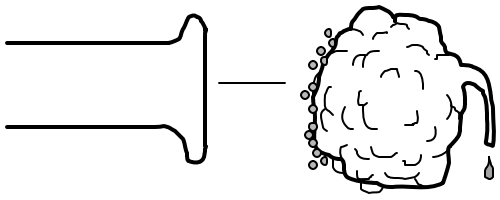
Nerve Transmission: Nerve to Skeletal Muscle



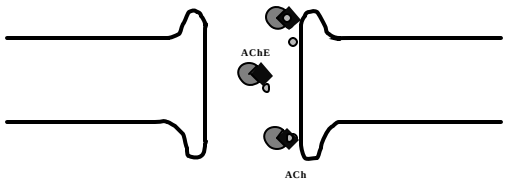
Nerve Transmission: Nerve to Smooth Muscle



Nerve Transmission: Nerve to Exocrine Gland



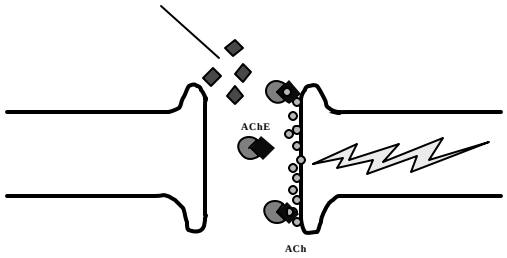
Stop Impulse: The Role of Acetylcholinesterase (AChE)



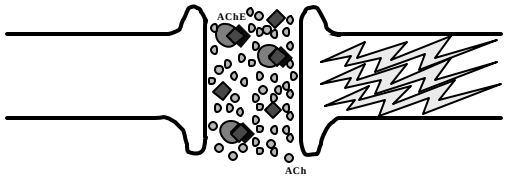
Toxicological effect of nerve agents

- **Nerve agent binds to and inhibits acetylcholinesterase (AChE)**
- **Acetylcholine (ACh) is not destroyed**
- **ACh continues to stimulate receptor**

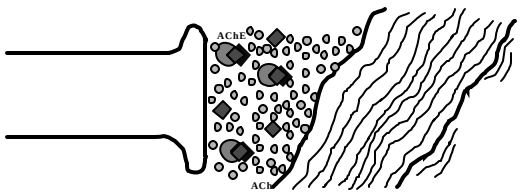
Exposure to Nerve Agent



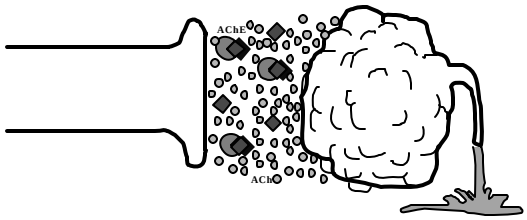
AChE Inhibition



AChE Inhibition: Effects on Smooth Muscle



AChE Inhibition: Effect on Exocrine Glands



Clinical effects of nerve agents

(Stimulation of muscarinic receptors)

"DUMBELS"

D - diarrhea

U – urination

M – miosis

B – bronchoconstriction, bronchorrhea

E – emesis

L – lacrimation

S - salivation

Clinical effects of nerve agents

Stimulation of nicotinic receptors on skeletal muscle

- **fasciculations, twitching**
- **muscular contraction**
- **muscle fatigue, flaccid paralysis**

Cause of death from nerve agents: Anoxia

- **Airway obstruction (secretions, bronchoconstriction,)**
- **Paralysis of respiratory muscle**
- **CNS depression of respiration**

Treatment for Exposure to Nerve Agents

- **Decontamination**
- **Ventilatory support**
- **Antidotes**
- **Anticonvulsive therapy**

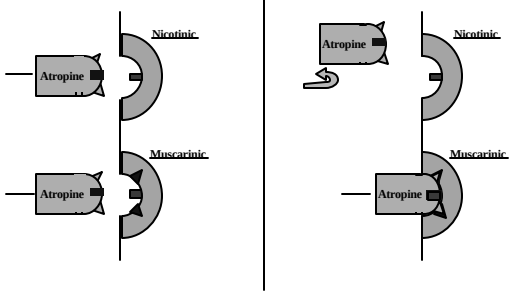
Antidotes for nerve agent exposure

- **Atropine (muscarinic sites)**
- **Oximes (nicotinic sites)**

Therapeutic Action of Atropine

- **Administer atropine iv/ im**
- **Atropine binds to ACh muscarinic receptors**
- **ACh cannot bind to receptors**
- **Reverses effects of ACh on smooth muscles, exocrine glands, and cholinergic nerves**

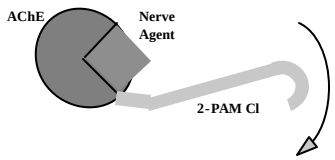
Interaction of Atropine with Receptors



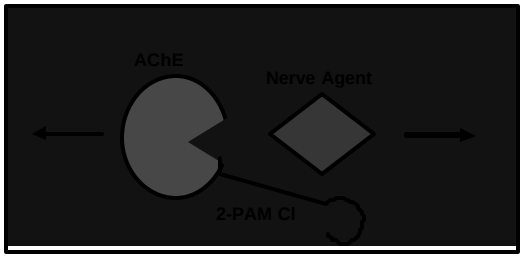
Therapeutic Action of Oximes

- **Administer Pralidoxime chloride (2-PAM) iv/im**
- **2-PAM chemically reacts with nerve agent bound to AChE**
- **Chemically altered nerve agent dissociates off AChE**
- **Regenerated AChE hydrolyzes ACh**
- **Reverses effects of ACh at nicotinic sites (skeletal muscle)**

Action of Pralidoxime Chloride (2-PAM Cl)



Action of Pralidoxime Chloride (2-PAM Cl)



Military Issue Antidotes
"MARK I Auto-Injectors"

References

- **http://ccc.apgea.army.mil/products/textbook/HTML_Restricted/index.htm**
- **http://www.emedicine.com/**