Medical Management of Biochemical Weapons Casualties: *An Introduction*

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- *When the drum beats to quarters is now a time of fearful expectation, and it is now the surgeon feels how much the nature of the wounds which might be brought to him ought to have occupied his mind in previous study.*

Sir Charles Bell, 1855

Objectives

- Review the history of biochemical weapons
- Understand the major types of chemical weapons available and the principles of medical management
- Understand the major types of biological weapons available and the medical management of those most likely to be employed in a civilian attack

Terrorism: the use of violence or the threat of violence to effect political change

•

Osama bin Laden

Sheikh Ahmed Yassin

Von Clauswitz (1780-1831)

- *"War is a continuation of 'Politik' (Policy or Politics) – by other means"*

עֶשֶׂר מַכּוֹת שֶׁהֵבִיא הַקָּדוֹשׁ
בָּרוּךְ הוּא עַל הַמִּצְרִים בְּמִצְרַיִם

וְאֵלּוּ הֵן

דָּם — צְפַרְדֵּעַ
כִּנִּים — עָרוֹב
דֶּבֶר — שְׁחִין
בָּרָד — אַרְבֶּה
חוֹשֶׁךְ — מַכַּת בְּכוֹרוֹת

רַבִּי יְהוּדָה הָיָה נוֹתֵן בָּהֶם סִימָנִים

דְּצַ"ךְ עַ"דַ שְׁ"ב בְּאַ"חַ"ב

Delium 423 BCE

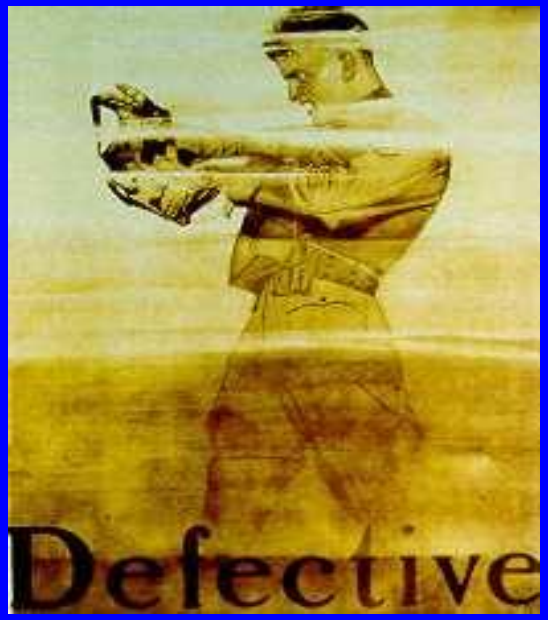
Plague – Caffa 1346

Smallpox and the French and Indian War

General Jeffrey Amherst approved
Exchanging smallpox infested
Blankets with Huron Indians
In 1763 during Pontiac's rebellion
Resulting in decimation of the
Indian foe.

Fritz Haber (1868-1934)

- Introduced chlorine gas
- Introduced phosgene gas
- Following World War 1 developed Hydrogen cyanide – Zyklon B


Defective

World War 1 Casualties

United Kingdom

- Phosgene
- 20, 015 casualties
- 1895 deaths (9.4%)
- Mustard
- 160, 970 casualties
- 4,167 deaths (2.5%)

United States

- Phosgene
- 6834 casualties
- 66 deaths (1%)
- Mustard
- 27,711 casualties
- 599 deaths (2.1%)

World War 1 Casualties

- One third of the 5 million WW1 casualties due to chemical weapons
- Pulmonary agents (chlorine and phosgene) were the most lethal
- The largest number of chemical casualties were due to mustard (all in the last year of the war)

The Interwar Years

- 1925 Geneva Protocol- Use of chemical and biological weapons is forbidden
- 1935 Eritrea- Italy uses mustard bombs to defeat Ethiopian troops
- 1936 Germany-Gerhart Schrader at IG Farben synthesizes TABUN an organophosphate anticholinesterase
- 1938 Germany- Schrader synthesizes a new compound- SARIN- 10x as potent as TABUN
- 1943 Germany – Nerve agent SOMAN synthesized

SS John Harvey
Bari Mustard Disaster 2 Dec 1943

617 casualties with a 14% fatality rate

Biological Warfare: Plague

- *Ningpo, China Oct. 1940 Japanese plane released 5kg of fleas*
- *99 bubonic deaths followed by rodent die-off*
- *Chang-the, China Nov 1941- lone Japanese plane released "strange particles—thousands of plague deaths ensue*

Dr. Shiro Ishii
Unit 731

Vx

- Synthesized at Imperial Chemical Company 1953
- 1000 x more toxic than Sarin when applied to skin—a drop the size of a pinhead could cause death within 15 minutes

Yemen Civil War
1962-1970

- Egyptians dropped mustard gas on multiple occasions
- January 1967, Kitaf, bombs dropped upwind of town. 95% of population of Kitaf dead within 50 minutes. All animals dead. Probable nerve agent
- Additional attacks against Gahar, Gahas, Hofal, Gadr, Gadafa in 1967

Iran-Iraq War 1980's

- Mustard Agents used extensively
- Severe casualties evacuated to European hospitals
- UN panel estimated that 45,000 Iranians injured by Iraqi chemical weapons

Halabja - 1983

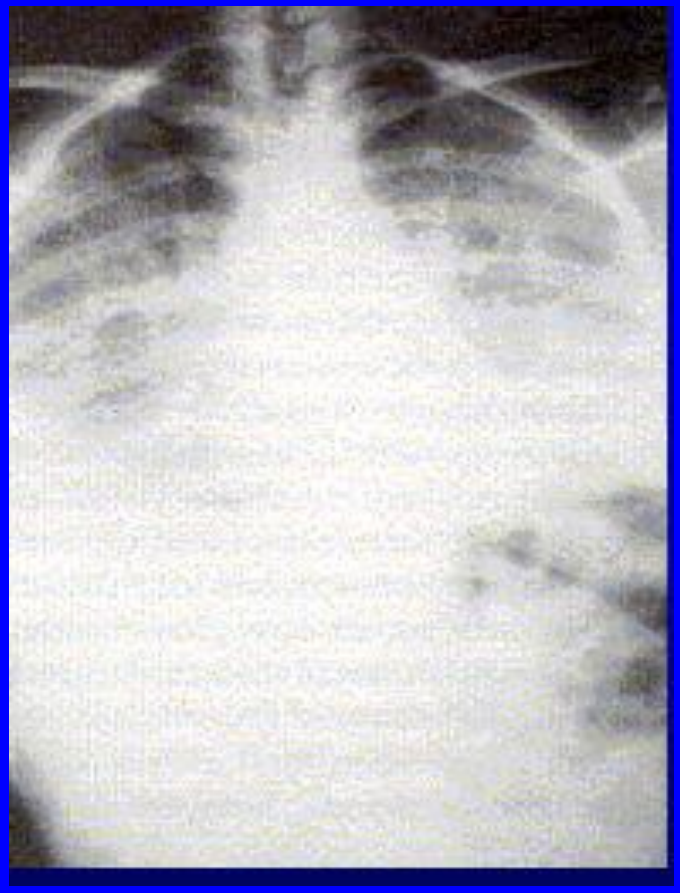
- Saddam Hussein gassed Kurdish villagers in Northern Iraq
- > 5,000 casualties
- Gas was a fast acting vapor – either cyanide or a nerve agent

Major Chemical Threats

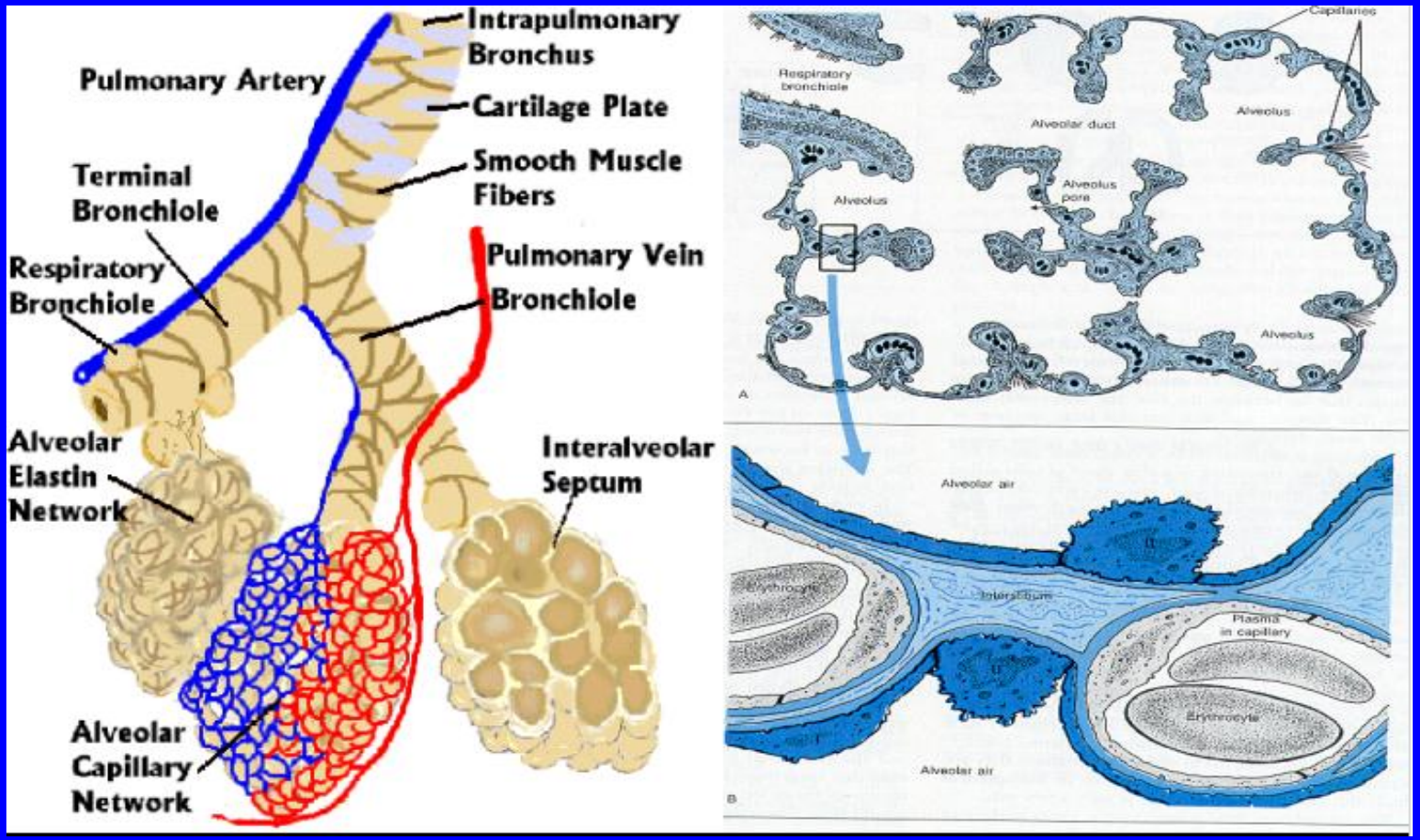
- Pulmonary Agents
- Cyanide Agents
- Vesicants
- Nerve Agents
- Riot control and incapacitating agents
- Toxic industrial chemicals

Pulmonary Agents

- Chlorine
- Phosgene
- PFIB (perfluoroisobutylene)



Pulmonary Agents - Pathophysiology



Clinical Considerations

- Pulmonary Agents cause pulmonary edema
- Latent period- onset delayed by hours, objective signs appear later than symptoms
- Sudden death may occur due to airway obstruction or bronchospasm

Clinical Considerations

- Pneumonia common 3-5 days after injury
- Effects exacerbated by exertion
- No specific therapy

Clinical Considerations

- Mild exposure: Chest tightness, cough, exertional dyspnea
- Moderate exposure: above symptoms plus hoarseness, stridor and pulmonary edema within 2-4 hours
- Severe exposure: Massive pulmonary edema within 1 hour

Cyanide

Zyklon B (hydrocyanic acid)

Cremation Pits Auschwitz
1944

Cyanide - Military Operations

- Difficult to weaponize
- Very volatile - blows away
- Weapons inefficient – cyanide payload destroyed in 50% of munition delivery explosions

Current Threats

- Focused Targets: Terrorist attacks, homicides, suicides
- Household products: silver polish, rodenticides
- Industrial Hazards: chemical processing industry, metal plating, iron and steel mills, gold and silver mines

Hydrogen Cyanide

- **Colorless liquid or gas**
- **Odor of bitter almonds**
- **Vapor density lighter than air**
- **Boils at 70 degrees F and freezes at 7 degrees F**
- **Highly water soluble**
- **Nonpersistent**

$HCN \rightleftharpoons H^+ + CN^-$

Hydrogen Cyanide

- Colorless liquid or gas
- Odor of bitter almonds
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- Boils at 70 degrees F and freezes at 7 degrees F
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- Nonpersistent

$CNCl \rightleftharpoons CN^- + Cl_2$

Cyanogen Chloride

- Colorless gas or liquid
- Pungent, biting odor
- Vapor density heavier than air
- Boils at 59 degrees F, freezes at 20 degrees F
- Slightly water soluble
- Nonpersistent

Chemistry of CN^-

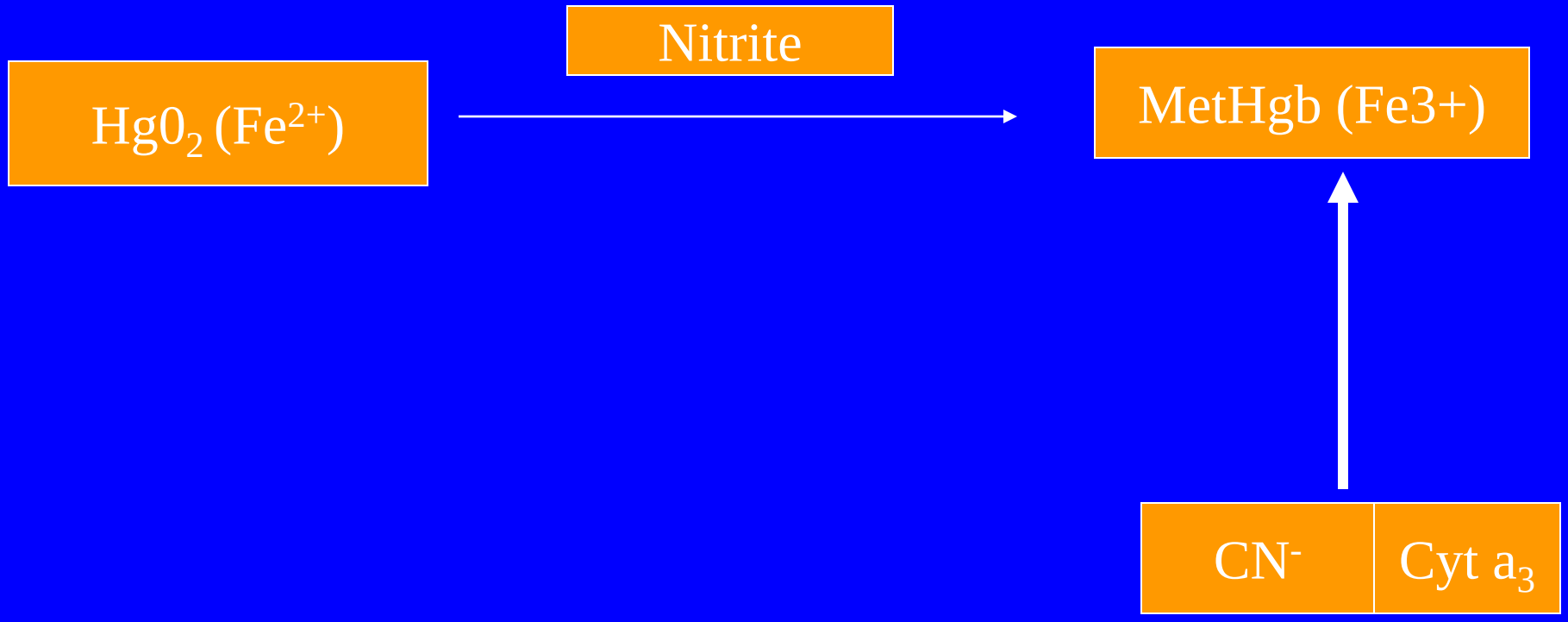
- High affinity for ions of transitional metals
  - Cobalt
  - Iron
    - Cytochromes (Fe 2^+, Fe 3^+)
    - Heme in Methemoglobin (Fe 3^+)

Pathophysiology

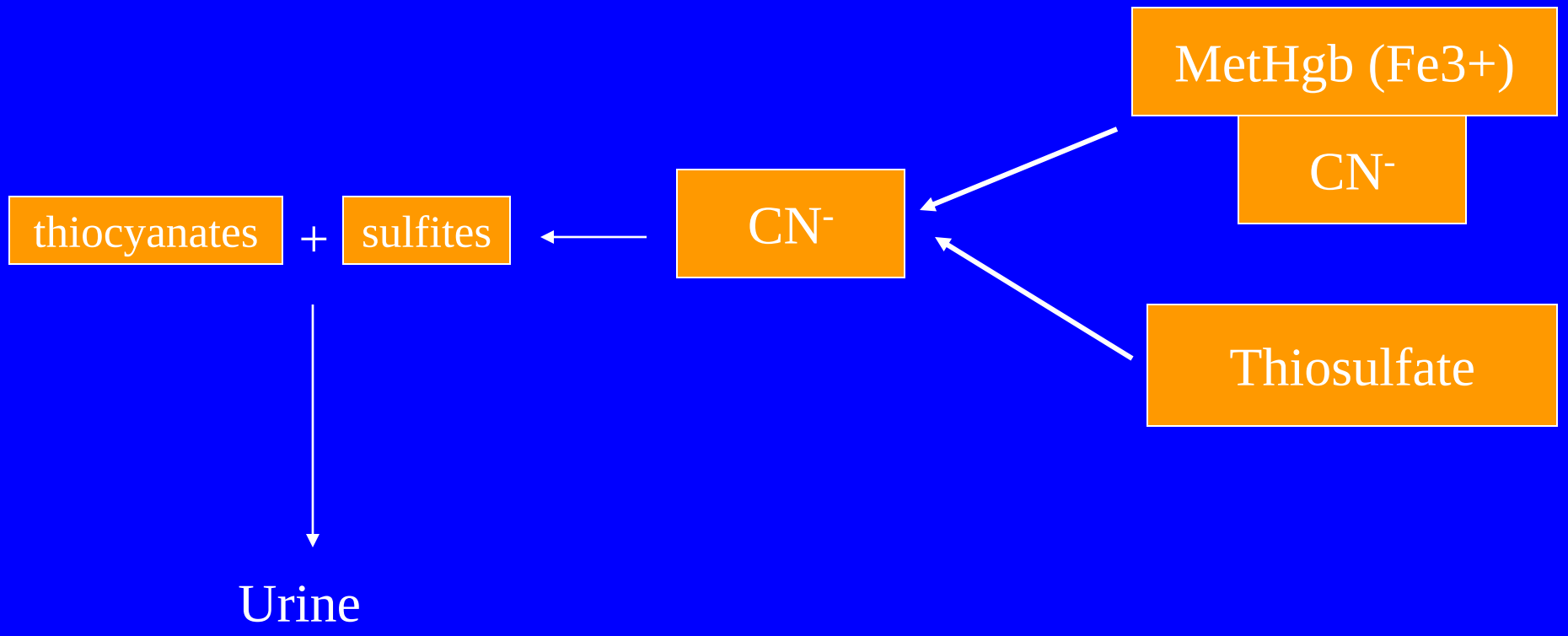
CN^- interrupts oxidative phosphorylation by binding to cytochome a_3 in cytochrome oxidase

- Stable but not irreversible binding
- CN^- has higher affinity for Fe^{3+} in metHb

Antidote to Cyanide Poisoning



Antidote to Cyanide Poisoning



Classic Clinical Presentation Hydrogen Cyanide Moderate Exposure

- Bright red venous blood and skin
- Odor of bitter almonds
- Profound metabolic acidosis

Hydrogen Cyanide
Severe Exposure

- Tachypnea
- Rapid Loss of Consciousness
- Apnea
- Cardiac Arrest

Treatment of Cyanide Poisoning

- Amyl Nitrite – 0.3 ml ampules for inhalation – marked vasodilation – do not use if casualty conscious and able to stand
- Sodium Nitrite – comes in a 3% solution; give 10 cc (300mg) iv over a 3 minute period in adults. 0.2 ml/kg in children not to exceed 10 ml.

Treatment of Cyanide Poisoning

- Sodium Thiosulfate: give 50 cc of a 25% solution (250 mg/cc) = 12.5 grams. Administer over a 10 minute period immediately after nitrite administration

Vesicants

- Mustards
- Lewisite
- Phosgene oxime

Mustards

- Oily liquid
- Light yellow to brown in color
- Vapor heavier than air
- Liquid heavier than water
- Low volatility-persistent
- Causes bone marrow suppression

Treatment - Decontamination

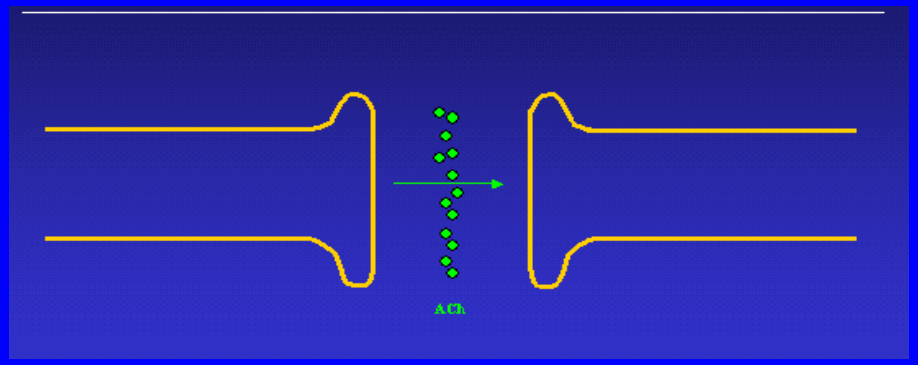
- Early decontamination protects casualty
- Late decontamination protects medical personnel and facility

Nerve Agents

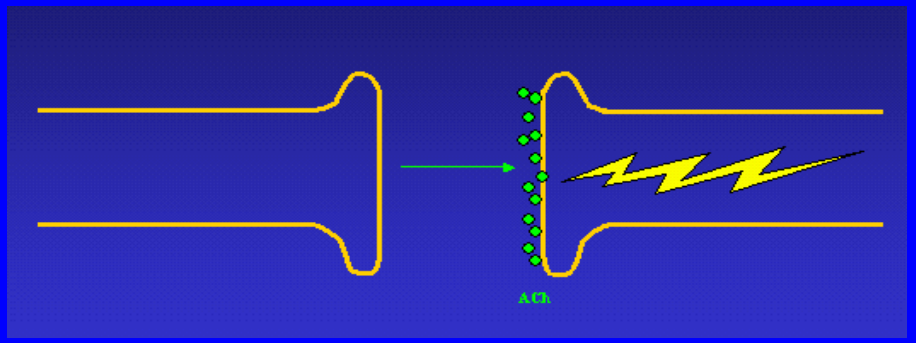
- Anti-cholinesterase
- Acetylcholine accumulates
- Effects due to excess Acetylcholine
  - Cholinergic crisis

Physical Properties of Nerve Agents

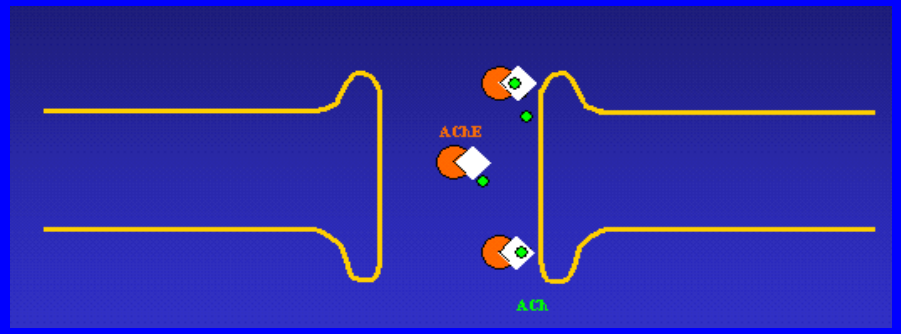
- Clear colorless liquid
  - Not nerve gas
- Boils > 150 ^{o} C
- Penetrates skin and clothing



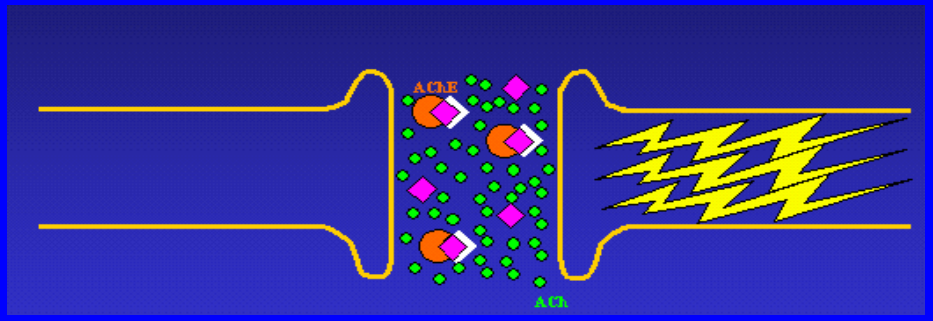
Acetylcholine crossing synapse



Acetylcholine binding to Receptor initiating post Synaptic transmission



Cholinesterase binding to acetylcholine



Cholinesterase inactivated Due to binding with nerve agent

Effects of Cholinergic Crisis

- Muscarinic
  - Smooth muscles
    - Bronchoconstriction
    - Miosis
    - GI smooth muscle constriction – nausea, diarrhea
  - Glands - increased secretions from
    - Eyes, nose, mouth, airway, GI tract
  - Heart - Bradycardia

Effects of Cholinergic Crisis

- Nicotinic
  - Skeletal muscle
    - Fasciculations, twitching, fatigue, flaccid paralysis
  - Preganglionic
    - Tachycardia, hypertension

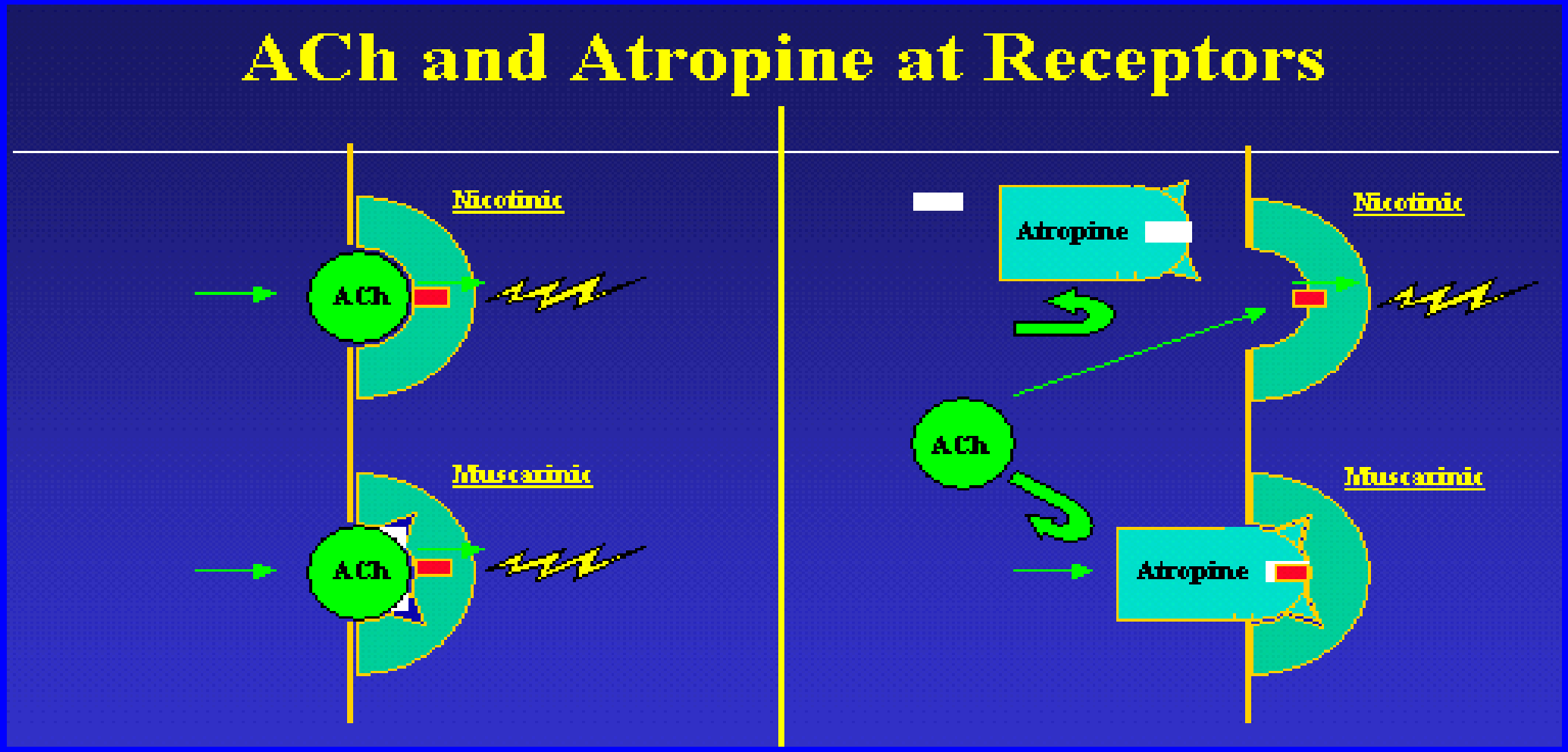
Heart Rate

- Muscarinic (vagal) - decrease
- Nicotinic (preganglionic) - increase
- May be high, low or normal

CNS Effects of Nerve Agents

- Large exposure
  - Loss of consciousness
  - Seizures
  - Apnea
  - Death
- Minor Exposure
  - Slowness in thinking, decision making
  - Poor concentration

Antidote to Organophosphates: Atropine for Muscarinic Receptors



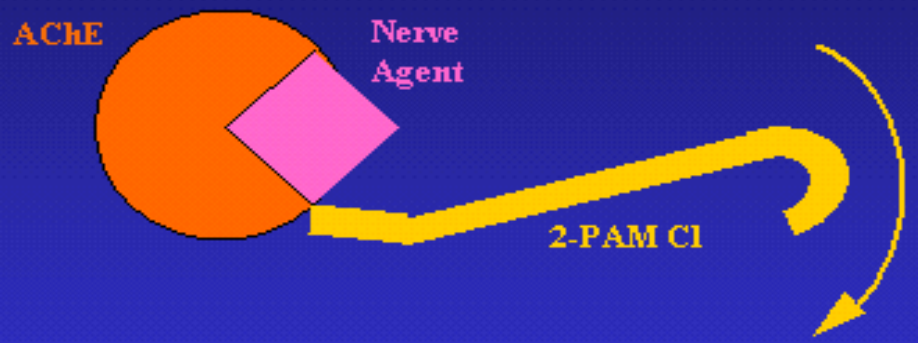
Atropine

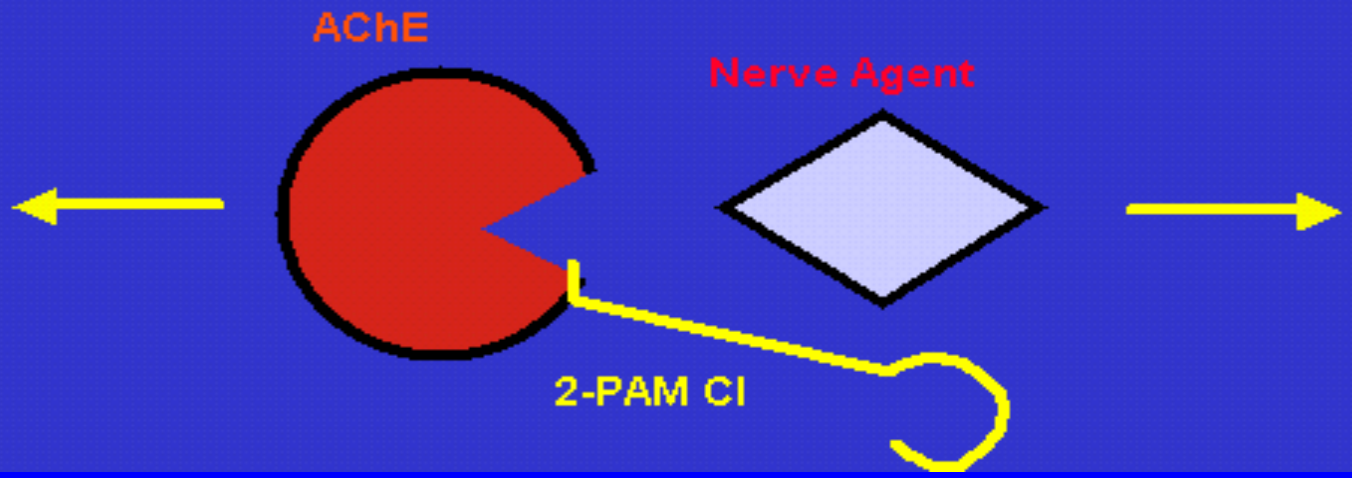
- Starting dose 2-6 mg
- 2 mg every 5 minutes until
  - Secretions dry
  - Ventilation improved
- Usual dose (severe casualty) 15 – 20 mg
  - 1000s of mgs in insecticide poisoning

Antidote to Organophosphates: Oximes at Nicotinic Receptors

- Effects at Nicotinic receptors
  - Increase skeletal muscle strength
- No effects at muscarinic receptors

Action of Pralidoxime Chloride (2-PAM Cl)





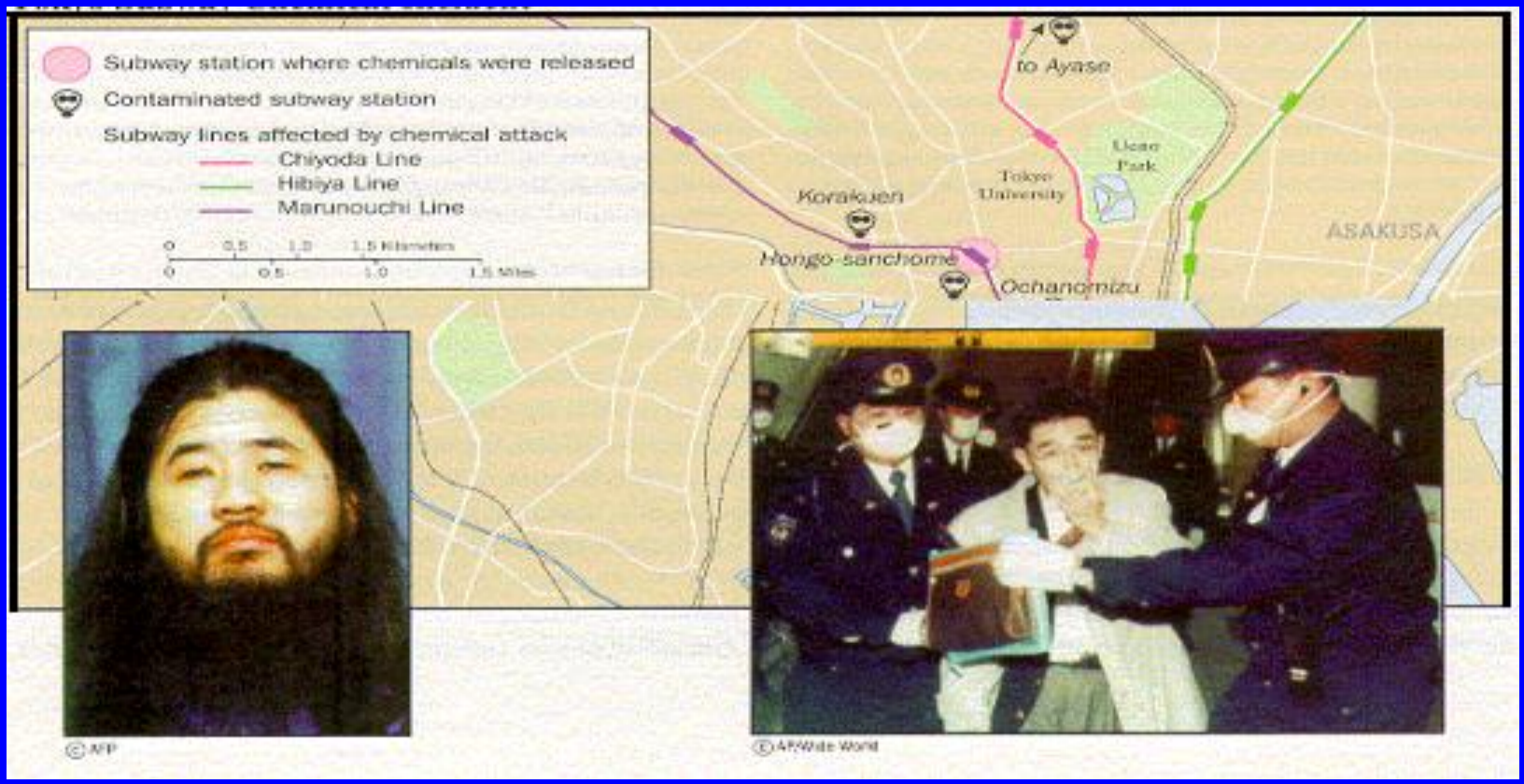
Oximes

- Remove agent from enzyme unless aging has occurred
- Aging: agent-enzyme complex changes
- Oximes cannot reactivate enzyme after aging
- Aging times: Soman 2 minutes, Sarin 3-4 hours, others longer

Dose of Pralidoxime Cl

- 1 gram iv over 20-30 minutes
- To be given immediately after atropine

Aum Shinrikyo Sarin Attack
Tokyo subway 1995



30% solution of Sarin

Numbers seeking care
278 Tokyo medical facilities

- 5510 total
- Mild 984
- Moderate 37
- Severe 17
- Deaths 12
- Status unknown >300

Major Chemical Threats

- Pulmonary Agents
- Cyanide Agents
- Vesicants
- Nerve Agents
- Riot control and incapacitating agents
- Toxic industrial chemicals

Biological Weapons

- Pathogens
- Toxins
- Biomodulators (e.g. Agent Orange)

Bioterrorism Pathogens

- Bacteria
  - B. anthracis
  - S. typhi
  - S. typhimurium
  - Shigella species
  - Y. pestis
  - V cholerae
  - Rickettsia prowazekii
- Toxins
  - Botulinum toxin
  - Mycotoxins
  - SEB
  - Ricin
- Viruses
  - Variola (smallpox)
  - VHF
    - Ebola/Marburg
    - Lassa Fever
    - CCHF

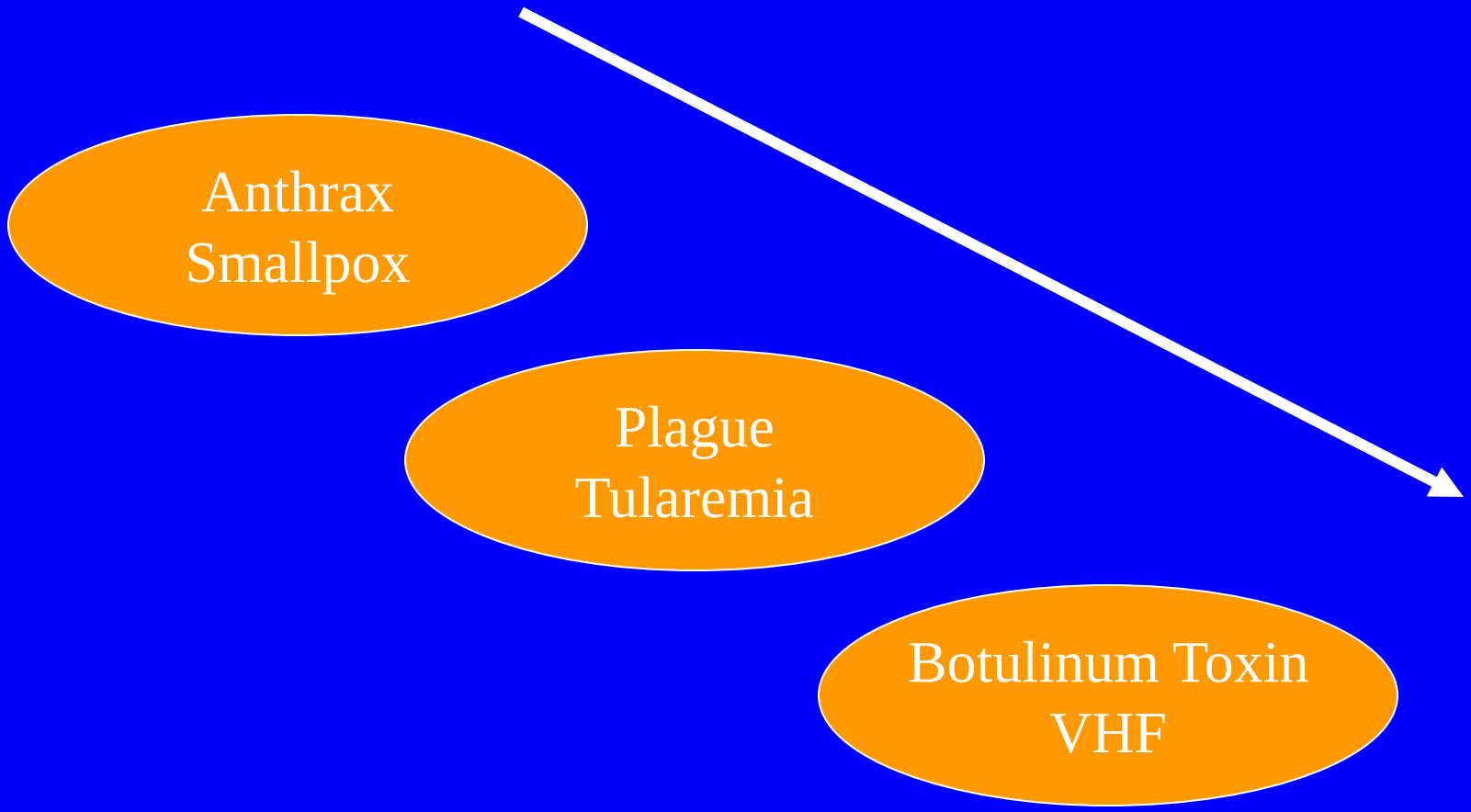
Portals of Entry of Biological Agents

- Respiratory Tract
- GI Tract
- Skin/Mucus Membranes

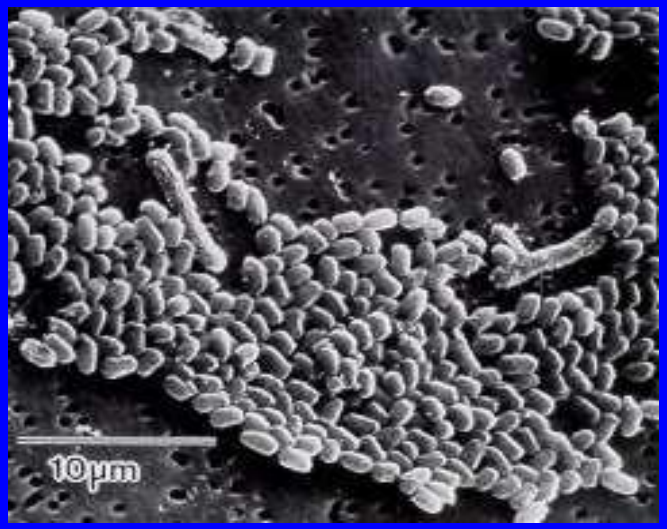
Disease from Aerosolized Biologic Agents of most concern

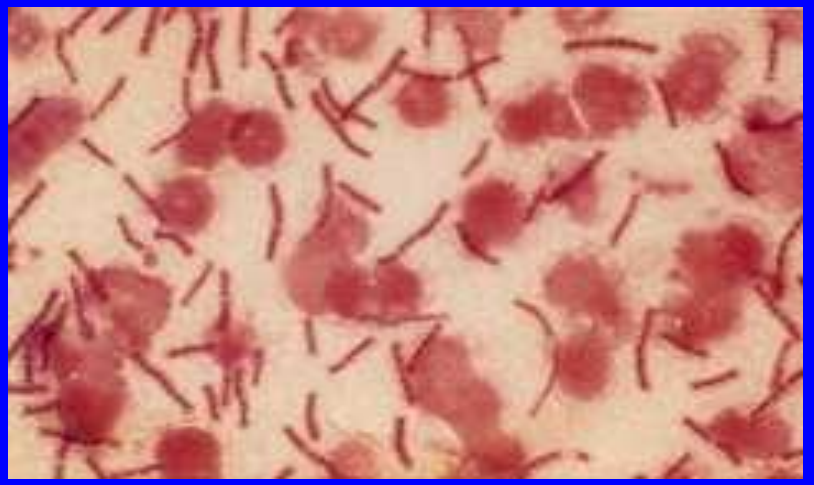
- Aerosolized droplets 1-5 microns optimal for reaching lower respiratory tract
- Aerosols of some agents produce pulmonary syndromes (anthrax, plague, Q fever, SEB)
- Aerosols of most agents produce systemic illness (botulinum, most viruses)

Agents of Greatest Concern



Anthrax





- Gram positive spore forming non-motile rod
- 1876 Robert Koch – germ theory of disease
- 1881 Louis Pasteur – first live bacterial vaccine

Epidemiology

- Reservoir: Soil
- Herbivores infected during grazing
- Transmission to humans
  - Contact with infect animals and products
  - Ingestion of contaminated meat
  - Inhalation – industrial and weapons settings

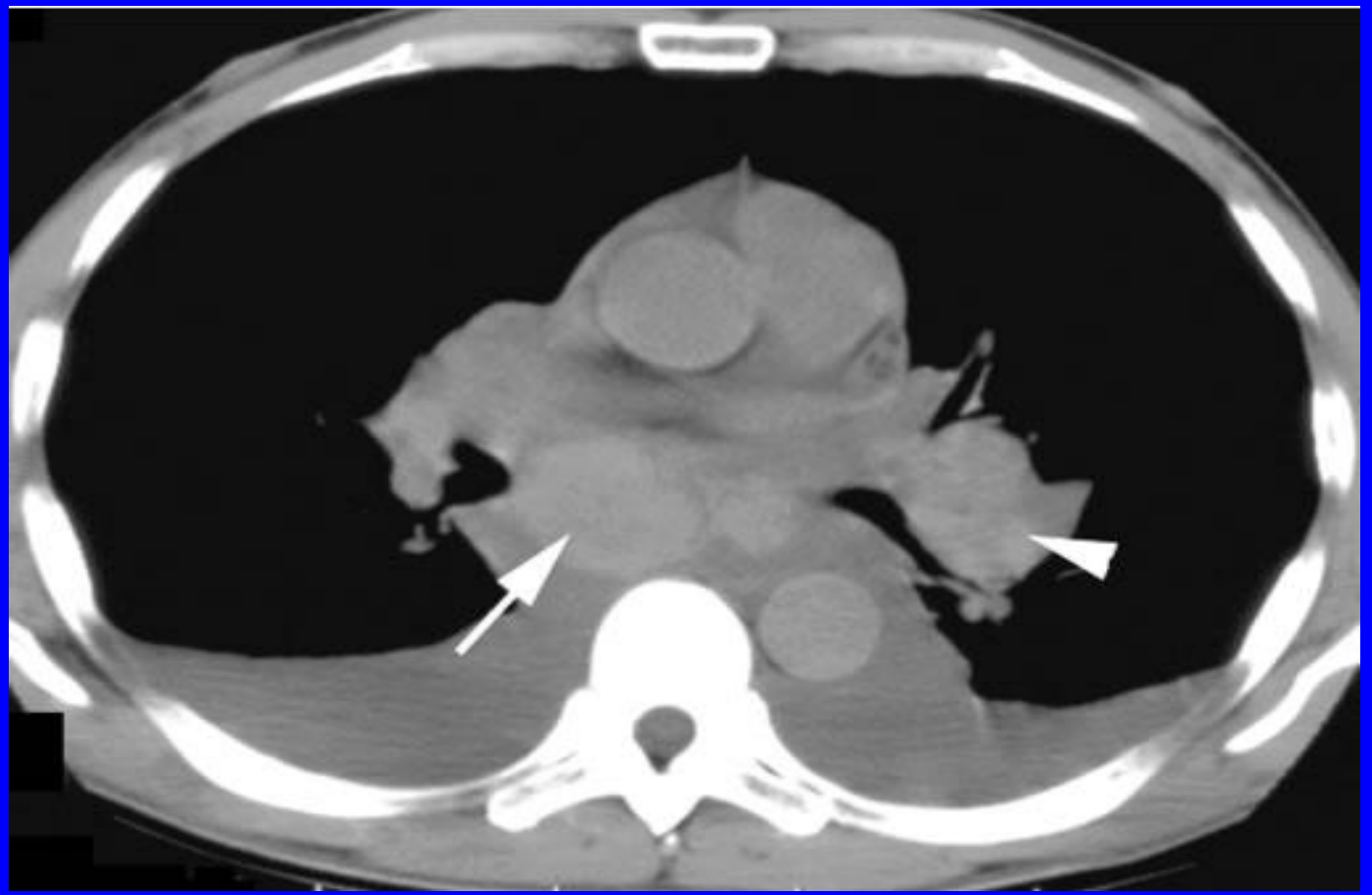
Cutaneous Anthrax

- Malignant pustule
- 95% of all Anthrax infections
- 80-90% complete resolution

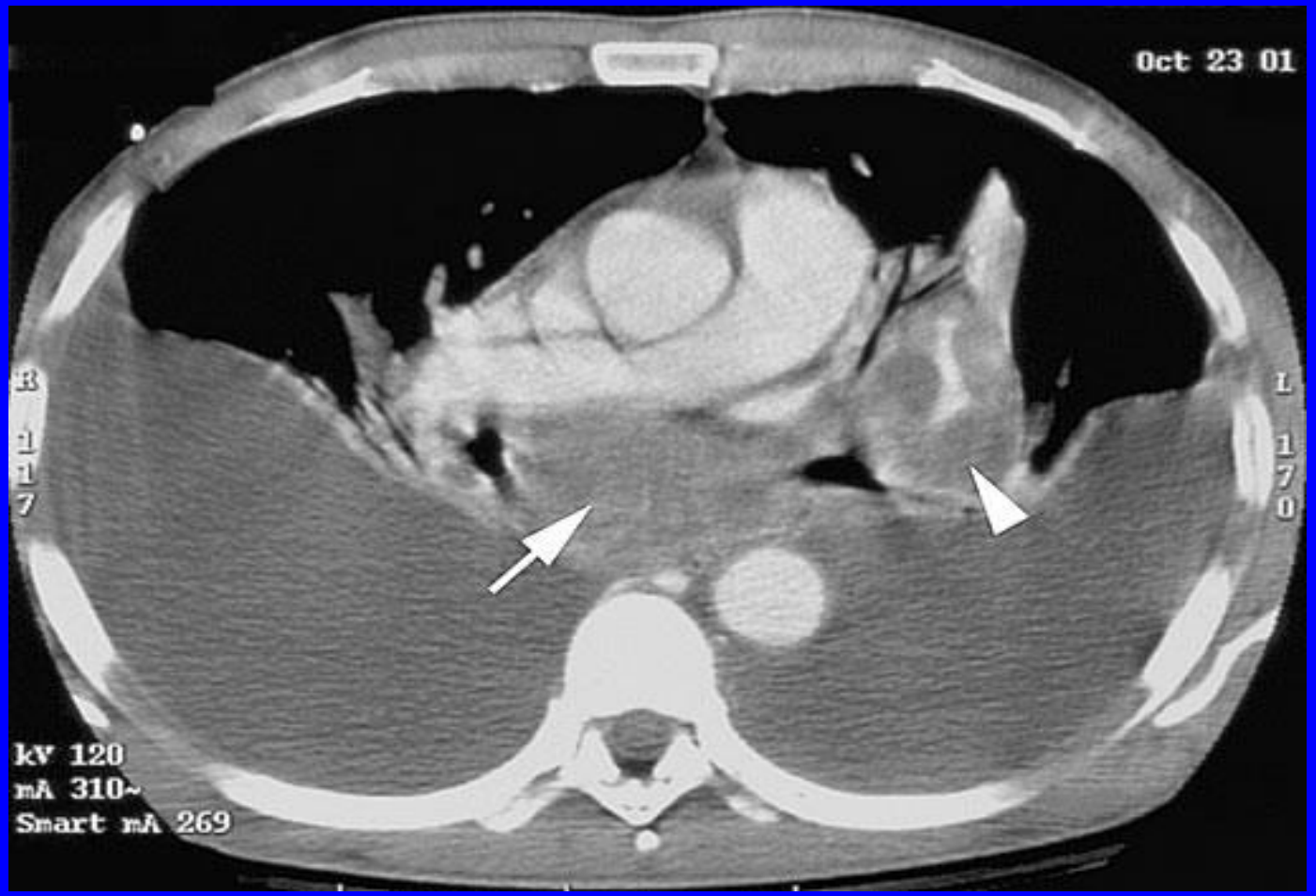
Anthrax Case 4 October 19, 2001

- 56 y.o. male postal worker
- 3 day history of fever, chills, malaise, chest heaviness, productive cough

Anthrax Case 4 October 19, 2001



Anthrax Case 4 October 23, 2001



Anthrax Treatment

- Post exposure prophylaxis: Ciprofloxacin 500 mg po bid 4-8 weeks
- Initial Inhalation Anthrax Treatment Protocol
  - Cipro 400 mg iv q 12h
  - or Doxycycline 100 mg iv q 12 h
  - Additional antimicrobials: Rifampin, Vanco, Imipenum, Clinda
- Vaccine: not available for civilian use

CDC. Update: Investigation of Bioterrorism-Related Anthrax and Interim Guidelines For Exposure Management and Antimicrobial Therapy, October 2001. MMWR 2001; 50:909-919.

Sverdlovsk – April 4-May 15, 1979

- < 1 gram of anthrax spores released via air vent without filter
- 77 patients infected
- 66 deaths (87%)

Smallpox - Variola

- Infectious via aerosol
- No routine Vaccination
- Decreased potency
- Limited supply
- Transmissible
- 30% mortality

Smallpox - Treatment

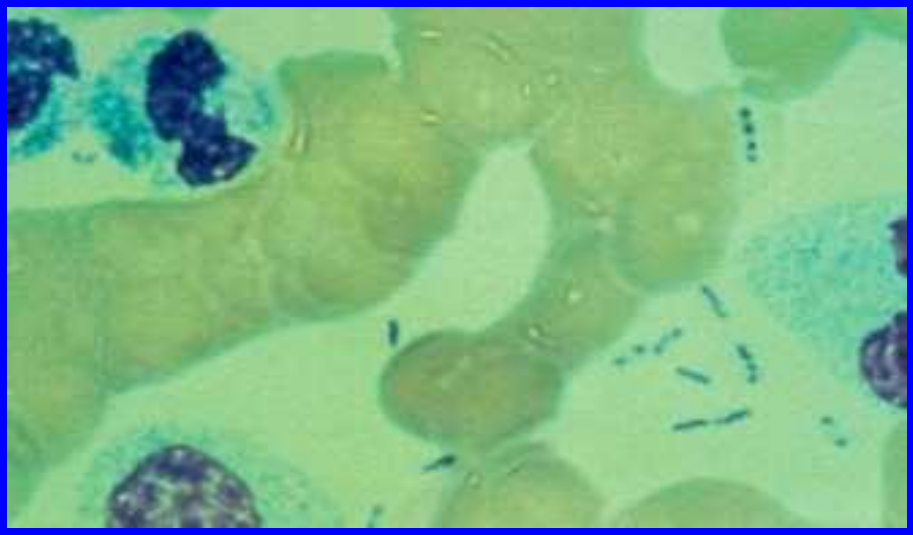
- Vaccination within 3-4 days of exposure can prevent the disease in many patients and prevent death in most
- After 7 days of exposure, most “experts” would give vaccinia immunoglobulin as well
- No specific antiviral therapy

Dark Winter War Game
June 22-23, 2001

- Scenario: Al Qaida terrorists spray smallpox from aerosol cans in 3 shopping malls in Oklahoma City, Atlanta and Philadelphia.
- By day 13 of the scenario, smallpox had spread to 25 cities in the US and 15 countries.
- 11,000 individuals infected and 2600 dead by Day 13.

Plague

- Reservoir >200 species of mammals
  - Rattus rattus
  - Squirrels, cats
- Vector > 80 species of fleas
- Person to person transmission via aerosol



Yersinia Pestis: Gram negative
Non-motile coccobacillus

Plague

Bubonic

Septicemic

Pneumonic

Pneumonic Plague

- Primary or secondary (incubation 2-3 days)
- High fever, chills, malaise
- Hemoptysis
  - Pneumonia progresses rapidly
  - Respiratory failure and circulatory collapse

Plague: Diagnosis

Otherwise healthy young person

Hemoptysis

Think Plague

Especially if GNCB in sputum

Plague: Treatment

- Streptomycin 15 mg/kg IM or IV qd x 10 days or
- Doxycycline 200 mg iv x1 then 100 mg iv q 12 h
- Cipro 500 mg po/iv bid should also be effective
- Chloramphenicol for meningitis
- No vaccine

Tularemia – Rabbit Fever

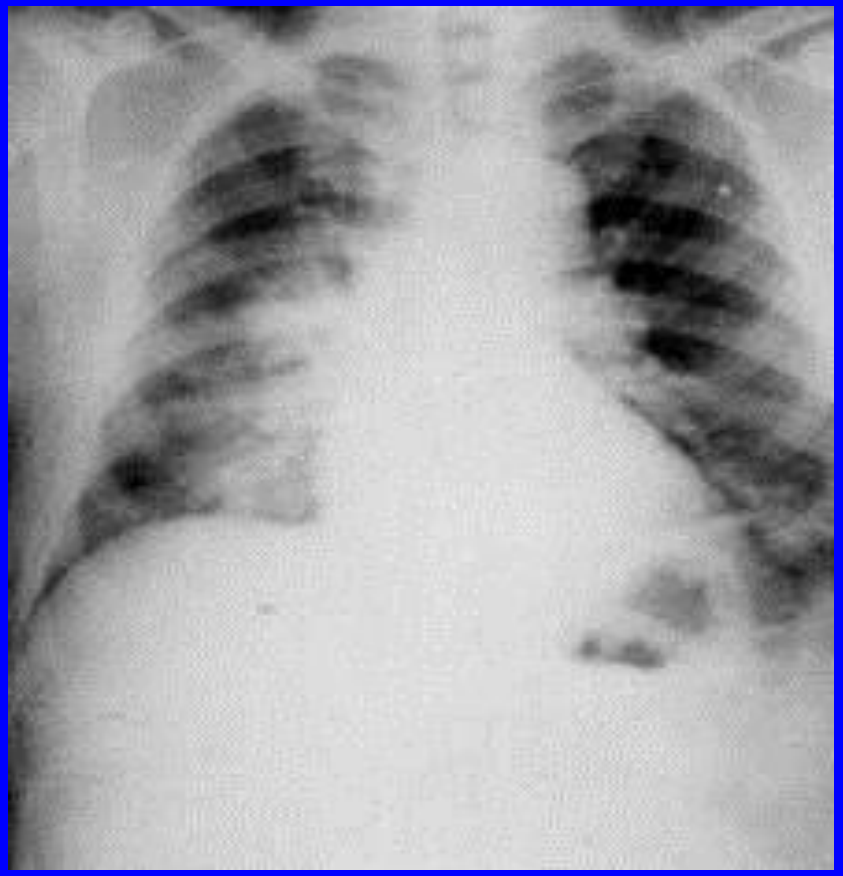
- Gram negative non-motile coccobaccillus
- Reservoir:
  - Rabbits, squirrels, muskrats, cats
- Vectors:
  - Ticks, deerflies

Tularemia: Clinical Presentation

- Ulceroglandular:
- Glandular
- Occuloglandular
- Pharyngeal
- Typhoidal: nonspecific febrile illness without localization

Pneumonic Tularemia

- After inhalation (biological weapon)
- Secondary hematogenous spread after typhoidal form
- Vaccine available



Tularemia: Treatment

- Post exposure prophylaxis
  - Doxycycline 100mg po bid or
  - Ciprofloxacin 500mg po bid
- For treatment of established infection
  - Gentamycin 5 mg/kg iv qd
- Vaccine available but not currently recommended for prophylaxis

Toxins Relevant to Biological Warfare

- Botulinum Toxin
- Staph Enterotoxin B (SEB)
- Ricin
- T3 Mycotoxins (Yellow Rain)

Mechanism of Action

- Enters pre-synaptic nerve terminal
- Prevents release of Acetylcholine
  - Neuromuscular junction-flaccid paralysis
  - Cholinergic autonomic blockade

Botulism: Clinical Features

- Latent period: 24-36 hours after inhalation
- Symmetrical descending bulbar paralysis
  - Blurred vision, diplopia, ptosis, photophobia
  - Dysphonia, dysphagia
  - Flaccid paralysis

Botulism: Treatment

- Antitoxin
- Ventilatory support
- Intensive Care
- Recovery may be prolonged (months)

Viral Hemorrhagic Fevers

- Acute febrile illness
- Malaise, myalgia
- Petechiae, ecchymoses
- Diffuse hemorrhage
- Shock

Pathogens

- Areaviridae
  - Lassa Virus
- Phlebovirus
  - Rift Valley Fever
- Nairovirus
  - Crimea-Congo Hemorrhagic Fever
- Hantavirus
- Filoviridae
  - Ebola HF
  - Marburg HF
- Flaviviridae
  - Yellow Fever
  - Dengue HF

Mode of Transmission in Biological Weapon

Aerosol

Treatment of VHF

- Strict Isolation
- Supportive Care
- Ribavirin (available from the CDC on a compassionate use basis) otherwise
- No specific treatment

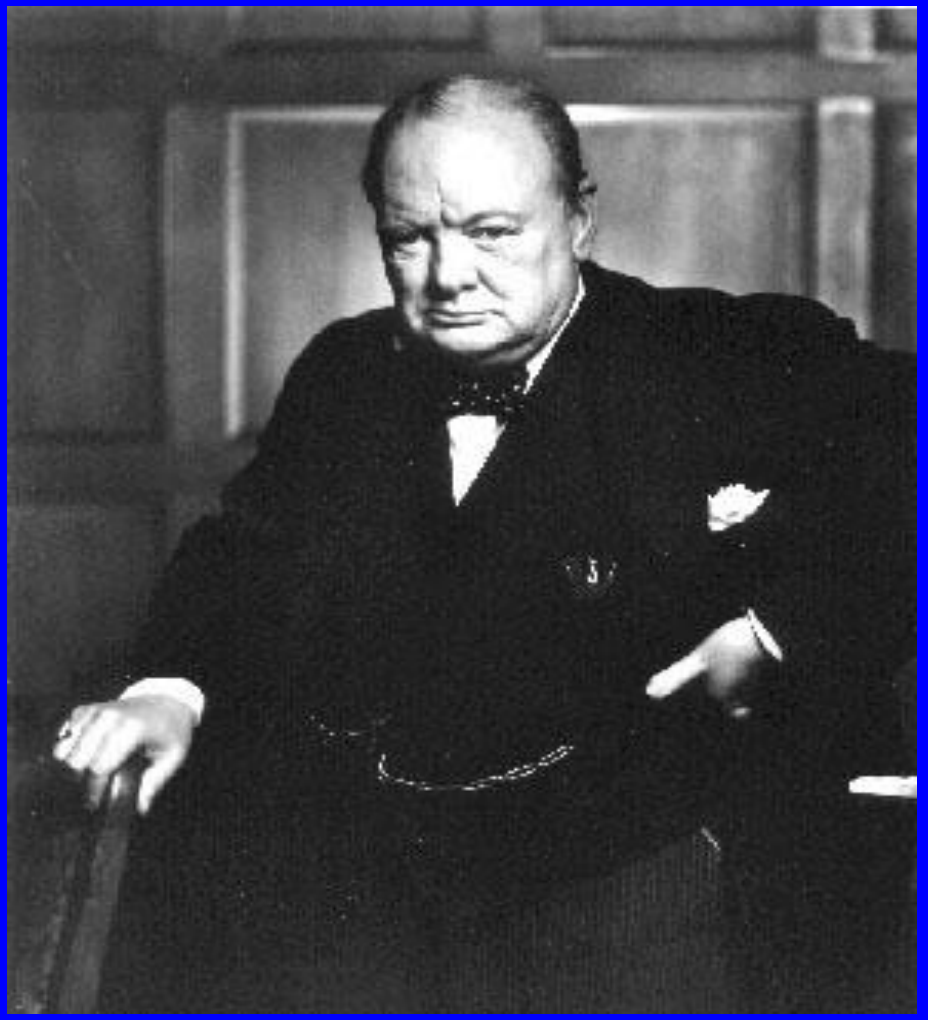
Chem-Bio Casualties

- Immediate Pulmonary
  - Phosgene
  - SEB
  - Vesicants
  - Cyanide
- Immediate Neurologic
  - Nerve Agents
  - Cyanide
- Delayed Pulmonary
  - Anthrax, Plague, Tularemia
  - Q Fever
  - Phosgene
  - SEB, Ricin, Vesicants
  - Phosgene
- Delayed Neurologic
  - Botulism
  - VEE

Further Study

- http://ccc.apgea.army.mil/Documents/HTML_Restricted/index.htm (Textbook of biochemical weapons)
- http://ccc.apgea.army.mil/ (US Army Institute of Chemical Defense)
- http://www.usamriid.army.mil/education/instruct.html (US Army Research Institute for Infectious Disease)
- http://www.medletter.com/freedocs/bioweapons.pdf (Medical Letter: Rx of Biological Weapons Pathogens)
- http://www.bt.cdc.gov/ (CDC homepage for bioterrorism)

In War, Resolution
In Defeat, Defiance
In Victory, Magnanimity
In Peace, Good Will



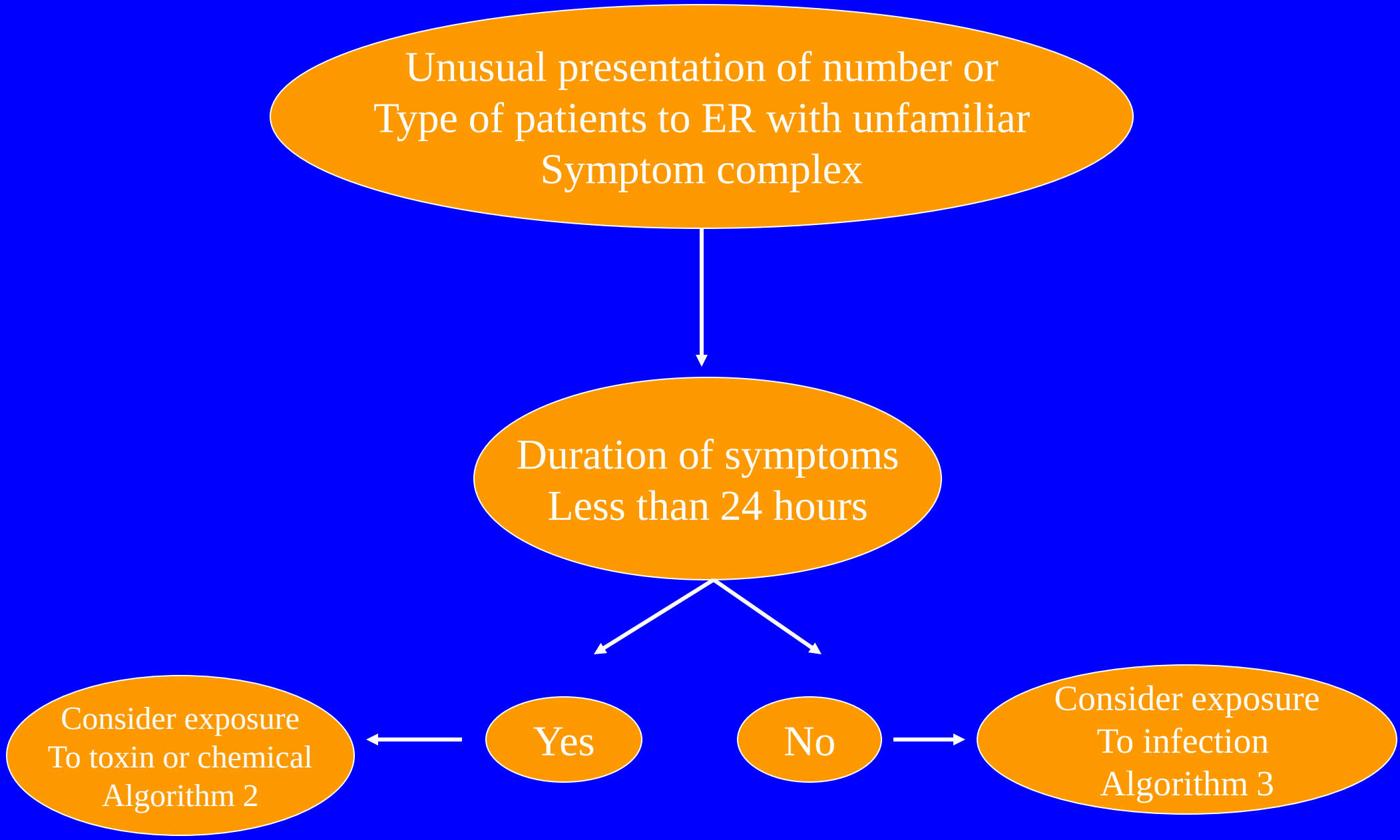
Winston S. Churchill

God Bless America

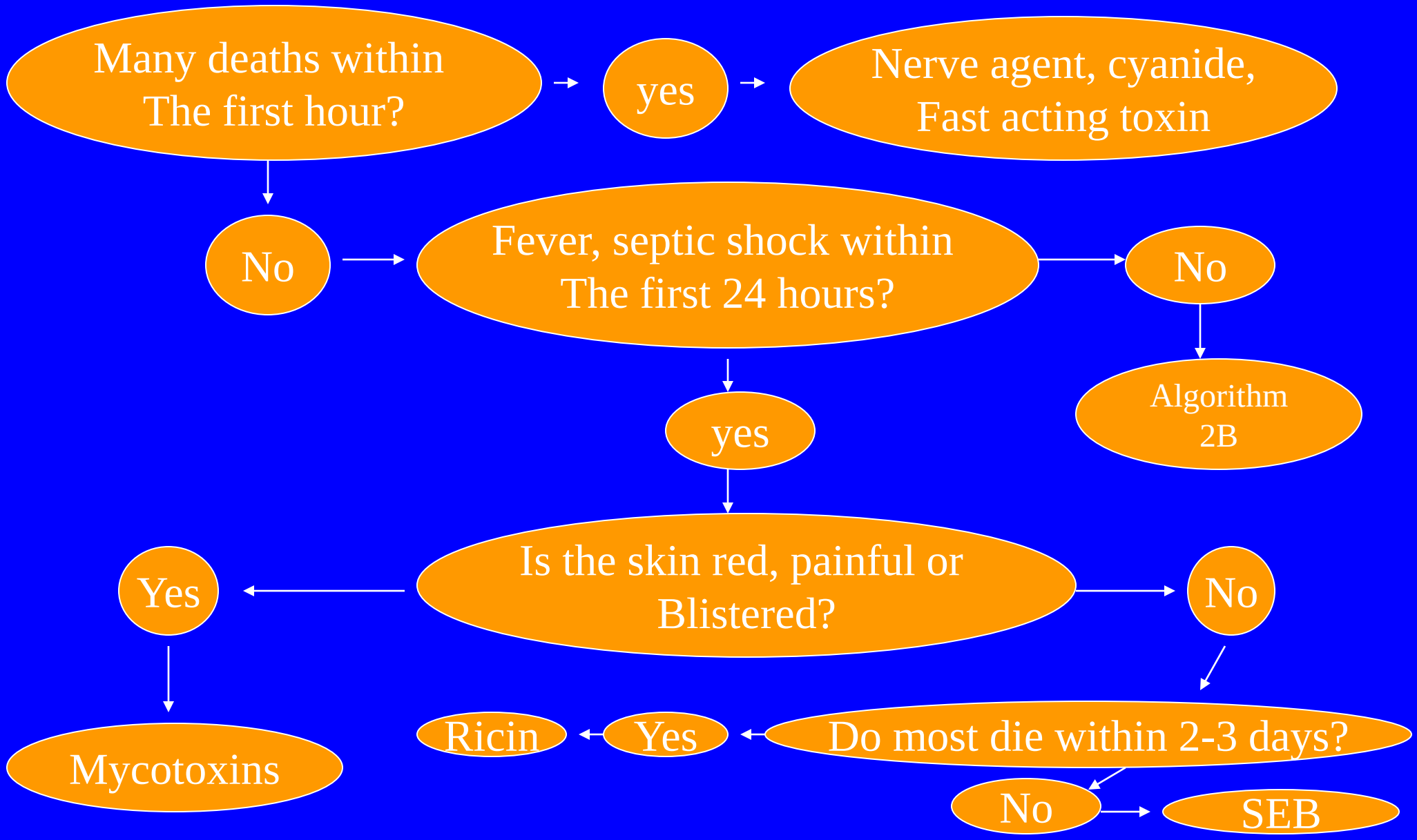
When you're wounded and left
on Afghanistan's plains,
And the women come out to
cut up what remains,
Jest roll to your rifle and
blow out your brains
An' go to your Gawd like
a soldier.

Anticholinesterases

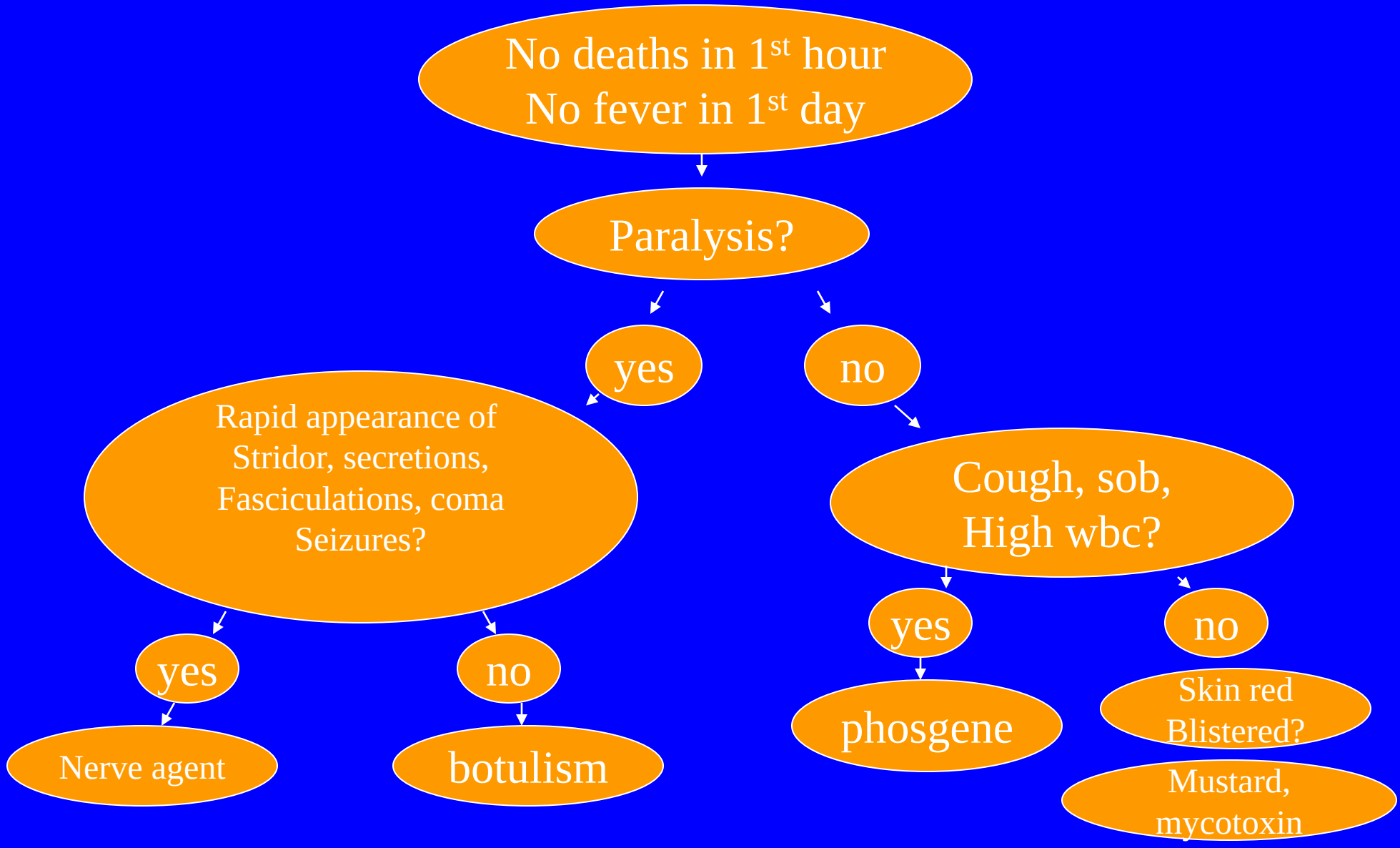
- Carbamates
  - Physostigmine (Antilirium)
  - Pyridostigmine (Mestinon)
  - Neostigmine (Prostigmine)
- Organophosphates
  - “Nerve Agents”
  - Malathion
  - Diazinon


Unusual presentation of number or
Type of patients to ER with unfamiliar
Symptom complex
Duration of symptoms
Less than 24 hours
Yes
No
Consider exposure
To toxin or chemical
Algorithm 2
Consider exposure
To infection
Algorithm 3

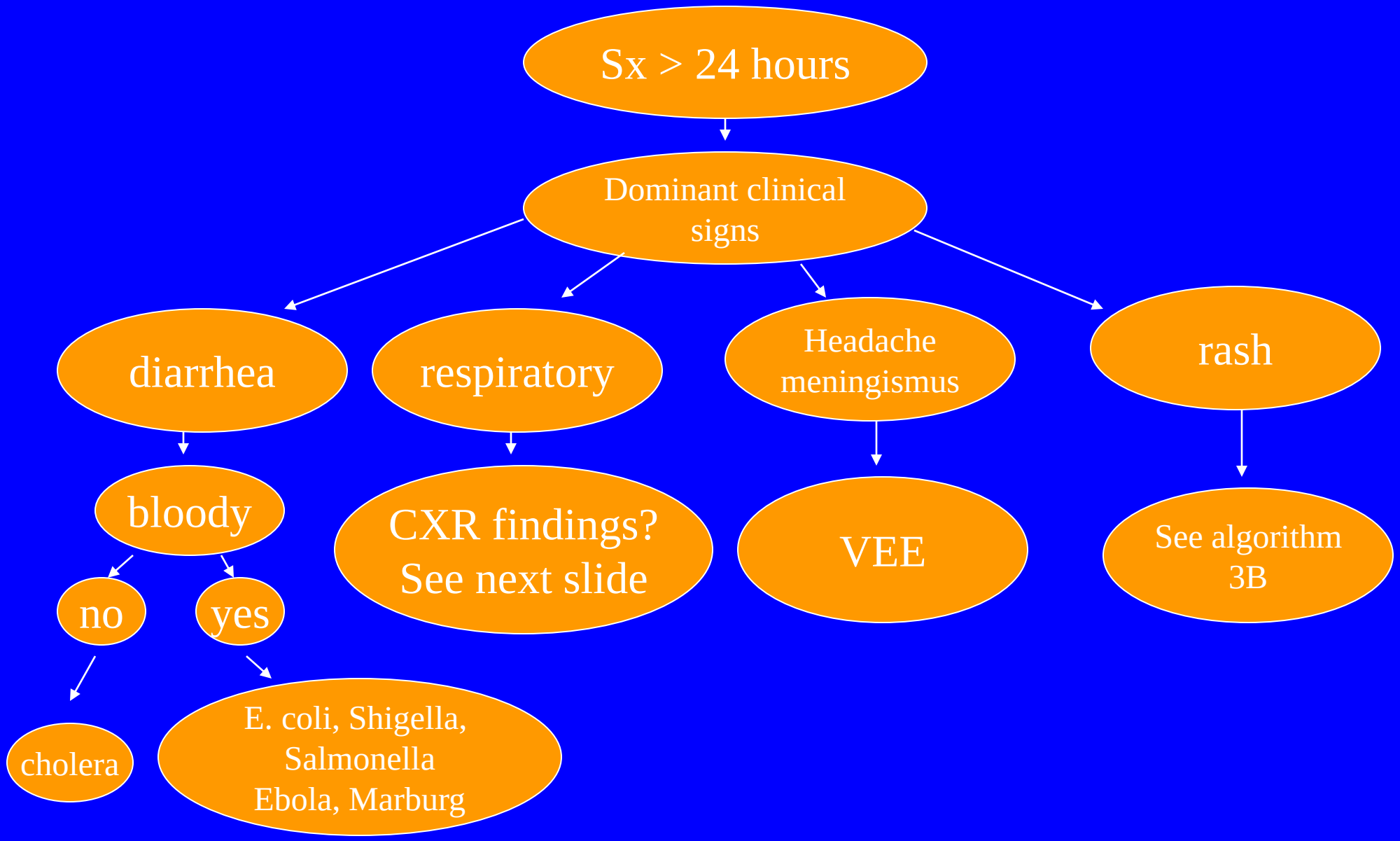
Algorithm 2A



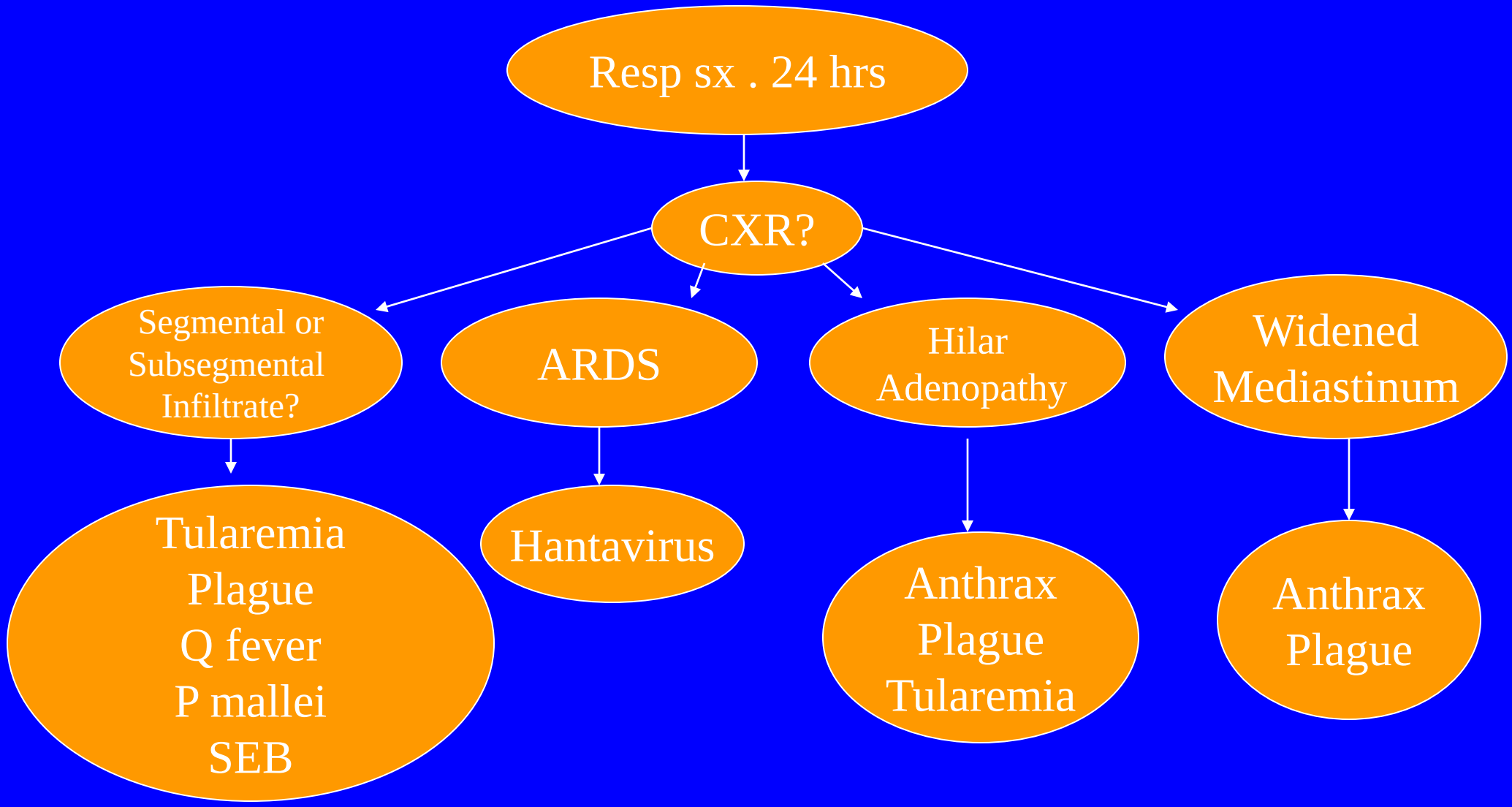
Algorithm 2B



Algorithm 3A



Algorithm 3A (continued)



Algorithm 3B