CYANIDE

U.S. ARMY MEDICAL RESEARCH INSTITUTE OF CHEMICAL DEFENSE

CHEMICAL CASUALTY CARE DIVISION

Objectives

- Distribution (occurrence) and history
- Physical and chemical properties
- Mechanism of action
- Clinical presentation
- Treatment

Distribution and History

- **Ubiquitous (in low concentrations)**
  - Interstellar space and prebiotic earth
  - Most living organisms
    - Man: < 0.20 mg / mL (8 mmol / L) in blood
- **Poisonous in higher concentrations**
  - Favorite of assassins and terrorists
  - CW agents: AC and CK

Do not confuse CN^- (cyanide ion) with CN (chloroacetophenone), a riot control agent

History and Military Use

- Ancient Egypt and Rome
- Scheele: Isolated Prussic acid (1782)
- Playfair: Advocated use during Crimean War
- Napoleon III: Proposed use in Franco-Prussian war
- WW I: French (Vincennite) and British
- Nazi Germany: Zyklon B
- Middle East: Apparent use in Hama and Halabja

Cyanide off the Battlefield

- **Terrorists**
- **Homicidal and suicidal use**
- **Judicial executions**
- **Combustion (plastics, cigarettes, vehicle exhaust)**
- **Industry (ore processing, chemical syntheses)**
- **Household products (silver polish, acetonitriles)**
- **Illicit manufacture of PCP**
- **Iatrogenic exposures: Sodium nitroprusside**
- **Pseudomonas infections**

Cyanogenic Glycosides in Plants

- **Amygdalin** (Laetrile®; bitter almonds, apricot seeds)
- **Prunasin** (cherry laurel water;
  also primary metabolite of amygdalin)
- **Dhurrin** (sorghum, bamboo shoots, other grasses)
- **Linamarin** (cassava [manioc], certain lima beans, linseed oil)
- Hydrolysis by ƀ-glucosidase in emulsin yields HCN

Diseases Related to Cyanide Exposure

- **Tropical ataxic neuropathy** (TAN)
- **Konzo** (upper-motor-neuron disease in Zaire)
- **Subacute combined degeneration** of the spinal cord
- **Retrobulbar neuritis** in pernicious anemia
- Dominantly and recessively inherited **optic atrophies**
- **Leber's hereditary optic atrophy** (LOA)
- **Tobacco amblyopia**

CN^-: Chemistry and Biochemistry

High affinity for ions of transitional metals

- **Cobalt**
- **Iron, especially ferric ion (Fe^{3+})**
  - **Cytochromes (Fe^{2+} and Fe^{3+})**
  - **Heme in methemoglobin (metHb) (Fe^{3+})**

Ability to react enzymatically with sulfanes ($S\text{-}S^-$)

Other reactions
(especially with carbonyl and sulfhydryl groups)

CN^-: Normal Metabolism

- CN^- + Vitamin B_{12a} ⇄ Cyanocobalamin (B_{12})
- CN^- + Sulfanes ($S\text{-}S^-$) → Thiocyanates (SCN^-) + Sulfates (SO_3^{2-})
  - Sulfane reaction catalyzed by rhodanese
  - Sulfane reaction essentially irreversible
  - Rate-limiting factor: Sulfanes (sulfur donors)
- Reactions with carbonyl and sulfhydryl compounds (directly [non-enzymatically] and via enzymes such as 3-mercaptopyruvate sulfur transferase [MPST])

AC: Hydrogen Cyanide

- **HCN** $\rightleftharpoons$ $H^+ + CN^-$
- **Highly water soluble, but only weakly acidic: Hydrocyanic (Prussic) acid**
- **Very volatile; vapor and gas 94.1% as dense as air and explosive**
- **Boiling point 25.6° C (78.1° F)**

AC: Hydrogen Cyanide

- Faint **"musty"** odor of **bitter almonds**, **peach pits**, or **burning rope** (ability to detect is genetically determined and is absent in up to 40-50% of the population)
- Onset time: **Seconds** with high inhaled concentrations
- **LCt_{50}: 2500-5000 mg-min / m^3** (varies with concentration of gas and duration of exposure)

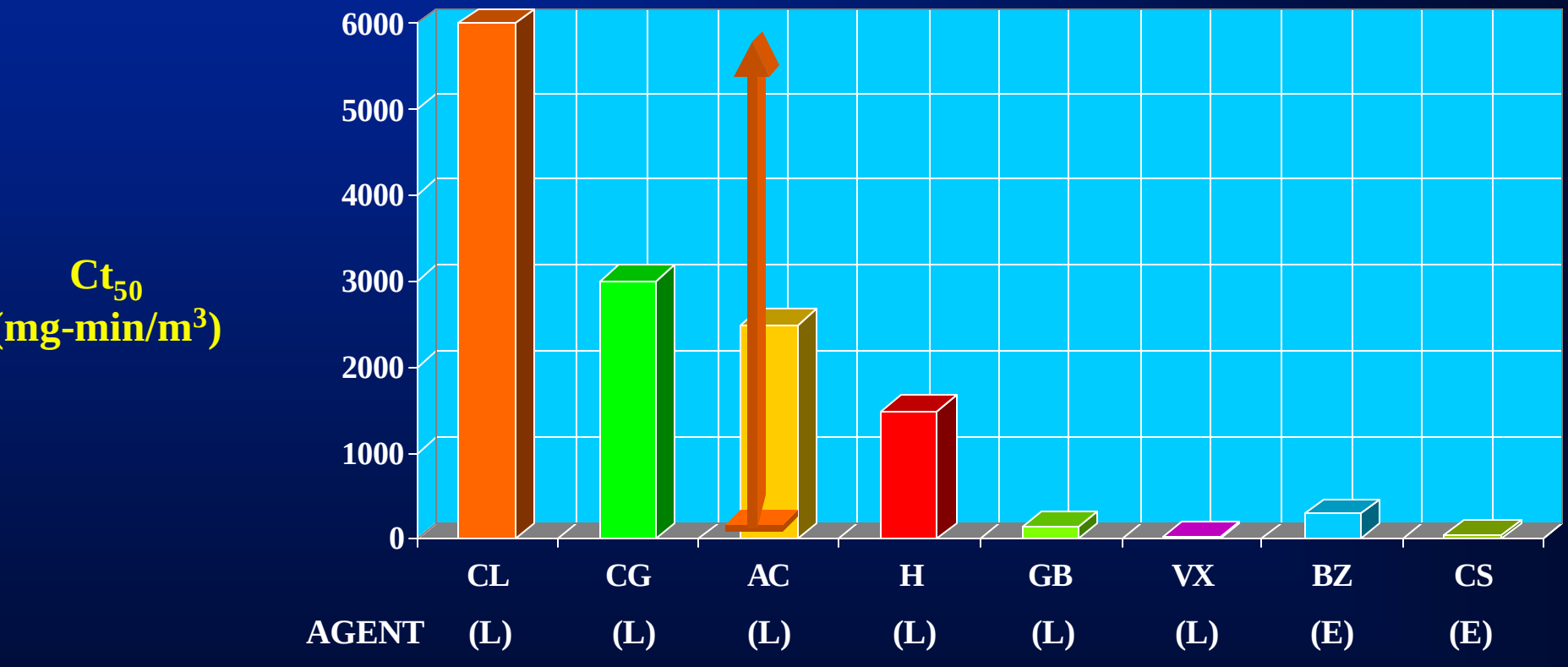
CK: Cyanogen Chloride

- **CNCl**  **CN^- + Cl_2**
- **Slightly water soluble**
- **Very volatile; vapor and gas heavier than air**
- **Boiling point 13.8° C (56.8 ° F)**

CK: Cyanogen Chloride

- **Pungent, biting odor masked by irritation of eyes, nose, and respiratory tract**
- **Onset time: Seconds with high inhaled concentrations**
- **LCt_{50}: 11,000 mg-min / m^3 at physiological pH**

Comparative Toxicity of Cyanide



Cyanide: Toxicokinetics (ADBE)

- **A**bsorption: **Inhalation > ingestion > percutaneous absorption**
- **D**istribution: **Wide distribution to all tissues via blood**
- **B**iotransformation: **Reactions with _____ and _____**
- **E**limination:
  - **Unchanged cyanide in breath, sweat, and urine**
  - **Thiocyanate and cyanocobalamin in urine**
  - **Iminothiocarboxylic acid (ITCA)**

Mechanism of Action

- A “blood agent”? (compare CO)
  - Reaction with Fe^{2+} in HbO_2 to form HbCN (quantitatively unimportant)
  - Elevation of blood levels of ammonia and of neutral and aromatic amino acids (probably a secondary event)
  - Lactic acidosis (predominantly a secondary event)

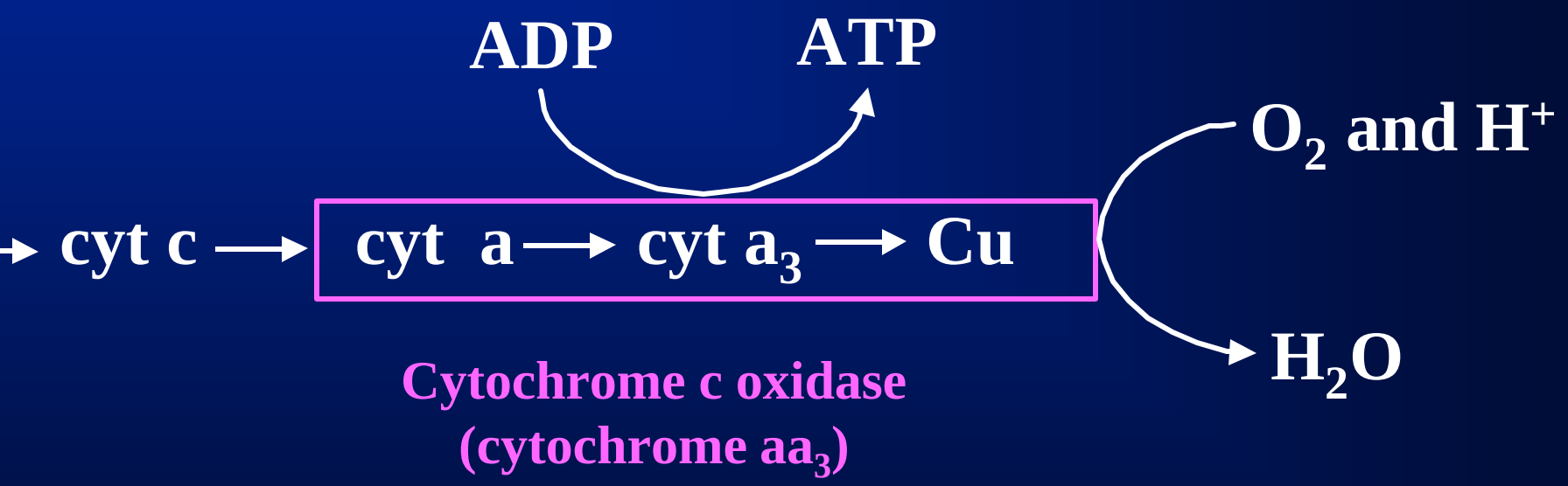
Mechanism of Action: The Classical Explanation

- Primary site of action: **Cells** rather than blood
- **Interruption of cellular respiration in mitochondria**
  - **Result: Histotoxic anoxia**

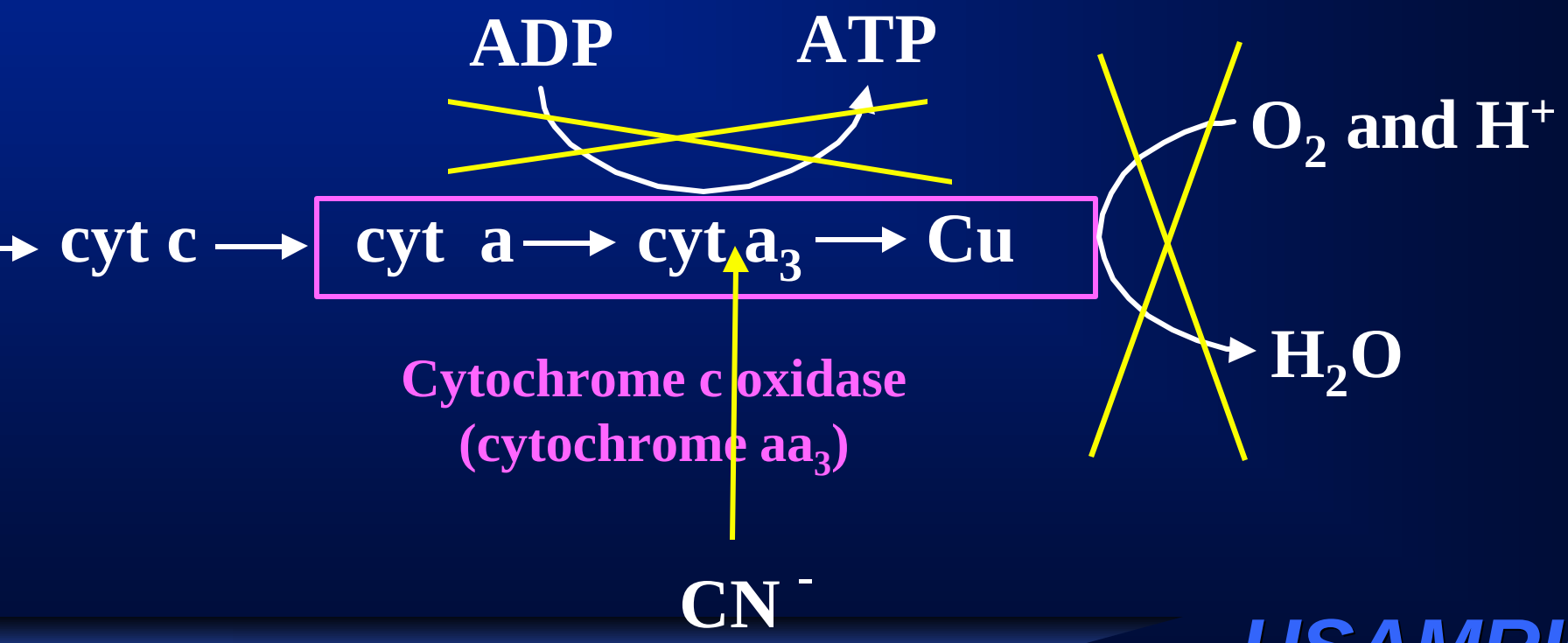
Classical Mechanism of Action

- **Binding of CN^- to cyt a_3 in mitochondria**
  - **Stable but not irreversible binding**
  - **CN^- has higher affinity for the Fe^{3+} in methemoglobin (metHb)**
- **Interruption of oxidative phosphorylation**

Oxidative Phosphorylation Chain (Terminal End)



Oxidative Phosphorylation Chain (Terminal End) with CN



Effects on Cells and Blood

- **No generation of ATP**;
  cessation of all processes dependent upon ATP

- **No extraction of O_2 from blood**;
  decreased AV O_2 difference

- **Pasteur shift to anaerobic glycolysis**;
  lactic acidosis and high anion gap

Effects at Organ Level

- **Carotid and aortic chemoreceptors**
  - **Intense stimulation from lack of usable oxygen**
    - **Results in neural stimulation of respiratory center and adrenal medulla**
- **CNS (nerve more sensitive than muscle)**
  - **Variation of sensitivity and effects within CNS**
  - **Respiratory-center failure (central apnea): USUAL MECHANISM OF DEATH**
- **Heart**
  - **Accumulation in left ventricle**
  - **Increased demand (from released catecholamines) in the face of reduced energy supply**
  - **Cardiac dysrhythmias and heart failure**

Clinical Presentation with High Doses

- **Rapid onset** when CN^- inhaled in high concentrations
  - With massive doses, collapse and death may be **nearly instantaneous** (apoplectic form)
  - **Onset** often in <u>10-18 seconds</u>
  - **Death** often in <u>5-8 minutes</u>

Progression of Symptoms and Signs

- Transient increase in rate and depth of respiration (from hypoxia of carotid and aortic bodies)
- Initial hypertension and tachycardia (from hypoxia of aortic body)
- Convulsions / rigidity / opisthotonus / trismus / decerebrate posturing (20 - 30 seconds)
- Respiratory depression and arrest (1 - 2 minutes)
- Bradycardia, hypotension, and cardiac arrest

Clinical Presentation: Skin

- Initial **flushing** and **diaphoresis** may occur
- Skin and breath may smell of **bitter almonds**
- Acrylonitrile-induced bullae
- Cyanide poisoning is NOT characterized by **cyanosis** early in its course!

Clinical Presentation: Other

- **Exposure to low concentrations**
  - **Onset may be delayed and gradual**
  - **Headache, anxiety, weakness, lightheadedness, vertigo, ataxia, nystagmus, muscle rigidity**
- **Ingestion**
  - **Hypersalivation**
  - **Acrid, burning, metallic, or constricting sensations**
  - **Epigastric pain (with some plant ingestions)**
  - **Hyperthermia (with some plant ingestions)**
  - **Nausea and vomiting (central effect; may also be seen following inhalation**

Clinical Presentation: Classic Signs

- Bright red venous blood, skin, and fundal vessels
- Profound metabolic acidosis with high anion gap
- Odor of bitter almonds
- Tachypnea, hypertension, and bradycardia without cyanosis
- Respiratory depression without cyanosis

Cyanide and ASBESTOS

- ***A***gent(s): Type(s) and toxicity (including LD_{50})
- ***S***tate(s): Solid? Liquid? Gas? Vapor? Aerosol?
- ***B***ody site(s): Where exposed / Route(s) of entry? [*absorption*]
- ***E***ffects: Local? Systemic? [*distribution*]
- ***S***everity: Mild? Moderate? Severe?
- ***T***ime course: Onset? Getting better/worse? Prognosis?
- ***O***ther diagnoses: Instead of? [*DDx*] In addition to?
- ***S***ynergism: Combined effects of multiple exposures or insults?

Treatment

- **Prerequisite:** ***Protect yourself!***
- **General supportive therapy**
- **Specific antidotal therapy**

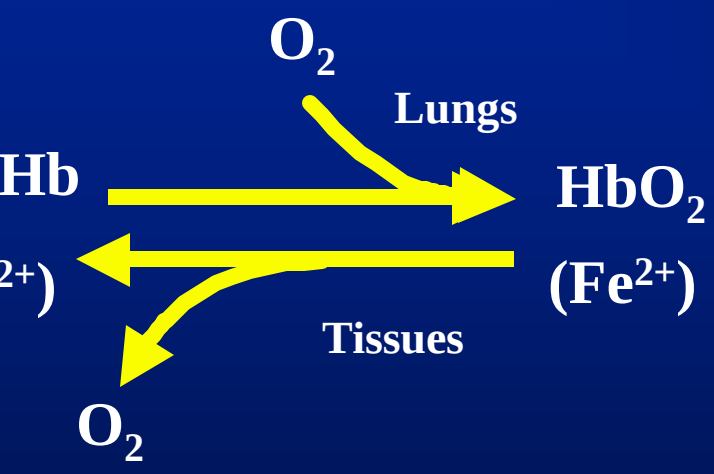
General Supportive Therapy

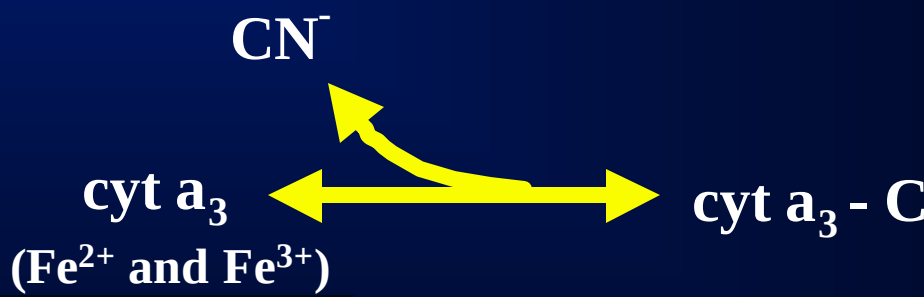
- **Termination of exposure**
  - **Removal of patient:**
    - **Physical removal, masking**
  - **Removal of agent**
    - **Decontamination (soap and water)**
    - **Gastric lavage with activated charcoal, 5% sodium thiosulfate, 0.1% potassium permanganate, or 1.5% hydrogen peroxide (ingestion)**
- **Airway, Breathing, and Circulation**
  (but beware unprotected mouth-to-mouth respiration)
- **100% oxygen (normobaric vs. hyperbaric)**
- **Correction of metabolic acidosis**
- **Observation for at least 24 to 48 hours**

Goals of Specific Antidotal Therapy

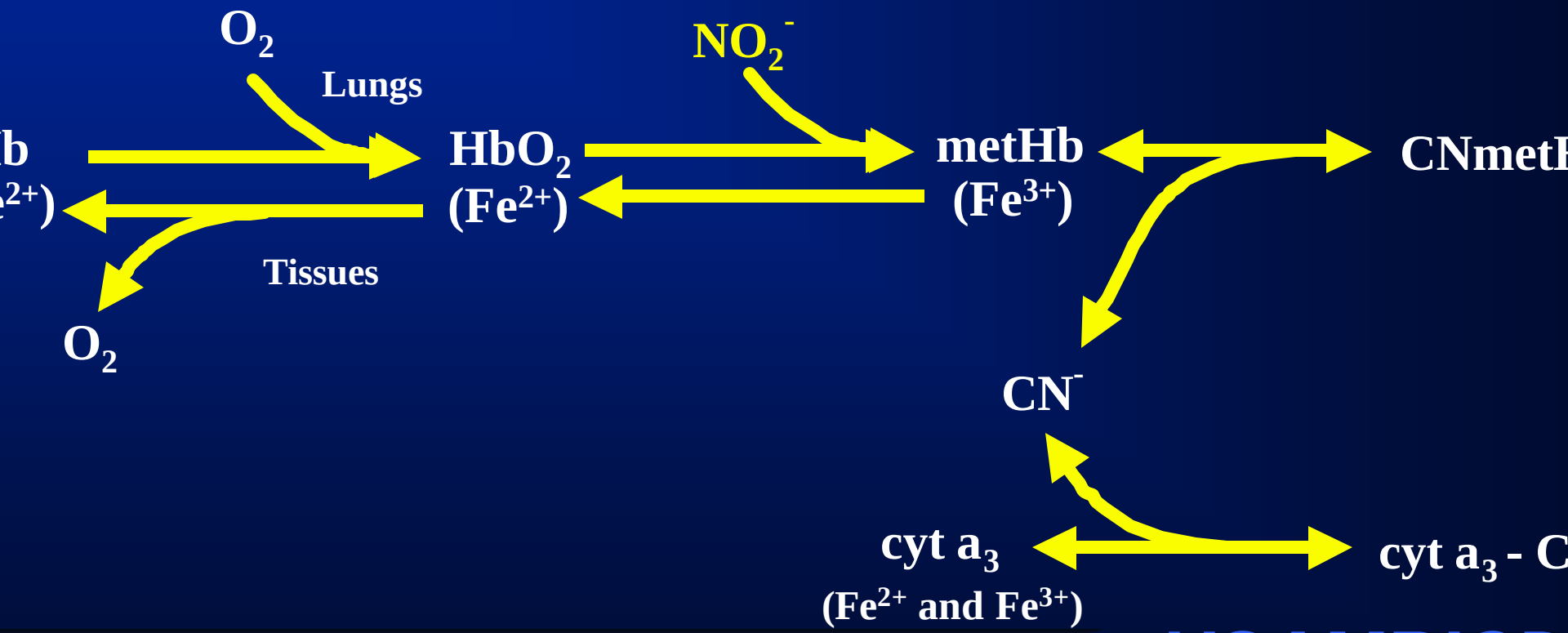
- **Displacement of CN^- from cytochrome a_3**
  - **Reaction of CN^- with metHb generated by nitrites or other metHb formers**
- **Enzymatic conversion of CN^- to thiocyanate**
  - **Administration of a sulfane (e.g., sodium thiosulfate) as a sulfur donor**

Cyanide and Cytochrome a_3





Displacement of CN^- from cyt a_3



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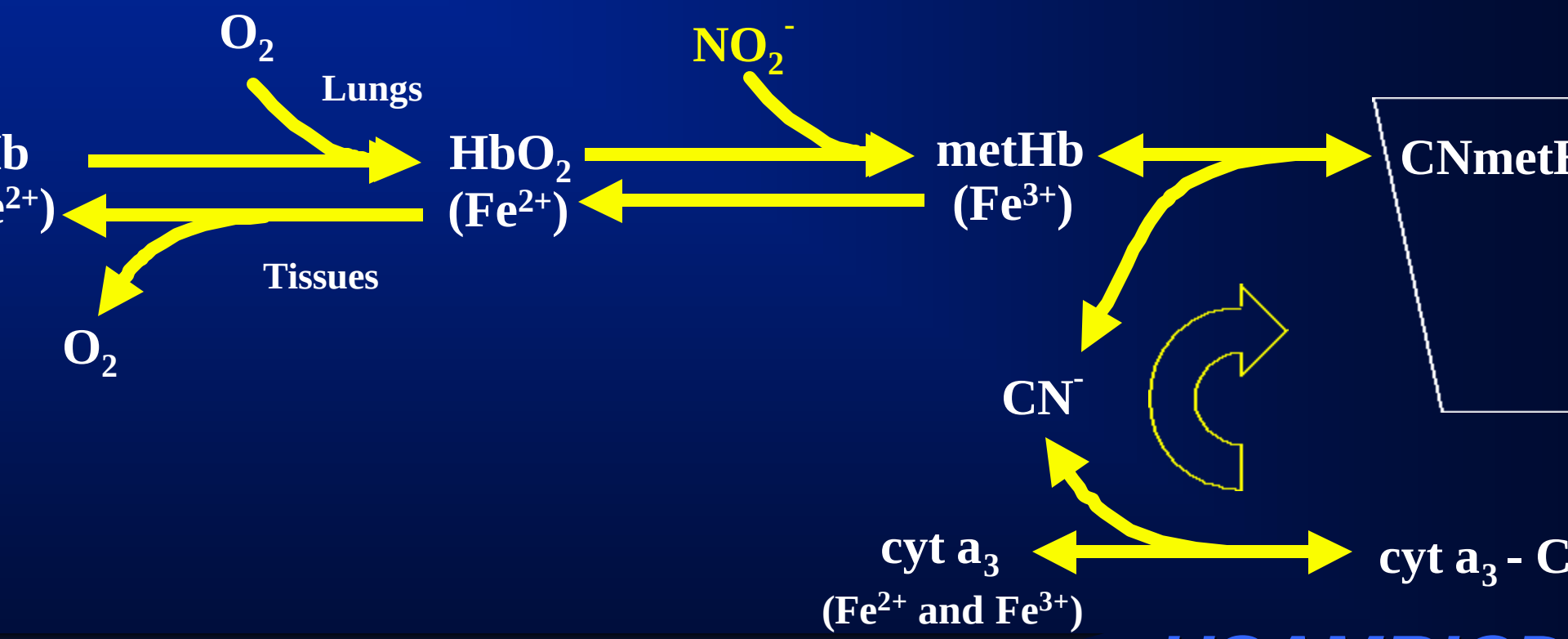


Amyl Nitrite: ($C_5H_{11}NO_2$)

- **Therapeutic effect noted as early as 1888**
- **One of three components of the commercially available cyanide antidote kit**
- **Given by inhalation by crushing vials**
- **Converts Hb (Fe^{2+}) to metHb (Fe^{3+}), but inhalation leads to variable metHb levels**

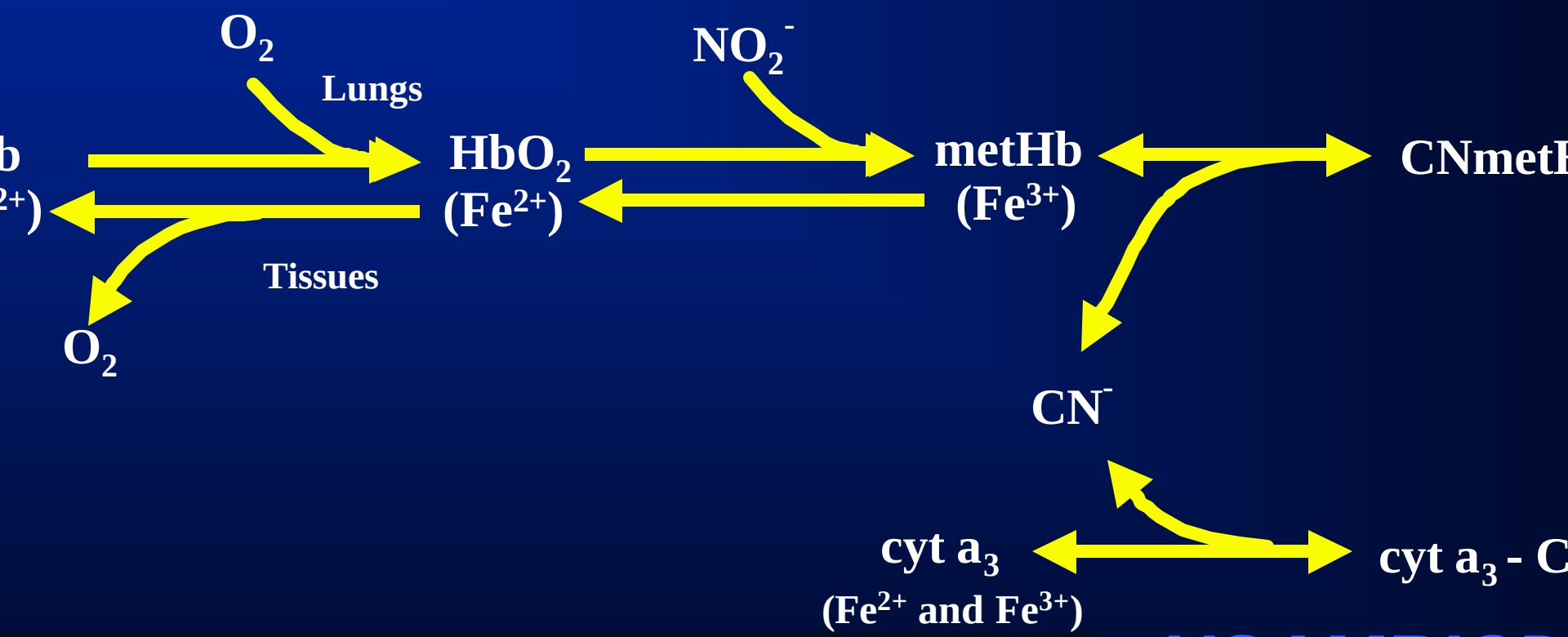
Sodium Nitrite ($NaNO_2$)

- Converts HbO_2 (Fe^{2+}) to metHb (Fe^{3+})
- Therapeutic effect seen before metHb generated
- Vasodilatory mechanism of action?
- Adverse effects
  - Methemoglobinemia (maintain <40% metHb)
  - Hypotension

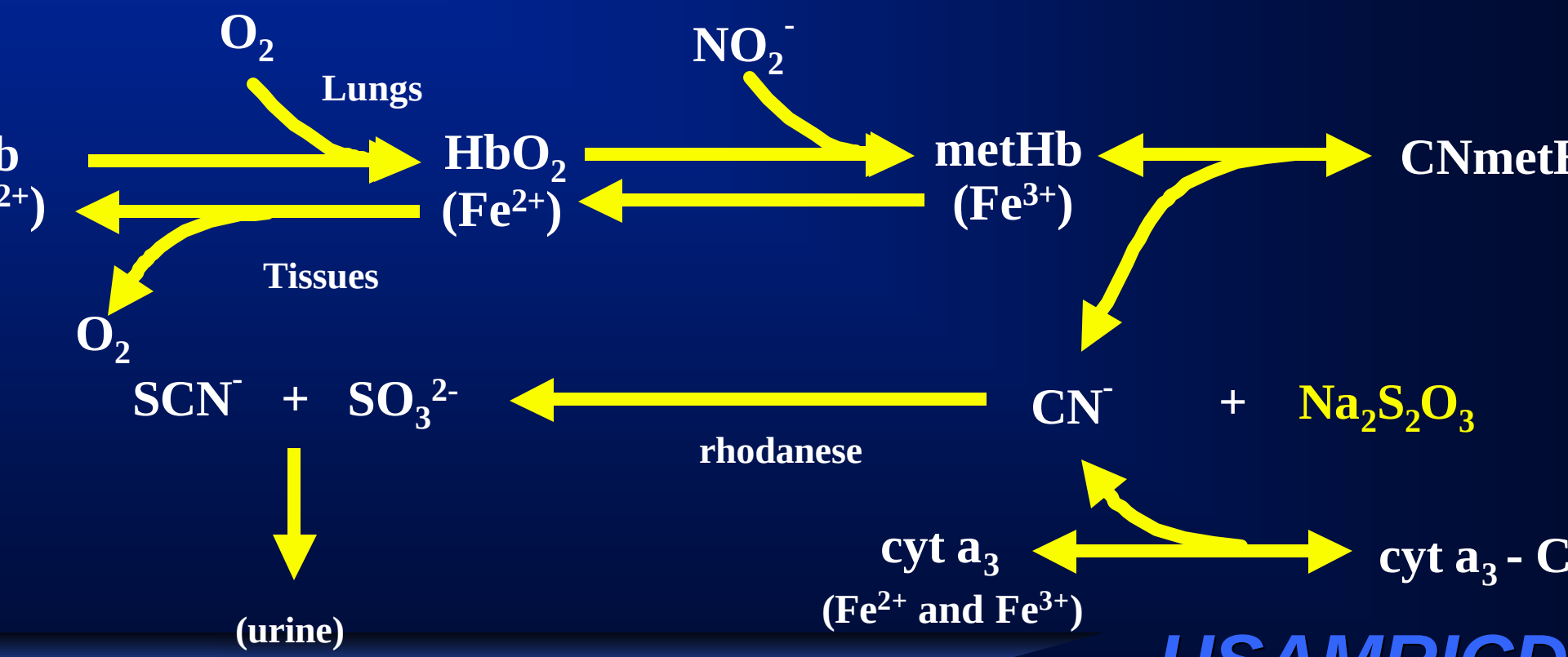
Sodium Nitrite: Administration

- 10 mL IV of a 3% soln (30 mg / mL) = 300 mg
- Administer over at least a 3-minute period
- Give half original dose if signs recur

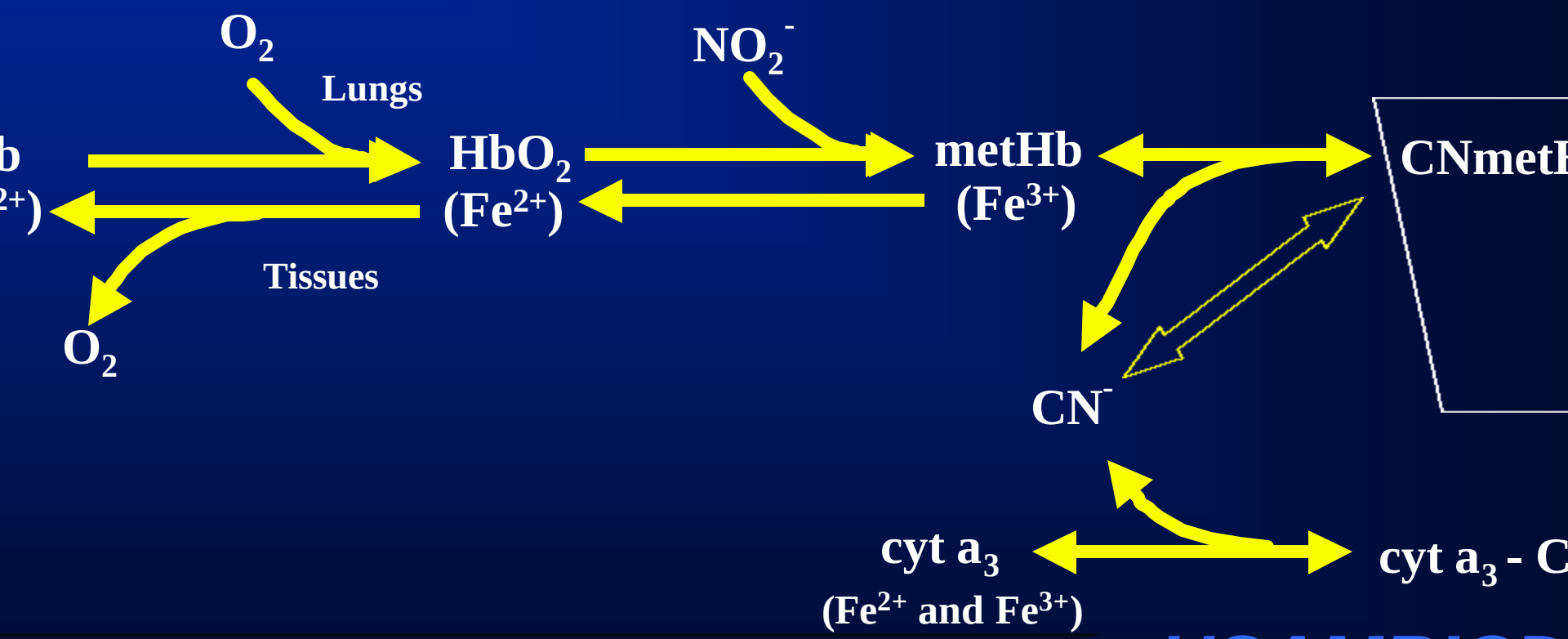
Displacement of CN^- from cyt a_3



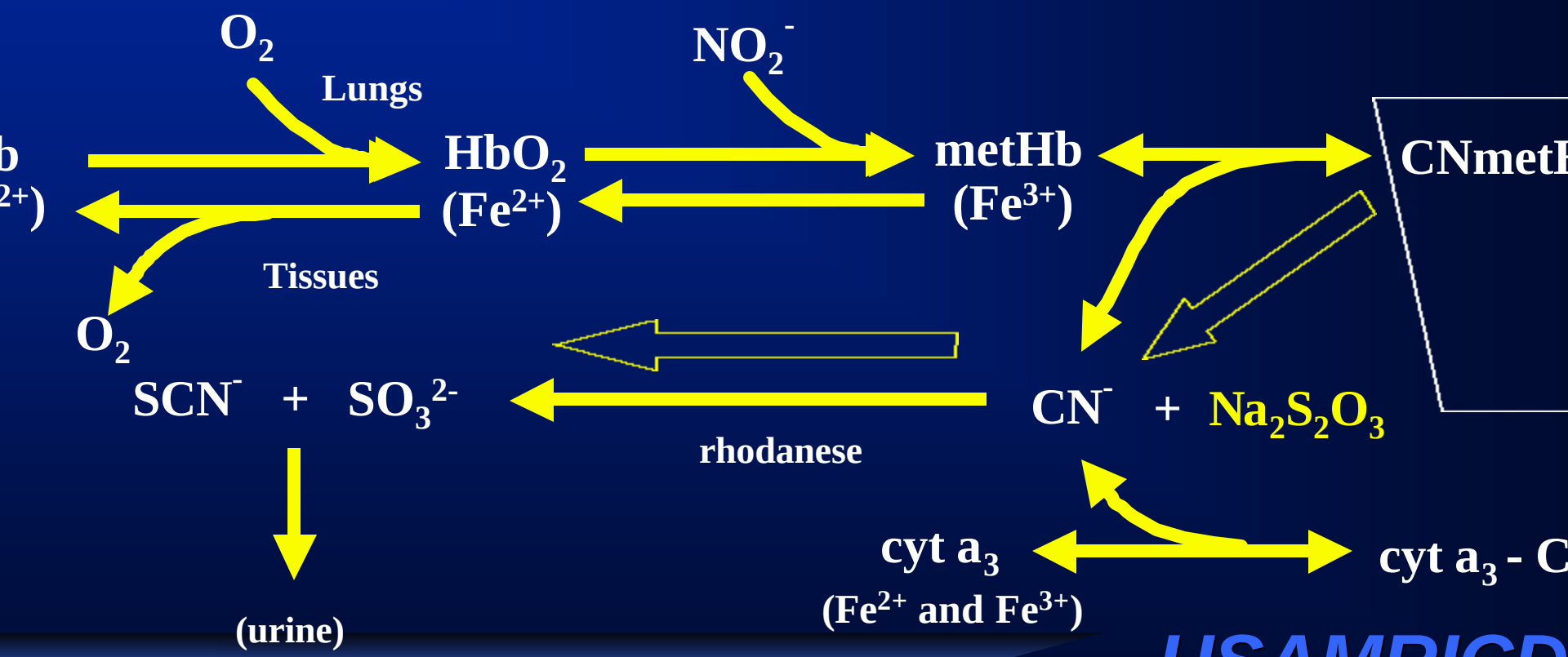
Conversion of CN^- to Thiocyanate



Displacement of CN^- from cyt a_3



Conversion of CN^- to Thiocyanate



Sodium Thiosulfate ($Na_2S_2O_3$)

- Enzymatically reacts with CN^- to form thiocyanate (SCN^-) and sulfite (SO_3^{2-})
- Irreversible reaction; thiocyanate excreted by kidney
- Adverse effects few and usually not serious
  - Nausea, vomiting, arthralgias, psychosis only with levels > 10 mg /dL

Sodium Thiosulfate: Administration

- 50 mL IV of a 25% soln (250 mg / mL) = 12.5 g
- Administer over a 10-minute period beginning immediately after nitrite administration
- Give half original dose if signs recur

Experience with Antidotes

- "The combination of sodium nitrite and sodium thiosulfate is the best therapy against cyanide and hydrocyanic acid poisoning. The 2 substances intravenously injected, one after the other, namely the nitrite followed by the thiosulfate, are capable of detoxifying approximately 20 lethal doses of sodium cyanide in dogs and are effective even after respiration has stopped. As long as the heart is still beating, the chances of recovery by utilizing this method are very good." -Chen et al.

Other Specific Antidotes

- **Other methemoglobin formers**
- **Cobalt compounds**
- **Miscellaneous compounds under investigation**
  - **Carbonyl compounds (pyruvate, alpha-ketoglutarate, glyoxal trimer)**
  - **Sulfhydryl compounds (e.g., mercaptopyruvate)**
  - **Calcium-channel blockers (e.g., diltiazem, verapamil)**
  - **Chlorpromazine**
  - **Naloxone, etomidate, etc.**

Other Methemoglobin Formers

- **4-Dimethylaminophenol (4-DMAP)**
  - **Forms metHb more rapidly than do nitrites**
  - **No hypotension, but metHb levels often too high**
  - **Local necrosis may occur after IM injection (give IV only)**
  - **Used in Germany**
- **Para-aminoproplophenone (PAPP)**
- **Para-aminooctanoylphenone (PAOP)**
- **Hydroxylamine (50 mg / kg IM effective in beagles)**
- **Primaquine analogs (8-aminoquinolines)**

Cobalt Compounds

- **Dicobalt edetate (Co_2 EDTA, Kelocyanor)**
  - **Chelates CN^-**
  - **Adverse effects**
    - **Angina pectoris, ventricular dysrhythmias, periorbital and laryngeal edema, convulsions**
  - **Used in the U.K., France, and the Netherlands**

Cobalt Compounds

- **Hydroxocobalamin (vitamin B_{12a})**
  - **Reacts stoichiometrically with CN^- to form cyanocobalamin (vitamin B_{12})**
  - **Difficult to administer adequate amounts**

Summary

- On the battlefield, usually a **vapor** or a **gas**
- **Variable potency (LCt_{50})** because of limited metabolism, but **rapidly acting** in high concentrations
- NOT primarily a "**blood**" agent; rather, probably a **cellular poison**
- **Nitrites** generate **metHb**, which "pulls" cyanide from cyt a_3 and combines with the cyanide (reversible reaction; temporary reservoir for bound cyanide)
- **Thiosulfate** irreversibly reacts with cyanide to form thiocyanate (excreted in urine)