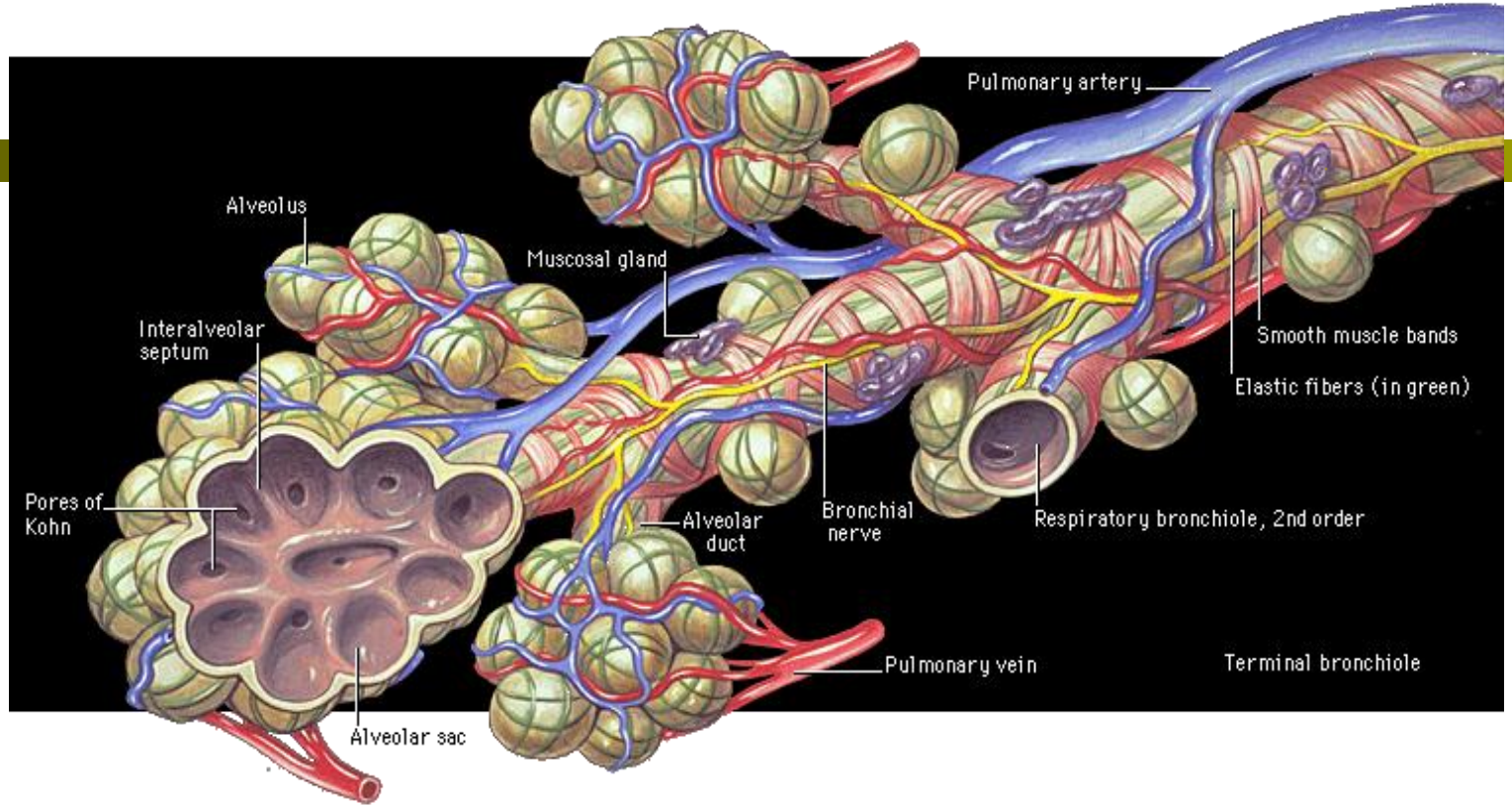
MEDICAL UNIVERSITY – PLEVEN
FACULTY OF PUBLIC HEALTH
CENTER FOR DISTANCE LEARNING

PULMONORY EDEMA - INDUCING COMPOUNDS



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Pulmonary edema

Two stages in the formation of pulmonary edema are recognized.

The first is **interstitial edema**. Widened lymphatics can be seen, and lymph flow increases. Pulmonary function is little affected at this stage.

The second stage is **alveolar edema**. Here, fluid moves across into the alveoli, which are filled one by one.

I. Increased Capillary Hydrostatic Pressure

(**hydrostatic pulmonary edema**)

This is the most common cause of pulmonary edema and frequently complicates heart disease, such as acute myocadial infarction, left ventricular failure and mitral valve disease. In all of these conditions, **left arterial pressure rises**, causing an increase in pulmonary venous and capillary pressure.

For relatively small increases in pressure, the edema fluid has a low protein concentration because the permeability of the capillary wall is preserved (**low-permeability edema**). With large increases of pressure, the protein concentration of the edema fluid is high (**high permeability edema**).

II. Increased Capillary Permeability

An increased capillary permeability also occurs in a variety of conditions. Toxins that are inhaled such as chlorine, sulfur dioxide, nitrogen oxides, ammonia cause pulmonary edema in this way.

In severe pulmonary edema, capillary fluid moves into the alveoli. The accumulated fluid in the alveoli and respiratory airways impairs the gas exchange function of the lung. With the decreased ability of the lungs to oxygenate the blood, the hemoglobin leaves the pulmonary circulation without being fully oxygenated. Cyanosis and shortness of breath result.

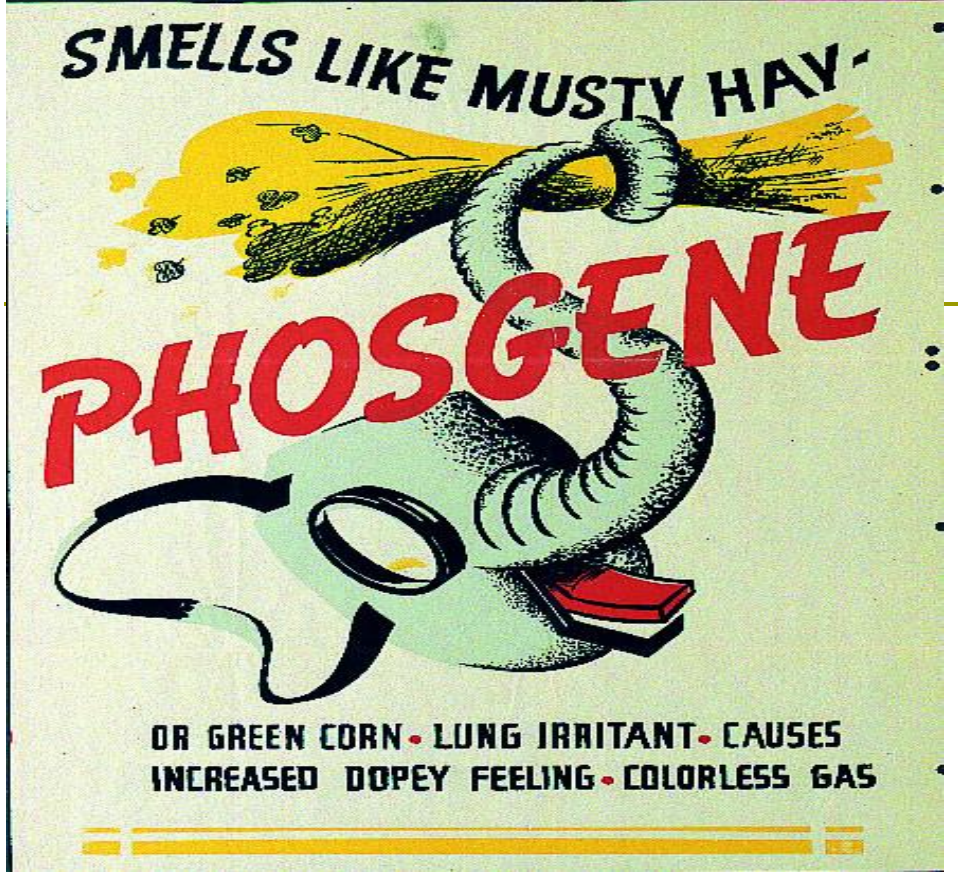
Clinical Features

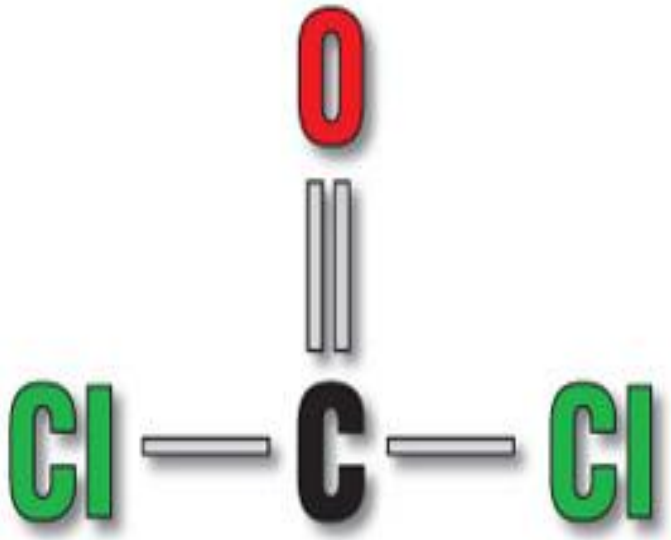
Dyspnea-difficulty breathing or shortness of breath. Breathing is typically rapid and shallow. A person with acute pulmonary edema is usually seen gasping for air. The pulse is rapid, the skin is moist and cool, and the lips and nail beds are cyanotic. Dyspnea and air hunger are accompanied by a cough productive of frothy – bloody sputum - the effect of air mixing with **serum albumin** and **red blood cells** that have moved into the alveoli.

The movement of air through the alveolar fluid produces fine crepitations called **crackles**. In more severe cases, rhonchi may be heard. In the terminal stage the breathing pattern is called the death rattle. Patients literally drown in their own secretions.

Increased pulmonary edema is the result of capillary damage from a diverse collection of disease and is more of an inflammatory infiltration than the watery edema of heart failure.

- The **most important compounds** of this group are:
  - **phosgene**
  - **chlorine**
  - **ammonia**
  - **nitrogen oxides**
  - **methyl isocyanide**
- **They cause:**
  - **hypoxia**
  - **dyspnea**
  - **pulmonary edema**.


SMELLS LIKE MUSTY HAY
PHOSGENE
OR GREEN CORN • LUNG IRRITANT • CAUSES
INCREASED DOPEY FEELING • COLORLESS GAS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PHOSGENE

I. Sources and use

- production **of plastics (polyurethane)**
- synthesis **of drugs (intermediate product)**
- **fires of some plastics (polyurethane, polyvinylchloride)**
- **decomposition product** of other **chlorinated chemicals (**as **freons)**. The decomposition requires specific **alkaline conditions** and **high temperature**
- **the metabolism** of some chlorinated compounds (**as chloroform**) results in the formation of **endogenous phosgene**

I. Sources and use

- **Phosgene (carbonyldichloride - $COCl_2$)** is:
  - a **colorless gas**
  - its odor is similar to **musty hay**
  - at room temperature is **slightly soluble** in water
- Phosgene **enters** the organism **primarily by:**
  - **inhalation**
  - **partially** by the **skin**

II. Mechanism of action

- The exact **mechanism** of action of phosgene **still remains obscure**.
- Because of its low solubility in water it reaches to deep part of the respiratory tract - to the alveoli.
- Phosgene **causes**:
  - **pulmonary congestion**
  - **degenerative changes in the epithelium** of the **upper respiratory system**
  - **lobular pneumonia**
  - **pulmonary edema**

II. Mechanism of action

- There are **several hypotheses** explaining toxic mechanism on **molecular level**:

1. The **phosgene acts by combination with water** and **forms hydrochloric acid**, which then produces **tissue damages**.
2. The **phosgene interacts with the amino groups of proteins to form diamides**.
3. The **phosgene interacts** with **chemical groups** in the macromolecules -**hydroxyl, sulphhydryl etc. -** a number of **enzymes** show decreased activities.

II. Mechanisms of action
Pathophysiologic mechanisms for explanation of the pulmonary edema

- **Damage of the blood-air barrier in the lung** and leak of **fluid** from the pulmonary capillaries
- Other pathogenic mechanism is so called **"neurogenic pulmonary edema"**. It explains the pulmonary edema caused by phosgene with massive vasoconstriction and production of edema.

- **Hystopathology**

The edema fluid is:

- classically **eosinophilic**
- with **high content of proteins**

The **epithelium of the terminal bronchioles is first damaged**.

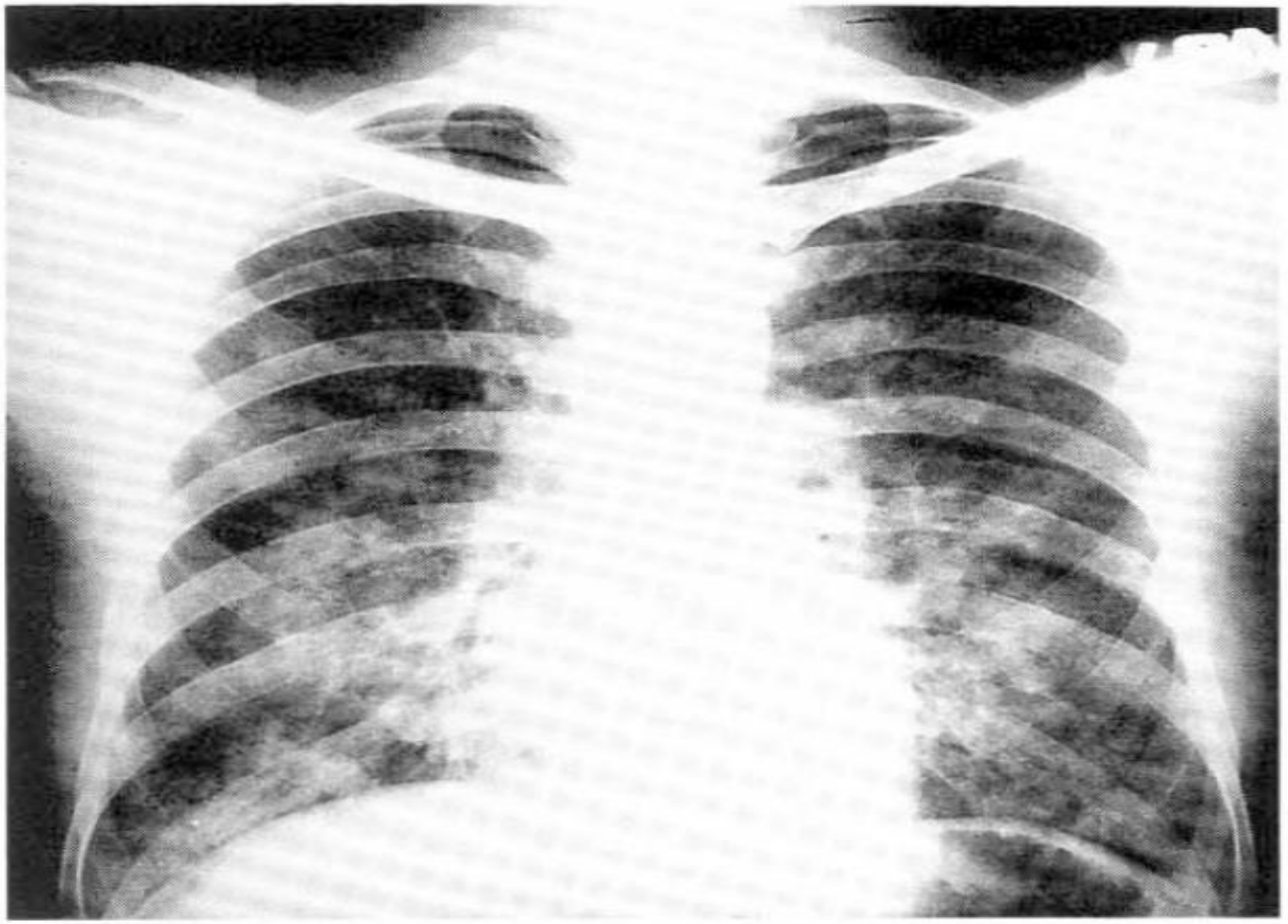
It is observed a **swelling of type II alveolar cells**.

III. Clinical presentation

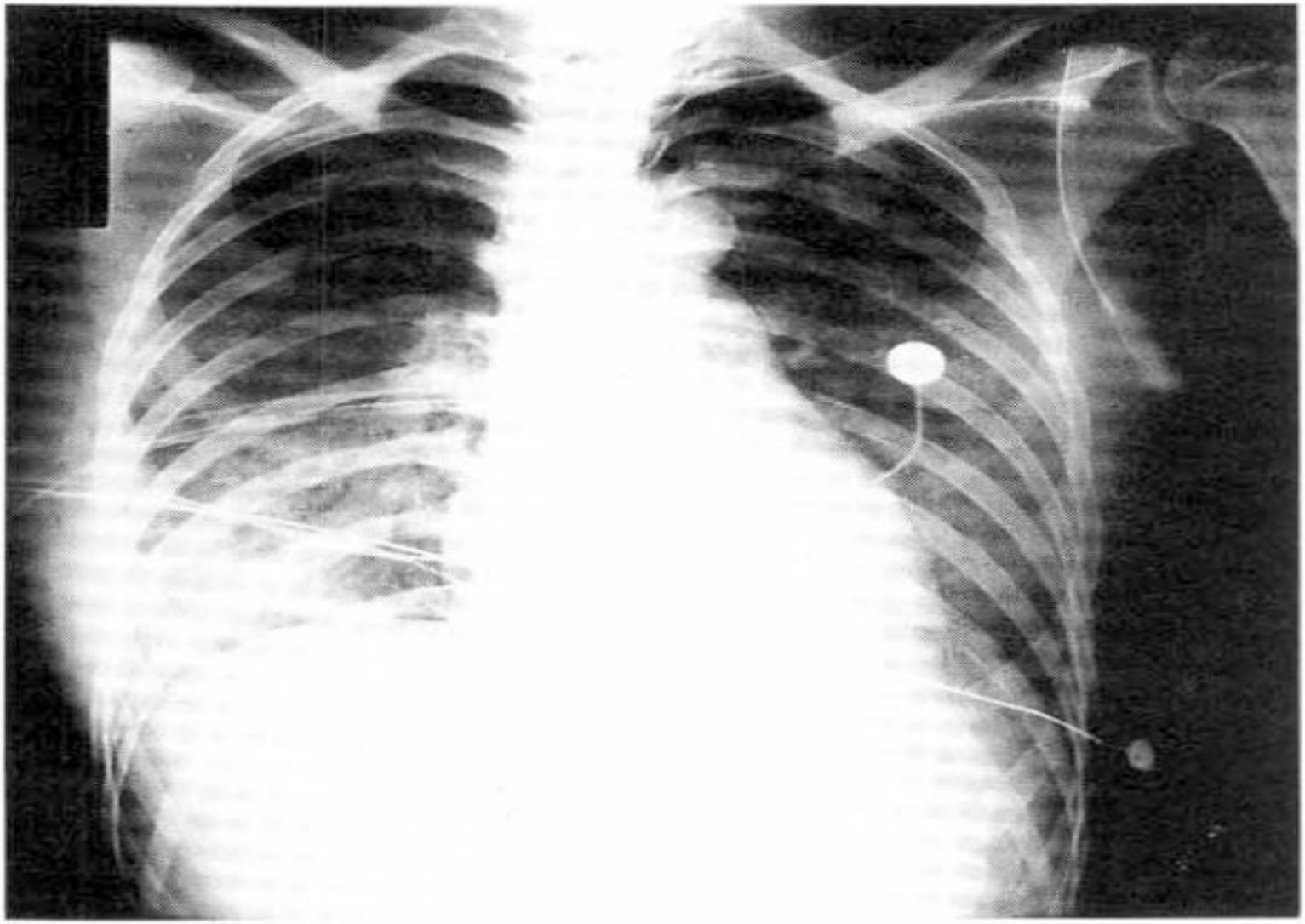
- The **early symptoms** and **signs** are:
  - **irritation**
  - **cough**
  - **lacrimation**
  - **feeling of tightness** of the chest
- **Latent period without chest signs follows the early symptoms.** This **period may last from 30 min to 24 h**.

  During the latent period is observed only: **increased rate of respiration and slow pulse.**
- **After the latent period appear:**
  - **painful cough**
  - **cyanosis**
  - **increasing quantities** of **initially whitish but later pink expectoration**

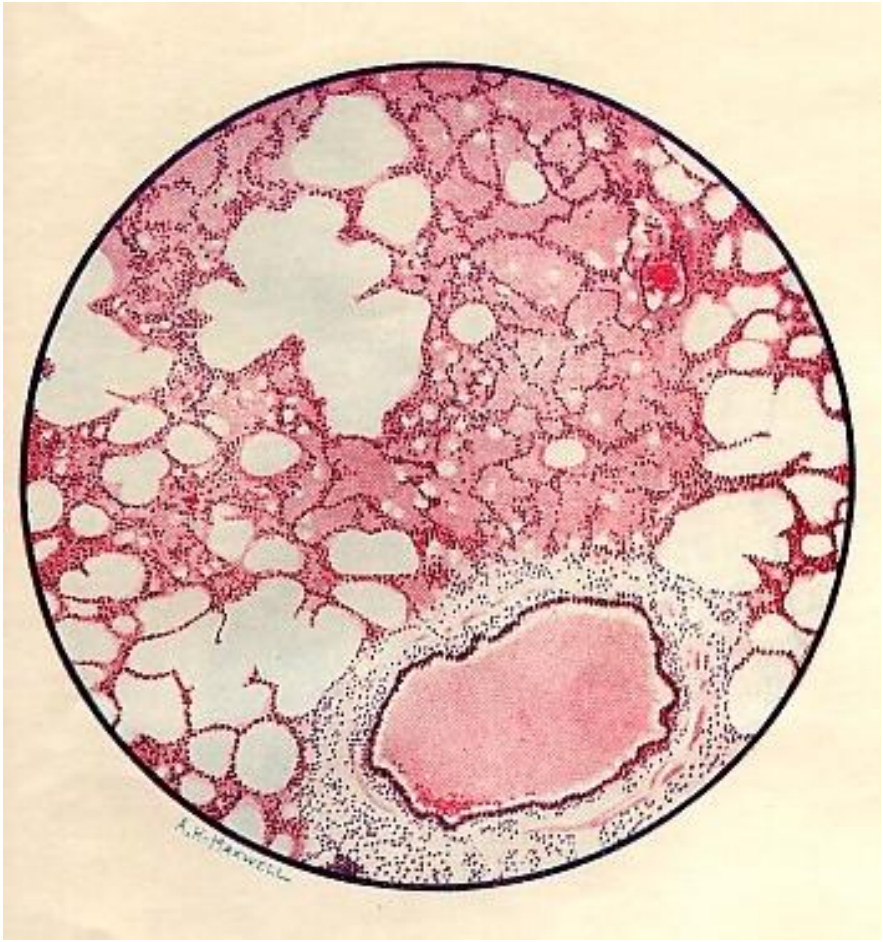
Bilateral pulmonary edema



PHOSGENE – Pulmonary edema



Phosgene



The main changes in the lung are:

- Congestion, and occasional thrombosis, of the network of pulmonary blood vessels.
- Abundant outpouring of inflammatory oedema fluid both into the tissues and into the air spaces of the alveoli and bronchi.
- Disruptive emphysema of the weakened lung tissue.

III. Clinical presentation

- The **cause of death** is **cardiac failure** and **circulatory collapse** caused by the **hypoxia**.
- The **phosgene does not appear to cause chronic health effects** in humans.
- **Early complications** after **acute poisoning:**
  - **acute cardiac failure**
  - **bronchopneumonia**
  - **thrombosis of legs**
- **Late complications:**
  - **pulmonary fibrosis**
  - **emphysema**
  - **bronchiectasis**

IV.Treatment

- **First**, the patients should be **removed from** phosgene exposure by **suitable protected rescuers**.
- **Treatment of pulmonary edema:**
  - **Bronchodilators, inhaled beta$_2$ adrenergic agonists and anticholinergic drugs (Albuterol + Ipratropium bromide – protect the airways from spasms and may reduce the amount of mucus)**
  - **diuretic drugs,** but they are largely ineffective against toxic pulmonary edema
  - **Steroids – not very effective**
  - **respiratory and cardiac** stimulants
  - **Antibiotics**
  - **oxygen therapy** in patients unable to maintain adequate arterial oxygen tension

IV.Treatment

- **No antidotes**
- Focus on airway, breathing, and circulation
- Proceed rapidly to intubation if necessary
- Provide supplemental oxygen for dyspnea, hypoxia, or crackles
- Provide positive-pressure ventilation
- **All persons thought** to have been **exposed to phosgene** should be confined to bed, to prevent acute and **fatal pulmonary edema.**

CHLORINE

I. Sources and use

Chlorine is used as:

- **bleaching agent in pulp mill facilities;**
- **production of resin and plastic manufacturing;**
- **disinfecting agent,** particularly in **wastewater treatment;**
- **in household bleaches;**
- **pharmaceuticals industry;**
- **metal extraction etc.;**

Chlorine is **a greenish-yellow gas** with a pungent, irritant odor. It forms **explosive compounds** with many **common substances**.

II. Mechanism of action

- **Chlorine enters the** organisms primarily by inhalation.
- **Chlorine atoms** react with **endogenous water** to form **hydrochloric (HCl)** and **hypochloric acid (HClO)**.
- The **hypochloric acid** rapidly **degrades** to **hydrochloric acid (HCl)** and **oxygen radicals**. These **toxic radicals cause** most of the observed **respiratory effects**.

III. Pathology

Postmortem changes after **fatal massive exposure** to chlorine:

- **destruction of the mucous membranes lining** of the **bronchi and bronchioles**;
- **focal and confluent** areas of **edema** in the **alveoli**;
- **patchy superimposed pneumonia**;
- **hyaline membrane formation;**
- **thromboses of the pulmonary vessels;**
- **ulcerative tracheobronchitis;**

IV. Clinical presentation

a) Acute form of poisoning

Signs and symptoms:

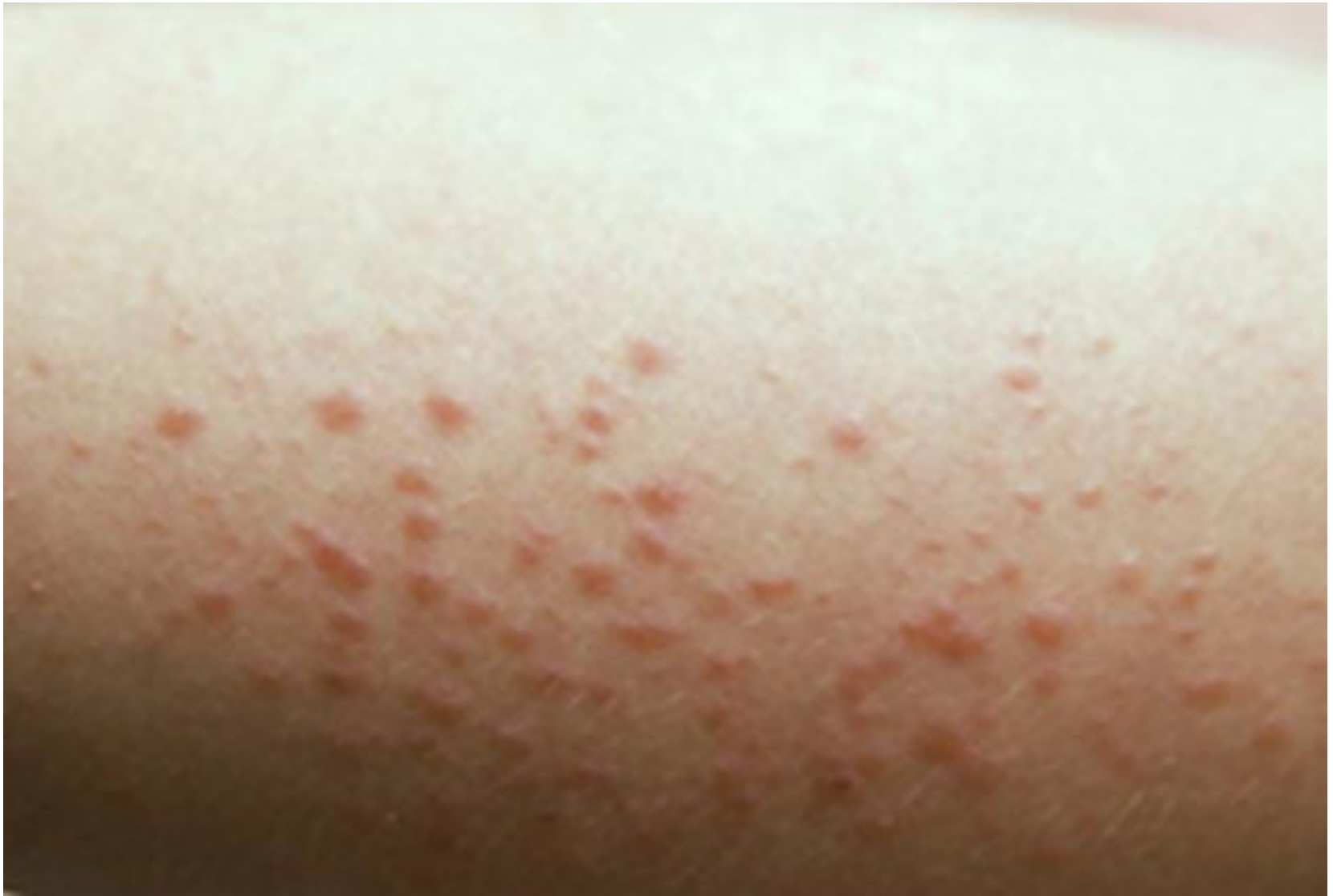
- **burning of the eyes and the nose;**
- **lacrimation;**
- **rhinorrhea;**
- **respiratory distress;**
- **nausea and vomiting;**

IV. Clinical presentation

All of the immediate signs and symptoms typically **pain and respiratory distress persist for up to 2 weeks.**

- **In condition of severe overexposure are observed:**
  - **Tracheobronchitis**
  - **pneumonia**
  - **pulmonary edema**
- **The usual symptoms of cough, dyspnea and chest pains start within 10 minutes** of the exposure; so, there **is not any latent period.**

Chlorine rash



IV. Clinical presentation

b) Chronic effects

Chronic exposure to low levels of chlorine very often produces **chronic inflammation** of **upper respiratory airways**.

V. Treatment

The treatment of acute chlorine gas inhalation **includes**:

- **removing the patients from the exposure;**
- **oxygen;**
- **use of nebulized bronchodilators;**
- administration of **mild sedatives**;
- **cough medication containing codeine;**
- inhaled and parenteral **corticosteroid therapy**;
- **suction to remove fluid** from the **respiratory tract**;
- **symptomatic drugs** and **supportive methods**;
- flushing the affected surfaces with water in case of dermal and ocular exposure;

Broncospasm

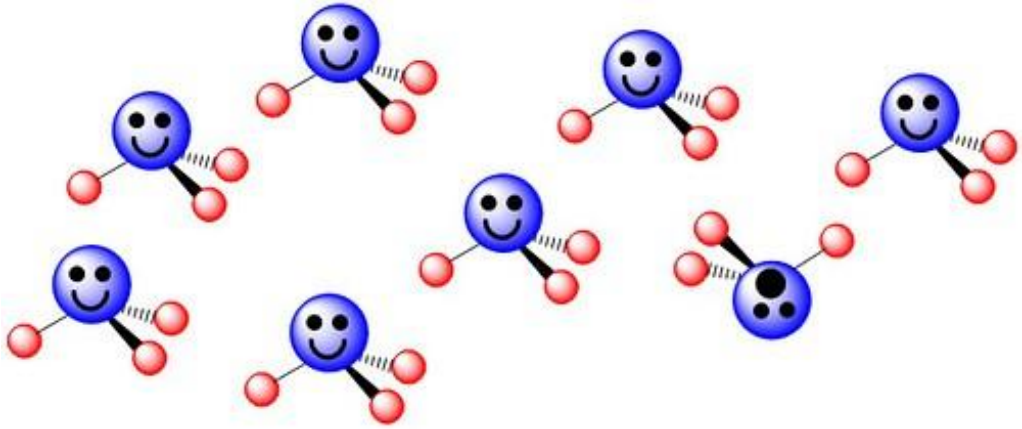
- Beta 2 agonists such as **albuterol (salbutamol)**. **Ipratropium** (anticholinergic) may be added to the treatment.
- May require **terbutaline** (short-acting beta 2 agonist) or **aminophylline (anticolinergic)**.
- **Nebulized lidocaine** (4% topical solution) may provide analgesia and reduce coughing.

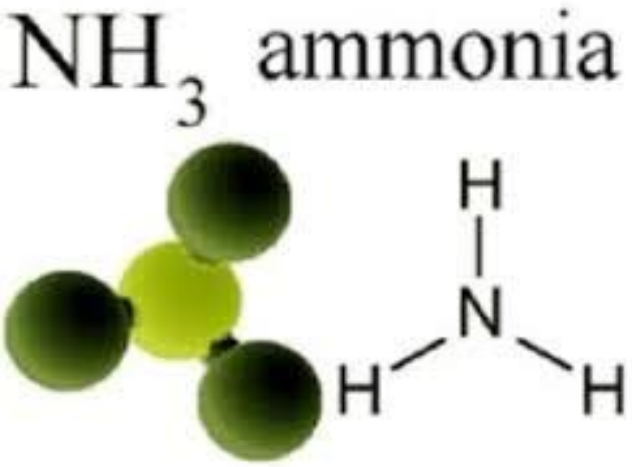
Sodium bicarbonate

- In the past, several authors used **nebulized sodium bicarbonate**.
- The mechanism of action is believed to be the **neutralization of hydrochloric acid** formed in the airways. Theoretically, **an exothermic reaction** may occur.
- Animal studies suggest nebulized sodium bicarbonate **may cause chemical pneumonitis.**

Differential Diagnosis (phosgene/chlorine

- **Riot control agents**
  - More intense irritation than phosgene or chlorine.
  - Not accompanied by odor of phosgene
- **Nerve agents**
  - Production of profuse secretions
  - Lack of cholinergic effects: profuse secretions; miosis,
  - Effects not delayed
- **Vesicants**
  - Predominately affects central rather than peripheral airways
  - Dyspnea accompanied by airway necrosis and obstruction
  - Pulmonary parenchymal damage usually manifests as hemorrhage rather than edema





AMMONIA

I. Sources and use

- Ammonia is a **widely used chemical:**
  - **in the manufacture of explosives, cyanides, plastics and synthetic fibers**
  - **as a coolant in refrigeration units**
  - **as a cleaning agent**
  - **as a fertilizer** (because of its nitrogen content)
- **Ammonia (NH_3)** is a **colorless gas**, with a **characteristic pungent odor**.
- **In mixture with air** it produces explosion.

II. Mechanism of action

- **Ammonia forms ammonium hydroxide (NH_4OH) with the moist respiratory tract lining.** This is an **exothermic reaction** that may cause **a thermal injury**.
- The formed ammonium **hydroxide readily dissociates** to yield **hydroxyl ions**.
- These **ions** cause **burn-resembling alkali burns**, which **result in liquefaction necrosis** and **deeper tissue penetration**.

III. Pathology

- **Histology examination** of the lung tissue shows:
  - **persistent inflammation**
  - **fibrous changes**
  - **obstruction of smaller airways** by mucus
- **2 to 5 days** after intoxication may be found:
  - upper airway infections
  - bronchopneumonia
- In fatally intoxicated persons are revealed:
  - **burns to the larynx** and **tracheobronchial tree**
  - **pulmonary hemorrhage**s
  - **pulmonary edema**.

IV. Clinical presentation

a) Acute effects of poisoning

- **The acute intoxication have two distinct clinical presentations:**
  - The ***first***, associated with very **high concentration of ammonia**, represents a **trancheobronchitis** with **massive swelling of the upper airways** and possible **laryngospasm and laryngeal edema.**
  - The **laryngospasm** is thought to be a **protective response to defend the lower airways.**
  - **The patients,** who **can be revived with endotracheal intubation or thracheostomy** usually, survive without **any severe chronic pulmonary damage**.

IV. Clinical presentation

- **The *second* form is associated with lesser concentration of ammonia and does not manifest acute respiratory distress.**
- **These patients rather gradually develop obstructive symptoms or pulmonary edema**

IV. Clinical presentation

b) Chronic effects

- **Chronic effects** may occur after acute exposure to ammonia. They are manifested as:
- **chronic bacterial infections;**
- **pulmonary fibrosis;**
- **bronchiectasis;**
- **obliterating bronchiolitis;**

V. Treatment

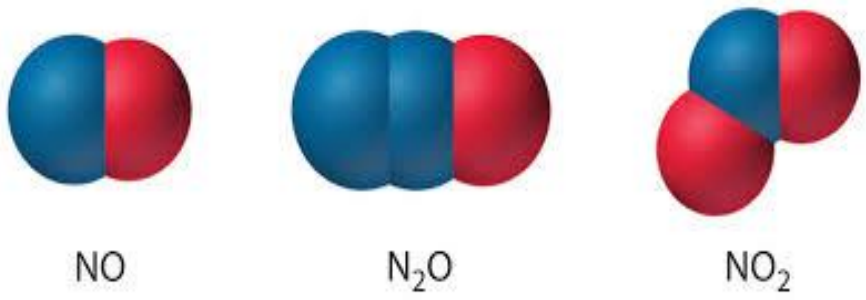
In case of accident the first aid treatment consists of:

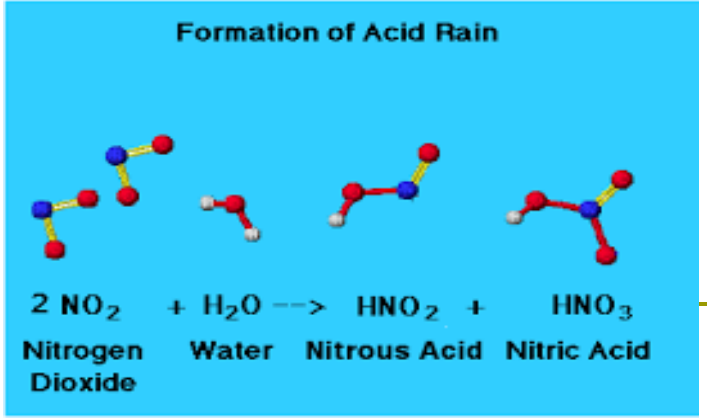
- **removing the patient** from the **source of exposure**
- **basic life support** measures
- **removing the ammonia from the eyes and skin** by **irrigating** with copious amount of water
- **removing of the contaminated clothing**

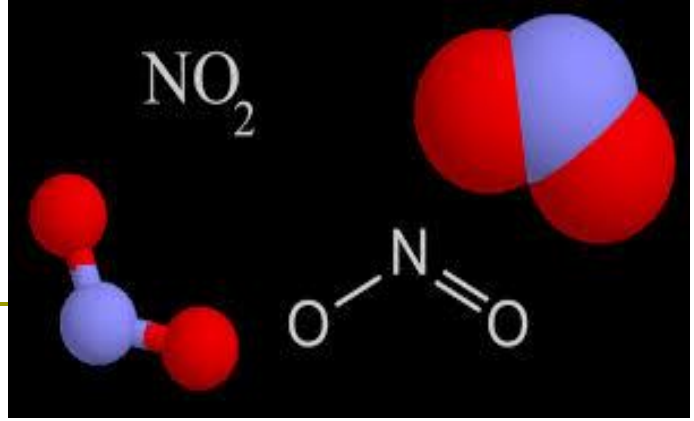
The **treatment in hospital**:

- **symptomatically**
- **pathophysiologically - treatment of pulmonary edema, cardiac failure** etc.
- **there is not any antidote** for ammonia

NITROGEN OXIDES







- **The oxides of nitrogen are an important group of compounds,** which may induce **pulmonary edema**.
- There are **five different oxidation states of nitrogen, so there are five nitrogen** oxides.
- The **nitrogen dioxide (NO_2) is the most toxic** of all oxides of the nitrogen.
- The nitrogen oxide may be present in the form of a **yellowish brown liquid** or a **reddish brown gas** with **pungent acrid odor**.
- **It reacts with water** to form **nitric and nitrous acid**.
- Nitrogen dioxide has an important role **in the formation** of **photochemical smog**, giving it a characteristic brown color.
- Nitrogen oxides are also **major contributors** to the formation of **acid rain**.
- Nitrogen oxides in combination with **sunlight** may promote the formation of **ozone.**

I. Sources of nitrogen oxides:

They are released by:

- **power plants**
- **oil refineries**
- **automobile exhaust systems**
- **stoves and furnaces**
- **kerosene space heaters**
- **cigarette smoke**

II. Mechanism of action

- The **severity of the effects** depends on:
  - the **concentration of the gas**
  - the **duration of exposure**
- The nitrogen dioxide has relatively low solubility in water and for this reason:
  - It has a weak effect on the **oropharyngeal mucosa**
  - It reaches the **lower airways, where it forms nitric acid.**
- **The formed nitric acid** dissociates to **nitrates and nitrites**, that can induce:
  - **direct local tissue inflammation**
  - **destruction of the mucous membranes of the airways**
- **The nitrates and nitrites** may initiate **peroxidation of lung lipids** by forming **oxygen free radicals**.
  - this mechanism causes the respiratory epithelium to become "leaky", resulting **in non-cardiogenic pulmonary edema**.

III. Clinical presentation

- **Acute overexposure** may result **in:**
  - **immediate death**
  - **pulmonary edema (usually later, within 48 hours)**
- Some **patients** who **recover** from the initial symptoms may:
  - **pass** into **latent period** lasting **2 to 6 weeks**.
  - **after the latent period the** patient suddenly relapse into a recurrence of **dispnea** due **to brochiolitis obliterance**.
  - most patients recover from this late recurrence but somebody may develop **progressive chronic bronchitis** and **emphysema** and die of respiratory failure.

III. Clinical presentation

- **Long-term exposure** to low levels of nitrogen **dioxide has not been shown** to cause chronic **bronchitis or emphysema**.
- However, there **are evidences that the long-term exposure** produces:
  - **diminished lung function**
  - more **infection of airways tract**
- **Diagnosis** depends on **an accurate, detailed occupational and medical history**.
- Because of the delayed onset of symptoms, people suspected of high-dose exposure should be **observed for** approximately **48 hours** for any signs of lung injury (**hypoxemia** or **tachypnea)**.

IV.Treatment

It involves:

- **administration of oxygen**
- possibly **assisted ventilation**
- **haemodynamic monitoring**
- **use** of **corticosteroids - to prevent a forming of pulmonary fibrosis**