respiratory tract toxicology

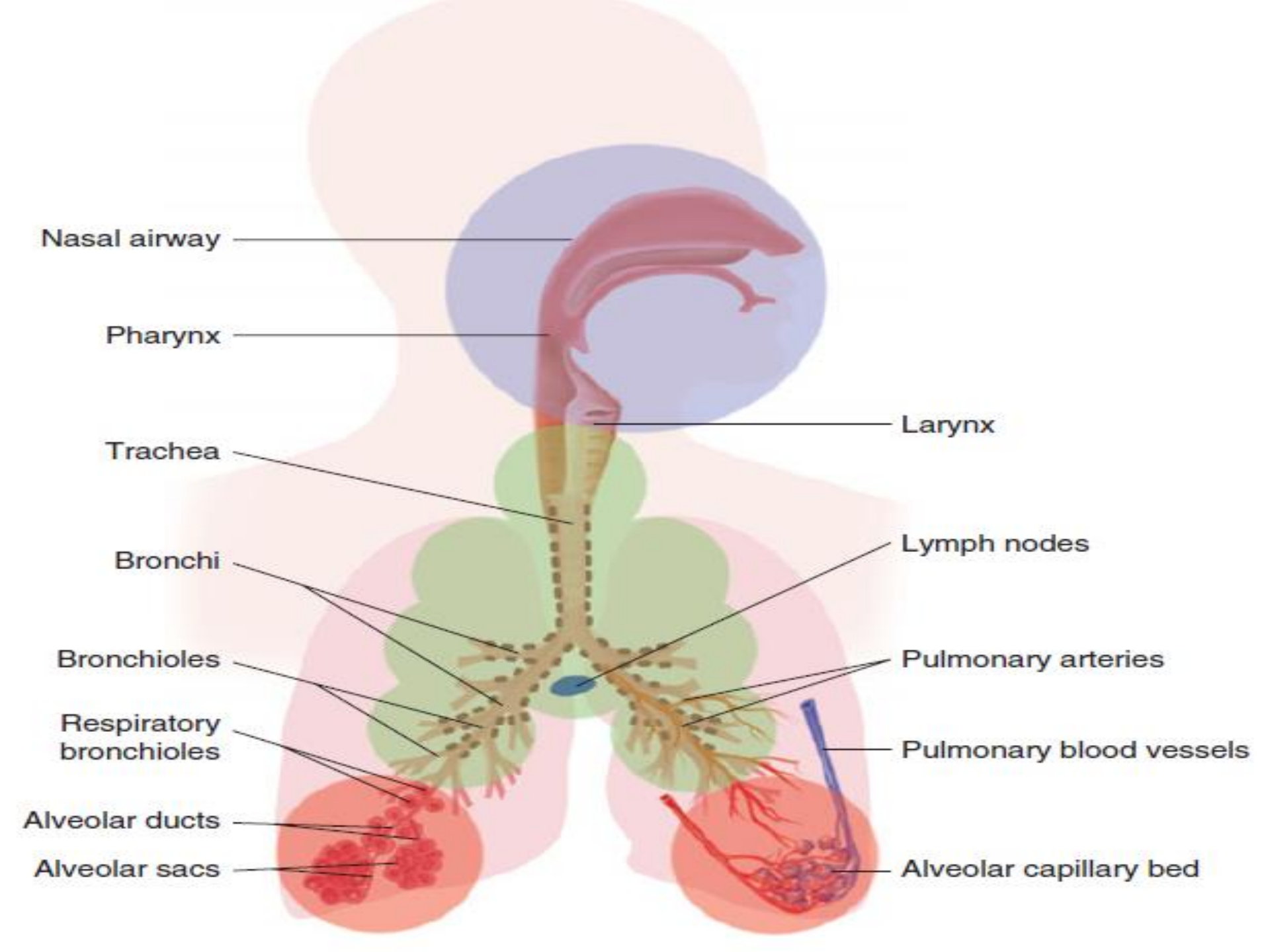
- **exposure to chemicals by inhalation can have two effects:**

- **on the lung tissues and on distant organs that are reached after chemicals enter the body by means of inhalation**

- **inhalation toxicology**
- **respiratory tract toxicology**

Lung Structure and Function

- Air enters the respiratory tract through the nasal and oral regions
- The nasal passages function as a filter for particles
- Air is warmed and humidified while passing through the nose.
- Highly water-soluble gases are absorbed efficiently in the nasal passages, which reach from the nostril to the pharynx.
- Nasal epithelia can metabolize foreign compounds. Cytochrome P450 isozymes 1A1, 2B1, and 4B1 have been localized in the nose in several species
- The nasal turbinates form a first defensive barrier against many toxic inhalants.


Nasal airway
Pharynx
Larynx
Trachea
Lymph nodes
Bronchi
Bronchioles
Pulmonary arteries
Respiratory bronchioles
Pulmonary blood vessels
Alveolar ducts
Alveolar sacs
Alveolar capillary bed

Conducting Airways

- The proximal airways (trachea and bronchi) of humans have a pseudostratified epithelium containing ciliated cells and two types of nonciliated cells : mucous and serous cells.

- Mucous cells :produce respiratory tract mucus They coat the epithelium with a viscoelastic sticky protective layer that traps pollutants and cell debris.
- The mucus layer is also thought to have antioxidant, acid-neutralizing, and free radical scavenging functions that protect the epithelial cells.

- Serous cells produce a fluid in which mucus may be dissolved, or upon which a mucus layer may be floated

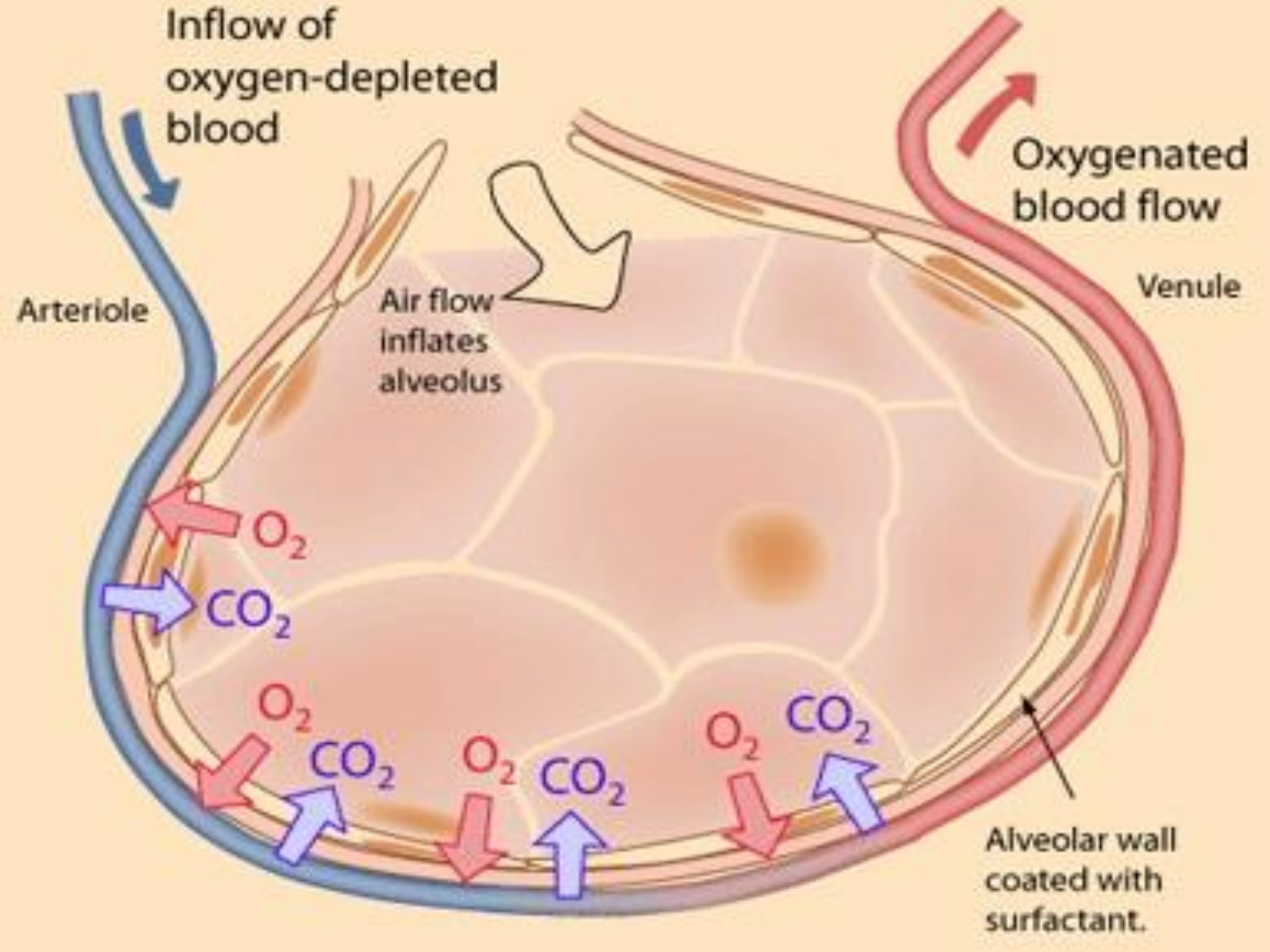
- The action of the respiratory tract cilia continuously drives the mucus layer toward the pharynx, where it is removed from the respiratory system by swallowing or expectoration

- **Gas exchange occurs in the alveoli**

- **adult human lungs contain an estimated 300 million alveoli.**

- **capillaries are organized in a single sheet. Capillaries are separated from the air space by a thin layer of tissue formed by epithelial, interstitial, and endothelial components.**

- **A variety of abnormal processes may thicken the alveolar septum and adversely affect the diffusion of oxygen to the erythrocytes.**


Inflow of oxygen-depleted blood
Oxygenated blood flow
Arteriole
Venule
Air flow inflates alveolus
O_2
CO_2
O_2
CO_2
O_2
CO_2
O_2
CO_2
Alveolar wall coated with surfactant.

GENERAL PRINCIPLES IN THE PATHOGENESIS OF LUNG DAMAGE CAUSED BY CHEMICALS

Toxic Inhalants, Gases

- In inhalation toxicology, exposure is measured as a concentration

- The sites of deposition of gases in the respiratory tract define the pattern of toxicity of those gases.

- Solubility, diffusivity, and metabolism/reactivity in respiratory tissues and breathing rate are the critical factors in determining how deeply a given gas penetrates into the lung

- ✓ Highly soluble gases such as SO_2 or formaldehyde do not penetrate farther than the nose (relatively nontoxic)
- ✓ insoluble gases such as ozone and NO_2 reach the smallest airways
- ✓ Very insoluble gases such as CO and H_2S efficiently pass through the respiratory tract and are taken up by the pulmonary blood supply to be distributed throughout the body.

- Particle size is usually the critical factor that determines the region of the respiratory tract in which a particle or an aerosol will be deposited.

- Large particles (larger than 5 μm) are usually trapped in the upper respiratory tract (nasopharyngeal region and large conducting airways),

- whereas smaller particles (0.2–5 μm)can be transported to the smaller airways and the alveoli .

Nanotoxicology

- There is intense current interest in the lung toxicity of nanoparticles, particles with diameters of <100 nm.

toxicological concerns reflect three major issues

1- the enormous surface area

2- include nanotubes, which are high axial ratio rods that provoke concerns that they might be far more toxic than spheres

3- host defenses

- It must be kept in mind that the size of a particle may change during inspiration before deposition in the respiratory tract.

- Materials that are hygroscopic, such as sodium chloride, sulfuric acid, and glycerol, take on water and grow in size in the warm, saturated atmosphere of the upper and lower respiratory tract.

Deposition of particles occurs primarily by

1. **interception, trajectory of a particle brings it close enough to a surface**
2. **impaction, airway bifurcation**
3. **sedimentation, gravitational force**
4. **diffusion , sub micrometer particles** it is an important deposition mechanism in the nose and in other airways and alveoli for particles smaller than about 0.5 μm.

- An important factor in particle deposition is the pattern of breathing. During quiet breathing, a large proportion of the inhaled particles may be exhaled. During exercise, when larger volumes are inhaled at higher velocities, deposition in airways increases.

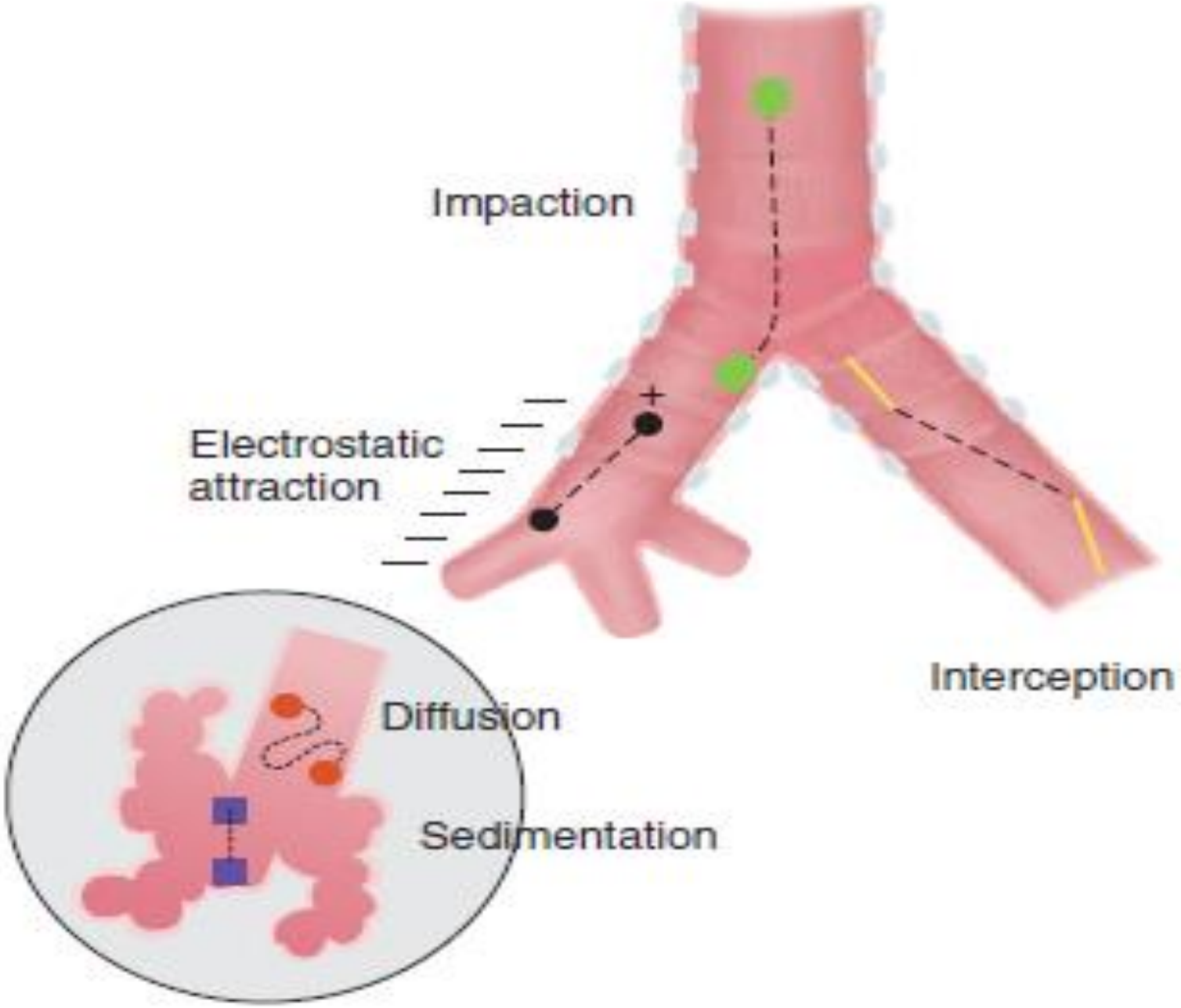


Figure 15-7. *Mechanism of particle deposition in the respiratory tract.*

Nasal Clearance

- **Particles deposited in the anterior portion of the nose are removed by extrinsic actions such as wiping and blowing**

Pulmonary Clearance

1.Particles may be directly trapped on the lining layer of the conducting airways(via the mucociliary escalator).

2. Particles may be phagocytized by macrophages and cleared via the mucociliary escalator.

3. Particles may be phagocytized by alveolar macrophages and removed via the lymphatic drainage.

4. Materials may dissolve from the surfaces of particles and be removed via the bloodstream or lymphatics.

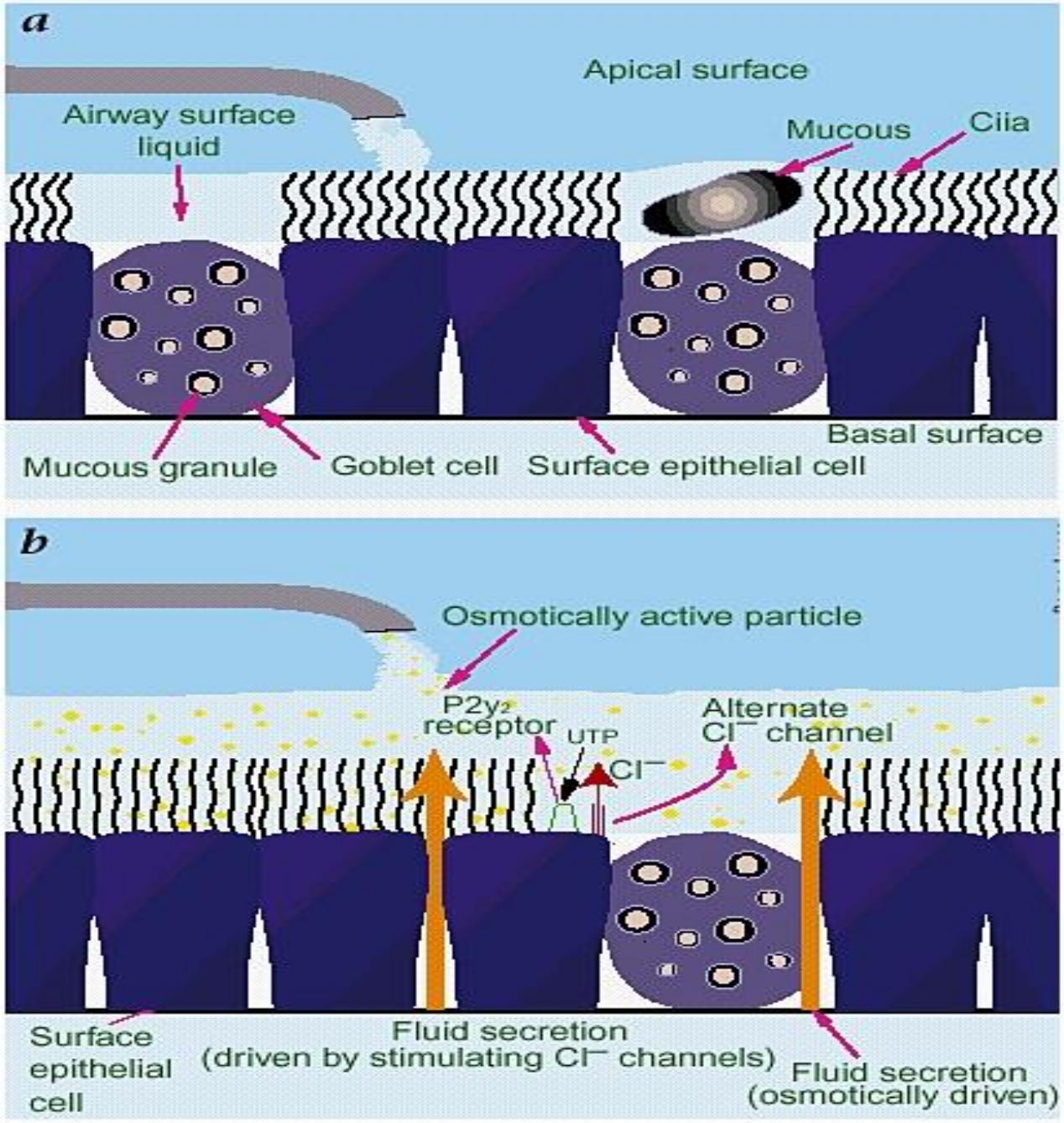
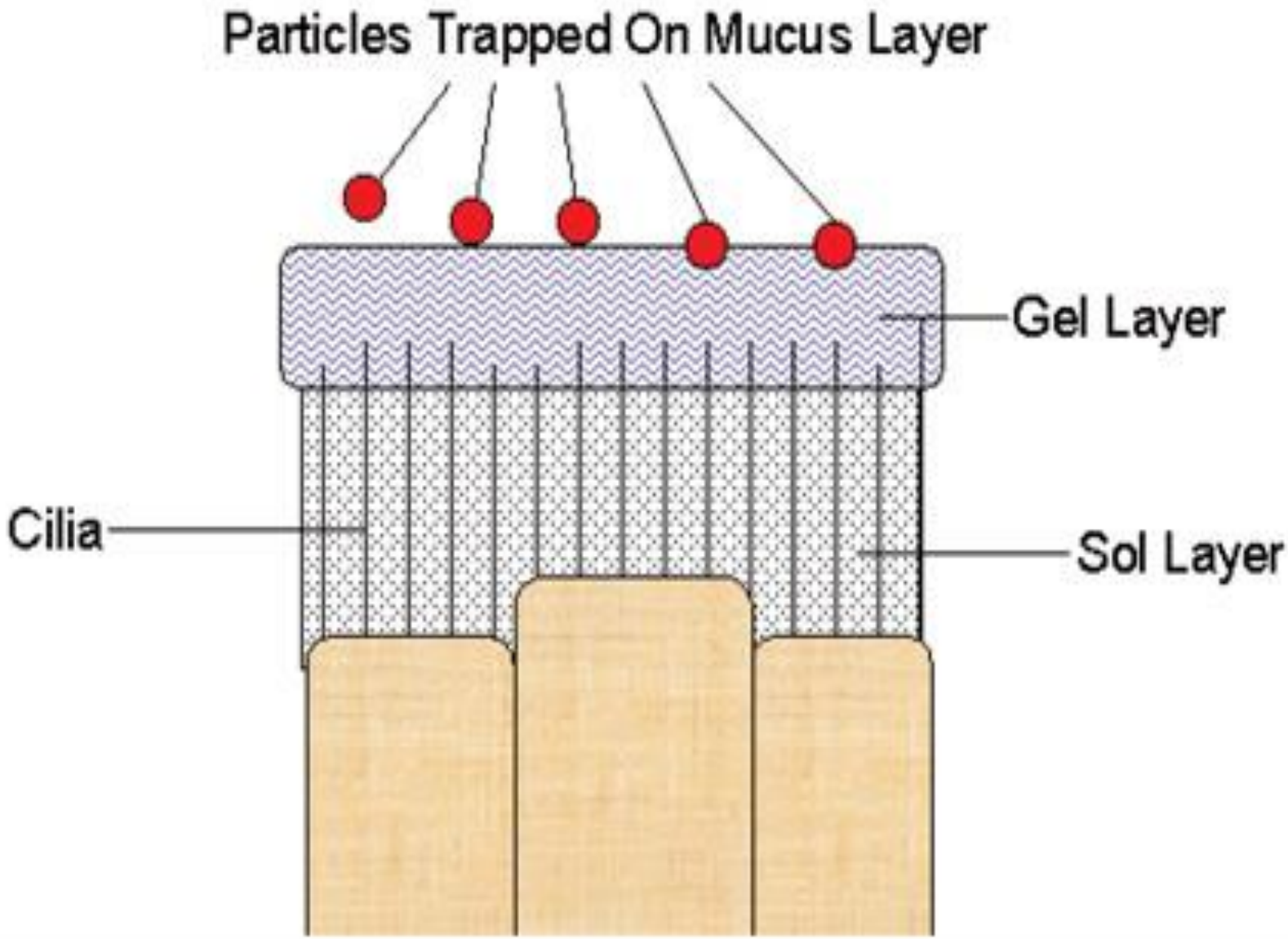

a
Apical surface
Airway surface liquid
Mucous
Cilia
Mucous granule
Goblet cell
Surface epithelial cell
Basal surface
b
Osmotically active particle
P2y2 receptor
UTP
Cl⁻
Alternate Cl⁻ channel
Surface epithelial cell
Fluid secretion (driven by stimulating Cl⁻ channels)
Fluid secretion (osmotically driven)

FIGURE 2

Mucociliary Clearance of the Nose



- **ACUTE RESPONSES OF THE LUNG TO INJURY**
- **Mechanisms of Respiratory Tract Injury**

1- Certain gases and vapors stimulate nerve endings in the nose, particularly those of the trigeminal nerve characterized by tickling, itching, and painful nasal sensations several irritants including acrolein, chlorine, formaldehyde

2- many acidic or alkaline irritants produce cell necrosis

3- inhalation of HCl, NO_2, NH_3, after a latency period of several hours, begins to leak, flooding the alveoli delayed pulmonary edema

4-ozone lesions are propagated by a cascade of secondary reaction products and by reactive oxygen species that arise from free radical reactions.

5- Metabolism of foreign compounds can be involved in the pathogenesis of lung injury.

cytochrome P450 1A1, 2B1, 2F1, 4B1, and 3A4 as well as NADPH cytochrome P450 reductase, epoxide hydrolase, and flavin-containing monoxygenases

- glutathione *S*-transferases and glutathione peroxidase.

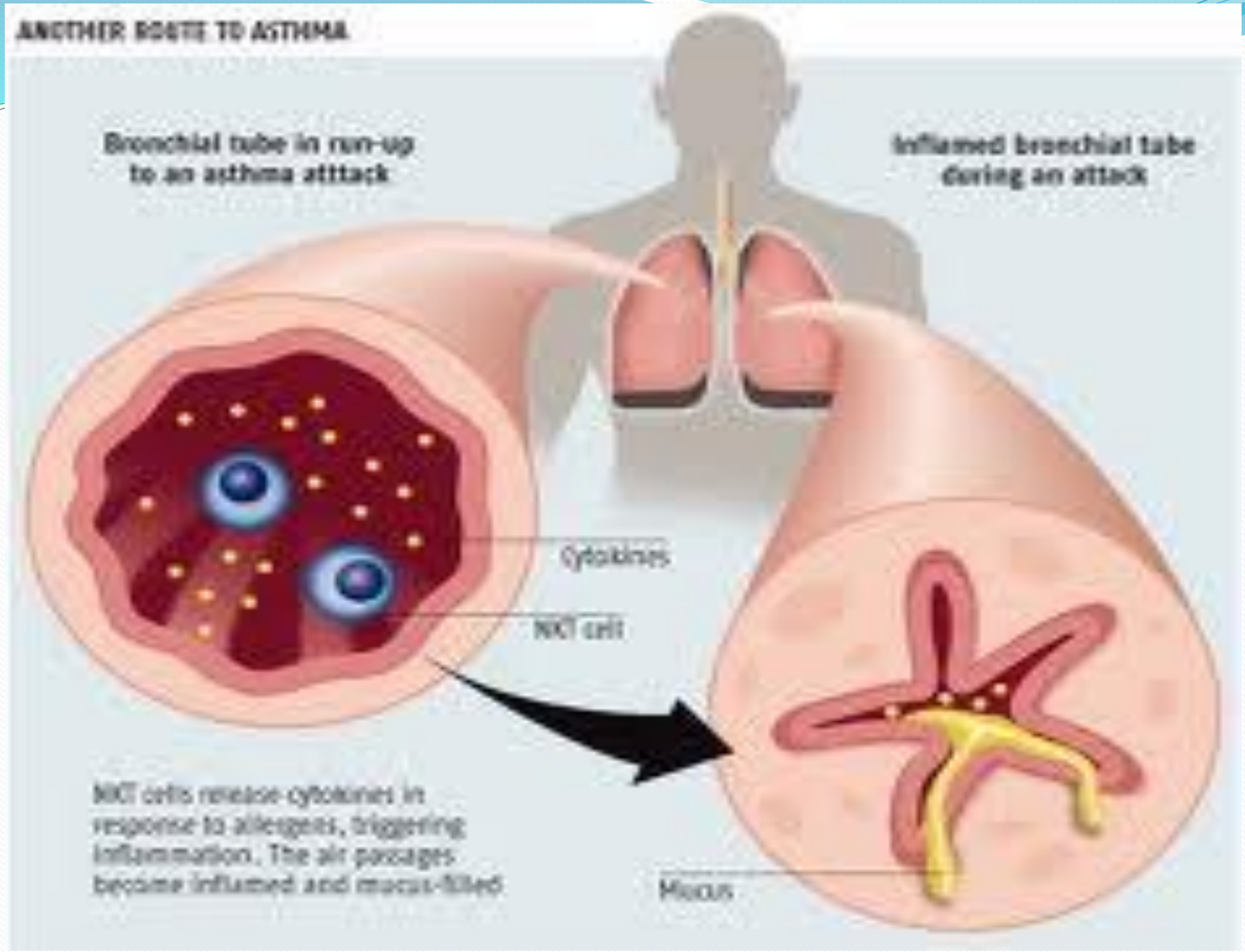
6-Bronchoconstriction can be evoked by irritants (acrolein, etc), cigarette smoke, or air pollutants, and by cholinergic drugs such as acetylcholine

Airway Reactivity

- Large airways are surrounded by **bronchial smooth muscles**, which help maintain airway tone and diameter during expansion and contraction of the lung. Bronchial smooth muscle tone normally is regulated by the **autonomic nervous system**

- Bronchoconstriction can be provoked **by irritants** such as cigarette smoke and air pollutants and by cholinergic drugs such as acetylcholine, histamine, leukotrienes , and substance P

- Bronchoconstriction causes a **decrease in airway diameter** and a corresponding increase in resistance to airflow. Characteristic associated symptoms include wheezing, coughing, a sensation of chest tightness, and dyspnea. Exercise potentiates these problems.


ANOTHER ROUTE TO ASTHMA
Bronchial tube in run-up to an asthma atttack
Inflamed bronchial tube during an attack
Cytokines
NKT cell
NKT cells release cytokines in response to allergens, triggering inflammation. The air passages become inflamed and mucus-filled
Mucus

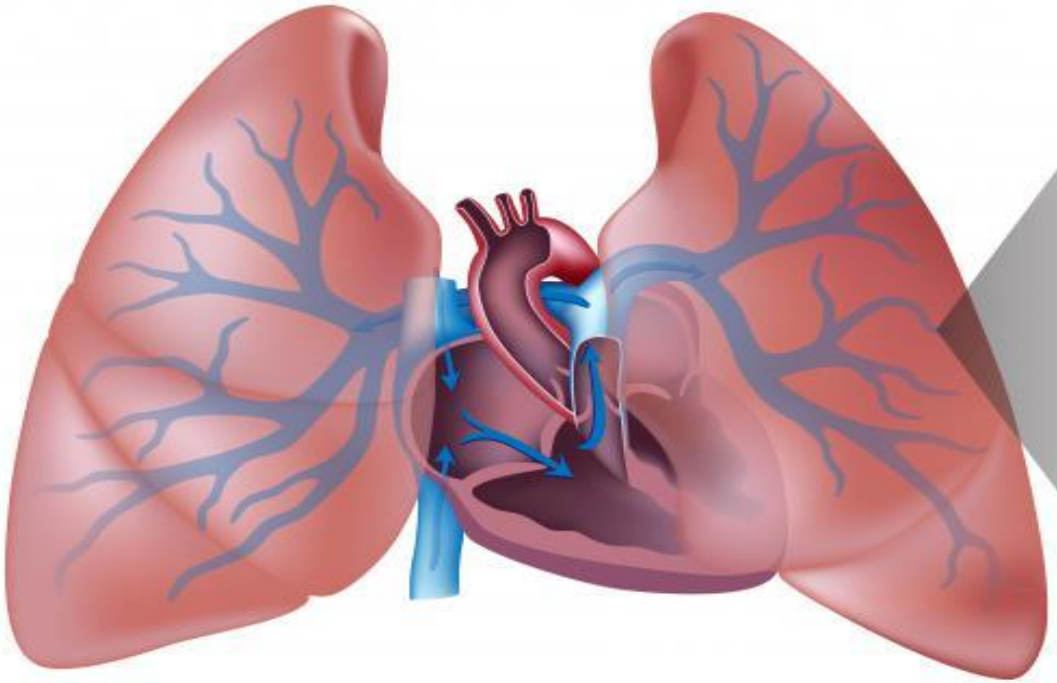
Pulmonary Edema

Toxic pulmonary edema represents an acute, exudative phase of lung injury that generally produces a thickening of the alveolar-capillary barrier , limits diffusive transfer of O_2 and CO_2.

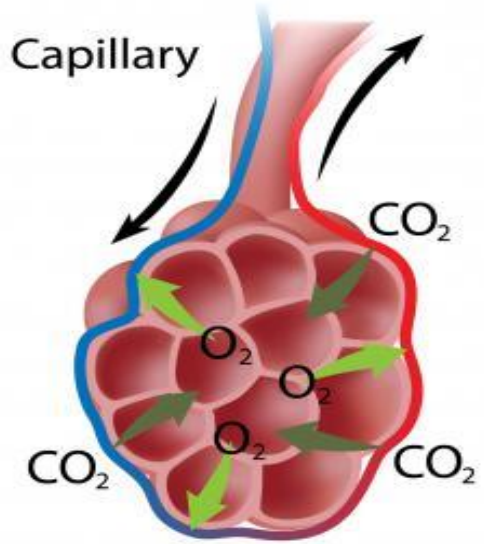
inflammatory cells and related immune responses in an edematous lung probably play a role

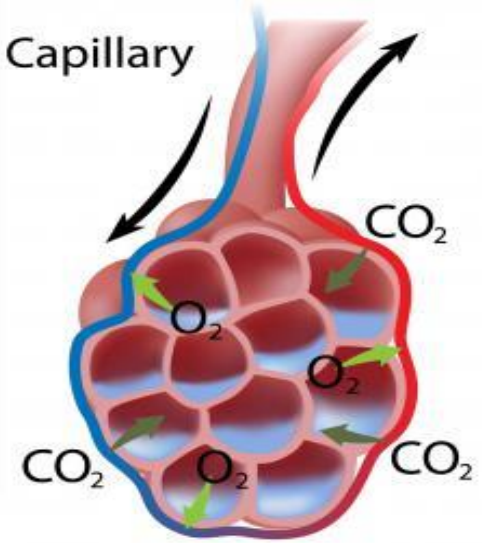
After exposure to some toxic chemicals in which the alveolar-capillary surface is denuded (such as alloxan), recovery is unlikely, whereas in situations of more modest injury (such as histamine administration), full recovery is readily achievable.

Pulmonary Edema



Normal



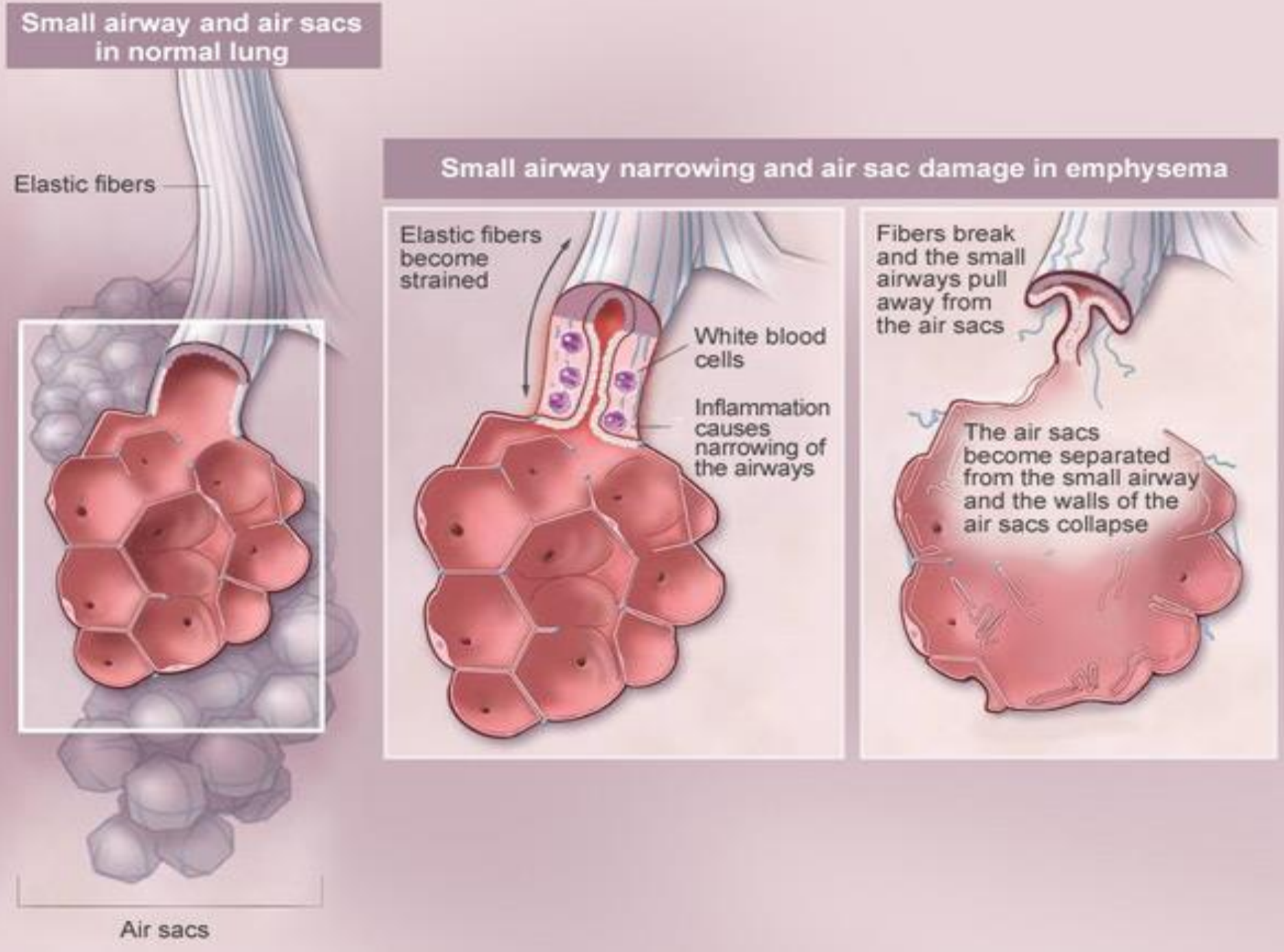


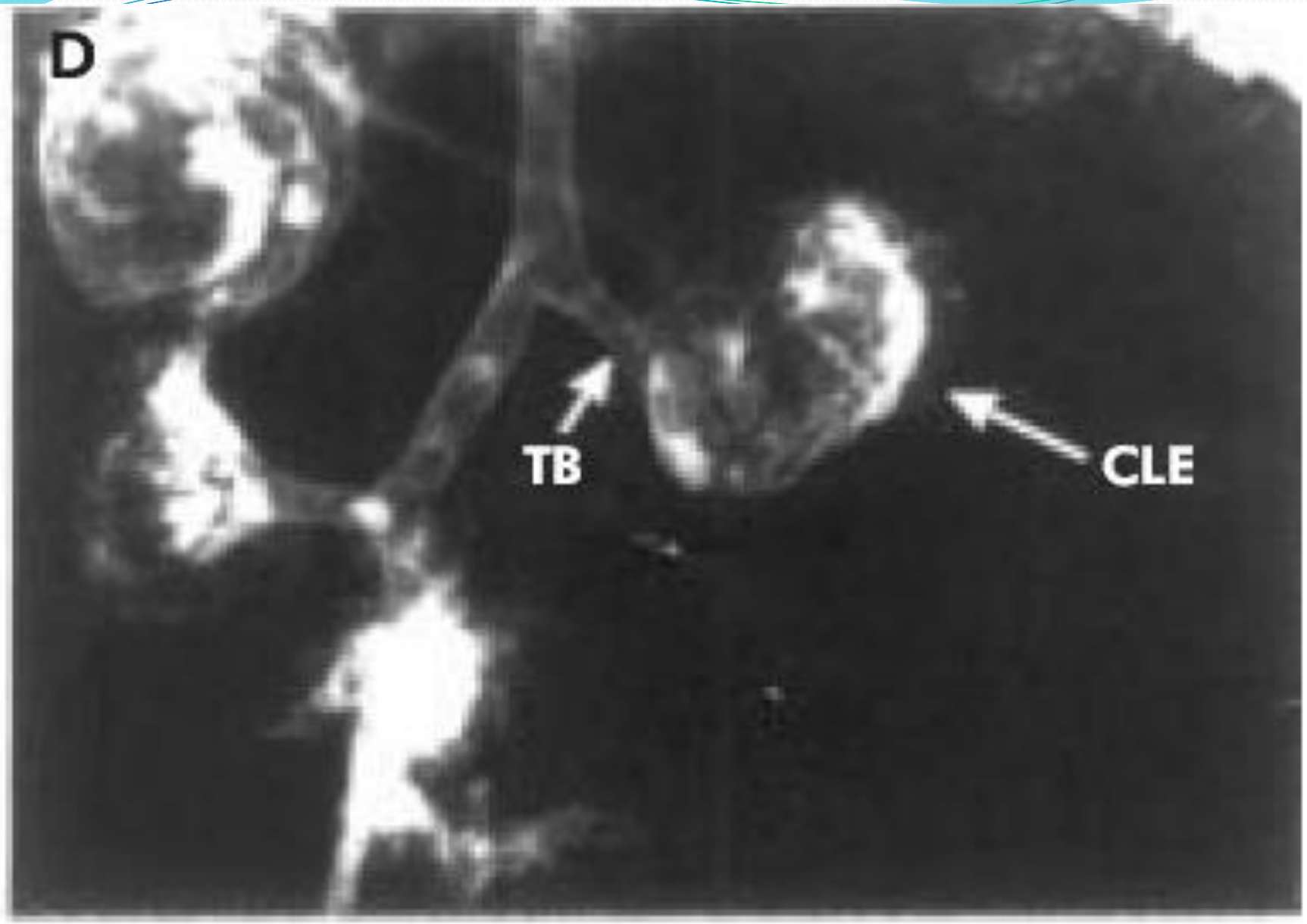
Buildup of fluid in the air sacs

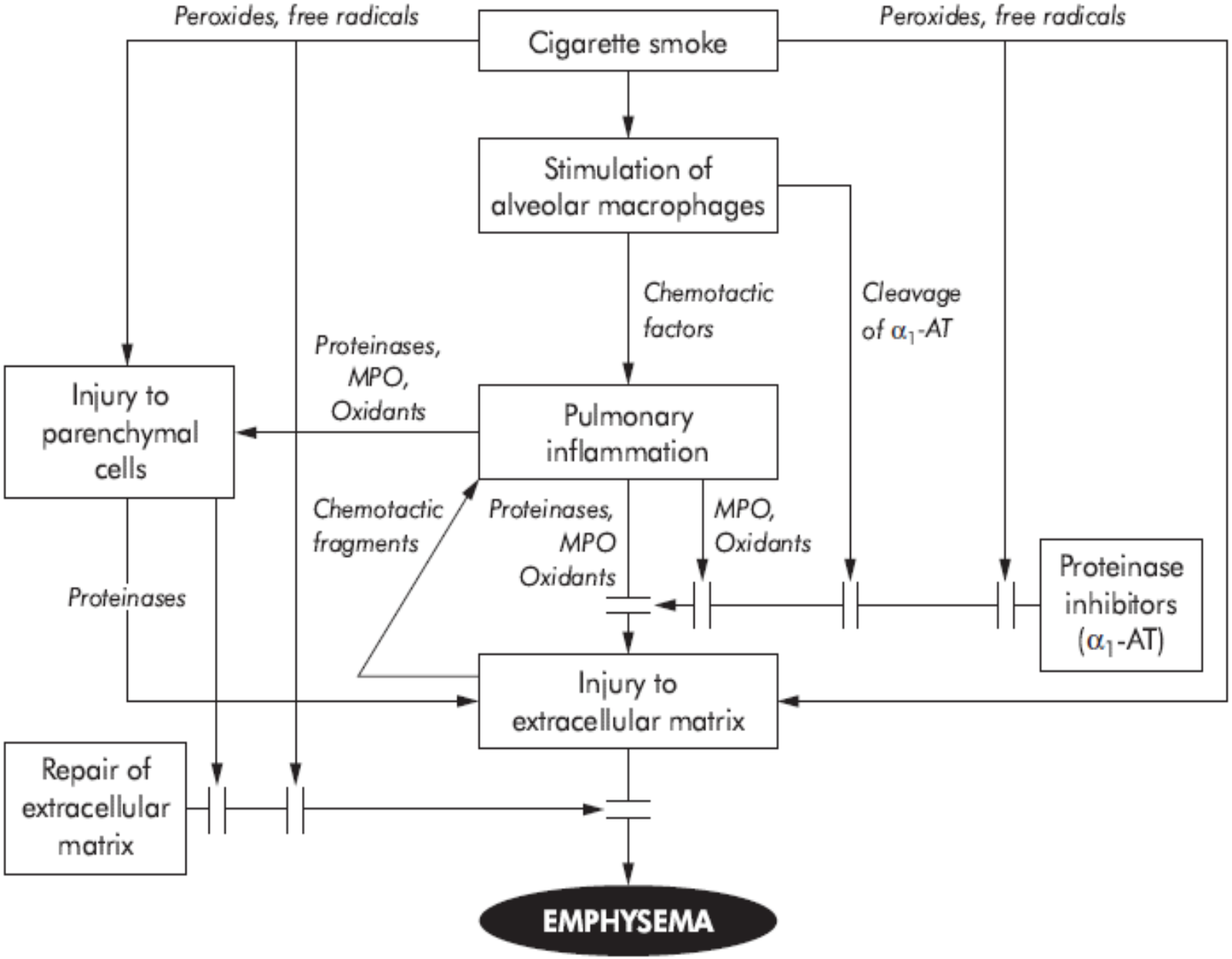
- **CHRONIC RESPONSES OF THE LUNG TO INJURY**

Emphysema

- **an abnormal enlargement of the airspaces distal to the terminal bronchiole accompanied by destruction of the walls without obvious fibrosis**
- **distended, hyperinflated lung that no longer effectively exchanges oxygen and carbon dioxid**
- **The major cause of human emphysema is cigarette smoke**
- **alpha-1-antiprotease deficiency – which has inhibitory activity over the neutrophil elastase**
- **As an individual ages, an accumulation of random elastolytic events can cause the emphysematous changes in the lungs that are normally associated with aging. Toxicants that cause inflammatory cell influx and thus increase the burden of neutrophil elastase can accelerate this process.**


Small airway and air sacs in normal lung
Elastic fibers
Air sacs
Small airway narrowing and air sac damage in emphysema
Elastic fibers become strained
White blood cells
Inflammation causes narrowing of the airways
Fibers break and the small airways pull away from the air sacs
The air sacs become separated from the small airway and the walls of the air sacs collapse


D
TB
CLE


Peroxides, free radicals
Cigarette smoke
Peroxides, free radicals
Stimulation of alveolar macrophages
Chemotactic factors
Cleavage of α_1-AT
Proteinases, MPO, Oxidants
Injury to parenchymal cells
Pulmonary inflammation
Chemotactic fragments
Proteinases, MPO Oxidants
MPO, Oxidants
Proteinase inhibitors (α_1-AT)
Proteinases
Injury to extracellular matrix
Repair of extracellular matrix
EMPHYSEMA

Fibrosis

increased focal staining of collagen fibers in the alveolar interstitium.

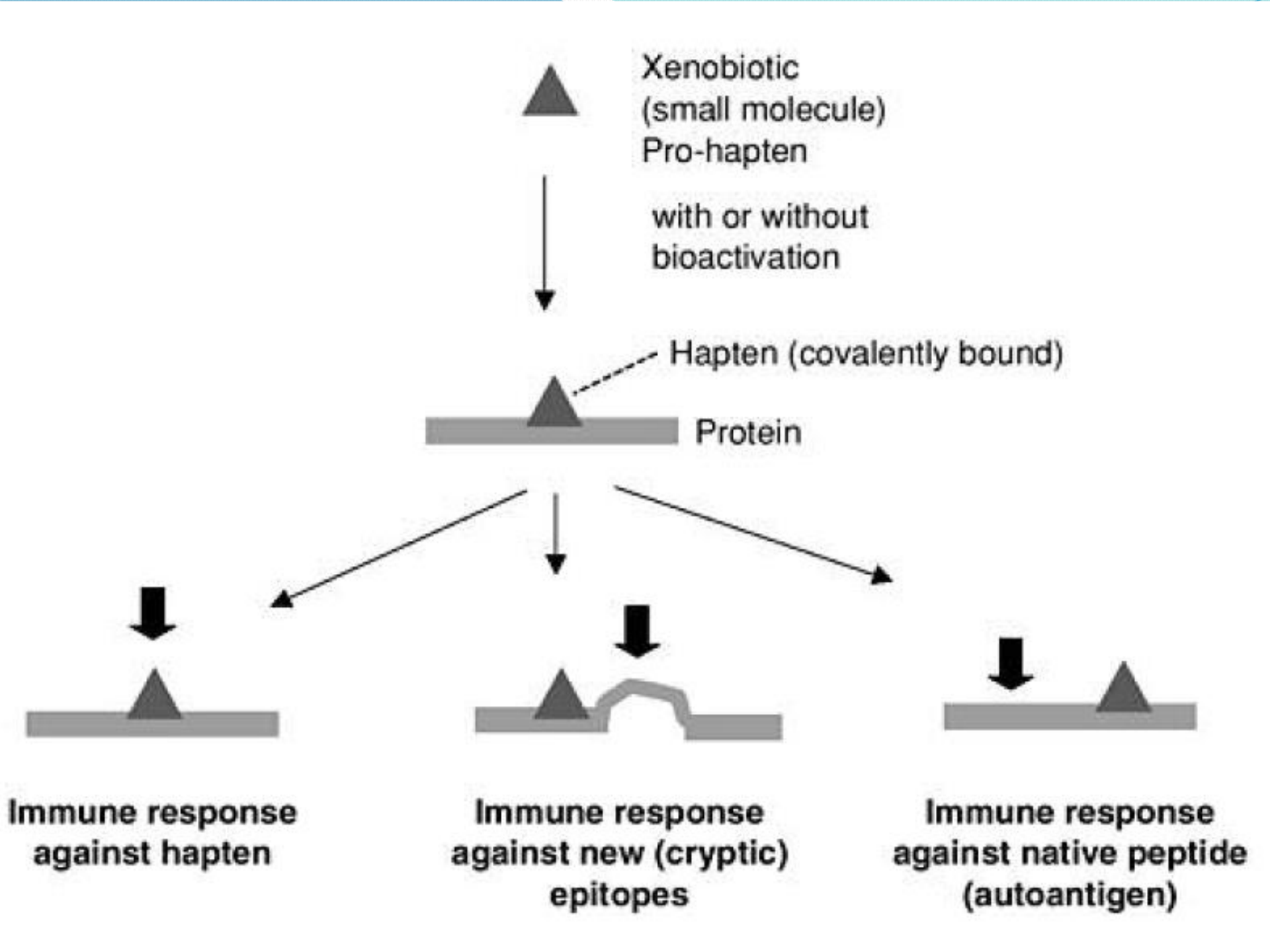
Types I and III collagen an approximate ratio of 2:1

Type III collagen is more compliant than is type I; thus , increasing type I relative to type III collagen may result in a stiffer lung

- **Asthma**

Asthma is characterized clinically by attacks of shortness of breath, which may be mild or severe. The clinical hallmark of asthma is increased airway reactivity

- Haptens hypothesis support such reactivity where haptenation of a peptide by a reactive xenobiotic or a reactive metabolite can induce a specific immune response by different mechanisms


Xenobiotic
(small molecule)
Pro-hapten
with or without
bioactivation
Hapten (covalently bound)
Protein
Immune response
against hapten
Immune response
against new (cryptic)
epitopes
Immune response
against native peptide
(autoantigen)

- **Lung cancer**
- exposure to many chemicals encountered in industrial settings pose a lung cancer risk

- Inhalation of asbestos fibers and metallic dusts or fumes, such as arsenic, beryllium, cadmium, chromium, and nickel, encountered in manufacturing operations has been associated with cancer of the respiratory tract Workers

- Formaldehyde is a probable human respiratory carcinogen

- welding fumes are suspected carcinogens. Smokers who inhale radon or asbestos fibers increase their risk of developing lung cancer several fold, suggesting a synergistic interaction between the carcinogens

- Damage to DNA is thought to be a key mechanism

- . Ionizing radiation leads to the formation of superoxide, which is converted through the action of superoxide dismutase to hydrogen peroxide. In the presence of Fe and other transition metals, hydroxyl radicals may be formed which then cause DNA strand breaks.

- Cigarette smoke contains high quantities of active oxygen species and other free radicals

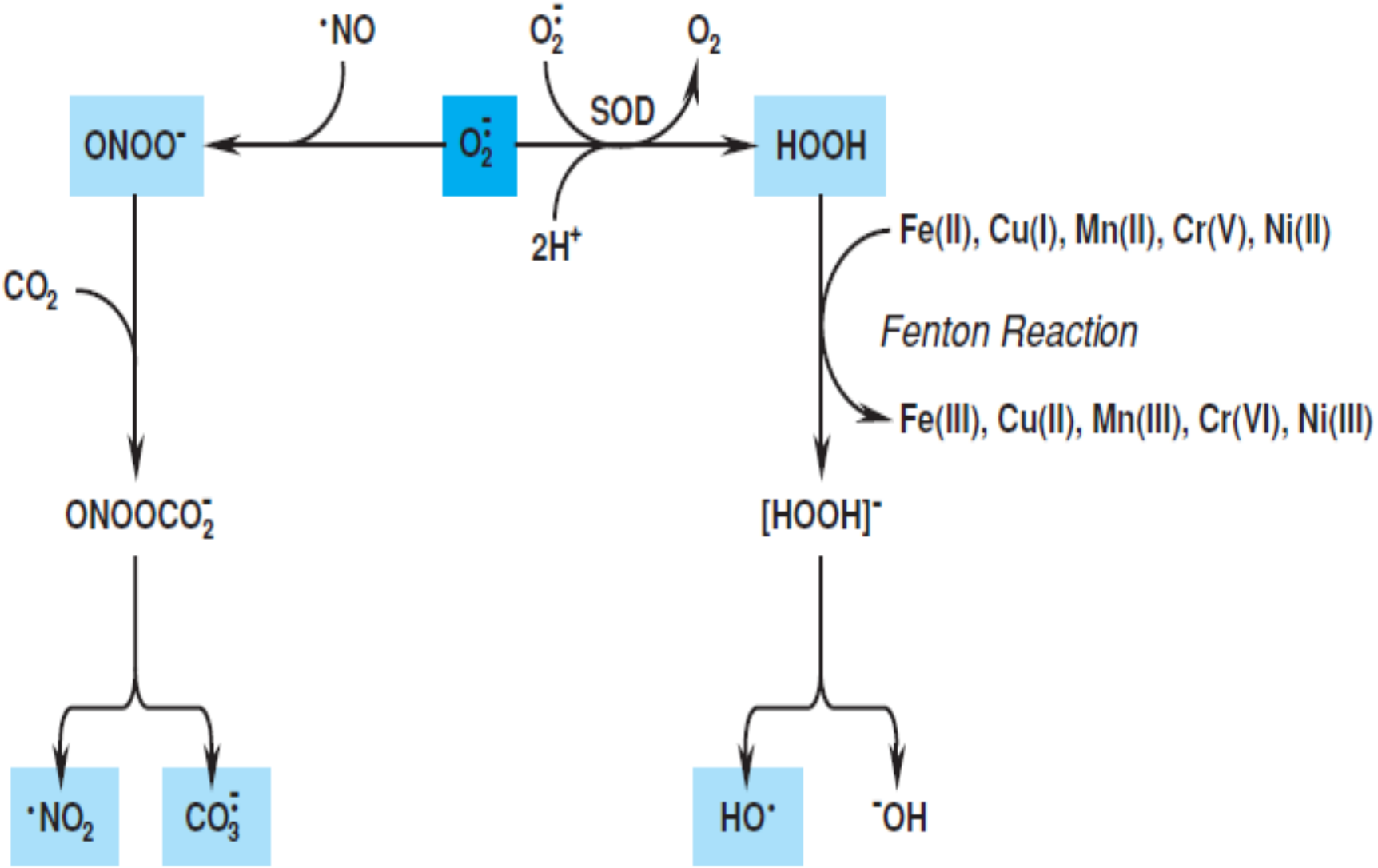


Figure 3-4. Two pathways for toxication of superoxide anion radical ($O_2^{\bullet-}$) via nonradical products ($ONOO^-$ and HOOH) to radical products ($^{\bullet}NO_2$, $CO_3^{\bullet-}$ and $HO^{\bullet}$).

AGENTS KNOWN TO PRODUCE LUNG INJURY IN HUMANS

Airborne Agents That Produce Lung Injury in Humans

Asbestos

- ✓ asbestos describes silicate minerals in fiber form
- ✓ mining operations and in the construction and ship building industries

- ❖ The hazards associated with asbestos exposure depend on fiber length:
- ✓ Fibers 2μm in length may produce asbestosis
- ✓ fibers 5μm long associated with mesothelioma
- ✓ fibers larger than 10 μm may lead to lung cancer
- ❖ Fiber diameter is another critical feature. Fibers with diameters larger than approximately 3 μm do not readily penetrate into the peripheral lung.

- ❖ For the development of mesothelioma(The most common anatomical site for mesothelioma is the pleura (the outer lining of the lungs and internal chest wall), fiber diameter must be less than 0.5 μm, because thinner fibers may be translocated from their site of deposition via the lymphatics to other organs, including the pleural surface

- Once asbestos fibers have been deposited in the lung, they may become phagocytized by alveolar macrophages.

- Short fibers are completely ingested and subsequently removed via the mucociliary escalator

- Longer fibers are incompletely ingested, and the macrophages become unable to leave the alveoli release mediators such as lymphokines and growth factors, which in turn attract immune-competent cells or stimulate collagen production

- triggering of an inflammatory sequence of events or
- production of changes that eventually lead to the initiation (DNA damage caused by reactive molecular species) or
- promotion (increase rate of cell turnover in the lung) of the carcinogenic process.

Naphthalene

- **Tar ,**petroleum, precursor chemical , cigarette smoke

- Naphthalene epoxides may subsequently be conjugated with glutathione and form adducts that are eliminated as mercapturic acids. The epoxide can undergo rearrangement to 1-naphthol with subsequent metabolism to quinones, which are potentially toxic compounds

- Smokers inhale substantial amounts of naphthalene in cigarette smoke

- Naphthalene metabolites bind covalently to cellular proteins that are important in normal cellular homeostasis and protein folding and this may be related to the mechanism of toxicity by this chemical.

- **Blood-borne Agents That Cause Pulmonary Toxicity in Humans**
- **Bleomycin**
- is a widely used cancer chemotherapeutic agent. Pulmonary fibrosis, often fatal, represents the most serious form of toxicity

- The sequence of damage includes necrosis of capillary endothelial and alveolar cells, edema formation and hemorrhage

- after 1–2 weeks) proliferation of type II epithelial cells, and eventually thickening of the alveolar walls by fibrotic changes

bleomycin hydrolase inactivates bleomycin.

activity of this enzyme is low in lung and skin

bleomycin-mediated release of cytokines such as TGF beta and TNF alpha

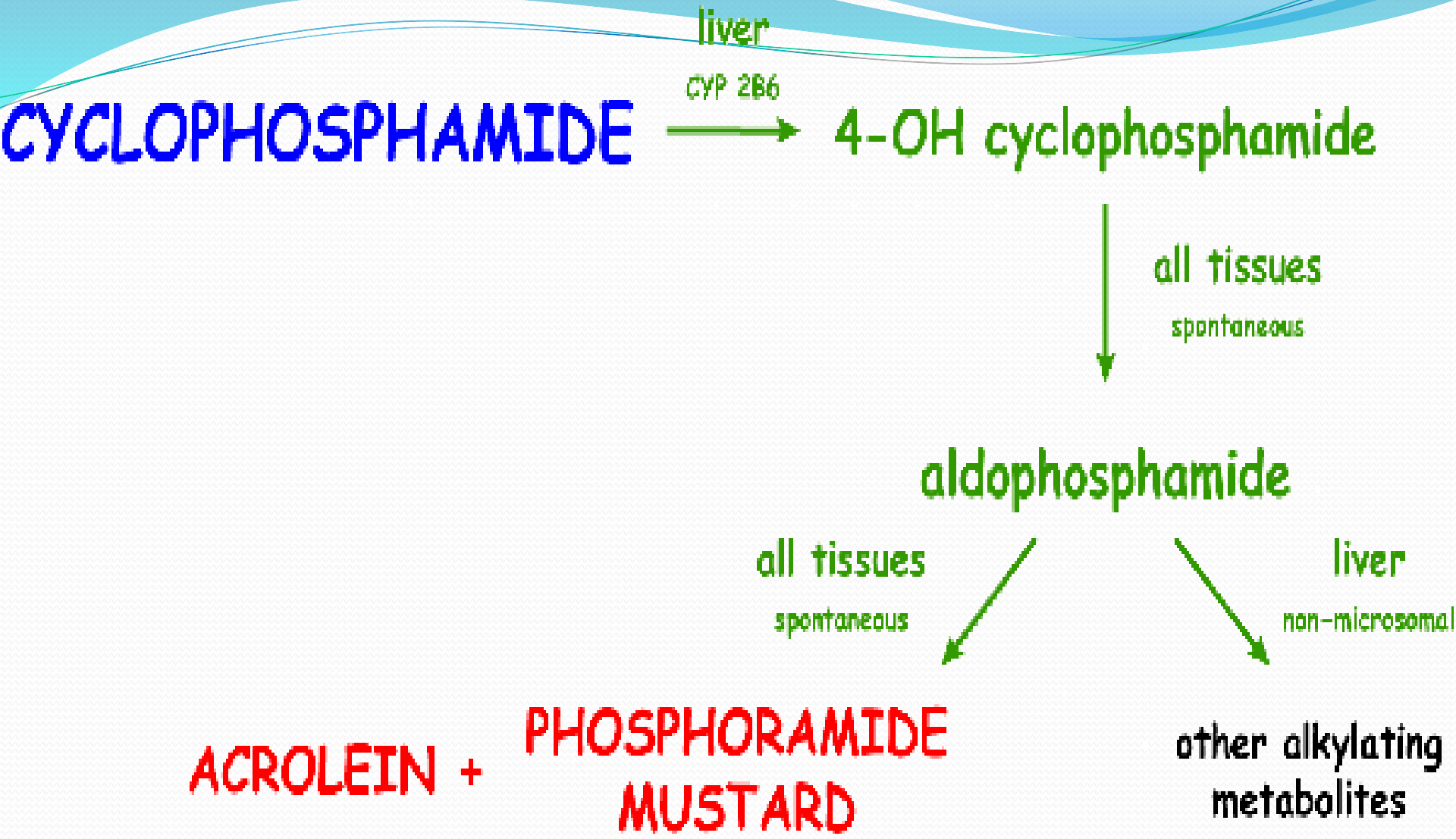
mRNA coding for fibronectin and procollagens are increased

stimulates the production of collagen in the lung

Cyclophosphamide

The undesirable side effects include hemorrhagic cystitis(MESNA) and pulmonary fibrosis

- Cyclophosphamide is metabolized by the cytochrome P-450 system to two highly reactive metabolites: acrolein and phosphoramide mustard. Cyclophosphamide and its metabolite acrolein initiate lipid peroxidation.


liver
CYP 2B6
CYCLOPHOSPHAMIDE
4-OH cyclophosphamide
all tissues
spontaneous
aldophosphamide
all tissues
spontaneous
liver
non-microsomal
ACROLEIN +
PHOSPHORAMIDE MUSTARD
other alkylating metabolites

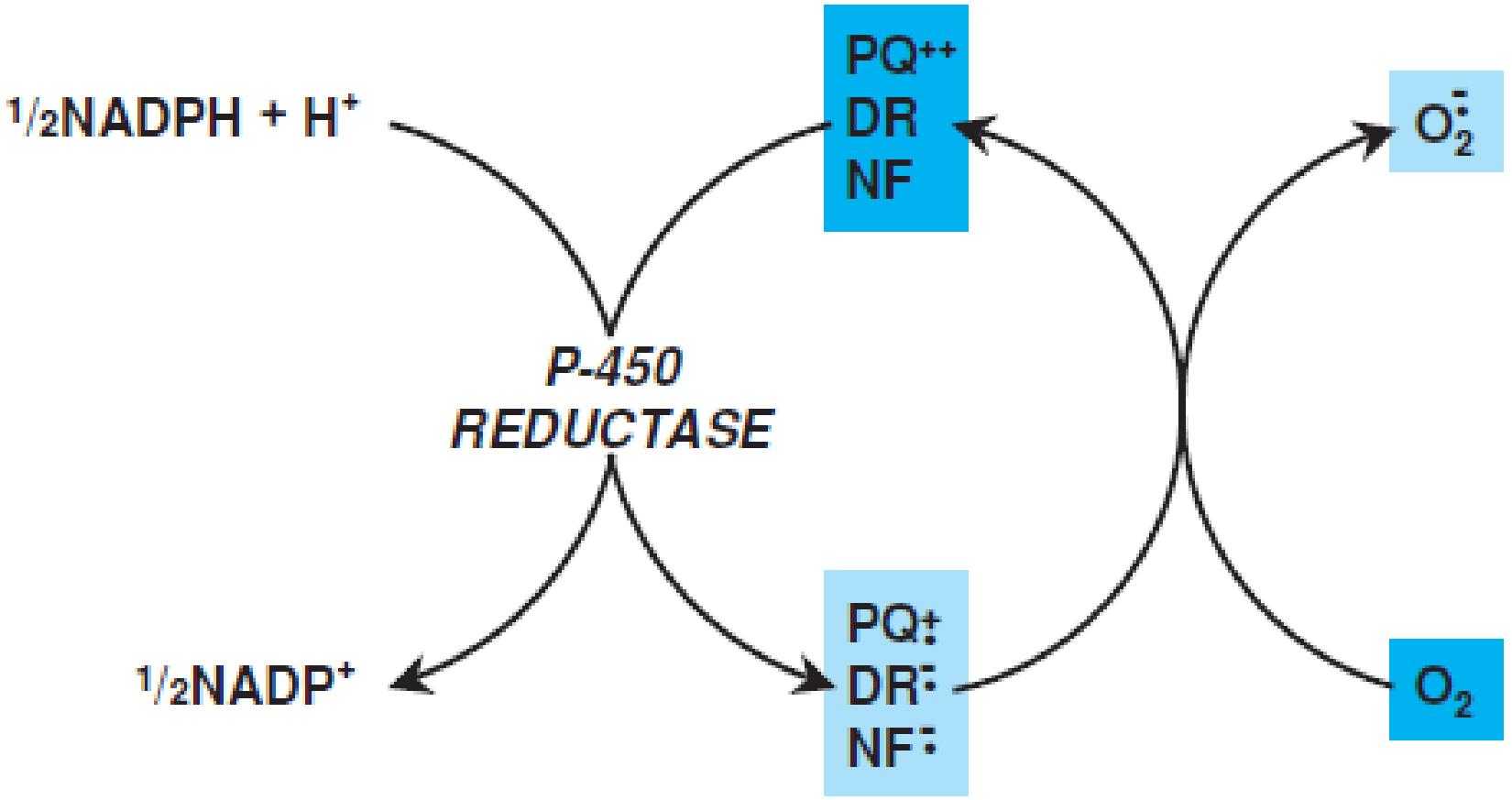


Figure 3-3. Production of superoxide anion radical ($O_2^{\bullet-}$) by paraquat (PQ^{++}), doxorubicin (DR), and nitrofurantoin (NF).