

## Defenses of the Respiratory System

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## Respiratory System Functions

- Gas exchange: Oxygen enters blood and carbon dioxide leaves
- Regulation of blood pH: Altered by changing blood carbon dioxide levels
- Voice production: Movement of air past vocal folds makes sound and speech
- Olfaction: Smell occurs when airborne molecules drawn into nasal cavity
- Protection: Against microorganisms by preventing entry and removing them

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## contd

Protective mechanism// defense mechanism

- Air conditioning
- Bronchial secretions help to trap the dust and other particles present in the inspired air
- Ciliary escalator help to remove the materials trapped by the bronchial secretion- expectorant
- Secretions of IgA- provides immunity
- Pulmonary alveolar macrophages engulf anything foreign coming in contact with them

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## Respiratory sys Functions contd

- Metabolic activity:
  - synthesis: proteins fat, carbohydrates etc.
    1. dipalmitoyl lecithin- component of surfactant synthesized.
    2. Mucopolysaccharides produced by goblet cells
    3. Synthesis of collagen and fibres
  - activation
    - angiotensin I to II: by the converting enzymes- endothelia of pul capillaries
  - inactivation: vaso active substance are removed – endothelial cells
    - Noradrenaline ///bradykinin ///5 H-T (serotonin) and some prostaglandins

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## contd

- Reservoir of blood: available for circulatory compensation
- Filter for circulation: fibrinolysis
  - thrombi, microaggregates etc
- Immunological:
  - IgA secretion into bronchial mucus
- Water balance
- Temperature regulation

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## The Respiratory Defense System

- Consists of a series of filtration mechanisms
- Removes particles and pathogens

Components of the Respiratory Defense System

- **Goblet cells** and **mucous glands**: produce mucus that bathes exposed surfaces
- **Cilia**: sweep debris trapped in mucus toward the pharynx (**mucus escalator**)
- **Filtration** in nasal cavity removes large particles
- **Alveolar macrophages** engulf small particles that reach lungs
- **Ig A secretion**

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## Defense Mechanisms

- Protect tracheobronchial tree & alveoli from injury
- Prevent accumulation of secretions
- Repair

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## Defense for

- **Incoming**
  - Every day about 10,000 L of air is inspired
  - Liquids, food particles, and bacteria that may be *aspirated* (accidentally inspired from the oropharynx or nasopharynx) into the airways
- **Contacting**
  - 50 to 100 m<sup>2</sup> of what may be the most delicate tissues of the body
- **Contactants**
  - Dust, pollen, fungal spores, ash, and other products of combustion; microorganisms such as bacteria; particles of substances such as asbestos and silica; and hazardous chemicals or toxic gases
- **Others**
  - Alveoli must be protected from the cold and from drying out.
  - The mucosa of the nose, the nasal turbinates, the oropharynx, and the nasopharynx

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## Depression of Defense Mechanisms

- Chronic alcohol is associated with an increase incidence of bacterial infections
- Cigarette smoke and air pollutants is associated with an increase incidence of chronic bronchitis and emphysema
- Occupational irritants is associated with and increased incidence of hyperactive airways or interstitial pulmonary fibrosis

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## Upper respiratory tract

- Nasal passages protect airways and alveolar structures from inhaled foreign materials
  - Long hairs (vibrassae) in nose (nares) filters out larger particles
  - Mucous coating the nasal mucous membranes traps particles (>10 microns)
    - Moistens air – 650 ml H<sub>2</sub>O/day
  - Nasal turbinates
    - Highly vascularized, act as radiators to warm air

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- **Particle Clearance**
  - Hairs in the nostril strains out particles larger than 10µm in diameter. Some escapes and settle in mucus membrane in nose and pharynx where they impact on the tonsils & adenoids (immunologically active lymphoid tissues)
  - Particles 2→10µm settle on walls of bronchi where they they initiate reflex bronchial constriction & coughing. Alternatively they are removed by the **Mucociliary Escalator**


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## The Upper Air Passages

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## Vibrissae

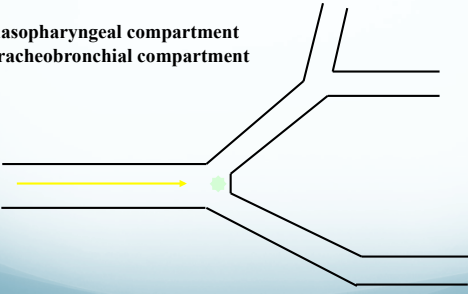


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## Impaction

The particle's momentum in air stream prevents it from making turn at a bifurcation.

nasopharyngeal compartment  
tracheobronchial compartment



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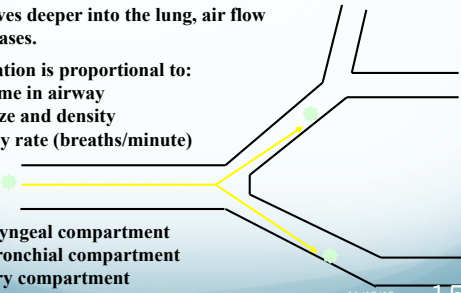
## Sedimentation

When gravitational forces on a particle are greater than air resistance and buoyancy, the particle will fall out of the air stream.

As air moves deeper into the lung, air flow rate decreases.

Sedimentation is proportional to:  
particle time in airway  
particle size and density  
respiratory rate (breaths/minute)

nasopharyngeal compartment  
tracheobronchial compartment  
pulmonary compartment



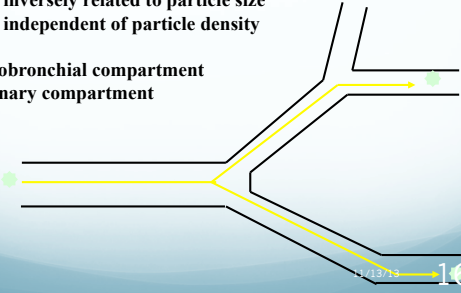
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## Diffusion

Particles have random motion, resulting in random impacts.

Diffusion coefficient is:  
inversely related to particle size  
independent of particle density

tracheobronchial compartment  
pulmonary compartment



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## Cough

- From trachea to alveoli sensitive to irritants
- Afferents utilize primarily CN X
- Process
  - 2.5 L of air rapidly inspired
  - Epiglottis closes and vocal chords close tightly
  - muscles of expiration contract forcefully which causes pressure in lungs to rise to 100 mm Hg
  - Epiglottis and vocal chords open widely which results in explosive outpouring of air to clear larger airways
    - at speeds of 75 – 100 MPH
  - Cough is ineffective at clearing smaller airways due to large total X-sectional area
    - can't generate sufficient velocity

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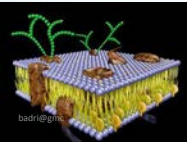
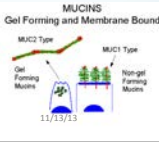
## Sneeze

- Sneeze reflex
  - Associated with nasal passages
  - Irritation sends signal over CN V to the medulla
    - Response similar to cough, but in addition uvula is depressed so large amounts of air pass rapidly through the nose to clear nasal passages
  - With sneeze and cough velocity of air escaping from the mouth & nose has been clocked at speeds of 75-100 MPH

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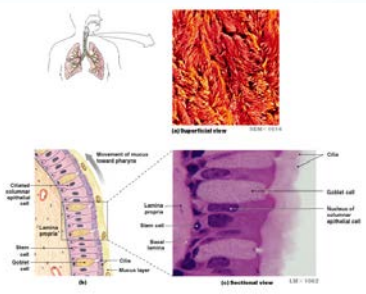
### Mucus

- Mucus is an aqueous suspension containing glycoproteins and ionic and lipid moieties produced by mucous glands and goblet cells; it functions to trap and clear particles, to dilute noxious substances, to lubricate the airways, and to humidify respired air.
- In a healthy individual, mucus is 95% water.
- Mucin contains highly functionalized glycoproteins forming an entangled "bottle brush" like structure.
- Mucus secretion is controlled by neuropeptides (Substance P, vasoactive intestinal peptide, and bombesin) and vagal stimulation (Ach) will increase secretion.





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### The Respiratory Epithelium



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**Goblet Cells**

**Basement Membrane**

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### Mucociliary Escalator

- The epithelium from the anterior third to the nose to the beginning of the respiratory bronchiole is ciliated.
- The cilia is bathed in a periciliary fluid where they beat at a rate of 10→15 Hz.
- On top of the cilia & periciliary layer rest a mucus layer, a complex mixture protein & polysaccharide secreted from specialised cells or glands in the conducting airway.
- Allows trapping of foreign bodies (in mucus) & transport out of airway (**ciliary beat**)
- Ciliary mechanism move particle out at rate of 16mm/min

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### The Villi



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### Mucociliary elevator

- Clears smaller airways
  - Mucous produced by goblet cells in epithelium and small submucosal glands
  - Ciliated epithelium which lines the respiratory tract all the way down to the terminal bronchioles moves the mucous to the pharynx
    - Swallowed or coughed out
    - Organisms in mucus are destroyed by acid environment in stomach if swallowed

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- Mucociliary clearance may be impaired by factors that damage ciliary function, by abnormalities in the biochemical properties of the mucus, or by changes in the quantity of mucus.
- Normal ciliary movement can be negatively affected by: cigarette smoke, anesthetic agents, bacterial products, viral infection, and eosinophilic byproducts.
- **In cystic fibrosis, mucus is abnormally viscous with markedly delayed mucociliary clearance.**
- In chronic bronchitis, the quantity of mucus is increased, at times overwhelming the mucociliary escalator.
- When the mucociliary clearance system is impaired, cough serves as a back-up system.

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## Immune reaction in the lung

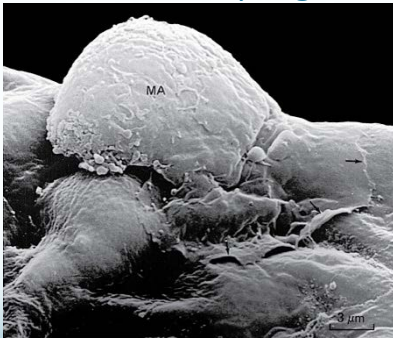
- Alveolar macrophages
  - Capable of phagocytosing intraluminal particles
  - Principal phagocytic cells in the distal air spaces
- Complement system
  - Small proteins found in the blood synthesized in the liver
    - Complements the ability of antibodies and phagocytic cells to clear pathogens from an organism
    - Part of the innate immune system along with macrophages

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## The Macrophage



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## Pulmonary Alveolar Macrophages

- Important component of pulmonary defense mechanism.
- Particles less than  $2\mu\text{m}$  can evade the mucociliary escalator and reach the alveoli
- Pul AM Are actively phagocytic and ingest these particles.
- Also process inhaled antigen for immunological attack
- Secrete substances that attract granulocytes
- When ingest large amount of substance in cigarette smoke & other irritants, will release lysosomal products and cause inflammation.

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## Immune rxn in the lung

- Antibodies associated with the mucosa
  - IgG- lower respiratory tract
  - IgA- dominate in upper respiratory tract
  - IgE- predominantly a mucosal antibody

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## Immune reaction in the lung (cont)

- Macrophages
  - present "pieces" of organisms to other effector cells through a series of interactions involving cytokines which promote a more vigorous/widespread immune response
- Humoral immune system
  - Antibodies
  - Accessory processes
    - Th2 activation, Cytokine production, germinal center formation, isotype switching, affinity maturation, memory cell generation
- Various lipoproteins and glycoproteins

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### Clearance in the Pulmonary Compartment

AM-mediated particle clearance  
endocytosis by lung epithelial cells  
absorption into blood

Type I cell    Type II cell  
Alveolus (Airspace)  
Alveolar Macrophage  
Fibroblasts  
Capillary Lumen

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### Other chemical substances released by airway epithelial cells to aid Lung Defense

- Immunoglobulin A (IgA)
- Collectins (surfactant)
- Protease & other peptides
- Chemokines & cytokines- recruit immune cells to site of infection

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### Particle Clearance Mechanisms

**The Nasopharyngeal Compartment**  
muciliary clearance (transport back to nasopharynx)  
mechanical clearance (sneezing, coughing, swallowing)  
absorption into circulation (soluble particles)

**The Tracheobronchial Compartment**  
muciliary clearance (transport to oropharynx)  
endocytosis into peribronchial region (insoluble particles)  
absorption into circulation (soluble particles)

**The Pulmonary Compartment**  
alveolar macrophage mediated clearance  
endocytosis by lung epithelial cells into interstitium  
absorption into circulation (soluble particles)

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### Schematic diagram of bronchoalveolar defense mechanisms

Mucociliary escalator  
Pulmonary arteriole  
Terminal bronchiole  
Respiratory bronchiole  
Alveolar sac  
Pleura

Bronchial-associated lymphoid tissue  
Centripetal lymphatics  
Bronchoalveolar junction

Alveolar macrophage  
Particle  
Cell and/or particle pathway  
Fluid absorption pathway

Source: Levitzky MG: Pulmonary Physiology, 7th Edition:  
<http://www.accessmedicine.com>

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### Integrated System for Defense of the Respiratory Tract

- **Natural mechanical defenses**
  - Filtration and impaction remove particles
  - Sneeze, cough, and bronchospasm expel particles
  - Epithelial barriers and mucus limit particle penetration
  - Mucociliary escalator transports particles cephalad
- **Natural phagocytic defenses**
  - Effected by airway, interstitial, and alveolar macrophages; polymorphonuclear leukocytes
  - Phagocytosis of particulates, organisms, and debris
  - Microbicidal and tumoricidal activities Degradation of organic particles
- **Acquired specific immune defenses**
  - Humoral immunity
    - Effected by B lymphocytes
    - Biologic activities mediated by specific antibody
    - Augments phagocytic and microbicidal defense mechanisms
    - Initiates acute inflammatory responses
  - Cell-mediated immunity
    - Effected by T lymphocytes
    - Biologic activities mediated by Delayed-type hypersensitivity reaction T cell cytotoxicity
    - Augments microbicidal and cytotoxic activities of macrophages
    - Mediates subacute, chronic, and granulomatous inflammatory responses

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### Cystic Fibrosis

- Defective gene at long arm of chromosome 7
- Encodes the cystic fibrosis transmembrane conductance regulator (CFTR)
- Regulates Cl<sup>-</sup> channel located on apical membrane of various epithelia
- Most common mutation is loss of phenylalanine residue in position 508

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- The function of the  $Cl^-$  channel is depress
- Sodium & water move out of airway leaving secretions sticky & inspissated
- Result in a reduced periciliary layer that inhibit function of the mucociliary escalator
- Get repeated pulmonary infection esp Pseudomonas aeruginosa & progressive fatal destruction of the lung

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## Cystic Fibrosis

"Woe is the child who tastes salty from a kiss on the brow, for he is cursed, and soon must die."  
-Northern European Folklore

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## Hallmarks of CF

- Very salty-tasting skin
- Appetite, but poor growth & weight gain
- Coughing, wheezing & shortness of breath
- Lung infections, e.g. pneumonia/bronchitis

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## Clinical Aspects

Cystic fibrosis affects the entire body

- Lungs and sinuses
- GI, liver and **pancreas**
- Endocrine system
- Reproductive system

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## From Mutation to Disease

The mutant form of CFTR prevents chloride transport, causing mucus build-up

Mucus clogs the airways and disrupts the function of the pancreas & intestines.

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## Effects of smoking

- Smoking reduces respiratory efficiency
  - Deposits tar & other chemicals
  - swelling of mucosal lining and increased production of mucus
    - Impedes airflow
  - destroys cilia and inhibits their movement
    - Reduces removal of excess mucus and debris

Smokers lungs  
Bodies The exhibition March 2006  
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## Smoking

- Nicotine constricts terminal bronchioles
  - Reduces airflow into and out of lung
- CO binds irreversibly to Hb
  - Reduces blood oxygen carrying capacity
- Destruction of elastic fibers (prime cause of emphysema)
  - Reduced lung compliance
  - Collapse of small bronchioles during exhalation
    - traps air in alveoli during exhalation
    - Reduces efficiency of gas exchange

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- Smoking contributes to lung disease
  - Impairs lungs' natural defense mechanisms –irritates airways & inhibits work of ciliary cells
- Smoking is leading cause of serious lung disease & certain types of cancer
  - Synergistic effect with other pulmonary carcinogens (asbestos, chromium/uranium compounds, arsenic)
  - Increases lung cancer risk by 15% + chronic asbestos exposure 4%= 60% risk NOT 29%
- Smokers develop lung disease & cancer more readily & diseases progress more rapidly

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## FILTRATION OF INSPIRED AIR

- **Impaction** Greater than 10 m in diameter are removed by impacting in the large surface area of the **nasal septum and turbinates** . Air entering the trachea contains few particles larger than 10 m, and most of these will impact mainly at the **carina or within the bronchi**.
- The nasal hairs, or **vibrissae** (larger than 10 to 15 microns )
- **Sedimentation** of particles 2 to 5 m by gravity in the smaller airways, where airflow rates are extremely low. Thus, most of the particles between 2 to 10 m in diameter are removed by impaction or sedimentation and become trapped in the mucus that lines the **upper airways, trachea, bronchi, and bronchioles**
- Smaller particles and all foreign gases reach the alveolar ducts and alveoli. Some smaller particles (0.1 m and smaller) are deposited as a result of **Brownian** motion due to their bombardment by gas molecules. The other particles, between 0.1 and 0.5 m in diameter, mainly stay suspended as **aerosols**, and about **80% of them are exhaled**.

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### REMOVAL OF FILTERED MATERIAL Reflexes in Airways

- Mechanical or chemical stimulation of receptors, nose, trachea, larynx, or elsewhere in the respiratory tract may produce
  - Bronchoconstriction to prevent deeper penetration of the irritant into the airways and may also produce a cough or a sneeze.
  - A sneeze results from stimulation of receptors in the nose or nasopharynx;
  - A cough results from stimulation of receptors in the trachea.
  - A deep inspiration, to near the total lung capacity, forced expiration against a closed glottis. Intrapleural pressure may rise to more than 100 mm Hg . The glottis opens suddenly, and pressure in the airways falls rapidly, resulting in compression of the airways and an explosive expiration, with linear airflow velocities approach the speed of sound. carry the irritant, along with some mucus, out of the respiratory tract.
  - In a sneeze, expiration is via the nose; in a cough, the expiration is via the mouth.
  - The cough or sneeze reflex is also useful in helping to move the mucous lining of the airways toward the nose or mouth. Coughs can be initiated by many causes, including postnasal drip from allergies or viral infections, asthma, gastroesophageal reflux disease, as an adverse effect of the very commonly prescribed angiotensin-converting enzyme inhibitors, mucus production from chronic bronchitis, infections, and bronchiectasis.

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### REMOVAL OF FILTERED MATERIAL, Mucociliary Escalator

- The entire respiratory tract, from the upper airways down to the terminal bronchioles, is lined by a **mucus-covered ciliated epithelium**, with an estimated total surface area of 0.5 m<sup>2</sup>. The only exceptions are parts of the pharynx and the anterior third of the nasal cavity.
- **Goblet cells and mucus-secreting glands**. Complex polymer of mucopolysaccharides. The mucous glands are found mainly in the submucosa near the supporting cartilage of the larger airways. In pathologic states, such as chronic bronchitis, the number of goblet cells may increase and the mucous glands may hypertrophy, resulting in greatly increased mucous gland secretion and increased viscosity of mucus.
- **The cilia** lining the airways beat in such a way that the mucus covering them is always moved up the airway, away from the alveoli and toward the pharynx. The mucus blanket appears to be involved in the mechanical linkage between the cilia. The cilia beat at frequencies between 600 and 900 beats per minute, and the mucus moves progressively faster as it travels from the periphery. In small airways (1 to 2 mm in diameter), linear velocities range from 0.5 to 1 mm/min; in the trachea and bronchi, linear velocities range from 5 to 20 mm/min. Studies have shown that ciliary function is inhibited or impaired by cigarette smoke.
- **The "mucociliary escalator"** is an especially important mechanism for the removal of inhaled particles that come to rest in the airways. Material trapped in the mucus is continuously moved upward toward the pharynx. This movement can be greatly increased during a cough, as described previously. Mucus that reaches the pharynx is usually swallowed, expectorated, or removed by blowing one's nose. It is important to remember that patients who cannot clear their tracheobronchial secretions (an intubated patient or a patient who cannot cough adequately) continue to produce secretions.

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### DEFENSE MECHANISMS OF THE TERMINAL RESPIRATORY UNITS

#### • Alveolar Macrophages

- Large mononuclear ameboid cells Inhaled particles engulfed and destroyed by their lysosomes. Most bacteria are digested in this manner.
- However, particles such as **silica**, is not degradable by the macrophages and may even be toxic to them. If the macrophages carrying such material are not removed from the lung, the material will be re deposited on the alveolar surface on the death of the macrophages. The mean life span of alveolar macrophages is believed to be 1 to 5 weeks. The main exit route of macrophages carrying such non digestible material is migration to the muco ciliary **escalator** via the pores of Kohn and eventual removal
- Particle-containing macrophages may also migrate from the alveolar surface into the septal interstitium, from which they may enter the lymphatic system or the mucociliary escalator. Macrophage function has been shown to be inhibited by **cigarette smoke**.
- Also important in the lung's immune and inflammatory responses. They secrete many enzymes, arachidonic acid metabolites, immune response components, growth factors, cytokines, and other mediators that modulate the function of other cells, such as lymphocytes.

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### DEFENSE MECHANISMS OF THE TERMINAL RESPIRATORY UNITS

#### • Other Methods of Particle Removal or Destruction

- Some particles reach the mucociliary escalator because the alveolar fluid lining itself is slowly moving upward toward the respiratory bronchioles.
- Others penetrate into the interstitial space or enter the blood, where they are phagocytized by interstitial macrophages or blood phagocytes or enter the lymphatics.
- Particles may be destroyed or detoxified by surface enzymes and factors in the serum and in airway secretions. These include *lysozymes*, found mainly in leukocytes and known to have bactericidal properties; *lactoferrin*, which is synthesized by polymorphonuclear lymphocytes and by glandular mucosal cells and is a potent bacteriostatic agent; *alpha<sub>1</sub> antitrypsin*, which inactivates proteolytic enzymes released from bacteria, dead cells, or cells involved in defense of the lung (e.g., neutrophil elastase); *interferon*, a potent antiviral substance that may be produced by macrophages and lymphocytes; and *complement*, which participates as a cofactor in antigen-antibody reactions and may also participate in other aspects of cellular defense.
- Finally, many biologically active contaminants of the inspired air may be removed by antibody-mediated or cell-mediated immunologic responses.

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