SESSION-SPECIFIC OBJECTIVES

• List the **four classes** of environmental and occupational lung diseases
• List the specific diseases in each class
• Explain the mechanisms by which toxicants cause each disease
• List factors that determine **balance between lung tissue repair and pathologic remodeling after toxicant exposure**
• Define circumstances under which lung disease is the outcome
Tissue Injury, Repair and Remodeling

- Inflammation
  - Macrophage
  - Vessel
  - Alveolus
  - Airway Lumen

- Fibrosis
  - Growth factors
  - Proteinases

- Repair
  - Proteinases

- Emphysema
  - Growth factors

Depending on the original events, repair can also lead to destruction of the lung tissue.

We hope repair will go in this direction to restore to original normal condition.

Collagen, fibroblasts activity --> fibrosis and scarring within the lung.

Large number of events including growth factor, cytokines released can lead to lung tissue injury.

Loss of alveolar septa and lead to destruction of lung tissue --> emphysema (imbalance between proteases and anti-proteases).
Fibrosis and Emphysema - inappropriate responses to injury

“The same factors (i.e., cytokines, growth factors, proteinases) that mediate tissue repair following injury also mediate fibrogenesis…”

“…it is the aberrant expression of these factors - either in magnitude or timing - that favors disease progression over healing”

Key takeaway: molecules/factors that initiate the repair response can also lead to injury including fibrosis/destructions
Environmental and Occupational Lung Diseases

- Obstructive Airway Diseases
- Hypersensitivity Pneumonitis
- Fibrotic Diseases
- Lung Cancer

all of the lung disease we talk about today are related to environmental and occupational exposures

e.g. emphysema

allergic to environmental material. A hypersensitivity reaction (Type II), different from asthma (Type I hypersensitivity)
Obstructive Lung Disease (Diseases of the Airways)

- Occupational and environmentally-induced asthma
- Reactive airways dysfunction syndrome (RADS)
- Chronic bronchitis (a component of COPD)
- Byssinosis (Cotton worker’s disease)
- Bronchiolitis obliterans

meaning decrease in air flow in the airways and air trapping

cause severe morbidity and even mortality

related to cotton dusts and pts may experience SOB at work when they are exposed to cotton dusts. Symptoms would not show up if pts are away from work, for example, during the weekends. (used to be very prevalent in N.C.)

similar to asthma
Airway Remodeling and Fibrosis in Asthma

From 2010 lecture: asthma is a reversible airway disease, with both acute and chronic components, caused by:
1. constriction of airway smooth muscles
2. increased mucous production that would block off the lumen and reduce air flow
3. asthma attack is reversed when the allergens are removed
4. prolonged exposure/chronic asthma can lead to airway remodelling that leads to fibrosis
Asthma: An Obstructive Lung Disease with Acute and Chronic Components

Asthma encompasses both the **acute** physiologic response of **broncho-constriction** caused by **allergen** challenge as well as the **chronic** aspect of **airway inflammation** and remodeling.

Both acute and chronic aspects contribute to airway obstruction.

*both of the acute and chronic aspects contribute to the airway obstruction where the chronic aspect is generally irreversible*
Asthma is generally an allergic disease with some exceptions.

**Immunological mechanism**
- antibody-dependent hypersensitivity: an IgE-mediated type I allergic reaction

**Non-immunologic mechanisms**
- pharmacologic agents (e.g. aspirin)
- epithelial disruption (e.g. viral infection)

From 2010 lecture: Extrinsic form: caused by external allergens. Intrinsic form: overly reactive airway that has a genetic component to it.
Mechanisms of Occupational and Environmental Asthma

Aspects of Chronic Airway Remodeling

- sloughing of bronchial epithelium
- mucous cell hyperplasia and excessive mucus production
- airway fibrosis
- airway smooth muscle cell growth
- inflammatory cell infiltration (eosinophilia)

Steps involved in the chronic airway remodeling:

- Metaplasia--mucous cells (goblet cells) replace the epithelium in smaller airways. (goblet cells normally only exist in larger airways.)

Especially in the extrinsic form of asthma (allergen related).
Pathology of asthma

- Pulmonary artery
- Bronchiole
- Alveoli
- Bronchiolar epithelium
- Smooth muscle
- Mucus

Mucus plug is abnormal--obstruction
You will see the goblet cells in next slide
A bit more prominent than it should be, part of the remodeling process
Pathology of asthma

- Smooth muscle
- Epithelium
- Mucus
- Inflammatory cells
- Eosinophils

- Contraction of the SMC results in bronchial constriction typical of asthma
- Again, in pts with allergen caused asthma, there are often eosinophils (granular cells stained red)

- Lots of goblet cells in the epithelium (also part of the chronic inflammation process as discussed 2 slides ago)
Agents causing Environmental and Occupational Asthma

- **high-molecular weight allergens**: (sensitizing agents, IgE-mediated, >1000 daltons)
  - plants
  - bacterial (endotoxin)
  - house dust mite
  - cockroach

- **low-molecular weight compounds**: (IgE-mediated “hapten” mechanism or IgE-independent mechanism)
  - anhydrides
  - metals
  - penicillin
  - diisocyanates

*cause of Byssinosis (cotton dust caused obstructive disease)*
*antigens in the proteins in the mite*
*meaning they typically bind to another protein to cause immunogenic effects*
Cellular Mechanisms of Asthma

DC cells have a very important role in the development of asthma: allergen passing through an injured mucousal layer will attach to DC. DC can then directly interact with mast cells to trigger granules release. DC cells also present the ag to lymphocytes -->TH2 particularly important in asthma pathology and airway remodeling, as well as plasma cells IgE production. IgE can bind to the allergen

From: Lambrecht et al., The Immunologic Basis of Asthma, Marcel Dekker, Inc. 2003
Once TH2 cells are activated by the antigen, presenting DC cells, they can act as an amplification system and produce cytokines, growth factors, and chemokines, to recruit cells including neutrophils and eosinophils. Granules released from eosinophils can trigger smooth muscle constriction, etc. There might also be smooth muscle hyperplasia, fibroblasts lay down collagen--->airway remodeling.

From: Lambrecht et al., The Immunologic Basis of Asthma, Marcel Dekker, Inc. 2003
Cellular Mechanisms of Asthma: Chronic Airway Remodeling Involving Interleukin-13 and Growth Factors

From: Ingram and Bonner, Current Molecular Medicine Reviews, 2006
Reactive Airways Dysfunction Syndrome (RADS)

- Definition: an asthma-like syndrome with a non-immunologic basis induced by high-dose exposure to irritant substances that cause airway epithelial damage.

- Examples of irritants that cause RADS:
  - chlorine
  - ammonia
  - sulfuric acid

Individuals normally don't have previous airway symptoms (e.g., asthma) until exposure to the irritants.
Chronic Obstructive Pulmonary Disease (COPD) = chronic bronchitis + emphysema

Chronic Obstructive Pulmonary Disease (COPD) - 4th highest cause of death in the USA with a mortality 14 times that of asthma. The single most important factor is cigarette smoke.

Chronic Bronchitis/bronchiolitis - A component of COPD, but can occur in the absence of emphysema. Caused by a variety of occupational and environmental insults, including metal-induced oxidative stress, bacterial pathogens, viruses.

Emphysema - proteolytic degradation of alveolar walls due to an imbalance in proteinase/anti-proteinase system. Neutrophil elastase is a major mediator of alveolar wall destruction. Emphysema usually occurs with chronic bronchitis.

2010 lecture: alpha1-anti-trypsin (blood) inhibits protease activity. There is a congenital defect where patients don't make this enzyme. Cigarette smoking can increase protease activity while at the same time inhibit alpha-1-anti-trypsin activities--> imbalance. More on the later COPD lecture.
Chronic Obstructive Pulmonary Disease

With emphysema, the walls of alveoli are damaged by inflammation. Alveoli can lose their natural elasticity, become overstretched and rupture. Several adjacent alveoli may rupture, forming one large space instead of many small ones.

Chronic bronchitis is a chronic inflammation and thickening of the walls of your bronchial tubes, which narrows them. It often induces cough spells.

holes in alveoli. holes get larger and larger. lungs lose elastic recoil

small airway lumen and wall thicker. mucous plugging often present. cause air way obstruction and air trapping
Chronic Bronchitis/Bronchiolitis

- **Definition:** Non-allergic airway disease characterized by mucus cell hyperplasia, chronic airway remodeling, and fibrosis.

- **Examples of irritants that cause bronchitis:**
  - Cigarette smoke
  - Bacterial endotoxins and viral infections
  - Air pollution particulate matter
  - Metal-induced oxidative stress
  - Ozone: contributing factor, not major compared to cigarette smoking
Vanadium Pentoxide ($V_2O_5$)-induced Bronchiolitis

administration of metal induces small airway disease--bronchiolitis (in animal model)

dark purple staining for mucin--should not be here in normal circumstances

these are goblet cells (goblet cells hyperplasia in small airway diseases)

Alcian blue PAS stain highlighting mucin-filled goblet cells
Vanadium Pentoxide ($V_2O_5$)-induced Bronchiolitis

Walters and Bonner (2005) Air Pollutants & the Respiratory Tract: Lung Biology in Health and Disease, Vol. 204
Causes of *Bronchiolitis Obliterans*

- Postinfectious (e.g., adenovirus)
- Fumes and toxins (*S. androgynus*)
- Drug reactions (e.g., penicillamine)
- Chronic allograft rejection (lung, B.M.)
- Collagen vascular disorders (esp. RA)
- Inflammatory bowel disease
- Bronchiectasis, CF, asthma
Bronchiolitis Obliterans: A tissue response to injury

what used to be the bronchiole (we can tell because it is adjacent to the pulmonary artery on the left). A circular mass of fibrous tissue with no lumen or epithelium cells at all. Periphery has smooth muscle cells, there are inflammatory cells at the very edge, resulting in obliteration.
Environmental and Occupational Lung Diseases

- Obstructive Airway Diseases
- Hypersensitivity Pneumonitis
- Fibrotic Diseases
- Lung Cancer
Hypersensitivity pneumonitis: Allergic Response Leading to Fibrosis

Genetic Susceptibility is a Major Factor

- Immune mechanism and pathology:
  - Infiltrative disease involving recurrent exposure and sensitization (elevated IgG).
  - Diffuse mononuclear inflammation of terminal bronchioles and alveoli. Small poorly formed granulomas.

- Examples:
  - Thermophilic actinomycetes mediate farmers’ lung disease
  - Avian proteins (Bird-fancier’s or pigeon breeder’s lung).
  - Chronic Beryllium Disease

Another example would be molds growing in the air conditioning system

Only a small % of individuals exposed to a certain environmental factor actually develop the disease

Now in good control

Frequently associated with a few giant cells in the interstitium

Usually with fever and chills
Hypersensitivity pneumonitis

2010 lecture notes:
lymphocytes infiltration and airway centered inflammation is diagnostic of hypersensitivity pneumonitis
Treatment:
1. avoid the allergen
2. steroids

lymphocytic infiltration of the alveolar septum causing thickening of the alveolar wall
occasional giant cells forming loose granulomas (hard to find but characteristic)
Macrophage Presentation of Beryllium to Helper T Lymphocyte via Major Histocompatibility Complex (MHC)

Be\(^{+2}\) exposure

Beryllium taken in by macrophages and presented on cell surface by HLA-DP\(\beta_1\) gene product

Macrophage activation of T lymphocytes result in cytokine release that lead to granuloma formation which can cause damage to the lung

HLA-DP\(\beta_1\) gene product

Glu-69

helper T lymphocyte
non-necrotising Granuloma formation. In this case it is much more well formed granuloma when compared to hypersensitivity pneumonitis. If fact, this has to be distinguished from sarcoidosis. (berylliosis is even more rare than sarcoidosis)
Environmental and Occupational Lung Diseases

- Obstructive Airway Diseases
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- Fibrotic Diseases
- Lung Cancer
Pulmonary Fibrosis

Fibroblasts

Type I epithelial cell

Infiltrating Fibroblasts

Macrophage

Red blood cells

Endothelial cell

Important effector cells. They are the first to be exposed to the pathogen and their subsequent interaction with the epithelium cells and fibroblasts are important for the pathology.

Proliferation of fibroblast within the interstitium and production of collagens by the fibroblasts
Mechanisms of Lung Fibrosis

Environmental agents
- Chemotherapeutic drugs

Reactive oxygen species
- Repetitive exposure can lead to injury

Epithelial injury
- FGF-7
- Limited exposure can lead to normal repair
- Restoration of epithelium
- Myofibroblast apoptosis
- Tissue repair

Macrophage/lymphocyte activation
- HB-EGF
- FGF-2, PDGF, EGF

Myofibroblast proliferation
- TGF-β

Collagen deposition
- Tissue remodeling & fibrosis

Small amount of exposure to ROS normally lead to repair and tissue replacement. But prolonged exposure can activate the macrophages and lymphocytes that lead to myofibroblasts proliferation and production of collagen.
Communication is everything

“If cytokines are the language through which cells communicate, then fibrosis is the result of a conversation where words were spoken too loudly and repeated too often…”
Cytokine/Growth Factor Cascades in Lung Fibrosis

Asbestos, Silica, Bleomycin

Increased IL-1β & TNF-α

Increased PDGF and PDGF Receptors

Fibroblast growth

TGF-β Auto-induction

Increased TGF-β

Fibroblast collagen deposition

Increased CTGF

Fibroblast growth and chemotaxis
Platelet-derived Growth Factor Signaling in Lung Fibrosis


[Diagram showing interactions between platelet-derived growth factor (PDGF) and other molecules in lung fibrosis]

- First exposure to pathogen, for example, asbestos fiber.
- Inhaled, inorganic particles or fibers.
- Platelet derived growth factor normally binds to alpha-2 macroglobulin molecule and lead to proteinase activities. However, if the signal from the Macrophage are "repeated too loud of too often", PDGF binds to fibroblast cell membrane molecules instead and signals for fibroblasts proliferation and collagen production.

- If production and degradation are imbalanced, it can lead to proliferation and inflammation.
Pneumoconiosis - Occupational Lung Fibrosis

Dust in the lung: disease caused by exposure to excessive amount of dust

Silica fibers in the lung. Interaction of macrophages lead to cytokine, ROS production that lead to fibrosis.

Silicosis

Highly pigmented fibrosis in coal worker’s lung

Coal Worker’s Pneumoconiosis
DIFFUSE ALVEOLAR DAMAGE OXYGEN TOXICITY

Acute phase

Organizing phase

Even normal lungs with extensive 100% O2 exposure may be damaged. Pts with lung diseases are even worse susceptible to ROS injuries.

Over time, the hyaline membrane will be replaced by fibrous tissue.
BLEOMYCIN-INDUCED PULMONARY FIBROSIS

result from ROS

thickening of the interstitium from fibrosis

characteristic hyperplasia of alveolar Type II cells lining the . potential confusion with: cancer, viral inclusion bodies

chemotherapy agent
Death by Asbestos

exposure not too often now. It has not eliminated since it was used in insulation materials

darker staining-->proliferation of epithelial tissue in response to injury

fibrosis

airspace

collagen accumulation
the process starts in the bronchiole wall. this is the bronchiole epithelium lining the smaller airways.

asbestos bodies in the wall of the bronchiole.

excess fibrous tissue.

high power view
ASBESTOS (FERRUGINOUS) BODIES

protiens and Fe deposit on the asbestos body by the macrophages because the macrophage can not entirely take the fiber up

macrophage

asbestos body inside the macrophage
Visualizing Early Asbestos-Induced Cell Proliferation in rats using Bromodeoxyuridine Immunohistochemistry

- Terminal bronchiole and alveolar sacks
- Cells undergoing division
- Lots of mitotic cells
- This is a terminal bronchiole (direction from top down) and giving rise to two alveolar sacs one on the left and one on the right
- Alveolar duct bifurcation
Asbestos Deposition and Early Responses in the Rat Lung

EM showing a lower power view of a lung from an experimental animal exposed to asbestos for a short period of time (less than a day)

this is a nice view of a bronchiole merging into alveolar ducts/sacs
Asbestos fibers on the surface of the alveolar duct. (They like to land on branch points) Macrophage activities seen on next slide.
At the alveolar duct bifurcation we saw earlier, these macrophages are trying to "eat up" the asbestos fibers through phagocytosis. They will show up within 24 hrs.
Early Fibrotic Lesion Development at Fiber Deposition Sites

1. Asbestos deposition
   - Asbestos fiber coming in with the airflow tend to pack at the first alveolar duct bifurcation

2. Macrophage accumulation
   - Macrophage activated producing TGF beta, IL1 (macrophage factor) and PDGF

3. Fibrogenesis
   - Cytokines and growth factors produced by the macrophages will induce fibroblasts proliferation and prosis, end up with a litter scar at the location
Macrophage-Mediated Particle Clearance

1) **mucociliary escalator**: upward movement of particulate material by combined action of trapping particles in mucus, then upward beating of cilia on airway epithelial cells, then material is expelled or swallowed.

2) Macrophage-mediated: macrophages engulf particles and deposit them on mucociliary escalator or enter the lymphatic system.

- phagocytosis, deposit them on mucociliary escalator or going into the lymphatics and clean up the foreign particles that way
- they can destroy the virus and bacterial, but stuff like asbestos fibers or silica can not destroyed by macrophages
Major Factors Influencing Repair versus Disease

- Deposition site of inhaled toxicant
- Severity of injury by inhaled toxicant
- Reactivity and solubility of inhaled toxicant
- Persistence of inhaled toxicant
- Immune response and genetic susceptibility

- If trapped in LOWER respiratory track→ more likely to get disease
- Dose of pathogen exposure
- 3.g. asbestos fibers particularly persistent. Persistent ones are more likely to cause injury
Environmental and Occupational Lung Diseases

- Obstructive Airway Diseases
- Hypersensitivity Pneumonitis
- Fibrotic Diseases
- Lung Cancer
Asbestos-related Diseases

- Asbestosis
- Carcinoma of the Lung
- **Mesothelioma**
  - Pleural
  - Peritoneal
- Benign Asbestos-Related Pleural Diseases (Pleural Plaques)
- Other Cancers (Larynx)

- Increased risk of carcinoma with smoking and asbestosis
- Asbestos exposure and smoking have synergy and multiply the risks for lung cancer
- 80-90% asbestos related
- Tend to need an even higher exposure
- Scars may form
- Larynx gets hit twice: 1 when you breath the asbestos fiber in. 2. on the mucociliary escalater when you try to clean the fibers out
Asbestos-Induced Lung Cancer

- radiation fibrousis (from treatment for lung cancer)
- pigmentation with nodules of fibrosis
- silicosis due to exposure to silica
- asbestosis
- and emphysema (smoker)
- large squamous cell carcinoma

ONE lung with many different pathogenesis!
Asbestos-Related Mesothelioma

classic asbestos related mesothelioma of the pleural--->grow like a sheath

regional lymph node involvement. This lung is extremely injured and respiration is greatly limited
MECHANISMS OF ASBESTOS-INDUCED CARCINOGENESIS

• **Mesothelioma**
  – Clastogenic mechanism
  – Reactive oxygen species (ROS)
  – Growth factors/cytokines

  If put mesothelial cells with asbestos fibers in vitro, there is interference with normal mitotic divisions
  --> chromosome fragmentation etc

• **Lung Cancer**
  – *Synergistic* effect with *cigarette smoke*
  – ROS, growth factors, cytokines

  The exposure need not be too high

  5 fold risk increase with high dose asbestos. 10 fold with smoking. 50 fold with both combined