Restrictive lung diseases other heterogeneous group of disorders characterized by reduced lung compliance and reduced forced vital capacity (FVC). The unifying pathogenic factor is characterized by injury to the alveoli with activation of macrophages and release of fibrogenic cytokines such as TGF-β. There are several ways to classify them, the easiest would be to classify them as granulomatous disorders, fibrosing disorders, smoking associated restrictive lung diseases and disorders with a predominance of eosinophils.

Two broad categories
- Interstitial lung disease
- Chest wall disease

**Interstitial Lung disease**

Group of disorders that result in inflammation and fibrosis of alveolar walls (septa) with similar clinical, radiographic, and physiologic features

- Symptoms: Dysepnea
- Physical exam: Tachypnea, fine “dry” crackles, no wheezing
- Physiology: reduced oxygen diffusing capacity, decreased lung volume and compliance
- Secondary pulmonary hypertension can result in right sided heart failure (cor pulmonale)
- Chest Radiography: Diffuse infiltration by small nodules, irregular lines, or ground glass shadows
- End stage disease results in “honeycomb lung”

- Major categories, etiologies of chronic interstitial lung disease – Robbins Table 12-3 (Robbins Basic Pathology)

**Sarcoidosis**

Definition:
- Multisystem disease of unknown etiology
- Characterized by non-caseating granulomas
- Diagnosis of exclusion because other diseases may present as non-caseating granulomas: TB, fungal infection, berylliosis

Pathogenesis:
- Unknown, however evidence suggests disordered immune regulation in genetically predisposed individuals exposed to certain environmental agents
  - CD4 T-cell driven

Clinicopathologic Correlation:
- Characteristically develops in adults less than age 40, African Americans
- Pulmonary Disease:
  - Lungs common site of involvement
  - CXR with interstitial fibrosis, ± hilar lymphadenopathy
Spectrum of symptoms: asymptomatic; shortness of breath; dry cough; progressive, permanent lung dysfunction

Nonspecific symptoms include fever, anorexia, night sweats, weight loss

- Ocular disease:
  - Uveitis, iritis, iridocyclitis, choroiditis, optic nerve involvement

- Skin:
  - Erythema nodosum – very tender erythematous skin plaques and nodules.
  - Lupus pernio – papulonodules/plaques in areas affected by cold (nose, ears, cheeks); often with beaded appearance on nasal rim

- Heart:
  - Restrictive cardiomyopathy
  - Conduction abnormalities

- Liver, bone marrow, CNS involvement, Bell’s Palsey (CN VII)
- Other findings:
  - Hypercalcemia – granulomas autonomously convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D which increased calcium absorption
  - Hypergammaglobulinemia (manifestation of T-cell dysregulation)
  - Elevated ACE (Angiotensin converting enzyme)
  - Cutaneous anergy to skin tests like PPD
  - Histologic finding (noted in First Aid) – the granulomas (in particular the giant cells of the granulomas) may contain inclusions
    - Schauman bodies – laminated concretions composed of calcium and proteins
    - Asteroid bodies – stellate (star-shaped) inclusions

Treatment:
- Steroids

Course/Prognosis:
- 65-70% of patients recover with minimal manifestations
- 20% of patients have permanent loss of lung or vision function
- Deaths
  - 10-15% due to cardiac or CNS complications
  - Majority of deaths are due to progressive pulmonary fibrosis and cor pulmonale

**Idiopathic Pulmonary Fibrosis (IPF)**
Also known as “Usual interstitial pneumonia”, “cryptogenic fibrosing alveolitis”

**Etiology:**
Causative agent is unknown – see Robbins figure 15-13
Repeated cycles of epithelial activation/injury by some unidentified agent lead to abnormal epithelial repair and fibroblastic proliferation resulting in fibrosis

**Morphology:**

**Gross:**
- Scarring of pleural surfaces
- Fibrosis of lung parenchyma which appear as firm, rubbery, white areas
- Findings most prominent subpleural and along interlobular septa

**Microscopic**
- Honeycomb fibrosis represents the destruction of alveolar architecture and formation of cystic spaces lined by pneumocytes type II and bronchial epithelium
- There may be mild to moderate inflammation (mostly lymphocytes, some plasma cells) in fibrotic areas.

Note: the histologic picture of “usual interstitial pneumonia” which is required for the diagnosis of IPF can be seen in other diseases, in particular collagen vascular disease such as rheumatoid arthritis, systemic lupus erythematosus, and progressive systemic sclerosis. Correlation with clinical history is critical.

**Clinicopathologic correlation**
- Men > women, typically 40-70 years old at presentation
- Initial presentation is dyspnea on exertion + dry cough
- “Velcro” crackles on physical exam
- Gradual deterioration despite treatment (with immunosuppressants such as steroids, cyclophosphamide, azothioprine).
- Definitive treatment is lung transplant
- Mean survival is 3 years after diagnosis
  - As the pathogenesis of IPF is better elucidated, novel treatments, such as therapies neutralizing TBF-1, enhancing telomerase activity or delaying telomere shortening, or augmenting caveolin-1 may be developed?

**Pneumoconioses**

Definition: The accumulation of dust in the lungs and the tissue reaction to its presence
  - Result of organic and inorganic particles and chemical fumes and vapors.
  - Common pathologic feature is pulmonary fibrosis.
  - Overall incidence is decreasing with regulations limiting exposures in the workplace.
Lung Diseases Caused by Air Pollutants: See Robbins Table 15-6

Pathogenesis:
- Development of pneumoconiosis depends on pollutant concentration, size and shape, solubility and reactivity, individual susceptibility, additional effects of other irritants.
  - Most dangerous particles range from 1 to 5 μm in diameter because they reach the terminal small airways and sacs and settle in their linings.
- Macrophages endocytose and trap particles. Reactive particles trigger release of inflammatory mediators from macrophages which initiate fibroblast proliferation and activation. End result – collagen deposition and fibrosis.

Coal Worker’s Pneumoconiosis
- Greatest exposure to coal miners
- Coal mine dust = coal + trace metals + inorganic minerals + crystalline silica
- Disease progresses with continued exposure to coal
- Associated diseases
  - Anthracosis
    - Inhaled carbon pigment is engulfed by alveolar/interstitial macrophages. Accumulates in connective tissue, pleural lymphatics, lymph nodes
    - Seen in urban dwellers, tobacco smokers and coal miners
    - No sequelae
  - Coal macules and nodules
    - Accumulations of dust laden macrophages
    - Not many symptoms
  - Progressive Massive Fibrosis
    - Results from coalescence of coal nodules leading to haphazard fibrosis, large scars (2-10cm) with dense collagen and pigment
    - Results in progressive dyspnea, pulmonary dysfunction, pulmonary hypertension, cor pulmonale
    - No increased risk of bronchogenic carcinoma
    - No increased susceptibility to tuberculosis
  - Caplan Syndrome
    - Aka “rheumatoid pneumoconiosis”
• Form of Coal Worker Pneumoconiosis associated with rheumatoid arthritis
• Suggestion that presence of rheumatoid arthritis is a host factor that modifies response of an individual to coal mine dust exposure
• Radiology – the nodules may cavitate

Asbestosis
Asbestos is the smallest naturally occurring fiber
  • Serpentine chrysotile fibers are curly and flexible. They represent most of the fibers used in industry
  • Amphibole fibers are straight, brittle, fibrogenic. They are more pathogenic than chrysotile fibers, in particular in induction of mesothelioma.
• Occupational exposures: shipbuilding, roofing, plumbing, mining, milling, and fabrication; installation of insulation
• Environmental exposure is also potentially hazardous: there is increased incidence of asbestos-relate cancer in family members of asbestos workers.
• Asbestos has an oncogenic effect:
  ◦ Acts as tumor initiator and promoter (mediated by reactive free radicals)
  ◦ Adsorbs toxic chemicals (tobacco smoke)
• Asbestos has a fibrogenic effect.

Asbestos related diseases:
  • Parenchymal interstitial fibrosis (asbestosis)
    ◦ Distinguished from other forms of diffuse interstitial fibrosis by presence of asbestos bodies:
      ▪ Asbestos bodies are golden brown, beaded or fusiform rods (resemble dumbbells) with a translucent center. Consist of asbestos fibers coated with an iron containing proteinaceous material. Iron is thought to derive from phagocyte ferritin.
      ▪ Often seen within macrophages
    ◦ Clinicopathologic correlation:
      ▪ Patients develop dyspnea, cough. May progress to respiratory failure, cor pulmonale, death.

  • Localized fibrous pleural plaques:
    ◦ Most common manifestation of asbestos exposure
    ◦ Well circumscribed plaques of dense collagen usually on parietal pleura and domes of diaphragm.
    ◦ Do not correlate with level of exposure to asbestos.
Lung Pathology_Part III

- Usually asymptomatic and commonly discovered as a radiographic finding.

- **Pleural effusions**
  - Pathogenesis:
    - Thought to be due to mechanical irritation by fibers permeating the pleura and a having direct cytotoxic effect on the surface mesothelial cell layer
  - Effusions are usually small, may be bloody
  - Prognosis usually good though the effusions do often recur spontaneously

- **Bronchogenic carcinoma**
  - Asbestos is associated with 5 fold increase in lung carcinoma
  - 55 fold increase when associated with smoking
  - Asbestos related cancers are morphologically indistinguishable from other forms of lung cancer (small cell and non-small cell)

- **Malignant Mesotheliomas (additional details to follow in Lung Path_PartIV handout)**
  - Arise from visceral or parietal pleura
  - Latent period after asbestos exposure is long – 25 to 40 years
  - Pathogenesis:
    - Asbestos fibers settle near mesothelium
    - Reactive oxygen free radicals induce DNA damage
    - Associated with deletions of chromosome 1p, 3p, 6q, 9p or 22q.

**Silicosis**
Most prevalent occupational disease
- Associated occupations include sandblasting, quarrying, mining, stone cutting, foundry work, ceramics
- Crystalline forms of silica (quartz) are more fibrogenic than exposure to amorphous forms
  - **Simple nodular silicosis**
    - Upper zones of lungs with concentric hyalinized collagen with a whorled appearance
    - Fibrotic lesions may be present in hilar lymph nodes (rim of calcification around lymph nodes may be seen radiographically as “eggshell calcification”)
    - Often incidental finding on chest-x ray
Lung Pathology_Part III

- Progressive Massive Fibrosis
  - Coalescence of nodules
  - Progressive dyspnea, pulmonary HTN, cor pulmonale

- Silicosis is associated with increased susceptibility to tuberculosis
  - Pathogenesis: postulated that silicosis depresses cell mediated immunity and silica may inhibit ability of pulmonary macrophages to kill phagocytosed mycobacteria
  - Nodules may have central necrosis when complicated by TB

Debate - Is silica carcinogenic? Is it associated with the development of bronchogenic carcinoma?

See Table 1 for Summary of Pneumoconiosis

Table 1

<table>
<thead>
<tr>
<th>Agent</th>
<th>Exposure</th>
<th>Clinical</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestos</td>
<td>Shipbuilding, roofing, Plumbing</td>
<td>Subdiaphragmatic and pleural plaques, calcify</td>
<td>Lower lobes, Interstitial fibrosis, Pleural plaques, increased risk of bronchogenic carcinoma, mesothelioma Ferruginous bodies</td>
</tr>
<tr>
<td>Coal</td>
<td>Mining, Industries, urban dwellers</td>
<td>Nothing specific, fibrosis, Caplan Syndrome-Assocn with RA</td>
<td>Upper lobes, Anthracosis, to simple macules to progressive massive fibrosis</td>
</tr>
<tr>
<td>Silica</td>
<td>Foundries, Sandblasting, mines</td>
<td>Susceptibility to TB: Silicotuberculosis Egg shell calcification of hilar lymph nodes</td>
<td>Upper lobes Hyalinized whorled nodules</td>
</tr>
<tr>
<td>Beryllium</td>
<td>Aerospace industry</td>
<td></td>
<td>Upper lobes Granulomatous inflammation</td>
</tr>
</tbody>
</table>

Hypersensitivity Pneumonitis (not covered in lecture but here for your reference)

V. Ananthanarayanan
2017
Aka: Allergic alveolitis

Etiology:
- Abnormal hypersensitivity response from spores of thermophilic bacteria, fungi, animal proteins, bacterial products
  - Farmer’s lung: exposure to dusts from harvested, humid hay that permits proliferation of thermophilic actinomycetes
  - Pigeon breeder’s lung (bird fancier’s disease): exposure to proteins from serum, excrement, feathers of birds
  - Humidifier (air conditioner) lung: exposure to thermophilic bacteria in heated water reservoirs

Pathogenesis:
- Immunologically mediated response to an extrinsic antigen that involves both immune complex and delayed type hypersensitivity reactions.

Morphology:
- Interstitial pneumonitis (lymphocytes, plasma cells, macrophages)
- Noncaseating granulomas

Clinicopathologic Correlation:
- 4-6 hours after exposure patients develop fever, dyspnea, cough, leukocytosis
- Diffuse and nodular infiltrates on CXR
- Progression to chronic fibrotic lung disease prevented by removal of environmental agent