ILD: Definition

1. ILD is not one disorder
2. Strictly speaking, an ILD involves the interstitium. Anatomic structures other than the interstitium can be involved:
   “alveolitis”
   “vasculitis”
   “peri-bronchial disease”

What Conditions Belong to “ILD”?

1. Diffuse abnormalities on chest radiology
   “Diffuse Parenchymal Lung Disease” (DPLD) is the more general and preferred term.
2. Similar clinical presentations
3. Similar physiological consequences
4. Generally, chronic non-infectious, non-neoplastic disease involving the lung parenchyma including the interstitium.
**Classification of Diffuse Parenchymal Lung Disease**

- **Systemic Disease**
  - DPLD

**Classification of Diffuse Parenchymal Lung Disease**

- **Systemic Disease**
  - DPLD
  - Known Cause & Other

**Classification of Diffuse Parenchymal Lung Disease**

- **Systemic Disease**
  - DPLD
  - Known Cause & Other
  - Granulomatous

**Classification of Diffuse Parenchymal Lung Disease**

- **Systemic Disease**
  - DPLD
  - Known Cause & Other
  - Granulomatous
  - Sarcoid
  - Chronic hypersensitivity pneumonitis
  - Drugs Pneumoconioses EG

**Classification of Diffuse Parenchymal Lung Disease**

- **Systemic Disease**
  - DPLD
  - Known Cause & Other
  - Granulomatous
  - Idiopathic Interstitial Pneumonia (IIP)

**Survival for UIP vs NSIP**

- **Years**
  - 0
  - 2
  - 4
  - 6
  - 8
  - 10

- **Alive (%)**
  - UIP
  - NSIP

- **Others**

**Years**

- 0
  - 2
  - 4
  - 6
  - 8
  - 10

- **Alive (%)**
  - UIP
  - NSIP
  - Others
**COMPARATIVE MORTALITY RATES**

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>5-YEAR MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>85%</td>
</tr>
<tr>
<td>IPF (UIP)</td>
<td>50-70%</td>
</tr>
<tr>
<td>CHF</td>
<td>50%</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>38%</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>13%</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Prevalence of ILD**

<table>
<thead>
<tr>
<th></th>
<th>MALE</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational/</td>
<td>20.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Environmental</td>
<td>1.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Drug &amp; Radiation</td>
<td>7.1</td>
<td>11.6</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>20.2</td>
<td>13.2</td>
</tr>
<tr>
<td>IPF</td>
<td>10.1</td>
<td>14.3</td>
</tr>
<tr>
<td>Pulm Fibrosis (Not IPF)</td>
<td>8.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>8.3</td>
<td>8.8</td>
</tr>
</tbody>
</table>

(per 100,000/year)

*Am J Respir Crit Care Med 1994; 150: 967-972.*

**Epidemiology of IPF**

- **Incidence**
  - Estimated 31,000 New Patients per Year in the United States
- **Prevalence**
  - Estimated 5,000 Current Patients in the United States


**ILD: CLINICAL HISTORY**

- Insidious onset
- Preceding URI
- Occupational Exposure and Cigarette Smoking
- Progressive Dyspnea with Exertion (DOE)
- Paroxysmal cough

**ILD: PHYSIOLOGIC FINDINGS**

- Pulmonary function
  - Restrictive ventilatory defect
    - Reduced total lung capacity (TLC) & FVC
    - Normal or increased FEV₁/FVC ratio

*Adapted from ATS/ERS, Am J Respir Crit Care Med. 2002;166:144-64.*

**ILD: PHYSICAL FINDINGS**

- Tachypnea
- Basilar crackles
- May have digital clubbing
- Low lung volume, cyanosis, tachycardia

*Adapted from ATS/ERS, Am J Respir Crit Care Med. 2002;166:144-64.*
**Pulmonary Function Testing**

<table>
<thead>
<tr>
<th></th>
<th>Obstructive</th>
<th>Restrictive</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>100%</td>
<td>50%</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>FEV1</td>
<td>50%</td>
<td>50%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>43%</td>
<td>90%</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>TLC</td>
<td>100%</td>
<td>65%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>RV</td>
<td>105%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>FRC</td>
<td>95%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>DICO</td>
<td>50%</td>
<td>50%</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>

**ILD: PHYSIOLOGIC FINDINGS**

- Pulmonary function
  - Impaired gas exchange
    - Desaturation with exercise (pulse oxymetry)
    - Decreased $\text{Pa}_2$
    - Increased A-a gradient
    - Decreased $\text{DL}_{CO}$

Adapted from ATS/ERS. Am J Respir Crit Care Med. 2000;161:646-664.

**Six Minute Walk Testing in ILD**

Patient encouraged to walk at a maximal pace with as many stops as necessary

Oxygenation (desaturation) and symptom scores are measured

Desaturation may occur in other conditions
  - Pulmonary hypertension
  - Severe COPD
  - Heart failure

**ILD: PLAIN CHEST X-RAY**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Desaturation</th>
<th>4-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP (IPF)</td>
<td>Yes</td>
<td>35% n=83, p=0.0018</td>
</tr>
<tr>
<td>No</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>NSIP</td>
<td>Yes</td>
<td>66% n=22, p=0.0089</td>
</tr>
<tr>
<td>No</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
ILD: Early HRCT Findings

ILD: Traction Bronchiectasis

ILD: HONEYCOMBING

ILD: Case Presentation

50 year old man with “rapidly progressive IPF” transferred to CUMC 1/03

Pulm Hx: Cigarette smoking @ 1.5 ppd, teens - 45
Pneumonia 2/02, with full recovery

PMH: Gout
OA

Occupation: Mason

Case Presentation: HPI

7/97-12/00: Subtle bibasilar infiltrates
9/02: Persistent cough
Mild DOE
11/02: Extensive infiltrates, Restrictive PFT’s
Case Presentation: HPI

12/02: Surgical Lung Biopsy (Lingula & SS-LLL)
12/02: Predisone 60 mg/d (0.7 mg/kg/d)
12/02: URI, oral antibiotics
Acute decompensation
Dexamethasone 30 mg/d

Case Presentation: Clinical Course

3/03: Prednisone 25 mg/d
Pulmonary Rehabilitation
Less Dyspneic

4/03: Transplant Evaluation
PA 25/13 (17)
PCW (2)

7/03: Off Prednisone
Full-time work
SpO2 95 - 83% with stair climbing

Case Presentation: PFT’s

<table>
<thead>
<tr>
<th>DATE</th>
<th>1/03</th>
<th>3/03</th>
<th>4/03</th>
<th>7/03</th>
<th>9/03</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>2.5L (59%)</td>
<td>2.6</td>
<td>3.0</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>FEV1</td>
<td>2.2L (63%)</td>
<td>2.3</td>
<td>2.7</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>F/I-V</td>
<td>88%</td>
<td>88%</td>
<td>90%</td>
<td>90%</td>
<td>91%</td>
</tr>
<tr>
<td>TLC</td>
<td>3.7L (61%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC</td>
<td>2.0L (65%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCO</td>
<td>7.8L (24%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO2 (R)</td>
<td>92%</td>
<td>89%</td>
<td>92%</td>
<td>95%</td>
<td>91%</td>
</tr>
<tr>
<td>SpO2 (EX)</td>
<td>81%</td>
<td>79%</td>
<td>83%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT</td>
<td>1365'</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case Presentation: Exercise Physiology

<table>
<thead>
<tr>
<th>CPET</th>
<th>1/03</th>
<th>10/03</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIME</td>
<td>7 min</td>
<td>8 min</td>
</tr>
<tr>
<td>MAX WORK</td>
<td>65 watts</td>
<td>60 watts (32%)</td>
</tr>
<tr>
<td>VO2-max</td>
<td>12.2 ml/min/kg (37%)</td>
<td>11.1 (34%)</td>
</tr>
<tr>
<td>VE/VCO2</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>MVV</td>
<td>86 L/min (58%)</td>
<td>124 (85%)</td>
</tr>
</tbody>
</table>
**Progression of IPF: Acute Exacerbation vs Slow Decline**

**Traditional View of UIP/IPF Progression**

- **Acute Exacerbation vs Slow Decline**

**FVC = forced vital capacity**

Am J Respir Crit Care Med. 2003;261(1 Suppl):S1-S105.

**Pathological Sections Demonstrating UIP**

- **a. Peripheral accentuation of the disease**
- **b. Transition into uninvolved lung**
- **c. Low power pathology**
- **d. High power image of fibroblastic focus**

Courtesy of Kevin O. Leslie, MD.

Slide courtesy of Alain Borczuk, MD.

**Myofibroblast Proliferation in UIP**

**Multiple Hypotheses for the Pathogenesis of IPF**

- **Inflammation causes fibrosis**
- **Noninflammatory (multiple hit) hypothesis:** fibrosis results from epithelial injury and abnormal wound healing in the absence of chronic inflammation
- **Vascular remodeling:** aberrant vascular remodeling supports fibrosis, and may contribute to increased shunt and hypoxemia
- **Abnormalities in host defense.**


**Inflammatory Hypothesis**

- **Inflammation causes fibrosis**
  - Inflammatory concept was dominant in the 1970s and 1980s
  - IPF resulted from unremitting inflammatory response to injury culminating in progressive fibrosis
  - Role of inflammation remains controversial
  - Lack of efficacy of corticosteroids

Noninflammatory (multiple hit) Hypothesis

Recurrent pulmonary injury → Epithelial/endothelial injury and apoptosis → Loss of basement membrane → Failure of epithelialization/endothelialization → Fibroblast proliferation → Progression fibrosis with loss of lung architecture

Vascular Remodeling Hypothesis

- Aberrant vascular remodeling supports fibrosis and may contribute to increased shunt and hypoxemia
  - Increased angiogenesis results from imbalance of pro-angiogenic chemokines (IL-8, ENA-78) and anti-angiogenic, IFN-inducible chemokines (IP-10)
  - Vascular remodeling leads to anastomoses between the systemic/pulmonary microvasculature, increasing right-to-left shunt, contributing to hypoxemia

Defects in Host Defense Mechanisms May Contribute to Fibrosis

- Defects in endogenous host defense mechanisms (eg, IFN-g, PGE2 production) that limit fibrosis after acute lung injury may contribute to progressive fibrosis

IPF: Potential Contributing Pathways

Goals:
- Diagnosis
- Monitoring disease progression
- Coordination of therapy
- Clinical trials
- Investigative research
### Composition of the multi-disciplinary group

<table>
<thead>
<tr>
<th>Role</th>
<th>Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonologists</td>
<td>Clinical coordinators</td>
</tr>
<tr>
<td>Lung pathologists</td>
<td>Physical therapists</td>
</tr>
<tr>
<td>Chest radiologists</td>
<td>Respiratory techs.</td>
</tr>
<tr>
<td>Exercise Physiologists</td>
<td>Outside consultants</td>
</tr>
<tr>
<td>Rheumatologists</td>
<td>Cardiologists</td>
</tr>
<tr>
<td>Transplant physicians</td>
<td>Thoracic surgeons</td>
</tr>
<tr>
<td>Basic researchers</td>
<td>(Medical Informatics)</td>
</tr>
</tbody>
</table>

### Potential system-wide goals & projects:

- **Data base**
  - Diagnosis, natural history, pathogenesis
- **Diagnosis**
  - Central review of cases, clinical conferences
- **Coordination of care**
  - Clinical trials, transplant/tertiary care
- **Basic research**