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.

ILD: Thickening of the Interstitium
ILD: Thickening of the Interstitium

ILD: Cellular and Fibrotic

Slides Courtesy of Alain Borczuk, MD
Classification of Diffuse Parenchymal Lung Disease

Systemic Disease

DPLD

Known Cause & Other

Drugs
Pneumoconioses
Eosinophilic granuloma

Classification of Diffuse Parenchymal Lung Disease

DPLD

Systemic Disease

Granulomatous

Sarcoid
Chronic hypersensitivity pneumonitis

Known Cause & Other

Drugs
Pneumoconioses

EG

Idiopathic Interstitial Pneumonia (IIP)

Classification of Diffuse Parenchymal Lung Disease

- DPLD
- IIP
  - UIP (IPF)
  - Non-UIP
  - Cellular
  - Fibrotic
- NSIP

Survival for UIP vs NSIP

- Years
- Alive (%)

### 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 ofILD

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

**Estimated 83,000 Current Patients in the United States**

**Estimated 31,000 New Patients per Year in the United States**

---

**ILD: CLINICAL HISTORY**

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

---

ILD: PHYSICAL FINDINGS

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

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. 2000;161:646-664.
Pulmonary Function Testing

Examples:

<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 \( \text{Pa}_{\text{O}_2} \)
    - Increased A-a gradient
    - Decreased \( \text{DL}_{\text{CO}} \)

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

---

Six Minute Walk Testing in ILD

Primary end-point is distance walked

6MWT distance is often used as an endpoint in clinical trials for ILD therapy

Degree of desaturation may have prognostic significance
Desaturation during initial 6MWT predicts decreased survival:

<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%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>69% n=83, p=0.0018</td>
</tr>
<tr>
<td>NSIP</td>
<td>Yes</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>100% n=22, p=0.0089</td>
</tr>
</tbody>
</table>

ILD: PLAIN CHEST X-RAY
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: HRCT
### Case Presentation: Clinical Course

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
</table>
| 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</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</td>
<td>2.3</td>
<td>2.7</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>F/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</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC</td>
<td>2.0L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCO</td>
<td>7.8L</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></td>
<td>79%</td>
<td>83%</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>1/8/03</th>
<th>10/7/03</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

Respiratory Function/Symptoms vs Years

FVC = forced vital capacity

Step Theory of UIP/IPF Progression

Respiratory Function/Symptoms vs Years

Acute exacerbation

FVC vs Years

50%

Pathological Sections Demonstrating UIP

Myofibroblast Proliferation in UIP

Slide courtesy of Alain Borczuk, MD.
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 re-epithelialization/re-endothelialization
- Fibroblast proliferation
- ECM deposition
- Release of profibrotic growth factors (TGF-b, PDGF, IGF-1)
- Progressive 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 (e.g., IFN-γ, PGE2 production) that limit fibrosis after acute lung injury may contribute to progressive fibrosis.


IPF: Potential Contributing Pathways
Potential Therapeutic Targets

- Inflammation
  - Anti-oxidants
  - Cytokines
- Epithelial Restoration
  - Mitogens
  - Stem cell progenitors
- Aperrent Vascular Remodeling
  - Angiostatic molecules
- Fibroproliferation
  - Growth factors inhibitors
  - Chemokine antagonists
- Host Defense
  - Interferon-gamma
  - Prostaglandin-E2


Center for Interstitial Lung Disease

A multi-disciplinary group at NY-Presbyterian Hospital, based in the Jo-Ann LeBuhn Center for Chest Disease

Goals:
- Diagnosis
- Monitoring disease progression
- Coordination of therapy
- Clinical trials
- Investigative research
**Center for Interstitial Lung Disease**

### Composition of the multi-disciplinary group

<table>
<thead>
<tr>
<th>Pulmonologists</th>
<th>Clinical coordinators</th>
</tr>
</thead>
<tbody>
<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**