# Interstitial Lung Disease 2008


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Columbia University Medical Center


# 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"?

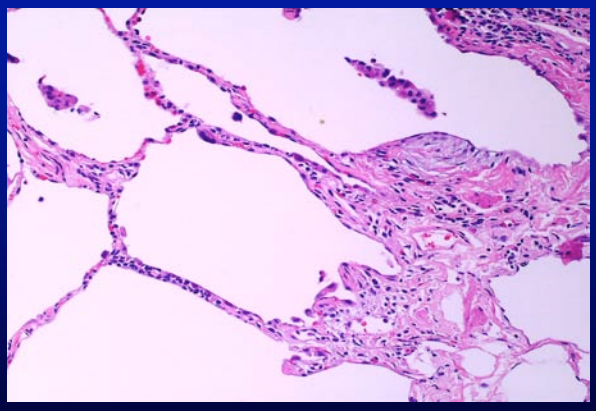
1. Diffuse abnormalities on chest radiology
   "Diffuse Parenchymal Lung Disease" (DPLD) is the more general and preferred term.

2. Similar clinical presentations

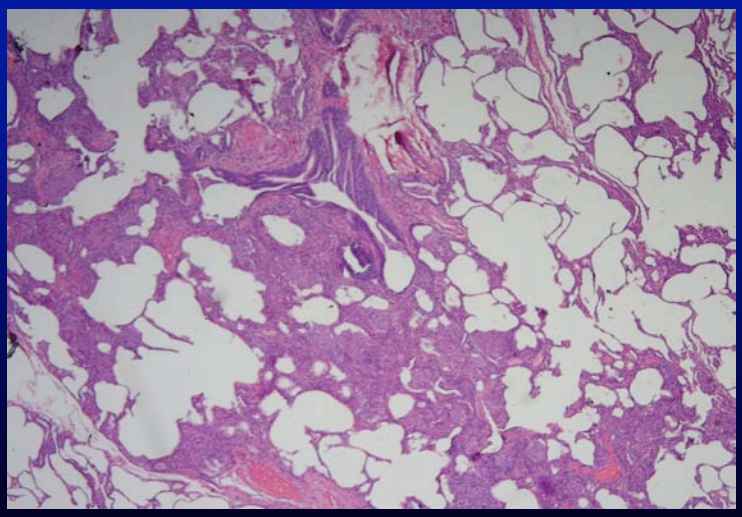
3. Similar physiological consequences

4. Generally, chronic non-infectious, non-neoplastic disease involving the lung parenchyma including the interstitium.

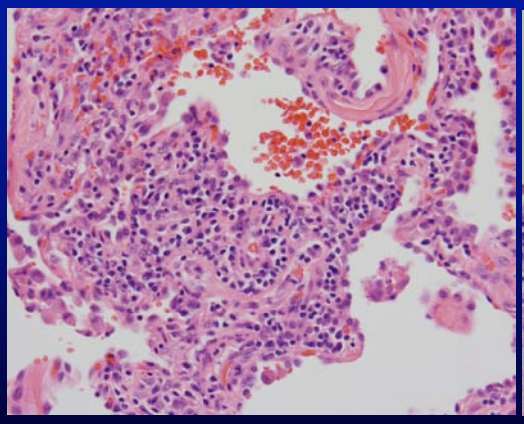
## ILD: Thickening of the Interstitium

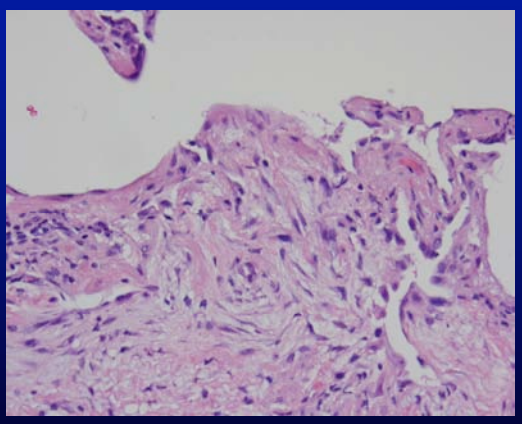


# ILD: Thickening of the Interstitium



# ILD: Cellular and Fibrotic





Slides Courtesy of Alain Borczuk, MD

# Classification of Diffuse Parenchymal Lung Disease

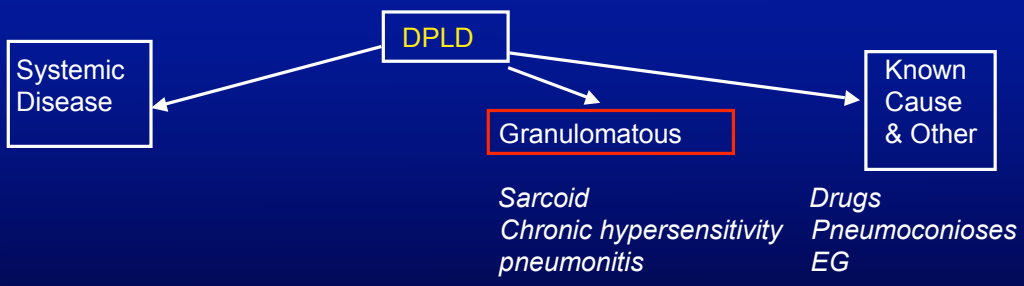

Am J Respir Crit Care Med (2002)165:277-304

# Classification of Diffuse Parenchymal Lung Disease


*Drugs*
*Pneumoconioses*
*Eosinophilic granuloma*

Am J Respir Crit Care Med (2002)165:277-304

# Classification of Diffuse Parenchymal Lung Disease

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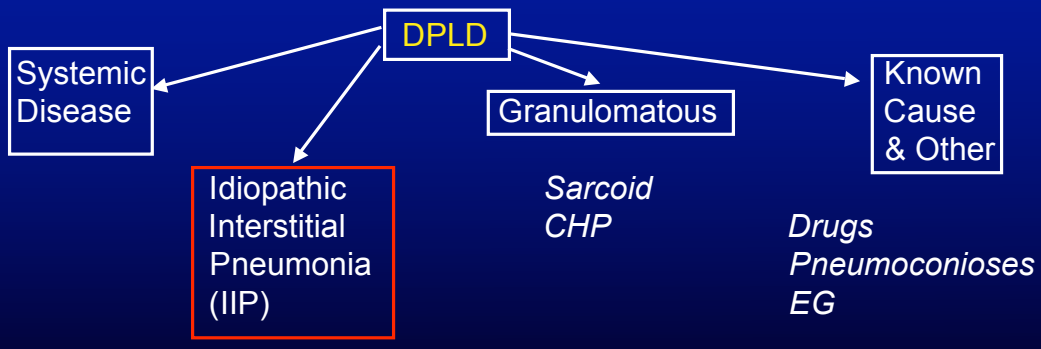


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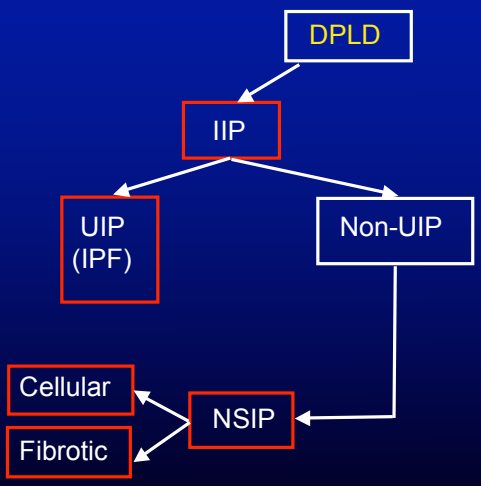


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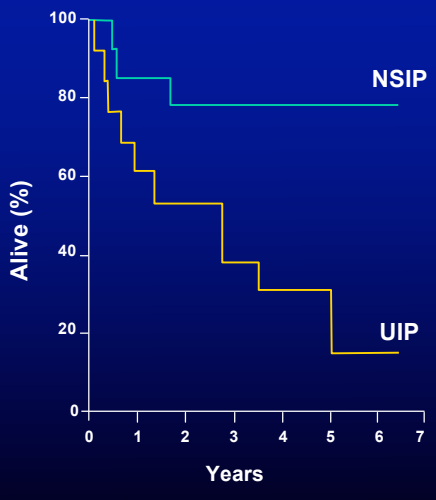
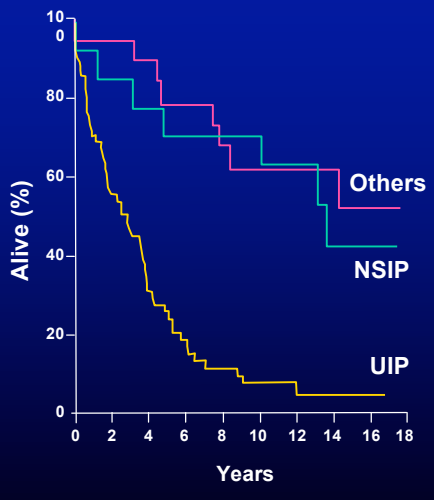
# Survival for UIP vs NSIP




Daniil ZD, et al. *Am J Respir Crit Care Med*. 1999;160:899-905.

Bjoraker JA, et al. *Am J Respir Crit Care Med*.1998;157:199-203.

## COMPARATIVE MORTALITY RATES

| DISEASE | 5-YEAR MORTALITY |
|---|---|
| Lung Cancer | 85% |
| IPF (UIP) | 50-70% |
| CHF | 50% |
| Colorectal Cancer | 38% |
| Breast Cancer | 13% |
| Prostate Cancer | 2% |

## Prevalence of ILD

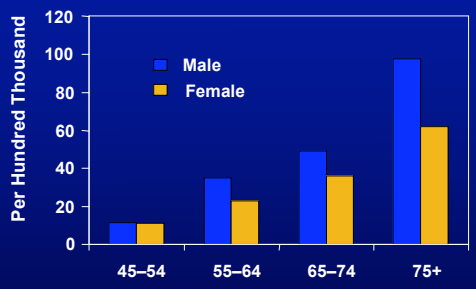
| | MALE | FEMALE |
|---|---|---|
| Occupational/ Environmental | 20.8 | 0.6 |
| Drug & Radiation | 1.2 | 2.2 |
| Rheumatologic | 7.1 | 11.6 |
| IPF | 20.2 | 13.2 |
| Pulm Fibrosis (Not IPF) | 10.1 | 14.3 |
| Sarcoidosis | 8.3 | 8.8 |

(per 100,000/year)

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

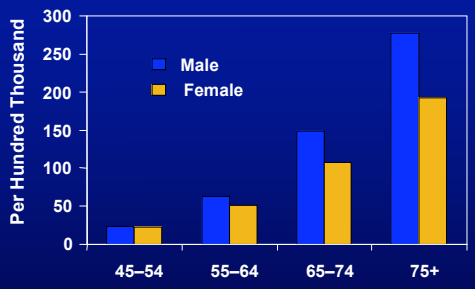
# Epidemiology of IPF

## Incidence




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

## Prevalence




Estimated 83,000 Current Patients in the United States

Weycker D, et al. Prevalence, Incidence, and Economic Costs of Idiopathic Pulmonary Fibrosis. Paper presented at: CHEST 2002, November 2-7, 2002; San Diego, CA.

# 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 $FEV_1$/FVC ratio**

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

## Pulmonary Function Testing

*Examples:*

| | Obstructive | Restrictive | Normal |
|---|---|---|---|
| FVC | 100% | 50% | >70% |
| FEV1 | 50% | 50% | >80% |
| FEV1/FVC | 43% | 90% | >70% |
| | | | |
| TLC | 100% | 65% | >80% |
| RV | 105% | 60% | |
| FRC | 95% | 55% | |
| DICO | 50% | 50% | >80% |

## ILD: PHYSIOLOGIC FINDINGS

- **Pulmonary function**
  - **Impaired gas exchange**
    - **Desaturation with exercise (pulse oxymetry)**
    - **Decreased $Pa_{O2}$**
    - **Increased A-a gradient**
    - **Decreased $DL_{CO}$**

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**

## 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

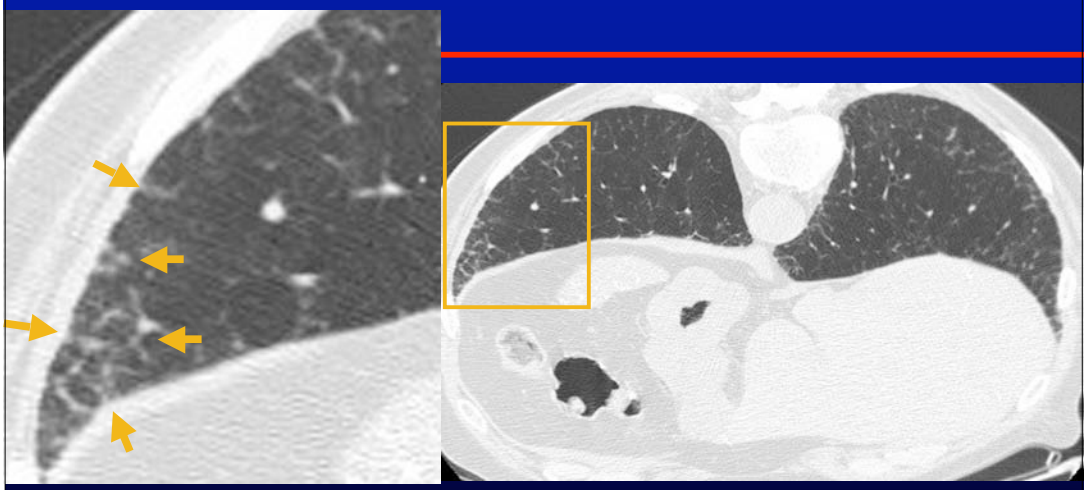
Degree of desaturation may have prognostic significance

## Desaturation during initial 6MWT predicts decreased survival:

| Disease | Desaturation | 4-Year Survival | |
|---|---|---|---|
| UIP (IPF) | Yes | 35% | |
| | No | 69% | n=83, p=0.0018 |
| NSIP | Yes | 66% | |
| | No | 100% | n=22, p=0.0089 |

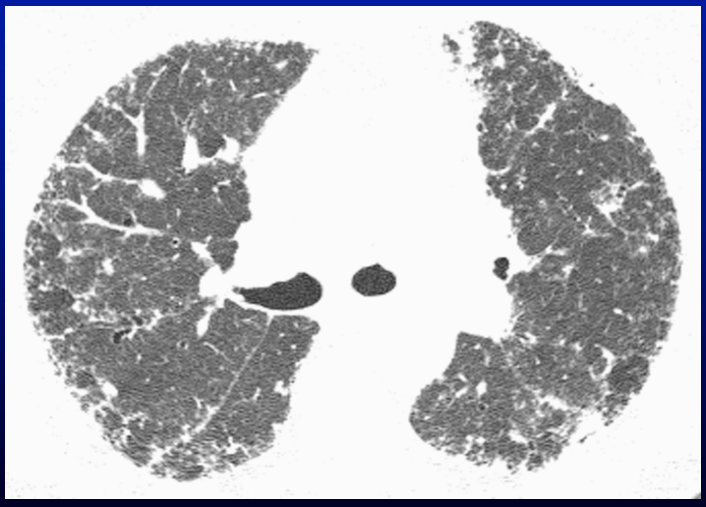
## ILD: PLAIN CHEST X-RAY

# ILD: Early HRCT Findings



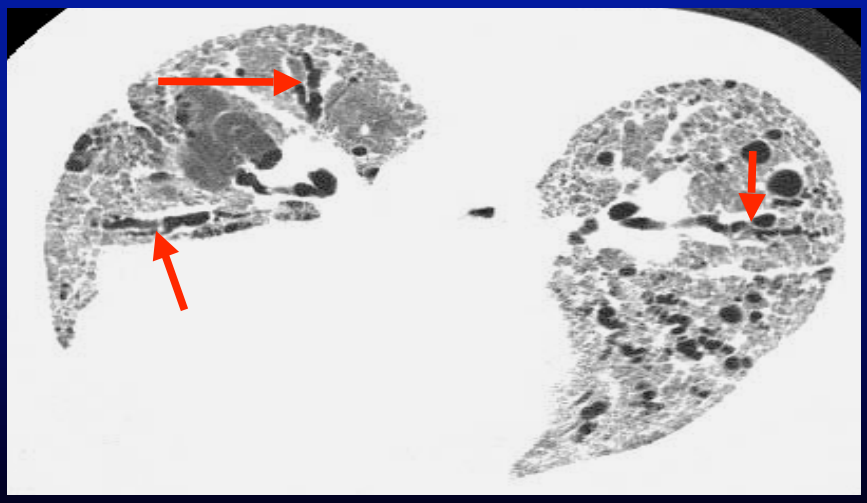
Courtesy of David A. Lynch, MD.

# ILD: Early HRCT Findings



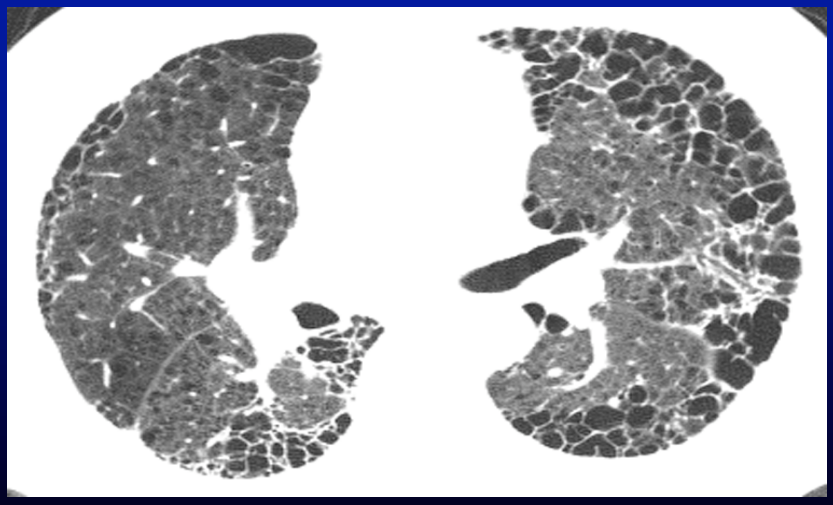
Courtesy of David A. Lynch, MD.

# ILD: Traction Bronchiectasis



Courtesy of W. Richard Webb, MD

# ILD: HONEYCOMBING



Courtesy of W. Richard Webb, MD.

## 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

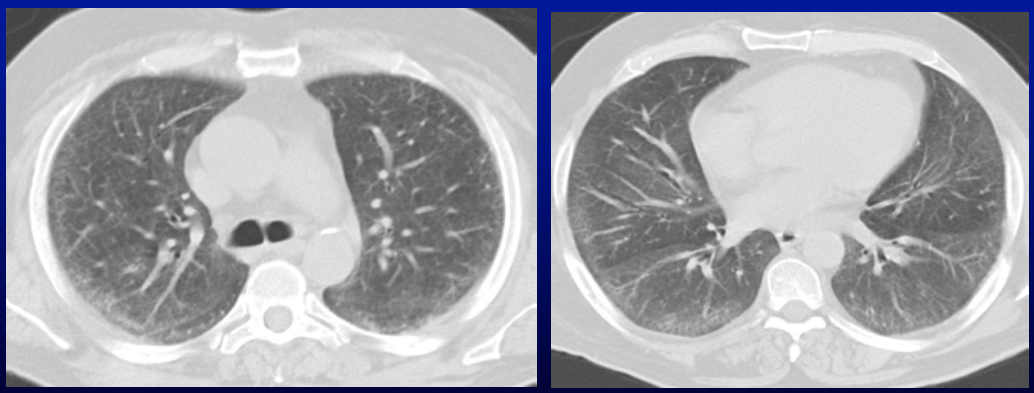
9/02: Persistent cough
Mild DOE

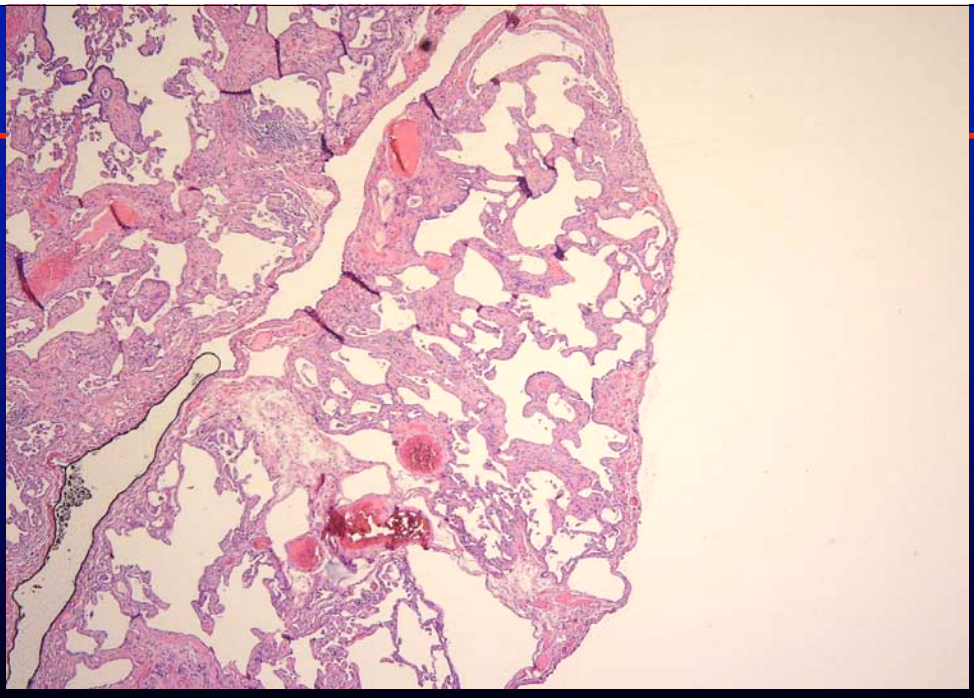
11/02: Extensive infiltrates, Restrictive PFT's

## Case Presentation: HPI

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

## CASE PRESENTATION: HRCT





## 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

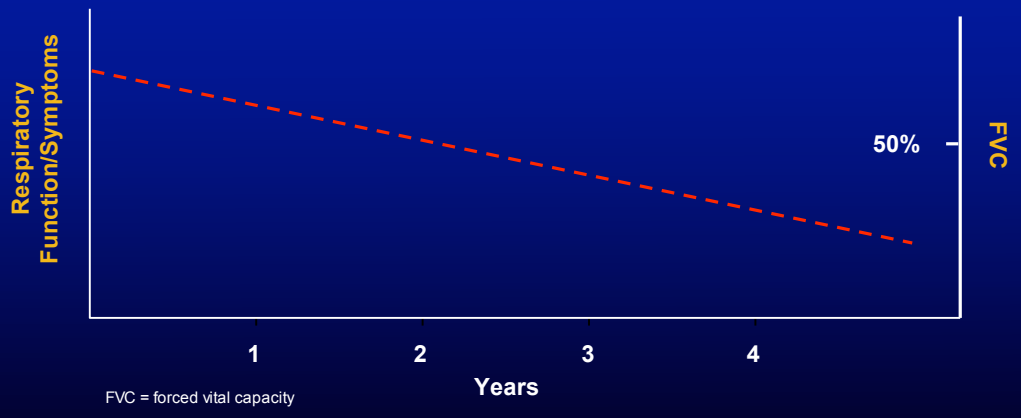
| DATE: | 1/03 | 3/03 | 4/03 | 7/03 | 9/03 |
|---|---|---|---|---|---|
| FVC | 2.5L (59%) | 2.6 | 3.0 | 3.1 | 2.9 |
| FEV1 | 2.2L (63%) | 2.3 | 2.7 | 2.8 | 2.7 |
| F/V | 88% | 88% | 90% | 90% | 91% |
| TLC | 3.7L (61%) | | | | |
| FRC | 2.0L (65%) | | | | |
| DLCO | 7.8L (24%) | | | | |
| SpO2 (R) |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

## Case Presentation: Exercise Physiology

| CPET | 1/8/03 | 10/7/03 |
|---|---|---|
| TIME | 7 min | 8 min |
| MAX WORK | 65 watts | 60 watts (32%) |
| VO2-max | 12.2 ml/min/kg (37%) | 11.1 (34%) |
| VE/VCO2 | 47 | 51 |
| MVV | 86 L/min (58%) | 124 (85%) |

# Progression of IPF: Acute Exacerbation vs Slow Decline

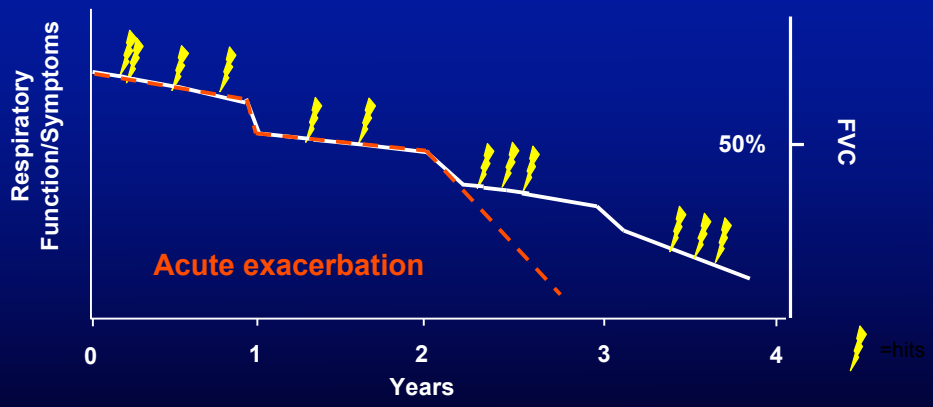
## Traditional View of UIP/IPF Progression




FVC = forced vital capacity

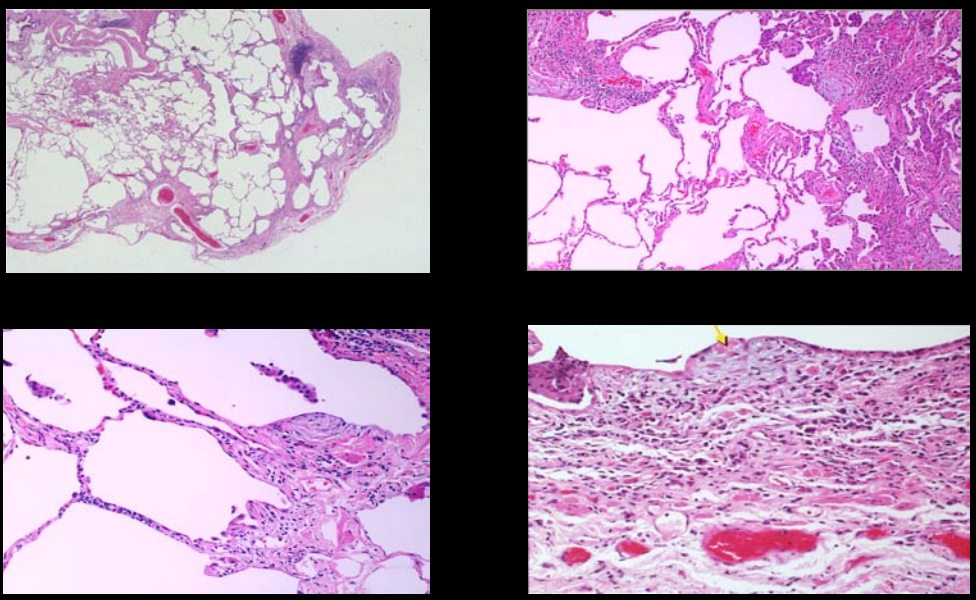
# Progression of IPF: Acute Exacerbation vs Slow Decline

## Step Theory of UIP/IPF Progression

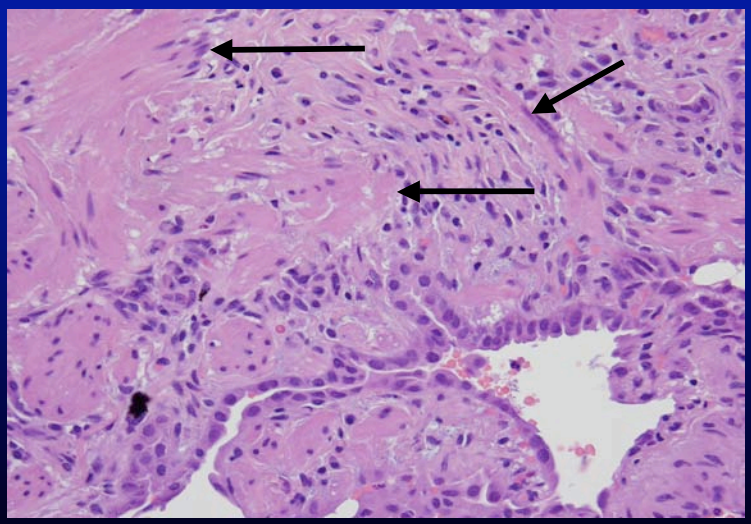



*Am J Respir Cell Mol Biol.* 2003;29(3 suppl):S1-S105.

## 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.*

Noble PW, Homer RJ. *Clin Chest Med*. 2004;25:749-758, vii.
Raghu G, Chang J. *Clin Chest Med*. 2004;25: 621-636, v.
Strieter R. *Am J Respir Cell Mol Biol*. 2003;29(3 suppl):S67-S69.

## 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


Noble PW, Homer RJ. *Clin Chest Med*. 2004;25:749-758, vii.
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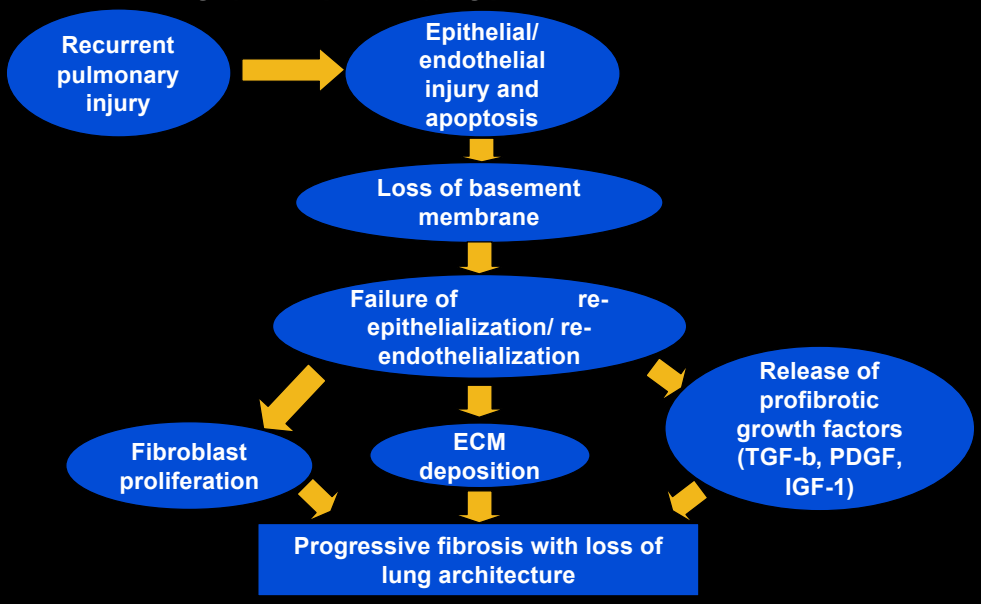
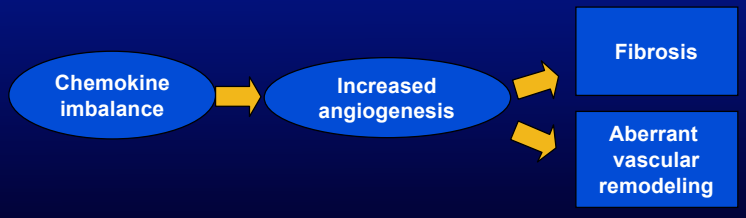
## Noninflammatory (multiple hit) Hypothesis




# 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

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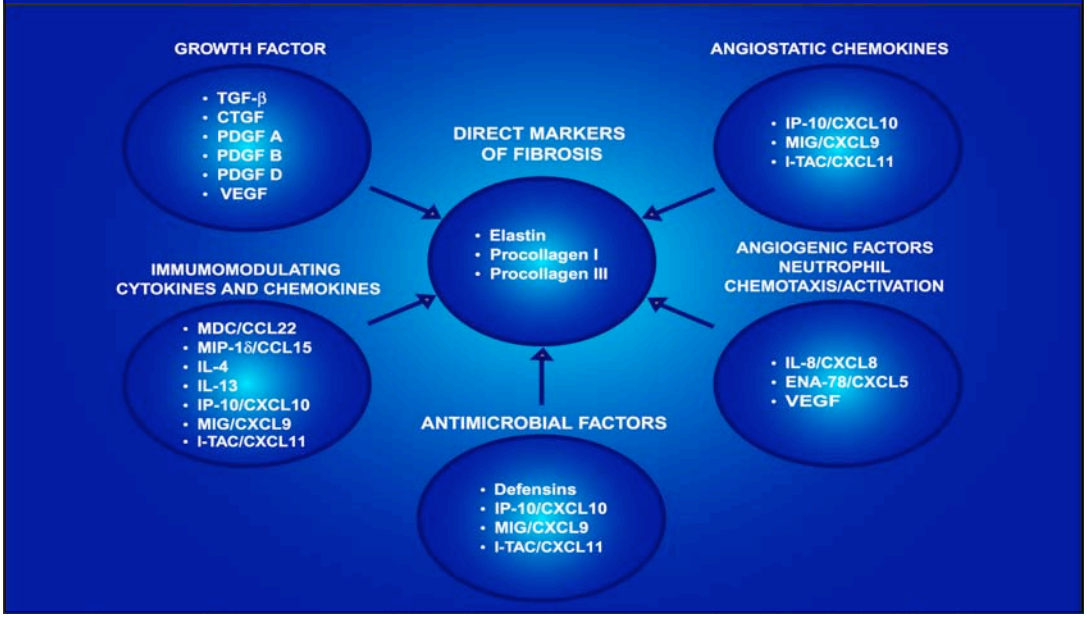
Strieter RM, et al. *Am J Respir Cell Mol Biol*. 2003;29(3 suppl):S67-S69.

## Defects in Host Defense Mechanisms May Contribute to Fibrosis

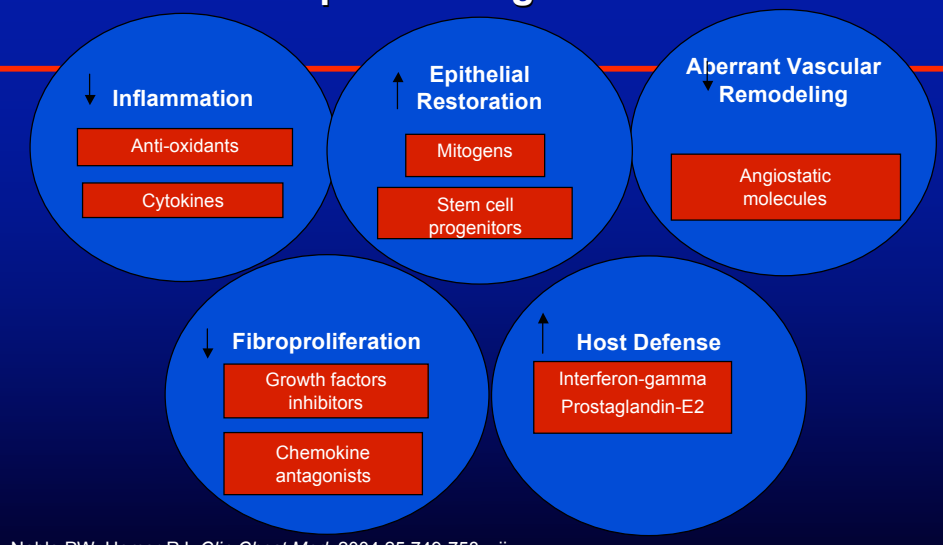
- Defects in endogenous host defense mechanisms (eg, IFN-g, PGE2 production) that limit fibrosis after acute lung injury may contribute to progressive fibrosis

Noble PW, Homer RJ. *Clin Chest Med*. 2004;25:749-758, vii

## IPF: Potential Contributing Pathways



## Potential Therapeutic Targets





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Selman M, et al. *Drugs*. 2004; 64:405-430.
Burdick MD, et al. *Am J Respir Crit Care Med*. 2005;171:261-268.


## 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

- Pulmonologists
- Lung pathologists
- Chest radiologists
- Exercise Physiologists
- Rheumatologists
- Transplant physicians
- Basic researchers
- Clinical coordinators
- Physical therapists
- Respiratory techs.
- Outside consultants
- Cardiologists
- Thoracic surgeons
- (Medical Informatics)

## Center for Interstitial Lung Disease

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