Diffuse Parenchymal Lung Disease

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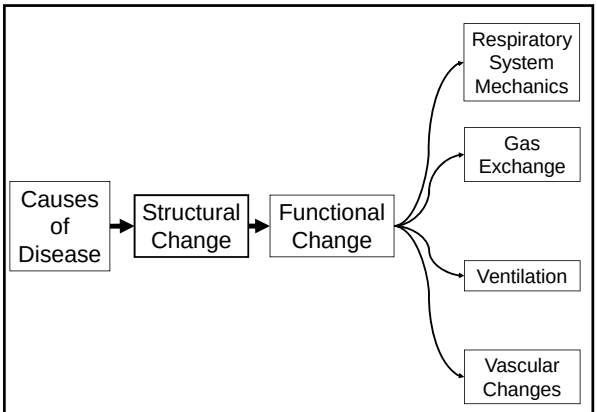
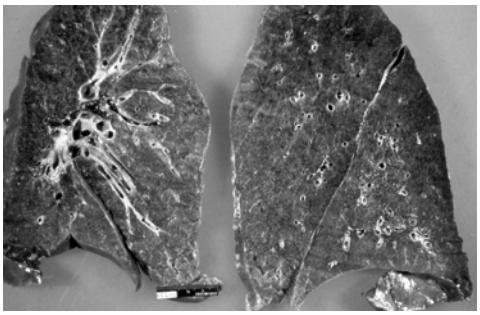
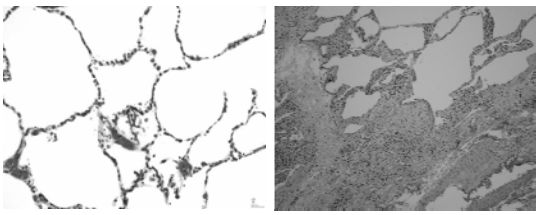


Compartments of the Lung



Courtesy *Alain Borczuk, MD*

Parenchymal Inflammation and Fibrosis



Normal Lung

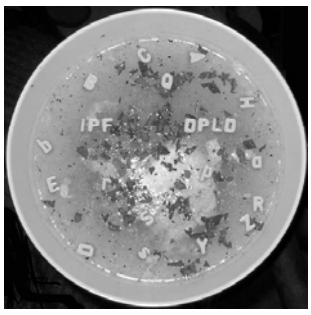
DPLD

Courtesy *Alain Borczuk, MD*

Overview

- Terminology and classification scheme
- Pathophysiology
- Clinical manifestations
- Pathogenesis
- Management

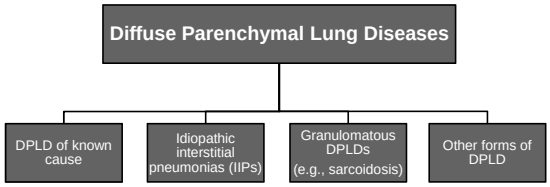
Alphabet Soup



Terminology

- Diffuse parenchymal lung disease (DPLD)
  A group of non-infectious, non-neoplastic lung diseases each characterized by varying degrees of inflammation and/or fibrosis of the parenchyma of both lungs.
- Interstitial lung disease (ILD)
  Old term for DPLD
- Idiopathic interstitial pneumonias (IIPs)
  A group of 7 DPLDs of unknown cause
- Idiopathic pulmonary fibrosis (IPF)
  The most common IIP (full definition to follow)
- Pulmonary fibrosis
  Non-specific term denoting bilateral parenchymal fibrosis

Spectrum of DPLD



ATS/ERS Guidelines for IIP. *AJRCCM* 2002:165:277-304.

Known Causes of DPLD

- Drugs (chemotherapy, antibiotics)
  – www.pneumotox.com
- Radiation
- Connective Tissue Diseases
- Occupational/Environmental
  – Inorganic antigens (Pneumoconioses)
  – Organic antigen (Hypersensitivity Pneumonitis)

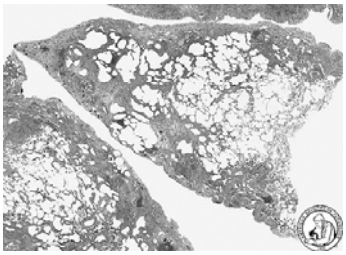
Idiopathic Interstitial Pneumonias
Classified by *histologic pattern*

Clinical-Radiologic-Pathologic Diagnosis	Histologic Pattern
Idiopathic pulmonary fibrosis (IPF)	Usual interstitial pneumonia (UIP)
Non-specific interstitial pneumonia (NSIP)	Non-specific interstitial pneumonia
Cryptogenic organizing pneumonia (COP)**	Organizing pneumonia
Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD)
Respiratory bronchiolitis-ILD (RB-ILD)	Respiratory bronchiolitis
Desquamative interstitial pneumonia (DIP)	Desquamative interstitial pneumonia
Lymphoid interstitial pneumonia (LIP)	Lymphoid interstitial pneumonia

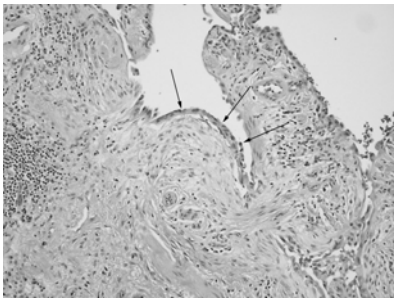
**Formerly known as *bronchiolitis obliterans-organizing pneumonia (BOOP)*

ATS/ERS Guidelines for IIP. *AJRCCM* 2002:165:277-304.

Usual interstitial pneumonia is the histologic pattern of IPF



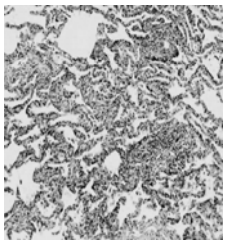
Fibroblastic foci are a key histological finding in UIP



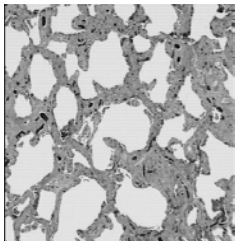
Visscher & Myers. *Proc Am Thorac Soc* 2006;3:322-9.

Non-specific interstitial pneumonia

Cellular NSIP

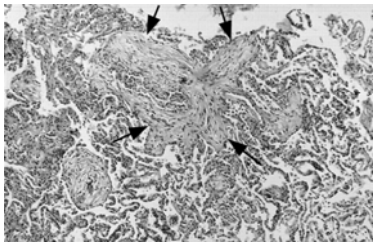


Fibrotic NSIP



Leslie K. O. Chest 2005;128:513S-519S

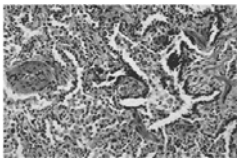
Cryptogenic Organizing Pneumonia



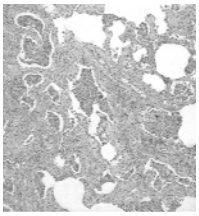
Lynch DA, et al. *Radiology* 2005;236:10-21.

RB-ILD and DIP are *smoking related diseases*

RB-ILD



DIP



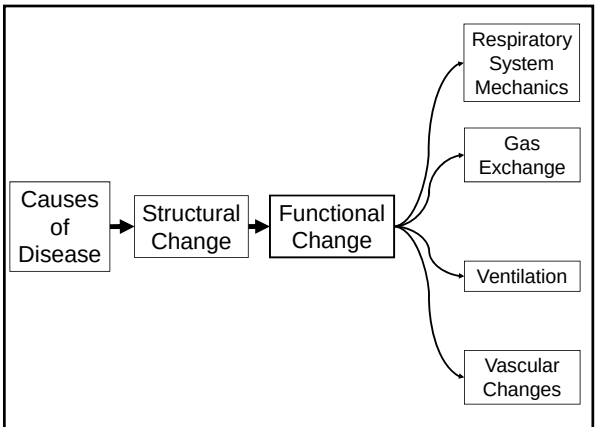
Ryu JH,et al. *Eur Respir J* 2001;17:122-32.
Caminati & Harari. *Proc Am Thorac Soc* 2006:3;299-306.

Selected other DPLDs

- Sarcoidosis
- Eosinophilic pneumonias
- Lymphangioleiomyomatosis
- Langerhan's cell histiocytosis

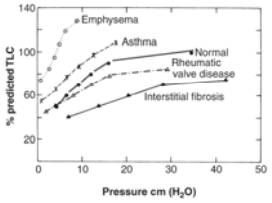
Related Diseases Involving the Lung Parenchyma

- Alveolar filling diseases
  - Pulmonary edema
  - Acute respiratory distress syndrome (ARDS)
  - Alveolar proteinosis
  - Diffuse alveolar hemorrhage
- Vascular diseases
  - Lymphangitic carcinomatosis
  - Pulmonary vasculitis

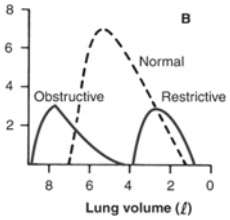


Respiratory System Mechanics in DPLD

Pressure-Volume Curves



Reduced Lung volumes



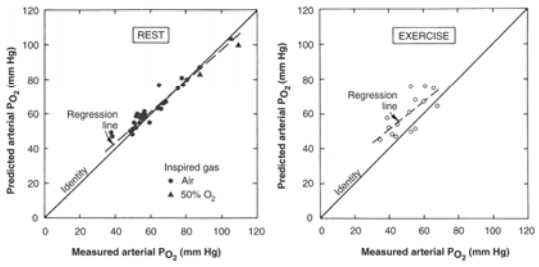
West, JB. Pulmonary Pathophysiology: The Essentials, 2008

DPLD leads to a *restrictive ventilatory defect*

- Reduced lung volumes
  - Total lung capacity**
  - Forced vital capacity
  - FEV_1
- Typically, no airflow obstruction

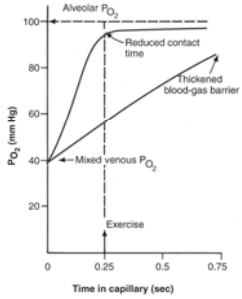
**Reduced TLC = restrictive ventilatory defect

Gas exchange in DPLD



West, JB. Pulmonary Pathophysiology: The Essentials, 2008

Changes in pulmonary capillary PO_2



West, JB. Pulmonary Pathophysiology: The Essentials, 2008

DPLD leads to *impaired gas exchange*

- V/Q mismatch
- Diffusion impairment *only with exercise*
- Shunt does *not* play a role

What about *ventilation* and *vascular changes*?

- Alveolar hyperventilation
  - Hypoxemia
  - Abnormal mechanics and load
- Vascular disease is common
  - Intimal hyperplasia
  - Medial hypertrophy
  - Pulmonary hypertension is typically not severe

Clinical Manifestations of DPLD

DPLDs share many clinical features

Similarities

- Dyspnea
  - progressive
  - exertional
- Cough
  - non-productive
- Bibasilar crackles
- Restrictive ventilatory defect
- Impaired gas exchange
- Abnormal lung imaging

Differences

- Extrapulmonary findings
  - sarcoidosis
  - connective tissue disease
- Pattern on lung CT
- Histopathology

Case

Case

- 54 year old man comes to see you because of two years of dyspnea
  - First, while mowing his lawn
  - Then, more dyspneic than his wife in the gym
  - Now dyspneic with most activities at home.
- Dry cough (no sputum) and occasional joint pains.
- No wheezing or hemoptysis.
- No fever or chills.
- No chest pain, orthopnea, PND, or edema.
- No rash, visual changes, Raynaud's phenomenon, dysphagia, or heartburn

Case

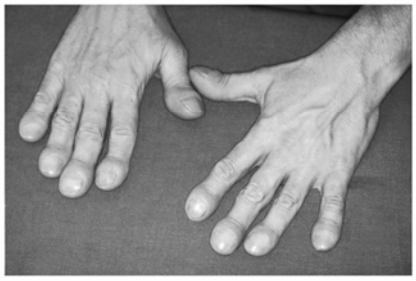
- Past medical history
  - Osteoarthritis
  - Hypercholesterolemia
- Past surgical history
  - None
- Medications
  - Simvastatin, multivitamin, acetaminophen
- No known drug allergies

Case

- Family history
  - No lung disease
  - Mother 85 yo – alive and well
  - Father died at 74 with heart failure
  - Sister with ovarian cancer
- Social history
  - Smoked one pack per day for 35 years (35 packyears). Quit 3 years ago
  - No alcohol or drug use
  - No pets, humidifiers, or hot tubs
  - Real estate agent. No military or construction work

Exam

- BP 118/80 mm Hg; pulse 103; RR 28; T 99.7°
- S_pO_2 92% breathing room air.
- No JVD.
- Rapid, shallow breathing. Chest symmetric. No accessory muscle use. Bibasilar crackles halfway up bilaterally. No wheezes or rhonchi.
- S1, S2 were normal. Regular rhythm. No murmur, rub, or gallop.
- No cyanosis.



NEJM, 2001

PFTs

New York Presbyterian Hospital
Columbia Presbyterian Medical Center
622 West 168th Street New York, NY 10032

Adult Pulmonary Diagnostic Unit

Patient:
Age: **Gender: Male**
Height: 68 in (173 cm) **Weight: 193 lb (87.5 kg)**
Body Mass Index: 29.24

Spirometry		Ref	Pre Meas	Pre % Ref
FVC	Liters	4.55	2.94	65
FEV1	Liters	3.63	2.30	63
FEV1/FVC	%	80	78	
FEF25-75%	L/sec	3.57	2.18	61
FEF25%	L/sec	7.79	6.48	83
FEF50%	L/sec	4.28	3.38	79
FEF75%	L/sec	1.62	0.72	44
PEF	L/sec	8.31	7.99	96
MVV	L/min	140	128	92
PIF	L/sec	3.85	5.21	136
FIF50%	L/sec	4.85	5.08	105
FET100%	Sec		7.26	

Lung Volumes				
VC	Liters	4.55	3.09	68
TLC	Liters	6.60	4.50	68
RV	Liters	2.04	1.41	69
RV/TLC	%	31	31	
FRC PL	Liters	3.37		
FRC N2	Liters	3.37	2.59	77
FRC He	Liters	3.37		
Vtg	Liters			

Diffusion				
DLCO	mL/mmHg/min	33.6	10.7	32
DL Adj	mL/mmHg/min	33.6	10.6	31
VA	Liters		3.72	
DLCO/VA	mL/mHg/min/L	5.21	2.87	55

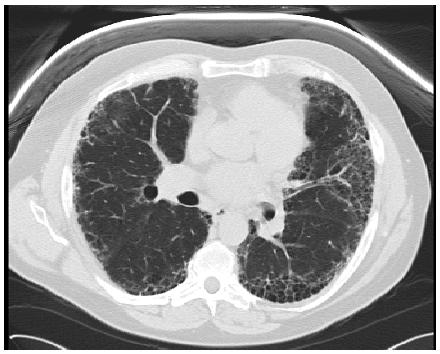
Arterial Blood Gases

Level		Sit@12:42
FIO2	%	21.00
pH		7.43
PCO2	mmHg	36.2
PO2	mmHg	69.3
HCO3	meq/L	24.4
Hb	gm/dL	15.0
%HbCO	%	1.0
SaO2	%	93.6
P(A-a)O2	mmHg	38.4

Six-minute walk test

- Distance walked : 1778 ft
- Resting S_pO_2: 93%
- Exercise S_pO_2: 88%

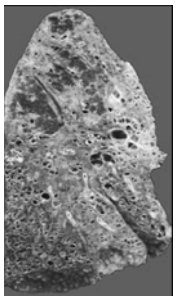
Normal chest CT



Questions

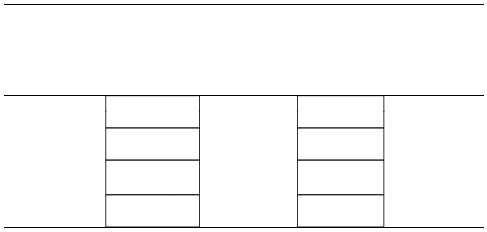
- Why does he have dyspnea?
- What are the mechanisms of hypoxemia in this patient?
- Why did oxyhemoglobin saturation decrease during exercise?
- What's the diagnosis?

Idiopathic pulmonary fibrosis



- Most common IIP
- Prototypical form of DPLD
- Usual interstitial pneumonia
- Risk factors
  - Older age
  - Male gender
  - Cigarette smoking
  - Family history

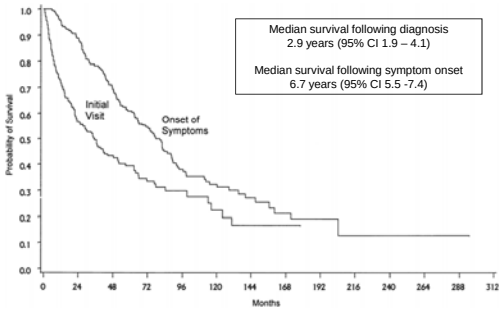
Epidemiology of IPF



*PYO = patient-years of observation

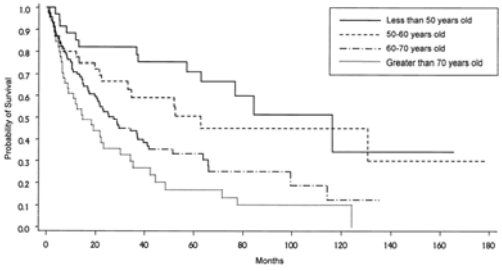
Coultas et al. *Am J Respir Crit Care Med* 1994;150:967-72.

Survival in IPF



King et al. *Am J Respir Crit Care Med 2001;*164:1171-81.

Age Influences Survival in IPF

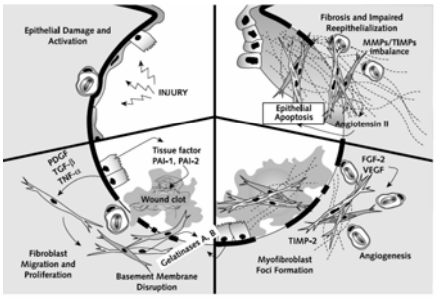


King et al. *Am J Respir Crit Care Med 2001;*164:1171-81.

Proposed Causes of IPF

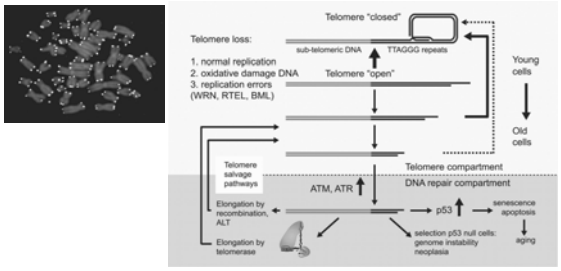
- Cigarette smoking
- Viral-induced inflammation
- Occult environmental/occupational exposures
- Gastroesophageal reflux

Pathogenesis of IPF



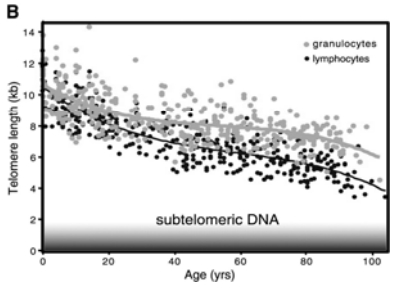
Selman, M. *Ann Int Med*. 2001

A Role for Telomere Length in IPF



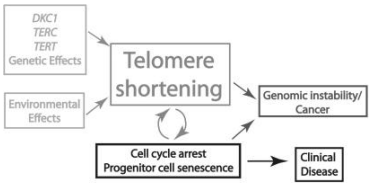
Aubert, G. et al. Physiol. Rev. 88: 557-579 2008

Telomere Length Decreases with Age



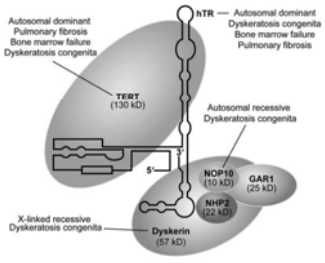
Aubert, G. et al. Physiol. Rev. 88: 557-579 2008

Telomeres and cellular senescence



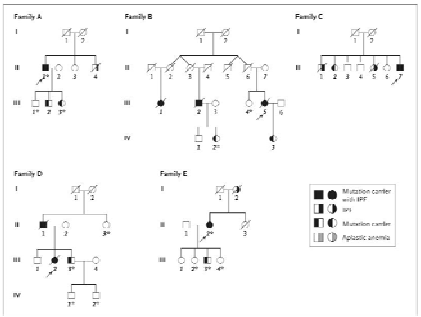
Aubert, G. et al. Physiol. Rev. 88: 557-579 2008

Telomerase mutations are associated with pulmonary fibrosis



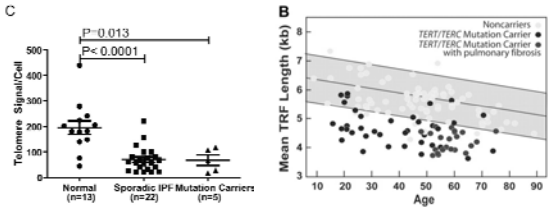
Garcia et al. *Nucleic Acids Res* 2007; 35:7406-16

Telomerase mutations in familial IPF



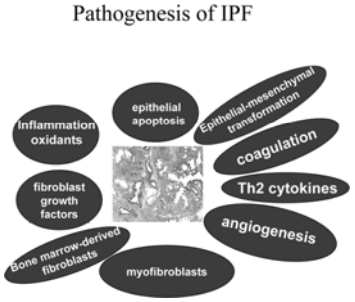
Armanios et al. *NEJM* 2007;356:1317-26

Telomere length is reduced in IPF



Alder JK et.al. PNAS 2008;105:13051-13056
Cronkhite, JT. et al. AJRCCM 2008;178:729-37

Other mediators in IPF



Noble and Homer. AJRCCM 2005:33:113-120

What about other DPLDs?

- Injurious triggers
  - Autoimmune mediated inflammation
  - Drug-induced injury
  - Radiation-induced injury
  - Eosinophil degranulation
  - Hypersensitivity reaction

Management of DPLD

- Biopsy often required to make a diagnosis
  - Surgical lung biopsy
  - Transbronchial lung biopsy (less useful)
- Oxygen therapy
- Pulmonary rehabilitation

Treatment of DPLD

- Injury avoidance
  - Inhaled agents
  - Offending drug
- Anti-inflammatory therapy
  - Treat underlying inflammatory diseases
  - Trial of corticosteroids for documented parenchymal inflammation
  - Steroid-sparing agents
- Lung transplantation