

# Lung Disease in Systemic Sclerosis: New Insights and Treatment Options

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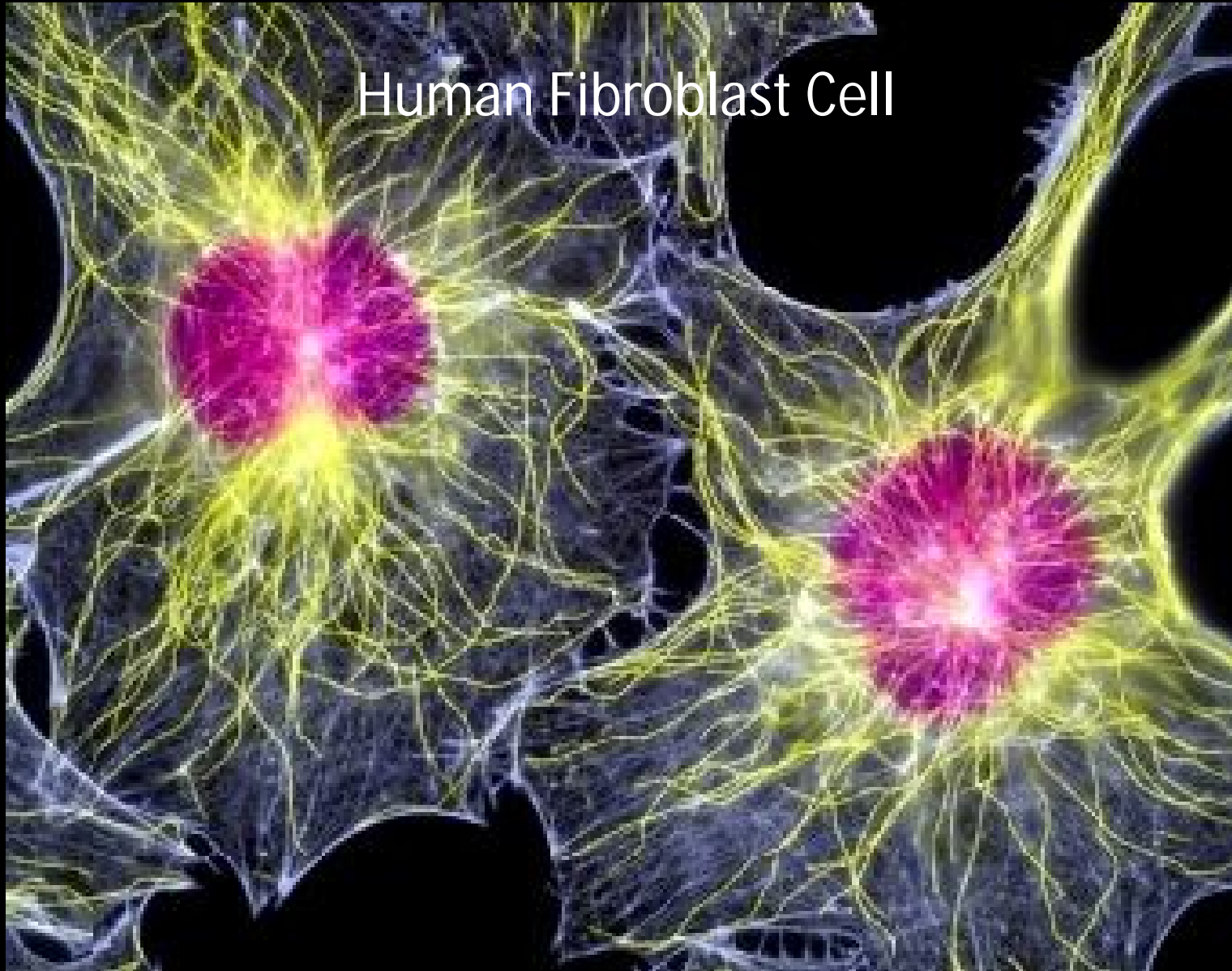
# Lung Disease in Systemic Sclerosis: New Insights and Treatment Options

- Pathophysiology
- Lung Disease
- Current therapies
- Future targets for therapy

Man knows much more than he  
understands.

ALFRED ADLER

# Human Fibroblast Cell



# Systemic Sclerosis Pathophysiology: What goes wrong?

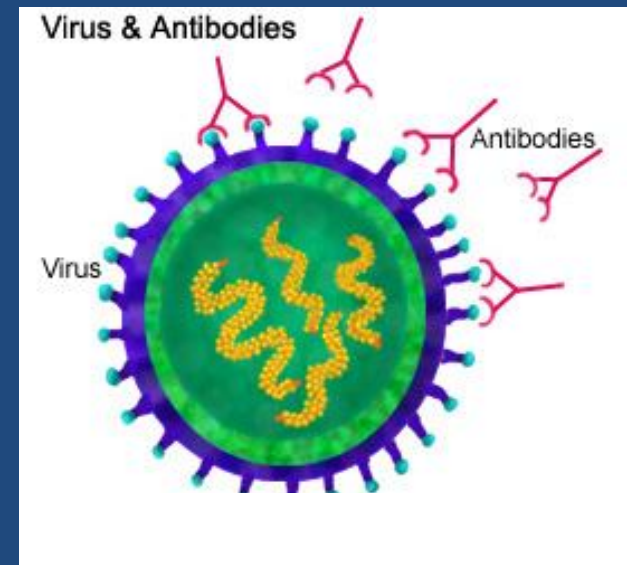
- Auto antibodies
- Skin thickening
- Abnormal blood vessels

# Systemic Sclerosis Pathophysiology: What goes wrong?

- Auto antibodies
- Skin thickening
- Abnormal blood vessels

# Auto Antibodies

- Self-made proteins
- Attach and “attack”
- Auto antibodies attack self
- Most common ABs in SSc
  - Scl-70
  - Anti-centromere
  - U3-RNP



# Other Auto-Immune Diseases

- Rheumatoid arthritis
- Sjogren's disease
- Systemic lupus
- Inflammatory bowel disease
- Thyroid disease
- Celiac sprue
- Etc., etc., etc.



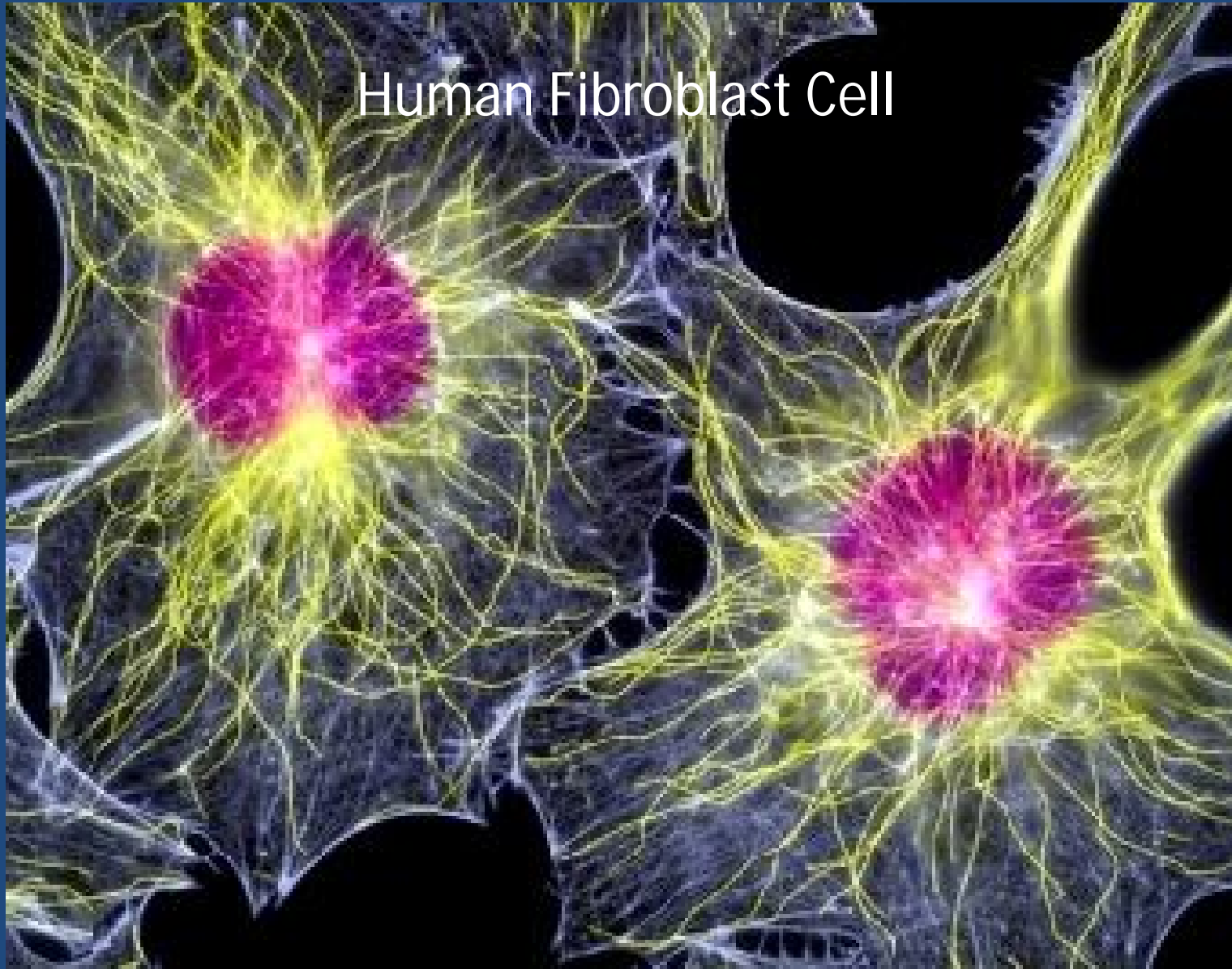
# How do we know the immune system is involved in SSc?

- Auto antibodies >90% pts with SSc
- Immunologic activation is present
  - Elevated levels of growth factors, chemokines, cytokines, white blood cells
- Suppressing the immune system may help in some patients

# Pathophysiology: What goes wrong?

- Auto antibodies
- Skin thickening
- Abnormal blood vessels

# Human Fibroblast Cell

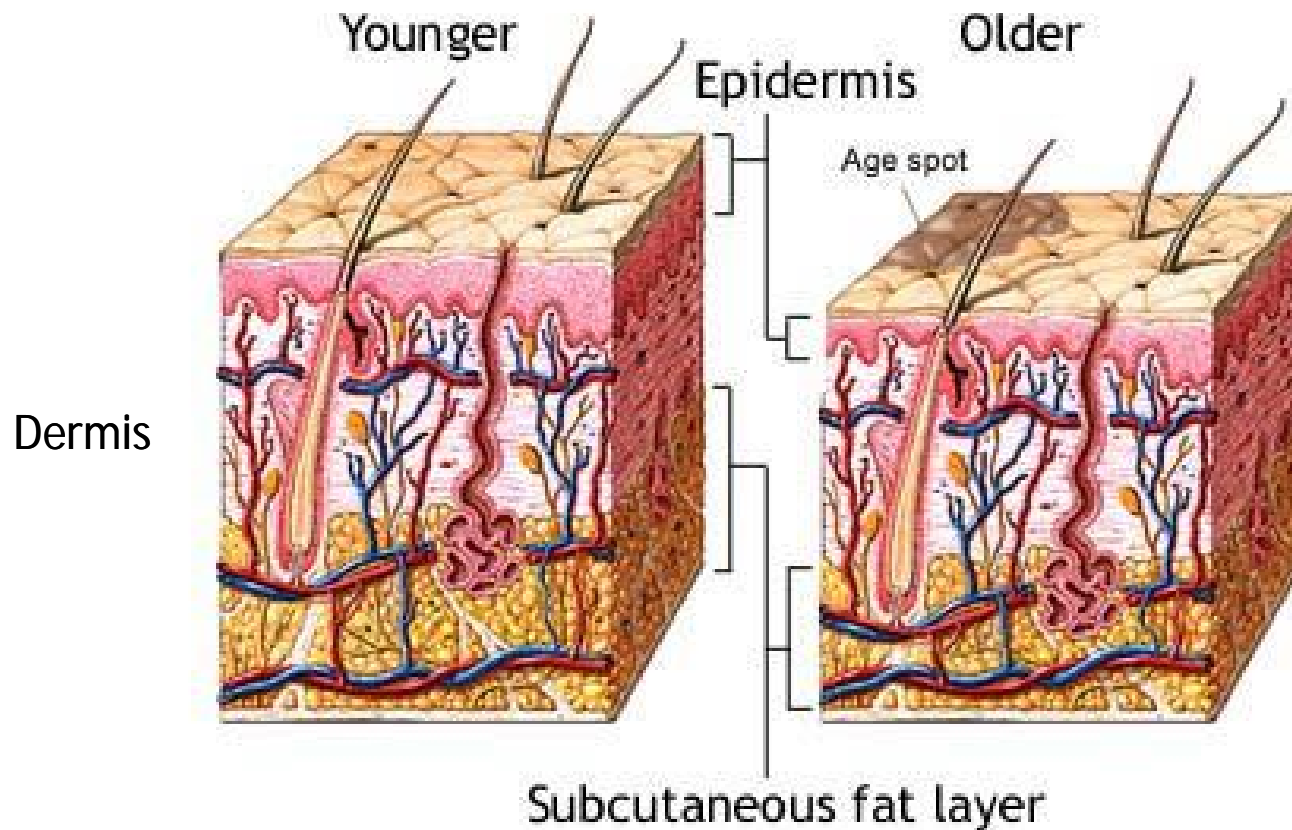




- Made by fibroblasts
- 25-35% of all protein in the body
- Only made by animals
- Gives structure to tendons, skin, bones, cartilage

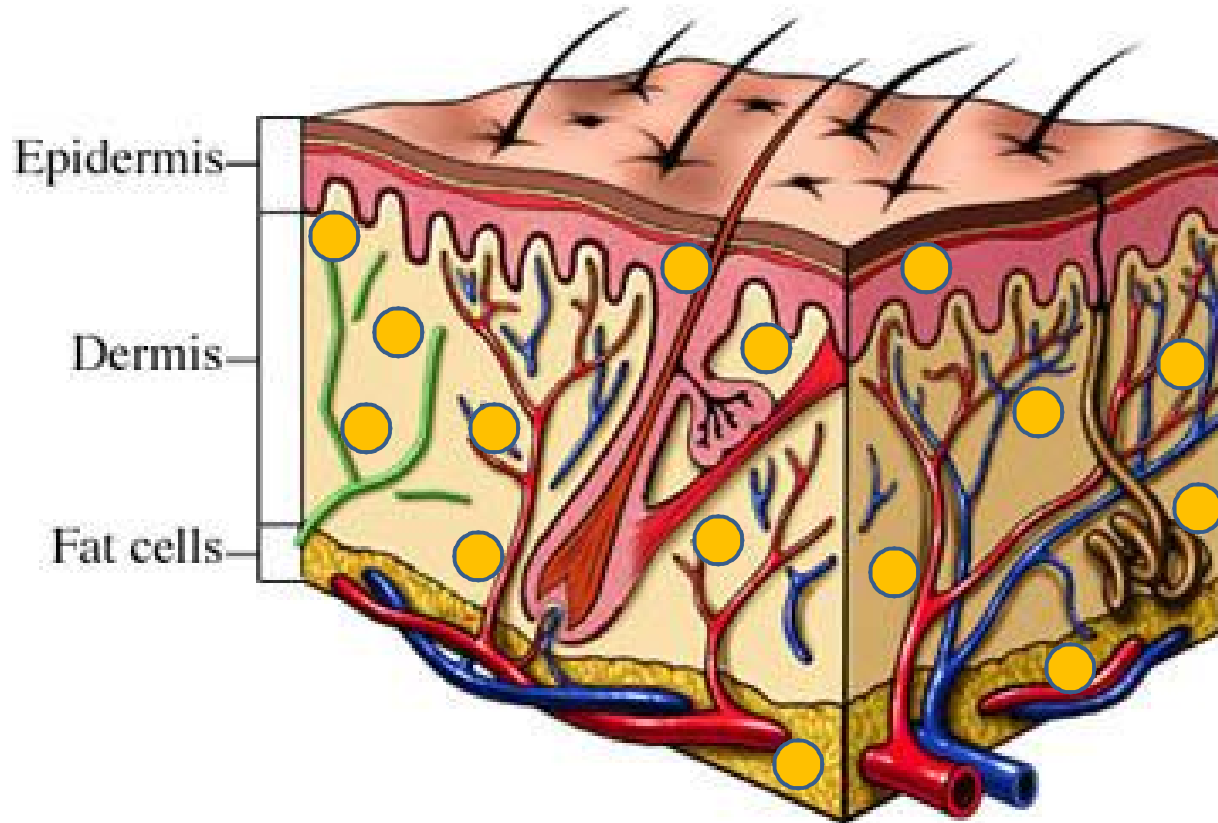


# Normal Aging



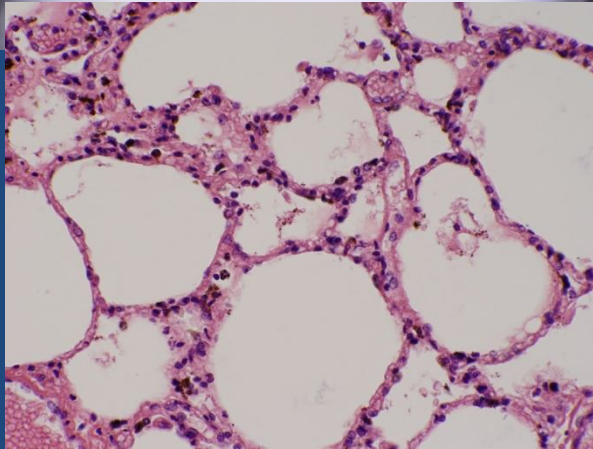
- Thinning of all layers of the skin
- Loss of collagen support in the epidermis and dermis

# Scleroderma Skin Changes

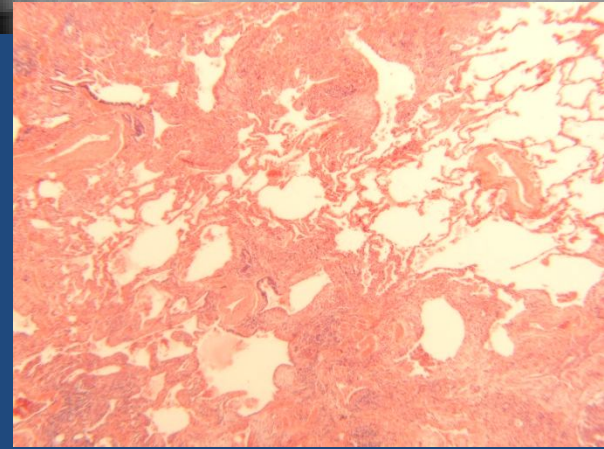


● = Collagen

Normal Lung



Interstitial Lung Disease





# Pathophysiology: What goes wrong?

- Auto antibodies
- ~~Skin thickening~~ Fibroblasts gone wild
- Abnormal blood vessels

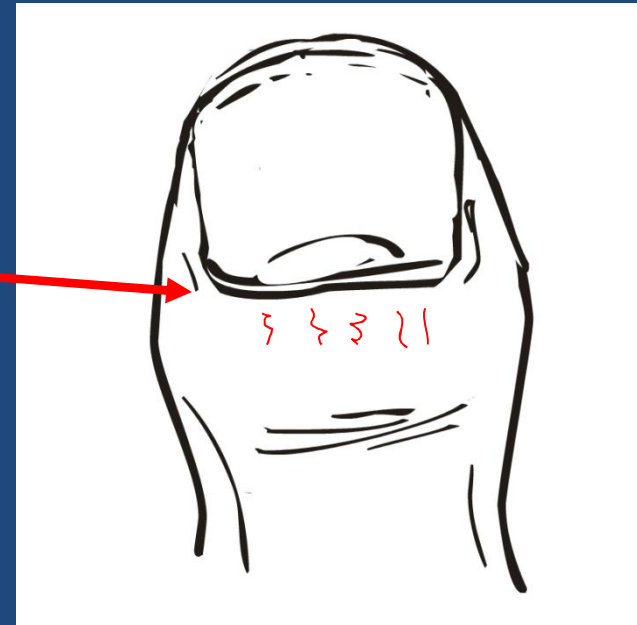
# Pathophysiology: What goes wrong?

- Auto antibodies
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Nailfold



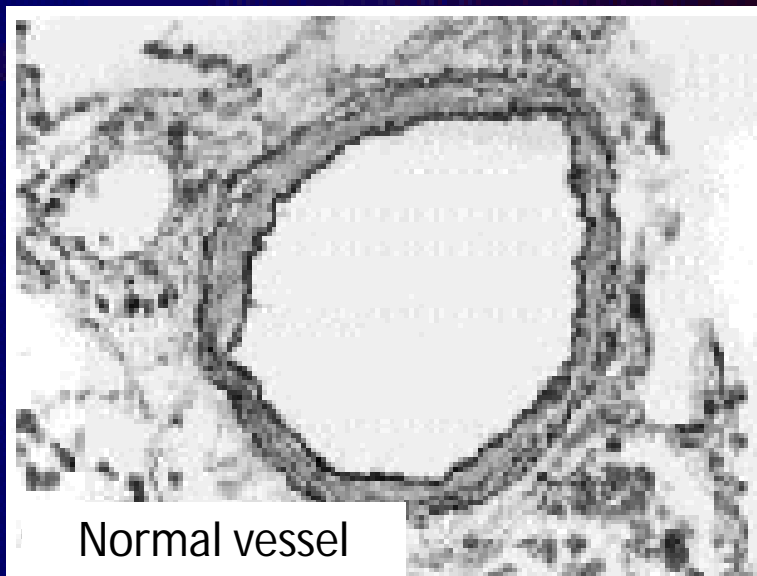
### Nailfold Capillaroscopy

- increased diameter
- reduced numbers
- increased visibility
- bushy and bizarre shapes
- punctate haemorrhages

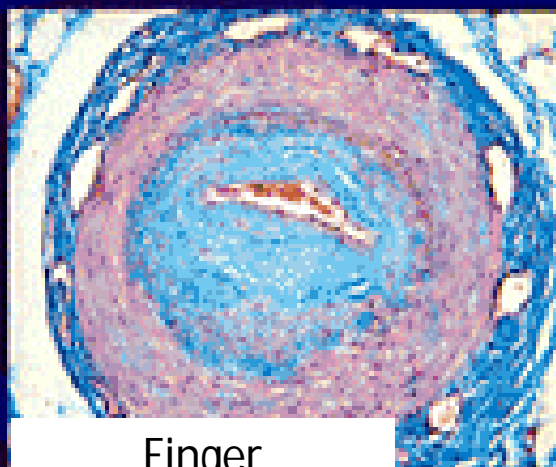
# Common vascular pathology in multiple sites



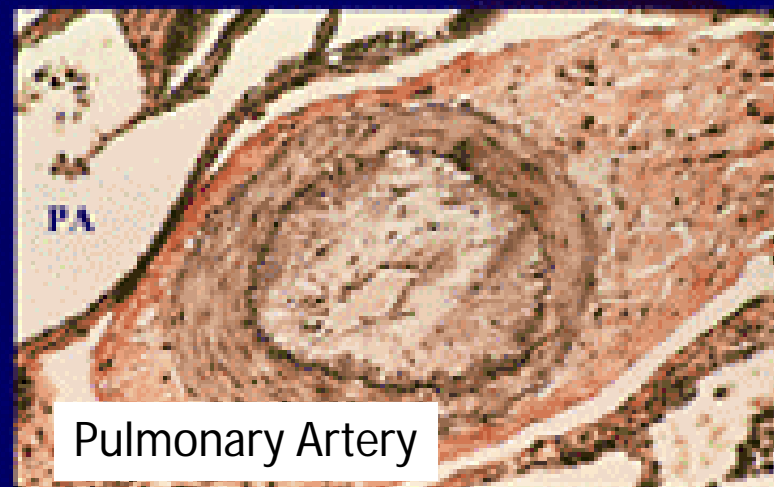
Kidney



Normal vessel



Finger



Pulmonary Artery

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- Pathophysiology
- Lung Disease
- Current therapies
- Future targets

# Clinical Signs of Lung Involvement

- Shortness of breath
- Cough
- Fatigue
- Chest tightness or discomfort
- Exercise intolerance

# Non-Pulmonary Causes of Symptoms

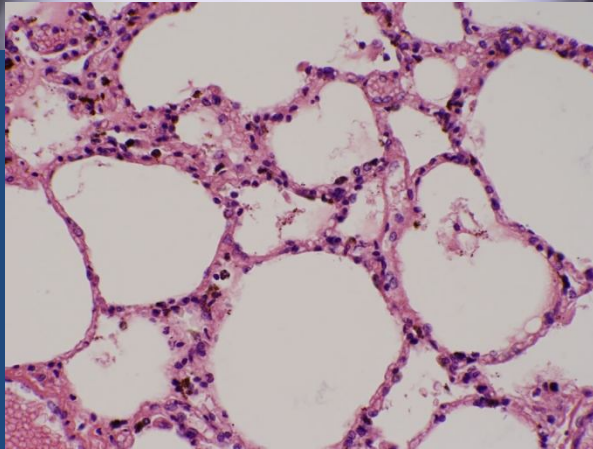
- Anemia
- Chest restriction due to skin involvement
- Arthritis/Fibromyalgia
- Obesity
- Heart disease



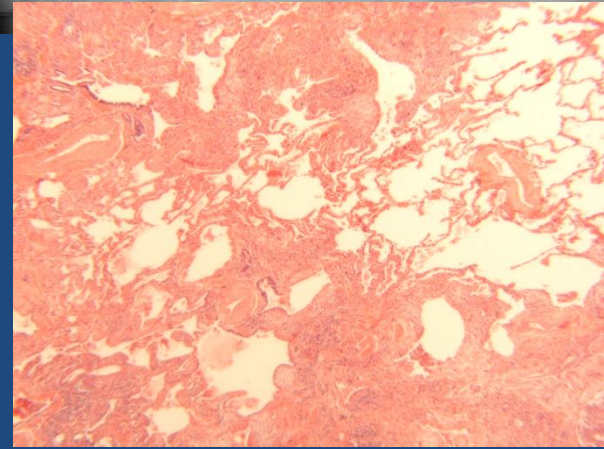
# Systemic Sclerosis and Lung Disease

- Interstitial lung disease
- Pulmonary hypertension
- Less common lung conditions
  - BOOP, alveolar hemorrhage, bronchiectasis

Normal Lung

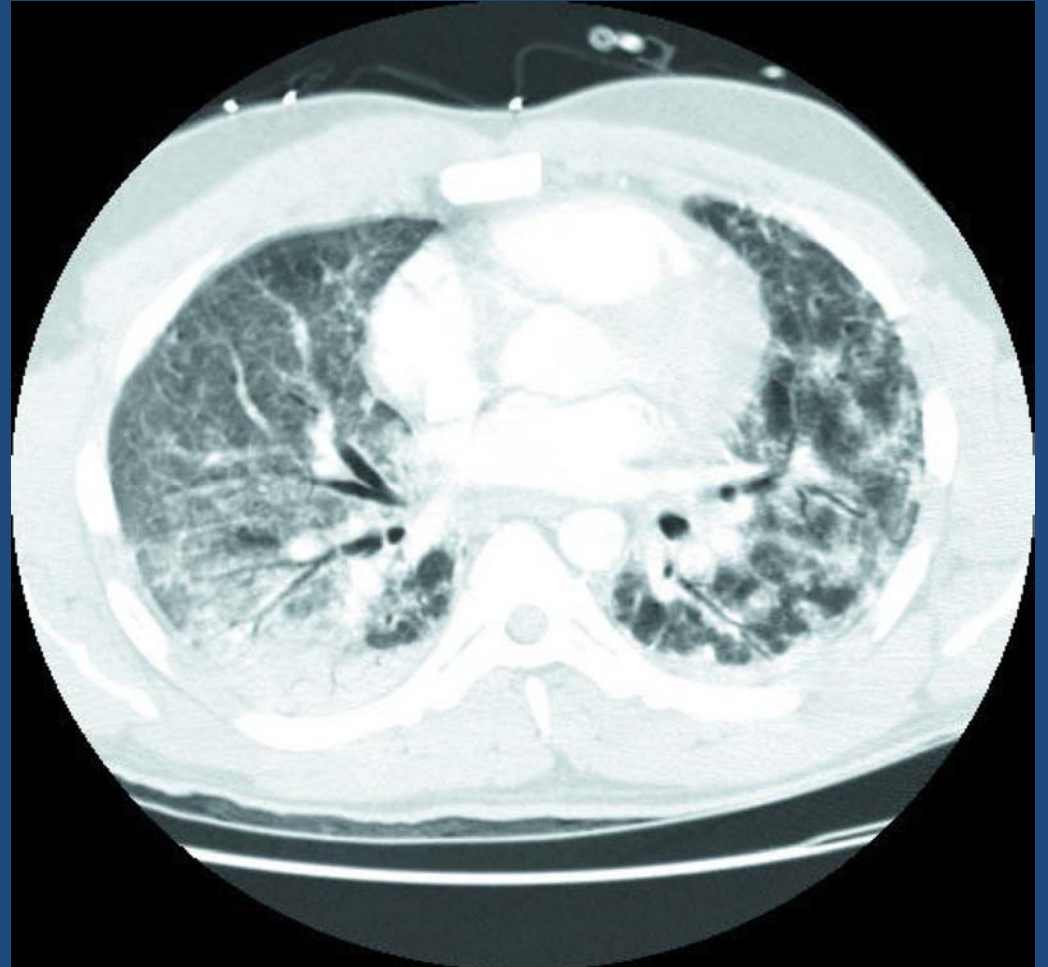


Interstitial Lung Disease



## Diagnosing ILD

- High Resolution Cat Scan (HRCT)
- Pulmonary function testing
- Bronchoscopy
- Lung biopsy



# Interstitial Lung Disease

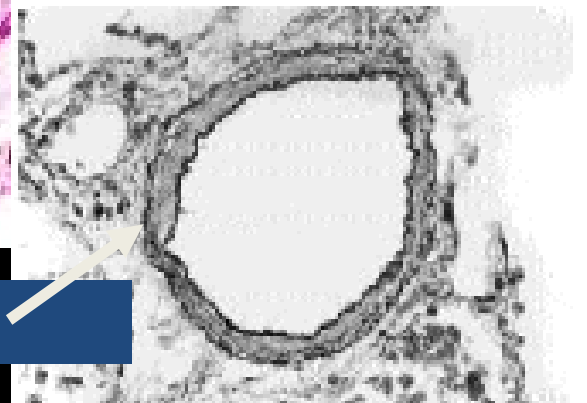
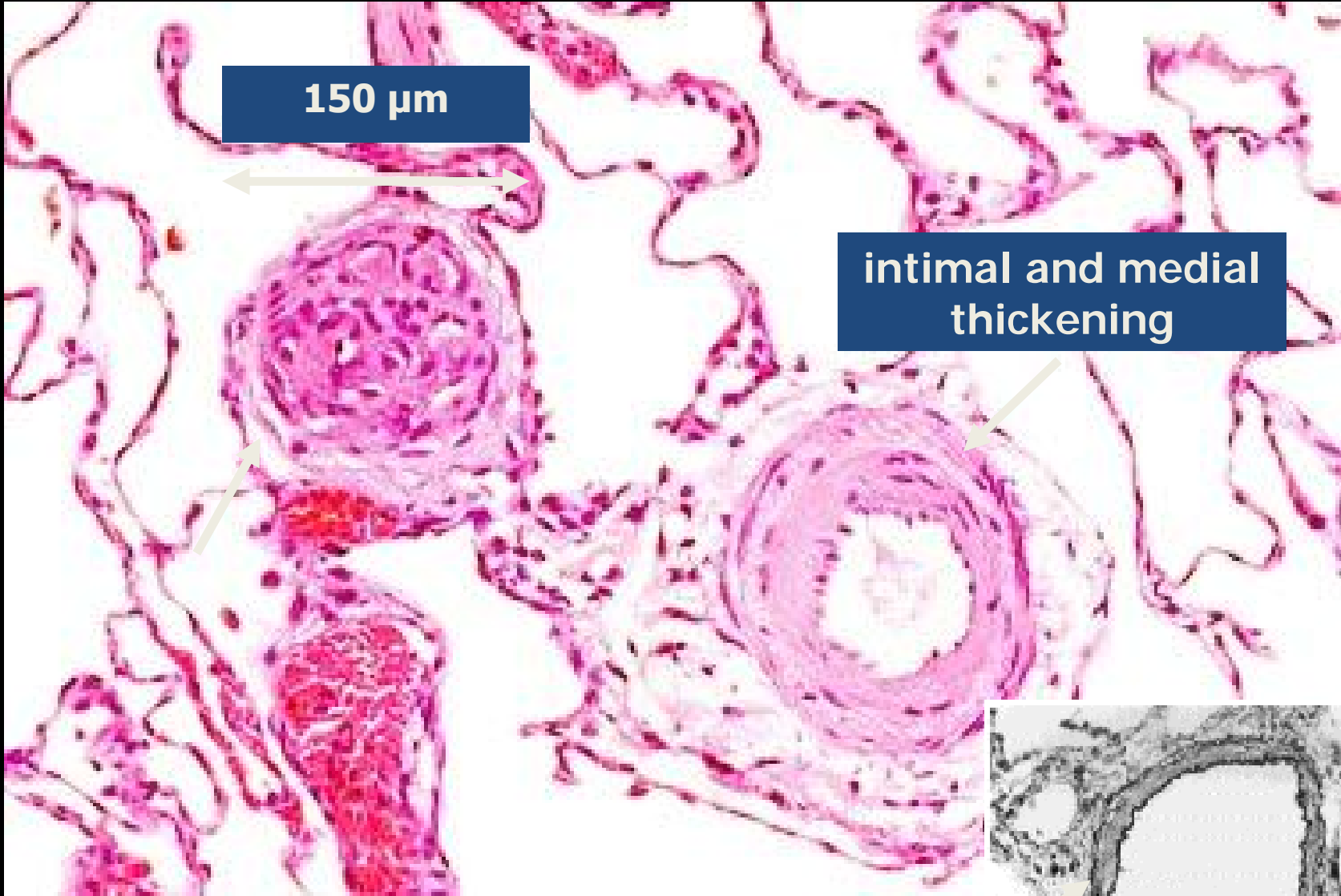
- Increased fibroblasts and collagen in the walls of the air sacs of the lung
- Other names: Scleroderma lung, pulmonary fibrosis, fibrotic lung disease

# Interstitial Lung Disease

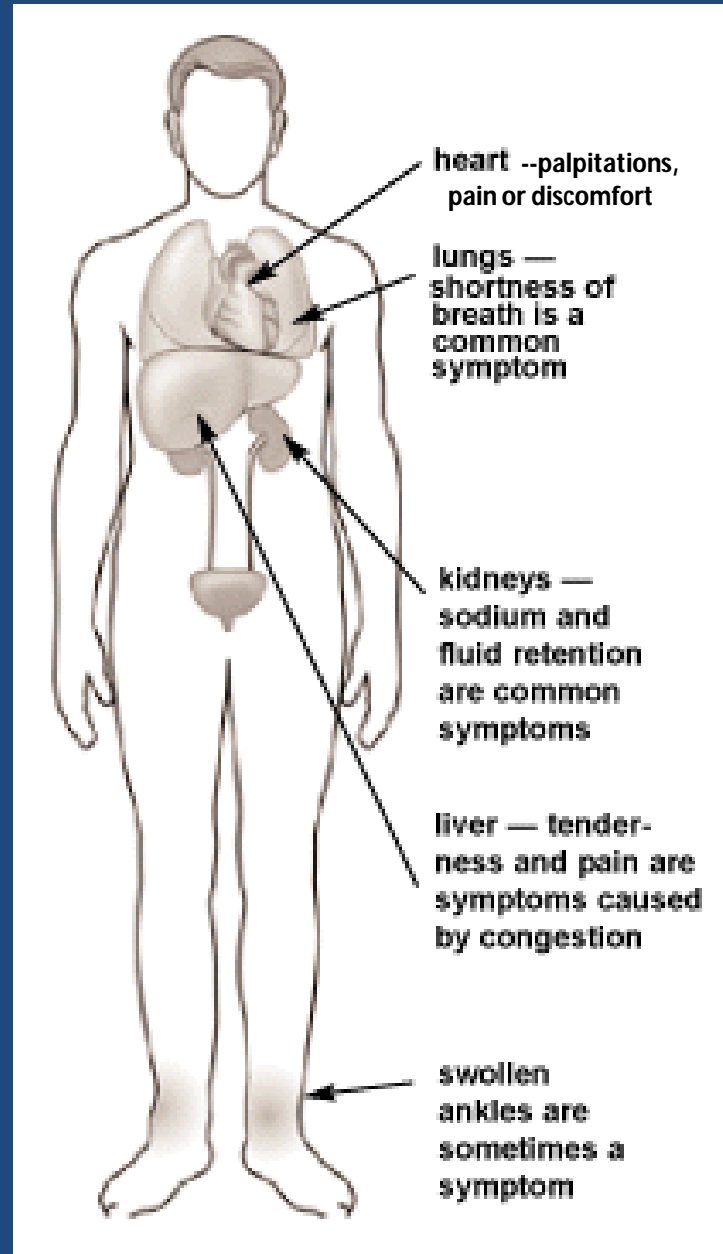
- 55-90% of all SSc patients have ILD
- Associated with Scl-70 antibody
- GERD/aspiration is a cofactor
- Progressive disease:
  - >20% on initial CT increases risk for progression
  - more common with dcSSc
  - warrants consideration of treatment

# Pulmonary Hypertension = Pulmonary Artery Hypertension (PAH)

- Increased fibroblasts and collagen in the arteries of the lung
- Obstruction to flow:
  - Increased pressure in the blood vessels
  - Back-up of fluid in the legs
  - Impaired oxygen uptake



# Symptoms of Pulmonary Hypertension

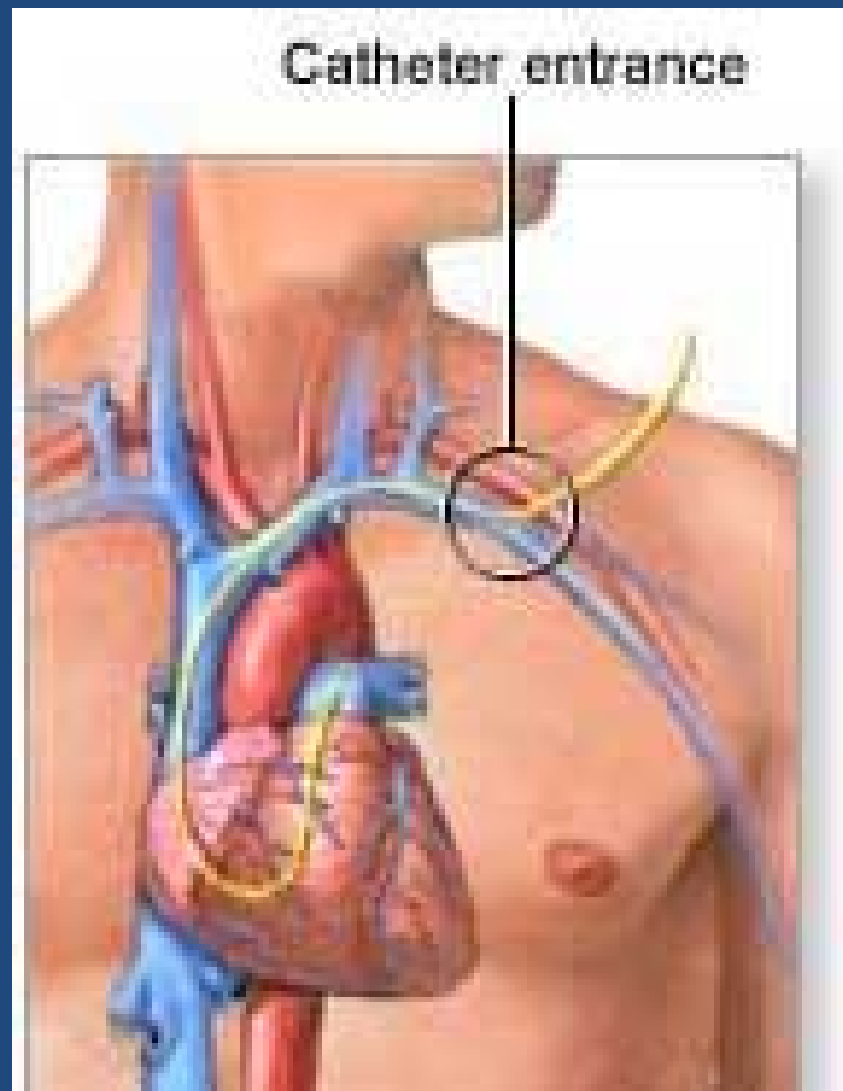




# Pulmonary Artery Hypertension (PAH)

- Prevalence estimates 5-50% in SScI
- Higher prevalence in limited systemic sclerosis (lcSScI) versus diffuse cutaneous (dcSScI)
- Associated with anticentromere antibody
- May occur with or without ILD

## Right Heart Catheterization: Confirms pulmonary artery hypertension



# Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study

Denton, et al.

Q J Med 2010;103:109-115.

## Historical (1990-1993) vs. Contemporary (2000-2003)

	Diffuse cutaneous (dcSSc)	Limited cutaneous (lcSSc)
5-yr survival	Improved 15% (84%)	No change (92%)
Pulmonary Fibrosis	7% vs. 38%	3% vs. 16%
Pulmonary Hypertension	<1% vs. 7%	1% vs. 8%
ANA	No change (98%)	No change (92%)

# Early Detection of Lung Involvement

- At Diagnosis: Pulmonary function testing (PFT), echocardiogram, 6 minute walk test, CT scan of the chest, overnight oxygen test
- Annual Screening: PFTs and echocardiogram

# Why Screen?

- The age of nihilism is over
- Effective treatments for PAH are here
- Major paradigm switch:
  - Treatment focus is more than immunosuppression
  - Future therapies are not just science fiction
  - Clinical trials are available

# Lung Disease in Systemic Sclerosis: New Insights and Treatment Options

- Pathophysiology
- Associated Lung Disease
- **Current therapies**
- Future targets

# Scleroderma Treatments

- Immune Suppression
- Biologic Therapies
- Antifibrotic Agents
- Transplantation
  - stem cell transplant
  - lung

# Immune Modulating for Interstitial Lung Disease

- Chemotherapies
  - Cyclophosphamide (cytoxan)\*, mycophenylate (cellcept), azathioprine (imuran), methotrexate<sup>-</sup>
- Biologic
  - Anti-tumor necrosis factor (infliximab), anti-CD 20 (rituxumab)

\*positive study, <sup>-</sup>negative study



# Cyclophosphamide versus Placebo in Scleroderma Lung Disease

*Scleroderma Lung Study Research Group. NEJM 2006; 354:2655.*

- Oral cyclophosphamide x 1 year versus placebo

## Results:

- 145/158 completed at least 6 months of treatment
- 2.53% improvement in lung function in cyclophosphamide group at 12-months
- Higher rate of side effects in treatment group

## Unanswered questions:

- Is 2.53% lung function clinically meaningful
- Is iv cyclophosphamide as effective with less risk of side effects ?
- Is there a better way to choose which patients are at risk for progressive disease

# Anti-Fibrotic Therapies

- Penicillamine<sup>-</sup>—blocks collagen cross-links
- Relaxin<sup>-</sup>—smooth muscle relaxant
- ET-1 blockade (Bosentan)<sup>-</sup>—blocks biologic cascade
- Pirfenidone

\*positive study, -negative study

# Current Clinical Trials

- SCOT trial: Scleroderma  
Cyclophosphamide Or stem cell  
Transplantation
- ASTIS: Autologous Stem cell  
Transplantation International Scleroderma  
Trial

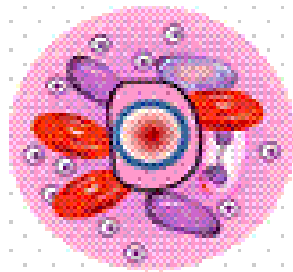
# Why might stem cell transplant work?

- The immune system may not recognize self as abnormal and will stop attacking

## The Autologous Transplant Process

### 1. Collection

Stem cells are collected from the patient's bone marrow or blood.



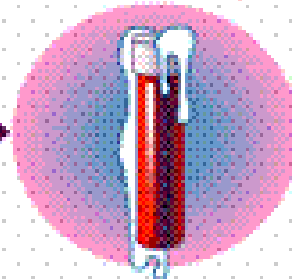
### 2. Processing

Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.



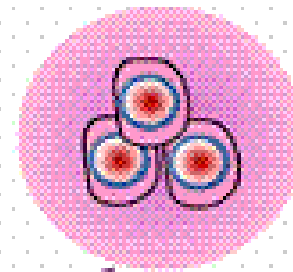
### 3. Cryopreservation

Blood or bone marrow is frozen to preserve it.



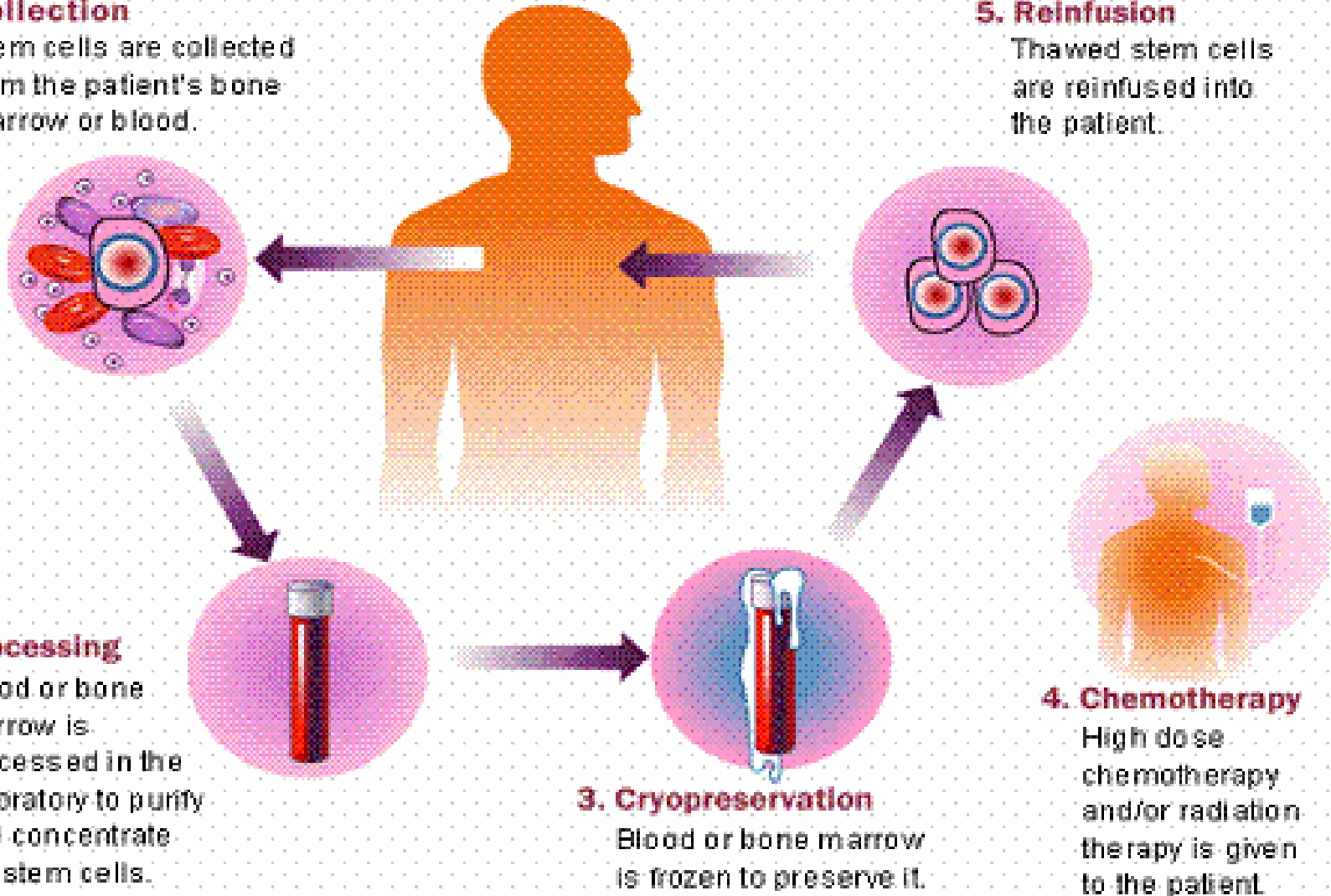
### 5. Reinfusion

Thawed stem cells are reinfused into the patient.



### 4. Chemotherapy

High dose chemotherapy and/or radiation therapy is given to the patient.



# Autologous Stem Cell Transplant

- Vonk, et al. Netherlands and France.
  - 81% with clinical benefit
  - 73% with more than 25% reduction in skin score
  - 5 year survival 96.2%, 7 year survival 85%
  - Less treatment related complications than prior experience

# Current Therapies for PAH

**Supplemental Oxygen**

**Diuretics**

**Anticoagulation**

**Calcium Channel Blockers**

**Prostacyclins--Intravenous epoprostenol/remodulin (Flolan/Remodulin), subcutaneous treprostinil (Remodulin), inhaled iloprost or remodulin (Ventavis/), oral remodulin (clinical trials)**

**Endothelin-1 receptor blocking agents--bosentan (Tracleer), ambrisentan (Letaris)**

**Oral phosphodiesterase 5 (PDE5) inhibitors--sildenafil (Revatio), tadalafil (Adcirca)**

**Lung Transplantation**

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## Oral phosphodiesterase 5 (PDE5) inhibitors:

sildenafil (Revatio)

tadalafil (Adcirca)



Severity



# Lung Transplants

- Significant risks
- More commonly done for ILD than PAH
- Exhaust other options before considering
- Timing: Not too well and not too sick

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# Clinical Research Trials

- <http://clinicaltrials.gov>
- 60+ trials current or future enrolling SScI pts
- Approx. 50% are treatment trials

# Future Targets: Anti-growth factors

- Tyrosine Kinase Inhibitors—
  - Imatinib (Gleevec) and others
  - Block a pathway that lead to fibrosis
  - Clinical trials underway for use in skin, PAH and ILD

# Summary

- Screening for lung disease is important for both asymptomatic and symptomatic patients
- Discuss treatment options with your pulmonary physician
- Treat progressive disease
- Early treatment may be important
- Stay tuned...

If you think you can win, you can win.  
Faith is necessary to victory.

WILLIAM HAZLITT





**Endothelin receptor antagonists**

Bosentan  
Ambrisentan

**PDE-5 inhibitors**

Sildenafil, Tadalafil

**Prostacyclins**

Epoprostenol  
Treprostinil  
Iloprost

