Environmental Pathology II: Mechanisms of Lung Injury

APPROVED

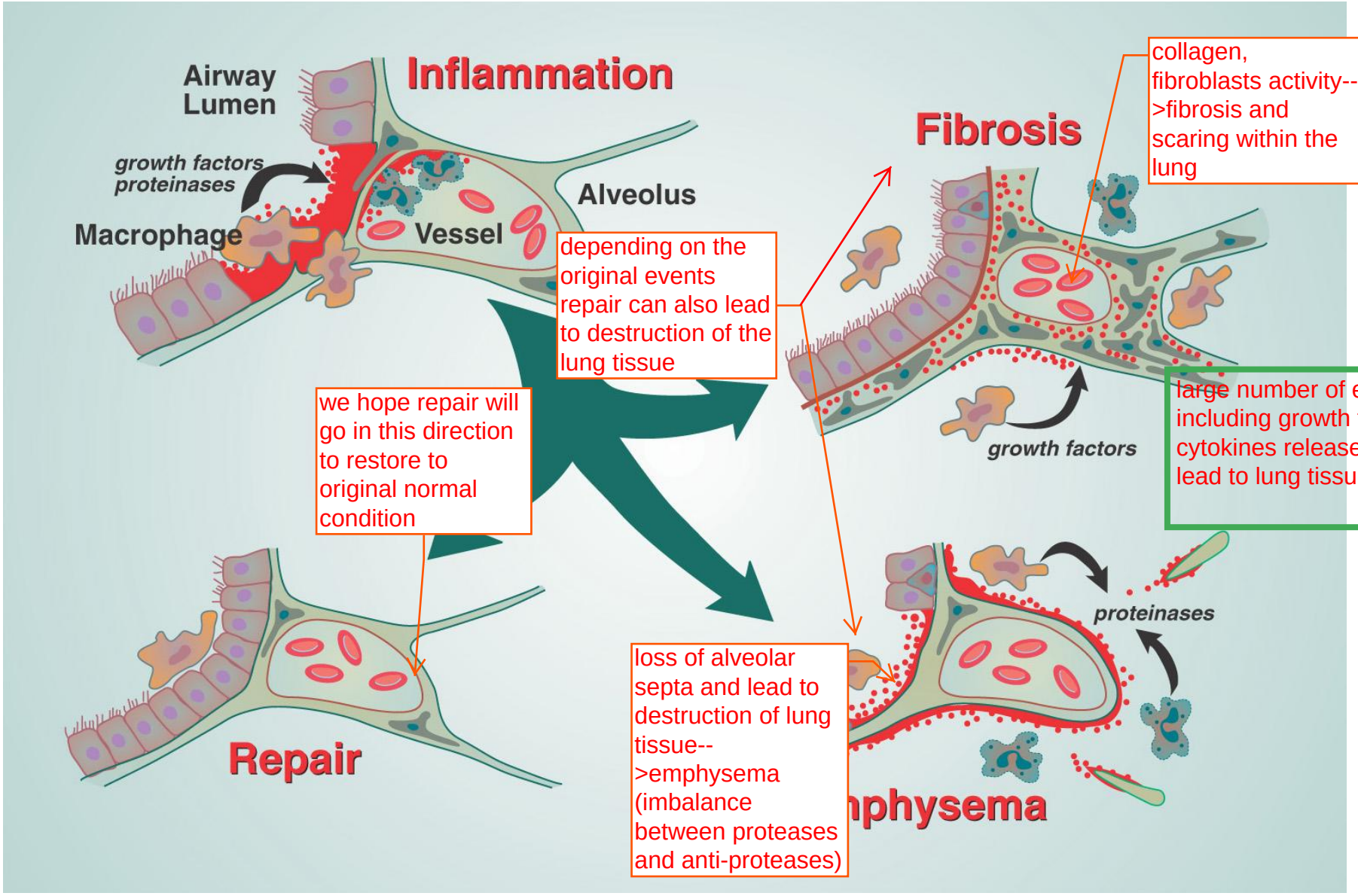
March 24th, 2011

Victor L. Roggli, MD
Department of Pathology

SESSION-SPECIFIC OBJECTIVES

- **List the four classes of environmental and occupational lung diseases**
- **List the specific diseases in each class**
- **Explain the mechanisms by which toxicants cause each disease**
- **List factors that determine balance between lung tissue repair and pathologic remodeling after toxicant exposure**
- **Define circumstances under which lung disease is the outcome**

Tissue Injury, Repair and Remodeling



Fibrosis and Emphysema - inappropriate responses to injury

"The same factors (i.e., cytokines, growth factors, proteinases) that mediate tissue repair following injury also mediate fibrogenesis…"

"…it is the aberrant expression of these factors - either in magnitude or timing - that favors disease progression over healing"

Key takeaway: molecules/factors that initiate the repair response can also lead to injury including fibrosis/ destructions

Environmental and Occupational Lung Diseases

- Obstructive Airway Diseases
- Hypersensitivity Pneumonitis
- Fibrotic Diseases
- Lung Cancer

e.g. emphysema

allergic to environmental material. A hypersensitivity reaction (Type II), different from asthma (Type I hypersensitivity)

all of the lung disease we talk about today are related to environmental and occupational exposures

meaning decrease n air flow in the airways and air trapping

Obstructive Lung Disease (Diseases of the Airways)

cause severe morbidity and even mortality

- Occupational and environmentally-induced asthma
- Reactive airways dysfunction syndrome (RADS)
- Chronic bronchitis (a component of COPD)
- Byssinosis (Cotton worker's disease)
- Bronchiolitis obliterans

similar to asthma

related to cotton dusts and pts may experience SOB at work when they are exposed to cotton dusts. Symptoms would not show up if pts are away from work, for example, during the weekends. (used to be very prevalent in N.C)

Airway Remodeling and Fibrosis in Asthma

From 2010 lecture: asthma is a reversible airway disease, with both acute and chronic components, caused by
1. constriction of airway smooth muscles
2. increased mucous production
that would block off the lumen and reduce air flow
3. asthma attack is reversed when the allergens are removed
4. prolonged exposure/chronic asthma can lead to airway remodelling that leads to fibrosis

Asthma: An Obstructive Lung Disease with Acute and Chronic Components

smooth muscle constriction

Asthma encompasses both the acute physiologic response of broncho-constriction caused by allergen challenge as well as the chronic aspect of airway inflammation and remodeling.

Both acute and chronic aspects contribute to airway obstruction.

both of the acute and chronic aspects contribute to the airway obstruction where the chronic aspect is generally irreversible

Asthma is generally an allergic disease with some exceptions

Immunological mechanism

- antibody-dependent hypersensitivity: an IgE-mediated type I allergic reaction

From 2010 lecture: Extrinsic form: caused by external allergens
Intrinsic form: overly reactive airway that has a genetic component to it

Non-immunologic mechanisms

- pharmacologic agents — e.g. asprin
- epithelial disruption — e.g. viral infection

Mechanisms of Occupational and Environmental Asthma

Aspects of Chronic Airway Remodeling

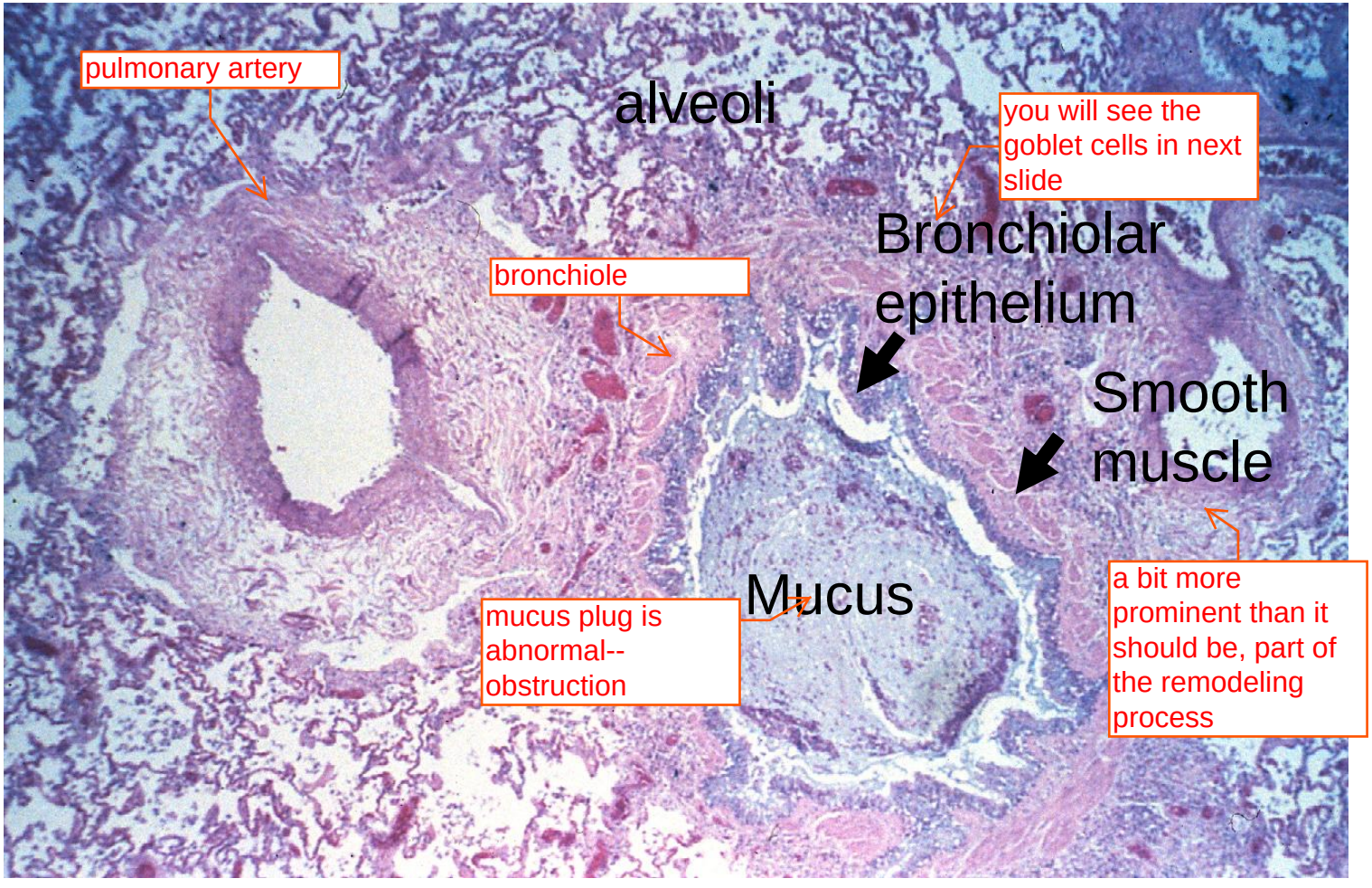
steps involved in the chronic airway remodeling

- sloughing of bronchial epithelium
- mucous cell hyperplasia and excessive mucus production
- airway fibrosis
- airway smooth muscle cell growth
- inflammatory cell infiltration (eosinophilia)

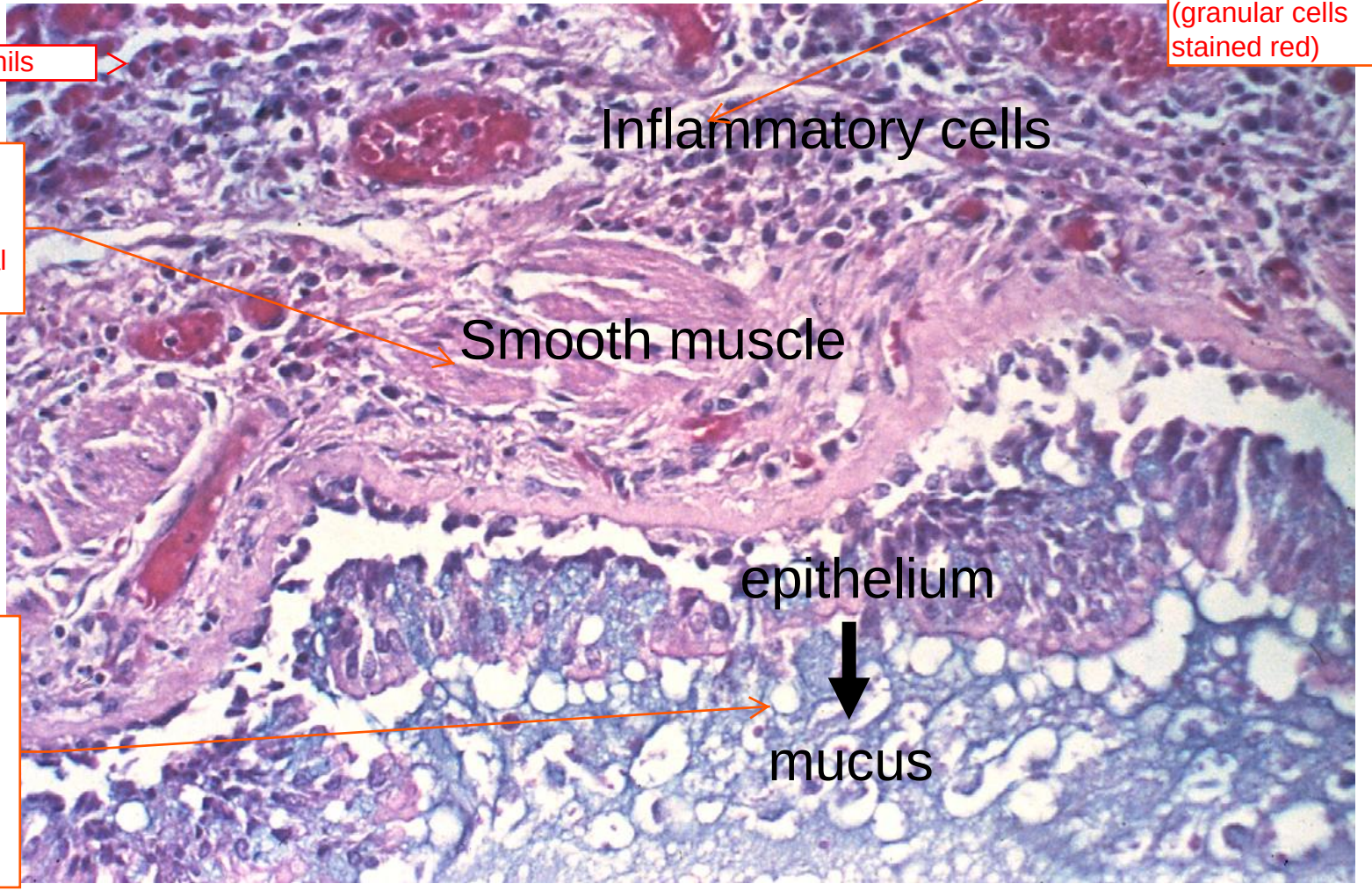
metaplasia--mucous cells (goblet cells) replace the epithelium in smaller airways. (goblet cells normally only exist in larger airways.)

especially in the extrinsic form of asthma (allergen related)

Pathology of asthma



Pathology of asthma



again, in pts with allergen caused asthma, there are often eosinophils (granular cells stained red)

eosinophils

contraction of the SMC results in bronchial constriction typical of asthma

ots of the goblet cells in the epithelium (also part of the chronic nflammation process as discussed 2 slides ago)

Agents causing Environmental and Occupational Asthma

- high-molecular weight allergens: (sensitizing agents , IgE-mediated, >1000 daltons)
  - plants
  - bacterial (endotoxin)
  - house dust mite
  - cockroach
- low-molecular weight compounds: (IgE-mediated "hapten" mechanism or IgE-independent mechanism)
  - anhydrides
  - metals
  - penicillin
  - diisocyanates

pollens

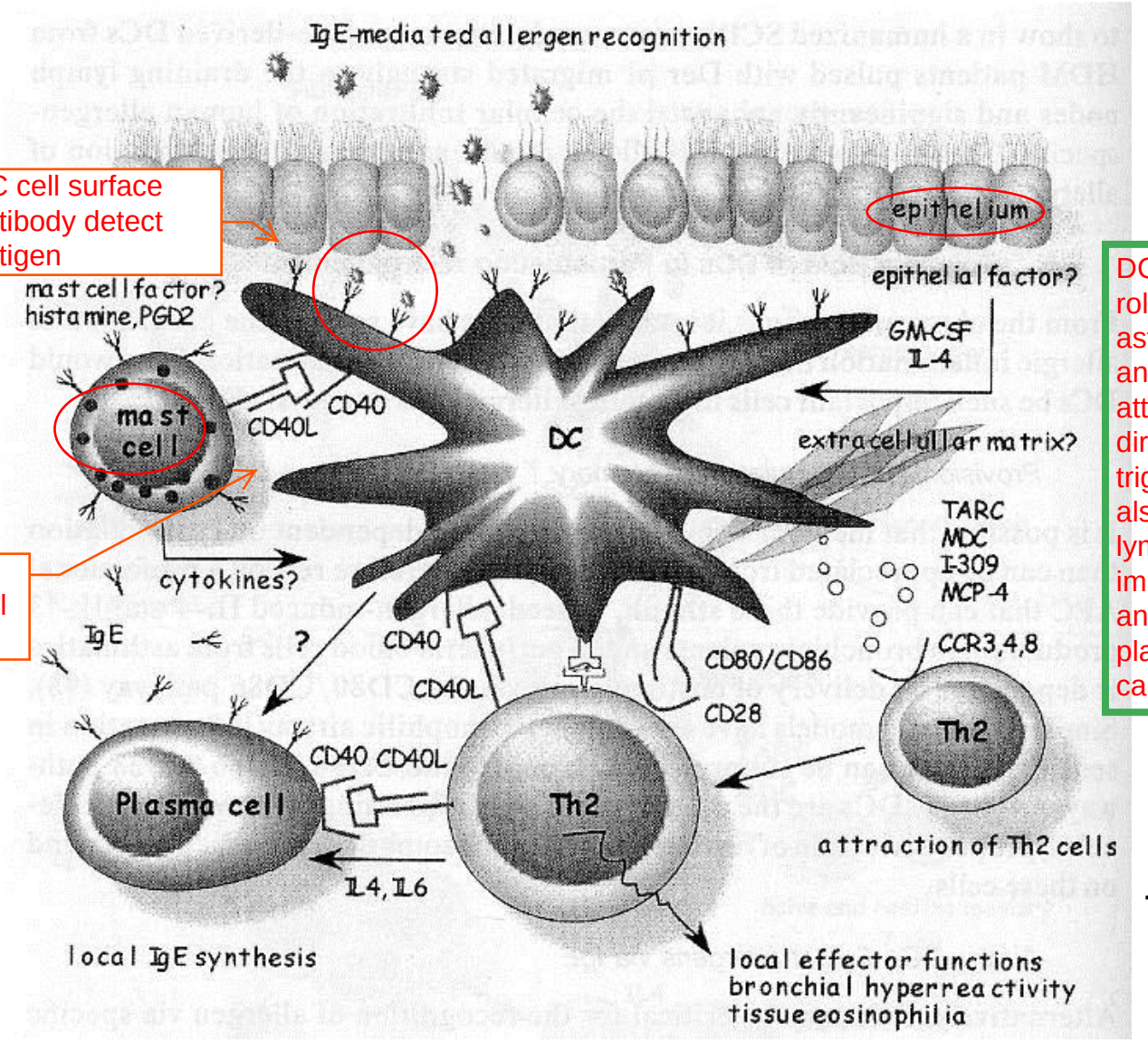
cause of Byssinosis (cotton dust caused obstructive disease)

antigens in the proteins in the mite

cobalt

meaning they typically bind to another protein to cause immunogenic effects

Cellular Mechanisms of Asthma



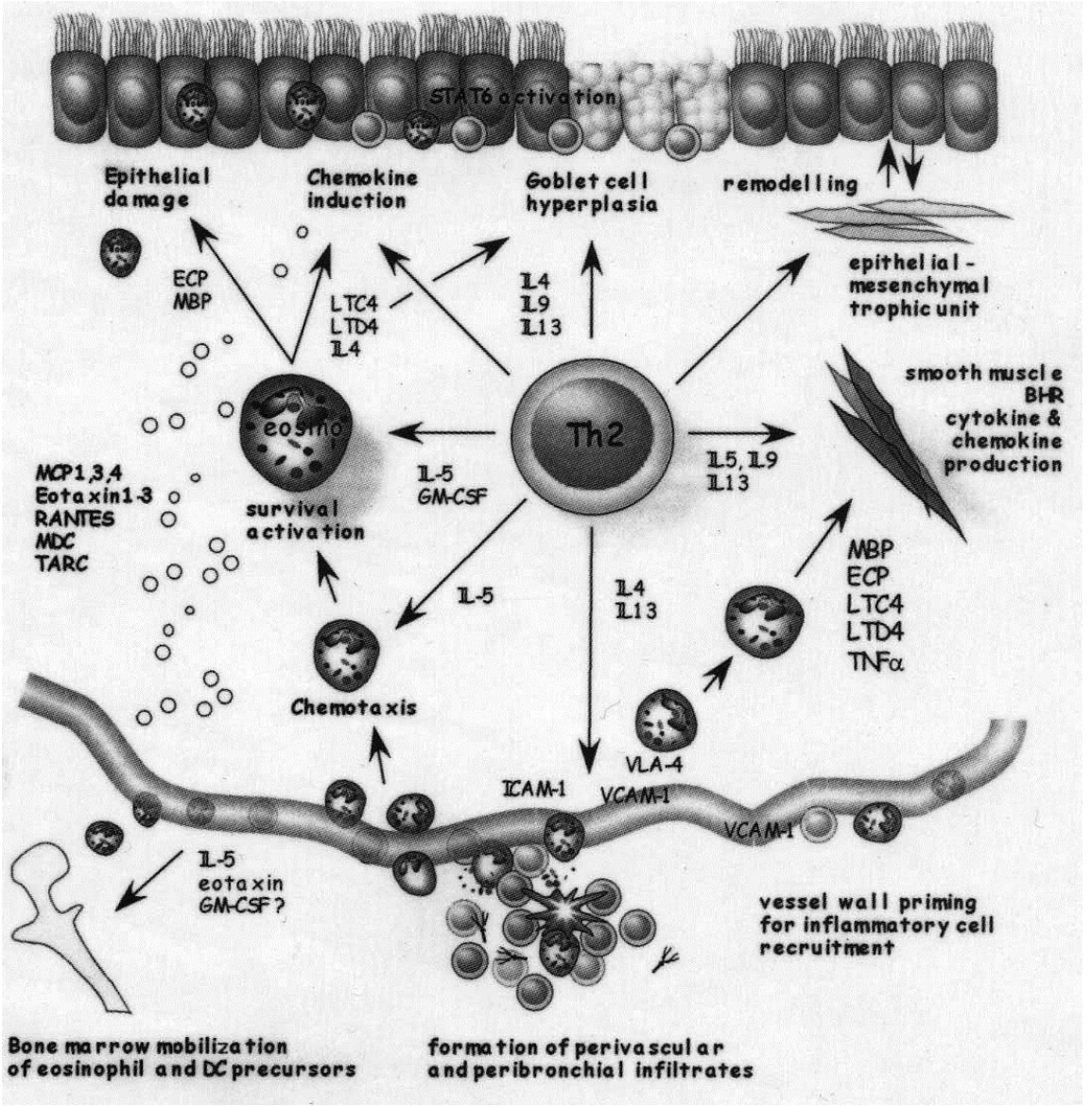
DC cell surface antibody detect antigen

communication between mast cell and DC cells

DC cells have a very important role in the development of asthma: allergen passing through an injured mucousal layer will attach to DC. DC can then directly interact with mast cells to trigger granules release. DC cells also present the ag to lymphocytes -->TH2 particularly important in asthma pathology and airway remodeling, as well as plasma cells IgE production. IgE can bind to the allergen

From: Lambrecht et al., The Immunologic Basis of Asthma, Marcel Dekker, Inc. 2003

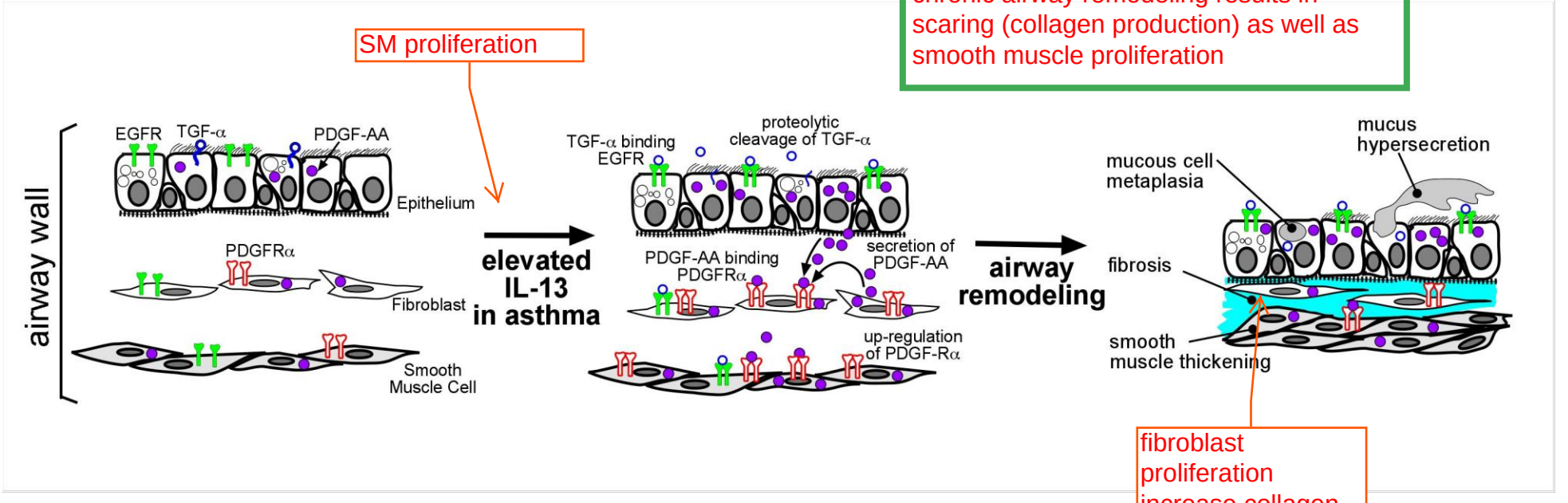
Cellular Mechanisms of Asthma



once TH2 cells are activated by the ag presenting DC cells, they can act as an amplification system and produce cytokines, growth facters and chemokines, to recruit cells including neutrophils and eosinophils. Granules released from eosinophils can trigger smooth muscle constriction etc. There might also be smooth muscle hyperplasia, fibroblasts lay down collagen-->airway remodeling.

From: Lambrecht et al., The Immunologic Basis of Asthma, Marcel Dekker, Inc. 2003

Cellular Mechanisms of Asthma:
Chronic Airway Remodeling Involving Interleukin-13 and Growth Factors



From: Ingram and Bonner, Current Molecular Medicine Reviews, 2006

Reactive Airways Dysfunction Syndrome (RADS)

- Definition: an asthma-like syndrome with a non-immunologic basis induced by high-dose exposure to irritant subtances that cause airway epithelial damage.
- Examples of irritants that cause RADS:
- chlorine
- ammonia
- sulfuric acid

individuals normally don't have previous airway symptoms (e.g. asthma) until exposure to the irritants

COPD has two components: 1. airway components: bronchitis
2. lung components: emphysema. pts usually have both components to some degree

Chronic Obstructive Pulmonary Disease (COPD) = chronic bronchitis + emphysema

Chronic Obstructive Pulmonary Disease (COPD) **- 4th highest cause** of death in the USA with a mortality 14 times that of asthma. The single most important factor is cigarette smoke.

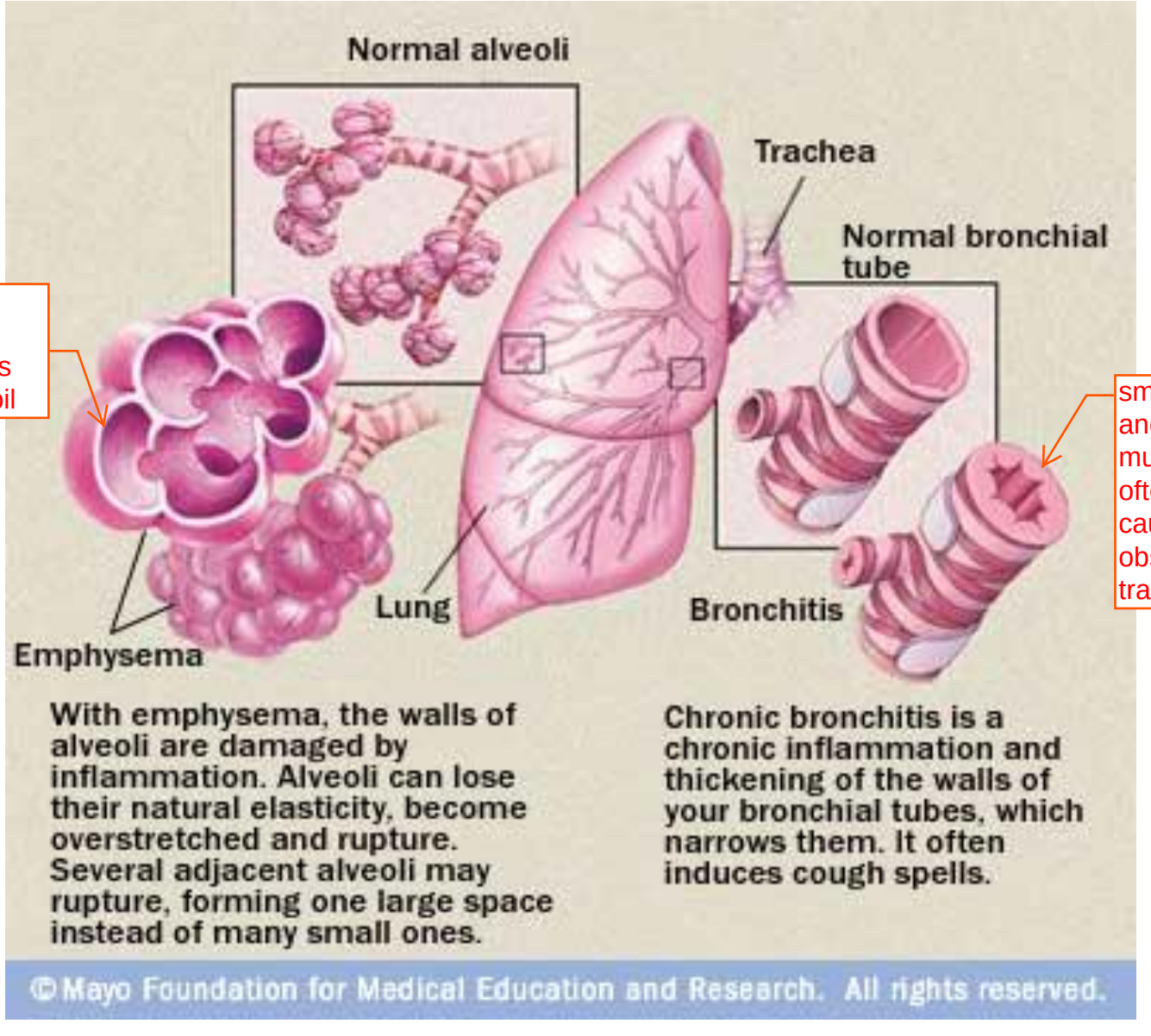
smokers can have either components of the COPD or both

Chronic Bronchitis/bronchiolitis - A component of COPD, but can occur in the absence of emphysema. Caused by a variety of occupational and environmental insults, including metal-induced oxidative stress, bacterial pathogens, viruses.

Emphysema - proteolytic degradation of alveolar walls due to an imbalance in proteinase/anti-proteinase system. Neutrophil elastase is a major mediator of alveolar wall destruction. Emphysema usually occurs with chronic bronchitis.

2010 lecture: alpha1-anti-typsin (blood) inhibits protease activity. There is a congenital defect where patients don't make this enzyme. Cigarette smoking can increase protease activity while at the same time inhibit alpha-1-anti-trypsin activities--> imbalance. More on the later COPD lecture

Chronic Obstructive Pulmonary Disease



holes in alveoli. holes get larger and larger. lungs lose elastic recoil

small airway lumen and wall thicker. mucous plugging often present. cause air way obstruction and air trapping

Chronic Bronchitis/Bronchiolitis

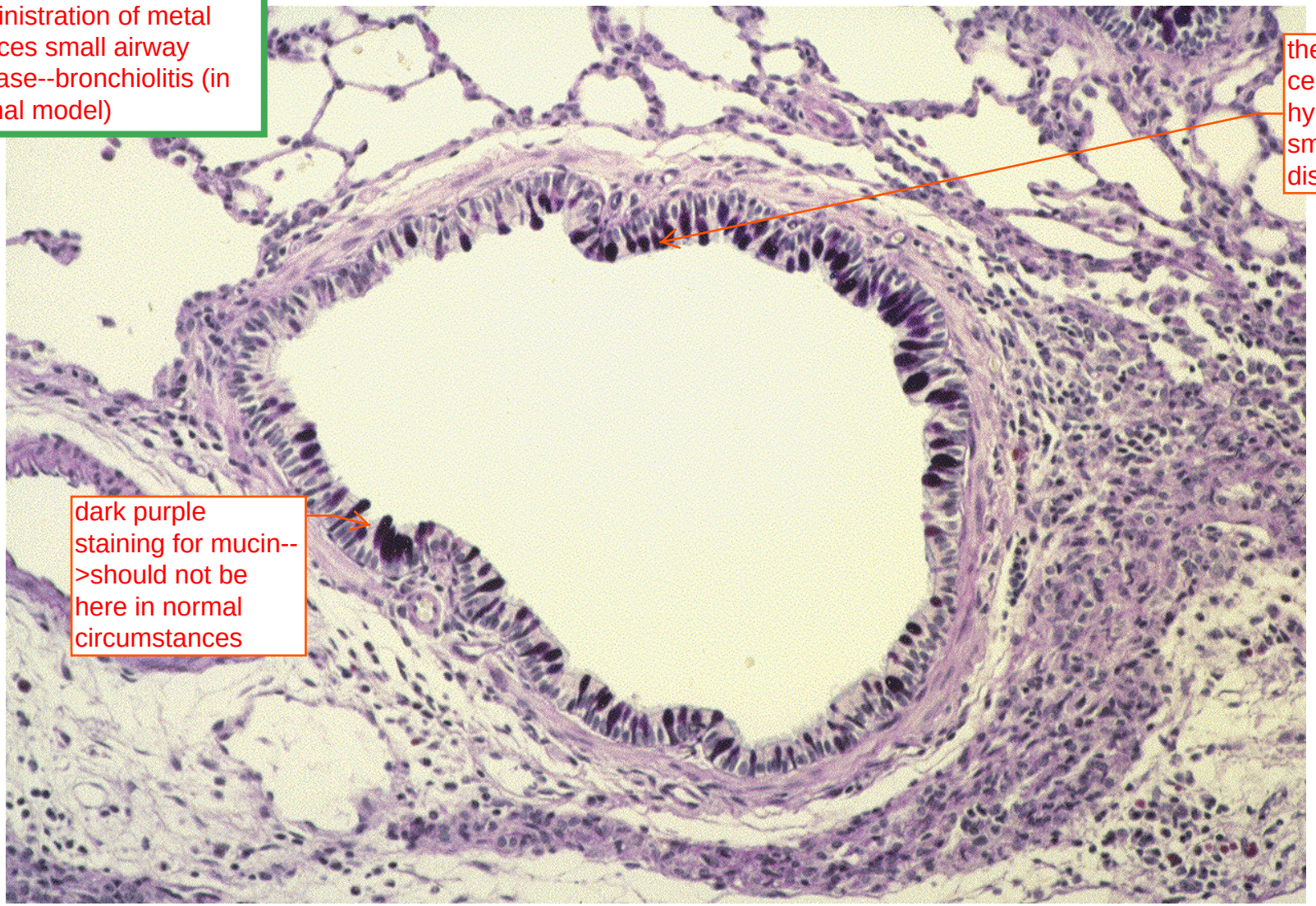
- Definition: Non-allergic airway disease characterized by mucus cell hyperplasia, chronic airway remodeling, and fibrosis.
- Examples of irritants that cause bronchitis:
- Cigarette smoke
- Bacterial endotoxins and viral infections
- Air pollution particulate matter
- Metal-induced oxidative stress
- ozone

contributing factor, not major compare to cigarette smoking

incomplete combustion, super hot summers

Vanadium Pentoxide (V_2O_5)-induced Bronchiolitis

administration of metal induces small airway disease--bronchiolitis (in animal model)

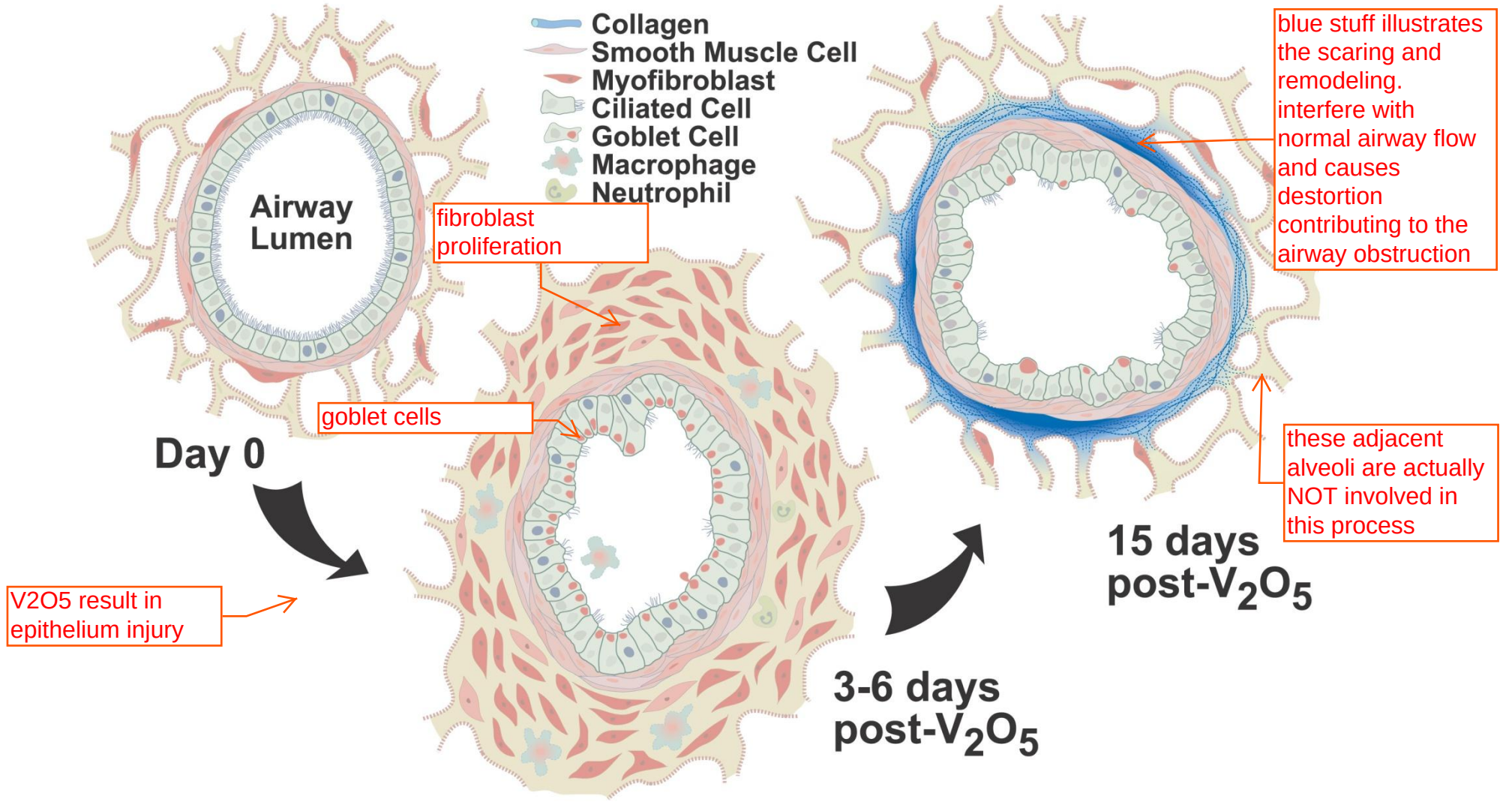


these are goblet cells (goblet cells hyperplasia in small airway diseases)

dark purple staining for mucin-->should not be here in normal circumstances

Alcian blue PAS stain highlighting mucin-filled goblet cells

Vanadium Pentoxide (V_2O_5)-induced Bronchiolitis



Walters and Bonner (2005) Air Pollutants & the Respiratory Tract: Lung Biology in Health and Disease, Vol. 204

Causes of Bronchiolitis Obliterans

- Postinfectious (e.g., adenovirus)
- Fumes and toxins (*S. androgynus*)
- Drug reactions (e.g., penicillamine)
- Chronic allograft rejection (lung, B.M.)
- Collagen vascular disorders (esp. RA)
- Inflammatory bowel disease
- Bronchiectasis, CF, asthma

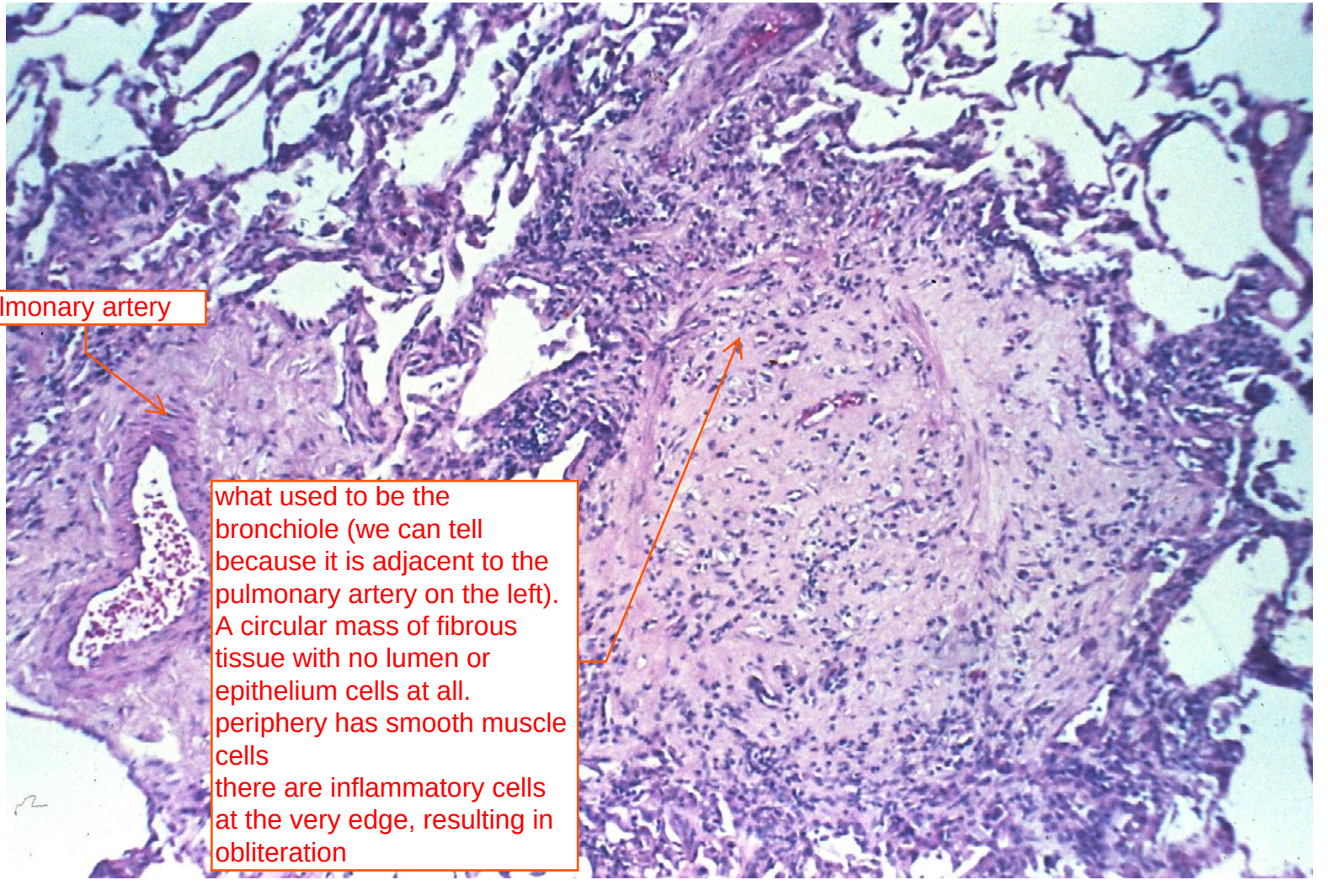
severe lesion. for example, Adenovirus infection in children causes necrosis in the epithelium and subsequently fibrosis and leads to bronchiolitis

e.g. 1. ammonia
2. Androgynus (a weight loss substance) caused bronchiolitis obliterans outbreak in Taiwan esp. in young women

transplants. in the lung the host cells attacking the allograft cells. or in the BM transplant case, essentially a GVHD

ulcerative colitis

Bronchiolitis Obliterans:
A tissue response to injury



Environmental and Occupational Lung Diseases

- Obstructive Airway Diseases
- Hypersensitivity Pneumonitis
- Fibrotic Diseases
- Lung Cancer

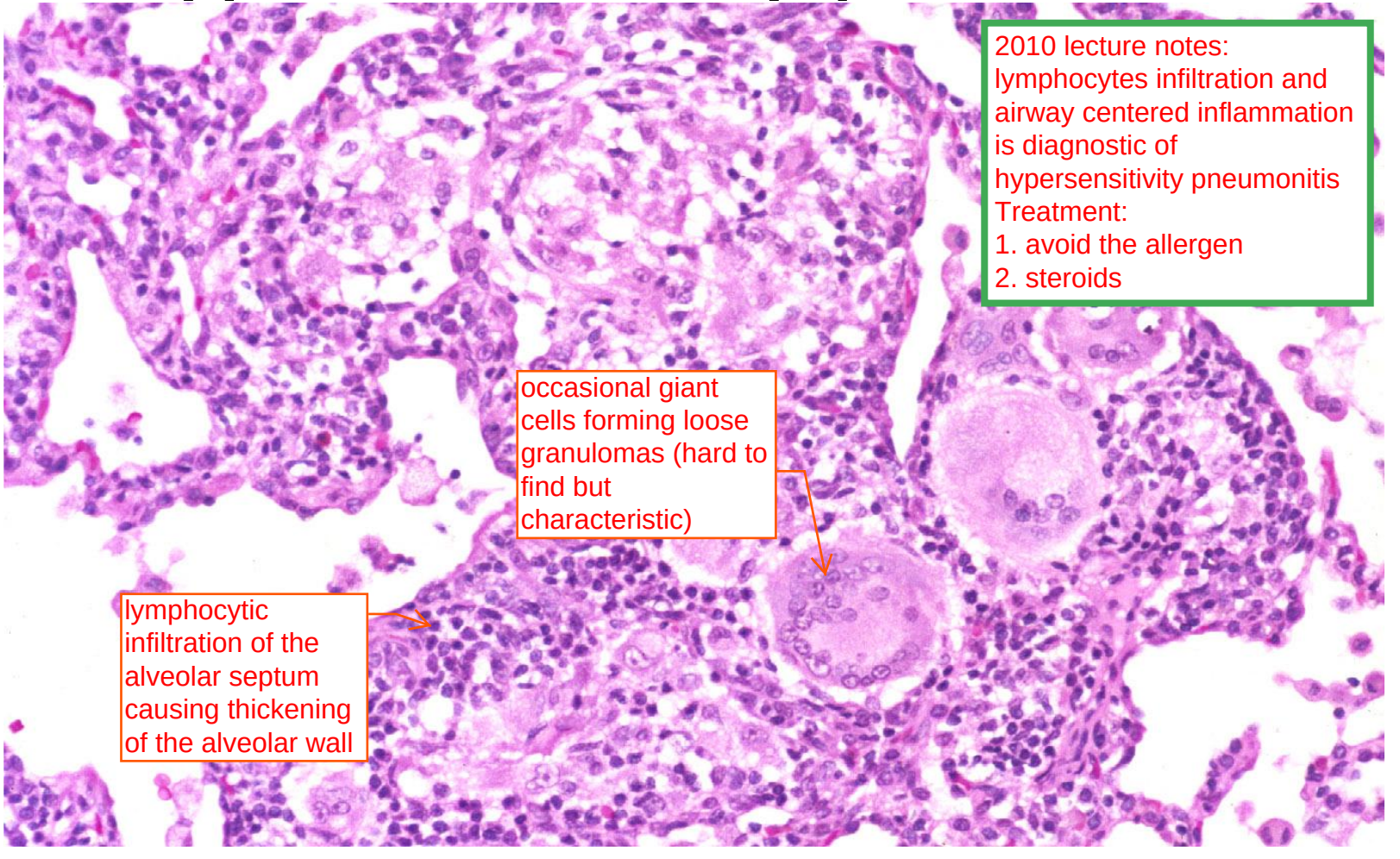
Hypersensitivity pneumonitis: Allergic Response Leading to Fibrosis

Genetic Susceptibility is a Major Factor

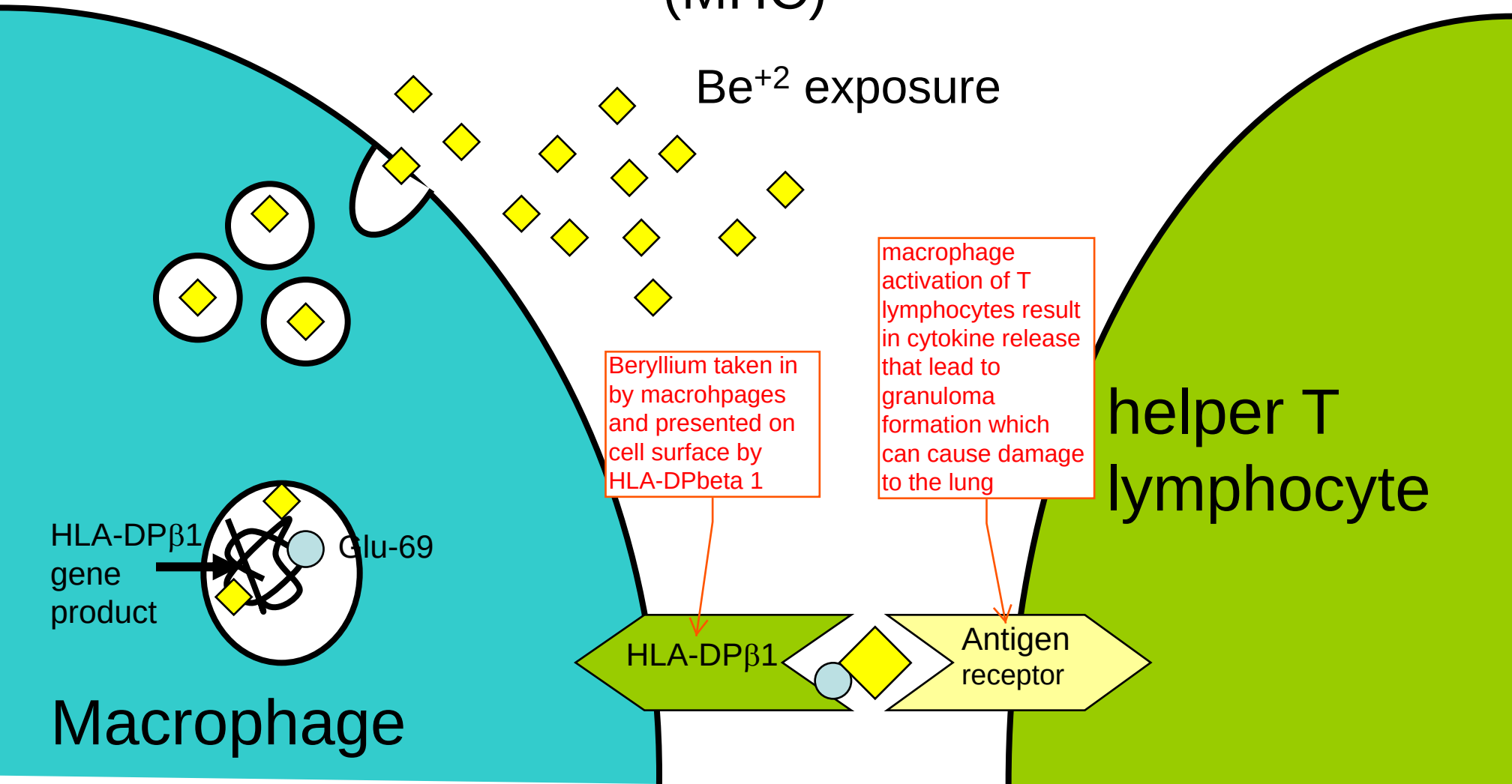
- immune mechanism and pathology:
  - Infiltrative disease involving recurrent exposure and sensitization (elevated IgG).
    - usually with fever and chills
  - Diffuse mononuclear inflammation of terminal bronchioles and alveoli. Small poorly formed granulomas.
    - frequently associated with a few giant cells in the interstitium
- examples:
  - Thermophilic actinomycetes mediate farmers' lung disease
    - now in good control
  - Avian proteins (Bird-fancier's or pigeon breeder's lung).
  - Chronic Beryllium Disease
    - another example would be molds growing in the air conditioning system

only a small % of individuals exposed to a certain environmental factor actually develop the disease

Hypersensitivity pneumonitis

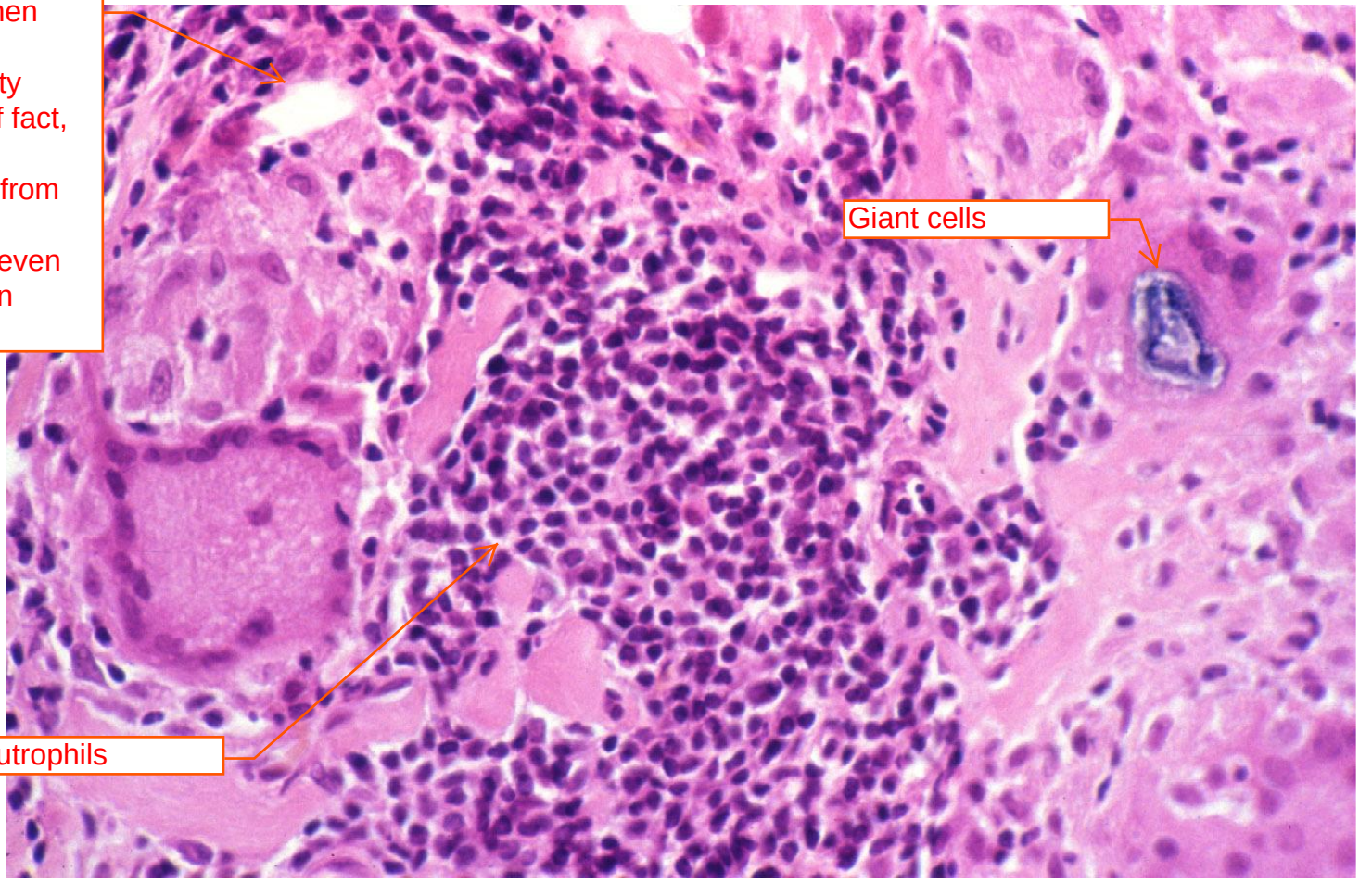


Macrophage Presentation of Beryllium to Helper T Lymphocyte via Major Histocompatibility Complex (MHC)



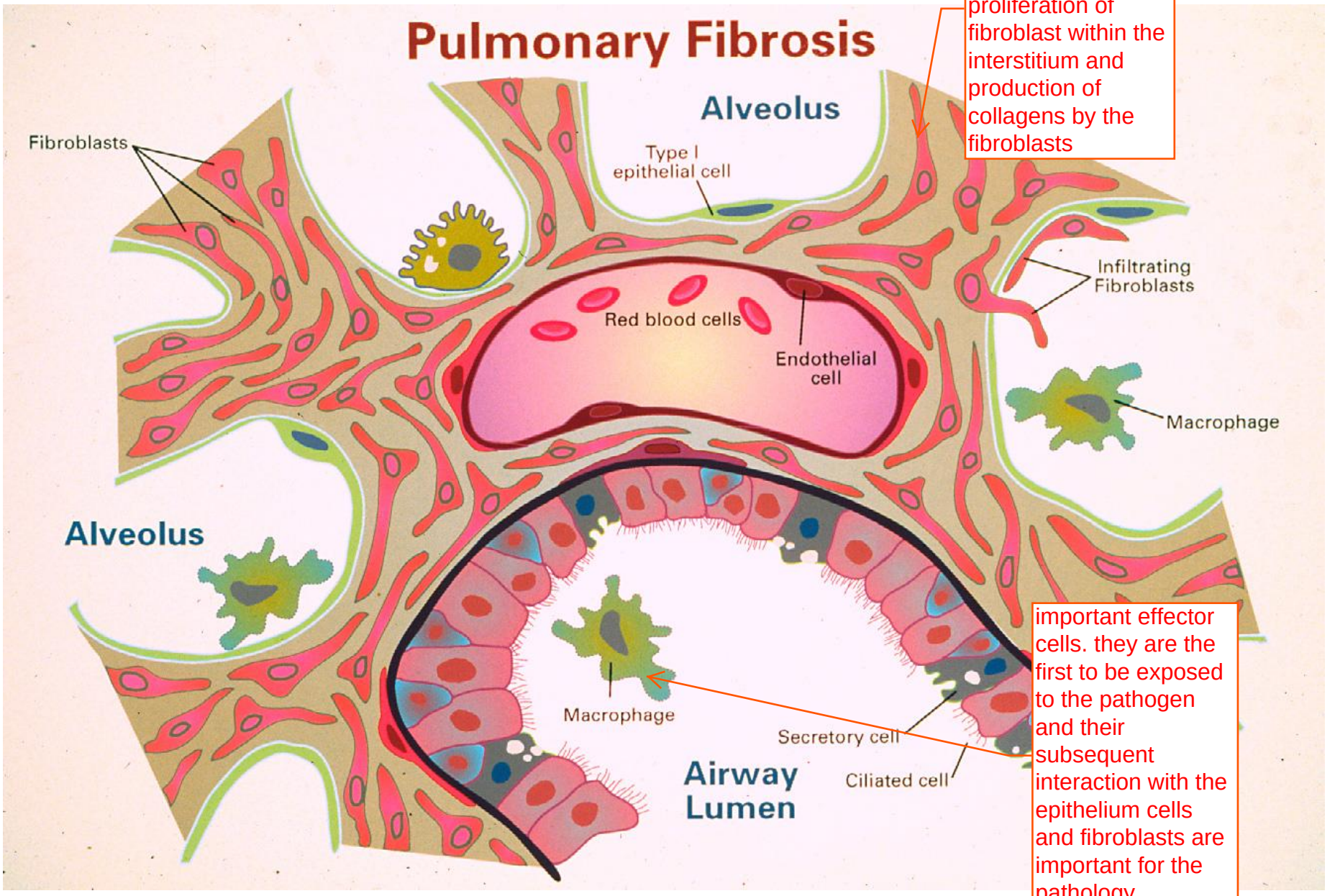
BERYLLIOSIS

non-necrotising Granuloma formation. In this case it is much more well formed granuloma when compared to hypersensitivity pneumotitis. If fact, this has to be distinguished from sarcoidosis. (berylliosis is even more rare than sarcoidosis)

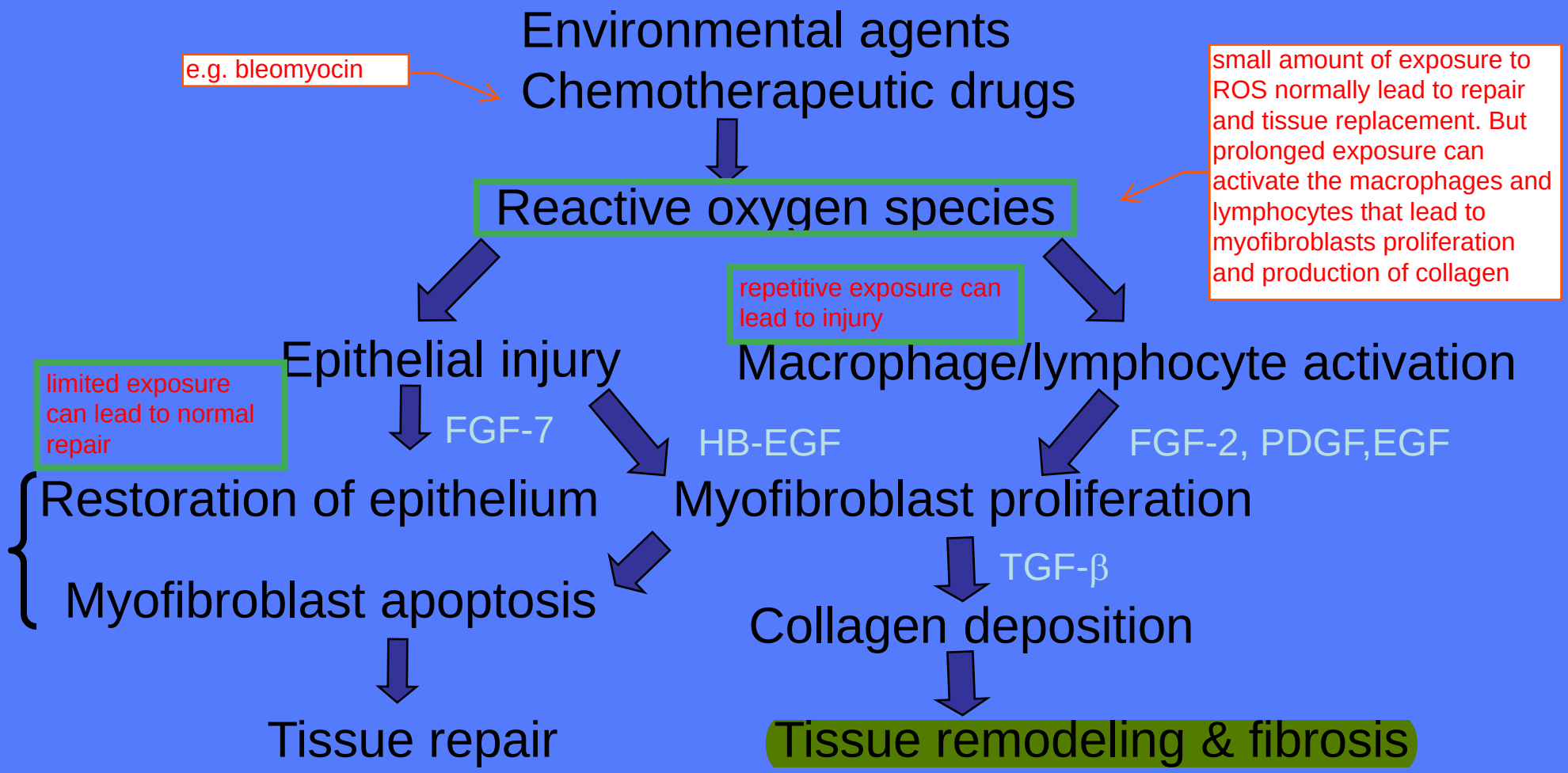


Environmental and Occupational Lung Diseases

- Obstructive Airway Diseases
- Hypersensitivity Pneumonitis
- Fibrotic Diseases
- Lung Cancer


Pulmonary Fibrosis
Alveolus
Fibroblasts
Type I epithelial cell
proliferation of fibroblast within the interstitium and production of collagens by the fibroblasts
Infiltrating Fibroblasts
Red blood cells
Endothelial cell
Macrophage
Alveolus
Macrophage
Secretory cell
Ciliated cell
Airway Lumen
important effector cells. they are the first to be exposed to the pathogen and their subsequent interaction with the epithelium cells and fibroblasts are important for the pathology

Mechanisms of Lung Fibrosis



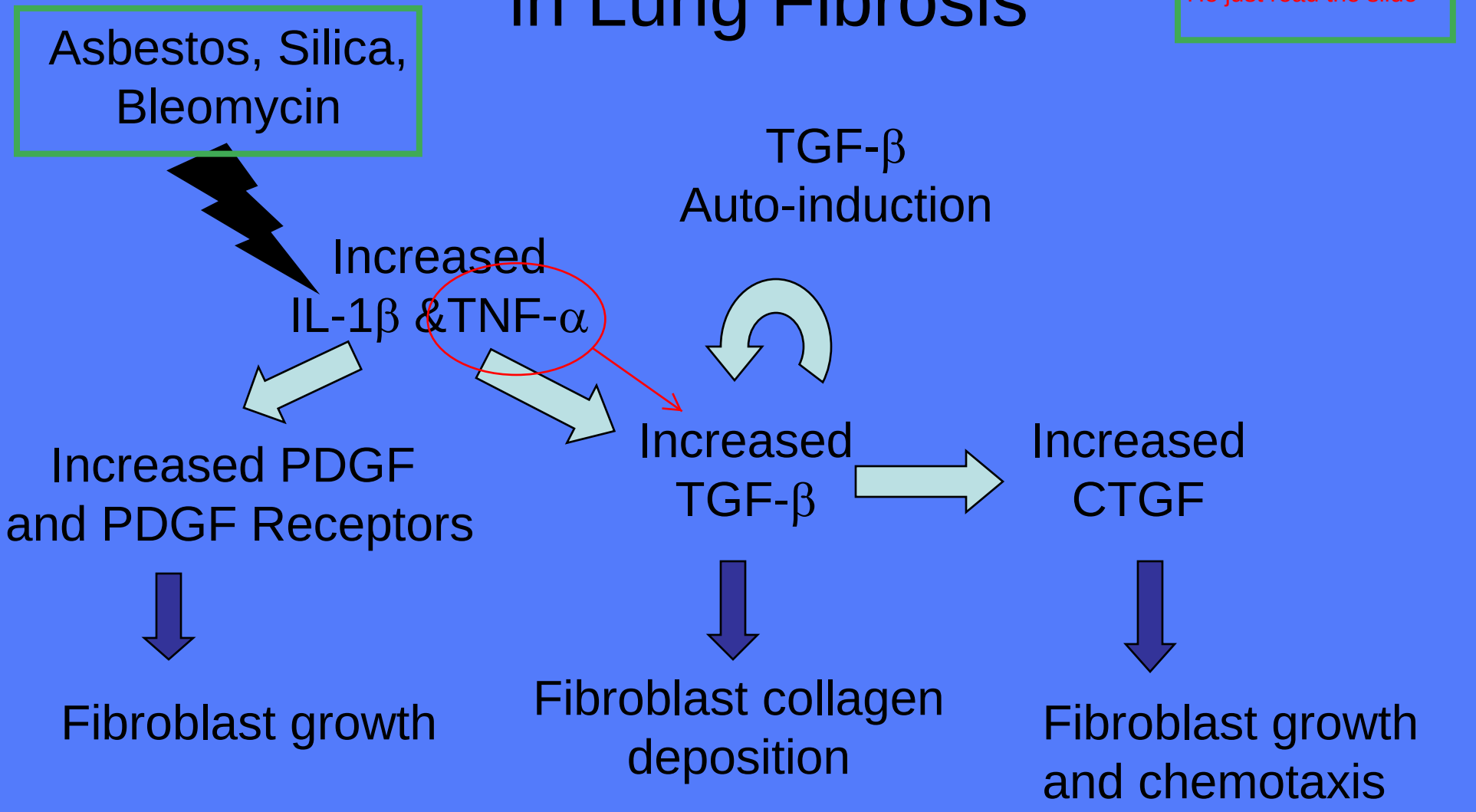
Communication is everything

“If cytokines are the language through which cells communicate, then fibrosis is the result of a conversation where words were spoken too loudly and repeated too often…”

basically too frequent release of too much cytokines leads to fibrosis

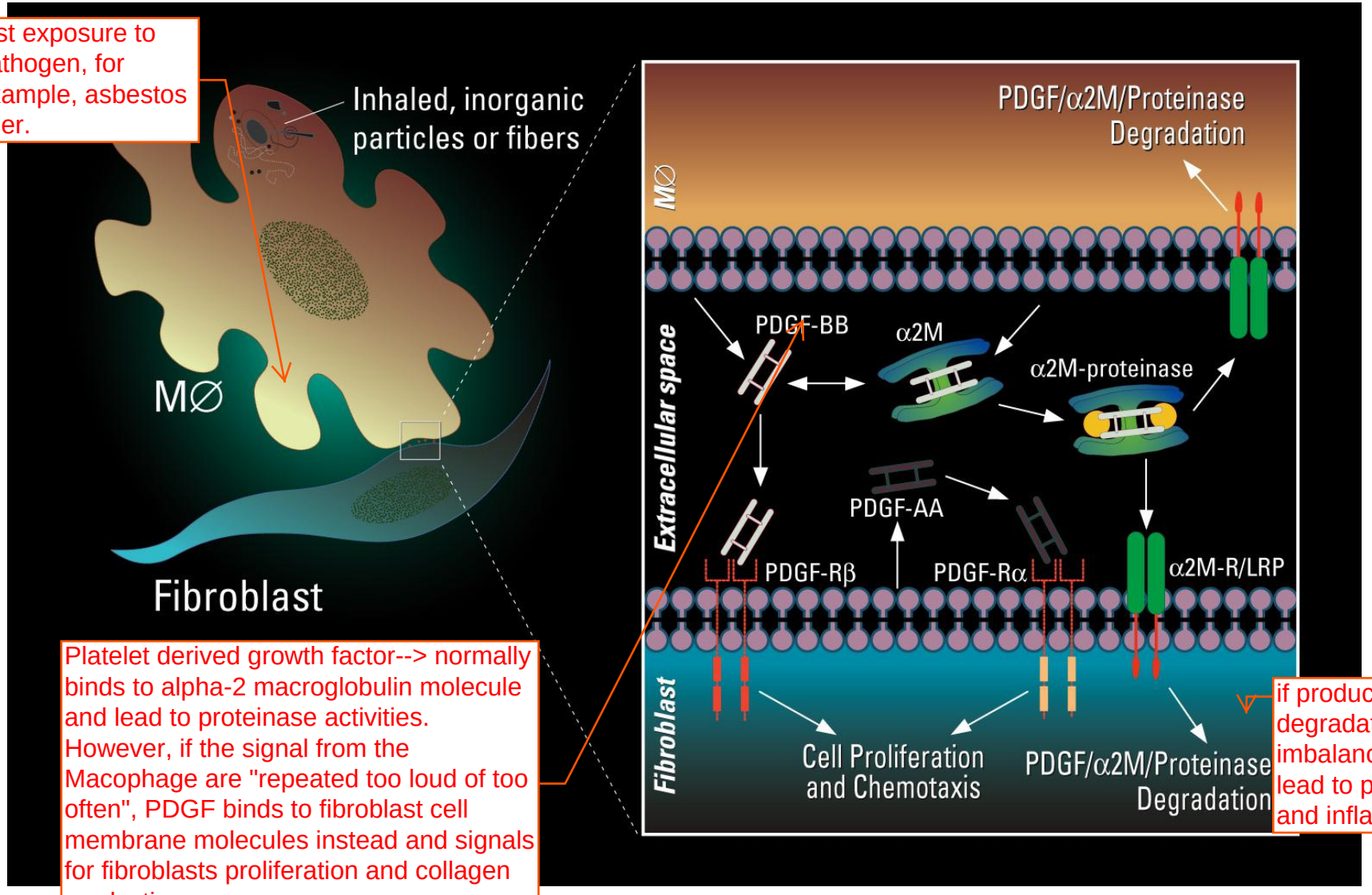
Cytokine/Growth Factor Cascades in Lung Fibrosis

He just read the slide



Platelet-derived Growth Factor Signaling in Lung Fibrosis

first exposure to pathogen, for example, asbestos fiber.



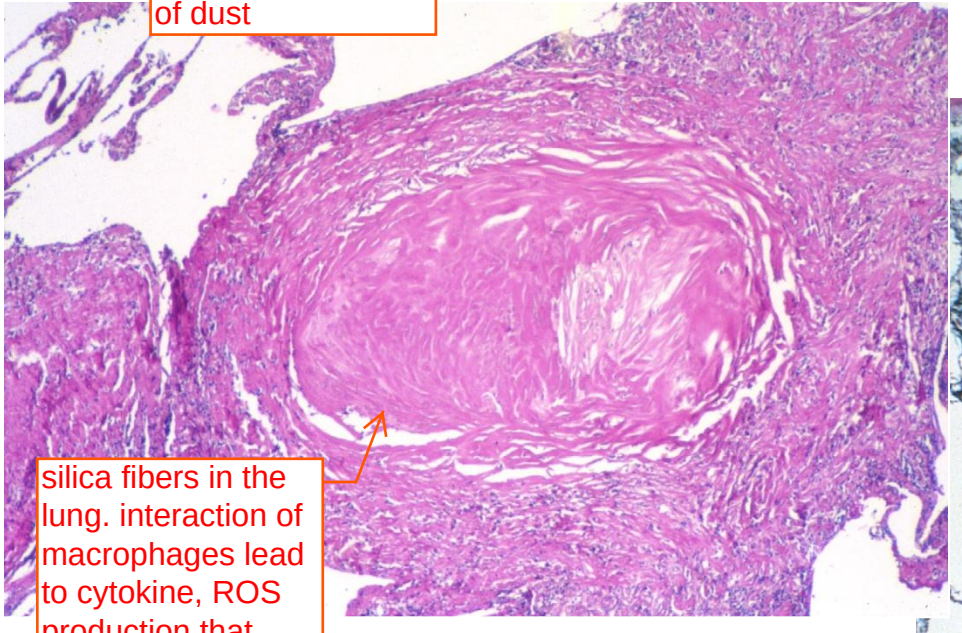
Platelet derived growth factor--> normally binds to alpha-2 macroglobulin molecule and lead to proteinase activities. However, if the signal from the Macophage are "repeated too loud of too often", PDGF binds to fibroblast cell membrane molecules instead and signals for fibroblasts proliferation and collagen production

if production and degradation are imbalanced, it can lead to proliferation and inflammation

R. Brody. (1993) Cytokine Binding Proteins. In *"Lung Biology in Health and Disease (Vol. 51): Cytokines of the Lung"*.

Pneumoconiosis - Occupational Lung Fibrosis

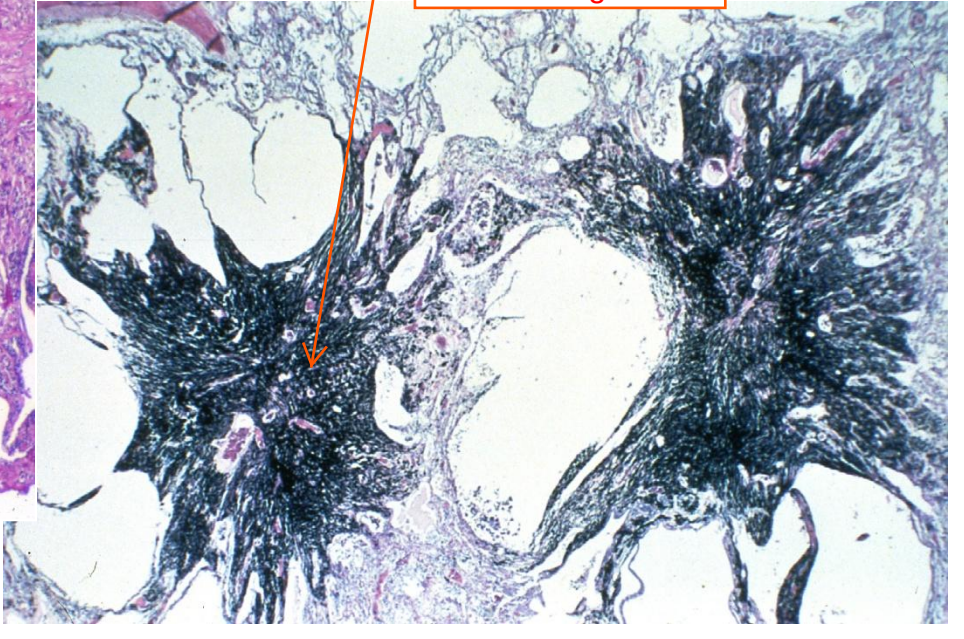
dust in the lung: disease caused by exposure to excessive amount of dust



silica fibers in the lung. interaction of macrophages lead to cytokine, ROS production that lead to fibrosis.

Silicosis

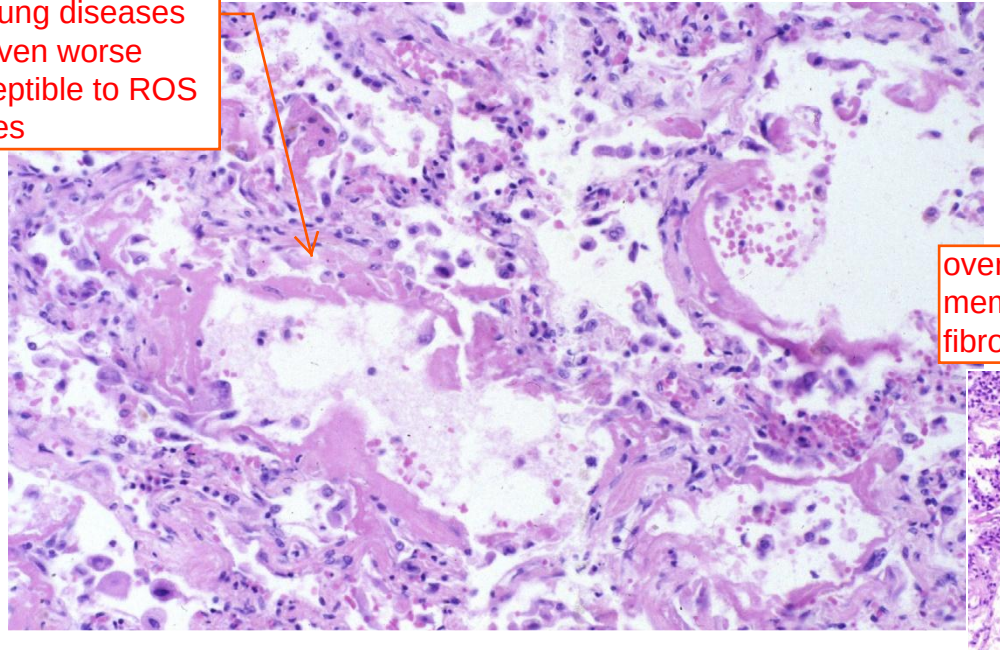
highly pigmented fibrosis in coal worker's lung



Coal Worker’s Pneumoconiosis

DIFFUSE ALVEOLAR DAMAGE OXYGEN TOXICITY

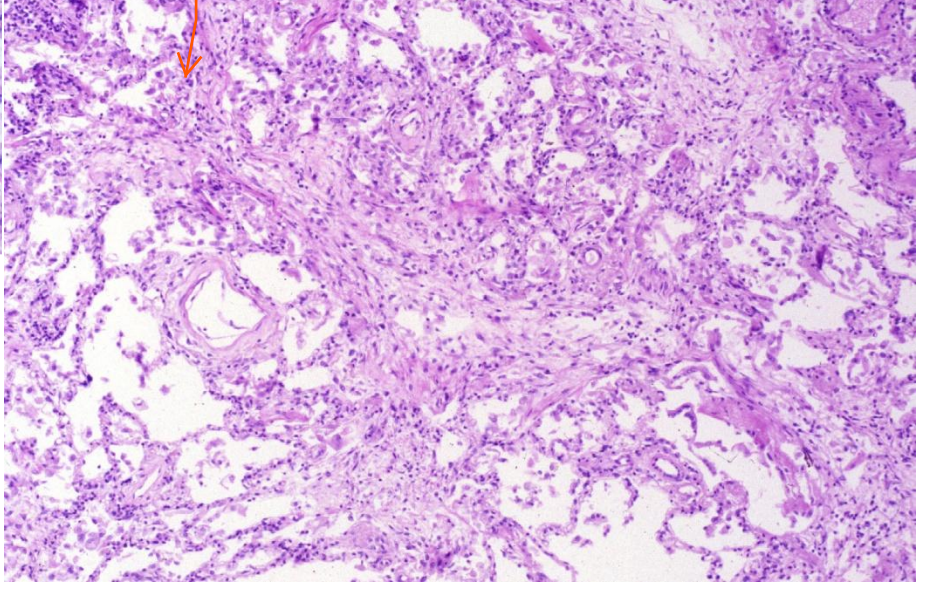
even normal lungs with extensive 100% O2 exposure may be damaged. pts with lung diseases are even worse susceptible to ROS injuries



Acute phase

Organizing phase

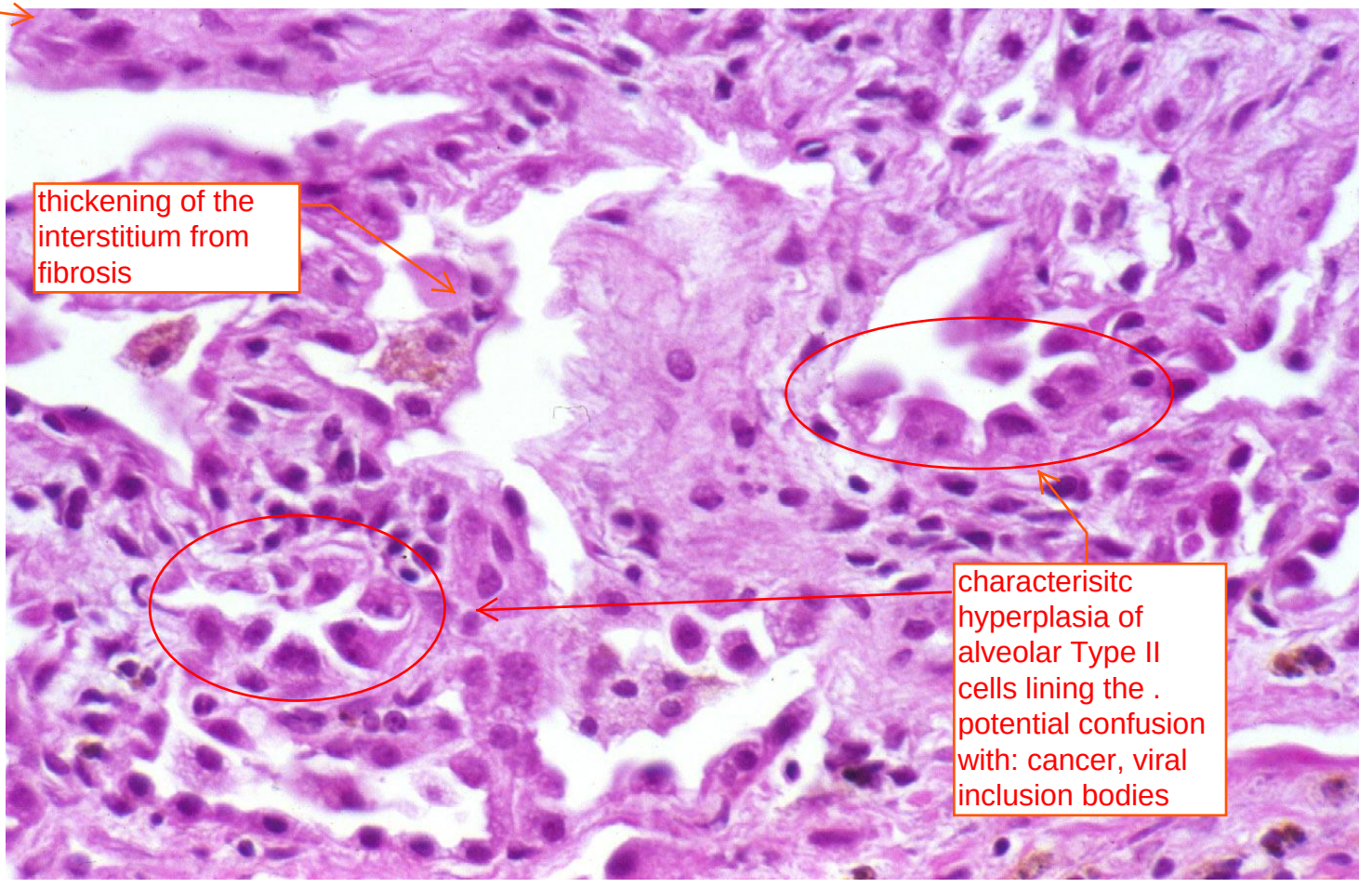
over time, the hyaline membrane will be replaced by fibrous tissue



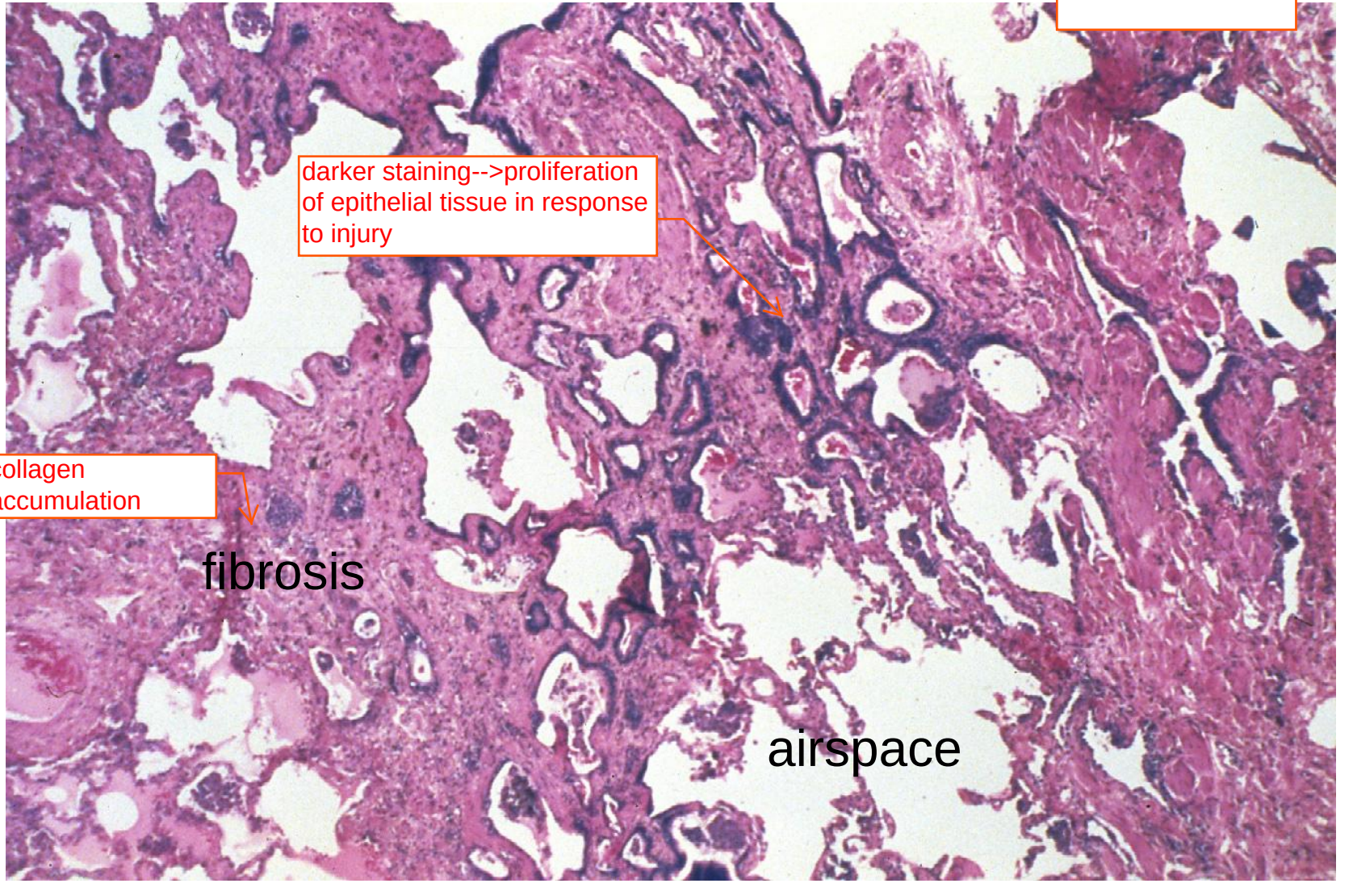
chemotherapy agent

BLEOMYCIN-INDUCED PULMONARY FIBROSIS

result from ROS

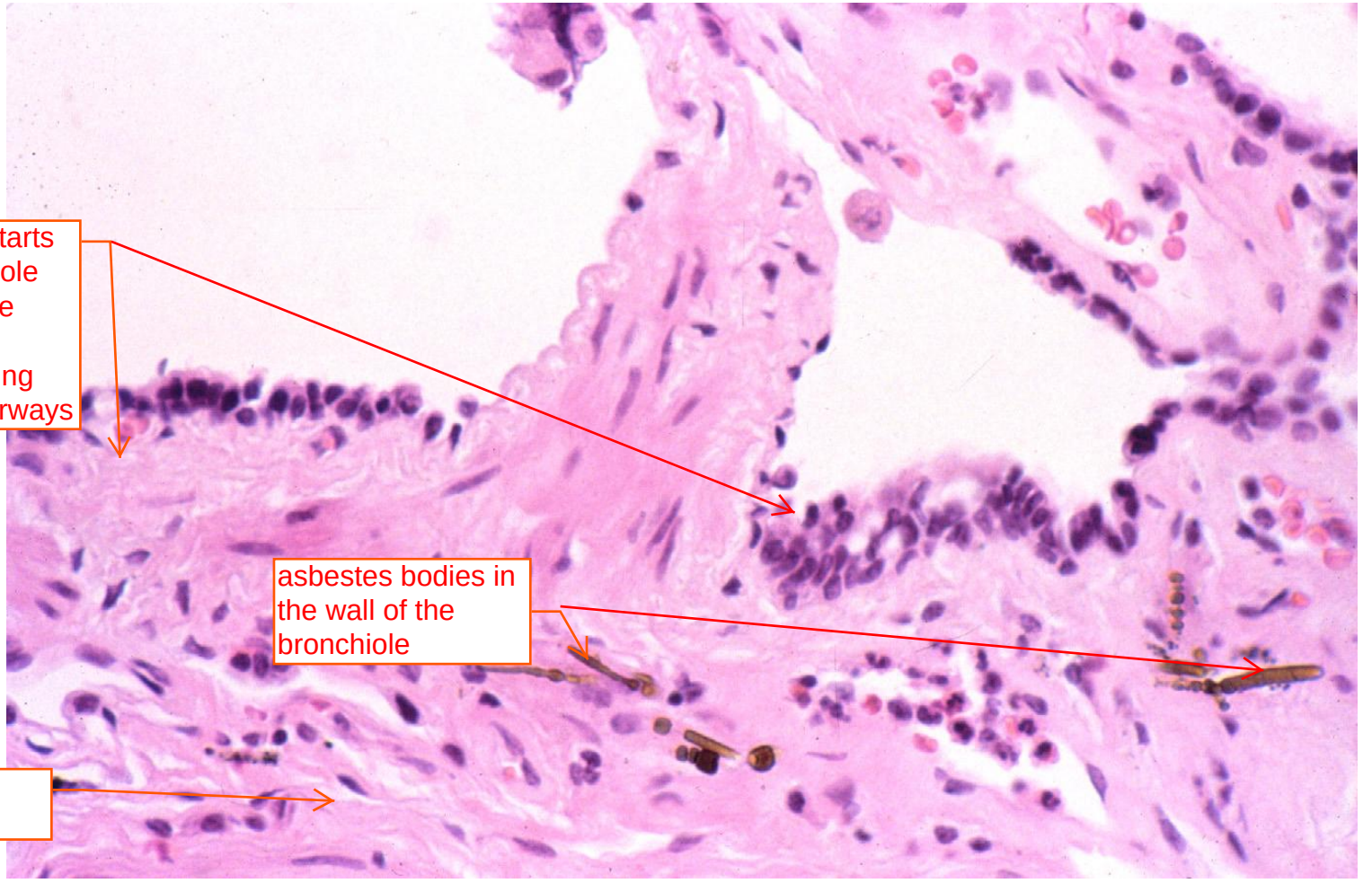


Death by Asbestos



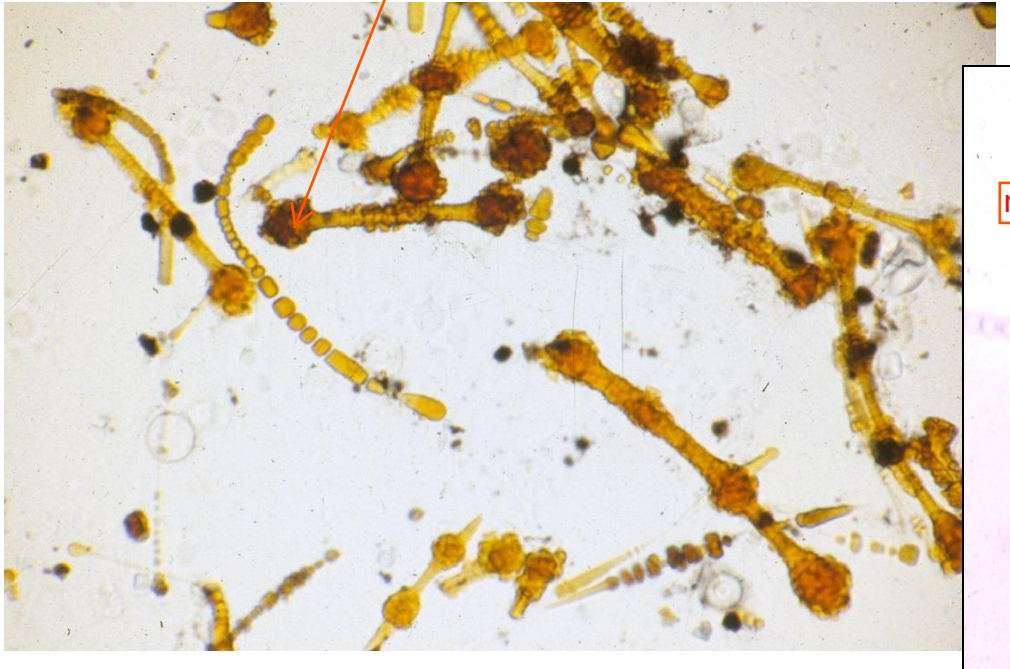
ASBESTOSIS

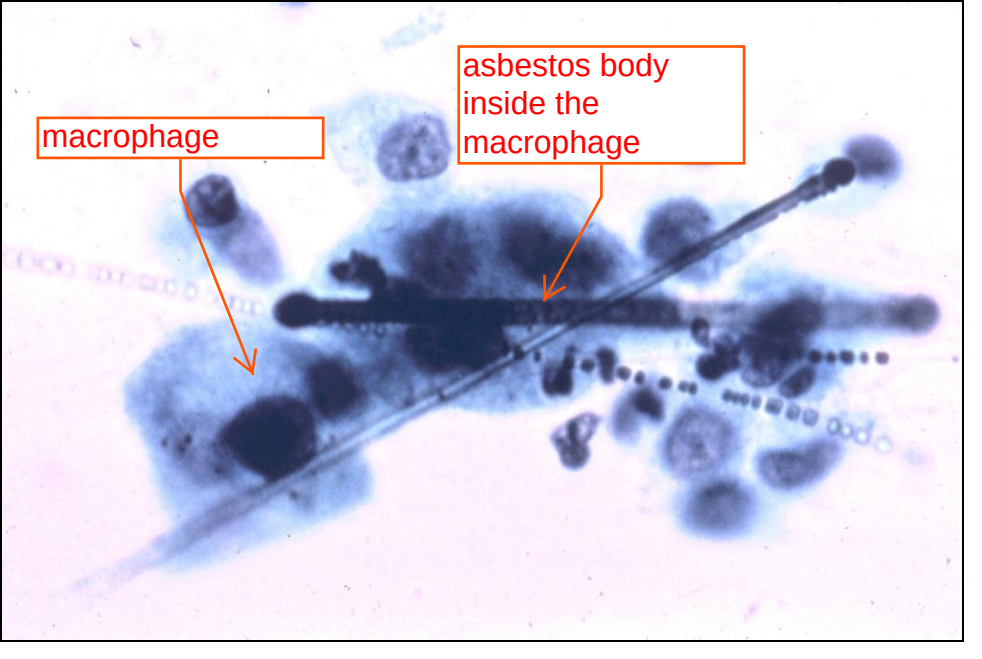
high power view



ASBESTOS (FERRUGINOUS) BODIES

protiens and Fe deposit on the asbestos body by the macrophages because the macrophage can not entirely take the fiber up



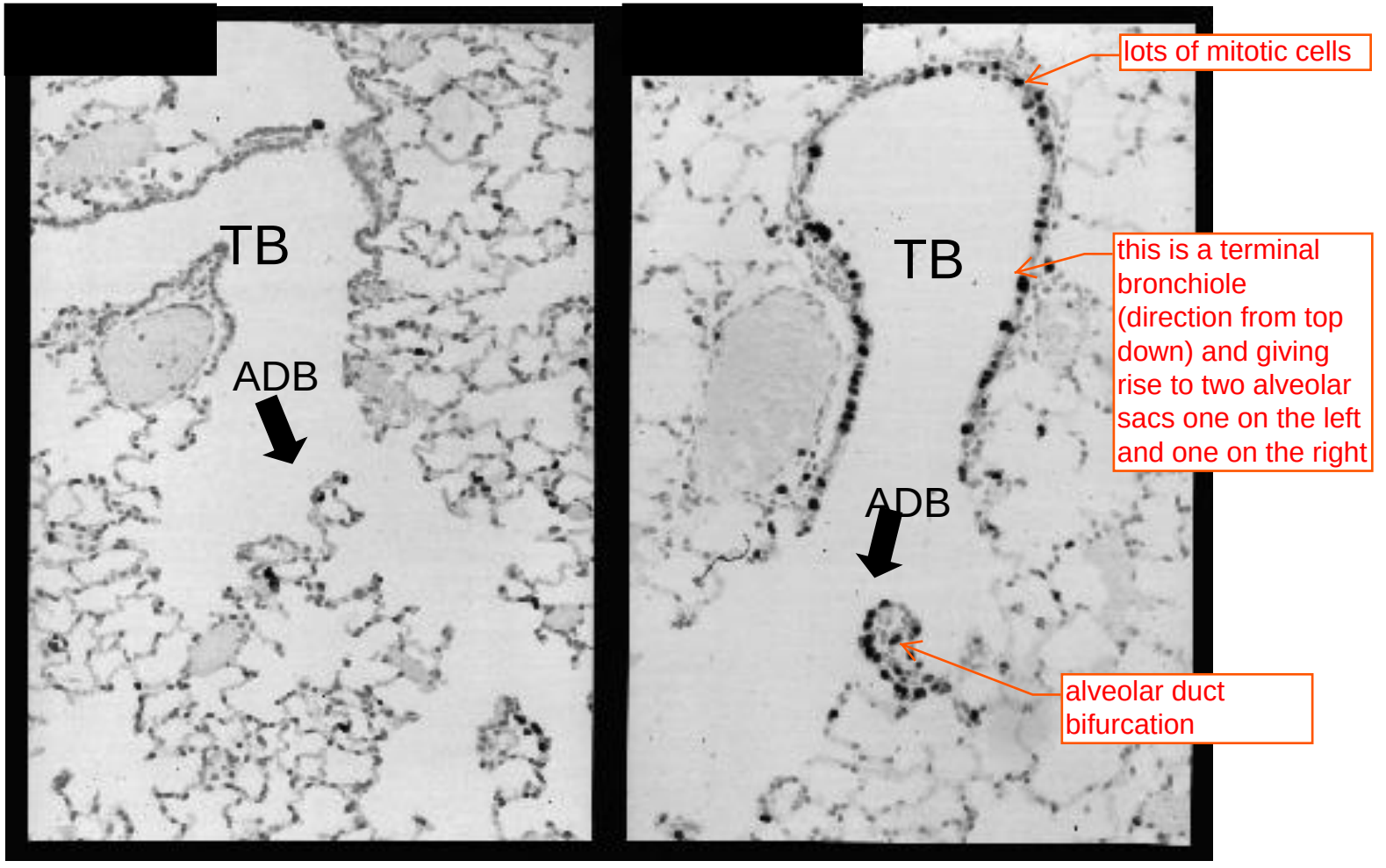


activities focused on the terminal respiratory unit
-->Terminal bronchiole and alveolar sacs

Visualizing Early Asbestos-Induced Cell Proliferation in rats

show cells undergoing division

using Bromodeoxyuridine Immunohistochemistry



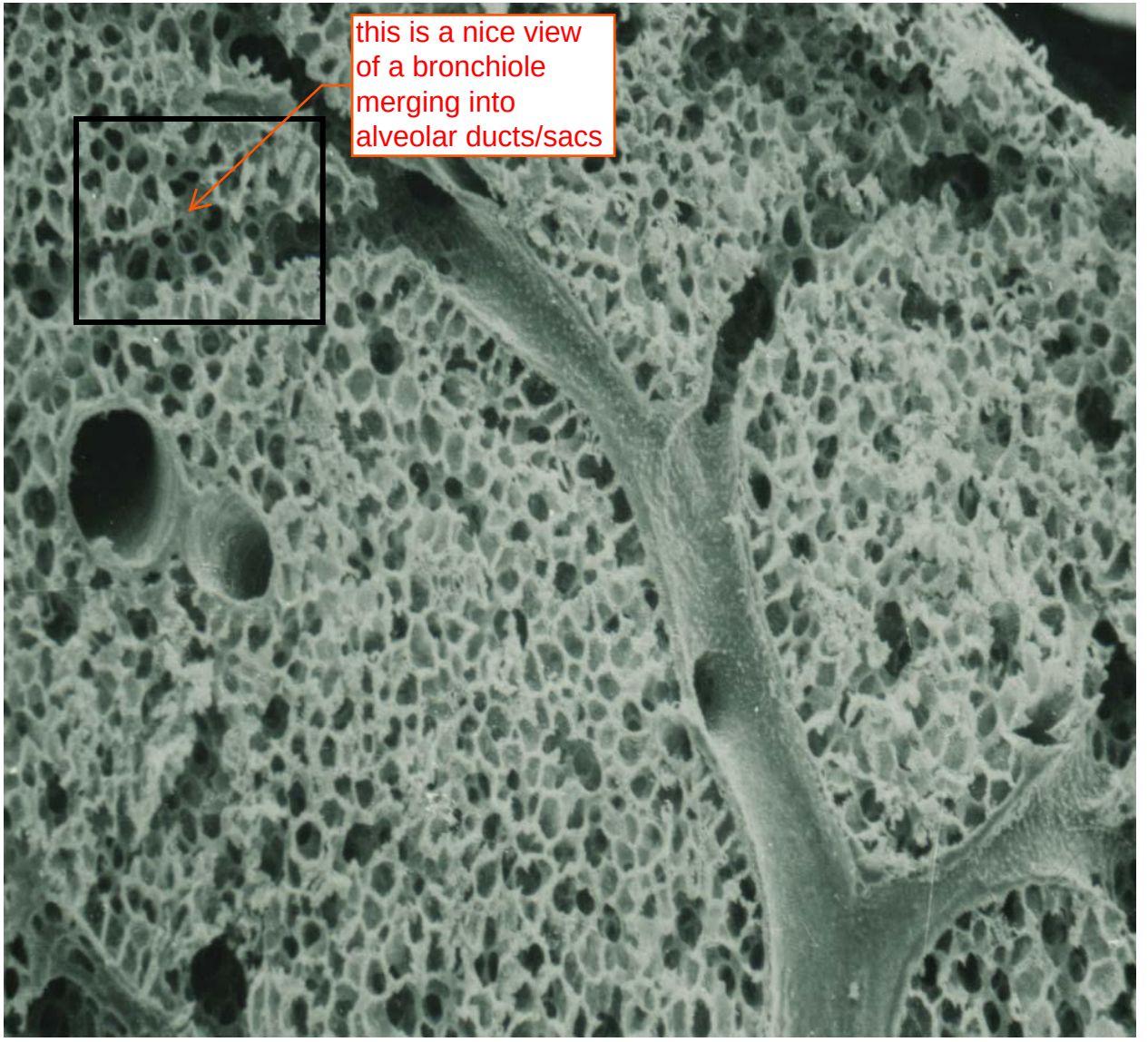
lots of mitotic cells

this is a terminal bronchiole (direction from top down) and giving rise to two alveolar sacs one on the left and one on the right

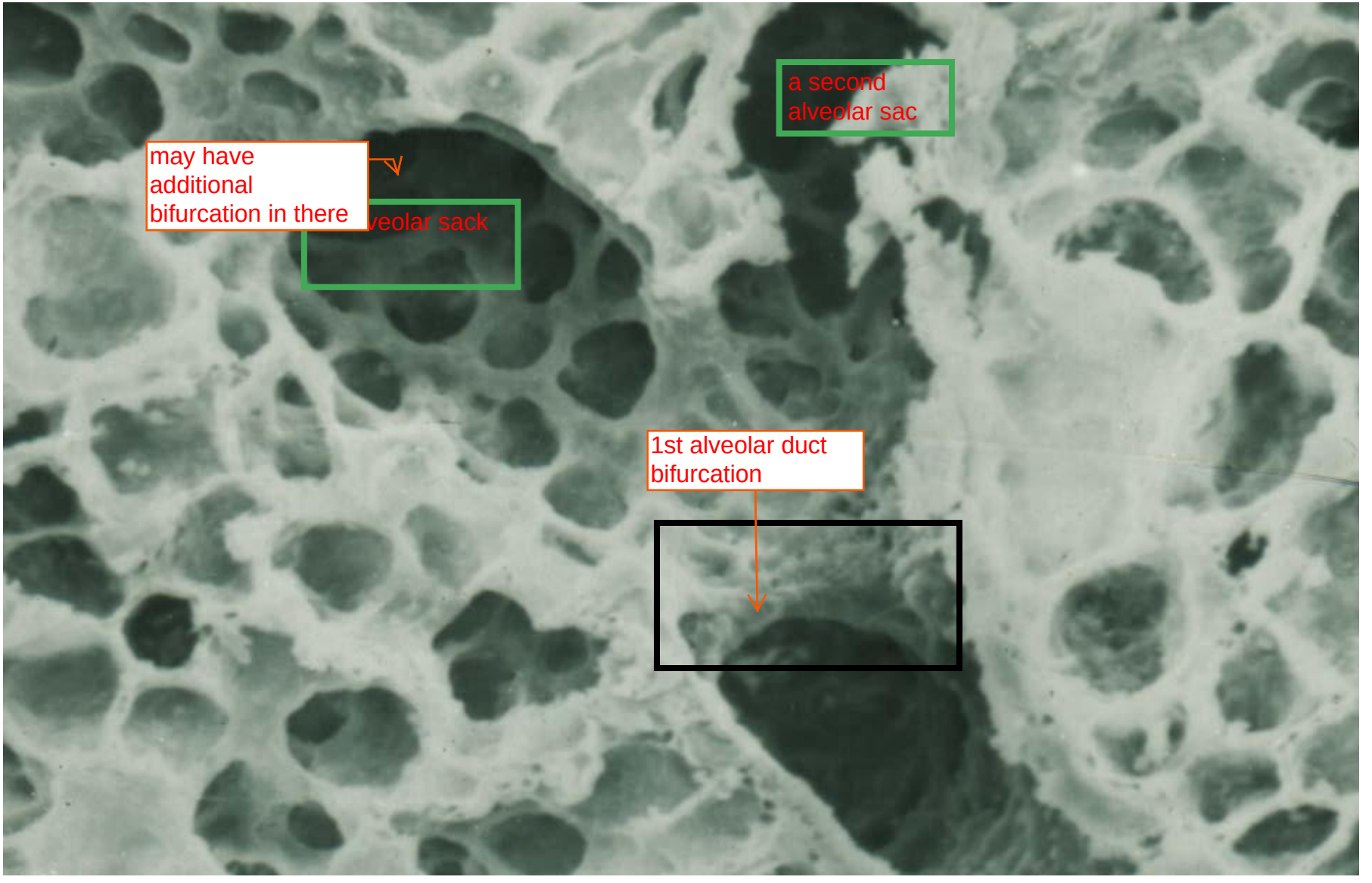
alveolar duct bifurcation

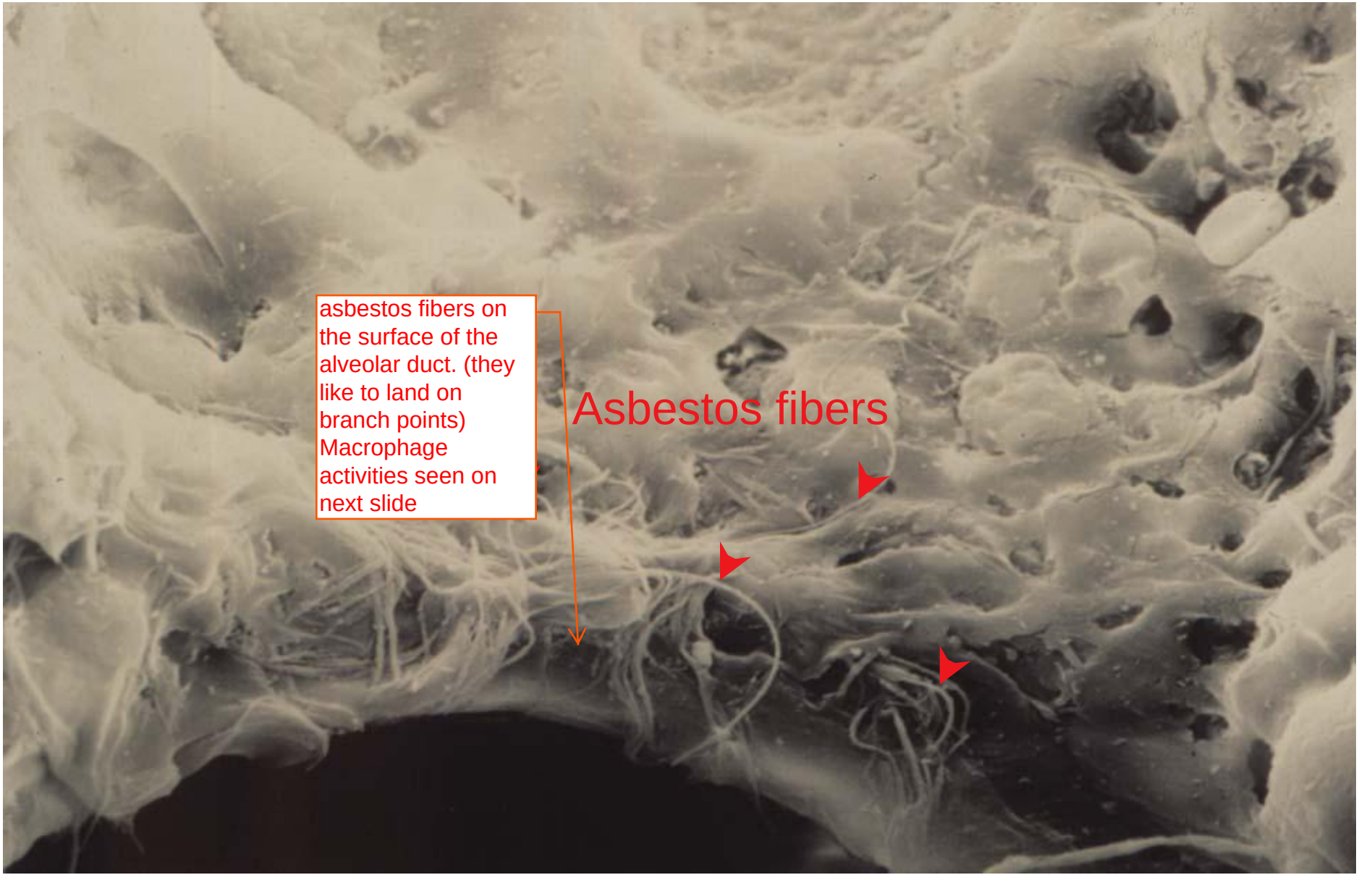
Asbestos Deposition and Early Responses in the Rat Lung

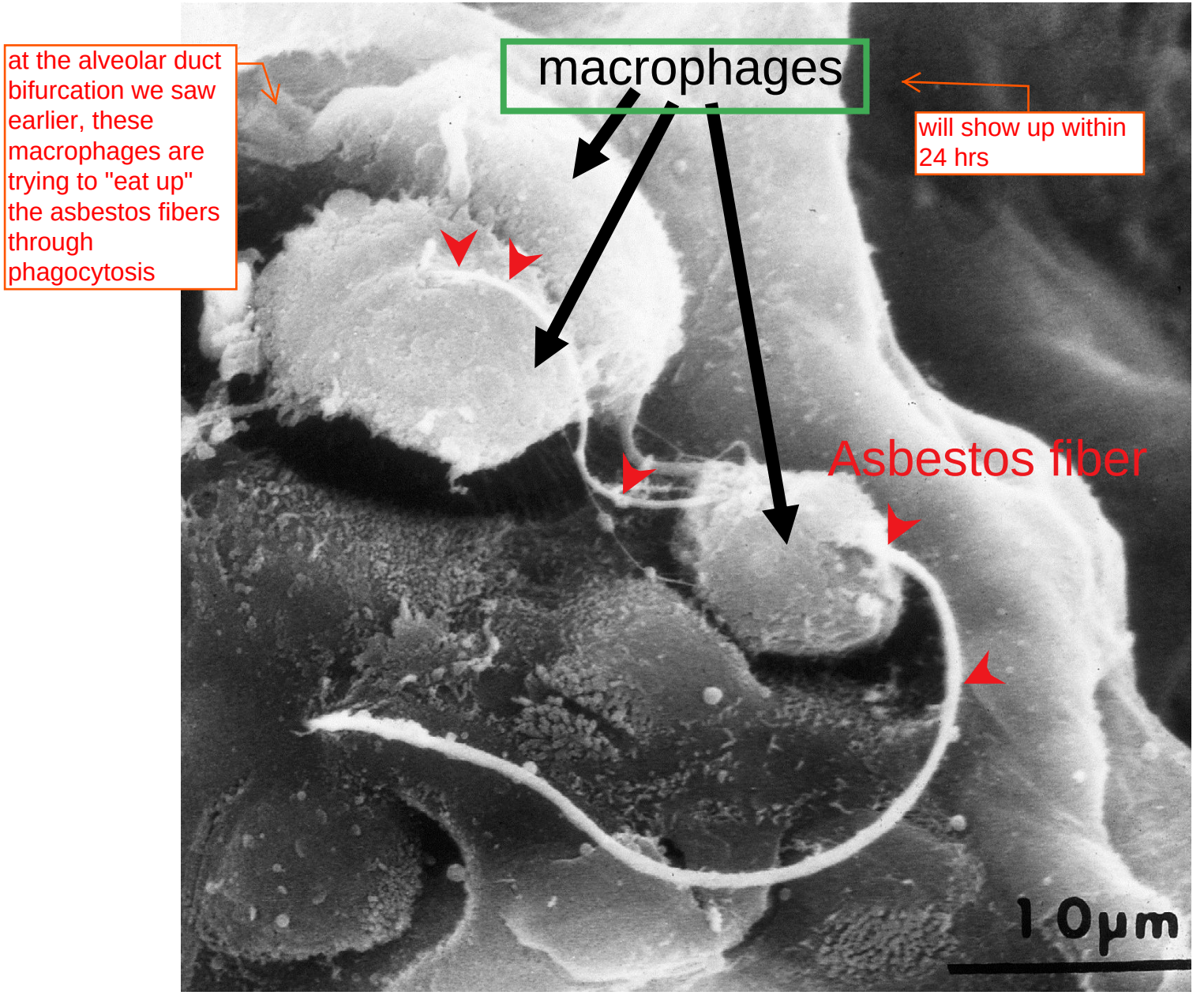
EM showing a lower power view of a lung from an experimental animal exposed to asbestos for a short period of time (less than a day)



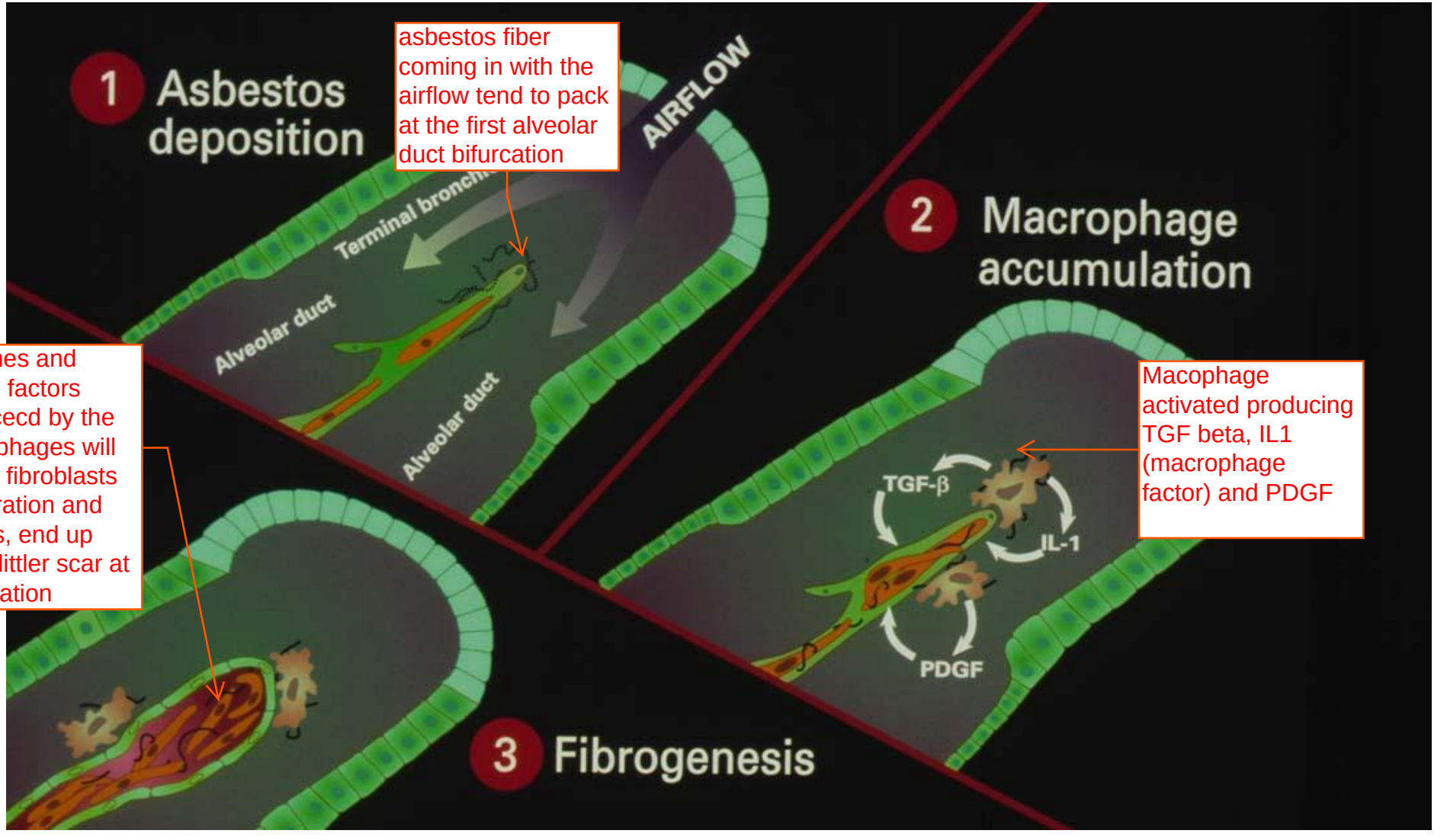
Asbestos Deposition and Early Responses in the Rat Lung



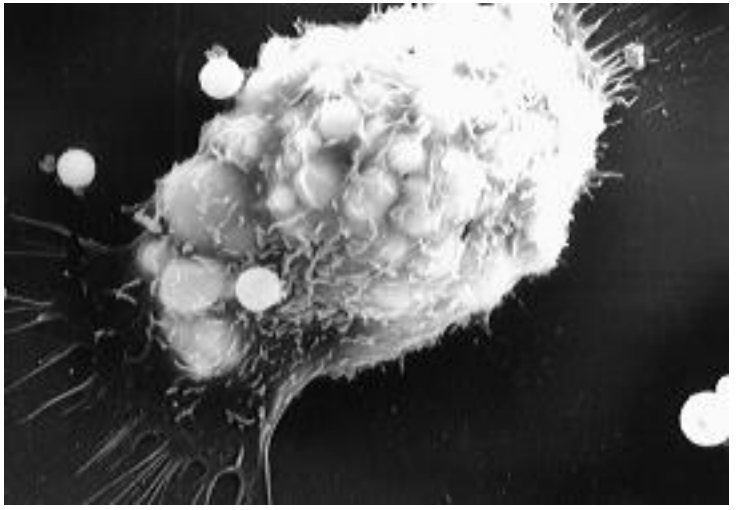

asbestos fibers on the surface of the alveolar duct. (they like to land on branch points) Macrophage activities seen on next slide
Asbestos fibers


at the alveolar duct bifurcation we saw earlier, these macrophages are trying to "eat up" the asbestos fibers through phagocytosis
macrophages
will show up within 24 hrs
Asbestos fiber
10µm

Early Fibrotic Lesion Development at Fiber Deposition Sites



Macrophage-Mediated Particle Clearance



phagocytosis, deposit them on mucociliary escalator or going into the lymphatics and clean up the foreign particles that way

1) mucociliary escalator: upward movement of particulate material by combined action of trapping particles in mucus, then upward beating of cilia on airway epithelial cells, then material is expelled or swallowed.
2) Macrophage-mediated: macrophages engulf particles and deposit them on mucociliary escalator or enter the lymphatic system.

they can destroy the virus and bacterial. but stuff like asbestos fibers or silica can not destroyed by macrophages

Major Factors Influencing Repair versus Disease

- Deposition site of inhaled toxicant
- Severity of injury by inhaled toxicant
- Reactivity and solubility of inhaled toxicant
- Persistence of inhaled toxicant
- Immune response and genetic susceptibility

if trapped in LOWER respiratory track--> more likely to get disease

dose of pathogen exposure

3.g. asbestos fibers particularly persistent. persistant ones are more likely to cause injury

Environmental and Occupational Lung Diseases

- Obstructive Airway Diseases
- Hypersensitivity Pneumonitis
- Fibrotic Diseases
- Lung Cancer

Asbestos-related Diseases

- Asbestosis
- Carcinoma of the Lung
- Mesothelioma
  - Pleural
  - Peritoneal
- Benign Asbestos-Related Pleural Diseases (Pleural Plaques)
- Other Cancers (Larynx)

increased risk of carcinoma with smoking and asbestosis

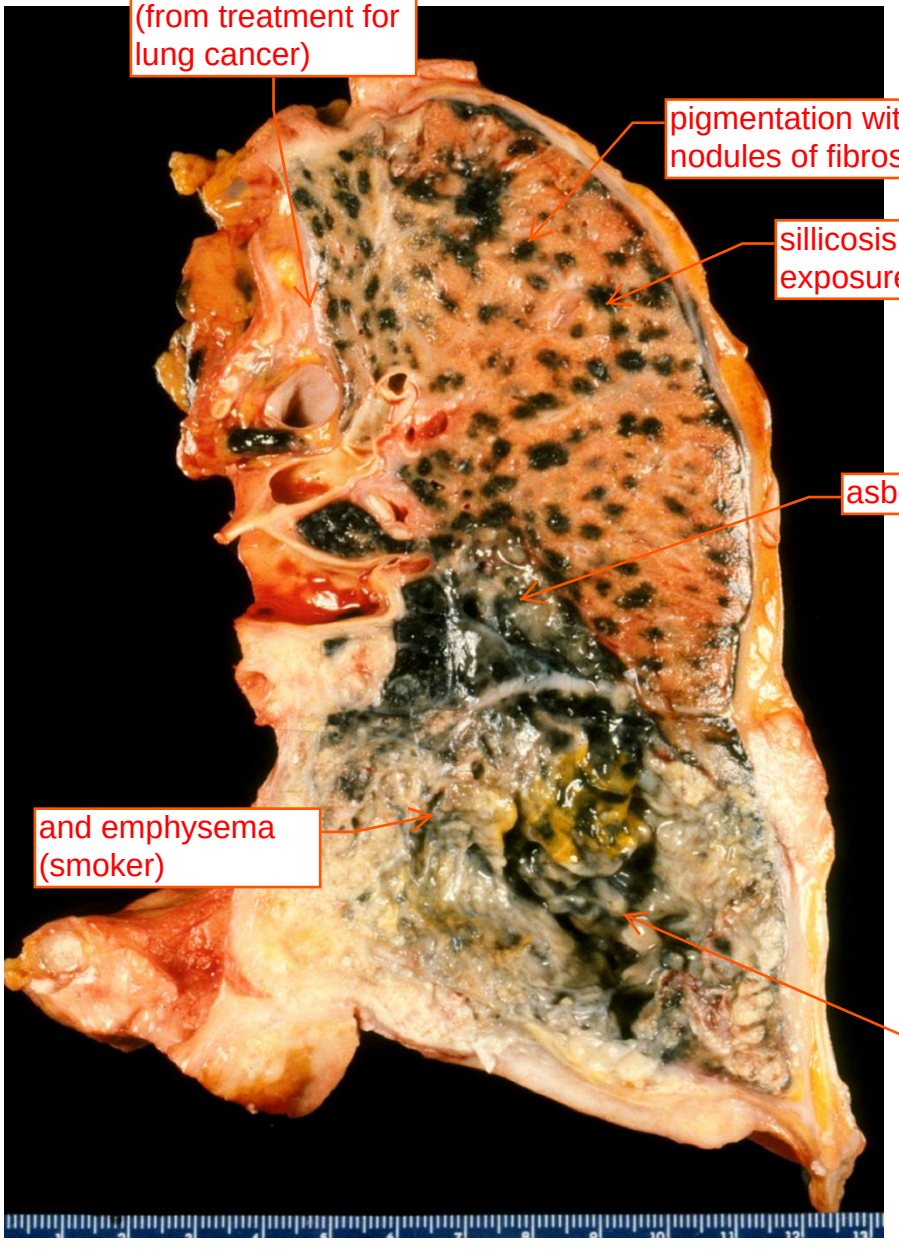
asbestos exposure and smoking have synergy and multiply the risks for lung cancer

80-90% asbestos related

tend to need an even higher expsoure

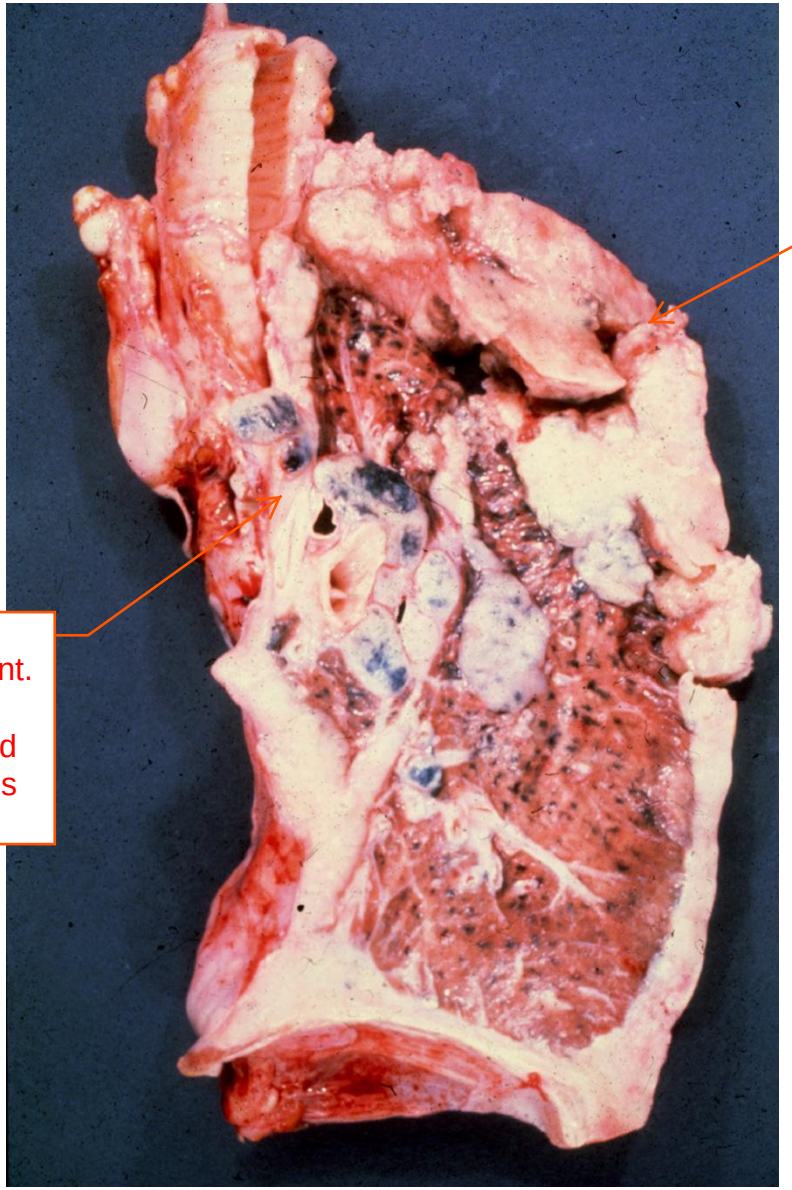
scars may form

larynx gets hit twice:1 when you breath the asbestos fiber in. 2. on the mucocilliary escalater when you try to clean the fibers out



ONE lung with many different pathogenesis!

Asbestos-Induced Lung Cancer



classic asbestos related mesothelioma of the pleural-->grow like a sheath

regional lymph node involvement. This lung is extremely injured and respiration is greatly limited

Asbestos-Related Mesothelioma

MECHANISMS OF ASBESTOS-INDUCED CARCINOGENESIS

- **Mesothelioma**
  - **Clastogenic mechanism**
  - **Reactive oxygen species (ROS)**
  - **Growth factors/cytokines**
- **Lung Cancer**
  - **Synergistic effect with cigarette smoke**
  - **ROS, growth factors, cytokines**

if put mesothelial cells with asbestos fibers in vitro, there is interference with normal mitotic divisions -->chromosome fragmentation etc

may result in mutations that lead to malignancy

the exposure need not be too high

5 fold risk increase with high dose asbestos. 10 fold with smoking. 50 fold with both combined