PATHOGENESIS OF BRONCHIAL OBSTRUCTION - ASTHMA, COPD

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1. ASTHMA

- Definition by GINA (Global Initiative for Asthma):

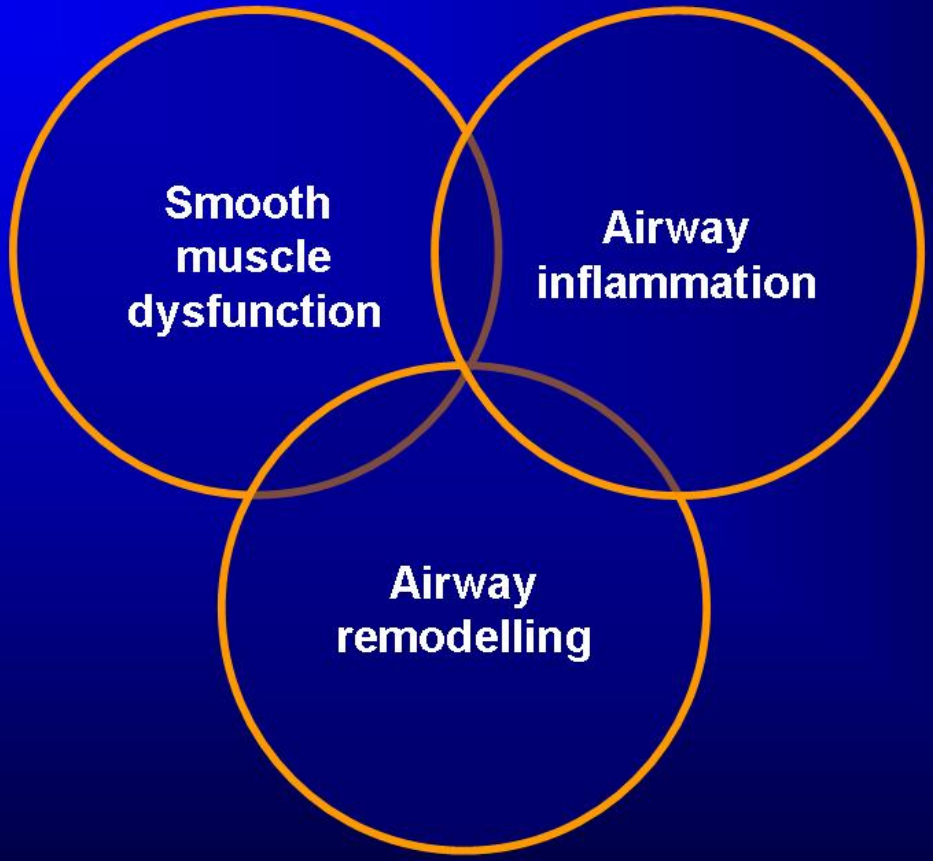
  Asthma is a chronic inflammatory disorder of airways. Many cells and mediators are involved in this process – eosinophils, mast cells and T-lymphocytes. Chronic inflammation is connected with bronchial hyperresponsivness and leads to episodes of wheezing, coughing, tightness in the chest, breathlessness, shortage of breath specially at night and in the morning. This episodes are usually connected with variable obstruction which is reversible spontaneously or by treatment.

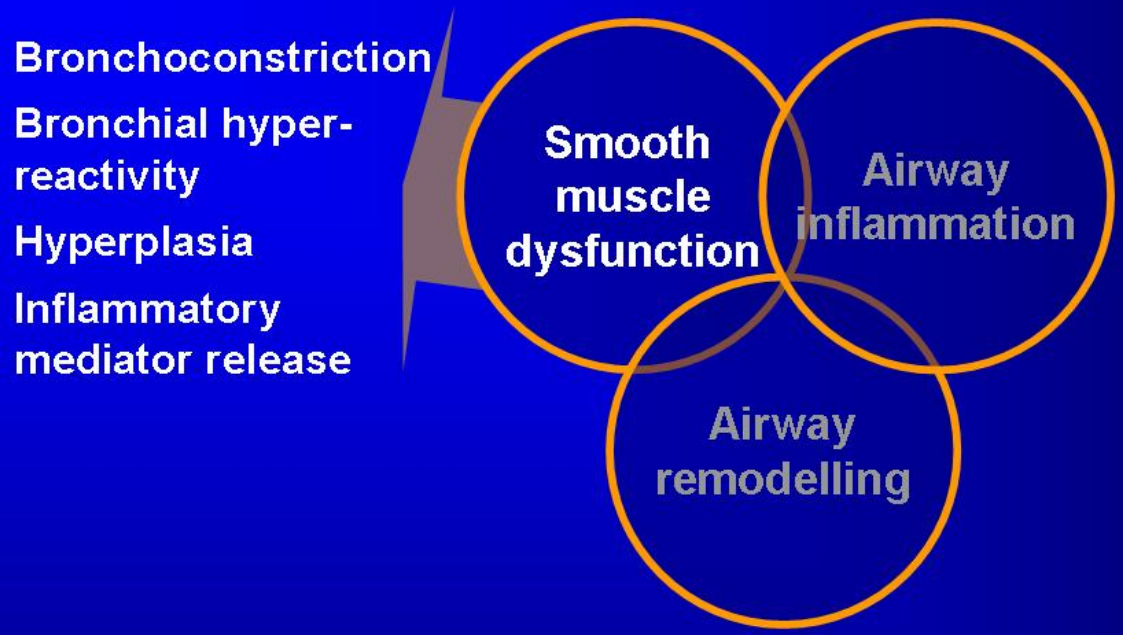
- **Allergic asthma** = asthma induced by immunological mechanisms. IgE induced asthma – IgE antibodies triggers early and late-phase of response, T-lymphocytes late and delayed responses.
- **Non-allergic asthma** = asthma induced by non-immunological triggers
- **Intermittent x persistent**

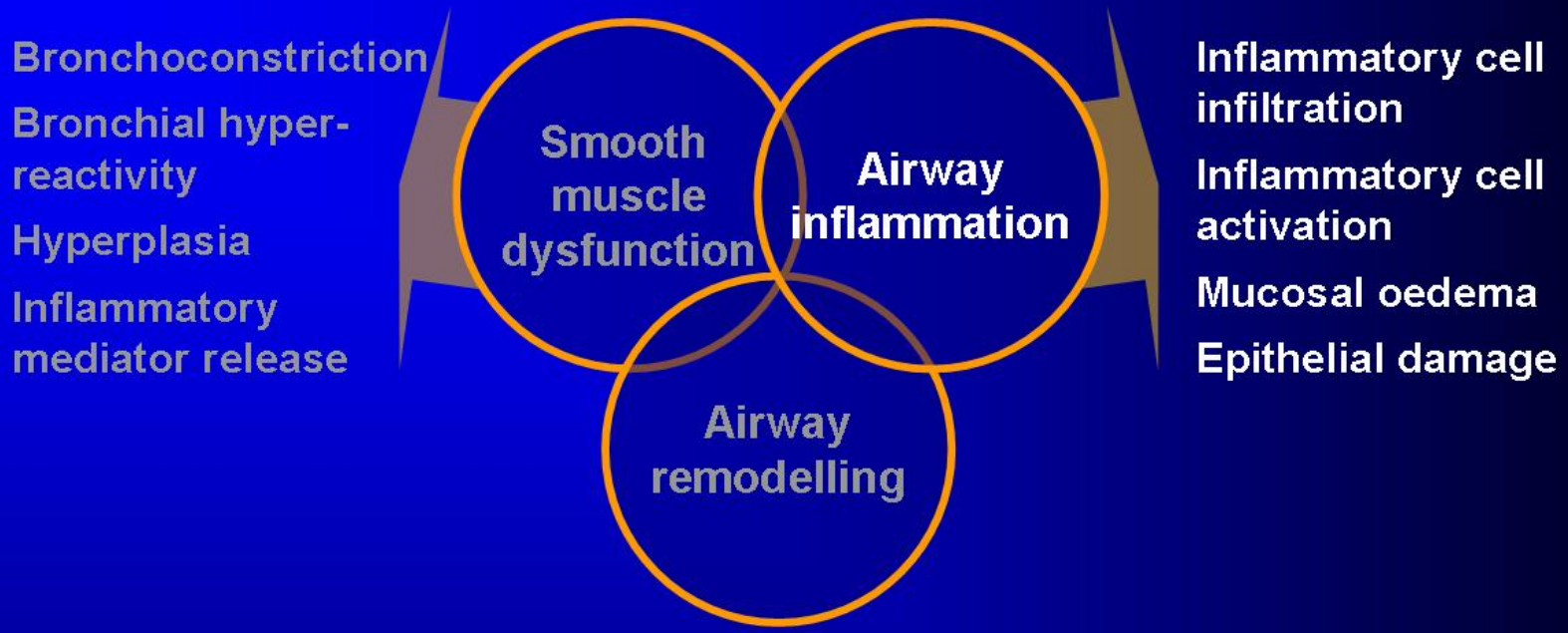
Inflammation causes obstruction of airways by:

- Acute bronchoconstriction
- Swelling of bronchial wall
- Chronic production of mucous
- Remodeling of airways walls

Asthma pathophysiology




Bronchoconstriction
Bronchial hyper-reactivity
Hyperplasia
Inflammatory mediator release
Smooth muscle dysfunction
Airway inflammation
Airway remodelling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Inflammatory cell activation
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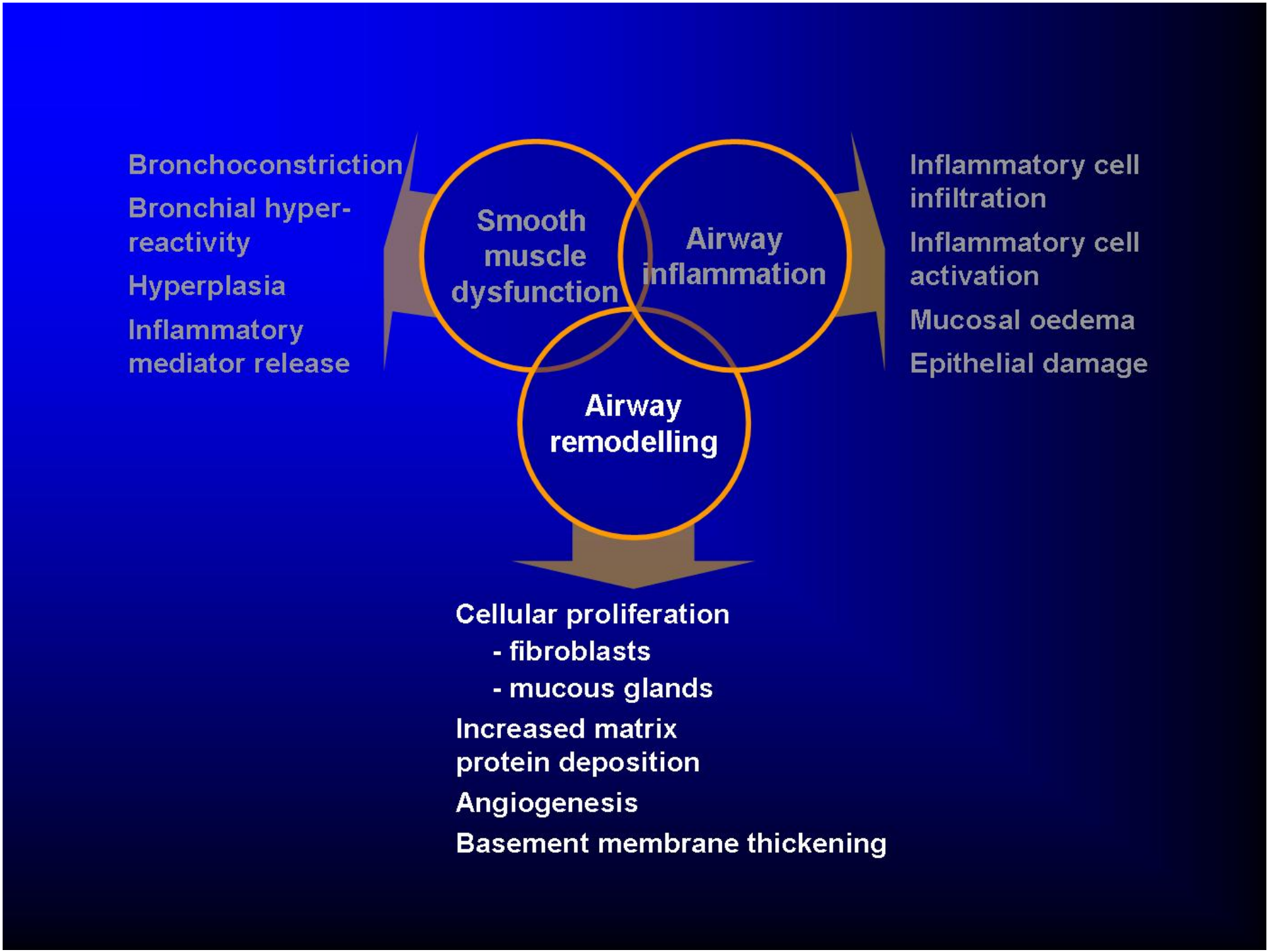
Epithelial damage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Epithelial damage
Cellular proliferation
- fibroblasts
- mucous glands
Increased matrix protein deposition
Angiogenesis
Basement membrane thickening

Risk factors:

- **individual predisposition** (genetic variability – 5. a 11. chromosome - atopy, bronchial hyperreactivity, male or female, nation)
- **environment** – exposition to allergens and professional chemicals which lead to sensitivity, viral and bacterial infection, food, smoking, social and economic society, number of family members, psychosomatic influence

Cells involved in chronic allergic inflammation

- 1. Eosinophils
- 2. Mast cells
- 3. T-lymphocytes
- 4. Neutrophils
- 5. Basophils

Histology

- **Histopathology** findings during biopsy examination have not clear affinity to course of disorder and changes of pulmonary function. Also bronchial hyperreactivity does not correlate with histology findings

Inflammation

Acute inflammation

↓

Symptoms
of bronchoconstriction

Remodeling of airways

↓

Ongoing
obstruction of
airways

Chronic inflammation

↓

Exacerbation
nonspecific
hyperreactivity

Therapy and obstruction

- Changes of **ventilation parameters** exist in patients with proper anti-inflammatory therapy

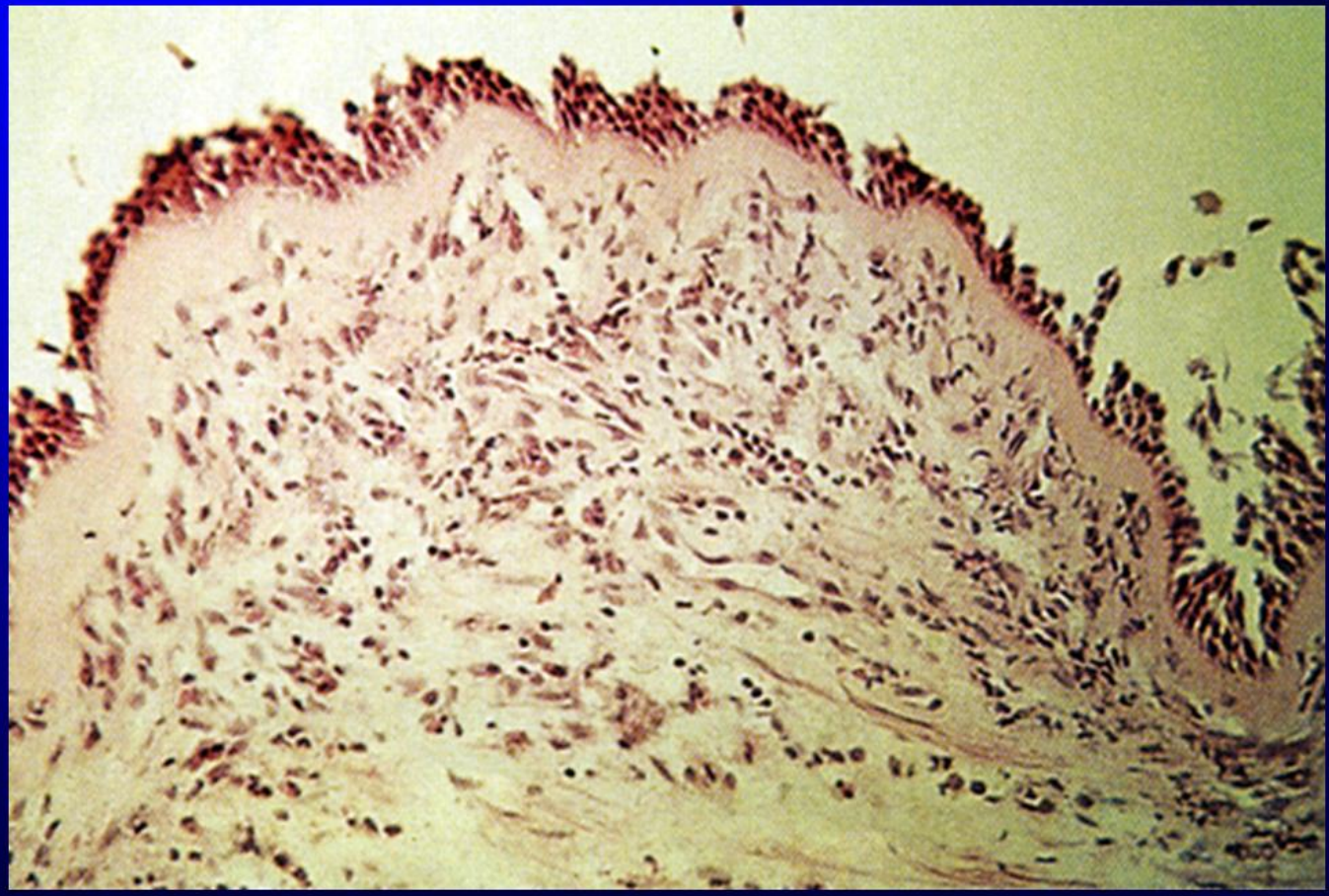
x

- **the obstruction of airways** is not proven in all asthmatic patient.

Remodeling

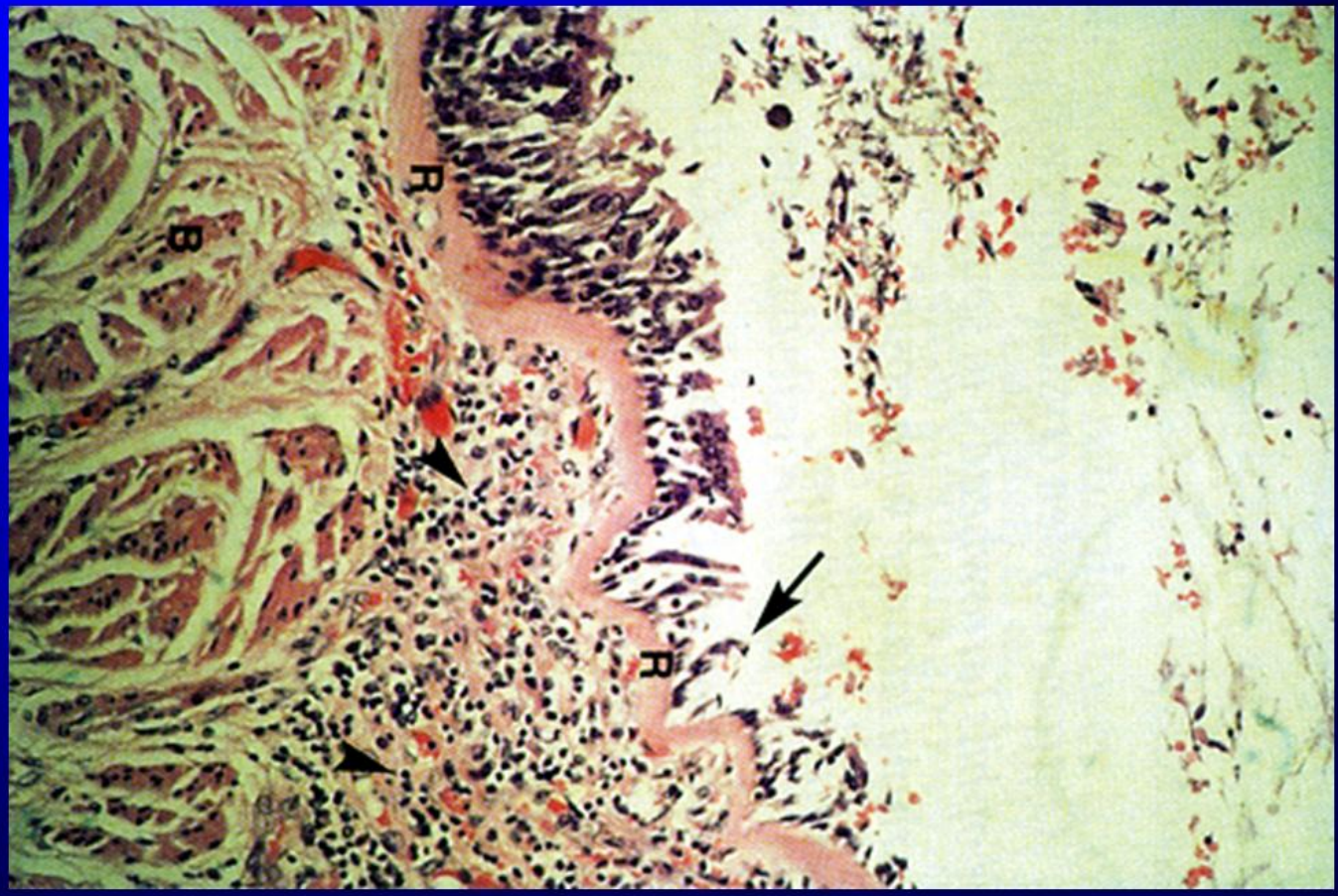
- destruction of brush epithelium in airways
- swelling of the bronchial wall
- stimulation of proliferation of fibroblasts
- deposition of collagen in lamina reticularis of basal membrane
- hypertrophy of smooth muscles
- hyperplasia of goblet cells

Loss of surface epithelium in mild asthma



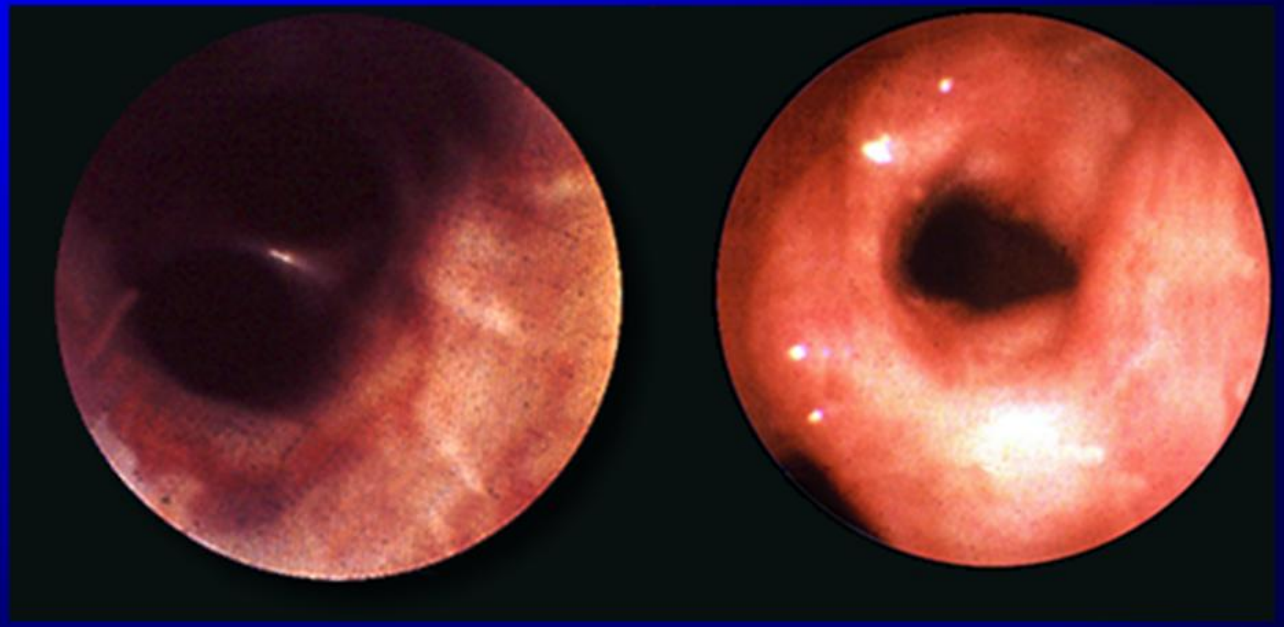
Jeffery, 2000

Epithelial damage in fatal asthma



Jeffery, 2000

Allergen induced mucosal oedema

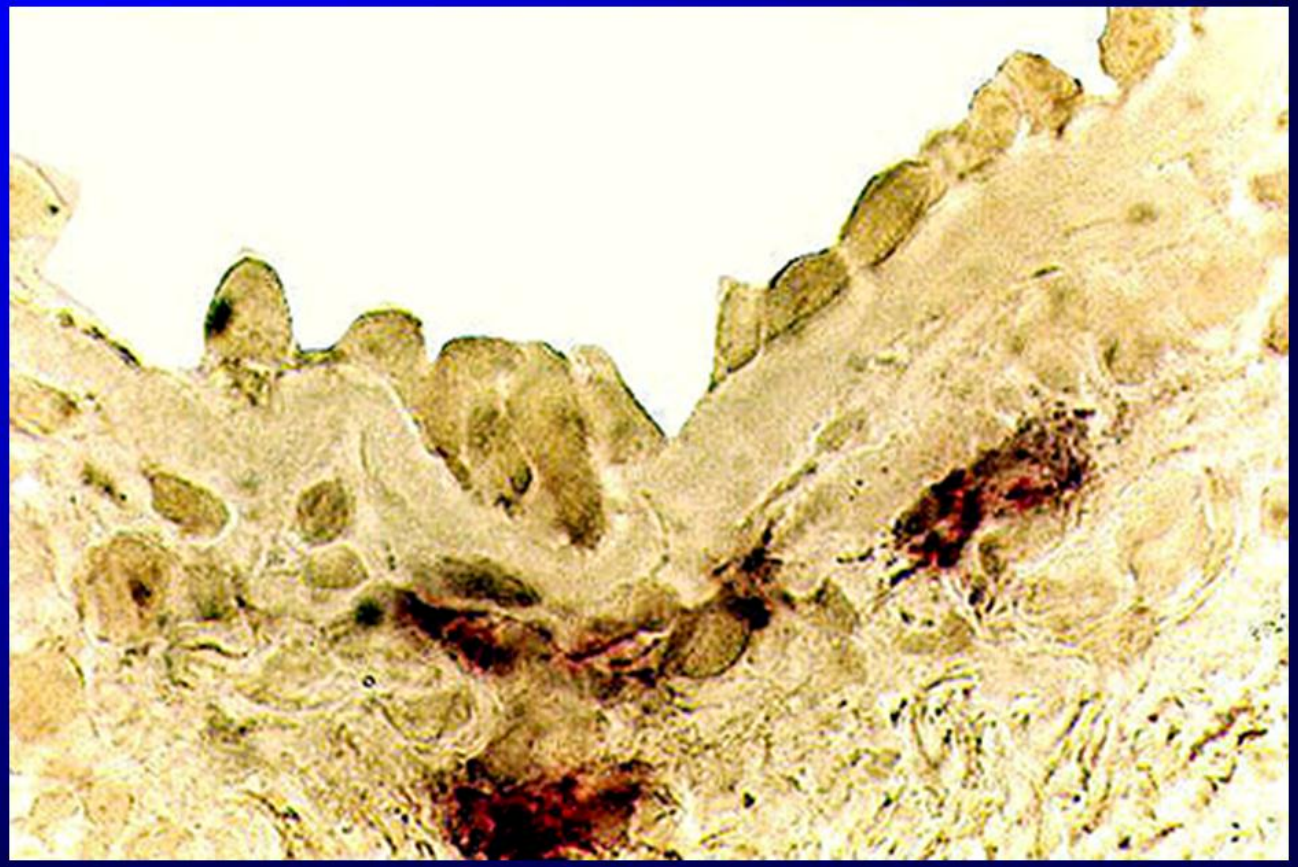


Time zero

6 hours

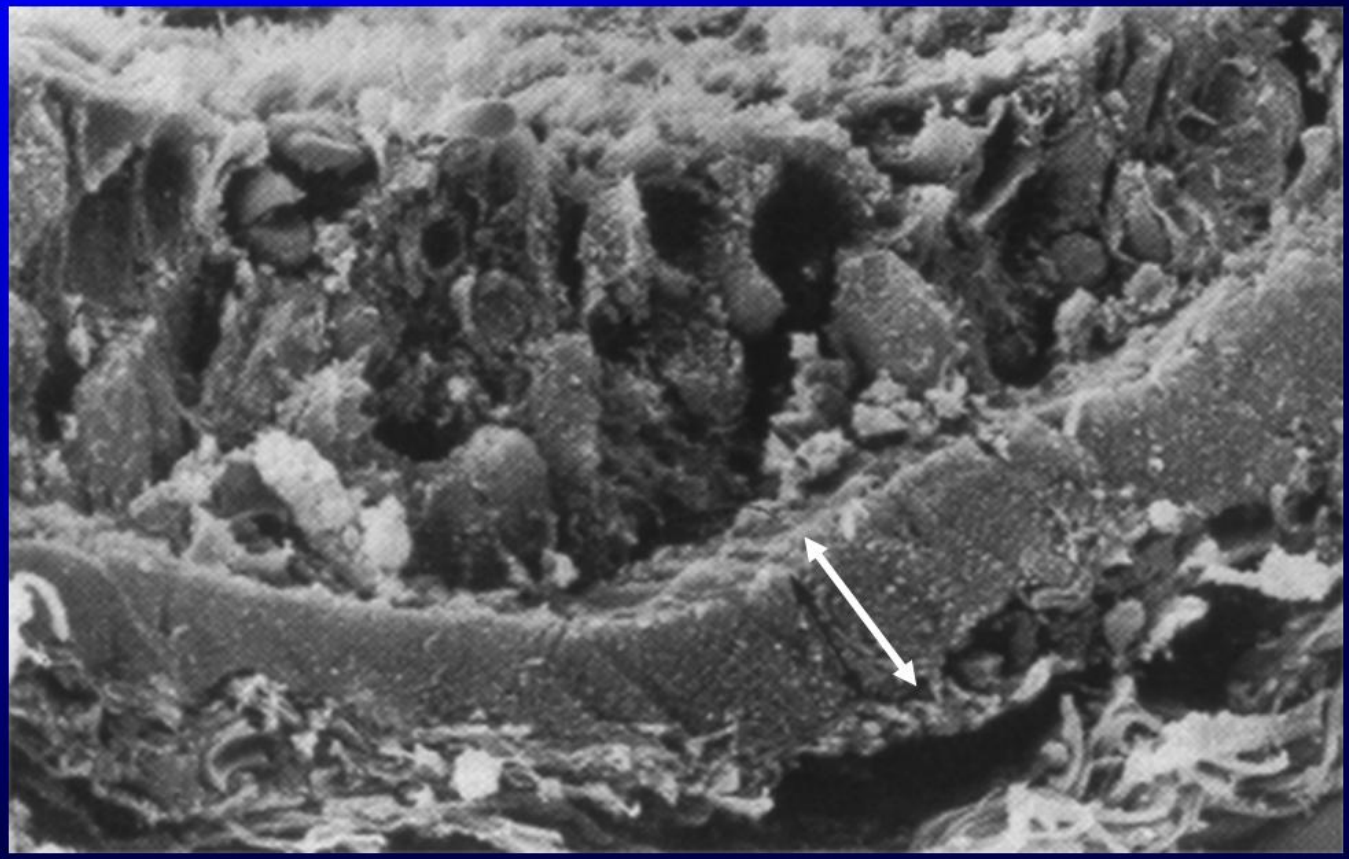
Photograph courtesy of Dr P Howarth

TGF-beta expression by fibroblasts



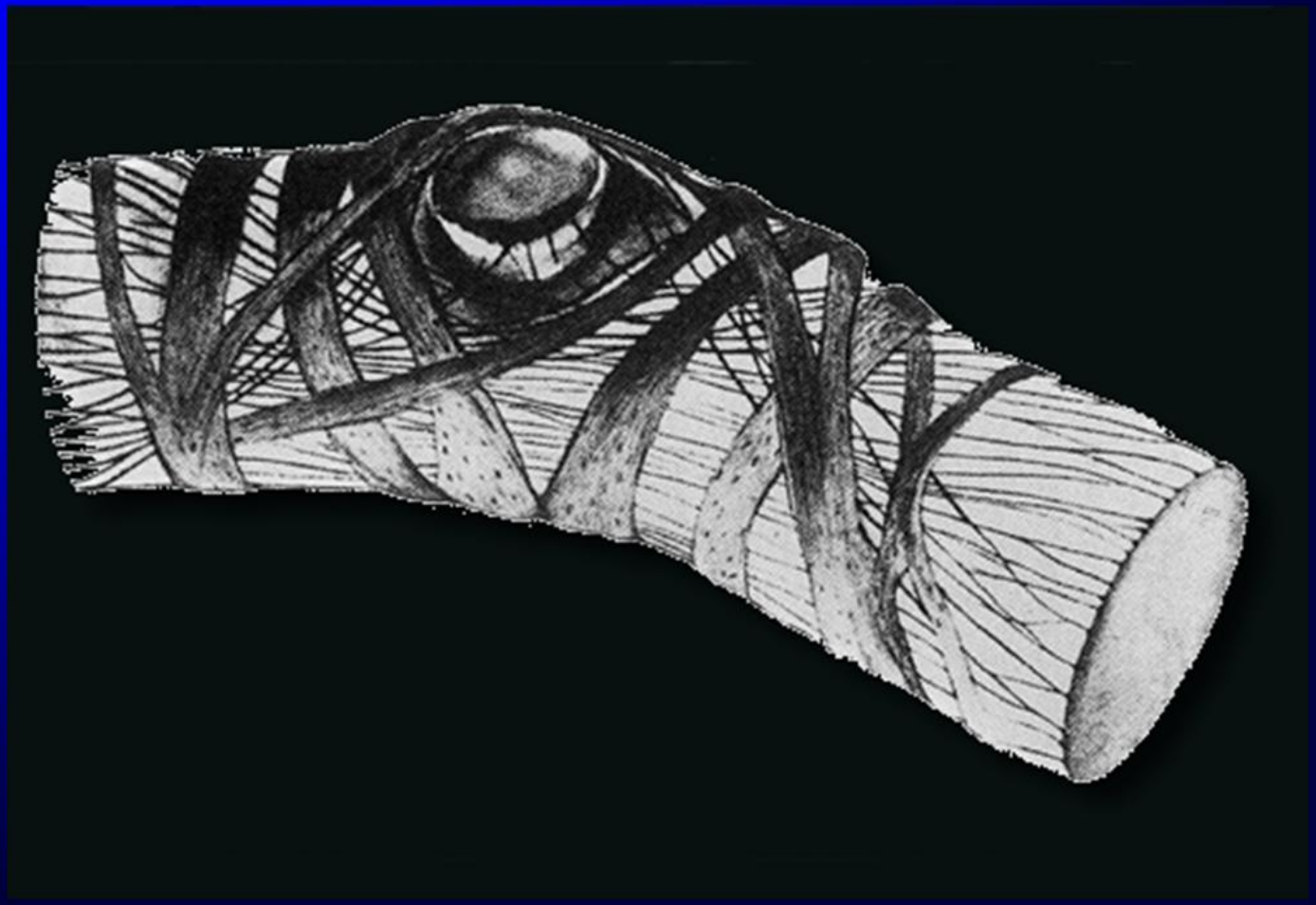
Photograph courtesy of Profesor A M Vignola

Basement membrane thickening in asthma



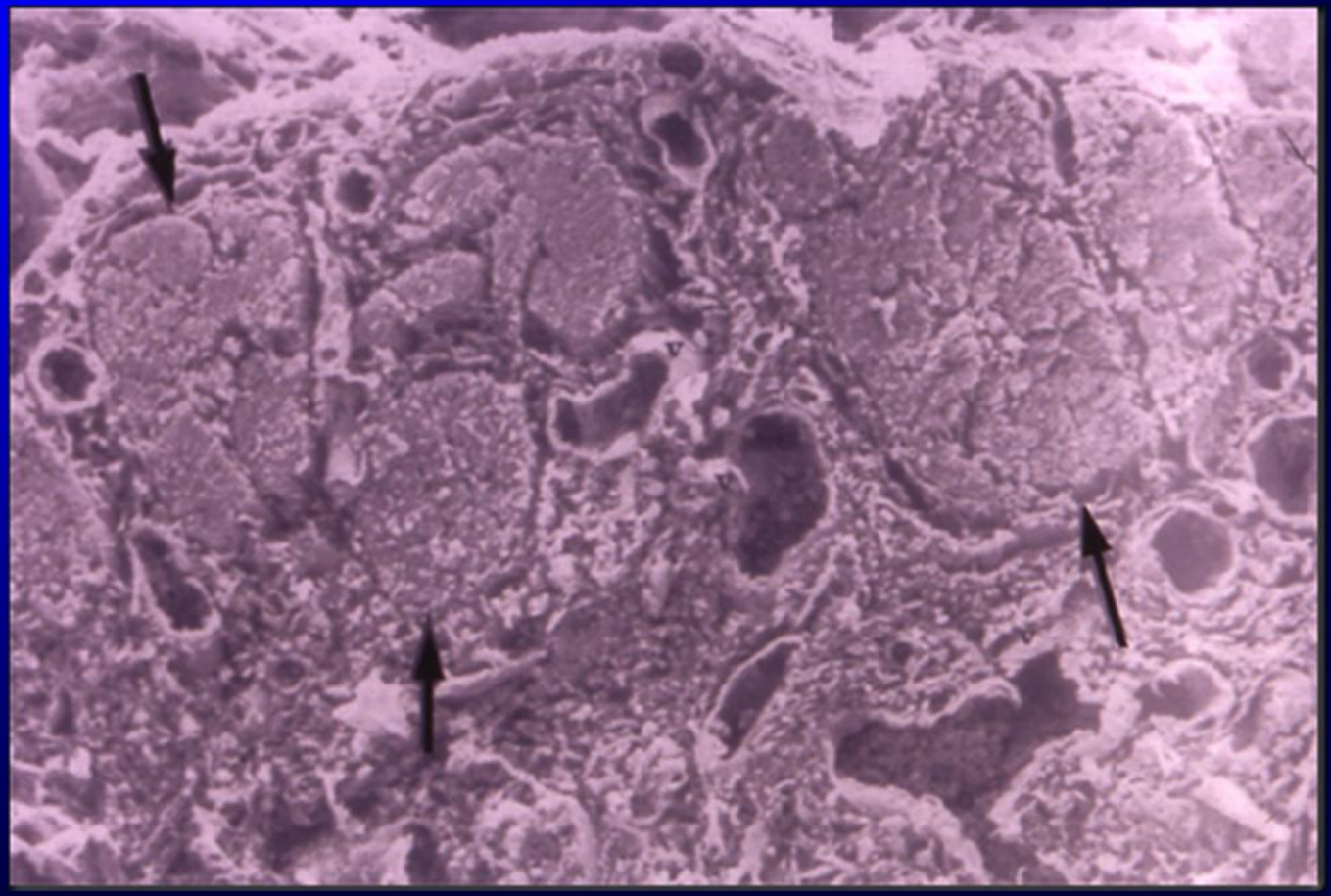
Jeffery, 1999

Airway wall bronchial smooth muscle



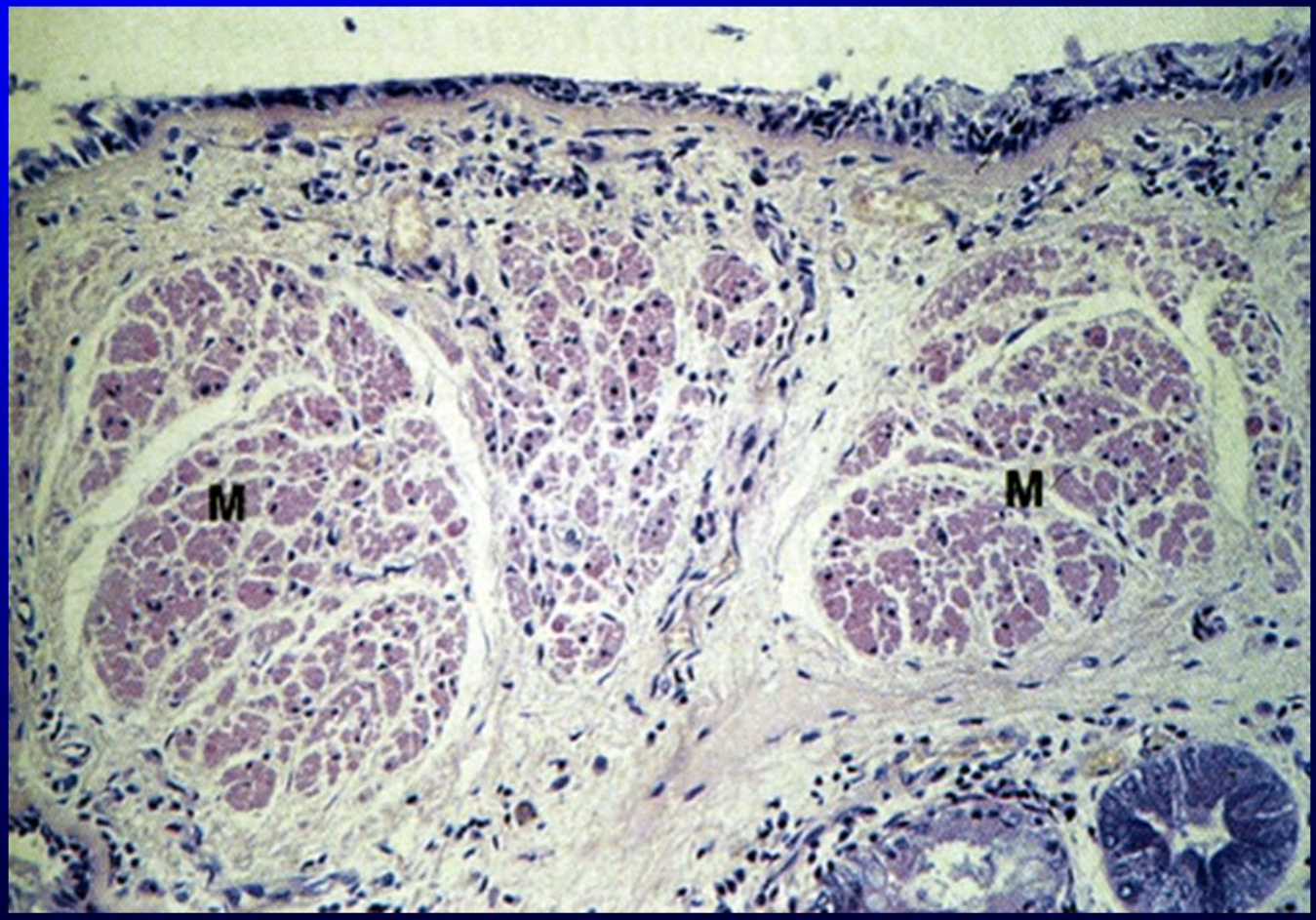
Reproduced from Miller 1937

Bronchial smooth muscle enlargement



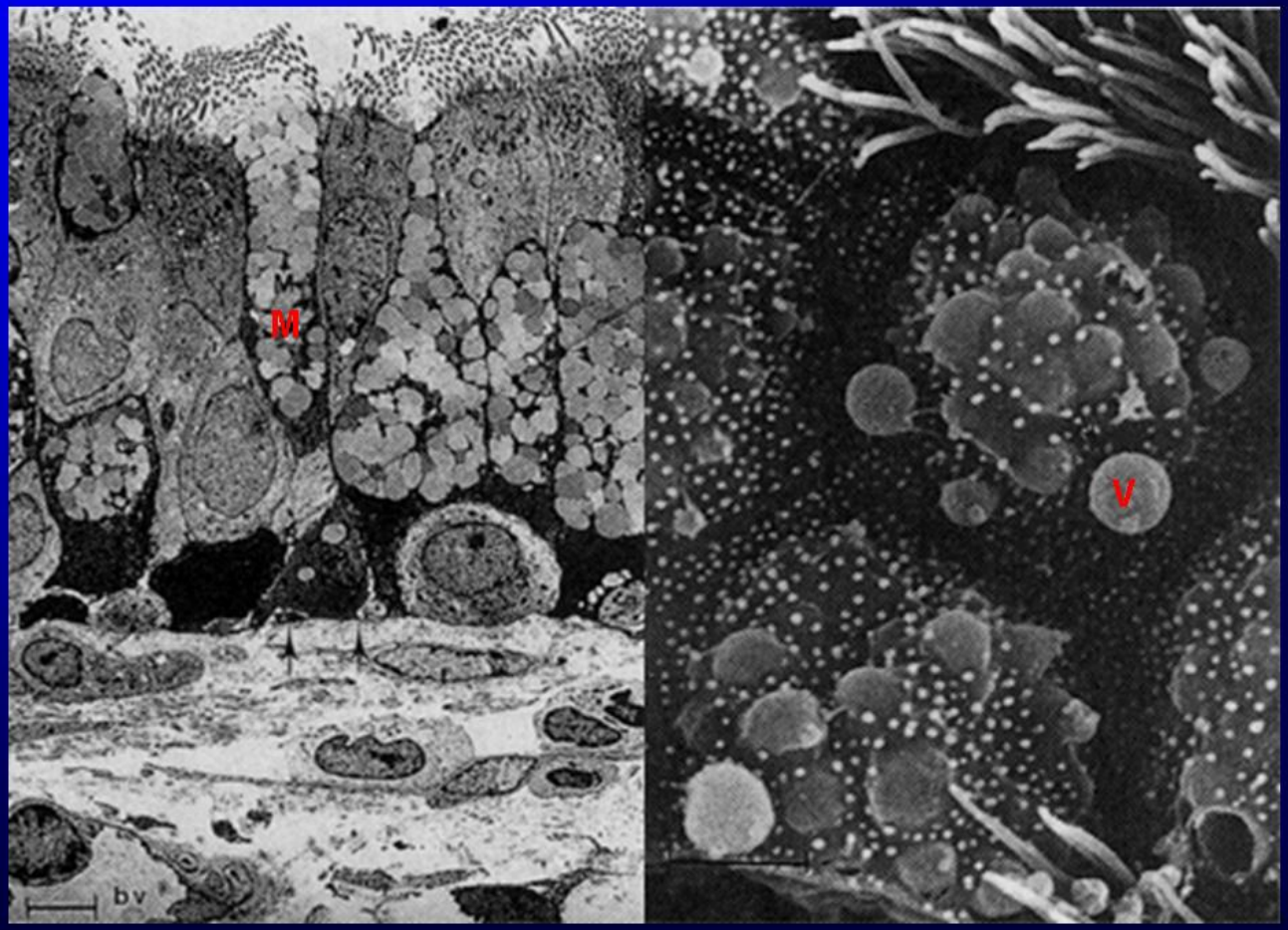
Jeffery, 2000

Airway smooth muscle cell proliferation



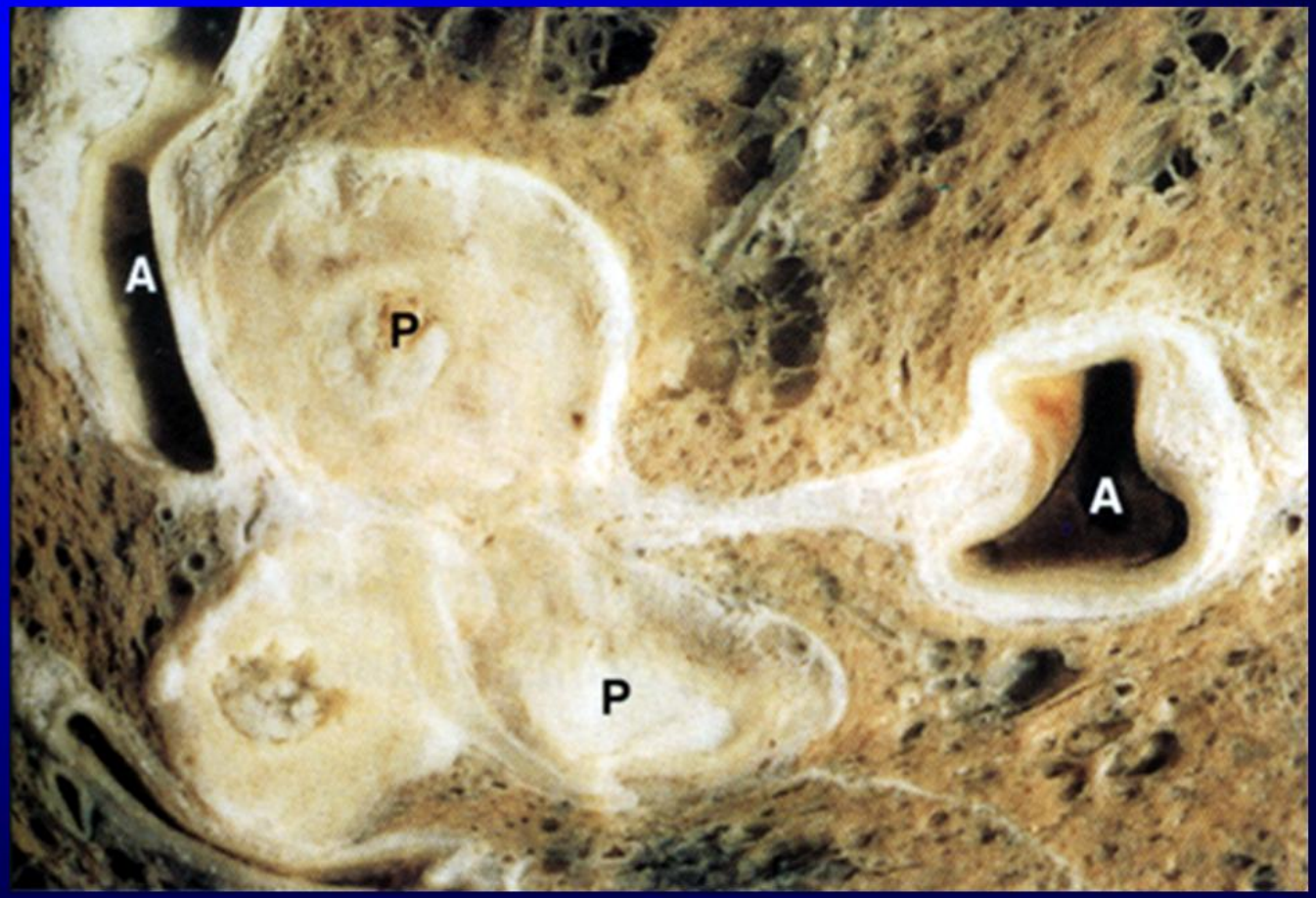
Jeffery, 2000

Mucous gland hyperplasia in asthma



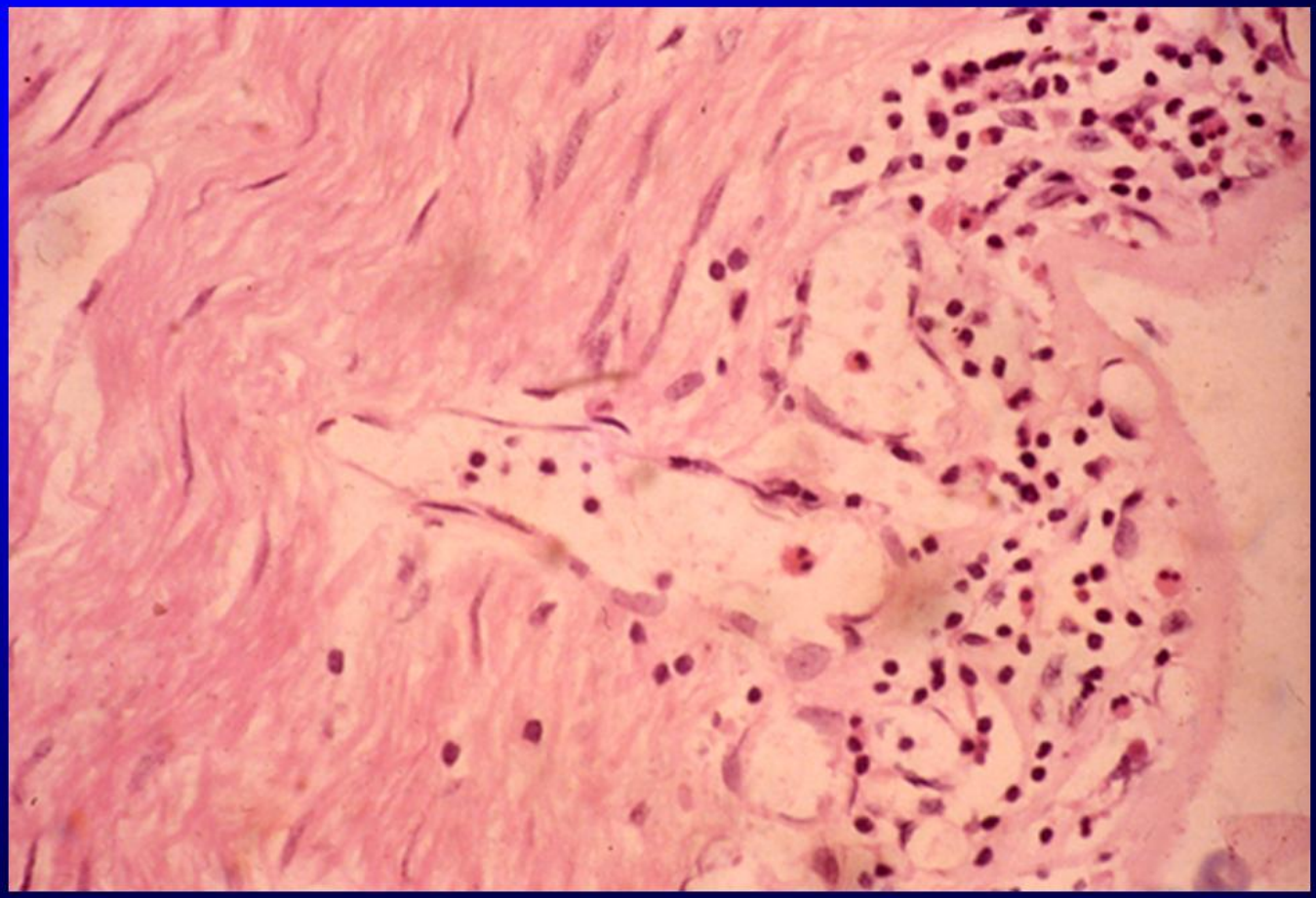
Jeffery, 1999

Airway mucus plugs in fatal asthma

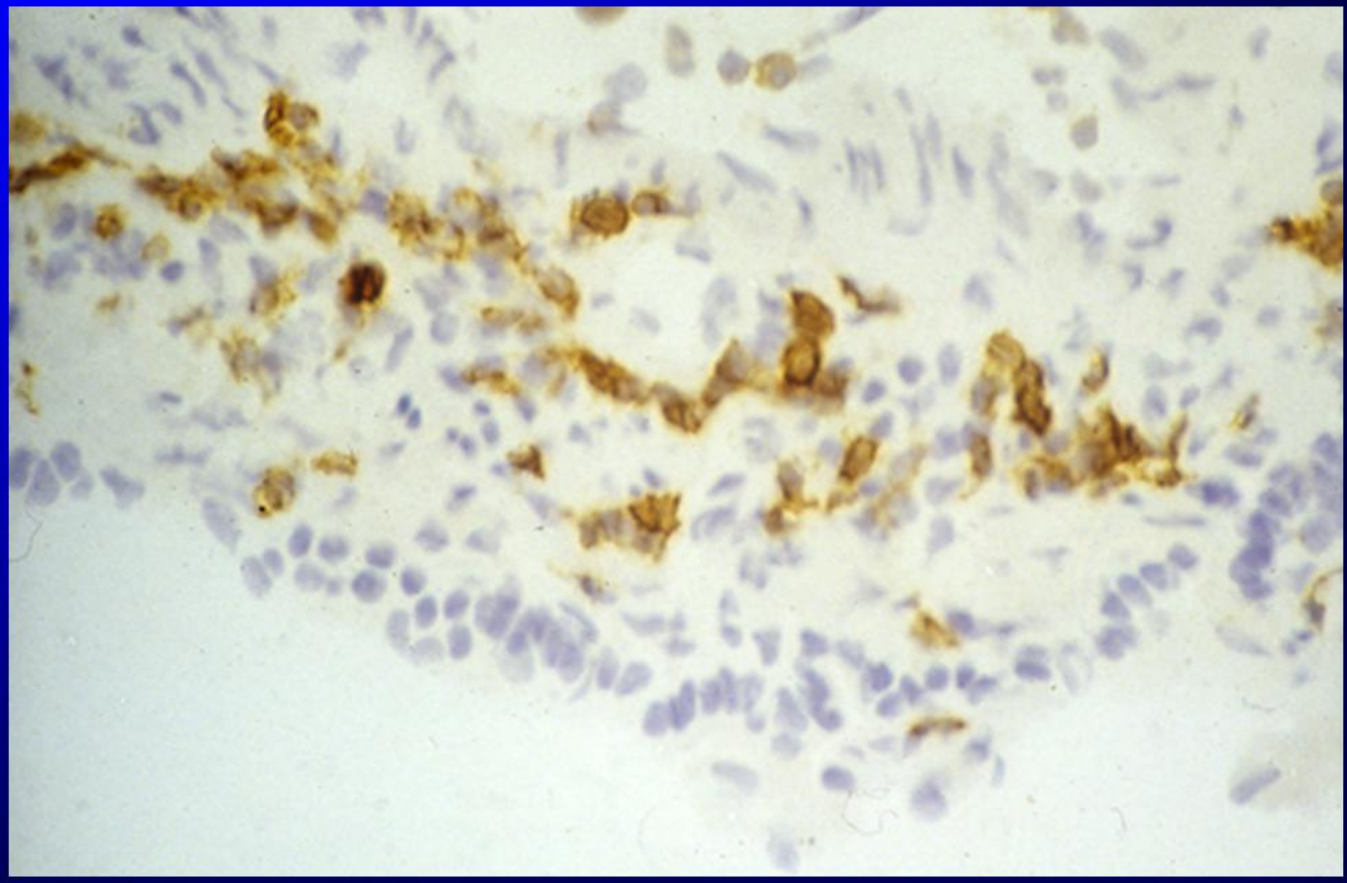


Jeffery, 2000

Chronic inflammation in asthma



Increased CD4(+) T-cells



Photograph courtesy of Dr J Wilson

Subepithelial structures:

- thickness of basal membrane
- increasing deposition of extracellular matrix under epithelium
- deposition of collagen I., III., IV., V. and VII. in reticular membrane
- increasing deposition of proteoglycans (lumican, biblycan, decorin, fibromodulin, hyaluron, versica)
- tenascin (corresponds with activity of chronic inflammation)
- fibronectin

Pathogenetic process of inflammation

Increasing number of smooth muscles fibres

Sever bronchospasms during exacerbation

Increasing number of mucous glands

Increase of mucous secretion during exacerbation

Ongoing of inflammatory cells

Inflammation

Release of fibrogenetic factors

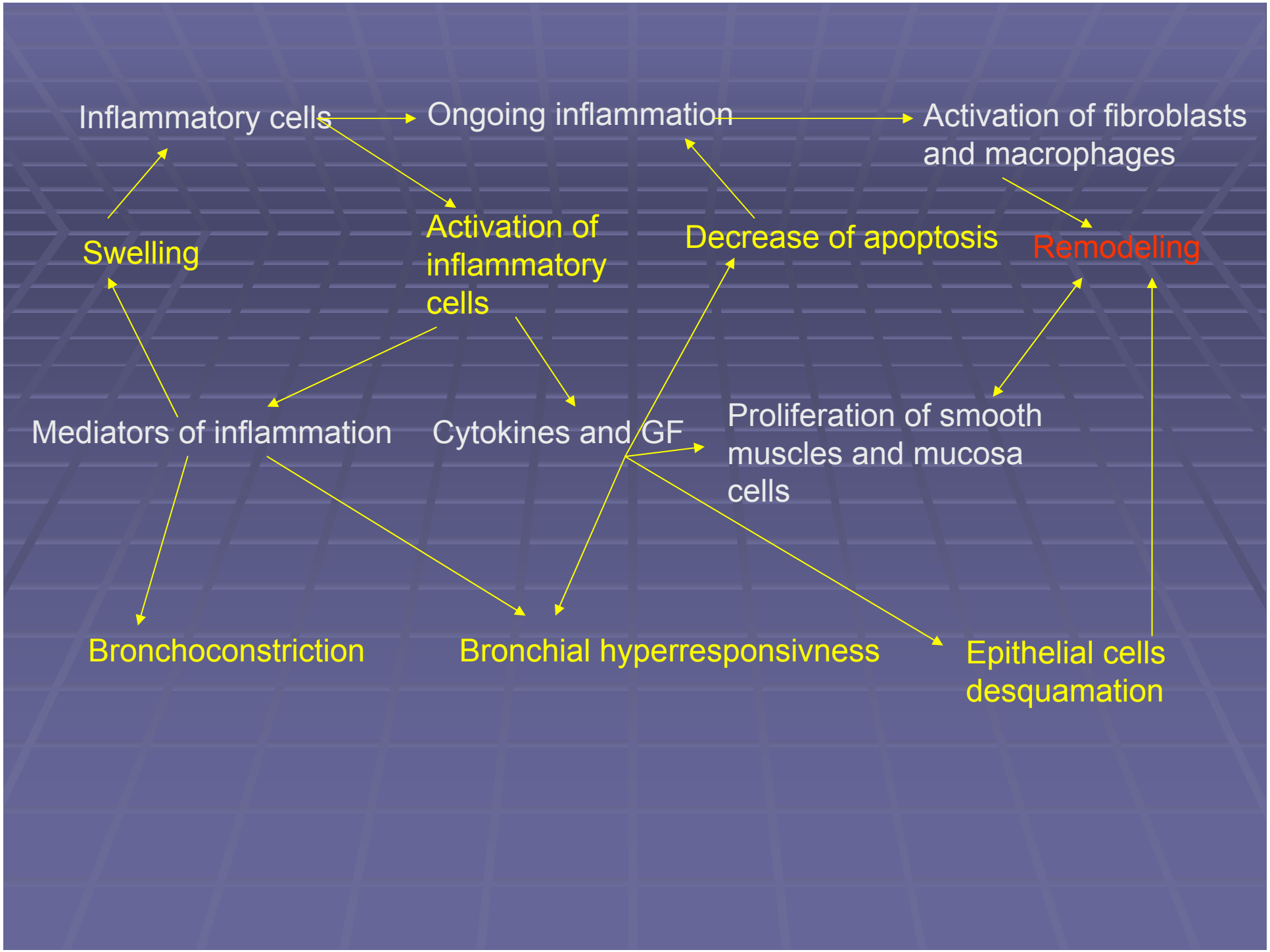
Deposition of collagen in basal and epithelial membranes

Elastolysis

Decrease of elasticity of the wall

Pathophysiological and clinic consequences

- in some patients the grade of remodeling not necessarily correlates with bronchial hyperreactivity
- remodeling correlates with plasma level of eosinophils, but does not correlate with the grade of bronchial hyperreactivity nor with period and severity of asthma
- long period of asthma is connected with collagen and fibronectin deposition and with lowering of bronchial hyperreactivity
- decrease of FEV1 although the proper therapy
- no correlation between thickening of the reticular membrane and the period of asthma and decrease of FEV1 in adults


Inflammatory cells
Ongoing inflammation
Activation of fibroblasts and macrophages
Swelling
Activation of inflammatory cells
Decrease of apoptosis
Remodeling
Mediators of inflammation
Cytokines and GF
Proliferation of smooth muscles and mucosa cells
Bronchoconstriction
Bronchial hyperresponsivness
Epithelial cells desquamation

Functional changes during acute asthmatic attac

- Increased working activity of breathing muscless
- Increased RV and FRC
- Arterial hypoxemia
- Low grade hypocapnia
- Imbalance between ventilation and perfussion

Functional changes during acute asthmatic attac

- During accute asthmatic attack are not involved all bronchioli at the same time
- During obstruction we can see increased resitence in distribution of inspired air
- That is the reason for hyperventilation of surrounding alveoli
- Hypoxemia and triggers from lungs causes an increased ventilaiton activity- mild hypocapnia is then the result of these changes

Functional changes during acute asthmatic attac

- Relative hyperventilation of some alveoli in which is an increased pAO2 but it is not sufficient for compensation of low oxygen amount in alveoli which are hypoventilated due to bronchoconstriction, oedema and mucus creation

Functional changes during acute asthmatic attac

- Increased FRC, RV, TLC, DLCO,
- Decrease of dynamic compliance C dyn
- During an inspiration we can observe decrease of systolic pressure and decreases the amplitude of puls wave -
- pulsus paradoxus – decrease of blood pressure more than 10 mmHg

Classification of asthma:

- **A. Atopic (allergic) asthma**

  in combination with allergic rhinitis, atopic dermatitis, genetic predisposition

  confirmation of spec. IgE antibodies, prick tests, inhalation challenge

- **B. Endogenous asthma**

  without specific known influence, obviously in women after exposition to cold weather, refract to the standard therapy

- **C. Exercise induced asthma**

  physical exercising, provocation by inhalation of chemicals, cold or hot weather

- **D. Aspirin induced asthma**

  typical triads-nasal polyps, urticaria and asthma induced by application of aspirin

  other drugs

- **E. Allergic bronchopulmonary aspergillosis**

  aspergillus acts as an allergen challenge in atopic people and induces aspergillus asthma or alergic bronchopulmonary aspergillosis

  in the chest radiography are intermitent infiltrates in lungs, the viscosity of mucous is increased and mucous plugs, bronchiectasia

- F. **Gastroesophageal reflux**

  bronchospasm induced by reflex
- **G. Sinobronchial syndrome**

  combination of sinusitis with nasal polyps and with asthma
- **H. Professional asthma**

  induced by inhalation and exposition to industry chemicals
- **CH. Asthmatic equivalent**

  dry cough, irritating, without breathlessness

Classification of Asthma Severity:

Step 1. Intermitent asthma

- Symptoms less than once a week
- Brief exacerbations
- Nocturnal symptoms not more than twice a month
- PEF or FEV1 > 80%, variability < 20%

Step 2. Mild Persistent Asthma

- Symptoms more than once a week but less than once a day
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than twice a month
- PEF or FEV1 > 80%, variability 20-30%

Step 3. Moderate Persistent Asthma

- Symptoms daily
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than once a week> 1x per week
- Daily use of inhaled short-acting-β2-agonist
- PEF or FEV1 between 60- 80%, variability > 30%

Step 4. Severe Persistent Asthma

- Symptoms daily
- Frequent exacerbations
- Limitation of physical activities
- Frequent nocturnal symptoms
- PEF or FEV1 < 60%, variability > 30%

New Classification according to Asthma Control

- 1. Controlled Asthma
- Daytime symptoms none (twice or less/week)
- Limitations of activites none
- Nocturnal symptoms/awakening none
- Need for reliever/rescue treatment none (twice or less/week)
- Lung function (PEF or FEV1) normal
- Exacerbations none

- 2. Partly Controlled
- Daytime symptoms more than twice week
- Limitations of activites any
- Nocturnal symptoms/awakening any
- Need for reliever/rescue treatment more than twice/week
- Lung gunction (PEF or FEV1) <80% predicted or personal best
- Exacerbations one or more/year

- 3. Uncontrolled
- Daytime symptoms three or more/week
- Limitations of activites three or more/week
- Nocturnal symptoms/awakening three or more/week
- Need for reliever/rescue treatment three or more/week
- Lung gunction (PEF or FEV1)
- Exacerbations one in any week

Examination methods:

History

- variable – seasonal, diurnal, exercise
- breathlessness, cough, wheezing, rhinitis
- physical examination – normal, hyperinflation with sounding se percussion, prolonged breath-out, dry phenomenon, pulsus paradoxus, running of supraclavicular area, silent lungs

Spirometry

- diagnosis, to monitor treatment, estimation and prevention, examination before an operation
- basic– searching – PEF (Peak Exspiratory Flow)
- index of variability

$$PEF = \frac{\text{the highest-the lowest} \times 100}{0{,}5 \times (\text{the highest} + \text{the lowest})}$$

- - FVC, FEV1, FEV1%FVC
- enlarged – spirometry, curve of flow-volume, bronchial challenge tests
- puls oxymetry, rhinomanometry

- **Pletysmography**
  - referential method for measuring of resistance, breathing work, compliance and DLCO
  - isoterm conditions , two phases- measuring of intrathoracal volume of gas and measuring of airways resistance

- **Bronchomotoric challenge**
  - bronchodilatation test – test of reversibility of bronchial obstruction
  - salbutamol 200-400 ug, ipratropium 80 ug
  - bronchoconstriction test – bronchial hyperreactivity
  - histamin 1g na 100 ml of 0,9% NaCl, methacholin, acetylcholin, adenosin-5-monofosfát, hypertonic NaCl

- **RTG**
  - normal, hyperinflation
- **Bronchoscopy**
  - Endobronchial biopsy – submucosis
  - Bronchoalveolar lavage – phenotypic differentiation from peripheral blood, express CD69

- **Induced sputum**
  - Hypertonic NaCl
  - Number of eosinophils in sputum corresponds to bronchial biopsy and BAL
- **ECP**
  - ECP levels in induced sputum corresponded to symptoms score and inversely proportional to PEF.
  - Significant inflammation –15 ug/l, compensation of asthma - 23 ug/l

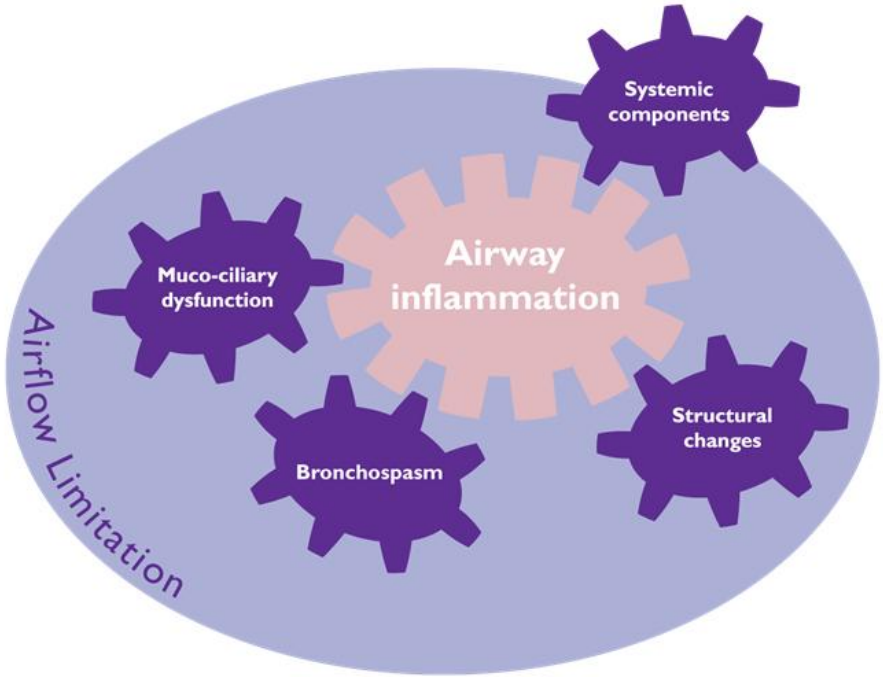
- **Measuring of breath-out condensated gas**
  - LTB4, cysteinyl leukotrienes, NO –increased in untreated patients, dependent on flow, lower flow-higher NO, constantly 50 ml/s
  - Low production of NO in cilia dyskinesis, cystic fibrosis, correlation with findings in biopsy and eosinophils in sputum
- **Blood gases**

2. COPD

Definition by GOLD (Global Initiative for Chronic Obstructive Lung Disease):

- **COPD is characterized by decreasing flow in airways (bronchial obstruction) which is not completely reversible. Bronchial obstruction is in the progress and is connected with abnormal inflammatory response of lungs caused by toxic pollutants.**

COPD is a multicomponent disease with inflammation at its core leading to mortality



- ↓Lung function
  - ↑ Symptoms
    - ↑ Exacerbations
      - ↓ Exercise tolerance
        - ↓ Health status and ↑ morbidity
          - Mortality

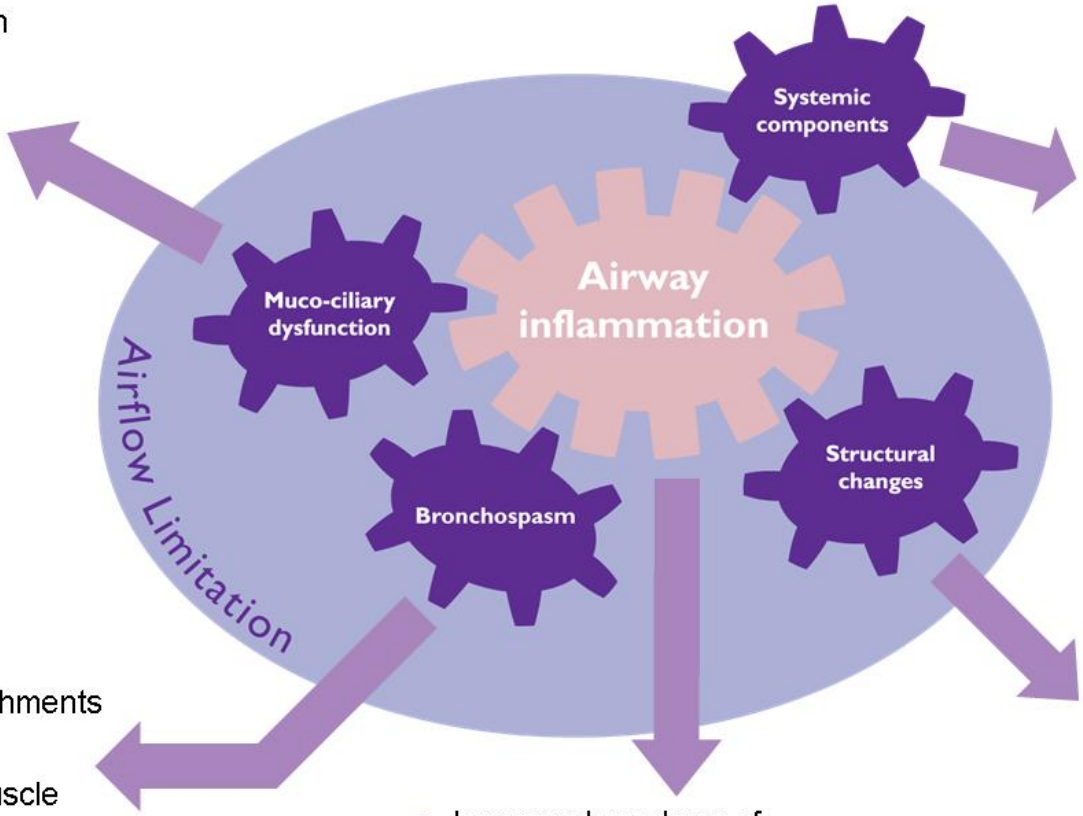
Agusti. Respir Med 2005
Agusti et al. Eur Respir J 2003
Bernard et al. Am J Respir Crit Care Med 1998

Chronic bronchial obstruction

- Combination of disorder of small airways (**obstructive bronchiolitis**) and destruction of lung tissue (**emphysema**)
- Chronic inflammation – remodeling and narrowing of small airways
- Destruction of lungs and inflammation lead to lose of connection of alveoli with small airways
- Decrease of elasticity

Pathophysiological features of COPD

- Mucus hypersecretion
- Reduced mucociliary transport
- Mucosal damage



- Poor nutritional status
- Reduced BMI
- Impaired skeletal muscle
  - weakness
  - wasting

- Loss of alveolar attachments
- Loss of elastic recoil
- Increased smooth muscle contraction

- Increased numbers of inflammatory cells/activation
- Elevated inflammatory mediators: IL-8, TNF-α, LTB-4 and oxidants
- Protease/anti-protease imbalance

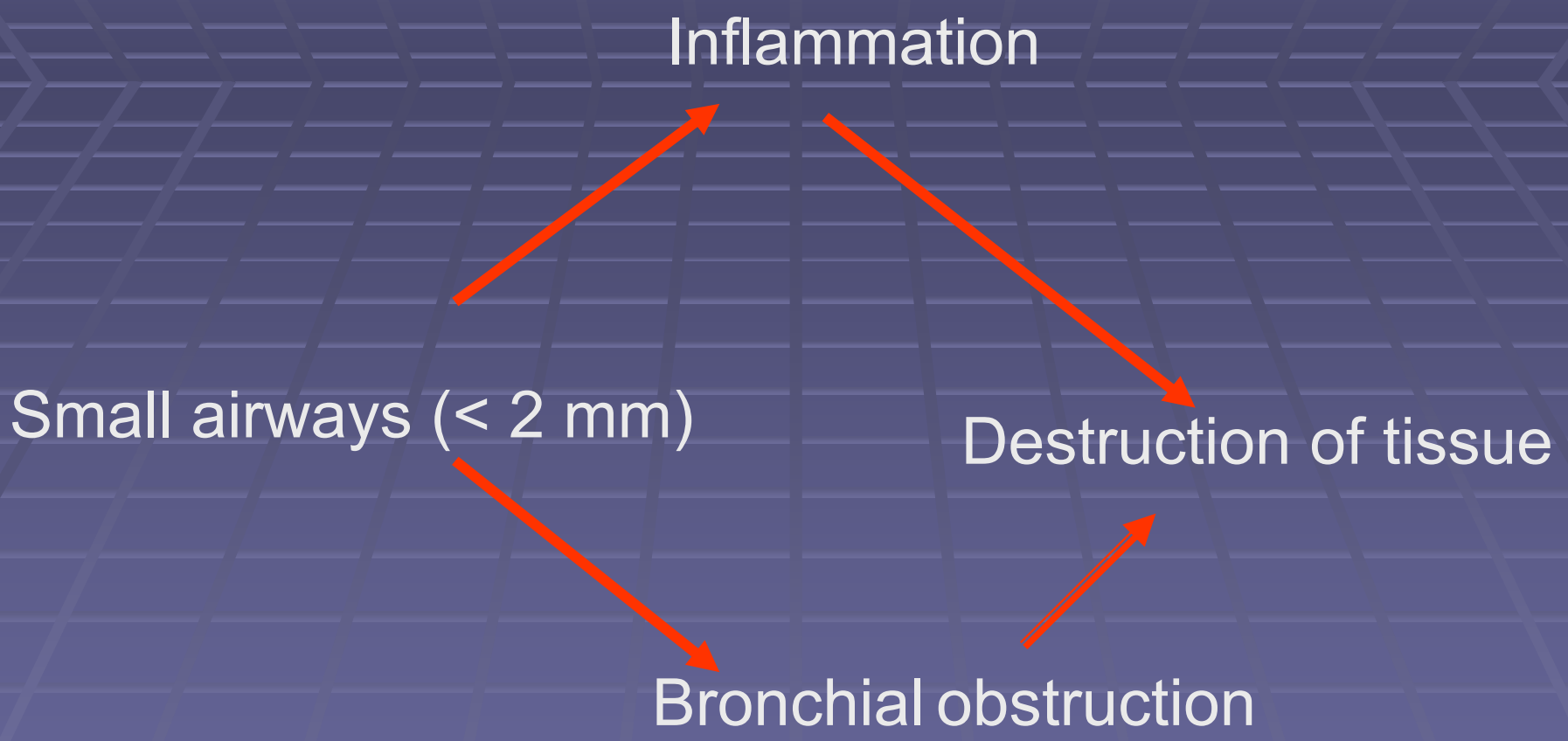
- Goblet cell hyperplasia/ metaplasia
- Mucous gland hypertrophy
- Increased smooth muscle mass
- Airway fibrosis
- Alveolar destruction

IL = interleukin
LTB-4 = leukotriene B4
TNF-α = tumour necrosis factor- α

Risk factors

- **Genetic factors** (e.g. deficiency of α1-antitrypsin, ABO secretion status, microsomal epoxid hydroxylase, glutathion S-transferase, α1- antichymotrypsin, complementary part GcG, TNF- α, microsatelit instability), hyperreactivity of airways, growth of lungs
- **Exposition to tobacco smoke**, professional dust and chemicals, air pollution in environment and in buildings, infection, social and economic status

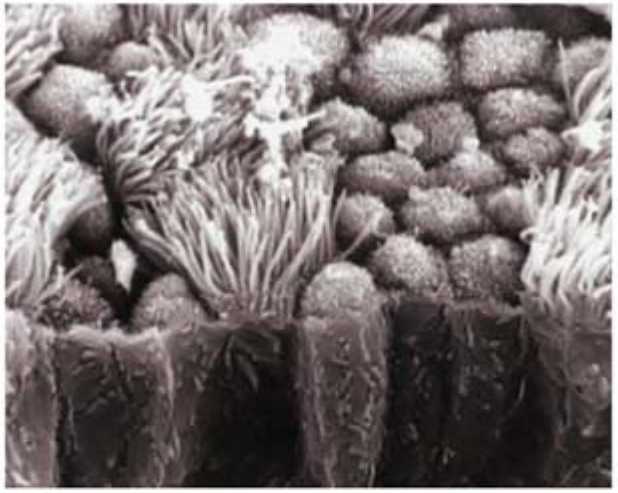
Pathogenetic mechanisms of COPD



Pathophysiology of COPD: mucociliary dysfunction

Mucociliary dysfunction

- Mucus hypersecretion
- Increased mucus viscosity
- Reduced mucociliary transport
- Mucosal damage



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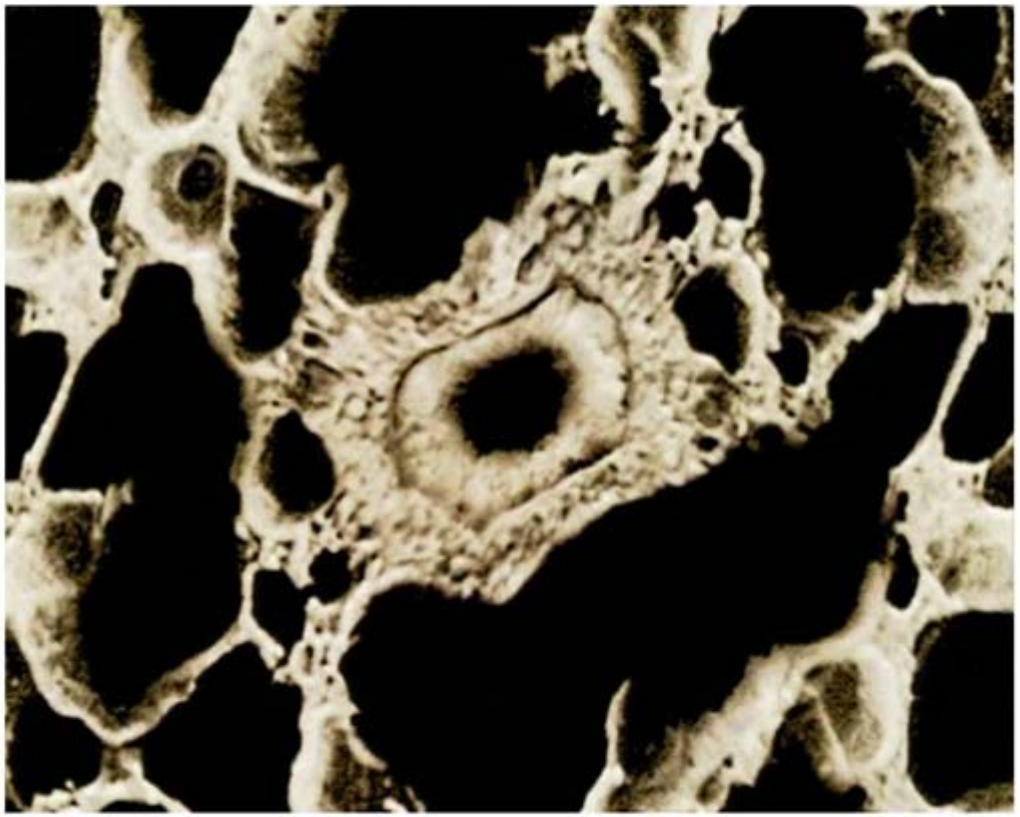
Agusti Respir Med 2005

Pathophysiology of COPD: structural changes

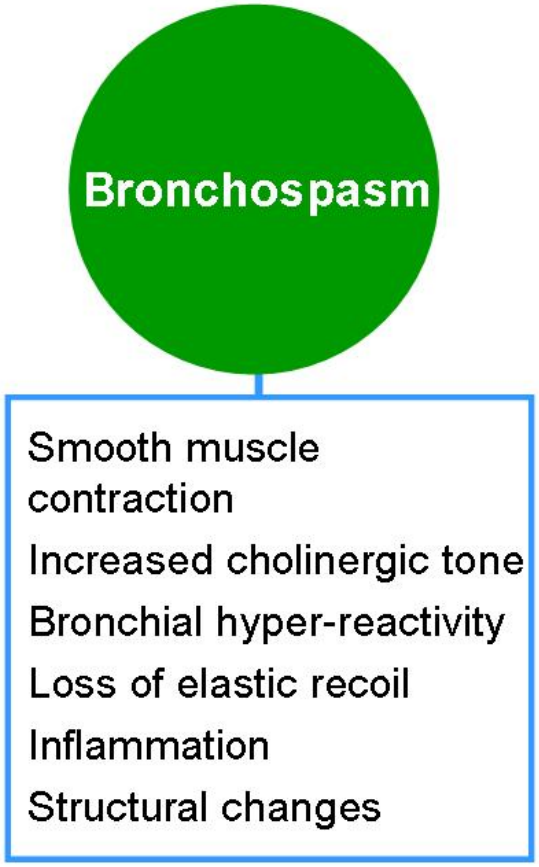
Structural changes

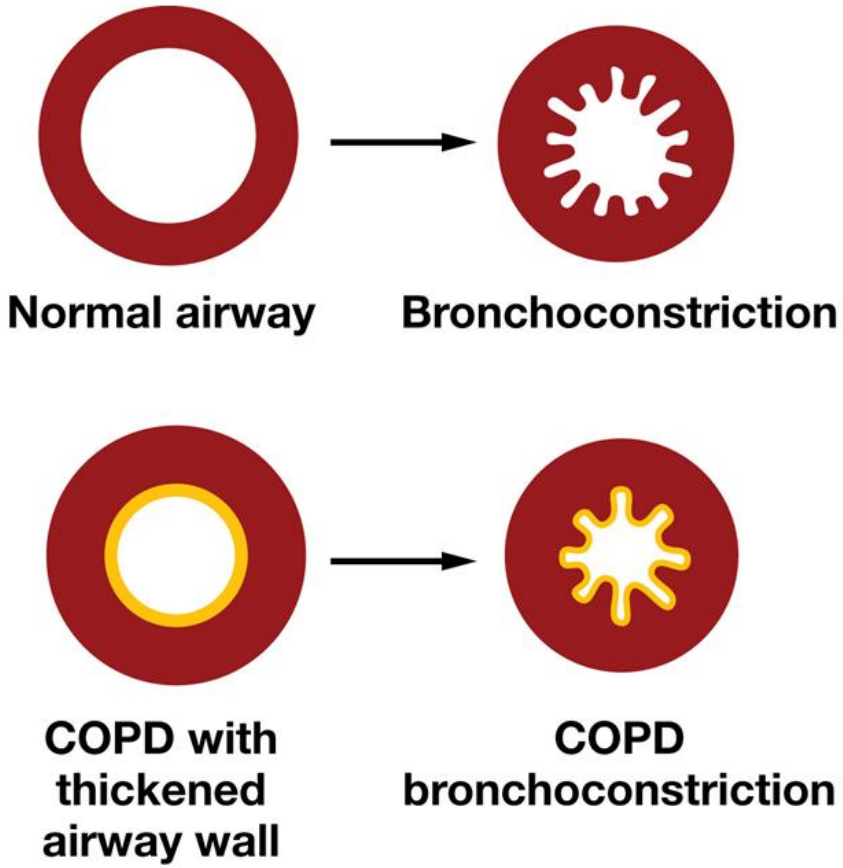
- Alveolar destruction
- Epithelial hyperplasia
- Glandular hypertrophy
- Goblet cell metaplasia
- Airway fibrosis



Jeffery. Thorax 1998

Pathophysiology of COPD: bronchospasm

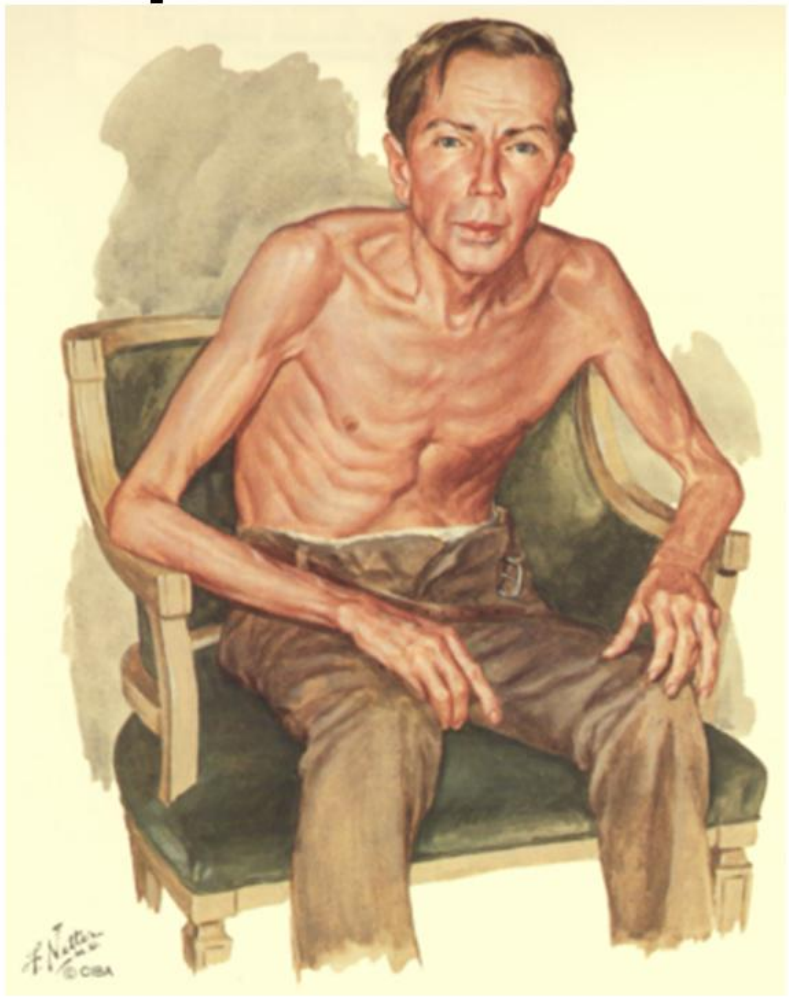




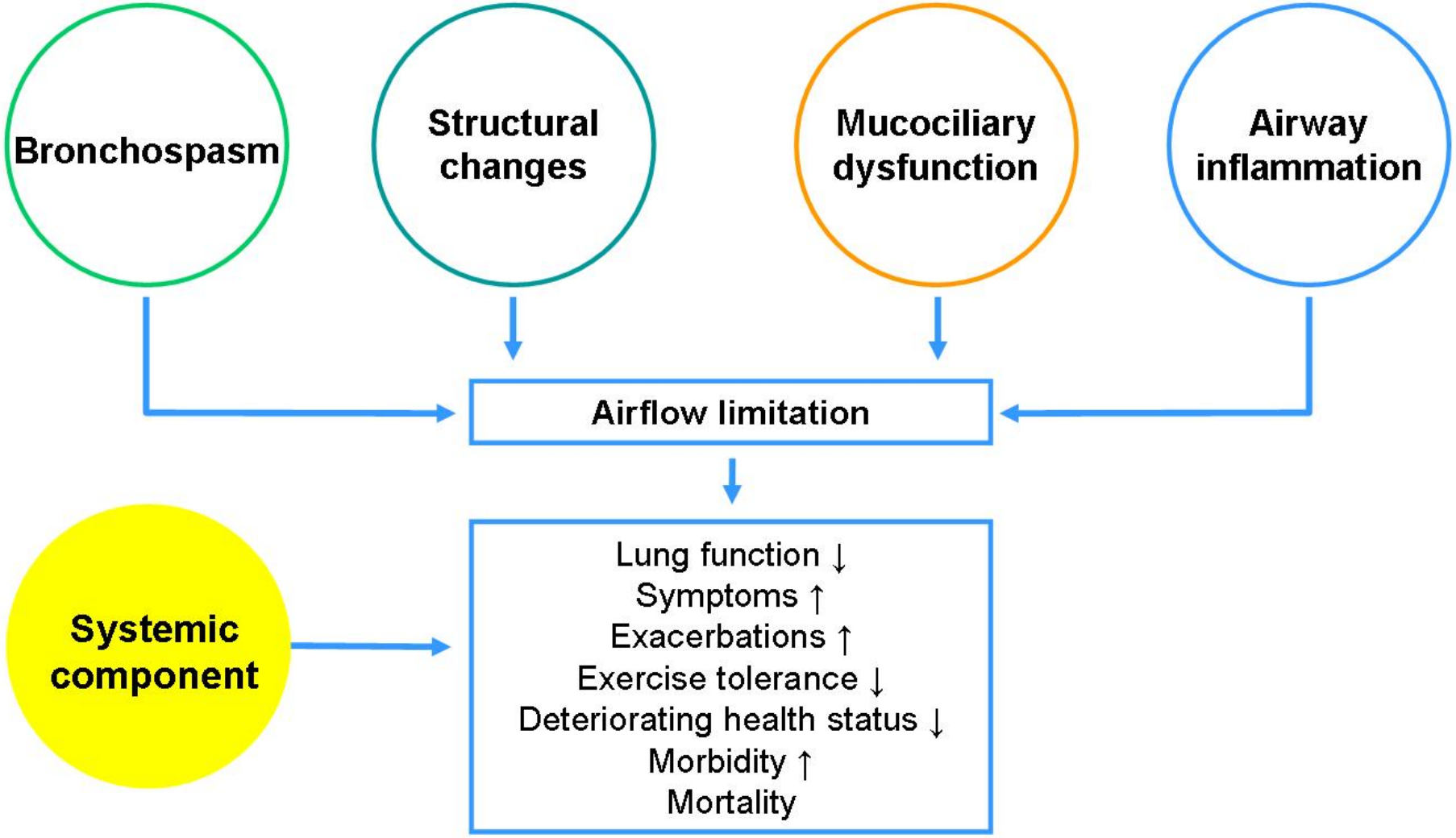
Pathophysiology of COPD: systemic component

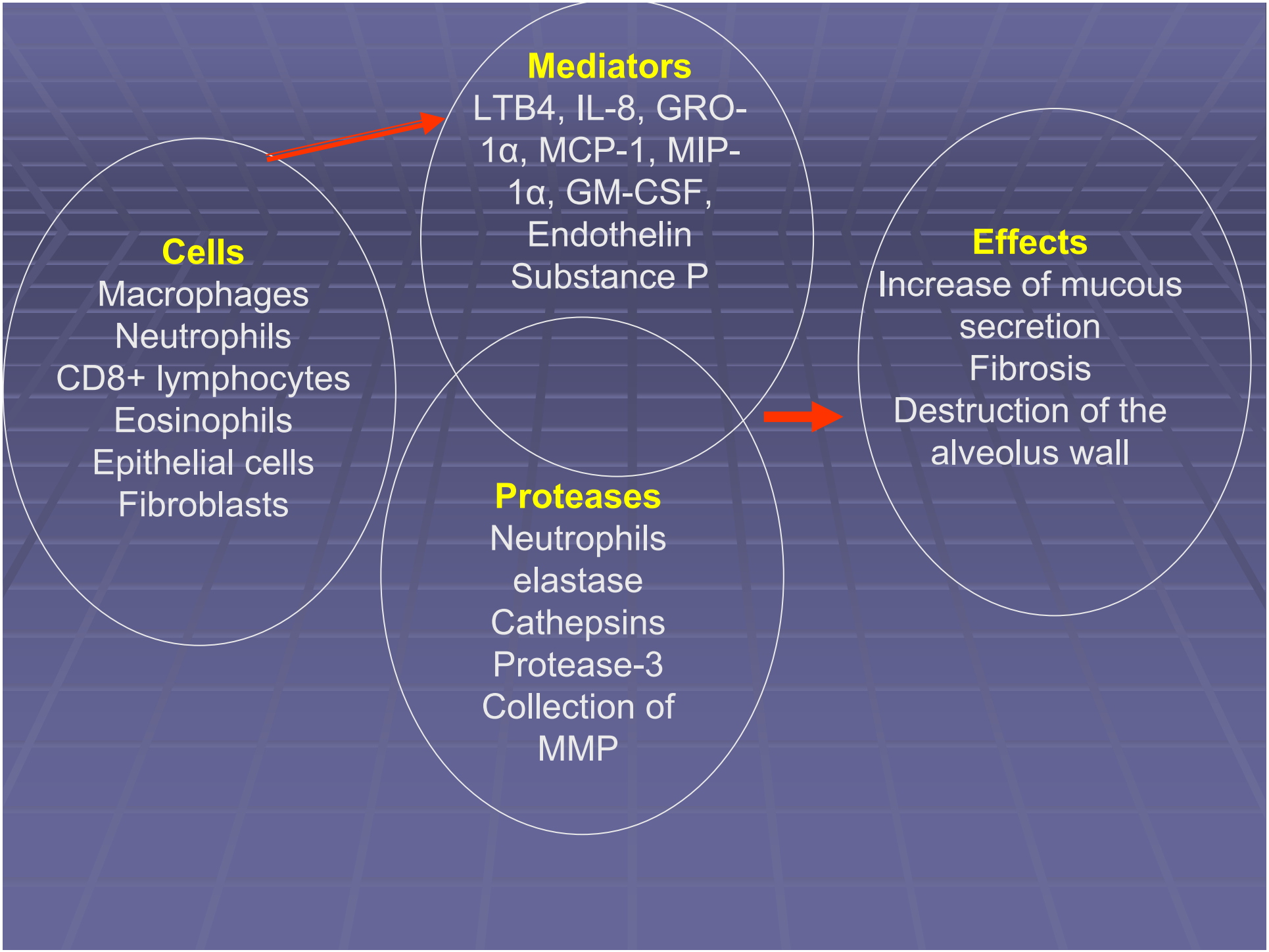
Systemic component

- Systemic inflammation
- Poor nutritional status
- Reduced BMI
- Impaired skeletal muscle
  - weakness
  - wasting
- Impact on other organs e.g. cardiovascular disease



Pathophysiological features of COPD




Mediators
LTB4, IL-8, GRO-1α, MCP-1, MIP-1α, GM-CSF, Endothelin Substance P
Cells
Macrophages
Neutrophils
CD8+ lymphocytes
Eosinophils
Epithelial cells
Fibroblasts
Proteases
Neutrophils elastase
Cathepsins
Protease-3
Collection of MMP
Effects
Increase of mucous secretion
Fibrosis
Destruction of the alveolus wall

Pathogenesis of COPD

- **pollutants in environment ---inflammation**
- **smoking of cigarettes** – stimulation of macrophages and epithelial cells to produce TNF- α, IL-8 and LTB4
- exhalations from cars, dust from grain
- **instability between proteases and anti-proteases in lungs**
- Laurell and Eriksson –1963 – deficiency of α1-antitrypsinu and emphysema

- **oxidative stress**
- hydrogen peroxide, NO – directly measured oxidants produced during smoking of cigarettes
- isoprostan F2 α-III, marker of oxidative stress in lungs, bronchoconstriction
- changes in central and peripheral bronchi, lung tissue and vessels
- peripheral bronchi are the major place of the obstruction

- centrilobular type of emphysema
- changes include: increased secretion of mucus, the function of cilia is disturbed, obstruction, hyperinflation of lungs, disturbed gas exchange – firstly hypoxaemia (due to irregularity of ventilation and perfusion), then hypercapnia, pulmonary hypertension and cor pulmonale

Classification of COPD grading:

Grade 0 – high risk

- normal spirometry
- chronic symptoms

Grade I – mild

- FEV1/FVC < 70%
- FEV1>80%
- Chronic symptoms are or are not present (cough, sputum)

Grade II – moderate

- FEV1/FVC < 70%
- 50% < FEV1< 80%
- Chronic symptoms are or are not present (cough, sputum, breathlessness)

Grade III – severe

- FEV1/FVC < 70%
- 30% < FEV1< 50%
- Chronic symptoms are or are not present (cough, sputum, breathlessness)

Grade IV – the most severe

- FEV1/FVC < 70%
- FEV1 < 30% or FEV1< 50% and respiratory failure or clinical symptoms of cor pulmonale

Examination methods:

- **Clinics**

  History, physical examination, inspection, palpation, percussion, auscultation

- **Spirometry, bronchodilatation challenge and test of reversibility by corticosteroides**

  if FEV1 after application of bronchodilatators is < 80% and FEV1/FVC <70%, the bronchial obstruction is not fully reversible

  patient is treated for 6-12 month with inhalation corticosteroides and FEV1 is increased about 200 ml and about 15% before treatment, the test is positive

- **RTG, CT, HRCT**

  hyperinflation – flat diaphragm, enlargement of retrosternal space, increased transparency of lungs, quick loosing of pulmonary vessels bed
- **Blood gases**

  in patients with FEV1< 40%

  in patients with clinical symptoms of respiratory failure, right heart failure

- **Pulmonary hemodynamics**
  pulmonary hypertension, cor pulmonale
- **Hematocrit**
- **Screening for deficiency of α1-antitrypsin**
  COLD started before 45 years

COPD and asthma are both inflammatory diseases, although the cells and mediators differ

	Stable COPD	COPD exacerbations	Asthma
Characteristic inflammatory cells	$CD8^+$ T-cells	$CD4^+$ T-cells	$CD4^+$ T-cells
	Macrophages	Eosinophils	Eosinophils
	Neutrophils	Neutrophils	Mast cells
Inflammatory mediators	TNF-α	RANTES	RANTES
	IL-8	IL-6	IL-4
	Elastase	IL-8	IL-5
			IL-13

GOLD Guidelines 2005
Barnes et al. Eur Respir J 2003