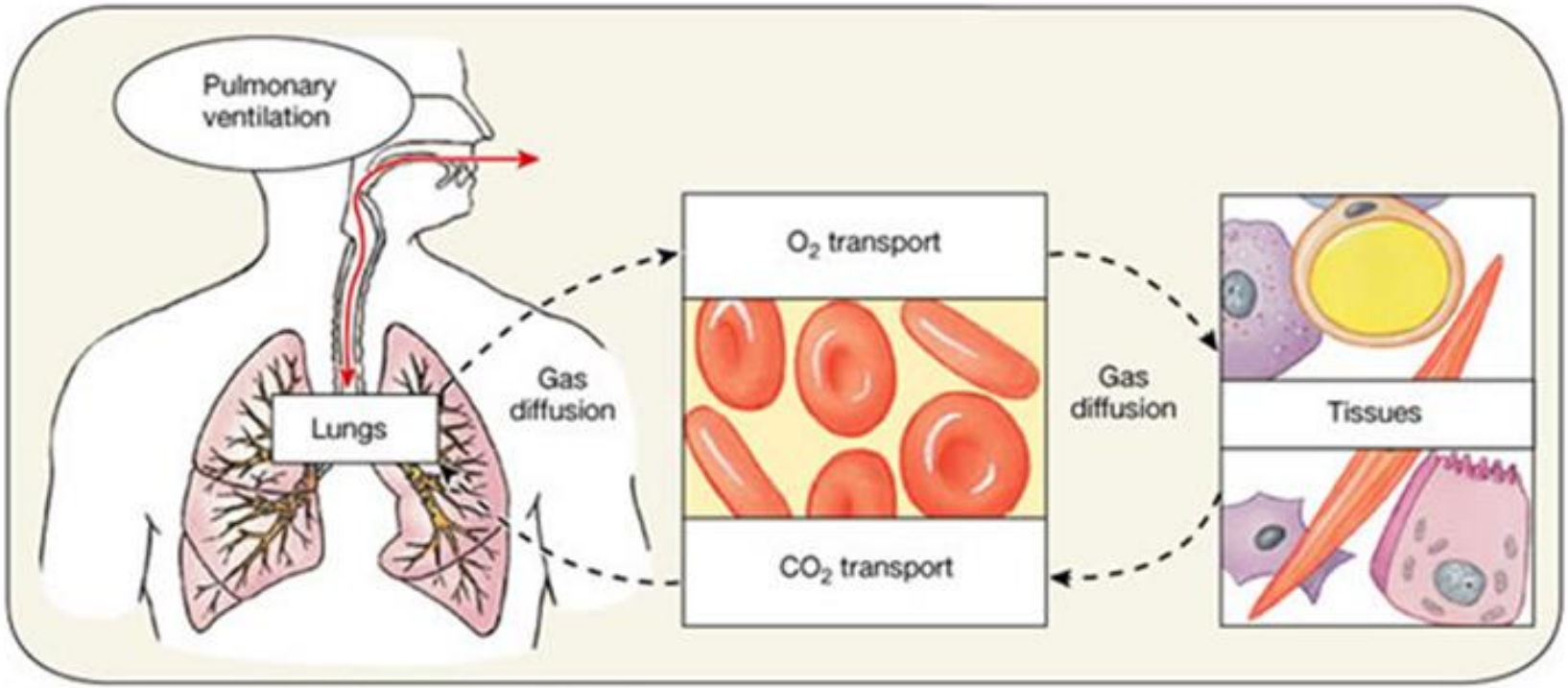
Pathophysiology of the respiratory system II - common diseases

Respiratory insufficiency
Classification of respiratory diseases
- ventilation disease
- diffusion diseases
- perfusion diseases

Chronic obstructive pulmonary disease (COPD)
Bronchial asthma

Respiration & gas exchange in the lungs

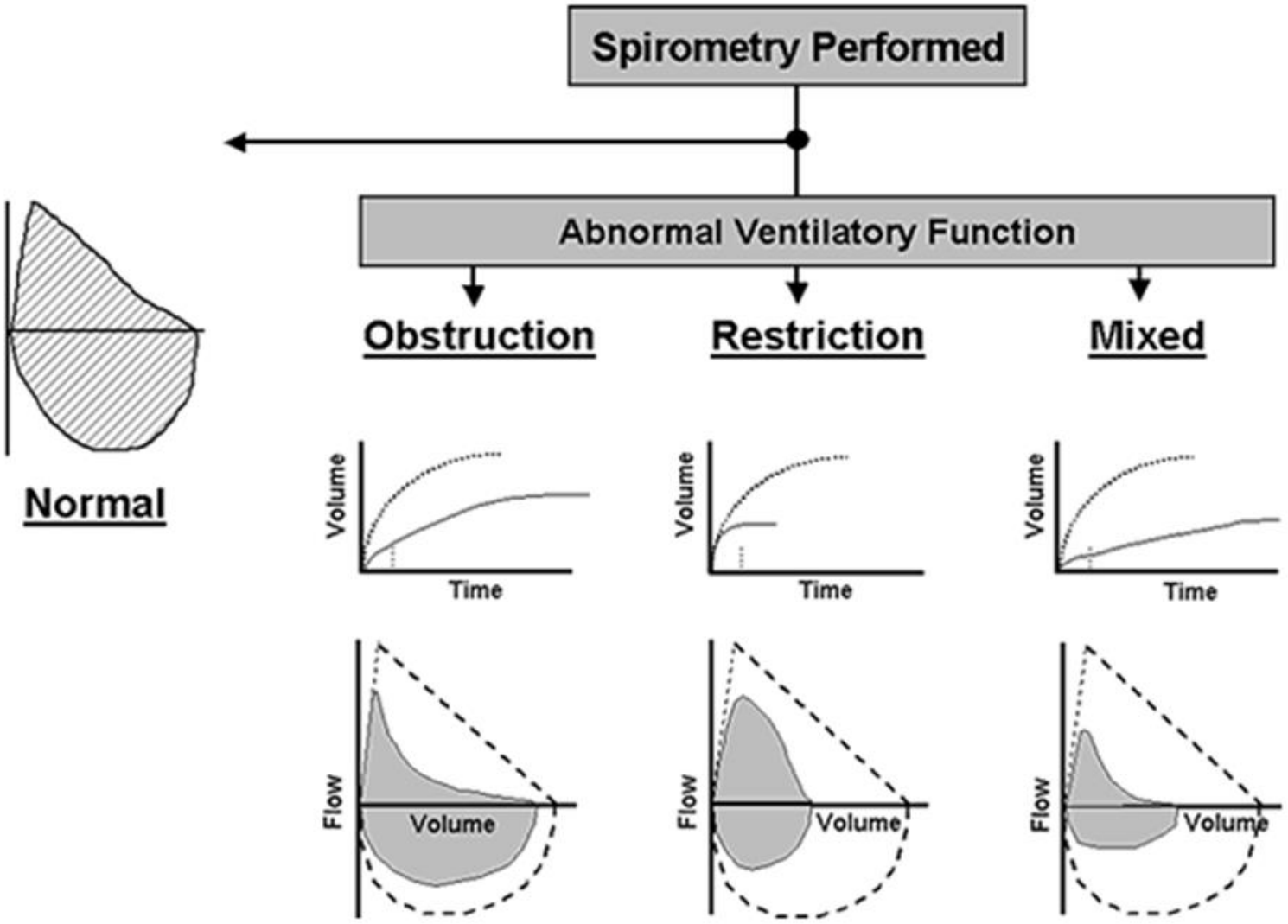
- **ventilation** = a mechanical process
  - breathing in narrower sense
- **diffusion** = a chemical process
  - across the alveolo-capillary membrane according to pressure gradients
- **perfusion** = a circulatory process
  - regulation of blood flow in the pulmonary bed



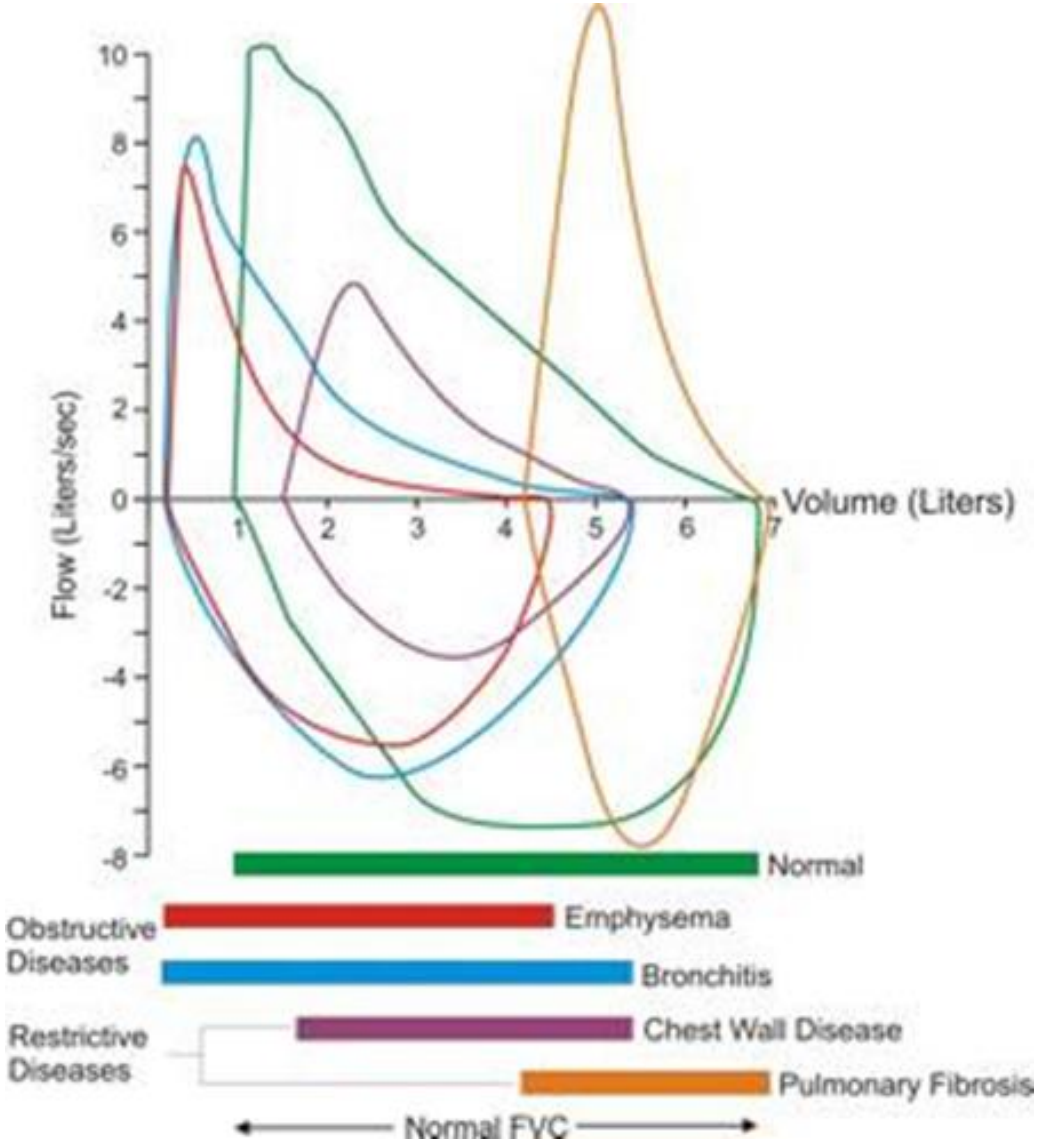
Classification of respiratory diseases

- (1) **Ventilation diseases**: local or global hypoventilation
  - hypoventilation (usually extrapulmonal cases) (↓ V_A/Q ratio) $V'_A = (V_T - V_D) \times f$
    - CNS (intoxication with depression of resp. center, head trauma, …)
    - paralysis of resp. muscles, myasthenia gravis
    - obstruction of upper airways
  - obstruction diseases = narrowing of airways (↓ V_A/Q ratio (shunt), spirometry **norm. FVC, ↓FEV1**)
    - localized obstruction
      - » bronchial obstruction (foreign body, tumor, inflammation, lymph nodes, ..)
      - » atelectasis
    - generalized obstruction
      - » reversible (bronchial asthma)
      - » irreversible (COPD, cystic fibrosis)
  - restriction diseases = reduction of lung parenchyma or respiratory movements (spirometry ↓ **FVC, norm. FEV1**)
    - parenchymal (sarcoidosis, idiop. pulmonary fibrosis, pneumoconiosis, bronchopneumonia)
    - extra-parenchymal (deformities of chest and spine)
  - combined
- (2) **Diffusion diseases**: thickening of alveolo-capillary membrane
  - lung fibrosis
  - pneumoconiosis
    - silicosis, asbestosis,…
  - bronchopneumonia
- (3) **Perfusion diseases** (Q): ↑ V_A/Q ratio (deadspace)
  - lung embolism
  - hypotension

Spirometry in ventilation diseases

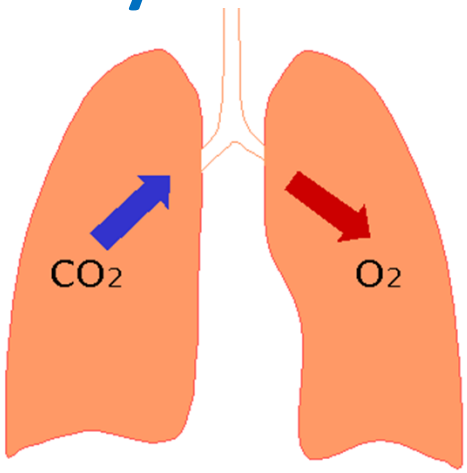


Flow-volume loops in various respiratory diseases



RESPIRATORY INSUFFICIENCY

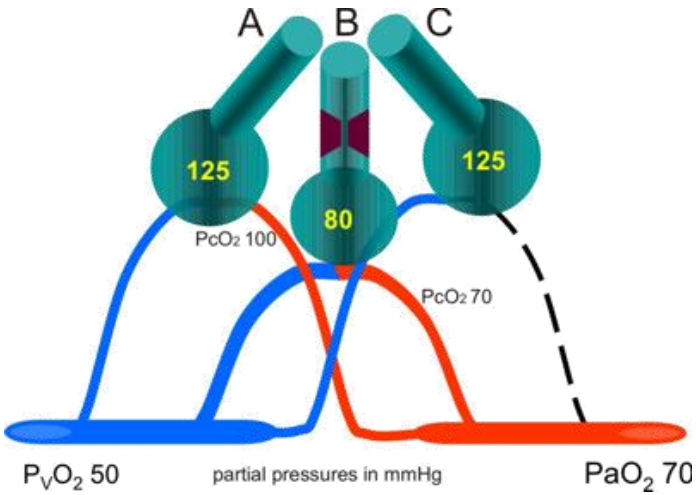
Respiratory insufficiency

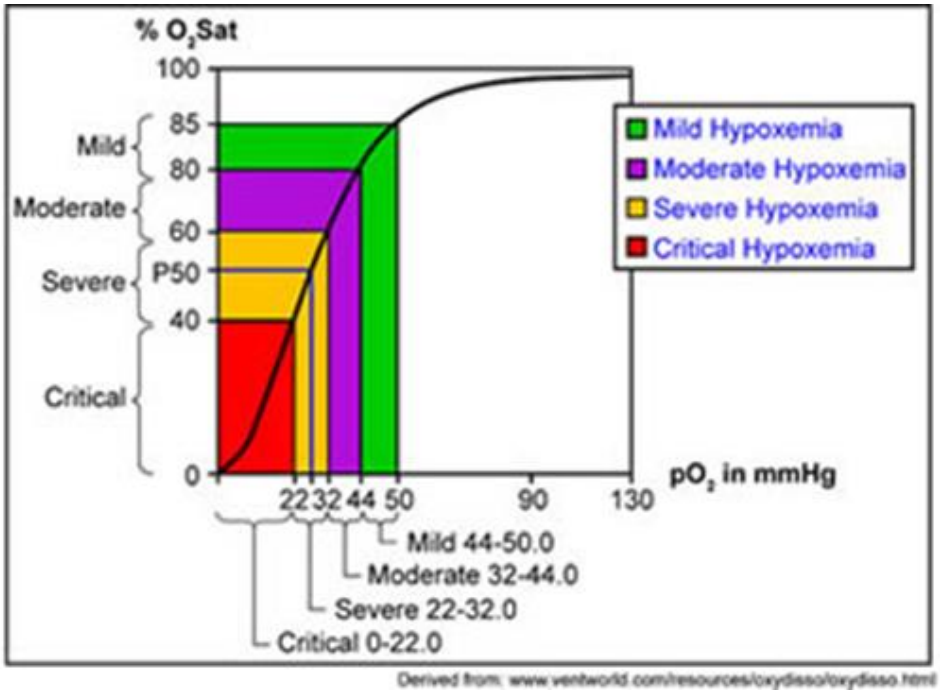


- basically all types of respiratory disorders can lead to RI
  - severity of disease is graded according to its effect to gas exchange
- the aim of the respiration is to maintain optimal values of blood gases by way of their exchange with environment, therefore the main criteria of resp. insufficiency are blood gases values
  - ↓paO_2 (hypoxemia) is a constant component of RI
    - a thus decrease of Hb saturation
      - pulsion oxymetry!
  - ↑$paCO_2$ (hypercapnia) sometimes, often normo- or even hypocapnia
- classification of resp. insufficiency
  - type I or partial or hypoxemic (↓paO_2 <10 kPa and normo or ↓$paCO_2$)
    - failure of oxygenation
  - type 2 or global or ventilatory (↓paO_2 <8kPa and ↑$paCO_2$ >6 kPa)
    - failure of mechanical ventilation
      - compensated – normal blood pH (compensatory increase of hydrogen carbonates)
      - decompensated – decrease of blood pH < 7,36 (respiratory acidosis)

Why O_2 and CO_2 behave differently

- majority of lung diseases with variable V_A/Q mismatch causes hypoxemia
- the presence of hypercapnia is influenced by
  - different diffusibility of O_2 compared to CO_2
    - diffusion diseases usually do not lead to hypercapnia on their own
  - rate of equilibration of O_2 and CO_2 in lung capillary
    - increased velocity of flow in capillary have a grater effect on O_2
  - different forms of transport of O_2 and CO_2 in blood
    - hyperventilation lowers PCO_2, however since hemoglobin becomes saturated on 100% already during normal ventilation, further increase has no effect





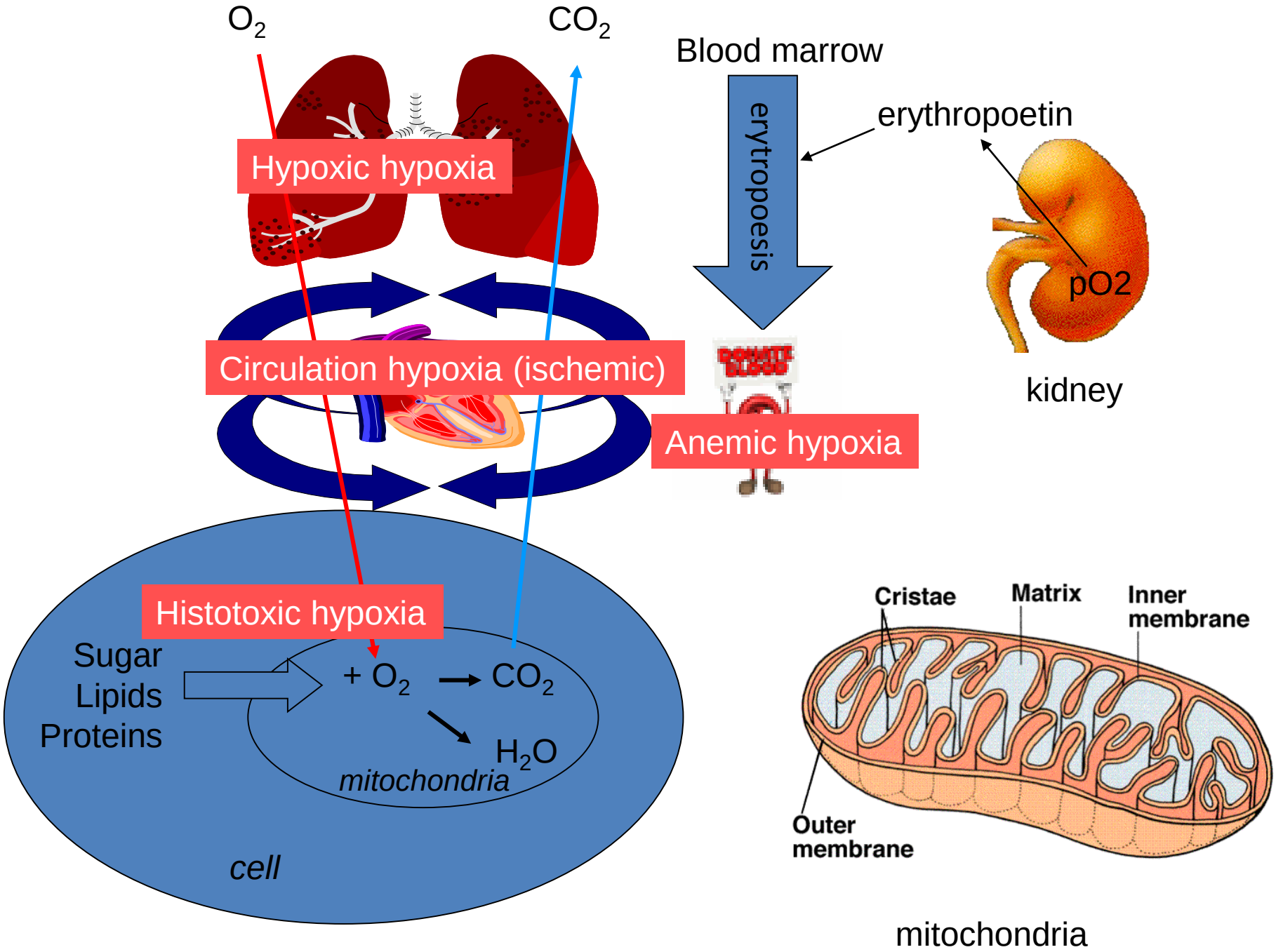
Respiratory insufficiency

- extra-pulmonary causes of low paO_2 (hypoxemia/hypoxia) are not usually classified as RI
  - cardiovascular (heart disease with right-to-left shunt)
  - circulation hypoxia
- classification of RI
  - latent RI: normal blood gases at rest, abnormal during exercise
  - manifest RI: blood gases pathological in rest
- time course:
  - acute: abrupt onset
    - aspiration of foreign body, pneumothorax, asthma attack
  - chronic: slowly progressing, variable compensation
    - COPD, lung fibrosis, cystic fibrosis
  - chronic with acute exacerbations:
    - COPD

- diagnostics of resp. insufficiency
  - examination of blood gases and acid-base balance (Astrup)
    - arterial blood (a.radialis, a. cubitalis, a. femoralis)
    - arterialised blood (ear lobe)
    - capillary blood (fingers) – imprecise
  - parameters:
    - blood pH – normally 7.36-7.44
      - i.e.[H+] = 35-44 nM
    - paO_2 – partial pressure of oxygen
      - 10-13 kPa (75-95 mmHg)
    - $paCO_2$ – partial pressure of carbon dioxide
      - 4.8-6 kPa (36-45 mmHg)
    - HCO_3 – hydrogen carbonates
      - 22,0-26,0 mmol/l
    - BE – base excess
      - normally 0
    - $SatO_2$ – saturation of Hb (normally > 90%)
    - Mean PvO2
      - 6 kPa (45 mmHg)
    - Mean PvCO2
      - 6.1 kPa (46 mmHg)

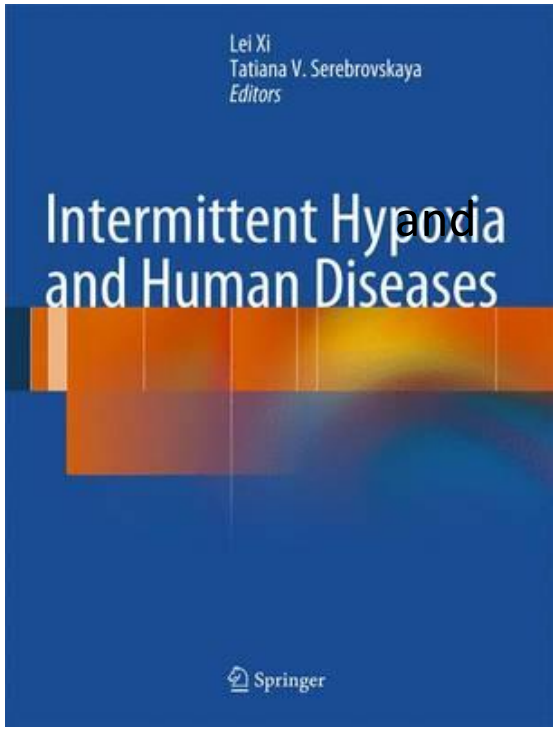
Generalized hypoxia

- = deficiency of O_2 in the organism (↓paO_2 <10kPa/75mm Hg)
- types:
  - (1) hypoxemic hypoxia = **↓ arterial PO_2** - leads to central cyanosis
    - causes of hypoxemia
      - ↓ PO_2 in inspired air (PO_2 (high altitude, low FiO_2)
      - hypoventilation due to damage of respiration center
      - diffusion impairment (fibrosis, emphysema)
      - anatomical shunting of non-oxygenated blood (heart)
      - ventilation-perfusion mismatch
  - (2) anemic hypoxia = **normal arterial PO_2**
    - ↓ concentration of hemoglobin
      - anemia, leukemias
    - abnormal hemoglobin with low ability to bind oxygen
      - carbonylhemoglogin (COHb)
      - methemoglobin
  - - (3) circulatory hypoxia = **normal arterial PO_2** – leads to peripheral cyanosis
    - decreased cardiac output
    - decreased of systemic blood pressure
    - (local tissue ischemia)
    - microcirculation defects
  - - (4) histotoxic hypoxia – **normal arterial PO_2** , ↑ venous PO_2
    - Intoxication with cyanides, cobalt, …)

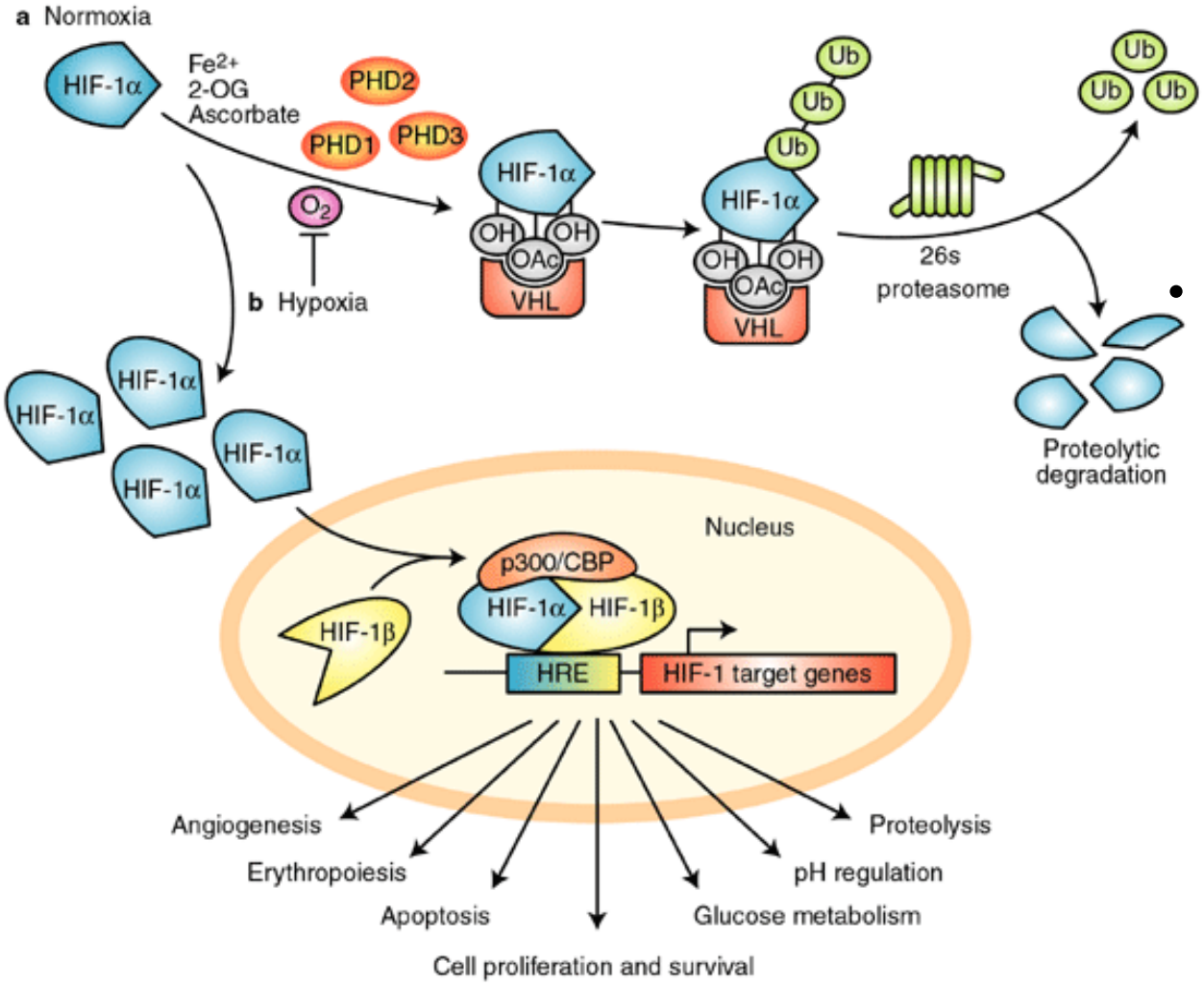

O_2
CO_2
Hypoxic hypoxia
Circulation hypoxia (ischemic)
Histotoxic hypoxia
Sugar
Lipids
Proteins
+ O_2
CO_2
H_2O
mitochondria
cell
Blood marrow
erythropoesis
erythropoetin
pO2
kidney
Anemic hypoxia
Cristae
Matrix
Inner membrane
Outer membrane
mitochondria

Intermittent, chronic intermittent and chronic hypoxia

- **Intermittent** hypoxia
  - an effective stimulus for evoking the respiratory, cardiovascular, and metabolic to some extent beneficial
    - they may provide protection against disease as well as improve exercise performance in athletes
- Long-term consequences of **chronic intermittent** hypoxia (such as OSA) may have detrimental effects
  - hypertension, cerebral and coronary vascular problems
  - ↑ right ventricular heart mass, pulmonary vascular remodeling and pulmonary hypertension
  - developmental and neurocognitive deficits neurodegeneration
- **Chronic** hypoxia induces proliferation of the vasculature due to angiogenesis (up-regulation of VEGF) but can also change the integrity of vessels, leading to changes in vascular permeability (e.g. contribution to acute mountain sickness)

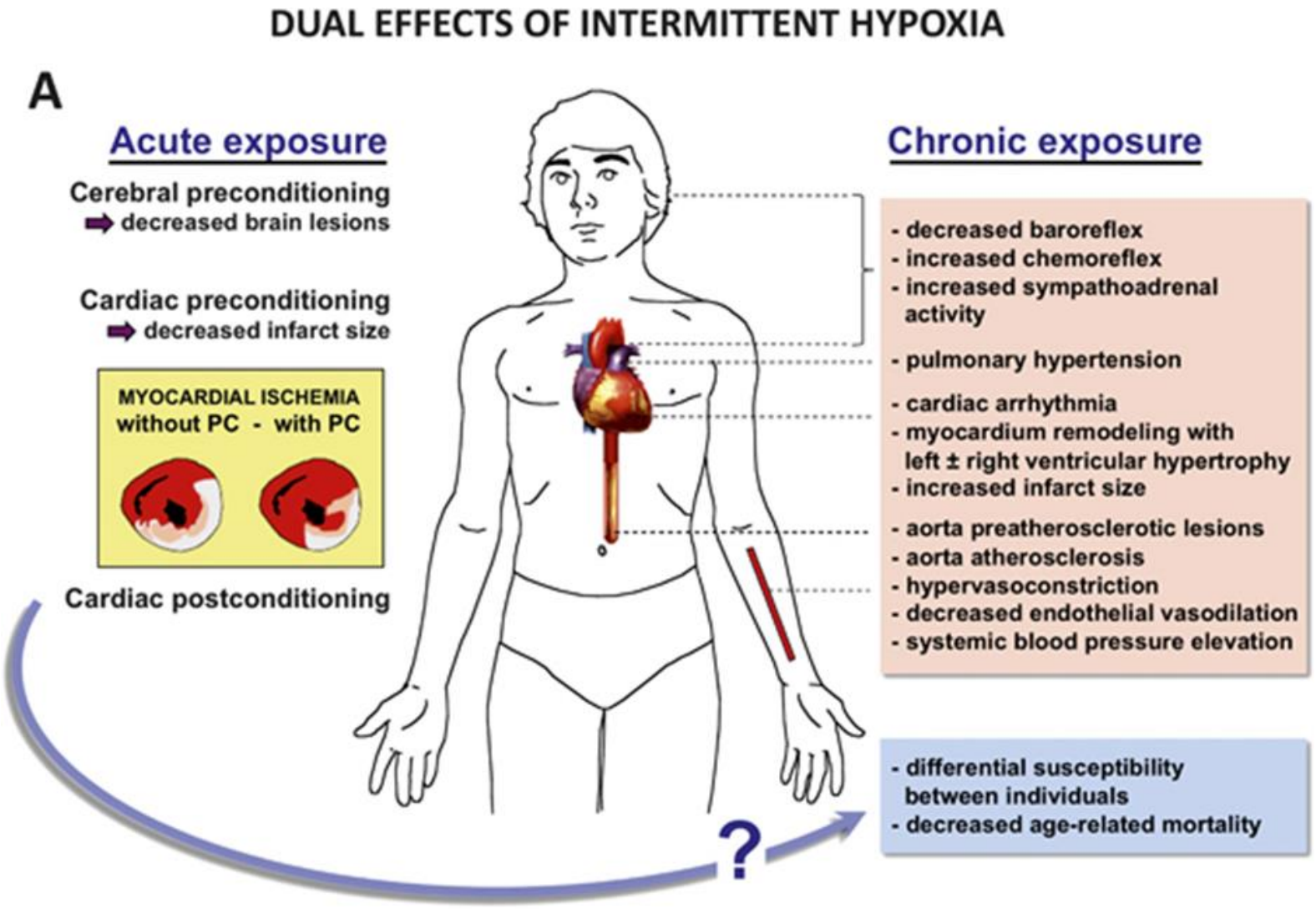


Hypoxia and gene transcription

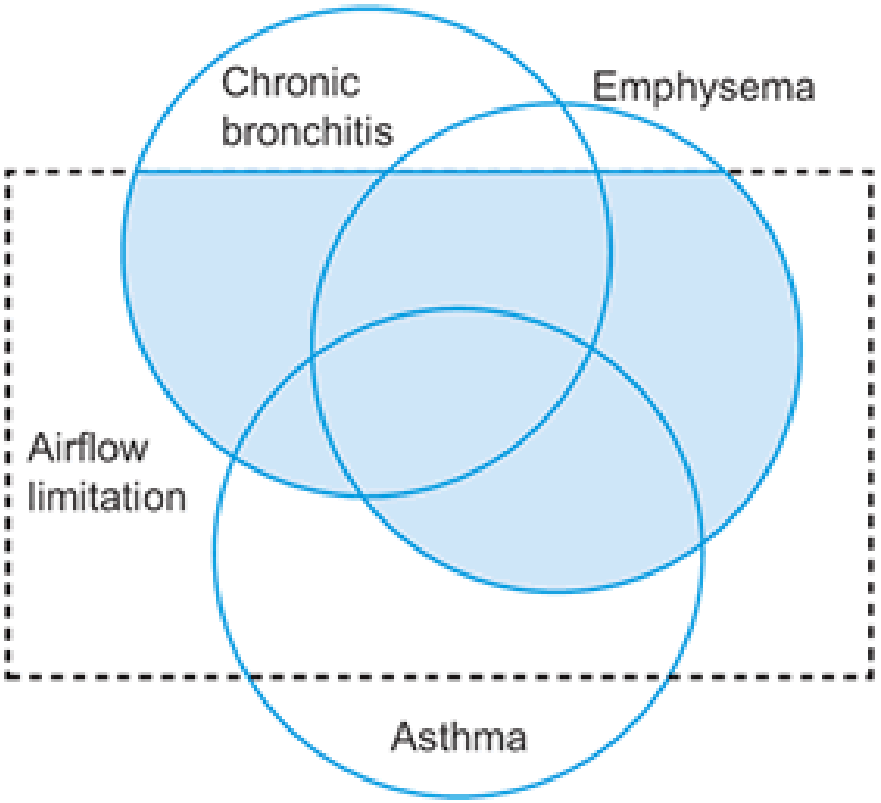


HIF-1α regulation by proline hydroxylation

- The ability of hypoxia to promote persistent adaptations is due in part to its ability to induce changes in gene transcription
- The regulation of the expression of a wide variety of genes involved in hypoxic adaptations is largely due to activation of a hypoxia-sensitive transcription factor, hypoxia-inducible factor 1 (HIF-1)
  - HIF-1 is a heterodimer of HIF-1 alpha and HIF-1 beta
  - oxygen levels directly regulate the expression of the HIF-1 component in a dose-dependent manner

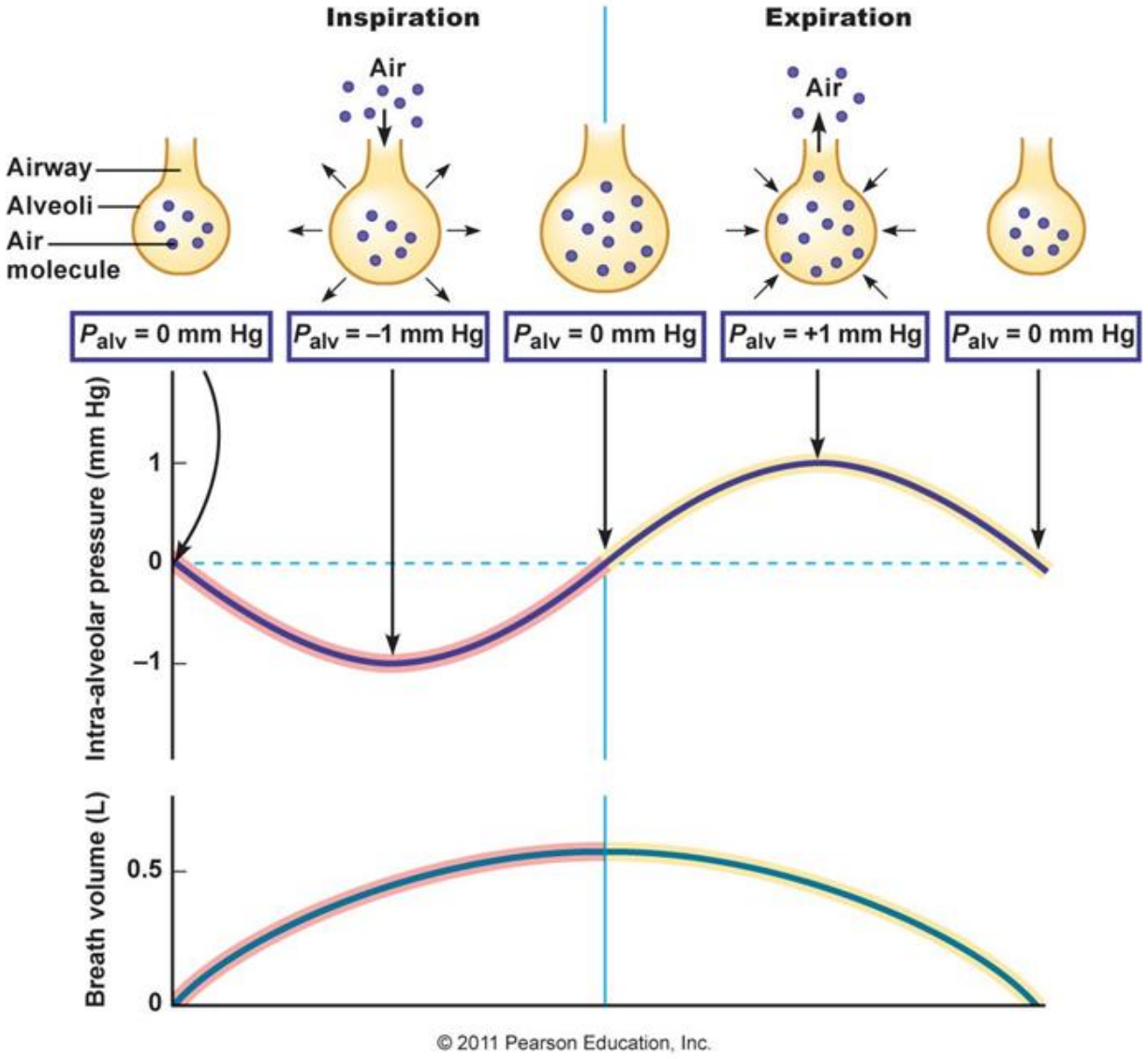


According to the severity and duration of exposure, intermittent hypoxia (IH) may have either beneficial effects, involving pre- and postconditioning, or detrimental effects as in sleep apnea. It is not clear whether pre-/postconditioning-like phenomena occur during chronic exposure and contribute to the differential susceptibility between patients for IH-related consequences and/or to the age-related decline in mortality observed in sleep apnea patients



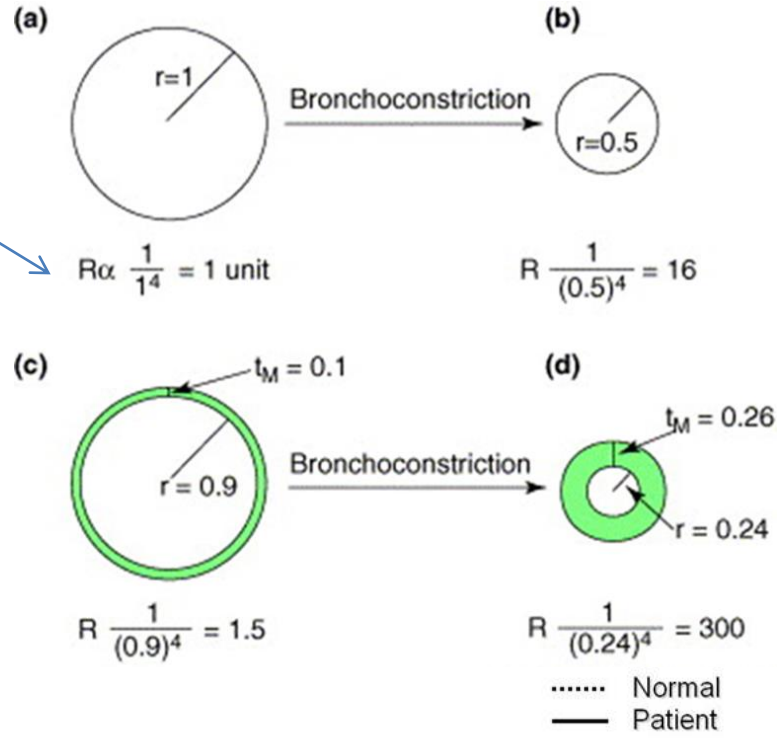
MOST COMMON OBSTRUCTION DISEASES

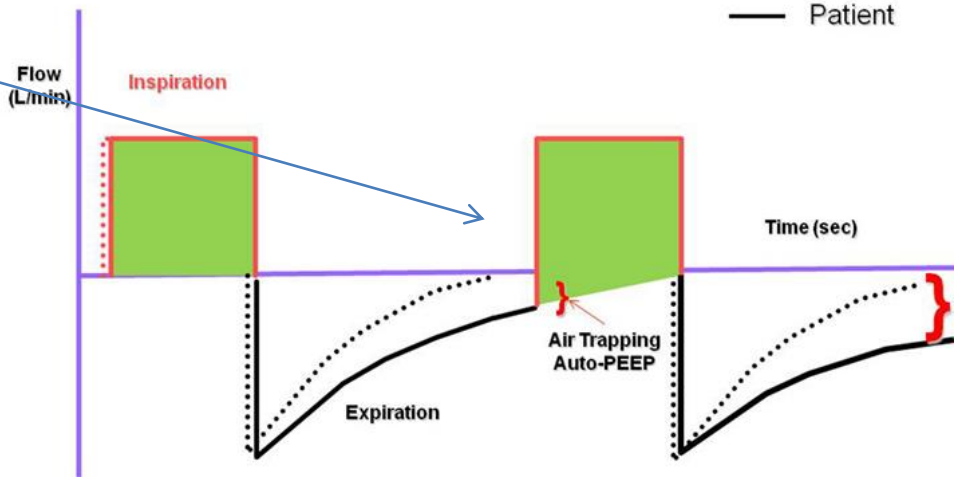
Breathing = periodical changes in preassures and resistances



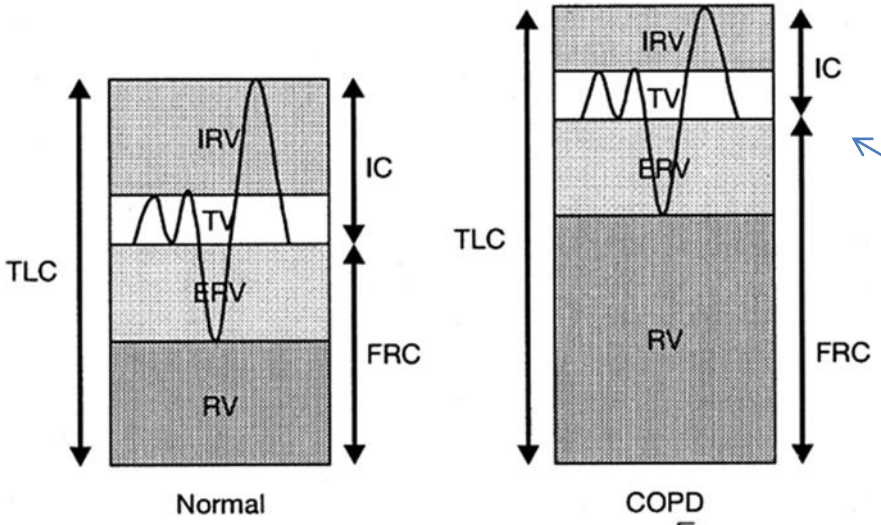
Ventilation disorders due to bronchial obstruction – basic pathophysiological characteristics

- obstruction in airways massively increases their **resistance** (dynamic resistance)
  - Hagen-Poiseuille law $R = \frac{8nl}{\pi r^4}$
- since inspirium is an active process (muscles and negative alv. and transthoracic pressure overcome resistances) but expirium passive one, obstruction leads to an **impairment of expiration**
- participation of auxiliary respiratory muscles leads to
  - dynamic compression, air trapping and **hyperinflation of the lungs**
    - ↑ residual volume (FRC, RV, TLC)
  - ↑ breathing effort and thus **dyspnea**
- ↓dynamic ventilatory parameters (spirometry)
  - more time needed to exhale FVC (↓FEV1)

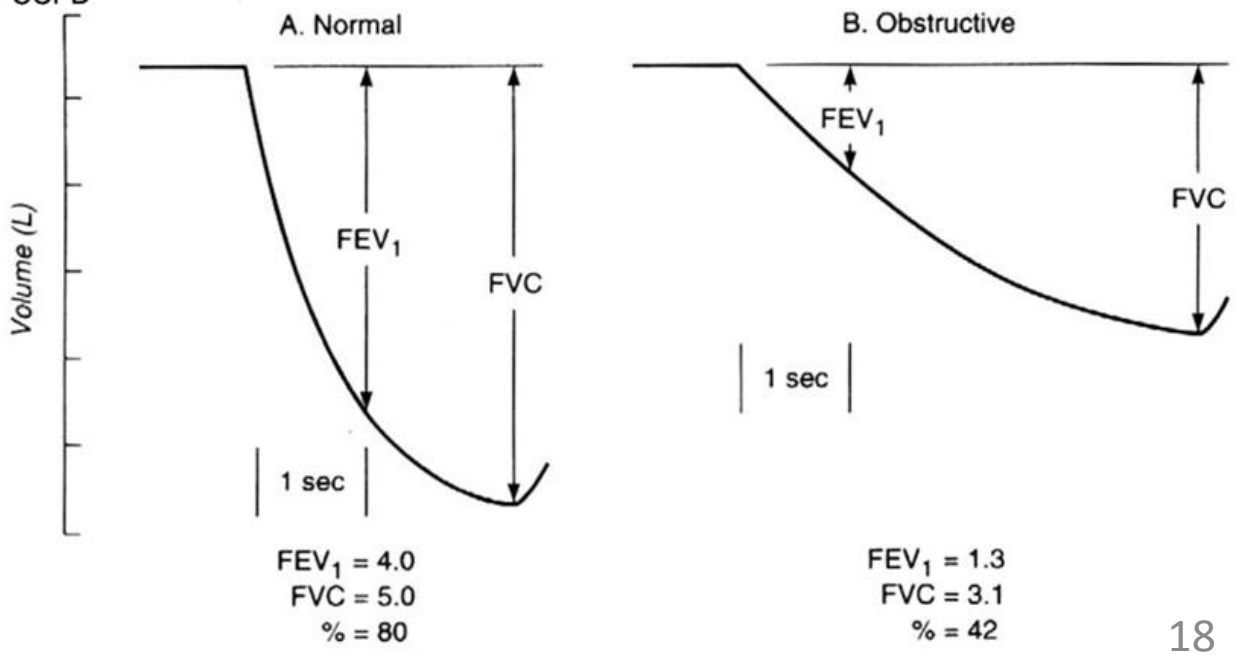




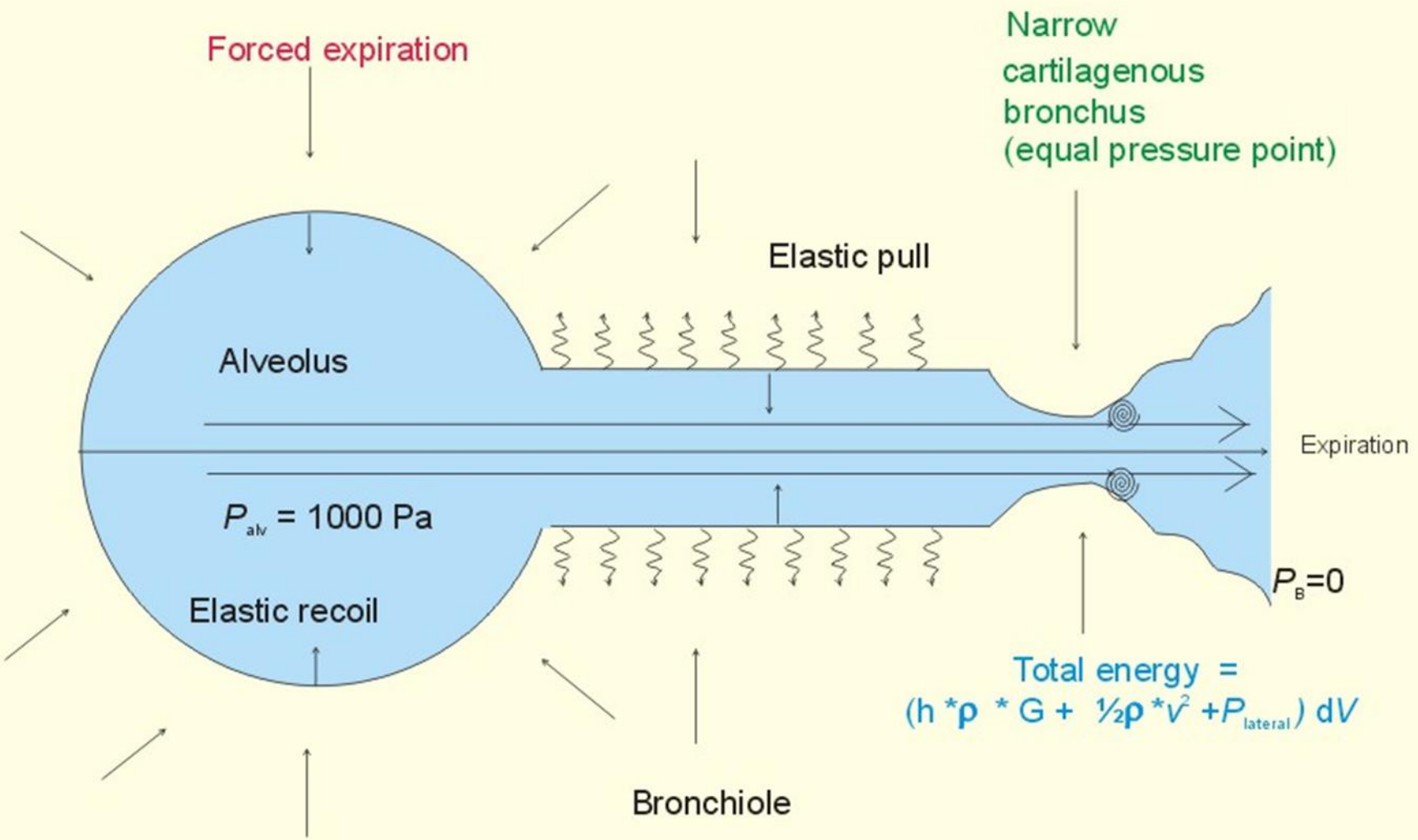
Ventilation disorders due to bronchial obstruction – basic pathophysiological characteristics



shift towards inspiration reserve volume with greater static resistances of airways (increased breathing effort)



Dynamic Airway Collapse



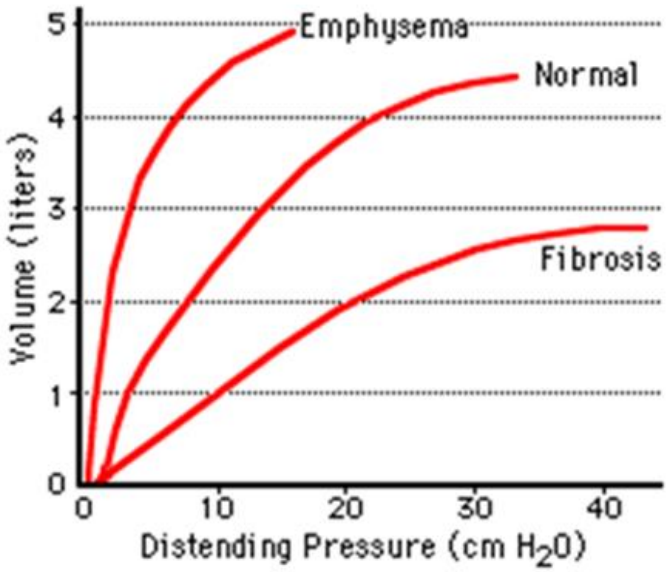
Expiratory effort --- Increased kinetic energy --- Reduced lateral pressure --- Dynamic Airway Collapse

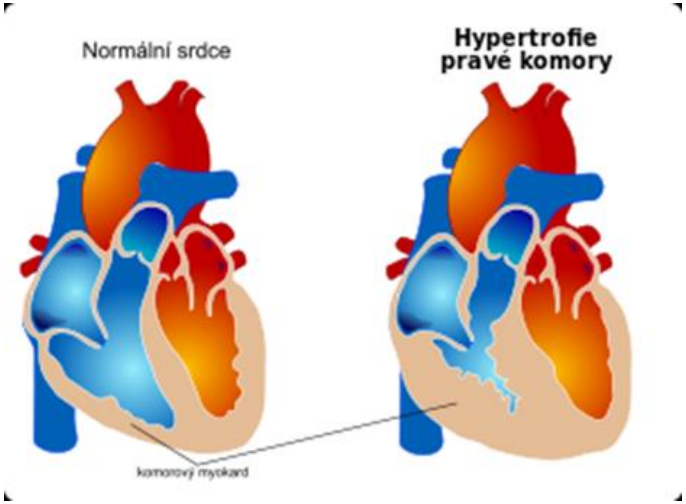
Fig. 13-5

KMc

Ventilation disorders due to bronchial obstruction – basic pathophysiological characteristics

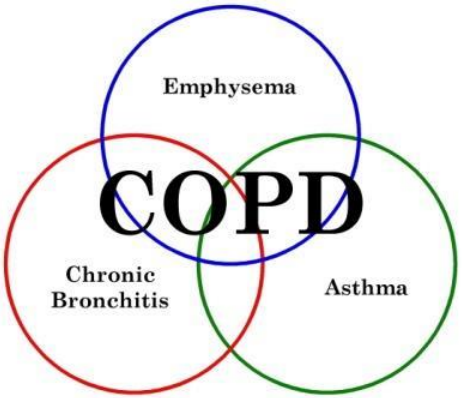
- ↓V_A **but variable ventilation-perfusion mismatch**
  - more bronchitis = more „shunting“(↓ V_A/Q)
  - more emphysema = more „deadspace“(↑ V_A/Q)
- destruction of alveolar septa (emphysema)
- both abnormalities contribute to **resp. insufficiency**
  - hypoxemia develops due to ↓V_A, and loss of diffusion area for oxygen
- event. hypercapnia and resp. acidosis develops due to ↓V_A, increasing shunt and breathing effort (production of CO_2)
- **hypoxic vasoconstriction** in pulmonary circulation (and event. destruction of septa and capillaries in emphysema) leads to its remodelation
  - secondary **pulmonary hypertension**
  - and event. cor pulmonale (isolated hypertrophy of right ventricle)

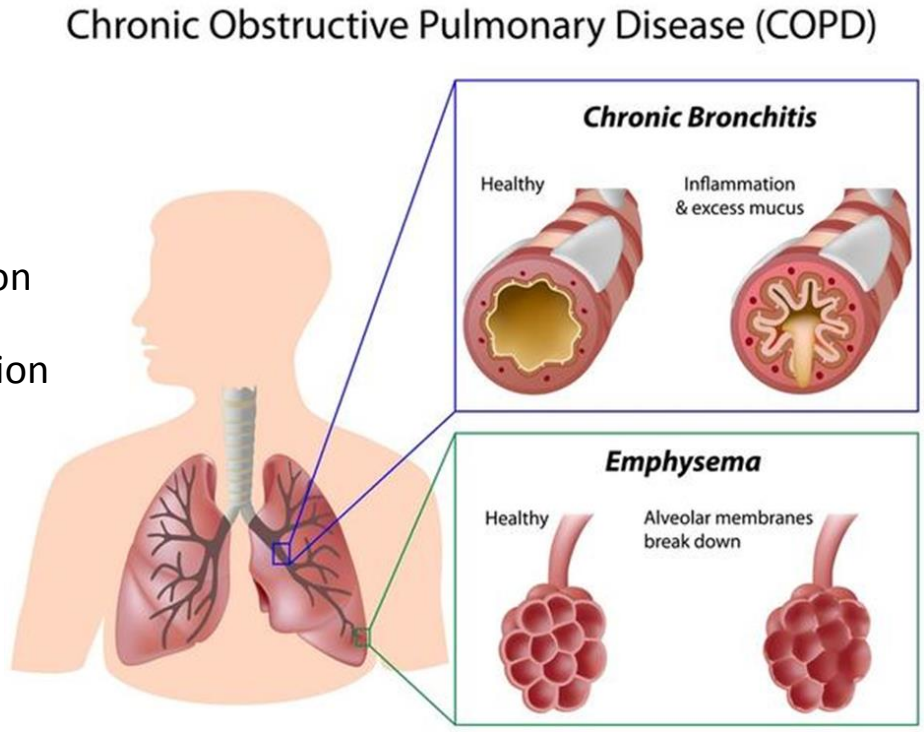




Chronic obstructive pulmonary disease (COPD)

- COPD is not solely **pulmonary** disease but **systemically** manifested syndrome
- definition of pulmonary component of COPD:
  - permanent bronchial obstruction, not fully reversible, usually progressive, characterized by abnormal inflammatory response to environmental harmful stimuli
  - bronchial obstruction in COPD is caused by individually variable combination of:
    - **chronic bronchitis** (with excessive resp. secretion)
    - **pulmonary emphysema** (i.e. destruction of lung parenchyma)
    - **obstructive bronchiolitis** (with obstruction of small airways)
- systemic component comprises:
  - changes in pulmonary vasculature
  - hypoxic hypoxia



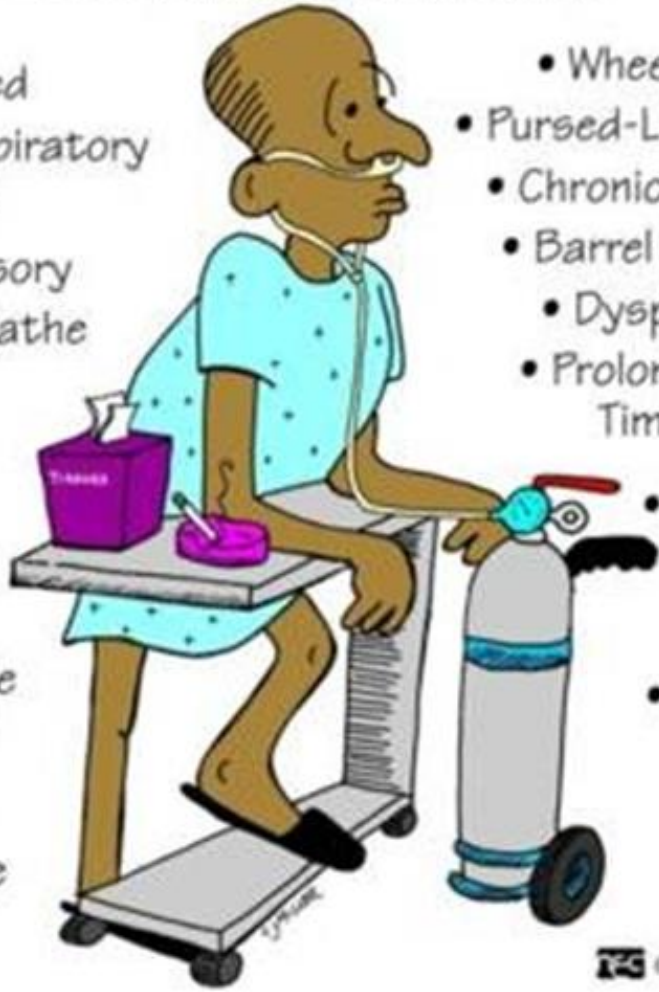


COPD

CHRONIC AIRFLOW LIMITATION

"EMPHYSEMA AND CHRONIC BRONCHITIS"

- Easily Fatigued
- Frequent Respiratory Infections
- Use of Accessory Muscles to Breathe
- Orthopneic

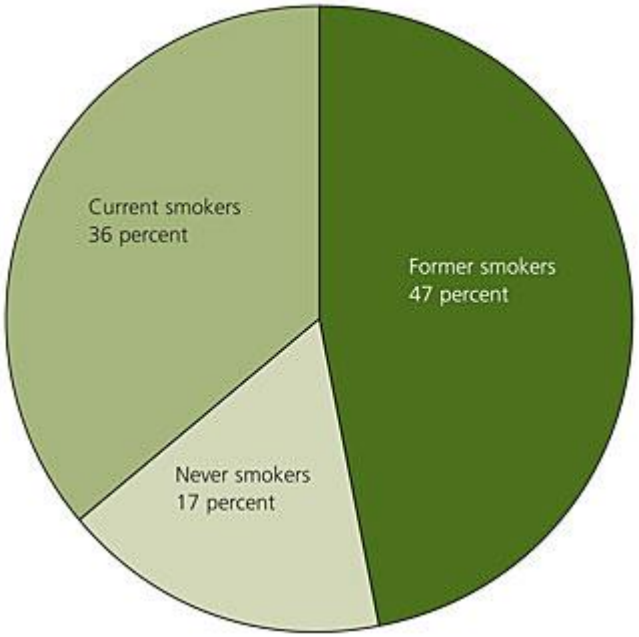


- Wheezing
- Pursed-Lip Breathing
- Chronic Cough
- Barrel Chest
- Dyspnea
- Prolonged Expiratory Time
- Bronchitis - Increased Sputum
- Digital Clubbing
- Cor Pulmonale (Late in Disease)
- Thin in Appearance

World COPD Day 2012
November 14, 2012

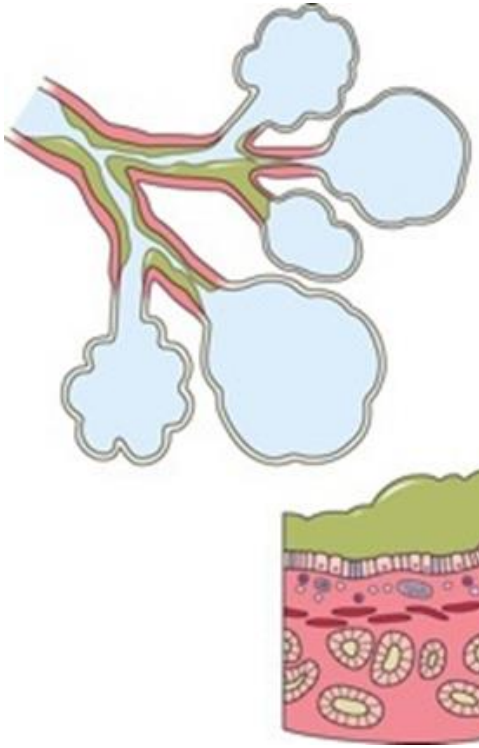
COPD

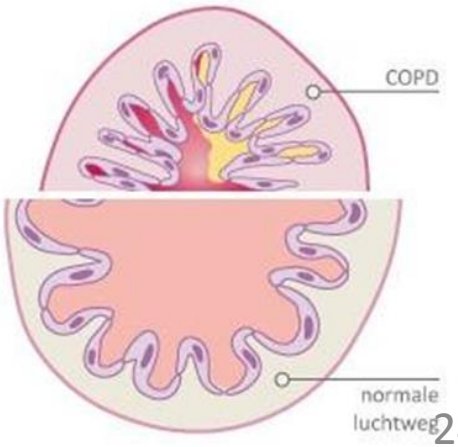
- COPD is one of the most frequent chronic illnesses and one of the commonest causes of mortality worldwide
  - 4th place leading cause of death in countries with high prevalence of smoking
    - after MI, tumors and stroke
- **85-90% of COPD patients are smokers**
  - Incidence is increased up to twentyfold in smokers compared to non-smokers
  - even more so in workers exposed to air pollution



Chronic bronchitis (∅ >2mm) and bronchiolitis (∅ <2mm)

- symptomatic definition
  - hypersecretion of mucus and chronic productive cough that continues for at least 3 months of years for at least 2 consecutive years
- however patients typically suffer from chronic bronchitis without obstruction for a long time and only then develop bronchial obstruction (i.e. COPD)
  - there are of course patients with COPD without clinical signs of chronic bronchitis
  - some chronic bronchitis cases never progress to COPD
- in manifest COPD presence of chronic bronchiolitis is obligatory dominantly responsible (together with pulmonary emphysema) for obstruction
  - chronic persistent inflammation of small airways (∅ ≤ 2 mm)
  - the ratio between chronic bronchiolitis and pulmonary emphysema is entirely individual

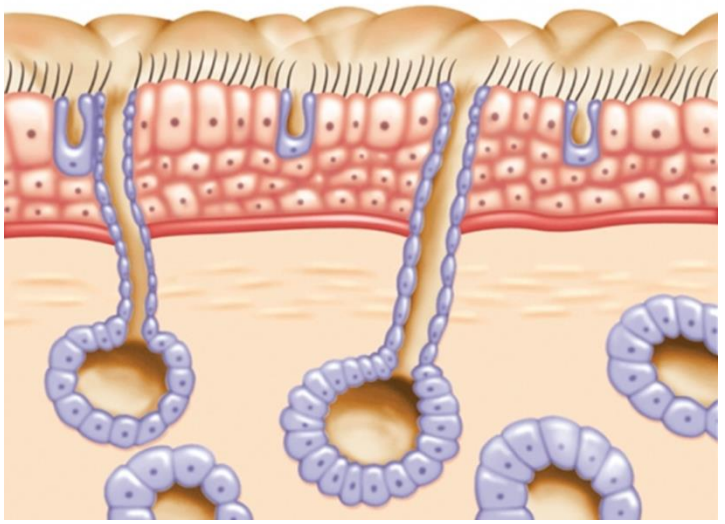


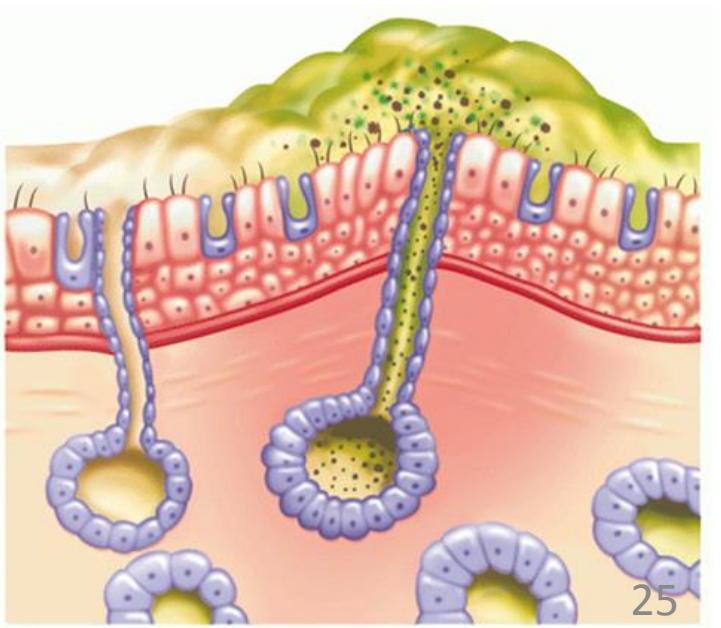


Chronic bronchitis – pathological anatomy

- inhaled irritants not only increase mucus production but also increase the size and number of **mucous glands** and **goblet cells** in airway epithelium
  - mucus produced is thicker and more tenacious than normal
  - sticky mucus coating makes it much more likely that bacteria, such as H. influenze and S. pneumoniae, will become embedded in the airway secretions, there they reproduce rapidly
- **cilia** function is impaired, reducing mucus clearance further
  - lung´s defense mechanisms are therefore compromised, increasing susceptibility to pulmonary infection and injury
- **bronchial wall** becomes inflamed and thickened from edema and accumulation of inflammatory cells
- initially chronic bronchitis affects only the larger bronchi, but eventually all airways are involved
- thick mucus and hypertrophied bronchial smooth muscle obstruct the airways and lead to closure, particularly during expiration, when the airways are narrowed
  - airways collapse early in expiration, trapping gas in the distal portions of the lung.
  - obstruction eventually leads to ventilation-perfusion mismatch, hypoventilation (increased PaCO2) and hypoxemia

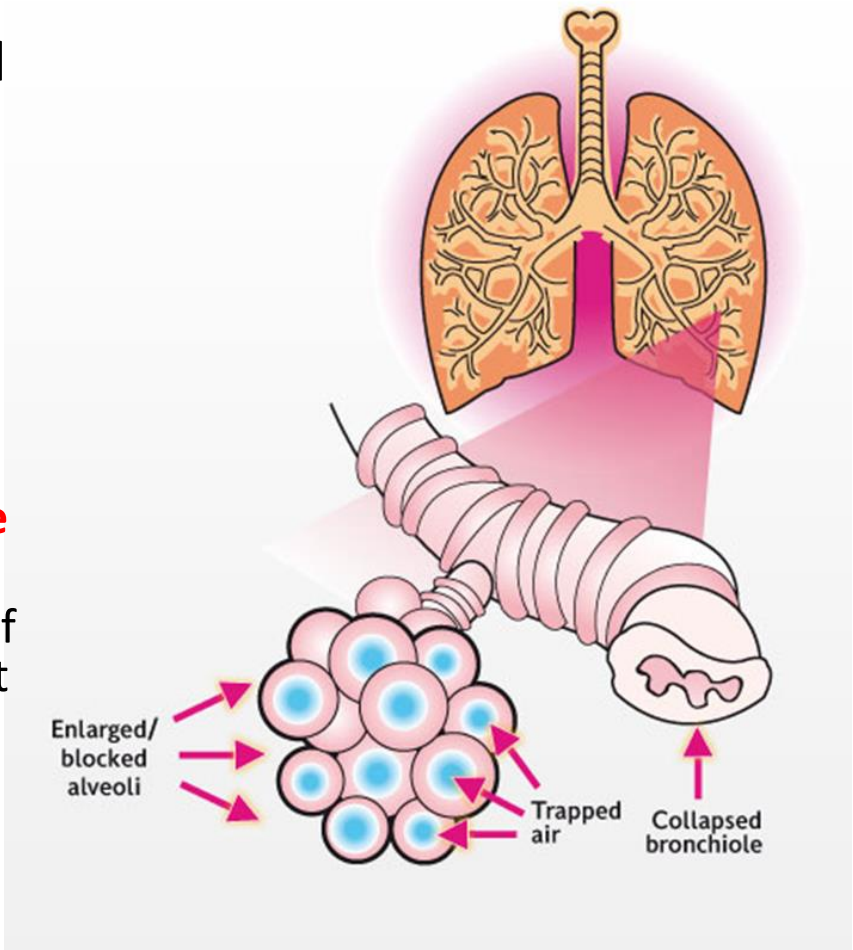
normal



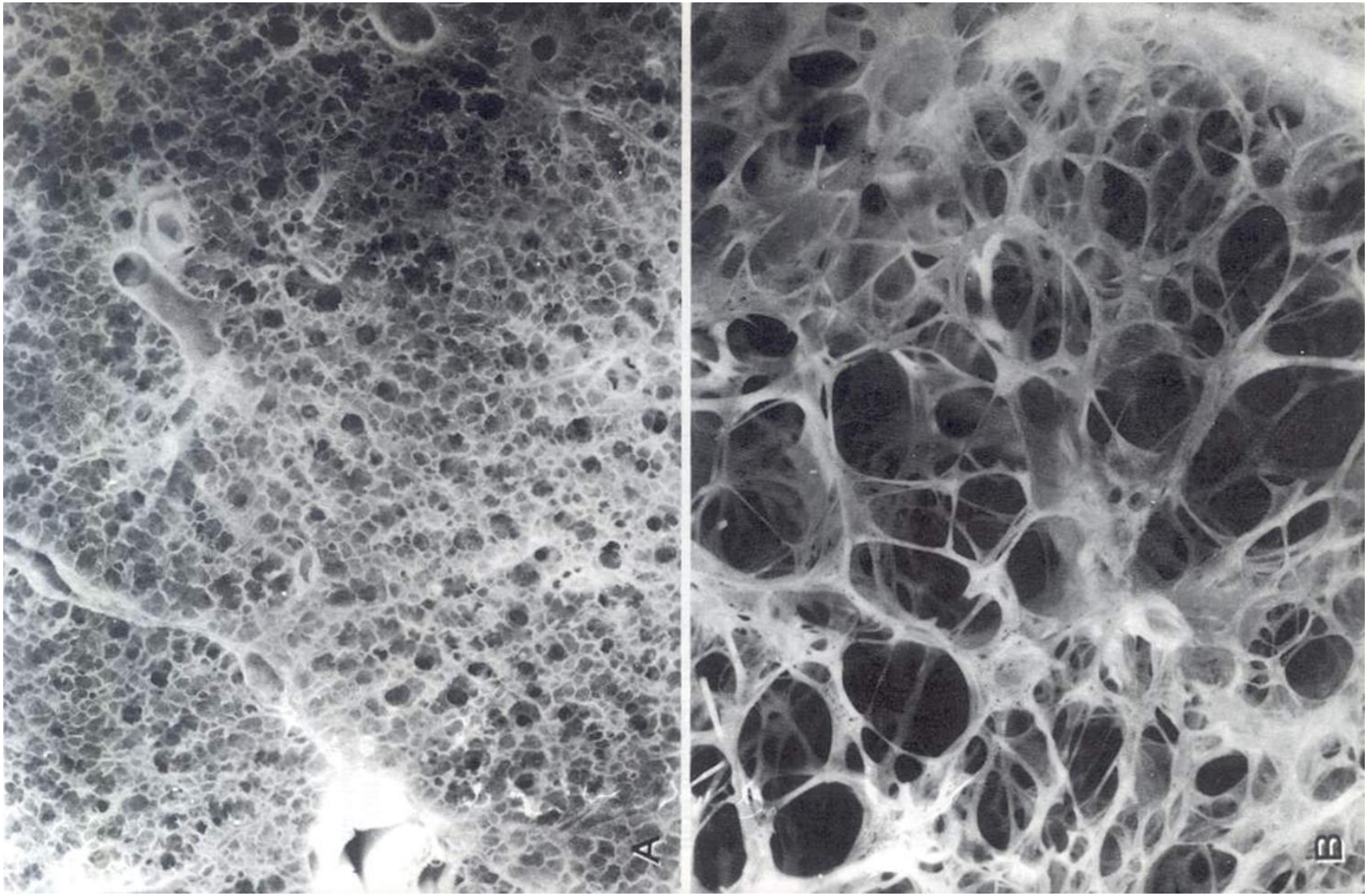


Lung emphysema

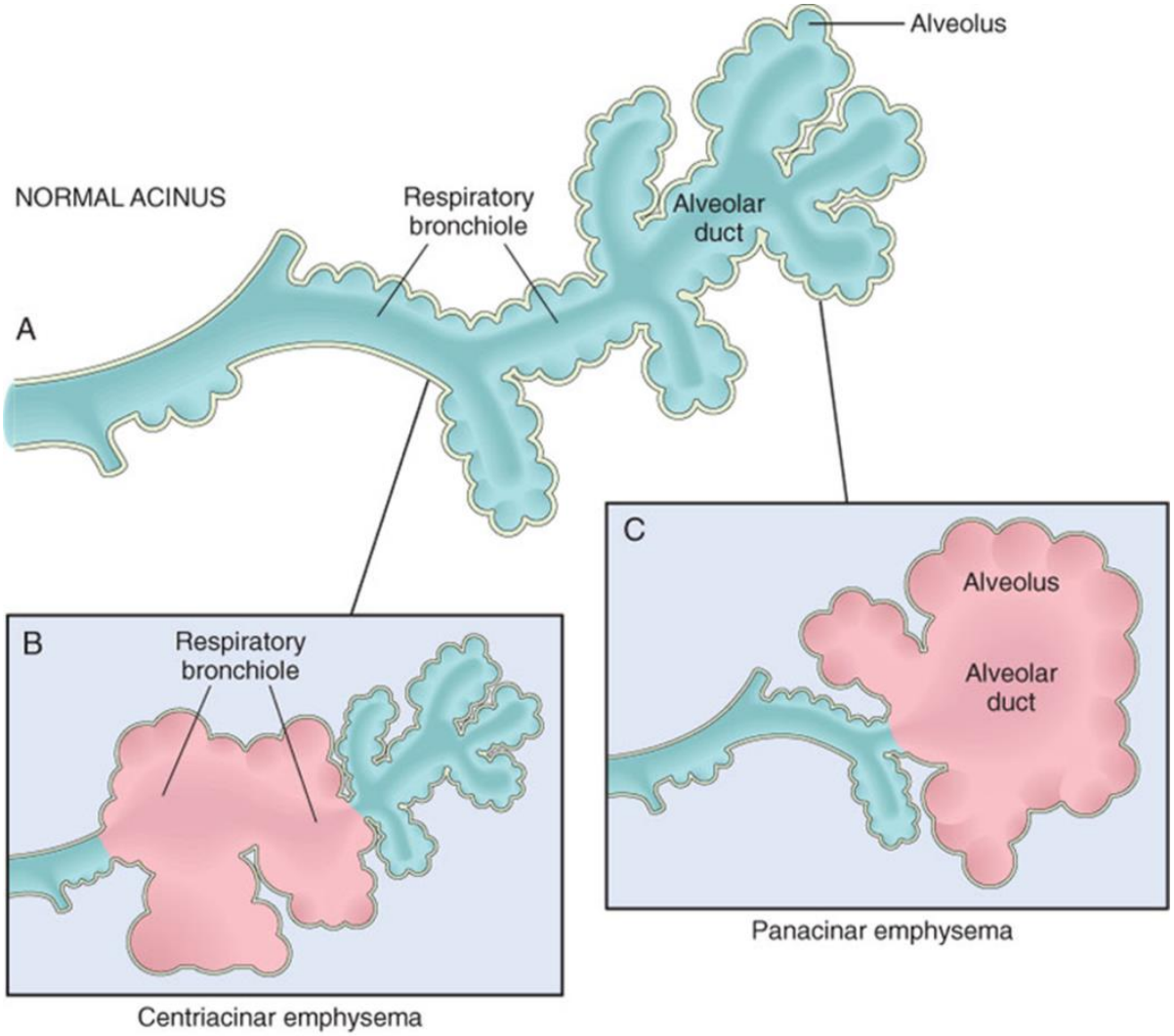
- abnormal permanent enlargement of gas-exchange airways = acini (i.e distally from terminal bronchioles) accompanied by **destruction of alveolar walls** and without obvious fibrosis
  - obstruction results from changes in lung tissues, rather than mucus production and inflammation, as in chronic bronchitis
- functional consequence:
  - major mechanism of airflow limitation is **loss of elastic recoil** leading to the **collapse of small airways** during expiration
  - expiration becomes difficult because loss of elastic recoil reduces the volume of air that can be expired passively,
  - combination of increased RV (and FRC) in the alveoli and diminished caliber of the bronchioles causes part of each inspiration to be trapped in the acinus
  - **hyperinflation** of alveoli causes large air spaces (bullae) and air spaces adjacent to pleura (blebs) to develop



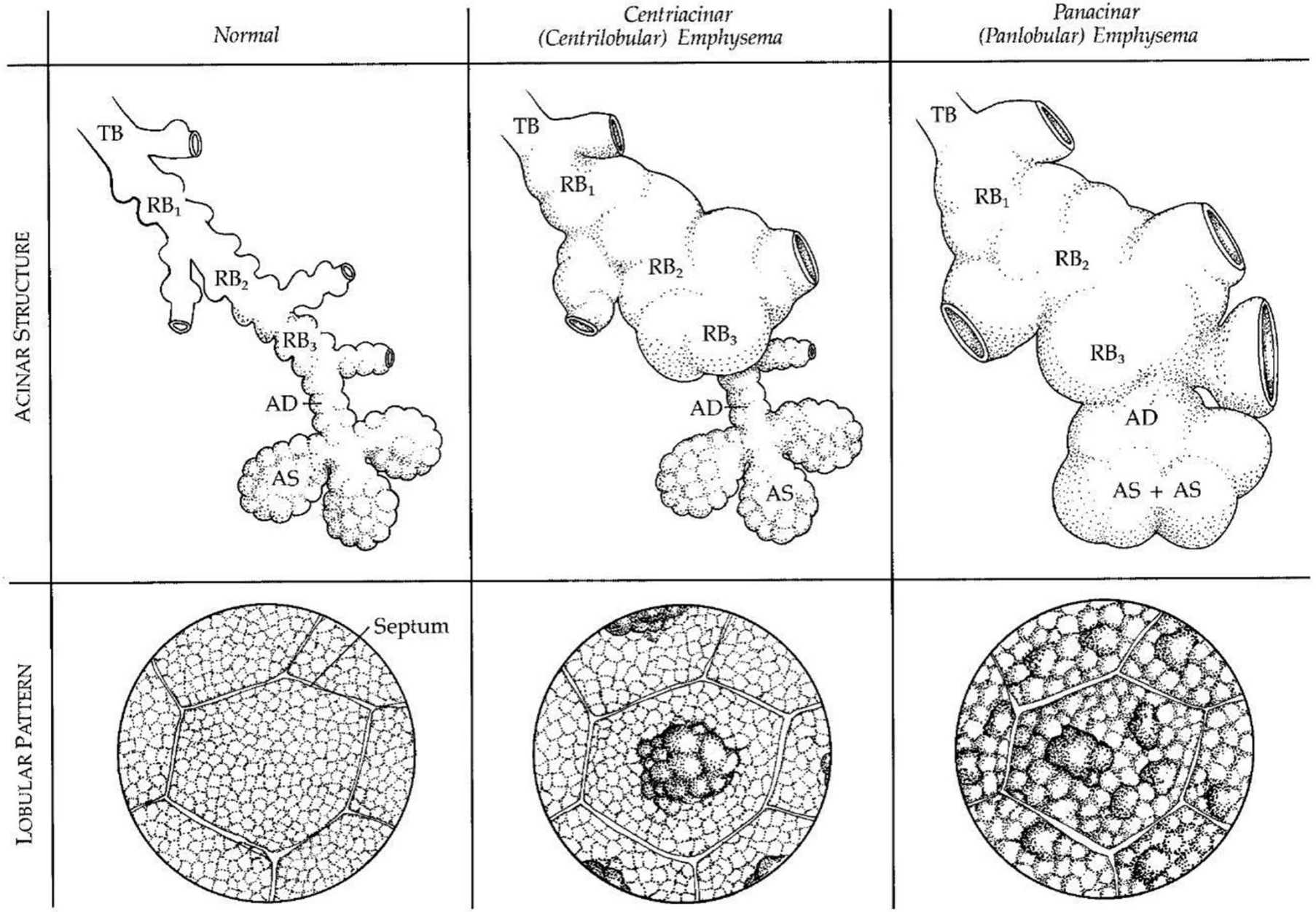
Healthy (left) vs. emphysematous lung (right)



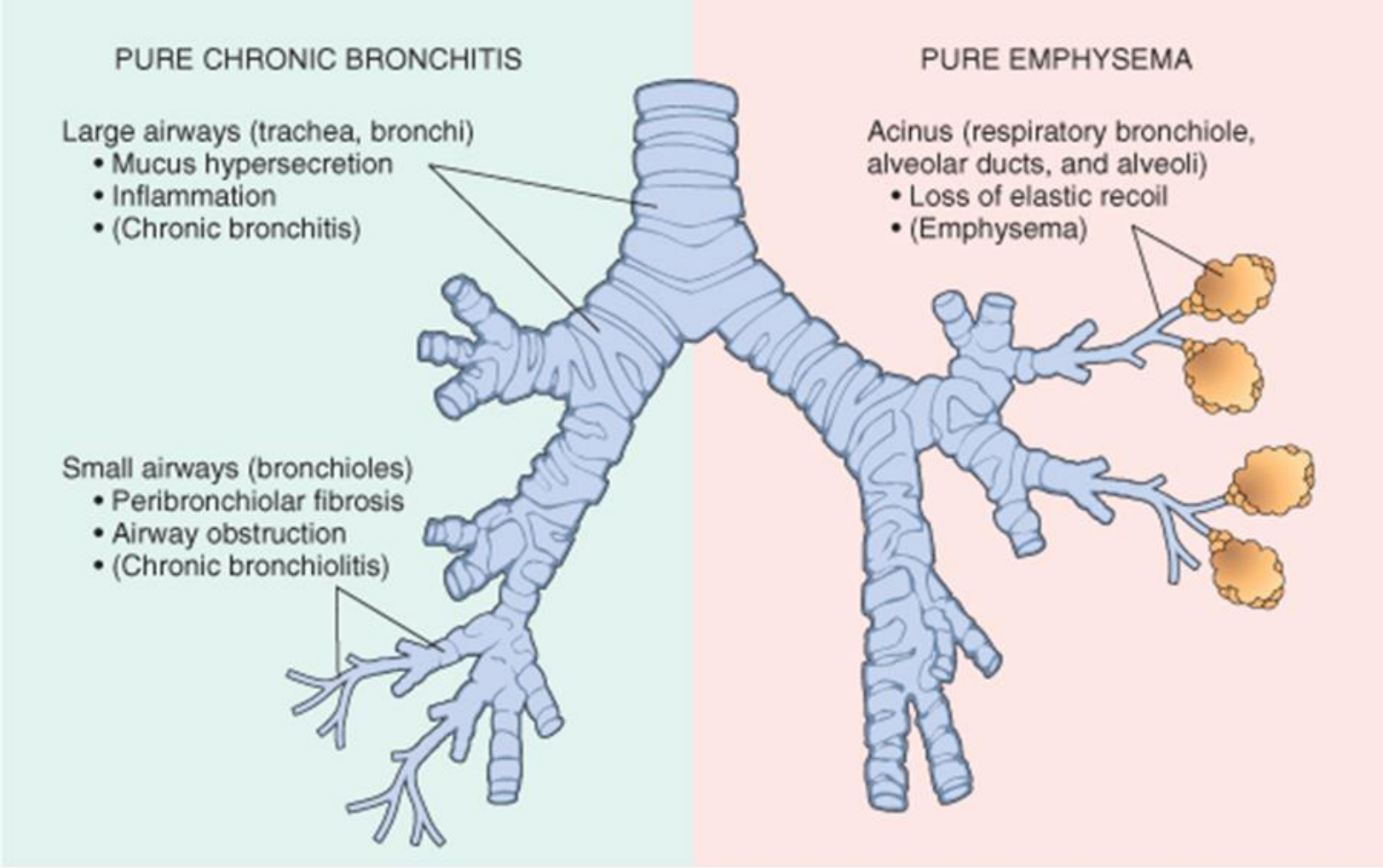
Emphysema types in COPD

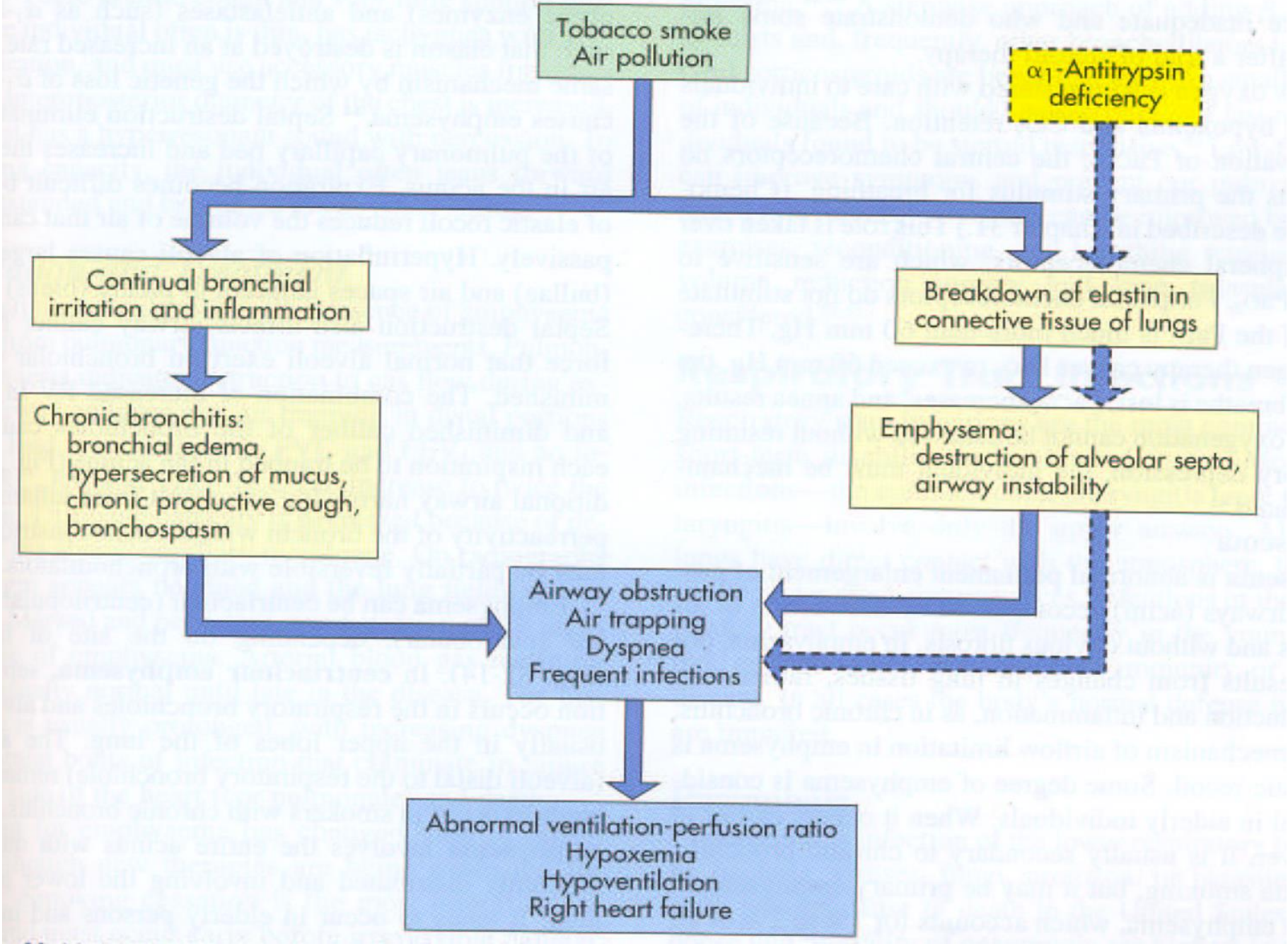


- Centrilobular (centriacinar):
  - septal destruction occurs in the respiratory bronchioles and alveolar ducts, usually in the upper lobes of the lung
  - alveolar sac (alveoli distal to the respiratory bronchiole) remains intact
  - tends to occur in smokers
- 2) Panacinar (panlobular):
  - involves the entire acinus with damage more randomly distributed and involving the lower lobes of the lung
  - tends to occur in patients with α1-antitrypsin deficiency


Normal
Centriacinar
(Centrilobular) Emphysema
Panacinar
(Panlobular) Emphysema
ACINAR STRUCTURE
LOBULAR PATTERN
TB
RB1
RB2
RB3
AD
AS
AS + AS
Septum

Variable overlap in COPD

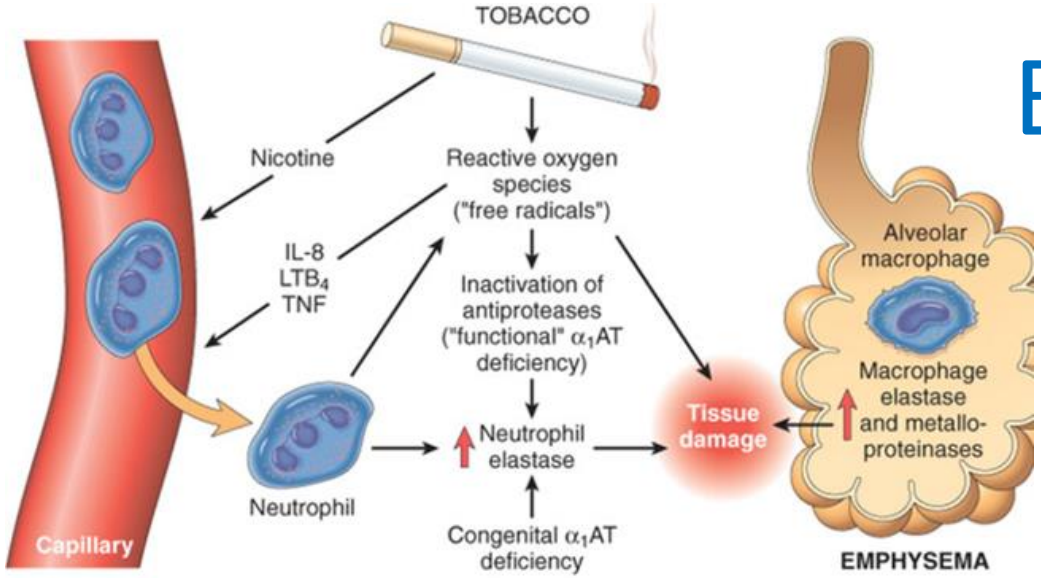


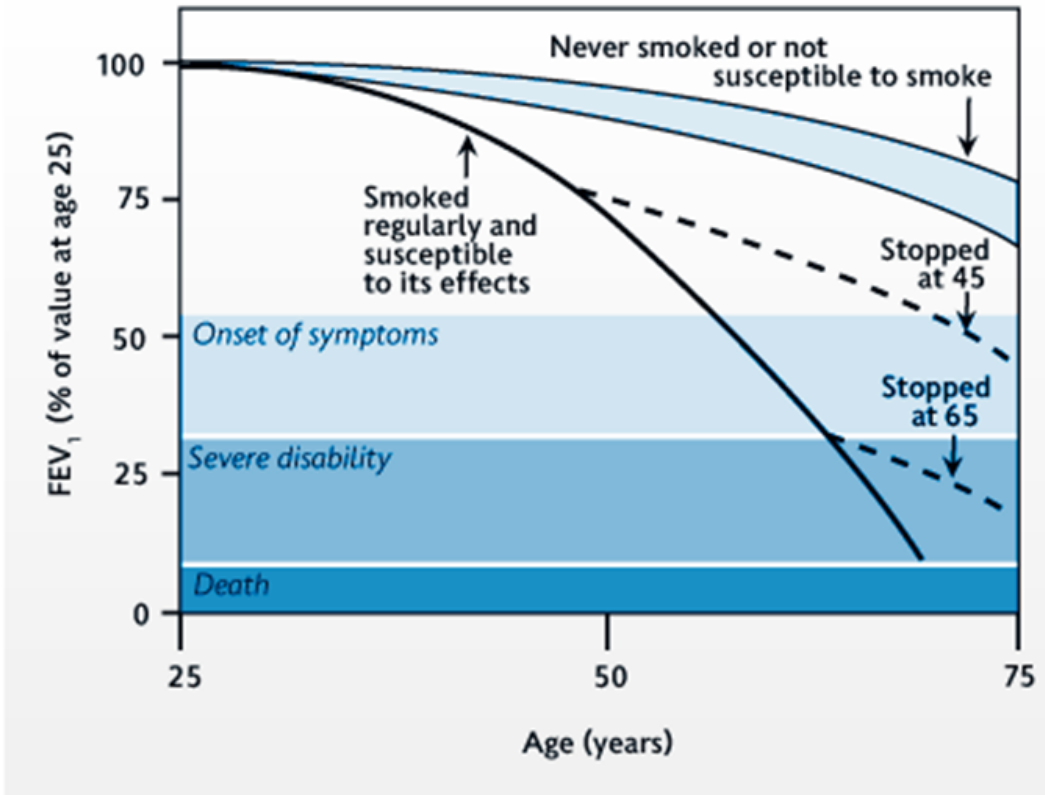

Tobacco smoke
Air pollution
α1-Antitrypsin deficiency
Continual bronchial irritation and inflammation
Breakdown of elastin in connective tissue of lungs
Chronic bronchitis:
bronchial edema,
hypersecretion of mucus,
chronic productive cough,
bronchospasm
Emphysema:
destruction of alveolar septa,
airway instability
Airway obstruction
Air trapping
Dyspnea
Frequent infections
Abnormal ventilation-perfusion ratio
Hypoxemia
Hypoventilation
Right heart failure

Etiology of COPD - multifactorial

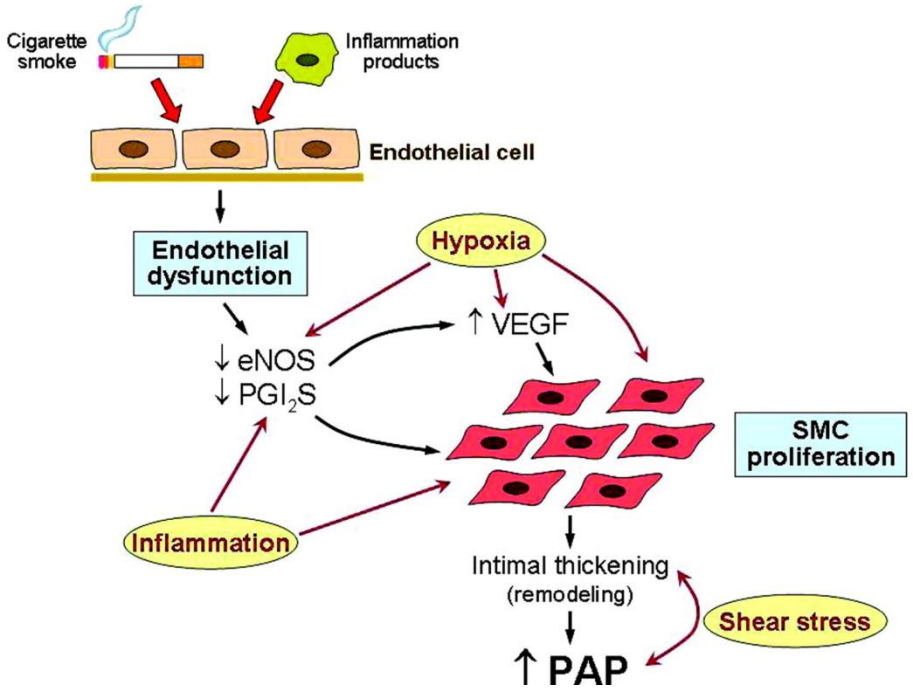
- smoking
  - cigarette smoke and air pollution, tip the normal balance of elastases (proteolytic enzymes) and antielastases (such as α1-antitrypsin) so that elastin is destroyed at an increased rate
  - ↑ number of neutrophil granulocytes in inflammed airways
    - source of elastases and proteases favoring emphysema development
  - tissue injury due to reactive oxygen and nitrogen species
    - healing with the participation of macrophages (source of matrix metaloprotinases)
  - hypertrophy of mucus glands and thus CHB
  - impairment of surfactant
- airway hyper-reactivity
- genetics (= variable consequencies in two persons with equal „smoking“ history)
  - α1-antitrypsin deficiency
    - α1-antitrypsin inhibits neutrophil elastase which has the ability to destruct lung tissue
    - identified more than 75 alleles in the gene for α1-antitrypsin
  - other genes
    - pro-inflammatory cytokines, growth factors, protease/antiprotease balance, antioxidants etc.
- exposure to other air pollutants (dust, smoke, professional exposure, car traffic fumes, biomass burning etc.)
  - the most risky are small particles ≤ 2.5 μm
- recurrent lower airways and lung infections

Effect of smoking



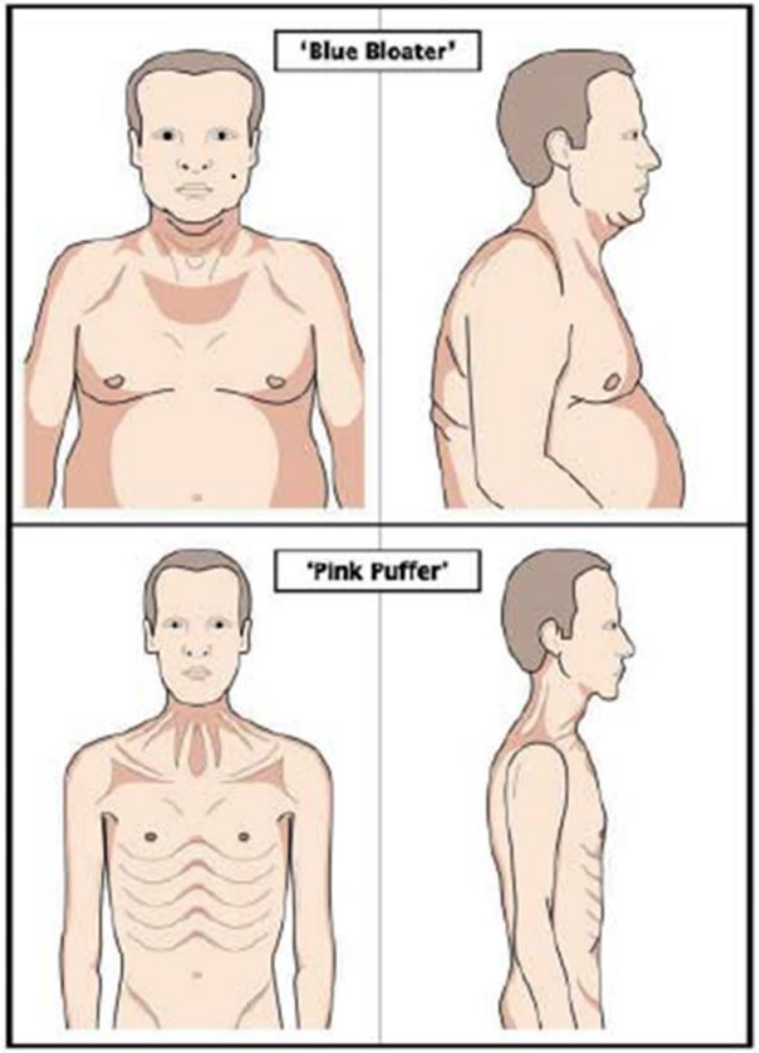


Pulmonary vessels in COPD



- remodelation (i.e. wall thickening, lumen narrowing and increased resistance) present very early in the time course of COPD
  - endothelial dysfunction
    - due to oxidative stress
  - hyperplasia of tunica intima
    - cells (inflammatory cells and SMCs) as well as ECM
  - hypertrophy of tunica media
- gradually hypoxia and loss of capillaries (emphysema) contributes to remodelation as well
  - vasoconstriction
  - later pre-capillary form of secondary pulmonary hypertension
- cor pulmonale

Clinical heterogenity of COPD



- Type A – “pink puffer” - dominance of emphysema
  - patients with emphysema are able to maintain a higher alveolar minute ventilation (“puffers”) than those with chronic bronchitis
    - therefore they tend to have a higher PaO2 and lower PaCO2 and are indeed „pink “
  - a thin, tachypneic patient using accessory muscles and pursed lips to facilitate respiration
    - thorax is barrel-shaped due to hyperinflation
  - there is little cough and very little sputum production (in „pure“ emphysema)
- Type B – “blue bloater”– dominance of bronchitis
  - bronchitis patients are often „blue“ due to hypoxemia (and central cyanosis)/hypercapnia
  - they regularly exhibit right heart failure due to an increase in pulmonary artery pressure impairing right ventricular function
    - this leads to peripheral edema (“bloaters”)

TABLE 22-2 Characteristics of Emphysema and Chronic Bronchitis

Characteristic	Type A Pulmonary Emphysema ("Pink Puffers")	Type B Chronic Bronchitis ("Blue Bloaters")
Smoking history	Usual	Usual
Clinical features		
Barrel chest (hyperinflation of the lungs)	Often dramatic	May be present
Weight loss	May be severe in advanced disease	Infrequent
Shortness of breath	May be absent early in disease	Predominant early symptom, insidious in onset, exertional
Decreased breath sounds	Characteristic	Variable
Wheezing	Usually absent	Variable
Rhonchi	Usually absent or minimal	Often prominent
Sputum	May be absent or may develop late in the course	Frequent early manifestation, frequent infections, abundant purulent sputum
Cyanosis	Often absent, even late in the disease when there is low PO_2	Often dramatic
Blood gases	Relatively normal until late in the disease process	Hypercapnia may be present Hypoxemia may be present
Cor pulmonale	Only in advanced cases	Frequent
		Peripheral edema
Polycythemia	Only in advanced cases	Frequent
Prognosis	Slowly debilitating disease	Numerous life-threatening episodes due to acute exacerbations

COPD stages

Stage I: Mild

Spirometry shows mild airflow limitation (FEV_1 ≥80% predicted; FEV_1/FVC <0.70). Primary symptoms are chronic cough and sputum production

Stage II: Moderate

Spirometry shows a worsening airflow limitation (FEV_1 ≥50% and <80% predicted; FEV_1/FVC <0.70). Patients often experience dyspnea, which may interfere with their daily activities.

Stage III: Severe

Spirometry shows severe airflow limitation (FEV_1 ≥30% and <50% predicted; FEV_1/FVC <0.70). Symptoms of cough and sputum production typically continue, dyspnea worsens, and repeated exacerbations occur.

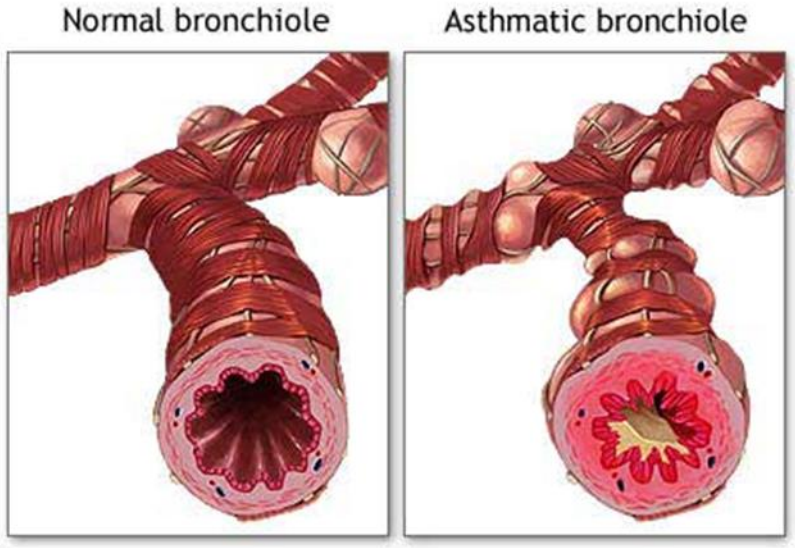
Stage IV: Very Severe

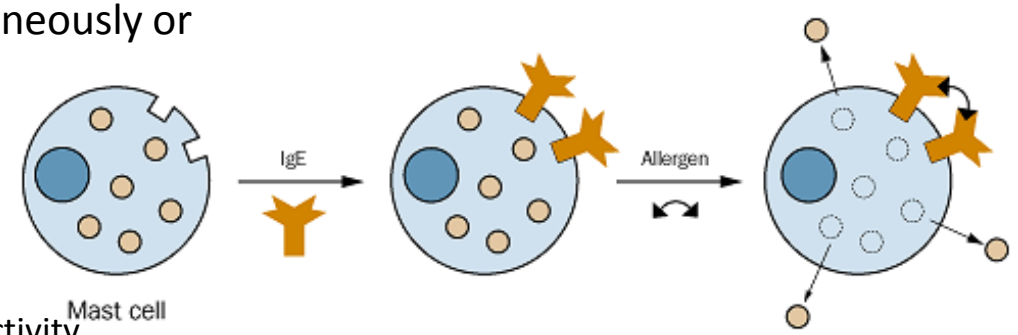
Spirometry shows very severe airflow limitation (FEV_1 <30% predicted or FEV_1 <50% predicted; FEV_1/FVC <0.70 plus chronic respiratory failure). Complications such as respiratory failure or heart failure may develop.

1. Rodriguez-Roisin R, Anzueto A, Bourbeau J, et al; GOLD Executive Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2009). Global Initiative for Chronic Obstructive Lung Disease Web site: http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed March 8, 2010.

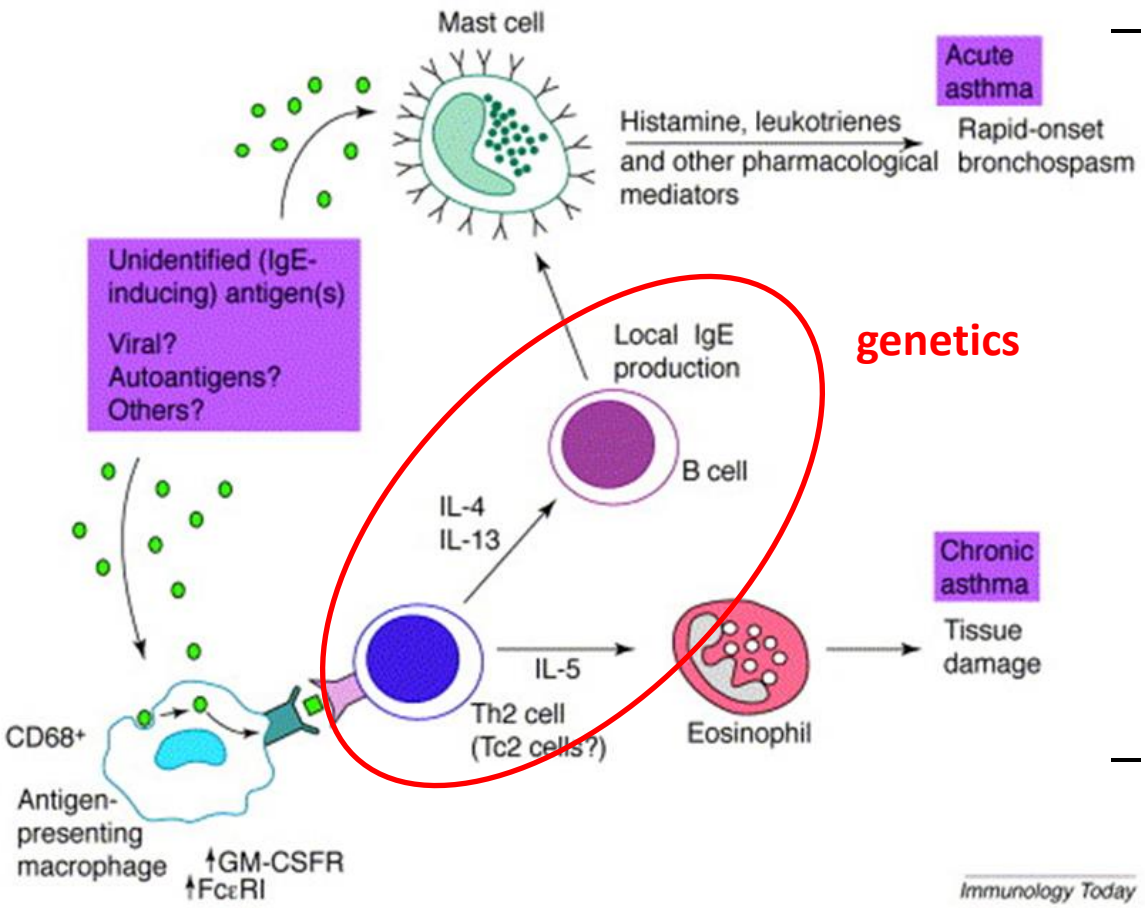
Bronchial asthma

- prevalence
  - 5-10% children
  - ~ 5% adults
- definition (GINA 2006)
  - a **chronic inflammatory disorder** of the airways in which many **cells** play a role
  - chronic inflammation causes an associated increase in **airway hyper-responsiveness** that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning
  - these episodes are usually associated with widespread but variable **airway obstruction** that is often reversible either spontaneously or with treatment
- types
  - allergic (extrinsic)
    - IgE-mediated bronchoconstriction
  - non-allergic (intrinsic)
    - IgE-independent = bronchial hyperreactivity
      - damage of epithelium
      - increased sensitivity to bronchoconstrictive agents



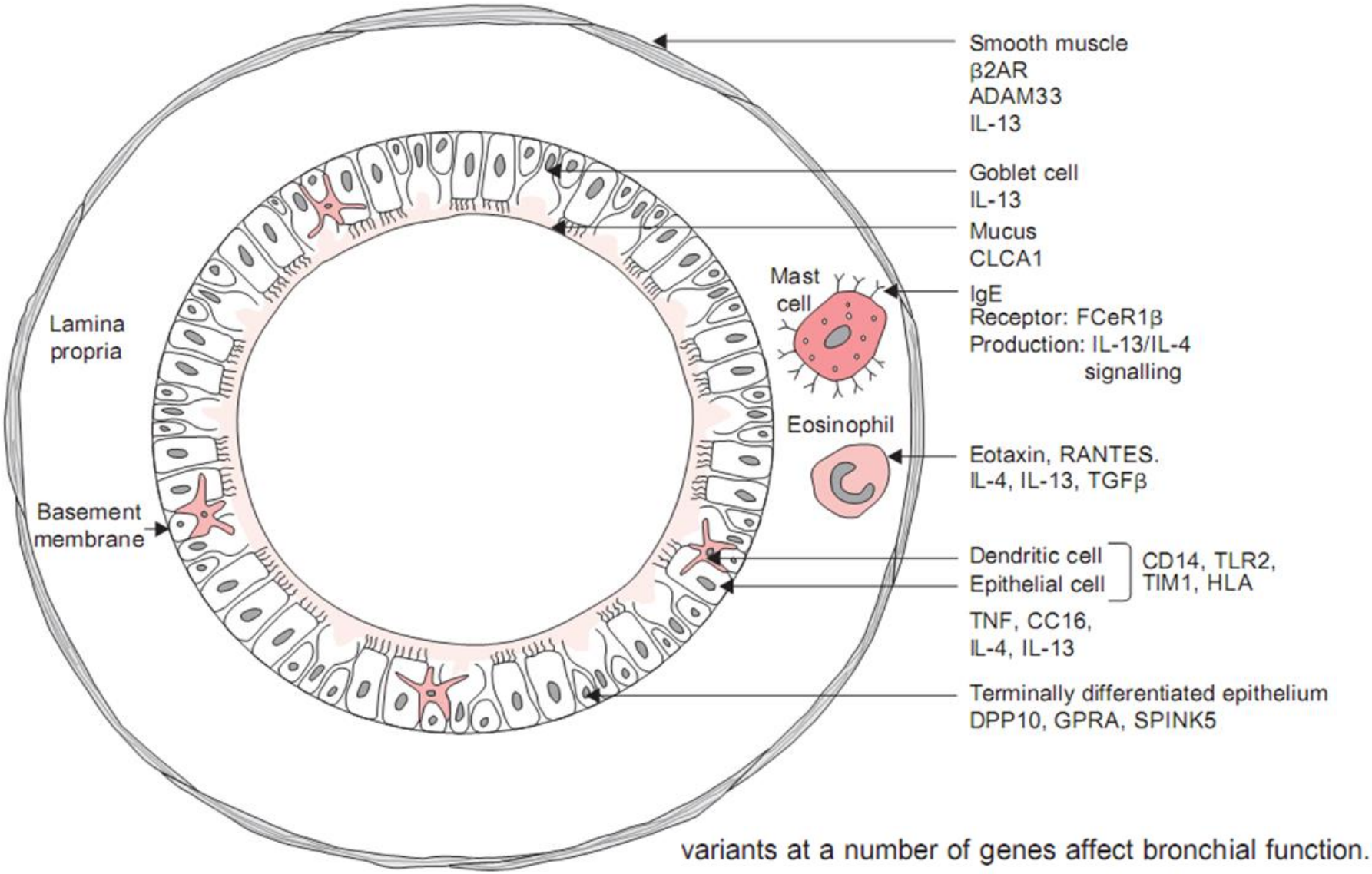


IgE-mediated asthma



- due to the **atopy**
  - genetic predisposition to the alteration of immune response towards immunopathological reaction of type 1
    - ↑ formation of IgE
    - ↑ activity of CD4+Th2 cells (cytokines IL-4, 5, 6, 13)
    - altered Ag presentation by APC
    - different reactivity of target cells to mediators (histamine)
    - ↓ suppressor activity of T cells
    - ↑ number of mast cells
    - ↑ concentration of FcεR1 on their surface
  - IgE antibodies directed often against (aero)allergens
    - domestic (dust mites)
    - pollen
    - infection agents (bacteria, viruses)
    - others

Polygenic nature of asthma



variants at a number of genes affect bronchial function.

Sensibilisation phase in atopic subjects

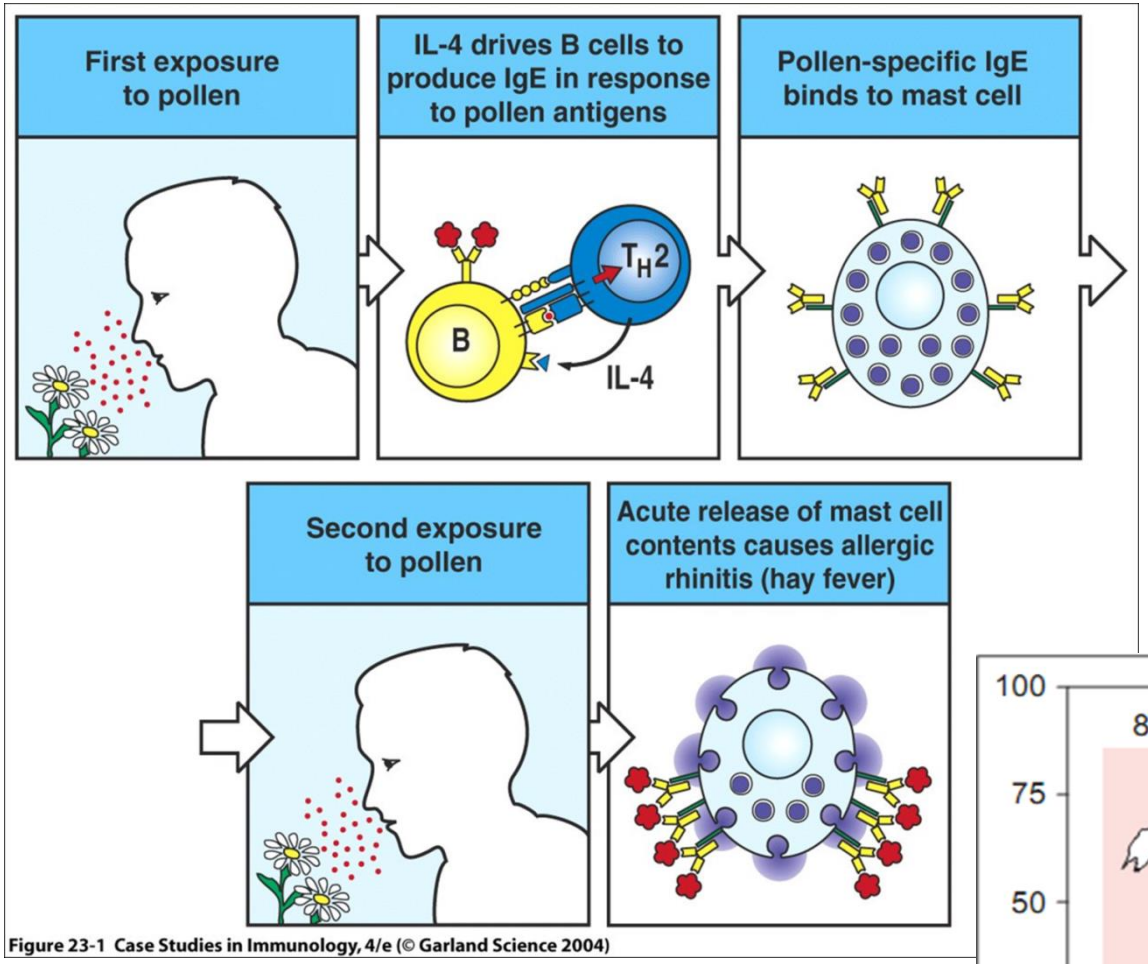
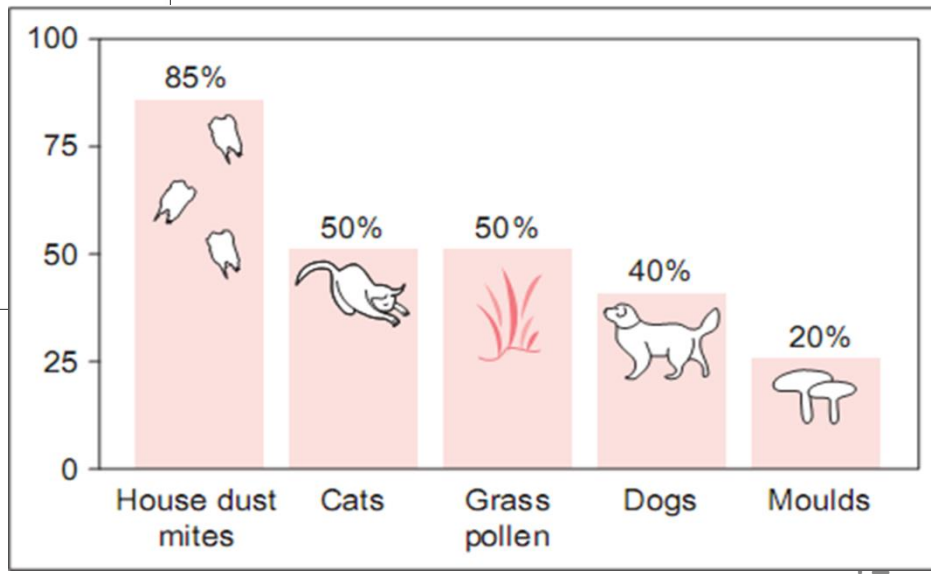
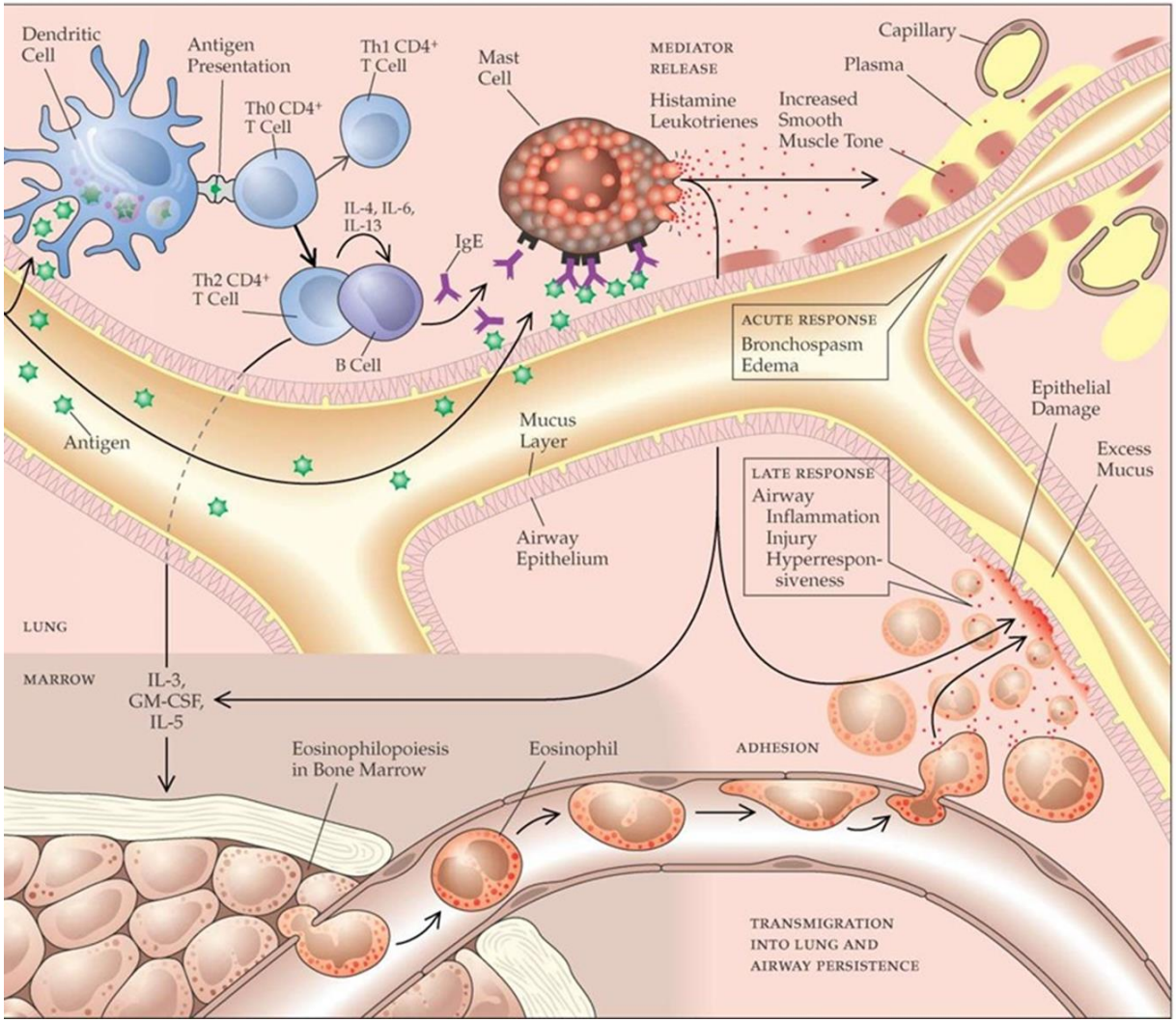


Figure 23-1 Case Studies in Immunology, 4/e (© Garland Science 2004)

Proportions of asthmatic children sensitized to common allergens



Pathogenesis of allergic asthma



Inhaled antigen is processed by dendritic cells and presented to Th2 CD4+ T cells. B cells are stimulated to produce IgE, which binds to mast cells. Inhaled antigen binds to IgE, stimulating the mast cell to degranulate, which in turn leads to the release of mediators of the immediate response and the late response. Histamine and the leukotrienes produce bronchospasm and airway edema. Released chemotactic factors, along with factors from the Th2 CD4+ T cells, facilitate eosinophil traffic from the bone marrow to the airway walls. These late responses are proposed to lead to excessive mucus production, airway wall inflammation, injury, and hyperresponsiveness. (GM-CSF—granulocyte-macrophage colony-stimulating factor; IFN-γ—interferon gamma; IL—interleukin)

Table 7.1 Characteristics of Th1 and Th2 cells

	Th1	Th2
Cytokines	• IL-2, IFN-γ • IL-3, GMCSF	• IL-4, IL-5, IL-10, IL-13 • IL-3, GMCSF
Main receptors	• IL-12Rβ, IL-18R • CXCR3, CCR5	• CCR4
Effector functions	• Macrophage activation • Complement-binding • Opsonization • Neutrophil activation	• Production of IgE • Production of neutralizing antibodies • Suppression of macrophage activation • Eosinophil activation, proliferation, maturation, recruitment

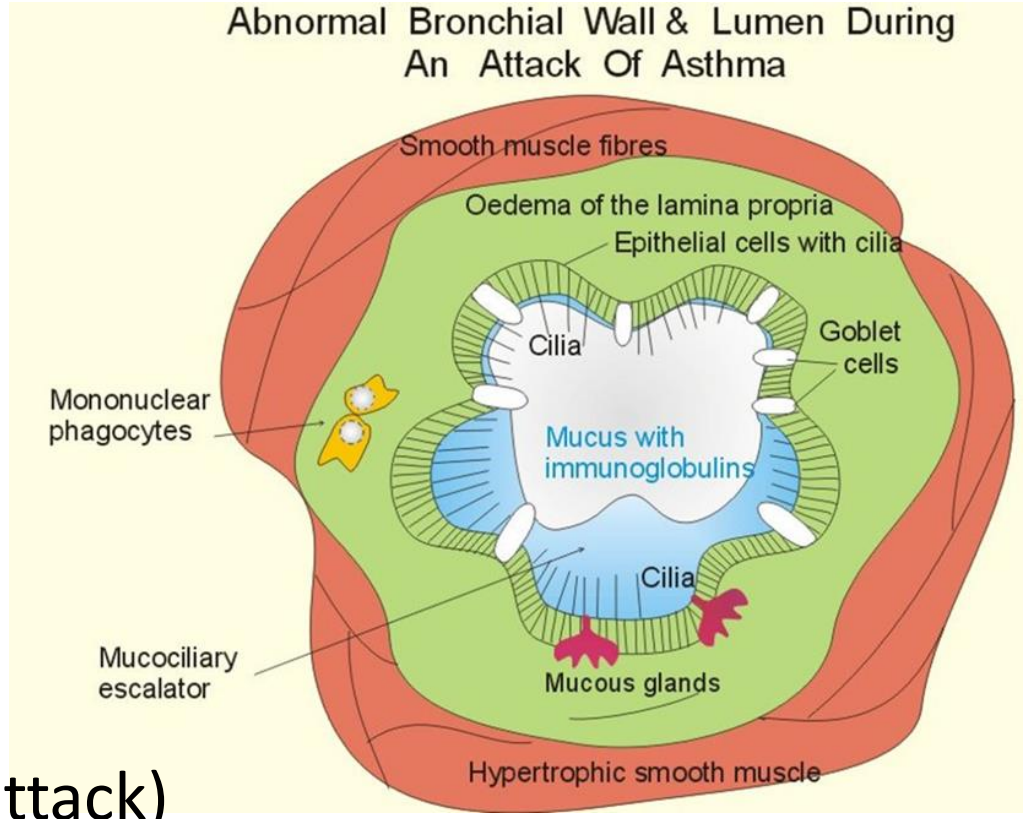
GMCSF, granulocyte macrophage colony stimulating factor; IL, interleukin; IFN, interferon; IgE, immunoglobulin E.

Table 7.2 Characteristics of regulatory T (Treg) cells

nTreg	aTreg: Th3	aTreg: Tr1
• T cell: T cell/APC contact • Generated in thymus • CD4+, CD25hi, CD45RO+, GITR+, CTLA4+, CD103+, Foxp3+ • Protect against autoimmunity • 5–10% of CD4+ T cells	• Soluble/membrane TGF-β • Generated in periphery (post-thymic) • Variable CD25 expression • Inhibit Th1 and Th2 responses	• Soluble IL-10 • Generated in periphery • (post-thymic) • Variable CD25 expression • Inhibit Th1 and Th2 responses

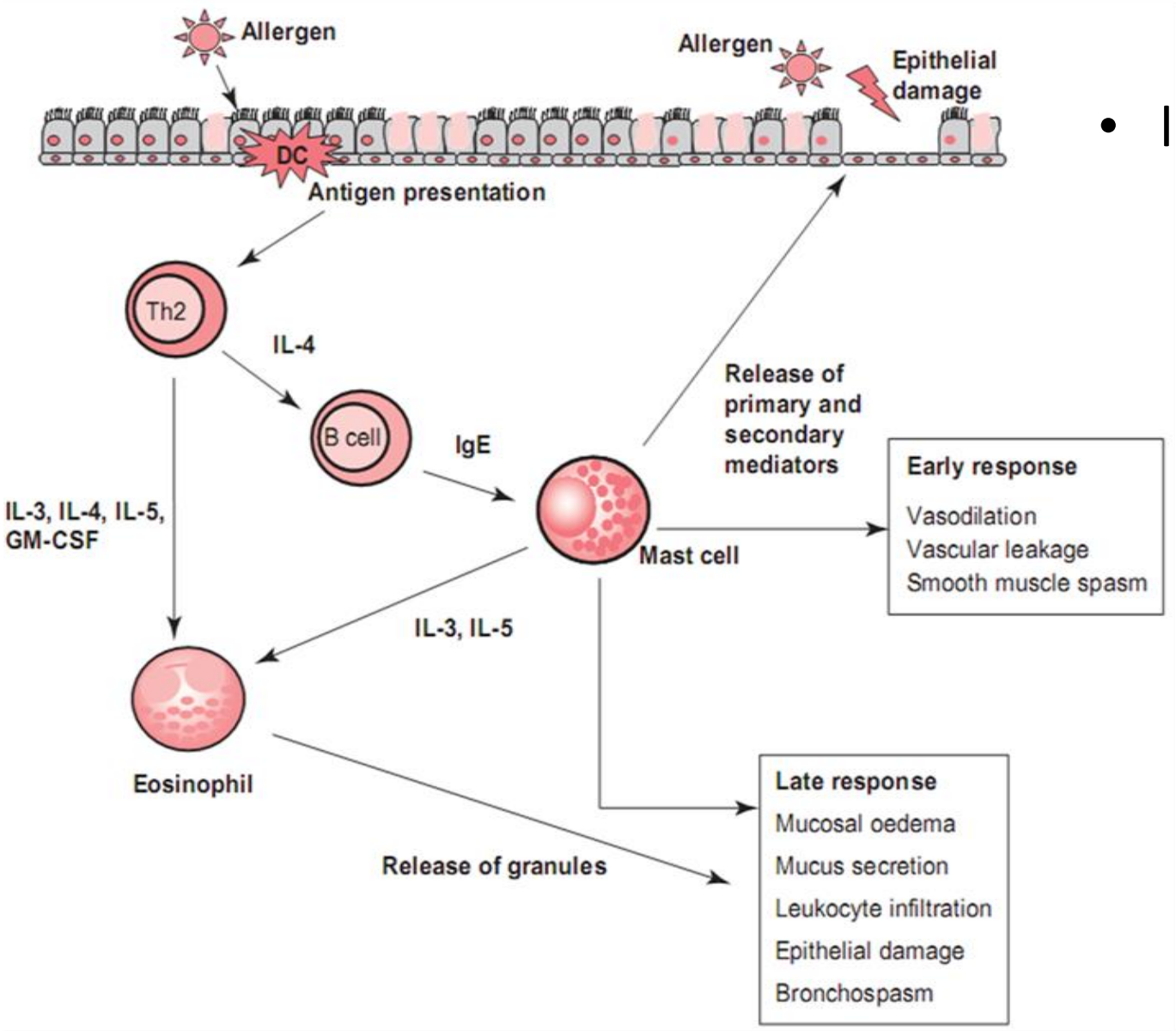
Major characteristics of subsets of CD4+ Treg cell bases on cell-surface markers, immunosuppressive cytokine secretion and suppressive action. nTreg, natural Treg; aTreg, adaptive Treg; Th, T helper cell; Tr1, T-regulatory cell type 1; APC, antigen-presenting cell, TGF, transforming growth factor; IL, interleukin. (From Van Oosterhout AJ, Bloksma N (2005). Regulatory T-lymphocytes in asthma. *Eur Resp J*, **26**:918–932.)

Asthma – acute, late and chron. phase



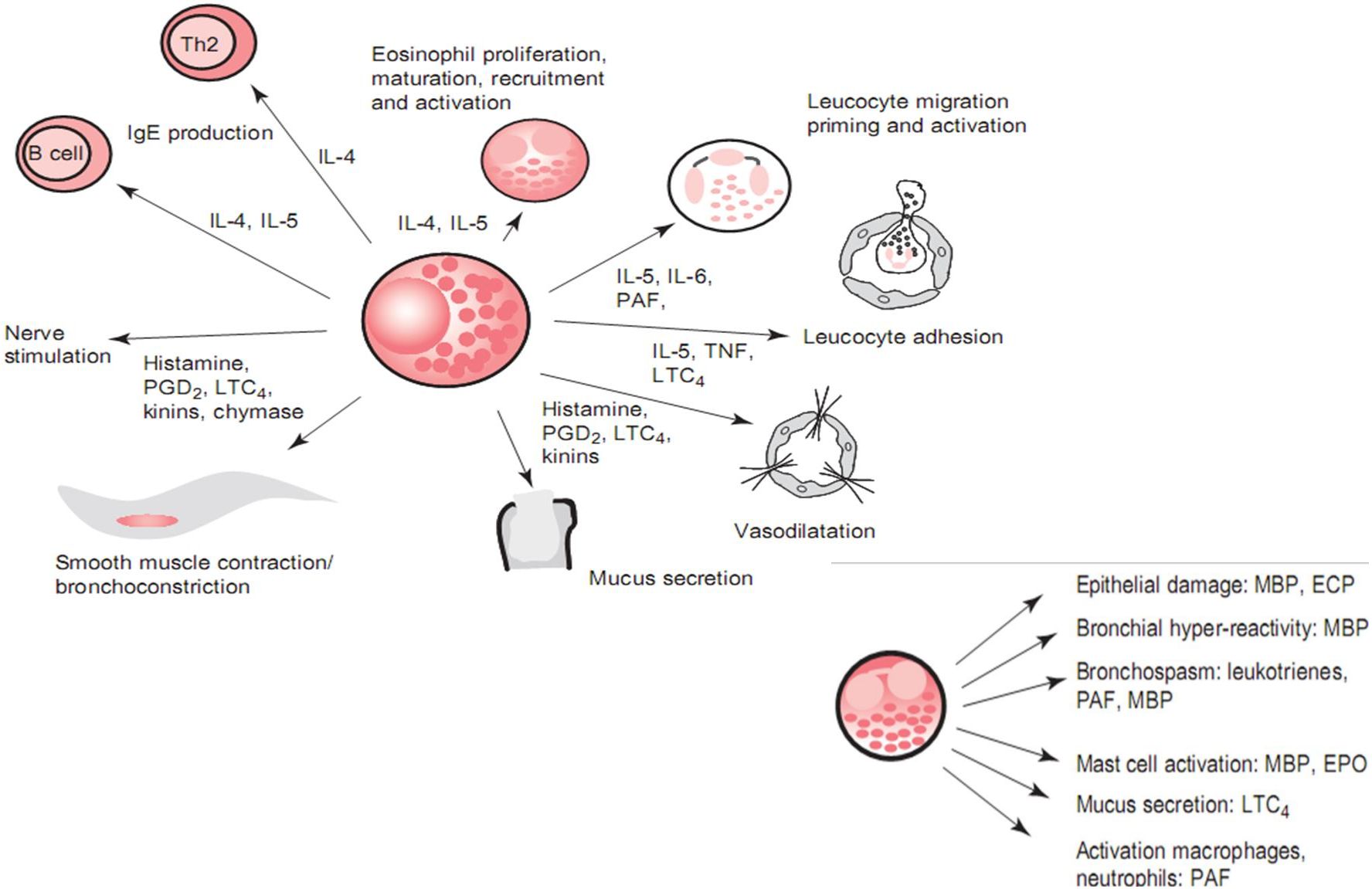
- early phase (acute attack)
  - 15-30 min, mediators of mast cells (**histamine**)
    - immediate biological response but as wells as chemotaxis of other cell types
  - ↑ secretion of mucus, edema of the bronchial wall
  - contraction of SMCs (bronchospasms)

Asthma – acute, late and chron. phase

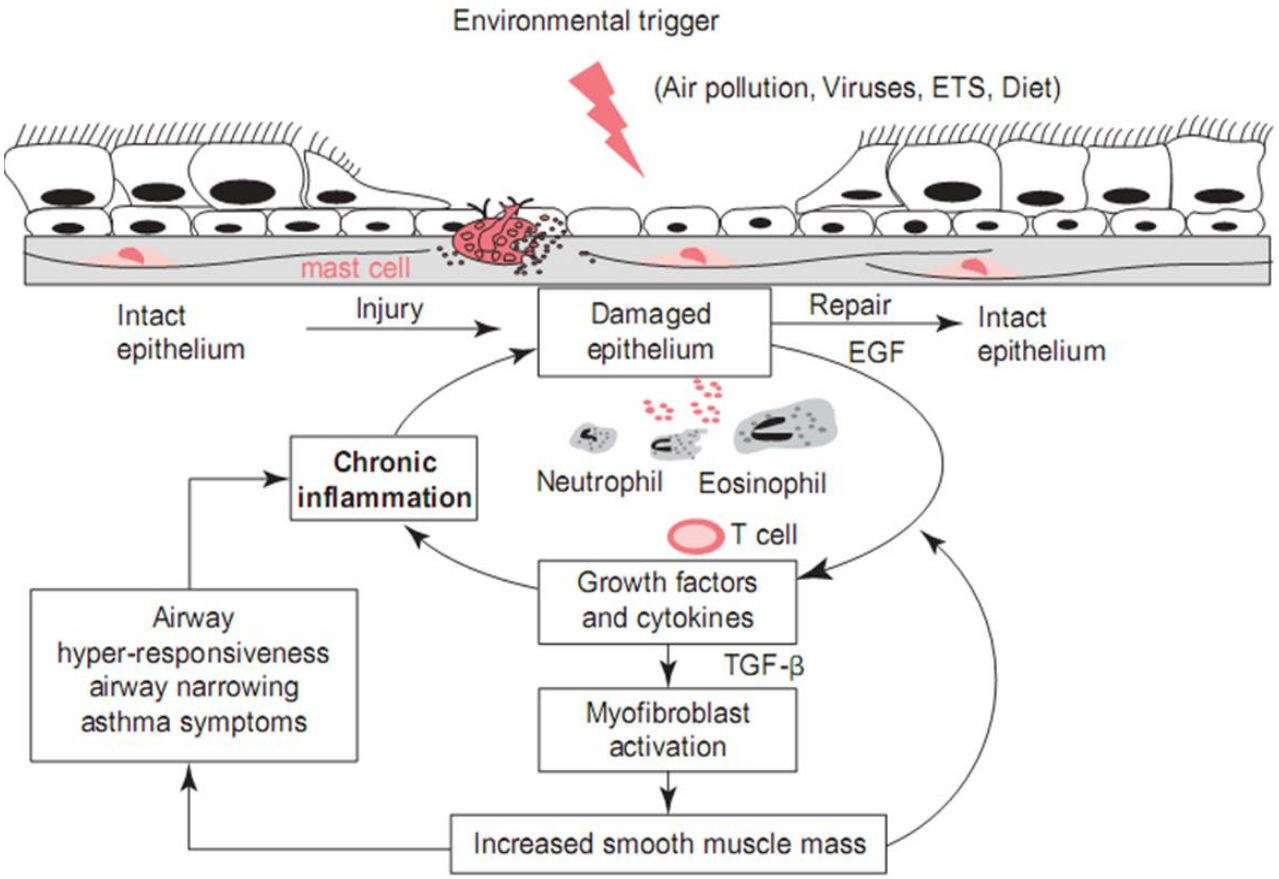


- late phase
  - after 4-8 hrs
  - mediators of neutrophils, **eosinophils**
    - **leukotrienes** C, D and E, basic and cationic protein etc.
  - inflammation (hyperemia, edema), hypersecretion of mucus, event. destruction of epithelium

Mediators of mast cells and eosinophils

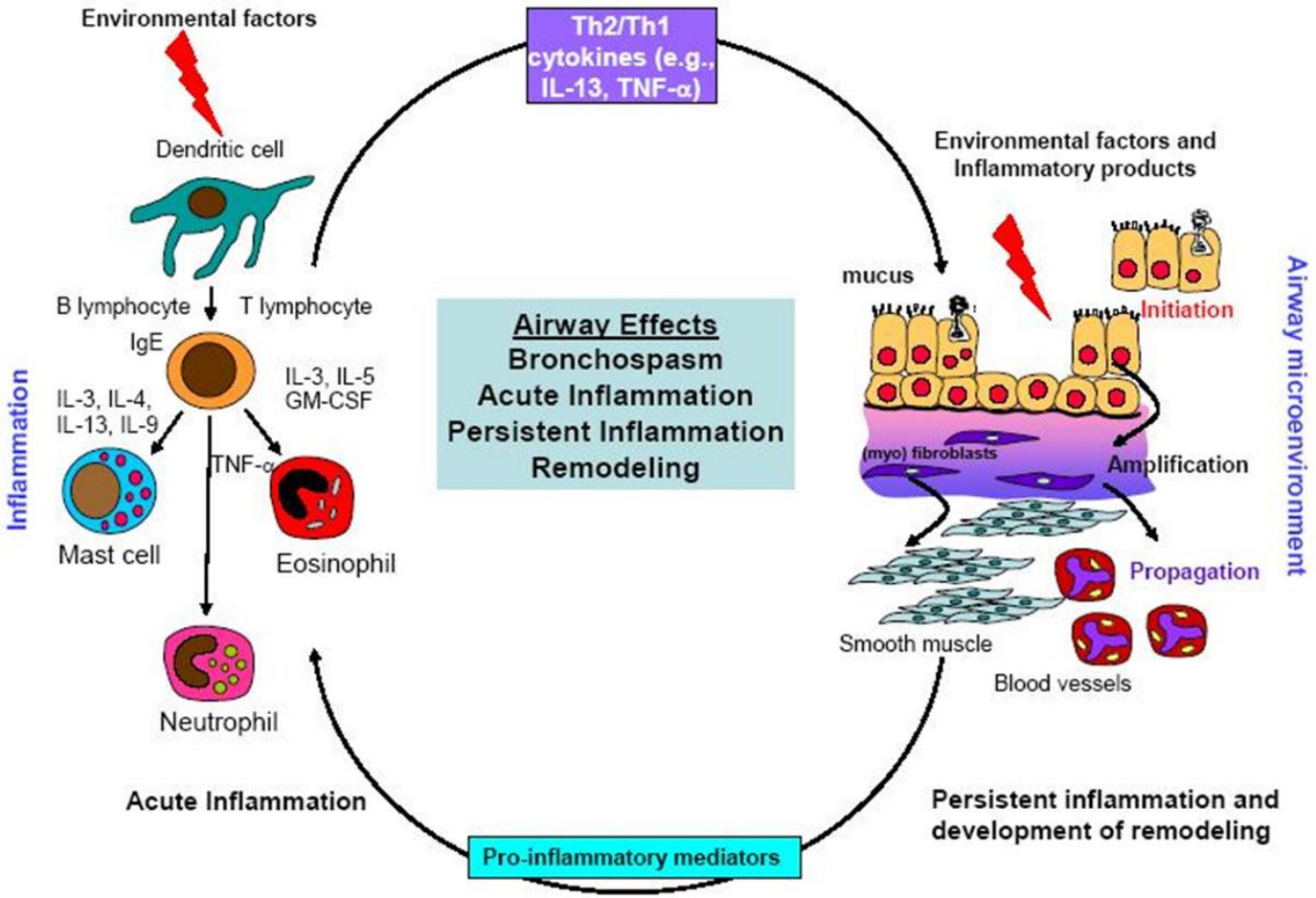


Asthma – acute, late and chron. phase



- chronic phase
  - chronic inflammation + repair processes lead to irreversible structural (**remodelation**) and functional (**hyper-reactivity**) changes of airways constituting a vicious cycle
  - epithelium
    - ↓ cilia, desquamation
    - hypertrophy of mucus glands and hyperplasia of goblet cells
  - basal membrane
    - fibrotisation in subepithelialspace (collagen)
  - muscle layer
    - hypertrophy and hyperplasia of SMCs

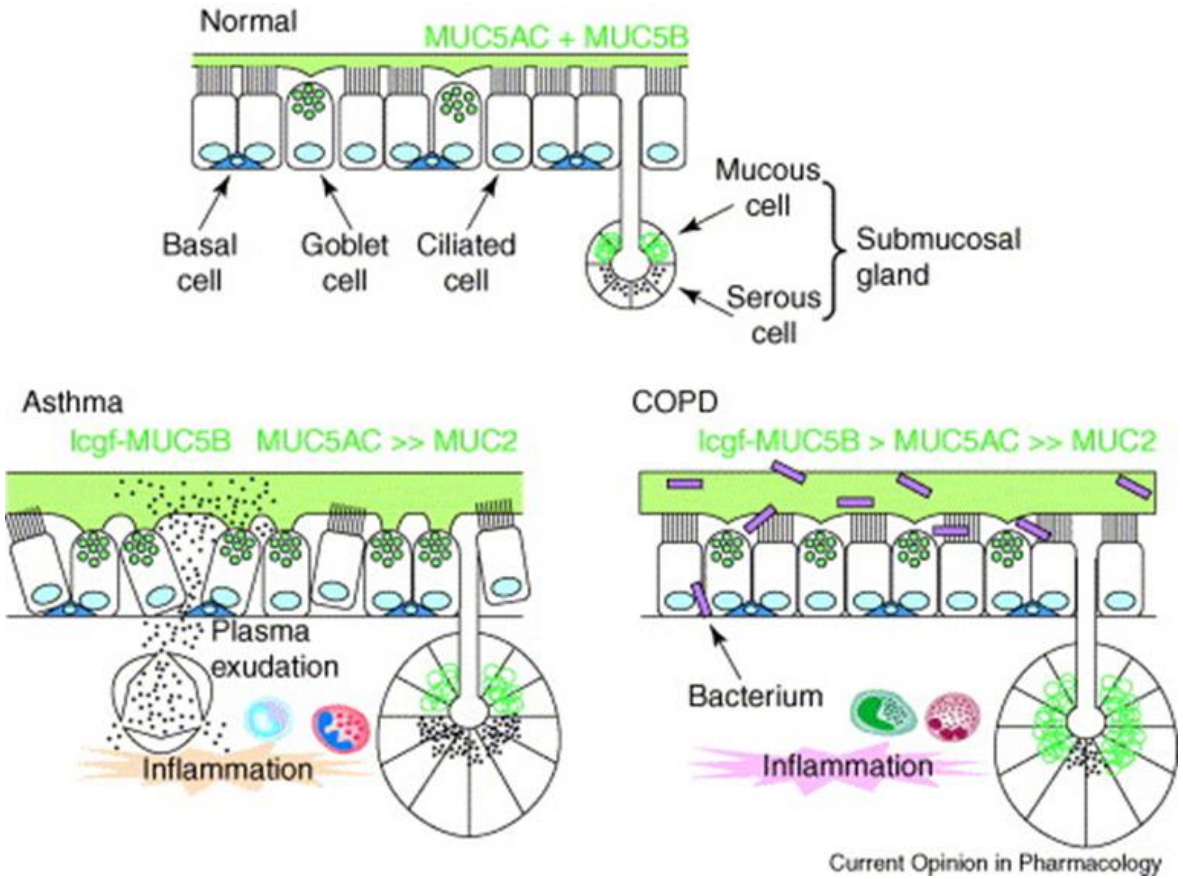
FIGURE 2–2. FACTORS LIMITING AIRFLOW IN ACUTE AND PERSISTENT ASTHMA



Key: GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL-3, interleukin 3 (and similar); TNF-α, tumor necrosis factor-alpha

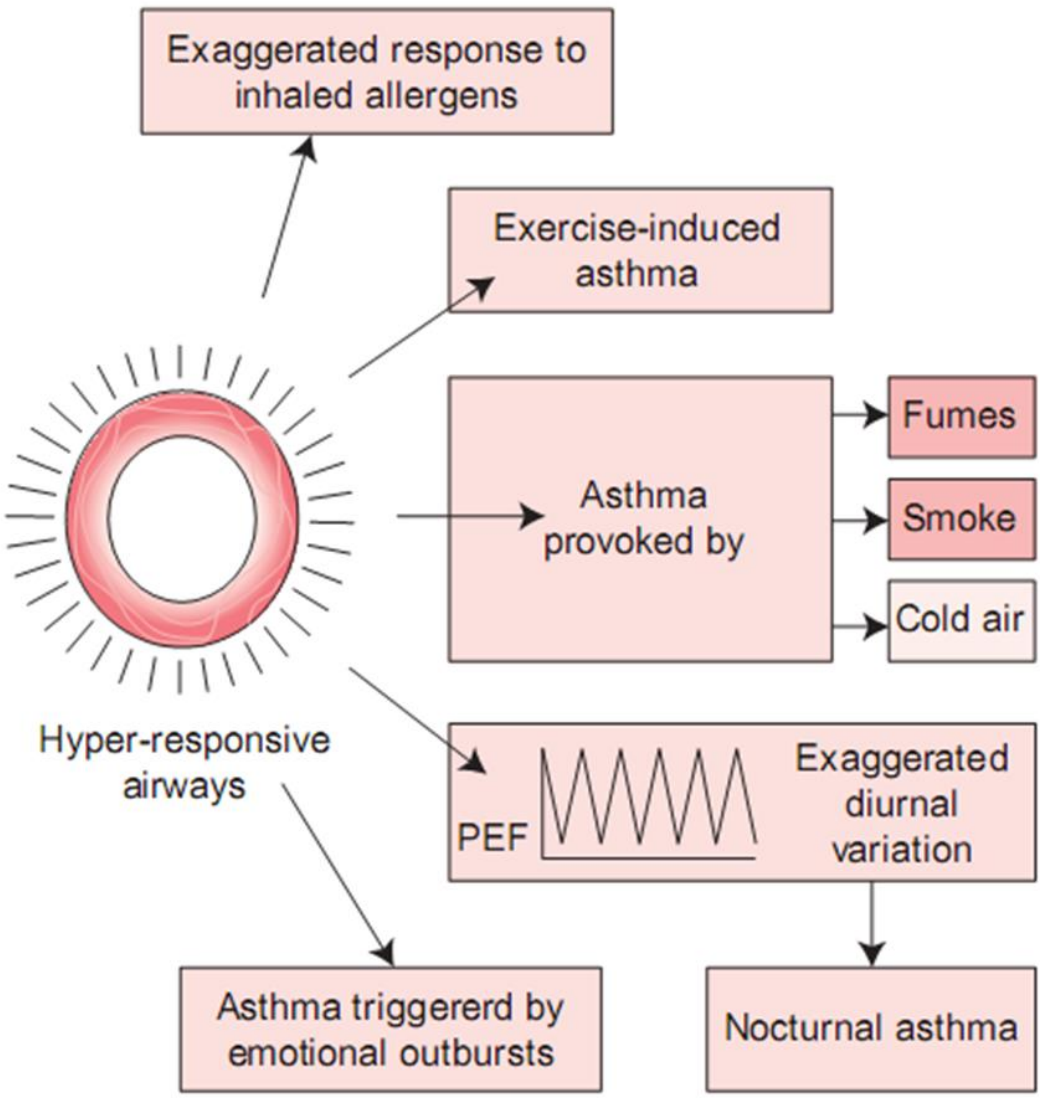
Source: Adapted and reprinted from The Lancet, 368, Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults, 780–93. Copyright (2006), with permission from Elsevier.

Mucus pathophysiology in asthma and COPD: similarities and differences



- In asthmatics, there is increased luminal mucus, a similar or increased ratio of mucin (MUC) 5B (low charge glycoform [lcgf]) to MUC5AC, small amounts of MUC2, epithelial 'fragility', marked goblet cell hyperplasia, submucosal gland hypertrophy (with normal mucous to serous cell ratio), 'tethering' of mucus to goblet cells, and plasma exudation. Airway inflammation involves T lymphocytes and eosinophils. In COPD, there is increased luminal mucus, an increased ratio of lcgf MUC5B to MUC5AC, small amounts of MUC2, goblet cell hyperplasia, submucosal gland hypertrophy (with an increased proportion of mucous to serous cells), and respiratory infection (possibly owing to reduced bacterial enzymatic 'shield' from reduced serous cell number). Pulmonary inflammation involves macrophages and neutrophils.

The hyper-responsive airways in asthma respond to a wide-range of provoking factors



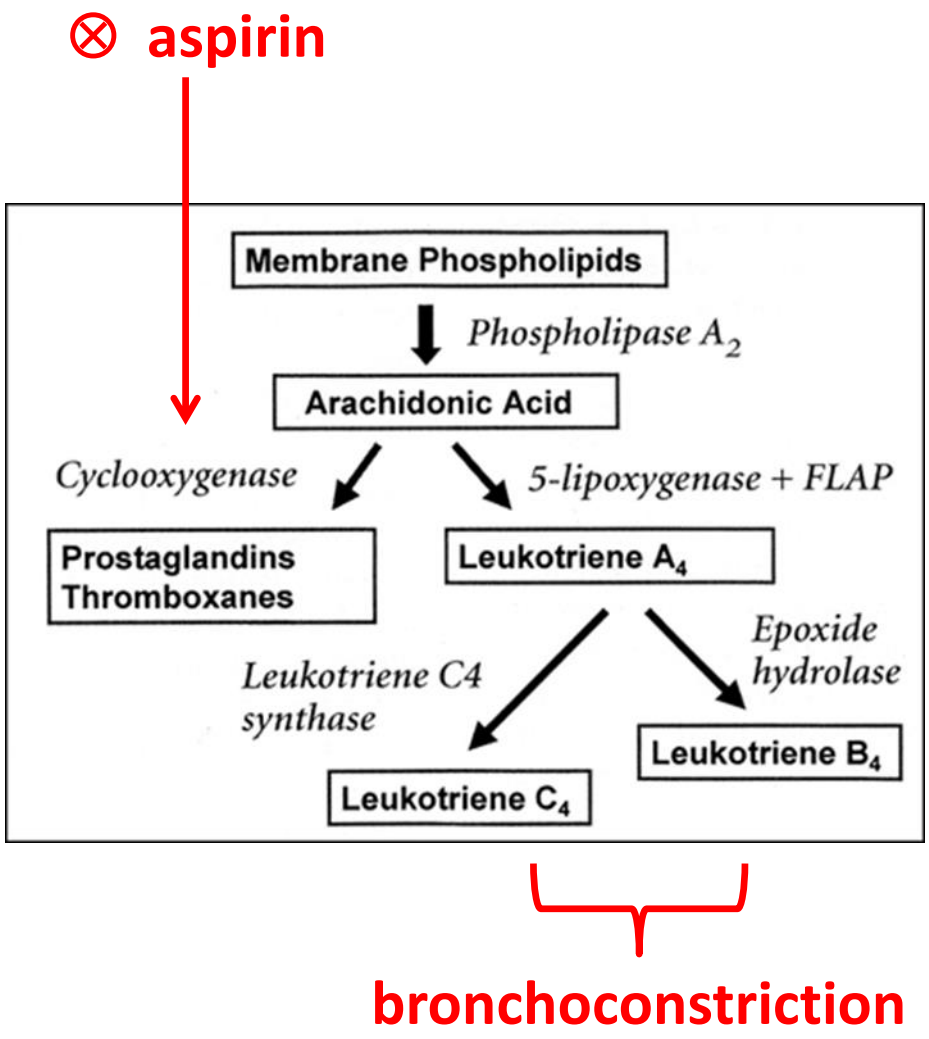
- parasympathetic nerve endings are close to the surface
  - damage leads to their exposure and increase of bronchoconstriction potential
- bronchomotoric tests
  - bronchodilations tests - reversibility of bronchial obstruction
    - salbutamol 200-400 ug
    - ipratropium 80 ug
  - bronchoconstriction test – bronchial hyperreactivity
    - histamine 1g in 100 ml of physiol. soution
    - metacholin

Table 1.4 Stimuli that can provoke asthma symptoms

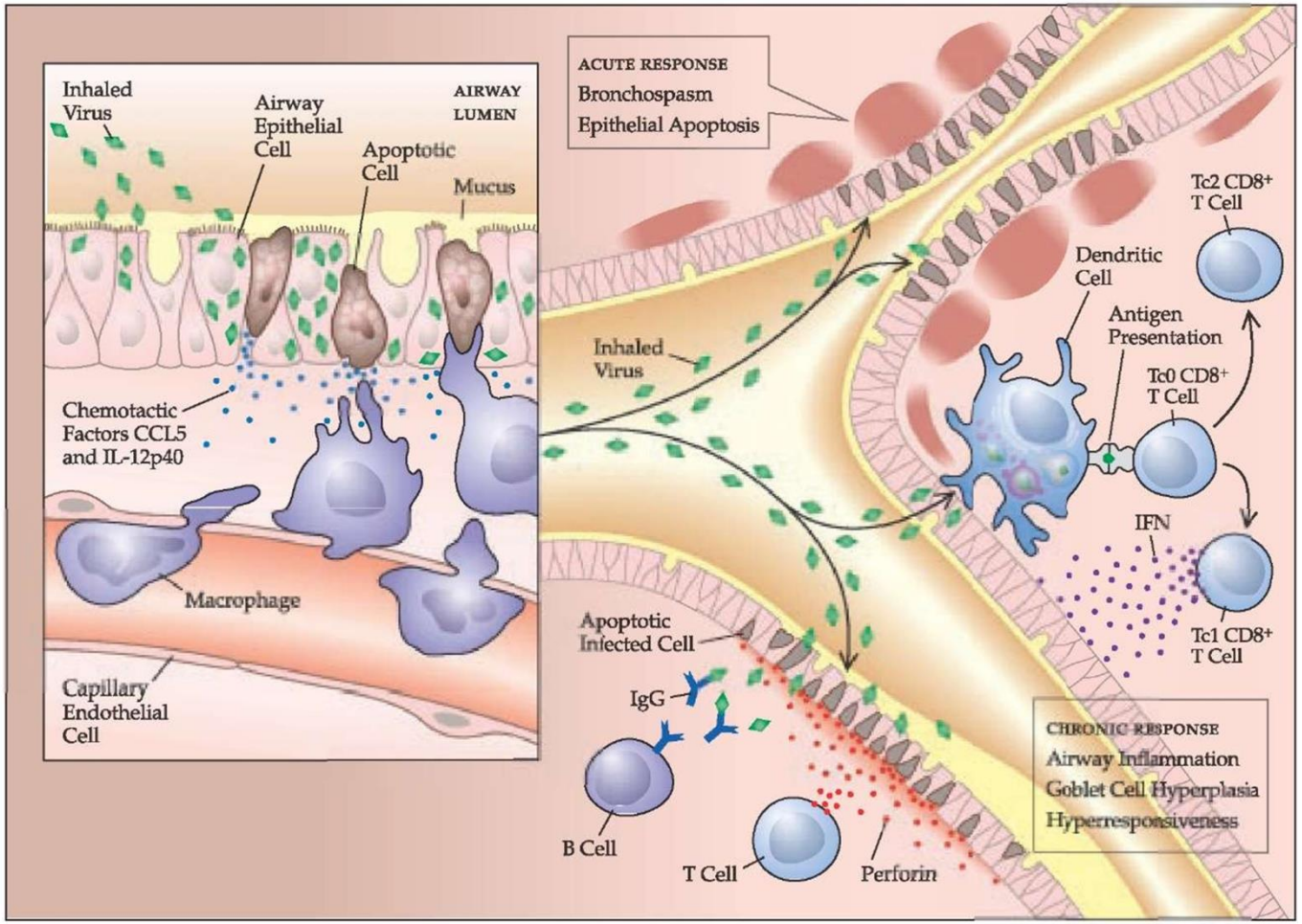
- Cold air
- Exercise
- Climate, including changes in temperature and humidity, e.g. fog
- Air pollution, both indoor and outdoor
- Fumes, including smoke, perfume, sprays
- Allergens, including house dust mite, cat, dog, moulds
- Medications, including
  - β-blockers used for heart disease and high blood pressure
  - non-steroidal anti-inflammatory drugs such as aspirin used for pain relief or arthritis
- Emotion, including stress and loss (bereavement)
- Hormonal, such as premenstrual and during pregnancy
- Night-time and early morning
- Foods, including preservatives, such as tartrazine (orange colouring), monosodium glutamate (used in Chinese food), sulphites (included in some wines) and allergens such as peanuts, shellfish
- Workplace exposure to agents to which individuals become sensitized
- Alcohol
- Viral respiratory tract infections such as the common cold and influenza

Aspirin-induced asthma (AIA)

- typical features:
  - first manifestation in 3rd-4th decade, more often women
  - whole year persisting cold
  - nasal polyps and blockade
- frequency:
  - ~10% of adult cases of asthma is in fact AIA
    - in general population 0.3-0.9%
- „aspirin trias“
  - sensitivity to ASA
  - asthma
  - persisting rhinosinusitis with nasal polyposis and eosinophilia



Pathogenesis of virus-induced asthma



Inhaled virus infects epithelial cells and leads to apoptosis of some of them. The release of chemotactic factors promotes the recruitment of macrophages into the lung parenchyma, where they ingest the dead epithelium. An acute response consisting of bronchospasm occurs at this time. Similar to allergic asthma, the inhaled virus is processed by dendritic cells and presented to Th2 CD8+ T cells. These cells produce copious amounts of IFN-γ. Perforin released from the T cells leads to apoptosis of infected cells. B cells produce IgG, which is capable of neutralizing the virus. These events are thought to be related to the chronic response, which consists of airway inflammation, goblet cell hyperplasia, and airway hyperresponsiveness. (IFN-Y—interferon gamma; IL—interleukin; CCL—chemokine ligand)

Asthma – clinical manifestation

- During full remission
  - individuals are asymptomatic and pulmonary function tests are normal
- During partial remission
  - no clinical symptoms but pulmonary function tests are abnormal
- During attacks
  - dyspnea and ↑respiratory effort, wheezing, non-productive coughing, tachycardia and tachypnea
- Diagnosis
  - spirometry
    - ↓ expiratory flow rate, forced expiratory volume (FEV1), and forced vital capacity (FVC)
    - ↑ FRC and total lung capacity (TLC)
  - blood gas analysis shows respiratory inssuficiecy
    - initially partial (i.e. hypoxemia with respiratory alkalosis)
    - later global (i.e. hypercapnia and respiratory acidosis)