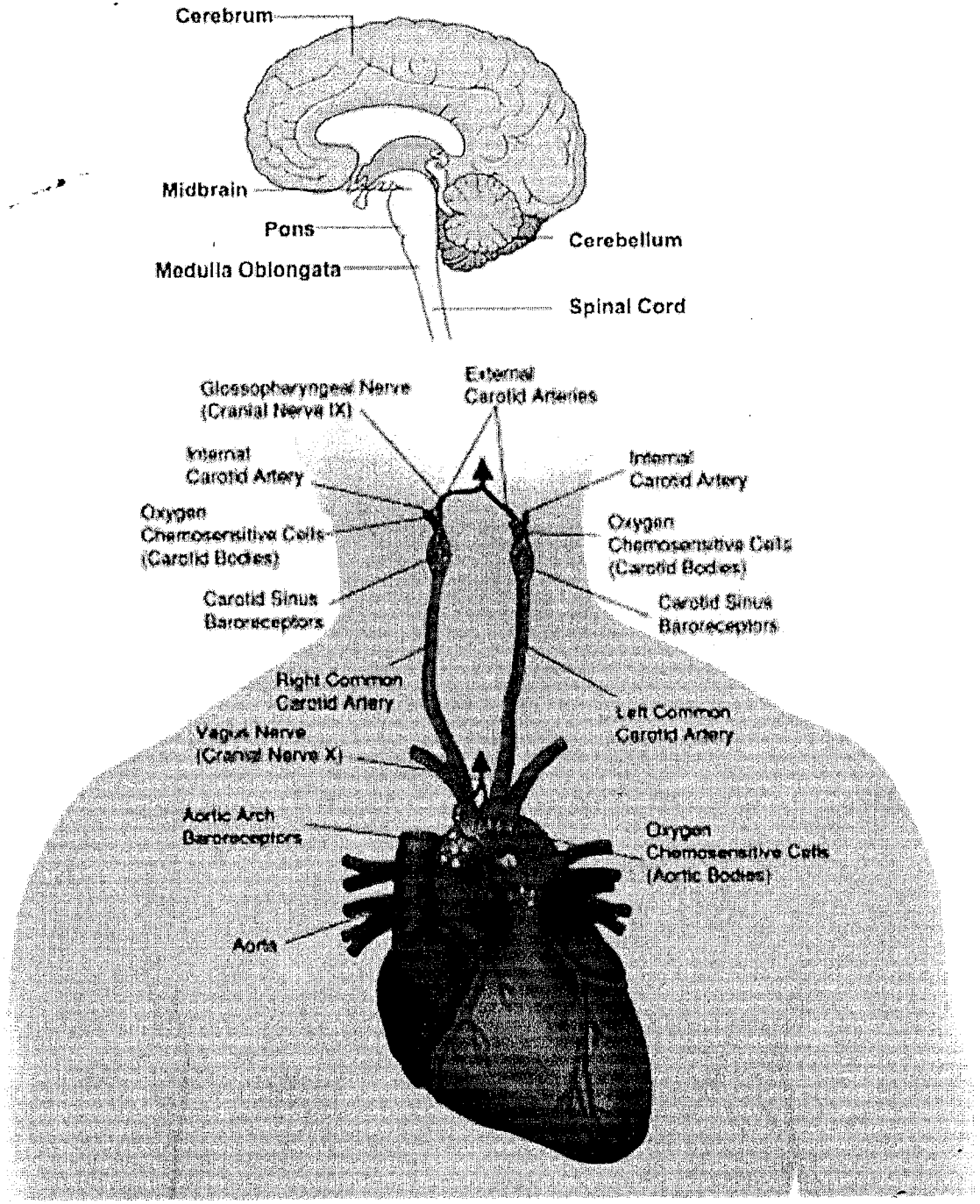
Bronchial Asthma

Regulation Of Respiration

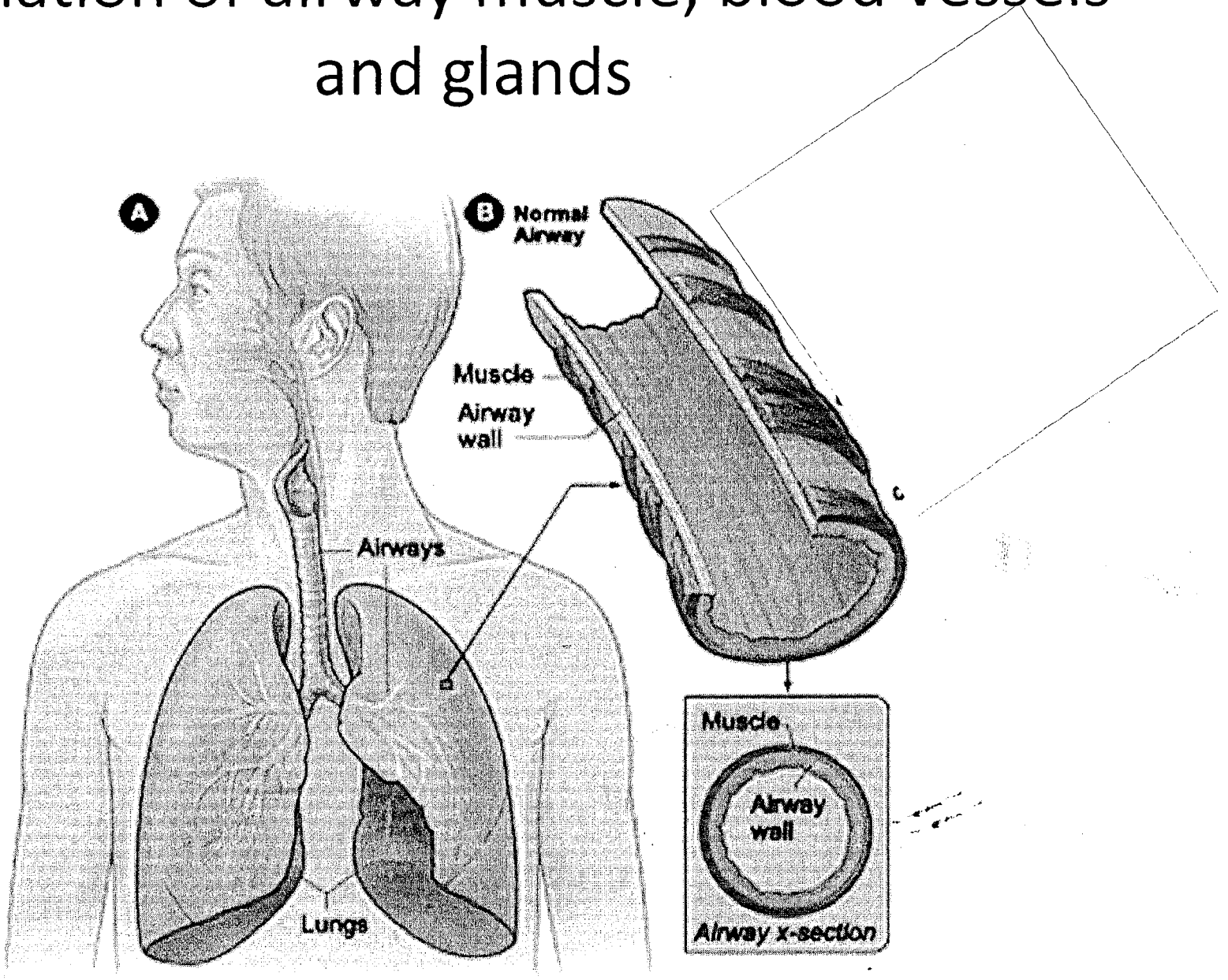
- Spontaneous rhythmic discharges from the respiratory centre in the medulla, modulated by input from pontine and higher central nervous system (CNS) centres and vagal afferents from the lungs.

- Various chemical factors affect the respiratory centre, including the partial pressure of carbon dioxide in arterial blood (P_Aco_2) by an action on medullary chemoreceptors, and of oxygen (P_AO2) by an action on the chemoreceptors in the carotid bodies.

- Voluntary control (connections between the cortex and the motor neurons innervating the muscles of respiration).


Cerebrum
Midbrain
Pons
Medulla Oblongata
Cerebellum
Spinal Cord
Glossopharyngeal Nerve (Cranial Nerve IX)
External Carotid Arteries
Internal Carotid Artery
Internal Carotid Artery
Oxygen Chemosensitive Cells (Carotid Bodies)
Oxygen Chemosensitive Cells (Carotid Bodies)
Carotid Sinus Baroreceptors
Carotid Sinus Baroreceptors
Right Common Carotid Artery
Left Common Carotid Artery
Vagus Nerve (Cranial Nerve X)
Aortic Arch Baroreceptors
Oxygen Chemosensitive Cells (Aortic Bodies)
Aorta

Regulation of airway muscle, blood vessels and glands



Regulation of airway muscle, blood vessels and glands

Afferent pathways

- Irritant receptors respond to exogenous chemicals, inflammatory mediators and physical stimuli (e.g. cold air).

Efferent pathways

- Parasympathetic nerves cause bronchoconstriction and mucus secretion through M3 receptors.
- Sympathetic nerves innervate blood vessels and glands, but not airway smooth muscle.
- β2-adrenoceptor agonists relax airway smooth muscle, inhibit mediator release from mast cells, and increase mucociliary clearance.
- Inhibitory non-noradrenergic non-cholinergic (NANC) nerves relax airway smooth muscle by releasing nitric oxide.

Bronchial Asthma

- A common **long term inflammatory disease** of the airways of the lungs. It is characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm in response to irritant stimuli that are too weak to affect non-asthmatic subjects.
- Acute attacks are reversible, but the underlying pathological disorder can progress in older patients to a chronic state superficially resembling COPD (where the obstruction is either not reversible or at best incompletely reversible, by bronchodilators).

Asthma is **characterised** by:

- Inflammation of the airways
- Bronchial hyper-reactivity
- Reversible airways obstruction

Etiology

- 235–330 million people worldwide are affected by asthma, and approximately 250,000–345,000 people die per year

- Cause of asthma is unknown but many factors play a part:

  - Genetic factors: Asthma tends to run in the family
  - Environmental factors: pollen, dust, mold, tobacco smoke
  - Other potential triggers
    - Occupational exposure: chemicals and gases
    - Medications (such as aspirin and beta blockers…)

Asthma: Early Clinical Manifestations

- Expiratory & inspiratory wheezing
- Cough
- Dyspnea
- Anxious
- Increased respiratory & heart rate
- Prolonged expiratory phase [1:3 or 1:4]

Asthma: Severe Clinical Manifestations

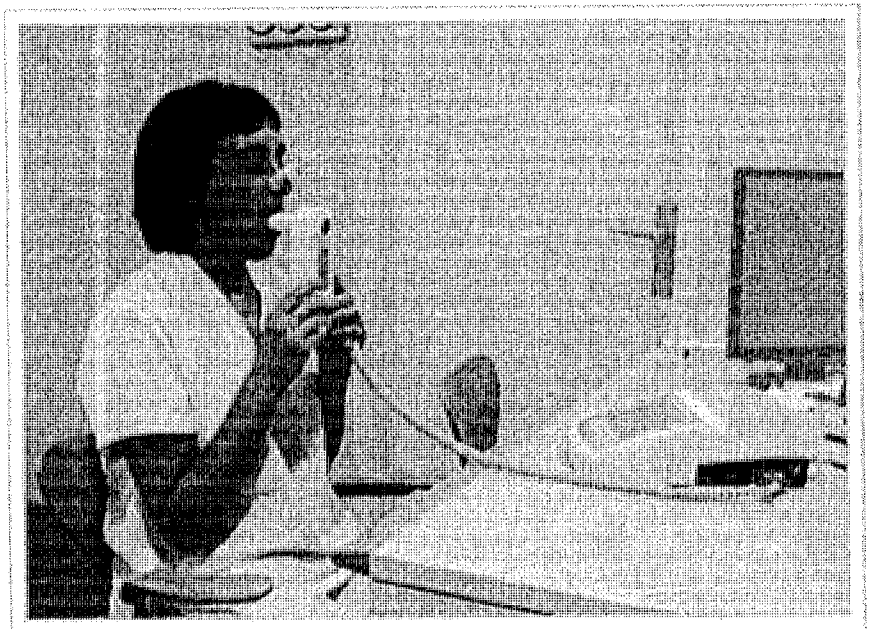
- Hypoxia (Cyanotic nail beds)
- Confusion
- Increased heart rate & blood pressure
- Respiratory rate up to 40/minute & pursed lip breathing

Diagnosis and Classification

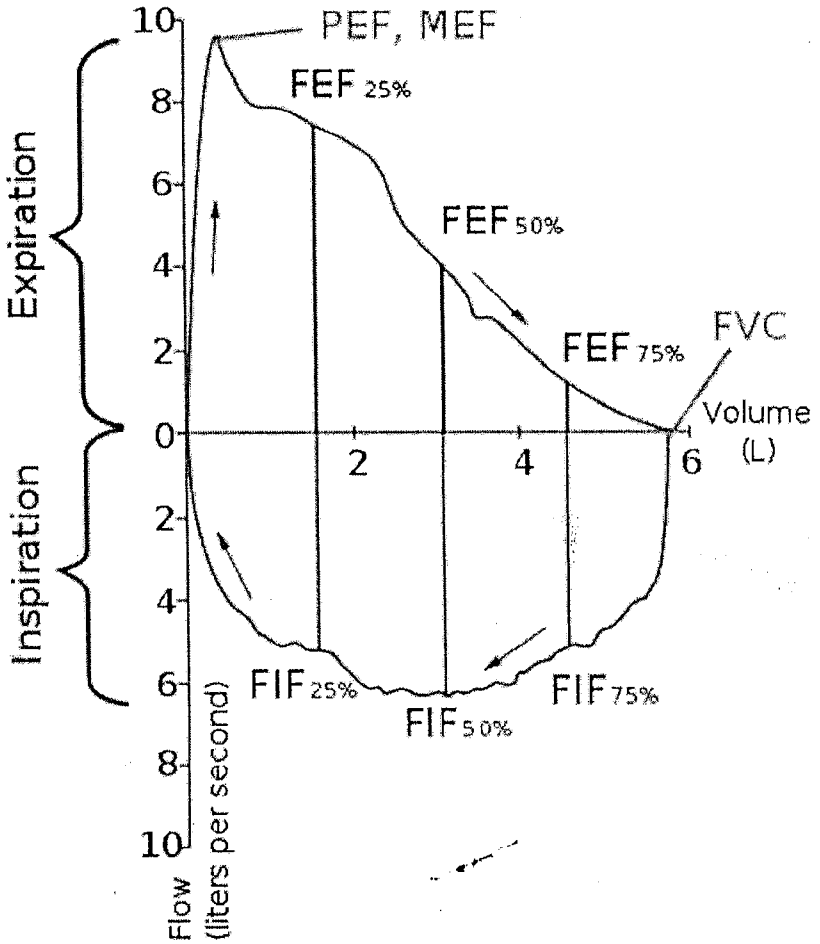
- Diagnosis is usually based on the pattern of symptoms, response to therapy over time and spirometry. Asthma is classified according to the frequency of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate.

Spirometry

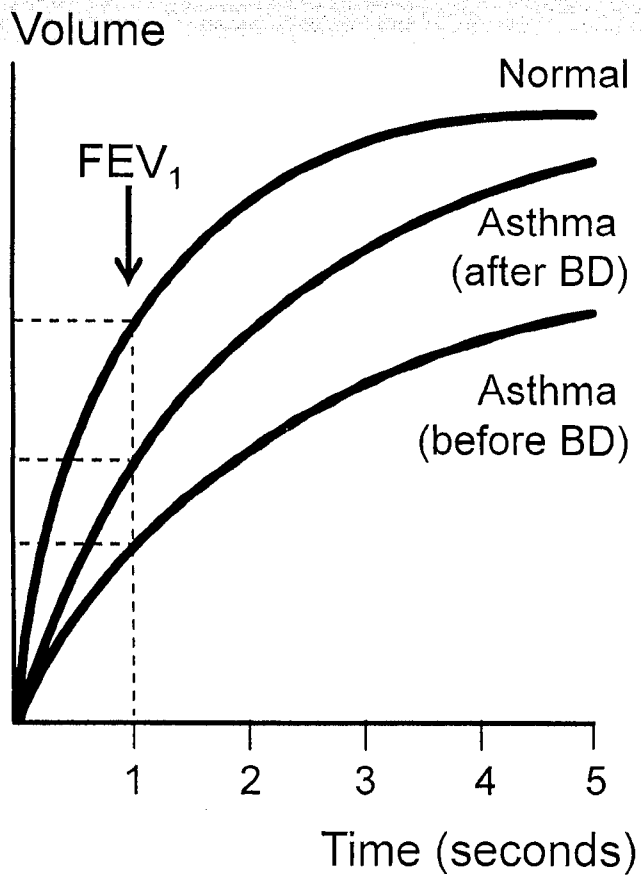
Medical diagnostics



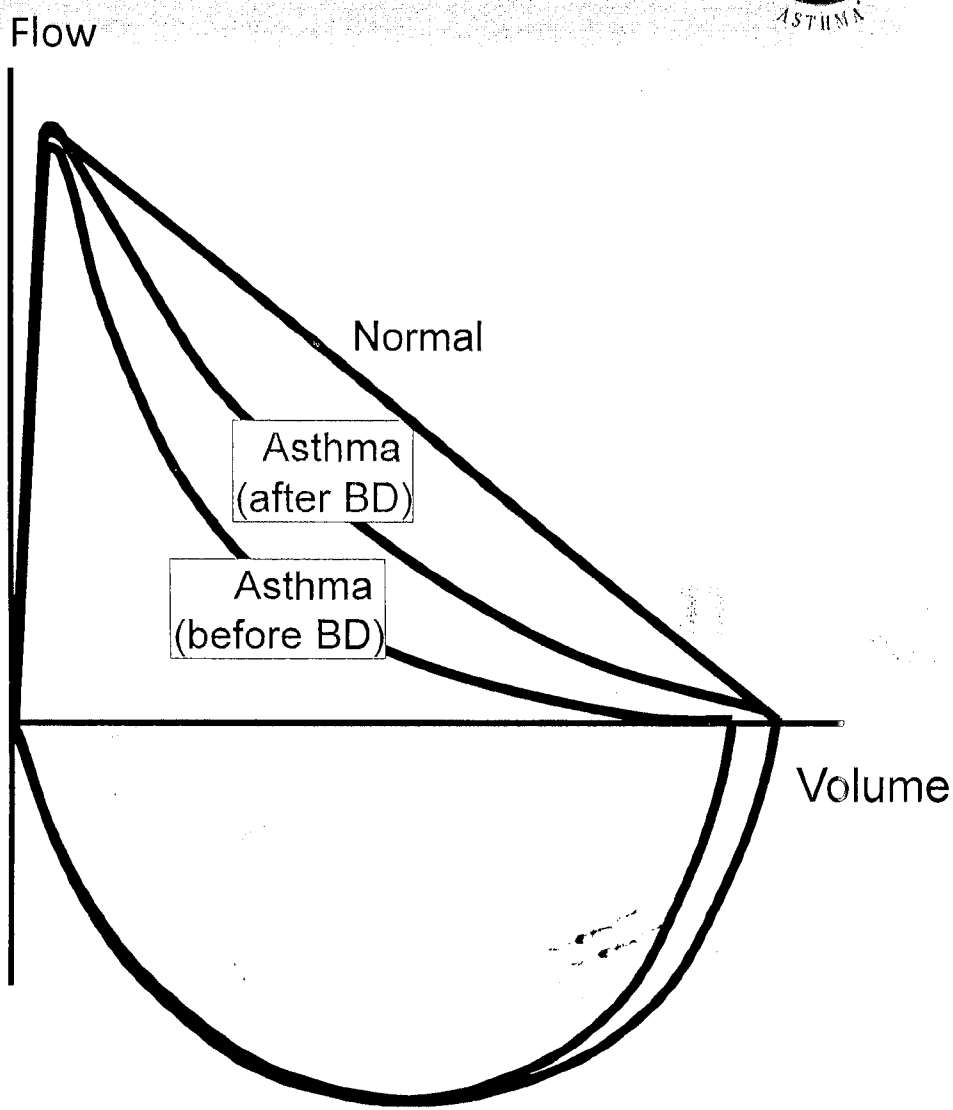
Doing spirometry



Typical spirometric tracings



Note: Each FEV_1 represents the highest of three reproducible measurements



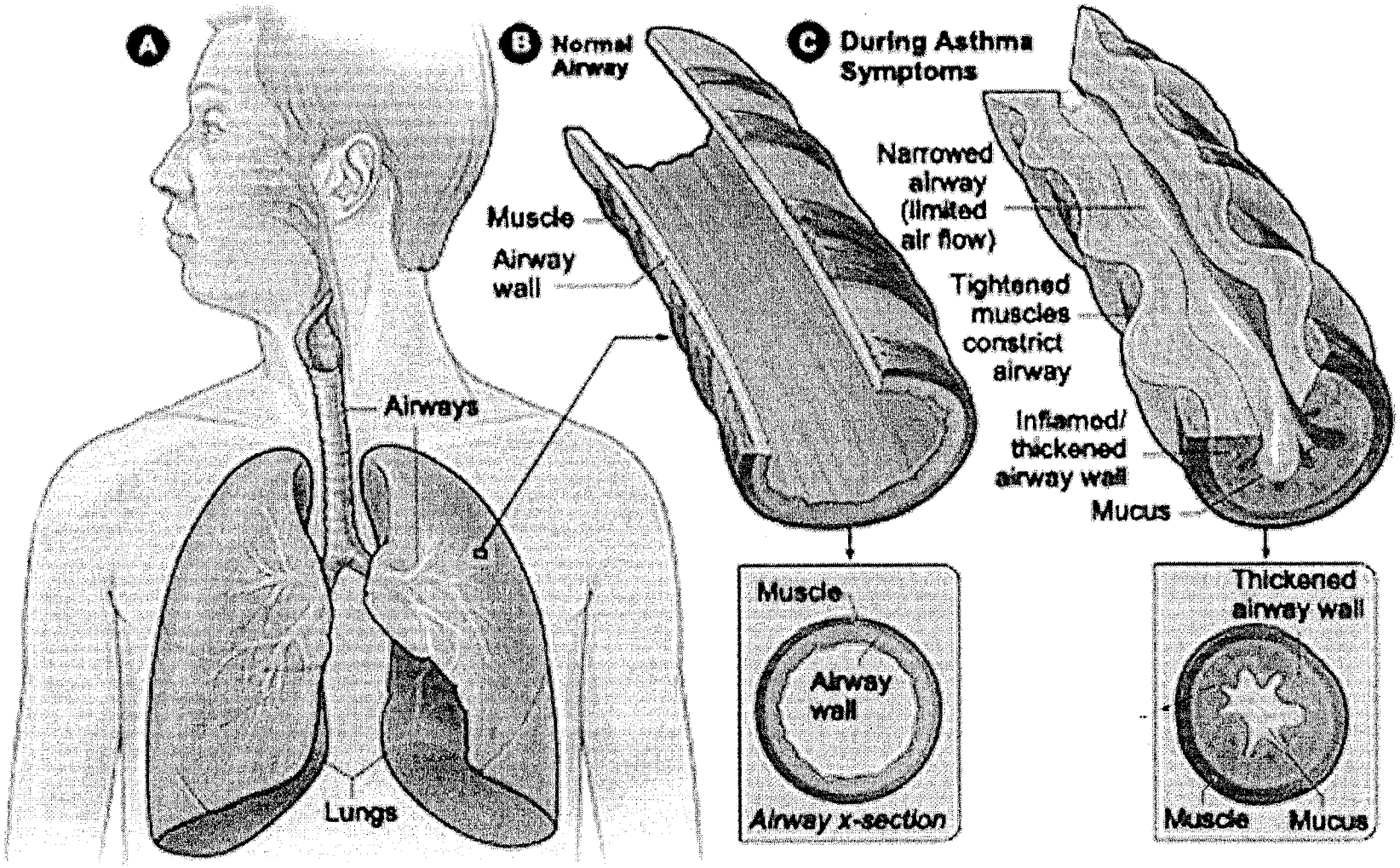
Clinical classification (≥ 12 years old)[7]

Severity	Symptom frequency	Night time symptoms	%FEV_1 of predicted	FEV_1 Variability	SABA use
Intermittent	≤2/week	≤2/month	≥80%	<20%	≤2 days/week
Mild persistent	>2/week	3–4/month	≥80%	20–30%	>2 days/week
Moderate persistent	Daily	>1/week	60–80%	>30%	daily
Severe persistent	Continuously	Frequent (7×/week)	<60%	>30%	≥twice/day

Diagnosis and Classification

- Diagnosis is usually based on the pattern of symptoms, response to therapy over time, and spirometry. Asthma is classified according to the frequency of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate.
- At risk- breathing test normal, mild symptoms
- Mild- breathing test shows mild limitation, increasing symptoms
- Moderate- person will typically seek care for symptoms, shortness of breath with significant exertion, lung tests abnormal
- Severe (status asthmaticus) - shortness of breath with limited activity, lung tests abnormal
- It may also be classified as atopic or non-atopic (*allergic* and *non-allergic)* where atopy refers to a predisposition toward developing a type 1 hypersensitivity reaction.

Pathophysiology of Bronchial Asthma



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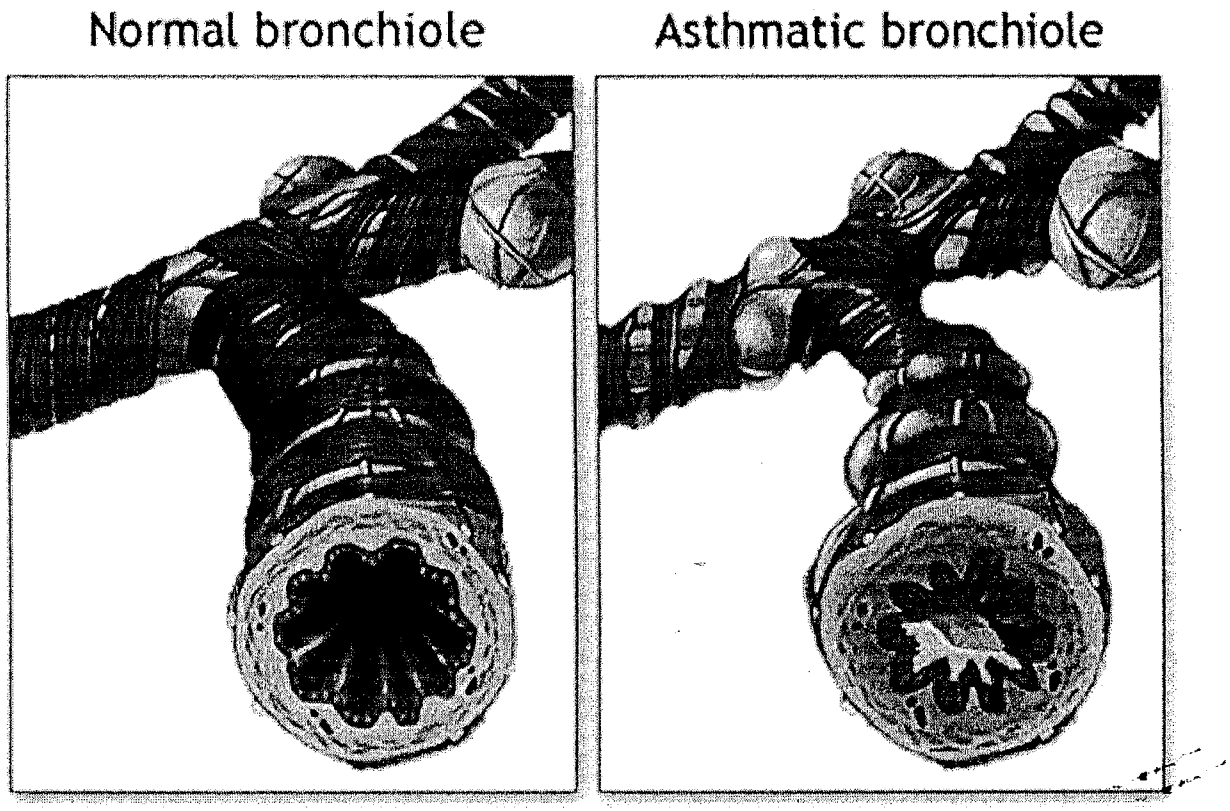
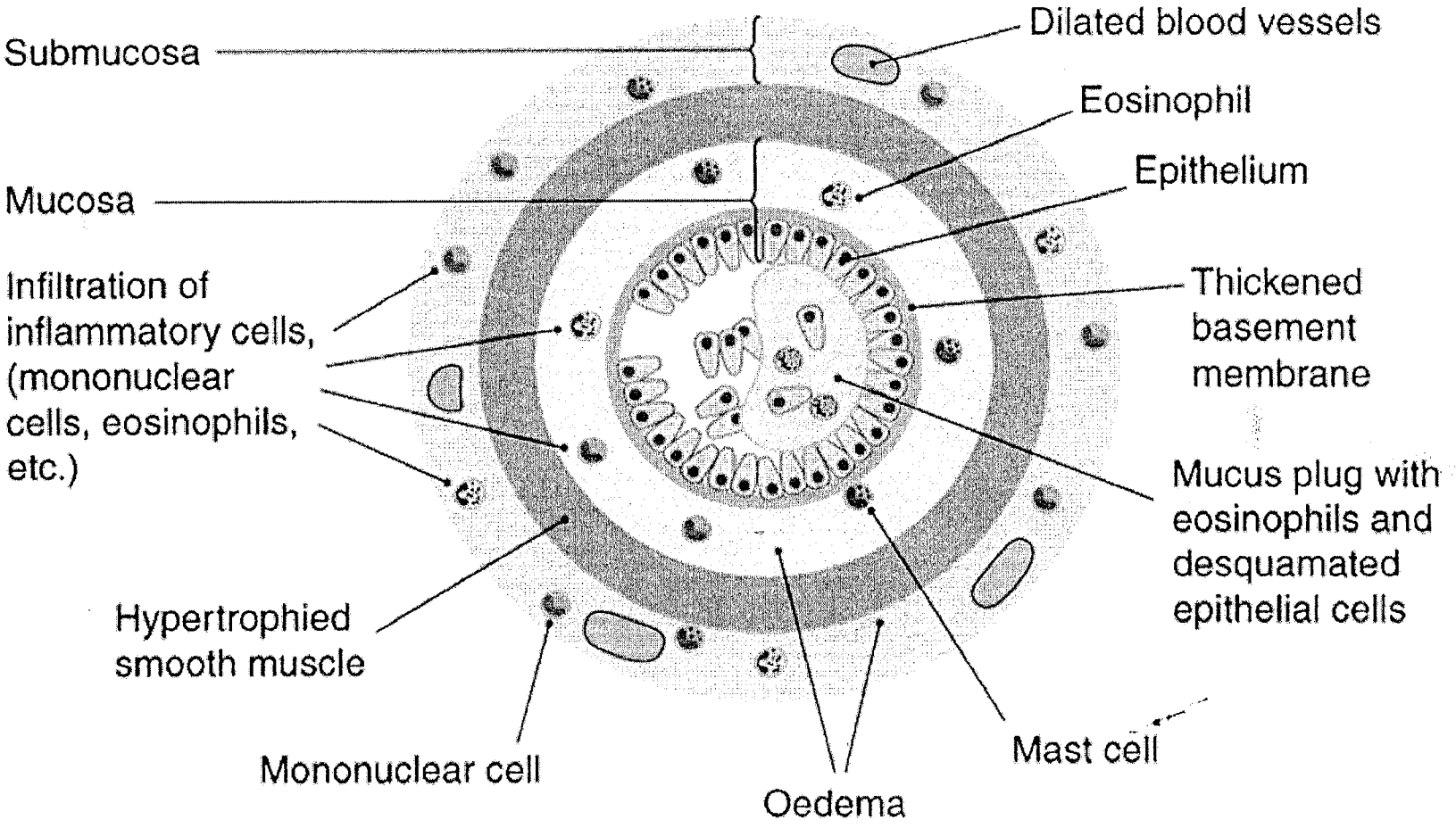
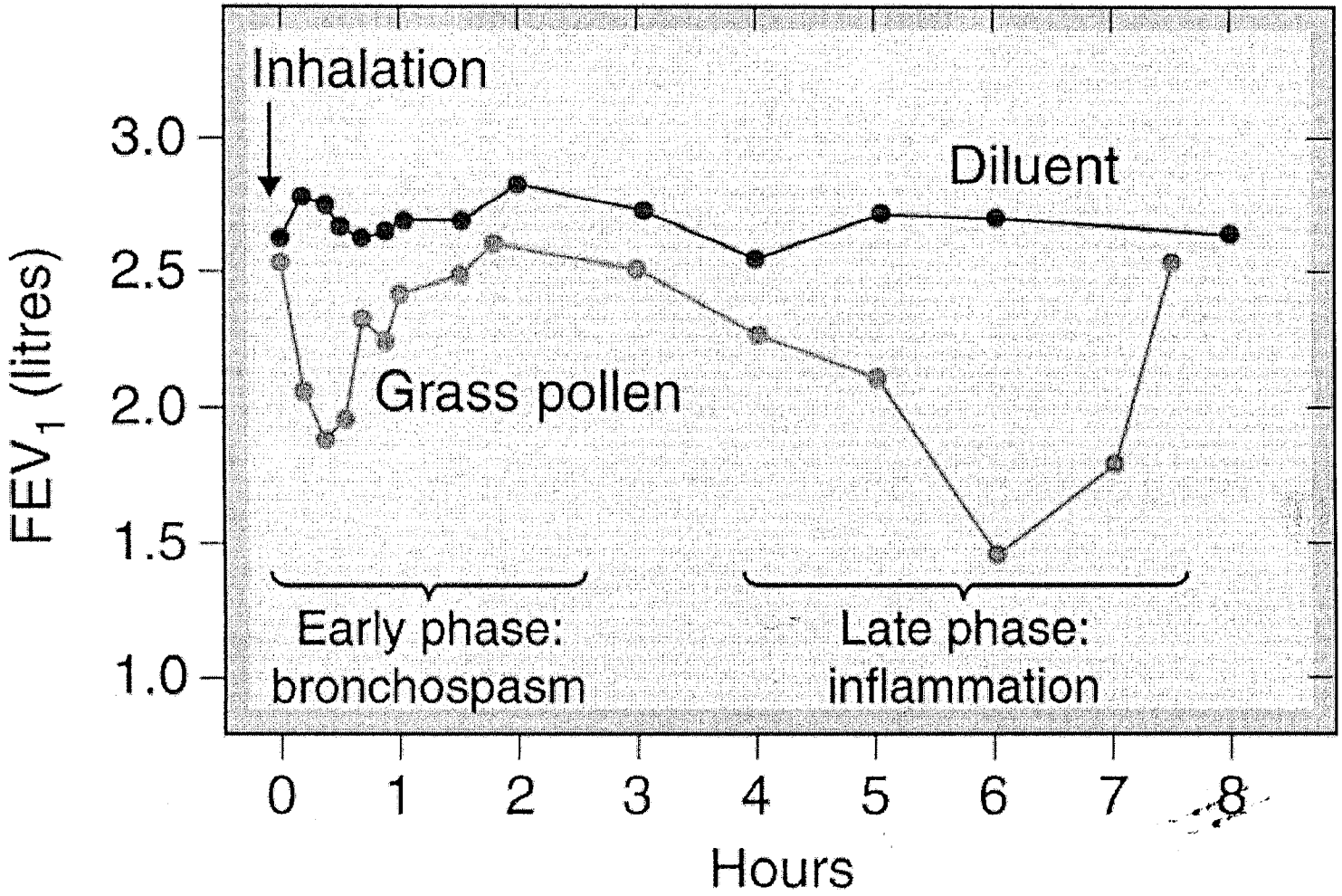


Pathophysiology of Bronchial Asthma



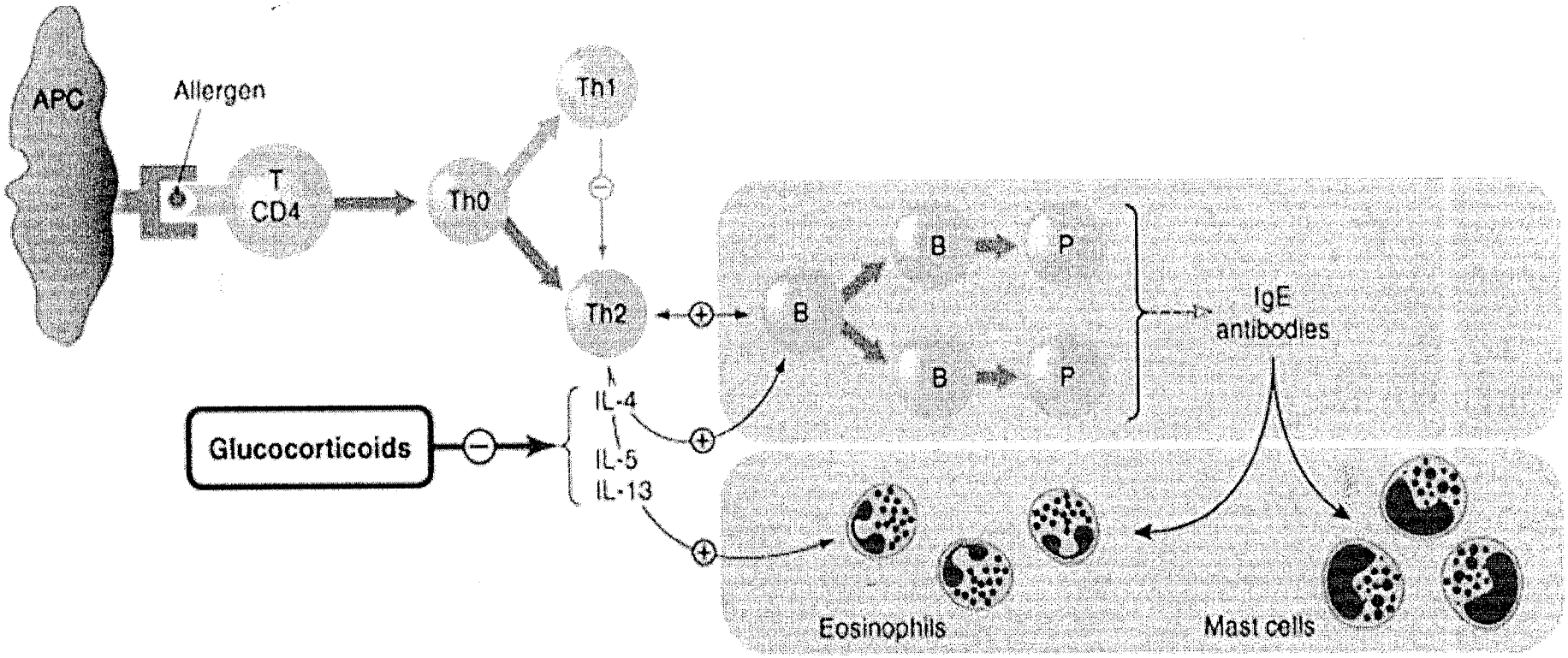
Schematic diagram of a cross-section of a bronchiole, showing changes that occur with severe chronic asthma.

Development of allergic asthma



Two phases of asthma demonstrated by the changes in forced expiratory volume in 1 second (FEV_1) after inhalation of grass pollen in an allergic subject.

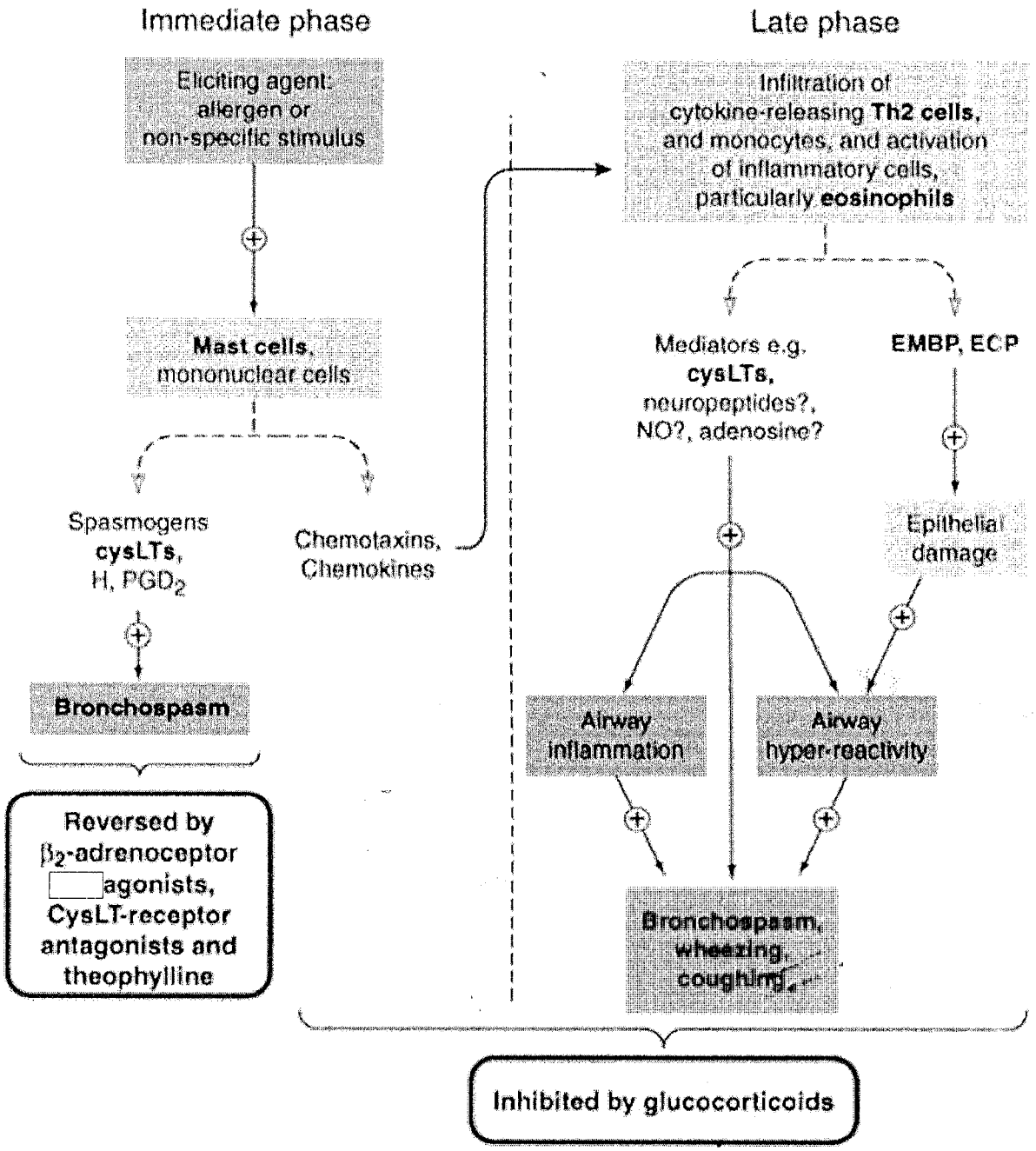
Pathophysiology of Bronchial Asthma



The part played by T lymphocytes in allergic asthma.
In genetically susceptible individuals, allergen (green circle) interacts with dendritic cells and CD4+ T cells, leading to the development of Th0 helper lymphocytes, which give rise to a clone of helper Th2 lymphocytes. These then (i) generate a cytokine environment that switches B cells/plasma cells to the production and release of IgE; (ii) generate cytokines, such as interleukin (IL)-5, which promote differentiation and activation of eosinophils; and (iii) cytokines (e.g. IL-4 and IL-13) that induce expression of IgE receptors. Glucocorticoids inhibit the action of the cytokines specified. APC, antigen-presenting dendritic cell; B, B cell; P, plasma cell; Th, T-helper cell.

Immediate and late phases of asthma, with the actions of the main drugs.

CysLTs, cysteinyl leukotriene (Leukotrienes C_4 and D_4); ECP, eosinophil cationic protein; EMBP, eosinophil major basic protein; H, histamine; iNO, induced nitric oxide



- **Pathogenesis** involves exposure of genetically disposed individuals to allergens; activation of Th2 lymphocytes and cytokine generation promote:
  - differentiation and activation of eosinophils
  - IgE production and release
  - expression of IgE receptors on mast cells and eosinophils.
- **Important mediators** include leukotriene B4 and cysteinyl leukotrienes (C4 and D4); interleukins IL-4, IL-5, IL-13; and tissue-damaging eosinophil proteins.

Treatment of Asthma

CLASSIFICATION	BRONCHO-CONSTRICTIVE EPISODES	RESULTS OF PEAK FLOW OR SPIROMETRY	LONG-TERM CONTROL	QUICK RELIEF OF SYMPTOMS
Intermittent	Less than 2 days per week	Near normal*	No daily medication	Short-acting β_2 agonist
Mild persistent	More than 2 days per week, not daily	Near normal*	Low-dose ICS	Short-acting β_2 agonist
Moderate persistent	Daily	60% to 80% of normal	Low-dose ICS + LABA OR Medium-dose ICS	Short-acting β_2 agonist
Severe persistent	Continual	Less than 60% of normal	Medium-dose ICS + LABA OR High-dose ICS + LABA	Short-acting β_2 agonist

ICS = inhaled corticosteroid. LABA = long-acting β_2 agonist.

Guidelines for the treatment of asthma. In all asthmatic patients, quick relief is provided by a SABA as needed for symptoms. *Eighty percent or more of predicted function.

Treatment of Asthma

Controller drugs:
prevent asthma attacks and/or reduce severity

- ❑ **Bronchdilators:**
- **Certain sympathomimetics (e.g., salmeterol)**
- Methylxanthines (theophylline)
- Muscarinic receptor antagonists
- ❑ **Anti-inflammatory agents**
- Corticosteroids
- Leukotriene synthesis inhibitors (zileuton)
- Leukotriene antagonists (zafirlukast)
- Cromoglicate and nedocromil
- Histamine H_1-receptor antagonists
- Antibodies

Antiasthma drugs:

1. Bronchodilators :

- β2-Adrenoceptor agonists (e.g. salbutamol) are first-line drugs
  - They act as physiological antagonists of the spasmogenic mediators but have little or no effect on the bronchial hyper-reactivity.
  - They relax bronchial muscle whatever the spasmogens involved. They also inhibit mediator release from mast cells and TNF-α release from monocytes, and increase mucus clearance by an action on cilia
  - Usually given by inhalation of aerosol, powder or nebulised solution, but some may be given orally or by injection. A metered-dose inhaler is used for aerosol preparations.

Two categories of β_2-adrenoceptor agonists are used in asthma:

Short-acting β_2-agonists (salbutamol= albuterol, terbutaline) is given by inhalation; its effects start immediately and last 3-5 hours, and it can also be given by intravenous infusion in status asthmaticus.

Long-acting β_2-agonists (salmeterol, formoterol) to prevent bronchospasm (e.g. at night or with exercise) in patients requiring long-term bronchodilator therapy. They are given regularly by inhalation; their duration of action is 8-12 hours.

Unwanted effects:

- Tachycardia, Dysrhythmias, peripheral vasodilatation
- Tremor
- hyperglycemia
- Tolerance