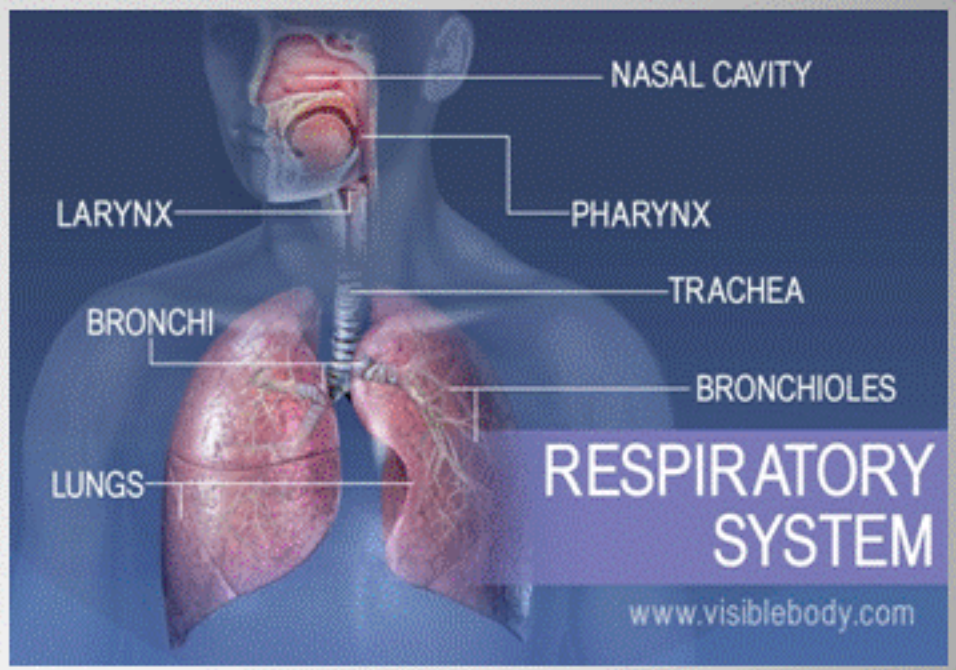
DRUGS ACTING ON RESPIRATORY SYSTEM

Anti-Asthmatic drugs



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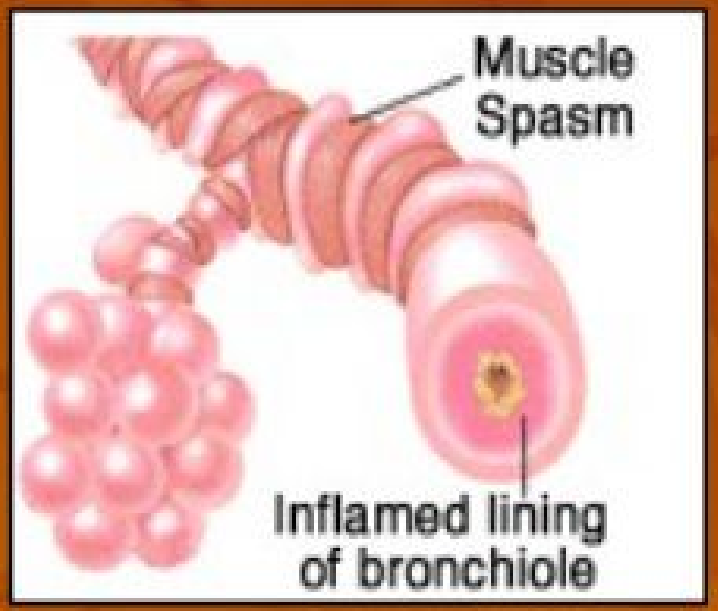
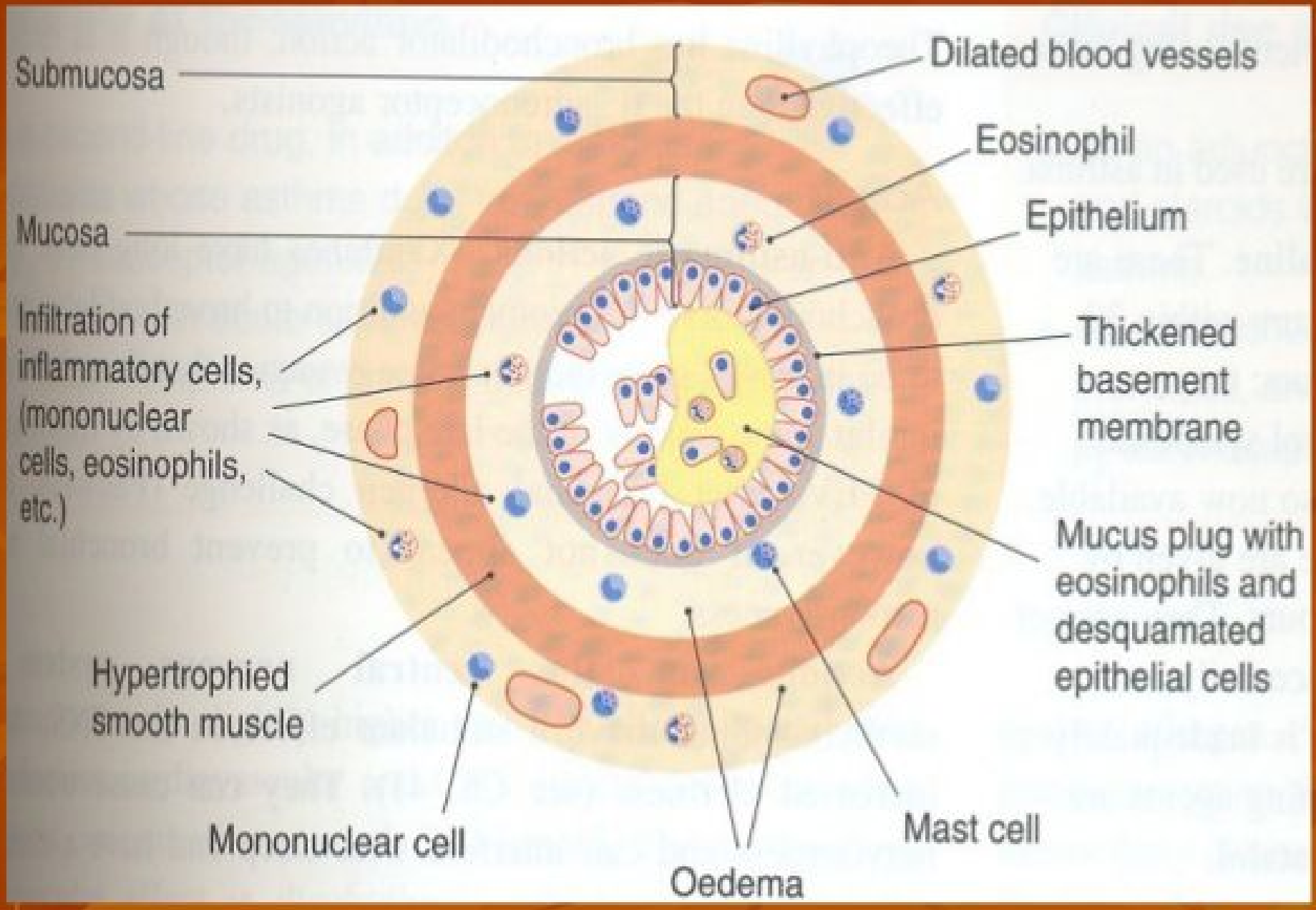
INTRODUCTION



ASTHMA

- Chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.
- In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are associated with widespread but variable airflow obstruction that is reversible either spontaneously, or with treatment.

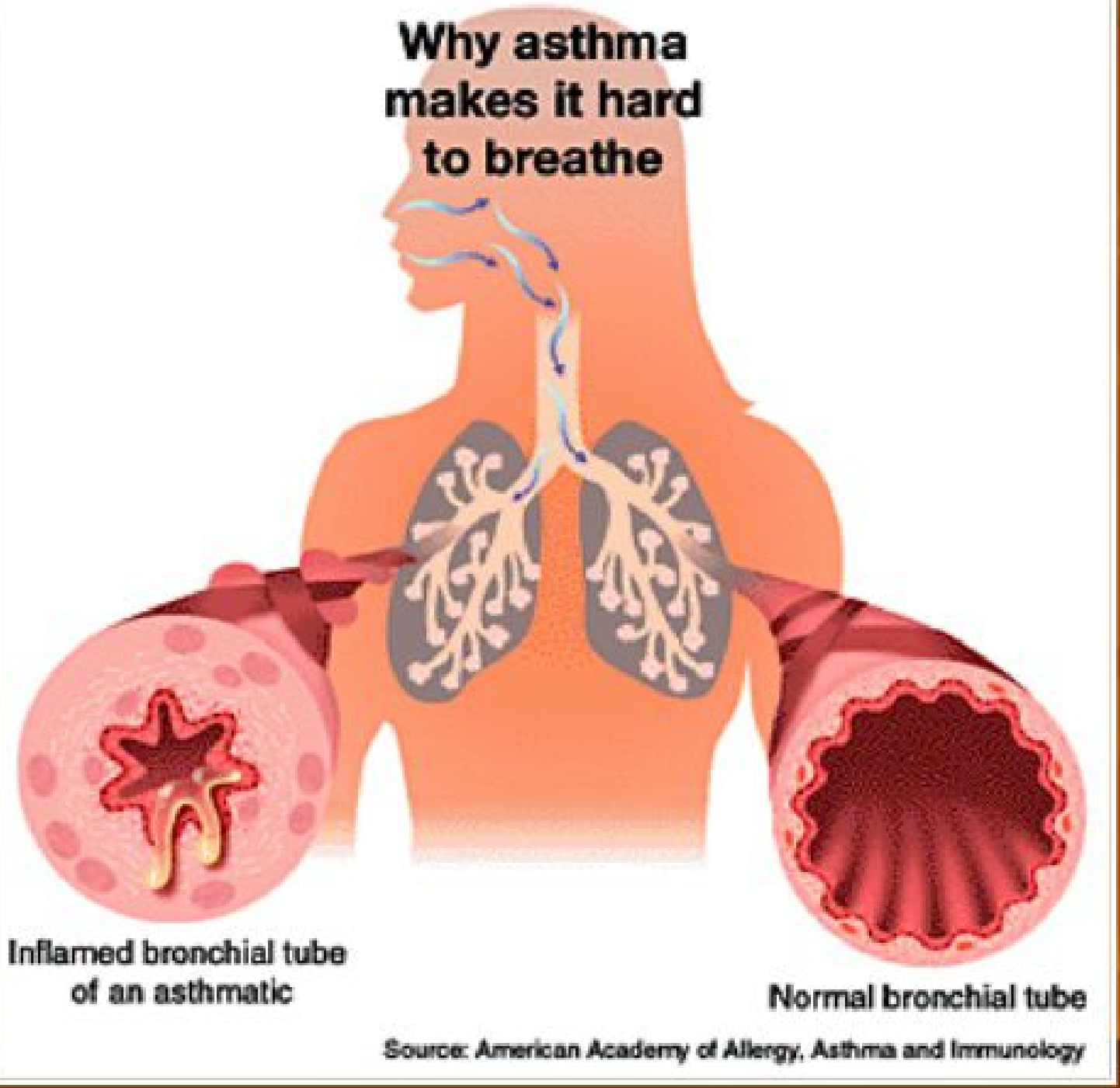

Submucosa
Mucosa
Infiltration of inflammatory cells, (mononuclear cells, eosinophils, etc.)
Hypertrophied smooth muscle
Mononuclear cell
Oedema
Mast cell
Dilated blood vessels
Eosinophil
Epithelium
Thickened basement membrane
Mucus plug with eosinophils and desquamated epithelial cells

ASTHMA

- Most common chronic condition in children
- #1 cause of school absenteeism
- Morbidity and mortality highly correlated with poverty, urban air quality, indoor allergens, lack of patient education, and inadequate medical care
- About 5000 deaths annually.

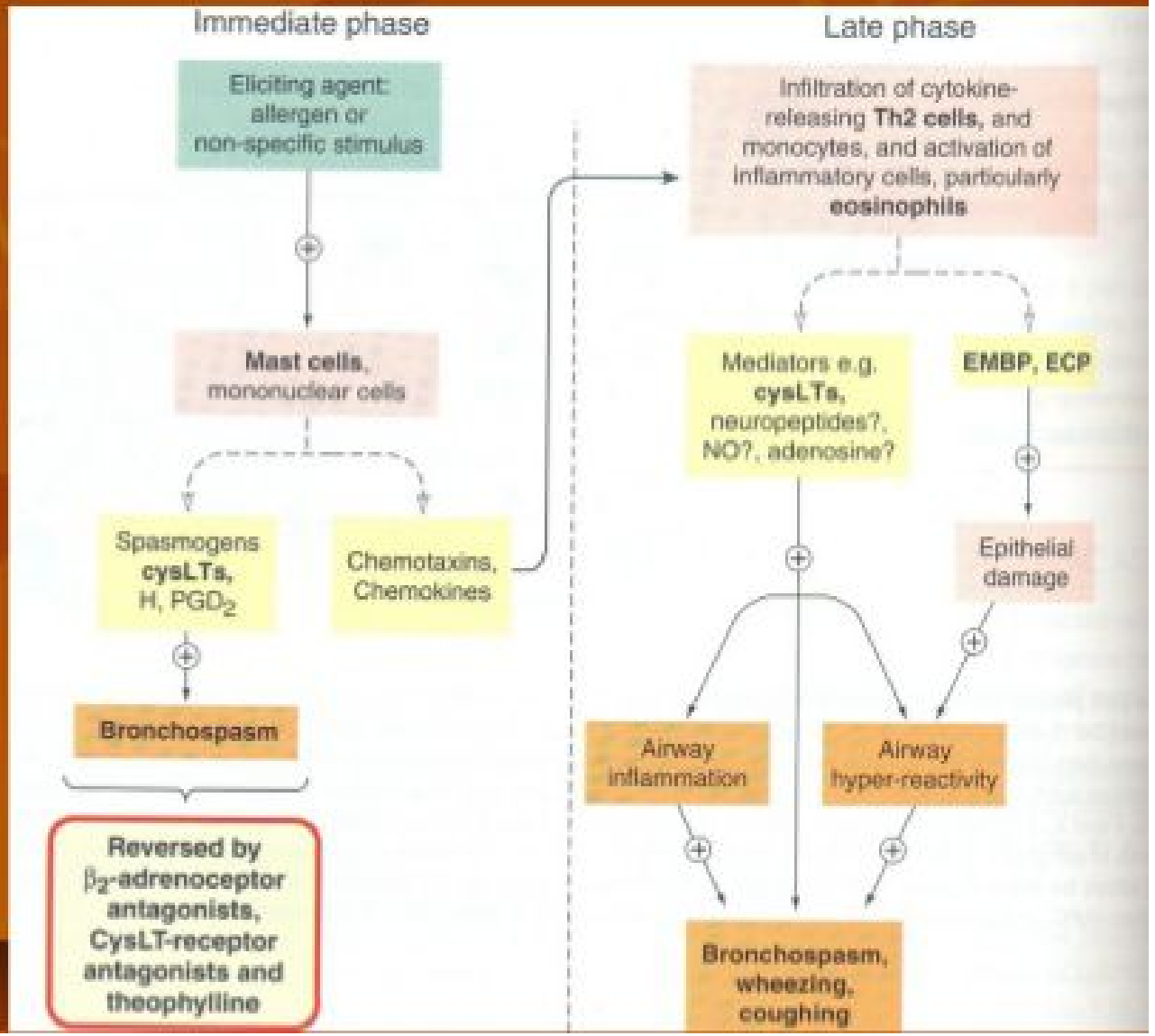
SIGNS & SYMPTOMS OF ASTHMA

- Usually associated with airflow obstruction of variable severity.
- Airflow obstruction is usually reversible, either spontaneously, or with treatment.
- The inflammation associated with asthma causes an increase in the baseline bronchial hyper responsiveness to a variety of stimuli.


Why asthma makes it hard to breathe
Inflamed bronchial tube of an asthmatic
Normal bronchial tube
Source: American Academy of Allergy, Asthma and Immunology

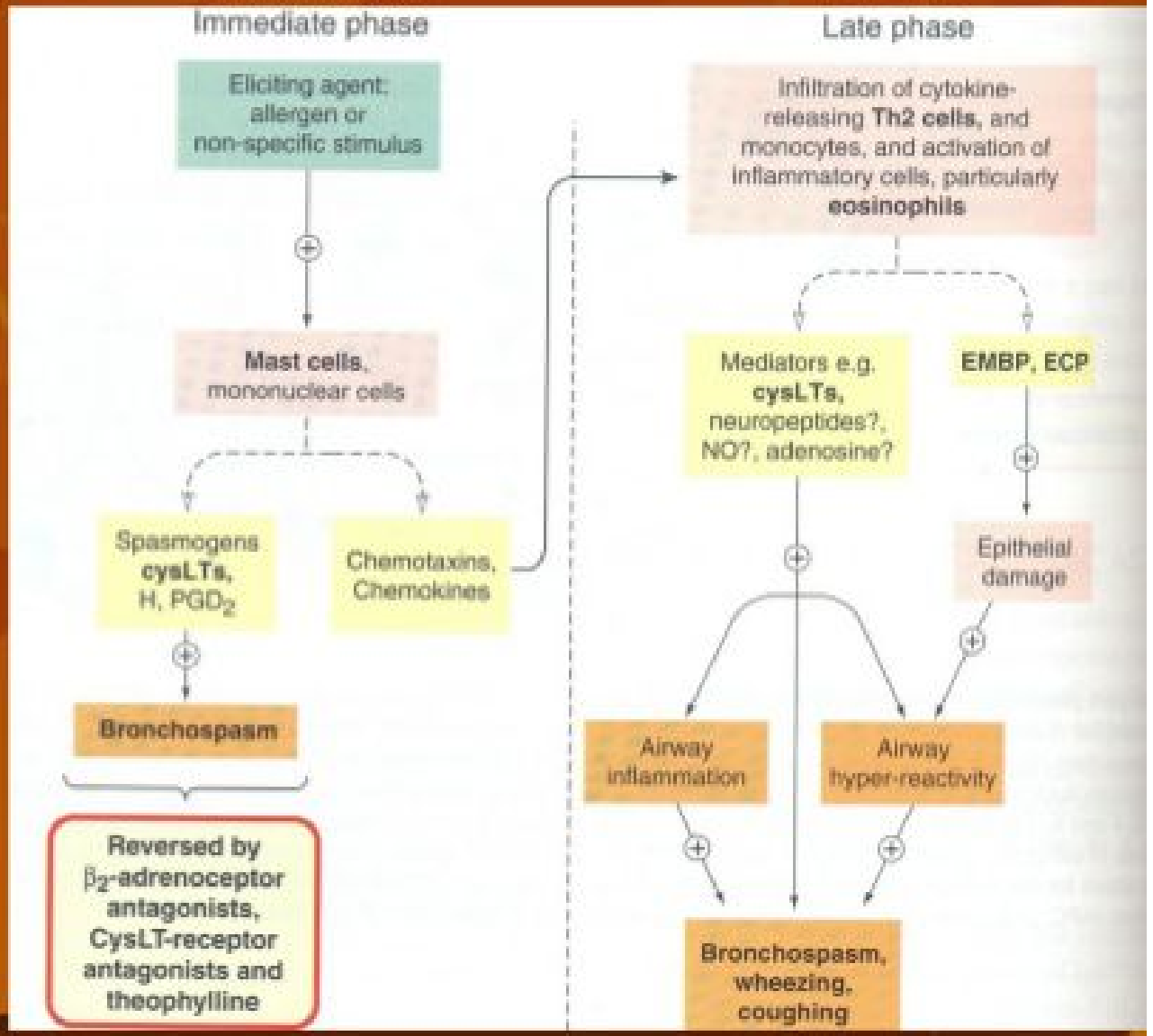
PATHOGENESIS OF ASTHMA

- The early reaction is immediate bronchoconstriction produced by histamine, tryptase, and other neutral proteases, leukotrines C4 and D4 and prostaglandins
- These agents diffuse throughout the airway wall and cause vascular leakage



PATHOGENESIS OF ASTHMA

- Late bronchoconstriction occurs after 2-8 hours by TH2 lymphocytes and interleukins 4, 5, 9 and 13, attracting and activating eosinophils and stimulating IgE production by B lymphocytes



ASTHMA TRIGGERS

- Allergens
  - Dust mites, mold spores, animal dander, cockroaches, pollen, indoor and outdoor pollutants, irritants (smoke, perfumes, cleaning agents).
- Pharmacologic agents; ASA, beta-blockers.
- Physical triggers (exercise, cold air, distilled water, and sulfur dioxide).
- Diseases; GERD, viral and bacterial URI, rhinitis.
- Physiologic factors

TREATMENT OF ASTHMA

- Global Initiative for Asthma (6-point plan)
  - Educate patients to develop a partnership in asthma management
  - Assess and monitor asthma severity with symptom reports and measures of lung function as much as possible
  - Avoid exposure to risk factors
  - Establish medication plans for chronic management in children and adults
  - Establish individual plans for managing exacerbations
  - Provide regular follow-up care

CLASSIFICTION OF DRUGS USED IN ASTHMA

A) Short term relievers used for relief of acute bronchoconstriction:

1. Beta Adrenergic agonists
2. Methylxanthines
3, Anrimuscrinic agents

CLASSIFICTION OF DRUGS USED IN ASTHMA

1. Beta Adrenergic agonists:

(i) Drugs acting on both β1 and β2receptors:

- Epinephrine
- Ephedrine
- Isoproterenol

(ii) Beta2 selective drugs:

- Albuterol
- Terbutaline
- Metaproterenol
- Pirbuterol
- Bitolterol
- Salmoterol
- Formoterol

CLASSIFICTION OF DRUGS USED IN ASTHMA

2. Methylxanthines:

- Theophylline
- Theobromine
- Caffeine

3. Antimuscarinic agents:

- Ipratropium

CLASSIFICTION OF DRUGS USED IN ASTHMA

B) Long term controllers for reduction of symptoms and prevention of attacks:

1. Corticosteroids
2. Leukotriene pathway antagonists
3. Inhibitors of mast cell degranulation

CLASSIFICTION OF DRUGS USED IN ASTHMA

1. Corticosteroids:

- Prednisolone
- Hydrocortisone
- Beclomethasone
- Triamcinolone
- Fluticasone
- Budesonide
- Mometasone

CLASSIFICTION OF DRUGS USED IN ASTHMA

2. Leukotriene pathway antagonists:

- Zileuton
- Zafirlukast
- Montelukast

3. Inhibitors of mast cell degranulation:

- Cromolyn sodium
- Nedocromil

PHARMACODYNAMICS OF B-ADRENERGIC RECEPTORS

- Beta-2 receptors are the predominant receptors in bronchial smooth muscle
- Stimulate adenylyl cyclase, which increases synthesis of cAMP which leads to relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity
- Inhibits release of mast cell mediators such as histamine, leukotrienes, and prostaglandin-D2.
- Beta1-receptors are predominant receptors in heart, but up to 10-50% can be beta2-receptors.

BETA ADRENERGIC AGONISTS

a) Non selective beta adrenergic agonists:

Epinephrine:

- It stimulates alpha and beta1as well as beta2 receptors.
- It is an effective rapid acting bronchodilator when injected S/C (0.4 mL of 1:1000 solution) or inhaled as a microaerosol from a pressurised canister (320 mcg/ puff).
- Adverse effects tachycardia, arrythmias and worsening of angina pectoris.

BETA ADRENERGIC AGONISTS

Ephedrine:

- Used in asthma for longest time.
- Longer duration and lower potency than epinephrine.
- Not much used nowadays due to development of β2-selective agents.

Isoproterenol:

- A potent bronchodilator , producing effect in 5 minutes.
- Duration of action 60-90 minutes.
- High doses associated with cardiac arrhythmias leading to death.

BETA-2 ADRENERGIC AGONISTS:

Short acting β-2 selective adrenergic agonists:

- Short acting drugs eg albuterol, terbutaline, and perbuterol are available as metered-dose inhalers. They are potent bronchodilators.
- Bronchodilation is maximal within 15-30 minutes and persists for 3-4 hours.
- Toxic effects are minimized when these drugs are delivered by inhalation.

BETA-2 ADRENERGIC AGONISTS

Long acting beta-2 selective agonists:

- Salmeterol, a potent selective beta-2 agonist, that achieves its long duration of action as a result of high lipid solubility. This increaes the affinity of the drug for the beta adrenoceptors.
- The drug appears to interact with inhaled corticosteroids to improve asthma control.
- Long acting drugs should not be used in acute bronchospasm.

METHYLXANTHINES

Theophylline:

- Narrow therapeutic index/Maintain 5-20 mcg/mL
- Variability in clearance leads to a range of doses that vary 4-fold in order to reach a therapeutic dose.

Mechanism of action:

- Smooth muscle relaxation (bronchodilation).
- Suppression of the response of the airways to stimuli.
- Increases force of contraction of diaphragmatic muscles.
- Interacts with many other drugs.

METHYLXANTHINES

- Previously used to be main-stay of asthma therapy.
- The bronchodilation produced by theophylline is the major therapeutic action in asthma.
- Most preparations of theophylline are well absorbed from GIT.
- For oral therapy with prompt- release formulation the typical dose is 3-4 mg/kg every 6hours.

METHYLXANTHINES

Adverse effects of theophylline:

- Anorexia, nausea, vomiting, abdominal discomfort, headache and anxiety may occur.
- Higher levels may cause seizures or arrythmias.
- Toxic levels may occur in patients with liver disease.

METHYLXANTHINES - EFFECTS

(A) CNS effects:

- Mild cortical arousal with increased alertness and deferral of fatigue
- Caffeine containing beverages cause nervousness and insomnia in unusually sensitive patients and bronchodilation in patients with asthma.
- Medullary stimulation and convulsions .
- Nervousness and tremors are toxic effects of larger doses.

METHYLXANTHINES - EFFECTS

(B) Cardiovascular effects:

- Direct positive chronotropic and inotropic effects on the heart.
- In unusually sensitive patients few cups of coffee can cause arryhthmias but in normal persons high doses administered parenterally produce only sinus tachycardia and increased cardiac output.
- Relaxation of vascular smooth on larger doses except cerebral vessels where they cause contraction.
- Ordinary consumption raise peripheral vascular resistance and BP slightly, probably by releasing catecholamines.
- Increases viscosity of blood in some cases.

METHYLXANTHINES - EFFECTS

(C) Effects on GIT:

- Stimulation of gastric acid and digestive enzymes secretion.

(D) Effects on kidney:

- Weak diuresis (especially theophylline).

(E) Effects on smooth muscles:

- Bronchodilation.
- Also inhibits antigen-induced histamine release.

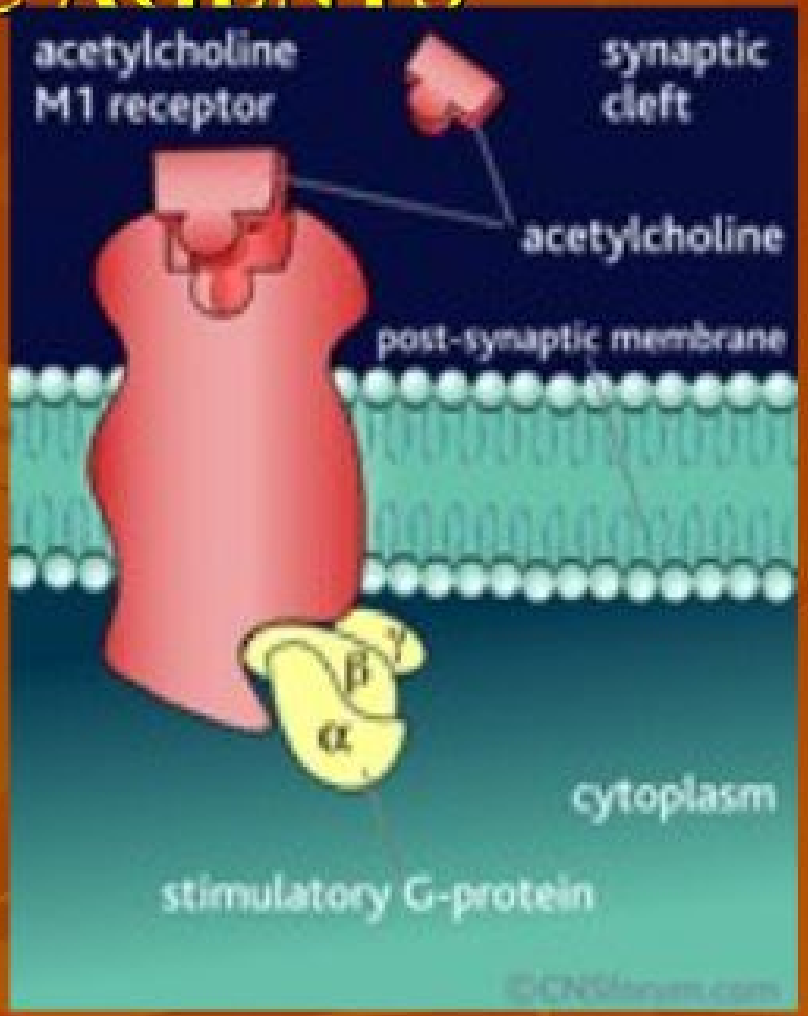
(F) Effects on skeletal muscles:

- Strengthening of contraction.

ANTIMUSCRINIC AGENTS

MOA:

- Muscarinic antagonists competitively inhibit the effect of acetylcholine at muscarinic receptors ie block the contraction of airway smooth muscle and the increase in the secretion of mucus.



ANTIMUSCRINIC AGENTS

- Ipratropium bromide a quaternary ammonium derivative of atropine is used .It is delivered in high doses by inhalation route.

Clinical uses:

- Addition of Ipratropium enhances the bronchodilation produced by nebulized Albuterol in acute severe asthma.
- In patients intolerant of inhaled beta agonist agents.

ANTIMUSCRINIC AGENTS

- **Atropine** is effective intravenously as well asaerosol, effect lasting for 5 hours
- **Adverse effects** of antimuscrinics include urinary retention, tachycardia, loss of visceral accommodation and agitation.

LONG TERM CONTROLLERS

CORTICOSTEROIDS:

- They reduce bronchial reactivity, cause contraction of engorged vessels in bronchial mucosa, and inhibition of the infiltration of asthmatic airways by lymphocytes , eosinophils and mast cells.
- Oral and parenteral corticosteroids are reserved for patients who require urgent T/M.

CORTICOSTEROIDS

Adverse effects of inhaled coticosteroids:

- High doses of inhaled steroids may cause adrenal suppression .
- Oropharyngeal candidiasis.
- Hoarseness
- Risks of cataracts and osteoporosis in adults over the long term use.
- Transient slowing of rate of growth in children.

CORTICOSTEROIDS

Clinical Uses:

- Used in emergency.
- Regular controller therapy is maintained with aerosol corticosteroids.
- Urgent treatment started with prednisolone 30-60 mg orally or methylprednisolone 1 mg/kg I/V.
- In most patients discontinued in 10 days.
- Aerosol therapy decreases the systemic side effects.

Pharmacotherapy

- Mast cell stabilizers (cromolyn/nedocromil)
  - Inhibits release of mediators from mast cells (degranulation) after exposure to specific antigens
  - Blocks Ca2+ ions from entering the mast cell
  - Safe for pediatrics (including infants)
  - Should be started 2-4 weeks before allergy season when symptoms are expected to be effective
  - Can be used before exercise (not as good as ICS)
  - Alternate med for persistent asthma

- Mast cell stabilizers
- Cromolyn and Nedocromyl
- MOA
- An alteration in the function of delayed chloride channels in the cell membrane results in:
- Inhibition of the early response to an antigenic challenge of mast cells
- Inhibition of the inflammatory response of eosinophils to inhalation of allergens.

- Cromolyn or Nedocromil when taken regularly 2-4 puffs 2-4 times daily by patients with nonseasonal asthma, reduces symptomatic severity and the need for bronchodilator medication.
- Addition of nedocromil to a standard dose of an inhaled corticosteroid appears to improve asthma control.

- Adverse effects
- Minor throat irritation, cough, and mouth dryness and rarely chest tightness and wheezing.
- Serious adverse effects dermatitis, myositis, or gastroenteritis occurs in less than 2% of patients.
- Very few cases of pulmonary infiltration and anaphylaxis have been reported.

Pharmacotherapy

- Leukotriene receptor antagonists
  - Leukotriene-mediated effects include:
    - Airway edema
    - Smooth muscle contraction
    - Altered cellular activity associated with the inflammatory process
  - Receptors have been found in airway smooth muscle cells and macrophages and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells) and nasal mucosa

- Leukotriene pathway inhibitors
- Zileuton a 5- lipoxygenase inhibitor
- Montelukast, Zafirlukast LTD4 – receptor antagonists.
- They improve asthma control.
- They are given orally can be given in patients who comply poorly with inhaled therapies.
- Montelukast can be used in children as young as 6 years of age. It can be taken without regards to meals and only once-daily convenient dosage.


Thank You