Pathophysiology of Asthma

By

Jagadish Prasad Mishra

4th sem M.B.B.S.

Asthma:-

It is a syndrome characterized by airflow obstruction that varies markedly, both spontaneously and with treatment.

Symptoms-wheezing, breathlessness, cough, chest tightness

Prevalence-10-12% adults, 15% children

Developed country>Developing country

Risk Factors

Endogenous Factors

Genetic predisposition

Atopy

Airway hyperresponsiveness

Gender

Ethnicity?

Obesity?

Viral infections

Environmental Factors

Indoor allergens

Outdoor allergens

occupational sensitizers

Passive smoking

Respiratory infections

Triggers:-

- **Allergens-Dermatophagoides species(dust mite), environmental exposure, grass pollen, ragweed, tree pollen, fungal spores, pets furs, cockroaches etc**
- **Virus infection-upper respiratory tract virus such as rhinovirus, respiratory syncytial virus, coronavirus etc**
- **Pharmacological agents-beta blockers, ACE inhibitors, aspirin**
- **Exercise(may exacerbate)**
- **Physical factors-cold air, hyperventilation**
- **Food**
- **Air pollutants-sulfur dioxide, irritant gases**

Contd….

- **Irritants-household sprays paint fumes**
- **Occupational factors**
- **Hormonal factors-fall in progesterone thyrotoxicosis**
- **Gastrointestinal reflex**
- **stress**

Types of asthma-

- **Atopic asthma-classical type I IgE mediated hypersensitivity, allergen sensitization, seen from childhood, +ve history of asthma in family, skin test +ve**
- **Non-atopic asthma-no allergen sensitization, no such history, skin test –ve, virus infection?**
- **Drug induced asthma-sensitive to certain drugs like aspirin, NSAIDS etc**
- **Occupational asthma-stimulants such as fumes, organic and chemical dusts(wood, cotton), gas(toluene), penicillin products etc**
- **Exercise induced asthma-begins after exercise and stops after 30 minutes, worsen in cold and dry climate**

pathogenesis

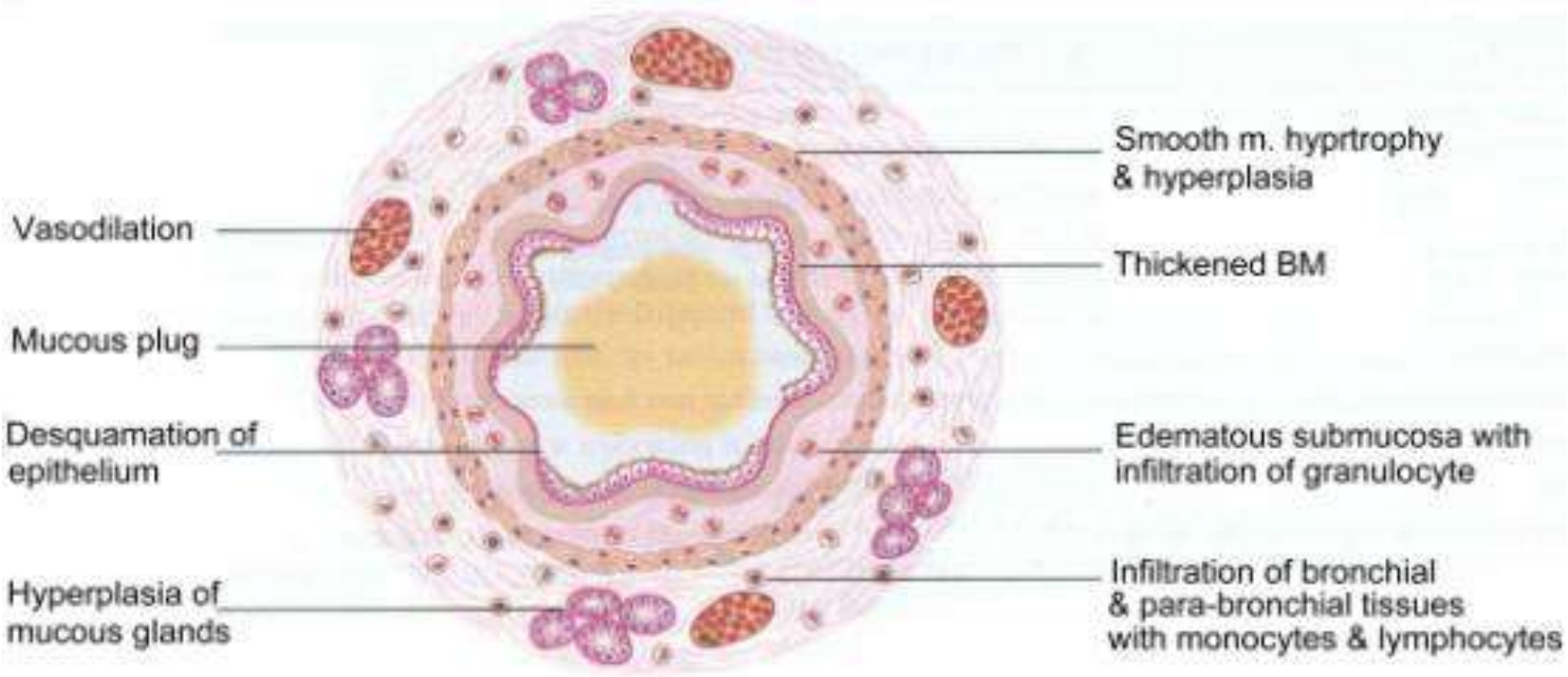
- pathology
- Inflammation
- Inflammatory mediators
- Effects of inflammation
- Airway remodeling

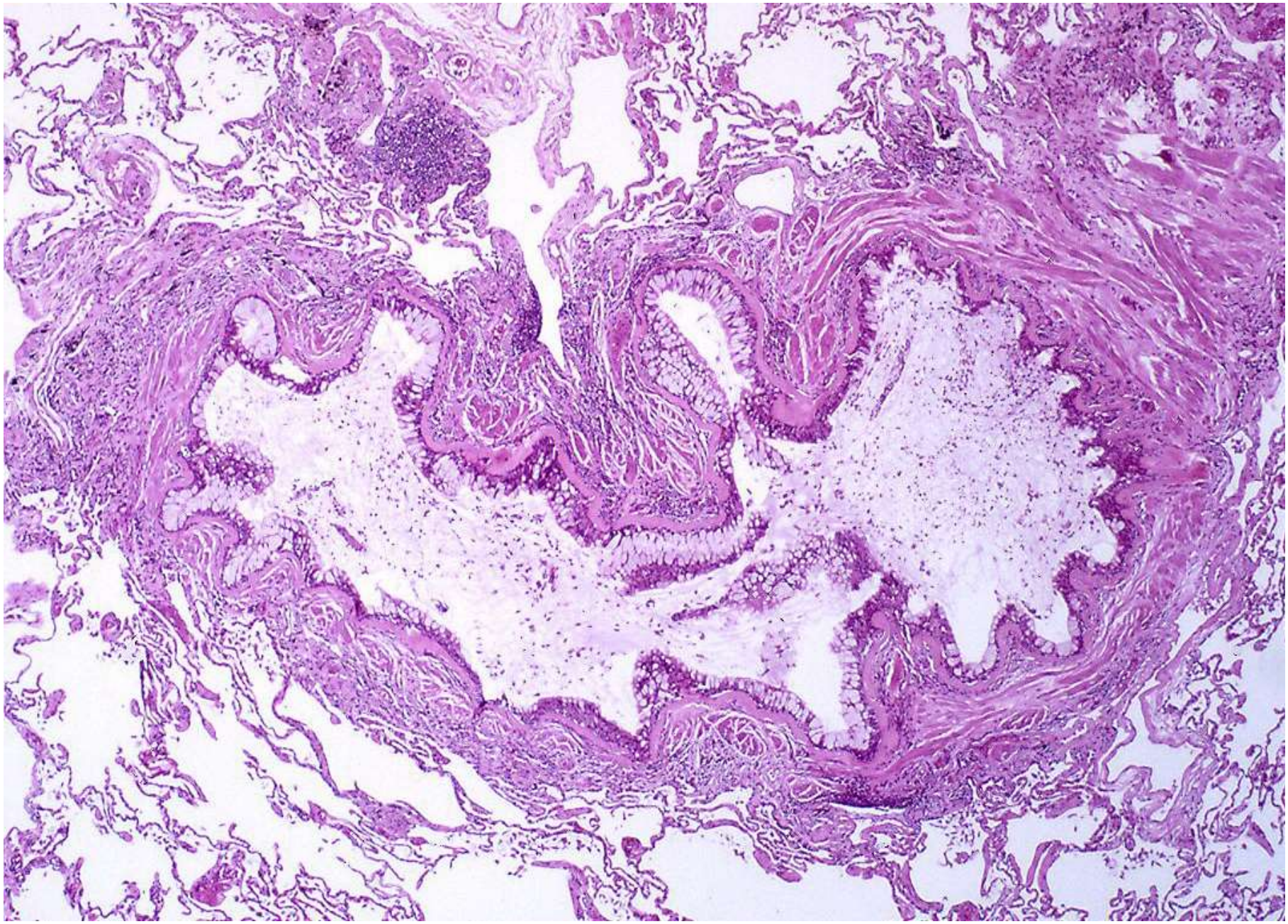
pathology

- Chronic inflammation of lower airways
- Mucosal infiltration of activated eosinophils and T lymphocytes
- Thickening of basement membrane
- Goblet cell metaplasia
- Smooth muscle hypertrophy and thickening
- Shedding of epithelium
- Occlusion of airway by mucosal plug

Contd..

- Vasodilatation and leakage
- Angiogenesis
- Lung parenchyma not affected



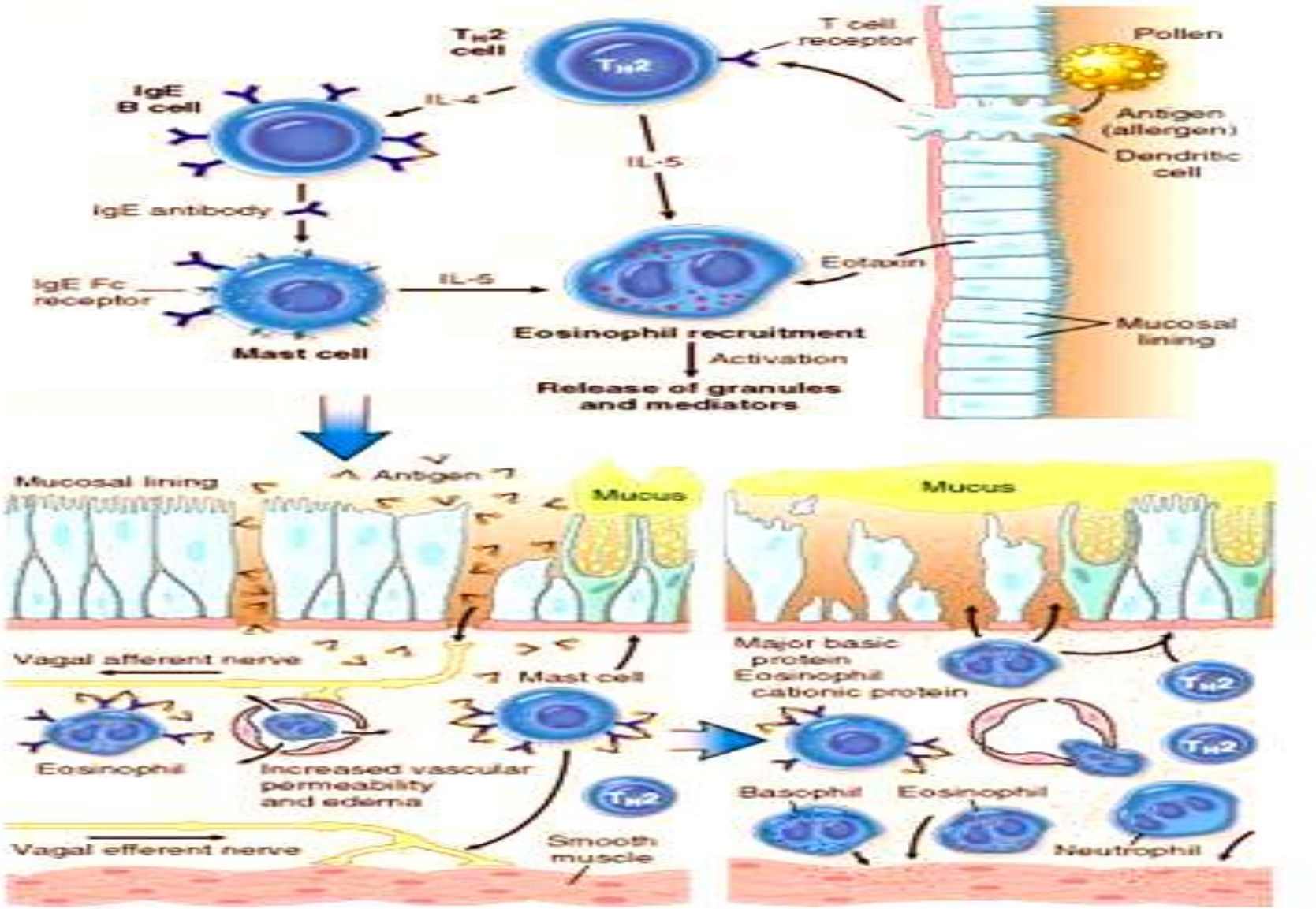


Inflammation

- Allergic type of inflammation occurs
- From trachea to terminal bronchiole
- Predominantly in bronchi
- Airway hyperresponsiveness
- Cells involved in inflammation-mast cell macrophages dendritic cell eosinophils neutrophils T lymphocytes and structural cells
- Early phase reaction-mediated by granules release from mast cell, bronchoconstriction, vasodilation and increase permeability

Contd…

- **Late phase reaction-inflammation with recruitment of eosinophils, T lymphocytes, neutrophils, macrophages etc and subsequent release of mediators.**



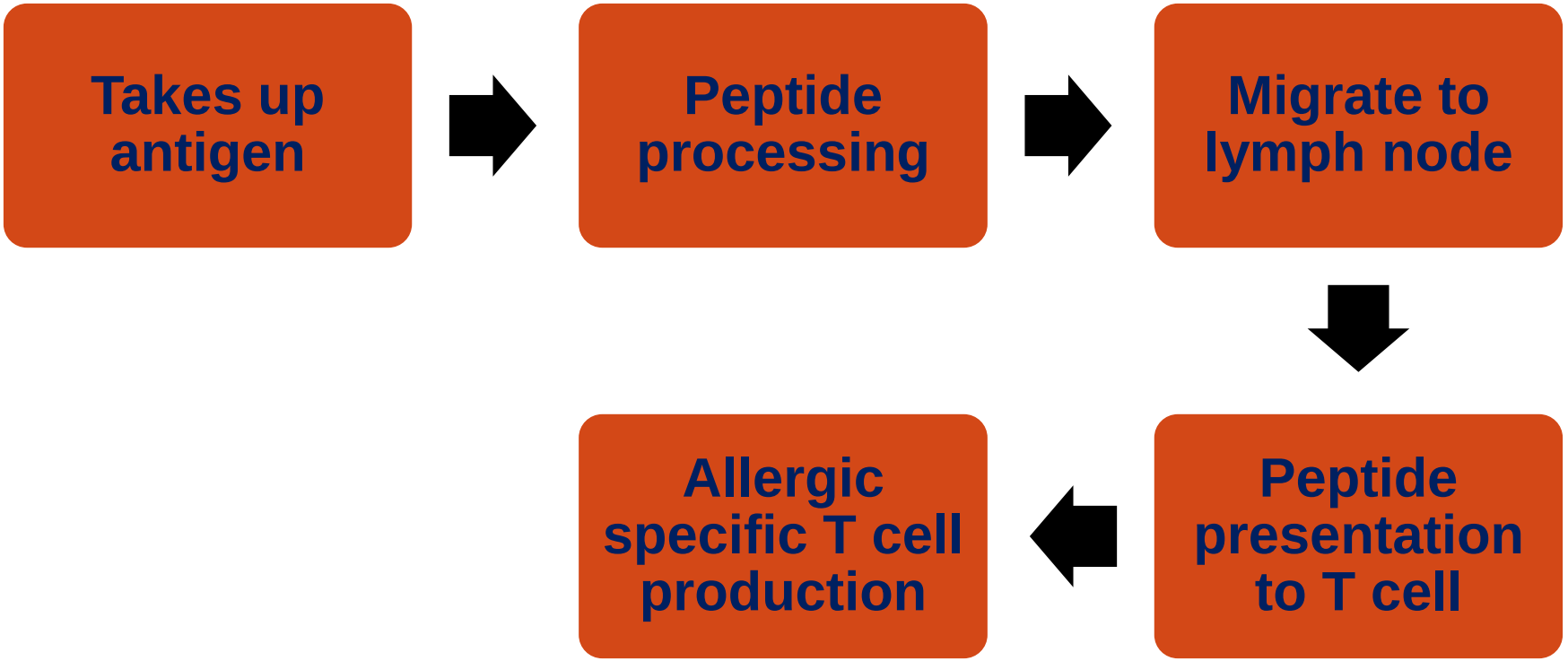
D. IMMEDIATE PHASE (MINUTES)

E. LATE PHASE (HOURS)

Contd…

- **Mast cell-activated by IgE dependant mechanism, initiate acute bronchoconstriction action by releasing histamine, prostaglandinD2,leukotrienes etc**
- **Macrophage-activated by low affinity IgE receptor, produce various inflammatory mediators**
- **Dendritic cell-macrophage like major APC in airways, TSLP(Thymic stromal lymphopoietin) by epithelial cell induced chemokine release for TH2 cells**

Dendritic cell antigen presentation



Contd…

- **Eosinophils-infiltration is characteristic feature of asthma, activated by IL-5, causes exacerbation of asthma by producing mediators**
- **Neutrophil-activated and infiltration**
- **T cell-release cytokines, causes recruitment of eosinophils, also causes maintenance of mast cells, in asthma TH2 cell produce IL-5(eosinophil recruitment) IL-4, IL-13(increase IgE production and mucus secretion).CD4+ cell also involved**
- **Structural cells-epithelial cells(TSLP), fibroblasts etc**

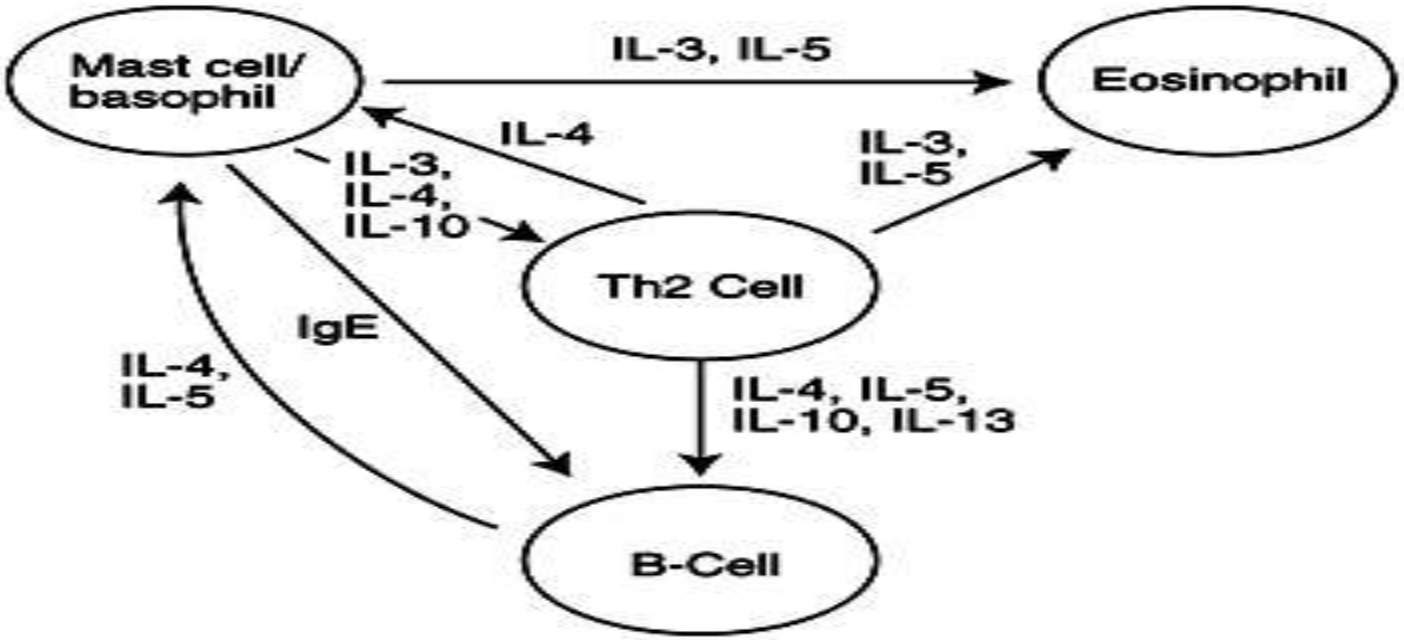
Inflammatory mediators-

- **Histamine, prostaglandin D2, cysteinly leukotrienes-cause smooth muscle contraction, increased microvascular leakage, increased mucus secretion, act as chemoattractant for inflammatory cells**
- **Cytokines- IL-4, IL-5, IL-13-causes allergic inflammation, IL-1beta, TNF-alpha-amplification of inflammation, TSLP(Tymic stromal lmphopoietin)-from epithelial cells act as chemoattractant for TH2 cells, IL-10, IL-12-anti inflammatory**
- **Chemokines-attract inflammatory cells, Eotaxin(CCL11) attract eosinophil via CCR3 receptor, TARC(CCL17) and MDC (CCL 22) from epithelial cell attract TH2 cell via CCR4.**

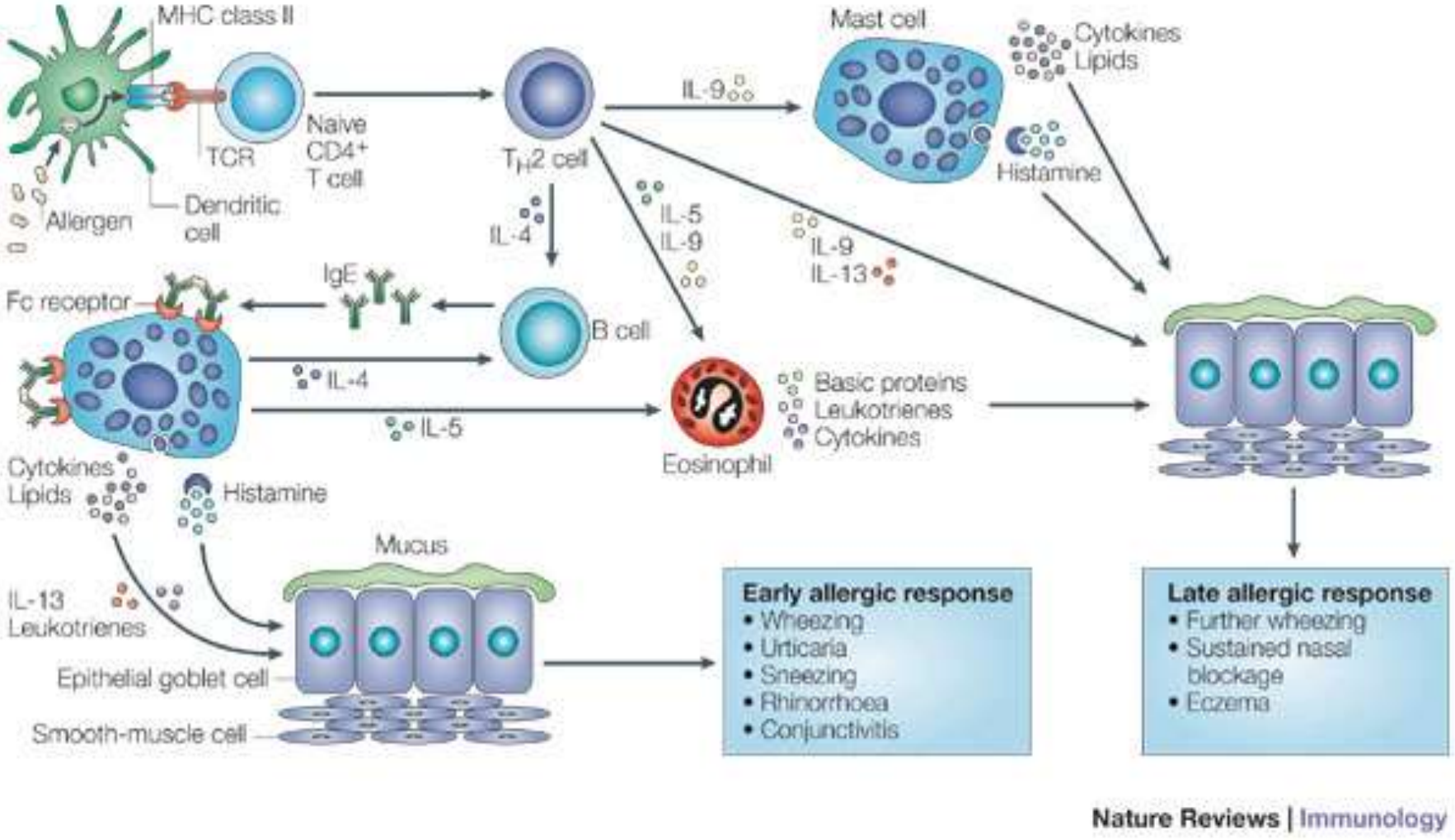
Contd…

- **Oxidative stress-increase in ROS production**
- **NO-act as relaxant but mainly causes vasodilatation leading to leakage**
- **Transcription factor-NF-kB, activator protein-1**

Figure 1: Interactions of Th2 Cells with Other Cells.



Various inflammatory mediators-

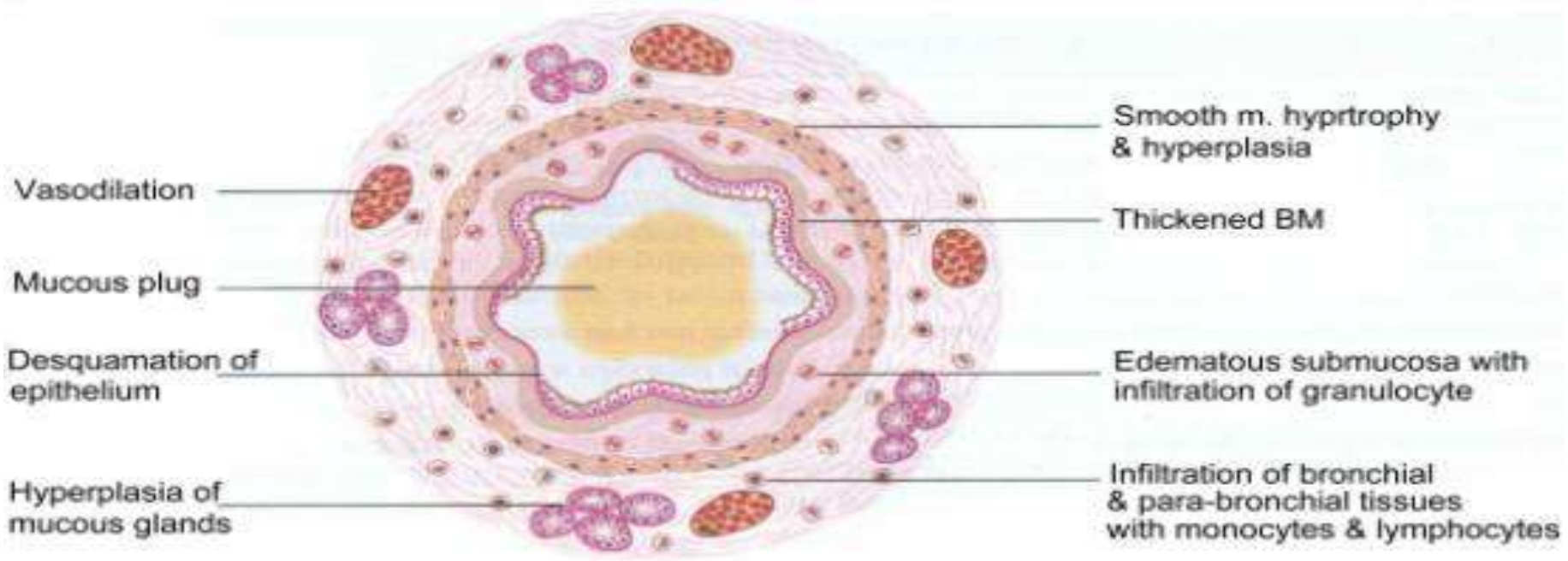


Effects of inflammation-

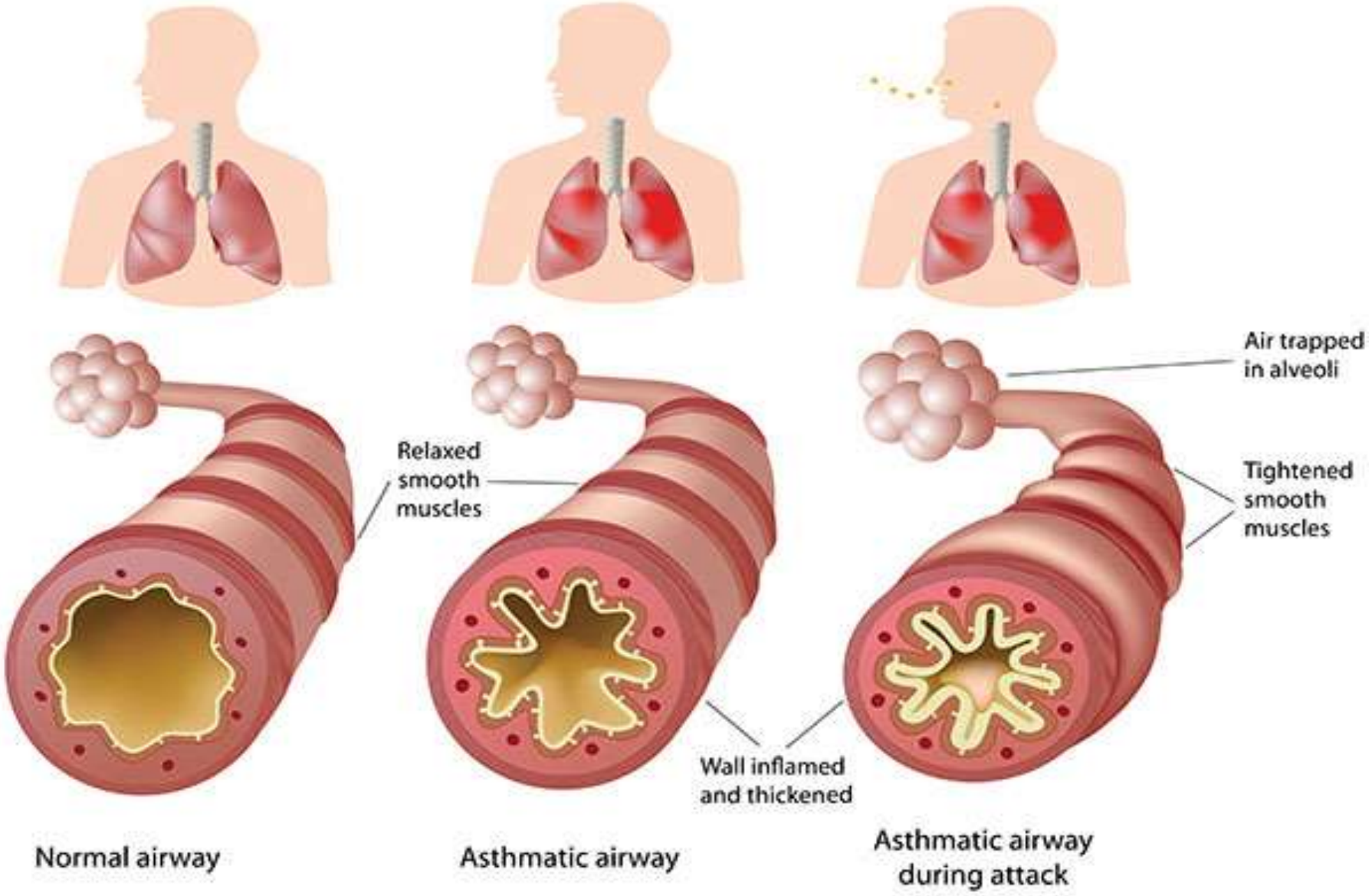
- **Epithelium-dysfunction, damage, loss of enzyme, loss of relaxant factors, loss of barrier function**
- **Fibrosis- subepithelial fibrosis, basement membrane thickening, deposition of III and V collagen(by factors release from eosinophil)**
- **Smooth muscle- increased responsiveness to constrictor mediators, in chronic cases hypertrophy/hyperplasia by growth factors released by inflammatory mediators**
- **Vascular response-vasodilation, angiogenesis, microvascular leakage**

Contd….

- **Mucus hypersecrection-** by goblet cell hyperplasia, increase in mucus plug, leading to blocking of airway
- **Neural effect-**reflex cholinergic bronchoconstriction by increased muscarinic action

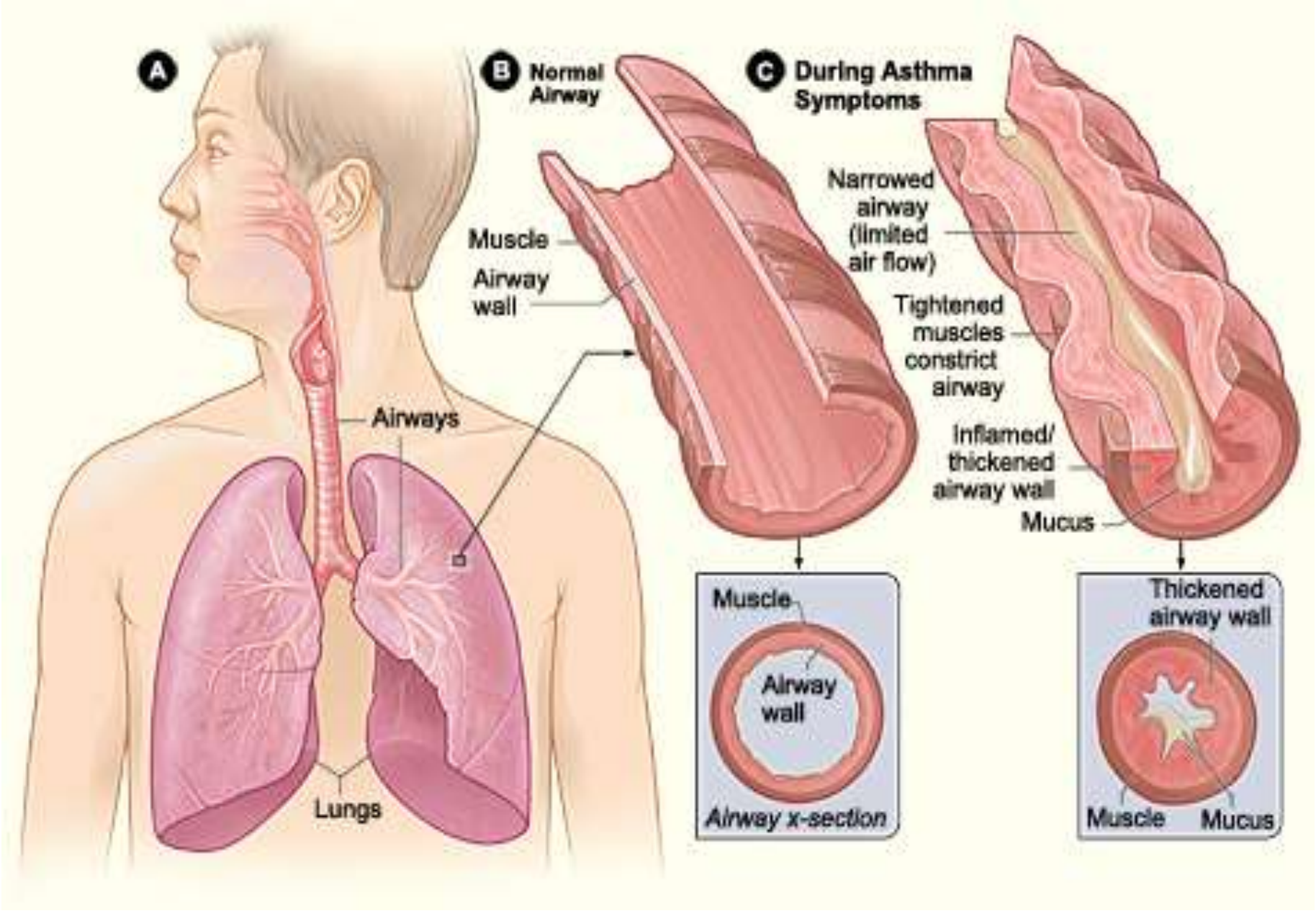


Asthma and Your Airways

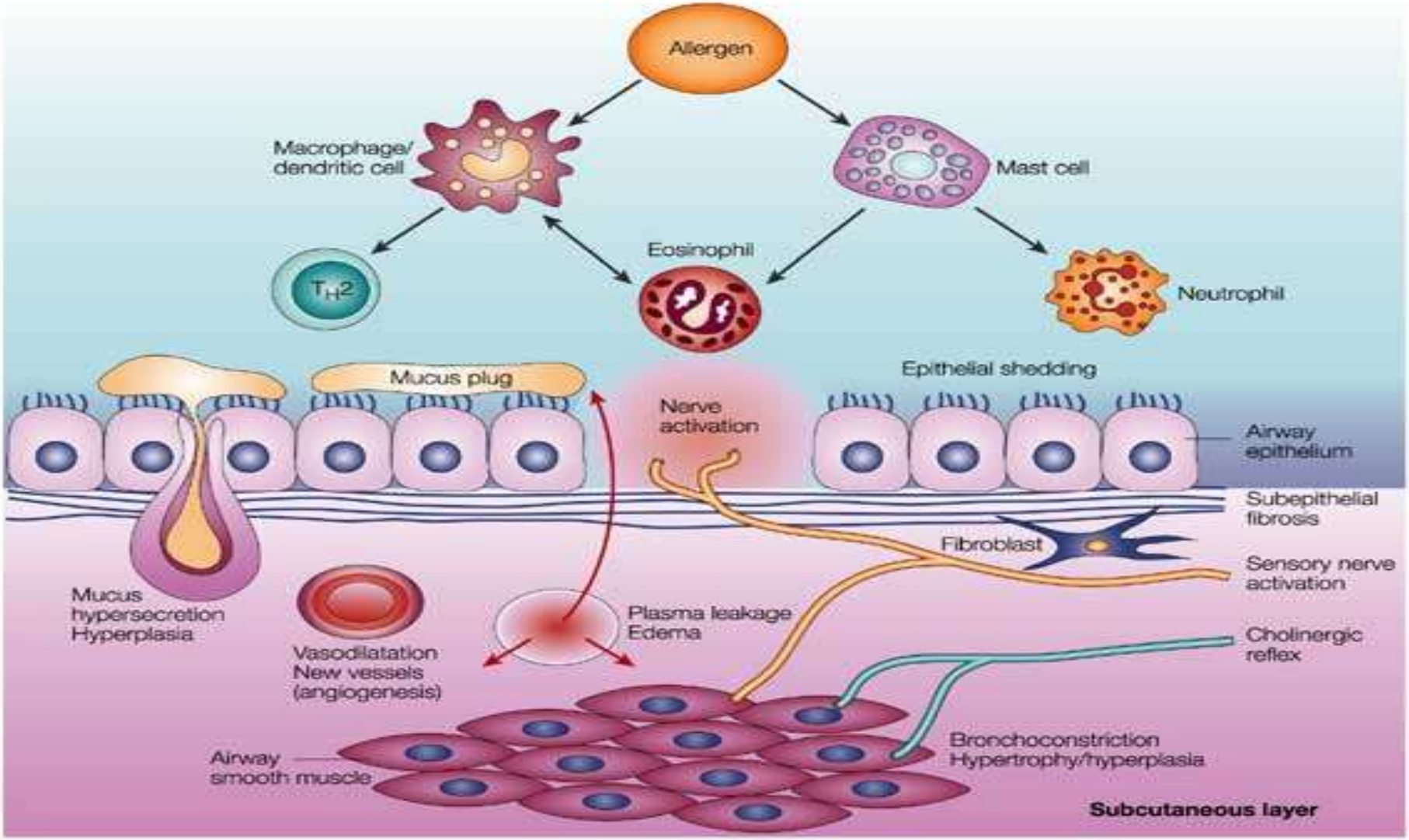


Airway remodeling:-

- Several changes can be seen
- Irreversible narrowing of lumen
- Decline in lung function
- Smooth muscle hyperplasia
- Fibrosis


A
B Normal Airway
C During Asthma Symptoms
Muscle
Airway wall
Airways
Lungs
Narrowed airway (limited air flow)
Tightened muscles constrict airway
Inflamed/ thickened airway wall
Mucus
Muscle
Airway wall
Airway x-section
Thickened airway wall
Muscle
Mucus

Pathophysiology of asthma-

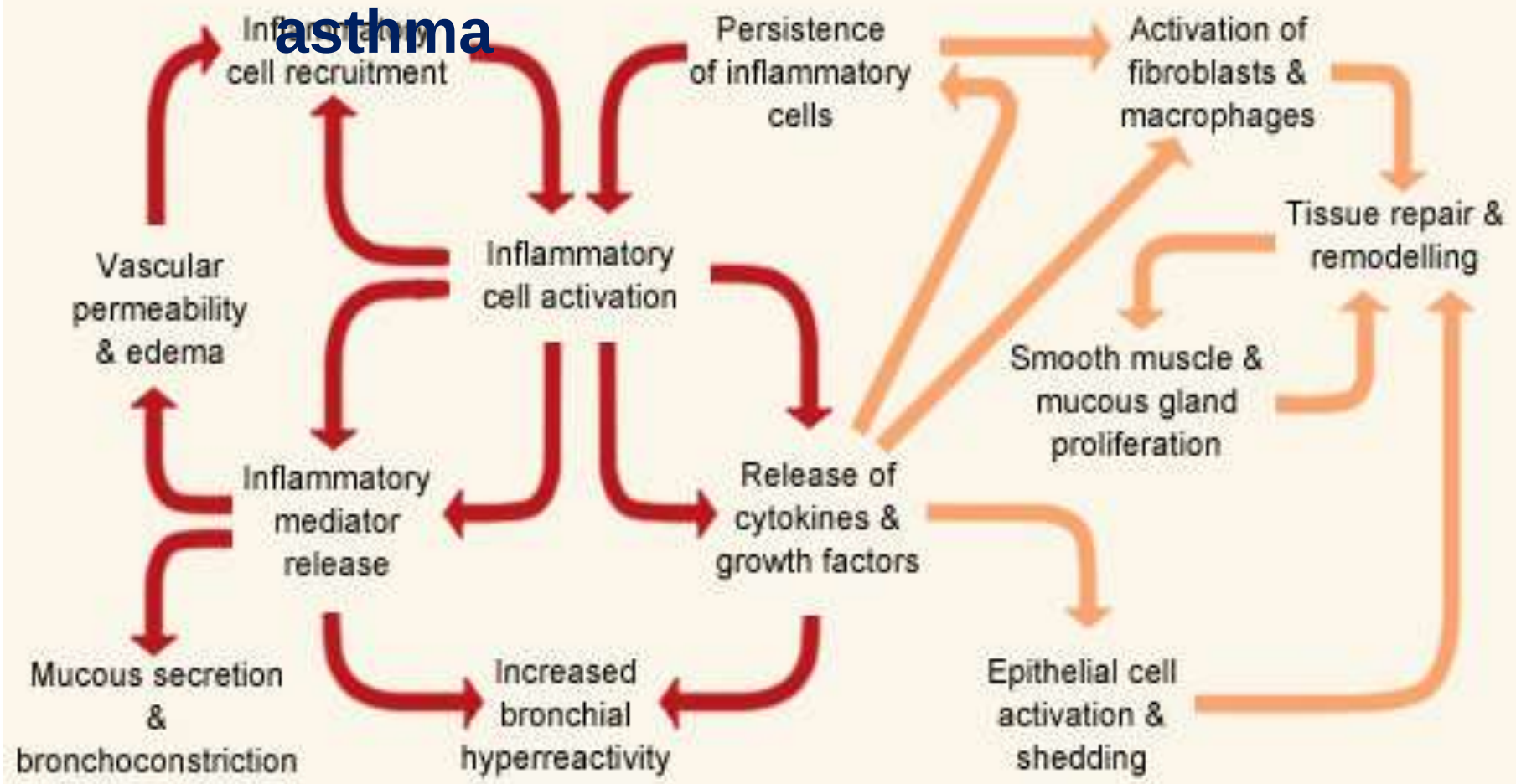


Nature Reviews | Drug Discovery

Summary-

- Asthma is chronic inflammatory disorder with airway hyperresponsiveness and airway obstruction.
- various risk factors and triggers
- Types-atopic and non-atopic
- Eosinophilic infiltration and thickening of B.M.
- Hyperplasia of gland and vasodilatation
- IgE dependant mast cell activation and release of various mediators
- Early and late phase reactions with dendritic cell and TH2 cell
- Various mediators-cytokine, chemokines, PGs etc
- Epithelium shedding, fibrosis, hypertrophy of muscle and increased permeability
- Airway remodeling

Overall pathophysiology af asthma



Adapted from:

Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodelling. 2000. Am J Respir Crit Care Med, 161: 1720-1745

Thank you