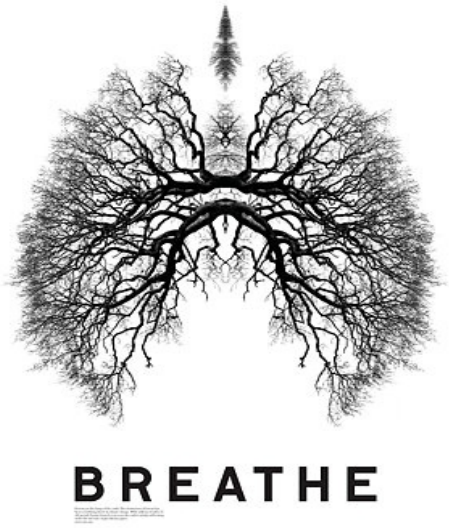
Introduction to Lungs
&
Bronchial Asthma



@pathology434

Objectives:

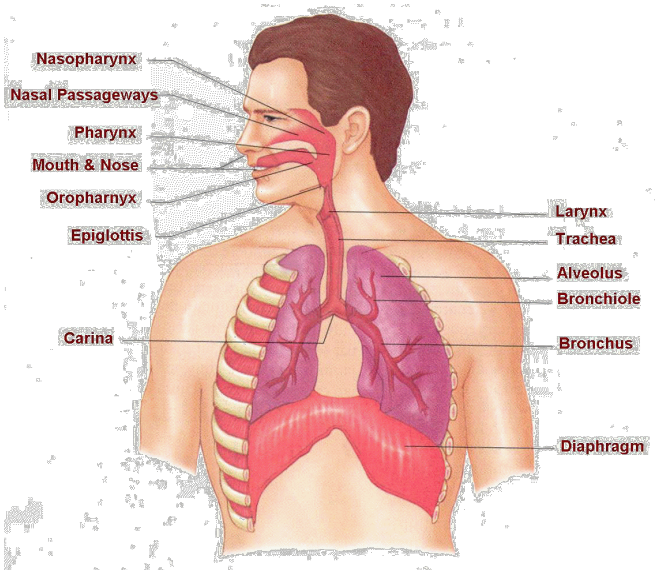
- Understanding asthma as an episodic, reversible bronchoconstriction caused by increased responsiveness of the tracheobronchial tree to various stimuli.
- Knowing that asthma is divided into two basic types: extrinsic or atopic allergic and intrinsic asthma.
- Understanding the morphological changes seen in the lungs in cases of severe asthma.

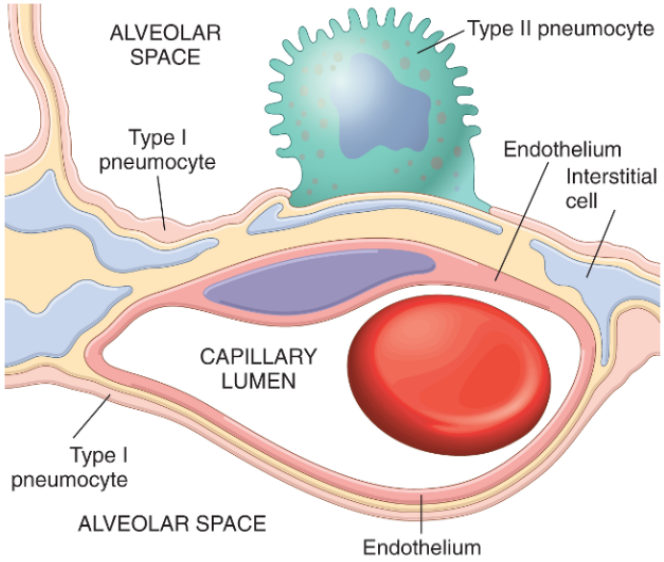
Contents:

- Definitions of asthma as one of the chronic obstructive airway diseases.
- Types and pathogenesis of extrinsic (immune) asthma and extrinsic (non-immune) asthma.
- Clinical presentation and pathological changes seen in the bronchial tree in cases of asthma.
- Complications of asthma: superimposed infection, chronic bronchitis and pulmonary emphysema.
- Definition and manifestations of status asthmaticus.

Important note: During the previous blocks, we noticed some mistakes just before the exam and we didn't have the time to edit the files. To make sure that all students are aware of any changes, please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: **Pathology Edit**

Introduction to Lungs.





Anatomy of the respiratory tract: ***Nose*** → ***Nasopharynx*** → ***Larynx*** → ***trachea*** divides to give the ***main bronchi*** → ***bronchioles*** (lacks cartilage and submucosal glands in their walls) → ***terminal bronchioles*** → ***respiratory bronchioles*** → ***alveolar ducts*** → *(Acinus)* ***alveolar sacs*** → ***alveoli***.

- Part of the nasopharynx is lined by **squamous epithelium**, while the lower portion of the respiratory tract is lined by **pseudostratified ciliated columnar epithelium** with **goblet cells** and **neuroendocrine cells**.

Histology of the alveoli:

- Alveolar epithelium contains a continuous layer of two principal cell types:
  - flattened, platelike **type I pneumocytes** covering 95% of the alveolar surface.
  - Rounded **type II pneumocytes** which synthesize **surfactant** and are the main cell type involved in repair of alveolar epithelium after damage to type I pneumocytes.
- The **capillary endothelium** and basement membrane.
- The **pulmonary interstitium** is composed of fine elastic fibers, small bundles of collagen, a few fibroblast-like cells, smooth muscle cells, mast cells, and rare mononuclear cells.
- Macrophages.

The lung is covered by two layers:

1. Parietal pleura → adjacent to the rib cage and muscles.
2. Visceral pleura → adjacent to the lungs.

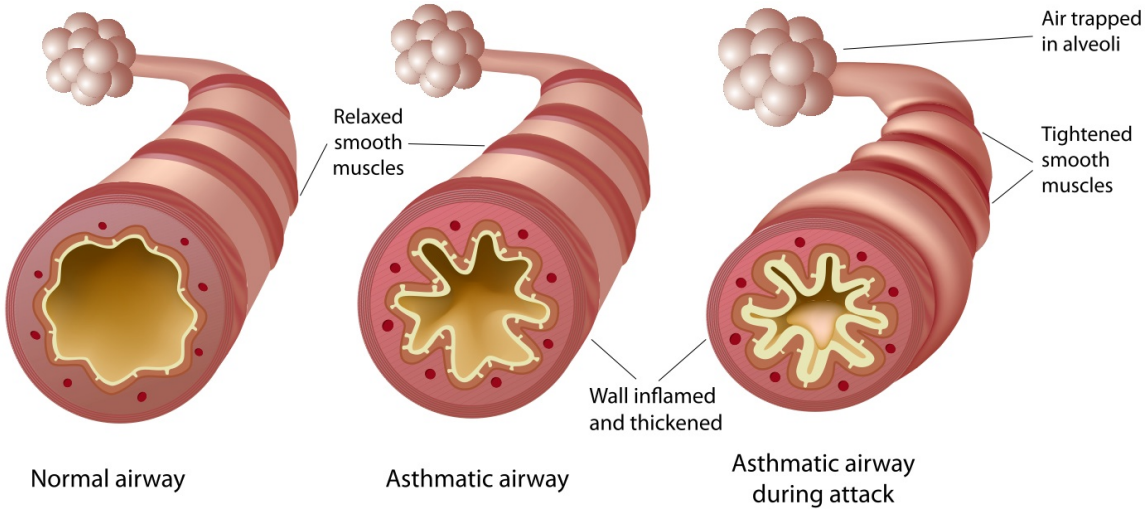
Between these two layers we have the **pleural cavity**, which contains 3-5 ml of fluid that may be used as a diagnostic tool. (E.g by aspiration).

Lung diseases are classified to:

- **Obstructive lung disease:** Patients have difficulties expiring air. E.g: bronchial asthma, emphysema, chronic bronchitis, and Bronchiectasis.
- **Restrictive lung disease:** Patients have difficulties inspiring air. Interstitial fibrosis is a good example.

Other lung diseases: Congenital lung disease (genetic, non-genetic), Infections, Inflammation, Neoplasia.

What is Asthma?



Asthma: is a chronic inflammatory disorder that causes recurrent episodes of attacks.

Connect to Pharmacology: The bronchial smooth muscles are controlled by M3 and Beta 2 receptors. An M3 agonist would cause bronchospasm, while a beta2 agonist will cause bronchodilation. In the pharmacology of asthma, the bronchospasm is treated by a beta2 agonist or by a muscarinic antagonist.

Hallmarks of the disease:

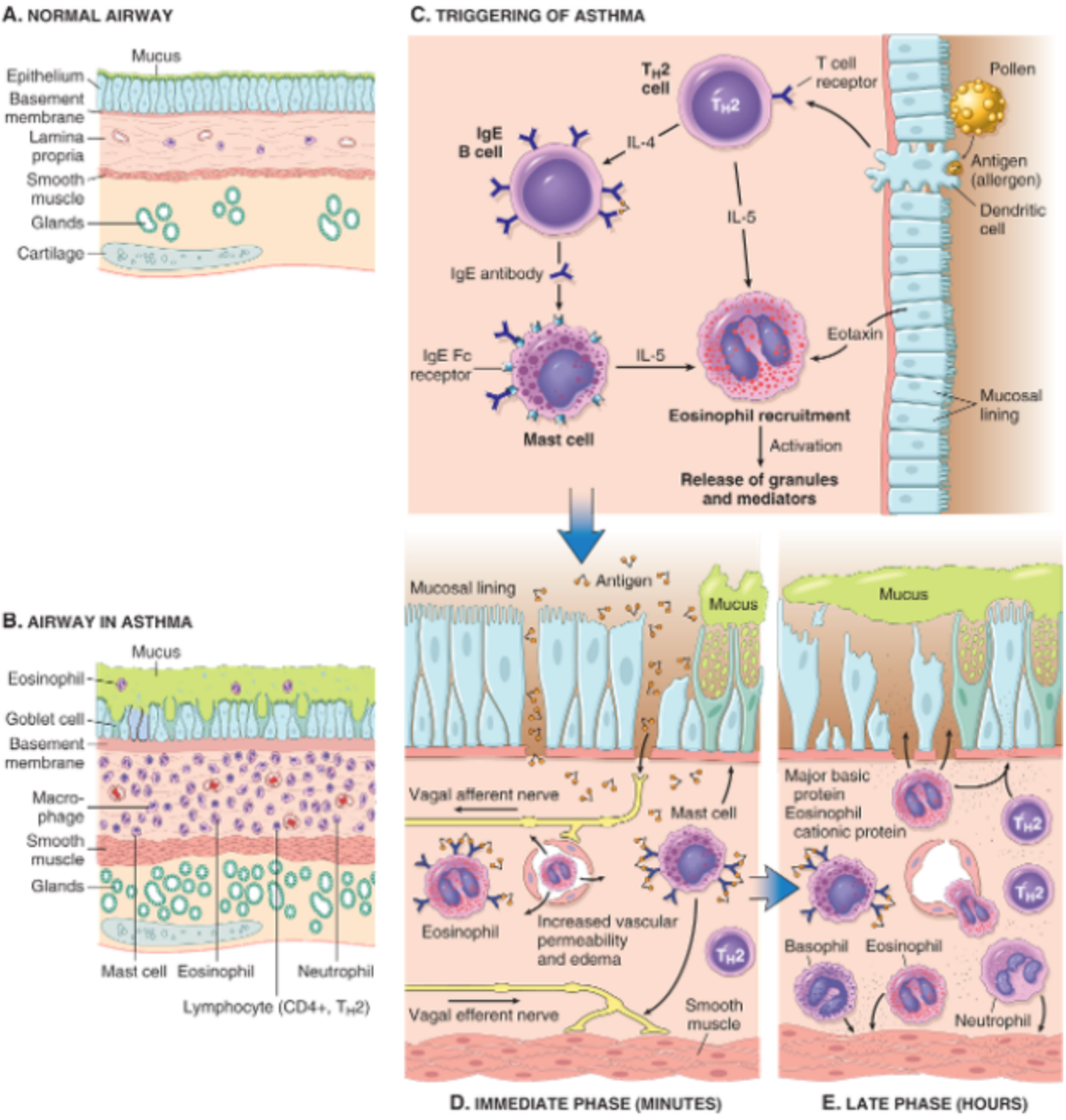
The hallmarks of the disease are: chronic **reversible airway obstruction**, chronic **bronchial inflammation with eosinophils**, bronchial smooth muscle **hypertrophy** and **hyper reactivity**, and **increased mucus** secretion.

Symptoms:

- Dyspnea[1].
- Wheezing [2] "because the lumen of the bronchi is narrowed"
- Dry cough.
- Tightness of chest.

[1] Shortness of breath
[2] High pitched whistling sound made when breathing.

Pathogenesis of asthma.



The major etiologic factors of asthma are:

1) Genetic predisposition to type **1 hypersensitivity.**
2) Acute and chronic airway inflammation.
3) Bronchial hyperresponsiveness to a variety of stimuli.

The inflammation involves many cell types and inflammatory mediators, but the excessive reaction of **type 2 helper T (T_H2) cells** is very important in the pathogenesis of asthma. When environmental antigen enters the tissue **T helper 2 cells** (Th2) produces:

1. **IL-4** → IgE production.
2. **IL-5** → activates eosinophils which play a major part in the pathogenesis of asthma. Because they produce basic proteins, which cause asthma and damage bronchial wall and incite inflammation and induce contraction of bronchial smooth muscles.
3. **IL-13** → mucus production.

What happens after IgE & eosinophils are produced?
The same old story: IgE attaches to mast cells and causes sensitization. After that, at **a second exposure**, the antigen attaches to the sensitized mast cell causing degranulation of its contents. After the degranulation of mast cells, different molecules are produced. The reaction occurs in two phases:

Please note that these phases are not completely separate, you should think of phase 1 as how the reaction starts, and think of phase 2 as how does the reaction ends. These two stages overlap.

1) **Phase1: the early stage:**
   - Bronchoconstriction
   - Increased mucus production
   - Vasodilation

2) **Phase2: the late phase:**
   - Inflammation with eosinophils, neutrophils, and T cells.
   - Epithelial cells produce chemokines that attract more Th2 cells and worsen the inflammatory process.

Connect to pharmacology: The management of asthma depends on bronchodilators at the early phase of this disease and steroids at the late phase. Bronchodilators include Beta2 adrenergic agonists or M3 cholinergic antagonists. Steroids are potent anti-inflammatory agents that are used to stop the inflammatory process during the late phase.

- These repeated attacks lead to changes in the bronchial wall, known as **airway remodeling**.
- Airway remodeling includes **bronchial smooth muscle** and **mucous glands** **hypertrophy**, and increased deposition of **collagen**.
- Finally, we will just point out that there are some genes that may make the patient susceptible to asthma. One of these genes is found on **chromosome 5**. This gene is responsible of the production of IgE in many ways. As you would imagine, a person overexpressing this gene would definitely be susceptible to asthma.

Types of asthma.

1) **Extrinsic (Atopic asthma)**
   - **Mediated by IgE and is a classic example of type 1 hypersensitivity.**
   - Usually begins in childhood and a positive family history is common (congenital).
   - **Most common** type of asthma.
   - The asthma attacks are usually **preceded by allergic issues** such as allergic rhinitis or eczema.
   - The disease is triggered by environmental antigens such as pollens or whatever. So the best treatment is to avoid the triggers

How it is diagnosed?

a) **Skin prick test** with the antigen causes an immediate reaction.
b) **Serum radioallergosorbent** (I dare you to read this word five times in a row) test. Shortly known as **RASTs**. This test identifies IgE for specific allergens..

2) **Intrinsic (non-atopic asthma)**
   - This type does not have evidence of allergy.

Extra information: if this type is not allergic, does it share the same pathogenesis we have talked about?
Quote from Robbins Basic Pathology, Ninth edition, page 470, second line, fourth word: "*Although the connections are not well understood, the ultimate humoral and cellular mediators of airway obstruction (e,g, eosinophils)* ***are common to both atopic and nonatopic asthma****, so they are treated in the same way.*" So yes, they have a similar pathogenesis.

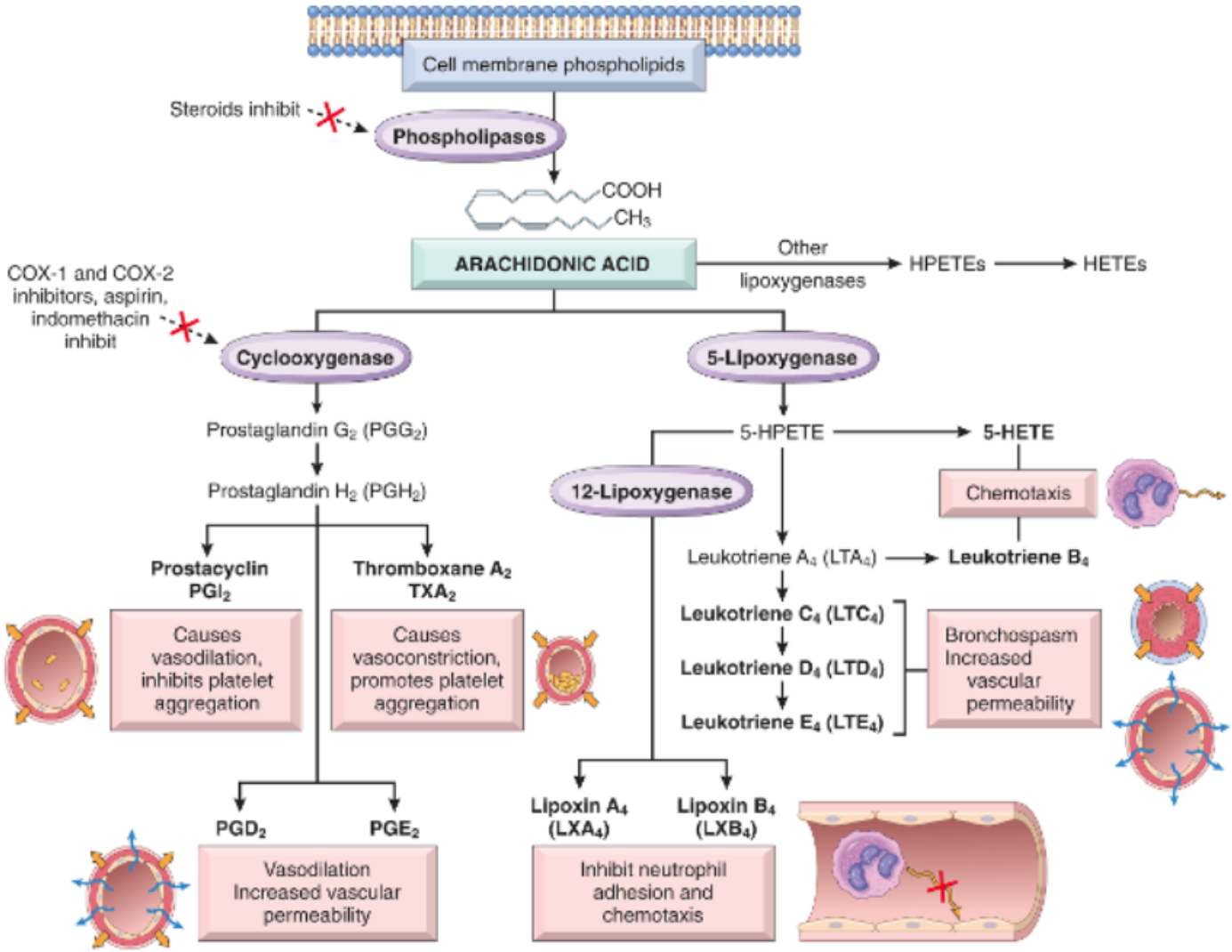
3) **Drug induced asthma**

NSAIDs, and especially **aspirin** may provoke asthma.

Connect to pharmacology: There are two questions that come up to us regarding this matter.

a) What is the mechanism of drug induced asthma?
Let us go back to the mechanism of action of NSAIDs. Arachidonic Acid may be metabolized by cyclooxygenase (COX) or lipooxygenase (LOX). Using NSAIDs, we block COX to eliminate the production of prostaglandins that are pyretic agents and cause pain. When we block COX, where does all of the Arachidonic Acid go to? It goes to LOX. Recall that LOX produce Leukotrienes B4,C4, & D4**. Leukotrienes C4 & D4 cause bronchospasm** and they are related to SRSA. SRSA is the Slow Reacting Substance of Anaphylaxis.

b) Why especially aspirin?
Because aspirin irreversibly binds to COX and Arachidonic Acid can't compete with it on the active site of COX.



4) Exercise Asthma.

5) Occupational Asthma.
Stimulated by fumes, dusts, and other chemicals.

Clinical features.

- Asthma attacks are characterized by severe **dyspnea** and **wheezing**.
- Status **asthmaticus** is a severe attack of asthma which may last for days. it is a medical emergency. This is a severe episode of asthma symptoms and lasts for long periods of time. The patient as a result of this becomes hypoxic. Hospital care is necessary [3]because this condition may be fatal.
- As an **obstructive disease**, the problem is with expiring air out of the lungs.

***Connect to physiology*:** The text is just to help you understand but what you need to know is written in the conclusion.

- **FEV1:** Forced Expiratory Volume in one second: It is the amount of air the subject can blow in one second. What do you think would happen with this number in asthma?
- Well, since it is an obstructive disease, there must be problems with air coming out of the lung. This will make the patient able to expire less air. Thus, **FEV1 will be decreased**.
- **FVC:** Forced Vital Capacity: this is the total lung volume – residual volume. In patients with obstructive lung disease, there is no problem with the amount of air in the lungs. In fact, there may be an increase in the amount of air in the lung because when the patient can't exhale the air, it will stay inside the lung causing hyper inflation. FVC **will be normal or slightly increased**.
- **PEF:** Peak Expiratory Flow: This is the ratio between FEV1/FVC. Since FEV1 is decreased, and FVC is normal or increased, the ratio between them would be **lower than normal**.

Conclusion: In COPD and asthma patients, FEV1 is less, FVC is normal or increased, and PEF is lower than normal.

Histological findings.

Histological findings of the sputum (on a histological slide):

- **Curschmann spirals:** collection of mucus with a special shape.
- **Charcot Leyden crystals:** something that looks like crystal but made up of eosinophil protein.
- Large numbers of **eosinophils** (especially in atopic asthma).

Findings after autopsy:

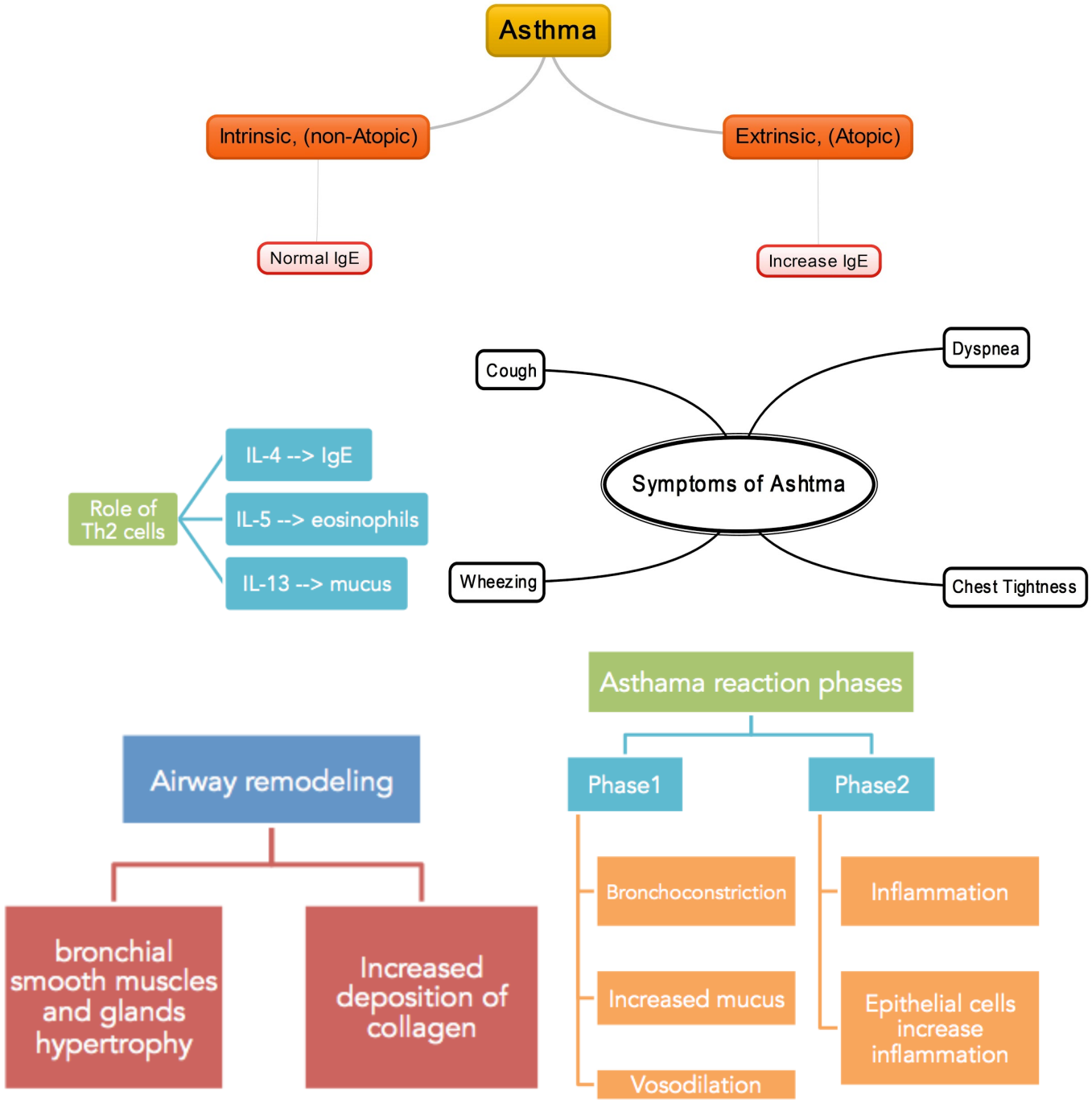
- Increased goblet cells
- Hyperplastic smooth muscles
- Fibrosis of the basement membrane (in severe forms of asthma)

Complications of the disease:

- Mucus plugs are favorable places for bacterial growth. Thus, patients may become at **increased risk of infections. Secondary infection "secondary bronchitis"**
- **Secondary emphysema**
- Pneumothorax: collection of air in the pleural cavity. Possibly caused by the infections we have just talked about.
- We talked about airway remodeling and status asthmaticus and how it may be life threatening.

[3] Is a must

Summary.



- **Genetic susceptibility chromosome 5.**

MCQ's.

1- What are the most common bronchial asthma symptoms?
a)Tightness of chest, dyspnea and shortness of breath
b)Wheezing with cough
c)High grade fever with cough
d)Both a and b

2-Which of the following best describes asthma?
a)Autoimmune disease
b)An infectious disease
c)An atopic disease
d)A malignant disease

3- Which of the following results are most probably of an asthmatic patient?
a)Productive cough
b)Allergy against pollens
c)Elevation of FEVI and FEVI\VC ratio in the Pulmonary Function Test (PFT)
d)Presence of Curschmann spirals in sputum.

4- What is the classic pathological feature of asthma?
a)Worsening in warm weather
b)Bronchial hyperreactivity
c)Weakened tracheal cartilage
d)Loss of surfactant

5-Which of the following is NOT a feature of asthma?
a)Bronchial smooth muscle hypertrophy
b)Mucus plugs
c)Toxic tubular injury
d)Reversible bronchospasm

6-Asthma is a hereditary disease:
a)True
b)false
c)True in some cases
d) False in some cases

7- Which of the following explains the pathogenesis of atopic asthma?
a)IgG mediated disease
b)IgA mediated disease
c)IgE mediated disease
d)T-cell mediated disease

8- Which of the following interleukins is responsible of activation and stimulation of eosinophils in asthma pathogenesis?
a)IL-5 b)IL-3 c)IL-4 d)IL-13

10-Which of the following is the best diagnostic tool of asthma?
a)Chest x-ray
b)Sputum culture
c)Pulmonary function test
d)Complete blood count

11-Non allergic asthma most commonly:
a)Arise in childhood
b)Arise in late ages

12- A 18 year old female patient came to the ER with shortness of breath. Her mother said that she was taking painkillers for her dysmenorrhea her medical student friend told her about. She took a couple of tablets two hours ago.Clinical examination revealed wheezing sounds upon breathing. What is the underlying mechanism of her presenting symptoms?
a) Decreased production of PGE2
b) Bronchospasm due to autonomic activity of the drug
c)Pharmacologic competition with arachidonic acid
d)Excessive blood loss leading to shock

13- A 15 year old female came to the clinic for routine check up. History taking revealed that she was taking a drug for her xerostomia (dry mouth). The patient explained that she was feeling some discomfort while breathing. The patient also pointed out that her brother has asthma. How can the drug she takes contribute to asthma?
a) Excessive saliva may enter the lungs and increase mucus
b)The drug stimulates Th2 cells and may increase IL production
c) The drug exhibits an beta2 antagonist effect
d) The drug exhibits a muscarinic agonist effect

Answers & explanation.

1) D
2) C → it is an atopic disease. If you answered a, remember that an autoimmune disease is the body reacting to its own tissues. In autoimmune diseases, the antigen is from the same body. This is not the case with asthma as the antigen isn't from the body.
3) D → You could argue that B may be the answer, but we believe that D is more specific for asthma. An allergy to pollens may be a simple rash for example.
4) D
5) C
6) Both C & D are correct.
7) C
8) A
9) A
10) C → if you answered B check again because culturing is for infections. If you have answered D, CBC would be helpful to detect elevated eosinophils for example. However, it is extremely non specefic. The best answer is using PFT.
11) B

12) C → NSAIDs are commonly used for dysmenorrhea. NSAIDs compete with AA on the same receptor (pharmacologic antagonist). It specifically competes on COX enzymes. Increased leukotriene production may have contributed to this patient's symptom of shortness of breath or asthma attack. If you have anwered A, it is correct that NSAIDs decrease PGE2 production but it has nothing to do with the asthma attack she is having. If you have answered B, you must know that autonomic means related to sympathetic or parasympathetic actions. NSAIDs don't work on these. If you have answered D, please note that normal blood loss during the menstrual cycle is 20-60 ml and it is not significant and shouldn't lead to hypovolemic shock (around 1 liter).

13) D → Xerostomia usually occurs due to Sjogren syndrome. A muscarinic agonist, namely cevimeline, is given for such patients to increase salivation. Drugs given for Sjogren syndrome (xerostomia) are usually M3 selective because we don't want them to act on the heart (M2) or the gastric acid secretions (M1). However, M3 receptors are still found on the Eye (stimulation = miosis and accommodation, antagonist such as atropine causes mydriasis and cycloplegia). Anyways, M3 receptors are also found in the lungs and stimulation of M3 receptors causes bronchospasm. This is why the best answer is D. If you have answered C, you are on the right track but you have missed the context of the question. Beta 2 antagonists definitely cause bronchospasm but in the context of this question, a beta 2 antagonist will not help in xerostomia. If you have anwered A, good job in realizing that the drug used is an M agonist and increases saliva production. However, the salival would enter the GI and not the respiratory system due to the glottis

More questions.

1. COPD is a group of diseases characterized by ?
Airflow obstruction , decrease in forced expiratory volume (FEV1).

2.Restrictive pulmonary diseases (RPD) is a group of diseases characterized by ?
Reduce lung capacity due to either chest wall or skeletal abnormalities.

3. Which antibody involve in extrinsic asthma ? And which type of reaction is mediated by ?
IgE, type 1 hypersensitivity reaction.

4. What is the most common type of asthma ?
Atopic (extrinsic).

5. Which test use to diagnosis of atopic asthma ?
Radioallergosorbent (RAST) & skin prick test.

6.What is the clinical features of asthma ?
Severe dyspnea, wheezing, difficulty in expiration.

7. What does the sputum contain histologically ?
Curschmann spirals, numerous eosinophils and charcot leyden crystals (collection of crystalloid made up of eosinophil protein).

8. How do we know the charcot leyden crystals came from the lung or not ?
If there is alveolar macrophage that's mean it is from the lung.

9. what is the airway remodeling ?
Sub-basement membrane thickening and hypertrophy of bronchial glands and smooth muscles.

10. Why aspirin can cause asthma ?
Aspirin inhibit the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxygenase route , thereby shifting the balance of production toward leukotriene like (C4, E4, D4) and that cause bronchospasm

11- what is the characteristics of asthma ?
asthma is chronic inflammatory disorder characterized by coughing, wheezing, breathlessness

12. In sputum histology test of asthmatic patient what we should see ?
Eosinophil, thickened mucosa

13. Why status asthmaticus lead to the death ?
because it's associated with acidosis, hypercapnia (increase CO2 level), and severe hypoxia

14. which viruses can cause intrinsic (non atopic) asthma ?
Parainfluenza virus, and rhinovirus

Contact us on: Pathology434@gmail.com
Twitter: **@Pathology434**

Good Luck!

محمد الخراز
مها الربيعة
عمر الرهبيني
سارة محمد الجاسر
رزان الصبحي
حسين الكاف