بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

PATHOLOGY

MID | Lecture 3

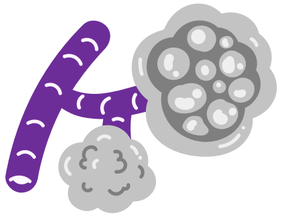
Asthma and Bronchiectasis

Written by: Moawyah Alzghoul
Abdalrahman Qatatsheh

Reviewed by: Mahmoud Aljunaidi

﴿ وَلَقَدْ نَعْلَمُ أَنَّكَ يَضِيقُ صَدْرُكَ بِمَا يَقُولُونَ ﴿٩٧﴾ فَسَبِّحْ بِحَمْدِ رَبِّكَ وَكُن مِّنَ السَّاجِدِينَ ﴾

سبحان الله وبحمده، سبحان الله العظيم



بسم الله الرحمن الرحيم، هذا الملف كتب بنية الأجر لزميلنا عمر عطية عودة المرابي نسأل الله أن يتغمده بواسع رحمته وأن يثبته عند السؤال وأن يصبر أهله ويربط على قلوبهم.
الله يرحمك يا عمر ويجعل مثواك الجنة.

قال تعالى:"﴿ يَا أَيُّهَا النَّاسُ اتَّقُوا رَبَّكُمْ وَاخْشَوْا يَوْمًا لَّا يَجْزِي وَالِدٌ عَن وَلَدِهِ وَلَا مَوْلُودٌ هُوَ جَازٍ عَن وَالِدِهِ شَيْئًا ۚ إِنَّ وَعْدَ اللَّهِ حَقٌّ ۖ فَلَا تَغُرَّنَّكُمُ الْحَيَاةُ الدُّنْيَا وَلَا يَغُرَّنَّكُم بِاللَّهِ الْغَرُورُ (33) إِنَّ اللَّهَ عِندَهُ عِلْمُ السَّاعَةِ وَيُنَزِّلُ الْغَيْثَ وَيَعْلَمُ مَا فِي الْأَرْحَامِ ۖ وَمَا تَدْرِي نَفْسٌ مَّاذَا تَكْسِبُ غَدًا ۖ وَمَا تَدْرِي نَفْسٌ بِأَيِّ أَرْضٍ تَمُوتُ ۚ إِنَّ اللَّهَ عَلِيمٌ خَبِيرٌ (34)﴾"
- سورة لقمان

اللهم لا تقبض أرواحنا إلا وأنت راضٍ عنّا ولا حول ولا قوة إلا بالله.

ادعوا له، رحمه الله وغفر له وأسكنه فسيح جناته.

دعاء عن روح الزميل الراحل

III- ASTHMA

https://pixy.org/1266846/

III. ASTHMA

- Chronic inflammatory disorder of the airways

- Causes recurrent episodes of **wheezing**, **Dyspnea**, **chest tightness and cough** particularly at **night** and/or **early in the morning.**

Asthma, its hallmarks are:

1. **Intermittent and reversible** airway obstruction (**bronchospasm**, that is neither continuous nor permanent)
2. Chronic bronchial **inflammation** with **eosinophils**.
3. Bronchial **smooth muscle cell hypertrophy and hyper-reactivity**.
4. Increased **mucus secretion**.

MAJOR FACTORS:

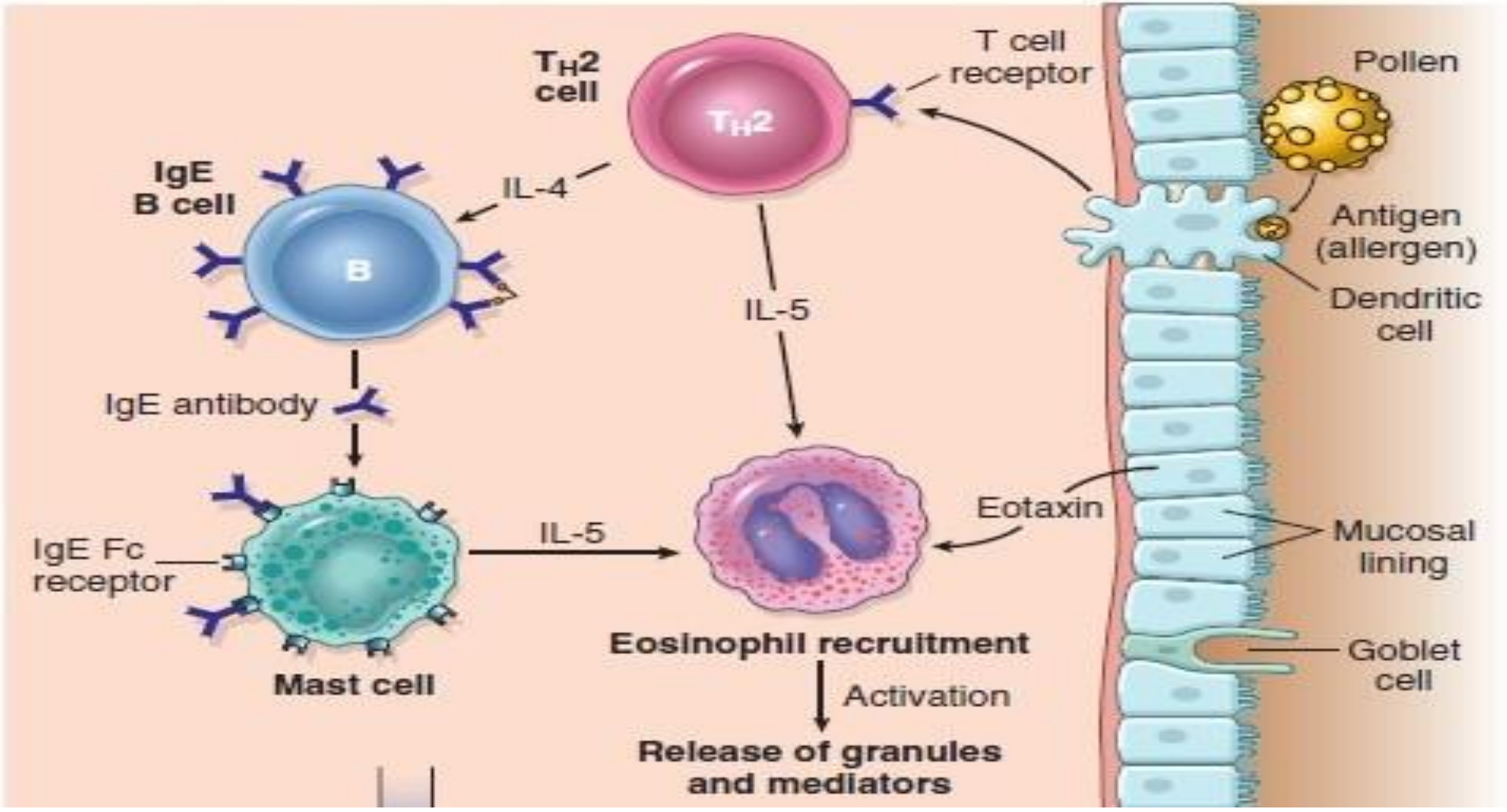
- ✓ **Genetic predisposition** to type I hypersensitivity (atopy).
- ✓ Acute and chronic **airway inflammation.**
- ✓ Bronchial hyper-responsiveness to a variety of stimuli.

CAN BE TRIGGERED BY:

- Respiratory **infections** (especially viral).
- Airborne **irritants** (smoke, fumes).
- **Cold air.**
- **Stress.**
- **Exercise.**

PATHOGENESIS

سبحان الله


C TRIGGERING OF ASTHMA
T_H2 cell
T_H2
T cell receptor
Pollen
IgE B cell
B
IL-4
Antigen (allergen)
Dendritic cell
IL-5
IgE antibody
IgE Fc receptor
IL-5
Eotaxin
Mucosal lining
Goblet cell
Mast cell
Eosinophil recruitment
Activation
Release of granules and mediators

Pathogenesis

❖ Initial airway response after the **first exposure** to an inhaled allergen:

1. The allergen will be recognized by an Antigen Presenting Cell (**Dendritic cells**) in the epithelial lining.

2. As a results, **TH2** lymphocytes will be activated, releasing several cytokines, leading to **B-cell** activation and subsequent IgE production through **IL-4** and **IL-13** action, **eosinophils** activation and recruitment via **IL-5**, increased mucus production and secretion through **IL-13**.

3. IgE antibodies coat the **submucosal mast cells**, and upon **re-exposure** of mast cells by the same allergen, two waves of rection happen:
   A. **Early or immediate reaction**.
   B. **Late reaction**.

The Early-Phase Reaction

A. The early-phase reaction is dominated by:

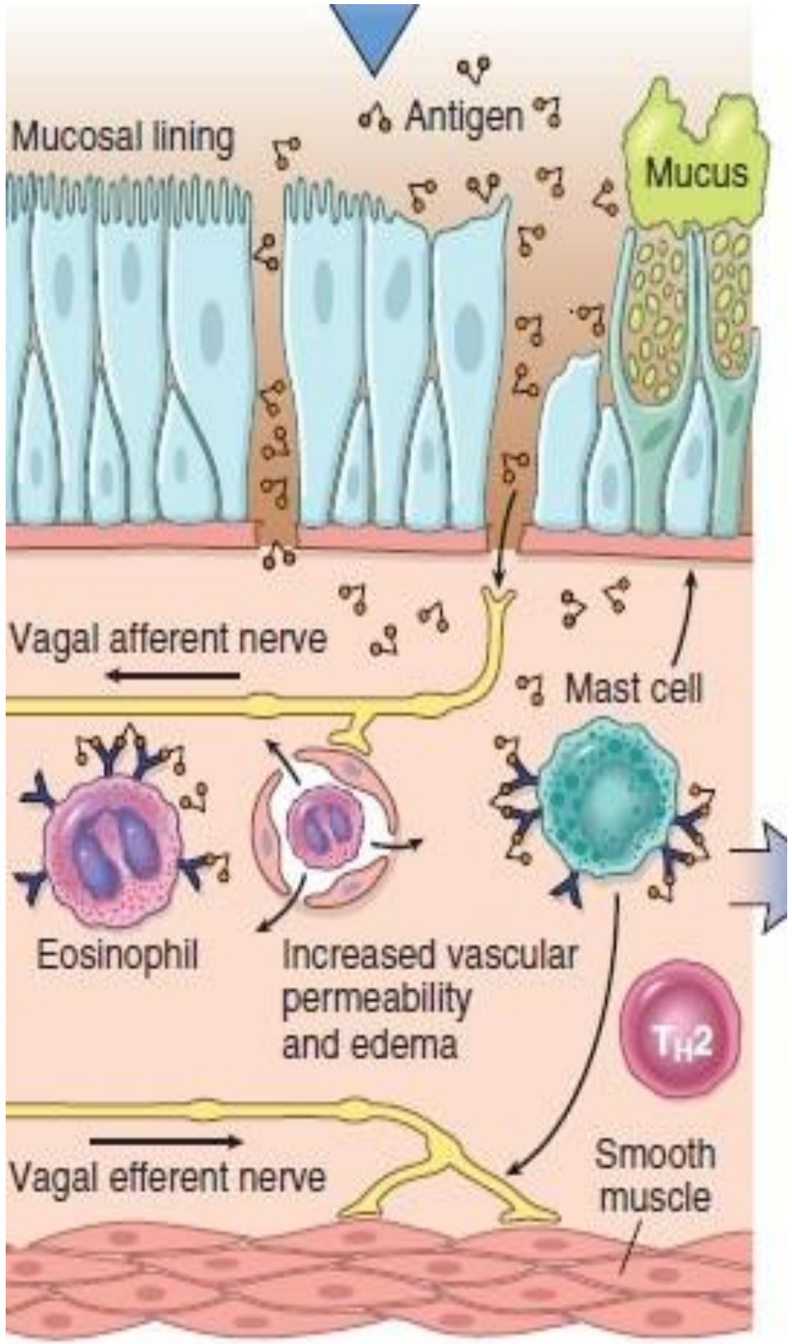
- **Bronchoconstriction**, triggered by histamine, prostaglandin D2, leukotrienes C4/D4/E4, as well as by the neural reflex pathways.
- **Increased mucus** production.
- **Vasodilation**.

The Early-Phase Reaction

- On **re-exposure** to antigen (ag) → immediate reaction

- Triggered by Ag-induced **cross-linking of IgE** bound to Fc receptors **on mast cells.**

- Mast cells **release** preformed **mediators** that directly and via neuronal reflexes **induce**:
  - Bronchospasm.
  - Increased vascular permeability.
  - Mucus production.
  - Recruitment of leukocytes.



D IMMEDIATE PHASE (MINUTES)

The Late-Phase Reaction

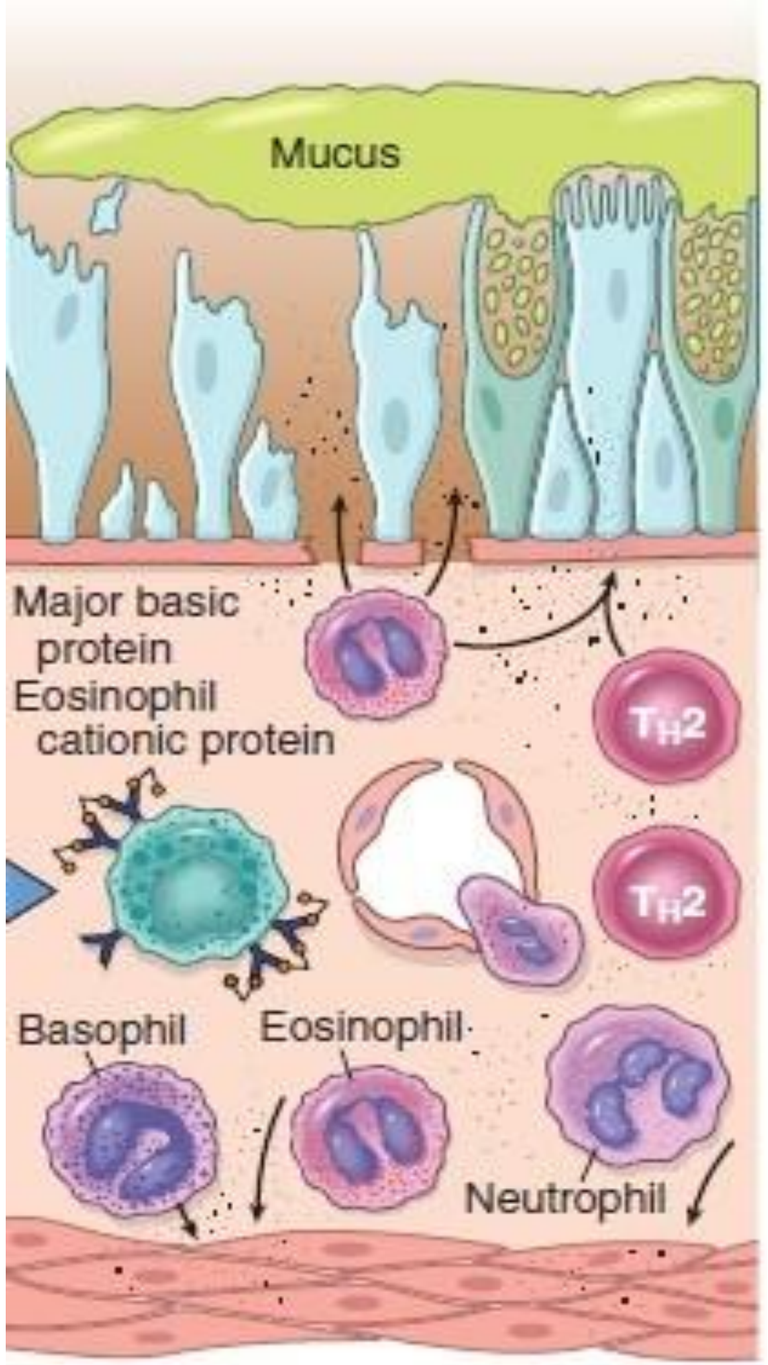
B. The late-phase reaction is inflammatory:

Inflammatory mediators → stimulate epithelial cells to produce chemokines (eotaxin, potent chemoattractant and activator of eosinophils) → recruit TH2 cells, eosinophils, and other leukocytes → amplifying the inflammatory reaction.

The Late-Phase Reaction

- **Leukocytes recruited** to the site of reaction (neutrophils, eosinophils, and basophils; lymphocytes and monocytes) **release mediators** → initiate the late phase of asthma.

➢ Eosinophils release **major basic protein** and **eosinophil cationic protein** that cause **damage** to the epithelium.



Pathophysiology of Airway Remodeling in Chronic Asthma; a late-phase sequela.

- **Repeated bouts of inflammation** lead to structural changes in the bronchial wall → called **airway remodeling**, including:
  - Hypertrophy of bronchial smooth muscle.
  - Hypertrophy of Mucus glands.
  - Increased vascularity.
  - Deposition of subepithelial collagen.

Morphological Characteristics of the Asthmatic Airway

Increased number of **mucus-secreting goblet cells.**
Hypertrophy of submucosal glands.
Accumulation of mucus in the bronchial lumen.
Thickened basement membrane.
Intense chronic **inflammation** composed of cells depicted in the image below.
Hypertrophy and hyperplasia of smooth muscle cells.

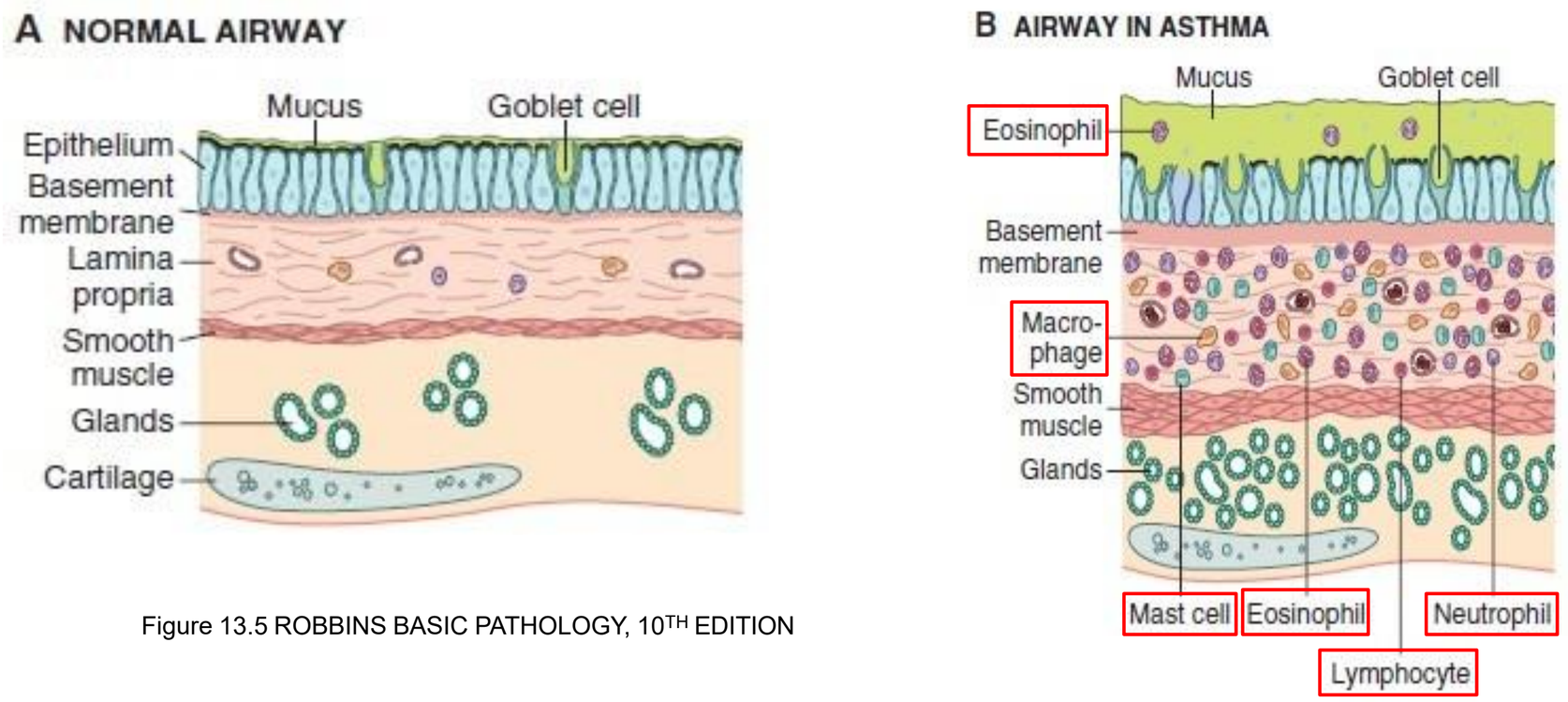
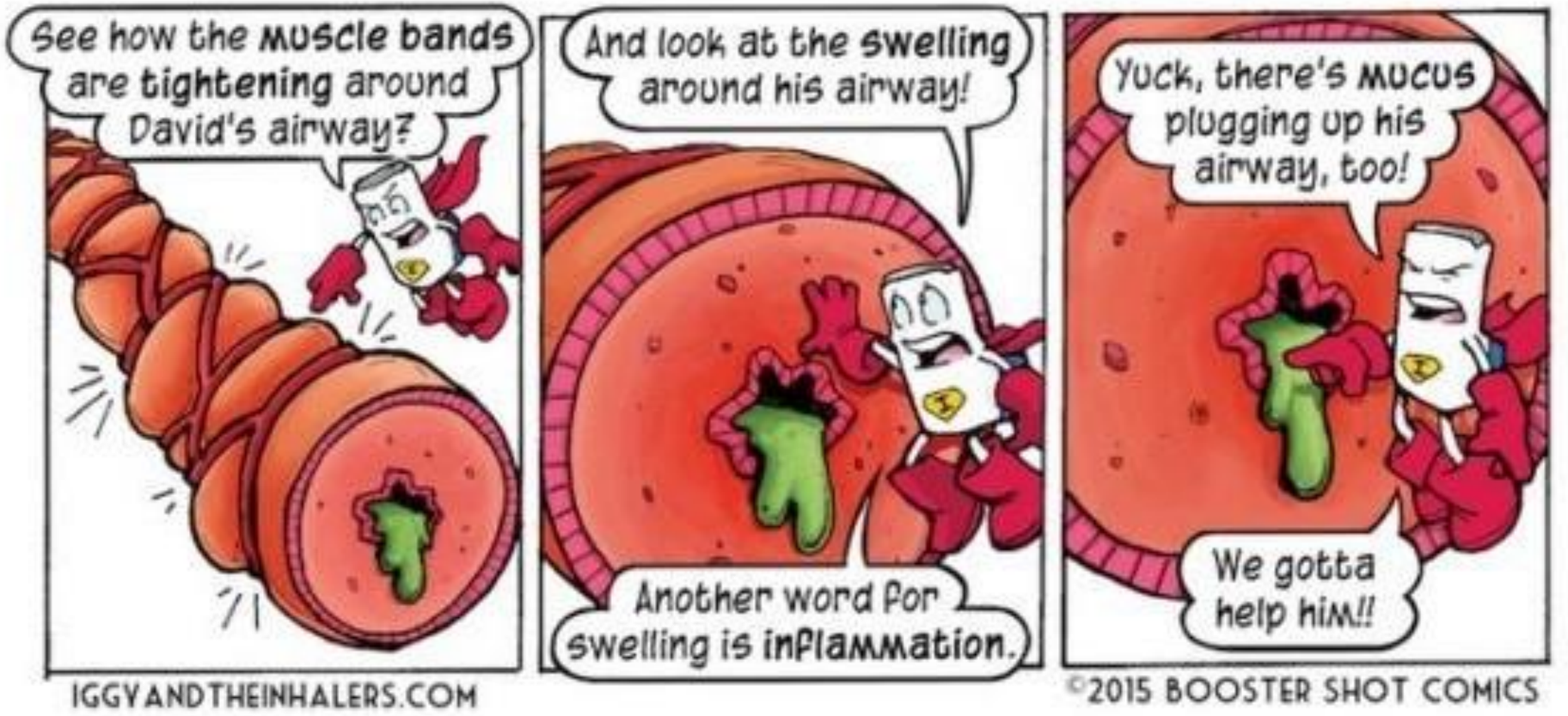


Figure 13.5 ROBBINS BASIC PATHOLOGY, 10TH EDITION



https://anonhq.com/doctor-creates-animation-videos-comic-books-make-asthma-less-scary-kids/

TYPES OF ASTHMA

لا إله إلا الله وحده لا شريك له

1- ATOPIC ASTHMA:

- The **most common**.
- Classic example of **type I IgE–mediated hypersensitivity** reaction.
- Beginning in **childhood**.
- **Positive family history** of atopy and/or asthma attacks are preceded by allergic rhinitis, urticaria, or eczema.
- Attacks are **triggered by allergens** in dust, pollen, animal dander (material shed by furry or feathered animals), or food, or by infections.

Immunopathogenesis of Atopic Asthma: Sensitization and Response

- The initial exposure to the antigen → **excessive activation** of type 2 helper cells (T_{H2}) → Cytokines production:
  - **IL-4** and **IL-13** stimulate **IgE production**.
  - **IL-5** activates **eosinophils**.
  - **IL-13** also stimulates **mucus production**.

- IgE coats submucosal mast cells → release of Mast cell– derived mediators upon re-exposure → produce two waves of reaction:
  A. Early (immediate) phase of reaction.
  B. Late phase of reaction.

ATOPIC ASTHMA: Diagnosis

1. **Skin test with the antigen**: immediate wheal-and-flare reaction:
   - "Skin prick test" is the most common allergy skin test used in the clinic.
   - A series of tiny drops of the **allergen** are placed on patient's back or hand, then a **needle prick** is introduced in the skin beneath each drop, if the patient is **allergic**, he/she will get **red and itchy rash** especially at the skin prick sites, otherwise, nothing happens.

https://www.alpfmedical.info/causative-agent/type-i-hypersensitivities-immediate-igemediated.html

2. **Serum radioallergosorbent tests** (RASTs): a blood test using radioimmunoassay to detect specific IgE antibodies, to determine the substances a subject is allergic to.

2- NON-ATOPIC ASTHMA:

- **No evidence of allergen sensitization.**
- **Negative** skin test, unlike **atopic** asthma.
- A positive **family history** of asthma is **less common**.
- Triggered by:
  - **Viral respiratory infections** (rhinovirus, parainfluenza virus).
  - **Inhaled air pollutants** (sulfur dioxide, ozone, nitrogen dioxide).

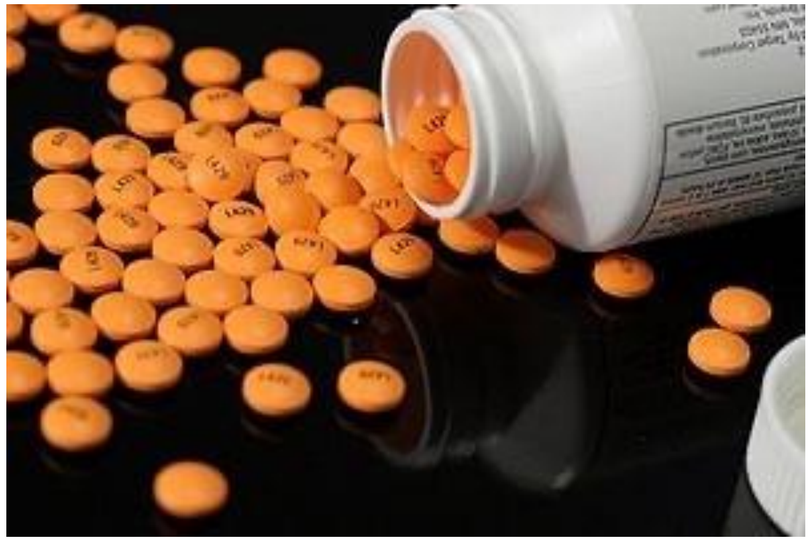
✓ Although the connection between these exposures and non-atopic asthma is still not well-understood, the ultimate **humoral and cellular mediators** of airway obstruction are the **same** in both atopic and non-atopic variants, so they are **treated in a similar way.**

3- DRUG-INDUCED ASTHMA:

- Eg: Aspirin induced asthma:

  Patients with aspirin hypersensitivity present with recurrent rhinitis, nasal polyps, urticaria, and bronchospasm.

- The **precise pathogenesis is unknown,** but may involve some **abnormality in prostaglandin metabolism** from inhibition of cyclooxygenase by aspirin.



https://en.wikipedia.org/wiki/Aspirin_exacerbated_respiratory_disease

4- OCCUPATIONAL ASTHMA:

- **Triggered** by **fumes** (epoxy resins, plastics), animal substances, **organic and chemical dusts** (wood, cotton, platinum), **gases** (toluene), and other chemicals.
- Farmers, animal handlers, manufacturers of foam mattresses, bakers, food processors, cotton workers and manufacturers of metals, are all at risk of developing this type of asthma.
- Asthma attacks usually **develop after repeated exposure to the antigen.**

https://www.hopkinsmedicine.org/health/conditions-and-diseases/asthma/occupational-asthma

MORPHOLOGY

سبحان الله وبحمده
سبحان الله العظيم

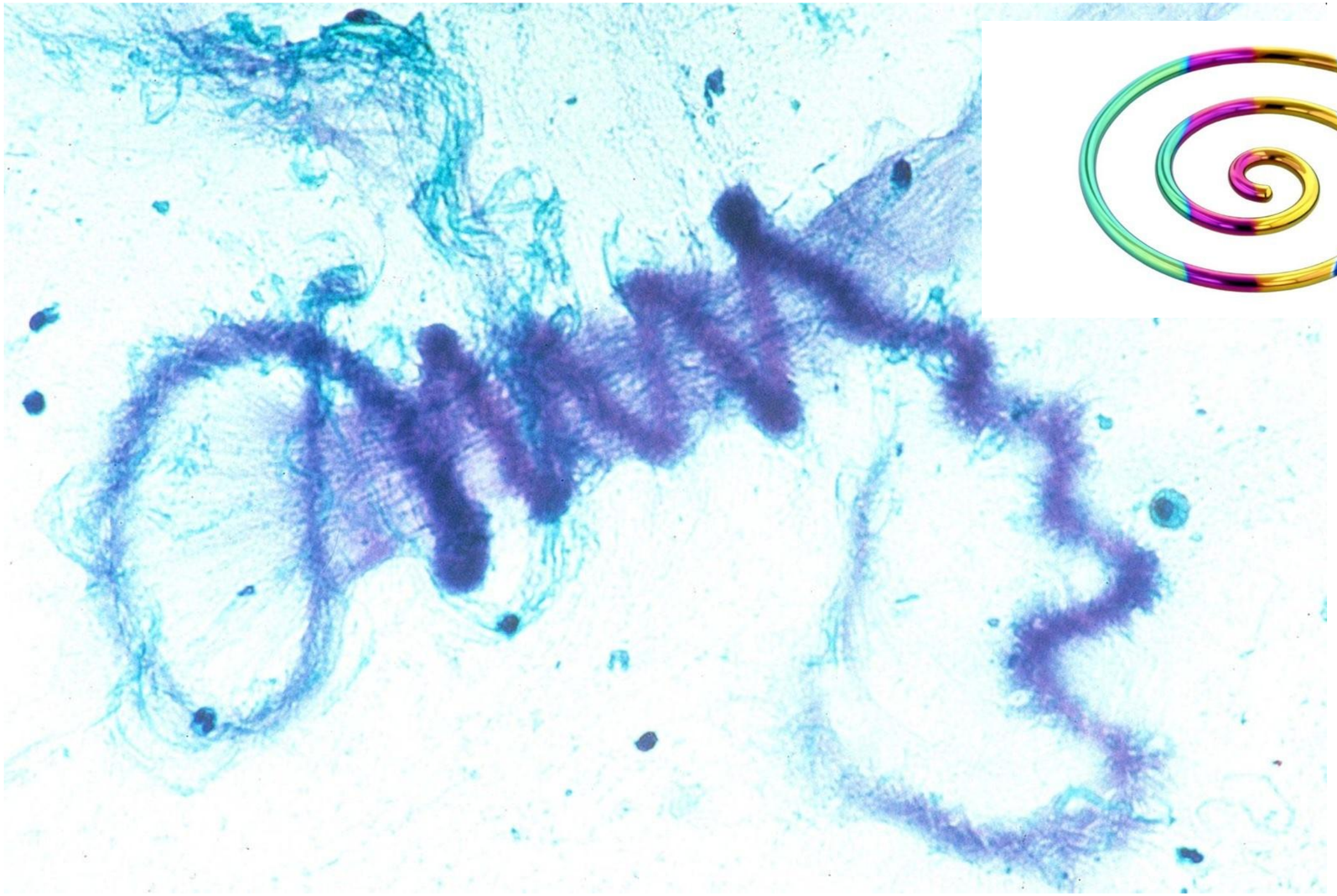
MORPHOLOGY

- Occlusion of bronchi and bronchioles by **thick mucous plugs.**
- Mucous plugs contain **whorls of shed epithelium** called **Curschmann spirals.**

https://www.nikonsmallworld.com/galleries/199-photomicrography-competition/curschmanns-spiral-in-sputum-specimen

MORPHOLOGY

Curschman Spirals in sputum



https://anatometal.com/jewelry/spirals/

https://www.nikonsmallworld.com/galleries/1996-photomicrography-competition/curschmanns-spiral-in-sputum-specimen

MORPHOLOGY

Fig. 13.11 Bronchial biopsy specimen from an asthmatic patient showing:

- **Sub-basement membrane fibrosis** marked by the yellow star.
- **Eosinophilic inflammation marked by red star**.
- **Smooth muscle hyperplasia and hypertrophy** marked by the green arow.

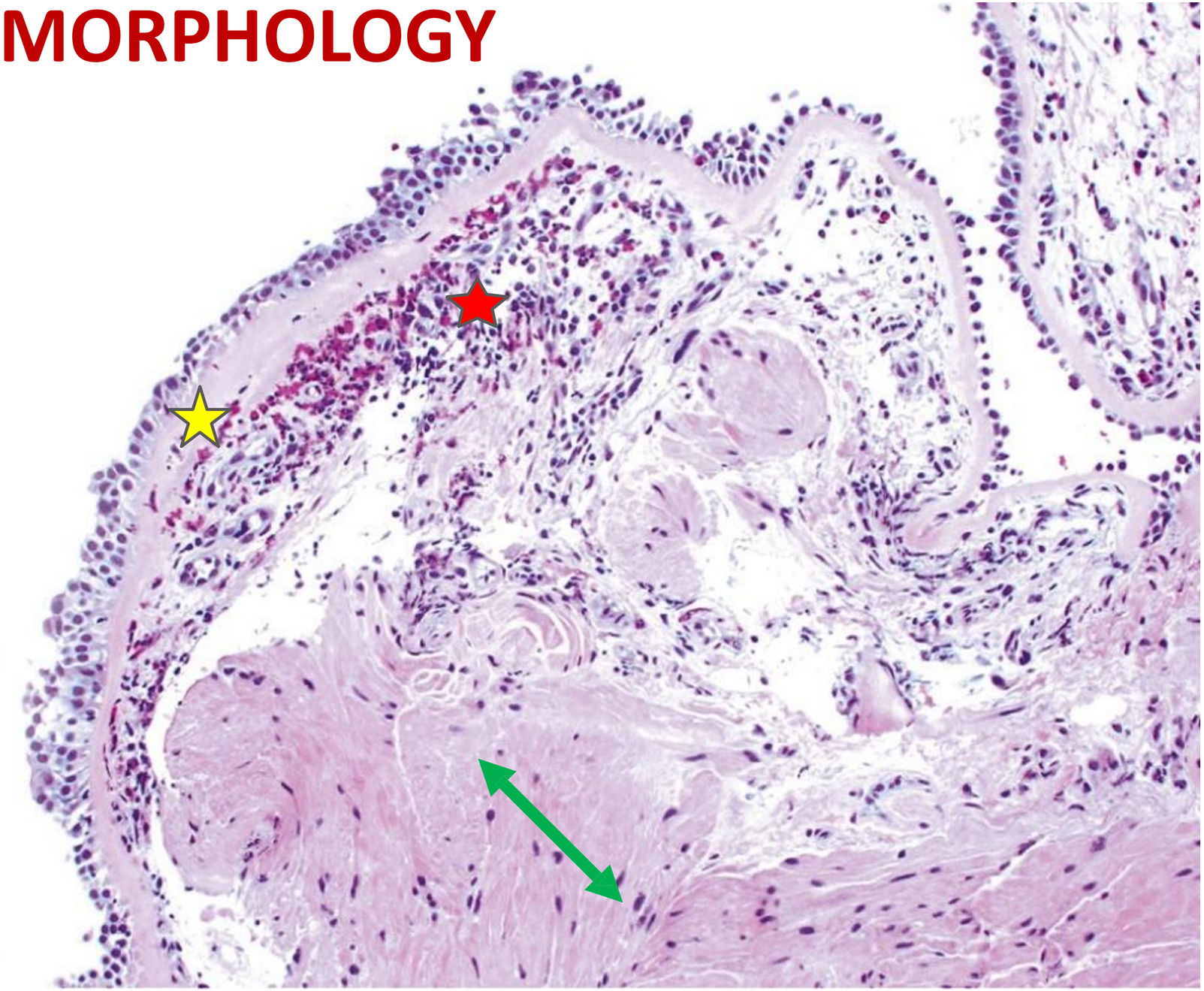
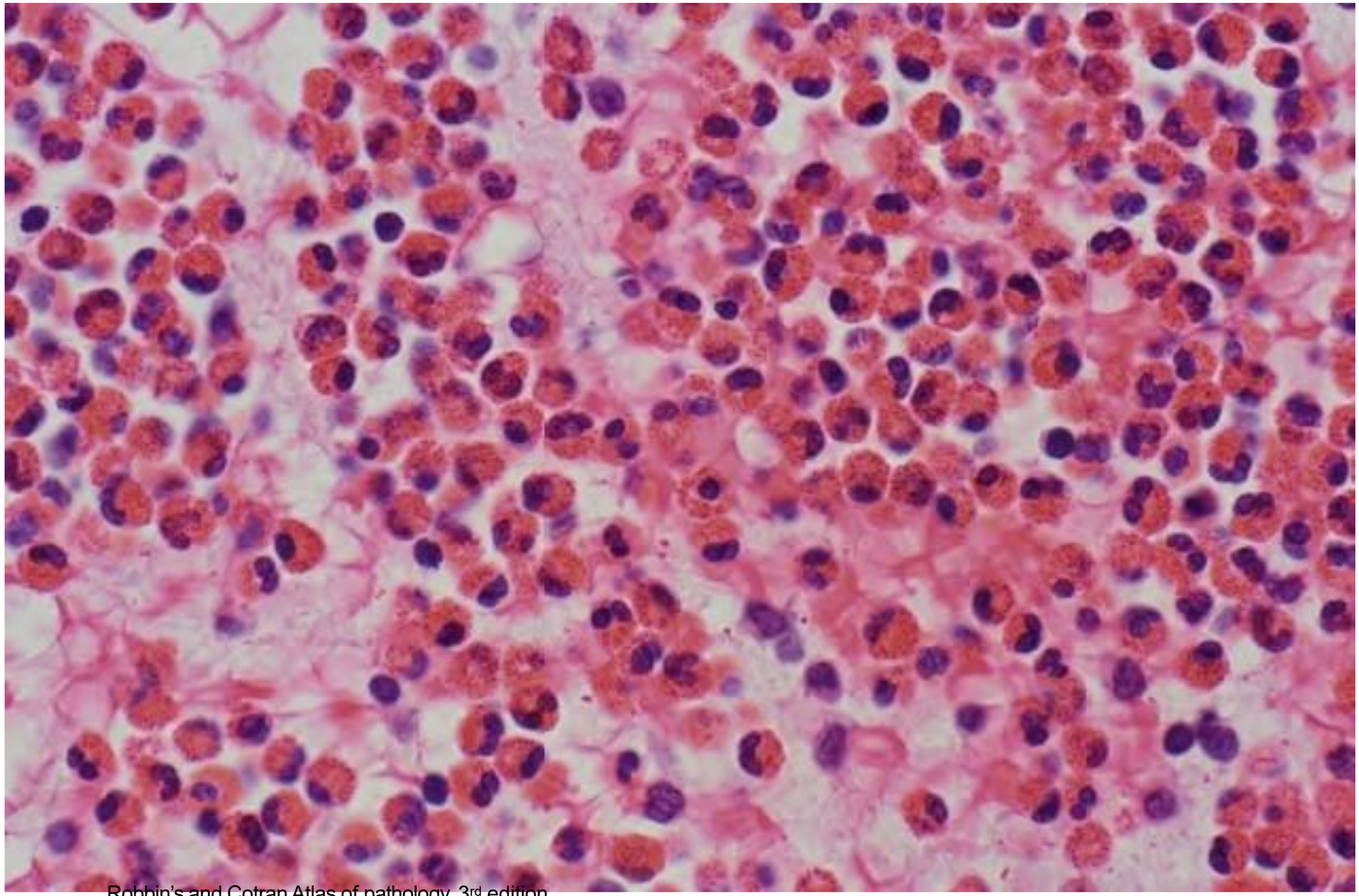


Figure 13.5 ROBBINS BASIC PATHOLOGY, 10TH EDITION

- Eosinophils are the characteristic inflammatory cells in asthma.

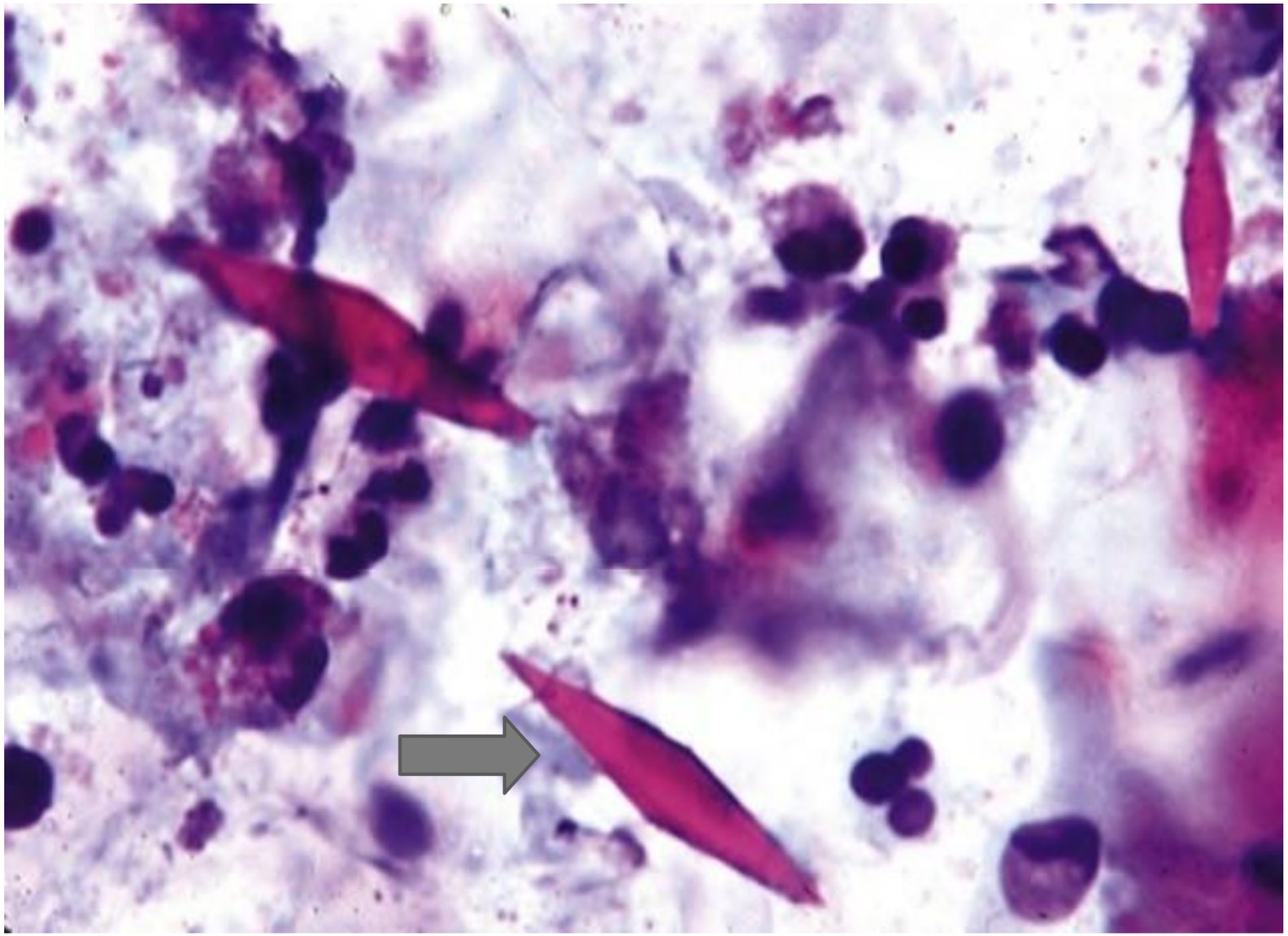


Robbin's and Cotran Atlas of pathology, 3rd edition

MORPHOLOGY

Charcot-Leyden crystals

Charcot-Leyden crystals:
crystalloids made up of the eosinophil protein **galectin-10**



Robbin's and Cotran Atlas of pathology, 3rd edition

MORPHOLOGY

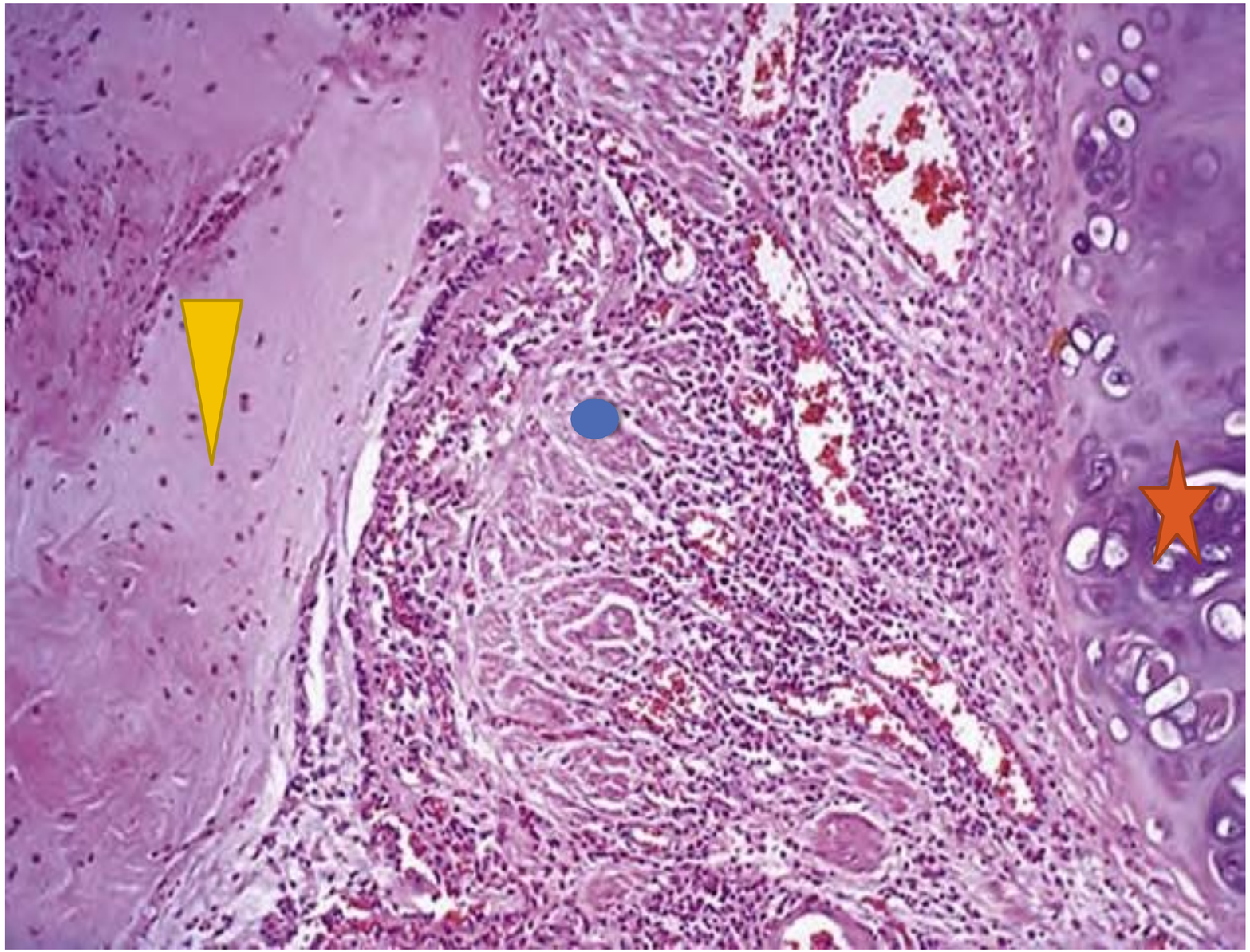
Morphological Consequences of Recurrent Airway Inflammation

- **Airway remodeling** (the characteristic morphological change in bronchial wall after recurrent episodes), including:
  - Thickening of airway wall.
  - Sub-basement membrane fibrosis.
  - Increased submucosal vascularity.
  - An increase in size of the submucosal glands and goblet cell metaplasia of the airway epithelium.
  - Hypertrophy and/or hyperplasia of the bronchial muscle.

- In severe or fatal cases → **distension of lungs** due to air trapping, with small areas of **atelectasis**(recall L1).

MORPHOLOGY

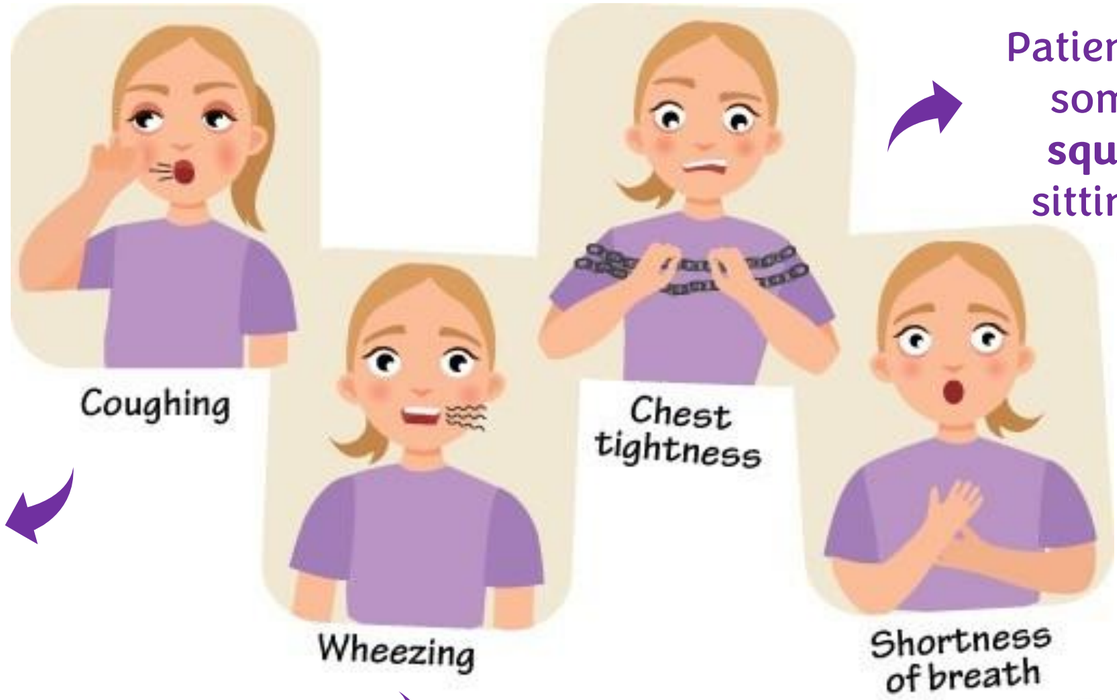
- This figure shows a predominantly **expanded submucosa** marked by the blue circle, sandwiched between the **bronchial cartilage** on the right marked by the red star and **bronchial lumen** stuffed and **filled with mucus** marked on the left by the yellow triangle. The **submucosa is widened** due to smooth muscle hypertrophy, edema fluid and inflammatory cells, especially eosinophils.



Robbin's and Cotran Atlas of pathology, 3rd edition

CLINICAL FEATURES OF ASTHMATIC ATTACKS

- **Asthma** is usually associated with **expiration difficulty**, and is **reversible**, **EXCEPT** in severe advanced cases.
- Each episode lasts from one to several hours and **subsides** either spontaneously or with therapy.
- **The intervals between these attacks are free of respiratory difficulties.**



Patients may feel something is **squeezing** or sitting on their chest.

Often **worse at night or early in the morning.**

Wistling sound especially during expiration, sometimes can be heard easily without a stethoscope.

Patients cannot catch their breath or breathe deeply enough.

https://allergyasthmanetwork.org/what-is-asthma/asthma-symptoms/

Status asthmaticus:

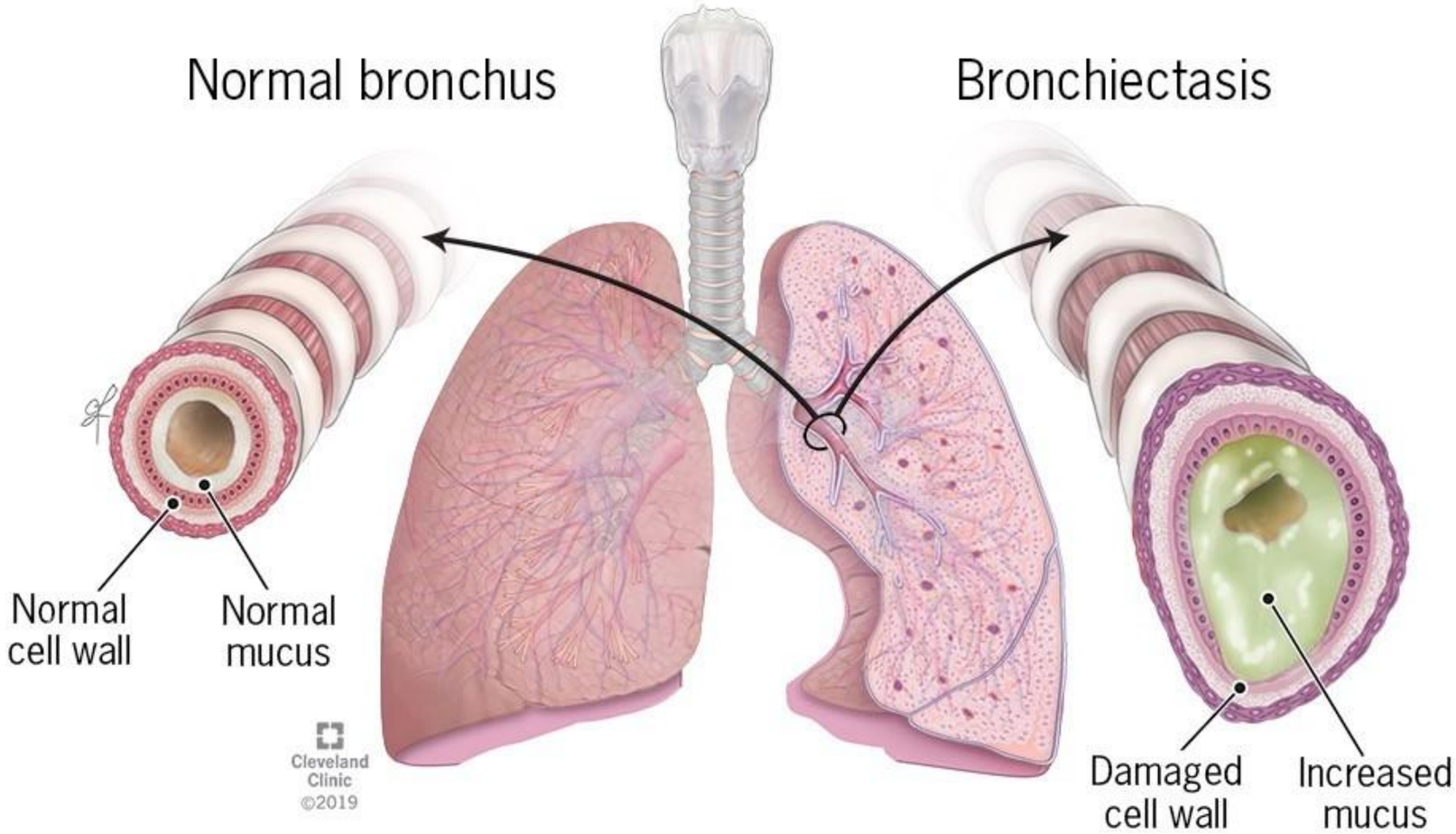
- **Severe paroxysmal** (sudden) **asthmatic attack** that does not respond to therapy, persisting for days or weeks, and might be associated with **hypercapnia**, **acidosis**, and severe **hypoxia**. This type of attacks might be fatal in some patients.

https://nurseslabs.com/status-asthmaticus-nursing-management/

MANAGEMENT:

- **Standard therapies include:**
  - **Anti-inflammatory drugs** (glucocorticoids).
  - **Bronchodilators** (beta-adrenergic drugs)
  - **Leukotriene inhibitors** (leukotriene receptors antagonists or leukotriene modifiers).
    - ✓ These agents prevent the **leukotrienes-induced bronchospasm**, as well as **blocking** the effect of some immune mediators like **IL-4** and **IL-5**, the latter effect can be helpful in some patients.

IV- BRONCHIECTASIS



https://my.clevelandclinic.org/health/diseases/21144-bronchiectasis

لا حول ولا قوة إلا بالله

BRONCHIECTASIS

- **Permanent** dilation of **bronchi and bronchioles** caused by destruction of smooth muscle and the supporting elastic tissue.
  - Permanent: It's an **irreversible dilation**.

- Typically results from or is associated with **chronic necrotizing infections.**

- It is not a primary disorder, as it always occurs **secondary to persistent infection or obstruction.**

BRONCHIECTASIS

- The condition is characterized by the **irreversible (permanent) dilation of the airways.**
- It mainly affects **bronchi** and **bronchioles.** This distinguishes it from emphysema, which is defined as permanent dilation of the airways distal to the terminal bronchioles.

❖ **Pathogenesis:**

– The underlying mechanism typically involves **chronic necrotizing infections,** that induce the destruction of bronchial walls' smooth muscle and elastic tissue, leading to the loss of structural support.

BRONCHIECTASIS

- **Clinically**: cough and expectoration of copious amounts of (غزير/كثيف) purulent sputum.
  - Purulent sputum usually contains WBCs, cellular debris, and mucus.
  - It is typically **yellow-green** and can be seen in conditions such as **bronchiectasis** or **lung abscess**.

- **Diagnosis**: appropriate history and radiographic demonstration of bronchial dilation.

BRONCHIECTASIS

PATHOGENESIS

❖ Two **intertwined** processes contribute to bronchiectasis:

1. **Obstruction.**

   Obstruction impairs clearance of secretions → **superimposed infection** → inflammatory damage to the bronchial wall + the accumulating exudate → airways distention → irreversible dilation.

2. **Chronic infection.**

   Persistent necrotizing infection in the bronchi or bronchioles → poor clearance of secretions, obstruction, and inflammation with **peribronchial fibrosis** and **traction on the bronchi** → irreversible dilation.

Further Explanation in the next slide.

BRONCHIECTASIS

PATHOGENESIS - Explanation

- **Obstructions** caused by foreign bodies, for example, **impair the clearance of secretions**, leading to their **accumulation** and providing a **favorable medium for superimposed infections.** Consequently, the secretions and the bronchial wall become infected, **inducing inflammatory reactions**. This inflammation results in **tissue damage**, especially to the bronchial wall, and the accumulation of exudate, which further distends the airways, leading to irreversible dilation.

- Conversely, a **persistent necrotizing infection** in the bronchi or bronchioles may lead to **poor clearance of secretions**; this is usually followed by **obstruction** due to the accumulation of secretions and inflammation with bronchial wall damage, resulting again in full-blown bronchiectasis.

As we learned it's a secondary process that happens due to another primary disorder.

BRONCHIECTASIS

❖ **The conditions that most commonly predispose to bronchiectasis include:**

1. **Bronchial obstruction**:
   - By tumors, foreign bodies, and impaction of mucus OR as a complication of atopic asthma and chronic bronchitis.
   - ✓ Bronchiectasis is localized to the obstructed lung segment.
2. **Congenital or hereditary conditions:**
   A. **Cystic fibrosis:**
      - **Widespread** severe bronchiectasis.
      - Due to obstruction caused by **abnormally viscid mucus and secondary infections**.
      - Cystic fibrosis is a hereditary disease that affects the lungs and digestive system; in this disease, the body produces **thick and sticky mucus** that may block the lungs and obstruct the pancreas.

BRONCHIECTASIS

❖ **The conditions that most commonly predispose to bronchiectasis include:**

2. Congenital or hereditary conditions:

B. Immunodeficiency states:

- Due to recurrent bacterial infections.
- Can be localized or diffuse.

C. Primary ciliary dyskinesia (immotile cilia syndrome):

- Rare autosomal recessive disorder.
- Caused by inherited abnormalities of cilia which impairs the mucociliary clearance of the airways, leading to persistent infections.
- Associated with bronchiectasis + sterility in males.

3. Necrotizing, or suppurative, pneumonia:

- Particularly with virulent organisms such as **Staphylococcus aureus** or **Klebsiella spp**.

BRONCHIECTASIS

MORPHOLOGY, MACROSCOPIC:

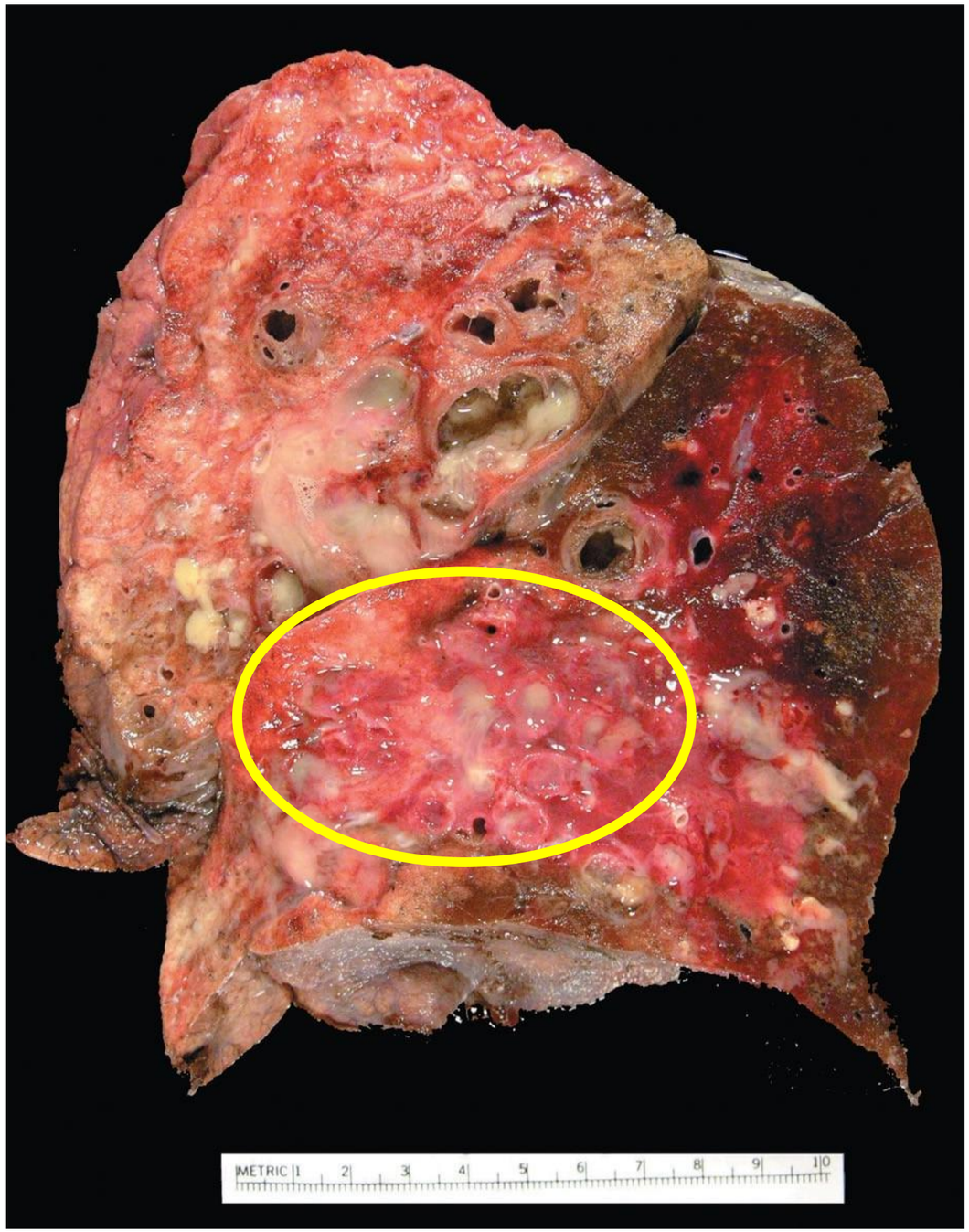
- Usually affects: **Lower lobes bilaterally**, particularly the vertical air passages.
- **Most severe** involvement in **distal bronchi and bronchioles**.
- The airways may be dilated to as much as **four times** their usual diameter.

BRONCHIECTASIS

MORPHOLOGY, MACROSCOPIC:

- **Markedly dilated bronchi filled with purulent mucus.**

- This figure shows the **gross appearance** of a lung that is involved by **bronchiectasis in a patient with cystic fibrosis** who underwent lung resection for lung transplantation.
- As you can appreciate the cut surface of the lunge shows **marked dilation of the bronchi** and those bronchi are stuffed and filled with **purulent mucus**, yellow circle.



BRONCHIECTASIS

MORPHOLOGY, MICROSCOPIC(1):

❖ The histologic findings vary with the activity and the chronicity of the disease:

➢ In full-blown **active cases**:

- **Intense** acute and chronic inflammatory **exudate** within the walls of the bronchi and bronchioles.
- **Desquamation of lining epithelium** and extensive **ulceration**, due to severe inflammation.
- **Mixed flora are cultured** from the sputum.

  The usual organisms include *staphylococcus*, *streptococcus*, *pneumococcus* enteric organisms and anaerobic bacteria.

BRONCHIECTASIS

MORPHOLOGY, MICROSCOPIC(2):

➢ **When healing occurs:**

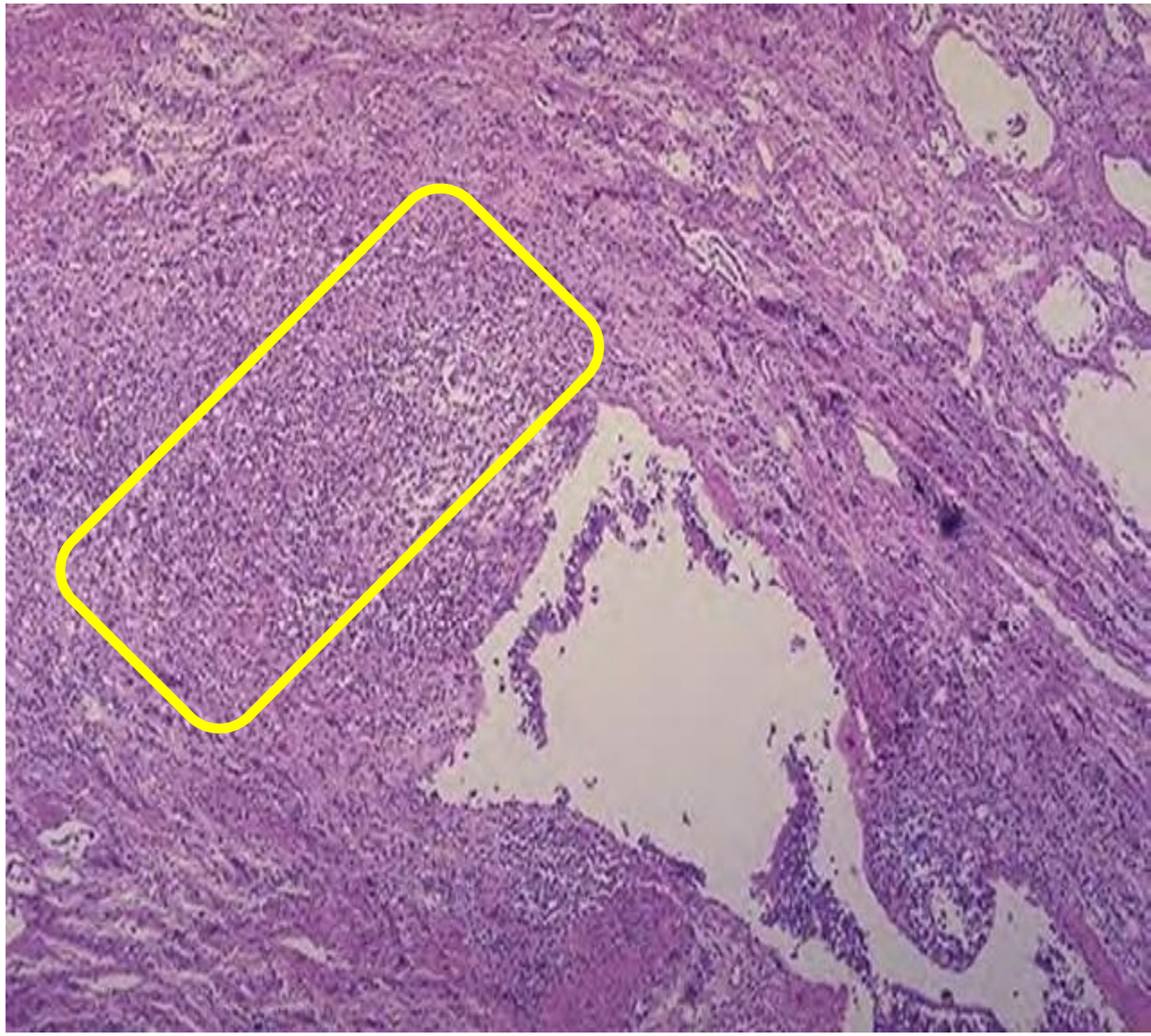
- The lining epithelium **may** regenerate completely. Sometimes, it cannot be repaired completely, and abnormal dilation and scarring persist.
- **Fibrosis of bronchial and bronchiolar walls**, as what is seen in chronic cases.
- **Peribronchiolar fibrosis**, also in chronicity.
- **Abscess formation in some cases**; necrosis destroys the bronchial and bronchiolar walls, producing an abscess cavity.

BRONCHIECTASIS

MORPHOLOGY, MICROSCOPIC:

Figure 5-34: Bronchiectasis, microscopic dilated bronchus in which the mucosa and bronchial wall are not seen clearly because of the necrotizing inflammation with tissue destruction.

- Extensive necrotizing inflammation, yellow box.
- The mucosal lining cannot be defined; mostly it is desquamated.



Robbin's and Cotran Atlas of pathology, 3rd edition

BRONCHIECTASIS

CLINICAL FEATURES

- Severe, persistent **cough with mucopurulent sputum**.
- Other symptoms: dyspnea (shortness of breath), rhinosinusitis, and hemoptysis.
  - Symptoms often **episodic.**

- **Precipitated** or induced by **upper respiratory tract infection** (URTI).

- **Severe widespread bronchiectasis:** significant obstructive ventilatory defects, hypoxemia, hypercapnia, pulmonary hypertension, and **cor pulmonale.**

- However, with current treatment, outcomes have been improved and severe complications such as brain abscess or cor pulmonale are less frequent.

The underlined word is hyperlinked

IN SUMMARY:

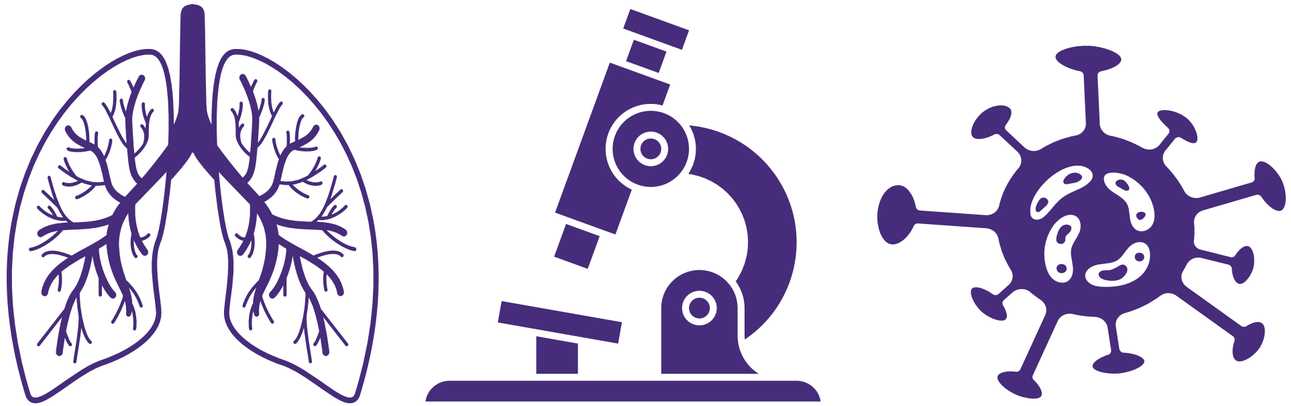
Table 13.1 Disorders Associated With Airflow Obstruction: The Spectrum of Chronic Obstructive Pulmonary Disease

Clinical Entity	Anatomic Site	Major Pathologic Changes	Etiology	Signs/Symptoms
Chronic bronchitis	Bronchus	Mucous gland hypertrophy and hyperplasia, hypersecretion	Tobacco smoke, air pollutants	Cough, sputum production
Bronchiectasis	Bronchus	Airway dilation and scarring	Persistent or severe infections	Cough, purulent sputum, fever
Asthma	Bronchus	Smooth muscle hypertrophy and hyperplasia, excessive mucus, inflammation	Immunologic or undefined causes	Episodic wheezing, cough, dyspnea
Emphysema	Acinus	Air space enlargement, wall destruction	Tobacco smoke	Dyspnea
Small airway disease, bronchiolitis*	Bronchiole	Inflammatory scarring, partial obliteration of bronchioles	Tobacco smoke, air pollutants	Cough, dyspnea

*Can be present in all forms of obstructive lung disease or by itself.

الحمد لله

THANK YOU!



PATHOLOGY QUIZ LECTURE 3

رسالة من الفريق العلمي

الموت واعظ القلوب، والزاجر عن الذنوب، فلم نجد واعظًا للقلوب كالموت، ولم نذكر زاجرًا عن الذنوب كالموت؛ قال النبي صلى الله عليه وسلم: «كفى بالموت واعظا»، «من لم يتعظ بالموت فلا واعظ له».

كتب الله الموت على جميع الخلائق، فالموت كأس الكل شاربه، وبالموت تفنى أعمار الخلائق؛ فلا مفر منه، قال تعالى: ﴿قل إنَّ المَوْتَ الذي تفرُّونَ منْهُ فإنهُ مُلاقيكمْ ثمَّ تُردُّونَ إلى عالِمِ الغيْبِ والشَّهادَةِ فيُنبِّئكم بما كنتمْ تعْملونَ[8]﴾.

فالموت حق، وعلينا الإستعداد فهم السابقون ونحن اللاحقون، قال عليه الصلاة والسلام: (أكثروا ذكر هادم اللذات: الموت).

أعملوا صالحا وادعوا لمن سبقنا بالرحمة والمغفرة.

رحم الله زميلنا عمر عطية وأسكنه فسيح جناته، وألهم أهله الصبر والسلوان.

رحمنا الله وإيّاكم.

سُورَةُ آلِ عِمْرَانَ

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

كُلُّ نَفْسٍ ذَآئِقَةُ ٱلْمَوْتِ ۗ وَإِنَّمَا تُوَفَّوْنَ أُجُورَكُمْ
يَوْمَ ٱلْقِيَـٰمَةِ ۖ فَمَن زُحْزِحَ عَنِ ٱلنَّارِ وَأُدْخِلَ ٱلْجَنَّةَ
فَقَدْ فَازَ ۗ وَمَا ٱلْحَيَوٰةُ ٱلدُّنْيَآ إِلَّا مَتَـٰعُ ٱلْغُرُورِ ﴿١٨٥﴾

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			