Bronchial Asthma

OBJECTIVES:

- ✓ Define bronchial asthma (BA).
- ✓ Know the two types of asthma
  1. Extrinsic or atopic allergic.
  2. Intrinsic asthma.
- ✓ Understand the pathogenesis of BA.
- ✓ Understand the morphological changes (gross and microscopic) seen in the lungs in asthmatic patient.
- ✓ Know the manifestation and clinical course of BA.
- ✓ List the complications of BA.
- ✓ Define status asthmaticus.
- ✓ Know the prognosis and prevention of BA.

Editing File

Black: original content.
Red: Important.
Green: AlRikabi's Notes.
Grey: Explanation.
Blue: Only found in boys slides.
Pink: Only found in girls slides.

Pathology Teamwork 438
MED438 KING SAUD UNIVERSITY
Reviewed by Razan AlRabah & Ibrahim ALDakhil

Overview: By Dr.AlRikabi

Before we start we need to revise the **anatomical** structure and **histology** of the respiratory tract:

Lining	Part of the nasopharynx is lined by squamous epithelium, while the lower portion of the respiratory tract is lined by Pseudostratified columnar ciliated epithelium with goblet cell & Neuroendocrine cells Clara cells are found in the terminal bronchioles.
Alveoli	• Type I pneumocytes: Flattened, platelike cells covering 95% of alveolar surface, it's important in gas exchange. • Type II pneumocytes: Secrete surfactant that keeps alveoli open by decreasing the surface tension, it's also involved in repair of alveolar epithelium after damage to type 1 pneumocytes. • Alveolar macrophage (also called carbon lading or anthracotic macrophage) • Capillary endothelium and basement membrane • Pores of Kohn: holes in the walls of adjacent alveoli.
Lungs anatomy	**The lungs are covered by 2 layers:** 1)Parietal pleura: attached to the inner surface of the thoracic cavity. 2)Visceral pleura: covers the surface of each lung. Between these two layers there is the pleural cavity. What is pleural effusion? Accumulation of fluid within the pleural cavity, with heaviness on the side and difficulty breathing.

- **What's the difference between Bronchi and Bronchioles?**
  Bronchi has cartilage and more glands, while bronchioles has NO cartilage.
- To differentiate between sputum and saliva: Sputum contains macrophages, while saliva does not.

Lung diseases are classified into: "We will study them in details in the coming lectures"

1. Chronic **obstructive** pulmonary disease like: bronchial asthma - chronic bronchitis - emphysema - bronchiectasis.
2. **Restrictive** lung disease: will affect pulmonary acini + connective tissue within parenchyma. Eg: Lung volume reduction (incapable of expanding)
3. **Infectious**: viral pneumonia, bacterial pneumonia & TB.
4. **Tumors:** Mostly malignant. Main cause: smoking.
5. Pulmonary **Tuberculosis**.

Bronchial Asthma

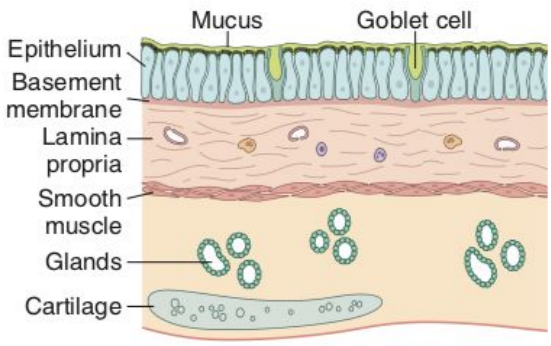
Definition: a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing[1], breathlessness, chest tightness and cough.

Hallmarks of Bronchial Asthma

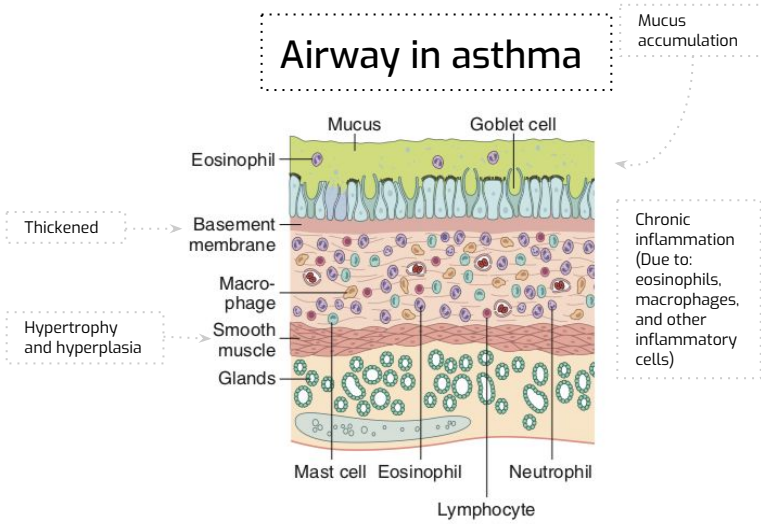
- Intermittent and reversible airway obstruction
- Chronic bronchial inflammation with eosinophils
- Bronchial smooth muscle cell hypertrophy[2] and hyper-reactivity[3]
- Increased mucus secretion

Airway comparison

Normal airway



Airway in asthma



[1]why does the asthmatic patient wheeze? **Wheezing occurs when the small airways of the lungs become narrow or constricted. This makes it difficult to breathe, and can cause a whistling sound when breathing out.**

[2]why there is a bronchial smooth muscle hypertrophy? Because with repeated contraction the muscle size will increase.

[3]what do we mean by hyper-reactivity? Some of the stimuli that trigger attacks in patients would have little or no effect in persons with normal airways.

[4]**Generally, -Productive cough → Obstructive**(Asthma is an exception it could be productive or non-productive)
-Dry cough → Restrictive

Pathogenesis of Bronchial Asthma

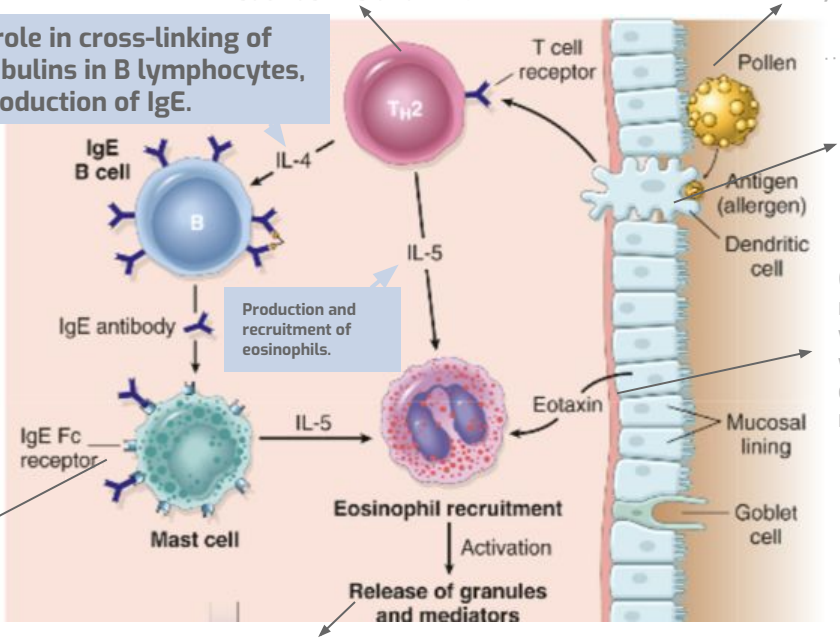
Step1: Triggering of asthma

1. Antigen enters the body.

2. Recognized by the dendritic cell or any other APC.

3. Activate TH2 cell and the release of cytokines such as IL-5 and IL-4.

will play a role in cross-linking of immunoglobulins in B lymphocytes, promote production of IgE.



6. Injured bronchial mucosal lining cells will secrete eotaxin which helps in the eosinophils recruitment.

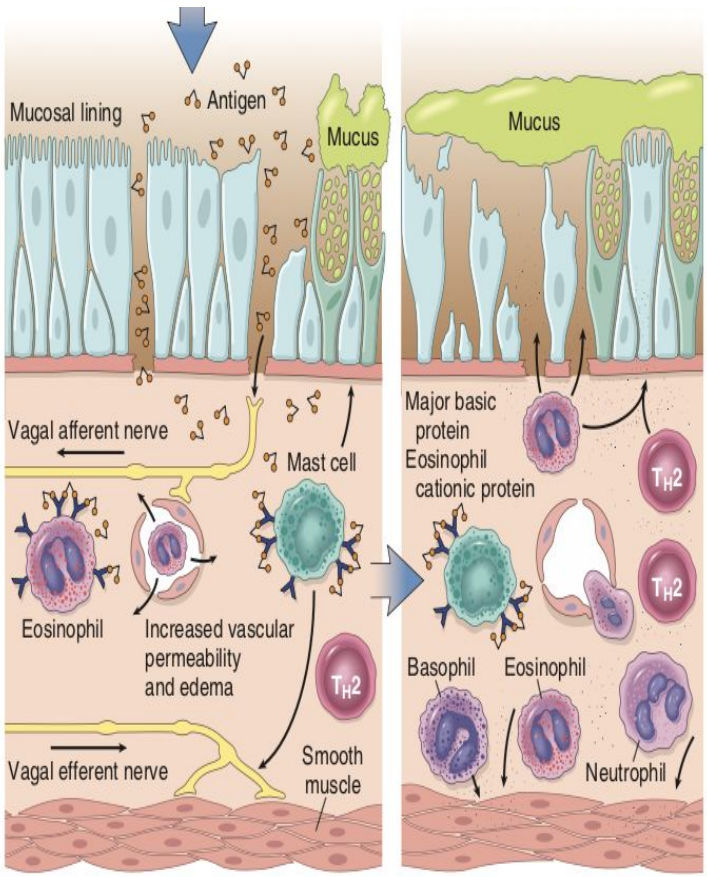
4. igE attach to mast cell and stimulate the release cytokines such as histamine and IL-5

5. Eosinophils will release the granules and mediators which are toxic to epithelial cells.

Step2: immediate phase (minutes)

1- Re-exposure to antigen (Ag)
2- immediate reaction is triggered by: Ag-induced cross-linking of IgE bound to Fc receptors on mast cells.
3- Mast cells release preformed mediators that directly and via neuronal reflexes induce:

- **Bronchospasm.**
- **Increased vascular permeability.**
- **Mucus production.**
- **Recruitment of leukocytes.**



Step3: Late phase (hours)

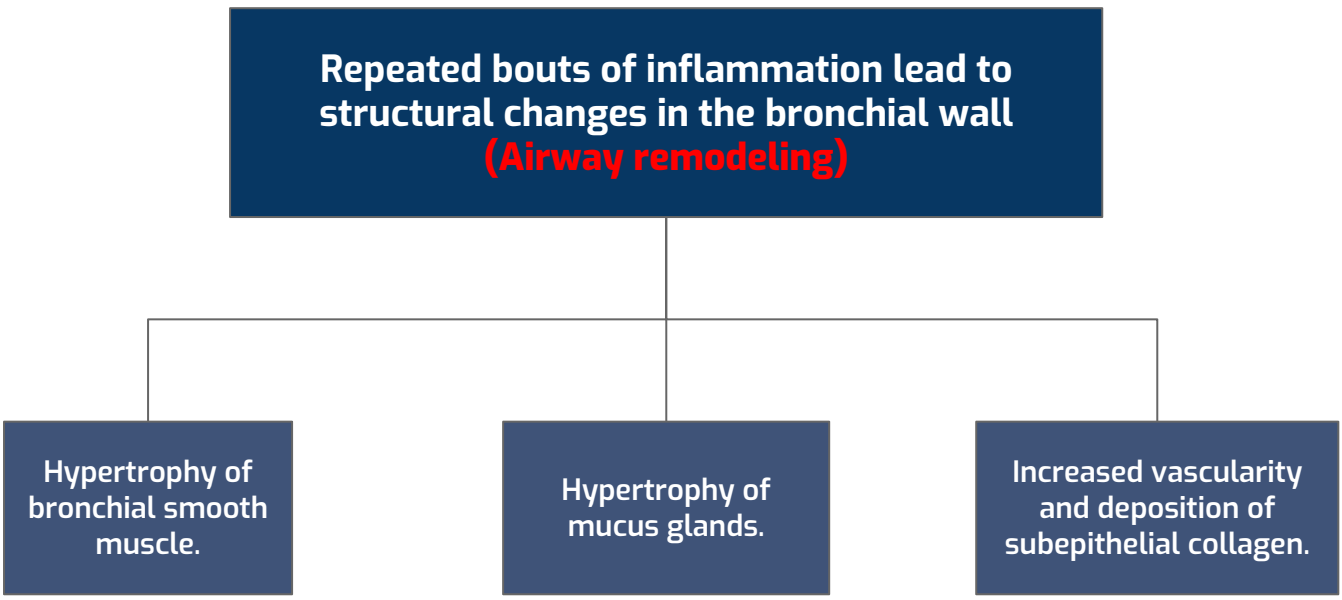
Leukocytes recruited to the site of reaction:
- neutrophils,
- eosinophils,
- basophils
- lymphocytes
- monocytes
These cells will release additional mediators that initiate the late phase of asthma.

Several factors released from eosinophils (e.g., major basic protein, eosinophil cationic protein) also cause damage to the epithelium.

Pathogenesis of Bronchial Asthma (CONT.)

Cytokines produced by Type 2 helper T (TH2) cells:

Cytokine	Function
IL-4	Stimulate IgE production.
IL-5	Activates eosinophils which play a major part in the pathogenesis of asthma. Because they produce basic proteins, which cause asthma, damage bronchial wall, incite inflammation, and induce contraction of bronchial smooth muscles.
IL-9	Damages the bronchial epithelium directly.
IL-13	Stimulates IgE and mucus production.



In the first exposure to the allergen it will start the sensitization of igE with no symptoms but in the second exposure the igE already exists, so it will lead to IgE mediated reaction which has two phases. The first one starts within minutes and is called the acute phase. After 4-8 hours the late phase will start.

Types of Bronchial Asthma

1- Extrinsic asthma (Atopic):	2- Intrinsic asthma (Non-Atopic):
Bronchospasm is induced by inhaled antigens	A disease in which the bronchial hyper-reactivity is induced by non-immune mechanisms
Atopic/allergic Asthma 70%	Non-atopic/Not allergic Asthma 30%
Type 1 hypersensitivity reaction* mediated by IgE, induced by exposure to extrinsic antigen/allergens e.g. food, pollen, dust, etc, So the best treatment is to avoid the triggers.	Initiated by diverse, non-immune mechanisms.
Family history: positive Skin test: positive	Family history: uncommon Skin test: Negative

3- Drug-induced asthma:	4- Occupational asthma
• NSAIDs, and especially aspirin may provoke asthma. • Patients with aspirin sensitivity present with recurrent rhinitis, nasal polyps, urticaria, and bronchospasm. • The precise pathogenesis is unknown but is likely to involve some abnormality in prostaglandin metabolism stemming from inhibition of COX by aspirin. • Beta blockers may also cause bronchospasm (major pathology in asthma) in some patients.	• Stimulated by fumes, dusts, and other chemicals. • Asthma usually develop after repeated exposure to the inciting antigen(s).

*usually preceded by allergic issues such as allergic rhinitis, allergic conjunctivitis, and eczema.

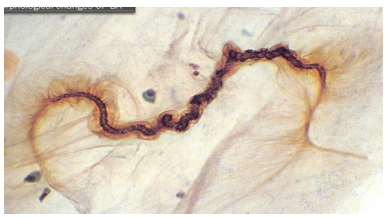
Bronchial Asthma

Diagnosis (of extrinsic asthma) By:

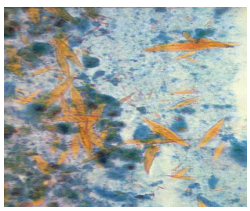
- **Skin test** using antigen: positive (immediate wheal and flare reaction)
- **Radioallergosorbent test (RAST):** presence of IgE in the blood.
- **Spirometry:** pulmonary function test
- **Sputum sample**

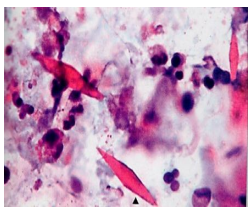
Histological findings of the sputum (Must be bronchial secretion not saliva):

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

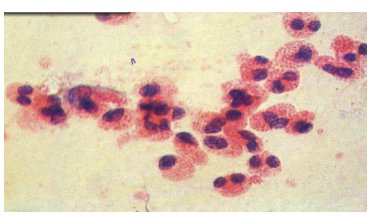


Curschmann's spiral





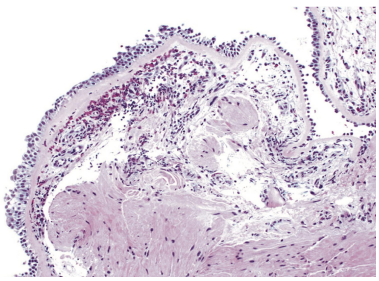
Charcot–Leyden Crystals
(rhomboid shape)



Bronchial Asthma

Morphology

- 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



Bronchial biopsy specimen from an asthmatic patient

Clinical features

"usually attacks last from 1 to several hours and subside either spontaneously or with therapy"

- Dyspnea
- increase in residual volume and anteroposterior diameter due to air trapping
- Wheezing(2)
- Status asthmaticus(1)
- Cough → nocturnal(3) and/or morning cough
- Difficult expiration
- Tightness of chest
- Subtle deficits can be detected by pulmonary function tests.

(1)Severe paroxysm that does not respond to therapy and persist for days and weeks.
(2)Due to bronchoconstriction and mucus plugging, which leads to trapping of air in distal airspaces and progressive hyperinflation of the lungs.
(3) at night

Bronchial Asthma

Complications:

Airway remodeling	Pneumothorax[1] and Pneumomediastinum[2]
Superimposed infections	Status asthmaticus[5]
May develop to other COPD[4]	In some cases cor pulmonale[3] and heart failure develop

Prognosis of Asthma

- **Remission** (reduce,decrease):
  - 50% of cases of childhood asthma resolve spontaneously but may recur later in life.
  - Remission in adult-onset asthma is less likely.
- **Mortality:**
  - Death occurs in ~0.2% of asthmatics.
  - It is usually (but not always) preceded by an acute attack and about 50% are more than 65 years old.

Prevention of Asthma

- **Control of factors** contributing to asthma severity:
  Exposure to *irritants* or *allergens* has been shown to increase asthma symptoms and cause exacerbations.
- **Skin test:**
  - Results should be used to assess sensitivity to common indoor Allergens.
  - All patients with asthma should be advised to avoid exposure to allergens to which they are sensitive.

[1] Leakage of air into the pleural cavity.
[2] Abnormal presence of air or another gas in the mediastinum.
[3] Abnormal enlargement of the right side of the heart as a result of disease of the lungs or the pulmonary blood vessels.
[4] Chronic bronchitis, Bronchiectasis, Emphysema; we'll take them in details next lecture.
[5] A medical emergency with acute severe breathlessness (Overinflated lungs because of severe obstruction and air trapping) which requires immediate intensive care including intermittent positive-pressure ventilation.

Summary

Bronchial Asthma: Episodic attacks of bronchoconstriction (Reversible).

	Anatomical site	Pathologic changes	Etiology	Signs/Symptoms
Asthma	Bronchus	- Smooth muscle hypertrophy, & hyperplasia. - Excessive mucus. - Inflammation.	Immunologic or undefined causes.	- Episodic wheezing. - Cough. - Dyspnea.

Types

- **Extrinsic asthma**:
  Type 1 Hypersensitivity reaction, IgE, childhood. family history of allergy.
- **Intrinsic asthma**:
  BA is associated with aspirin, exercise, cold induced, viral infection. No history of allergy.

Morphology

- Hypertrophy of bronchial smooth muscle & hyperplasia of goblet cells & eosinophils, thickened Basement membrane.
- Mucous plug & Curschmann spirals & Charcot-Leyden crystals.
- Remodeling with sub-basement membrane fibrosis
  and hypertrophy of muscle layer

Complications

- Superimposed infection
- Chronic bronchitis Complication
- Pulmonary emphysema
- Status asthmaticus (Overinflated lungs with severe obstruction and air trapping)

Dr. AlRikabi's notes

Bronchial asthma

Definition: Inflammatory disorder of the airway, which is characterized by increased responsiveness of the bronchial mucosa and bronchial wall to various stimuli, it's also characterized by episodic attacks and it's reversible, which means that it can be reversed by avoiding the stimuli.

Signs and symptoms:

- Dyspnea."Most serious"
- Wheezing.
- Cough."Not a major symptom"

Asthma has two major types:

Extrinsic(Atopic):

- Common in children.

Intrinsic(Non-atopic):

- Usually happens in adults.
- These patients don't have history of hypersensitivity.
- Usually come after exercise(exercise induced intrinsic asthma): Exercise causes dehydration which will increase the osmolality of the sputum which is associated with secretion of certain chemical mediators(especially Leukotrienes C4,D4,E4 which will cause bronchospasm).
- Aspirin (block PGs—> enhance leukotrienes C4, D4, E4—> bronchoconstriction)

Pathogenesis

1) Entry of antigen, then it is engulfed by APCs and presented to T-lymphocytes, especially CD4.
2) Activates the CD4 T-lymphocytes and transform them into TH2 cells.
3) TH2 cells start secreting these cytokines:

- **IL-4**: will stimulate the B-lymphocytes to secrete IgE(has a main role in hypersensitivity type 1), this IgE will bind to certain receptors on mast cells, then the antigen will come and bind to the antibody, then the mast cell will release the granules(which contain histamine, serotonin and other chemical mediators) which will cause vasodilation and edema.
- **IL-5**: Can be secreted by T&B lymphocytes, it will facilitate the recruitment of eosinophils, which will also release their granules(has major basic proteins) which will cause damage to the bronchial epithelium, then the damaged epithelium will secrete eotaxin which will recruit more eosinophils.
- **IL-9**: Act directly on the bronchial epithelium and will cause damage to it.
- **IL-13**: Same action as IL-4.

Pathological changes in asthma:

- Hyperplasia/ Hypertrophy and spasm(due to stimulation and irritation of the nerves endings specially nerves from the vagus nerve)
- Excessive mucus secretion with accumulation of eosinophils.

QUIZ

1- which of the following activate eosinophils in bronchial asthma?
A- IL-4
B- IL-5
C- IL-28
D- Th2

2- A 35-year-old man has a 5-year history of episodic wheezing and coughing. The episodes are more common during the winter months, and he has noticed that they often follow minor respiratory tract infections. In the period between the episodes, he can breathe normally. There is no family history of asthma or other allergies. On physical examination, there are no remarkable findings. A chest radiograph shows no abnormalities. A serum IgE level and WBC count are normal. Which of the following is the most likely mechanism that contributes to the findings in his illness?
A- Accumulation of alveolar neutrophilic exudate
B- Bronchial hyperreactivity to chronic infammation
C- Emigration of eosinophils into bronchi
D- Hyperresponsiveness to Aspergillus spores
E- Secretion of interleukin (IL)-4 and IL-5 by T cells

3- which of the following is a clinical feature of bronchial asthma
A- Increase vertical-horizontal diameter
B- Increase residual volume
C- Breakdown of alveoli
D- Underinflated lungs with severe obstruction

4- A pharmaceutical company is designing agents to treat the recurrent bronchospasm of bronchial asthma. Several agents that are antagonistic of bronchoconstriction are tested for efficacy in reducing the frequency and severity of acute asthmatic episodes. An inhaled drug reducing which of the following mediators is most likely to be effective in treating recurrent bronchial asthma?
A- Th1 cytokines
B- Vasoactive amines
C- Th2 cytokines
D- Leukotrienes
E- Prostaglandins

5- A study of people with atopic asthma reveals that they develop pathologic changes in their airways with repeated bouts. These changes include smooth muscle and mucus gland hypertrophy. It is observed that the late-phase inflammatory response to allergens potentiates epithelial cell cytokine production that promotes airway remodeling. Which of the following immune cells is most important in this excessive inflammatory response to allergens?
A- B lymphocyte
B- Cytotoxic lymphocyte
C- Natural killer cell
D- TH1 lymphocyte
E- TH2 lymphocyte
F- TH17 lymphocyte

1- B | 2- B | 3- E | 4- C | 5- E

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Thank you

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