Lecture series : General outline

1  Asthma: interactions between allergens & epithelium
2  Allergic inflammation: Th2 cells, IL-4 and mast cells
3  Allergic inflammation: Th2 cells, IL-5 and eosinophils
4  Inhibiting allergic airways inflammation
5  Key mediators of allergic airways inflammation
6  Bronchodilators and Airway Hyperresponsiveness
The aim of these lectures is to:

- develop an understanding of the cellular and molecular pathways that cause airway dysfunction in asthma, and
- discuss pharmacologic approaches aimed at treating (and preventing?) asthma

Overview of Respiratory Pharmacology lectures

Causes & consequences of airway narrowing in asthma

- contraction of ASM
- thickening of the airway wall - inflammation & remodelling
- hypersecretion of mucus
  - airway narrowing (obstruction)
  - symptoms > breathlessness, cough, wheeze

Key cells, pathways & mediators in narrowing

Pharmacotherapy of asthma

<table>
<thead>
<tr>
<th>Relievers</th>
<th>Preventers</th>
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<tbody>
<tr>
<td>Current therapies</td>
<td>Future therapies?</td>
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<tr>
<td>MUC5B</td>
<td>New corticosteroids</td>
</tr>
<tr>
<td>Mucus</td>
<td>IL-4 inhibitors</td>
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<tr>
<td>Antagonists</td>
<td>IL-5 inhibitors</td>
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<tr>
<td>Muscarinic antagonists</td>
<td>Macrolides</td>
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Systemic Pharmacology 3320
**What is asthma?**

1. An airways disease in which exposure to various provoking stimuli (triggers) make airways narrow too much and too easily.

These triggers don’t cause narrowing in nonasthmatic people.

<table>
<thead>
<tr>
<th>Exposure to triggers</th>
<th>Asthmatic</th>
<th>Nonasthmatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g.</td>
<td>Airways narrow</td>
<td>Airways don’t narrow</td>
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<tr>
<td>allergen</td>
<td></td>
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<tr>
<td>respiratory virus</td>
<td></td>
<td></td>
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<tr>
<td>exercise</td>
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<tr>
<td>drugs, incl. aspirin</td>
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<tr>
<td>irritants, smoke</td>
<td></td>
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<tr>
<td>extreme emotions</td>
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<tr>
<td>etc. …</td>
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</tbody>
</table>

**What is asthma?**

2. In asthma, airway narrowing can cause bronchial obstruction and airflow limitation, which leads to symptoms of

- wheezing 🎭
- breathlessness, 🎭
- chest tightness, and
- nighttime or early morning coughing.

These symptoms are variable, intermittent, worse at night and provoked by triggers including exercise.

The difficulty of breathing for an asthmatic is likened to an non-asthmatic jogging for two minutes and then trying to breathe through a drinking straw.
What is asthma?

3. **Airway narrowing** (↓ internal diameter of airway) caused by:
   - contraction of airway smooth muscle (bronchoconstriction)
   - inflammation of the airway wall (swelling in airway wall)
   - hypersecretion of mucus into the airway lumen.

![Diagram showing normal and asthmatic airways]

What is asthma?

4. **Chronic inflammatory airways disease** characterized by acute episodes or attacks, called ‘exacerbations’

![Graph showing airway dysfunction and chronic asthma]

During chronic asthma airway function may not return to normal *(see red areas).*
A chronic inflammatory airways disease characterized by acute episodes or attacks.

Asthma symptoms are reversible, either spontaneously or with treatment.

**What is asthma?**

4. Asthma ...

- is one of the most common chronic inflammatory diseases, affecting about 300 million people worldwide
- is a disease of unknown cause, although genetic, environmental & developmental influences exist
- is currently not curable or preventable
- is not a single disease, rather there exist distinct asthma phenotypes – our focus will be on *allergic* asthma (most prevalent phenotype; >50%)
- therapies that manage symptoms are available, but 5-10% of patients have severe disease that fails to respond to conventional therapy – new therapies/strategies needed
What are the pathologic features of asthma?

**Gross pathology**

Lung slice from non-asthmatic person

- Airway lumen is clear, allowing gases to easily flow in & out of lungs

Lung slice from person that died during severe asthma attack

- Airway lumen is blocked, reducing the flow of gases in & out of lungs

Note: the thin-walled tubes are blood vessels

Mucus plugs → narrow airway lumen → over-inflation of lung (severe asthma)

Low magnification of asthmatic lung slice

Higher magnification of asthmatic lung slice
What are the pathologic features of asthma?

Gross pathology

Mucus plug removed from asthmatic airways

Asthmatic lung slice

What are the pathologic features of asthma?

Nonasthmatic airway

goblet cell

cartilage

basement membrane

blood vessels

submucosal glands

epithelium

lumen

smooth muscle

... also nerves, etc.
What are the pathologic features of asthma?

Asthma is a syndrome in which there are recurrent, episodic bouts of *airway narrowing*

*Airway narrowing* is caused by:

1. contraction of airway smooth muscle (ASM)
2. thickening of the airway wall - inflammation and remodelling
3. hypersecretion of mucus

These factors contribute to the airway narrowing experienced by people with asthma in response to a *trigger* such as an airborne allergen

A/Professor Peter Henry
People with allergic asthma

- allergen induces an inappropriately large immune response
- inflammation of the airways (chemicals released from resident and inflammatory cells)
- wheeze, cough, chest tightness

People without asthma

- allergen largely ignored
- at worst, weak response low levels of IgG
- no symptoms

Why do people with allergic asthma develop these inappropriately large immune responses to allergens? It is not clear, but it seems the immune system is ‘tricked’ into reacting to these innocuous allergens in the same way as it does to signals derived from parasites such as worms and ticks.

The response of the immune system to aeroallergens in asthma is a complex multicellular process ...
Allergic inflammation occurs within the airway wall ...

Major Structures within the Airway wall

1. Epithelium
   - epithelial cells
   - antigen presenting cells (APCs)
   - sensory nerves
2. Blood vessels
3. Resident inflammatory cells (e.g. mast cells, lymphocytes)
4. Submucosal glands (SG)
5. Airway smooth muscle
6. Post-G parasympathetic nerves (innervate SG & airway smooth muscle)
The journey of an inhaled allergen ...

Allergens are inhaled and the first cells they come in contact with are the epithelial cells ...

Many different types of epithelial cell.

Ciliated epithelia: 200-300 cilia/cell which beat and move the mucus toward the mouth.

Mucous-producing epithelia: produce mucus that covers the airways.

Basal cells: attach epithelial cells to basement membrane (not shown).

The view from inside the airway lumen ...

Scanning electron micrograph showing bulging tops of mucus-secreting & ciliated cells.
Beating cilia move the overlying rafts of mucus...

Interactions of allergens with epithelial cells...

- To the asthmatic airways, allergens are foreign invaders.
- Most inhaled allergen is trapped by mucus and swept away by the rapidly beating cilia.
- If not, then the allergen meets the next line of defense, the tight junctions between the cells of the epithelium.
Tight junctions act as ‘gate-keepers’, controlling outward flow of fluid and the inward flow of macromolecules such as allergens.

**How do the inhaled allergens get past the tight-junctions?**

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### 5 key revision points

1. **Asthma** is a chronic inflammatory airways disease characterized by acute episodes or attacks. The aim of therapy is to reduce the ............... , ............... , and ............... of episodes.

2. **Asthma** is associated with reduced airway lumen size caused by .................. & ........................................................................

3. People whose asthma is triggered by agents such as pollens, animal dander & house dust mite have ............. asthma.

4. The ............... cells line the airway lumen, and consist of ............... & ............ cells.

5. Airway defence mechanisms against inhaled allergens include the ........ sheet and ................... which act as a seal between neighbouring epithelial cells.
Lecture 1: Outcomes

At the completion of this lecture you will be able to:

- define asthma in terms of symptoms, triggers and causes of airway narrowing
- describe the major gross and microscopic pathologic features of asthmatic airways
- describe the major structures within the airway wall.

Notices (for PHAR3321)

- Read and understand the handout for our lab sessions on 28th, 29th and 30th August.
- A pre-lab on-line quiz is to be completed prior to attending the lab session. It is now open & will close at 11:00 AM Monday 28th August.
- The quiz will cover:
  - general aspects of the lab session
  - drugs used in the lab session
  - the process of allergic inflammation
  Use lab handout, lecture material and online resources.
- Once you start the quiz on the LMS (PHAR3321), you will have 1 hour to complete it and you will get one attempt at it.
- The quiz will be in the MCQ/cloze test format (31 questions) and will count for 10% of your lab mark.