Treatment of Bronchial Asthma

Lecture 2

Doctor 019

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Definition of Asthma

- ***Chronic inflammatory disorder with intermittent narrowing of the airways.***
- ***Characterized by wide variations, over short periods of time, in the resistance to flow in the intrapulmonary airways.***

Factors in the Treatment Strategy

- **Asthma is a *chronic* condition**
- **The goal of therapy is *normal function***
- **Asthma is *heterogeneous* in terms of:**
  - **Cause or trigger mechanism.** some people get asthma from peanuts, some by smoking, etc..
  - **Extent of bronchoconstriction *and***
  - **Degree of inflammation.**
- **The course is *unpredictable.***
- **Therapy must be *individualized.***

Every patient has their own way of therapy

Risk of Not Treating Asthma

- **Deterioration of the condition.**
- **Accelerated decline in the function of the patient's lungs as measured by PFT's.**

PFT: pulmonary function test

- **Increased number of attacks of asthma.**
- **Poorer response to therapy if started late.**
- **Increased mortality from asthma.**

mortality of asthma is relatively low
So, if a patient died from asthma, it's probably the doctor's fault (and will probably get punched :')

Goals of Therapy in Asthma

- **Minimal symptoms even during sleep.**
- **No, or infrequent, acute episodes.**
- **No ED visits or missed days in school or work.** **ED: emergency department**

نعطيه حبوب مثلاً ، أحسن ما يستخدم بخاخات

- **Rare need for beta-agonist inhaler therapy.**
- **No limitation of activities – even sports.**
- **Peak flow rate variability less than 20%.**
- **FEV_1 consistently >80% of predicted range.**
- **No or minimal adverse effects from drugs.**

Pathogenesis

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- **Early Asthmatic Response:**

Allergens provoke IgE production.

The tendency to produce IgE is genetically determined.

Re-exposure to the allergen causes antigen-antibody interaction on the surface of the mast cells leading to:

Release of stored mediators.

Synthesis of other mediators.

Also, activation of neural pathways.

All lead to bronchoconstriction.

Prevented by bronchodilators.

Pathogenesis

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- **Late Asthmatic Response:**

4-5 hours later.

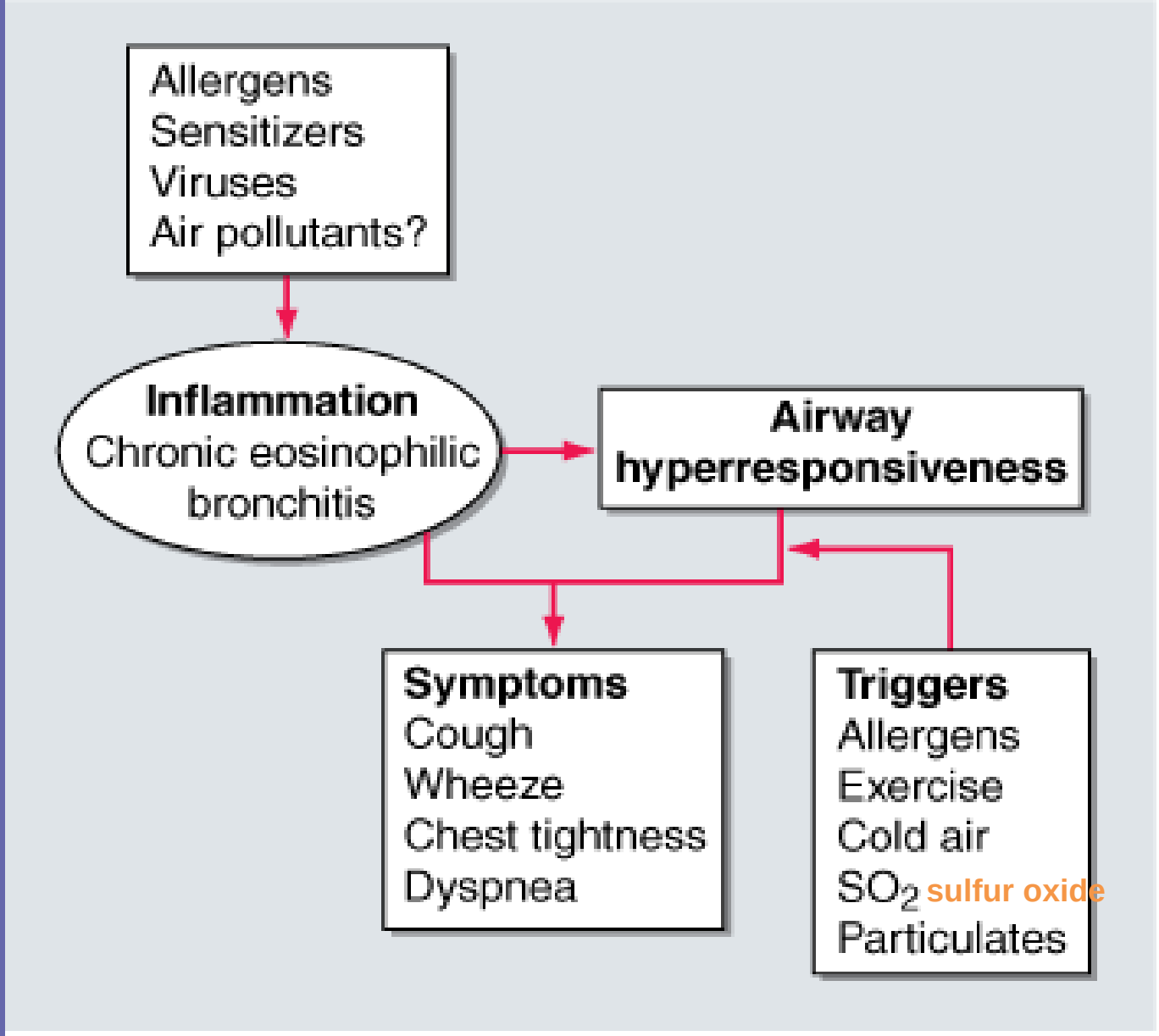
More sustained phase of bronchoconstriction.

Influx of inflammatory cells and an increase in bronchial responsiveness.

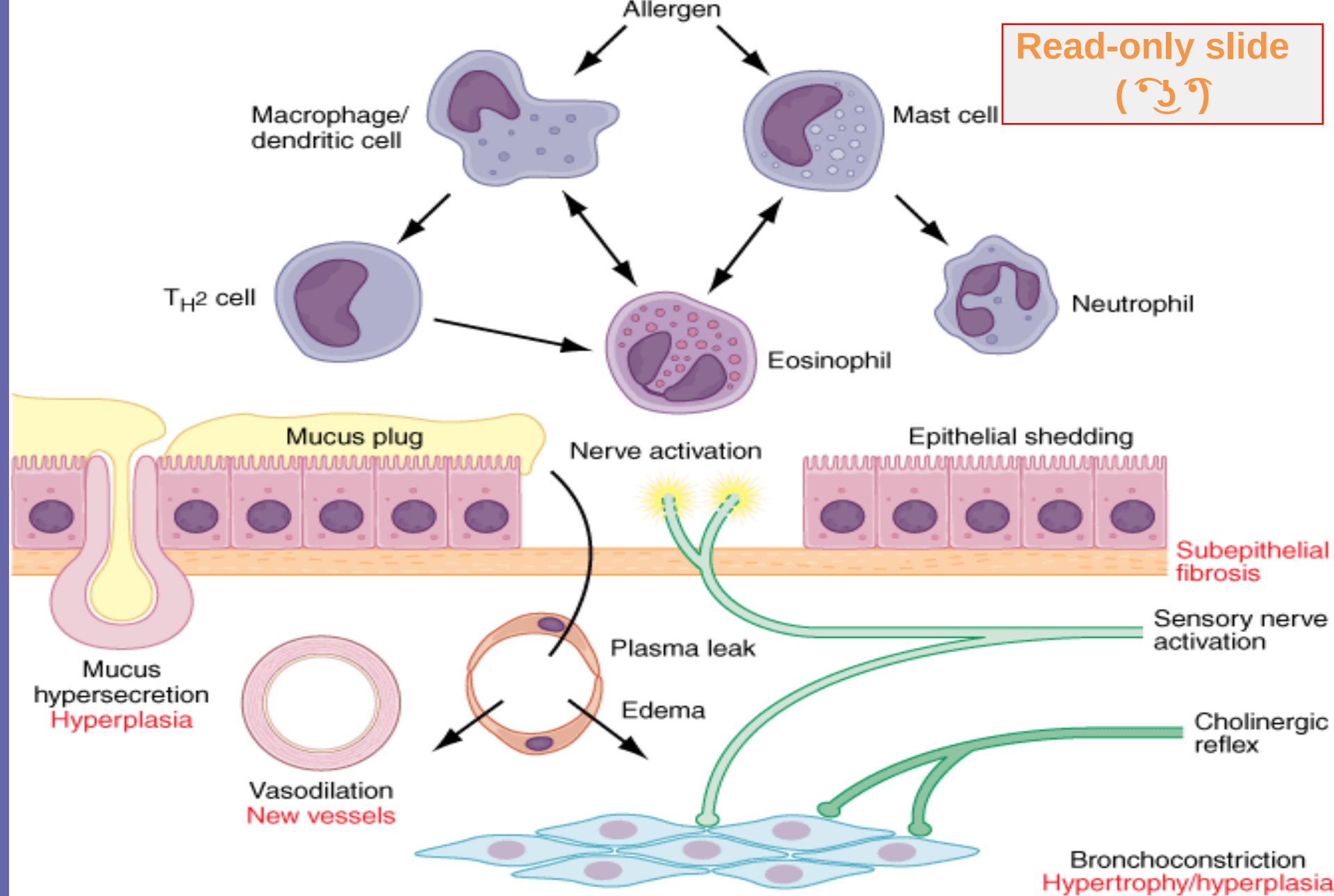
The mediators here are cytokines produced by TH2 lymphocytes, especially interleukins: 5, 9, and 13.

These will stimulate IgE production by B lymphocytes, and directly stimulate mucus production.

Prevented by corticosteroids.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com



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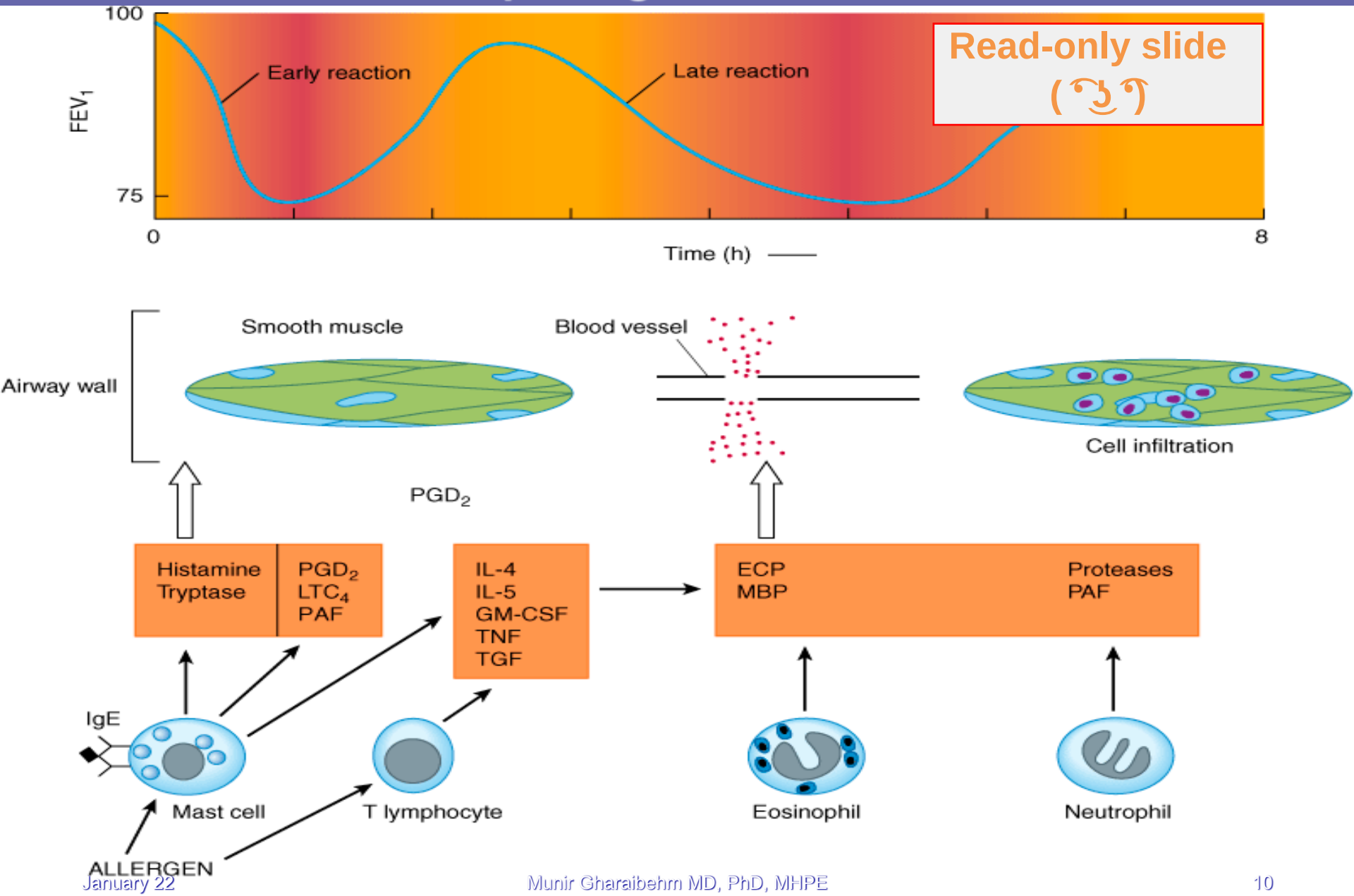
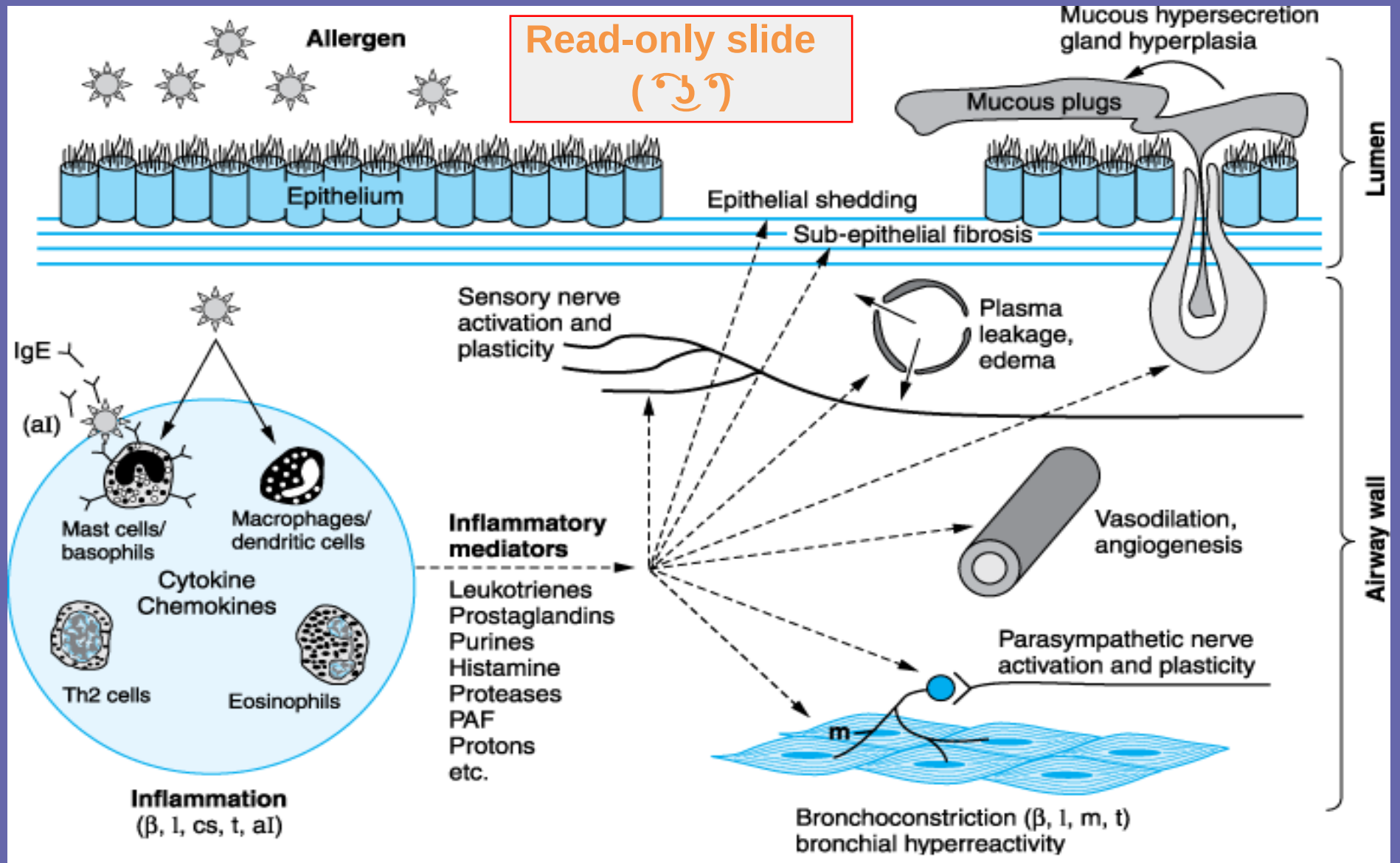
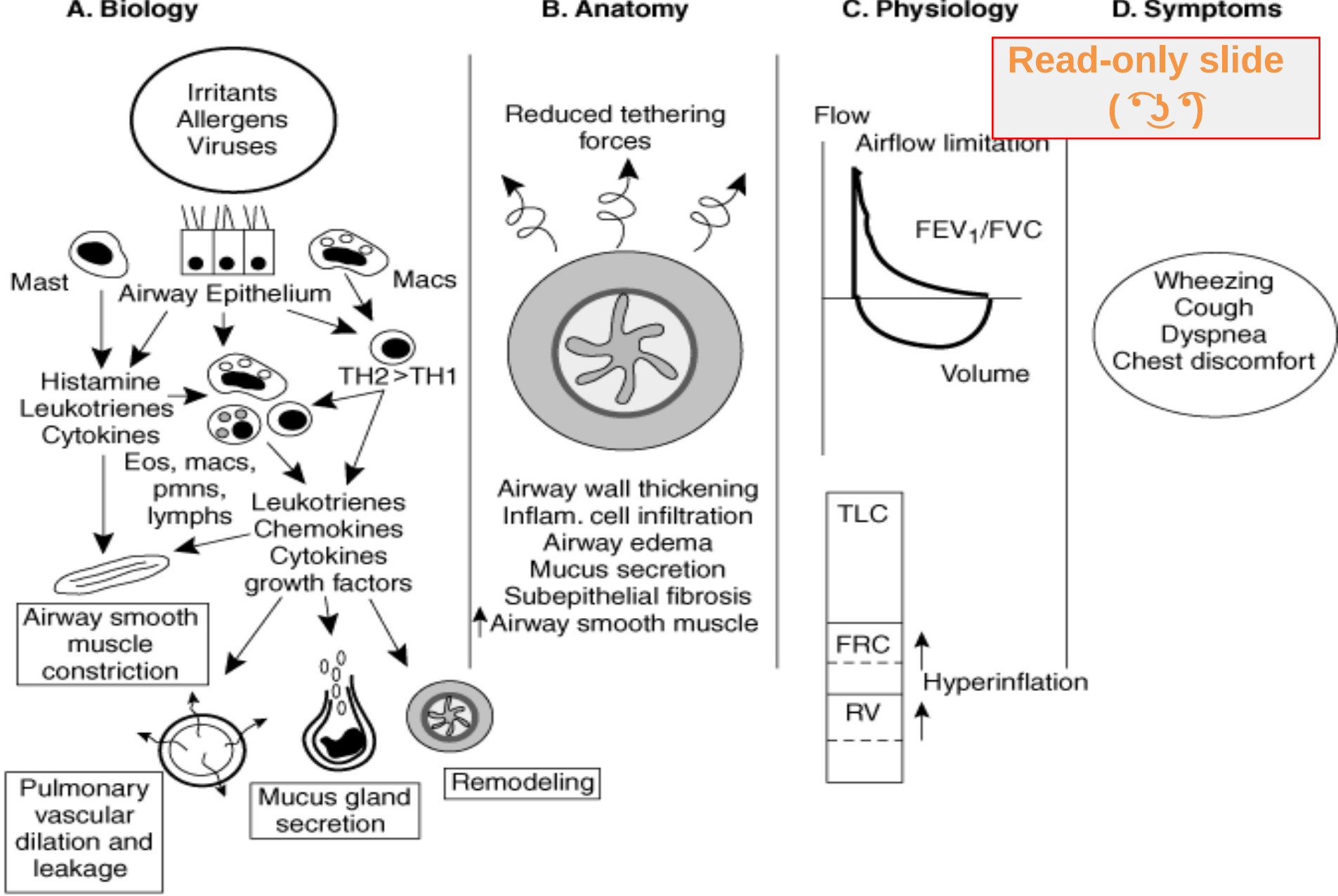
Immunopathogenesis of asthma.



Simplified view of allergic inflammation in the airways.





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Histopathology of a small airway in fatal asthma

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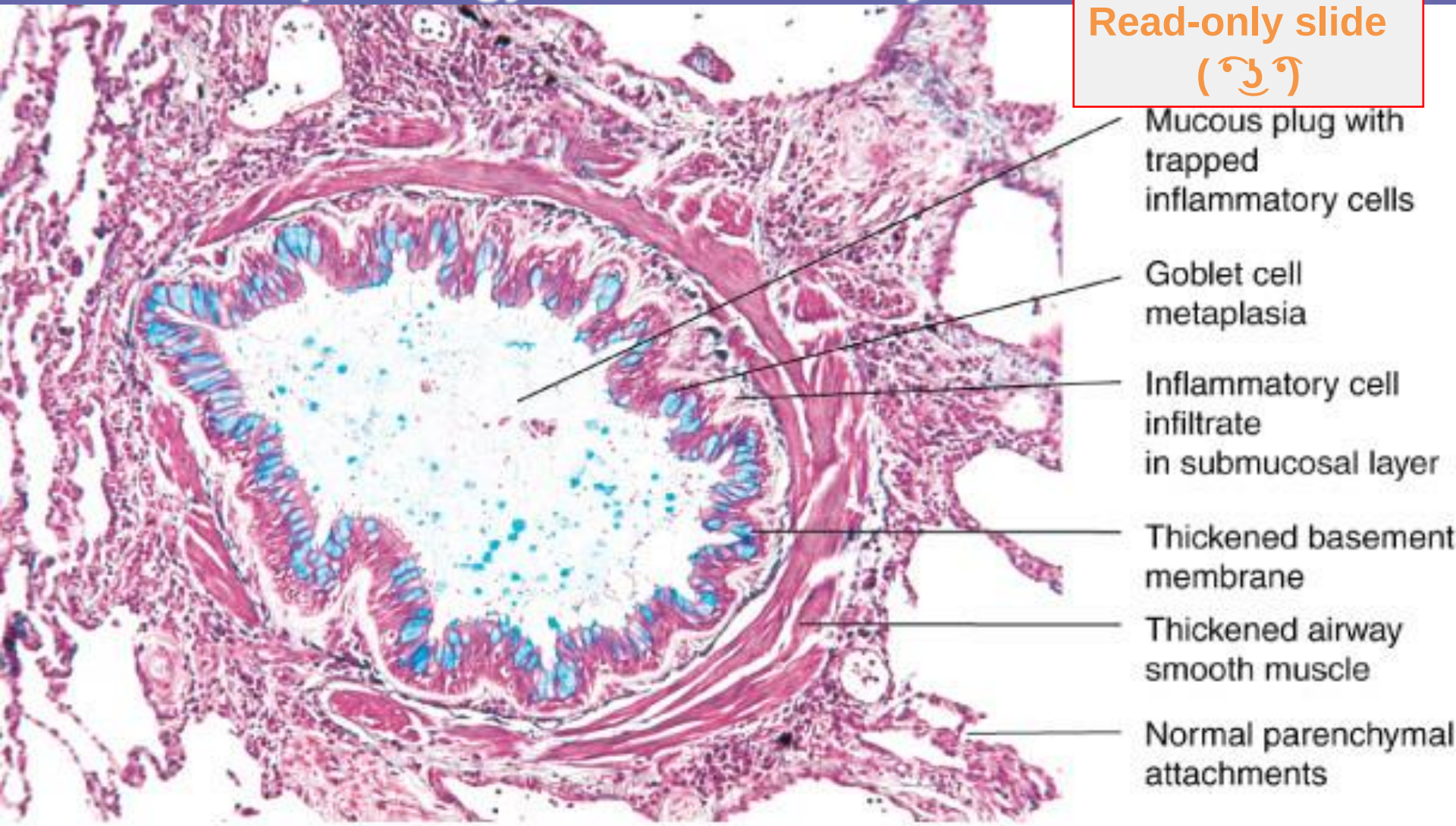

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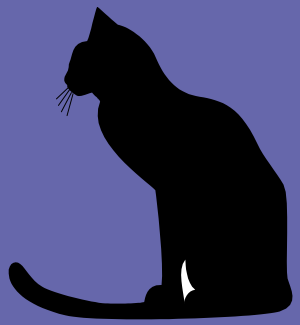
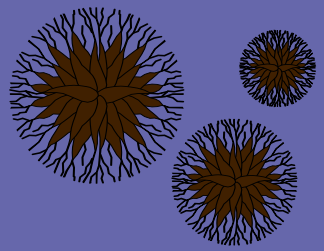
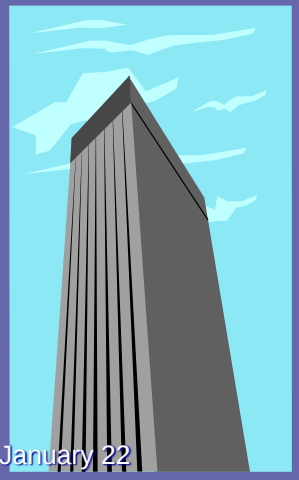
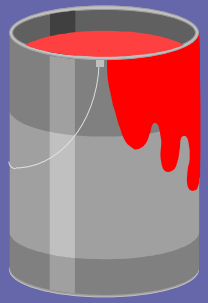
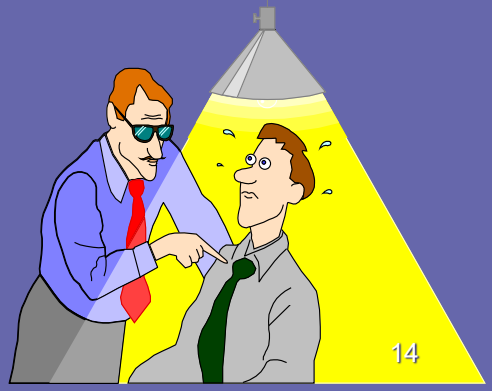
Asthma Triggers











Asthma Triggers

- Exercise / cold air
- Cigarette smoke
- Stress / anxiety situations زي التحقيقات الجنائية
- Animal dander's (cats, dogs etc..)
- Allergens (grass, trees, molds, cockroach)
- Pollutants (sulfur dioxide, ozone, etc…)
- Fumes/toxic substances
- Medications (ASA, NSAID's, others)

ASA: acetylsalicylic acid (aspirin)

Diagnosis of Asthma - Subjective

- ✓ **Cough** - usually in spasms and to the point of vomiting - nighttime worse than daytime. if the patients coughs more in night so there's high probability that they have bronchial asthma
- ✓ **Cough** may follow exposure to cold air, exercise, URI (common cold), or exposure to an allergen. URI: upper respiratory infection
- ✓ **Dyspnea** > cough or wheezing > sputum. the patient is irritated from dyspnea more than coughing,weezing or sputum
- ✓ **Past history** of bronchiolitis as a child.
- ✓ **Family history** of asthma is common

Diagnosis of Asthma - Objective

- Reduced FEV_1 and FEV_1/FVC ratio — spirometry
- Reduced Peak Expiratory Flow Rate (FEFR)
- Reversibility with Bronchodilators — if the patient gets better after bronchodilators they probably got bronchial asthma
- Heightened response to Methacholine Test.
- Increase in expired Nitric Oxide. — NO is an indication of inflammation
- Increase in Inflammatory mediators and their metabolic products in body fluids

Regarding 4th point:
Methacholine is like acetylcholine, it's a parasympathetic which causes constriction.
Methacholine test is a challenge test, so the patient shouldn't have bronchoconstriction at the moment, and you want to diagnose them,
You give the patient methacholine in very low doses, then they'll have bronchoconstriction, which is short lived.
Extra: Methacholine challenge test is performed to evaluate how "reactive" or "responsive" your lungs are.

خرافات وأفكار خاطئة

Myths and Misconceptions

- ✓ **Patient and physician "Steroid-o-phobia".**

  Short course of steroids helps in preventing patients deterioration. Steroids should be used in patients with corona

- ✓ **Asthma is an emotional illness.**

- ✓ **Asthma is an acute disease.**

  Asthma isn't an acute disease, even if it's gone for some years, it'll come back!!

- ✓ **Asthma medications are addictive.**

  Some people believe all medications are addictive, which is totally false.

- ✓ **Asthma medications become ineffective if they are used regularly.**

- ✓ **Asthma is not a fatal illness / It does not kill.**

Index of Severity

Peak Expiratory Flow Rate

	% Predicted	Lability (%)
		variability
		It should be stable in normal people whenever they did the test
Normal	> 90	< 10
Mild	70 - 90	10 - 20
Moderate	50 - 70	20 - 30
Severe	30 - 50	30 - 50
Very Severe	< 30	> 50

Overview of the changing therapy of asthma by decade

تطوّر العلاج

1960's

it's a derivative of xanthine products, such as caffeine or tea
They inhibit the phosphodiesterase enzyme (which breaks down cAMP), if you inhibit the breakdown of cAMP this means accumulation of cAMP, which will produce bronchodilation

epinephrine, adrenaline & noradrenaline increase cAMP

Aminophylline, Epinephrine, Ephedrine

derived from plant Ephedra sinica.
It causes release of catecholamin (epinephrine, norepinephrine) so it will cause bronchodilation, CNS stimulation, cardiac stimulation

1970's

like aminophylline

Beta-agonists, Theophyllines,

steroids

Beclomethasone, Cromolyn,

Ipratropium anticholinergic

Survey of the changing therapy of asthma by decade

1980's

Same as before, but we obliterated theophylline because it causes cardiac stimulation

Beta-agonists, Inhaled Corticosteroids, Cromolyn, Ipratropium

1990's

Inhaled Corticosteroids, Beta-agonists, Theophylline, Leukotriene Inhibitors

Survey of the changing therapy of asthma by decade

2000's

LABA: long acting beta agonist
LTRA: Leukotriene receptor antagonists

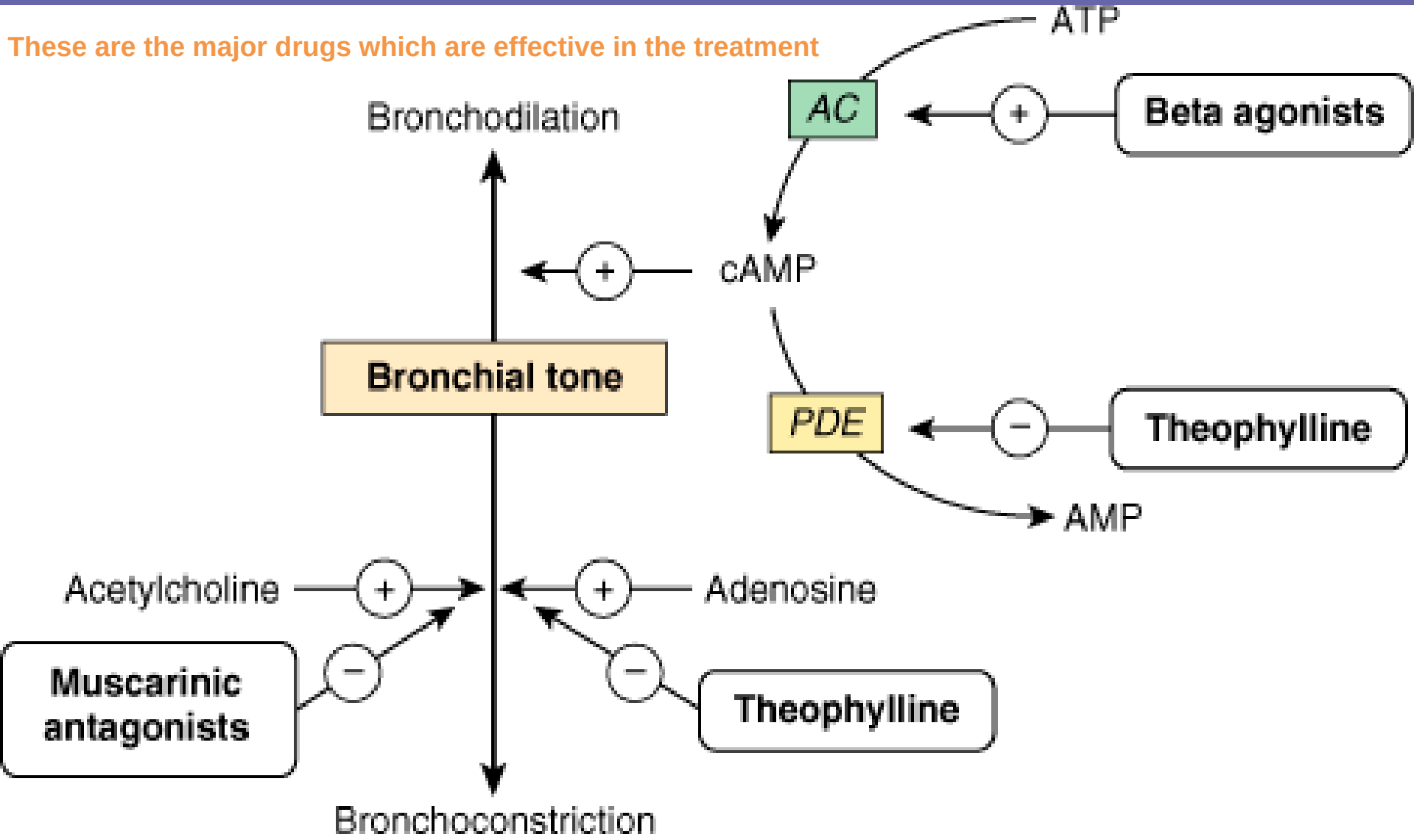
Corticosteroids + LABA, LTRAs, Theophylline, Cromolyn, Ipratropium, Tiotropium

like Ipratropium, but with some modifications

2010's

Prevention including gene therapy.

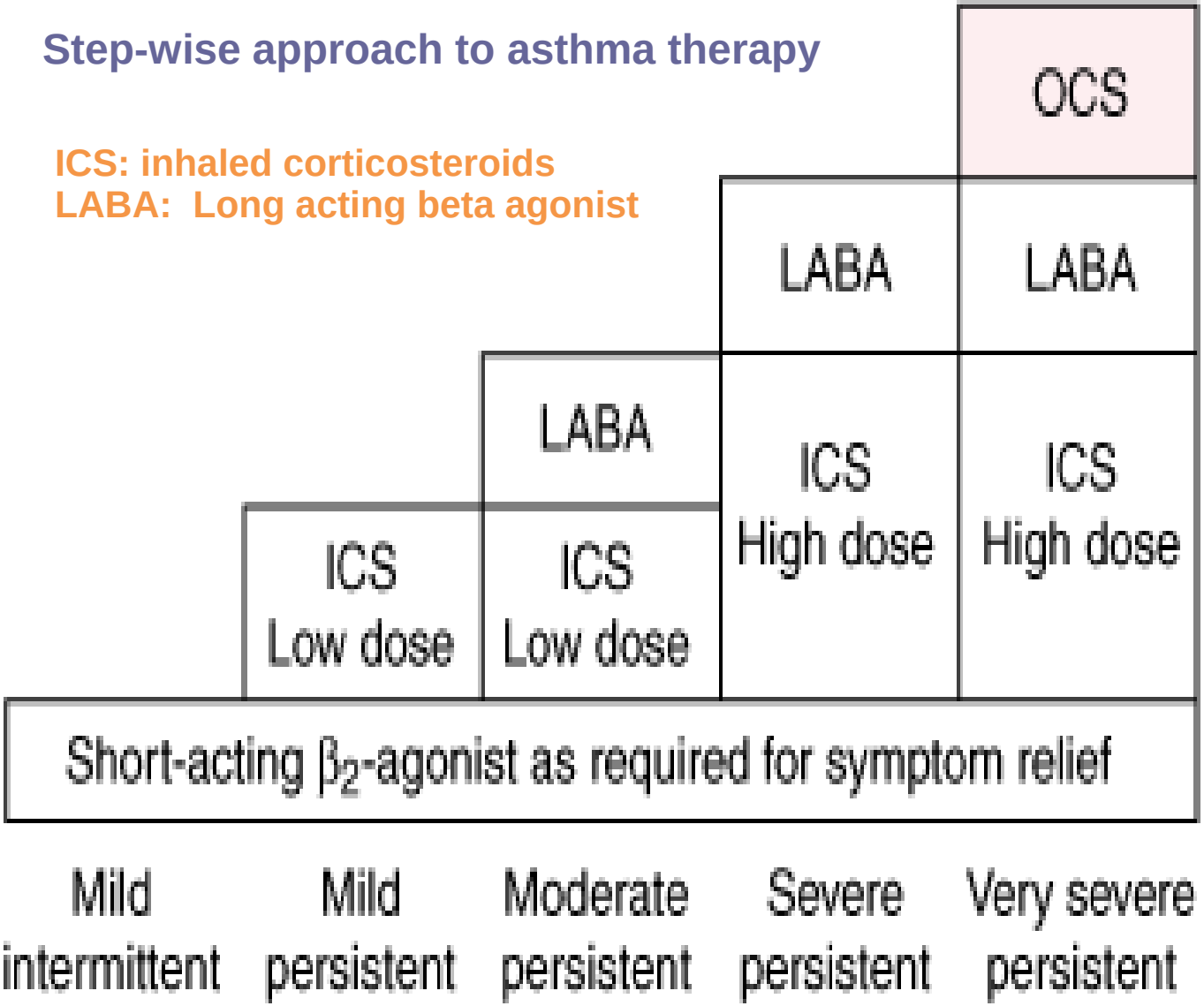
These are the major drugs which are effective in the treatment



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Step-wise approach to asthma therapy

ICS: inhaled corticosteroids
LABA: Long acting beta agonist



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Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

Relievers / Controllers

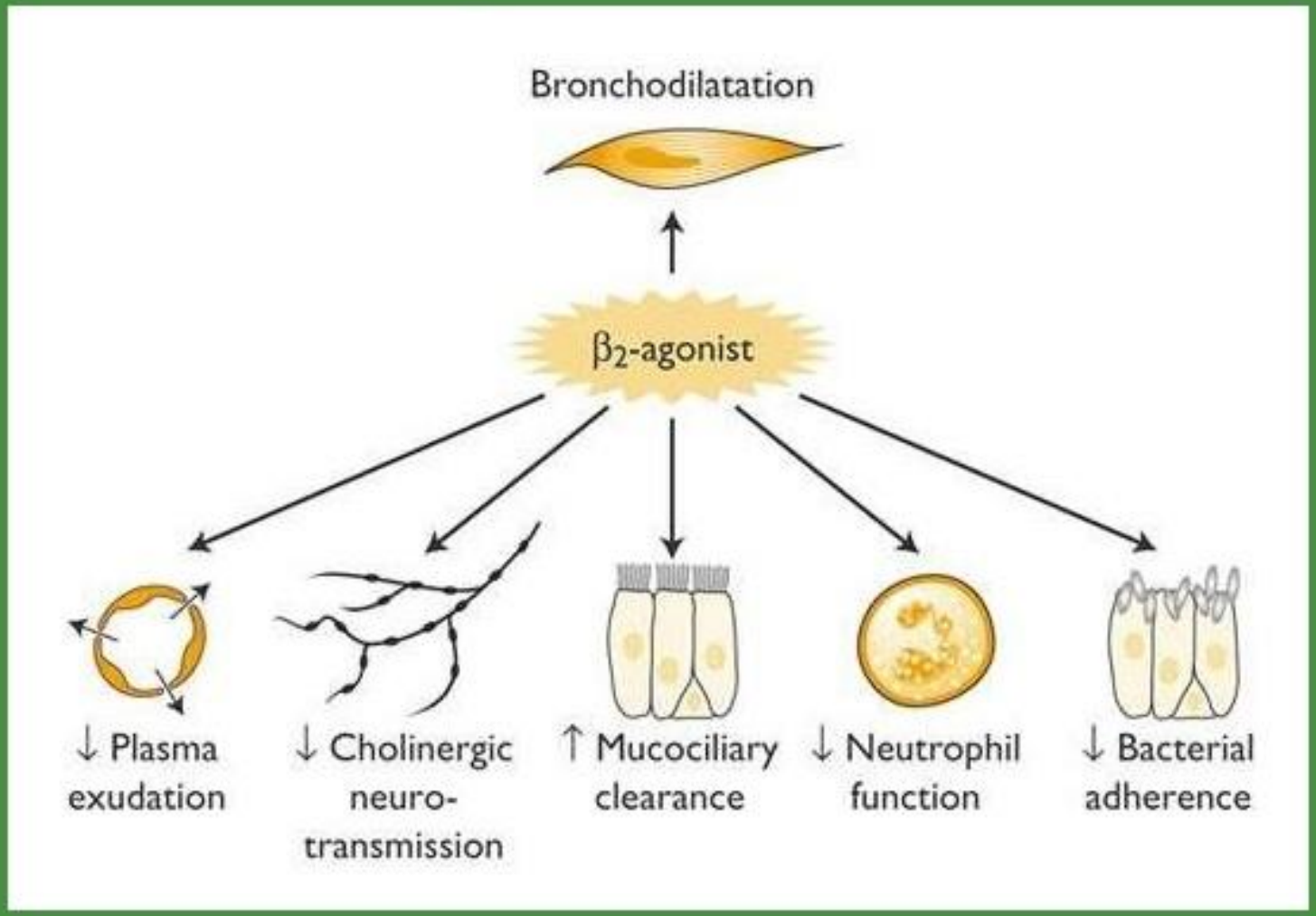
- **Quick relief medications:**
  - Inhaled Short acting Beta-2 Agonists
  - Inhaled Anticholinergics
  - Systemic Corticosteroids
- **Long-term control medications:**
  - Topical (inhaled) Corticosteroids
  - Inhaled Cromolyn Na and Nedocromil
  - Oral Methylxanthines (Theophyllines)
  - Inhaled Long-acting Beta-2 Agonists (LABA)
  - Oral Leukotriene modifiers (LTRA)

Beta 2-Adrenergic Agonists

actions of beta 2 adrenergic agonist:

- ✓ Medications of choice for acute exacerbations
  - ✓ Actively relax airway smooth muscle.
  - ✓ Inhibit release of inflammatory mediators.
  - ✓ Enhance muco-ciliary activity.
  - ✓ Decrease vascular permeability.
  - ✓ Inhibit eosinophil activation.

Role of beta agonists in asthma and COPD



β2 agonists have other beneficial effects including inhibition of mast cell-mediator release, prevention of microvascular leakage and airway edema, and enhanced mucocillary clearance. The inhibitor effects on mast cell actions suggest that β2 agonists may modify acute inflammation.

Beta 2-Adrenergic Agonists

- **Molecular Actions:**

Increase cAMP.

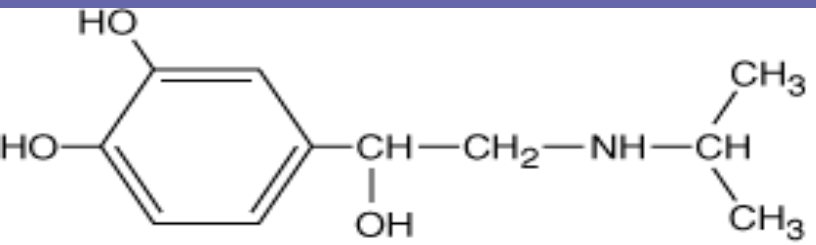
Activate protein kinase A.

Phosphorylate kinases.

All lead to decreased cytosolic Ca++.

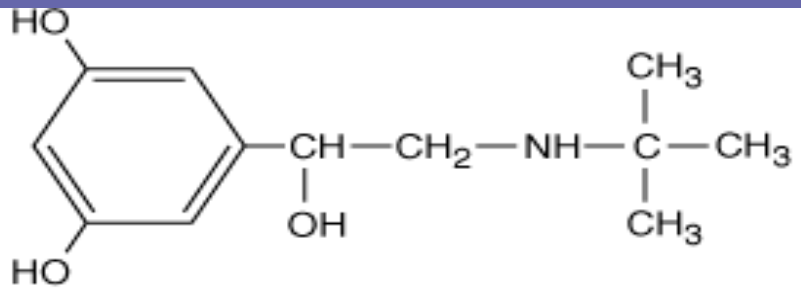
Calcium is responsible for contraction of smooth muscles, so increasing cAMP will decrease Ca++

Beta2-Selective Drugs



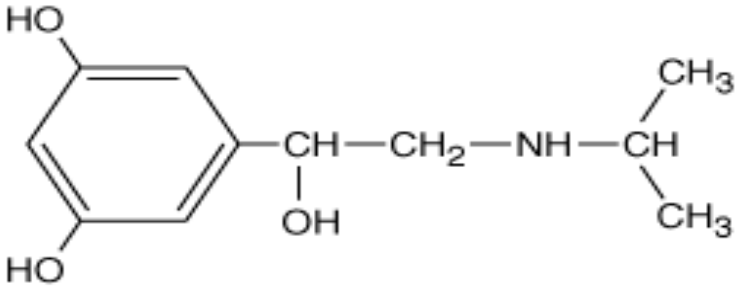
Isoproterenol

works on Beta 1 & Beta 2



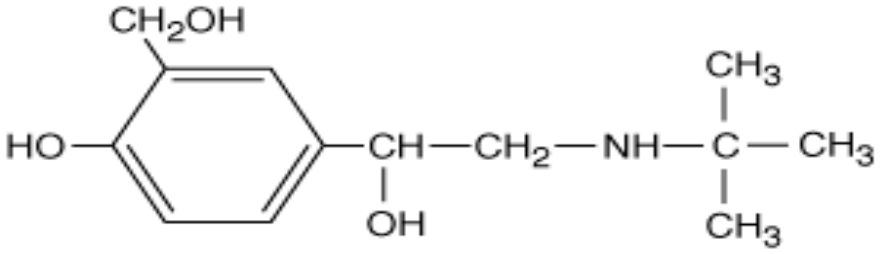
Terbutaline

Beta 2 selective



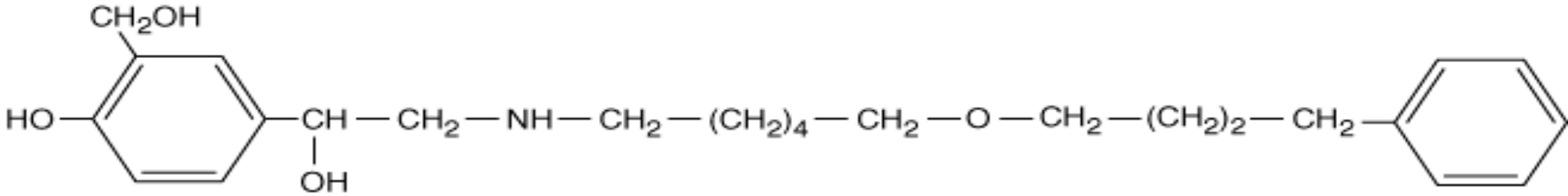
Metaproterenol

Beta 2 selective



Albuterol (salbutamol)

Beta 2 selective



Beta 2 selective

Salmeterol

Beta 2-Adrenergic Agonists

- **Epinephrine:**

Obtained from bovine (البقر) adrenal gland.

Stimulates α, β1 and β2 receptors.

Not effective orally.

Subcutaneous. In emergency, in a situation called status asthmaticus (persistance of acute attacks of bronchial asthma), also it's used in anaphylactic shock

Epinephrine will raise the blood pressure, and cause bronchodilation, so it'll relieve bronchial asthma

Distribution and Actions of B1/B2 receptors

Organ	B1	B2
Heart	+ inotropic and chronotropic	
Blood Vessels		Vasodilation and Hypotension
Bronchi		Bronchodilation
Uterus		Tocolysis Tocolysis: relaxes pregnant's uterus
Skeletal Muscles		Tremor
Fat tissue	Lipolysis (B3)	
Carbohydrate Metabolism		Glycogenolysis

Beta 2-Adrenergic Agonists

- **Isopreterenol:**

Stimulates β1 and β2 receptors.

First (1960s) convenient, pocket- sized multidose inhalers.

Considerable tachycardia and pounding. خـفـقـان

Short acting Beta 2-Adrenergic Agonists

- **Albuterol(Salbutamol).** USA UK Short acting beta 2 agonist
- **Terbutaline.**
- **Pirbuterol.**
- **Metaproterenol.**
- **Isoetharine.**

Rapid onset: 3-5 minutes.

Maximal effect: 30-60 minutes.

Duration: 4-6 hours.

Long -acting Beta 2-Adrenergic Agonists(LABA)

- **Salmeterol.**
- **Formoterol.**

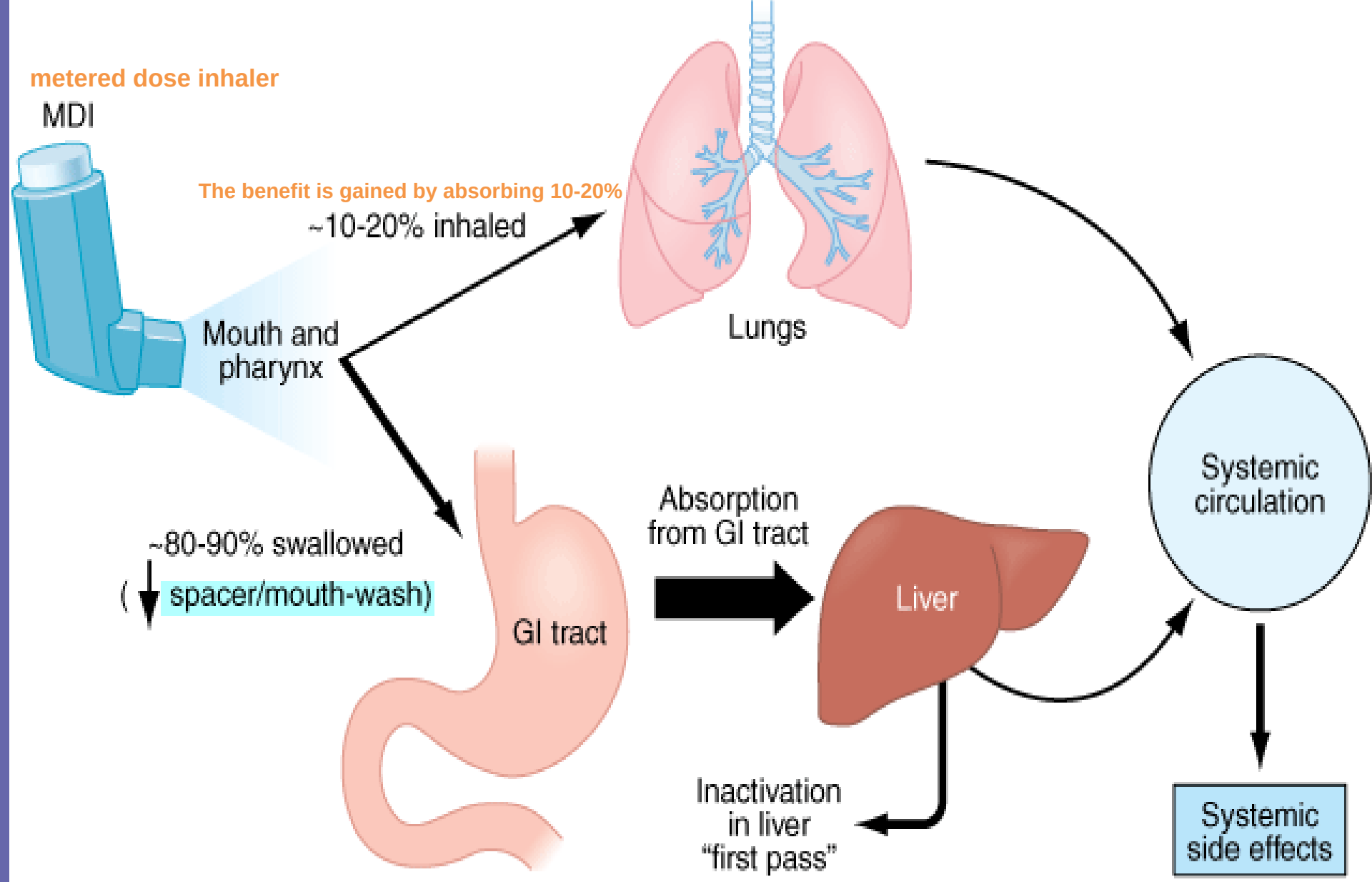
Long-acting inhaled bronchodilators:12 hours.

Suppress nighttime attacks.

Controllers with steroids.

No tachyphylaxis.

metered dose inhaler



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Problems of Metered Dose Inhalers(MDI)

- Cap not removed prior to use in some patients
- Timing of canister actuation to inspiration is critical - only first air in gets to the right place
- Inspiration too rapid - should take 4 - 5 seconds
- Nasal inspiration contains no medication
- Spacers not used, despite evidence of their great utility

➢ To use MDI's correctly requires instruction

Spacer

- A large volume chamber attached to a MDI, used to decrease the deposition of drug in the mouth.
- Serves to reduce the velocity of the injected aerosol before it enters the mouth and allows large drug particles to deposit in the device.
- The smaller, high velocity drug particles, are more likely to reach the target airway tissue.
- Rinsing the mouth can also decrease systemic absorption and oropharyngeal candidiasis.

Beta 2-Adrenergic Agonists

- ✓ Medications of choice for acute exacerbations
  - ✓ Actively relax airway smooth muscle
  - ✓ Enhance muco-ciliary clearance
  - ✓ Decrease vascular permeability

However, short-acting formulations are to be used on a p.r.n. basis only - regular use is associated with diminished control

P.R.N.: it stands for 'pre re nata', which means that the administration of medication is not scheduled. Instead, the prescription is taken as needed.

Beta 2-Adrenergic Agonists

- **TOXICITY:**
- Nervousness, Anxiety, Tremor
- Due to vasodilation, may increase perfusion of poorly ventilated lung units and might transiently decrease PaO2.
- Tachyphylaxis. Tolerance, which is reduced effectiveness
- Increased mortality due to cardiac toxicity.

because they're Beta 2 selective, not Beta 2 specific.
Beta 2 selective drugs work on Beta 1 & Beta 2, but they work on Beta 2 more than Beta 1. But with increasing dose, you lose the selectivity and they'll work on Beta 1 and cause cardiac stimulation!

"A Nested Case-Control of the Relation Between Beta-Agonists & Death and Near Death From Asthma"

- All deaths and Beta agonist use were studied for 1 year.
- As Beta Agonist use increased, risk of death increases.
- For each canister per month increase in use, the risk of death doubled.

- Conclusion:

  Use of beta 2-Agonist drugs, as a class, is associated with an increased risk of death

Beta 2-Adrenergic Agonists

Patients homozygous for glycine at the B-16 locus of the β receptor improved with regular use of albuterol or salmeterol.

Patients homozygous for arginine at the B-16 locus of the β receptor(found in 16% of Caucasians and more frequently in blacks) deteriorated with regular use of albuterol or salmeterol