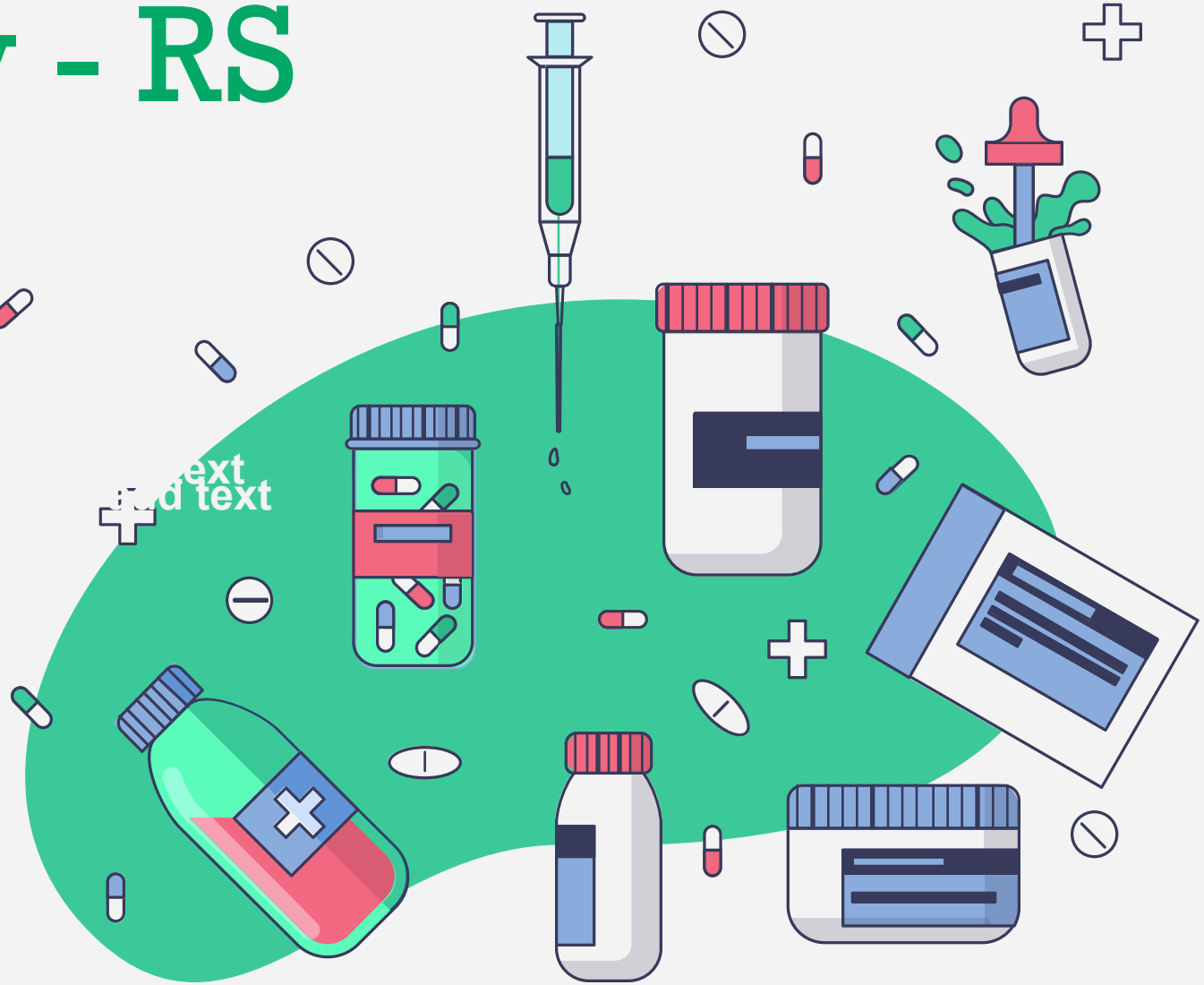
Pharmacology - RS

Done By

Leen Anwer AlHadidi
& Samah Freihat

Corrected By

Dana Alkhateeb



النادي الطلابي
كلية الطب

Treatment of Bronchial Asthma

Dr Munir Gharaibeh, MD, PhD, MHPE

Department of Pharmacology

School of Medicine

December 2021

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.**
  - **Extent of bronchoconstriction *and***
  - **Degree of inflammation.**
- **The course is *unpredictable*.**
- **Therapy must be *individualized*.**

Acute attack can be relieved by itself but it might deteriorate

Risk of Not Treating Asthma

- **Deterioration of the condition.**
- **Accelerated decline in the function of the patient's lungs as measured by PFT's.** Pulmonary function test
- **Increased number of attacks of asthma.**
- **Poorer response to therapy if started late.**
- **Increased mortality from asthma.**

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.**
- **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.**

Emergency department

Pathogenesis

- **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.

الدكتور ما رح يسأل عن الباثو بالامتحان
يسعد مساكم

Pathogenesis

- **Late Asthmatic Response:**

4-5 hours later.

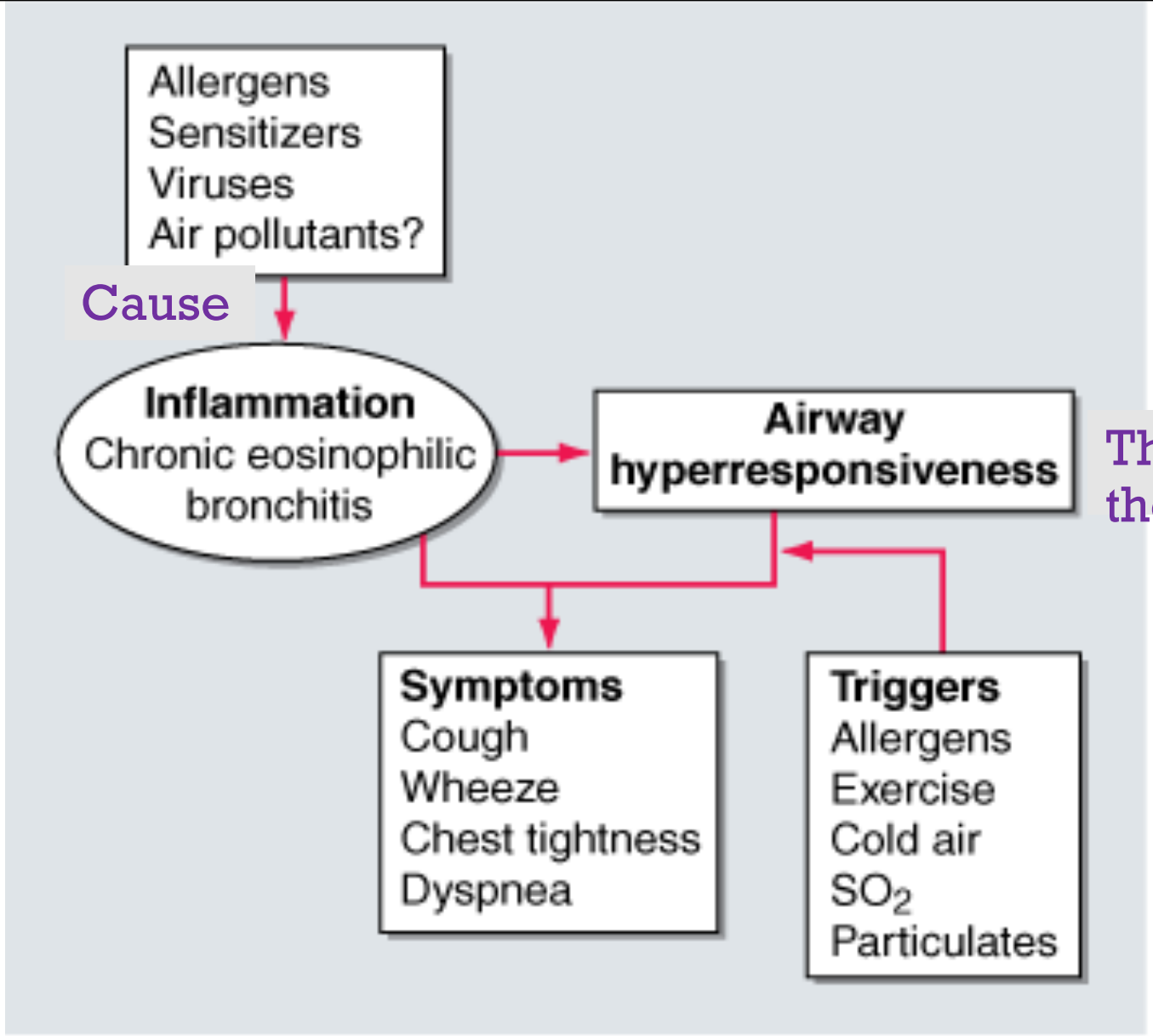
More sustained phase of bronchoconstriction.

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.

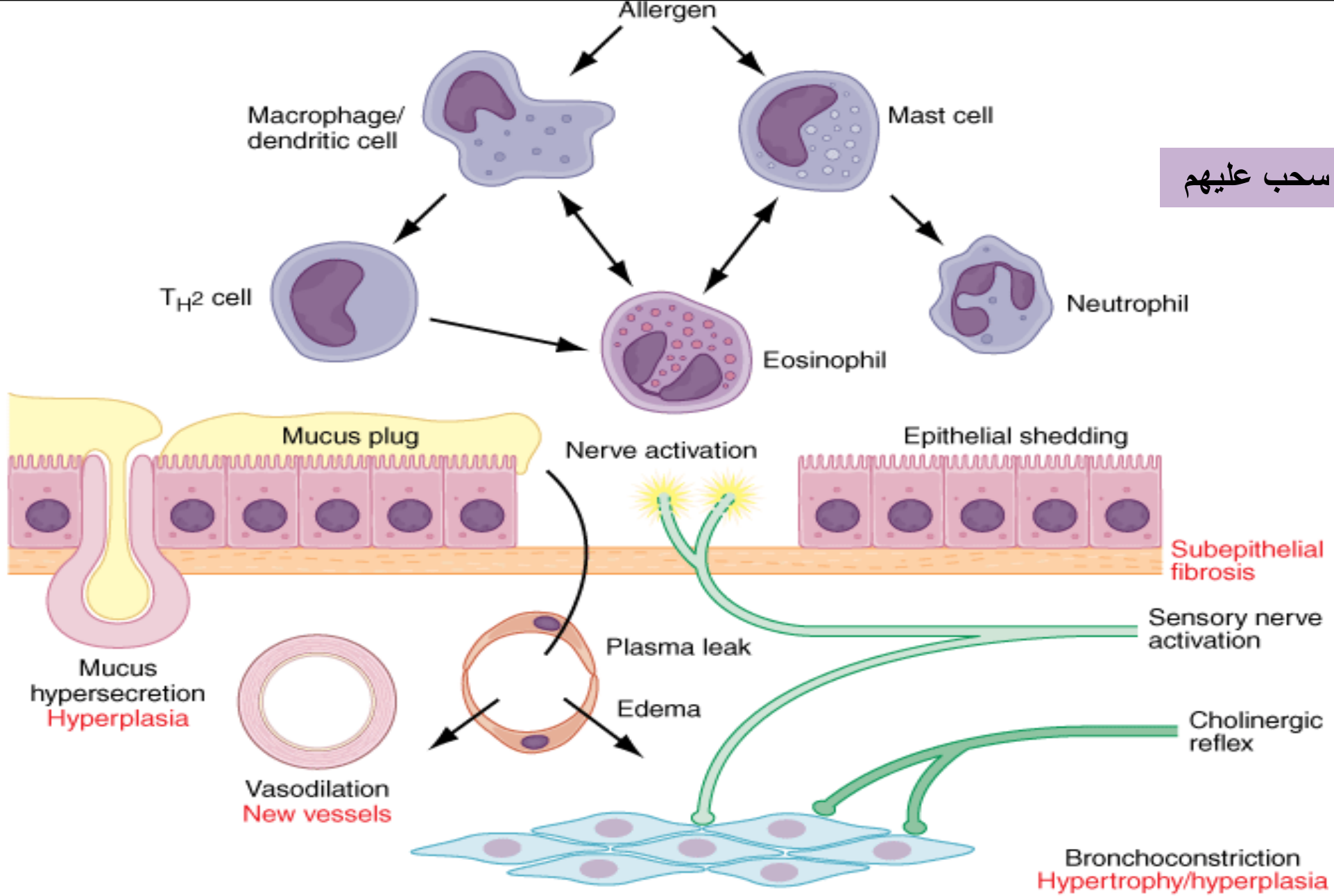
Prevented by corticosteroids.



The inflammation will increase the responsiveness of the airway

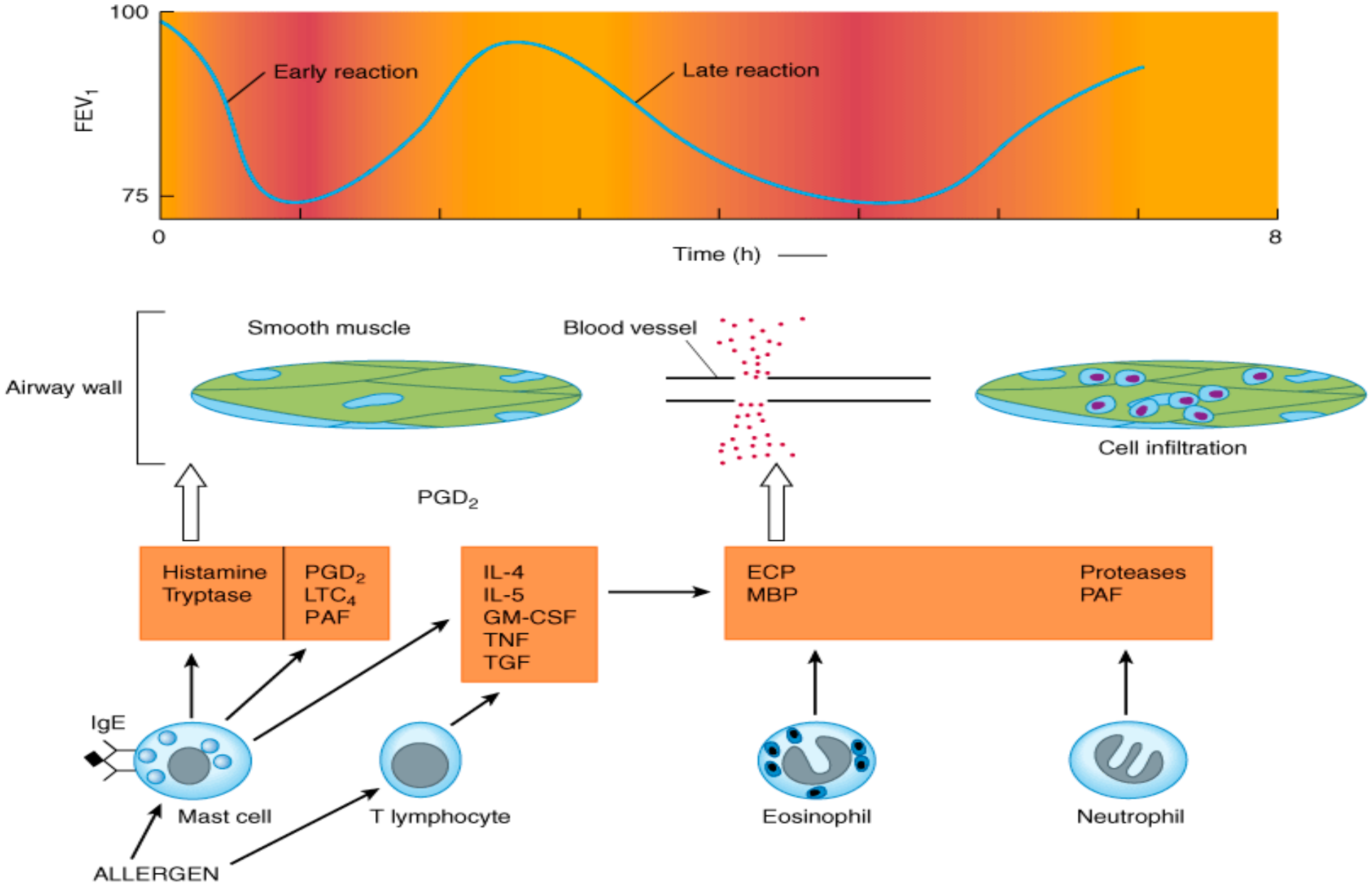
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

الدكتور سحب عليهم



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

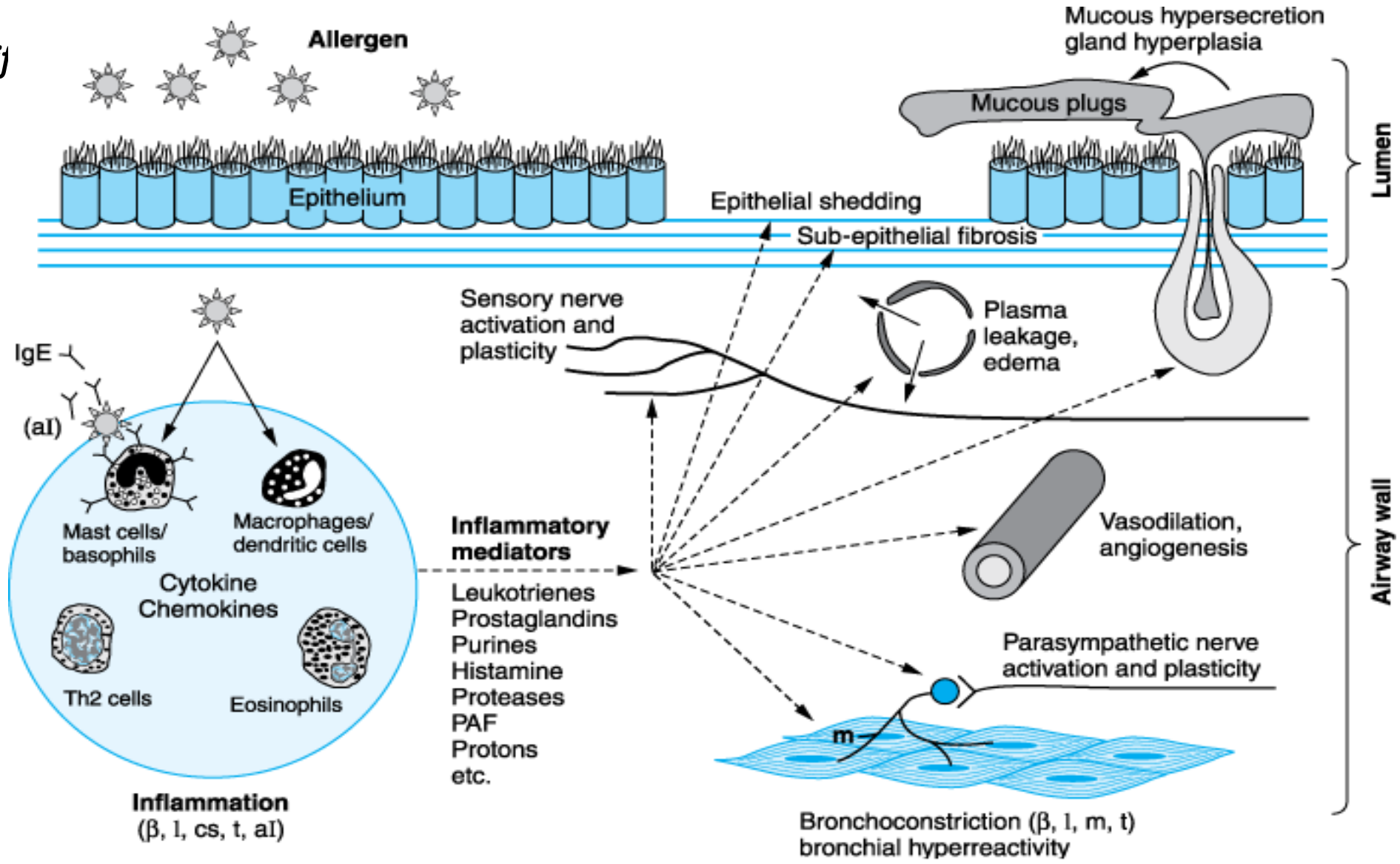
Immunopathogenesis of asthma.



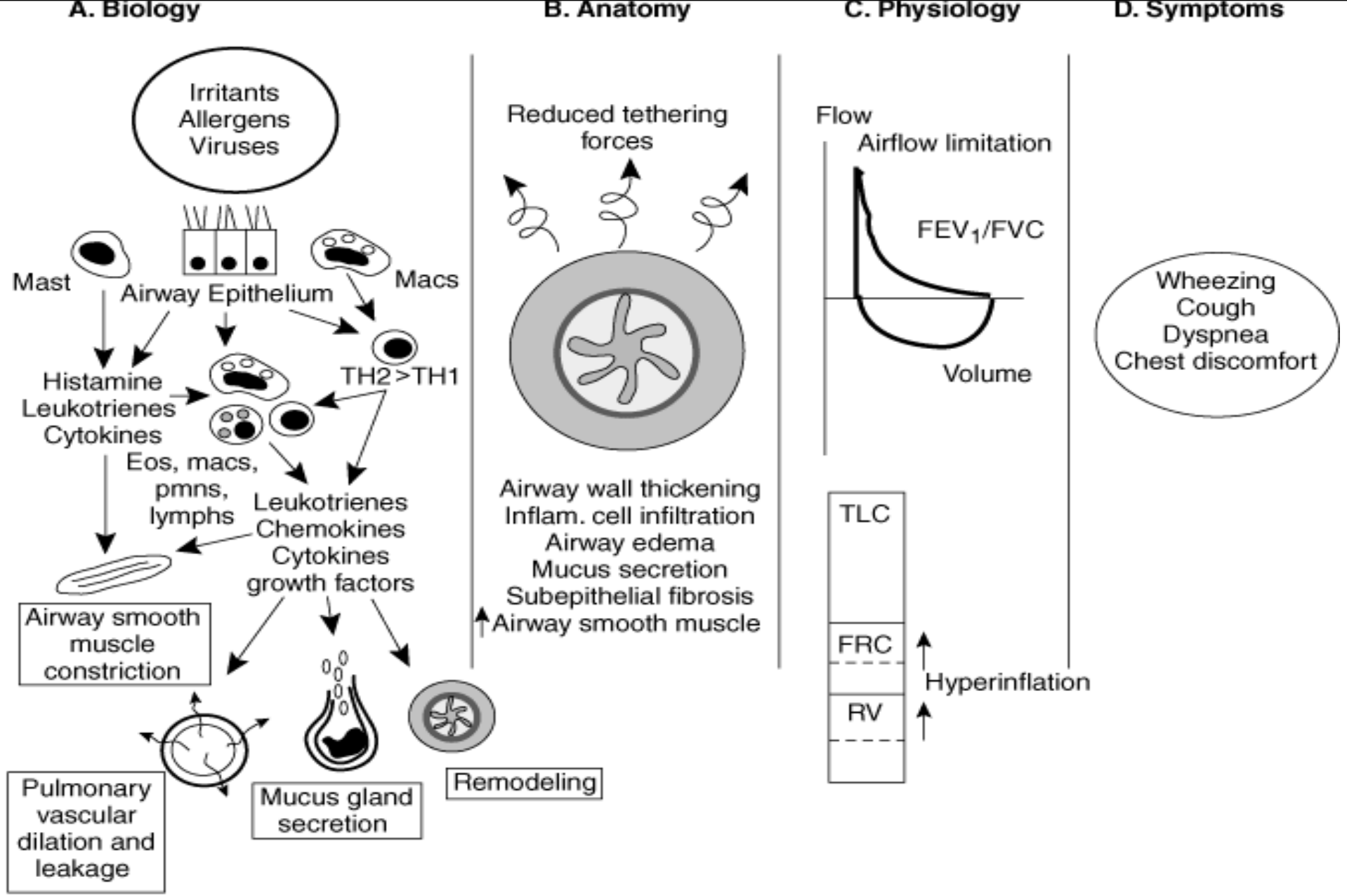
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Simplified view of allergic inflammation in the airways.

Simplij



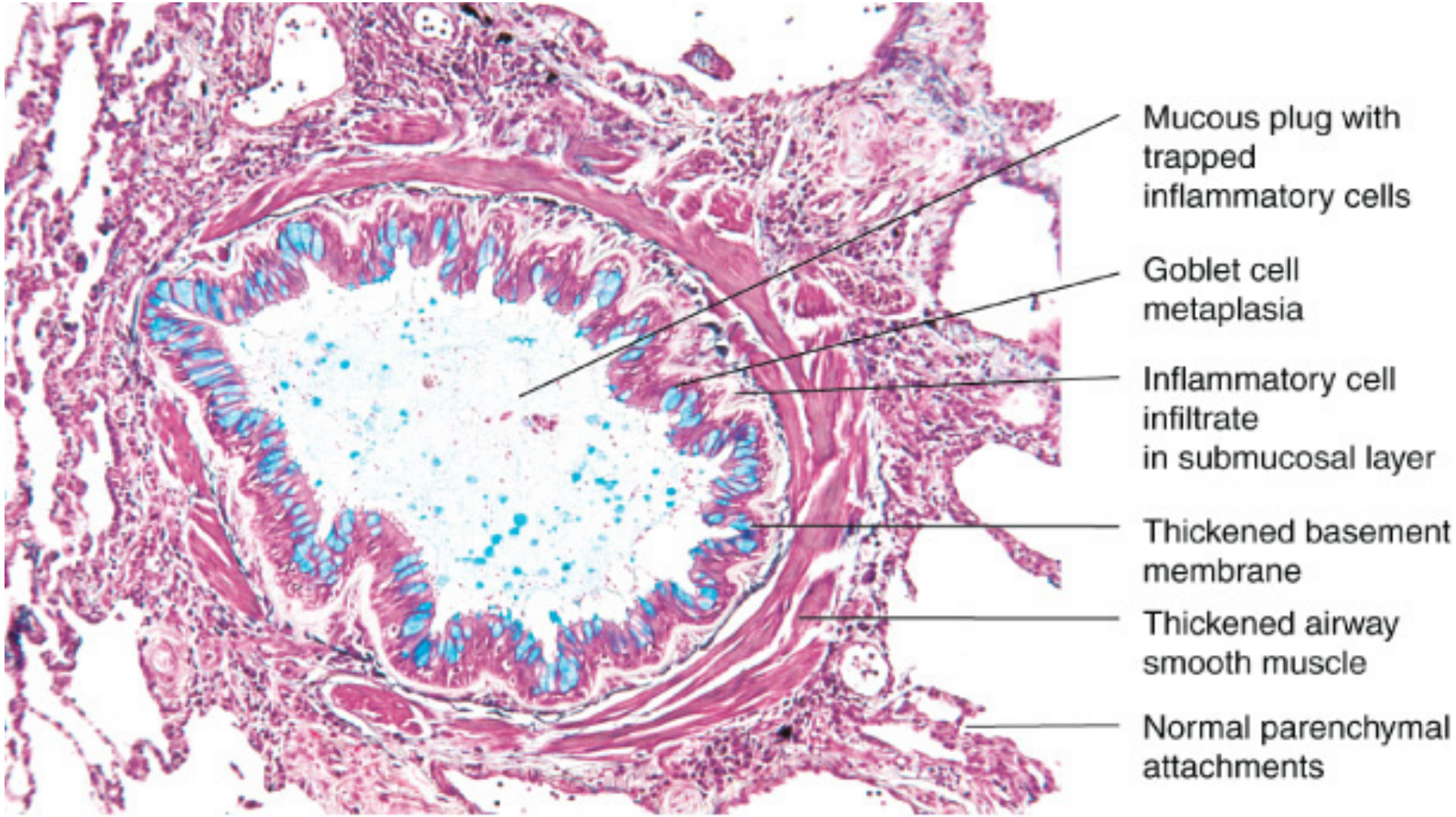
Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com



Source: Hanley ME, Welsh CH: *Current Diagnosis & Treatment in Pulmonary Medicine*: http://www.accessmedicine.com

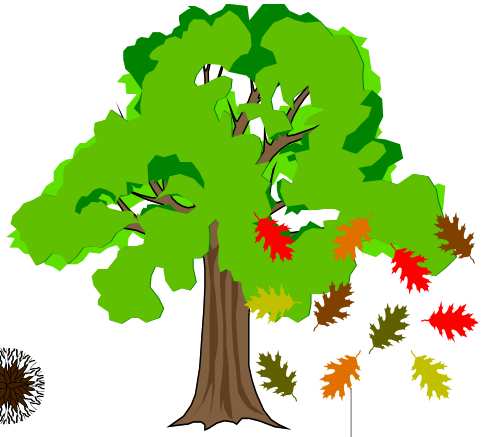
Histopathology of a small airway in fatal asthma

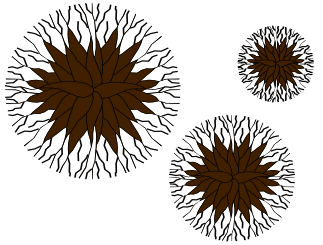
الدكتور ضل ساحب لهون

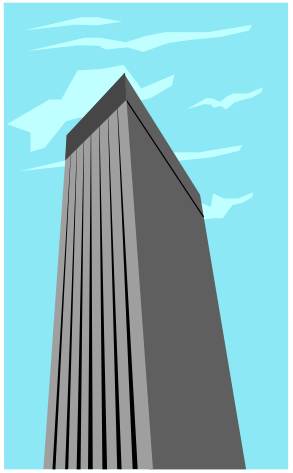


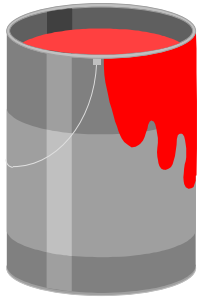
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

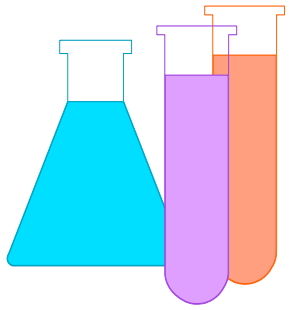
Asthma Triggers











Asthma Triggers

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

Aspirin

Diagnosis of Asthma - Subjective

Severe cough

✓ Cough - usually in spasms and to the point of vomiting
- nighttime worse than daytime.

✓ Cough may follow exposure to cold air, exercise, URI (common cold), or exposure to an allergen.

✓ Dyspnea > cough or wheezing > sputum.

Inflammation and infection because of obstruction

✓ Past history of bronchiolitis as a child.

✓ Family history of asthma is common

Diagnosis of Asthma - Objective Spirometry

- **Reduced FEV1 and FEV1/FVC ratio**
- **Reduced Peak Expiratory Flow Rate (FEFR)**
- **Reversibility with Bronchodilators**
- **Heightened response to Methacholine Test.** Parasympathetic activator
- **Increase in expired Nitric Oxide.** Indication of inflammation
- **Increase in Inflammatory mediators and their metabolic products in body fluids**

  Eosinophilia , CRP

Myths and Misconceptions

خرافاااات

- ✓Patient and physician “Steroid-o-phobia”.
- ✓Asthma is an emotional illness.
- ✓Asthma is an acute disease.
- ✓Asthma medications are addictive.
- ✓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 (%)	قياس التذبذبات في القراءة في أوقات مختلفة
Normal	> 90	< 10	أقل من ١٠٪ اختلاف في القراءات
Mild	70 - 90	10 - 20	
Moderate	50 - 70	20 - 30	
Severe	30 - 50	30 - 50	
Very Severe	< 30	> 50	أكثر من ٥٠٪ اختلاف كبير بالقراءات

Overview of the changing therapy of asthma by decade

1960's

Aminophylline, Epinephrine, Ephedrine

Phosphodiesterase inhibitor (Xanthine products) in coffee , tea & cacoa

Injection increases CAMP

Releases catecholamines release epinephrine and NE
⬆️ CAMP
CNS stimulation and heart stimulation

1970's

Beta-agonists, Theophyllines,

Beclomethasone, Cromolyn, Ipratropium

Steroids

Anticholinergic

Phosphodiesterase enzyme breaks down CAMP
If we use phosphodiesterase inhibitor we increase accumulation of CAMP ➡️ bronchodilation

Survey of the changing therapy of asthma by decade

1980's

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

Long acting ßeta agonist

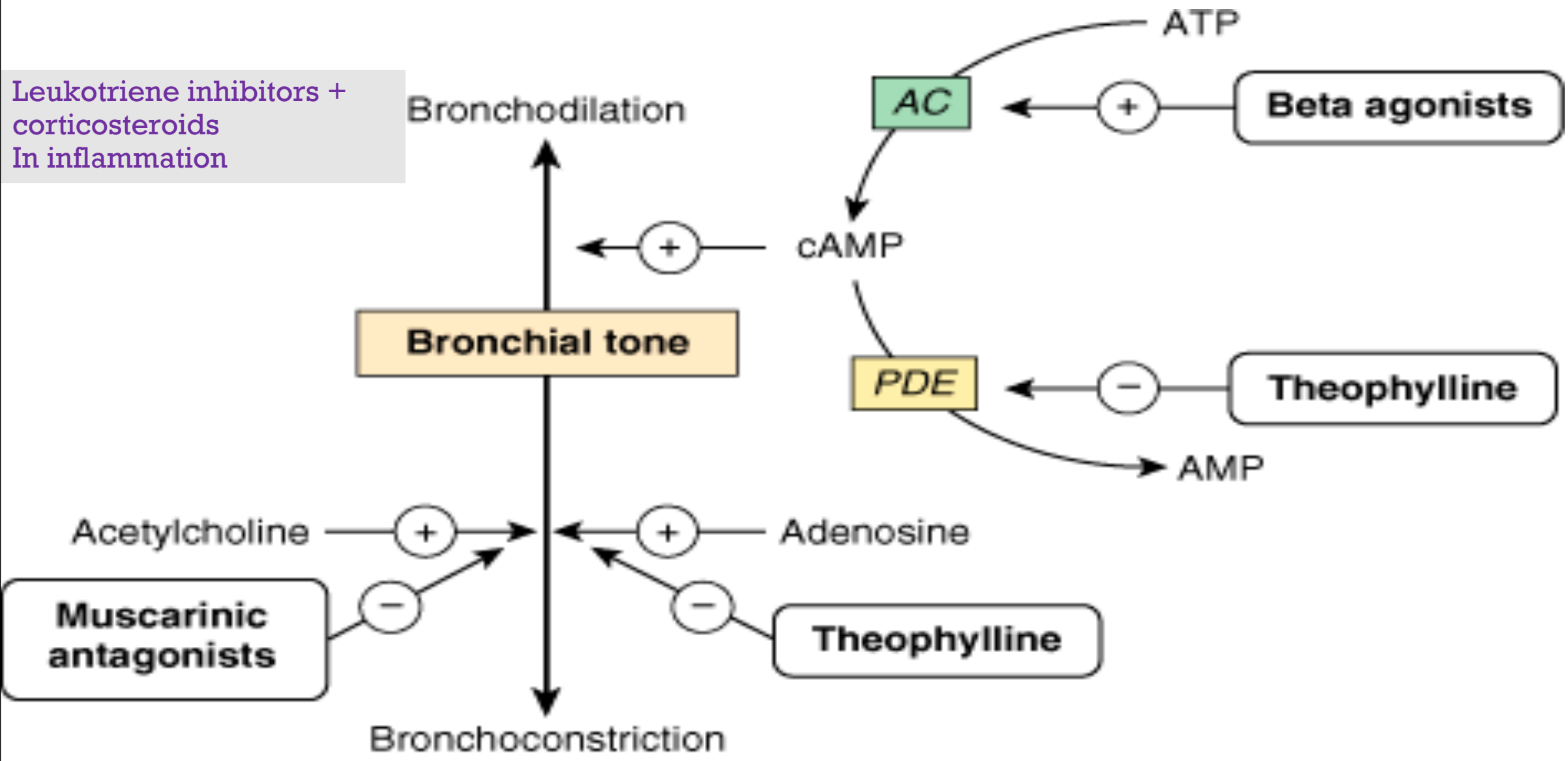
Corticosteroids + LABA, LTRAs, Theophylline, Cromolyn, Ipratropium, Tiotropium

Leukotriene receptor antagonist

2010's

Prevention including gene therapy.

Leukotriene inhibitors + corticosteroids
In inflammation



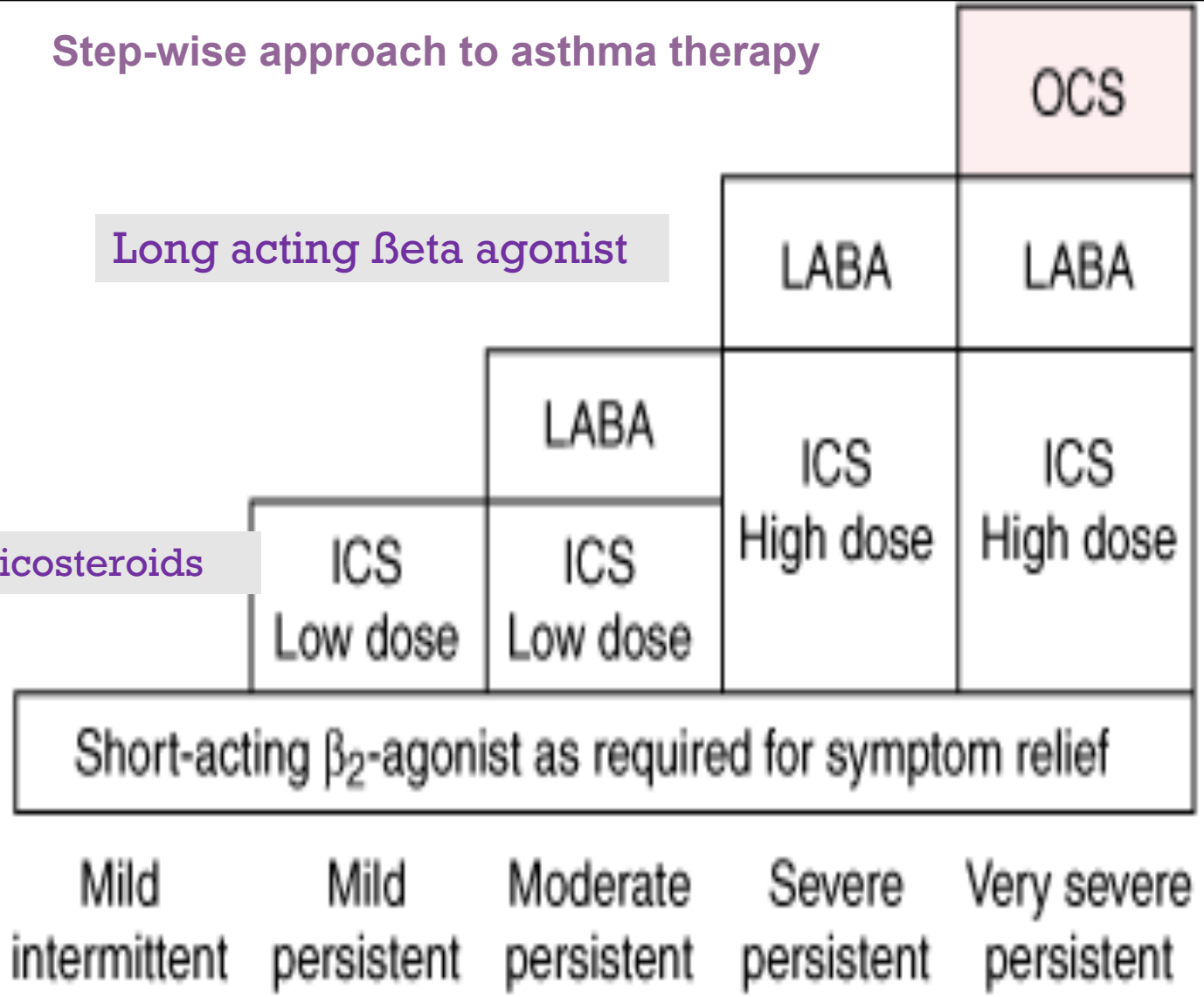
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Step-wise approach to asthma therapy

Oral corticosteroids

Long acting ßeta agonist

Inhaled 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

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)

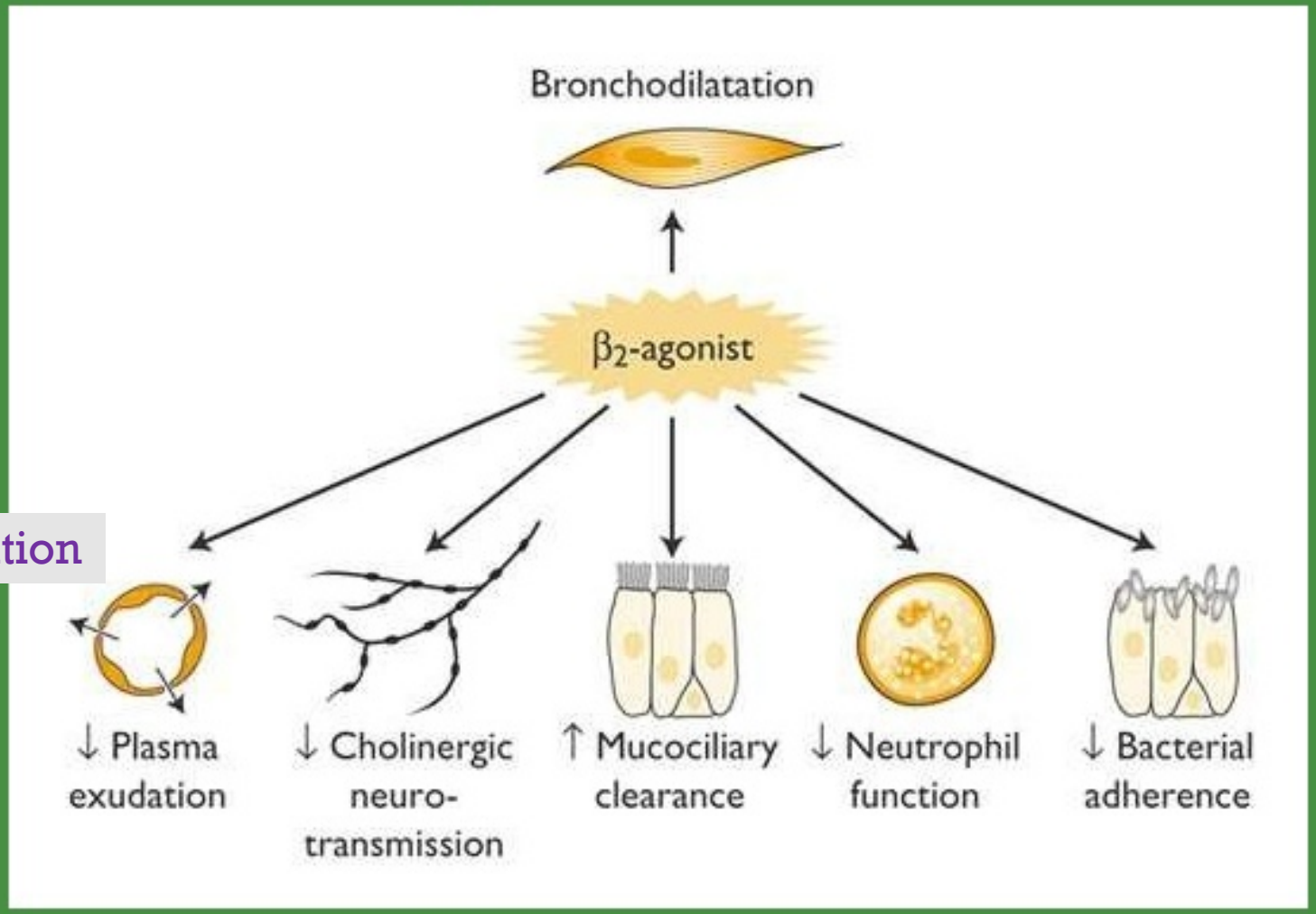
Severe bronchoconstruction + inflammation
we give corticosteroids systemically, starts with high dose for a few days then reduce the dose

Beta 2-Adrenergic Agonists

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

Not only dilate the bronchi

Role of beta agonists in asthma and COPD



Beside bronchodilation

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.

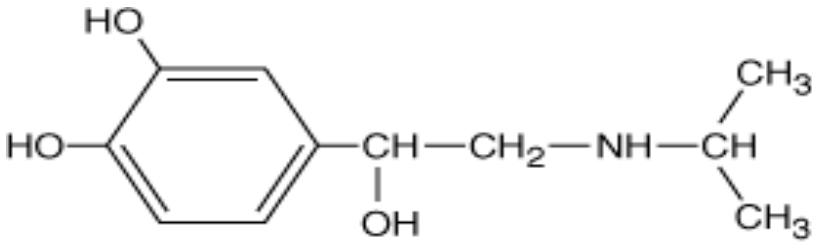
Activate protein kinase A.

Phosphorylate kinases.

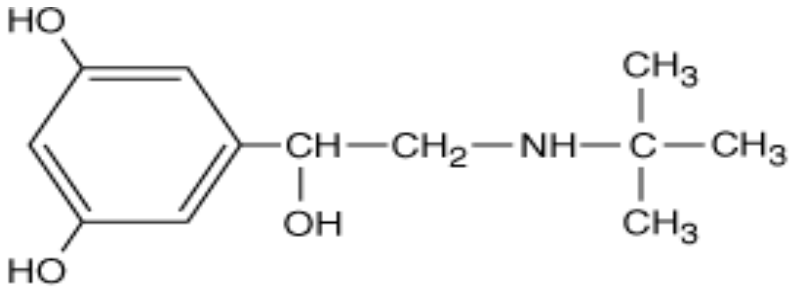
All lead to decreased cytosolic Ca++.

Beta2-Selective Drugs

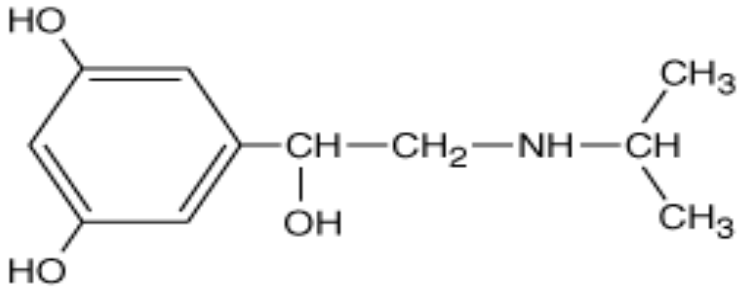
Epinephrine + NE ➡️ work on alpha and beta receptors While isoproternol work on Beta receptors (B1 , B2) ➡️ cardiac stimulation (arrhythmia)



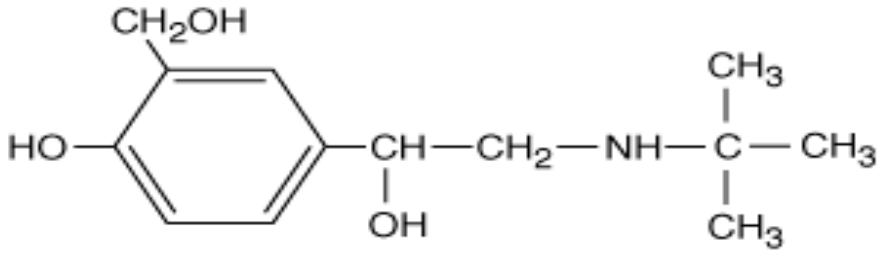
Isoproterenol



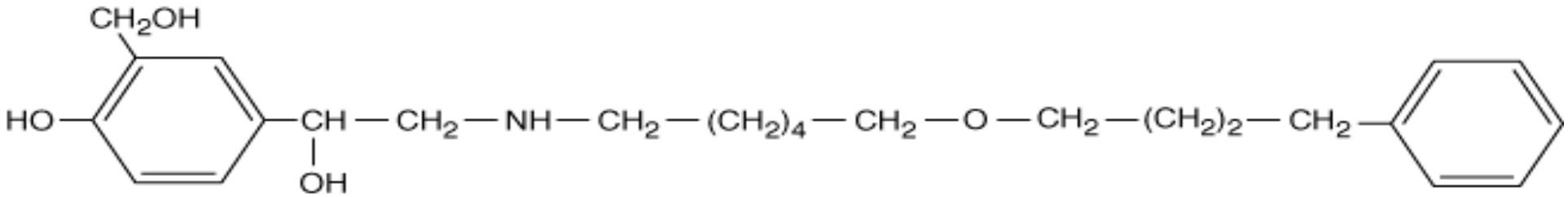
Terbutaline



Metaproterenol



Albuterol (salbutamol)



Salmeterol

Beta 2-Adrenergic Agonists

- **Epinephrine:**

Obtained from bovine adrenal gland.

Stimulates α, β1 and β2 receptors.

Not effective orally.

Subcutaneous.

1) In emergency (status asthmaticus) (peresistance of acute attack of the bronchial asthma)
2) anaphylactic shock

Anaphylactic shock : release of histamine which cause bronchoconstriction and vasodilation
Epinephrine ➡️ physiological antagonist not pharmacological antagonists because it doesn't work on histamine receptors

Distribution and Actions of B1/B2 receptors

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

Relaxes the pregnant uterus , delay labor

Produce glucose from glycogen

Beta 2-Adrenergic Agonists

- **Isopreterenol:**

Stimulates β1 and β2 receptors.

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

Cause Considerable tachycardia and pounding. خفقان

Short acting Beta 2-Adrenergic Agonists

- Albuterol(Salbutamol). **Ventolin** الاسم التجاري
- Terbutaline.
- Pirbuterol.
- Metaproterenol.
- Isoetharine.

Rapid onset: 3-5 minutes.

Maximal effect: 30-60 minutes.

Duration: 4-6 hours.

2-3 times a day

Long -acting Beta 2-Adrenergic Agonists(LABA)

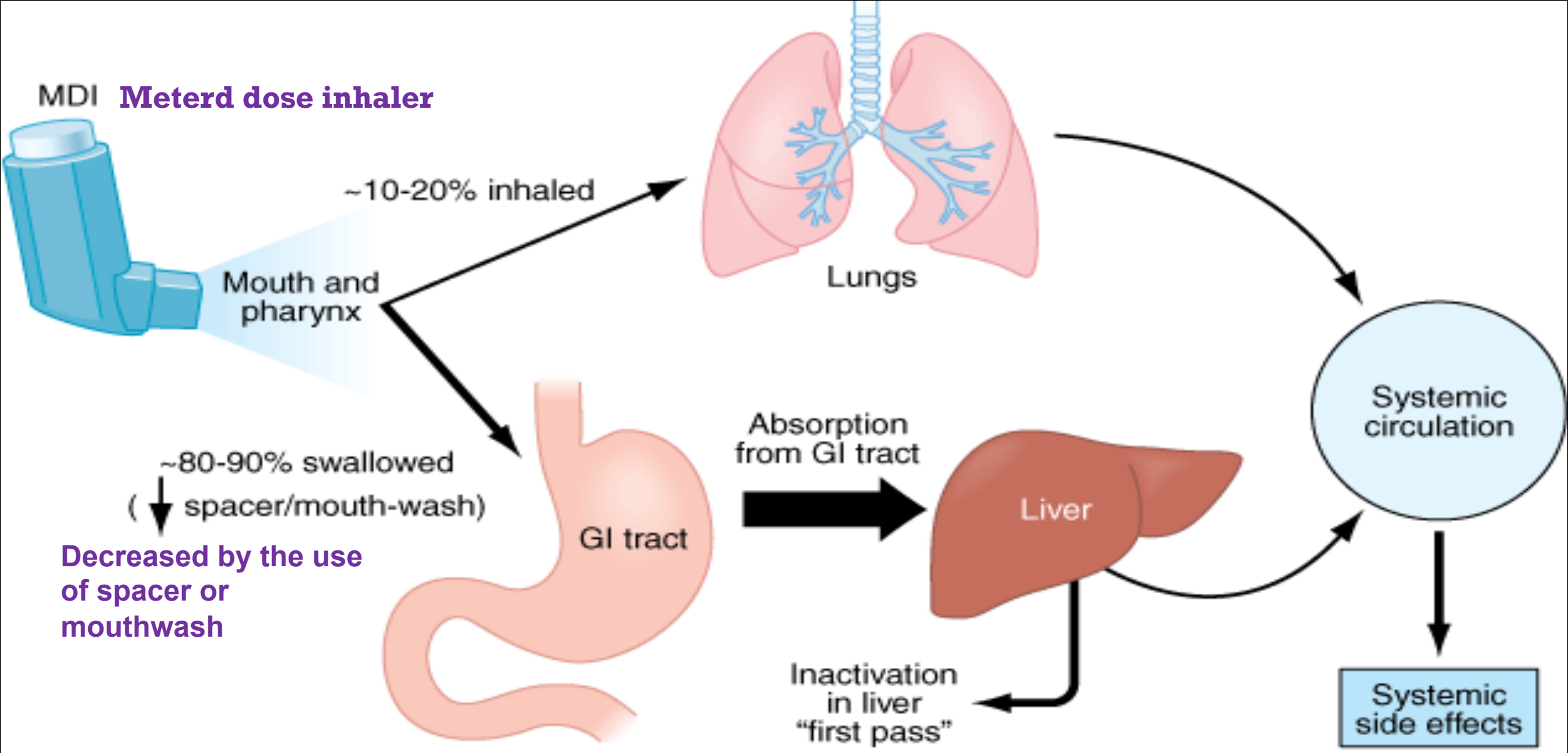
- **Salmeterol.**
- **Formoterol.**

Long-acting inhaled bronchodilators:12 hours.

Suppress nighttime attacks.

Controllers with steroids.

No tachyphylaxis.



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

Problems of Metered Dose Inhalers(MDI)

How to use it? Breathe out completely press canister once then breathe slowly

- 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.**

Large particles more likely to be swallowed and reach GI tract and cause side effect

- **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 = pro re nata which means that the medication is taken when the situation needs
Ex . Exercise

Beta 2-Adrenergic Agonists

We have Beta receptors in the brain so if we use it in high dose it will cross the blood brain barrier and cause side effects

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

They are beta 2 selective not beta 2 specific (meaning that is a drug works on beta 2 and beta 1 but more effective in beta 2.
when we increase the dose we lose the selectivity and calls 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.**

Ex : instead of using ß2 agonist two times a day , using it four times this will double the risk of death

Conclusion:

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

Beta 2-Adrenergic Agonists

Genetic variation

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