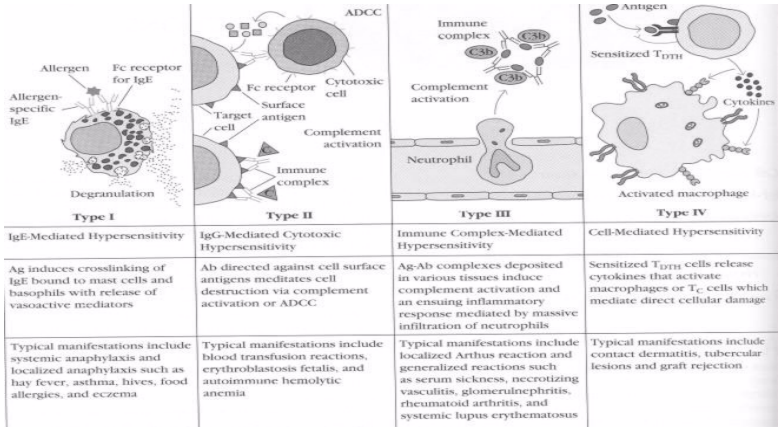
PATHOPHYSIOLOGIC FEATURES OF ALLERGIC CONDITIONS

Lecture from pathological physiology
October 21, 2004

Immunopathologic reactions



Type I	Type II	Type III	Type IV
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_{DTH} cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

Kuby et al., 2000

Definition of basic conceptions

- **Hypersensitivity**

A reaction to something inthe environment which most exposed persons tolerate. The mechanisms can be

- **immunological (e. g.allergy)**
- **or other (i. e. non-allergic hypersensitivity)**

Although the word hypersensitivity implies an increased response, the response is not always heightened but may, instead, be an inappropriate immune response to an antigen.

Atopy

- **Atopy – a hereditary predisposition to the development of immediate hypersensitivity reactions against common environmental antigens with tendency to produce IgE antibodies to extremely small amounts of naturally occuring allergens.**

The abnormal IgE response of atopic individuals is at least part genetic – it often runs in families

Atopic individuals have abnormally high levels of circulating IgE and also more than normal numbers of circulating eosinophils.

These individuals are more susceptible to allergies such as hay fever, eczema and asthma.

Allergy

- **Allergy** – is a reaction of hypersensitivity mediated by immunologic mechanisms

Allergic reactions may develop inthe course of

either humoral or cell-mediated response

Allergen refers specifically to nonparasitic antigen capable of stimulating type I hypersensitive responses in allergic individuals.

Allergy

- Allergy due to IgE antibodies
  - I. type of hypersensitivity
  - in subjects with atopy
  - AB, rhinitis, urticaria, food allergies, insect allergies, anaphylaxis….
- Allergy due to non-IgE mechanisms
  - III. type of hypersensitivity
  - anaphylaxis mediated by immune complexes
  - serum sickness
- Allergy due to cells
  - IV. type of hypersensitivity,
  - allergic contact dermatitis
  - non-IgE associated atopic dermatitis

Allergic diseases - today

- Allergic diseases come under one group of multifactorial (civilisation) diseases

„Allergy“ – from Greek („allos ergeia“) = altered reaction´s ability (von Pirquet,1906)

„anaphylaxis“ – from Egypt 2140 b.c.

Asthma - this term was used in Homer´s Illiada
- Hippocrates, Galen

Rhinitis – this term is known from 1533

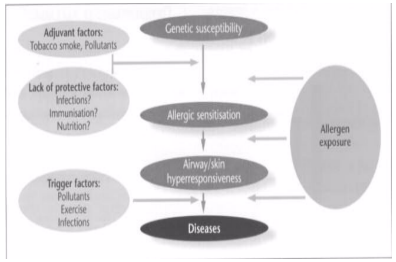
Development of allergy during life

- Allergic diseases result from the association of a genotype (innate, hereditary) and acquired factors related to the environment and lifestyle. They depend on the intensity of allergenic contact and immunologic reactivity (IgE secretion):

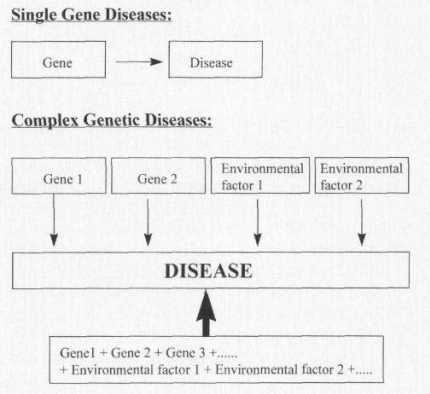
⇨ Genetic susceptibility

⇨ Allergen sensitisation

⇨ Trigger factors



GENETIC PREDISPOSITION



A single „allergy chromosome“ is not thought to exist, rather, the genetics of allergy are polygenic and influence various aspects of the diseases such as IgE secretion, cytokine interaction and receptors.

Prasad M, Chest 1997

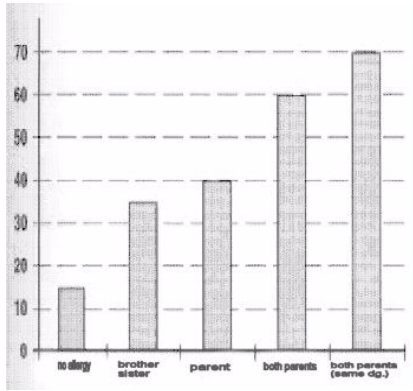
Bomprezi et al. 2003

Potential risk factors for allergic disease

A family history of allergic disease is a strong risk factor with a pronounced organ or disease specifity

This hereditary tendence to develop AB, AR or AD was named „atopy“ by Coca in 1923

Polygenic inheritance patterns have been confirmed by developments in molecular genetics, in particular human genome mapping



Špičák et al. 2004

Genetic predisposition for allergic disease

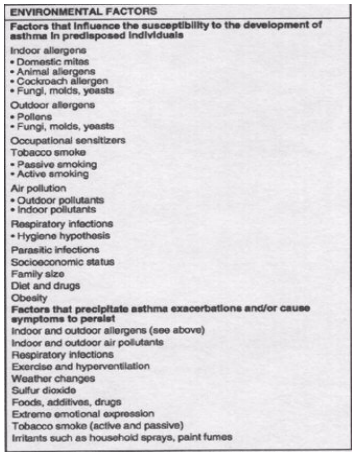
Locus*	Candidate genes
2 pter	Unknown
2q33	CD28, IGBP5
3p24.2-p22	CCR4
4q35	IRF2
5p15	Unknown
5q23-q33	IL-3, IL-4, IL-5, IL-13, IL-9, CSF 2, GRL1, ADRB2, CD14
6p21.1-p23	HLAD, TNFA
7p15.2	TCRG, IL-6
7q35	TCRB
9q31.1	TMOD
11p15	Unknown
11q13	FCER1B, CC16/CC10
12q14-q24.33	STAT 6, IFNG, SCF, IGF1, LTA4H, NFYB, BTG1
13q14.3-qter	TPT1
14q11.2-q13	TCRA/D, MCC
14q32	IgHG
16p12.1	IL4R
16q22.1-q24.2	Unknown
17p11.1-q11.2	C-C chemokine cluster
19q13	CD22
21q21	Unknown
Xq28/Yq28	IL9R
12q	NOS1
5q31	β_2-agonist receptor
11q13	GSTP1

Environmental factors

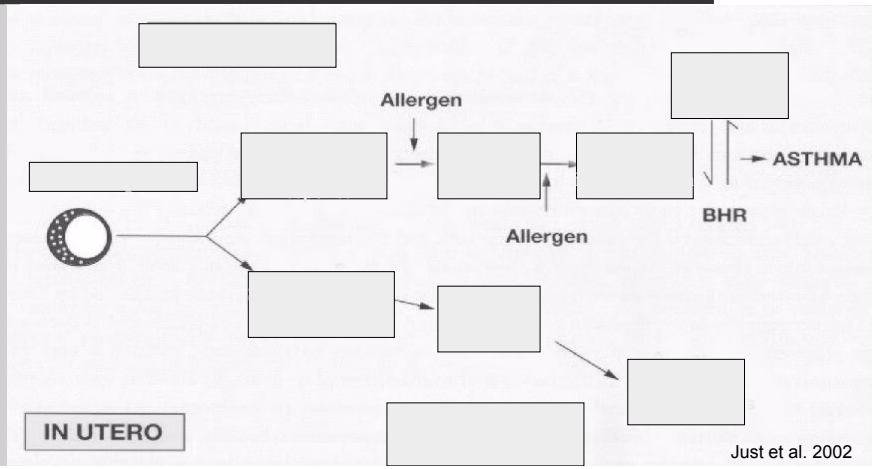
Environmental factors modify the likelihood that allergic diseases will develop inpredisposed invididuals. These factors include…

Some environmental factors can also exacerbate disease, these are also called precipitating factors (triggers)

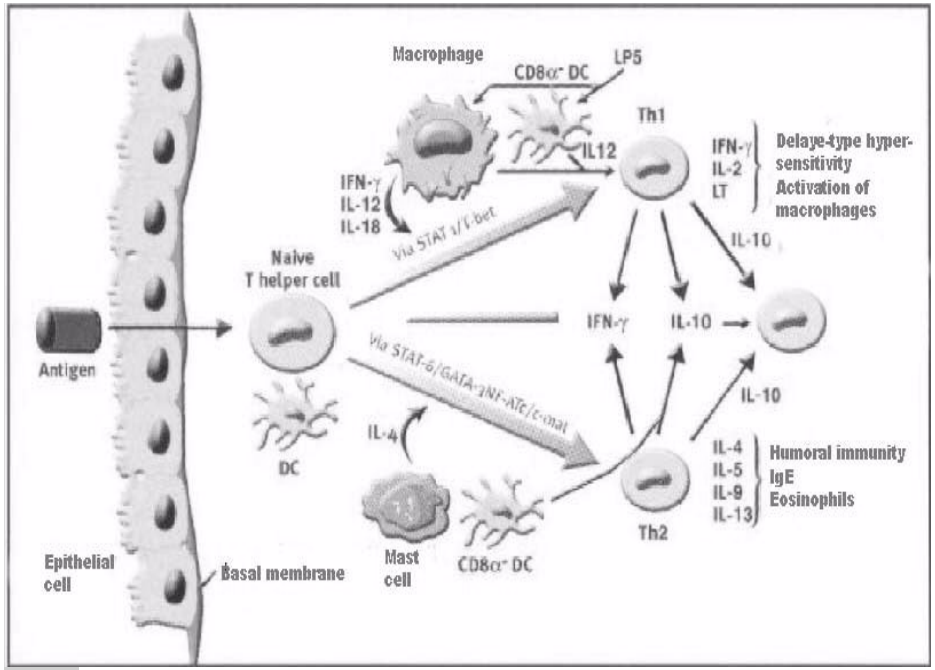
- allergens, exercise, cold air, drugs, irritant gases, weather changes and extreme emotional expression.



Th1/Th2 balance in utero a po narození



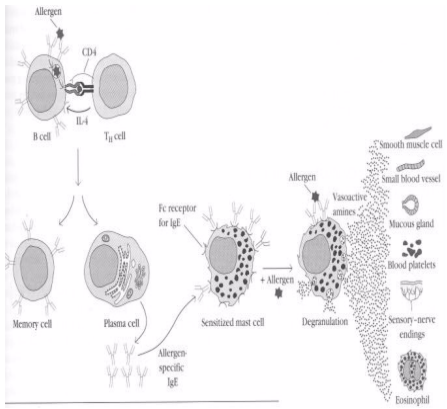
Just et al. 2002



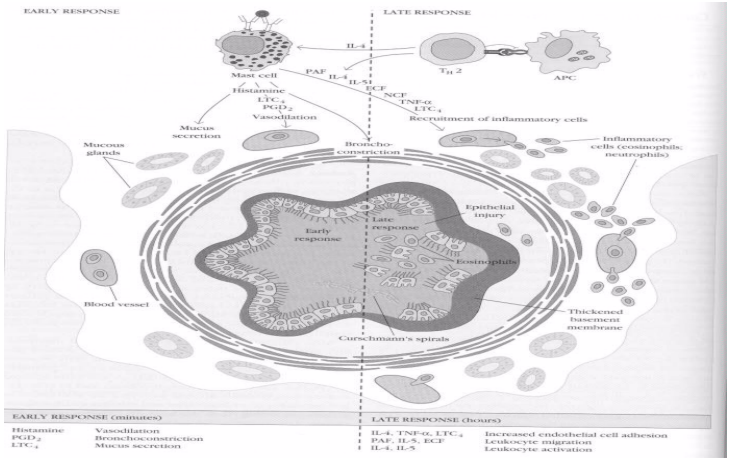
Bousquet et al. 2002

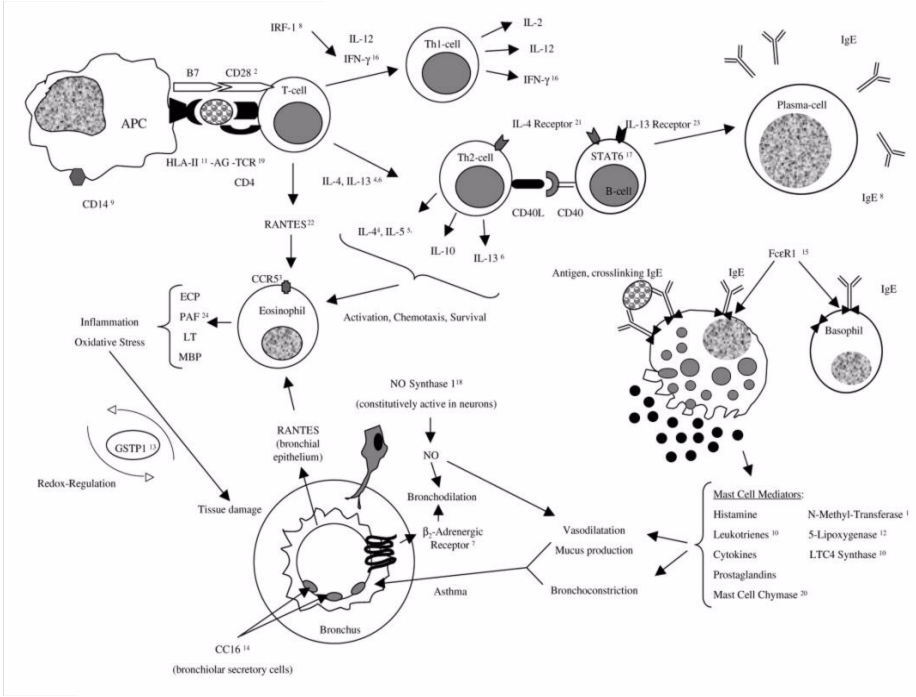
General mechanism underlying a type I hypersensitive reaction

- **Exposure to allergen activates B cells to form IgE-secreting plasma cells.**
- **The secreted IgE molecules bind to IgE-specific Fc receptors on mast cells and blood basophils.**
- **Second exposure to the allergen leads to crosslinking of the bound IgE, triggering the release of pharmacologically active mediators, amines from these cells.**
- **They cause smooth muscle contraction, vasodilatation ….**

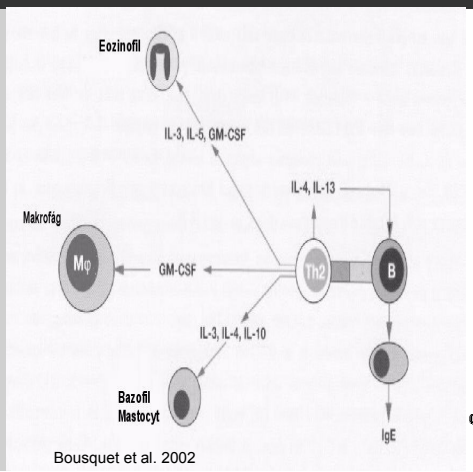


The early and late inflammatory response in allergic disease (asthma)

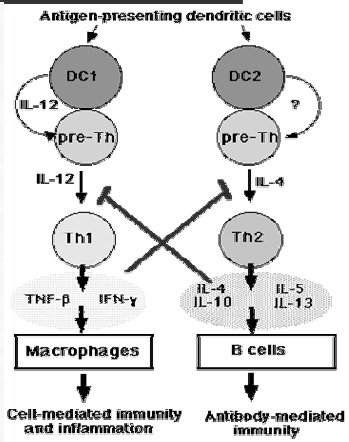




The central role of Th cells in pathophysiology of allergic diseases

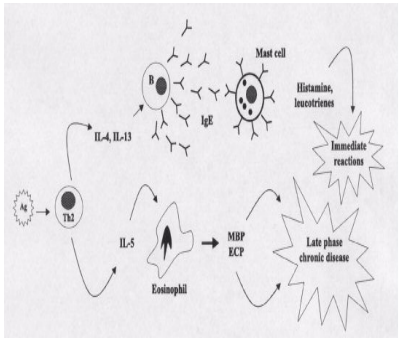


Bousquet et al. 2002



Th2 paradigm in atopic diseases

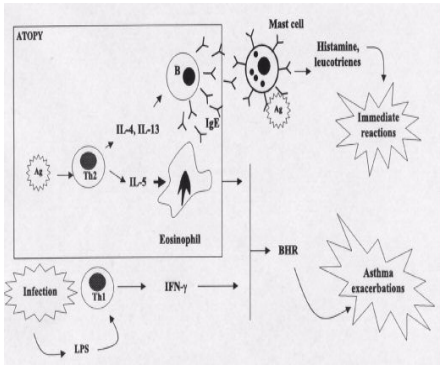
Once into the organism, the allergen triggers a Th2 activation. This activation leads to IgE production by B cells and to the early phase of allergic response via the release of vaso- and broncho-active mediators by mastocytes and other effector cells. In parallel, IL-5 activates eosinophils, leading to the late phase reaction and if allergen exposure is prolonged, to the chronic disease, via the production of MBP and ECP.



El Biaze et al. 2003

Th1 paradox in atopic diseases

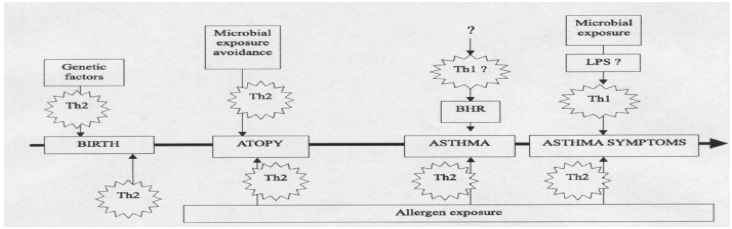
The Th2 activation is relevant for the inception of atopy. Another kind of inflammation, in which Th1 cells are present, is necessary to induce the development of the disease and inpatients , the triggering of symptoms.



El Biaze et al. 2003

Natural history from atopy to asthma (hypothesis)

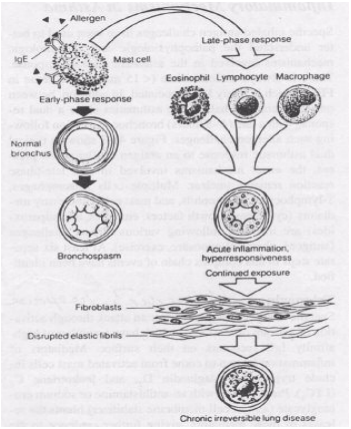
The immune system is skewed at birth to a Th2 activation, in as muchas genetic factors predisposing to atopy are present. Atopy develops in response to allergens in case of early microbial avoidance, according to hygiene hypothesis. Later, allergen exposure always stimulates the Th2 activation, but bronchial hyperreactivity and asthma are associated to Th1 activation. Once asthma is present, symptoms are triggered during microbial exposure via a additional Th1 activation.



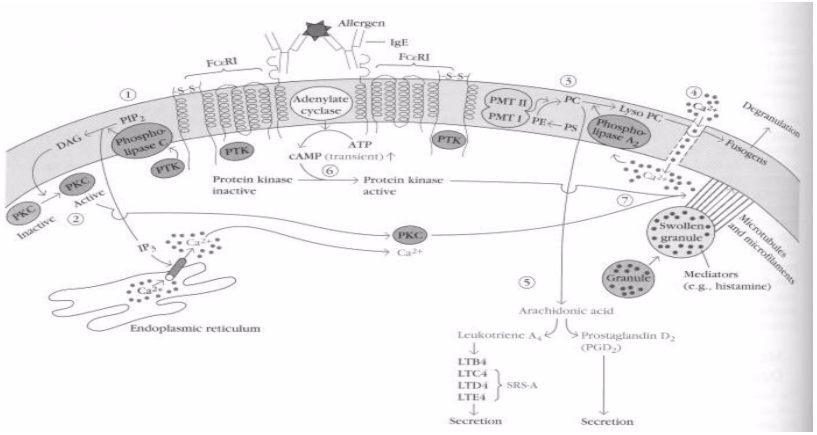
El Biaze et al. 2003

Mast cell

The mast cell plays a central role in initiating both the early-phase asthmatic response, which results inbronchospasm , and the late-phase response, which results in inflammation and hyperresponsiveness as well as some chronic irreversible changes.



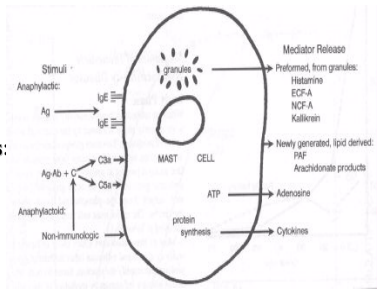
Mast cells
activation and degranulation



Mast cell-mediators

- **Preformed (from granules) mediators:**
  - histamine, heparin, chymase, tryptase, proteases, eosinophil, chemotactic factor and neutrophil chemotactic factor
- **Newly generated (lipid derived) mediators:**
  - leukotrienes, prostaglandins, PAF, bradykinin and various cytokines:

*** TNF-alfa (activation of fagocytes)**
*** TGF-beta (fibrotisation)**
*** IL-5 (stimulation of the production of eosinophils)**
*** IL-6 (e.g. stimulation of the production Ig, incl. IgE)**



Biologic effects of histamine

H1 receptors:

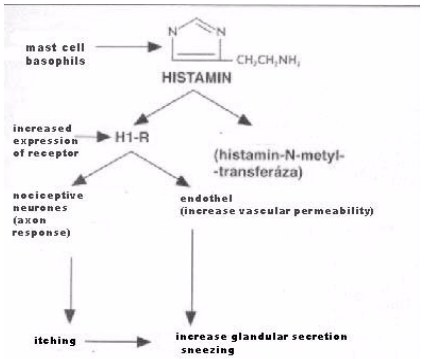
- **Bronchoconstriction, vasodilatation**
- **Increased vascular permeability**
- **Increased bronchial mucus secretion**
- **chemotactic factor for eosinophils and neutrophils**

H2 receptors:

- **Increased production of HCl**

H3 receptors:

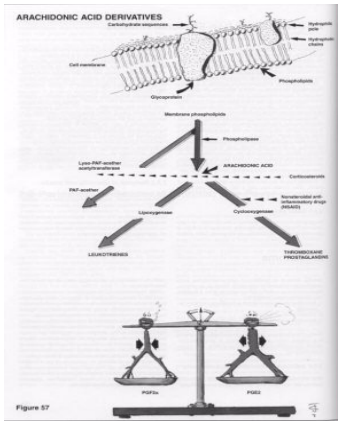
- **especially in CNS**



Špičák et al. 2004

The secondary mediators of mast cells

- **Prostaglandins:**
  - **PGD2: vasodilation, increased vascular permeability, contraction of pulmonary smooth muscles, activation of eosinophils, chemotaxis**
- **Leukotrienes:**
  - **LTC4, LTD4, LTE4 (SRS-A): Increased vascular permeability, contraction of pulmonary smooth muscles**
  - **LTB4: chemotaxis of granulocytes**
- **PAF (platelet-activating factor):**
  - **key chemotactic factor**

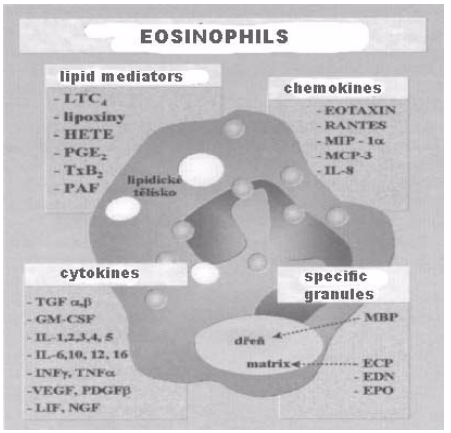


Basophils

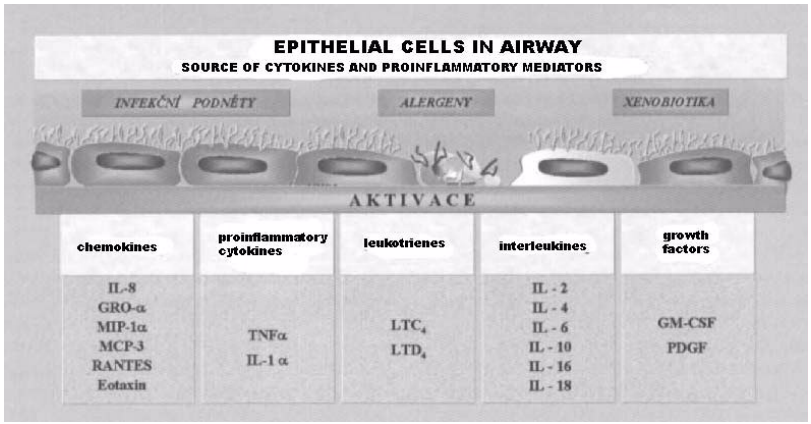
- **Basophils are granulocytes that circulate in the blood of most vertebrates, in humans, they account for 0,5-1,0% of the circulating white blood cells.**
- **Their granulated cytoplasm stains with basic dyes, hence the name basophil.**
- **They release pharmacologically active substances from their cytoplasmatic granules. These substances play a major role in certain allergic responses.**

Eosinophils

- **IL-5 is a basic factor for their differenciation**
- **LTB4, IL16, eotaxin (from T-cells and mast cells) are chemotactic factors for eosinophils**
- **They produce several**
  - **proinflammatory mediators (basic peptides, TNF, PG, LT, cytokines)**
  - **reactive O2 metabolites**
  - **enzymes (for example elastase, colagenase…)**

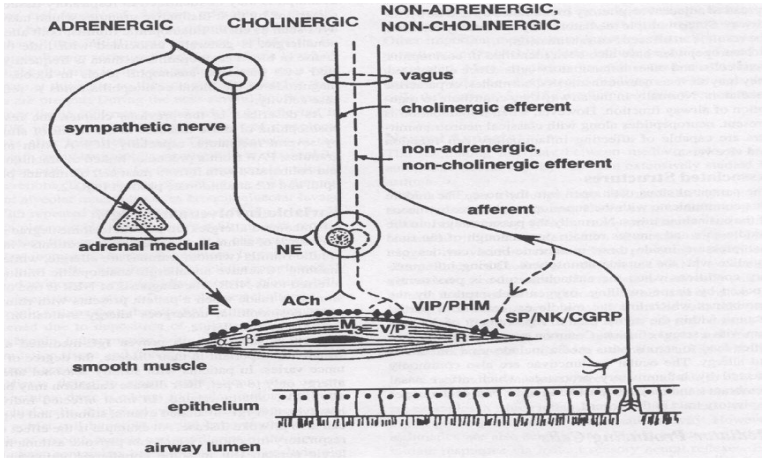


The role of epithelial cells in allergic inflammation



Krejsek et al. 2004

Innervation of human airway smooth muscle



Clinical manifestation: Anaphylaxis

- **A severe, often life-threatening, systemic allergic reaction may variably involve the skin, the GIT, the respiratory tract and the cardiovascular system**
- **Allergic x Non-allergic**

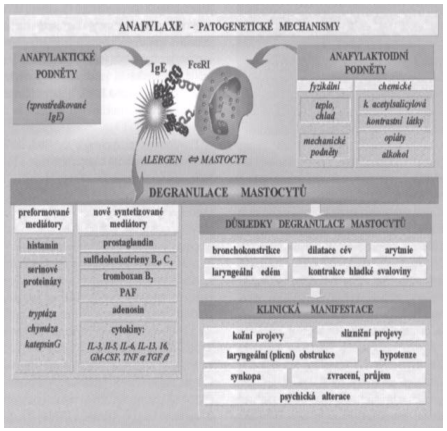
  ↙ ↘

  IgE non-IgE

- **Etiopathogenesis:**

  - drugs, - food, - venom

  - latex,



Krejsek et al. 2004

Allergic rhinitis

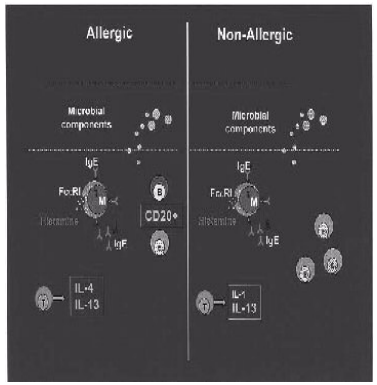
- **The most common atopic disorder, affecting 10 20% of populations is allergic rhinitis, commonly known as hay fever**

- **This results from the reaction of airborne allergens with sensitized mast cells in the conjunctivae and nasal mucosa to induce the release of pharmacologically active mediators from mast cells; these mediators then cause localized vasodilation and increased capillary permeability**

- **The symptoms include watery exudation of the conjunctivae, nasal mucosa, and upper respiratory tract, as wll as sneezing and coughing**

- **In 50% patients with rhinitis can develop asthma = conception ⇓**

  one airway – one disease



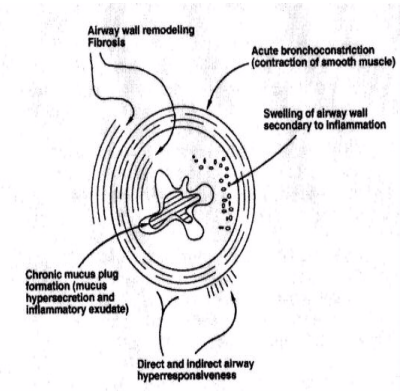
Atopic dermatitis (allergic eczema)

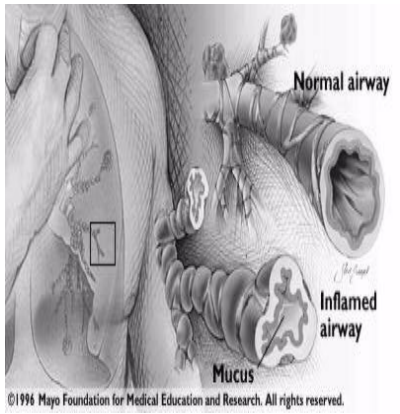
- It is an inflammatory disease of skin that is frequently associated with a family history of atopy
- The disease is observed most frequently inyoung children, often developing during infancy
- Serum IgE levels are often elevated
- Unlike a delayed-type hypersensitive reaction, which involves Th1 cells, the skin lesions inatopic dermatitis have Th2 cells and an increased number of eosinophils

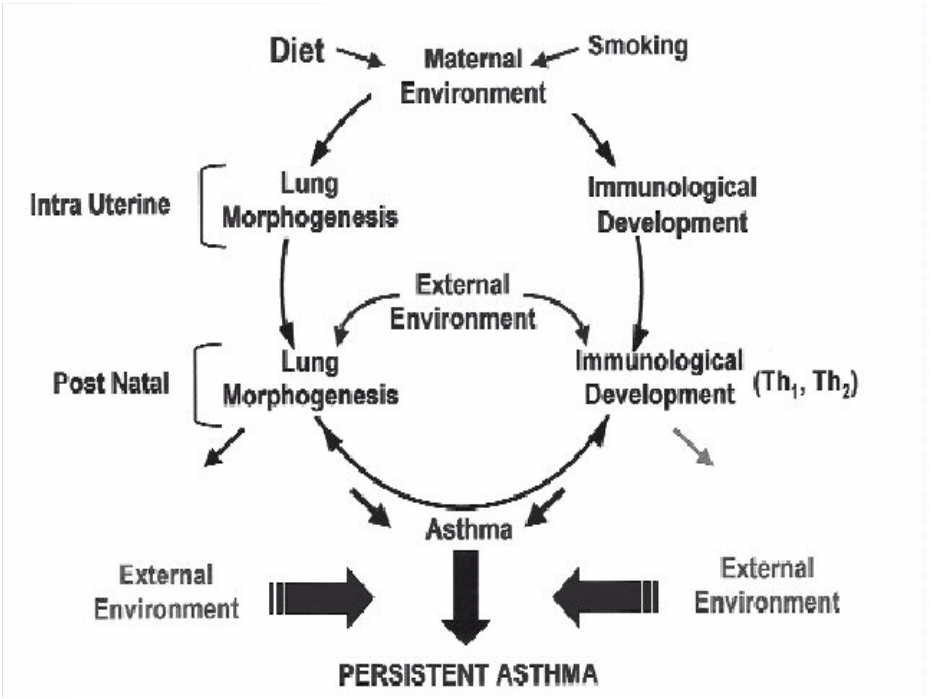
Asthma - definition (GINA 2002)

- Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.
- The chronic inflammation causes an associated increase inairway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or inthe early morning.
- These episodes are usually associated with widespread but variable airway obstruction that is often reversible either spontaneously or with treatment.

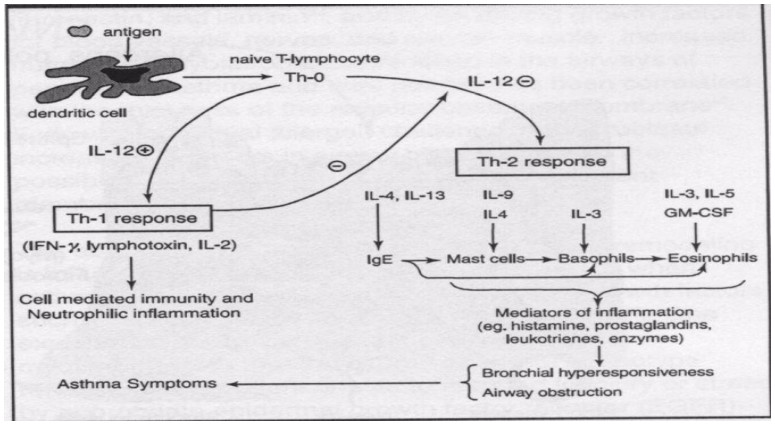
Factors that contribute to airflow limitation in asthma



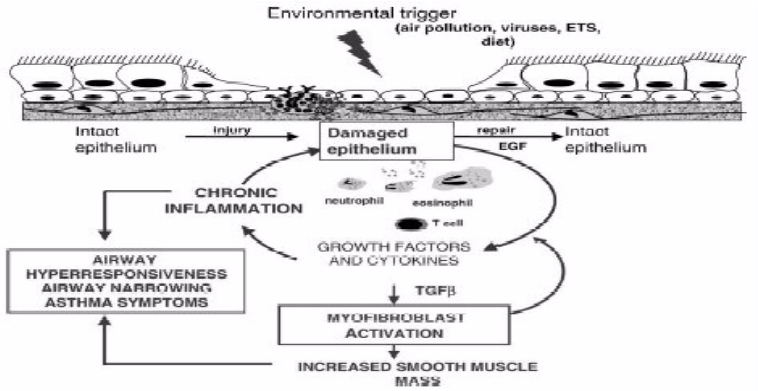




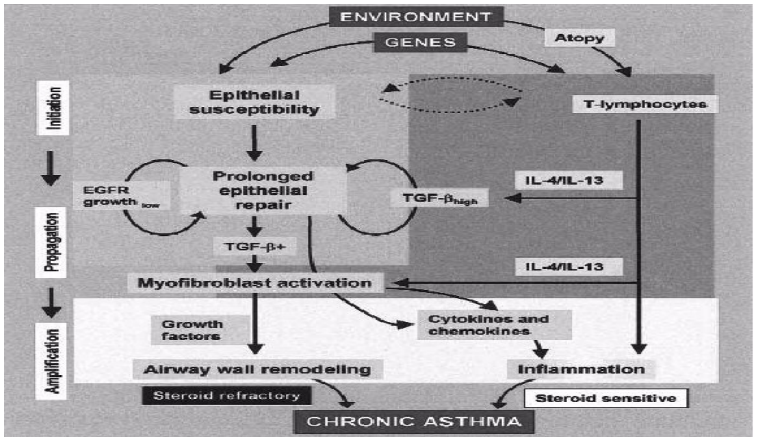
Pathogenesis of asthma



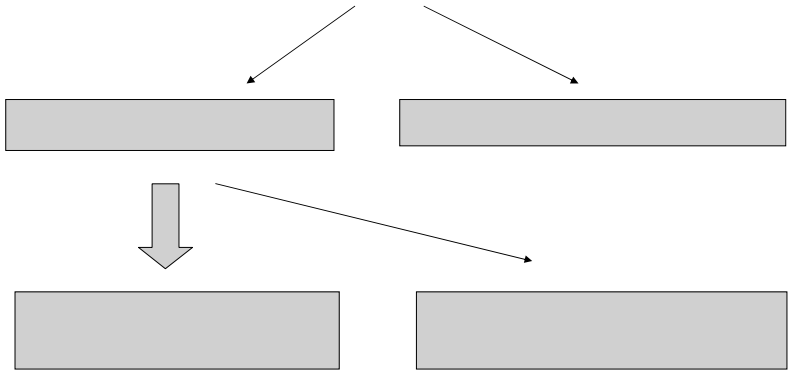
Inflammation and remmodelation of tissues in asthmatics



New paradigma of asthma pathogenesis



Types of asthma



Urticaria and angioedema

Urticaria (hives) typically appear as pruritic, reddened cutaneous elevation that blanch with pressure.

Histologically, small venules and capillaries inthe superficial dermis are dilated, and localized edema due to vascular permeability is present

A low-grade inflammatory infiltrate may be present and tends to correlate incellularity and composition with the phase and severity of the skin lesion.

Angioedema results from a similar process deeper inthe dermis and subcutaneous tissues, swelling is more extensive, and erythema and itching are less prominent or absent.

Food allergies

- Various foods also induce localized anaphylaxis inallergic individuals (AB, AR, AD, urticaria …)
- Allergen crosslinking of IgE on mast clls along the upper or lower gastrointestinal tract can induce localized smooth-muscle contraction and vasodilation and thus such symptoms as vomiting or diarrhea.
- Mast cell degranulation along the gut can increase the permeability of mucous membranes, so that the allergen enters the bloodstream. Various symptoms can ensue, depending on where the allergen is deposited. For example, some individuals develop asthmatic attacks after ingesting certain foods. Other develop atopic urticaria, commonly known as hives, when a food allergen is carried to sensitized mast cells inthe skin, causing swollen (edematous) red (erythematous) eruption. This response is called a wheal and flare reaction.

Drugs allergy

Drugs allergy

IgE mediated mediated

non-IgE

Non -allergic drug hypers.

- Activation of complement (anestetics, RTG drugs)
- aspirin intolerance (block of COX enzyme)

Diagnosis of allergic diseases

- Anamnesis – familiar, personal, occupational, social…
- Physical examination
- Skin tests (prick-tests, intradermal tests)
- Lung function measurements (spirometry, PEF)
- Total IgE level, specific (sIgE) levels

Treatments

Goals:

- To reverse of acute attacks
- To control recurrent attacks
- To reduce bronchial inflammation and the associated hyperreactivity
- + elimination of allergens (if it is possible)

Drugs:

- Allergen-specific immunotherapy
- Bronchodilator (Beta agonists, Anticholinergic agents, Theophylline)
- Immunosuppressant (corticosteroids)
- Others (Leukotriene modifiers, antihistamine, e.g.)

Allergen-specific immunotherapy

- Specific immunotherapy (SIT) using allergen extracts has been administered in many countries for the treatment of allergic diseases.

- Mechanisms of action:

  - Although the mechanisms of action of SIT have not been fully defined, some studies suggest that SIT may shift the immune system´s balance from Th2 to Th1 cells, with increased production of interleukin (IL-12) and interferon gamma (IFN-gamma). SIT also increases the anti-inflammatory cytokine IL-10.

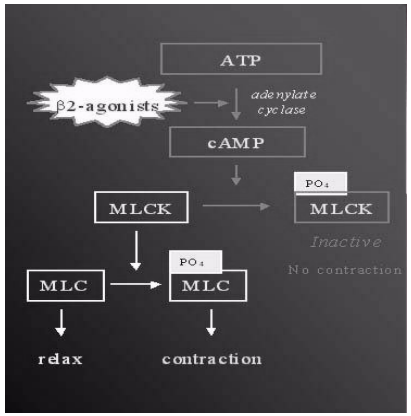
Bronchodilator

Beta2 agonists

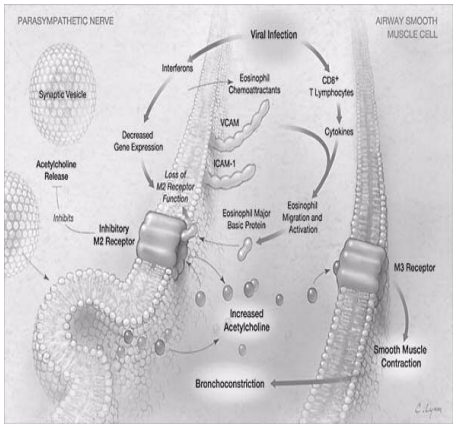
- selective β2 agonists

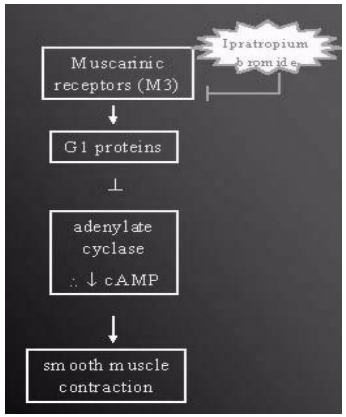
- albuterol (short acting)

- salmeterol, formoterol (long lasting)

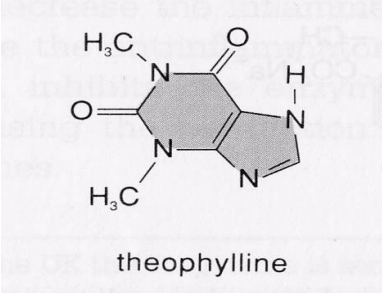


Anticholinergic agents





Methylxanthine



Eg. Theophylline

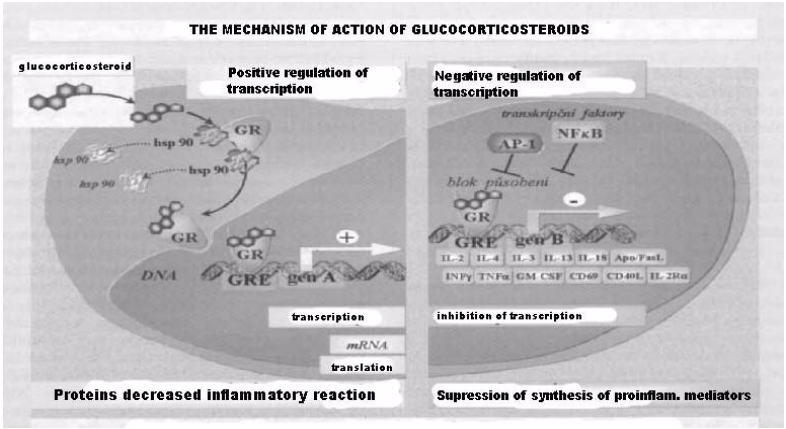
(similar to caffeine)

- **Inhibits phosphodiesterase and therefore increase cAMP**
- **Reduce intracellular calcium**
- **Cause membrane hyperpolarisation to prevent activity of smooth muscle**
- **Decrease of infiltration of eosinophils into epithelium**

Corticosteroids

- **Inhibit the attraction of inflammatory cells to the site of allergic reaction**
- **Block leukotriene synthesis**
- **Inhibit cytokine production and adhesion protein activation**
- **Reverse β2 receptor down-regulation**

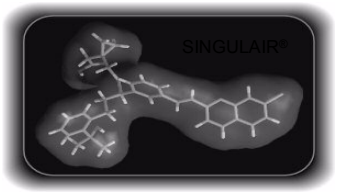
The mechanisms of action of corticosteroids



Krejsek et al., 2004

Leukotriene mediators

- **Inhibitors of 5-lipoxygenázy**
- **Antagonists of cysteinyl LT receptors**



eg. SINGULAIR® (montelukast sodium): leukotriene D4 receptor antagonist