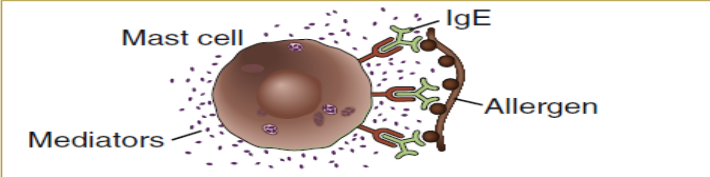
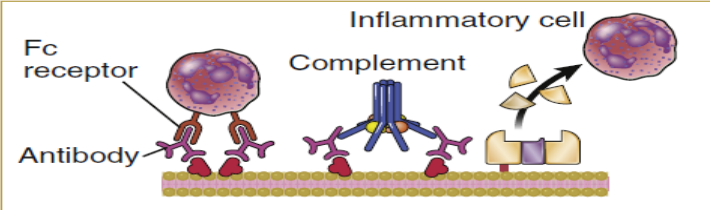
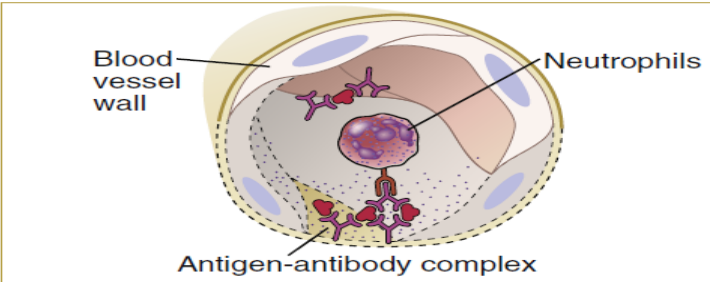
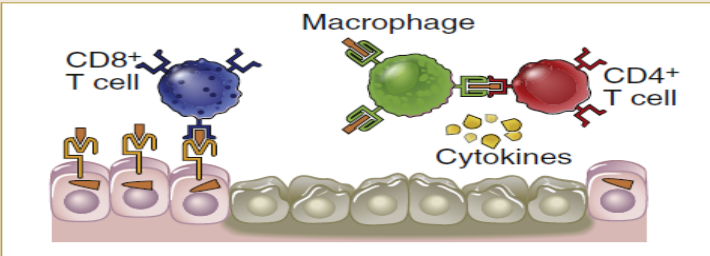


# Hypersensitivity disorders

*Diseases caused by excessive or inadequate immune response*

- Disorders caused by immune responses are called **hypersensitivity diseases**.
- Immune response to the self or foreign antigens can be disturbed (qualitatively inadequate) or uncontrolled (quantitatively changed) – **reactions of hypersensitivity**.
- The immune response can be directed toward self antigens – **autoimmunity**.

# Types of hypersensitivity

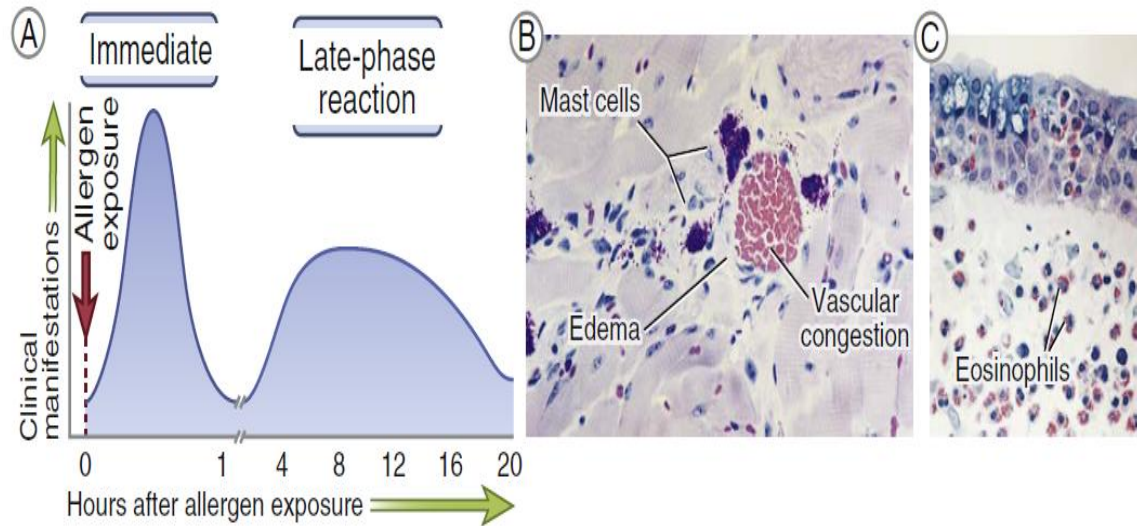
Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	<p>Th2 cells, IgE antibody, mast cells, eosinophils</p> 	<p>Mast cell–derived mediators (vasoactive amines, lipid mediators, cytokines)</p> <p>Cytokine-mediated inflammation (eosinophils, neutrophils)</p>
Antibody-mediated diseases (Type II)	<p>IgM, IgG antibodies against cell surface or extracellular matrix antigens</p> 	<p>Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages)</p> <p>Opsonization and phagocytosis of cells</p> <p>Abnormalities in cellular function, e.g., hormone or neurotransmitter receptor signaling</p>
Immune complex–mediated diseases (Type III)	<p>Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane</p> 	<p>Complement- and Fc receptor–mediated recruitment and activation of leukocytes</p>
T cell-mediated diseases (Type IV)	<p>1. CD4<sup>+</sup> T cells (cytokine-mediated inflammation) 2. CD8<sup>+</sup> CTLs (T cell–mediated cytotoxicity)</p> 	<p>1. Macrophage activation, cytokine-mediated inflammation</p> <p>2. Direct target cell lysis, cytokine-mediated inflammation</p>

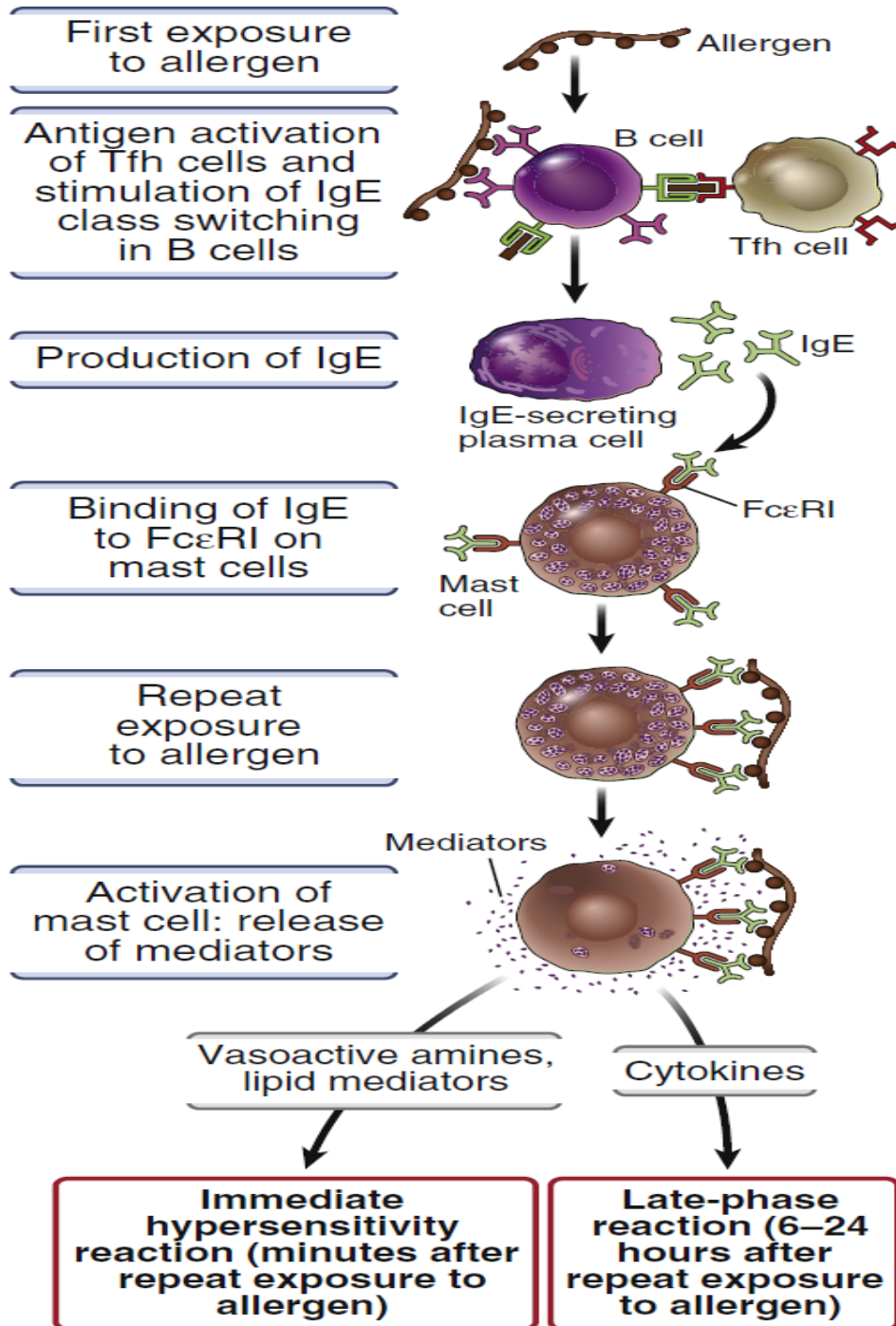
# Immediate hypersensitivity (type I) Allergy, Atopy

Ag + IgE + mast cell → rapid reaction of blood vessels (**vasodilation**) and smooth muscles (**constriction**), **inflammation**

20% of the population

- allergic rhinitis
- food allergy
- bronchial asthma
- anaphylaxis





# Production of IgE

The immune system of some people (atopics) in contact with proteins (allergens) responds atypically: through the activation of **Th2** lymphocytes.

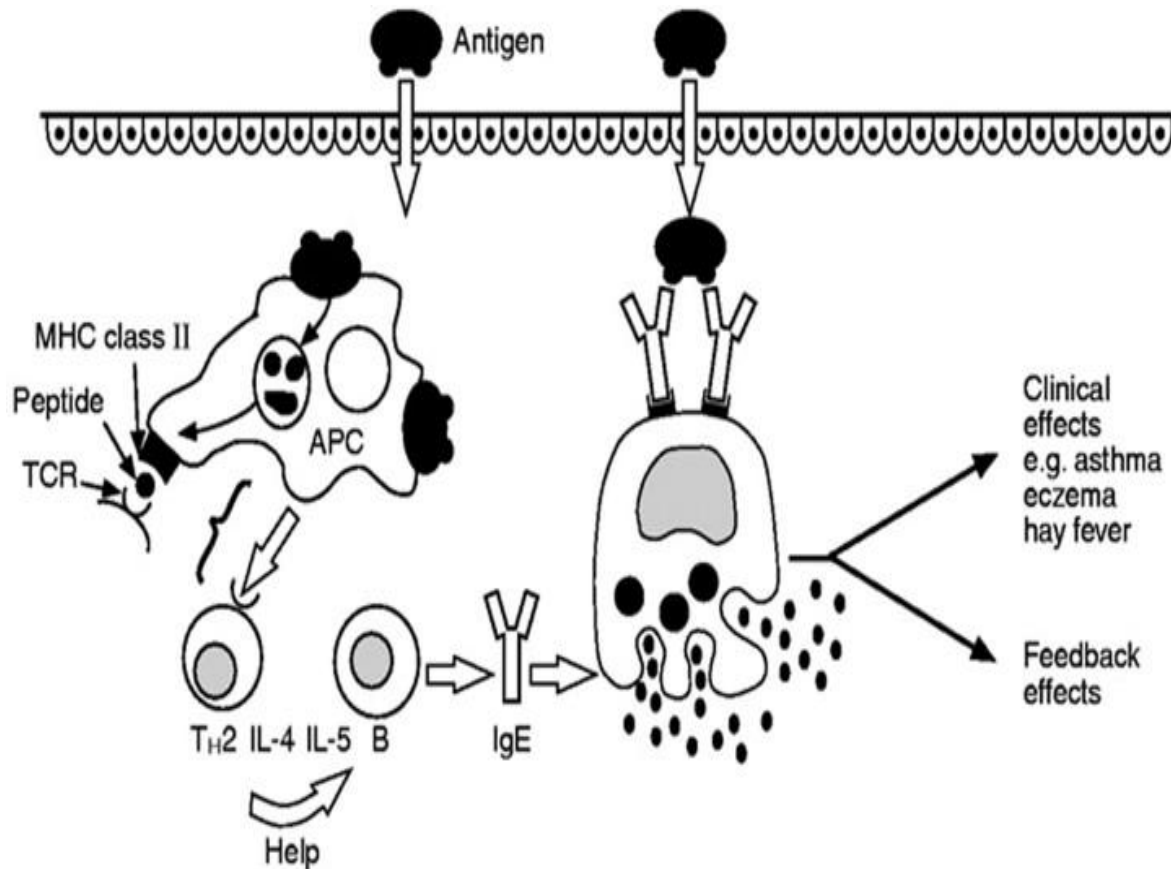
The most common allergens are:

- pollen
- some food
- insect toxins
- animal dander
- some protein-bound drugs (e.g. penicillin)
- *Dermatophagoides*



The cytokines that produce **Th2** lymphocytes (IL-4 and IL-13) act on specific B lymphocytes to produce IgE.

# Atopy



IL4

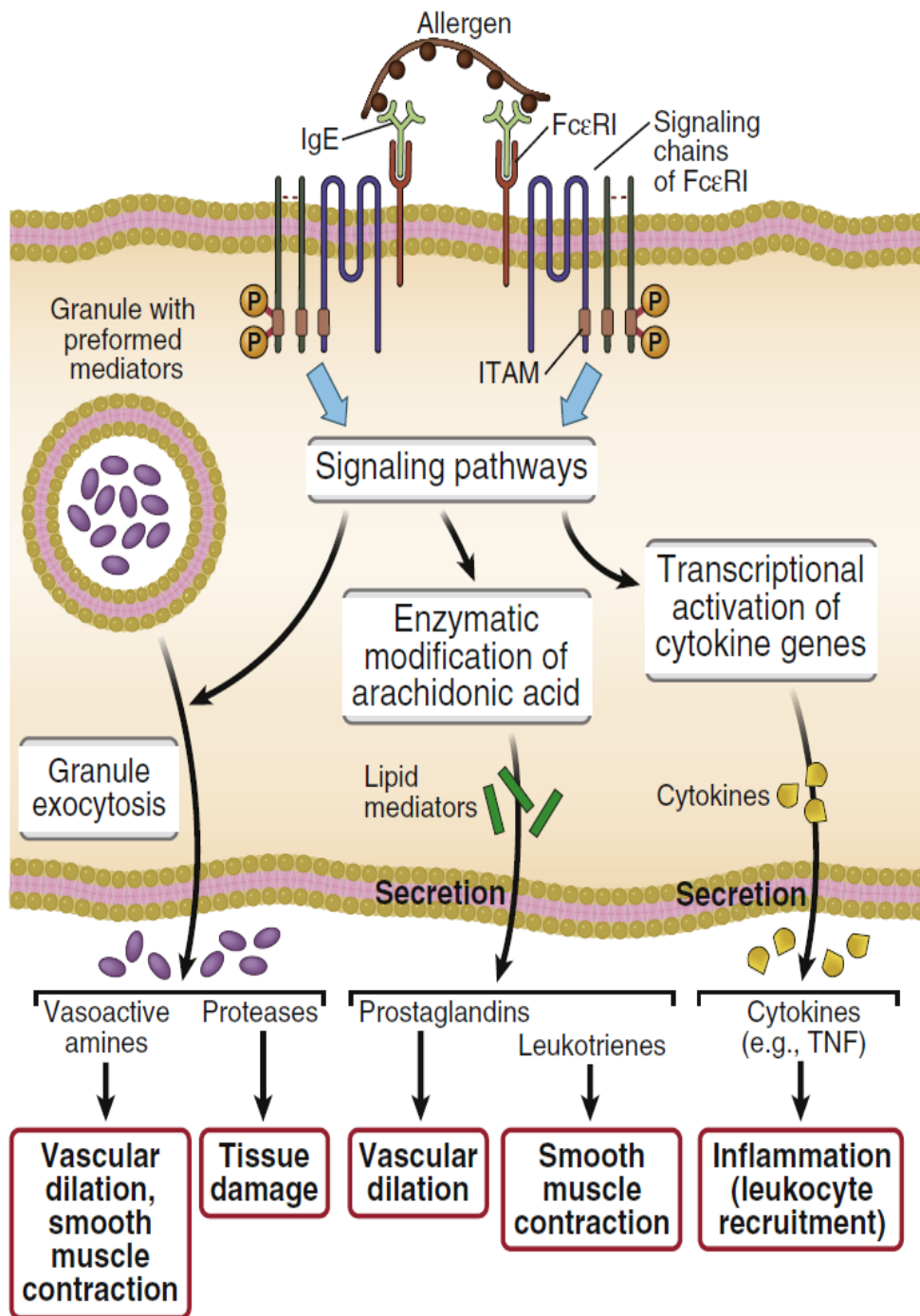
IL5

IL13

**MHC II** - expression  
of allergens as  
dominant epitopes

# Mast cell activation and secretion of mediators

- **IgE**, created during the response to an allergen, binds for **high-affinity Fc receptors** (for  $\epsilon$  chains of these antibodies) expressed on mast cells – **Fc $\epsilon$ RI**.
- In other words, in atopic patients, mast cells are coated (sensitized) by IgE that are specific to the allergen(s).
- **Repeated exposure** to the allergen **activates mast cells to release and synthesize mediators**.
- Mast cells are present in all connective tissues, and which mast cells will be activated depends on the route of allergen entry.



**Mast cells release three types of mediators:**

**Vasoactive amines and proteases** (previously synthesized). They are released promptly from the granules. These mediators are histamine, serotonin, proteases...

**Cyclooxygenase and lipoxygenase pathway metabolites** of arachidonic acid (newly generated and secreted). These mediators are prostaglandins (PG), leukotrienes (LT) and platelet-activating factor (PAF).

**Cytokines**

IL-4, TNF, IL-5 ...

## Clinical manifestations of immediate hypersensitivity reactions

Clinical syndrome	Clinical and pathological manifestations
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; inflammation of upper airways, sinuses
Food allergies	Increased peristalsis due to contraction of intestinal muscles
Asthma	Airway obstruction caused by bronchial smooth muscle hyperactivity; inflammation and tissue injury
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) caused by vascular dilation; airway obstruction due to laryngeal edema

# Therapy

Syndrome	Therapy	Mechanism of action
Anaphylaxis	Epinephrine	Causes vascular smooth muscle cell contraction, increases cardiac output (to counter shock), and inhibits bronchial smooth muscle cell contraction
Asthma	Corticosteroids	Reduce inflammation
	Leukotriene antagonists	Relax bronchial smooth muscle and reduce inflammation
	Beta adrenergic receptor antagonists	Relax bronchial smooth muscles
Various allergic diseases	Desensitization (repeated administration of low doses of allergens)	Unknown; may inhibit IgE production and increase production of other Ig isotypes; may induce T cell tolerance
	Anti-IgE antibody	Neutralizes and eliminates IgE
	Antihistamines	Block actions of histamine on vessels and smooth muscles
	Cromolyn	Inhibits mast cell degranulation
	Antibodies that block cytokines and their receptors: anti-IL-5 and anti-IL-5R (asthma), anti-IL-4R (atopic dermatitis)	Block actions of cytokines

# Diseases caused by antibodies and immune complexes (type II and type III hypersensitivity)

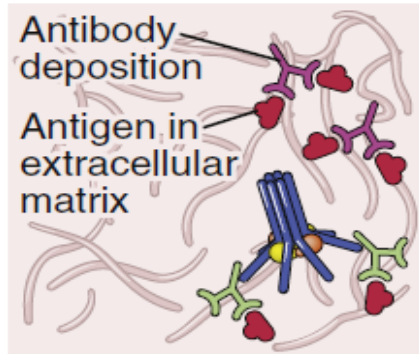
Antibodies can cause disease:

- by binding to target antigens on cells and tissues (components of the extracellular matrix). These diseases are usually **specific for a particular tissue or organ**
- by forming antibody-antigen complexes (immune complexes) that are deposited in blood vessels at places of turbulence (branches of blood vessels) or high pressure (renal glomeruli and joint synovium). These diseases are usually **systemic**: *vasculitis, arthritis and nephritis*

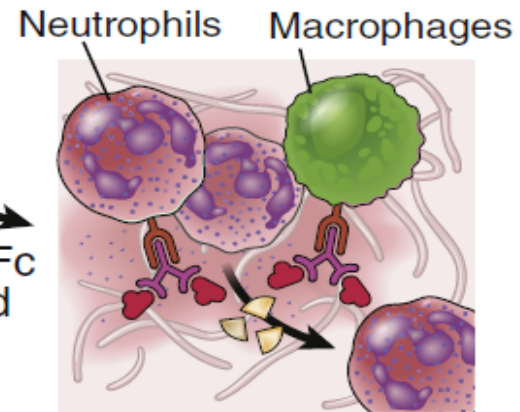
## Mechanism of antibody deposition

## Effector mechanisms of tissue injury

### Ⓐ Injury caused by anti-tissue antibody

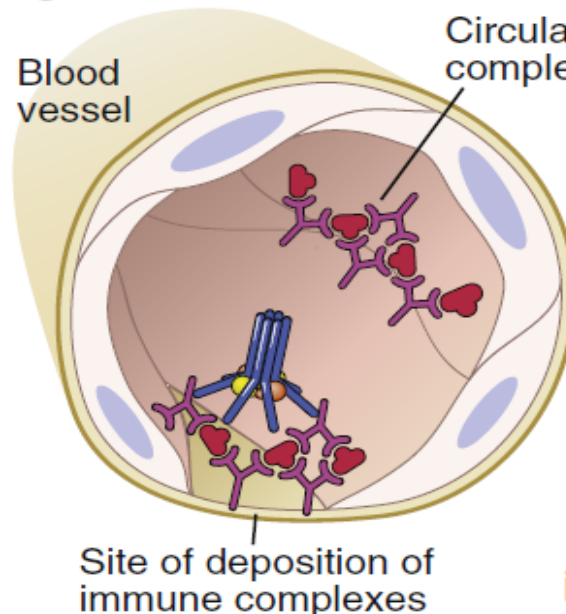


Complement- and Fc receptor-mediated recruitment and activation of inflammatory cells

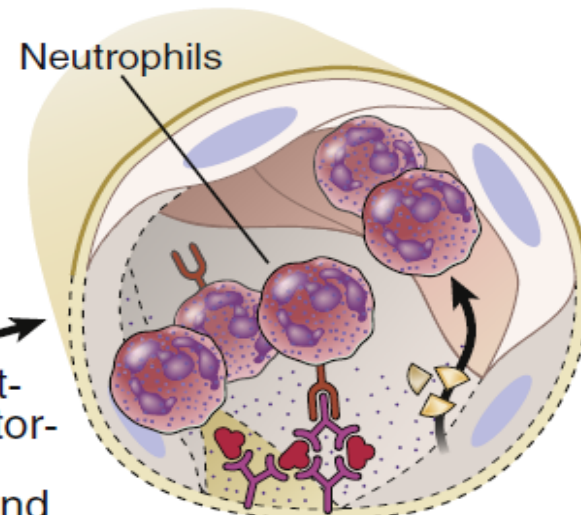


**Tissue injury**

### Ⓑ Immune complex-mediated tissue injury



Complement- and Fc receptor-mediated recruitment and activation of inflammatory cells



**Vasculitis**

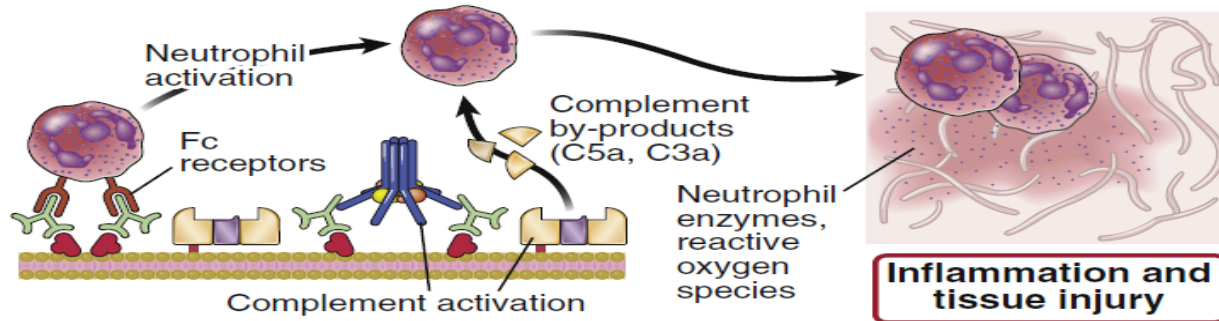
# Etiology

The antibodies that cause disease:

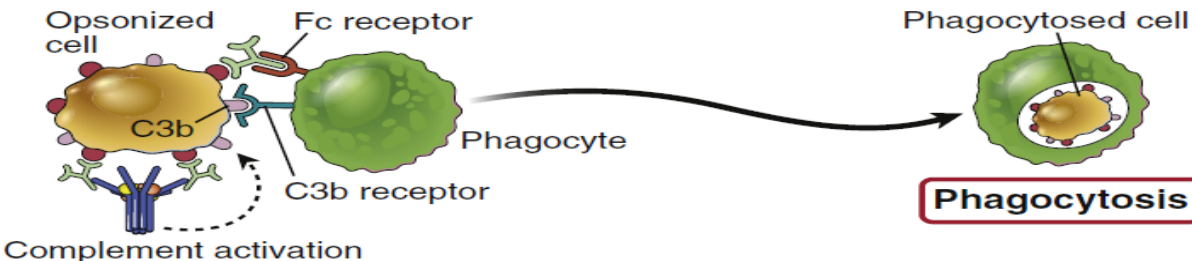
- are most often autoantibodies against self antigens
- are rarely specific for foreign antigens:
  - antigens of microorganisms
    - poststreptococcal sterile sequelae:  
*febris rheumatica and post-streptococcal glomerulonephritis*, occur as a consequence of the cross-reaction - **antigenic mimicry**
    - immune complexes of antibodies and antigens of microorganisms such as viruses (e.g. the hepatitis virus) or parasites (e.g. malaria)
  - xeno serum antigens (serum sickness)

# Effector mechanisms of antibody-mediated diseases

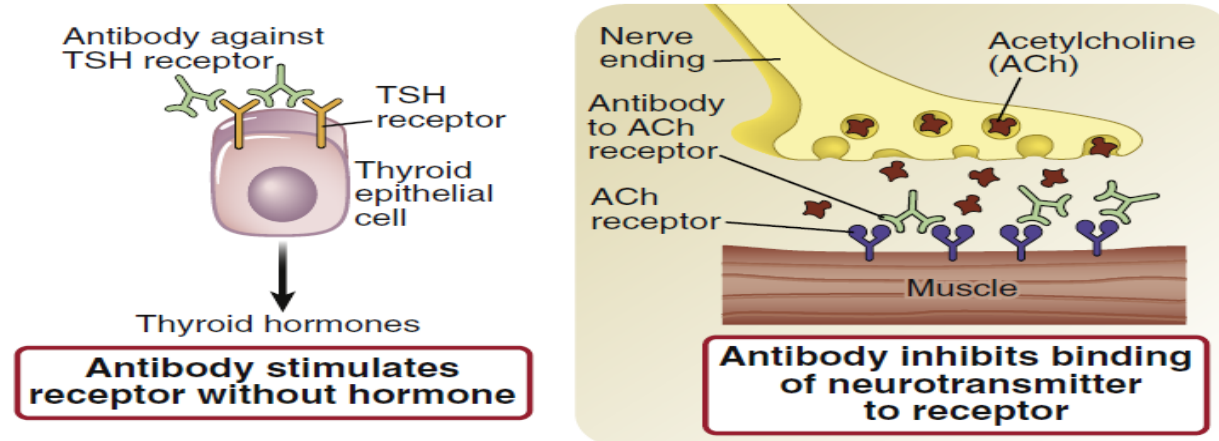
## (A) Complement- and Fc receptor–mediated inflammation



## (B) Opsonization and phagocytosis



## (C) Abnormal physiologic responses without cell/tissue injury



# Antibody-mediated diseases (type II hypersensitivity)

Antibody-mediated disease	Target antigen	Mechanisms of disease	Clinicopathologic manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune (idiopathic) thrombocytopenic purpura	Platelet membrane proteins (gpIIb/IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Goodpasture syndrome	Collagen in basement membranes of kidney glomeruli and lung alveoli	Complement and Fc receptor-mediated inflammation	Nephritis, lung hemorrhage
Graves disease (hyperthyroidism)	Thyroid stimulating hormone (TSH) receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated disruption of intercellular adhesions	Skin blisters (bullae)
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B <sub>12</sub>	Anemia due to abnormal erythropoiesis, nerve damage
Rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis

# Immune complex diseases (type III hypersensitivity)

Immune complex disease	Antibody specificity	Clinicopathologic manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	In some cases, microbial antigens (e.g., hepatitis B virus surface antigen); most cases unknown	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s)	Nephritis
Serum sickness (clinical and experimental)	Various protein antigens	Systemic vasculitis, nephritis, arthritis
Arthus reaction (experimental)	Various protein antigens	Cutaneous vasculitis

Immune complexes contain cationic antigens that bind to the negatively charged components of the basement membrane of the blood vessels of the kidney glomeruli.

# Therapy

- **Corticosteroids**
- **Plasmapheresis** is used to reduce levels of circulating antibodies
- **Intravenous IgG (IVIG) pooled from healthy donors**
- **Blockade of CD40 or its ligand**
- **Antibody specific for CD20**
- **Induction of tolerance**

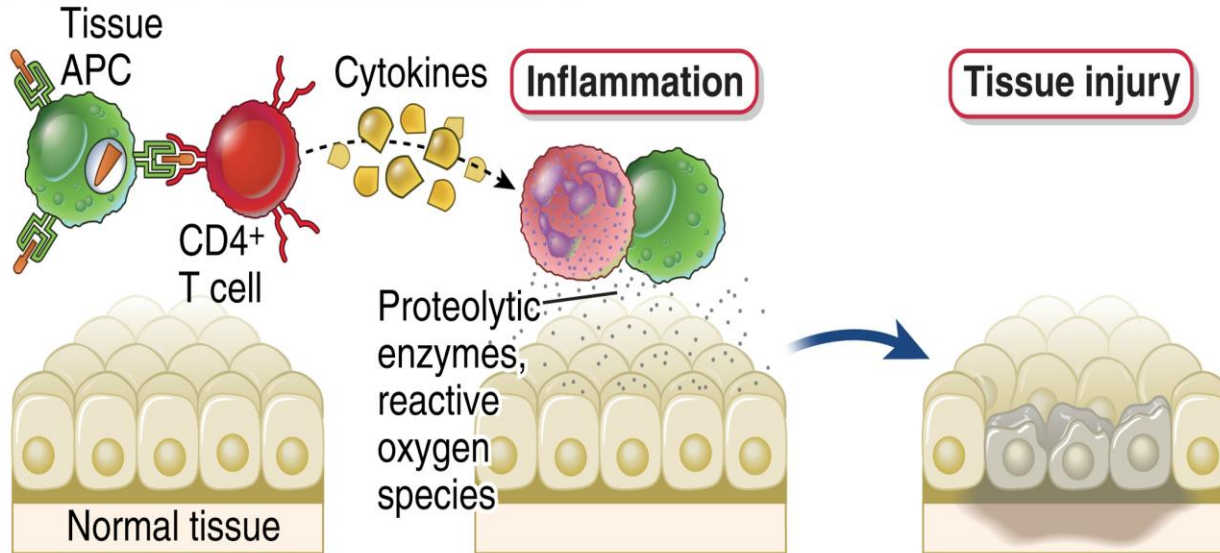
## **Diseases caused by T lymphocytes (type IV hypersensitivity)**

# Etiology

- Most of these diseases are probably the result of autoimmunity.
- Autoimmune reactions are usually directed against cellular antigens that have limited tissue distribution, and these diseases are usually not systemic but **organ specific**.
- In addition, the tissue may be damaged during the "normal" response of T lymphocytes to the microorganism:
  - TBC
  - Hepatitis C
  - Myocarditis (*Coxsackivirus B*)
  - Superantigens

# Pathogenesis

## A Cytokine-mediated inflammation



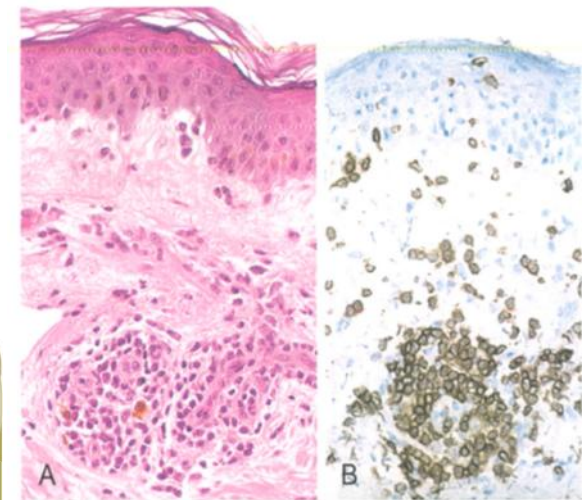
CD4<sup>+</sup> lymphocytes  
(DTH)

Th1 → IFN $\gamma$  → Mo/MF

Th17 → IL-17 → N

CTL

## B T cell-mediated cytotoxicity



# Diseases caused by T lymphocytes

Disease	Specificity of pathogenic T cells	Clinicopathologic manifestations
Multiple sclerosis	Myelin proteins	Demyelination in the central nervous system, sensory and motor dysfunction
Rheumatoid arthritis	Unknown antigens in joint	Inflammation of synovium and erosion of cartilage and bone in joints
Type 1 diabetes	Pancreatic islet antigens	Impaired glucose metabolism, vascular disease
Crohn disease	Unknown, ? role of intestinal microbes	Inflammation of the bowel wall; abdominal pain, diarrhea, hemorrhage
Psoriasis	Unknown	Chronic skin inflammation
Contact sensitivity (e.g., poison ivy, drug reaction)	Modified skin proteins	DTH reaction in skin, rash
Chronic infections (e.g., tuberculosis)	Microbial proteins	Chronic (e.g., granulomatous) inflammation

These diseases are usually chronic and progressive.

All these diseases today are classified in **chronic inflammatory diseases**.

Tissue injury causes release and alteration of self proteins, which may result in reactions against these newly encountered proteins - **epitope spreading**.

# Therapy

- Corticosteroids
- Cytokine antagonists (TNF- $\alpha$ )
- Immunosuppressive drugs (cyclosporin, rapamycin.....)
- Blockade of the costimulator (B7)
- Induction of tolerance - IVIG