

Basic Immunology

Allergies and hypersensitive reactions

Cellular and molecular mechanism.
T cell mediated macrophage activation =
Type IV. hypersensitive reaction (DTH).

Immune system

RECOGNITION

SELF

NON-SELF

altered SELF

normal immune-homeostasis

TOLERANCE

ELIMINATION



AUTOIMMUNITY

TUMORS

IMMUNO
DEFICIENCIES

HYPERSENSITIVE
REACTIONS

ALTERED immune-homeostasis = IMMUNOPATHOLOGY

Hypersensitive reactions

- **Pathological overreactions of the immune response with severe tissue damage (necrosis) in the effector phase.**
- **The immune system itself initiates these diseases.**
- **Different background mechanisms.**
- **Gell and Coombs distinguished 4 types of reactions originally (1963). More recently these were further subdivided.**
- **Significance:**
 1. **Allergic diseases**
 2. **Autoimmune diseases**

Based on the immunological mechanisms we distinguish 4 types of hypersensitive reactions

Immunoglobulin-mediated

- Type I.** Atopy or Allergy
(IgE-mediated immediate form)
- Type II.** Humoral cytotoxic immune reactions
(IgG against cellular antigens)
- Type III.** Immunocomplex-diseases
(soluble self or non-self antigens)

Cell-mediated

- Type IV.** T cell-mediated → Th1- and Tc- cytokines
(DTH=**D**elayed **T**ype **H**ypersensitivity)

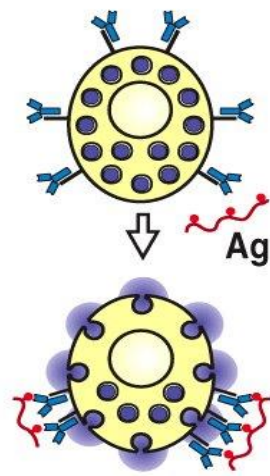
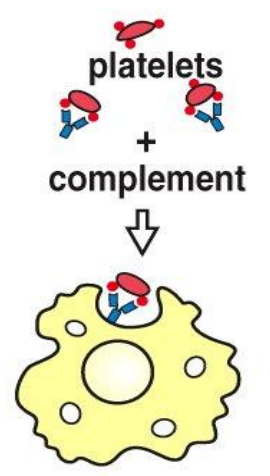
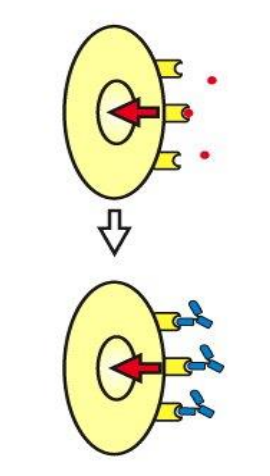
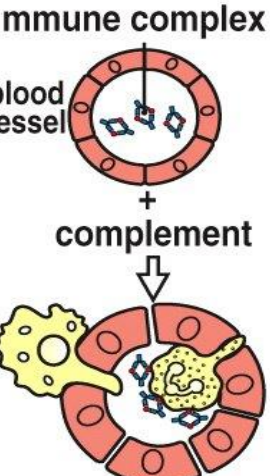
	Type I	Type II		Type III	
Immune reactant	IgE	Type II a	IgG	Type II b	IgG
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen
Effector mechanism	Mast-cell activation	Complement, FcR ⁺ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, Phagocytes	Complement, Phagocytes
					
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg, penicillin)	Chronic urticaria (antibody against FCεR1α)	Serum sickness, Arthus reaction	

Figure 12-2 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

	Type IV		
	Type IV a T _H 1 cells	Type IV b T _H 2 cells	Type IV c CTL
Immune reactant	Type IV a T _H 1 cells	Type IV b T _H 2 cells	Type IV c CTL
Antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Macrophage activation	IgE production, Eosinophil activation, Mastocytosis	Cytotoxicity
	<p>IFN-γ T_H1</p> <p>chemokines, cytokines, cytotoxins</p>	<p>IL-4 IL-5 T_H2</p> <p>eotaxin</p> <p>cytotoxins, inflammatory mediators</p>	<p>CTL</p>
Example of hypersensitivity reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

Figure 12-2 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Classification of hypersensitivity reactions

Melanie C. Dispenza, M.D., Ph.D.

Table 1 Modern classification of hypersensitivity reactions*

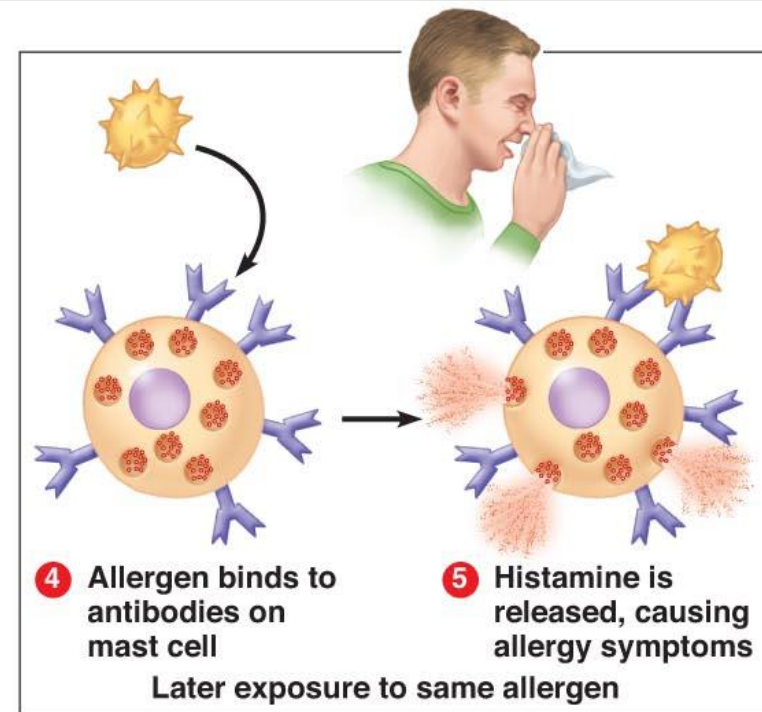
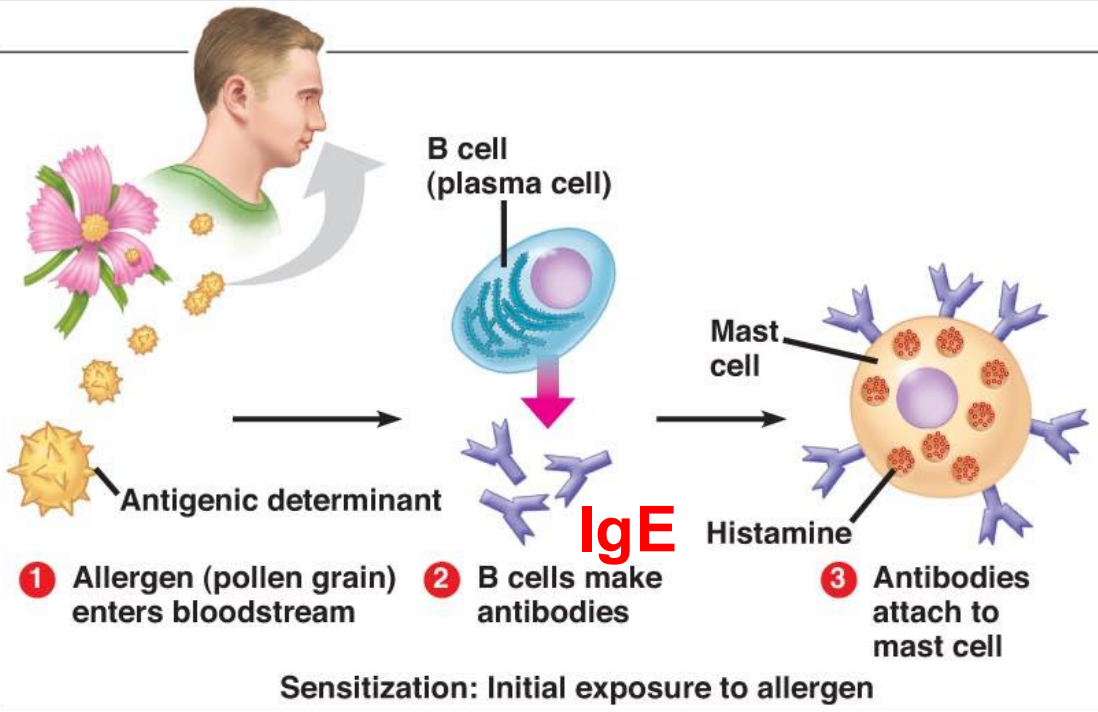
Classification Type	Immunologic Mechanisms	Clinical Examples
I	Mast cell-mediated reactions IgE-dependent (anaphylactic)	Anaphylaxis, angioedema, urticaria, asthma, allergic rhinitis
	IgE-independent (nonimmunologic or anaphylactoid)	Reactions to iodinated contrast reagents and some biologics
IIa	Antibody-mediated cytotoxic reactions (IgG/IgM antibodies); complement often involved	Immune cytopenias
IIb	Antibody-mediated cell-stimulating reactions	Graves disease, chronic idiopathic (spontaneous) urticaria
III	Immune complex-mediated complement activation	Serum sickness, drug-induced lupus, vasculitis
IVa	Th1 cell-mediated macrophage activation	Type 1 diabetes, contact dermatitis (with type IVc), tuberculin test reactions
IVb	Th2 cell-mediated eosinophilic inflammation	Maculopapular exanthems, DRESS syndrome, persistent asthma, allergic rhinitis
IVc	Cytotoxic T cell-mediated reactions	SJS and/or TEN, bullous exanthems
IVd	T cell-mediated neutrophilic inflammation	AGEP, Behçet's disease

IgE = Immunoglobulin E; Th = T-helper cell; DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; AGEP = acute generalized exanthematous pustulosis.

**Adapted from Ref. 14.*

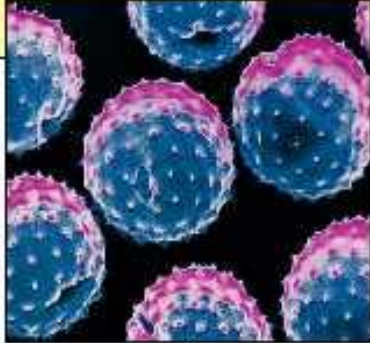



**Type I., immediate hypersensitivity;
Allergy, Atopy**

Basic mechanism



Allergens

Figure 10.1a

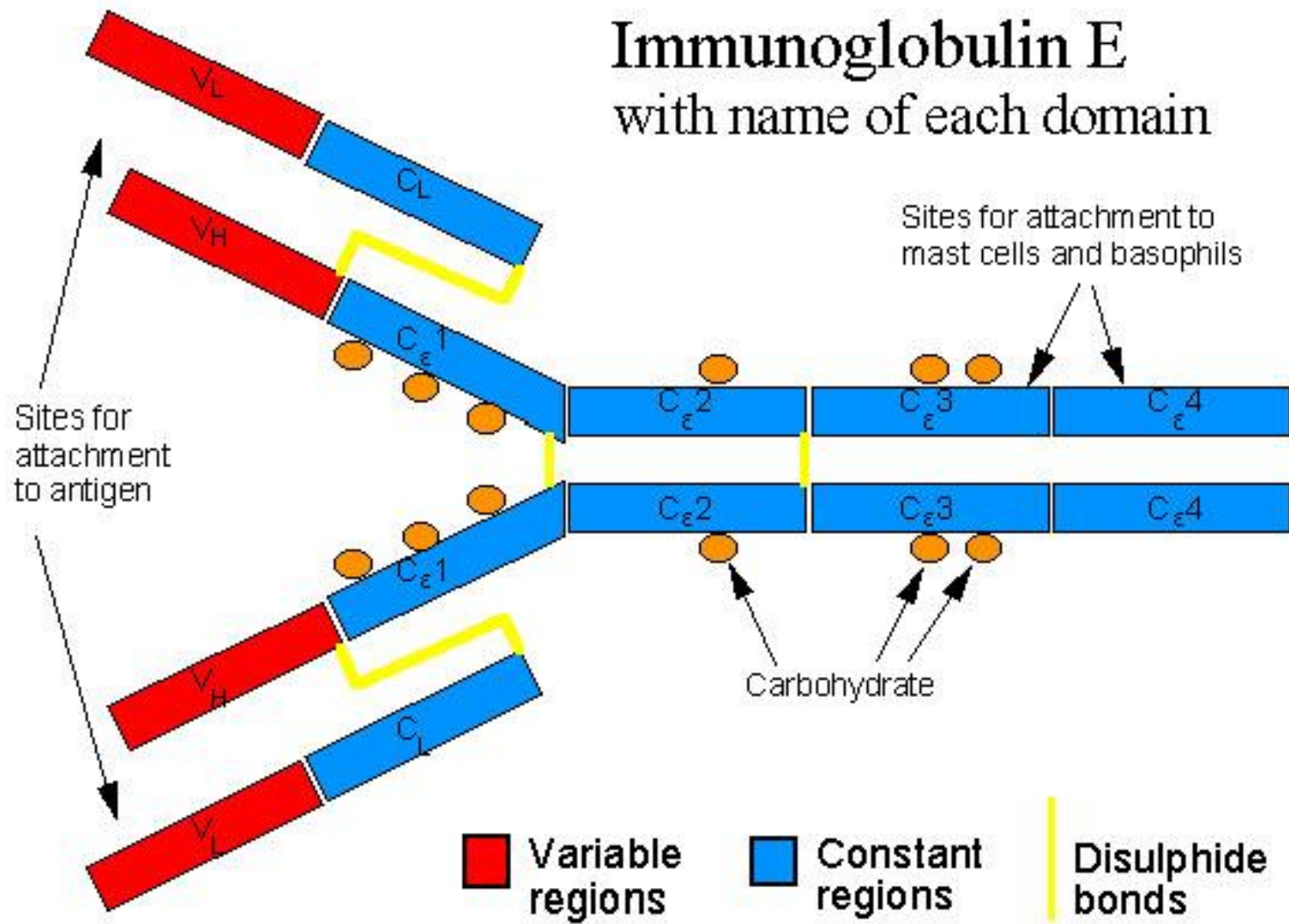
Common sources of allergens		
Inhaled materials Plant pollens Dander of domesticated animals Mold spores Feces of very small animals eg house dust mites	 pollen	 house dust mite
Injected materials Insect venoms Vaccines Drugs Therapeutic proteins	 wasp	 drugs

Food antigens (milk, soy, gluten, nuts, additives etc.)

Most important characteristics of inhaled allergens which enhance IgE production through Th2 activation

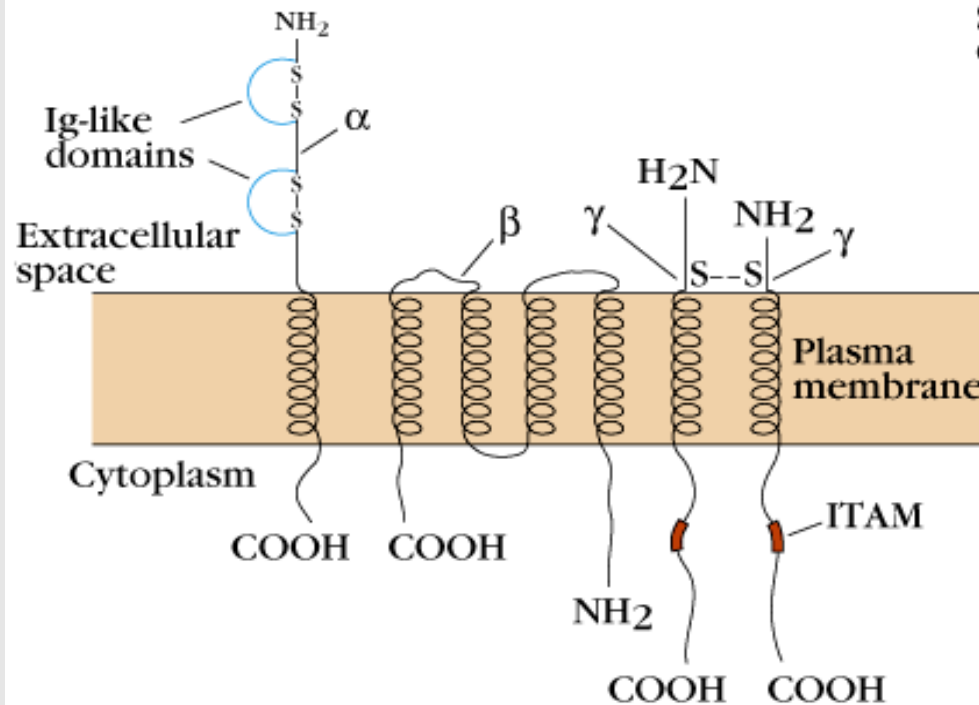
Proteins	only proteins elicit T cell response
Enzyme activity	often proteases
Low dose	enhance activation of IL-4-producing CD4-Th2 cells
Low molecular weight	the allergen can easily diffuse from the particle into the mucus.
Good solubility	the allergen can be released easily from the particle
Stabile	the allergen can be released even from exsiccated particles
Contain peptides that are able to bind to self MHCII	important at the first exposure for T cell activation

Immunoglobulin E with name of each domain

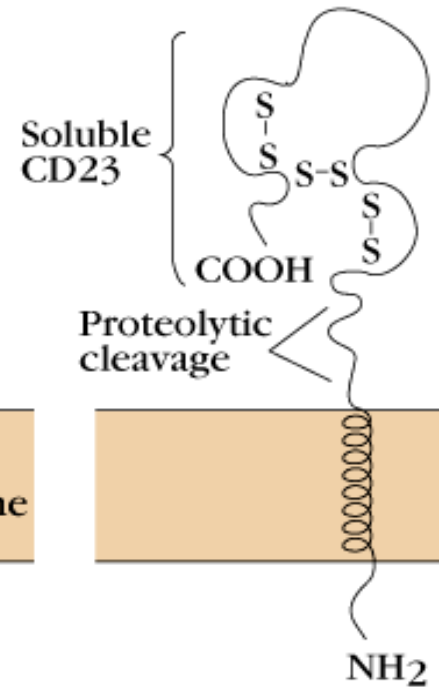


IgE-Receptors

(a) FcεRI:
High-affinity IgE receptor



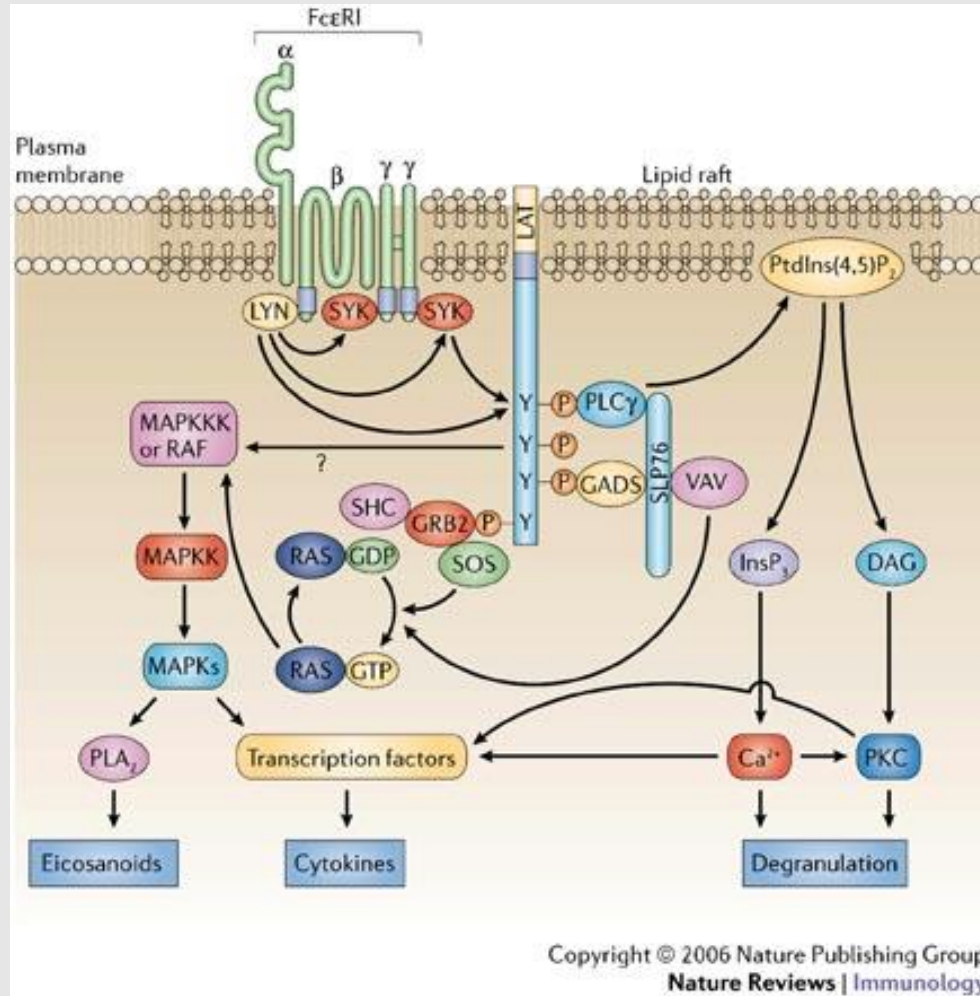
(b) FcεRII (CD23):
Low-affinity IgE receptor



**mast cells, basophil gr,
activated eosinophil gr**

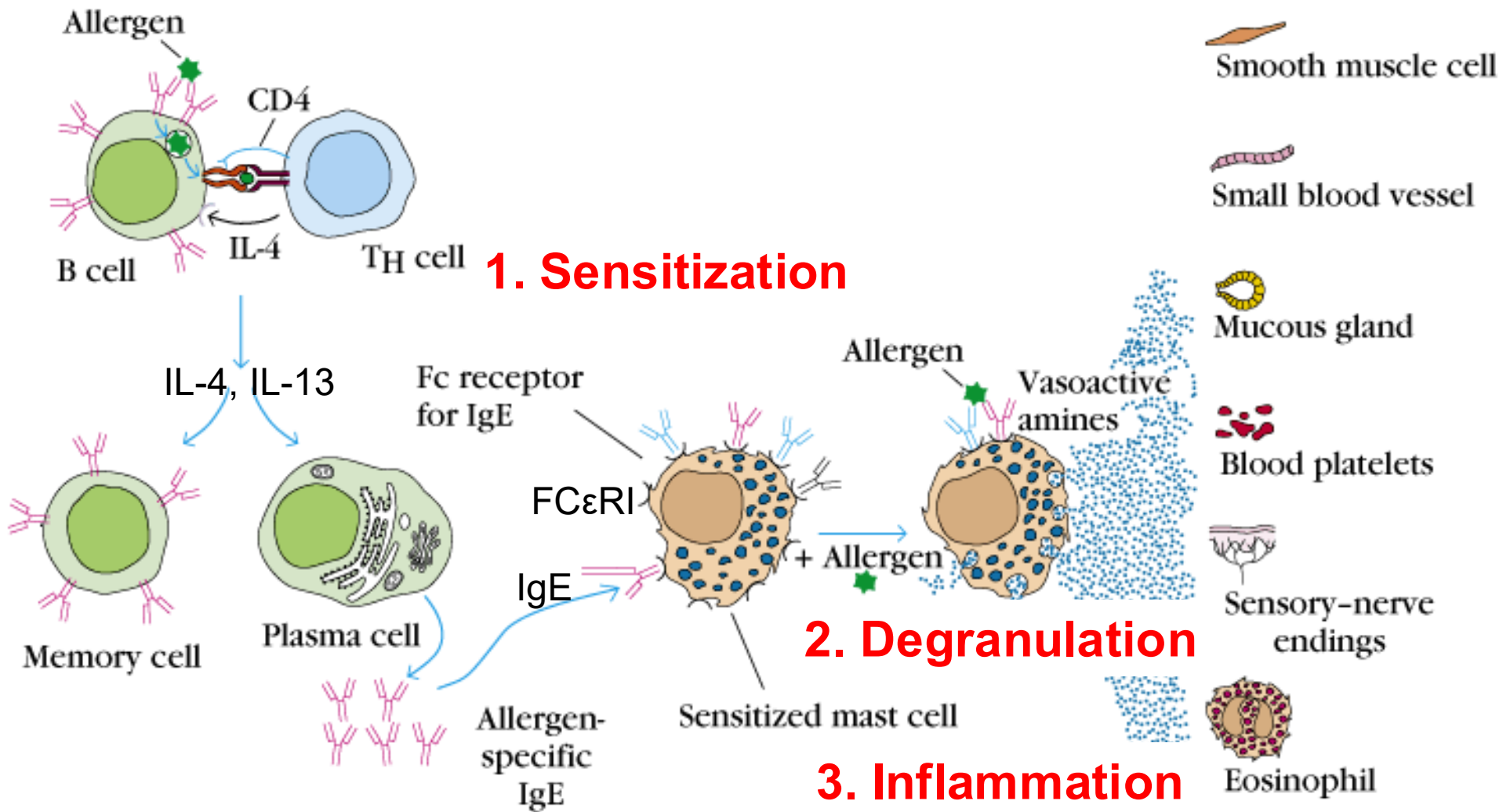
**eosinophil gr,
follicular B cells**

Fcε-Receptor signaling

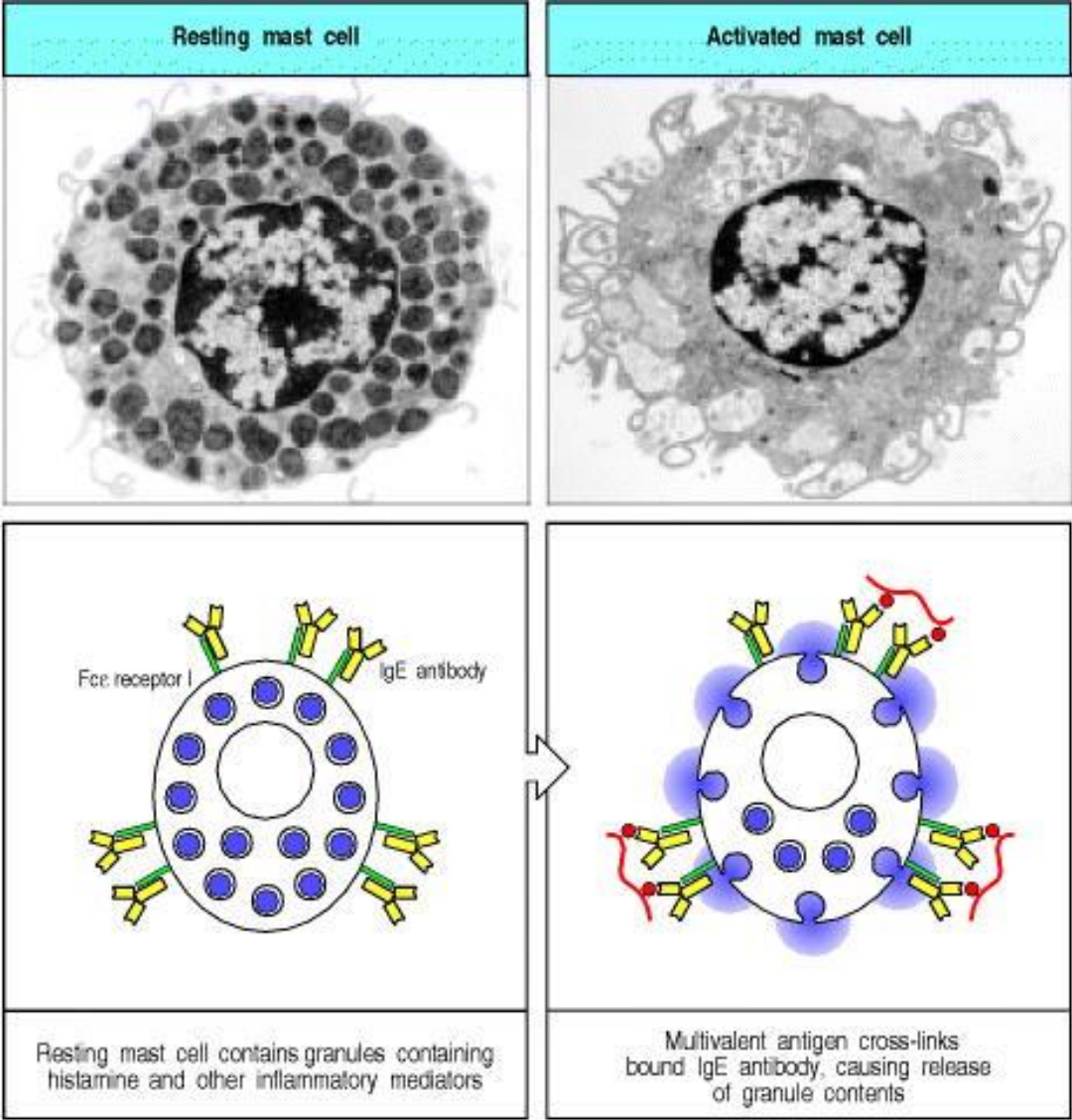


Gilfillan *et al.* *Nature Reviews Immunology* 6, 218-230 (March 2006) | doi:10.1038/nri1782

Mechanism of Type I. hypersensitivity



Degranulation of mast cells



Pharmacologic Mediators of Immediate Hypersensitivity

Preformed mediators in granules

histamine	bronchoconstriction, mucus secretion, vasodilatation, vascular permeability
tryptase	proteolysis
kininogenase	kinins and vasodilatation, vascular permeability, edema
ECF-A (tetrapeptides)	attract eosinophil and neutrophils

Newly formed mediators

leukotriene B ₄	basophil attractant
leukotriene C ₄ , D ₄	same as histamine but 1000x more potent
prostaglandins D ₂	edema and pain
PAF	platelet aggregation and heparin release: microthrombi

Antigen-IgE binding enhances IgE production

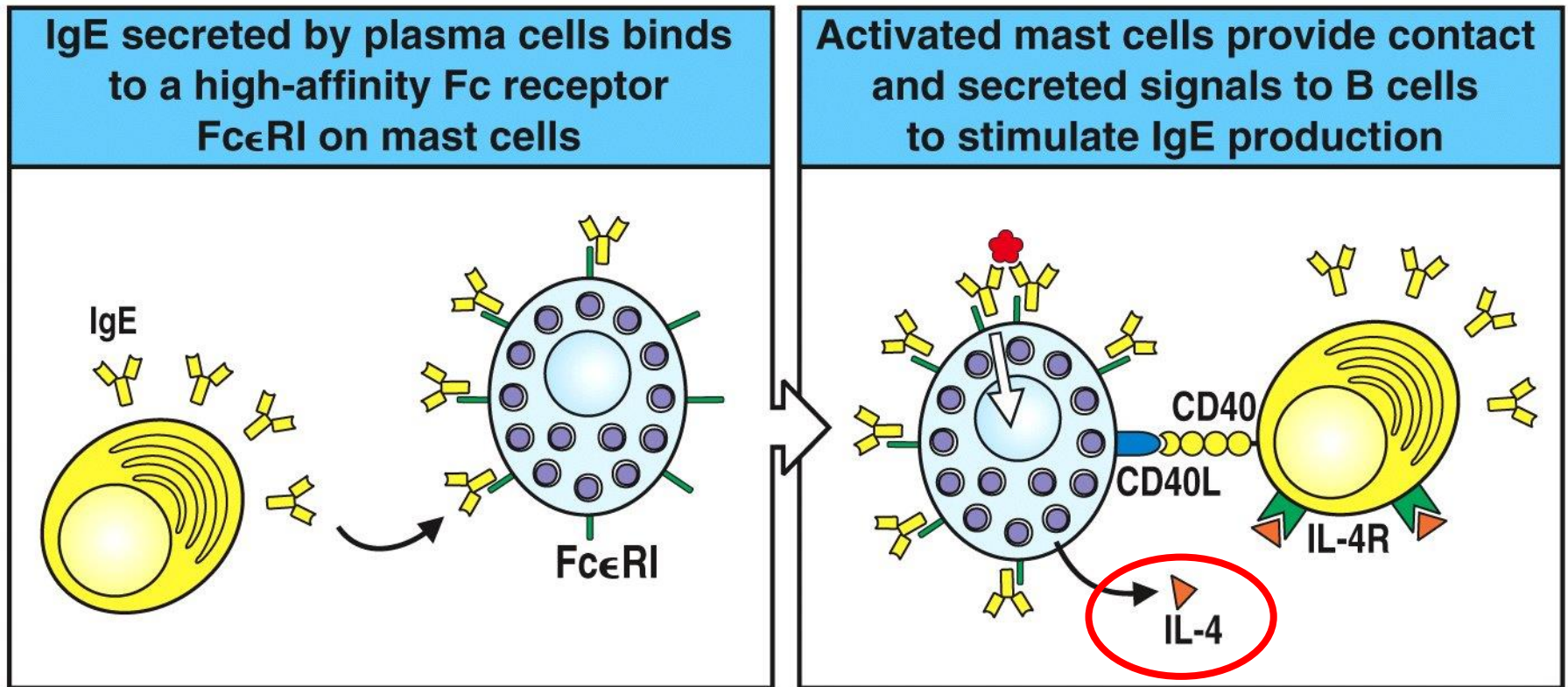


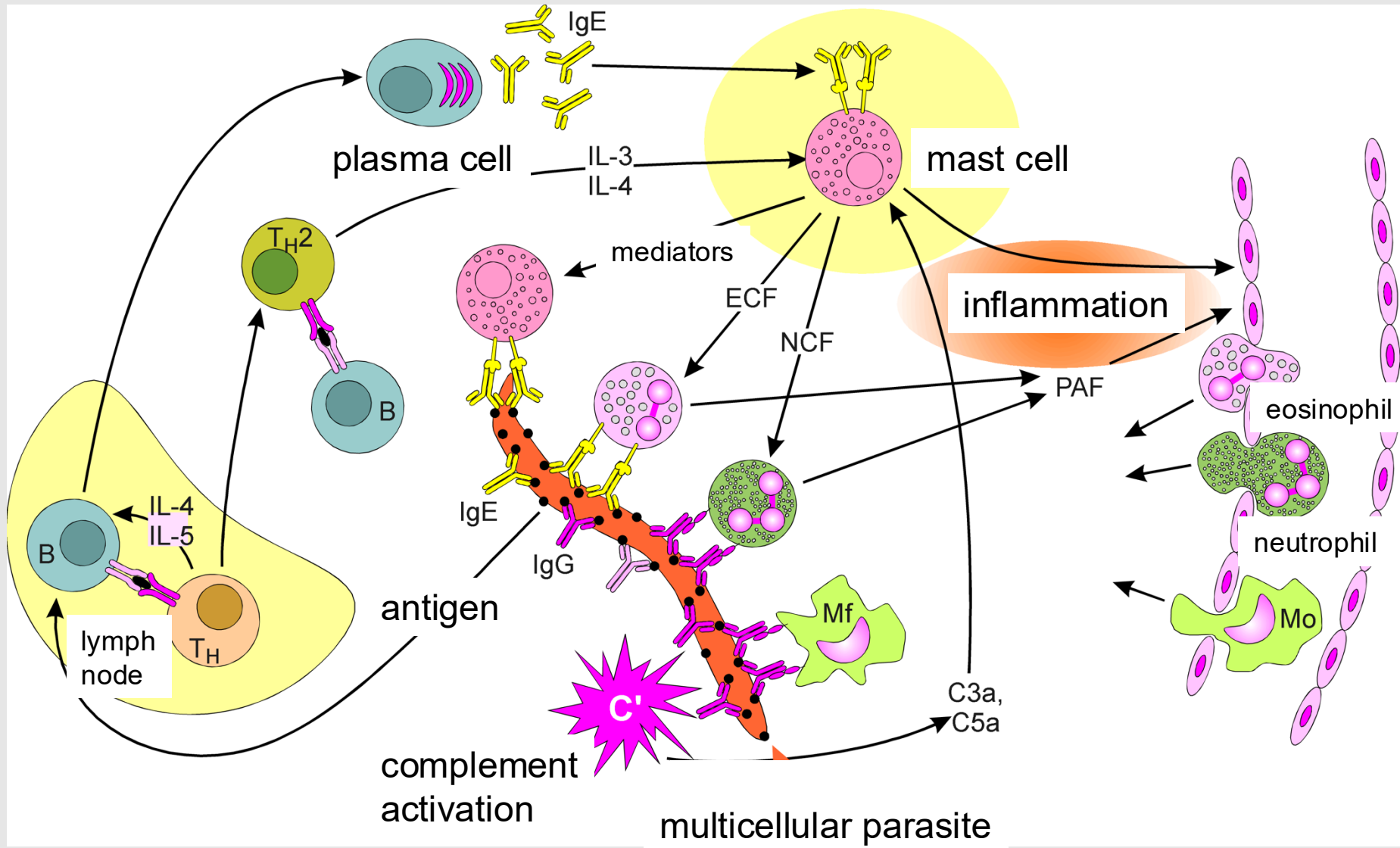
Figure 12-7 Immunobiology, 6/e. (© Garland Science 2005)

Late phase:

Upon cytokine effect: recruitment of neutrophils and eosinophils, stimulation of B cells

IL-3, IL-5, GM-CSF → local eosinophil proliferation → **Inflammation**

Physiological role of the IgE response in the protection against parasites and fungi



Shistosoma mansoni (bilharzia)

Type I. diseases

- **Systemic anaphylaxia - anaphylactic sock**
- **Allergic rhinitis (=Hay fever)**
- **Allergic conjunctivitis**
- **Allergic asthma**
- **Urticaria**
- **Ekzema (atopic dermatitis)**



Allergy – Environmental factors

Atopic allergy and asthma is the most frequent in the economically well-developed countries.

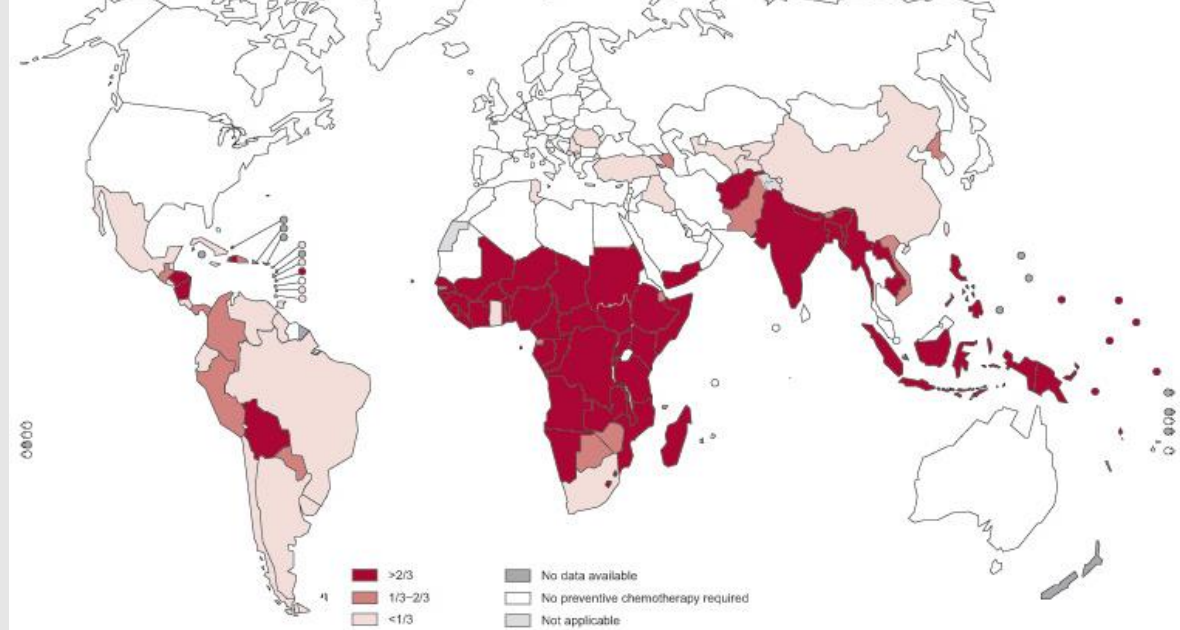
- changes in the infectious diseases in early childhood („**Hygiene-theory**” / „**Old Friends Hypothesis**”)
- **Environmental pollution** (air pollution in industrial regions, traffic)
- Altered allergen concentrations
- Changes in the **diet** (chemicals)
- Changes in the gut **microbiota**

Global prevalence of Allergic Rhinitis



Hygiene-theory

Global prevalence of Soil Transmitted Helminths



Hygiene-theory

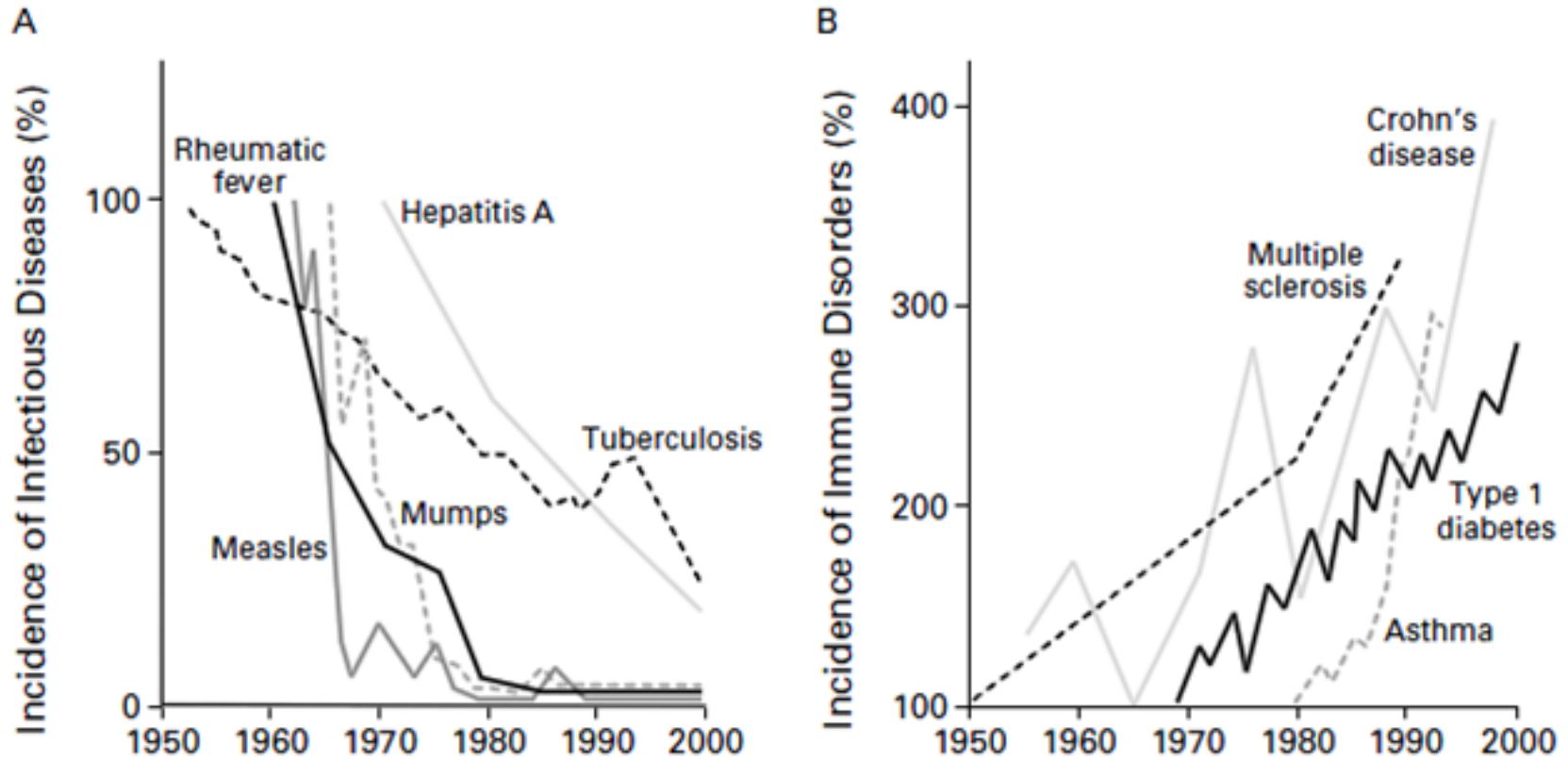
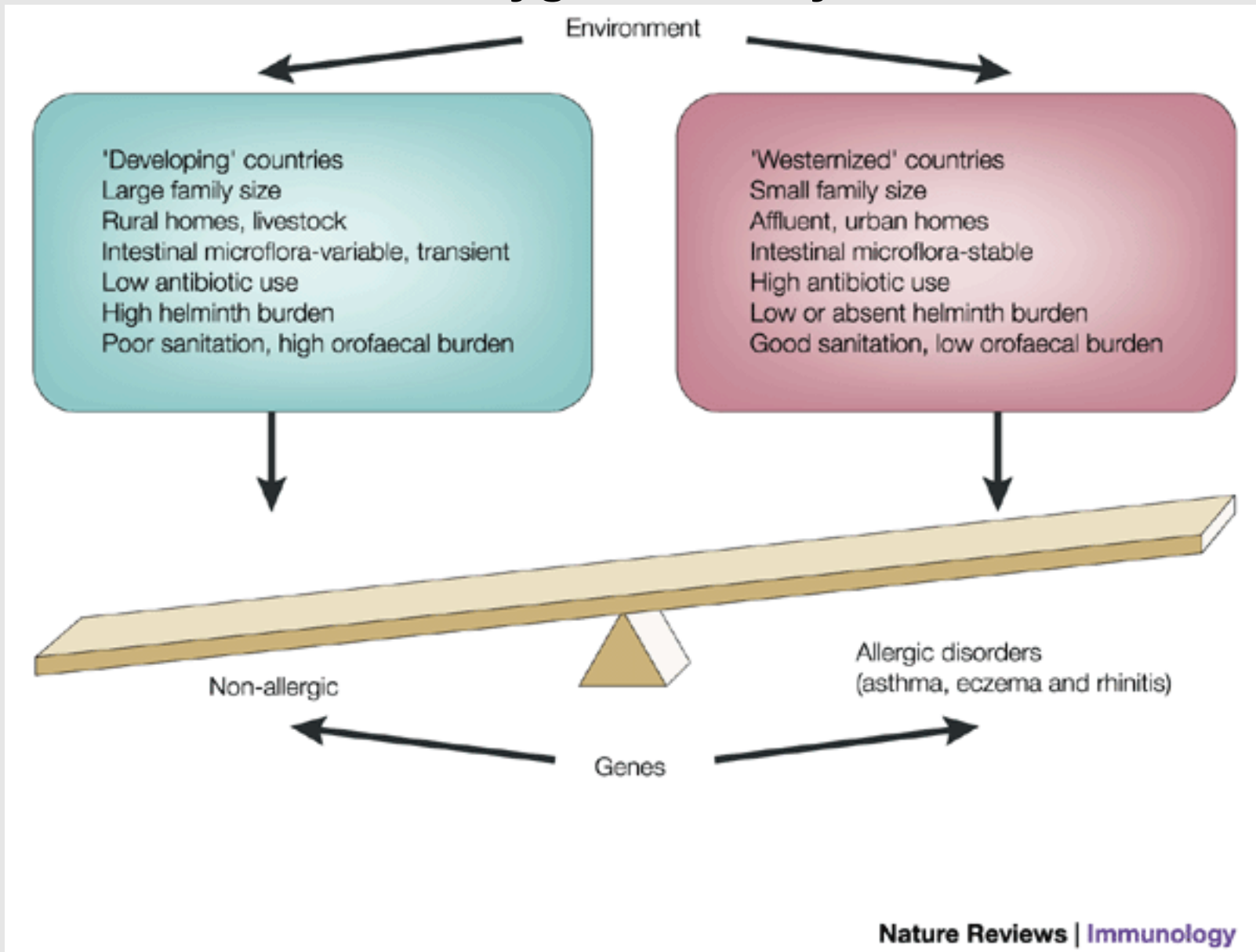


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

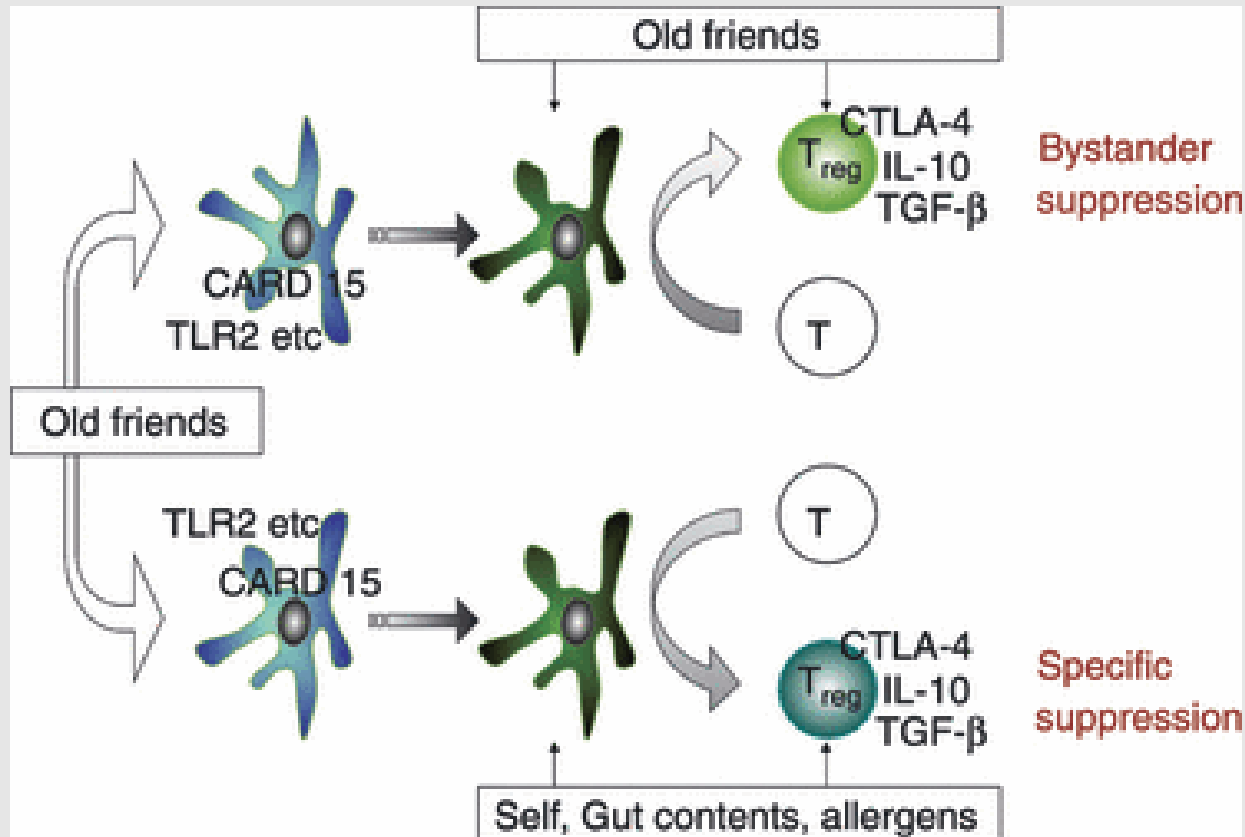
Hygiene-theory



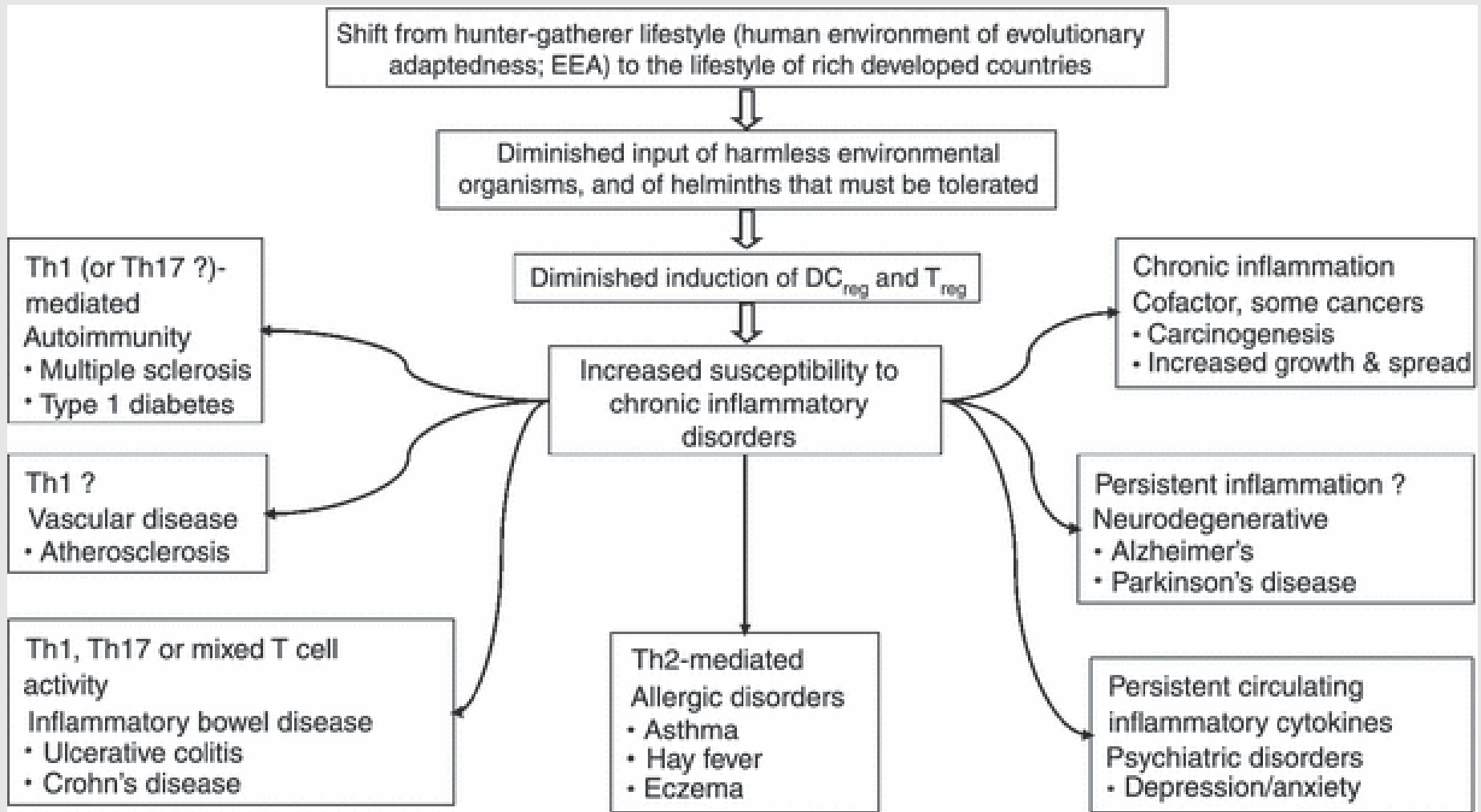
In: Marsha Wills-Karp, Joanna Santeliz & Christopher L. Karp: [The germless theory of allergic disease: revisiting the hygiene hypothesis.](#) *Nature Reviews Immunology* 1, 69-75 (October 2001)doi:10.1038/35095579

Old Friends hypothesis

“Old Friends”=Organisms such as helminths and environmental saprophytes, that are part of mammalian evolutionary history.



In: Review series on helminths, immune modulation and the hygiene hypothesis: The broader implications of the hygiene hypothesis. *Immunology*, Volume 126, Issue 1, pages 3-11, 8 DEC 2008 DOI: 10.1111/j.1365-2567.2008.03007.x <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2567.2008.03007.x/full#f2>





Atopy

- increased susceptibility to allergic disease (eg. hay fever, asthma)
- strong IgE-answer to environmental antigens
- high **IgE** and **eosinophilia** in the blood
- Genetic background:
 - **Chromosome 11q** – high affinity Fc ϵ R β -chain polimorfism
 - **Chromosome 5q** - IL-3, IL-4, IL-5, IL-9, IL-13 and GM-CSF genes
IgE isotype switch, eosinophil granulocyte survival, mast cell proliferation
 - **IL-4 promoter** – increased activity
higher IgE cc.
 - **IL-4-receptor** α -chain gain-of-function mutation – increased signaling strength

Therapeutic possibilities

- **Allergen free environment**
- **Antihistamines**
- **Desensitization**
- **Membrane-stabilizing drugs**
- **Non-specific immunosuppression**
- **CD23 (inhibiting IgE receptor) - activation**

Diagnosis:

1. Intradermal skintest

2. ELISA: allergen-specific IgE measurement

Allergen-specific skin tests

Prick test
IgE-mediated immediate reaction



Reading: 30 min

DTH:



Reading: 48h

Type II. hypersensitivity
antibody-mediated cytotoxic form

Type II hypersensitivity- cytotoxic reactions

- antibody and cell-mediated cytotoxicity
- complement-mediated lysis
- IgG and IgM
- K-cells, platelets, neutrophils, eosinophils and macrophages
- Examples:
 - ❑ Rh antigen
 - ❑ transfusion reactions
 - ❑ autoimmune haemolytic anemia
 - ❑ hyperacute graft rejection
 - ❑ reactions to tissue antigens

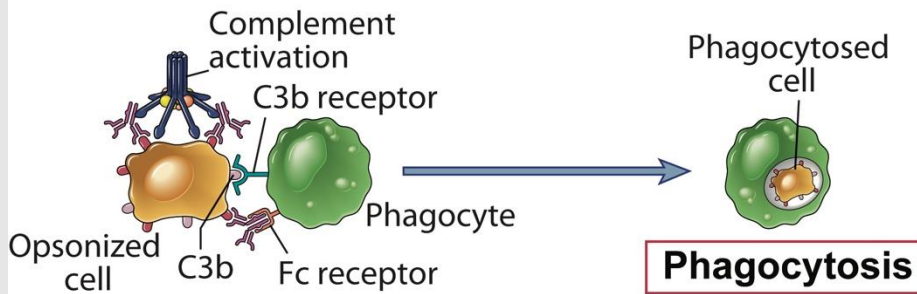
Type II. diseases

- **Antigens** are usually endogenous, sometimes exogenous chemicals (haptens), which can bind to cell surface.
- Drug-induced-hemolytic anemia, - granulocytopenia, - thrombocytopenia
- **Diagnosis**: circulating antibodies and immunofluorescence on biopsy from the lesion
- **Therapy**: anti-inflammatory- and immunosuppressive drugs

Type II. hypersensitivity

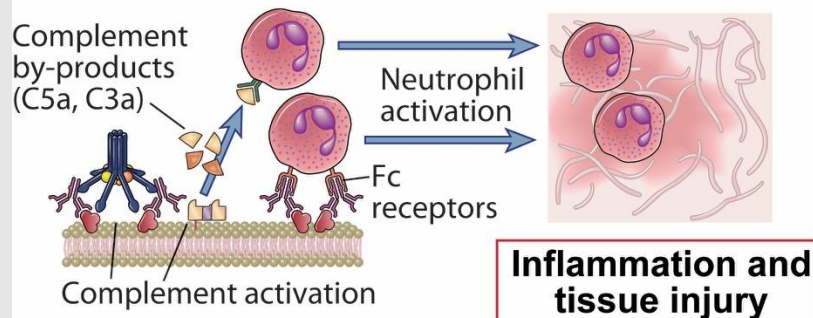
Type II a

Opsonization and phagocytosis



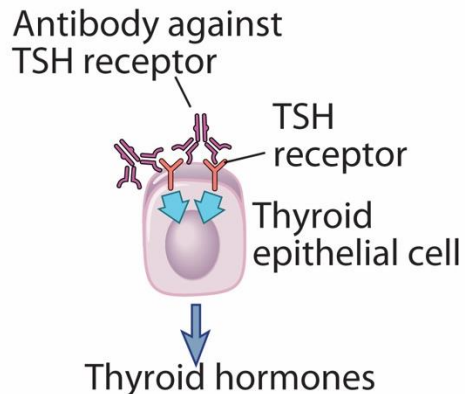
ADCC and complement-mediated lysis

Complement- and Fc receptor – mediated inflammation

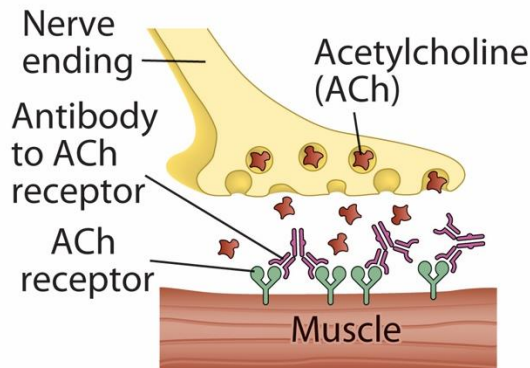


Type II b

Abnormal physiologic responses without cell/tissue injury



Graves (Basedow) disease

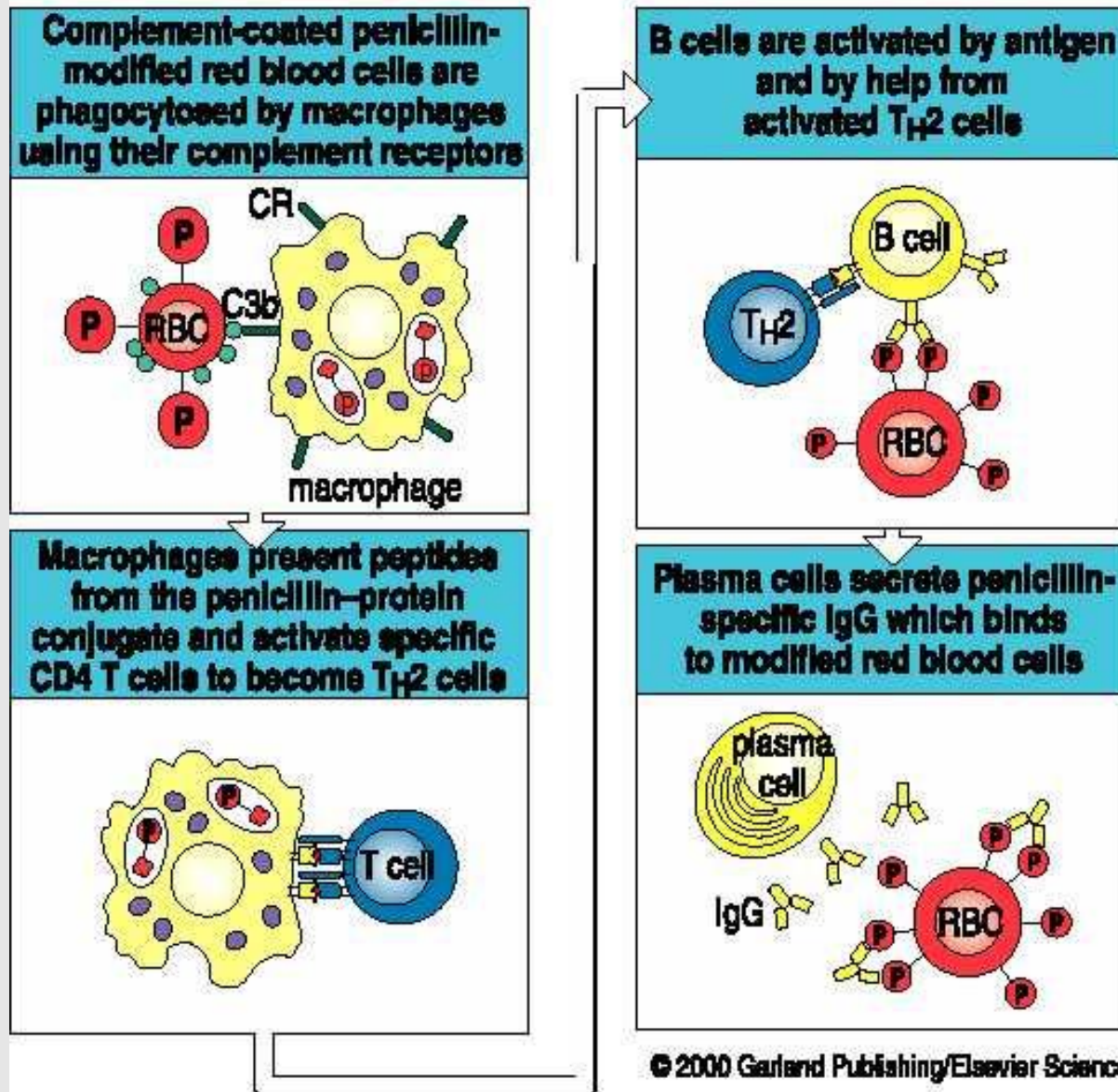


Antibody inhibits binding of ligand to receptor

Myasthenia gravis

Type II. hypersensitivity -

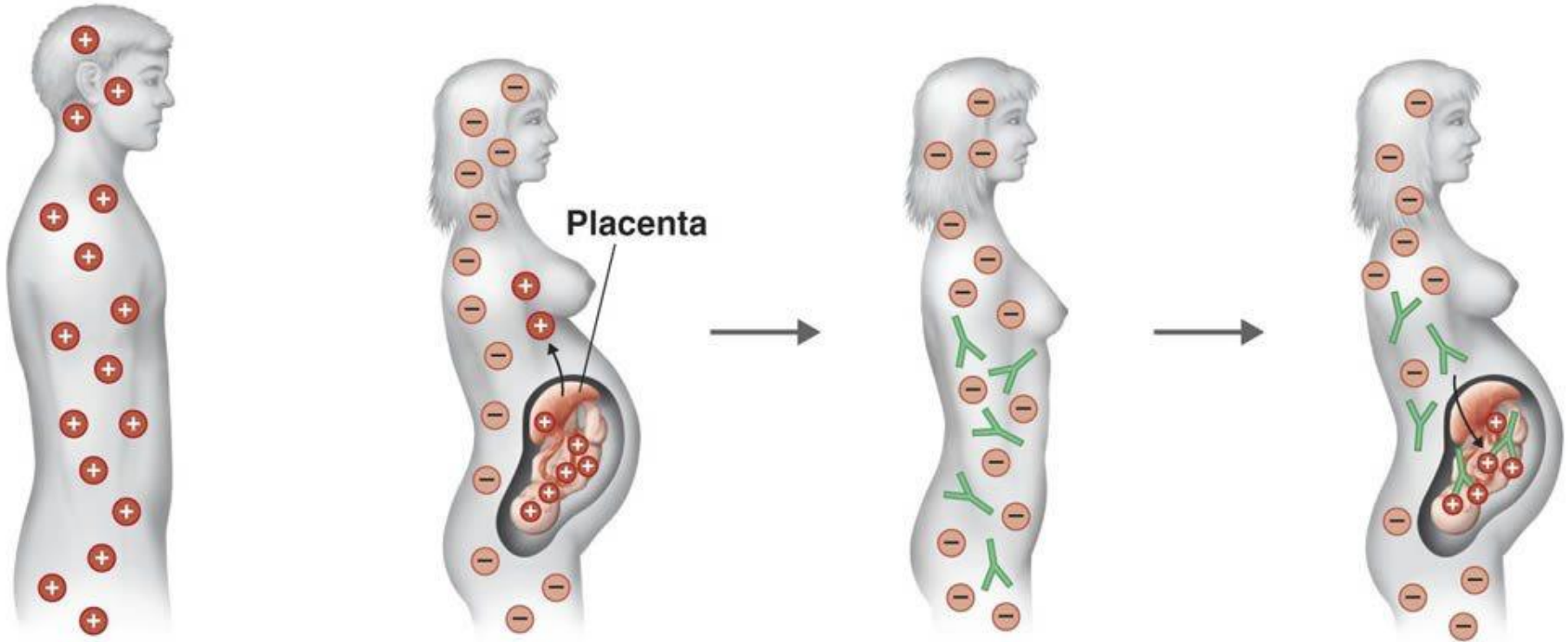
Figure 10.26



Drug-induced hemolytic anemia

Hemolysis

Rh incompatibility



1 Rh⁺ father.

2 Rh⁻ mother carrying her first Rh⁺ fetus. Rh antigens from the developing fetus can enter the mother's blood during delivery.

3 In response to the fetal Rh antigens, the mother will produce anti-Rh antibodies.

4 If the woman becomes pregnant with another Rh⁺ fetus, her anti-Rh antibodies will cross the placenta and damage fetal red blood cells.

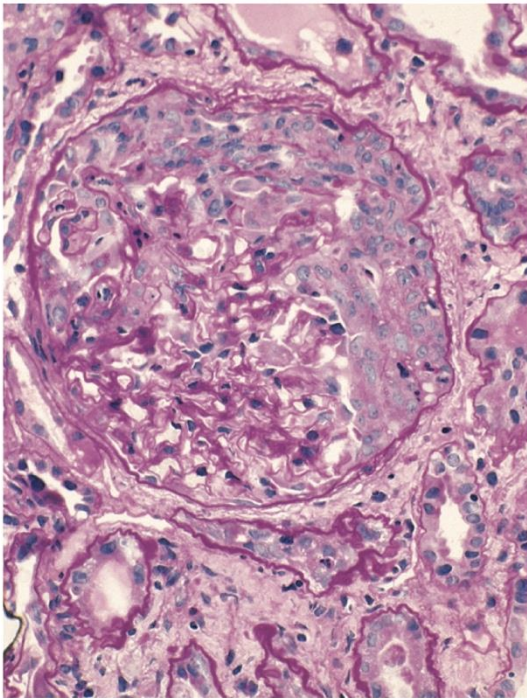
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Prophylaxis: anti-RhD antibody prophylaxis after delivery

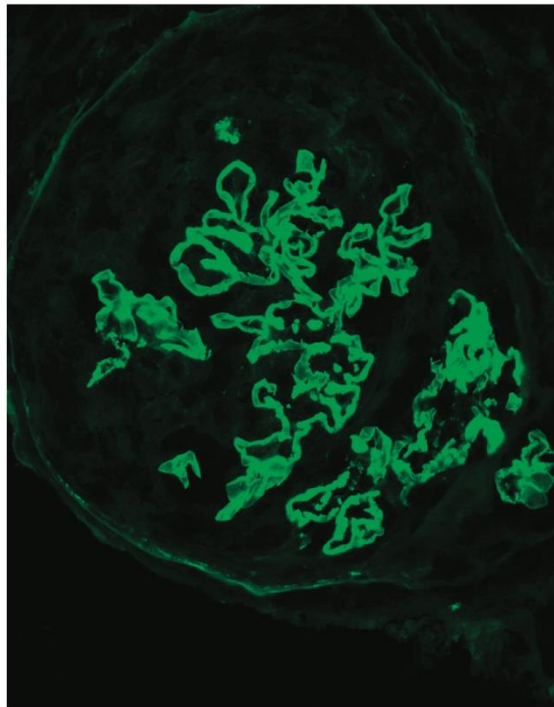
Antibody-mediated Glomerulonephritis (1)

Goodpasture-syndrome

Anti-basement membrane antibody-mediated glomerulonephritis



Light microscopy



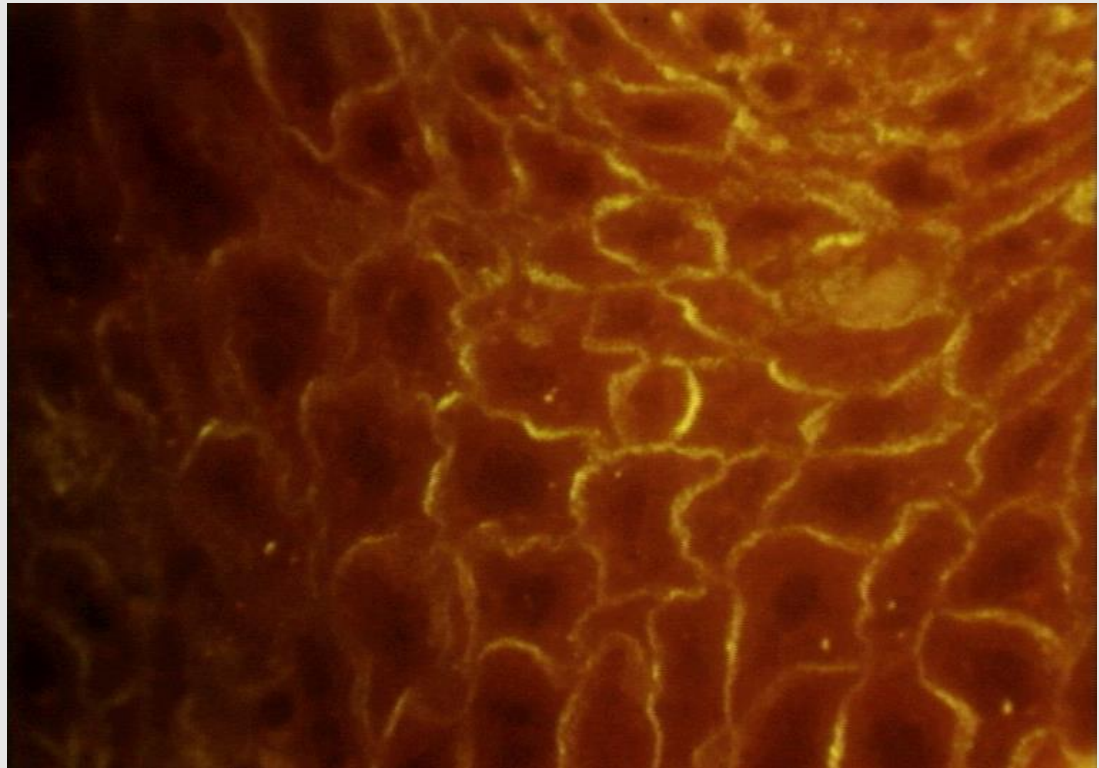
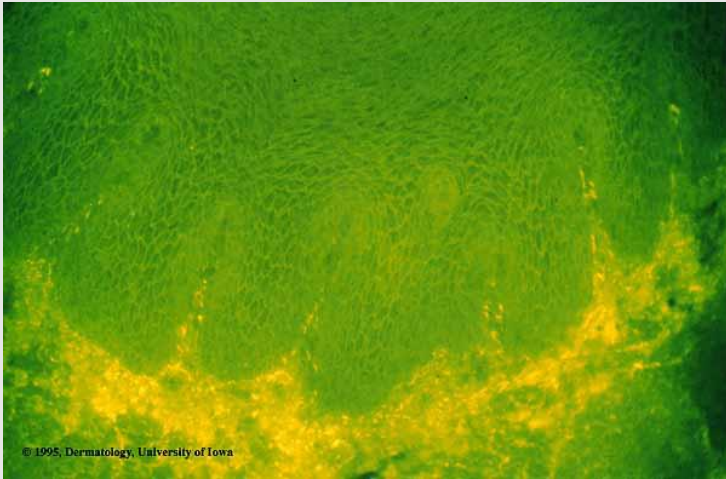
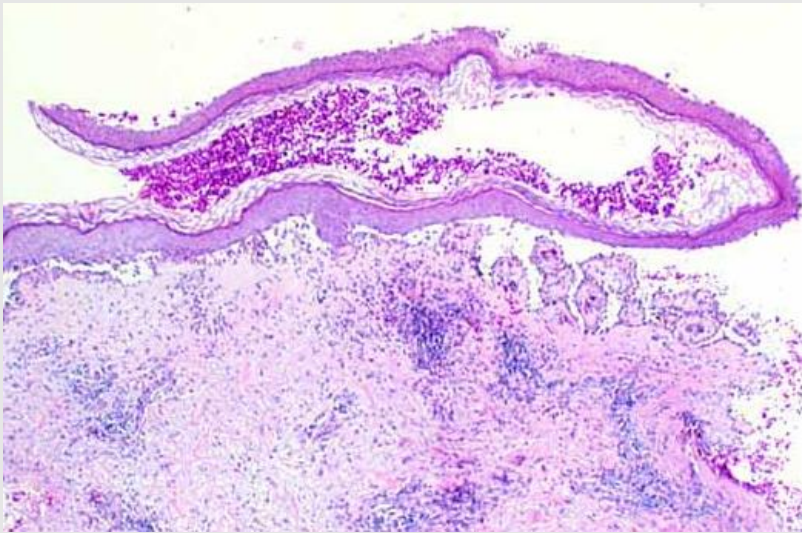
Immunofluorescence

The pathologic lesion contains antibodies, complement and neutrophils.

Staining is **smooth** and **linear**.

Pemphigus vulgaris

Target antigen: skin
intercellular proteins: cadherin,
desmosome
Symptoms: blisters in the skin



Type III. hypersensitivity

Immunocomplex disease

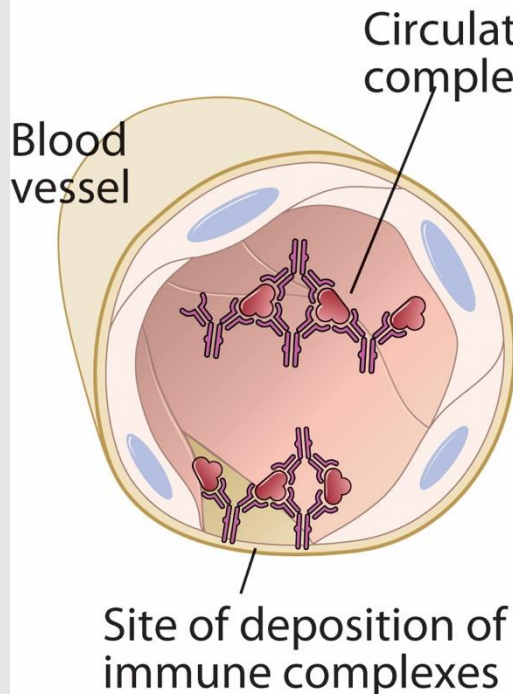
Type III. hypersensitivity

- **Immunocomplex disease**
- **Antigens** are exogenous (chronic bacterial, viral or parasitic infections) or endogenous tissue molecules (Autoimmun diseases)
- **Antigens are soluble.** The pathologic lesion contains antibody and complement factors.
- **Tissue damage caused by** neutrophils (inflammation) and platelets (thrombosis).

Types of Antibody-Mediated Diseases

Immune complex – mediated tissue injury

Mechanism of antibody deposition



Effector mechanisms of tissue injury

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



Neutrophil granule enzymes, reactive oxygen intermediates

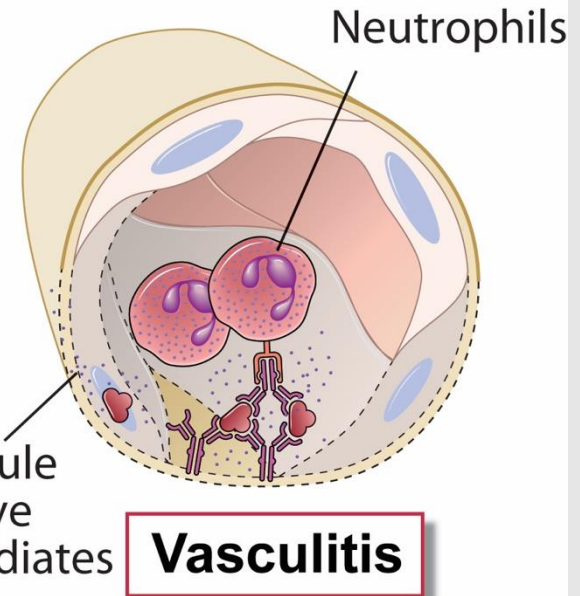


Fig. 18-1B

Diseases

- Caused by **dissolved immunocomplexes**. The outcome of the disease is influenced by the size of the immunocomplexes.
- might be **general** (eg. serum sickness) or **organ-specific**:

Skin (SLE, Arthus-reaction)

Lung (Aspergillosis, Farmer's lung)

Blood vessels (Polyarteritis)

Limbs (RA)

Kidneys (lupus Nephritis)

- **3-10 hours** needed for the development

For **diagnosis** immunocomplexes have to be verified in tissue biopsy.

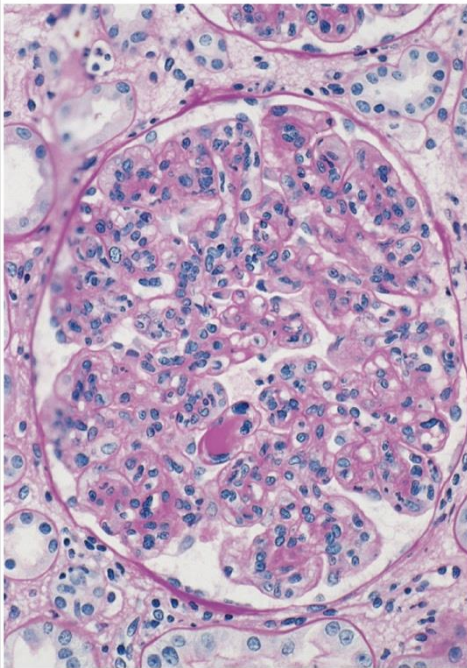
Granular staining is characteristic.

Immunocomplexes and low complement concentration in the serum.

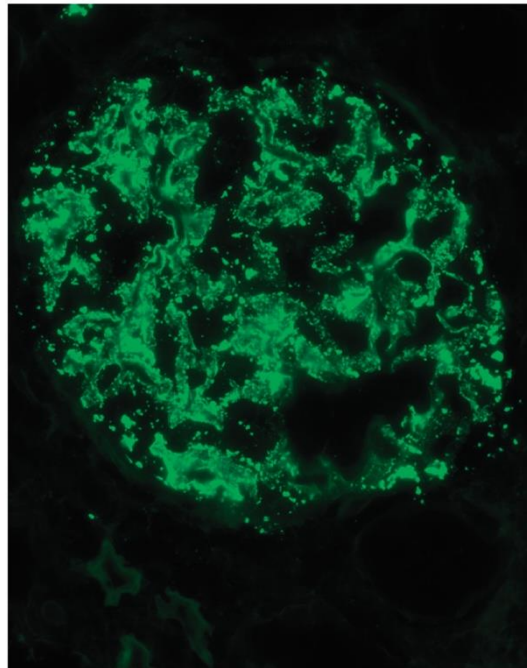
Arthus-reaction: immunocomplex-mediated vasculitis

Antibody-mediated Glomerulonephritis (2)

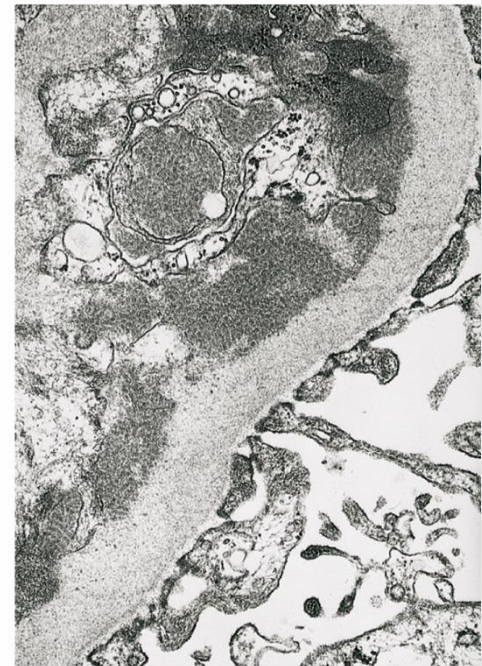
Immune complex-mediated glomerulonephritis



Light microscopy



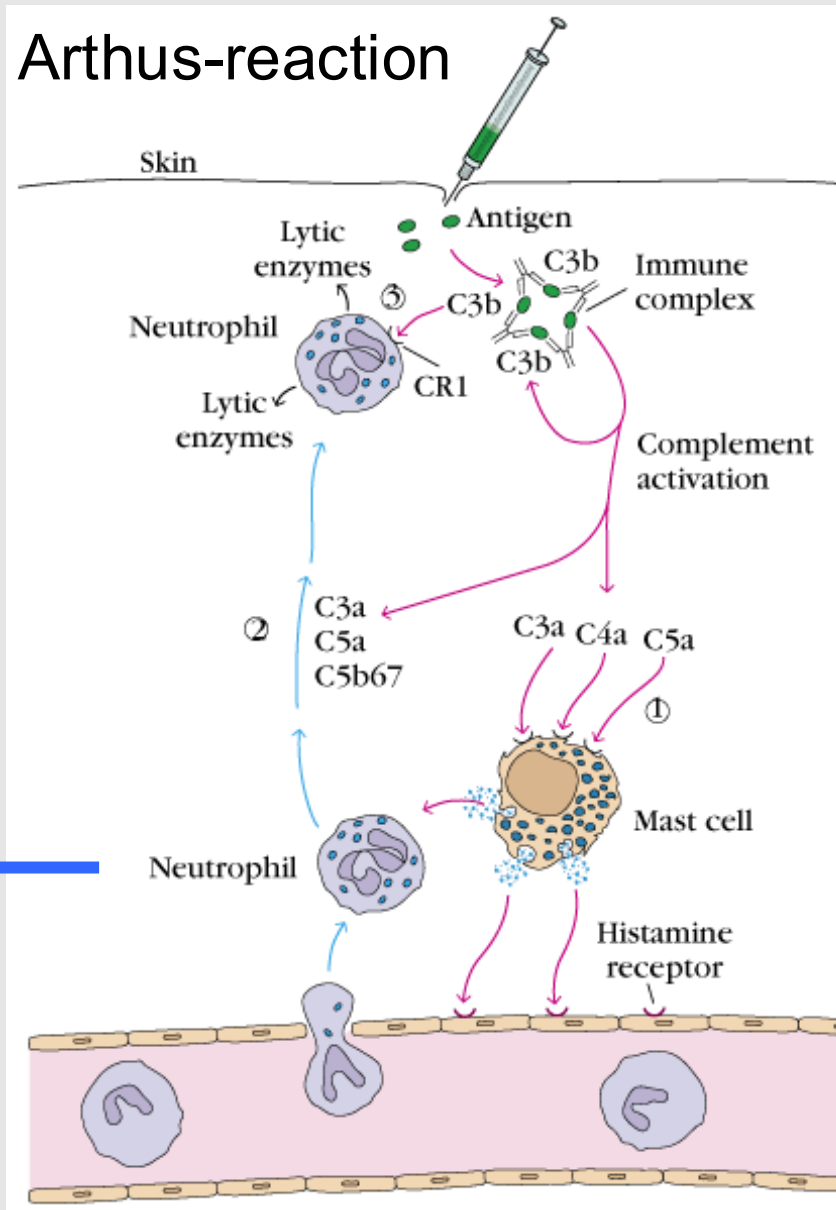
Immunofluorescence



Electron microscopy

Fig. 18-3B

Type III. hypersensitivity



Type III. hypersensitivity

Disease	Symptom	Therapy
Serum sickness (GN, Arthritis, Vasculitis)	fever, limb pain, dermatitis, lymphadenopathia, proteinuria, breathing insufficiency	Clearance of immunocomplexes, supportive treatment
Polyarteritis nodosa	Pain, high blood pressure	Immunosuppression
SLE, RA	Polyarthralgia (limb pain), face redness (dermatitis), lung- and kidney failure	Immunosuppression
allergic bronchopulmonary Aspergillosis	Asthma, recurrent fever, chest pain	Corticosteroids against inflammation
Some cancers	Similar to serum sickness	Tumor excision

Type IV. hypersensitivity

Delayed type hypersensitivity (DTH)

TABLE 14-3 INTRACELLULAR PATHOGENS AND CONTACT ANTIGENS THAT INDUCE DELAYED-TYPE HYPERSENSITIVITY

Intracellular bacteria

Mycobacterium tuberculosis

Mycobacterium leprae

Listeria monocytogenes

Brucella abortus

Intracellular fungi

Pneumocystis carinii

Candida albicans

Histoplasma capsulatum

Cryptococcus neoformans

Intracellular parasites

Leishmania sp.

Intracellular viruses

Herpes simplex virus

Variola (smallpox)

Measles virus

Contact antigens

Picrylchloride

Hair dyes

Nickel salts

Poison ivy

Poison oak

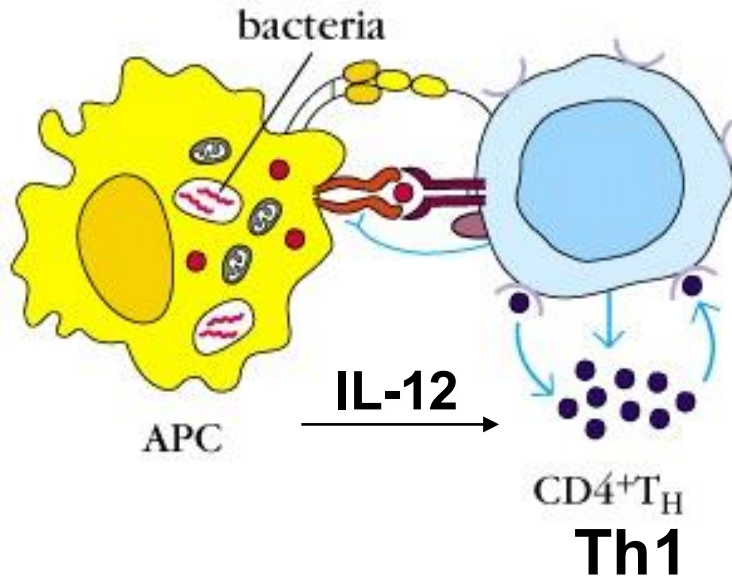
Self tissue antigens

Alloantigens (Transplantation)

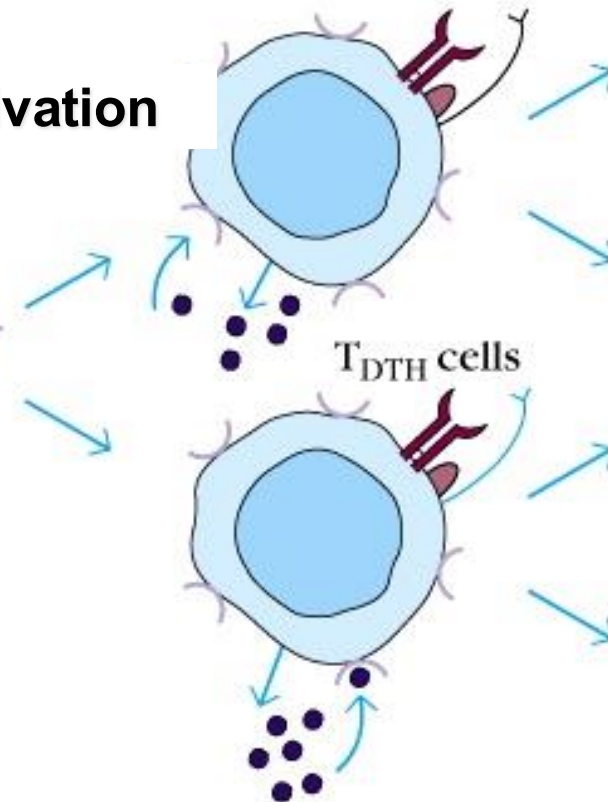
Phase 1 and 2 of DTH

(a) Sensitization phase

1. Sensitization



2. Activation



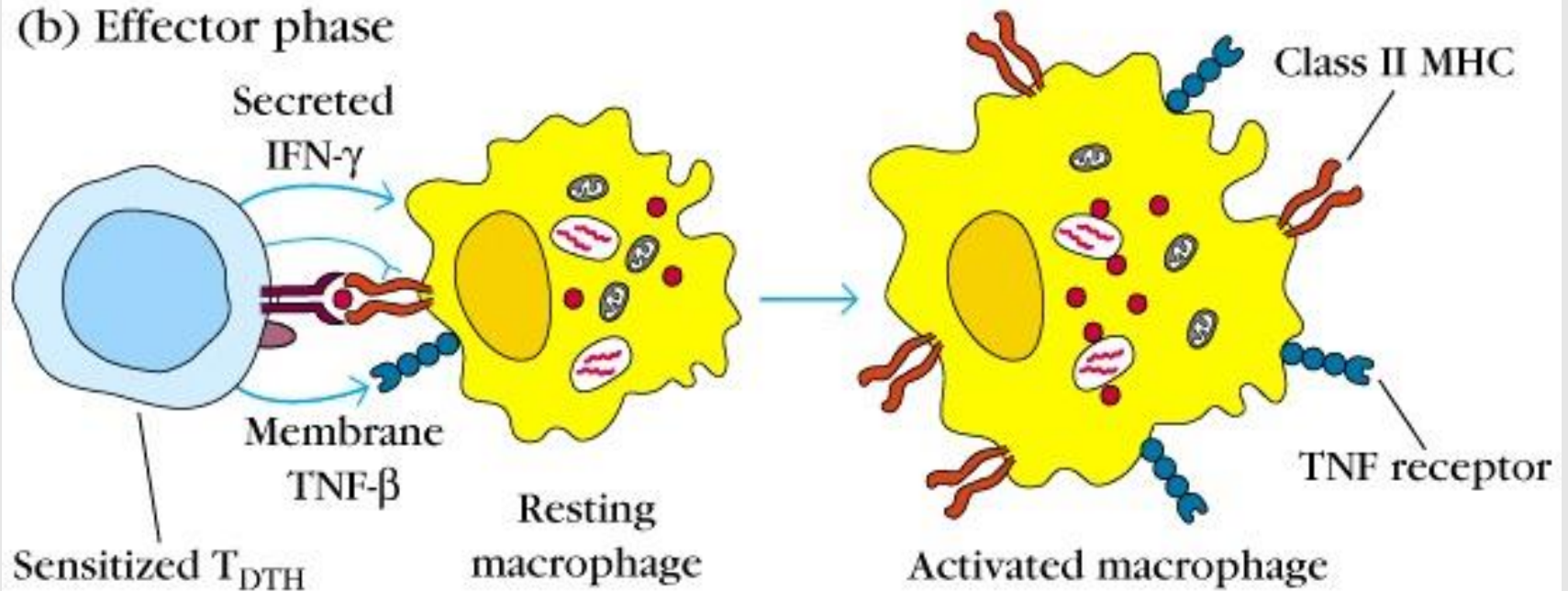
Antigen-presenting cells:
Macrophages
Langerhans cells

T_{DTH} cells:
T_H1 cells (generally)
CD8⁺ cells (occasionally)

1. Sensibilization: 1-2 weeks after the first antigen contact. APCs (Langerhans-cells, endothel cells or macrophages) produce IL-12 and induce Th1-cell differentiation.

2. Activation: Th1-activation, proliferation, rarely CD8⁺ CTL-activation.

2. contact with the antigen



T_{DTH} secretions:

Cytokines: IFN- γ , TNF- β , IL-2,
IL-3, GM-CSF
Chemokines: IL-8, MCAF, MIF

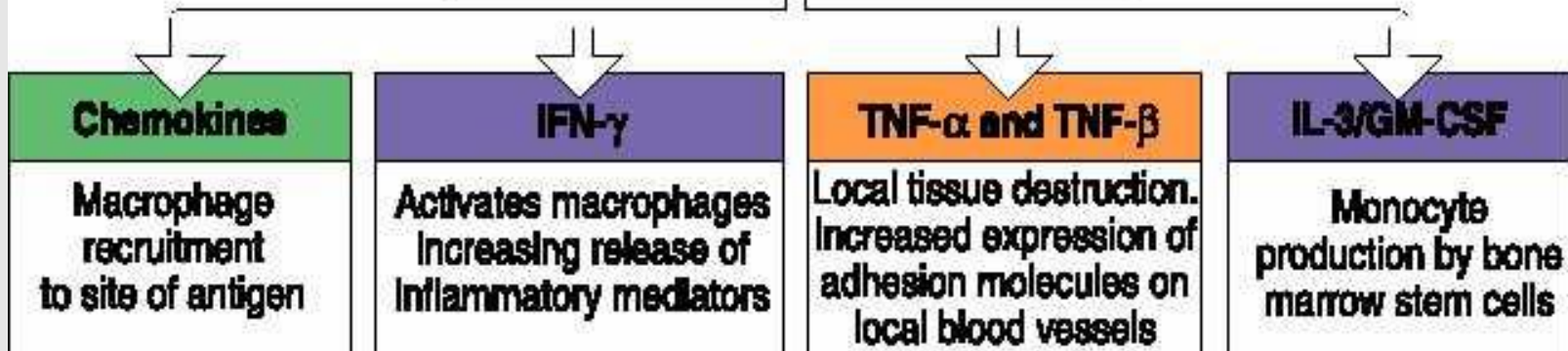
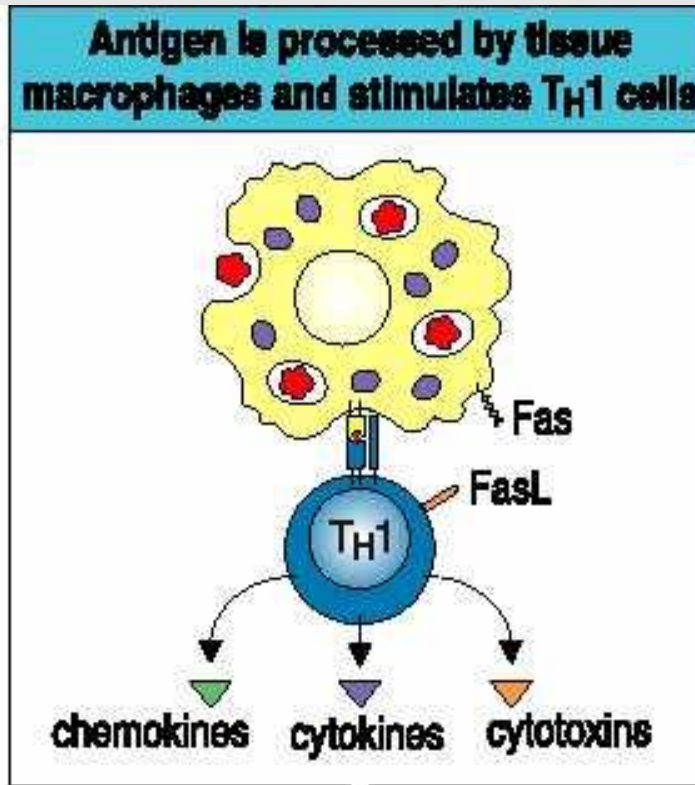
Effects of macrophage activation:

↑ Class II MHC molecules
↑ TNF receptors
↑ Oxygen radicals
↑ Nitric oxide

Effector phase: 2. antigen stimulus leads to Th1-cell activation, cytokine secretion (24h), recruitment of macrophages and other non-specific inflammatory cells (48-72h). From the infiltrating cells only 5% is T cell, 95% is non-specific.

Type IV. hypersensitivity

Figure 10.34



Stages of macrophage activation

Resting

Activated

Hyperactivated

----->IFNgamma-----

----->LPS, Immuncomplex
double stranded RNA

Phagocytosis

Antigen presentation

Tumor cell and
parasite killing

Chemotaxis

Tumor cell binding

Proliferation

decreased prolif.

No proliferation.

No cytotoxicity

No APC

MHC II -,

MHC II+, O₂ high

MHCII -, O₂high

O₂ low

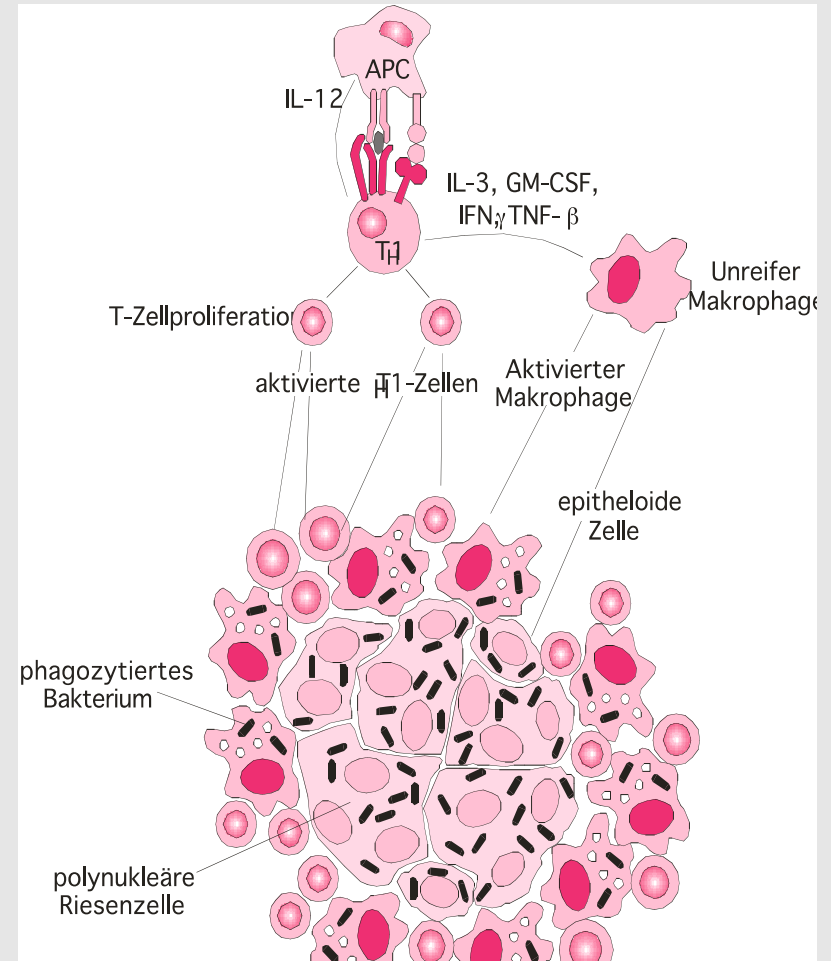
TNF, cytotoxic

Protease secretion

4. phase of DTH

- **Granulomatous-reaction**: if the intravesicular pathogen survives in the cells it induces a prolonged DTH response – **chronic infection**
- → continuous macrophage activation leads to cytokin- and growth factor production and granuloma formation.
- Giant cells, epitheloid cells, tissue damage, necrosis, fibrosis.

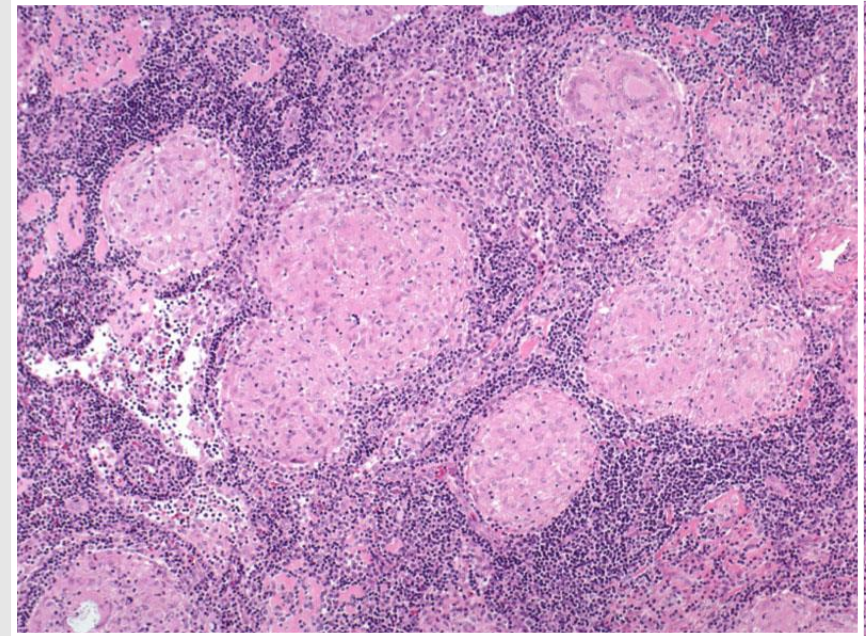
The structure of granulomas



Diseases

- **Infections:** intracellular bacteria eg. *Mycobacterium tuberculosis*, *M. leprae*; Viruses: *Herpes simplex*
- **Contact dermatitis, atopic ekzema**
- **Autoimmun diseases:** Type 1 Diabetes Mellitus, Rheumatoid arthritis, Inflammatory bowel disease (IBD), Multiple sclerosis, Peripheral neuritis, Autoimmune myocarditis
- **Transplant rejection:** allogeneic tissue transplantation

Type IV. hypersensitivity – Tuberculous granulomas



Poison ivy (Toxicodendron) Contact dermatitis



Comparison of Different Types of hypersensitivity

	type-I (anaphylactic)	type-II (cytotoxic)	type-III (immune complex)	type-IV (delayed type)
antibody	IgE	IgG, IgM	IgG, IgM	None
antigen	Exogenous	cell surface	soluble	tissues & organs
response time	15-30 minutes	minutes-hours	3-8 hours	48-72 hours
appearance	weal & flare	lysis and necrosis	erythema and edema, necrosis	erythema and induration
histology	basophils and eosinophil	antibody and complement	complement and neutrophils	monocytes and lymphocytes
transferred with	antibody	antibody	antibody	T-cells
examples	allergic asthma, hay fever	erythroblastosis fetalis, Goodpasture's nephritis	SLE, farmer's lung disease	tuberculin test, poison ivy, granuloma