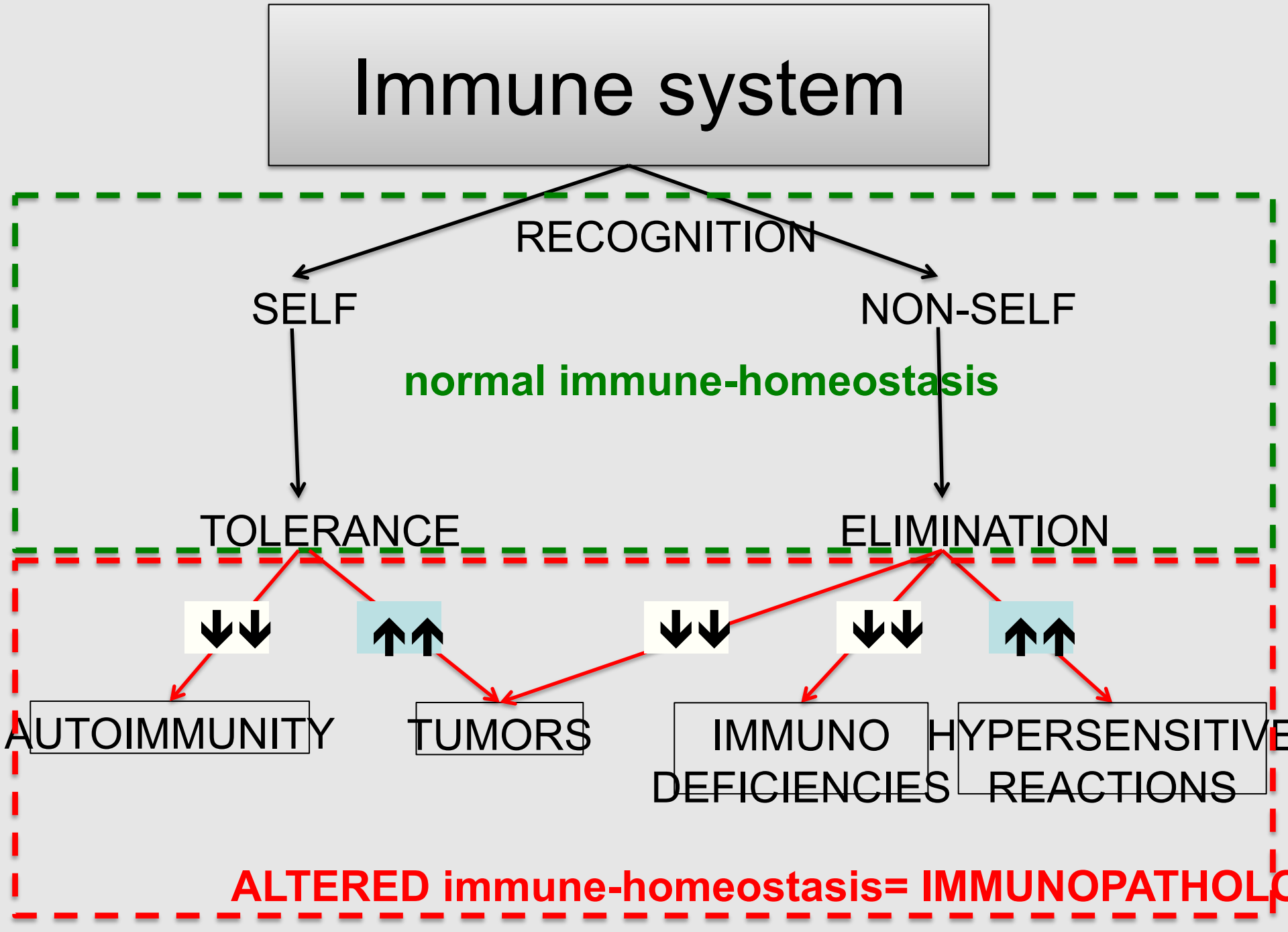
Basic Immunology

Allergies and hypersensitive reactions

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


Immune system
RECOGNITION
SELF
NON-SELF
normal immune-homeostasis
TOLERANCE
ELIMINATION
AUTOIMMUNITY
TUMORS
IMMUNO DEFICIENCIES
HYPERSENSITIVE REACTIONS
ALTERED immune-homeostasis= IMMUNOPATHOL

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. Immuncomplex-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)

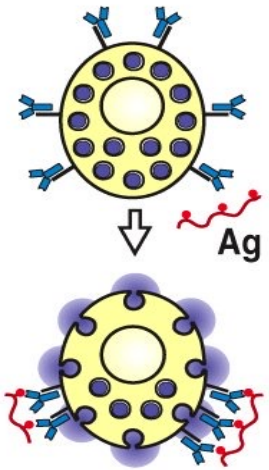
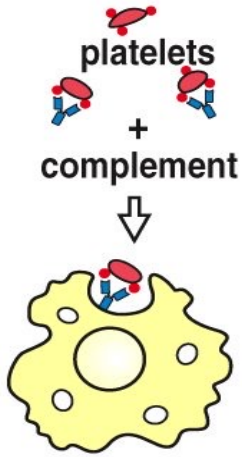
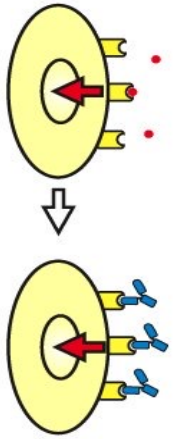
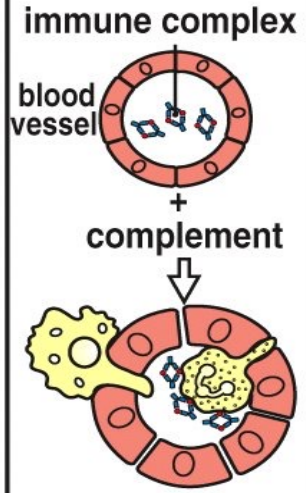
	Type I	Type II		Type III
Immune reactant	IgE	Type II a IgG	Type II b	IgG
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, Phagocytes
				
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)

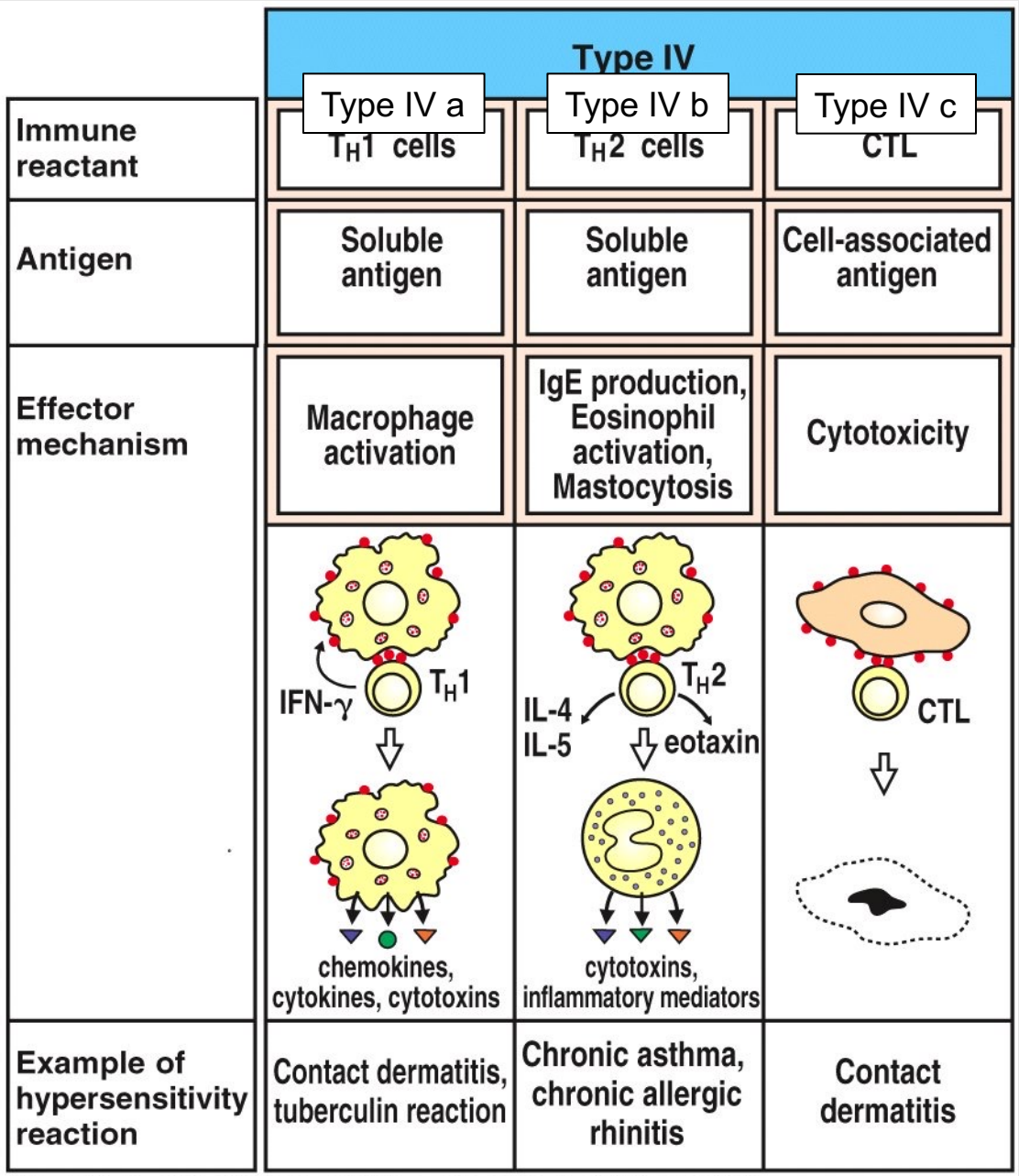


Figure 12-2 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Classification of hypersensitivity reactions

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

Table 1 **Modern classification of hypersensitivity reactions***

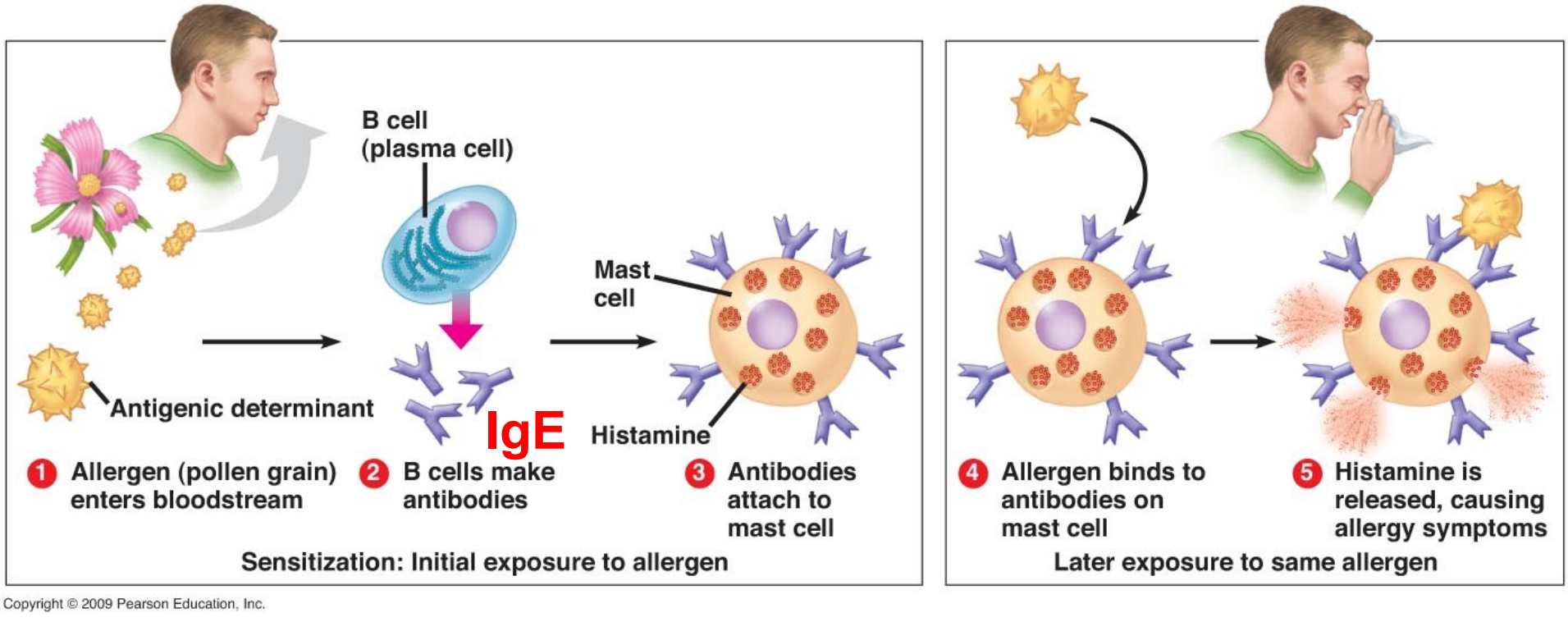
Classification Type	Immunologic Mechanisms	Clinical Examples
I	Mast cell-mediated reactions	
	IgE-dependent (anaphylactic)	Anaphylaxis, angioedema, urticaria, asthma, allergic rhinitis
	IgE-independent (nonimmunologic or anaphylactoid)	Reactions to iodinated contrast reagents and some biologics
IIa	Antibody-mediated 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.*

In: (Allergy Asthma Proc 40:470–473, 2019; doi: 10.2500/aap.2019.40.4274)

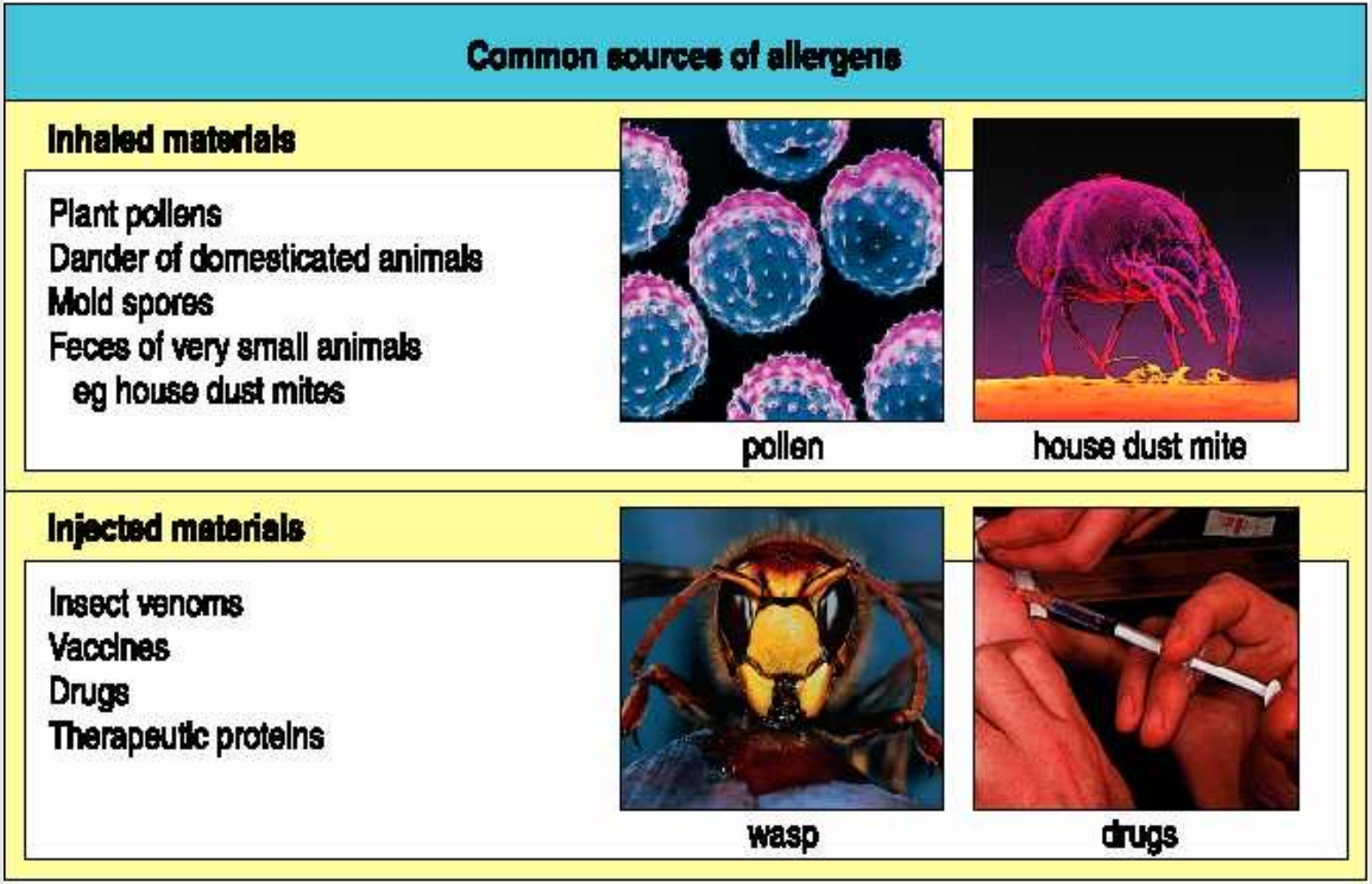
Type I., immediate hypersensitivity; Allergy, Atopy

Basic mechanism



Allergens

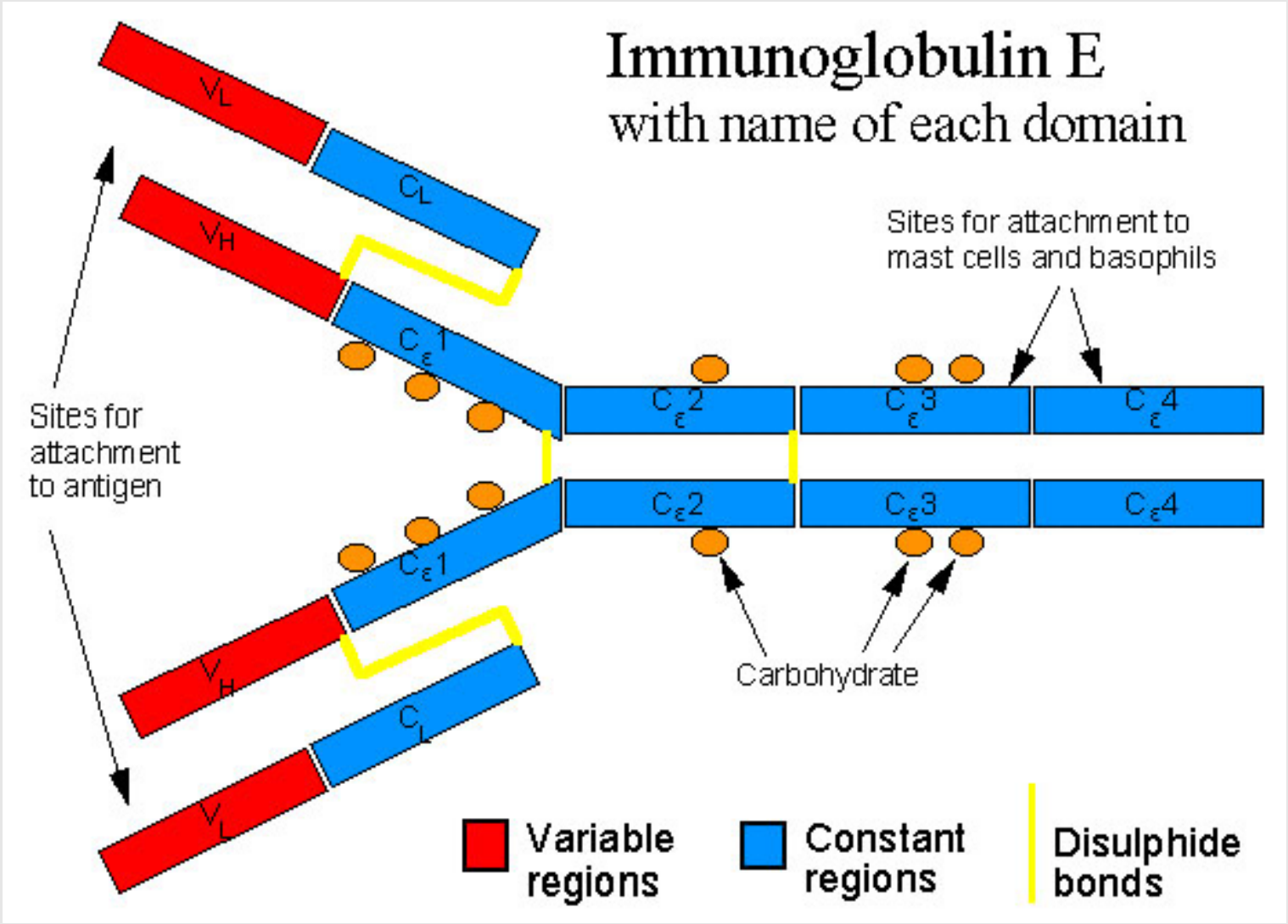
Figure 10.1a



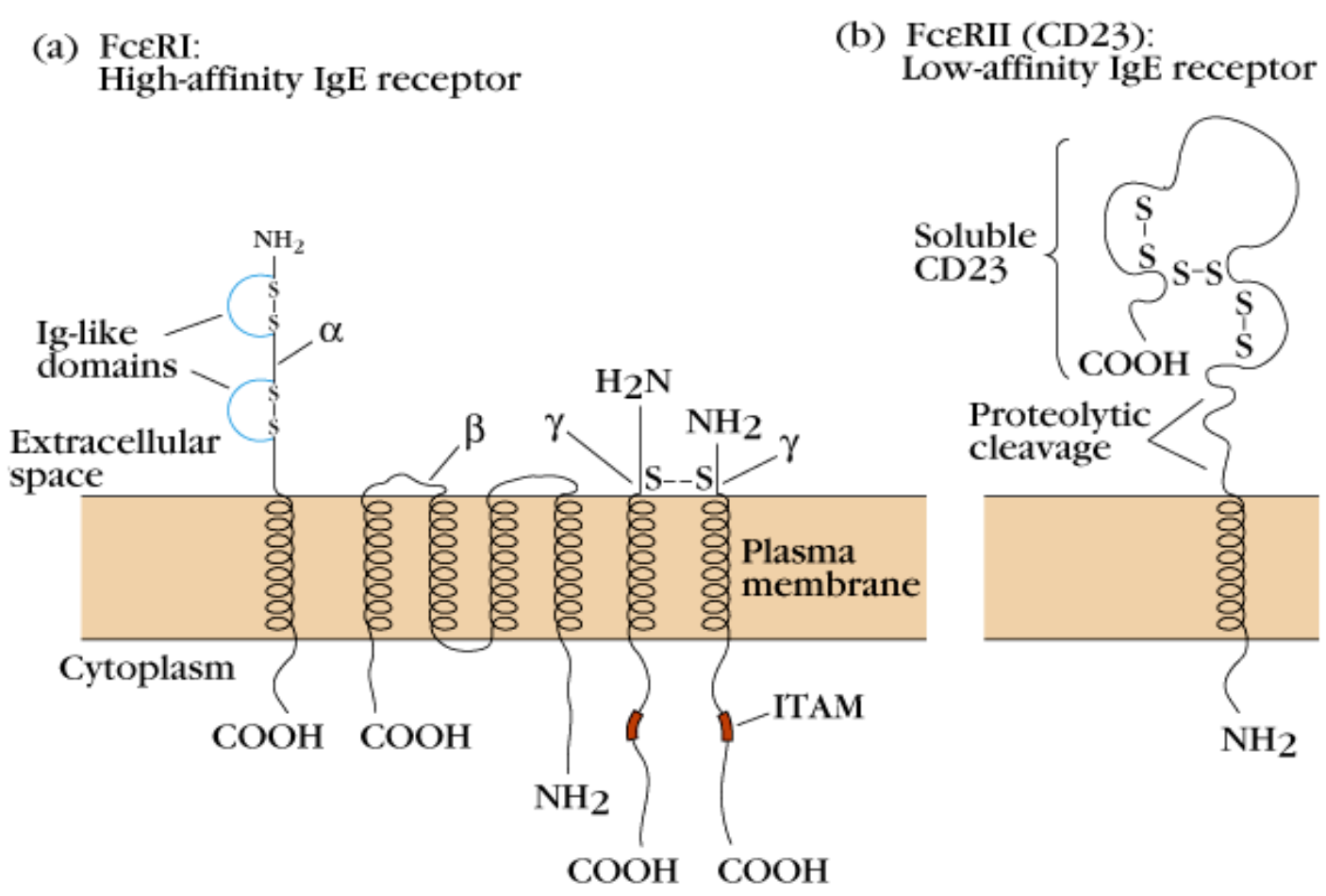
Food antigens (milk, soy, gluten, nuts, additives etc.)

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

Proteins	only proteins elicit T cell response
Enzime 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
V_L
C_L
V_H
$C_\varepsilon 1$
Sites for attachment to mast cells and basophils
Sites for attachment to antigen
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
$C_\varepsilon 1$
V_H
C_L
V_L
Carbohydrate
Variable regions
Constant regions
Disulphide bonds

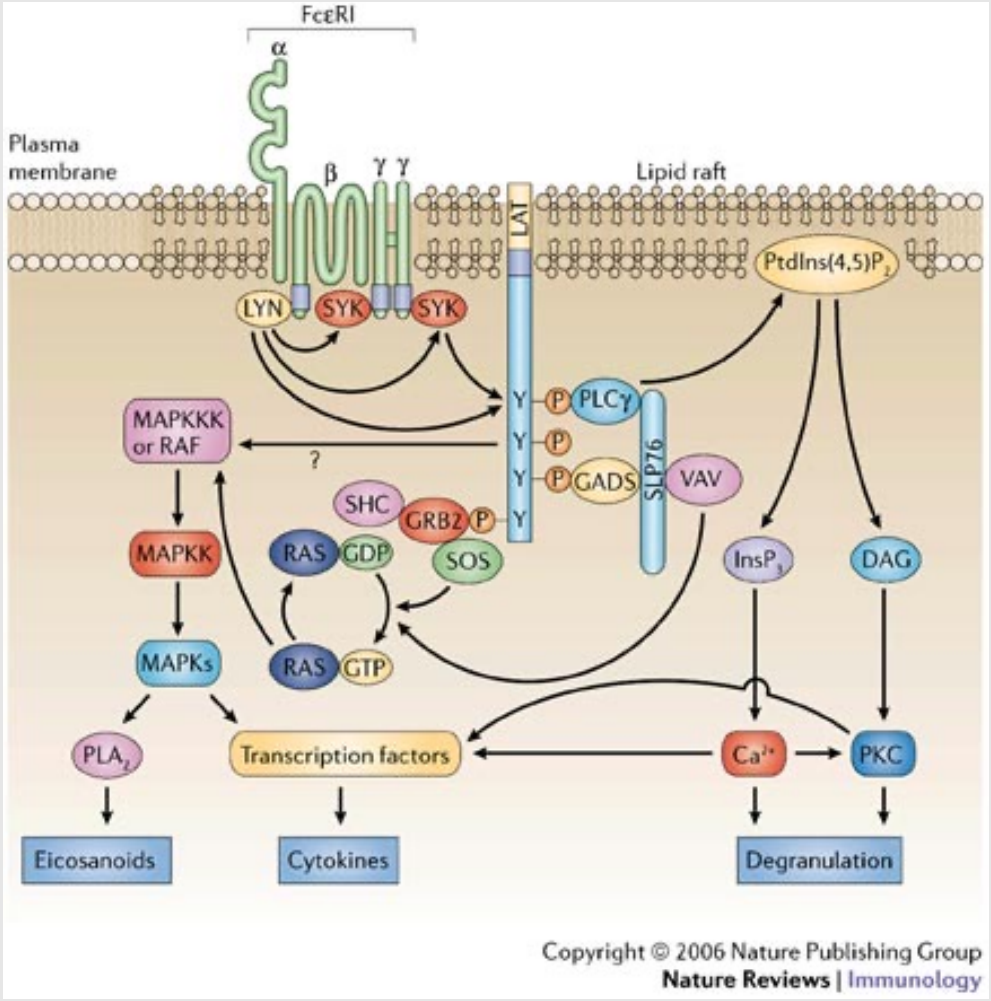
IgE-Receptors



mast cells, basophil gr, activated eosinophil gr

eosinophil gr, follicular B cells

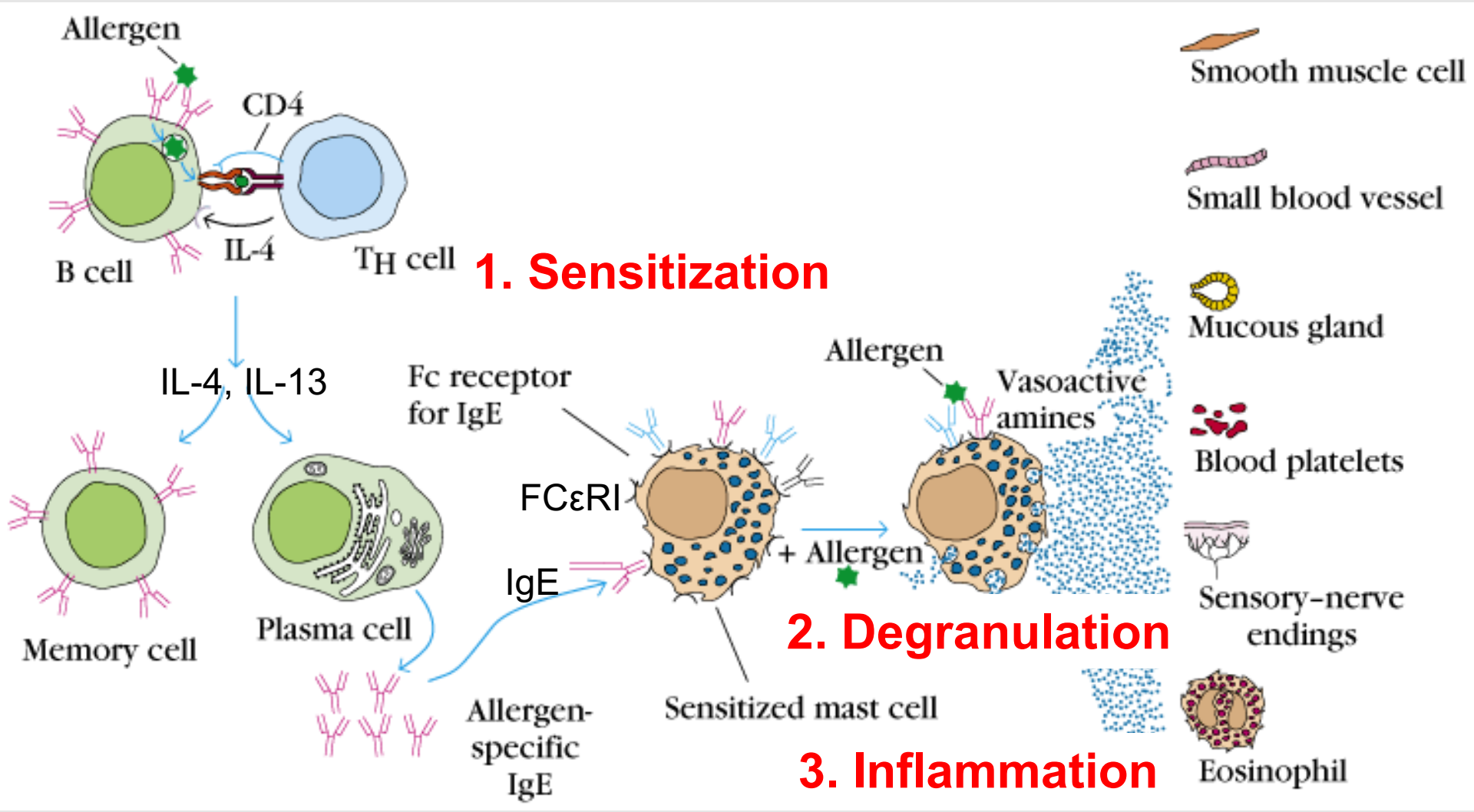
Fcε-Receptor signaling



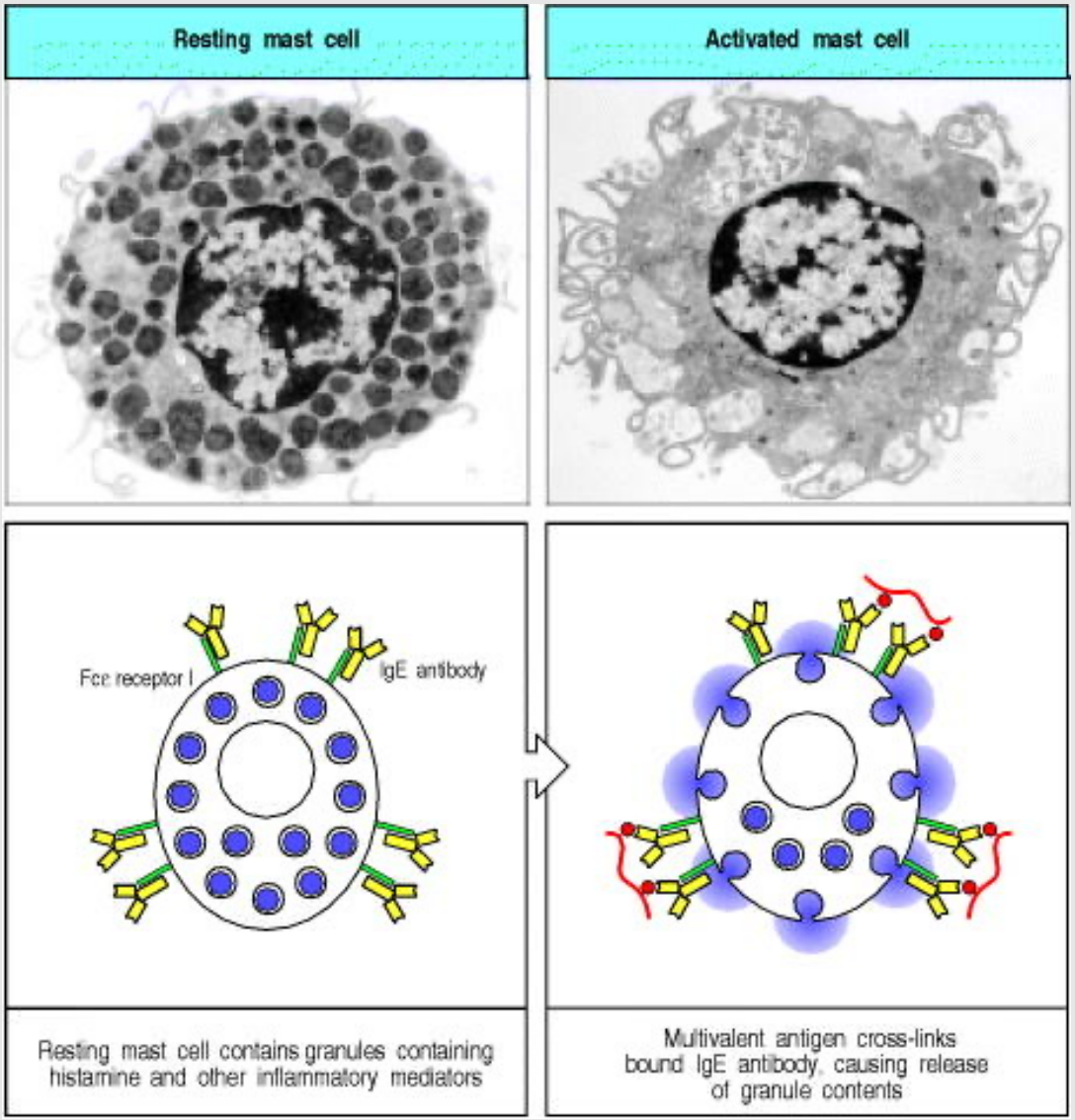
Gilfillan *et al. Nature Reviews Immunology* 6, 218-230 (March 2006) | doi:10.1038/nri1782

nature REVIEWS IMMUNOLOGY

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

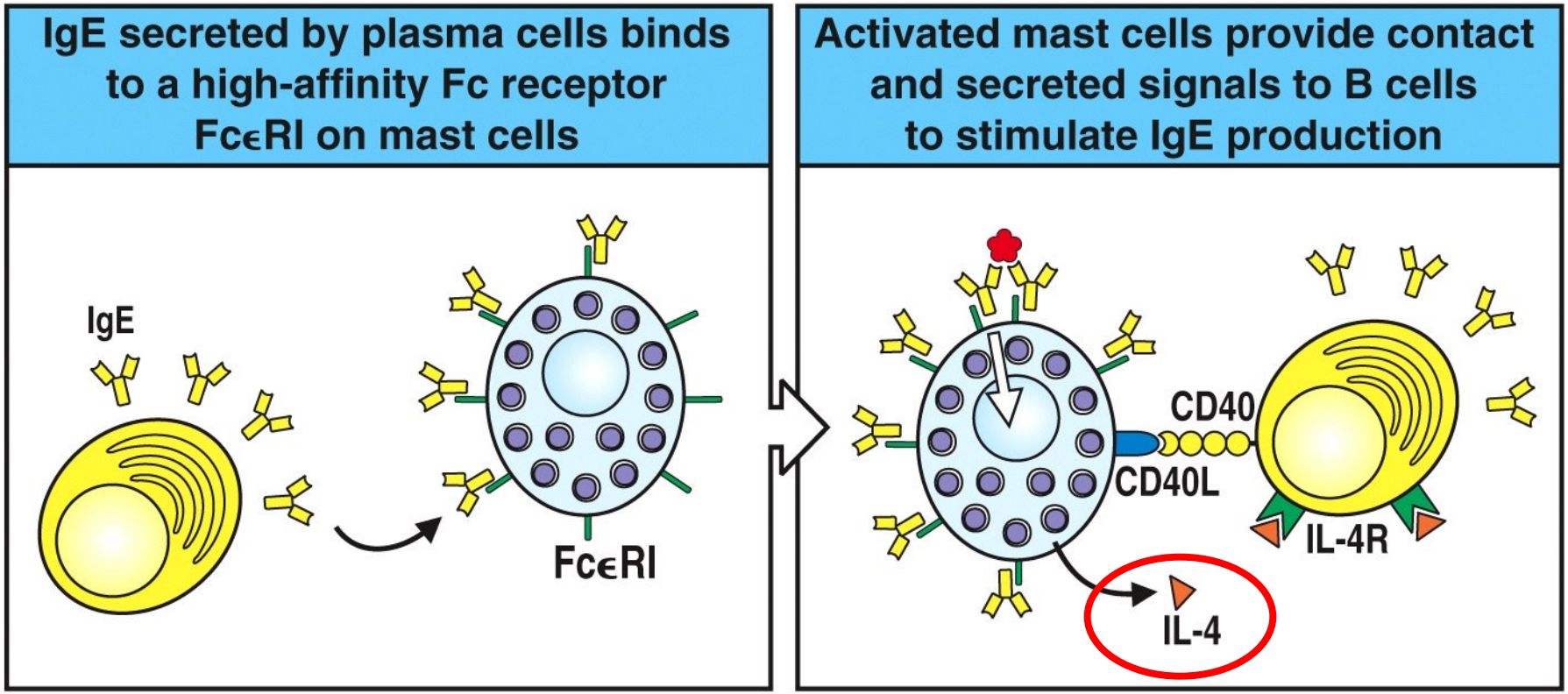
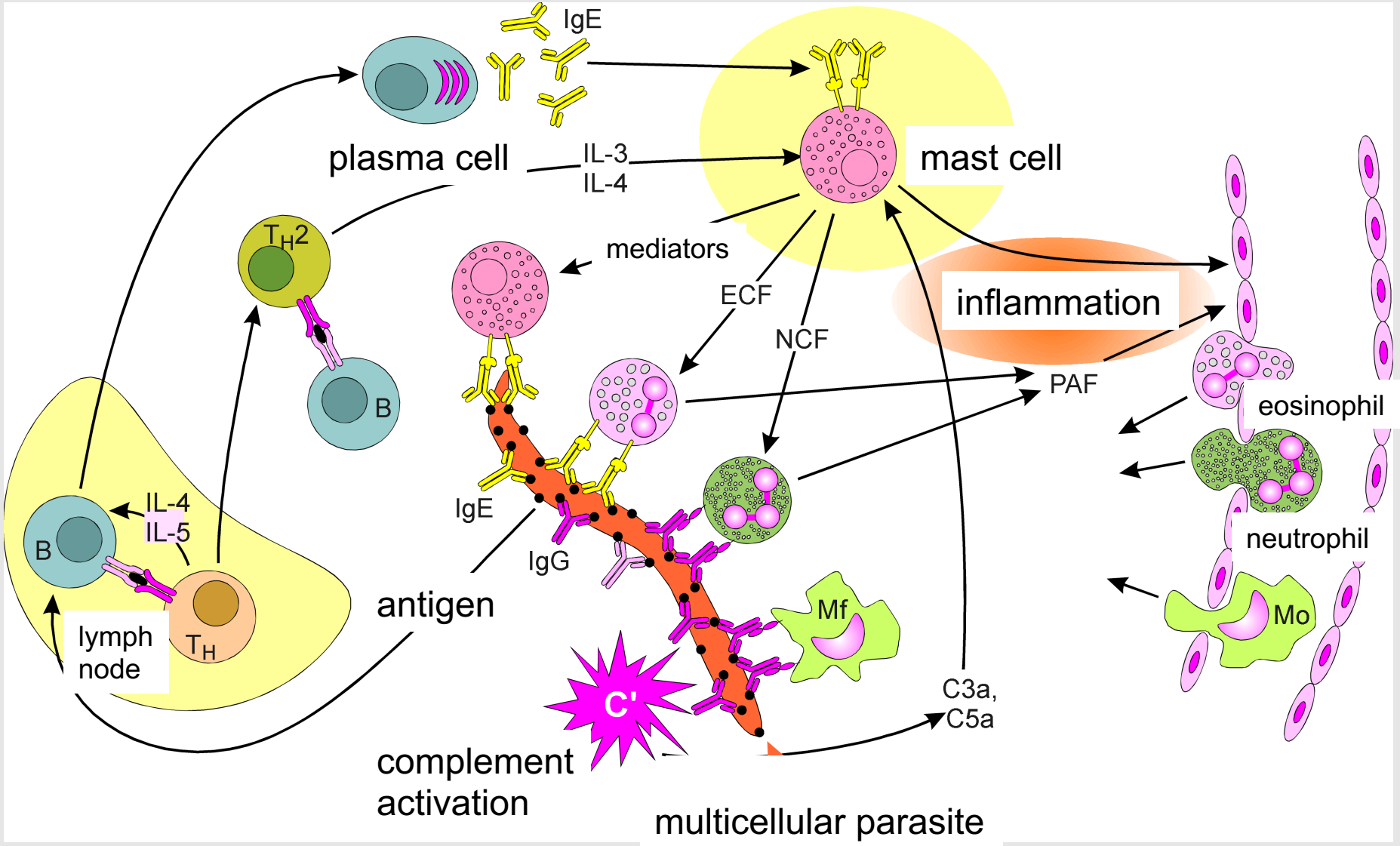


Figure 12-7 Immunobiology, 6/e. (© Garland Science 2005)

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 parazites 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

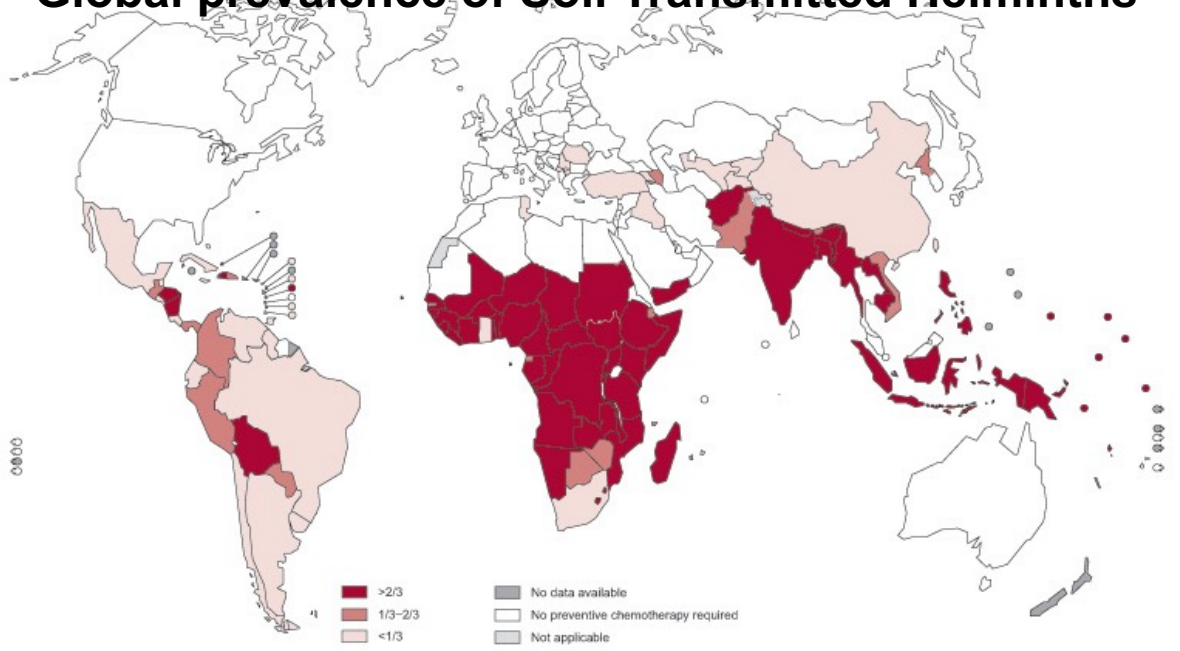
Atopic allergy and asthma is the most frequent in the economically well-developed countries.

- **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**

Hygiene-theory

Global prevalence of Allergic Rhinitis

Global prevalence of Soil Transmitted Helminths



Hygiene-theory

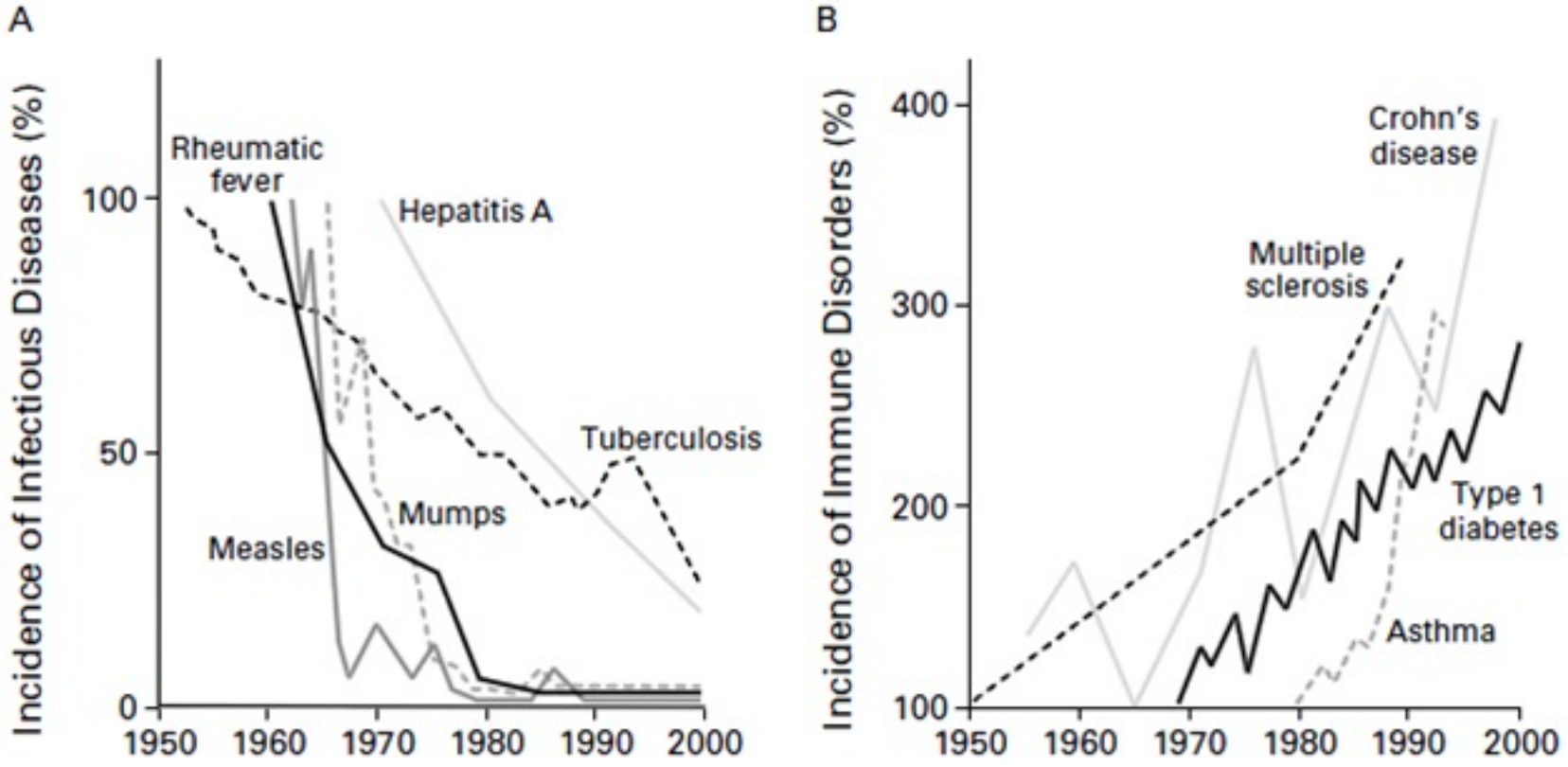
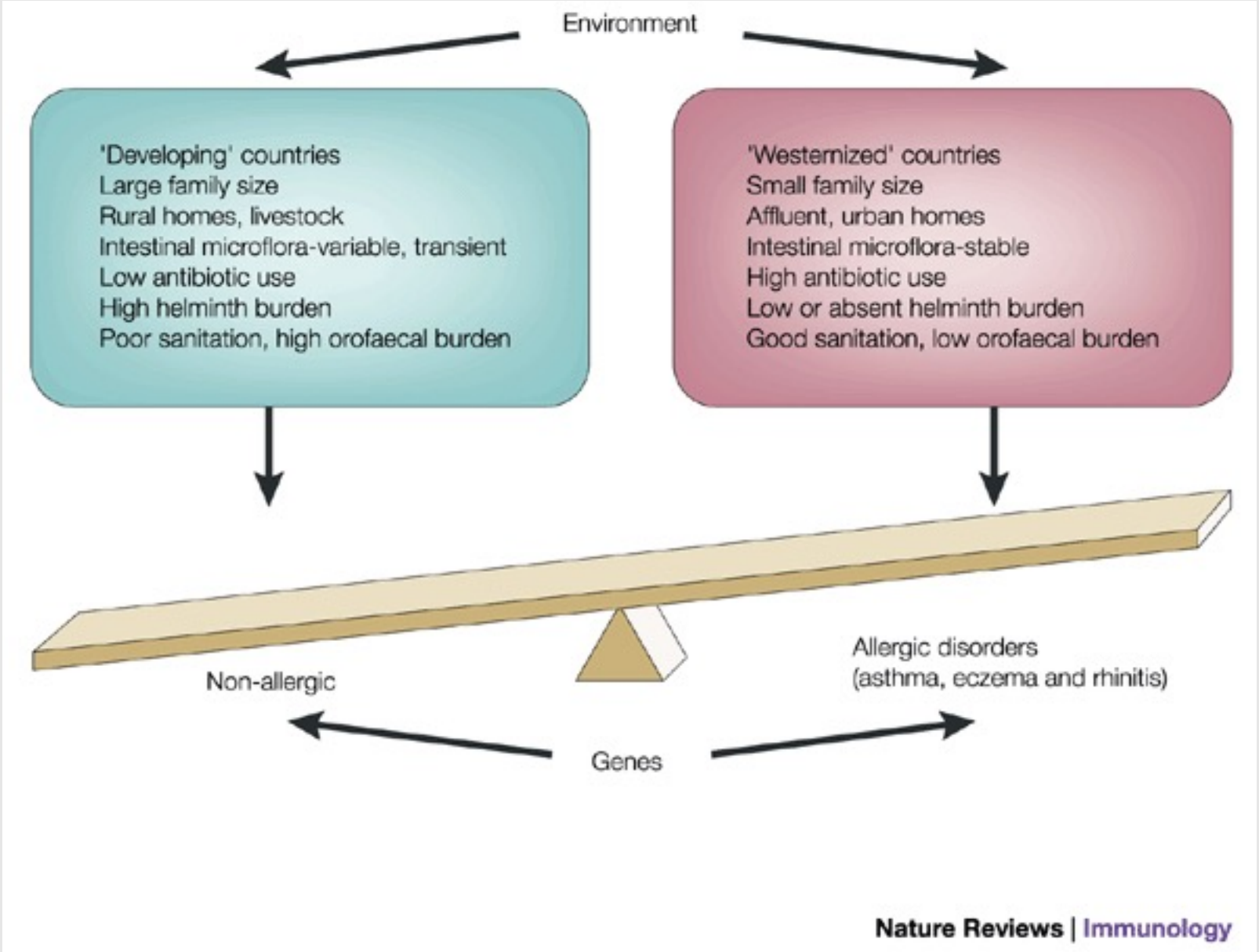


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

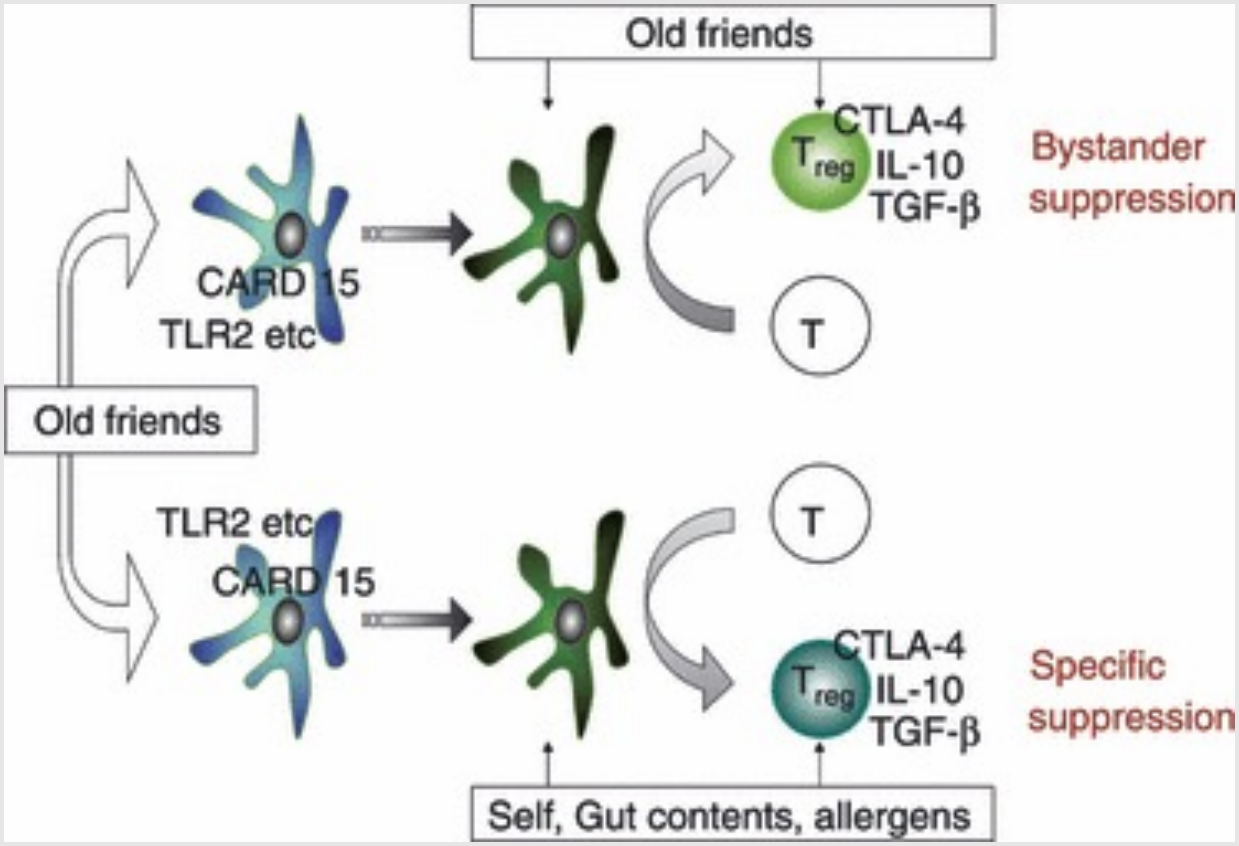
Hygiene-theory



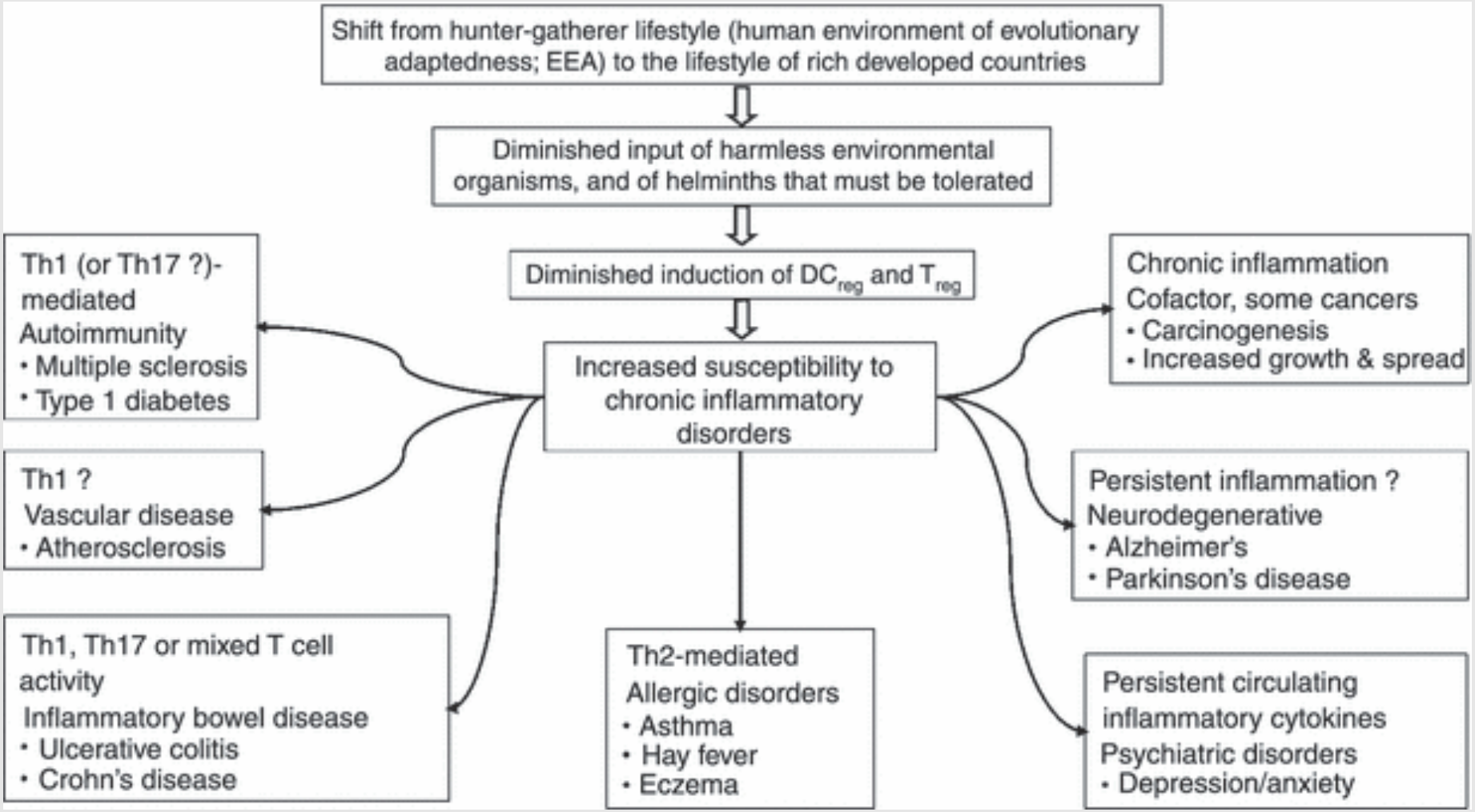
In: Marsha Wills-Karp, Joanna Santeliz & Christopher L. Karp: **The germless theory of allergic disease: revisiting the hygiene hypothesis.** *Nature Reviews Immunology* **1**, 69-75 (October 2001)doi:10.1038/35095579

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



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

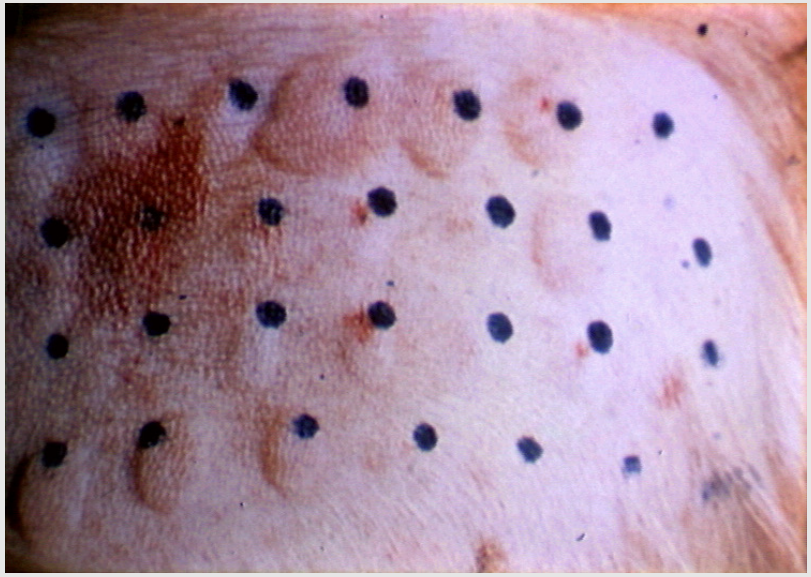
Atopy

- increased susceptibility to allergic disease (eg. hay fever, asthma)
- strong IgE-answer to environmental antigens
- high **IgE** and **eosinophylia** in the blood
- Genetic background:
  - **Chromosome 11q** – high affinity FcεR 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

Type II. hypersensitivity

antibody-mediated cytotoxic form

Type II hypersensitivity- cytotoxic reactions

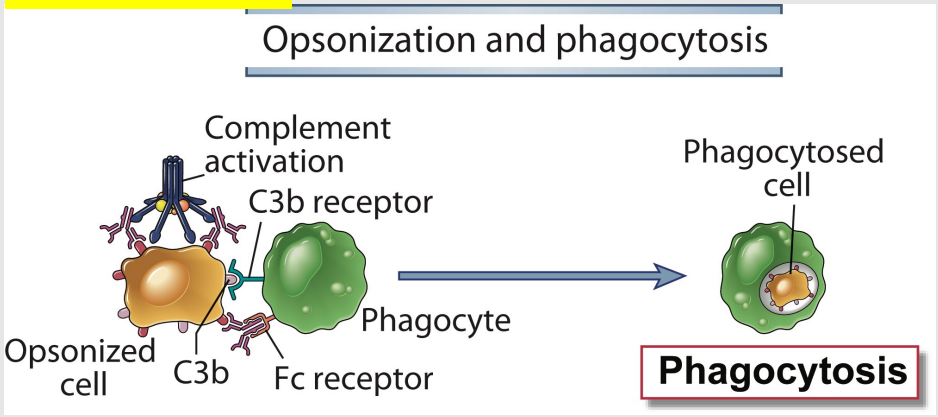
- antibody and cell-mediated cytotoxicity
- complement-mediated lysis
- IgG and IgM
- K-cells, platelets, neutrophils, eosinophils and macrophages
- Examples:
  - Rh antigen
  - transfusion reactions
  - autoimmune haemolytic anemia
  - hyperacute graft rejection
  - reactions to tissue antigens

Type II. diseases

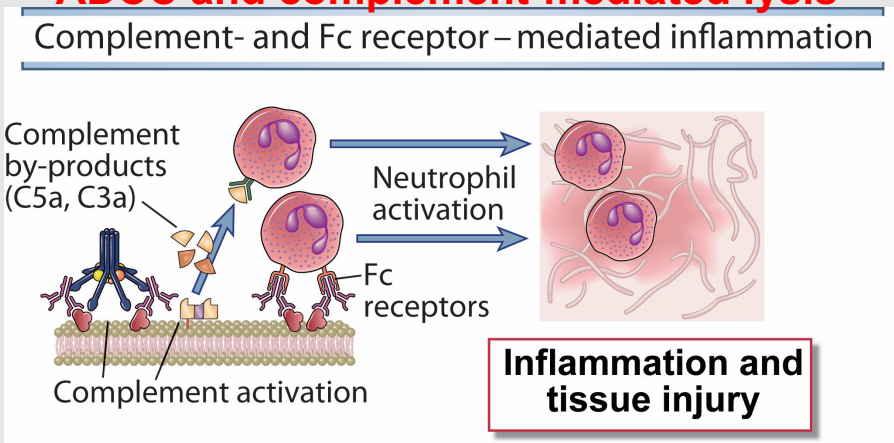
- **Antigens are usually endogenous, sometimes exogenous chemicals (haptens), which can bind to cell surface.**
- **Drug-induced-hemolitic anemia, - granulocytopenia, - trombocytopenia**
- **Diagnosis: circulating antibodies and immunfluorescence on biopsy from the lesion**
- **Therapy: anti-inflammatory-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

Type II. hypersensitivity

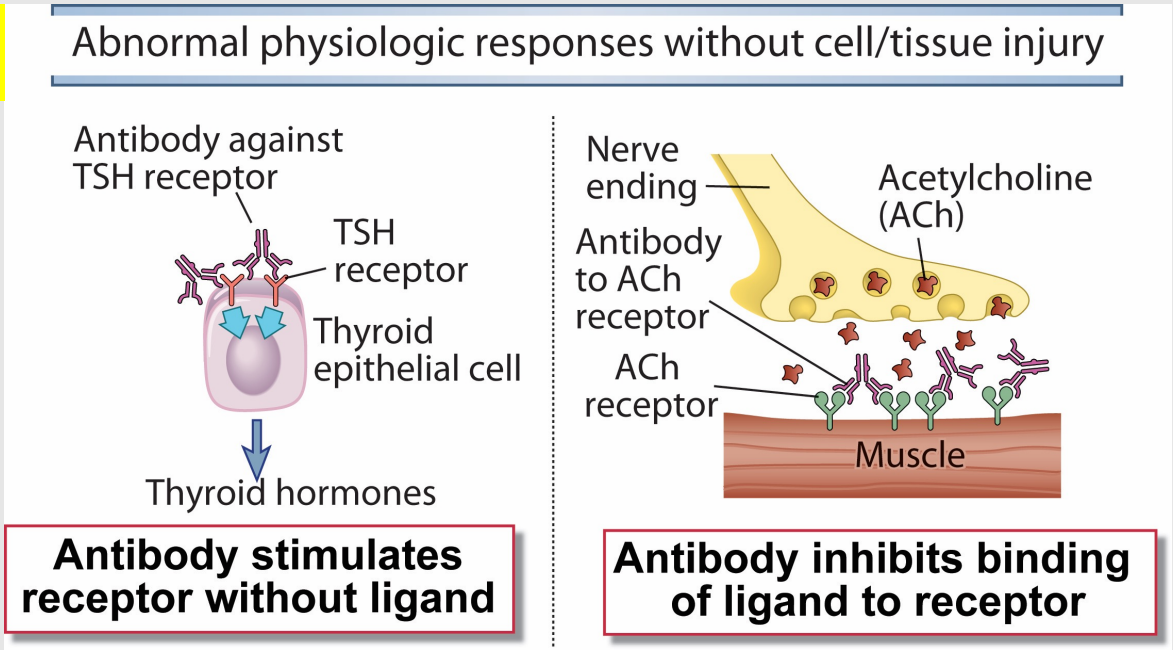
Type II a



ADCC and complement-mediated lysis



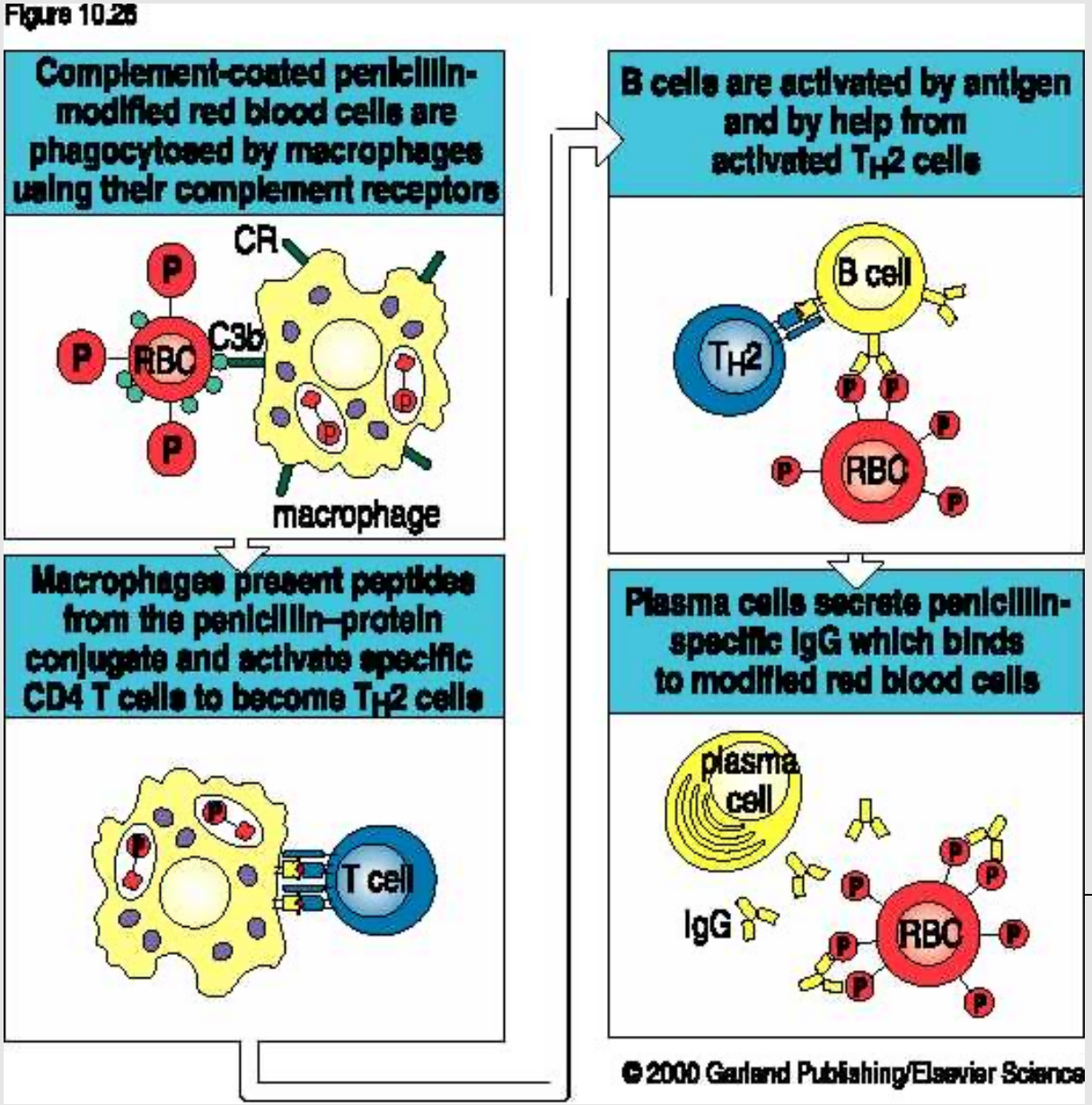
Type II b



Graves (Basedow) disease

Myasthenia gravis

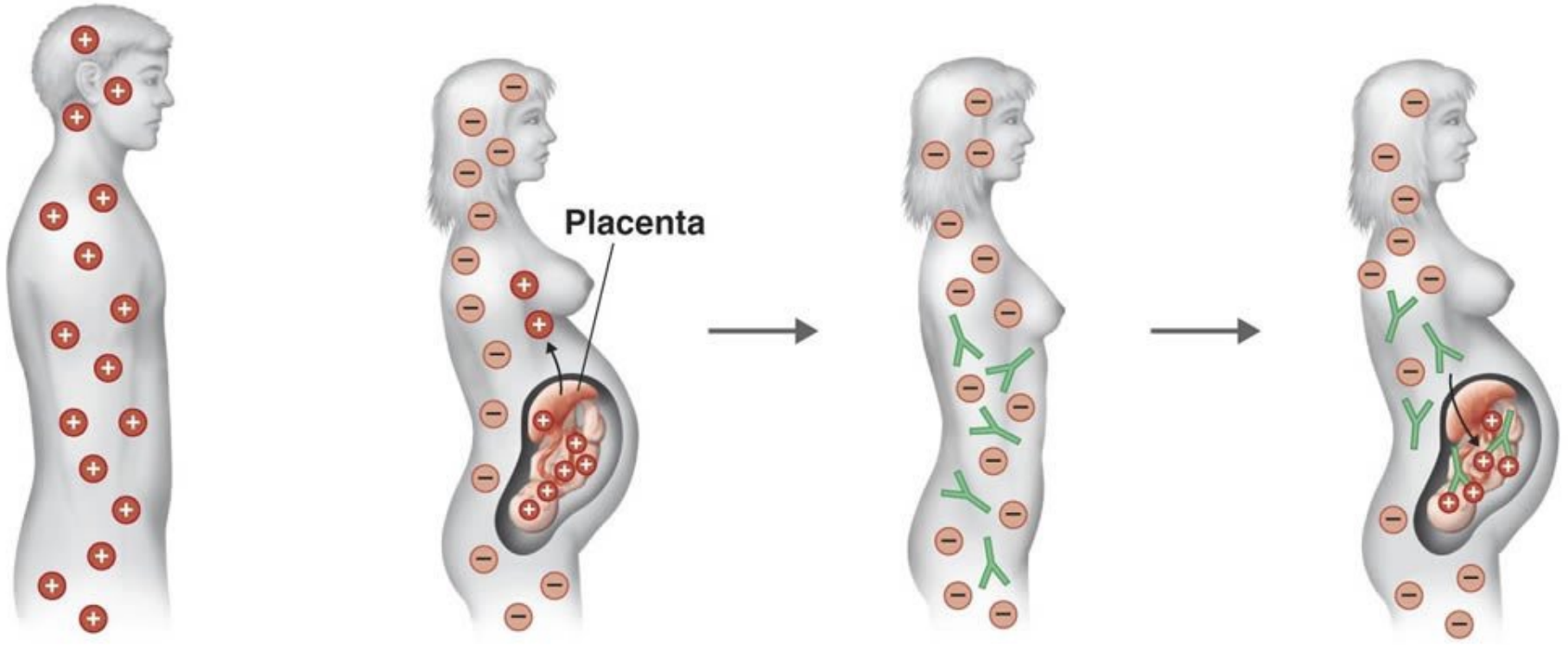
Type II. hypersensitivity -



Drug-induced hemolytic anemia

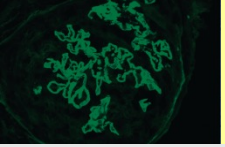
→ **Hemolysis**

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.

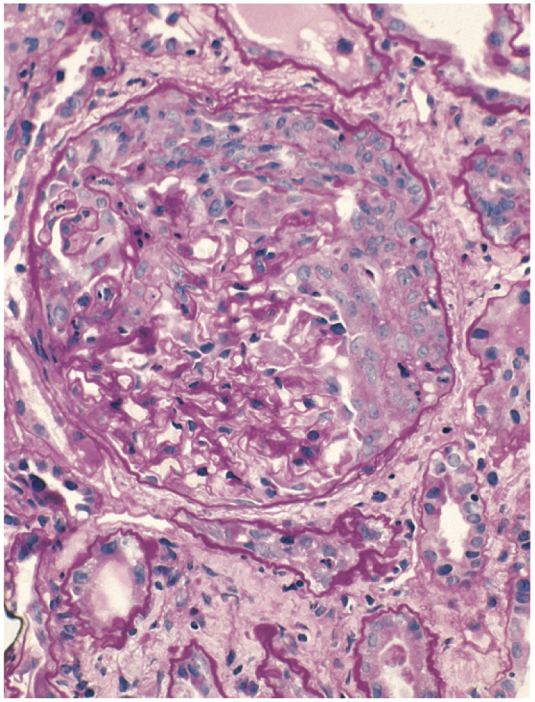
Prophylaxis: anti-RhD antibody prophylaxis after delivery



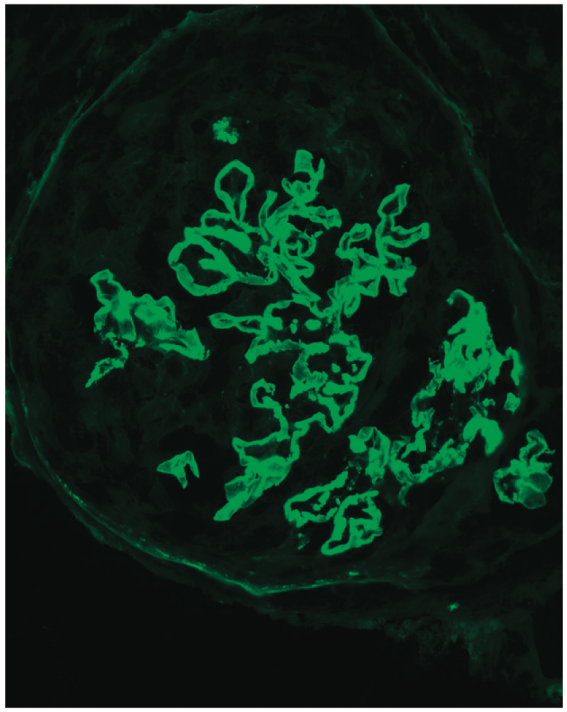
Antibody-mediated Glomerulonephritis (1)

Goodpasture-syndrome

Anti-basement membrane antibody-mediated glomerulonephritis



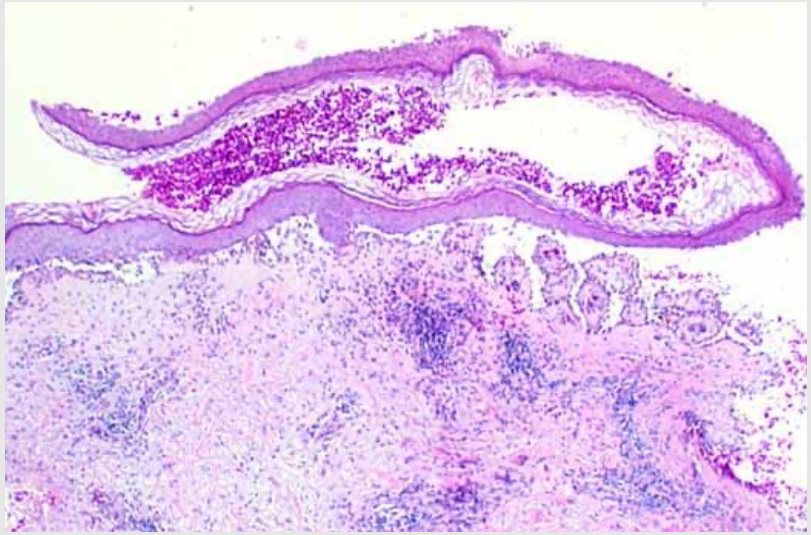
Light microscopy



Immunofluorescence

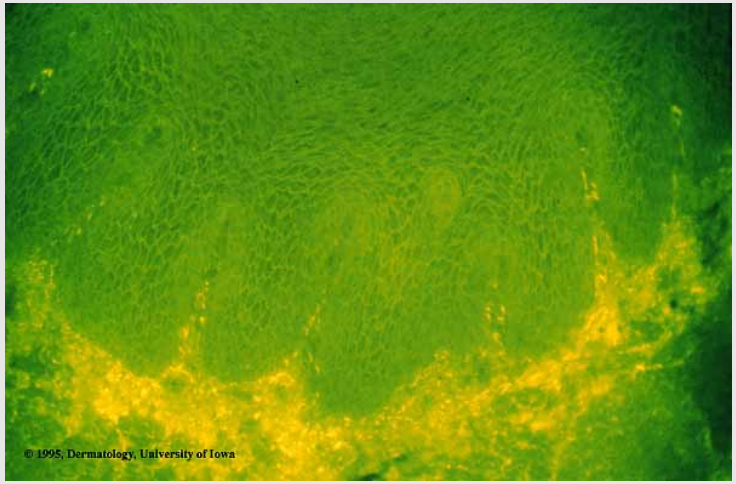
The pathologic lesion contains antibodies, complement and neutrophils.

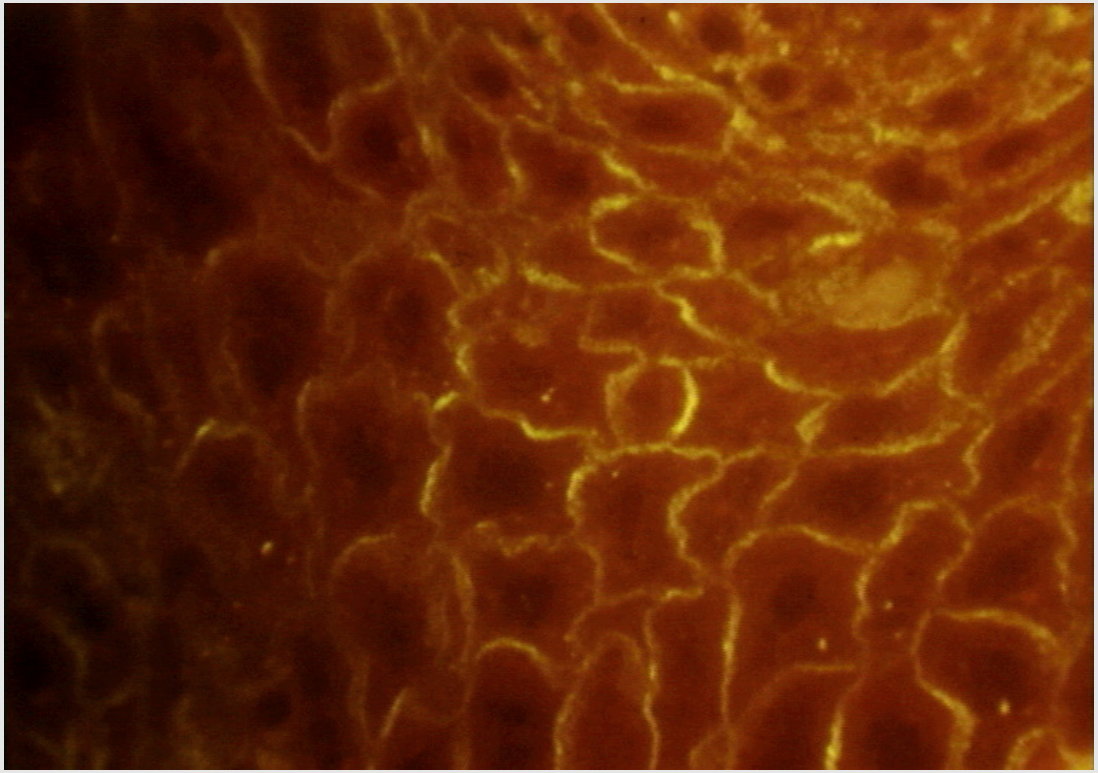
Staining is smooth and linear.



Pemphigus vulgaris

<u>Target antigen:</u> skin intercellular proteins: cadherin, desmosome
<u>Symptoms:</u> blisters in the skin





Type III. hypersensitivity

Immuncomplex disease

Type III. hypersensitivity

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

Types of Antibody-Mediated Diseases

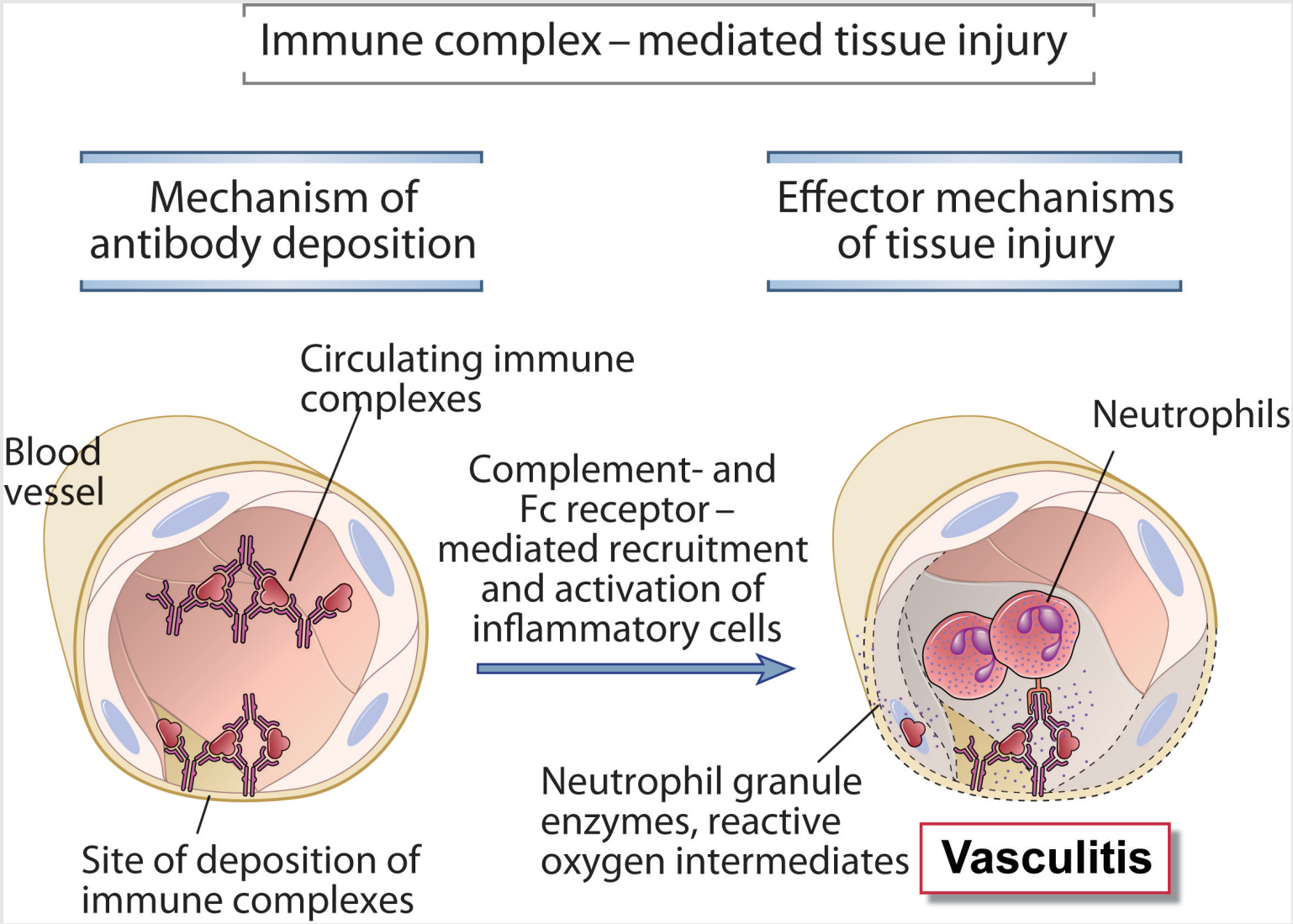


Fig. 18-1B

Diseases

- Caused by dissolved immuncomplexes. The outcome of the disease is influenced by the size of the immuncomplexes.
- 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 immuncomplexes have to be verified in tissue biopsy.

Granular staining is characteristic.

Immuncomplexes and low complement concentration in the serum.

Arthus-reaction: immuncomplex-mediated vasculitis

Antibody-mediated Glomerulonephritis (2)

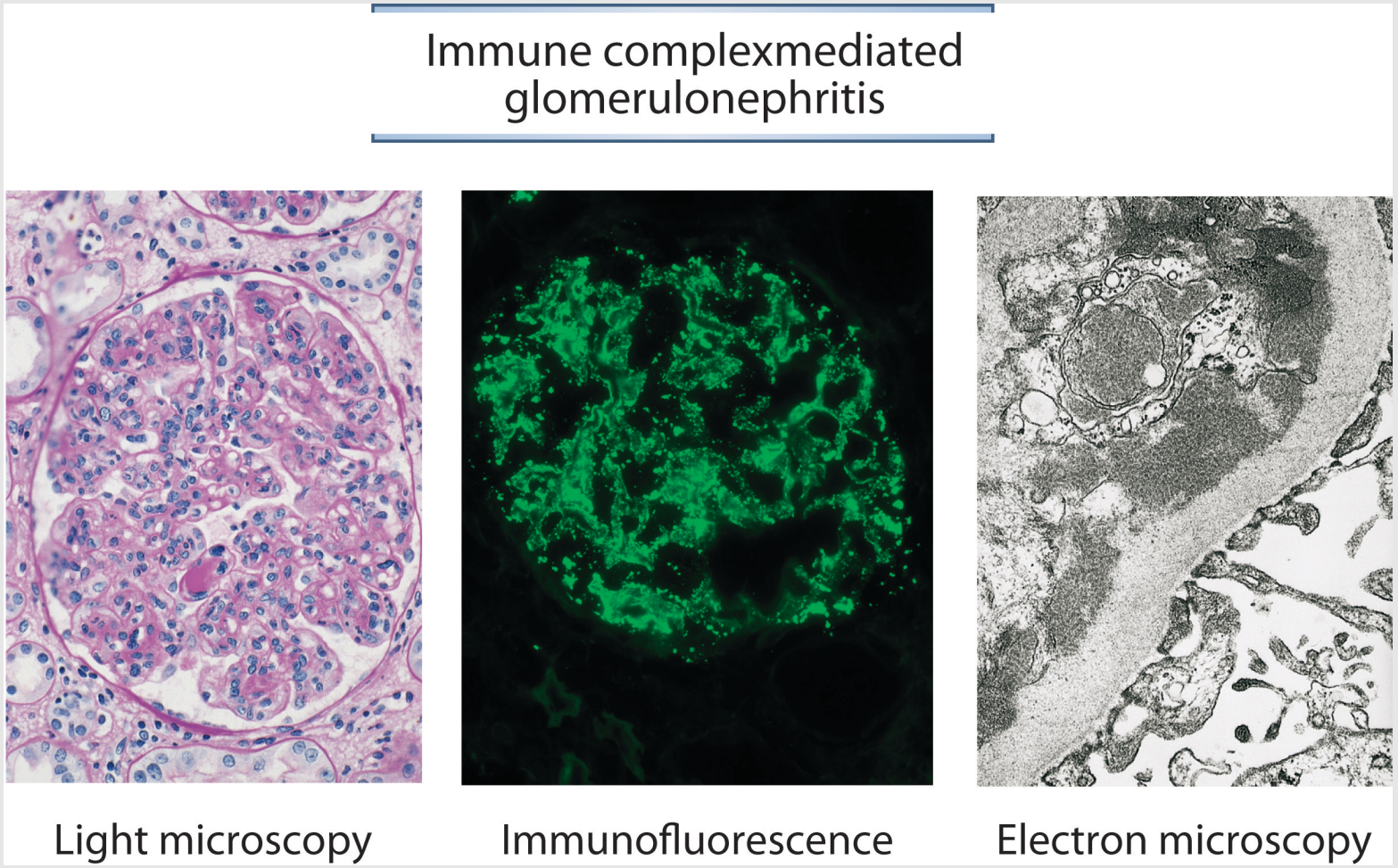
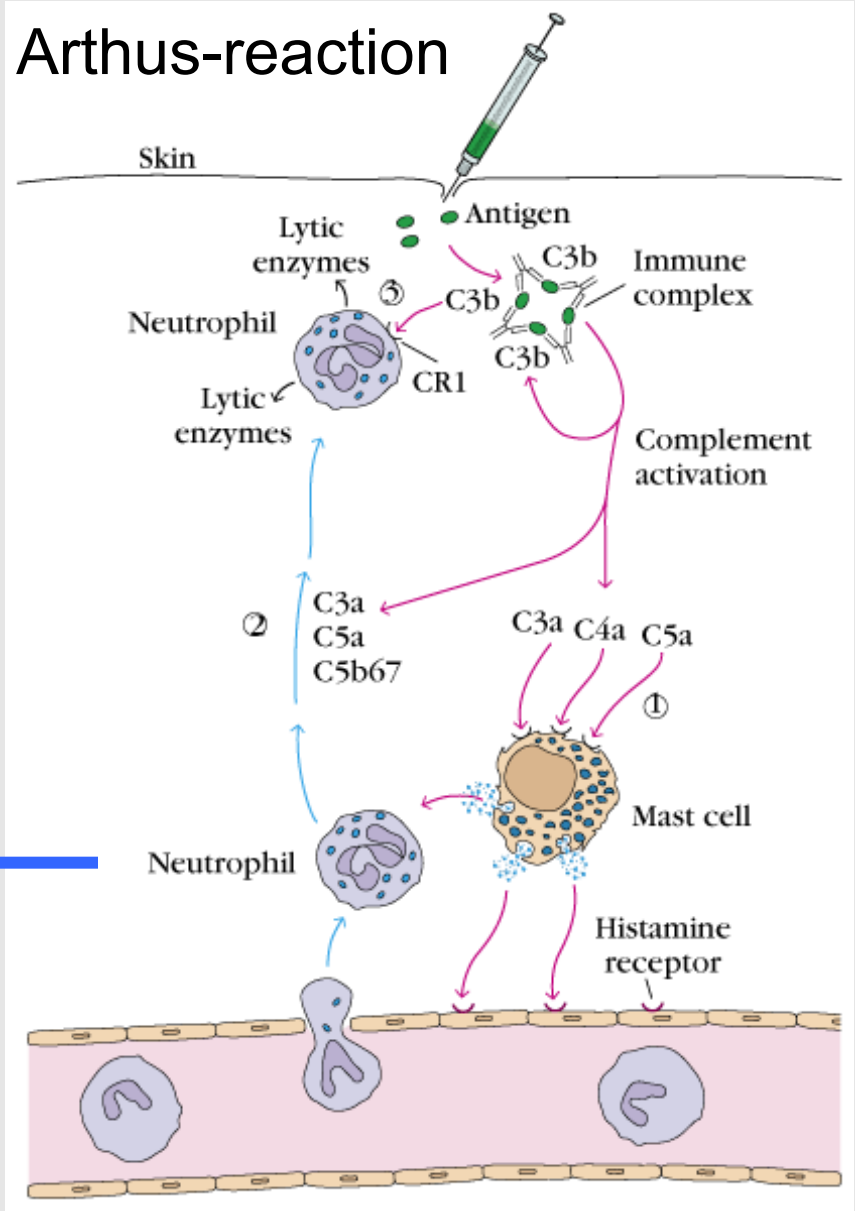


Fig. 18-3B

Type III. hypersensitivity



Local inflammation

vasculitis

Type III. hypersensitivity

Disease	Symptom	Therapy
Serum sickness (GN, Arthritis, Vasculitis)	fever, limb pain, dermatitis, lymphadenopathia, proteinuria, breathing insufficiency	Clearance of immuncomplexes, supportive treatment
Polyarteritis nodosa	Pain, high blood pressure	Immunosupression
SLE, RA	Polyarthralgia (limb pain), face redness (dermatitis), lung- and kidney failure	Immunosupression
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)

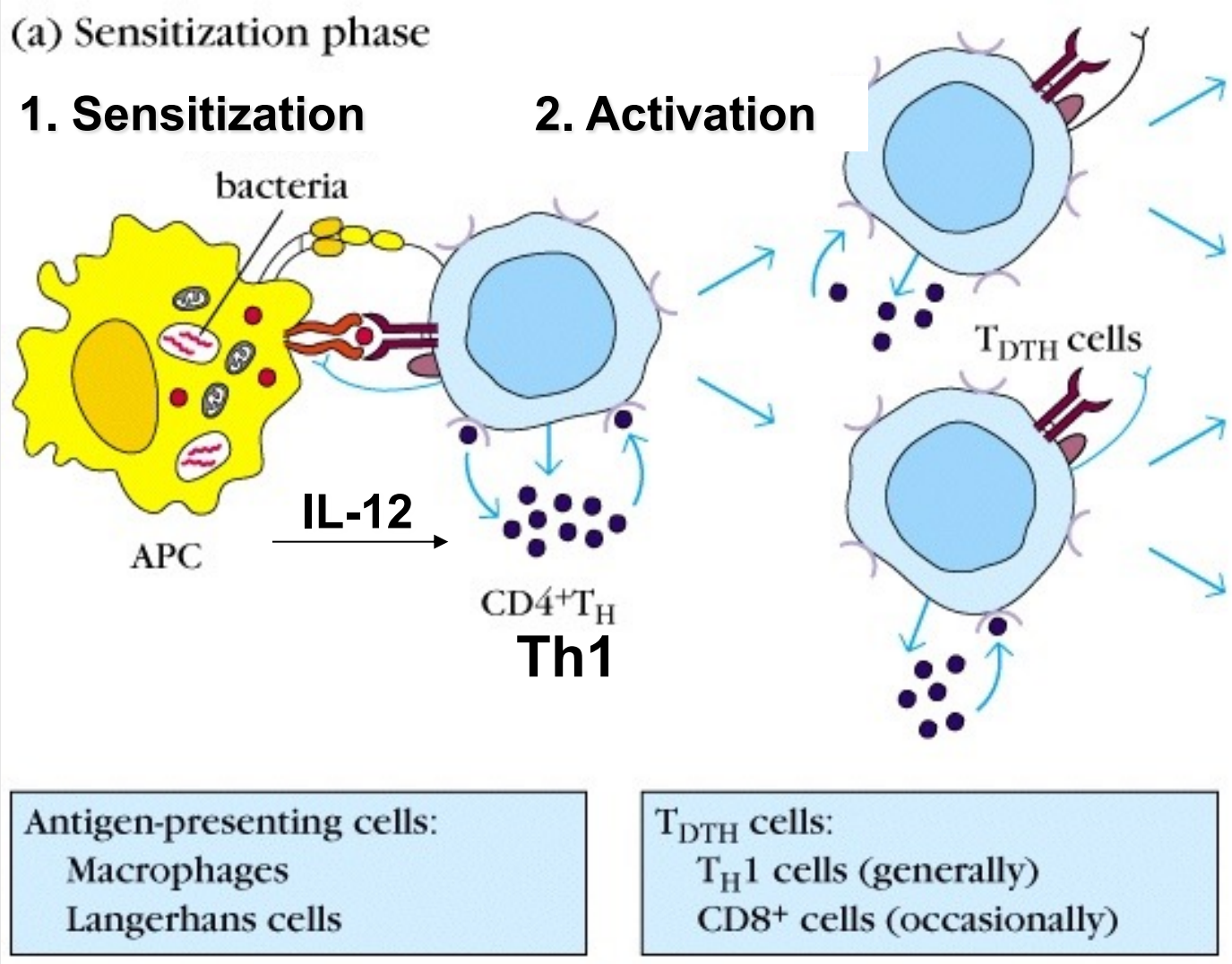
TABLE 14-3 INTRACELLULAR PATHOGENS AND CONTACT ANTIGENS THAT INDUCE DELAYED-TYPE HYPERSENSITIVITY

Intracellular bacteria	Intracellular viruses
Mycobacterium tuberculosis	Herpes simplex virus
Mycobacterium leprae	Variola (smallpox)
Listeria monocytogenes	Measles virus
Brucella abortus	Contact antigens
Intracellular fungi	Picrylchloride
Pneumocystis carinii	Hair dyes
Candida albicans	Nickel salts
Histoplasma capsulatum	Poison ivy
Cryptococcus neoformans	Poison oak
Intracellular parasites	
Leishmania sp.	

Self tissue antigens

Alloantigens (Transplantation)

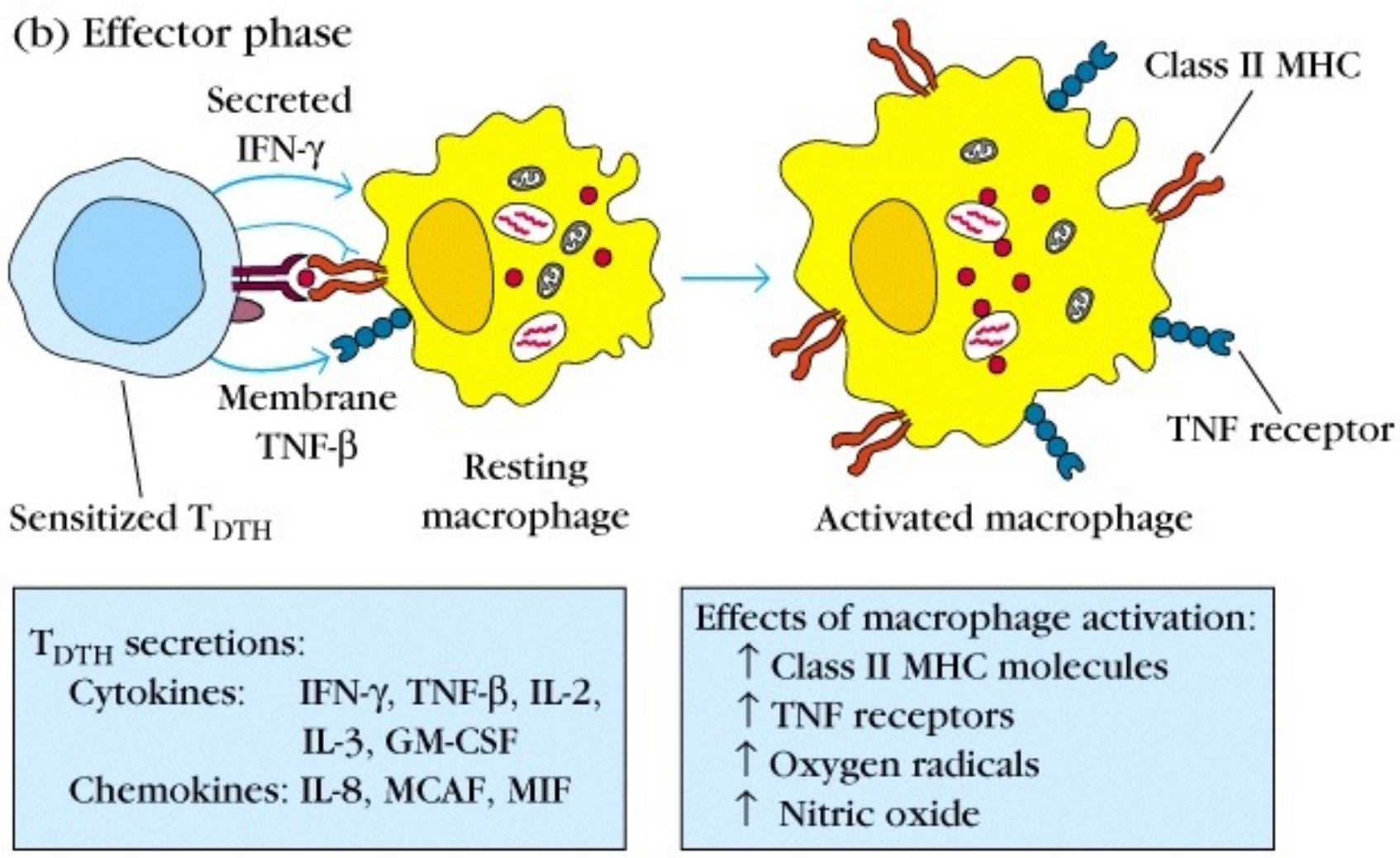
Phase 1 and 2 of DTH



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.

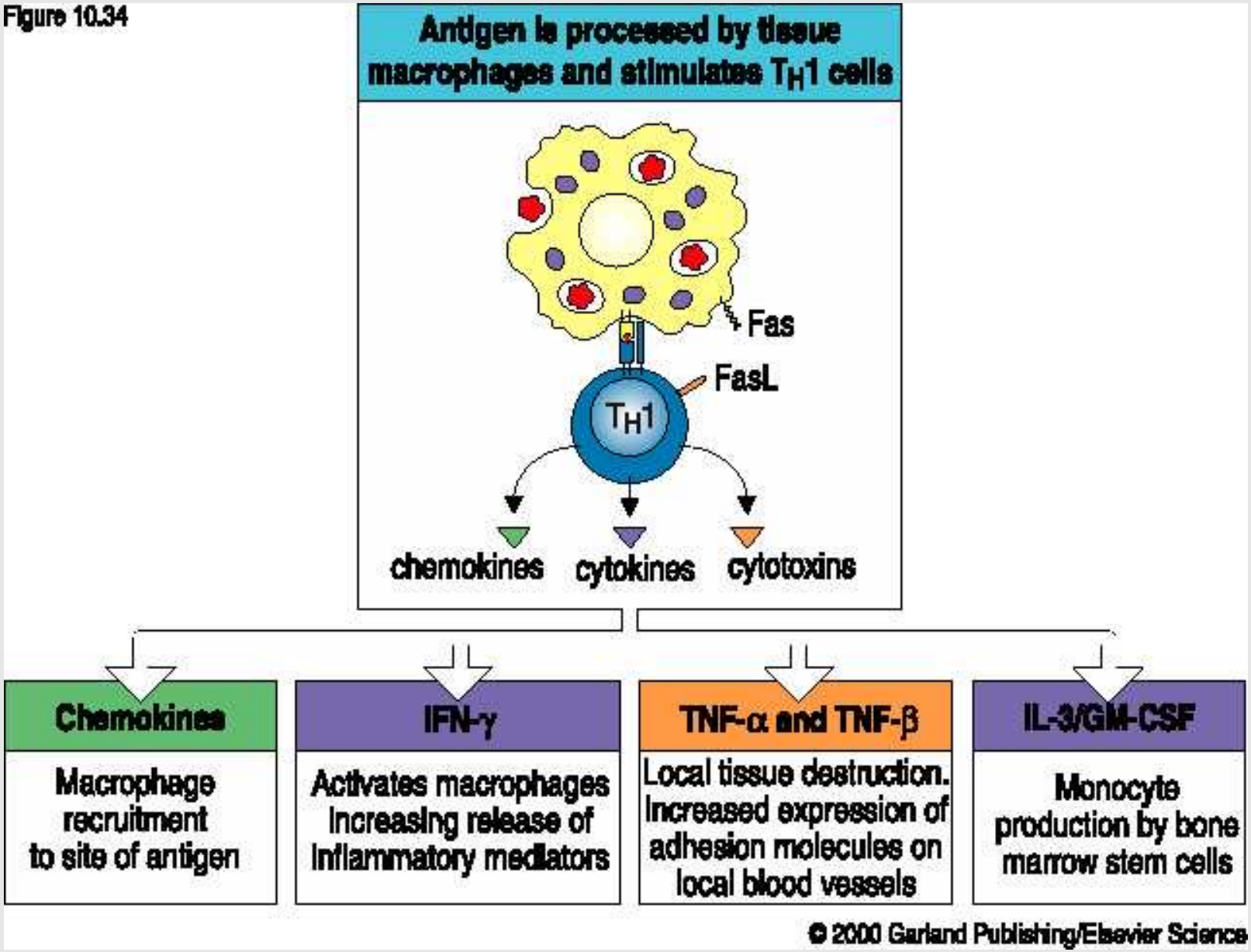
2. Activation: Th1-activation, proliferation, rarely CD8+ CTL-activation.

2. contact with the antigen



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



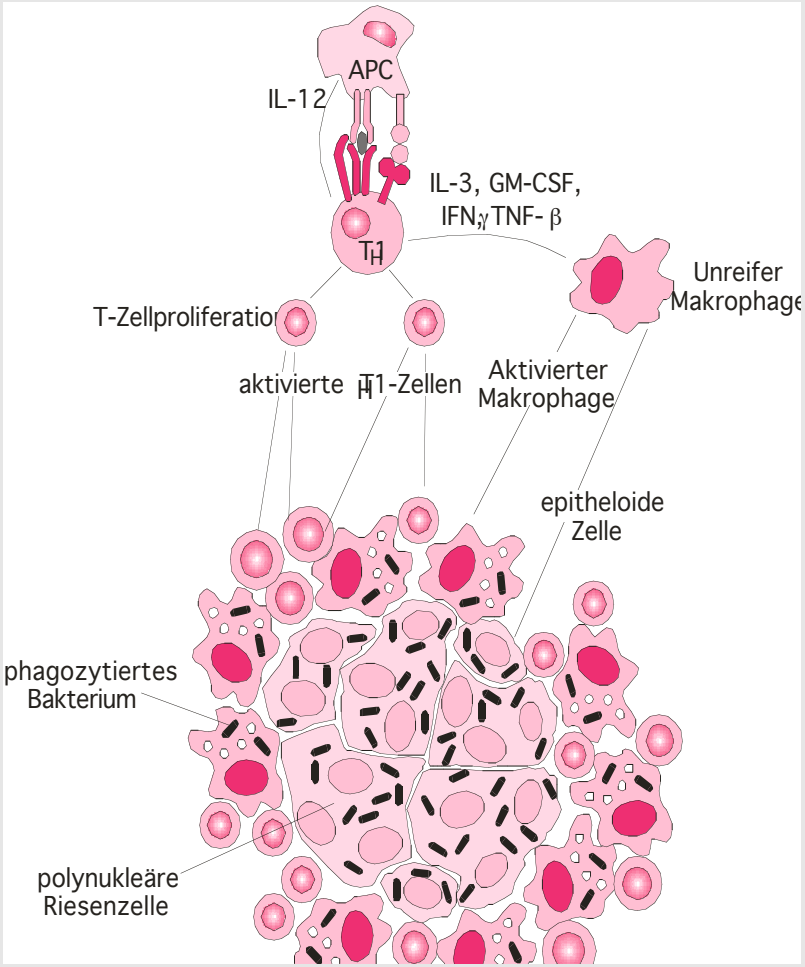
Stages of macrophage activation

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

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

The structure of granulomas

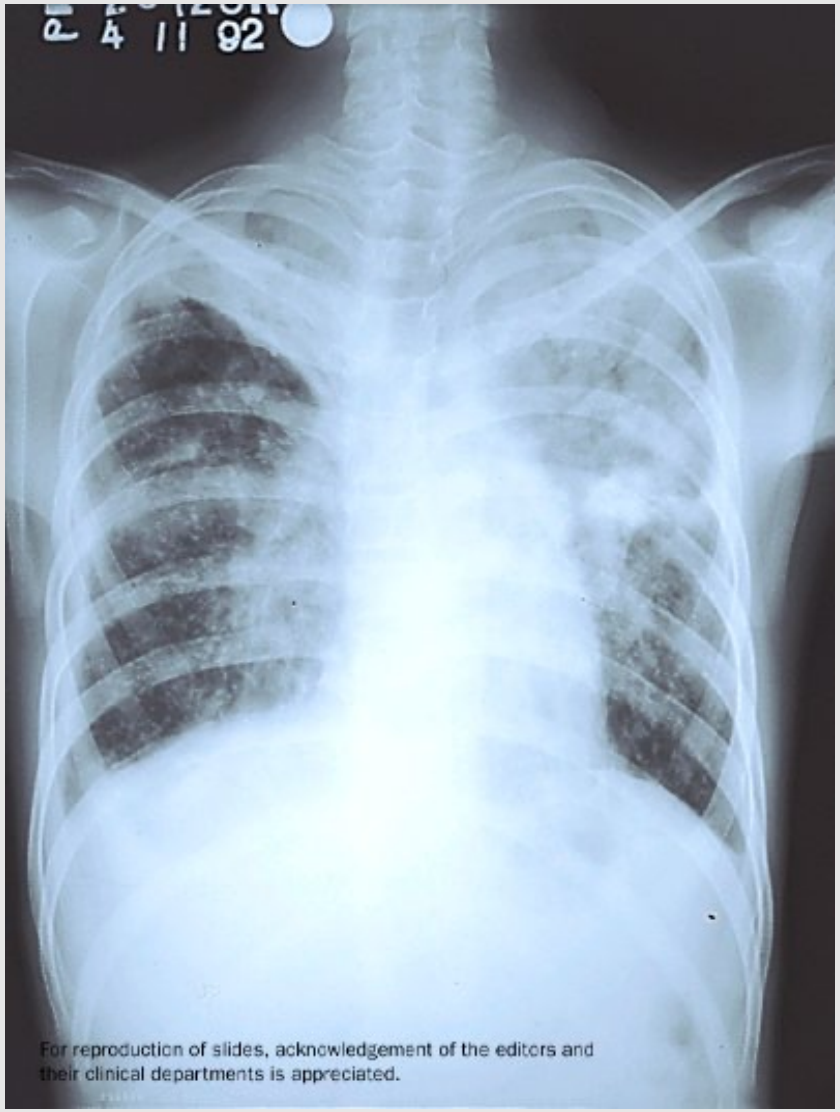


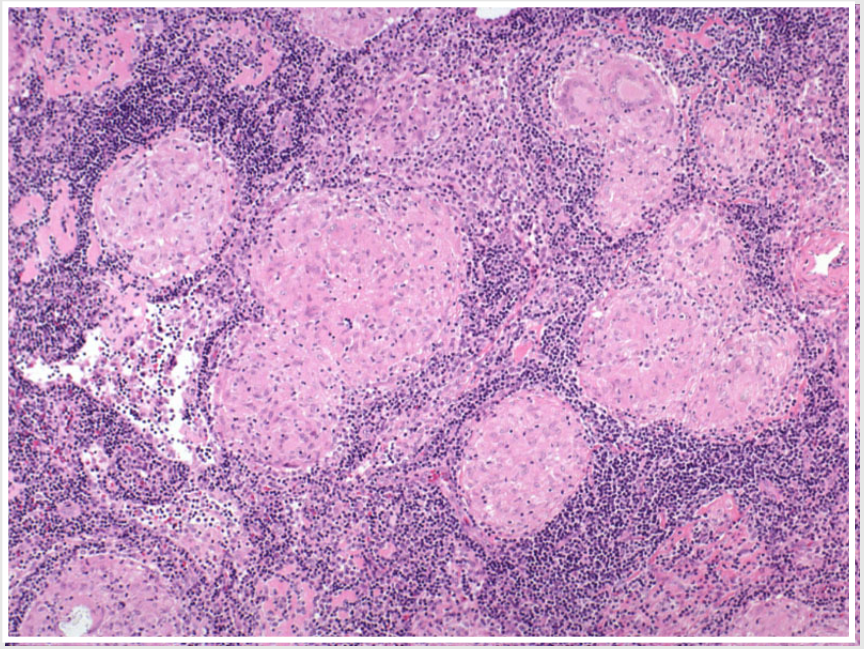
Diseases

- 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: allogen tissue transplantation

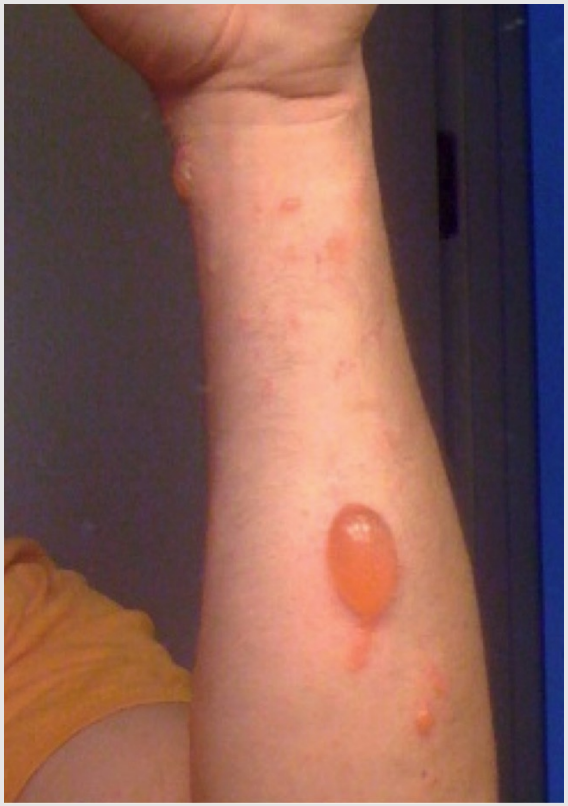
Type IV. hypersensitivity –

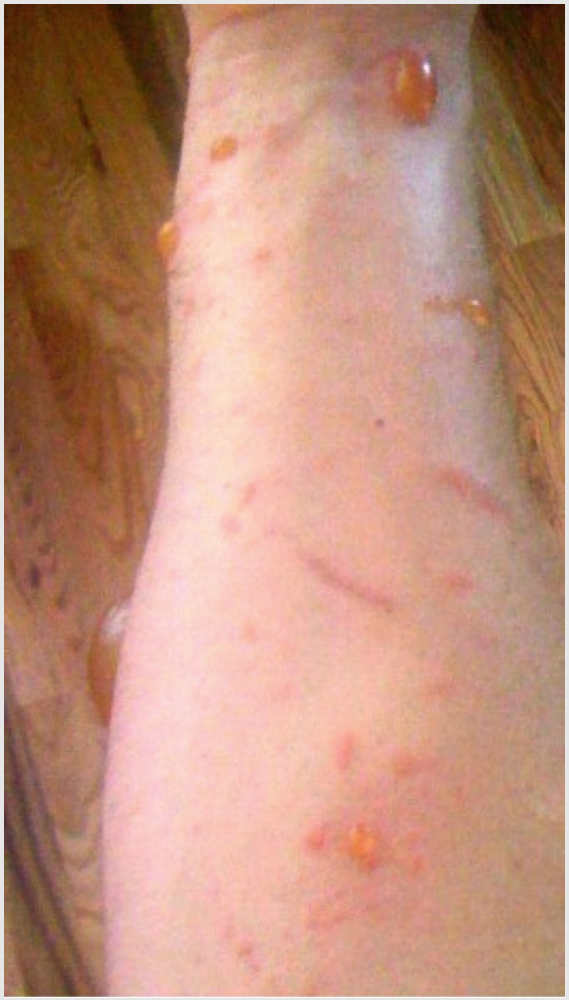
Tuberculotic granulomas





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