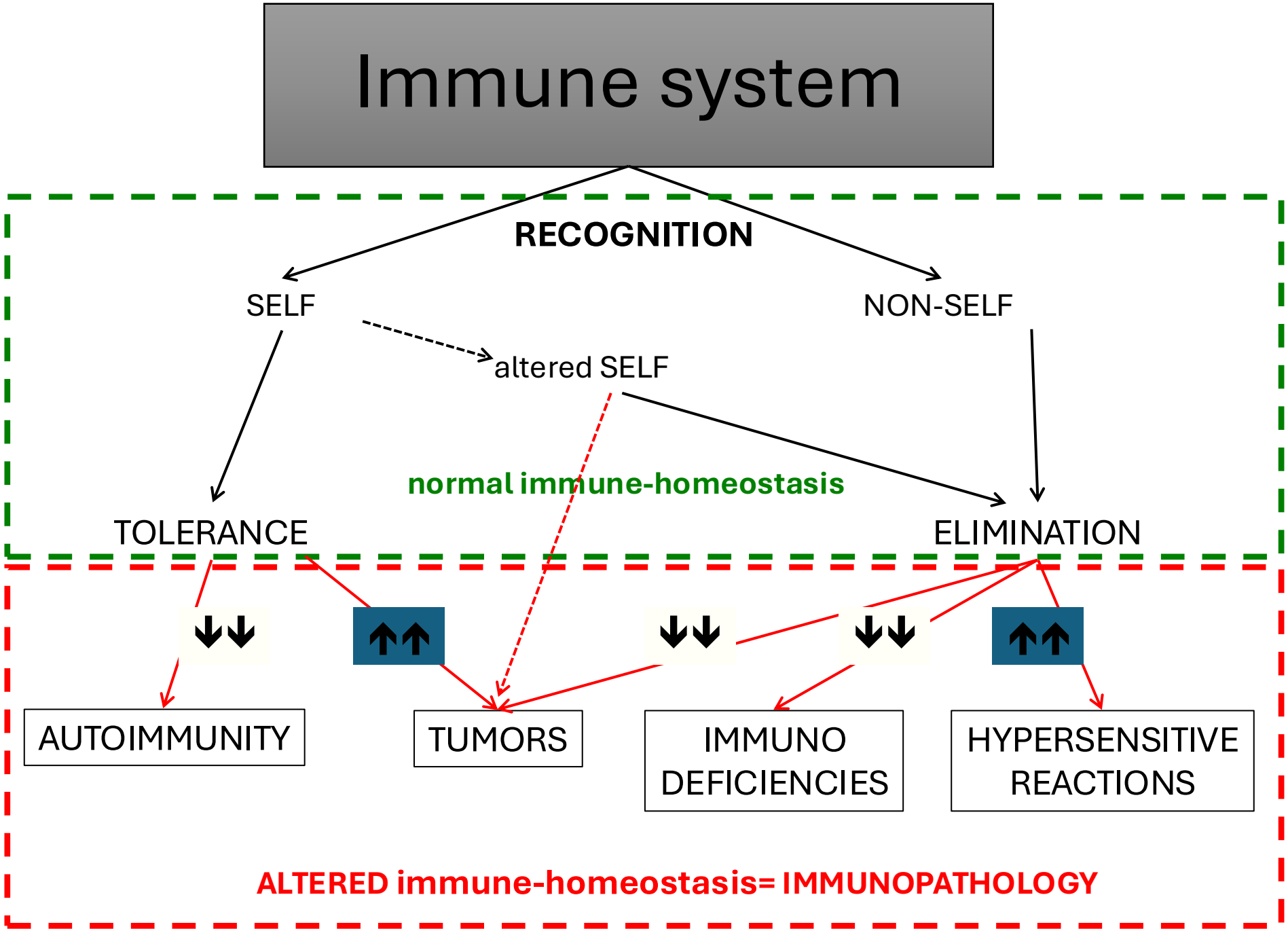
Basic Immunology

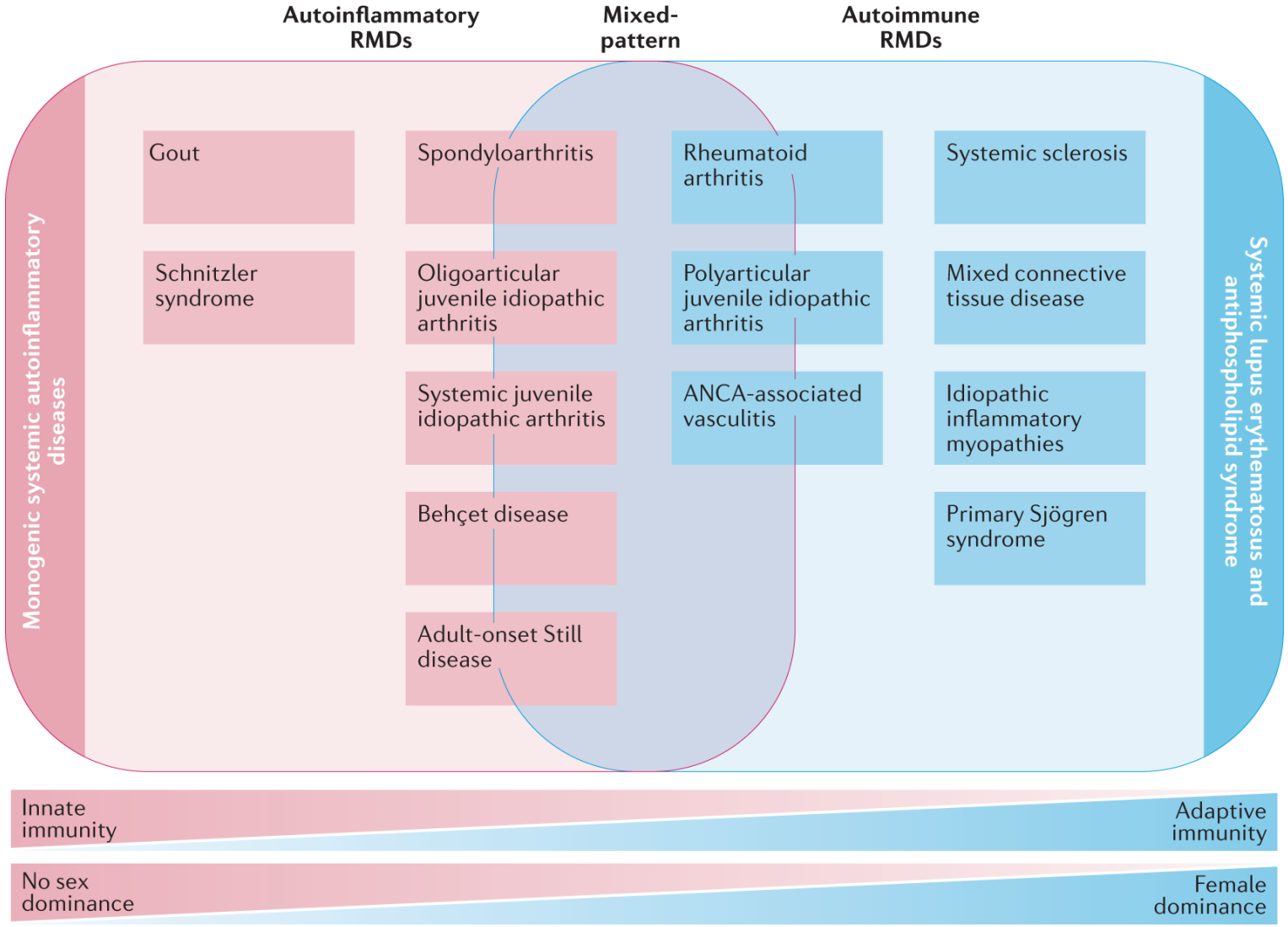
Allergies and hypersensitive reactions

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

Lectures 21.-22.


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

Rheumatic- and musculoskeletal diseases (RMD)



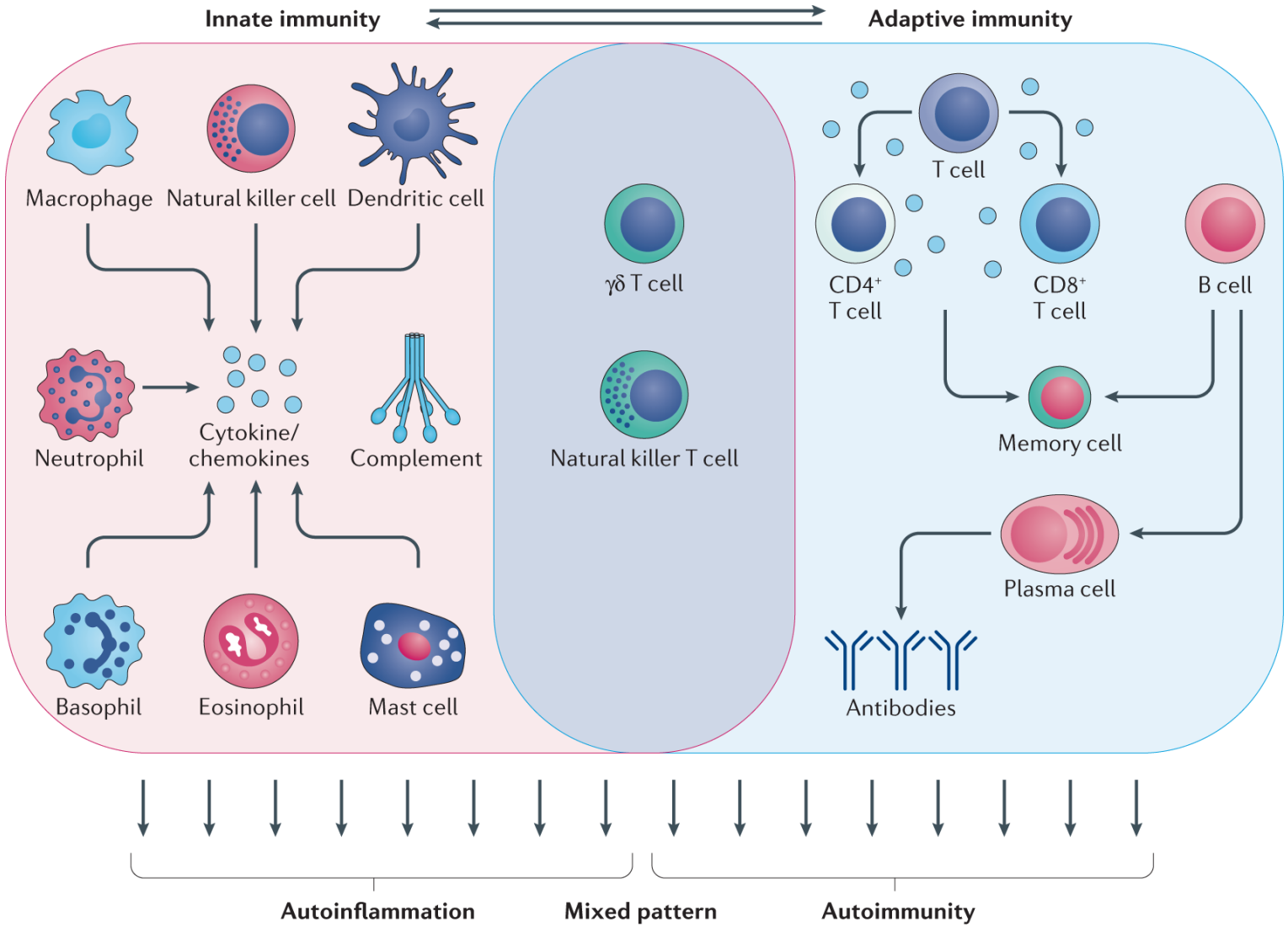
Review Article | Published: 02 August 2021

Autoinflammation and autoimmunity across rheumatic and musculoskeletal diseases

Zoltán Szekanecz ✉, Iain B. McInnes, Georg Schett, Szilvia Szamosi, Szilvia Benkő & Gabriella Szűcs

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Autoinflammation und Autoimmunität



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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=Delayed Type Hypersensitivity)

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)

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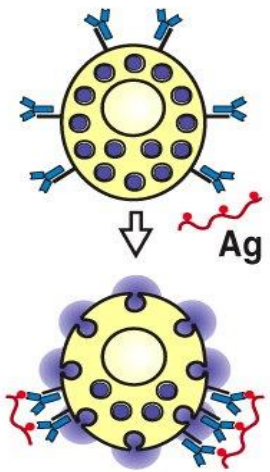
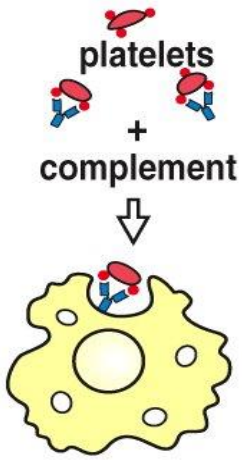
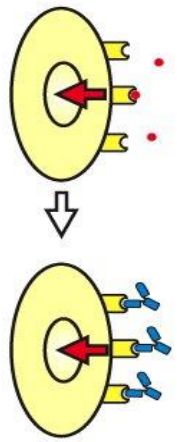
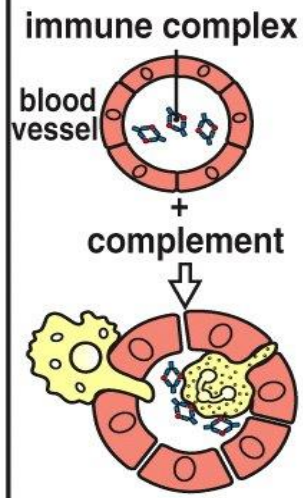
	Type I	Type II		Type III
Immune reactant	IgE	Type II a IgG	Type II b	IgG
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, Phagocytes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

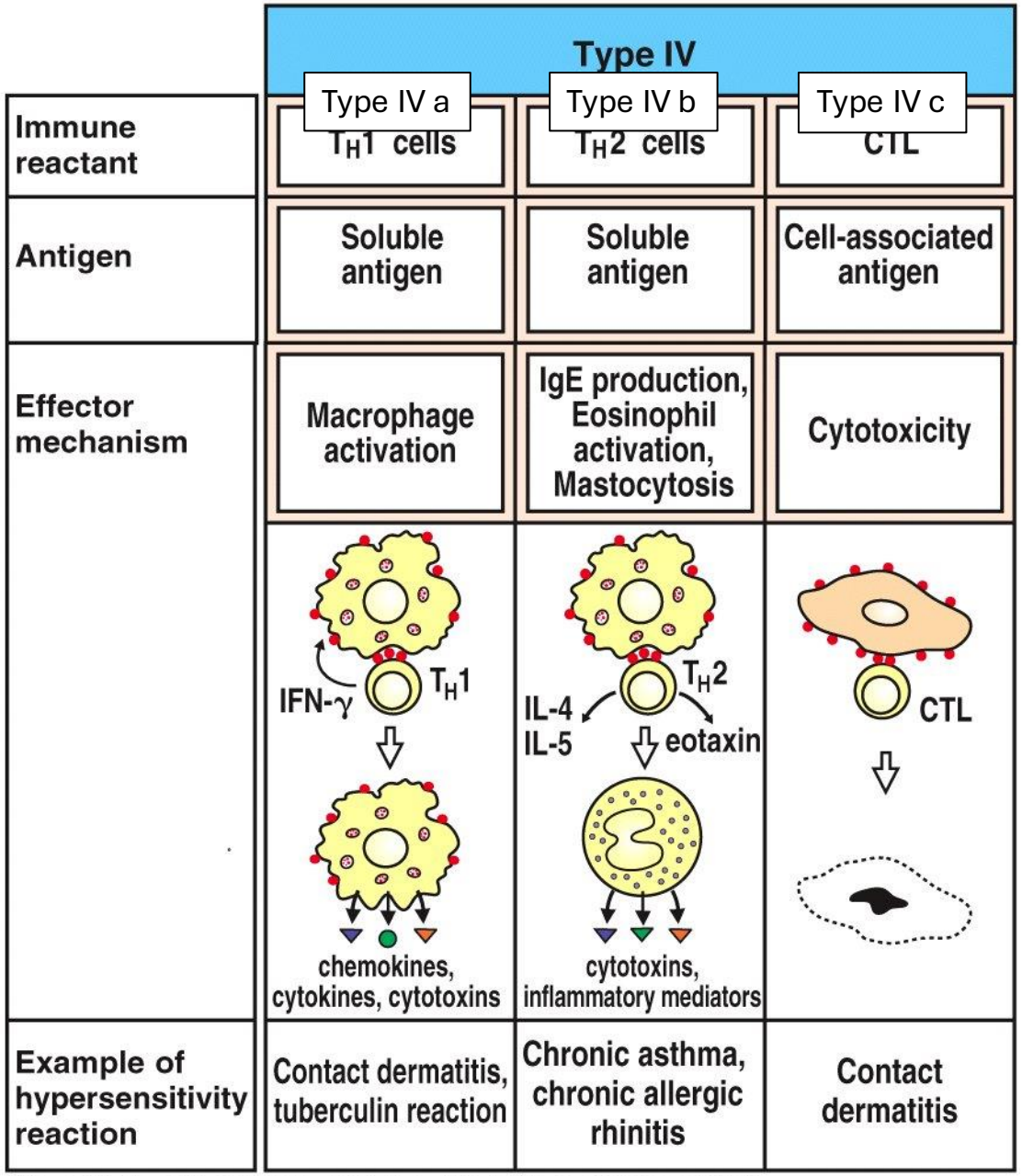
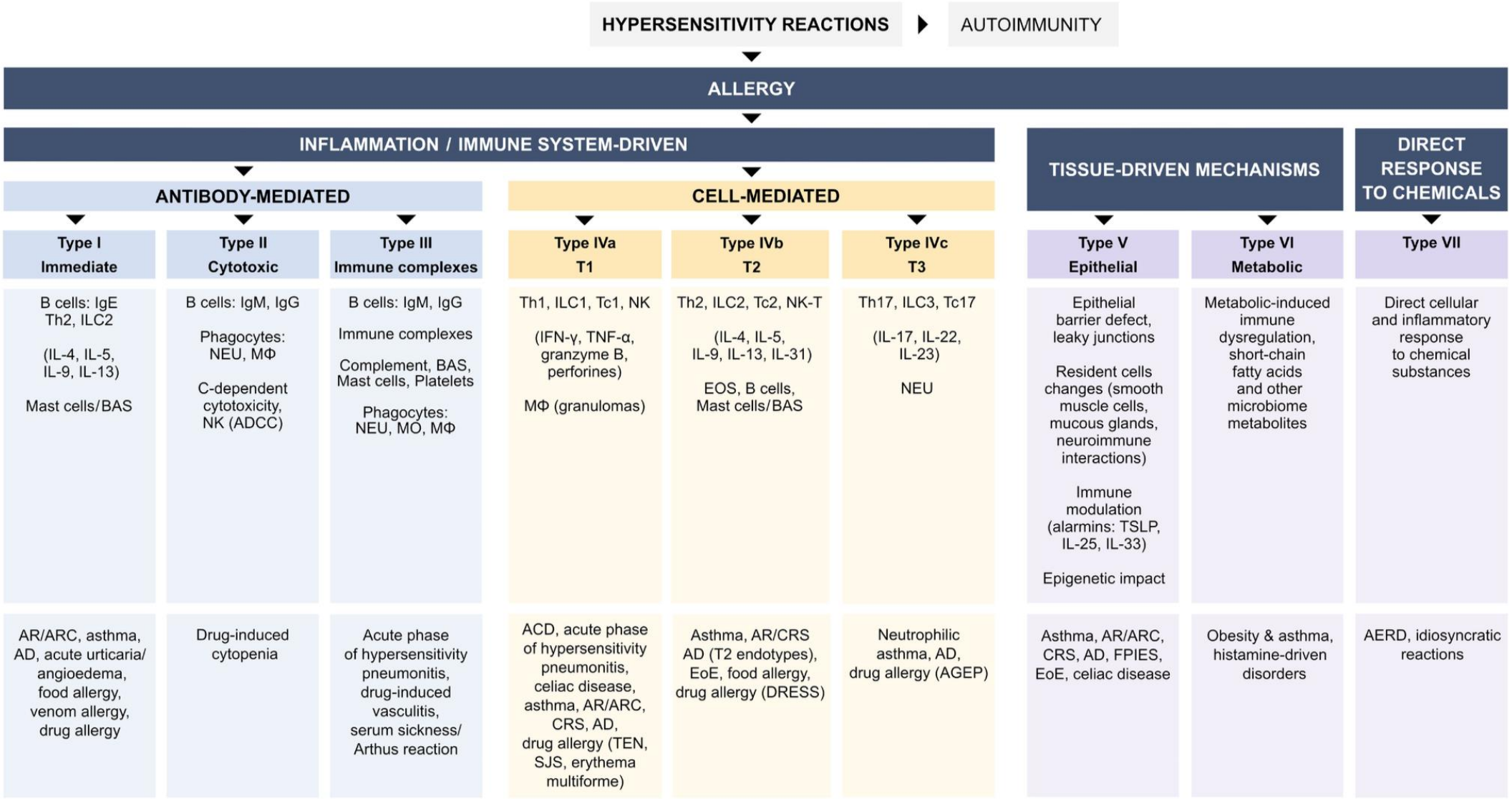


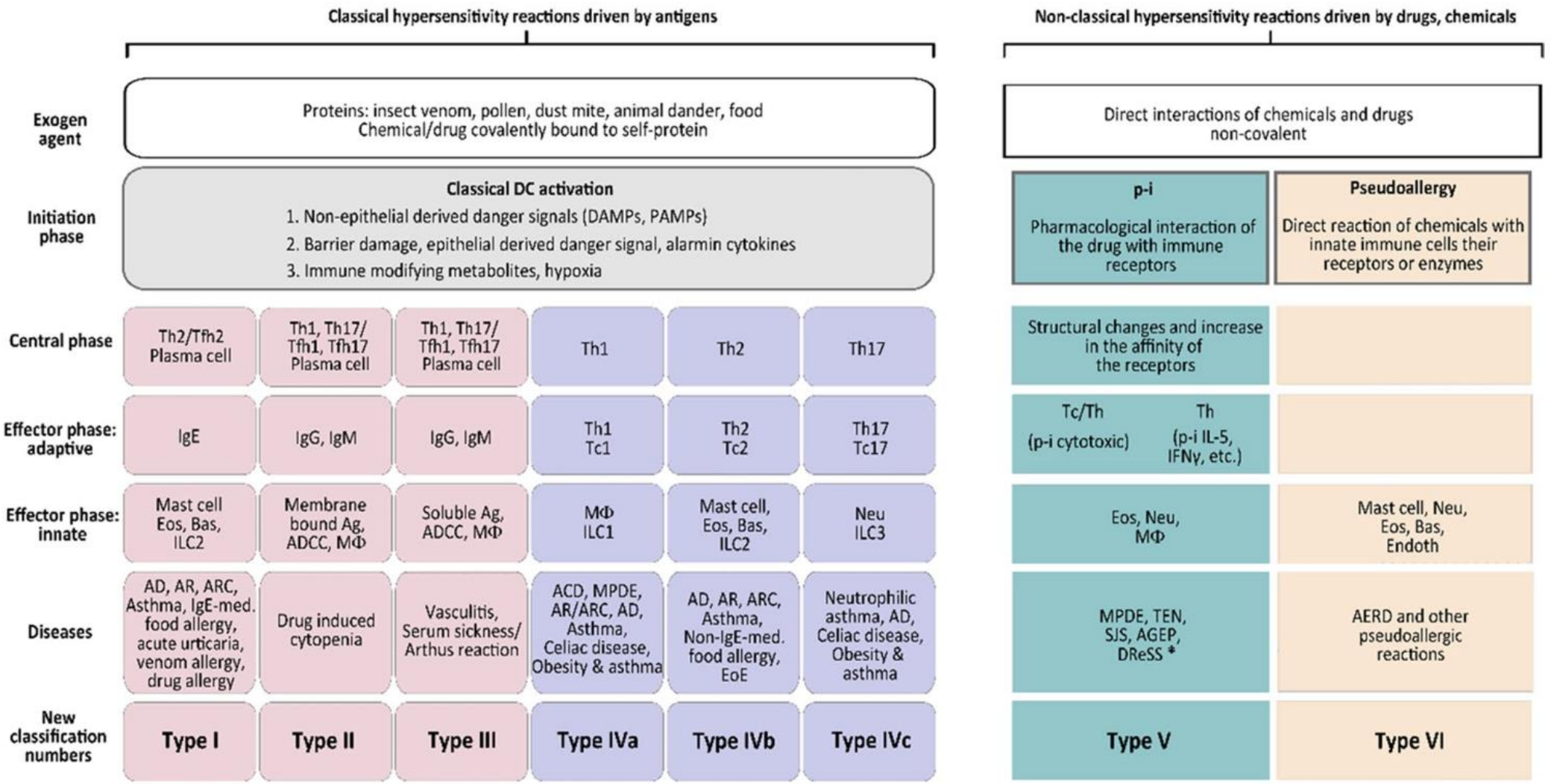
Figure 12-2 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

2023 Classification – Jutel and colleagues

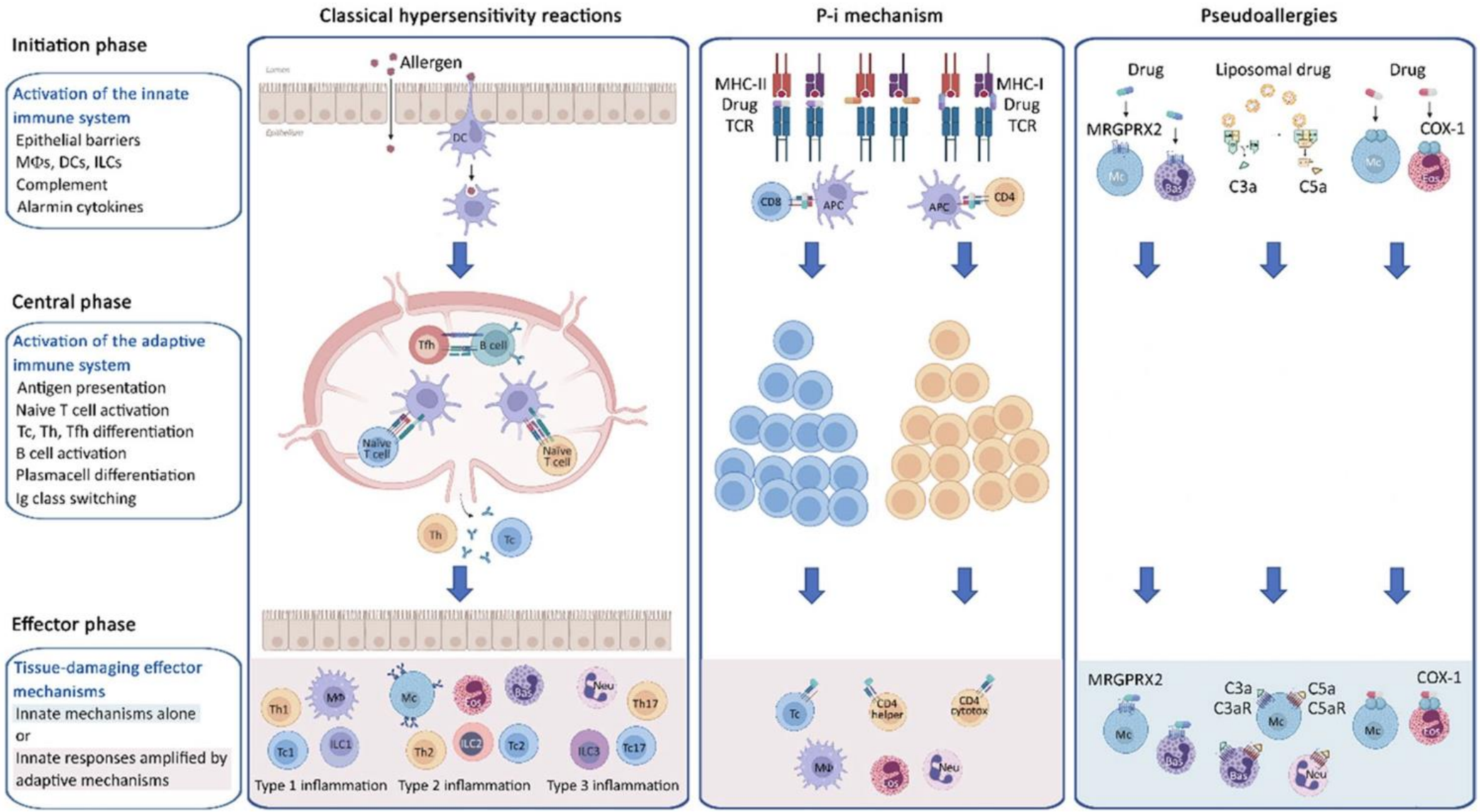


Allergy. 2023;78:2851–2874. wileyonlinelibrary.com/journal/all

2026 Classification – Szegedi and colleagues



ACD, Allergic contact dermatitis; AD, atopic dermatitis; AERD, aspirin exacerbated respiratory disease; AGEP, acute generalised exanthematous pustulosis; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; DReSS, drug reaction with eosinophilia and systemic symptoms; EoE, eosinophilic oesophagitis; MPDE, maculopapular drug eruptions; SJS, Stevens-Johnson syndrome;

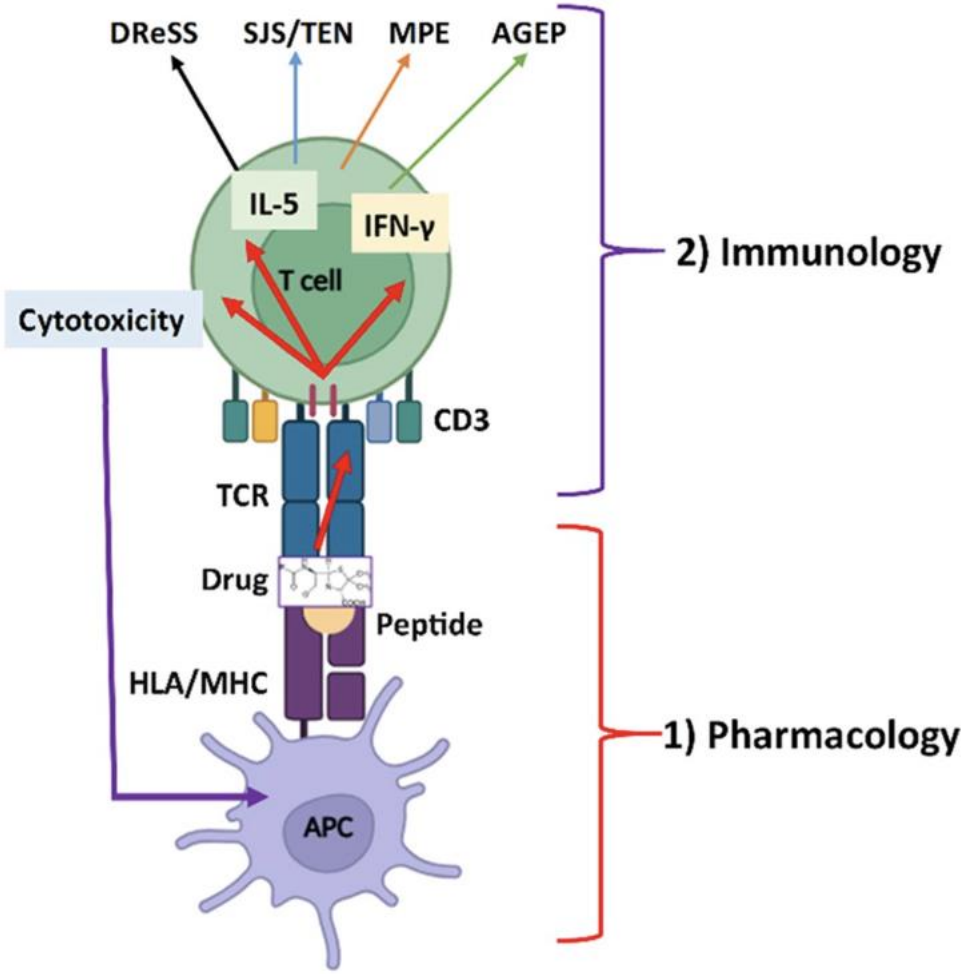

Classical hypersensitivity reactions
P-i mechanism
Pseudoallergies
Initiation phase
Activation of the innate immune system
Epithelial barriers
MΦs, DCs, ILCs
Complement
Alarmin cytokines
Central phase
Activation of the adaptive immune system
Antigen presentation
Naive T cell activation
Tc, Th, Tfh differentiation
B cell activation
Plasmacell differentiation
Ig class switching
Effector phase
Tissue-damaging effector mechanisms
Innate mechanisms alone
or
Innate responses amplified by adaptive mechanisms
Allergen
DC
Tfh
B cell
Naive T cell
Th
Tc
Th1
MΦ
Tc1
ILC1
Mc
Th2
ILC2
Tc2
Bas
Eos
Neu
Th17
ILC3
Tc17
Type 1 inflammation
Type 2 inflammation
Type 3 inflammation
MHC-II
Drug
TCR
MHC-I
Drug
TCR
CD8
APC
APC
CD4
Tc
CD4 helper
CD4 cytotox
MΦ
Eos
Neu
Drug
MRGPRX2
Mc
Bas
Liposomal drug
C3a
C5a
Drug
COX-1
Mc
Eos
MRGPRX2
Mc
Bas
C3a
C3aR
C5a
C5aR
Mc
Bas
Neu
Mc
COX-1
Eos

The “p-I” Concept
(Pharmacological Interaction with Immune Receptors (p-i)Mechanism)

A non-covalent binding develops between a drug- and MHC- or TcR molecule.

Superantigen-like activation.

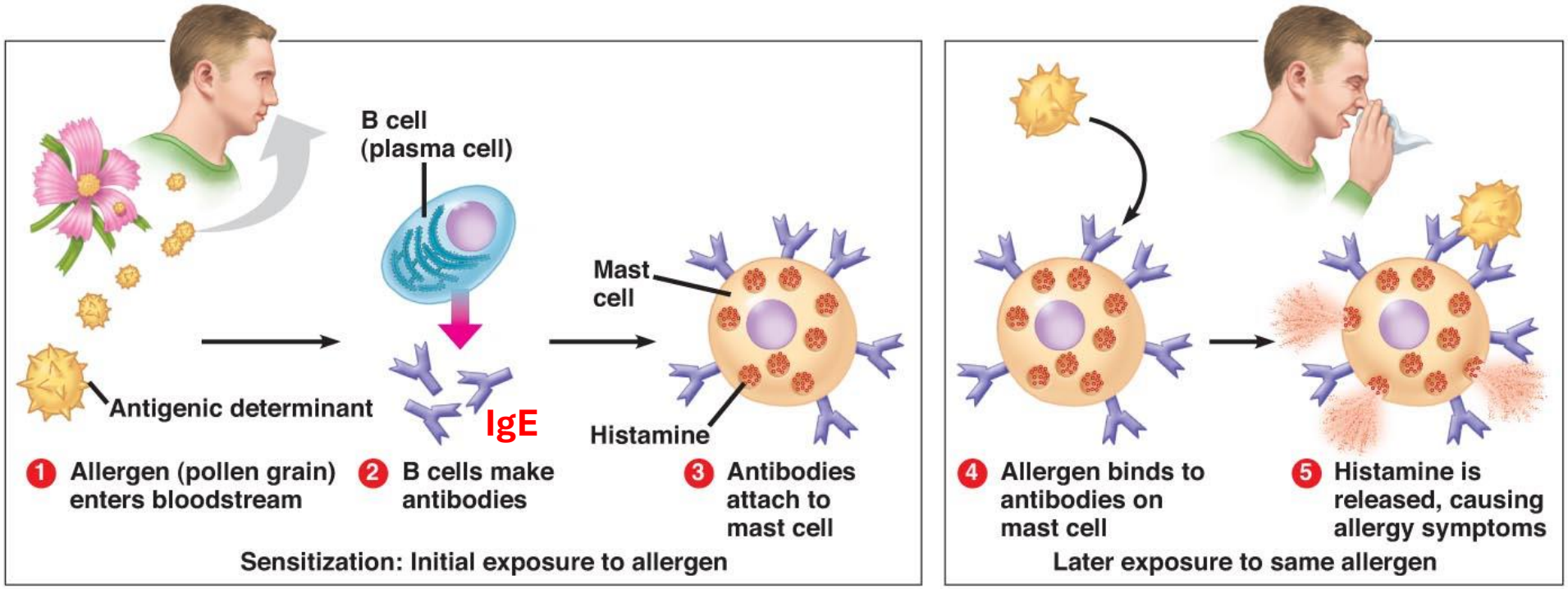
Very intensive T cell activation leads to severe generalised skin lesions.



AGEP, acute generalised exanthematous pustulosis; DReSS, drug reaction with eosinophilia and systemic symptoms; MPDE, maculopapular drug eruptions; SJS, Stevens-Johnson syndrome;

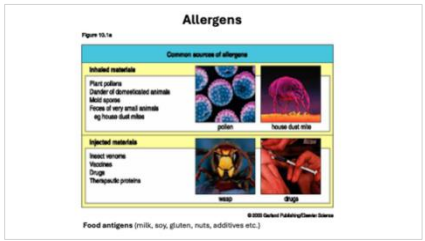
Type I., immediate hypersensitivity;
Allergy, Atopy

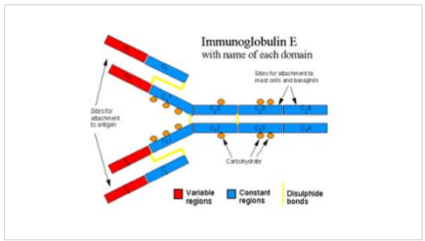
Basic mechanism

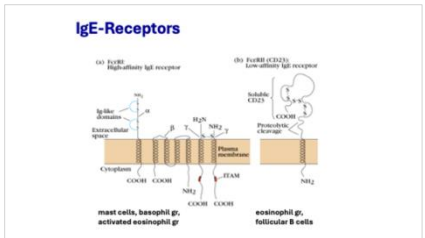


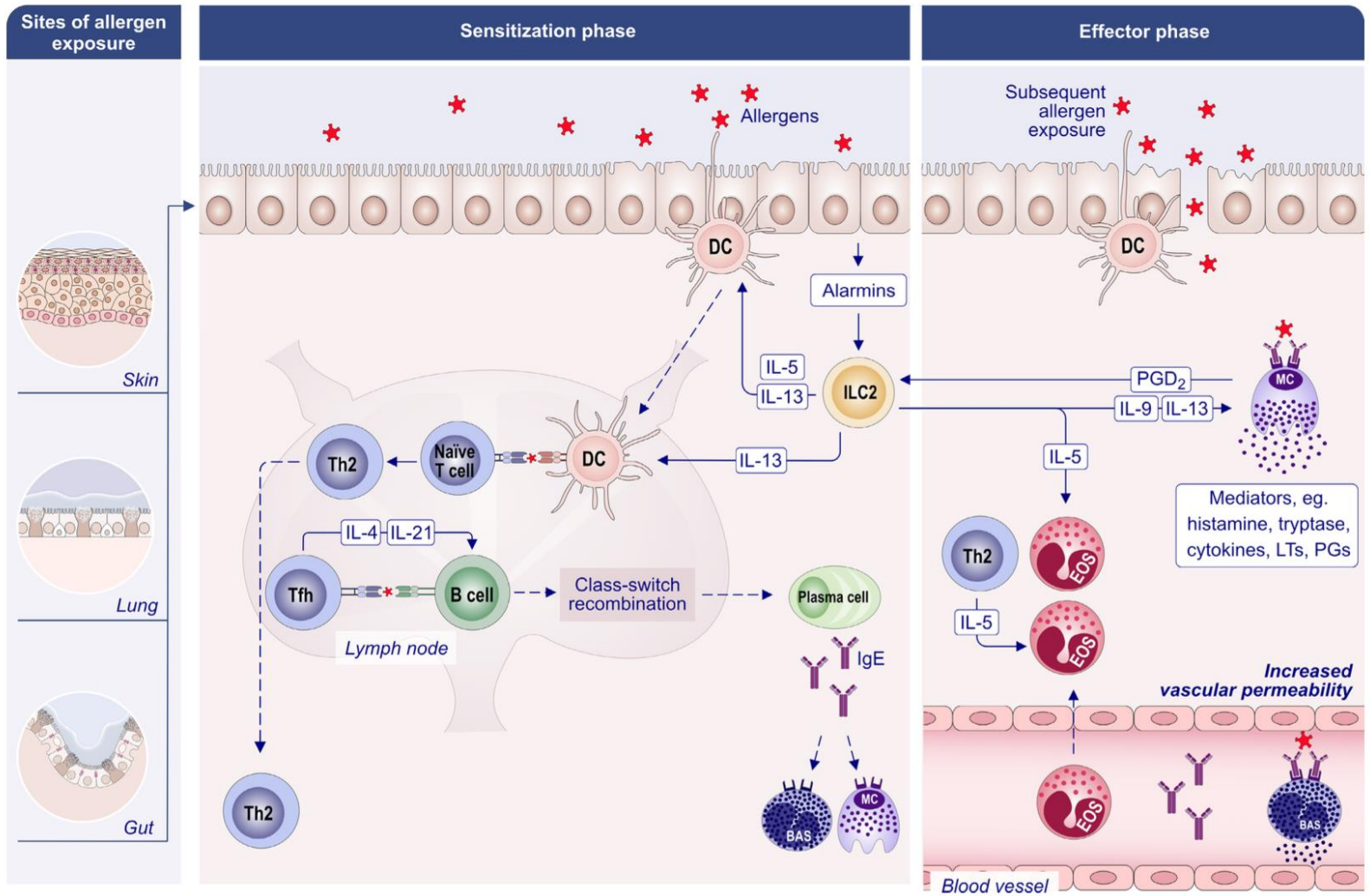
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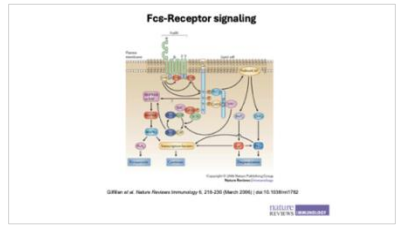
Dictionary:
”Allergy” – Clemens von Pirquet (1906), Greek: “allos” – other, different; “ergon” – work, reaction
“Atopy” - Arthur F. Coca and Robert A. Cooke, Greek: “topos” – place; “atopos” – out of place, strange

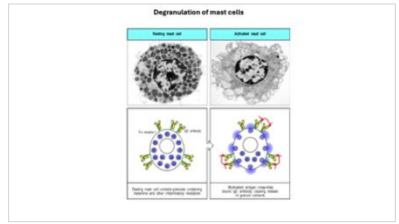

Allergens
Food antigens (milk, soy, gluten, nuts, additives etc.)

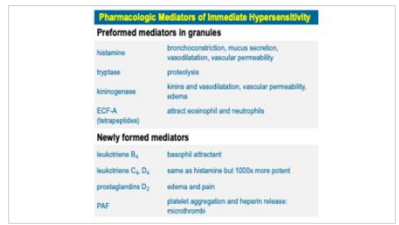

Immunoglobulin E
with name of each domain
Variable regions
Constant regions
Disulphide bonds

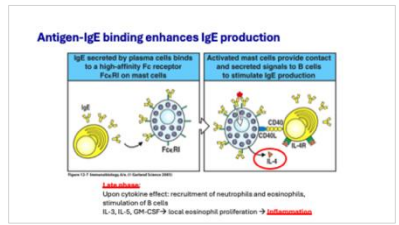

IgE-Receptors
mast cells, basophil gr, activated eosinophil gr
eosinophil gr, follicular B cells


Sites of allergen exposure
Sensitization phase
Effector phase
Skin
Lung
Gut
Allergens
DC
Alarmins
IL-5
IL-13
ILC2
Th2
Naïve T cell
DC
IL-13
IL-4
IL-21
Tfh
B cell
Class-switch recombination
Plasma cell
IgE
Lymph node
Th2
MC
BAS
Subsequent allergen exposure
DC
PGD2
IL-9
IL-13
MC
IL-5
Mediators, eg. histamine, tryptase, cytokines, LTs, PGs
Th2
EOS
IL-5
EOS
Increased vascular permeability
EOS
BAS
Blood vessel


Fcε-Receptor signaling

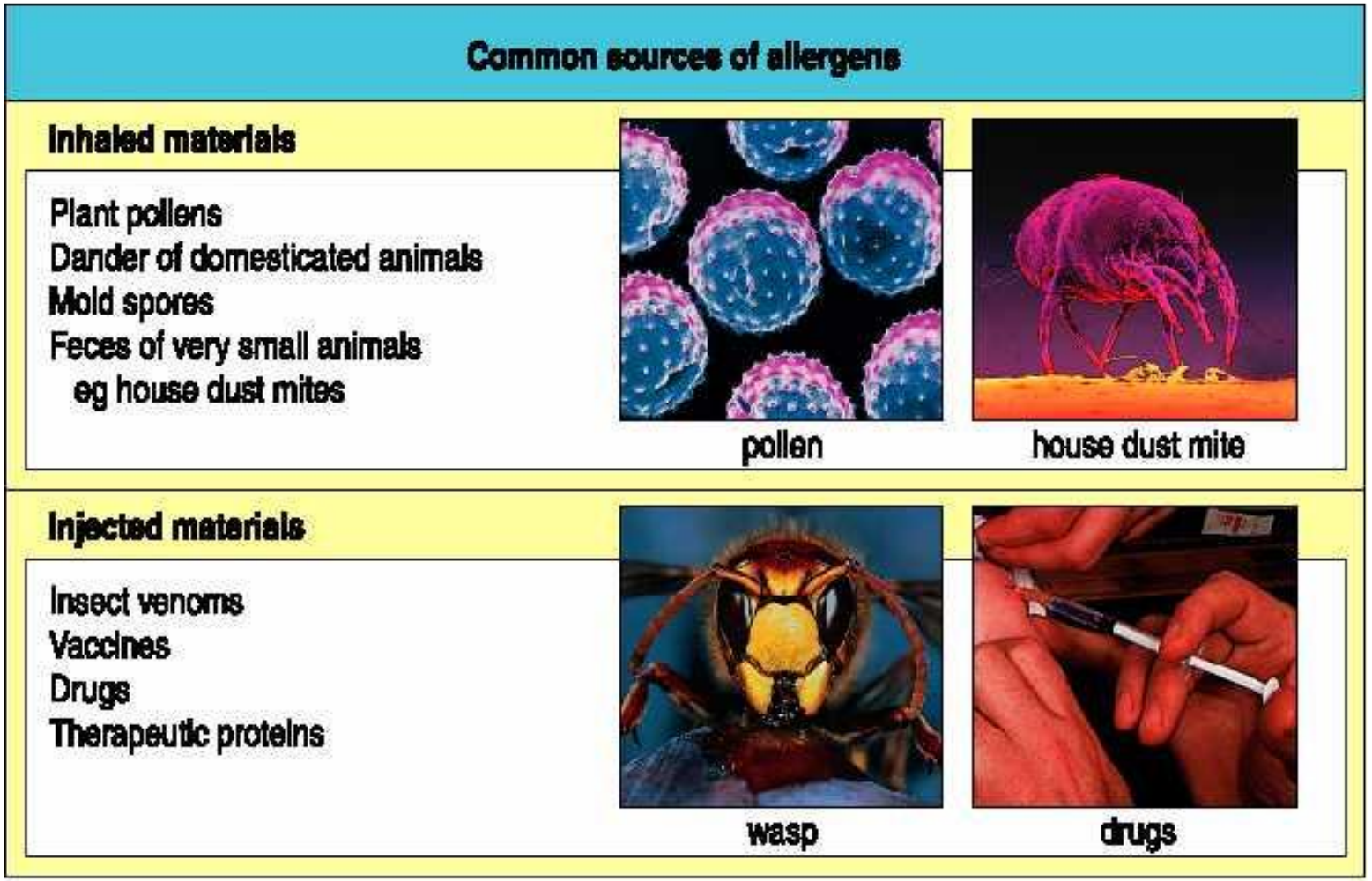

Degranulation of mast cells


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 B4
basophil attractant
leukotriene C4, D4
same as histamine but 1000x more potent
prostaglandins D2
edema and pain
PAF
platelet aggregation and heparin release; microthrombi


Antigen-IgE binding enhances IgE production
IgE secreted by plasma cells binds to a high-affinity Fc receptor FcεRI on mast cells
Activated mast cells provide contact and secreted signals to B cells to stimulate IgE production
IgE
FcεRI
CD40
CD40L
IL-4R
IL-4
Late phase:
Upon cytokine effect: recruitment of neutrophils and eosinophils, stimulation of B cells
IL-3, IL-5, GM-CSF → local eosinophil proliferation → Inflammation

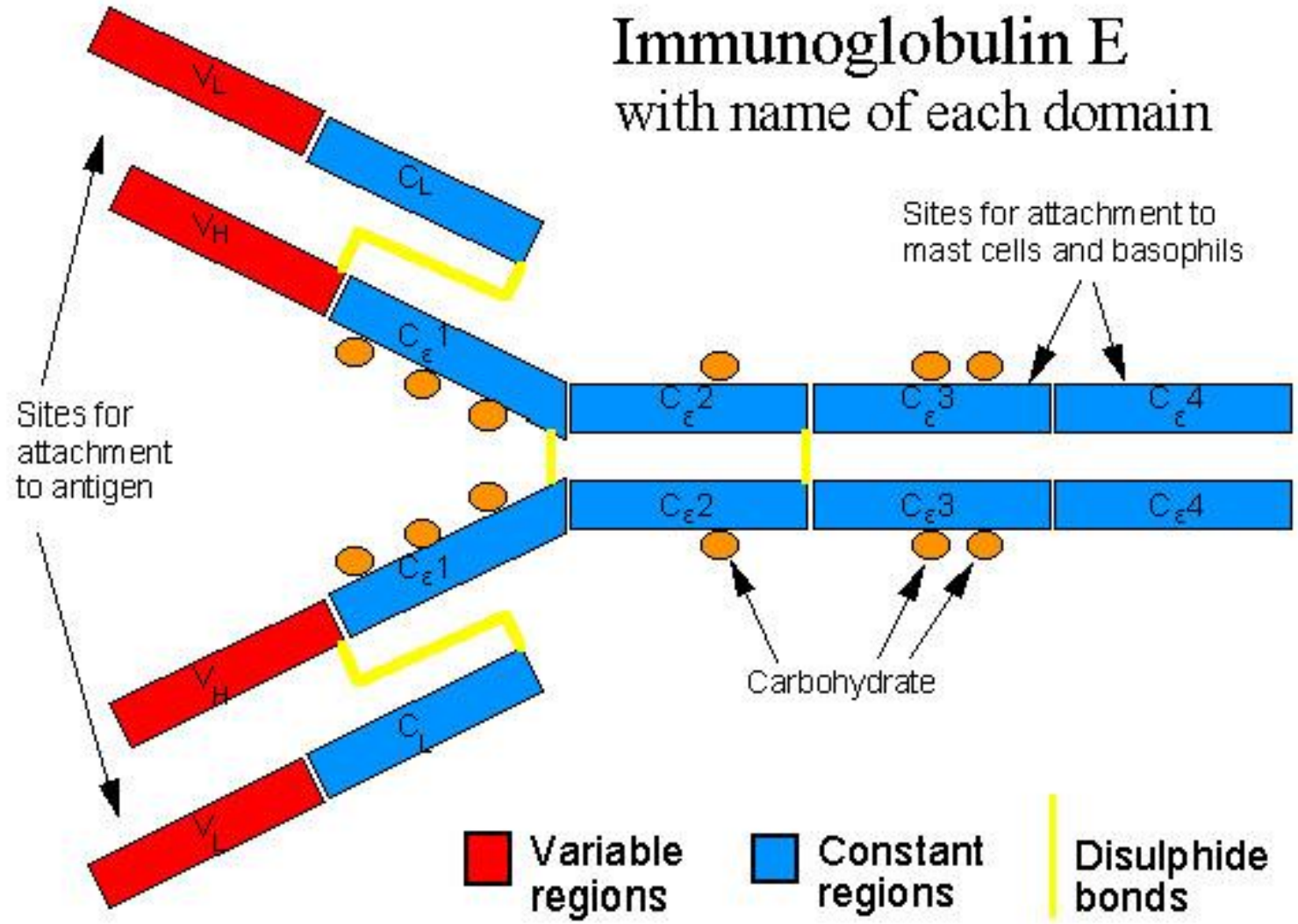
Allergens

Figure 10.1a

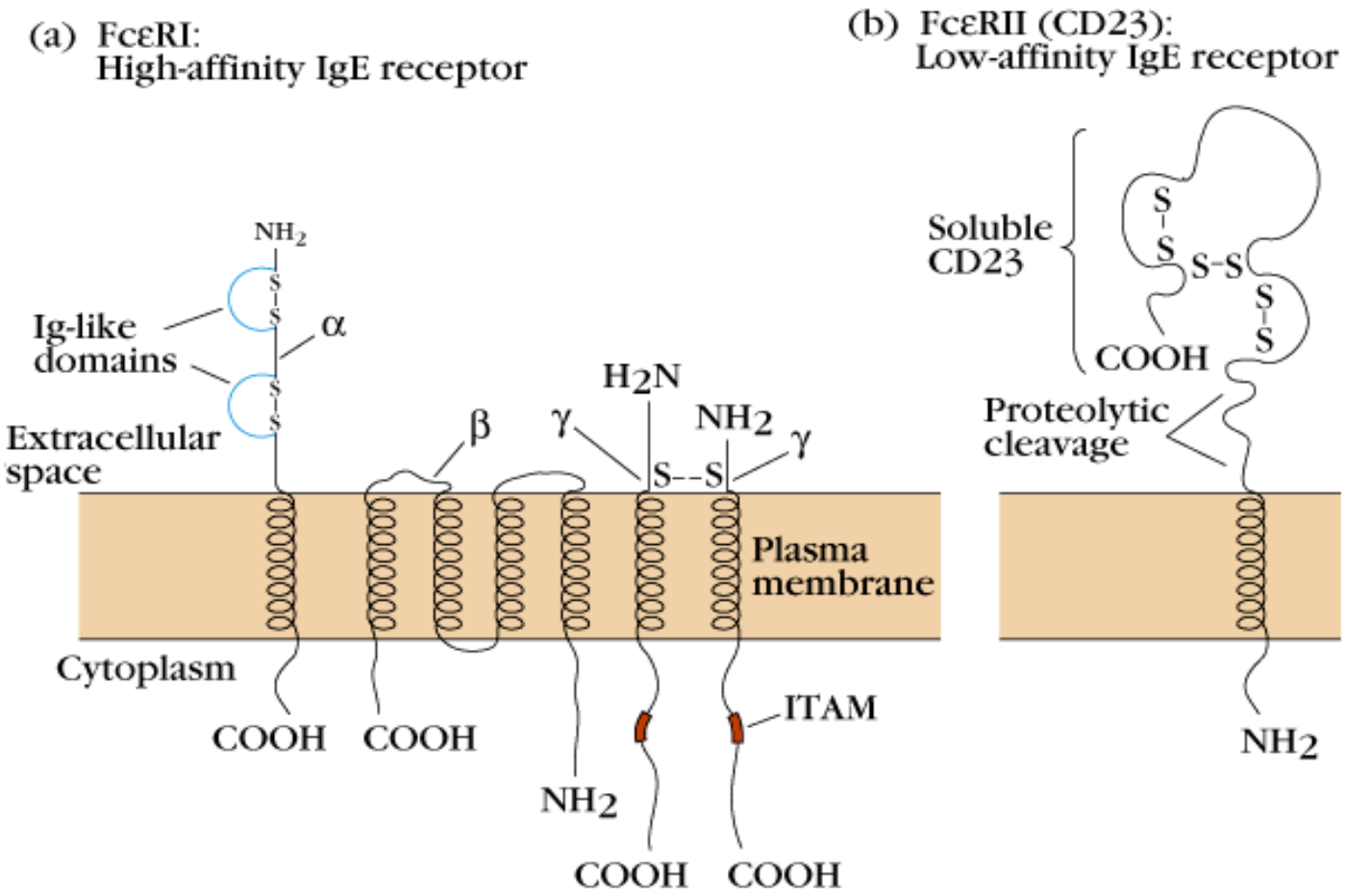


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Food antigens (milk, soy, gluten, nuts, additives etc.)


Immunoglobulin E
with name of each domain
Sites for attachment to mast cells and basophils
Sites for attachment to antigen
Carbohydrate
Variable regions
Constant regions
Disulphide bonds

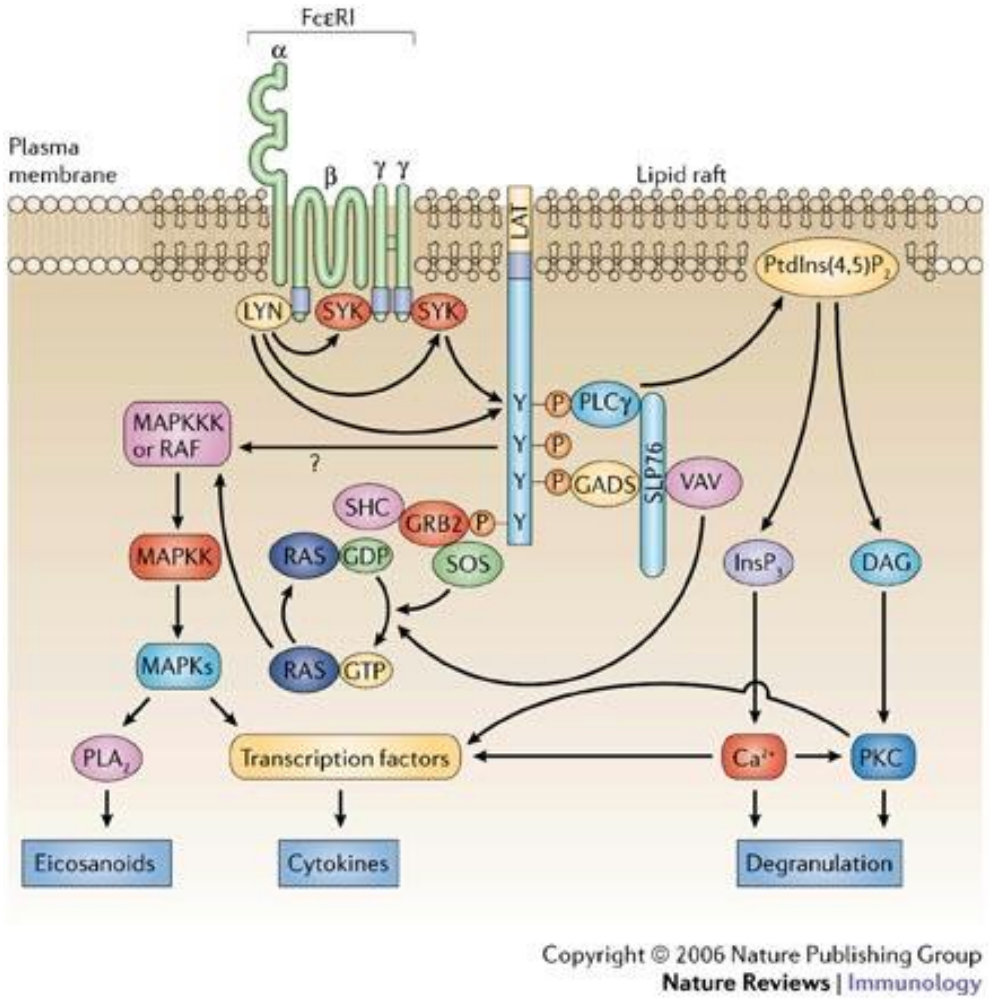
IgE-Receptors



mast cells, basophil gr, activated eosinophil gr

eosinophil gr, follicular B cells

Fcε-Receptor signaling

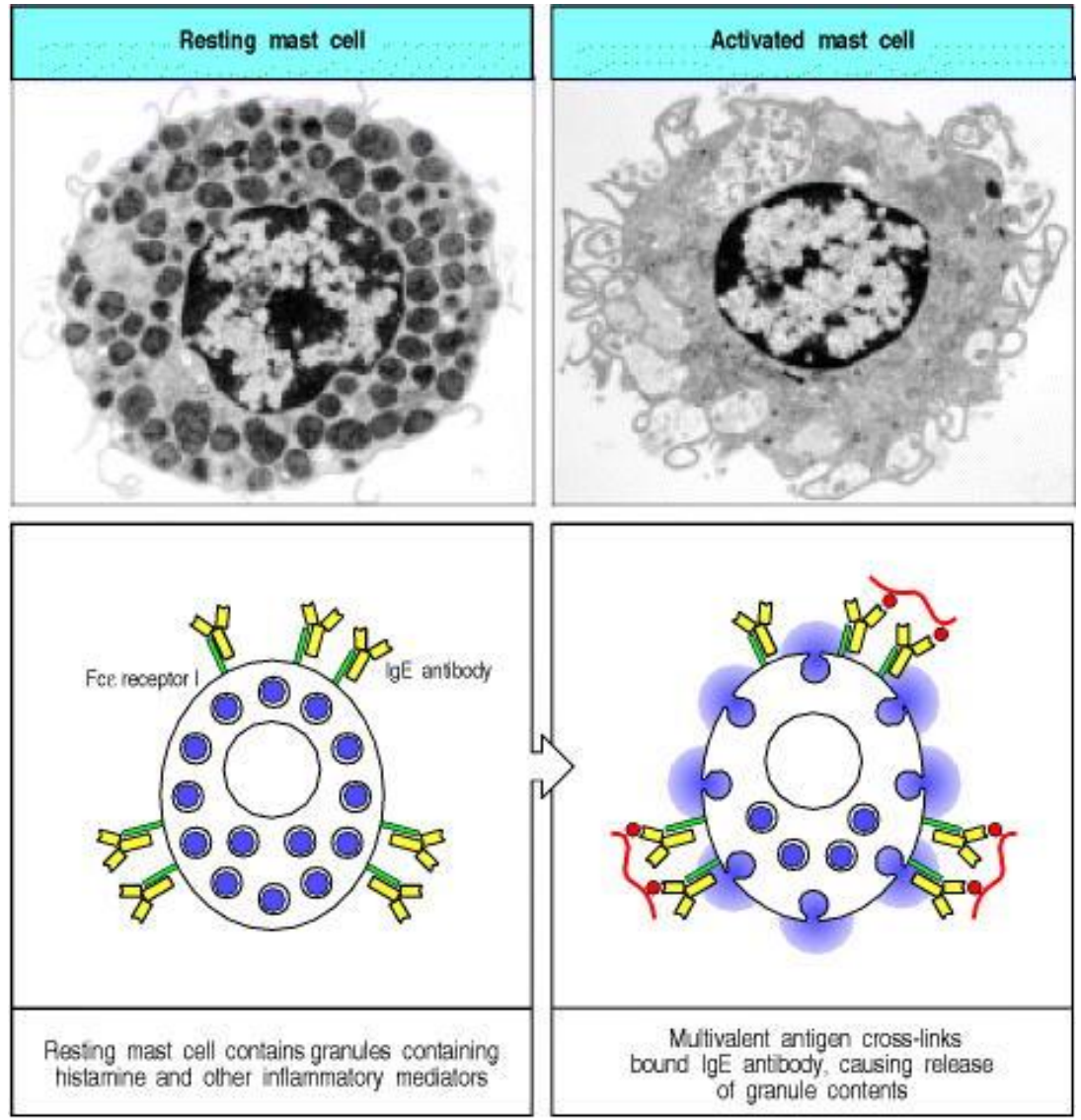


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Gilfillan *et al. Nature Reviews Immunology* 6, 218-230 (March 2006) | doi:10.1038/nri1782

nature REVIEWS IMMUNOLOGY

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

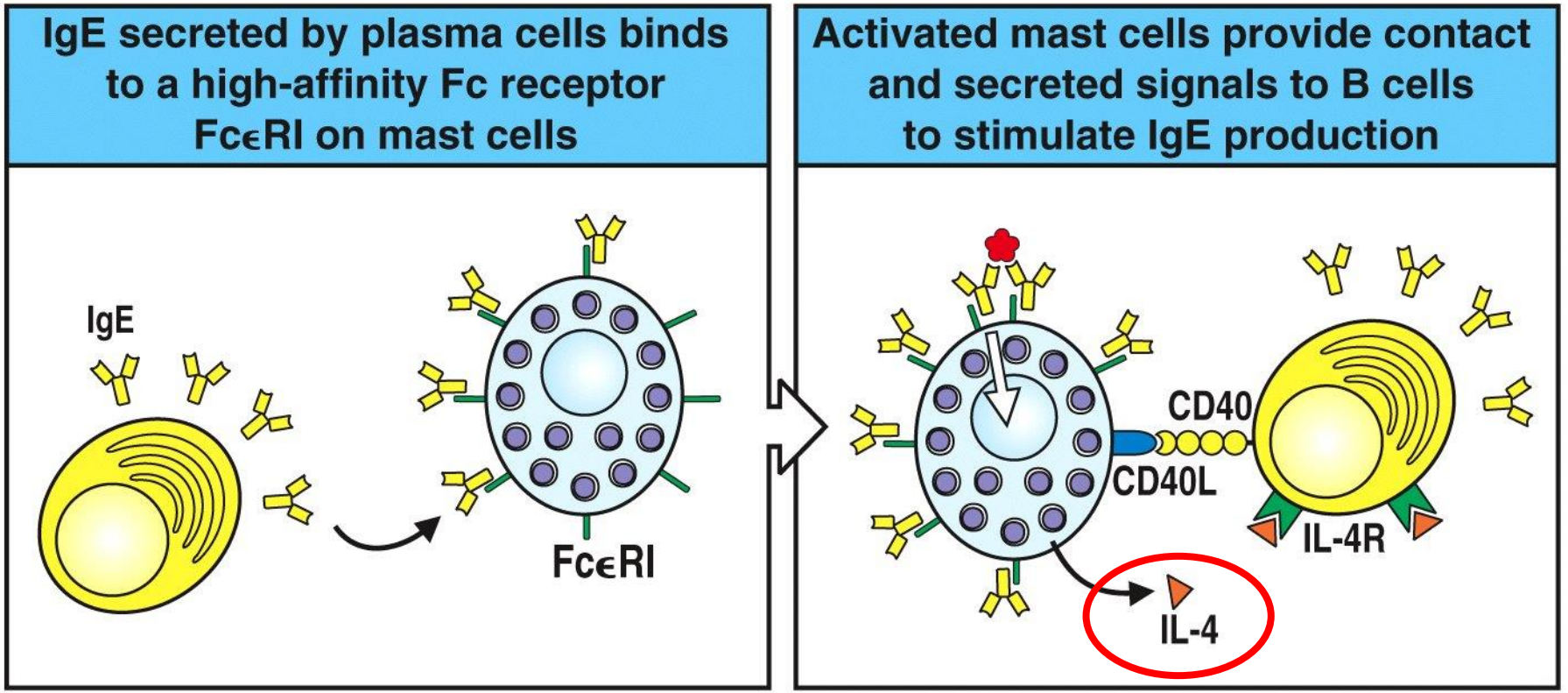


Figure 12-7 Immunobiology, 6/e. (© Garland Science 2005)

Late phase:

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

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

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.

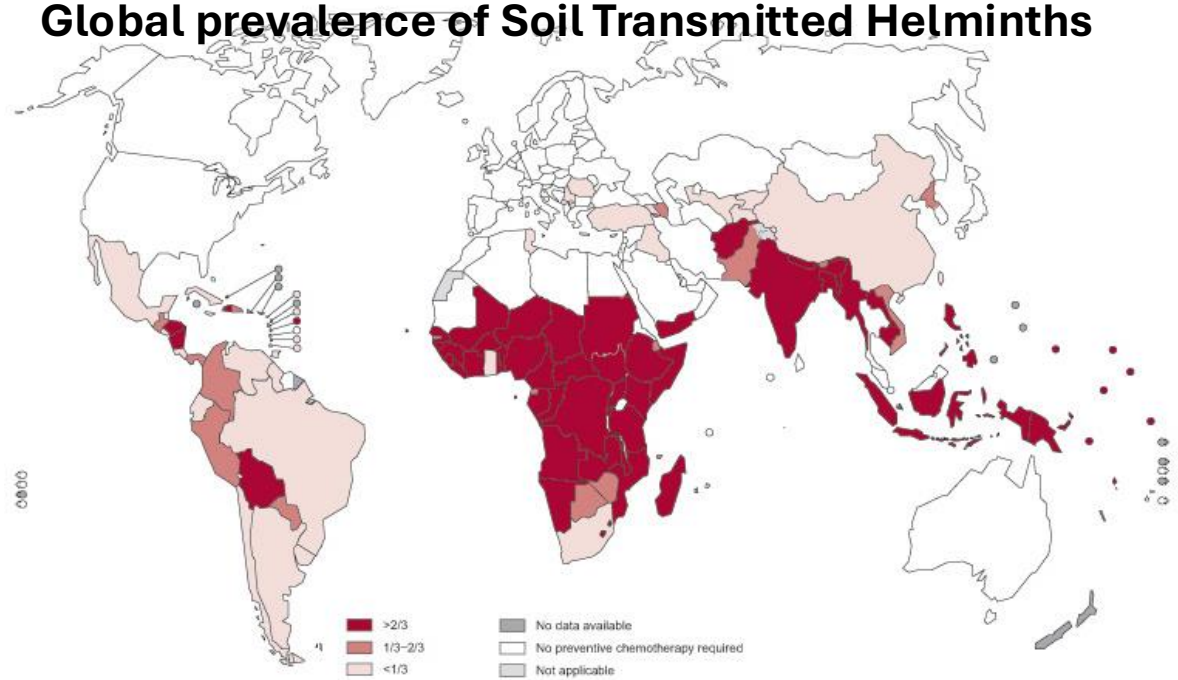
- **changes in the infectious diseases in early childhood („Hygiene-theory" / „Old Friends Hypothesis")**
- **Environmental pollution (air pollution in industrial regions, traffic)**
- **Altered allergen concentrations**
- **Changes in the diet (chemicals)**
- **Changes in the gut microbiota**

Global prevalence of Allergic Rhinitis



Hygiene-theory

Global prevalence of Soil Transmitted Helminths



Hygiene-theory

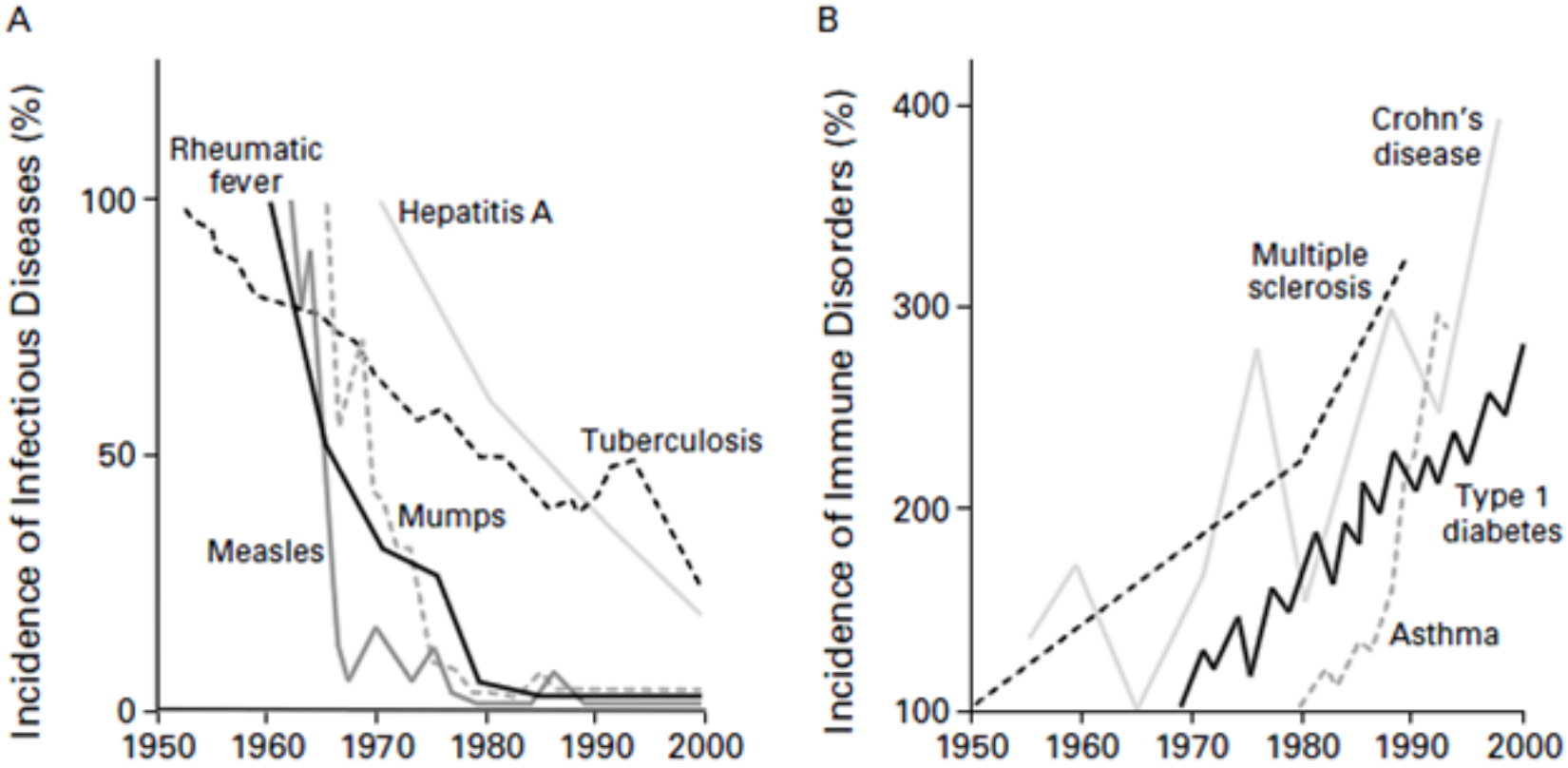
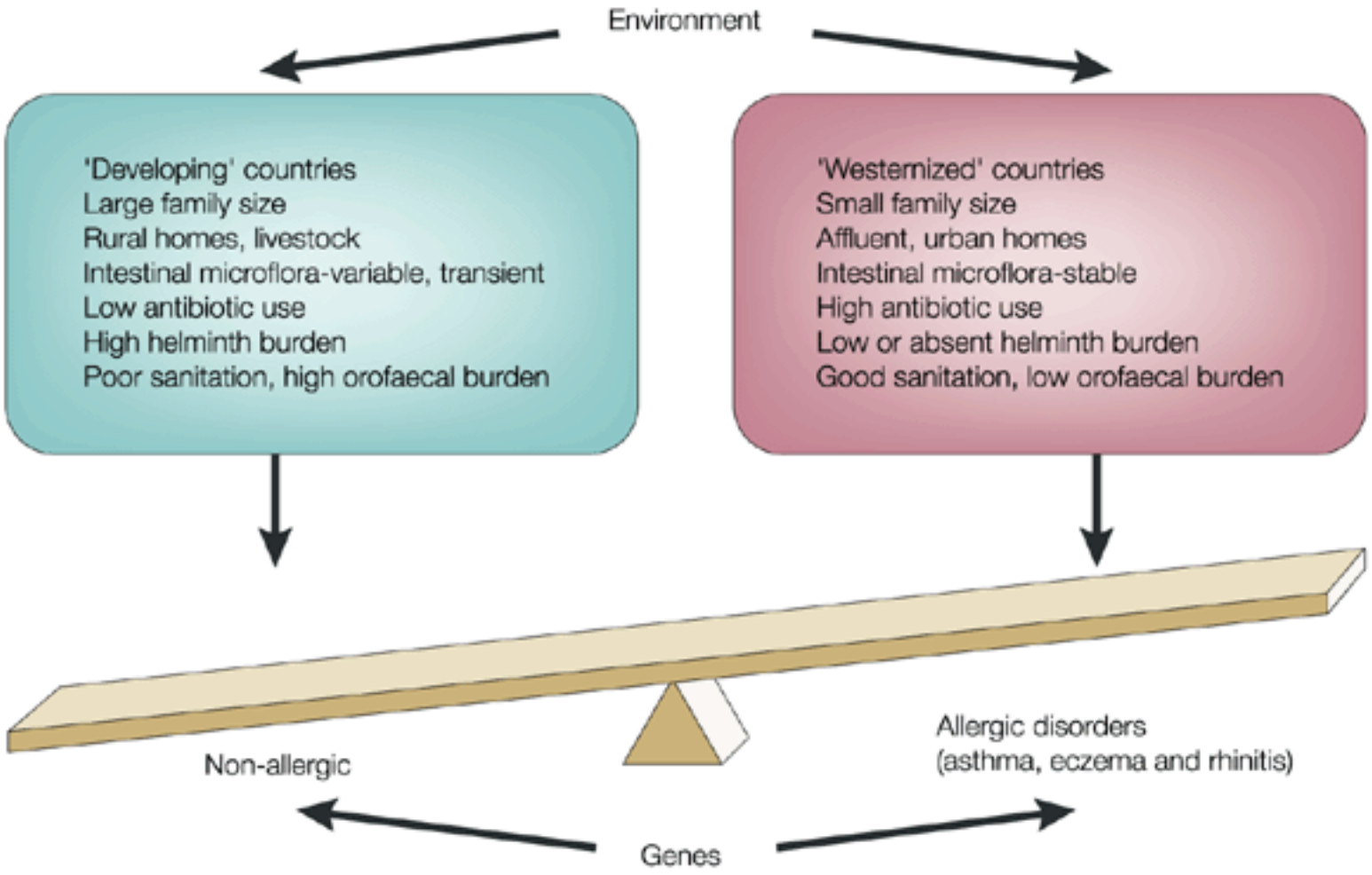


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

Hygiene-theory

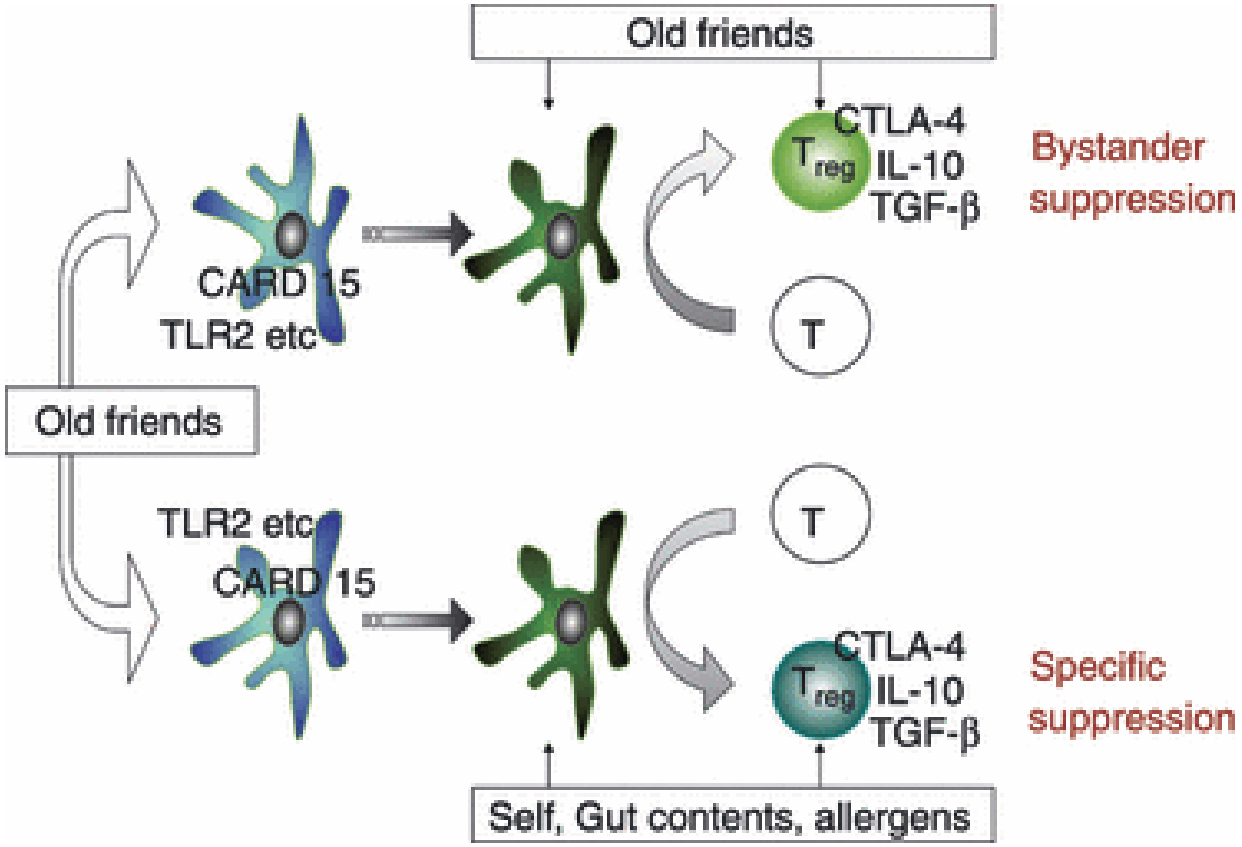


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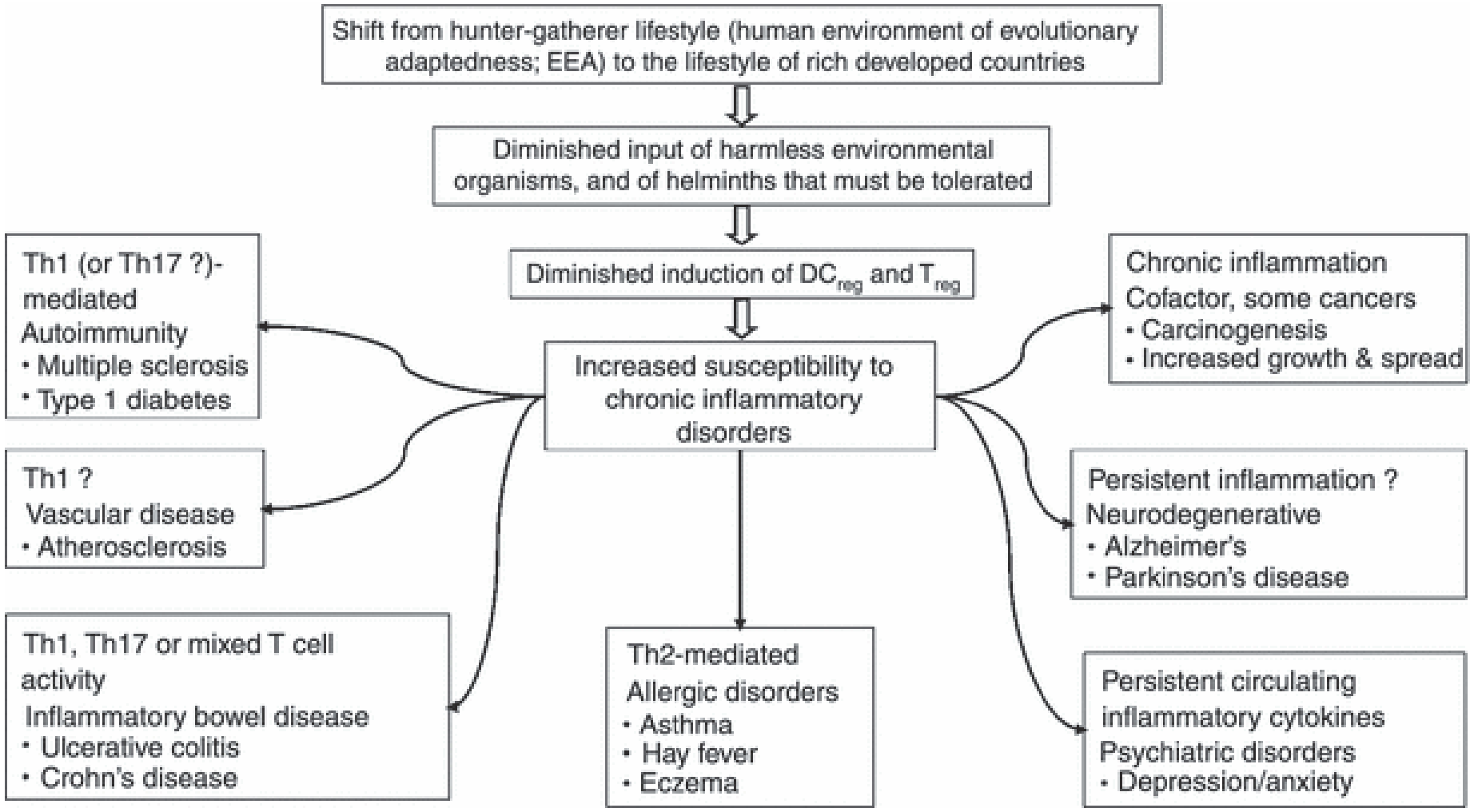
In: Marsha Wills-Karp, Joanna Santeliz & Christopher L. Karp: The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nature Reviews Immunology* **1**, 69-75 (October 2001)doi:10.1038/35095579

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

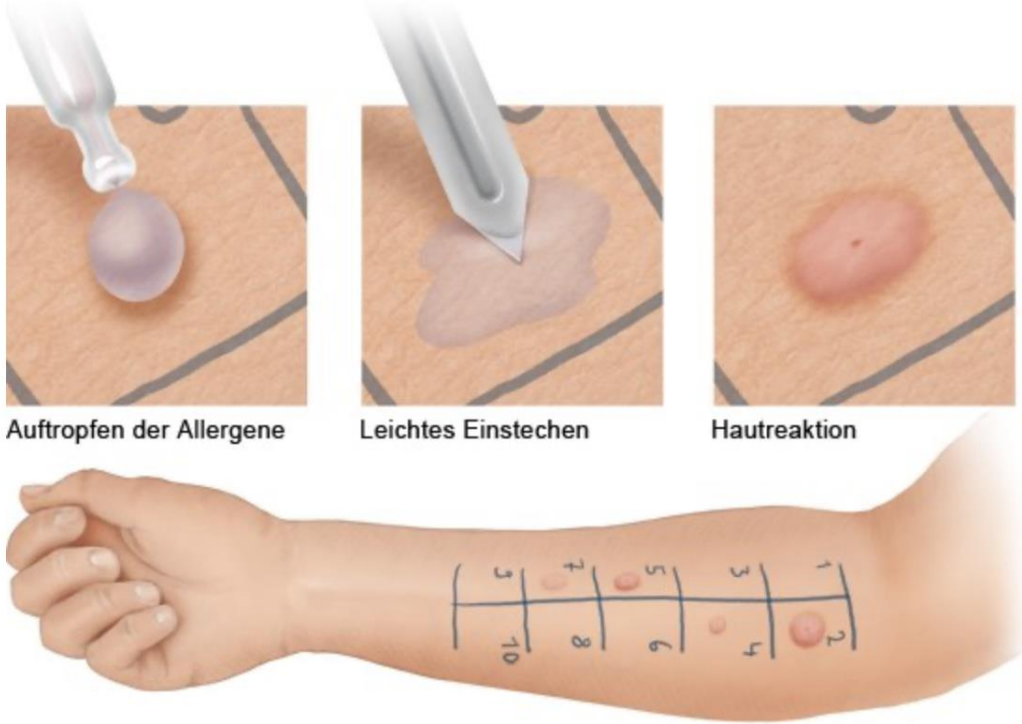
- increased susceptibility to allergic disease (eg. hay fever, asthma)
- strong IgE-answer to environmental antigens
- high **IgE** and **eosinophylia** in the blood
- Genetic background:
  - **Chromosome 11q** – high affinity FcεR β-chain polimorfism
  - **Chromosome 5q** - IL-3, IL-4, IL-5, IL-9, IL-13 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

Diagnostics

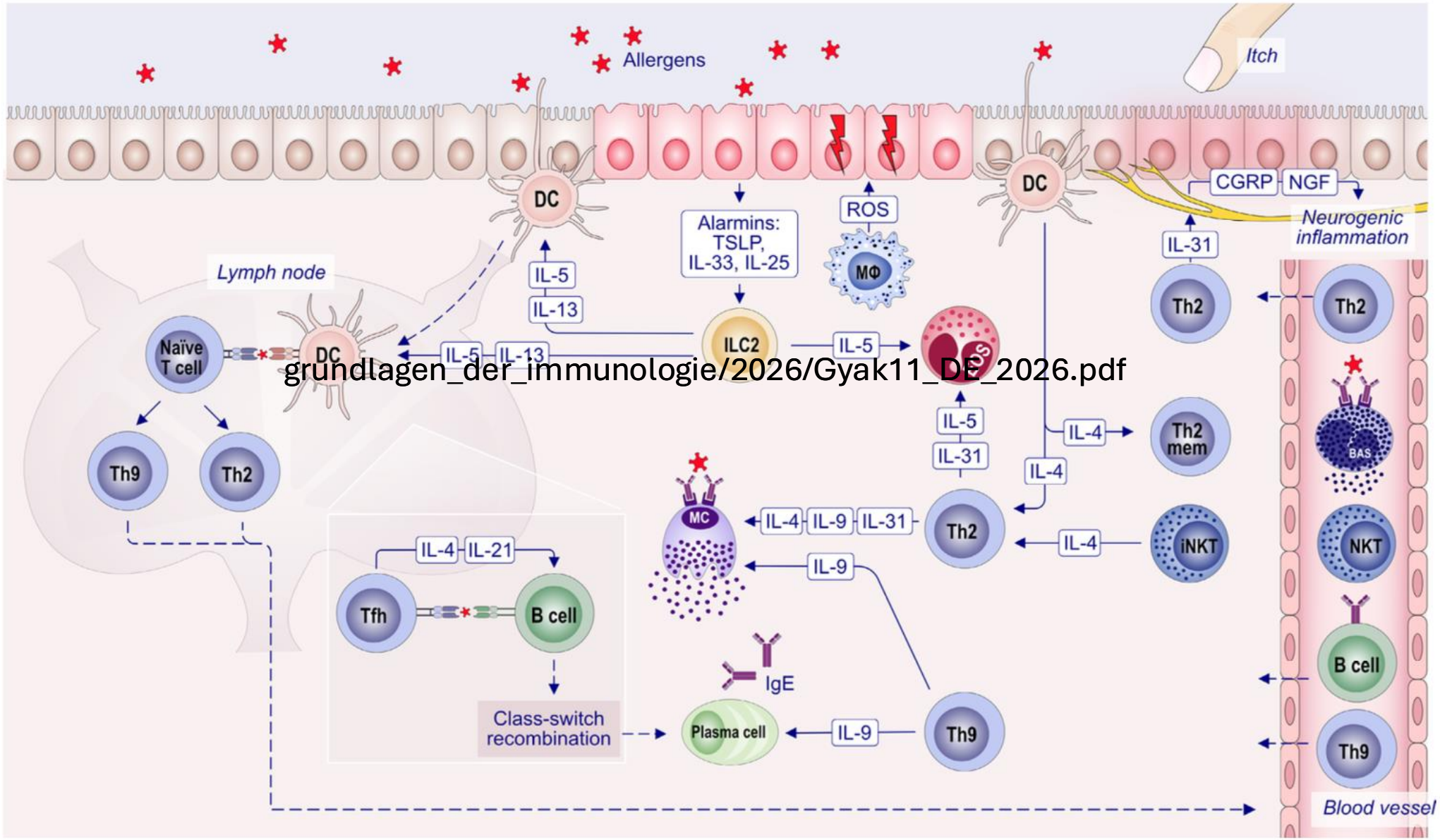
1. **Intradermal skintest (Prick test)**



Ablauf des Prick-Tests und Ergebnisse auf heller Haut

2. **ELISA: allergen-specific IgE measurement**

Typ IVb reaction



grundlagen_der_immunologie/2026/Gyak11_DE_2026.pdf

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

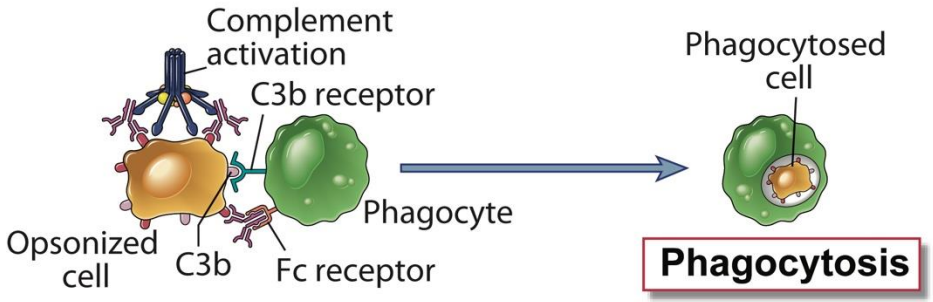
- **Antigens are usually endogenous, sometimes exogenous chemicals (haptens), which can bind to cell surface.**
- **Drug-induced-hemolitic anemia, - granulocytopenia, - trombocytopenia**
- **Diagnosis: circulating antibodies and immunfluorescence on biopsy from the lesion**
- **Therapy: anti-inflammatory-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

Type II. hypersensitivity

Type II a

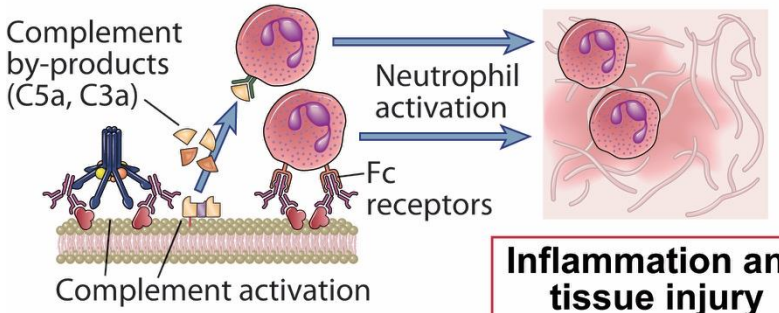
ADCC and complement-mediated lysis

Opsonization and phagocytosis



Phagocytosis

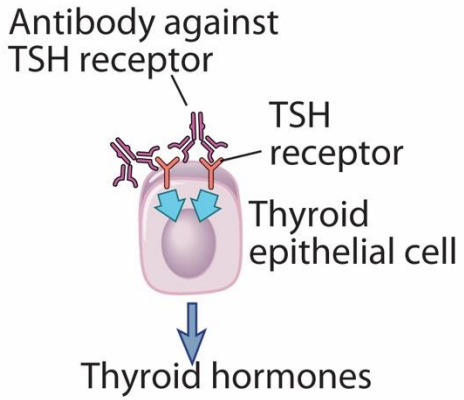
Complement- and Fc receptor – mediated inflammation



Inflammation and tissue injury

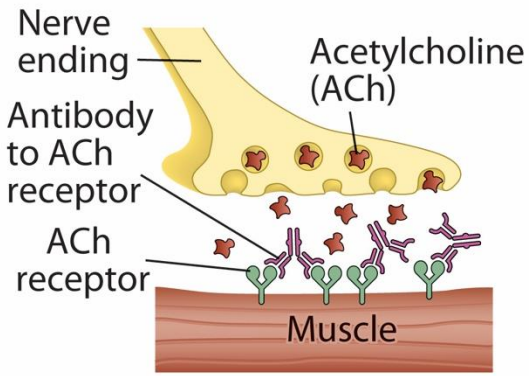
Type II b

Abnormal physiologic responses without cell/tissue injury



Antibody stimulates receptor without ligand

Graves (Basedow) disease

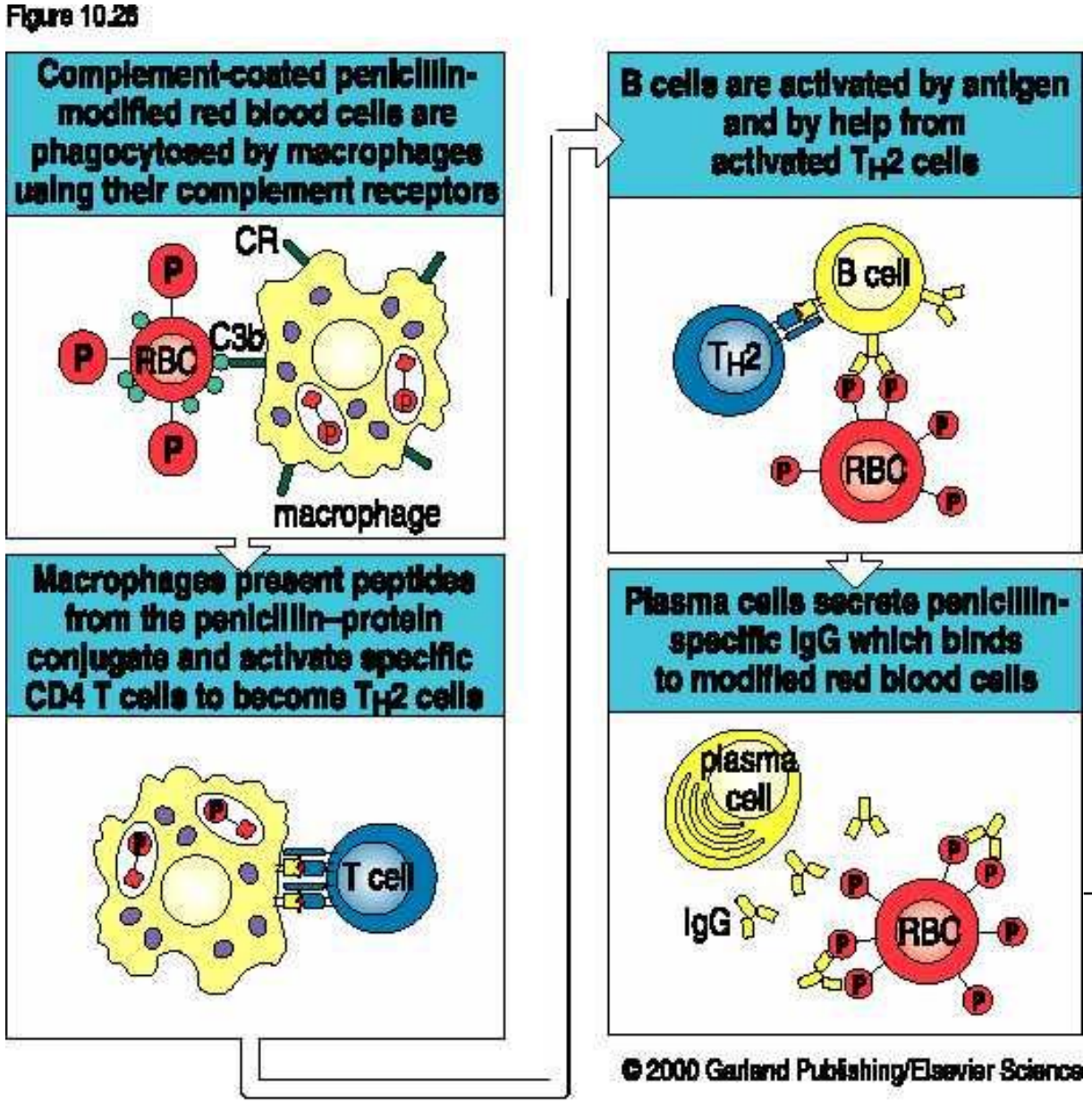


Antibody inhibits binding of ligand to receptor

Myasthenia gravis

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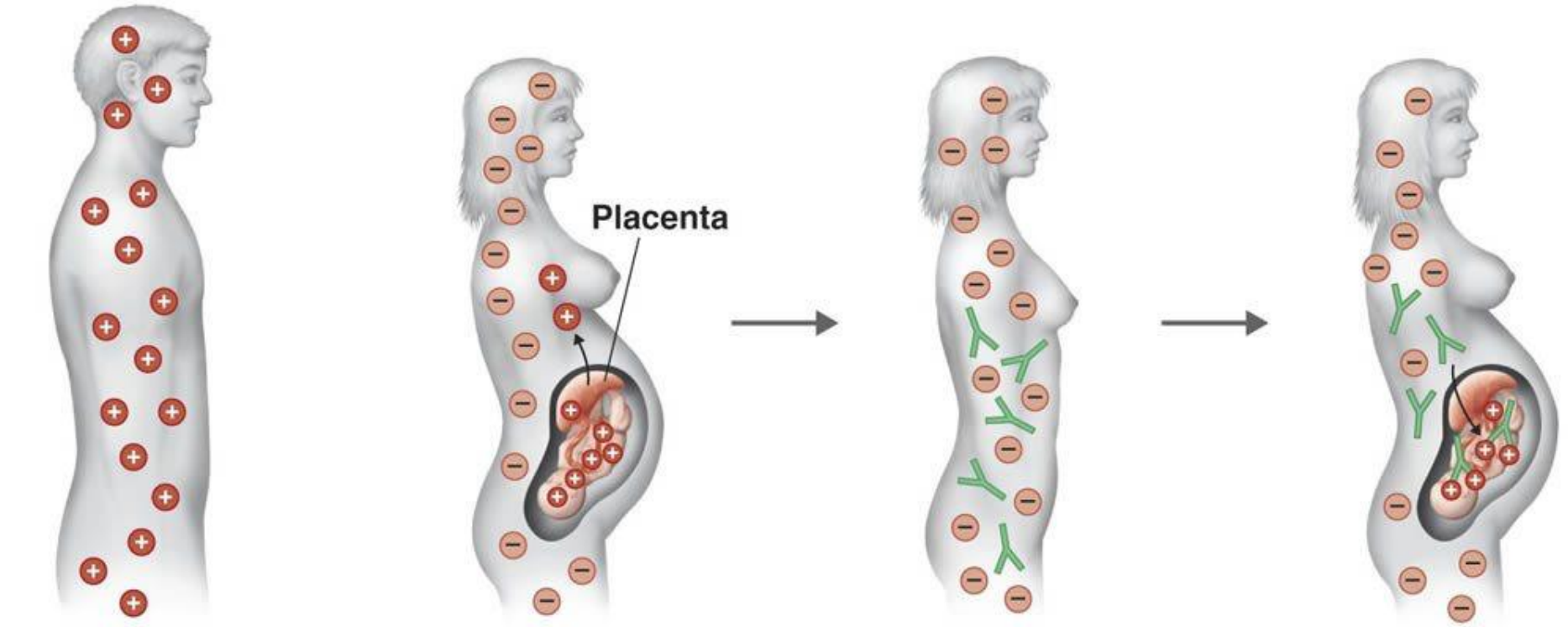
Type II. hypersensitivity -



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.

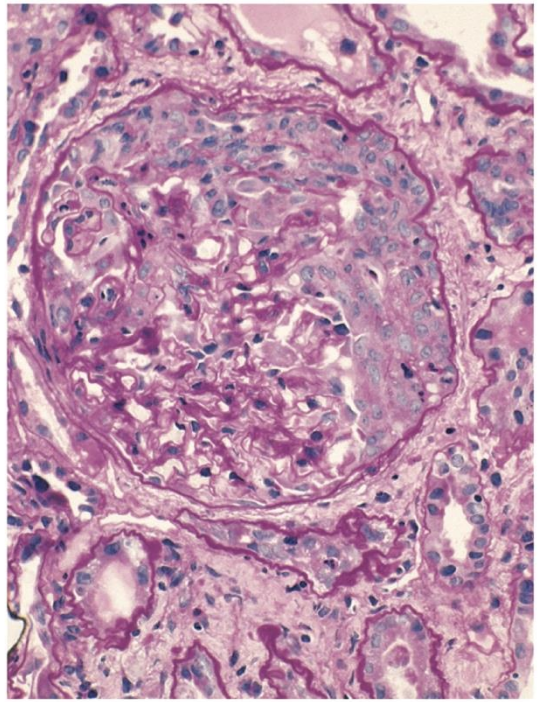
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Prophylaxis: anti-RhD antibody prophylaxis after delivery

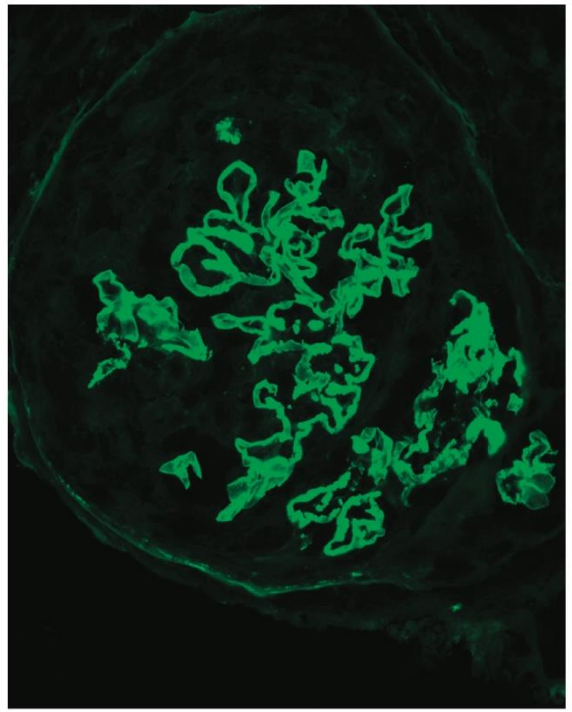
Antibody-mediated Glomerulonephritis (1)

Goodpasture-syndrome

Anti-basement membrane antibody-mediated glomerulonephritis



Light microscopy

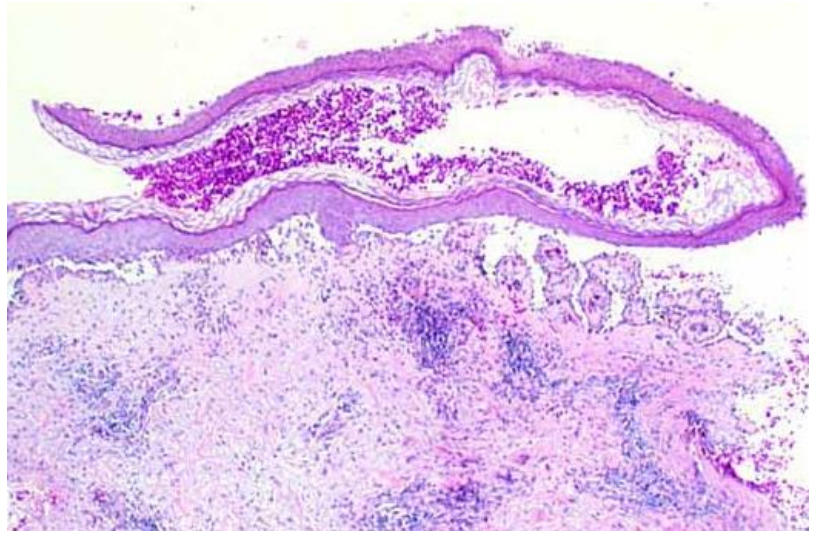


Immunofluorescence

The pathologic lesion contains antibodies, complement and neutrophils.

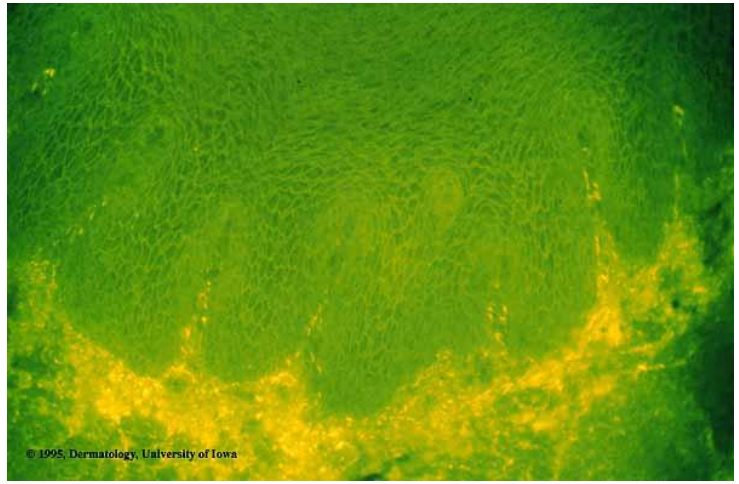
Färbung ist glatt und linear.

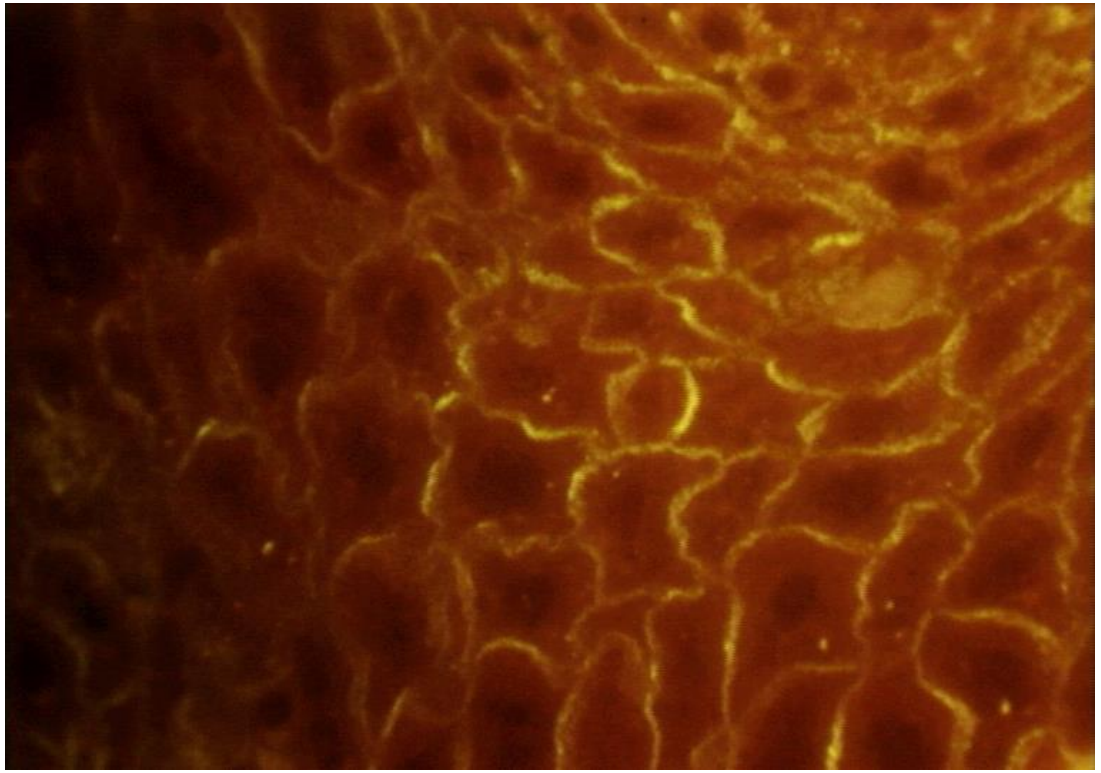
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Pemphigus vulgaris

<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

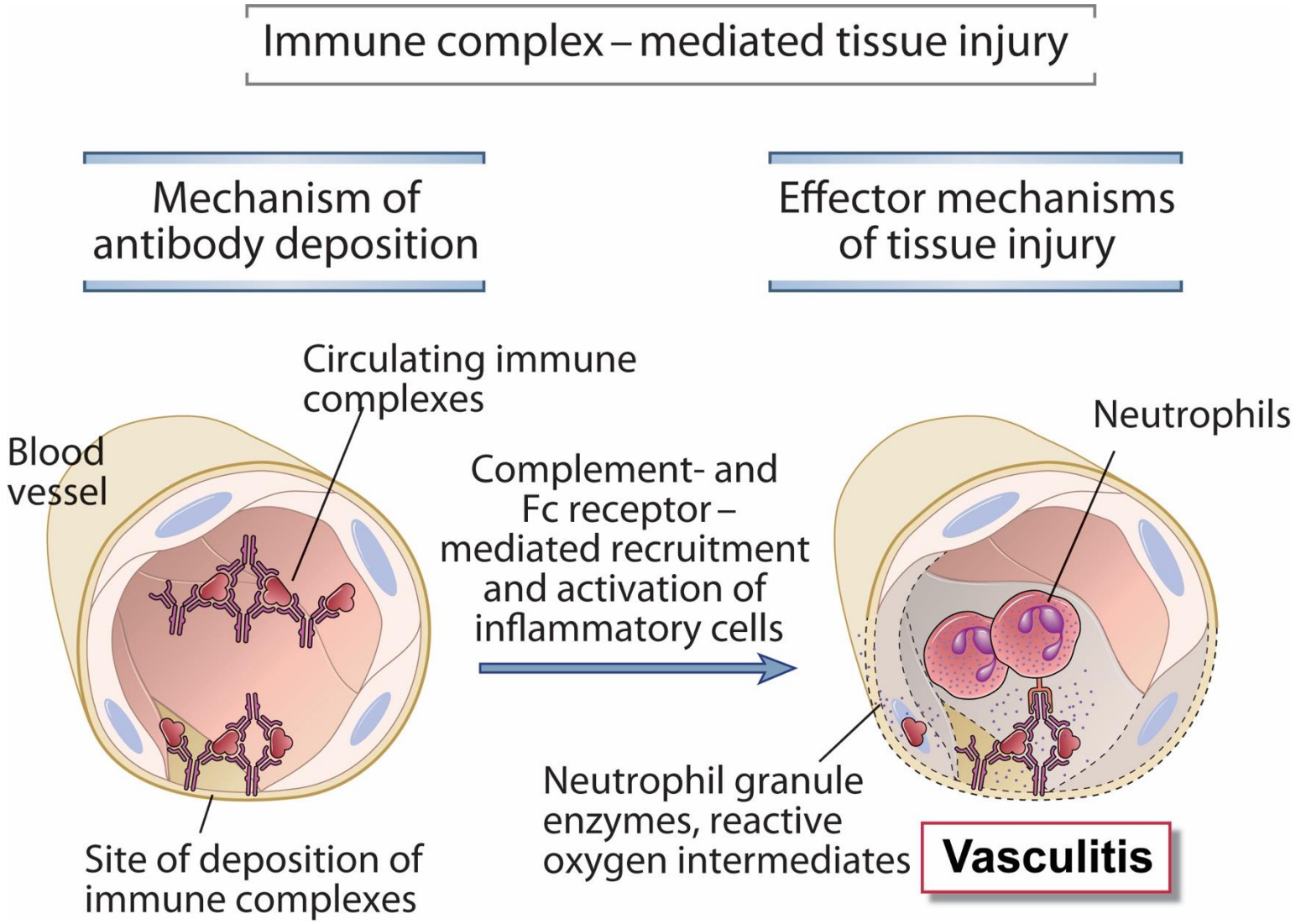


Fig. 18-1B

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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)

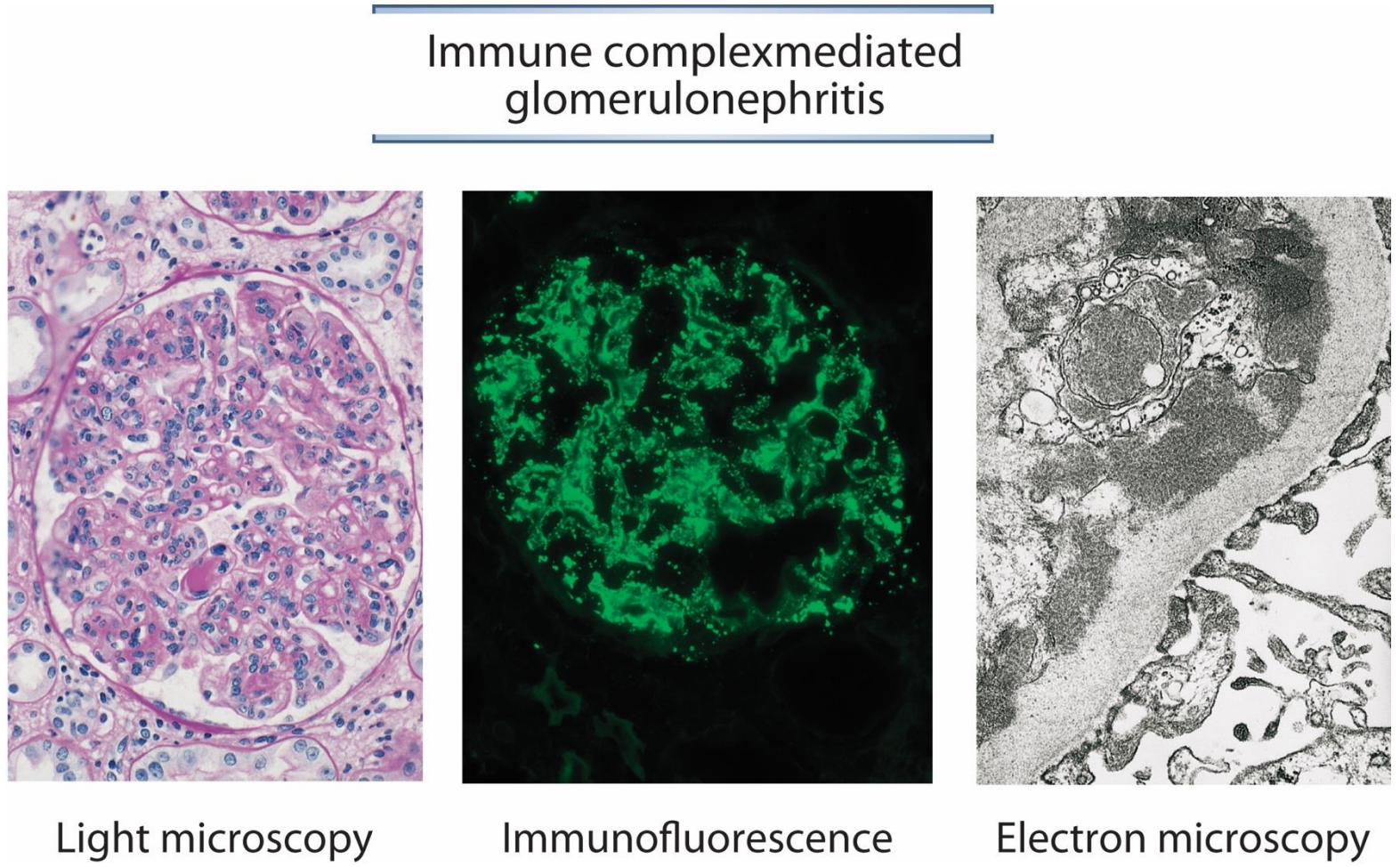
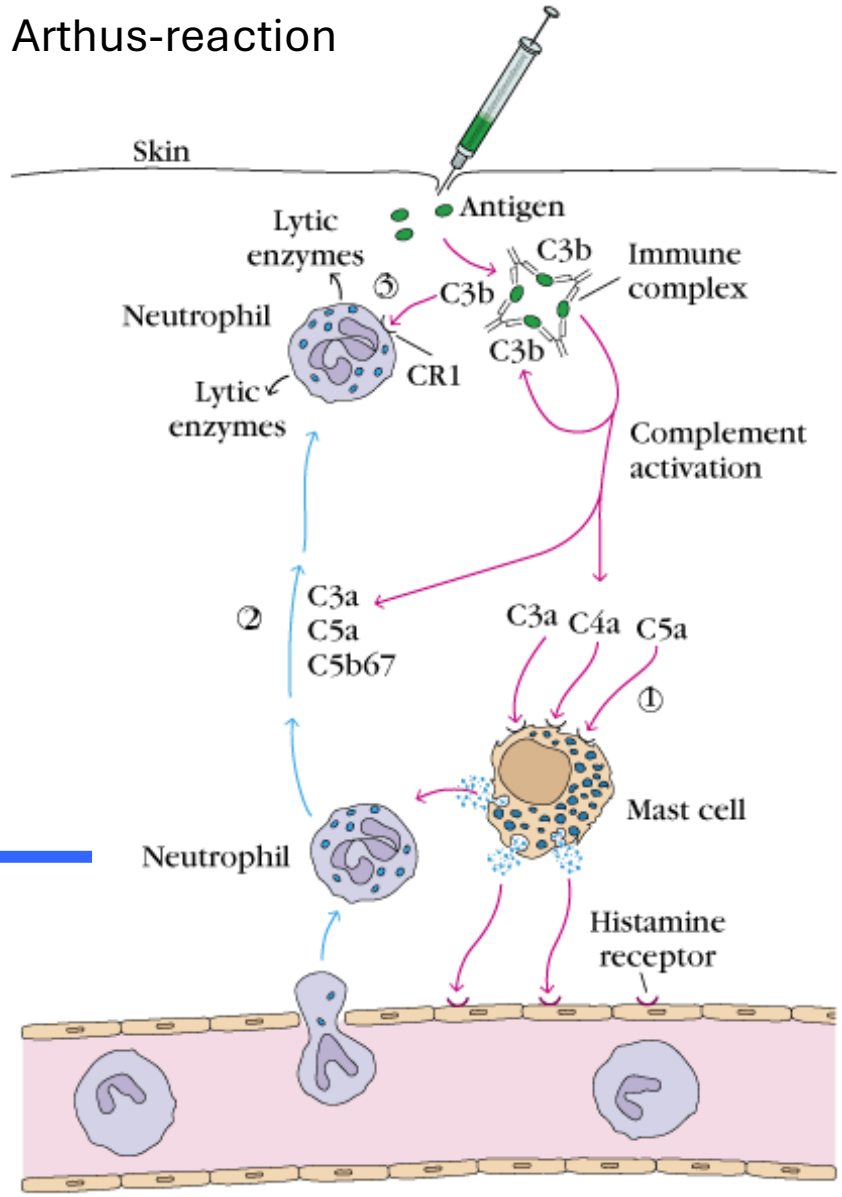


Fig. 18-3B

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Type III. hypersensitivity

Arthus-reaction



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

*Clemens von Pirquet observed after diphteria-antitoxin therapy with horse serum (1911.)

Type IV. hypersensitivity

Delayed type hypersensitivity (DTH)

See in Lectures 17-18. Celular immune mechanisms