Hypersensitivity

Lecture 12

Hypersensitivity – allergy immunedeficiency

Deficiency of regulatory function immune system

Occasionally even healthy immune system react not correctly – hyperactively

1963 – Coombs a Gell classifiction

acc.to the type of ethiological immune mechanism

Worldwide , influenced

Sensitivity is – individual (genetic,exposition – smoking, home pets)

immunological base of some clinical sy is not always clearly defined – intolerance, opium, intoxication by sea fruits - dif.dg

Terms

- Allergy – disease, during which the immune reaction to the antigen (alergen) is based on inflamation of tissues that leads to the changes of the function without elimination of antigen
- Allergen – antigen starting allergic reaction – chemicals – natural or synthetic
- Different types of chemicals – different mechanism of allergy
- HyperSenzitivita – too strong answer to antigen
- Exposition to allergen
- Types and phases of allergic reactions
- Atopic – person prepared to react in allergic – hypersensitive way via IgE

Types of alergic-hypersensitive reactions

Acc. Coombs and Gell – based on immunological mechanisms

4 types:

1. type – early reaction, atopy
2. type – cytotoxic reaction
3. type – reaction from immunocomplexes
4. type – delayed type hypersensitivity reaction - DTH

- Possibility of existence of several reactions together

Phases of hypersensitive reactions

A) Sensibilisation:

Exposition to antigen induce stage (with specific antibodies or sensibilised lymphocytes), that is clinically seen only after the next exposition to the same antigen – the time of sensibilisation is not always known

B) Fase of activity:

- reexposition,
- binding of specific effectors (Ab, cells)
- production and release of cytokines,
- clinical symptomatology

Immunological way

1) IgE-mastocyt-mediators

- early *reaction (type 1)*

2) IgG or IgM-complement-neutrofil

- *cytotoxic reaction (type 2)*

- *reaction from immunokomplexes (type 3)*

3) Sensibilised effektor Tlymohocyte - TDH
delayed hypersensitivity – lymfokines

- *delayed type, cell reaction (type 4)*

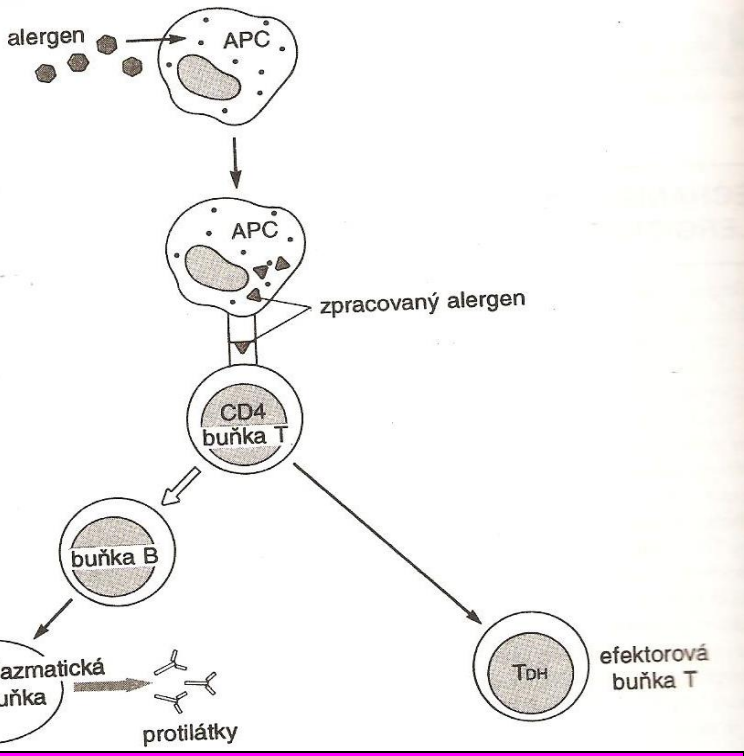
A) SENSIBILISATION
Ag and APC

Processing of antigen

Contact with CD4 TH cells TH1?TH2

B cells change to plasma cell
Productionof IK

Production of sensiibilised TDH cells



B) EFFECTOR PHASE

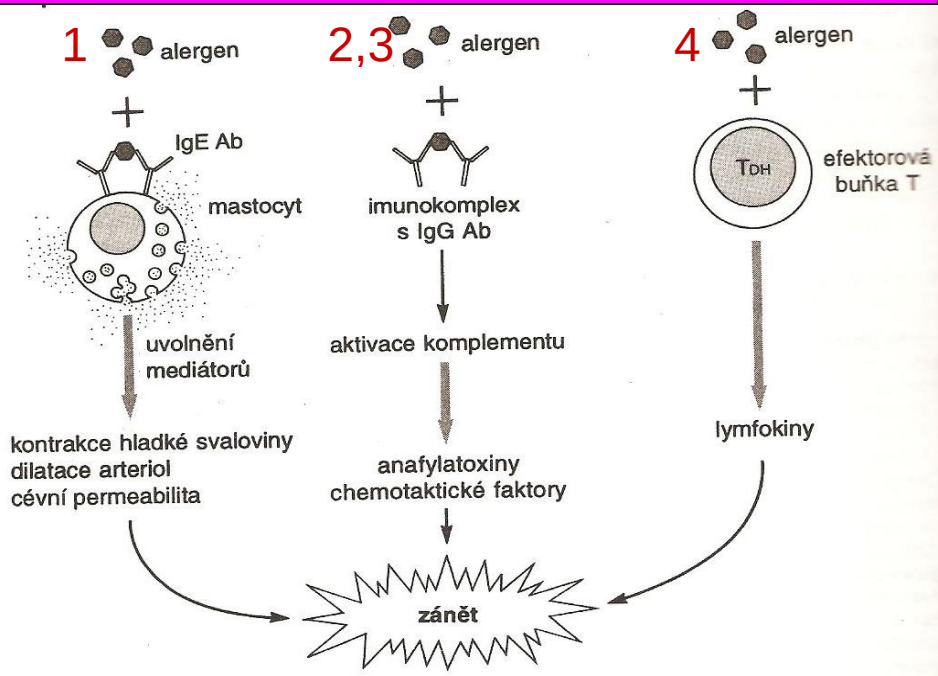
Alergen +

+ IgE
Mastocyt
mediatores

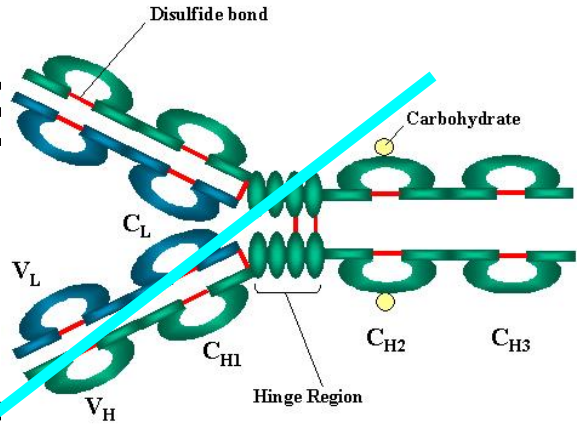
+ IgG/IgM
complement
anafylatoxines
C5

+ Tbb
lymfokines

clinical symptoms



Structure of antibodies



2 identical heavy and 2 identical light
disulfidic bound
- between heavy and light – betwee… 2 heavy
- inter-chain … intra-chain

Variable and constant regions

existence of **hypervariable regions- HVR (or complementarity determining regions. <u>Ab with different specificity have different HVR regions – regions with variaty of amino acids, that represent direct contact with Ag</u>**

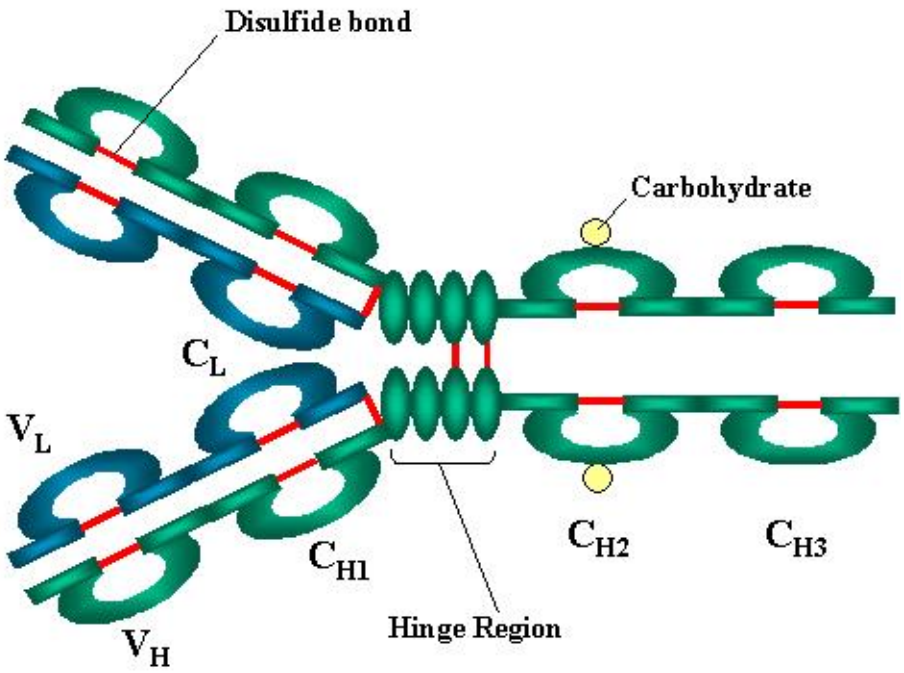
flexible joint region -

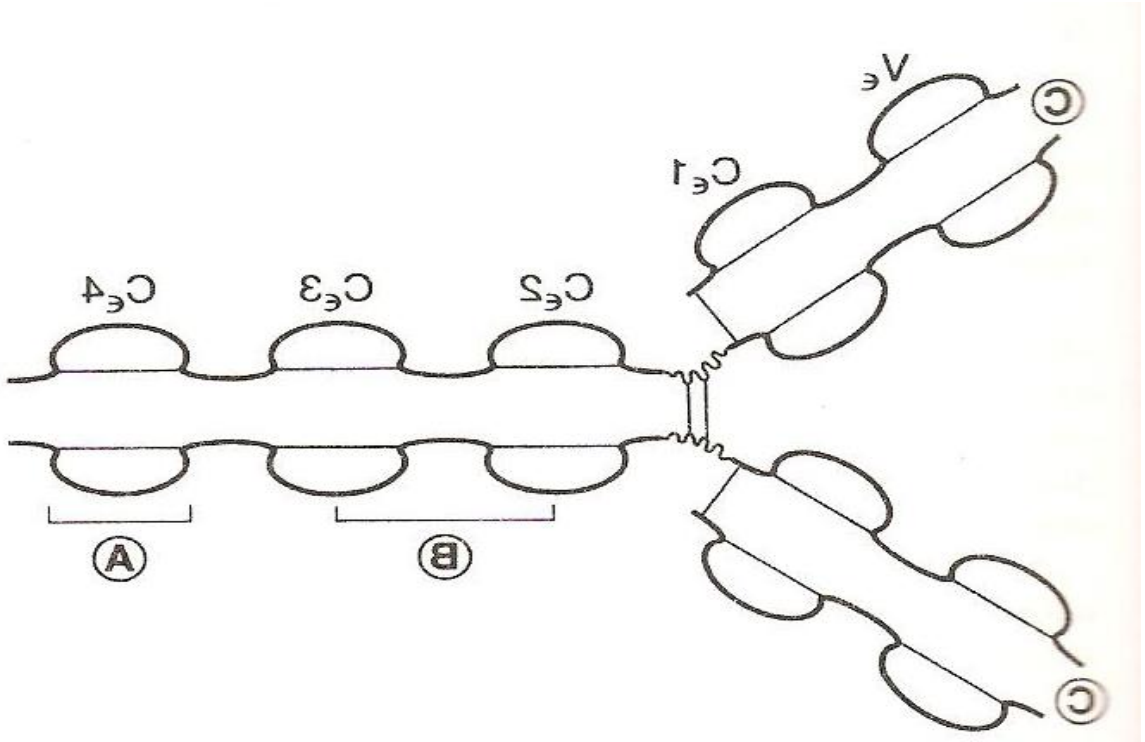
Domains – nor heavy nor light are flat.,

IgE

- Monomer
- Exceptional structure

- similar to IgG – monomer bit on H chain in constant region there are 3 domains ($Fc_{epsilon}$ 2-4) $Fc_{epsilon}$ 2 and 3 bind on specific receptors of mastocytes receptor mastocytov ($Fc_{epsilon}RI$)


Disulfide bond
Carbohydrate
C_L
V_L
C_{H1}
V_H
Hinge Region
C_{H2}
C_{H3}


A
B
C
C
$C_{\epsilon 4}$
$C_{\epsilon 3}$
$C_{\epsilon 2}$
$C_{\epsilon 1}$
V_ϵ

1.type – early reaction – atopic (4 fázy)

Sensibilisation

Exposition to antigen results in antibody answer – synthesis of specific IgE antibodies

Why and when IgE and atopy?

Way of enter – the same

Type of molecule – the same

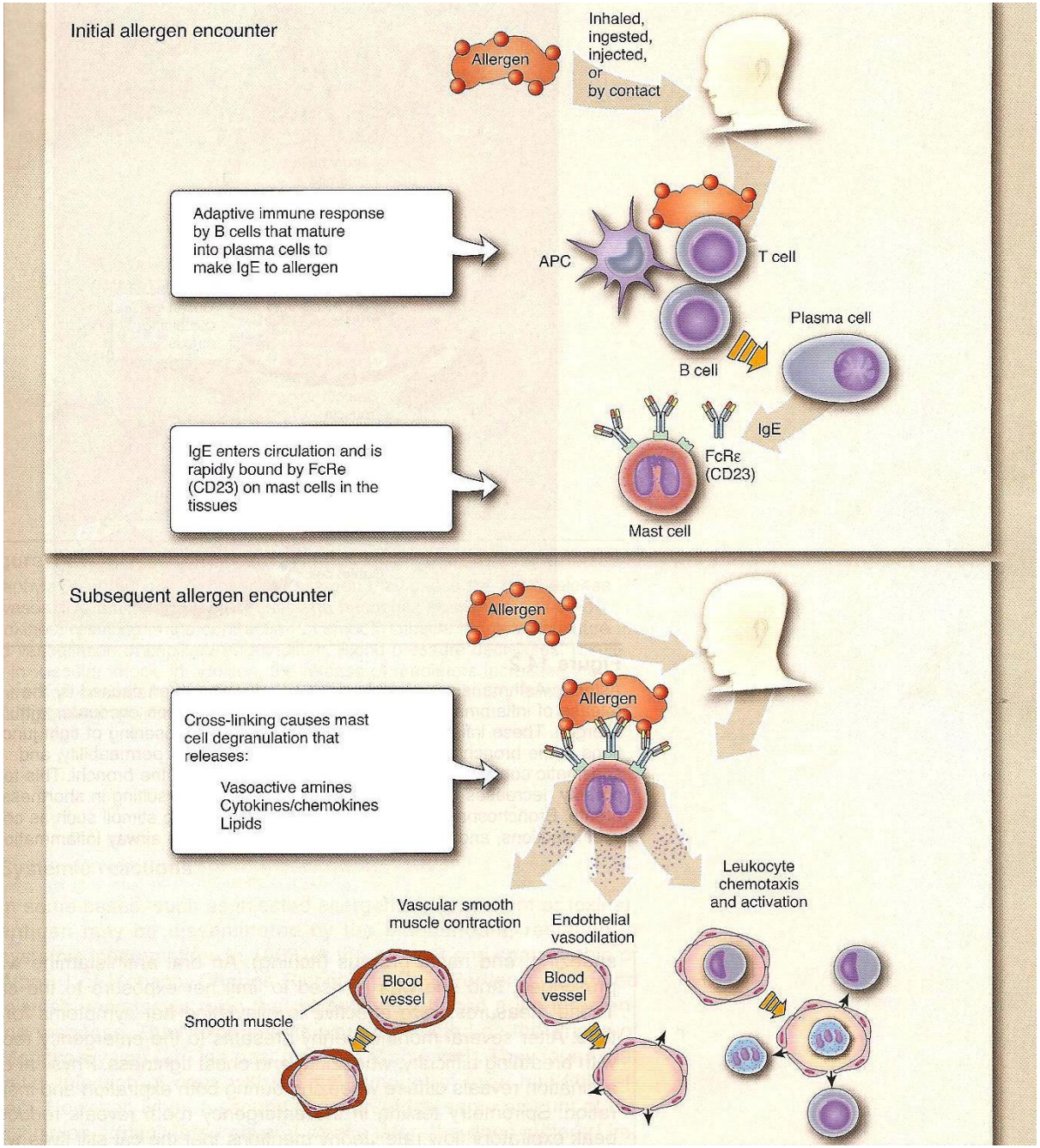
The size of the dose is important – very small amout of Ag

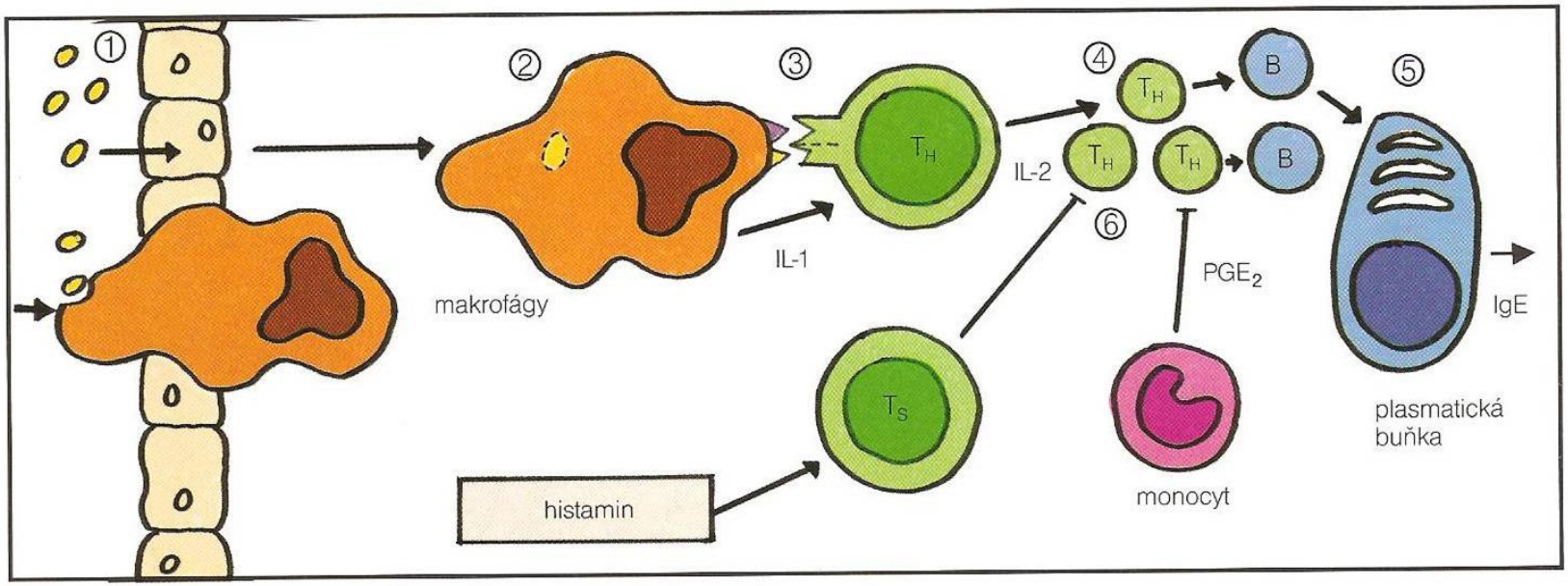
General characteristic of immunity – past contacts, stimulation of immunity, exposition to ag in postnatal period (type Th1 or Th2, theory of hygiene)

1.type – early reaction (4 fázy) cont.

- IgE adhere by their Fc fragment on the surface of mastocytes, that are in circulation
- Second exposition to ag (10-14 days later) –
  - immediate bound to Fab fragment of IgE present on mastocytes,
  - degranulation of vasoactive amines (histamín, sérotonín), lipid mediators, chemotactic substances
- Clinical symptomatology caused by effect of mediators (smooth musles contraction, vasodilatation, increased vessel permeability, bronchospasm, oedema, anaphylactic shock)

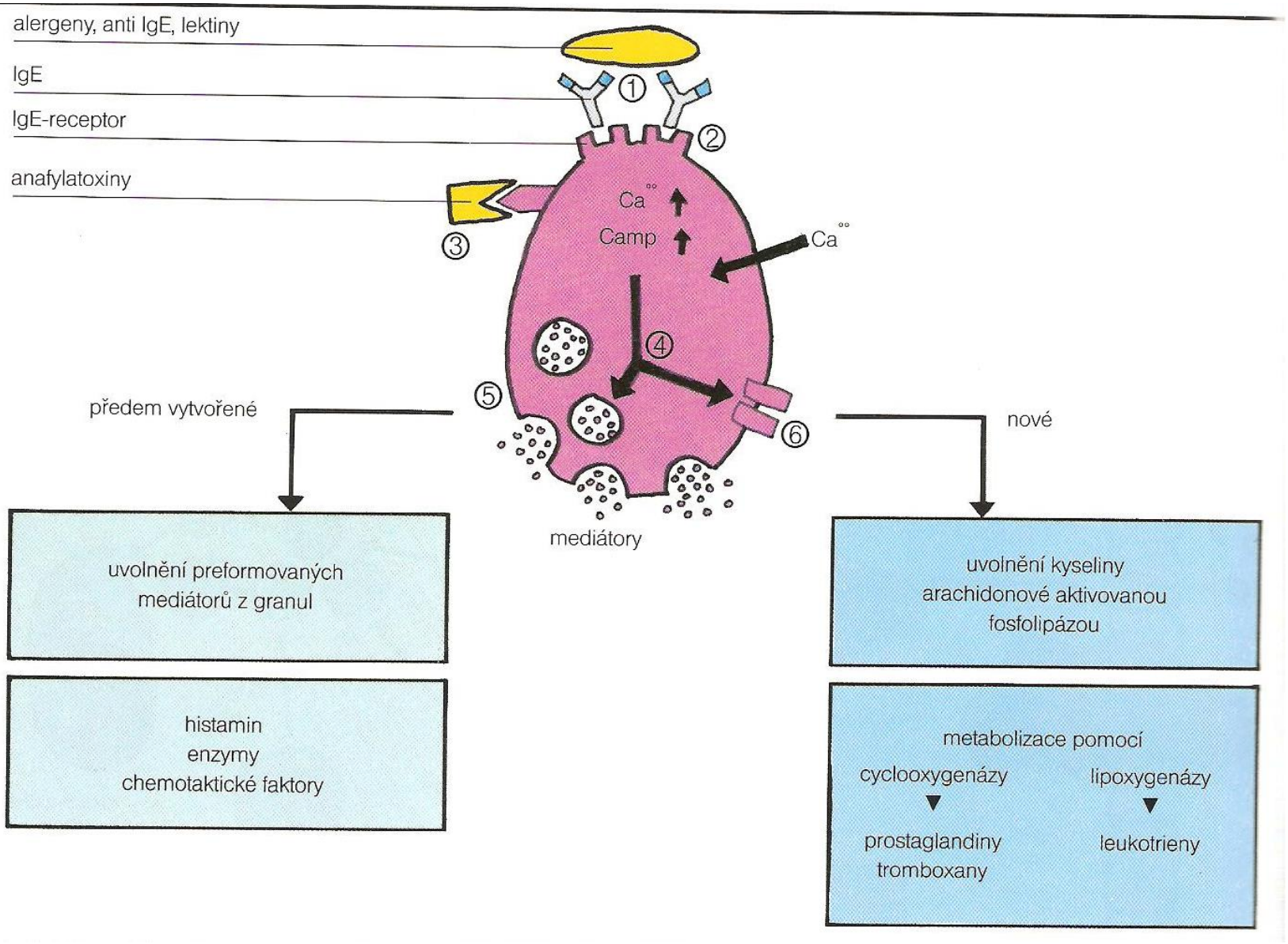
- Allergy to drugs, molds, insect bite
- Tested by – i.c. application


Initial allergen encounter
Allergen
Inhaled, ingested, injected, or by contact
Adaptive immune response by B cells that mature into plasma cells to make IgE to allergen
APC
T cell
B cell
Plasma cell
IgE
IgE enters circulation and is rapidly bound by FcRe (CD23) on mast cells in the tissues
FcRε (CD23)
Mast cell
Subsequent allergen encounter
Allergen
Allergen
Cross-linking causes mast cell degranulation that releases:
Vasoactive amines
Cytokines/chemokines
Lipids
Leukocyte chemotaxis and activation
Vascular smooth muscle contraction
Endothelial vasodilation
Blood vessel
Smooth muscle
Blood vessel



Contact of the mucous membrane – phagocyosis by macrophages – presentation to Thelper cells – IL2- and clonal selection – influence and help B cells to change to plasma cells producing IgE

– Thelper cells are controled by Tsupresor cells. In atopics the deficiency of controlled mechanism – lack of supressors lead to hyperproduction of IgE



IgE are bound on basofils in tissue and mastocytes

After reexposition – the alergen is bound to Fab fragment of IgE bound on the mastocyte, that leads to the production of signal and degranulatio of vasoactive amines from the mastocyte, that has the clinical effect (increase of permeability,

2.type – cytotoxic reaction

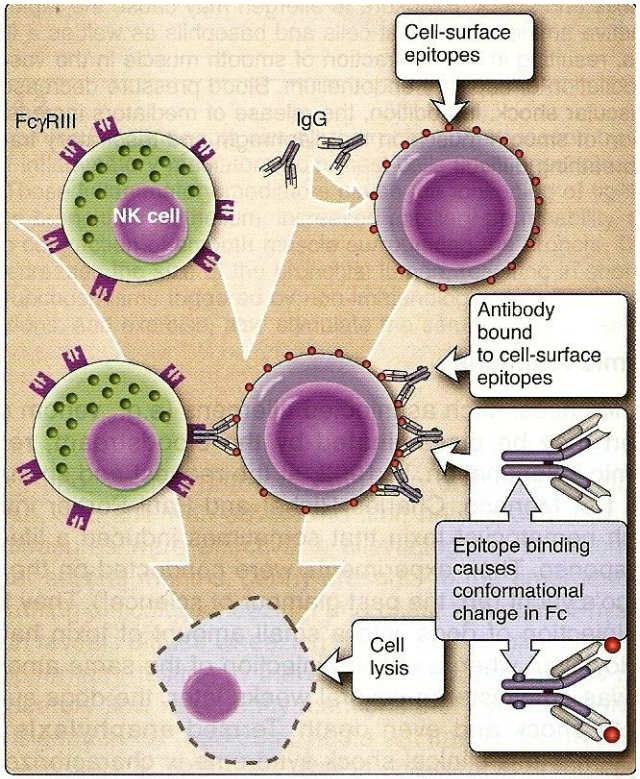
- Antibodies against antigens on the surface of self cells or tissues as the result of

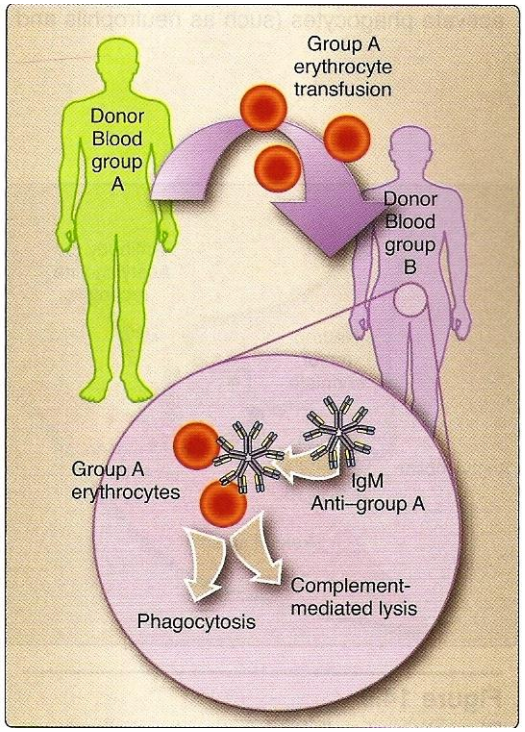
- deficiency of tolerance
- cross reactivity of antibodies against exogenous antigens, that have similar structure as self cell superficial structures
- bound of foreign antigens on the surface of self cells

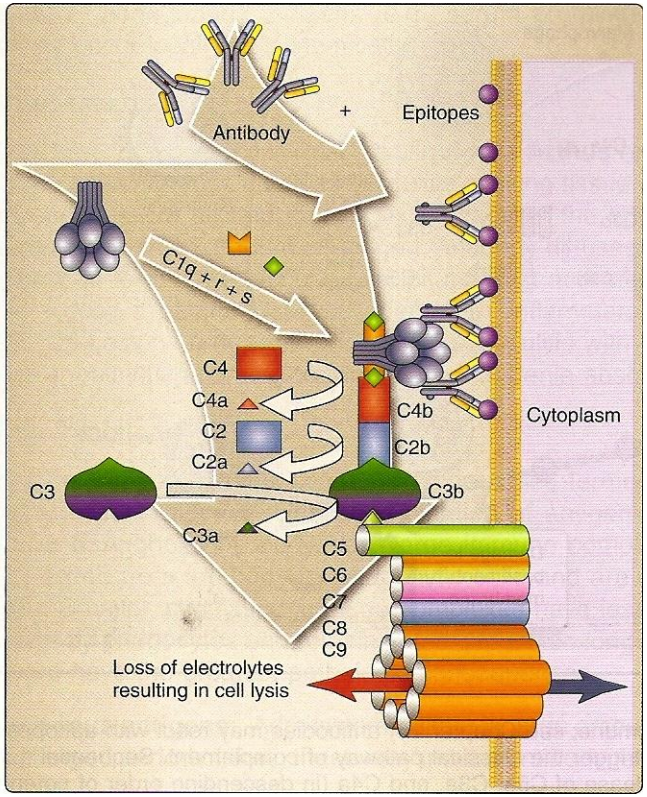
- Mechanism of destruction: opsonisation of antigen on the surface of the cell with IgG, NK cells are bound by Fc fragment of antibody and cause lysis of cell, activation of complement and lysis of the cell
- Examples:

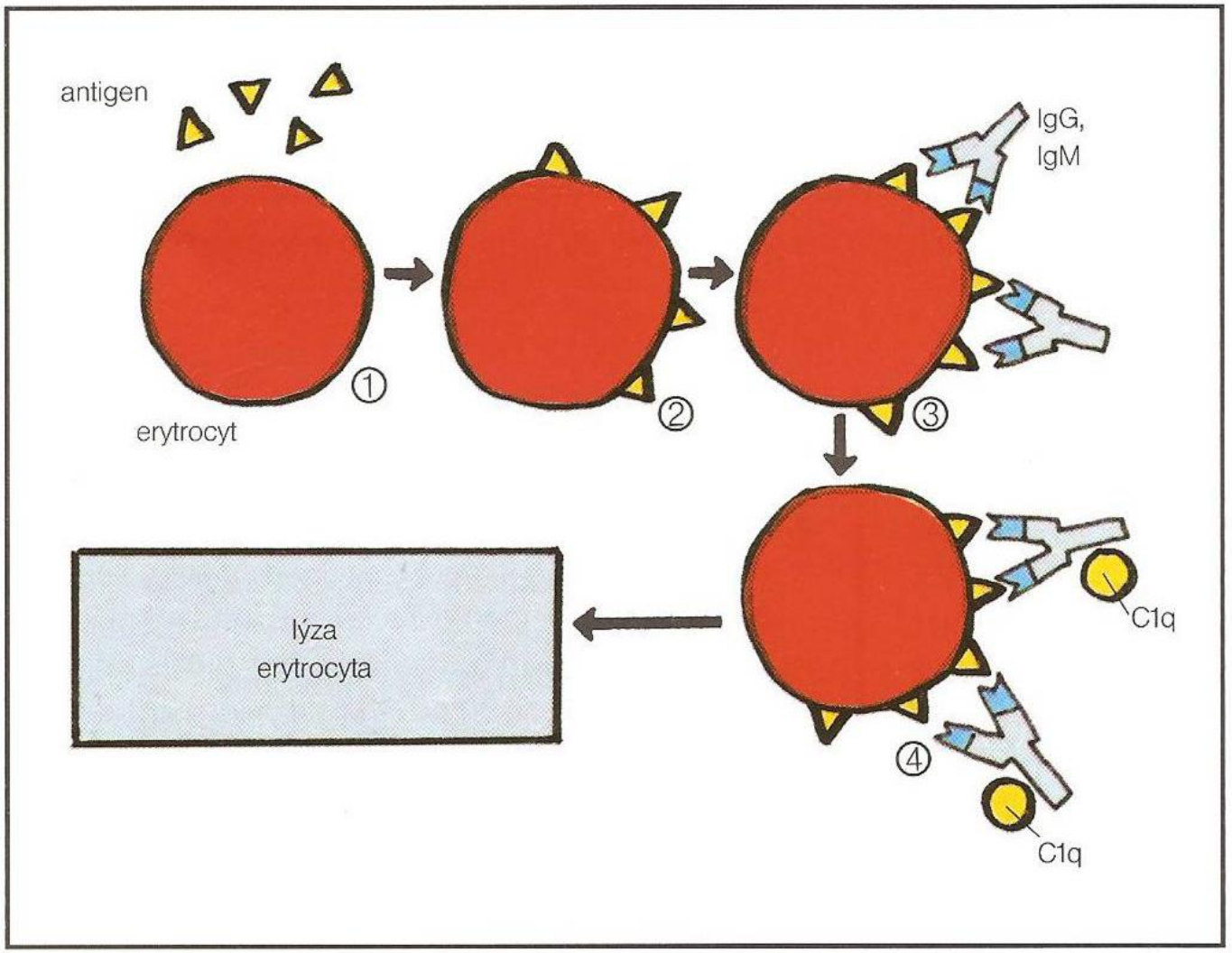
Pemfigus – IgG antibodies react with intracellular substances between epidermal cells

Haemolytical anaemia – ex.: PNC, Goodpastureov sy , Morbus hemolyticus neonatorum, posttransfusion reaction, cold aglutinins, early rejection of graft


Cell-surface epitopes
FcγRIII
IgG
NK cell
Antibody bound to cell-surface epitopes
Epitope binding causes conformational change in Fc
Cell lysis


Group A erythrocyte transfusion
Donor Blood group A
Donor Blood group B
Group A erythrocytes
IgM Anti–group A
Complement-mediated lysis
Phagocytosis

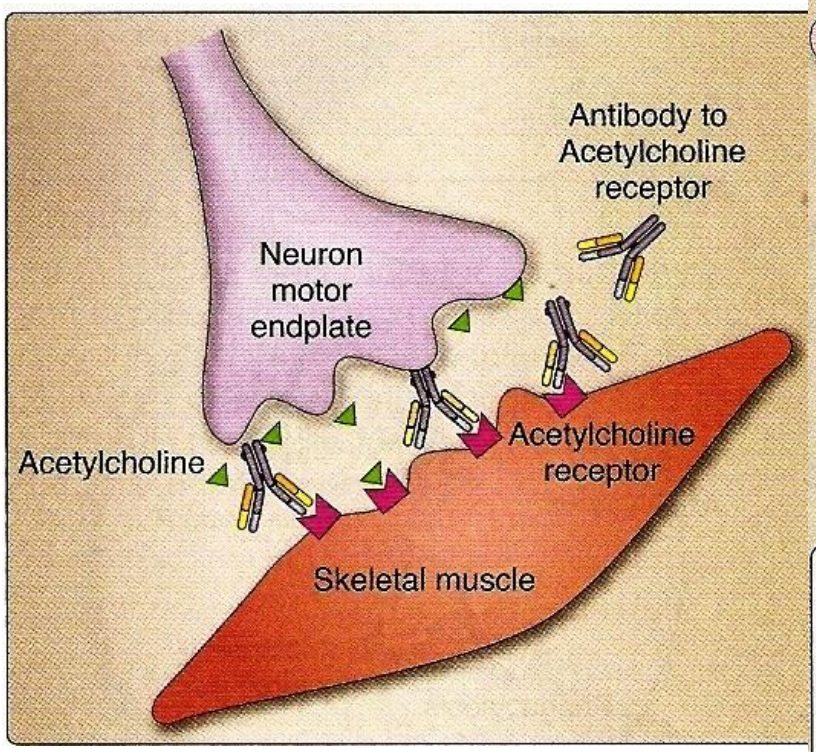

Antibody
+
Epitopes
C1q + r + s
C4
C4a
C2
C2a
C3
C3a
C4b
C2b
C3b
Cytoplasm
C5
C6
C7
C8
C9
Loss of electrolytes resulting in cell lysis

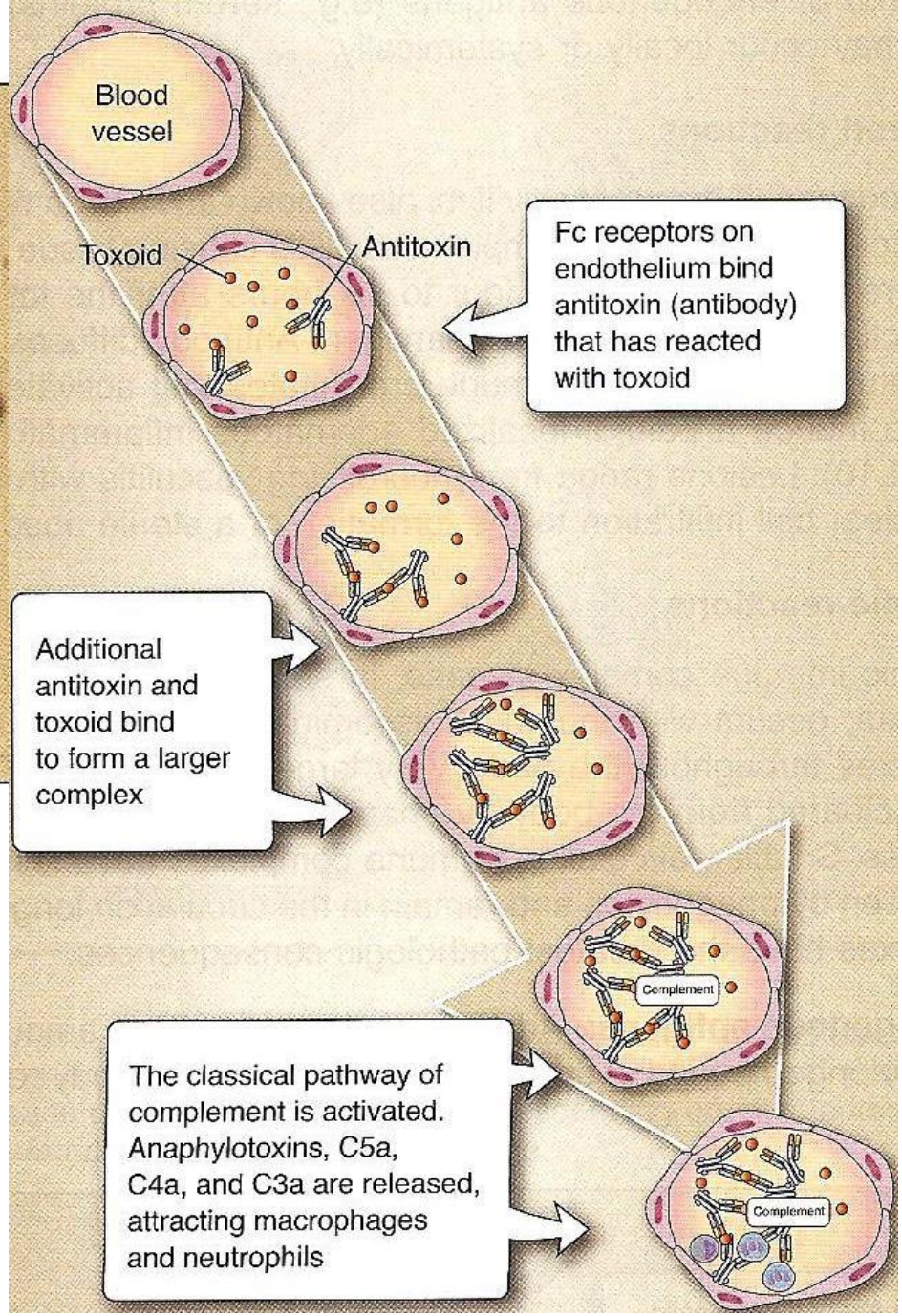


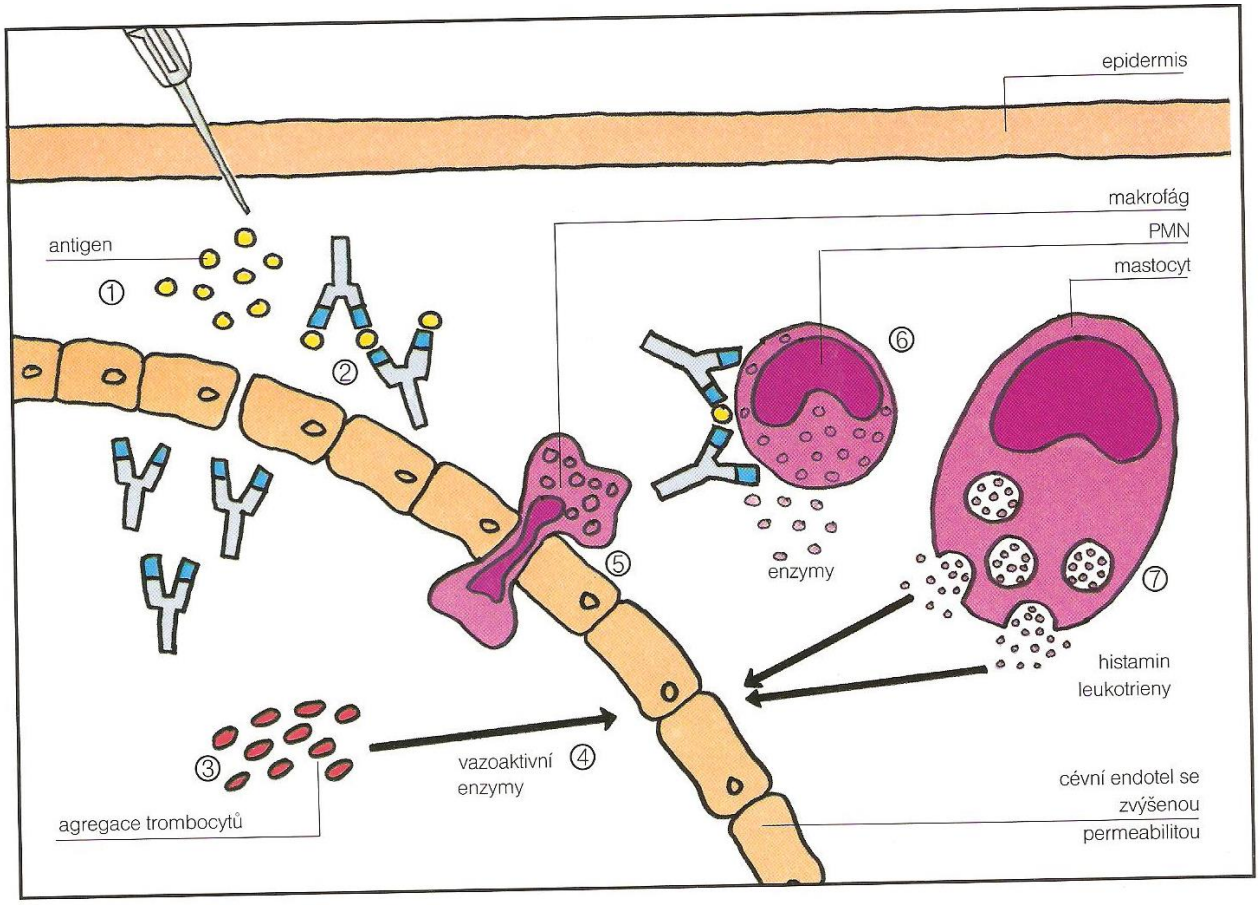
Drug induced haemolytical anaemia: Antigen (PNC) is bound on erytrocytes. Antibodies IgG/IgM are specifically bound that activates C1q leading to lysis of the cell - haemolysis

3.type hypersensitivity from immunocomplexes

- Circulating antibodies produce in time of sensibilisation react with free antigen (present in blood in time of reexposition) that leads to the production of circulating immunocoza vzniku cirkulujúcich imunokomplexov (CIK)
- They are usually eliminated by macrophages
- The disease strarts if CIK are deposited in tissue and/or if complement is activated (production of anaphyltoxins and chemoattractants)
- Usually after chronical exposition ot antigen – longlasting load of macrophages(chronical streptococcal infection, autoimmune diseases, LE, alergic alveolitis)
- Depends on the type of Ag an Ab and size of immunocomplexes (small are in circulation, big are eliminated by macrophages, medium can be deposited)


Antibody to
Acetylcholine
receptor
Neuron
motor
endplate
Acetylcholine
Acetylcholine
receptor
Skeletal muscle


Blood
vessel
Toxoid
Antitoxin
Fc receptors on endothelium bind antitoxin (antibody) that has reacted with toxoid
Additional antitoxin and toxoid bind to form a larger complex
Complement
The classical pathway of complement is activated. Anaphylotoxins, C5a, C4a, and C3a are released, attracting macrophages and neutrophils
Complement



Arthus reaction – local reaction of immunocomplexes – test for existence or risk of the 3rd type of hypersensitivity (serzm serum disease)

Injected antigen + IgG = IK — activation of complement, agregation of trombocytes, release of mediators, increase of permeability of vessels, local oedem, PMNL

Value of CIK – activity of the disease (40j normal value)

4. type - delayed type hypersensitivity

- 1.- 3. type are expressed within minutes after reexposition (20 minutes – to several hours)
- 4. type
  – after more that 12 hrs
  – late type – there are 4 clinical subtypes
  a) Jones Mote
  b) kontact allergy
  c) tuberculin reaction
  d) granulomatouse reaction

Prejavia sa

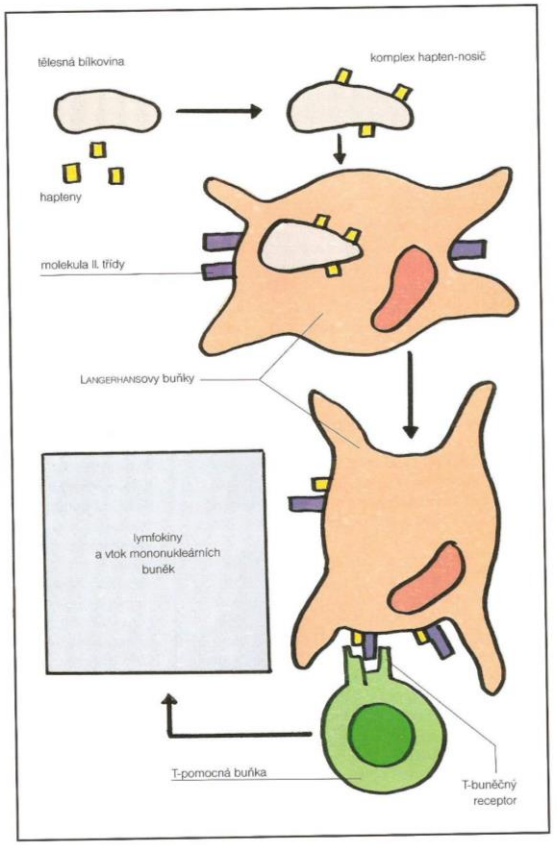
za 1 – 3 dni

za 14 a viac dní

Jones Mote – cutaneous basofil hypersensitivity

- Very inferquent
- Locel reaction
- Basofilic infiltration under epidermis
- Induced by soluble antigens
- After 24 hrs oedem of the skin that persists one week

Kontaktná alergia, dermatitída, kontaktný ekzém



- Po kontakte kože s alergénom
- MX po 2-3 dňoch
- Nízkomolekulárne haptény
  –prenikajú kožou
  – viažu sa na telesné proteiny
  –senzibilizácia,
  –aktivita Langerhansových buniek:

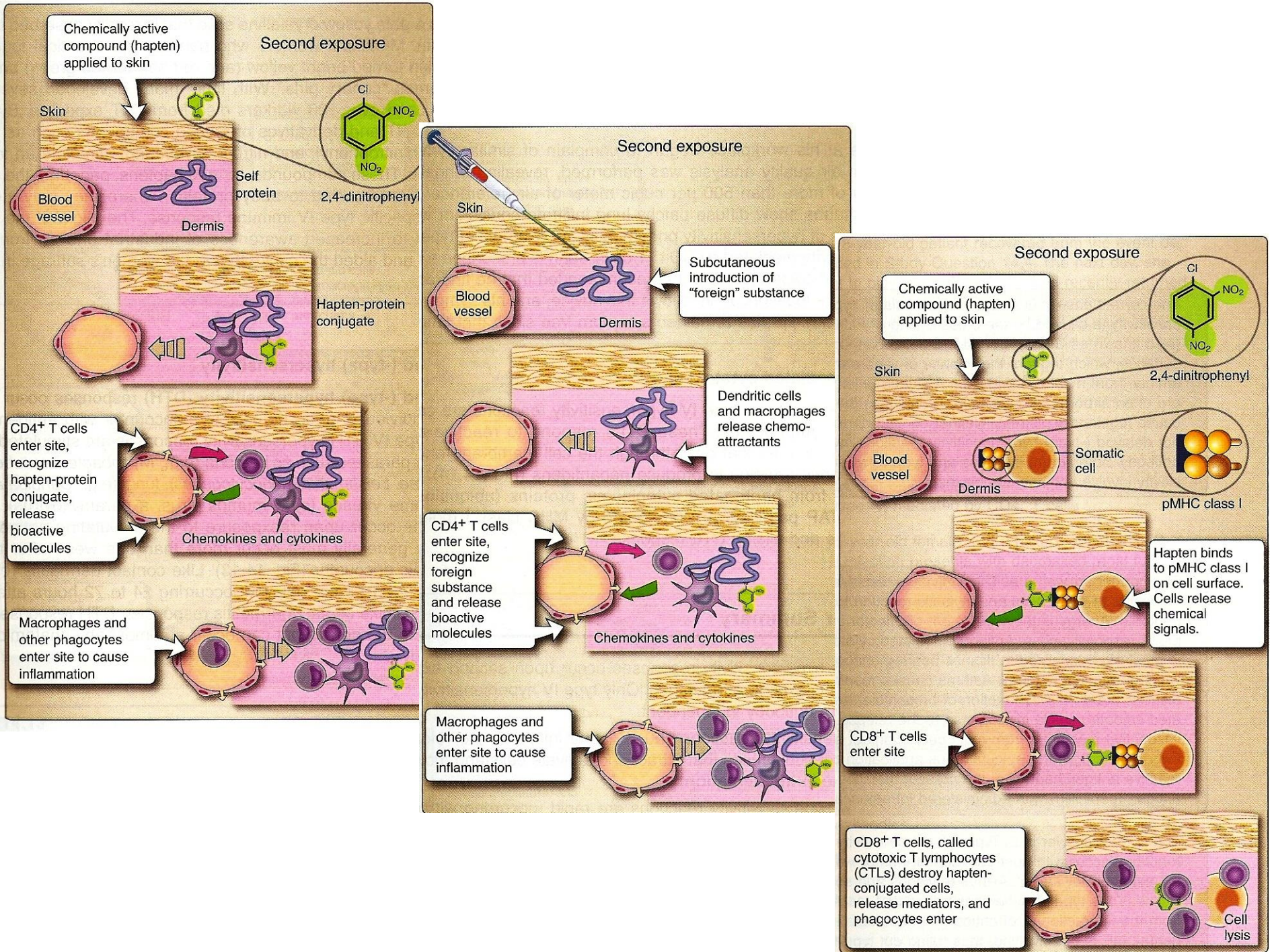
fungujú ako fagocyty,

tkanivové makrofágy

APC – uvoľnenie lymfokínov,

mononukleárny infiltrát, pľuzgieriky

epidermálna reakcia


Second exposure
Chemically active compound (hapten) applied to skin
Skin
Self protein
2,4-dinitrophenyl
Blood vessel
Dermis
Hapten-protein conjugate
CD4+ T cells enter site, recognize hapten-protein conjugate, release bioactive molecules
Chemokines and cytokines
Macrophages and other phagocytes enter site to cause inflammation
Second exposure
Skin
Subcutaneous introduction of "foreign" substance
Blood vessel
Dermis
Dendritic cells and macrophages release chemo-attractants
CD4+ T cells enter site, recognize foreign substance and release bioactive molecules
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Somatic cell
pMHC class I
Hapten binds to pMHC class I on cell surface. Cells release chemical signals.
CD8+ T cells enter site
CD8+ T cells, called cytotoxic T lymphocytes (CTLs) destroy hapten-conjugated cells, release mediators, and phagocytes enter
Cell lysis

Tuberkulínová reakcia

- Robert Koch

Subkutánna aplikácia tuberkulínu (lipoprotein mykobaktérií)
pocit ochorenia s teplotou a lokálny edém a indurácia

Dnes: presne odmerané množstvo na testovanie špecifickej imunity proti mykobaktériám

Do 24 hodinách edém a indurácia 15 mm infiltrácia monocytmi a makrogágmi. Pri pretrvávaní antigénnej expozície – až granulomatózny zápal

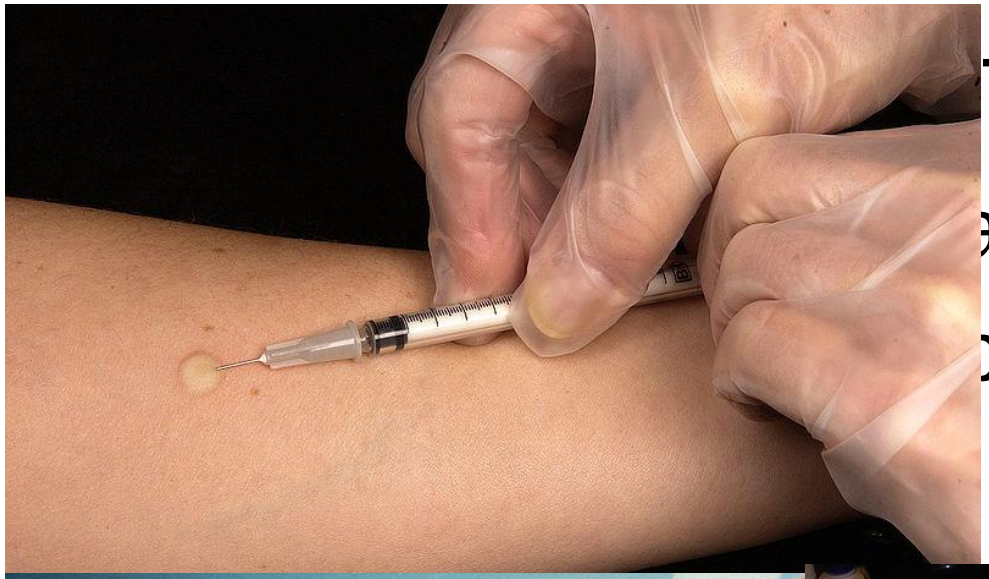
Anergia – negatívna tuberkulínová reakcia napriek expozícii (pri aplikácii spolu s kortisonom)

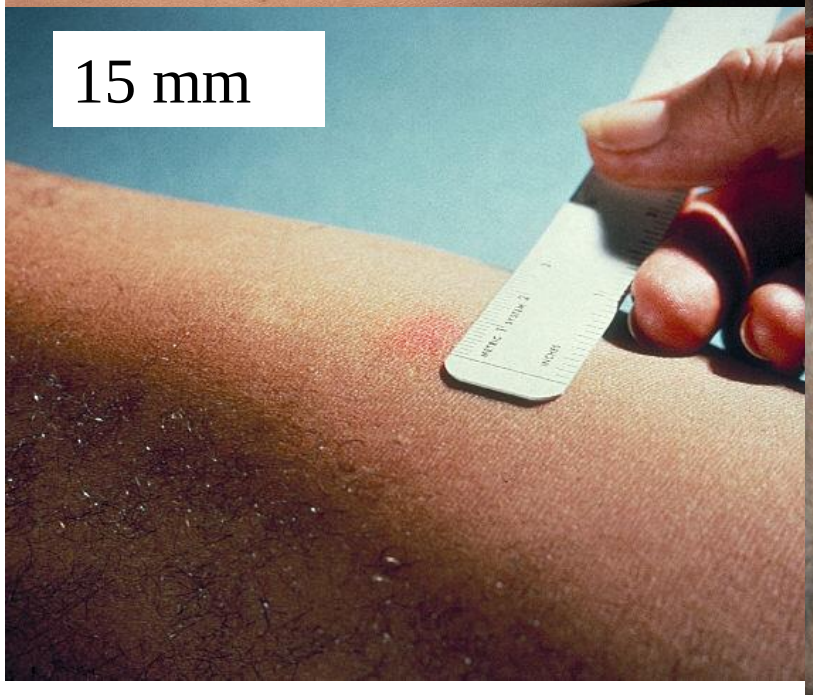
Mantoux test

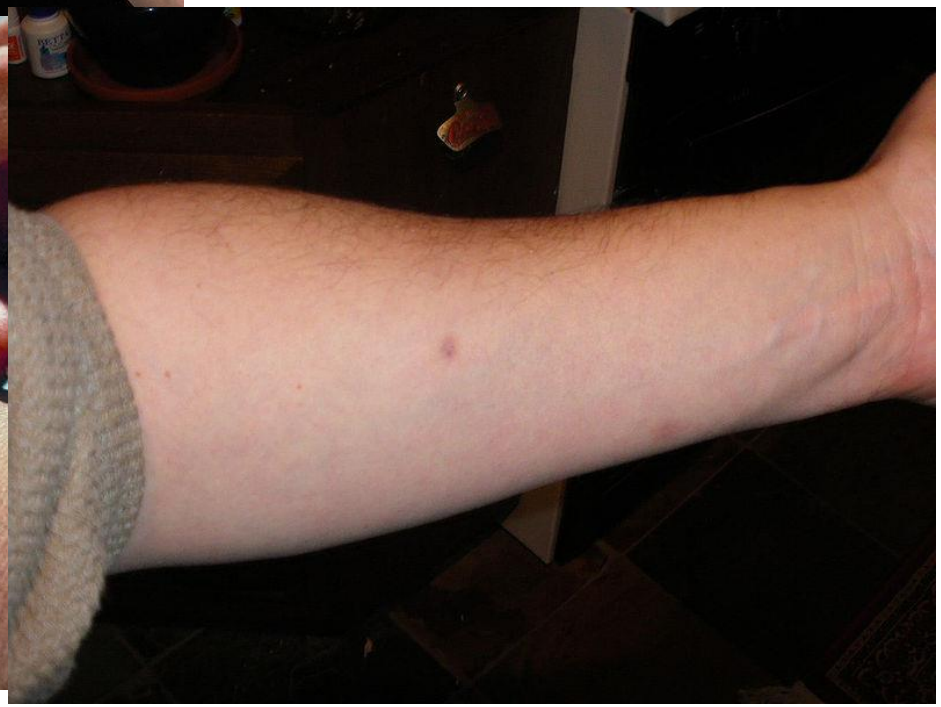
- 0 – 15 mm – anergia (neprítomnosť špecifickej bunkovej imunity) preočkovanie
- 15 mm – primeraná reakcia, edém a indurácia
- 15 a viac – hyperergia – pravdepodobná kontinuálna stimulácia - existencia expozície antigénu – ochorenie, kontakt – depistáž, rtg aj v okolí.

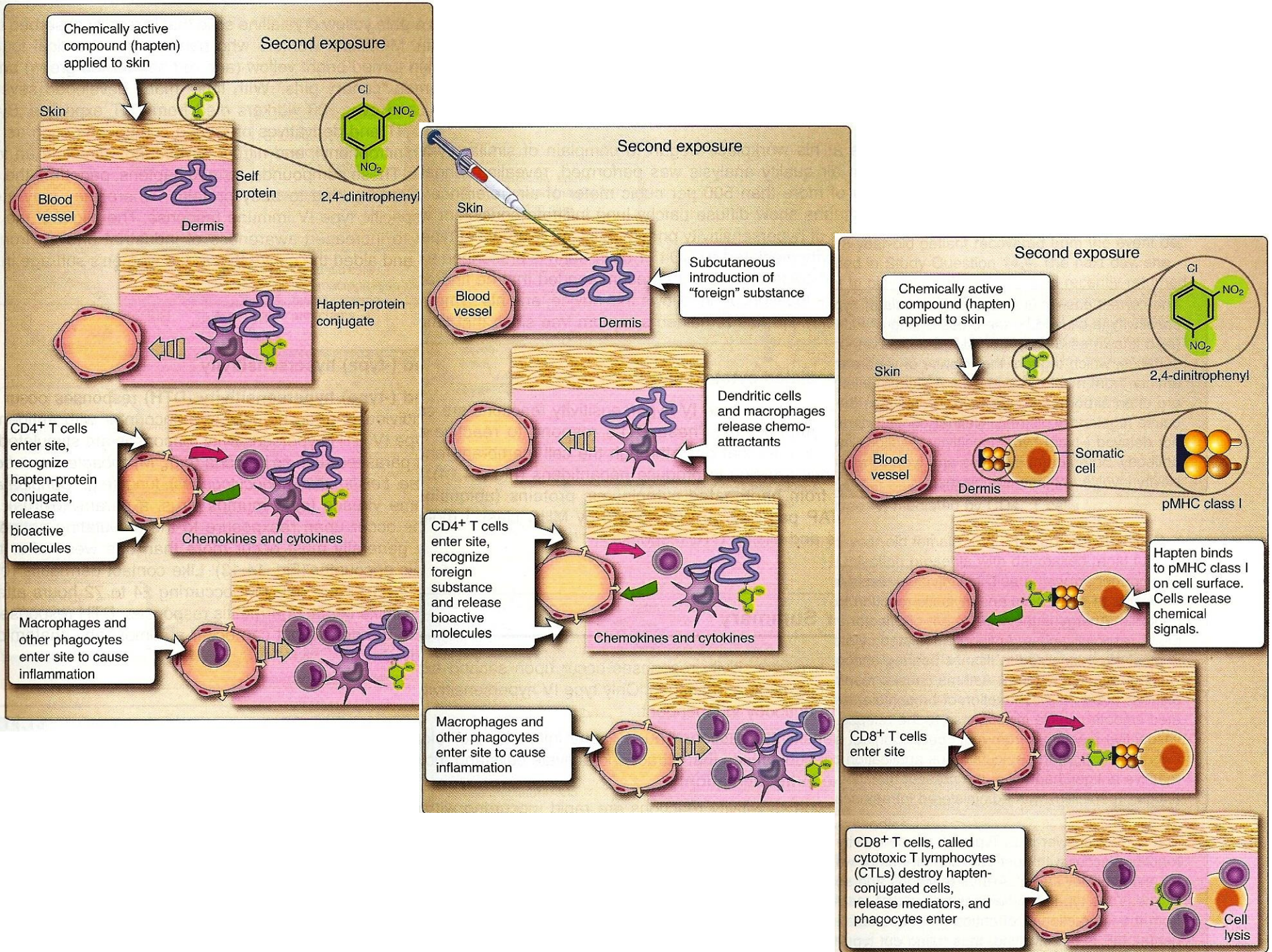
Matoux skin test reading

- application
- positive





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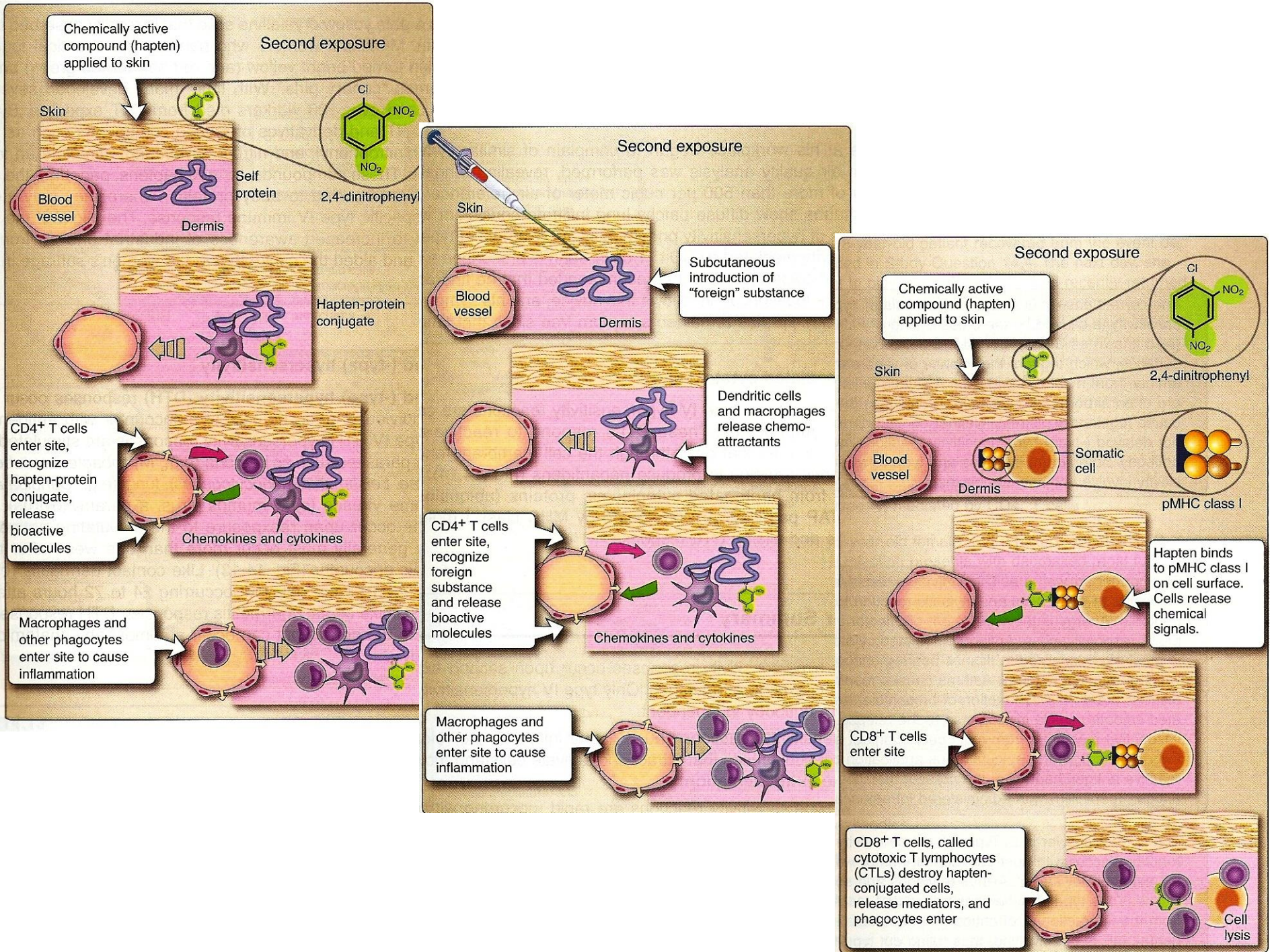
Granulomatózna reakcia

- Pri dlhodobej stimulácii (perzistencia i.c. mikroorganizmov, imunokomplexov, anorganických častíc – latex – ktoré sú príliš veľké pre makrofágy) –vznikajú granulomy
- Antigén – lymfocyt – lymfokín – makrofág aktivovaný makrofág – epiteloidná bunka (bez fagozómov) – obrovské bunky spojením epiteloidných – neostatočné zásobovanie centra – nekróza. Jadro je obklopené lymfocytmi a fibroblastami – syntéza kolagénu - fibrotizácia

Makrofág s prežívajúcou baktériou priťahuje ďalšie makrofágy a lymfocyty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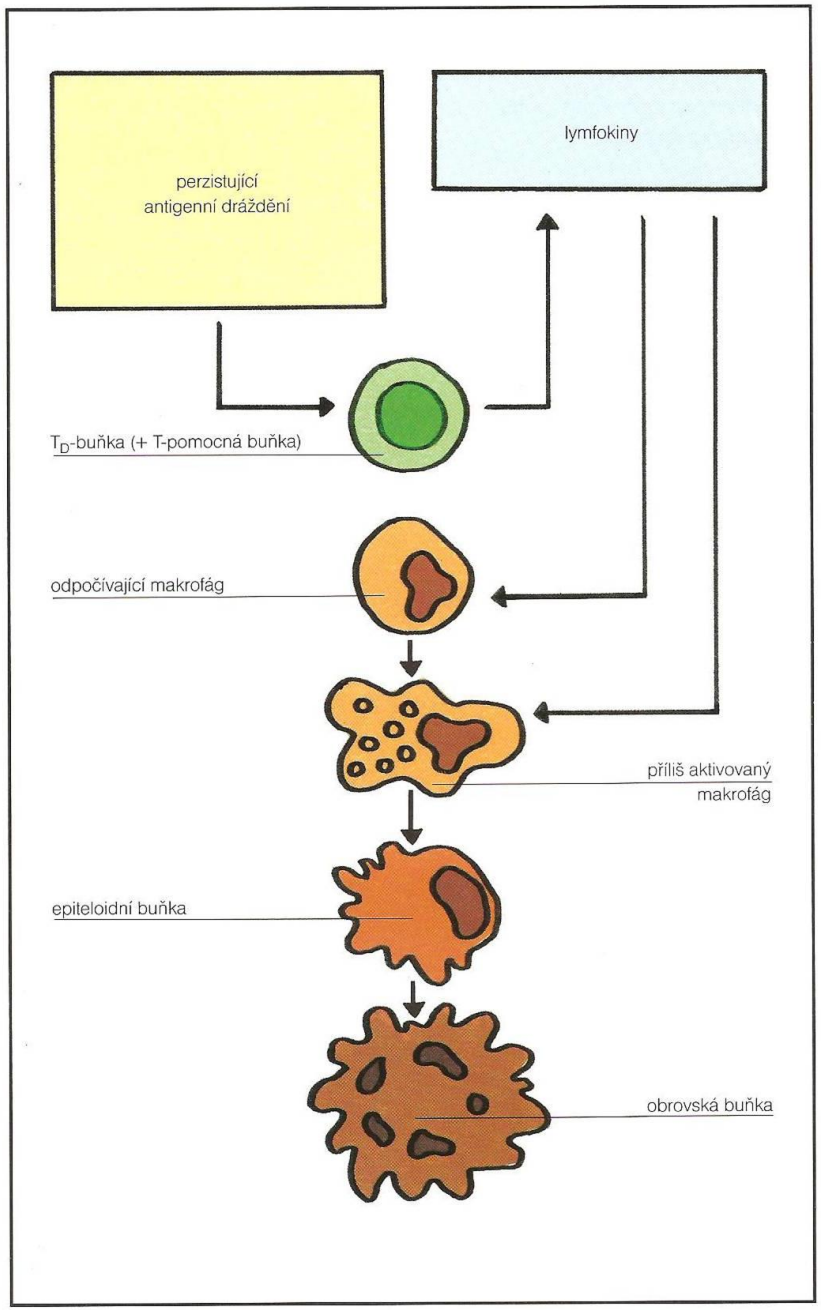
perzistující
antigenní dráždění
lymfokiny
T_D-buňka (+ T-pomocná buňka)
odpočívající makrofág
příliš aktivovaný
makrofág
epiteloidní buňka
obrovská buňka

4.typ – reakcia opozdeného typu - charakteristika

- Aplikácia antigénu (vlastnosti – i.c. parazit) vyvolá tvorbu senzibilizovaných T lymfocytov
- Opakované aplikácia LD antigénu s.c. – erytém a indurácia
- Prenos séra na druhého jedinca a podanie LD – nezaistí ochranu
- Prenos T lymfocytov na druhého jedinca a podanie LD – zaistí ochranu
- Reakcia na 2. podanie antigénu je pomalá viac ako 48 - 72 hodín, mediovaná T lymfocytmi a makrofágmi (po 2. podaní antigénu **spolu** s 1.podaním LD iného i.c. paratzita – ochrana proti obidvom)