Hypersensitivity

Lecture 10

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 bases

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 effector Tlymohocyte - TDH
delayed hypersensitivity – lymfokines

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

A) SENSIBILISATION
Ag and APC

Processing of antigen

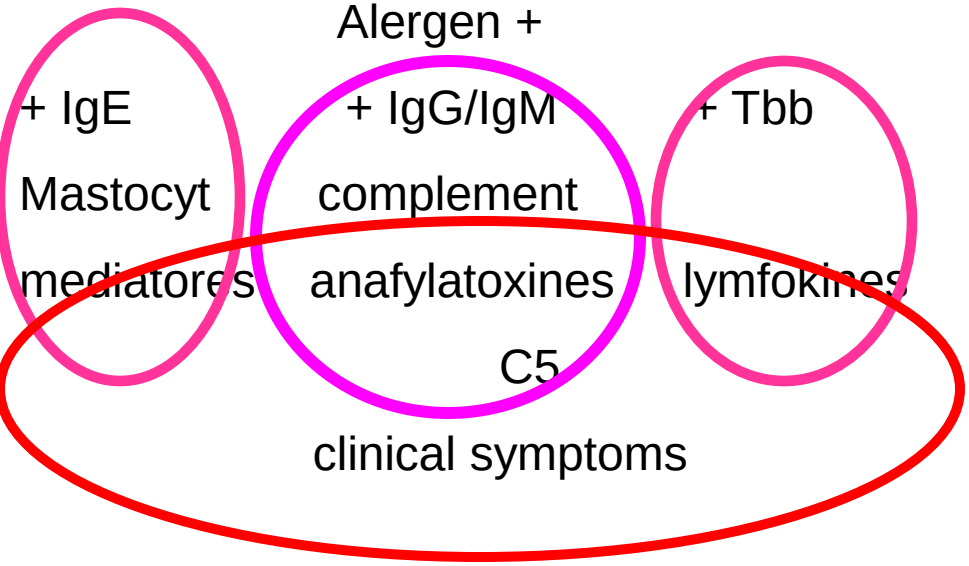
Contact with CD4
Th cells Th1?Th2

B cells change
to plasma cell
Productionof IK

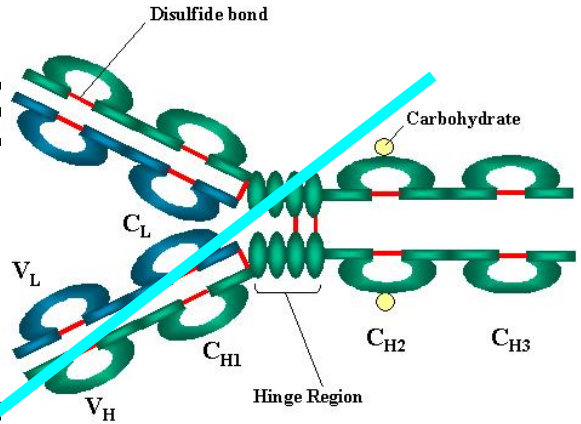
Production of
sensiibilised TDH cells

B) EFFECTOR PHASE

1 2,3 4



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>**

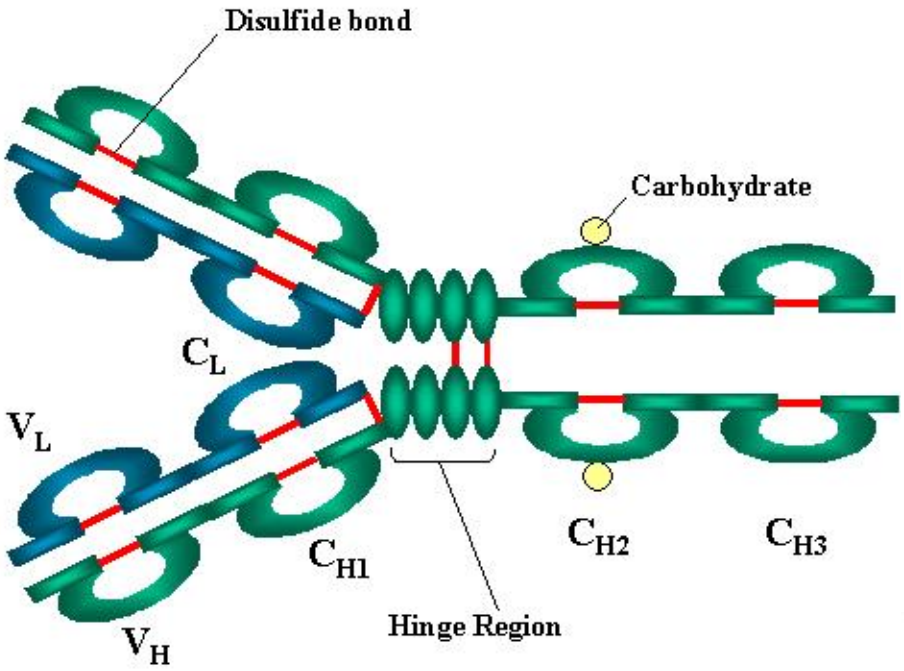
flexible joint region -

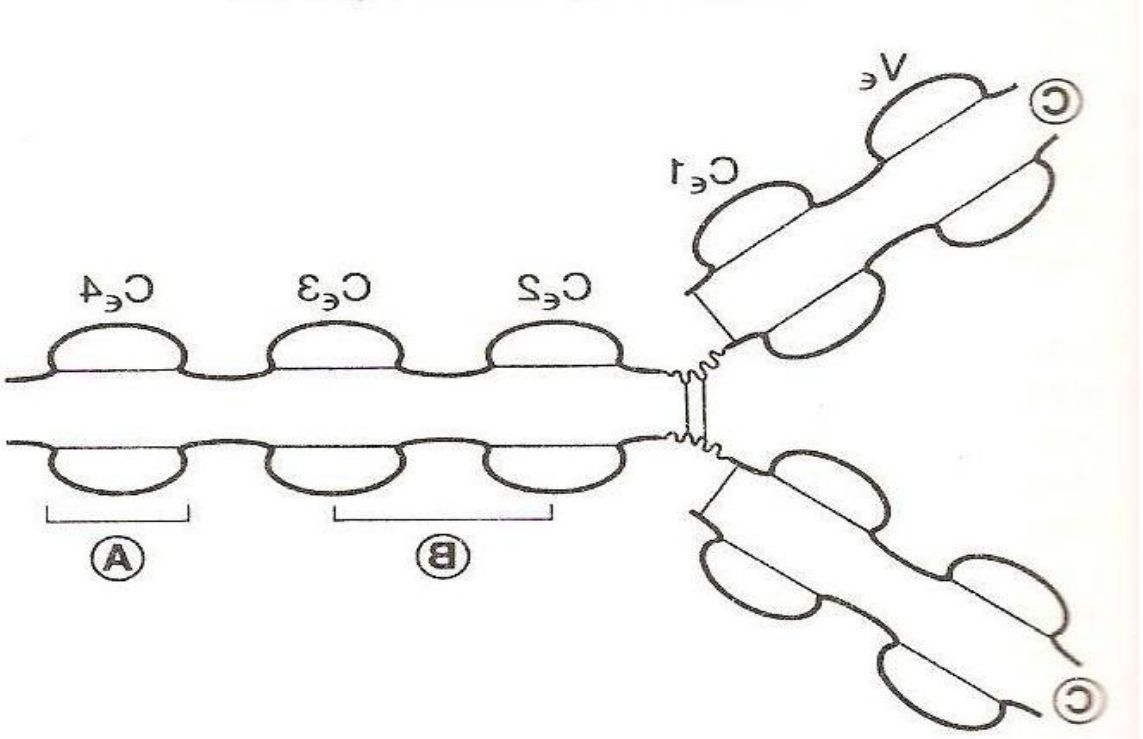
Domains – nor heavy nor light are flat.,

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}
C_{H2}
C_{H3}
Hinge Region
V_H


A
B
C
C
V_e
C_{e1}
C_{e2}
C_{e3}
C_{e4}

1.type – early reaction – atopic

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

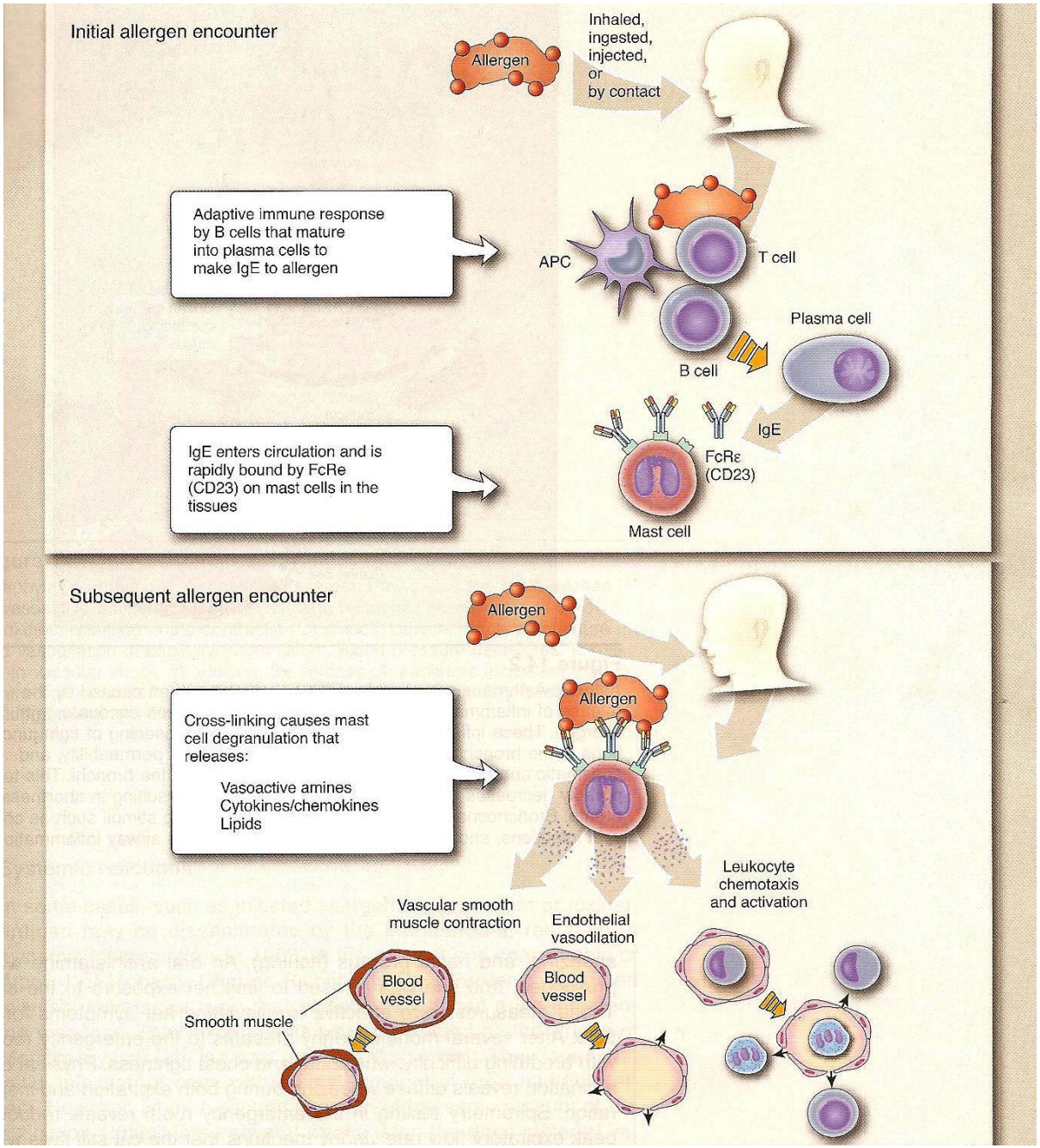
The size of the dose is important – very small amout of Ag

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 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, bronchospasm...).

2.type – cytotoxic reaction

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

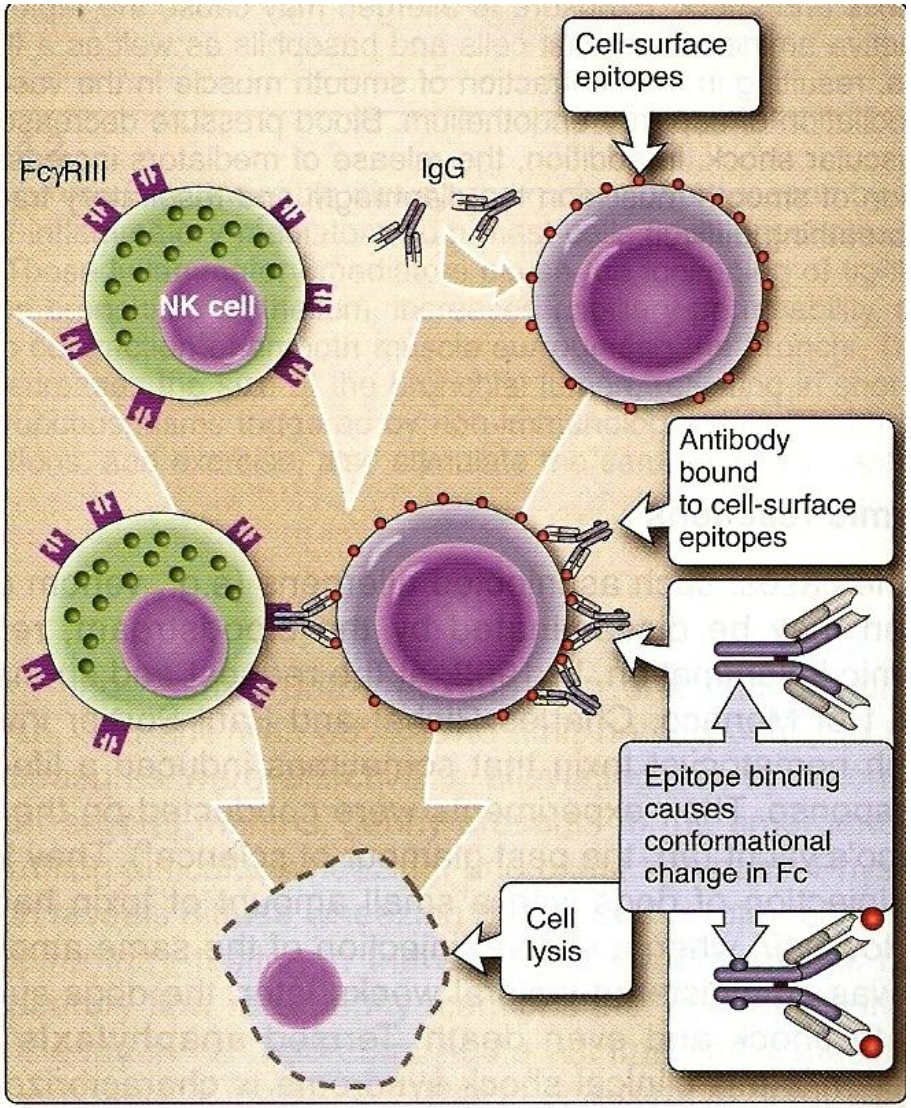
- deficiency of tolerance
- cross reactivity of antibodies against exogenous antigens, that have similar structure as self cell superficial structures
- bound of foreign antigens on the surface of self cells

- 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:

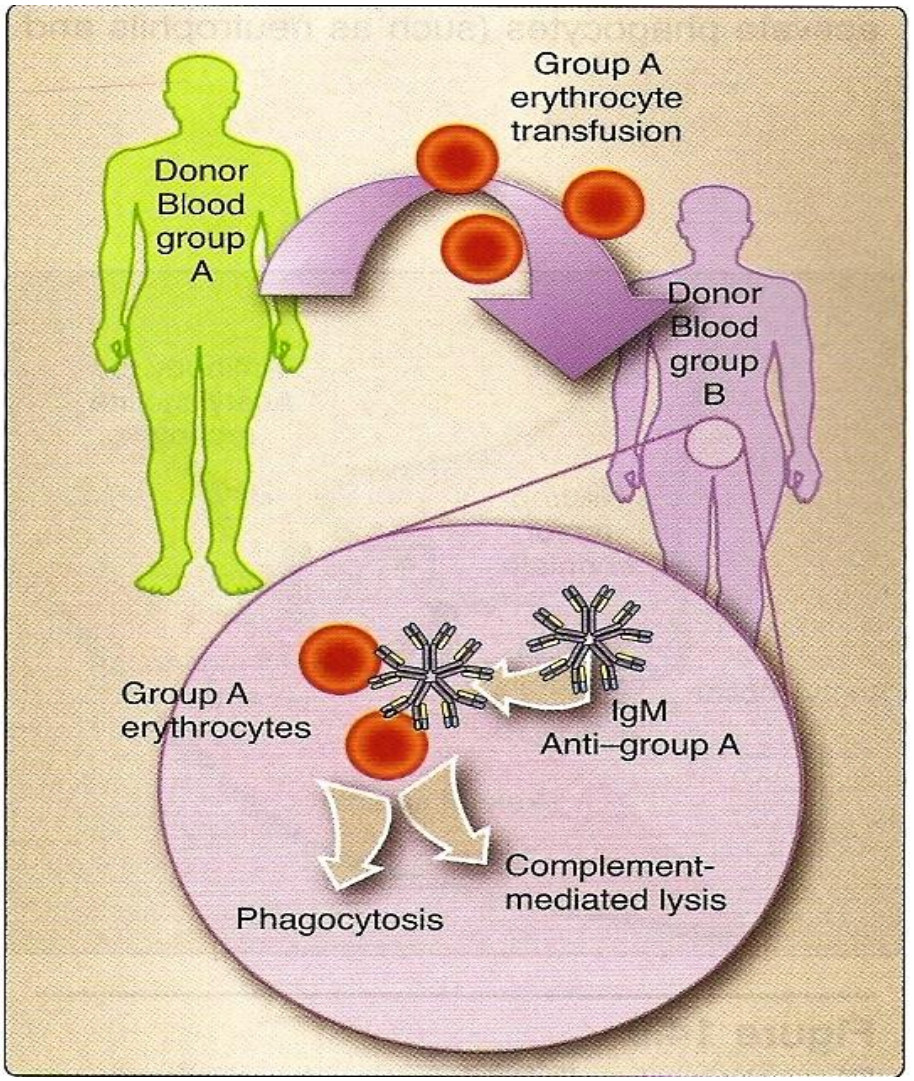
Pemfigus – IgG antibodies react with intracellular substances between epidermal cells

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

ADCC



Bad blood transfussion



Drug induced haemolytical anaemia:

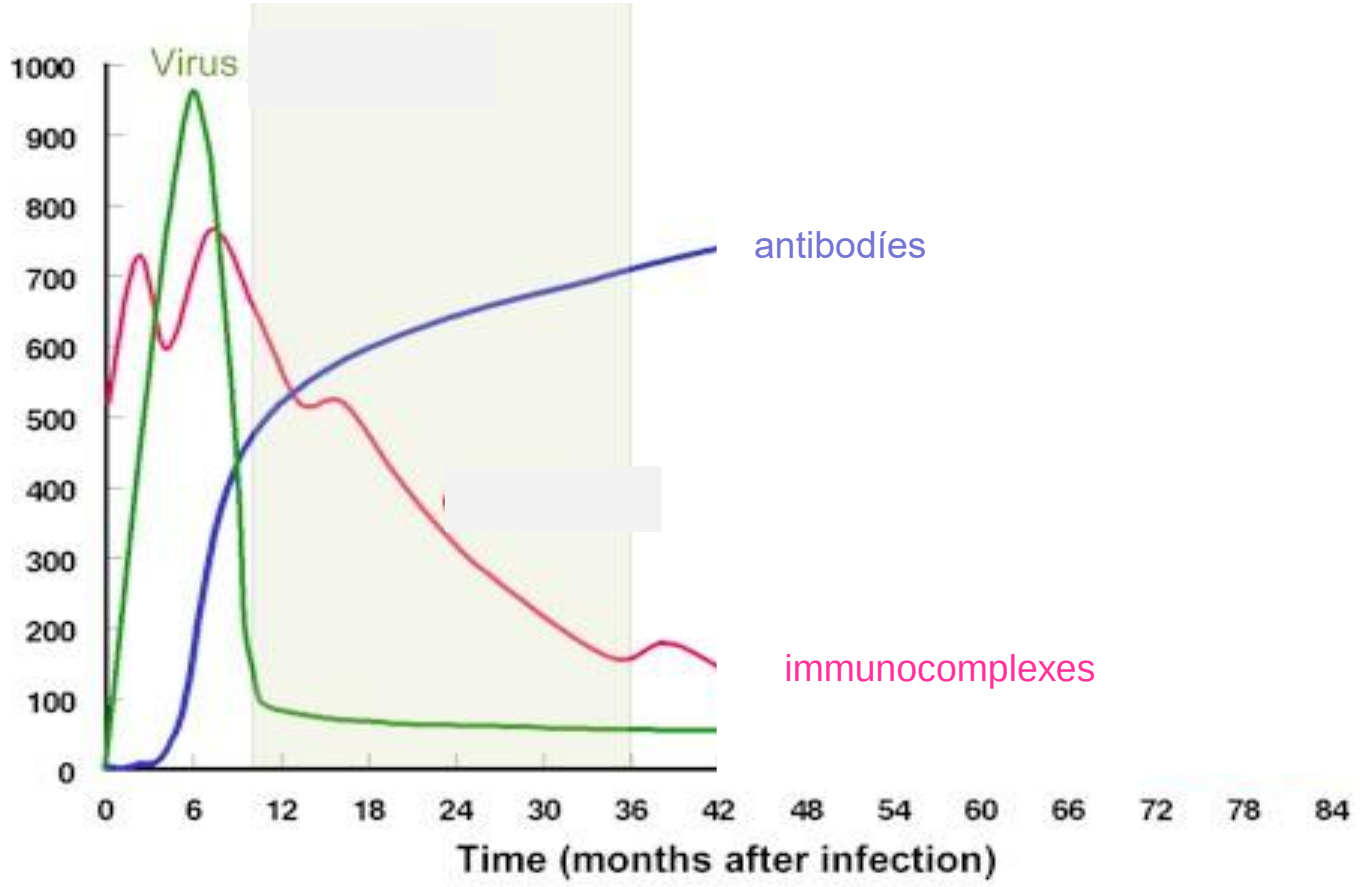
Antigen (PNC) is bound on erytrocytes. Antibodies IgG/IgM are specifically bound that activates C1q leading to lysis of the cell - haemolysis

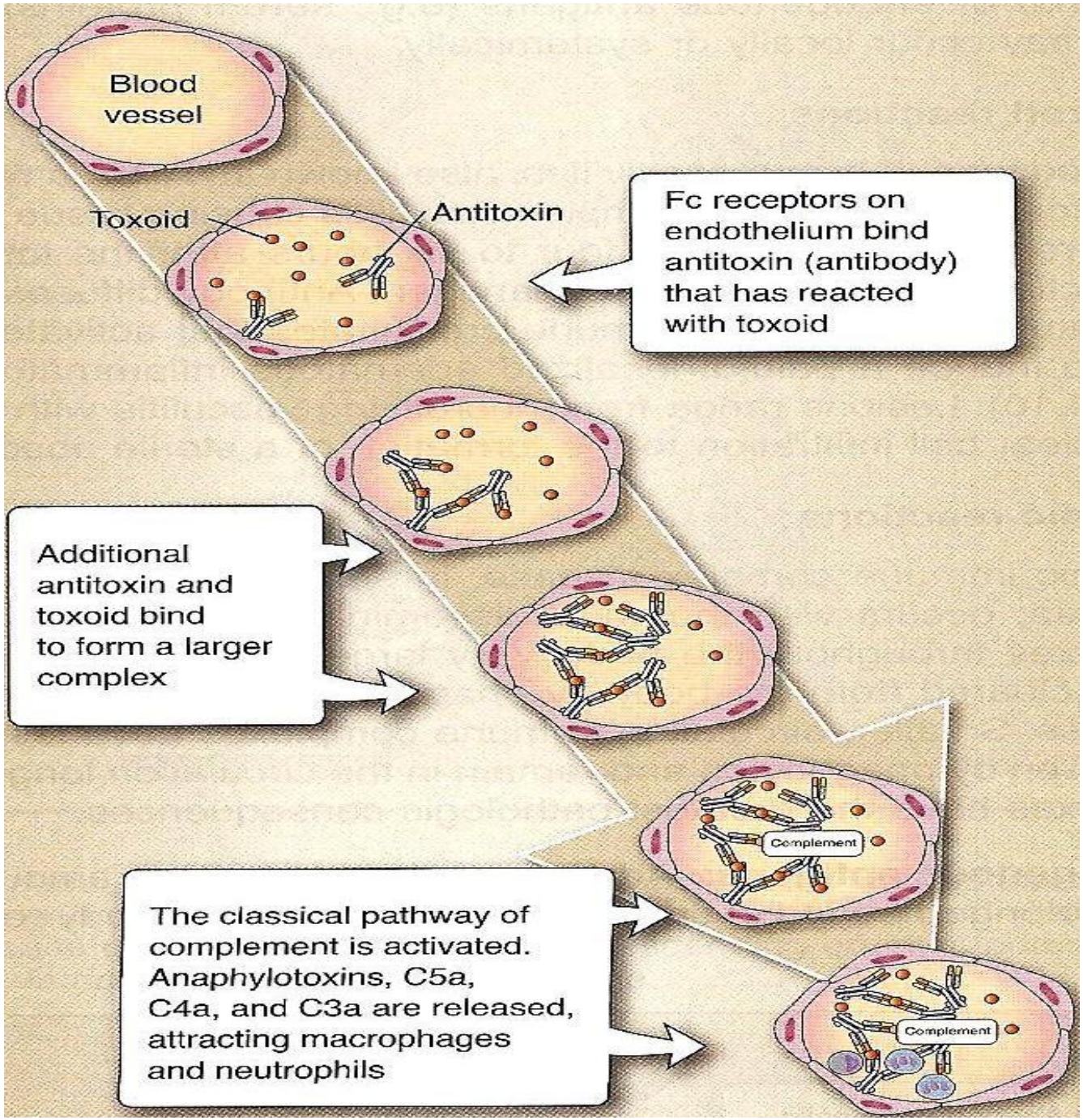
3.type hypersensitivity from immunocomplexes

- **Circulating antibodies** produced in time of sensibilisation react with **free antigen** (present in blood in time of reexposition) this leads to the production of circulating **immunocomplexes** (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)

Immunocomplexes deposit:
Usually after **chronical** exposition ot antigen – longlasting load of macrophages (**streptococcal infection – deposition of immunocomplexes to bas.membrane of glomeruli** - **GNFT**, *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)




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
– skin test
- local reaction of immunocomplexes
–detection of existence of antibodies and the risk of the 3rd type of hypersensitivity (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

expressed after

1 – 3 days

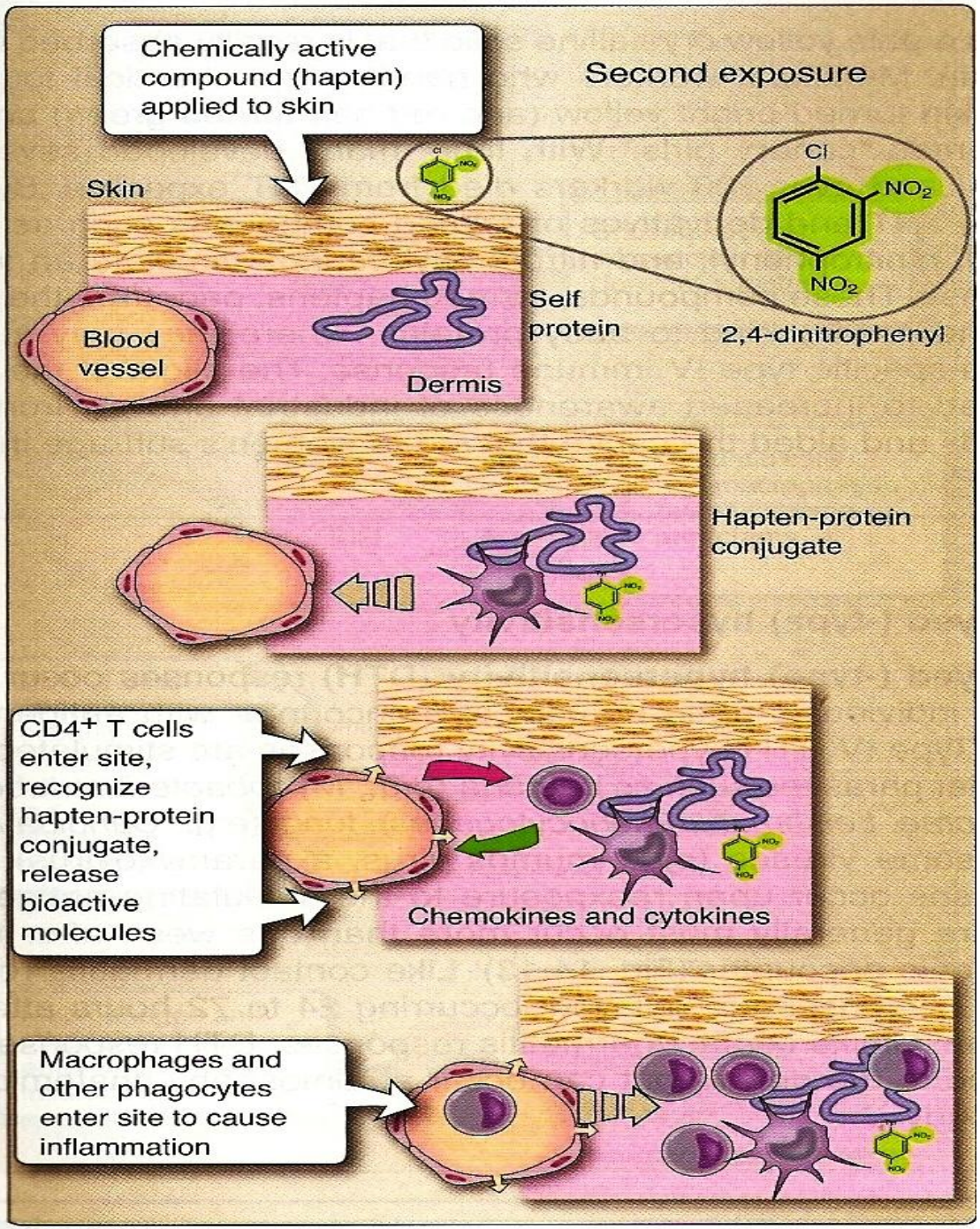
More than 14 days

Jones Mote – cutaneous basofil hypersensitivity

- Very infrequent
- Local reaction
- Induced by soluble antigens
- Lead to basofilic infiltration under epidermis
- After 24 hrs oedem of the skin that persists one week

Contact allergic dermatitis, contact eczema

- Contact of the skin with allergen
- MX after 2-3 days
- Low molecular weight haptens
  – penetrate the skin
  – bind on the body proteins
  – sensibilisation
  – activity of Langerhans cells: (fagocytosis, tissue macrophages, APC) – release lymphokines that leads to mononucleare infiltrate
  epidermal reaction


Chemically active compound (hapten) applied to skin
Second exposure
Skin
Cl
NO2
NO2
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

Tuberculin reaction

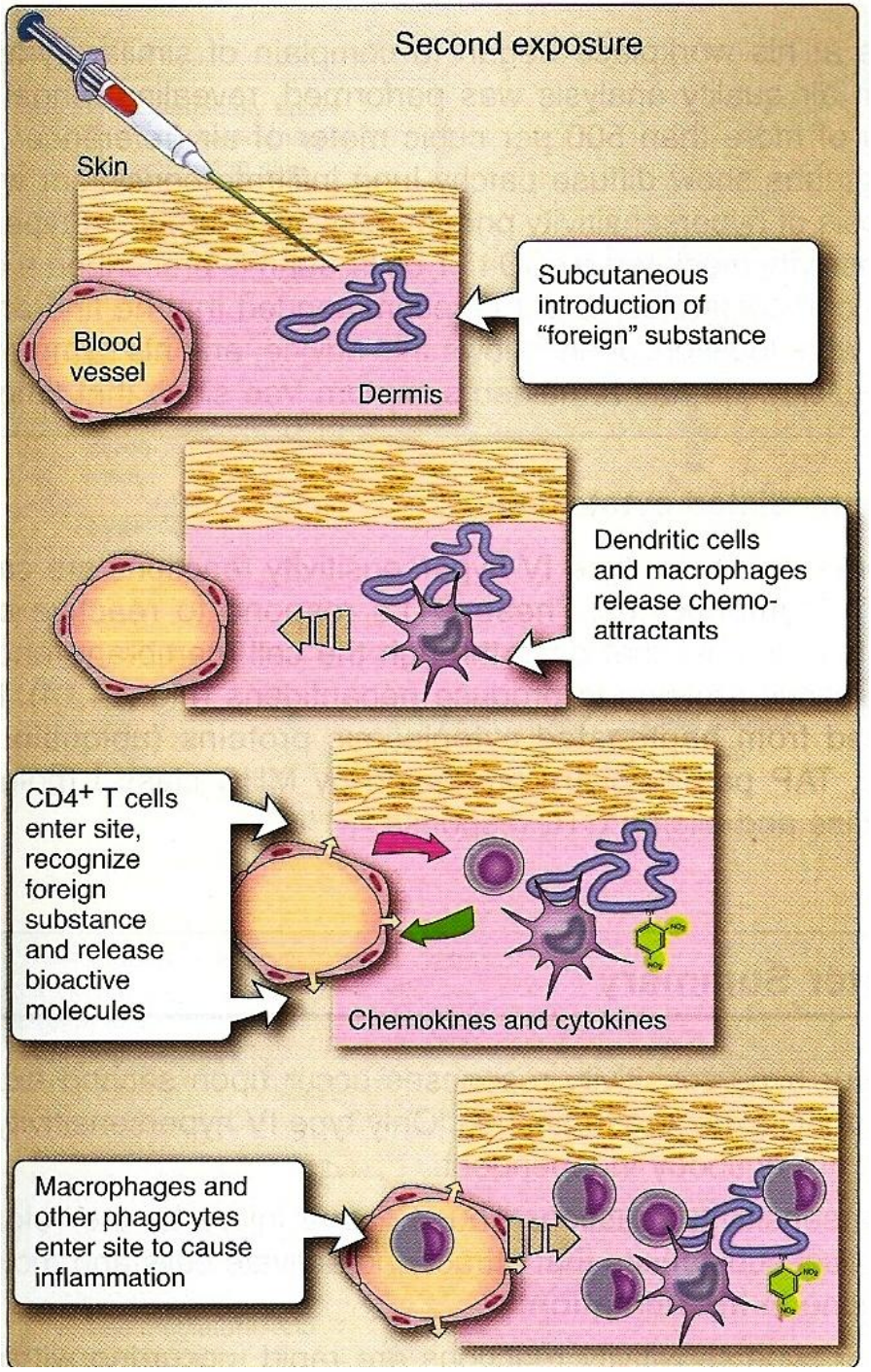
- Robert Koch

Subcutaneous application of tuberculin – PPD (lipoprotein of mycobacterium)

24 hrs after application: edema and induration

Infiltration with monocytes, makrophages, if longer exposition granulomatouse inflamation

- **Mantoux** – in vivo detection of specific cell immunity after exposition to antigen


Second exposure
Skin
Blood vessel
Dermis
Subcutaneous introduction of "foreign" substance
Dendritic cells and macrophages release chemo-attractants
CD4+ T cells enter site, recognize foreign substance and release bioactive molecules
Chemokines and cytokines
Macrophages and other phagocytes enter site to cause inflammation

Matoux skin test reading







Measurement of induration

- 0 – 15 mm – negative, not enought, vaccination, revaccination
- 15 mm – OK, positive (after vaccination ?)
- 15 and more – too much, possible activity

Granulomatouse reaction

- After longlasting stimulation (persistence of i.c. microorganisms, immunocomplexes, anorganic particules – latex, that are to big for macrophages) – granulomas
- Antigen – lymphocyte – lymphokines – macrophage activated macrophage – epiteloid cell (witout phagosomes) – giant cells with fused epiteloid – necrosis.- fibrotisation