Host-parasite relationship
Pathogenictiy and virulence
Pathomechanism, molecular pathogenesis, virulence factors
Infection and diseases, vaccines

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Definition of the host and the parasite

- **Host:** macroorganism, usually multicellular
  phylogenetically higher level,
  eukaryote (animal, plant)
  (it could be prokaryote)
- **Parasite:** Living on/in the host → damages → can cause disease
  obtaining necessities of life from the host
  - **non living:** unique protein (prion), nucleic acid (viroid)
  - **non living/living:** virus
  - **prokaryote:** bacterium
  - **eukaryote:** microscopic fungi, protozoa, helmiths

  } microorganism, microbes

  - vast majority of microorganisms live in the environment, minor fraction is parasite
  - **biologically there is no sharp distinction between normal and pathogenic**

Host-parasite relationship

- **Host:** able to exist independently or might depend on microbes
- **Microorganisms:**
  - saprophytes live in the environment
  - **symbiosis:** macro- and microorganism live together (association)
    - **mutualism:** advantageous for both (reciprocal benefit)
    - **commensalism:** do not damage each other (neutral)
    - **parasitism:** advantageous for microorganism (unilateral benefit)
      damages to macroorganisms → disease

Commensalism and mutualism in human as host

- **Normal microbe flora** (bacteria, microscopic fungi)
  - on skin and mucous membranes, in gut and vagina → colonisation
  - **host cell : microbe cell number = 1:10**
  - no entry, no penetration, no colonisation inside cells, tissues, organs
  - (in the blood: occasionally, transiently)
- **Viruses:** no exogenous normal virus flora
  - (but: latent viruses /episomal, integrated/ can be shed symptomless)
  - **Human endogenous retroviruses (HERV)**
    - 8% of the genome = self
    - they code for vital functions (e.g. placenta)
- **Protozoa, helminths:** never found in the normal flora

Advantages of commensalism/mutualism

- **For microorganisms**
  - shelter and food
  - colonisation, but no entry (penetration) into tissues
  - (through wounds, very rarely → disease)
- **For the host (human)**
  - to prevent colonisation of harmful microbes (parasites)
    - Occupying surface and cell receptors
    - Producing antimicrobial compounds
      (e.g. lactic acid in vagina, antibiotics)
  - processing/degrading food components
    - Producing useful metabolites (vitamin K or B_{12})

Parasite microorganisms

- Inducing pathogenic conditions → diseases **(>1400 species!)**
- **Damages for human:**
  - entry/penetration from surfaces into tissues → invasivity
  - passively through wounds (damaged tissue integrity)
  - actively (enzymes)
  - multiplication/replication in tissues → pathogenic effects → disease
- **Types of parasitism** (pathogenicity, being pathogenic)
  - **obligate parasites:** in defined host (range of hosts)
    always pathogenic, never found in the normal flora
  - **facultative parasites:** depending on the condition of both host and microbe, presence of predisposing /risk factors, members of the normal flora
  - **opportunistic parasites:** member of the environment, not pathogenic for healthy people, take advantage in case of host disorders (usually immunosuppression)

Predisposing/risk factors enhancing infection I

- **For facultative pathogens**
  - **physical ← mental stress**
  - **acute diseases, wounds, burns**
  - **chronic debilitating conditions**
    Diabetes, alcoholism, drug abuse, nutritional defects, tumours, leukaemia (combined with immune suppression, see later)
  - calculi (urinary tract, bile stone)
  - urinary tract obstruction
  - certain work conditions
- **Medical interventions (diagnostic and/or therapeutical)** – iatrogenic
  - changes in the normal microbe flora ← antibiotics, other drugs
  - surgery, oral surgery (entry of normal, facultative or opportunistic pathogens)
  - prosthetics, catheters (biofilm!)
- **Nosocomial infections**
  - in any health care facility, any source of infection, anybody (patients, staff, visitors)

Predisposing/risk factors enhancing infection II

- **For opportunistic microbes**
  - immune deficiencies/defects
  - physiologically weak (newborns, pregnancy, elderly)
    immunosenescence determining life expectancy: ≈105 years
- **Congenital/connatal immune deficiencies**
  - T lymphocytes = cellular immunity ↔ intracellular pathogens, protozoa, helminths
  - B lymphocytes = humoral immunity ↔ bacteria, fungi, protozoa
  - complex (T+B cells)
  - innate immunity (phagocyte functions, interleukin production)
  - complement system
- **Acquired immune deficiencies**
  - medication (corticosteroids, cytostatic drugs)
  - radiation (environment, medical)
  - tumours, leukaemia (virus)
  - infections – **especially those replicating in immune cells**
    viruses: HHV-6, HHV-7, HIV in CD4+ T cells and macrophages
    EBV in B cells
    several bacteria, protozoa in macrophages

Specificity of pathogenicity, pathogenic ability

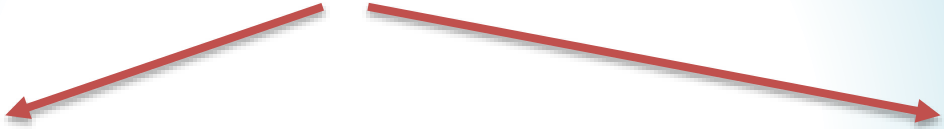
- **Pathogenicity**
  - **ability of the whole population of a given microbe species to elicit disease in a given host or range of hosts**
  - species specific, defined genetically in both host(s) and microbe (yes or no, qualitative)
  - Koch postulates → molecular Koch postulates (determination at molecular level)
- **Virulence**
  - **in the level of pathogenicity**
  - ability to elicit disease by a smaller population (tribe, strain, type) of the species
  - genetically determined in the smaller population only (quantitative)
- **High virulence ↔ low virulence ↔ avirulent (virulence is lost)**
  - **increasing virulence:** mutations, GMO, bioterrorism
  - **decreasing virulence:** mutations, attenuation

Quantitation of virulence

- Virulence can be measured (number of germs)
- How many microbe (or group of microbes) defined among standard circumstances induces pathological conditions (disease, death) = **dosis, dose**
  - **ID_{50} = infective dose** inducing disease in 50% of hosts (e.g. in susceptible experimental animal)
  - **DL_{50} = dosis lethalis** causing death in 50% of hosts
  - DL_{90}, DL_{100}, ID_{100} etc.
  - **$TCID_{50}$ = tissue culture infecting dose** damaging 50% of cultures
- **Small number of germs (1-10^2) → disease = high virulence**
  - 1 calicivirus particle → enteritis (resistant to environmental conditions)
- **Large number of germs (≥ 10^5) → disease = low virulence**
  - ≥ 10^5 cholera bacterium → enteritis (extremely sensitive to acidic pH)

Factors determining virulence

- **Constituents or products of microbes**
  - genetically determined (but phenotypically dependent)
- **Examples of bacterial virulence factors**



Non-toxic

Cell surface constituents

- capsule (see later)
- flagella, cilia → motility
- fimbriae → specific ligands (adhesins)
  - sex fimbriae (conjugation)
- pili → adherence to host cells
- invasins → specific ligand to enter cells
- glycocalyx/extracellular mucoid substances → biofilm

Extracellular enzymes

- damaging host cells

Toxic

- exotoxins
- endotoxin (lipopolysaccharide, LPS)

Non-toxic virulence factors of bacteria

- **Capsule**
  - polysaccharide
  - polypeptide (Bacillus anthracis, D-glutamic acid)
- **Role of the capsule**
  - protection
    - mechanical, physico-chemical
    - biological - **anti-phagocytic**
      - masking, hiding other antigens
  - antigen variations in one species - immune evasion
  - adhesion to host cells

Non-toxic virulence factors of bacteria: extracellular enzymes

- Secreted from living bacteria → exert effect on host cells
- Examples
  - **Antiphagocytic effect**
    - leukocidines
    - coagulase
    - haemolysins
    - proteases
  - **Facilitating invasion**
    - **solubilising cells, tissues of the host**
    - streptokinase (fibrinolysin) – (surgery: cleaning wounds)
    - collagenase
    - hyaluronidase

Toxic virulence factors: exotoxins

Secreted by living bacteria → effect on host cells

Major characteristics

- polypeptides (mostly A+B subunits), good antigens
- well defined structure and effect
- some of them are coded by bacteriophages

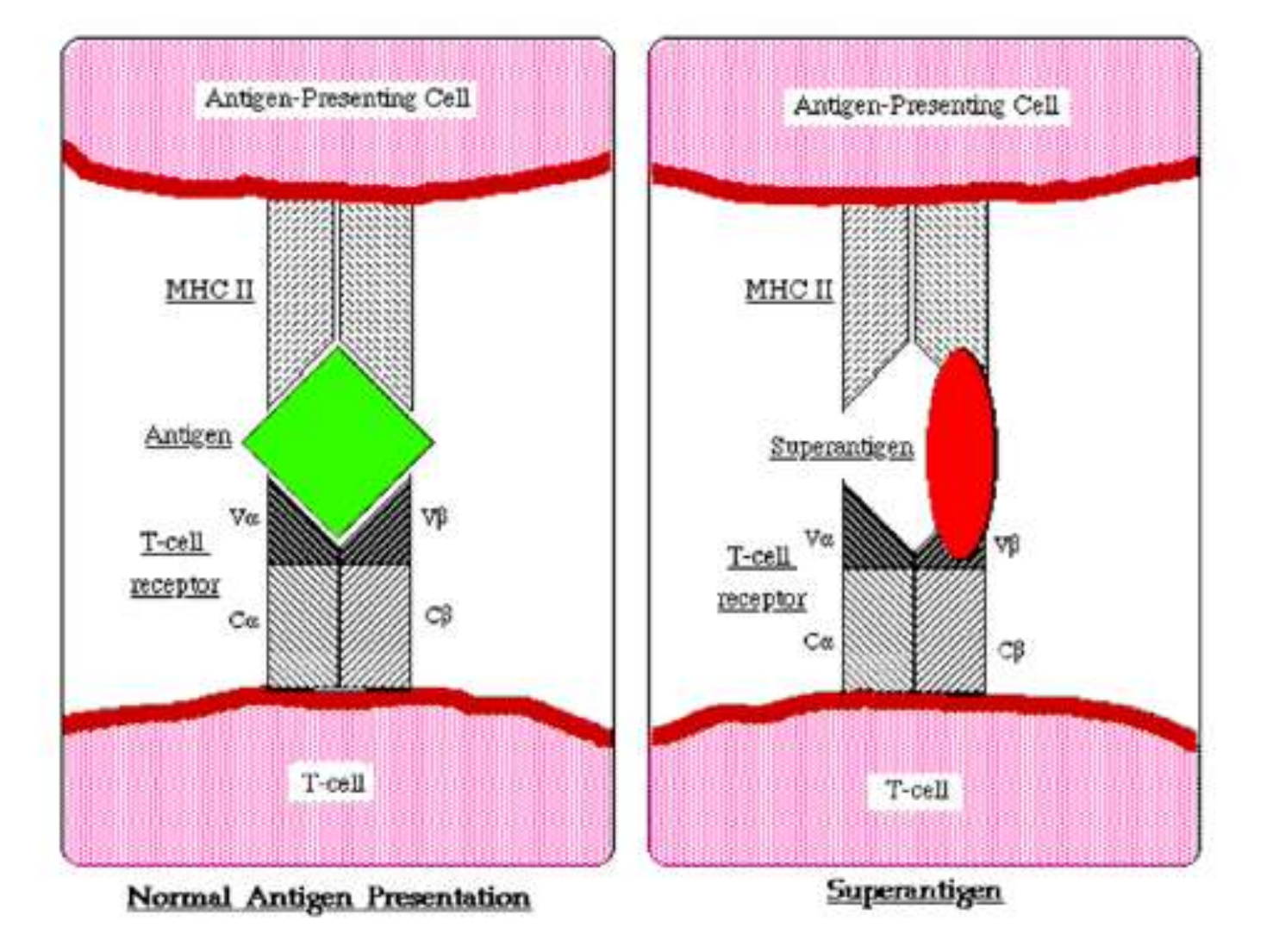
Effect on the host

- **effect on host surfaces (extracellularly acting)**
  - membrane damage (pore formation → loss of nutrients → cell death
  - superantigens: APC MHCII + TCR binding → cytokine production → toxic shock (*Staphylococcus aureus*: toxic shock syndrome toxin, TSST)
- **intracellularly acting**
  - A+B toxin (A: toxic effect or the opposite, B: cell surface binding)
  - inhibition of protein synthesis (diphtheria)
  - overproduction of mediators, neurotransmitters (acetylcholine → tetanus)
  - hypersecretion (cholera toxin: Na^+, Cl^-, etc. → diarrhoea

Measurement of toxicity

- DLM = dosis lethalis minima kills all experimental animals (ng – µg)

Superantigens



Endotoxin (lipopolysaccharide, LPS)

Gram negative bacteria – cell wall

Major characteristics

- heat stable, conserved in many Gram- bacteria, weakly immunogenic (as antigen)

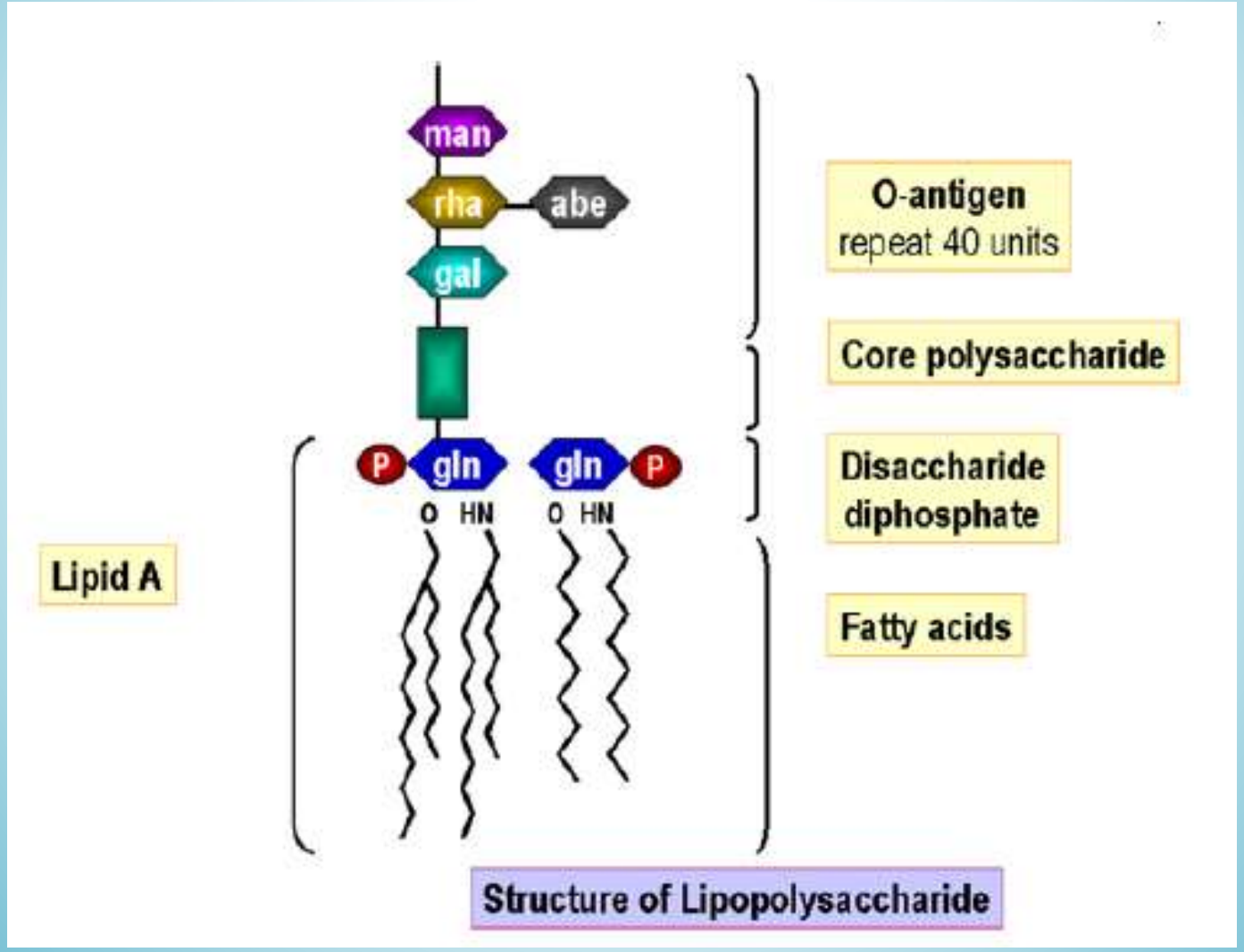
Importance

- recognition by innate immunity:
- pathogen associated molecular pattern (PAMP)
- LPS → LPS binding protein → macrophages, B cells, PMNL, platelets CD14 and TLR4 binding → cell activation → overproduction of inflammatory mediators (IL-1, -8, TNF-α)

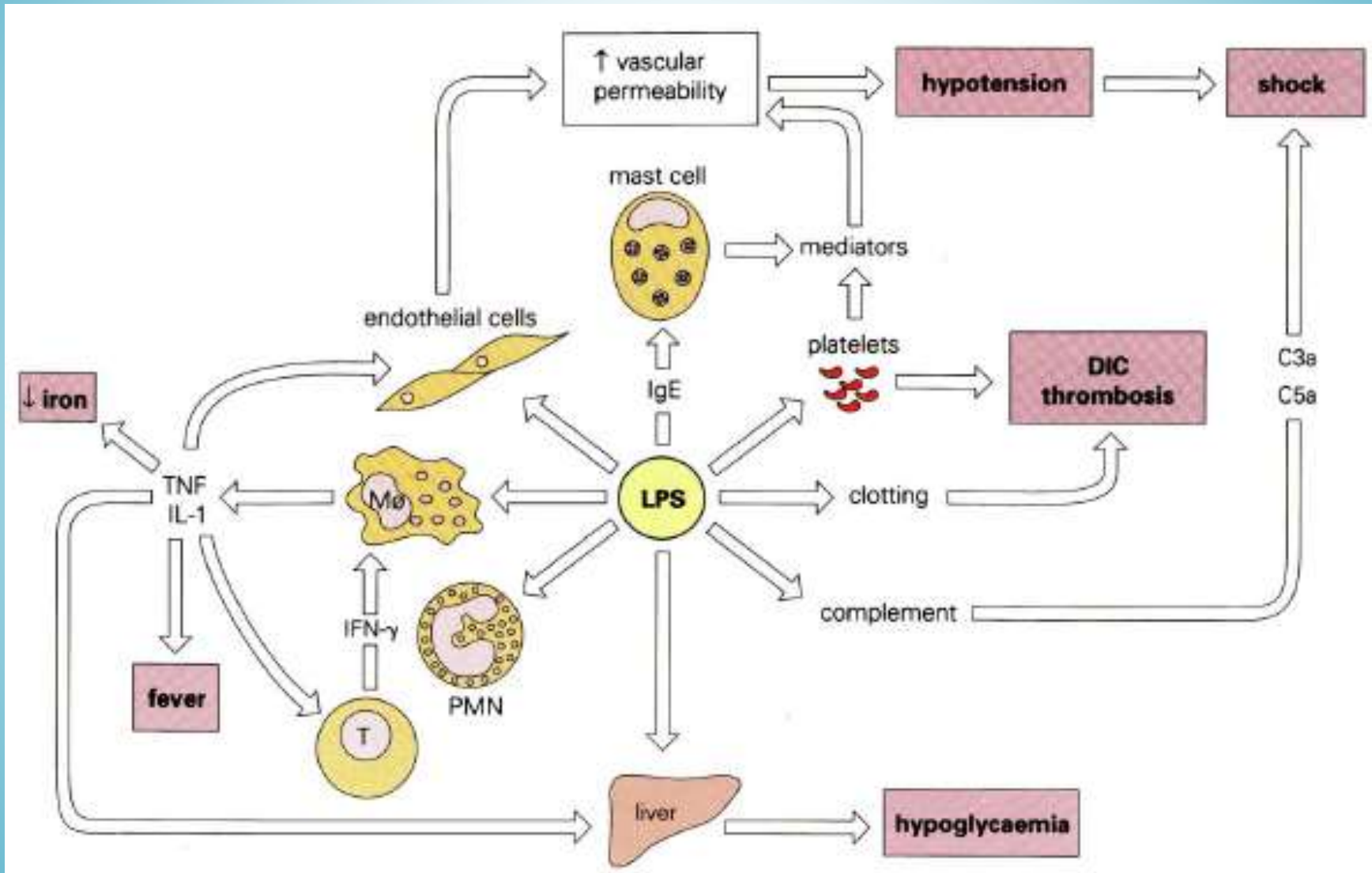
Biological effects:

- **beneficial:** **small amount is immunostimulant (essential for innate immunity) eliciting inflammation → isolation of infective agents**
- **malignant:** large amount exerts systemic effects
  fever, vascular permeability → hypotension, acute phase proteins, hypoglycaemia, cytokine storm, DIC, thrombosis → shock →death

Structure of LPS



Effects of endotoxin



Mims: Medical Microbiology Fig. 16.6

Onset of infection

Infection: entry and replication of microorganism in macroorganism

Source of infection

- **Exogenic** – infected, symptomless
  ill
  carrier
  } **human, animal**
  – environmental vehicles (soil, water, food, etc.)
  – reservoir: animals (rodents and insects) or humans or vehicles **carrying pathogenic microbes permanently**
- **Endogenic** – from the normal flora (skin, mouth, gut, vagina)
  – activation of latent/persistent microbes

Contagious infections: from human to human

Non-contagious infections: not from human to human

1st infection = primary infection → repeated (secondary) infection

Transmission of infection

Horizontal spread

- **Direct contact**
  - human-human, animal-human
- **Indirect contact**
  - contaminated environment, objects

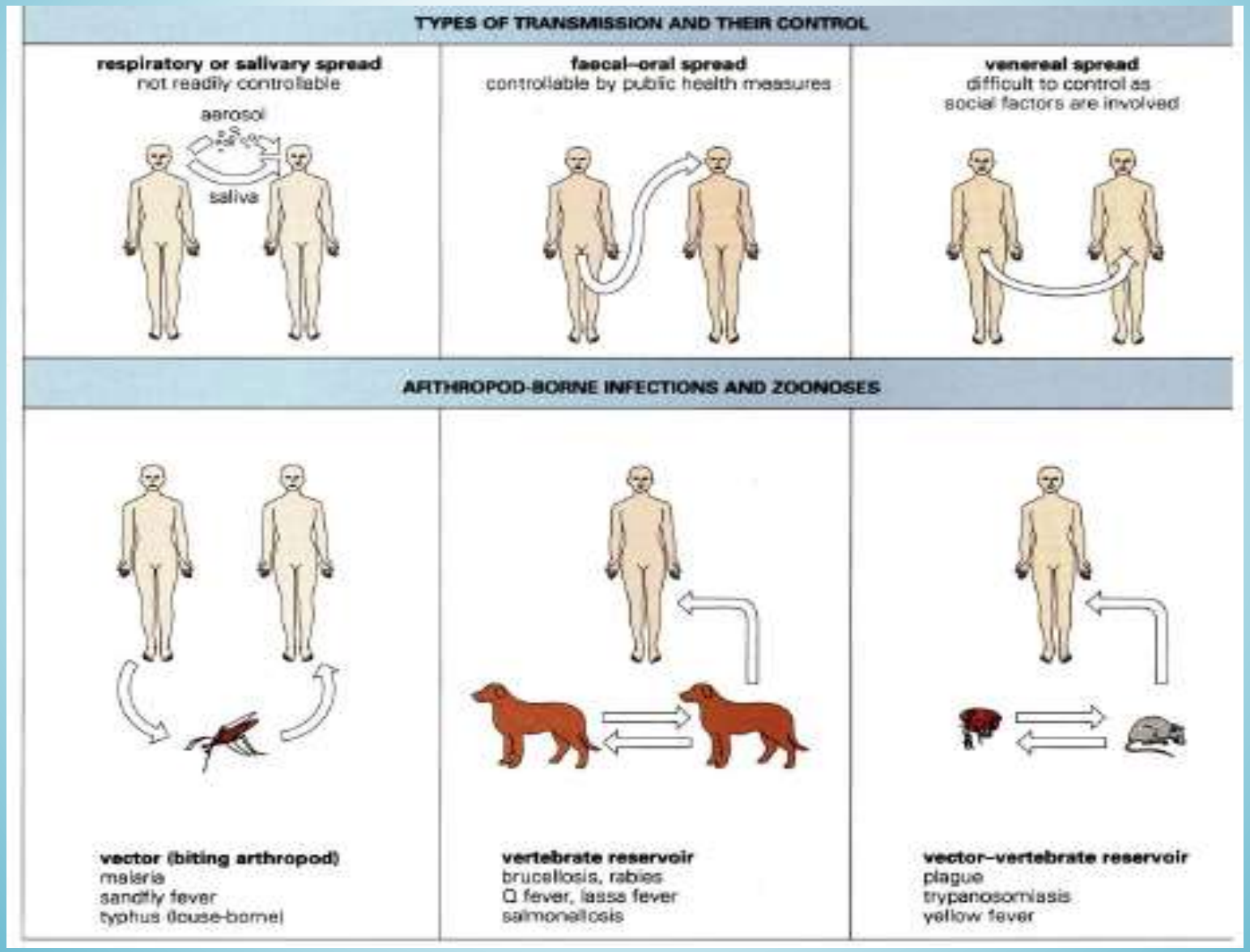
} skin, mucous membranes (sexual organs)

- **Vehicles**
  - air-blow – coughing, sneezing, talking → droplet aerogenic infections
  - contaminated water, food alimentary/oral infections
  - blood sucking insects (lice, fleas, ticks, mosquitos) vector (arthropod → host /direct percutan transmission/ → arthropod)
- **Iatrogenic infections**
  - direct percutaneous infections by contaminated blood/cell/organ donation, equipments

Vertical spread

- **Next generations:** transplacental, diaplacental → connatal infection (immediate or late manifestation)

Types of transmission



Infection process: entry

Portals of entry (attachment and penetration)

- skin and mucous membranes
  injuries (damage of integrity)
  direct penetration (arthropods)
- respiratory tract (epithelial or immune cells)
- gastrointestinal tract (epithelial or immune cells)
- urogenital tract (ascending)

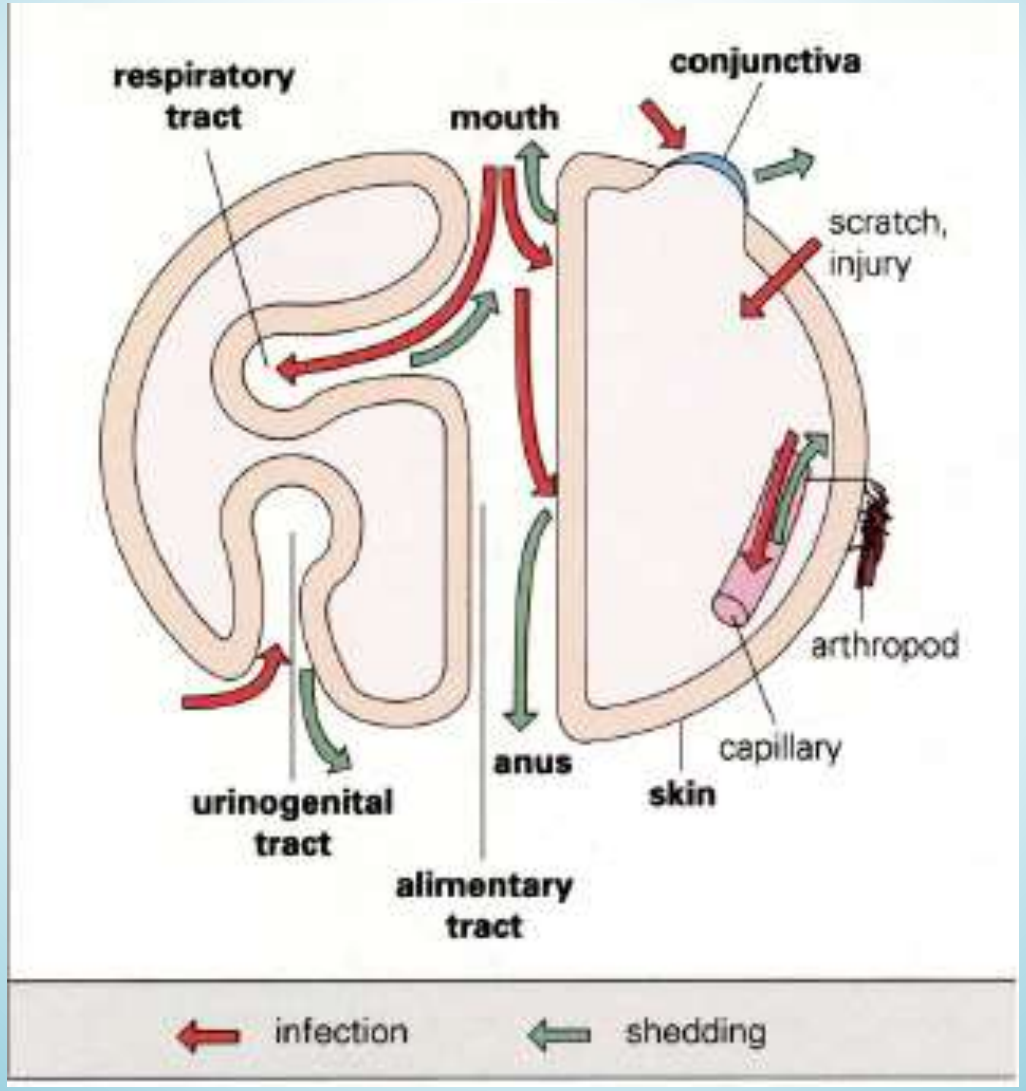
Iatrogenic infections

- skin, mucous membranes – wounds
- implanted cells, tissues, organs
- devices – syringes, canules, prosthetics, catheters (urinary tract!)

Nosocomial infection

- in any healthcare setting, any source, any transmission, any portal of entry, any host (patients, staff, visitor)

Microbial infection and shedding



Infection process: colonisation, dissemination

Colonisation

- irreversible, at or near to the site of entry
- multiplication of microbes
- local infections (tetanus bacterium, wart viruses)

Dissemination

- spreading in the body – invasion → generalised infection
- tissue damage, in the blood (haematogenic), in the lymphatics (lymphogenic), canalicular (respiratory tract), ascending (urogenital tract)

Consequence

- microbes are found far from the portal of entry
- large quantity → several pathogenic effects → disease

Incubation time

- symptomless period between the moment of infection (frequently unknown) to the onset of symptoms/disease outbreak
- **few hours – more months (HBV)**
- **several years – decades (protozoa, tumour viruses, prions)**

Infection process: generalization

Dissemination, invasion

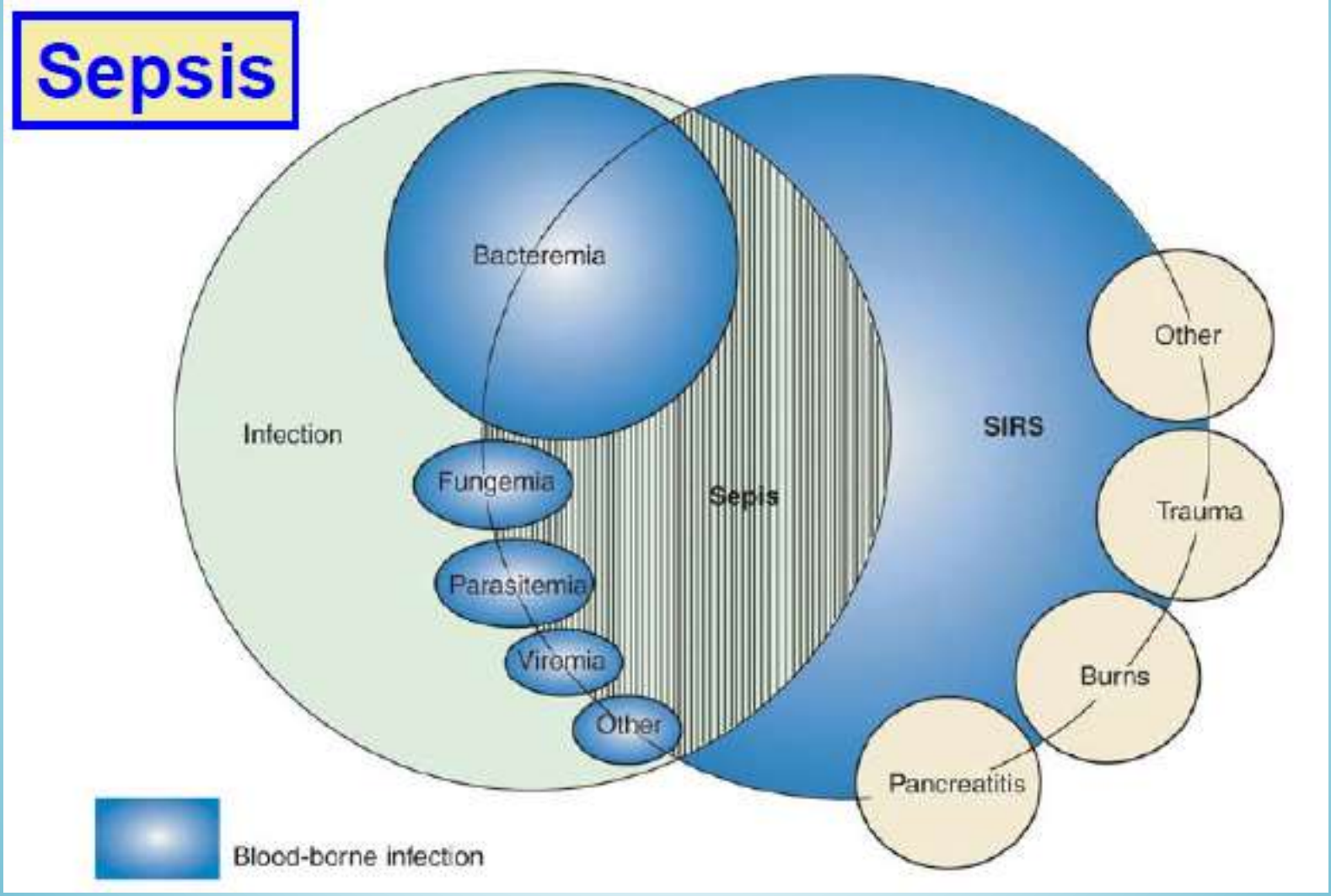
Extremely harmful if found in the bloodstream:

- bacterium – bacteriaemia
- virus – viraemia
- parasite (protozoon, helmith) – parasitaemia
- fungus – fungaemia
- toxin – toxaemia

Sepsis

- **Infection → systemic inflammatory response syndrome (SIRS)**
  generalized weakness, malaise, warm skin, rash
  high (>38°C) or low (<36°C) body temperature
  tachycardia (>90/min)
  tachypnoe (>20/min)
  WBC (10-12x10^9/L)
- **Aggravation:** organ hypoperfusion
- **Septic shock:** hypotension (systolic BP <90mmHg) resistant to medications
- **Death:** multi organ dysfunction syndrome (MODS)

Sepsis


Sepsis
Bacteremia
Infection
Fungemia
Parasitemia
Viremia
Other
Sepis
SIRS
Other
Trauma
Burns
Pancreatitis
Blood-borne infection

Infection process: outcome

Symptomless

- subclinical, silent, inapparent (or very mild, non-specific symptoms)
- quick elimination of the pathogen
- **very important:** symptomless infections in childhood result in lifelong immunity (e.g. toxoplasma) or cross immunity (HSV-1/HSV-2)
- **Latent** – the pathogen remains in the body, activates upon intrinsic/extrinsic factors
- **Persistent** – Viral forms of latency – episomal (herpes) or integrated (retroviruses)
  The pathogen activated regurarly, shed symptomless
  (but infects others!)
- **Carrier state** – the pathogen is shed continuously w/o symptoms (source of infection)

Manifest infection, manifestation of disease - symptoms are detected

- Acute (fulminant = extremely rapid course)
- Subacute
- Chronic

Infection process: outcome

Acute
Chronic

→ The pathogen disappears from the body → reconvalescence → clinical recovery

Times of microbial and clinical recovery are different!

Acute (mainly fulminant) → The pathogen remains in the body

Chronic → No pathogen in the body, but irreversible damages

→ death

The above courses are natural processes

Treatment (medication, antibiotics, vaccination, etc.) profoundly alters disease course!

Defence mechanism against pathogenic microbes

Unspecific factors

Inhibition of attachment, entry and facilitation of removal

- skin integrity
- upward synchronised movement of cilia in the respiratory tract
- pH – skin – organic acids, sebum
  vagina – lactic acid (Lactobacilli) pH 4-5
  stomach – HCl, pH 1-2
- enzymes – tear – lysozyme + blinking
  mouth, gastrointestinal tract
- osmolarity – urine flow
- accelerated peristaltic movement, vomiting

The role if immune system in the antimicrobial defense

Functions of the immune system

- **recognition of pathogenic microbes** (foreign, non-self)
- **innate immunity – immediate onset of aspecific defense mechanisms**
- depending on innate immunity: **onset of adaptive immunity**
- recognition of antigens, their presentation
- activation of signal transmission among different immune cell subsets (interleukines, chemokines)
- mobilisation of the effector cells in the cellular and humoral immune system
- destruction of microorganisms and infected cells
- elimination of debris produced from microbes, infected cells and unnecessary immune cells
- **establishment of immune memory**

Primary infection = first encounter between the macro- and microorganism: above reactions

Secondary/repeated infection by the same microbe: activation of immune memory

Recognition of pathogenic microbes

Monocytes, macrophages, neutrophil phagocytes, dendritic cells

- **Cell surface receptrors** (C-type lectin, TLR1,2,4,5,6)
- **Endosomal receptors** (C-type lectin, TLR3,7,8,9)

Recognized molecules

- Conserved **structures missing in mammalian organisms**
  pathogenic associated molecular pattern (PAMP)
  LPS, Gram positive bacterial cell wall peptidoglycan, lipoteichoic acid, flagellin, N-formylmethionin, hypomethylated CpG-DNA, ss/dsDNA, ss/dsRNA
- **Intracellular components of lysed infected** (virus, bacteria, protozoa) **cells**
  damage associated molecular patterns (DAMP)
  nuclear polypeptides, mitochondrial DNA, reactive oxygen radicals, matrix proteins, heat shock proteins

Activation of the innate immunity

Augmented signal transduction from receptors → cascade of events

- activation of **interferon regulatory factors (IRF)** → production of interferons (IFN-α,-β,-γ,-λ) → activation of IFN-stimulated genes (ISG, several hundreds) in immune and adjacent cells, infected cells
- formation of **intracellular inflammasomes** (RIG-I, NLRP3, etc.) and stress granules = protein complexes
- **protein kinase R (PKR) activation** → RNaseL activation →degradation of foreign RNA
- **caspase activation** → programmed cell death of infected cells
- release of **pro-inflammatory mediators** (e.g. IL-1,-2,-8, TNF-α) GM-CSF, G-CSF: phagocyte attraction

First signs of manifesting innate immunity

- **Onset of inflammation**
  - **localisation of infecting agents**, preventing systemic infection/damage
  - **increased circulation** and permeability of capillary membranes → oedema
  - **local and systemic effects of mediators**
    pro-inflammatory cytokines (IL-1,-8,-11, TNF-α, etc.)
    anti-inflammatory cytokines (TGF-β, IL-4,-6,-10, etc.)
    attraction of immune cells/phago-, monocytes, macrophages, lymphocytes, etc.
  - **acute phase reaction** (systemic effect: fever, malaise)
  - production of **C-reactive protein (CRP):** opsonisation and/or aggregation of bacteria

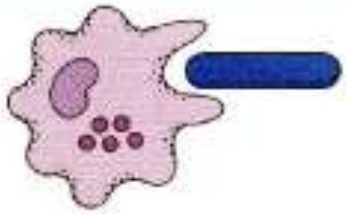
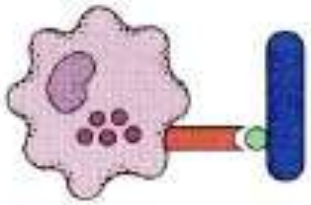
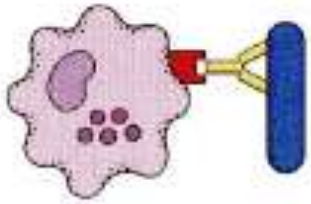
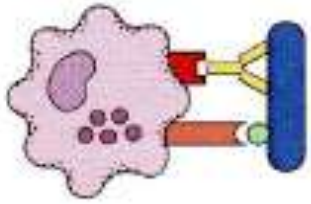
Contribution of the complement system to innate immunity

Activation and effect through different routes

- **Bacterial cell wall mannose** → mannose binding lectin (MBL) → MASP1/MASP2 protease activation → C4/C2 split → C3 convertase → production of C3a and C3b fragments

- **C3a and C5a – neutrophil granulocyte chemotaxis**
- **C3b – opsonisation:**
  bacterium + C3b molecule + phagocyte complement receptor enhanced phagocytosis
- **C5b-C9 - binding Gram negative bacterial lipids** → bacteriolysis bacteriocidia

Opsonisation

phagocyte	opsonin	binding
1 	–	±
2 	complement C3b	+ +
3 	antibody	+ +
4 	antibody and complement C3b	+ + + +

The role of phagocytes in the innate immunity

Phagocytosis

- G-CFS, GM-CSF – augmented production, chemotaxis, tissue entry
- main role: kill extracellular pathogens

Steps of action

- binding (opsonisation +/-) → engulfment and internalisation → phagosome + lysosome fusion → killing in phagolysosome →

oxygen dependent (O_2^-, NO^-)

oxygen independent (enzymes: lysosyme, lactoferrin, defensins)

→ digestion of killed microbes → cell death, debris → constituents of pus

Natural killer cells

Role

- to attach and destroy infected cells

Natural killer (NK) cells

- large, granular lymphocytes
- TCR expression + Fc (CD16) receptor+, MHC-

Mechanism of killing

NK cell receptors + foreign antigen on target cells
FasL + Fas
} Binding →

Production of perforin: pore formation in cell membrane of target cells
granzyme – intracellular induction of apoptosis

Adaptive immune response

Role

- selective destruction of pathogenic microbes
- antigen dependent
- different course in primary and secondary infections (immune memory)

Course

- internalisation of antigens into antigen presenting cell (APC: MØ, DC)
- proteolysis → peptide subunits carrying epitopes
- presenting subunits on MHC-I or MHC-II molecules to effector cells
- activation of effector cells
- destruction of microorganism: by antibodies ← **humoral immunity**
- destruction of infected cells:
- destruction of eukaryotic pathogen:

} cytotoxic cells ← **cellular immunity**

Adaptive immune response: activation of effectors cells I

Cellular immunity

- **cytotoxicity:** naive $CD8^+$TCR + APC MHC-I antigen peptide → activation → binding infected cells → perforin/granzyme → cell destruction
- **helper function:** naive $CD4^+$TCR + APC MHC-II antigen peptide → activation → cytokine production
  - Th1 – boosting cellular immunity
  - Th2 – boosting humoral immunity

Humoral immunity

- **B cells:** BCR + Ag (repetitive epitopes) → activation
  BCR + Th2 cytokines + Ag → activation

  Plasma cells → antibody = immune globulin (Ig) production + immune memory

Adaptive immune response: activation of effectors cells II

γ/δ T cells

- Phylogenetically early γ and δ TCR + Ag recognition w/o MHC restriction → cytotoxic effects, cytokine production
- γ/δ T cells + MHC-like CD1 + Ag → activation of Th1 cells → cytokine production – mucosal immunity

T_{reg} (regulatory T cells)

- Control of immune reaction to inhibit immune reactions against self Ag
- Abnormal functions in the elderly (immunosenescence)

Humoral immunity

Antibody classes

- **IgM** – produced in primary infection: rapid but transient effect
- **IgG** – later in the course of primary infections, lifelong existence (seroconversion)
  Rapid production at high level in secondary infections
- **IgA** – dimer, on the surfaces of the mucous membranes → mucosal immunity
  MALT (BALT, GALT)
  inhibition of binding of microbes to mucosal cell receptors
- **IgD** – "natural" antibody
- **IgE** – in allergic reactions

Functional groups

- **Anti-adhesive antibodies**, IgA – Gram+ bacteria: lipoteichoic acid
  – Gram- bacteria: pili
- **Neutralising antibodies** – binding microbes (virions), exotoxins, enzymes
- **Opsonising antibodies** – Gram+ bacteria, capsule antigens → promoting phagocytosis

Immune reactions against extracellular bacteria I

Activation of the innate immunity

- Gram- bacterial LPS: macrophage activation → cytokine production
- Gram+ bacterial peptidoglycan: complement activation (alternative route)

Complement activation → opsonisation

- Phagocyte Fc receptor + antibody Fc + complement → rapid, efficient internalisation

Major role of antibodies

- IgM/IgG binding → direct bacteriocidia
- IgM – opsonisation, agglutination, lysis
- IgG – **neutralisation** (bacteria, toxins)
- Polysaccharide antigens → IgM (T independent B cell activation)
- *S. aureus* TSST → $CD4^+$ T cell activation → cytokine storm

Immune reactions against extracellular bacteria II

Immune evasion by bacteria

- **Defense strategies of microbes to avoid immune reactions**
  - Inhibition of innate immunity
    weak TLR binding – *S. typhi, Y. pestis, Francisella*
  - Capsule – New antigenic variations
    Masking other antigens (O)
  - *S. aureus* – Fibrin cover
    Protein A: blocks Ig Fc fragment, host cell Ag mimicry
    Catalase: inactivation of lysosomal enzymes
    Leukocidin: membrane damage of phagocytes
  - *S. pyogenes* – Streptolysin: damages lysosomal membranes
    M protein: C3 inactivation

Immune reactions against intracellular bacteria

Infection and survival in phagocytes and macrophages

- Immune defense: mostly cellular immunity
- $CD4^+$ Th1 dominance → IL-12, TNF-α, IFN-γ production → MØ activation
- MØ MHC-I – Ag-expression: $CD8^+$ T cell and NK cell activation → cytotoxycity
- APC MHC-II – Ag-expression → B cell activation → antibody production

Immune evasion by bacteria

- *M. tuberculosis*: **macrophage damage**, inhibition of activation by IFN-γ
- *M. tuberculosis*, Legionella, Chlamydia: **inhibition of the fusion between phagosome – lysosome**
- Shigella, Listeria, Rickettsia: **damages to lysosomal membrane**
- Salmonella, Coxiella: **inhibition of lysosomal enzymes**
- Neisseria, enteric bacteria: **Inhibition of complement activation** ("serum resistance")
  Inhibition of opsonisation
- *Neisseria meningitidis* B: **self antigen mimicry**

Immune defense against virus infections

Viruses = intracellular parasites!

Definitive role of innate immunity

- NK cells activated by IL-12 destroy infected cells very early

The role of antibodies

- unenveloped viruses + Ab → phagocytosis
- enveloped viruses + Ab → lysis of virions
- neutralising antibodies

Destruction of infected cells

- phagocyte MHC-II Ag presentation → Activation of B cells
  → Activation of $CD4^+$ T cells → cytokine production

- many types of infected cells: MHC-I Ag presentation → $CD8^+$ T cells activation
- cells + Ab + complement → lysis, phagocytosis
- ADCC: antibody dependent cellular cytotoxicity (NK Fc receptor + Ab binding)

Immune evasion by viruses

- **Replication in immune cells (**HIV, HHV-6, HHV-7 in $CD4^+$ cells)
- **Persistence:** episomal (*Herpesviridae*), integration (*Retroviridae*)
- **Cell-to-cell spread** avoiding antibodies (*Herpesviridae*)
- **Antigen variations** - shift (influenzaviruses, rhinoviruses)
- **Inhibition of MHC synthesis** (adenoviruses, cytomegalovirus U18 gene product)
- **Interleukin mimicry** (Epstein-Barr virus vIL-10)
- **Complement fragment neutralisation** (HSV-1 – C3b)

Immune defense against protozoa and helminths I

In common speech

- parasite = helminths, protozoa, arthropods (known for centuries)
- medical parasitology
- (microbes = bacteria, viruses, microscopic fungi)

Protozoa: single cell eukaryotes (microscopic size)

Helmiths: multicellular organisms (microscopic – extremely large size)

Immune defense

- inefficient, hardly known → chronic debilitating diseases

Innate immunity

- direct damage – phagocytosis
- alternative complement activation – lysis

Adaptive immuity

- cellular immunity against intracellular parasites
  - cytotoxic T cells
  - IFN-γ activated macrophages

Immune defense against protozoa and helminths II

Adaptive immunity

- **Humoral immunity** against extracellular parasites
  - Complement activation, antibodies: **opsonisation, ADCC, neutralisation**
  - Helminths: Local inflammation, granuloma = localisation → fibrosis
    IgE and IgE-dependent cytotoxicity, allergy
    Th2 cytokine dominance (IL-4, IFN-γ, TNF-α)

Immune evasion by parasites

- Replication inside cells (WBC, liver: malaria, MØ: toxoplasma)
- Protecting shell from host polypeptide (Schistosoma in the lung)
- Enzyme production (Leishmania: antibody digestion)
- Inhibition of phagolysosome fusion (*Toxoplasma gondii*)
- Solubilisation of phagolysosome membrane (*Trypanosoma cruzi*)
- Shift in antigen structure (vegetative forms/cysts)
- Generalized immune suppression

Immunisation I

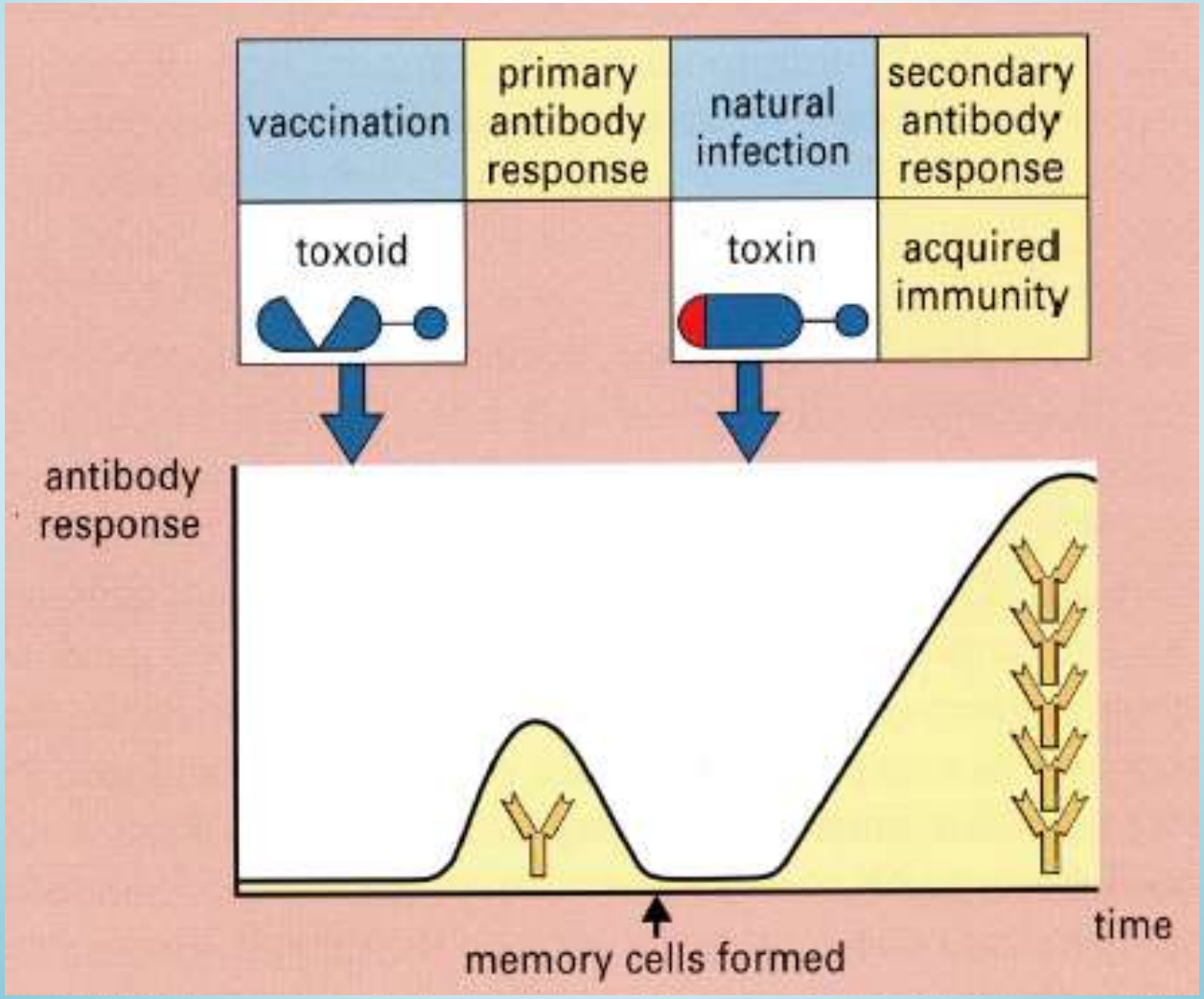
Aim: Immunisation, vaccination – **to protect against invading pathogens**
Different by historical times, geographical regions, target populations

Forms: Active = to mimic primary infection – establishment of adaptive immunity
Passive = to substitute antibodies

Active immunisation

- Introduction of antigen(s) in harmless form → primary infection → immune memory
- Killed microbes
- Living, attenuated (avirulent) microbes
- Attenuated toxins (toxoid)
- Components of microbes (antigen molecules: capsule polysaccahride, polypeptides)
  - **Artificially produced (HPV L1, HBV surface antigen)**
  - DNA vaccination (future)
- Adjuvants
- Slow effect (booster injections), lifelong effect

Active immunisation



Immunisation II

Passive immunisation

- Introduction of antibodies
- Natural: foetus, breast milk (IgG, IgA)
- Artificially: antibodies produced in animals, human (poly-/monovalent), “γ-globulin”
- Immediate but transient effect, no immune memory

Immunomodulation

- Immune therapy (oncology), anti-cytokine MAbs

Immunisation III

Risks and side effects of immunisation

- Reaction (normal) → complication (rare biological effects) → accident (by the product or application)
- **Active immunisation**
  - Living attenuated microbes: generalization (post-vaccination encephalitis)
  - (mutants → reversion: e.g. poliomyelitis virus)
  - Further mutations: loss of antigenicity (BCG)
- **Passive immunisation**
  - Animal serum → hypersensitivity type I (anaphylaxia) and type III (Arthus reaction, serum sickness)

Contraindications

- Acute infectious diseases (including incubation time)
- Immune system disorders, some forms of allergy
- Pregnancy (living attenuated microbes)
- Intervals between vaccination (weeks)

Controlling

- Public health authorities

Abnormal immune reactions: hypersensitivity

Hypersensitivity reactions

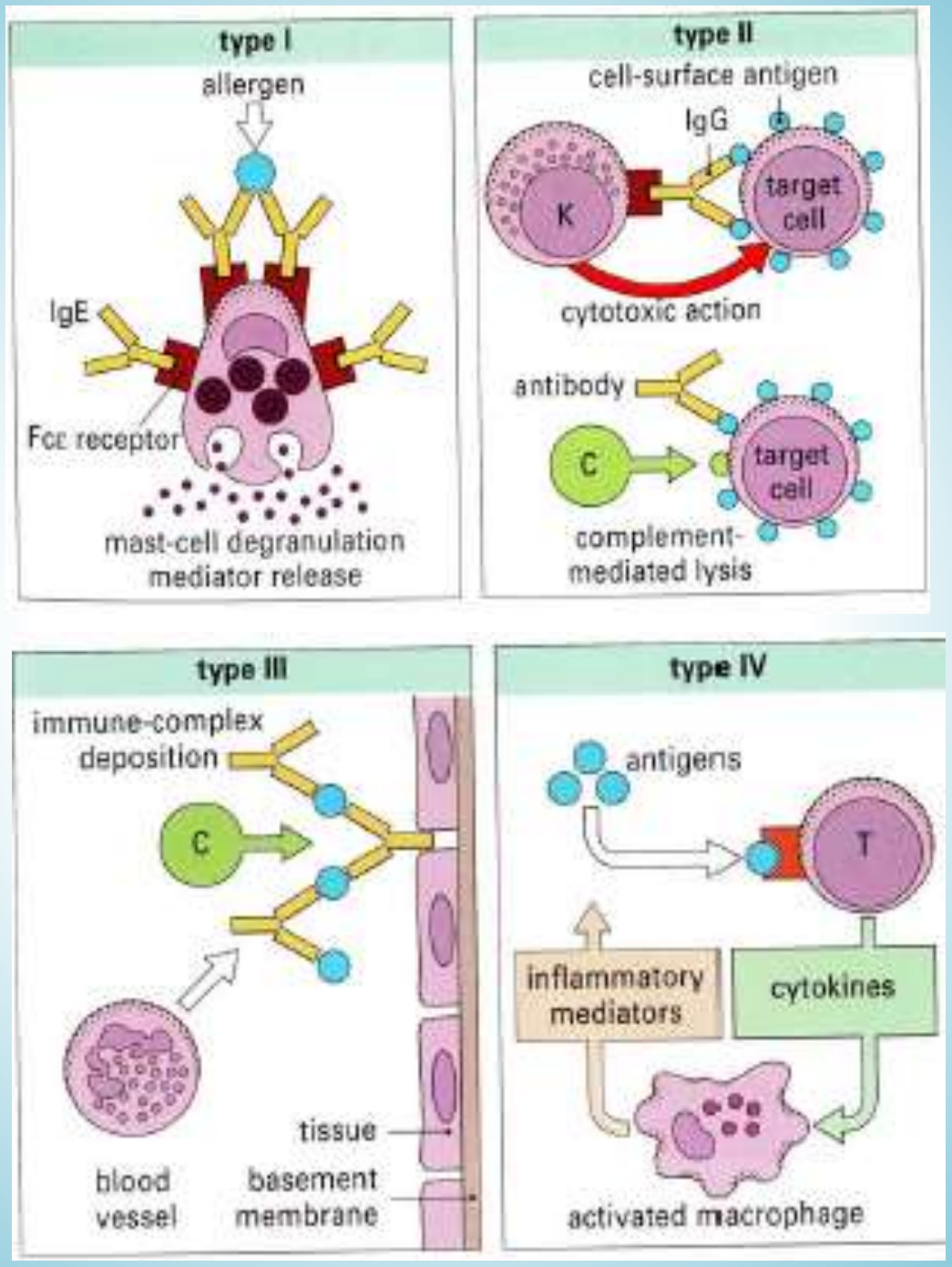
Early types

- **Type I Anaphylaxis**
  - Sensibilisation with Ag (microbes or products, pollen, metals, hay, chemicals, etc. → IgE production → allergy, release of bioactive/vasoactive mediators + Th2 cytokines → shock (death)
  - Generalized or local (skin)
- **Type II Cytotoxic**
  - Cell surface Ag + IgM/IgG → complement mediated lysis, NK activity, ADCC
  - Haptens, drugs, Rh incompatibility
- **Type III Immune complex (Arthus) reaction, serum sickness**
  - Immune complexes are deposited in tissues → complement activation → chemotaxis of PMNL → local tissue damage, inflammation
  - (Kidney: glomerulonephritis)

Late type

- **Type IV Cell mediated hypersensitivity**
  - Intrcellular Ag → Th1 cytokine production → local inflammation → macrophage/T cell concentration → granuloma
  - Tuberculin allergy, Mantoux test

Hypersensitivity reactions



Autoimmunity and immune tolerance

Immune tolerance

- No immune response to a particular antigen/antigens
- Most important: self antigens
- Clonal selection, clonal allergy – established in foetus

Automimmunity

- Immune reactions to self (own) antigens
- Released of sequestered antigens (cell damage)
  mumps virus → damage of testicular cells → inflammation → infertility
- Cross reacting antibodies (microbial antigen ≡ self antigen)
  Streptococcus M protein – heart muscle
  adenoviruses – α-gliadin
  Klebsiella – HLA-B27
  Treponema pallidum – cardiolipin
  Campylobacter jejuni – gangliosides

Blocking antibodies, idiotype network

- Variable (V) region of antibodies ≈ foreign (?) → anti-idiotypic antibodies → binding → blocking → termination of antibody response