Immune system disorders

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Outline

- Introduction to the function of immunity
- Immunodeficiency
  - Primary
  - Acquired
- Failure of immune tolerance
  - Autoimmunity
  - Allergy: Anaphylaxis

Immune system

- complex cellular and humoral system is able to:
  - recognize foreign **antigens** (a specific **sensory function**)

What is antigen?

- **Anti**body **gen**erator
  - Unique molecule which is able to generate adaptive immune response against itself (cellular and humoral)

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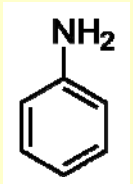
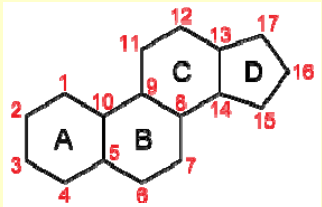
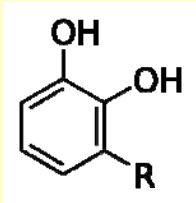
- Protein / peptide
- Polysaccharide
- Combination of protein or polysaccharide with
  - each other
  - **lipids** (LPS)
  - **nucleic acids**
  - other organic molecules (e.g. aniline, steroids, urushiol – poison ivy,)
    - hapten







pentadecylcatechol
e.g. R=$C_{15}H_{31}$

Immune system

- complex cellular and humoral system is able to:
  - recognize foreign **antigens** (a specific **sensory function**)
  - organize defense (**self-controlling and regulatory function**)
  - effectuate suppression or elimination of „the invader“ (**effector functions**)

Role of immunity

- Recognition and discrimination of self and foreign molecules
  - Immune defense
    - Elimination of “danger”, i.e. pathogenic microorganisms and altered self
  - Immune tolerance
    - Tolerance of “safe”, i.e. self and common environmental antigens

Immune system disorders

- Immunodeficiencies
  - Frequent infectins
  - Increased risk of malignancies
  - Frequently associated with autoimmunity/allergy
- Failure of immune tolerance
  - Autoimmunity
  - Allergy
  - Transplantation consequences (graft rejection, GVHD)

Prenatal development is normal in the absence of the immune system

Immunodeficiency

Primary (inborn)

Acquired

Clinical Significance of Immunodeficiency

- Primary immunodeficiencies
  - More than 70 diseases (male / female ~ 2 / 1)
  - Incidence of serious primary immunodeficiencies ~1:1200 (all ~ 1:400 - 1:800)
  - Frequently associated with
    - Autoimmunity
    - Lymphoreticullar malignancies
- **Secondary immunodeficiencies**
  - **are more frequent** then primary
  - the mechanisms are complex

Primary immunodeficiencies

Innate immunity defects

Failure of antigen recognition, presentation and non-specific killing of microbes

Adaptive immunity defects

defects in differentiation and antigen-specific activation of lymphocytes

Primary immunodeficiencies

- Most have recessive type of inheritance (often X-linked)
- Diagnosed usually on the basis of medical history (frequent infections)
- First immunodeficiency was described on 1952 (Ogden C. Bruton)

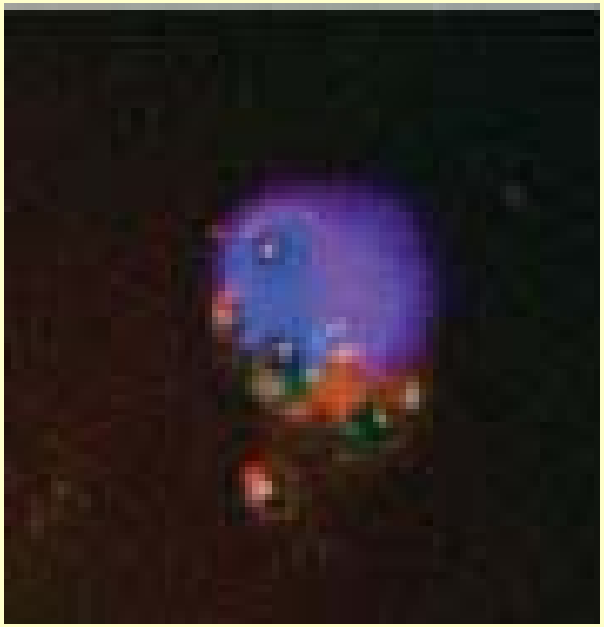
Innate immunity defects

Phagocyte defects

Complement defects

Defects of receptors and signaling pathways of innate immunity

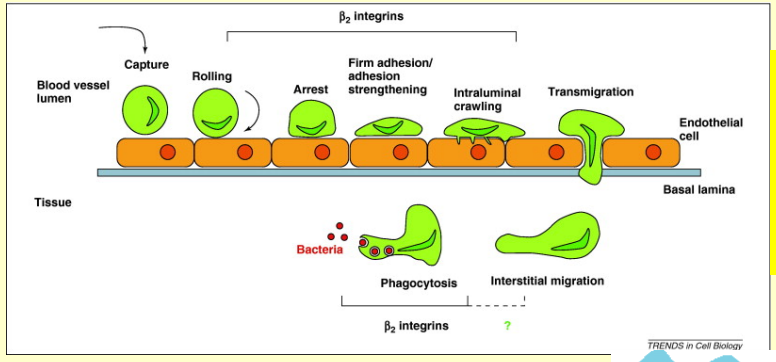
Phagocyte defects



Phagocytosis
Macrophage (blue staining)
engulfing dead neutrophils
(white spots)

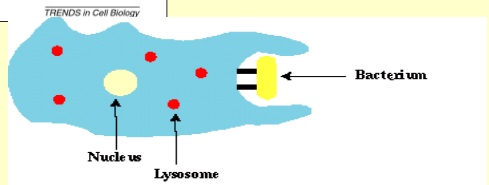
Critical steps in phagocytosis

- Leukocyte recruitment and migration
- Target recognition and phagosome formation
- Vesicle fusion (phagosome – lysosome)
- Target digestion and killing

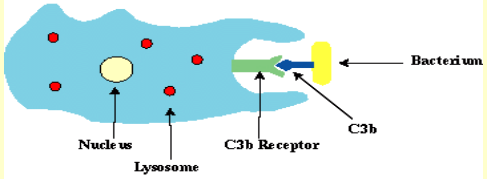


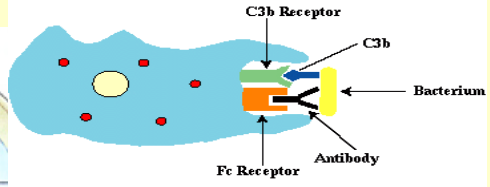
- Adhesion molecules
- Cytokines
- Chemokines

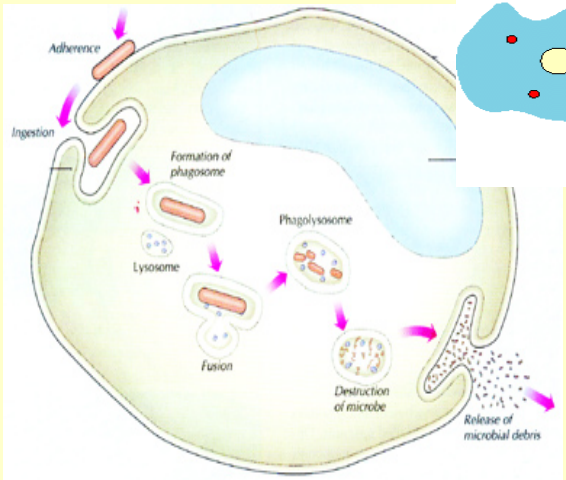
Direct PRRs



Indirect opsonized pathogen







- Digestion enzymes
- Oxidative burst (ROS)

Phagocytosis defects

Persistent bacterial infection

- Adhesion defects
- Defects in intracellular vesicle processing
- Defects in production of enzymes or ability to generate ROS

Adhesion defects

- Defect of leukocyte migration, adhesion, and phagocytosis
- Generalized pyogenic bacteria infections

- Some causes:
  - Defects in the leukocyte integrins (e.g. common β2 subunit (CD18)
  - Defects in the selectin ligand (e .g. sialyl-Lewis^x)

Chronic granulomatose disease

- Rare (~1:200 000)
- Five types distinguished by the gene that is involved
- Mutations in genes that code subunits of an enzyme complex called NADPH oxidase (production of ROS).
- Defective intracellular killing of pathogens (bacteria)

- Defective macrophage activation result in chronic stimulation of CD4 T cells

- Chronic intracellular and extracellular bacterial infections (result in granulomas)

Chediak Higashi sy

- Chronic granulomas
- mutation of LYST gene (lysosomal trafficking regulator gene)
- intracellular vesicle fusion defect

Complement defects

What is complement?

- Blood plasma proteins activated sequentially on response to various stimuli

- Complement activation
  - classical pathway by antigen-antibody complex
  - mannos-binding lectin pathway
  - alternative pathway by some bacterial components

Complement function

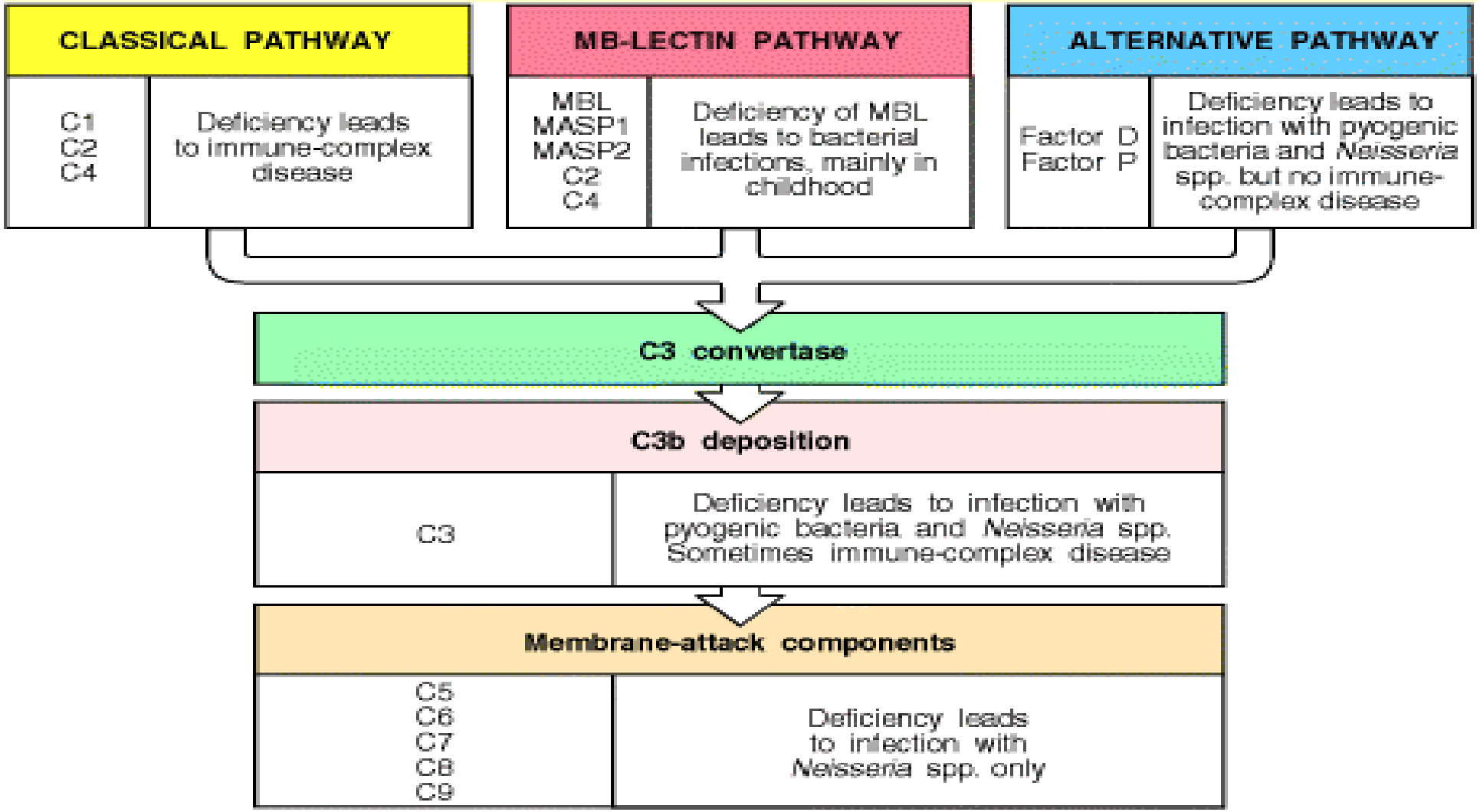
?

Complement function

- Cell lysis (bacteria, somatic cells)
- Amplification of phagocytosis (opsonisation)
- Leukocyte chemotaxis (migration signal)

Defects in complement components

susceptibility to certain infections and accumulation of immune complexes



Defects of receptors and signaling pathways of innate immunity

Defects of receptors and signaling pathways of innate immunity

- **IFNγ receptor deficiency**
  - OMIM:209950, OMIM:107470, OMIM:600263, OMIM:209950, OMIM:147569
- **IL-12 receptor deficiency**
  - OMIM:209950, OMIM:601604
- **IL-12 p40 subunit deficiency**
  - OMIM:209950, OMIM:161561
- **TLR3 deficiency**
  - OMIM:603029, OMIM:603029

OMIM = Online Mendelian Inheritance in Man

Adaptive immunity defects

Combined immunodeficiencies

Predominantly antibody immunodeficiencies

Other well defined immunodeficiencies

WHO classification of primary immunodeficiencies

J. Immunol. Published online November 16, 2009 suggested novel classification

General causes of adaptive immunity defects

- Failure of T and/or B lymphocyte development, differentiation and maturation
- Failure of antigen-dependent differentiation of T and/or B cells
- Failure of T – B lymphocyte communication

Cell mediated and humoral immunity defects

Consequences of defects in cell mediated immunity

- Disseminated viral infections
  - mainly HSV, VZV, CMV
- Fungal infections (cutaneous, mucosal or systemic)
- Failure of antibody response to T-cell dependent antigens (proteins)
  - if CD4 Th lymphocytes defect

Consequences of defects in antibody immunity

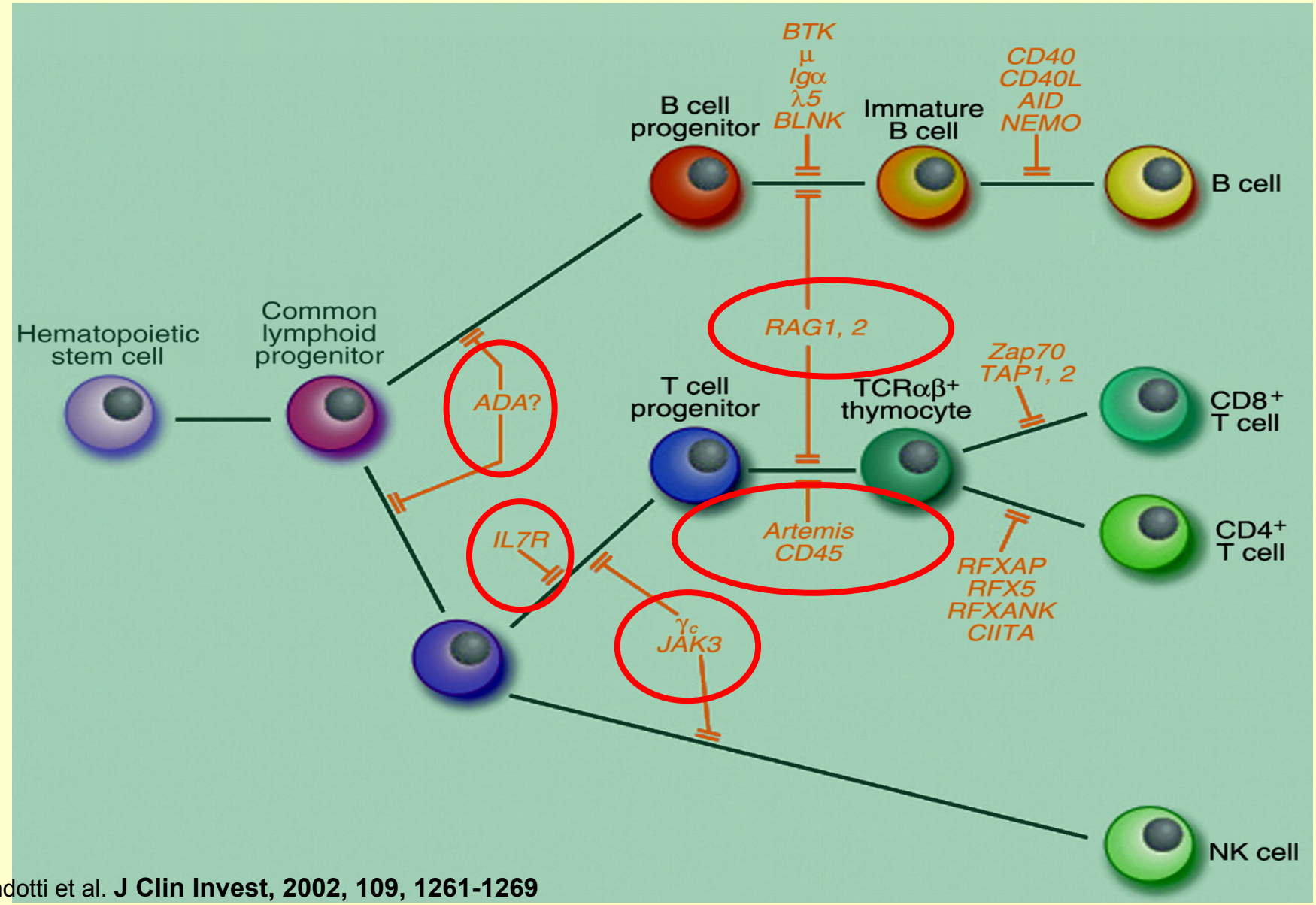
- Pyogenous bacteria infections
  - respiratory, neural system, bacteriemia
- Almost normal response to viral infections (e.g. Rubeola, Varicella-zoster)
  - Exceptions
    - HBV infection – progressive fatal course
    - Polyomyelititis immunization
    - Adenoviral encephalomyelitis

Combined immunodeficiencies

Combined immunodeficiencies (CID and SCID syndromes)

- Failure of cell mediated and humoral immunity
- Susceptibility to severe fungal, bacterial and viral infections
- Caused by mutations in genes responsible for differentiation of T, B and NK cells
- Incidence 1:100 000 – 1:1 000 000

Molecular defects known to be responsible for SCID sy



Candotti et al. **J Clin Invest, 2002, 109, 1261-1269**

Combined immunodeficiencies

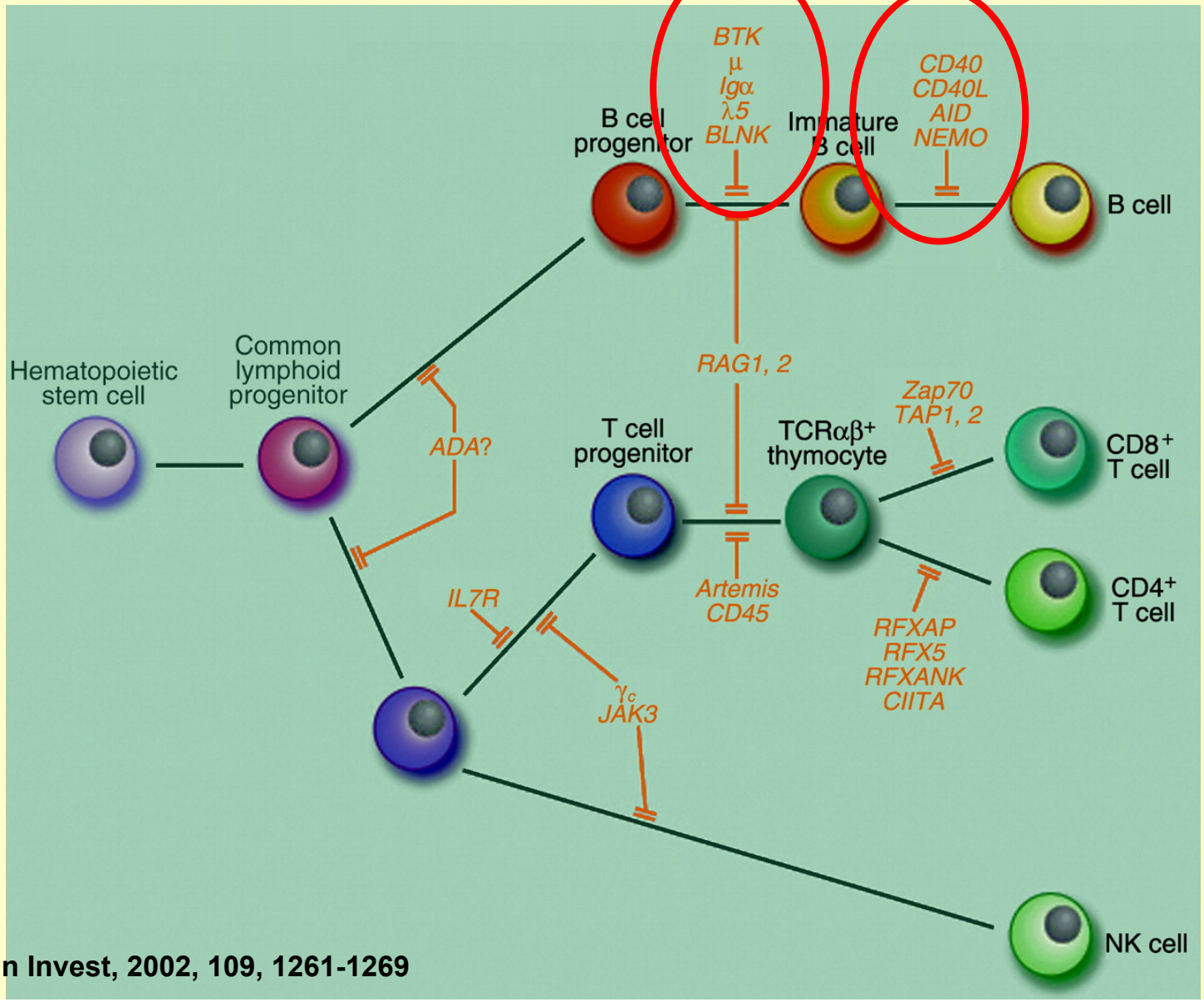
- SCID X-linked
  - deficiency of common γ chain of IL2, 4, 7, 9, 15 receptors
- SCID autosomal recessive
  - JAK3 deficiency
  - Adenosin deaminase (ADA) deficiency
  - Purine nucleoside phosphorylase (PNP) deficiency
  - MHC II deficiency

Predominantly antibody immunodeficiencies

Predominantly antibody immunodeficiencies

- **X-linked agammaglobulinemia (Bruton)**
- Autosomal recessive hypogammaglobulinemia
  - mutation of Ig heavy chain gene
  - mutation of κ chain
- **Selective IgA deficiency**
- **CVID**
- Selective deficiency of IgG subclasses (with or w/o IgA deficiency)
- Ig deficiency with hyper IgM

Molecular defects known to be responsible for defects in humoral immunity



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Bruton's X-linked agammaglobulinemia

- First described immunodeficiency (Ogden C. Bruton, 1952)
- Defect of *Btk* gene function (Bruton's tyrosin kinasa)
  - growth and differentiation of pre B lymphocytes
- Frequent infections with pyogenic bakteria (e.g. *Streptococcus pneumoniae*)
- Mycoplasma infections - arthritis

Selective IgA deficiency

- Incidence: 1:600 - 1:700 (Caucasians)
- Serum IgA <50 μg/mL (normal or > IgM a IgG)
- Differentiation block of the B lymphocytes into IgA producing plasma cells (normal α-heavy chain)
  - inner defect of B lymphocyte differentiation
  - dysfunction of helper T lymphocytes (IL-5, TGF-β)
  - inability of B lymphocytes to respond to differentiation signals from T lymphocyte

Selective IgA deficiency

- Variable clinical manifestation:
  - Without clinical manifestation
  - Higher frequency of respiratory infections and gastrointestinal infections
  - Frequent severe infections of respiratory tract and GIT (may lead to permanent tissue damage)

Increased incidence of bronchial asthma, atopy, and arthritis

Common variable immunodeficiency (CVID)

- Heterogeneous group of disorders (20-30)
  - prevalence 1:50 000
- B-lymphocytes normal counts of polyclonal immature B lymphocytes
- Pathogen stimulated antibody response is insufficient
- cause?
  - Failure of differentiation of B cells to plasma cells
- Autoimmunity in 20% of CVID pts.

Other well defined immunodeficiencies

Other well defined immunodeficiencies

- Wiskott-Aldrich sy
- DiGeorge sy
- Ataxia telangiectasia

Wiskott-Aldrich sy

- WAS gen pX chromosome (WASp, 1994)
  - Eczemas
  - Thrombocytopenia (bloody diarrhea)
  - Recurrent infections
- Low levels of IgM (IgA, IgE elevated)
- Normal B cell count
- Defect in anti-LPS antibody generation
- Reduction of T cells (with time)

DiGeorge sy

- Isolated defect of T lymphocytes
  - Ig levels are often normal
  - Ig response is insufficient (IgG and IgA)
- Congenital thymic aplasia with other birth defects (e.g. heart and vessel malformation)

- Deletion of part of chromosome 22q11 or > 10p (responsible gene unknown)
- Immune defect is getting better with age

Ataxia telangiektasia

- ATM gene mutation (recessive)
- ~ 1% of heterozygotes
  - but incidence 1:10 000-100 000
- Defect in the ability to repair DNA breaks (= defect in the TCR and BCR rearrangement)
  - Imunodeficiency (respiratory infections ~ COPD)
  - Cerebellar ataxia (poor coordination)
  - Muscle atrophia
  - Telangiectasia: dilated small blood vessels
  - Tumors

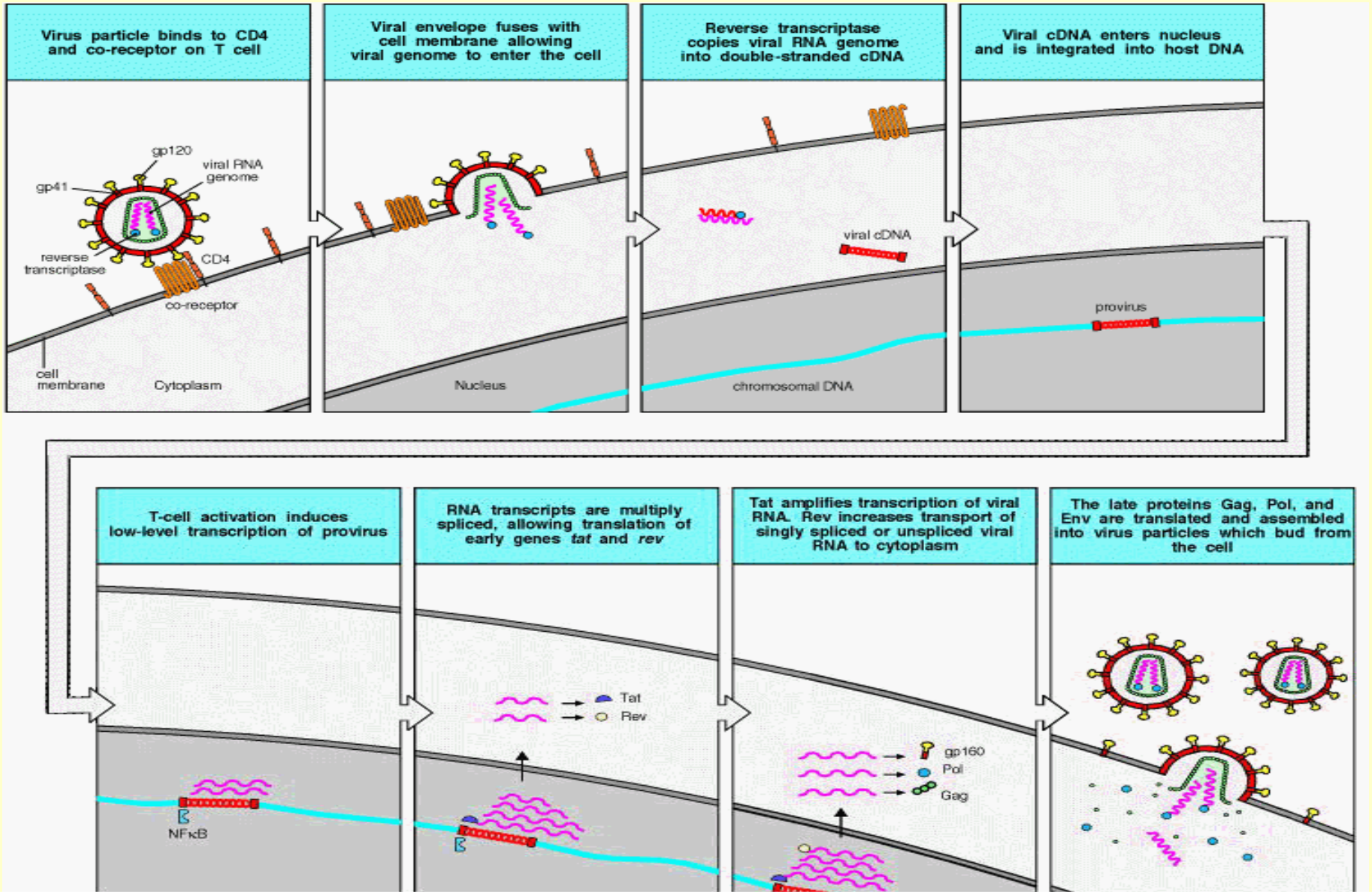
Acquired immunodeficiencies

Inhibition of immune reactions by pathogen

- Permanent destruction of the immune system (HIV, HLTV)
- Temporal depression of the immune system:
  - acute viral infections suppress cellular immunity for several days to a few weeks
  - serious bacterial infections inhibit the ability of neutrophils to respond to chemotactic agents
  - Parasitic worm infections (e.g. schistosomiasis) may lead to deviation of immune response (Th1>Th2) resulting in decreased ability to form antibodies after antigenic challenge

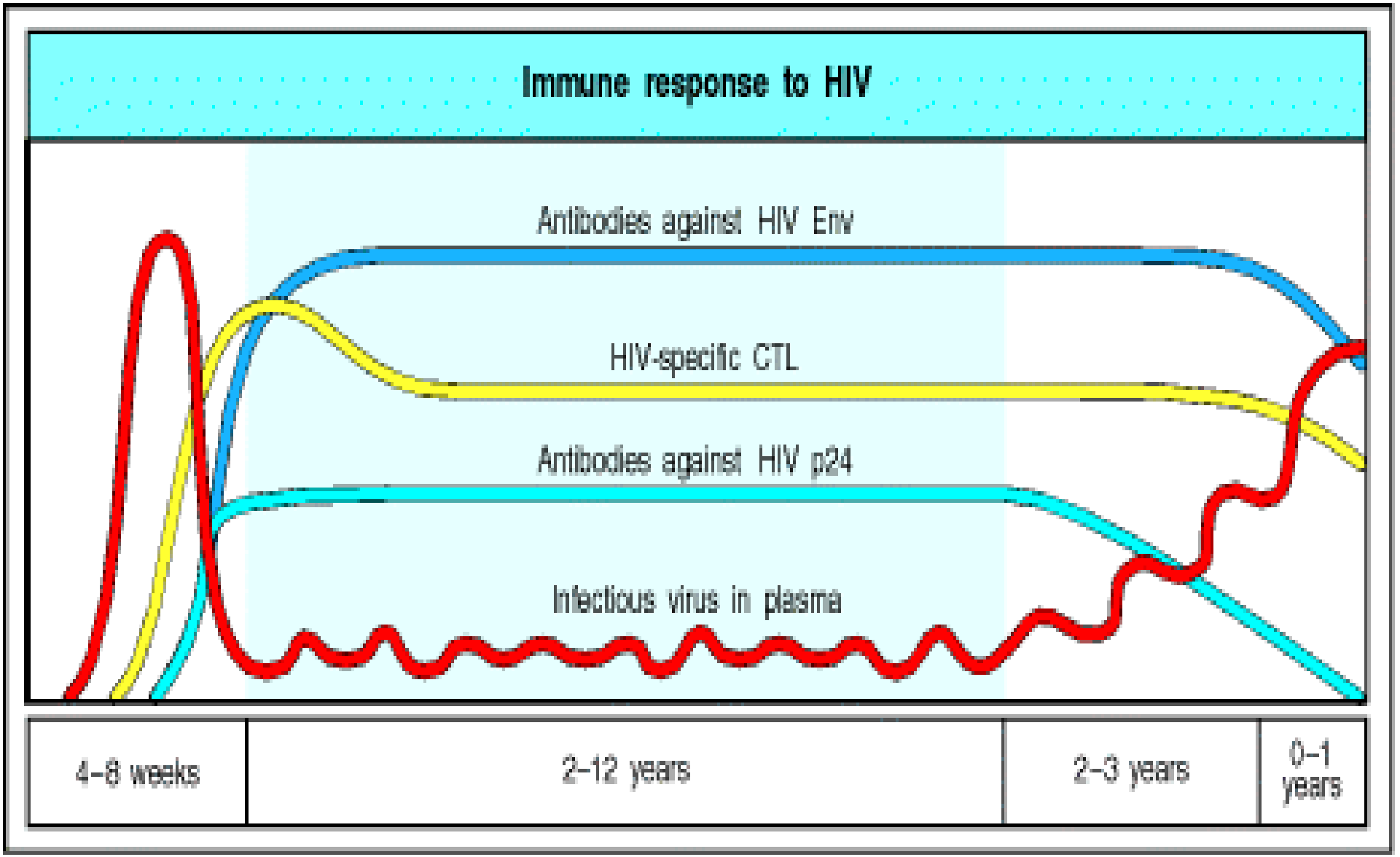
HIV Infection and AIDS:

Infection of CD4+ T cells (Th) + other cells with CD4

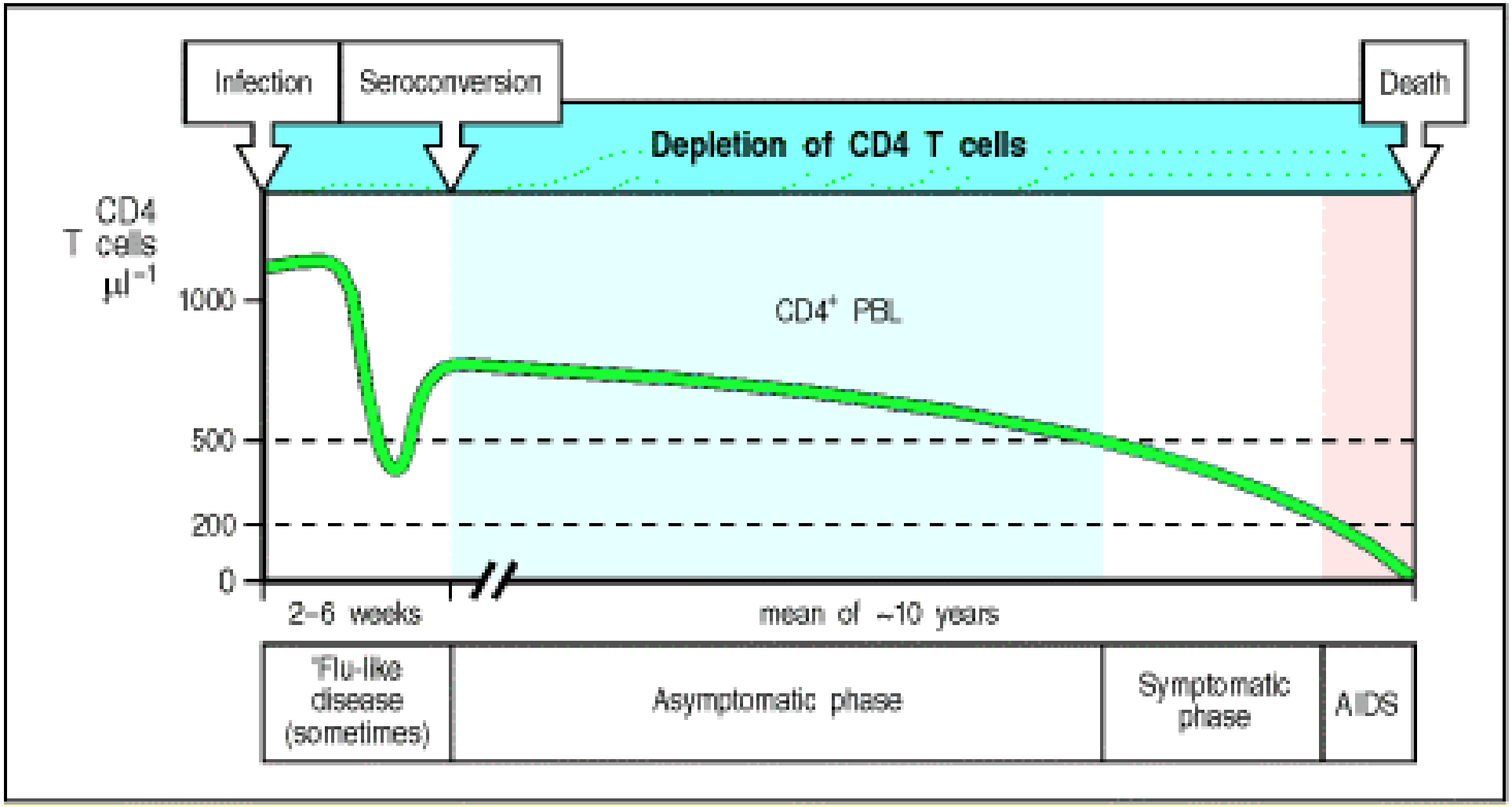


The immune response to HIV

immune response controls but does not eliminate HIV



The typical course of untreated infection with HIV (gradual decrease of CD4+ T cells)



Consequences of HIV infection

- Susceptibility to opportunistic infection:
  - Viral infections (e.g. cytomegalovirus, HSV, KSV)
  - Parazites (lung pneumocystsis, toxoplasmosis)
- Diarrhea (HIV and other infections)
- Increased risk of tumors
  - Kaposiho sarcoma, lymphomas
- Dementia (virus penetrates into the CNS)

Staphylococcus infections

- Production of superantigens
  - e.g. enterotoxin a toxic shock syndrome toxin-1
- Superantigens bind to TCR of most T cells and cause nonspecific polyclonal activation = rapid proliferation and subsequent cell death (apoptosis, AICD)

  → generalized immunosupression

Measles virus infection

- Cause:
  - Infection and damage of dendritic cells (APC) → defect in activation of T lymphocytes
- Consequences:
  - Transient immunodeficiency T and B cell functions are affected (especially DTH)
- May last several months after the infection
- Susceptibility to mycobacterial infekctions

Malnutrition

- World leading cause of immunodeficiency
- Protein-calorie malnutrition
  - profound deficiency in the production and function of T cells
- Iron or vitamin A deficiency
- Respiratory and gastrointestinal infections

Malignant disorders of lymphoreticular tissues

- Malignant myeloma / plasmocytoma
- Lymphoma
- Leukemia (ALL, AML, CLL)
- etc

Damage to immune system by external factors

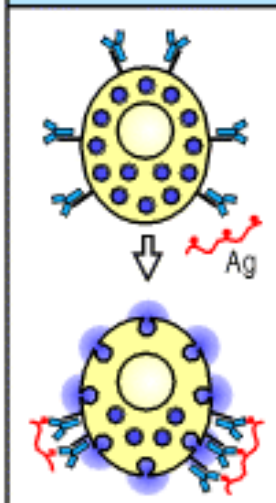
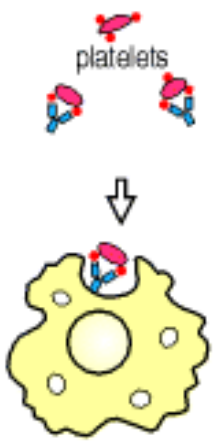
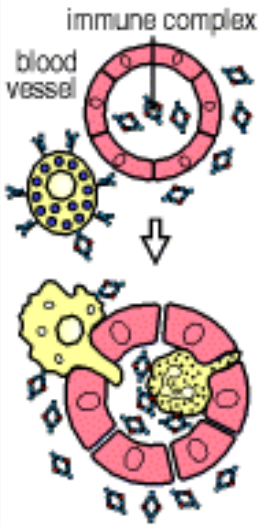
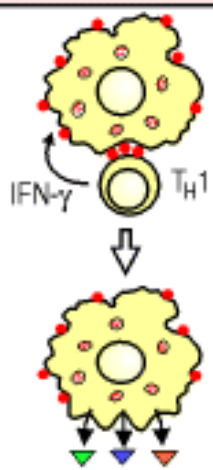
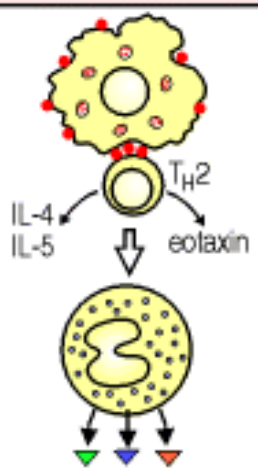
- burns, trauma, chemotherapy, ionizing radiation

Failure of immune tolerance

Autoimmunity

Allergy and hypersensitivity

Types of pathologic immune reactions

	Type I	Type II	Type III	Type IV		
Immune reactant	IgE	IgG	IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	FcR^+ cells (phagocytes, NK cells)	FcR^+ cells Complement	Macrophage activation	Eosinophil activation	Cytotoxicity
						
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g., penicillin)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

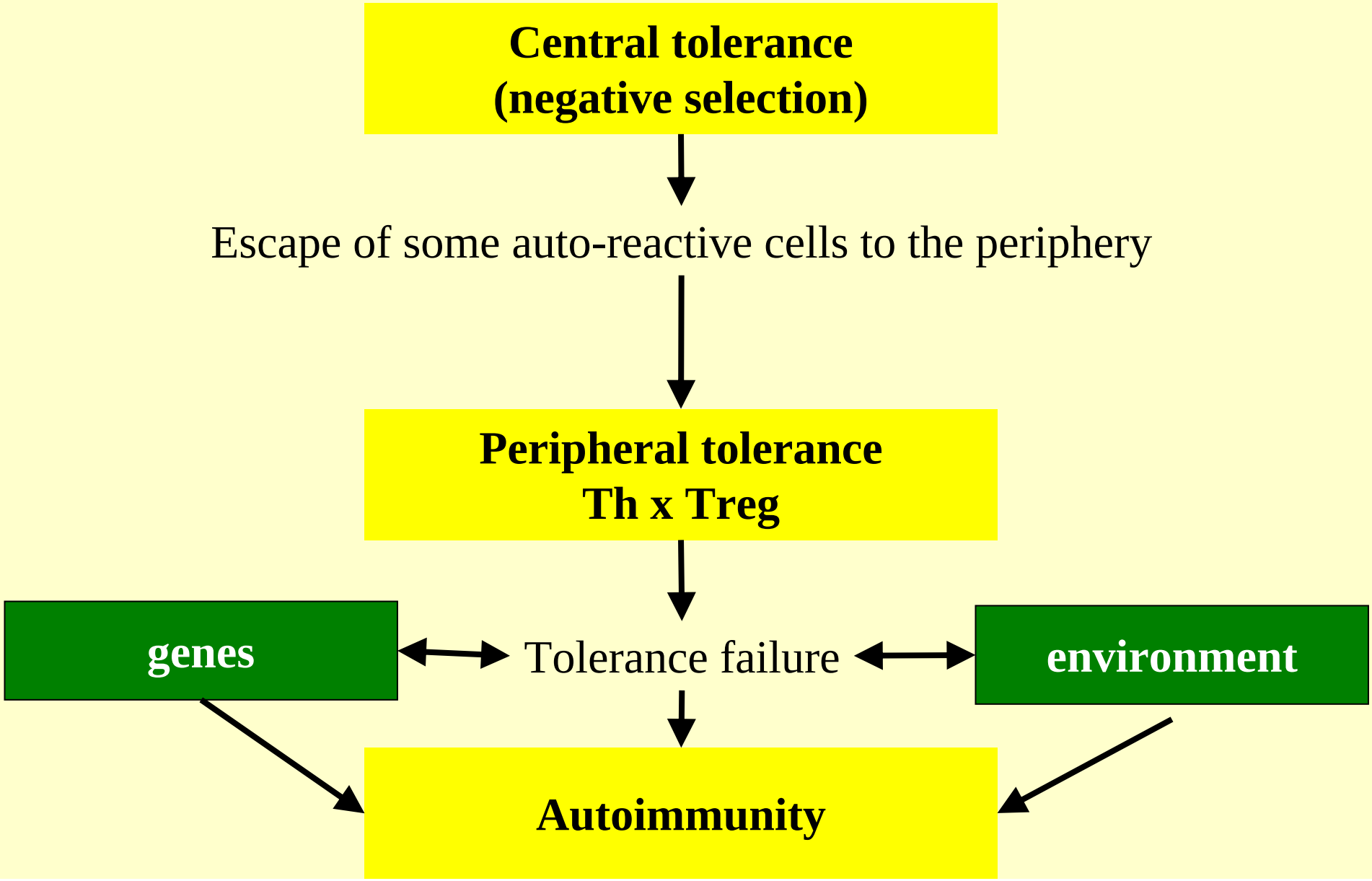
Autoimmunity

Pathologic immune reaction to self (auto) antigens resulting in the damage of cells and tissues

Clinical significance of autoimmune diseases

- More than 80 diseases
- ~ 5% of population
- Clinically manifested usually in middle age
- High morbidity and mortality
- Women are affected more often
- With some exceptions:
  - DM type 1, Ankylosing spondilitis, Polyarteritis nodosa

Development of Autoimmune Disease



Mechanisms of autoimmune damage

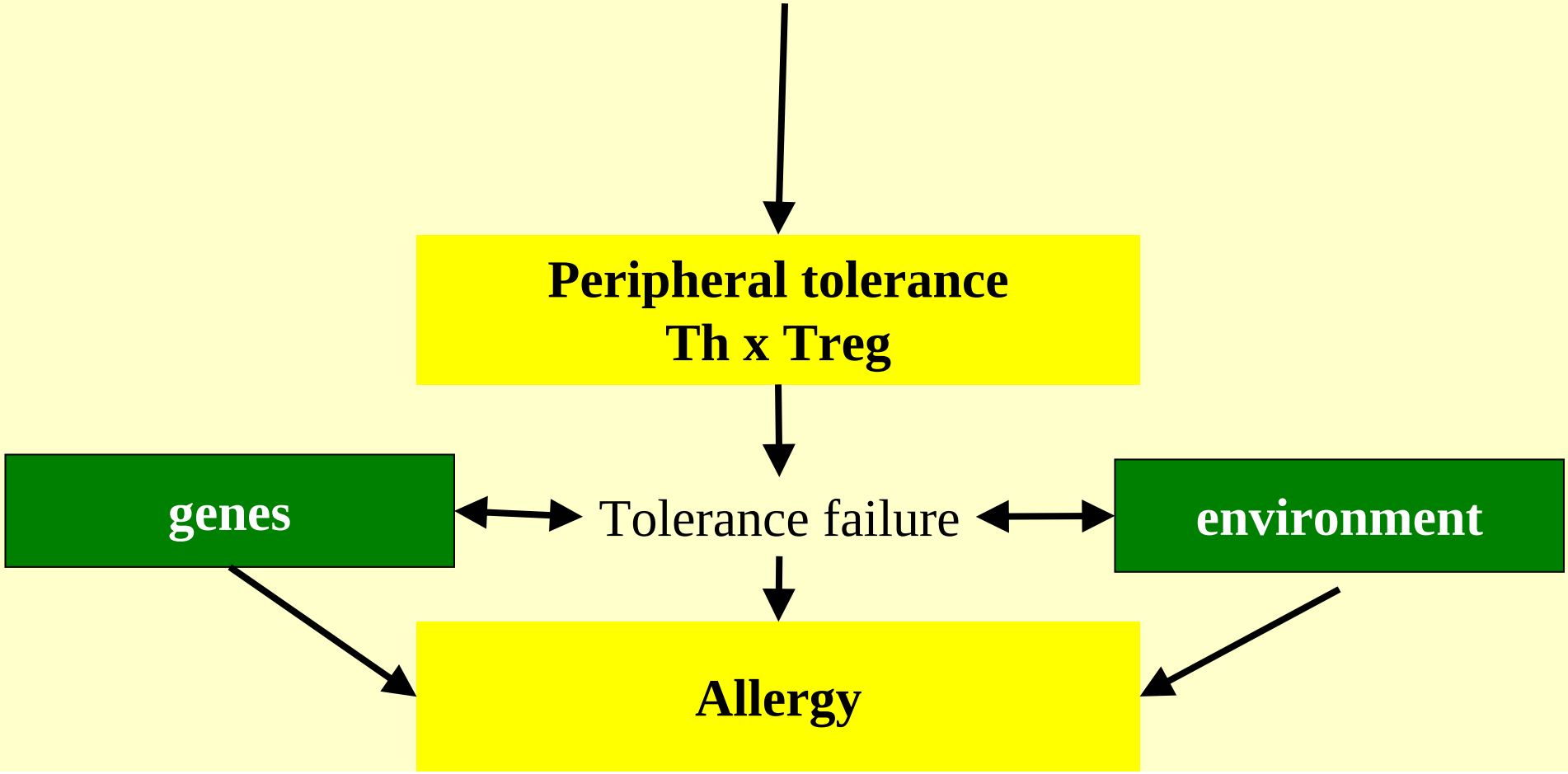
- **Antibody mediated damage**
  - Lysis of cells
  - Interaction with cell receptor
  - Immunocomplex deposition
  - Antibody-dependent cell cytotoxicity (ADCC)
- **T lymphocyte mediated damage**
  - CD4+ T cells mediated or activated CD8+ CTL
- **Non-specific inflammatory mechanisms**

Alergy / Hypersensitivity

Pathologic immune reaction to "harmless" environmental antigens (allergens)

Development of Allergy

T and B cells with the ability to recognize common environmental antigens are in the periphery

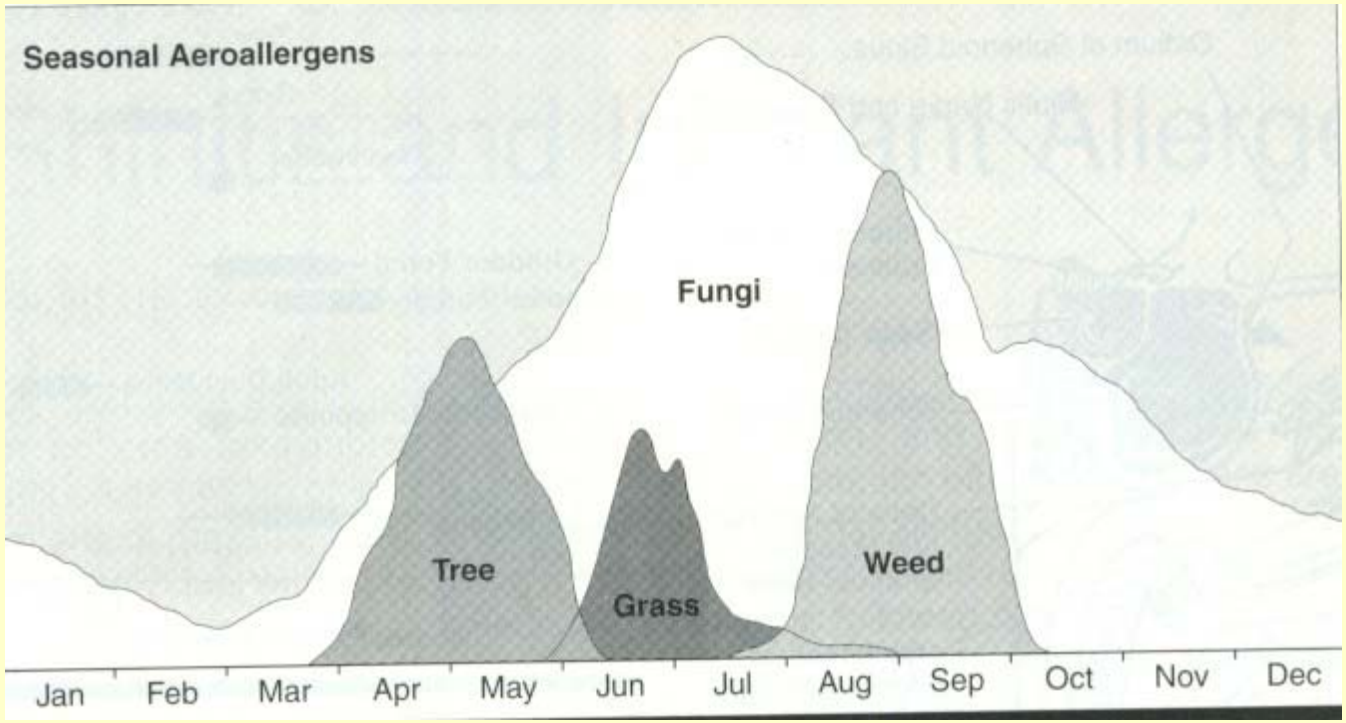


IgE mediated allergy (Type I reaction)

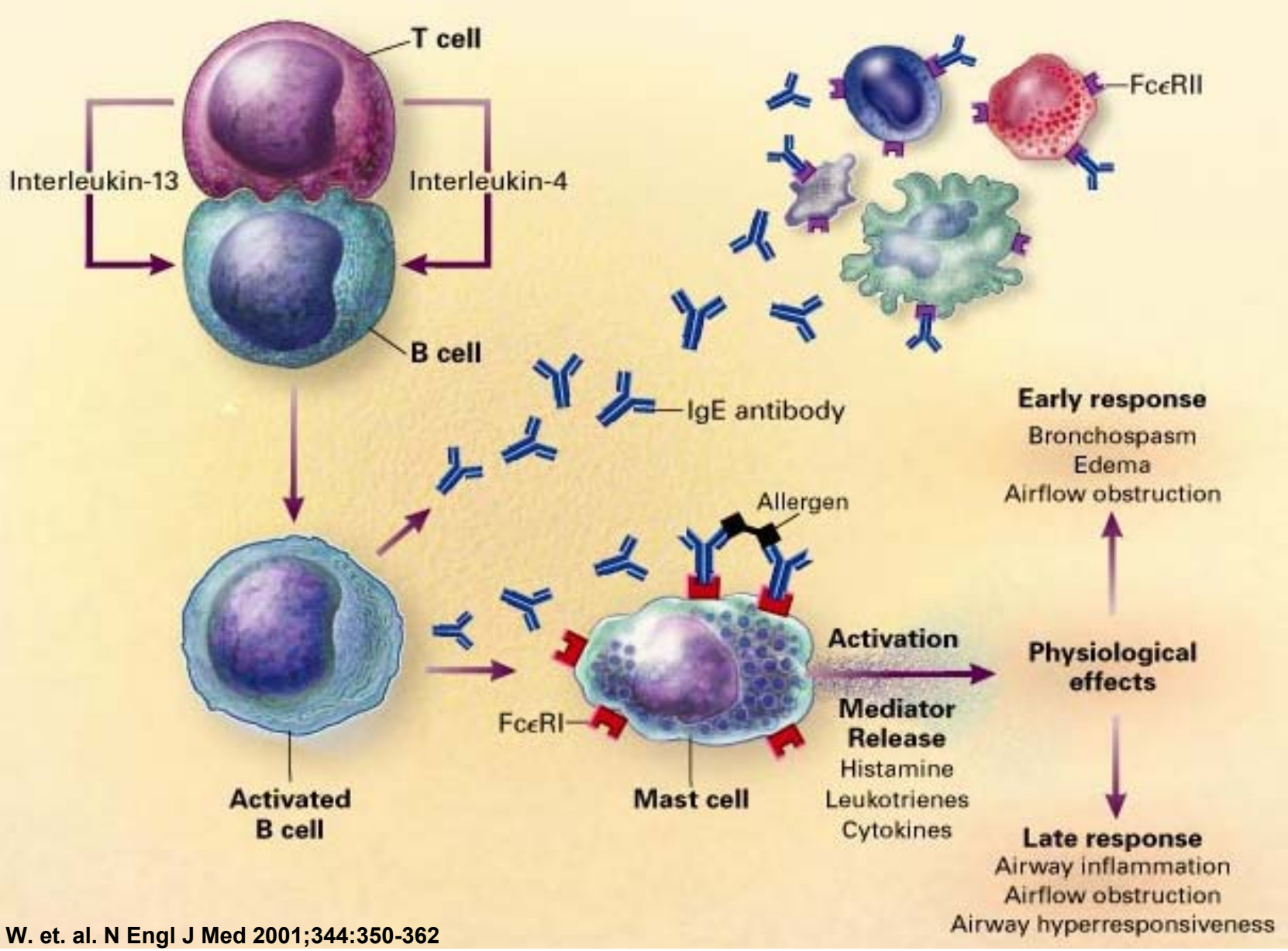
Syndrome	Common allergens	Route of entry	Response
Systemic anaphylaxis	Drugs Serum Venoms Peanuts	Intravenous (either directly or following oral absorption into the blood)	Edema Increased vascular permeability Tracheal occlusion Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Insect bites Allergy testing	Subcutaneous	Local increase in blood flow and vascular permeability
Allergic rhinitis (hay fever)	Pollens (ragweed, timothy, birch) Dust-mite feces	Inhalation	Edema of nasal mucosa Irritation of nasal mucosa
Asthma	Danders (cat) Pollens Dust-mite feces	Inhalation	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Tree nuts Peanuts Shellfish Milk Eggs Fish	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis (rarely)

ALLERGENS

- **Year-round symptoms:**
  - **Dust mites**
  - **Pets hair**
  - **Cockroaches**
  - **Mice excrements**
- **Latex**
- **Seasonal:**

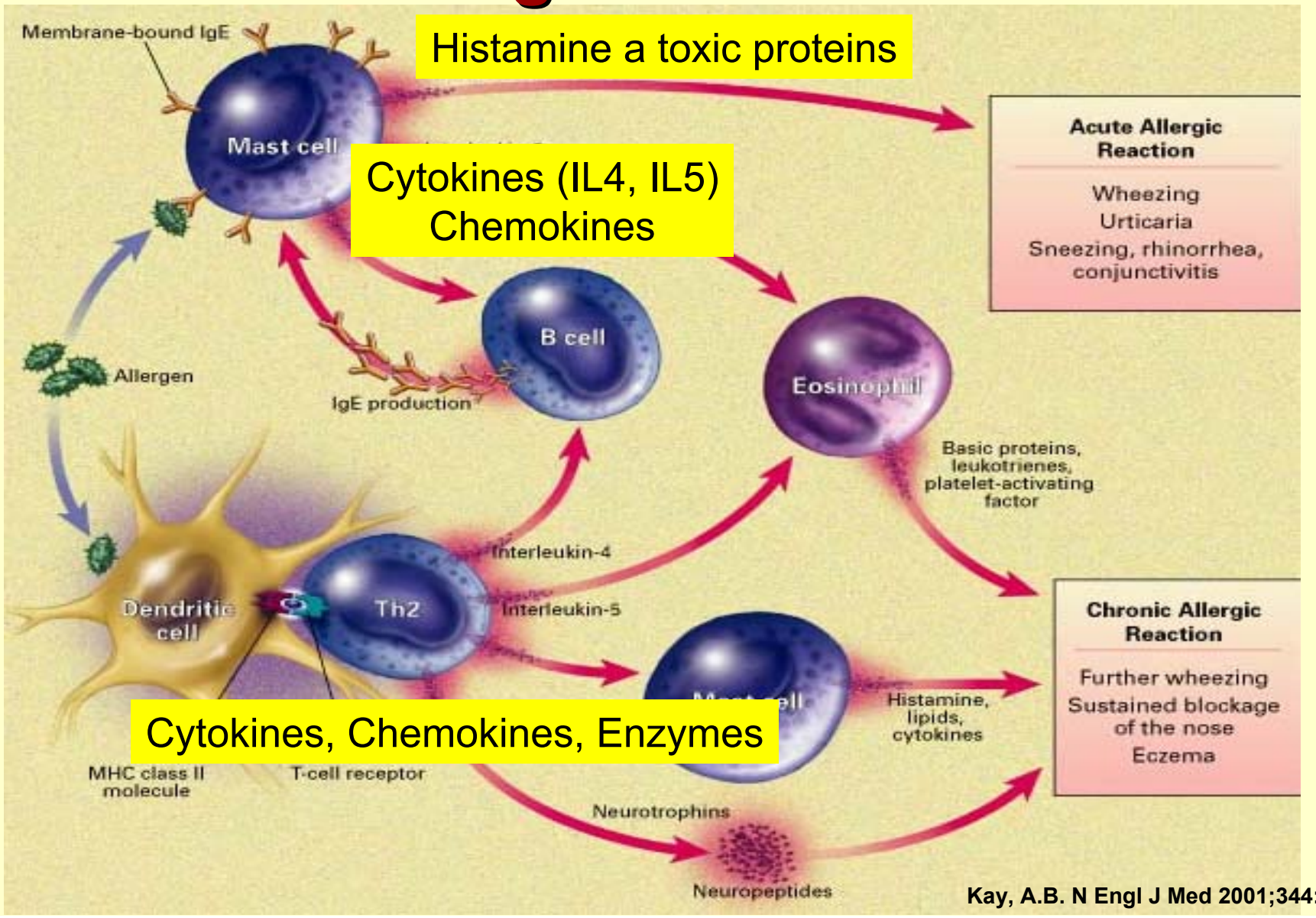


Interactions between CD4 T Cells and B Cells Are Important in IgE Synthesis



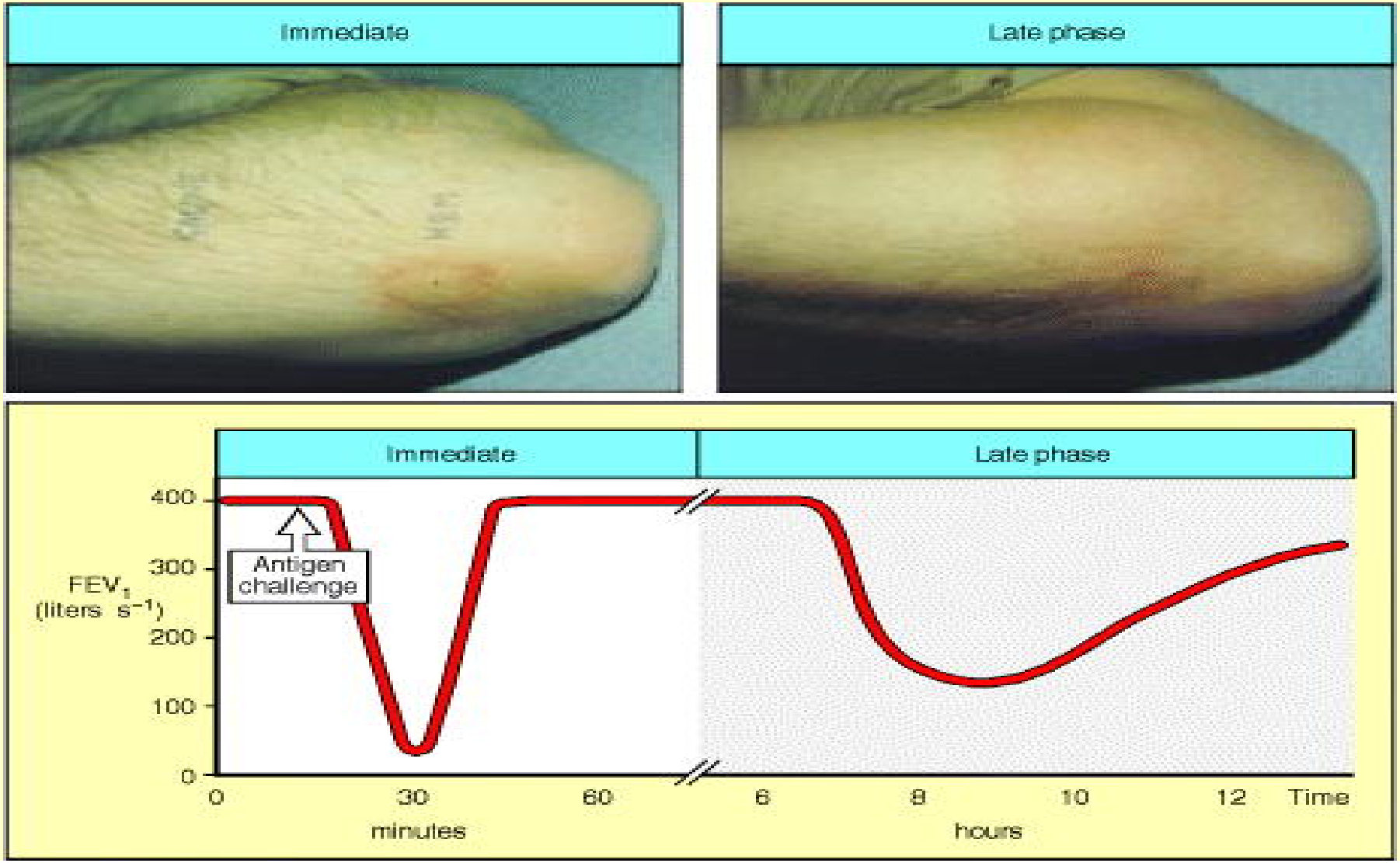
Busse, W. W. et. al. N Engl J Med 2001;344:350-362

Pathways Leading to Acute and Chronic Allergic Reactions



Kay, A.B. N Engl J Med 2001;344:30-37

Allergic reactions can be divided into an immediate response and a late-phase response



Molecules released by mast cells on activation

Class of product	Examples	Biological effects
Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodel connective tissue matrix
Toxic mediator	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction
Cytokine	IL-4, IL-13	Stimulate and amplify T_H2 cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
	TNF-α (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium
Chemokine	MIP-1α	Attracts monocytes, macrophages, and neutrophils
Lipid mediator	Leukotrienes C4, D4, E4	Cause smooth muscle contraction Increase vascular permeability Stimulate mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Molecules released by eosinophils on activation

Class of product	Examples	Biological effects
Enzyme	Eosinophil peroxidase	Toxic to targets by catalyzing halogenation Triggers histamine release from mast cells
	Eosinophil collagenase	Remodels connective tissue matrix
Toxic protein	Major basic protein	Toxic to parasites and mammalian cells Triggers histamine release from mast cells
	Eosinophil cationic protein	Toxic to parasites Neurotoxin
	Eosinophil-derived neurotoxin	Neurotoxin
Cytokine	IL-3, IL-5, GM-CSF	Amplify eosinophil production by bone marrow Cause eosinophil activation
Chemokine	IL-8	Promotes influx of leukocytes
Lipid mediator	Leukotrienes C4, D4, E4	Cause smooth muscle contraction Increase vascular permeability Increase mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Anaphylaxis

- Reaction to antigen-induced IgE-mediated release of active substances in previously sensitized individual

- The cause is pathologic immune reaction type I. (IgE hypersenzitivity)

Reaction to active substances

- Vasodilatation
- Increased Capillary Permeability
- Smooth Muscle Spasm

Vasodilatation

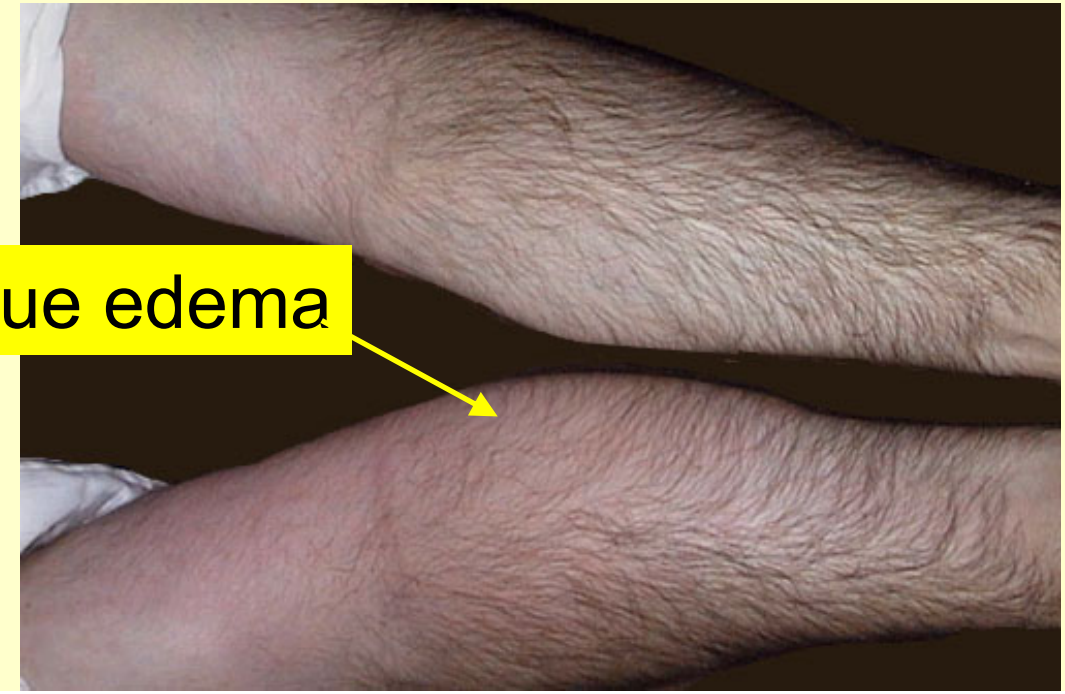
- Decreased peripheral vascular resistance
  - Hypotension
  - Tachycardia
  - Peripheral hypoperfusion (hypoxia)

Hypovolemic shock

Hypoxia

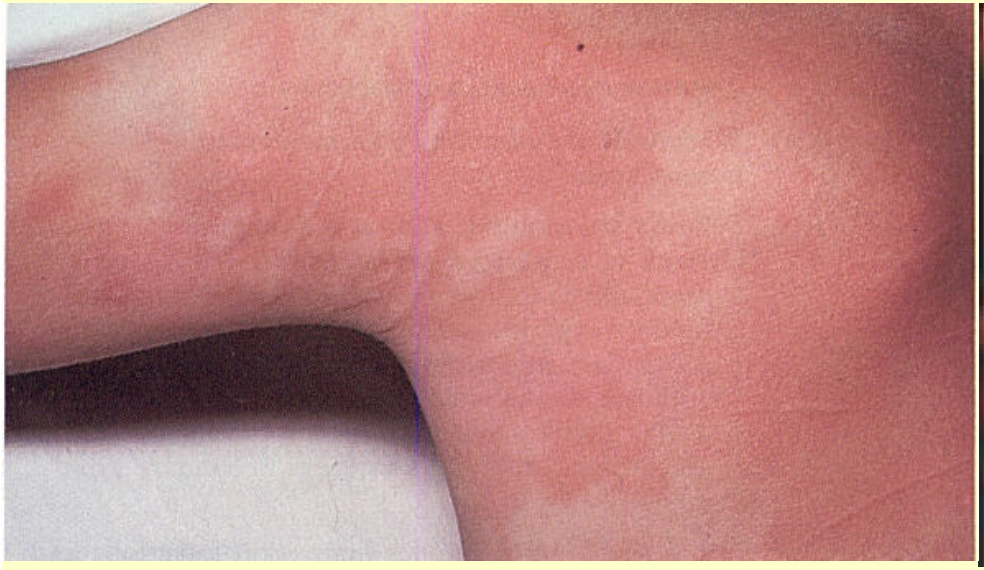
Increased Capillary Permeability

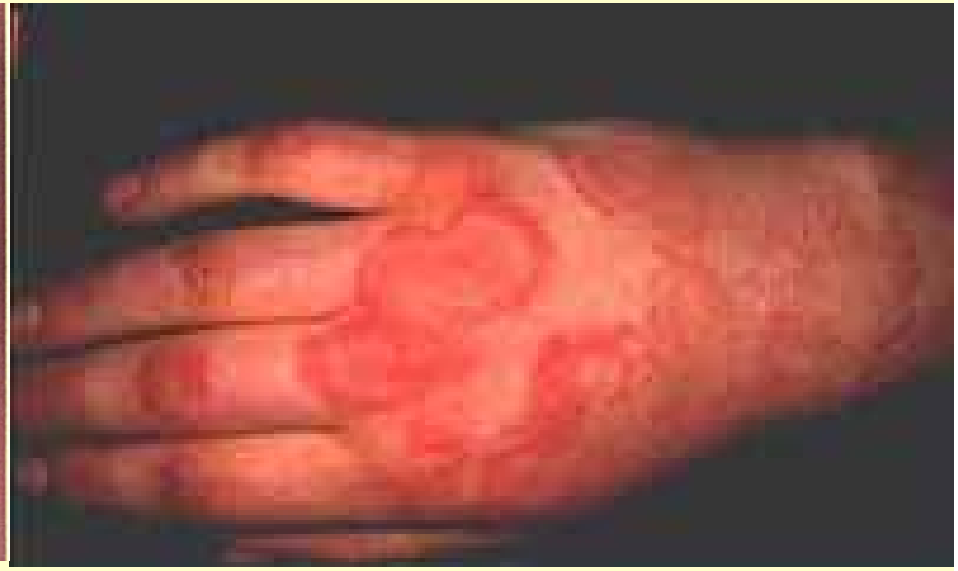
- Fluid leakage from vascular space
  - Tissue edema



Increased Capillary Permeability

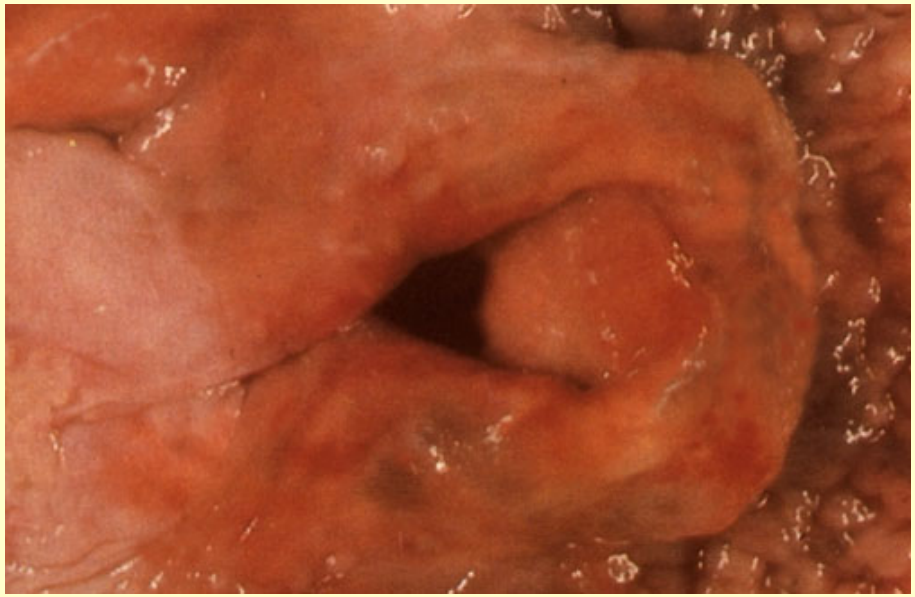
- Fluid leakage from vascular space
  - Tissue edema
  - Hives (urticaria)





Increased Capillary Permeability

- Fluid leakage from vascular space
  - Tissue edema
  - Hives (Urticaria)
  - Laryngeal edema



Increased Capillary Permeability

- Fluid leakage from vascular space
  - Tissue edema
  - Hives (Urticaria)
  - Laryngeal edema
  - Decreased intravascular volume

Airway obstruction

Hypovolemic shock

Hypoxia

Smooth Muscle Spasm

- Bronchospasm
  - shortness of breathGI Tract Spasm
- GI tract spasm
  - nausea, vomiting, cramping, diarrhea
- Bladder Spasm
  - Urinary urgency, incontinence

Cause of death in anaphylactic reaction

- Laryngeal edema and respiratory failure > 70%
- Failure of circulation > 25%
- Other causes < 5% (CNS, MI)

THERAPY!!

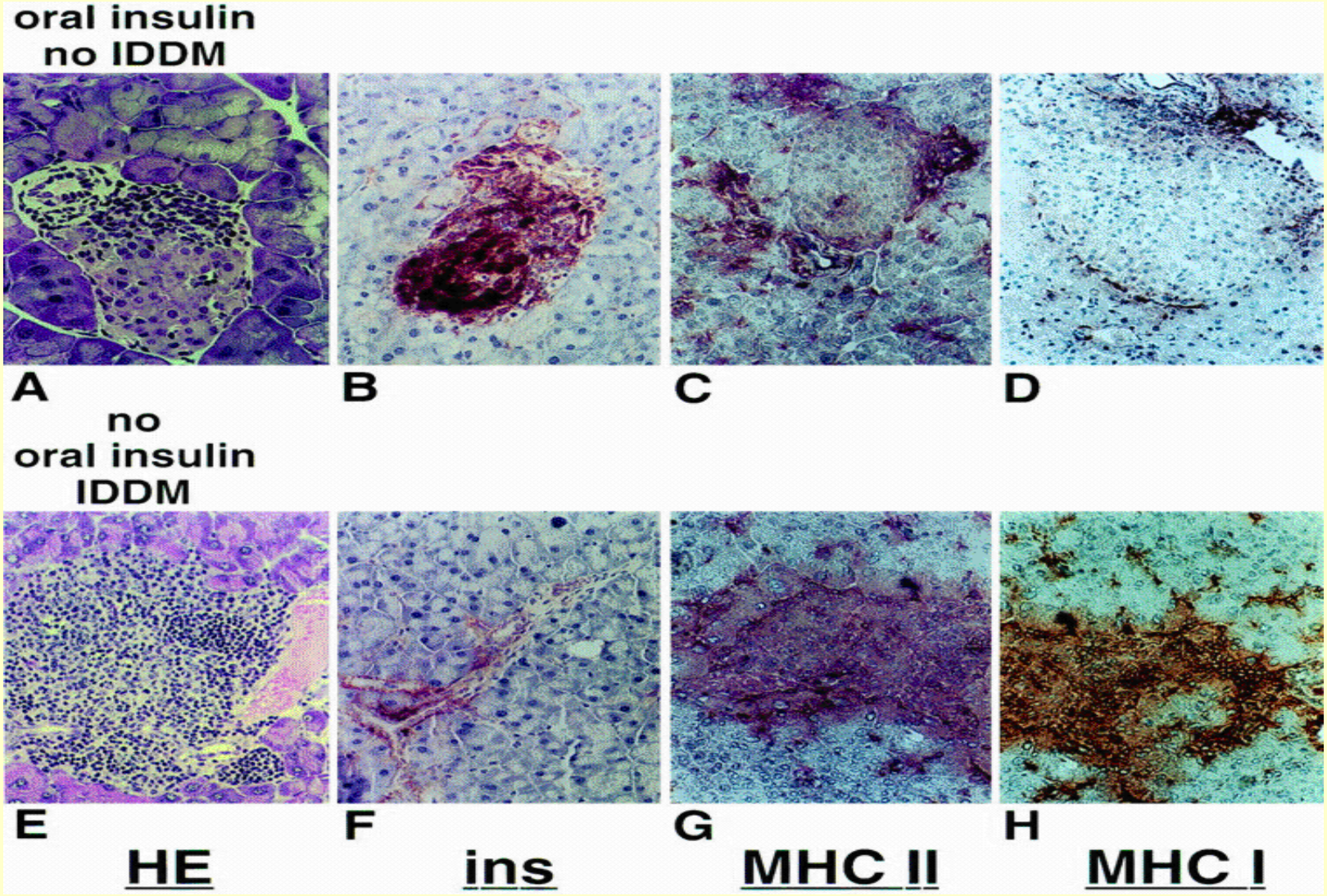
THERAPY OF AUTOIMMUNE AND ALERGIC DISEASES - current

- Anti-inflammatory drugs (NSAID, steroids)
- Blockers of tissue damage mediators
  - antihistaminics
  - antagonists of leucotriens and their receptors
  - biological therapy – antibodies to proinflamatory cytokines and cells (e.g. TNFα-R or anti-TNFα, anti alpha 4 integrin, interferon beta-1)
- Immunosuppression (Cyclosporine)
- Plasmapheresis
- Desensitization by increasing doses of allergen

THERAPY OF AUTOIMMUNE AND ALERGIC DISEASES - experimental

- (Re-) induction of immune tolerance
  - mucosal administration of antigen
    - clinical studies:
      - DM type I. prevention – insulin
      - RA – bovine collagen type II
      - MS – bovine myelin
  - i.v. administration of antigen
  - repeated administration of low antigen doses parenterally
    - clinical studies of DM type I. prevention - insulin

Oral administration of insulin: experimental therapy of viral infection induced DM type I



von Herrath MG., *et al.*, J. Clin. Invest. 1996. 98:1324-1331

THERAPY OF AUTOIMMUNE AND ALERGIC DISEASES - experimental

- Blocking of inflammation and co-stimulation
  - Blockers of co-stimulatory molecules
  - Antagonists of inflammatory cytokines
    - e.g. inhibitors of IL-1, TNF, IL17A, IL12
  - Administration of inhibitory molecules
    - e.g. IL-10
- Blockers of lymphocyte migration
  - e.g. anti-$\alpha 4\beta 7$ (used successfully in the cotton-top tamarine model of chronic intestinal inflammation)

THERAPY OF AUTOIMMUNE AND ALERGIC DISEASES - experimental

- Imunablation and autotransplantation of hematopoietic stem cells (BM CD34+ cells)
  - clinical studies in late stages of life threatening autoimmune diseases, e.g. SLE, MS, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura

End of the Lecture