

INTRODUCTION TO RHEUMATOLOGY



The origins of Rheumatology

- Concept of rheuma (revma) first appeared in the literature in the I century BC.
- Word "rheuma" has Greek origin.
- Rheuma refers to "a substance that flows", probably formed from phlegm.
- This is the "primary juice," by definition of the ancients, which was formed in the brain and flowed in different parts of the body, causing illnesses.

The origins of Rheumatology



- In 1642, French physician Dr. G. Baillou introduced term "rheumatism".
- He suggested that arthritis can be a manifestation of systemic disease.

The origins of Rheumatology

- In 1940, Bernard Comroe suggested the term **"rheumatologist."**



- In 1949, Hollander uses the term **"rheumatology"** in his textbook "Arthritis and Allied Conditions".



The origins of Rheumatology

- In 1928, in the USA Dr. Pemberton organized the American Committee for the treatment of rheumatism,
- It was renamed the American Association for the Study and Treatment of rheumatic diseases (1934),
- Followed by the American Association of rheumatic (1937) and, finally, the American Rheumatology Association (1988).



History of the discovery of some rheumatic diseases

Acute rheumatic fever



- Rheumatism has a long history.
- First written information about it was found in Hippocrates' works.
- At the beginning of XX century all the joint diseases were considered to be “reumatism”.

Acute rheumatic fever

- Classic works devoted to the ARF, have been written by Bullarom (Jean-Bapite Bomllard) and Walter B. Cheadle and published in 1836.
- They distinguished “rheumatic arthritis” and “carditis”.
- At one time Lasegue said: “Rheumatism licks the joints but bites the heart.”
- S. Botkin showed that ARF affects many organs: kidneys, skin, nervous system, liver and lungs.

Acute rheumatic fever

- In 1904 morphologist **Ludwig Aschoff** first discovered and described the morphological substrate of rheumatic fever - a kind of **cell granuloma**.
- In 1929 Talalayev showed that rheumatic granuloma Aschoff is only one of the stages of rheumatic granuloma.
- It has **3 phases: exudative phase, cell proliferation and sclerosis**.
- So now the rheumatic granuloma is called **Aschoff Talalayev**.



Acute rheumatic fever

- In 1933, **Rebecca Lancefield** divided into groups **hemolytic streptococci**, helping researchers clarify the epidemiology of the disease.
- For the first time **Dignostic criteria** of ARF were developed by Dr. TD Jones (T Duckett Jones) and published in **1944**.
- Later they were adopted and revised by the American Heart Association.



Rheumatoid arthritis

- ❑ The earliest signs of rheumatoid arthritis were found in 4500 BC. They were found on the remains of skeletons of Indians in Tennessee, USA.
- ❑ The first paper describing the symptoms of rheumatoid arthritis dates back to 123 year.
- ❑ The first clinical description of this pathology in 1800 made Augustine, Jacob Landry-Beauvais (Augustin-Jacob Landre-Beauvais). The author called the disease a variant of gout - a "simple asthenic gout" (goutte asthenique primitif).
- ❑ Benjamin Brodie described the slow progression of synovitis by involving joint capsule and tendon sheath.

Rheumatoid arthritis



- A. Garro (A. Garrod) suggested the term "rheumatoid arthritis" in 1858 and differentiated it from gout in 1892, the disease got its present name.

Systemic lupus erythematosus

- The name **LUPUS**, the Latin version as Lupus erythematosus, comes from 2 words:
 - Latin "lupus", which means wolf
 - "Eritematozus" - red, because of its similarity to the bite injuries hungry wolf.
- This disease has been known to doctors since 1828, when French dermatologist Biett described skin symptoms.
- In 1845, Austrian dermatologist Ferdinand von Hebra described a rash of "butterfly" type on her nose and cheeks.
- In 1872 dermatologist Kaposi observed that some patients with skin symptoms also have internal organs involvement .



Systemic lupus erythematosus

- In 1948, William Hargraves described the LE-cells. This discovery allowed doctors to identify many patients with systemic lupus erythematosus.
- In 1956, Professor from Switzerland Peter Miescher described antinuclear antibodies (ANA).
- In 1958, Professor George Friou published works about introduction of the immunofluorescent technique to detect antinuclear antibodies (ANA).
- He showed that a substance in the serum of patients with SLE reacted with the nuclei of cells and that the substance was gamma globulin and the target in the nucleus was DNA complexed with histones.

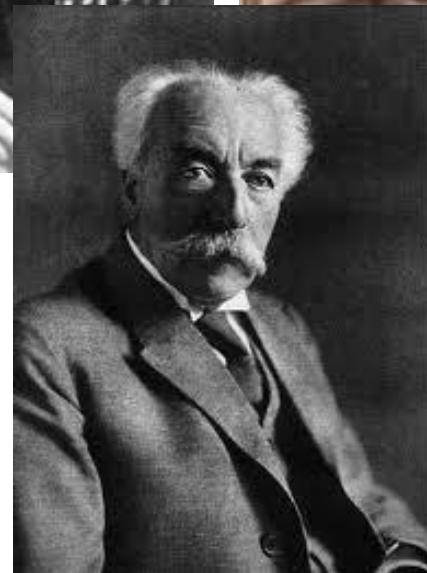
Spondyloarthropathies (ankylosing spondylitis)

- The archaeological study of Egyptian mummies found the disease, which is now called ankylosing spondylitis.
- The first historical description of the disease in the literature refers to 1559, when Realdo Colombo described the two skeletons with typical changes of ankylosing spondylitis in his book "Anatomy."
- 100 years later, in 1693, an Irish physician Bernard Connor described the skeleton of a man with signs of scoliosis, in which the sacrum, hip bone, lumbar vertebrae and 10 thoracic vertebrae with ribs are fused into one bone.



Spondyloarthropathies (ankylosing spondylitis)

- In the late 1890s, Russian doctor, Vladimir Bekhterev and French doctors Adolf Strumpell and Pierre Marie described ankylosing spondylitis.
- Linking disease to a MHC gene class I HLA-B27 belongs to the Americans Lee Schlosstein, Rodney Bluestone and Paul Terasaki, as well as the Britains Derrick Brewerton, Caffrey and Nicholls.



Classification of rheumatic / musculoskeletal syndromes in different years

Rheumatology as a specialty

- Rheumatology as an independent scientific and practical discipline was formed 45 years ago.
- **Rheumatology** is a sub-specialty in internal medicine and pediatrics, devoted to diagnosis and therapy of rheumatic diseases.
- Clinicians who specialize in rheumatology are called **rheumatologists**.

Rheumatology as a specialty

- Rheumatic diseases are one of the most common pathologies of the human body.
- Rheumatologists deal mainly with clinical problems involving joints, soft tissues, autoimmune diseases, vasculitis and heritable connective tissue disorders.

The origins of classification of Rheumatic diseases

- Theoretical basis for combining various diseases in the same group was **connective tissue involvement**.
- In different diseases we can meet pathology of derma, tendons, ligaments, cartilage, bones as well as pathology of special types of connective tissue (synovial and serous membranes, basal membranes of blood vessels and epithelium, etc.).

Types of collagen

Table 1

Collagen Type	Principle Tissue Distribution	Cells of Origin
I	Loose and dense ordinary connective tissue; collagen fibers	Fibroblasts and reticular cells; smooth muscle cells
	Fibrocartilage	
	Bone	Osteoblast
	Dentin	Odontoblasts
II	Hyaline and elastic cartilage	Chondrocytes
	Vitreous body of the eye	Retinal cells
III	Loose connective tissue; reticular fibers	Fibroblasts and reticular cells
	Papillary layer of dermis	
	Blood vessels	Smooth muscle cells; endothelial cells
IV	Basement membranes	Epithelial and endothelial cells

The origins of Rheumatology

- The American College of Rheumatology (ACR) is an organization for physicians, health professionals, and scientists that advances rheumatology through programs of education, research, advocacy and practice support.
- The European League Against Rheumatism (EULAR) is the organisation which represents the patient, health professional and scientific societies of rheumatology of all the European nations.

Classification of Rheumatic diseases

- **Acute rheumatic fever**
- **Diffuse connective tissue diseases**
 - ▣ Rheumatoid arthritis
 - ▣ Systemic lupus erythematosus
 - ▣ Progressive systemic sclerosis
 - ▣ Polymyositis/ Dermatomyositis
 - ▣ Sjogren's disease.
 - ▣ Mixed connective tissue disease
 - ▣ Idiopathic juvenile arthritis

Classification of Rheumatic diseases

- **Seronegative spondyloarthropathies**
 - Ankylosing spondylitis
 - Psoriatic arthrytis
 - Reactive arthritis
 - Enteropathic arthritis
 - Undifferentiated spondyloarthropathies
- **Infectious arthritis**
 - Lyme's diseese
 - Septic arthritis
 - Tbs arthritis
 - Hepatitis B and C
 - HIV et. al

Classification of Rheumatic diseases

□ Systemic vasculitis

- Polyarteritis nodosa
- ANCA associated vasculitis:
 - Churg Strauss syndrome
 - Wegener's granulomatosis
 - Microscopic polyangiitis
- Hemorrhagic vasculitis (Henoch Schonlein purpura, hypersensitivity vasculitis)
- Takayasu's arteritis
- Kawasaki disease
- Horton's disease (giant cell arteritis).
- Obliterate trombangitis (Vinivartera-Biurger disease).

Classification of Rheumatic diseases

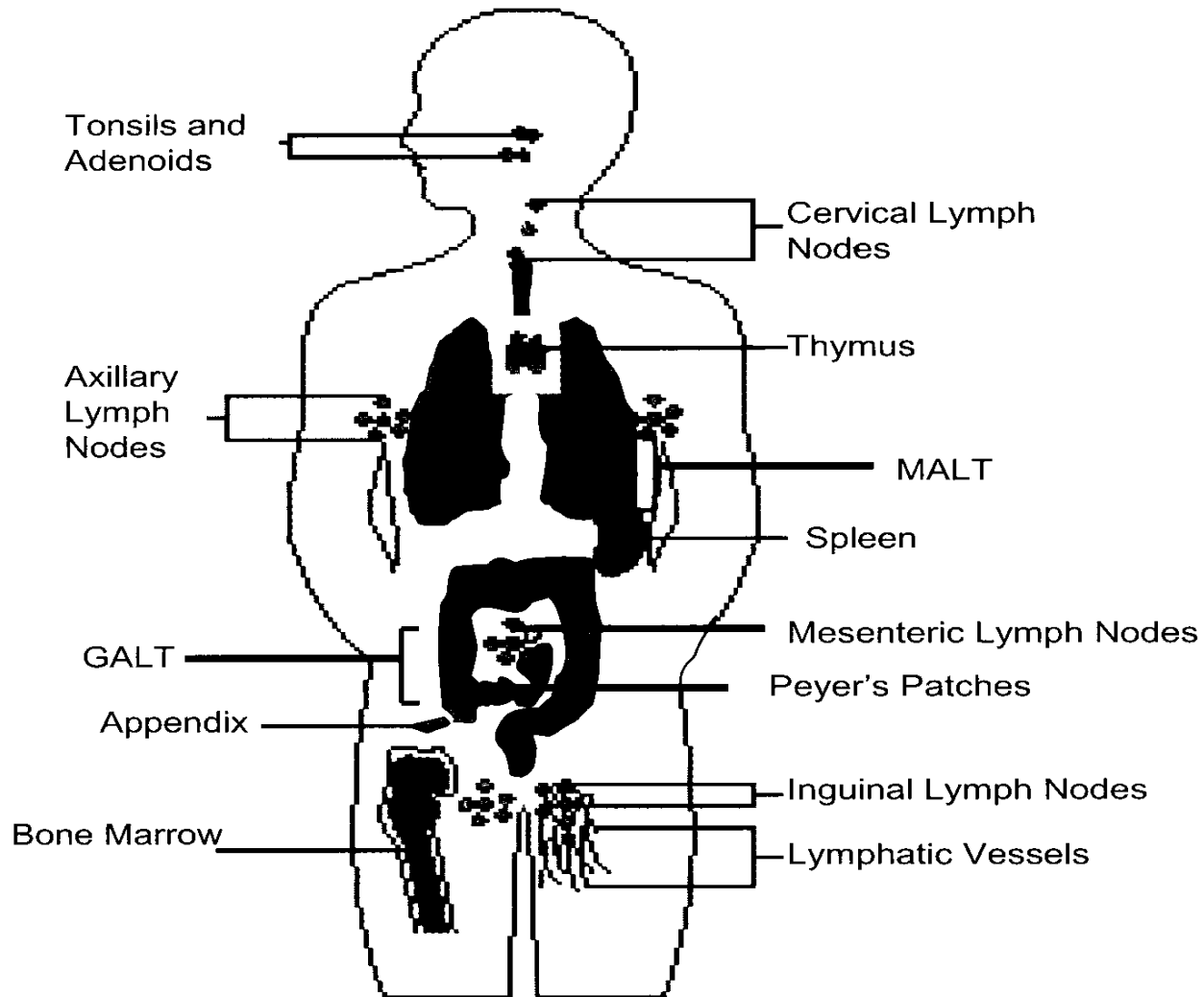
- Rheumatic diseases (associated with metabolic and endocrine diseases)
 - ▣ Crystal-induced arthropathy (gout and pseudogout)
 - ▣ Arthropathy in endocrine diseases (diabetes mellitus, acromegaly, hyperparathyroidism, thyroid diseases)
- Osteoarthritis
- Bone and cartilage disorders: Osteoporosis, osteomalacia
- Neuropathic disorders: Charcot joint, carpal tunnel syndrome

Clasificarea bolilor reumatice

- Non-articular rheumatism:
 - ▣ Fibromyalgia
 - ▣ Tendons and fascia diseases:
 - Tendinitis and tenosynovitis
 - Bursitis
 - Capsulitis
- Hematological disorders: Haemoglobinopathies, leukaemia, lymphoma, haemophilia
- Neoplasms: paraneoplastic syndromes
- Miscellaneous disorders: Familial Mediterranean fever, Sarcoidosis, Behçet disease
- Hereditary diseases of conjunctive tissue and bones

Immune reactions in rheumatology

Immune system tissues

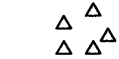


Immune system components

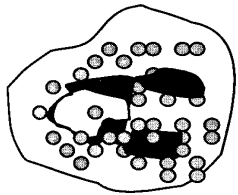
Innate Immunity



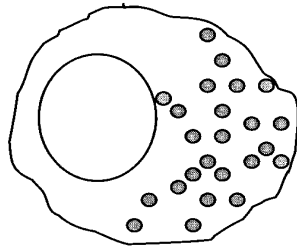
Epithelial Cells



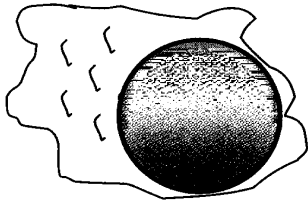
Complement



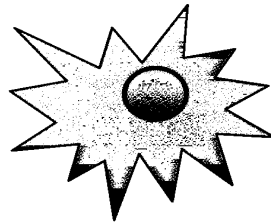
Neutrophil



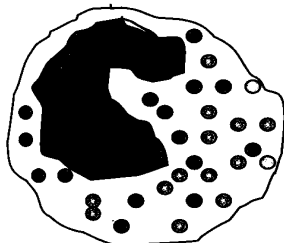
Natural Killer Cell



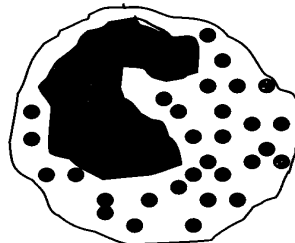
Macrophage



Dendritic Cell

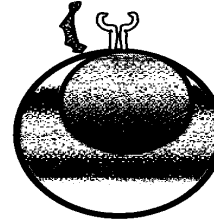


Eosinophil

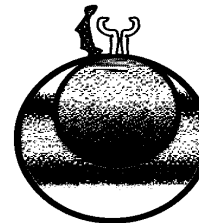


Mast Cell

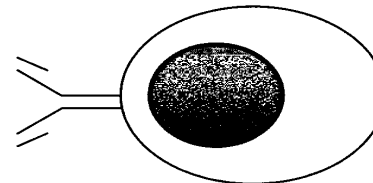
Adaptive Immunity



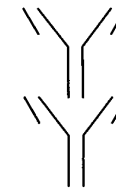
CD8+ T Cell



CD4+ T cell



B Cell



Immunoglobulins

Innate immunity

- Is also known as **non-specific immune system** and first line of defense.
- Comprises the cells and mechanisms that defend the host from infection by other organisms in a non-specific manner:
 - Cell barrier
 - Phagocytosis
 - Cytotoxic action of NK cells
 - Activity of complement

Adaptive (aquired) immune system

- Is composed of highly specialized, systemic cells and processes that eliminate or prevent pathogen growth.
- The cells of the acquired immune system are T and B lymphocytes.

Immune response

Cells with regulatory role:

- Th lymphocytes - amplify immune response;
- T reg (Ts) lymphocytes - limitate intensity of immune response;
- Tcs (contra supressor) lymphocytes – realize functional balance between Th și Ts.

Cells with role :

- B lymphocytes - humoral immune response ;
- Tc lymphocytes – cell immunity.

Immune response

- Immune response is defined as any response of the immune system to an antigenic stimulus leading to determination and neutralization of aggressor structure.
- Contact between Ag and immune cell is followed by its multiplication and differentiation resulting in specific Ig formation (humoral response) or sensitized T lymphocyte appearance (cell response).
- Effects of this contacts is called ***primary immune response***.

Immune response

Immune response consists of several stages:

- Ag perception, processing and presentation;
- Ag recognition;
- Co stimulatory molecules recognition;
- Lymphocyte activation;
- Execution and Ag elimination;
- Decline of immune response (homeostase re-establishing);
- Ag memory maintaining

Cellular immunity Humoral immunity

Antigen (Ag) intruder

Inhibits

Triggers

Inhibits

Adaptive defenses

Innate defenses

Surface barriers

Internal defenses

Ag-infected body cell engulfed by dendritic cell

Becomes

Ag-presenting cell (APC) presents self-Ag complex

Activates

Naive CD8 T cells

Activates

Naive CD4 T cells

Activated to clone and give rise to

Activated to clone and give rise to

Memory CD8 T cells

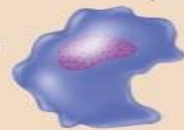
Cytotoxic T cells

Induce co-stimulation

Memory CD4 T cells

Helper T cells

Cytokines stimulate



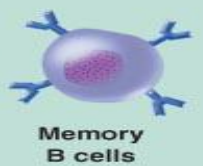
Nonspecific killers (macrophages and NK cells of innate immunity)

Together the nonspecific killers and cytotoxic T cells mount a physical attack on the Ag

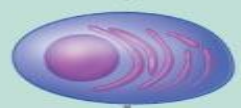
Free Ags may directly activate B cell

Antigen-activated B cells

Clone and give rise to



Memory B cells



Plasma cells (effector B cells)

Secrete



Antibodies (Igs)

Circulating Igs along with complement mount a chemical attack on the Ag

Co-stimulate and release cytokines

Present Ag to activated helper T cells

Immune reactions

- The reaction resulting from the recognition and binding of an antigen by its specific antibody or by a previously sensitized lymphocyte is called **immune reaction**.
- Although the immune system generally is protective, the same immunologic mechanisms that defend the host at times may result in severe damage to tissues and, occasionally, may cause death.

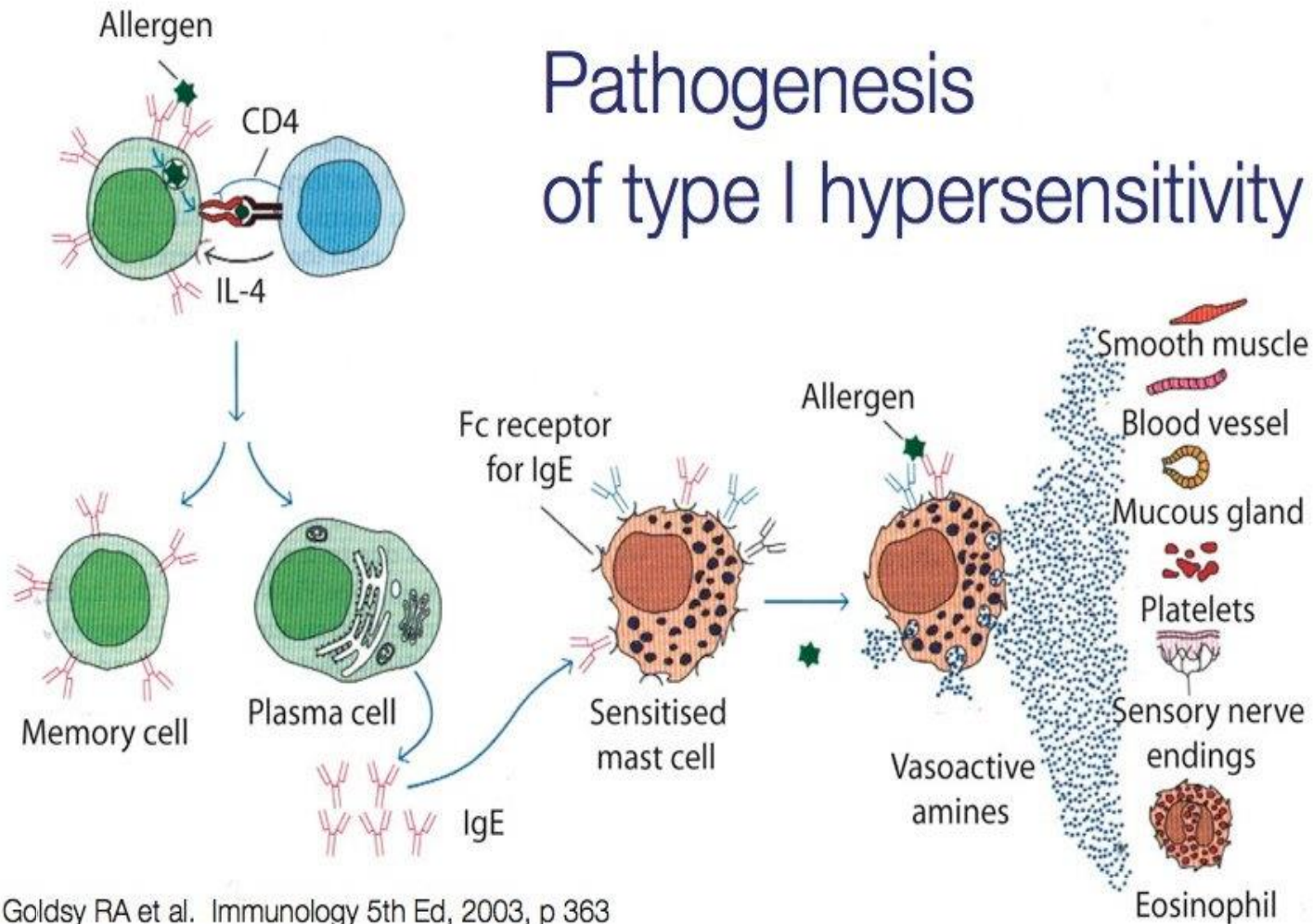
Immune reactions

- Cell and Coombs have classified these damaging immunologic reactions (also called hypersensitivity reactions) into **four major types**:
 - ▣ immediate hypersensitivity (type I) reactions,
 - ▣ cytotoxic (type II) reactions,
 - ▣ immune complex-mediated (type III) reactions,
 - ▣ delayed hypersensitivity (cell-mediated, type IV) reactions.
- Roitt describes immune reaction of type V, similar to type II, just Ab fixes on the cell modifying its function but not destroying it.

Anaphylaxis or immediate hypersensitivity reactions (type I)

- Ag leading to this type of reactions are called **allergens**.
- They can be: some proteins (hormones, enzymes, insects' poison), blossom dust, animal products (feather, skin desquamation), home dust, food allergens, some therapeutic agents etc.
- Most of the people do not react at these Ag.
- This immune reaction in most cases takes place due **genetically determined IgE hyperproduction**.
- IgE production is firmly under the control of IgE-specific T cells, which can produce both IgE-potentiating and IgE-suppressing factors.
- Genetic predisposition to immediate hypersensitivity reactions is called **atopy**.

Anaphylaxis or immediate hypersensitivity reactions (type I)



Goldsy RA et al. Immunology 5th Ed, 2003, p 363

a. First contact

b. Sensibilization

c. Repeated exposure

Anaphylaxis or immediate hypersensitivity reactions (type I)

- Ig implicated in this type of reactions belong to **Ig E** and are called **reagins**.
- They are secreted by plasmocytes located at respiratory tract and gastrointestinal mucosal levels.
-
- After secretion Ig E are fixed on mastocytes and basophiles membrane.
- A new exposure to Ag will lead to Ag joining with specific Ab (Ig E) on the surface of mastosites and basophiles with immune complex formation.

Anaphylaxis or immediate hypersensitivity reactions (type I)

Immune complex formation on the surface of mastocytes and basophiles will start 2 processes:

- **Cell degranulation** with release of pharmacologically active substances, or mediators (histamine, serotonin, neutrophile hemotactic factor, proteases);
- **De novo synthesis** of some mediators in the cell membrane from arachidonic acid that will lead to platelets aggregation, vasoactive amines release, increase of vascular permeability, bronchial spasm, mucus secretion, strong vasodilatation)

Anaphylaxis or immediate hypersensitivity reactions (type I)

- Target areas for anaphylaxis are the tissues with big number of mastocytes: lungs, vascular endothelium, gastrointestinal tract.
- Clinical manifestations will vary as a function of localization, circumstances and intensity.

Cytotoxic (type II) reaction

- Cytotoxic reactions involve primarily:
 - Either the combination of IgG or IgM antibodies with epitopes on cell surface or tissue
 - or the adsorption of antigens or haptens to tissue or cell membrane, with subsequent attachment of antibodies to the adsorbed antigens.

Cytotoxic (type II) reaction

- Either mechanism may lead to one of the following destructive processes:
 - ▣ Activation of complement, with subsequent lysis or inactivation of target cells.
 - ▣ Phagocytosis of target cells, with or without complement activation.
 - ▣ Lysis or inactivation of target cells via effector lymphoid cells.

Cytotoxic (type II) reaction

- ❑ Target cells usually are blood cells, vascular endothelial cells, kidneys.
- ❑ As a function of target cells this type of reaction can have multiple clinical presentations:
 - ❑ 1. Transfusion reactions: Intravascular hemolysis of red blood cells usually is associated with ABO system incompatibility.
 - ❑ 2. Extravascular hemolysis of red blood cells almost invariably is associated with Rh incompatibility.
 - ❑ 3. Autoimmune hemolytic disease. Warm antibody hemolytic anemia, cold antibody hemolytic anemia, and paroxysmal cold hemoglobinuria.

Cytotoxic (type II) reaction

- 4. Hemolytic disease of the newborn: Erythroblastosis fetalis occurs when Rh-negative mother gives birth to an Rh-positive infant, the Rh antigen having been acquired from an Rh-positive father.
- 5. White blood cell lysis
 - a. Systemic lupus erythematosus (SLE)
 - b. Granulocytopenia
 - c. Idiopathic thrombocytopenic purpura (ITP)
- 6. Nephrotoxic nephritis. Goodpasture's syndrome
- 7. Bullous diseases. Characterized by antibody and complement deposition in squamous intercellular spaces and along the basement membrane of the skin.

Cytotoxic (type II) reaction

- There are some situations when joining of the specific Ag to a cell does not determine cellular lysis, but increases or depresses its function.
- Some authors (Roitt) consider this situation to be an independent type of immune reactions called type V. The others treat it as a variant of type II reaction.

Type III: Immune Complex Mediated Reactions

- This type of reaction is determined by **Ag-Ab immune complexes presence at tissue level.**
- The pathogenesis of immune complex disorders involves an interplay of antigen, antibody, complement, and neutrophils.
- Immune complexes can be formed locally or can be brought with blood flow, if not eliminated from circulation by monocyte-macrophage system.
- In both cases the following inflammatory events are identical.

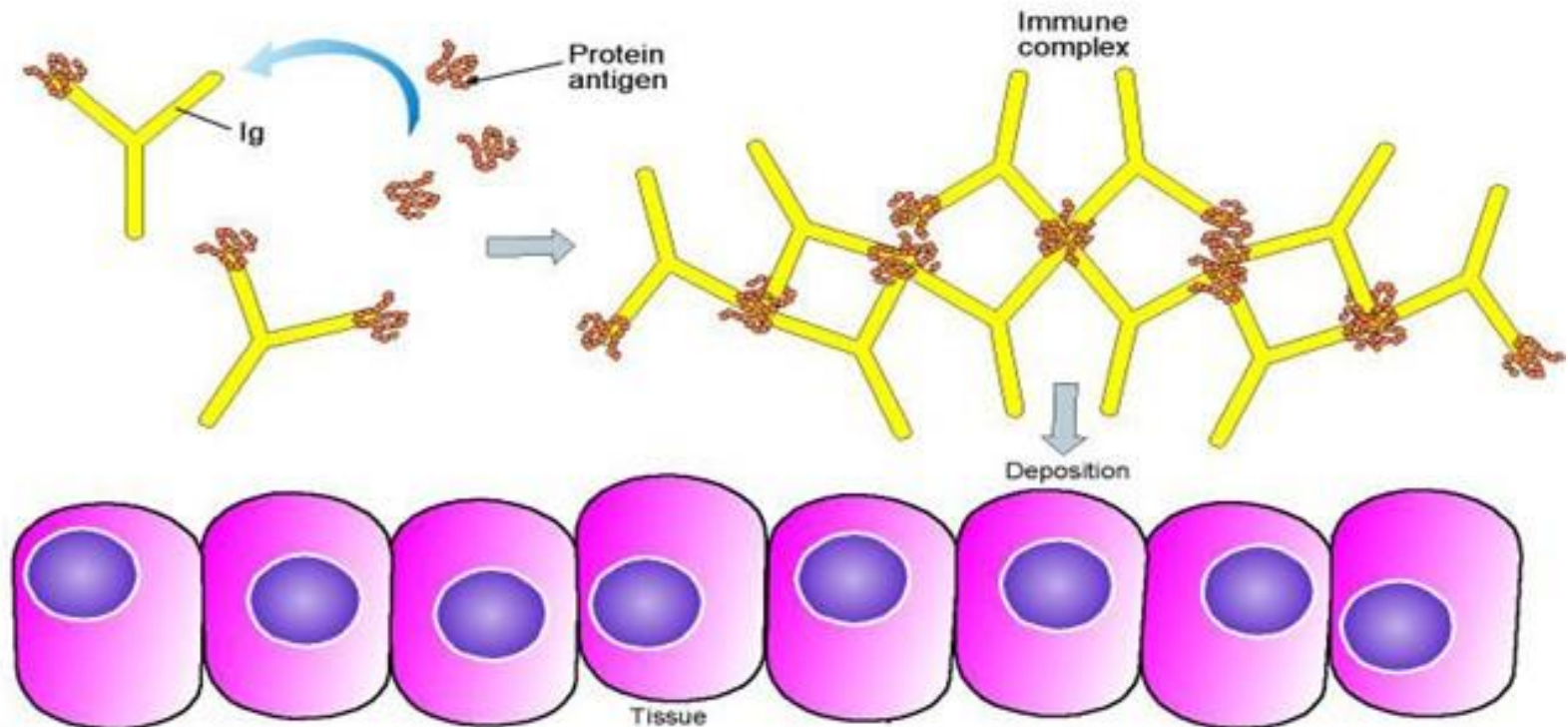
Type III: Immune Complex Mediated Reactions

- Ag implicated in this process can be various:
 - **endogen** (proper structures become non-self: nuclear Ag, tubular renal Ag) or
 - **exogen** (a big number of microbial or viral structures).
- Implicated Antibodies have to be able to activate complement and belong either to **IgG** or to **IgM** classes.

Type III: Immune Complex Mediated Reactions

Type 3 - immune complex hypersensitivity

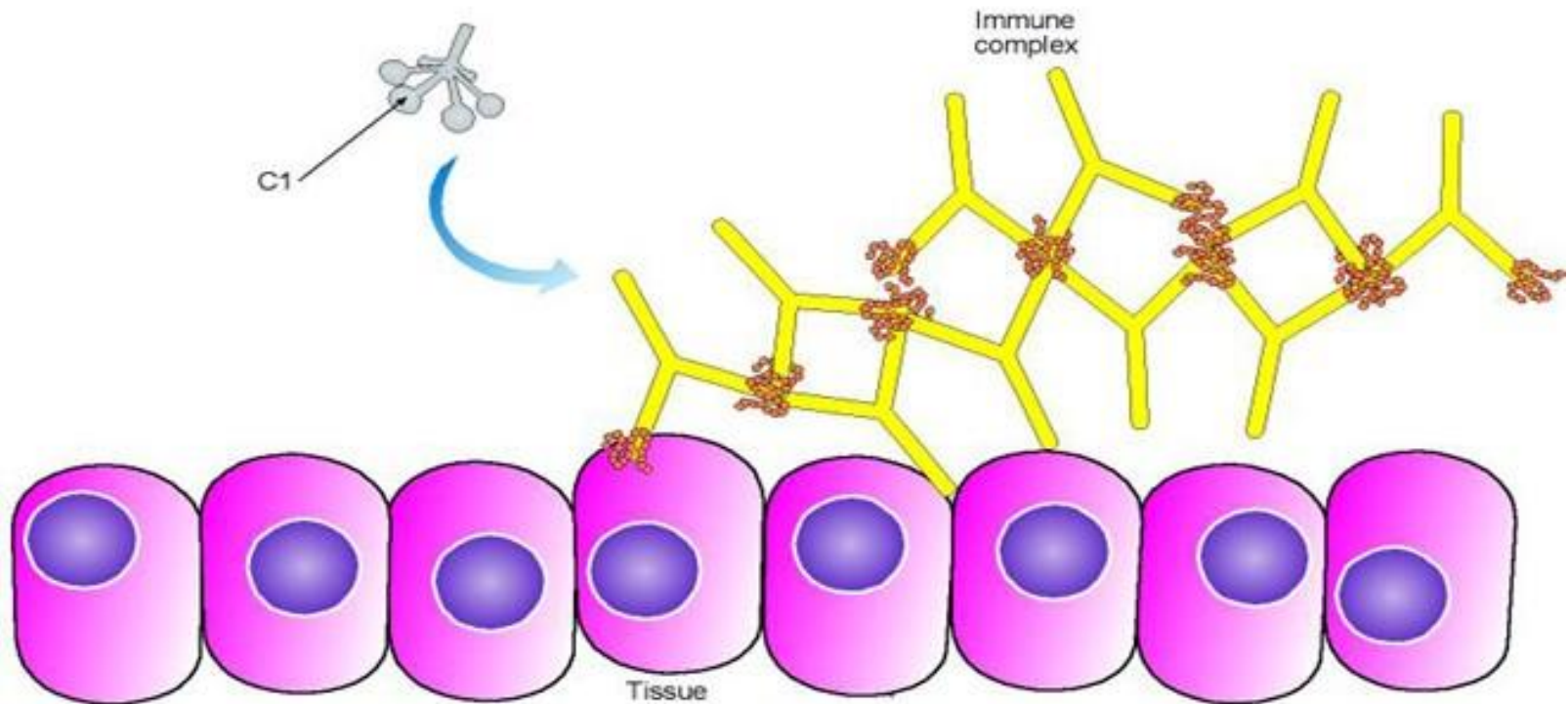
Figure 3a



Binding of multiple IgM or IgG antibodies to soluble antigen causes an insoluble complex to form which is deposited at the surface of tissue.

Type III: Immune Complex Mediated Reactions

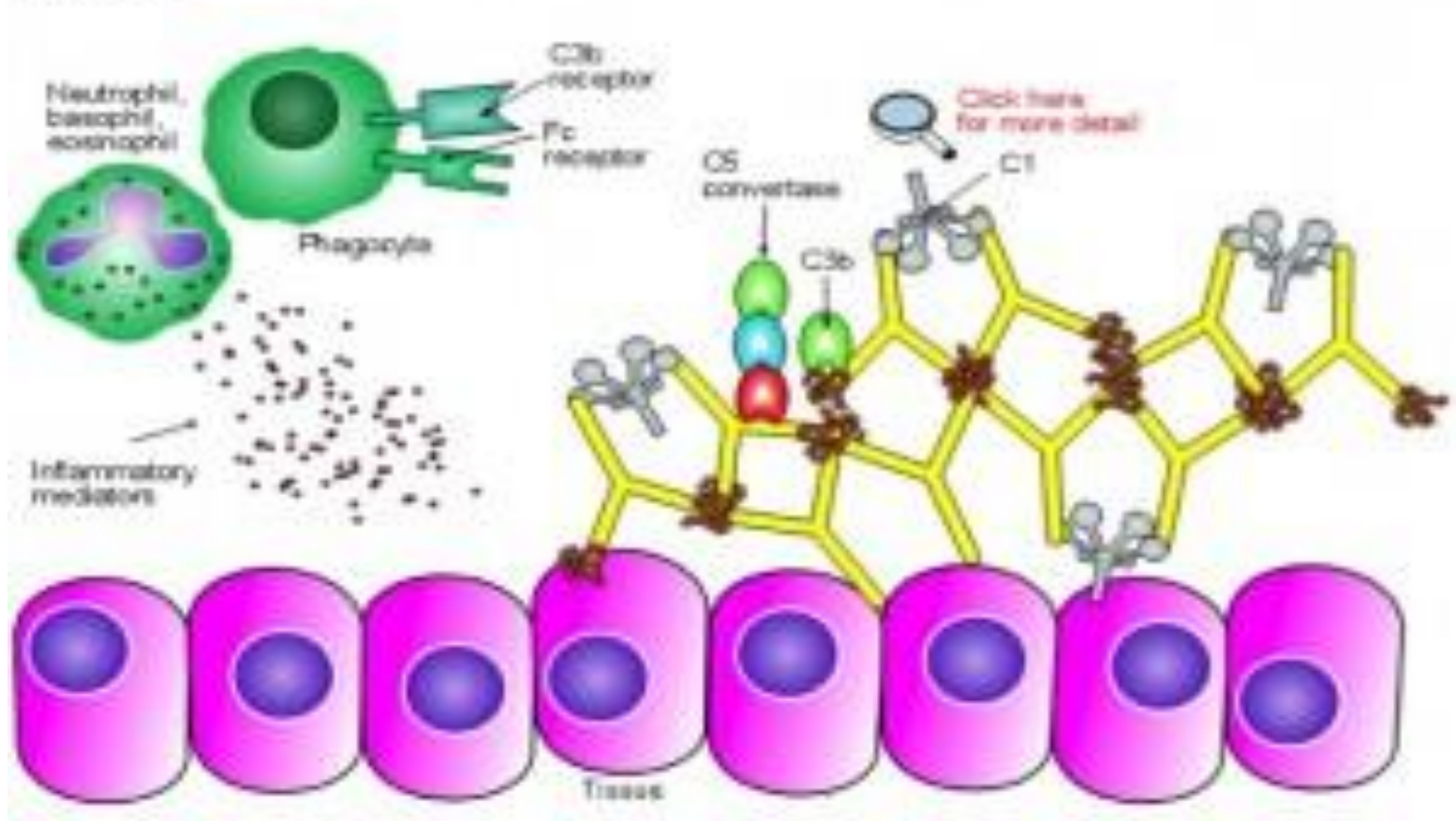
Figure 3b



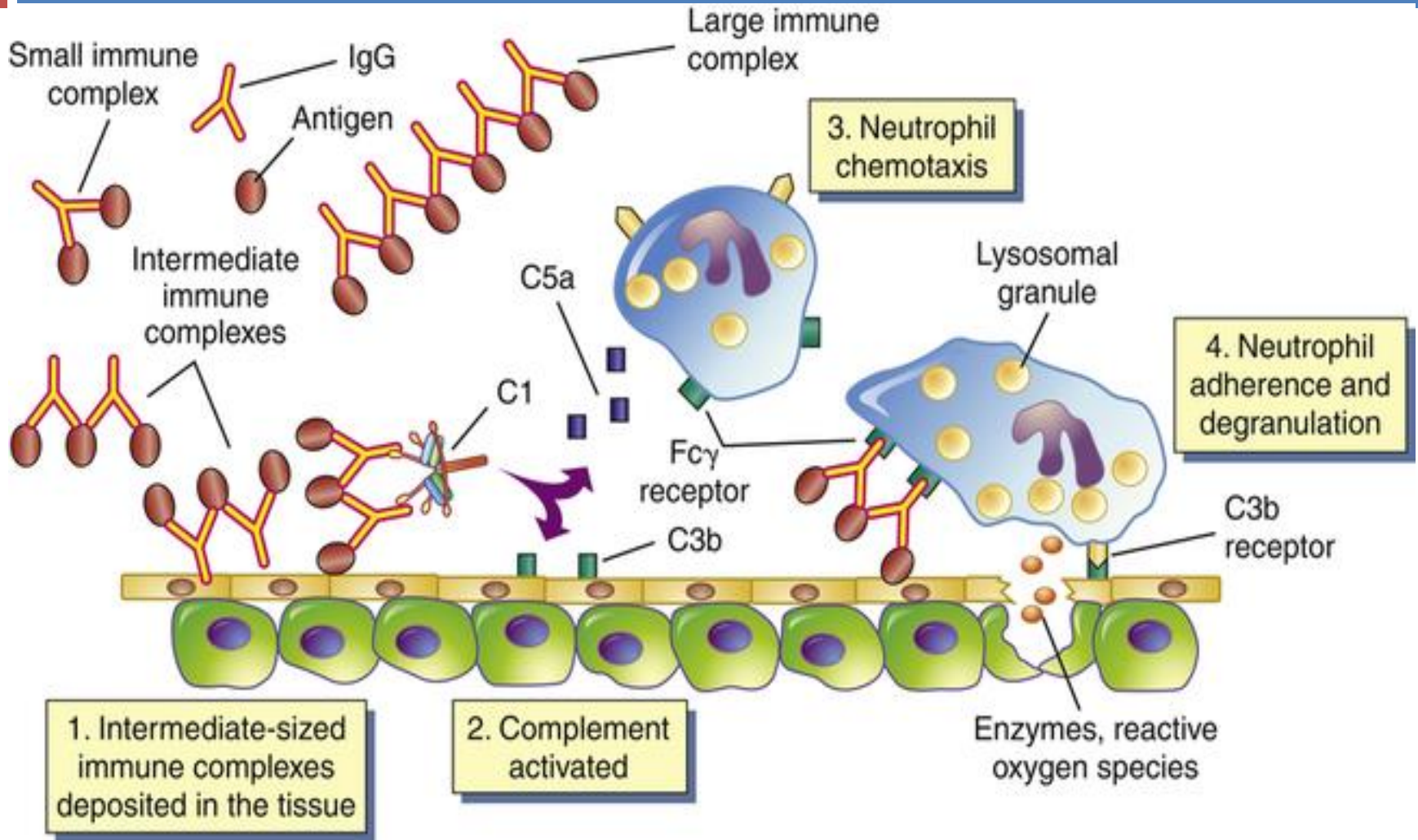
The classical complement pathway is initiated by the recruitment of C1 complement protein that binds the Fc domain of bound IgM or IgG.

Type III: Immune Complex Mediated Reactions

Figure 3c



Type III: Immune Complex Mediated Reactions



Type III: Immune Complex Mediated Reactions

- The mechanism begins with soluble Ag-AB immune complex (IC) formation.
- This generally occurs in the region of antigen excess.
- Medium size immune complexes are involved in lesion formation, because being soluble they escape phagocytosis.
- They penetrate the endothelium of blood vessel walls (probably with the aid of vasoactive amines released from platelets and basophils), and are deposited on the vascular basement membrane.

Type III: Immune Complex Mediated Reactions

- Complement activation (following IC formation), results in C3a, C4a and C5a fragments, which are anaphylotoxines.
- C5a and C5b67 are chemotactic for neutrophils and the neutrophils then infiltrate the area and release lysosomal enzymes that destroy the basement membrane of the vessels.
- Platelets also make a contribution interacting through Fc receptor on their membrane with IC.
- This leads to platelets aggregation and microthrombs formation.

Type III: Immune Complex Mediated Reactions

- Platelets and basophiles release vasoactive amines, that increase vascular permeability and cell growth factor.
- Clinically, this type of reaction can have many aspects: Arthus reaction, serum sickness, hypersensitivity pneumonitis, poststreptococcal glomerulonephritis, autoimmune diseases (Rheumatoid arthritis and SLE).

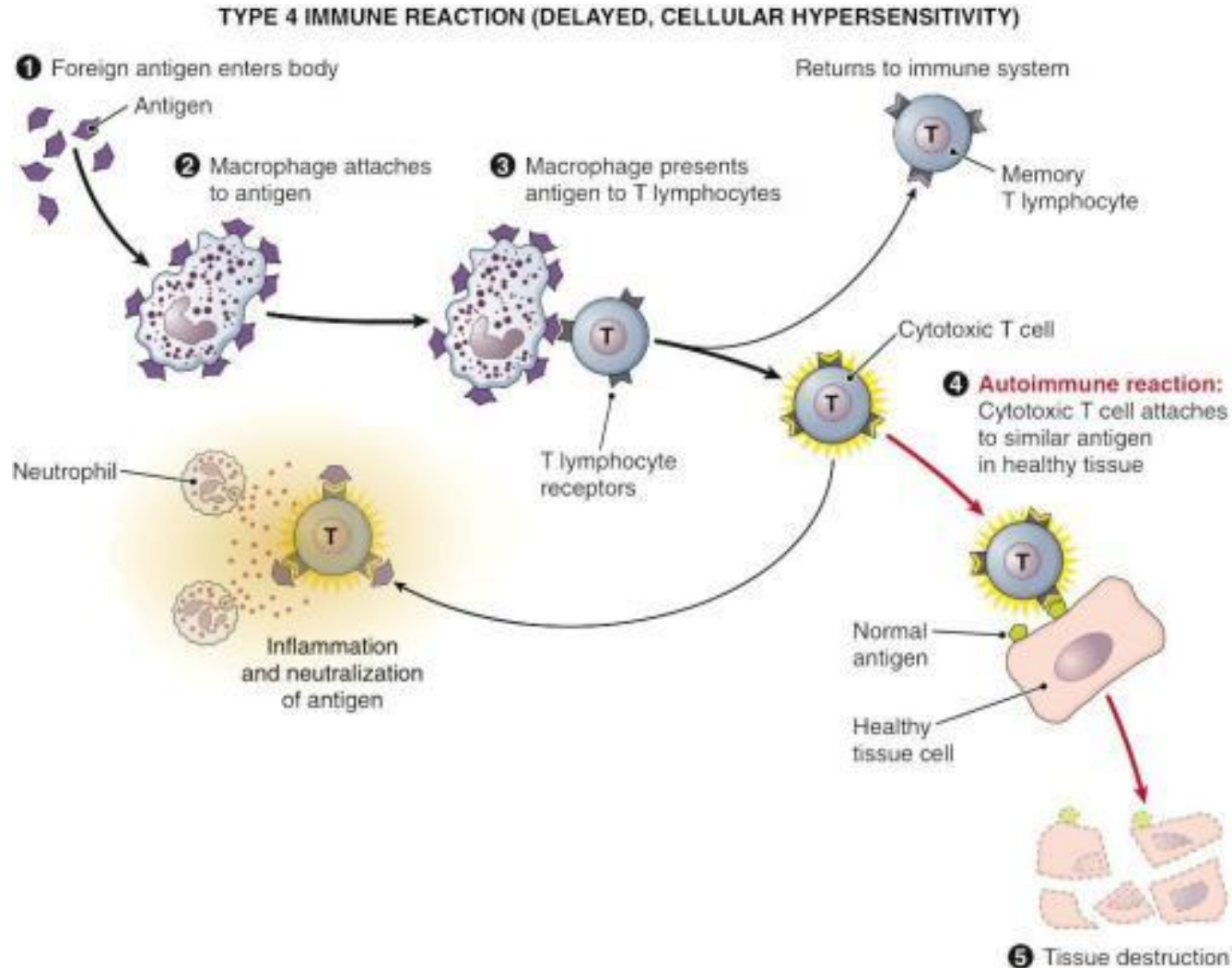
Type IV: Cell Mediated Reactions

- Cell mediated immune reaction is attributed to a condition with increased immunization, determined by an Ag that begins an immune cellular response.
- Key role in this type of reaction plays a sensitised T lymphocyte and T lymphocyte produced cytokines, released after the contact with Ag .
- Neither Ab nor Complement are implicated.

Type IV: Cell Mediated Reactions

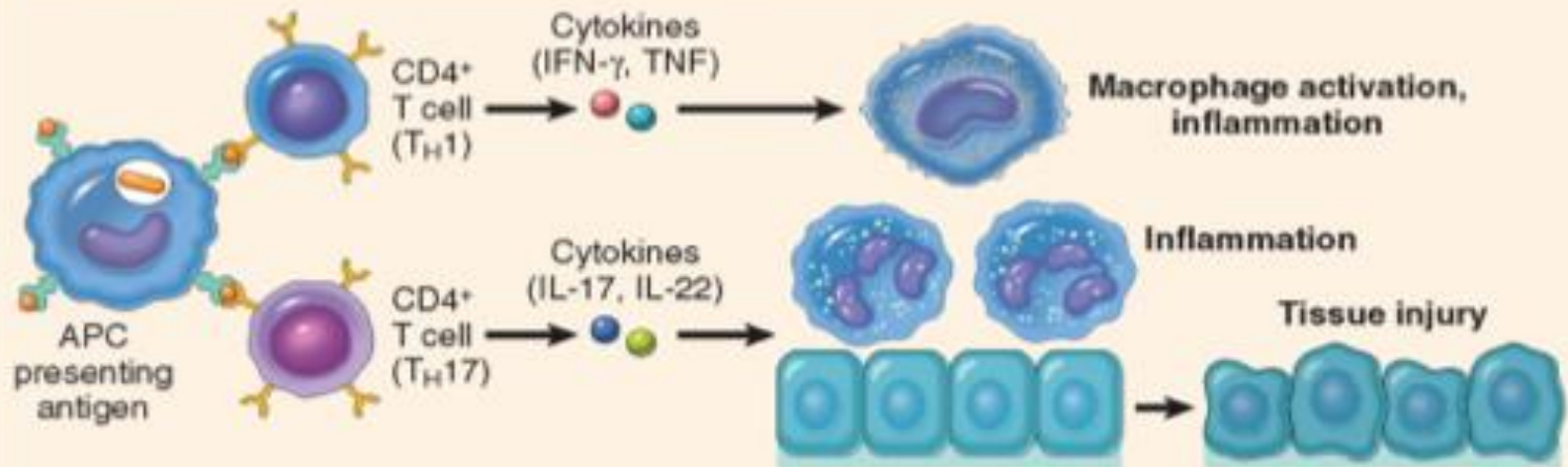
- Cell mediated immune reactions consists of 2 aspects: ***delayed hypersensitivity and cellular cytotoxic response.***
- Each is realized by a different type of sensibilised lymphocyte.
- Both are delayed reactions, clinical manifestations appear in several days after exposure to Ag.

Type IV: Cell Mediated Reactions

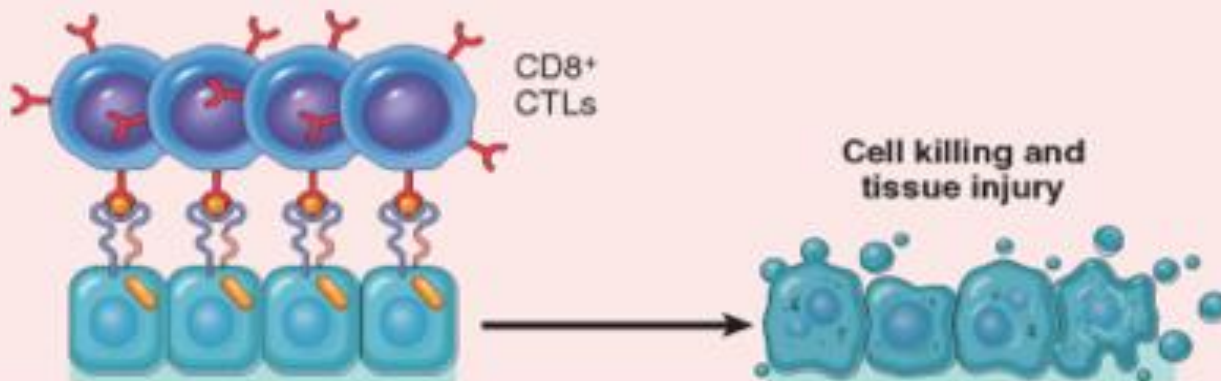


Type IV Hypersensitivity

A. Delayed-type hypersensitivity and immune inflammation



B. T cell-mediated cytotoxicity



Delayed hypersensitivity

- Lymphocytes responsible for this process are named ***Tdth*** (***delayed-type hypersensitivity***) and act via other cells (ex. Mf) that are stimulated and directly produce tissue damage. Tdth have CD4+ determinants on the surface.
- After this interaction, Tdth CD4+ lymphocytes produce lymphokines: IFN- γ , MAF (Macrophage Activating Factor, stimulating antibacterial and cytotoxic MF activity, MCF (Macrophage Chemotactic Factor, stimulating MF infiltration), IL-2, TNF-P (lymphotoxine).

Delayed hypersensitivity

Out of them the most important role plays *IFN- γ* , having the following functions:

- Viral replication inhibition;
- To increase expression of MHC molecules on the cell surface, including MF, improving Ag presentation to Tdth lymphocytes;
- To increase expression of Fc receptors on MF;
- To stimulate macrophagal phagocytosis;
- To elevate NK cell activity

Delayed hypersensitivity

- Activated **macrophages** release a lot of biologic active products: cytokines (IL-1, IL-6, TNF- α), proteases, lysosomal enzymes .
- IL-1 and IL6 activate and stimulate other lymphocytes and macrophages, provoke fever, increase serum concentration of acute phase reactants and of some complement fractions, stimulating acute inflammation.
- Besides, IL-1 increases cellular adhesion.

Delayed hypersensitivity

- As the result of interaction with Ag circulating lymphocytes are attracted and activated by lymphokines produced by Tdth lymphocytes
- In activated MF increases production of active oxygen metabolites and lysosomal enzymes.
- This leads to increased antibacterial cell capacity, and contributes to inflammation and tissue lesion.
- **Clinical examples** of delayed hypersensitivity are: contact dermatitis, tuberculine reaction, granulomatous reaction.

Cellular cytotoxic response

- This type of immune reaction is realized with the help of Tc lymphocytes. These may act in two ways:
 1. IFN- γ secretion and
 2. Direct destruction of target cells, such as viral or tumoral cells.

Cellular cytotoxic response

- Tc lymphocytes release cytokines from cytoplasmic granulas, proteases and lymphotoxine.
- Direct action is their particularity (Tc vsTdth).
- It is considered, that Tc lymphocyte mechanism of action includes elaboration and activation of endonuclease, capable to fragment DNA of target cells.

Cellular cytotoxic response

Cytotoxicity developed by **Nkcells** is cellular, without Ab intervention.

- Immune reaction of type IV has many clinical examples:
 - citolysis in endemic hepatitis,
 - acute cellular rejection,
 - multiple sclerosis

To remember!

- ✓ Body protection against external aggression and recognition of proper structures is realized through innate and adaptive mechanisms interacting between them.
- ✓ Immune system includes all the cells and soluble factors implicated in adaptive immunity appearance.
- ✓ Lymphocytes represent a cellular component of immune system. Different subtypes of lymphocytes express many receptors having a role in their migration, activity, initiation and control of humoral or cell-mediated immune response.

To remember!

- ✓ Immune response represents all the mechanisms helping to recognize and neutralize aggressive structures.
- ✓ When immune response is exaggerated it loses its protective role and becomes dangerous for the host, generating an immune reaction leading to the system body damage.

A horizontal bar at the top of the slide, divided into a red section on the left and a blue section on the right.

Laboratory studies

The values of laboratory data

- Laboratory tests may help in diagnosis and confirmation of data obtained by history taking and examination, but are not independently diagnostic criteria.
- In addition, laboratory tests can help monitoring disease activity, but they are meaningful only when correlated with clinical outcome.

Laboratory studies in rheumatic diseases

- Anemia
 - ▣ Normochromic - Correlation with disease activity
 - ▣ Iron - NSAID-associated gastrointestinal pathology
 - ▣ Hemolytic - SLE, APS
 - ▣ Aplastic - Citostatic, phenylbutazone, D-penicillamine, etc.
- Leukocytes
 - ▣ Leukocytosis - A high activity of inflammation, with Still, the infection
 - ▣ Leukopenia - SCR (lymphopenia), with m-Felty (neutropenia)
- Platelets
 - ▣ Thrombocytosis - The high activity of inflammation
 - ▣ Thrombocytopenia - SLE, APS

Laboratory studies in rheumatic diseases

- CPK, LDH - Increase - Inflammatory myopathies
- Transaminases, bilirubin - Increase - Pathology of the liver with "rheumatologic" manifestations of the toxicity of drugs (methotrexate, NSAIDs)
- Uric acid - Hyperuricemia – Gout
- Calcium, vitamine D - Osteoporosis
- Markers of inflammation
 - Increased ESR - Active inflammation in various diseases, a diagnostic criterion for polymyalgia rheumatica and giant cell arteritis, intercurrent infection
 - Increased CRP - activity of inflammation, joint destruction, SLE - intercurrent infection
- Uroscopy
 - Microhematuria – nephritidis (SLE, systemic vasculitis), toxic drugs
 - Proteinuria – nephritidis (SLE, systemic vasculitis, amyloidosis), the toxicity of drugs

The value of immunological tests in rheumatic diseases

Test	Disease	Diagnosis in typical clinic manifest	Dif-Diagnosis	Scrinig	Monitoring
Anti-nuclear	SLE	+++	++	-	?
Anti-DNA	SLE	+++	+	-	+++
Anti-body -Sm, RNP	SLE, Mixt path	+++	+++	-	-
C3, C4	Nephropaties in SLE	++	++	-	+++
CH50	SLE	+	+	-	+
Anti CCP	RA	+++	+++	+++	+
Rheumatoid factor	RA	+++	+	?	+

The value of immunological tests in rheumatic diseases

Test	Disease	Diagnosis in typical clinic manifest	Dif-Diagnosis	Scrinig	Monitoring
CRP	RA	+	+	-	+++
ASL-O	ARF	++	++	-	+
ANCA	Vasculitidis	+++	++	-	+
Anti-phosfolipides	APhS	+++	++	-	+
HLA B-27	AS	++	-	-	-

The disease, in which can increase the RF in the serum

- ❑ Subacute bacterial endocarditis
- ❑ Leprosy
- ❑ Chronic inflammatory disease of unknown etiology
- ❑ Tuberculosis
- ❑ Syphilis
- ❑ Sarcoidosis
- ❑ Lyme Disease
- ❑ Periodontal disease
- ❑ Interstitial lung disease
- ❑ Viral diseases
- ❑ Liver disease
- ❑ Rubella
- ❑ Cytomegalovirus
- ❑ Mixed cryoglobulinemia

Autoantibodies in rheumatic diseases

Type	Description	Clinical interface
Anti –ds DNA	Antibodies to double strand of DNA, have greater specificity than antibodies to ssDNA	Highly specific for SLE, rarely detected in other diseases and in healthy people
Anti – Histon	Most diagnostic tools are not shared by antibodies to the five main types of histones	SLE, lupus medication, other autoimmune diseases
Anti – ENA	Typical diagnosticum to 2 extractable nuclear antibodies (Sm and RNP - ribonucleoprotein)	Highly specific for SLE
Anti – SSA/Ro	ribonucleoprotein	SLE (especially subacute cutaneous lupus), lupus neonatal syndrome Shogren
Anti – SSB/La	ribonucleoprotein	Shogren's syndrome, lupus erythematosus, SLE newborn

Autoantibodies in rheumatic diseases

Type	Description	Clinical interface
Anti – centromer	Antibodies to the centromere / kinetochore region of chromosome	Limited scleroderma (CREST)
Anti – Scl 70	Antibodies to topoisomerase 1 DNA	scleroderma
Anti – Jo-1	Antibodies to the transfer-RNA synthetase	Poly / dermatomyositis, particularly in patients with interstitial lung disease, Raynaud's phenomenon, cracked skin of hands (mechanical arm), arthritis, and resistance to therapy
Anti – PM-Scl	Antibodies to nuclear components of granular	Polymyositis / scleroderma Overlap syndrome
Anti – Mi-2	Antibodies to nuclear antigens of unknown function	dermatomyositis

The main indications for diagnostic arthrocentesis

- Monoarthritis
- Trauma with effusion into the joint cavity
- Suspicion of purulent arthritis
- Suspicion of microcrystalline (urate, hydroxyapatite) arthritis
- Unclear diagnosis

The value of radiology in rheumatic diseases

Disease	Thorax	Hand and foot	Sacroiliac	Knee joints	other
Rheumatoid arthritis	+	+++	+	+	The thoracic spine
Osteoarthritis	-	++	+++	+++	-
AS	-	-	+++	-	Lumbar spine
Reactive arthritis	-	++	+++	-	Heel bone
SLE	+++	++	++	-	-
Scleroderma	+++	++	-	-	The Esophagus
Gout	-	++	-	-	-
Osteoporosis	-	-	-	-	Densitometry, spine

Minimum set of laboratory tests to diagnose the causes of joint pain

- The total blood count,
- platelets
- ESR
- Bilirubin
- Transaminase
- CK
- Creatinine
- Uric acid
- Urinalysis, daily urine for protein
- Microscopic analysis of synovial fluid, including crystals
- CRP
- rheumatoid factor
- antinuclear factor
- Anti-DNA
- A/b to extractable nuclear antigen (RNP)
- ANCA
- ASL-O
- Determination of chlamydial antigen
- A/b to B.burgdorferi
- HLA B-27

Application of the morphological study (biopsy) in diagnosis of rheumatic diseases and their complications

- Polymyositis
- Sjogren's disease
- Diffuse eosinophilic fasciitis
- Systemic vasculitis
- Secondary amyloidosis
- Differential Diagnosis in subcutaneous sites (rheumatoid nodule / tophi)
- Differential diagnosis of suspected tumor of the synovial

Drugs used to treat rheumatic diseases

Non-steroidal anti-inflammatory drugs for treatment of rheumatic diseases

Medication	Dose	Possible side effects
Diclofenac potassium	100-200 mg/24 h, divided into 2-4 reception	For all NSAIDs: abdominal pain, or stomach, cramps, discomfort, edema (oedema), diarrhea, vomiting, dizziness, allergic reactions
Diclofenac sodium	100-200 mg/24 h, divided into 2-4, or 100 mg in the form of retard	
Etodolak	800-1200 mg/24 h, divided into 2-4 reception. In the form of retard 1 dose 400-1000mg/24 h	
Ibuprofen	1200-3200 mg/24 h, divided into 3-4 reception	
Indomethacin	50-200 mg/24 h, divided into 2-4, either in the form of retard 75 mg 1 times a day, 75 mg 2 times daily	
Ketoprofen	200-225 mg/24 h divided into 3-4 reception or retard-150-200 mg/24 h 1 times	
Meloxicam	7.5 -15 mg/24 h 1 times per day	
Naproxen	500-1500 mg/24 h divided 2 reception	
Nimesulide	100-200 mg/24 to 1-2 reception	
Piroxicam	20 mg/24 h in 1-2 reception	
Etoricoxib	60-120 mg once a day	
Celecoxib	200-400 mg once a day	

Classification

Salicylates

- Aspirin Diflunisal
- Na.salicylate salicylamide

Para-aminophenol

- Acetaminophen

Phenyl Acetic acid

- Diclofenac
- Ketorolac

Oxicams

- Piroxicam

Pyrazolone derivatives

- Phenylbutazone Oxyphenbutazone
- Analgin Azapropazone

Propionic acid derivatives

- Ibuprofen Ketoprofen Flurbiprofen
- Naproxen

Fenamates

- Mafenamic acid
- Flufenamic acid

Preferential COX-2 inhibitors

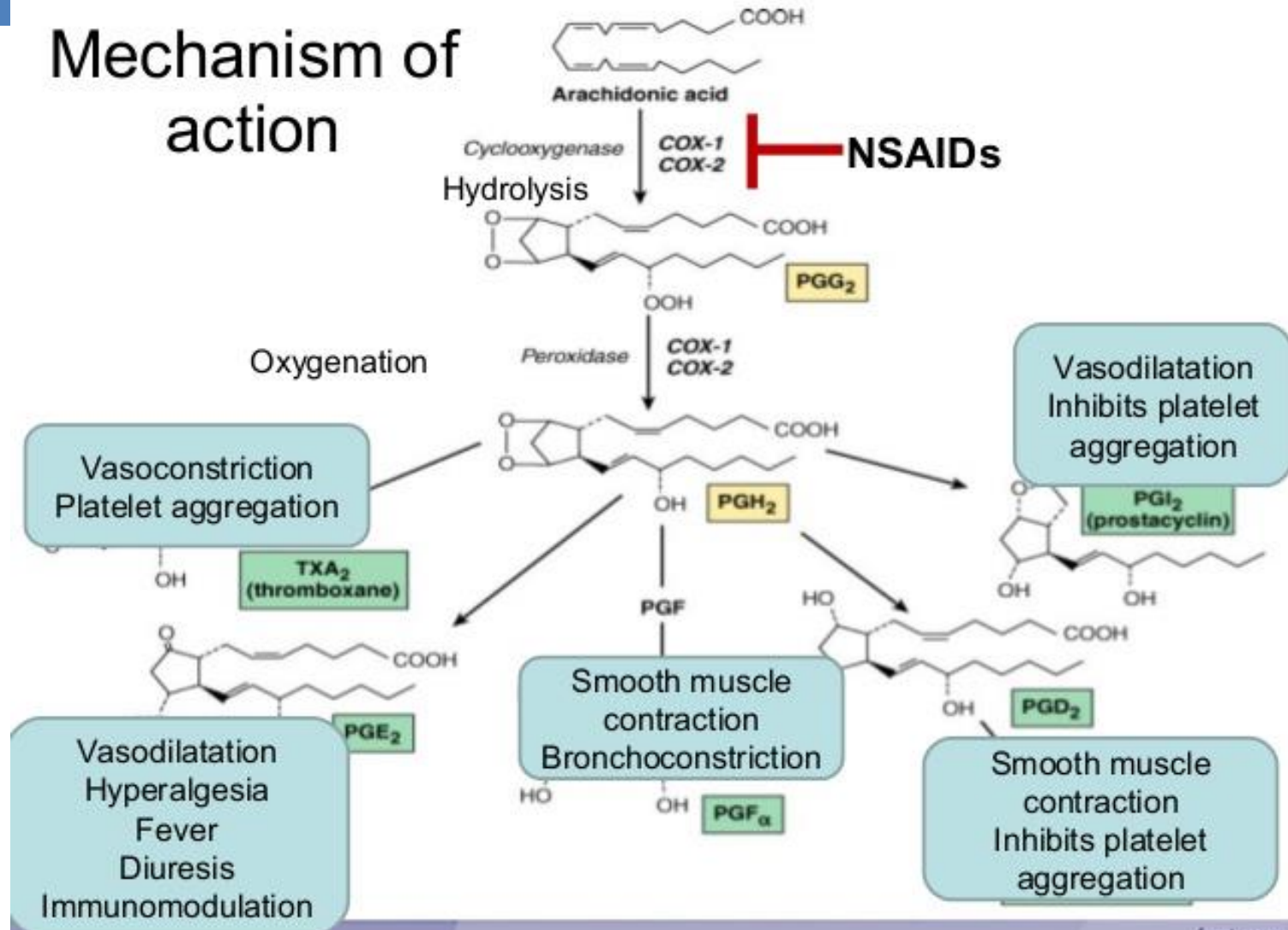
- Nimesulide
- Meloxicam Nebumatone

Selective COX-2 inhibitors

- Celecoxib Rofecoxib
- Paracoxib Lumiracoxib Valdecoxib

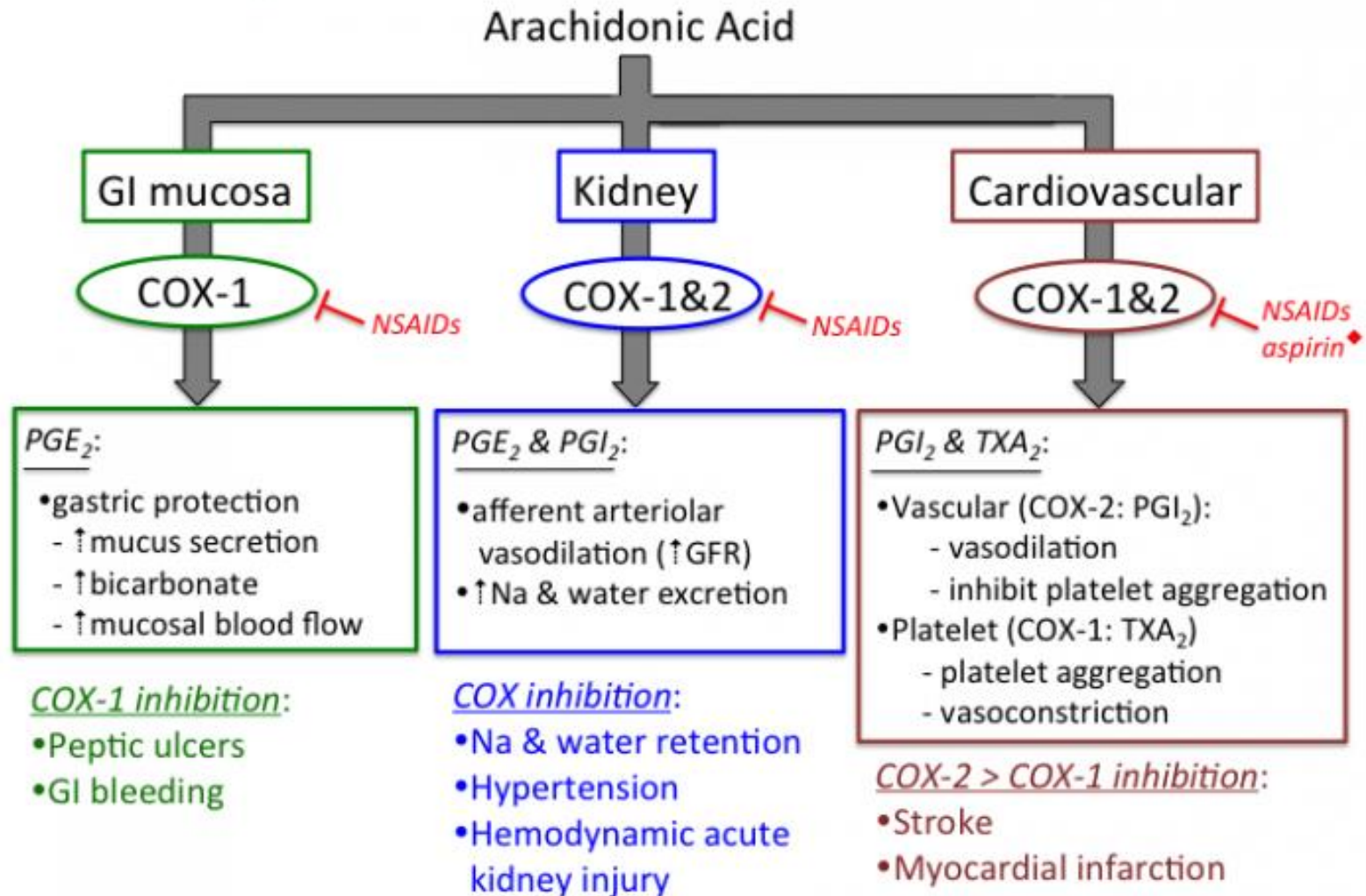
NSAIDs mechanism of action

Mechanism of action



NSAIDs side effects

NSAID Side Effects:



♦ Low dose aspirin irreversibly inhibits platelet COX-1

Non-steroidal anti-inflammatory drugs for treatment of rheumatic diseases

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Nimesulide	100-200 mg/24 to 1-2 reception	
Piroxicam	20 mg/24 h in 1-2 reception	

Prevention and treatment of **GASTROINTESTINAL** pathologies resulting from receiving NSAIDS

•**Antacids**

- have no data about their effectiveness

•**H2-blockers**

- Cure duodenal injury duodenal injury in Warn high doses were effective at the level of the stomach and eliminate symptoms caused by NSAIDS

- Improve semiology

•**Proton pump inhibitors**

- are effective for the prevention and treatment of gastroduodenal injury

- improve semiology

Risk factors for the development of renal failure in the application of NSAIDs

High risk

Reducing the volume of circulating blood, such as significant bleeding or hemodynamic disturbances on the type of shock

Severe heart failure

Cirrhosis of the liver with / without ascites

Clinically significant dehydration

Low - medium risk

true kidney disease

diabetic nephropathy

nephrotic syndrome

hypertensive nephropathy

beginning of anesthesia

The controversial risk

advanced age

Corticosteroids

- Corticosteroids are widely used in the treatment of inflammatory forms of arthritis and related systemic autoimmune diseases.
- In addition to their strong anti-inflammatory effect, they regulate a wide range of metabolic, immunological and central nervous system function.
- For systemic therapy have been issued numerous synthetic derivatives, but the prednisone, prednisolone, and methylprednisolone are used most widely.

Corticosteroids

Form	Relative anti-inflammatory potential	Equivalent dose (mg)	Elimination half-life (h)
Hydrocortisone	1	20	8-12
Cortisone	0,8	25	8-12
Prednisone	4	5	12-36
Methylprednisolone	5	4	12-36
Prednisolone	5	4	12-36
Dexamethasone	20-30	0,75	36-54

Corticosteroids type of therapy

Methylprednisolone

- **Low dosages** – 4-8 mg per day
- **Medium dosages** - 1 mg per kg per day (60-80 mg)
- **High dosages** – Puls therapy (15mg/kg per day) – 1000 mg – 3 consecutive days, then switch to medium dosages

Side effects of long-term Corticoid Therapy

□ Frequent

- Hypertension
- Negative calcium balance and secondary hyperparathyroidism
- Negative nitrogen balance
- Obesity, moon-like face, supraclavicular fat accumulation in the area, fat accumulation in the form of a mountain on his back,
- Slowing of wound healing, erythema face, thin, fragile skin, blue striae, petechiae and ecchymosis
- Acne
- Growth retardation in children
- Adrenal insufficiency, resulting in suppression of the hypothalamic-pituitary-adrenal system
- Hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis
- Sodium retention, hypokalemia
- Increased risk of infection, neutrophilia, lymphopenia
- Osteoporosis, compression fractures of vertebrae, Osteonecrosis
- Mood changes such as euphoria, emotional lability, insomnia, depression, increased appetite
- Subcapsular cataract

Side effects of long-term Cortico-Therapy

□ **Medium frequency**

- Metabolic alkalosis
- Diabetic ketoacidosis, hyperosmolar diabetic coma
- Peptic ulcer (usually the stomach), gastric bleeding
- "Silent" intestinal perforation
- Increased intraocular pressure and glaucoma
- Mild intracranial hypertension or pseudotumor of the brain
- Spontaneous fractures
- Psychosis

Side effects of long-term Cortico-Therapy

□ Rare

- ▣ Sudden death in the rapid introduction of high-dose, pulse therapy
- ▣ Valvular damage in SLE
- ▣ In susceptible patients may develop heart failure
- ▣ Cellulitis (after cancellation)
- ▣ Hirsutism or virilism, impotence, secondary amenorrhea
- ▣ Hepatomegaly as a result of fatty liver
exophthalmos
- ▣ Allergies to synthetic corticosteroids (urticaria, angioedema)

DMARDs –

Disease modifying antirheumatic drugs

- Disease modifying antirheumatic drugs (DMARDs) - the basic drugs from diverse groups that reduce the symptoms of rheumatoid arthritis (RA) and other inflammatory autoimmune diseases.
- In addition, there is increasing evidence that treatment with DMARD, especially if applied early in the course of the disease, can delay the progression of cartilage and bone destruction.
- When the RA is not responding to treatment DMARD, biological therapy can be applied. Biologicals alter the action of cytokines

DMARDs –

Disease modifying antirheumatic drugs

- **When to start** - an understanding that changes in the joints can occur within the first 12 months of the debut of RA, led to the earlier introduction of DMARD and more aggressive combination of DMARDs.
- **Monotherapy** - Methotrexate is considered standard therapy for DMARD.
- **Combination therapy** – Joining of one or two DMARD therapy with methotrexate for the background is often used in an attempt to improve clinical response in those patients who did not give an answer to monotherapy with methotrexate. The most commonly used combinations of DMARD - "triple therapy" (methotrexate + hydroxychloroquine +sulfasalazin) or methotrexate plus a biological agent.

DMARDs –

Disease modifying antirheumatic drugs

Medication	Dosage	Possible side effects
Methotrexate	7.5-20 mg/week	Discomfort in the stomach, skin rash, headache, photosensitivity, increased transaminase, leukopenia, ulcers in the mouth, weakness, fatigue
Leflunomid	10-20 mg/day in 1. Treatment begins with a dose of 100 mg support screens from 3 consecutive days	Diarrhea, dizziness, hair loss, hypertension, increased transaminase, leukopenia, rash on the skin
Sulfasalazine	500-3000 mg daily in 2-4 reception	Abdominal pain, diarrhea, increased sensitivity, reduced appetite, nausea, vomiting, rash on the skin
Hydroxychloroquine	200-600 mg daily in 2-1 reception	Violation of, diarrhea, rash

DMARDs –

Disease modifying antirheumatic drugs

Medication	Dosage	Possible side effects
Cyclophosphamide	50-150 mg per day in single dose	Hematuria, hair loss, leukopenia, amenorrhea, nausea, vomiting
Mycophenolate Mikofenolat	1.5-day	Diarrhea, moderate leukopenia
Azathioprine	50-150 mg/day in 1-3 reception	Leukopenia, increased transaminase

Metotrexate mechanism of action

- Developed as a folic acid analogue.
- Methotrexate inhibits purine and pyrimidine synthesis.
- Suppression of transmethylation reactions with accumulation of polyamines.
- Reduction of antigen-dependent T-cell proliferation.
- Promotion of adenosine release with adenosine-mediated suppression of inflammation.

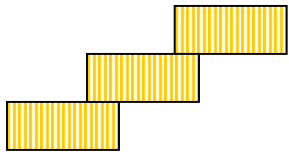
DMARDS mechanism of action

- **Leflunomide** is a selective inhibitor of de novo pyrimidine synthesis.
- **HCQ** increase pH within intracellular vacuoles and alter processes such as protein degradation by acidic hydrolases in the lysosome, assembly of macromolecules in the endosomes, and posttranslation modification of proteins in the Golgi apparatus. As a result, antimalarials diminish the formation of peptide-MHC protein complexes required to stimulate CD4+ T cells and result in down-regulation of the immune response against autoantigenic peptides.

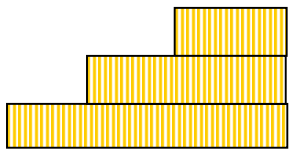
DMARDS mechanism of action

- Cyclophosphamide a cytotoxic agent, significantly decreases antinuclear antibody levels, glomerular cell proliferation, and immunoglobulin staining in the glomeruli.
- Mycophenolate mofetil - an inhibitor of inosine monophosphate dehydrogenase (IMPDH). This is the rate-limiting enzyme in de novo synthesis of guanosine nucleotides. T- and B-lymphocytes are more dependent on this pathway than other cell types are.

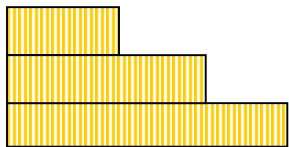
Treatment strategies with drugs



1. Sequential monotherapy



2. Step-up (ascending) combination therapy



3. Step-down (descending) combination therapy



4. Combination with a biological agent

Biological therapy

- One of the most important achievements of the pharmacotherapy of inflammatory rheumatic diseases associated with the development of entirely new group of drugs, which are called "biological" agents.
- Their mechanism of action is associated with suppression of synthesis of "inflammatory" cytokines, playing a fundamental role in the immunopathogenesis of these diseases, especially RA.

Immunomodulating and proinflammatory effects of cytokines in the pathogenesis of inflammatory rheumatic diseases (1)

- **Vascular endothelial cells** - enhance the expression of adhesion molecules (ISAM-1, VSAM-1, E-selectin) through the activation of NF- κ B stimulate angiogenesis, leading to disruption of anticoagulant activity (stimulation of the synthesis of tissue factor, suppression of synthesis of thrombomodulin).
- **Lymphocytes** - contribute to the development of lymphoid tissue, modification of SV44 and the ability to bind to the ligand.
- **Dendritic cells** - cells induce the maturation and migration from nonlymphoid organs to secondary lymphocyte organs.
- **Neutrophils and platelets** - contribute to activation.

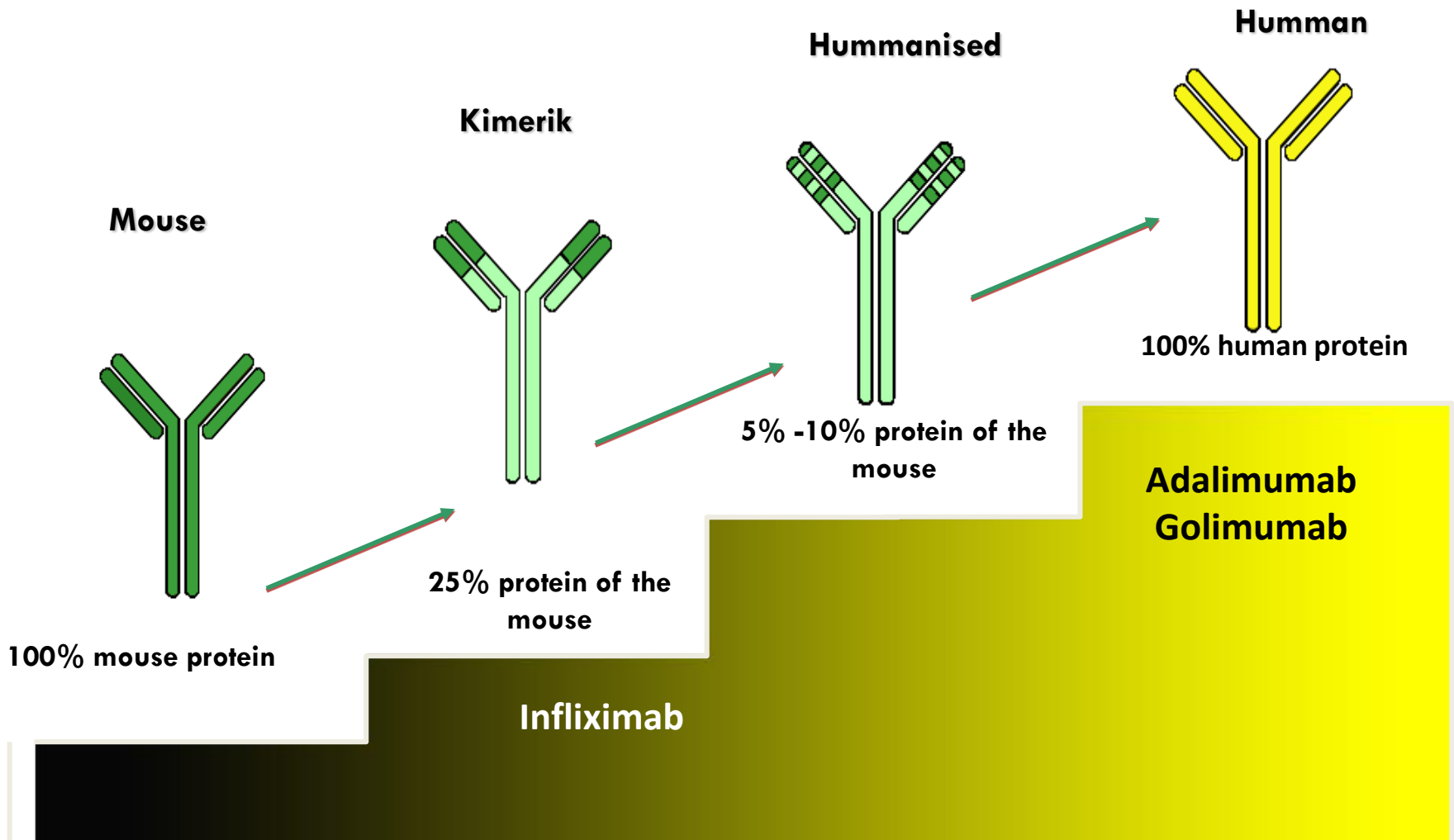
Immunomodulating and proinflammatory effects of cytokines in the pathogenesis of inflammatory rheumatic diseases (2)

- **Fibroblasts and synoviocytes** - lead to proliferation.
- **Pro-inflammatory cytokines** - in addition induce the synthesis of IL-1, IL-6, granulocyte-macrophage colony-stimulating factor.
- **Other pro-inflammatory mediators** - induce the synthesis of PGE2 through activation of COX-2, leukotrienes, platelet activating factor, nitric oxide and reactive oxygen species.
- **Metalloproteinases** - induce the synthesis of collagenase, gelatinase, stromelysin.
- **Other effects** - increase pain, induce cachexia, induce fever, mobilize calcium from the bones; modulate apoptosis.

Biological therapy

- The particular interest is the use of monoclonal antibodies.
- These drugs have very high specificity, which provides a selective effect on certain links in the immunopathogenesis of disease, minimally affecting normal functioning mechanisms of the immune system.
- This can significantly reduce the risk of "generalized" immunosuppression, which is typical of many drugs, especially glucocorticoids and cytotoxic drugs.

Monoclonal antibody to TNF- α



Biological therapy

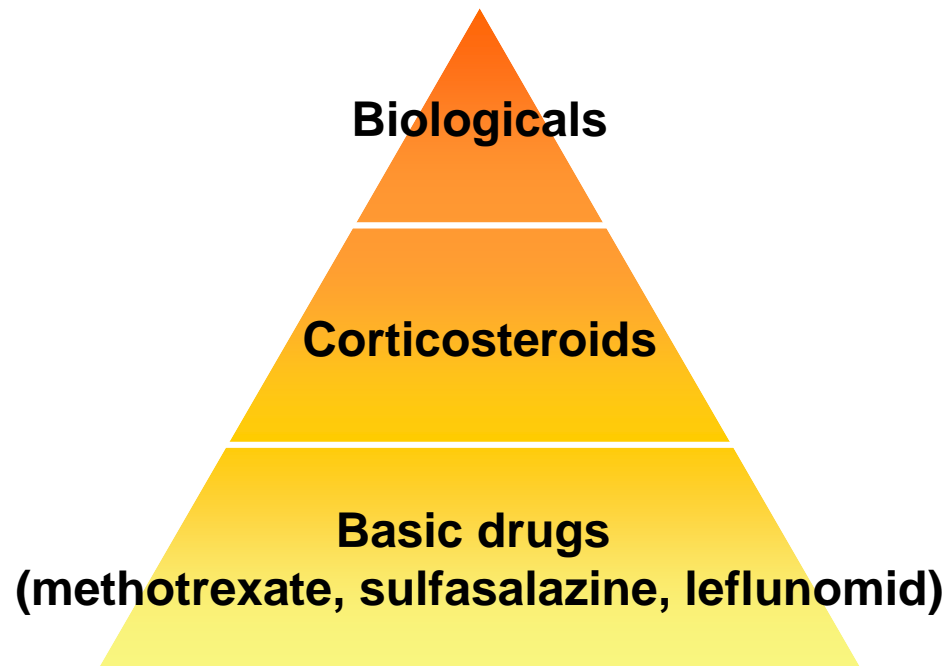

- The main target for anticytokine monoclonal antibody therapy is:
 - TNF-alpha (infliximab, adalimumab, etc.)
 - IL-6 (tocilizumab)
 - CD20 B cells (rituximab)
 - IL-1, IL-2, etc.

Contraindications of biological therapy

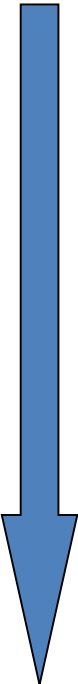
- ❑ Congestive heart failure
- ❑ Severe infection
- ❑ Latent tuberculosis
- ❑ Malignant neoplasms
- ❑ Pregnancy and lactation.

The need for biological specimens

The gravity of the condition of the patient



The number of patients



THANK YOU!