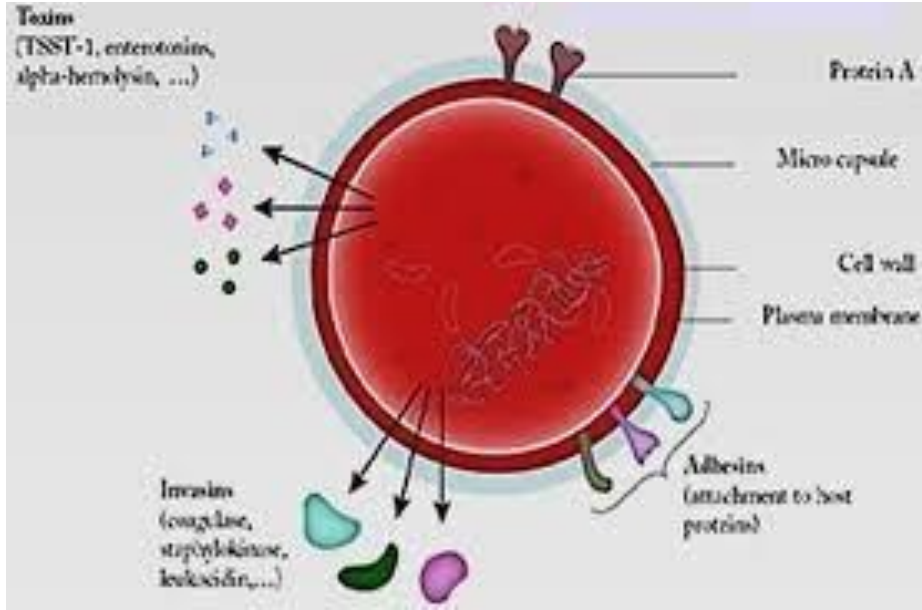
Practical 8
The concept of infection. Immunity and its types: innate (non-specific) and acquired (specific) immunity. Innate (nonspecific) immunity, its features and factors.

- *Infection or infectious process* cover pathological process occurring in macroorganism as a result of entry and reproduction of microorganism. The similar processes caused by protozoans, helminthes and insects are called invasion (lat, invazio – attack). The interaction of microorganisms with macroorganisms in the infectious process manifests itself pathogenetically and clinically as an infectious disease.
- ***Infectious process conditions*** • Pathogenic microorganism • Sensitive macroorganism • Environmental conditions
- ***The role of microorganism in infectious process :*** Saprophytic microorganisms live in environment, human and animal organisms as commensals without causing disease (greek, sapros – decay and phyton - plant). Pathogenic microorganisms (lat, pathos – suffering, genos - origin) enter sensitive macroorganism and cause infectious disease. Opportunistic microorganism can cause disease only under certain conditions. Their ability to cause disease is dependant on host macroorganism status.
- *Pathogenicity* is ability of microorganism to cause pathological process or disease. Pathogenicity is genetic feature of microorganims and specific for the majority of microorganisms in other words, each pathogenic microorganism causes specific disease. Pathogenicity may vary within the same species. The degree of pathogenicity is expressed in *virulence* (Latin, virulentus - toxic). For viruses, the term "infectivity" is used instead of "virulence". Change of virulence – weakening or strengthening may be phenotypic or genotypic. Once the factor causing the change of virulence disappears, the virulence returns to its previous level. If the virulence change is due to genetic factor it is passed from one generation to another. Cultivation of microorganisms under unfavourable conditions, long-term cultivation on artificial media, passage in animal organism with weak sensitivity, impact of physical and chemical factors may cause weakening of virulence. Stabile weakening of virulence – attenuation is used in vaccine preparation. Passage of microorganism in organism of sensitive animal may strengthen the virulence. It may be due to selection of virulent population of microorganisms.

- Virulence of microorganisms in the laboratory is usually assessed in laboratory animals, especially white mice. For this purpose, lethal and infectious doses are determined.
- **Lethal dose** – the lowest number of microorganism or toxin causing death of certain number of animals over a period of time.
- **Absolute lethal dose** (DCL - dosis certa letalis) – the lowest number of microorganism or toxin causing death of 100% animals.
- **Minimal lethal dose** (DLM - dosis letalis minima) – the lowest number of microorganism or toxin causing death of the majority (approximately 90%).
- **Median lethal dose** (LD50) – the number of microorganism or dose of toxin causing death of a half of experimental animals. This dose is commonly used for evaluation of virulence.
- **Infective dose**s are İD100 and İD50.



Pathogenicity factors of microorganisms-morphological structures:
Pili, fimbriae– adhesion
Capsule, microcapsule– protection from phagocytosis
Cell wall components (lipoteichoic acids, M-protein) – chemoattraction, adhesion, complement activation, protection from phagocytosis.
Cell wall components(lipopolisaccharide) - endotoxin

Pathogenicity factors of microorganisms:
 Adhesion – specific connection of microorganism to sensitive cell.
 Colonization - multiplication of microbe on surface of sensitive cell.
 Penetration – ability of some pathogens to enter in cells (epithelial, leucocites, lymphocites etc.).
 Invasion – entry of microbe through mucous membrane and connective tissue into necessary tissues (neuraminidase, hyaluronidase)

- **Adhesion** (lat, adhesis – stick) – ability of microorganism to stick cells and tissues. It is supported by pilis and otherstructures(adhesins and ligands). On the other hand there special structures of macroorganism cells called receptorswhich are able to interact with microbes. Adhesion of microorganismsis ligand-receptror mediated phenomenon.
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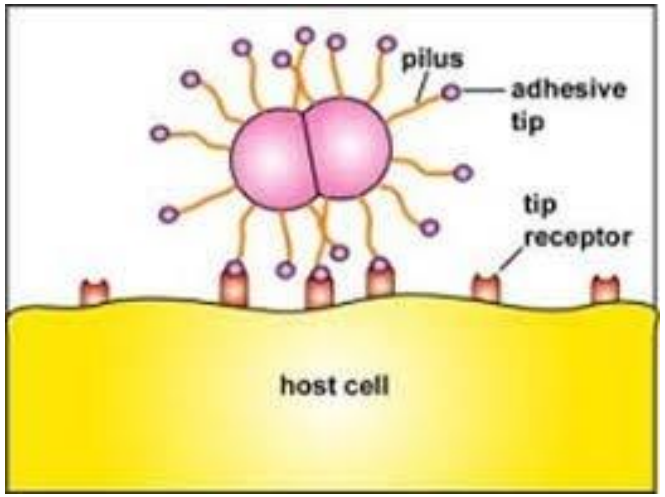
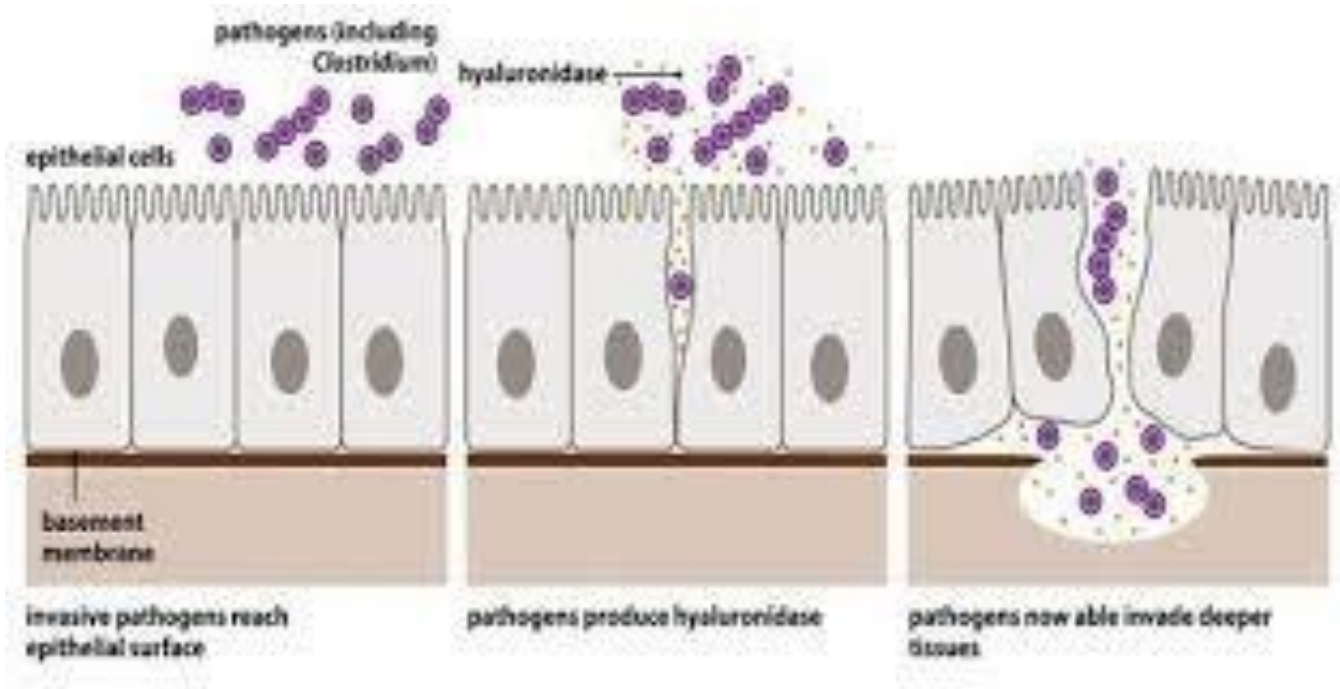
- After adhesion microorganisms begin to multiply on certain areas –**colonization**. First, microorganism colonize skin and mucous membranes. Colonization may occur both inside and outside the cell. For example, cholera causing microbe colonizes surface, while dysentery causing bacteria multiply inside the cell.
- Ability to penetrate is related to invasiveness of microorganism. *İnvasiveness* - is ability to enter cells and tissues. Colonization of skin and mucose membranesis not always limited to surface layers. Pathogenicity of some bacteria (Shigellae, iersinia etc.) is related to their ability for penetration. Penetration is mediated by special factors among which invasins – special proteins of outer layer are well studied. Interaction of invasins with cell surface receptors – integrins results with endocytosis(“swallowing”).
- Many pathogenic microorganisms especially bacteria have pathogenic factors preventing phagocytosis – microcapsule, capsule, slime layer. Some microorganisms synthesise substances weakening phagocytosis or breaking down chemoattractants. There are also factors preventing intracellular killing of bacteria:
- • Substanses inhibititng fusion of phagosome with lysosome
- • Protection from oxydasing factors of phagososmes
- • Resistance to lysosomal enzymes
- • Factors causing lysis of phagosome(exp. listeriolysin);
- • Some microorganisms (trypanosomes) can leave phagolysosome thus preventing themselves from phagocytosis
- These factors support survival of microorganismsinside the pahgocytesincomplete phagocytosis. This phenomenon enables spread (dissemination) of microbe in organism through blood and lympha.



- **Agression enzymes**
- Invasiveness is closely linked with ability to produce enzymes – aggression ferments. They commonly break down membrane of cells, extracellular substance enabling spread of microorganism in tissues. Hyaluronidase, Lesitinase (phospholypase), Neuraminidase, Collagenase, Plasmacoagulase, Fibrinolysin ,Citolysins (hemolysins), leucosydins, IgA1-proteases.
- Many pathogenic microorganisms especially bacteria have pathogenic factors preventing phagocytosis – microcapsule, capsule, slime layer. Some microorganisms synthesise substances weakening phagocytosis or breaking down chemoattractants.
- One of the most important pathogenic factors of bacteria are their toxins. • Two main groups of toxins exist: exotoxins and endotoxins.
- Each infectious disease has its own pathogen (etiological factor), in other words, each pathogenic microorganism causes only a certain disease (or diseases).
- - Bacterial infections, viral infections, mycoses
- - Protozoosis, helminthosis, infestations
- Infectious disease is contagious.
- - Contagious index – a ratio of infected people number to number of people which were in contact with infection source.
- Infectious acquired immunity disease has periodical course is formed after infectious disease.



- According to the mechanisms of action Exotoxins can be divided into several groups: • toxins affecting the cytoplasmic membrane; • toxins affecting intracellular targets • Superantigens
- ***Toxins acting on cytoplasmic membrane of host cell:*** 1) Toxins with enzymatic hydrolysis activity (for example, alphatoxin of C. perfringens with phospholipase activity hydrolyzesthe cell membrane); 2) Some toxins cause cell lysis by disrupting the selective transport of ions by forming pores in the cytoplasmic membrane. For example, S. pyogenes O-streptolysis, E. coli hemolysis, L. monocytogenes O-listeriolysis, S. aureus alpha-toxin act by this mechanism.
- ***Toxins acting on intracellular target***s: Act after entering the host cell. These toxins are synthesized as a functionally inactive single polypeptide chain or protoxin. They are activated under the influence of macroorganism tissue and cell proteases. Structurally these toxins are 2-component molecules - A-B (English, the initials of the words "active" and " binding "). Fragment B binds to specific receptors on the surface of host cells and have no toxic effect, it enables transfer of A-component inside the cell. A-fragment has toxic activity.
- ***Superantigen***s activate lymphocytes, mainly Tlymphocytes, by non-specific (polyclonal) activation.Unlike specific (monoclonal) activation, most lymphocyte clones are involved in non-specific (polyclonal) activation, resulting in hypersecretion of cytokines. S. aureus enterotoxins and toxin shock syndrome toxin, streptococcal scarlet fever toxin, etc. have superantigenic properties.

Exotoxins	Endotoxins
Synthesized by living microbial cells and accumulates in high concentrations in a liquid culture medium.	*Gram-negative bacteria are part of the cell wall and are removed after the bacterial cell is destroyed.*
Produced by both gram negative and gram positive bacteria.	*Exist only in gram negative bacteria*
Proteins with molecular weight 10000-900000 D.	*Lipopolisacharide complex. Toxicity is related to lipid A.*
Relatively thermolabile – rapidly destroyed by 60 C and higher.	*Relatively thermostable and do not lose their toxicity for one hour at a temperature higher than 60 C.*
High antigenic properties	*Weak antigenic properties*
Some factors cause their conversion to anatoxins.	*Do not convert to anatoxins.*
High toxicity.	*Low toxicity.*
Do not cause fever.	*Cause fever by mediating interleukin-1 production.*
Production may be coded by extrachromosomal genes.	*Production is coded by chromosomal genes.*
Selective effect on organs and tissues.	*Have no selective action.*

- ***The role of macroorganism in infectious process* : Age** («child infections»)/ **Nervous system condition/ Endocrine system condition/ Nutrition/ Sex/ Genetic factors/ Immune system condition/ Normal microbiota role**(colonization resistance)
- Each infectious disease has its own pathogen (etiological factor), in other words, each pathogenic microorganism causes only a certain disease (or diseases).
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- ***Infection source***
- **Antroponoses**- the source of infection are people
- **Zoonotic** infections- the source of infection are animals
- **Sapronoses** - the source of infection is the environment
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- ***Infection mechanisms***
- **Air-droplet mechanism -** the causative agent is mainly localized in the upper respiratory tract spreads to environment when talking, sneezing, coughing and infects through air-droplet, air-dust mechanism. Respiratory tract pathogens are transmitted through this mechanism. Sneezing
- **Fecal-oral mechanism** - the causative agent is mainly localized in the intestines, excreted in the environment with feces and transmitted by an alimentary route (food, water). Intestinal infections are transmitted by this mechanism.
- **Contact mechanism**– pathogens are localized in different places and spread through different ways. - Direct and indirect infections possible.
- **Transmissive mechanism -** The causative agent is in the blood of a person or an animal and is transmitted by blood-sucking insects (malaria, smallpox, etc.). - Parentheral infection can also be attributed to the transmissive mechanism.
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- ***Infectious process stages***
- **The incubation period, or latent period,** covers the period from the entry of a pathogenic microbe into an organism until the first signs of the disease are observed. In most diseases, the latent period lasts 1-2 weeks. **Prodromal (Greek, prodromos - evangelist)**, or the period of awareness is a period after the latent period, with non-specific symptoms (fever, headache, weakness, malaise).
- **The period of clinical manifestations,** beginning after the prodromal period, is accompanied by the symptoms characteristic of each infectious disease. - General signs, characteristic symptoms, pathognomonic symptoms. **Reconvalescence period** - decresase of symptoms and recovery of organism functions. - *healing, microbe carriage, chronic form, lethal.*
- ***Infectious disease forms :***
- Depending on the origin - exogenous infection, endogenous infection, or autoinfection
- Depending on the location of the causative agent in the body - Focal infection, generalized infection Distribution of the causative agent and its toxin in the body - Bacteremia (sepsis), virusemia, toxemia Depending on number of he pathogen - monoinfection, mix-infection
- Superinfection- infection with the same agent before the disease is cured
- Reinfection - infection with the same agent after complete recovery of the infectious disease
- Recidive - recurrence of syptoms without new infection

- **Immunity**
- • greek, «immunitas» - exemption from obligations, privilegy
- • Immunity – processes and mechanisms supporting inner stability of organism by protecting it from pathogens and other genetically foreign substances

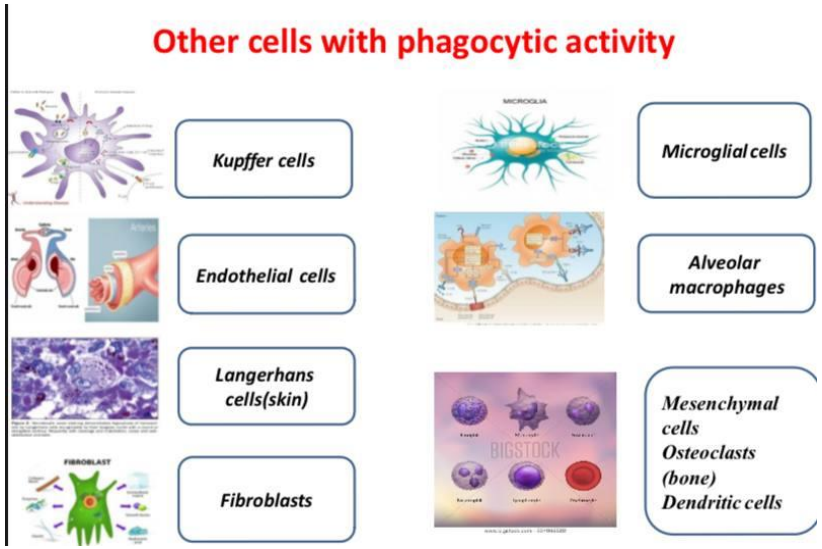
- Types of immunity:
- *Innate or species immunity* – organism is insensitive to antigen and passes this feature to next generation . *Acquired immunity* - formed after exposure of the organism to microorganisms or other antigens, is not transmitted from generation to generation.

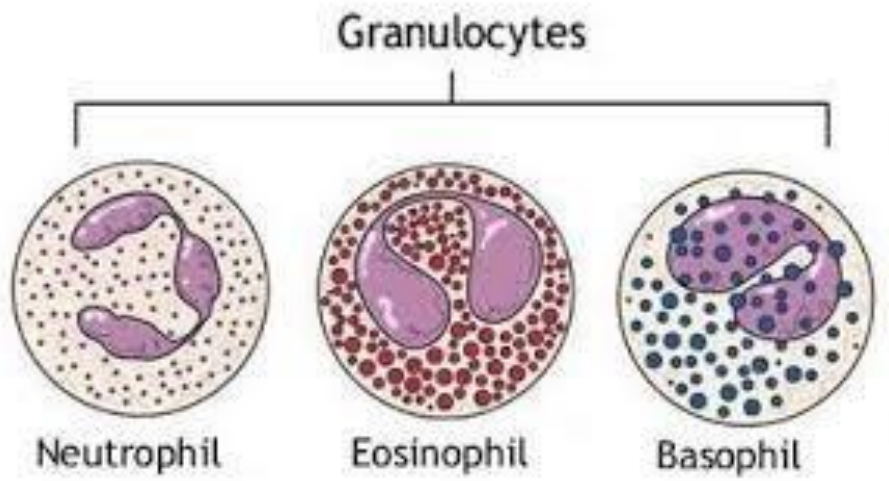
- ***Immunity manifestation :***
- **Antibacterial , Antiviral , Antitoxic , Antifungal, Antiprotozoan, Transplantation, Antitumor**
- **,Sterile and non-sterile, Non-specific and specific immunity**

- ***Sterile*** immunity the complete elimination of pathogens from the body. ***Nonsterile*** immunity can not eliminate microorganism from the organism, in other words it exists only in presense of pathogen and disappears when the pathogen leaves macroorganism.Thus, it is also called infection immunity. Nonsterile immunity is observed in tuberculosis, siphylis etc.
- ***Specific immunity*** : The activity of specific factors depends on the type of antigensthat enter the body. A specific defense factor formed against any antigen cannot protect the body from other antigens, in other words, these factors have specificity.
- Types of ***non-specific immunity***:
- Non-specific defense factors can be divided into specialized and non-specialized, humoral and cellular. Specialize defense factors primary function is defense of organism, while the primary function of non-specialized factors(non-specific resistance)is not defense.
- Humoral factors- dissolved substances, Cellular factors consist of different cells.

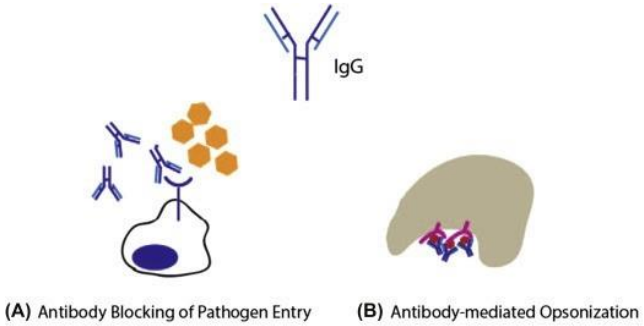
- ***Non-specialized defense factors or non-specific resistance:***
- Skin and mucous membranes are outer barriers of organism. The integrity of skin and mucous membranes and their impermeability for foreign antigens is vital for defense: Alteration of integrity increases possibility of entering microorganisms.
- There are many non-specific humoral defense factors in body tissues and blood. They usually have an antimicrobial effect or are involved in the activation of other immune factors. Non-specific humoral defense factors include secretory immunoglobulins, complement system proteins, lysozyme, C-reactive protein, transferrin, interferon and IFN.

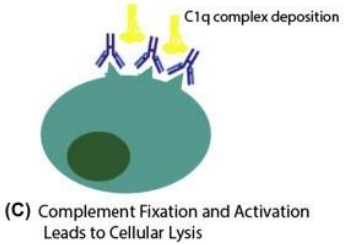
- ***Phagocytes***
- Phagocytosis (greek, phagos-engulf, cytos-cell) absorption and neutralization of microorganisms, cells with altered antigenic features, foreign bodies by neutrophils and macrophages. The process of phagocytosis has three steps- migration, ingestion and killing (killing). The process begins with the migration of phagocytes to the object of phagocytosis. It occurs through chemotaxis of phagocytes induced by chemoattractants - metabolic products of microorganisms, tissue and cellular debris etc.

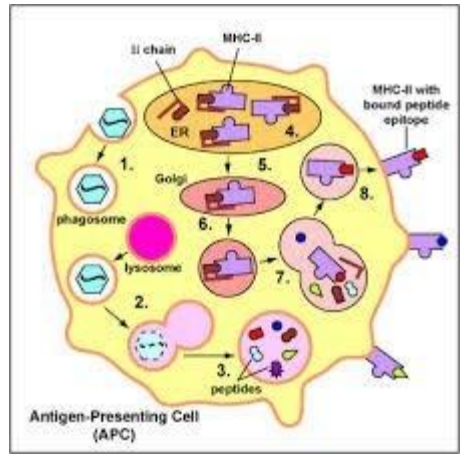


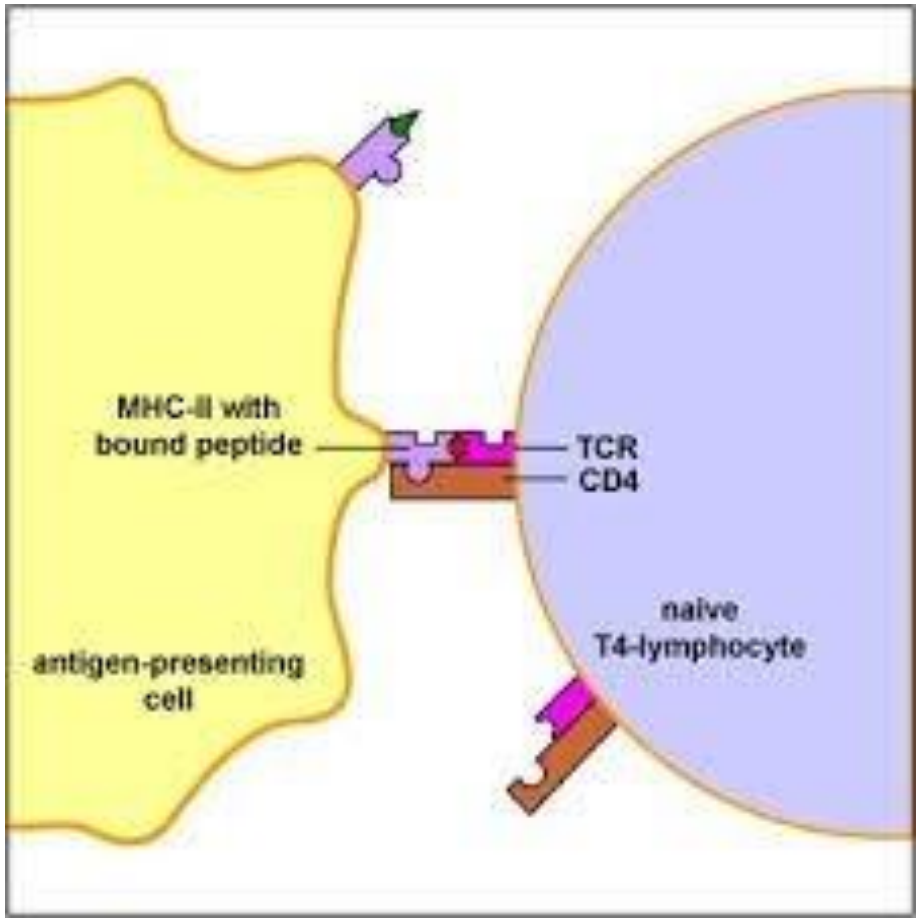


- Opsonization – attachment of antibodies and complement to the object of phagocytosis – plays an important role in phagocytosis. Opsonized object is easily recognized by phagocytes as they have special receptors for opsonins. Phagocytosis may occur without opsonization as well however with low efficacy.
- Objects attached to the pahgocytes membrane are surrounded by pseudopods resulting with formation of phagosome(vacuoles) in protoplasma. Then, after fusion of phagosome with lysosome phagolysosome is formed and the object is processed and disintegrated by phagocyte enzymes. Complete digestion of engulfed microorganism by phagocytes is called complete phagocytosis. The processing of some microbes in phagocytes occurs without opsonization. At some conditions even activated phagocytes can not process these objects resulting in incomplete phagocytosis characteristic for granulomatous infections(tuberculosis, brucellosis etc.)
- Various mechanisms are envolved in illing of microorganisms in phagocytes: oxygen-dependent and non-oxygen-dependent mechanisms. The oxygen-dependent mechanism begins immediately after phagosome formation and destroys objects inside the phagocyte with oxygen radicals. Absorption of the object is accompanied by a "respiratory explosion" in phagocytes, resulting in the formation of free oxygen radicals- superoxide radicals and hydrogen peroxide.
- Antigen presenting cells(APC) :Functionally monocytes and macrophages have 2 subpopulations: first- perform only phagocytosis, second – phagocytosis and presentation of antigen to lymphoid cells. The latter cells called antigen presenting cells(APC) process antigen, present it to T and B-lymphocytes thus participating in formation of specific immunity.









- ***İnflammation reactions***
- The entry of foreign bodies into the body, including bacteria, causes defensive inflammatory reactions. These responses are characterized by appropriate clinical signs - hyperemia, swelling, fever and pain. Inflammatory reactions include an increase in blood flow velocity, an increase in capillary permeability, the passage and accumulation of fluid from from blood vessels to the interstitial areas. The increase in capillary permeability is due to the action of some chemical mediators, especially histamine, prostaglandins and leukotrienes. The pain is mainly caused by the mediator bradykinin. Neutrophils and macrophages migrate to the site of infection earlier (first) than other cells. It should be noted that neutrophils dominate in acute purulent infections, while macrophages - mainly in chronic or granulomatous processes. Microorganisms - inducers of the inflammatory response are phagocytosed by of polymorphonuclear neutrophils (PNLs) and macrophages. PNL makes up about 60% of leukocytes in the blood, the amount of which increases significantly during infection (leukocytosis). However, it should be noted that in some infections of bacterial origin (for example, typhoid fever), on the contrary, a decrease in the amount of leukocytes (leukopenia) is observed.