Basic tasks of clinical immunology. Principles of functioning of the immune system, clinical and laboratory evaluation of its disorders.

Professor Vladimir Babadzhan
- Primary lymphoid organs: maturation of lymphocytes.
- Secondary lymphoid organs: trap antigens & provide sites for mature lymphocytes to interact with that antigen.
- Tertiary lymphoid tissues: cutaneous associated lymphoid tissues.
# Lymphoid Organs

## Central or Primary

- Provide the appropriate microenvironment for development and maturation of lymphocytes

  - Thymus
  - Bone Marrow

## Peripheral or Secondary

- Sites where mature lymphocytes interact effectively with the antigens.

  - Spleen
  - Lymph nodes
  - MALT
Primary Lymphoid Organs

- Immature lymphocytes generated in bone marrow mature, becomes specific for a particular antigen in central lymphoid organs.

- Such educated cells are immunocompetent cells.
  - T cells arise in thymus.
  - B cells in bone marrow.
Bone Marrow

- All lymphocytes originate in bone marrow.
- T lymphocytes develop in thymus.
- B lymphocytes develop in bone marrow itself.

(In birds, bursa of Fabricius – primary site associated with B cell maturation)
Origin and Development of Immune Cells

**BONE MARROW**

- **Stem cells**
  - noncommitted dividing

- **Progenitor cells**
  - committed dividing

- **Lymphoid**
  - thymus
  - bursa equivalent

- **Myeloid**
  - Monocyte: 3-5%
  - PMN: 70%
  - eosinophil: <3%
  - basophil: <2%

**BLOOD**

- **T cell**: 90%
- **B cell**: 10%

**TISSUE**

- Cell Mediated Immunity
  - B
  - Humoral Immunity
  - MP
  - mast
Thymus

Functions:
- Production of thymic lymphocytes.
- Major site of lymphocyte proliferation.
- Thymus (T) dependent lymphocytes or T cells – immunocompetent.
- Important in development of CMI.

Thymus dependent areas of peripheral lymphoid organs:
- White pulp of spleen.
- Paracortical areas of lymph node.

Effects of thymectomy or congenital thymic aplasia:
- Deficient CMI (Di George syndrome)
- Increased chance of getting infectious diseases
- Diminish antibody response towards thymus dependent antigens.
Peripheral Lymphoid Organs

Lymph node

- B-cell activation
- Afferent lymphatic vessels
- Paracortex
  - Initial T-cell and B-cell activation
- Cortex
- Medulla
  - Plasma-cell secretion of antibody

- Germinal center
- B-cell proliferation and differentiation
- Secondary follicle

Efferent lymphatic vessel
Lymph Node

- Placed along the course of lymphatic vessels.

- Phagocytose foreign materials including microorganisms especially from local tissues.

- Help in the proliferation and circulation of T & B cells.

- Histology:
  - Macrophages & dendritic cells
  - Cortex & paracortex
  - T helper cells - paracortex
  - B cells - cortex
  - Plasma cells - medulla
Lymphoid Organs

Functions:
- Defense
- Homeostasis
- Surveillance
The normal individual has two levels of defence against foreign agents. The first type is named *natural* or *innate* immunity. This type of immunity is sometimes referred to as non-specific but broadly specific. The second type of immunity is *adaptive* or *acquired* immunity and is confined to vertebrates.
INNATE IMMUNITY

PHYSICAL BARRIERS
Skin, mucous membrane

CELLS
granulocytes, monocytes, macrophages

CHEMICAL BARRIERS
pH, lipids, enzymes

ACQUIRED IMMUNITY

HUMORAL
B cells
antibodies

CELL MEDIATED
T cells
interleukines

MP
Physical barriers are the first line of defense against infection. The skin and mucous membranes provide a continuous surface which must be breached and back this up with mechanical protection through cilia and mucous. **Physiological factors** such as pH, temperature and oxygen tension limit microbial growth. The acid environment of the stomach combined with microbial competition from the commensal flora inhibits gut infection. **Protein secretions** into external body fluids such as lysozyme also help resist invasion. Soluble factors within the body such as complement, interferons and collectins and other "broadly specific" molecules such as C-reactive protein are of considerable importance in protection against infection. **Phagocytic cells** are critical in the defense against bacterial and simple eukaryotic pathogens. **Macrophages** and **Polymorphonuclear leucocytes (PMN)** can recognise bacterial and yeast cell walls through broadly specific receptors (usually for carbohydrate structures) and this recognition is greatly enhanced by activated complement (opsonin).
Nonspecific Immunity

- **Granulocytes**
  - Polymorphonuclear leukocytes (PMN, neutrophils)
  - Eosinophils
  - Basophils (blood)
  - Mast Cells (tissues)

- **Mononuclear Phagocytes**
  - Monocytes (blood)
  - Macrophages (tissue)

(allergic and hypersensitivity reactions)
Functions of Phagocytic Leukocytes (mono, MP and PMN)

- **Localization and Removal of Foreign Substances** (Inflammation and wound healing)
  - **Chemotaxis**: directed migration to site of injury; chemical mediators (chemotactic factors)
  - **Phagocytosis**: ingestion of foreign substances
  - **Metabolic destruction**: digestion and killing
    - Oxygen-dependent (MPO, ROI, RNI)
    - Oxygen-independent (cationic proteins, lysozyme, TNF, porphorins)
Immune Functions of Macrophages

- Antigen processing and presentation
- Tumor Cytotoxicity
- Tumor Surveillance
Antigen Processing and Presentation

Ingestion of antigen

Processing of Ag

Epitope displayed on MHC

Peptide
Macrophage (APC)

MHC Class II

CD4

Peptide Antigen

TCR

CD4 Th Cell

Cytokines
Dendritic Cells

- Antigen presenting cells
- Pleomorphic, have long needle like processes
- Present in blood & peripheral lymphoid organs
- Little or no phagocytic activity
Mucosa Associated Lymphoid Tissue (MALT)

GALT - Lymphoid tissues in gut. From adenoids & tonsils to the follicles in the colon

BALT - Lymphoid tissues in respiratory tract.
Cell Mediated Immunity

- Mediated by **T lymphocytes** which release soluble mediators (**interleukines**)

- Important in host defense against viruses, certain bacteria, fungi, transplant rejection and tumor surveillance; Type IV (delayed type) hypersensitivity (DTH) reactions

**T Cells:** derived from precursor cells in bone marrow; mature in thymus; become educated
Cells of Immune System

- Central cells of the immune system -
  - LYMPHOCYTES
  - They are responsible for:
    1. adaptive immunity.
    2. immunological aspects of diversity, specificity, memory & self / nonself recognition.

- Functions of other WBCs
  1. engulf and destroy micro organisms
  2. present antigens.
  3. secrete cytokines.
Lymphocytes educated by central lymphoid organs

Stimulated T cells produce lymphokines

Stimulated B cells divide & transform into plasma cells which synthesize antibodies

Surface markers

- Reflect various stages of maturation & differentiation of lymphocytes & other leucocytes
- Each surface marker given a CD (Cluster of Differentiation) number

CD 4 – Helper T cells
CD 8 – Suppressor T cells or Cytotoxic T cells
CD 19 – B cells
CD16 – natural killer cells
T Lymphocyte Types

- Helper cells (CD4 cells)
- Cytotoxic cells (Killer T cells, CD8 cells)
- Suppressor cells (CD8 cells)
- Natural killer cells (NK-cells, CD16)
- Memory cells
Helper T-Cells (CD4 cells)

- Master “on-switch” of immune system
- Recognize antigens
- Secrete lymphokines that activate all other immune system cells
- Stimulate B-cells to begin antibody production
T-helper cells

**Th1 cells:** T helper inflammatory cells
- Involved in cell-mediated allergies, e.g. poison ivy
- Promote rejection of transplanted tissue
- Stimulated by cell-bound antigen, and secrete lymphokines

**Th2 cells:** Stimulate B cells to produce antibodies
Cytotoxic (Killer) T-Cells (CD8 cells)

- Respond to presence of antigens and lymphokines produced by CD4 cells
- Seek out, bind to, and destroy:
  - Cells infected by viruses
  - Some tumor cells
  - Cells of tissue transplants
- Can deliver lethal hits on multiple cells in sequence
Suppressor T-Cells (CD8 cells)

- Produce **interleukines** that inhibit proliferation of B and T cells
- Downregulate or dampen immune response
Antigen Recognition by T Cells

- Specific T cell receptor
- T cells are MHC restricted; only recognize antigen and MHC protein
- T-helper cells (CD4) recognize processed antigen and piece of self (MHC II)
- Cytotoxic T cells (CD8) recognize processed antigen and nonself (MHC I)
T – Cell Maturation

- CD4 cells = MHC II Restriction - TWO types – TH1 & TH2. TH1 – secrete γ interferon & IL – 2, which activate macrophages & T cells promoting CMI. TH2 – secrete IL – 4, IL – 5, IL – 6 = stimulate B cells to form Abs.

- CD8 cells = MHC I Restriction – can kill & lyse target cells carrying new or foreign Ags = down regulate immune response.
Natural Killer Cells
NK cells

- Cytotoxic towards malignant &
  - virus infected cells
- Natural or non immune
- Destroy cells by apoptosis
- Active in severe combined immunodeficiency diseases

- Important cells in:
  - immune surveillance & natural defense
  - against virus infected & malignant cells.
History

Name **histocompatibility complex** because of its discovery based on transplantation experiments.

- Human MHC antigens are found on surface of leucocytes hence synonymous with Human Leukocyte Antigens (HLA) & MHC complex of genes with the HLA complex.
HLA Complex

- HLA complex of genes located on short arm of chromosome 6.

- It is comprised of three separate clusters of genes:
  1. HLA class I \( \rightarrow \) A, B & C loci.

  2. Class II or D region \( \rightarrow \) DR, DQ & DP loci.

  3. Class III or the complement region \( \rightarrow \) genes for complement components C2 & C4 of the classical pathway, properdin factor B of alternative pathway, heat shock proteins, tumor necrosis factors C.
HLA Molecules

MHC class I molecule

- peptide-binding groove
- $\alpha_2$
- $\alpha_1$
- $\alpha_3$
- $\beta_2$-microglobulin

MHC class II molecule

- peptide-binding groove
- $\beta_1$
- $\beta_2$
- $\alpha_1$
- $\alpha_2$
There are 2 basic types of T cell

<table>
<thead>
<tr>
<th>Accessory Molecule</th>
<th>T cell</th>
<th>MHC restriction</th>
<th>Function</th>
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<tbody>
<tr>
<td>CD4</td>
<td>T helper</td>
<td>Class II</td>
<td>Cytokine production help for B cells and cytotoxic T cells</td>
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<tr>
<td>CD8</td>
<td>T cytotoxic</td>
<td>Class I</td>
<td>Cytokine production cytotoxic lysis of infected or tumour cells</td>
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</table>
Memory T-Cells

• Have previously encountered specific antigens
• Respond in enhanced fashion on subsequent exposures
• Induce secondary immune response
Humoral Immunity

Mediated by **B lymphocytes** which produce **antibodies** or **immunoglobulins (Ig)** in response to antigen challenge

**Antibodies**: glycoproteins; selective, highly specific; found in $\gamma$–globulin fraction of serum (humoral=blood)

**Five Classes**: physical, chemical and antigenic differences
Classes of Antibodies

**IgM:** primary immune response (7%); Type III hypersensitivity reaction; immune complexes; B cell receptor

**IgG:** secondary immune response, B memory cells (70%)

**IgA:** external secretions, produced locally against bacteria and viruses (15%)

**IgE:** Type I hypersensitivity reactions, minute amounts

**IgD:** umbilical cord blood, primitive recognition or regulation; B cell receptor
Kinetics of Antibody Production

Primary response

Secondary response

Antibody titer in serum (arbitrary units)

Initial exposure to antigen

Second exposure to antigen

IgG

IgM

Time (days)
Summary of the phases of the immune response

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<th>Phase</th>
<th>Immediate</th>
<th>Early</th>
<th>Late</th>
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<td>Duration</td>
<td>0-4hrs</td>
<td>4-96hrs</td>
<td>&gt;96hrs</td>
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<tr>
<td>Type</td>
<td>Innate</td>
<td>Innate (inducible)</td>
<td>Specific</td>
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<td>Key molecules</td>
<td>Complement</td>
<td>Complement</td>
<td>IgM and IgG antibody</td>
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<td></td>
<td>Histamine etc</td>
<td>IL-1, TNFalpha, IL12</td>
<td>IL2, IL4, IL12, IFN gamma</td>
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<td></td>
<td>IFNalpha/beta</td>
<td>(\text{IFNalpha/beta})</td>
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<tr>
<td></td>
<td></td>
<td>MBP, CRP</td>
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<tr>
<td>Key cells</td>
<td>Macrophages</td>
<td>Macrophages</td>
<td>T cells</td>
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<tr>
<td></td>
<td>Mast cells</td>
<td>Neutrophils</td>
<td>B cells</td>
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<tr>
<td></td>
<td>Neutrophils</td>
<td>NK cells</td>
<td>Macrophages</td>
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</table>
Cytokines and NK cells combine to provide early defense against virus infections
Summary of Immunity to different types of pathogens

<table>
<thead>
<tr>
<th>class</th>
<th>subclass</th>
<th>key immune mechanisms</th>
<th>memory?</th>
<th>example</th>
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<tbody>
<tr>
<td>Extracellular</td>
<td>bacterial</td>
<td>complement (alternative pathway)</td>
<td>No</td>
<td>Staph aureus</td>
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<td></td>
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<td>phagocytosis via innate receptors</td>
<td>No</td>
<td>Strep pneumoniae (capsule -ve)</td>
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<tr>
<td></td>
<td></td>
<td>IgM/IgG antibody/ complement (CP)</td>
<td>Yes</td>
<td>Staph aureus</td>
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<tr>
<td></td>
<td></td>
<td>IgG/IgM iC3bR/FcγR phagocytosis</td>
<td>Yes</td>
<td>Strep pneumoniae (capsule+ve)</td>
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<tr>
<td></td>
<td>helminths</td>
<td>IgG/ADCC (granulocytes+eosinophils)</td>
<td>Yes</td>
<td>Schistosoma mansoni</td>
</tr>
</tbody>
</table>
Summary of Immunity to different types of pathogens

<table>
<thead>
<tr>
<th>class</th>
<th>subclass</th>
<th>key immune mechanisms</th>
<th>memory?</th>
<th>example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracellular</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>bacteria + protozoa</td>
<td></td>
<td>activated macrophage (by NK cells)</td>
<td>No</td>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>activated macrophage (by T&lt;sub&gt;H&lt;/sub&gt;1 cells)</td>
<td>Yes</td>
<td>Leishmania major</td>
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<tr>
<td></td>
<td></td>
<td>cytotoxic T cell</td>
<td>Yes</td>
<td>Chlamydia trachomatis</td>
</tr>
<tr>
<td>viruses</td>
<td></td>
<td>interferon α/β</td>
<td>No</td>
<td>Influenza virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NK cell killing</td>
<td>No</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytotoxic T cell killing</td>
<td>Yes</td>
<td>Smallpox (Variola major)</td>
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<tr>
<td></td>
<td></td>
<td>activated macrophage (by T&lt;sub&gt;H&lt;/sub&gt;1 cells)</td>
<td>Yes</td>
<td>Herpes Simplex virus</td>
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<tr>
<td></td>
<td></td>
<td>neutralising antibody</td>
<td>Yes</td>
<td>Influenza virus</td>
</tr>
</tbody>
</table>
ANTIINFECTIOUS IMMUNITY

Nonspecific immunity (innate)

- mechanical barrier (skin, mucous membranes)
- chemical factors (ph)
- system of uninuclear phagocytes (macrophages)
- NK-cell
- neutrophylies, eozinophyliss, basophylies
- Humoral factors (lysosine, interferones, complement, colectin, pentracsine)

Specific immunity (acquired)

- specific passive immunity
  - natural (a/t through a placenta and milk)
  - artificial (a/t, immunoglobulins)
- specific active immunity
  - natural (after the carried infection)
  - artificial (vaccination)
PRINCIPLES OF DETERMINATION OF IMMUNE STATUS:

- estimation;
- determining the connection of quantitative indexes with their functional activity;
- determining the connection of immunological mechanisms with the clinical features of disease;
- account of connection of individual reactivity with genetic factors;
- comparing of indexes of immune status of organism to the norm;
- looking after the state of immune status in dynamics.
Immunological investigations

- anamnesis
- Objective inspection
- Laboratory investigations
  - screening
  - Specifying


Prolifer. act. T- & B-Lymph in reaction blasttransformaton on mytogenes or agents. B-Lymph, carrying surface. Ig IL, TNF-α, CIK. Activation of NK-cells. Complement titer Phagocytising cell function
### Variants of changes of laboratory indexes of immunity

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Indexes of immunogramm</th>
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<tbody>
<tr>
<td>Signs of infectious syndrome</td>
<td>Decline of natural resistance, level of T-cell, IRI&lt;1.5 due to T-helpers, decline of level of V-lymphocytes, immunoglobulins.</td>
</tr>
<tr>
<td>Signs of allergic syndrome</td>
<td>Decline of level of T-cell, IRI &gt;3.5 due to the increase of T-helpers and decline of T-suppressor-cell, increase of V-lymphocytes and level of IGE, positive tests of hypersensitiveness of immediate or slow type.</td>
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<tr>
<td>Signs of autoimmune syndrome</td>
<td>Decline of level of T-cell, IRI&gt;3.5 due to the considerable increase of level of T-helpers and decline of level T-suppressor-cell, increase of level of V-lymphocytes, Circulatory immune complexes, decline of indexes of phagacytosis and complements, presence of specific autoantibodies.</td>
</tr>
<tr>
<td>Combined violations</td>
<td>mixed changes with approximately equivalent defects.</td>
</tr>
<tr>
<td>Index</td>
<td>Result</td>
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<tr>
<td>--------------</td>
<td>--------</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>102</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>3,1</td>
</tr>
<tr>
<td>Platelets</td>
<td>160</td>
</tr>
<tr>
<td>ESR</td>
<td>42</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
</tr>
<tr>
<td>Stick-nuclear</td>
<td></td>
</tr>
<tr>
<td>Segment-nuclear</td>
<td></td>
</tr>
<tr>
<td>43-71 %</td>
<td></td>
</tr>
<tr>
<td>2000-6500</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>9</td>
</tr>
<tr>
<td>8480</td>
<td>900</td>
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<tr>
<td>Immunological indexes</td>
<td>Result</td>
</tr>
<tr>
<td>T- lymph. CD3%</td>
<td>49</td>
</tr>
<tr>
<td>The abs. number</td>
<td>446</td>
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<td>T-help. CD4%</td>
<td>29</td>
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<td>263</td>
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<td>T-suppress. CD8%</td>
<td>21</td>
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<td>191</td>
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<td>Immune regulatory index</td>
<td>CD4/CD8</td>
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<td>NK-cells CD16%</td>
<td>25</td>
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<tr>
<td>The abs. number</td>
<td>227</td>
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<td>B-lymph. CD22%</td>
<td>23</td>
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<tr>
<td>The abs. number</td>
<td>209</td>
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</tbody>
</table>

**Immunogram in acute bacterial infection (pneumonia), the patient L., 22 years old**
Immunogram during acute viral infection. Patient 26 years old.

<table>
<thead>
<tr>
<th>Index</th>
<th>Result</th>
<th>Rate</th>
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</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>134</td>
<td>F- 115-145. M- 132 - 164 g/l</td>
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<tr>
<td>Erythrocytes</td>
<td>3,9</td>
<td>F – 3,7-4,7. M-4,0-5,1x10^{12}/l</td>
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<tr>
<td>Platelets</td>
<td>270</td>
<td>150 - 320x10^9/l</td>
</tr>
<tr>
<td>ESR</td>
<td>18</td>
<td>2-15 mm/h</td>
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<tr>
<td>Leukocytes</td>
<td>10,2</td>
<td>4-9x10^9/l</td>
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<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Stick-nuclear</th>
<th>Segment-nuclear</th>
<th>Eosinophils</th>
<th>Basophils</th>
<th>Monocytes</th>
<th>Lymphocytes</th>
<th>Large granular</th>
<th>Plasmocytes</th>
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<tr>
<td>43-71 % 2000-6500</td>
<td>1 -4% 80-400</td>
<td>0,5 - 5% 80-370</td>
<td>0-1% 20-80</td>
<td>3 - 9% 90-720</td>
<td>25 -37% 1600-3000</td>
<td>1-5% 80-500</td>
<td>0- 1% 20-80</td>
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<tr>
<td>36</td>
<td>5</td>
<td>31</td>
<td>0</td>
<td>11</td>
<td>43</td>
<td>10</td>
<td>0</td>
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<tr>
<td>3670</td>
<td>510</td>
<td>3160</td>
<td>0</td>
<td>1120</td>
<td>4390</td>
<td>1020</td>
<td>0</td>
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<thead>
<tr>
<th>Immunological indexes</th>
<th>Result</th>
<th>Rate</th>
<th>Immunological indexes</th>
<th>Result</th>
<th>Rate</th>
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<tr>
<td>T-lymph. CD3 %</td>
<td>60</td>
<td>50 - 80</td>
<td>IgG</td>
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<td>8,0-18,0 g/l</td>
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<td>1000-2200</td>
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<td>T-help. CD4 %</td>
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<td>33-46</td>
<td>IgM</td>
<td>3,25</td>
<td>0,2-2,0 g/l</td>
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<td>The abs. number</td>
<td>1053</td>
<td>309-1571</td>
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<tr>
<td>T- suppress. CD8 %</td>
<td>36</td>
<td>17-30</td>
<td>IgA</td>
<td>2,07</td>
<td>0,3-3,0 g/l</td>
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<td>282-999</td>
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<td>Immune regulatory index</td>
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<td>1,4-2,0</td>
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<td>65</td>
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<td>12-23</td>
<td>Power activity</td>
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<td>B-lymph. CD22 %</td>
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<td>17-31</td>
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<td>The abs. number</td>
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