

Ministry of health care of Ukraine
Highest state scientific institution of the Ukraine
«Ukrainian medical stomatological academy»

"Approved"
at a meeting of the Department of
Experimental and Clinical Pharmacology with
Clinical Immunology and Allergology
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**Methodical guidance for students' self-directed
work when preparing for practical session**

Academic subject	Clinical Immunology and Allergology
Semantic module №1	Immunological status. Immunodeficiency diseases and immune-pathology
Topic №1	The structure and principles of functioning of the immune system. Non-specific immunity. Specific immunity. Understanding of imagedetecting receptors.
Year of study	5
Faculty	medical

Poltava 2017

1. Relevance of theme:

Clinical immunology studies the diseases associated with dysfunction of the immune system, and diseases in which the immune response plays leading role. At present clinical immunology is a clinical and laboratory discipline that deals with the study, diagnosis and treatment of patients with diseases or pathological processes that occur as a result of violations of immune mechanisms, as well as those cases where the immunological manipulation are central to the treatment or prevention of disease.

2. Learning objectives:

1. To master the subject and objectives of clinical immunology at the present stage.
2. Develop the concept of the modern achievements of Clinical Immunology and Allergology.
3. Know us clinical immunology with other disciplines and practical activities of a doctor.
4. To master the material factors of innate immunity: cell (monocyte-macrophage system, and granulocyte killer cells), humoral (complement system, cytokines, etc.).
5. Master the knowledge of the antigens and their characteristics, specific immunity, its features, stages of formation and cooperation of immune cells involved in the immune response.
6. To study the main population T- and B-lymphocytes and subpopulations (T-helper type 1 and 2, T-Regulatory) lymphocytes stages of their maturation and differentiation of their function.
7. Substantiate the clinical value of knowledge of immunoglobulins, their structure, function, for thymus-dependent and thymic-independent mechanisms of antibody synthesis, structure and properties of circulating immune complexes.
8. To analyze the clinical and diagnostic information about the major histocompatibility complex: its structure, properties, functions, regulation of immunity.

3. Basic knowledge, skills necessary for studying the subject (interdisciplinary integration)

The name of the previous disciplines	These skills
Anatomy	Knowing the structure of the thymus and lymphatic nodes, plaques, spleen, bone marrow. Spend examination of patients.
Normal physiology	To know the functioning of the central and peripheral organs of the immune system. About know the basics of clinical and laboratory studies.
Biochemistry	Learn the basics of biochemical laboratory studies. Action and effect of cytokines of different groups of biologically active substances.
Microbiology and virology	Know the immune response, diagnostics bacteriological and viral infections. About know the basics of special microbiological methods.
Therapy	Know the pathogenesis and clinical manifestations of allergic diseases and secondary immunodeficiencies. To be able to collect immunological and allergic history.
Phthisiatry	Learn the mechanisms of development of glue dependence immune response and the course of the clinical manifestations of tuberculosis.
Infectious diseases	Learn the pathogenesis, clinical manifestations of bacterial and viral infections. To be able to diagnose bacterial and viral infections.

4. Tasks for work during preparation for the classes.

4.1. The list of key terms, parameters, characteristics which the student is to assimilate while preparing for the class:

Term	Definition
Clinical immunology	Clinical and laboratory discipline that deals with the examination, diagnosis and treatment of patients with pathological processes that develop as a result of violation of the immune mechanisms.
Antigen present cell	The cell is able to present to sup with the proce us IAOD minutes peptide together with MHC molecules of the second class for cutting T-cell antigenras of knowledge feeling receptors on CD4 T-glue.
Interleukin	The group of molecules that are part of the cytokines that are produced by cells of the immune system and are called the "hormones of the immune system cells.
Plasmacyte	End this paragraph in the differentiation antigen about whether to actively secrete large amounts of antibodies.
Respiratory burst	Increased metabolism of oxygen, which is observed in phagocytes after their activation.

4.2. Theoretical questions for the class:

1. The object and purpose of clinical immunology and allergy. History of immunology. The main directions of development.
2. Cell protection congenital factors and their interaction in the implementation of the immune response.
3. Cleaning effect as part of immunobiological surveillance. The main types of killer cells, their function and properties. The role of granulocyte blood cells in the immune response.
4. Humoral factors of innate immunity.
5. The antigens: structure, function. Haptens.
6. T lymphocytes - helper 1 and type 2. The value of the functional balance between the T-helper cells (Th1 \ Th2).
7. B-lymphocytes. Key markers and function. The structure of the receptor that recognizes the antigen. The concept of T-dependent and T-independent immune response types.
8. Modern understanding of the structure and function of the major histocompatibility complex.

Content topics

Key examples of pathologies in the diagnosis and treatment of which requires the participation of Clinical Immunology.

1. Immunodeficiencies
 - primary
 - secondary
 - HIV inducative
2. Allergic diseases (including asthma)
3. Diseases of the collagen and connective tissue
 - vasculitis
 - large collagen
 - Eosinophilic fasciitisies
4. The immune endocrinopathies
 - thyroiditis
 - thyrotoxicosis
 - diabetes type I
 - Primary adrenal insufficiency
 - poliendocrinopatie

5. Blood Diseases

- autoimmune hemolytic anemia
- idiopathic thrombocytopenic purpura
- pernicious anemia
- plasma cell disease
- amyloidosis

6. Diseases of the nervous system

- multiple sclerosis
- Gullian-Barre syndrome
- myasthenia gravis

7. Tumors of the immune system

- lymphoma
- neoplasia associated with immunodeficiency

8. Immuneconcentrated skin pathology

9. Immuneconcentrated renal pathology

10. Immuneconcentrated pathology of the gastrointestinal tract

11. Diseases of immune complexes

12. Cancer Immunotherapy

13. Transplantation of organs and bone marrow.

The main function of the immune system - protection against all genetically foreign - based on its ability to recognize "their" and "foreign". The action of the immune system is directed not only at the foreign, coming from outside (such as bacteria), but also on its own altered cells. Disorders of the immune system lead to various diseases - from urticaria and allergic rhinitis to rheumatoid arthritis and malignancy.

The bodies of the immune system

The immune system is represented by a set of organs and tissues, including the central decided to allocate, where the maturation of lymphocytes and peripheral, which are to be mature lymphocytes.

By the central authorities of the immune system are the thymus and bone marrow, in utero - and the liver.

1. **Bone marrow.** All immune cells derived from bone marrow stem cells that differentiate into lymphocytes, granulocytes, monocytes, erythrocytes and megakaryocytes. In the bone marrow occur earliest antigendependent maturation and differentiation of B-lymphocytes. Reducing the number of stem cells and their differentiation disturbances lead to immunodeficiency.

2. **The thymus** develops from the third and fourth pharyngeal pouches and is located in the mediastinum. The thymus is a differentiation of bone marrow cells - predecessors of T-lymphocytes and their transformation into mature T lymphocytes. Part of maturing T-cells and is directed against self antigens. Furthermore, thymus produces a number of hormones (e.g., thymosin), which regulate differentiation and function of T lymphocytes.

Peripheral organs of the immune system - is the lymph nodes, spleen, lymph follicles tract. These bodies are linked by blood and lymph vessels. Moving to these vessels, cells receive information about the antigen and transmit it to all organs of the immune system.

1. **Lymph nodes** - peripheral organs of the immune system, located along lymphatic vessels. They retain antigens and prevent their spread. Lymph node stroma formed by loose connective tissue in the parenchyma of his distinguished cortex and medulla. Cortical substance - dependent B-Zone - contains lymph follicles, consisting mainly of B-lymphocytes. T cells are arranged in advant feeling paracortical T-dependent area.

2. **Spleen** delays and destroys antigens circulating in the blood. Lymphoid tissue splenic white pulp represented islets which like lymph nodes have follicular structure and divided into B- and T-dependent areas.

3. **Lymph follicles of the intestinal tract** - it tonsils, lymph follicles and actually Peer

plaque. Lymph follicles are also divided into B- and T-dependent areas. A large amount of lymphocytes is also in the lamina propria and epithelium cells among the small and large intestine.

It is extremely important for understanding the mechanisms of the immune response on the part of both innate and acquired immunity have specific understanding that the substance can claim the title of "**antigen**".

By antigens should include substances having two main properties: 1) *Immunogenicity* - ability to induce a specific immune response, whereby antibodies are produced by immune cells or 2) *antigenicity* - the ability to react specifically with antibodies or cells produced by the introduction of the antigen. Immunogenic substances are always antigens, while antigens are not always immunogenic them.

Mechanisms of immunity

Specific factors include the protection of humoral and cellular links of immunity. Phagocytosis and mediating complement destruction of cells are nonspecific protection factors. Despite the fundamental difference between the nonspecific factors of protection against specific lies in the ability to recognize the antigen and to keep the memory of it, functionally they are closely related. Thus, development of an immune response is not possible without the involvement of macrophages, while lymphocytes macrophage activity is regulated. The following are key figures for non-specific and acquired, specific immunity.

Natural non-specific immunity - is primarily *mechanical barriers and physiological factors*. Further it is possible to allocate *the chemical and biochemical reactions*, inhibiting the development of infections in the body. (See. Table)

The factors of nonspecific protection

<i>Humoral factors:</i>	<i>Cellular factors:</i>
- Lysozyme	- Neutrophils
- Complement	- Monocytes
- Milking immune cytokines (I and FN / p, FNP-but IL-1R, GM-CSF, and others.);	- Macrophages
- Kallikren-system systems	- Natural killer cells
- Factor Hageman	- Dendritic cells
- Natural antibodies	- Eosinophils
- Gostrofase proteins	- Blood basophils
-peptide-Antibiotics	- Mast cells
- Eicosanoids	- Platelets
- Platelet activating factor	- Red blood cells

The factors of nonspecific protection from such action include the waste products of the sebaceous glands that contain antimicrobial factors in the form of fatty acid enzyme lysozyme contained in the various secrets of the body and has the ability to destroy Gram-positive bacteria; low acidity certain physiological secrets that prevent colonization of microorganisms different organism. For example, the acidic pH of the urine, vaginal secretions, gastric supports the ability to resist pathogenic microorganisms.

The next component of innate immunity is *cell covering* mononuclear phagocytes (monocytes, tissue macrophages), granulocytes - neutrophils, eosinophils, basophils (peripheral blood and mast cells or tissue) and *killer cells*.

A feature of the PC and K-cells is the ability to lyse target cells without prior sensitization, which distinguishes them from the cytotoxic T lymphocyte killers. Morphologically, the natural killer cells are large, with granules and low density, whereby they

belong to the large granular lymphocytes.

Target cells PC cells are virtually all cells containing core, however, the greatest activity PC cells show relative tumor and virus infected cells. Since PC cells destruction of the target cells do not require the participation of the antibody and presence of complement, this type is called *spontaneous cytolysis cell-mediated cytotoxicity*.

PC-cells express on their surface receptors for interferon and IL-2.

The next cells involved in the mechanisms of the innate (natural) immunity, is a K-cells. They carry on their surface receptors for IgG Fc-fragment and capable of antibody-dependent cellular cytotoxicity (AZKOTS). Finally, in the mechanisms of innate (natural) immunity involves LAK cells. These include normal lymphocytes activated under the influence of IL-2, which acquired the ability to carry Keeling s second effect.

Another important part of innate immunity is *humoral immunity*. It has long been known that a normal intact serum is able to kill and lyse many Gram-negative bacteria. This is due primarily to the presence of so-called serum of *natural antibodies*. These natural antibodies binding to microbes that enter the body, facilitate activation of the complement system and the destruction of microbes. It is known that the wall (membrane) of bacterial cells composed of two layers. The outer layer contains lipopolysaccharides, and internal - peptidoglycans. Antibodies and complement (due to its activity stenous) layer bacterial lipopolysaccharide destroy target cells and then using the lysozyme present in blood serum - peptidoglycan layer.

An important humoral (serum) factor of innate (natural) immunity is *properdin* - a protein that is different from natural antibodies and complement. It activates the complement system through the alternative.

Another factor of innate immunity is the *β -lysine* - an antibacterial protein, released from platelets as a result of the destruction. It is - active primary protective factor against gram-positive bacteria.

An important role in innate antimicrobial humoral immunity play *interferons* - proteins produced by the virus-infected cells, they protect the other portion of the cells from virus infection.

Interferons - glycopeptide family, who are divided into two types.

Type I includes α - and β -IFN. A-IFN family consists of about 20 proteins produced mainly by leukocytes and macrophages, so the α -IFN is also called leukocyte.

β -IFN produced mainly by fibroblasts, so he called fibroblast. Two known IFN- β : β 1 and β 2. Now β 2 - IFN identified IL-6. The ability to produce α -, β -interferon also are T- and B-lymphocytes, endothelial and epithelial cells PC cells.

Type II interferons called γ -IFN. Its produced by activated Th1 cells and PC.

There are the following biological effects of interferon: a) an antiviral b) antiproliferative (antitumoral) c) Immunomodulatory d) antibacterial.

Complement consists of over 20 with a protein - the complement components detected in the blood and on the surface of certain cells. Complement plays an important role in the defense against foreign he destroys bacteria and viruses infected own cells involved in the regulation of inflammatory and immune responses. Some fragments of the complement components, for example C3b are opsonins. Phagocytosed opsonized cells faster because phagocytes actively bind to these cells via corresponding receptors. Complement components can be divided into three groups:

- 1) components that trigger the classical pathway of complement activation;
- 2) components that trigger alternative pathway of complement activation;
- 3) effector components.

The specific (adaptive) immune system can be divided into two components, a humoral and cellular

The humoral immunity. Antigenoral men of knowledge receptors of B-lymphocytes are immunoglobulin molecules. When the antigen binding to the corresponding receptor and under the influence of cytokines produced by monocytes, macrophages and T-lymphocytes, the

activation of B cells, which begin to divide and differentiate into plasma cells. Part of activated B-lymphocytes are transformed into memory cells that provide quick and effective immune response when re-exposed to the antigen. There are 4 stages of **the primary immune response**. In the first step, which takes 3-4 days to a corresponding antigen antibodies in serum absent. In the second stage there are M appear, and after 10-14 days after exposure to the antigen - IgG. In the third stage the antibody level remains constant. The fourth stage of the primary immune response usually routinely stretched for months. It is characterized by a gradual decline in antibody levels. **Secondary repeated immune response** develops with repeated exposure to the antigen. Antibodies of mainly IgG, appears faster than in the primary immune response. It should also be noted that they dissolve more slowly than IgM. The main characteristic of the immunoglobulin shown in the table.

KEY FEATURES OF IMMUNOGLOBULIN

Ig	Max - in blood serum	Part of the total number - va Ig,%	Activation to ompleme - NTA (To classical path)	Function	Poluras Period - pad, day
IgM	0.7 - 2 g / l	≈ 10	+	Pentamer. Produced in the fetus. It represents the earliest antibodies mainly directed not against viruses and gram negative bacteria; enhances phagocytosis. It has feedback IgG synthesis	About 4-5
IgG IgG1 IgG2 IgG3 IgG4	7- 16 g / l	≈ 70 60 total IgG thirty 7 3	+ (Addition IgG4)	The monomer thimic-dependent. It is the later antibodies against bacterial polysaccharide antigens (G2> G1), enhances phagocytosis, crosses the placenta, neutralizes toxins	About 21
IgA	1.0 - 3.5 g / l	≈ 15	-	Serum - monomer, secretory - dimer; thimic-independent. Protects mucosa (secretory IgA), neutralizes viruses and bacterial toxins	About 5-6
IgE	20-120 IU	6	-	Monomer. It induces allergy, anaphylaxis; implementing protection against parasites, it activates tissue basophils. Produced by plasma cells, tonsils, adenoids, mucosal	About 2-3
IgD	3-170 mg / l	1.	-	Monomer. Responsible for the differentiation of lymphocytes	About 2-3

Antibody diversity. To detect all varieties environmental antigens the immune system must produce at least 10^8 antibodies of different specificities. Antibody specificity, i.e. ability to recognize any one antigen, determined by amino acid sequence of the variable regions of heavy and light chain heavy chain.

One of the most important biological functions of immunoglobulin - the antigen binding and the formation of **immune complexes (IC)**, which is a physiological process that

permanently runs in humans and directed to maintaining the constancy of its internal environment. IR Education - one of the components of a normal immune response. It should be completed by neutralization or elimination of the antigen. However, IR may be recorded in the vessels and cause an inflammatory reaction in certain conditions. Localization IR depends on the creation and circulation with subsequent deposition in the tissues; in the latter case acquiring a generalizing process in nature, this may lead to the development of immunocomplex pathologies.

During the last years shown that diseases which are associated with IC, many: autoimmune disease, glomerulonephritis, cancer, infectious diseases, bacterial, viral and parasitic etiology, some skin, lung, eye diseases, and the like. This prompted the search for methods of determining the infrared in biological fluids. Today they offered more than 30.

Cell-mediated immunity. Main characteristics of cellular and humoral immunity presented table.

Main characteristics of cellular and humoral immunity	
humoral immunity	Cellular immunity
antibody-mediated	cell-mediated
Effector cells - B cells	Effector cells - T lymphocytes
Passive immunity is generated when you enter serum entry	Passive immunity is generated when you enter the entry of lymphocytes
The basis of the antibacterial immunity	The basis of the antiviral, anticancer, antifungal immunity

Cellular immunity is mediated by cytotoxic T lymphocytes and T helper cells. Cytotoxic T cells directly in contact with foreign cells and destroy them, and T-helper cells produce biologically active substances - **cytokines**, activating macrophages. By the ability to produce a variety of cytokines and participate in the regulation of cellular and humoral immunity T helper type are divided into two - Th1 and Th2. First produce interferon and interleukin-2 and stimulate proliferation of cytotoxic T lymphocytes; activates macrophages, interleukins produce second-4 - 5, -6, stimulate the proliferation and differentiation of B-lymphocytes as well as synthesis of various classes of antibodies (Table).

By the term "**cytokine**" merged so-called growth factors regulating proliferation, differentiation and function of blood cells, including immune cells. The table shows the main types of interleukins, which are essential in the work of doctors.

Table 1

Cytokines

Name	Produced:	Mechanism of action:
IL-1 (α , β) - endogenous pyrogens, lymphocytes activating factor	Macrophages, epithelial, endothelial, glial cells, fibroblasts	It stimulates the production of IFN- γ , TNF, IL-6,8. It activates granulocytes, NK. It induces fever. It has a synergistic effect with IL-4
IL-2 - a growth factor of T lymphocytes.	Tx-1	Enhances IFN- γ production, TNF, IL-6,8. Induces T, B-LF. It stimulates the maturation of the LAC
IL-3-colony-stimulating factor	CD-4, mast cells, thymic epithelial cells	Enhances proliferation of neutrophils, erythrocytes.
IL-4-B-exercise therapy. stimulating factor	Tx-2	An antagonist of IFN- γ , IL-1,6,8, FTS. It inhibits the cytotoxicity of T-LF., Macrophages. Enhances proliferation of mast cells.
IL-5-eosinophilic factor	Tx-2	Enhances the function of eosinophils, B-LF., IgA Products, IgE.

IL-6 is a proinflammatory effect	Macrophages, T, B-LF, fibroblasts, endothelial, epidermal, cells hondro-, osteocytes	Enhances production gostrofaznih proteins induces fever. Stimulates B-LF, stem cells, CD4, 8
IL-7	Fibroblasts, endothelial cells, T-LF., Timur stromal cells	Increases the number of B-LFK, Stimulates T-LF.
IL-10	Tx-2	Suppress function Tx-1, of NK, monocytes, reduced IFN- γ production, TNF, IL-1, 8
IL-11 platelet factor	Fibroblasts, bone marrow stromal cells	It stimulates thrombopoiesis
IL-12 is a proinflammatory effect	B LF, monocytes, macrophages	Differentiation into Th1 Tx0 stimulates NK, cytotoxic T LF. It increases the level of IFN- γ .
Necrotic factor (α , β) - PNP	Different cells, mainly - by monocytes, macrophages, B- and T-LF.	Low concentration FNP α - enhances adhesion nf. in the area of inflammation, activates the respiratory burst in LF. High concentration FNP α (kaheksina) - causes tumor necrosis. Activates macrophages, NK, produce IL-1,6. TNF- β (lymphotoxin) - induced apoptosis target cells.

Major histocompatibility complex - a group of genes and their encoded cell-cell surface antigens, which play a crucial role in the recognition of foreign and development of the immune response. Major histocompatibility complex HLA person got the name of (human leukocyte antigen). **HLA class I antigens** are required for recognition of transformed cells by cytotoxic T lymphocytes. An important function of **HLA class II antigens** - providing interaction between T-lymphocytes and macrophages in the immune response. Helper T cells recognize foreign antigen only after its processing by macrophages compound with HLA Class II antigens and for the appearance of this complex macrophage surface. The ability of T cells recognize foreign antigens only in combination with HLA antigens are called restriction on HLA. Determination of HLA class I and II antigens has great value in clinical immunology and is used, for example, the selection of donor-recipient pairs before organ transplantation.

Materials for students' self-directed work

A. Tests to verify the initial level of knowledge

1. Ligant - is:

- A. The structure, which is responsible for communication with the receptor +
- B. The structure of the nuclear substance cells
- C. structure, which is responsible for the activation of the interferon receptor dependent
- D. The structure connecting the heavy and light chain immunoglobulin

2. Main properties of Toll-like receptors:

- 1. The anti-tumor effect;
- 2. Compatibility of specific and nonspecific immunity +
- 3. The property to suppress the action of superantigens
- 4. The combined effects of HLA-I and II of the action item.

3. Acquisition, specific immunity is presented:

- a) the natural barriers
- b) a helper cell +
- c) phagocytosis

d) Immunoglobulin A +

4. What does not belong to a specific immune response:

a) cell-mediated immunity +

b) immunity neutrophil

c) humoral immunity

d) immunity NK cells +

5. The main regulatory factors specific cell-mediated immunity are:

a) B cells

b) macrophages

c) T-cells +

d) eosinophils

e) none of the above

f) all of the above.

6. A property is the ability of the immunoglobulin to bind directly to the antigen:

a) yes b) no c) only caused by infectious.

7. Or cross the placenta IgG?

a) Yes +

b) No

c) in the initial stage of pregnancy.

8. allergic reactions greatest value of immediate type are:

a) sensitization to allergens

b) the presence of antibodies Ig E +

c) the presence of IgG antibodies

d) the presence of slow type hypersensitivity.

9. Of HLA - is:

1. human leukocyte antigen +.

2. The antigens HLA Class I and Class III

3. The antigens HLA class I and class II +

4. The antigens and HLA class I and class of cytotoxic lymphocytes

10. Eosinophilic factor is:

1. IL-2

2. IL-5 +

3. IL-7

4. IL-12

11. Major histocompatibility complex is:

1. human leukocyte antigen +

2. The antigens HLA Class I and Class III

3. The antigens HLA class I and class II +

4. The antigens and HLA class I and class of cytotoxic lymphocytes

B. Test for students' self-directed work.

1. Fundamentals of antibacterial protection of the body are:

1. T lymphocytes

2. + lymphocytes

3. Antibodies +

4. Immunocompetent cytotoxic cells

2. Fundamentals of anti-virus protection of the body are:

1. T lymphocytes +

2. B lymphocytes

3. Antibodies

4. Immunocompetent + cytotoxic cells

Task 1.

What are the main distinctive features of Th 1 type of cell and its basic functions.

Answer

Th1 produce alpha, IFN-gamma. They are key regulators of cellular immunity.

Task 2.

What is the mechanism of "inclusion" of platelets in the process of immune response, and what forms of pathogens, they primarily operate?

Answer:

Platelets have receptors for Fc-fragment of immunoglobulins and complement component C3. They have cytotoxic effect on platelet protozoal infections.

Task 3.

It is known that for some active generalizing forms of inflammation signs of hepatosplenomegaly. What is the main pathogenetic mechanism of participation with the complement system?

Answer:

Macrophages in liver and spleen process inactivating pathogenic immune complexes actively connected complement system due to the presence of receptors on their surface C3 of complement fragment.

Task 4.

What are the main distinctive features of Th2 type and its basic functions.

Answer

Producing IL-4, IL-5. They are main regulators of humoral immunity.

Task 5.

Male, 37 years old, in the treatment of periodontitis (without the use of anesthetic and antibiotics) noted the development of edema of the lips. The general state of health did not suffer (it was moderately expressed feeling the impression of fullness in the area). Given the theme of class that you ask the question the teacher to make the diagnosis? Specify the pathogenesis of this disease.

Answer:

Question: "What is the pathogenetic mechanism in the patient?" Given unchanged the overall health of the patient - the diagnosis: "Hereditary angioedema with C1 inhibitor deficiency of complement fragment".

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Methodical guidelines composed by

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