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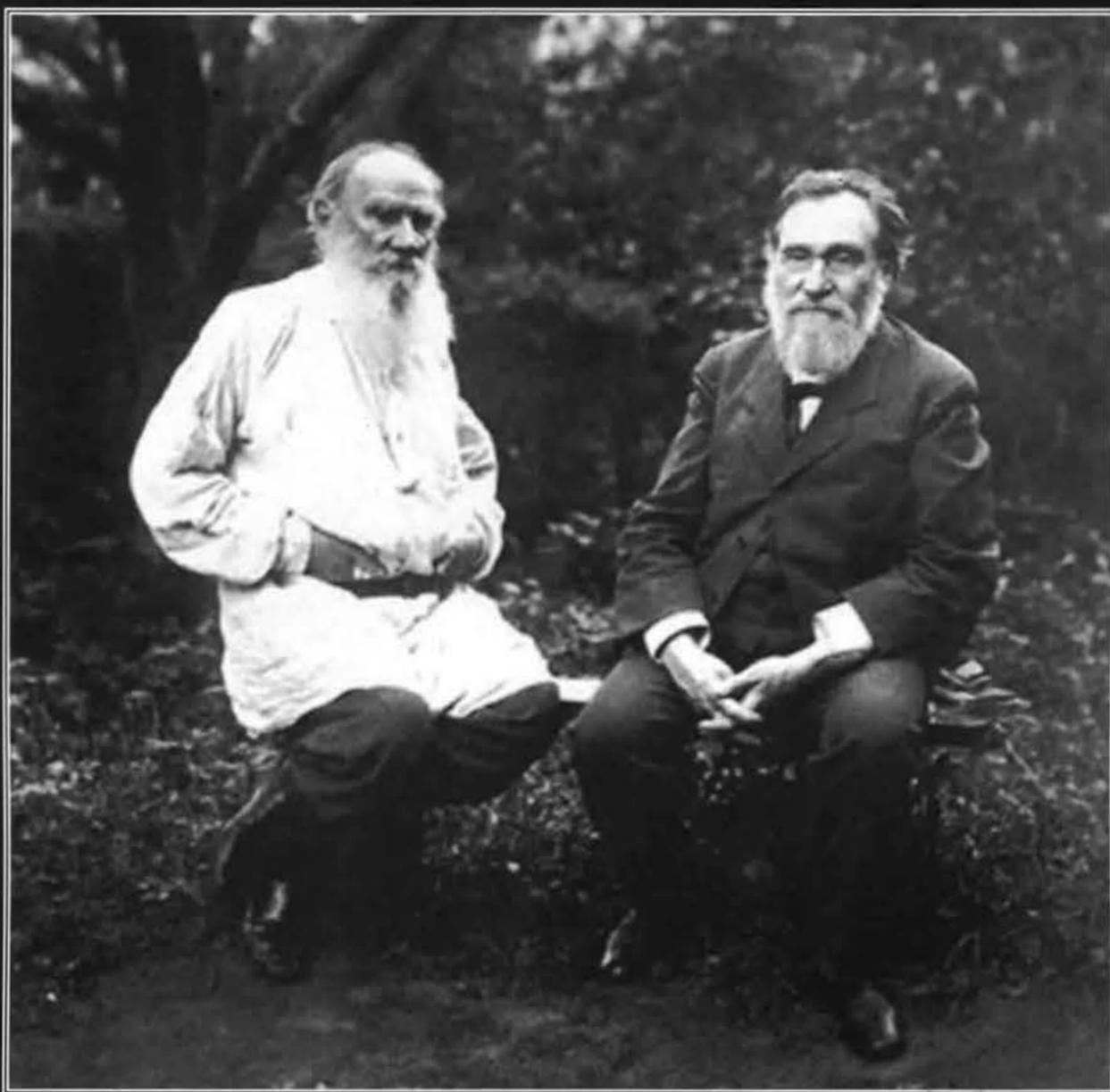


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Immunophysiology, natural autoimmunity and human health

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ABSTRACT

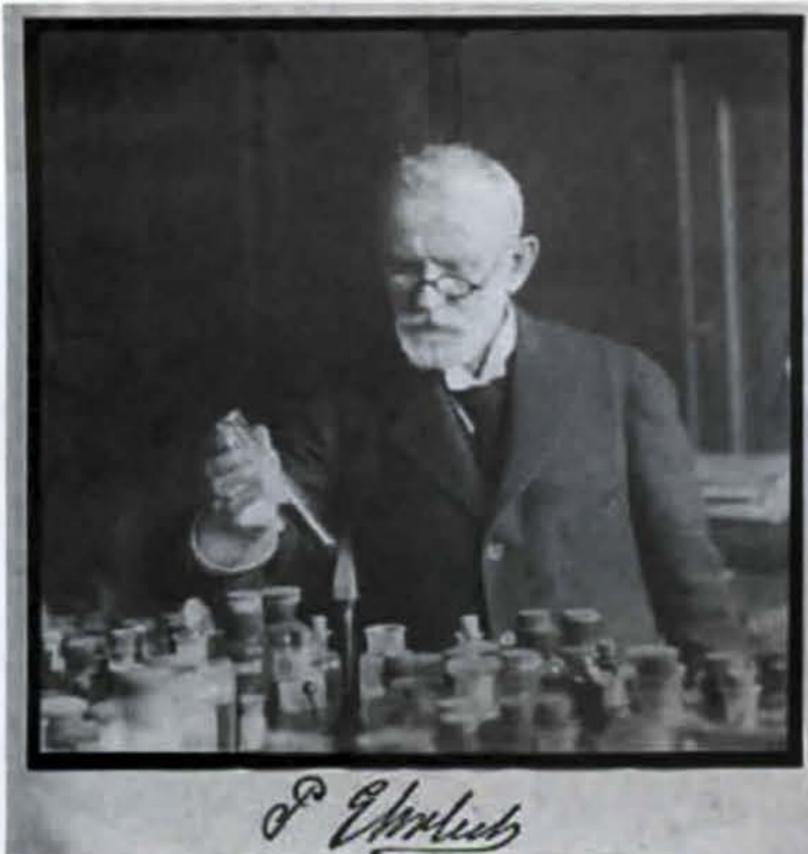
Pathological processes in any organ usually lead to activation of apoptosis of specialized cells and rise of extracellular concentration of specific antigens. These events usually take the role of trigger for secondary rise of production of autoantibodies with appropriate specificity. These kinds of autoimmune reactions are sanogenic in essence, aiming to augmentation of effectiveness of clearance of affected organs. Much more rarely, the primary rise of autoantibody production (not related to real needs of organism and not associated to pre-existing disease of organ or tissue) can be detected. Such situations are pathogenic and may be accompanied by different clinical consequences. The rates of physiologic, adaptive (secondary) autoimmune reactions to pathogenic (primary) autoimmune reactions may be evaluated at least as 9 to 1. Secondary quantitative changes in autoantibody production (specific for any pathology) should be considered as a universal marker for virtually all chronic diseases and may be detected months or years before the appearance of clinical signs of disease. Therefore analysis of quantitative changes in the serum content of natural autoantibodies may become an effective instrument for early pre-clinical and even pre-nosologic detection of pathological processes with different organic location and cellular targeting. Future investigations in this field may result in revision of the main paradigm of medicine (DISEASE – TREATMENT), and transition to the new one (prognosis – prevention).

Key-words: regulatory autoantibodies, physiologic autoimmunity, immunculus.

Introduction

Historically, immunology was formed as a branch of applied microbiology, therefore “microbiological” points of view were reproduced for decades because generations of specialists in immunology were educated by microbiologists. None the less, let us consider a not quite inconceivable situation: let us imagine – the founders of immunology were not microbiologists (Louis Pasteur, Paul Ehrlich and others) but physiologists (for example, Ivan Pavlov, Walter Cannon and others) (Pic. 1), and this field has been initially developed in the frame of general physiology.

In such an alternative historical reality, the immune system could probably be considered mostly as the system responsible for maintenance of molecular homeostasis, and terms such as “sense of antigenicity”, “immune analyzer”, “immune image”, “immune reflex” (instead of secondary immune response) etc., could become quite usual. In this case, the term “immunity” could be associated rather not with the habitual alerted guard, busy with permanent war against microbes, but with a much more peaceful image of housekeeper, busy with utilization and neutralization of factors harmful for homeostasis, mostly endoge-



Pic. 1. Historical founders of immunology a) Louis Pasteur (1822-1895), b) Paul Ehrlich (1854-1915) during experiments. c) I-van Petrovich Pavlov (1849-1936) walking in front of the building of Historical Faculty of the St.-Petersburg University.

nous in origin. Indeed, over a century ago, Elia Mechnikoff had proposed that the main predestination of the immune system is not the "Struggle" against Non-Self. During the 10th International Medical Congress (Berlin, 1896), he had claimed that it would be wrong to consider immunity as a gendarme of an organism. Its participation in a constant struggle Host-against-Parasite is no more than a particular case of a much wider biological predestination of the immune system – which is dynamic participation in self-maintenance, self-reparation, and self-optimization, and maintenance of a harmony state under the constant pressure of Environment¹. Unfortunately, his lone voice was not heard at that time, and similar ideas were revived only recently. For example, Polly Matzinger²

in her "danger hypothesis" imply that the immune system in the least "think" about Self/Non-Self discrimination, but securing rather of a whole organism homeostasis. Her hypothesis, surmises that the immune system is involved in elimination/blocking not "foreigners" but "harmfulness" and provide the ground for explanation of various phenomena, now unexplained, such as constant presence of abundant "normal" microbial flora ("foreigners"!) in each healthy organism, or pregnancy (why any healthy women provides development of semi-allogenic fetus and did not destroy it?), etc. Transfer of accent from a defensive role to homeostatic function of the immune system leads to re-evaluation of some habitual views, touch upon, for example, phenomena of physiological au-

toimmunity and general meaning of natural autoantibodies (auto-Abs).

Regulatory autoantibodies

Auto-Abs should be attributed to typical recognizing molecules and we should bear in mind that all regulatory processes in organism are based upon specific intermolecular recognition. By means of production of specific auto-Abs to any regulatory molecule and its receptor, the immune system may influence upon mechanisms of cellular proliferation, differentiation and dying, as well as any other genetically determined events in molecular and cellular levels³. For example, specific Abs against chromatin receptors of endocrine cells penetrates into nuclei of cells *in vitro* and *in vivo*, and influence upon specific mRNA transcription and production/secretion of hormones^{4,5}. It was supposed that endogenous inter- and intracellular molecules-communicators (messengers), their receptors hand by hand with auto-Abs of according specificity form a complicated supra-molecular system which provides co-ordinate realization of genetic programs in different cells⁴. Idiotype-antiidiotypic mechanisms may be the cause for appearance of *auto-antiidiotypic Abs*, their CDR region could be stereochemically similar to receptor-binding part of ligands (hormones, neurotransmitters, drugs, etc). Such *auto-antiidiotypes* could, at least partially, reproduce the biologic activity of original molecules. Many experimental and clinical data directly indicates the reality of these phenomena: Abs with specific activity similar to hormones, trophic factors, enzymes, drugs of different classes, etc. have been described^{5,7,9,10}. Supposedly by anti-idiotypic mechanism, *the immune system may reproduce biologically active copies OF ANY (!) biologically active molecule*. Is it something like a real embodiment of ancient myth about Panacea (Πανάκεια, Panakeia – all-healing)? In applying to the immune system, the term “*Immunocea*” may be proposed. Could unique wideness and effectiveness of IVIG therapy be partly related to effects of “*Immunocea*”?

Clearance function of the immune system

One of the most basic (evolutionary initial) homeostatic function of the immune system is its involvement in general clearance function⁸. Immune-mediated clearance seems to be an archetype of the immune system functioning and includes elimination of

fickle objects such as viruses, bacteria, fungi, but in the first place, this function is directed to utilization of emerging products of millions of dying cells every moment. Many activities of the immune system could be derived from this ancient function.

With the lapse of time Mechnikoff, it is widely accepted that clearance of products (endogenous and exogenous in origin) intended to utilization, is carried out by macrophages, but this is only half true. Why so? On macrophages' surface, there are TL-receptors (bind some typical patterns of molecules of bacterial wall) and scavenger-receptors (bind some lipoproteins – self and non-self in origin)¹⁰. However, if we were told about self-molecules with abnormal changes in their structure, which should be utilized, or about waste products of apoptosis of self-cells – we would face evident obstacles because macrophages can not “notice” most of them. Macrophages, as such, can not discern normal serum albumin from defective one, or senescent erythrocyte from new one, as well as most of the products of apoptotic cells of liver, lungs, kidneys, etc. None the less, this issue – what macrophage has to gobble and what it should not be touched – has been determined quite effectively with using of specialized signatures, “tags”, attached to utilized items – namely auto-Abs. Specific auto-Abs have been attached to any product which should be “gulp down” by macrophages, and first of all to waste products of apoptosis¹¹. In their turn, macrophages bind Abs-Antigen complexes (soluble, as well as, particulate ones) by means of superficial Fc-receptors and take them up efficiently by pinocytosis or endocytosis. Metaphorically speaking, Abs-opsonines executes the role of scent mark for “blind” dog (macrophage) and help to the last “to recognize” effectively the objects intended to utilization.

Autoantibodies and physiologic autoimmunity

Nota bene: Production of Abs is regulated (feedback principle) by the quantity of according antigens (processed and available for recognition by immunocompetent cells)¹². Increase of discharge of waste products is a pre-requisite for elevated synthesis of specific Abs-signatures, and consequent utilization of them by macrophages. Individual intensity of apoptosis/replacement of different specialized cells is roughly the same in any healthy adult. Nearly same levels of production of antigenic waste products is probably the main reason for nearly same serum levels of

very different (in terms of specificity) auto-Abs in each healthy individuals, practically independent from gender and age^{3,11}. In opposite, pathological changes in heart or lungs, kidneys or liver, and other organs lead to abnormal rise of "cardiotropic", "pulmotropic", "renotropic", etc. auto-Abs¹³, because, practically, any disease in its early beginning is accompanied by notable rise of apoptosis in certain populations of specialized cells and massive release of specific antigens. Excessive emission of apoptotic debris (including usually "hidden" intracellular tissue-specific antigens) is able to trigger elevated production of auto-Abs of according specificity⁸. This kind of easily detected secondary autoimmune reaction should be considered as adaptive in essence because these events are directed to restoration of disturbed homeostasis by means of intensification of clearance of involved organs and activation of reparative processes (many auto-Abs do stimulate DNA synthesis, increase mitotic rate and other signs of reparation)^{3,8,9,11}. That is if the content of "cardiotropic", "hepatotropic", etc., auto-Abs in blood serum of investigated person put in the normal range – this result will indicate that apoptotic rates in heart, liver, etc., did not exceed physiological rates. On the other hand, in case of long-term rise in synthesis of, for example, "pulmotropic" auto-Abs – it may be considered as supposed marker of present or forming pathologic process in the lungs, even if there are no evident clinical symptoms of lung pathology at investigation. In our practice, we confront situations when specific changes (rise) in serum auto-Abs content appear months or even years before the first clinical signs of the different somatic diseases, not always considered as autoimmune in origin¹⁴. Thereby, elevation of auto-Abs seems to be the earliest sign of incipient development of pathology. Why so? Probably, it may be related to enormous excess of specialized cells in any organ (used for providing of functional reliability)¹¹. As a result, any chronic pathological process by nearly any etiology will reach the stage of organ insufficiency only after a prolonged silent period – when potential of regeneration will be exceeded by long-lasting degenerative events. Signs of functional insufficiency (as peculiar biochemical changes and clinical symptoms) will appear at this stage. So, biochemical and pathophysiological deviations reflect the appearance of perceptible functional organ insufficiency. On the contrary, changes in auto-Abs content have appeared long before, because they are related not to organ functional failure, but abnormal activation of apoptotic events. Early pre-di-

sease changes in any organ may potentially be revealed also by histological investigation of biopsy specimens. However, somebody would hardly use such (biopsy and histology) an approach for wide population investigations/observations for aims of disease prognosis and prevention.

Based upon our own clinical experience and literature data^{14,15} we insist: in an overwhelming majority of cases, an abnormal rise of serum content of auto-Abs with different antigen specificity is a secondary event (reflection), induced by primary damage of tissue/organ. This kind of autoimmune reactions should be considered as sanogenic, which is positive in essence. However, autoimmune diseases, related to abnormal elevation of auto-Abs production and/or excessive activation of effector lymphocytes are also a reality. How sanogenic (positive) and pathogenic (negative) autoimmune reactions can be differentiated? It seems that primary autoimmune reactions (that is, the ones not conditioned by real needs of organism), in most cases, are pathogenic. Besides, in theory, secondary immune activation sometimes may be inadequate in intensity, or incorrectly targeted, or inadequately regulated, and in each case the result may be rather harmful for organism. These pathogenic situations are often named by the generalized term "allergy"¹¹.

From a didactical point of view, we suppose to use the term "autoimmunity", preferably, in relation to physiologic autoimmune processes. Adaptive immune reactions (secondary mostly) should be clearly distinct from "autoallergic" (primary mostly) pathogenic immune reactions. We propose to use the term "autoallergy" for non-conditioned by real needs of organism abnormal rise of production of many cytokines and/or auto-Abs (provoked by viruses, bacteria, chemicals or other harmful causes). This term may be used not only for the designation of classical allergic disorders but, also, for typical autoimmune diseases.

Thus:

1. Primary pathological changes in any organ usually lead to activation of apoptosis in populations of specialized cells and are reflected by secondary (adaptive, compensatory) rise of production and blood serum content of auto-Abs with according specificity. This reaction of the immune system is sanogenic.

2. Secondary quantitative changes in auto-Abs production may be easily detected for months or years before appearance of early clinical signs of disease, and should be considered as universal marker/sign of nearly any (not only autoimmune/autoallergic) chronic disease, including those, which (in the

view of modern medicine) usually are not characterized by immune changes.

3. Much more rarely, physicians meet with primary rise of auto-Abs production, mostly induced by different external stimuli and does not relate to initial damage in organs and tissues. Such situations are pathogenic in essence and may lead to immune-mediated pathological changes (autoallergy, autoallergic diseases). This possibility should be taken in mind, however, in our own practice, an average frequency of adaptive (secondary) and pathogenic (primary) autoimmune reactions have not exceeded 95: 5.

Clinical examples

Patient B.C. (29 y, female). Pregnancy 9-10 wks, symptoms of threatening miscarriage, abnormal blood coagulation, signs of decrease of placental blood flow (doppler). Leucopenia. Serum level of auto-Abs against beta2-Glycoprotein I is below of population norm (data obtained by manufacturer. Serologic markers of anti-phospholipid syndrome had not been revealed.

Results of multiparametric diagnostic investigation by ELI-P-Complex Kit ("Immunculus", Russia); obtained data has presented in % from population norm: auto-Abs against choriogonadotropin -51% from population norm; auto-Abs against dsDNA -31; auto-Abs against beta2-Glycoprotein I -4% auto-Abs against collagen -45%; auto-Abs against Fc-fragment of IgG -26%; auto-Abs against insulin -49%; auto-Abs

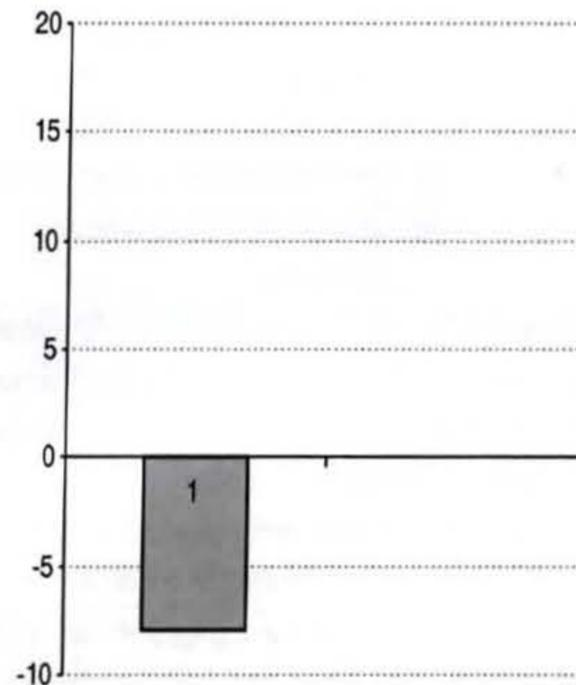


Fig. 1. Serum level of auto-Abs against beta2-Glycoprotein I in investigated samples below of population norm (accepted as zero level).

against thyroglobulin -42%; auto-Abs against S100 protein -35%; auto-Abs against SPR06 -46%; auto-Abs against ANCA -63%; auto-Abs against Trm03 -58%; auto-Abs against Kim05 -64%. Average Individual Immune Reactivity (AIIR) is -45% to population normal level (that is prominent immune suppression takes place); Level of reactivity related to auto-Abs against beta2-Glycoprotein I is +76% compare to AIIR. Conclusion: prominent serologic markers of anti-phospholipid syndrome had been revealed by using multiparametric kits for analysis of individual profile (or pattern) of serum immune reactivity, but not with

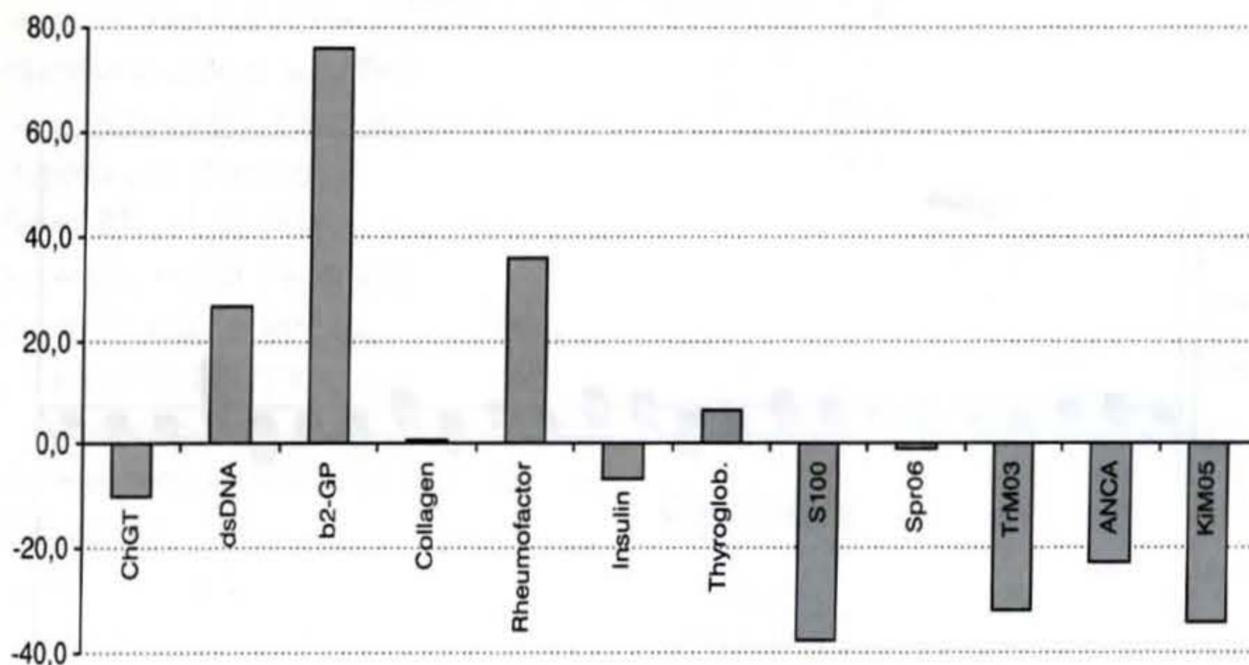


Fig. 2. Serologic markers of anti-phospholipid syndrome had been revealed in the same sample by using multiparametric kits (ELI-P-Complex Method) for analysis which is based upon individual profile of serum immune reactivity compare to individual average level of immune reactivity (accepted as zero level), but not with monoparametric kit based upon comparison of patient serum reaction with "population norm data".

monoparametric kits for single antibody level evaluation in comparison with "population norm" (Fig. 1, 2).

Catamnestic clinical observations: Miscarriage occurred at 12-13 weeks of pregnancy, most probably in relation to anti-phospholipid syndrome and placental blood flow disturbances.

Patient M.N. (48 y, male); complains for indefinite weakness and indisposition; 4 episodes of abnormal elevation of blood pressure (up to 160/100) were noted during the last 4-5 months.

Results of multiparametric diagnostic investigation by ELI-Viscero-Test-24 Kit ("Immunculus", Russia) in % from population norm (Fig. 3, 4): auto-Abs against dsDNA +1% from population norm; auto-Abs against beta2-Glycoprotein I +12%; auto-Abs a-

gainst Fc-fragment of IgG +5%; auto-Abs against heart antigen beta2-adrenoreceptor -9%; auto-Abs against heart antigen Com -3%; auto-Abs against platelets antigen Trm -3%; auto-Abs against small vessel antigen ANCA -5%; auto-Abs against kidney antigen Kim +38%; auto-Abs against kidney antigen Kis +25%; auto-Abs against lung antigen Lus -8%; auto-Abs against lung antigen Lum -8%; auto-Abs against stomach wall antigen Gam -14%; auto-Abs against intestine wall antigen Itm +7%; auto-Abs against liver antigen HMMP -3%; auto-Abs against liver antigen Hes -8%; auto-Abs against insulin -11; auto-Abs against insulin receptors -9; auto-Abs against TSH receptors -8; auto-Abs against thyroglobulin -14%; auto-Abs against adrenal antigen Adr-QC -12; auto-Abs against prostate/spermal

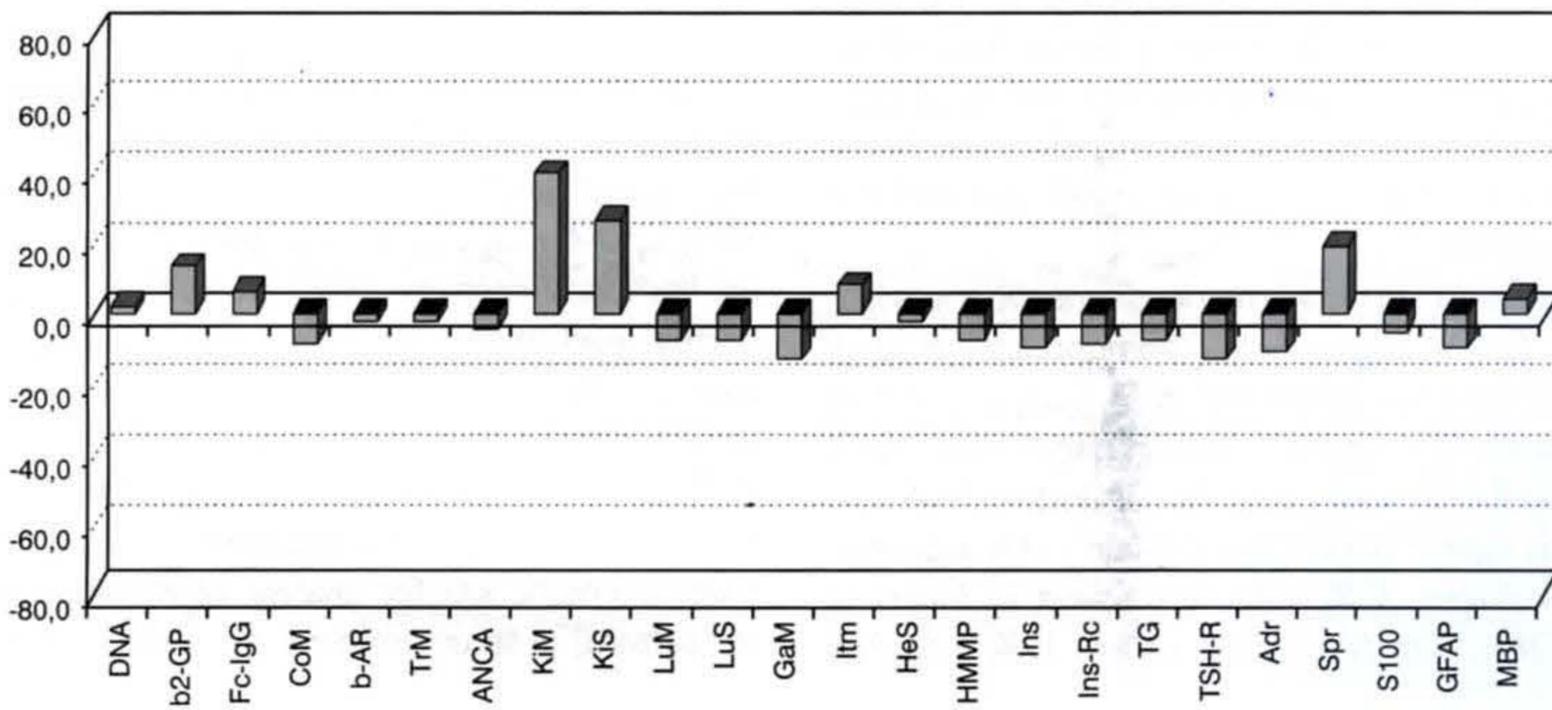


Fig. 3. ELI-Viscero-Test data before treatment.

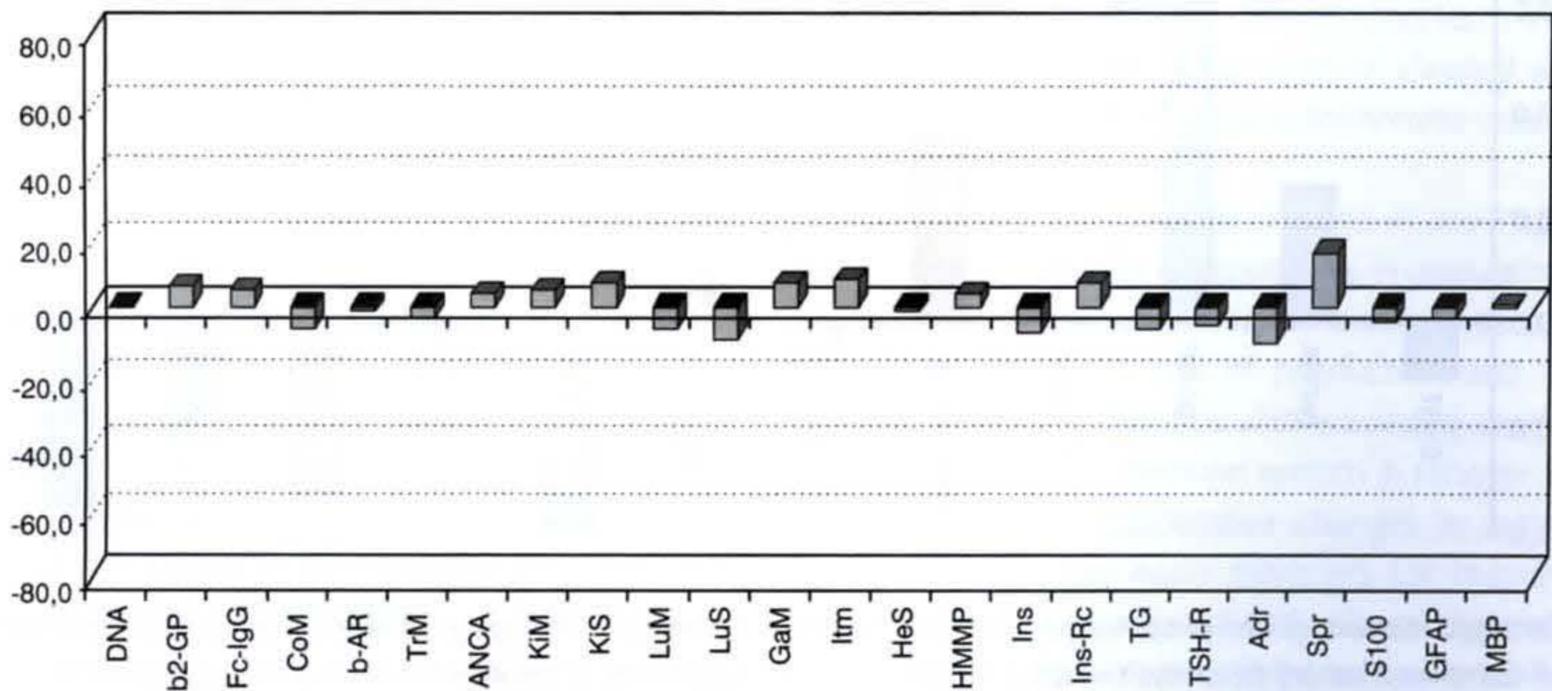


Fig. 4. ELI-Viscero-Test data 6 months later, after treatment.

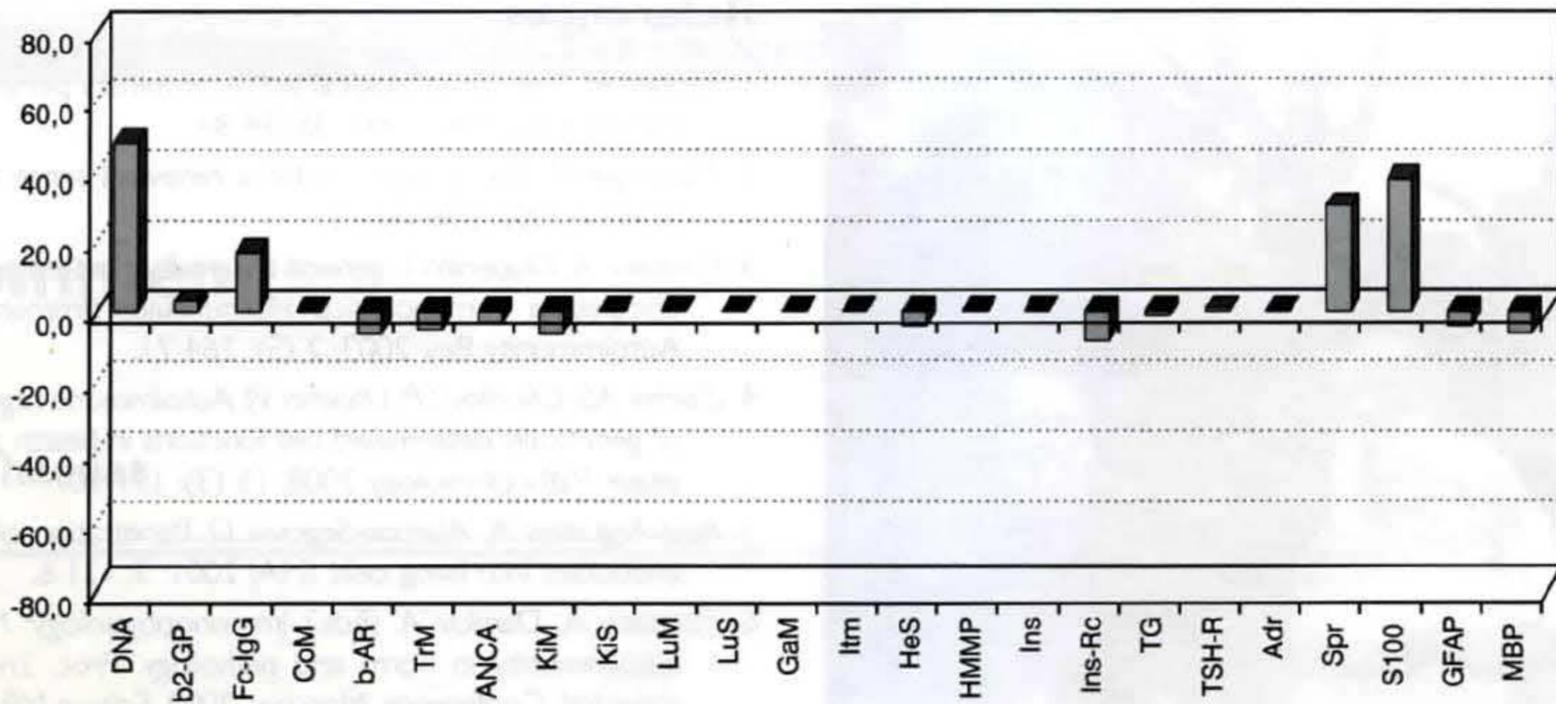


Fig. 5. ELI-Viscero-Test data of patient with very early stage of prostatic gland cancer.

antigen SPR +18; auto-Abs against S100 protein -6%; Abs against astrocyte's protein GFAP -11%; Abs against myelin protein MBP +3%. Average Individual Immune Reactivity (AIIR) is -1% to population normal level (normal level of general immune reactivity); Prominently elevated immune reactivity against kidney cells, and against prostate antigen were found (Fig. 3, 4). Additional investigation of urine revealed a moderate bacteriuria and pyuria. Antibacterial treatment was effective and bacteriuria/leucocyteuria disappeared. Arterial blood pressure also became normal (during 18 months of regular observation no episodes of abnormal elevation of blood pressure were noted). *Conclusion:* Early stage of arterial hypertension of kidney origin was revealed; treatment of kidney inflammatory process was effective and resulted also in successful control of early stage of chronic arterial hypertension of renal origin.

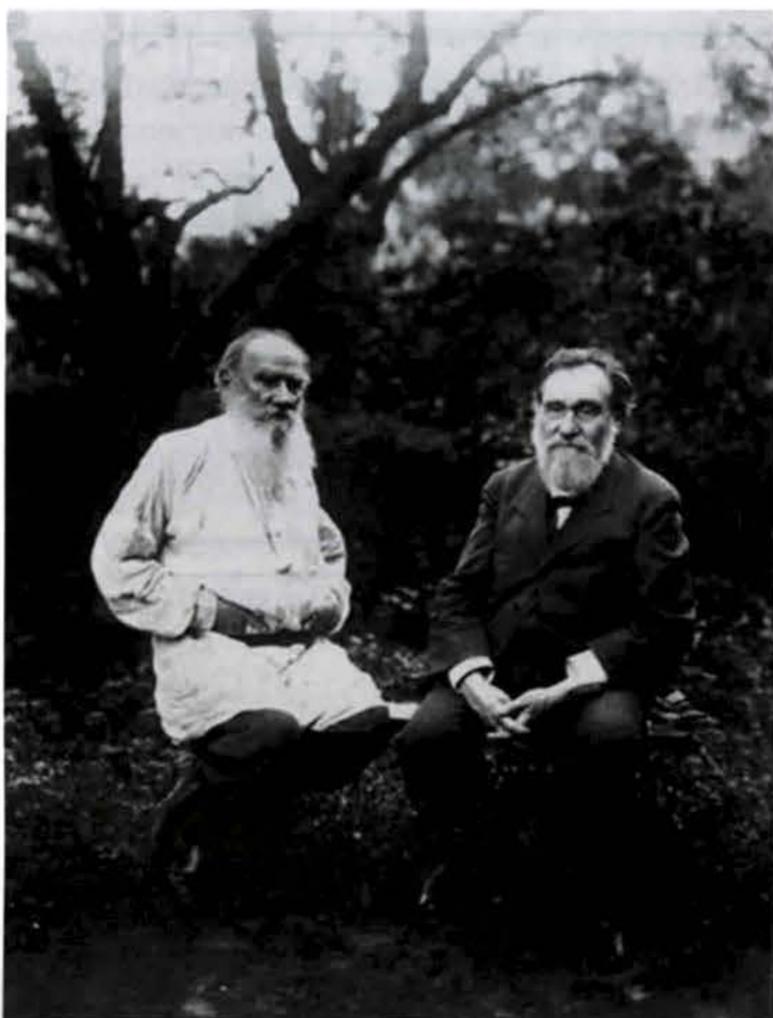
Patient B.R. (64 y.o., male); considered himself a healthy person (without any complains).

Results of multiparametric diagnostic investigation by ELI-Viscero-Test-24 Kit ("Immunculus", Russia) in % from population norm (Fig. 4): auto-Abs against dsDNA +46% from population norm; auto-Abs against beta2-Glycoprotein I +1%; auto-Abs against Fc-fragment of IgG +15%; auto-Abs against heart antigen beta2-adrenoreceptor -11%; auto-Abs against heart antigen Com -8%; auto-Abs against platelets antigen Trm -7%; auto-Abs against small vessel antigen ANCA -5%; auto-Abs against kidney antigen Kim -8%; auto-Abs against kidney antigen Kis -13%; auto-Abs against lung antigen Lus -16%; auto-Abs against lung antigen Lum -

12%; auto-Abs against stomach wall antigen Gam -14%; auto-Abs against intestine wall antigen Itm -11%; auto-Abs against liver antigen HMMP -6%; auto-Abs against liver antigen Hes -12%; auto-Abs against insulin -11; auto-Abs against insulin receptors -10; auto-Abs against TSH receptors -3; auto-Abs against thyroglobulin -1%; auto-Abs against adrenal antigen Adr-QC -2; auto-Abs against prostate/spermal antigen SPR +28; auto-Abs against S100 protein +36%; Abs against astrocyte's protein GFAP -6%; Abs against myelin protein MBP -8%. Average Individual Immune Reactivity (AIIR) is -2% to population normal level (normal level of general immune reactivity); Prominently elevated immune reactivity against kidney cells, and against prostate antigen were found (Fig. 5). Additional investigation of prostatic gland with PET revealed abnormally intensive accumulation of glucose in gland tissue; blood level of prostate-specific antigen was at upper norm level; cancer in situ (histology investigation of biopsy sample) was diagnosed in the prostate gland. Patient was treated surgically. Three years later any signs of malignancy were absent. *Conclusion:* Very early stage of prostatic cancer was revealed; treatment was effective.

Concluding remarks

Precision multi-parametric investigations of abnormal changes in content of plurality of auto-Abs may become an effective instrument for early pre-clinical revealing of changes, which can lead to disease, with the aim of timely intervention and prevention of future disease development. Future successes in this area may become the ground for revision of the main



Pic. 2. Founder of the idea of physiological autoimmunity E. E. Mechnikoff (1845-1916) and supporter of ideas of preventive medicine L. N. Tolstoy (1828-1910) during conversation. 01 August 1909, "Yasnaya Poljana" estate.

paradigm of modern medicine (DISEASE – TREATMENT) and transition to the new one (PROGNOSIS – PREVENTION). Of course, for transformation of the desire into reality not only effective, pre-clinical diagnostic methods should be elaborated, but also algorithms of individualized preventive measures (effective and socially realizable) should be proposed and accepted by general medical practice.

Many years ago Leo Tolstoy¹⁶ had bitterly written: "each individual has own peculiarities, and his own new disease, not known to medicine ... Field of medicine is practically not investigated... All known medications may help 1/1000 from expected". Elia Mechnikoff was a little more optimistic: "There are no incomprehensible in nature, but a lot of not comprehend so far" (Pic 2).

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