Biochemistry (Moscow), Vol. 67, No. 5, 2002, pp. 600-608. Translated from Biokhimiya, Vol. 67, No. 5, 2002, pp. 721-731.

DISCUSSION

The Immunological Homunculus (Immunculus) in Normal State and Pathology

A. B. Poletaev

Laboratory of Molecular Medicine, Medical and Ecological Fund "Chernobyl-Test", ul. Zuryupy 3, Moscow, 117418 Russia; fax: (095) 336-70-01; E-mail: vtchernn@rol.ru

Received April 2, 2001
Revision received June 4, 2001

Abstract—The immunculus is considered as the system (general network) of constitutively expressed natural autoantibodies against different extracellular, membrane, cytoplasmic, and nuclear self-antigens (ubiquitous and organ-specific). It is specially noted that the repertoires of natural autoantibodies are surprisingly constant in healthy persons, independent of gender and age, and characterized by only minimal individual peculiarities (individual immune fingerprints). On the other hand, abnormal metabolic changes which precede the clinical manifestation of different diseases showed easily detected changes, rather quantitative than qualitative, in the systems of natural autoantibodies in patients' sera (immunculus distortions). This phenomena could supposedly be used for "mapping" the state of physiological norm in terms of the millions of natural autoantibody repertoires, and for elaboration of the methods for early (preclinical) detection of potentially pathogenic metabolic changes. Could the individual features of the general network of constitutively expressed natural autoantibodies reflect the functional state of the body and be used for "mapping" of normal and pathological functional state? Could the changes in production of some biologically active natural autoantibodies not only reflect the state of the body, but be used for partial compensation of functional deficiency of certain molecular systems? These and related questions are discussed in this article. The research project "immunculus" is proposed for international cooperative investigations.

Key words: natural autoantibodies, immune regulation of physiological functions, immunculus, mapping of autoantibodies repertoires, diagnostics.

NATURAL AUTOANTIBODIES

During the last 10 to 15 years efforts of many researchers in the field of neuroimmune and immunoendocrine interactions and other aspects of immunoregulation of physiologic functions have been concentrated mainly on the analysis of the biological activity of different interleukins, interferons, and chemokines. However, the unique character of the immune system on the molecular level is determined not so much by dozens of cytokines, the majority of which are produced also by cells of different types in many organs and tissues [1, 2], as by its ability to produce a huge number of antibodies (Ab) and antigen-specific cellular receptors, including anti-SELF Ab (or auto-Ab) and anti-SELF receptors of T- and B-lymphocytes.

The presence of natural (physiological) autoantibodies (nAAb) in the body of healthy persons was first demonstrated by Besredka about 100 years ago [3] and later by Landshteiner [4], but only recently nAAb have become a real object of scientific research.

In the 60s to 70s immunology rested upon a nearly unbreakable base of Bernet's clonal-selection theory [5], and auto-Ab findings in healthy persons, contradicting this theory, were found discouraging, and thus were practically ignored. The situation started to change following the appearance of the immune network theory [6], postulating that the immune system of healthy individual can produce Ab to a variety of antigens of their own body, i.e., nAAb. In the 80s to 1990 experimental confirmations of the presence in the blood serum of healthy persons of hundreds of nAAb specifically directed to hormones, receptors, intercellular matrix components, cytoskeletal proteins, DNA, histones, enzymes, components of the main histocompatibility complex, and other endogenic compounds appeared [4, 7]. Many publications indirectly show that nAAb to any endogenic antigens at some concentration are present in the body of healthy persons and can be revealed by using suitable methods of Ab detection. It was clearly confirmed when expressing libraries of genes of the human B-lymphocytes were used (Professor W. J. Harris, Aberdeen University, Scotland, U. K., personal communication).

0006-2979/02/6705-0600$27.00 ©2002 MAIK "Nauka/Interperiodica"

For some time it was considered that nAAb are exclusively low-affinity polyreactive molecules of IgM class [8]. However, in subsequent experiments it was shown that half or more of nAAb circulating in the blood of the healthy adults belong to IgG class [9]. Besides, a significant part of such nAAb is monospecific and their specific affinity can reach the values of 10^{-11} M and higher [8, 10].

It was established that nAAb synthesis is programmed by constitutively expressing Ig genes almost without undergoing somatic mutagenesis [4]. Accordingly, in contrast to large differences in individual sets of antibodies to xenogenic antigens, nAAb repertoires are very similar in all healthy persons of different age and gender and are formed primarily during the intrauterine period [4]. Those very small individual differences (immune fingerprints) of nAAb repertoires, typical for the normal condition, are determined mostly during the first months of the baby's life under the influence of repertoires of maternal nAAb of IgG class, actively transferred transplacentally and performing the role of some kind of matrices which tune the offspring's nAAb repertoires (phenomenon of epigenetic immune imprinting [11]). Accordingly, pathologic shifts in the repertoires of maternal (but not paternal) nAAb of IgG class, sometimes substantial under different forms of pathology in a pregnant woman, can define for years the corresponding abnormal changes in the production of nAAb of her baby and may lead to the formation of different pathologic changes in the child [11].

In the 60s when studying one of the main forms of thyrotoxicosis, Graves disease, in the blood of many sick persons the presence of factor LATSS (Long-Acting-Thyroid-Stimulating-Substance) was detected. The latter with high-affinity bound to thyrotropin (TTH) receptors on the cells of the thyroid gland [12]. As a result, abnormal elevation of synthesis and secretion of thyroid hormones was noted in such patients. LATTS was identified as auto-Ab specifically interacting with the binding sites of TTH receptors. During the 70s much hope was placed on the possibility of using tests for the presence of LATSS in patients' blood sera for diagnostic purposes. However, to the researchers disappointment it appeared that such auto-Ab (functionally similar to TTH) are present in blood of not only sick persons but healthy ones as well, and differences in their serum contents are only quantitative [12].

The analogous situation, approximately at the same time, was repeated with "taraxein fraction", supposedly responsible for mental deviations in schizophrenic patients. Taraxein was identified as auto-Ab to some nuclear antigens in neurons of the septal area of brain neurons [13, 14]. The administration of such partly purified Ab in the general blood flow of human volunteers or monkeys brought about phenomena of transitory acute psychosis accompanied by electroencephalographic changes and behavior deviations with hours or days duration [14]. It seemed that with some more efforts the schizophrenia puzzle would end. But the situation with LATSS repeated exactly and corresponding auto-Ab has been detected in the blood sera of healthy persons as well, though in lower concentrations [15].

Thus, it was clearly demonstrated as useless to attempt to create diagnostic methods the basis of the detection of some unique special "pathogenic" variants of auto-Ab, qualitatively new in their antigenic specificity, i.e., not synthesized in the normal state. But does this mean that detection of not qualitative but quantitative changes in the production of many variants of auto-Ab (nAAb) cannot be informative for diagnostic purposes?

IMMUNCULUS AS THE MIRROR OF THE STATE OF THE BODY

In accordance with a remarkable hypothesis of Cohen and Young, the molecular specificity of the body is reflected in sets of anti-self receptors of autoreactive T-lymphocytes, the totality of which forms the "immunological homunculus" [16]. Information now available allows thinking about the realization of this fruitful idea in the functional sense. At that, it is reasonable to somewhat expand the frames of initial hypothesis of Cohen and Young and to include in idea "immunological homunculus" or "immunculus" not only as autoreactive T-cells, but also the general network of circulating nAAb.

Originally the idea of the homunculus as the mirror of the anatomical body structure was proposed and based in detail by neurologists. The homunculus is presented by the populations of neurons of the sensory-motor cerebral cortex topically controlling different parts of the human body [17]. In doing so, the homunculus, as the neurologists understand it, is not only a mirror passively reflecting anatomical structures of the body but also one of the mechanisms for the control of their activity. The illustration of the controlling functions of the central neurons representing the homunculus serve clinical observations of patients with insults, wounds, or tumors of the brain, which leads to lack of certain neuron populations and is accompanied by different motor and sensory dysfunction: speechlessness, disability to perform arbitrary motions, dysfunction of separate organs, etc. [17].

If the homunculus of neurologists means the reflection of the individual anatomy (three-dimensional structure) of the body on the level of populations of the brain's neurons, immunculus reflects rather not the anatomical structures, but individual peculiarities of the antigenic (molecular) composition and metabolic transformations accompanying the living activity of the body. In other words, the principal difference between homunculus and immunculus lies in the fact that the first is mostly "the

mold of the anatomy" (body's structural state), while the second is "the mold of physiology" (body's functional state). Accordingly, the idea of "immunculus" is much more virtual and probably is more difficult to perceive, but it is not less real and important in the biological (and medical) sense.

As noted above, remarkable uniformity of nAAb repertoires in healthy persons is established in early ontogenesis and lasts for decades [4]. At the same time, many diseases (possibly the majority) are accompanied by significant deviations in the production and serum contents of these nAAb. We suppose that detailed analysis of serum content of many thousands of nAAb against different antigens of the human body (membrane, cytoplasmic, nuclear, extracellular; ubiquitous, as well as organ- and tissue-specific) and characteristic nAAb changes (rather quantitative than qualitative), may become a precision instrument for the evaluation of the functional state of the body in general and its specialized components in particular.

According to our observations the serum content of nAAb of IgG class interacting with some proteins involved in embryonic development (these nAAb are detected by ELI-P-Test [18]) is very similar in all investigated healthy women. At the same time, the content of such Ab in women suffering from repeated miscarriages, infertility, or giving birth to newborns with developmental defects, significantly differs from the physiologic norm [18, 19]. The more stable and prominent deviations in the content of corresponding nAAb usually correspond to the more significant disturbances of the woman's reproductive functions. In other words, serum content of such "embryotropic" nAAb is one of the physiologic constants reflecting the state and condition of the reproductive functions. The importance of the evaluation of the content of "embryotropic" nAAb in planning pregnancy and using (in case of necessity) specialized treatment-and-prophylactic measures is evident.

Another example: healthy persons of both sexes are characterized by remarkably similar levels of serum content of nAAb of IgG class to some proteins of nervous tissue ("neurotropic" nAAb) and corresponding anti-idiotypic Ab revealed by the ELI-N-Test method. However, for patients suffering from different forms of neurological and mental diseases the content of such Ab was usually changed, and the normal idiotypic/anti-idiotypic balances are disturbed [20]. It is significant that if newborns are evaluated by neonatologists as healthy but are characterized by long-lasting deviations in repertoires of "neurotropic" nAAb, 6 to 36 months later 60 to 70% of such babies reveal neurological problems [21].

It is important to note that uncoordinated (pathologic) changes in the relative content of different antibodies to proteins of nervous tissue rather than the abnormal increase of production of some particular antibodies are the most characteristic feature of many forms of psycho- and neuropathology [20]. According to the data obtained in our laboratory [20, 21] as well as experimental data of other researchers [22], certain nearly the same levels of antibodies to different proteins of the nervous tissue are present in the blood of somatically, psychically, and mentally/neurologically healthy persons, while the relative content of such antibodies in the norm may vary within rather limited bounds—thus indirectly demonstrating the presence of some mighty (network) mechanisms called upon to ensure maintenance of production, secretion, and catabolism of such antibodies within the necessary physiologic frames. In cases of pathological changes, for example, the major part of the patients with diagnoses of schizophrenia, epilepsy, multiple sclerosis, manic-depressive disorder and other forms of the nervous system pathology feature significant quantitative differences of serum immunoreactivity to lots of proteins of brain cells, reflecting the combined discoordination (both increase and reduction as compared with the physiologic norm) of the levels of synthesis, secretion or catabolism and utilization of different antibodies interacting with the brain cells [20]. In other words, during different forms of nervous system pathology uncoordinated changes of the quantitative characteristics of synthesis and secretion of antibodies produced by many clones of immunocompetent cells are noted, rather than signs of autoimmune aggression on the part of one or several clones of lymphocytes (as considered earlier [14]).

It should be underscored that pathologic changes in the compositions of nAAb ("embryotropic", "neurotropic" or others), as a rule, represent a reaction on non-physiology changes in synthesis or degradation of the respective endogenous compounds-antigens [23] and appear at the initial (pre-clinical) stages of pathology, during physiologically compensated metabolic disturbances. These long-lasting changes in the nAAb repertoires could be detected much earlier (sometimes months and years) than clinically manifested (pathophysiological) deviations will appear. This fact reflects the secondary nature of the clinical signs of pathology, which begins to show only on the far gone stages of the initial changes of molecular and cellular level under the conditions of progressively increasing insufficiency of the physiologic compensatory mechanisms. Evidently, an interesting peculiarity is exercised in this, peculiarity which qualitatively differs the principles of the functional reliability of the complicated biological systems from the technical or electronic systems—phenomenon which can be designated as "pyramids of stability". Its essence may be formulated in the following way: for a long time violations at the molecular level (deviations in the normal content of these or those biologically active molecules) may practically not to affect at the cellular level of organization, i.e., upon reaching certain threshold values practically not to influence on the functioning of these or those cells of the organism; in its turn violations at the cellular level of

organization (for example, death of significant number of the cells of this or that organ and tissue according to the mechanisms of necrosis or apoptosis) upon reaching of certain quantitative threshold may be practically invisible at the organism-wide (whole) level. In other words, for living systems it turns out to be characteristic higher reliability and stability of every subsequent level of organization as compared with the preceding one. These observations fully agree with the well-known statement that "... any disease is a drama in two acts, the first of which takes place under put off candles in the silence of our organs and only in the second one pain and other visible manifestations of the disease turn to appear".

Quantitative mapping of the serum repertoires of thousands nAAb, accumulation of the respective data banks are a wide field of activities for researchers and clinicians. The result of these researches may be working out of principally new diagnostic technologies for "early notification", i.e., preclinical diagnosis of the pathologic metabolic changes typical for reversible stages of pre-disease.

REGULATORY IMMUNCULUS

In accordance with some estimations 20 to 30% of clones of specialized immunocompetent cells during the whole life produce 20 through 30 thousand nAAb molecules per minute [24]. As a result, a few grams of nAAb of different specificity are produced in the body of any healthy individual daily. Should this phenomenon be considered as nonsense, as an example of potentially hazardous wastefulness of the body? Such biological irrationality could hardly be preserved during evolution. It is more logically to suppose that nAAb are normal (physiological) components of the body taking part in the realization of biologically significant regulatory functions.

According to Galaktionov [2], the process of multicellular organism evolution was going both along the road of increasing the absolute quantity of somatic cells and along the road of strengthening specialization and differentiation of separate groups of cells. At the same time, the immune system evolution was connected with the multicellularity in general, rather than with the anti-infectious protection. To our mind, it will be not superfluous to add to this a remark about the fact that evolution of the multicellularity phenomenon was closely coupled not only with the increase of the organism cell number and their differentiation, but also with the rise of the role and significance of the regulation of the intercellular and intersystem interactions. In so doing, an important role belongs to the immune system in general and in particular to such of its products as natural antibodies.

It should be noted that Ab equally with T- and B-cellular receptors, molecules of the main histocompatibility complex, adhesins, integrins, growth factors receptors, Thy-1 molecules, myelin-associated glycoprotein, carcinoembryonic antigen, and others refer to a wide superfamily of immunoglobulins. Criteria for referral to the superfamily is the domain organization and expressed homology of their primary structure with the known immunoglobulins [2]. In the functional plan the main feature uniting the superfamily representatives is their participation in the regulation of the ordered intercellular interaction by establishing specific intermolecular contacts (homo- or heterophilic). In the evolutionary aspect, genes of these molecules are descendants of the common gene coding the structure of the ancestor homodomain membrane protein at the dawn of the appearance of multicellular organisms, providing "intercellular couplings" by homophilic cooperation with the same molecule on the surface of the adjacent cell. As a result of tandem duplications of the ancestor gene during evolution there appeared multiple loci controlling the production of different immunoglobulin-like molecules of intercellular adhesion. Amplified genes were expressed in cells of different types, giving space for mutation drift bringing changes into the structure of their products, changing affinity and specificity of intermolecular contacts regulating intercellular interaction [2]. The latest evolutionary acquisition were molecules of Ab, which kept the main functional sign of the superfamily representatives, namely, capability to participate in homeostatically expedient very specific intermolecular interactions securing regulated cooperation of different types of cells. In contrast to the majority of other representatives of the superfamily, rigidly tied to the cell membrane structures, Ab obtained freedom for displacement and, accordingly, significantly greater possibilities for performing intercellular and intersystem distant communications.

In the 1950s Grabar proposed a "sewage" role of nAAb which may bind and block very different potentially hazardous products of catabolism [25]. Similar views were held by Kovalev in his conception of immunochemical homeostasis [23].

However, it seemed to us as an unjustified restriction to bring the role of these molecules only to the function of a "scavenger". It was shown experimentally that nAAb against many hormones, trophic factors, and regulatory peptides (insulin, nerve growth factor, VIP, cytokines, etc.) are constantly synthesized in the body of healthy persons and protect these very labile molecules from premature degradation [9]. Such nAAb provide transportation of biologically active molecules to specialized binding sites where the dissociation of antigen–Ab complexes take place and the peptides interact with their respective receptors, binding the ligands with more affinity than Ab. The protector role of nAAb is revealed here not only in prevention of peptides from premature proteolysis but also in preventing their ineffective diffuse "spreading" throughout many sites with low affinity unspecific binding [26]. As a result, biological effectiveness of peptide

communicators increase prominently. For example, activity of somatotropin, which is present in the blood circulation as a complex with a specific Ab, turns out to be 200 to 400% higher than that of the free hormone [26].

In their turn, specialized receptor structures of cells can also be targets for specific anti-receptor nAAb. Besides the mentioned TTH receptor-binding thyroid-stimulating nAAb, nAAb against insulin receptors, against estrogen receptors [27], against acetylcholine, serotonin, dopamine, norepinephrine receptors are described [28].

The fact that Ab can modulate functions of intranuclear estrogen receptors *in vivo* [27], reflects the biological permeability of Ab and suggests that even the most "closed" compartments of living cells are accessible for Ab.

The findings of recent years are very important for understanding the principles of the biological activity of nAAb, primarily how "hidden" in the seemingly deepest cells compartments antigens turn out to be accessible for rather large molecules of the antibodies. These findings suggest the presence of effective mechanisms of translocation or directed Ab transport both through the histohematic barriers and through the membrane structures of live cells [29, 30]. As a result of specific energy-dependent transcytosis [31] Ab gain access to the respective target antigens, expressing not only on the surface membranes, but intracellularly as well, including inside isolated cytoplasmic organelles, for example mitochondria [32] or inside the nuclei of live cells. Principally it is important to have confirmations that Ab feature the ability not only to penetrate into the intracellular cells compartments, but also specifically to interact here with corresponding antigens *in vivo* [7, 33]. Interacting with different membrane, cytoplasmic, and nuclear target antigens, changing their conformational characteristics, blocking, or activating certain functional sites of the latter, Ab turn out to be a universal instrument capable specifically and reversibly to change the functional activity of its molecular targets.

Previous ideas that histohematic and cellular barriers are something like the impenetrable "Chinese Wall" for circulating Ab became things of the past. Nevertheless, probably there is some kind of selectivity of the barriers with reference to Ab of certain specificity (as well as to Ab belonging to different classes of immunoglobulins). Possibly it helps to perform something like selector functions ensuring preferred arrival of the required specificity antibodies to tissues, organs, and cells enriched in the respective target antigens. Just as lymphocyte homing takes place (the latter is based upon some membrane marker molecules in high endothelial cell and some tissue-specific features of lymphocytes [1, 2], and has provided a peculiar immunocompetent cell transport to the desired place and at the desired time). Undoubtedly, an analog of such homing underway not at the cellular (lymphocytes) but at the molecular level (molecules of Ab) could make a major contribution to the realization of their regulatory functions. Recent observations concerning the fact that Ab to vasopressin, introduced into the paraventricular nucleus of the rat hypothalamus, are selectively accumulated by live neurons synthesizing particular peptides, but not other nearby cells, serve as an additional illustration to the aforesaid [34]. It is worth noting that some endogenous compounds, which themselves practically fail to penetrate through histohematic barriers, in complex with Ab acquire characteristics of additional permeability (trans-barrier permeability). For instance, molecules of the nerves growth factor, incapable of passing through the blood–brain barrier in their free state, acquire this ability if they are present in the general circulation in the form of NGF–IgG complexes [35]. It is quite possible that these data illustrate another aspect of Ab biological activity connected with the provision of the trans-barrier transfer of biologically active compounds.

Antibodies have been described which influence the functions of membrane ion channels [36], i.e., are able to influence transmembrane transport of various ions and, by means of this kind of activity, to modulate the excitability of living cells. Excessive production of such Ab may be the cause of development of some forms of neurological (neuromuscular) pathology, for example Lambert–Eaton syndrome [37].

If we consider nAAb as regulatory factors, potentially able to modulate the activity of target molecules and thus to influence various cellular and physiological functions, we should bear in mind that "anti-tubulin", anti-histone", "anti-insulin" and any other Ab, strictly speaking, are not directed to protein molecules as such. Antigen-binding sites of Ab are able specifically to interact with only small portions of the target proteins (epitopes). On that ground, scores of different (in the variants specificity) Ab can potentially bind with dozens of different epitopes of one and the same protein molecule. Biological effects of Ab with different epitope specificity can be opposite sometimes. For example, inhibition of the growth of neuronal processes by anti-NGF Ab is well-studied and documented [38]. At the same time, using combinations of Ab to different epitopes of NGF receptors, it is possible to achieve modulation of the whole activity spectrum of NGF itself from mainly trophic influence up to induction of neuronal differentiation [39]. Ab to some antigens of oligodendrocytes are causally related to the development of demyelinating diseases [40]. At the same time, the ability of some anti-oligodendrocyte nAAb to induce remyelination is also described. It is supposed that such Ab may be used in the therapy of multiple sclerosis [41].

Depending on the epitopic specificity of Ab the consequences of the Ab–receptor cooperation may so differ that from the pharmacological point of view they should be ascribed to different classes of compounds. Ab–receptor binding may lead to the receptor activation and induc-

tion of the secondary intercellular events of the molecular level; in this case Ab should be considered as the receptor agonists. Other Ab to the same type of receptors, but binding to different sites (epitopes) of the latter, may inhibit or block the receptor functions, i.e., stand as specific receptor antagonists [24]. The result of the Ab–receptor interactions may be quite unexpected events on the organ and cellular level. For example, some variants of Ab to thyrotropin receptor may stimulate mitotic activity and growth of thyroid gland cells, i.e., to advance as inducers of proliferation [42]. Ab may not only stimulate but also inhibit cellular proliferation [43], and cause dystrophic and atrophic changes by mechanisms of programmed cell death (apoptosis) of both normal and malignant cells [44], or, on the contrary, to block apoptosis [45].

Realization of the principle of partial epitope specificity of cooperation repeatedly multiplies precision and selectivity of regulatory potencies of nAAb as to polyfunctional regulatory macromolecules. Let us note that epitopes can be not only linear (sections of successive monomers of the polymeric molecule), but conformational as well, formed by linearly distant, however space-approaching sections of the primary structure of macromolecules [46].

Significantly less studied however perhaps not less important is the aspect of Ab activity connected not with the modulation of the target antigen functions, but with the biological activity of Ab molecules per se, depending on the giant number of the possible structure variants of their own active centers represented by hyper-variable sections of their Fab-fragments. It is established that some Ab, as such, possess their own enzymatic activity (so-called "abzymes"). Among other things, there is a description of Ab displaying activity of superoxide dismutases, stimulating hydrolysis of phosphoinositides, catalyzing transfer of the acyl grouping, formation and segregation of carbon–carbon bonds, catalyzing stereospecific aminolysis, hydrolysis of aromatic amides, and cyclization, as well as possessing proteolytic activity [24, 47]. With regard to the giant number of possible variants of the active center of Ab, theoretically, evidently, it is possible for them to display ANY variant of enzymatic activity.

There are no theoretical prohibitions on the existence of molecules of Ab whose conformational structure of the active centers can sterically repeat (principle of molecular mimicry) the functional fragments of the structure of any other biologically active molecules, in particular the fragments of the receptor-binding sites of various "classical" communicators (endogenic neuromediators, neuromodulators, and hormones). Such Ab could functionally replace the respective intercellular communicator molecules and, thus, to fill in their deficiency in case of necessity. Ab characterizing such ligand-like activity have actually been described in recent years. Previously we have already talked about Ab able "to substitute" thyroid-stimulating hormone [12]. Besides, there were described Ab "mimicking" substance P, insulin, serotonin, norepinephrine, estrogens, gangliosides and other biologically active ligands [24, 28] and able to activate the respective receptors in living cells, increasing the production of the secondary messengers and inducing cascades of the coupled intracellular rearrangements. At that, as Erlanger notes [48], for the formation of practically the same space-functional conformations, the active centers of anti-idiotypic Ab quite not obligatory should have close to "mimicked" antigen sets of amino acid residues because very similar functional conformations can be present in the proteins which differ between each other in 137 out of 141 residues of amino acids.

All this repeatedly widens the potential possibilities of Ab to appear as regulators, modulators, tuners, doublers and direct participants of the broadest circle of biological processes.

In general, it should be admitted that the area of potential biological activity of nAAb is exceptionally wide. Moreover, one should not reject the possibility that Ab molecules cannot only modulate the activity of their targets but, functionally compensate (to some extent, to replace in necessity) the shortage of certain hormones, enzymes, or trophic factors.

Are there any contradictions between the proposition about the nAAb regulatory functions and the ideas about potentially aggressive role of auto-Ab originating from Paul Ehrlich's idea of "horror autotoxicus"? Let us consider an explanatory example: if secretion of hormones of thyroid gland (or any other) exceeds the tolerable physiologic level, pathology is developing—hyperthyroidism with its characteristic symptomatic of thyrotoxicosis. Reduction of the thyroid hormonal secretion below the tolerable threshold also inevitably leads to pathology with the clinical picture of hypothyroidism. This example illustrates the general biological rules—for molecules, performing the regulatory functions, it is necessary to maintain certain "golden mean" of concentrations, while their content coming both beyond the upper and lower physiological boundaries is fraught with pathologic consequences. The situation with nAAb is evidently the same. Condition of the norm, in this case as well, is certain concentration "golden mean". And if the content of various nAAb fall outside of the compensating limits, there can develop pathologic changes in the form of destructive auto-aggressive autoimmune diseases (in case of Ab excess), or in the form of less studied disorders depending on shortage of secretion of certain types of nAAb. For example of the latter may serve the embryo development stoppage accompanying some regulatory nAAb shortages in the blood of the pregnant woman [19, 49, 50]. Low (sub-threshold) content of nAAb to some proteins of brain cells is a feature of some of the nervous system disorders [20, 51].

Recognizing, after Abramov [52], that consideration of the immune system exclusively from the positions of the main factor determining the resistance of the organism to infectious diseases represents not more than historical interest, and that the concept of the immunological supervision and discrimination of "SELF" and "NON-SELF" needs certain revision and reprocessing, it seems for us as important to take one more step. Namely, to recognize its participation (together with nervous and endocrine systems as a competent participant of the "Big Three") in the regulation and cooperation of the common for the organism homeostatic processes. At that, the latter is realized with the use of not only different types of leukins, but specialized molecules of Ab as well, capable to distinguish, reversibly cooperate, and in a required manner to change the functional characteristics of a giant number of autoantigens, expressing on the surface and in the intracellular compartments of the cells of different organs and tissues.

It could be supposed that the key features of immunity as a biological phenomenon are identification, actualization, and dynamic maintenance of the "SELF" complexity during the individual lifespan. The "SELF" protection (including protection from pathogenic microbes) is no more than one of derivative from the main biological function of the immune system. This conclusion is similar to the ideas of Mechnikoff [53], who supposed that the "phagocyte system" (immune system in modern terms) is designed not so much as to struggle with pathogenic microorganisms, but to dynamically maintain the "state of harmony" or "state of health" (preservation of optimal homeostasis) under the constant disharmonizing environmental pressure. According to Mechnikoff, immunocytes should not be considered as "body gendarmes". Their participation in the interspecies struggle of "host–parasite" is only a particular episode of the global biological function of the phagocyte (immune) system, with the latter designed to take part in the strive (since earliest times) for the organism for self-optimization, self-maintenance, and self-reparation [54].

According to Ershov [55], homeostasis appeared at the same time when the chemical evolution was to be completed by the biological one. And the first system of the homeostasis maintenance became the genetic code. With the appearance of the genetic code life went from the condition of the unstable equilibrium to the stable non-equilibrium which is being preserved hundreds of millions of years. However, at a certain evolutionary stage, when genome reached the size of some 10^6 base pairs, statistical probability of appearance of reading mistakes (transcription and translation) lead to the fact when the genetic code stopped guaranteeing homeostasis of the prokaryotic cell. It entailed the appearance of the complicated systems of the genome correction and reparation which lead to the subsequent increase of the latter sizes. With the appearance of the eukaryotic cells, multicellular organisms, and then vertebrates (the genome sizes of some 10^9-10^{12} pairs), the main load in the maintenance of the dynamic homeostatic equilibrium between the organism and the environment fell on the intracellular and intercellular regulatory molecules including natural autoantibodies.

Accordingly changes in the nAAb content may reflect launching of the original compensation mechanisms aimed at softening the growing pathologic changes at the molecular level. Taking into consideration the versatile biological activity of many thousands of nAAb, it is possible to admit that immunculus, as a mold of the body's functional state, may to revealed the ability of partial compensation of various molecular systems functional deficiency at the expense of adaptive quantitative changes of certain nAAb production. It increases compensatory-homeostatic potential of the body and extends "inertia of health".

Thus, the research area fragmentarily outlined above could become a basis for wide research within the scope of possible project "Immunculus". This project is capable of presenting an alternative (or rather to be additive) to the famous scientific project "Human Genome". It is known that the genetic code ensures "information base" of formation and maintenance of highly-ordered molecular structures (proteins) organization of the body cells during individual lifespan. At that, peculiarities of the genetic program are vertically transferred from both parents to children. In turn, immunculus supposedly participates in basic mechanisms of ordered functional integration of the preformed systems of the body cells of different types. In so doing, the vertical information transfer about the immunculus structure takes place as well. However, unlike genetic information, this transfer is performed only between the mother and fetus/baby according to the mechanism of epigenetic immune imprinting at the expense of transplacental active transfer of maternal antibodies of IgG class for tuning the primordial nAAb-producing cells of her offspring [11]. Evidently, both intracellular structural (ensured by genome) and intercellular/intersystem functional (ensured by immunculus) homeostasis are the basis for the normal activity of the healthy organism.

Performance of wide experimental and analytical works on "mapping" of healthy individuals' immunculus and creation of the respective computer data bases ("maps" of nAAb against different self-antigens) will permit the expression of the functional norm of any organ and tissue and the human body as a whole in terms of quantities of different constitutively synthesizing nAAb. It could permit the elaboration of the technology of effective "preclinical diagnosis" based on the early revealing of changes in nAAb repertories indicative for the beginning of pathologic metabolic changes having not reached the level of the clinical manifestation. That is, it might permit

the diagnosis of many diseases to be brought to a qualitatively new level. It could be supposed that observations indicative of the biological activity of nAAb and the latter possible participation in the regulation of the most different homeostatic events of the molecular-cellular level, allow us to hope that realization of project "Immunculus" will give theoretical foundation not only for the new approaches to early diagnosis but also may be useful for the creation of the new technologies of prophylactic and treatment of many serious diseases, based on specifically "address" regulating actions on separate components of the immunculus.

Some works of the last decade aimed at comparative study of the serum contents of "embryotropic" [19] and "neurotropic" [20, 21] nAAb in the patients and healthy people, as well as at the analysis of clinically significant consequences of abnormal production of such nAAb, can be regarded as the initial steps in the realization of the project.

REFERENCES

1. Haitov, P. M., Ignateva, G. A., and Sidorovich, I. G. (2000) *Immunology* [in Russian], Meditsina, Moscow.
2. Galaktionov, V. V. (1998) *Immunology* [in Russian], Moscow University Publishers, Moscow.
3. Besredka, M. (1901) *Ann. Inst. Pasteur*, **15**, 758-763.
4. Lacroix-Desmazes, S., Kaveri, S. V., Mouthon, L., Ayouba, A., Malanchere, E., Coutinho, A., and Kazatchkine, M. D. (1998) *J. Immunol. Meth.*, **216**, 117-137.
5. Bernet, M. (1971) *Cellular Immunology* [in Russian], Nauka, Moscow.
6. Jerne, N. K. (1974) *Ann. Immunol. (Inst. Pasteur)*, **125**, 373-389.
7. Poletaev, A. B. (1995) in *Monoclonal Antibodies in Neurobiology* (Shtark, M. B., and Starostina, M. V., eds.) Aspekt, Novosibirsk, pp. 37-45.
8. Casali, P., and Notkins, A. L. (1989) *Immunol. Today*, **10**, 364-368.
9. Bendtzen, K., Svenson, M., Jonsson, V., and Hippe, E. (1990) *Immunol. Today*, **11**, 167-169.
10. Avrameas, S. (1991) *Immunol. Today*, **12**, 154-158.
11. Vabyschevich, N. K., Poletaev, A. B., Budykina, T. S., and Zamaleeva, R. S. (1998) *Med. Konsultatsiya*, **2**, 14-17.
12. Teppermen, J., and Teppermen, H. (1989) *Physiology of The General Metabolism and Endocrine System* [Russian translation], Mir, Moscow.
13. Heath, R. G., Krupp, I. M., Byers, L. W., and Liljekvist, J. I. (1967) *Arch. Gen. Psychiatry*, **16**, 10-23.
14. Heath, R. G., Krupp, I. M., Byers, L. W., and Liljekvist, J. I. (1967) *Arch. Gen. Psychiatry*, **16**, 24-33.
15. Knight, J. G., Knight, A., Menkes, D. B., and Mullen, P. E. (1990) *Biol. Psychiat.*, **28**, 467-474.
16. Cohen, I. R., and Young, D. B. (1991) *Immunol. Today*, **12**, 105-110.
17. Pribram, K. (1975) *The Languages of The Brain* [in Russian], Progress, Moscow.
18. Poletaev, A. B., and Vabyschevich, N. K. (1997) *Vestnik Ross. Assots. Akusherov Ginekol.*, **4**, 21-25.
19. Poletaev, A. B., and Morozov, S. G. (2000) *Human Antibodies*, **9**, 216-222.
20. Poletaev, A. B., Morozov, S. G., Gnedenko, B. B., Zlunikin, V. M., and Korzhenevskey, D. A. (2000) *Autoimmunity*, **32**, 33-38.
21. Poletaev, A. B., Budykina, T. S., Gnedenko, B. B., Kluchnikov, S. O., and Morozov, S. G. (1998) *Med. Konsultats.*, **4**, 1-4.
22. Norendran, A., and Hoffman, S. A. (1989) *J. Neuroimmunol.*, **24**, 113-123.
23. Kovalev, I. E., and Polevaya, O. Yu. (1985) *Biochemical Principles of Immunity against Low-Molecular-Weight Chemical Compounds* [in Russian], Nauka, Moscow.
24. Kulberg, A. Y. (1986) *Molecular Immunology* [in Russian], Meditsina, Moscow.
25. Grabar, P. N. (1968) in *The Problems of the Organism Reactivity in Pathology* (Ado, A. D., ed.) Meditsina, Moscow, pp. 35-52.
26. Wang, B. S., Lumanglas, A. L., Szewczyk, E., McWilliams, W., Loullis, C. S., and Hart, I. C. (1992) *Mol. Immunol.*, **29**, 313-316.
27. Borovski, A., Gyling, M., Muquardt, C., Body, I. I., and Leclercq, G. (1991) *Endocrinology*, **128**, 3283-3292.
28. Azizov, R. G. (1997) *Immunopharmacological Investigations of The Neural–Immune Interactions*: Doctoral dissertation [in Russian], NII BIKhS RAN, Staraya Kupavna.
29. Landor, M. (1995) *Ann. Allergy, Asthma Immunol.*, **74**, 279-283.
30. Ritchie, T. C., Fabian, R. H., and Coulter, J. D. (1985) *Brain Res.*, **343**, 252-261.
31. Ikonen, E., Parton, R. G., Hunziker, W., Simons, K., and Dotti, C. G. (1993) *Curr. Biol.*, **3**, 635-644.
32. Berg, P. A., and Klein, R. (1990) *Springer-Semin. Immunopathol.*, **12**, 85-99.
33. Isenberg, D. A., Rahman, M. A., Ravikarjan, C. T., and Kalsi, J. K. (1997) *Immunol. Today*, **18**, 149-153.
34. Burlet, A. J., Leon-Henry, B. P., and Robert, F. R. (1987) *Exp. Brain. Res.*, **65**, 629-638.
35. Albeck, D., Rose, G. M., and Veng, L. (1996) *Soc. Neurosci. Abst.*, **22**, 752.
36. Barhanin, J., Meiri, H., Romey, G., Pauron, D., and Lazdunski, M. (1985) *Proc. Natl. Acad. Sci. USA*, **82**, 1842-1846.
37. Sher, E., Canal, N., Piccolo, G., Gotti, C., Scoppetta, C., Evoli, A., and Clementi, F. (1989) *Lancet*, **8664**, 640-643.
38. Johnson, E. M., Gorin, P. D., Osborne, P. A., Rydel, R. E., and Pearson, J. (1982) *Brain Res.*, **240**, 131-140.
39. Maliartchouk, S., Zheng, W.-H., and Saragovi, H. U. (1997) *Soc. Neurosci. Abst.*, **23**, 336.
40. Laman, J. D., Thompson, E. J., and Kapos, L. (1998) *Immunol. Today*, **19**, 489-491.
41. Asakura, K., Miller, D. J., Pease, L. R., and Rodriguez, M. (1998) *J. Neurosci.*, **18**, 7700-7708.
42. Prabhakar, B. S., Fan, J. L., and Seetharamaiah, G. S. (1997) *Immunol. Today*, **18**, 437-440.
43. Kusch, A. A., Belyavskiy, A. V., Schumay, E. P., and Tugizov, S. M. (1988) *Dokl. AN SSSR*, **300**, 968-970.
44. Ageenko, A. I. (1994) *The Face of Cancer* [in Russian], Meditsina, Moscow.

45. Estus, S., Zaks, W. J., Freeman, R. S., Gruda, M., Bravo, R., and Johnson, E. M. (1994) *Soc. Neurosci. Abst.*, **20**, 432.
46. Syren, K., Lindsay, L., Stoehrer, B., Jury, K., Luhder, F., Bekkeskov, S., and Richter, W. (1996) *J. Immunol.*, **157**, 5208-5214.
47. Kovaliov, I. E., and Shipulina, N. V. (1996) *Khim.-Farm. Zh.*, **30**, 3-12.
48. Erlanger, B. F. (1989) *Immunol. Today*, **10**, 151-152.
49. Takeuchi, S. (1990) *Am. J. Reprod. Immunol.*, **24**, 108-119.
50. Bose, R., Ming, Y., and Nan, P. (1991) *Immunol. Invest.*, **20**, 441-449.
51. Morozov, S. G. (1997) *Antibodies to Proteins of Nervous Tissue during Nervous and Psychiatric Diseases (Immunochemical and Clinico-Immunological Research)*: Doctoral dissertation [in Russian], NII Pitaniya, RAMN, Moscow.
52. Abramov, V. V. (1988) *Interactions of the Nervous and Immune Systems* [in Russian], Nauka, Novosibirsk.
53. Metchnikoff, E. (1968) *Immunity in Infective Diseases*, Johnsom Reprint (original published 1901), New York.
54. Tauber, A. I. (1991) *Perspect. Biol. Med.*, **35**, 74-86.
55. Ershov, F. I. (1996) *The Interferon System in Norm and Pathology* [in Russian], Meditsina, Moscow.