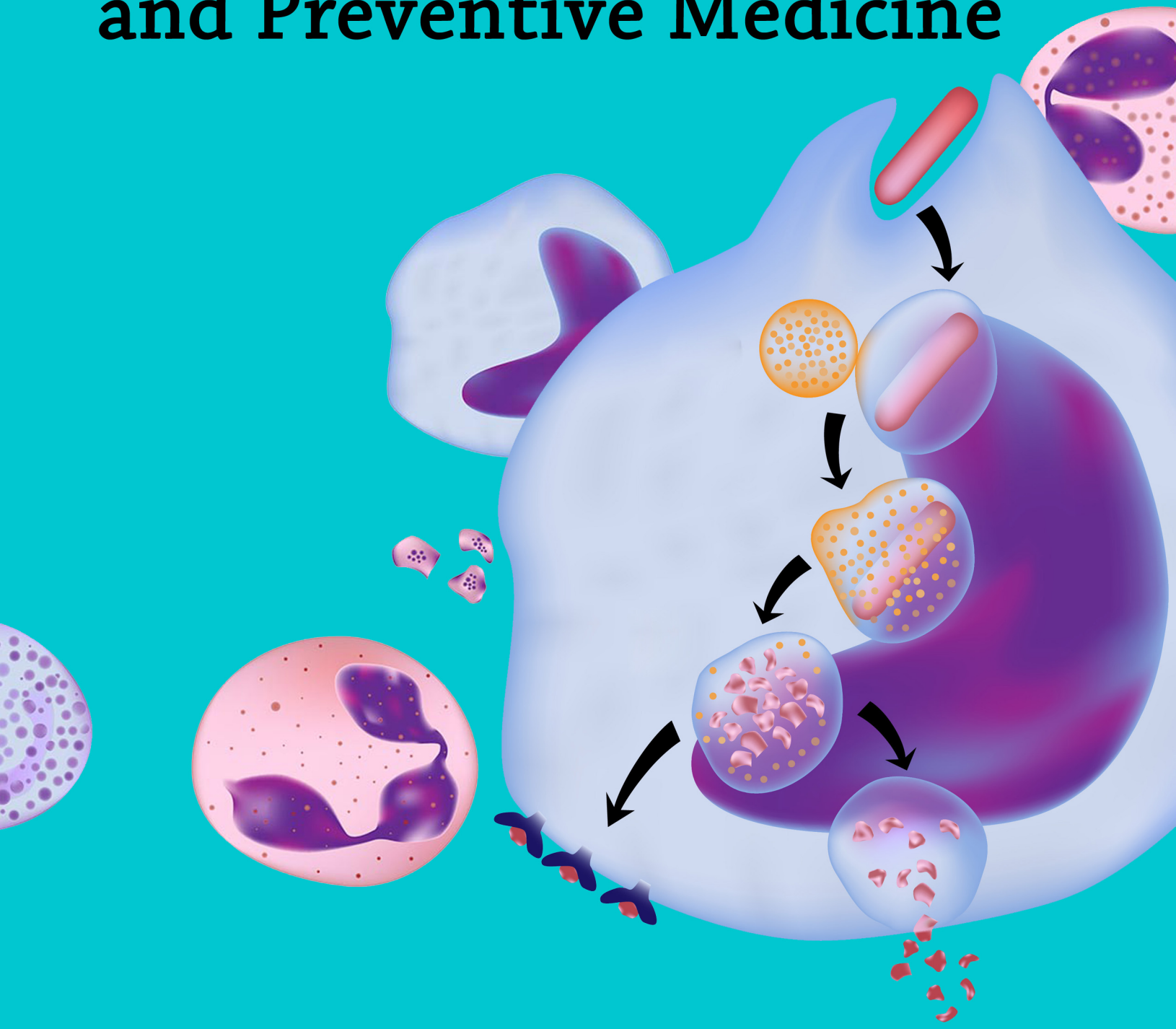
eISBN: 978-1-60805-724-5
ISBN: 978-1-60805-725-2

# Physiologic Autoimmunity and Preventive Medicine



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# Physiologic Autoimmunity and Preventive Medicine

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# FOREWORD

## FEW WORDS ABOUT PREVENTIVE MEDICINE

*The prediction and prevention are not a field for scholastic speculations,*
*but concrete activity on preserving of human health and active longevity*

According to the Bible, Noah's grandfather, Methuselah lived 969 years. It is easier to believe and accept that, by calculations of gerontologists, the biological resource of a human body lasts for not less than 120 years. The well-known medieval physician Paracelsus considered that the person could live 600 years. Haller and Hufeland (XVIII century) limited human life age to 200 years. Ilya Mechnikov and Alexander Bogomolets talked about 160 years. But how many people will live at least 100 years, do you know?

The fact that the overwhelming majority of us do not live 60-80 years until our biological limit characterizes pessimistically contemporary state of medicine, nobody knows why, called “public healthcare”. The modern medicine (in a traditional Western variant) does not protect human health or, otherwise, talk round corners. The modern medicine is the medicine of “repair”, the medicine of tablets and a scalpel. This is not the fault made by healthcare policy makers, or by physicians. It historically determined. The basic paradigm of medical aid involuntarily formed throughout many centuries.

Today “the repair medicine” also includes such a significant segment like disaster medicine and military medicine. However, it is rather a small segment of contemporary medicine, which focused not on wounds, traumas or life-threatening infections, but on chronic and slowly developing cardiovascular, malignant, endocrine, neurological, and other diseases. Understanding of the crisis in the current healthcare situation is an incentive to reflect on alternative ways of the development of medicine, or rather, about the formation of a real healthcare - medicine of prevention.

It is worth saying that “tablet strategy” practically exhausted. Today the average investment for one pharmaceutical compound from its development to market

launch requires more than 1 billion dollars. Thus, not only practical physicians, but also pharmacologists recognize that “tablet strategy” is effective in not more than 30% of cases maximum. Some specialists consider that the inefficiency or the harmfulness of pharmaceuticals reaches 85% (from the lecture by Vitaly Prutsky, the Head of Information Management in R&D “AstraZeneca” in Russia and Eastern Europe, 2012).

It is interesting that captain Jacques Margeret employed to tsar Boris Godunov wrote in his book titled “Estat de l'empire de Russie, et grande duche de Moscovie” dated 1606, “Many Russians live until 90-100 and 120 years and face illnesses only in an old age. Thus, nobody accepts medicines with the exception of the tsar and top noblemen”.

So the way of healthcare development surely guides ours society to a deadlock. What shall we do?

**PREVENTIVE MEDICINE IDEA**

The preventive medicine (PM) is an alternative healthcare ideology and methodology. Its essence refers to the personified management of physiological health state and organism reserves. The main objective is the high-grade healthy human life prolongation up to natural, biologically restricted limits. The main task is to not to cure illnesses, but to reveal any deviations of organism to lead to diseases and take the targeted actions to prevent illnesses.

The philosophy of the preventive medicine differs essentially from the traditional Western medicine philosophy so long as it based not on the paradigm of “repair” but maintenance managing of the human health.

We consider that in order to solve today’s and tomorrow’s acute demographic problems along with the healthy birthrate ensuring, the morbidity and mortality decrease, the high-grade healthy and efficient life prolongation it is necessary, not in words, but in practice, to get down to the PM concept formation and to the practical step development for its implementation.

## PRACTICAL IMPLEMENTATION OF PM CONCEPTION AS A CHALLENGE FOR STATE AND GOVERNMENT

The task includes the creation of new technologies and techniques, and their application in the clinical practice, the management system construction for mutual relations between citizens, medical organizations, companies, institutions, and the state regulating or supervisory agencies involved in the medical service sector.

It is necessary to adjust the activity range for different organs in state management, education, fundamental science, clinical practice, and medical business. The task complexity requires the construction of optimal connective trajectories (profiles) between a considerable quantity of dotted interdisciplinary and interdisciplinary competences.

In our opinion, the decision of such a global problem is quite possible nowadays with the help of "Strategy Project Principle" for the development and implementation of the predictive and preventive medical technologies and practices as strategic management models.

We consider necessary to accept from the first steps not separate techniques, but complete concept project with 15-30 year planning horizon. It will allow revise and manage simultaneously the whole cycle of healthcare development. This conception will be capable to be changed and developed in time in accordance with current events and circumstances. The project principal offered by us ensures the management system from the moment of the innovative mainstream, formation or scientific idea appearance until the moment of rendering high qualitative certificated healthcare service for each concrete person.

We suppose practical fulfillment of PM project should include the following basic sections:

1. Organizational, technical and personnel support; the solving of vocational training issues for highly qualified professional specialists in close inter/interdisciplinary sectors (physicians, researchers,

# PREFACE

Historically immunology formed as a branch of applied microbiology and generations of specialists in immunology educated by microbiologists. Therefore, "microbiological" points of view concerning predestination of the Immune System (ISYS) reproduced for decades. Essence of such views may be impressed by the phrase: *the main function of the ISYS (or for precision – Adaptive Immune System) is the constant struggle against any non-selfness which gets into the host-organism (foreign antigens in microbes, cells, or particles)*.

This position does not permit to answer a lot of questions. For example:

1. Why ISYS is not struggling against numerous representatives of the "normal" microflora?

2. Why ISYS is not fighting against thousands paternal antigens expressed fetus?

3. If antigens which had not been presented to ISYS during early ontogenesis should be considered as ***non-self antigens***, why ISYS does not reject the lactating breast expressing a lot of milk' neo-antigens?

4. If ***the main function of the ISYS is the constant struggle*** why and how ISYS is involving in maintenance of general homeostasis, in regulation of tissue growth, reparation, and differentiation, in general morphogenesis and fetal development?

5. If any of autoreactivity is the sign of pathology, why autoantibodies and self-reactive lymphocytes presented in each healthy individual during all lifespan?

6. Restricted (microbiological) view about immunity has become a touchable obstacle now for practical introduction some new ideas and methods, related to pre-nosologic detection of different chronic diseases.

These and other "difficult questions" have been considered in the eBook. An attempt to take a look upon immunity from an unusual angle, and re-evaluate the biological meaning of the immune system from physiological point of view undertaken.

It is especially important: if we have to consider the immunity-autoimmunity phenomena from the position of physiology (see Chapter 1) – it automatically gives us a new ground for real construction of amazing building of future individualized prognostic-&-preventive medicine. Appropriately authors of each chapter of the eBook have to do somehow with the subject.

Let us touch the idea of preventive medicine shortly. It is well known that ancient Greek's God of treatment, Asclepius had two daughters – Panacea (Πανάκεια, Panakeia) – she was able to treat any disease – and Hygieia, Ὑγιεία or Hygēa (she was able to prevent any disease). According to the legend some ancient Chinese doctors had received their salary only if their patients – members of Emperor's family – were healthy, and be deprived if patients were ill. Thereby the idea of preventive medicine should not be considered only as fashionable trend of recent years. But in spite of the long history this idea remains an idea, and the main occupation of modern medicine, as well as centuries ago, is not prevention but treatment of manifesting diseases. This state is directly related to inability for ordinary physician to peep into the future of observed patient and to forecast the future disease absent now.

Do consider the typical sequence of main blocks of events leading to the disease.

1) Influence of factors/agents which may become the trigger of the disease in some conditions (will be or not potentially hazard factors initiate the disease partially related to the features of individual genotype, intensity and duration of action),

2) Compensated (pre-disease) but steady changes on the molecular level,

3) Compensated (pre-disease) but steady functional changes on level of cells populations,

4) Compensated (pre-disease) but steady morphological (structural) changes on level of cells populations,

5) Partially compensated functional and morphological changes on level of tissue/organ (first signs of the disease)

6) Stages of functional decompensation – clinically developed disease

7) Recovery with more or less full rehabilitation, or death

These stages clearly indicate for evident necessity to reveal and evaluate some defined molecular changes (the Stage-2) for maximally early prediction of high-probably future disease. While most complicated and precision technologies revealing of tissue defects may operate at the best from the Stage-4.

Many hopes of practical medicine laying for achievements of molecular genetic turned to be overestimated, mostly because great influence/contribution of epigenetic factors in the development of most of the diseases. It is not concern cohort of monogenic diseases, but total contribution of the lasts in population's morbidity, and mortality is far below of 1%. Modern genetic methods may be valuable for the evaluation of probability of heart disease, or diabetes, or epilepsy, *etc.*, expressed as individual risk level above or below of an average. However, the development of disease and the risk of disease are not considered adequate.

On the other hand, there are molecules-markers (biomarkers). Everybody is aware of such markers as abnormal blood glucose level, higher bilirubin, or steady elevated protein in urine, *etc.* Some biomarkers reflect peculiar changes in the main systems of the organism and many cases may be more robust and more certain pre-clinical indicators for the future or presenting disease.

Natural autoantibodies with certain antigen specificity may also be considered as prognostic useful and universal molecular markers. Steady changes in production and blood serum content of these molecules have been related directly with tissue damage of any origin and any location [1], and related to any (not only “autoimmune”!) presenting now or leading to the development of the disease [2].

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*Physiologic Autoimmunity and Preventive Medicine,* **2013, 3-20** 

# CHAPTER 1

# The Main Principles of Adaptive Immune System Function: Self-Recognition, Self-Interaction, and Self-Maintenance

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**Abstract:** The immune system is a natural component of and direct participant in the physiological activity of healthy organisms. The main forms of physiological activity of the immune system are based on the intrinsic abilities of self-identification, self-maintenance, self-regulation, and self-reparation – that is, on recognizing components of the "self", *i.e*., natural autoimmunity. The most ancient and homeostatically important function of natural autoimmunity is autoclearance. A multitude of immune functions, including those related to antimicrobial defense, derived from the basic function of autoclearance. Pathological processes of any kind in any organ are usually accompanied by apoptosis/necrosis of the resident cells and, accordingly, by increased extracellular concentration of intracellular components. These events induce the secondary rise in production of autoantibodies with appropriate specificity (opsonines), which provides augmentation of clearance by facilitating the efficacy of macrophage-dependent consumption of debris in the affected organ. This phenomenon is sanogenic in nature and adaptive in essence. Therefore, secondary changes in production and serum content of tissue-specific autoantibodies can be considered the universal and earliest detectable marker of any chronic disease.

**Keywords:** The Immune System, immunophysiology, innate immunity, adaptive immunity, natural autoimmunity, autoantibodies, immune autoclearance.

## THE IMMUNE SYSTEM AND MICROBES

All known eukariotic organisms, from the most primitive forms to the complex mammals, coexist with a multitude of viruses and bacteria. T- and B-lymphocytes appeared only at the later stages of evolution—from cartilaginous fishes forward [1]. Nevertheless, any multicellular organism is in constant contact with pathogenic microbes, yet effectively resistant to infection, even when lacking an

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adaptive immune system (AdIS). Therefore, it is doubtful that antimicrobial activity is the main function of the AdIS. Rather, the innate immune system (InIS), which appeared much earlier phylogenetically and is still present in superior vertebrates, is more likely to be the main antimicrobial defender. And the key mission of the "young" AdIS is self-identification and mutually coordinated adjustment of multiple cellular, subcellular, and epicellular components, as well as continuous molecular screening and participating in molecular and cellular homeostasis throughout an individual's life. While the AdIS certainly can participate in extermination of potentially dangerous microorganisms, nevertheless, this type of activity seems to be more accessory than priority.

One important feature of the interaction between the AdIS and microbes that was revealed recently is selectivity [2]. As a result of this phenomenon, homeostatically neutral microorganisms (the main component of the microbiota in host-organisms) are ignored by the immune system; the potentially useful ones are even guarded, and only those deemed hazardous become the subjects of attack [2]. This distinction by the immune system is not determined by the usual suspect - "foreignness" of microbes - but instead depends on the extent of potential danger to homeostasis in general. Mechanisms of such selectivity remain to be elucidated; regardless, noted phenomena seemingly indicate that antimicrobial activity of the immune system is not reliant solely on the "non-selfness" of microbes, as they are all aliens. Rather, it depends upon the ratio of potential "hazard" to "utility"—a reasonable criterion to use when determining an organism's needs.

## THE DESTINY OF THE ADIS

It has been known since Norbert Wiener's time that a regulatory switch can modulate the function of a complicated system only a) if provided with an internal "image" (model) of the system as a whole and b) when informed by multiple feedback mechanisms. Consequently, as one of the main participants in the control and regulation of bodily functions (neuro-immuno-endocrine regulatory meta-system [3]), the immune system, namely AdIS, needs both a model of the regulated object ("complete image" of the organism) and multiple feedback stimuli. In other words, to provide self-recognition and self-preservation, the AdIS

requires special mechanisms for the identification of the organism's native structures. The main instrument for such self-recognition is provided by the "immunculus" (or self-reactive entity), based on a complicated and interconnected network of natural autoantibodies (auto-Abs) [4]. The original idea that the immunculus served as an image of the organism's antigenic state was established by the hypothesis of an immunologic homunculus proposed by Irun Cohen [5], which was later revised [6].

In accordance with the main idea of the immunculus, the sum of natural auto-Abs with different antigenic specificities could be likened to a *sui generis* mosaic picture, formed by a great number of separate "bits of smalt". Quantitative change in each "bit of smalt" directly depends on changes in expression and secretion of according self-antigens. The immune system can use this image therefore as permanent means of constantly screening the current antigenic situation in various compartments of the body and for comparing the presented state to the desired (optimal) one. Substantial and prolonged deviations from the optimal molecular/antigenic state of an organism lead to secondary changes (deformations) in the general structure of the image/immunculus and to induction of multiple compensatory and reparation mechanisms aimed at restoring molecular and functional homeostasis. This is why the immunculus may be considered not only a passive "mirror" of the organism's condition but rather an active gyroscope-like "device", intended for maintenance of molecular/antigenic and metabolic homeostasis [6]. In addition to the network of natural auto-Abs, antigen-specific autoreactive T- and B- lymphocytes also contribute to this phenomenon. Thus, both molecular (auto-Abs) and cellular elements (autoreactive lymphocytes) are permanently present in any healthy organism throughout its life and form the interconnected system of self-recognition.

The desired, non-destructive level of physiologic autoimmunity is ensured by mechanisms that control for the state of autoimmune activity—a system of internal security. Lymphocytes that express any autoreactive receptors of too great affinity will be eliminated by negative selection, as well as lymphocytes that do not express anti-self receptors, and receptors of insufficient affinity to self-antigens (positive selection) are removed by regulatory mechanisms. Consequently, any initial clone of T- and B-lymphocytes successfully passing

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*Physiologic Autoimmunity and Preventive Medicine,* **2013, 21-45** 

# CHAPTER 2

# The Integrative (Co-Operative and Defensive) Function of the Immune System and its Role in Preventive Medicine

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**Abstract:** The goals of preventive medicine from the immunologic perspective should continue to be aimed at increasing the number of vaccinations against dangerous infectious diseases and various types of virally-induced cancer. In the future, we can perhaps hope to find treatments that would prevent rejections of transplanted organs or even cure autoimmune diseases. These hopes are justified by well-documented research of immunosuppressive regulatory cells over the past decades. However, the missing link is the way how we can control them to do what we desire in each clinical setting. So far, all we therapeutically have is still an unsatisfactory crude "off-switch" for the immune system in terms of glucocorticoid hormones or other general immunosuppressants. We need better control at both, the intracellular and extracellular therapeutic levels. The help might come if we "think" before we try novel therapies. One way how we might improve planning research and clinical trials would be to see the function of the immune system from a different perspective. Here I try to help that by discussing various suggestions about how the immune system works. My suggestion is the Integrity hypothesis, which sees the role of the immune system in checking the normalcy of tissue architecture and communication. I propose that natural cooperation exists side by side with natural selection, so that the immune system represents a search engine for potential commensal microorganisms in addition to its defensive function.

**Keywords:** Immunity, function, theory, immunoregulation, Danger, Self-nonself, Integrity, Pattern-recognition, homeostasis, commensal, symbiont, co-operativity, rejection, protection, cancer, T-cells, B-cells, APC, DC, Treg.

## INTRODUCTION

A hallmark of good preventive health care includes successful immune defenses against many infectious diseases, and conversely a tolerance of an organ transplant without affected immunity. Immunology as a science started as a wish aimed to explain physiologic processes underlying the success of first

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vaccinations by Edward Jenner over 200 years ago. Remarkably, although we know an impressive amount of details, we still wonder about the general rules that guide our immunity, and the medical profession seems to be still under the influence of the William Harvey's advice: "Don't think; try!". Have we been so lucky to discover simple ways to boost our microbial defenses by such early vaccinations? Namely, recent difficulties in preparing vaccines against for example malaria or AIDS virus just illustrate what kind of challenges may lay still ahead. It is remarkable that after many years of research we still question how the immune system should maximally damage pathogens, while minimally injuring our own tissues.

Many immunologists use words like xeno-transplantation and xeno-reactivity in describing experiments in which foreign cells, tissues and organs were used. Transplanted organs, however, will mostly be rejected by the immune system. Thus, successful transplantation still requires complete immunosuppression. And only in rare, yet unresolved circumstances would organs such as liver be accepted as if they were of self origin.

*Xeno*, a word derivative from the Greek language (*xeinos*, in old Greek), is used to mean alien, guest, or stranger. Interestingly, in the Greek version of "Odyssey" by Homer, *xeinos* was sometimes used to mean host, and even friend! This wider interpretation has interesting parallelism with theories about the function of the immune system - especially the recent ones like Stranger [1-3], Danger [4-8] and Integrity [9-13]. The goal of immunologists is to succeed in creating an organ transplant such that the foreign tissue can be accepted as a friendly well-integrated guest, never becoming a dangerous stranger; and all this with an uncompromised defense system.

In order to achieve this goal, we must first have in depth understanding of the molecular and cellular foundations of the immune system in humans. I believe that the current foundation (Self-Nonself discrimination theory [14-24]) - which is claimed to be the simplest explanation of the function of the immune system - is in fact an oversimplification, and I will try to persuade the reader about it in the current article. My solution is the Integrity hypothesis, which, in addition to the known function in defense, proposes that the immune system provides an "asylum" to potential commensal microorganisms [11].

The main reason for not knowing how to control the regulatory cells is insufficient knowledge, probably, as a consequence of not doing the proper experiment. We are doing it the hard way – by brute force: *i.e.* sequencing all genes, analyzing all possible cellular functions in various circumstances, hoping that eventually someone will get the right idea on how to handle the immune system. Can we take a short cut? Yes, we can, and we could be inspired by experiments based on new hypotheses. Firstly, the Stranger theory [1] hoped to identify pathogenic identity as a characteristic feature of microorganisms dividing them into harmful and non-harmful micro-aliens. That is difficult to understand as different species have different pathogens. Thus, pathogenicity is a relative feature in nature. Yet, there are molecular patterns characteristic for pathogens of a particular species. This is important information for an organism that is in dire need to be defended. Discriminating between pathogenic or non-pathogenic species is, I believe, too complicated to be solely explained by the self-nonself discrimination principle. Furthermore, there is basically no need to accommodate the existence of suppressor (regulatory) cells in making a difference between pathogens and harmless species of microorganisms by the immune system. If we increase the complexity of the system with a new theory, then we can possibly include them (as their existence is experimentally documented). The Danger theory [4] aimed at such a goal, suggesting that the local immune-cell environment contributes to the regulation of immune response [7]. I would suggest even going one step further with the Integrity hypothesis: namely, the co-operative function of the system should be included. This could be achieved by a cross-talk between cells of the innate and adaptive immunity that effectively make decisions whether to reject, neglect or protect a microorganism that penetrates our body. We understand quite a bit of the rejection mechanism, which is the immune response or defense. Neglection and protection is sparsely documented, but in it we could find a place for regulatory cells that can protect useful commensals and (“decide” to) neglect irrelevant ones [11].

The Integrity hypothesis was built on top of Danger [4] and Stranger [1] theories and these in turn used the legacy of Self-Nonself discrimination theory [14, 17, 19, 20]. These 'newcomers' aim to “fine tune” scientific research about cellular signaling and homeostatic factors. They could lead us to find how to control the

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# CHAPTER 3

# The Hallmarks of Physiologic Antibody Immunity in Cardiac Diseases and its Impact to Personalized Medicine

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**Abstract:** Immune system plays a great physiological role in maintaining of heart tissue homeostasis. This concerns numerous proteins, expressed in myocardium in norm (heart proteomics) and, of course, their "fingerprints" in mirror of immunculus (heart immunomics of main immunogenic region B-epitopes). In this chapter we tried to reveal the problem of cardiac specific proteins, their impact in heart physiology and local autoimmunity, the mechanisms of their formation and approaches for highly specific immunotherapy, based on their profiles in dynamics of pharmacological treatment. Here we discuss implications of antibody therapy and antibody elimination, peptide therapy and immunomodulation under guidance of physiological immunity, partially based on recently received data.

**Keywords**: Cardiology, inflammatory heart diseases, heart proteomics, heart immunomics, B-epitope, antibody profiles, preventive medicine.

## CONTEMPORARY ISSUES OF DIAGNOSTICS IN CLINICAL CARDIOLOGY

Diagnostical algorithm of study the patients with recently originated congestive heart failure (CHF) demands exclusion of the inflammatory nature of myocardial lesion. Considering that the myocarditis is, first of all, morphological diagnosis, verification of endomyocardial biopsy is necessary. Traditional intravital morphological diagnostics is based on analysis of 4-6 biopsy samples. But only the usage of 17 biopsy samples gives correct diagnosis in 80% of cases, that is possible only postmortem [1, 2].

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But not only the number of endomyocardial biopsies complicates diagnostics of myocarditis. It should be noted that the signs of chronic inflammation were detected as in dilated cardiomyopathy (DCM) and myocarditis. For example, T-lymphocyte infiltration is found in up to 48% of cases with DCM [3].

There are similar pathways of pathogenesis activation *via* viral, bacterial and immune-mediated triggers. Besides, circulating antibodies are found in both pathologies. IgG antibodies giving a diffuse cytoplasmic staining pattern of myocytes, and a negative pattern on skeletal muscle, were found in about one-third of myocarditis/DCM patients and their symptom-free family members [4]. Heart Failure Association of the European Society of Cardiology in 2009 organized an expert workshop, where immune alterations were mentioned among principal goals for further investigations [5]. Some authors propose that myocarditis and DCM may represent different consequent stages of carditropic autoimmune disease based on the model of AAB response to cardiac myosin [6], presenting deviations from normal level.

## HEART EPIGENETICS AND PROTEOMICS IN PHYSIOLOGICAL NORM

Russian cardiologist Kovalyov was the first scientist to make heart proteomics [7]. There were found 312 abundant proteins, 40 of them were identified [8]. Each protein was characterized according to several parameters, including molecular weight, isoelectric point, name, partial sequence, subcellular localization, and genetic as well as embryonic changes.

Since then important proteomic data was obtained by McKenna, Van Eyk, Muller-Werdan, Goette, Choong-Chin Liew [4, 9-12] and others.

Changes to the cardiovascular system arise from or have the potential to alter, collectively or individually, proteomes of cardiac muscle and components of the vascular system, including smooth muscle and endothelial cells [9]. Traditional proteomic methods of mapping and identifying proteins give researchers the ability to develop protein databases. Global changes may be identified by protein profiling by comparison to either experimental controls or protein databases or

both. Modified proteins are identified, as is the nature of each modification, and in some cases, the actual site of these modifications may be determined. The next logical step would be to link information about proteome changes directly to functional consequences of these changes.

Many of these advances, however, are contributing toward improved reliability of 2-D gel protein databases. Pioneering proteomic work by the laboratories of Dunn and Jungblut led to the creation of numerous online 2-D databases of human, dog, mouse, and rat myocardium [9]. They are only partially complete (with roughly 200 proteins identified), but they provide a foundation for the inventory of these particular tissues. These freely accessible works in progress are tremendously important, because they provide researchers with a basis for visualization of changes in protein patterns resulting from the conditions of their particular study. For proteomics to fulfill its potential, comprehensive protein inventories must be prepared for the variety of species and tissues studied in cardiovascular research, and they must remain freely accessible.

In some cases protein identification is not so principal as tissue protein profiling. Simply monitoring a protein profile after resolution by one or more separation methods is often sufficient to address whether two or more experimental conditions induce the same protein changes. This is advantageous when determining, for example, molecular pathways of action by multiple drugs in pharmaceutical drug discovery programs. Direct comparison of their protein profiles or "protein signatures" facilitates rapid screening of differences between various treatments without an absolute necessity for protein identification [13].

Several studies were produced to find proteomic markers for various types of cardiac pathology.

## HEART EPIGENETICS AND PROTEOMICS IN DIAGNOSTICS OF INFLAMMATORY AND DEGENERATIVE DISEASES OF MYOCARDIUM

Although traditional proteomics and protein profiling provide important research information, the ultimate goal of developing proteomic techniques for

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# CHAPTER 4

# Autoimmunity *vs.* Autoallergy in Immunoneuroendocrine Regulation and Dysregulation

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**Abstract:** Autoimmunity and its contradictory nature in autopathokinesis have drawn attention from the emergence of immunology as a science. The properties of antibodies towards nuclear antigens of endocrine cells are both theoretically and clinically hot topics as are their applications in the modulation of genetically determined cell functions. In this chapter we discuss the history of physiological autoimmunity concept, the difference and borders between physiological *autoimmunity* and pathological *autoallergy*, regulatory potential of the first and pathogenic implications of the last one. The review of our data on antibody production after immunization of animals with some nuclear antigens is given, characterizing their properties and the mechanisms of their intracellular penetration and association with nuclear targets. There are data on the presence of similar autoantigens and corresponding autoantibodies in the blood sera of intacts. The antibodies towards chromatin components appear to be able to penetrate into the nuclei of the endocrine cells and act there through mechanism(s) different from hormonal regulators, at least in adrenals. They stimulate or inhibit proliferation, translation and transcription, hormone biosynthesis in target cells. This suggests that autoimmunity is one of the mechanisms in the physiological regulation of cellular morphogenesis and genetically determined functions. Physiological autoimmunity thus contributes to the bringing-together and co-tuning of genetic information reading, adaptive immune system is regarded as a tool for self-construction of multicellular organism and for support of multicellularity. At the same time, however, the literature on autoimmunity has mostly been concentrated on eliciting a particular disease only. Special reconsideration of these statements is given, the concept of Immunacea is coined, immunoneuroendocrine regulatory meta-system is reviewed, penetration of antibodies into living cells is discussed, some aspects of fetal-maternal immune relations are considered, and link of human microbiome to autoimmunity is emphasized.

**Keywords:** Autoimmunity, autoallergy, counter-immune response, endocrinopathies, immunoneuroendocrine meta-system, Immunacea, intracellular

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penetration of antibodies, Hashimoto's disease, marfanoid phenotype, microbiome, pregmunity, prolactin, receptor-agonistic autoantibodies, self-tolerance.

## INTRODUCTION

Autoimmune response permanently attracted the attention of pathophysiologists from the very first steps of Immunology because the phenomenon of autoimmunity comprises in itself the key contradiction of Pathophysiology as a science. Autoimmunity is the phenomenon brightly expressing the unity, mutual penetration and relativity of injury and defense. It concentrates the idea of *autopathokinesis* or disease self-driving due to imperfection of defense, which is highly meaningful for the whole science of Pathology. The first autoimmune endocrine disorder (struma lymphomatosa or chronic autoimmune thyroiditis - AIT) was described by Hakaru Hashimoto 100 years ago, in 1912 [1]. To that moment I.I. Mechnikov's school already coined an idea of endocrine cell regulation by means of antibodies ("*cytotoxins*") [2-4].

## FROM "PHYSIOLOGICAL INFLAMMATION" TO AUTOIMMUNE SELF-REGULATION

Even until now in the world literature autoimmunity is often considered just as a pathological mechanism able to elicit some kind of disease. For a long time, practically, from the moment of its origination, the classical Immunology, addressing to the problem of autoimmunity, was restrained with the principle of «Horror autotoxicus», attributed to Paul Ehrlich and Julius Morgenroth [5]. This concept claims that no antibodies can be formed against self components in a healthy organism. Such a view was in contradiction with the evolutionary concept of immunity, formulated by I.I. Mechnikov (1845-1916), who from the very beginning of Immunology, interpreted the role and function of immune cells much broader, then just responsibilities of gendarmes or border guards aimed exclusively on the aliens. Contemporaries of Mechnikov, which co-authored with him the essentials of new science, mostly microbiologists or immunochemists by their interests, insisted on this "anti-alien" priority [6]. But as early as in 1892 I.I. Mechnikov published small paper on the existence of Darwinian struggle "within

a body", *i.e.* between cellular elements of the same Metazoan organism [7]. According his idea, immunity and specialized cells, responsible for it, are evolutionary required first of all not as warriors against aliens, but in order to keep peace within own body of an individual, by means of harmonization of the contradictions between elements of self. In this fruitful concept immune system looks like product of inherent imperfection of the body and serves for permanent self–construction and remodeling of multicellular self organism in ontogenesis, by means of "physiological inflammation" or (as it was named later by I.I. Mechnikov and his pupils) – "natural autoimmunity" (Fig. **1**) [2, 7–8].

We feel some resemblance between this early Mechnikov's idea and recent concept of Integrity coined by Z. Dembić (see Chapter 2); especially regarding his assumption that similar molecular signals regulate the response of immune cells and establish intercellular assembly in multicellular tissues of Metazoa.

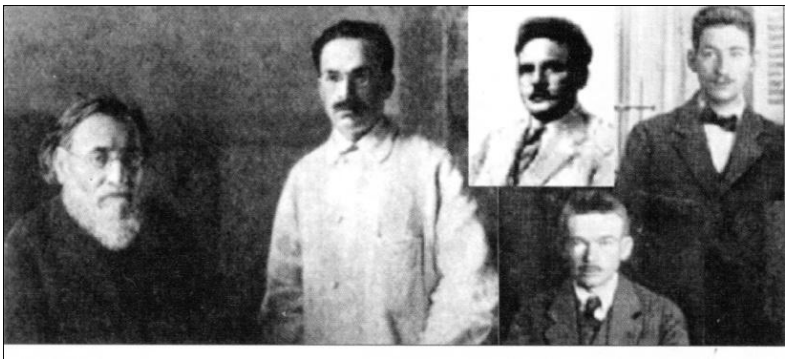

**Figure 1:** Founders of physiological autoimmunity theory, left to right: Ilya Il'ich Mechnikov and his pupils: Alexandr Mikhailovich Bezredka, Yefim Semyonovich London (portrait), Alexandr Alexandrovich Bogomolets (sitting) and Leonid Ruvimovich Perel'man. Photo-montage from [28]: Here and everywhere below reproduced from original publication by permission of its editor-in-chief.

Almost immediately after the declaration of "*Horror autotoxicus*" principle, I.I. Mechnikov's disciple Ye. S. London (1869-1938) [3] as well as P. Uhlenhuth [9] have obtained under experimental condition autoantibodies, accordingly, against sperm and a crystalline lens. Another Mechnikov's pupil A.M. Besredka has found natural antibodies towards self red blood cells [10]. Few years later, K. Landsteiner and J. Donath have described the very first human autoimmune disease – *paroxysmal cold anemia-hemoglobinuria* [11].

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*Physiologic Autoimmunity and Preventive Medicine*, **2013, 167-198** 

# CHAPTER 5

# Autoimmune Phenomena through the View of Predictive, Preventive and Personalized Medicine

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**Abstract:** Type 1 diabetes (T1D) is a severe autoimmune disease characterized by the destruction of the pancreatic beta-cells. The genetic predisposition to T1D and a vast variety of triggering factors initiate autoimmune processes culminating in the appearance of autoantibodies (autoAbs). The destruction of β-cells of the islets of Langerhans occurs as a result of infiltration of immune system cells. The metabolic changes, the activity of autoantibodies and the protein and genetic markers are considered as the predictors of insulin dependent diabetes mellitus 1(IDDM 1). Multiple sclerosis (MS) is an autoimmune disease characterized by the progression of neurological disturbances which result from the interaction between the processes of inflammation and neurodegeneration. The estimated median incidence of MS worldwide is 2.5 per 100,000, and prevalence is estimated at approximately 1.5 million cases. The onset of MS usually falls at the age between 20 and 40. Women are affected approximately twice as often as men [1]. Preventive medicine and predictive medicine are understood as a complex of measures, aimed at prevention and prediction of diseases, as against the therapeutical and palliative medicine, which remedy disorders or treating their symptoms. The basic methods of the preventive medicine are subclinical diagnostics, using the molecular approaches. Such diagnostics are based on the detection of bioindicators of hidden pathology long before the actual manifestation of symptoms of the disease. Genomics, proteomics and cytomics are the basic methods of prediction, which help to estimate susceptibility to diseases and prevent them.

**Keywords:** Autoimmune disorders, Multiple sclerosis, Type 1 diabetes, autoantibodies, genomics, HLA genes, diagnostics, proteomics, prediction, metabolites.

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## 1. INTRODUCTION

An autoimmune disorder is a malfunction of immune system that causes the body to attack its own organs, tissues and cells. There are actually millions of people suffering from autoimmune diseases worldwide and the prevalence is rising, for example, autoimmune diseases affect approximately 5 percent of the population in Western countries, that illustrate a fascinating but poorly understood group of disorders [2].

In this review, we define an autoimmune disease as a clinical syndrome caused by the activation of T cells or B cells, or both, in the absence of (known as *autoimmune syndrome*) or under the pressure of an ongoing infection (known as *postinfectious autoimmune syndrome/PIFAS*).

Etiology of autoimmune disorder is diverse and symptoms vary greatly depending on which disorder develops and which part of the body is affected. Infections can induce autoimmune diseases and PIFAS, in particular, in several experimental settings, some of which have clinical counterparts. A variety of mechanisms have been invoked to explain these observations, including *molecular mimicry* and an increase in the immunogenicity of autoantigens caused by inflammation in the targeted organ or targeted tissue [3]. Over 80 clinically distinct autoimmune disorders are known and the most common include T1D, systemic lupus erythematosus (SLE), Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purpura, myasthenia gravis, rheumatoid arthritis, *etc.* We will consider genetic susceptibility to autoimmune disease, some of the environmental and internal triggers of autoreactivity, changes in pathologic processes as the disease progresses, and selected mechanisms of tissue injury to generate a chronic autoimmune inflammation to demand for the updated and newer therapeutic approaches.

The problem of autoimmunity and autoimmune disorders now becomes one of the main reasons of the healthcare spending. The development of subclinical diagnostic algorithms of diagnostic and monitoring of autoimmune diseases will play significant role in screening and identifying targeted tissue or organ defects at the stages when the defects would be still reversible.

Since there is no fundamental difference between the structure of self antigens (or autoantigens) and that of foreign antigens, lymphocytes evolved not to distinguish self from foreign, as some have speculated, but to respond to antigen only in certain microenvironments, generally in the presence of inflammatory cytokines [4]. Since autoreactivity is physiologic, the challenge is to understand how it becomes a pathologic process and how immune-related molecular and cellular tools contribute to tissue injury. For clinicians, autoimmune diseases appear to be either systemic (as in the case of SLE or rheumatoid arthritis/RA), or tissue-specific (or disseminated like MS), or organ-specific (as in the case of T1D). This classification is useful in deciding on therapy, which may differ according to the pathogenic mechanism. In some organ-specific or tissue-specific diseases, autoreactivity against a ubiquitous (organ-specific or tissue-specific) autoantigen develops, but the disease is restricted to a particular organ (like autoimmune myocarditis/AIM or autoimmune thyroiditis/AIT) or a tissue (T1D or MS). Presumably, the autoantigen has greater accessibility in affected tissues, although the patterns of lymphocyte migration may also determine sites of inflammation [5]. In this review, we would focus on two broadly known clinical models of autoimmunity, both are tissue-specific autoimmune disorders provoked mostly by the initial PIFAS, *i.e.*, T1D and MS.

T1D is an autoimmune, chronic, multifactorial disease characterized by the destruction of the pancreatic beta-cells associated with appearance of autoAbs and infiltration of the pancreas with self-reactive T cells. The destruction of the pancreatic beta-cells leads to high glucose levels in blood (hyperglycemia) and systemic metabolic and immune-related failures [6,7]. Epidemiologic studies have demonstrated that genetic factors are crucial determinants of susceptibility to T1D. There are plenty of triggering factors, which initiate autoimmune processes in individuals with genetic predisposition to T1D. Most variants of T1D are multigenic, with multiple susceptibility genes working in concert to produce the abnormal phenotype. Some of these genes confer a much higher level of risk than others; for example, the major histocompatibility complex (MHC/HLA) makes an important contribution to T1D susceptibility. Since Charcot first described MS as a clinical entity in 1868, attempts have been made to identify factors underlying the development of the disease. Studies of twins, adopted children, and the

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*Physiologic Autoimmunity and Preventive Medicine,* **2013, 199-207** 

# CHAPTER 6

## Autoantibodies: Serum Content or Profiles?

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**Abstract:** "…The initial paradigm "one autoantibody for one disease" does not appear to be useful any longer. An autoantibody profile does seem to offer more diagnostic and prognostic power than the determination of single autoantibody specificity" (P-L. Meroni). Why is it so? Fruitfulness of the idea for identification of autoantibody depends on reactivity patterns (autoantibody signatures or profiles) illustrated by analyses of few examples where clinical and laboratory symptoms corresponded to changes in profiles of serum auto-Abs and mismatched to single auto-Ab serum evaluation. Author proposes that future "mapping" repertoires of thousands of natural auto-Abs as the profiles will lead to the appearance of principally new technologies in clinical as well as pre-clinical diagnosis of different chronic diseases.

**Keywords:** Natural autoimmunity, immune network, serum autoantibodies, laboratory diagnostic, profiles of autoantibodies.

### WHICH INFORMATION MAY BE OBTAINED FROM THE ANALYSIS OF SERUM PROFILES OF AUTOANTIBODIES?

Evaluation of human autoantibodies (auto-Ab) with different antigen specificity has been carried out around the world in a large number of clinical laboratories. The specialized kits for an assessment of blood serum content of auto-Ab against DNA, cardiolipin, beta2-glycoprotein I, collagen, thyroglobulin, *etc.*, were provided by dozens of companies. All commercially offered kits intended for detection of separate auto-Ab in serum samples are considered as markers of certain autoimmune diseases. However, our practice as well as observations of our colleagues, indicate that this approach may be ground for incorrect clinical conclusions. The serum auto-Abs investigated in patients with immunodeficiency

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or with polyclonal immune activation may lead to arraneous results more often. In contrast, analysis of changes in a relative ratio of different auto-Abs (*i.e.*, profiles of serum immune reactivity of investigating person) can provide an objective assessment of the clinical picture regardless of whether patient under observation manifests an immunodeficiency, immune activation or exhibits a normal immune reactivity. This approach was applied for methods of the ELI-Test group (Abbreviation from Enzyme-Linked-Immuno-Tests), which elaborated, on the investigation of health state of the population of radioactive polluted areas soon after Chernobyl Disaster (1986). Now ELI-Tests have successfully been applied in Russia for the routine clinical investigation of auto-Abs in patient's blood serum for diagnostic and prognostic needs [1, 2]. These methods provide the possibility to analyze individual profiles of some dozen markers of auto-Abs of IgG class present in serum samples.

Let us consider some of the clinical cases observed in our laboratory.

*Case 1*. Pregnant woman 32 years old, clinically healthy; third pregnancy; clinical signs of a possibility of miscarriage had appeared at 4-5 weeks of gestation. abnormal rise was observed in her blood coagulation (hypercoagulation) already applied during additional investigation. Also noted was the deterioration of placental blood flow. In spite of already applied treatment, the spontaneous interruption of her pregnancy took place at 12-13 weeks of pregnancy. Clinical and laboratory data were typical for antiphospholipid syndrome (APS), but only low serum levels of auto-Abs against cardiolipin and against β2-Glycoprotein-I were found during repeated investigations of blood serum at 6 and 10 weeks of pregnancy by standard ELISA Kits ("Orgentec", Germany). In contrast, abnormal rise of auto-Abs against β2-Glycoprotein-I (that is a marker sign of APS) was revealed when changes in the relative content (profiles) of multiple auto-Abs were analyzed by ELI-Tests technology instead of a separate evaluation of auto-Abs against cardiolipin and β2-Glycoprotein-I in the serum sample. In this case, the relative elevation of auto-Abs against β2-Glycoprotein-I had manifested in a woman with prominent immune suppression. Which in principle, could not be revealed using standard kits.

Clinical conclusion. The Pregnant woman was characterized by symptomatology as a typical case for antiphospholipid syndrome. This diagnosis was confirmed by

data about the relative rise of level of auto-Abs against β2-Glycoprotein-I in her blood serum sample comparing to many other natural auto-Abs. Common immunochemical methods of analyzing the serum auto-Abs to cardiolipin and β2-Glycoprotein-I were not informative (*i.e.* marker signs of APS were not found) because prominent immune suppression observed in woman.

*Case 2*. Male 52 years old; main complaints during the visit to a physician were "heavy head", headache and muscular pain during the last 2 or 3 days; body's temperature was in normal range. A day before he applied to a laboratory for investigation of serum level of antibodies against DNA because of being "*afraid of the inheritable risk of SLE in his case"*. An official laboratory conclusion was presented. In accordance to the conclusion, serum level of IgG auto-Abs against dsDNA was found to have been elevated significantly. Profiles of 24 IgG auto-Abs with different antigen specificity were analyzed in his serum sample by means of ELI-Viscero-Test Kit and specialized PC software ("Immunculus", Russia). Elevation of immune reactivity of auto-Abs against dsDNA was not evidenced in profiles. Small relative elevation of immune reactivity of ANCA (a marker of small vessels vasculitis) and auto-Abs against liver mitochondrial antigens were noted in profiles. Important feature was general immune activation reflected by the rise of production and level of many auto-Abs with different specificity. Acute viral infection was found to have been (infectious mononucleosis) developed clinically in patient few days later. It may be assumed that anti-dsDNA antibodies and profiles of 24 IgG auto-Abs (including auto-Abs to DNA) can be measured by ELISA in patient serum samples obtained during the prodromal period of acute viral infection.

Clinical conclusion. Clinical and laboratory data indicate generalized immune activation in patient's organism, related to acute viral infection, accompanied by polyclonal immune activation and elevated production of numerous auto-Abs with different antigen specificity, including auto-Abs against DNA.

Both examples clearly illustrate the restrictions related to the evaluation of the serum content of the auto-Abs with any separate antigen specificity. Measurement of separate auto-Abs content may provide clinically reliable information if the individual activity of the immune system is normal. In contrast, it is applicable to

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# CHAPTER 7

# Autoimmune Thyroiditis: A New Comorbidity of the Most Prevalent Endocrine Disease, Its Prevention and Prediction

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**Abstract:** Hashimoto's thyroiditis as most prevalent autoimmune endocrine disorder of nowadays is detailed, with data on its natural history, etiology, pathogenesis and co-morbidity. A review of authors' original papers is given, establishing the clinical pathophysiological hypothesis, initially coined in 2002, about regular transition of adolescent hypothalamic syndrome (obesity with rose striae) with age into early metabolic syndrome, complicated by autoimmune thyroiditis. Some evidences are obtained, that witness for marfanoid phenotype and chronic disequilibrium between local, autacoid-mediated and systemic, hormone-mediated regulation, typical for inherited connective tissue disorders, may promote this transition. Pathogenetic role of hyperprolactinemia and cytokine misbalance in transition of physiologic anti-thyroid autoimmunity into autoallergic disease is evaluated. Prevention, early recognition and prediction of autoimmune thyroiditis course, as well as preventive treatment of its complications are reviewed.

**Keywords:** Aging, adolescents, adiponectin, autoimmune thyroiditis, cytokines, Dupuytren's contracture, Hashimoto's disease, hypothyroidism, iodine, leptin, marfanoid phenotype, Marfan syndrome, metabolic syndrome, obesity, prevention, prolactin, rose striae, Simpson-Page syndrome, transforming growth factor.

## INTRODUCTION

It has been repeatedly noticed in the history of medicine that a disease initially considered being rare or endemic, with time appeared to be universally spread and socially important. One of the example is HIV infection, which was proposed to call "4 H's syndrome" in 1983, when its nature was still unknown (its first victims

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were Haitians, homosexuals, hemophiliacs and heroin addicts only) [1].

Autoimmune thyroiditis (AIT) can be regarded as the unique non-infectious example of this kind, described as a rare endemic thyroid ailment 100 years ago [2], and nowadays appeared to be, probably, most universally spread human auto-allergic disease, one of the most acute problems for preventive medicine.

## Centenary of Hashimoto's Disease

The very first proven antibody-mediated auto-allergic human disorder was described just 8 years before AIT [3]. To that moment the concepts of humoral and cellular immunity were newborn, a role of plasma cells, recently found by P.G. Unna [4], as a source of antibodies was not known, the existence of T-lymphocytes was not even supposed. At the same time, an outstanding Russian pathophysiologist, many times credited above (see Chapter 4) – Ye.S. London (1904) already suggested the unitary theory of humoral and cellular immunity, postulating that both have the same source [5]. Thyroidology to that moment already had like 75 years of development passed as an area of clinical medicine, but absolutely irrelevant to Immunology. Diffuse toxic goiter was known [6] and related to nervous disorders, although more than half a century still had to pass before the future discovery of thyroid-stimulating antibodies [7]. Thanks to research of newly (1909) Nobel-crowned E. Th. Kocher, the concept of iodine-deficient etiology of endemic goiter, earlier suggested by G.A. Chatin, has got a broad recognition [8, 9]. But the pathologists knew colloid goiter only, resulted from thyroid hyperplasia in lack of iodine. Yet, goiter was common in some areas, where iodine deficit could not exist at all: for example, on Kyushu island of Japan, famous for the birthplaces of iodine-containing mineral deposits and for seafood attraction of its inhabitants.

A young surgeon, Hakaru Hashimoto (1881-1934) together with Prof. Sakurai (histologist) and Prof. Nakayama (pathologist) during 1907-1910 took part in pathohistological studies of partially removed thyroid glands. Hakaru was medical doctor in 3$^{rd}$ generation (Fig. **1**), the first graduate from recently established Kyushu Imperial University at Fukuoka and clinical resident of the first Japanese neurosurgeon, pupil of Jan Mikulicz-Radecky, Hayari Miyake (1867-1945).

**Figure 1:** Hakaru Hashimoto in the year of his discovery (1912); courtesy of Dr. Hiroshi Satoh, Kyushu University.

In 4 women of middle age (2 of them suffered from hypothyroidism) he found in thyroid glands the unknown pathomorphological signs [2]. H. Hashimoto has noticed that in difference with common colloid goiter, these thyroid specimens contained local infiltrates with lymphoid and plasma cells. Formation of lymphoid follicles started from germinal centers. The author has depicted the changes of thyrocytes with marked diffuse fibrosis around the lymphoid follicles, giant eosinophilic cells and even lymphatic vessels, newly structured within thyroid gland. The picture did not fit with the diagnosis of Graves' disease, von Mikulicz's disease, Riedel's chronic thyroiditis, infectious thyroid involvement. By the way, normally lymphocytes are very rare in thyroid parenchyma [10]. Earlier the findings like this were never mentioned. Hashimoto prophetically concluded that there must be some exogenous factor, provoking accumulation of lymphocytes in thyroid. He was sure in discovery of a new disease and called it "lymphomatous goiter" (lat.: struma lymphomatosa). The results of his

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