

Professor Shoenfeld's Mosaic of Life and Kaleidoscope of Research

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Мозаика жизни и калейдоскоп научных исследований профессора Шенфельда

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Summary

This article presents the biographical data of Professor Shoenfeld, the features of his scientific path, and the scope of his professional interests, which can be useful as an example of professionalism, professional dedication and passion for young Russian doctors and scientists. Professor Yehuda Shoenfeld is a world-renowned scientist, specializing in the field of Autoimmunity. He is a member of the editorial boards of 42 journals and an author of 2058 articles on various aspects of medicine. Y. Shoenfeld is an honorary professor at several European universities, his exceptional contribution to medical science has been marked by numerous awards. The article also contains data on the cooperation of the professor with the St. Petersburg State University, the creation of the laboratory of Mosaic of Autoimmunity and the work within this scientific collaboration.

Key words: Yehuda Shoenfeld, autoimmune disease, ASIA syndrome, antiphospholipid syndrome, systemic lupus erythematosus, helminths, laboratory of Mosaic of Autoimmunity

Резюме

В этой статье представлена биография профессора Шенфельда, особенности его научного пути и сферы его профессиональных интересов, которые могут быть полезны в качестве примера профессионализма, профессиональной самоотдачи и увлеченности для российских врачей и ученых. Профессор Иегуда Шенфельд — всемирно известный ученый, специализирующийся в области аутоиммунитета. Он является членом редколлегий 42 журналов и автором 2058 статей по различным аспектам медицины, почетным профессором нескольких европейских университе-

тов. Его выдающийся вклад в медицинскую науку отмечен многочисленными наградами. В статье также содержатся данные о сотрудничестве профессора с Санкт-Петербургским государственным университетом, создании лаборатории мозаики аутоиммунитета и работе в рамках этого научного сотрудничества.

Since 2017 Professor Yehuda Shoenfeld has headed the first laboratory of Mosaic of Autoimmunity at the St. Petersburg State University, Russia. The laboratory was organized with the support of the grant of the Government of the Russian Federation (contract 14.W03.31.0009 form February 13, 2017) on the allocation of a grant for state support of scientific research performed under the guidance of leading scientists.

Professor Yehuda Shoenfeld is a founder and director of the Zabudovich Center for Autoimmune Diseases (Sheba Medical Center, Tel Aviv, Israel), Head of the Laura Schwarz-Kipp Department for the Study of Autoimmune Diseases (Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel).

Y. Shoenfeld is the undisputed world leader in the field of one of the newest medical disciplines — Autoimmunology, which is being developed with his active and significant participation. He is the author of 2058 articles, including many papers published in leading world journals such as "the New England Journal of Medicine", "Nature", "Lancet", "PNAS USA", "Journal of Clinical Investigation", "Journal of Immunology", "Blood", "FASEB", "Journal of Experimental Medicine", "Circulation", "Cancer", "Clinical Reports" and others. He is an author and editor of 62 books, including the classic editions of the "Mosaic of Autoimmunity", "Infections and Autoimmunity", studied by physicians all over the world, and the textbooks "Autoantibodies" and "Diagnostic Criteria for Autoimmune Diseases", released by leading world publishers such as Elsevier and Wiley Blackwell. In 158 books, the professor is the author of certain chapters. Under the guidance of Professor Y. Shoenfeld, 15 patents were issued for the diagnosis and treatment of not only autoimmune diseases but also oncology and several others.

The professor is a member of the editorial boards of 42 journals in the field of rheumatology and autoimmunity, internal diseases, pediatrics, experimental and clinical pathology. He is the founder and editor of the leading Israeli medical journal in English — Israel Medical Association Journal (IMAJ), and also the co-founder and co-editor of the most influential autoimmunity journals — Autoimmunity Reviews (impact factor 8.745) and the Journal of Autoimmunity (impact factor 7.6). For the last twenty years, Professor Shoenfeld has been the editor-in-chief of Harefuah (the leading Israeli medical journal in Hebrew), and the Israeli Medical Encyclopedia (10 volumes,

Ключевые слова: Иегуда Шенфельд, аутоиммунное заболевание, синдром ASIA, антифосфолипидный синдром, системная красная волчанка, гельминты, лаборатория мозаики аутоиммунитета



Prof. Yehuda Shoenfeld

5000 articles). The professor organized almost 60 international congresses on autoimmune diseases and rheumatology in various countries, including Russia.

Y. Shoenfeld is a Doctor of Medicine, Master of Clinical Research, a member of more than twenty scientific and professional societies from different countries and regions, uniting specialists in immunology, oncology, rheumatology, internal diseases, physiology, pharmacology, and vaccination. In some of them, he is a member for more than 45 years. He is an honorary member of the British Royal College of Physicians and Master of the American College of Rheumatology. In 2004, Professor Y. Shoenfeld was awarded the Carol Nachman Prize for the outstanding innovative research in the field of clinical and experimental rheumatology. He is an honorary member of the Hungarian Association of Rheumatology, the Society of Rheumatology of Argentina and Mexico, the Slovenian Academy of Sciences and Arts and the New York Academy of Sciences, an honorary doctor of the universities of Debrecen (Hungary), Pleven (Bulgaria) and Hasselt (Belgium), honorary professor of the universities of Ljubljana (Slovenia) and Alt-Herborn (Germany). Professor Y. Shoenfeld was awarded the gold medal of the Slovak Society of Physicians, the Nelson Prize in Humanities at the University of California, the European League against Rheumatism Award for the disclosure of the most

important aspects of the etiology and pathogenesis of the antiphospholipid syndrome (APS), as well as the Israeli Prizes for the “Contribution to the Development of Medical Hebrew”, “OMETZ for Outstanding Contribution to Medicine”, and for the “Outstanding Contribution to Science throughout Life — in the field of internal diseases”. In May 2019 Professor Shoenfeld has elected to be the full member of Israeli Academy of Science, which includes 13 Nobel Prize winners.

Today, according to the Scopus database, Professor Y. Shoenfeld’s Hirsch Index is considered to be 107 (<https://www.scopus.com/authid/detail.uri?authorId=36879964800>), which represents not only the huge amount of his scientific work but also the incredible demand and relevance of the published data.

Considering the diversity of scientific research of Professor Y. Shoenfeld from the beginning of his scientific career to the present days, it is difficult to find a system or an organ, the study of which the scientist would not pay tribute. He is one of the most renown clinical pathophysiologists and immunologists of our time.

The most significant directions of research of Professor Y. Shoenfeld are presented in Figure 1.

Professor Shoenfeld was born in 1948 in the family of a lawyer in the Slovak city of Topolcany (then — Czechoslovakia). Shortly after his birth, his parents moved to the newly created State of Israel, where Y. Shoenfeld graduated from school and in 1965 entered the medical faculty

of the Hebrew University of Jerusalem. From this moment on, the mosaic of life and the kaleidoscope of scientific research by Professor Y. Shoenfeld began to take shape.

His life as a researcher can be divided into periods. Being a university student, then a doctor, paratrooper and a military doctor, resident doctor, head of the clinical department and head of the medical center, he did not interrupt scientific research and made a number of world-famous discoveries (Fig. 2).

The first period (1965–1972) was dedicated to the university studies and military service, where a student, and then as paratrooper and a military doctor performed his first studies on osteogenesis imperfecta, cancer treatment, issues of military health, sport and extreme medicine, professional overload and the occurrence of asthenia, rehabilitation methods, etc. His papers of this period were widely accepted, and their high scientific level may, for example, be shown by the fact that his publications on the health issues of saunas are widely cited even in the homeland of this rehabilitation method in Finland.

Y. Shoenfeld successfully graduated from the Medical Faculty of the Hebrew University in Jerusalem and defended his dissertation “Osteogenesis Imperfecta” (1972) under the guidance of Professor A. Fried.

The second period of the scientific career of Y. Shoenfeld (1973–1984) was associated with postgraduate education and advanced training in Israel (Tel Aviv University and Beilinson Medical Center in Petah-Tikva) and in the

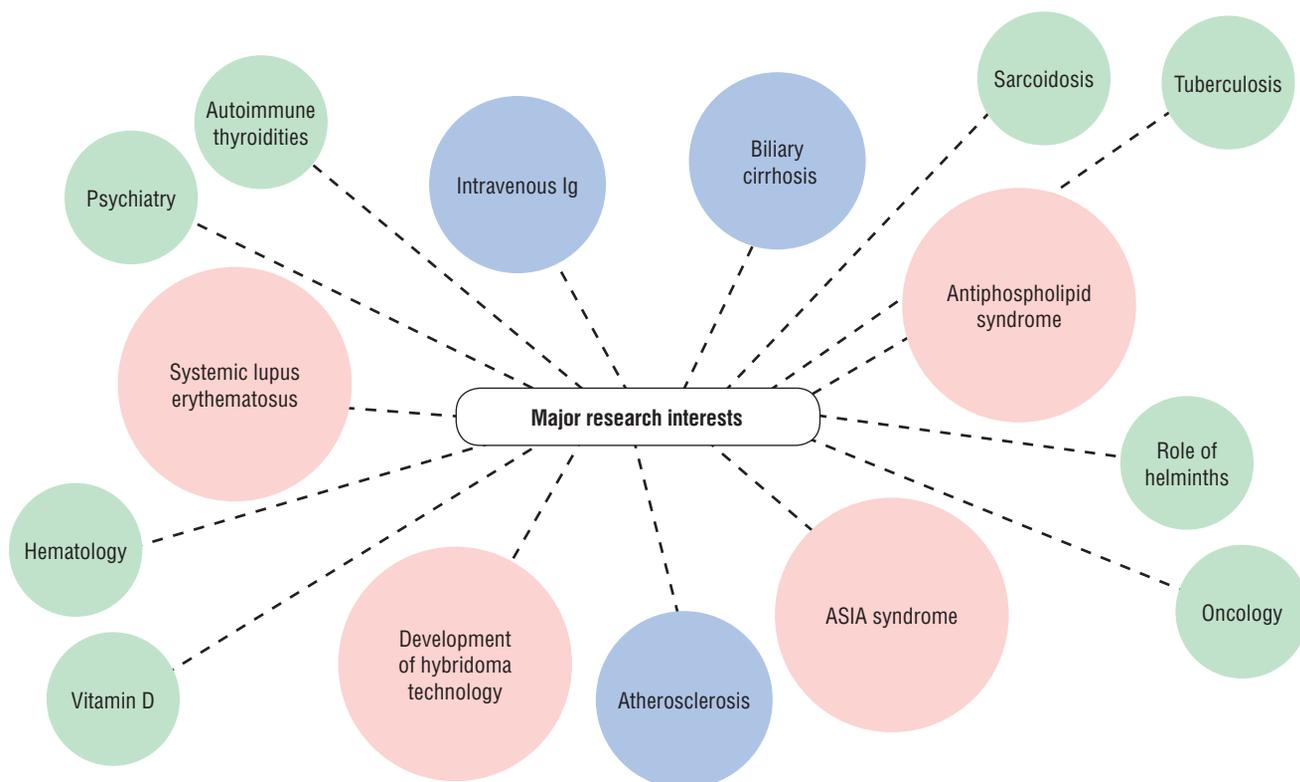


Figure 1. Spectrum of research areas tackled by Professor Shoenfeld

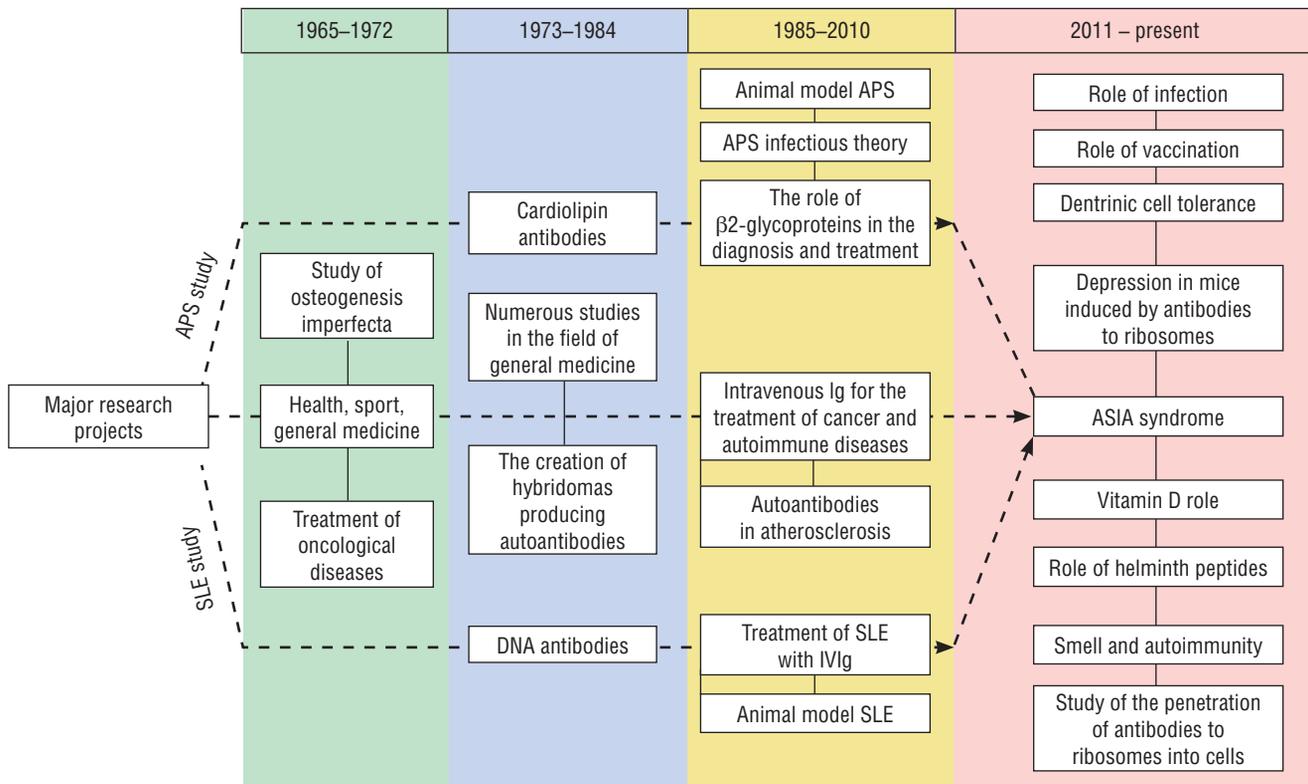


Figure 2. Timeline of scientific research of Professor Y. Shoenfeld

USA (hematological centers and clinics of several universities, including Tufts University, Cornell and University of California, under the guidance of prominent American scientists — immunologists and hematologists: E. Beutler, R. S. Schwartz and R. L. Nachmann). In 1980, Y. Shoenfeld graduated from the master's program in internal medicine, and then he began his medical and teaching work. Already at the beginning of his career, he showed tremendous ability to work, creativity and great interest in many areas of medicine, so, during the post-graduate study period, he published up to 20 articles per year tackling various medical disciplines.

Since 1974, Professor has taught environmental physiology, and then, for many years at the University of Tel Aviv, internal diseases. It was the time when his first research of autoimmune pathogenesis of diseases began, among which the systemic lupus erythematosus received the most attention.

After a year of practice as a senior doctor at the Beilinson Hospital (Rabin Medical Center, Petah-Tikva, Israel, 1984), Professor Y. Shoenfeld headed the "D" Department of Medicine and the outpatient department of the Clinical immunology and Allergology at the Soroka Medical Center (Beer-Sheva, Israel, 1984–1985). The scientist began to study in detail the role of autoimmune mechanisms in the pathogenesis of such diseases as systemic lupus erythematosus (SLE), antiphospholipid syndrome

(APS), primary biliary cirrhosis and others and identified some autoantibody characteristic of these diseases, which is now applied in medical practice all over the world.

Following the postulates of Henle and Koch, developed in the last quarter of the XIX century, in his research Professor Y. Shoenfeld applied a similar principle. Proving the etiology of autoimmune diseases, he discovered typical autoantibodies, then created experimental models of diseases, confirming the role of these antibodies. After that, this knowledge was used to create new methods of diagnosis, treatment, and prevention of various autoimmune diseases.

The key research of Professor Shoenfeld in the field of studying SLE was the creation of its experimental model using autoantibodies infusion to the double-stranded DNA, which is one of the main evidence of the autoimmune origin of this disease [1].

The results of studies of autoantibodies to DNA in SLE were presented in the articles by Shoenfeld et al., published in the *Lancet*, one of the most cited journals [2, 3]. During this period, his books were also published describing the new ideas about the pathogenesis of SLE and APS [4, 5].

In the studies of APS, very significant results were achieved, namely, the role of autoantibodies to the cardiolipin cofactor, anti β 2-glycoprotein I and cross-infection provocation in the etiology and pathogenesis of this

disease. These data are used to justify the treatment, prevention, and diagnosis of the APS. On this basis, models of the APS in animals were created by infusion of the corresponding autoantibodies [6].

From 1985 to 1989, Prof. Shoenfeld led the Department of Hybridomas and the Laboratory of Autoimmune Diseases at the Soroka Medical Center, collaborating with the Faculty of Health Sciences at Ben-Gurion University (Negev, Beer Sheva, Israel). At this time, an important study was performed on the creation of the world's first human hybridomas producing monoclonal antibodies [7].

Nowadays, the professor and his colleagues begin to study the effect of intravenous polyclonal donor immunoglobulin in the treatment of various immunopathological diseases [8]. Several patents were issued for intravenous immunoglobulin preparations for the treatment of certain oncological diseases, such as lymphoma, melanoma, sarcoma, and others (patents No. 5.562.902, 5.965.130, 00964595.3-2402/1220687).

In 1989, while working at the Department of Medicine "B" at the Sheba Medical Center and at the Faculty of Medicine at Tel-Aviv University, the professor develops the principle of "mosaic of autoimmunity", which implies a systemic approach to various autoimmune diseases. It was this concept that became the basis for the creation of a new branch of medicine — autoimmunology.

In 1990, Yehuda Shoenfeld became a professor at the University of Tel Aviv. His clinical and scientific work focuses on autoimmune and rheumatological diseases. Since 2003, he has worked as the head of the department for the study of autoimmune diseases named after Laura Schwarz-Kipp at the Sackler Medical Faculty of the University of Tel Aviv. Since 2011 he is a founder and head of the Center for Autoimmune Diseases, named after Zabludovich, which has become an internationally recognized leading institution in the field of applied and fundamental aspects of autoimmunology. The center was founded at the expense of funds raised from patrons and grateful patients. The work in the established center is based on medical practice and continuation of translational research with the involvement and training of specialists from various fields all over the world.

In 1995, Professor Y. Shoenfeld published new data on the role of autoimmunity in the pathogenesis of atherosclerosis, and the possibility of its immunotherapy was proved [9]. Later his articles on the pathogenesis of accelerated development of atherosclerosis in autoimmune diseases were published in the journal "Nature Reviews Rheumatology" (impact factor 12.188) [10, 11].

Y. Shoenfeld also pays attention to infectious diseases. So, he investigated autoimmune disorders in tuberculosis and confirmed the predisposition to the development of tuberculosis with a reduced level of vitamin D. Further, various autoantibodies were found that reflects the pres-

ence of autoimmune pathology in patients with active tuberculosis. The autoantibodies level usually decreases after treatment with anti-tuberculosis drugs [9, 12].

Professor Y. Shoenfeld proclaims the principle: "Everything is autoimmune until proven otherwise", and later, together with the famous American autoimmunologist Noel Rose, he postulates the important role of interactions of the organism and microflora in the origin of diseases including autoimmune: "Everything is infectious until proven otherwise".

Being a follower of the Nobel Prize winner I.I. Mechnikov (1908), who worked at St. Petersburg State University for 7 years, Professor Y. Shoenfeld summarizes and develops the ideas of the influence of external factors and nutrition on the formation of human microbiota and the immune response that determine life expectancy. He is creating a new concept, based on a polyetiological approach to the development of autoimmune diseases with a combination of the external trigger factors and the immunogenetic predisposition of the individual. This approach has allowed an innovative view at the prevention, diagnosis, and treatment of many diseases.

Having great clinical experience, in 2011, Professor Shoenfeld summarizes ideas about the role of adjuvants and adjuvant-like substances of endogenous and exogenous origin as trigger factors that contribute to the development of a systemic autoimmune-inflammatory syndrome. He studied the effects of silicone, vaccine components, plastic surgery dermal fillers (hyaluronic acid, acrylamide and methacrylate), dental amalgam, aluminum, and other xenobiotics and pollutants, including a number of foreign materials widely used in medicine, such as metal implants, etc. [13].

The result of this research was the presentation to the scientific community a new syndrome named by Shoenfeld: an autoimmune inflammatory syndrome induced by adjuvants (ASIA), which Professor Y. Shoenfeld considers his second most significant achievement. Since 2012, according to the suggestion of the World Congress on autoimmunity, this syndrome has been named after him and is known by eponym — Shoenfeld syndrome. Professor Y. Shoenfeld, for the first time, also formulated the concept of the so-called hyperferritinemic syndrome.

Today, Professor Shoenfeld is working with his students, studying the role of helminths in the pathogenesis of autoimmune diseases. There was determined the effect of certain secretory-excretory products of parasitic worms on autoimmune processes. The professor and co-authors obtained conjugate of the secretory-excretory products of helminths — phosphorylcholine and human immunoregulatory taftsin tetrapeptide (taftsin-phosphorylcholine), able to provide therapeutic and preventive effect in experimental therapy in a number of models of autoimmune diseases that have been shown to lupus

nephritis, experimental autoimmune colitis and arthritis, temporal arteritis, and recently — with the participation of scientists from St. Petersburg State University — for multiple sclerosis. The results of the research of Professor Y. Shoenfeld were patented (patent number 61/590830) and presented in the article “Will worms cure rheumatoid arthritis?”, which was published in the journal “Nature Reviews Rheumatology” [14, 15].

A large amount of time the professor devotes to the training of young specialists and the delivering of his own unique experience. His Center for Autoimmune Diseases, affiliated with the University of Tel Aviv, performs not only research and clinical functions, but also serves as an institution of postgraduate education, forming personnel for a new branch of medicine — autoimmunology.

Today, 50 Shoenfeld’s students are working as heads of departments in leading medical centers and clinics in Israel, and all have the title of professor. The main aim of the professor’s participation in the megagrant of the Russian Government was the possibility of transferring his experience to Russian specialists, educating young scientists, as well as expanding cooperation with Russian colleagues, conducting joint scientific research. Professor Shoenfeld first visited St. Petersburg State University by the invitation of L.P. Churilov, who was the coordinator of the organizing committee of the International Medical and Biological Conference of Young Researchers “Fundamental Science and Clinical Medicine — Homo and Health” in 2015, where the Professor had a series of guest lectures. Acquaintance with the physiologists and clinicians from St. Petersburg State University convinced him to start joint research projects.

Historically, the question of autoimmunity diseases has always been given special attention at the St. Petersburg State University. A student of two great Russian pathologists, S.M. Lukyanov and I.I. Mechnikov, Professor E.S. London (1869–1939) developed his ideas about physiological autoimmunity, autoimmune infertility and neuroimmune interactions, and obtained models of a number of autoimmune diseases. Under the leadership of Professor Y. Shoenfeld, a new laboratory was created here in 2017, called the “laboratory of Mosaic of Autoimmunity”, as part of the grant of the Government of the Russian Federation. The name is largely symbolic, and not only because it reflects the principle proclaimed by Shoenfeld in the clinical pathophysiology of autoimmune diseases. For many years, the rector of St. Petersburg University was the founder of mosaic art in Russia — M.V. Lomonosov, and the laboratory itself was created precisely in the rooms where the classic of the theory of autoimmunity E. London worked at the beginning of the XX century.

Research on the etiology, pathogenesis and experimental therapy of multiple sclerosis, the study of the role

of autoimmunity diseases on the thyroid gland and brain function, and the autoimmune links of the pathogenesis of sarcoidosis were launched in the laboratory. They occur in close cooperation with the clinical bases of St. Petersburg State University, in particular — the Research Institute of Phthisiopulmonology, as well as in collaboration with the Institute of Experimental Medicine.

A model of experimental allergic encephalomyelitis has been developed in mice and the ways of its experimental therapy have been achieved. Also, have been obtained results that conclude that the preliminary administration of taftsin-phosphorylcholine inhibits the development of experimental allergic encephalomyelitis. For the first time was shown the effectiveness of the method of experimental therapy for autoimmune disease of the central nervous system.

As part of a studies under the guidance of Professor Y. Shoenfeld, evidence was found for the role of adjuvant-like factors in etiology and autoimmune mechanisms in the pathogenesis of sarcoidosis. For the first time, the features of the subpopulation composition of follicular T-helpers and T-regulators were traced. This may show a common feature between sarcoidosis and ASIA syndrome.

A connection was found between a number of immunoendocrine marks and manifestations of psychiatric pathology in patients with Hashimoto’s chronic autoimmune thyroiditis. A correlation was found between the levels of prolactin and antibodies to thyroid antigens, as well as mental disorders. Cases of autoimmune encephalitis with autoimmune thyroiditis, mistakenly diagnosed as schizophrenia are described. A number of psychopathological reactions were reproduced in experimental mice by the administration of immunoglobulins from schizophrenic patients with comorbid autoimmune thyroiditis.

An analysis of the autoimmune diseases epidemiological data in Russia was carried out and the extreme heterogeneity of the geographical distribution of immunopathies in different subjects of the Russian Federation was shown, as well as the patterns correlated with urbanization factors, in particular with the development of the road network.

Dysfunction of immunological reactivity in silicone mammoplasty associated with changes in prolactin regulation was described, which can lead to the development of autoimmune and sarcoid reactions.

According to the results of research, dozens of articles were published in international journals and dozens of reports were presented at European and World Conferences and Congresses in Paris, Lisbon, Harbin and Florence. More than thirty young scientists and students of St. Petersburg State University and other Russian scientific institutions were given the opportunity to begin their



Figure 3. Participants of the 2nd St. Petersburg Academy of Autoimmunity (2018)



Figure 4. Professor Y. Shoenfeld in the Zabludovich Center for Auto-immune Diseases with a deputy head of the Laboratory of Mosaic of Autoimmunity L.P. Churilov

scientific work in cooperation with the established laboratory of Mosaic of Autoimmunity, together with leading world experts in the field of autoimmunity.

In 2017, Professor Shoenfeld and his laboratory organized and successfully held the First St. Petersburg Congress on Autoimmunity “The Bridge between East and West”. In September 2018, the Second Academy of Autoimmunity was held at St. Petersburg State University, which was attended by 50 leading specialists on autoimmunity from 11 countries (Great Britain, Germany, Greece, Israel, Italy, Spain, the Netherlands, Russia, France, USA, Switzerland), including the leading pathologist of our time — Professor Abul M. Abbas (University of California). More than 600 Russian and foreign students, postgraduates, clinical residents, doctors and scientists were students of the Academy (Fig. 3). Among the lecturers and participants of the congress were 7 members of the Russian Academy of Sciences.

In 2019, from 11 to 13 October, the Fourth St. Petersburg Academy of Autoimmunity, supported by the Russian Foundation for Basic Research, is planned at



Figure 5. Shoefeld's seminar in the conference hall of the Laboratory of Autoimmunity Mosaic with colleagues and young scientists from St. Petersburg State University and PSPbGMU

St. Petersburg State University under the guidance of Professor Shoefeld.

In 2017, published the first edition of the "Guidelines on autoimmune diseases for general practitioners", edited by Y. Shoefeld, P.L. Meroni and L.P. Churilov (St. Petersburg: ELBI-Medkniga; 2017. 416 p.).

Today, the professor is in all his intellectual brilliance and excellent physical shape meets with colleagues at his Center for Autoimmune Diseases in Israel (Fig. 4).

Professor Shoefeld is actively planning new research, not just dreaming, but implementing his plans! "Do today what you can do tomorrow!" — this is his life principle and motto, which serves as a farewell to the younger generation.

In March 2019, the third year of creative and scientific work began in the megagrant under the guidance of Pro-

fessor Shoefeld, which we hope will open up even more opportunities for understanding the complex mechanisms of the kaleidoscope of autoimmunity.

All the laboratory staff and participants in research wish Professor Shoefeld life energy, new discoveries, many years of inspired creativity, and sincerely thank for the new knowledge and experience that the professor generously shares with Russian colleagues.

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