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. (7 figs, bibl.: 94 refs).

Keywords: aging, adolescents, adiponectin, autoimmune thyroiditis, cytokines, Dupuytren's contracture, Hashimoto H., 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 examples 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 V) – 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 3rd 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 Sato, 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 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 observations were

published (1912) in a trustworthy German journal [2]. In this paper, he discussed in detail (and with profound knowledge of a subject) all data on thyroid, available to that period. Inspired by his teacher, Miyake, who highly appreciated articles by von Mikulicz, Hashimoto even anticipated the probable kinship of a new nosological entity with von Mikulicz' disease and Graves' disease because "round-nucleated cells" were known for ability to infiltrate various glands in all of them. It is especially valuable because still many years had to pass before recognition of autoimmune nature for all these nosological forms. Later H. Hashimoto had to abandon scientific career, left university and accepted to himself all care of family and rural medical practice of his deceased father. The brilliant début article, which immortalized his name, remained his sole academic paper forever. In 1934 this countryside family practitioner perished from abdominal typhoid fever, caught from a patient [11-13]. It was a fateful recapitulation of a previous tragedy: death of a discoverer of another autoimmune thyroid disorder Dr. Karl Adolph von Basedow (1799-1854), who perished from epidemic typhus infected on autopsy of his patient [14].

We believe that it was specifically H. Hashimoto, who has described one hundred years ago, in 1912 the first cell-mediated human autoimmune disease. Delayed type of hypersensitivity (DTH), in fact, was medically described as early as in E. Jenner's publications on smallpox vaccination [15]. But, before H. Hashimoto not a single DTH-mediated autoimmune disease was known. Autoimmune endocrine disorders were not yet described to 1912 also, although Ye.S. London already demonstrated that autoallergy may alter gonads and cause infertility [5]. It means that H. Hashimoto can be referred to as a pioneer of Immunoendocrinology: indeed he has intentionally emphasized the lymphoid specifics of freshly discovered goiter variant, though lymphocytes in that epoch were not yet recognized as immunocytes! The true value of Hashimoto's discovery had to wait for appreciation during many years. But as soon as in 30ies validity triumphed: Allen Graham, a surgeon from Cleveland, Ohio has confirmed Hashimoto's point of view and priority in 2 papers for reliable journals published in English (1931-32) and proved that lymphomatous struma with thyroid fibrosis outcome is not a Riedel's struma, but a separate nosological form. Moreover, he coined an eponym: "Hashimoto's goiter" [16]. From thereafter papers and textbooks started

to mention this name regularly, first in the USA, later in Britain. The disease was recognized as a separate nosological entity, but still was regarded as rare one, and by no means was it related to mass cases of seemingly "sporadic" hypothyroidism, observed by practitioners beyond the iodine-deficient regions.

In 1956 the coryphaei of Immunology Ernst Witebsky and Noel R. Rose created the first model of Hashimoto's disease in rabbits by means of immunization with marker antigen of thyrocytes – thyroglobulin. Thus, for the first time in the history of Pathophysiology they proved in principle the very possibility of experimental modeling for autoimmune diseases [17-18]. Later I. Roitt and D. Doniach revealed antithyroid autoantibodies in clinical patients with Hashimoto's disease and formulated the auto-allergic concept of "struma lymphomatosa" [19-20]. The broadest spreads of this illness, especially among females, finally attracted the attention of health professionals in 1962, and it happened beyond the area, where it was initially registered: I. Doniach & E.D. Williams, basing on the data of continuously performed autopsies of English women perished from different reasons, revealed the picture of Hashimoto's disease in thyroid glands of 15-25% of all cases examined [21].

Comorbidity of AIT with Marfanoid Phenotype and Simpson-Page' Syndrome

Why ordinary family practitioner from a remote Japanese village has got global recognition? The point is that incidence of AIT starting from 2nd half of 60ies in XX century constantly increased, comprising a lion's share of the total thyroid pathology. It became not only medical, but also global social problem, like diabetes mellitus. AIT nowadays is the most important reason of hypothyroidism worldwide, standing far ahead of endemic goiter by quantity of its victims. According to our data, the frequency of AIT diagnosis on admission to hospital among St. Petersburg adolescents-draftees increased more than 5-fold since 1987 till 2002 [22]. During 1960ies Hashimoto's disease was mentioned in world literature of PubMed database 292 times, in 90ies – already 1792, and now this request in PubMed gives 5218 references, 3028 of them within the last decade [23].

In our Department of Pathology the research of AIT was started in fact from the moment of its foundation (1997). Since Jan 1st 1998 till June 15th 2012 we have consulted 51 736 persons between 1 and 90 years old, suffering from AIT. The majority of them stay under our dynamic medical follow-up during 1-14 years. As a result of research and treatment, we have collected considerable clinical-pathophysiological database and refined several concepts of etiology, pathogenesis and treatment of AIT, in particular: role of Chernobyl disaster sequels, roles of hyperprolactinemia, marfanoid phenotype, chronic systemic excess of some cytokines, relation to early metabolic syndrome (MS) *etc*. Observing the patients of different age with AIT, we have noticed among them huge percentage of adolescents and young adults with either juvenile dyspituitarism (Simpson-Page' syndrome, hypothalamic syndrome of adolescence, obesity with rose striae, see: Fig**. 2** below), or *vice versa*, those with obvious hypotrophy. Their clinical examination brought us to some curious results: it appeared that overwhelming majority of such patients (regardless of their body mass and fatness status) displayed the combination of various signs of non-syndromal connective tissue dysplasia (CTD) of marfanoid phenotype (MF): rather tall height, long arms with the elements of arachnodactyly, fairly short legs, backbone and chest deformations, transversal type of flat foot, benign joint hypermobility, skin hyperelasticity, interdigital membranes, positive thumb and wrist tests (Walter-Murdoch symptom), mitral valve prolapse, false chordae in left ventricle, deformations of gallbladder, right-side nephroptosis, myopia with astigmatism, wrong dentition *etc* [24]. Classical Marfan syndrome occurs in our AIT cohort 74 times more often then in local population. Interestingly, the adolescents of both sexes after decrease of their body mass (as a result of effective treatment) converted into patients with typical habitus of marfanoid CTD [Fig**. 2**].

At the same time, they often displayed autoantibodies against thyroid gland in titers, increasing with age [Fig. **3**], as well as clinical-laboratory manifestations of hypothyroidism of varying severity. We have separated a cohort of 195 marfanoid male adolescents-draftees of the identical age [25] and revealed in their blood significant increase of T$_3$ level (to 2,25±0,06 *vs.* 1,74±0,06 nM/L in controls), decrease of T$_4$ (107,6±0,1 *vs.* 124,4±3,3 nM/L) and raise of TSH (2,14±0,13 *vs.* 0,99±0,06 µU/ml). Diagnostic titers of antithyroid autoantibodies presented in 11,

5% of cases. Half of draftees had the ultrosonographic images of thyroid typical for AIT: hypo-echogenic irregular structure with micro-nodules and cysts. One third of adolescents manifested so called "subclinical" hypothyroidism.
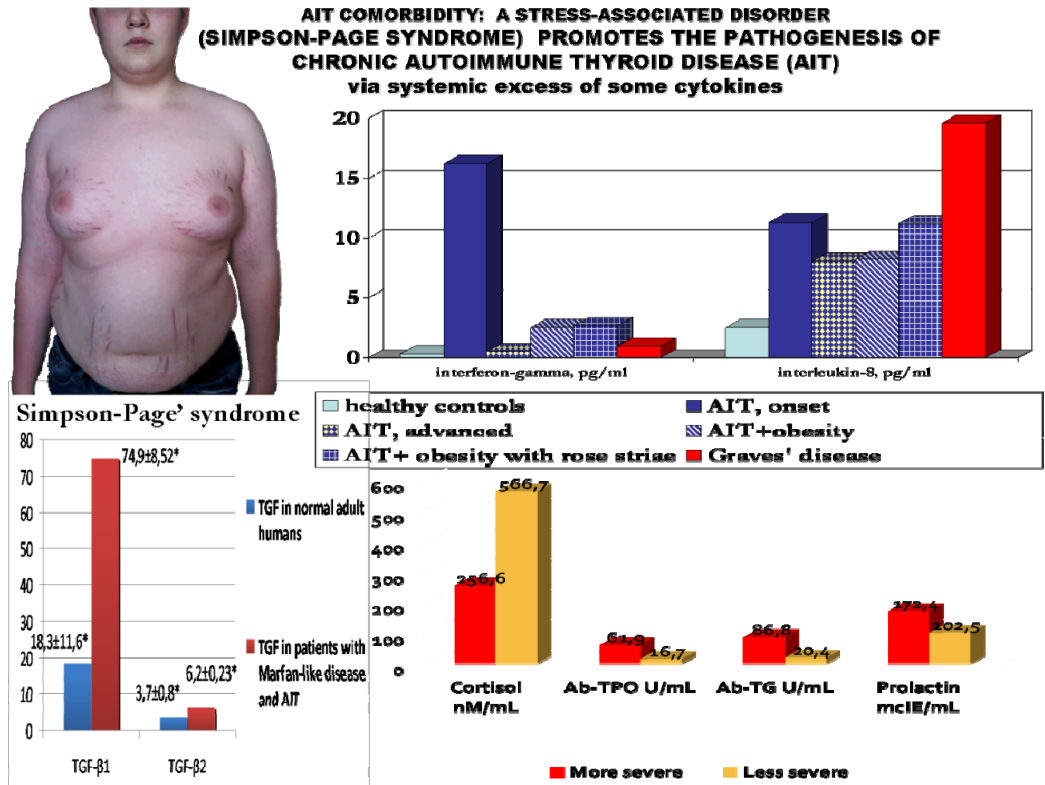
Figure 2: Habitus of a typical patient with SPS-CTD-AIT comorbidity (in left upper corner) and content of several cytokines (TGFβ1/β2, interferon-γ, IL-8); hormones (prolactin, cortisol) and autoantibodies towards thyroid antigens (thyroperoxidase – Ab-TPO and thyroglobulin – Ab-TG) in blood of patients and controls (everywhere p<0,05 with controls).

Exploring 194 persons with CTD (14-50 years of age) we revealed significant decrease of T_3 and T4 blood levels, raise of TSH level, noteworthy growth of anti-TG and anti-TPO autoantibody titers in their blood, compared to healthy donors of the same age. In group of 40 marfanoid persons with overt hypothyroidism the difference with healthy donors was even sharper. With aging the production of thyroid hormones by CTD patients tended to decrease, with appropriate increase of blood TSH, anti-TG and anti-TPO autoantibody levels [Fig. **3**]. This tendency was accompanied by increase of thyroid gland volume (estimated by

ultrasonography). These data may witness for gradual progressing of AIT in CTD patients to the outcome of overt hypothyroidism [25-26].

In Hashimoto's thyroiditis combined to marfanoid habitus autoimmunity towards thyroid significantly (asterisks) increases with age, bold dashed horizontal line marks diagnostic titer of autoantibodies.
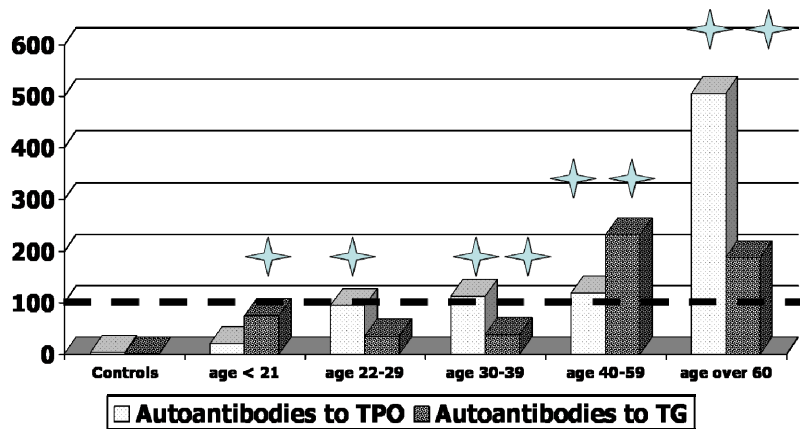

Figure 3: Age dynamics of autoantibodies towards thyroid antigens in AIT-CTD. *) – p<0, 05 with controls. Dashed line marks cut level of diagnostically significant autoantibodies titer.

LEPTIN in AIT marfanoid patients
BMI of primary and secondary obesity groups differs N/S
Secondary obesity in Simpson-Page' syndrome manifests highest leptin
level among all AIT marfanoid patients, asterisk marks p<0,05 to healthy & to
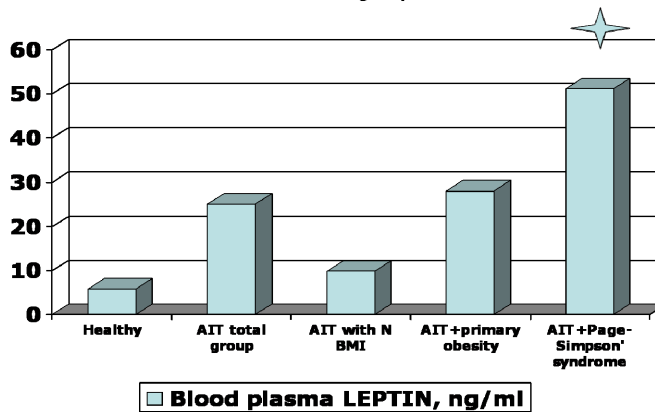total AIT group

Figure 4: Content of leptin in blood of AIT-CTD patients, accompanied by either STS, or common obesity, or normal body mass. *) – p<0, 05 with controls.

Conflict of Autacoid and Hormonal Regulation in AIT-SPS-CTD Patients

Checking the parameters of cytokine and hormonal regulation in adolescent patients with comorbidity of AIT, SPSand CTD, we registered in systemic blood significantly excessive concentrations of both TGFβ1 and β2 [Fig. **2**], as well as absolute and relative (per unite of body mass index, BMI) hyperleptinemia [Fig. **4**] [26-27]. SPS and hypothyroidism both are regarded by many authors as typical pseudo-cushingoid stress-associated disorders or diseases of overstressed adaptation [28]. It is particularly right for the highly stressful period of adolescence, critically sensitive one in the ontogenesis of endocrine system [29]. Inhibiting influence of stress on thyroid function is well known, as well as stimulating one – on the production of sympathetic-adrenal agonist leptin (especially among the young obese persons) [28-30]. Taking into account these influences and also the fact of glucocorticoid-mediated inhibition of some TGFβ effects (systemic excess of this cytokine is a proven key pathogenetic link of full Marfan syndrome [31]), one may suggest that patients with SPS have conditions for compensatory hyperproduction of TGFβ, thyroid dysfunction and hyperleptinemia, which all were registered in our study. There are tight interrelations between leptin and thyroid (including leptin production stimulation by TSH, thyroliberin production stimulation by leptin, presence of leptin receptor on thyroid cells, stimulation of their growth and function by leptin, suppression of leptin production by thyroid hormones and hyperleptinemia in hypothyroidism) [32-34]. Because of this we proposed that the excess of leptin in our patients facilitated the thyroid dysfunction [35]. Moreover, leptin is a proven stimulator of Th1, macrophages of 1st type and autoimmune delayed hypersensitivity reactions. These links are most important in AIT pathogenesis and, also they trigger inflammatory changes in adipose tissue [34, 36]. Correlation of leptin level and autoimmune thyroid disease in obese patients has been already confirmed [37]. However, in a Polish study the adolescents with AIT did not display overt elevation of leptin level, although the levels of TSH and leptin correlated [38]. Presumably, the explanation is that, unlike our patients, their cohort was not selective for marfanoid habitus. It looks like in *marfanoid* SPS adolescents; *in particular*, the disorders of leptin regulation of autoimmunity promote the pathogenesis of AIT. Hence, there must be some other factor, related to CTD and able to render permissive effect on the leptin stimulation of AIT development.

It is not by chance that comparing the levels of TSH and thyroid function in marfanoid and non-marfanoid SPS patients, we found that in marfanoid ones, TSH concentration was greater and latent hypothyroidism was registered more often (52% *vs.* 39%, respectively) [27].

Key role may belong to other cytokine – TGFβ, which systemic action is sharply excessive not only in classical full Marfan syndrome [31], but also, according to our data [Fig. **2**], in non-syndromal CTD [27]. We have registered weak negative correlation between TGFβ blood concentration and titer of antithyroid autoantibodies and negative correlation between TGFβ and TSH blood concentrations [26-27]. This can be related to greater degree of AIT and hypothyroidism in smaller levels of immunosuppressive TGFβ. But, TGFβ renders unequivocal effects on the course of AIT: its compensatory anti-inflammatory potential and relation to Treg differentiation and function [39] does not exclude neither its ability to stimulate migration of lymphocytes into thyroid, not its enhancing effect of fibrosis. Recently a variant of chronic thyroiditis was described with the predominance of fibrosis, depending on IgG$_4$ autoantibodies, but with less prominent lymphoid infiltrates ("fibrotic") [40]. Also TGFβ may stimulate the development of experimental AIT [39, 41]. The induction of TGFβ production within thyroid by *iodides* is of special significance [42]. Earlier many authors (see chapter V above), beginning from N.R. Rose *et al.*, have demonstrated that the excessive consumption of iodine provokes AIT both in humans and in experimental animals. We also have similar data [43-44]. The trend of TGFβ action over autoimmunity depends on permissive context, created by other bioregulators [39].

In our co-morbid patients the permissive background for excessive systemic action of TGFβ1/β2 was definitely pro-inflammatory. Firstly, it is due to leptin excess, which is typical, for example for post-partum thyroiditis and contributes into its pathogenesis [45]. Secondly, in SPS we have revealed hyperangiotensinogenemia [46], which could be very essential for marfanoid patients because it was proven that *via* chymase activation angiotensin II promotes TGFβ activation and TGFβ-dependent vascular pathology, including aneurisms, typical both for MF and Marfan syndrome [47]. Finally, in AIT we have revealed the excess of an acute phase reactant – ceruloplasmin, which is

related to chronic systemic excess of inflammatory autacoids and manifestation of oxidative stress [48-49].

We suppose that in marfanoid SPS patients there is a "struggle" between contradictory and, in many aspects, opposite immunoregulatory influences of leptin and TGFβ for prevalence over physiological anti-thyroid autoimmunity. But, while these autacoids balance their effects on autoimmune process, at the same time they both promote the development and consolidation of marfanoid habitus, co-stimulating the axial dolichomorphic growth of mesodermal derivates [36, 50]. Stress always means "stealing" of energetic and plastic resources from insulin-dependant mesenchymal derivates on behalf of the cells holding non-insulin dependant GLUT-transporters [28, 51]. The dysplastic connective tissue in CTD probably gets more prone to these deprivation effects of chronic stress. This link can consolidate mutually provocative actions of SPS and CTD. The skin striae are observed regularly in both disorders (and in some other stress-associated states), as a typical manifestation of energetic and substrate deprivation of connective tissue [52].

We also revealed in autoimmune thyroid disease some more characteristic changes in systemic action of cytokines [53] [Figs. **2, 4** above, and **(5-6)** below].

It appeared that AIT (mainly – in the beginning) is accompanied by clear increase in systemic level of γ-interferon (which serves as an inducer of aberrant MHC-II proteins expression on the thyrocytes, provokes autoallergy and can be in turn induced by leptin) [40]. Moreover, in advanced AIT its level tends to decrease, but not in AIT accompanied with obesity and SPS. In AIT there is much more significant γ-interferon systemic response, than in von Basedow-Graves' disease, apparently because of cellular T_{h2}-dependent autoallergic mechanisms prevailing in Hashimoto's disease over humoral ones, typical for von Basedow-Graves disease. Systemic concentrations of pro-inflammatory IL-8 and TNFα were also increased in AIT (last one mostly in advanced cases and first one – in the onset of AIT). IL-8 level in systemic circulation was especially noticeably elevated in AIT-SPS-obesity co-morbid individuals. At the same time, von Basedow-Graves' disease was characteristic for definitely higher systemic levels of both IL-8 and TNFα, than Hashimoto's disease [Figs. **2** above, and **(6)** below]. The

compensatory increase of anti-inflammatory IL-10 in systemic circulation was characteristic for von Basedow-Graves' disease only, but absent in AIT groups. Moreover, only in combination of SPS and AIT concentration of IL-10 was close to that of controls [Fig. **6** below], but all other AIT groups even had significant decrease of this parameter [53]. Similar data on the systemic excess of IL-8, TNFα and γ-interferon in AIT were also reported by N.N. Tsybikov *et al.* [54].

The exophthalmia was proven to be characteristic for the "Graves-like" phenotype of transgenic mice, having adiponectin *excess* [55]. But the habitus of Graves' disease patients is definitely "anti-metabolic" – *i.e.* they display many clinical and laboratory signs opposite to that of typical MS. Adiponectin is involved in Graves' ophthalmopathy pathogenesis and also is abundant in some autoimmune endocrinopathiae (Hirata disease) [40]. Due to this, we hypothesized that adiponectin excess may be observed in von Basedow-Graves' disease [56] and interested in content of this autacoid (known inhibitor of MS pathogenesis) both in cases of von Basedow-Graves' disease and in various comorbidities of AIT. In début of AIT and, especially, in von Basedow-Graves' disease we revealed significantly greater absolute and relative (per unite of BMI compared to controls) systemic concentrations of adiponectin. But in advanced AIT and, most strikingly, in combination of AIT with SPS level of adiponectin paradoxically decreased. In AIT-SPS comorbidity it was not only significantly lower, than in controls, but also obviously lower than in AIT combined with common obesity (in spite of the same BMI in last 2 groups). The difference was especially noticeable when calculated per unit of BMI [57]. In all groups of AIT adiponectin levels were lower than among von Basedow-Graves' patients [Fig. **5**]. It means that autacoid regulation in SPS-AIT comorbidity is distinct from that of common AIT not only because of obesity peculiar to SPS, but due to some other specifics of this stress-related adolescent disorder. Stress-associated tendency to hypoadiponectinemia in adolescents also was revealed by P. Pervanidou *et al.* [58].

Both AIT and MS are rightfully called social diseases of our century. The great prevalence of both disorders inevitably causes their comorbidity, not only because of high spread, but also due to common pathogenetic links and close clinical signs. MS is closely related to different kinds of endocrine autoimmunity [40]. We have examined 400 adult patients with AIT and hypothyroidism of various

severity (200 males and 200 females, between 22 and 79 years old) and in 206 of them (51, 5%) registered the set of manifestations typical for MS [59]. At present, MS is regularly reported in pediatric and adolescent patients, which phenomenon was for the first time noticed as early as in 1994 [60]. On the basis of many years of continuous observations we suggested that most important risk factors of juvenile MS (JMS) are SPS and marfanoid CTD. The main mechanisms, establishing the transformation of SPS into JMS in marfanoid CTD individuals, is chronic excessive systemic action of the mesenchymal autacoids, mentioned above, and also the impact of AIT, which gets promoted on this basis [26].

ADIPONECTIN: POSSIBLE MEDIATOR OF GRAVES' DISEASE & PROTECTIVE FACTOR
IN COURSE OF HASHIMOTO'S THYROIDITIS (AIT) , NOT ACTING IN CO-MORBID
SIMPSON-PAGE' SYNDROME, BUT STILL ACTING IN GRAVES-von BASEDOW' DISEASE
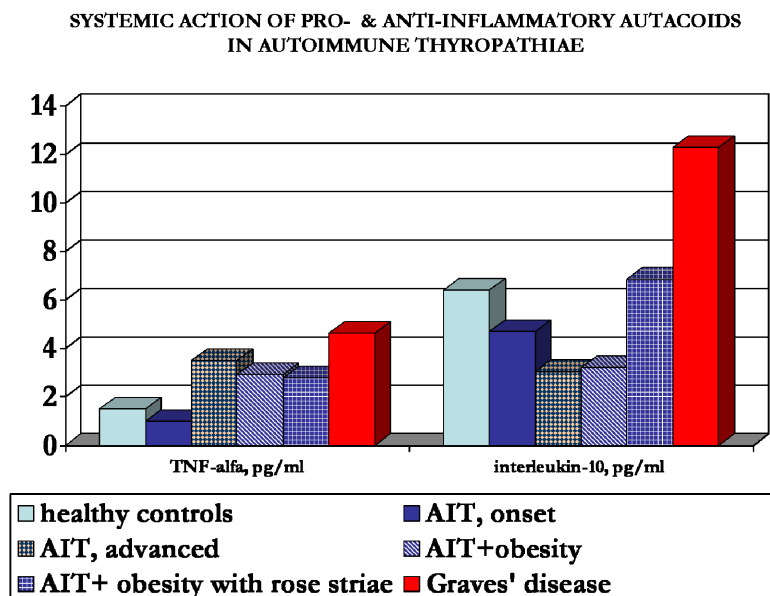AND IN THE ONSET OF AIT WITHOUT SIMPSON-PAGE' SINDROME
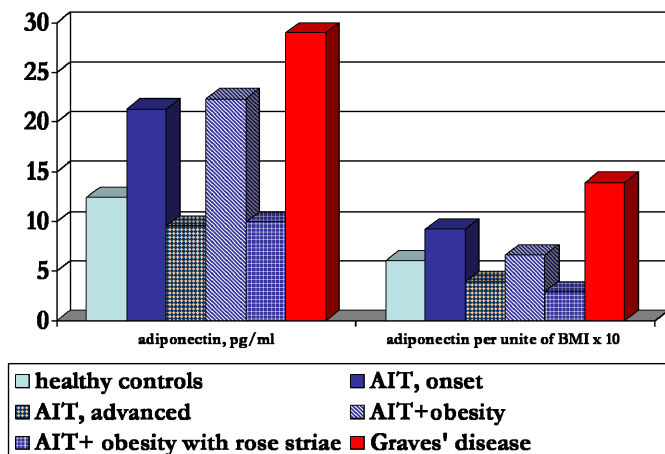
Figure 5: Systemic action of adiponectin in AIT (n=30) - in the onset and peak of disease; AIT with CTD & SPS (n=40), AIT with common obesity, or in Graves' disease (n=20) – compared to healthy controls(n=22). Everywhere P<0,01 with controls.

Comorbidity of AIT-SPS-CTD as a Precursor of Early Metabolic Syndrome

In 2002 we coined a concept that SPS in fact should be regarded as JMS or its precursor and postulated the regular transformation of SPS into JMS [46, 61-62]. The investigation of 250 adolescents with SPS revealed that over 70% of them displayed to the moment of examination (or developed in catamnaesis) 4 to 5 signs of MS according IDF classification (*i.e.* arterial hypertension, dyslipidemia, android obesity, intolerance to glucose, hyperinsulinemia *etc*.). Moreover, according modified Ghent criteria, all of them had the signs of marfanoid CTD.

We demonstrated (according Japanese Thyroidological Association criteria) the presence of AIT with all above mentioned signs of cytokine dysregulation in this group of patients [26-27]. Other endocrine peculiarities of such adolescents were hypercortisolism, hyperaldosteronism, hyperreninemia, excess of angiotensin II and, which was the most typical: Increasing hyperprolactinemia and progressing hypothyroidism with raise of TSH level [26, 46].

Figure 6: Systemic action of proinflammatory TNFα and anti-inflammatory interleukin-10 in AIT (n=30) - in the onset and peak of disease; AIT with CTD & SPS (n=40), AIT with common obesity, or in Graves' disease (n=20) – compared to healthy controls (n=22). Everywhere P<0,05 with controls.

Hypercytokinemia with involvement of mesenchymal autacoids: TGFβ, leptin, TNFα, some interleukins and interferons, acute phase reactants, as well as lack of adiponectin, or hypothyroidism – all are firmly proven links of inflammatory changes in adipose tissue, inducing insulin resistance of lipocytes, muscles, vascular walls and liver, hypothalamic dysfunction and thus – facilitating the formation of MS. The role of TGFβ is principally important because of its ability to induce TAK-kinases, involved both in pro-inflammatory activity and in decrease of insulin sensitivity. Also, many of these changes are proven atherogenic factors [40, 63-66].

In co-morbidity of CTD, SPS and AIT we found all these signs of misbalance between local autacoid and systemic hormonal regulation. These changes, in our opinion, are responsible for key steps in transformation of SPS into early MS. SPS may fade away with aging, but AIT proceeds increasingly through lifetime. Probably, it is thyroid disorder which consolidates this comorbidity *via* hypothyroidism, well proven risk factor of MS [66]. The adolescents with CTD and SPS have skin rose striae in 100% of cases. During transformation of this comorbidity in JMS they frequently develop Dupuytren's contracture (DC) [26, 59]. We regard both *rose striae and DC* as the most important stigmata of comorbidity, described here. First of them reflects the metabolic deprivation of the dysplastic connective tissue in hypercortisolism, typical for SPS [26, 28, 52], second one depends on action of TGFβ [67], which we found in surplus in blood of these patients [27].

The disorders of interaction between central neuroendocrine and local autacoid regulation in CTD are important in pathogenesis of these disorders. But, in our opinion, exceptional contribution belongs to noticeable hyperprolactinemia, observed in AIT patients [Figs. **2** above and **7**]. Hyperprolactinemia results from prolactoliberin-like action, caused by thyroliberin, which in turn is produced in attempt to compensate for hypothyroidism developing in AIT patient. These two liberins partially share the domens of their action [68]. Excess of prolactin causes in patients with AIT mastalgia, mastopathy, masculine gynecomastia and infertility. We have a long successful experience of fertility re-establishment in AIT patients of both sexes by means of suppression of hyperprolactinemia with thyroxinotherapy [69]. The regular occurrence of reproductive dysfunction in autoimmune thyroid disease was reported also by Y. Shoenfeld *et al.* [70]. They related it to multiple target autoimmune disorder, vitamin D deficiency, possible extrathyroid immune mediated effects, for example, on uterus. But, in our opinion hyperprolactinemic mechanism is most potent and plays the main part in these complications of AIT.

Hyperprolactinemia obviously alters fertility, both in males and females, suffering from AIT, being the significant factor of risk for fibromatosis and even for cancer of breast [69, 71]. Besides that, the stimulating influence of prolactin on immune system is very essential, including its ability to promote the autoimmune

processes, which was shown in several non-organospecific autoimmune diseases [72-73]. We demonstrated in marfanoid AIT patients **[**fig. **2** above**]** that the higher was the blood level of prolactin and lower – the blood level of cortisol, the greater were the titers of anti-thyroid autoantibodies [26, 53, and 57]. Aggravating effect of hyperprolactinemia was noticed also in autoimmune lymphocytic hypophysitis [40].
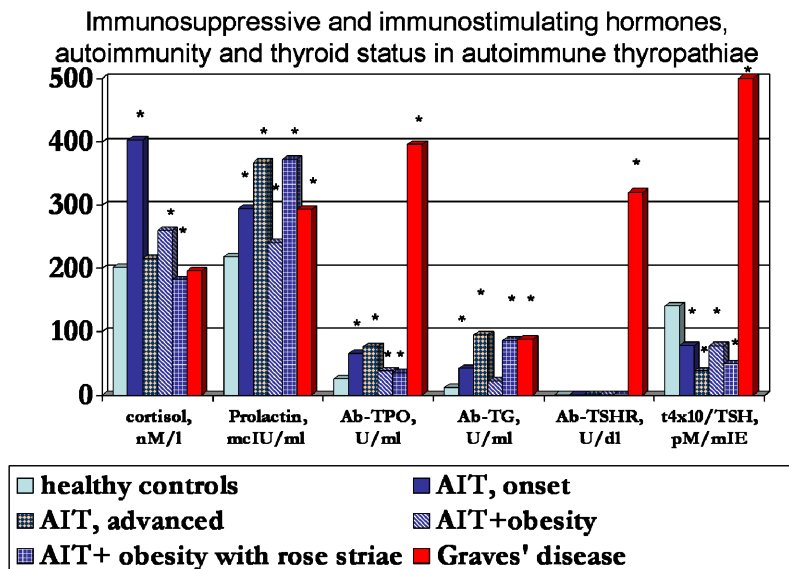
Figure 7: Parameters of hormonal (prolactin, cortisol, TSH) and autoimmune (autoantibodies to: thyroglobulin – TG, thyroperoxidase – TPO, TSH receptor– TSHR) regulation in controls (n=22), in onset of AIT and on the height of AIT (n=17), in AIT combined to SPS (n=40) or common obesity (n=30); and in Graves' disease (n=20). (*) – p<0,05 with controls.

We have noticed that the spectrum of autoallergy in marfanoid AIT patients is getting broader with the progressing of their MS. Our study of autoimmunity spectrum in them made with A.B. Poletaev's ELI-Viscerotest method [74] revealed that in some cases in plus to AIT markers these patients with age develop increased levels of autoantibodies towards adrenals, platelets, liver, CNS antigens *etc.* An example is a case of a male patient S., who has marfanoid habitus and suffered from AIT since adolescence. To the age of 25 he developed in plus high level of antisuprarenal antibodies with decrease of physiological autoimmunity against myelin. In several cases of AIT and MS treatment of hypothyroidism with L-thyroxin provided not only substitution effect and achievement of euthyroidism,

but also immune modulating action, with decrease in anti-thyroid and some other (for example, anti-platelet) autoantibodies. Unlike glucocorticoids, thyroid hormones allowed to achieve this without general immune depression. We described few cases when thyroxinotherapy was much more effective in suppression of autoallergy, than even prednisolone treatment [75]. It was demonstrated earlier by A.Sh. Zaichik that hypothyroidism inhibits the programmed cell death [76], for example, in adrenocortical apoptosis by default. Due to this, we explained immunomodulation *via* thyroid hormones taking into account that withdrawal of autoreactive lymphoid clones also requires apoptosis [77]. That's why during progressing of AIT (because of coming hypothyroidism) the apoptotic-mediated renewal of tissues will occur more slowly. This is manifested in the picture of hypothyroidism: for example, there is inhibition of the epidermal stratum corneum renovation, which causes so called geroderma, typical for these patients. Thyroid hormones control expression of keratin as well as transglutaminase and plasminogen activator in epidermocytes, last 2 agents responsible for shedding process [78]. Inhibition of CNS cells apoptosis accounts for disorder of synaptic re-modeling in brain of hypothyroid cretins [79]. We suspect that apoptotic withdrawal of autoreactive lymphocytes in hypothyroidism also slows down. Direct stimulation of apoptotic process in human lymphocytes with thyroid hormones was shown *in vitro* [80]. Hypothyroidism *via* this mechanism may promote the increase of anti-thyroid autoantibodies' titers, cause lymphocytosis (typical for AIT) and facilitate the broadening of autoallergy spectrum with age. By the way, lymphocytosis was included into the list of MS manifestations from the very beginning of MS concept [81]. Hypothyroidism and variety of autoimmune disorders, growing with age, was demonstrated, for example, in Turner's syndrome (45X0) [40].

In conclusion, here we presented some data that demonstrate the existence of chronic conflict between *central* neuroendocrine (prolactin, cortisol) and *local* autacoid (leptin, TGFβ, pro-inflammatory and anti-inflammatory cytokines) forms of regulation in comorbidity of marfanoid CTD, SPS and AIT [82].

We suppose that this conflict serves as the main driver of the progressive course of disease, leading to hypothyroidism and to early MS [83].

Prevention and Prediction for AIT and for its Complications

Thyroxinotherapy may restore the normal course of apoptotic cell withdrawal, thus improving not only geroderma and cognitive brain functions of a patient, but also autoimmunity regulation [26, 74-75, and 84].

In our practice, thyroid hormones display the ability to prevent autoallergy, MS and immuno-metabolic senescence [43, 75, 84-85]. In chapter V [Fig. **6** of Chapter V] we already mentioned that in 100 families, where we observed a comorbidity of CTD, SPS and AIT through several generations, the auto-allergic disorders in children started long before overt and even before latent hypothyroidism [74]. We interpret this as an indirect witness for inherited basis of the AIT-SPS-CTD comorbidity explored. The alleles involved in this comorbid constellation are not yet known. But this does not obstacle the possibility of early recognition and prophylaxis.

Pathogenesis of AIT and formation of its comorbidity are well studied, and treatment of this disease with synthetic thyroid hormone (Levothyroxine) is highly effective not only in respect of AIT itself, but also its serious complications, particularly, hypothyroidism and related disorders. There is evidence of complete cure of AIT after thyroxinotherapy, started early. Immunosuppressive treatment is not indicated in AIT due to adverse effects: immune modulation with thyroid hormones is preferable, especially in youngest and most aged groups of patients. In fact early effective treatment of AIT with Levothyroxine is at the same time valuable way to prevent early MS, atherosclerosis and, generally speaking, foresee and avert accelerated pathological metabolic senescence [85]. The idea to prevent precocious aging by means of thyroid function improvement is not new one. It dates back to classical works by Victor Horsley (end of XIX century) and Arnold Lorand (1911) [86-87]. Now it seems to resurrect due to obvious link between aging, autoimmunity and thyroid regulation [75, 85]. Thyroid hormones and resveratrol, resembling them in structure, are even able to stimulate the expression of sirtuins (survival genes) [88].

To predict and prevent AIT itself, a physician should take into account proven facts related to its etiology [40].

To conclude all aforementioned data, we may delineate several most important contingents, which stand under high risk of early complicated AIT. These are:

- Marfanoid individuals with non-syndromal CTD and/or Marfan syndrome, MASS-phenotype and related disorders. It looks like in all these anomalies defective connective tissue can not establish appropriate barriers in order to prevent conflict between local autacoid-driven and systemic neuroendocrine regulatory mechanisms;

- Adolescents with SPS (juvenile dyspituitarism or obesity with rose striae). It looks like stress-associated metabolic deprivation and hyperprolactinemia in this disorder may facilitate both early AIT and hypothyroidism with transformation into MS;

- Individuals misusing iodine and iodine-containing drugs (Amiodarone, Nexterone, Cordarone) or biologically active iodized food amendments because of AIT provocation and disorder of pituitary-thyroid feedback mechanism under the influence of iodine excess [29. 84] (see also above chapter V). This group most probably includes also individuals exposed to radionuclides and to iodine prophylaxis with huge doses of non-radioactive iodine after nuclear disasters. We have under our constant prolonged medical follow-up a group of 596 persons, exposed to radionuclides and to massive iodine prophylaxis in 1986, immediately after Chernobyl disaster (migrants from that area or so called "liquidators"). Among them in 25 years elapsed we observed much greater prevalence and severity of AIT and hypothyroidism, than among local St. Petersburg residents of the same age [22, 89]. Similar data on increased prevalence of AIT and greater incidence of CTD among children born to families of exposed persons as well as in patients after high consumption of iodine were recently reported by Ukrainian researchers [90-92].

1. Patients treated for chronic hepatitis, malignancies or other diseases by interferons and/or other kinds of cytokine therapy are under increased risk of AIT and should be medically followed up for thyroid

status, because of pathogenetic roles of interleukins and other cytokines in AIT, which was demonstrated by many other authors, including us [27, 40, 54, 57, 82, 92].

2. Patients with thyroid disorders and their close relatives, as well as those, whose HLA haplotype or genome contain alleles predisposing to autoallergy and specifically to AIT, should abstain from iodine-containing drugs and have to prefer vitamin-mineral compositions without iodine. Iodized cooking salt is useful exclusively in districts with proven endemic iodine deficit, but not everywhere [29, 84].

3. All above mentioned contingents have to be under special medical monitoring with periodical medical check-ups. Medical team for their follow-up must include an endocrinologist-thyroidologist. Related laboratory program shall involve thyroid autoimmunity monitoring, preferably with "ELI-test" method.

4. Early and advanced symptoms of AIT are very versatile and may involve all organs and systems. Due to this correct diagnosis of AIT may be delayed, if the physicians of various specialties will put the diagnoses by means of search and reasoning within the limits of their specialization only. Manifestations of AIT and hypothyroidism are often observed during many years (being factually "written on patient's face"), but misinterpreted as "dermatological", "psychiatric", "gastroenterological" or "dental" problems (although dry skin, depression and phobiae, constipation or chronic cheek biting – all may be typical signs of AIT!).

That's why early diagnosis and effective preventive treatment of AIT are only possible if all medical doctors, regardless of their profile, will be well-educated in Thyroidology. The presence of anti-thyroid autoantibodies *per se* is not an equivalent of autoimmune thyroid disease; healthy individuals also produce them [fig. **7** above]. It means that early clinical manifestations as well as dynamics of antibody titers are very essential for diagnosis.

In conclusion we need to coin the following verdict: Because physiological neuroendocrine regulation is inseparable from immune one, <u>every</u> endocrine disorder may have an autoallergic variant.

Self-recognition and interaction with self ligands is a major kind of immune system activity both in health and in disease [93-94], so anti-thyroid autoantibodies are most common among normal individuals and AIT is most widespread somatotype-related autoimmune disease of nowadays.

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COMPETING INTERESTS' STATEMENT

The authors declare no competing financial interests

REFERENCES

[1] Treichler P.A. AIDS, Gender, and Biomedical Discourse: Current Contests for Meaning / In: Fee E., Fox D.M. AIDS: the Burdens of History. Berkley-LA-Oxford, UC Press, 1988.
[2] Hashimoto H. Zur Kenntnis der lymphomatösen Veränderung der Schilddrüse (Struma lymphomatosa), Archiv f klin Chir (Berlin) 1912; 97:219–250.
[3] Donath J, Landsteiner K. Über paroxysmale Hämoglobinurie. Münch Medizin Wochensch 1904; 51: 1590-1593.
[4] Unna PG. Über plasmazellen, insbesondere beim Lupus. Monattsschrift f prakt Dermatol 1891;12: 296.
[5] London ES. Selected Works. Leningrad, Nauka Publ 1968, pp. 1-234 P. [in Russian]
[6] von Basedow K.A. Exophthalmos durch Hypertrophie des Zellgewebes in der Augenhohle. Wschr ges Heilk 1840; 220: 197.
[7] Beall GN, Solomon DS. Inhibition of long acting thyroid stimulator by thyroid particulate fractions. J Clin Invest 1966; 45(4): 552-61.
[8] Kocher Th. Über Kropfextirpation und ihre Folgen. Arch f klin Chirurg 1883;29: 254.
[9] Chatin A. Recherches de l'iode dans l'air, les eaux, le sol et les produits alimentares des Alpes de la France et du Piemont. Cr Acad Sci 1852;34: 51.
[10] Vinogradova YE, Shinkarkina AP, Poverennyi AM. Autoimmune thyroiditis in the diseases of blood system. Ter Arkhiv 2003;75(12): 83–92. [in Russian]

[11] Amino N, *et al.* Hashimoto's disease and Dr. Hakaru Hashimoto. Endocrine J 2002; 49: 393–7.

[12] Hashimoto K. Hakaru Hashimoto – a family memory. In: Nagataki S, *et al.* Eds. 80 years of Hashimoto disease. Amsterdam a.e, Elsevier Sci Publ 1993; pp. 7 – 9.

[13] Sawin CT. The Heritage of Dr. Hakaru Hashimoto (1881-1934). Endocrine J 2002; 49: 399– 403.

[14] Stroev YuI. From Karl von Basedow – to Eugeniy Bazarov. Med –XXI vek 2008; 2(11):121-33.

[15] Jenner E. An Inquiry into the Causes and Effects of the Variolae Vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of the Cow Pox. London, S. Low 1798.

[16] Graham A. Riedel's struma in contrast to struma lymphomatosa. West J Surg 1931;39: 681–89.

[17] Witebsky E, *et al.* Chronic thyroiditis and autoimmunization. JAMA 1957; 164: 1439-1447.

[18] Witebsky E, Rose NR. Studies on organ specificity. IV Production of rabbit thyroid antibodies in the rabbit. J Immunol 1956;76: 408 – 16.

[19] Roitt IM, *et al.,* Auto-anibodies in Hashimoto's disease (Lymphadenoid goiter). Lancet 1956;2: 820–821.

[20] Roitt IM, Doniach D. Human auto-immune thyroiditis. Serological studies. Lancet 1958;2: 1027 – 33.

[21] Williams ED, Doniach I. The post-mortem incidence of focal thyroiditis. J Path Bact 1962; 83: 255–264.

[22] Churilov LP, *et al.* Autoimmune thyroiditis– actual problem of current endocrinology. Vestn S-Petergurgsk Univ Ser. 11. Meditsina 2006; 2: 3–25. [in Russian]

[23] Stroev YuI, Churilov LP. 100 years of single Hakaru Hashimoto's academic paper immortalized its author. Actual Probl Transp Med (Odessa) 2012; 2(28): 67 – 70. [in Russian]

[24] Churilov LP, *et al.* Hypotrophy in juvenile draftees – actual social problem. In: Erman MV, Ed. Health of the Young. St.Petersburg, SPbSU Publ 2005; pp 16–17. [in Russian]

[25] Mudzhikova OM. The characteristics of immuno-endocrine reactivity in patients with non-syndromal connective tissue dysplasia. Fundam nauka klin med 2006; 9: 222-223. [in Russian]

[26] Stroev YuI, *et al.* Clinical Pathophysiology of early metabolic syndrome: Pathogenetic roles of juvenile dyspituitarism, connective tissue dysplasiae and autoimmune thyroiditis. Patol fiziol experim terap 2011;3:3–14. [in Russian]

[27] Kalashnikova AV, *et al.,* Role of autacoids in pathogenesis of endocrine disorders in non-syndromal systemic dysplasia of connective tissue. Vestn S.-Petergurgsk Univ Ser 11 Meditsina 2009; 4: 3 – 25. [in Russian]

[28] Tsigos C, Kyrou I, Chrousos GP. Stress, Visceral Obesity, and Metabolic Complications. Ann NY Acad Sci 2006;1083:77— 110.

[29] Stroev YuI, Churilov LP. Endocrinology of Adolescents. Saint Petersburg. ElBi-SPb Publ 2004; 1-384. [in Russian]

[30] Brydon L, *et al.* Stress-induced cytokine responses and central adiposity in young women. Int J Obes (Lond) 2008; 32(3):443 - 50.

[31] Judge DP, Dietz HC. Marfan's syndrome. Lancet 2005; 366:1965—76.

[32] Iglesias P, Díez JJ. Influence of thyroid dysfunction on serum concentrations of adipocytokines. Cytokine 2007;40(2): 61—70.

[33] Novak K, *et al.* Rat thyroid gland express the long form of leptin receptors, and leptin stimulates the function of the gland in euthyroid non-fasted animals. Intern J Molec Med 2002; 9: 31-5.

[34] Matarese G, Leiter EH, La Cava A. Leptin in autoimmunity: many questions, some answers. Tissue Antigens 2007;70(2): 87—95.

[35] Pisareva SV, Stroev YuI, Churilov LP. Leptin as immunoneuroendocrine regulator of metabolism. Trudy Mariinsk Boln 2004;3: 112—120. [in Russian]

[36] Matarese G, Sanna V, Fontana S, Zappacosta S. Leptin as a Novel Therapeutic Target for Immune Intervention. Curr Drug Targets — Inflammat and Allergy 2002;1(1): 1322.

[37] Marzullo P, *et al.* Investigations of thyroid hormones and antibodies in obesity: leptin levels are associated with thyroid autoimmunity independent of bioanthropometric, hormonal, and weight-related determinants. J Clin Endocrinol Metab 2010;95(8): 3965—72.

[38] Bossowski A, *et al.* Analysis of serum adiponectin, resistin and leptin levels in children and adolescents with autoimmune thyroid disorders. J Pediatr Endocrinol Metab 2010:23(4): 369—77.

[39] Fondal WJr, *et al.,* Transforming growth factor-beta has contrasting effects in the presence or absence of exogenous interleukin-12 on the *in vitro* activation of cells that transfer experimental autoimmune thyroiditis. J Interferon Cytokine Res 2001;21(1):971—80.

[40] Eisenbarth GS, Ed. Immunoendocrinology: Scientific and clinical aspects. New York and elsewhere, Springer – Humana Press, 2011.

[41] Herder Ch, *et al.* Transforming Growth Factor-β1 and Incident Type 2 Diabetes: Results from the MONICA/KORA case-cohort study, 1984—2002. Diab Care 2009;32(10): 1921—23.

[42] Yamazaki K, *et al.* Iodide-induced chemokines and genes related to immunological function in cultured human thyroid follicles in the presence of thyrotropin. Thyroid 2010;20: 67-76.

[43] Churilov LP, Stroev YuI., Wenlong Zhao. Sanogenic vs Pathogenic Effect of Iodine on the Organism and Ageing. In: Prevention of Age-related Diseases. Shanghai : EPU-Fudan Univ Publ 2009; pp. 50—52.

[44] Se He Wang, Baker J.R. Immunopathogenesis of thyroiditis. In: Eisenbarth GS, Ed. Immunoendocrinology: Scientific and Clinical Aspects. NewYork *et al.*, Springer Humana Press 2011; 443-455.

[45] Mazzoitti G, *et al*. High leptin levels in women developing postpartum thyroiditis. Clin Endocrinol 2004; 60(2): 208—13.

[46] Stroev YuI, *et al.* Obesity in Adolescents. St. Petersburg, ElBi-SPb Publ 2003; pp. 1-216.

[47] Takai S, Jin D, Miyazaki M. Chymase as an important target for preventing complications of metabolic syndrome. Curr Med Chem 2010;17(28):3223—29.

[48] Zaichik ASh, *et al.,* mmune response as sanogenic and pathogenic factor in development of auto-allergic and infectious diseases. In: Petrov SV *et al*, Eds. Selected Lectures of Leading Scholars, Faculty of Medicine, St. Petersburg State University. St. Petersburg, Univ. Publishers 2005; pp. 12–27.

[49] Stroev YuI., Churilov LP. Autoimmune thyroiditis and redox-potential of the organism. Zah patol ta patolohichn fiziol (Luhan's'k). 2010; 5(2): 68. [in Russian]

[50]   Livshits G, Trofimov S, Pantsulaia T. Genetic variation of circulating leptin is involved in genetic variation of hand bone size and geometry. Osteoporosis internat 2003;14(6): 476—83.

[51]   Zaichik ASh, Churilov LP. General Pathophysiology with the Principles of Immunopathology, 4th edition. St.Petersburg, ElBi-SPb. Publishers, 2008. [in Russian]

[52]   Stroev YuI., Churilov LP. Skin striae: new concepts of pathogenesis and diagnostical value of an old symptom. Med - XXI vek 2008; 2 (11): 50—55. [in Russian]

[53]   Stroev YuI, *et al.* Immunoneuroendocrine interactions in Hashimoto's thyroiditis. III International symposium: Interactions of the Nervous and Immune Systems in Health and Disease. St.Petersburg: Russia, 2011; pp. 65–66.

[54]   Tsybikov NN, *et al.* Content of pro-inflammatory cytokines, endothelin-1 and autoantibodies against them in autoimmune thyroiditis. Dalnevost med zh 2009; 3:17–19. [in Russian]

[55]   Combs TP, Pajvani UB, Berg AH. A transgenic mice with a deletion in the collagenous domain of adiponectin sisplays elevated circulating adiponectin and improved insulin sensitivity. Endocrinology 2004;145: 367–85.

[56]   Mudzhikova OM, Stroev YuI, Churilov LP. Connective tissue, somatotype and thyroid gland. Vestn S-Petergurgsk Univ Ser 11 Meditsina 2009; 2: 3—25. [in Russian]

[57]   Churilov LP, Stroev YuI. The autoimmune thyroiditis: centennial jubilee of the social disease. In: Poletaev AB, Skurydin SV. Immunophysiology. Autoimmunity in Health and Disease. Contribution to Predictive and Preventive Medicine. Moscow, PCP Preventive Medicine Publ 2012; pp. 50–64.

[58]   Pervanidou P, *et al.* The immediate and long-term impact of physical and/or emotional stress from motor vehicle accidents on circulating stress hormones and adipo-cytokines in children and adolescents. Stress 2008;11(6): 438 – 47.

[59]   Stroev YuI, *et al.,* Autoimmune thyroiditis as a risk factor of the metabolic syndrome. Med acad zh RAMN 2012; Spec. Issue: 44 – 47. [in Russian]

[60]   Bao W, *et al.* Persistence of multiple cardiovascular risk clustering related to syndrome X from childhood to young adulthood: the Bogalusa Heart Study. Arch Intern Med 1994;154: 1842-47.

[61]   Stroev YuI, *et al.* Thyroid status in adolescents with hypothalamic syndrome of pubertal period. Trudy Mariinsk Boln 2002;I: 49—51. [in Russian]

[62]   Stroev YuI, Churilov LP, Bel'gov AYu. On the possibility of the transformation of hypothalamic syndrome of pubertal period into metabolic cardiovascular X-syndrome. Bull VA Almazov Res Inst Cardiol 2004; 2(1): 229. [in Russian]

[63]   Stroev YuI, Tsoy MV, Churilov LP, Shishkin AV. Classical and modern concepts of metabolic syndrome. II. Pathogenesis. Vestn S-Petergurgsk Univ Ser 11 Meditsina 2007;4: 3—14. [in Russian]

[64]   Osborn O, Olefsky JM. The cellular and signaling networks linking immune system and metabolism in disease. Nature (Med) 2012;18(3): 363– 74.

[65]   Vettor R, *et al.,* Review article: adipocytokines and insulin resistance. Aliment Pharmacol Ther 2005; 22(Suppl 2): 3—10.

[66]   Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab 2003; 88: 2438-44.

[67]   Kloen P, *et al.* Transforming growth factor-beta: possible roles in Dupuytren's contracture. J Hand Surg (Am) 1995; l:101—108.

[68] Zaichik ASh, Churilov LP. Pathophysiology. V.II. Pathochemistry. Endocrine & Metabolic Disorders. 3rd edition. St. Petersburg, ElBi Publishers 2007. [in Russian]

[69] Maximova AV, *et al.,* Hashimoto's autoimmune thyroiditis, hypothyroidism, prolactin and female reproduction system. Actual Probl Transp Med (Odessa) 2011; 2(24): 122–130. [in Russian]

[70] Twig G, Shina A, Amital H, Shoenfeld Y. Pathogenesis of infertility and recurrent pregnancy loss in thyroid autoimmunity. J Autoimmun 2012; 38(2-3): J275-J281.

[71] Giustarini E, *et al.* Thyroid autoimmunity in patients with malignant and benign breast diseases before surgery. Eur J Endocrinol 2006; 154(5): 645 -649.

[72] Orbacha H, Schoenfeld Y, Hyperprolactinemia and autoimmune diseases. Autoimm Rev 2007;6: 537-542.

[73] Shabanova SSh., Alekberova ZS. Neuroendocrinology and autoimmunity: Current perspectives. Nauch-pract. Revmatol 2010;1: 24 – 31. [in Russian]

[74] Poletaev AB, *et al.,* Immunophysiology *versus* Immunopathology: natural autoimmunity in human health and disease. Pathophysiology 2012; 19(3): 221-231.

[75] Churilov LP, Stroev YuI, Mudzhikova OM. Ageing, thyroid and autoallergy: New insight into pathogenesis and treatment. Wien Klin Wochenschr 2009; 121(7—8, suppl 1): 70—71.

[76] Zaichik A.Sh. The changes in specific cellular functions under the influence of antibodies. Tsitologiya 1978; 20(9): 22—26. [in Russian]

[77] Coico R, Sunshine G, Benjamini E. Immunology: A short course. 5th edition. Hoboken, Wiley, 2003.

[78] Safer JD. Thyroid Hormone Action on Skin. Dermato-Endocrinol 2011;3(3): 211–215.

[79] Singh R, *et al.* Hypothyroidism alters the expression of Bcl-2 family genes to induce enhanced apoptosis in developing cerebellum. J Endocrinol 2003; 146: 39–46.

[80] Mihara S, *et al.* Effects of thyroid hormones on apoptotic cell death of human lymphocytes. J Clin Endocrinol Metab 1999;84(4): 1378–85.

[81] Kylin E. Studien über das Hypertonie-Hyperglykamie-Hyperurikamie syndrome. Zentralbl f Inn Med 1923;44: 105— 127.

[82] Churilov LP, *et al.* Immunoendocrine interactions in acute and chronic disorders as a manifestation of conflict between systemic and local regulation. Tavrich Med Biol Vestnik (Sympheropol') 2012; 15(3) 230–32. [in Russian]

[83] Stroev YI, Churilov LP. Adolescent Obesity with Rose Striae as a Juvenile Form of Metabolic Syndrome Characteristic for Marfanoid Individuals and Related to Autoimmune Thyroiditis. J Diabetes 2011; 3(1s): 80-81.

[84] Stroev YuI, Churilov LP. The heaviest bio-element (on the occasion of 200 years since the discovery of iodine). Biosphera 2012; 4(3): 313 – 342. [in Russian]

[85] Stroev YuI, *et al.* Diabetes mellitus type II as equivalent of accelerated metabolic ageing: markers and role of thyroid hormones in therapy. In: Prevention of Age-related Diseases. Shanghai : EPU-Fudan Univ Publ 2009; pp. 10—11.

[86] Lorand A. Old age deferred. 5th edition. Whitefish, Kessinger Publ, 2003.

[87] Churilov LP, Stroev YuI. The Life as a Struggle for Immortality: History of Russian Gerontology with an Immunoendocrine Bias. Ann Tradit Chin Med 2013; 6: 81–137.

[88] Engel N, Mahlknecht U. Aging and anti-aging: Unexpected side effects of everyday medication through sirtuin1 modulation. Int J Mol Med 2008; 21: 223–32.

[89] Churilov LP, *et al.,* Remote consequences of Chernobyl disaster impact on thyroid gland of St. Petersburg residents. Immunoneuroendocrine interactions in Hashimoto's thyroiditis. Ist

Russian Congress in Chronobiology and Chronomedicine (with International Contribution). Vladikaukaz: Russia, 2008; p. 89. [in Russian]

[90] Korenev NM, *et al.,* Health status of children born to families of parents irradiated due to Chernobyl disaster. Zdorov'e rebionka 2012; 6(41): 66–70. [in Russian]

[91] Abaturov AE, *et al*. Chronic autoimmune thyroiditis in children. Zdorov'e rebionka 2009; 1(16): 96–100. [in Russian]

[92] Chekalina NI, *et al*. Modern conceptions on autoimmune thyroiditis: Etiology and pathogenesis. Visnyk VDNZU Ukr Med Stomat Acad (Poltava) 2012; 12(4): 229 – 32. [in Ukrainian]

[93] Zaichik ASh, Poletaev AB, Churilov LP. "Self" recognition and interaction with "self" as a main activity form of adaptive immune system. Vestn S.-Petergurgsk Univ Ser 11 Meditsina 2013; 1: 3 – 25. [in Russian]

[94] Zaichik ASh, Poletaev AB, Churilov LP. Natural autoantibodies, immunological theories and preventive medicine. Vestn S.-Petergurgsk Univ Ser 11 Meditsina 2013; 2: 3 – 25. [in Russian]