The Changing Face of Autoimmune Disease: From *JAMA* to *IMAJ*

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Through the years, our understanding of autoimmunity and autoimmune disease has changed profoundly. Once thought to be rare, we now know that autoimmunity plays a significant role in the pathogenesis of many of our most common and troublesome illnesses. Autoimmune thyroiditis has provided an excellent model for studying the basis of autoimmune disease. Human thyroiditis can be duplicated in experimental animals, either by immunization with the major autoantigen, thyroglobulin, or by selective inbreeding of spontaneously susceptible animals. The genetic traits predisposing to susceptibility have been elucidated in experimental animals and promise to provide the tools for recognizing humans with heightened susceptibility. With greater understanding of the immunogenetics and immunopathogenesis of the disease, it should be possible to develop benign strategies for intervention before damage is no longer reversible.

In 1951, one of us (N.R.R.), working as a junior investigator with Professor Ernest Witebsky at the University of Buffalo, undertook a detailed study of the antigenic properties of thyroglobulin, the principal protein product of the thyroid gland. We found that this molecule can function as an autoantigen; that is, it can induce an antibody response in the very same animal from which it was taken. Even more surprising was the appearance of inflammatory lesions in the thyroid gland, producing a typical picture of thyroiditis. The appearance of the inflamed thyroids in autoimmunized rabbits, dogs and guinea pigs was so reminiscent of chronic lymphocytic thyroiditis in humans that we proposed that the human disease was caused by auto-immunization. We then proceeded to demonstrate antibodies to thyroglobulin in the sera of several patients with thyroiditis [1].

At the time, the doctrine of *horror autotoxicus* reigned supreme and our finding met with great skepticism. Antigens of a few "sequestered" tissues, such as the lens, testis and brain, were known to induce autoimmune disease. That a non-sequestered, autologous antigen could induce a human autoimmune disease turned that prevailing immunologic dogma on its head. The findings were sufficiently revolutionary that Witebsky decided that they should be reported in a major medical journal. By coincidence, Dr. John Talbot, former Chairman of Medicine at the University of Buffalo and a close colleague of Witebsky, had just become editor of the *Journal of the American Medical Association* (*JAMA*). Talbott begged Witebsky to send him an article of fundamental significance in order to enhance the scientific stature of the journal. A lengthy article, describing both the studies on experimental animals and the parallel investigations of humans with chronic thyroiditis, was assembled in June 1955 and finally appeared in June 1957 [1]. As predicted, the article had a major impact on immunologic thought — as demonstrated by its frequent citations in the medical literature, leading to its selection as a "citation classic" [2].

The *Israel Medical Association Journal* (*IMAJ*) is being reborn under the dynamic leadership of Professor Yehuda Shoenfeld, very much the way *JAMA* was revitalized under Dr. Talbot nearly half a century ago. It seems appropriate, therefore, to look back over some of the major discoveries associated with autoimmune thyroiditis as the prototype of a large group of autoimmune maladies. There is an inherited risk of developing any of these disorders. Autoimmune thyroiditis provided the first example of an autoimmune disease associated with a particular genetic trait, the major histocompatibility complex [3]. The goal of this article is to illustrate how information on genetic predisposition has evolved over the past four decades. Identifying subjects at greatest risk of developing autoimmune disease may soon permit interventions to interrupt the pathological process before irreversible damage to the target organ ensues.

Inheritance of Thyroid Autoimmunity

Often, major advances in medical science follow the observations of astute clinicians. Thus, Reginald Hall and his associates in 1960 [4] pointed out the marked clustering of thyroid diseases in certain families. Hall and Stanbury [5]

in 1967 further showed that even clinically euthyroid relatives of patients with autoimmune thyroid disease, including chronic thyroiditis and Graves' disease, have antibodies to thyroglobulin or other thyroid antigens much more frequently than age- and sex-matched controls. In a large-scale study, Roitt and Doniach [6] in 1967 found that 45% of euthyroid female relatives of patients with thyroiditis or myxedema have one or more of the thyroid autoantibodies, and 32% of euthyroid male relatives are positive. In contrast, controls matched for age and sex gave only 12–14% positive reactions. These studies show that there is a hereditary tendency to develop autoimmunity to thyroid antigens.

Other clinicians recorded an extraordinarily high incidence of other autoimmune diseases in patients with autoimmune thyroid disease. Irvine [7] in 1965 and Ardeman and colleagues [8] in 1960 demonstrated a significantly heightened incidence of antibodies to thyroid antigens in patients with pernicious anemia or atrophic gastritis. Conversely, patients with thyroiditis or myxedema had a high incidence of antibodies to gastric antigens or intrinsic factor. Similar associations were reported with idiopathic adrenal insufficiency, idiopathic parathyroid disease, and the insulin-dependent form of diabetes mellitus. High titers of autoantibodies were also found in a large proportion of patients with Sjögren's syndrome. These observations suggest that individuals with one form of autoimmunity are prone to develop another distinct autoimmune response.

It must be remembered, however, that members of a family share not only a gene pool, but also nutritional practices, environmental pollutants and infectious agents. Stronger evidence that these associations are hereditary is based on the numerous studies in identical twins, in which concurrence of autoimmune thyroid disease far exceeds that seen in non-identical twins [9,10]. In addition, there is a high frequency of thyroid autoimmunity in patients with chromosomal aberrations, particularly trisomy 21 (Downs' syndrome), as well as in mothers of these patients [11]. These clinical observations provided the rationale for a more searching investigation of the genetic factors that affect susceptibility to autoimmune thyroid disease in experimental models.

Thyroiditis in Experimental Animals

Because of the large number of inbred strains available, mice are well suited for detailed studies of genetic predisposition to autoimmune disease. Lymphocytic thyroiditis can be induced in mice by injection of purified mouse thyroglobulin combined with complete Freund's adjuvant. The disease is characterized by production of circulating autoantibodies to thyroglobulin and infiltration of the thyroid gland with mononuclear cells, simulating the appearance of chronic lymphocytic thyroiditis of humans. Our first genetic investigation [3] showed that, despite the many genetic differences between different strains of mice, susceptibility to autoimmune thyroiditis correlates with the MHC[1] of the mouse. The same pattern of autoantibody response and thyroid inflammation, regardless of the strain's genetic background, was evident in congenic mice bearing the same histocompatibility type. When we mated good-responder and poor-responder mice, the F_1 hybrid response was equivalent to the good-responder parent, showing that susceptibility to thyroiditis is a dominant trait. In the F_2 generation, responsiveness to thyroglobulin segregated and all good responders were of the good-responder parental MHC haplotype.

To ensure that the response was due to recognition of mouse thyroglobulin and not to susceptibility to the adjuvant effects of Freund's mixture, we repeated some of the experiments, using bacterial lipopolysaccharide as adjuvant [12]. The same mouse strains were susceptible to thyroiditis, showing that the response is not dependent upon the adjuvant used. The experiments were also instructive in demonstrating that thyroglobulin is effective as an autoantigen, even when administered intravenously if accompanied by a lipopolysaccharide injection, eliminating the possibility that denaturation due to emulsification in Freund's adjuvant is responsible for its autoantigenic properties.

We next established that responsiveness to thyroglobulin is dependent upon the T cells [13]. The experiments were carried out by immunizing mice depleted of T cells by adult thymectomy and irradiation followed by reconstitution with bone marrow cells that had been treated to remove T cells. First, we found that response to mouse thyroglobulin requires the presence of T cells. Next, we could show that when poor-responder mice were thymectomized, lethally irradiated, and restored with good-responder bone marrow and good-responder thymus cells, they developed severe disease and high titers of autoantibody. On the other hand, recipients of poor-responder thymus cells developed moderate to poor responses to thyroglobulin.

To determine more precisely the location of genes responsible for the response to thyroglobulin, we tested a large number of intra-H-2 recombinants [14,15]. The major genetic control of the immune response to thyroglobulin in mice localized to the centromeric (left) side of the H-2 complex and, more precisely, in the I-A subregion. Good responses were associated with I-A^k, I-A^s and I-A^q loci. Using other recombinant strains differing only at *D*-end alleles, we showed that *D* genes exerted a modifying role on the severity of thyroiditis. Animals with *I-A* genes encoding good response developed severe or mild disease depending upon their allele at the *D* locus. These experiments suggest that MHC class II genes are involved in the initial recognition of thyroglobulin, whereas MHC class I genetic traits regulate the effectors of thyroid lesions. This hypothesis was strengthened by the *in vitro*

[1] MHC = major histocompatibility complex

demonstration that MHC-class I-restricted cytotoxic T cells can directly injure mouse thyrocytes *in vitro* [16].

The obese strain chicken provides a model of spontaneous autoimmune thyroiditis not requiring deliberate immunization with thyroglobulin. As such, it closely resembles the human chronic lymphocytic thyroiditis. In the chicken, the MHC is the *B* locus, which encodes for both a blood group and tissue antigen. Although the OS[2] flock is not fully inbred, two alleles, B^{12} and B^{5}, are found in the greatest frequency. Greater pathology and higher antibody titers were observed in $B^{13}B^{13}$ and $B^{13}B^{15}$ birds than in their $B^{5}B^{5}$ siblings [17]. The influence of the *B* allele on the development of disease was also evident in crosses between the OS and parental CS chickens [18]. There were, however, marked differences between different families of birds, suggesting that non-MHC genes play an additional regulatory role in the immune response [19]. One set of non-MHC genes that distinguished OS chickens from their normal counterparts acted through the thymus, suggesting that a thymic abnormality contributes to inordinate susceptibility of OS birds to the multiple autoimmune processes [20]. A second abnormality that may account for the development of spontaneous thyroiditis in OS chickens was found in its thyroid gland and related to the ability of the thyroid follicular cells to take up iodine and incorporate it into thyroglobulin [21,22].

On the basis of these findings, we suggested that the spontaneous development of autoimmune disease depends upon the coincidence of at least three different types of genetic lesions, which happen to be fixed in the OS strain by selective breeding [23]. These lesions include a heightened immune response to thyroglobulin, encoded by MHC-associated genes and at least two types of non-MHC traits, one involving thymic maturation and the balance of helper and regulatory T cells, and the second influencing the uptake of iodine and its incorporation into thyroglobulin. Animals that inherit all three defects are the ones most likely to develop early and severe disease.

Autoimmune Thyroiditis in Humans

Since the autoimmune thyroiditis shows strong familial clustering, a heightened susceptibility is probably inherited [24]. Yet, most investigators agree that autoimmune disease is due to a combination of genetic and environmental stimuli. To detect the strongest inherited traits, we decided to study groups of families that each had a child with chronic lymphocytic thyroiditis. Our hypothesis was that if children develop an autoimmune disease at an early age, they have more of the genetic predisposing factors leading to autoimmunity than adults who get the disease later in life.

The evidence obtained from studies in the children with CLT[3] supports our hypothesis [25]. When thyroid autoimmunity is found in both parents, over 70% of the offspring (omitting the proband) developed thyroid autoimmunity; if only one parent had autoantibodies, only 50% of the clinically normal siblings had thyroid autoantibodies. If neither had autoantibodies, only 30% of the siblings showed autoantibodies. The data suggest a distinct "gene-dosage effect" due to the accumulation of genetic factors.

Table 1. Proband haplotypes shared by siblings and thyroid autoimmunity

HLA-A and -B	Siblings	With AB		Subclinical disease	
shared with proband	Total No.	No.	%	No.	%
Both haplotypes	19	17	90	6	32
One haplotype	13	9	70	1	8
No haplotype	9	5	56	0	0

On a populational basis, we previously found no association with particular HLA class I haplotypes with CLT. Within a family, however, autoantibodies and subclinical disease of siblings share the HLA A and B haplotype with the juvenile proband with CLT. Our work suggested that different HLA haplotypes would predispose to autoimmunity in different families and we predicted that the class II genes represented would be more informative.

A first step in testing this hypothesis was to select 10 patients with juvenile CLT and to perform HLA-DR typing to determine if overexpression of particular alleles was apparent [Table 1]. HLA-DR typing was performed at the DNA level, using sequence-specific oligonucleotide probes [26]. Six of the 10 patients carried the DR4 allele for a frequency of 30%, a higher allele frequency ($P=0.05$) than found in the general population (approximately 17% allele frequency). Even though the sample size is small, we believe that this indicates a trend that may have biological significance. Three DR4 subtypes were represented, DRB *0401, *0402 and *0403. Other DR allele frequencies in this juvenile population (DR7=15%; DR1=15%; DR3=15%; DR11, 12, 13, 14, 15 each 5%) were not significantly different from the expected frequency. Thus genetic factors are more prominent in patients with earlier age of onset, probably because younger patients encounter fewer non-genetic risk factors than adults.

We have been able to follow these families for over 15 years and were also able to ascertain that additional siblings have developed disease [27]. Even when no overt disease developed, some siblings were found by biochemical markers to have subclinical thyroid disease. We were able to ascertain a significant association between a particular HLA class II allele and thyroid autoimmunity as determined by the presence of autoantibodies, although the susceptibility allele differed in different families.

Immune Pathogenesis of Autoimmune Thyroid Disease

The T-cell receptor recognizes antigen as short linear fragments of proteins processed and presented by anti-

[2] OS = obese strain

[3] CLT = chronic lymphocytic thyroiditis

gen-presenting cells in context with MHC class II for helper/inducer cells. We suggest that different MHC restrictions are related to the recognition of different fragments of thyroglobulin. Therefore, the MHC restriction may differ in different families as well as in groups with different racial backgrounds. The cognate antigenic peptide may favor different T-helper cell responses (e.g., T_h1 vs T_h2) if bound to different MHC class II molecules. These issues bear on the relationship of particular determinants of thyroglobulin and the consequences of the autoimmune response: benign autoimmunity expressed only as circulating autoantibodies or as pathogenic autoimmunity in the form of autoimmune thyroid disease.

The immunopathogenesis of autoimmune thyroid disease is an unresolved issue. Both autoantibodies and cellular immunity contribute to disease. There are at least two studies in which human thyroid autoantibodies produced antibody-dependent, cell-mediated cytotoxicity, showing they have the potential to damage thyroglobulin-coated cells [28,29]. In addition, serum from thyroiditis patients may damage cultured thyrocytes by antibody-dependent cell-mediated cytotoxicity [30]. Immune complexes have also been identified in glands from patients with chronic thyroiditis [31]. The T cell role in thyroid damage may occur through different mechanisms. The T cell can show direct cytotoxic effects [32–34] or produce cytokines, such as TNF-β, which promote thyroid cell damage.

Several investigations, using anti-thyroglobulin monoclonal antibodies, have shown that there are qualitative differences between the epitope specificities of thyroglobulin autoantibodies of thyroiditis patients and those found in normal individuals [35]. Based on the results of their studies, Ruf et al. [35] hypothesized that immunoregulation in autoimmune diseases failed with respect to selected epitopes on the thyroglobulin molecule. Our own work, delineating particular fine specificities of Tg autoantibodies in patients with CLT and in euthyroid individuals, clearly shows a striking difference in the pattern of the B cell responses [36]. Antibodies from patients and from many normal individuals reacted with conserved epitopes of Tg, but patients recognized additional, species-limited determinants.

Future Strategies for Treatment/ Prevention

Using thyroiditis as a model has an advantage over other autoimmune endocrinopathies, such as Type I autoimmune diabetes, since the relevant antigen for inducing thyroid disease is known to be thyroglobulin. We have thus learned a great deal about the genetics of the immune response. If we can identify particular associations within the MHC class II loci that confer susceptibility and identify its corresponding peptide, future strategies can be envisioned for immuno-intervention. Indeed, we showed many years ago that genetically determined spontaneous thyroiditis in the BUF rat could be completely suppressed by timely intravenous administration of rat thyroglobulin in the absence of adjuvant [37].

We believe that we are on the verge of new and exciting innovations in our search for effective measures to control thyroiditis and other autoimmune diseases whose pathogenic antigen can be identified. These approaches involve using our rapidly growing genetic data banks to identify subjects at inordinate risk of developing an autoimmune disease. Knowledge of the precise antigenic determinants that instigate the pathologic autoimmune process, together with identification of the MHC restriction elements required for their presentation, will permit us to suppress or divert the harmful response before irreversible damage has been done.

The past half century of research on autoimmune disease — from *JAMA* to *IMAJ* — has indeed been a remarkable chapter in medical science.

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Capsule

Geomagnetic activity and cardiovascular parameters

Multidirectional changes in the natural history of many cardiovascular syndromes have been linked to different levels of daily and monthly geomagnetic activity (GMA). Previous studies have found that in periods of high GMA there were more admissions for acute myocardial infarction and more cases of anterior wall myocardial infarction. Results also showed a higher outpatient mortality and a trend towards higher hospital mortality from acute myocardial infarction; higher diastolic arterial pressure in healthy subjects and in treated hypertensive patients; higher prolactin and 17-corticosteroid levels in the peripheral blood; more severe migraine attacks and more admissions for CVA and cerebrovascular insufficiency in male patients; and changes in many blood coagulation cellular gradients (platelet count, basophils in the peripheral blood), a rise in platelet aggregation and fibrinogen level and a drop in leukocyte adhesiveness. In studies by E. Stoupel et al., periods of low GMA showed a related increase (negative correlation) in in-hospital non-MI-related cardiovascular deaths. Only in times of lowest GMA did inferior wall myocardial infarction exceed anterior wall myocardial infarction. Low GMA was also associated with higher levels of growth hormone and 11-ketosteroids in the peripheral blood, more sudden deaths, some increase in electrical heart instability/hourly number of ventricular and supraventricular extrasystoles, and higher rate of ventricular tachycardia.

The monthly occurrence of pregnancy-induced hypertension was negatively correlated with GMA level. Gender differences were noted in some of the parameters. Other studied parameters did not show changes related to GMA. These included hemoglobin level, electrolyte level, heart beat and pulse rate. Moreover, cardiovascular fluctuations that were related to the level of GMA also showed differences in the rising and dropping parts of the 11 year cycle of solar activity. It has been suggested that some of the changes observed in many clinical syndromes may be related to the concomitant activation of the serotoninergic system.

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