Editorial

Infection and Autoimmune Thyroid Disease

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In many different ways, it is difficult to tolerate oneself. But if we fail, autoimmune disease may develop. Immunologically speaking, the body has a number of ways to recognize external danger, and this results in a fierce immune attack on the culprits. These reactions, however, may sometimes go astray and damage not only the external cause of the danger, such as bacteria, but also the endogenous standby—oneself. Luckily, or by design, depending on your point of view, there are multiple controls to help us tolerate ourselves and prevent self-immolation, and only when these systems fail do we develop autoimmune disease. Elimination, via apoptosis, of T and B cells with a high avidity to self is the overall goal that has to be maintained throughout life. This may occur centrally in the thymus (1), where almost all self-antigens can be found at low levels, or peripherally at the site where self-antigens are normally expressed. Any T and B cells that escape early removal are kept suppressed by specific T regulatory cells (2). Some of us are more apt to develop autoimmune reactions than others, and much has been written about the role of genetics and the environment in the susceptibility and subsequent development of these complex disorders.

The autoimmune thyroid diseases (AITD) are very common examples of autoimmune disease in our population varying from thyroid overactivity (Graves' disease) to underactivity (Hashimoto's thyroiditis) and afflicting up to 10% of the population (3, 4). Familial clustering of AITD, exemplified by high sibling risk ratios (5), can actually be explained by both genetic and/or environmental influences. One of the commonest claims of evidence for the environment being important in the precipitation of AITD is the fact that identical twins are not always in synchrony. Although nonidentical twins have an expected low concordance for AITD of about 2%, identical twins have a concordance of only about 20–40% rather than 100% (6). These types of data seen in many autoimmune diseases suggest that genes are not the only causative factor. But of course, life is more complicated than such a simplistic approach because the immune systems of identical, monozygous twins are far from identical. The variable (V) genes of T cell receptors and Igs undergo random rearrangements throughout life, and so identical twins become less similar as time goes by and different environmental stimuli are experienced (7). Hence, it is quite amazing that the concordance rate for AITD remains so high in identical twins, and this provides evidence for the powerful effects of non-V genes, such as the major histocompatibility genes, CTLA-4, PTPN22, *etc.* (8) on susceptibility and development of autoimmunity. However, such observations leave room for the possibility that the environment is also an important component in the etiology of autoimmune disease. Indeed, exploring a unique 756 twin pair data set, Hansen *et al.* (9) in 2006, using thyroid autoantibodies as a marker for AITD, determined, via structural equation modeling, that only 60–70% of the risk for such markers was genetic. I do not have enough insight to accept the validity of such model-fitting procedures, especially in the absence of family data, but it certainly does appear as though genetics cannot account for all susceptibility to these common thyroid diseases.

So this logic leaves the environment as a secondary but likely important cause. And we are very familiar with some environmental precipitants (summarized in Table 1) (10). These include irradiation, as with the children of Chernobyl who developed increased thyroid autoantibodies (11, 12), and radioiodine treatment, which may precipitate Graves' disease (13), and iodine, itself or within amiodarone, which can precipitate AITD (14, 15). Smoking has also been shown to be an important factor, especially in Graves' ophthalmopathy (16, 17), and stress, although less well documented, is widely considered a precipitator by its effects on immune reactivity (18, 19). Yet these types of additive causes can account for only a small fraction of patients developing these disorders, leaving more environmental causes to be determined. What about infection (20)? The mechanisms by which infection may, theoretically, induce an autoimmune response are many (Table 2), and this makes infections an attractive hypothesis for disease initiation. Yet here we run into some difficulties because the literature is weak and polluted.

The often quoted role of yersinia enterocolitica being associated with, and precipitating, AITD has fallen into disrepute (21), as have reported retroviral infection (22). With such lack of evidence, investigators would normally search for an animal model to strengthen the hypothesis. But here the literature is also

Abbreviations: AITD, Autoimmune thyroid diseases; TLR, Toll-like receptors.

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TABLE 1. Environmental influences on AITD

Fetal size
Iodine intake
Selenium intake
Hormones
Female sex
Oral contraceptives
Pregnancy and parity
Fetal microchimerism
Stress
Direct trauma
Seasonal variation
Allergy
Smoking
Drugs
Amiodarone, antiretrovirals, campath anti-CD52
Interferon-α, IL-2, granulocyte-macrophage colony-stimulating factor
Irradiation
External
Radioactive iodine
Nuclear fallout
Viral infections
Bacterial infections
Lack of infections: the hygiene hypothesis

quiet. Although the Coxsackie B4 virus has been shown to induce type 1 diabetes in mice and the encephalomyocarditis virus can induce autoimmune myositis (23), the data for autoimmune thyroiditis is surprisingly sparse and dated. Avian leukosis virus has been used to induce chicken thyroiditis with a heavy lymphocytic infiltrate (24), and almost 20 yr ago, Penhale and Young (25) in Australia used a rat thymectomy model of autoimmune thyroiditis to show that keeping the animals in a germ-free environment made them much less susceptible to developing thyroiditis. These data, from both human and animal studies, suggest that infection could precipitate or accelerate AITD development. Such information, however, does not fit with the growing acceptance of what has become known as the hygiene hypothesis (23, 26).

The hygiene hypothesis implies that the immune system is educated by multiple exposures to different infections allowing it to better control autoimmune responses. Thus, improved living standards have been associated with decreased exposure to infections and an increased risk of autoimmune disease including allergy and type 1 diabetes mellitus (23, 27). Bacille Calmette-Guérin infection in an immunized mouse model of Graves' disease impaired the development of hyperthyroidism (28), agreeing with a variety of studies where infection has prevented, rather than accelerated, the development in animal models of type 1 diabetes, collagen-induced arthritis, and autoimmune encephalitis (23). Any useful addition to this sparse literature on AITD and the hygiene hypothesis should be welcome. In this month's issue of the *Journal*, Kondrashova *et al.* (29) add another report to their epidemiological studies of two childhood populations that they consider to have similar genetic backgrounds, one Finnish and wealthy and one Russian with a much lower economic status, and that are geographically close. These investigators have previously reported a much higher rate of microbial infections in the lower economic population and with this a much reduced prevalence of type 1 diabetes mellitus, celiac disease, and allergies (27). They now report a much reduced prevalence of thyroid autoantibodies in the lower economic population, using thyroid antibodies as a marker of future AITD. Their data agree with the hypothesis that multiple infections prevent the development of thyroid autoimmunity by exposing children to a wide variety of external antigens. Of course, their conclusions are also associated with a number of problems: 1) the frequency of thyroid autoantibodies in children is very low, around 4% in most studies, so that the entire difference between the groups in this report was based on only 12 children; 2) the iodine status of the two populations was not documented and may be critical, especially because different iodine intakes have been associated with different thyroid autoantibody rates (30); and 3) the assumption of genetic homogeneity was based on data of human leukocyte antigens, which we know are not major genetic influences on AITD (8), and there may be other important genetic differences between the two populations.

Putting aside these concerns, data from these types of analyses do agree with the hygiene hypothesis, suggesting that lack of infections dilutes the capacity of the immune system to avoid autoimmune responses. Such is the state of play: either infections enhance AITD or infections protect you. Take your pick. Most likely, the truth lies in between. We need multiple exposures to infection to train our immune system to perform well. But some infections are still able, in susceptible individuals, to break tolerance and allow autoimmune disease to develop. Here the role of the Toll-like receptors (TLR) appears to be an important area for further work (31). TLR recognize pathogen-associated molecular patterns, and their engagement activates the native immune system. This may provide a common pathway for immune education. Lack of this experience may lead to aberrant activation of autoimmune cells if they survive tolerance mechanisms. And so the possibility of infections being important mediators or inhibitors of autoimmune disease remains tantalizing. But such a possibility remains a long way from prime time.

TABLE 2. Some potential mechanisms by which infection may influence AITD

Molecular mimicry: recognizing an epitope on an external antigen such as a bacterium as self
Polyclonal T cell activation by superantigens present in bacteria
TLR activation by virus and heat-shock protein effects
Enhanced thyroid expression of human leukocyte antigen molecules allows enhanced self-antigen presentation

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