Autoimmune Endocrinopathies: Aspects of Pathogenesis and the Role of Immune Assays in Investigation and Management

Robert Volpé

It has been hypothesized over many years that the autoimmune endocrine diseases are each due to antigen-specific defects in suppressor (regulatory) T lymphocyte function. There is now increasing evidence in studies of autoimmune thyroid disease and insulin-dependent diabetes mellitus that suppressor cells are activated by irrelevant antigens but respond inadequately to specific relevant antigens. These inadequate responses are insufficient in themselves to precipitate the autoimmune disease; further insults from the environment increase the deficiencies in regulatory cell activity, adding to the genetically induced dysfunction, i.e., specific defects in antigen presentation. Diagnostic procedures for autoimmune endocrine diseases include tests of target cell function and the detection of various antibodies, which are becoming increasingly useful in prediction, diagnosis, and management of these diseases.

Indexing Terms: diabetes mellitus/Hashimoto thyroiditis/Graves disease

In this review of the immunological aspects of the autoimmune endocrinopathies, I focus particularly on autoimmune thyroid disease (AITD) and insulin-dependent diabetes mellitus (IDDM), and on the immunological assays utilized in the investigation, diagnosis, and management of patients with these conditions.

Genetic and Environmental Factors

The disturbance(s) in immunoregulation that lead to organ-specific endocrine diseases are partly genetic and partly environmental in nature (2–3). Autoimmune endocrine diseases (and those nonendocrine autoimmune disorders with which they are associated) (Table 1) tend to aggregate in families, and more than one of these maladies may occur concomitantly within the same patient or her/his family. The modes of inheritance of these disorders do not follow simple genetic rules, and environmental factors such as stress, infection, trauma, drugs, nutrition, smoking, and aging may distort the penetrance and expressivity of these conditions (by acting on the immune system) (4). The finding that the autoimmune endocrinopathies occur preferentially in individuals who have inherited certain major histocompatibility (MHC) gene markers [in humans, the human leukocyte antigen (HLA) system] definitely establishes the genetic influences in these disorders (5, 6). Most of these autoimmune diseases seem to be more prevalent in women than in men; this may be due in part to the influence of one gene on another (7) and in part to hormonal factors (8).

Immune regulation in autoimmune endocrinopathies. Table 2 depicts the HLA associations that have been observed in various autoimmune disorders (9). The HLA system (essential for antigen processing and presentation) is an important factor in the pathogenesis of these disorders; indeed, I consider the HLA genes to be crucial to the development of autoimmune diseases and possibly to their amplification (5, 6). The development of these diseases (including the disturbance in target cell function) depends on complex interactions among the antigen(s) on the target cells, the antigen-presenting cells, the CD4 helper/inducer T lymphocytes, T effector lymphocytes, the CD8 suppressor (regulatory)/cytotoxic T lymphocytes, B lymphocytes, antibodies, and various cytokines. In turn, these elements stimulate the target cells to express molecules of various types, e.g., intercellular adhesion molecules, heat-shock proteins, class I and class II MHC antigens, and other autoantigens that further modify the immune process. Controversy still abounds about the nature of the autoimmune process, the role of the antigen and of antigen presentation, and the involvement of microorganisms in these mechanisms (10, 11).

In theory, the factors that might account for the development of an organ-specific autoimmune process

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Table 1. Nonendocrine organ-specific autoimmune disorders associated with endocrinopathies.

<table>
<thead>
<tr>
<th>Endocrinopathy</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves (Basedow, Parry) disease</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>Vitiligo</td>
</tr>
<tr>
<td>Idiopathic Addison disease</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Insulinopenic diabetes mellitus</td>
<td>Sjogren syndrome</td>
</tr>
<tr>
<td>Autoimmune oophoritis and orchitis</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Autoimmune hypoparathyromid</td>
<td>Idiopathic thromocytopenic purpura</td>
</tr>
<tr>
<td>Autoimmune hypophysitis</td>
<td>Chronic active hepatitis</td>
</tr>
<tr>
<td>Infertility due to antisperm antibodies</td>
<td>Primary biliary cirrhosis</td>
</tr>
</tbody>
</table>

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would include: (a) an antigenic stimulus (however initiated, and including molecular mimicry) that would reciprocate and (or) even maintain the disorder, involving microorganismic antigens with homology to target all autoantigens, or with actual infections of the target self; (b) a precipitating antigenic stimulus, but coupled with an underlying immune abnormality; (c) abnormal antigen-specific induction of subsets of T lymphocytes because of an abnormal HLA-related gene or genes resulting in an operational disorder within the T lymphocytes ("operational" is meant to suggest that the abnormality of T-cell function may not be due to any molecular defect in or on these cells, but rather is induced by a disorder in antigen presentation to these T cells); (d) mutation of appropriate T or B lymphocytes to form an abnormal clone or clones of lymphocytes interactive with a particular target organ (these would be autonomous and not subject to normal immunoregulation, although there is no evidence for such a mutation); and (e) a specific inherent defect in immunoregulation, robably due to somewhat reduced specific antigenic induction of regulatory (suppressor) T lymphocytes by virtue of a disorder in presentation of the specific antigen; this would probably be due to abnormality(ies) of HLA-related gene(s). In this last hypothesis, the only additional necessity for precipitating the particular disease would be the presence of the antigen without any need for it to be abnormal in quality or quantity; availability of the antigen via an antigen-presenting cell, e.g., the macrophage; the appearance and (or) availability of target-cell-directed clones of helper T lymphocytes and B lymphocytes; and perturbation of the immune system by such factors as stress, trauma, infection, rags, smoking, and aging, which would be superimposed on the partial antigen-specific abnormality. In my view, the current evidence favoring the last hypothesis is increasingly compelling and is presented briefly below (12-14).

Suppressor (regulatory) T lymphocytes. Although clonal deletion of autoreactive T lymphocytes in the thymus plays an important role in the development of tolerance to self antigens, many autoreactive T lymphocytes reach the periphery, where they remain unresponsive to self antigens. Both anergy and active suppression have been postulated as explanations for this unresponsiveness (15). Anergic T lymphocytes identified in the periphery do not account for the observation that adoptive transfer of T lymphocytes from mice tolerant to a given antigen reduced the immune response to that same antigen in syngeneic recipients (16). The best explanation for this result is that some T lymphocytes can suppress immune responses.

The previous skepticism regarding the nature or even existence of suppressor (regulatory) T lymphocytes has now largely been laid to rest (13). There is increasing evidence for a role for these cells in preventing autoimmune disease, and for a deficiency of these same cells in causing these disorders (3).

There is no definitive evidence that a target cell abnormality or target cell injury or infection is necessary to induce these diseases (12), although this notion has its advocates (10, 11). Moreover, the idea that molecular mimicry (i.e., homologies between microorganismic antigens and autoantigens) might play a role, although a popular notion (10), has not been established, and there is evidence against that hypothesis (12). I believe that no abnormalities, injuries, or infections of the target cell are required in the development of these diseases (12). What is required is that the normal target cell antigen(s) be available to the T lymphocytes through antigen-presenting cells. The immunoregulatory disturbance is then quite sufficient to produce the disorder itself by virtue of the genetic abnormality of specific antigen induction of suppressor (regulatory) T lymphocytes, plus environmental factors playing on the immune system. Many membrane antigens circulate in solubilized form [e.g., the thyrotropin (TSH) receptor] and are thus available to the immune system (17). Indeed, normal peripheral tolerance is maintained by low concentrations of autoantigen, which then activate suppressor (regulatory) T cells (13); thus, genetic defects of specific antigen presentation (presumably of MHC and related genes) would result in the specific autoantigen failing to activate the regulatory cells. This may prove to be the fundamental basis of organ-specific autoimmune disease.

Autoimmune Thyroid Disease

TheAITDs include Graves disease (GD) and Hashimoto thyroiditis (HT) as well as variants of the latter (1, 2, 18-21). The clinical expression of these entities may be markedly different, yet there are genetic and pathogenic elements that are similar, if not identical, in both. Some investigators consider these two conditions to be opposite ends of a spectrum of the same disorder (1, 2). There are, however, elements that differ between these conditions and even between the variants of thyroiditis.

Table 2. Associations between HLA and autoimmune endocrinopathies and other related autoimmune disorders.

<table>
<thead>
<tr>
<th>Condition</th>
<th>HLA</th>
<th>Frequency, %</th>
<th>Relative risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic Addison disease</td>
<td>D/DR3</td>
<td>69</td>
<td>26.3</td>
</tr>
<tr>
<td>Graves disease</td>
<td>D/DR3</td>
<td>56</td>
<td>26.3</td>
</tr>
<tr>
<td>Autoimmune diabetes</td>
<td>D/DR3</td>
<td>56</td>
<td>26.2</td>
</tr>
<tr>
<td>D/DR4</td>
<td>75</td>
<td>32.2</td>
<td>6.4</td>
</tr>
<tr>
<td>D/DR2</td>
<td>10</td>
<td>30.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>D/DR3</td>
<td>50</td>
<td>28.2</td>
</tr>
<tr>
<td>Wegener syndrome</td>
<td>D/DR3</td>
<td>78</td>
<td>26.3</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>D/DR3</td>
<td>64</td>
<td>23.8</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>D/DR3</td>
<td>53</td>
<td>26.3</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>Dw5</td>
<td>25</td>
<td>5.8</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Dw5</td>
<td>70</td>
<td>14.6</td>
</tr>
</tbody>
</table>

* Increase in frequency of the disease in individuals carrying the indicated LA antigen compared with the frequency of the disease in individuals lacking a given antigen.

Adapted with permission from Svejgaard et al. (9).
GD is defined here as hyperthyroidism caused by the stimulation of the TSH receptor (TSHR) by an antibody (thyroid-stimulating antibody, TSAb). An appropriate new designation would be autoimmune thyrototoxicosis.

Autoimmune thyroiditis was first described by Hashimoto (22), who reported four patients with goiter in whom the thyroid histologic appearance manifested diffuse lymphocytic infiltration, atrophy of parenchymal cells, fibrosis, and an eosinophilic change in some parenchymal cells (Askanazy or Hurthle cells). In the "chronic fibrous" variant, fibrosis predominates and lymphocytic infiltration is less evident. In lymphocytic thyroiditis of childhood and adolescence, fibrosis, Askanazy cells, and germinal centers are less obvious than in the adult form, and thyroid antibodies tend to be lower in titer, or even absent. Postpartum thyroiditis occurs a few months after delivery as a transient form of autoimmune thyroiditis; although it generally clears (almost) completely, it may later culminate in a chronic form. In idiopathic myxedema the gland is atrophied, rather than hypertrophied. There is also an atrophic asymptomatic form, which is occult, and often discovered only at autopsy. Those persons with no clinical features, but with circulating thyroid antibodies, can also be shown to have occult autoimmune thyroiditis; some of these individuals may be in a state of "compensated hypothyroidism" (2). Although there may be subtle genetic and pathologic differences between these variants, the pathogenesis at least is similar; the term autoimmune thyroiditis is acceptable as a generic term for this group of diseases.

HT has increased in frequency over the past generation, perhaps owing to increased iodine intake over this time. [One possible mechanism to account for this observation relates to the increased immunogenicity of highly iodinated thyroglobulin, although the role of this in human AITD remains unclear (23, 24).] About 3% of the population has some functional deficiency of the thyroid secondary to autoimmune thyroiditis whereas up to 16% of elderly women have some degree of thyroid lymphocytic infiltration, usually not recognized clinically (2). About two-thirds of goiters in euthyroid adolescents are due to lymphocytic thyroiditis. GD is also common, occurring in ~1% of the population (2).

In both GD and HT there are several aspects that suggest the participation of an autoimmune process (Table 3). The overlap between GD and HT has long been recognized. Indeed, these diseases frequently aggregate in the same families. There are several reports of identical twins in which one has GD and the other HT. In fact, these two conditions can cohabit the same thyroid gland; the clinical expression will depend upon which condition predominates (2). Since there remain severe genetic, immunologic, laboratory, and clinical elements that differ between these maladies, they should still be considered separate entities.

Initial Observations

In studies of autoimmune thyroid disease, the initial observations included thyroid autoantibodies in the serum patients with HT (25), the induction of experimental thyroiditis in rabbits (26), and the presence of an abnormal thyroid stimulator in the serum of some pa

<table>
<thead>
<tr>
<th>Stigma</th>
<th>GD</th>
<th>HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic infiltration in thyroid</td>
<td>Frequently present</td>
<td>Almost invariable</td>
</tr>
<tr>
<td>Immunoglobulins in thyroid stroma</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Type of infiltrating lymphocytes in thyroid</td>
<td>B and T lymphocytes, some unidentified lymphocytes</td>
<td>B and T lymphocytes, some unidentified lymphocytes</td>
</tr>
<tr>
<td>Immune complexes in circulation</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Thymic enlargement</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Lymphadenopathy and splenomegaly</td>
<td>Infrequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Relative lymphocytosis</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Hypergammaglobulinemia</td>
<td>Occasional</td>
<td>Occasional</td>
</tr>
<tr>
<td>Benefit from corticosteroid therapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thyroid-stimulating immunoglobulin</td>
<td>Almost all</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Exopthalmos</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Evidence of cell-mediated immunity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Evidence for a defect in suppressor T lymphocytes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Examples of autoimmune diseases in patients</td>
<td>Pernicious anemia, diabetes mellitus, myasthenia gravis, Addison disease, idiopathic thrombocytopenic purpura, vitiligo</td>
<td>Pernicious anemia, diabetes mellitus, myasthenia gravis, Addison disease, chronic active hepatitis, Sjögren disease</td>
</tr>
<tr>
<td>Thyroid antibodies in relatives</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Thyroid and other autoimmune diseases in relatives</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>HLA genes (Caucasians)</td>
<td>HLA-B8 and Dw3</td>
<td>Atrophic form: HLA-B8 and DRw3</td>
</tr>
<tr>
<td>Animal models</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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ments with GD, capable of stimulating the guinea pig thyroid gland (27). This was termed long-acting thyroid stimulator (LATS) and was found to be an IgG. It is now termed thyroid-stimulating antibody (TSAb).

Immunoreactivity

The various antibodies that may be detected in AITD and their possible functions are documented in Table 4 and Fig. 1. TSAb has received the most attention because it stimulates thyroid cells, resulting in hyperthyroidism; it is directed against epitope(s) on thyroglobulin. The radioligand assay that measures binding of IgG to TSHR (by inhibition of binding of labeled TSH) generally refers to as thyrotropin-binding-inhibitory immunoglobulin (TBII). In patients with GD specifically, there is a close correlation between TBII and TSAb, which may be useful in the diagnosis of that condition (2). However, whereas TSAb represents a SHR antibody demonstrable by the TBII assay, some gGs positive in the TBII assay will not stimulate the thyroid cells, and some even inhibit TSH activity in vivo and in vitro (thyroid stimulating-blocking antibody), i.e., causing or contributing to hypothyroidism (2). This test typically is associated with atrophic thyroiditis (2). This antibody has also been associated with transient neonatal hypothyroidism, because of its passive placental transfer to the fetus (2). Although at present only functional assays (i.e., stimulation vs inhibition) differentiate between the two antibodies, evidence suggests that they bind to different epitopes on TSHR (29).

By use of assays measuring the generation of cAMP in human or FRTL-5 (fetal rat thyroid) thyrocytes, several laboratories have demonstrated TSAb in the sera of 95% of patients with untreated GD (2) (Table 5). TSAb concentrations in pregnant GD patients may increase in the first trimester, but they tend to decline in the third trimester and may sometimes temporarily disappear; in some cases, however, although the very high concentrations may become reduced, TSAb may remain markedly increased throughout pregnancy. In such instances there is a very real possibility of the fetus or newborn developing hyperthyroidism. In the fetus, this is due to passive placental transfer of the antibody, and the hyperthyroidism will gradually decline in the neonate over several weeks, making treatment necessary for only this length of time (2). After delivery, maternal TSAb might rebound to higher concentrations once again, sometimes leading to postpartum GD. TSAb tends to decline in many patients with long-term antithyroid drug therapy. Although this, along with regression of the goiter, might suggest that the patient is in remission, this remission may be short-lived, and the continued presence of TSAb is associated with a high relapse rate after discontinuance of the medication (2). TSAb becomes further increased after 131I therapy for several months as a result of the radiation-induced release of thyroid antigens, including TSHR, and then

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Antibody (function)</th>
<th>Antibody detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyoglobulin</td>
<td>Thyroglobulin antibody (no clear function)</td>
<td>Precipitin technique; tanned red cell hemagglutination; immunofluorescence on fixed thyroid sections; competitive binding RIA; coprecipitation with 125IThyroglobulin; microELISA; plaque-forming assay</td>
</tr>
<tr>
<td>PO</td>
<td>TPO (microsomal) antibody (cytotoxic in conjunction with lymphocytes)</td>
<td>Complement fixation; immunofluorescence on unfixed thyroid sections; cytotoxicity test on cultured thyroid cells; competitive binding; RIA; tanned red cell hemagglutination; microELISA</td>
</tr>
<tr>
<td>Second colloid component antigen(s)</td>
<td>CA2 antibody (no clear function); Membrane antibodies (cytotoxic with lymphocytes)</td>
<td>Immunofluorescence on fixed thyroid section; Immunofluorescence on viable thyroid cells; hemadsorption; binding assays</td>
</tr>
<tr>
<td>Thyroid and triiodothyronine</td>
<td>Thyroid hormone antibodies (bind and prevent hormone action)</td>
<td>Antigen-binding capacity</td>
</tr>
<tr>
<td>Antigen not defined</td>
<td>Growth-stimulating and growth-inhibiting antibodies (may induce or inhibit thyroid growth)</td>
<td>Effects on DNA content per thyroid cell nucleus or on G6PD activity per cell</td>
</tr>
<tr>
<td>SHR-related antigen</td>
<td>TSHR antibodies (may stimulate or inhibit thyroid cells, or neither)</td>
<td>Stimulatory assays; current terms include human thyroid stimulator, human thyrotropin-stimulating Ig (T5I); (TSAb) LATS bioassay; colloid droplet formation in human thyroid slices; stimulation of human thyroid adenylate cyclase in vitro; cytochemical assay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Binding assays: LATS protector assay; inhibition of 125I-thyrotropin binding to human thyroid membranes (TBII); fat cell membrane radioligand assay.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibitory assays: TSHR stimulation-blocking antibody</td>
</tr>
</tbody>
</table>

Table 4. Classification of antigens, antibodies, and assays used.

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G6PD, glucose-6-phosphate dehydrogenase.
Complement-fixing thyroid positive normal much patients a the titrations.

nify thyroiditis in antibodies various cells, permission.

immune CytOtoiCity non-complement-fixing Other Thus Reprinted shown shown that the presence of TPO antibodies was the

only positive result in 64% of all patients with hypothyroidism, whereas thyroglobulin antibodies were found in only 1% of such patients (31). The widespread practice of performing both tests increases the costs without diagnostic benefit (31). Even low titers of TPO antibodies correlate with thyroid lymphocytic infiltration (2Tables 6 and 7). High titers are highly suggestive of AITD, and very high titers are virtually diagnostic of AITD; nevertheless, a minority of patients with these disorders have only low titers or no detectable thyro antibodies. The recent expression of recombinant TP in the baculovirus system now permits screening by a ELISA for AITD (32).

Low titers of TPO antibodies are also observed in some cases of papillary thyroid carcinoma, nontoxic goiter, and subacute thyroiditis, as well as in many patients with no clinical evidence of thyroid disease (2). When such antibodies are detected in women before or in early pregnancy, later development of postpartum thyroiditis can be predicted; moreover, these antibodies show a transient higher increase in parallel with functional abnormalities that occur with postpartum thyroiditis (2). Thyroid antibodies in HT with increase TSH values generally decline with thyroxine TSH-sur

Table 5. Significance of TSAb.

| 1. Positive in ~95% of patients with GD. |
| 2. Positive transiently in some cases of silent and subacute thyroiditis and after acute yersiniosis (cross-reactivity). |
| 3. Declines in 3rd trimester of pregnancy, rebounds thereafter. |
| 4. If still high in late pregnancy, may cause fetal and neonatal Go. |
| 5. Rises further after 131I therapy for GD for several months. |
| 6. Usually (not invariably) declines with antithyroid drug therapy. |
| 7. If positive after antithyroid drug course, relapse of GD almost invariable. |

8. Positive test helps to diagnose euthyroid exophthalmos.

Table 6. Significance of thyroglobulin antibodies (Tg Ab) and TPO Ab. |

| 1. Tg Ab not as useful as TPO Ab (antimicrosomal Ab). |
| 2. Tg Ab rarely present without TPO Ab; TPO Ab often present without Tg Ab. |
| 3. TPO Ab correlates with thyroid dysfunction. |
| 4. Even low titers of TPO Ab correlate with thyroid lymphocytic infiltration (autopsy studies). |
| 5. High titers highly suggestive of AITD; very high titers virtually diagnostic of AITD; some AITD patients have low titers or none. |
| 6. Low titers also observed in some cases of papillary thyroid carcinoma, nontoxic goiter, and subacute thyroiditis. |

Table 7. Significance of TPO antibodies. |

| 1. Not cytotoxic per se, but correlate with thyroid damage. |
| 2. Decline in HT patients with increased TSH upon thyroxine treatment. |
| 3. Often decline in GD patients with thionamides, rise after 131I treatment. |
| 4. In early pregnancy, often predict postpartum thyroiditis. |
| 5. Rise further with postpartum thyroiditis, fall months later. |
pressive therapy (2). They also often decline in patients with GD treated with antithyroid drugs (2) (Tables 6 and 7).

Antibodies to the thyroid hormones themselves are of clinical importance only when the thyroid gland is incapable of responding to excess TSH. In such instances, antibodies to thyroxine and triiodothyronine reduce the free moiety; the addition of exogenous thyroid hormone may not yield the expected clinical improvement until the hormone binding sites on the antibody are saturated. Moreover, in the presence of these antibodies, thyroid hormone concentrations may misleadingly appear very high or low (depending on the assay system used) and may be very inconsistent with the clinical presentation (1, 2). Antinuclear antibodies are also found in AITD, as are antibodies to cell membranes and antibodies to a colloid component other than thyroglobulin. Whether there are thyroid growth-promoting or growth-inhibiting antibodies, separate from TSHR antibodies, remains controversial (2).

Autoantibodies to gastric antigens, islet cell antigens, and others are found more commonly in patients with AITD by virtue of the inheritance of more than one disease-susceptibility gene situated in proximity on chromosome 6. Antibodies against certain bacteria, such as Yersinia enterocolitica, are encountered commonly in AITD. They appear to arise from an artifact of homology between thyroid and bacterial antigens, and do not signify the presence or relevance of actual bacterial infection (2, 12).

T Lymphocytes

Studies of numbers and functions of T lymphocytes have been two-pronged, i.e., those of generalized (non-specific) suppressor T lymphocytes and those of antigen-specific suppressor T lymphocytes (1, 2, 18, 33). The term “generalized” refers to those studies of suppressor T-cell numbers or functions unrelated to those cells interacting with specific target cells, and having to do with measurements of total CD8+ CD11b+ cells (which have suppressor, but no cytotoxic activity), or by measuring the impact of such cells on total IgG production. Generally, there is a reduction in the number and function of generalized suppressor T lymphocytes in the hyperthyroid phase of GD, and these tend to normalize as thyroid function improves. This will occur whatever the form of therapy, and does so even if TSAb remains strongly positive (34). With some exceptions, results usually are normal in euthyroid HT.

The observation that there also is a reduction in such suppressor T lymphocytes in toxic nodular goiter (35), but less marked than in GD, suggests that hyperthyroidism has to be severe and perhaps prolonged to have such an effect, and there is evidence supporting this view (34). Thus the reduction in generalized suppressor T lymphocytes does not seem to be a primary or specific event, and appears to be secondary to the hyperthyroidism itself; by its additive effect superimposed on the antigen-specific defect in suppressor T lymphocytes, this reduction may act as a perpetuating and amplifying mechanism in the disease (34). Moreover, environmental factors such as stress, infection, drugs, smoking, and aging may have similar adverse effects on generalized suppressor T lymphocyte function, and thus may precipitate the malady by a similar additive effect (1, 2, 4, 36, 37).

Studies of antigen-specific suppressor T lymphocyte functions have yielded different results (2, 18, 33). The idea that there could be an antigen-specific disorder in suppressor T lymphocytes seems more rational than that of a generalized disturbance; the latter would result in multiple clinical disorders of immunoregulation and thus would not accord with genetic observations that AITD appears much more frequently in families in which the propositor also has AITD rather than other autoimmune disorders. There are now several studies indicating the presence of an organ-specific defect in suppressor T lymphocytes in AITD, in which the observation does not relate to the thyroid function of the patient (i.e., whether that patient is hyperthyroid, euthyroid, or hypothyroid) (13, 38–49). These studies have determined the impact of these cells specifically on antibodies directed against the target cell, or by reducing the sensitization of (helper) T cells against their specific antigen(s), without having a generalized effect as described above. (Of course, under some conditions, e.g., hyperthyroidism, both effects may coexist.) More recently, it was demonstrated that thyroid-specific antigens will not sufficiently activate CD8+CD11b+ T lymphocytes (“pure” suppressor cells) from patients with autoimmune thyroid disease as well as irrelevant antigen does, whereas normal CD8+CD11b+ T lymphocytes respond equally to relevant and irrelevant antigen (50). Moreover, TSHR will not activate CD8 T cells from patients with GD as well as it does control CD8 cells (from healthy persons, those with HT, those with nontoxic goiter, and those with IDDM). Conversely, glutamic acid decarboxylase (GAD-65), the putative antigen of the pancreatic beta cells, will not activate IDDM CD8 cells as much as it does CD8 cells from GD patients, HT patients, and healthy persons (51). In animal models of AITD, there is also increasing evidence for a role for suppressor (regulatory) T lymphocytes (13). The antigen-specific suppressor cell defect, which is partial or relative (40, 47–51), and which may relate to H-2-receptor-bearing suppressor T cells (39, 45), may be due to an abnormality of specific antigen presentation, resulting in reduced specific suppressor cell activation (see Fig. 2).

Role of Thyroid Antigen

There is no evidence of an alteration in the thyroid antigen in patients with AITD (2, 12). AITD appears to be primarily a disorder of immunoregulation, with the organ dysfunction resulting from an antigen-specific attack mounted by inadequately suppressed lymphocytes directed toward these specific cellular targets. The antigen must be available and must be presented to the T lymphocytes for this assault to occur. This requires expression of HLA-DR antigens on the antigen-presenting cells [macrophages and dendritic cells; thyroid cells also
It is proposed that the fundamental defect relates to reduced activation by specific antigen (Ag) (via an abnormality of specific Ag presentation by histocompatibility genes) of suppressor (regulatory) T lymphocytes (Ts). Precipitating factors from the environment may cause a reduction in nonspecific T function, thus adding to the Ag-specific Ts dysfunction. The result is to reduce suppression of thyroid-directed T helper (Th) and T effector (Te) (Tn, and Teo) cells and allow them to be activated in the presence of Ag-presenting cells (APC) and the thyroid Ag(s) (which must "drive" the process, activating the Th). Th may then act directly on the thyrocyte through the production of cytokines, which are essential at every stage of this process; the Th may cooperate with cytotoxic cells to produce thyroid damage. The activated Th will produce interferon-gamma (IFN-\(\gamma\)) close to the thyocytes, causing the latter to express MHC class II Ags, which may allow the thyocytes to secondarily become an APC, or conversely, may be protective. Th will also "help" specific B lymphocytes to produce thyroid autoantibodies (Abs), which may add to the pathological process. TSHR Abs play a major role in causing thyroid stimulation (TSAb in GD) or thyroid inhibition. TSAb or TSH will enhance IFN-\(\gamma\)-induced thyrocyte HLA-DR expression, and also increase thyroid Ag presentation, further stimulating Th. Excess thyroid hormone further reduces nonspecific Ts function and numbers, allowing further Th activation. These secondary processes thus tend to self-perpetuate the disease. Reprinted with permission (51).

may express HLA-DR and act as antigen-presenting cells (2, 52). However, thyrocyte HLA-DR expression is a secondary event, and macrophages, lymphocytes, and the production of interferon-\(\gamma\) are all necessary for the thyroid cells to express HLA-DR after the initiation of the immune assault (12). It has been suggested that the thyroid cell might be damaged by some external stimulus, then express HLA-DR as a consequence, and thus precipitate autoimmune thyroid disease (11), but this notion does not withstand close scrutiny (12). Rather, the evidence is consistent with the idea that the thyroid cell is initially normal, and expresses HLA-DR [as well as heat-shock protein-72 and intercellular adhesion molecule-I, further amplifying the immune disorder (53)] as a consequence of the immune disturbance. As mentioned above, the notion that the primary event might be infective (10, 11) is entirely speculative; I have argued that the thyroid cell is a passive captive to immunological events in AITD (12). I have postulated that the condition results from a disorder in immunoregulation, with environmental factors precipitating the disease by nonspecific effects on the immune system (4) adding to the genetically induced partial defect.

Genetic Control of the Immune Response

In mice, genes that map in the region corresponding to the HLA-D locus in humans are responsible for controlling the response of helper or suppressor T lymphocytes to a given antigen (5). In humans, GD is associated with HLA-DR3 (Caucasians), goitrous HT is associated with HLA-DR5, and atrophic thyroiditis with HLA-DR3 (6). However, persons bearing HLA-DR2 have only a moderate increase in relative risk and thus this clearly does not represent the "disease susceptibility gene." Recently, the frequency of subjects positive for HLA-DQ\(\alpha\)1*0501 was found to be significantly increased among Caucasian GD patients, markedly increasing their relative risk (54). However, patients with an autoimmune response to the TSHR (involving either stimulating or blocking antibodies) are genetically different in terms of HLA from patients whose thyroid autoimmune response does not involve TSHR antibodies (55). Even so, other genes are undoubtedly involved in the pathogenesis of these disorders, but they are not well defined, nor is their role understood (55).

Nature of GD Remission

More than one form of clinical remission occurs in GD (2). Surgical or \(^{131}\)I destruction of sufficient tissue may prevent recurrence. Conversely, continuous immunological thyroid destruction may bring about clinical remission, or even hypothyroidism. The latter may also result from a change in the nature of a TSHR antibody from stimulating to a blocking antibody (2). Another important form of remission is one in which all immunologic stigmata of the disease disappear, including thyroid antibodies, TSAb, and evidence of sensitization of T lymphocytes (56). This form of remission may occur only in patients with a less severe defect in immunoregulation in such patients, hyperthyroidism is initiated by some environmental insult acting on the immune system, converting an occult specific suppressor T lymphocyte defect to an overt one. This is reversible when that circumstance is overcome. The restoration of a euthyroid state by whatever means (antithyroid drugs, \(^{131}\)I, or surgery) should further relieve the situation because the effects of hyperthyroidism on the immune system will be reversed. Moreover, rest, the passage of time, the clearing of infection, the use of sedation, and other nonspecific measures will allow the partially defective immunoregulatory system to be restored to its previous functional capacity (2, 18).

Those persons with a presumed severe defect would not be expected to enter an immunological remission, no matter how long their antithyroid drugs were continued. Only those remissions associated with spontaneous or iatrogenic thyroid destruction would occur in this group.

Implications for Therapy for GD

Improvements in our understanding of the immune nature of GD have led to few changes in the management of this disease. However, because patients with very large goiters rarely achieve immunological remission, some selection for long-term antithyroid drug treatment can be made. Antithyroid drugs may themselves be immunosuppressive (20, 57, 58), although it is difficult to reconcile this proposal with the fact that many patients continue to manifest immunologic activ
ity throughout the course of treatment, no matter what the dosage of drug and no matter how well the hyperthyroidism is controlled. Also, because of the short duration of action of the drugs, it is difficult to comprehend how a long-term remission after cessation of therapy would persist. Moreover, the normalization of thyroid function is attended by normalization of the suppressor/helper T-lymphocyte ratio (2). Thus it seems more likely that the action of the antithyroid drugs on thyroid cells is more decisive in bringing about remission, rather than any direct immunosuppressive effect (59). Indeed, evidence indicates that antithyroid drugs bring about remissions by a direct effect on thyocytes, reducing thyrocyte-immunocyte signaling (60, 61).

The use of $^{131}$I therapy de novo also is associated with immunological perturbations, namely, a transient increase in TSAb and other thyroid autoantibodies, followed by an ultimate decline (2). This may be due to the liberation of thyroid antigens, stimulating the already disturbed immune system.

Subtotal thyroidectomy is often associated with a decline in TSAb activity, perhaps because most of the offending thyroid-committed lymphocytes are removed with the gland (2). Recurrences after surgery who have to be associated with (a) sufficient remaining thyroid parenchyma to respond to TSAb, and (b) sufficient remaining thyroid-committed lymphocytes to mount the immune attack.

GD ophthalmopathy will not be discussed here, since its pathophysiology is not well understood, and there are no immune assays of general credence for use in diagnosis and management.

**Immunology of IDDM**

**Genetics**

IDDM tends to aggregate in certain families. The concordance rate in identical twins is ~50%; the disparity of the age of onset in the concordant twins suggests that the disease occurs at random in those predisposed to develop it (1, 2, 62–64). This implies that there is a genetic factor and a nongenetic factor, which has prompted the search for environmental factors in the development of this disease, such as viruses, drugs, and nutrition. The most compelling evidence that IDDM in humans could be caused by a virus was the isolation of a coxsackie B4 virus from a child who had died with diabetic ketoacidosis and overwhelming viral infection (65). However, a more recent pathologic examination of the islets of Langerhans of this child demonstrated evidence of previous chronic beta cell damage that had preceded the acute viral infection (66).

Although there are experimental models that indicate that viruses may induce diabetes mellitus in vulnerable animals by infecting the islets, the evidence is not compelling in humans (1, 2, 62–64). However, it is of considerable interest that ~20% of children with congenital rubella will develop diabetes mellitus in later life (57–64, 67). This form of diabetes is somewhat atypical in that it is often non-insulin-dependent, although it usually does occur in patients who are HLA-DR3- and (or) DR4-positive, and many express islet cell antibodies (ICA). In these cases, the diabetes does not occur at the time of the infection, but years later, and the same children have a high incidence of thyroid autoantibodies, probably due to an effect of viruses on the immune system in genetically predisposed individuals. Another putative environmental factor may be a bovine albumin peptide found in cow’s milk that cross-reacts with islet cell antigen, and has been proposed as a precipitating factor in inducing IDDM in susceptible individuals (68). This proposal has recently been refuted (69).

The genetic predisposition relates to genes in the region of the HLA-DR alleles residing on chromosome 6. Type I diabetes is associated with the HLA alleles DR3 and DR4 (5, 6, 62–64). Of persons with IDDM, ~95% are positive for these alleles, as opposed to 40% of normal persons. Moreover, when siblings are identical for the HLA genes, the risk of diabetes is increased 90-fold, whereas a sibling having only one of the HLA loci in common with the diabetic sibling possesses a 37-fold increased risk (62–64). On the other hand, an HLA nonidentical sibling has a risk for IDDM similar to that of the general population. However, as withAITD, the presence of these genes does not ensure the development of IDDM, as 40% of the population have these same genes and only a small proportion of them develop diabetes, unless they happen to be members of families in whom diabetes is already present. Moreover, there are patients with IDDM who have neither DR3 or DR4 alleles. Thus it is thought that the diabetogenic genes reside close to these genes in linkage disequilibrium with them. In most Caucasians with IDDM, HLA-DQ$\beta$ sequences tend to share the common characteristic of not encoding aspartic acid at the 57 amino acid position of the HLA-DQ$\beta$ peptide chain (70). However, more recently, the HLA-DQ 3.2 (DQ$\beta$ 1*0302) gene has been found to be the most prevalent susceptibility gene in Caucasian IDDM patients (71), although it is not sufficient by itself to precipitate the disease. Other genetic and environmental factors are also required to induce IDDM.

Patients with IDDM often manifest autoantibodies to other organs, with an increased incidence of certain other organ-specific autoimmune diseases, most commonly AIITD; these are generally related to HLA-DR3 alleles.

**Immune Phenomena**

In most patients with IDDM, ICA precede overt diabetes, sometimes by many years, and occult changes in glucose metabolism may precede the overt expression of the condition (62–64). Various ICA have been described, with various methods of detection (72, 73). Several groups have reported that up to 80% of patients have these antibodies at or before the onset of disease (72, 73). Indeed, the presence of ICA combined with a decrease in the first phase of insulin secretion (<179 pmol/L) is predictive of the development of IDDM within 12 months, with a 95% probability (74). However, some relatives who have developed such antibodies have not
gone on to develop overt diabetes (75). Nevertheless, of relatives with a single positive ICA test, 50% will develop IDDM within 10 years (76, 77). The predictive value for health of negative ICA results is virtually 99% (77). Strongly positive and persistent ICA (>40 Juvenile Diabetes Fund units) is the best predictor of forthcoming IDDM, particularly when combined with decreased insulin secretion (78–81). The predictive value of ICA for development of IDDM within 10 years in first-degree relatives of patients with IDDM increases from 40% at low concentrations of ICA to 100% at high concentrations, whereas the respective sensitivities of the test are 88% and 31% (82). Thus, the risk of IDDM in relatives of probands increases with the titer of ICA, is greater in multiple families, and is increased in those <10 years of age with positive ICA (83). Positive ICA values also correlate with the rapid loss of C-peptide secretory capacity in newly diagnosed IDDM patients (84). Conversely, not all patients who develop overt IDDM are positive for these antibodies (85, 86). The ICA may be markers of ongoing beta cell destruction, but it is unlikely that they are pathogenic themselves. It is more likely that cytotoxic T lymphocytes, in conjunction with macrophages, induce the beta cell damage directly, including mediation by cytokines produced locally by the immunocytes (87).

Although the precise antigen has not been finally determined, a number of candidate autoantigens have been identified (72, 73), with GAD-65 as the leading contender (88). This enzyme catalyzes the conversion of glutamic acid to γ-aminobutyric acid, the major inhibitory neurotransmitter in the central nervous system (73). The response of IDDM T lymphocytes to GAD-65 directly reflects the risk of progression of clinical IDDM (96). However, it is not clear that antibodies to GAD have the same predictive value, as Harrison’s group has shown an inverse correlation of T cell responses to GAD and to antibodies to GAD (74, 96). In the acute, active phase of IDDM, there is an increase in activated T lymphocytes expressing the HLA-DR antigen (62–64, 89). Indeed, there is evidence of aberrant expression of HLA-DR antigens on the cell surface of some beta cells in IDDM (89); there is increasing evidence that HLA-DR expression on target cells is secondary to the immune assault itself, and is thus an intermediate step, rather than a primary precipitant (12).

The migration of lymphocytes from IDDM patients in vitro is inhibited by preparations of mammalian, including human, islets (42, 90). In studies with lymphocytes from IDDM patients, there is evidence of lymphocyte-mediated cytotoxicity against an insulinoma cell line; the lymphocytes also inhibit insulin release by isolated mouse islets (91).

Evidence for Organ-Specific Defect in Immunosuppression

Studies of nonspecific and specific suppressor cell function have been performed in animal models and human IDDM (41, 90–94). In one study, antigen-specific suppressor cell function was evaluated by suppressor cell activation with guinea pig islet cell homogenate, and measurements of cell proliferation rates demonstrated that specific suppressor cell activity was lower than in the control population (92).

T lymphocytes from patients with IDDM were mixed with T lymphocytes from patients with GD in the migration inhibition factor (MIF) test (41) to observe the response to human thyroid antigen and to human islet cell antigen. Lymphocytes from the IDDM patients alone produced MIF in response to islet cell antigen, but this was abrogated when GD T lymphocytes (positive in the MIF system against thyroid antigen, but negative against islet cell antigen) were added. Thus the GD lymphocytes acted as “normal” T lymphocytes in inhibiting the IDDM lymphocytic response to islet cell antigen. T lymphocytes from normal persons, but not those from other IDDM patients, also abrogate MIF production when added to the original IDDM T lymphocytes in response to the islet cell antigen. This would support the view that there is an organ-specific suppressor T lymphocyte defect in IDDM that is separate from that of GD (41). I mentioned earlier that the reduced activation of IDDM suppressor T lymphocytes by GAD (the putative beta cell antigen) is specific for this condition; the cells respond to irrelevant antigen normally (51). Other investigators have shown that the cytotoxic effect on isolated rat islets of lymphocytes from newly diagnosed type I diabetics could be abolished by the addition of lymphocytes from healthy persons, but not by lymphocytes from other diabetic patients (93). This also accords with the hypothesis of an organ-specific suppressor T-cell defect in IDDM.

In animal models of IDDM, there is also convincing evidence for a similar abnormality of suppressor T cell function [summarized in (94)]. Such an abnormality may prove to be fundamental to the pathogenesis of the disease.

Generalized Suppressor T Lymphocyte Function

Several reports indicate that a reduction in generalized suppressor T lymphocyte function or numbers in the early phase of diabetes mellitus appears to clear as the disease stabilizes (62–64). This may be analogous to the situation in severe hyperthyroidism in which there are similar findings. However, such generalized reductions in suppressor T lymphocyte function or numbers may arise from some preceding stress, or may be secondary to the stress of the metabolic disease itself. This may prove to be an important factor because it may be additive and superimposed on the organ-specific defect and thereby act as a precipitant or a perpetuating factor, later subsiding as the environmental and metabolic disturbances abate.

There is no convincing evidence for a target cell abnormality that precedes the disease and, like the thyroid cell in autoimmune thyroid disease, the beta cells may be passive captives to immune events. The combination of an antigen-specific reduction in activation of suppressor T cells plus any generalized disturbance in nonspecific suppressor T cell function or numbers resulting from variable environmental factors could additively precipi-
tate the disease. Thus, there is no need to invoke an antigenic disturbance in this theory. This would be in accord with the observation on transplanted pancreatic segments from three normal monozygotic twins (>15 years discordant) to their diabetic twinmates (95). No immunosuppressive therapy was provided because the recipients were monozygotic twins. At first the diabetic state cleared, but within 4 months, lymphocytic infiltration appeared in the grafts, with beta cell destruction. Thus, without any apparent antigenic stimulation other than the presence of the normal islets, the immune system still was abnormal and the disease recurred.

Immunotherapy

Interestingly, a fourth twin in the foregoing study, who also had been transplanted with a pancreatic segment, was treated prophylactically with azathioprine after the transplantation, and the diabetic state did not recur (95). This raises the issue of immunotherapy in the treatment of IDDM, before total destruction of the beta cells has occurred. Because beta cell destruction proceeds at a subclinical level for years before the onset of overt diabetes, it clearly would be of importance to predict which person is going to develop diabetes and to commence therapy before destruction of the beta cells is complete. This may soon be possible with new means of detecting antibodies or T lymphocyte response to islet cell antigens such as GAD (96). Cyclosporine, an immunosuppressive agent, when prescribed to newly diagnosed IDDM patients, will suppress the diabetic process, despite the considerable beta cell loss that has already occurred (97). Azathioprine has also proved similarly useful (98, 99). Indeed, insulin administration, given before the development of frank IDDM, might prevent or delay the onset by "resting" the beta cells and reducing the presentation of their antigen(s) (100). Immunotherapy with other models, e.g., T cell vaccination (101, 102) and oral vaccination with myelin basic protein (103), are being investigated. Recently, vaccination with GAD to susceptible but not yet diabetic mice prevented the development of IDDM (104, 105). This is an exciting development in the quest for a means of prevention for this very serious malady.

Insulin Resistance Due to Insulin Receptor Antibodies

Brief mention should be made of this rare entity, which is not genetically related to IDDM or to the other organ-specific endocrinopathies. Type B insulin resistance may be associated with profound hyperglycemia and acanthosis nigricans, although occasionally hypoglycemia may be noted when the insulin receptor antibodies manifest an agonist, rather than antagonist, effect on insulin action (106). However, insulin receptor antibodies may be seen in occasional IDDM patients (107).

Autoimmune Diseases of Adrenals, Gonads, Parathyroid, and Pituitary

Addison Disease

The original description by Addison (108) of 11 examples of this disorder included cases recognized as idiopathic (now known to be autoimmune) adrenal atrophy, as well as tuberculosis of the adrenal gland and metastatic carcinoma. Although tuberculosis once accounted for most cases of Addison disease, autoimmune adrenalitis has become the most common form of the condition in Western countries.

There is now ample evidence for an autoimmune basis for this disease (1, 2, 109) derived from histology of the adrenals, the finding of autoantibodies against the adrenal cortex in many patients with this condition, the association with other organ-specific autoimmune disease, study of HLA antigens, genetic studies, and experimental observations (1, 2, 109). In the human disease, both adrenal glands are very small, and difficult to locate at autopsy. The capsule is generally thickened and the cortex is usually completely destroyed. The remaining adrenocortical cells may be single or in small clusters. A mononuclear cell infiltrate is invariably, with lymphocytes, plasma cells, macrophages, and occasionally, germinal centers. The few remaining parenchymal cells are surrounded by the heaviest infiltration of lymphocytes, and a variable amount of fibrosis is evident (1, 2, 109).

Humoral immunity. Antiadrenal antibodies are detectable in about two-thirds of patients with autoimmune Addison disease (1, 2, 109). The means of detection have included the complement fixation test and immunofluorescence, but with recent identification of the actual antigens (21-hydroxylase in the adult disease, and 17-hydroxylase in type I childhood Addison disease (109)), Western blotting has been utilized. The adrenal antibodies tend to be more common in those patients with a short duration of disease, and in those who develop it at an early age. The titers of adrenal antibodies are much lower than for thyroid or gastric antibodies in patients with AITD or pernicious anemia, respectively, but they may persist for many years after adequate medical treatment. Such antibodies are found very rarely in the control population and are also quite rare in first-degree relatives of patients with Addison disease (providing that these relatives do not have idiopathic hypoparathyroidism). Adrenal antibodies occur in 25–30% of patients with idiopathic hypoparathyroidism.

In patients with Addison disease who have antidiadrenal antibodies, there also may be antibodies that react with ovary, testis, and steroid-producing cells in the placenta. These cross-reacting antibodies may be associated with primary ovarian failure. Although these are IgG antibodies and therefore can cross the placenta, there is no evidence that they are able to cause damage to the fetal adrenals.

In patients with autoimmune Addison disease, there is a high prevalence of antibodies to other organ antigens, including steroid-producing cells and parathyroid, thyroid, islet cell, and gastric antigens. There is also a higher prevalence of other overt organ-specific autoimmune diseases associated with these same antibodies (110, 115). Thus, in patients with autoimmune adrenal disease, careful consideration should be given to the probability that there will be other organ-specific autoimmune diseases, either in an overt or occult (serologic) form.
Genetic studies. Autoimmune Addison disease tends to be familial and is considered to be autosomal recessive, although the inheritance has not been completely determined. There is an increased incidence of HLA-B8 and DR3 in Caucasians, similar to that seen with GD. This is true, however, only with patients who do not have generalized candidiasis and hypoparathyroidism.

Ovarian Failure

Of women with autoimmune Addison disease, ∼25% have premature menopause or amenorrhea (1, 2, 109). Most of these women have circulating antibodies against steroid-secreting cells. Such antibodies are almost never detected in patients with amenorrhea that is not associated with Addison disease. The question arises whether autoimmune gonadal failure is a closely associated but separate organ-specific autoimmune disease, or whether it results from cross-reactive antigens shared by gonads and adrenals. Certainly, some steroid cell antibodies cross-react with adrenal, gonadal, and placental antigens. This would also explain the finding of antiovarian antibodies in some males with autoimmune aden failure. Sensitized T lymphocytes may be similarly cross-reactive (1, 2). In some instances, however, premature menopause, which is only occasionally of proven autoimmune etiology, may not be related to Addison disease.

Histologic features of the ovaries of patients with amenorrhea associated with autoimmune Addison disease will show lymphocytic infiltration and fibrous tissue, similar to that seen in AITD. Autoimmune testicular failure associated with Addison disease is quite uncommon, and generally is associated with polyendocrine autoimmune failure associated with candidiasis and hypoparathyroidism.

Hypoparathyroidism

Autoimmune hypoparathyroidism occurs mostly in children and adolescents and is often associated with mucocutaneous candidiasis (type I polyendocrine autoimmune disease). Thus it frequently is associated with Addison disease and other organ-specific autoimmune diseases (1).

The pathology is characterized by lymphocytic infiltration and atrophy. Antiparathyroid antibodies and evidence for cell-mediated immunity have been demonstrated (1).

Hypophysitis

There are increasing numbers of cases of autoimmune hypophysitis being reported, all in women between the third and eighth decade (2, 111). In many of these patients, the diagnosis was made at autopsy. A conspicuous feature of this condition has been its association with pregnancy and the postpartum state. In many of the reported cases, the disease was detected after delivery, with the longest interval after gestation being 14 months. Possibly, cases that have been diagnosed as postpartum Sheehan syndrome may instead often be examples of postpartum autoimmune pituitary disease, developing insidiously during and after pregnancy. Another prominent feature of autoimmune lymphocytic hypophysitis has been its association with other organ-specific autoimmune disorders such as HT, adrenalitis, and pernicious anemia.

Autoimmune Polyendocrine Disease

Theoretically, any patient with one expressed autoimmune endocrine disease showing serologic reactivity with another organ should be considered as potentially belonging to the polyendocrinopathies (112). Although many of these target organs are indeed endocrine glands, other nonendocrine organ-specific autoimmune diseases that are associated in increased frequency include pernicious anemia, myasthenia gravis, Sjögren disease, vitiligo, alopecia areata, chronic active hepatitis, idiopathic thrombocytopenic purpura, and rheumatoid arthritis (113). Those patients with overt autoimmune diseases of these organs would belong to the following categories: (a) candidiasis, hypoparathyroidism, Addison disease (two or three present); (b) Addison disease and AITD and (or) IDDM; and (c) AITD and IDDM, AITD and pernicious anemia, or AITD and vitiligo and (or) alopecia and (or) other organ-specific autoimmune diseases not falling into the above categories (114). Of these, only categories (b) and (c) are associated with definite HLA genes (112). Category (a), which seems to be the most severe form of autoimmune polyglandular endocrine failure, does not have any particular HLA type and generally occurs in children. Possibly, the putative suppressor T lymphocyte defect is more severe and more nonspecific than that seen in the other entities.

Various other, even rarer, polyendocrine autoimmune syndromes include central diabetes insipidus, autoimmune enteropathy, autoimmunity to gut hormone-secreting cells, and autoimmune directed against specific prolactin cells in the anterior pituitary (112).

The observation that all the disorders listed in Table 1 have a close association with one another and often are associated with specific HLA genes suggests a very similar pathogenesis for all these autoimmune entities. It well may be that each disease has separate genes and a separate organ-specific defect in immunoregulation. Probably, the defect is an organ-specific abnormality in suppressor T lymphocyte function, which is specific for each disease. The fact that some persons develop two or more of these diseases may be related to the inheritance of more than one closely related gene or sets of genes. Much remains to be learned about these disorders (114, 115).

Work cited from the author’s laboratory was supported by grants from the Medical Research Council of Canada (MT 859), and from the Wellesley Hospital Research Institute Foundation.

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CLINICAL CHEMISTRY, Vol. 40, No. 11(B), 1994 2145