REVIEW ARTICLE

MEDICAL PROGRESS

Autoimmune Polyendocrine Syndromes

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T HE AUTOIMMUNE POLYENDOCRINE SYNDROMES ARE DIVERSE, AND their diversity is a characteristic that is both clinically important and instructive when their basic immunologic features are considered (Table 1).[1-4] These syndromes include monogenic disorders (such as autoimmune polyendocrine syndrome type I, which has classic and characteristic disease associations[5]) and complex genetic disorders (such as autoimmune polyendocrine syndrome type II, in which the component diseases are more variable[6]). Some of the component disorders are common (e.g., thyroid autoimmunity and celiac disease), whereas others are rare (e.g., Addison's disease and myasthenia gravis). Some of the disorders are usually asymptomatic (e.g., celiac disease); others are symptomatic but typically diagnosed after years of illness (Addison's disease, which features severe fatigue and nausea, and pernicious anemia, which causes neuropathic symptoms); and still others are clinically dramatic at the time of diagnosis (type 1A diabetes, also known as immune-mediated diabetes and formerly called insulin-dependent diabetes). The term "polyendocrine" itself is a misnomer, in that not all patients have multiple endocrine disorders, and many have nonendocrine autoimmune diseases. Nevertheless, the recognition that patients in whom multiple autoimmune disorders are diagnosed may have a specific genetic syndrome, may be at increased risk for multiple autoimmune disorders, and may have relatives who have an increased risk should spur clinicians toward early diagnosis and treatment.[7]

A general question concerning the autoimmune polyendocrine disorders relates to the shared "antigen" that can result in the targeting of multiple tissues. In fact, it is likely that the affected organs and tissues do not share any specific molecule but rather have different molecules that are more or less likely to be targets when the immune system fails to maintain self-tolerance to a variety of molecules, in particular specific peptides within target organs (Fig. 1). In addition, specific genetic polymorphisms influence which specific diseases develop; for example, a polymorphism of the insulin gene related to the thymic expression of insulin alters the risk of type 1A diabetes but not the risk of other autoimmune disorders.[8]

ANIMAL MODELS OF PATHOGENESIS

In the simplest hypothesis for understanding organ-specific autoimmunity, the initial step is the loss of immunologic tolerance to a peptide within a specific molecule found in the target organ. Clones of the CD4 T cells that recognize the peptide then expand, and the specific cytokines produced by the clonal CD4 T cells favor inflammation (as when type 1 helper T [Th1]–cell clones produce cytokines such as interferon-γ) or favor autoantibody-mediated disease (as is the case predominantly with type 2 helper T [Th2]–cell clones).[9] The probability of T-cell autoreactivity is determined both in the thymus (the site of central tolerance) and in the periphery (the site of peripheral tolerance) and is strongly influenced by specific HLA alleles (Fig. 1).

Distinct HLA alleles probably contribute to disease by determining which peptides

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Feature	Autoimmune Polyendocrine Syndrome Type I	Autoimmune Polyendocrine Syndrome Type II	X-Linked Polyendocrinopathy, Immune Dysfunction, and Diarrhea
Prevalence	Rare	Common	Very rare
Time of onset	Infancy	Infancy through adulthood	Neonatal period
Gene and inheritance	*AIRE* (on chromosome 21, recessive)	Polygenic	*FOXP3,* X-linked
HLA genotype	Diabetes (risk decreased with HLA-DQ6)	HLA-DQ2 and HLA-DQ8; HLA-DRB1*0404	No association
Immunodeficiency	Asplenism, susceptibility to candidiasis	None	Overwhelming autoimmunity, loss of regulatory T cells
Association with diabetes	Yes (in 18%)	Yes (in 20%)	Yes (in majority)
Common phenotype	Candidiasis, hypoparathyroidism, Addison's disease	Addison's disease, type 1A diabetes, chronic thyroiditis	Neonatal diabetes, malabsorption

Table 1. Features of the Autoimmune Polyendocrine Syndromes.*

* The autoimmune polyendocrine syndromes differ in their prevalence, time of onset, inheritance, immune function, and disease associations. Such differences point to a heterogeneity in their pathogenesis, despite the underlying presence of genetic susceptibility to multiple autoimmune disorders.

are targeted and thus which tissue will be affected. The breakdown of self-tolerance is probably influenced by the milieu in which a peptide is presented. For example, inflammation induced by activation of the innate immune system (e.g., after infections) can favor loss of tolerance.[10] Such loss of tolerance is a likely explanation for the occasional presence of autoantibodies against multiple organs as well as autoimmune disease that sometimes occurs after interferon therapy.[11-13] The difference between a patient with a single disease and a patient with the autoimmune polyendocrine syndrome in whom one or more diseases develop over time is probably at least in part genetically determined; but it also should be recognized that disease penetrance, even among monozygotic twins, does not approach 100 percent (30 to 70 percent is usual), even in common autoimmune disorders.[14,15]

Genes that lower the set point for maintaining tolerance, such that T-cell expansion is more readily triggered after T-cell–receptor engagement, can cause autoimmune disorders such as the X-linked polyendocrinopathy, immune dysfunction, and diarrhea syndrome.[16] Another attractive hypothesis explaining the development of autoimmunity is that genes that increase thymic expression of peripheral self antigens, thereby favoring tolerance, would decrease the risk of disease.[17,18] Genes or environmental factors that increase normal T-cell regulatory function should prevent autoimmunity.[19] Infections

that activate the innate immune system can increase the risk of disease, whereas some infections are likely to decrease this risk, perhaps by stimulating regulatory T cells (the hygiene hypothesis).[20]

Studies in animal models have contributed to the understanding of polyendocrine autoimmune diseases. Three of the most important are mice that have undergone neonatal thymectomy (or thymectomy and radiation),[21] the BioBreeding (BB) rat, and the nonobese diabetic (NOD) mouse. Removing the thymus from an otherwise normal, three-day-old mouse results in lymphocytic invasion of multiple organs with attendant inflammation, leading to gastritis, oophoritis, and thyroiditis.[22] It is thought that in this model, which is dependent on specific timing of the thymectomy, the animal loses regulatory T lymphocytes that normally dampen the development of autoimmunity.

The NOD mouse, in which type 1A diabetes and sialitis develop spontaneously, has more than 15 genetic loci that contribute to disease,[23,24] including alleles of the major histocompatibility complex (MHC) and, in particular, those of I-A^{g7}, an HLA class II molecule.[25] A peptide composed of amino acids 9 through 23 of the insulin β chain is recognized by the T lymphocytes of NOD mice; T cells that are activated by the peptide then invade the pancreatic islets, and the ultimate result is type 1A diabetes.[26] This peptide, the B:9-23 self peptide, induces insulin autoantibodies when injected into
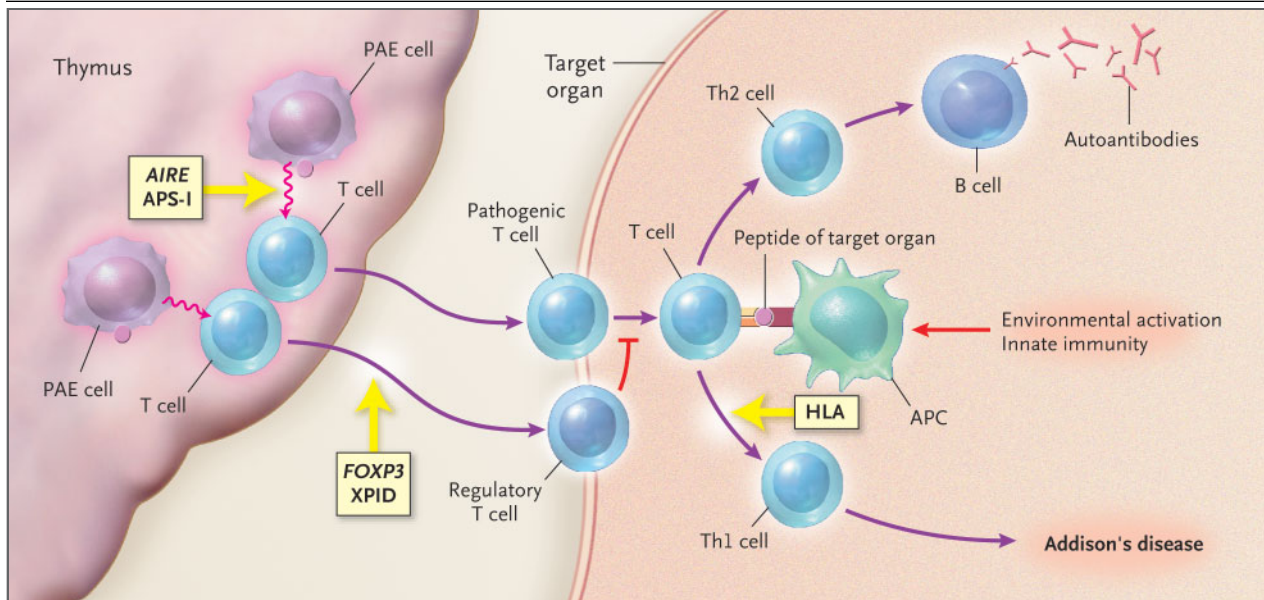
Figure 1. Pathogenic Model of Autoimmune Polyendocrine Syndrome Disorders.
Disease is determined by a subgroup of T cells that recognize one or more peptides of the target organ. These peptides are bound in the groove of HLA molecules and are presented to the T-cell receptor (TCR) of T lymphocytes. B lymphocytes stimulated by T cells produce auto-antibodies. Expression of "peripheral antigens," and thus peptides of target organs in the thymus, influence the balance between regulatory and pathogenic T cells. Innate immunity relates to the second signals that are required for activation of T lymphocytes by antigen-presenting cells (e.g., B7.1 on antigen-presenting cells and CD28 or cytotoxic T lymphocyte antigen 4 on T cells). *AIRE* denotes autoimmune regulator gene; APS-I autoimmune polyendocrine syndrome type I; XPID X-linked polyendocrinopathy, immune dysfunction, and diarrhea syndrome; PAE cell peripheral antigen-expressing cell in the thymus (probably both thymic epithelioid cells and macrophages or dendritic cells); APC antigen-presenting cell; Th2 cell type 2 helper T cell; and Th1 cell type 1 helper T cell.

normal BALB/c mice. When it is administered with polyriboinosinic-polyribocytidylic acid (poly-IC, a mimic of viral double-stranded RNA and an activator of the innate immune system), insulitis is induced; in special strains of mice, diabetes is induced.[26,27] In the NOD mouse, once autoimmunity is activated, insulin is only one of several islet antigens targeted by T lymphocytes; in particular, besides insulin, another beta-cell–specific antigen (islet glucose–related phosphatase) is a target of CD8 T cells.[28-30]

Both diabetes and thyroiditis develop spontaneously in the BB rat. Genes of the MHC are the major determinant of diabetes in the BB rat,[31] but for this strain of rats an autosomal recessive mutation of a gene causes severe T-cell lymphopenia.[32,33] Diabetes develops spontaneously in BB rats only if they have both lymphopenia and MHC alleles of the RT1-U type; the presence of other MHC alleles leads to thyroiditis when lymphopenia is present.[34] Thus, the manifestations of autoimmune disease depend both on the type of MHC alleles and the presence

or absence of lymphopenia, which is induced by a specific recessive mutation.

The most important general rule from animal models of autoimmune disease is that genes within the major histocompatibility complex, in particular immune-response genes (similar to the HLA-DQ and HLA-DR alleles in humans), are essential for disease targeting, and such targeting combined with abnormalities in immunoregulation leads to polyendocrine autoimmunity. Disease depends on cells derived from bone marrow, and major effectors are both CD4 and CD8 T lymphocytes; just as important, however, is that regulatory T lymphocytes can prevent disease.[19] Because they are inbred, each animal model can be viewed as just one example of what are genetically heterogeneous disorders in humans. Models with a mutated "causative" gene identical to the mutated gene in humans (e.g., scurfy mice, which have the same genetic mutation as that causing X-linked polyendocrinopathy, immune dysfunction, and diarrhea syndrome) will probably be better guides to pathogenesis and therapy than

are polygenic models, such as the NOD mouse, in which several effective therapies have not influenced progression to diabetes in humans.

SPECIFIC CLINICAL SYNDROMES

AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE I

Autoimmune polyendocrine syndrome type I is a dramatic autoimmune syndrome with characteristic disease associations[4,5] that often appear early in life, typically in infants with persistent candidal infection of the skin and mucous membranes without the systemic infection generally associated with severe immunodeficiency. The diagnosis of autoimmune polyendocrine syndrome type I is usually made later, when hypocalcemia due to hypoparathyroidism develops or Addison's disease is recognized in a young child. The syndrome is rare but has an increased prevalence in certain populations (e.g., inhabitants of Finland and Sardinia and Iranian Jews).

Mutations in an autoimmune-suppressor gene (*AIRE*, for autoimmune regulator), which encodes a transcription factor, cause the syndrome.[35-38] Persons with any two of several specific conditions — mucocutaneous candidiasis, hypoparathyroidism, and Addison's disease — almost always have *AIRE* mutations. Mutations in the *AIRE* gene cause many autoimmune diseases, and affected patients are at risk for the development of multiple additional autoimmune diseases over time, including type 1A diabetes, hypothyroidism, pernicious anemia, alopecia, vitiligo, hepatitis, ovarian atrophy, and keratitis. Affected patients may also have diarrhea or obstipation that may be related to the destruction of gastrointestinal endocrine cells (enterochromaffin and enterochromaffin-like cells).[39] Knockout of the *AIRE* gene in the mouse produces widespread autoimmunity, but the phenotype is relatively mild.[18,40] Nevertheless, study of this mouse model has led to the hypothesis that one function of the normal *AIRE* gene might be to enhance the expression of "peripheral" antigens in the thymus, thereby promoting tolerance.[18]

After diagnosis, patients with autoimmune polyendocrine syndrome type I require close monitoring. Monitoring can help prevent illness associated with delayed diagnosis of additional autoimmune diseases (e.g., Addison's disease and hypoparathyroidism, which can develop during adulthood) as well as oral cancer, which may develop if candidiasis is not treated aggressively, and infection due to asplenism, which is present in a subgroup of patients.[1]

AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE II

Autoimmune polyendocrine syndrome type II (also called Schmidt's syndrome with Addison's disease plus hypothyroidism) is much more common and more varied in its manifestations than autoimmune polyendocrine syndrome type I.[1,3,6,41] Symptomatic hypotension, which is a classic presentation of adrenal insufficiency in autoimmune polyendocrine syndrome type II, can be associated with a decrease in the insulin dose in a patient with type 1A diabetes. Such patients may also have hyperpigmentation and vitiligo as well as a several-year history of intermittent, severe hypoglycemia and intermittent, severe fatigue. Thus, the onset is insidious until the presenting hypotensive episode (Fig. 2). We are aware of one child who missed an entire year of school at the age of 10 years because of fatigue but did not receive the diagnosis of Addison's disease until the age of 17.

There is controversy between "splitters" and "lumpers" concerning syndrome classification.[2,3,7,42] Splitters consider each of the combina-
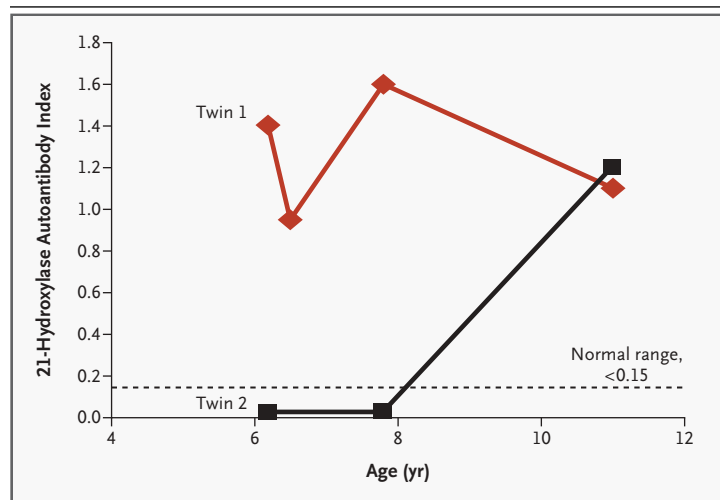
Figure 2. Results of Screening Tests for 21-Hydroxylase Autoantibodies in a Pair of Identical Twins.

The twins were screened for the autoantibody because a sibling had type 1A diabetes. Twin 1 had 21-hydroxylase autoantibodies on the initial test; Addison's disease developed by the age of 11 years, when the corticotropin level measured at 8 a.m. was elevated (at 195 pg per milliliter [43 pmol per liter]) and the peak cortisol level 60 minutes after cosyntropin stimulation was low (at 11 μg per deciliter [303 nmol per liter]) (normal range after stimulation, >18 μg per deciliter [497 nmol per liter]). Autoantibodies were detected in Twin 2 after the age of eight years; at the most recent assessment, his corticotropin and stimulated cortisol levels remained normal (19 pg per milliliter [4 pmol per liter] and 24 μg per deciliter [662 nmol per liter], respectively).

tions of disorders a separate syndrome: according to this approach, autoimmune polyendocrine syndrome type II refers to Addison's disease plus thyroid autoimmunity or type 1A diabetes; autoimmune polyendocrine syndrome type III refers to thyroid autoimmunity plus another autoimmunity (but not Addison's disease or type 1A diabetes); and autoimmune polyendocrine syndrome type IV refers to two or more other organ-specific autoimmune diseases. Lumpers, with whom we tend to agree, consider all the above combinations autoimmune polyendocrine syndrome type II (leaving only autoimmune polyendocrine syndrome type I and autoimmune polyendocrine syndrome type II). The disease is genetically complex, with parents, siblings, and offspring typically having multiple yet different autoimmune diseases.[43,44]

When a rare disorder, such as Addison's disease, occurs spontaneously, there is a high probability that other diseases are present or will develop. With a common autoimmune disorder such as hypothyroidism as the only disease, the development of additional autoimmune endocrine disorders is much less common. Diseases of intermediate prevalence, such as type 1A diabetes and celiac disease, are frequently associated with other autoimmune diseases. For example, approximately 1.5 percent of patients with type 1A diabetes have adrenal 21-hydroxylase autoantibodies, and are at high risk for Addison's disease, which develops in one third of these patients.[41,43,45] It is not clear what distinguishes a patient with a single disorder, such as isolated Addison's disease, from a patient with multiple additional autoimmune disorders. One factor may simply be time, since in many patients with Addison's disease additional disorders develop with increasing age.

X-LINKED POLYENDOCRINOPATHY, IMMUNE DYSFUNCTION, AND DIARRHEA

The syndrome of X-linked polyendocrinopathy, immune dysfunction, and diarrhea (known as XPID) is an extremely rare disorder characterized by fulminant, widespread autoimmunity and type 1A diabetes, which usually develops in neonates; it is often fatal.[46,47] The disorder is also known as XLAAD (X-linked autoimmunity and allergic dysregulation) and IPEX (immune dysfunction, polyendocrinopathy, and enteropathy, X-linked).[48,49] Recognition of the disease is important, since there is some evidence that bone marrow transplantation, with the development of mixed chimerism in the recipient, may reverse it. Studies in one patient who had a mutation in a gene called *Scurfin,* or *FOXP3,* as well as in the relevant animal model (scurfy mice), suggest that the mutated gene has an important role in setting the threshold for a response by T lymphocytes to T-cell–receptor engagement and that *FOXP3* controls the development of regulatory CD4+CD25+ T cells that are essential for the maintenance of tolerance to self tissue.[50]

OTHER SYNDROMES

Many syndromes include multiple endocrine disorders (Table 2). Recognition of these syndromes can aid early diagnosis and permit the initiation of specific therapy. For example, administration of a sulfhydryl-containing drug such as methimazole may be stopped when it is the cause of Hirata's disease (insulin-autoimmune syndrome with insulin-autoantibody–induced hypoglycemia),[51] or localized radiotherapy may be directed to a bone lesion or autologous bone marrow transplantation undertaken when the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) is present.[52-54]

| Table 2. Other Polyendocrine and Autoimmune Syndromes.	
Syndrome	**Component Diseases**
Chromosomal abnormalities (e.g., trisomy 21 and Turner's syndrome)	Chronic thyroiditis, type 1A diabetes, other disorders
POEMS syndrome (plasmacytoma)	Polyneuropathy, organomegaly, endocrinopathy, serum M protein, skin changes
Hirata's disease (HLA-DRB1*0406+ drug induction)	Insulin autoantibodies, hypoglycemia
Type B insulin resistance	Insulin-receptor autoantibodies, systemic lupus erythematosus (occasionally), hypoglycemia, hyperglycemia
Thymoma	Red-cell aplasia, myasthenia gravis, Graves' disease
Wolfram's syndrome (DIDMOAD)	Diabetes insipidus, diabetes mellitus, optic atrophy, deafness
Kearns–Sayre syndrome	External ophthalmoplegia, retinal degeneration, diabetes, thyroiditis, hypoparathyroidism

STAGES IN THE DEVELOPMENT OF AUTOIMMUNITY WITH ADDISON'S DISEASE

It is clear that autoimmunity precedes overt Addison's disease by years, as in many autoimmune endocrine disorders.[45,55,56] Figure 3 shows stages in

the hypothetical progression to Addison's disease[3] and the abnormalities characteristic of each stage. Many autoimmune disorders, even non–organ-specific diseases, are likely to have similar prodromes.[58,59] Hence, Addison's disease is an instructive model for end-organ failure in autoimmune polyendocrine syndromes.

GENETIC SUSCEPTIBILITY

In patients with autoimmune polyendocrine syndromes who have a single disorder such as Addison's disease or type 1A diabetes, the prevalence of additional autoimmune disorders is 30 to 50 times that in the general population.[60,61] The concurrence of more than one endocrinopathy presumably re-

sults from shared genetic susceptibility leading to loss of tolerance to multiple tissues.

As previously discussed, autoimmune polyendocrine syndrome type I is determined by autosomal recessive mutations in the *AIRE* gene. Addison's disease develops in 80 percent of patients with autoimmune polyendocrine syndrome type I, and type 1A diabetes develops in 18 percent.[5,62] In contrast to autoimmune polyendocrine syndrome type I, Addison's disease — either as part of autoimmune polyendocrine syndrome type II or as an isolated condition — is a complex genetic disorder with a specific HLA-DR and HLA-DQ genotype that confers high risk. The highest risk of the development of both Addison's disease and type 1A diabetes is
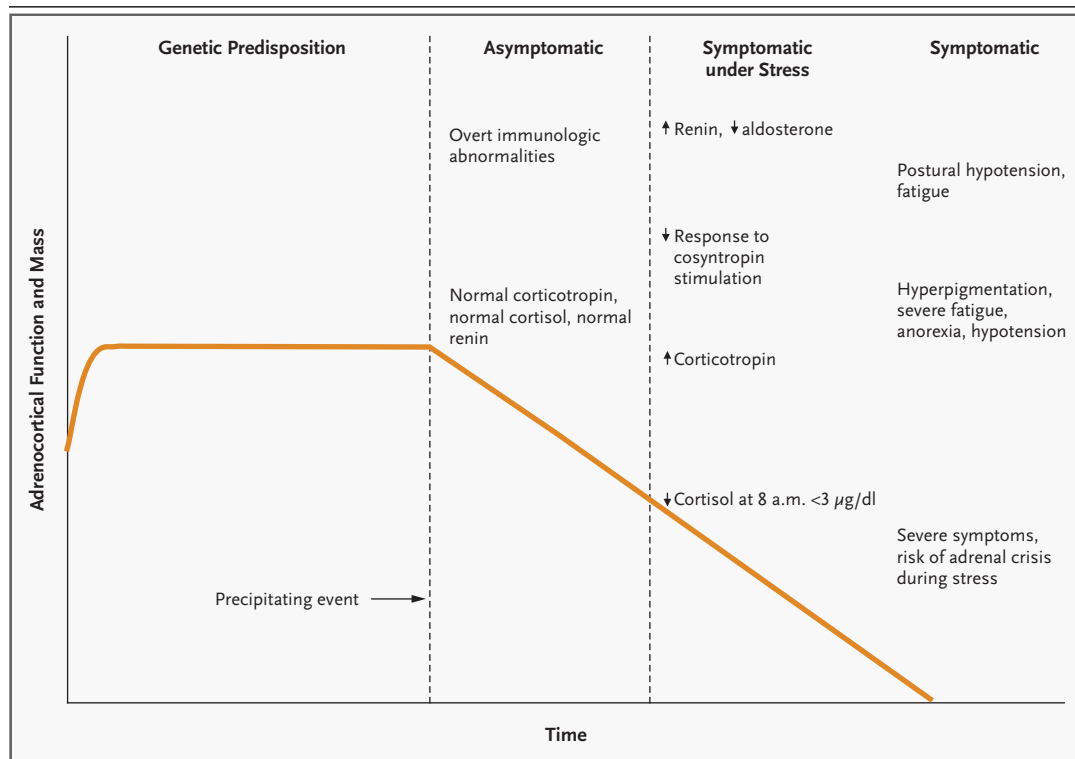
Figure 3. Stages in the Development of Addison's Disease.

Adrenocortical function is lost over a period of years as a patient's condition progresses to overt Addison's disease. In the first stage, a patient's HLA genotype plays the key role in his or her predisposition to the development of autoimmune polyendocrine syndrome type II. In the second stage, events that precipitate anti-adrenal autoimmunity occur, but they are currently unknown. In the third stage, which involves presymptomatic disease, 21-hydroxylase autoantibodies predict future disease. Finally, in the fourth stage, overt Addison's disease develops. An increased plasma renin level is one of the first metabolic abnormalities to occur and is followed by the sequential development of other metabolic abnormalities (a decreased cortisol level after cosyntropin stimulation, an elevated corticotropin level, and a decreased basal cortisol level). Finally, there are severe symptoms of adrenal insufficiency, such as hypotension; hypoadrenalism is likely if the cortisol level is less than 15 µg per deciliter (414 nmol per liter) during acute illness or if the basal cortisol level is less than 3 µg per deciliter (83 nmol per liter).[57] Upward arrows indicate an increase, and downward arrows a decrease.

associated with a heterozygous HLA-DR4–DQ8/ HLA-DR3–DQ2 genotype.[43,44] In Addison's disease, there is an additional, strong association with a mutated allele (5.1) of a nonclassic HLA molecule, MHC class I chain-related A (MIC-A).[63,64] It is likely that there are other genetic loci contributing to Addison's disease (e.g., cytotoxic T lymphocyte antigen 4),[65] but identifying the disease-predisposing genes to confirm the loci has proved difficult, as it has for type 1A diabetes.[66] The recent discovery of a vitiligo locus in a large family with thyroiditis[67] and the ongoing analysis of a family in which 21 members have type 1A diabetes and celiac disease[68] suggest that a subset of common autoimmune disorders are genetically heterogeneous with respect to key disease loci.

TRIGGERING OF AUTOIMMUNITY

A variety of factors can trigger autoimmune disease, and even a single disorder can have a variety of triggering factors. For example, administration of interferon alfa has been associated with the development of 21-hydroxylase autoantibodies, islet autoantibodies, and thyroid autoantibodies.[12,13] Type 2 interferons are likely to also be important for spontaneous disease and may underlie the ability of viral infections or poly-IC, which mimics the effects of viral RNA, to induce disease in animal models.[26] Triggering factors such as pregnancy may have special effects in patients with an autoimmune disease. For instance, postpartum thyroiditis develops in almost one third of patients with type 1A diabetes, and therefore patients with type 1A diabetes who are planning pregnancy should be tested for thyroid autoantibodies and monitored closely for thyroid abnormalities.[69] In one third of patients with multiple sclerosis who were treated with an experimental T-cell–depleting monoclonal antibody, Graves' disease developed as a striking and unexpected complication.[70]

Currently, common triggering factors are known for only a very few autoimmune disorders. The most dramatic of the known triggers are the gliadin peptides, which are associated with celiac disease. Prospective studies indicate that before transglutaminase autoantibodies appear, patients may have been consuming gliadin for several years, starting in infancy, suggesting that there may be additional factors that trigger the initial activation of disease.[71] An attractive hypothesis is that transglutaminase becomes a target as it deamidates glutamines of the gliadin peptides that induce disease. Gliadin pep-

tides may also become covalently bound to transglutaminase.[72]

ASSAYS FOR AUTOIMMUNE MARKERS

At present, assays for autoimmune T cells are in their infancy and not standardized,[73] although important progress is being made with tetramer and enzyme-linked immunospot (Elispot) assays.[74] Thus, for the earliest evidence of active autoimmunity we currently rely on assays to detect autoantibodies.[45,75,76] When the autoantibody is directly pathogenic (e.g., in disorders in which transplacental autoantibodies cause disease, such as Graves' disease and myasthenia gravis), this approach is logical. For T-cell–mediated disorders, which presumably constitute most of the autoimmune diseases in which glands are destroyed, autoantibody assays are primarily disease markers. Multiple workshops held by the Immunology of Diabetes Society suggest that to achieve specificities greater than 99 percent and high sensitivity, fluid-phase radioimmunoassays are required.[77] Such assays can use proteins that are transcribed and translated in vitro and simultaneously radioactively labeled; this approach is generally adaptable for assays for antibodies against most protein antigens.[75,78]

For the prediction of autoimmune diabetes in low-risk populations (e.g., general populations with a risk of diabetes of 1 in 300), even established radioimmunoassays indicate that people expressing a single autoantibody have a significantly lower risk than those with multiple islet autoantibodies[79-81] (Fig. 4). Autoantibodies to the enzyme 21-hydroxylase are present in more than 90 percent of patients with Addison's disease, and their detection almost always precedes the onset of disease.[43,45,82] A diagnosis of adrenal insufficiency in the absence of 21-hydroxylase autoantibodies requires a search for alternative causes of Addison's disease, such as tuberculosis or adrenoleukodystrophy. Figure 2 illustrates a case in twins: high levels of 21-hydroxylase autoantibodies were present in one twin beginning at the age of six years but were not found in his identical twin until five years later as indicated by the index in the 21-hydroxylase autoantibody assay of 0.15 or greater. The autoantibody assay index is calculated as (counts per minute [cpm] with the patient's serum − cpm with normal serum) ÷ (cpm with standard positive serum − cpm with normal serum). The first twin now has overt Addison's disease, and the second is being monitored with annual adrenal-function testing. The twins were first evaluated for

21-hydroxylase autoantibodies because they have a sibling with type 1A diabetes.

Twelve percent of patients with type 1A diabetes have transglutaminase autoantibodies.[83] One third of patients with type 1A diabetes who have the HLA genotype HLA-DR3–DQ2/HLA-DR3–DQ2 have transglutaminase autoantibodies.[83] Half of these patients have high levels of the autoantibodies and intestinal villous destruction, visible on examination of biopsy specimens. The levels of transglutaminase autoantibodies can fluctuate, and we recommend confirming the presence of high titers close to the time of planned biopsy. Approximately one third of patients with type 1A diabetes have thyroid autoantibodies. Chronic thyroiditis is very common, and a subgroup of patients can have thyroid dysfunction without these autoantibodies. For this reason, we monitor the level of thyrotropin. The combination of autoantibodies and a thyrotropin level greater than 5 mU per liter indicates a high risk of future development of hypothyroidism.

PROGRESSIVE METABOLIC ABNORMALITIES

As illustrated in Figure 2, patients in whom Addison's disease develops have a prodrome during which 21-hydroxylase autoantibodies are present. Betterle and coworkers[3] divide the progression to Addison's disease into stages, with an elevated plasma renin level as the first sign of adrenal damage. During this process, the adrenal reserve may be impaired, and we alert patients who have 21-hydroxylase autoantibodies about the symptoms and signs of adrenal insufficiency. In type 1A diabetes, the loss of first-phase insulin secretion in an intravenous glucose-tolerance test usually precedes the onset of overt diabetes; after diagnosis, loss of C-peptide secretion reflects continuing beta-cell destruction.[84] In thyroiditis, the presence both of autoantibodies against thyroid peroxidase and of elevations in the thyrotropin level above the normal range increases the risk of development of overt hypothyroidism.[85] Within 10 years of follow-up, approximately half the patients who are positive for autoantibodies against thyroid peroxidase and have type 1A diabetes have hypothyroidism.

SCREENING RECOMMENDATIONS

A high index of suspicion for additional autoimmune disorders in patients who have autoimmune polyendocrine syndrome type I or autoimmune polyendocrine syndrome type II, and their relatives,

is essential. Patients should be advised of the symptoms of the disorders for which they are at high risk: hypoglycemia (especially when they are receiving insulin therapy), fatigue, and hyperpigmentation (in some cases) for Addison's disease; polyuria, polyphagia, polydipsia, and nausea and vomiting with ketoacidosis for diabetes; coordination difficulties for pernicious anemia; and anemia, osteopenia, abdominal pain, and diarrhea for celiac disease. (Most patients with celiac disease are not symptomatic.) We give patients a sheet of information about associated disorders.

The constellation of disorders of autoimmune polyendocrine syndrome type I relates to immunodeficiency and chronic candidiasis as well as the frequent development of additional autoimmune
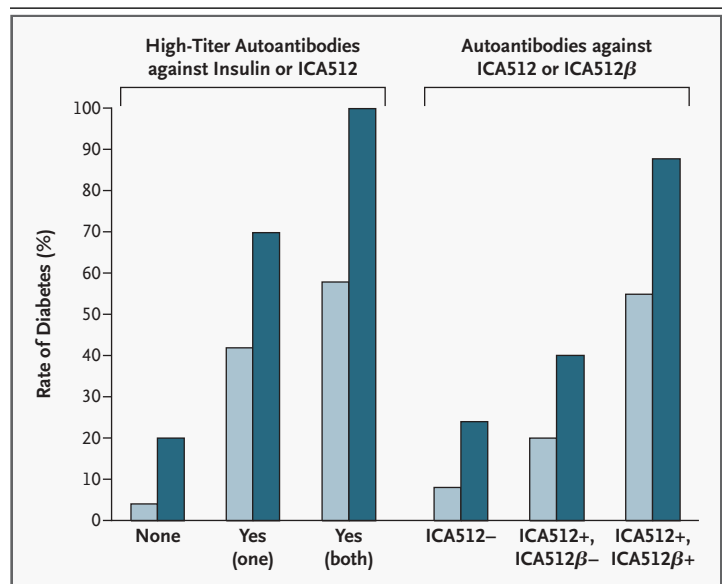
Figure 4. Rate of Progression to Type 1A Diabetes.
The graph shows the progression to type 1A diabetes four and eight years (light bars and dark bars, respectively) after the initial detection of islet autoantibodies in subjects who were first-degree relatives of patients with type 1A diabetes. The subjects are grouped according to the number of high-titer insulin autoantibodies or ICA512 autoantibodies detected (none, one, or both), as well as according to the presence or absence of autoantibodies against ICA512 or the related ICA512β. A determinant of progression to diabetes is the number of autoantibodies expressed, with differences in terms of specific autoantibodies. For example, the presence of autoantibodies against ICA512 and ICA512β conferred the highest disease risk in any combination, and a high titer of autoantibodies against insulin and ICA512 was associated with increased progression to diabetes. The titer of autoantibodies against glutamic acid decarboxylase did not influence the risk. A high titer was defined as a titer above the 25th percentile for ICA512 autoantibodies and above the 75th percentile for insulin autoantibodies. Adapted from Achenbach et al.[81]

disorders. It is important for follow-up to include aggressive treatment of candidiasis if needed, antibiotic prophylaxis if asplenism develops (e.g., if asplenism is detected by screening for Howell–Jolly bodies), tests for early detection of hepatitis (e.g., by screening for elevated serum levels of liver enzymes), and assessment for additional endocrine disorders with autoantibody and hormone testing.[1]

We recommend that patients with autoimmune polyendocrine syndrome type II and their first-degree relatives (and patients with "isolated" type 1A diabetes and Addison's disease) be periodically monitored for the development of hypothyroidism. The presence of autoantibodies against thyroid peroxidase usually precedes overt hypothyroidism. Given the high prevalence of thyroid disease due to autoimmunity, we measure thyrotropin with a sensitive assay able to detect both hypothyroidism and hyperthyroidism. Pediatric endocrinologists measure thyrotropin in their patients annually, but for adults, testing at five-year intervals may be sufficient if the initial thyrotropin level is normal and autoantibodies against thyroid peroxidase are absent. If those autoantibodies are present, however, adults should be screened yearly.

We also recommend screening for autoantibodies against 21-hydroxylase and transglutaminase. Currently, there is not enough information to define optimal intervals for testing, but anecdotal data indicate that autoantibodies can develop at any age, and thus we rescreen patients for autoantibodies even if their initial autoantibody tests are negative. Annual measurement of the corticotropin level and the level of cortisol both before and after cosyntropin stimulation (at 8 a.m.) in those with autoantibodies against 21-hydroxylase seems prudent to detect adrenal damage before a hypotensive crisis.[57]

The majority of persons identified in programs screening for autoantibodies associated with celiac disease, even those who have high levels of transglutaminase autoantibodies, are "asymptomatic." Recent studies suggest that many of them may be at risk for osteoporosis and may have detectable changes in growth and nutrition, as well as anemia.[86] Intestinal T-cell lymphomas develop in a subgroup of patients with symptomatic celiac disease. The level of transglutaminase autoantibodies often fluctuates in asymptomatic patients, and it is advisable to obtain a small-bowel biopsy specimen when the levels are high. ("High" levels are defined differently for different autoantibody assays. For example, with an autoantibody radioimmunoassay index,

with 99 percent of normal persons at an assay index below 0.05, a positive biopsy finding is associated with much higher levels — namely, an index greater than 0.5.[71]) Islet autoantibody determination in first-degree relatives of patients with autoimmune polyendocrine syndrome type II is best reserved for research settings, although appropriate rapid diagnosis of and therapy for new-onset diabetes are important, especially in young children.[87,88]

THERAPY

At present, the treatment of the polyendocrine autoimmune syndromes is dictated by the individual disorders. Knowledge of the syndromes allows early therapy of component disorders. An important clinical caveat is that in patients with suspected concomitant Addison's disease and hypothyroidism, thyroid replacement should not precede the necessary glucocorticoid replacement, since thyroid replacement may precipitate the hypotension and adrenal crisis due to the action of thyroxine in increasing hepatic corticosteroid metabolism. In addition, in a subgroup of patients with newly diagnosed Addison's disease who have moderately elevated levels of thyroid autoantibodies and thyrotropin levels below 30 μU per milliliter, thyrotropin levels may normalize after glucocorticoid replacement.

Obvious long-term goals are therapies that address the underlying autoimmunity associated with these disorders and, in particular, preventive therapies. Although prediction of type 1A diabetes is now possible, the preventive therapies studied to date have not altered disease progression,[89] although newer approaches are under study.[90,91] In contrast, for celiac disease, removal of gliadin from the diet is an effective treatment.[92,93] Autoimmunity can be an important barrier to transplantation, as noted by Sutherland and coworkers in a report of findings in identical twins; transplantation of the tail of the pancreas from a normal twin to a diabetic twin was associated with recurrent diabetes in the recipient.[94] With current immunosuppressive regimens, allogeneic pancreatic transplantation is possible,[95] and the results of islet transplantation have improved dramatically.[96] Nevertheless, a subgroup of islet transplants appear to succumb to autoimmune destruction.[97]

In the past decade, a wealth of new data have become available concerning the pathogenesis of rare as well as relatively common polyendocrine syn-

dromes. It has become clear that an imbalance between autoimmune effector and regulatory T lymphocytes is the major determinant of disease, that HLA alleles determine specific tissue targeting, and that an important research goal with respect to the entire constellation of disorders is the restoration of tolerance. Currently, for the clinician and family, recognition of the syndromes and early detection of the component disorders can contribute to the prevention of illness and, in some cases, death.

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