IPEX is caused by mutations in the *FOXP3* gene, which is also mutated in the Scurfy mouse, an animal model that shares much of the phenotype of IPEX patients. The FOXP3 transcription factor is expressed in regulatory T cells designated CD4+CD25+FOXP3+ (Treg). Lack of this factor causes a profound deficiency of this Treg population and results in rampant autoimmunity due to the lack of peripheral tolerance normally provided by these cells. Certain mutations may lead to varying forms of expression of the full syndrome, and there are rare cases where the *FOXP3* gene is intact but other genes involved in this pathway (e.g., CD25, IL-2Rα) may be causative.

THYMIC TUMORS

Thymomas and thymic hyperplasia are associated with several autoimmune diseases, with the most common being myasthenia gravis (44%) and red cell aplasia (20%). Graves' disease, T1D, and Addison's disease may also be associated with thymic tumors. Patients with myasthenia gravis and thymoma may have unique anti–acetylcholine receptor autoantibodies. Many thymomas lack AIRE expression within the thymoma, and this could be a potential factor in the development of autoimmunity. In support of this concept, thymoma is the one other disease with "frequent" development of anticytokine antibodies and mucocutaneous candidiasis in adults. The majority of tumors are malignant, and temporary remissions of the autoimmune condition can occur with resection of the tumor.

ANTI-INSULIN RECEPTOR ANTIBODIES

This is a very rare disorder where severe insulin resistance (type B) is caused by the presence of anti-insulin receptor antibodies. It is associated with acanthosis nigricans, which can also be associated with other forms of less severe insulin resistance. About one-third of patients have an associated autoimmune illness such as systemic lupus erythematosus or Sjögren's syndrome. Therefore, the presence of antinuclear antibodies, elevated erythrocyte sedimentation rate, hyperglobulinemia, leukopenia, and hypocomplementemia may accompany the presentation. The presence of anti-insulin receptor autoantibodies leads to marked insulin resistance, requiring more than 100,000 units of insulin to be given daily with only partial control of hyperglycemia. Patients can also have severe hypoglycemia due to partial activation of the insulin receptor by the antibody. The course of the disease is variable, and several patients have had spontaneous remissions. Therapy targeting B lymphocytes including rituximab, cyclophosphamide, and pulse steroids can induce remission of the disease.

INSULIN AUTOIMMUNE SYNDROME (HIRATA'S SYNDROME)

The insulin autoimmune syndrome, associated with Graves' disease and methimazole therapy (or other sulfhydryl-containing medications), is of particular interest due to a remarkably strong association with a specific HLA haplotype. Such patients with elevated titers of anti-insulin autoantibodies frequently present with hypoglycemia. In Japan, the disease is restricted to HLA-DR4-positive individuals with DRB1*0406. Curiously, a recent report demonstrated that five out of six Caucasian patients taking lipoic acid (sulfhydryl group) who developed insulin autoimmune syndrome were primarily DRB1*0403 (which is related to DRB1*0406); the sixth was DRB1*0406. In Hirata's syndrome the anti-insulin autoantibodies are often polyclonal. Discontinuation of the medication generally leads to resolution of the syndrome over time.

POEMS SYNDROME

POEMS (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M*-protein, and *s*kin changes; also known as Crow-Fukase syndrome; OMIM 192240) patients usually present with a progressive sensorimotor polyneuropathy, diabetes mellitus (50%), primary gonadal failure (70%), and a plasma cell dyscrasia with sclerotic bony lesions. Associated findings can be hepatosplenomegaly, lymphadenopathy, and hyperpigmentation. Patients often present in the fifth to sixth decade of life and have a median survival after diagnosis of less than 3 years. The syndrome is assumed to be secondary to circulating immunoglobulins, but patients have excess vascular endothelial growth factor as well as elevated levels of other inflammatory cytokines such as IL1-β, IL-6, and tumor necrosis factor α. A small series of patients have been treated with thalidomide, leading to a decrease in vascular endothelial growth factor. Hyperglycemia responds to small, subcutaneous doses of insulin. The hypogonadism is due to primary gonadal disease with elevated plasma levels of follicle-stimulating hormone and luteinizing hormone. Temporary resolution of the features of POEMS, including normalization of blood glucose, may occur after radiotherapy for localized plasma cell lesions of bone or after chemotherapy, thalidomide, plasmapheresis, autologous stem cell transplantation, or treatment with all-*trans*-retinoic acid.

OTHER DISORDERS

Other diseases can exhibit polyendocrine deficiencies, including Kearns-Sayre syndrome, DIDMOAD syndrome (*d*iabetes *i*nsipidus, *d*iabetes *m*ellitus, progressive bilateral *o*ptic *a*trophy, and sensorineural *d*eafness; also termed Wolfram's syndrome), Down's syndrome or trisomy 21 (OMIM 190685), Turner's syndrome (monosomy X, 45,X), and congenital rubella.

Kearns-Sayre syndrome (OMIM 530000) is a rare mitochondrial DNA disorder characterized by myopathic abnormalities leading to ophthalmoplegia and progressive weakness in association with several endocrine abnormalities, including hypoparathyroidism, primary gonadal failure, diabetes mellitus, and hypopituitarism. Crystalline mitochondrial inclusions are found in muscle biopsy specimens, and such inclusions have also been observed in the cerebellum. Antiparathyroid antibodies have not been described; however, antibodies to the anterior pituitary gland and striated muscle have been identified, and the disease may have autoimmune components. These mitochondrial DNA mutations occur sporadically and do not appear to be associated with a familial syndrome.

Wolfram's syndrome (OMIM 222300, chromosome 4; OMIM 598500, mitochondrial) is a rare autosomal recessive disease that is also called DIDMOAD. Neurologic and psychiatric disturbances are prominent in most patients and can cause severe disability. The disease is caused by defects in wolframin, a 100-kDa transmembrane protein that has been localized to the endoplasmic reticulum and is found in neuronal and neuroendocrine tissue. Its expression induces ion channel activity with a resultant increase in intracellular calcium and may play an important role in intracellular calcium homeostasis. Wolfram's syndrome appears to be a slowly progressive neurodegenerative process, and there is nonautoimmune selective destruction of the pancreatic beta cells. Diabetes mellitus with an onset in childhood is usually the first manifestation. Diabetes mellitus and optic atrophy are present in all reported cases, but expression of the other features is variable.

Down's syndrome, or trisomy 21 (OMIM 190685), is associated with the development of T1D, thyroiditis, and celiac disease. Patients with Turner's syndrome also appear to be at increased risk for the development of thyroid disease and celiac disease. It is recommended to screen patients with trisomy 21 and Turner's syndrome for associated autoimmune diseases on a regular basis.