

Master Answers for the Autoimmune Disease Small group

Master Answer for Cases 1A and 1B

There are multiple possible etiologies of autoimmune endocrinopathies, but regardless of the precise cause, there are two fundamentally different autoimmune **mechanisms** causing endocrine disease in the first 2 vignettes.

In the patient with hyperthyroidism, a **functional agonistic autoantibody**, either to the TSH receptor or to TSH itself, is produced by autoreactive B cells. These autoantibodies can bind to the TSH receptor **causing hyperstimulation, not destruction**, of the gland.

The specific immunopathogenesis of hyperthyroidism is speculative, but for discussion purposes, assume that a B cell clone capable of producing antibody specifically reactive for TSH or the TSH receptor and capable of mimicking TSH itself, is permitted to proliferate because of a deficiency of regulatory CD4, 25 T cells. The deficiency could be secondary to viral infection and depletion or to an autoimmune regulator (Aire) defect-the gene complex that forces the thymus to display endocrine self antigens so self-reactive T cells can be deleted before emigration. The autoreactive TSH clone, having emigrated from the thymus because the AIRE complex was not displaying TSH antigens, may be activated by sex hormones after puberty with or without the help of a viral infection.

Other poorly understood tolerance mechanisms could be altered by a virus and/or female sex hormones with identical results.

No matter what the mechanism, the clinical expression of the loss of suppression of that B cell clone is hyperthyroidism.

Conversely, **hypothyroidism** can and does occur by the same mechanisms that cause the loss of insulin production in the pancreas (see below).

In diabetes, the clinical picture is dominated by inability to produce adequate insulin for glucose metabolism because a **cellular mediated destructive attack** on the pancreas occurred. In the case of diabetes, certain viruses can bind and then infect hormone producing cells in the pancreas. The infected cells become susceptible to attack by NK & Th1 driven, IL-21 activated CD8 cells with antiviral specificity. In this circumstance, the immune system is doing what it has been taught to do in the face of viral infection.

Other possibilities include a theory that the infecting virus doesn't infect beta cells but has an antigen that shares an epitope with insulin or beta cells. Beta cells "look" like viral infected cells (mimicry) and are attacked by CD8 and CD4 and γ Th17 cell mechanisms.

Yet another possibility is that CD4,25, FoxP3 pancreatic beta cell specific T cells are preferentially destroyed by virus and tolerance to beta cells is lost.

Yet another possibility is that Beta cells are destroyed as "collateral damage" during a TIM1 response in neighboring pancreatic tissue

Yet another possibility is that the patient has a partial autoimmune regulator (Aire) defect that allowed beta cell reactive T cells to emigrate from the thymus during development and that these cells were activated by the viral infection- this one may prove to be true but suffice it to say, no one knows the cause of Type 1 diabetes yet!

Master answer for Case 2

The rapid onset of diffuse muscle weakness in a patient with **no** biopsy evidence of cellular mediated muscle destruction usually implies the presence of an autobody with specificity for the neuro muscular conduction system, in this case myasthenia gravis. The antibody present is specific for acetylcholine receptor (AcR) and there is strong evidence that a very similar disease can be experimentally reproduced in animals. The antibody binds to the AcR and downregulates it, decreasing the density of receptors at the neuromuscular junction and weakening transmission of impulses across it.

This situation is different than that found in hyperthyroidism. In myasthenia the autoantibody is an inhibitor, in hyperthyroidism the autoantibody is a promoter.

Patients with polymyositis, another autoimmune disease that cause symptoms similar to myasthenia, have a completely different etiology of their disease. Their T cells are attacking muscle fibers and pay no attention to the neuromuscular junction. Muscle biopsies in these patients are completely different than those in myasthenia because they have a **cellular mediated** autoimmune disease.

A major breakthrough was the discovery of massive numbers of AcR in eels. These AcR could be isolated in stable form and used for diagnosis and experimental studies of how the disease is caused. Once antibody was proven to be mediator of the disease, clinicians realized that mechanical removal of IgG (plasmapheresis) might at least ameliorate symptoms and prevent patients from requiring ventilatory support.

The loss of peripheral tolerance to AcR allows our normal complement of anti AcR-B cells, normally held in check by peripheral tolerance mechanisms, to expand and cause the disease. The loss of tolerance may be due to an underlying deficiency of CD4, 25⁺ regulatory T-Cells specific to the AcR in these patients. Whether the deficiency is

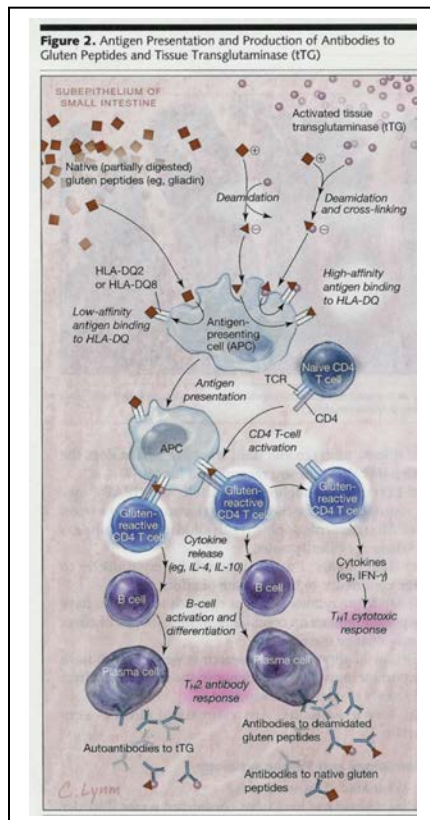
secondary an AIRE defect is unknown, but the inciting factor in many patients appears to be viral infection which unmask the defect and cause clinical disease.

Master Answer for Case #3

This patient has celiac sprue. This common autoimmune disease is also called non-tropical sprue or gluten sensitive enteropathy. The major symptoms arise from the patient's intolerance to gluten, specifically gliadin, a gluten component found in wheat, barley and rye. Beer has a lot of gliadins in it so Rush Week poses a serious threat to the patient with celiac disease.

The autoimmune destruction of small bowel villi function leads to nutrient malabsorption that then causes bloating, diarrhea and weight loss.

This autoimmune disease represents one of the best understood in terms of the **environmental** antigen that incites it, the **MHC loci that promote** it and the specificity of the pathogenic **T cells** localized in the small bowel. Although almost all the proteins in gluten are completely digested before arrival in the small bowel, one isn't. The latter is designated 33-mer and it is resistant to all known human digestive enzymes in the gut. The 33-mer then is loaded onto the MHC (HLA) DQ2 or DQ8 for presentation to submucosal CD4 T cells. Individuals with celiac sprue have either DQ2 (90-95%) or DQ8 (5-10%) - (**Do not memorize the precise alleles because you won't be asked for the specific ones on a test but you do need to know the causative significance of the fact that specific MHC alleles are associated with specific autoimmune diseases**). These 2 DQ loci are almost exclusively found in Caucasians and this explains the almost exclusive occurrence in Caucasians. The activated CD4 T cells then mediate the pathology by a typical Th1 immune reaction that culminates in loss of villi and function



The procedure was a small bowel biopsy and the histology on the left of the figure is typical of celiac disease. There are several autoantibodies found in celiac sprue. **None** of these autoantibodies appear to be directly associated **with disease causation**. One that is diagnostically helpful is anti-endomysial antibody that reacts with tissue transglutaminase. The antibodies are **IgA** (makes sense in a small bowel disease).

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Master Answer for Case #4

These three syndromes are the clinical realities of impaired immuno-regulation. The beneficial interactions between physician-scientists and basic researchers have never been more striking. Not only do these diseases confirm the predictions of basic research on the way immune responses are controlled but also provide a rational basis for devising new therapies to modify immune responses and control disease.

The FoxP3 defect in these patients was the key to understanding the critical importance of Tregs in immunology. These patients validated the much maligned concept of the regulatory T cell. In the IPEX syndrome the Fox defect appears limited to lymphoid tissue and CD4, 25 T cells in particular. Impaired T cell regulation was the operational defect and autoimmune disease was a predictable clinical outcome.

What else might the IPEX syndrome be telling us? The intractable diarrhea probably reflects regulatory defects in the gut mucosal immune system. The next frontier in clinical therapeutic immunology is the gut and these patients may provide an avenue for dissection of normal mucosal responses.

In the AIRE defect, you already can predict that there has been partial or complete loss of intra-thymic display of endocrine (and probably neuroendocrine) antigens which then allows you to expect and look for any number of endocrine deficiencies in these patients. Hypoparathyroidism (low calcium), hypothyroidism (deep voice) and ovarian/testicular dysfunction (infertility) are to be expected. The skin and bone abnormalities are likely due to loss of T cell control of bone and skin homeostasis.

What else might the AIRE syndrome be telling us? The frequent fungal defects would make one think some form of Th1 helper defect might also be present or that the ectodermal dysfunction is somehow thwarting innate immunity structural defenses in a way that the immune system can't fix.

Finally, in the Fas defect, the marked increase in CD3+, CD4- & CD8- cells confirms the evidence that antigen stimulated cells lacking a co-stimulatory signal are supposed to kill themselves by apoptosis. These patients can't do that and antigen bound T cells that have down-regulated their 4 or 8 surface markers but are unable to kill themselves "pile up" in lymphoid tissue and spleen.

What else might the Fas defect patients be telling us? Their B cells appear to be poorly regulated and inappropriate numbers of B cells mature to plasma cells and produce a wide range of IgG antibodies that are reflected by the presence of polyclonal

hypergammaglobulinemia. These patients may provide a window for further understanding B cell control.