

## Autoimmune Diseases of the Endocrine Glands

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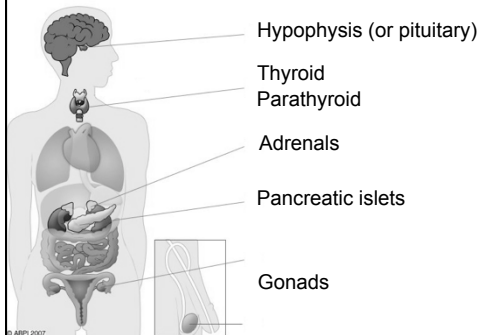
## The endocrine glands

Glands characterized by:

- absence of a duct system
- rich vascularization

Located in different areas of the body

## 6 "Classic" Endocrine Glands



## 6 "Classic" Endocrine Glands

Hypophysis (or pituitary) anterior	ACTH, TSH, LH, FSH, GH, PRL
posterior	ADH and oxytocin
Thyroid	T4, T3, and calcitonin
Parathyroids	PTH
Adrenals: cortex	Aldosterone, Cortisol, DHEA
medulla	Epinephrine and Norepinephrine
Pancreatic Islets	Insulin, glucagone, somatostatin
Gonads: testes	Testosterone, Inhibin
ovaries	Estrogens

## Autoimmune Endocrinopathies

- Endocrine glands can be affected by numerous autoimmune diseases
- These autoimmune endocrinopathies often cluster in the same family (familial aggregation) or in the same patient (co-morbidity)
- Knowledge of these diseases and their associations lead to earlier diagnosis and management

## Definition of Autoimmune Disease

- Condition where a functional and/or structural damage to normal components of the body is caused by humoral and/or cellular immune reactions
- Autoimmunity is the actual cause of the human disease, not the consequence or the harmless accompaniment

### Autoimmunity: the beginnings

- 1904: Donath & Landsteiner report that parossistic hemoglobinuria is caused by an antibody that binds to red cells at low temperatures, and then causes hemolysis at higher temperatures
- This observations is ignored because of the prevailing *horror autotoxicus* theory
- 1933: Thomas Rivers publishes an experimental model (injection of rabbit brains into monkeys) of the second autoimmune disease: multiple sclerosis
- 1951: William Harrington demonstrates (on himself) that thrombocytopenic purpura is caused by antibodies directed against platelets

### Description of Autoimmune Endocrinopathies

Chronologic order	Year	Endocrine disease	Author(s)
1	1951	Orchitis	Voisin & Barber
2	1956	Thyroiditis & Graves	Rose, Roitt, Adams
3	1958	Addison disease	Colover & Glynn
4	1962	Hypophysitis	Goudie & Pinkerton
5	1967	Hypoparathyroidism	Seeman
6	1968	Oophoritis	Irvine & Drury
7	1974	Type 1 DM	Bottazzo

### Diseases that will be discussed

- Type 1 diabetes mellitus
- Graves disease
- Hashimoto thyroiditis
- Addison disease
- Autoimmune hypoparathyroidism
- Autoimmune hypophysitis
- Autoimmune Polyendocrine Syndromes

### Diabetes Mellitus (DM)

- Group of metabolic disorders characterized by hyperglycemia resulting from:
  - defective insulin secretion (beta-cell loss): type 1
  - resistance to insulin action: type 2
  - Both
- Type 2 DM is the most common form (about 85% of all diabetic patients)

### Type 1 DM (beta cell loss)

- Type 1A: immune-mediate destruction of the pancreatic beta cells
- Type 1B: non-immune mediated forms of beta cell destruction, leading to absolute insulin deficiency
- There are about 1.5 million persons with type 1A in the US, 10% of which are children
- The incidence of type 1A DM is doubling approximately every 20 years, like that of asthma
- No cure available for type 1A DM. Treatment requires lifelong injections of recombinant insulin

### Genetic Susceptibility

- High concordance rate for monozygotic twins with type 1A DM: about 60%

		Twin 1	
		disease	no disease
Twin 2	disease	a	b
	no disease	c	<del>d</del>

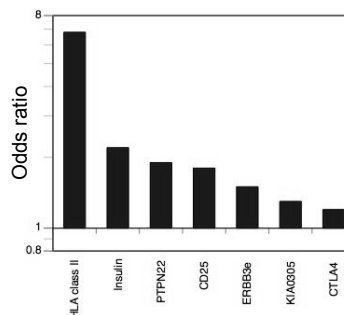
$$\text{Concordance rate} = \frac{a}{a + b + c}$$

Concordance rate (pairwise concordance): proportion of affected pairs among the pairs in which at least one twin has the disease

### Genetic Susceptibility

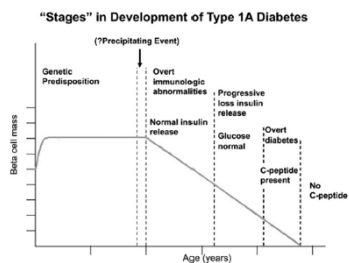
- The major determinant of genetic susceptibility is the class II locus of the Major Histocompatibility Complex (MHC, called HLA in humans): mainly DR and DQ
- GWA studies have identified numerous genetic loci that can modify the risk of developing type 1A DM

### Odds of developing type 1A DM



### Pathogenesis

- In a genetically susceptible individual, the development of diabetes occurs in stages.

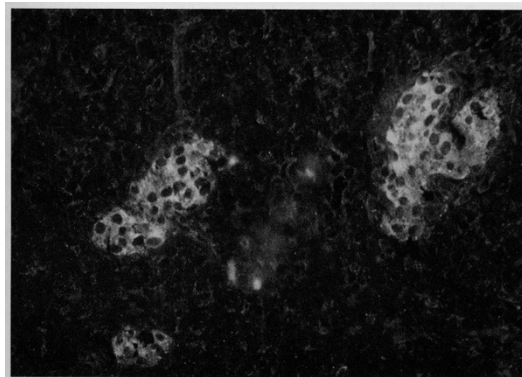


### Pathogenesis

- Much of what we know about the pathogenesis of type 1A DM comes from the study of the NOD mouse
- Type 1A DM is a T cell-mediated disease in which T cells infiltrate the pancreatic islets and ultimately kill the beta cells
- T cells, however, are not currently assessed in the clinical laboratory
- Thus, the diagnosis of autoimmunity in type 1A DM relies on serum autoantibodies

### Laboratory Assessment of autoimmune endocrinopathies

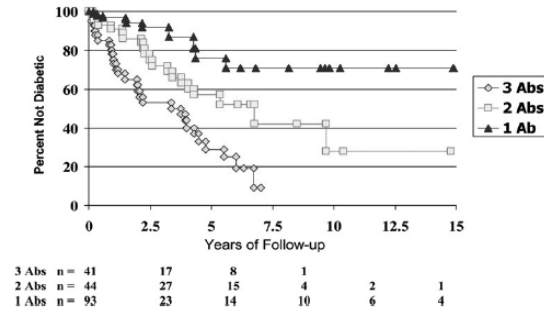
- Hormones to monitor the gland functions
- Autoantibodies to monitor the immunological pathogenesis
- Although T cells are fundamental for disease pathogenesis, T cell studies have yet to become part of the clinical laboratory



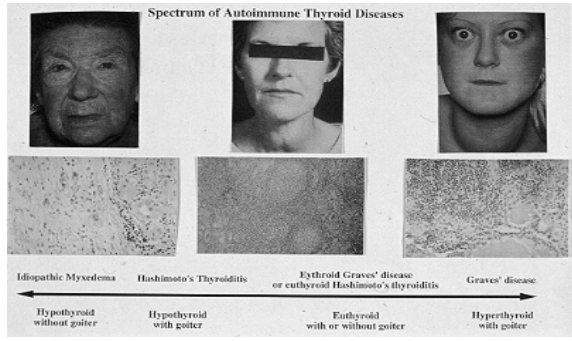
### Modern diabetes Ab tests

- Four antibodies are currently used to predict and monitor the development of type 1A DM:
  - GAD65 Abs (glutamic acid decarboxylase)
  - IA-2 Abs (Islet-associated antigen 2)
  - Insulin Abs
  - ZnT8 Abs (zinc T8 transporter)
- More Abs ==> faster DM development

### DM progression based on Abs

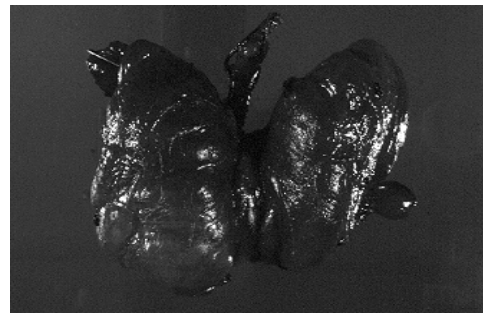


### Autoimmune Thyroid Diseases



### The thyroid in Graves disease

Big, smooth and soft



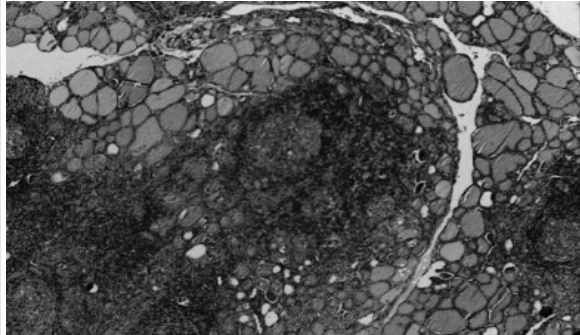
### Graves disease

- The hyperthyroidism is caused by autoantibodies that bind to and stimulate the thyrotropin (TSH) receptor on the surface of thyroid follicular cells
- The pathogenesis of ophthalmopathy and dermopathy is not known
- HLA DR3 increases the risk of developing Graves disease. Also polymorphisms in the CTLA-4 gene
- Concordance rate in monozygotic twins is low: ~25%
- Female sex remains the main risk factor

### TSH-R antibodies: Clinical Utility

- For diagnosis: little  
clinical criteria and thyroid hormone measurements (TSH and free T3) are sufficient for making the diagnosis
- For prognosis: important  
high levels of TSH-R Ab at the time of diagnosis suggest persistent hyperthyroidism  
high levels of TSH-R Ab at the end of a cycle of anti-thyroid drug therapy predict relapse after drug withdrawal
- For forecasting of neonatal hyperthyroidism: very important  
a high maternal titer of TSH-R Ab in the third trimester of pregnancy accurately forecasts neonatal Graves' disease

### Hashimoto thyroiditis



### Hashimoto's thyroiditis (various forms)

- Classic Hashimoto's thyroiditis
- Atrophic Hashimoto's thyroiditis (primary myxedema)
- Post-partum thyroiditis
- Silent (painless thyroiditis)
- Focal thyroiditis

### Classic Hashimoto's thyroiditis

- Middle-aged woman
- Goiter. At presentation euthyroid or hypothyroid (rarely hyperthyroid: Hashitoxicosis).
- Chronic course with almost universal development of hypothyroidism
- Dramatic improvement in quality of life since introduction of synthetic T4

### Hashimoto's thyroiditis: pathogenesis

- Unknown
- Importance of establishing an animal model (Rose and Witebsky, 1956)
- Importance of MHC haplotype and CD4+ T cells
- Role of thyroglobulin and thyroperoxidase antibodies: unclear

### TPO antibodies: Clinical Utility

- TPO antibodies are mainly measured to confirm a diagnostic suspicion of autoimmune thyroid disease
- TPO antibodies are an excellent marker of underlying autoimmune process in the thyroid gland
- In one exception, post-partum thyroiditis, the measurement of TPO antibodies is clinically crucial: the presence of TPOAb during pregnancy is a strong indicator of the development of post-partum thyroiditis

### TG antibodies: Clinical Utility

- Similarly to TPOAb, TG antibodies are measured mainly to They are only used to confirm a diagnosis of autoimmune thyroid diseases
- In one exception, follow-up of differentiated thyroid cancer, the measurement of TG antibodies is clinically crucial. In patients with differentiated thyroid cancer, after thyroidectomy and radioiodine therapy, the measurement of serum TG is useful to assess persistence or recurrence. TG antibodies may interfere with assays for TG, and therefore their presence should be sought when TG is measured

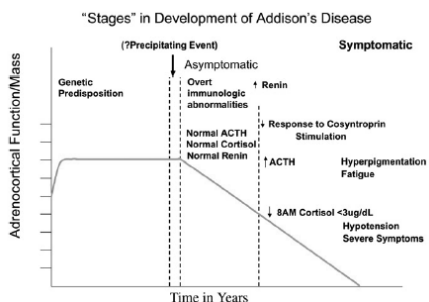
### Addison disease

- A primary adrenocortical insufficiency resulting in decreased levels of glucocorticoids, mineralcorticoids, and androgens and secondary elevation in ACTH
- Adrenal cortex becomes infiltrated with lymphocytes and eventually atrophic
- Autoimmunity is nowadays the most common cause of Addison disease (~80% of the cases), followed by tuberculosis
- Addison disease can occur in isolation or as part of the autoimmune polyglandular syndrome type 1 or 2

### Addison disease

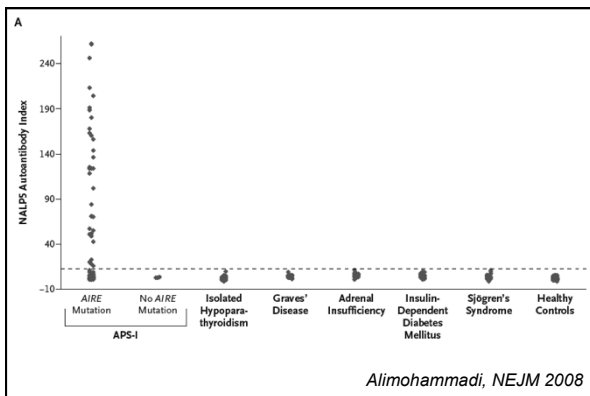
- Genetic predisposition:
  - MHC class II: the DR3 haplotype
  - MHC class I-related molecule A (allele 5.1)
- Antibodies to 21-hydroxylase are found in the majority of patients and predict the development of adrenal insufficiency

### Addison disease

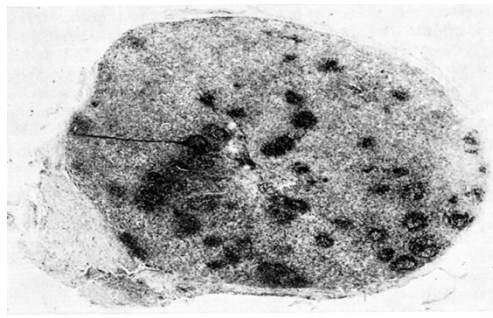


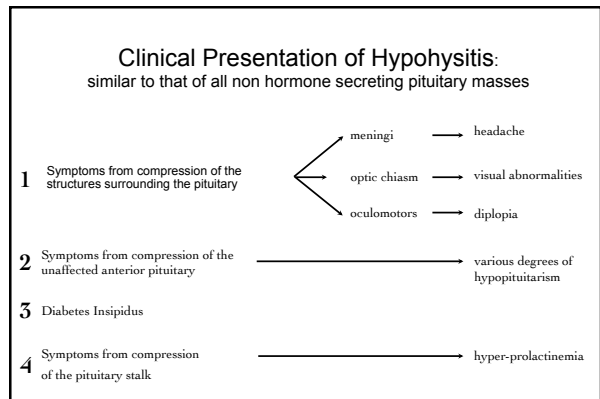
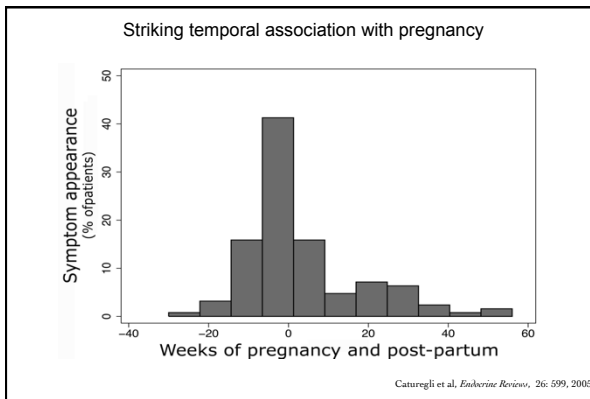
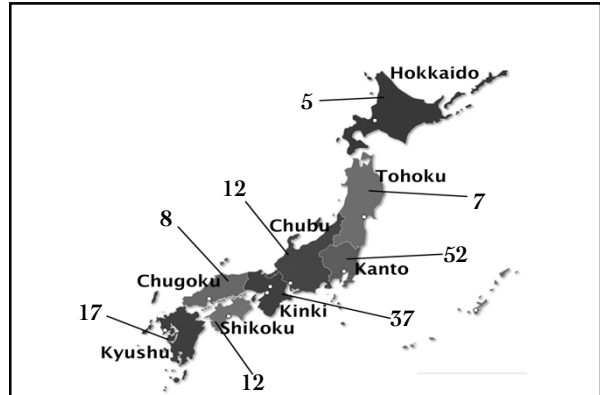
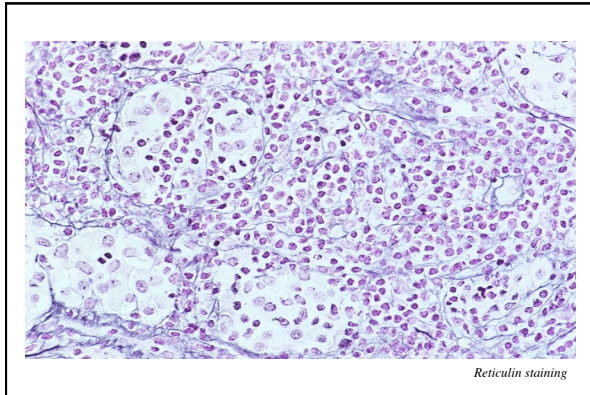
### Autoimmune hypoparathyroidism

- Rare but increasingly recognized
- Occurs in isolation or as common component of the autoimmune polyendocrine syndrome type 1
- It results in parathyroid hormone deficiency and thus hypocalcemia
- Traditionally diagnosed by exclusion, when no other causes of hypoparathyroidism and hypocalcemia can be identified
- More recently, antibodies to NALP5 have been uniquely identified



### Autoimmune Hypophysitis





the CTLA-4 connection

- Oncologists have begun to see hypophysitis
- Cancer patients treated with “boosters” of the immune response become susceptible to hypophysitis
- Example: patients with advanced melanoma<sup>1</sup>:
  - vaccinated with melanoma gp100 antigen
  - injected with an antibody that blocks CTLA-4
  - 5% develop hypophysitis

Blansfield, *J Immunother*, 26: 593, 2005

APS-1 (or, APECED)

- Single gene (monogenic) defect
- Most common in Finns, Iranian Jews, and Sardinians
- Characterized by various clinical features, mostly autoimmune in nature
- Present in children (2-3 years old), typically with mucocutaneous candidiasis involving mouth and nails (a non autoimmune feature)
- Children then develop hypotension and fatigue, from Addison disease, and hypocalcemia from hypoparathyroidism

### APS-1 (or, APECED)

- Caused by mutations in the AutoImmune Regulator gene (AIRE)
- It encodes a transcription factor expressed mainly in the thymus (medullary epithelial cells) that controls the presentation of self antigens to the developing T lymphocytes
- When the gene is mutated, tolerance to multiple self antigens is lost

### APS-2 (Schmidt-Carpenter syndrome)

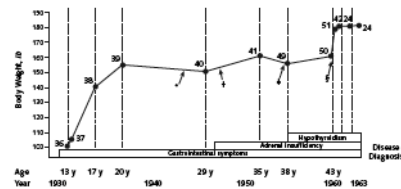
- More common than APS-1
- Affects adults, mainly women
- Defined by the presence of Addison disease plus autoimmune thyroid diseases or type 1A DM. Other diseases like pernicious anemia, hypophysitis, vitiligo can also be present
- Diseases can develop years to decade apart



HISTORY OF MEDICINE | Annals of Internal Medicine  
**Endocrine and Autoimmune Aspects of the Health History of John F. Kennedy**

Lawrence A. Mendel, MD, MPH  
 At the age of 42 years, John F. Kennedy was the youngest man ever elected president. Throughout both his presidency and his presidency, he was perceived as the epitome of youth and vigor. In fact, he had the most complete medical history of anyone to occupy the White House. The most complete of his 1960s medical records has provided researchers greater insight into the multiple medical conditions that afflicted Kennedy. A reconstruction of these records, created with other available sources, allows new understanding of his health history that can now be explored in the context of a varying autoimmune endocrine disorder.

Figure. John F. Kennedy's medical profile.



The time of diagnosis of gastrointestinal symptoms, adrenal insufficiency, and hypothyroidism are plotted against Kennedy's body weight at various ages. Ankle numbers at each solid circle are the reference from which body weight information was obtained.  
 \* Sinking of PT-109, August 1943.  
 † Addison disease diagnosed, September 1947.  
 ‡ Unsuccessful back surgery, October 1954.  
 § Suspected initiation of corticosteroid therapy, July to August 1960.

### IPEX syndrome

- Caused by mutations in the forkhead box protein 3 gene (FOXP3)
- Manifests in infants (first few months of life) with dermatitis, growth retardation, multiple endocrinopathies, and recurrent infections
- FOXP3 is a molecule that defines a subset of T lymphocytes called Treg. When mutated, Treg lose their ability to suppress other lymphocytes and the patient develops overwhelming autoimmunity
- Bone marrow transplantation is currently the only chance for survival