The Immune System and Endocrine Disorders

Immunopathology Unit.
College of Medicine & KSU Medical City

Objectives

- To recognize that many endocrine disorders are organ-specific autoimmune diseases.

- To understand the mechanisms of damage which take place at endocrine glands and their consequences.

- To know the important examples of autoimmunity which affect different endocrine glands and the pathogenesis of these disorders.

Many endocrine disorders are organ-specific autoimmune diseases.

In organ-specific autoimmune disease, the immune response is directed to a target antigen unique to a single organ.

the manifestations are largely limited to that organ.

The damage may be directly mediated by:

*Humoral (Antibodies) Immunity
the antibodies may
overstimulate or block
the normal function of the target organ

OR

*Cell-mediated Immunity (CMI).

Examples of Autoimmune endocrine diseases

Thyroid:

Hashimoto's disease :

Autoantibodies against thyroid peroxidase.

Primary myxoedema :

Atrophy of the thyroid.

Graves' disease :

Autoantibodies against Thyroid Stimulating Hormone receptor (TSH-R)

Pancreas :

Type I diabetes.

Adrenal :

Addison's disease.

Chronic endocrine disorder; adrenal glands
produce insufficient steroid hormones

Gonads :

Autoimmune oophoritis (inflammation of the ovaries).

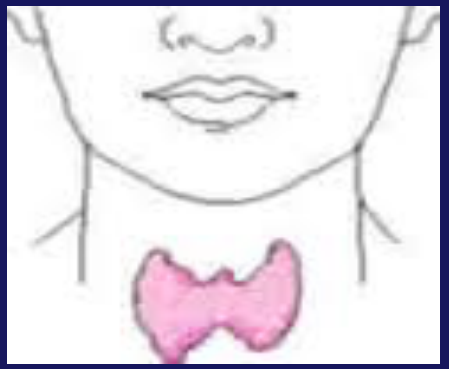
Autoimmune orchitis:

Testicular pain involving swelling, inflammation and infection

Pituitary:

Lymphocytic hypophysitis. Low production of one or more hormones by the pituitary gland due to autoantibodies and autoimmunity

1.Thyroid autoimmunity



Hypothyroidism

- Hashimoto's disease.
- Atrophic thyroiditis.

Hyperthyroidism

- Graves' disease.

A. Chronic Lymphocytic Thyroiditis (Hashimoto's Thyroiditis)

- Male: Female ratio is 1:3
- Associated with HLA II Predisposing effect: DR4 (DRB1*04-DQB1*03-DQA1*03). Protective role: DR13 (DRB1*13-DQB1*06-DQA1*01)

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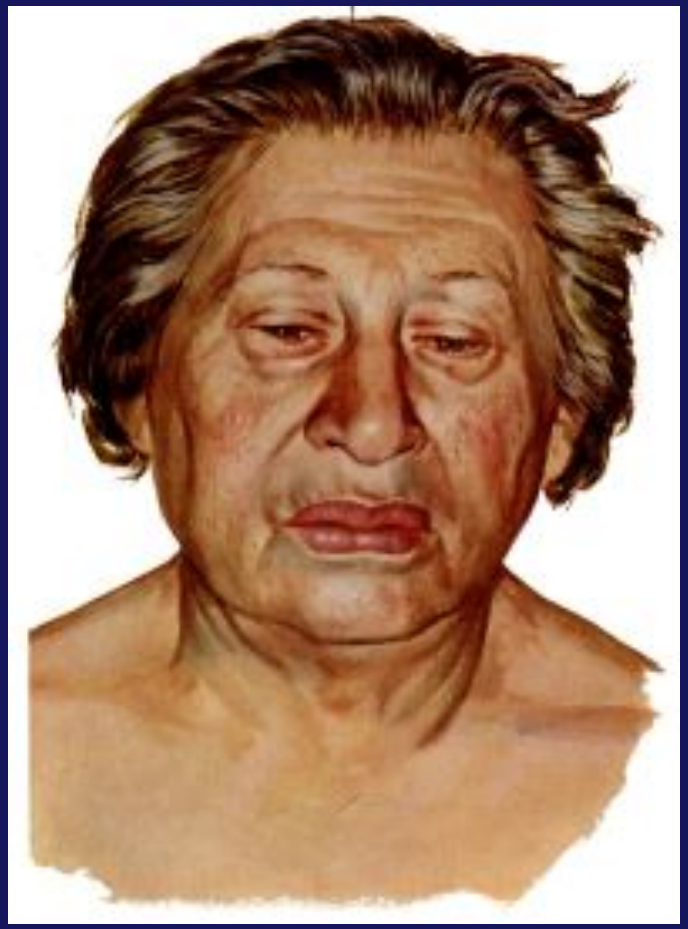
- Anti-thyroid peroxidase and anti-thyroglobulin antibodies.
- There will be symptoms of hypothyroidism.



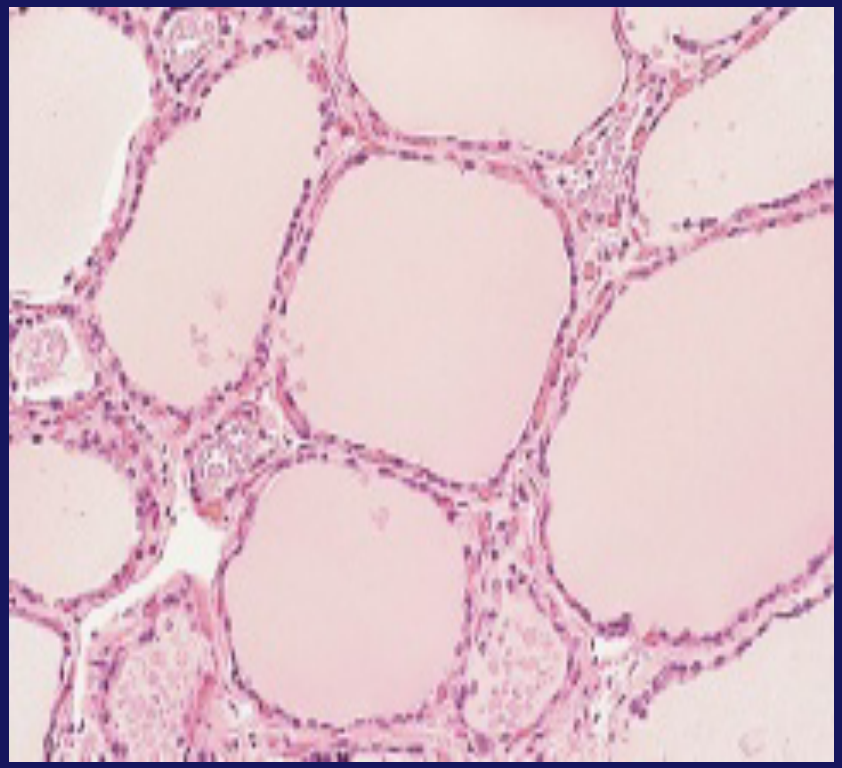
HASHIMOTO'S THYROIDITIS:

- Frequently seen in middle-aged women

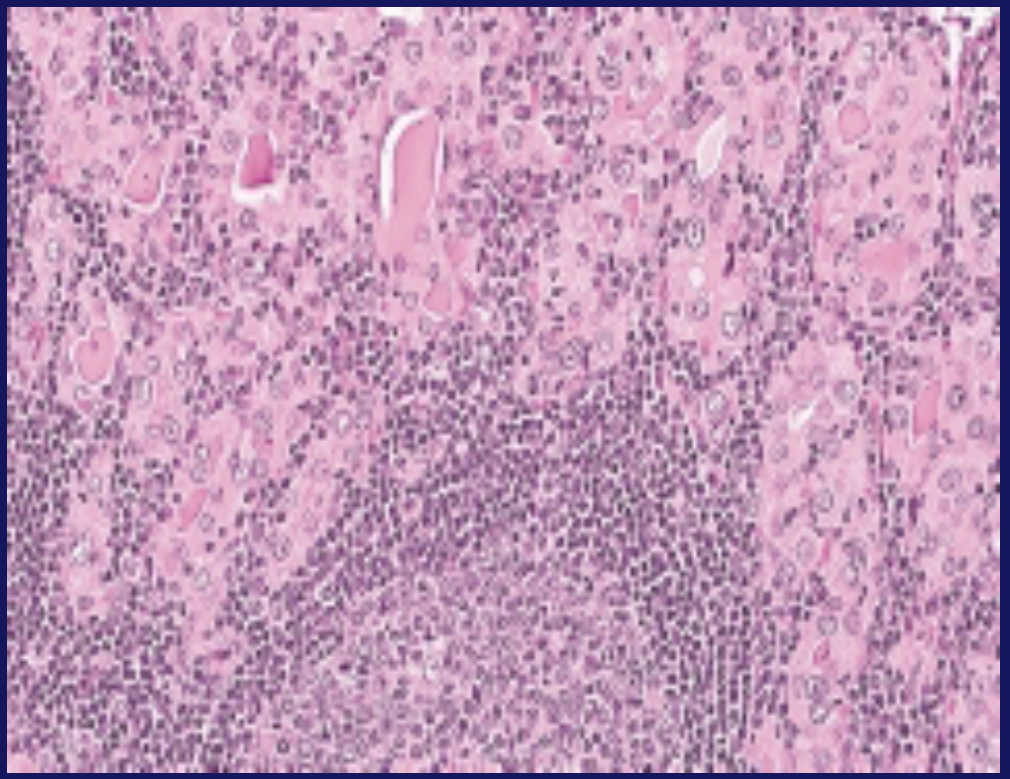
- Individuals produce auto-antibodies and sensitized TH_1 cells specific for thyroid antigens.

- The DTH response is characterized by:

an intense infiltration of the thyroid gland by lymphocytes, macrophages, and plasma cells, which form lymphocytic follicles and germinal centers.



Photomicrographs of (a) normal thyroid gland showing a follicle lined by cuboidal follicular epithelial cells



Hashimoto's thyroiditis showing intense lymphocyte infiltration.

[From Web Path, courtesy of E. C. Klatt, University of Utah.]

The ensuing inflammatory response causes:

A goiter, or visible enlargement of the thyroid gland,

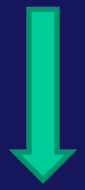
(a physiological response to hypothyroidism)

Antibodies are formed to a number of thyroid proteins, including:

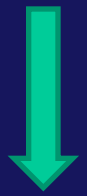
- thyroglobulin
- thyroid peroxidase

(both of which are involved in the uptake of iodine)

Binding of the auto-antibodies to these proteins.



interferes with iodine uptake
and leads to

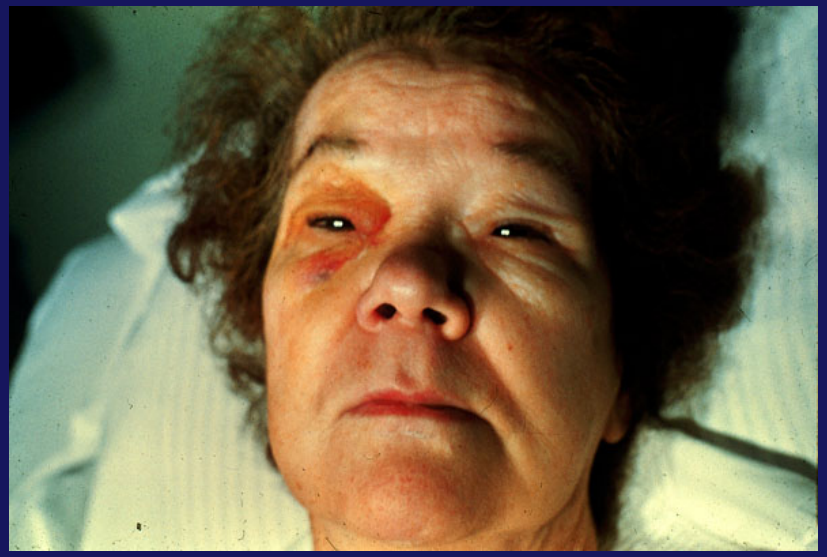


decreased production of thyroid hormones.

(hypothyroidism).

Clinical Features of Hashimoto's

- Fatigue, loss of energy
  Cold intolerance.
  Weight gain.
  Mental slowing.
  Enlarged thyroid.



B.Graves' Disease

- Less common than Hashimoto's disease.
- Male: Female ratio up to 1:7.
- Associated with HLA class II Predisposing effect for DR3 (DRB1*03-DQB1*02-DQA1*05) and a protective effect for DR7 (DRB1*07-DQB1*02-DQA1*02).

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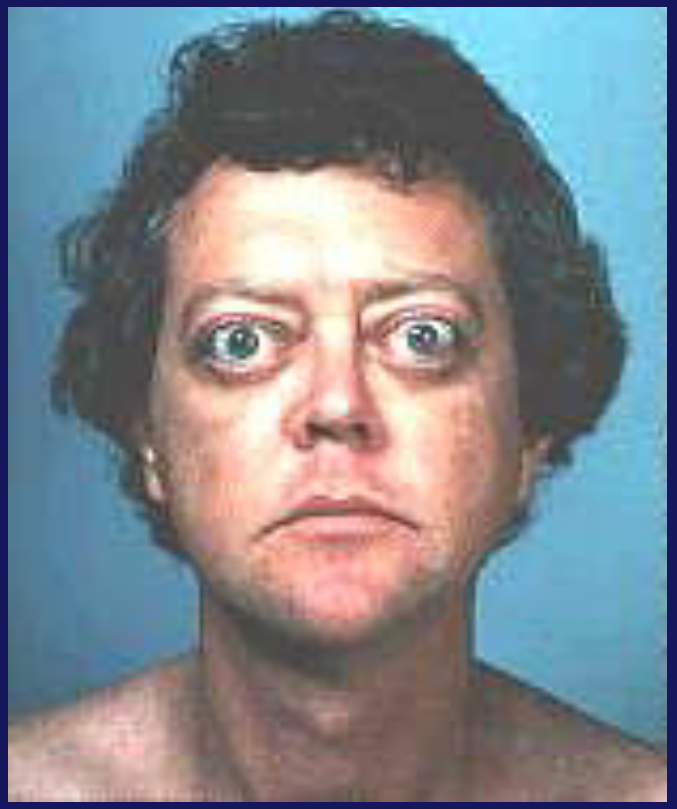


GRAVES' DISEASE :

The production of thyroid hormones is carefully regulated by thyroid-stimulating hormone (TSH), which is produced by the pituitary gland.

Binding of TSH to a receptor on thyroid cells activates adenylate cyclase and stimulates the synthesis of two thyroid hormones, thyroxine and triiodothyronine.

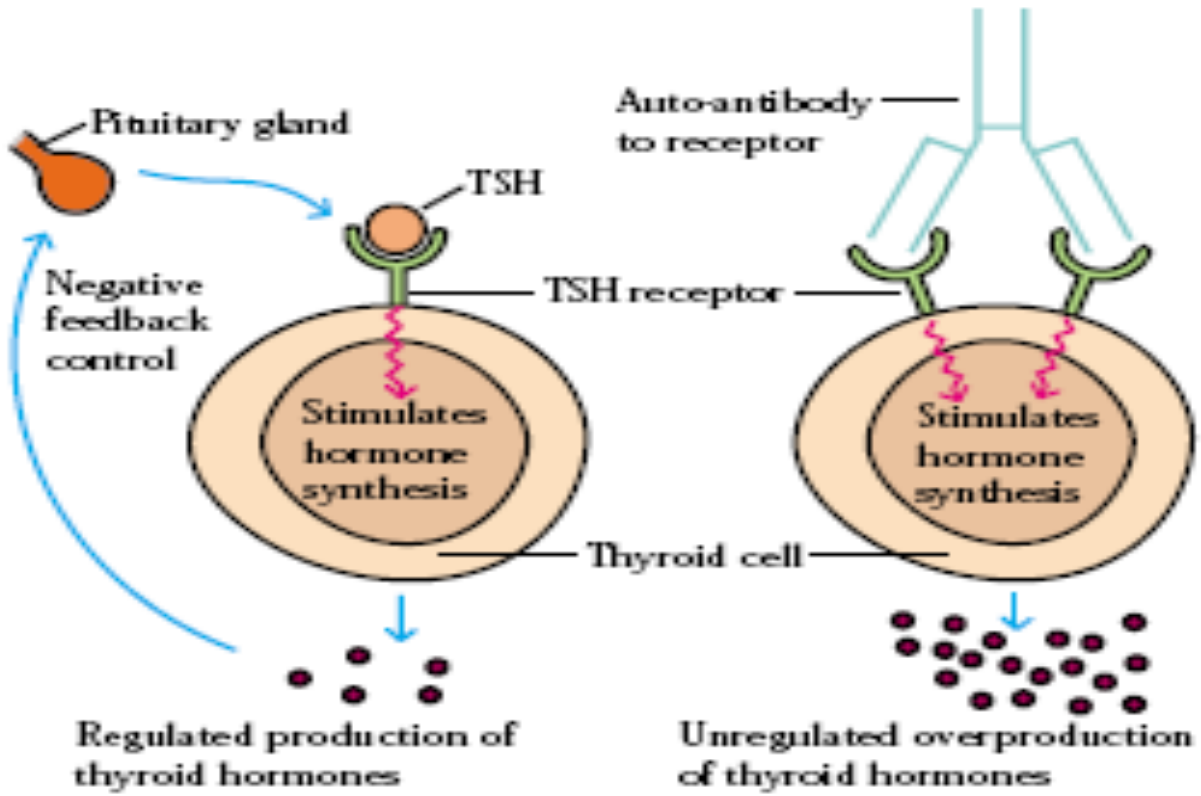


FIGURE 20-4 In Graves' disease, binding of auto-antibodies to the receptor for thyroid-stimulating hormone (TSH) induces unregulated activation of the thyroid, leading to overproduction of the thyroid hormones (purple dots).

In **Graves' disease auto-antibodies** bind the receptor for TSH and mimic the normal action of TSH, activating adenylate cyclase and resulting in production of the thyroid hormones.

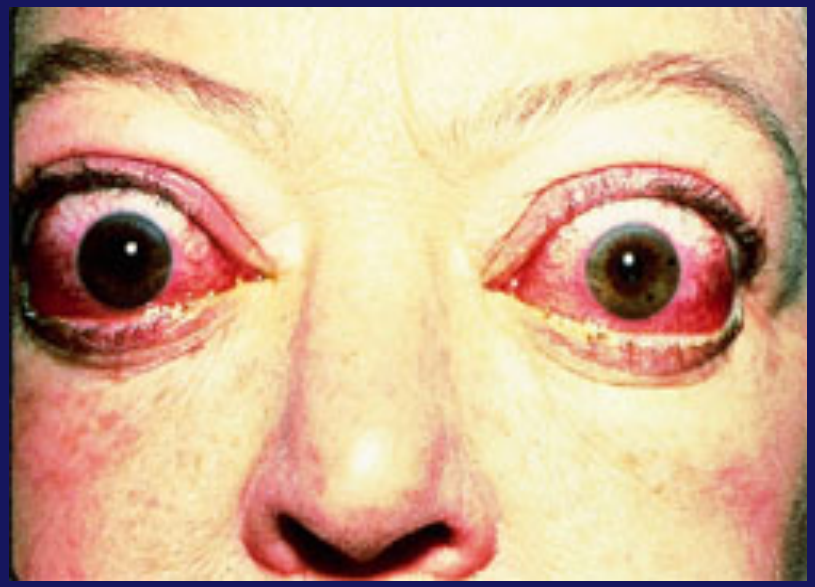
Unlike TSH

the autoantibodies are not regulated, and consequently they overstimulate the thyroid.

For this reason these auto-antibodies are called : long-acting thyroid-stimulating (LATS) antibodies.

Clinical Features of Graves' disease

- Agitation, sleep disturbance.
- Sweating, palpitations.
- Muscle weakness.
- Weight loss despite increased appetite.
- Goiter.
- Tremor.
- Ophthalmopathy.



2. Insulin-dependent diabetes mellitus (IDDM)

IDDM is an example of type IV hypersensitivity.

-Autoreactive T-cells invade the pancreatic islets and destroy the insulin-secreting beta cells.

- Macrophages become activated.

→This is frequently referred to as **insulitis**.

(Cell-mediated DTH response)

*** As A result:**

decreased production of insulin and consequently increased level of blood glucose.

Type 1 Diabetes Mellitus

Pathogenesis:

- Three mechanisms are responsible for the islet cell destruction:
  - Genetic susceptibility (HLA-DQ alleles).
  - Autoimmunity.
  - Environmental factors. Infections:
    Coxsackie virus??
    Echovirus??

Type I insulin- dependent diabetes.

pancreatic beta-cell autoreactive T cells (DTH & CTL) and autoantibodies.

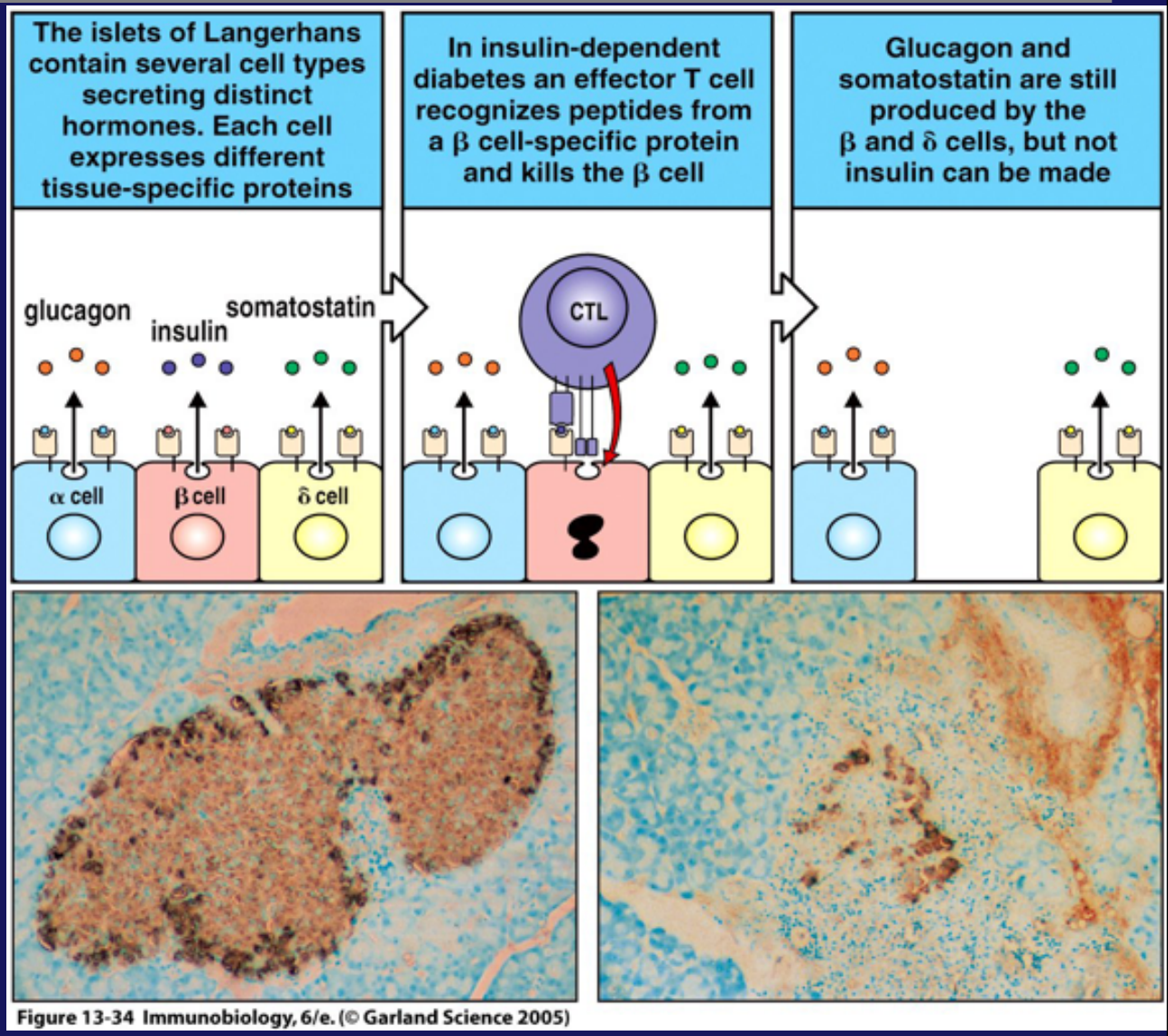


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

- **The most likely scenario is that viruses cause mild beta cell injury, which is followed by an autoimmune reaction against altered beta cells in persons with HLA-linked susceptibility.**

Type 1 IDDM patients (aprox.10%) are prone to other autoimmune disorders

3.Autoimmune adrenocortical failure, or Addison's disease.

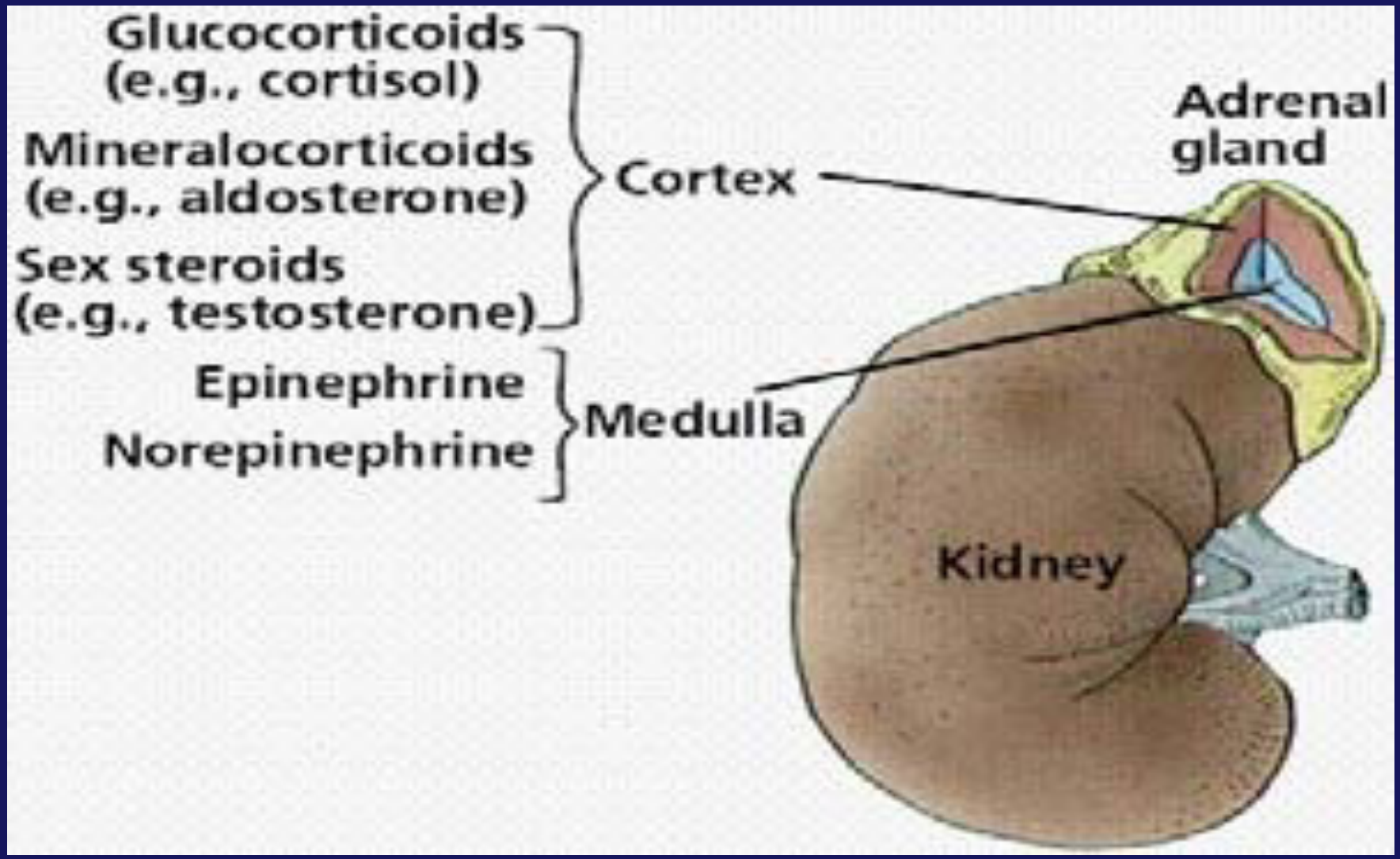
is a prototypical organ–specific autoimmune disorder.

It develops as a consequence of autoimmune destruction of steroid-producing cells in the adrenal gland.

A major autoantigen is **21-hydroxylase (21OH).**

which is involved in the biosynthesis of **cortisol** and **aldosterone** in the adrenal cortex .

Hormones of the adrenal glands :

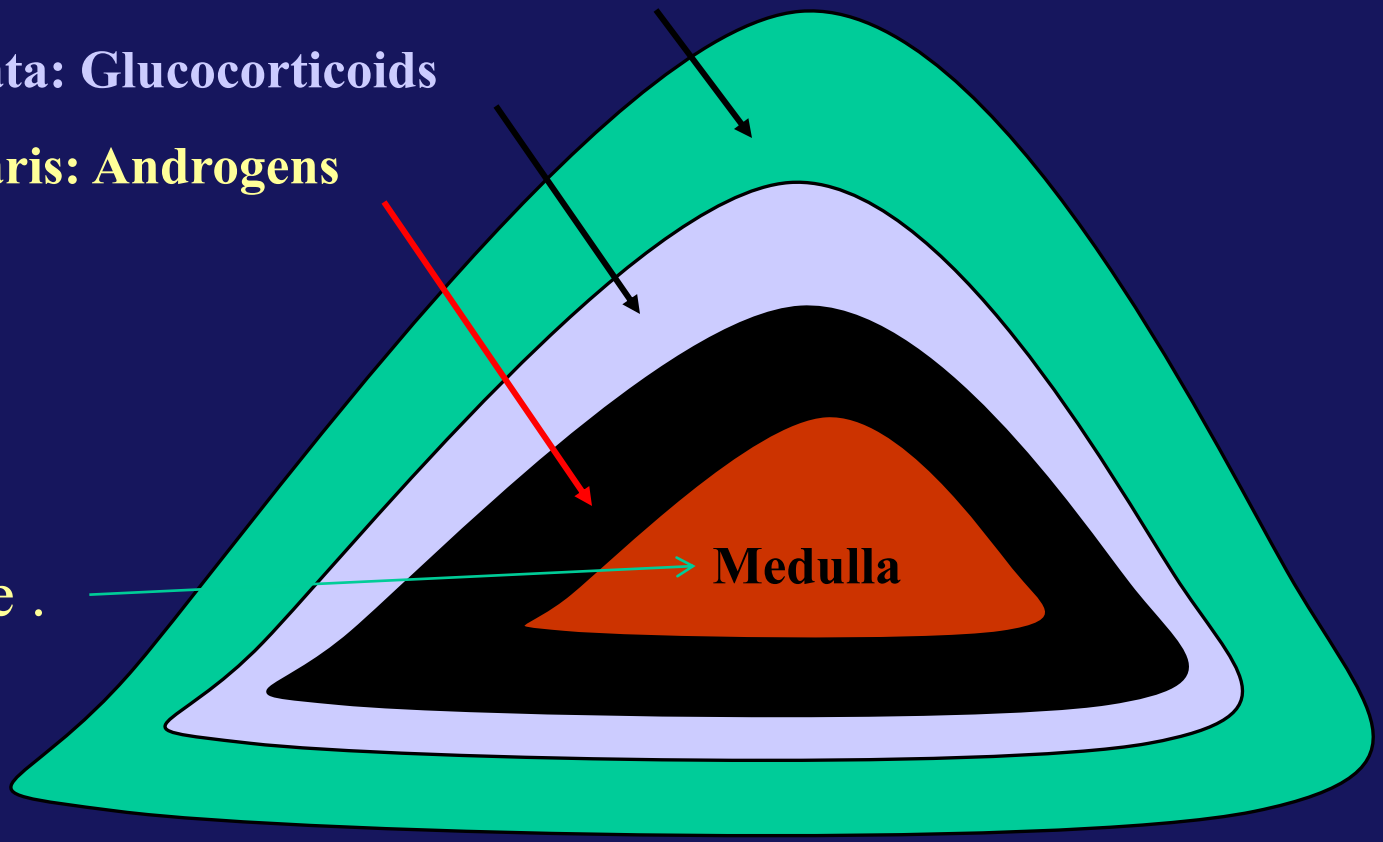


Adrenal Cortex

Zona Glomerulosa: Mineralocorticoids

Zona Fasiculata: Glucocorticoids

Zona Reticularis: Androgens



Epinephrine .

ADDISON'S DISEASE – GENETICS

- Female: Male ratio : 4:1

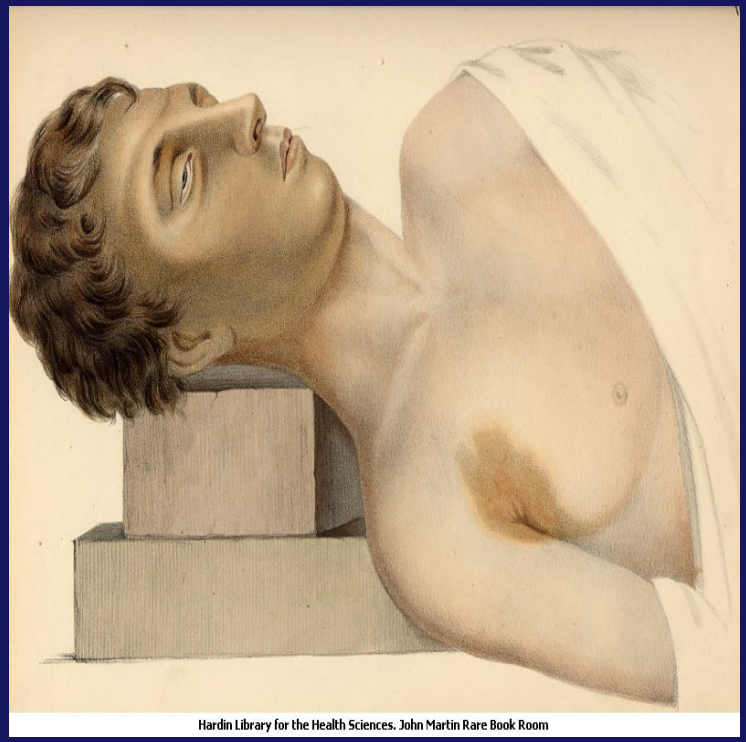
- Susceptibility genes:

HLA-DR3 and/or DR4
The most strongly associated DRB1*04 allele is DRB1*04:04

Primary adrenal insufficiency: symptoms & Physical findings

- Weakness
- Weight loss
- Poor appetite

  -Confusion
- Hyperpigmentation.
- Hypotension.
- Weak pulses.
- Shock.



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damage to the adrenal cortex may be caused by :

1. (autoimmune disease)
2. Infections .
3. Hemorrhage,
4. Tumors.
5. Use of drugs (anticoagulants).

T cell-mediated injury is likely to be central to pathogenesis.

Adrenal Autoantibodies may have a pathogenic role, as yet unclear , or could arise secondary to T cell-mediated tissue damage,