

Endocrine Block

Lecture one

The Immune System and Endocrine Disorders

IMMUNOLOGY

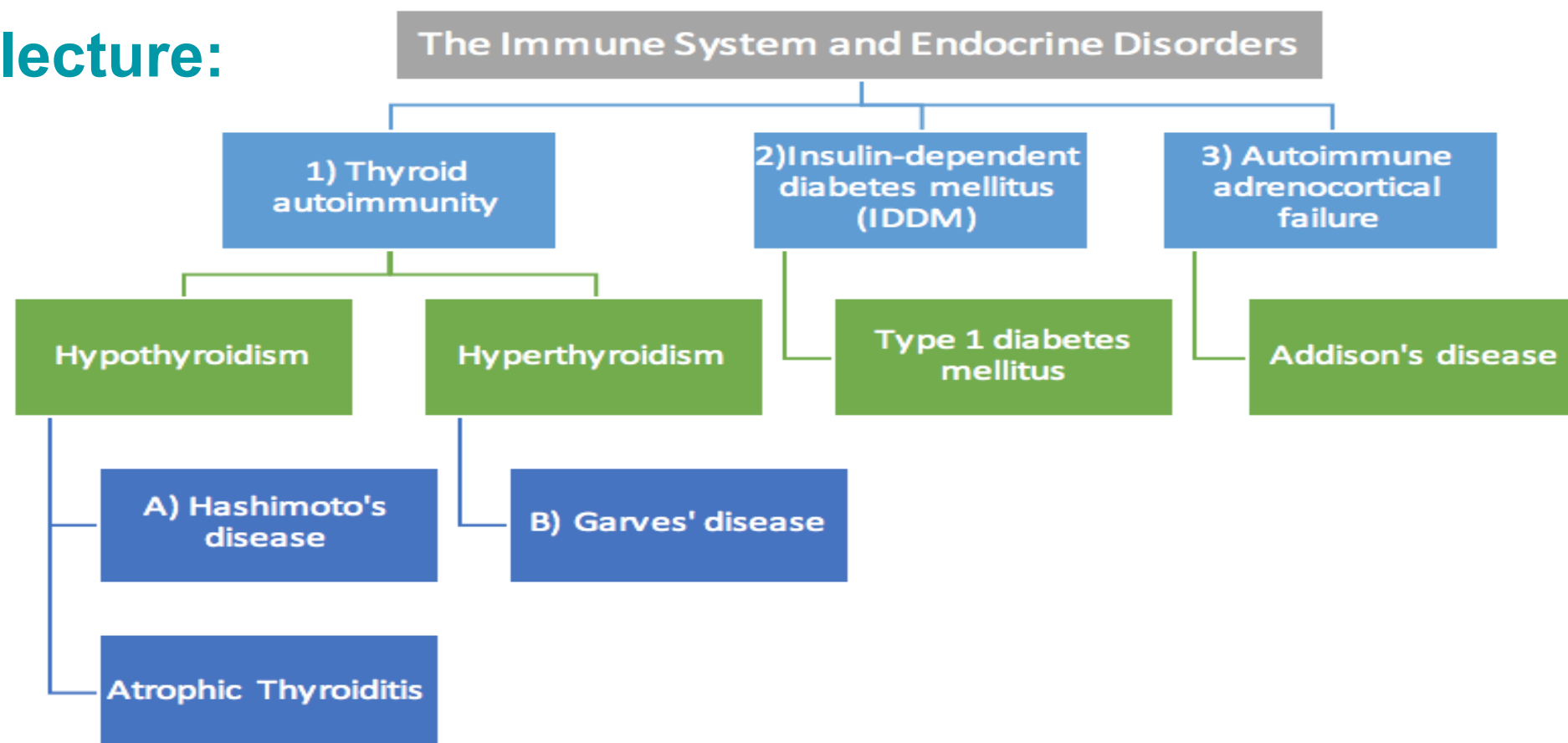
4 3 6 ' s T E A M W O R K

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.

- **Important.**
- Extra notes.
- **Doctor's notes**

Overview of the lecture:



Introduction

❖ Many endocrine disorders are **organ-specific** autoimmune diseases. leads to the function of the organ

organ-specific autoimmune diseases :

- 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: (could be either one or both of them)

- **Humoral (Antibodies) Immunity:**

the antibodies may **overstimulate** or **block** the normal function of the target organ

- **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.

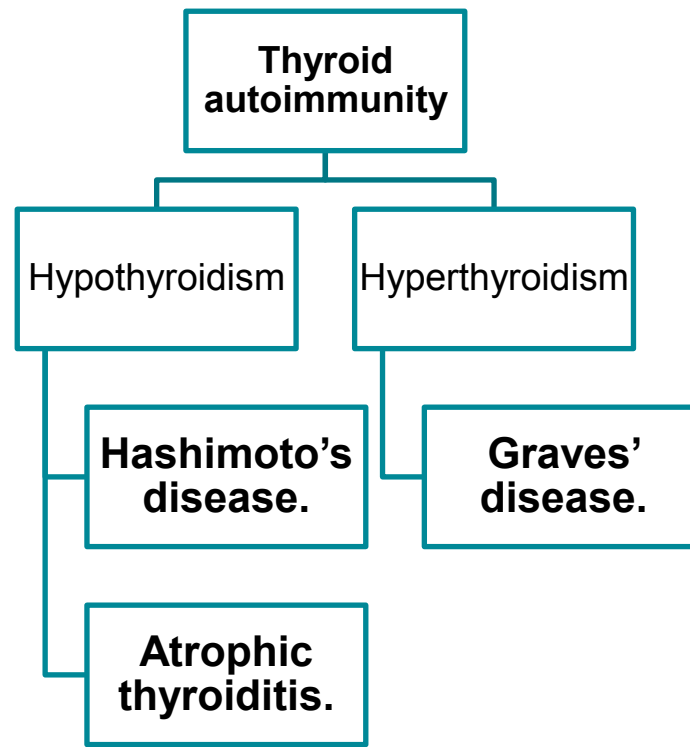
Pituitary

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

1) Thyroid autoimmunity

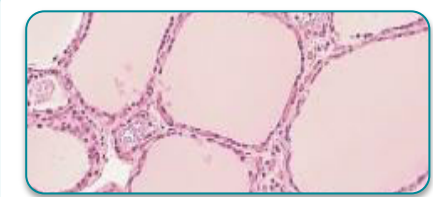
Autoimmunity is strongly associated with hypersensitivity type
Tissue damage = 2 (cellular antigen) ,3 (soluble antigen)

Why are females more susceptible to autoimmune diseases?
Hormones and genetics .

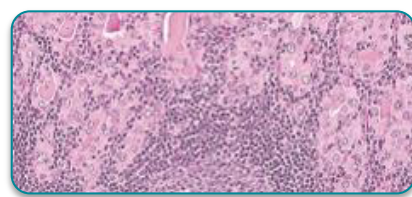


A) Hashimoto's Thyroiditis / Chronic Lymphocytic Thyroiditis:

- Male: Female ratio is 1:3, Frequently seen in middle-aged women.
- Associated with HLA II,
- Predisposing effect: **DR4** (DRB1*04-DQB1*03-DQA1*03). (more likely to get the disease)
- Protective role: **DR13** (DRB1*13-DQB1*06-DQA1*01) (less likely to get the disease) .
- There will be symptoms of hypothyroidism. *Subtypes are not important
- Individuals produce auto-antibodies and sensitized TH1 cells specific for thyroid antigens (Both Antibody mediated cellular mediated at the same time):
Anti-thyroid peroxidase and **anti-thyroglobulin antibodies**.



normal thyroid gland showing a follicle lined by cuboidal follicular epithelial cells



Hashimoto's thyroiditis showing intense lymphocyte infiltration.



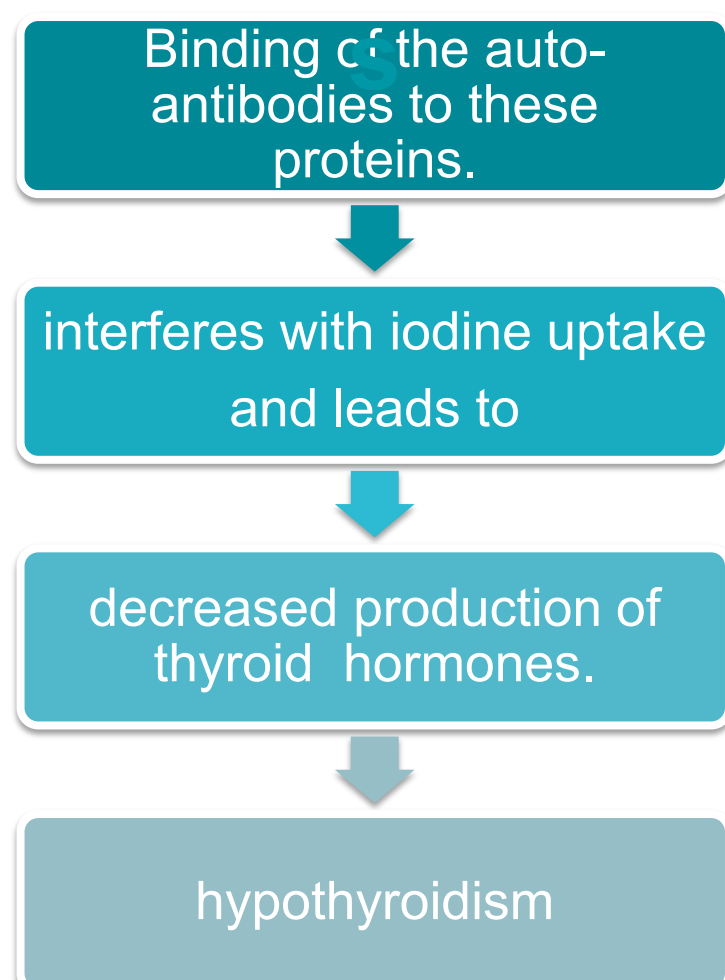
The DTH (Delayed Type (IV) Hypersensitivity) response is characterized by:

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

The ensuing inflammatory response causes:

- A **goiter** or **visible enlargement** of the thyroid gland. (a physiological response to hypothyroidism) .
- Formation of antibodies to thyroid proteins (**thyroid peroxidase** and **thyroglobulin**) both of **which are involved in the uptake of iodine**.

Pathogenesis



Clinical Features

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

*We highly recommend you to watch the videos next to hashimoto's, graves', type I DM and Addison's

1) Thyroid autoimmunity

Physiology of thyroid

- 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.

• Male: Female ratio up to 1:7.

• Less common than Hashimoto's disease.

B) Graves' Disease

• Associated with HLA class II protective effect for **DR7**
(DRB1*07-DQB1*02-DQA1*02).

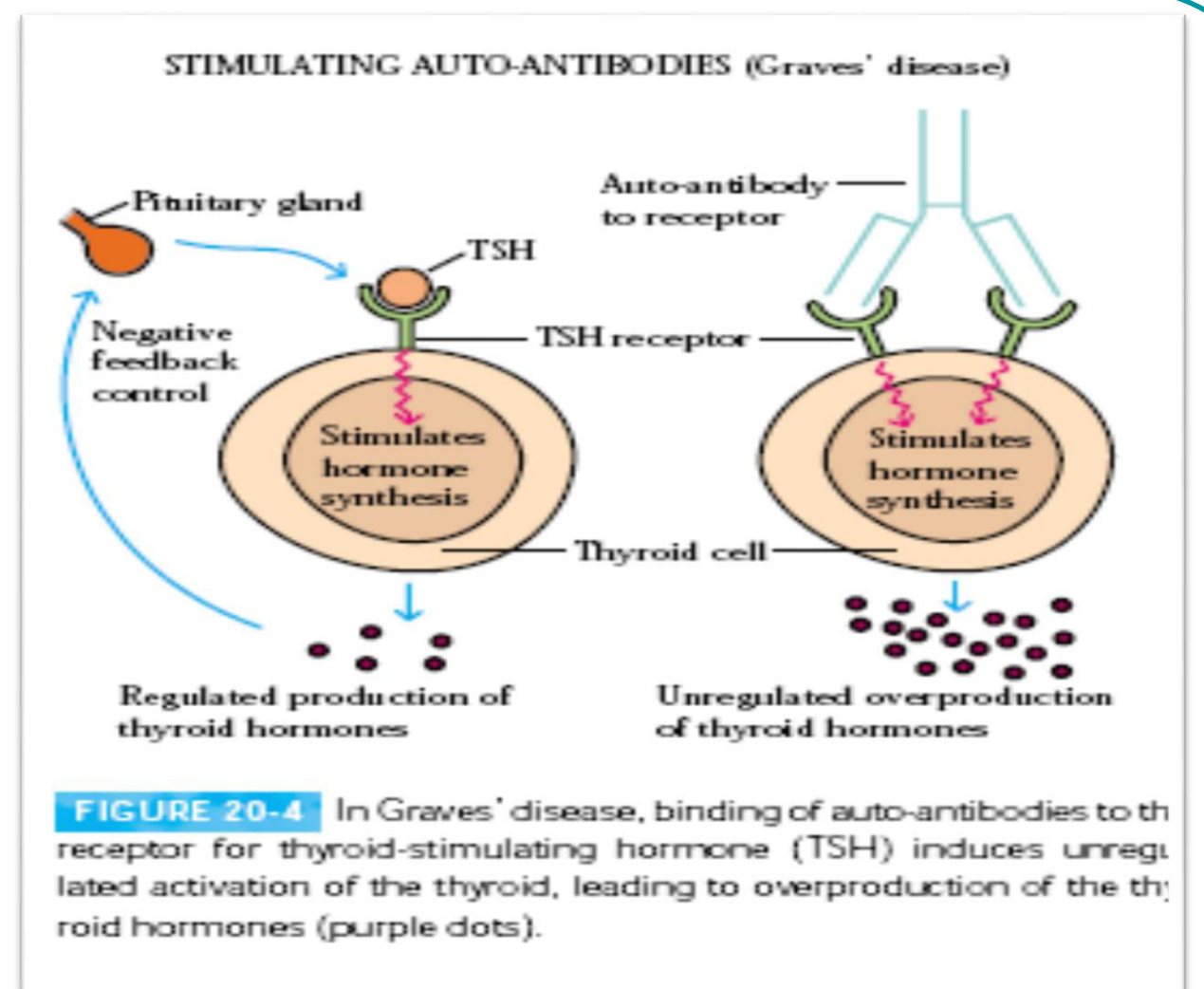
Associated with HLA class II Predisposing effect for **DR3**
(DRB1*03-DQB1*02-DQA1*05)

*Subtypes are not important

- 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. ***no -ve feedback, Continuous production**

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

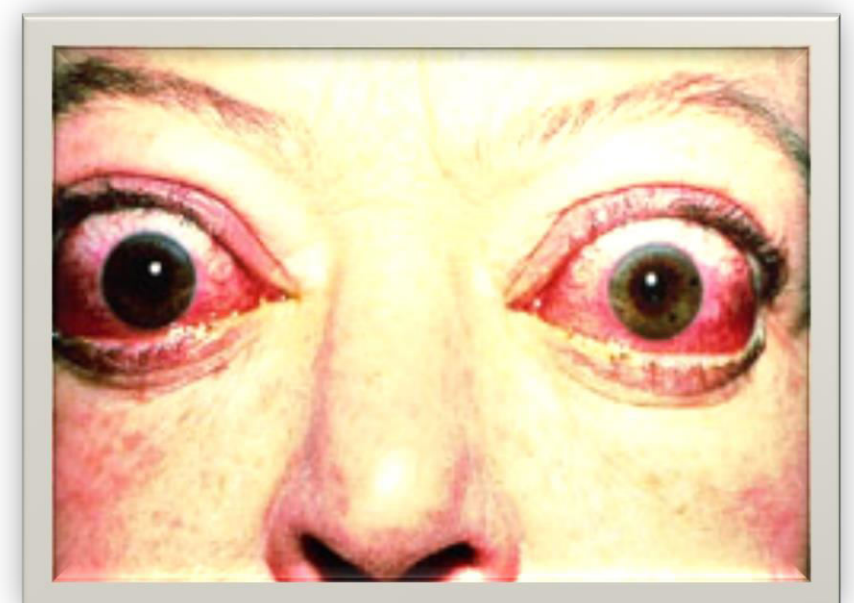
- For this reason these auto-antibodies are called long-acting thyroid-stimulating (**LATS**) antibodies.



Clinical Features of Graves' disease:

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

*exophthalmos



2) Insulin-dependent diabetes mellitus (IDDM)

Improper expression of Class II MHC on Non-antigen presenting cells

- 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 **at the site**. This is frequently referred to as **insulinitis**. (**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*) *under research



- 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 disorder

Beta cells improperly express of class 2 (remember that beta cells aren't APCs, so it's abnormal), cell antigens in beta cells then will be presented. T-cells (TH1) will come and attack the beta cells.

What makes beta cells express abnormal class II MHC?
Macrophages, produced IFN- γ which upregulates Class II MHC expression.

IFN- γ produced might be triggered by the viral infection

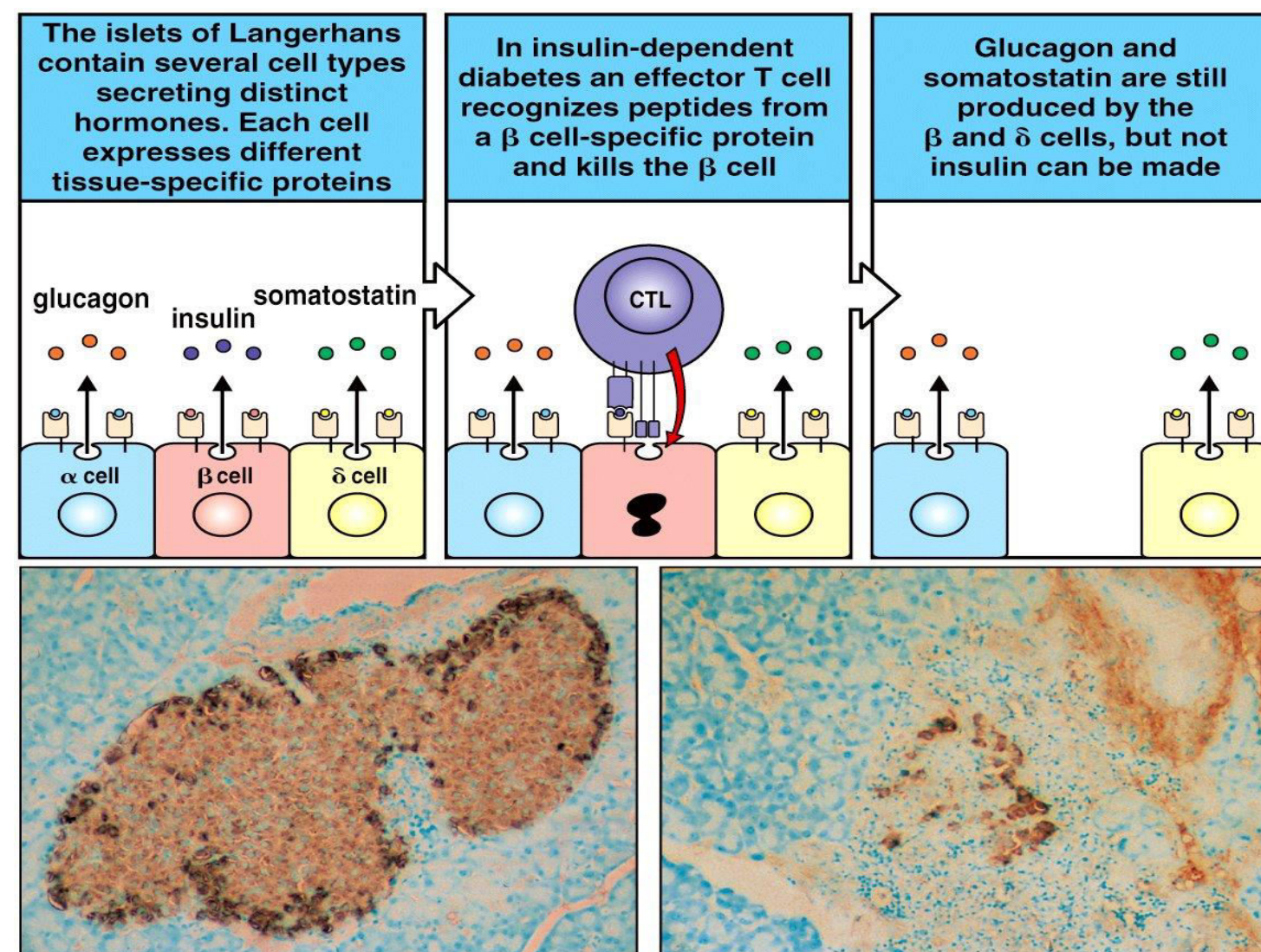


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

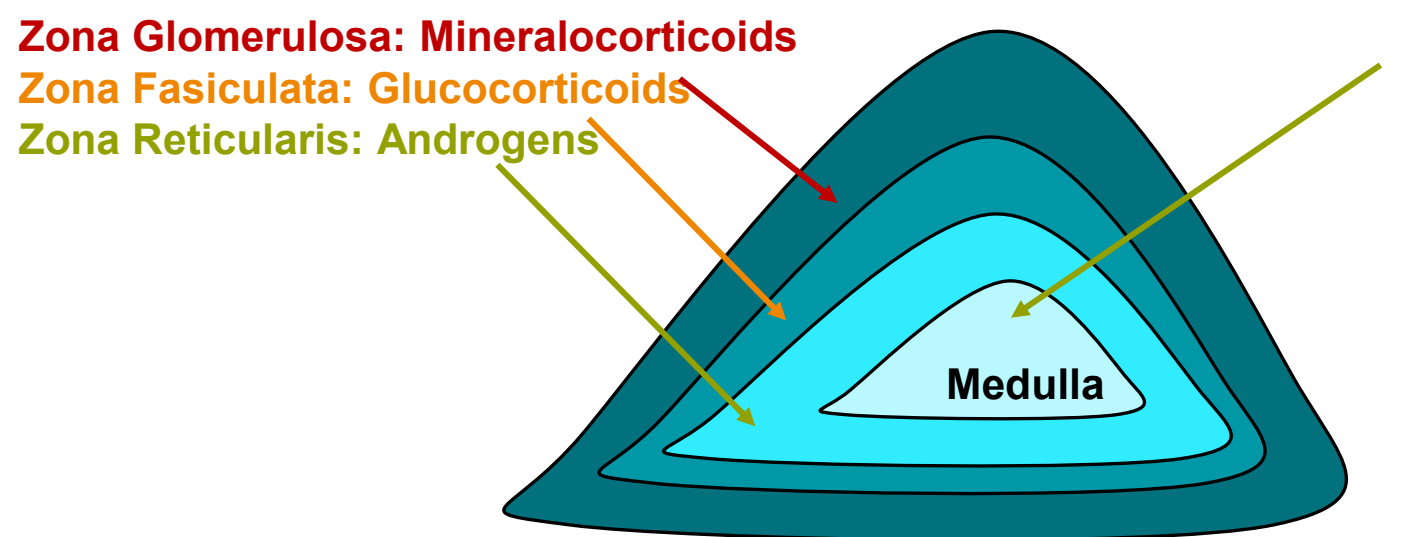
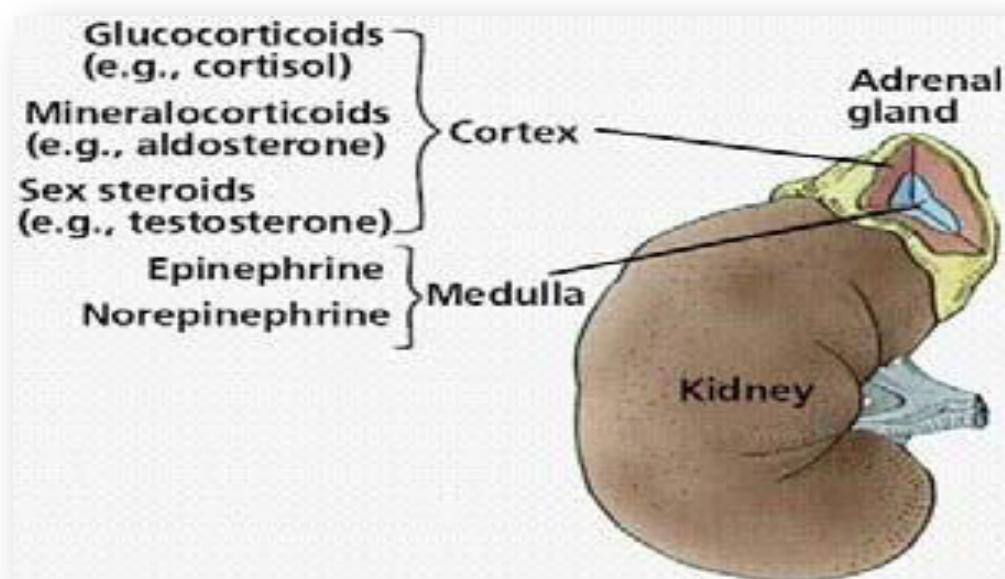
* pancreatic beta-cell autoreactive T cells (DTH & CTL) and autoantibodies.

3) Autoimmune adrenocortical failure



Named as 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)** important.
- which is involved in the biosynthesis of **cortisol** and **aldosterone** in the adrenal cortex .



Addison's disease

Genetics	Symptoms & physical finding in primary adrenal insufficiency	Etiology
<ul style="list-style-type: none"> - Female: Male ratio: 4:1 - Susceptibility genes: HLA-DR3 and/or DR4 - The most strongly associated DRB1*04 allele is (DRB1*04:04)*. <p>*subtypes</p>	<ul style="list-style-type: none"> <input type="checkbox"/> Weakness <input type="checkbox"/> Hyperpigmentation <input type="checkbox"/> Weight loss <input type="checkbox"/> Hypotension <input type="checkbox"/> Poor appetite <input type="checkbox"/> Weak pulses <input type="checkbox"/> Confusion <input type="checkbox"/> Shock. 	<ol style="list-style-type: none"> 1. (autoimmune disease)* 2. Infections . 3. Hemorrhage, 4. Tumors. 5. Use of drugs (anticoagulants). <p>*main one</p>

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.

Quiz

1- Atrophy of the thyroid is a feature of which of the following diseases?

- a) Hashimoto's disease b) Addison's disease c) Primary myxoedema d) Graves' disease

2- in which disease the auto-antibodies interferes with iodine uptake ?

- a) Hashimoto's disease b) Addison's disease c) Primary myxoedema d) Graves' disease

3- Hashimoto's Thyroiditis is an example of which type of hypersensitivity ?

- a) I b) II c) III d) IV

4- the protective role in Chronic Lymphocytic Thyroiditis is :

- a) DR4 b) DR3 c) DR 13 d) DR7

5- long-acting thyroid-stimulating (LATS) antibodies. Are present in which of the following ?

- a) Hashimoto's disease b) Addison's disease c) Primary myxoedema d) Graves' disease

6- in Insulin-dependent diabetes mellitus Autoreactive T-cells invade the pancreatic islets and destroy which pancreatic cells ?

- a) alpha b) beta c) gamma

7 – in Addison's disease the major autoantigen is :

- a) thyroid peroxidase b) TSH receptors c) 21-hydroxylase (21OH) d) beta cells

1-C
2-A
3-D
4-C
5-D
6-B
7-C



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