



**MEDICINE**  
KING SAUD UNIVERSITY

## Musculoskeletal Block

### Lecture One

## Mechanisms of Autoimmunity

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# IMMUNOLOGY

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

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### Objectives:

- Autoimmunity results from activation of immune response against self antigens.
- To learn how immunological tolerance (central and peripheral) is induced against self antigens for maintaining normal health.
- To gain understanding of various factors contributing to the breakdown of immunological tolerance and development of autoimmunity.
- Gender predilection in autoimmunity is a well known phenomenon and is briefly described.

- **Important.**
- Extra notes.
- **Females notes**
- **Males notes.**

Revised by

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# Autoimmunity

**Definition:** A condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue.

- Immune system has evolved to discriminate between:
  - **Self Ag** (originates within the body e.g. Blood group Ag, MHC Ag)
  - **Non-Self Ag** (Originate outside the body e.g. Bacteria).
- Mediated by auto-reactive T cells and auto-reactive B cells (auto-antibodies).

**Immunological tolerance:** is the failure to mount an immune response to an antigen. It can be:

Natural or "self" tolerance. it is the failure to attack the body's own proteins and other antigens.

Tolerance is a good thing , **when your tolerance fails you will have an autoimmune disease.**

**Tolerance to self is acquired by:**

**1- Deletion (clonal deletion):**

Deactivation of auto-reactive T cells and auto-reactive B cells by killing them. (Apoptosis)

**2- Functional inactivation (clonal anergy):**

Functional inactivation of developing lymphocytes that possess antigenic receptors with high affinity for self-antigens.

Anergy: State during which a cell can not become activated by exposure to its Ag. T & B cells become anergic when exposed to their Ag without costimulatory signal. \* To

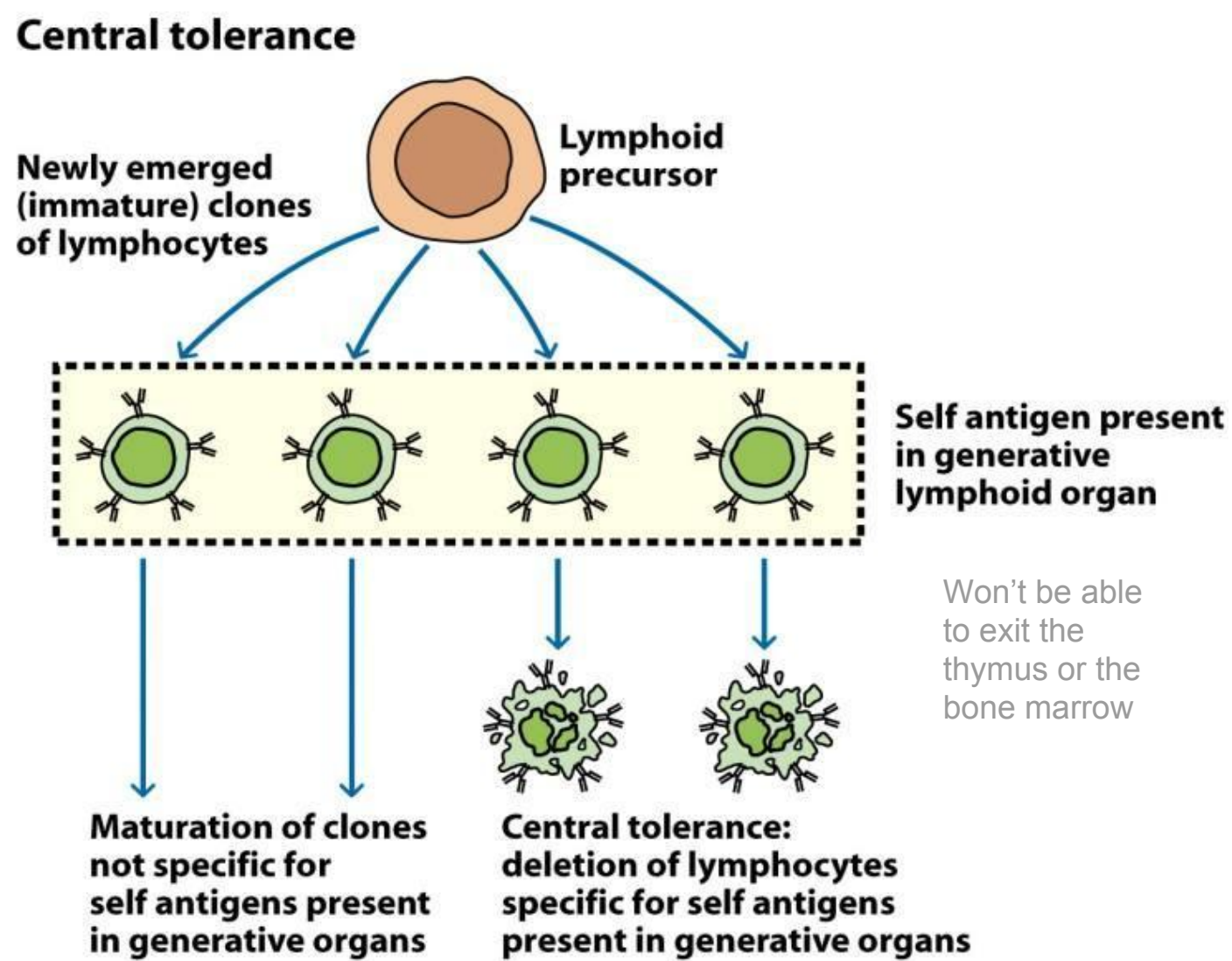
remember: Anergy = Lack of Energy.

# Self-Tolerance

**1- Central Tolerance:** established by deletion of lymphocytes in Primary lymphoid organs  
(Thymus & Bone marrow).

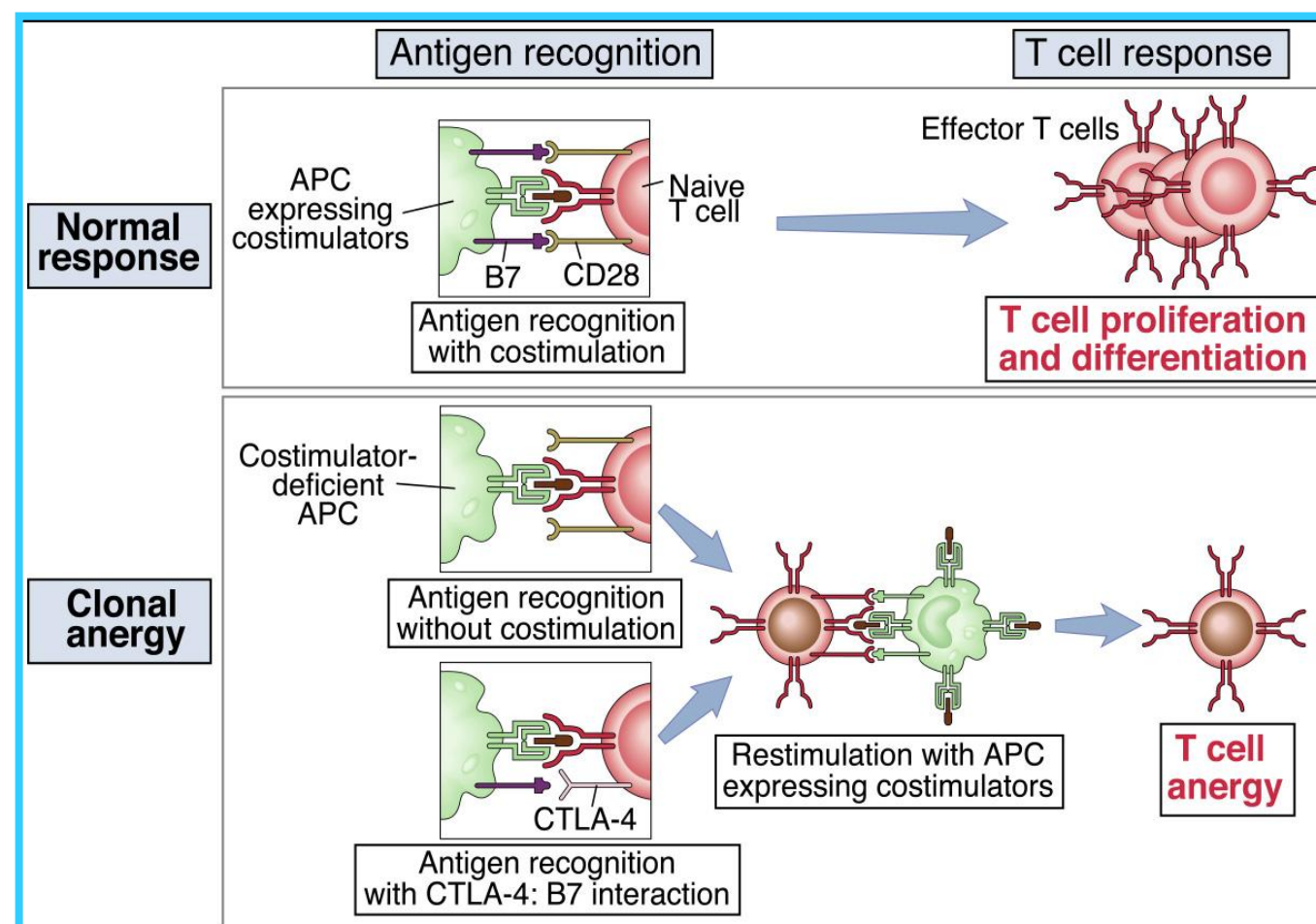
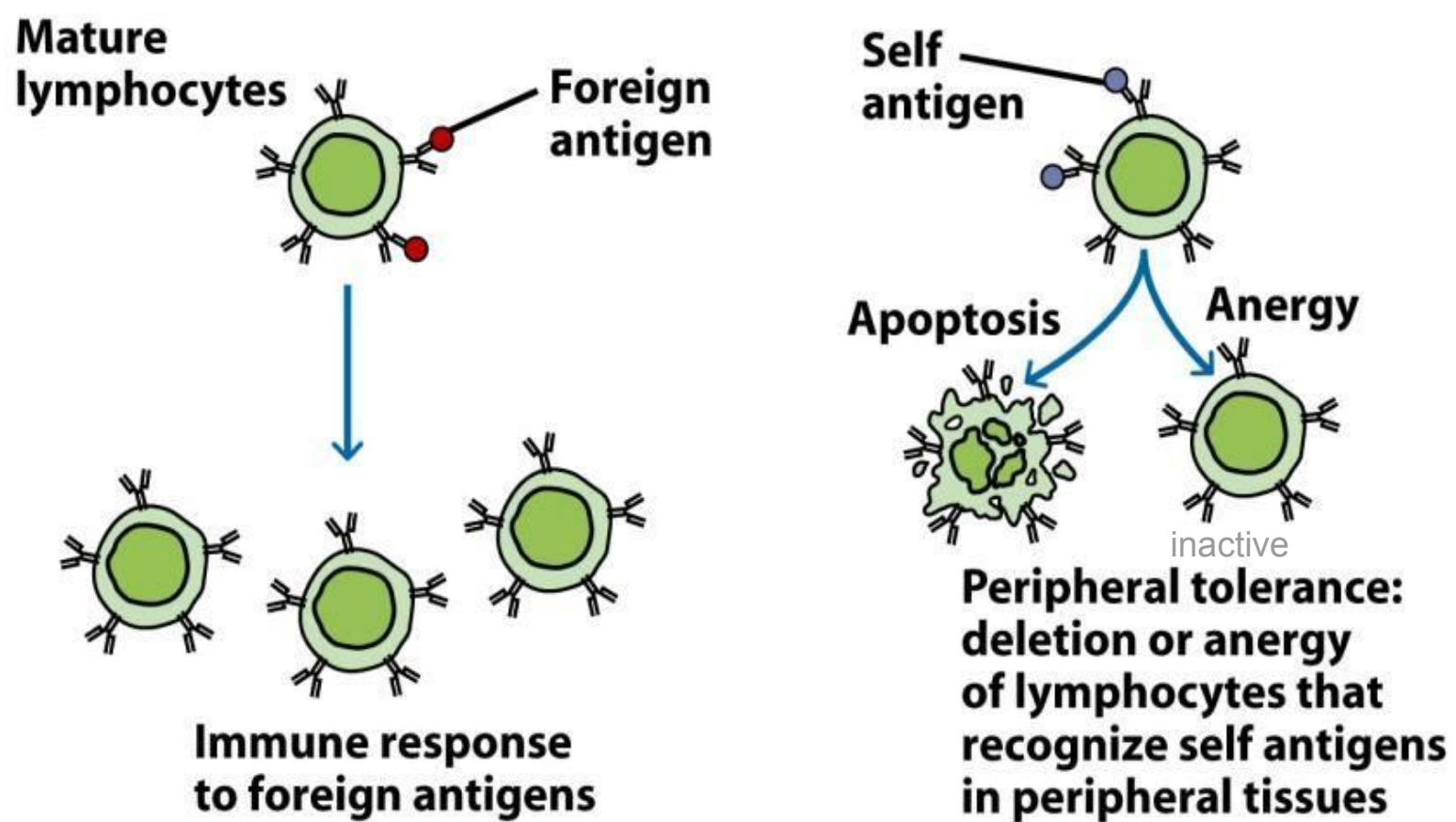
**2- Peripheral tolerance:** involves deletion, rendering anergic or actively suppressing escaped lymphocytes in Secondary lymphoid tissues (Peripheral tissues).

## 1- Central Tolerance:



## 2- Peripheral tolerance:

### Peripheral tolerance



## Failure of Immune Tolerance (Development of Autoimmunity):

### Induction of Autoimmunity “ Proposed Mechanisms ”:

- 1- Sequestered antigens.
- 2- Molecular mimicry.
- 3- Inappropriate class II MHC expression on non-antigen presenting cells.
- 4- Polyclonal B cell activation.

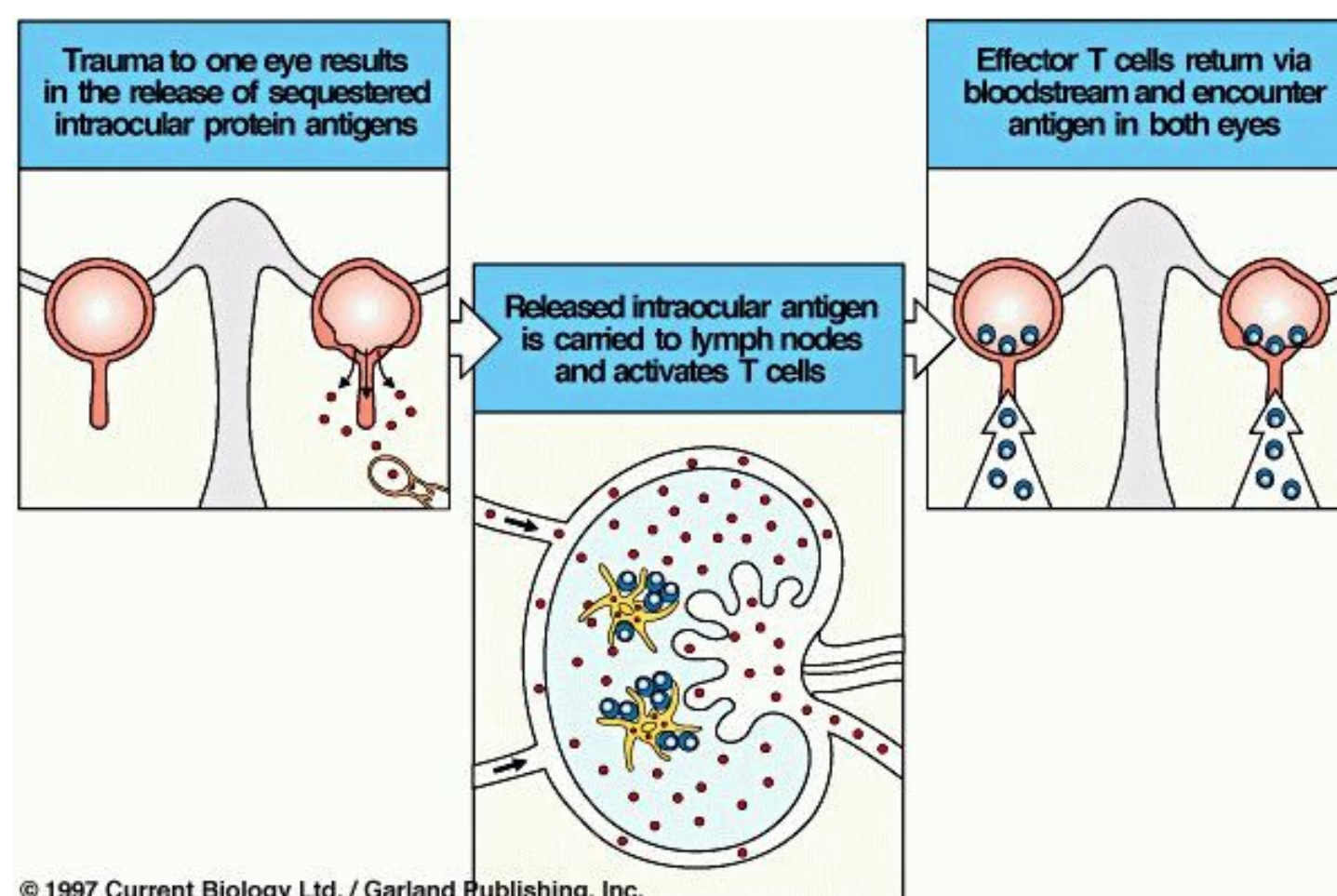
#### (1) Sequestered antigens

Some self-antigens are sequestered (hidden) in specialized tissues. They are isolated from the circulation of the blood and lymph. Therefore they are not in contact with the cells of the immune system (T-cells, B-cells) during a healthy state. But when body tissues are damaged by trauma, the hidden antigens are suddenly exposed to the immune system which results in their activation.

#### Examples of Sequestered Antigens:

- 1- **Myelin basic protein (MBP)** hidden by myelin sheath, when it is exposed to T-cells or B- cells it can cause multiple sclerosis (**MS**).
- 2- **Sperm-associated antigens** Anti-sperm antibodies are known to develop when sperm antigen exposed to B-cells after vasectomy (A vasectomy is done to prevent fertility in males).
- 3- **Lens and corneal** proteins of the eye following infection or trauma.
- 4- **Heart muscle antigens** following myocardial infarction.

#### Sympathetic ophthalmia: (التهاب العينين)



## (2) Molecular Mimicry

### (Cross-reacting Antigens)

It is basically the **similarity** or identity **between** a foreign antigen from either a **bacterium or a virus**, and a **self antigen**.

This phenomenon (molecular mimicry) can be the **initiating step** in a variety of autoimmune diseases in which this confusion is enough to auto-activate B and T cells to fight off the body's own antigens.

This phenomenon, known **as molecular mimicry**, occurs in a wide variety of organisms.

### Examples of Molecular Mimicry:

MOLECULAR MIMICRY BETWEEN PROTEINS OF INFECTIOUS ORGANISMS AND HUMAN HOST PROTEINS		
Protein <sup>a</sup>	Residue <sup>b</sup>	Sequence <sup>c</sup>
Human cytomegalovirus IE2	79	P D P L G R P D E D
HLA-DR molecule	60	V T E L G R P D A E
Poliovirus VP2	70	S T T K E S R G T T
Acetylcholine receptor	176	T V I K E S R G T K
Papilloma virus E2	76	S L H L E S L K D S
Insulin receptor	66	V Y G L E S L K D L
Rabies virus glycoprotein	147	T K E S L V I I S
Insulin receptor	764	N K E S L V I S E
<i>Klebsiella pneumoniae</i> nitrogenase	186	S R Q T D R E D E
HLA-B27 molecule	70	K A Q T D R E D L
Adenovirus 12 E1B	384	L R R G M F R P S Q C N
$\alpha$ -Gliadin	206	L G Q G S F R P S Q Q N
Human immunodeficiency virus p24	160	G V E T T T P S
Human IgG constant region	466	G V E T T T P S
Measles virus P3	13	L E C I R A L K
Corticotropin	18	L E C I R A C K
Measles virus P3	31	E I S D N L G Q E
Myelin basic protein	61	E I S F K L G Q E

\*الدكتور يقول  
افهموا مصطلح  
molecular  
mimicry  
فقط

## (3) Inappropriate Expression of Class II MHC Molecules

- Class II MHC ordinarily expressed on **antigen presenting cells**, such as macrophages, dendritic cells and B cells.
- Abnormal expression of MHC determinants allows the recognition of these auto-antigens by self-reactive T cells.
- This may occur due to the local **production of IFN- $\gamma$** , which is known to increase class II MHC expression on a variety of cells.
- The inducer of IFN- $\gamma$  under these circumstances could be a **viral infection**

## Type I Diabetes:

Pancreatic  $\beta$  cells express abnormally high levels of MHC I and MHC II

The theory of diabetes type I starts viral infection where there is abnormal expression of MHC II making it wrongly recognize B cells of pancreas which has insulin receptor that is similar to a viral antigen and killing B cells making pancreas unable to produce insulin.

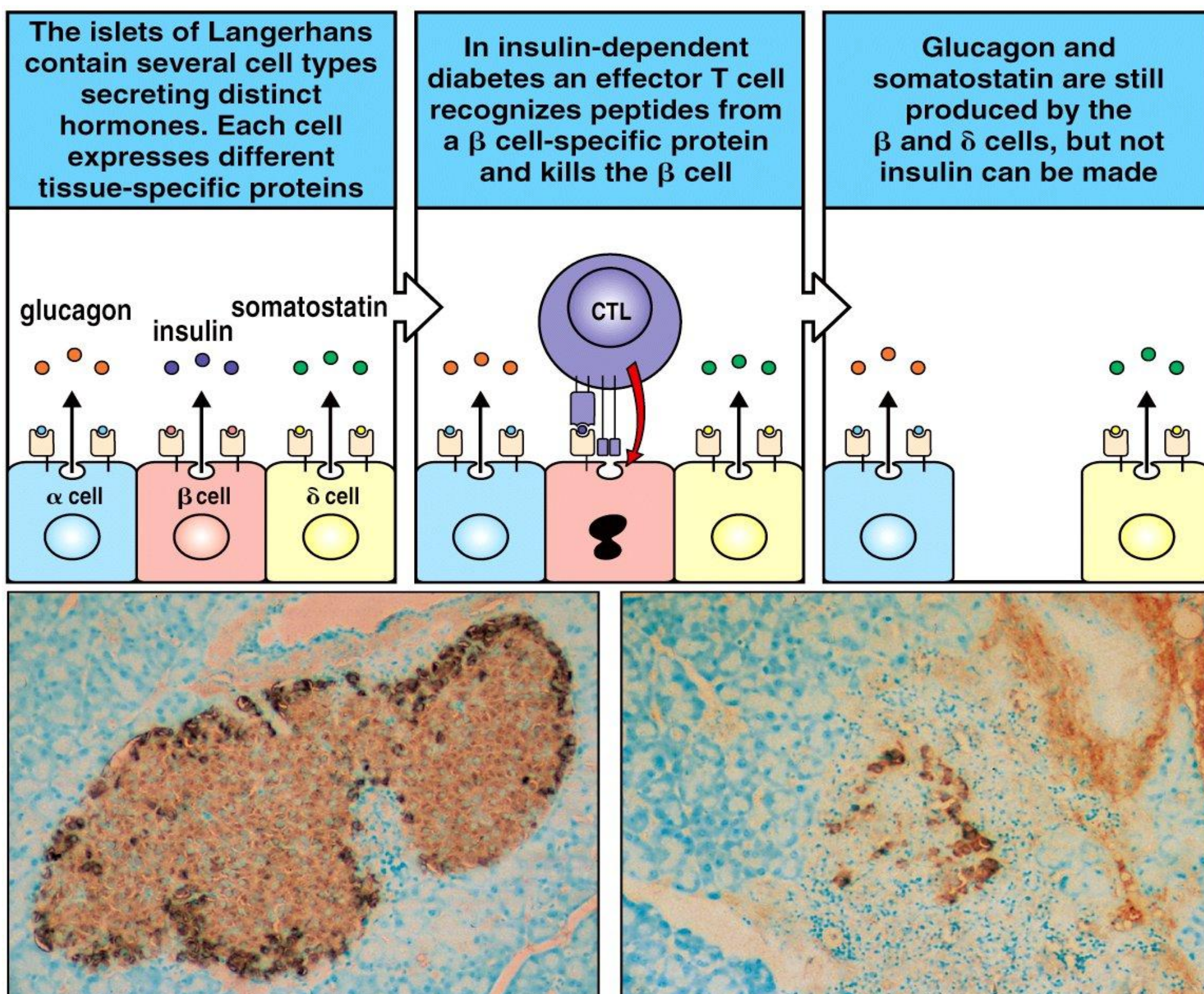
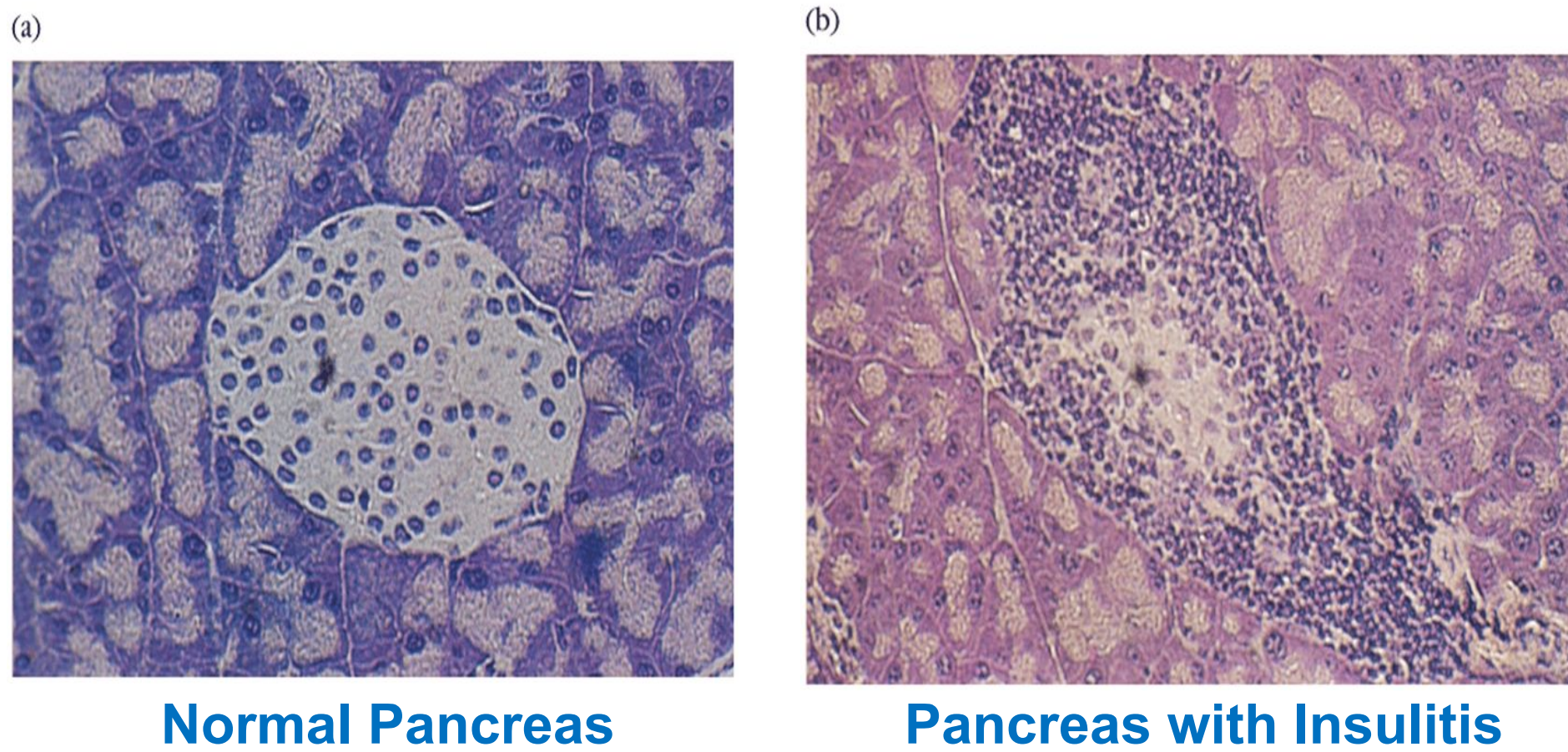


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

## (4) Polyclonal B cell Activation

**Viruses** and **bacteria** can induce nonspecific polyclonal **B cell** activation, including:

- Certain gram negative bacteria
- Herpes simplex virus.
- Cytomegalovirus
- Epstein Barr Virus
- Human immunodeficiency virus (HIV)

These viruses induce the **proliferation of numerous clones of B cells** to secrete IgM in the absence of a requirement for CD4 T cell help.

Polyclonal activation leads to the **activation of self-reactive B cells** and autoantibody production.

Patients with **infectious mononucleosis** caused by (EBV) and AIDS (HIV) have a variety of auto-antibodies.

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### Hormonal factors:

- About 90% of autoimmune diseases occur in women – cause not known
- In animal models estrogen can induce B cells to enhance formation of anti-DNA antibodies
- SLE either appears or exacerbates during pregnancy

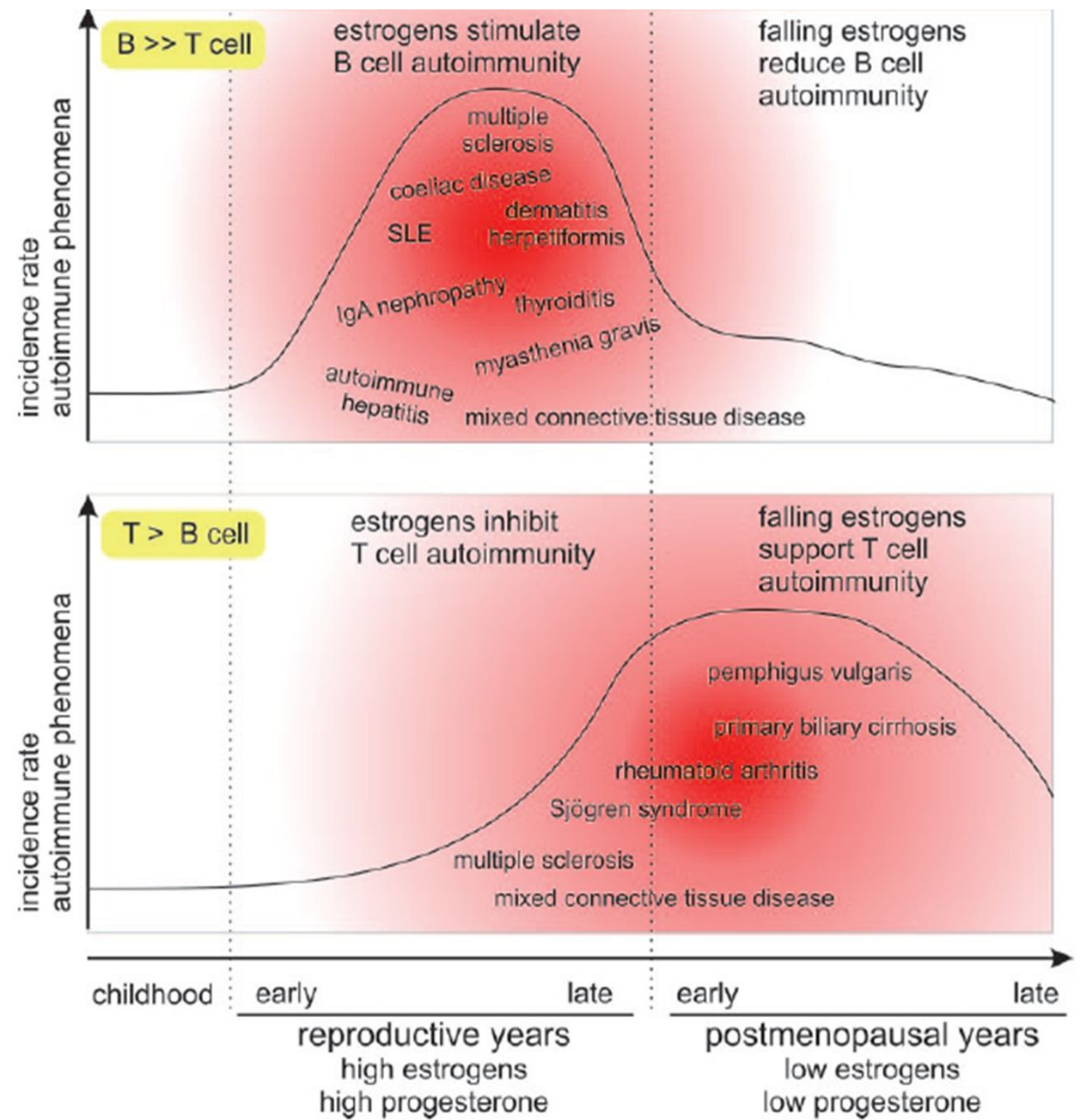
## Role of estrogen in autoimmune diseases:

- Estrogen stimulates B cells autoimmunity and inhibit T cells autoimmunity.

- Falling estrogens reduce B cell autoimmunity and support T cell autoimmunity.

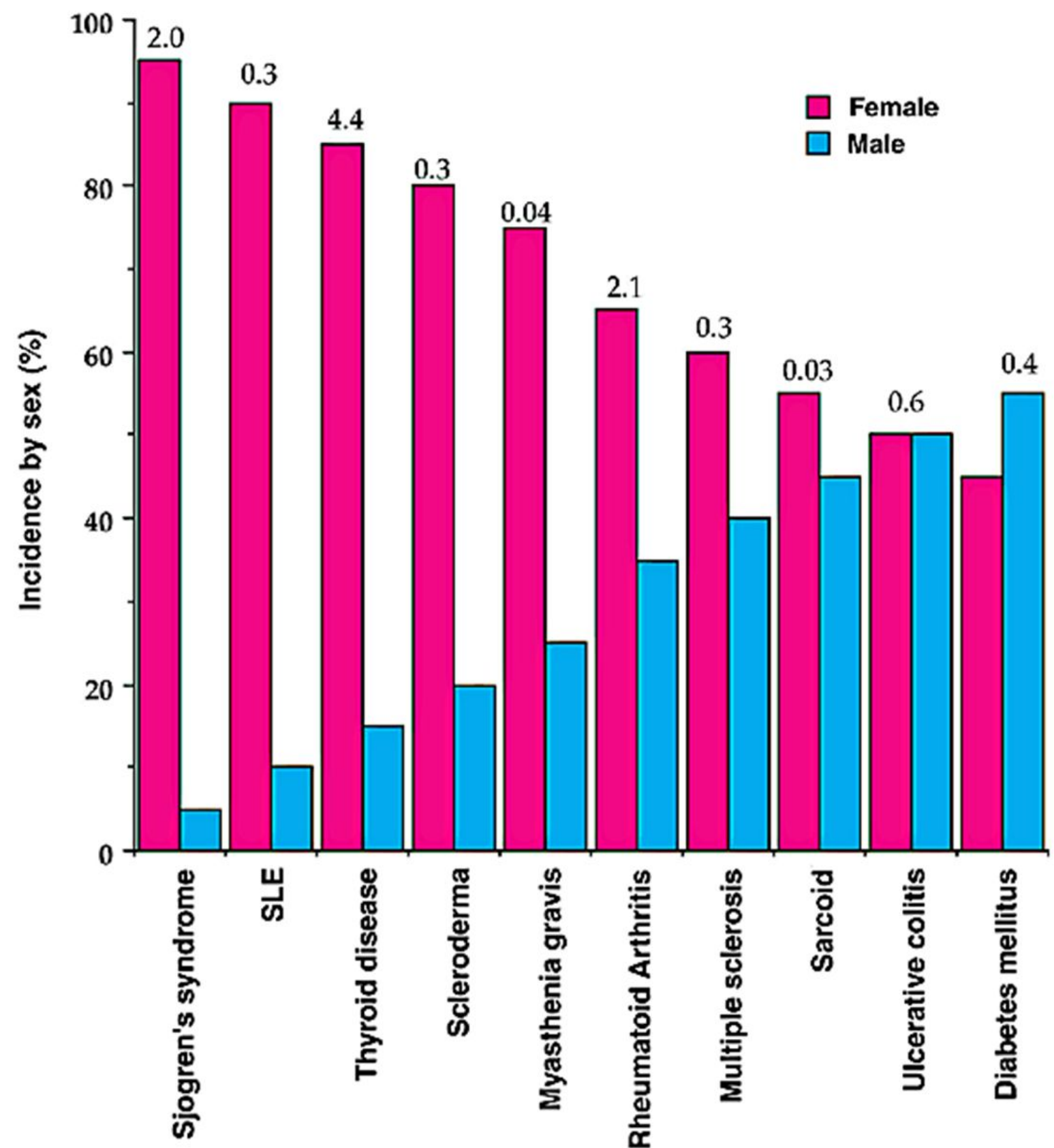
- Example of autoimmunity disease when B > T cells: SLE, MS, coeliac disease coeliac disease:

- Example of autoimmunity disease when T > B cells: diabetes, MS (multiple sclerosis)



## Statistics of autoimmune diseases by gender:

\* All autoimmune diseases occur in women more than men except diabetes mellitus (DM).





## Drug Induced Lupus Erythematosus:

Lupus erythematosus like syndrome develops in patients receiving a variety of drugs such as:

- Hydralazine (used for hypertension)
  - Procainamide (Used for cardiac arrhythmia)
  - Isoniazid (Antibiotic for tuberculosis)
  - Penicillin
  - Penicillamine
- Many are associated with the development of anti-nuclear antibodies (ANAs)
  - Renal and CNS involvement is uncommon (they're involved in SLE and that's what makes it dangerous)
  - **Anti-histone** antibodies are frequently present (histones are proteins found in eukaryotic cell nuclei that package and order the DNA into structural units called nucleosomes. They are the chief protein components of chromatin, acting as spools around which DNA winds.)

## Take home message

1. Normal healthy state is maintained by immunological tolerance against self antigens at central and peripheral levels.
2. Autoimmune diseases result from the breakdown of immunological tolerance to self antigens.
3. Certain autoimmune diseases exhibit strong association with female gender.

## Useful videos:

- Self vs nonself :  
[https://www.youtube.com/watch?v=afM6\\_VFaIss&index=2&list=LLhph2500OUDsKDIf2o-pH0A](https://www.youtube.com/watch?v=afM6_VFaIss&index=2&list=LLhph2500OUDsKDIf2o-pH0A)
- Tolerance :  
<https://www.youtube.com/watch?v=2liy8n4pUpE&index=1&list=LLhph2500OUDsKDIf2o-pH0A>

## MCQs:

**1- May be the initiating step in variety of autoimmune diseases:**

- a) Sequestered antigens.
- b) Molecular mimicry
- c) Inappropriate class II MHC expression
- d) Polyclonal B cell activation

**2- Some self-antigens are hidden in specialized tissues. Definition of:**

- a) Sequestered antigens
- b) Molecular mimicry
- c) Inappropriate class II MHC expression
- d) Polyclonal B cell activation

**3- Increase class II MHC expression on a variety of cells:**

- a) INF- alpha
- b) INF- beta
- c) INF- gamma

**4- In insulin-dependent diabetes an effector T cell recognizes peptides from:**

- a) Alpha cells
- b) beta cells
- c) gamma cells

**5- Estrogens stimulate T cells autoimmunity in reproductive years:**

- a) True
- b) False

1-B  
2-A  
3-C  
4-B  
5-B



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