

# **Mechanisms of Autoimmunity**

**Immunopathology Unit  
Department of Pathology  
College of Medicine**

# 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.

# Autoimmunity

A condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue

# Autoimmunity

Immune system has evolved to discriminate  
between

## Self and Non-self

Mediated by auto-reactive T cells and auto-reactive B  
cells (auto-antibodies)

**Tolerance to self is acquired by:**

**A) Deletion** (clonal deletion)

OR

**B) Functional inactivation** (clonal anergy)  
of developing lymphocytes that possess  
antigenic receptors with high affinity for self-  
antigens.

# **Self-Tolerance**

```
graph TD; A[Self-Tolerance] --> B[Central Tolerance (Thymus & Bone marrow)]; A --> C[Peripheral tolerance (Peripheral tissues)];
```

**Central Tolerance**  
**(Thymus & Bone marrow)**

**Peripheral tolerance**  
**(Peripheral tissues)**

# Central tolerance

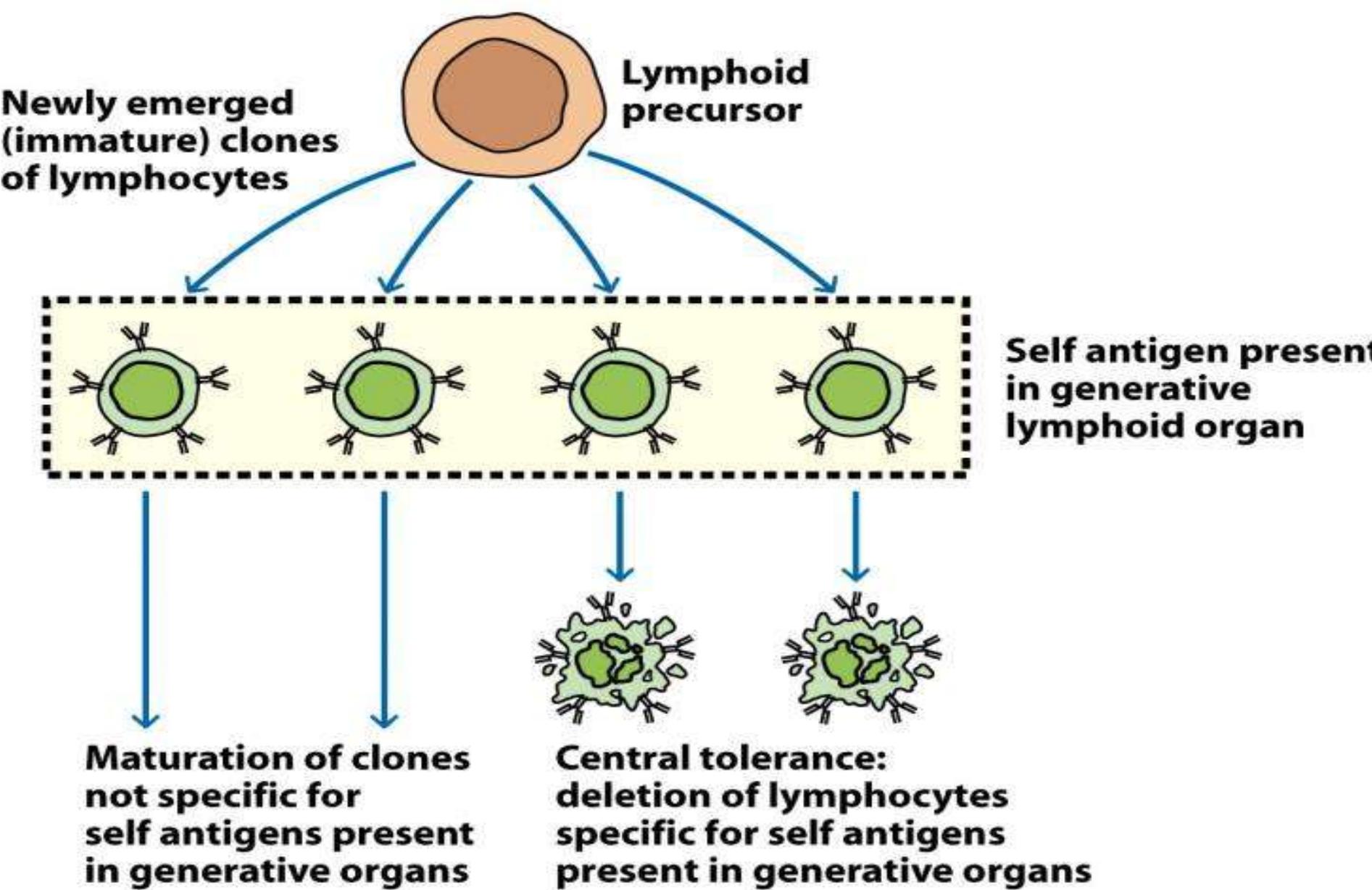
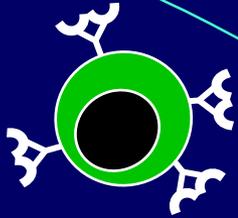
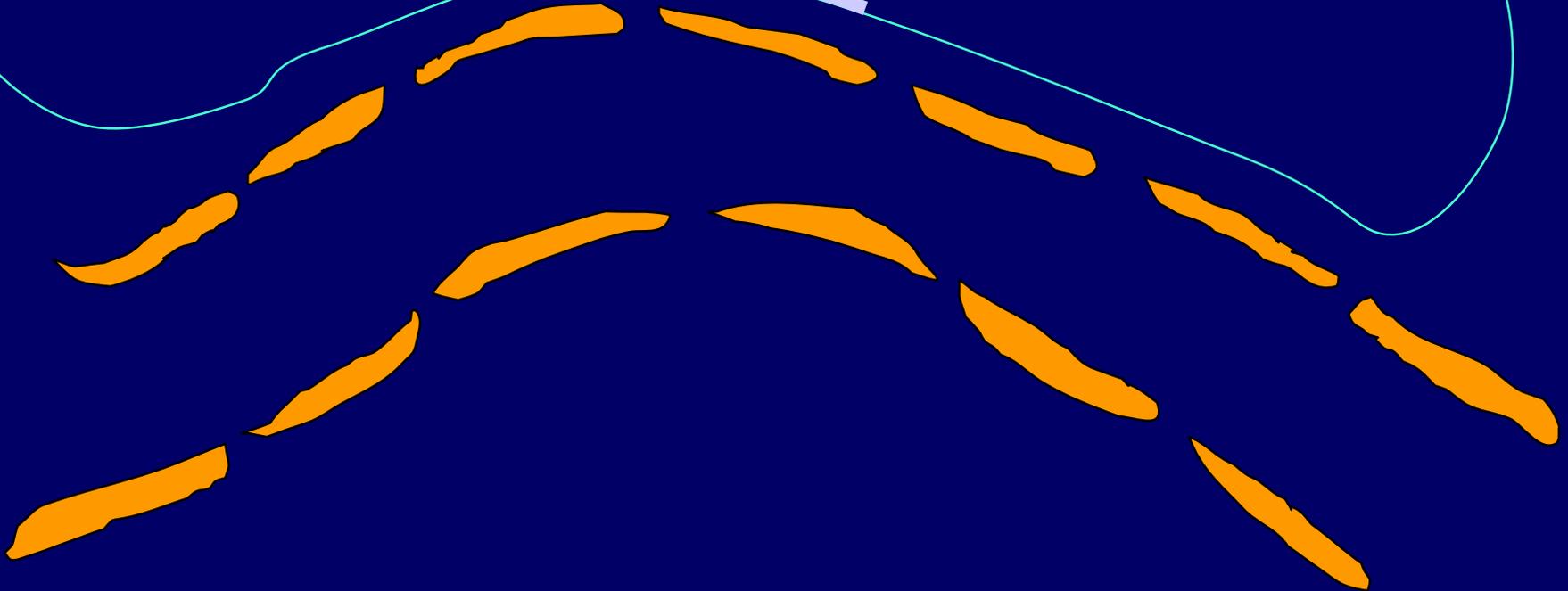


Figure 16-1a  
Kuby IMMUNOLOGY, Sixth Edition  
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Educated T-cell  
Autoreactive cell



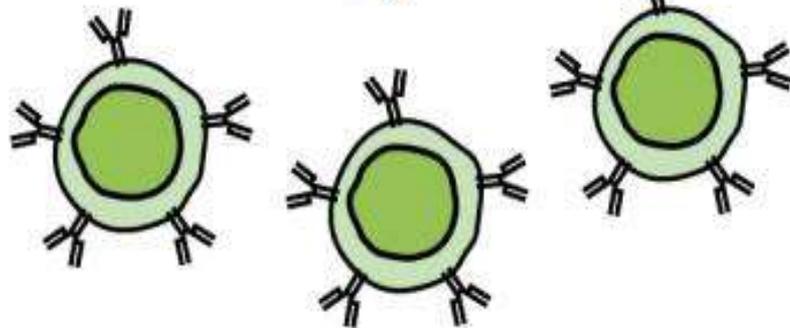
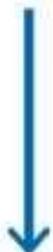
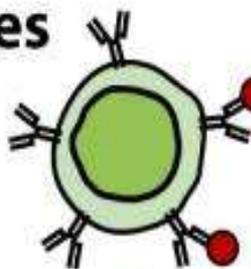
# Central Tolerance



# Peripheral tolerance

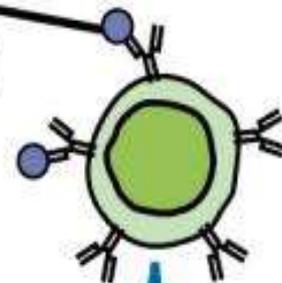
**Mature lymphocytes**

**Foreign antigen**



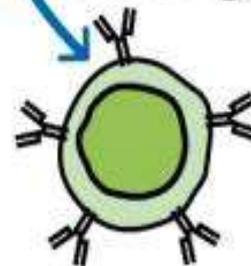
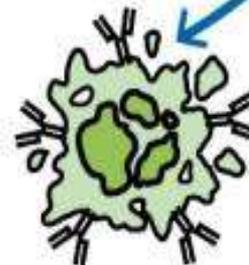
**Immune response to foreign antigens**

**Self antigen**



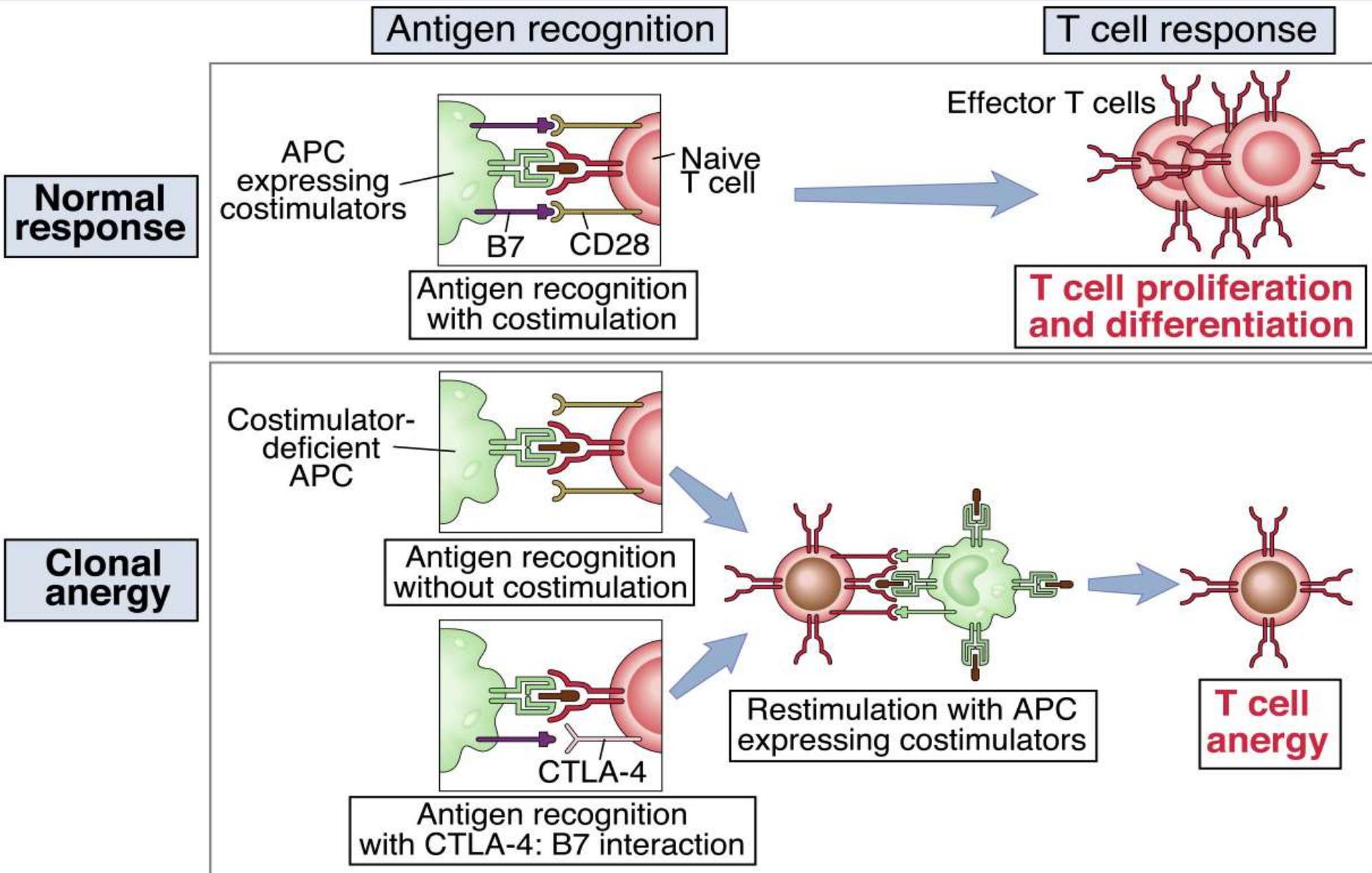
**Apoptosis**

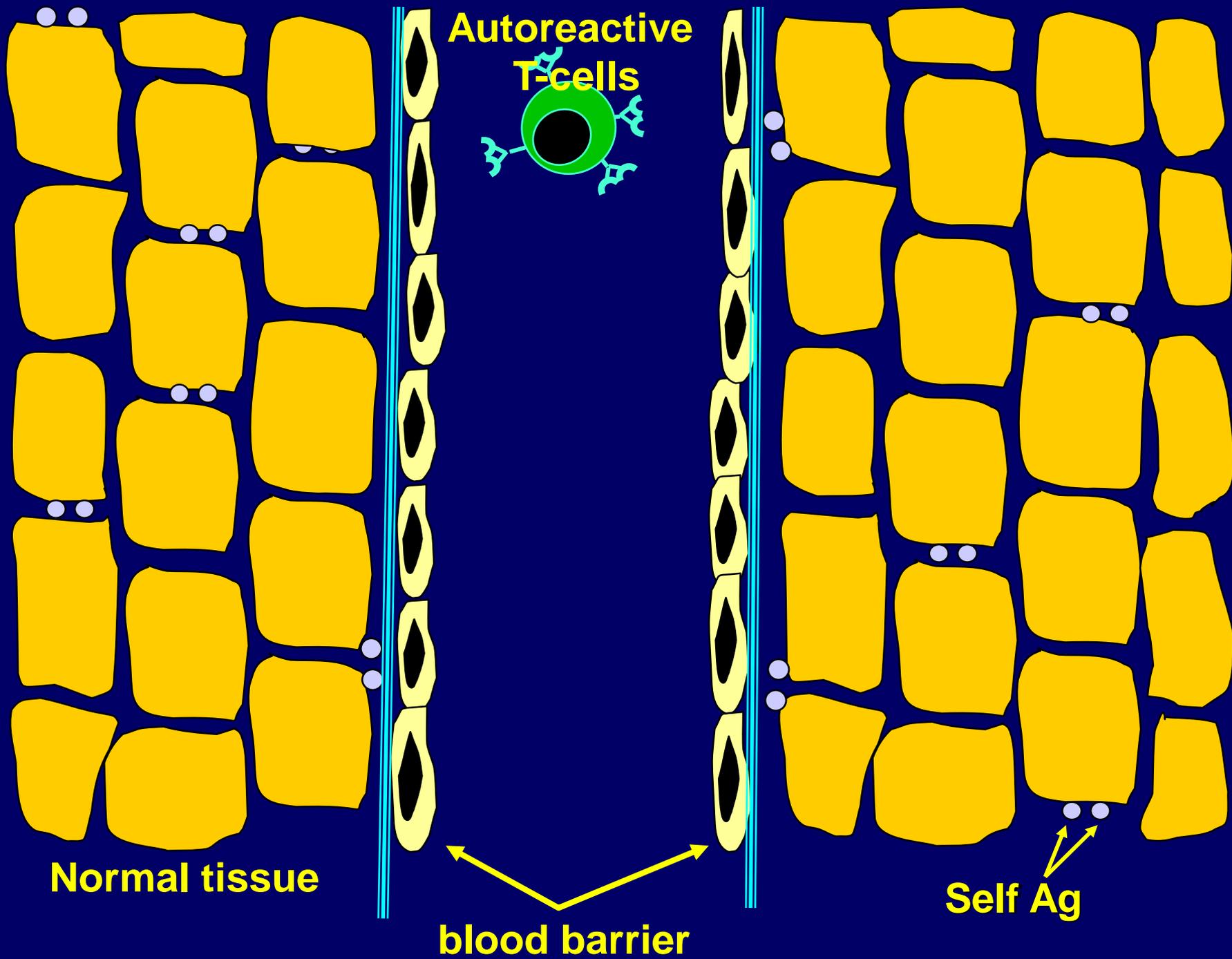
**Anergy**



**Peripheral tolerance: deletion or anergy of lymphocytes that recognize self antigens in peripheral tissues**

# Peripheral Tolerance of T Lymphocytes





**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 none-antigen presenting cells
4. Polyclonal B cell activation

# 1. Sequestered antigens

- Some self-antigens are sequestered (hidden) in specialized tissues.
- These are **not seen** by the developing immune system – will not induce self-tolerance.
- Exposure of T cells to these normally sequestered/tissue-specific self-antigens in the periphery results in their activation.

# Examples of **Sequestered** Antigens

**Myelin basic protein (MBP)**, associated with MS

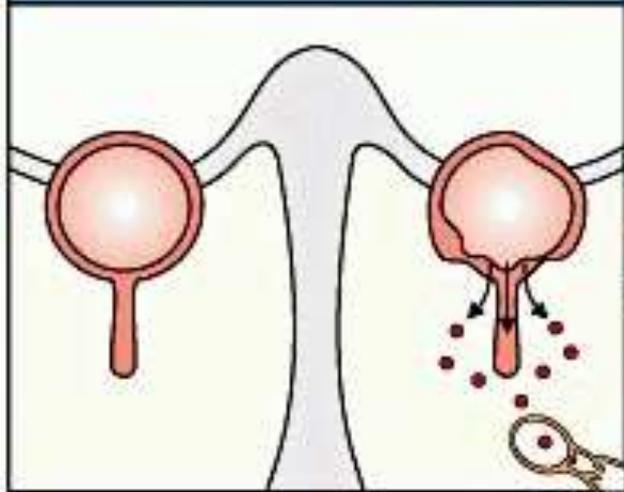
**Sperm-associated antigens** in some individuals following vasectomy

**Lens and corneal** proteins of the eye following infection or trauma

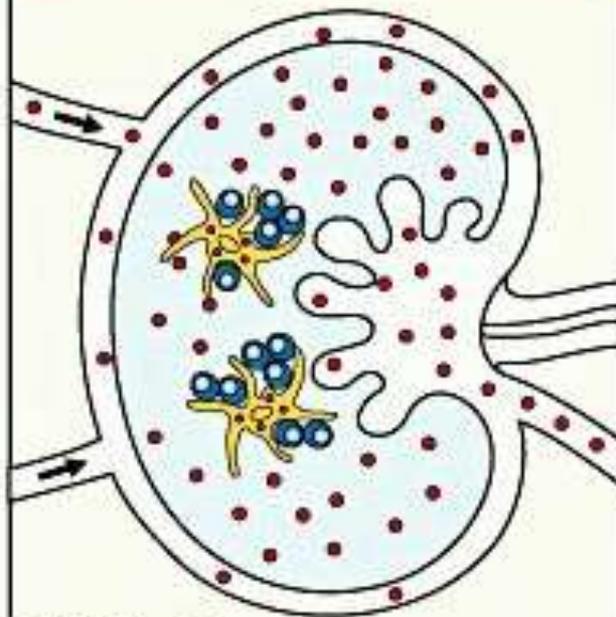
**Heart muscle antigens** following myocardial infarction

# Sympathetic ophthalmia

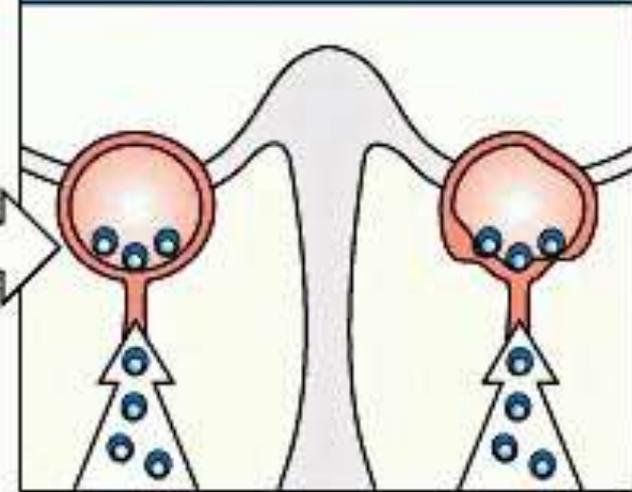
Trauma to one eye results in the release of sequestered intraocular protein antigens



Released intraocular antigen is carried to lymph nodes and activates T cells



Effector T cells return via bloodstream and encounter antigen in both eyes



## 2. Molecular Mimicry (Cross-reacting Antigens)

- Viruses and bacteria possess antigenic determinants that are very similar, or even identical, to normal host cell components.
- This phenomenon, known as *molecular mimicry*, occurs in a wide variety of organisms.
- Molecular mimicry may be the **initiating step** in a variety of autoimmune diseases.

# Examples of Molecular Mimicry

## MOLECULAR MIMICRY BETWEEN PROTEINS OF INFECTIOUS ORGANISMS AND HUMAN HOST PROTEINS

Protein*	Residue <sup>†</sup>	Sequence <sup>‡</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

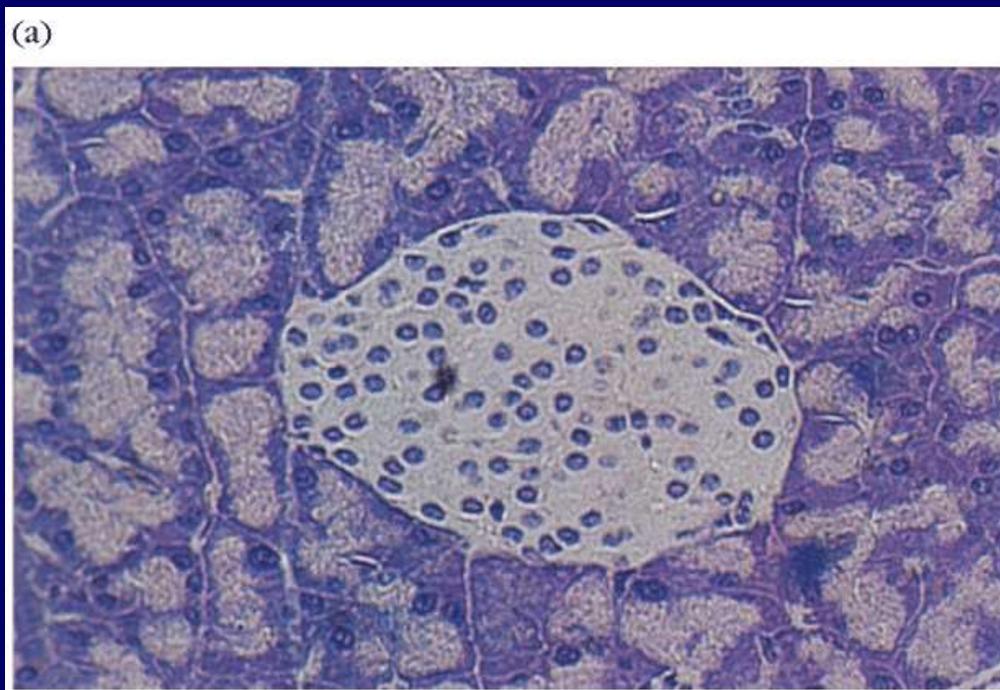
### 3. Inappropriate Expression of Class II MHC Molecules

- 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.

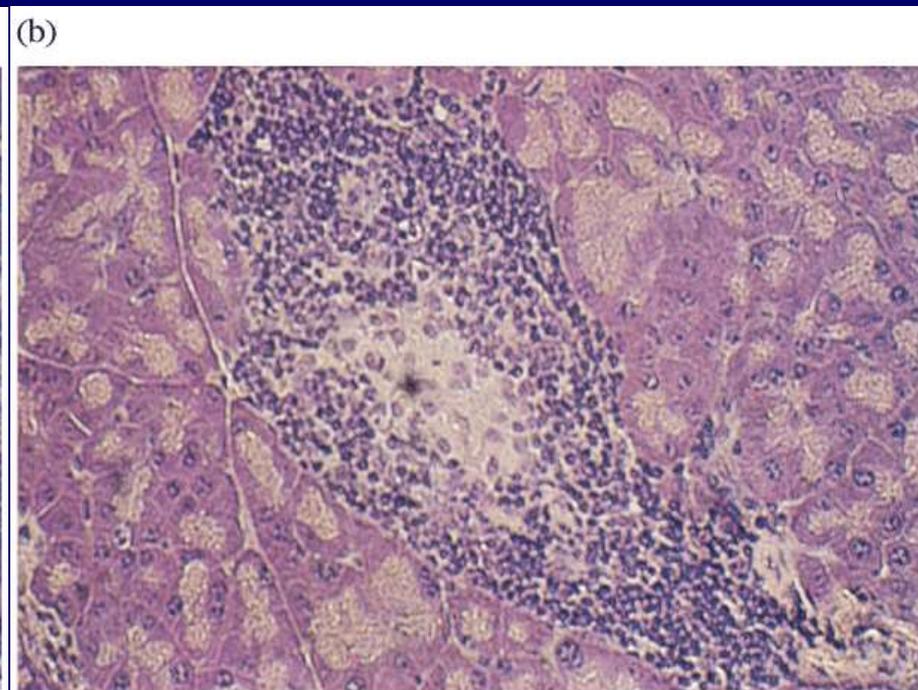
# Inappropriate Expression of Class II MHC Molecules

- 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 (?)



**Normal Pancreas**



**Pancreas with Insulinitis**

The islets of Langerhans contain several cell types secreting distinct hormones. Each cell expresses different tissue-specific proteins

In insulin-dependent diabetes an effector T cell recognizes peptides from a  $\beta$  cell-specific protein and kills the  $\beta$  cell

Glucagon and somatostatin are still produced by the  $\alpha$  and  $\delta$  cells, but not insulin can be made

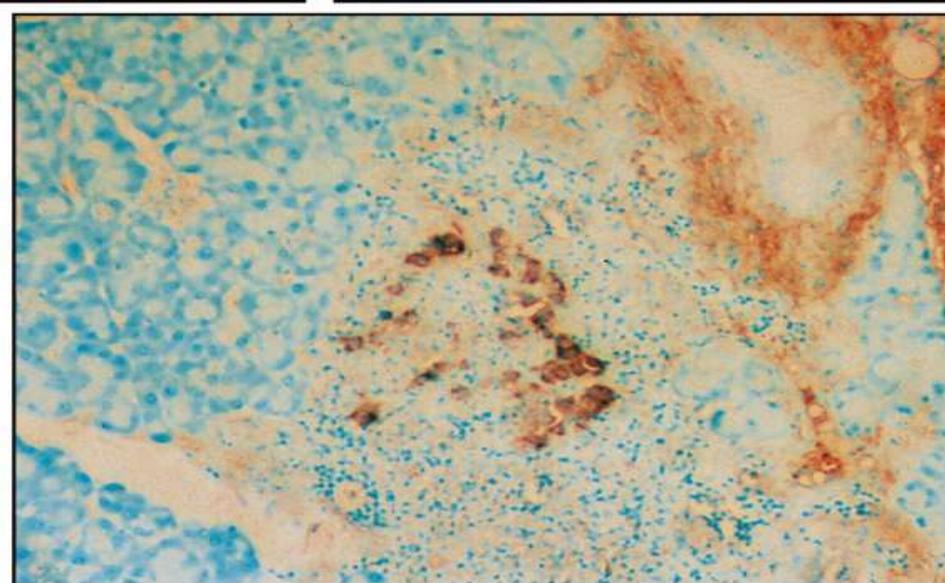
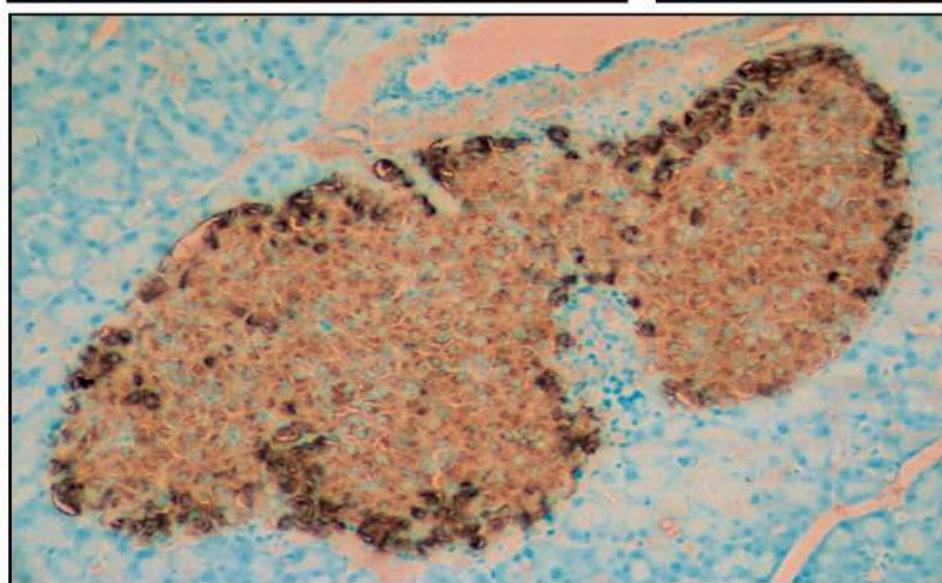
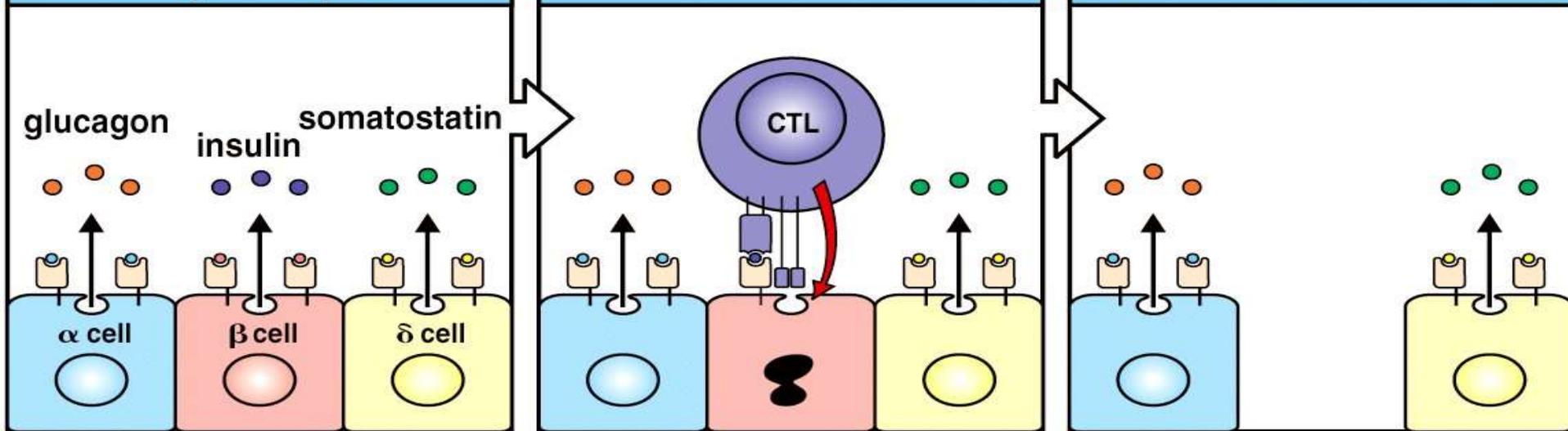


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

## 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)

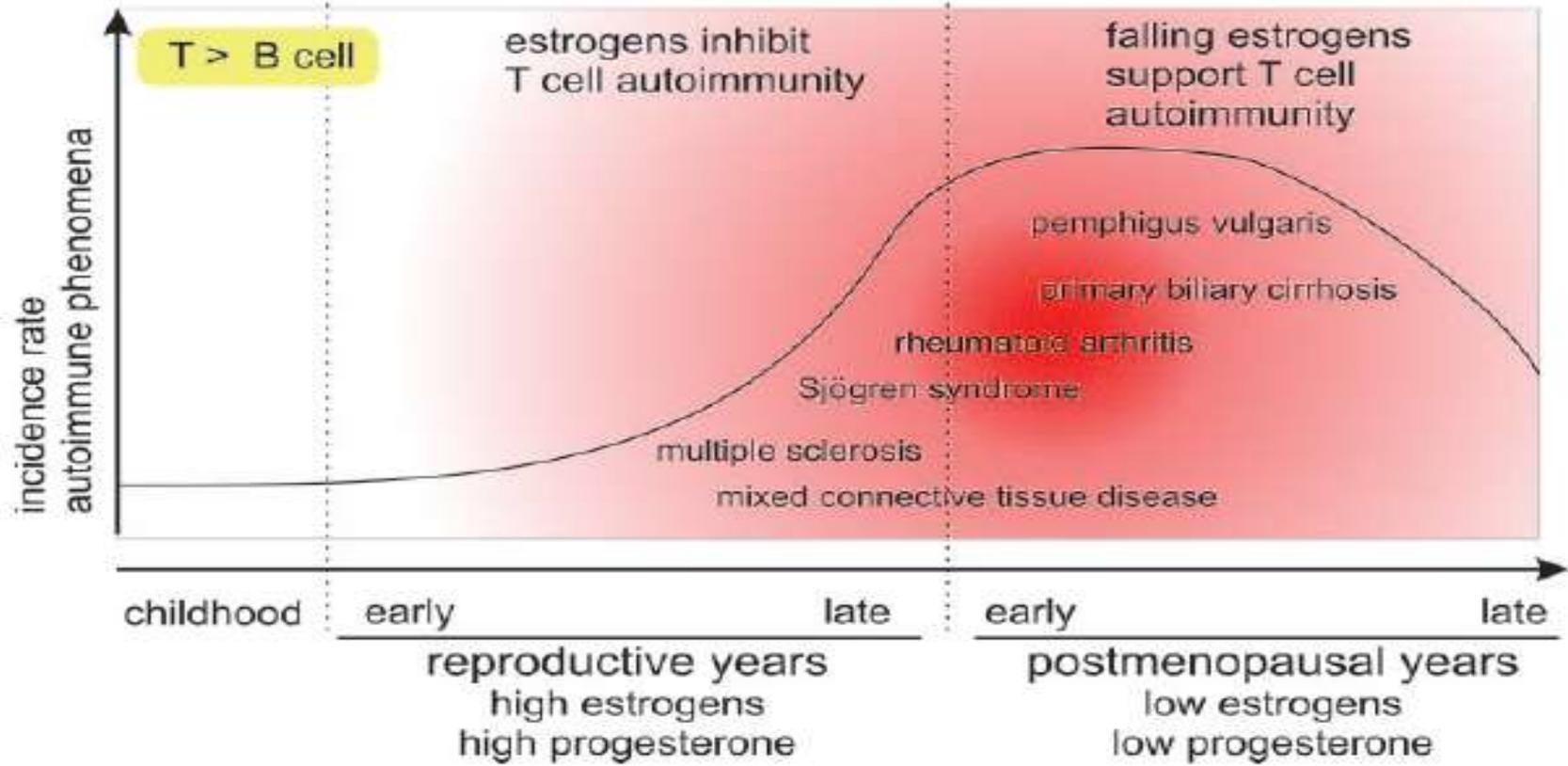
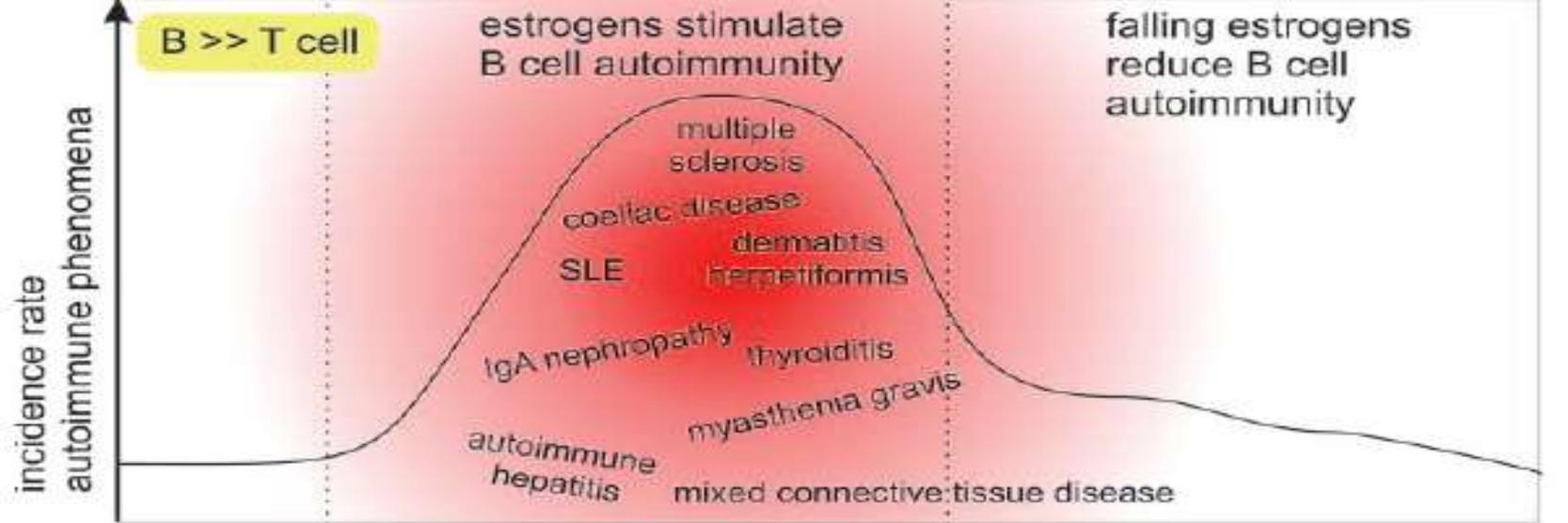
These viruses induce the **proliferation of numerous clones of B cells** to secrete IgM in the absence of a requirement for CD4 T cell help.

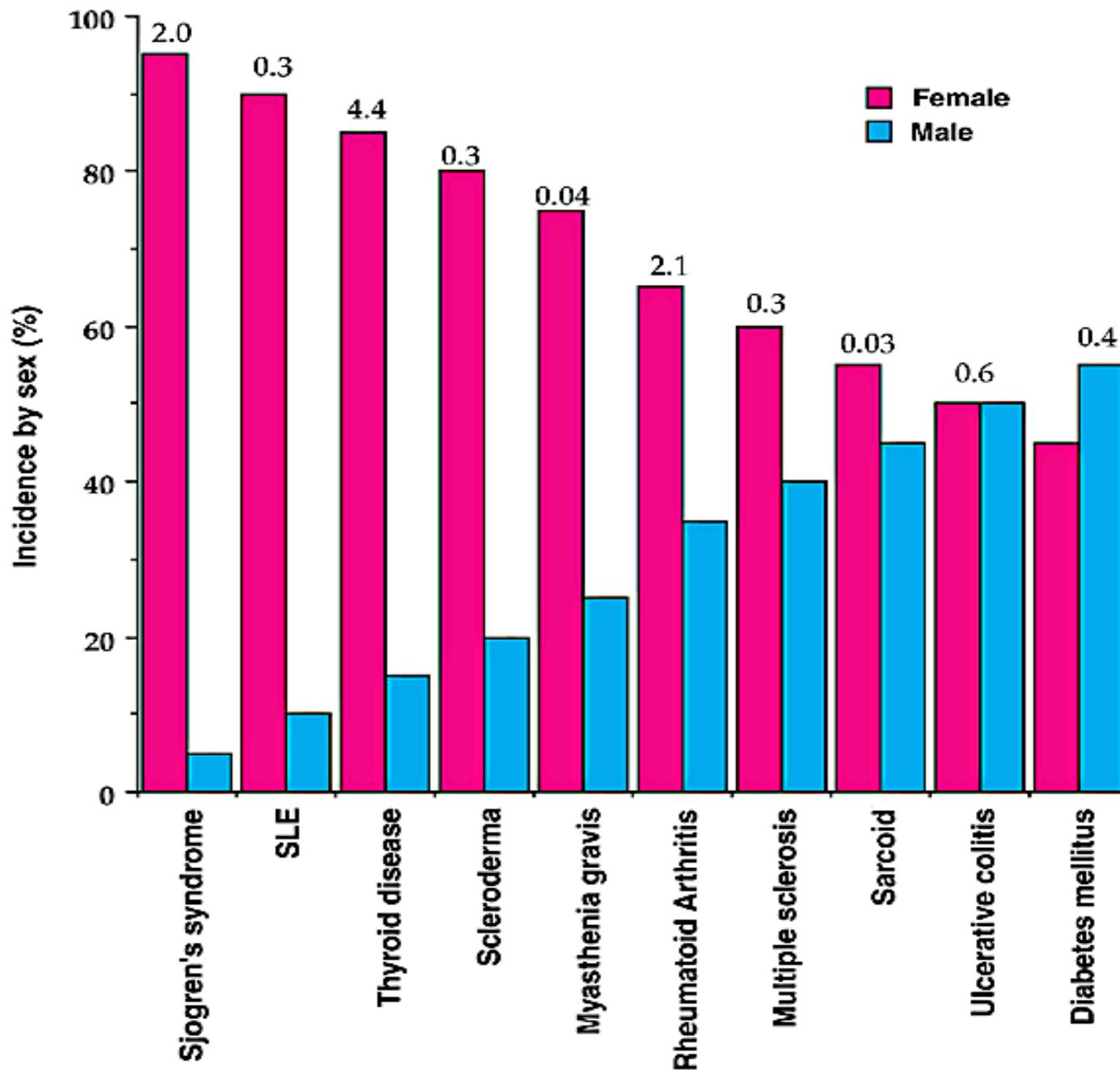
Polyclonal activation leads to the **activation of self-reactive B cells** and autoantibody production.

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

## • **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





# Drug Induced Lupus Erythematosus

- Lupus erythematosus like syndrome develops in patients receiving a variety of drugs such as
  - Hydralazine (used for hypertension),
  - Procainamide,
  - Isoniazid
  - Penicillin
- Many are associated with the development of anti-nuclear antibodies (**ANAs**)
- Renal and CNS involvement is uncommon
- **Anti-histone** antibodies are frequently present

# Take home message

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

**Thank you**