Mechanisms of Autoimmunity

Immunology Unit
Department of Pathology
College of Medicine

Reference

Kuby Immunology 7th Edition 2013

Chapter 16 Pages 517-520 & 531-534

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

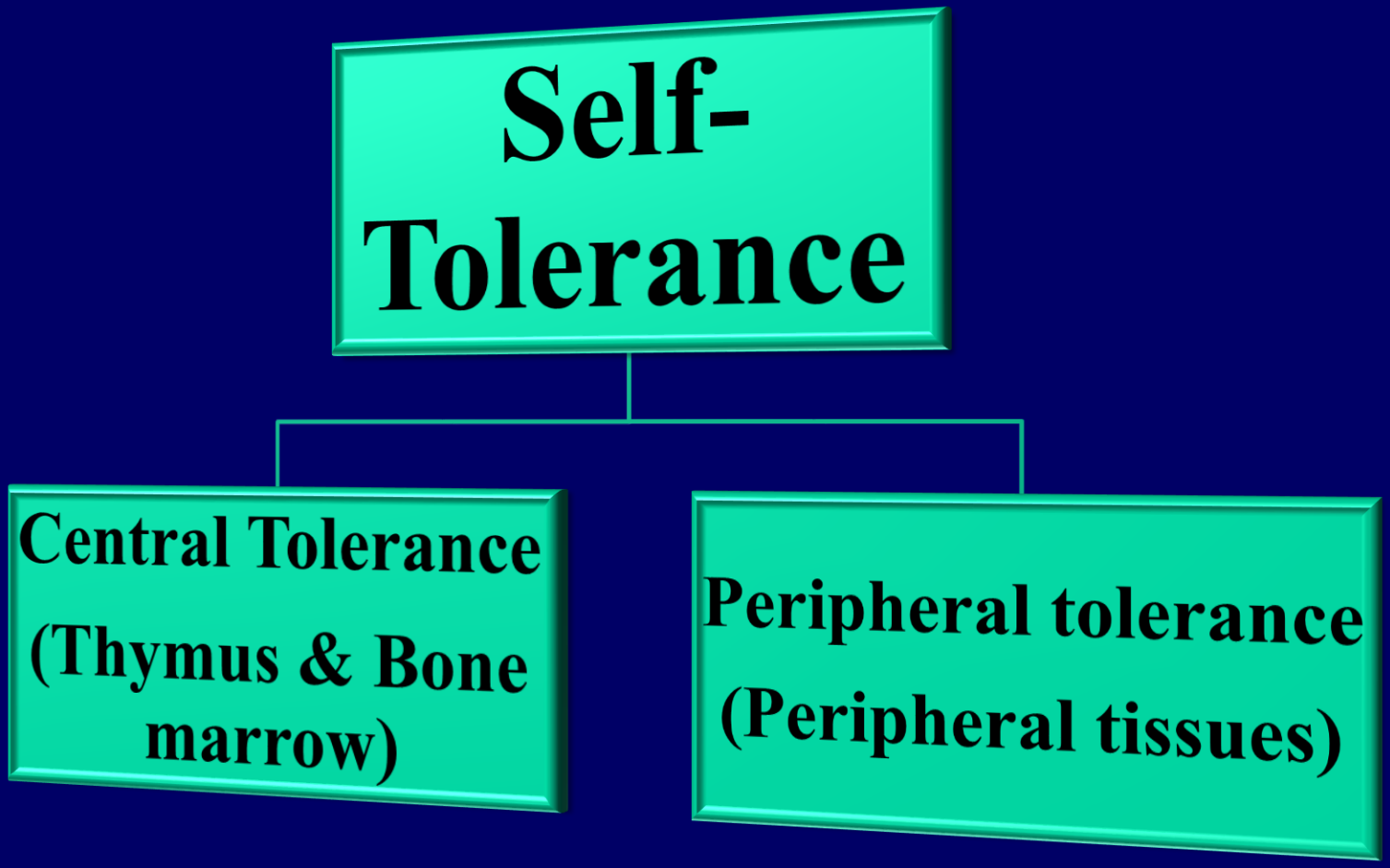
Immune system has evolved to discriminate between

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
Central Tolerance (Thymus & Bone marrow)
Peripheral tolerance (Peripheral tissues)

Central tolerance

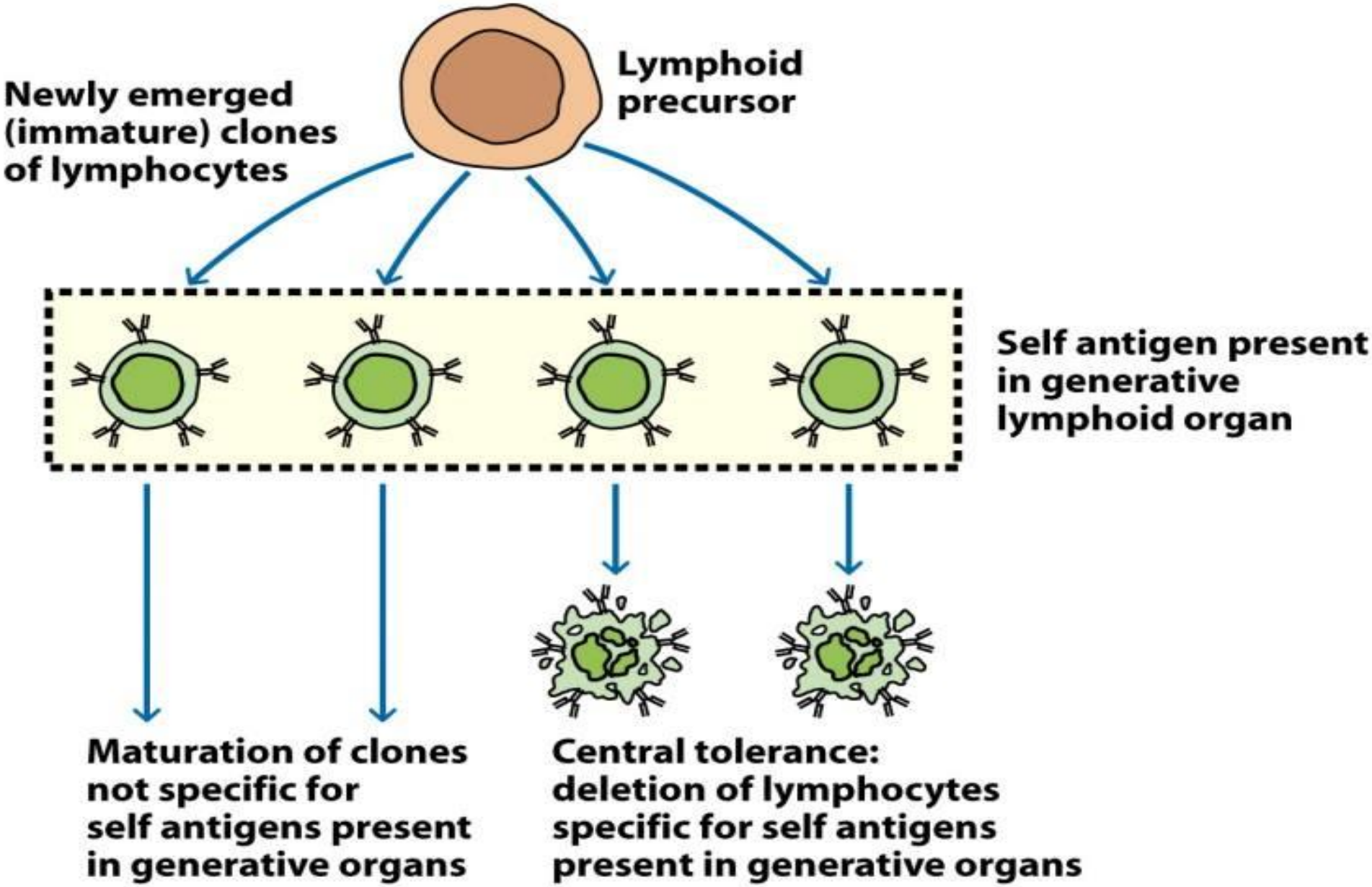
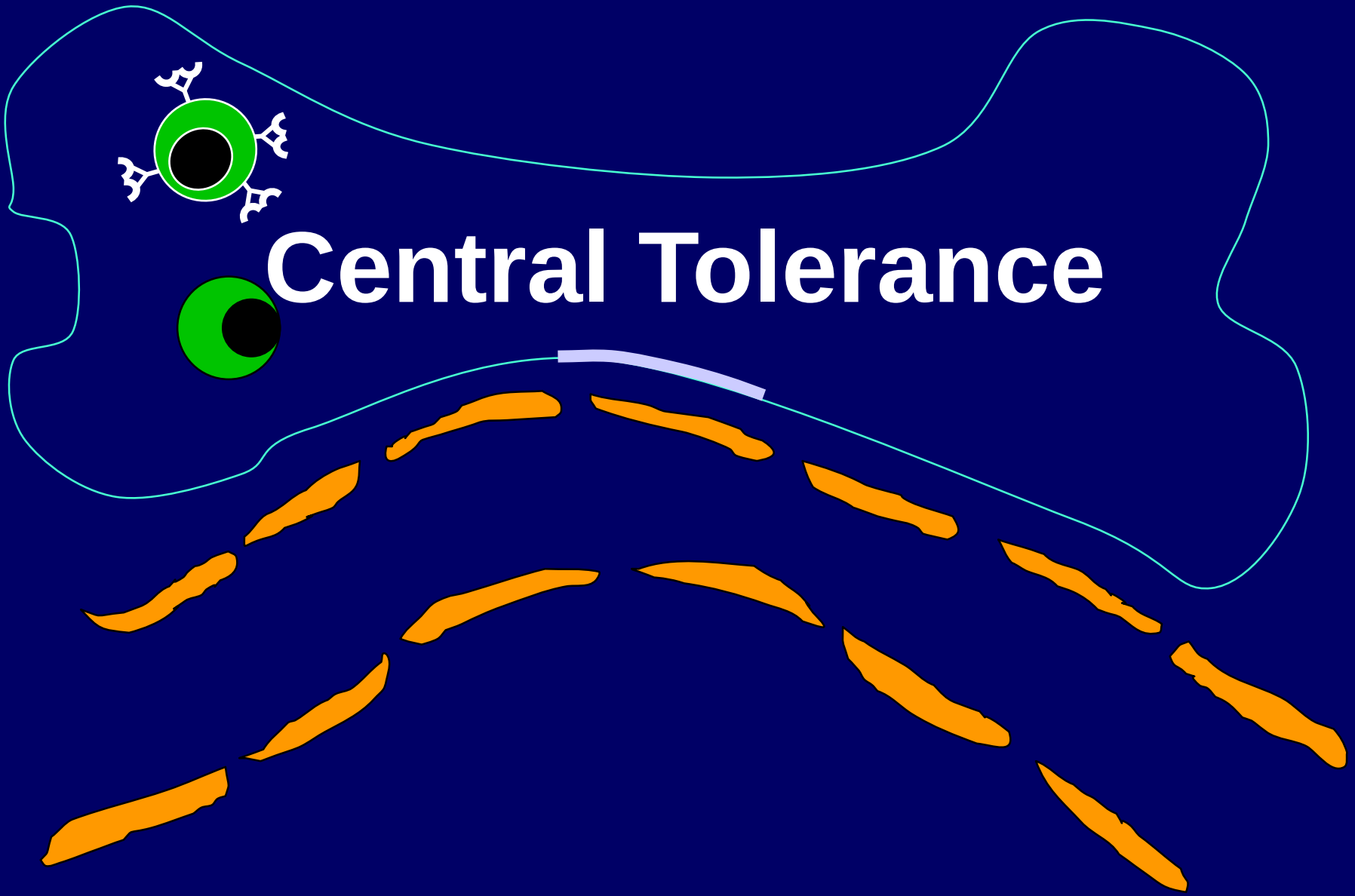


Figure 16-1a
Kuby IMMUNOLOGY, Sixth Edition

Educated T-cell
Autoreactive cell



Central Tolerance

Peripheral tolerance

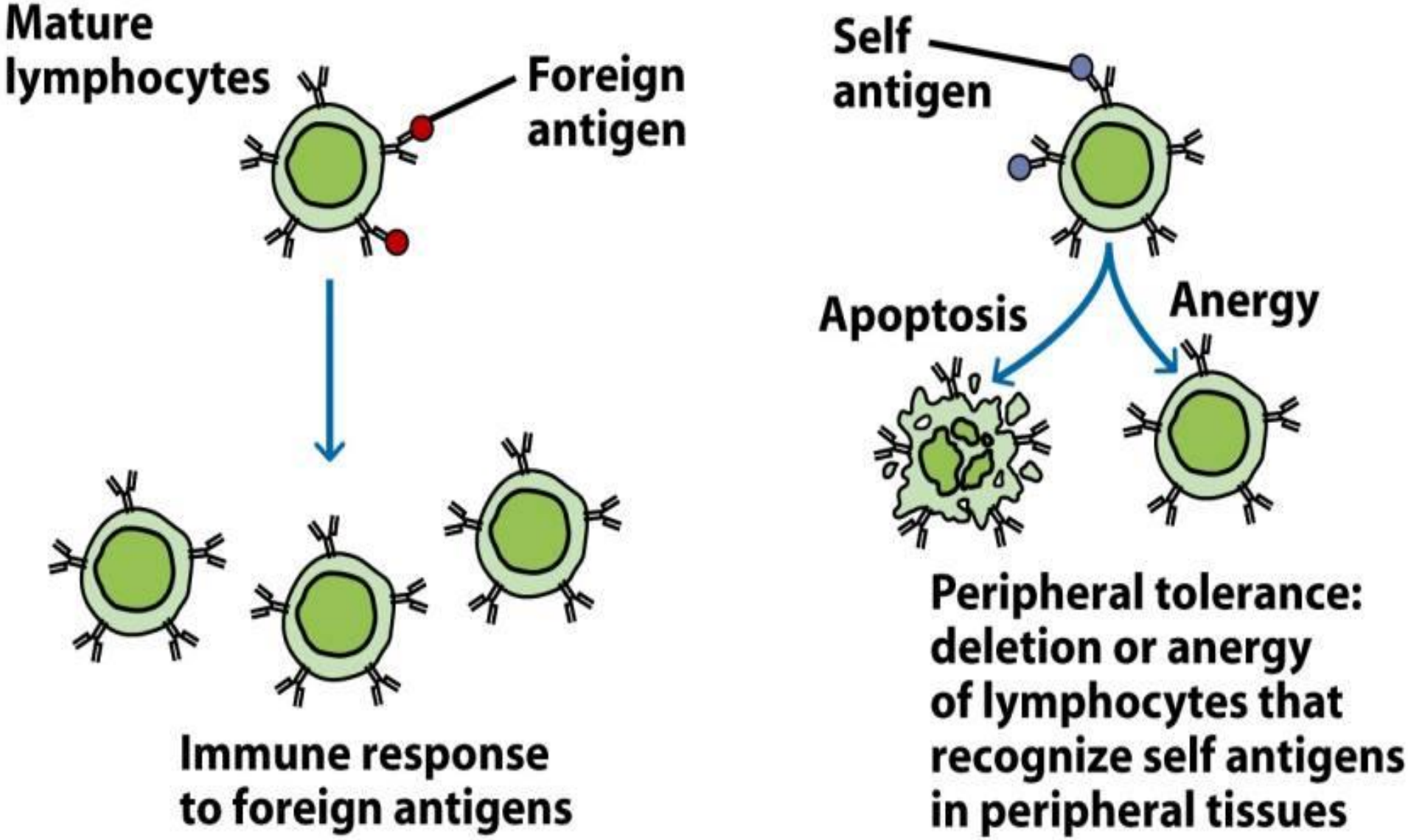


Figure 16-1b
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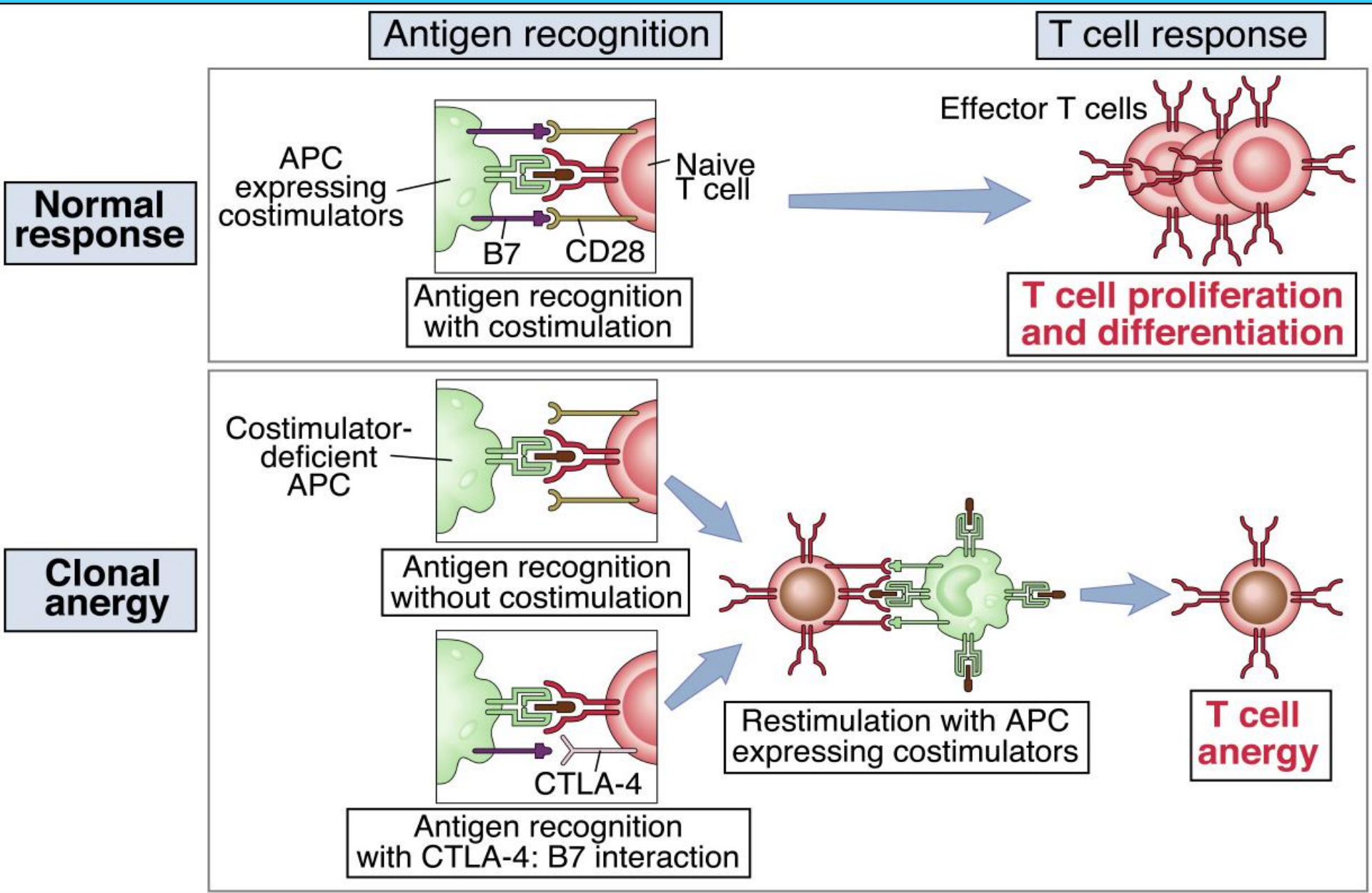
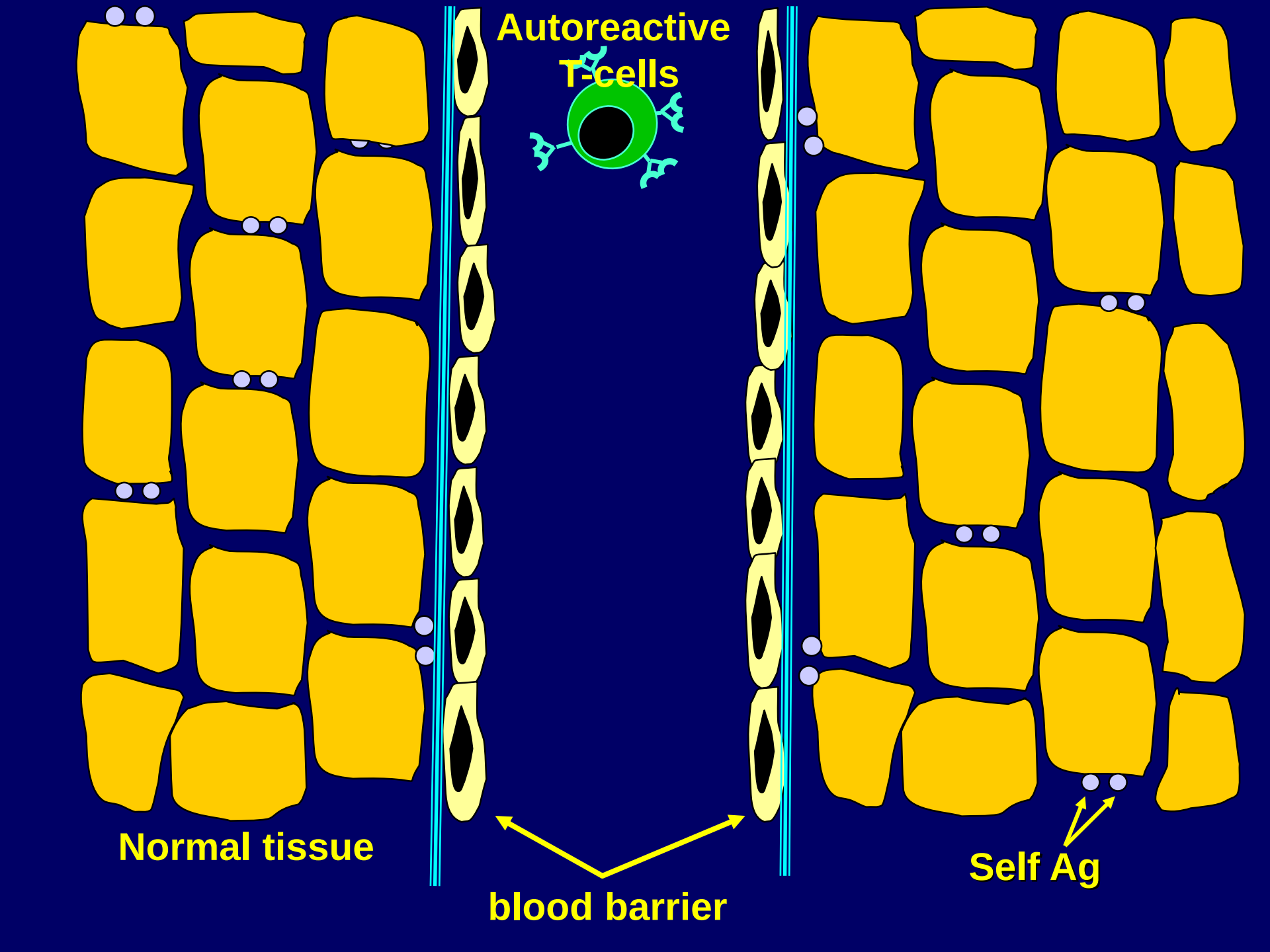
Peripheral Tolerance of T Lymphocytes




Autoreactive
T-cells
Normal tissue
blood barrier
Self Ag

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

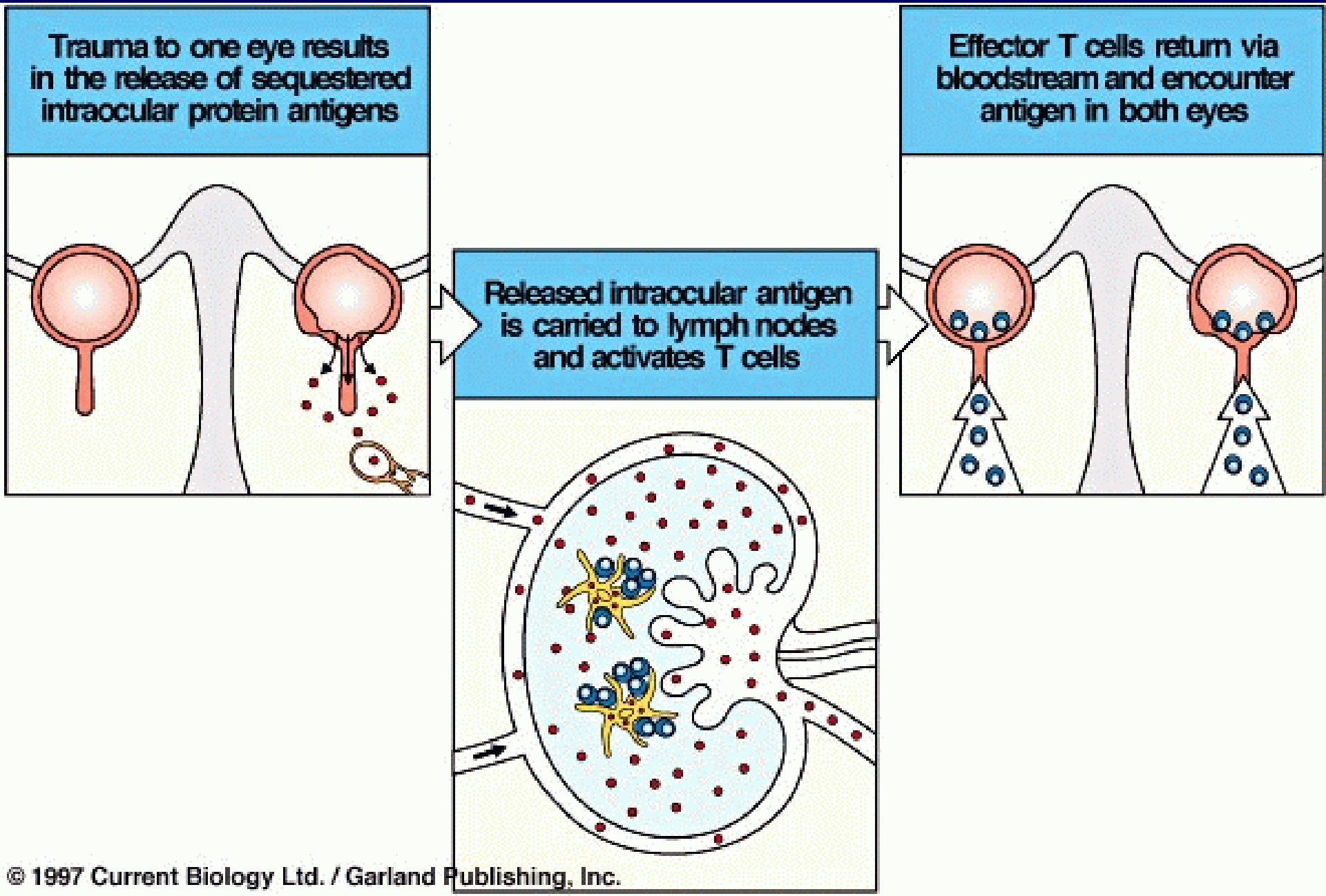
1. Sequestered antigens

- 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



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†	Sequence‡
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
Klebsiella pneumoniae 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
α-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

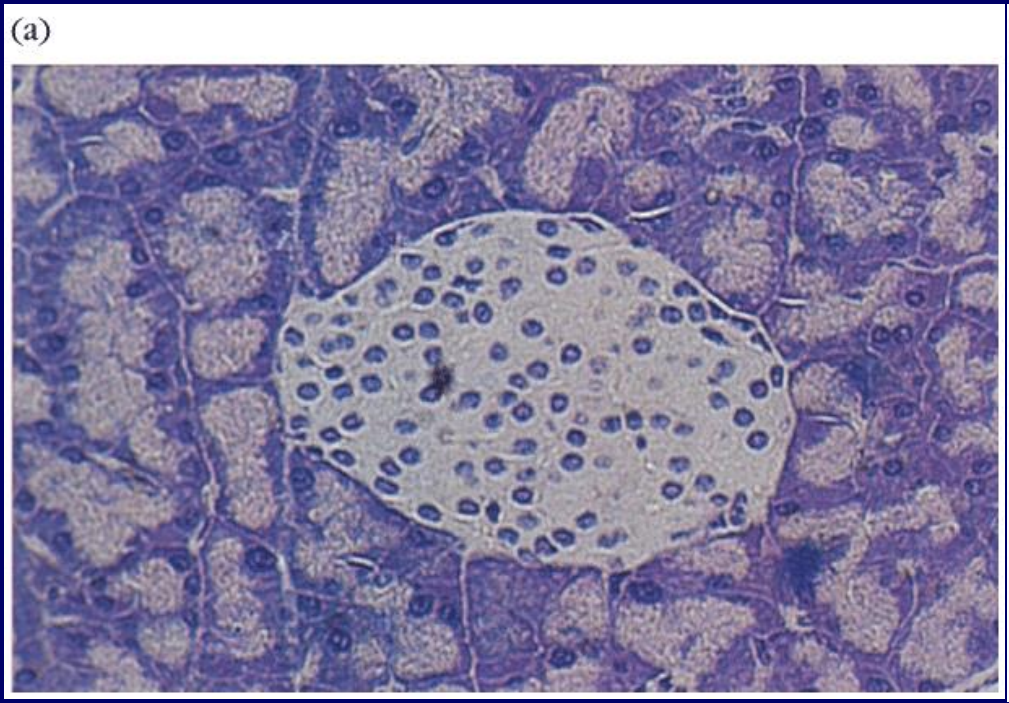
3. Inappropriate Expression of Class II MHC Molecules

- 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.

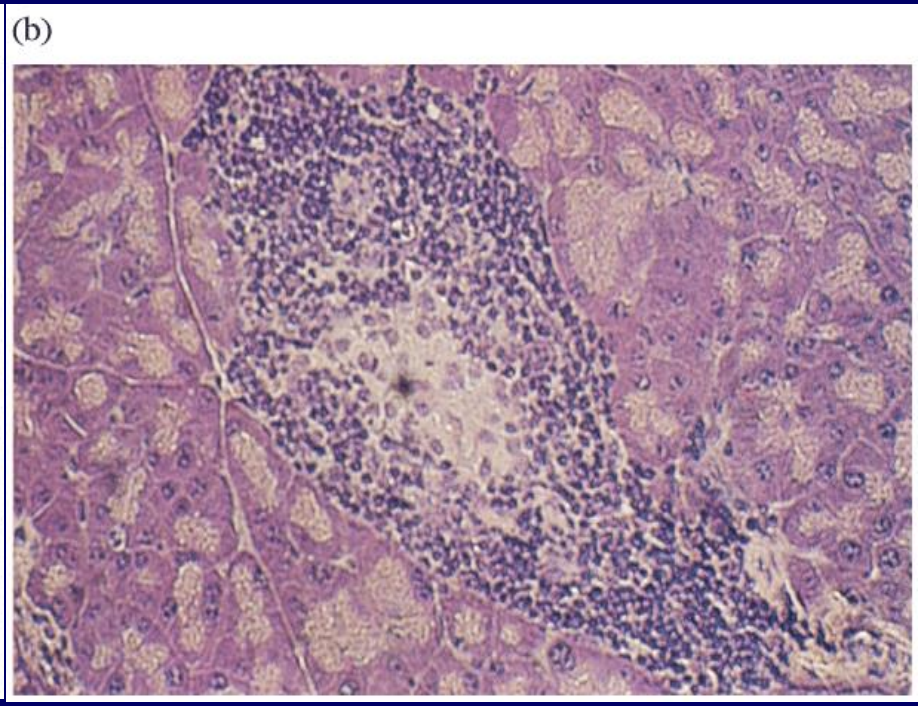
Inappropriate Expression of Class II MHC Molecules

- This may occur due to the local production of IFN-γ, which is known to increase class II MHC expression on a variety of cells.
- The inducer of IFN-γ under these circumstances could be a viral infection.

Type I Diabetes: Pancreatic β cells express abnormally high levels of MHC I and MHC II (?)



Normal Pancreas

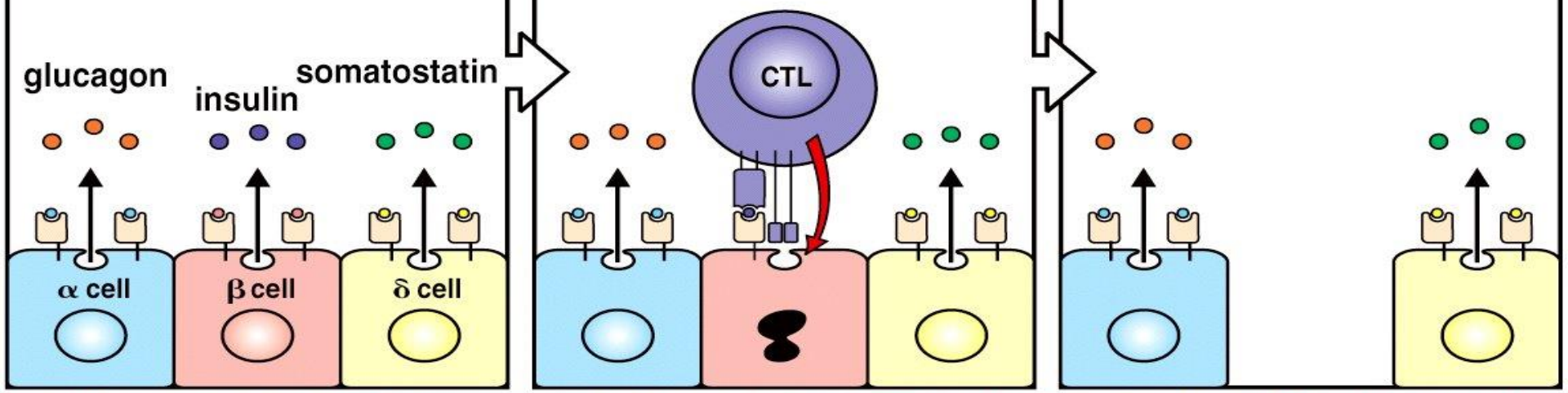


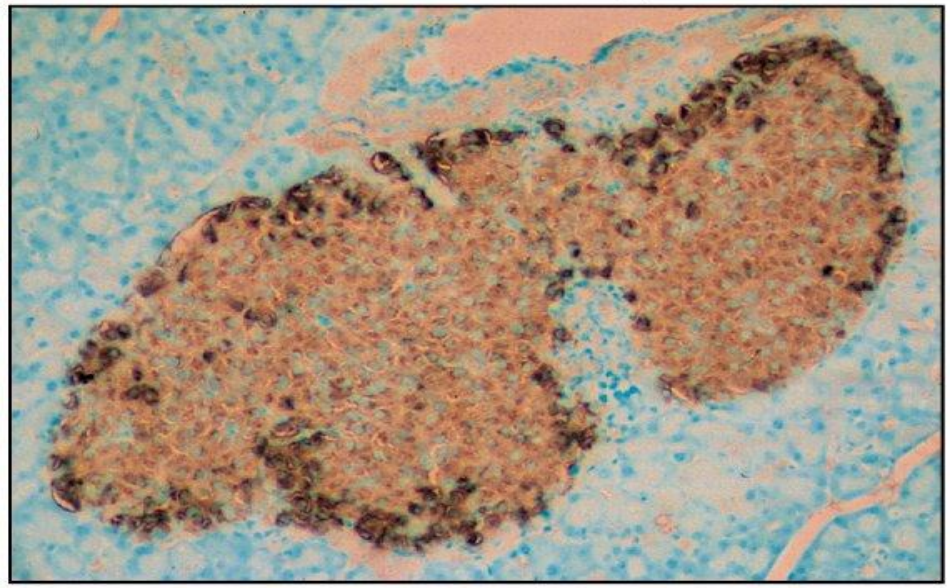
Pancreas with Insulitis

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 β cell-specific protein and kills the β cell

Glucagon and somatostatin are still produced by the α and δ cells, but not insulin can be made





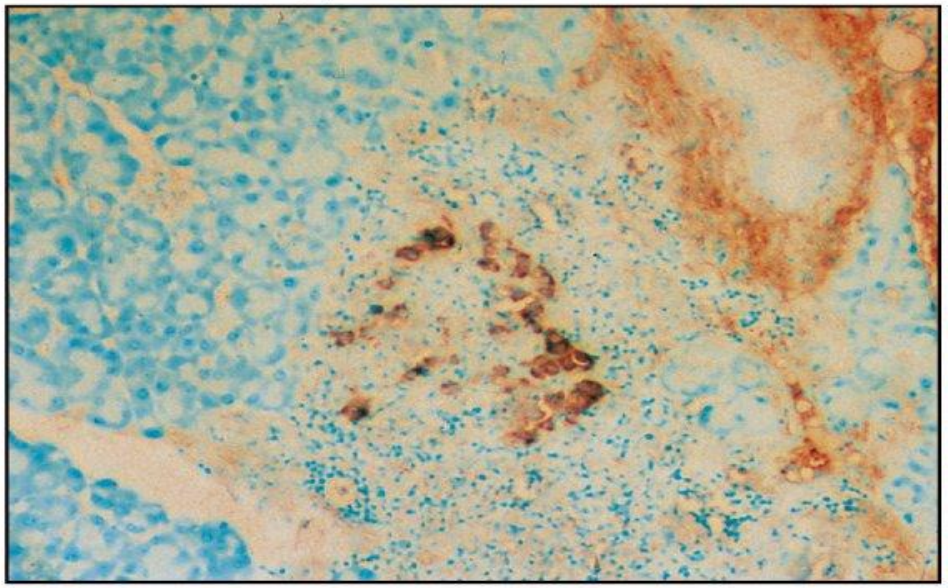


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

4. Polyclonal B Cell Activation

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

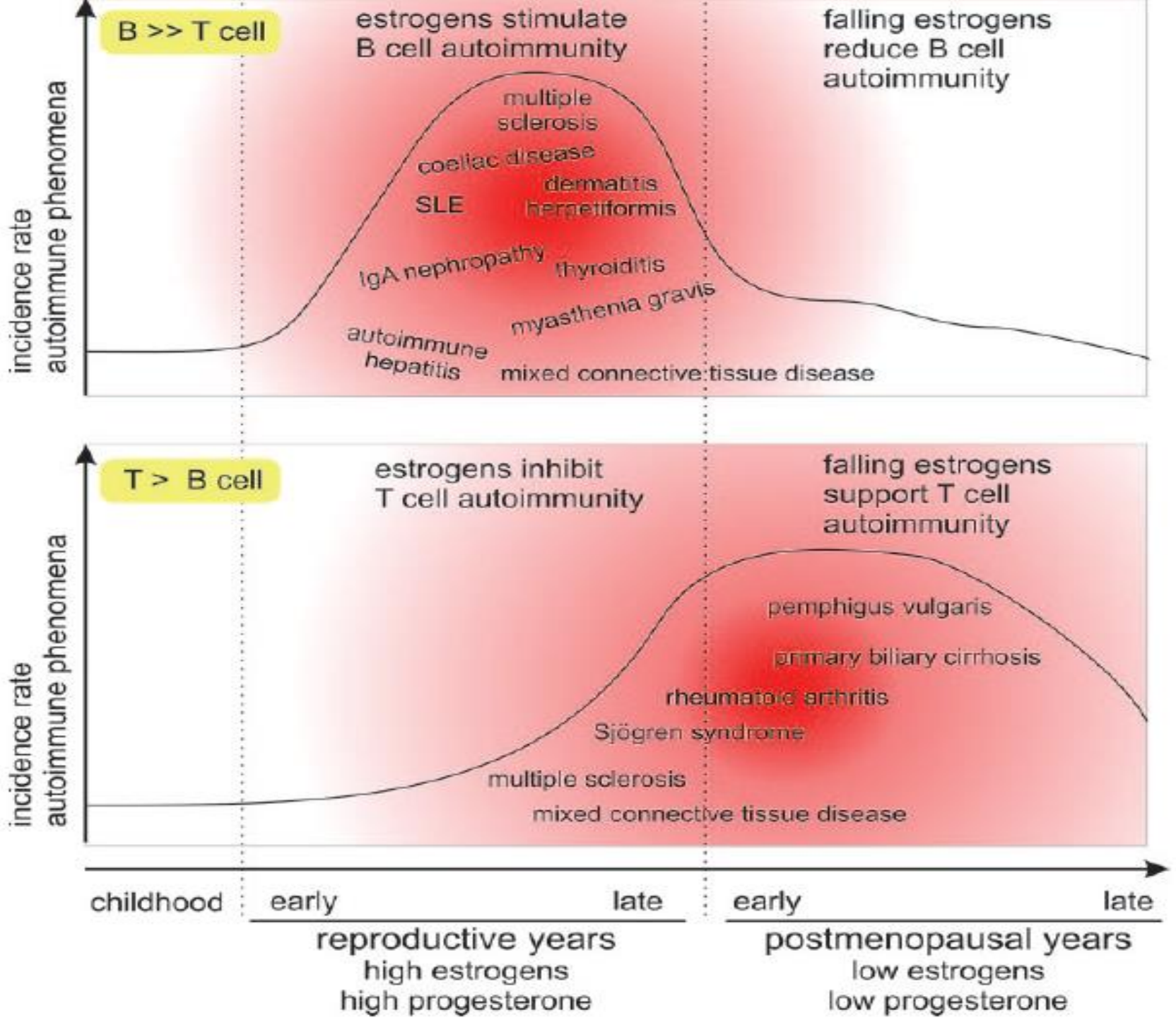
- Certain gram negative bacteria
- Herpes simplex virus.
- Cytomegalovirus
- Epstein Barr Virus
- Human immunodeficiency virus (HIV)

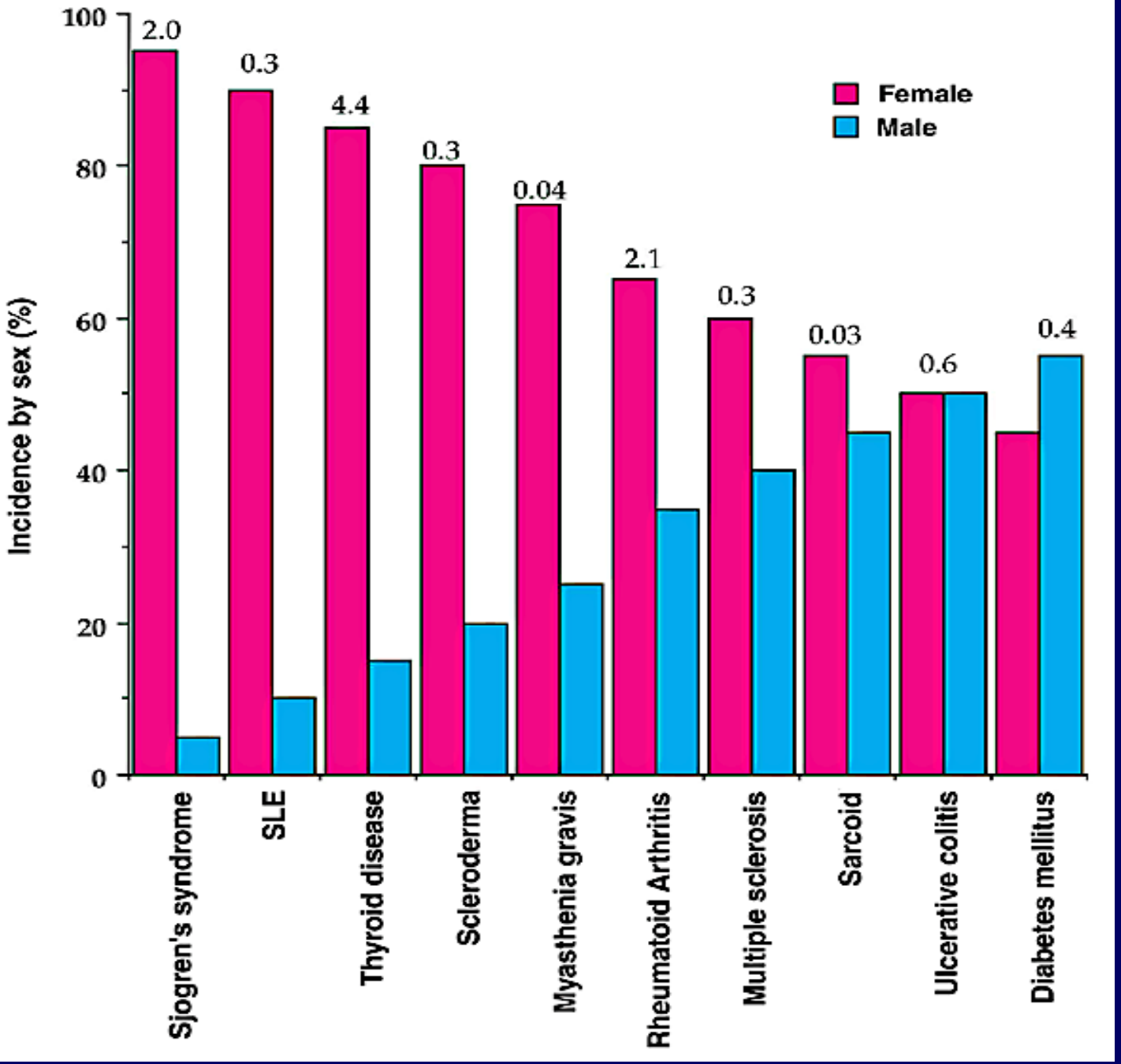
These viruses induce the proliferation of numerous clones of B cells to secrete IgM in the absence of a requirement for CD4 T cell help.

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


B >> T cell
estrogens stimulate
B cell autoimmunity
falling estrogens
reduce B cell
autoimmunity
incidence rate
autoimmune phenomena
multiple
sclerosis
coeliac disease
dermatitis
herpetiformis
SLE
IgA nephropathy
thyroiditis
myasthenia gravis
autoimmune
hepatitis
mixed connective tissue disease
T > B cell
estrogens inhibit
T cell autoimmunity
falling estrogens
support T cell
autoimmunity
incidence rate
autoimmune phenomena
pemphigus vulgaris
primary biliary cirrhosis
rheumatoid arthritis
Sjögren syndrome
multiple sclerosis
mixed connective tissue disease
childhood
early
late
early
late
reproductive years
high estrogens
high progesterone
postmenopausal years
low estrogens
low progesterone



Nature Immunology 2, 777 - 780 (2001)

Drug Induced Lupus Erythematosus

- Lupus erythematosus like syndrome develops inpatients 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