Mechanisms of Autoimmunity

Immunology Unit
Department of Pathology
College of Medicine, KSU

السلام عليكم
هذه النقاط المهمه الي اخدتها من
الدكتور حسب كلامه لي وفيه
مواضيع مفصل في نوتات التيم
لتسهيل الفهم والنقاط المهمه
هي باللون الاحمر
والله ولي التوفيق
Team immune

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

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

اهميتها ان السنترل من وين يفرز وهذا موجود بالنوتات

Peripheral tolerance

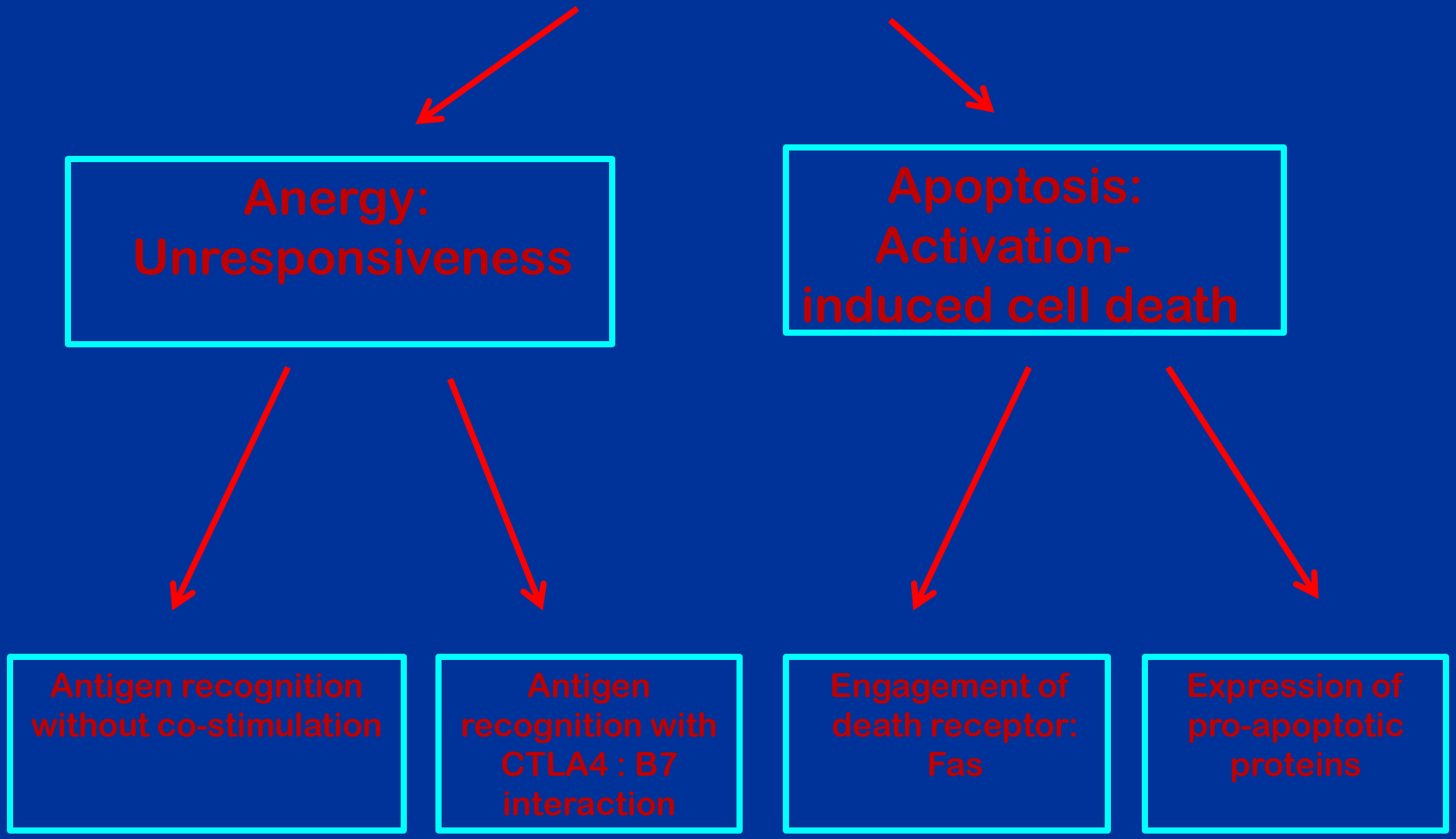
اهميتها ان البيرفرل من وين يفرز وهذا موجود بالنوتات

Educated T-cell
Auto-reactive cell

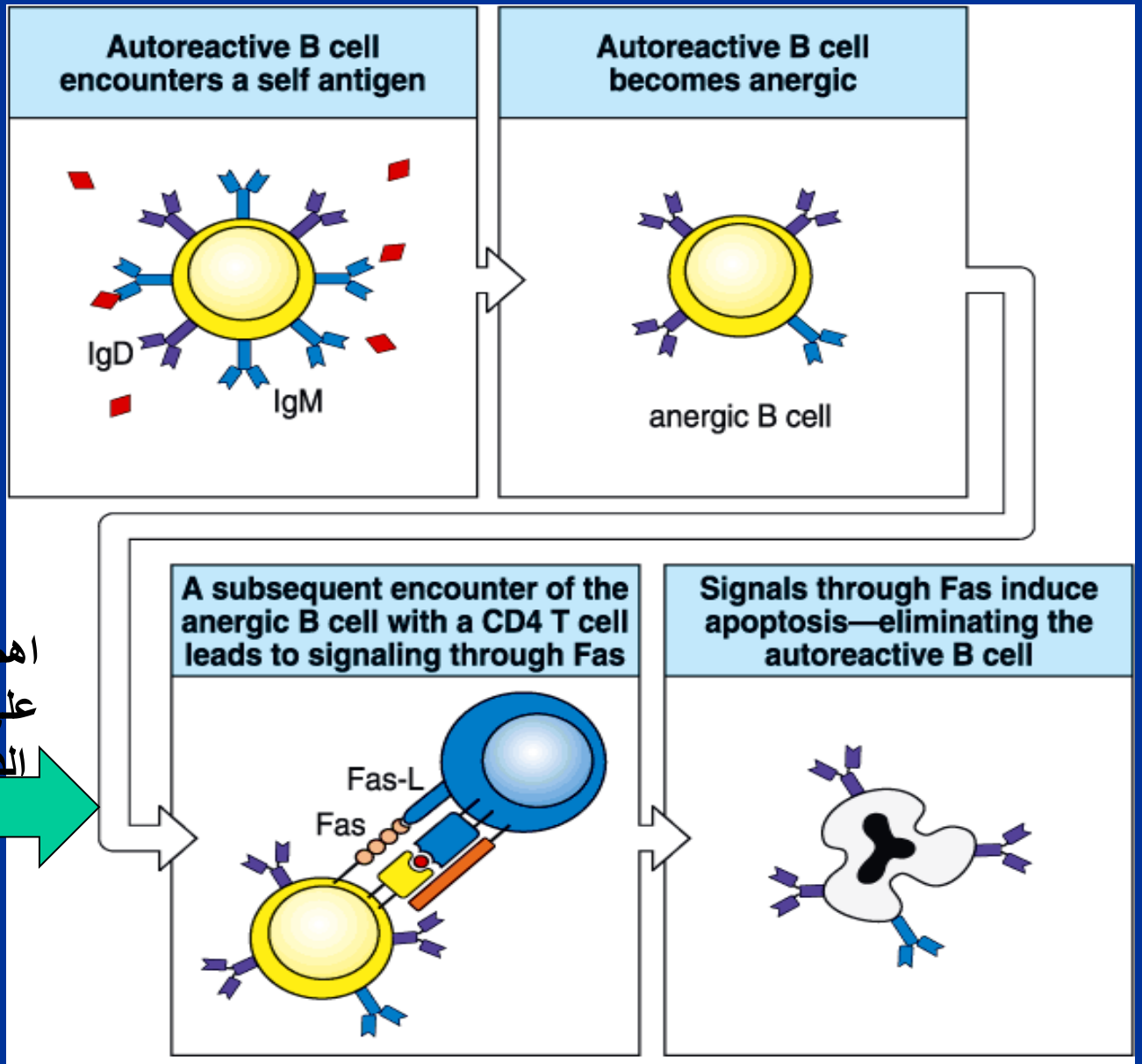
Central Tolerance

اللي لا زم تعرف منها انه
الانتجين اذا ما طلع من
الاورجن يضل فيه وهدا
موجود بالنوتات

Peripheral Tolerance of T Lymphocytes

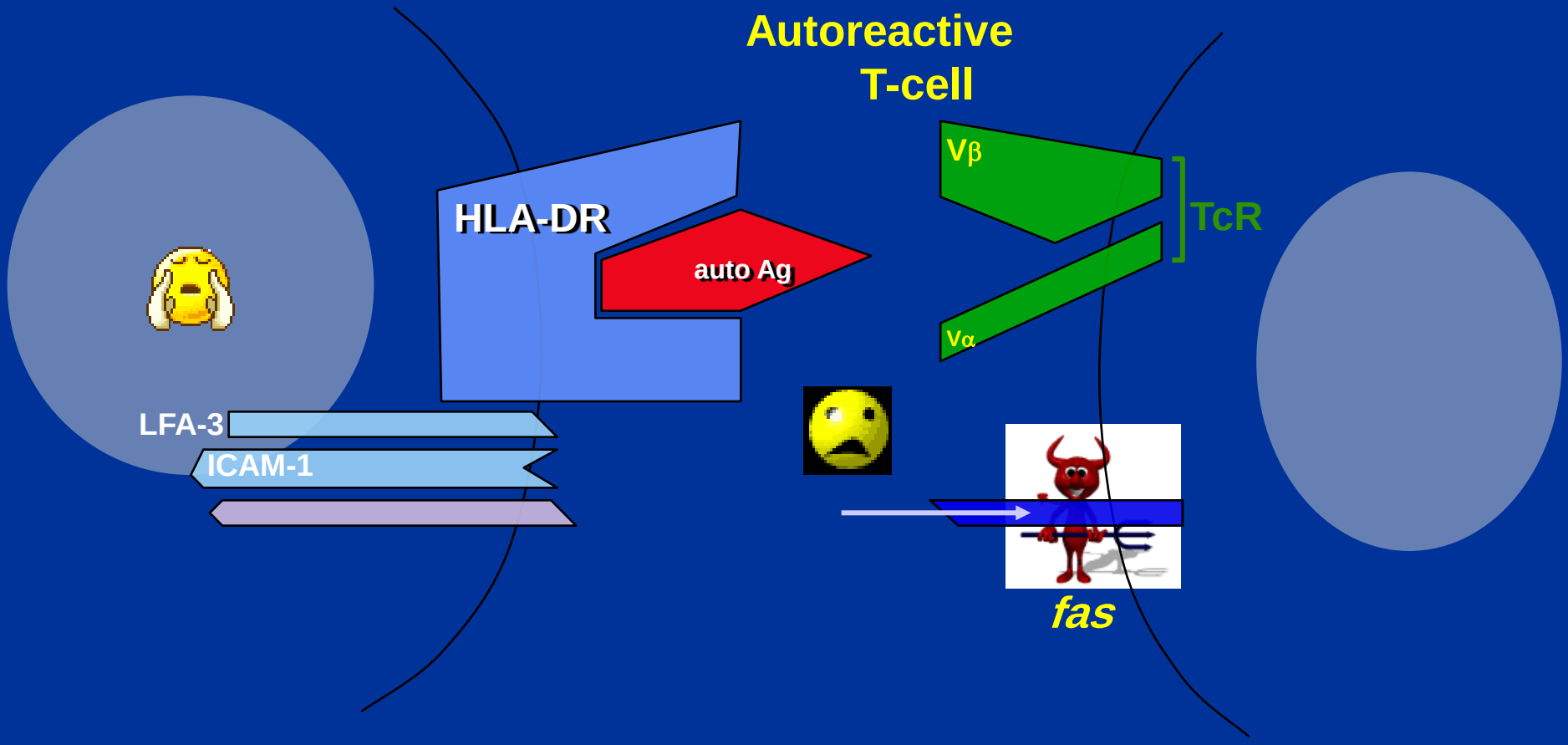


Peripheral B cell Tolerance Mechanisms



اهم نقطه على كلام الدكتور

Fig 13.38 © 2001 Garland Science

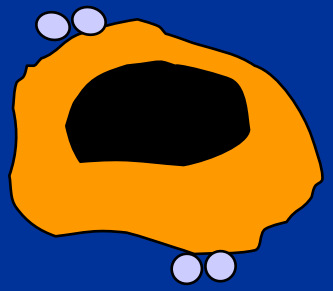


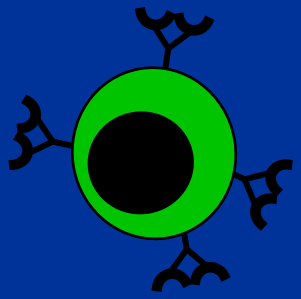
1. Lack of co-stimulator molecules – “anergy”

2. Stimulate *fas* ligand - program cell death “apoptosis”

Peripheral Tolerance

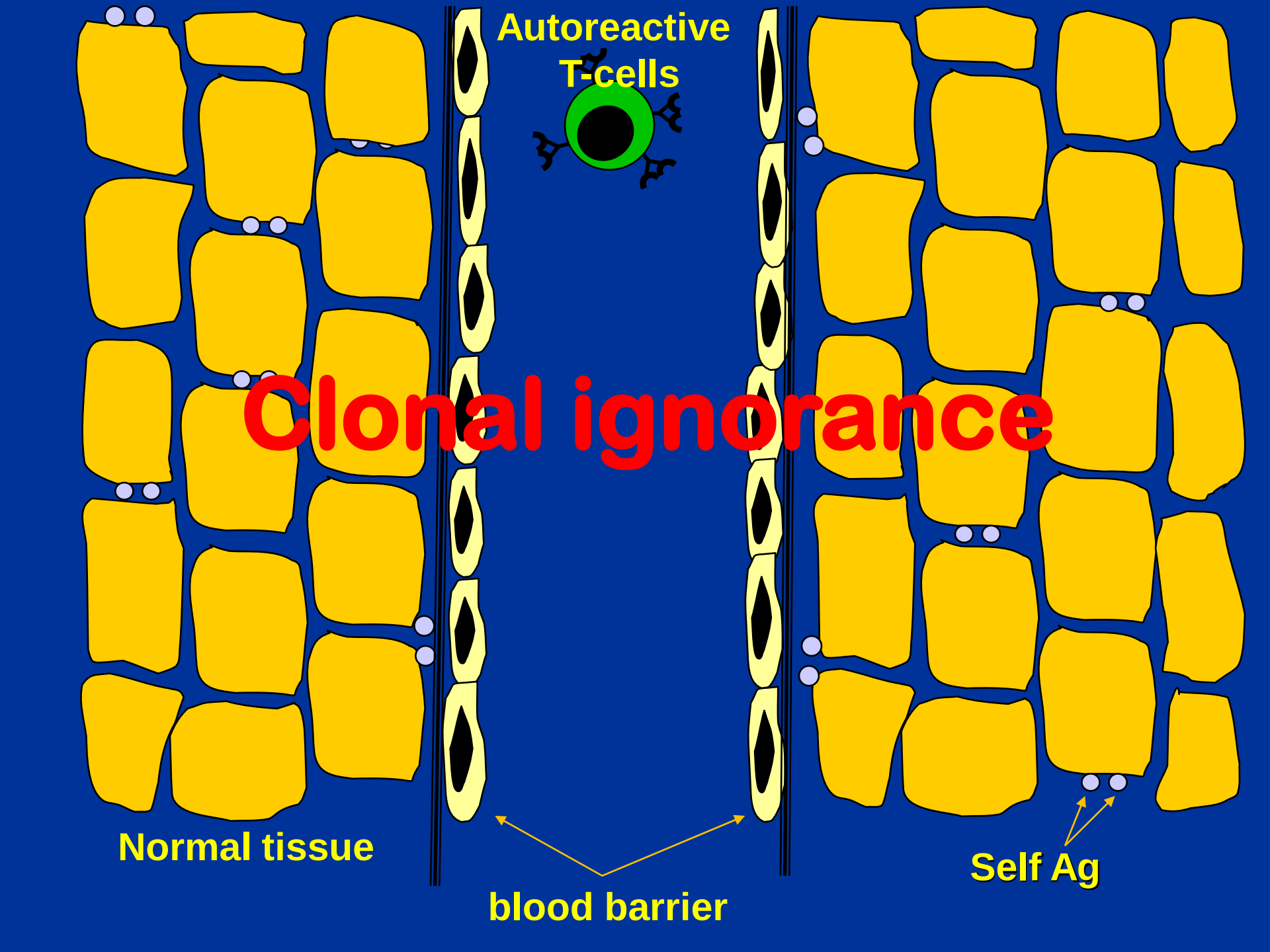
Host cell





Programed cell death
… or anergy…

Autoreactive cell


Autoreactive
T-cells
Clonal ignorance
Normal tissue
blood barrier
Self Ag

Failure of Immune Tolerance (Development of Autoimmunity)

Immunopathogenesis of autoimmunity

1. Release or exposure of sequestered (hidden) antigens
2. Molecular mimicry (cross-reaction)
3. Polyclonal B-cell activation
4. Inappropriate MHC expression on non-APC cells
5. Hormones
6. Drugs

1.Release or exposure of sequestered antigens

- Some self-antigens are sequestered 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

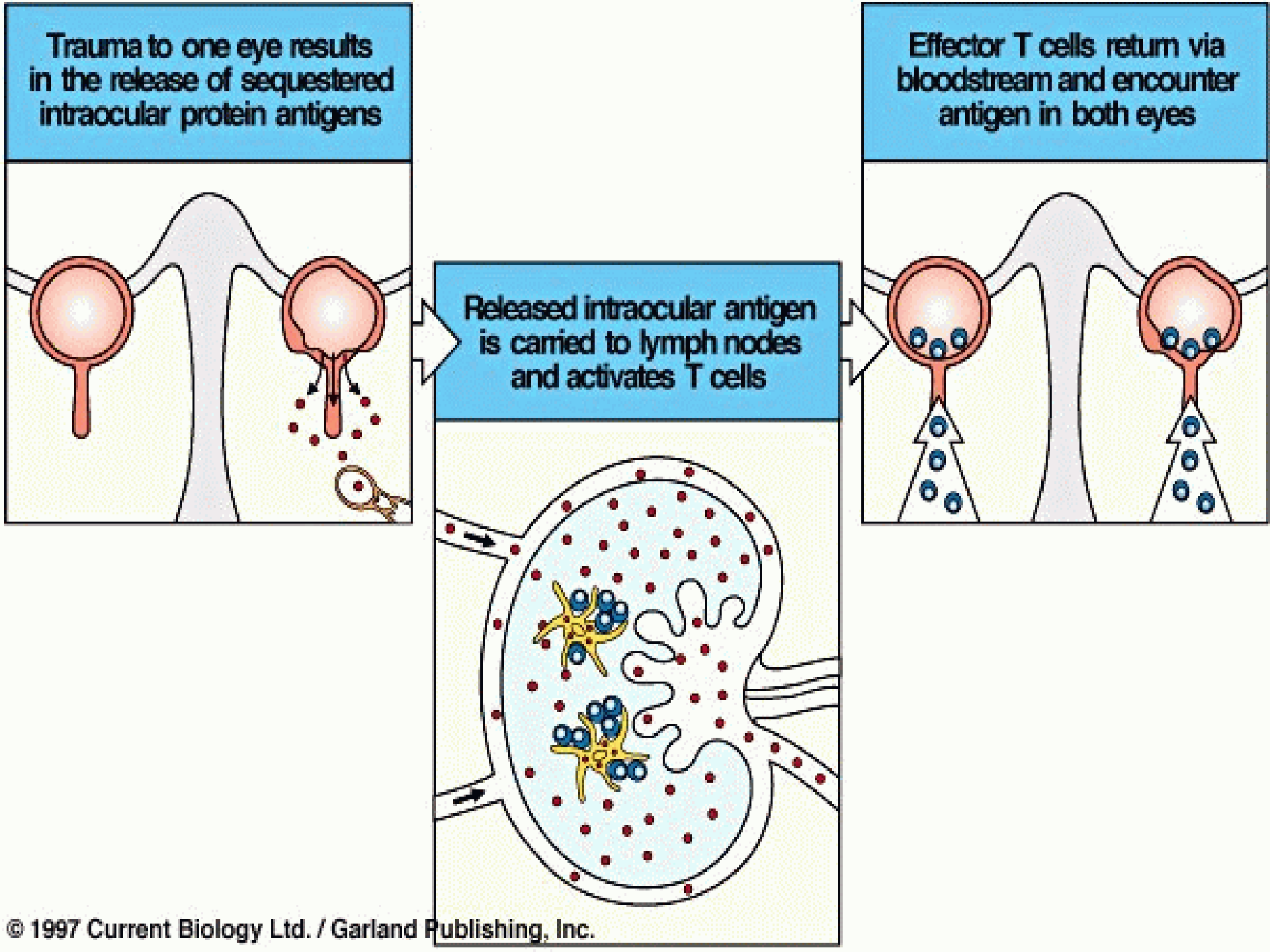
Examples of Sequestered Antigens

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



2.Cross-reacting Antigens (Molecular Mimicry)

- 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 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

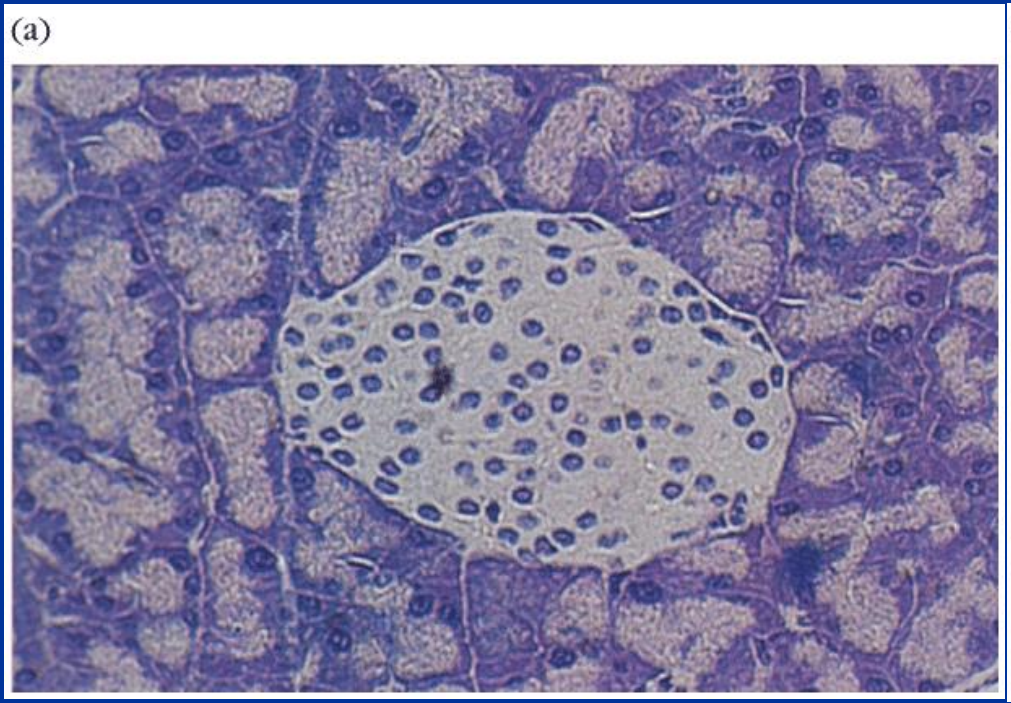
3. Inappropriate Expression of Class II MHC Molecules

- 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

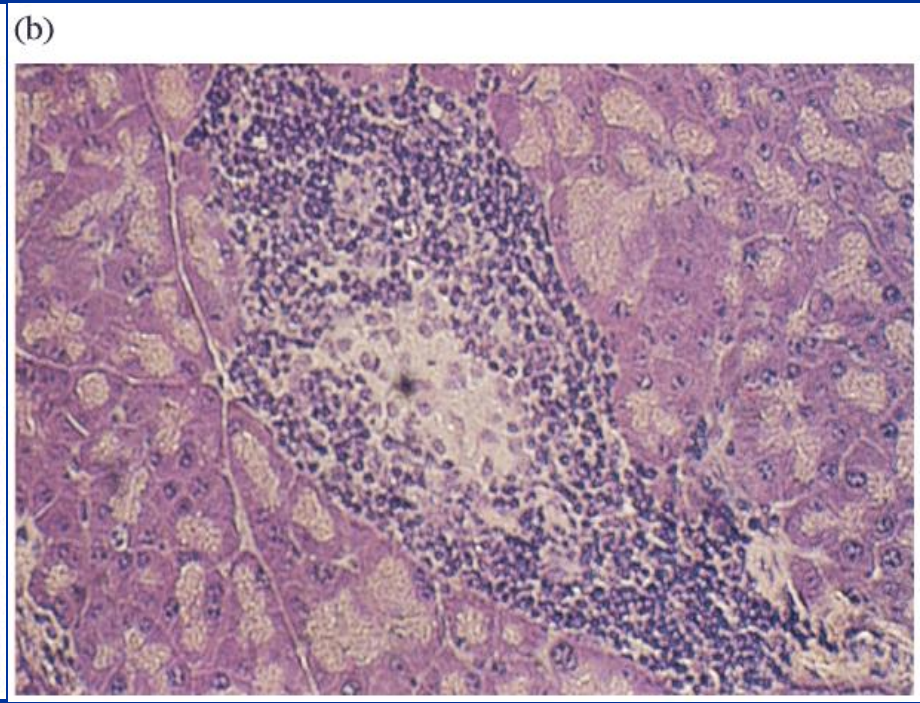
Inappropriate Expression of Class II MHC Molecules

- 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

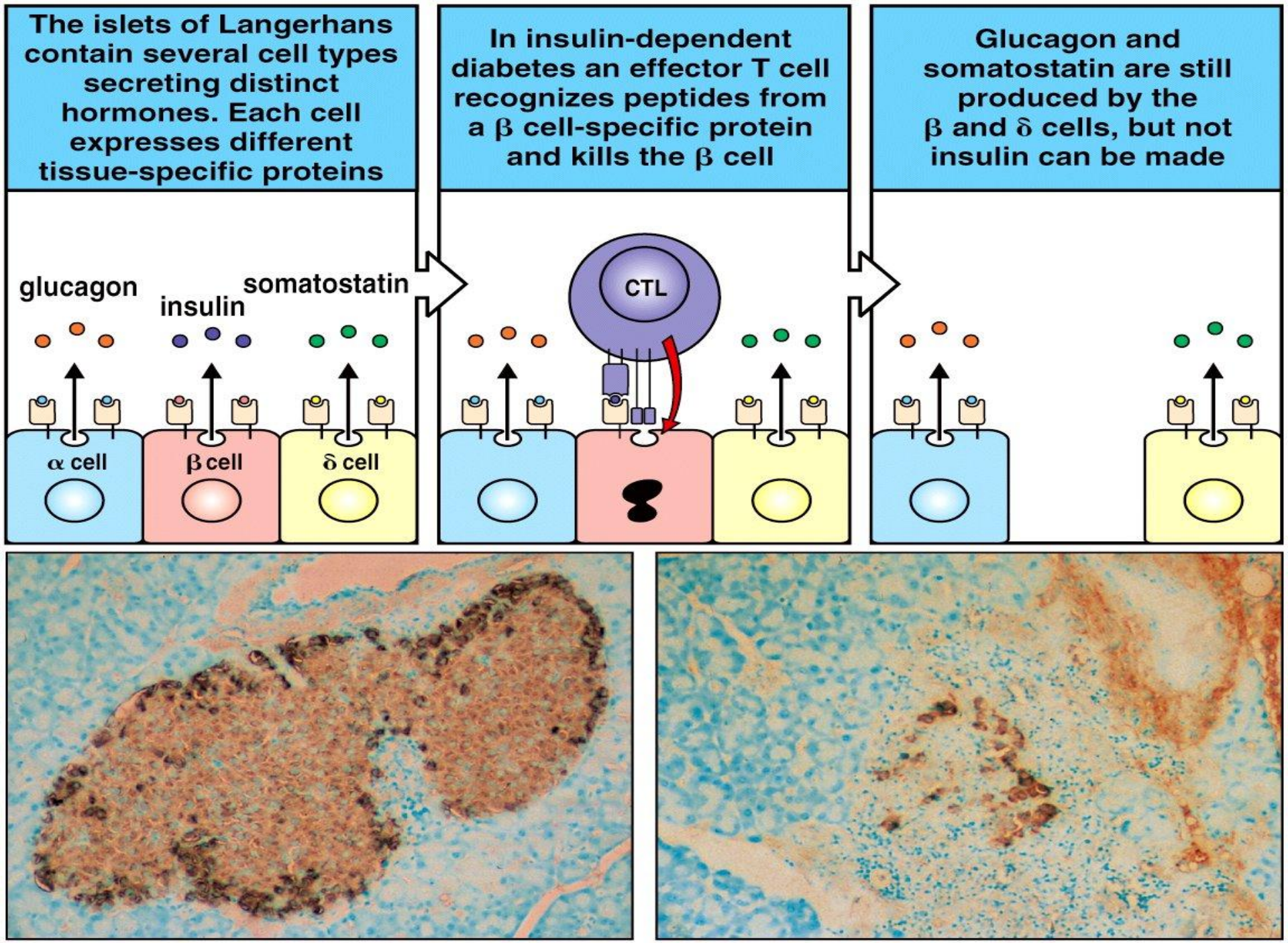


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

4. Polyclonal B Cell Activation

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

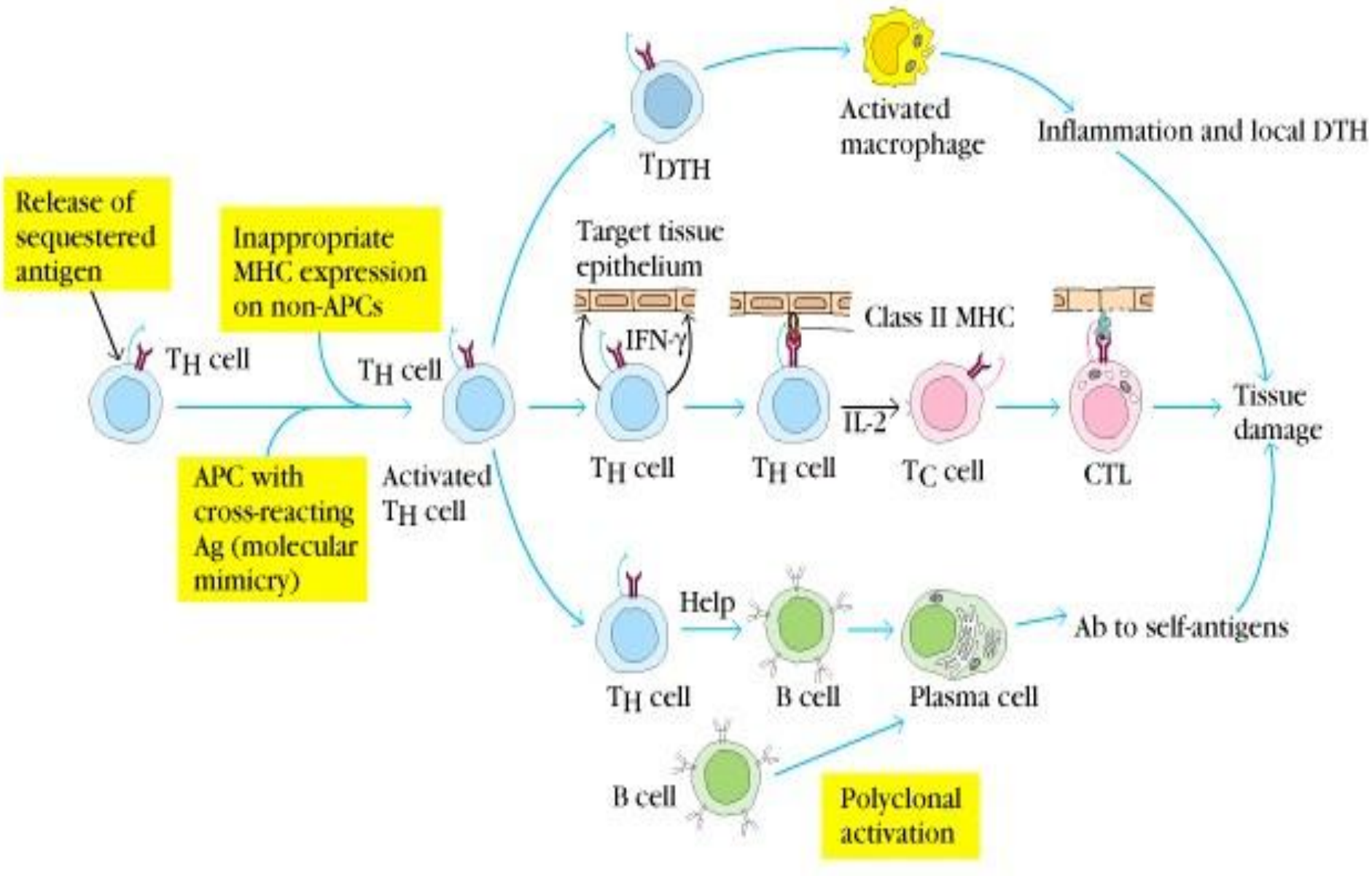
- Certain gram negative bacteria
- Herpes simplex virus
- Cytomegalovirus
- Epstein Barr Virus
- Human immunodeficiency virus (HIV)

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

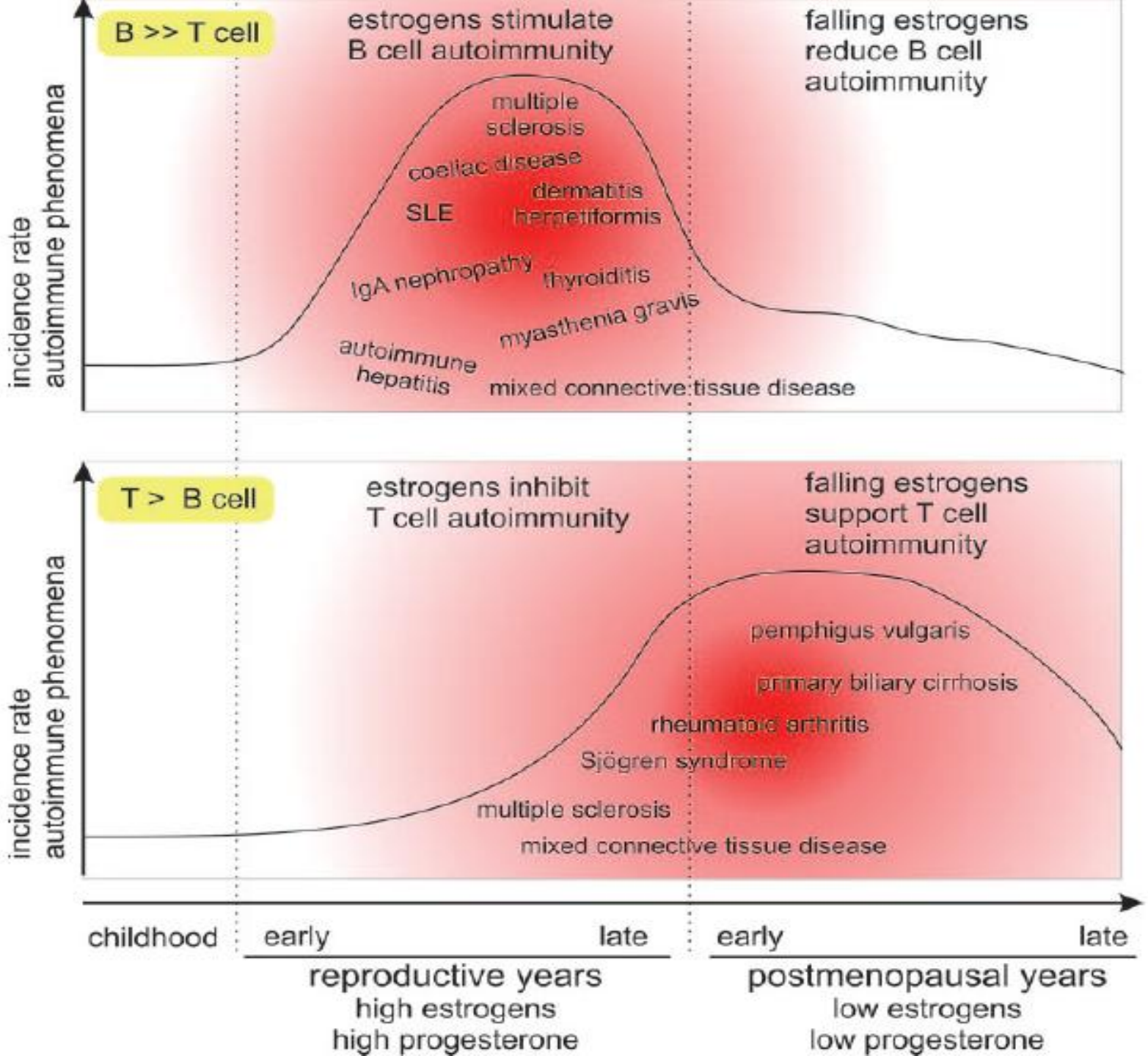
Patients with infectious mononucleosis (caused by EBV) and AIDS (HIV) have a variety of auto-antibodies

Summary of proposed mechanisms of autoimmunity



5. 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

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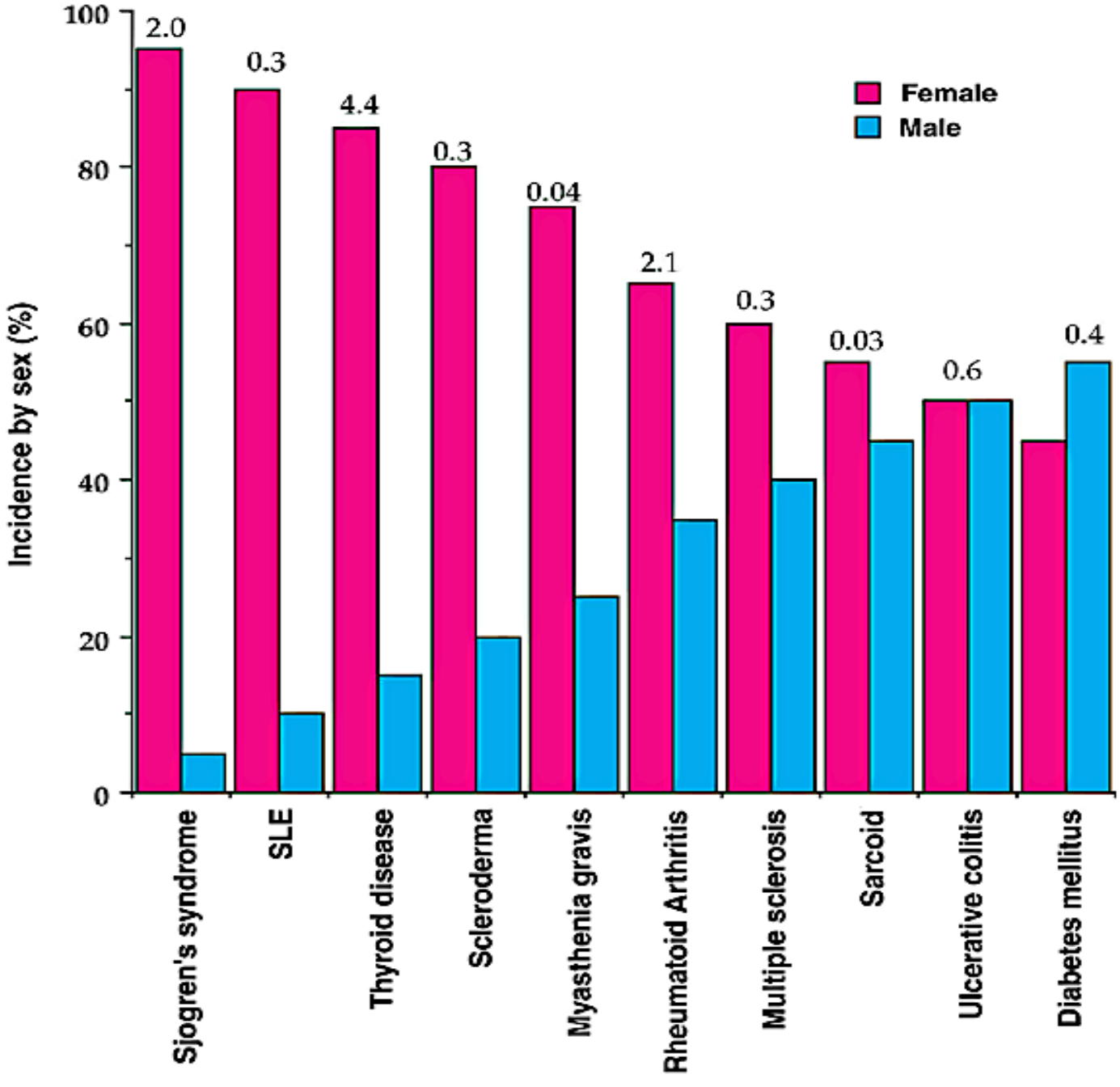

Nature Immunology 2, 777 - 780 (2001)

6. 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 ANAs
- Renal and CNS involvement is uncommon
- Anti-histone antibodies are frequently present

Thank you