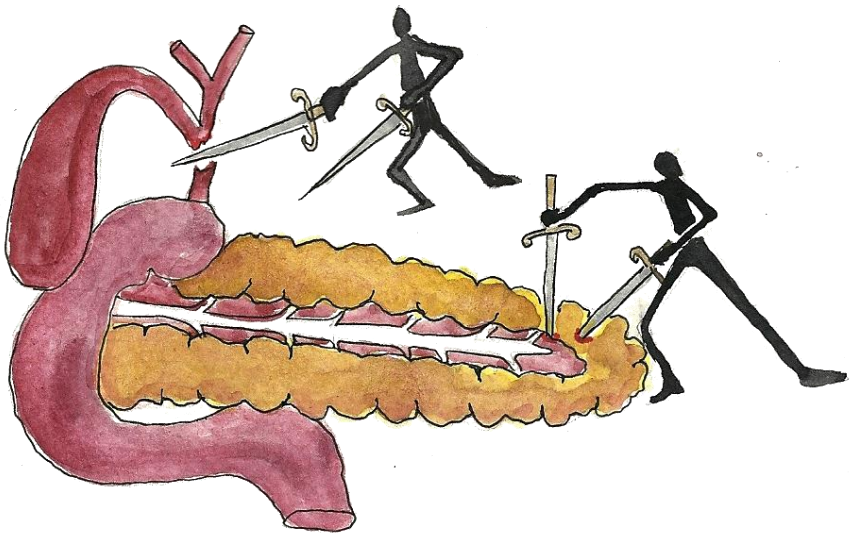
MECHANISMS OF AUTOIMMUNITY

LECTURE 1



AUTOIMMUNITY

- **A condition that occurs when the immune system mistakenly attacks and destroy the healthy body tissue.**
- **Immune system has evolved to discriminate between**

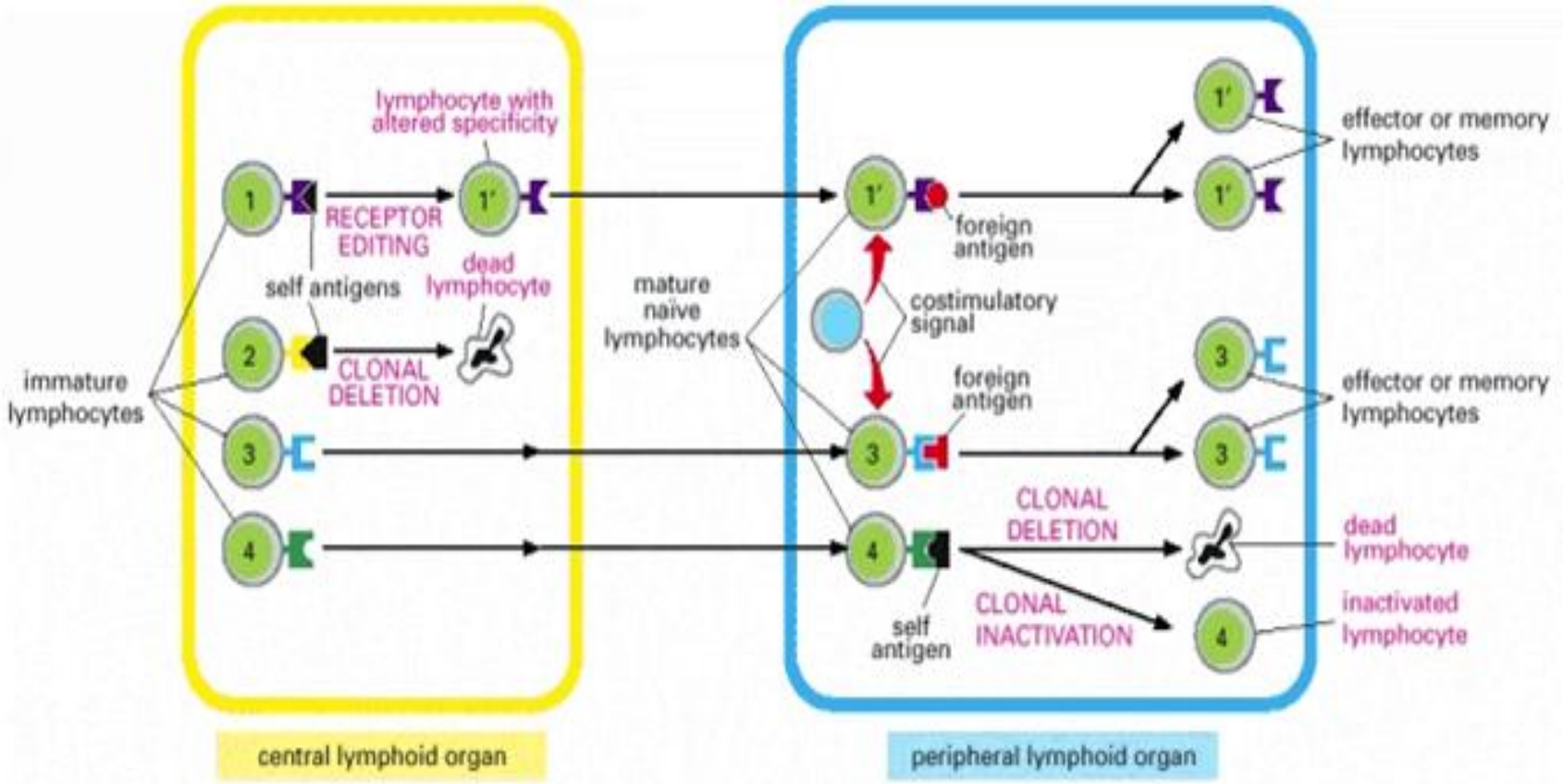
  Self and Non-self
- **Mediated by auto-reactive T cells and auto-reactive B cells (auto-antibodies)**

Tolerance to self is acquired by:

1. **Deletion (clonal deletion)**
2. **Functional Inactivation (clonal anergy):** of developing lymphocytes that possess antigenic receptors with high affinity for self-antigens.

SELF TOLERANCE

Central	Peripheral
Thymus & Bone Morrow	Spleen, Lymph nodes, etc.



FAILURE OF IMMUNE TOLERANCE
(DEVELOPMENT OF AUTOIMMUNITY)

Sequestered Antigens	Molecular Mimicry	Inappropriate Class II MHC Expression On Non-antigen Presenting Cells	Polyclonal B Cell Activation
Pathogenesis & Characteristics			
• Some self-antigens are sequestered (hidden) in specialized tissues.	• Viruses and bacteria possess antigenic determinants that are very similar, or even identical, to normal host cell components.	• Class II MHC ordinarily expressed on antigen presenting cells, such as macrophages, dendritic cells and B cells.	• 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.
• These are not seen by the developing immune system – will not induce self-tolerance.	• This phenomenon, known as *molecular mimicry*, occurs in a wide variety of organisms.	• Abnormal expression of MHC determinants allows the recognition of these auto-antigens by self-reactive T cells.	• Polyclonal activation leads to the activation of self-reactive B cells and autoantibody production.
• Exposure of T cells to these normally sequestered/tissue-specific self-antigens in the periphery results in their activation.	• Molecular mimicry may be the initiating step in a variety of autoimmune diseases.	• 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.	• Patients with infectious mononucleosis (caused by EBV) and AIDS (HIV) have a variety of auto-antibodies.

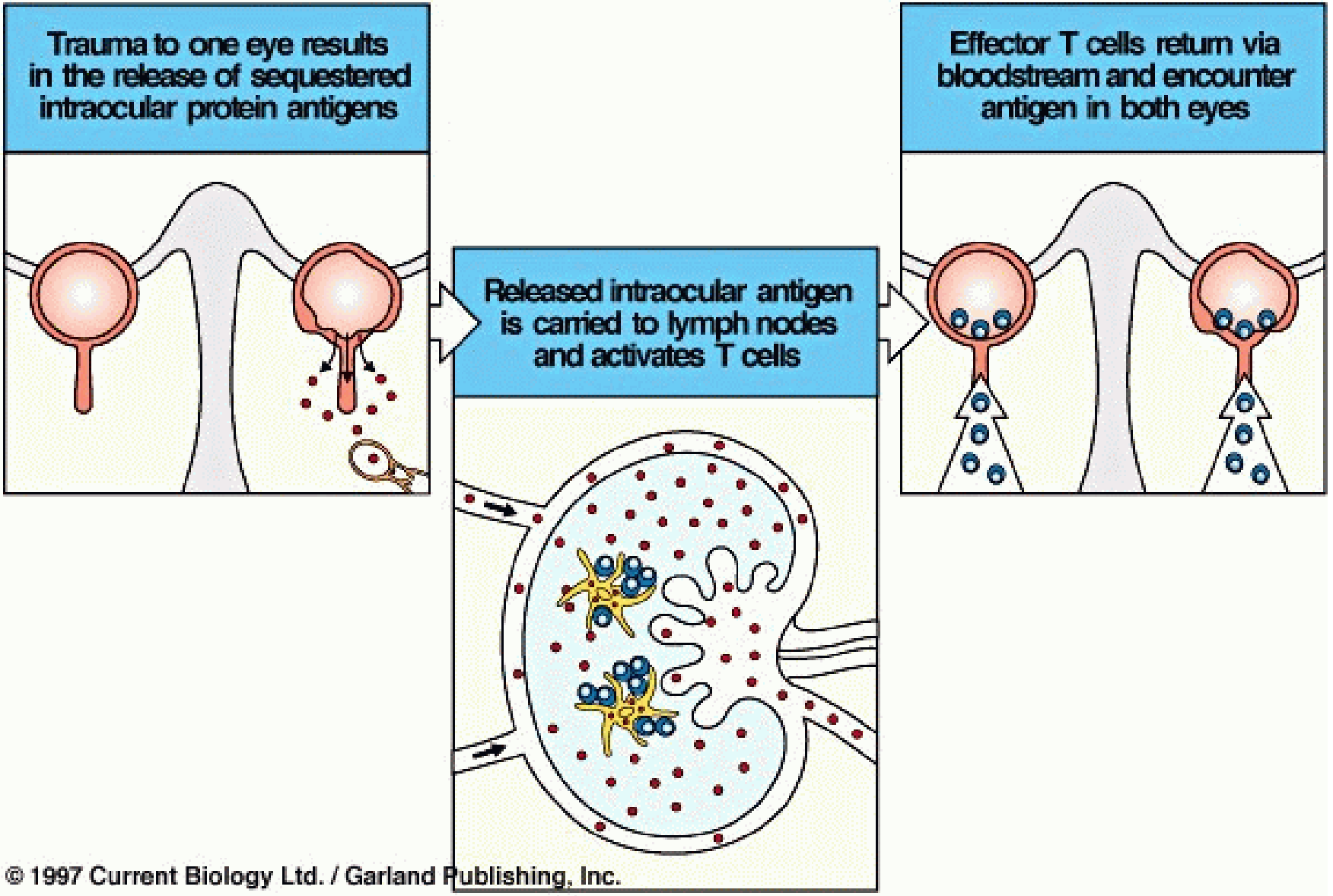
Cases and Examples

• Myelin basic protein (MBP), associated with MS	This table is not included, it's just for clarification	**Type I Diabetes:** Pancreatic β cells express abnormally high levels of MHC I and MHC II	**Viruses and bacteria can induce nonspecific polyclonal B cell activation, including:**
• Sperm-associated antigens in some individuals following vasectomy			• Certain gram negative bacteria
• Lens and corneal proteins of the eye following infection or trauma			• Herpes simplex virus.
			• Cytomegalovirus
• Heart muscle antigens following myocardial infarction			• Epstein Barr Virus
			• Human immunodeficiency virus (HIV)

TABLE 20-3 MOLECULAR MIMICRY BETWEEN PROTEINS OF INFECTIOUS ORGANISMS AND HUMAN HOST PROTEINS

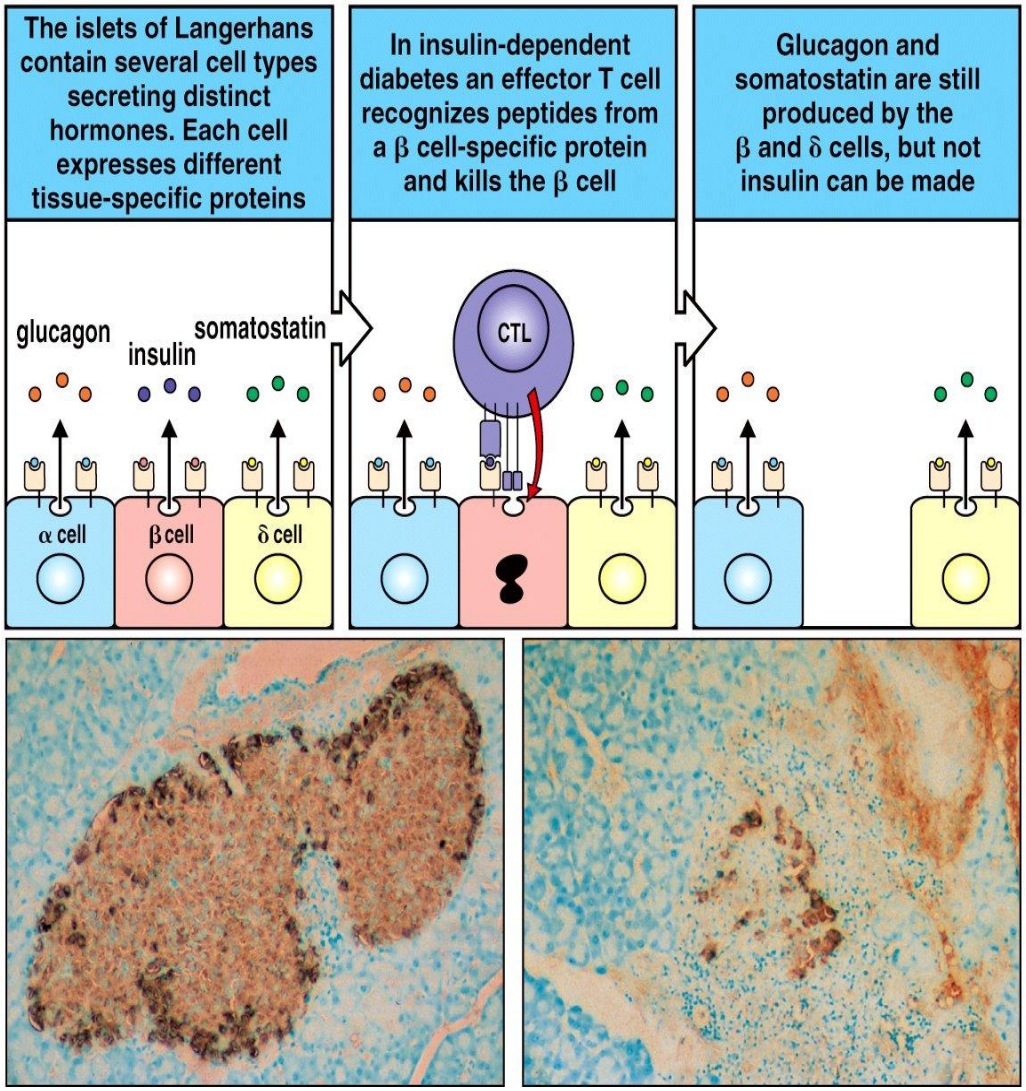
Protein*	Residue†	Sequence†
Human cytomegalovirus IE2	79	P D P L G R P D E D
HLA-DR molecule	60	V T E L G R P D A E
Poliovirus VP2	70	S T T K E S R G T T
Acetylcholine receptor	176	T V I K E S R G T K
Papilloma virus E2	76	S L H L E S L K D S
Insulin receptor	66	V Y G L E S L K D L
Rabies virus glycoprotein	147	T K E S L V I I S
Insulin receptor	764	N K E S L V I S E

SYMPATHETIC OPHTHALMIA

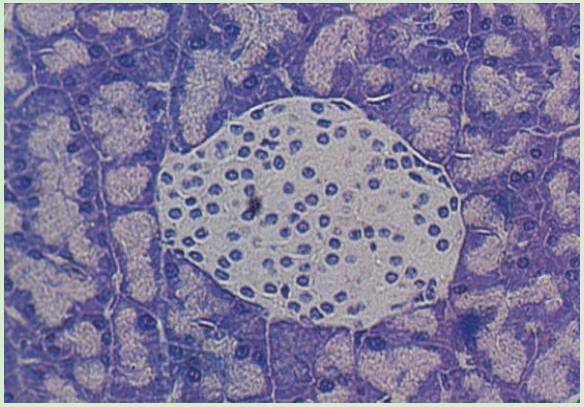


TYPE I DIABETES

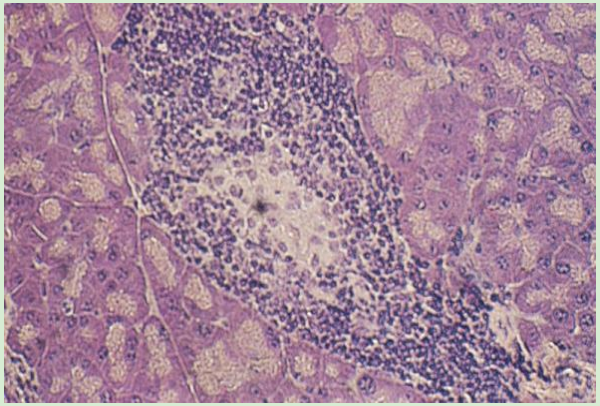
Pancreatic β cells express abnormally high levels of MHC I and MHC II



Normal Pancreas



Pancreas with Insulitis



Hormonal Factors

- About 90% autoimmune diseases occur in women, but the causes unknown.
- In animals models estrogen can induce B cells to enhance formation of anti-DNA antibodies.
- SLE (Systemic Lupus Erythematous) either appears or exacerbates during pregnancy.

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 .

REMEMBER

- Immunological Tolerance against self antigens is what keeps us healthy.
- Autoimmune diseases occur when immunological tolerance to self antigens in our body is disturbed.
- Certain autoimmune diseases are more common in female.