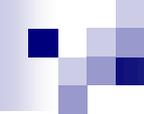




# Autoimmunity



# Outline

- History
- Definition
- Disease states
- Causes
- Immunopathology
- Diagnosis
- Treatment
- Mouse Models of human disease

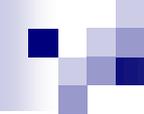
# Autoimmunity Origins

## **Horror autotoxicus:**

Literally, the horror of self-toxicity.

A term coined by the German immunologist Paul Ehrlich (1854-1915) to describe the body's innate aversion to immunological self-destruction.





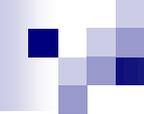
# History Continued

This concept of autoimmunity as the cause of human illness is relatively new, and it was not accepted into the mainstream of medical thinking until the 1950s and 1960s.



# Autoimmunity

- Basically means immunity to self
- A condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue.



# The “Immunology Definition”

# Failure of immune tolerance

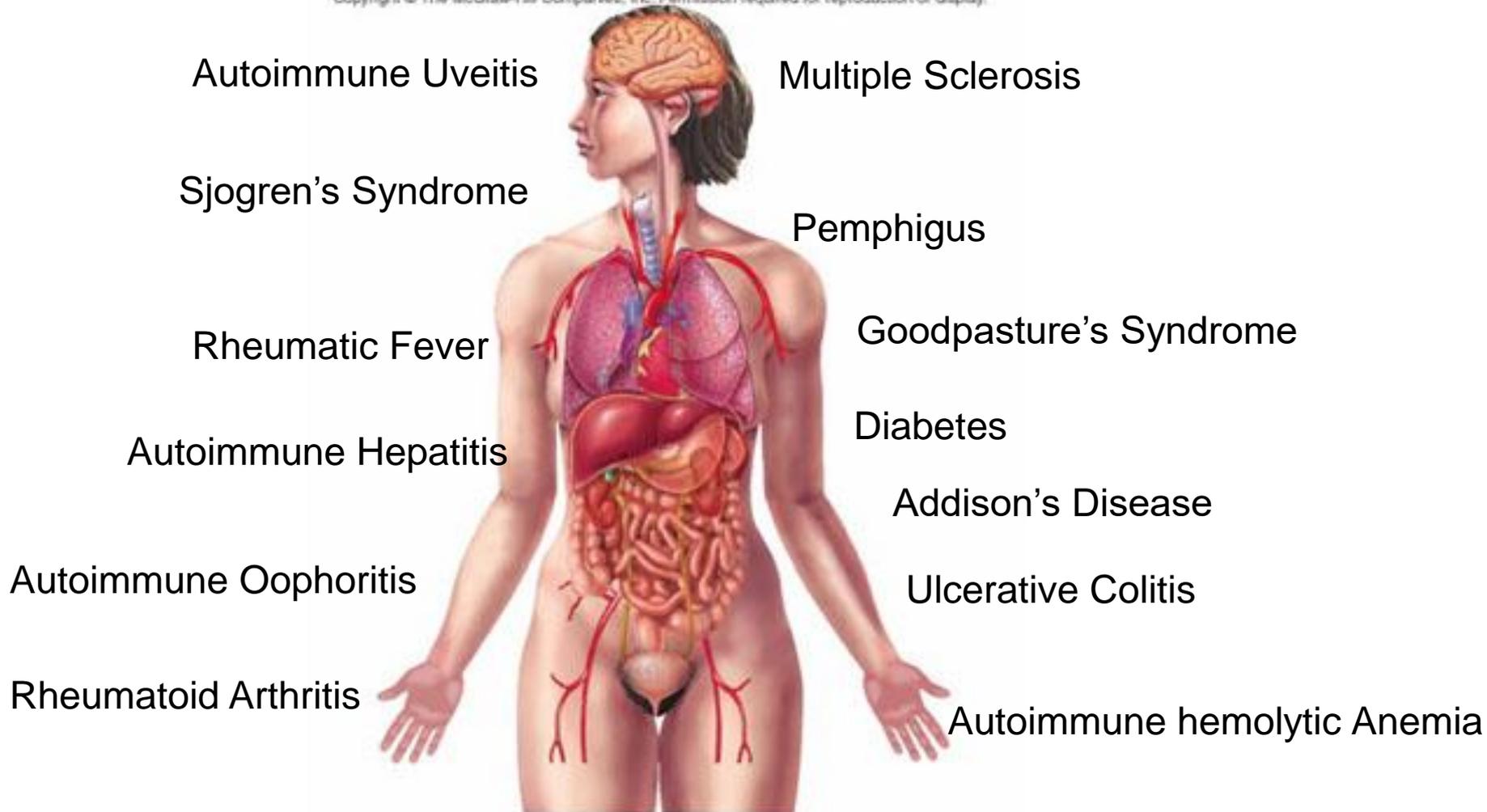
<b>Layers of self-tolerance</b>		
<b>Type of tolerance</b>	<b>Mechanism</b>	<b>Site of action</b>
Central tolerance	Deletion Editing	Thymus Bone marrow
Antigen segregation	Physical barrier to self-antigen access to lymphoid system	Peripheral organs (eg, thyroid, pancreas)
Peripheral anergy	Cellular inactivation by weak signaling without co-stimulus	Secondary lymphoid tissue
Regulatory cells	Suppression by cytokines, intercellular signals	Secondary lymphoid tissue and sites of inflammation
Cytokine deviation	Differentiation to T <sub>H</sub> 2 cells, limiting inflammatory cytokine secretion	Secondary lymphoid tissue and sites of inflammation
Clonal exhaustion	Apoptosis post-activation	Secondary lymphoid tissue and sites of inflammation

Figure 13-16 Immunobiology, 6/e. (© Garland Science 2005)

# Pick an organ, any organ . . .

Autoimmunity can affect ANY organ/organ system in the human body

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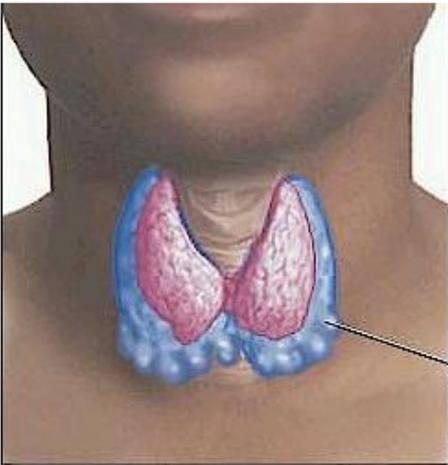
# Autoimmunity Classification

Can be classified into clusters that are either ***organ-specific*** or ***systemic***

Organ-specific autoimmune diseases	Systemic autoimmune diseases
Type I diabetes mellitus	Rheumatoid arthritis
Goodpasture's syndrome	Scleroderma
Multiple sclerosis	Systemic lupus erythematosus Primary Sjögren's syndrome Polymyositis
Graves' disease Hashimoto's thyroiditis Autoimmune pernicious anemia Autoimmune Addison's disease Vitiligo Myasthenia gravis	

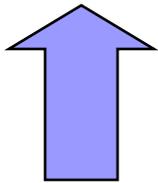
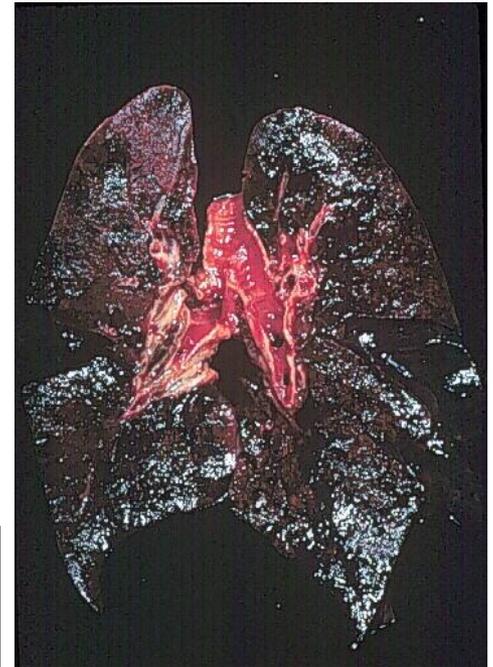
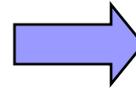
Figure 13-1 Immunobiology, 6/e. (© Garland Science 2005)

# Examples of Organ Specific



Enlarged, inflamed hypofunctioning thyroid (goiter)

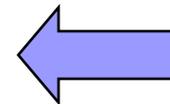
Lungs of a patient with Goodpasture's



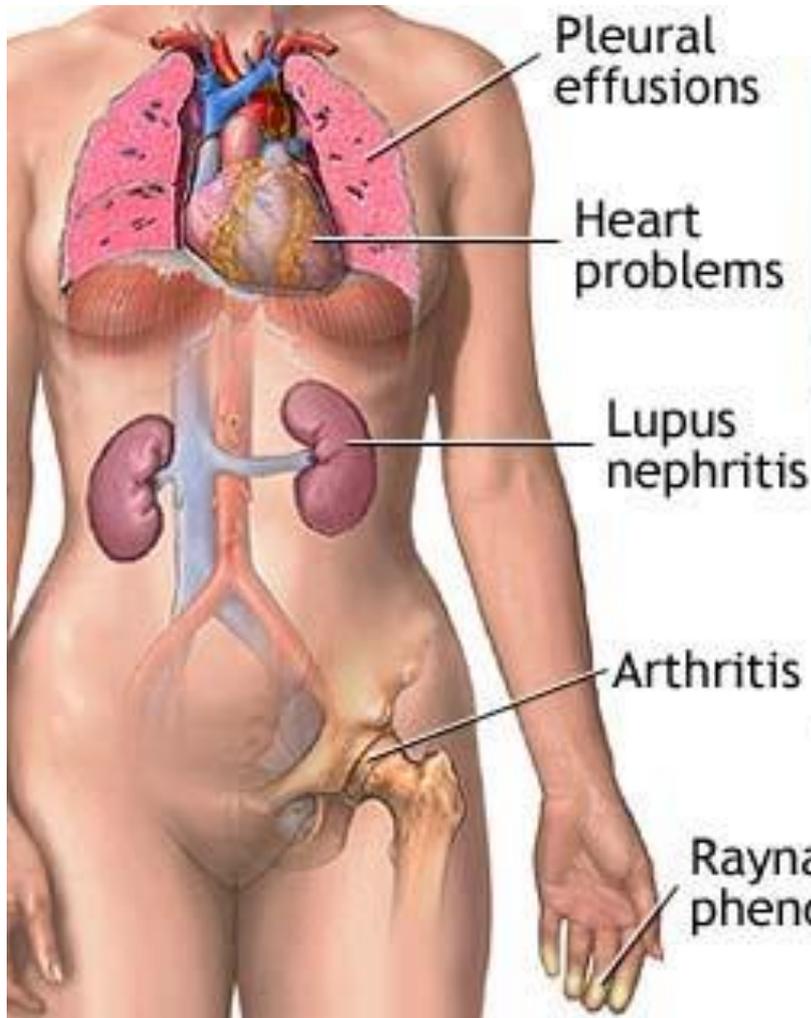
Hashimoto's disease (thyroiditis)



Vitiligo



# Examples of Systemic Autoimmunity



Butterfly rash



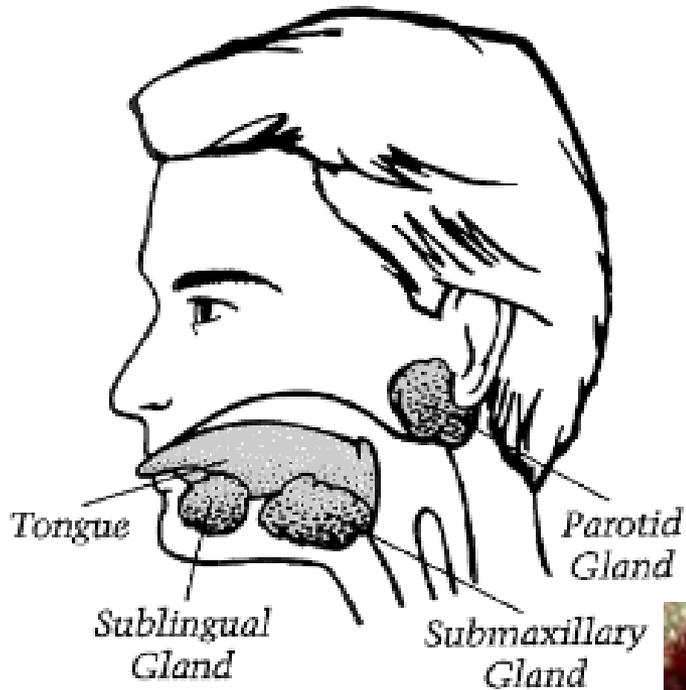
# SLE

Symptoms of systemic lupus erythematosus may vary widely with the individual

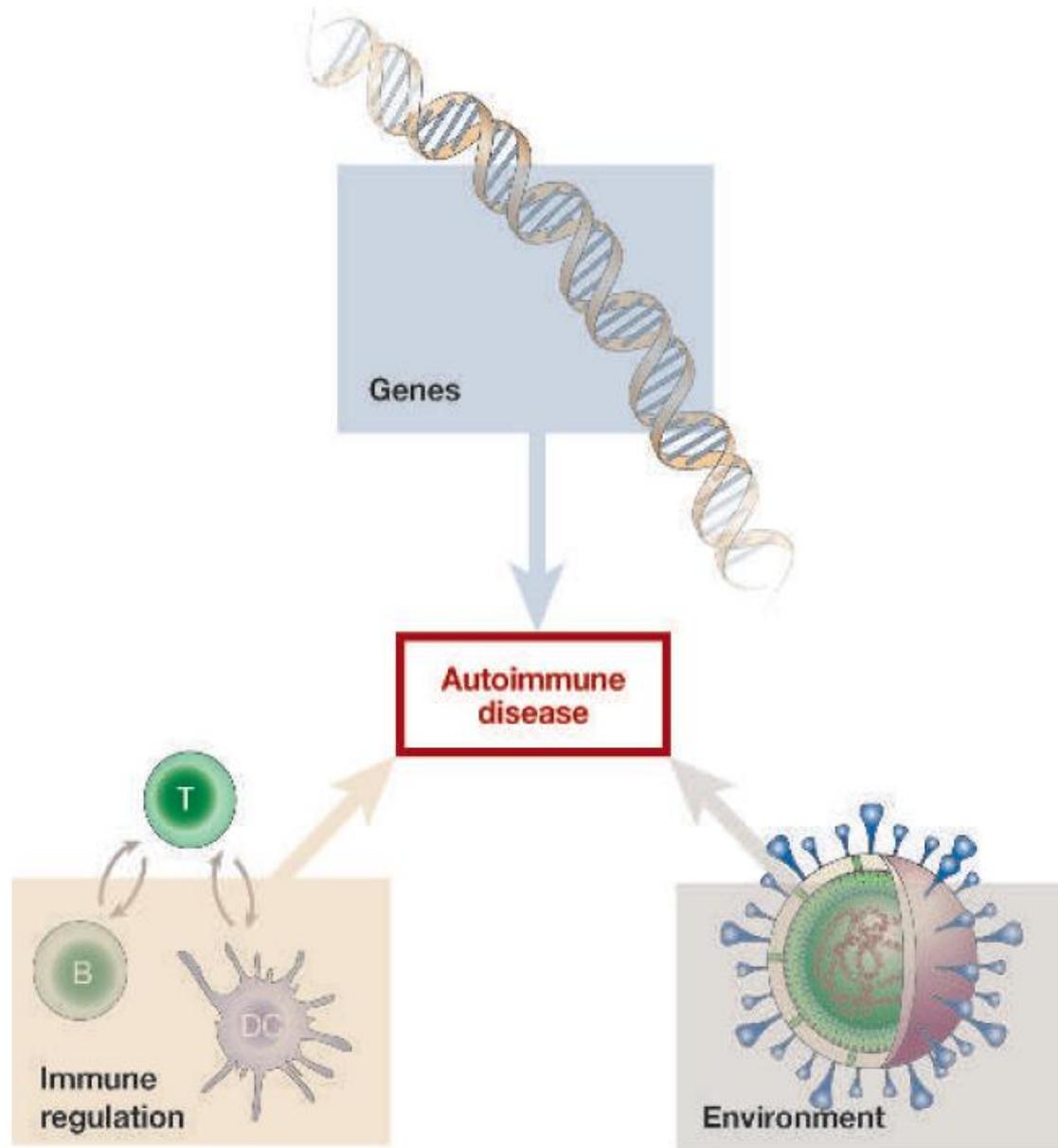


# Examples of Systemic Autoimmunity

## Sjogren's Syndrome



# Causes of Autoimmunity



# Genes and Autoimmunity

- The concept that a single gene mutation leads to a single autoimmune disease is the **EXCEPTION** not the rule.
- Because of this autoimmune diseases are generally classified as *complex* diseases as there is not a single “pinpoint-able” gene

# Exceptions to the Rule – Simple Genetic Autoimmune Illnesses

Disease	Gene	Mechanism
<b>APS-1</b> (Autoimmune polyglandular syndrome type 1)	<i>AIRE</i>	Decreased expression of self-antigens in the thymus, resulting in a defect in negative selection
<b>IPEX</b> (Immunodysregulation, polyendocrinopathy, enteropathy, X-linked)	<i>FOXP3</i>	Decreased generation of Tregs
<b>ALPS</b> (autoimmune lymphoproliferative syndrome )	<i>FAS, FASL</i>	Failure of apoptotic death of self reactive T or B cells

# Complex Disease and Genetics

There have been numerous disease associated genes or disease “susceptibility” genes linked to autoimmunity

## Associations of HLA serotype with susceptibility to autoimmune disease

Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5

Figure 13-20 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

# Complex Doesn't even begin to describe Autoimmune genetics

Table 1  
Altered gene expression patterns reported in autoimmune diseases

Diseases	Cell receptors adhesion molecules	Inflammatory molecules growth factors	Apoptosis/cell remodeling	Disease specific gene expression	Ref.
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SLE

MS

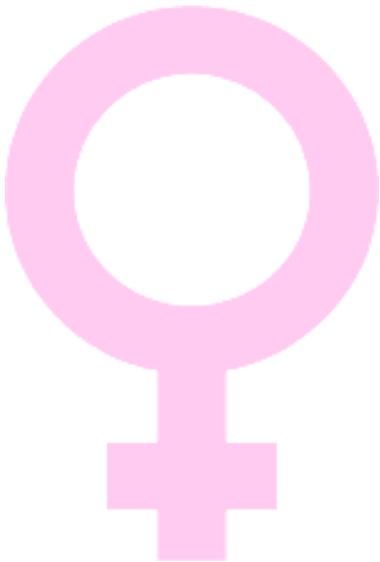
*Active plaques*

*Chronic plaques*

RA

# Environment

- Pathogens, drugs, hormones, and toxins are just a few ways that the environment can trigger autoimmunity



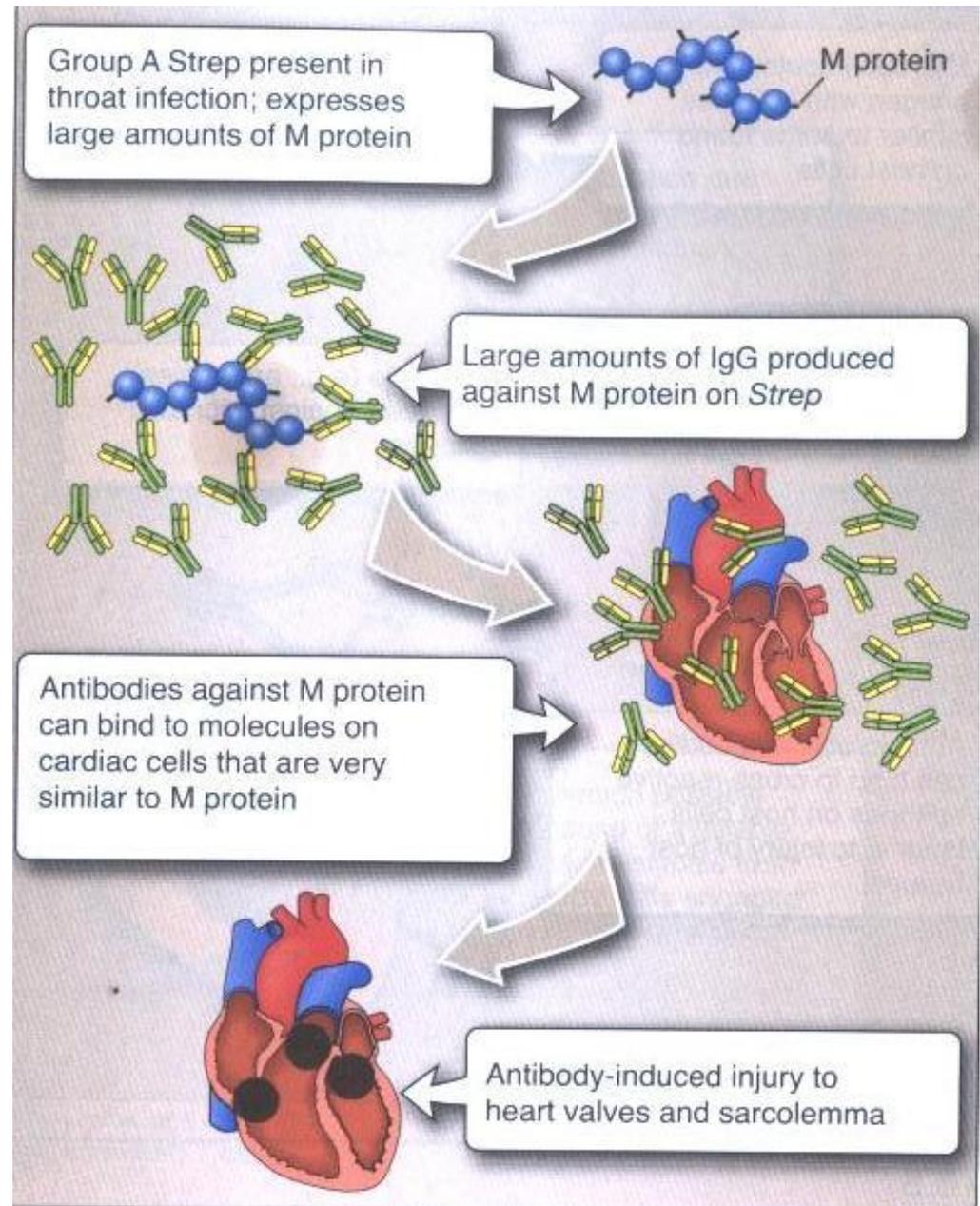
# Pathogens

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 ISSN 1080-0549/07/32(1):111-118/\$30.00  
 ISSN Online 1559-0267

Table 1  
 Main Examples of Molecular Mimicry Between a Pathogen and Auto-Immune Disease

Disease	Host antigens	Pathogens	References
Chagas' cardiomyopathy	Ribosomal protein 23 kD, myosin, B13 protein, Cha-peptide	<i>Trypanosoma cruzi</i>	3,4,8,9
Rheumatic fever	Cardiac myosin, tropomyosin laminin, vimentin, actin, keratin, N-acetyl-glucosamine	<i>Streptococcus pyogenes</i>	10-12
Myasthenia gravis	Acetylcholine receptor, neurofilaments	Herpes virus, <i>Hemophilus influenzae</i>	3,13,14
Multiple sclerosis	Myelin basic protein	Corona, measles, mumps, EBV, herpes	4,15-17
Guillain-Barré	Gangliosides, lipo-oligosaccharide	<i>Campylobacter jejuni</i>	18,19
Type 1 diabetes mellitus	Islet antigens:GAD 65, proinsulin carboxypeptidase H	Coxsackievirus B, Rotaviruses, Herpes, hepatitis C, rhino-, hanta retroviral	18,19
Ankylosing spondylitis	HLA-B27, type I, II, IV collagen	<i>Klebsiella pneumoniae</i> , chlamydia	4,22,23
Antiphospholipid syndrome	$\beta_2$ -glycoprotein-I	<i>Hemophilus influenzae</i> , <i>Neisseria gonorea</i> , Tetanus toxin, CMV	24,25
Systemic lupus erythematosus	Ro 60 kD, NMDA, dsDNA	EBV pneumococcal polysaccharide	26-29

Rheumatic fever is a classic example of molecular mimicry



# Drugs and Toxins

## ■ Drugs

- Examples: Procainamide (Pronestyl)
- Drug induced lupus

## ■ Toxins

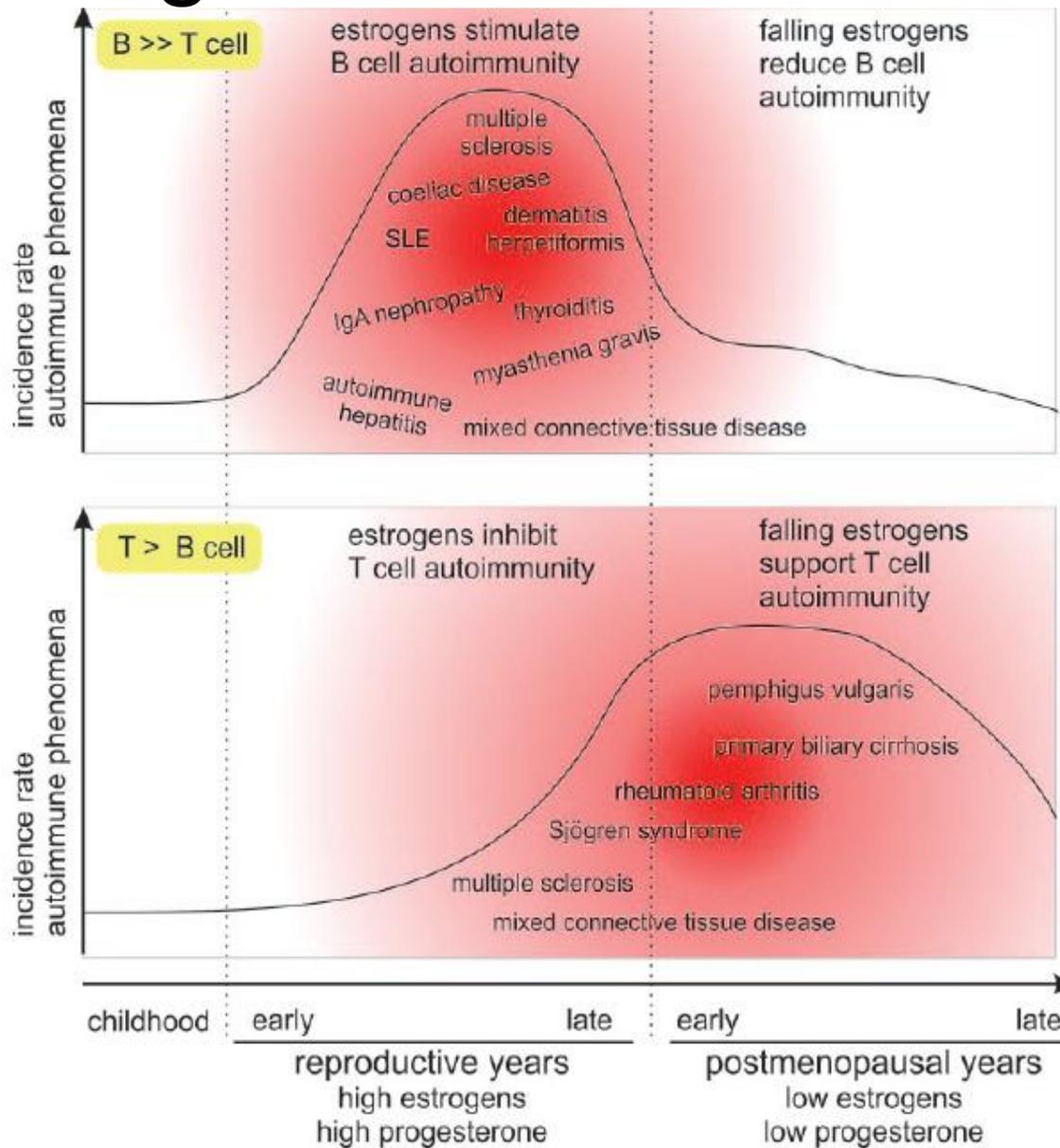
- Examples: Toxic Oil Syndrome
- Occurred in Spain in 1981 after people ate contaminated olive oil.
- People developed unique illness marked by lung disease, eosinophilia, and excessive IgE

# Hormones

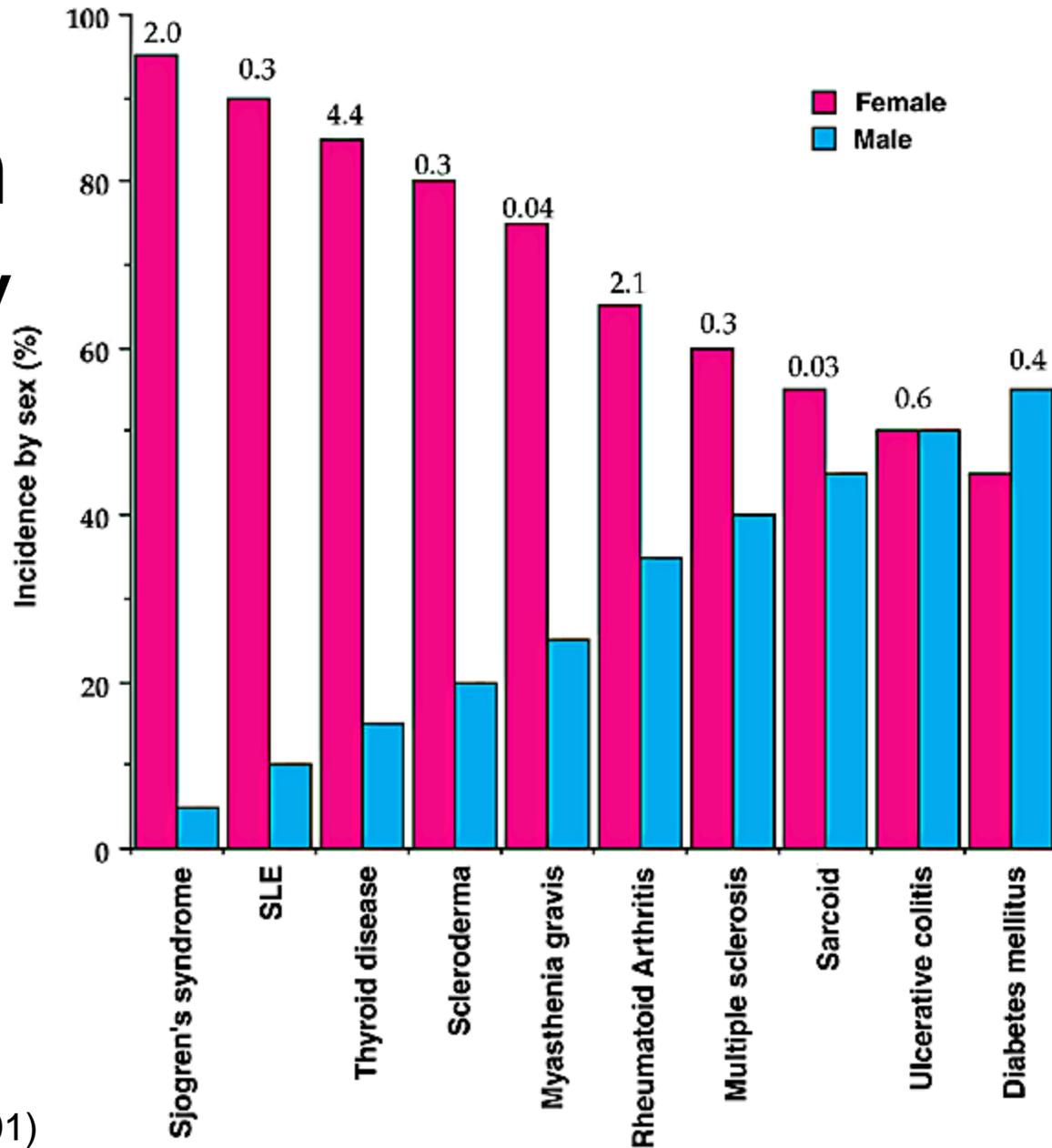
- Females are much more likely to develop autoimmune illness
- Rise in hormones associated with pregnancy may even cause abortion of the fetus (RSA)
- Endometriosis and preeclampsia are both thought to be autoimmune in nature

Hypothesis: estrogen response elements (EREs) in several genes

# Estrogens and Autoimmunity

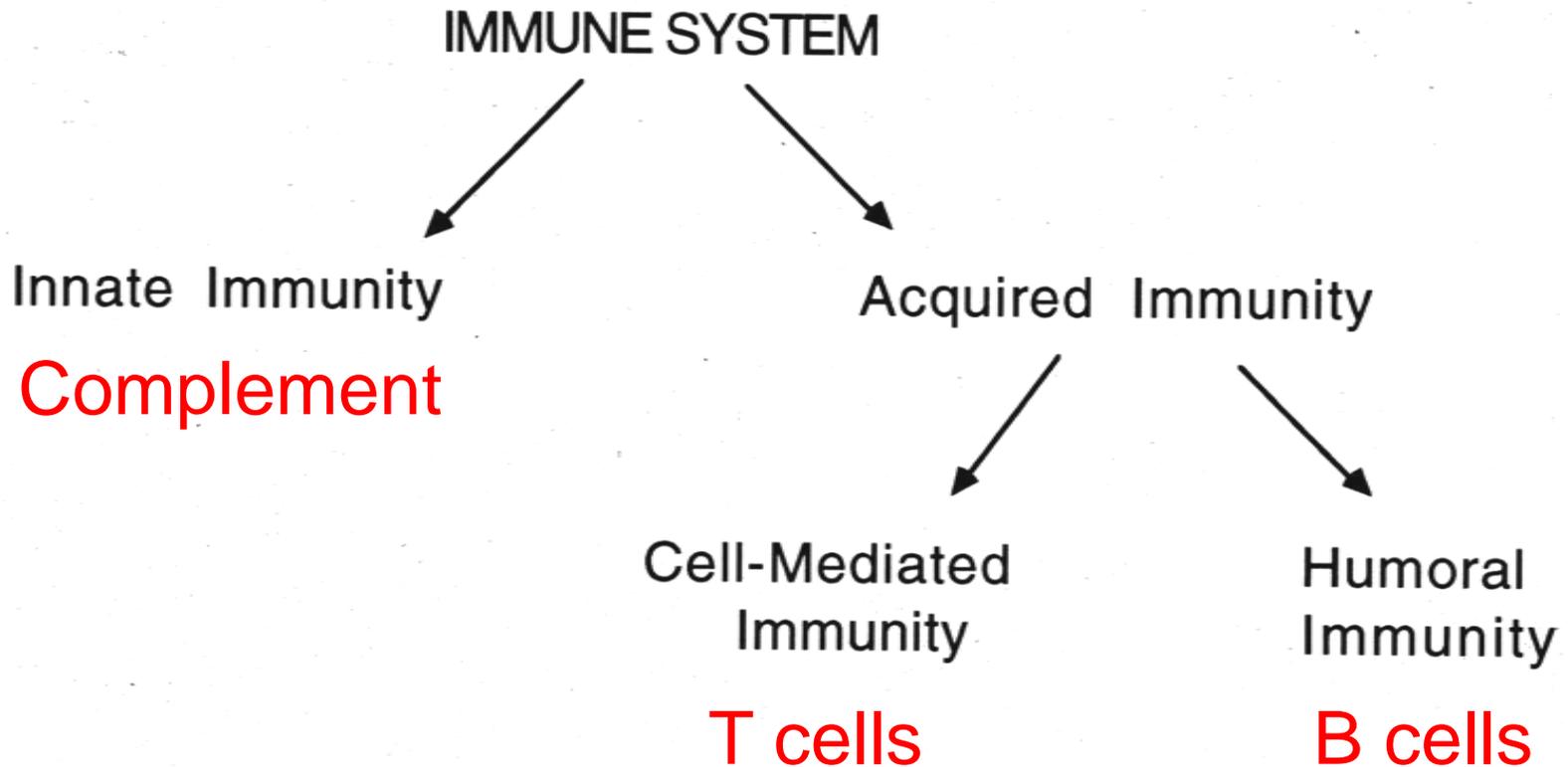


# Sex differences in autoimmunity



# Immune Regulation

A defect in any arm of the immune system can trigger autoimmunity

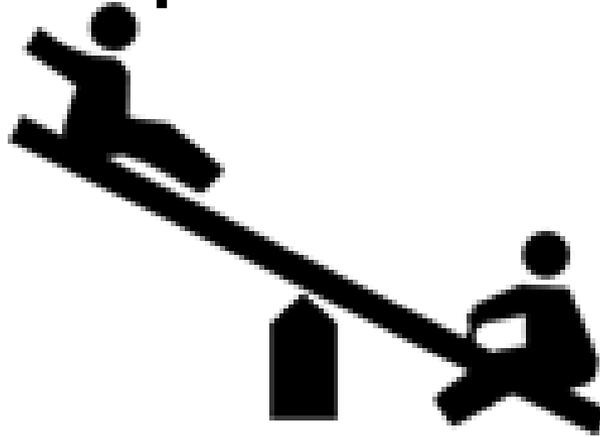


# Complement Deficiencies

- CD59 or CD55 –
  - Paroxysmal nocturnal hemoglobinuria
  - autoimmune hemolytic anemia
  - autoimmune thrombocytopenia
  - lupus lymphopenia
  
- Deficiencies in the classical complement pathway renders pts more likely to develop immune complex diseases
  - SLE
  - RA



# The Complement See-Saw



- The complement system is a mediator in both the pathogenesis and prevention of immune complex diseases
- It has a protective effect when functioning in moderation against pathogens; at the same time, the inflammation promoted by complement activation can result in cellular damage when not kept in check.

# B or T? That is the question?

Autoimmunity is hard to classify as strictly a B cell or T cell mediated disease as multiple arms of the immune system are involved



# Myasthenia Gravis

Disease marked by progressive weakness  
and loss of muscle control

Classified as a “B cell” Disease

Autoantibodies against nicotinic  
acetylcholine receptors



# Diabetes

Disease in which the body does not produce or properly use insulin

“ T cell” Disease

T cells attack and destroy pancreatic beta cells

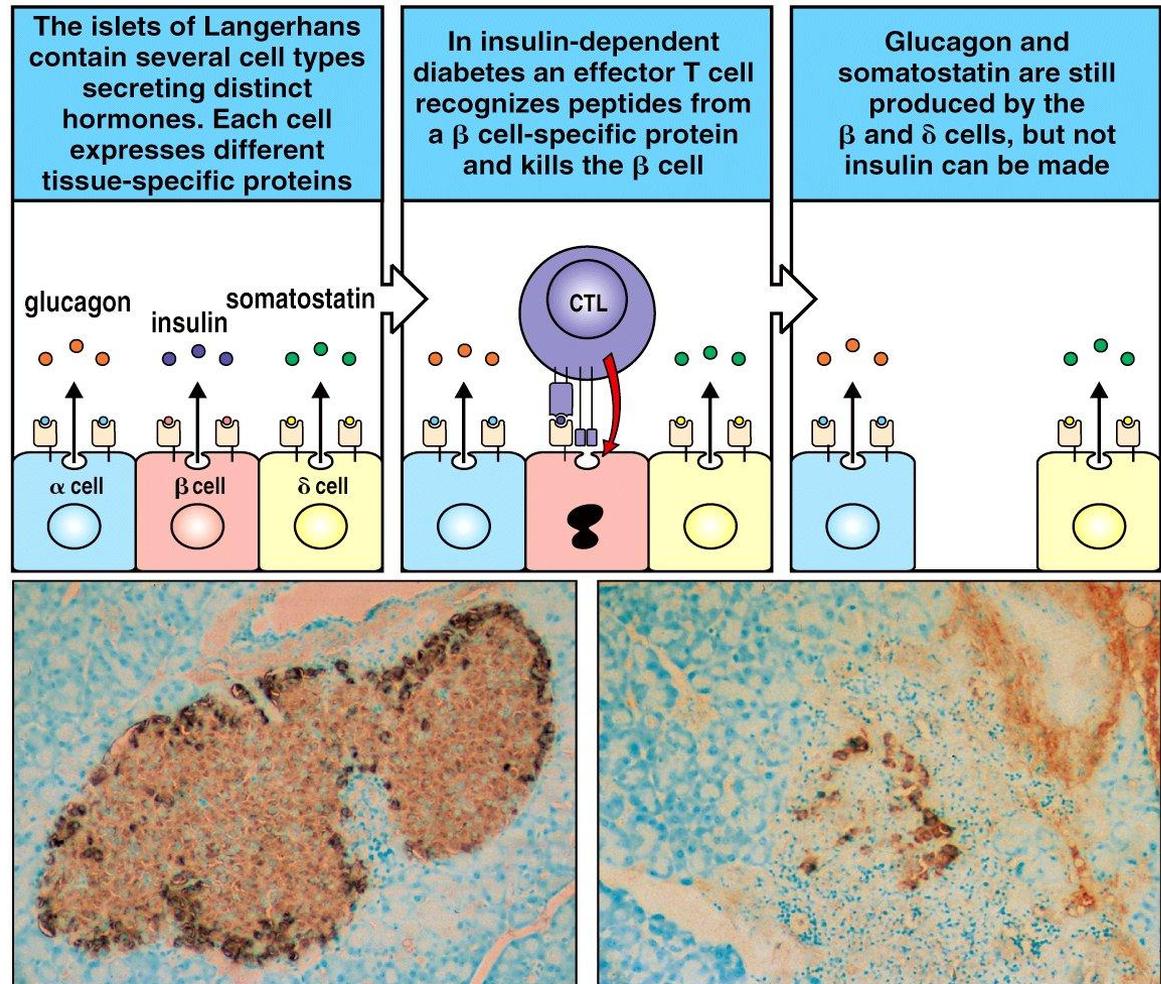


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

# Multiple Sclerosis

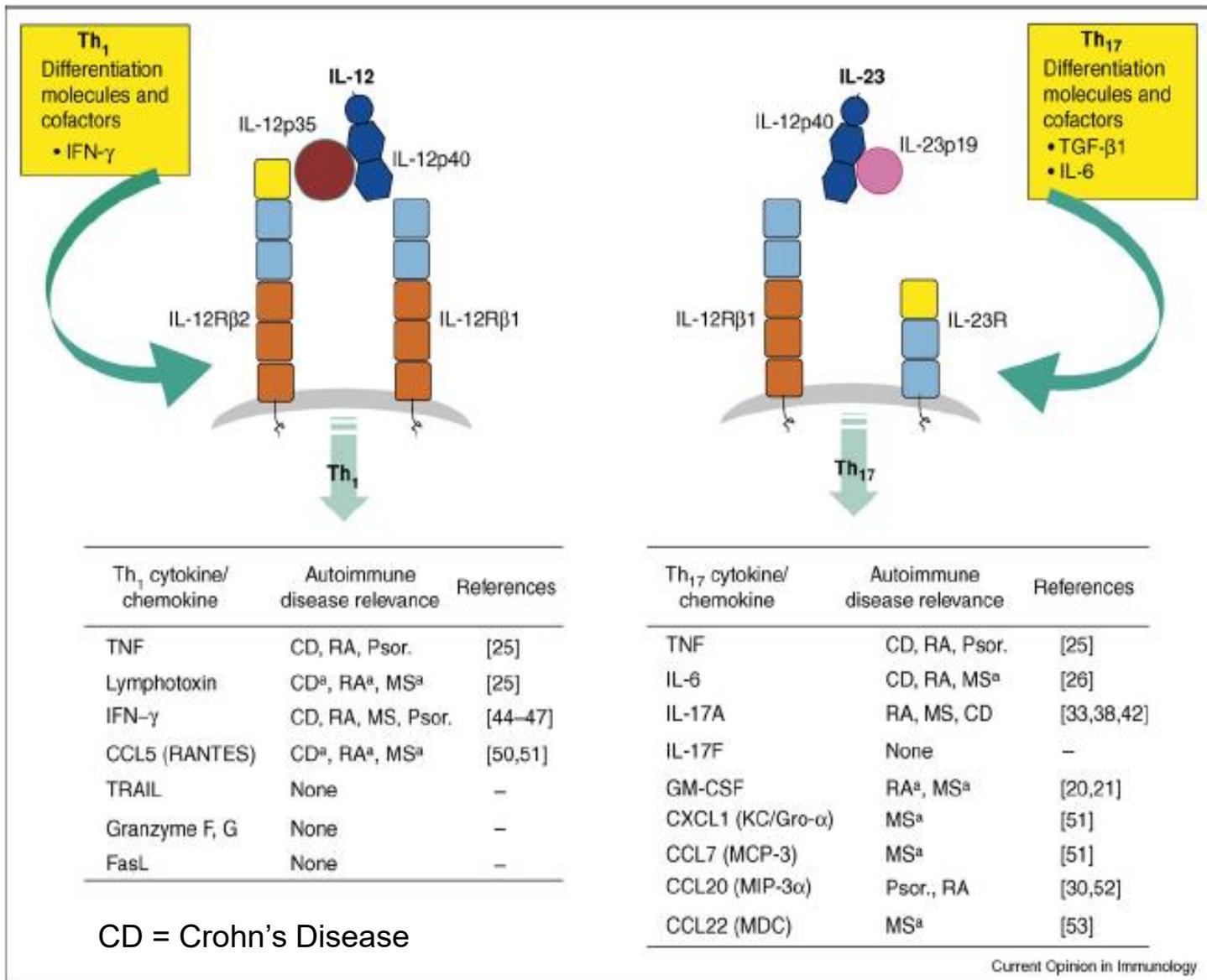
Central nervous system  
(brain and spinal cord)



In multiple sclerosis the myelin sheath, which is a single cell whose membrane wraps around the axon, is destroyed with inflammation and scarring

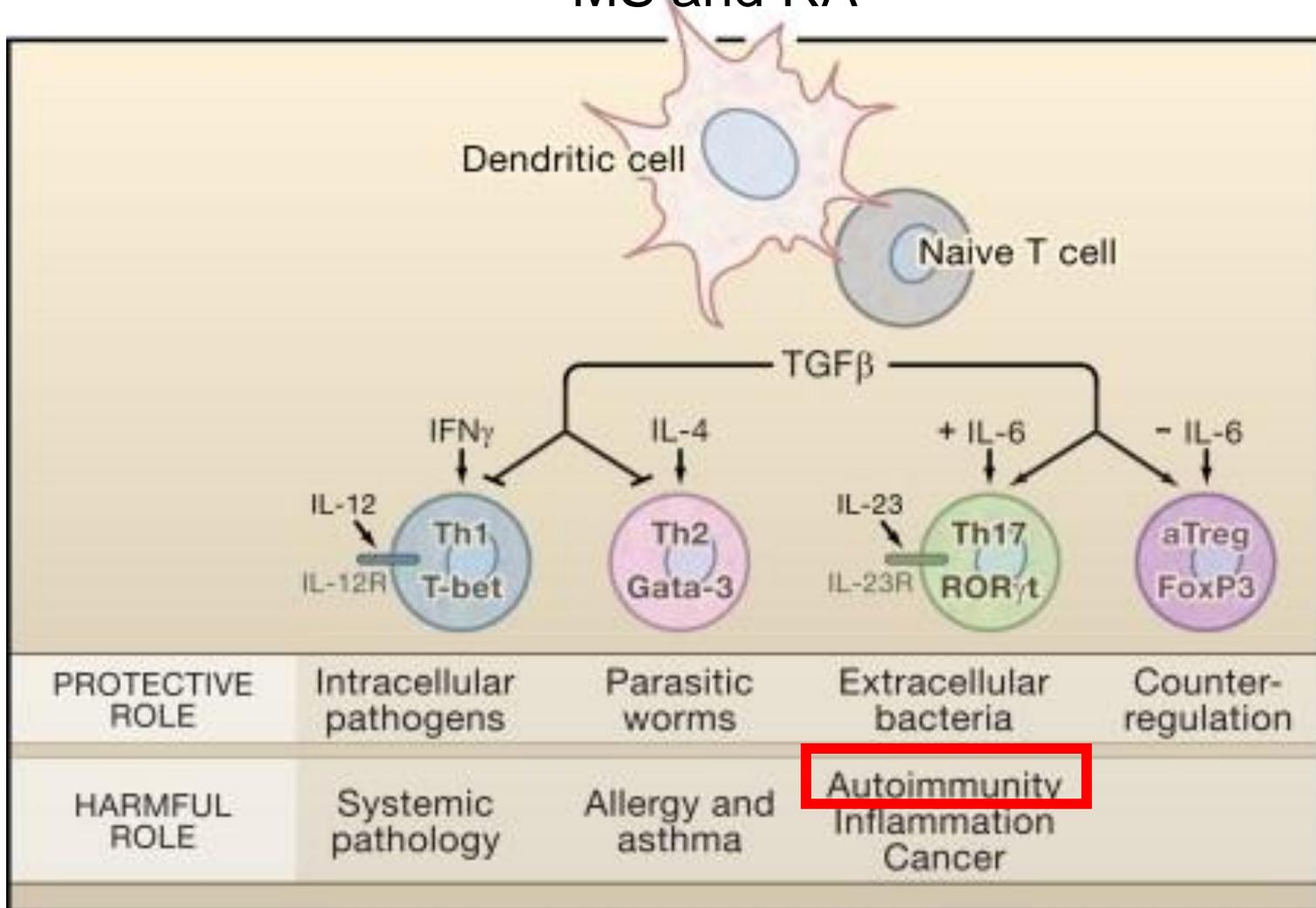
**MS patients can have autoantibodies and/or self reactive T cells which are responsible for the demyelination**

# Cytokine Dysregulation in Autoimmunity



# IL-17: The Autoimmunity Cytokine?

IL-17 KO mice – less susceptible to autoimmunity – especially MS and RA



# Symptoms

- Initial diagnosis may be missed in patients as diseases present with general symptoms
  - Fever, muscle ache, fatigue, joint pain
- Disease specific manifests
  - SLE – rash
  - Sjogren's – dry mouth, dry eyes



# Diagnosis

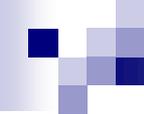
- General tests

- C Reactive Protein
- Autoantibody titers (anti DNA, anti phospholipids, etc)
- Presence of Rheumatoid Factor

- Disease specific tests

- Neurological exam – MS
- Fasting glucose - Diabetes





# Treatment

The key to treating  
autoimmunity is  
immunomodulation

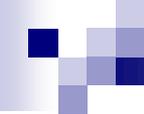
# Treatment Options

- Anti-inflammatory drugs
  - NSAIDS, Corticosteroids
- Immunosuppressant drugs
  - Methotrexate
- Radiation
- Plasmapheresis
- Cell Blocking Reagents
  - aCD20 (Rituxan)
  - aCD3 (Teplizumab)
- Cytokine Blocking Reagents
  - TNF (Humira, Enbrel)



# Mouse Models

Human Disease	Mouse Model
RA	Collagen Induced Arthritis (CIA)
MS	Experimental Autoimmune Encephalitis (EAE)
Ulcerative Colitis (UC)	Dextran Sodium Sulfate induced Colitis (DSS)
Diabetes	Non Obese Diabetic (NOD)
Lupus	MRL <sup>lpr</sup> (Lpr = lupus prone)



\*\*\*\*\*Remember\*\*\*\*\*

Autoimmunity is a failure of tolerance!

Knowing the tolerance mechanisms the immune system uses, will help you better understand autoimmune diseases!

## Failure of tolerance and disease Outcome

Type of tolerance	Mechanism
Central tolerance	Deletion Editing
Antigen segregation	Physical barrier to self-antigen access to lymphoid system
Peripheral anergy	Cellular inactivation by weak signaling without co-stimulus
Regulatory cells	Suppression by cytokines, intercellular signals
Cytokine deviation	Differentiation to T <sub>H</sub> 2 cells, limiting inflammatory cytokine secretion
Clonal exhaustion	Apoptosis post-activation

Figure 13-16 Immunobiology, 6/e. (© Garland Science 2005)