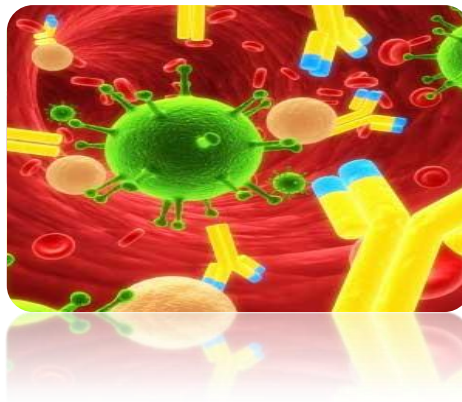


AUTOIMMUNITY

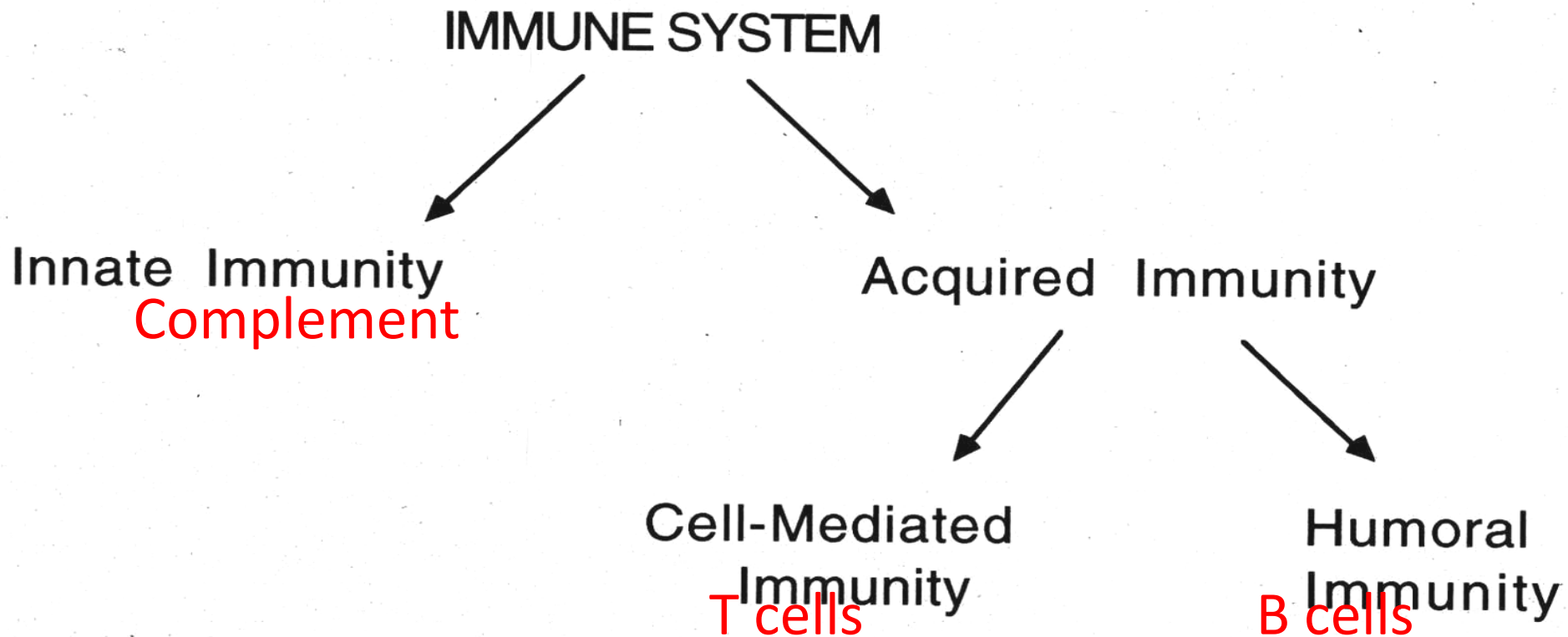
basics

Dr.T.V.Rao MD



Immune Regulation

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



DISORDERS OF THE IMMUNE SYSTEM

*

Immunodeficiency

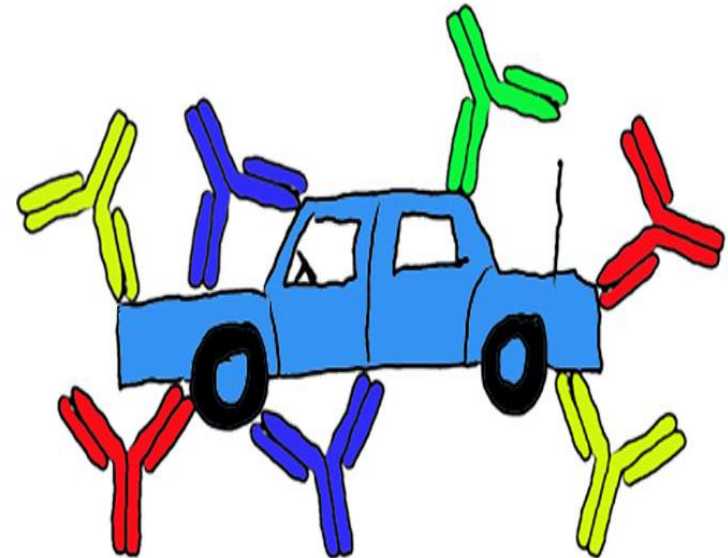
- **Too little**

* Hypersensitivity

- **Too much**

* **Autoimmunity**

- **Misdirected**



Autoimmunity

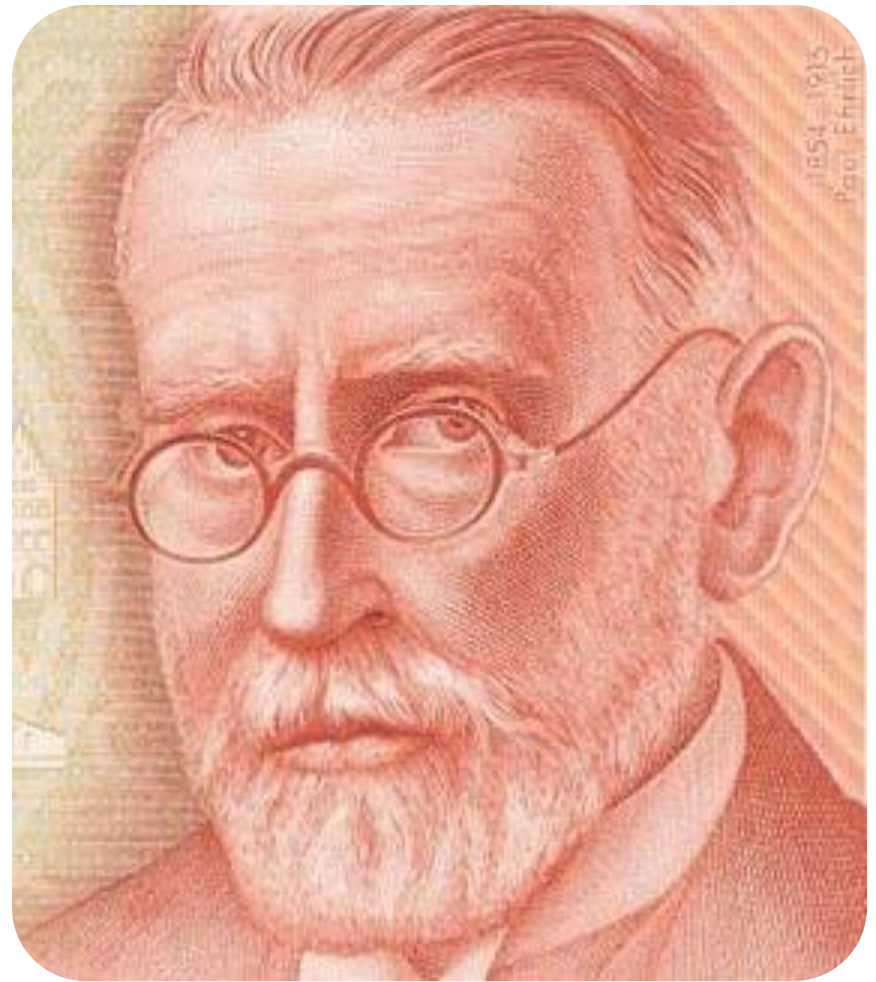
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Autoimmunity Origins

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.



Autoimmunity is

- **Autoimmunity** is the failure of an organism in recognizing its own constituent parts as *non self*, which allows an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an autoimmune disease. Autoimmunity is often caused by a lack of germ development of a target body and as such the immune response acts against its own cells and tissues.

Autoimmunity :

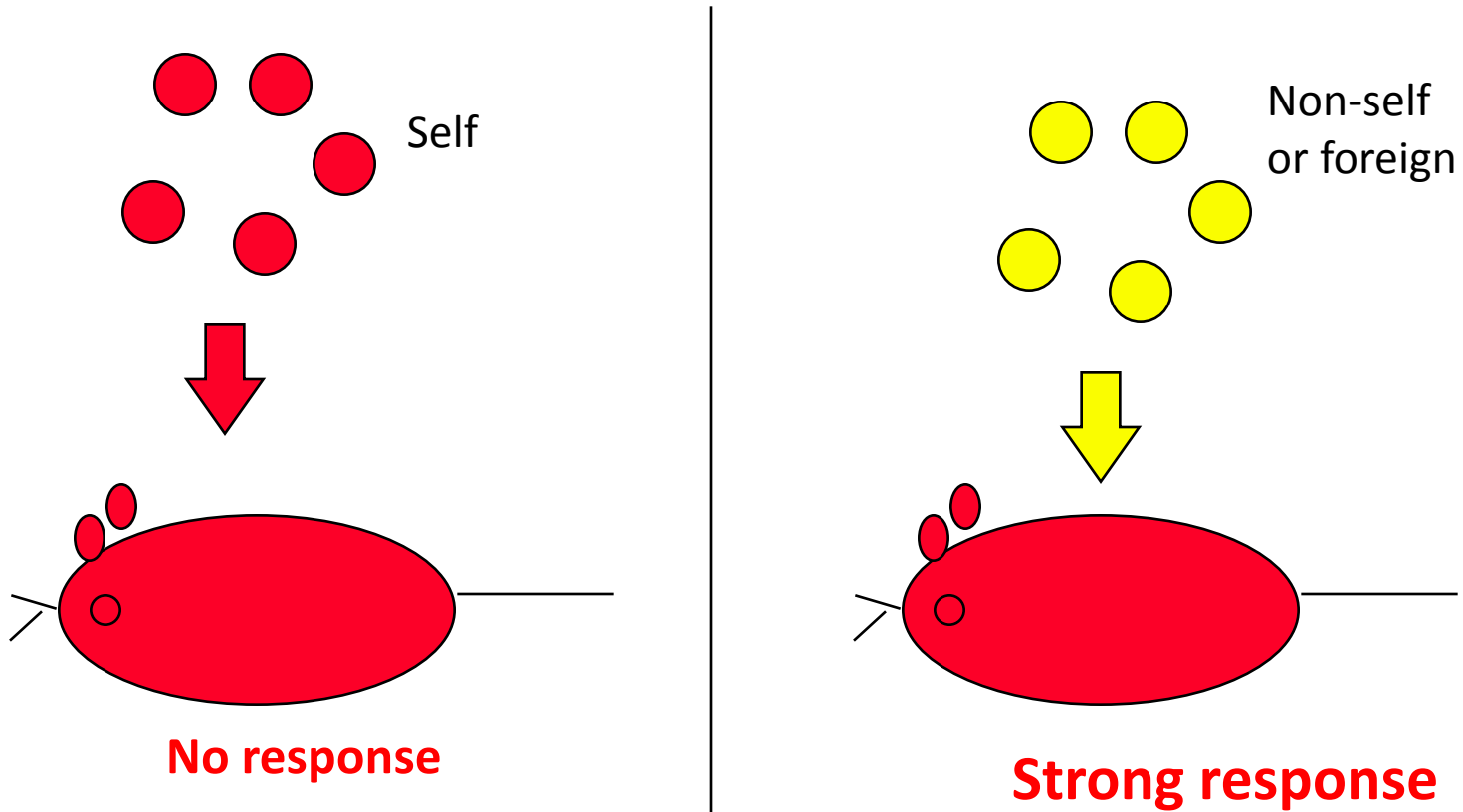
General principles and observations

- **Autoimmunity results from a failure or breakdown of the mechanisms normally responsible for maintaining self-tolerance in B cells, T cells, or both.**
- *The major factors that contribute to the development of autoimmunity are genetic susceptibility and environmental triggers, such as infections.*
- *Autoimmune diseases may be either systemic or organ specific.*
- *Various effector mechanisms are responsible for tissue injury in different autoimmune diseases.*
- *Epitope spreading: Autoimmune reactions initiated against one self antigen that injure tissues may result in the release and alterations of other tissue antigens, activation of lymphocytes specific for these other antigens, and exacerbation of the disease.*

AUTOIMMUNE DISEASES

- A Group of 60 to 80 chronic inflammatory diseases with genetic predisposition and environmental modulation
- Prevalence of 5% to 8% in US
- Prevalence is greater for females than males
 - 75% of cases
 - 4th largest disease class in women

Self-Nonself discrimination

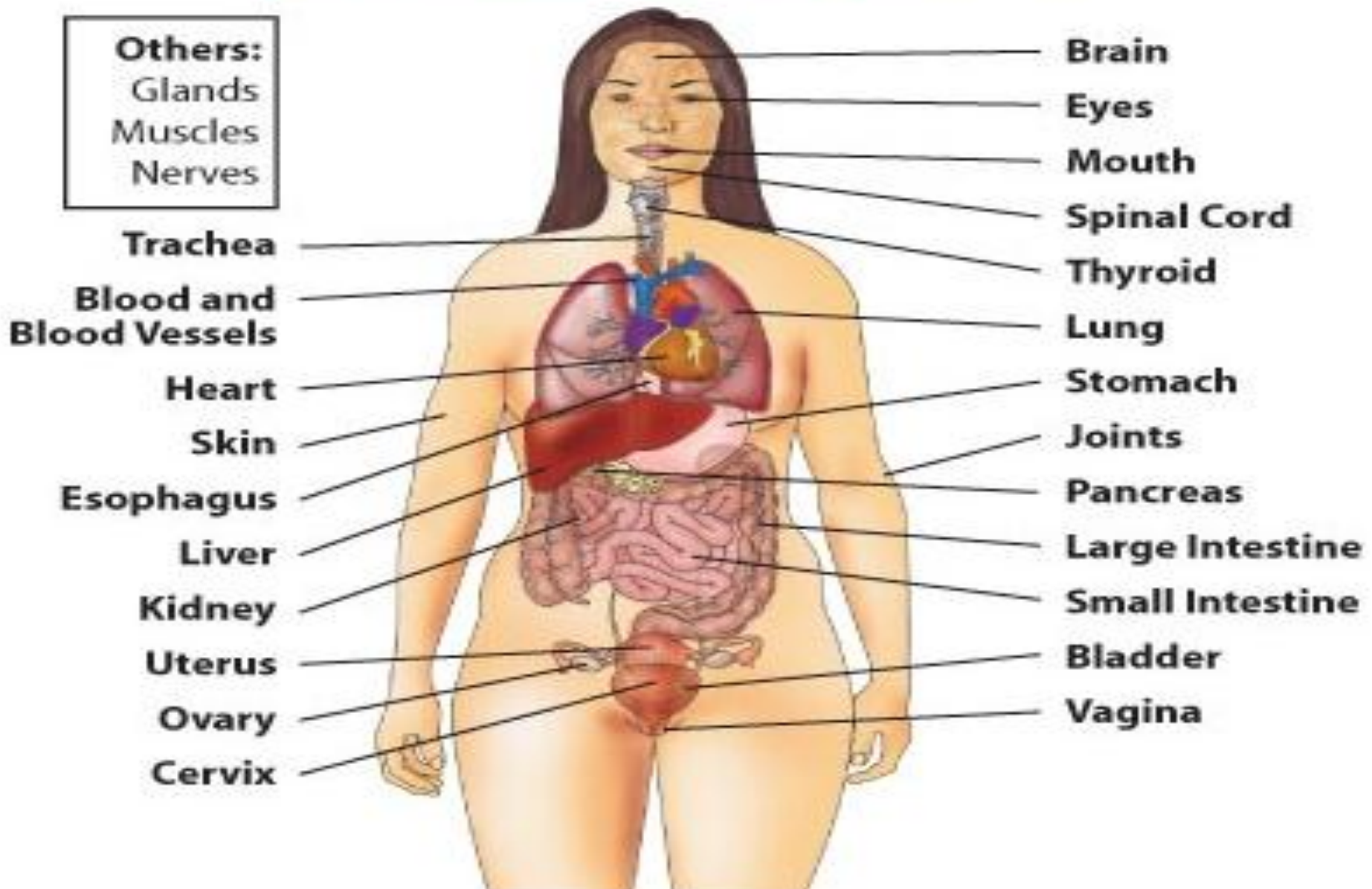


Autoimmunity

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



Body Parts That Can Be Affected by Autoimmune Diseases



Autoimmunity Classification

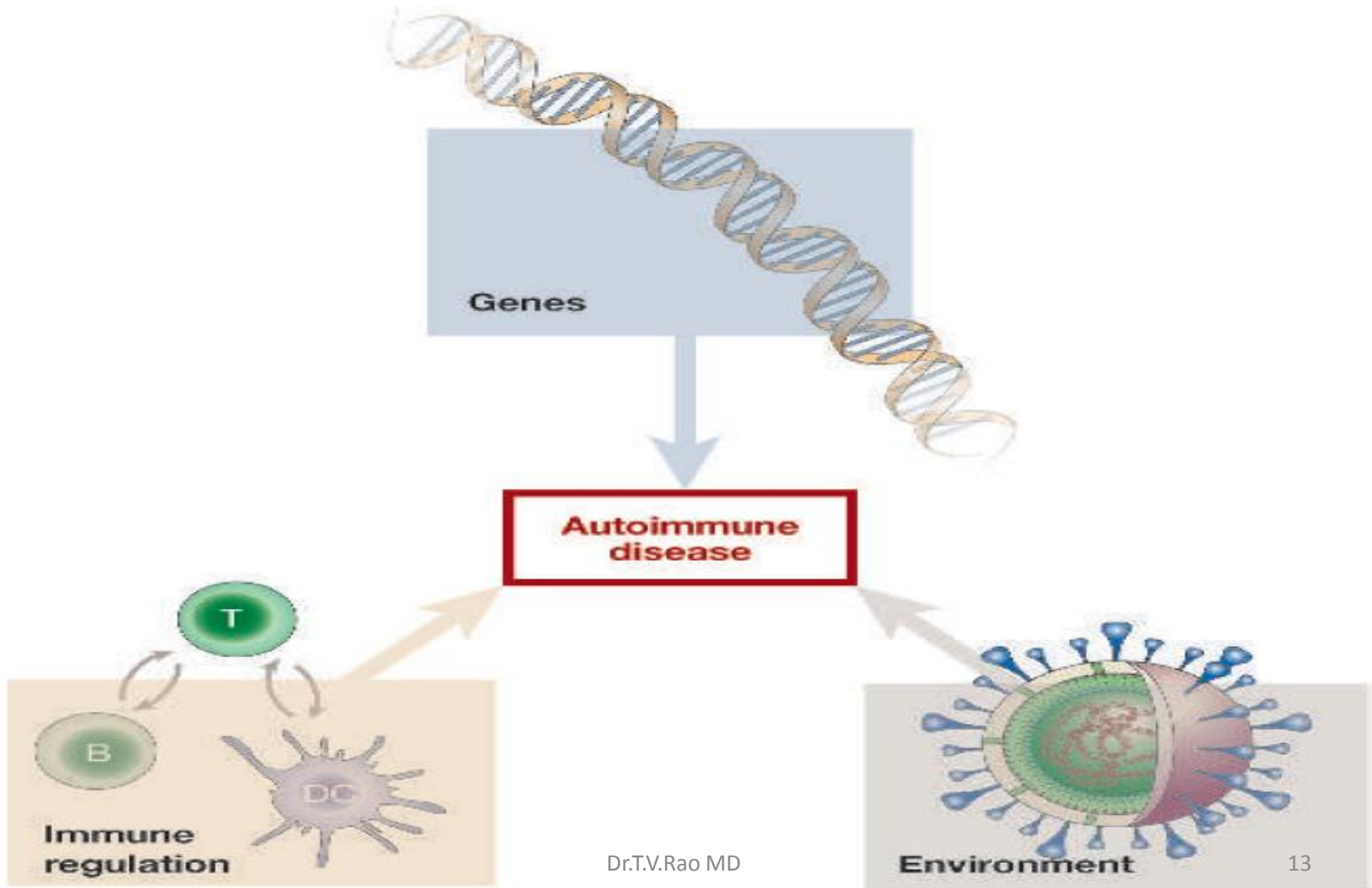
Can be classified into clusters that are either
organ-specific or systemic

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	

Major examples

- Prominent examples include Coeliac disease, diabetes mellitus type 1 (IDDM), systemic lupus erythematosus (SLE), Sjögren's syndrome, Churg-Straus Syndrome, Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purpura, rheumatoid arthritis (RA) and allergies.

Causes of Autoimmunity



Autoimmunity and Transplantation

- Autoimmunity is a destructive immune response against self antigens (how does this compare to hypersensitivities?)
- Once started, autoimmune diseases are hard to stop
Severity ranges from minor to lethal
- **Ehrlich predicted autoimmunity and called it *horror autotoxicus***

Mechanisms hypothesized to be involved in the breakdown of tolerance

- **Failure to delete auto reactive lymphocytes**
- Central tolerance failure
- Peripheral tolerance failure
- **Molecular mimicry**
- Abnormal presentation of self antigens
- Aberrant expression of major histocompatibility complex class II molecules
- Coupling of self and nonself antigens
- Overproduction of self antigens
- Disclosure of cryptic T-cell epitopes
- Release of sequestered self antigens
- Epitope spreading
- Polyclonal lymphocyte activation

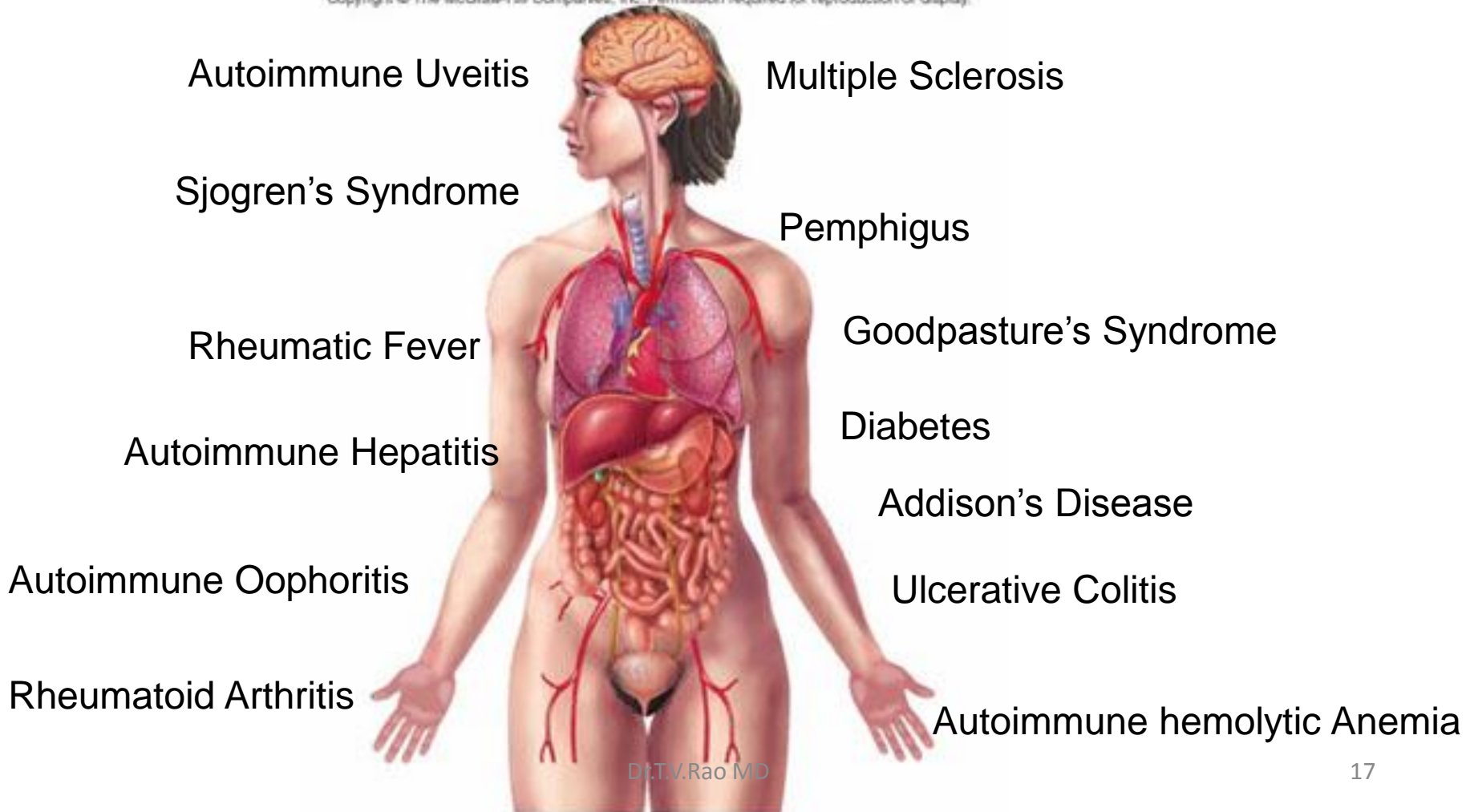
Putting the facts together

- Autoimmunity can be caused by immunological, genetic, viral, drug-induced, and hormonal factors.
- There are 4 immunological mechanisms of autoimmunity.
- All mechanisms cause abnormal B or T cell activation.
- Centrality of the *Ternary Complex*
- Most instances of autoimmune diseases occur with multiple mechanisms, which makes treatment difficult.

Pick an organ, any organ . . .

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

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Some autoimmune diseases may have a genetic component and are triggered by external factors (e.g., infection) or injury. Others are probably strictly caused by external factors (e.g., infection) or injury

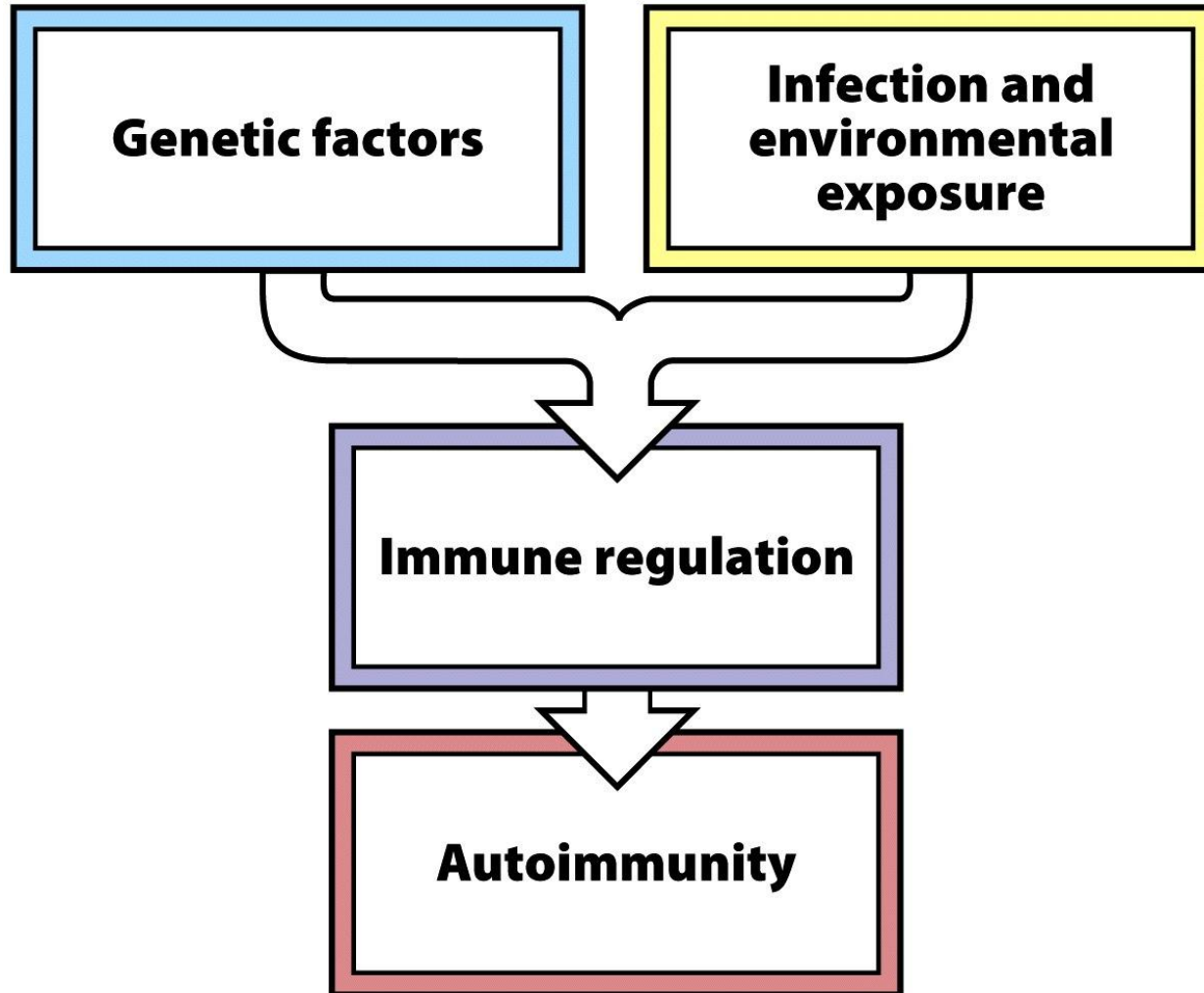
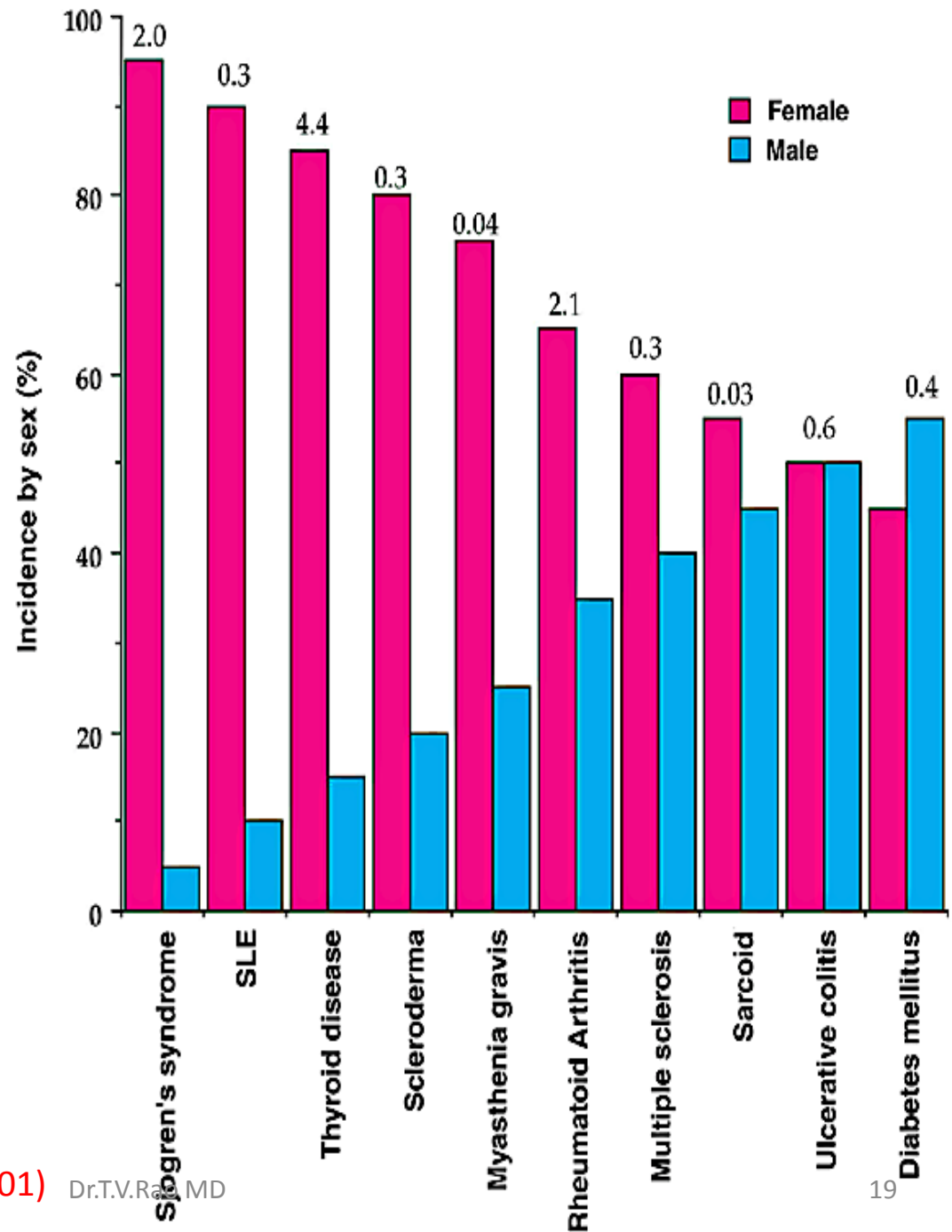


Figure 14-3 Immunobiology, 7ed. (© Garland Science 2008)

Sex differences in 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

Virus Infection Breaks Tolerance

Make hybrid gene of LCMV nucleoprotein (NP) expressed from insulin promoter

LCMV nucleoprotein (NP)



rat insulin promoter

Make transgenic mice that express NP only in the pancreatic β cells

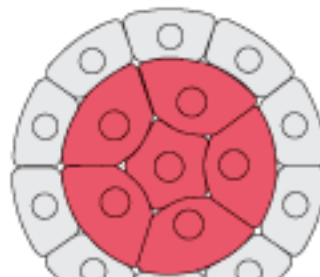


pancreas

NP-specific CD8 T cells are activated by LCMV infection

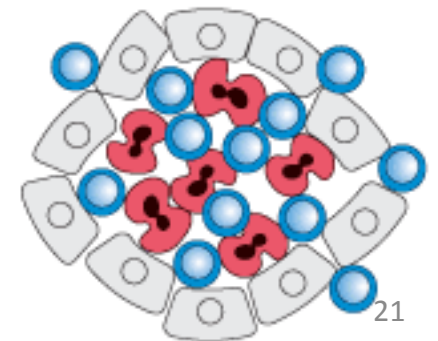


NP is expressed only in β cells and provokes no T-cell response

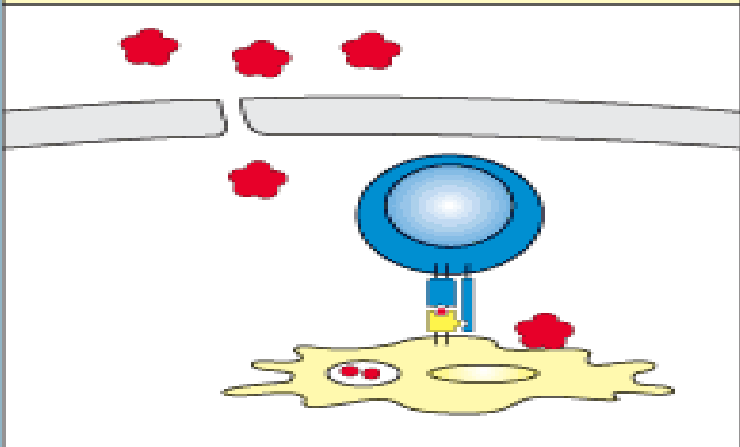
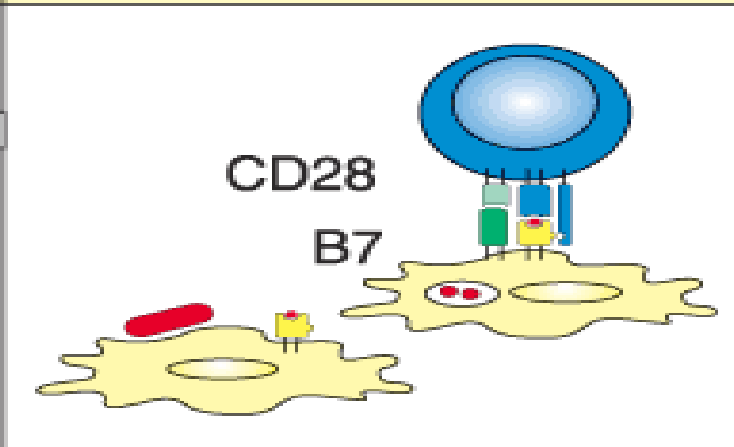


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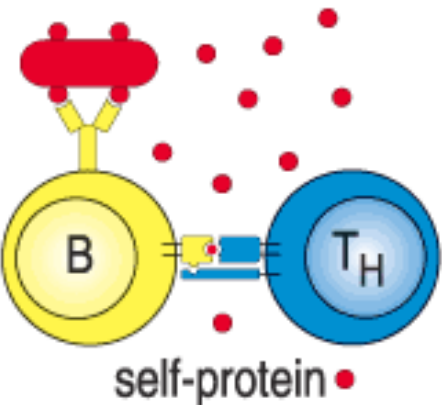
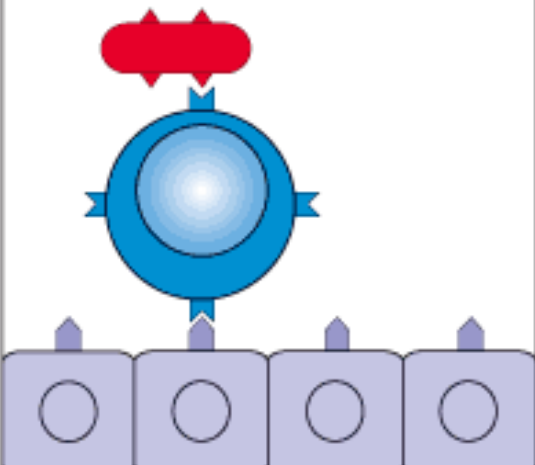
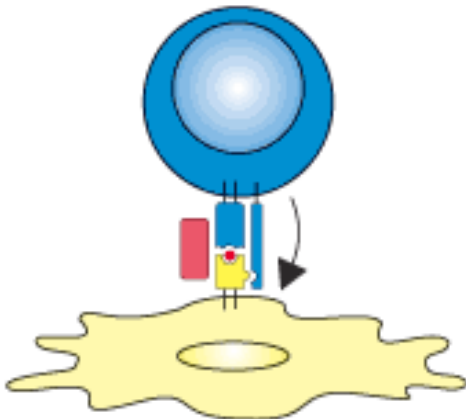
Activated CD8 T cells infiltrate islets and kill β cells expressing NP; this results in diabetes



Infections Break Tolerance

Mechanism	Disruption of cell or tissue barrier	Infection of antigen-presenting cell
Effect	Release of sequestered self antigen; activation of nontolerized cells	Induction of co-stimulatory activity on antigen-presenting cells
Example	Sympathetic ophthalmia	Effect of adjuvants in induction of EAE
	 <p>The diagram illustrates the mechanism of sympathetic ophthalmia. A grey horizontal line represents a tissue barrier. Above the barrier, several red flower-like shapes represent sequestered self-antigens. Below the barrier, a blue cell (antigen-presenting cell) is shown with a receptor (MHC) bound to one of these antigens. A yellow cell (T cell) is positioned below the blue cell, with its own receptor (TCR) interacting with the MHC-antigen complex.</p>	 <p>The diagram illustrates the effect of adjuvants in the induction of EAE. It shows two yellow cells (antigen-presenting cells). The cell on the left has a red oval (antigen) on its surface. The cell on the right has a blue cell (T cell) bound to its surface. The blue cell has a receptor (CD28) bound to a yellow structure (B7) on the antigen-presenting cell. Labels 'CD28' and 'B7' are placed near their respective components.</p>

Infections Break Tolerance

Mechanism	Binding of pathogen to self protein	Molecular mimicry	Superantigen
Effect	Pathogen acts as carrier to allow anti-self response	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
Example	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis
	 <p>A diagram showing a yellow B cell and a blue T_H cell. The B cell has a Y-shaped receptor on its surface. Red dots representing self-proteins are shown binding to the B cell's receptor. A blue line connects the B cell to the T_H cell, indicating an interaction. The label 'self-protein' with a red dot is at the bottom.</p>	 <p>A diagram illustrating molecular mimicry. A red pathogen is shown above a blue T cell. The pathogen has a shape that is very similar to the T cell's receptor. Below the T cell are four purple structures representing self-antigens, which the T cell's receptor is also designed to recognize.</p>	 <p>A diagram showing a superantigen mechanism. A large blue T cell is positioned above a yellow dendritic cell. A red superantigen molecule is bound to the dendritic cell's surface. An arrow points from the superantigen to the T cell, indicating its activation. The dendritic cell has a yellow receptor on its surface.</p>

Infections And Tissue Damage

Associations of infection with immune-mediated tissue damage

Infection	HLA association	Consequence
Group A <i>Streptococcus</i>	?	Rheumatic fever (carditis, polyarthritis)
<i>Chlamydia trachomatis</i>	HLA-B27	Reiter's syndrome (arthritis)
<i>Shigella flexneri</i> , <i>Salmonella typhimurium</i> , <i>Salmonella enteritidis</i> , <i>Yersinia enterocolitica</i> , <i>Campylobacter jejuni</i>	HLA-B27	Reactive arthritis
<i>Borrelia burgdorferi</i>	HLA-DR2, DR4	Chronic arthritis in Lyme disease

Exceptions to the Rule – Simple Genetic Autoimmune Illnesses

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

Autoimmune endocrine diseases

Thyroid

Hashimoto's disease (autoantibodies against thyroid peroxidase)

Primary myxoedema (atrophy of the thyroid)

Graves' disease (autoantibodies against TSH-R)

Pancreas

Type I diabetes

Adrenal

Addison's disease (chronic endocrine disorder; adrenal glands produce insufficient steroid hormones)

Gonads

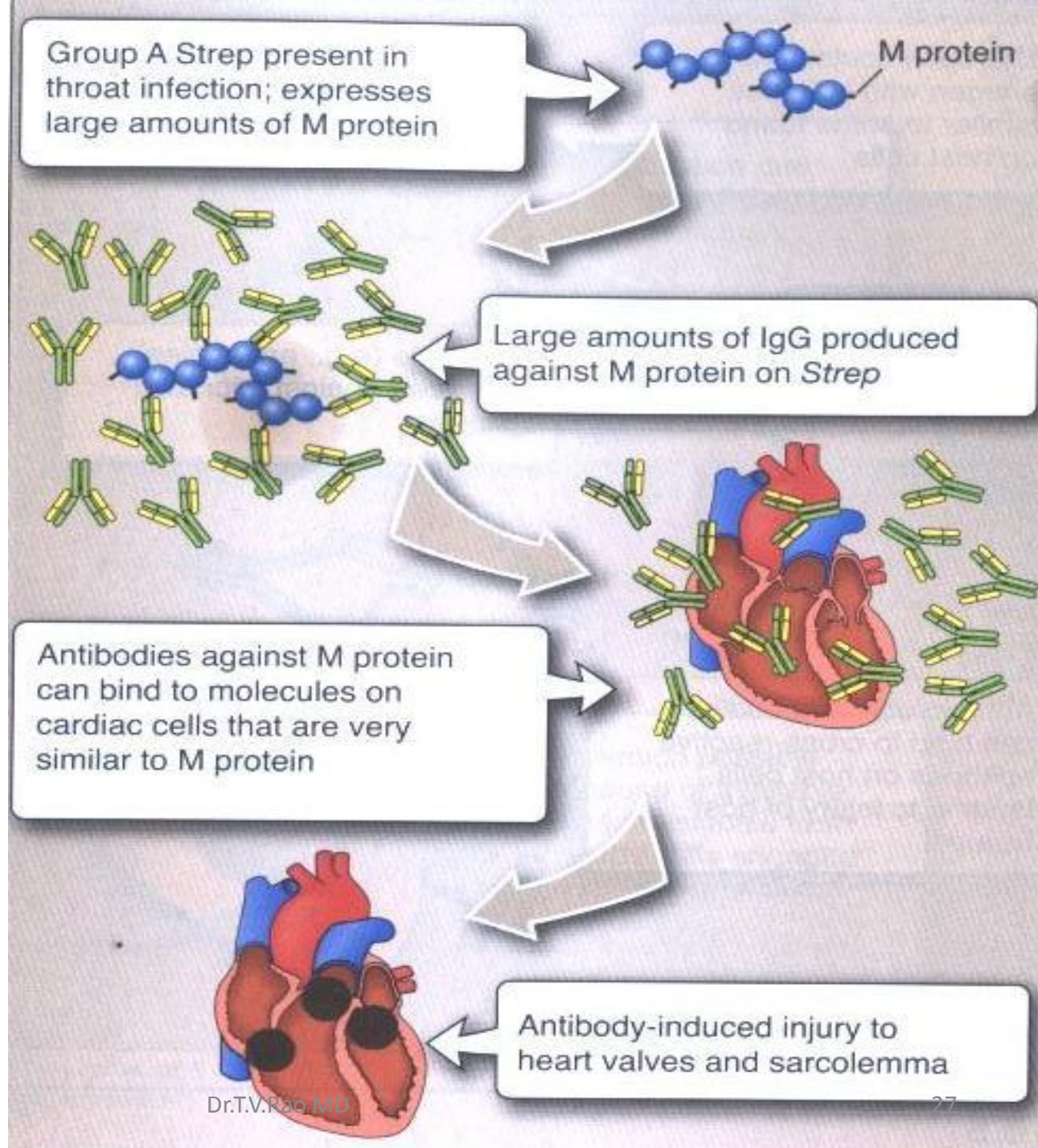
Autoimmune oophoritis (inflammation of the ovaries)

Autoimmune orchitis (testicular pain involving swelling, inflammation and infection)

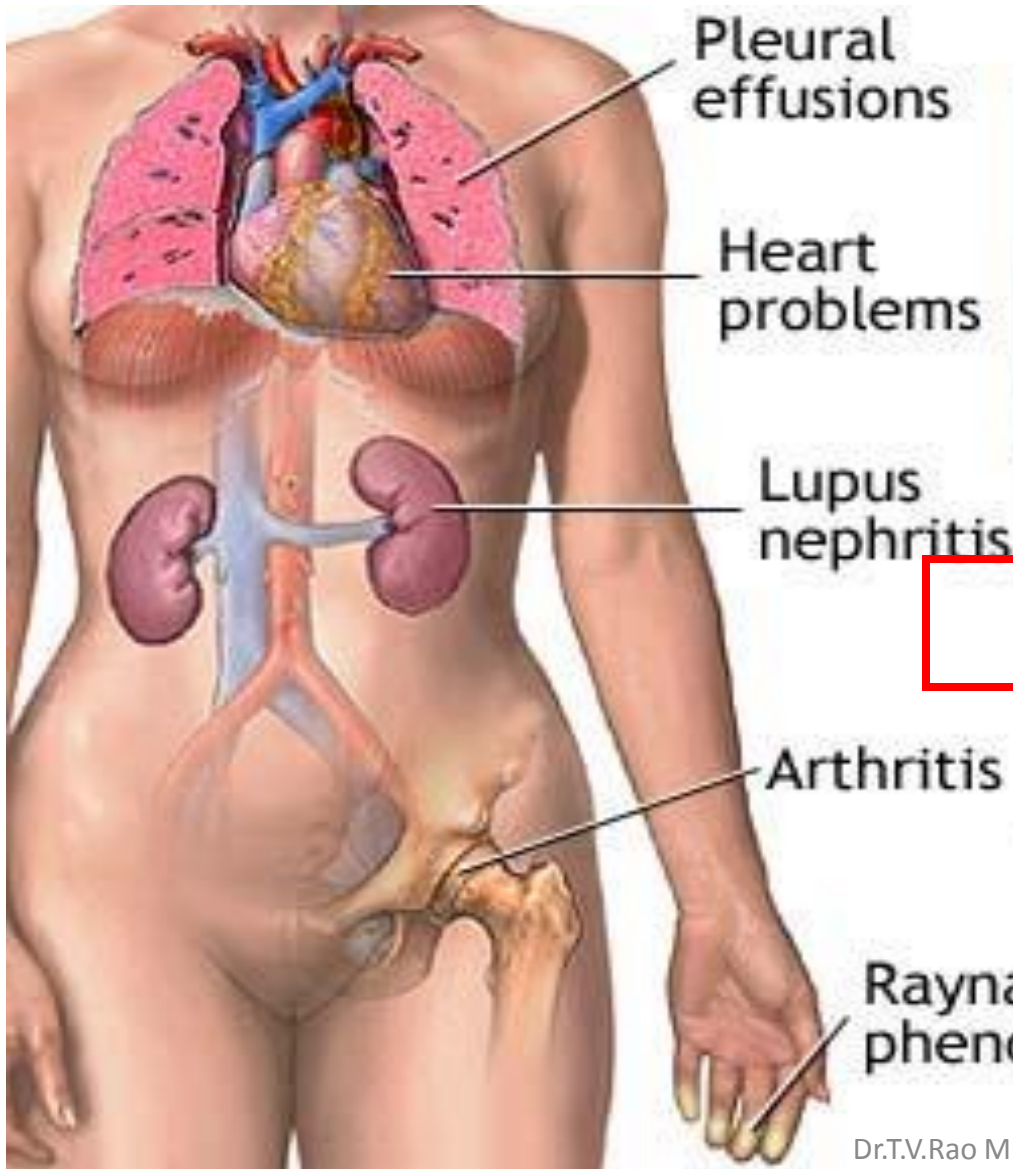
Pituitary

Lymphocytic hypophysitis (low production of one or more hormones by the pituitary gland due to autoantibodies and autoimmunity)

Rheumatic fever is a classic example of molecular mimicry



Examples of Systemic Autoimmunity

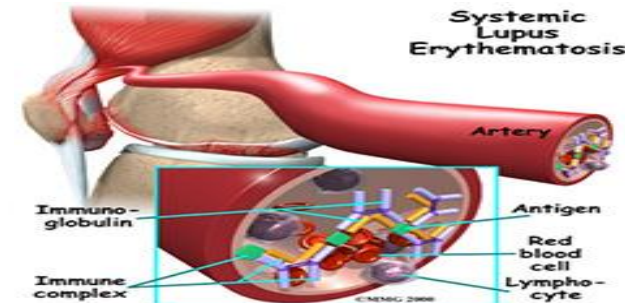


Butterfly rash



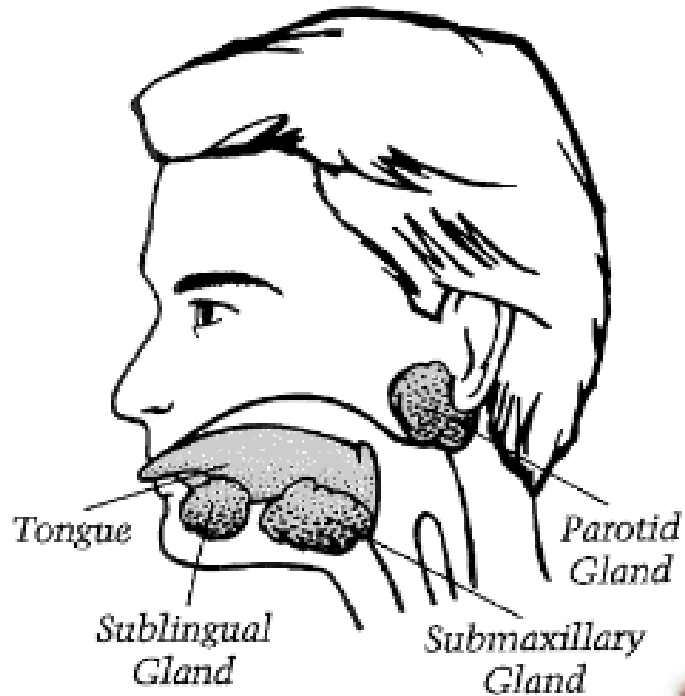
SLE

Symptoms of systemic lupus erythematosus may vary widely with the individual



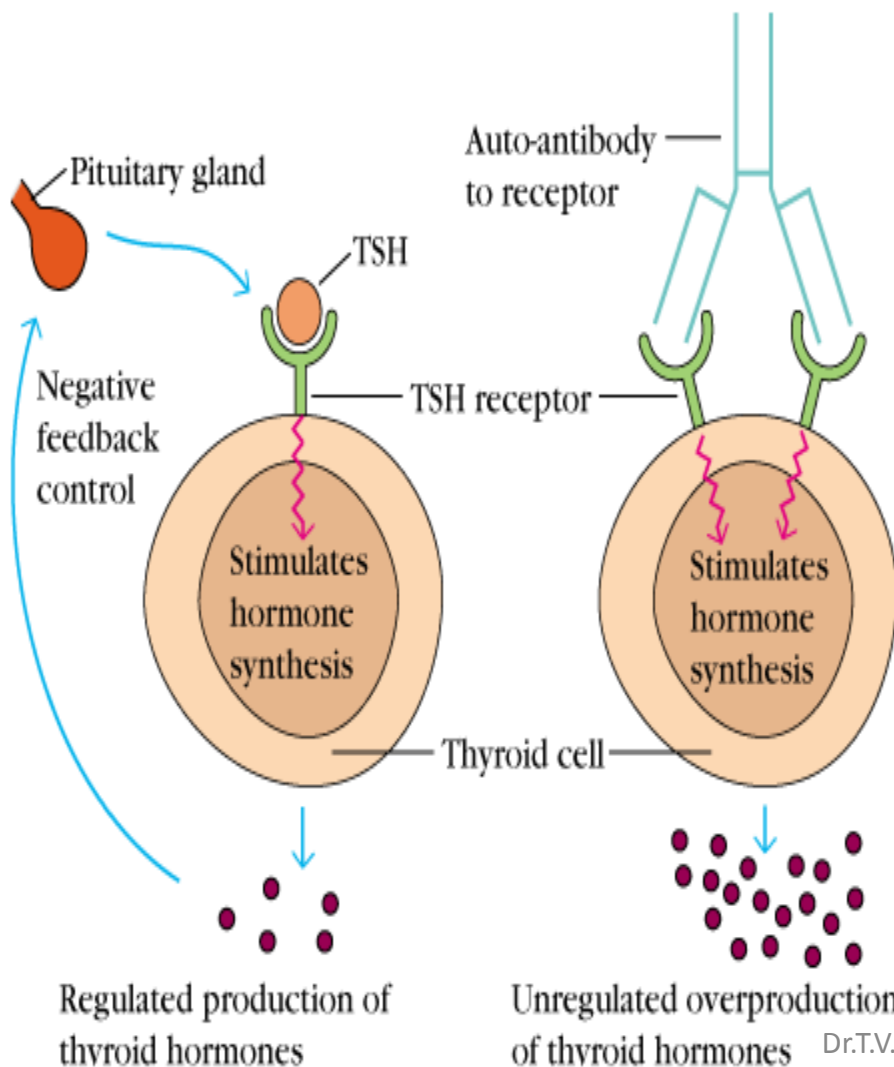
Examples of Systemic Autoimmunity

Sjogren's Syndrome



Grave's Disease

STIMULATING AUTO-ANTIBODIES (Graves' disease)



- Production of thyroid hormones is regulated by thyroid-stimulating hormones (TSH)
- The binding of TSH to a receptor on thyroid cells activates adenylate cyclase and stimulates the synthesis of two thyroid hormones: thyroxine and triiodothyronine
- A person with Grave's Disease makes auto-antibodies to the receptor for TSH. The binding of these auto-antibodies to the receptor mimics the normal action of TSH, without the regulation, leading to overstimulation of the thyroid
- The auto-antibodies are called long-acting thyroid stimulating hormones

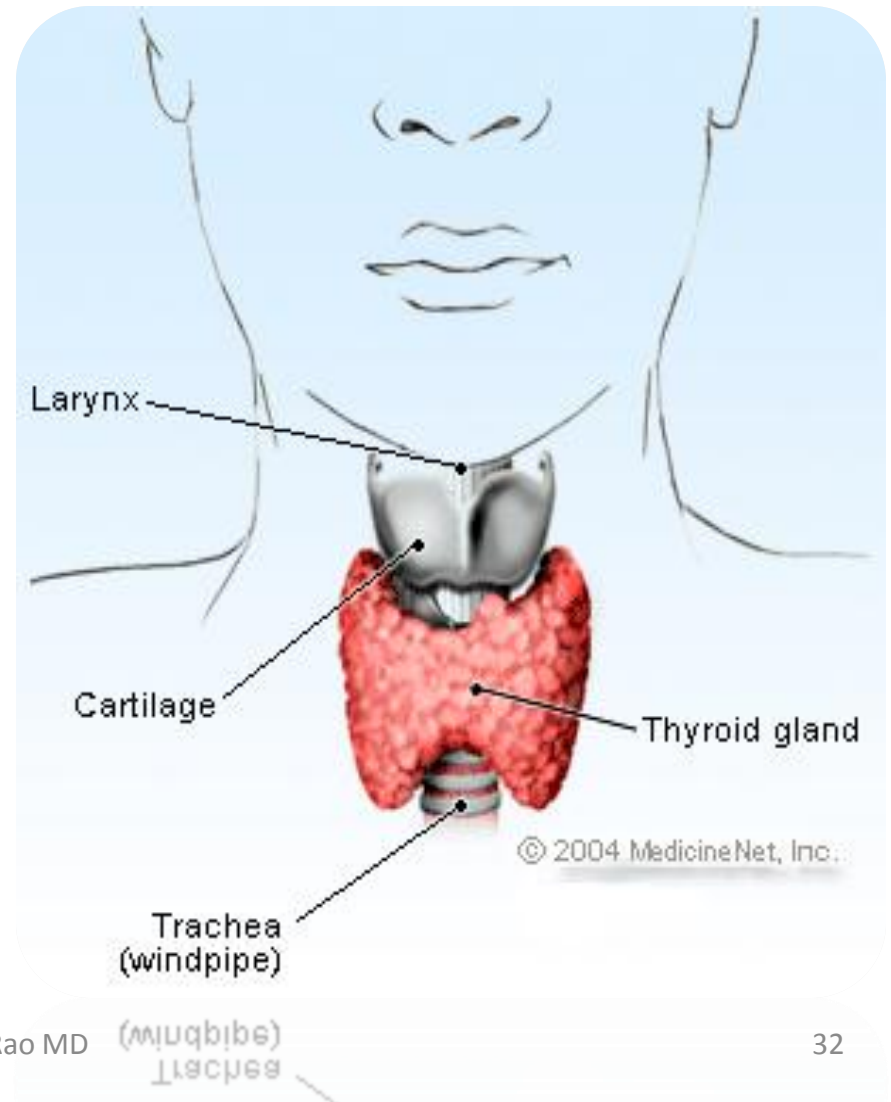
GRAVES' DISEASE

- **Risk factors**
 - HLADR3
 - Smoking for ophthalmopathy (5x)
- **Treatment**
 - Anti-thyroid drugs
 - Methimazole (Tapazole)
 - Radioactive iodine
 - I-131
 - Surgery
 - Thyroidectomy



HASHIMOTO'S DISEASE (THYROIDITIS)

- Alternative names
 - Chronic lymphocytic thyroiditis
 - Autoimmune thyroiditis
- Female to male ratio of 12:1
- Effector mechanisms
 - Autoantibodies specific for
 - Thyroglobulin
 - Thyroid peroxidase
 - CD8 T cells



HASHIMOTO'S DISEASE (THYROIDITIS)

- Most common cause of hypothyroidism in US
- Symptoms
 - Fatigue, cold intolerance, weight gain, depression, enlarged gland
- Laboratory diagnosis
 - T3,T4 (decrease) and TSH (increase) serum levels
 - Autoantibodies to
 - Thyroid peroxidase (TPO)
 - Thyroglobulin
- Treatment
 - Replacement therapy (Levothyroxine)

Rheumatoid arthritis particularly affects the small joints of the hands and feet

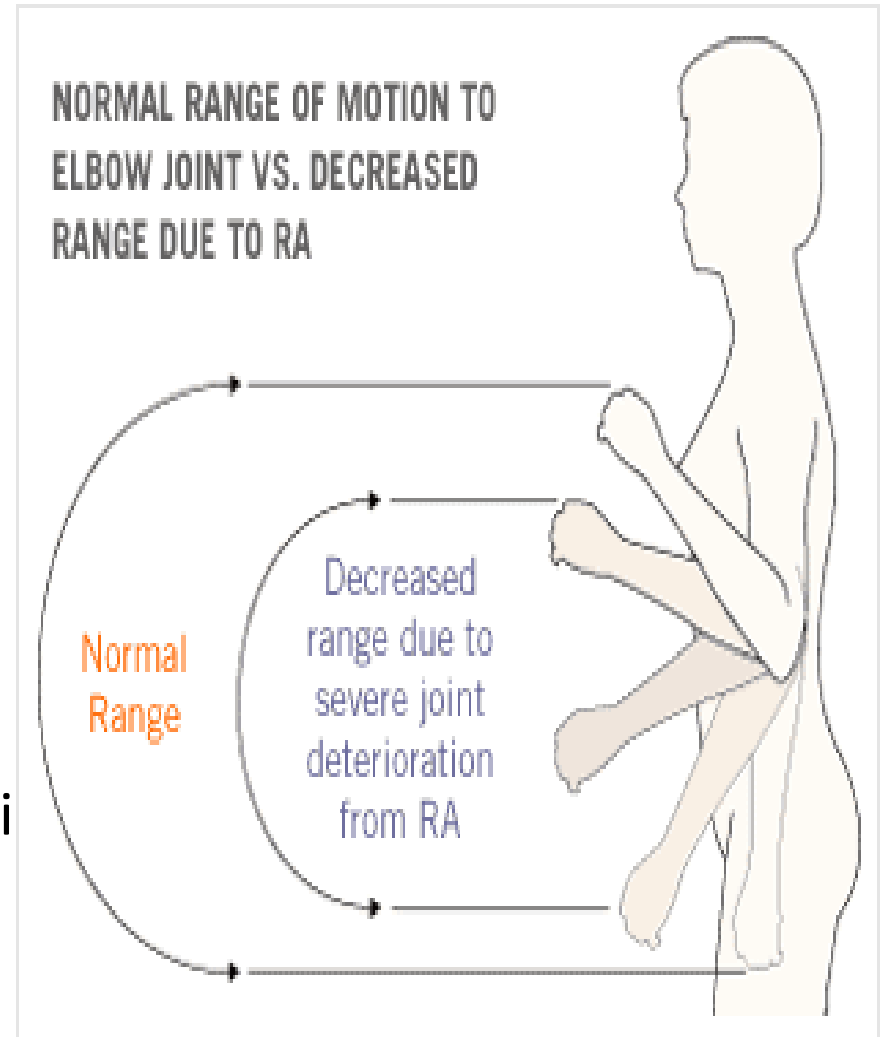




Typical rheumatoid joint deformities in the hands. There is wasting of the small muscles of the hand, swelling of the metatarsophalangeal joints and a small subcutaneous nodule on the little finger. The fingernail 'clubbing' is characteristic of the pulmonary fibrosis from which this patient also suffered.

CLINICAL FEATURES

- ❖ Onset: Insidious
- ❖ Main symptoms:
 - Pain
 - Stiffness – on waking and following inactivity
- Other symptoms:
 - Fatigue and lethargy
 - Low-grade fever
 - Weight loss Progressive decline



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)

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



Sex-based Differences in Autoimmunity

- **Differences can be traced to sex hormones**
 - hormones circulate throughout the body and alter immune response by influencing gene expression
 - (in general) estrogen can trigger autoimmunity and testosterone can protect against it
- **Difference in immune response**
 - ♀ produce a higher titer of antibodies and mount more vigorous immune responses than ♂
 - ♀ have a slightly higher cortisol secretion than ♂
 - ♀ have higher levels of CD4⁺ T-cells and serum IgM

Sex-based Differences

- **Estrogen**

- causes autoimmunity (generally)
- stimulates prolactin secretion (helps regulate immune response)
- stimulates the gene for CRH (corticotropin-releasing hormone) that promotes cortisol secretion
- causes more T_H1 -dominated immune responses (promotes inflammation)

- **Testosterone**

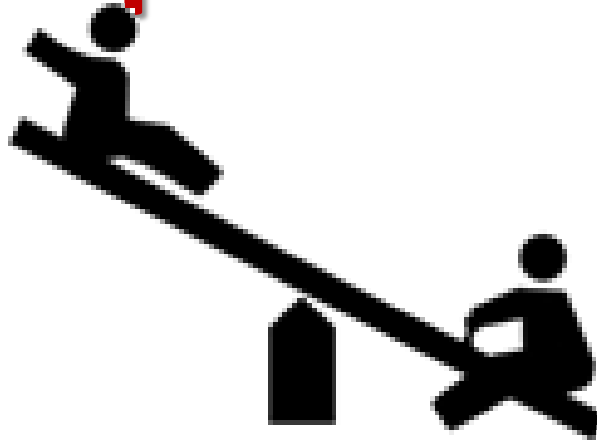
- can cause autoimmunity or protect against it

Sex-based Differences

- **Pregnancy**

- during this, ♀ mount more of a T_H2 -like response
- the change in hormones creates an anti-inflammatory environment (high cortisol levels)
- diseases enhanced by T_H2 -like responses are exaggerated and diseases that involve inflammatory responses are suppressed
- fetal cells can persist in the mother's blood or the mother's cells may appear in the fetus (microchimerism)
 - can result in autoimmunity if the fetal cells mount an immune response in the mother's body (or vice versa)

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.

Myasthenia Gravis

Disease marked by
progressive
weakness and loss
of muscle control

Classified as a “B cell”
Disease

Autoantibodies
against nicotinic
acetylcholine
receptors



Multiple Sclerosis

Central nervous system
(brain and spinal cord)

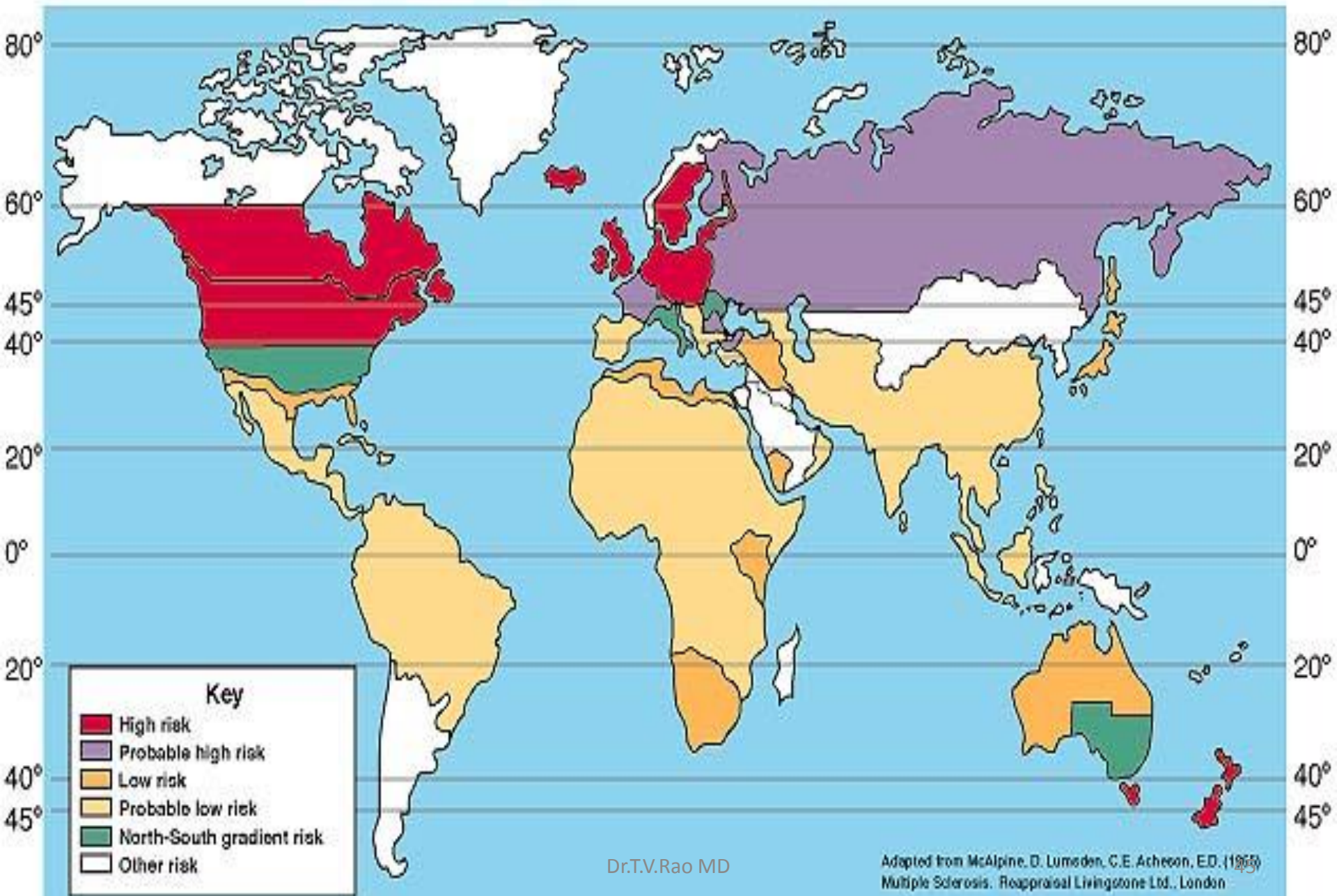


In multiple sclerosis the myelin sheath, which is a single cell whose membrane wraps around the axon, is destroyed with inflammation and scarring

ADAM.

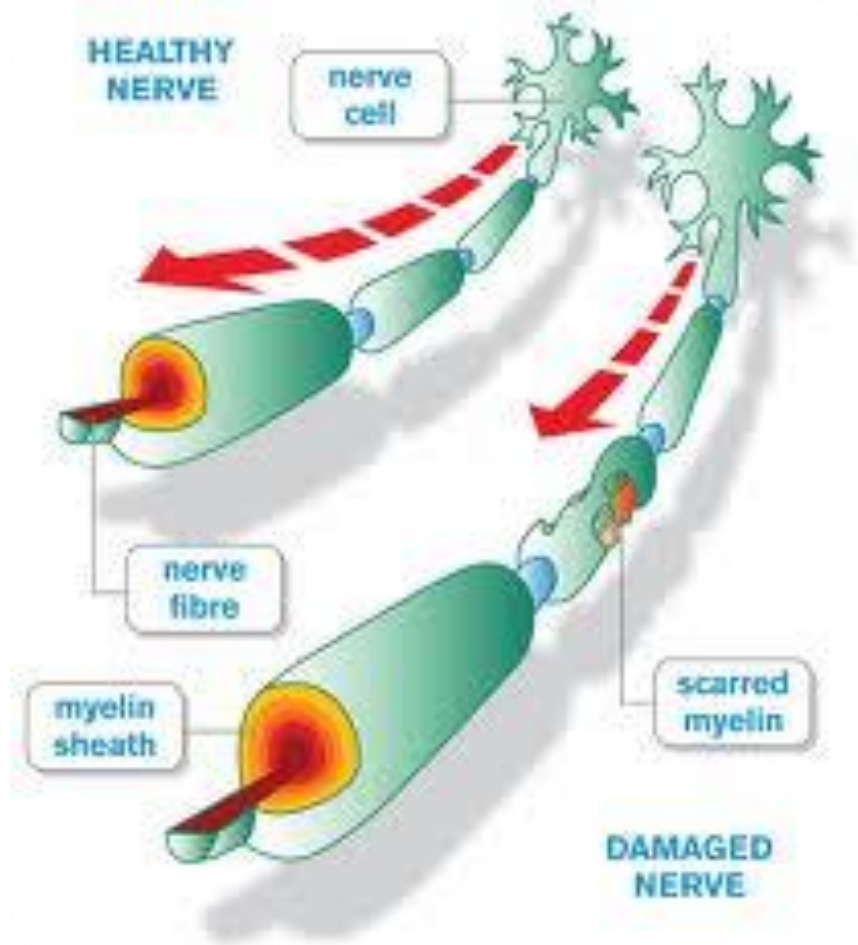
MS patients can have autoantibodies and/or self reactive T cells which are responsible for the demyelination

World Distribution of Multiple Sclerosis



MULTIPLE SCLEROSIS (MS)

- **Effector mechanisms**
 - Myelin basic protein is primary auto antigen for CD4 TH1 cells
- **Radiology diagnosis**
 - MRI for detecting demyelinating lesions (plaques)
- **Laboratory diagnosis**
 - High resolution protein electrophoresis for
 - Oligoclonal bands in CSF



SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- Chronic, multi-system inflammatory disease with protean manifestations and remitting course
- **Clinical manifestations**
 - Musculoskeletal (joint and muscle pain)
 - Dermatological (malar rash)
 - Renal (glomerulonephritis)
- **Female to male ratio of 9:1**
- **Etiology is unknown**
 - Genetics, race, hormones, environment



Figure 11-10 The Immune System, 2/e (© Garland Science 2005)

Diabetes

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

“T cell” Disease

T cells attack and destroy pancreatic beta cells

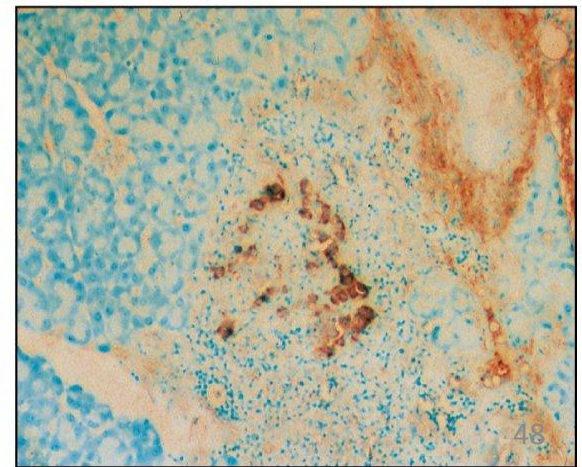
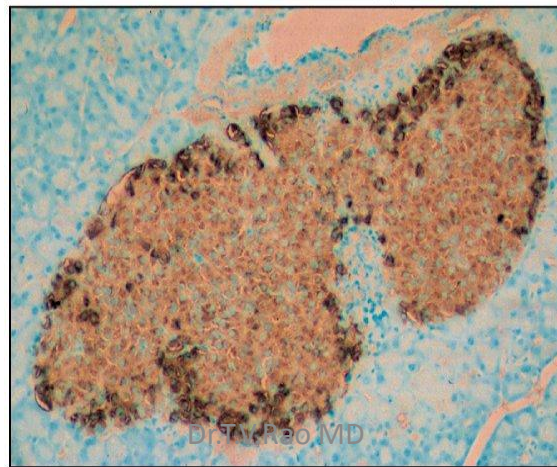
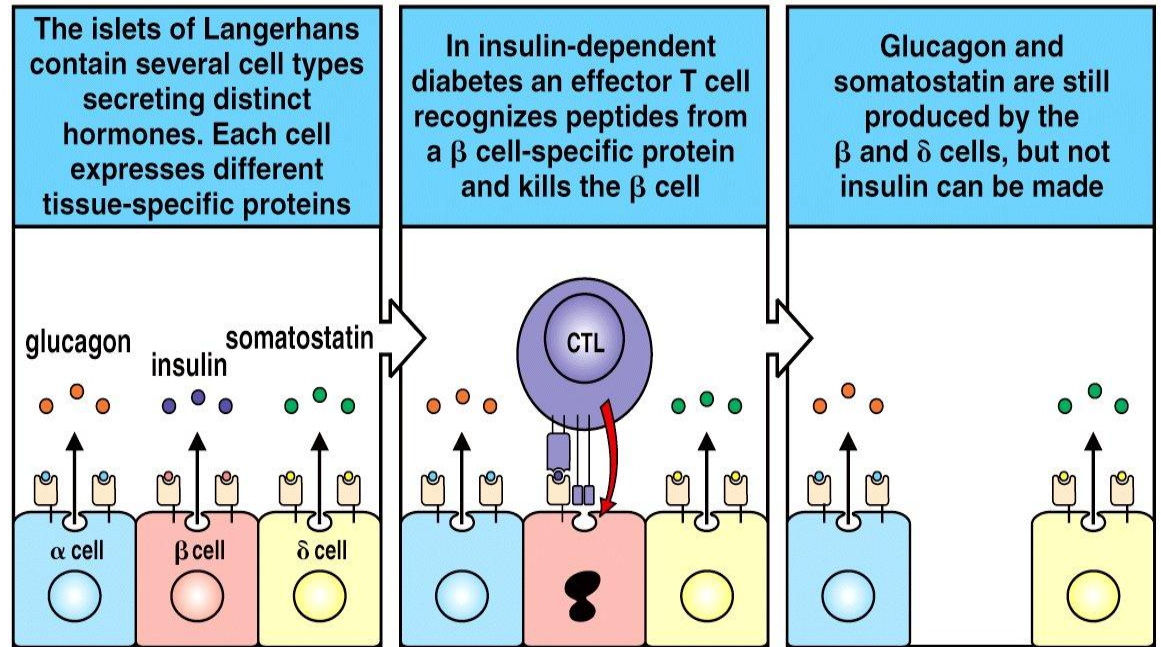
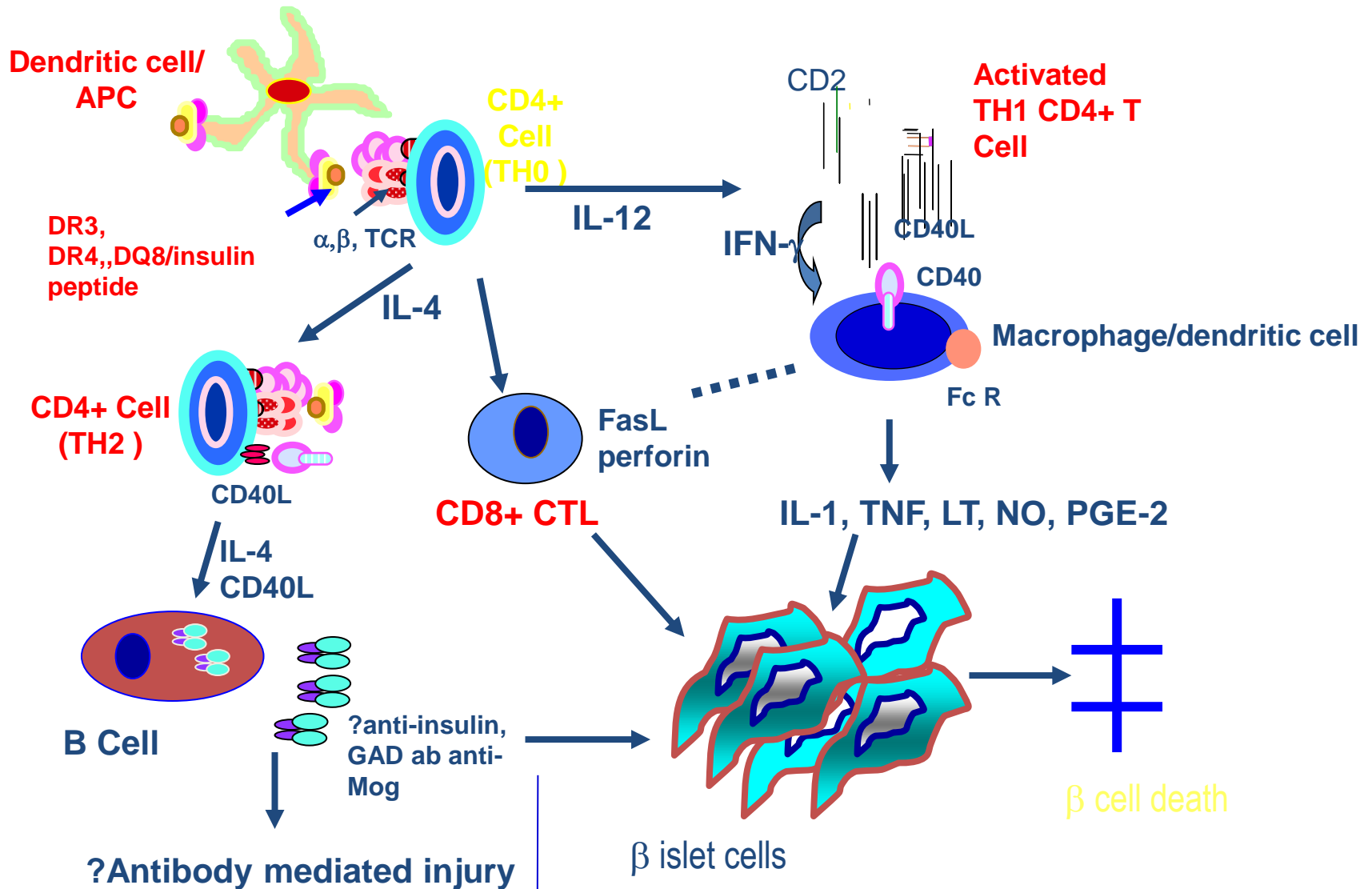
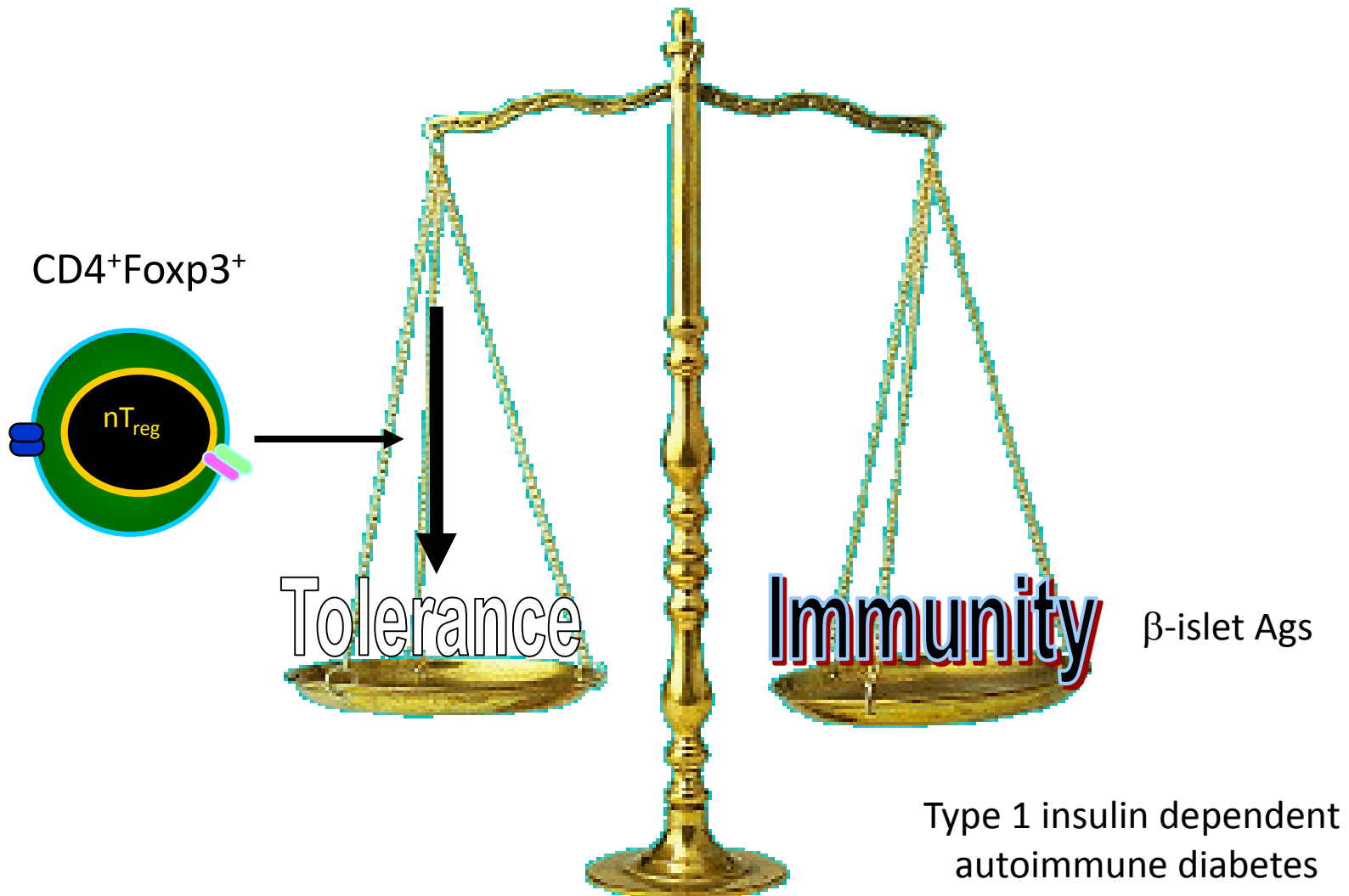


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

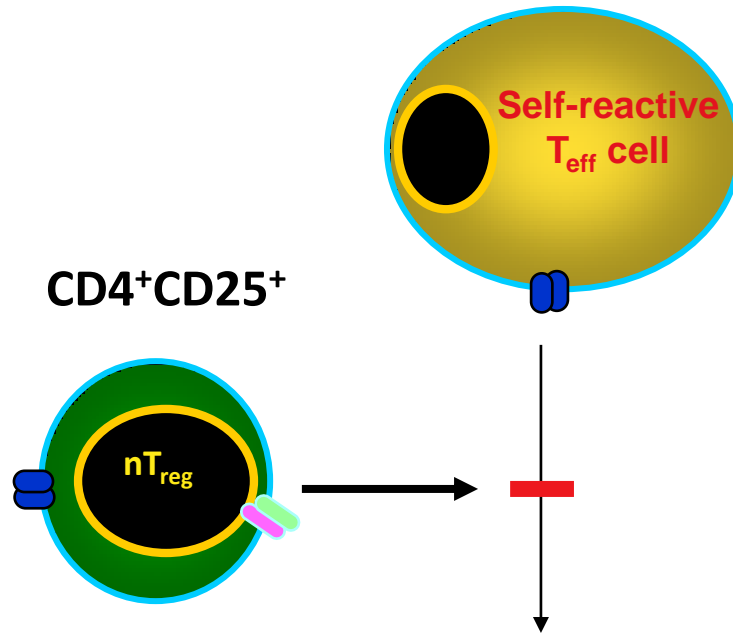
Immunopathophysiology of Diabetes



Balance of effector and regulatory mechanisms determines peripheral tolerance



Functional deficiency in CD4⁺CD25⁺ Treg cells in autoimmunity ?



Autoimmune disease:

Organ-specific - T1D, MS/EAE, Sjogren's, Thyroiditis
Systemic - SLE, APS, RA

Autoimmune Anemia's

- **Pernicious Anemia**

What is it?

- deficiency in vitamin B₁₂

What causes it?

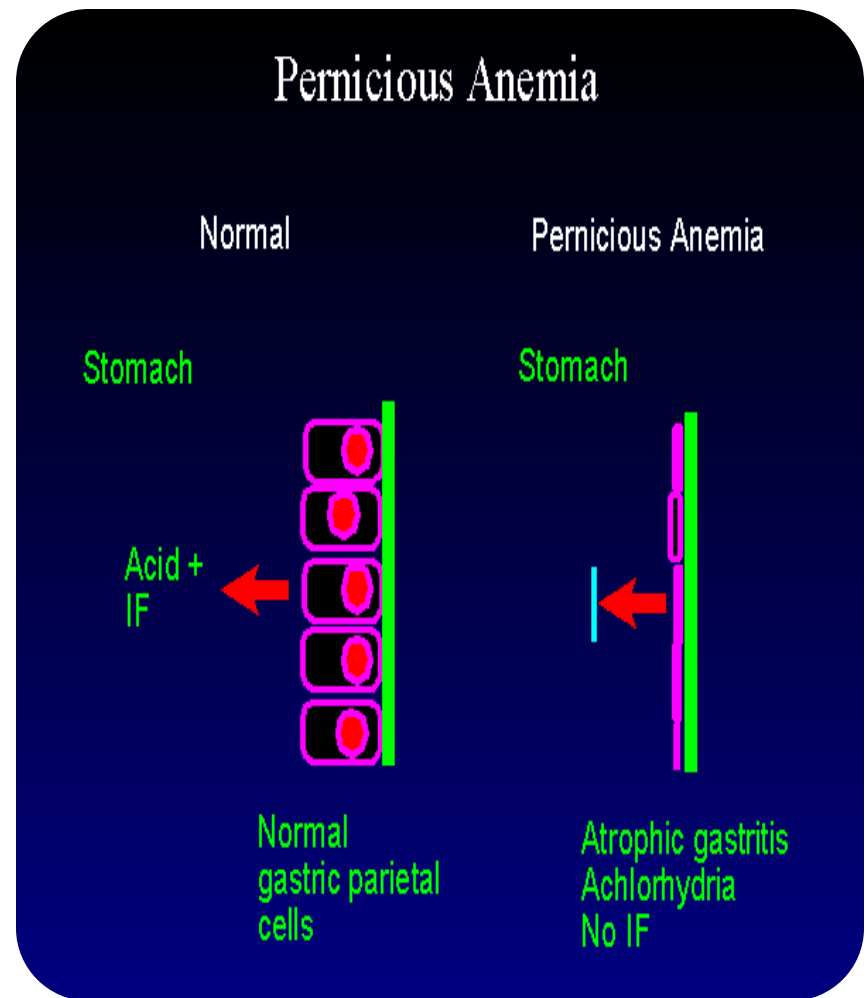
- auto-antibodies to intrinsic factor

What happens?

- B₁₂ remains in the stomach and is excreted

Treatment

- treated with injections of B₁₂



Hemolytic Anemia

Results from monoclonal antibodies to normal RBC constituents

- antibodies coat the erythrocytes, causing clumping, lysis, and premature clearance by the spleen
- can be induced by an “offending” agent (parasite, drug, or toxin) that adheres to the RBC
 - Drug-induced Hemolytic Anemia- drug binds to RBC’s and causes them to become antigenic
 - antibodies that develop from the drug recognize these cells and they are lysed

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 Options

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



Current Therapies

- Immunosuppressive drugs
 - corticosteroids, azathioprine
 - slows the proliferation of lymphocytes
- Cyclosporine A
 - blocks signal transduction mediated by the TCR (inhibits only antigen-activated T cells while sparing non-activated ones)
- Thymectomy
 - removal of thymus from patients with myasthenia gravis
- Plasmapheresis
 - removes antigen-antibody complexes for a short-term reduction in symptoms

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