

Autoimmunity



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.



What is autoimmunity?

- When the immune system is activated by self-antigens
- When the immune system no longer recognizes itself
- Generally is prevented by “self-tolerance”, where self-reactive antigens are eliminated
- But, the body cannot eliminate all self-reactive antigens because some help protect against foreign antigens!
- This means that everyone has some self-reactive antigens, only, they have not activated our antibodies...yet...

What is autoimmunity?

- When body mounts immune response against self, it is impossible for immune mechanism to eliminate antigen completely
- Result: a sustained response, chronic inflammation, tissue damage and sometimes death!

- ❑ Autoimmunity defines a state in which unresponsiveness to self terminates, leading to specific adaptive immune responses against self.
- ❑ Since self tolerance is somatically acquired, it is subject to failure particularly with the complexity of the issue.
- ❑ A remarkable number of autoreactive T and B cell clones are present in the healthy immune repertoire.

- ❑ Autoimmunity is not necessarily a sign of disease and it has become apparent that autoimmune responses are not as rare as once thought.
- ❑ In fact, current argument emphasizes that certain autoimmune responses are essential for the normal functioning and diversification of the immune response (CD-MHC, Id-anti-Id).
- ❑ Autoimmune diseases are not rare or exotic; autoimmune diseases and their sequelae occur with surprising frequency.

Normal Autoimmunity

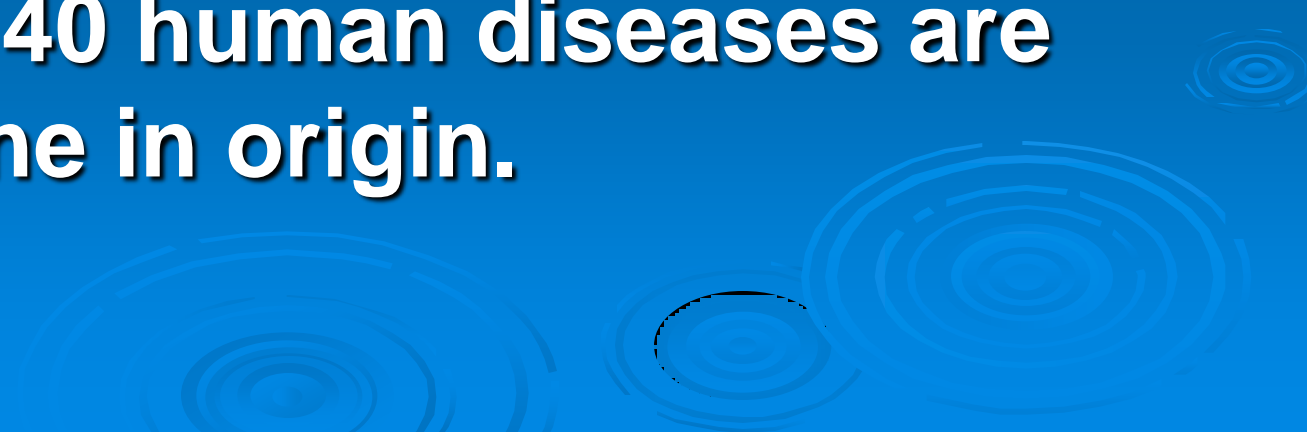
- ❑ Autoimmunity is an inherent property of the normal immune system
- ❑ Autoimmune diseases must be distinguished from the many instances of nonpathologic self recognition by the immune system.
- ❑ Autoimmunity is unlikely to reflect the failure of the main mechanisms of tolerance.

- ❑ Low titer, low affinity autoantibodies can be readily detected in the sera of normal individuals.
- ❑ Natural autoantibodies which are found in humans of all age groups, have a wide range of specificities
- ❑ They can bind to intracellular constituents, membrane proteins, serum proteins, and polypeptide hormones.

- ❑ Natural autoantibodies are produced by B1 (CD5⁺) cells regardless of antigen exposure.
- ❑ They are IgM of low affinity and extensive cross-reactivity.
- ❑ Activities include; binding to bacteria followed by activation of complement, cross reactivity with blood group antigens, and binding to normal cellular components.

- ❑ Natural autoantibodies may have a physiologic role such as elimination of degraded autoantigens, antigen presentation and prevention of autoimmune disease.
- ❑ The demonstration of autoimmunity as a cause of disease is difficult and requires the replication of disease manifestations by transfer of antibody or T-lymphocytes.
- ❑ An Experiment of nature is neonatal myasthenia gravis due to transplacental transfer of autoantibodies.

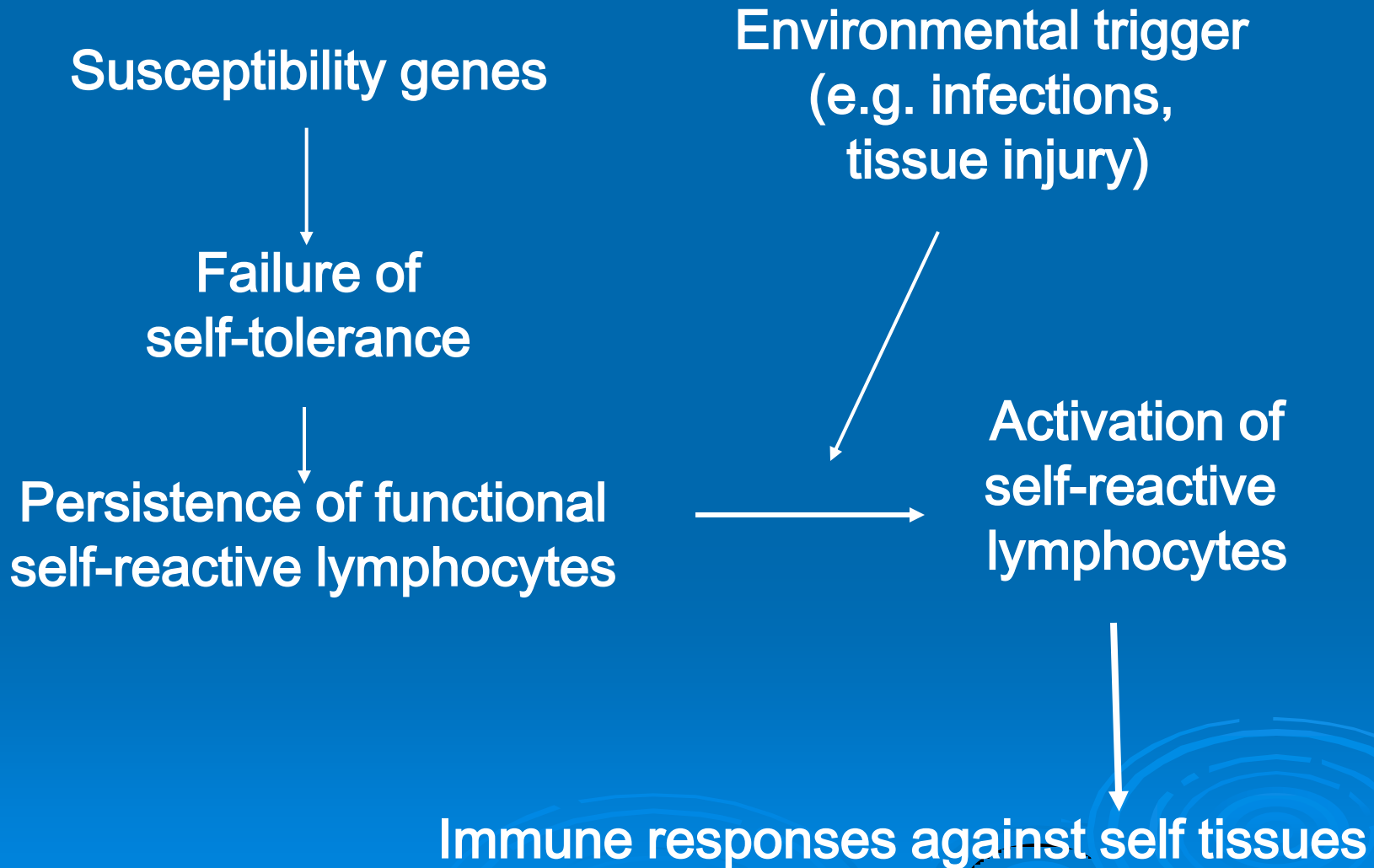
Significance of Autoimmune Diseases

- 5 % to 7% of adults are affected.
 - Two thirds are women.
 - More than 40 human diseases are autoimmune in origin.
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Significance of Autoimmune Diseases

- ❑ They should be distinguished from diseases accompanied by an immune reaction not triggered by self antigens
- ❑ Understanding of autoimmunity has greatly improved with the development of animal models and the identification of predisposing genes
- ❑ Nevertheless, the etiology of most human autoimmune diseases remains obscure

Pathogenesis of autoimmunity



Mechanisms

- ❑ Failure of Tolerance Induction
- ❑ Break down of peripheral Tolerance (Defects in CTLA-4, Defects in Fas or Fas ligands, Excess IL-2)
- ❑ Release of sequestered antigens
- ❑ Neoantigens: not truly self, modified self, denatured antigens, and antigens of transformed cells
- ❑ Epitope (Determinant) spreading: anti-myelin in MS
- ❑ Cryptic epitopes: exposed by conformational changes (IgM anti- IgG in rheumatoid arthritis)

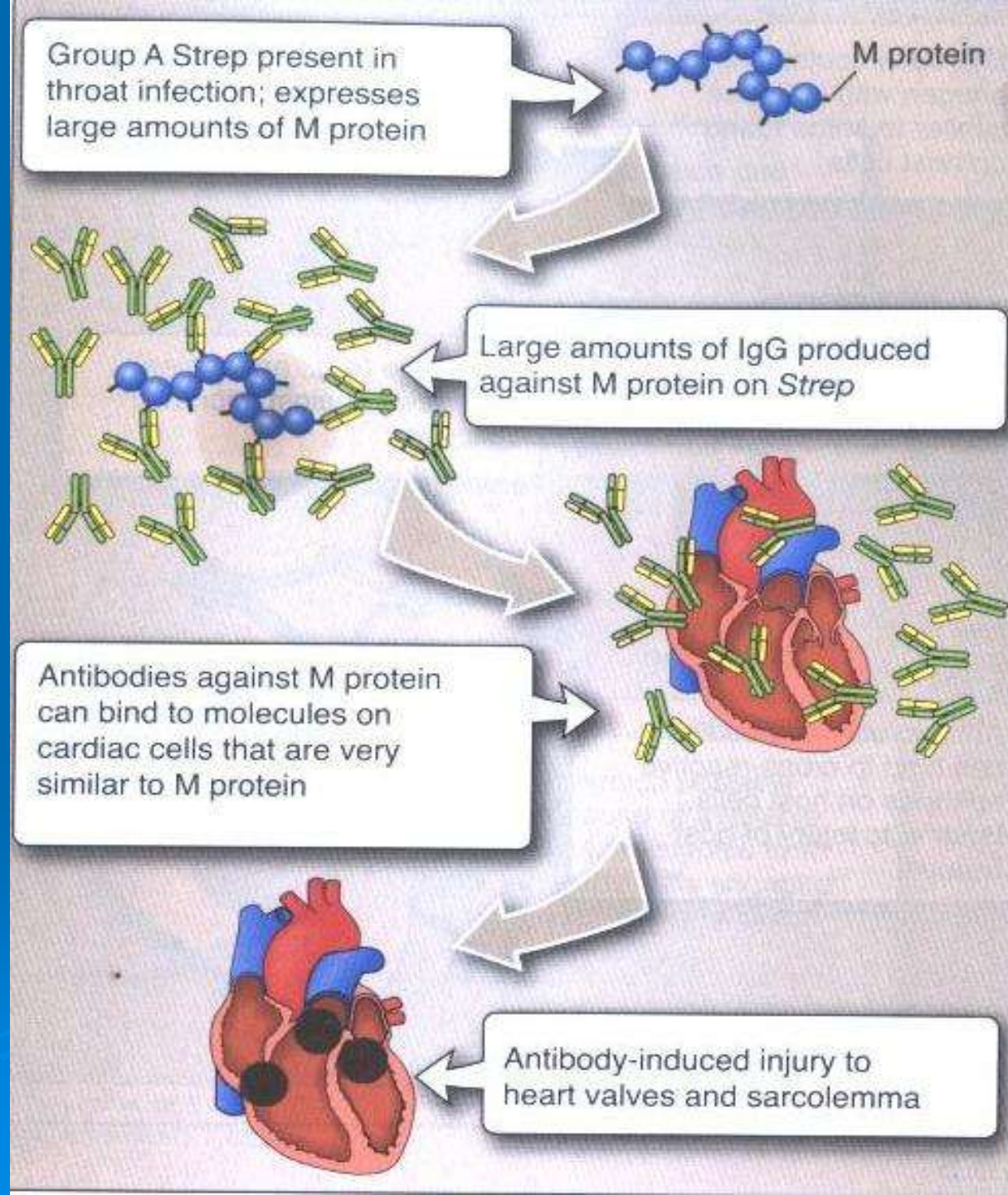
❑ **Molecular Mimicry**

- **Rheumatic fever:** Streptococcal M protein and antigens on sarcolemmal membrane and valves
- **IDDM:** Coxsackie and CMV antigens with GAD on β cells of the pancreas
- **Ankylosing spondylitis and reactive arthritis:** HLA-B27 with Klebsiella and Yersinia

❑ **T helper 1 –T helper 2 imbalance and cytokine milieu**

❑ **Polyclonal Activation (Superantigens bind TCR V β chain)**

Rheumatic fever is a classic example of molecular mimicry



Release of sequestered Ag

- ❖ Smoking can trigger Good pasture's syndrome
- ✓ Alveolar basement membrane normally not exposed to the immune system
- ✓ Smoking damages alveoli, exposes collagen
- ✓ Anti-collagen Ab damages lung and kidney

- ❖ Anti-sperm Ab produced in some men after vasectomy
- ❖ Injection of myelin basic protein (MBP) produces MS-like EAE in mice
- ❖ May be triggered by injury or infection

Immune stimulation

- Inflammation and secretion of IFN- γ which up-regulates MHC II
- Inappropriate MHC II expression e.g., on thyroid cells
- Activation of T and B responses to self Ag
- self Ag on MHC I; or MHC II
- Microbial infection stimulates APCs carrying self Ag
- High level of APCs with “second signal” breaks anergy

Induction of MHC class II expression facilitates autoimmunity

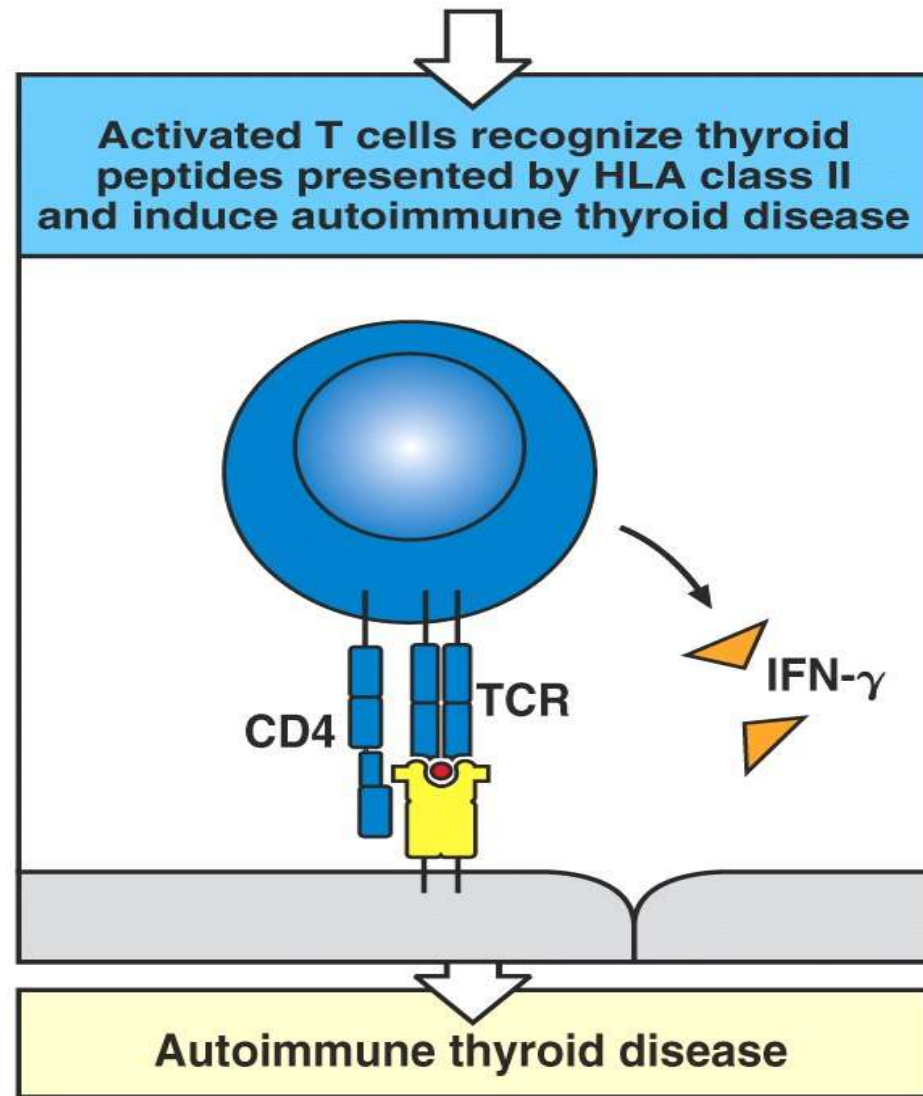
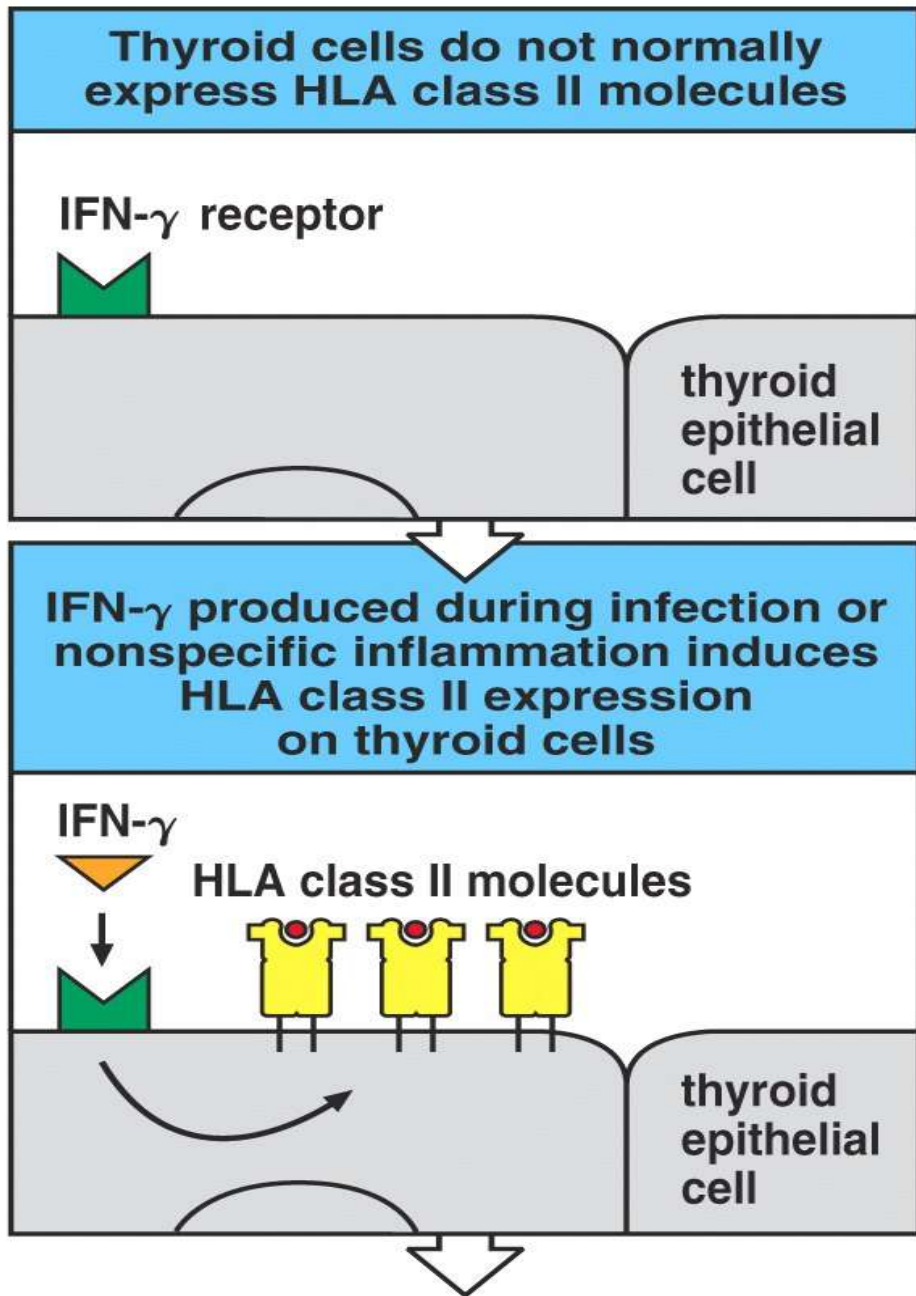
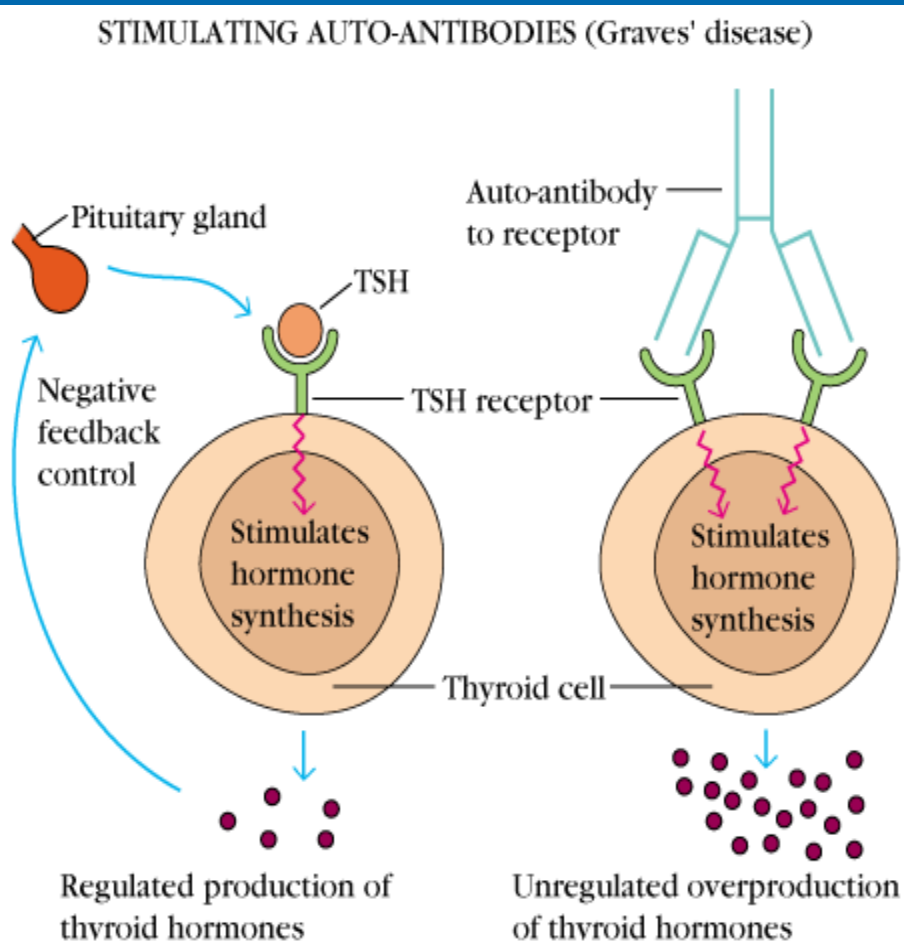


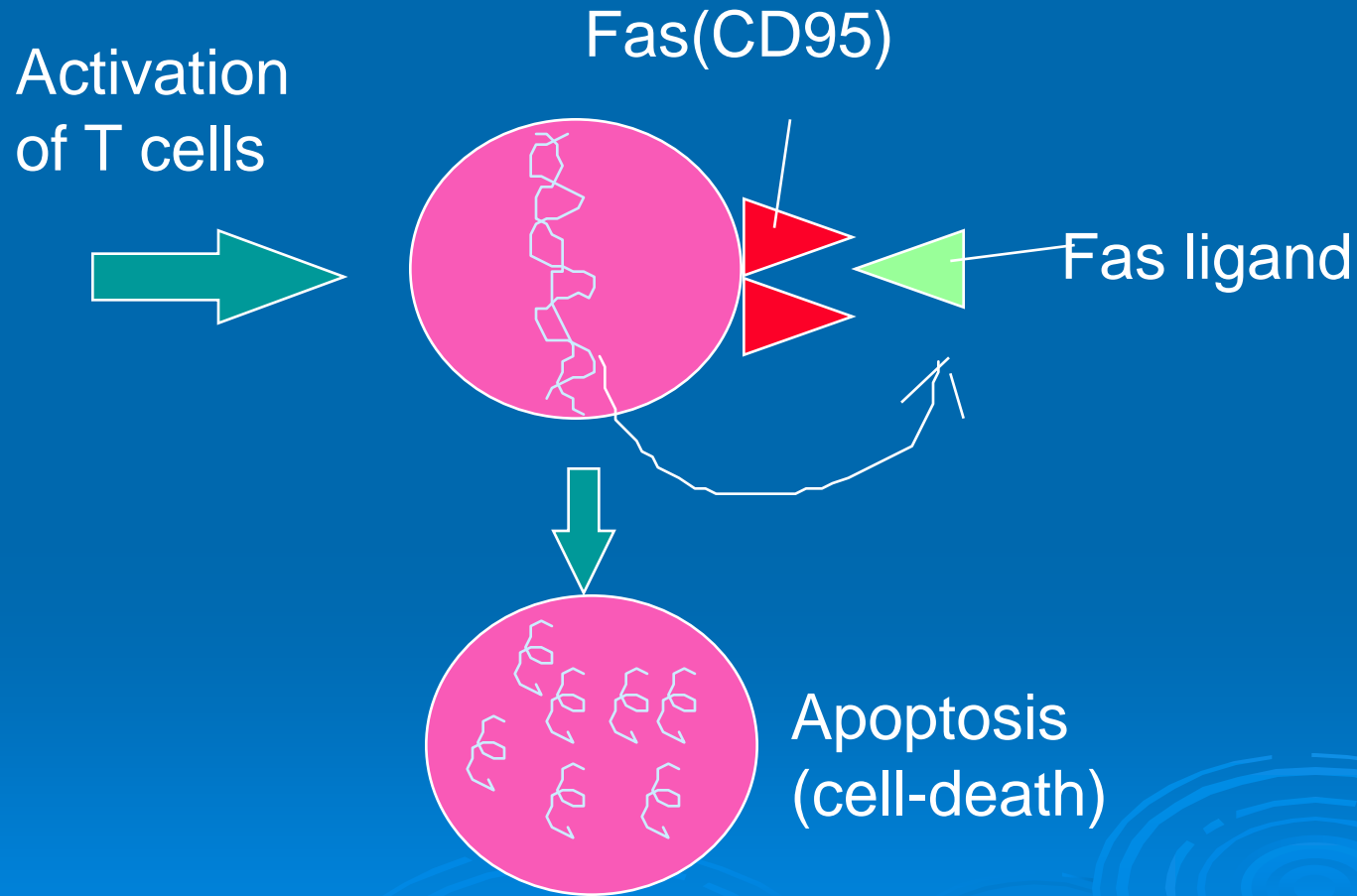
Figure 11-32 The Immune System, 2/e (© Garland Science 2005)

Grave's Disease

- Production of thyroid hormones is regulated by TSH
- The binding of TSH to a receptor on thyroid cells activates 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



What causes Autoimmunity? Defect in Fas and Fas ligand



ALPS

- Mutations in Fas or Fas ligand genes in humans leads to development of **Autoimmune lymphoproliferative syndrome** (ALPS).
- Patients with ALPS have chronic, nonmalignant lymphadenopathy and splenomegaly of childhood onset and an increased risk of B-cell lymphomas, autoimmune complications, increased numbers of normally rare α/β TCR+ CD3+CD4-CD8- or "double negative T cells"

Multiple sclerosis

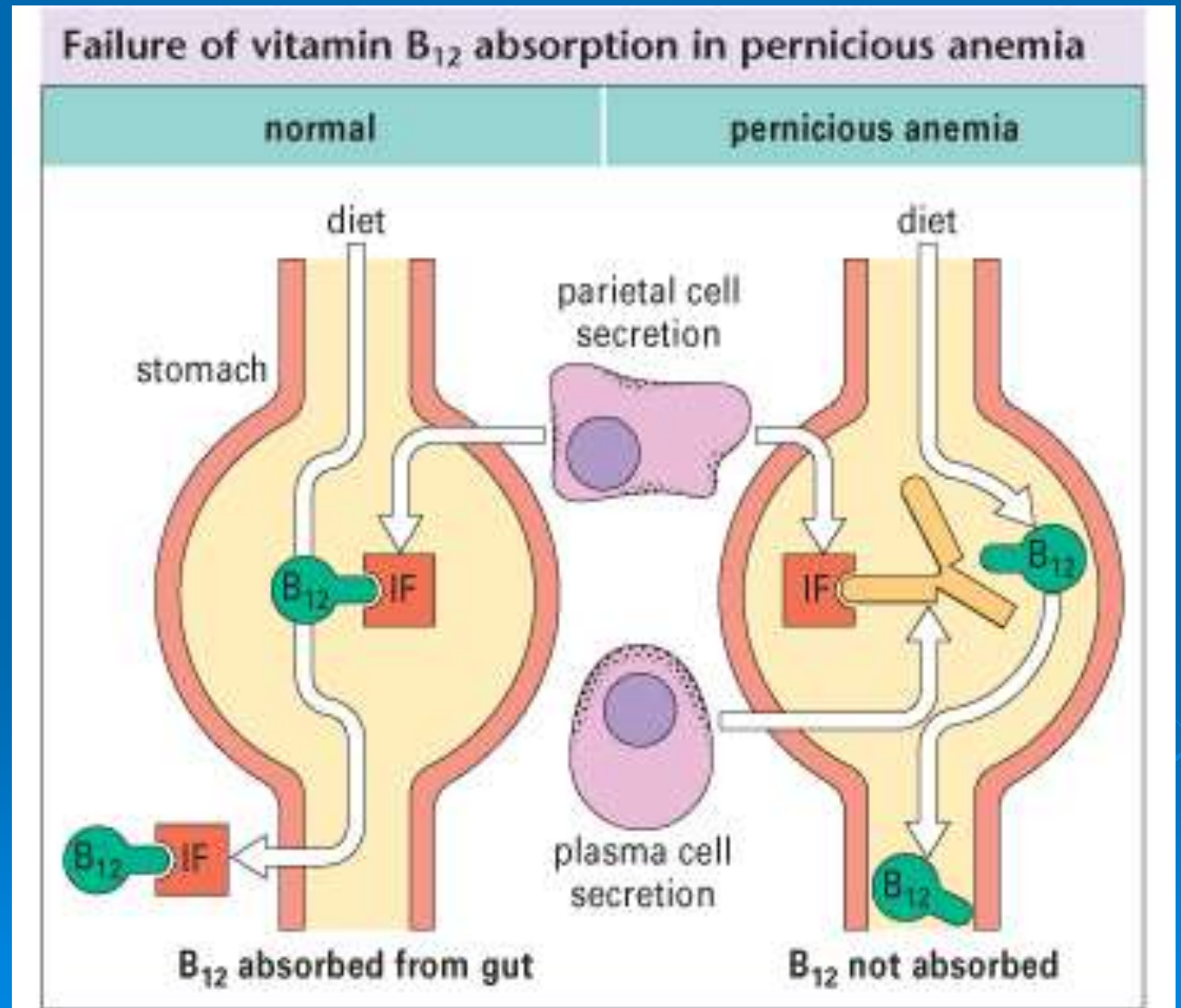
- One of the few autoimmune diseases caused by T cells. Abs are produced but their role is controversial.
- Mediated by Th17 cells.

Role of IL-17 in autoimmunity

- Unique T cells that produce IL-17 have been discovered that are distinct from Th1 and Th2 subsets.
- Such cells are called Th17 cells.
- Th1 cells differentiate in the presence of IL-12 and
- Th2 cells use IL-4.
- Th17 cells differentiate in the presence of TGF-beta and IL-6.
- Mice deficient in IL-17 do not develop EAE.

Pernicious Anemia

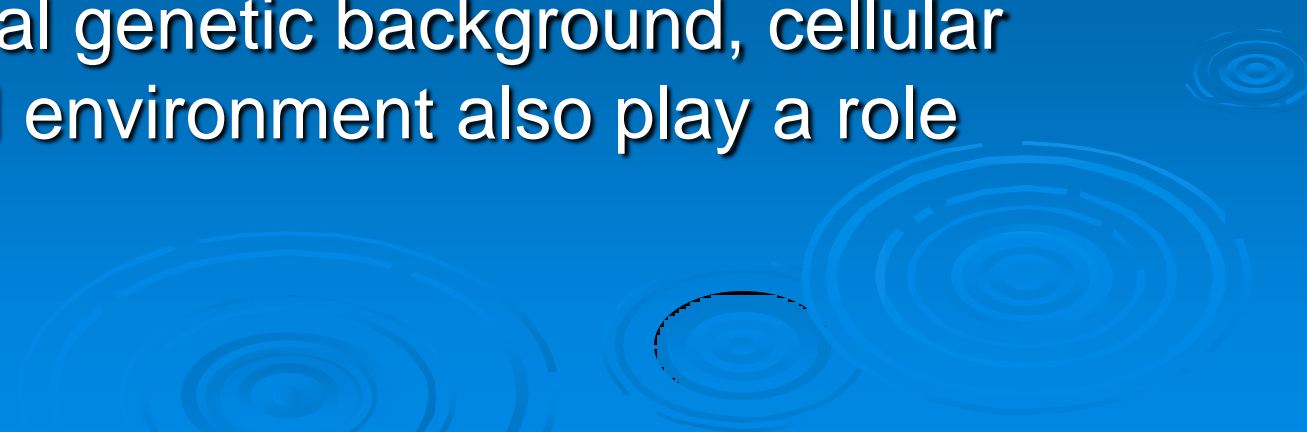
Ab against
intrinsic factor



Characteristics of Autoimmune Diseases

- 1) Systemic (Ab) or organ-specific (T Cells)
- 2) Variable course
- 3) Female preponderance
- 4) Overlapping manifestations
- 5) Immunosuppression
- 6) Diverse immunopathology
- 7) Constant antigens
- 8) Genetic susceptibility
- 9) Role of environmental factors

Factors Affecting Autoimmunity

- Familial studies suggest clear association between genetics and autoimmune disease
 - Also found to be more prevalent in women
 - However, studies between identical twins show that despite identical genetic background, cellular processes and environment also play a role
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AUTOIMMUNITY & LEFT-HANDEDNESS

- LEFT handed individuals more affected.
- 11% of left handed & 4% of right handed.
- Reasons for this are obscure.
- left-handedness & immune malfunction may both result from abnormal endocrine function in fetal life.

Examples of Organ-specific autoimmune Diseases

❑ Thyroid gland

- **Grave's disease** - autoantibodies against TSH receptor
- **Hashimoto's disease** (thyroiditis) - autoantibodies against thyroglobulin

❑ Pancreas: Insulin-dependent diabetes mellitus (IDDM)

❑ Adrenal gland

- **Addison's disease** (Hypoadrenocorticism):
 - Reduced production of glucocorticoids and/or mineralocorticoids as the result of atrophy of the adrenal gland.
- Serum from humans suffering from Addison's disease may contain auto-antibodies against adrenal cortex cells and the enzymes involved in steroid hormone metabolism.

SLE as an Example of Non organ-specific autoimmune Diseases

- ❑ Prototypic systemic autoimmune disease. Multiple autoimmune manifestations and generally high titer anti-nuclear antibody (seronegative cases have been described).
- ❑ Human SLE is more prevalent in females (oestrogens appear to aggravate the condition as does the hyperprolactinaemia of lactation).
- ❑ The clinical presentation of SLE involves polyarthrititis, mucocutaneous lesions, proteinuria and anaemia/thrombocytopaenia.

Autoantibodies against common components of human cells can cause systemic autoimmune disease

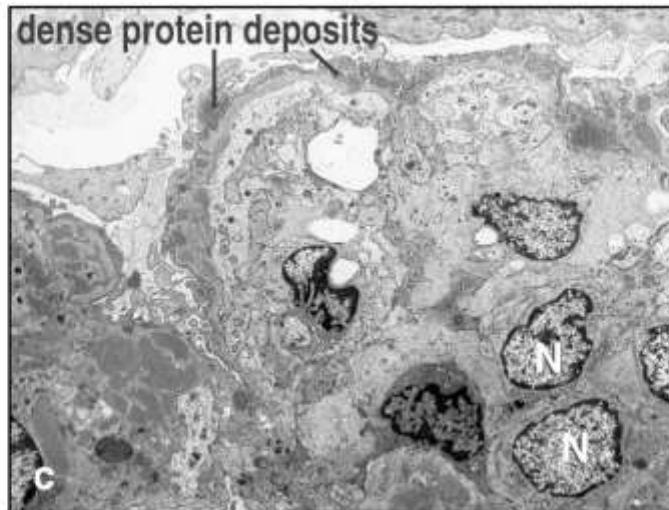
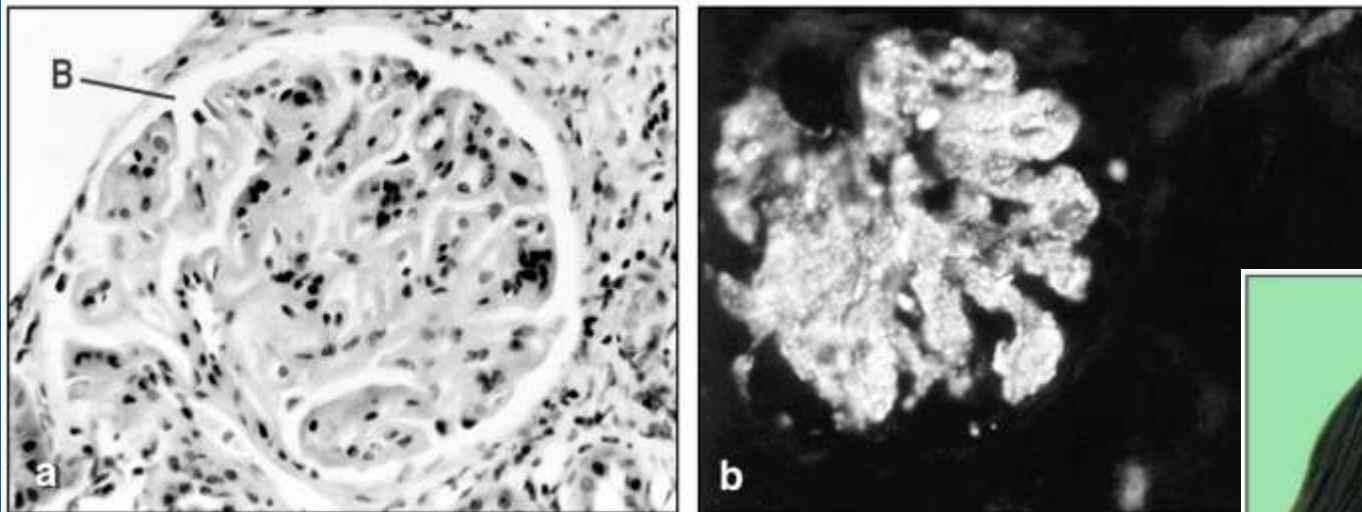


Figure 11-9 The Immune System, 2/e (© Garland Science 2005)

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

Most rheumatological diseases are caused by autoimmunity

Rheumatic diseases caused by autoimmunity

Systemic lupus erythematosus (SLE)
Rheumatoid arthritis
Juvenile arthritis
Sjögren's syndrome
Scleroderma (progressive systemic sclerosis)
Polymyositis–dermatomyositis
Behcet's disease
Ankylosing spondylitis
Reiter's syndrome
Psoriatic arthritis

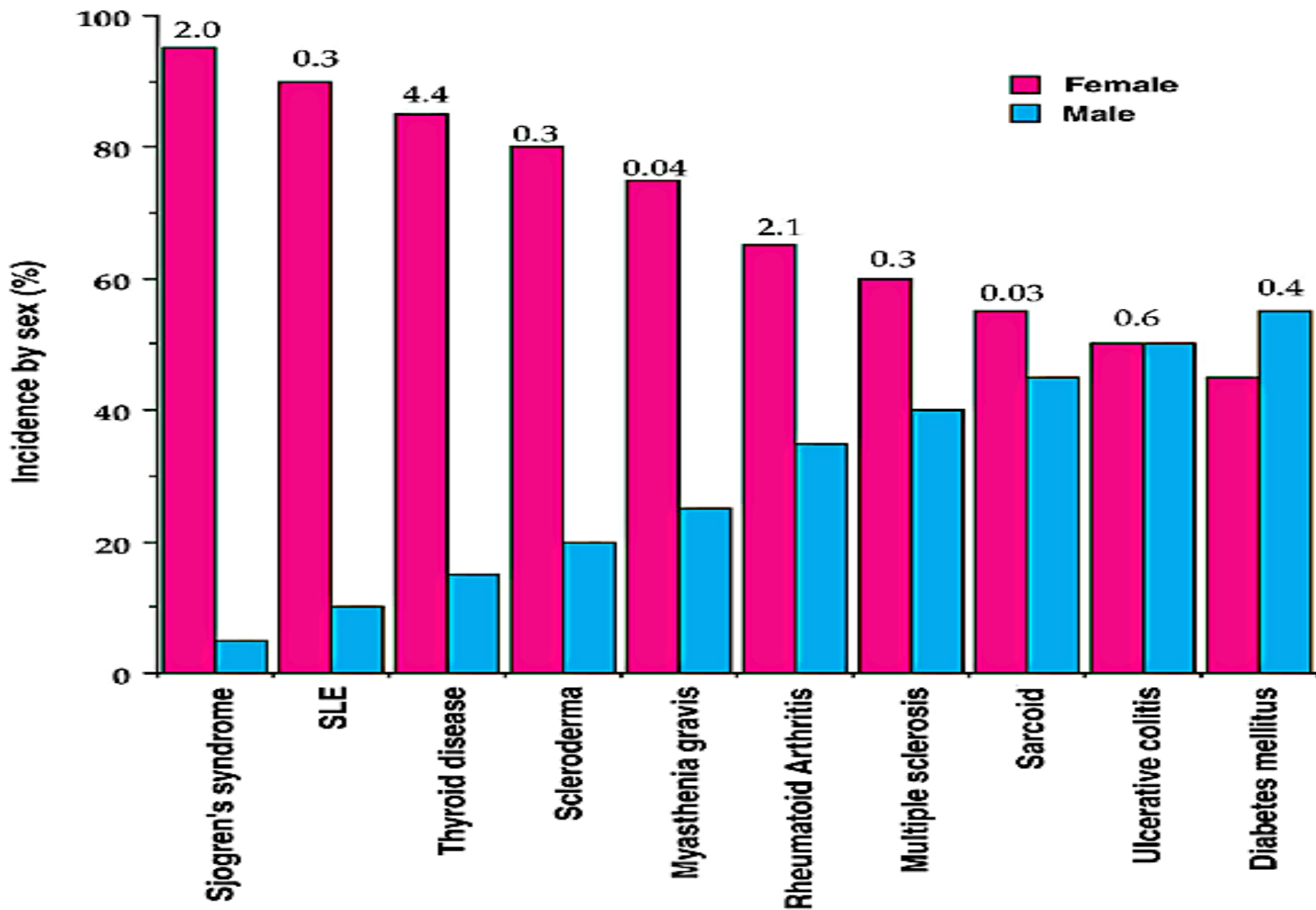


Figure 11-12 The Immune System, 2/e (© Garland Science 2005)

Female: Male Ratios in Some Autoimmune Diseases

- Multiple sclerosis 2:1
- Myasthenia gravis 2:1
- Diabetes 2:1
- Rheumatoid arthritis 4:1
- Graves' disease 7:1
- SLE 9:1
- Hashimoto's disease 50:1

Sex differences in autoimmunity



Immunopathologic Mechanisms

- ❑ **Tissue destruction:** in diabetes; CTLs destroy insulin-producing B-cells in pancreas
- ❑ **Antibodies block normal function:** in myasthenia gravis; Ab binds acetylcholine receptors
- ❑ **Antibodies stimulate inappropriate function:** in Graves' disease; Ab binds TSH receptor, mimics thyroid-stimulating hormone and activates unregulated thyroid hormone production
- ❑ **Antigen-antibody complexes affect function:** in Rheumatoid arthritis; IgM specific for Fc portion of IgG and IgM-IgG complexes deposited in joints leading to inflammation

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

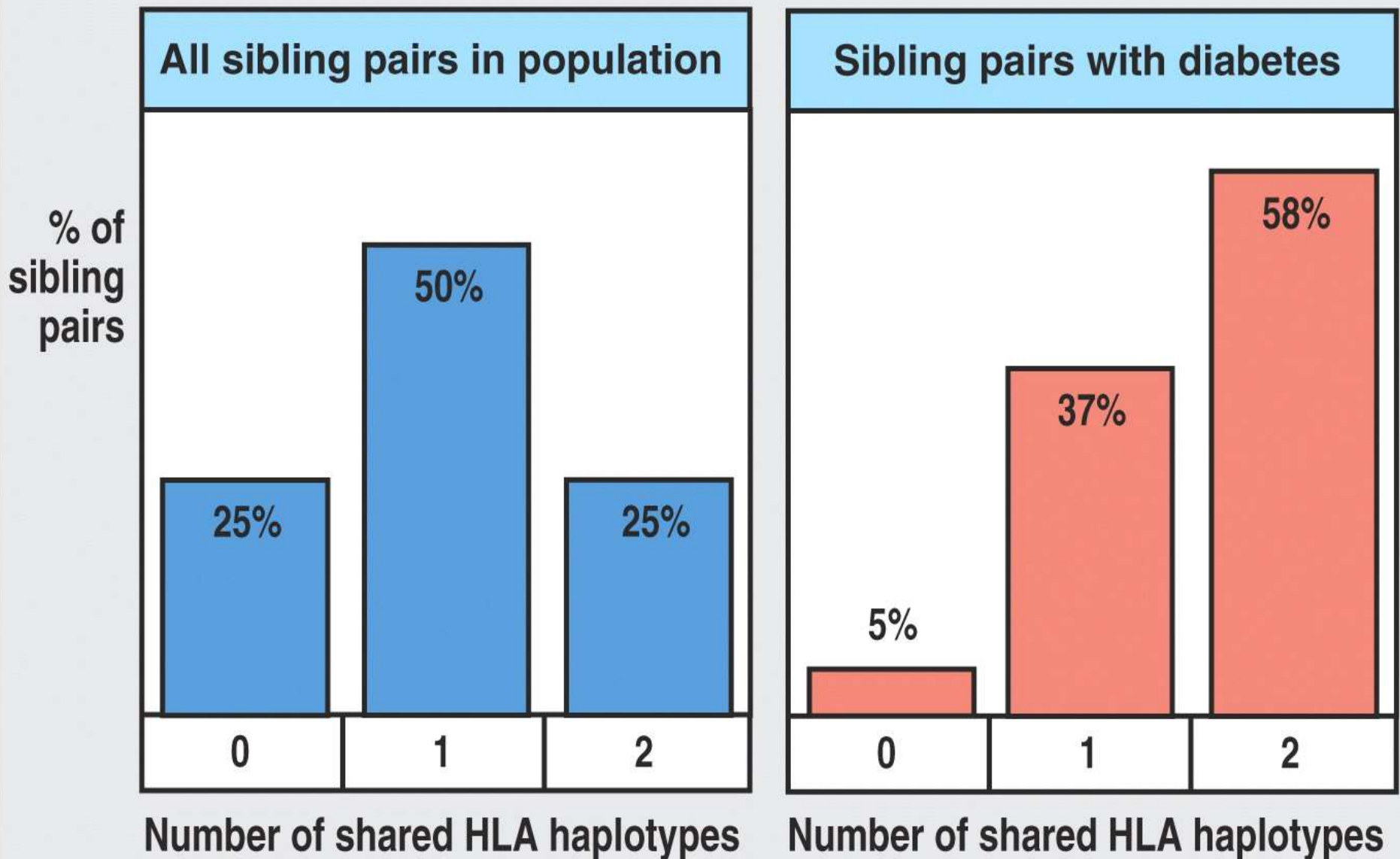
Exceptions to the Rule – Simple Genetic Autoimmune Illnesses

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

Genetics of autoimmunity

- Human autoimmune diseases are complex polygenic traits
 - Identified by genome-wide association mapping
 - Single gene mutations are useful for pathway analysis
- Some polymorphisms are associated with multiple diseases
 - May control general mechanisms of tolerance and immune regulation
- Other genetic associations are disease-specific
 - May influence end-organ damage

HLA is the dominant genetic factor affecting susceptibility to autoimmune disease



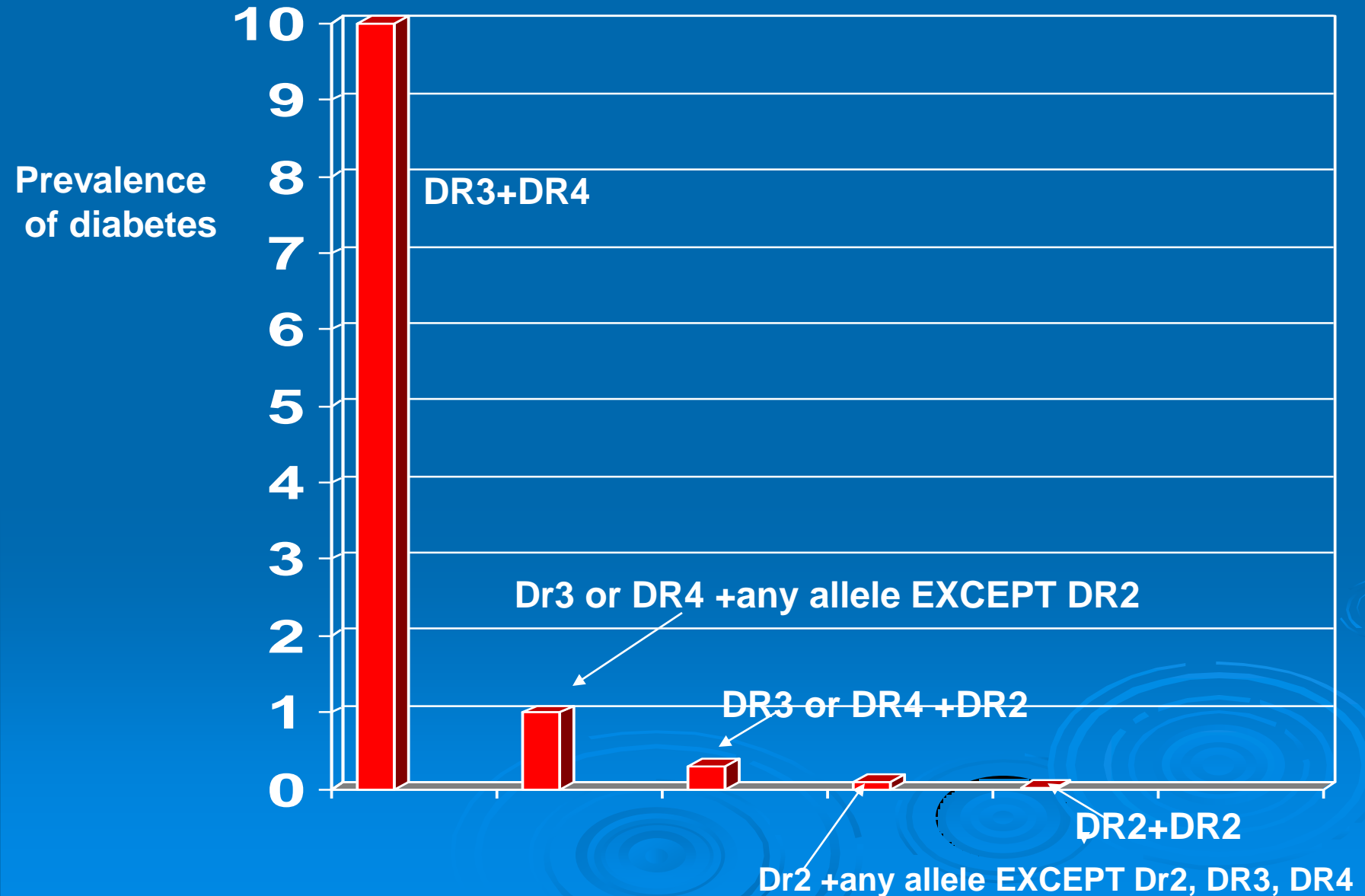
HLA Association and Autoimmune Diseases

- ❑ HLA-B8: Myasthenia gravis
- ❑ HLA-B27: Ankylosing spondylitis, Reiter's disease, acute uveitis
- ❑ HLA-Cw6: Psoriasis
- ❑ HLA-DR2: Goodpastures syndrome, MS
- ❑ HLA-DR3: Graves disease, MS, SLE, IDDM, Addison's disease
- ❑ HLA-DR4: IDDM, Pemphigus vulgaris, Rheumatoid arthritis
- ❑ HLA-DR5: Hashimoto's thyroiditis

Associations of HLA genotype with susceptibility to autoimmune disease

Disease	HLA allele	Relative risk	M/F
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10.04	<0.5
Good Pasteur's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4-5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10-20
Insulin-dependent diabetes mellitus	DR3 & DR4 DQ 2	3.2	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4-5

Population studies of HLA alleles in insulin-independent diabetes mellitus



Association with Infectious Processes

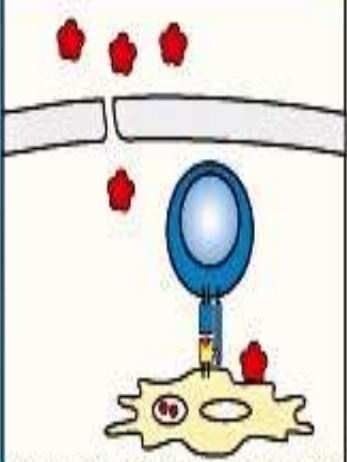
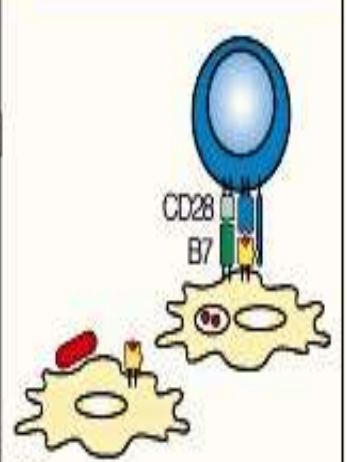
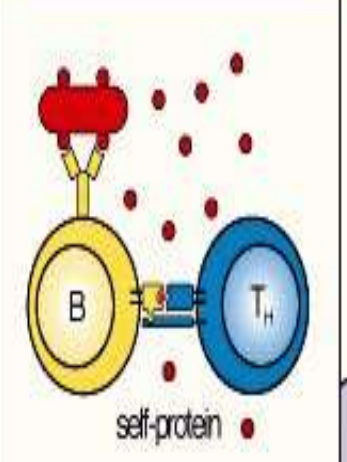
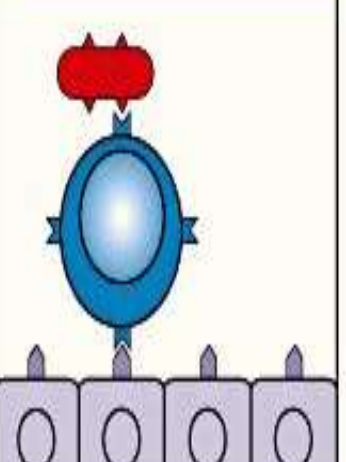
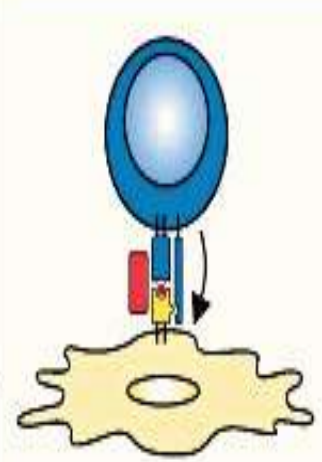
- SLE → HTLV-1, HIV-1
- IDDM → Coxsackie, Mumps, Rubella viruses
- Rheumatic fever → Streptococcus pyogenes
- Ankylosing spondylitis → Yersinia, Klebsiella
- Rheumatoid arthritis → EBV, HTLV
- Celiac disease → Adenovirus 12

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
Coxsackie A virus, Coxsackie B virus, echoviruses, rubella	HLA-DQ2, HLA-DQ8 DR4	IDDM

Figure 11-30 The Immune System, 2/e (© Garland Science 2005)

Several ways in which infectious agents could break self tolerance

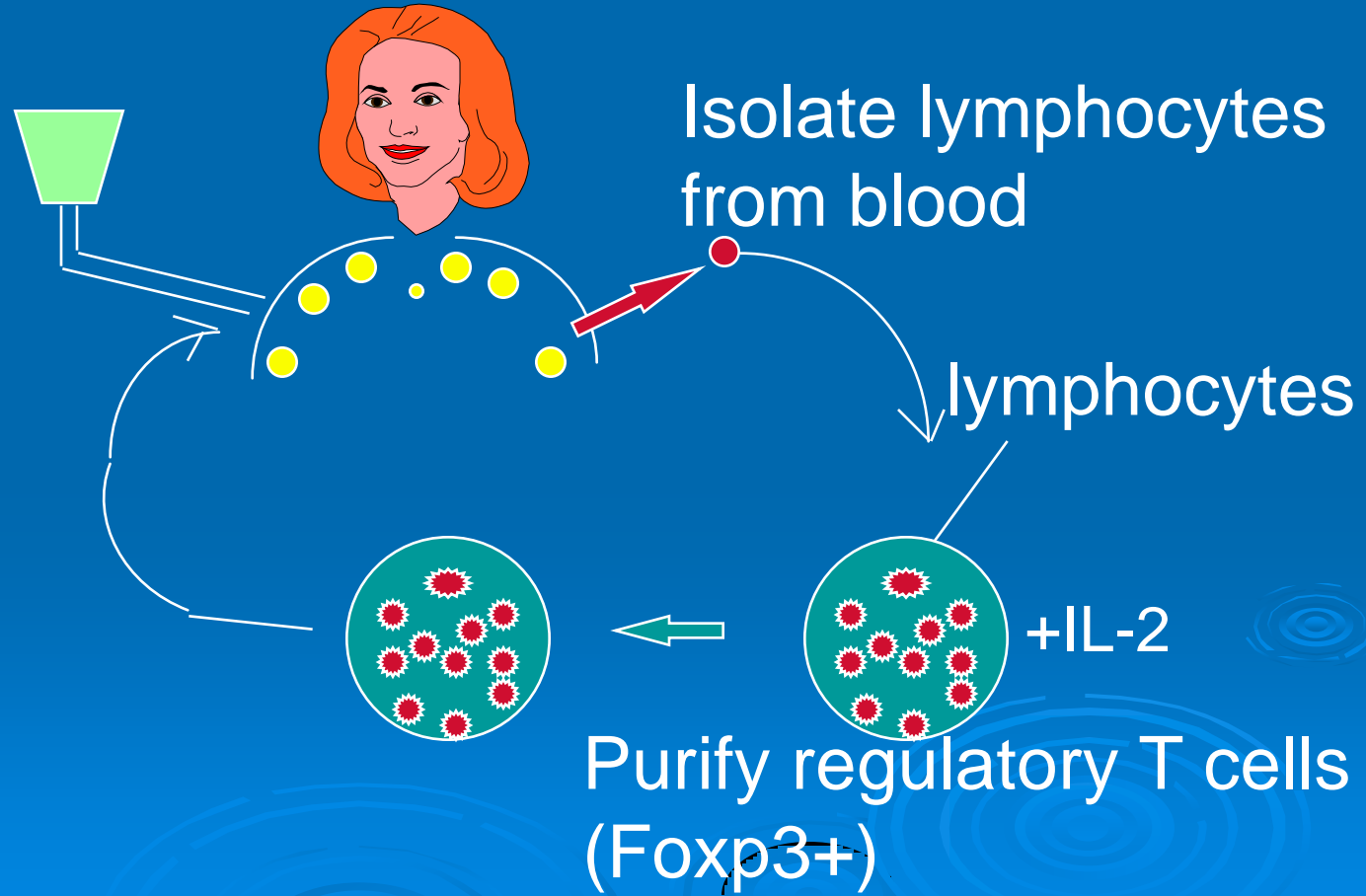
Mechanism	Disruption of cell or tissue barrier	Infection of antigen-presenting cell	Binding of pathogen to self protein	Molecular mimicry	Superantigen
Effect	Release of sequestered self antigen; activation of non-tolerized cells	Induction of co-stimulator activity	Pathogen acts as carrier to allow anti-self response	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
Example	Sympathetic ophthalmia	Effect of adjuvants: induction of EAE	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis
					

Treatment of Autoimmunity

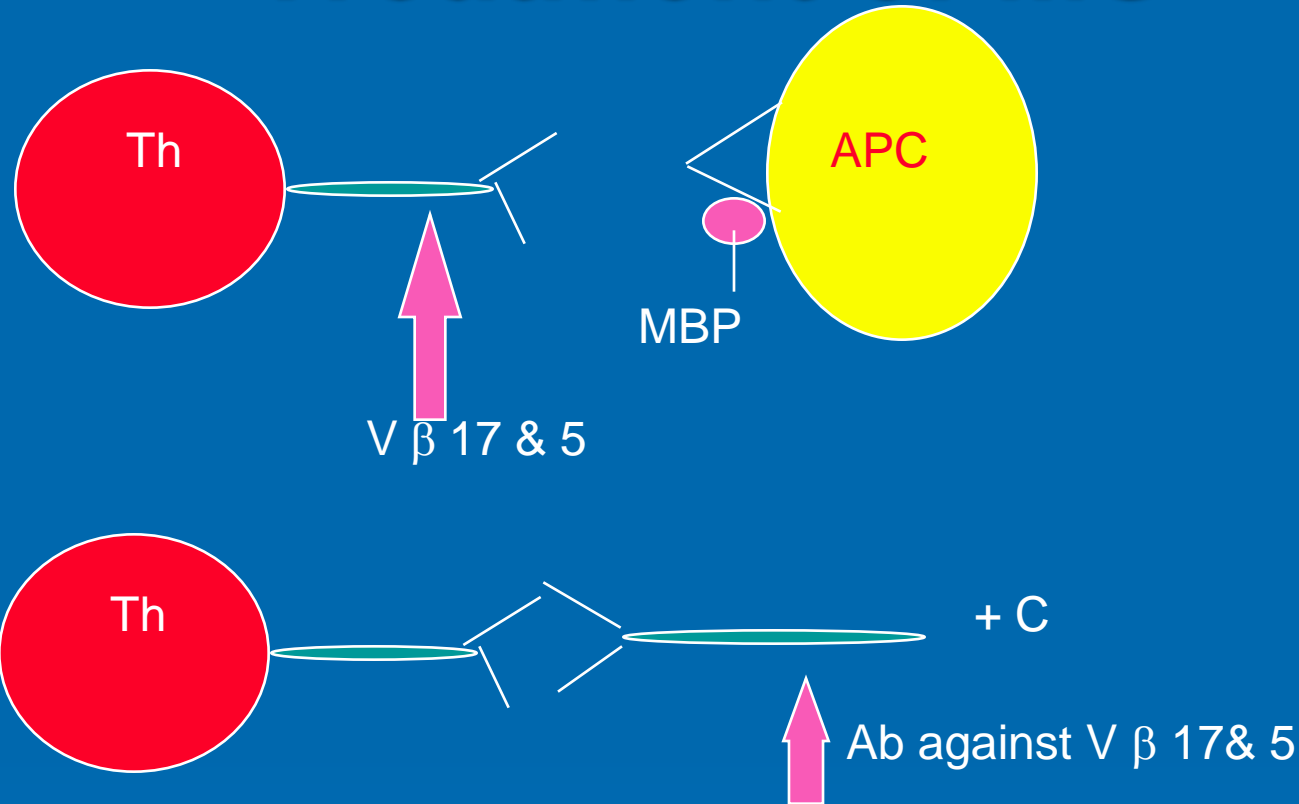
- **Immunosuppressive drugs**
 - **Corticosteroids, Azathioprine**
 - **Cyclosporine A**
 - **Anti-inflammatory**
- **Oral administration of myelin purified from cow brains--to treat MS.**
- **Transfer of regulatory T cells.**

Immunotherapy of autoimmune disease

Use of Regulatory T cells



Treatment of MS



- In MS, most T cells that respond to MBP use V β 17 and V β 5, TCR. Thus Abs against such T cells are being tested.

Treatment of Autoimmunity

- Use of beta-interferon to treat MS → blocks HLA expression.
- Use of Abs against TNF → suppresses arthritis pain for 5-10 weeks.
- Use of Abs against adhesion molecules → VLA-4, ICAM-1, etc.
- Use of Abs against CD4 Th.

Summary of Autoimmunity

- **Cause: Multiple—genetic, environmental, nutrition, infections, etc**
- **Breakdown in self-tolerance.**
- **Organ specific or Systemic.**
- **Majority are caused by autoAb production**
- **Treatment: Immunosuppressive drugs, Abs against TCR, cytokines, adhesion molecules, etc.**