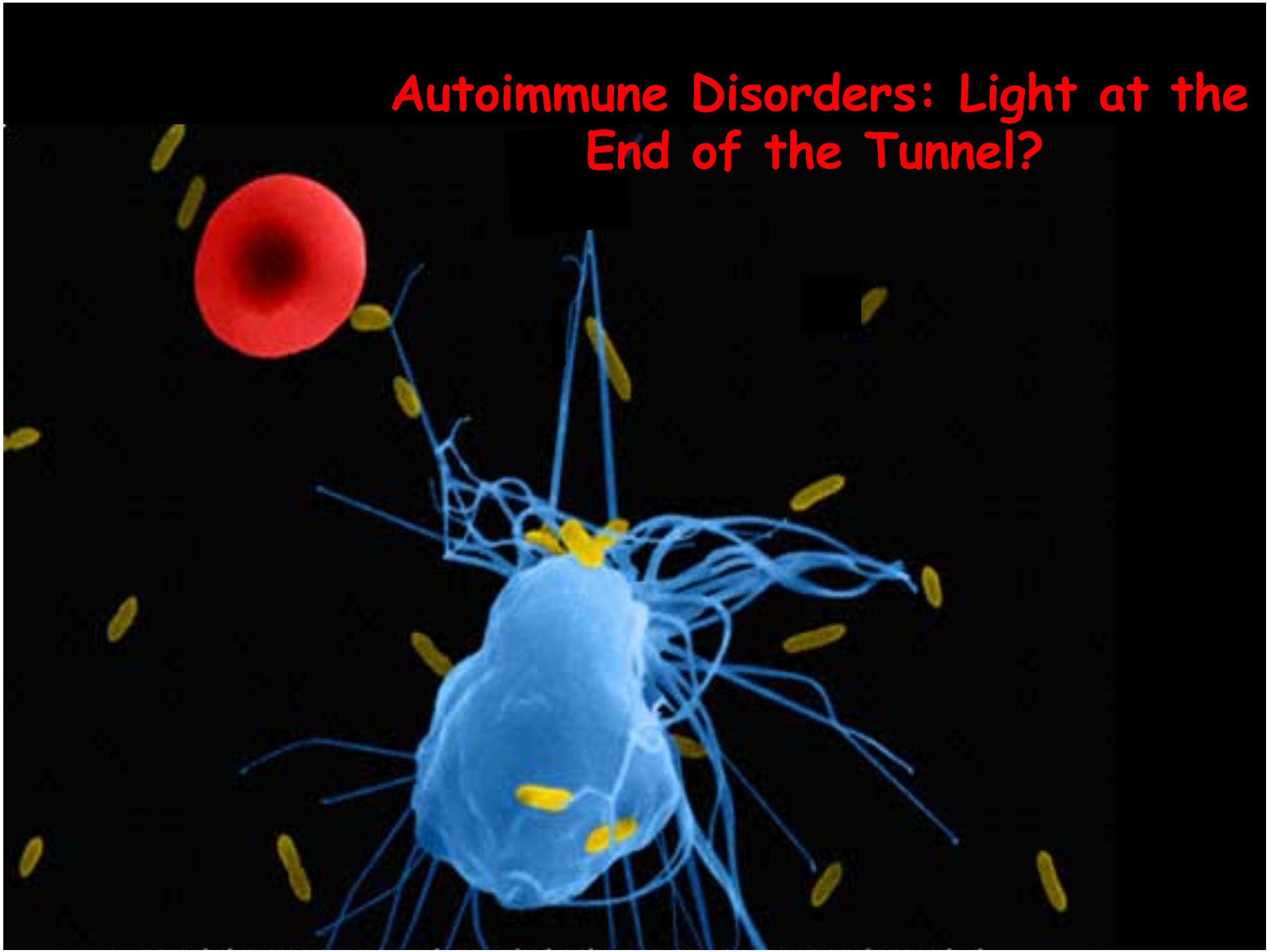
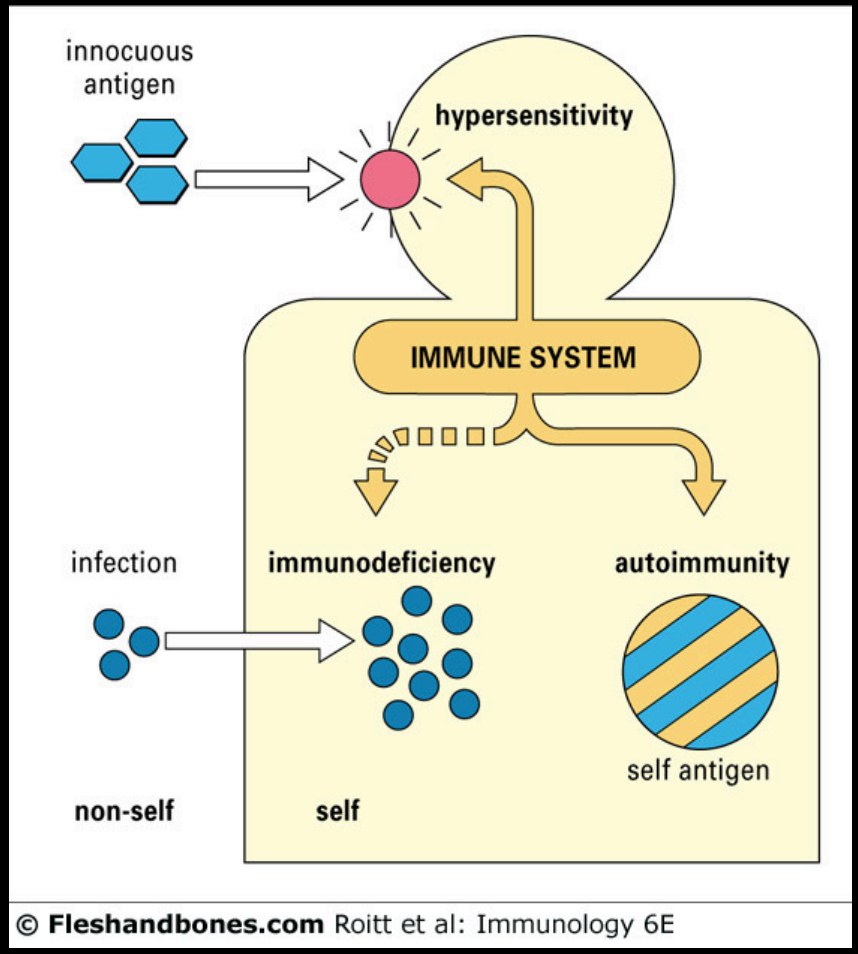
Autoimmune Disorders: Light at the End of the Tunnel?



Autoimmunity, one of three major mechanisms of 'inappropriate' immunity



What are autoimmune diseases?

The ability of the immune system to discriminate between 'self' and 'non-self' is a fundamental requirement for life.

The existence of self-tolerance prevents the individual's immune system from attacking normal cells and tissues of the body.

A breakdown or failure of the mechanisms of self-tolerance results in Autoimmunity.

Autoimmune Diseases

In autoimmunity, an immune response to self results in tissue injury. Autoimmune disorders are a diverse group of conditions, which occur due to abnormal stimulation and signaling within the immune system. "Self" versus "non-self" recognition is altered.

- There are ~80 different autoimmune diseases.
- Women are at 2.7x greater risk.
- Autoimmune diseases fit into Type II, III, and IV hypersensitivity-induced responses.
- Autoimmune diseases are not mediated by IgE (Type I hypersensitivity) antibodies.

How common are autoimmune diseases?

The prevalence values depend on the genetic background of the studied populations, on the geographical area, sizes of the populations, and definitions of the parameters that are being considered as positive signs of a disease.

Autoimmune diseases involve a multigenic predisposition.

For example, an individual who has an identical twin with SLE has a much higher frequency of developing SLE than a member of the general population (27-54% vs 0.1%)

How common are autoimmune diseases?

Cumulative data obtained from many different comprehensive epidemiological studies in the past 50 years estimate that the prevalence of autoimmune diseases is at the range of 3-9%.

Some autoimmune diseases are rare, while others, such as Hashimoto's disease, affect many people.

Fortunately, most diseases cause minor inconveniencies and are not life threatening (*e.g.*, Psoriasis, Vitiligo).

Many autoimmune diseases co-occur at greater than expected rates within proband patients and their families; this does not appear to be a uniform phenomenon across all diseases.

Recent Prevalence Data for Autoimmune Diseases, by Geographic Area

Hospital-based Data		Hospital and non-Hospital- based Data			
Denmark		Europe, North America, Australia, New Zealand		Asia, Middle East, Caribbean, South America	
Disease	Rate per 100,000	Study Area	Rate per 100,000	Study Area	Rate per 100,000
Systemic lupus	32	US, Spain, Greece	34-150	Saudi Arabia	19
Celiac disease	50	Greece, Netherland	180-350	Iran, Tunisia	140-280
		Iceland, Italy	740-1000	Brazil, Argentina	470-600
		Finland	1900	Turkey	900
Multiple sclerosis	182	US, Canada	177-358	Brazil, Argentina	4-20
		Italy, Greece, France	121-200	Jordan, Iran, Israel	11-62
		Norway, Portugal	46-50	Japan	13
Myasthenia gravis	18	Greece, Estonia, Croatia	8-15	Colombia	3
		UK, Netherlands, Sweden	8-15	Curacuo & Aruba	7
Sjögren disease	48	UK	3500	China	330-770
		Slovenia, Greece	600	Turkey	720-1560
Rheumatoid arthritis	381	France, Hungary, UK	310-810	Thailand, China	120-280

Main causative factors of autoimmune diseases

- **Genetic predispositon** - Many genetic loci affect the predisposition to autoimmune disease. Many autoimmune diseases show association with specific Major Histocompatability Complex (MHC) genes.

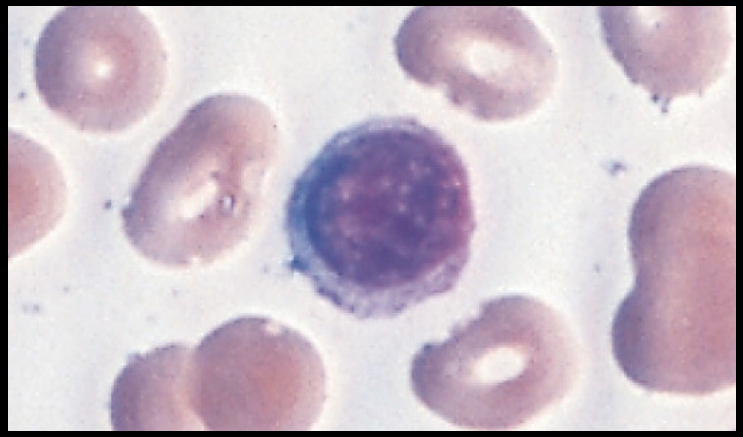
- **Gender** - Hormonal influences, especially sex hormones. In specific autoimmune diseases (SLE, MS), females are more commonly affected.

- **Environment** - Infections, especially viral, stress conditions, etc.

Susceptibility to Autoimmunity

- The best evidence for genetic factors in autoimmunity comes from identical twin studies.
- High concordance in twins suggests shared genetic or environmental factors.
- If a disease is restricted to monozygotic twins then genetic factors are important.
- In insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis, MS, and SLE, about ~20% of monozygotic twins show concordance, compared with <5% in dizygotic twins.

Autoimmune responses are mediated by the adaptive immune system



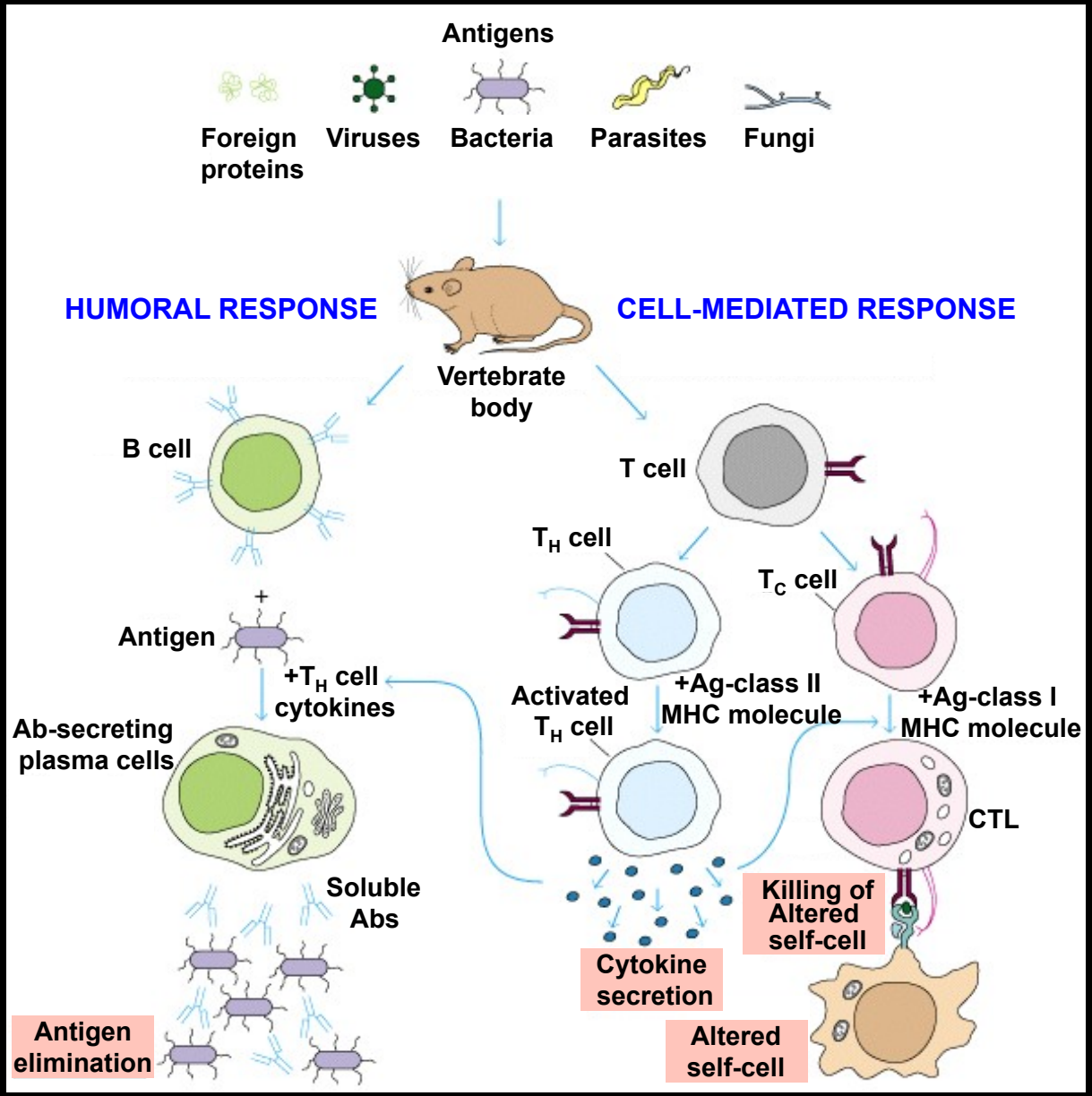
A blood smear showing multiple erythrocytes and a single resting lymphocyte

- Adaptive immune responses are mediated by lymphocytes
- Primary cells of the lymphatic system, also circulate in blood
- They respond in an antigen-specific manner
- They are ~30% of all blood leukocytes (white blood cells).
- Each lymphocyte has a unique antigen (Ag) receptor
- Are inactive until they meet a pathogen and undergo activation
- Memory of the adaptive immune response is provided by the lymphocytes

The adaptive immune system

The humoral response involves interaction of B lymphocytes (B cells) with antigen (Ag) and their differentiation into antibody-secreting plasma cells. The secreted antibody (Ab) binds to the antigen and facilitates its clearance from the body.

The cell-mediated responses involve various subpopulations of T lymphocytes (T cells) that recognize antigen presented on self-cells. T helper (T_H) cells respond to antigen by producing cytokines. Cytotoxic T (T_C) cells respond to antigen by developing into effector cytotoxic T lymphocytes (CTLs), which mediate killing of altered self-cells (e.g., virus-infected cells).



Self-tolerance depends on the concerted action of a variety of mechanisms that operate at different sites and stages of development

Central tolerance
Central deletion of newly formed T and B lymphocytes in the thymus and bone marrow.

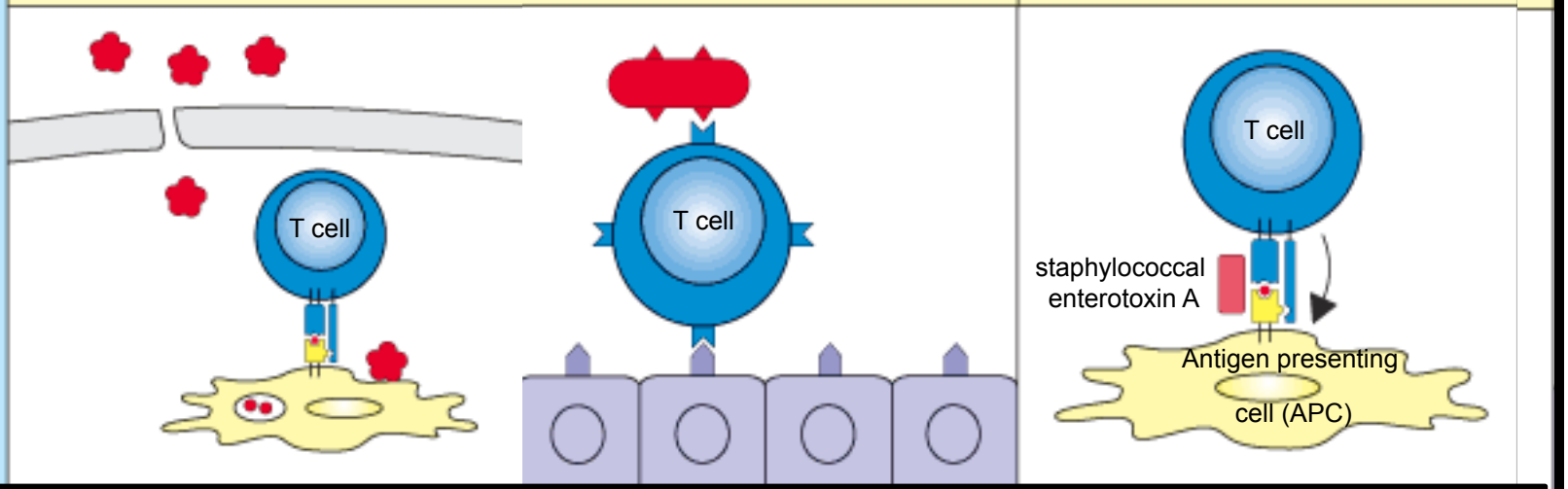
Peripheral tolerance
Cellular inactivation of adult lymphocytes, by 'weak' signaling that occur in the absence of costimulatory molecules.

Regulatory cells
Treg-mediated suppression of cytokine production.

Acquired tolerance
Immune system's adaptation to external antigens, such as the tolerance to fetal antigens during pregnancy. In adults, by repeated administration of very large doses of antigen, or small doses that are below the threshold required for stimulation of an immune response.

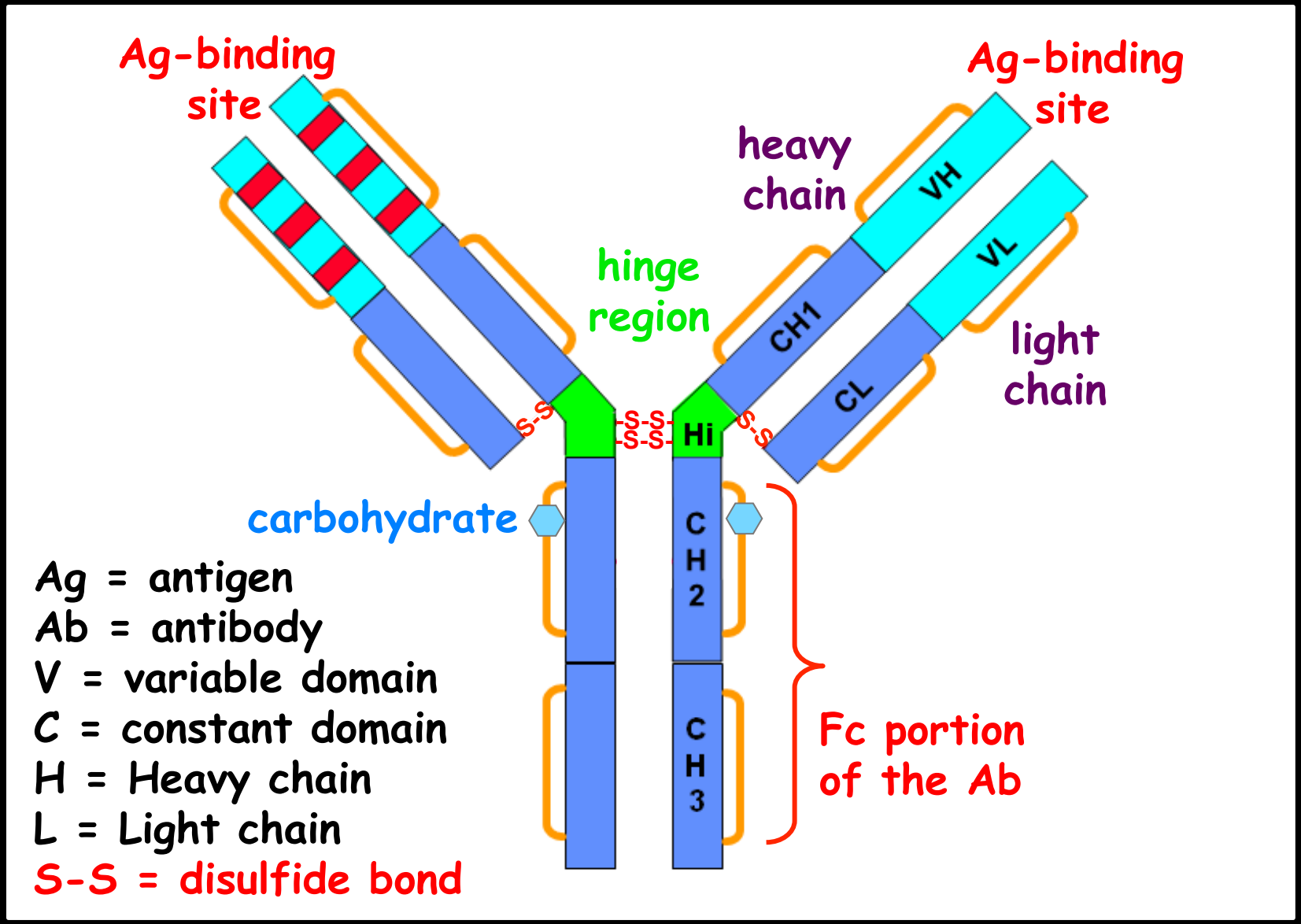
Mechanisms by which infectious agents can break self-tolerance

Mechanism	Disruption of cell or tissue barrier	Molecular mimicry	Superantigen
Effect	Release of sequestered self antigen; activation of nontolerized cells	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
Example	Sympathetic ophthalmia	Rheumatic fever Diabetes Multiple sclerosis	Rheumatoid arthritis



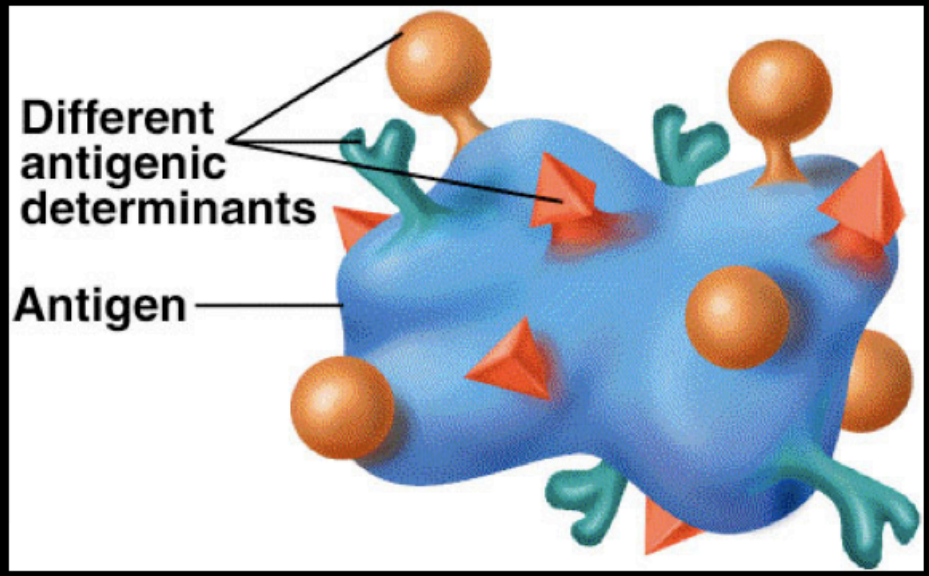
Immunobiology, Janeway et al., 4th Ed. Fig. 13.39a, p. 530 (5th, Fig. 13.42a)

Antibody Structure



Antibody molecules recognize and interact with small antigenic determinants (epitopes)

The specific site of an antigen that binds to an antibody is called an **antigenic determinant** or **epitope**.

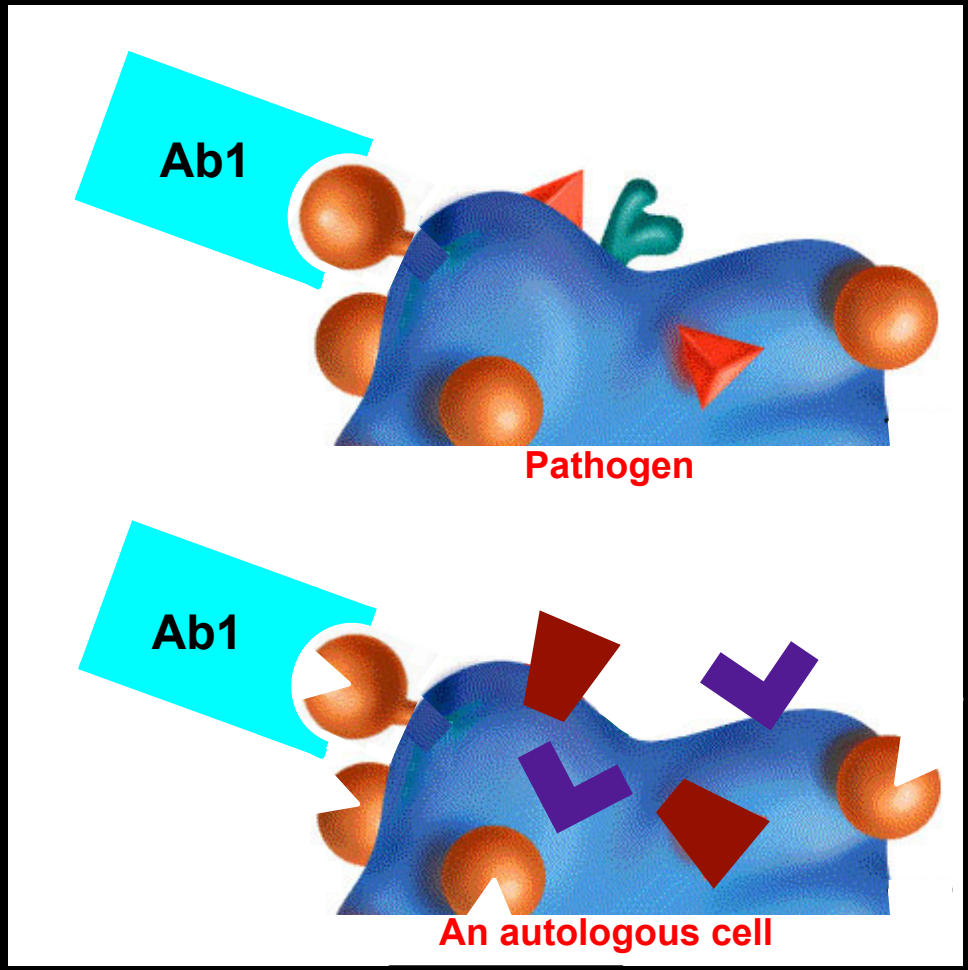


Most antigens have a variety of epitopes that generate a number of different antibodies that are called **polyclonal**.

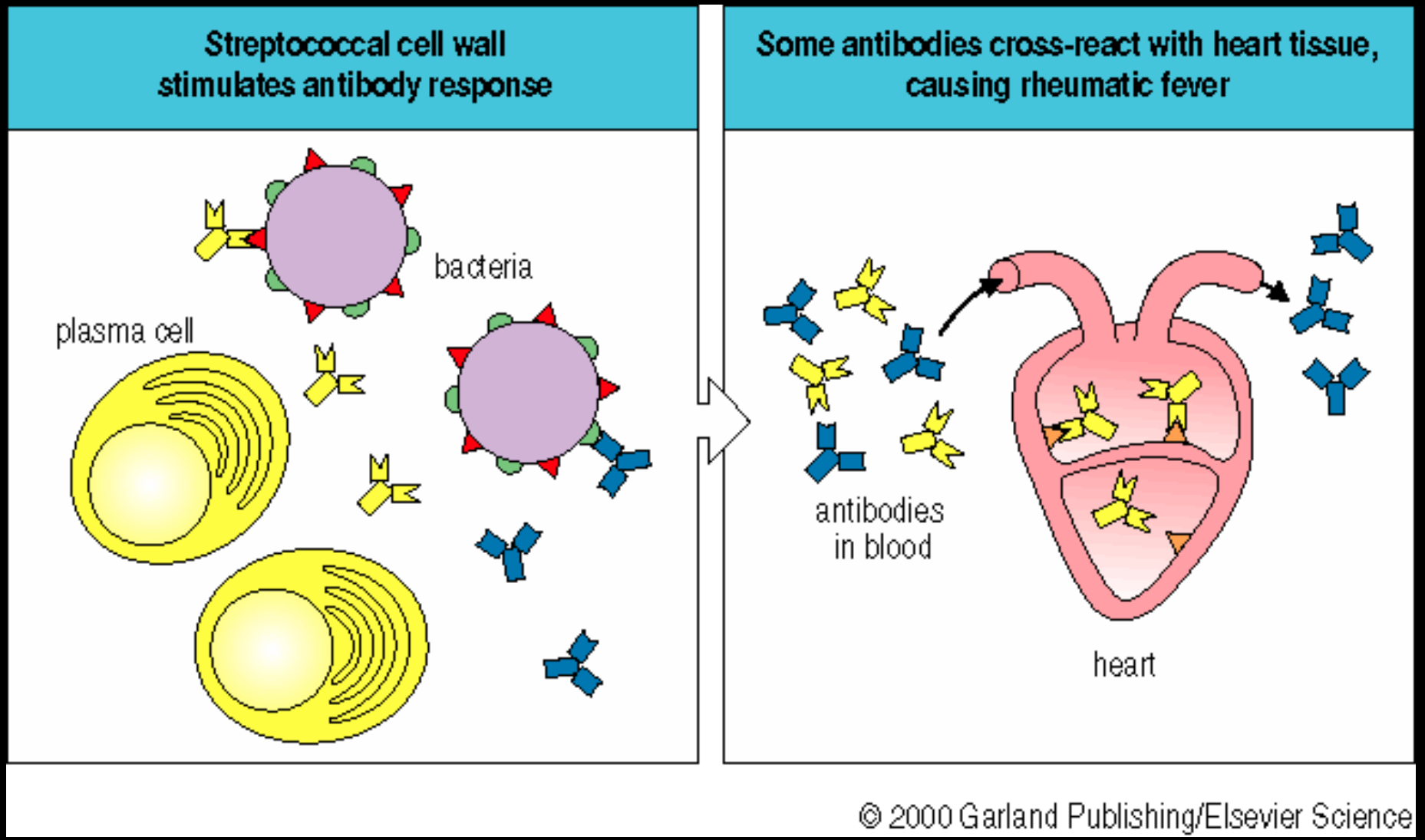
An immune response to a single epitope by one type of Ab producing cells is termed **monoclonal**.

Molecular mimicry

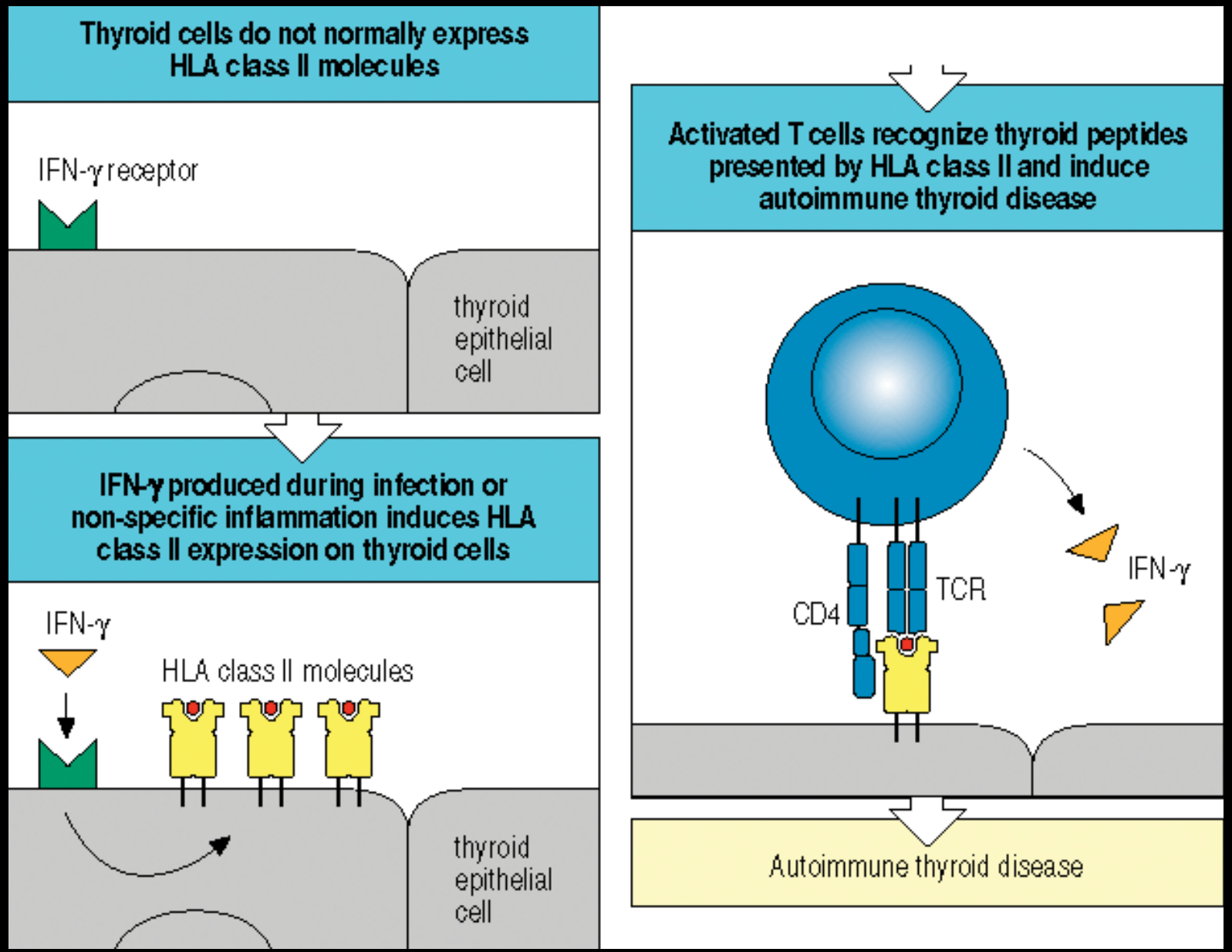
An antibody molecule that reacts against a specific epitope on a foreign antigen can cross-react against a similar epitope on a self protein



Rheumatic fever can occur following *Streptococcus* infection due to formation of cross reactive Abs that respond against heart, joints, skin, and brain tissue



A role for IFNγ in autoimmunity



Autoimmune Diseases

Organ specific autoimmune diseases:

Usually affect a single organ and the autoimmune response is directed against antigens within that organ.

e.g.: Type I diabetes mellitus, Goodpasture's syndrome, multiple sclerosis, Grave's disease, Hashimoto's thyroiditis, autoimmune pernicious anemia, myasthenia gravis, autoimmune Addison's disease, vitiligo.

Non-organ specific disorders:

Affect multiple organs and are usually associated with responses against self-molecules widely distributed throughout the body.

e.g.: SLE, Rheumatoid arthritis, scleroderma, Primary Sjogren's syndrome, polymyositis.

Immunobiology, Janeway et al., 5th Ed. Fig. 13.2, p. 504

Two types of autoimmune diseases

organ-specific	non-organ-specific

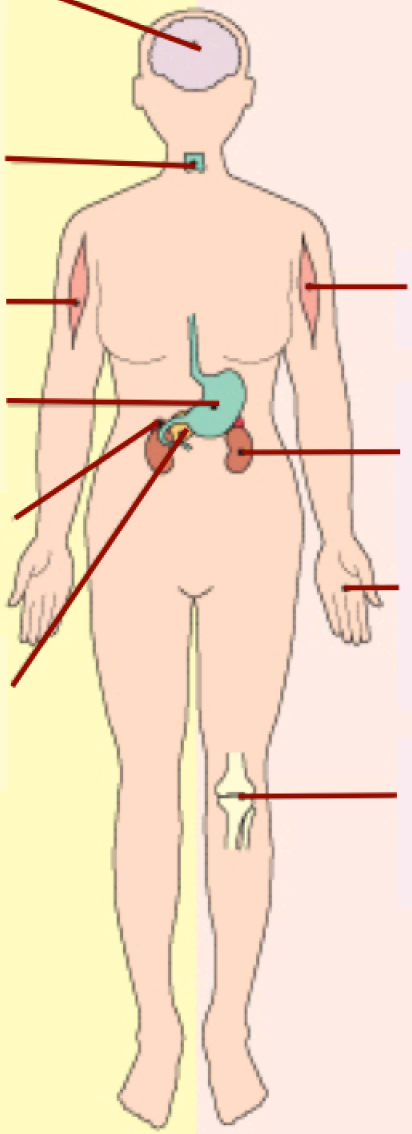
brain
multiple sclerosis

thyroid
Hashimoto's thyroiditis
Primary myxedema
thyrotoxicosis

stomach
pernicious anemia

adrenal
Addison's disease

pancreas
insulin-dependent diabetes mellitus



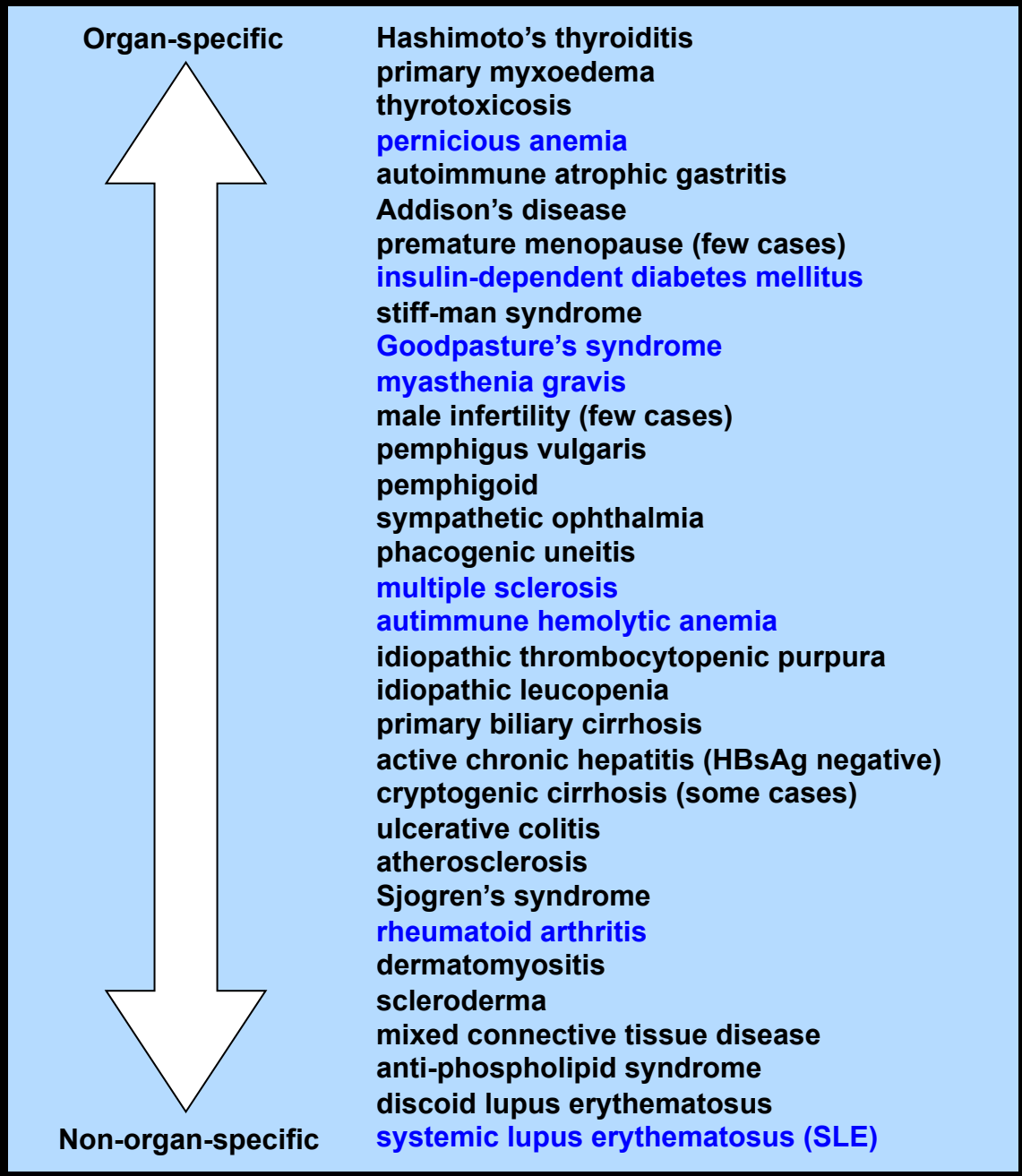
Muscle
myasthenia gravis

kidney
SLE

skin
Scleroderma
SLE

joints
rheumatoid arthritis

Autoimmune disease may be classified as organ-specific or non-organ-specific depending on whether the response is primarily against antigens localized to particular organs, or against widespread antigens.



Immunology, Roitt et al., 5th Ed. Fig. 28.3, p. 368

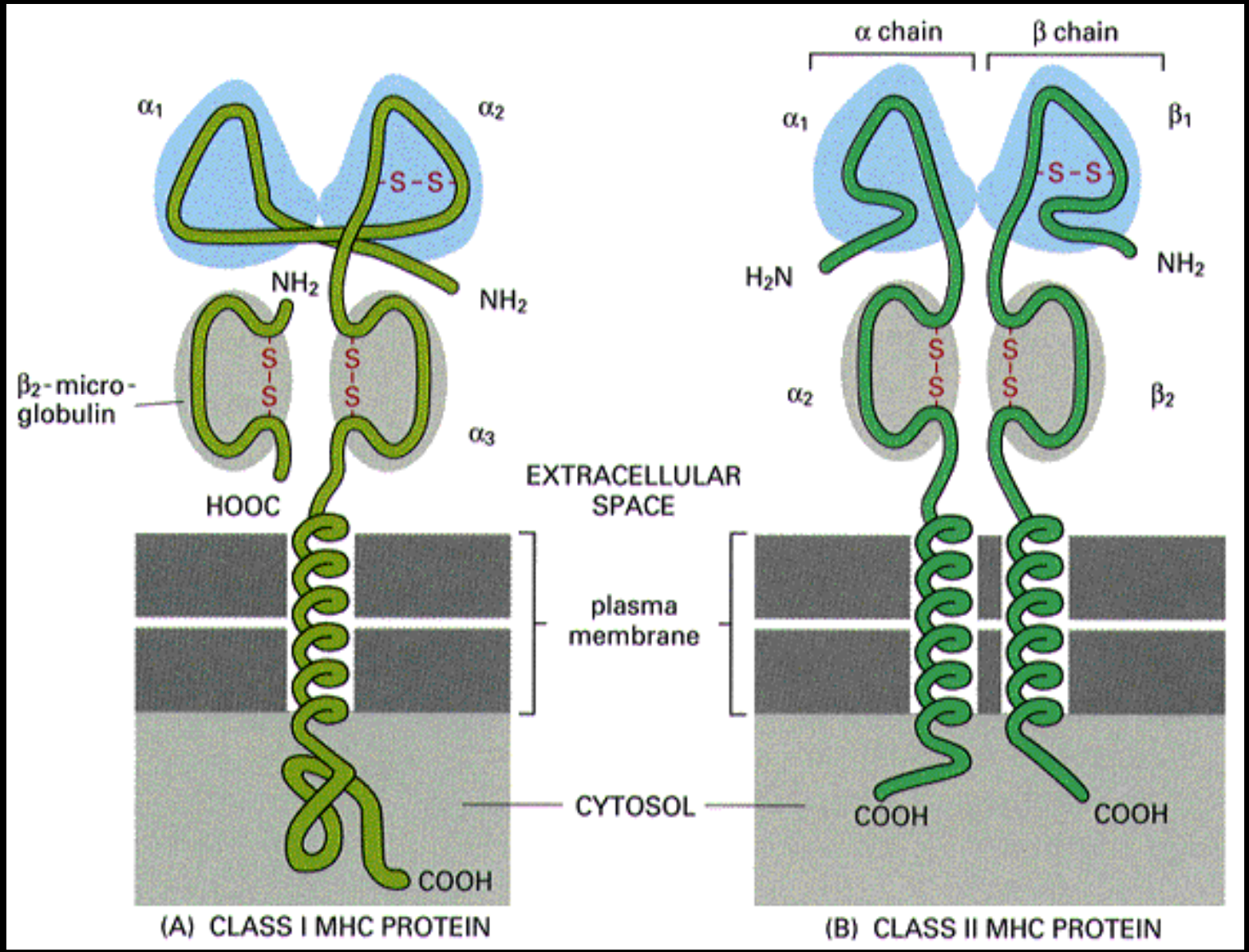
Autoimmune-induced tissue damages

- Autoimmune responses are initiated in the same way as normal adaptive immune responses.
- A self antigen is recognized on the target tissue by effector lymphocytes.
- Tissue damages can be mediated by effector mechanisms of both T and B lymphocytes (antibodies).
- In contrast to a regular immune response, an autoimmune response persists since the antigens cannot be permanently removed.

Why is MHC involved in susceptibility to autoimmune diseases?

- Autoimmune responses are mediated by T cells.
- T cells recognize Ags only when displayed by MHC molecules on the surface of antigen presenting cells.
- Some Human Leukocyte Antigen (HLA; human MHC) types preferentially bind self-antigens which can then be presented to T cells.

MHC class I and class II molecules

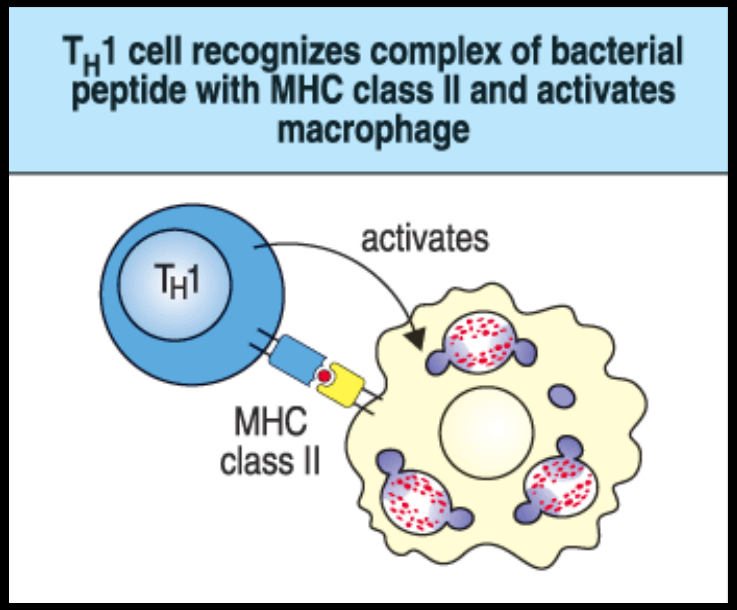


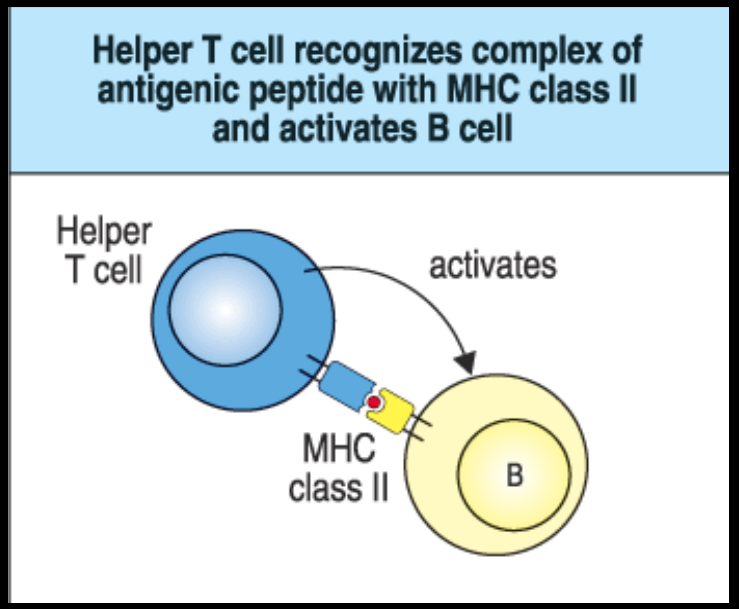
T cell recognition

T_H1 and T_H2 cells recognize antigen presented by MHC class II molecules.

On recognition of antigen on infected macrophages, T_H1 cells activate the macrophage, leading to the destruction of the intracellular bacteria.

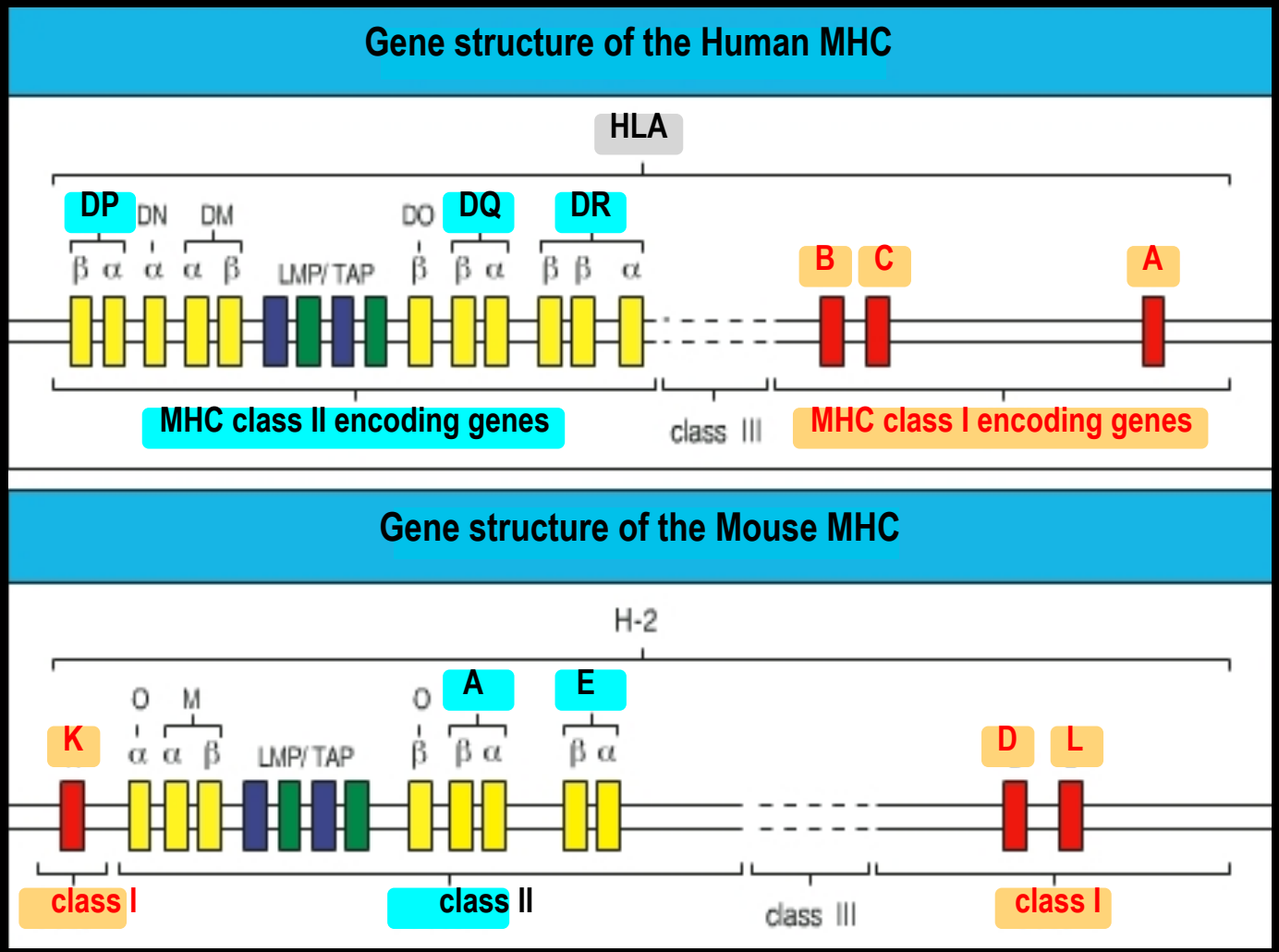
When T_H2 cells recognize antigen on B cells, they activate them to proliferate and differentiate into Ab-producing plasma cells.





Janeway *et al*., Immunobiology, 4th Ed., Garland Publishing, 1999, Fig. 1.30 (5th; Fig. 1.31, 2001)

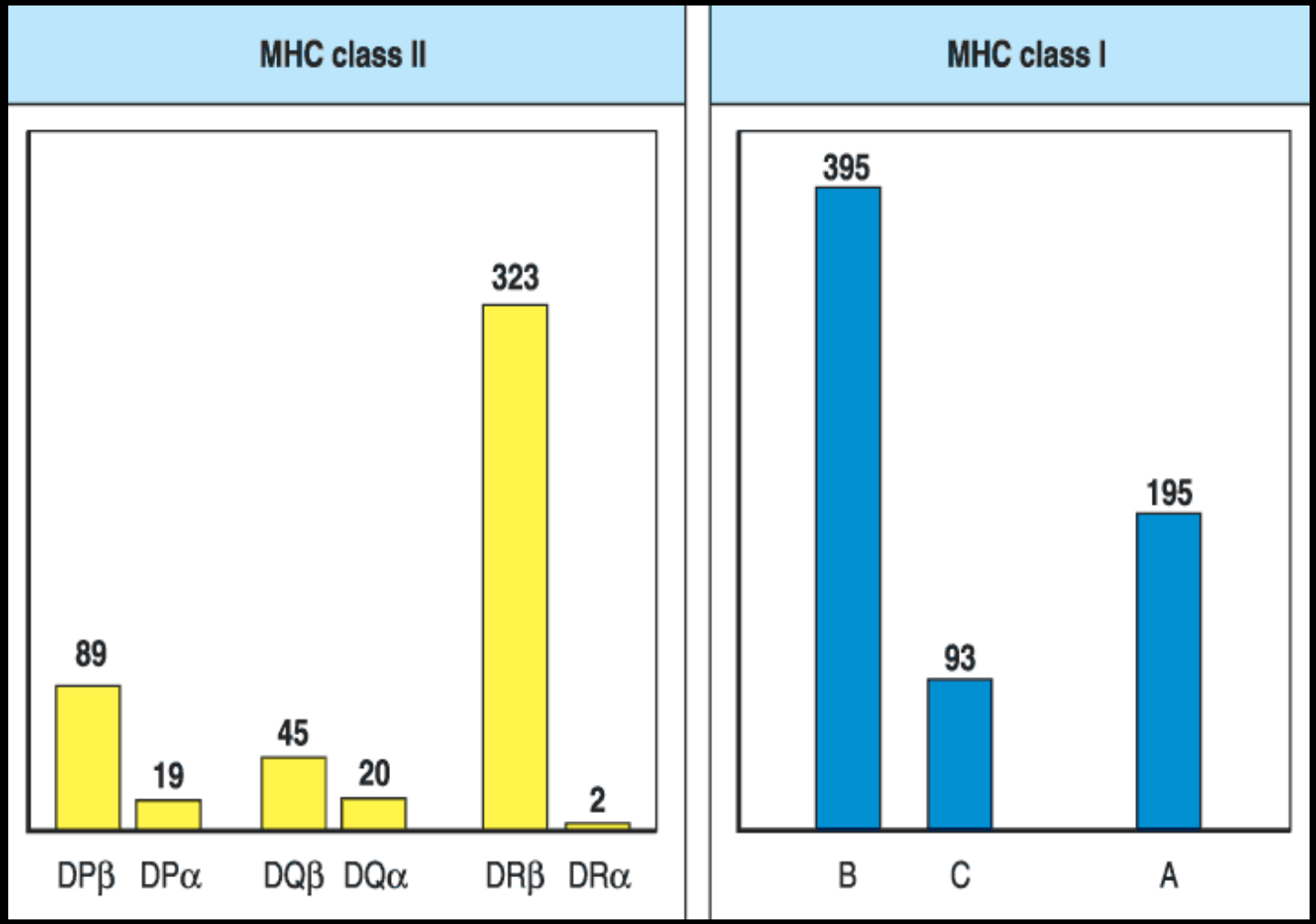
The genetic organization of the major histocompatibility complex (MHC) in humans and the mouse



Janeway *et al.*, Immunobiology, 4th Ed., Garland Publishing, 1999, Fig. 4.19

The human MHC genes are highly polymorphic

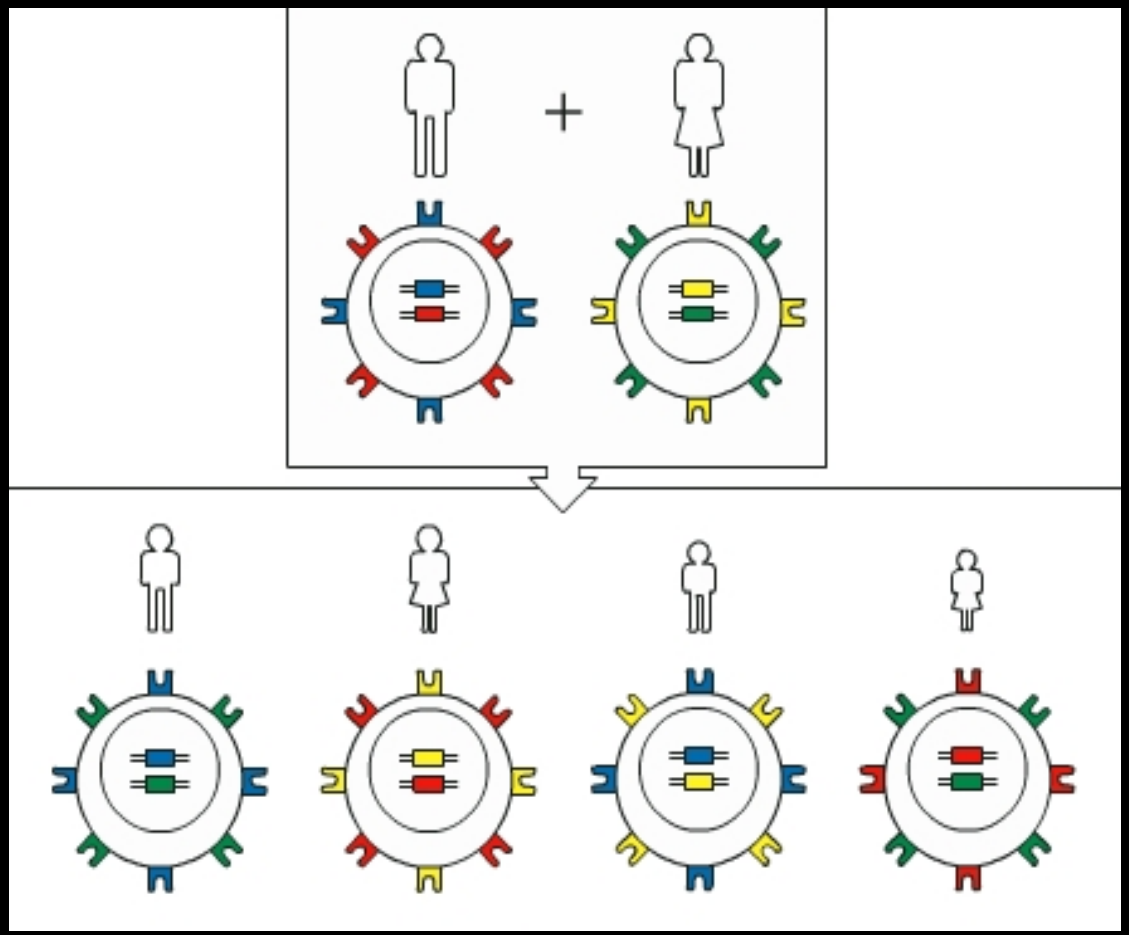
Numbers above the bars indicate the number of known alleles for the specific gene in the Caucasoid population



Janeway *et al*., Immunobiology, 4th Ed., Garland Publishing, 1999, Fig. 4.21 (5th; Fig.5.12, 2001)

Expression of MHC alleles is co-dominant

The MHC is so polymorphic that most individuals are likely to be heterozygous at each locus.



Janeway *et al*., Immunobiology, 4th Ed., Garland Publishing, 1999, Fig. 4.22. (5th; Fig. 5.13, 2001)

HLA-linked autoimmune diseases

Relative Risk - Ratio of antigen frequency in disease population to frequency in control population

Relative Risk

The statistical association between an autoimmune disease and a specific HLA gen is expressed as the relative risk. Relative risk is the ration between the incidence of the disease among carriers of the gene in question and the incidence among non carriers.

The relative risk of HLA-DR3+ individuals to develop Graves' disease

	DR3+	DR3−
Graves' disease +	4	2
Graves' disease −	1996	3998
Total	2000	4000

Frequency of Graves' disease among DR3+ individuals

$$\frac{4}{(4 + 1996)} = \frac{4}{2000} = 0.002$$

Frequency of Graves' disease among DR3− individuals

$$\frac{2}{(2 + 3998)} = \frac{2}{4000} = 0.0005$$

Relative risk $\frac{0.002}{0.0005} = 4$

Association of autoimmunity with HLA

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
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4–5

Immunobiology, Janeway et al., 4th Ed. Fig. 13.2, p. 492 (5th, Fig. 13.3)

Classification of autoimmune diseases

Autoimmune diseases can also be classified based on the immune mechanism which leads to the autoimmune response. There are three known mechanisms, also termed immunological hypersensitivity, that can induce autoimmunity.

- Type II - Cytotoxic/Stimulating (IgG/IgM-mediated)
- Type III- Arthus or Immune complex

  (IgG/IgM, immune complex-mediated)
- Type IV - Delayed type hypersensitivity

  (T cell-mediated delayed responses)

Some autoimmune diseases have multiple types of immunological hypersensitivity

Type II hypersensitivity-induced autoimmune diseases

Anti-cell surface antigen autoantibodies

- Binding of autoantibodies to cell surface molecules can lead to cell destruction (Type IIA), or to stimulation or inhibition of cell activities (Type IIB).

Autoimmune diseases due to type II hypersensitivity

Syndrome	Autoantigen	Consequence	
Antibody against cell-surface or matrix antigens (Type II)			
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes, anemia	Cellular destruction
Autoimmune thrombocytopenia purpura	Platelet integrin gpIIb:IIIa	Abnormal bleeding	
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage	
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin	
Acute rheumatic fever	Streptococcal cell wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves	Cellular destruction by cross-reactions
Graves' disease	Thyroid-stimulating hormone receptor	Hyperthyroidism	Cellular activation
Myasthenia gravis	Acetylcholine receptor	Progressive weakness	Cellular inhibition
Insulin-resistant diabetes	Insulin receptor (antagonist)	Hyperglycemia, ketoacidosis	Cellular inhibition
Hypoglycemia	Insulin receptor (agonist)	Hypoglycemia	Cellular activation

Immunobiology, Janeway et al., 4th Ed. Fig. 13.1, p. 490 (5th, Fig. 13.1)

Type IIA hypersensitivity-induced autoimmune diseases

Anti-cell surface antigen autoantibodies that induce cell cytotoxicity

- Initiated by the production of autoantibodies (IgM/IgG).
- Induced by autoantibody binding to intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (adsorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen).
- Mediated by a) complement activation and cell lysis, b) NK cell and macrophage activation that lyse the cells directly or following phagocytosis, respectively.

In diseases, such as autoimmune hemolytic anemia, Abs specific for cell-surface antigens can destroy cells

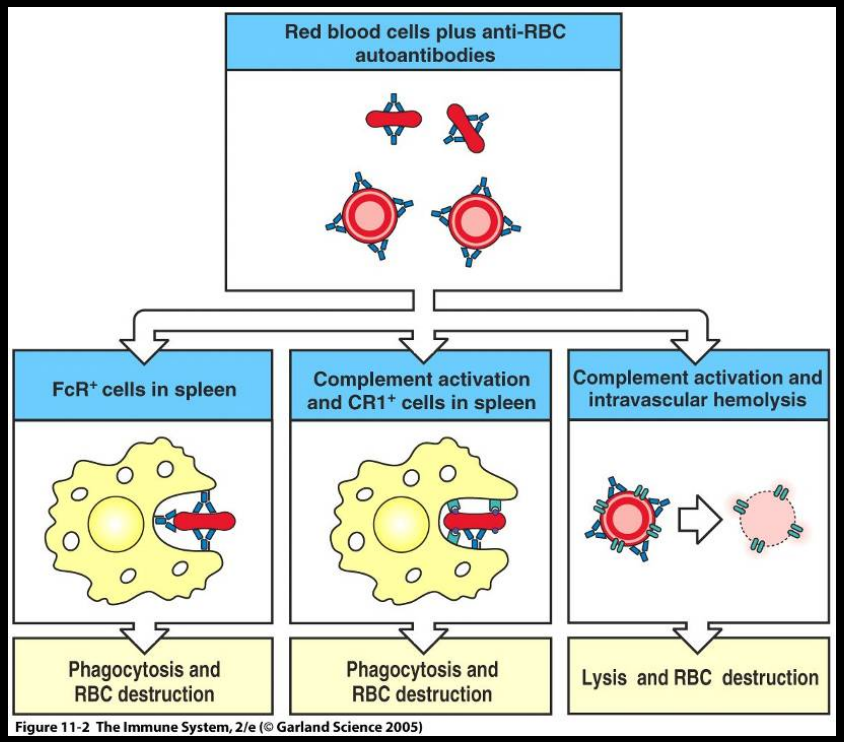
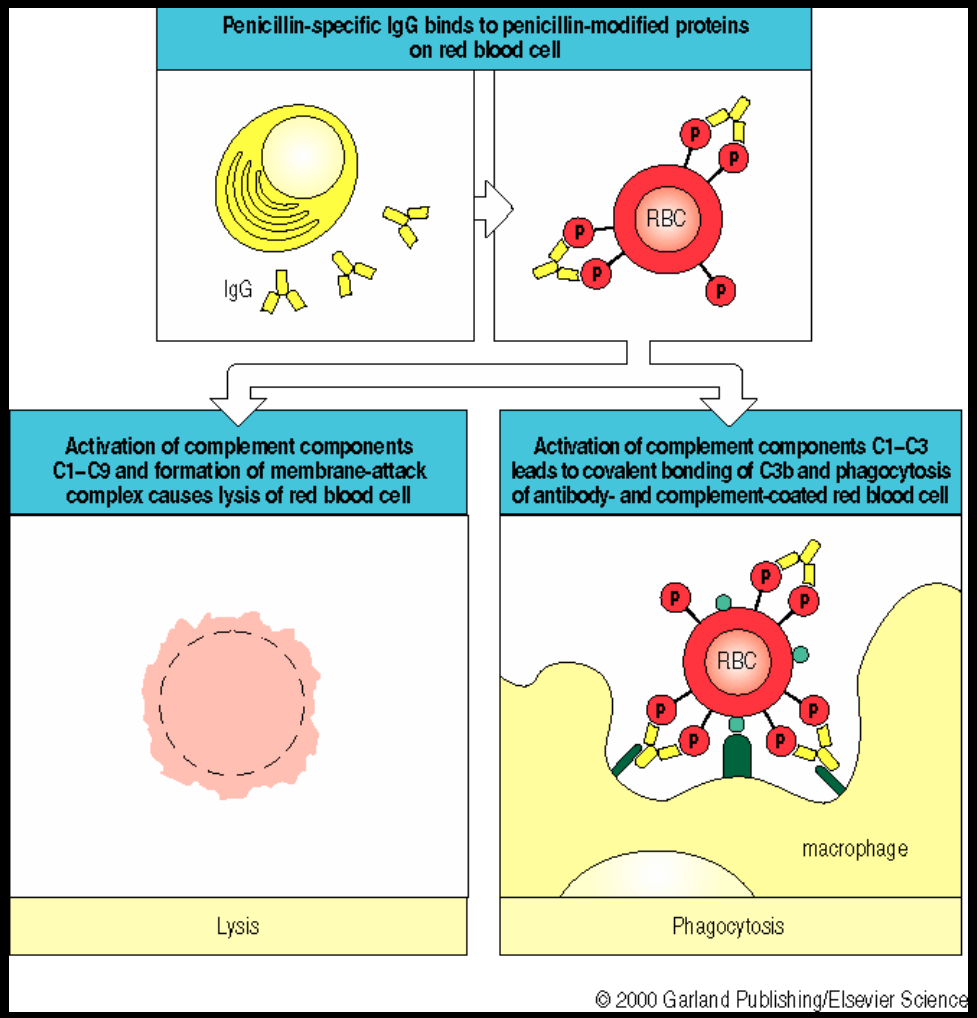


Figure 11-2 The Immune System, 2/e (© Garland Science 2005)

Immunobiology, Janeway et al., 4th Ed. Fig. 13.6, p. 496 (5th, Fig. 13.8)

Drug-induced autoimmune hemolytic anemia

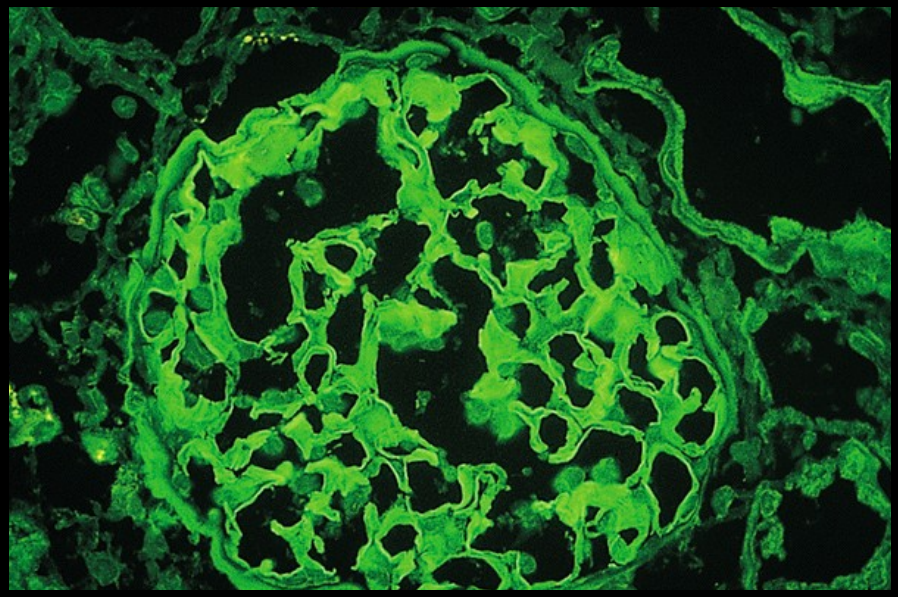


Drug (P=Penicillin) -modified red blood cells induce the production of antibodies, because the bound drug makes the cells look foreign to the immune system. Upon binding of these antibodies, the red blood cells become more susceptible to lysis or phagocytosis. Onset is dependent on the presence of specific antibodies.

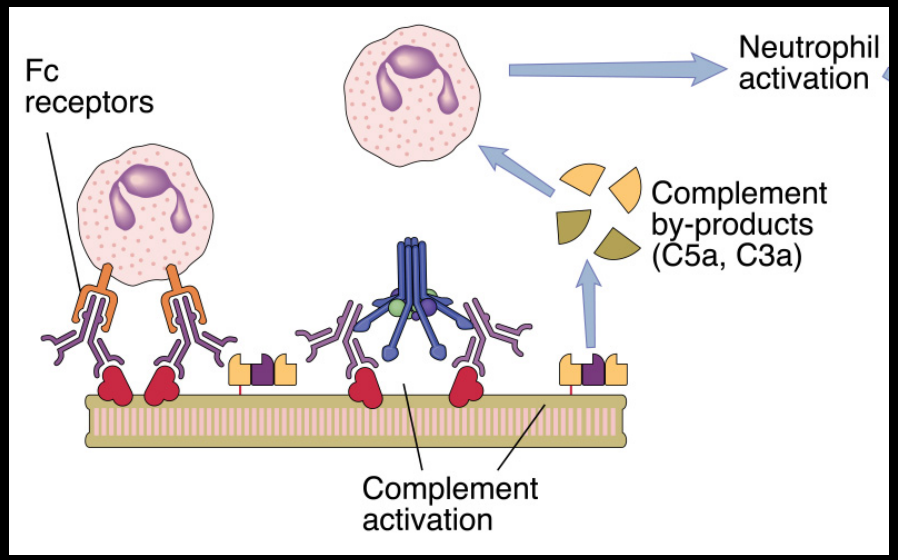
Goodpasture's Syndrome
Anti-glomerular basement antibody disease

- A disease caused by autoantibodies binding to basement-membrane antigens of the kidney glomeruli and the alveoli of the lungs.
- Complement activation leads to direct cell damage and inflammation due to the release of complement chemotactic factors (C5a).
- Damage to the kidney and lung basement membranes leads to progressive kidney damage and pulmonary hemorrhages.
- Death ensues several months after the onset of disease.
- Biopsies of patients reveal linear deposits of IgG and C3b along the basement membranes.

Goodpasture's Syndrome



Fluorescent anti-IgG staining of a kidney biopsy of a patient with Goodpasture's syndrome reveals deposits of IgG autoantibodies along the glomerular basement membrane.



Mechanism of tissue damage in Goodpasture's Disease: Deposition of IgG Abs in the kidney glomeruli, activation of complement and recruitment of inflammatory cells.

Type IIB hypersensitivity-induced autoimmune diseases

Some autoimmune Abs can cause abnormal physiological responses without cell/tissue injury

Stimulating or blocking anti-cell-surface receptor autoantibodies

- Initiated by the production of autoantibodies (IgM/IgG).
- Abs binding to a cell surface receptor stimulate the receptor by mimicking the action of the natural ligand.
- Abs binding to a cell surface receptor block the receptor and prevent its interaction with its natural ligand
- Abs cause abnormalities in tissue function with no tissue damage or inflammation.

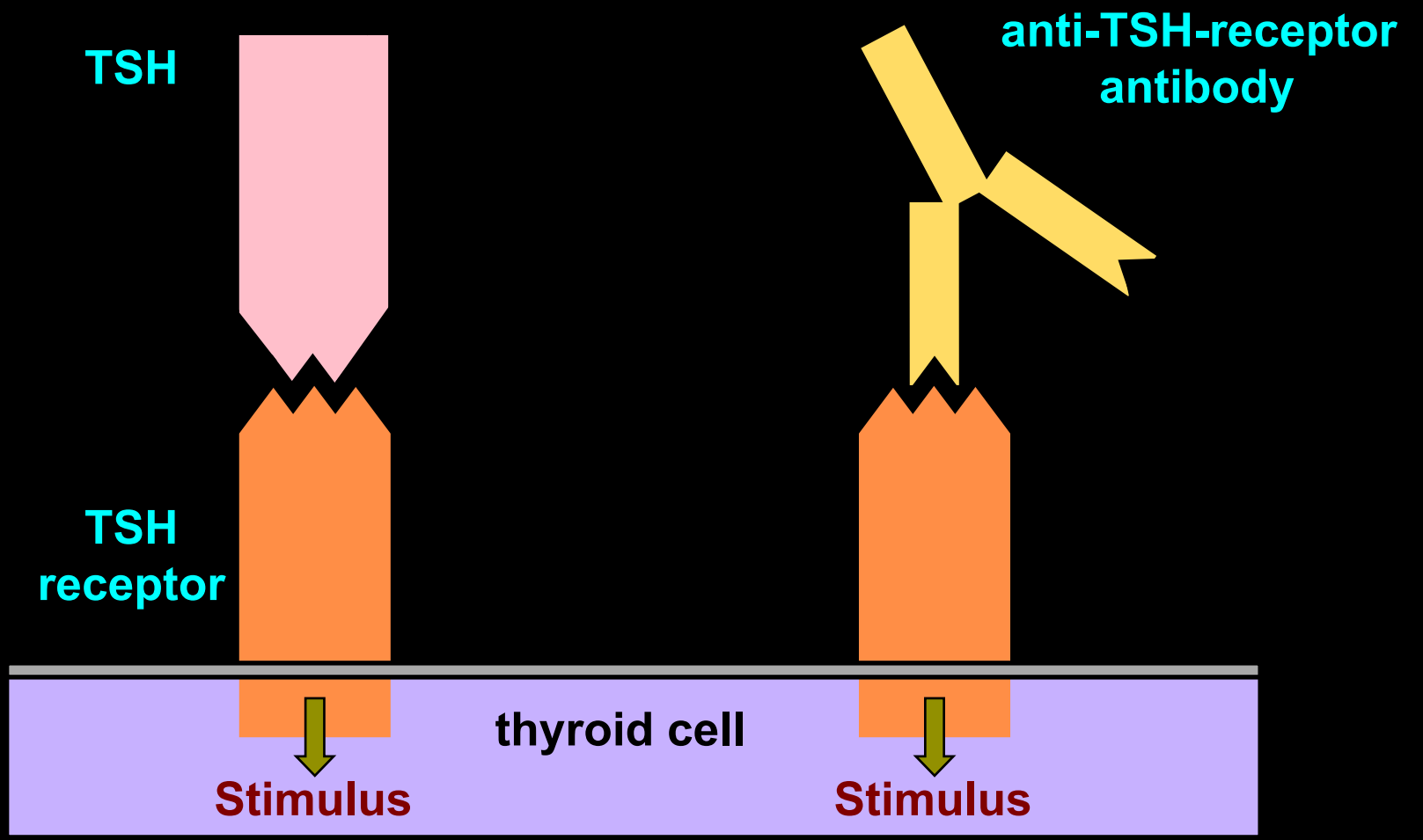
Autoimmune diseases caused by autoantibodies against cell-surface receptors

Diseases mediated by autoantibodies against cell-surface receptors		
Syndrome	Antigen	Consequence
Graves' disease	Thyroid-stimulating hormone receptor	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Progressive weakness
Insulin-resistant diabetes	Insulin receptor (antagonist)	Hyperglycemia, ketoacidosis
Hypoglycemia	Insulin receptor (agonist)	Hypoglycemia

These antibodies produce different effects depending on whether they are agonists (which stimulate) or antagonists (which inhibit) the receptor. Note that different autoantibodies against the insulin receptor can either stimulate or inhibit signaling.

Immunobiology, Janeway et al., 4th Ed. Fig. 13.9, p. 499 (5th, Fig. 13.11)

Graves' Disease: Autoantibodies directed against cell surface receptors

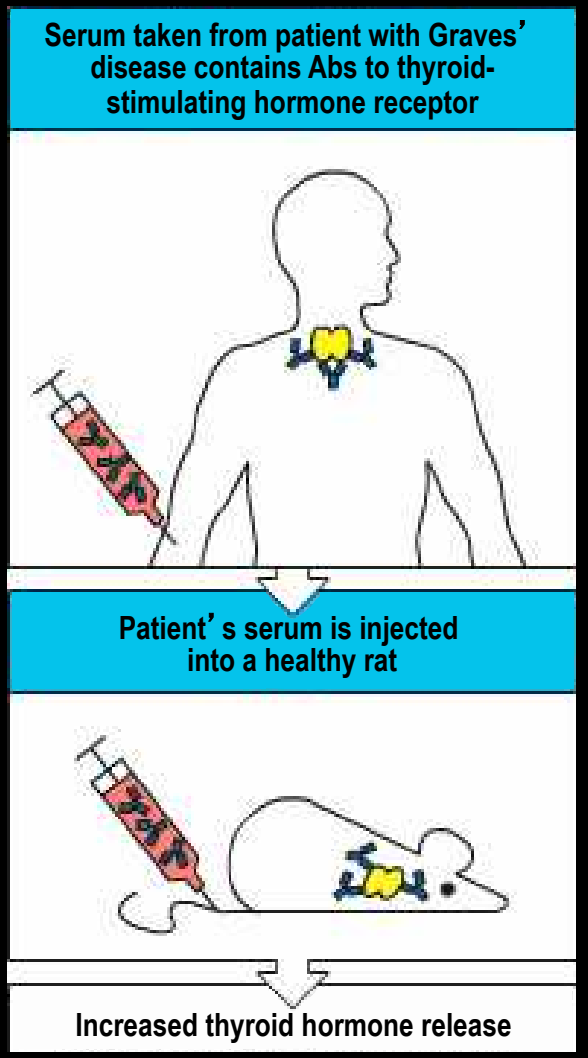


Thyroid cells are stimulated by TSH binding to its corresponding receptor. Abs to the TSH receptor, present in the serum of thyrotoxicosis (Graves' disease) patients, bind to the receptor in a similar manner, thereby delivering a comparable stimulus to thyroid cells, leading to overproduction of thyroid hormones.

Graves' Disease: Serum from autoimmune disease patients can transfer the same disease to experimental animals

When humans, mice and rats, share an autoantigen, the transfer of Abs from an affected human can cause the same symptoms in an experimental animal.

For example, Abs from patients with Graves' disease frequently produce thyroid activation in rats.



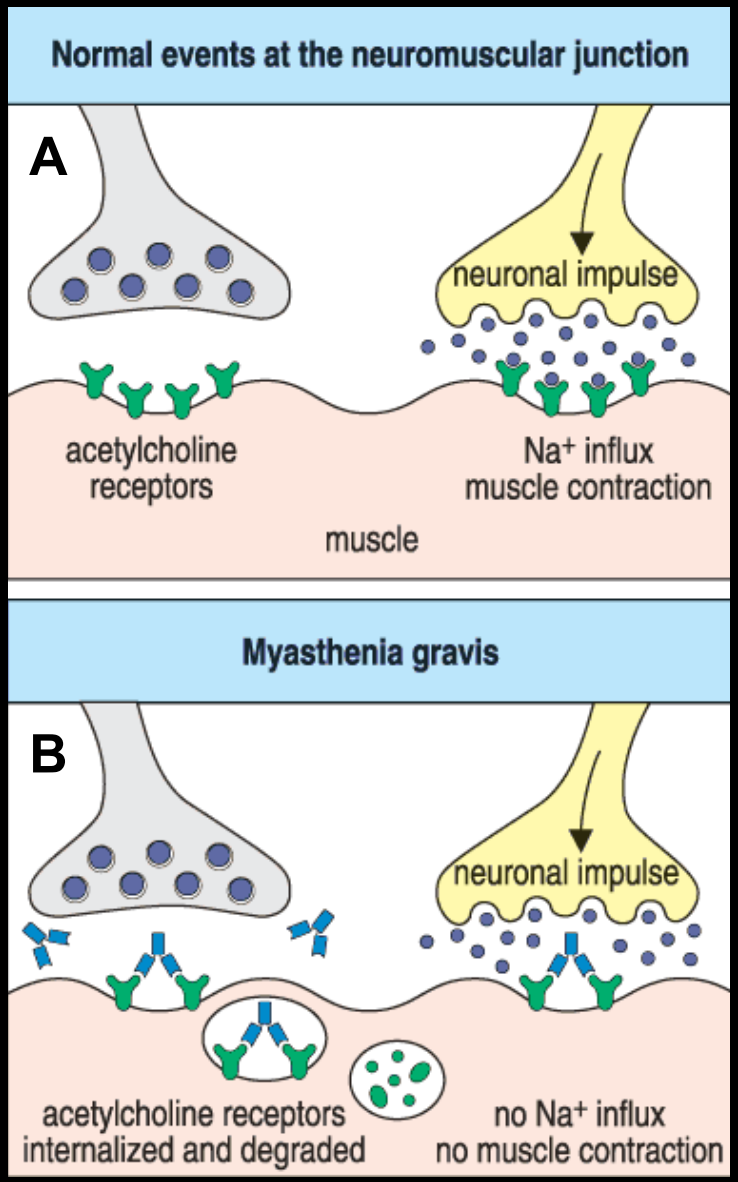
Immunobiology, Janeway et al., 4th Ed. Fig. 13.13, p. 502 (5th, Fig. 13.15)

In Myasthenia gravis autoantibodies inhibit receptor function

Autoimmune Abs inhibit ligand binding to receptors.

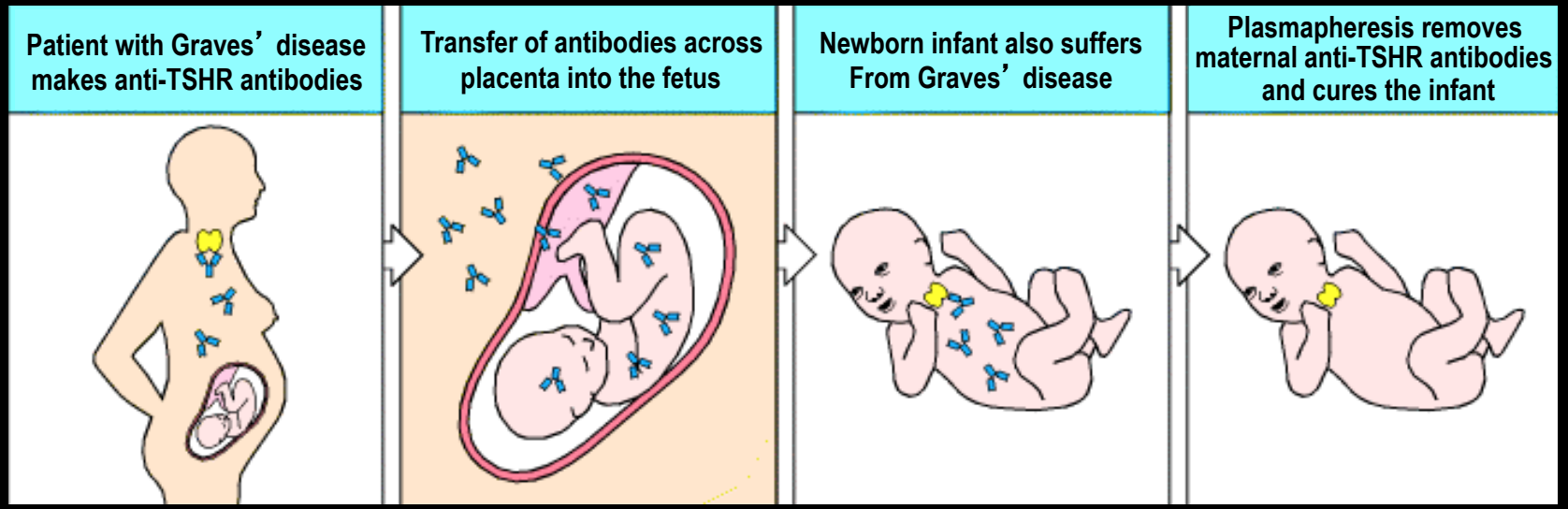
A. Under normal circumstances, acetylcholine released from stimulated motor neurons at the neuromuscular junction binds to acetylcholine receptors on skeletal muscle cells, triggering muscle contraction.

B. Myasthenia gravis is caused by autoantibodies against the alpha subunit of the acetylcholine receptor. Binding of autoantibodies to the receptor does not activate it but causes receptor internalization and degradation. As the number of receptors on the muscle is decreased, the muscle becomes less responsive to acetylcholine.



Immunobiology, Janeway et al., 4th Ed. Fig. 13.8, p. 498 (5th, Fig. 13.10)

Antibody-mediated autoimmune diseases can appear in the newborn of affected mothers as a consequence of trans-placental antibody transfer



In pregnant women, IgG Abs cross the placenta and accumulate in the fetus before birth. Babies born to mothers with IgG-mediated autoimmune disease frequently show symptoms similar to those of their mother during the first few weeks of life. Fortunately, there is little lasting damage as the symptoms disappear along with the maternal Abs. In Graves' disease, the symptoms are caused by Abs against the thyroid-stimulating hormone receptor (TSHR). Children of mothers making thyroid-stimulating Abs are born with hyperthyroidism, but this can be corrected by replacing the plasma with normal plasma (plasmapheresis), thus removing the maternal Ab.

Immunobiology, Janeway et al., 4th Ed. Fig. 13.15, p. 503 (5th, Fig. 13.17)

Type III hypersensitivity-induced autoimmune diseases

IgG/IgM immune complex-mediated disease

- The autoantigens are soluble and upon interaction with autoantibodies form soluble immune complexes.
- Occur when antigen-antibody complexes that are not adequately cleared by immune cells accumulate, giving rise to an inflammatory response and attraction of leukocytes.

Autoimmune Diseases due to Type III Hypersensitivity

Some common autoimmune diseases classified by immunopathogenic mechanism		
Syndrome	**Autoantigen**	**Consequence**
Type III immune-complex disease		
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, rash
Rheumatoid arthritis	Rheumatoid factor IgG complexes	Arthritis

Figure 11.1b

Immunobiology, Janeway et al., 4th Ed. Fig. 13.1b, p. 490 (5th, Fig. 13.1b)

Mechanisms of tissue injury in SLE

Production of small immune complexes

↓

Deposition in blood vessel walls,

basement membranes

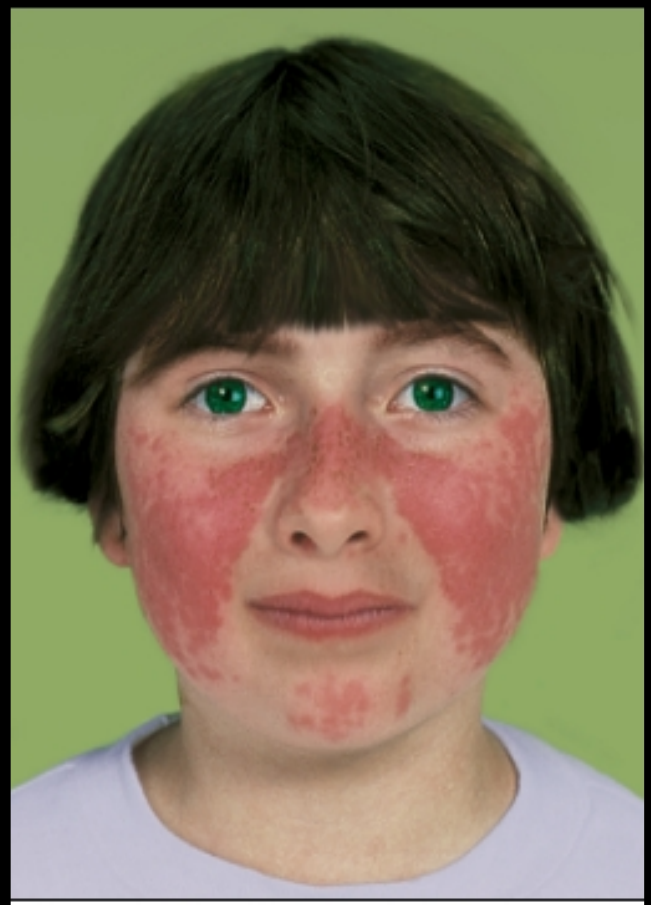
Renal glomerulus and other organs

↓

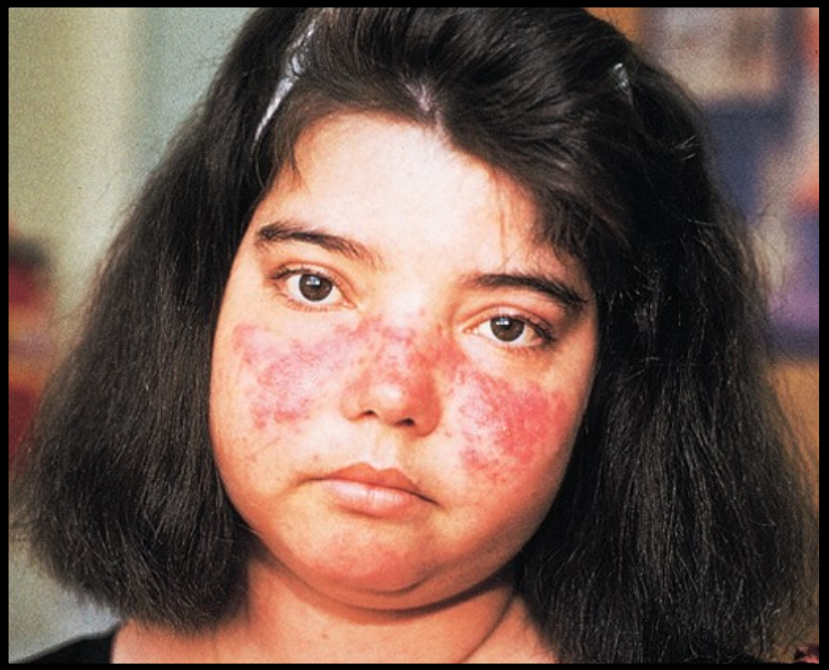
Activation of phagocytes

↓

Tissue damage



SLE is the most commonly known autoimmune disorder. This characteristic "butterfly" rash is made worse by exposure to sunlight. Lupus is a potentially fatal autoimmune disease that strikes 1 in 2,000 Americans and 10 times as many women as men.



Lupus Rash

Pernicious anemia

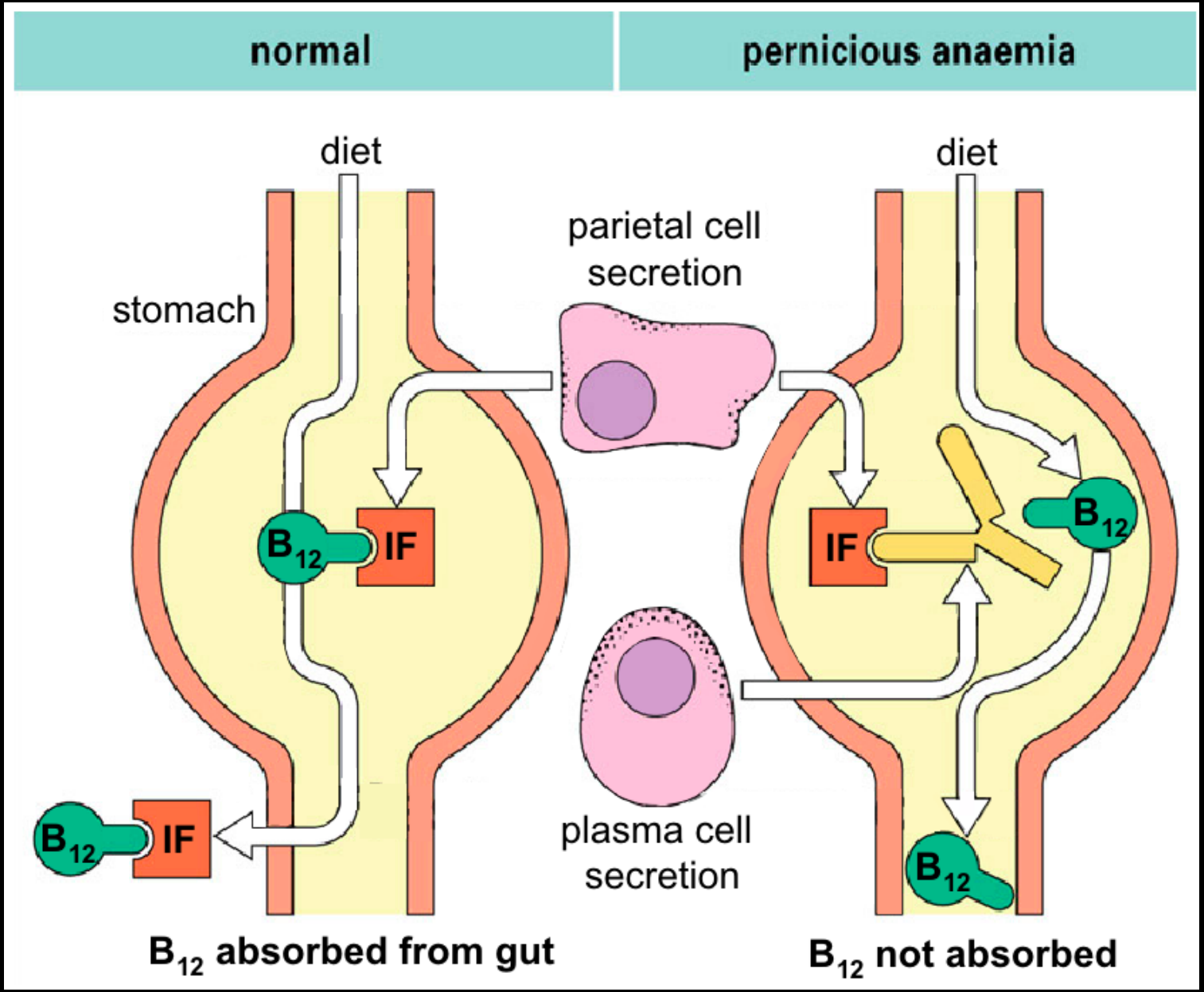
Described by Addison in 1849: fatigue, macrocytic anemia in well nourished individuals

Cause: Autoimmune destruction of parietal cells by autoantibodies to parietal cells and/or presence of autoantibodies to intrinsic factor. It results in B12 malabsorption.

Prevalence: 1.9 % of the elderly have PA (2.7% women, 1.4% men; 4.3% in Black women)

Increased incidence in American blacks, Northern Europeans

Often associated with other antibodies, e.g. anti-thyroglobulin in Hashimoto's thyroiditis



Immunology, Roitt et al., 5th Ed. Fig. 28.13, p. 372

Type IV hypersensitivity-induced autoimmune diseases

T cell-mediated delayed-type hypersensitivity diseases

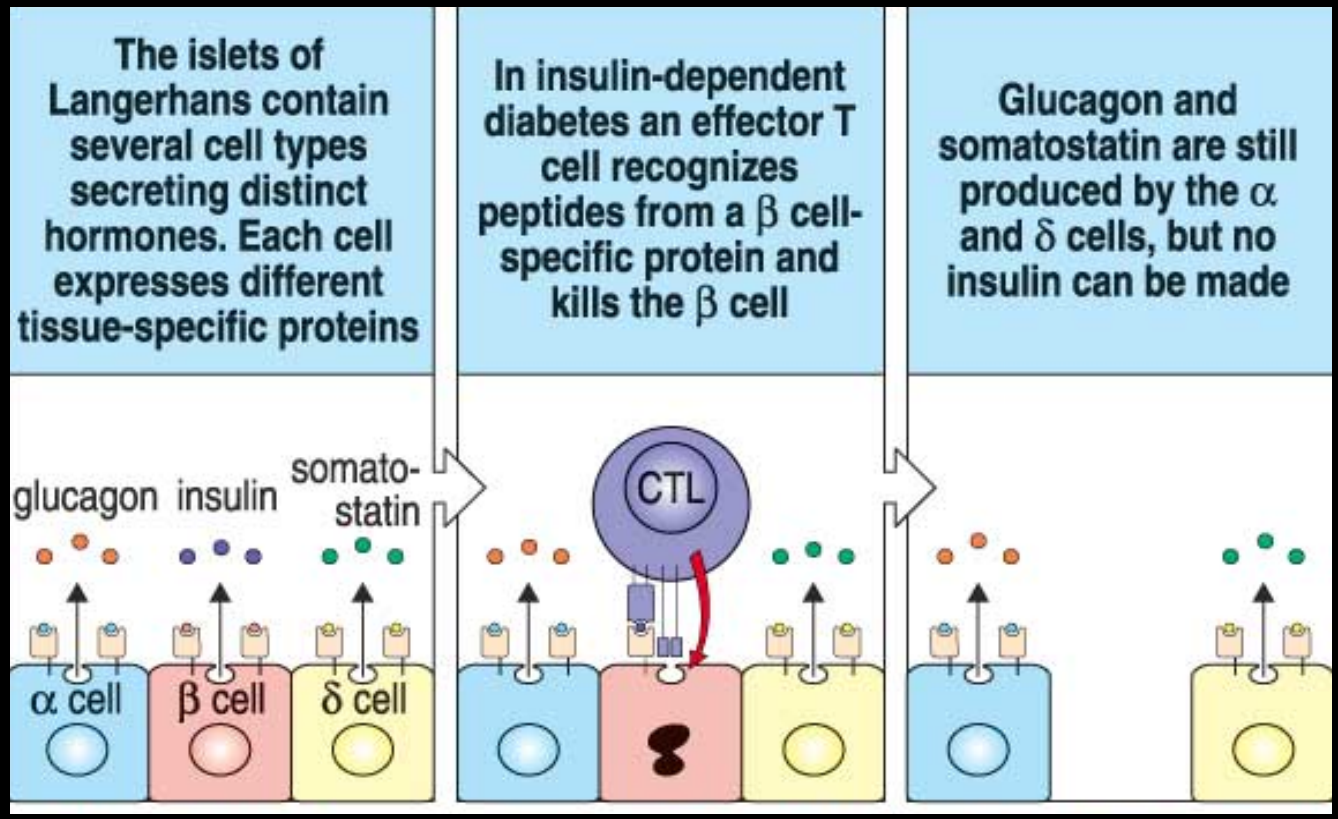
- Specific autoreactive T cells
- Direct damage to target cells by cytotoxic T cells

Autoimmune Diseases due to Type IV Hypersensitivity

Some common autoimmune diseases classified by immunopathogenic mechanism		
Syndrome	**Autoantigen**	**Consequence**
Type IV T cell-mediated disease		
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-Cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis	Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein	Brain invasion by CD4 T cells, weakness

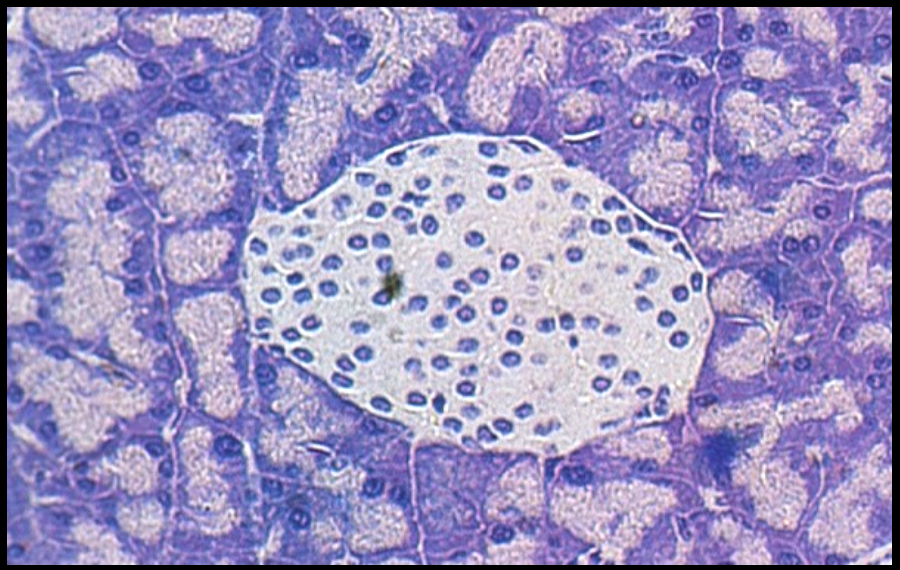
Immunobiology, Janeway et al., 4th Ed. Fig. 13.1c, p. 490 (5th, Fig. 13.1c)

Selective destruction of pancreatic β cells in IDDM

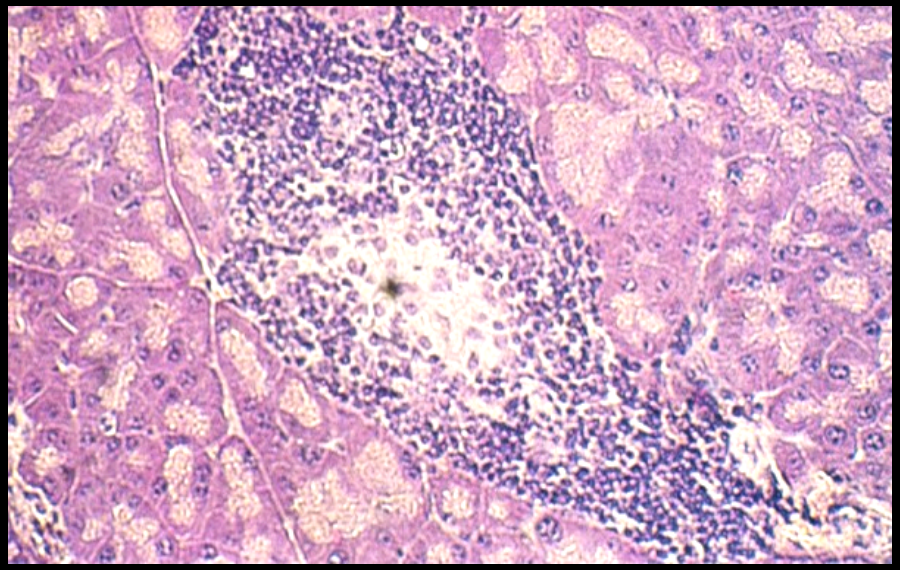


Immunobiology, Janeway et al., 4th Ed. Fig. 13.19, p. 508 (5th, Fig. 13.21)

Type I Diabetes



Islet of Langerhans in normal pancreas.

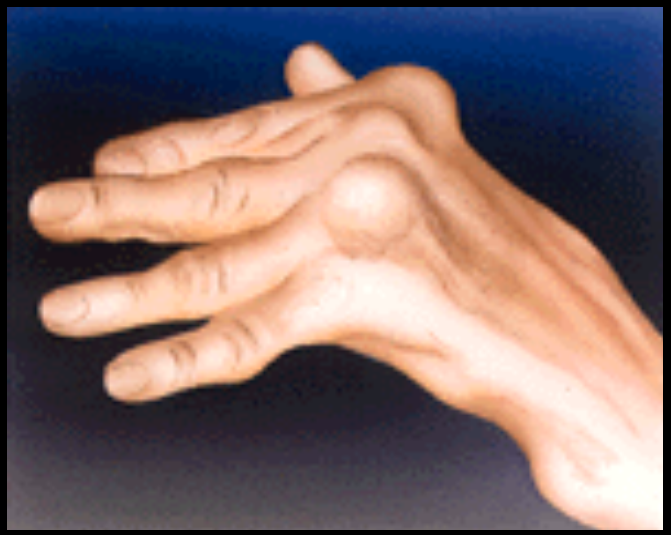


Islet of Langerhans from individual with insulin-dependent diabetes mellitus. Note the intense lymphocyte infiltration into the islet (insulitis).

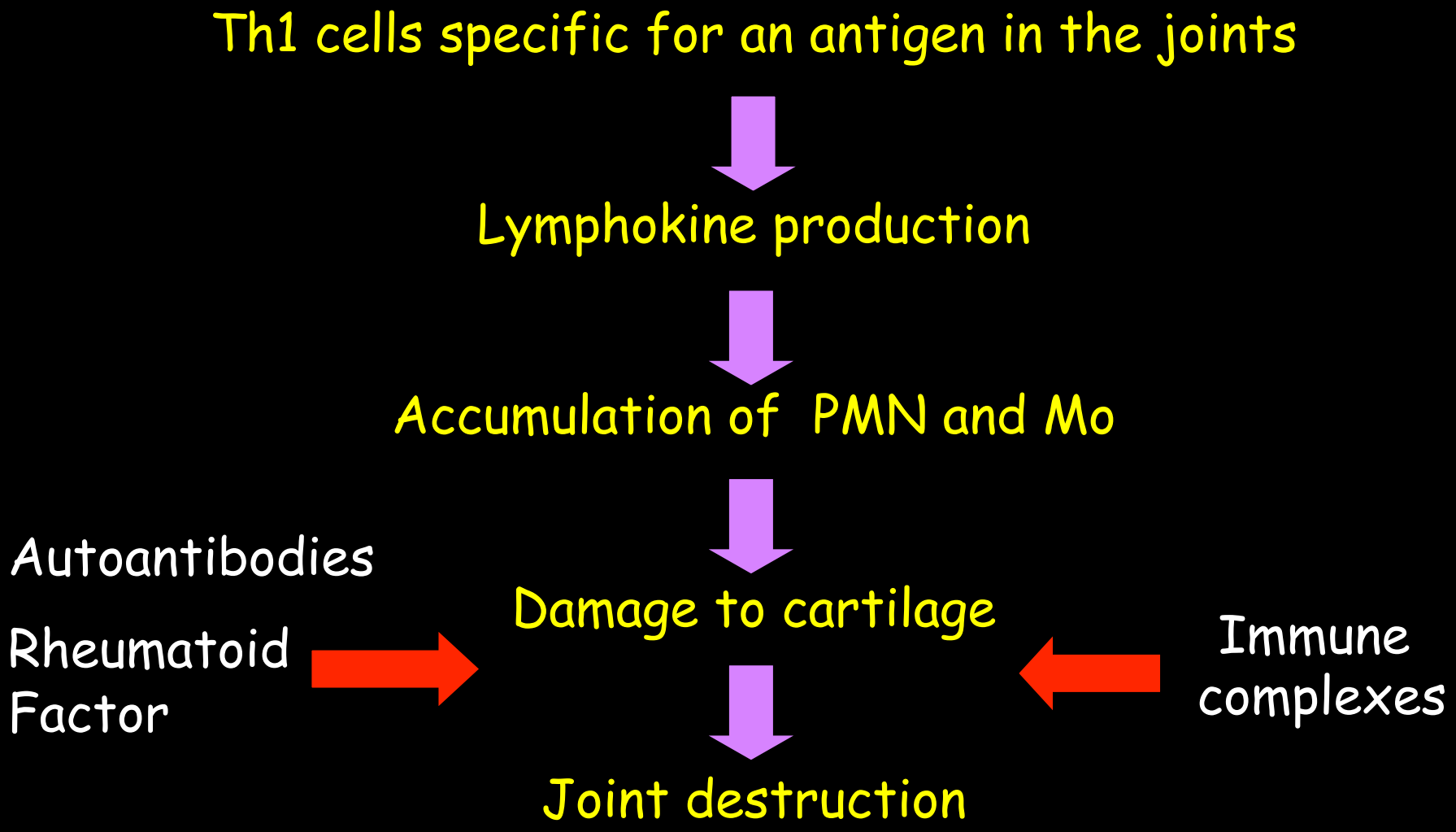
Rheumatoid arthritis

Among the most serious and disabling types of arthritis, 2.1 million Americans live with rheumatoid arthritis.

About one out of seven Americans exhibit some form of arthritis.

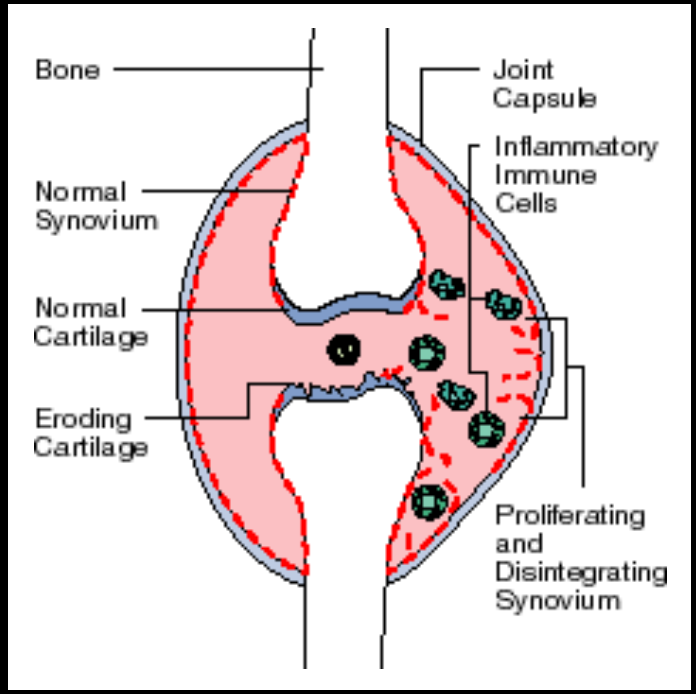


Rheumatoid Arthritis



Rheumatoid arthritis

Rheumatoid arthritis (RA) affects peripheral joints and may cause destruction of both cartilage and bone. The disease affects mainly individuals carrying the HLA-DR4 variant of MHC genes.



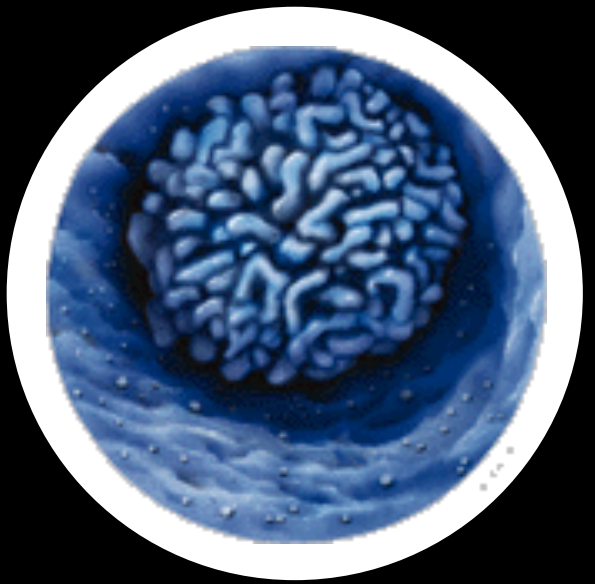
Example of inflammation and the role of cytokines in RA

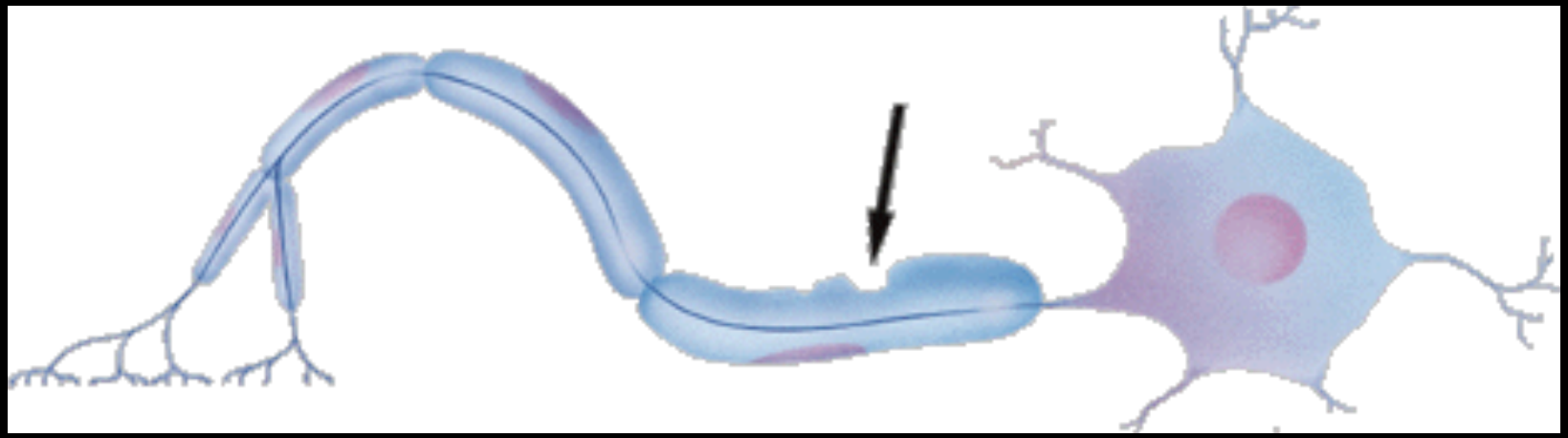
Tumor Necrosis Factor-alpha (TNFα):

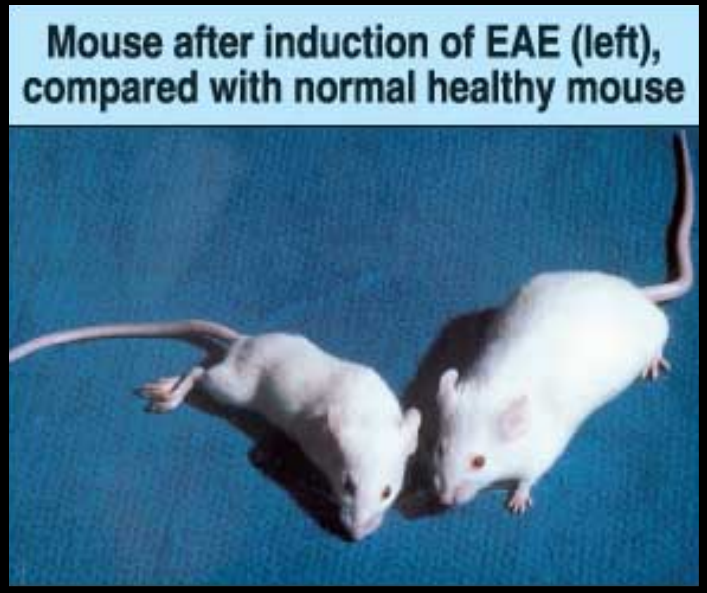
- Released by macrophages
- Increases vascular permeability
- Increases adhesion molecule expression on blood vessel endothelium
- Increases MHC expression

Multiple sclerosis

- Some populations, such as Gypsies, Eskimos, and Bantus, never gets MS.
- For susceptible populations, if one person in a family has MS, that person's first-degree relatives (parents, children, and siblings) have a 1-3% chance of getting the disease.
- Individuals with the HLA-DR2 variant of MHC genes are most susceptible to the disease.

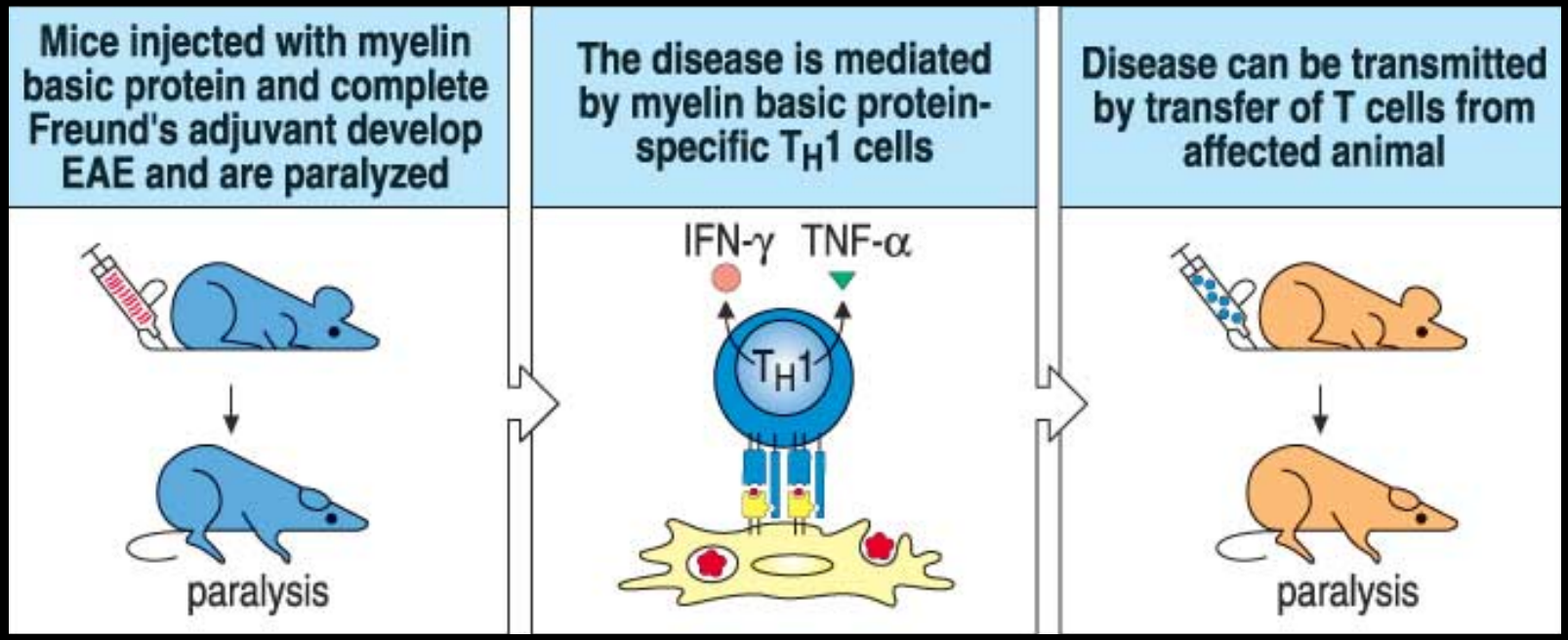






A mouse model for MS:

Induction of EAE (experimental allergic encephalitis), a model for multiple sclerosis



Immunobiology, Janeway et al., 4th Ed. Fig. 13.18, p. 507 (5th, Fig. 13.20)

At present, there is no cure for any of the autoimmune diseases.

What are the current optional treatments for autoimmune diseases?

1. Suppression of the immune response

This necessitates a delicate balance, controlling the disorder while maintaining the body's ability to fight disease in general.

The drugs most commonly used are anti-inflammatory corticosteroids.

Immunosuppressive drugs, such as **Cyclosporin A (CsA), FK506, or rapamycin, which inhibit the production of IL-2, an essential T cell growth factor.**

2. Immunotherapies

2a. Induction of T cell tolerance (by using altered peptide ligands).

2b. Cytokine-directed therapy, such as blocking of the tumor necrosis factor alpha (TNF-alpha).

TNF-alpha promotes the inflammatory response, which in turn causes many of the clinical problems associated with autoimmune disorders, such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, psoriasis.

Blocking TNF-alpha shows great promise as a new treatment for Rheumatoid arthritis.

3. Organ removal and hormone supplementation

- Removal of the thyroid in Graves' disease (hyperthyroidism)
- T3 and T4 treatment in hypothyroidism
- Treatment with insulin in IDDM, a more complicated treatment since the requirement for insulin is variable.