Basic Immunology

Lecture 23-24th

Immunological tolerance

Physiological and pathological autoimmunity.
Autoimmune diseases.

Immune tolerance

The first study in dizygotic twin cattle with a common placenta and shared mixture of each other's red blood cells described the life time tolerance between each other. R.E. Billingham and ***Peter Medawar*** in 1953 injected foreign cells into fetal or neonatal mice, and they could become accepting of future grafts from the same foreign donor. Theories of immune tolerance formulated by ***Sir Frank McFarlane Burnet*** and Frank Fenner, who were the first to propose the deletion of self-reactive lymphocytes to establish tolerance. Burnet and Medawar were ultimately credited for "the discovery of acquired immune tolerance" and awarded with ***Nobel Prize in Physiology or Medicine in 1960***. In their Nobel Lecture, Medawar and Burnet define immune tolerance as *"a state of indifference or non-reactivity towards a substance that would normally be expected to excite an immunological response."*

Cognitive paradigm of the immune tolerance

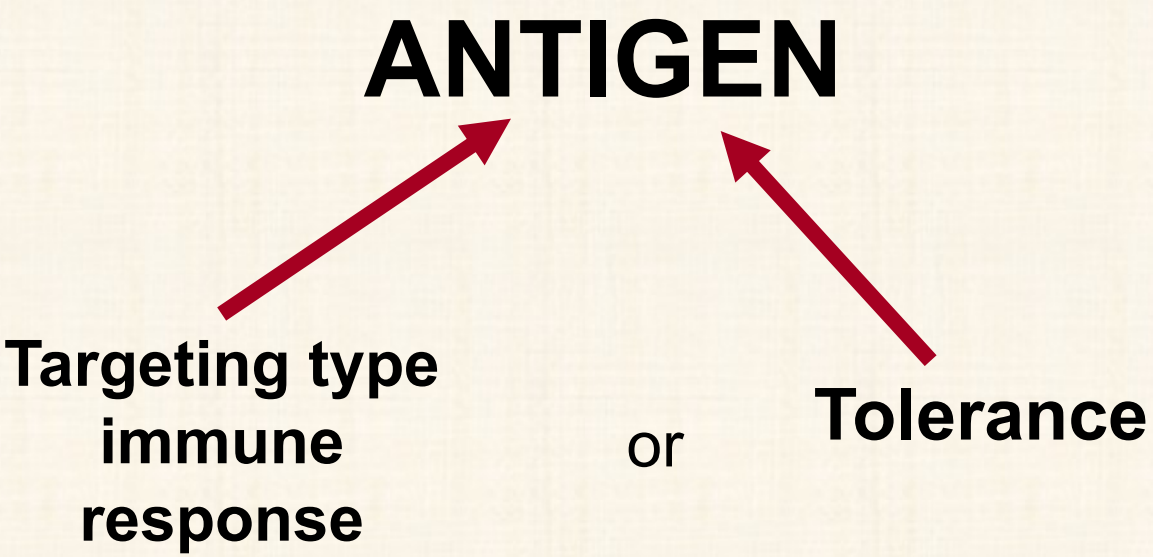
- In 1991, ***Irun Cohen*** proposed revising the clonal selection theory and replacing it with the **cognitive paradigm**.
- The natural autoimmune network is the *immunological homunculus*, which is the immune system's representation of the body.
- The particular self-reactivity comprising the homunculus could serve as a set of naturally occurring (auto)antibodies and cellular components of the natural immune system that act as biomarkers to help initiate and regulate tolerance and targeting-type immune response.

The natural immune system

- **The cognitive paradigm** based on a lot of data on natural autoimmunity existing healthy individuals. The presence of natural autoantibodies (nAAb) in the blood serum of healthy individuals without clinical symptoms of autoimmune diseases has long been known about.
- Some T cell subpopulations with invariant T cell receptor chains, such as gamma-delta (γδ) T cells, invariant natural killer T cells (iNKT) and mucosa-associated invariant T cells (MAIT), have been described, as have their role in the immune response and their association with the nAAb network and nAAb-producing B1 cells.
- It is now widely accepted that the cellular and humoral components of the natural immune system play a fundamental role in regulating both tolerating and targeting type immune responses.

TOLERANCE & AUTOIMMUNITY

- Upon encountering an antigen, the immune system can either develop an immune response or enter a state of unresponsiveness called **tolerance**.
- Immunological tolerance is thus the lack of ability to mount an immune response to epitopes to which an individual has the potential to respond.
- Targeting type and tolerating type immune responses composed by the same cellular and molecular components, the differences are in the effector phase only.
- Targeting type immune response or tolerance needs to be carefully regulated since an inappropriate response – whether it be **autoimmune** reaction to self-antigens or tolerance to a potential pathogen – can have serious and possibly life-threatening **immunodefficiencies**.



The immune system's network makes a permanent decision about whether to target or tolerate an antigen. The nature and occurrence of the antigen, as well as the immune system's current state, influence the type of response.

AUTOREACTIVITY **TOLERANCE**

Autoimmune diseases **Immunodeficiency**

The immune response, whether targeting or tolerating, needs to be carefully regulated, since an inappropriate response — whether an autoimmune reaction to self-antigens or tolerance to a potential pathogen — can have serious, possibly life-threatening, consequences.

TOLERANCE

- PASSIVE
- ACTIVE

AUTOIMMUNITY

- PHYSIOLOGIC REGULATION
- AUTOIMMUNE DISEASES

Mechanisms of the immunological tolerance

Central tolerance

- T cell mediated
- B cell mediated

Peripheral tolerance

- unresponsiveness
- local microenvironment mediated

Passive tolerance

Unresponsiveness: no MHC recognition or inhibited cellular differentiation.

- **Tolerance induced by the nature of the antigen**
- **Tolerance induced by the body**

Passive tolerance induced by the nature of the antigen

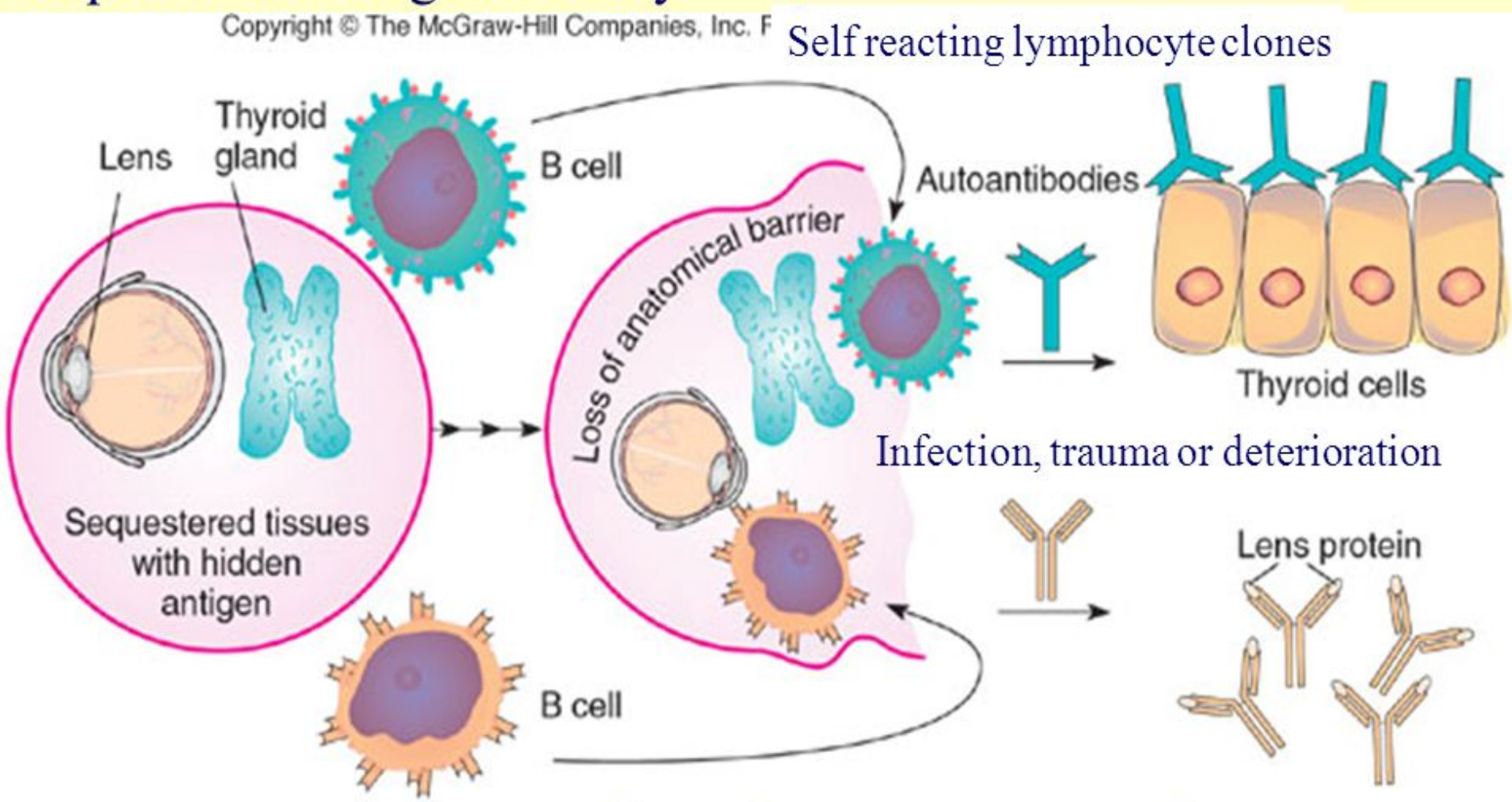
- chemical nature
- dose of the antigen
  - **low dose tolerance** (dominantly T cell mediated, long ranging)
  - **high dose tolerance** (B and T cell mediated, short ranging)
- mode of the administration

Tolerance induced by the body

- sequestered antigens
  - no MHC recognition
  - no antigen presentation
  - no systemic response
- clonal anergies
- heredited or acquired immunodeficiency
- exposure to radiation, chemotherapy drugs, or other agents that impair the immune system

Sequestered Antigen Theory

Sequestered behind anatomical barriers



(a) **Sequestered Antigen Theory**

Some tissues are not scanned by the immune system during embryonic growth.

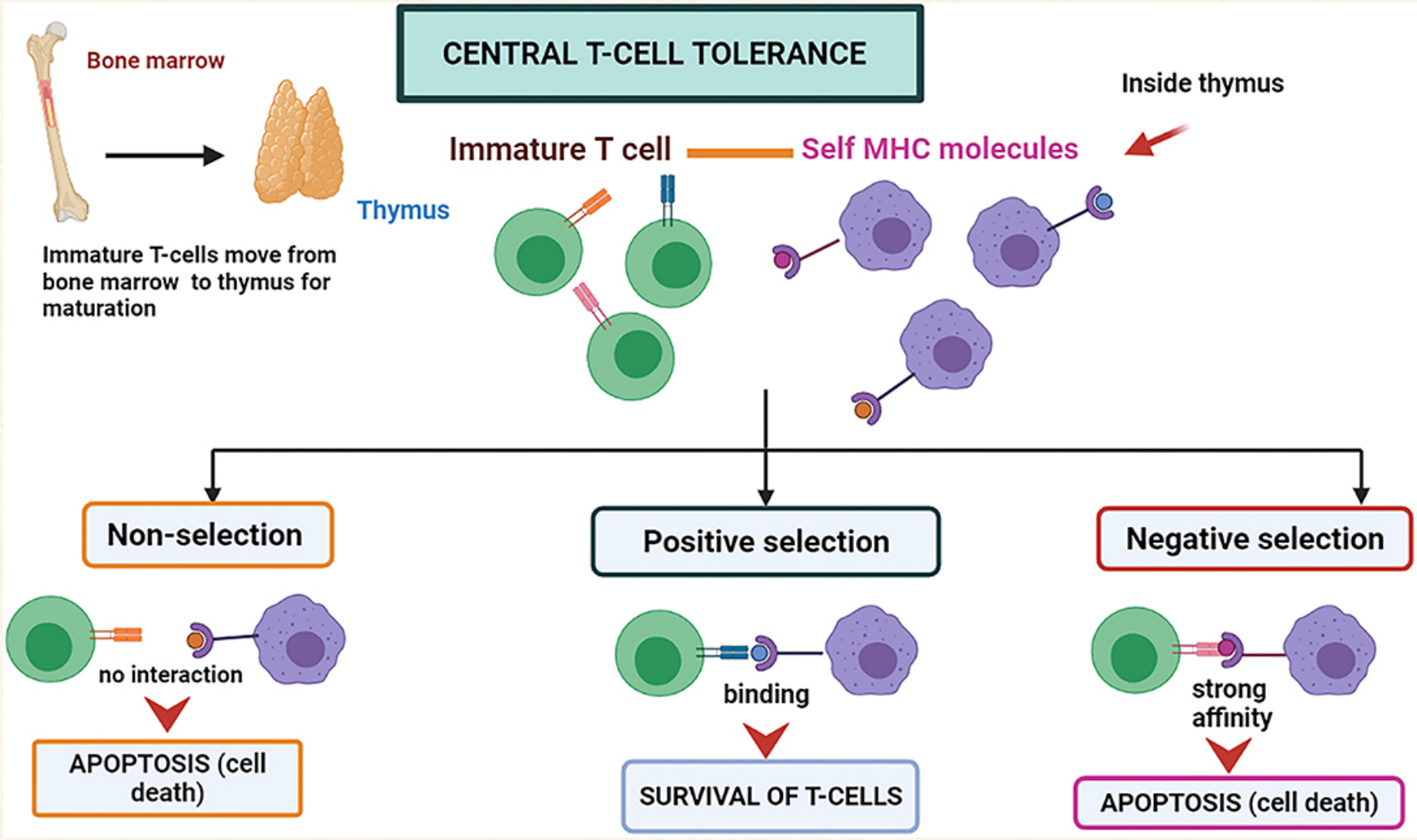
CNS, lens, thyroid & testes

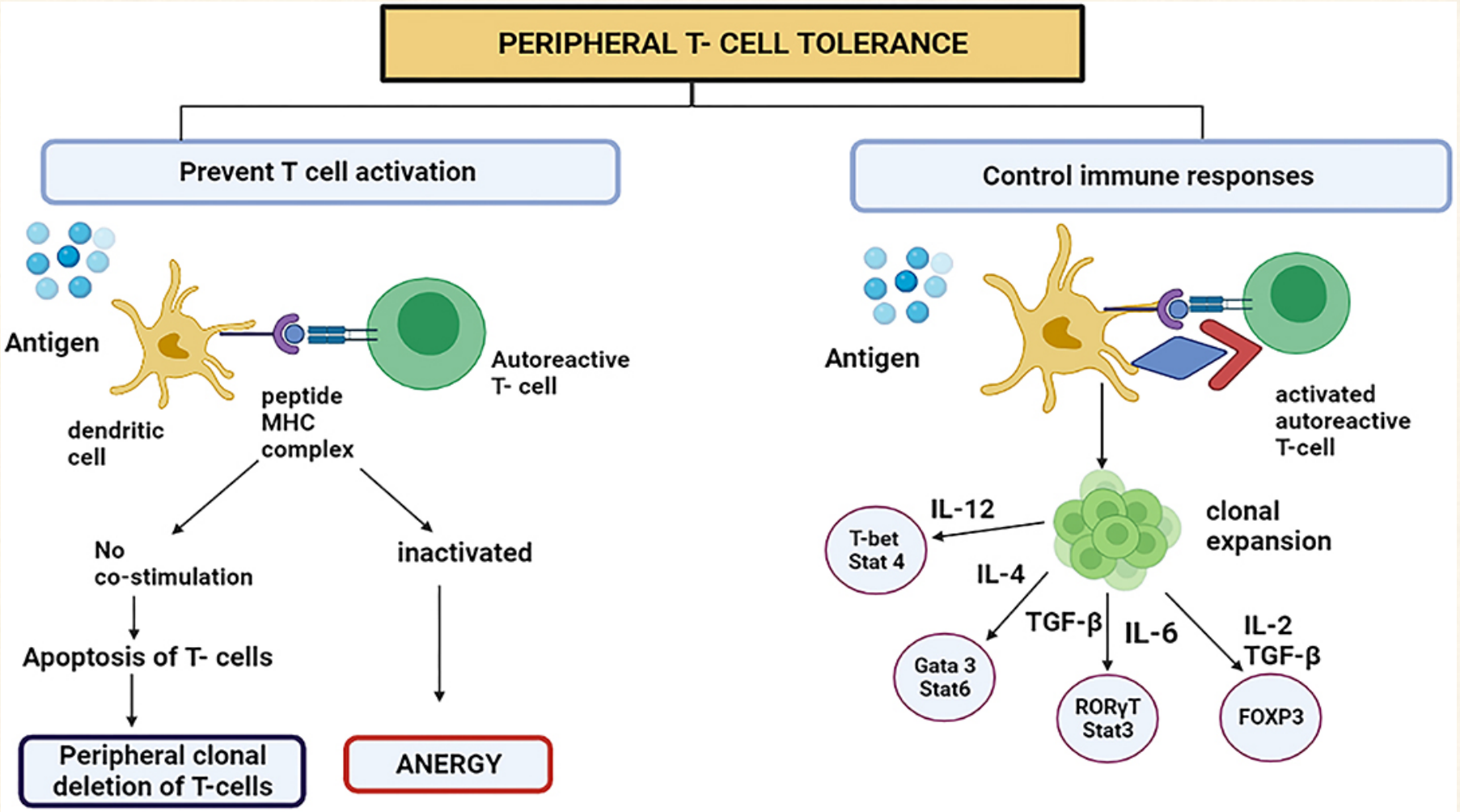
T-cell tolerance

Central Tolerance (selection in the Thymus)

Peripheral Tolerance (local microenvironment mediated)

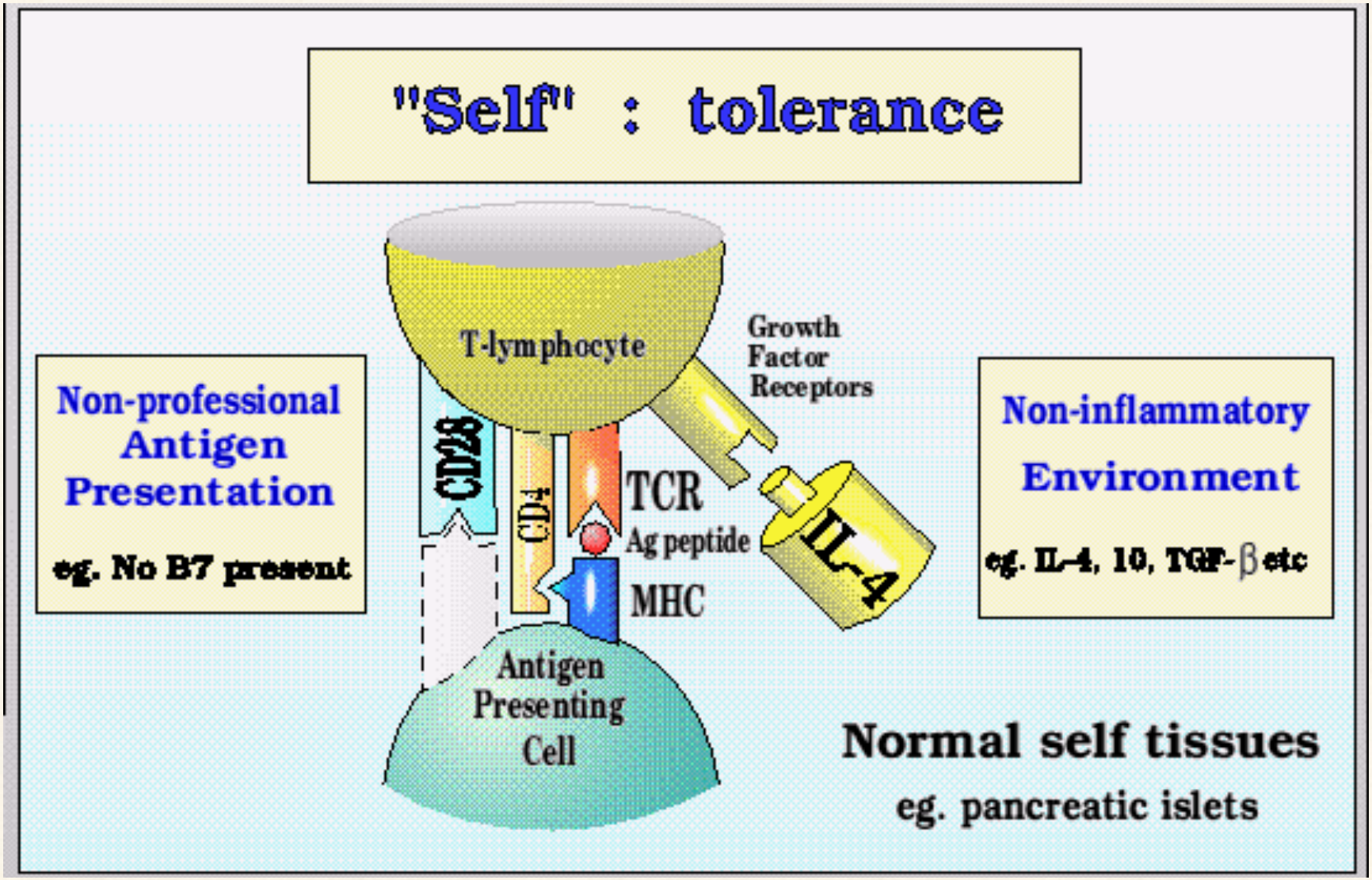
- Lack of co-stimulation
- Receipt of death signal (high dose of antigen)
- Control by regulatory T cells

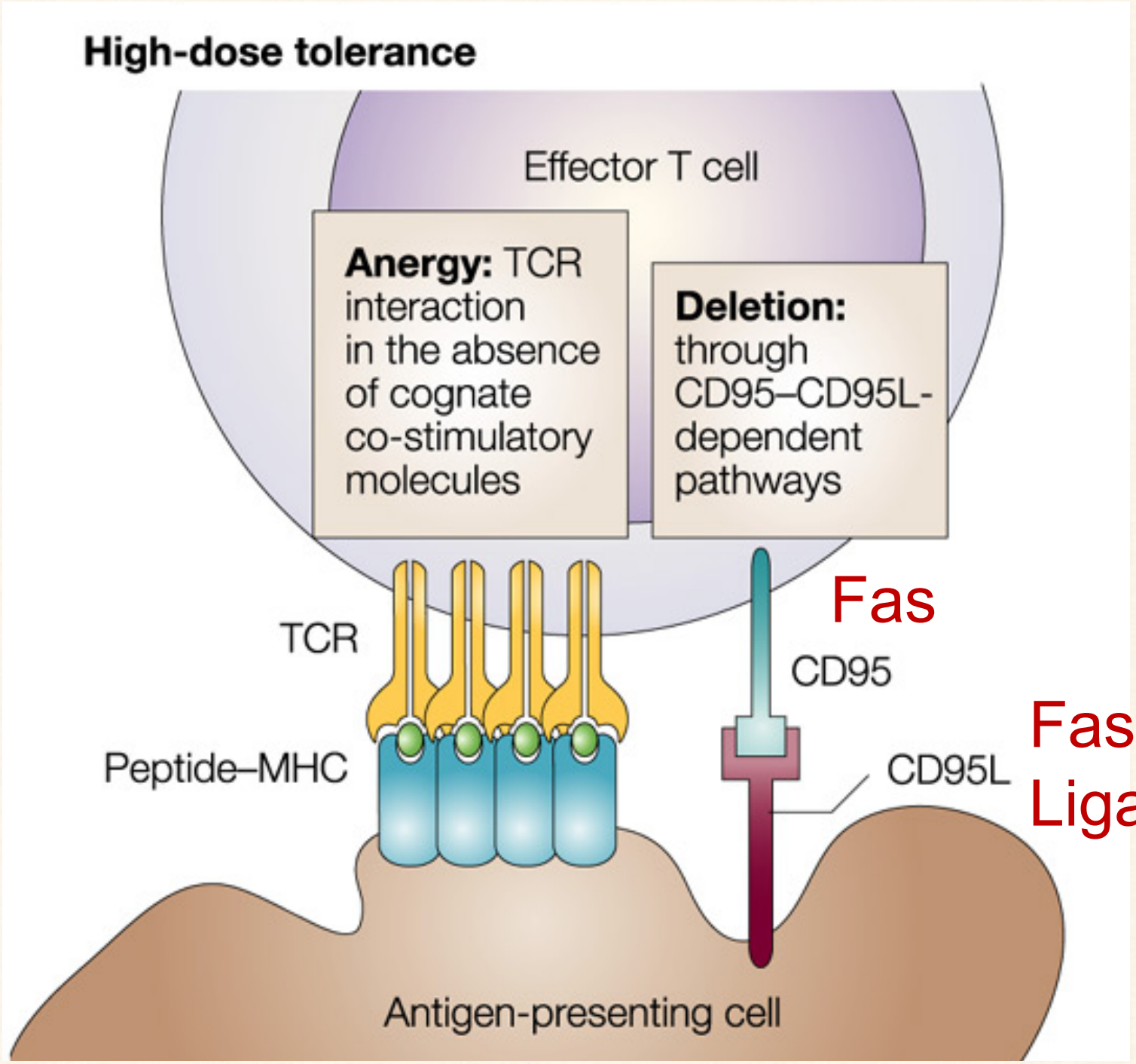

CENTRAL T-CELL TOLERANCE
Bone marrow
Thymus
Immature T-cells move from bone marrow to thymus for maturation
Inside thymus
Immature T cell
Self MHC molecules
Non-selection
no interaction
APOPTOSIS (cell death)
Positive selection
binding
SURVIVAL OF T-CELLS
Negative selection
strong affinity
APOPTOSIS (cell death)



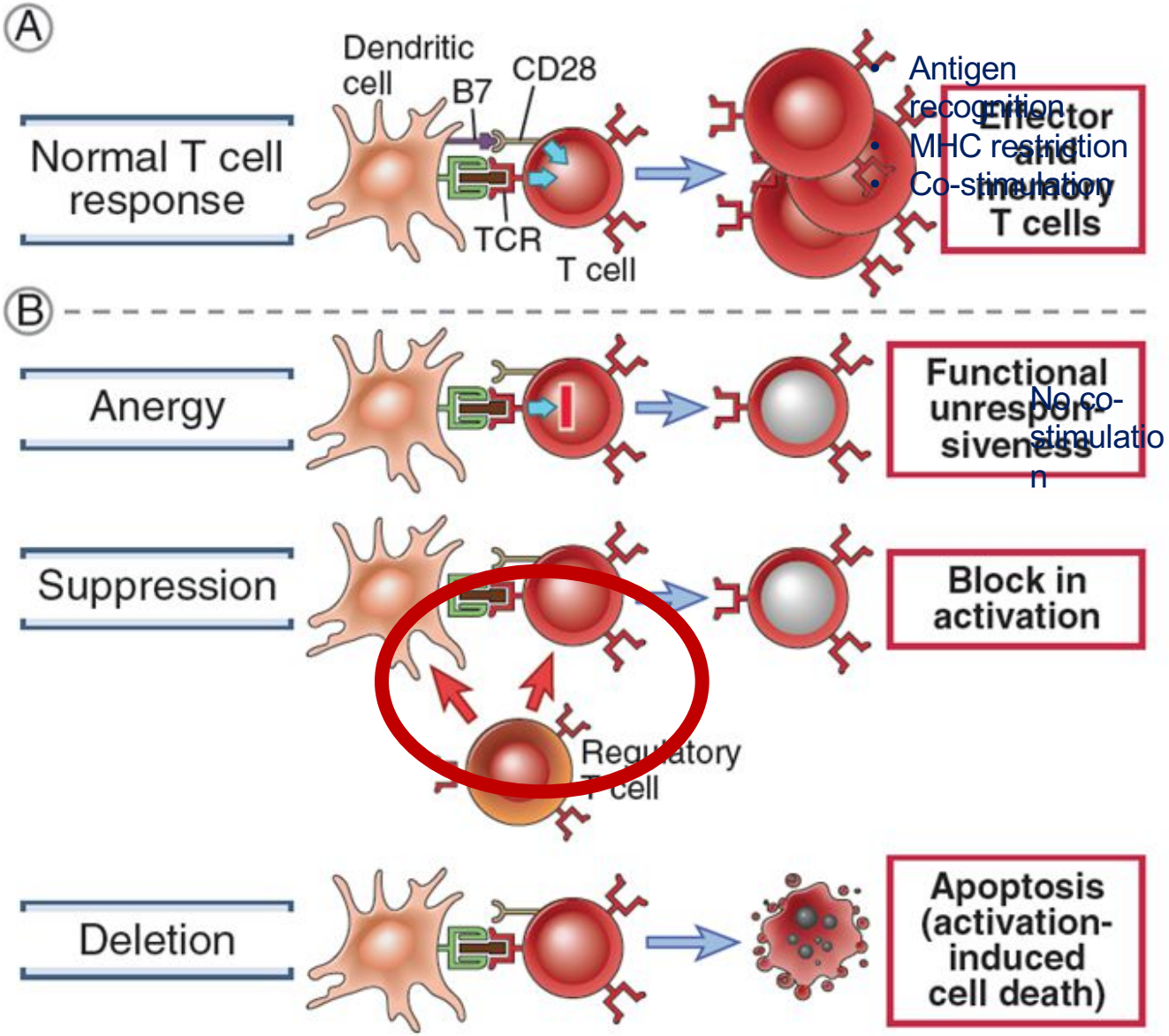
Peripheral T cell tolerance prevents T cell activation or controls the immune responses by switching on certain signaling pathways. However, to present T cell activation, the DC representing antigen either attaches to autoreactive T cell or starts apoptosis because the stimulatory component was absent on DC. This is called peripheral clonal deletion of T cells. If the T cell is inactivated, the process is called anergy.

Failed co-stimulation results low dose tolerance

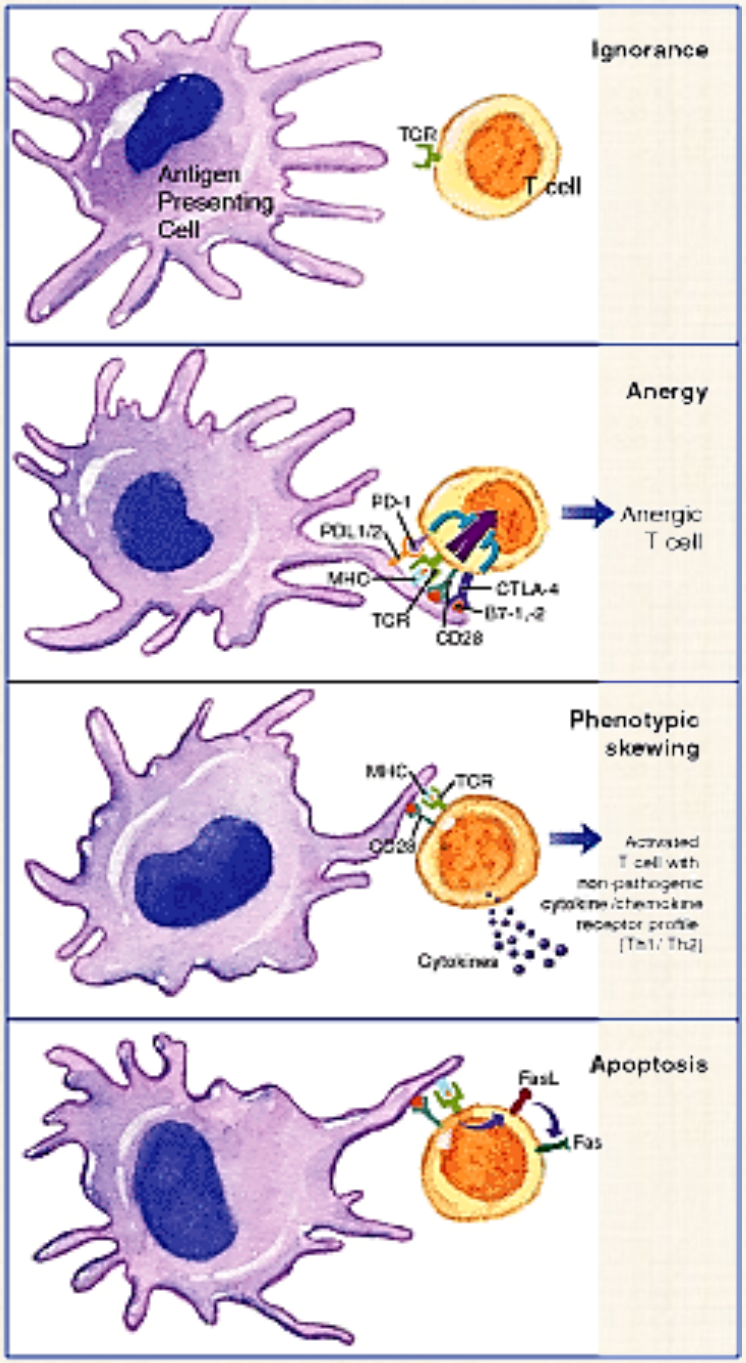



High-dose tolerance
Effector T cell
Anergy: TCR interaction in the absence of cognate co-stimulatory molecules
Deletion: through CD95–CD95L-dependent pathways
TCR
Peptide–MHC
Fas
CD95
CD95L
Fas Ligand
Antigen-presenting cell

Peripheral tolerance



Peripheral T cell tolerance



No response

(Sequestred antigens)

Anergy

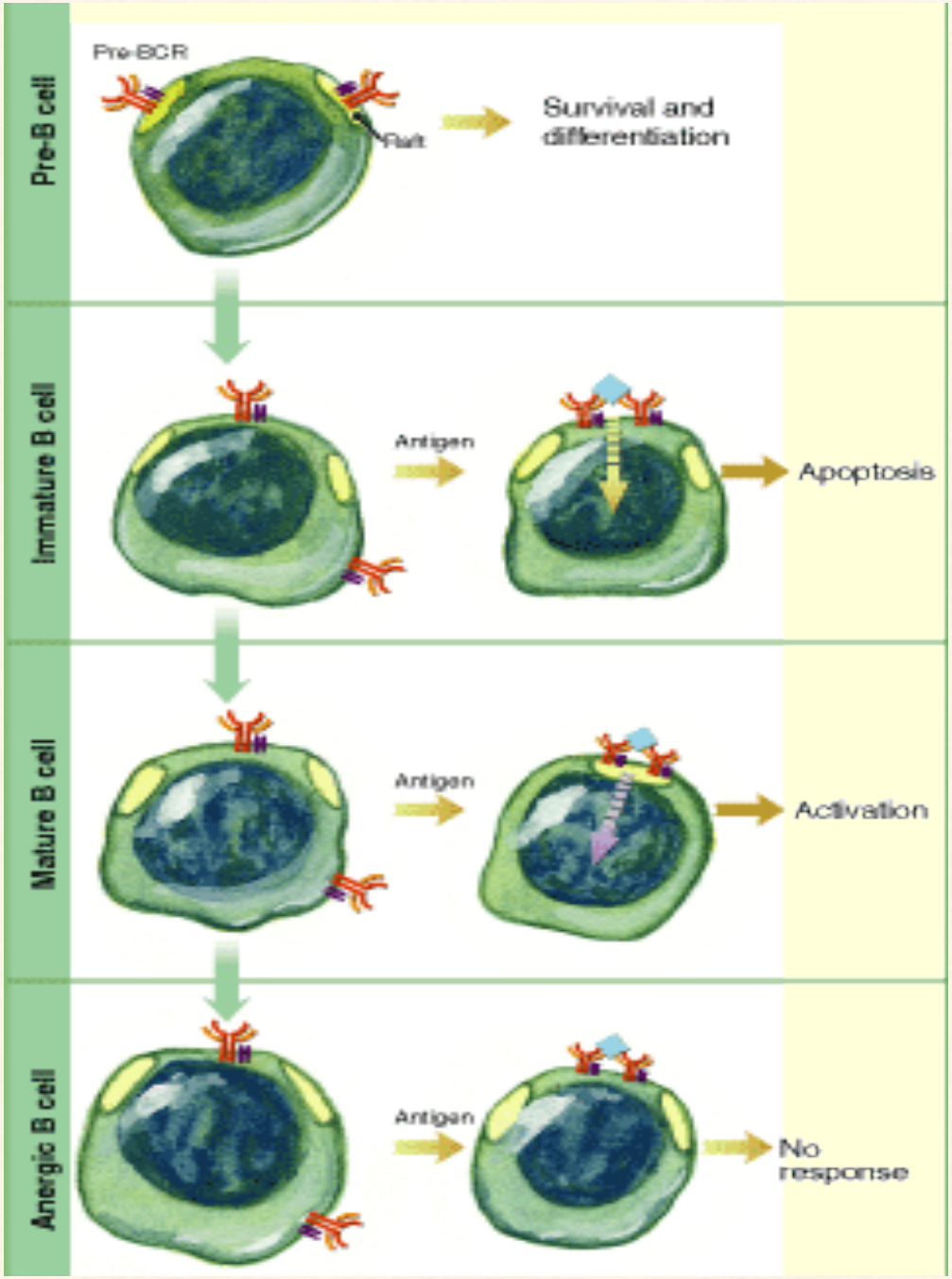
(Suppression by CTLA-4)

Anergy

(Th1/Th2 cross regulation)

Deletion

(High dose of antigen)

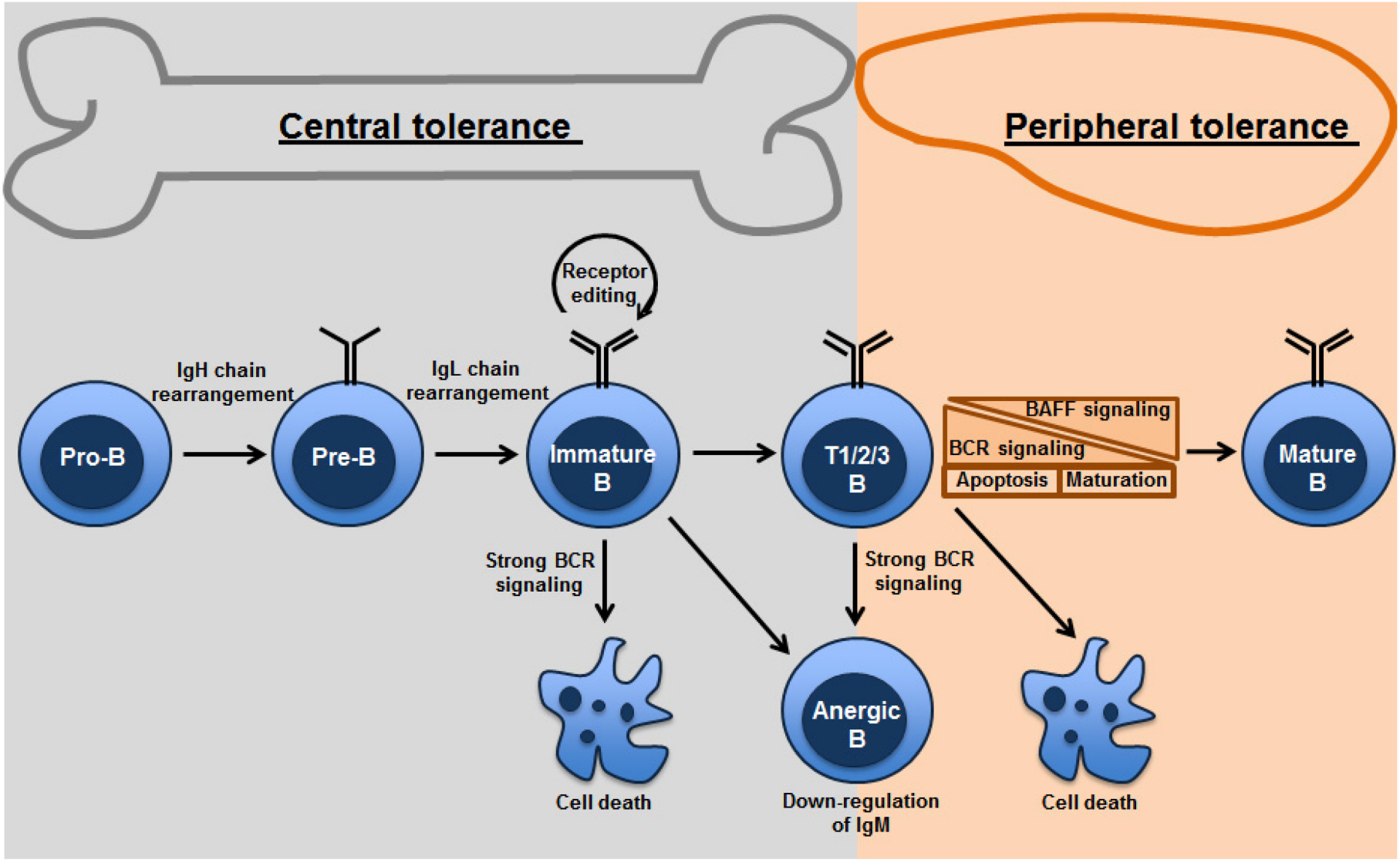


B-cell Tolerance

- Central tolerance

- Peripheral tolerance

Mechanisms of B-cell tolerance in bone marrow and periphery



ACTIVE TOLERANCE

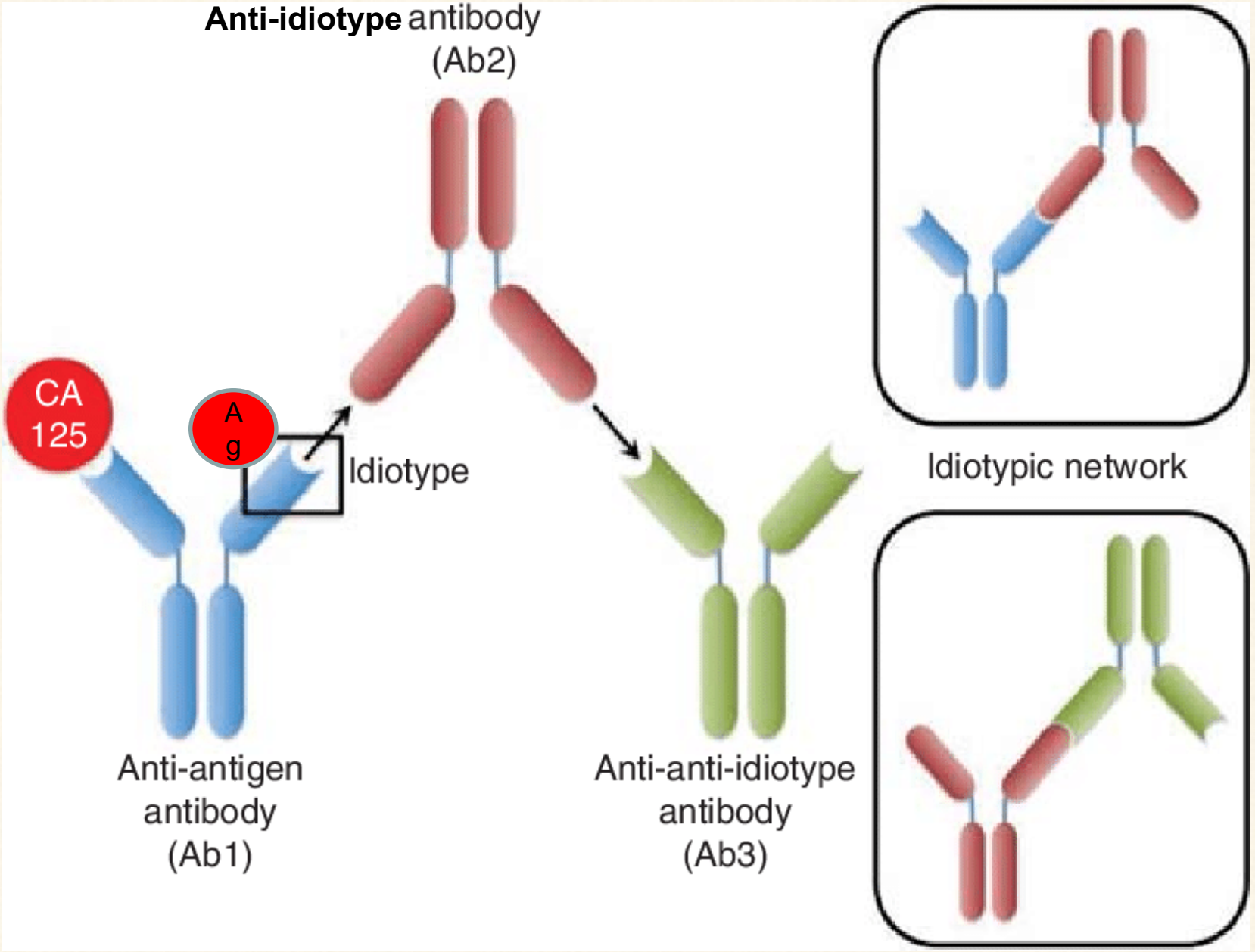
Anti-idiotype network

- Anti-idiotype antibodies against T cell and B cell receptors and immunoglobulins
- Antigen-specific inhibition and induction of memory

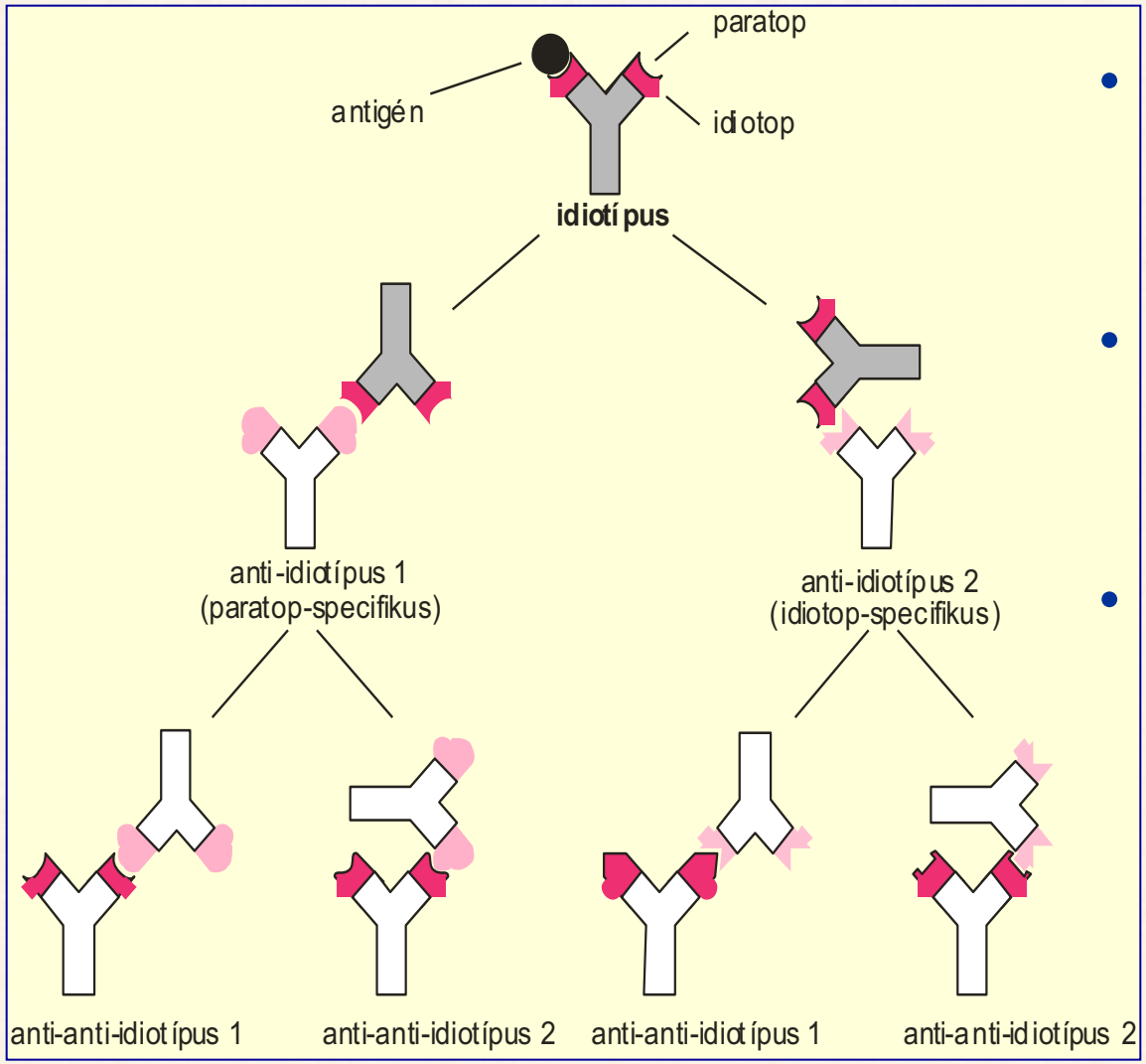
Natural immune system *("Immunological homunculus")*

- Low affinity IgM, IgG or IgA natural autoantibodies produced by CD5+ B1B cells
- γ/δ T, iγ/δT, ILCs1,2,3, MAIT, IEL, iNKT cells

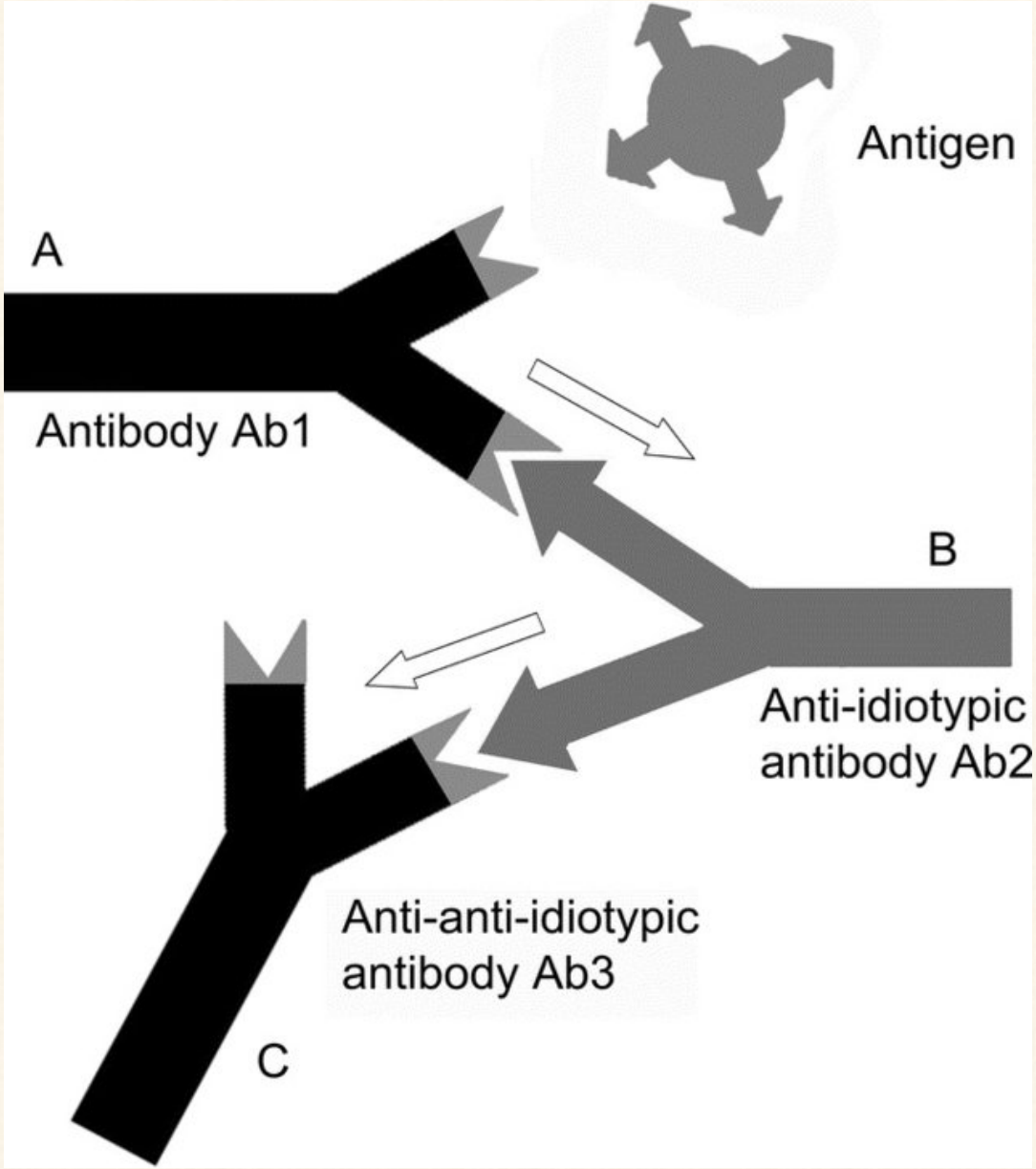
ANTI-IDIOTYPE NETWORK



Anti-idiotype network (*N. K. Jerne*)



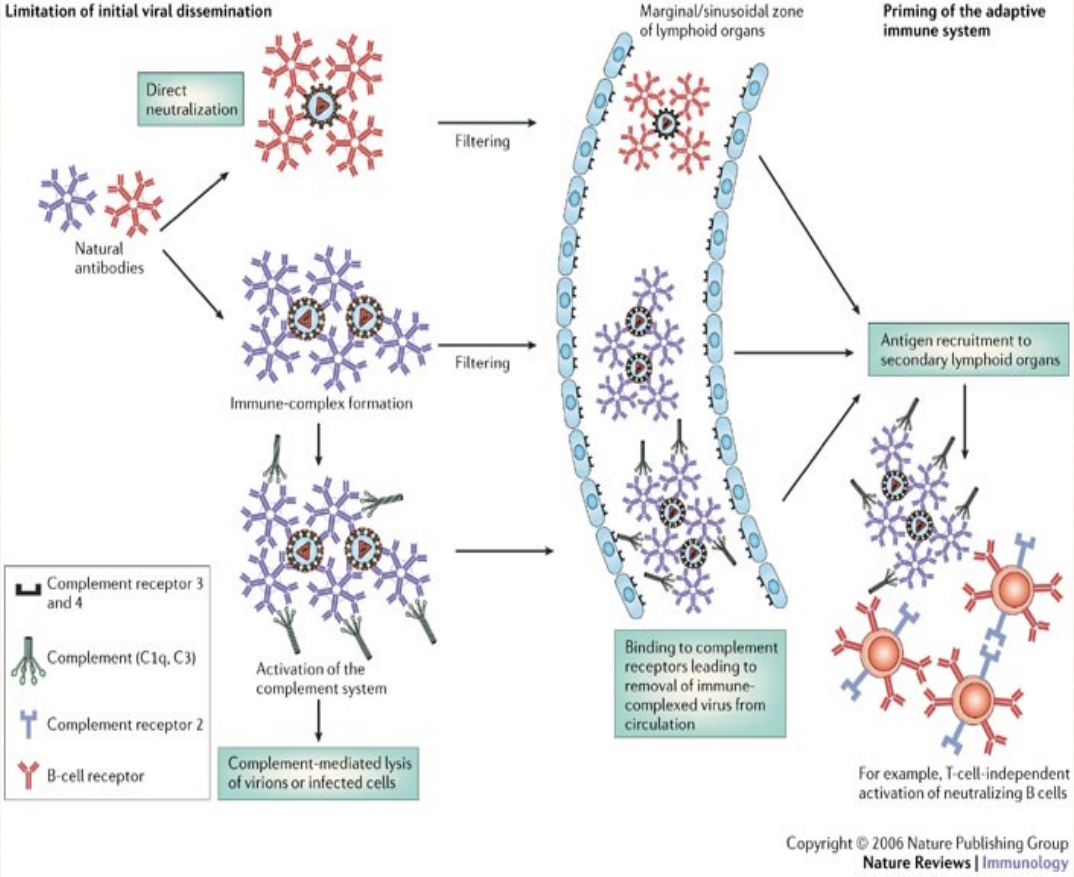
- **T- & B-cell suppression**
- **Functional memory formation**
- **Biological mimicri (insulin – *anti*-insulin – *anti-anti*-insulin ~ insulin)**



The anti-idiotypic network amplifies antigenic signals. (A) An antibody Ab1 is produced in response to a specific antigen. (B) With a defined idiotype, Ab1 induces the production of an anti-idiotypic antibody Ab2. This Ab2 may resemble the original antigen as an internal image. (C) Ab2 can stimulate the synthesis of an anti(anti-idiotypic) antibody Ab3 which principally is of the same specificity as Ab1.

Naturally occurring (auto)antibodies

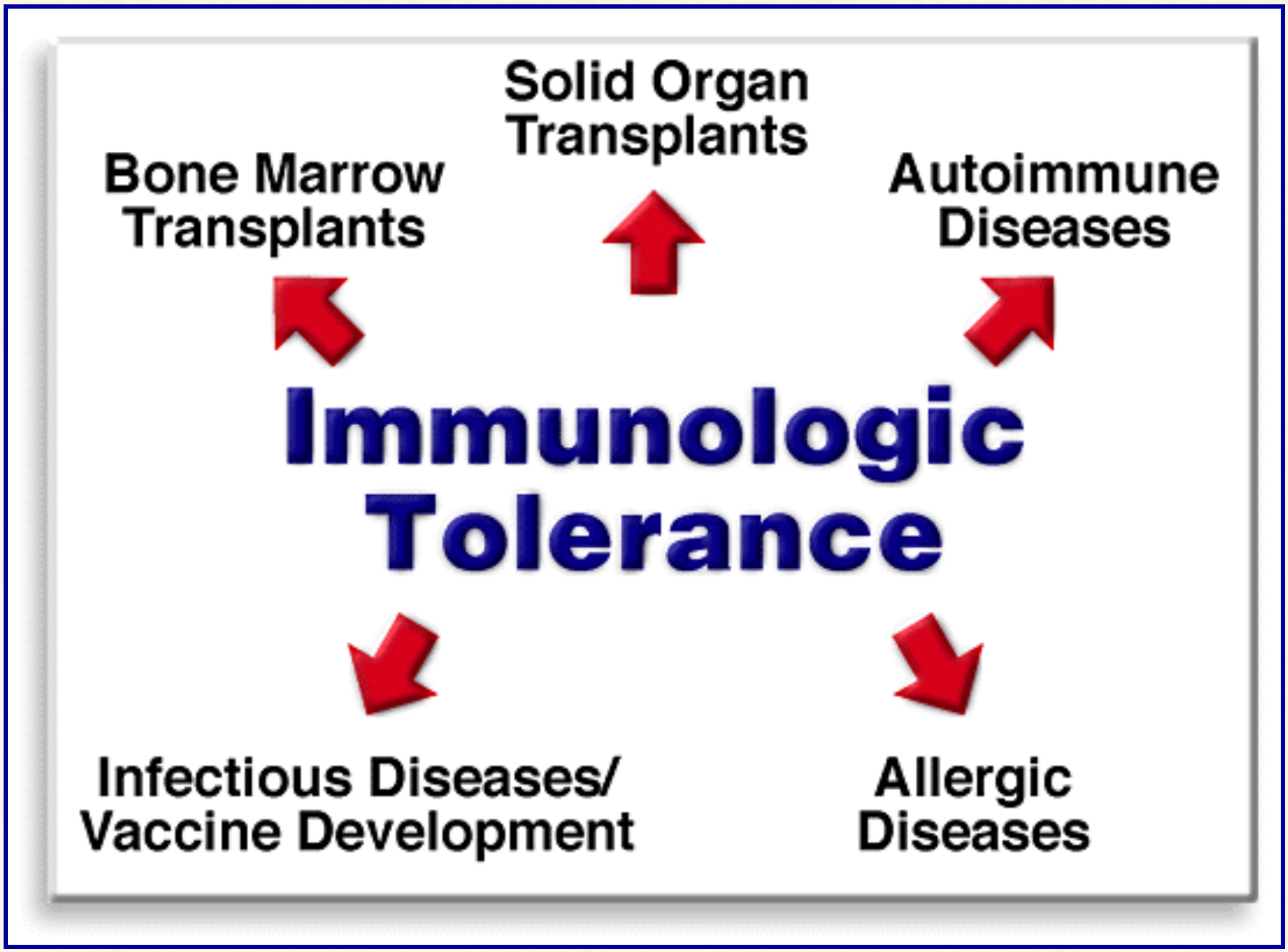
Natural autoantibodies may participate in a variety of physiological activities, from immune regulation, homeostasis and repertoire selection, to resistance to infections, transport and functional modulation of biologically active molecules. Autoantibodies of the **IgM (mostly)**, or IgG and IgA classes, **reactive with a variety of** serum proteins, cell surface structures and intracellular **structures, are 'naturally' found in all normal individuals.** Present in human cord blood and in 'antigen-free' mice, their variable region repertoire is selected by antigenic structures in the body and **remains conserved throughout life**. Encoded by germline genes with no, or few, mutations, natural autoantibodies are characteristically **'multireactive'** and do **not undergo affinity maturation** in healthy individuals.

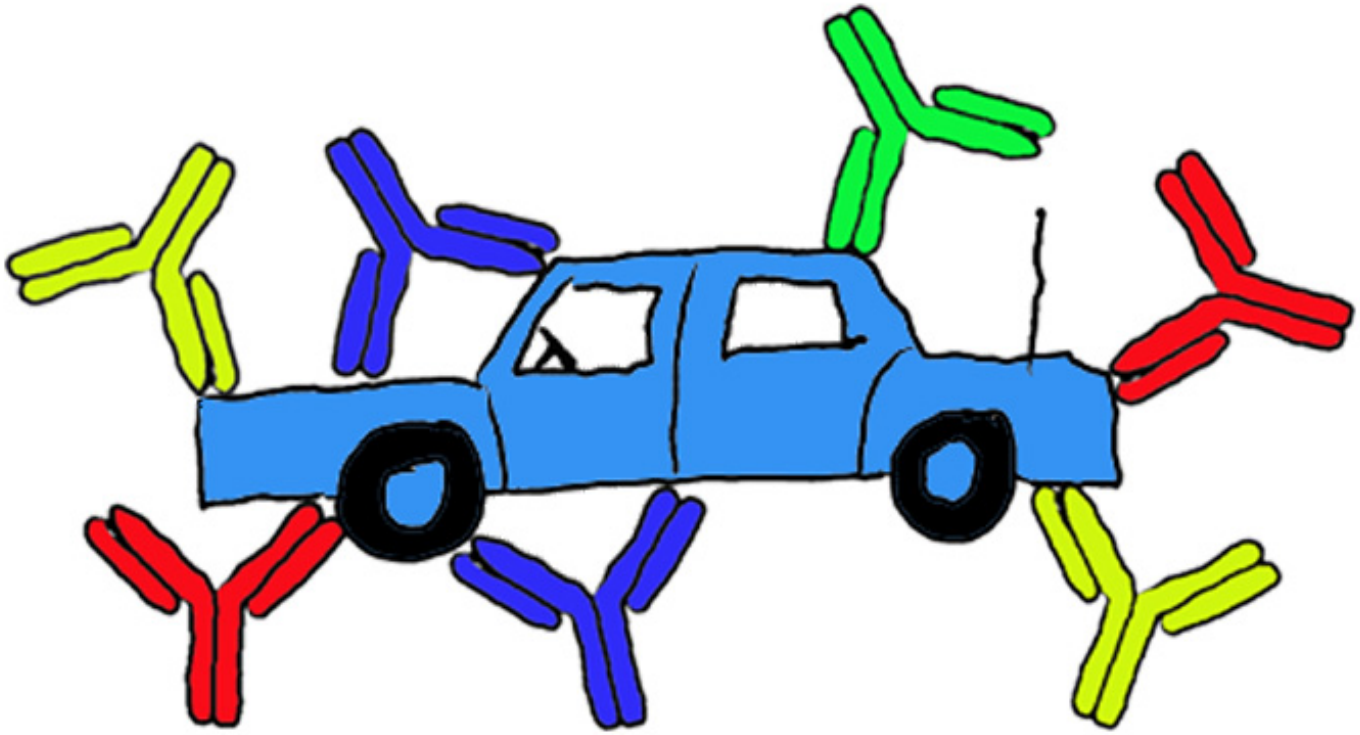


Natural antibodies provide an important link between the innate and adaptive immune systems. Before the adaptive immune system is activated, they restrict pathogen dissemination by direct neutralization, complement activation and elimination of them in the marginal/sinusoidal zone of secondary lymphoid organs. Moreover, natural antibodies favor priming of the adaptive immune system by contributing substantially to antigen recruitment in secondary lymphoid organs.

Antigens recognized by natural autoantibodies

Heatshock proteins	hsp65, hsp70, hsp90, ubiquitin
Enzymes	aldolase, citockrom c, SOD, NAPDH, citrate synthase, DNA topoisomarase I.
Cell membrane components	β2-microglobulin, spectrin, acetylcholin receptor
Cytoplasmic components	actin, myosin, tubulin, myoglobin, myelin basic protein
Nuclear components	DNS, histones
Plasma proteins	albumin, IgG, transferrin
Cytokines, hormones	IL-1, TNF, IFN, insulin, thyreoglobin


Solid Organ Transplants
Bone Marrow Transplants
Autoimmune Diseases
Immunologic Tolerance
Infectious Diseases/ Vaccine Development
Allergic Diseases



Autoimmunity

Autoimmune diseases affect 10% of the global population !

Autoreactivity/Autoimmunity

- **Paul Ehrlich**'s dictum (1900) of *horror autotoxicus* inhibited acceptance of the reality of autoimmune disease.
- The first autoantibodies were discovered in the 1940s, when antinuclear antibodies and rheumatoid factors were described as serum factors that could bind nuclear antigens and immunoglobulins, respectively.
- The discoveries of allergy and anaphylaxis were the first signs that the immune system was capable of self-damage. The studies on chronic thyroiditis and clinical laboratory breakthroughs led to the acceptance of autoimmune disease in the 1950s.
- Although autoimmunity was accepted as a pathological phenomenon, but the existence of self-reactive autoantibodies was also found in healthy individuals.

AUTOIMMUNITY

- **Physiological autoimmunity:** part of the normal immunological regulation
- **Pathological autoimmunity:** diseases caused by self reacting inflammatory immune responses with permanent tissue/organ injury

Pathomechanism of autoimmunity

- **Chronic inflammation and tissue necrosis**

  - **Cellular components:**

(T cells CD8 and Th1, NK, Mf, DC, Ne, Eo, Ba, Mc)

  - **Humoral components:**

(Ig+complement, ADCC, cytokines, chemokines, tissue hormones and mediators)

Pathomechanism of autoimmunity

- **Multifactor mechanism**

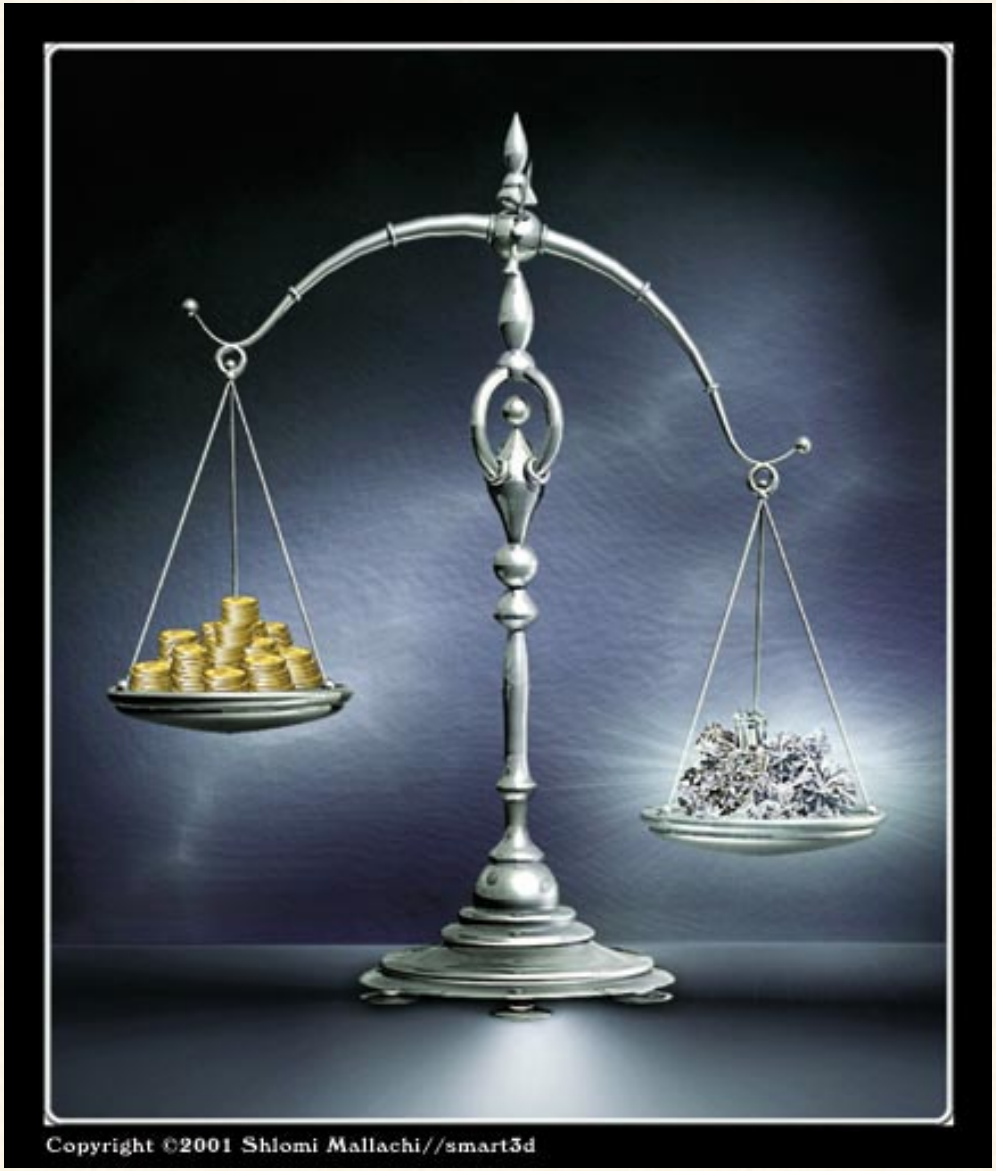
(general catastrophe of bio-regulation caused by external and internal factors)

- **Autoimmune *"steady state"*** (failure of dynamic balance on self tolerance and autoimmunity)

- **Role of infections** (molecular mimicry or inefficient natural antibody network)

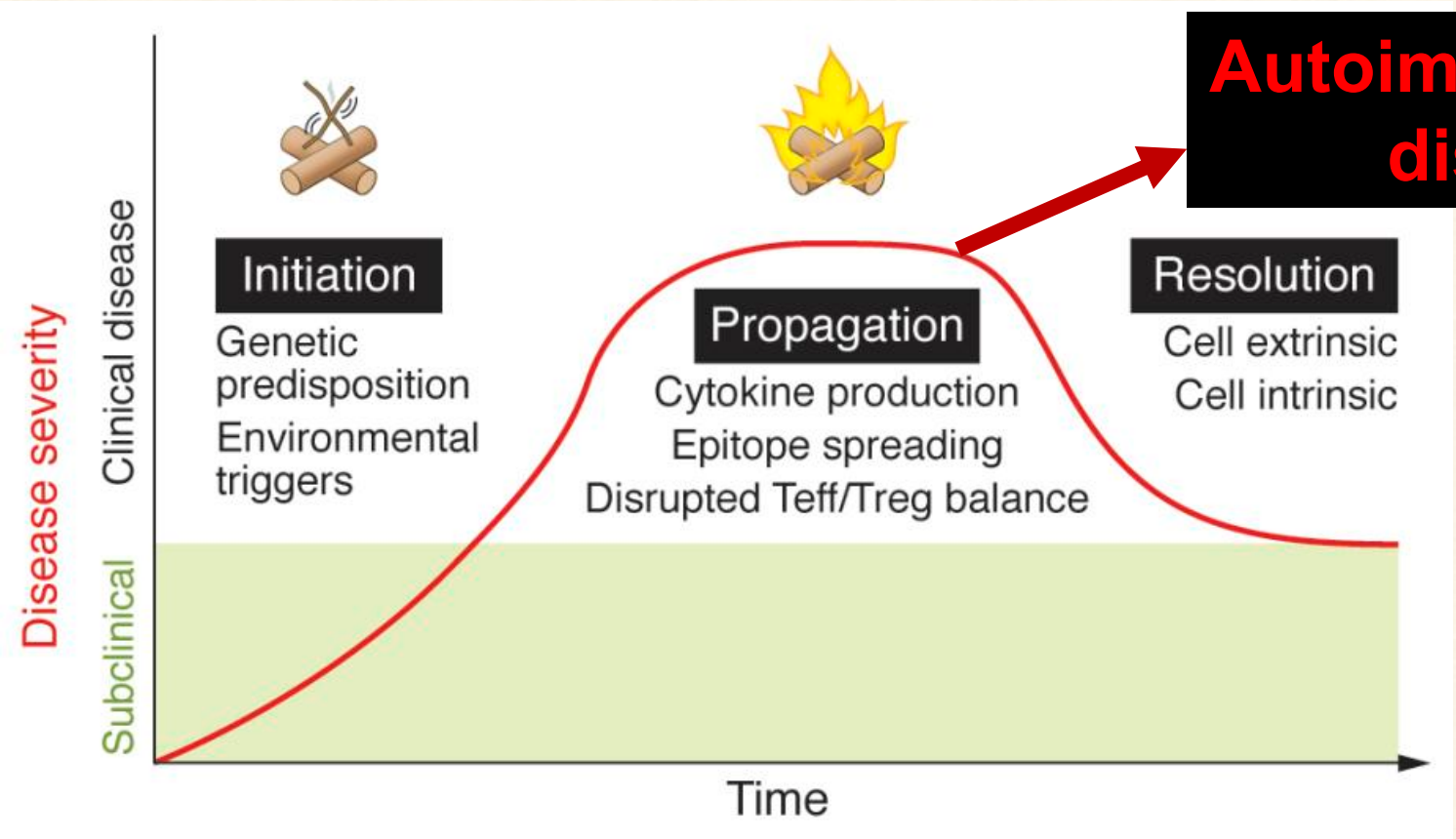
Autoimmune steady state

Self reacting immune response with tissues damages



Active tolerance and tissue repair

Progression of autoimmune reactions



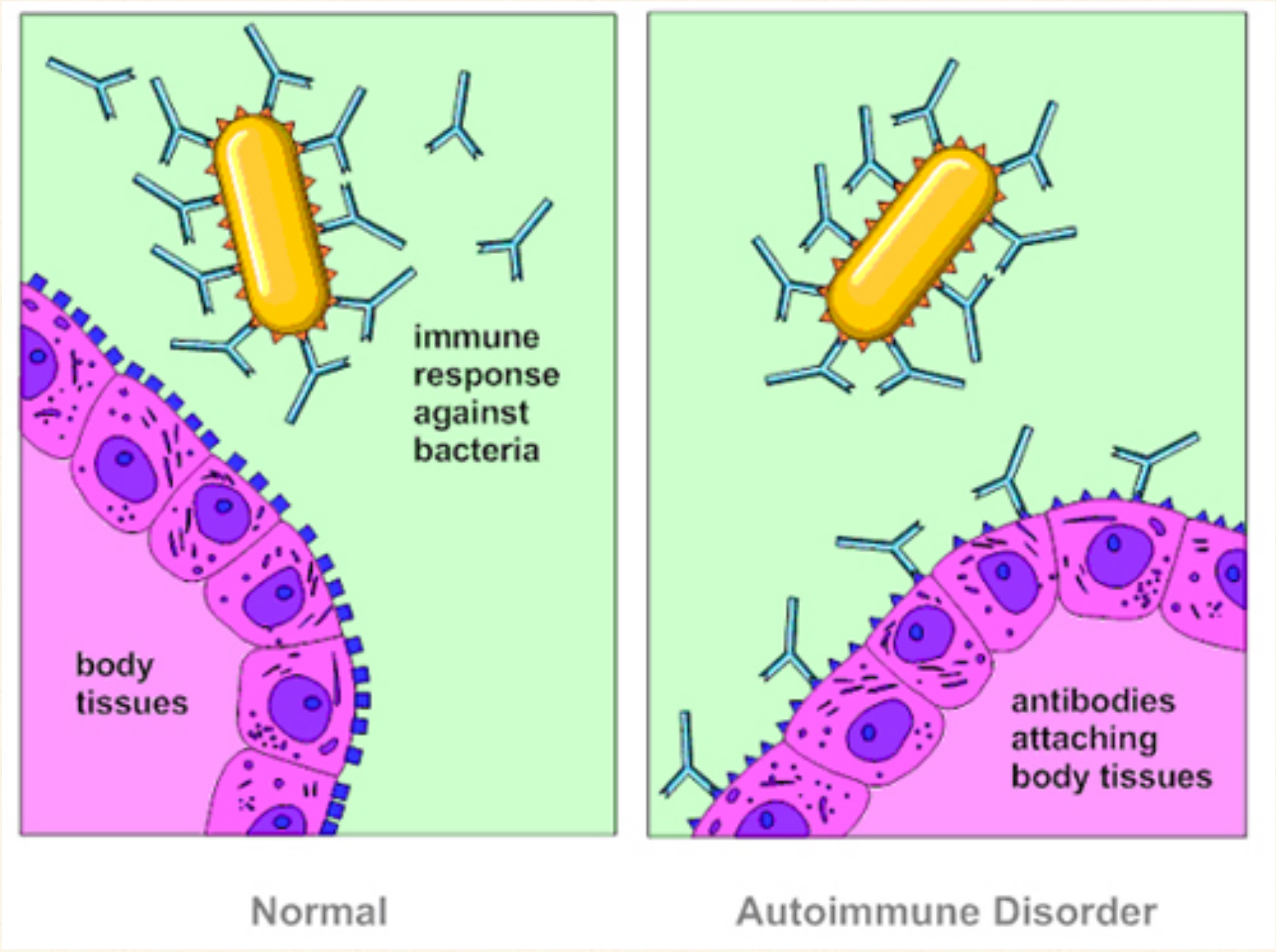
In the initiation phase are unaware of clinical symptoms. The clinical disease develops during the propagation phase characterized by inflammation and tissue damage. Autoimmune reactions resolve with the activation of inhibitory pathways and Treg mechanisms, or continue the propagation.

Pathomechanisms of autoimmune diseases

- Autoimmunity by the antigen

- Failed differentiation and selection of lymphocytes

- Genetic background


immune
response
against
bacteria
body
tissues
antibodies
attaching
body tissues
Normal
Autoimmune Disorder

Pathogens and human antigens	Peptid residues	Overlaping sequences
Human cytomegalovirus IE2	79	PDPLGRPDED
HLA-DR molecule	60	VTELGRPDAE
Poliovirus VP2	70	STTKESRGTT
Acetylcholine receptor	176	TVIKESRGTK
Papilloma virus E2	76	SLHLESLKDS
Insulin receptor	66	VYGLESLKDL
Klebsiella pneumoniae nitrogenase enzym	186	SRQTDREDE
HLA-B27 molecule	70	KAQTDREDL
Adenovirus 12 E1B	384	LRRGMFRPSQCN
Alfa-gliadin	206	LGQGSFRPSQQN
HIV p24	160	GVETTTPS
Human IgG	466	GVETTTPS
Measles virus P3	31	EISDNLGQE
Myelin basic protein	61	EISFKLGQE

Autoimmunity by the antigen

Tissue injury or inflammation, leading to:

- **Release of sequestered self antigens**

- **Structural alterations of self antigens**

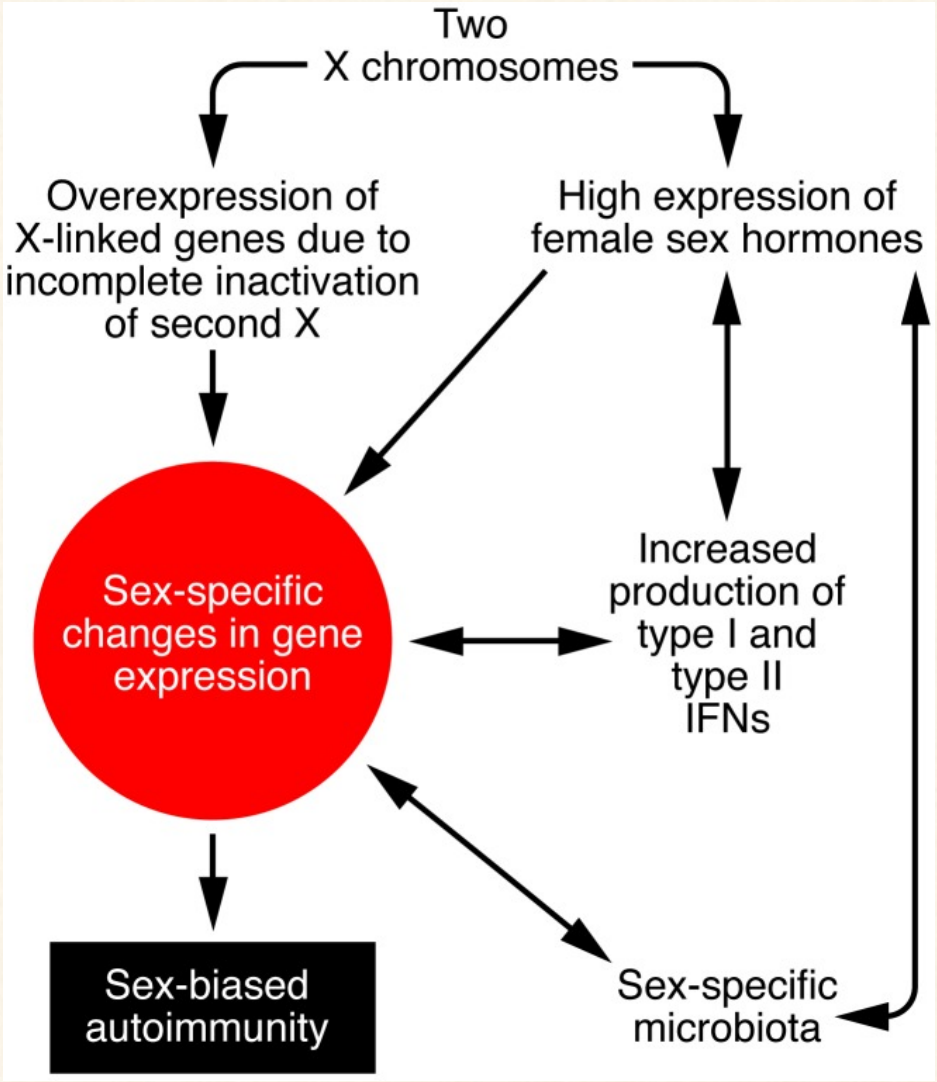
- **Increased costimulation on tissue APCs**

Autoimmunity by the failure of self tolerance

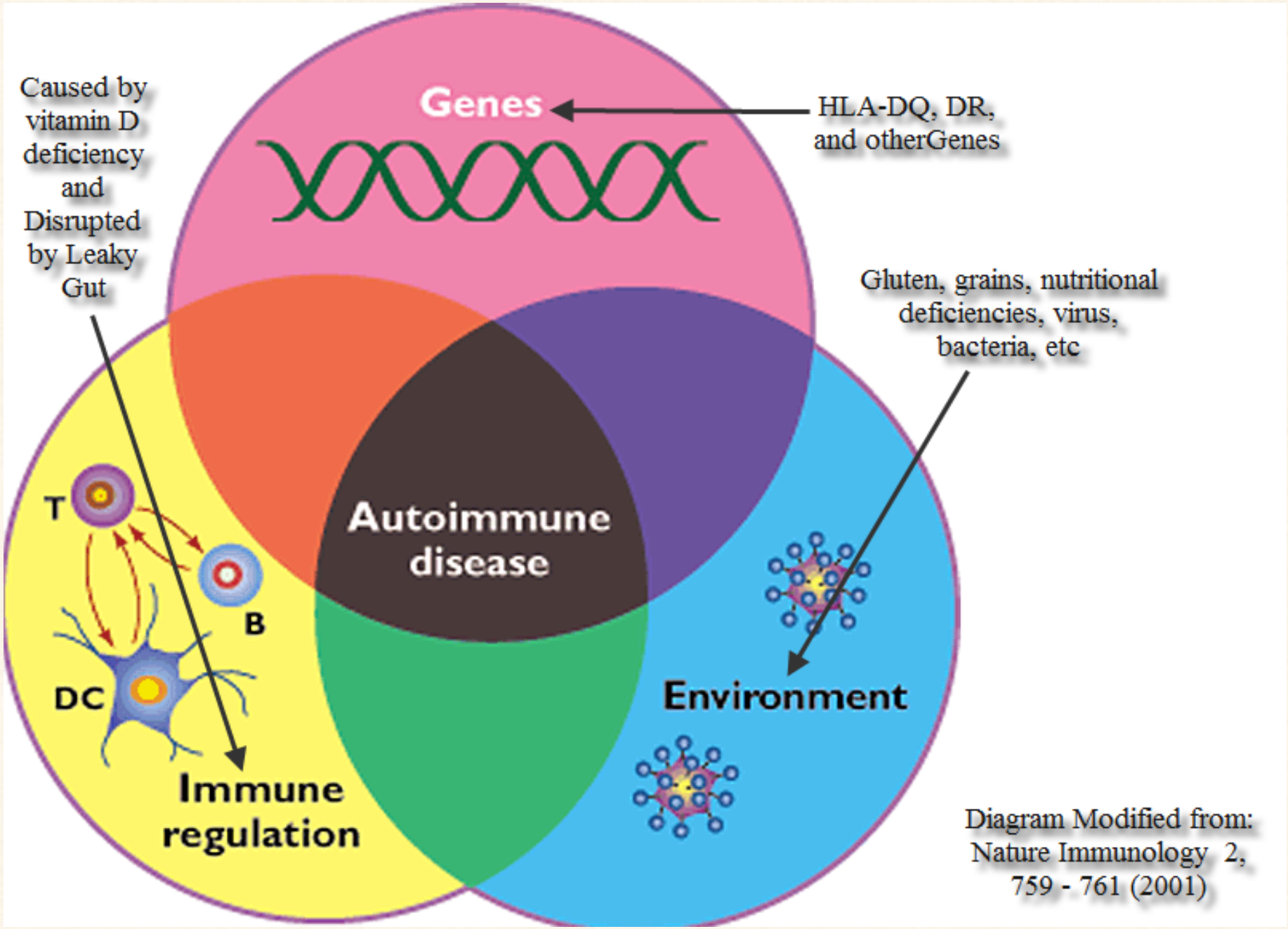
- Failed selection of lymphocyte repertoire
- Polyclonal activation of anergic self-reactive lymphocytes
- Stimulation by foreign antigens that cross-react with self

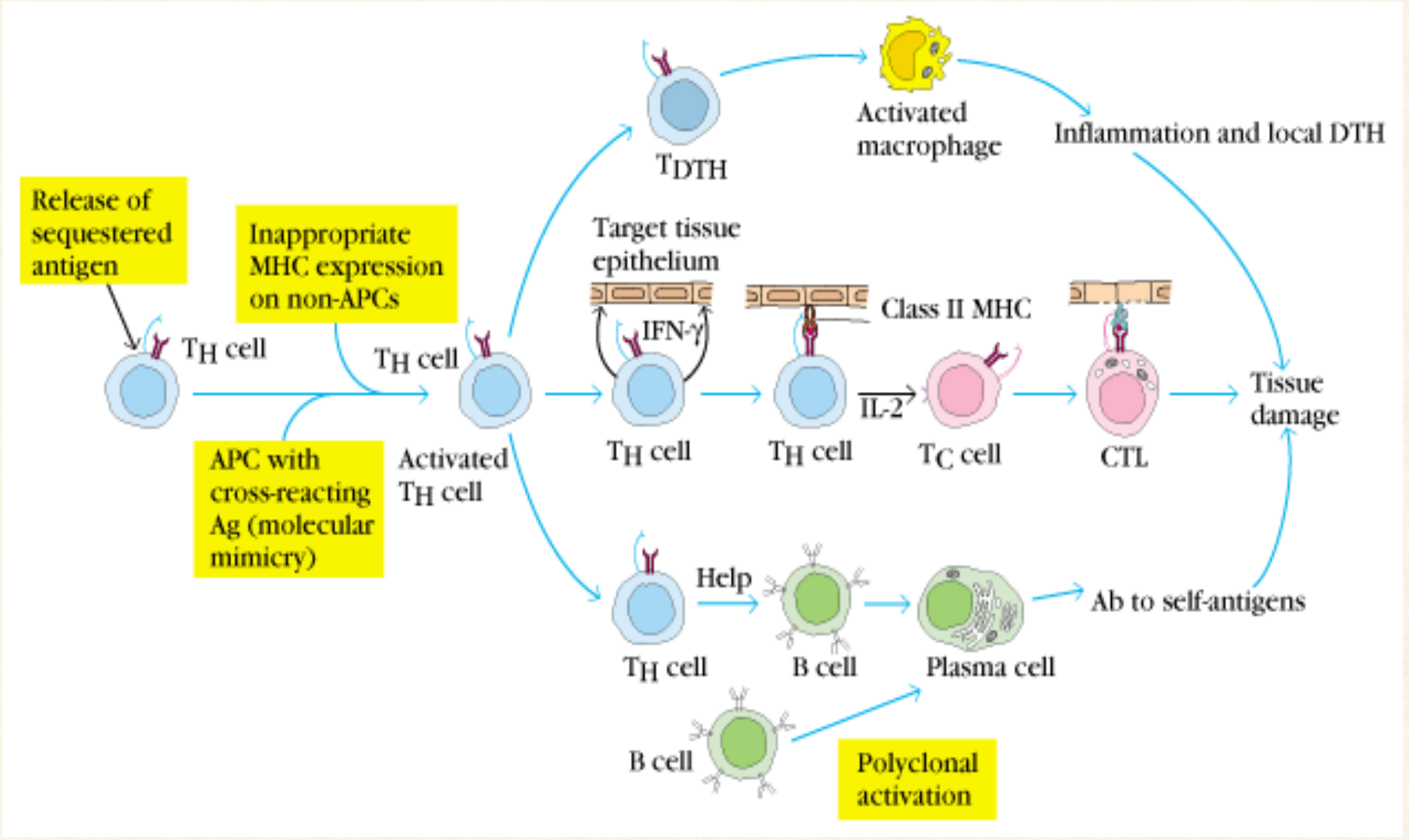
Associations of HLA serotype with susceptibility to autoimmune disease			
Disease	**HLA allele**	**Relative risk**	**Sex ratio (♀:♂)**
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5
Myasthenia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

Sex differences in autoimmunity



Autoimmune disease	Female/male ratio
Ankylosing spondylitis	1:2
Antiphospholipid antibody syndrome	5:1
Autoimmune chronic hepatitis	7:1
Celiac disease	1:1
Grave's disease	7:1
Hashimoto's disease	5-18:1
Multiple sclerosis	2:1
Myasthenia gravis	3:1
Primary biliary cirrhosis	10:1
Psoriasis	1:1
Rheumatoid arthritis	3:1
Sjogren's syndrome	9:1
Systemic lupus erythematosus	9:1
Systemic sclerosis	5:1


Caused by vitamin D deficiency and Disrupted by Leaky Gut
Genes
HLA-DQ, DR, and otherGenes
Gluten, grains, nutritional deficiencies, virus, bacteria, etc
T
B
DC
Autoimmune disease
Environment
Immune regulation
Diagram Modified from: Nature Immunology 2, 759 - 761 (2001)


Release of sequestered antigen
Inappropriate MHC expression on non-APCs
APC with cross-reacting Ag (molecular mimicry)
TH cell
TH cell
Activated TH cell
TDTH
Activated macrophage
Inflammation and local DTH
Target tissue epithelium
IFN-γ
TH cell
Class II MHC
TH cell
IL-2
TC cell
CTL
Tissue damage
Help
TH cell
B cell
Plasma cell
Ab to self-antigens
B cell
Polyclonal activation

Body Parts That Can Be Affected by Autoimmune Diseases

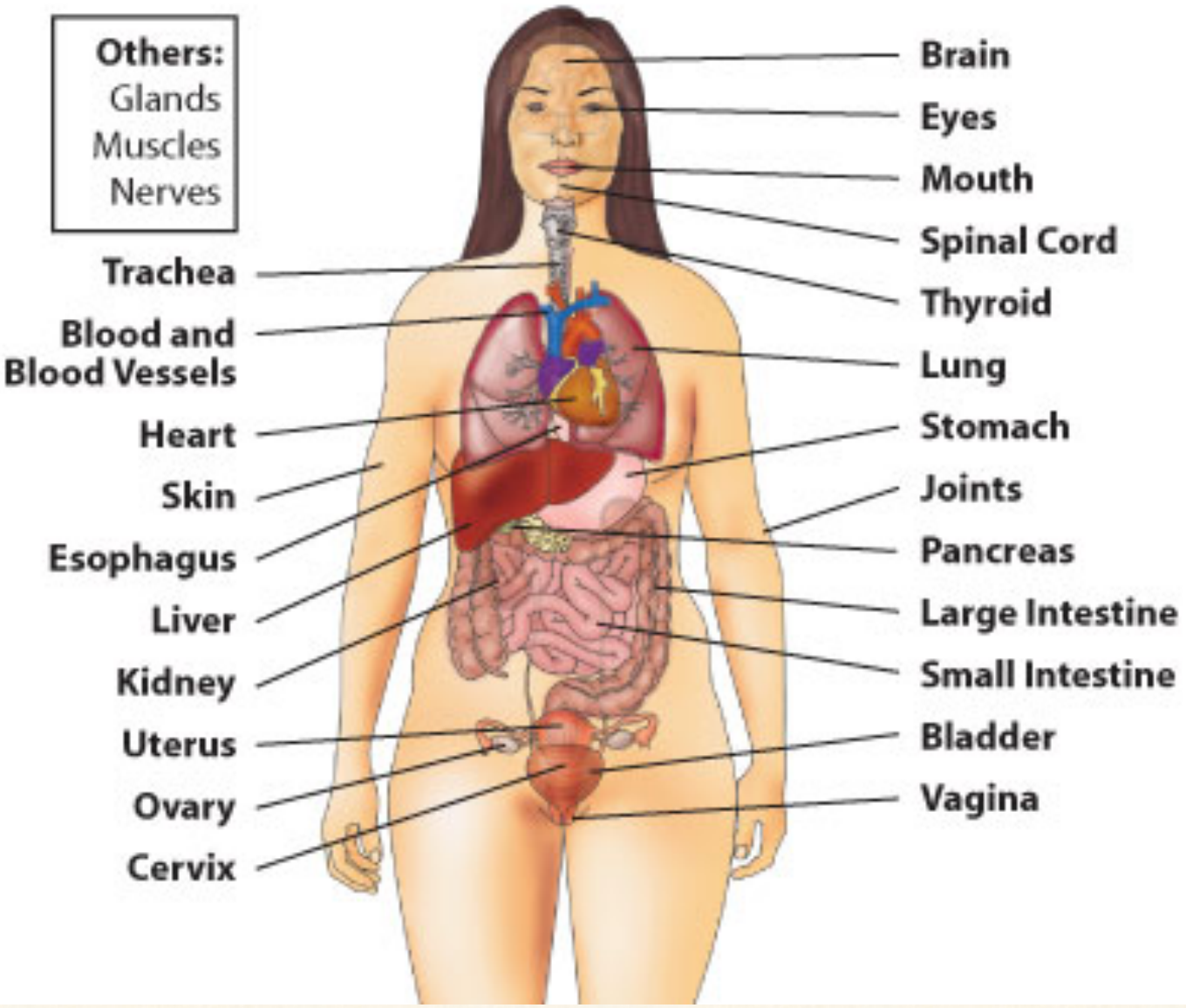
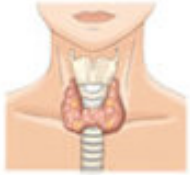


TABLE 20-1 SOME AUTOIMMUNE DISEASES IN HUMANS

Disease	Self-antigen	Immune response
Organ-specific autoimmune diseases		
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T_{DTH} cells, auto-antibodies
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_{DTH} cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
Systemic autoimmune disease		
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_{DTH} and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjogren's syndrome	Salivary gland, liver, kidney, thryoid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antobidies, immune complexes

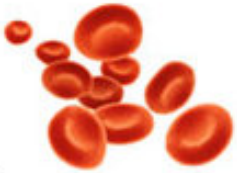
Autoimmune Diseases

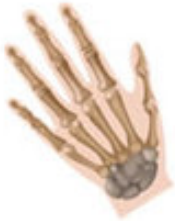
Brain
Multiple Sclerosis
Guillaun-Barre Syndrome
Autism



Thyroid
Thyroiditis
Hashimoto's Disease
Graves' Disease

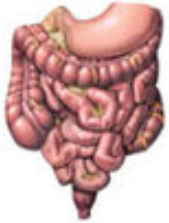
Blood
Leukemia
Lupus Erythematosus
Hemolytic Dysglycemia



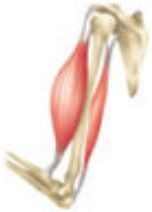


Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

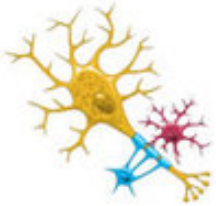
GI Tract
Celiac's Disease
Crohn's Disease
Ulceratic Colitis
Diabetes Type I



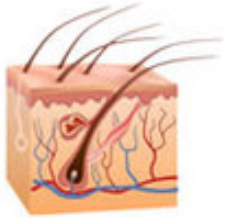
>100 Autoimmune Diseases



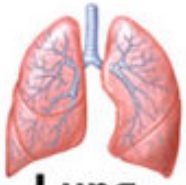
Muscles
Muscular Dystrophy
Fibromyalgia



Nerves
Peripheral Neuropathy
Diabetic Neuropathy

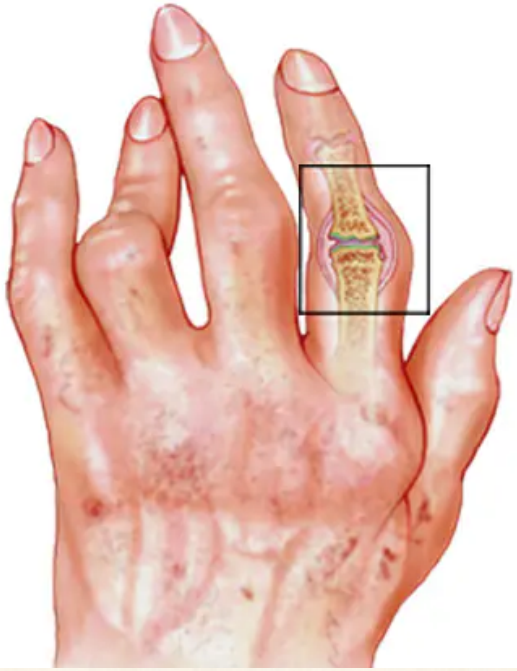


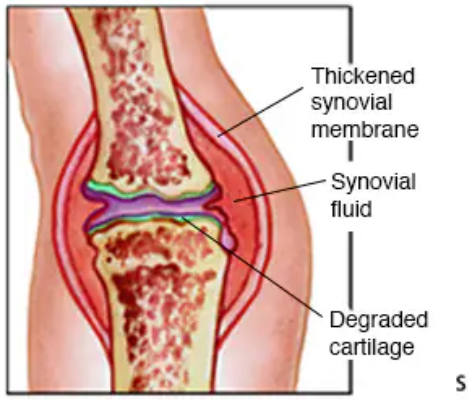
Skin
Psoriasis
Vitiligo
Eczema
Scleroderma

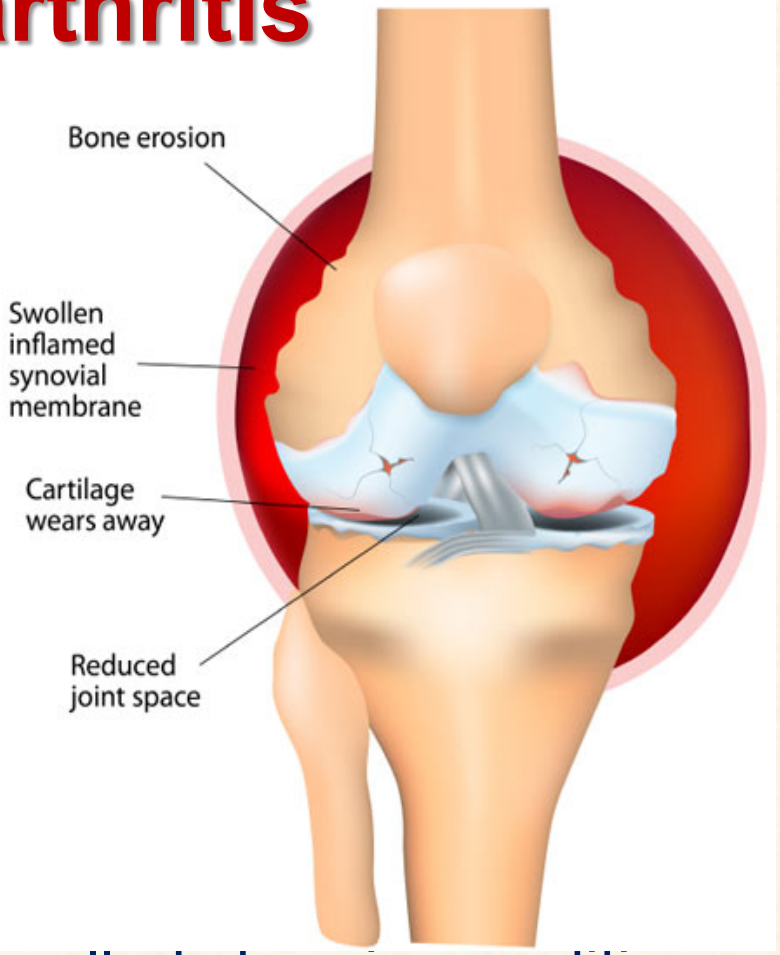


Lung
Fibromyalgia
Wegener's Granulomatosis

Rheumatoid arthritis

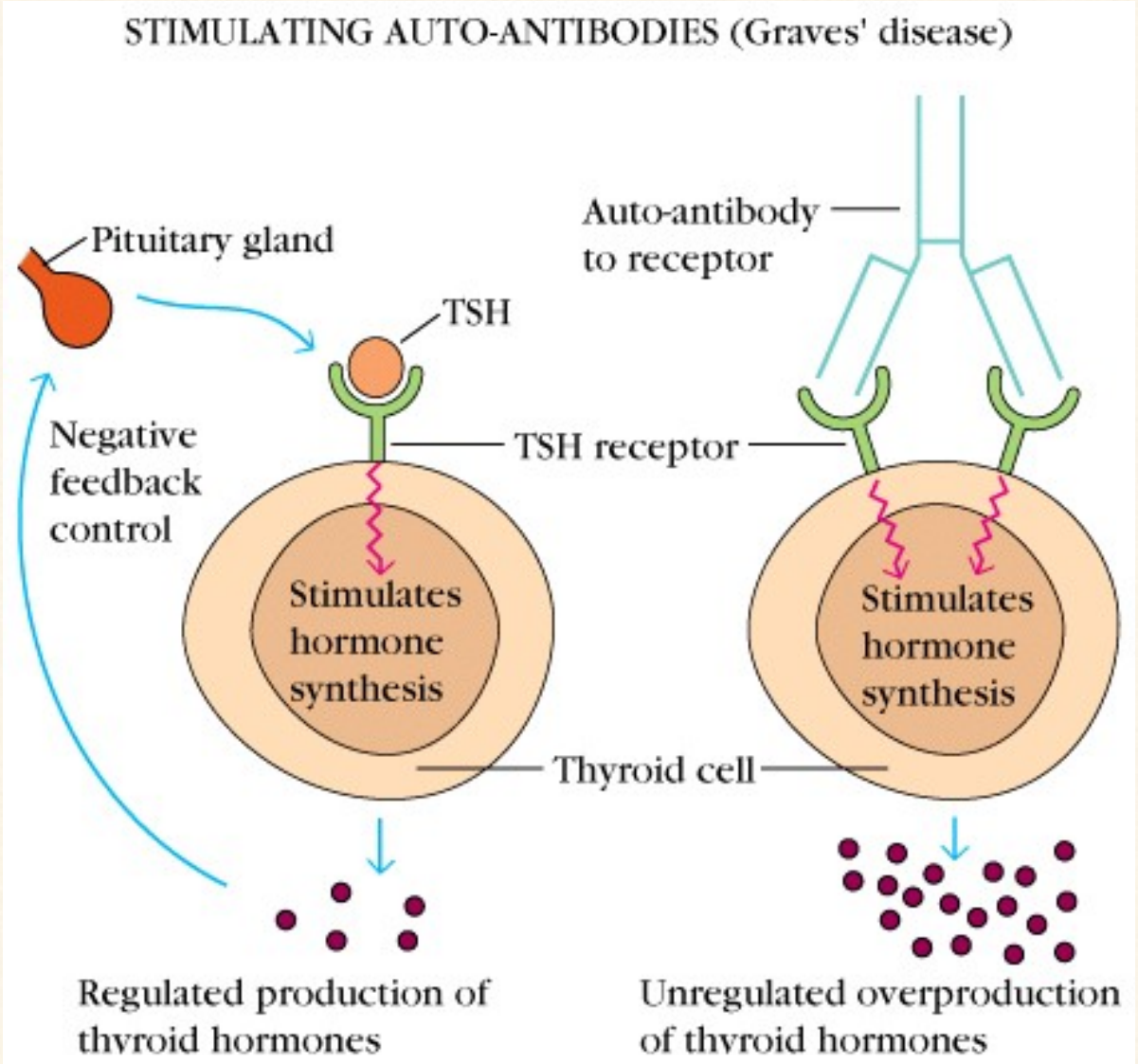




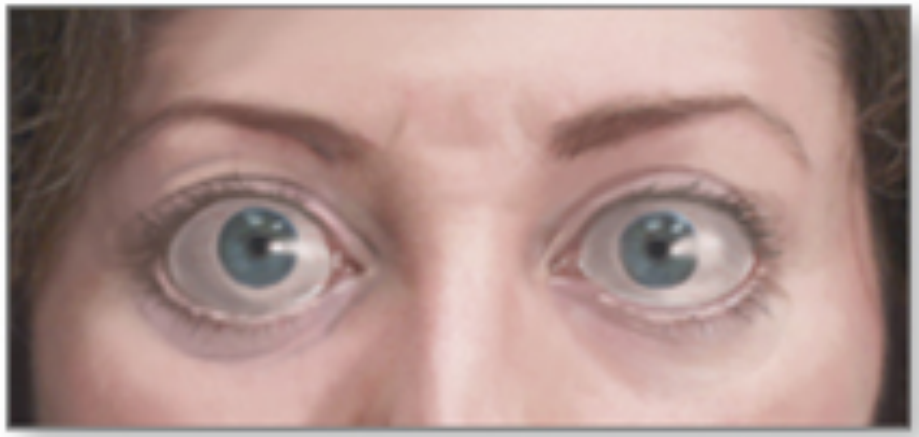


Rheumatoid arthritis is an ongoing, called chronic, condition that causes pain, swelling and irritation, called inflammation, in the joints. But it also can damage other parts of the body. These may include the skin, eyes, lungs, heart and blood vessels.

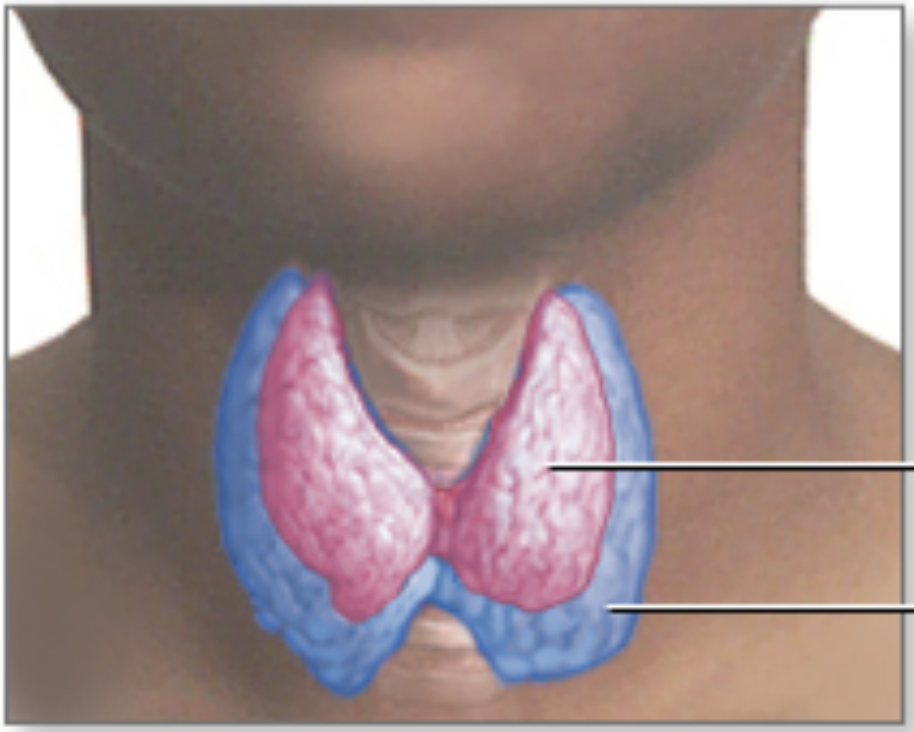
Grave's disease



In **Graves' Disease** a patient produces autoantibodies that bind to the receptors for thyroid-stimulating hormone (TSH). TSH is produced by the pituitary gland and the receptors for TSH are present on thyroid cells. Binding of these autoantibodies mimics the normal action of TSH which is to stimulate the production of two thyroid hormones, thyroxine and triiodothyronine. However, the autoantibodies are not under a negative feedback control system and therefore lead to overproduction of the thyroid hormones. For this reason these autoantibodies have been termed **long-acting thyroid-stimulating (LATS) antibodies**. Overproduction of thyroid hormones leads to many metabolic problems.



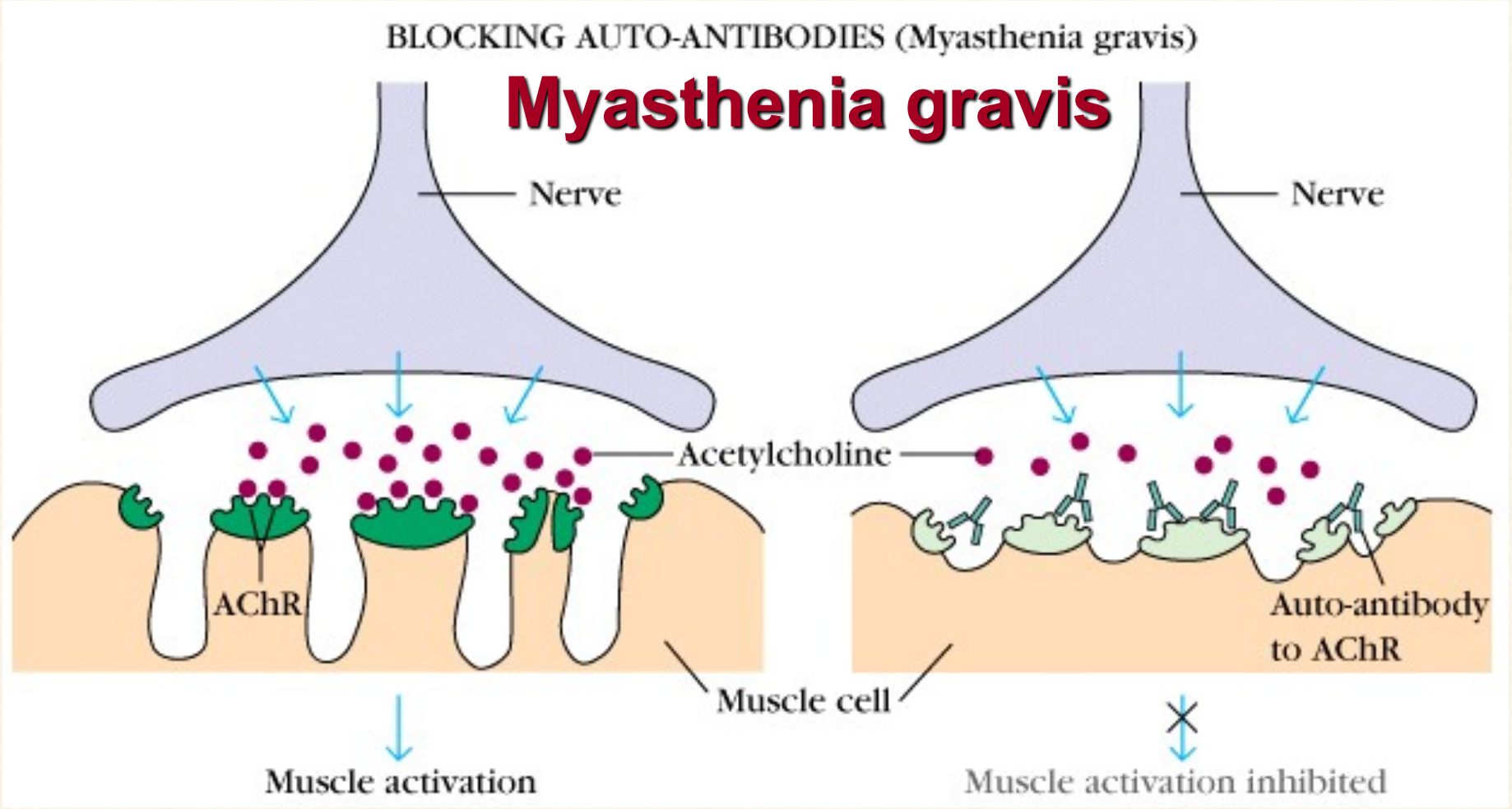
Exophthalmos (bulging eyes)



Diffuse goiter

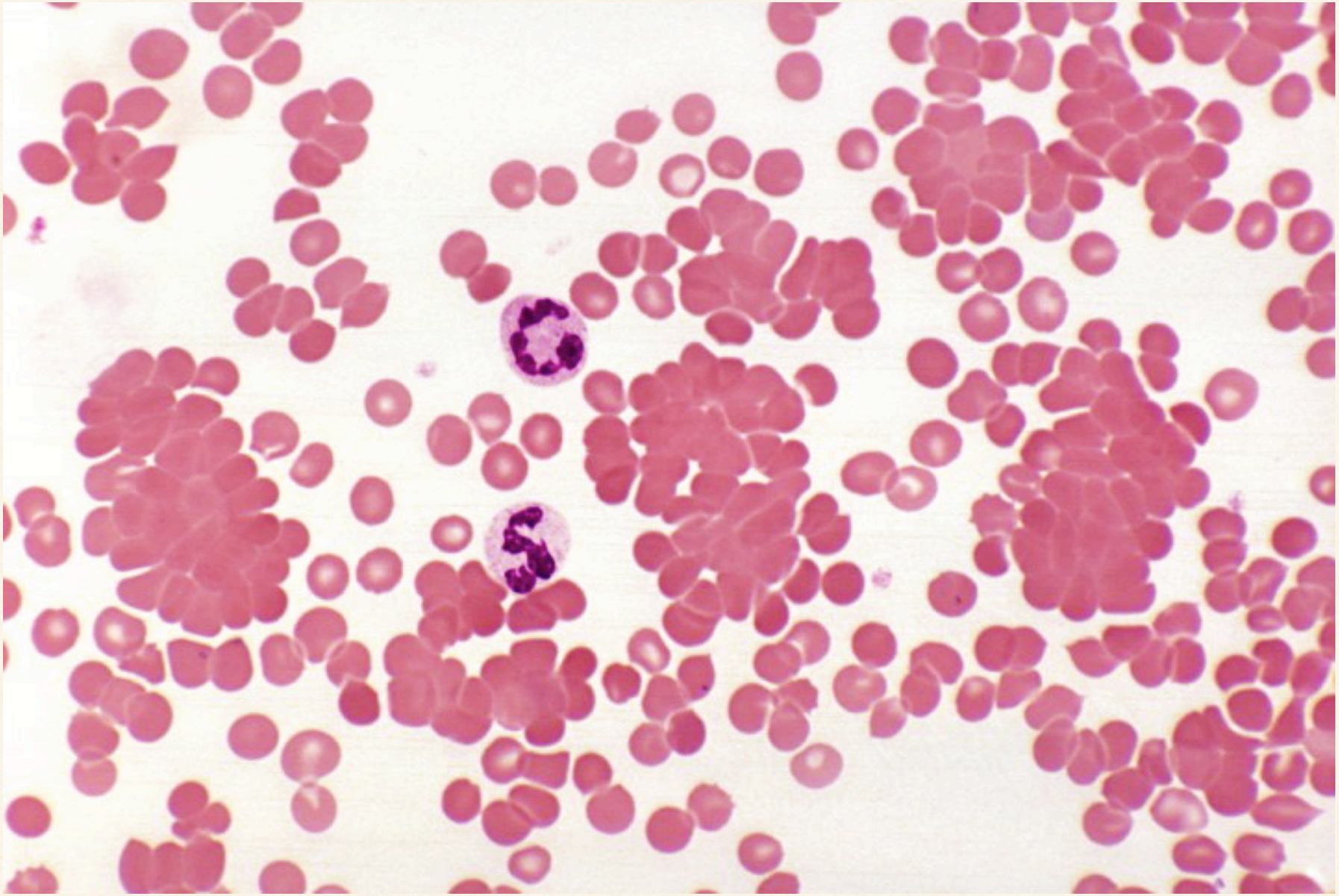
Graves' disease is a common cause of hyperthyroidism, an over-production of thyroid hormone, which causes enlargement of the thyroid and other symptoms such as exophthalmos, heat intolerance and anxiety

Myasthenia gravis

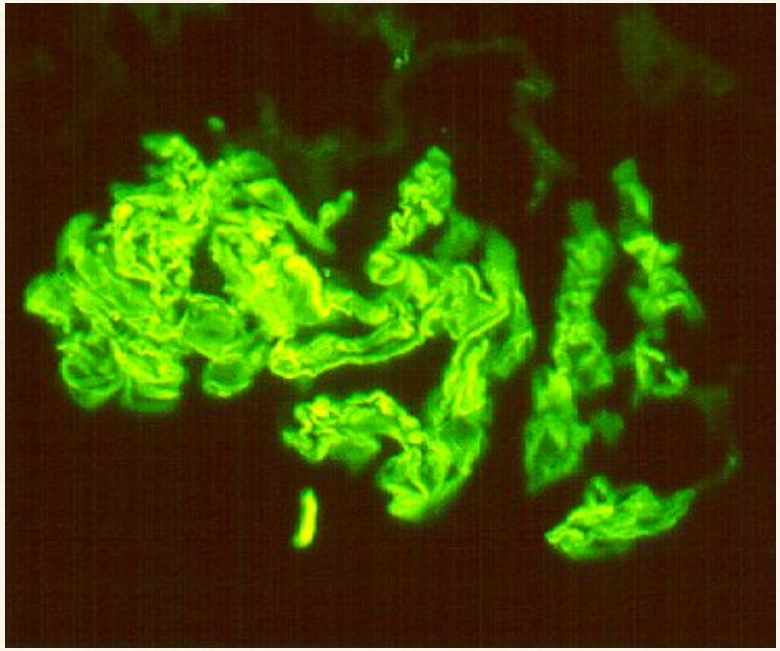


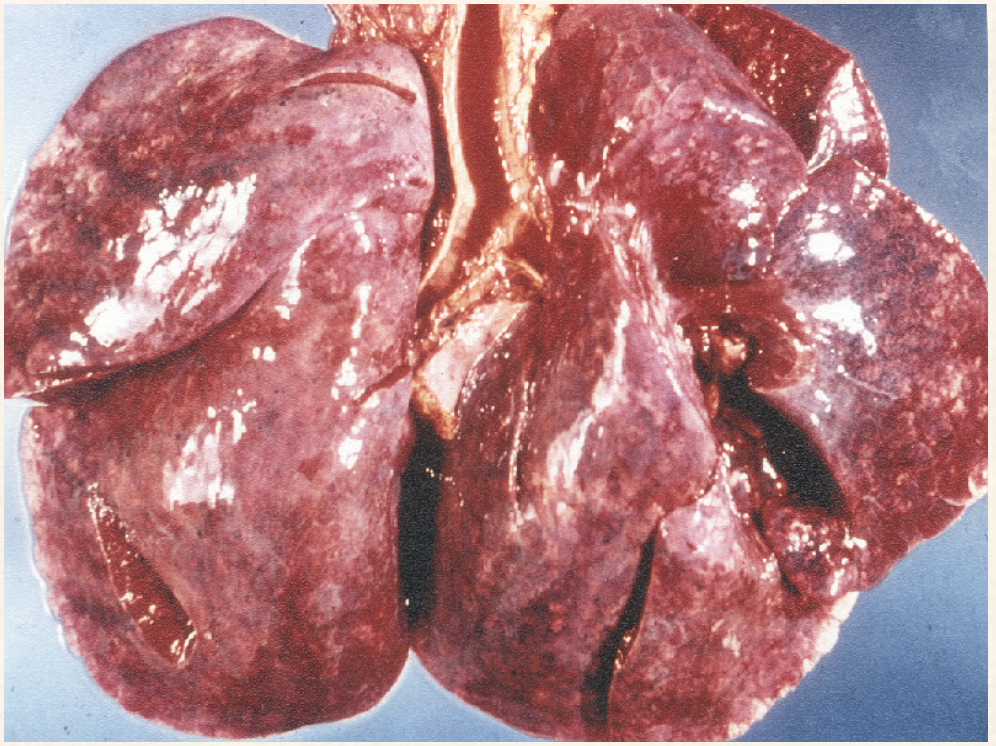
A patient with this disease produces autoantibodies to the acetylcholine receptors on the motor end-plates of muscles. Binding of acetylcholine in therefore blocked and muscle activation is inhibited. The autoantibodies also induce complement-mediated degradation of the acetylcholine receptors, resulting in progressive weakening of the skeletal muscles.

Autoimmune hemolytic anemia

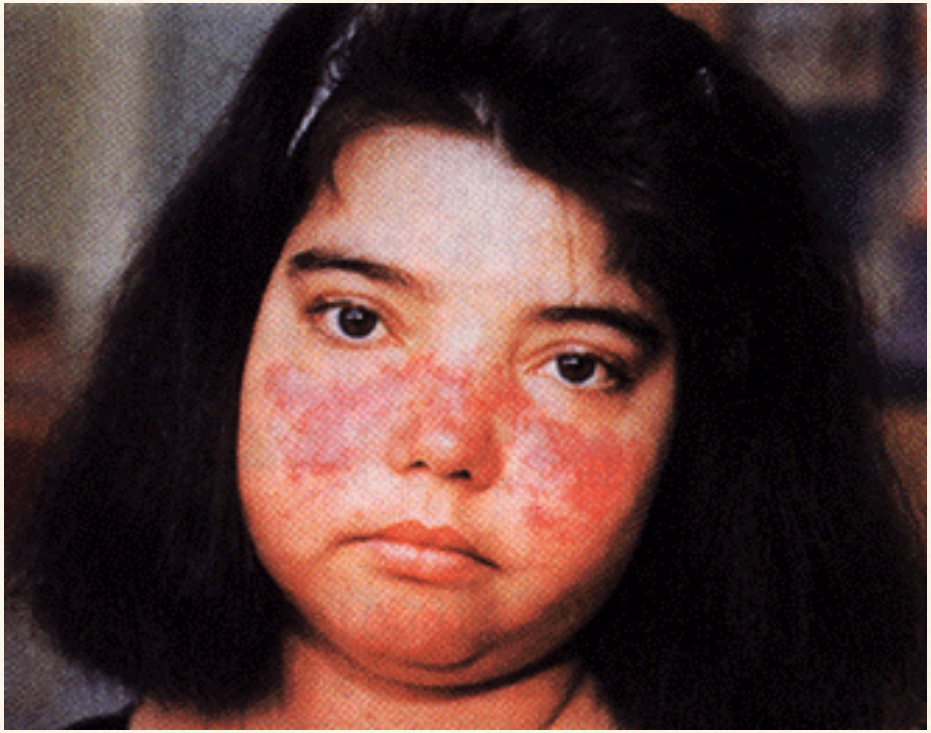


Goodpasture syndrom



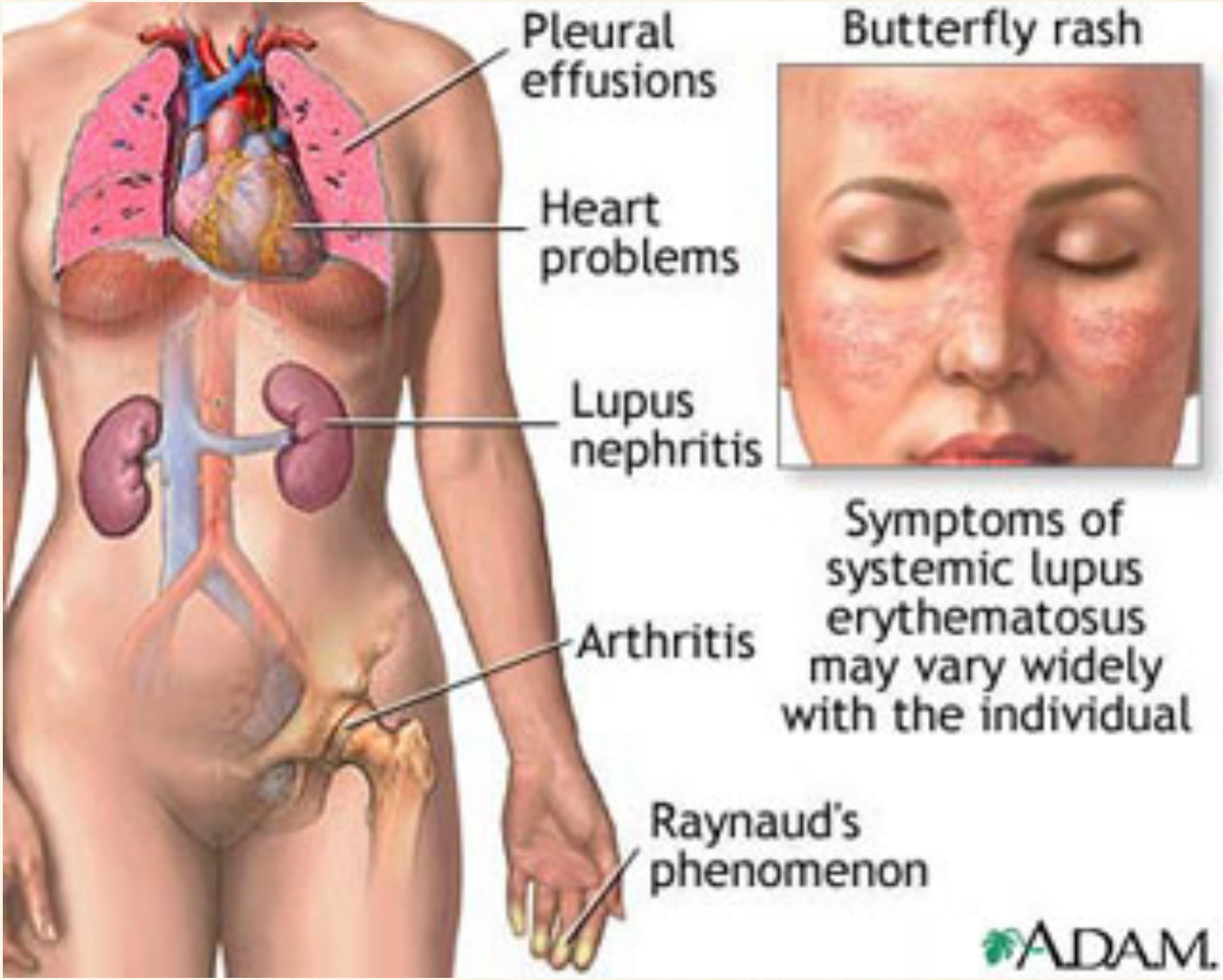


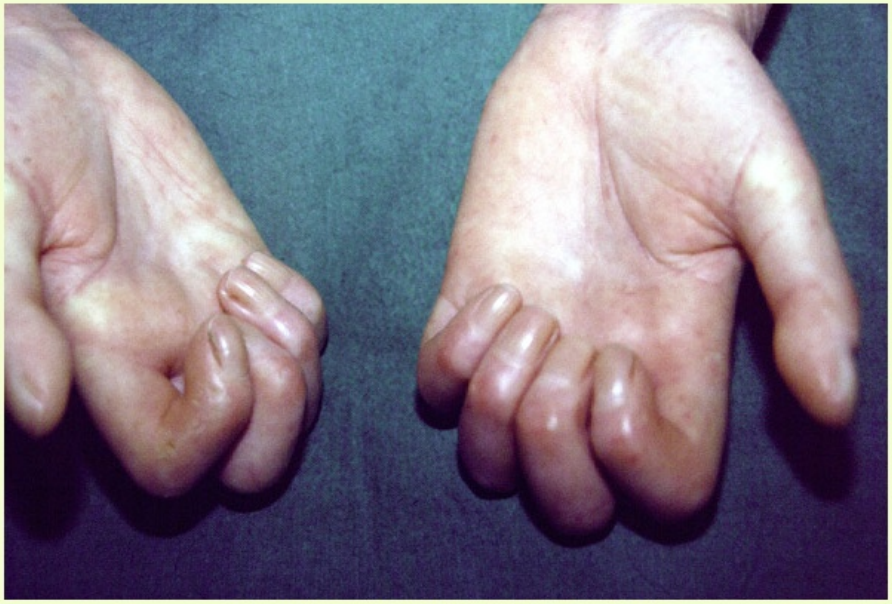
Autoantibodies are produced against alpha-3 subunit of type IV collagen in the basement membranes of glomeruli and lung causing bleeding necrosis.



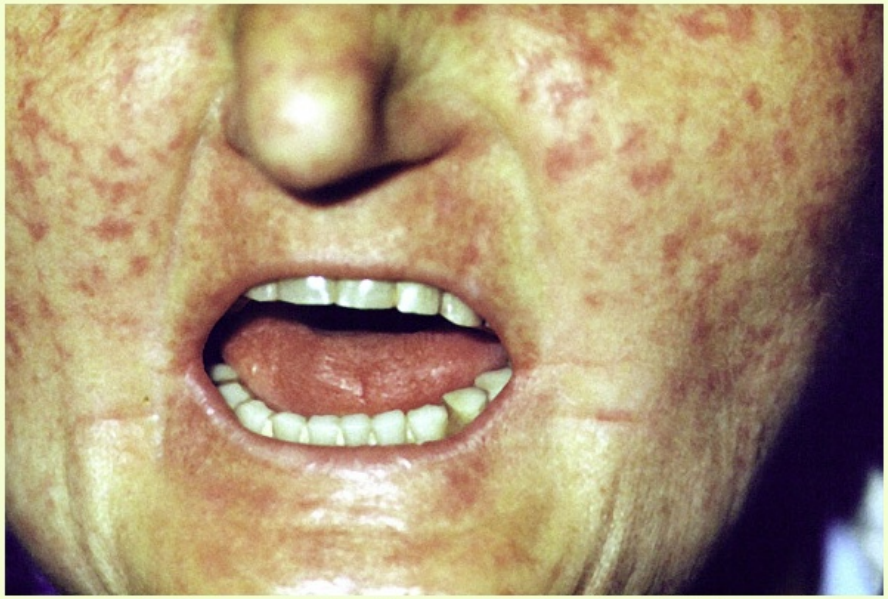
Characteristic "butterfly" rash over the cheeks of a young girl with SLE.

Systemic Lupus Erythematosus (**SLE**) is characterized by fever, weakness, arthritis, skin rashes, pleuritis, and kidney dysfunction. Affected individuals may produce autoantibodies to a range of tissue antigens such as DNA, histones, RBCs, platelets, leukocytes, and clotting factors. SLE typically appears in women between 20 and 40 years of age with a female:male ratio of 10:1. An example of complications arising from SLE is when immune complexes are deposited along the walls of small blood vessels. This deposition activates complement system, resulting in glomerulonephritis and damage to the blood-vessel wall (**vasculitis**) causing widespread tissue damage.


Pleural effusions
Heart problems
Lupus nephritis
Arthritis
Raynaud's phenomenon
Butterfly rash
Symptoms of systemic lupus erythematosus may vary widely with the individual
A.D.A.M.



Késôi, súlyos sclerodermás kézelváltozások



Csökkent maximalis oralis apertura ill. teleangiectasia SSc-ben

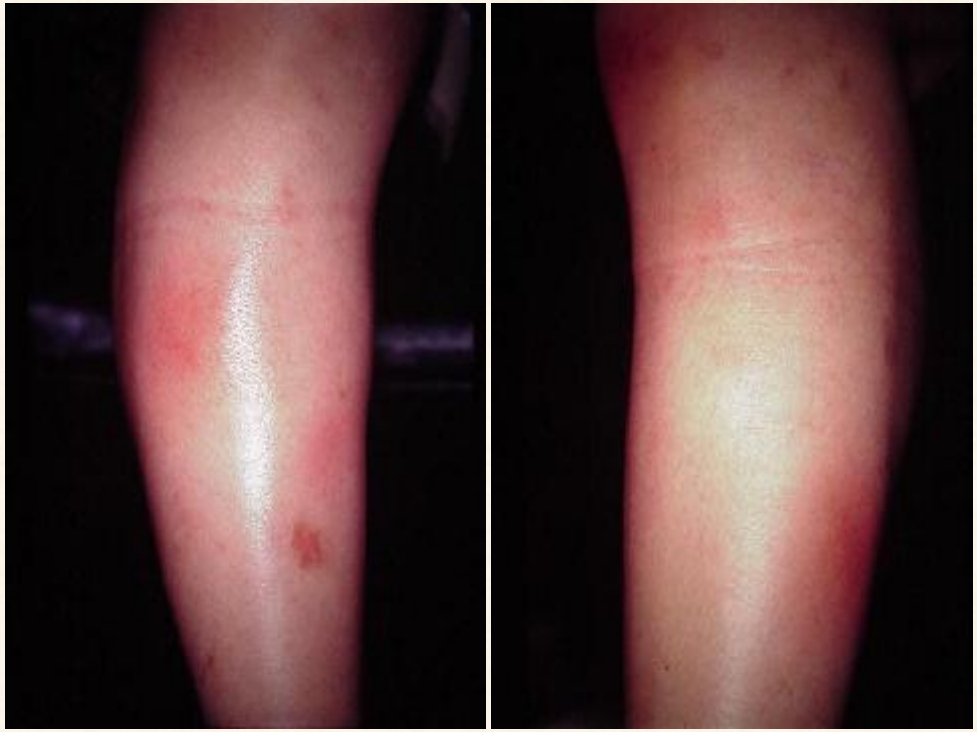
Diffuse cutaneous SSc **(dcSSc):** skin manifestation both on the extremities and on the trunk, severe internal organ involvement, **poor prognosis**

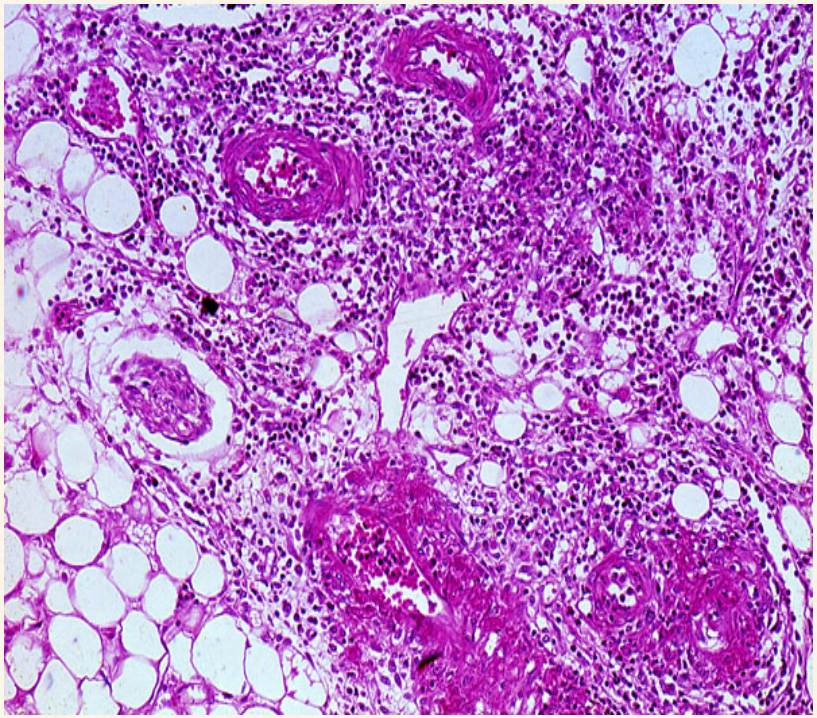
Limited cutaneous SSc **(lcSSc):** skin involvement only on the face and distal part of extremities, no internal organ involvement, **good prognosis**

The major autoantibody in SSc targets DNA topoisomerase I (Topo I or Scl-70)

Anti-Topo I autoantibodies are detected **mainly, but not exclusively** in dcSSc

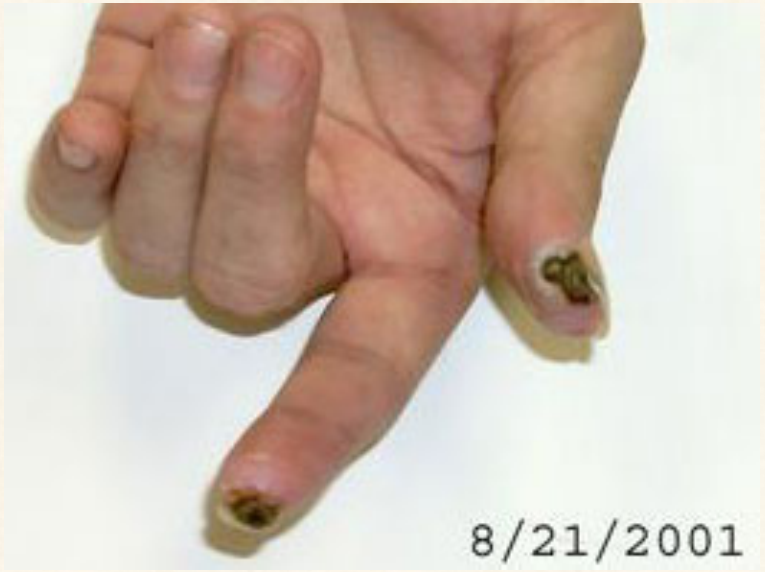
Periarteritis nodosa

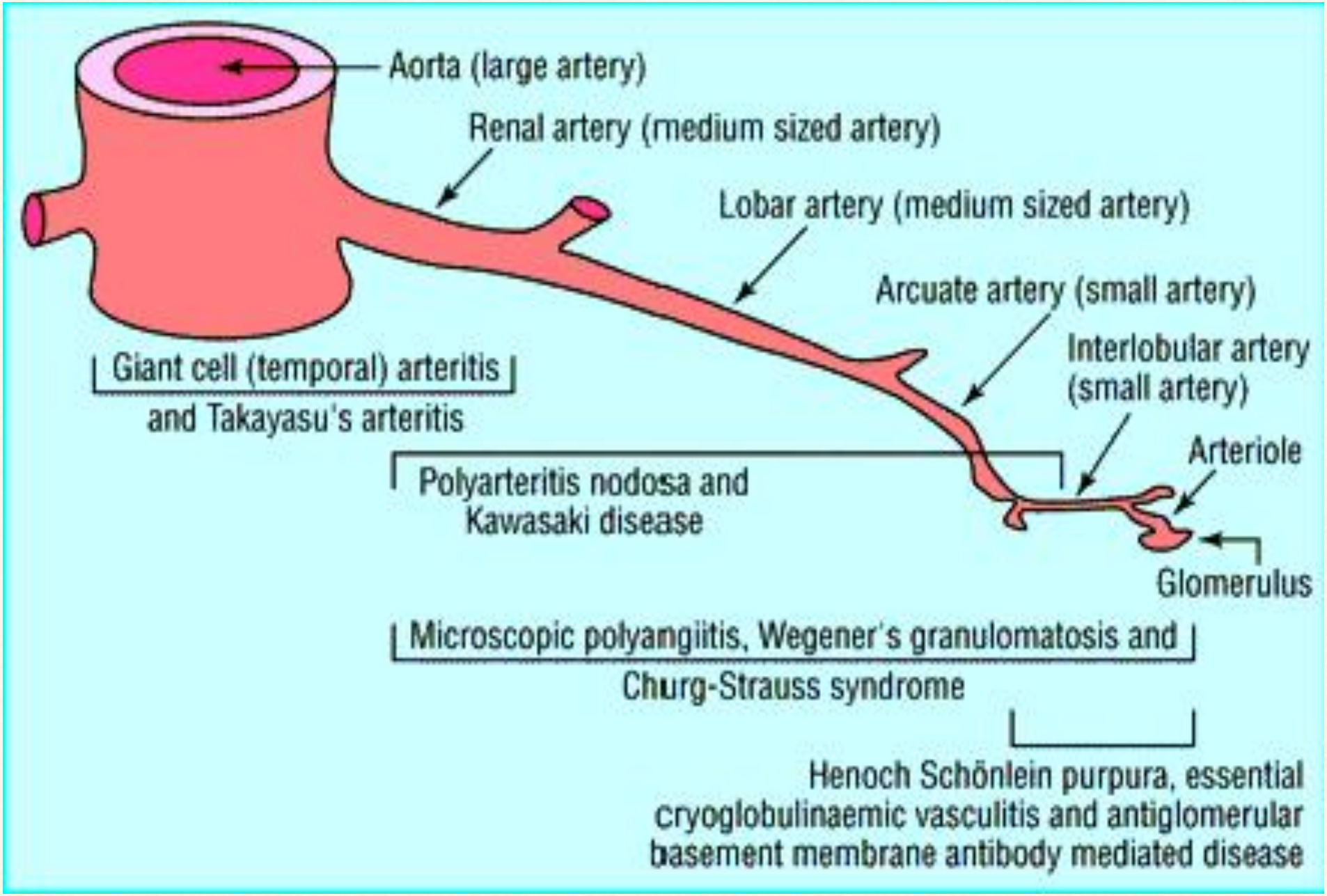




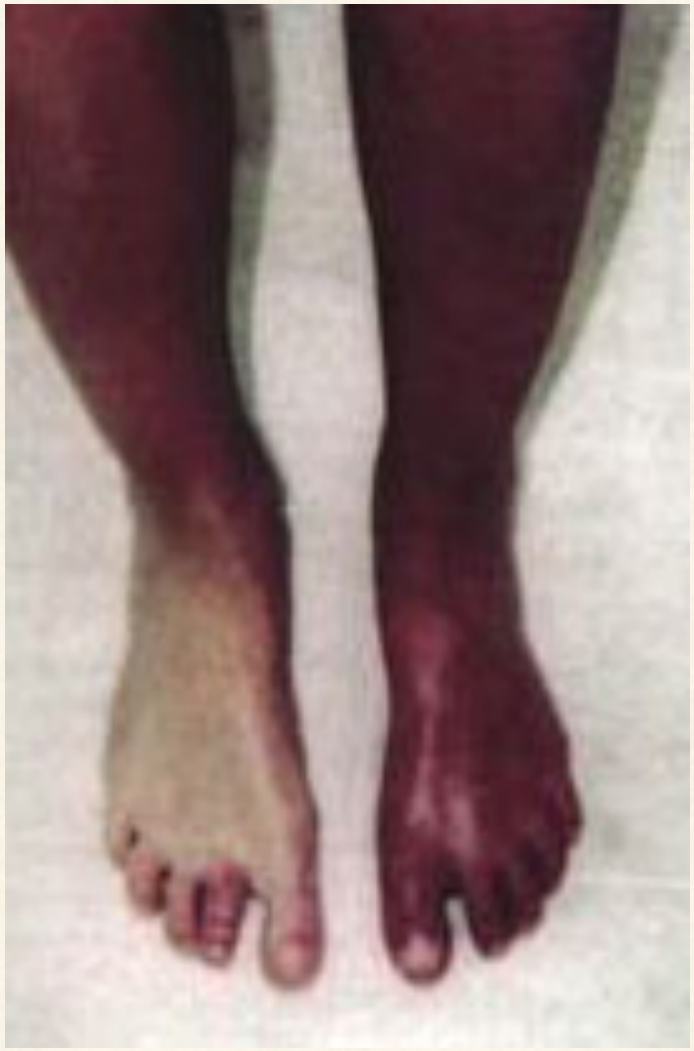
The medium sized arteries in the fat tissue appear magenta red because their wall is impregnated with fibrin (fibrinoid necrosis). There is also marked inflammation in the wall of these blood vessels extending into the perivascular connective tissue (arteritis and periarteritis).

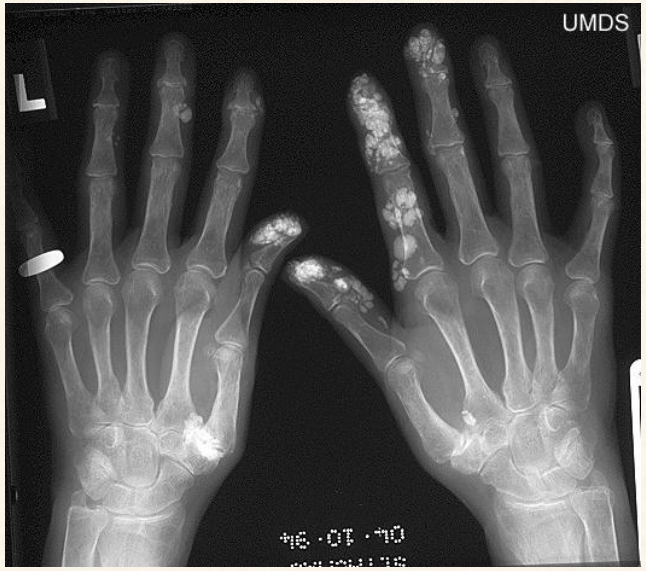
Periarteritis nodosa

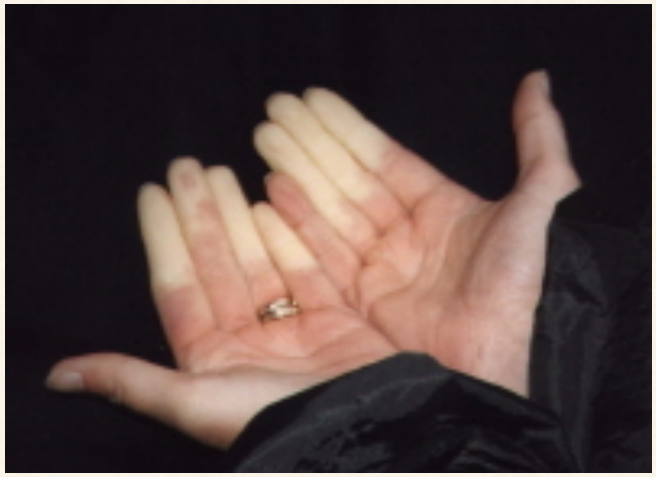



Aorta (large artery)
Renal artery (medium sized artery)
Lobar artery (medium sized artery)
Arcuate artery (small artery)
Interlobular artery (small artery)
Arteriole
Glomerulus
Giant cell (temporal) arteritis and Takayasu's arteritis
Polyarteritis nodosa and Kawasaki disease
Microscopic polyangiitis, Wegener's granulomatosis and Churg-Strauss syndrome
Henoch Schönlein purpura, essential cryoglobulinaemic vasculitis and antiglomerular basement membrane antibody mediated disease

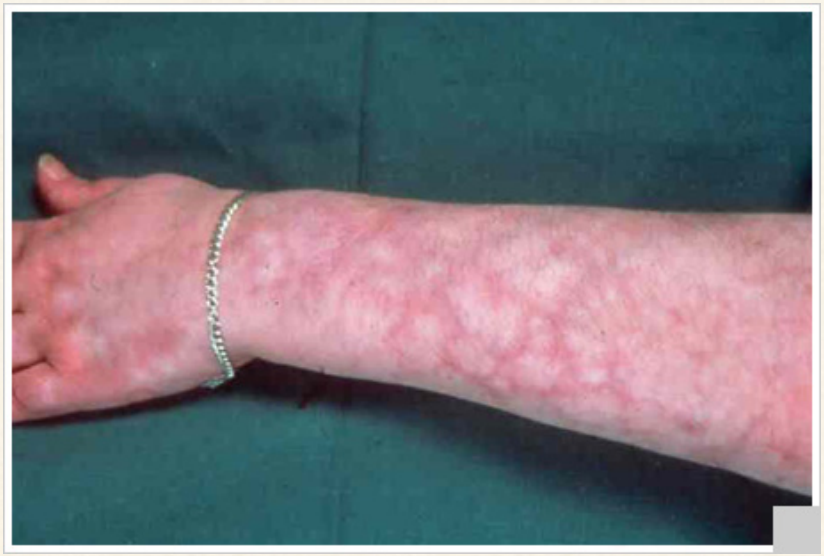
Raynaud's Syndrome

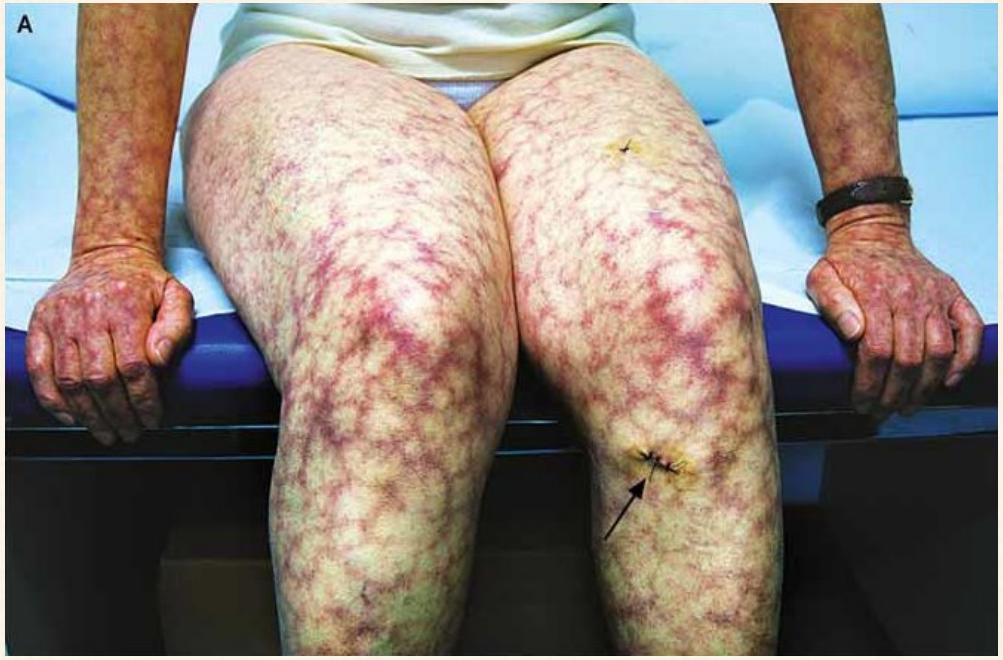


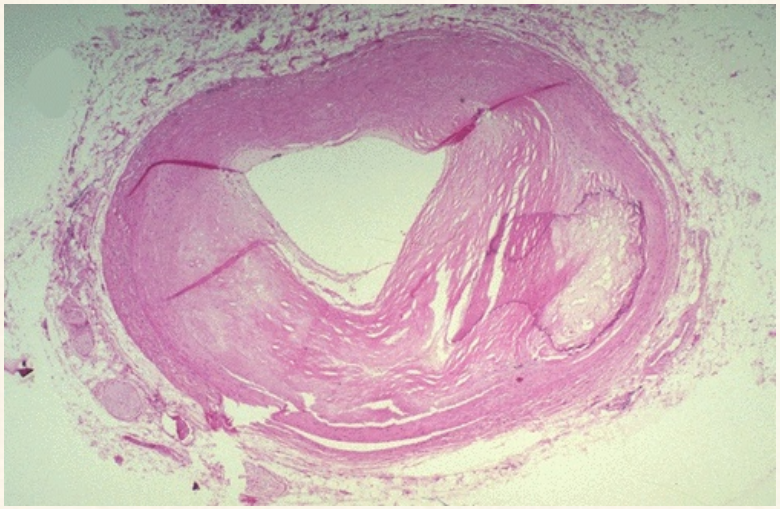




anti-Phopholipid syndrome

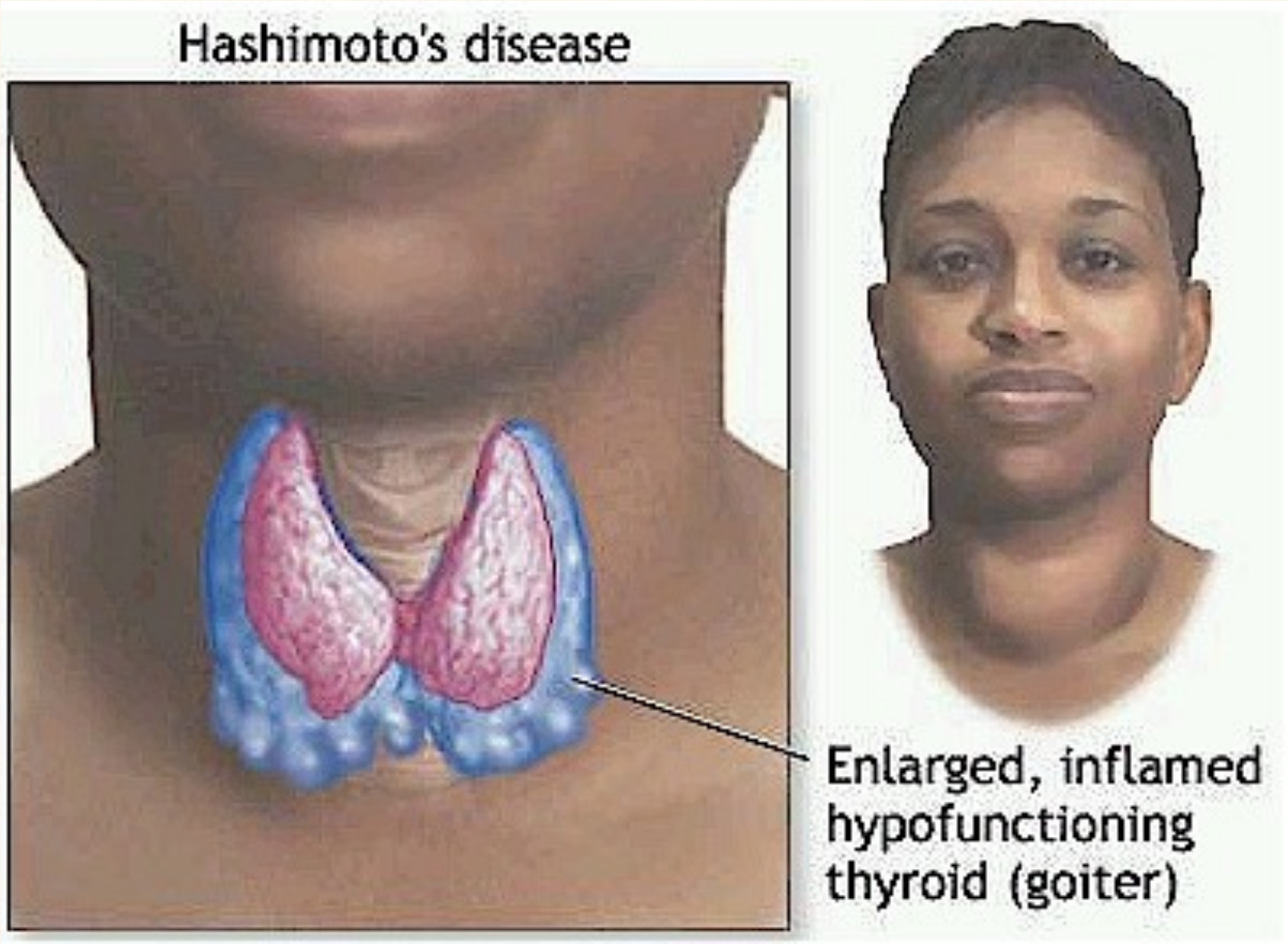




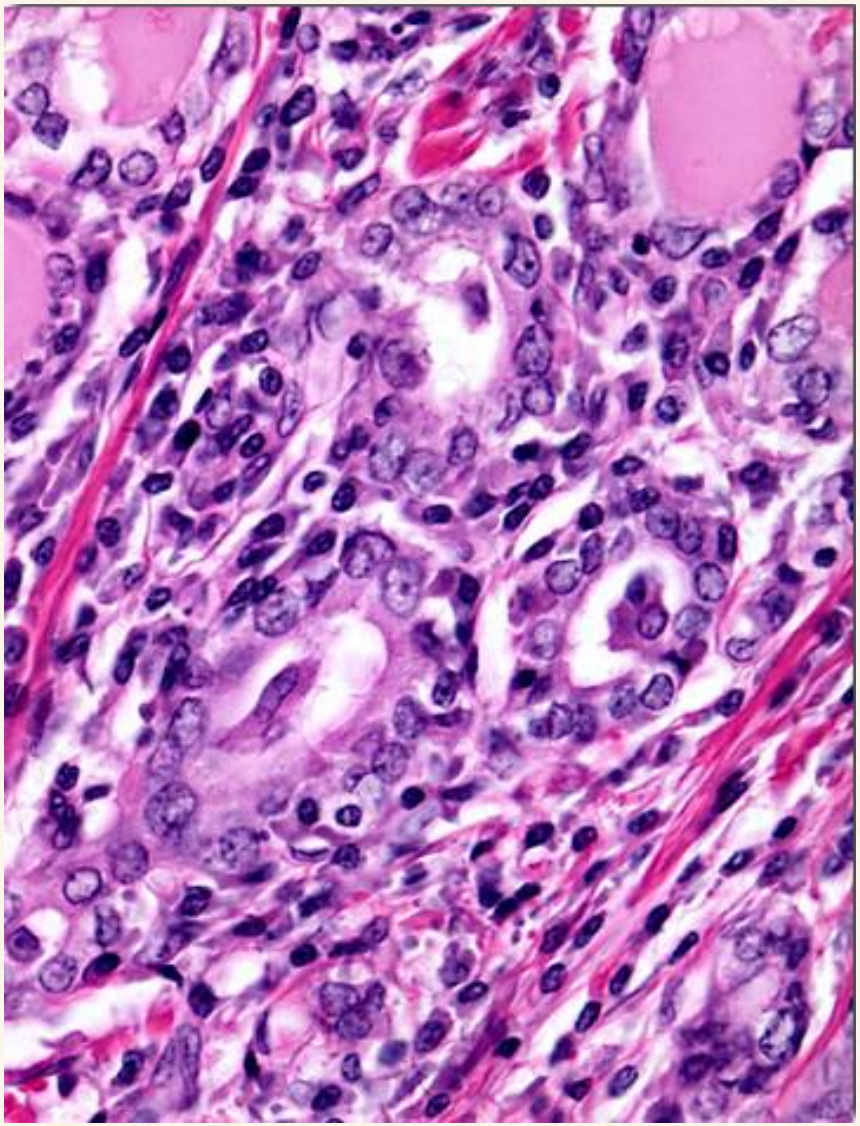


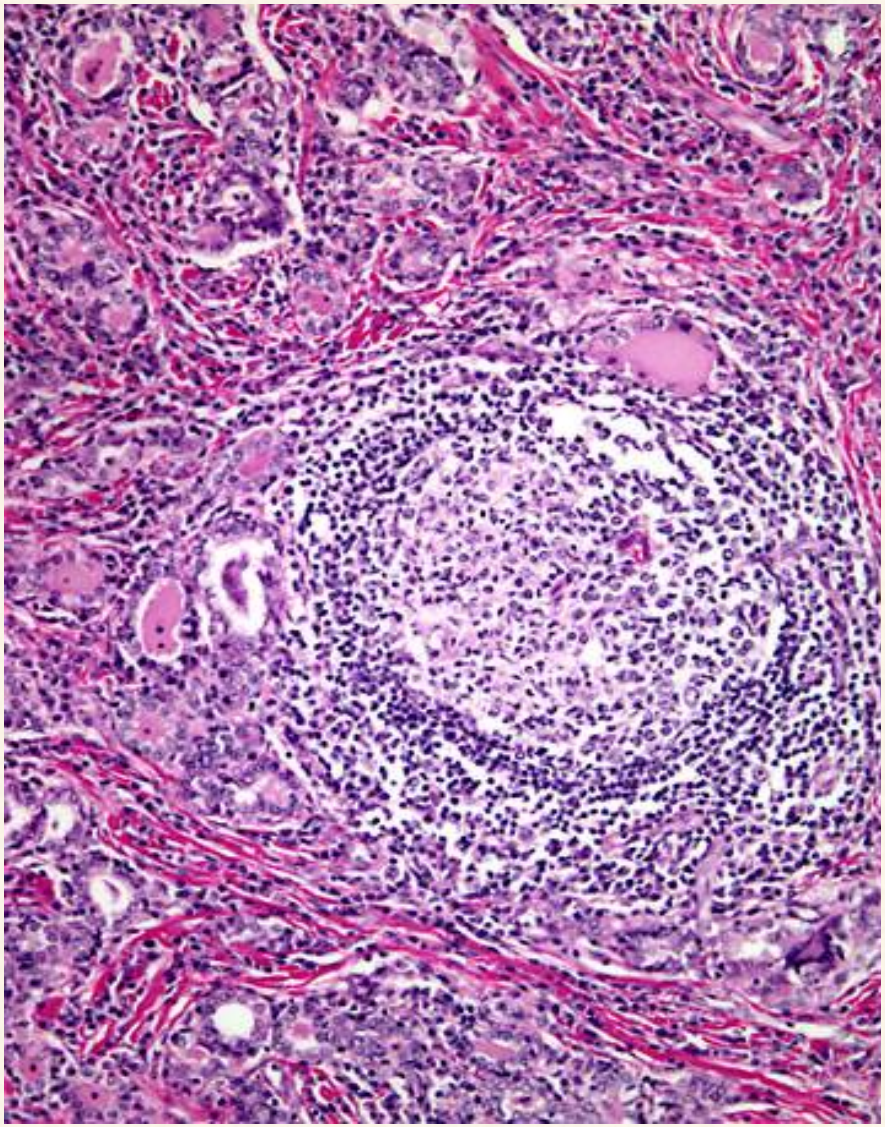
Livedo reticularis

Antiphospholipid Syndrome (APS, APLS, Hughes Syndrome, or Sticky Blood): abnormal antibodies linked to abnormal blood clots within veins and arteries.

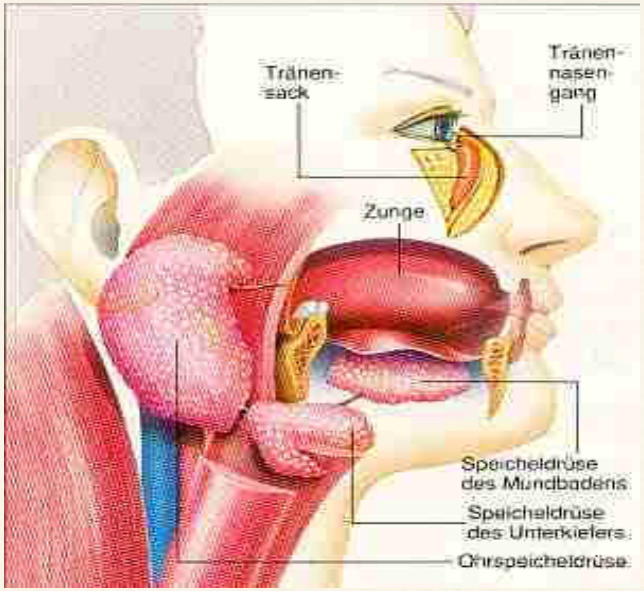

Hashimoto's disease
Enlarged, inflamed hypofunctioning thyroid (goiter)

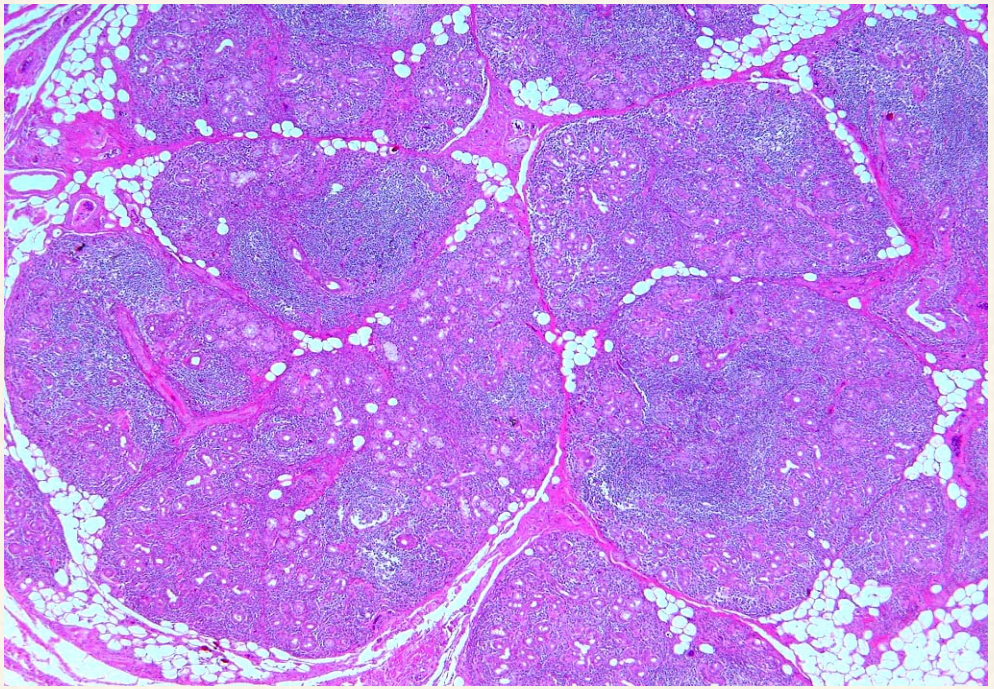
Hashimoto's disease

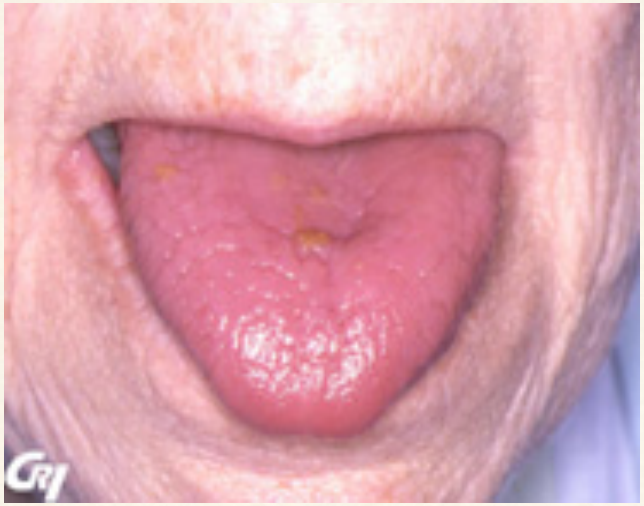


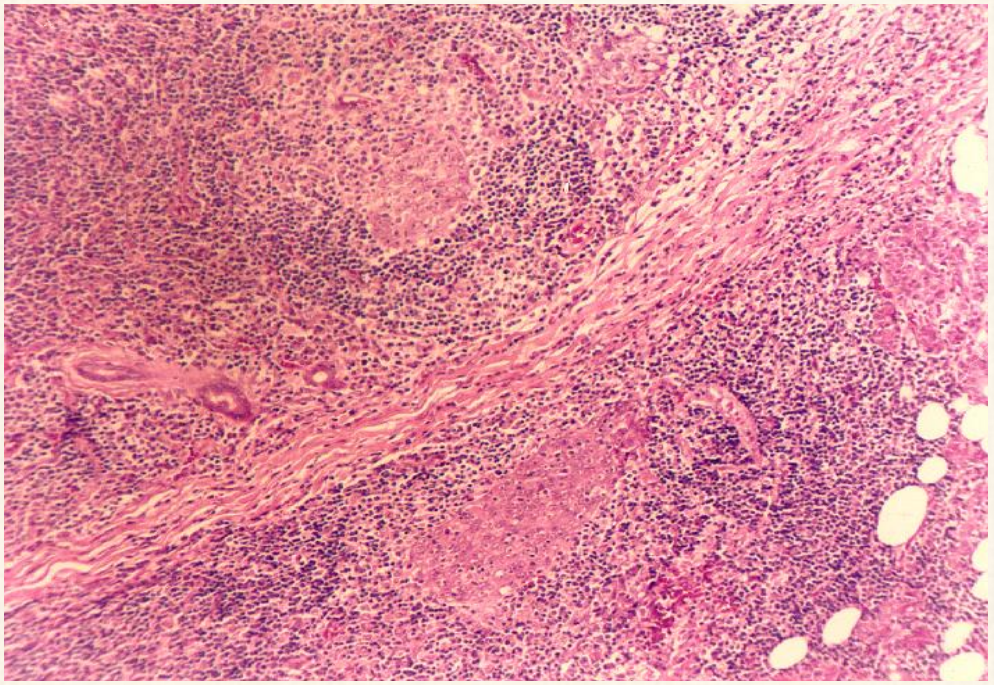


Sjögren syndrome

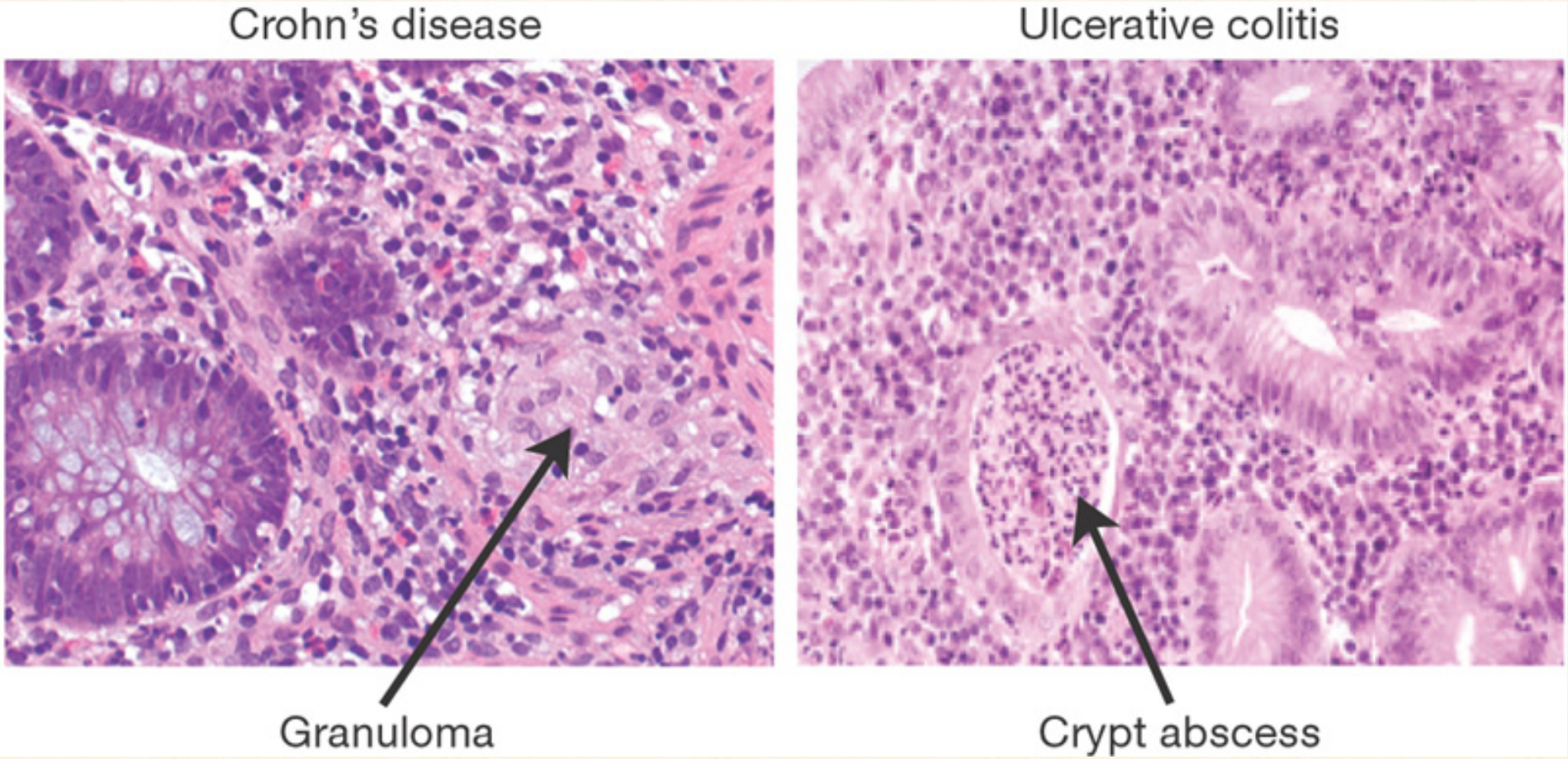




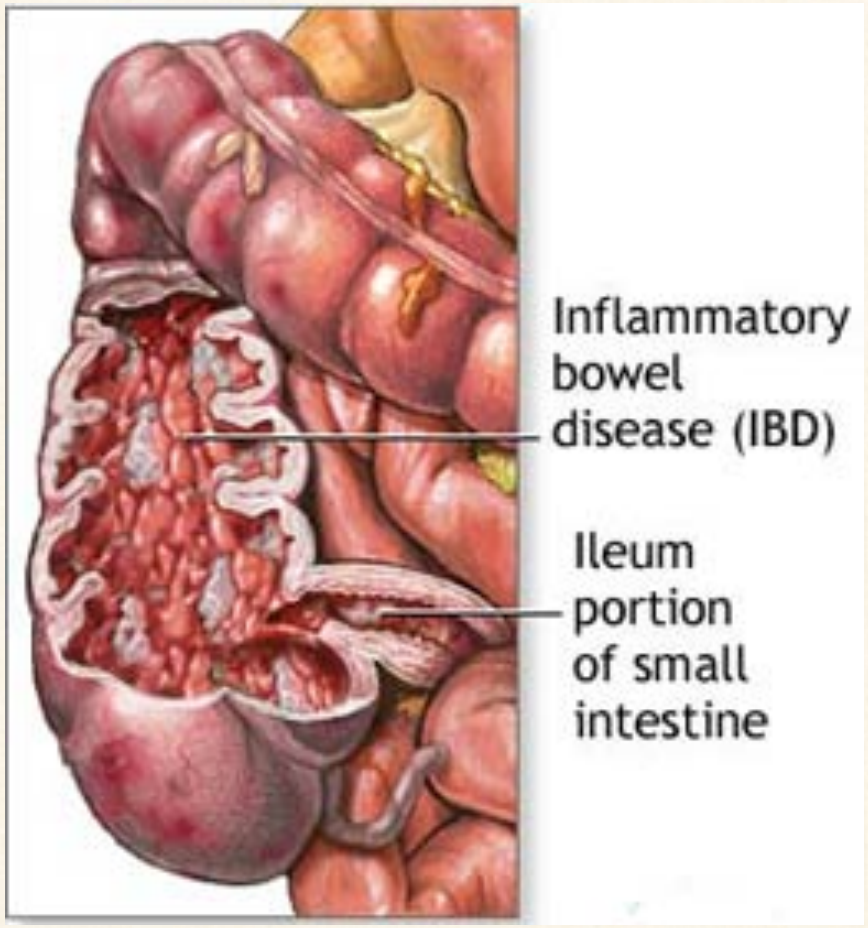


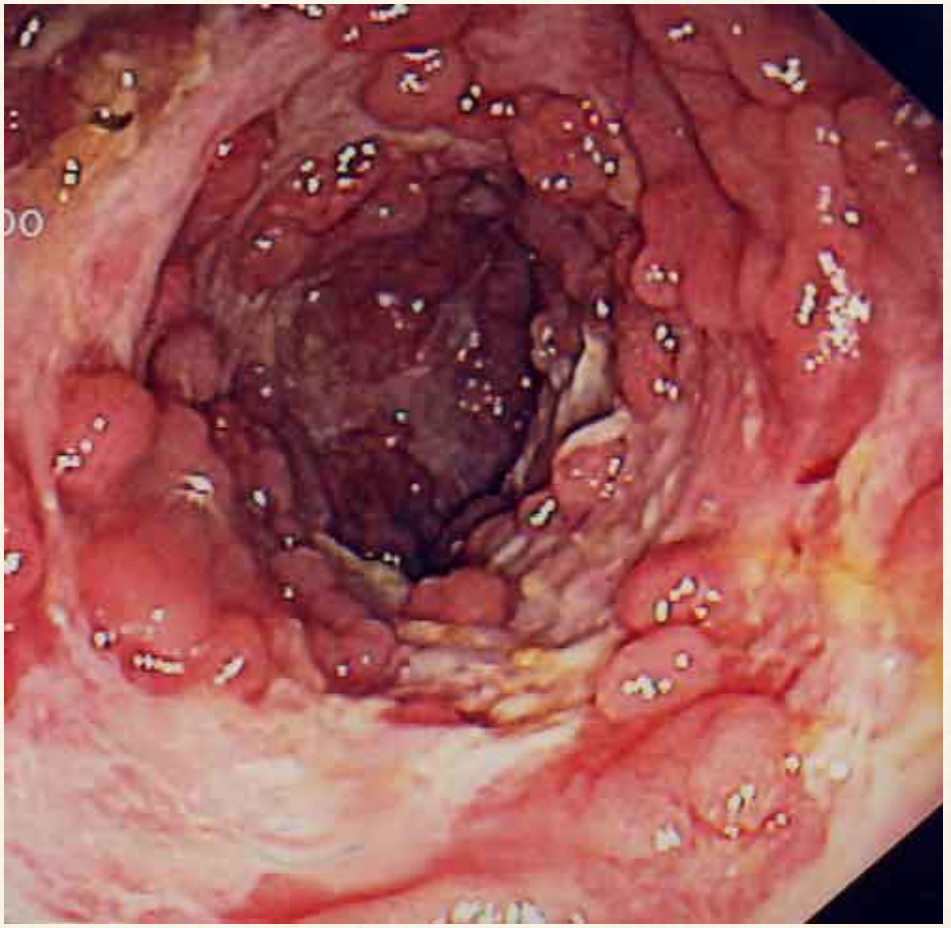


Inflammatory Bowel Diseases



Crohn's disease





Ulcerative colitis