DISEASES OF IMMUNITY

TOLERANCE & AUTOIMMUNITY

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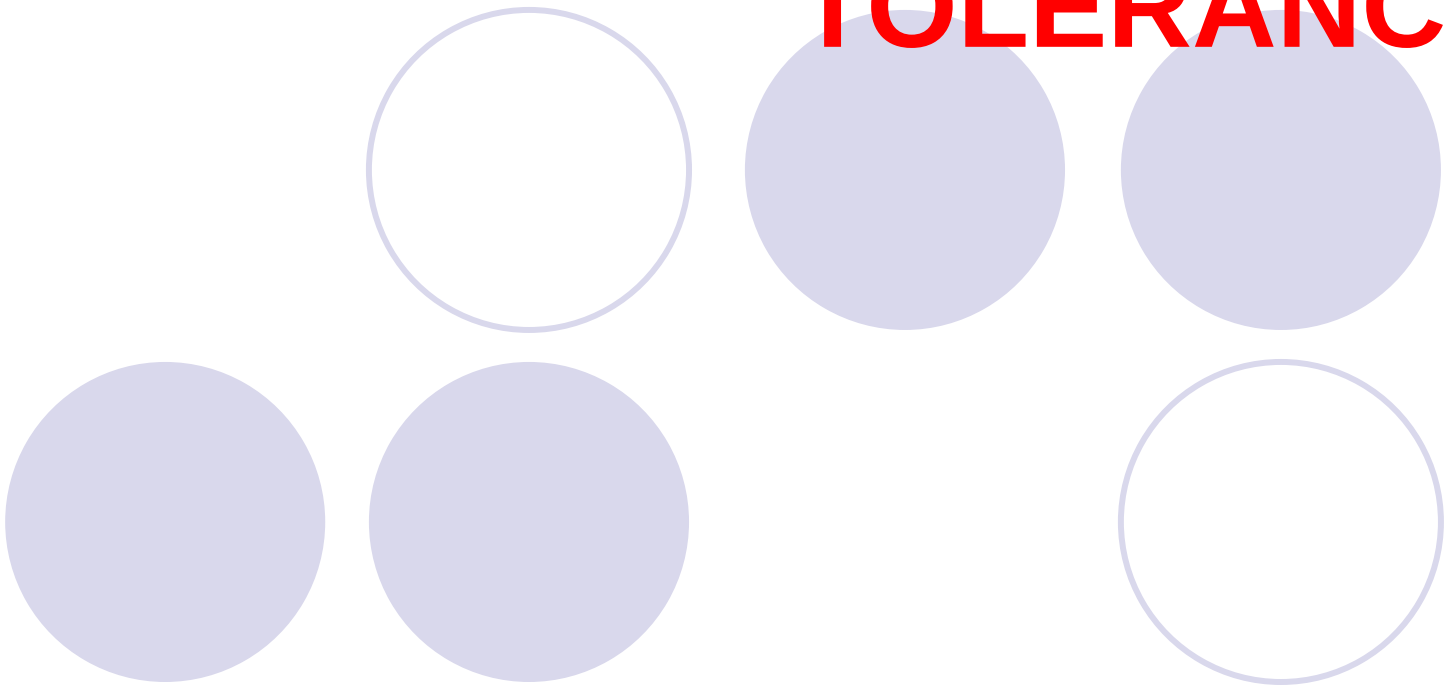
INTRODUCTION

- Immune system is a double edge sword
- Most of the times it is beneficial but some times it is harmful
- Two aspects will be discussed;
  - 1. How the immune system tolerates own tissues?
  - 2. How the body becomes intolerant to own tissues, when self Tolerance breaks?

DISEASES OF IMMUNITY

TOLERANCE



IMMUNOLOGIC TOLERANCE

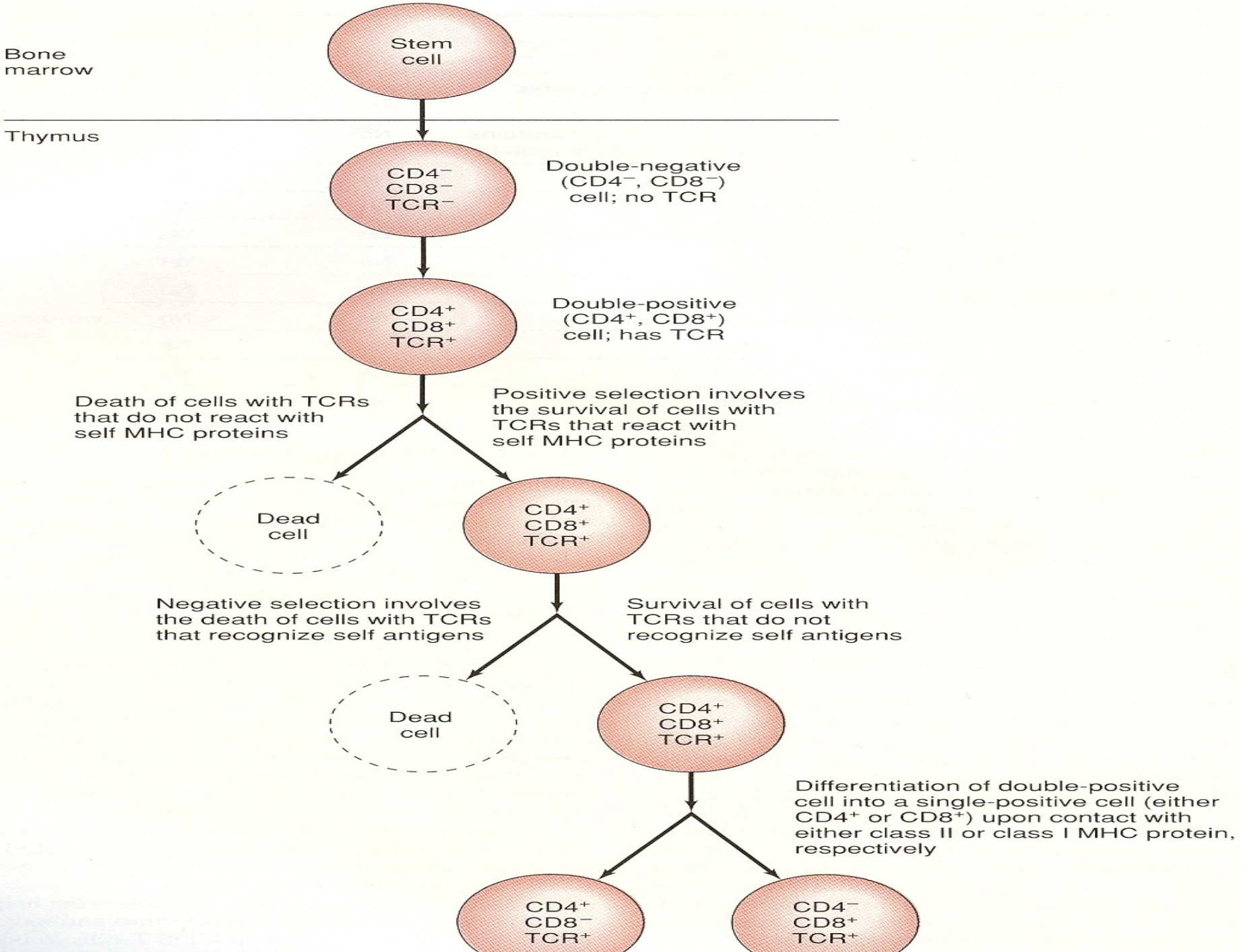
- "TOLERANCE" = Unresponsiveness
- "IMMUNOLOGIC TOLERANCE" = Unresponsiveness to an antigen
- "SELF-TOLERANCE" = Unresponsiveness to one's own antigens

INTRODUCTION

- **Immunological tolerance occurs when an immunocompetent host fails to respond to an antigen although immune system is functioning normally.**
- **<u>Basic Rule;</u> Antigens present during embryonic life are considered "self" and don't stimulate immune response, so we are tolerant to these antigens. Antigens encountered after maturity of immune system are considered "non-self"**
- **Although both T & B cells play a role, it is T cell tolerance that plays a major role.**

T CELLS TOLERANCE

- During T cell development in the thymus, the process of negative selection leads to the deletion of thymocytes whose T cell receptors have 'high affinity' for self antigens esp; MHC.
- Tolerance acquired within thymus is central tolerance & outside thymus is peripheral tolerance


Bone marrow
Stem cell
Thymus
CD4⁻ CD8⁻ TCR⁻
Double-negative (CD4⁻, CD8⁻) cell; no TCR
CD4⁺ CD8⁺ TCR⁺
Double-positive (CD4⁺, CD8⁺) cell; has TCR
Death of cells with TCRs that do not react with self MHC proteins
Positive selection involves the survival of cells with TCRs that react with self MHC proteins
Dead cell
CD4⁺ CD8⁺ TCR⁺
Negative selection involves the death of cells with TCRs that recognize self antigens
Survival of cells with TCRs that do not recognize self antigens
Dead cell
CD4⁺ CD8⁺ TCR⁺
Differentiation of double-positive cell into a single-positive cell (either CD4⁺ or CD8⁺) upon contact with either class II or class I MHC protein, respectively
CD4⁺ CD8⁻ TCR⁺
CD4⁻ CD8⁺ TCR⁺

B CELLS TOLERANCE

- B cell tolerance occurs;

  By clonal deletion during B cell development in the bone marrow.

- Tolerance in B cells is much less complete than T cells (So Autoimmue diseases are usually Ab mediated)

INDUCTION OF TOLERANCE

- Depends upon;
  1. *Immunologic maturity* of the host; In fetal periods grafts are accepted well
  2. *Structure & dose of Ag*; Simple Ag is tolerated well than a complex one. A very low/ high dose produces tolerance
  3. *T cells* become tolerant early & for longer time than B cells
  4. *Immunosuppresive therapy;* induces tolerance
  5. *Continuous presence of Ag;* Preserves tolerance

- What is immunologic tolerance?

- Briefly describe induction of tolerance.

MCQ's

I. Each of the following statement regarding immunologic tolerance is correct **except** ;

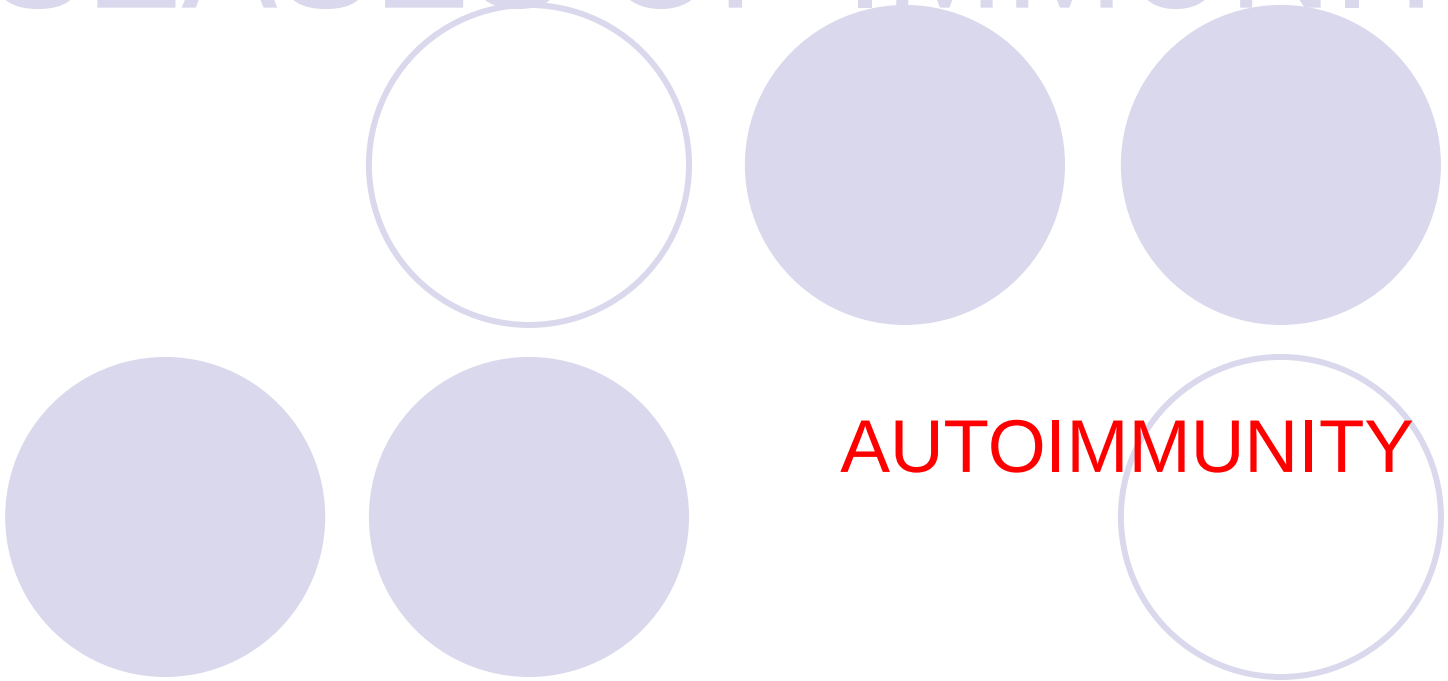
a. Tolerance is not Ag specific so immune paresis results in anergy against many antigens

b. Tolerance is induced more easily in T cells than B cells

c. Tolerance is more easily induced in neonates than adults

d. Tolerance is induced easily by simple molecules than complex molecules

DISEASES OF IMMUNITY



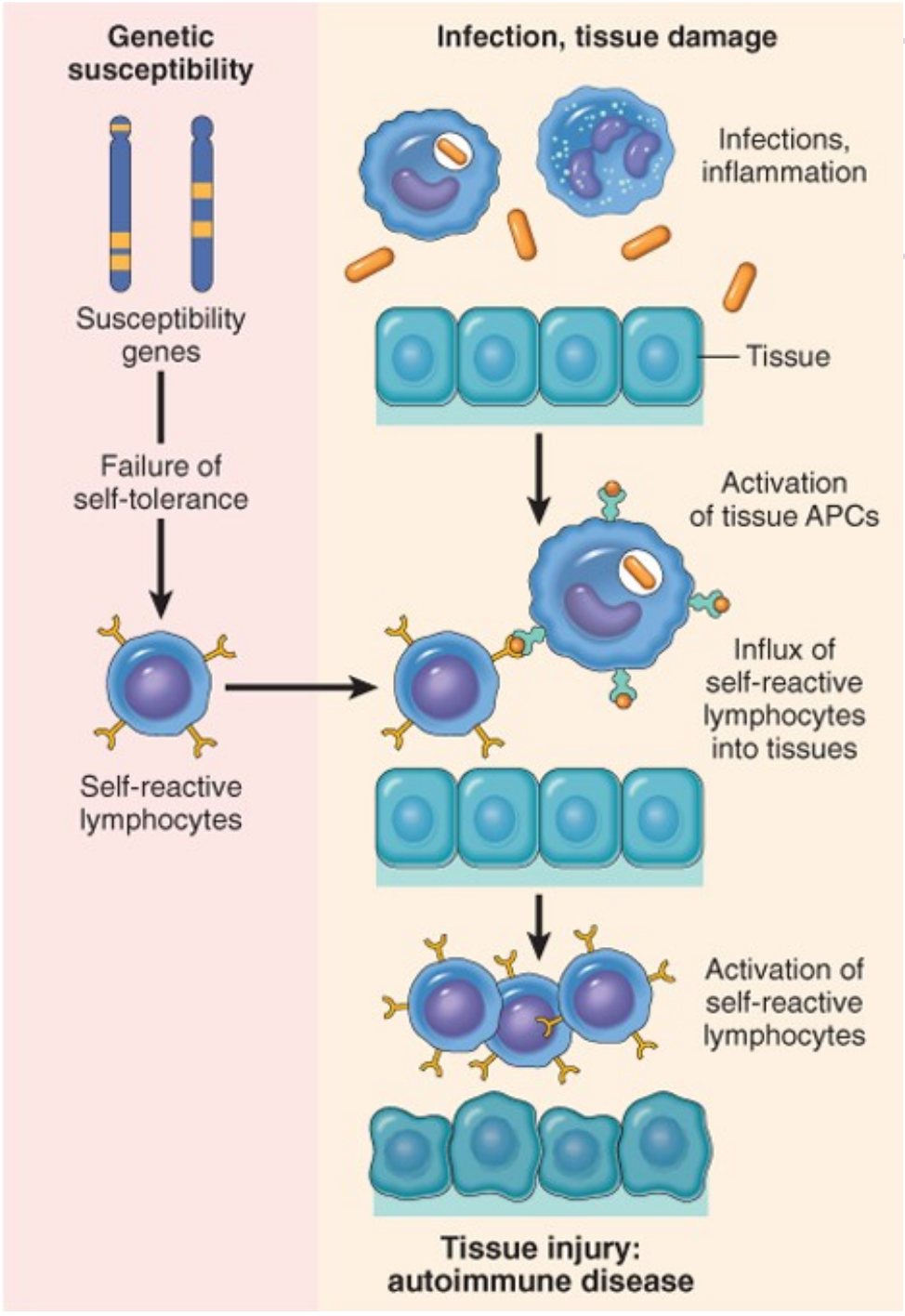
AUTOIMMUNITY

INTRODUCTION

- **“Autoimmunity” = Immune reaction against self**
- **Simply, Self-tolerance breaks down, causing disease**
- **Adult host exhibits tolerance to antigens present during fetal life that are recognized as “self”, but in certain situations the tolerance may be lost, resulting in autoimmunity**
- **The most important step in autoimmune disease is activation of self reactive helper (CD4+) T cells. Most reactions are Ab mediated**

AUTOIMMUNITY- PATHOGENESIS

1. Genes; HLA-B27: ↑ risk of ankylosing spondylitis & HLA-DR4: ↑ risk of rheumatoid arthritis (RA)
2. Endocrines; 90% autoimmune diseases occur in females
    1. Graves, Hashimoto's thyroiditis; common in Females
    2. Ankylosing spondilitis; common in Males
    3. RA; relieved during pregnancy
3. Environmental triggers/ Infections/ Drugs/ Diet
    1. Exposes hidden self-antigens
    2. Activate antigen presenting cells
    3. Most are multifactorial; Genes + Environment


Genetic susceptibility
Infection, tissue damage
Susceptibility genes
Infections, inflammation
Tissue
Failure of self-tolerance
Activation of tissue APCs
Influx of self-reactive lymphocytes into tissues
Self-reactive lymphocytes
Activation of self-reactive lymphocytes
Tissue injury: autoimmune disease

Microbe	Autoimmune Disease
1. Bacteria	
Streptococcus pyogenes	Rheumatic fever
Campylobacter jejuni	Guillain-Barré syndrome
Escherichia coli	Primary biliary cirrhosis
Chlamydia trachomatis	Reiter's syndrome
Shigella species	Reiter's syndrome
Yersinia enterocolitica	Graves' disease
Borrelia burgdorferi	Lyme arthritis
2. Viruses	
Hepatitis B virus[1]	Multiple sclerosis
Hepatitis C virus	Mixed cryoglobulinemia
Measles virus	Allergic encephalitis
Coxsackievirus B3[2]	Myocarditis
Coxsackievirus B4[3]	Type 1 diabetes mellitus
Cytomegalovirus	Scleroderma
Human T-cell leukemia virus	HTLV-associated myelopathy

MECHANISMS OF AUTOIMMUNE PATHOLOGY

1. **MOLECULAR MIMICRY; Many bacteria/ viruses are implicated as a source of cross reacting antigens- activating T/ B cells**
    1. **Strep pyogenes- Rheumatic fever**
    2. **Shigella- Reiter's disease**
    3. **Hepatitis B- Multiple sclerosis**
2. **ALTERATION OF NORMAL PROTEINS; Drugs can bind normal proteins and make them immunogenic (Procainamide- SLE)**
3. **RELEASE OF SEQUESTERED ANTIGENS; Sperms, brain, lens & uvea are sequestered and their antigens are not exposed to immune system (priviledged sites). DNA in sequestered sites, exposed after infections/ chemicals & radiations**
4. **"Sympathetic ophthalmia"**

AUTOANTIBODIES - CAUSE OR EFFECT?

- Almost all patients with autoimmune conditions have some autoantibodies present in their serum.
- They also have autoreactive T cells present.
- It is not known whether the autoantibodies play an important role in the disease/ are a secondary result of the tissue damage which has been caused by the disease process itself.

Examples of autoimmune disease

Graves' Disease (thyrotoxicosis)

Hashimoto's thyroiditis

pernicious anaemia

Addison's disease

insulin dependent diabetes mellitus

Goodpasture's syndrome

myasthenia gravis

multiple sclerosis(?)

autoimmune haemolytic anaemia

idiopathic thrombocytopenic purpura

rheumatoid arthritis

scleroderma

systemic lupus erythematosis (SLE)

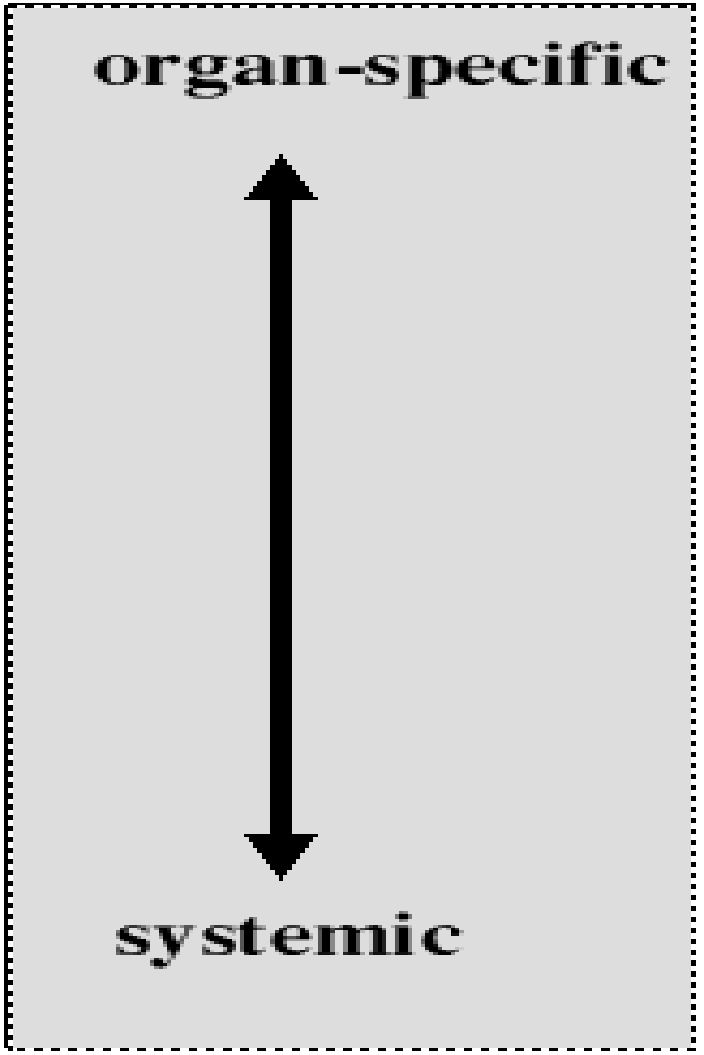
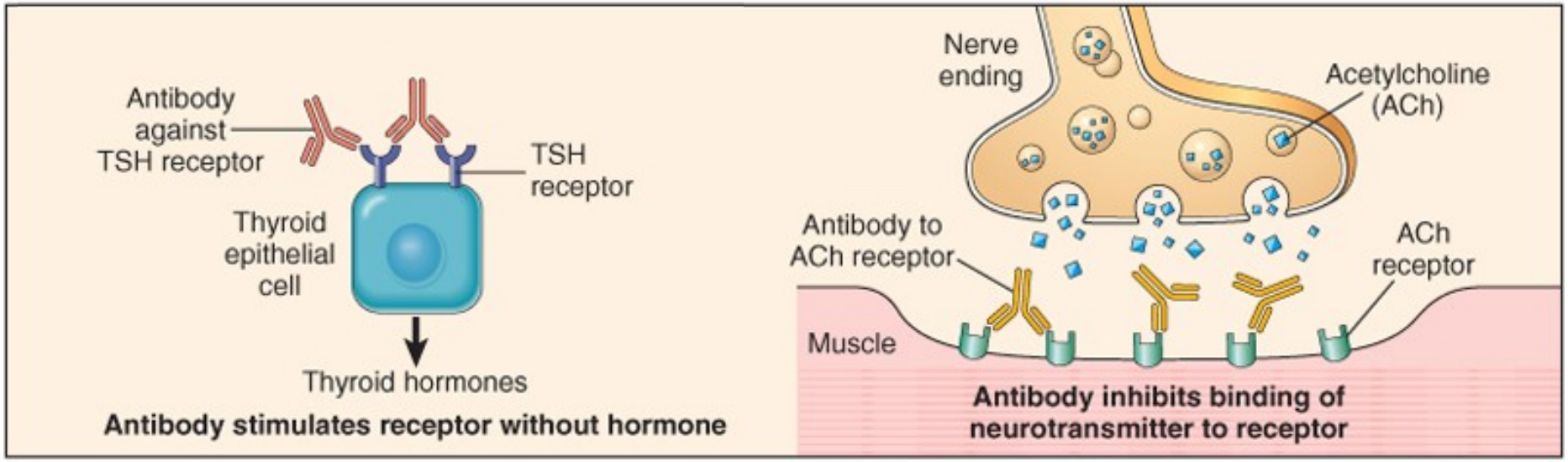


Table 66–1. Important autoimmune diseases.

Type of Immune Response	Autoimmune Disease	Target of the Immune Response
Antibody to receptors	Myasthenia gravis	Acetylcholine receptor
	Graves' disease	TSH[1] receptor
	Insulin-resistant diabetes	Insulin receptor
	Lambert-Eaton myasthenia	Calcium channel receptor
Antibody to cell components other than receptors	Systemic lupus erythematosus	dsDNA, histones
	Rheumatoid arthritis[2]	IgG in joints
	Rheumatic fever	Heart and joint tissue
	Hemolytic anemia	RBC membrane
	Idiopathic thrombocytopenic purpura	Platelet membranes
	Goodpasture's syndrome	Basement membrane of kidney and lung
	Pernicious anemia	Intrinsic factor and parietal cells
	Hashimoto's thyroiditis[2]	Thyroglobulin
	Insulin-dependent diabetes mellitus[2]	Islet cells
	Addison's disease	Adrenal cortex
	Acute glomerulonephritis	Glomerular basement membrane
	Periarteritis nodosa	Small and medium-sized arteries
	Guillain-Barré syndrome	Myelin protein
	Wegener's granulomatosis	Cytoplasmic enzymes of neutrophils
	Pemphigus	Desmoglein in tight junctions of skin
	IgA nephropathy	Glomerulus
Cell-mediated	Allergic encephalomyelitis and multiple sclerosis	Reaction to myelin protein causes demyelination of brain neurons
	Celiac disease	Enterocytes

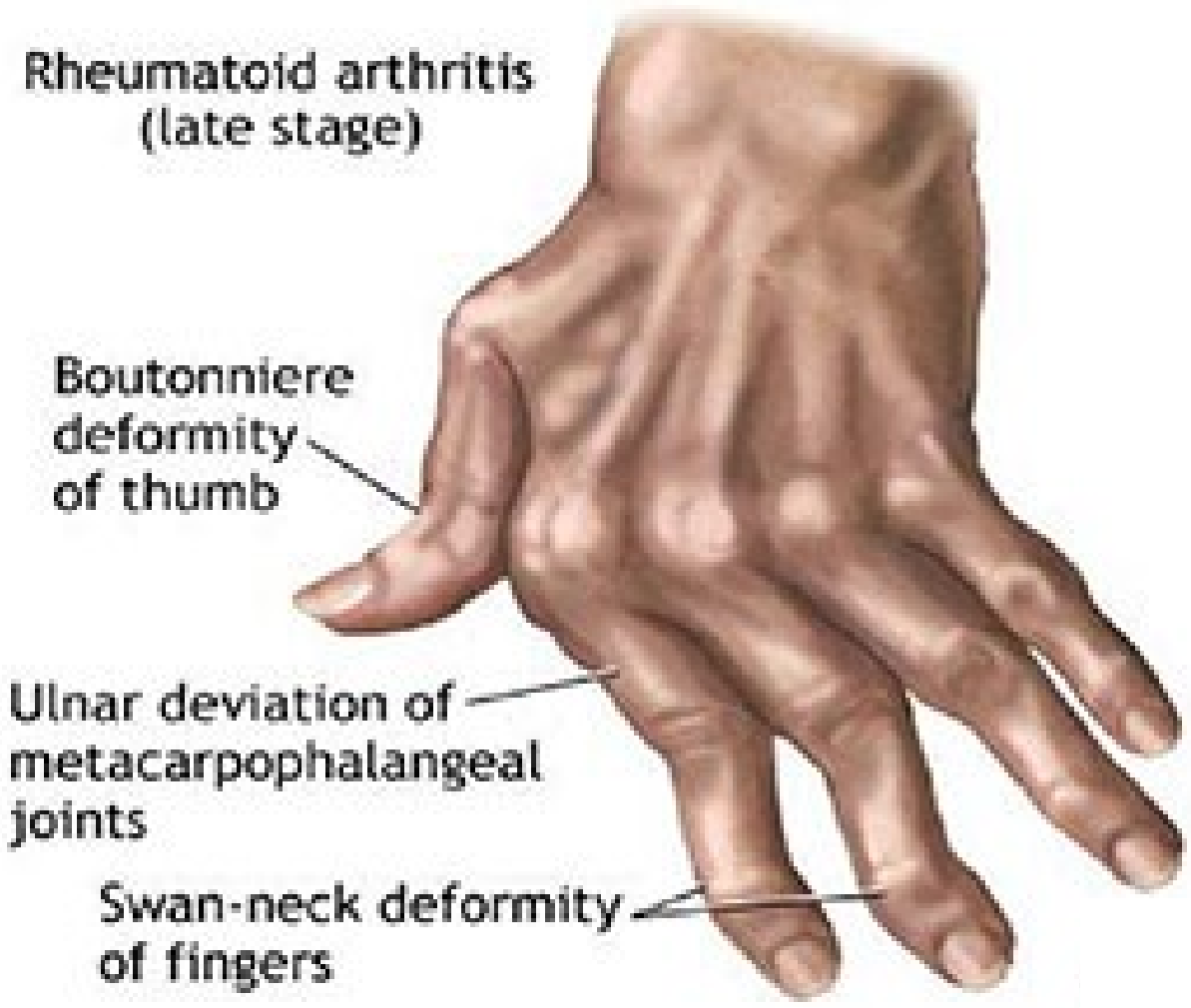
[1]TSH, thyroid-stimulating hormone.
[2]These diseases involve a significant cell-mediated as well as antibody-mediated response.

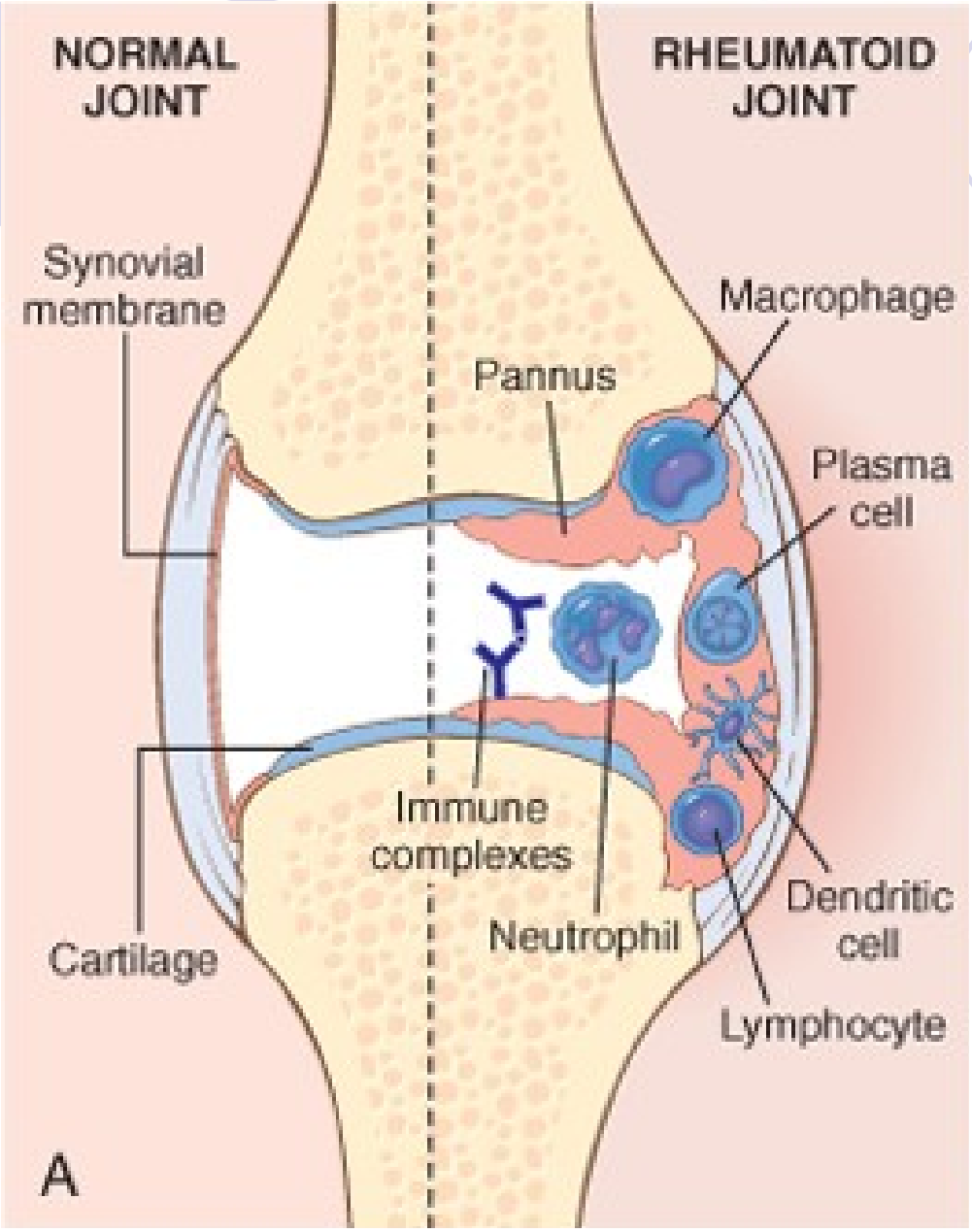
CELLULAR DYSFUNCTION



GRAVES DISEASE

MYASTHENIA GRAVIS


Rheumatoid arthritis
(late stage)
Boutonniere
deformity
of thumb
Ulnar deviation of
metacarpophalangeal
joints
Swan-neck deformity
of fingers


NORMAL JOINT
RHEUMATOID JOINT
Synovial membrane
Pannus
Macrophage
Plasma cell
Immune complexes
Neutrophil
Dendritic cell
Cartilage
Lymphocyte
A

ORAL CHANGES IN SJÖGREN SYNDROME

ATROPHIC PAPILLAE, DEEPLY FISSURED EPITHELIUM

ANGULAR CHEILITIS

MISSING TEETH AND MULTIPLE CARIES


Thank you