AUTOIMMUNE DISEASE PART II

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Lecture 5

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Two main mechanisms have been suggested to explain how environmental agents could promote the activation of autoreactive CD4 T cells by dendritic cells

1. **Molecular mimicry**
2. **Tissue damage**

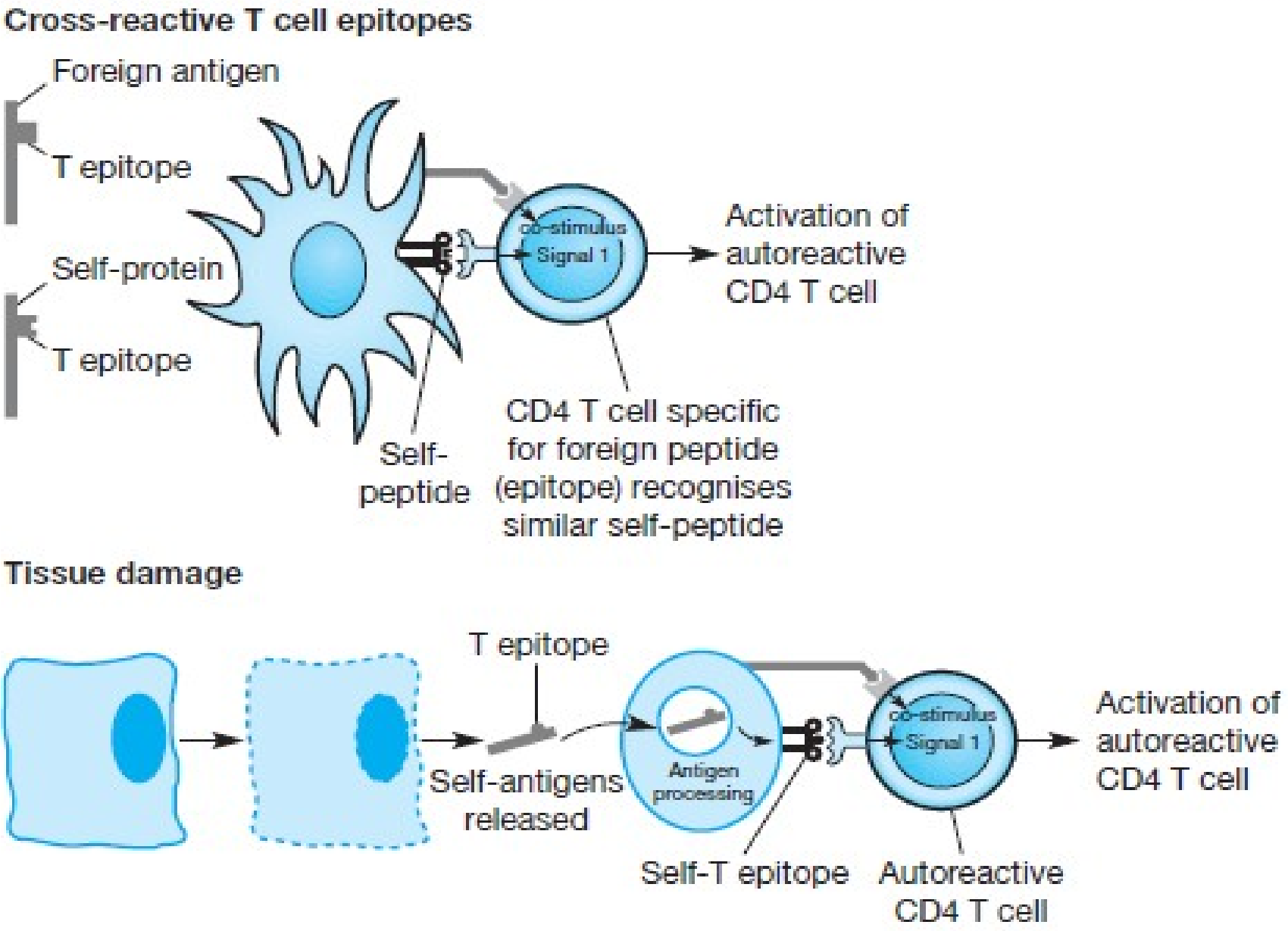
MOLECULAR MIMICRY

An environmental agent (such as an infectious organism) will b regarded as foreign by the immune system and dendritic cells will present antigenic peptides derived from the agent on their class II MHC.

If one of these antigenic peptides is very similar to a self-antigen peptide, CD4 T cells specific for that peptide will be activated to become Th. These can then react against self-peptides as well as those from the environmental agent and cause autoimmunity.

TISSUE DAMAGE

- The other is that tissue injury releases intracellular(sequestered) antigens that elicit an immune response.) Tissue damage, whether caused by a toxic substance or a pathogen, can lead to an inflammatory type of response with the production of cytokines and the release of self-antigens from damaged cells. These two factors can activate dendritic cells to present self peptides derived from the self-antigens on their class II MHC, which could then activate self-reactive CD4 T cells.


Cross-reactive T cell epitopes
Foreign antigen
T epitope
Self-protein
T epitope
co-stimulus
Signal 1
Activation of autoreactive CD4 T cell
Self-peptide
CD4 T cell specific for foreign peptide (epitope) recognises similar self-peptide
Tissue damage
T epitope
Self-antigens released
Antigen processing
co-stimulus
Signal 1
Activation of autoreactive CD4 T cell
Self-T epitope
Autoreactive CD4 T cell

Mechanisms

Avariety of mechanisms have been proposed for induction of :autoimmunity, including

1. **MOLECULAR MIMICRY**
2. **ALTERATION OF NORMAL PROTEINS**
3. **RELEASE OF SEQUESTERED ANTIGENS**
4. **EPITOPE SPREADING**
5. **NEOANTIGENS**
6. **LOSS OF SUPPRESSION**
7. **Infection.**

1.MOLECULAR MIMICRY

Various bacteria and viruses are implicated as the source of cross-reacting antigens that trigger the activation of autoreactive T cells or B cells. For example, Reiter's syndrome ,occurs following infections with *Shigella* or *Chlamydia*

The concept of **molecular mimicry** is a process in which infection by microbes is associated with the subsequent development of specific autoimmune disease.

The antigenic molecules on some infections agents are similar enough to some host-self molecules that B&T cell responses generated against the microbial antigens can results in damage to host cells bearing similar molecules.

One of the best-characterized examples of molecular mimicry:

Is the relationship between the M protein of *S. pyogenes*(the causative agents of strep throat) and the myosin of cardiac muscle.

Antibodies against certain M proteins cross-react with cardiac myosin, leading to rheumatic fever!!!!!!

Additional evidence supporting the molecular mimicry hypothesis includes the finding that:

there are identical amino acid sequences in certain viral proteins and certain human proteins. For example, there is an identical six–amino acid sequence in the hepatitis B viral polymerase and the human myelin basic protein.

MOLECULAR MIMICRY

- **Sharing of epitopes between an infectious agent and its host.**

- **Antibodies directed against the infectious agents starts reacting with normal self Ag.**

- **Triggers autoimmunity.**

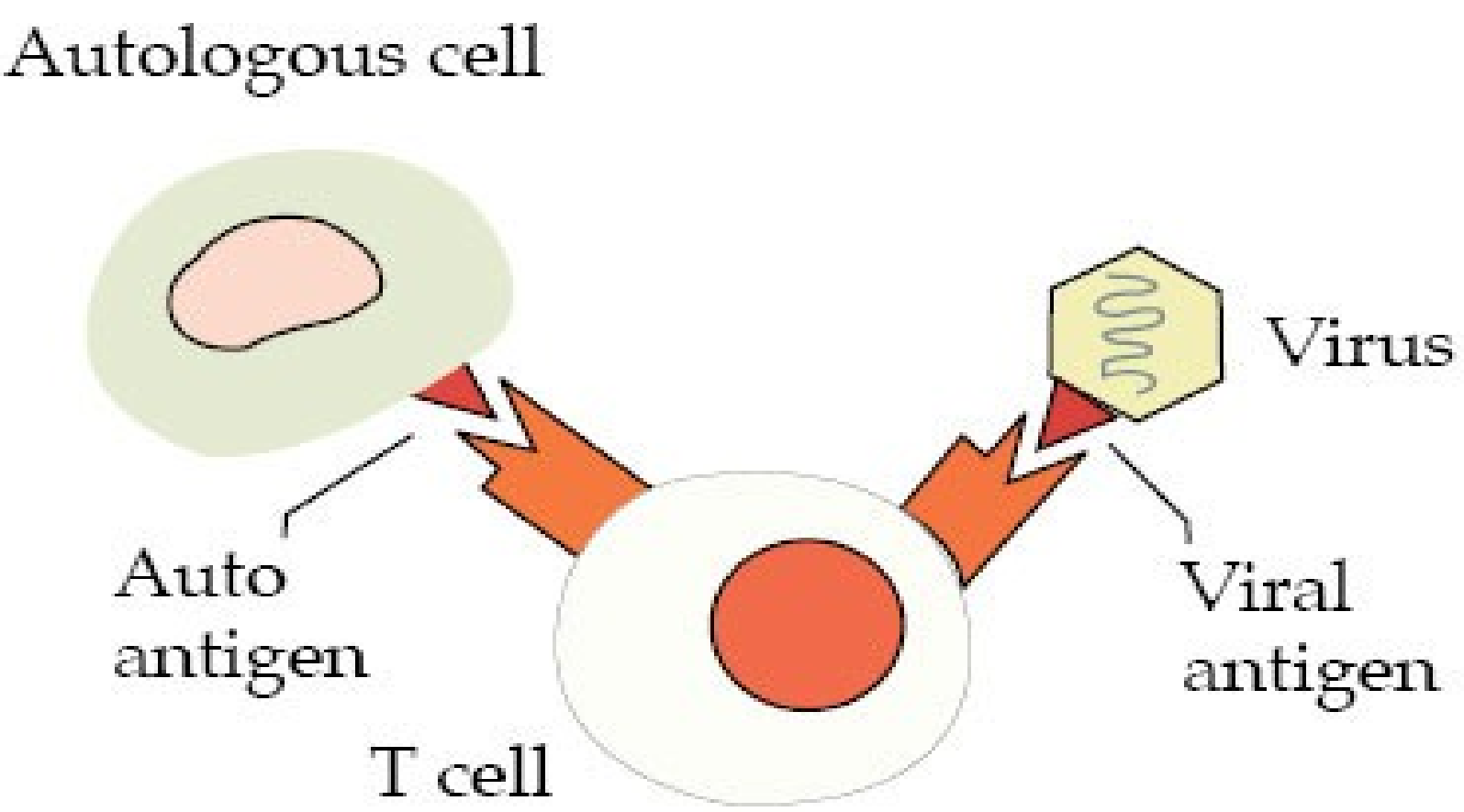


Fig. 1 : Diagram showing Molecular Mimicry Hypothesis. The molecular mimicry hypothesis suggest that a certain antigen (Viral / Bacterial) has a great degree of similarity with endogenous structures. Mistaken identity triggers the host immune system (autoantibodies) to attack the foreign as well as endogenous targets when infected with organism.

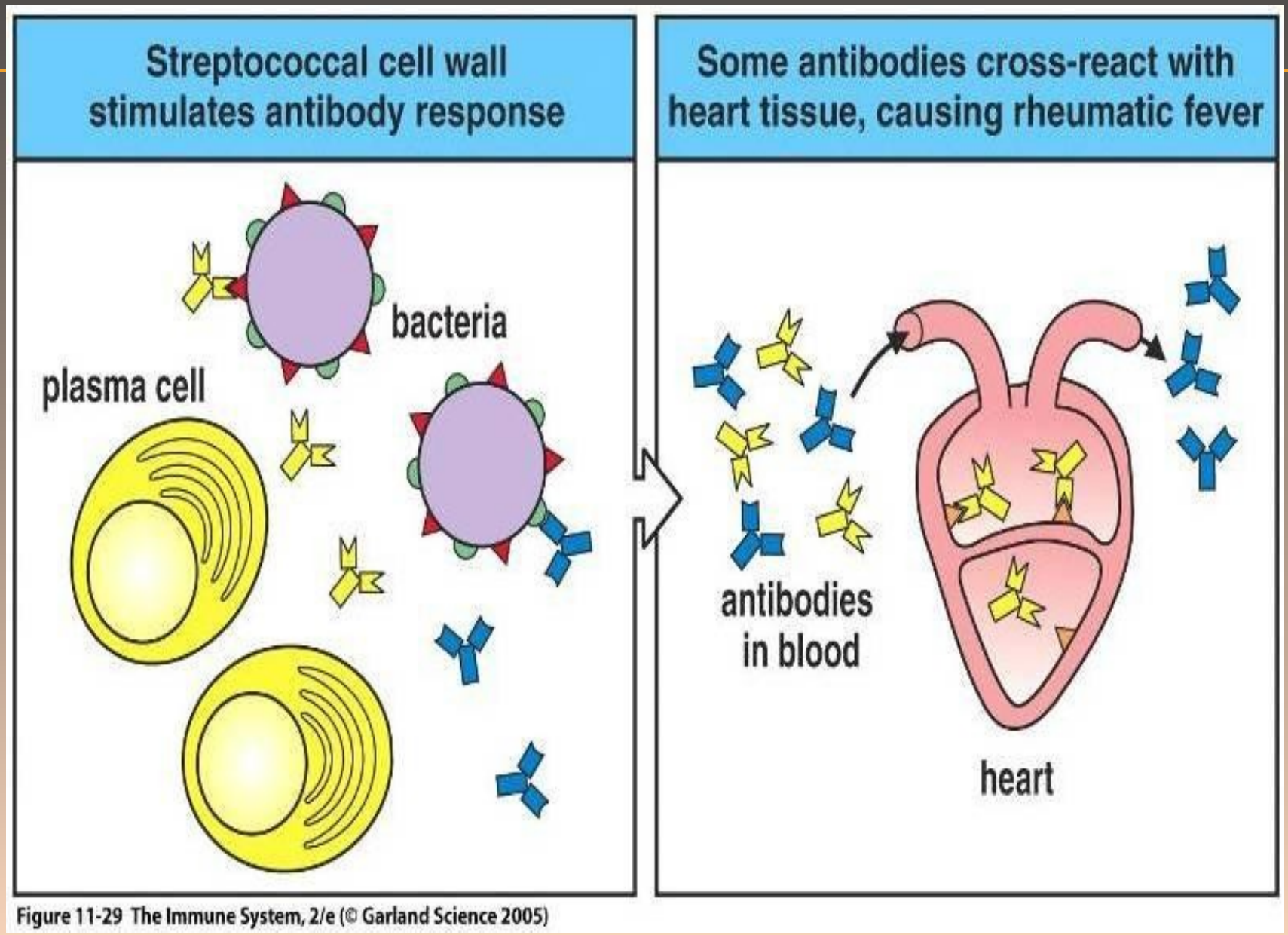


Figure 11-29 The Immune System, 2/e (© Garland Science 2005)

AG RELATED FROM HIDDEN LOCATION

Many self Ag are found in hidden location eg. C N S ,TESTES ,EYE (CORNEA)

organ damage

↓

Hidden Ag released

↓

Reaches blood stream

↓

Encounter Ag sensitive cells

↓

Stimulate autoimmunity

ANTIGEN GENERATED BY MOLECULAR CHANGES

- **Development of completely new epitopes on normal protein. eg RF immuno conglutinine.**

Mech. of formation of RF Ab + Ag

↓

new epitopes exposed on Fc region of Ab

↓

Stimulate the formation of Rf

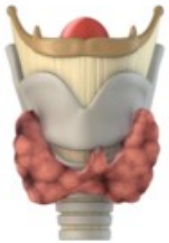
↓

Establishment of disease like rheumatiod artheritis and SLE

AUTOIMMUNE DISEASE

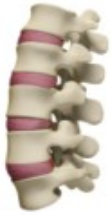
AUTOIMMUNE DISEASES

Brain
Multiple Sclerosis
Guillain-Barre Syndrome
Autism



Thyroid
Thyroiditis
Hashimoto's Disease
Graves' Disease

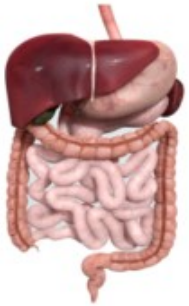
Blood
Leukemia
Lupus Erythematosus
Hemolytic Dysglycemia



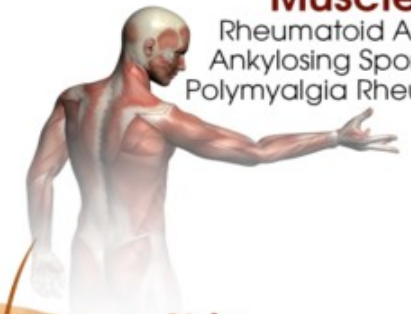
Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

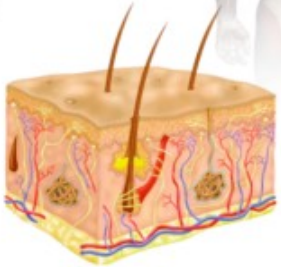
Over 100
Different Types of AutoImmune Disorders

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



Muscles
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

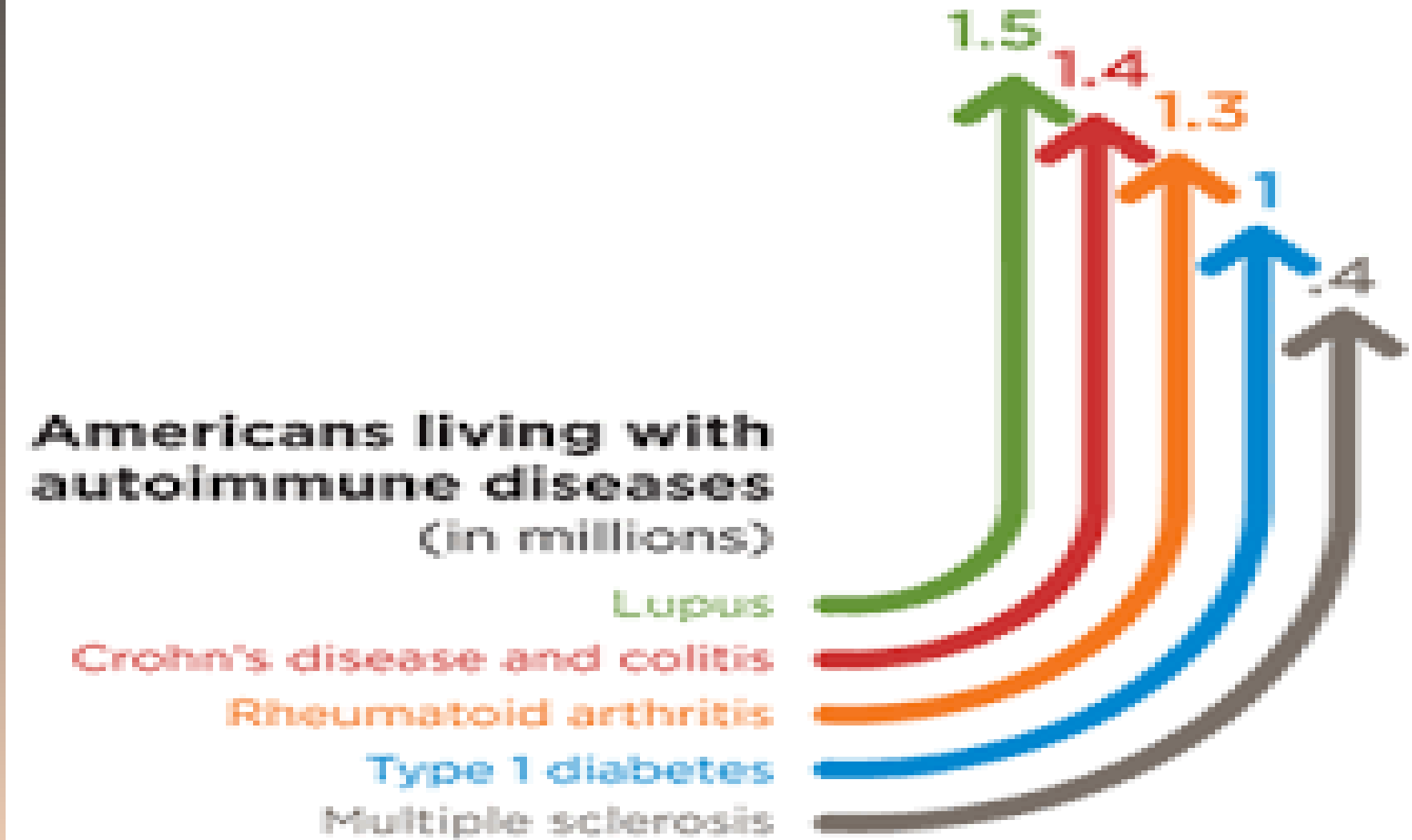




Skin
Psoriasis
Vitiligo
Eczema
Scleroderma

Nerves
Peripheral Neuropathy
Diabetic Neuropathy

Lung
Fibromyalgia
Wegener's Granulomatosis


Americans living with autoimmune diseases
(in millions)
Lupus
Crohn's disease and colitis
Rheumatoid arthritis
Type 1 diabetes
Multiple sclerosis
1.5
1.4
1.3
1
.4

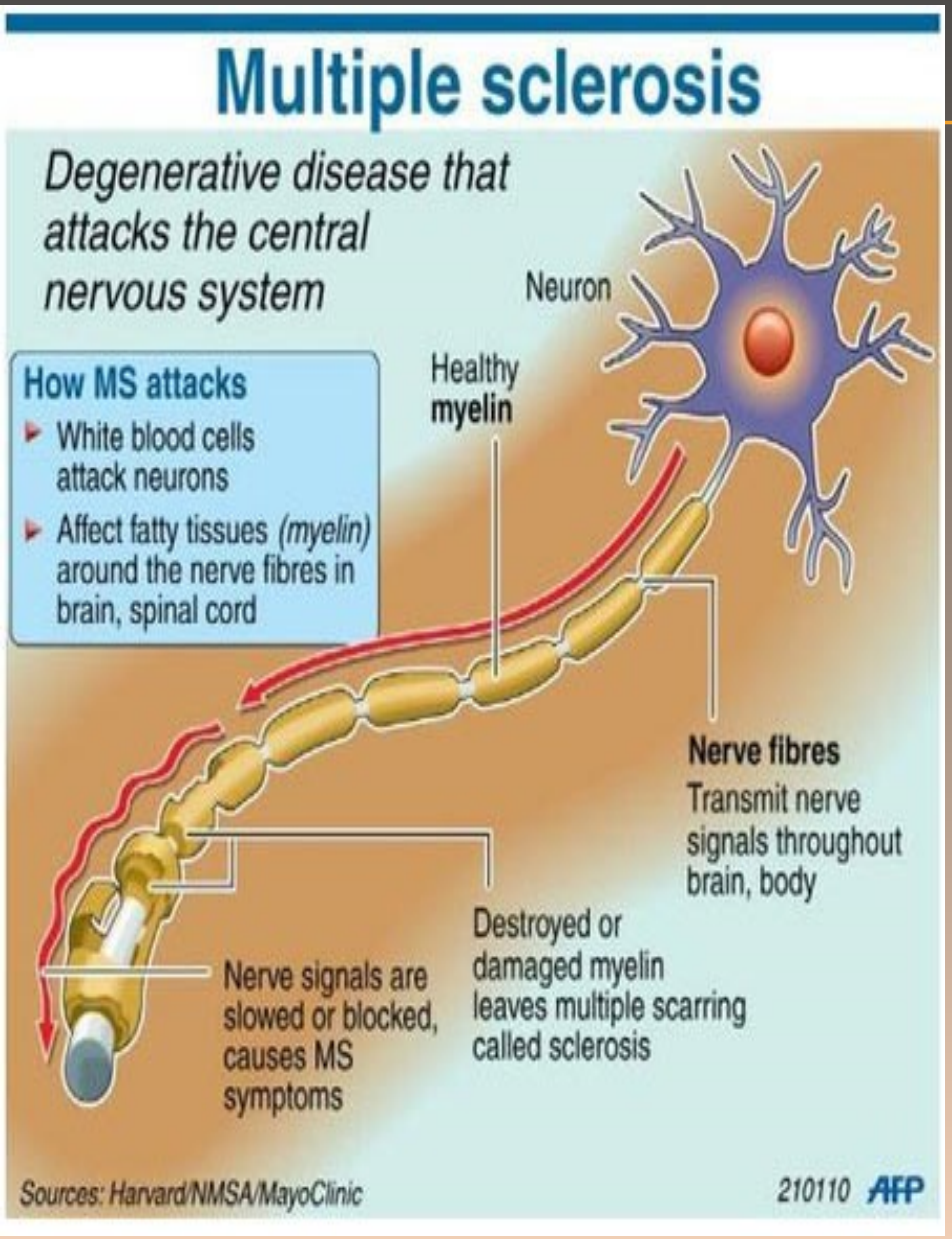
AUTOIMMUNE DISEASES

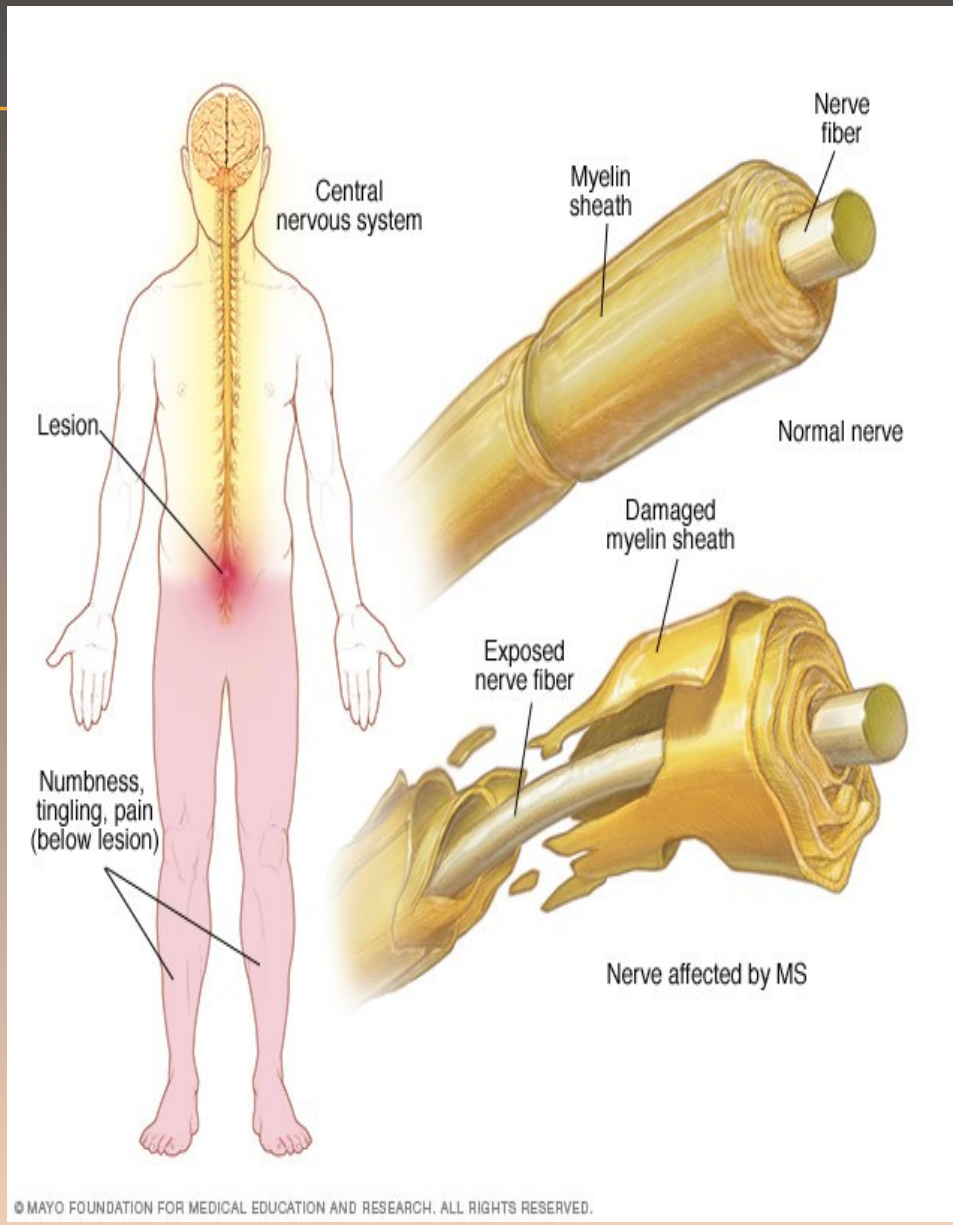
Some examples of autoimmune disease are described in more detail below:

I/ DISEASES INVOLVING PRIMARILY ONE TYPE OF CELL OR ORGAN

I/ Central nervous system (CNS) disorders

1. **Allergic Encephalitis**
2. **2.Multiple Sclerosis**


Multiple sclerosis
Degenerative disease that attacks the central nervous system
Neuron
How MS attacks
White blood cells attack neurons
Affect fatty tissues (myelin) around the nerve fibres in brain, spinal cord
Healthy myelin
Nerve fibres
Transmit nerve signals throughout brain, body
Destroyed or damaged myelin leaves multiple scarring called sclerosis
Nerve signals are slowed or blocked, causes MS symptoms
Sources: Harvard/NMSA/MayoClinic
210110 AFP


Central nervous system
Lesion
Numbness, tingling, pain (below lesion)
Nerve fiber
Myelin sheath
Normal nerve
Damaged myelin sheath
Exposed nerve fiber
Nerve affected by MS
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II/ ENDOCRINE DISORDERS

- **3.Chronic Thyroiditis**
- **4.Insulin-Dependent Diabetes Mellitus (IDDM)**

III/ BLOOD DISORDER

5.Hemolytic Anemias, Thrombocytopenias, and Granulocytopenias

6.Idiopathic thrombocytopenic purpura is.

IV/ Gastrointestinal tract disorders

7.Pernicious anemia

II/ DISEASES INVOLVING MULTIPLE ORGANS (SYSTEMIC DISEASES

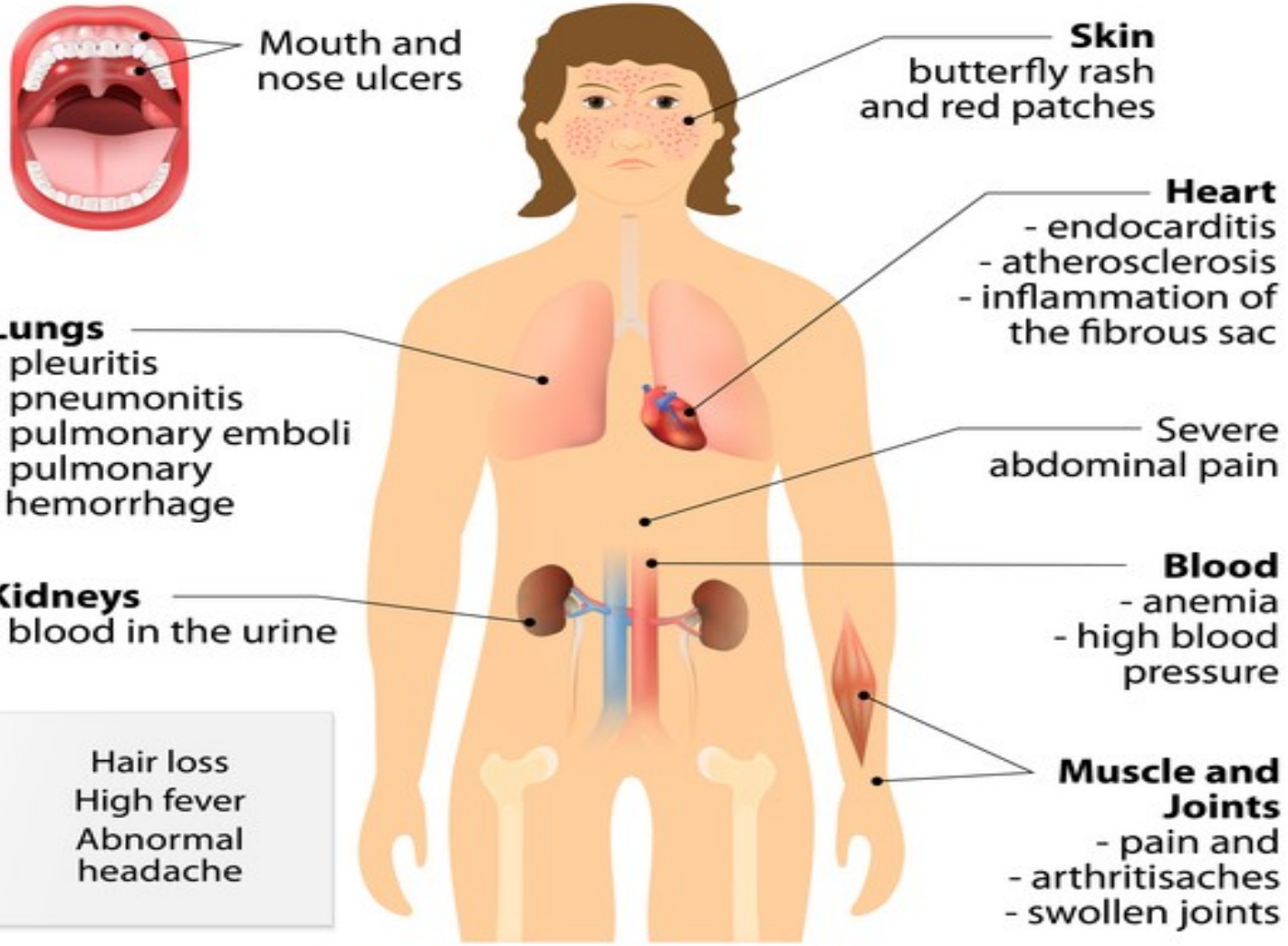
- RA
- Systemic Lupus Erythematosus

II/ DISEASES INVOLVING MULTIPLE ORGANS (SYSTEMIC DISEASES)

1.Systemic Lupus Erythematosus

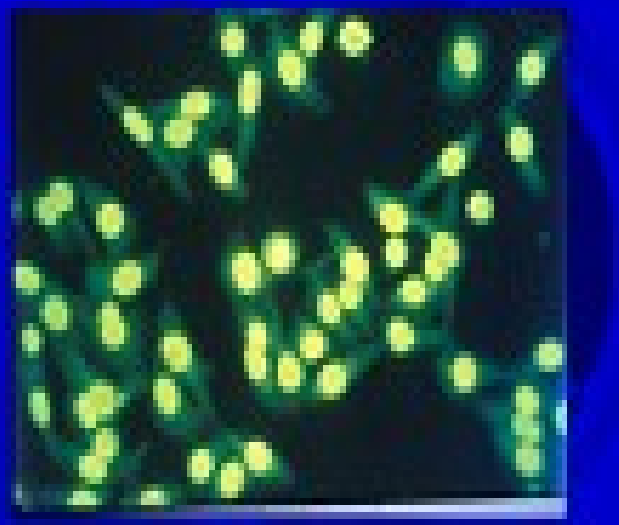
- In this disease, autoantibodies are formed against DNA, histones, nucleolar proteins, and other components of the cell nucleus.
- Antibodies against double-stranded DNA are the hallmark of systemic lupus erythematosus.
- The disease affects primarily women between the ages of 20 and 60 years. Individuals with HLA-DR2 or -DR3 genes are predisposed to systemic lupus erythematosus.
- Most of the clinical findings are caused by immune complexes that activate complement and, as a consequence, damage tissue. For example, the characteristic rash on the cheeks is the result of a vasculitis caused by immune complex deposition. The arthritis and glomerulonephritis commonly seen in systemic lupus erythematosus are also caused by immune complexes.
- The immune complexes found on the glomerulus contain antibodies (IgG, IgM, or IgA) and the C3 component of complement but not fibrinogen. However, the anemia, leukopenia, and thrombocytopenia are caused by cytotoxic antibodies rather than immune complexes.
- The diagnosis of systemic lupus erythematosus is supported by detecting antinuclear antibodies (ANA) with fluorescent antibody tests and anti-double-stranded DNA antibodies with ELISA.

Systemic lupus erythematosus



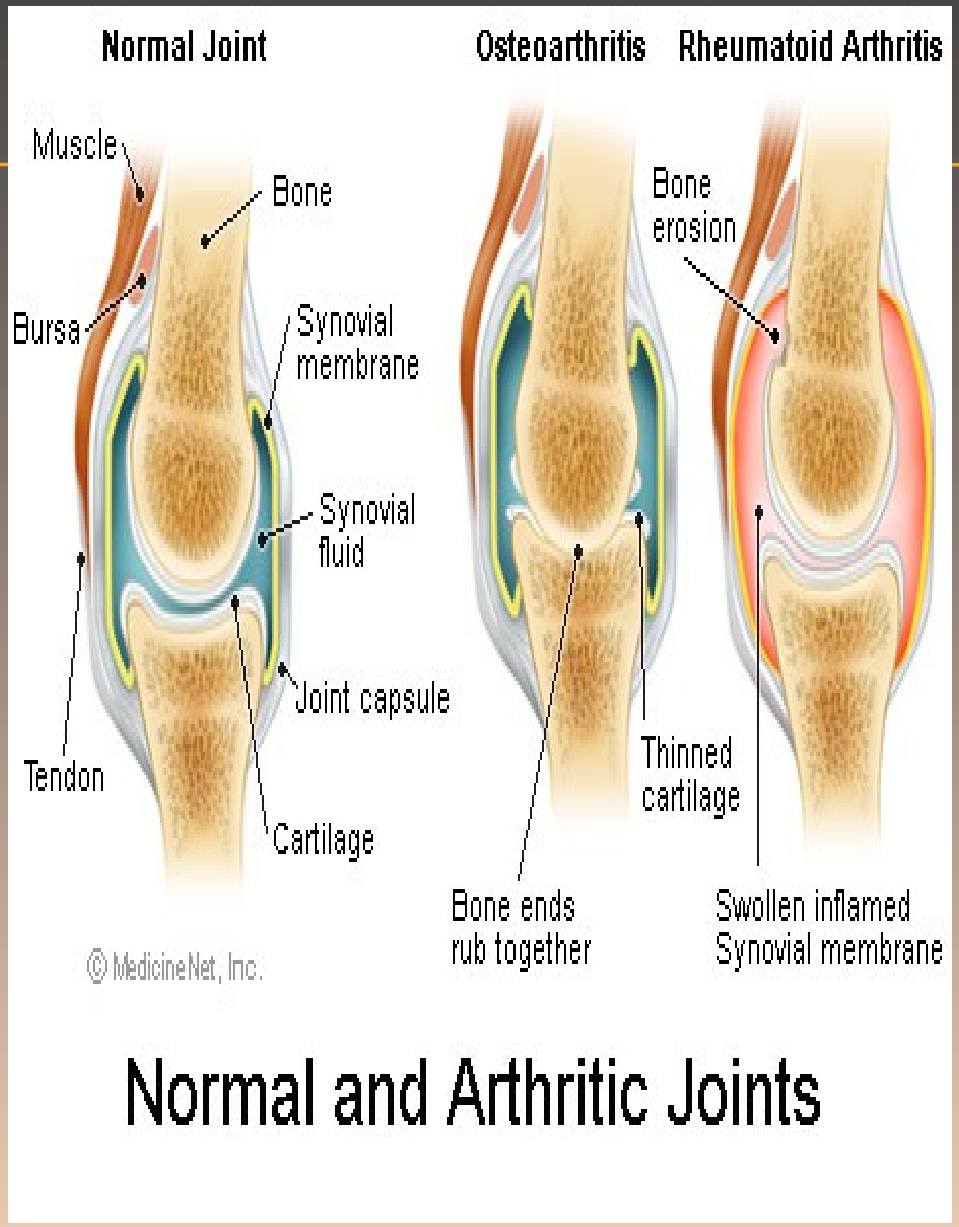
Systemic Lupus Erythematosis

A 27 year old woman presented with a visual field defect in the L. eye, head-aches and a facial rash. She had a positive ANA and proteinuria.



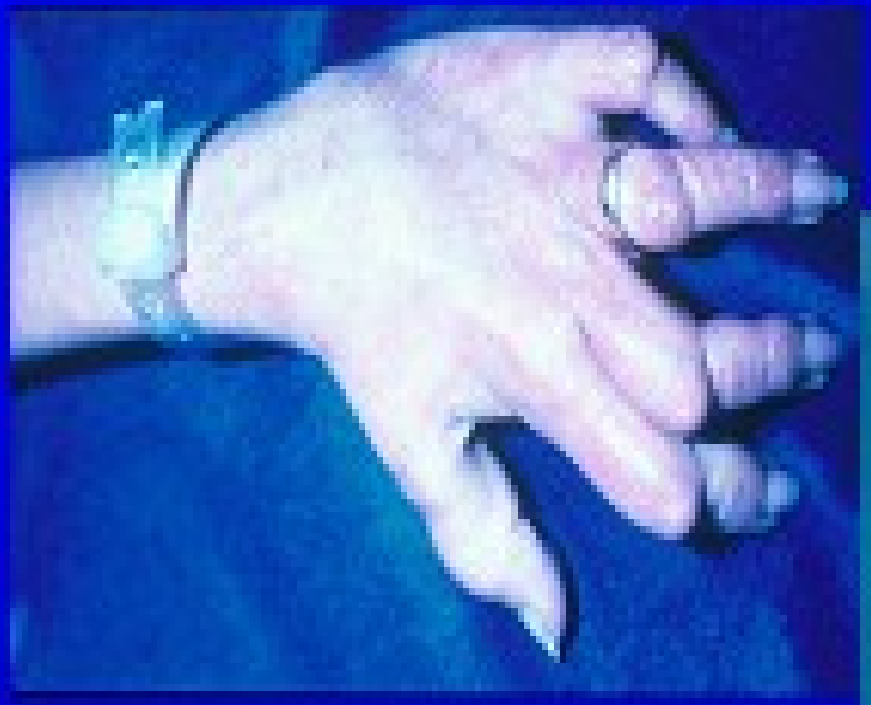
RHEUMATIOD ARTHRITIS

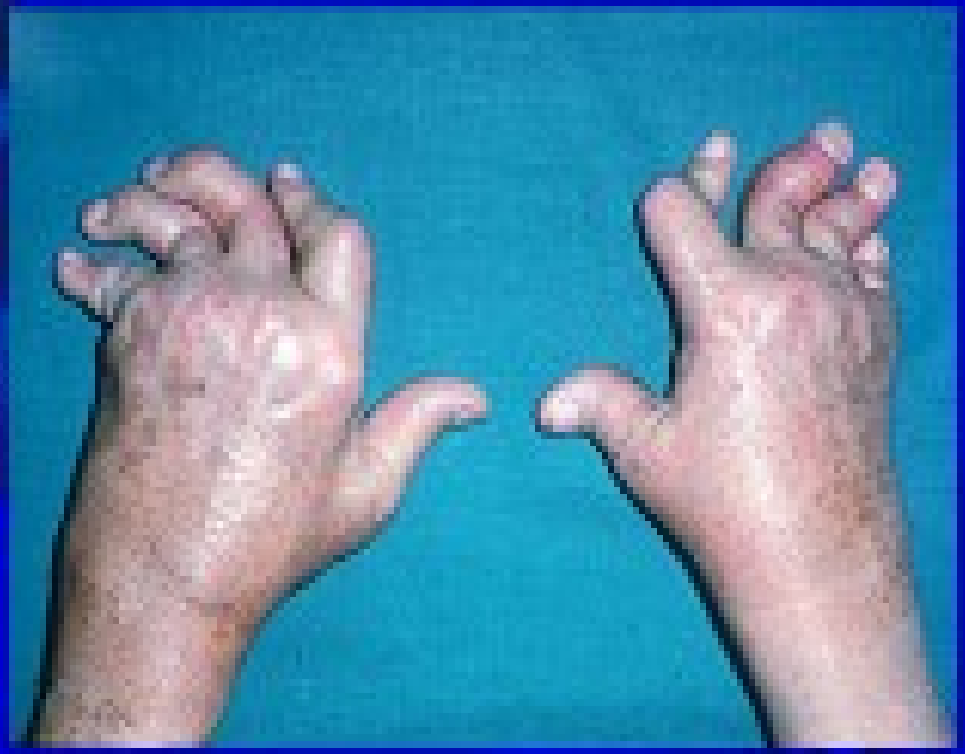
- Auto-immune disorder which results in inflammation of the synovial lining of the joint and cartilage destruction.
- This result in loss of function.
- Affects 1% of adults.



Normal and Arthritic Joints

Rheumatoid arthritis





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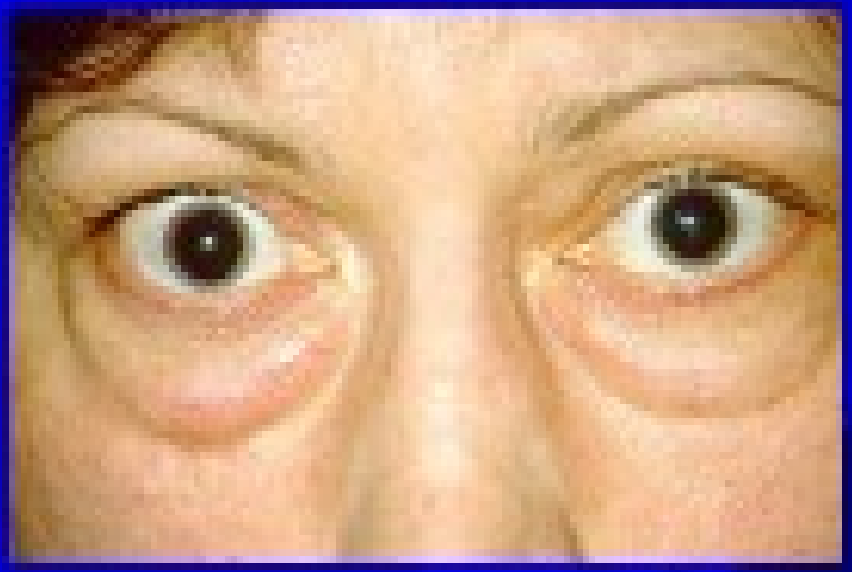
Autoimmune Thyroid diseasae



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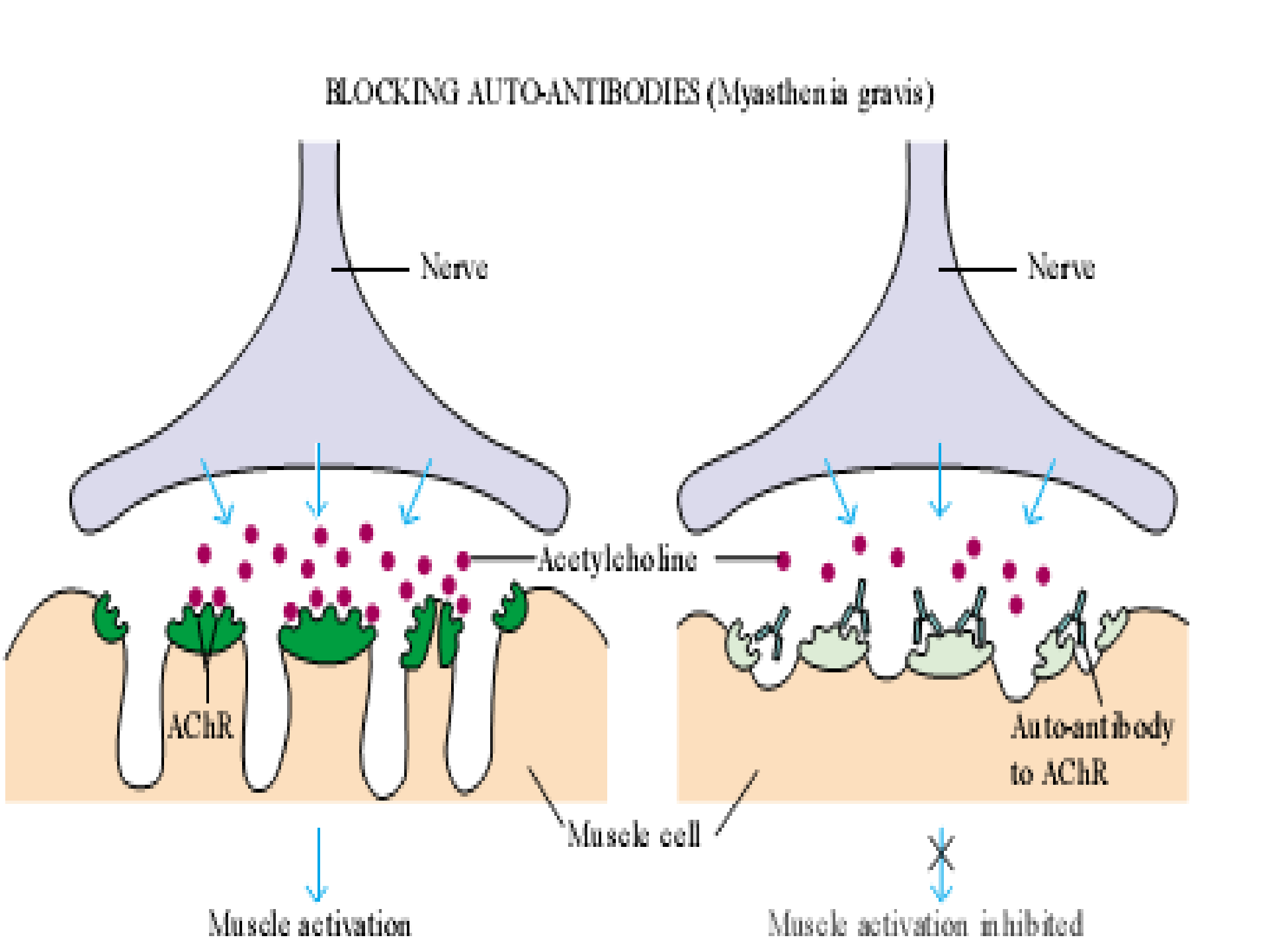
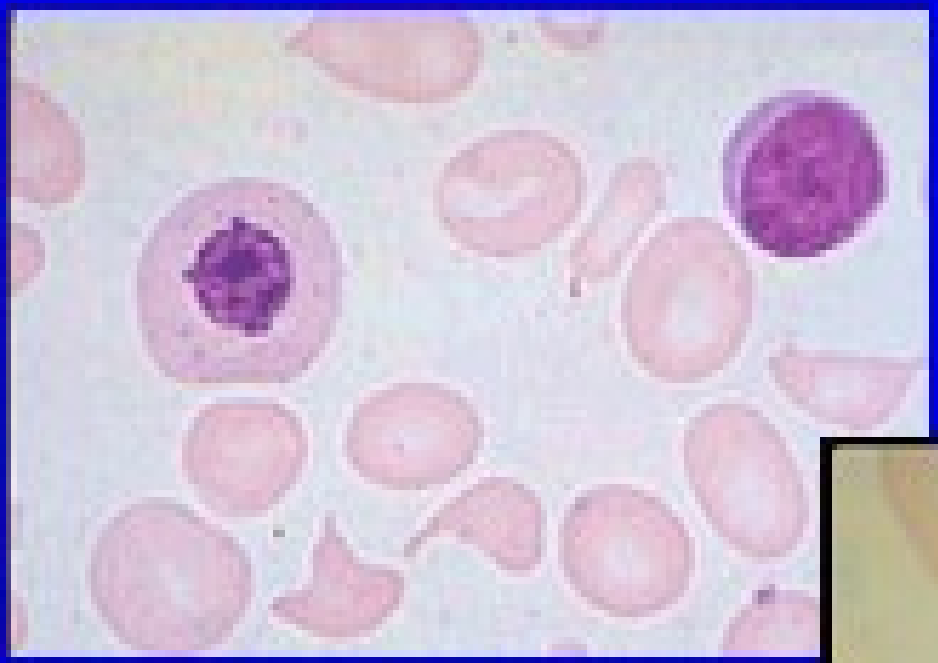
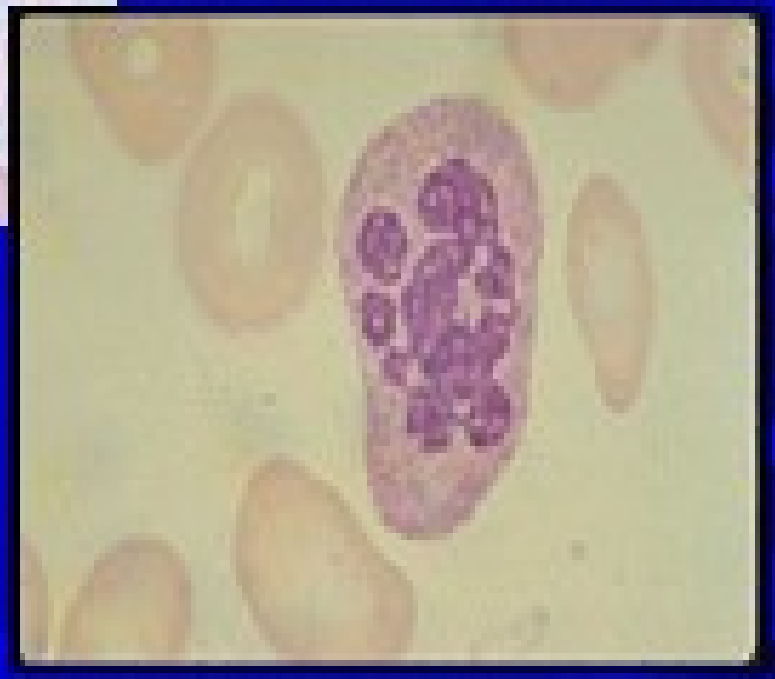

BLOCKING AUTO-ANTIBODIES (Myasthenia gravis)
Nerve
Nerve
Acetylcholine
AChR
Auto-antibody to AChR
Muscle cell
Muscle activation
Muscle activation inhibited

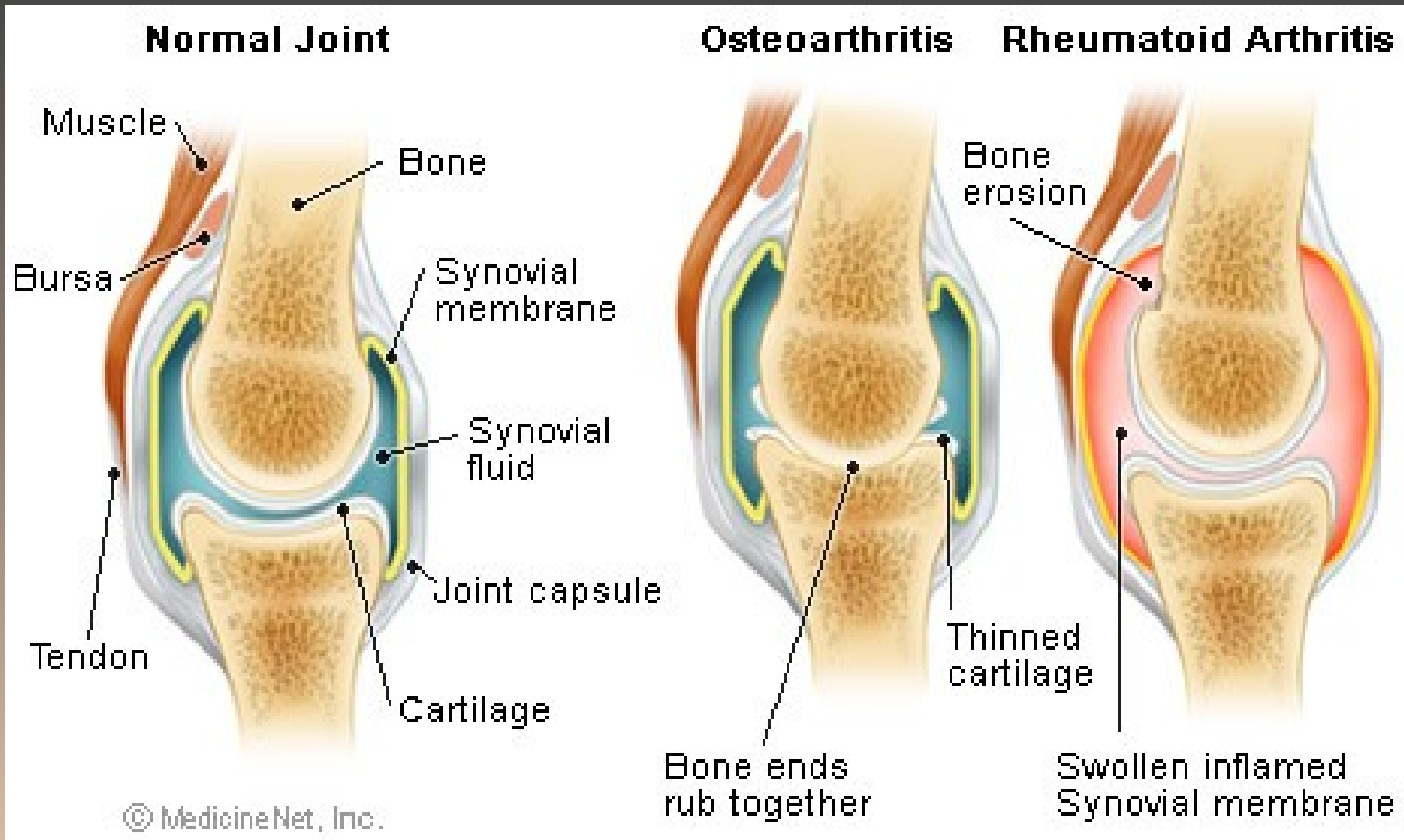
Pernicious anaemia



Macrocytic RBC

Hypersegmented PMN





Normal and Arthritic Joints

3.Rheumatic Fever

Group A streptococcal infections regularly precede the development of rheumatic fever.

Antibodies against the M protein of group A streptococci that cross-react withmyosin in cardiac muscle and proteins in joint and brain tissue are involved in the pathogenesis of rheumatic fever

Treatment

- The conceptual basis for the treatment of autoimmune diseases is to reduce the patient's immune response sufficiently to eliminate the symptoms.
- Corticosteroids, such as prednisone, are the mainstay of treatment, to which antimetabolites, such as azathioprine and methotrexate, can be added.
- The latter are nucleoside analogues that inhibit DNA synthesis in the immune cells.
- Immunosuppressive therapy must be given cautiously because of the risk of opportunistic infections.

TREATMENT FOR AUTOIMMUNITY

- Immunosuppression (e.g., prednisone, cyclosporin A)
- Removal of thymus (some MG patients)
- Plasmapheresis (remove Ab-Ag complexes)
- T-cell vaccination (activate suppressing T cells??)
- Block MHC with similar peptide
- anti-CD4 monoclonal Ab
- anti-IL2R monoclonal Ab

Definition and terminology of autoimmune disease

❖Autoimmune diseases are diseases that involve an immune response against one or more self-antigens.

❖These self-antigens are usually proteins that constitute part of the body; less often they are carbohydrates, lipids or DNA.

▪The self-antigens that the immune system responds to in an autoimmune disease are called **autoantigens** and the immune response against an autoantigen is called an **autoimmune response**.

▪The first disease to be identified as being autoimmune in origin was Hashimoto's thyroiditis in the mid-1950s.

- In this disease antibodies are produced against thyroglobulin and other thyroid-associated antigens.
- Antibodies against self-antigens are called **autoantibodies**
- and lymphocytes whose antigen receptors are specific for a self-antigen are called **autoreactive cells**.
- Nearly all autoimmune diseases involve the production of autoreactive CD4 T cells, which are also called **autoreactive Th cells**.
- Depending on the autoimmune disease there may also be the production of autoreactive B cells and/or autoreactive CD8 T cells.

THANK YOU