

# Autoimmune Diseases

Immunology Unit  
Department of Pathology  
College of Medicine

## **Reference**

**Kuby Immunology 7<sup>th</sup> Edition 2013**

**Chapter 16 Pages 525-531**

# Objectives

- To know that the inflammatory processes in auto immune diseases are mediated by hypersensitivity reactions (type II, III and IV)
- To know that autoimmune diseases can be either organ specific or may be generalized involving many organs or tissues
- To understand that the manifestations of autoimmune diseases depend upon the organ and the degree of damage inflicted on the target tissues

**Disease processes and tissue damage are due to Type II Type III and Type IV hypersensitivity reactions**

## SOME AUTOIMMUNE DISEASES IN HUMANS

Disease	Self-antigen	Immune response
<b>Organ-specific autoimmune diseases</b>		
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 <sub>DTH</sub> cells, auto-antibodies
Idiopathic thrombocytopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T <sub>DTH</sub> 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
<b>Systemic autoimmune disease</b>		
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T <sub>DTH</sub> and T <sub>C</sub> 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, thyroid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antibodies, immune complexes

## spectrum of autoimmune disease

organ specific



non-organ specific

Hashimoto's thyroiditis  
Primary myxoedema  
Thyrotoxicosis  
Pernicious anaemia  
Autoimmune atrophic gastritis  
Addison's disease  
Premature menopause (few cases)  
Insulin-dependent diabetes mellitus  
Goodpasture's syndrome  
Myasthenia gravis  
Male infertility (few cases)  
Pemphigus vulgaris  
Pemphigoid  
Sympathetic ophthalmia  
Phacogenic uveitis  
Multiple sclerosis (?)  
Autoimmune haemolytic anaemia  
Idiopathic thrombocytopenic purpura  
Idiopathic leucopenia  
Primary biliary cirrhosis  
Active chronic hepatitis (HBs Ag negative)  
Cryptogenic cirrhosis (some cases)  
Ulcerative colitis  
Sjögren's syndrome  
Rheumatoid arthritis  
Dermatomyositis  
Scleroderma  
Mixed connective tissue disease  
Discoid lupus erythematosus  
Systemic lupus erythematosus (SLE)

# Examples of Autoimmune Diseases Affecting Different Systems:

## **Nervous System:**

Multiple sclerosis  
Myasthenia gravis

Autoimmune neuropathies such as:  
- Guillain-Barré Syndrome (GBS)

Autoimmune uveitis

## **Blood:**

Autoimmune hemolytic anemia  
Pernicious anemia  
Autoimmune thrombocytopenia

## **Blood Vessels:**

Temporal arteritis  
Anti-phospholipid syndrome  
Vasculitides such as  
Wegener's granulomatosis  
Behcet's disease

## **Skin:**

Psoriasis  
Dermatitis herpetiformis  
Pemphigus vulgaris  
Vitiligo

## **Gastrointestinal System:**

Crohn's Disease  
Ulcerative colitis  
Primary biliary cirrhosis  
Autoimmune hepatitis

## **Endocrine Glands:**

Type 1 or immune-mediated diabetes mellitus  
Grave's Disease  
Hashimoto's thyroiditis  
Autoimmune oophoritis and orchitis  
Autoimmune disease of the adrenal gland

## **Multiple Organs, Musculoskeletal System**

Rheumatoid arthritis  
Systemic lupus erythematosus  
Scleroderma  
Polymyositis, dermatomyositis  
Ankylosing spondylitis  
Sjogren's syndrome

# Organ Specific Autoimmune Diseases

Mediated by **stimulating** or **blocking**  
auto-antibodies

- 1) Graves' disease (**Stimulating antibodies**)
- 2) Myasthenia gravis (**Blocking Antibodies**)



# 1. Graves' Disease (Thyrotoxicosis)

- Production of thyroid hormones is regulated by **thyroid-stimulating hormones (TSH)**

- The binding of TSH to a receptor on thyroid cells stimulates the synthesis of two **thyroid hormones**: thyroxine and triiodothyronine

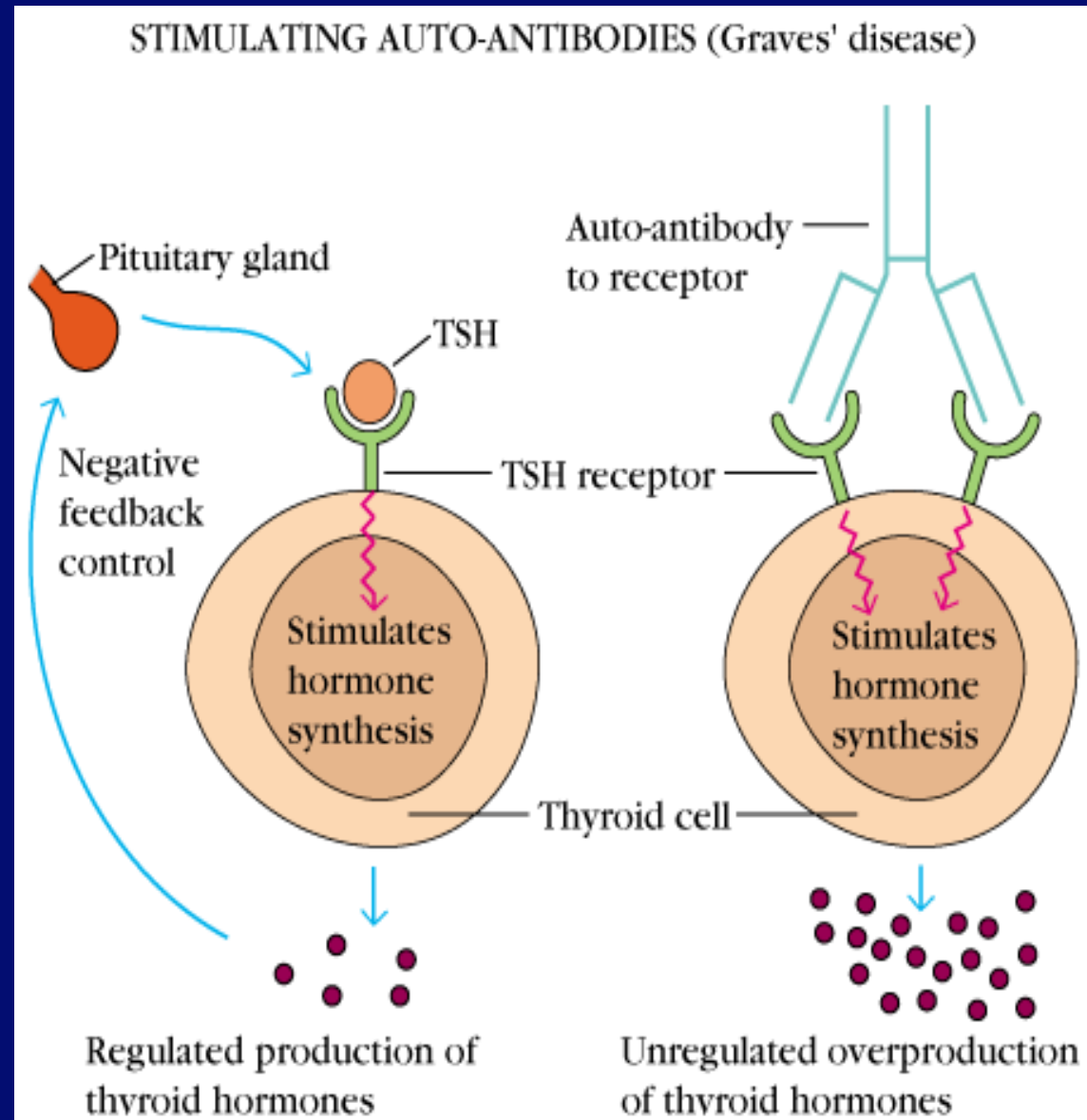




Fig. 1A



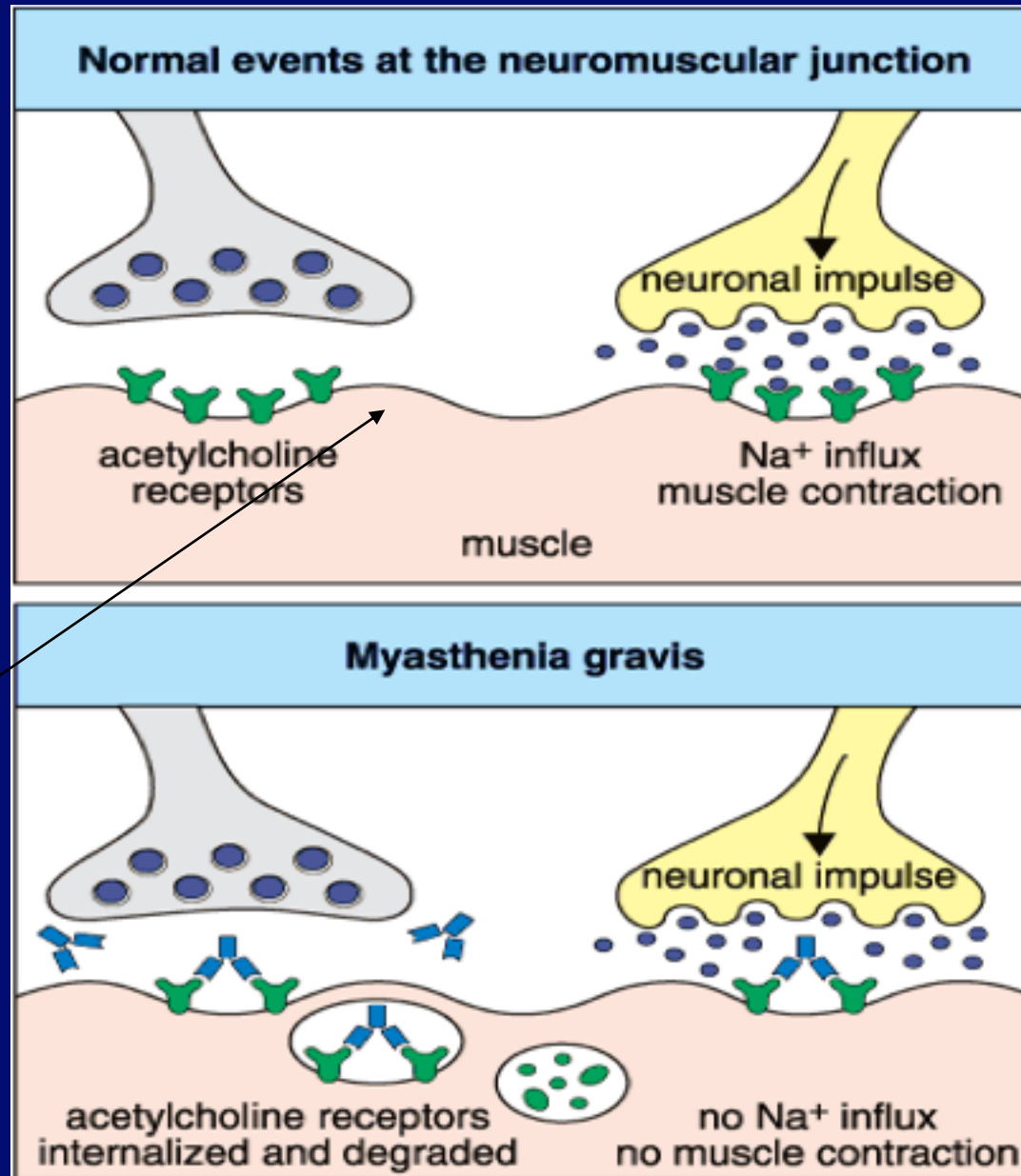
Fig. 1B

- A person with Graves' Disease makes **auto-antibodies to the receptor for TSH**.
- Binding of these auto-antibodies to the receptor **mimics** the normal action of TSH leading to over-stimulation of the thyroid gland

## 2. Myasthenia Gravis

- Clinically characterised by weakness and fatigability on sustained effort
- Antibodies directed against acetylcholine receptor (AChR)
- IgG Ab interact with the postsynaptic AChR at the nicotinic neuromuscular junction (NMJ)
- There is reduction in the number of functional AChR receptors by increasing complement mediated degradation of receptors

# Myasthenia gravis



Motor end-plates  
of muscles

Fig 13.10 © 2001 Garland Science

# Systemic Autoimmune diseases

## I. Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus is the prototype of systemic autoimmune disorder

The characteristic “**butterfly rash**” is made worse by exposure to sunlight

Lupus is a potentially fatal autoimmune disease



Figure 13.11 The Immune System, 3ed. (© Garland Science 2009)

Genetic + Environment factors

Pathogenic Auto antibodies  
-DNA/protein, RNA/protein complexes

Immune complexes

Complement activation

Chemotaxins

leukocytes  
mononuclear cells

Inflammatory factors  
IL-4, IL-6  
IL-10

Destruction of cells

## Symptom complex

### Constitutional

Fatigue:

Myalgia

Fever:

Weight change:

### Arthritis:

- migratory and asymmetrical. Only a few joints are usually affected, especially the hands

- Joint deformities including ulnar deviation, MCP subluxation, and **swan-neck deformities** caused by tendon laxity, rather than bony destruction.

### Dermatological: CNS:

- malar rash
- discoid lesions
- hair loss
- oral ulcers
- Raynaud's
- Nailfold erythema/crises
- livedo on hands/legs
- Bullous rash on legs
- dermatitis on fingers

- cognitive defects, anxiety, depression, psychosis, seizures, and/or neuropathies, cerebral punctate vasculitis

### Cardiovascular

- Pericarditis
- Verrucous endocarditis** => emboli
- CAD from steroids

### Pulmonary:

- Dyspnea and restrictive LFTs
- Pleurisy, pleural effusion, pneumonitis, interstitial lung disease, and pulmonary hypertension

### Renal:

- glomerulonephritis

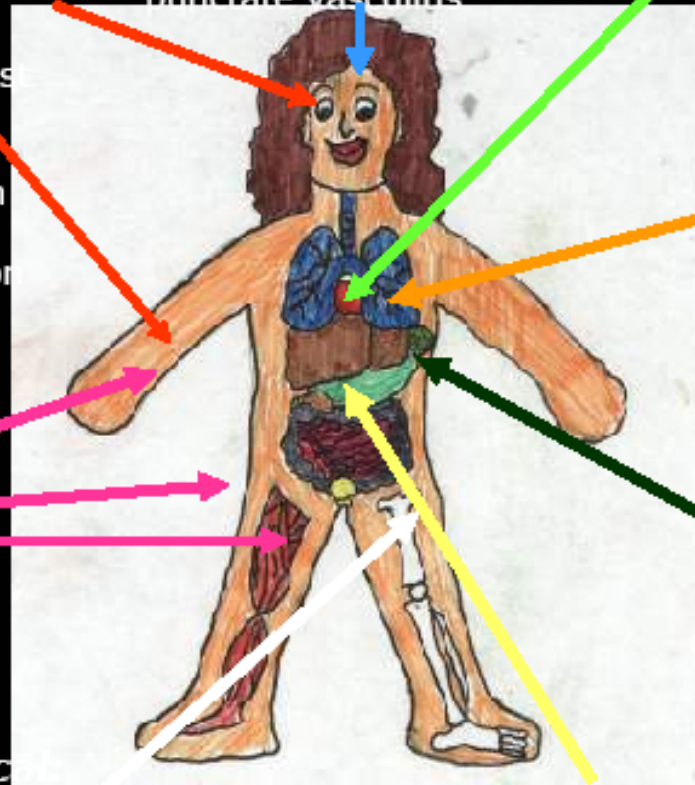
### Hematologic

- Anemia of chronic disease
- Asymptomatic leukopenia
- Thrombocytopenia
- lymphadenopathy

- Gastritis/peptic ulcer due to NSAID/corticosteroids

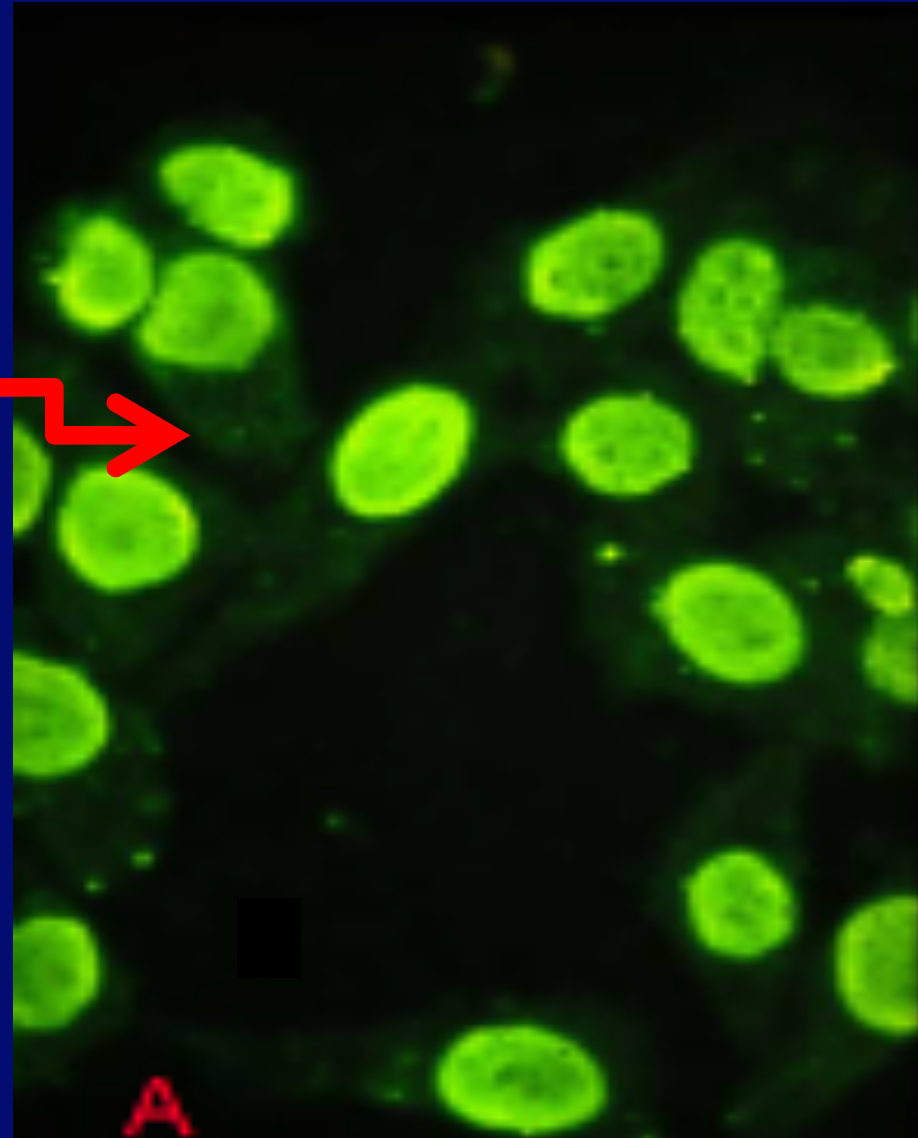
- Pancreatitis, peritonitis, and colitis: due to SLE vasculitis
- Lupoid hepatitis
- hepatosplenomegaly

### GI:



# Auto antibodies

- The anti-nuclear antibody (ANA) test is the best screening test for SLE and is determined by **immunofluorescence**
- The ANA is positive in significant titer (usually 1:160 or higher) in virtually all patients with SLE





## Significance of Autoantibodies in SLE

Antigen	SLE	Clinical Associations
ds DNA	70%	Nephritis (and flare)
Anti RNP	40%	Scleroderma, myositis
Histones	70%	Drug-Induced Lupus
SM Antigen	30%	Severe SLE
Anti ribosomal	20%	Psychosis, Depression
Antiphospholipid	50%	Clotting, fetal loss
SSA/Ro	35%	SCLE, Sjogren's, NLS
SSB/La	15%	SCLE, Sjogren's, NLS
Anti neuronal	60%	Active CNS lupus

# Other investigations

- Anti-double-stranded DNA titers
- Complement Levels (CH50, C3, C4)
- ESR
- CRP
- Complement Split products
- Decreased complement C1q

# Treatment

**NSAIDs**

**(Non-steroidal anti-inflammatory drugs)**

**Antimalarials (Hydroxychloroquine)**

**Immunosuppressive agents**

## 2. Rheumatoid Arthritis

- Rheumatoid arthritis is a common autoimmune disease in which the normal immune response is directed against an individual's own tissue, including the :
  - **Joints**
  - **Tendons**
  - **Bones**

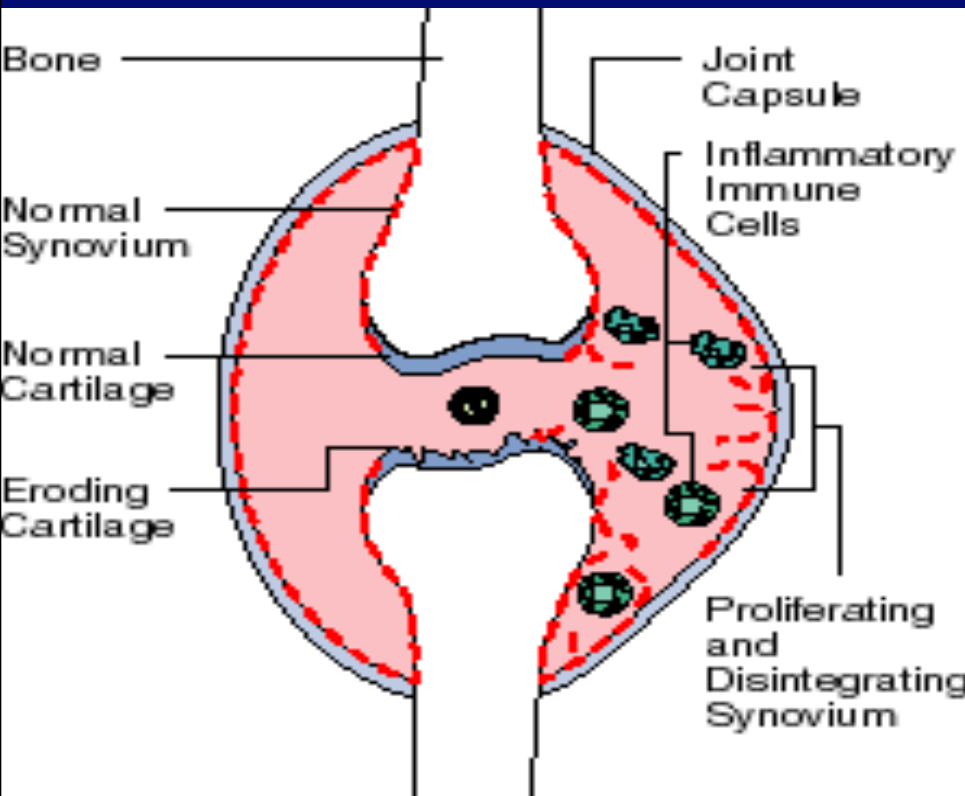
Resulting in inflammation and destruction of these tissues with progressive disability, systemic complications (cardiovascular, pulmonary ..) and early death.

# Rheumatoid Arthritis (*Contd.*)

- Both prevalence and incidence are 2-3 times greater in **women** than in men.
- The cause of rheumatoid arthritis is **not known**: complex interplay among genotype, environmental triggers.
- **Genetic factors: HLA-DR B1 locus** alleles that contain a common amino acid motif (QKRAA) in the HLA-DRB1 region, termed the shared epitope, confer particular susceptibility

# Rheumatoid Arthritis

Rheumatoid arthritis (RA) affects peripheral joints is characterized by an inflammation of the synovium: synovitis that may cause destruction of both cartilage and bone.



# Pathogenesis

(Type III hypersensitivity reaction)

Inflammatory cells produce pro inflammatory cytokines/  $\text{TNF-}\alpha$ , IL-1 that induce the secretion of metalloproteinases; which are known to cause joint destruction

T cell activation due to unknown antigens also contributes to the inflammation in RA

There is a lack of tolerance to citrullinated proteins and the appearance of autoantibodies directed against citrullinated proteins

# Pathogenesis

(Type III hypersensitivity reaction)

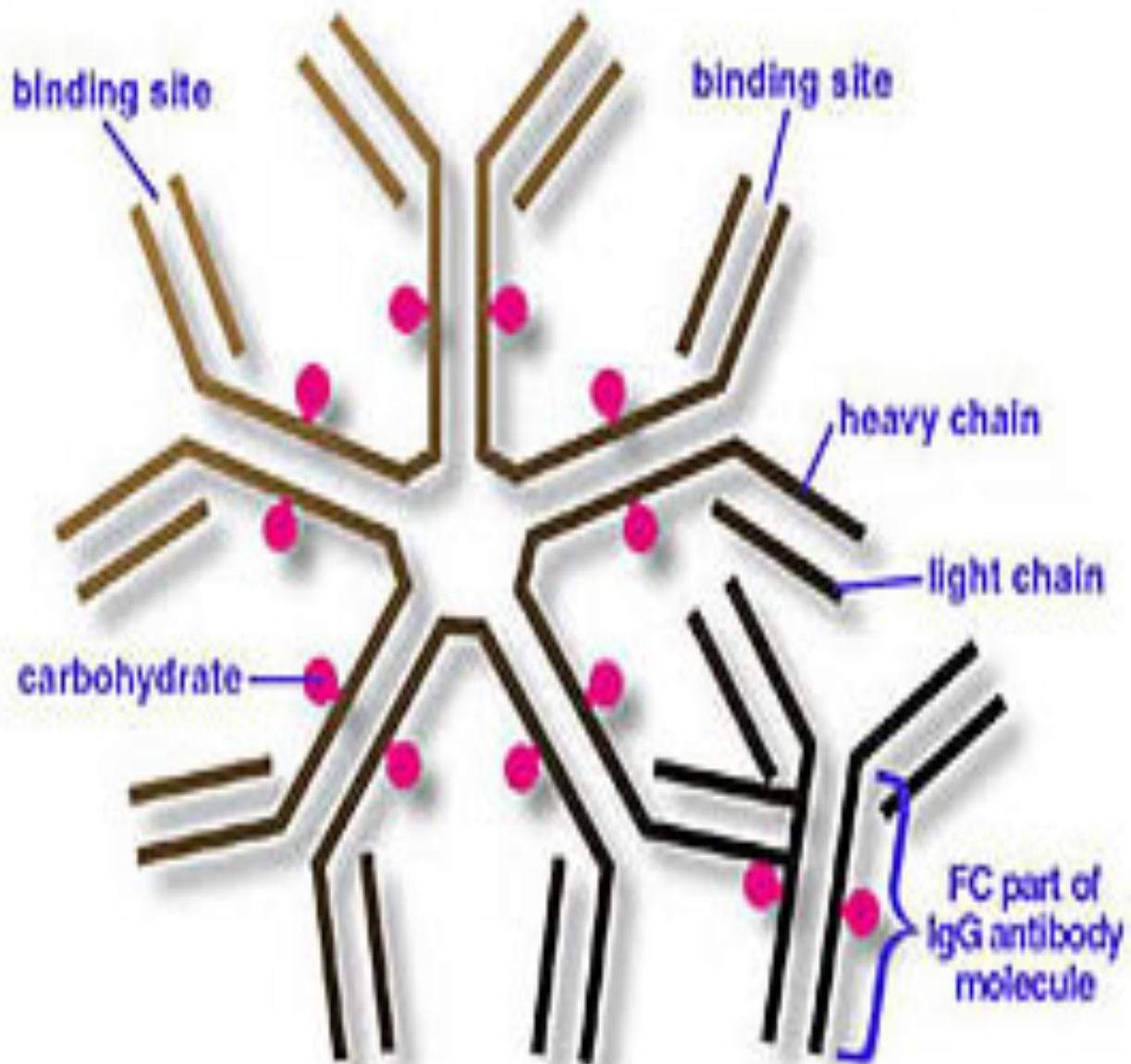
In rheumatoid arthritis, many individuals produce another group of auto-antibodies known as **rheumatoid factor**

These antibodies react with determinants in the **F<sub>C</sub> region of IgG**



# Rheumatoid Factor

The classic  
rheumatoid  
factor is an  
**IgM** antibody  
Directed  
against  
Fc  
part of IgG



# Pathogenesis

(Type III hypersensitivity reaction)

Such auto-antibodies bind to normal circulating IgG, forming **IgM-IgG complexes** which may be deposited in joints.

This leads to activation of synovial macrophages

The macrophages engulf the immune complexes and then release TNF and other pro-inflammatory cytokines e.g., IL-1

## Diagnosis:

- **Anti-citrullinated protein/peptides(ACP) antibodies/ anti-CCP : specific markers**
- **Rheumatoid factor**

## Medications

- **NSAIDS** (Non-steroidal anti-inflammatory drugs)
- **Disease-modifying drugs** (eg, gold, hydroxychloroquine, sulfasalazine, penicillamine)
- **Immunosuppressive therapy:**
  - Corticosteroids
  - Methotrexate
- **Surgery**
- **Physical therapy**

# Take home message

- The spectrum of autoimmune disorders is wide ranging from single organ involvement to a systemic disease
- The disease process is usually prolonged and is generally associated with significant morbidity and mortality
- The mainstay of the treatment is to maintain immunosuppression

**Thank you**