Immunology Team

Autoimmune Diseases

(2nd Lecture)

Musculoskeletal Block

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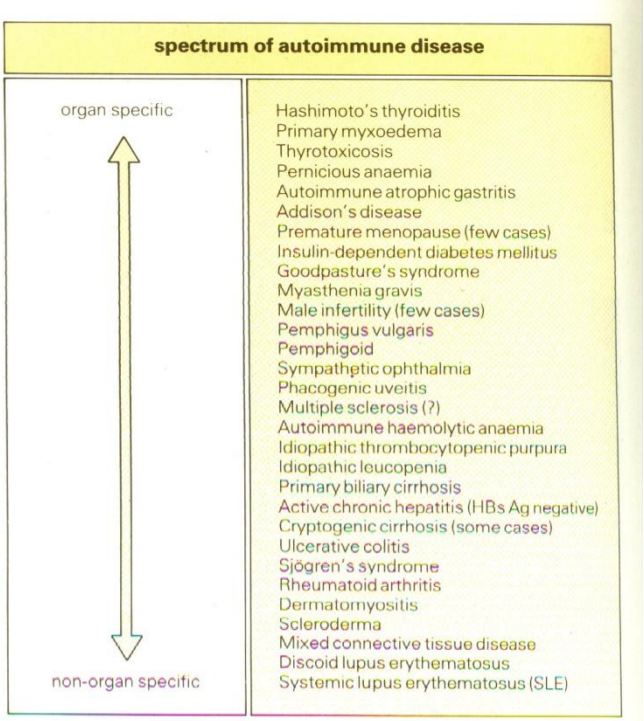
Autoimmune Diseases

Disease processes and tissue damage are due to Type II (IgG Ab to tissue antigens) Type III (Immune complex) and Type IV(Cell Mediated Immunity) hypersensitivity reactions .

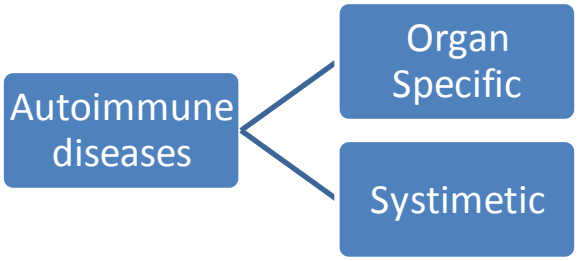
- We do not know the exact mechanism by which autoimmune disease happened.
- Autoimmune diseases could be: - Organ specific. – Systemic.

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, thyroid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antobidies, immune complexes



- At the top of the spectrum, the diseases are organ specific.
- At the bottom, the diseses are systimatic.
- In the middle, some diseases can be both: Systematic and Organ specific.



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

Autoimmune Diseases

Organ Specific

Mediated by stimulating or blocking auto-antibodies

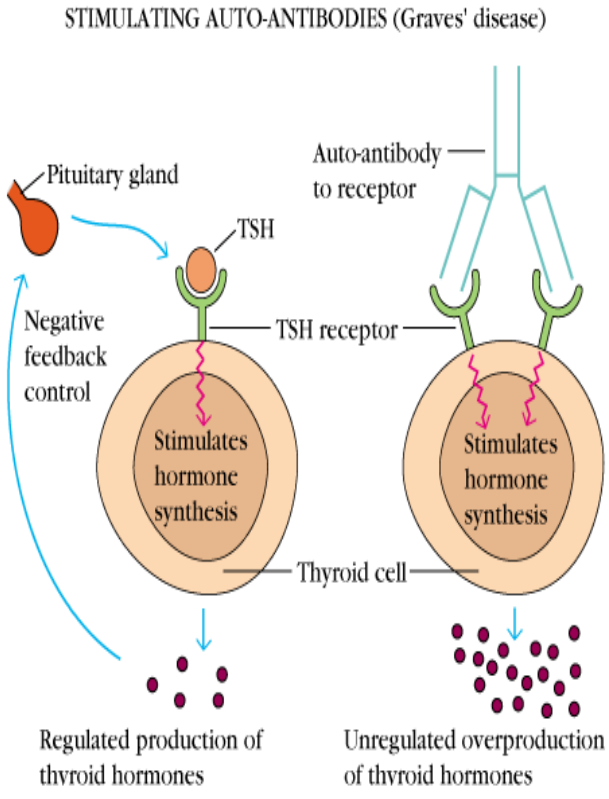
1) Graves' disease (Stimulating antibodies)
2) Myasthenia gravis (Blocking Antibodies)

1. Graves' Disease

1) Graves' Disease (Thyrotoxicosis)→ excessive release of thyroid hormone.
2) Production of thyroid hormones is regulated by thyroid-stimulating hormones (TSH)
3) The binding of TSH to a receptor on thyroid cells stimulates the synthesis of two thyroid hormones: thyroxin and triiodothyronine

Stimulating antibodies: By binding to the receptors and acting as an agonist

Blocking antibodies: Ab that blocks the receptors of the cell (inhibition) →preventing the agonist to do its work.

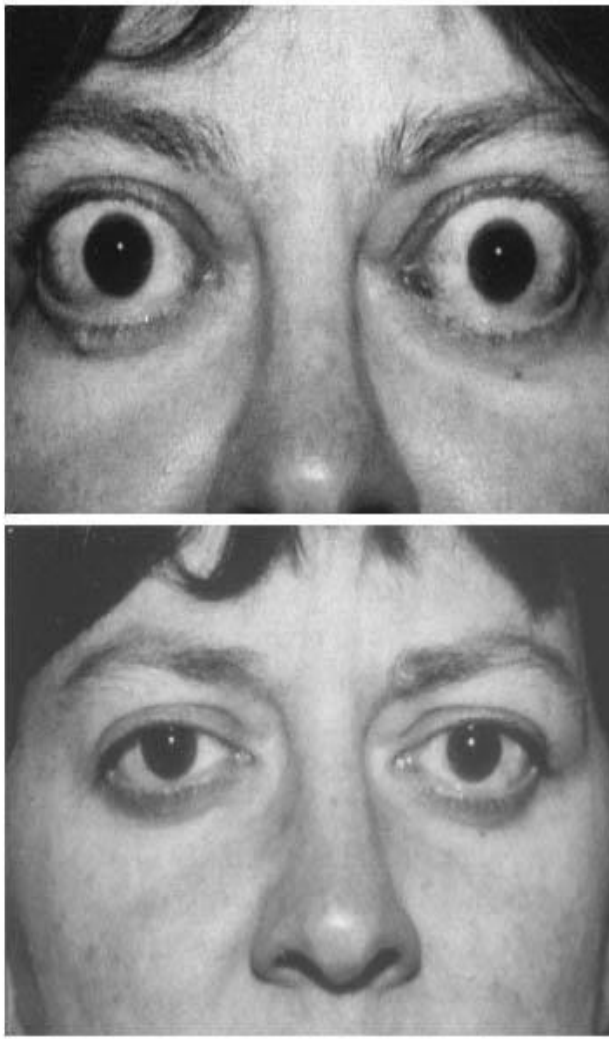


Explanation for the image:

- The right : Pituitary gland secrete Thyroid Stimulating Hormone (TSH) when thyroid hormones are needed→ TSH will bind to thyroid cells' receptors→ stimulate the gland to secrete its hormones, When the body does not need thyroid hormone, pituitary gland will stop its secretion of TSH which will end the stimulation of thyroid hormone and stops its secretion.
- In Graves disease (left): an auto antibody will mimic TSH and stimulate the thyroid gland. There is no termination → uncontrolled production of thyroid hormone, which will lead to over-stimulation of the thyroid gland.

- 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

Graves' disease: Treated by antithyroid, radioactive iodine or surgery.



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

- Main clinical signs of Thyroxicosis → Protrusion of the eyeball.
- Auto antibodies of Mysthenia Garvis → IgG.
- Antibody + Ach receptors = internalization.

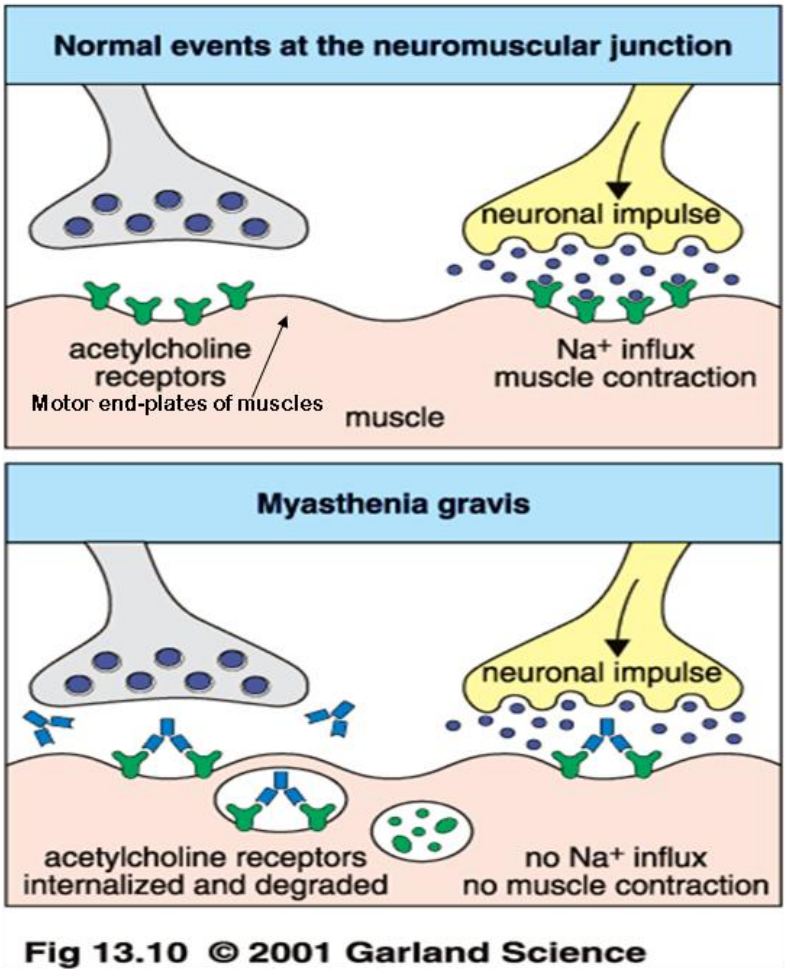


Fig 13.10 © 2001 Garland Science

Systemic Autoimmune Immune diseases

1. Systemic lupus erythematosis (SLE)

Systemic lupus erythematosis is the most common autoimmune disorder.

The characteristic "butterfly rash" is made worse by exposure to sunlight.

Lupus is a potentially fatal autoimmune disease .

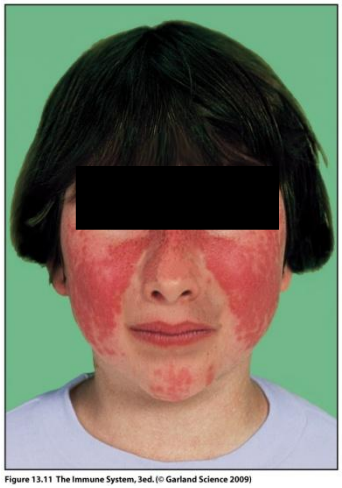
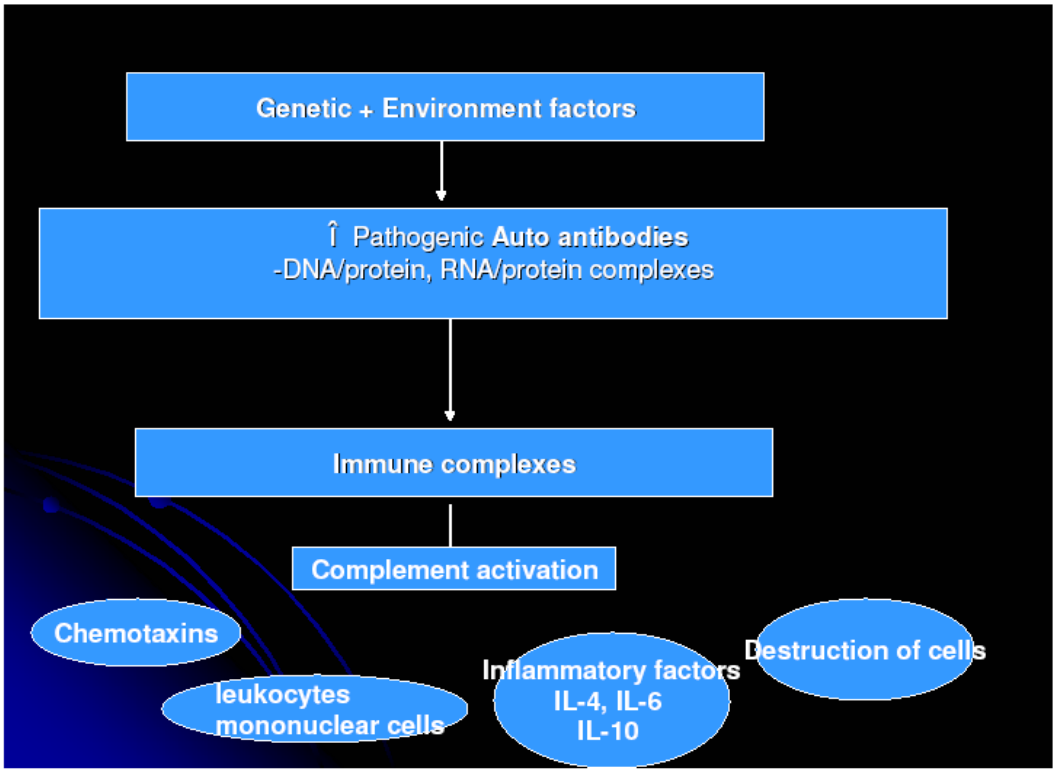
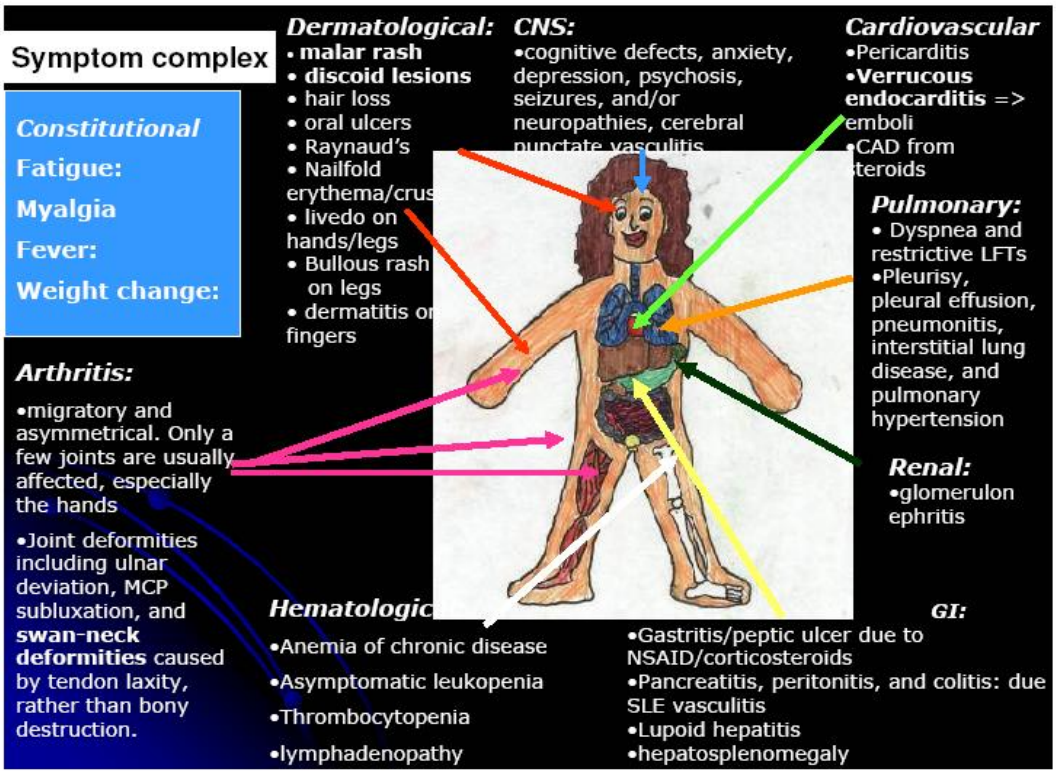


Figure 13.11 The Immune System, 3ed. (© Garland Science 2009)

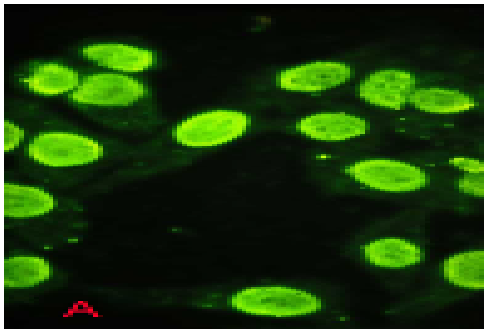
- Systemic lupus erythematosis (SLE) → Butterfly rash, Also it involves many organs.
- Why (SLE) is an autoimmune disease? Because it mainly directs against nuclear material.
- Diagnosis of (SLE) → Serum + Antibody against nuclear material = Immunofloracence appeared slid. (ELISA test).
- SLE → will produce antibodies not just for double stranded DNA .


Genetic + Environment factors
Î 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:
Dermatological:
• malar rash
• discoid lesions
• hair loss
• oral ulcers
• Raynaud's
• Nailfold erythema/crus
• livedo on hands/legs
• Bullous rash on legs
• dermatitis or fingers
CNS:
•cognitive defects, anxiety, depression, psychosis, seizures, and/or neuropathies, cerebral
Cardiovascular
•Pericarditis
•Verrucous endocarditis => emboli
•CAD from steroids
Pulmonary:
• Dyspnea and restrictive LFTs
•Pleurisy, pleural effusion, pneumonitis, interstitial lung disease, and pulmonary hypertension
Renal:
•glomerulon ephritis
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.
Hematologic
•Anemia of chronic disease
•Asymptomatic leukopenia
•Thrombocytopenia
•lymphadenopathy
GI:
•Gastritis/peptic ulcer due to NSAID/corticosteroids
•Pancreatitis, peritonitis, and colitis: due SLE vasculitis
•Lupoid hepatitis
•hepatosplenomegaly

Auto antibodies

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



Immunefluorescence

If the patient doesn't have the SLE, the slide will be just black without any green circles.

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 P	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

ESR: Erythrocyte Sedimentation Rate.

CRP: C- Reactive Protein.

Treatment

- NSAIDs (Non-steroidal anti-inflammatory drugs)
- Antimalarials (Hydroxychloroquine)
- Immunosuppressive agents

2. Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease in which the normal immune response is directed against an individual's own tissue, including the :

- Joints
- Tendons
- Bones

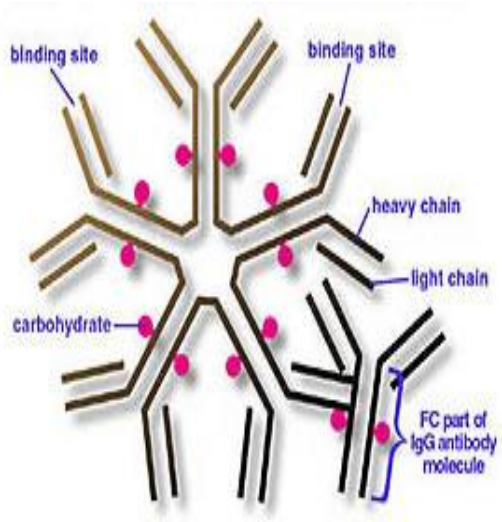
Auto reactive T cells & Auto antibody, both can cause Rhmatoid arthritis.

- Resulting in inflammation and destruction of these tissues
- The cause of rheumatoid arthritis is not known
  - Investigating possibilities of a foreign antigen, such as a virus
- Both prevalence and incidence are 2-3 times greater in women than in men

Pathogenesis

- (Type III hypersensitivity reaction)
- In rheumatoid arthritis, many individuals produce a group of auto-antibodies known as rheumatoid factor
- These antibodies react with determinants in the F_C region of IgG

Rheumatoid Factor



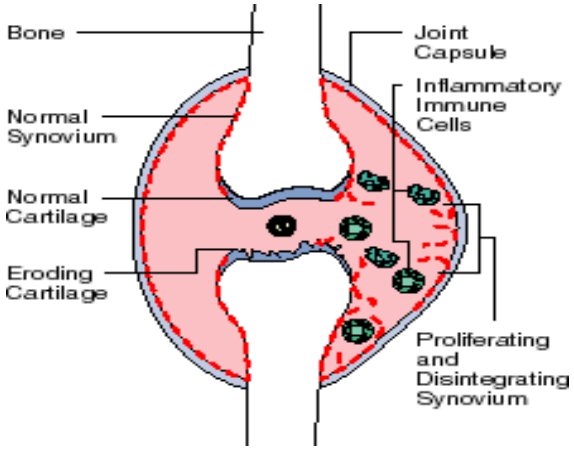
The classic rheumatoid factor is an IgM antibody with this kind of reactivity**.**

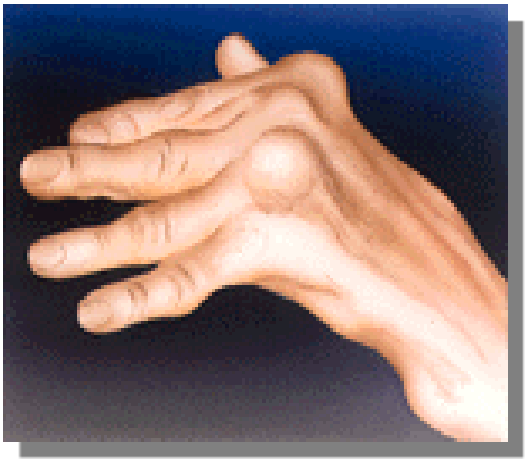
Rematoid factor: IgM → attached to → IgG - Fc part -.

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
- TNF induces 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





Rheumatoid arthritis (RA) affects peripheral joints and may cause destruction of both cartilage and bone.

Treatment and Prognosis

Medications :

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

Why doctors should be strict when following up their patients with autoimmune disease?

Because of the suppuration of immune system.