MEDICINE
KING SAUD UNIVERSITY

Revised by
شوق الأحمري & طراد الوكيل

Musculoskeletal Block

Lecture Two

Autoimmune Diseases

IMMUNOLOGY
436's TEAMWORK

Objectives:

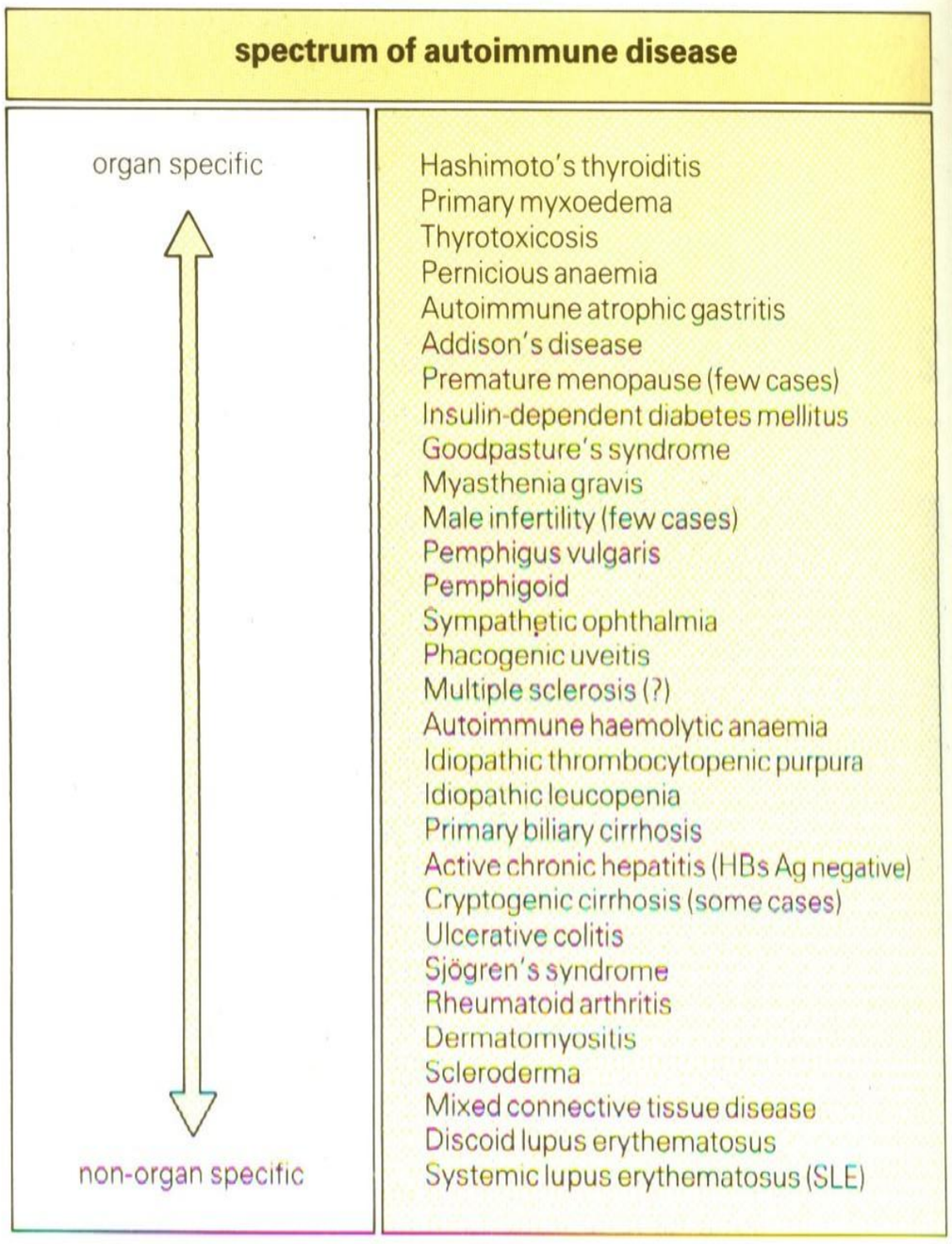
- To know that the inflammatory processes in autoimmune diseases are mediated by hypersensitivity reactions (type II, III and IV).
- To know that autoimmune diseases can be either organ specific or may be generalized involving many organs or tissues.
- To understand that the manifestations of autoimmune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

- **Important.**
- **Extra notes.**
- **Females notes**
- **Males notes.**

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
	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 (stimulati
Hashimoto's thyroiditis	Thyroid proteins and cells	T_{DTH} cells, auto-antibodi
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_{DTH} cells, auto-antibodi
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 comple
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



we are not required to memorize the tables. The point is just to know that there are (organ specific) and (non organ specific) disease.

Not important

Examples of Autoimmune Diseases Affecting Different Systems: important

Nervous System: Multiple sclerosis Myasthenia gravis Autoimmune neuropathies such as: - Guillain-Barré Syndrome (GBS) Autoimmune uveitis	**Skin**: Psoriasis Dermatitis herpetiformis Pemphigus vulgaris Vitiligo
Blood: Autoimmune hemolytic anemia Pernicious anemia Autoimmune thrombocytopenia	**Gastrointestinal System:** Ulcerative colitis Primary biliary cirrhosis Autoimmune hepatitis Crohn's Disease
Blood Vessels: Temporal arteritis Anti-phospholipid syndrome Vasculitides such as Wegener's granulomatosis Behcet's disease	**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

These diseases are mediated by stimulating or blocking auto- antibodies:

1) Graves' Disease (Thyrotoxicosis): (caused by **Stimulating antibodies**)

(By binding to the receptors and acting as an agonist leading to abnormal function).

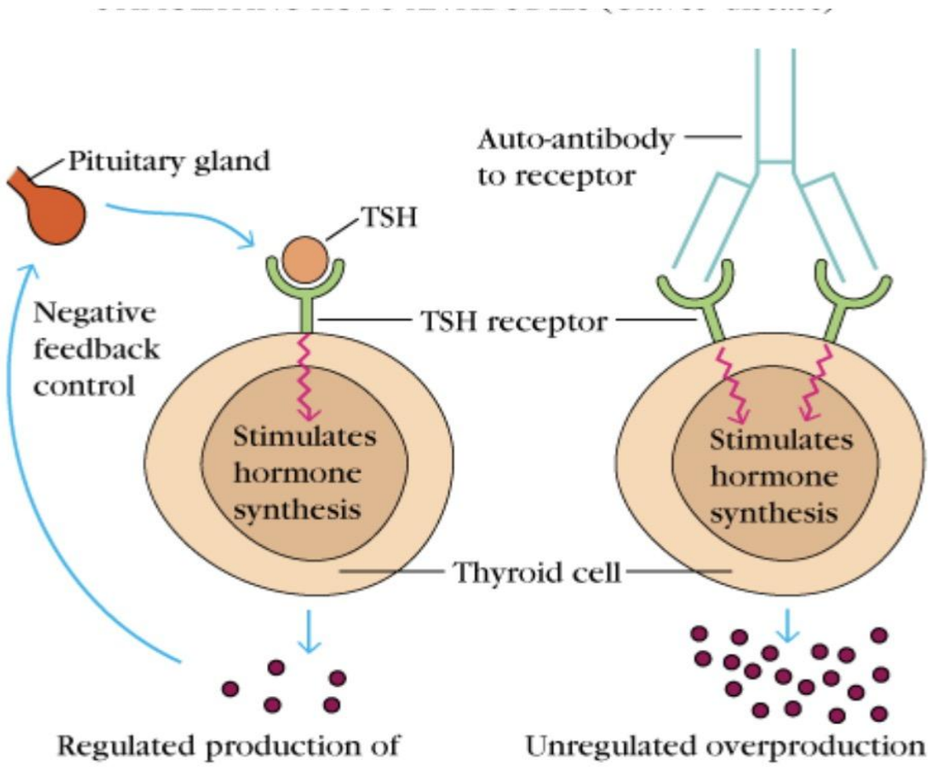
Production of thyroid hormones is regulated by thyroid- stimulating hormones (**TSH**) from the pituitary gland. The binding of TSH to a receptor on the thyroid cells stimulates the synthesis of **two thyroid hormones:**

1) Thyroxine.

2) Triiodothyronine.

- 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.

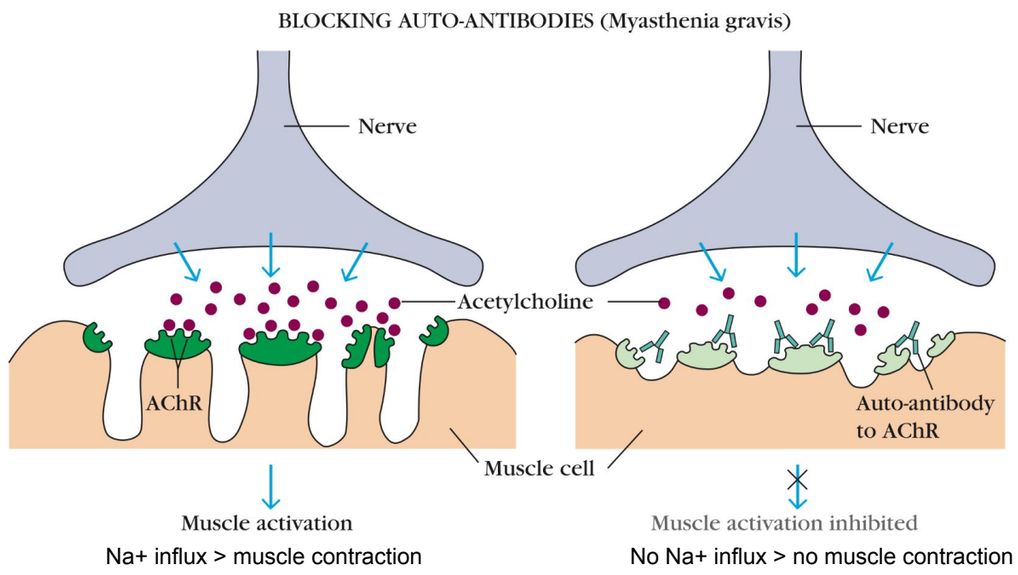
(يكون أجسام مضادة عملها شبيه بعمل الهرمون لتعمل عمله ويكون إنتاج مفرط)



2) Myasthenia gravis: (caused by **Blocking Antibodies**)

(The antibodies work on preventing the agonist from binding to the receptor leading to abnormal function).

- Clinically characterized 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.



Systemic Autoimmune diseases

1) Systemic lupus erythematosus (SLE):

Systemic lupus erythematosus is the prototype (the most common) of systemic autoimmune disorder

The characteristic “butterfly rash” is made worse by exposure to sunlight (photosensitive)

Lupus is a potentially **fatal** autoimmune disease

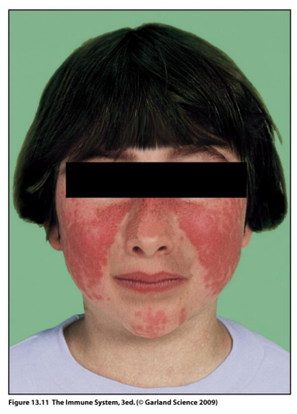


Figure 13.11 The Immune System, 3ed. (© Garland Science 2009)

Genetic + Environmental Factors > Pathogenic Autoantibodies (DNA/RNA + Protein complexes) >

Immune Complexes (antibody + antigen +complement) **> complement activation**

> • **Chemotaxins**

• **Leukocytes, mononuclear cells**

• **Inflammatory factors** (IL-4, IL-6, IL-10)

• **Destruction of cells**

Symptoms:

Constitutional fatigue
Myalgia
Fever
Weight change

Dermatological:
Malar rash
Discoid lesions
Hair loss
Oral ulcer
Raynauds’s
Nailfold, erthema
Livedo on hands/legs
Bullous rash on legs
Dermatitis on fingers

Cardiovascular:
Pericarditis
Verrucous endocarditis, emboli
CAD from steroids

CNS:
Cognitive defects, anxiety, depression, psychosis, seizures and neuropathies, cerebral punctate vasculitis

Hematological:
Anemia of chronic disease
Asymptomatic leukopenia
Thrombocytopenia
Lymphadenopathy

GIT:
Gastritis, peptic ulcer due to NSAID or corticosteroids
Pancreatitis, peritonitis and colitis due to SLE vasculitis
Lupoid hepatitis
Hepatosplenomegaly

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

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

Renal;
Glomerulonephritis

Investigations

1- 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 (Titer is a measurement of concentration of the antibodies (ratio)) (usually 1:160 or higher) in virtually all patients with SLE.

Significance of auto-antibodies is 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

2- Anti-double-stranded DNA titers (specific for SLE disease)

3- Complement Levels (CH50 (complement hemolysis)**, C3, C4)**

4- ESR (Erythrocyte sedimentation rate)

5- CRP (C-reactive protein) inflammatory marker

6- Complement Split products

7- Decreased complement C1q Why? Because as we said before we have continuous formation of immune

complexes (antigen + antibody) that activates the complement system (serum proteins) (specifically the classical pathway which contains C1q (note that q is subcomponent).

Treatment

1- NSAIDs (Non-steroidal anti-inflammatory drugs) to reduce the inflammatory symptoms

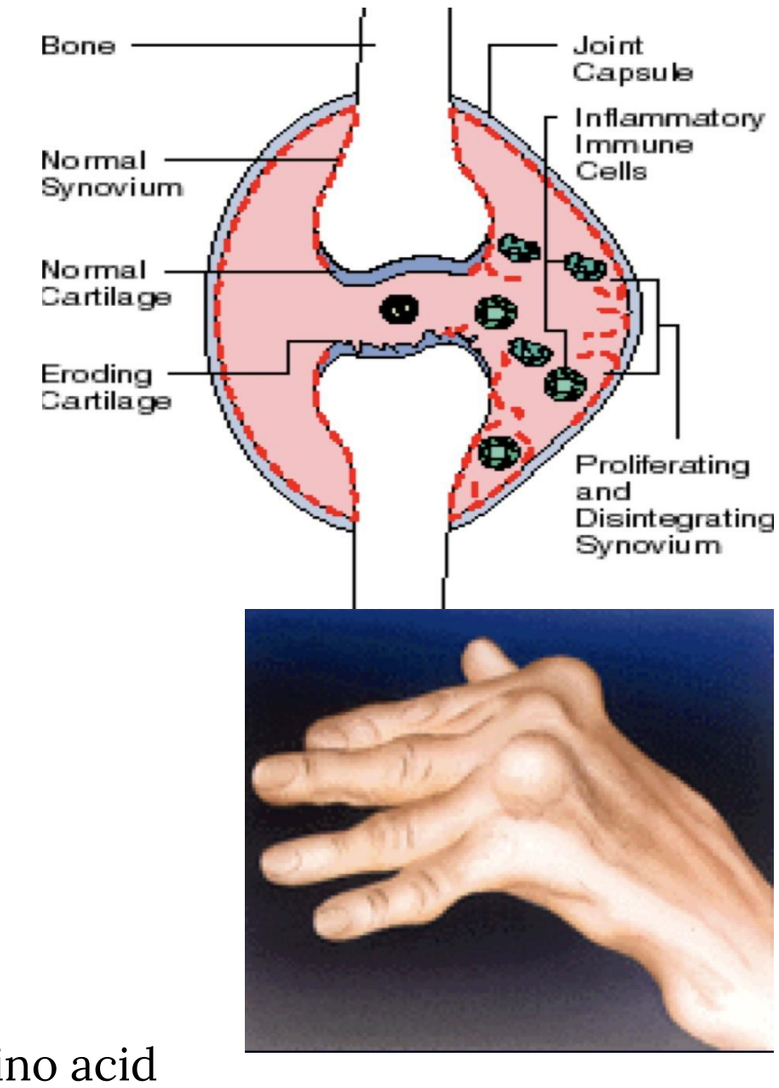
2- Antimalarials (Hydroxychloroquine) because they're also active in treating the symptoms of lupus

3- Immunosuppressive agents to decrease the harmful effect of auto-antibodies, but also decrease the natural immunity of the individual

2) Rheumatoid Arthritis:

- Rheumatoid arthritis is an autoimmune disease in which our immune system responds against an individual's own tissue, including:
  - Joints (weight bearing joints)
  - Tendons
  - bones

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



- Both prevalence and incidence are 2-3 times **greater in women** than in men. (because it's an autoimmune disease)

- The cause of rheumatoid arthritis is **not known (Idiopathic)** complex interplay among genotype, environmental triggers.

- **Genetic factors: HLA-DR B1 locus** alleles that contain a common amino acid motif (pattern) (QKRAA) in the HLA-DRB1 region, termed the shared epitope (the part of specific antigen to which an antibody attaches itself), confer (تمنح) particular susceptibility.

Pathogenesis:

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

(Type III hypersensitivity reaction)

Inflammatory cells produce pro inflammatory cytokines/ TNF-α, IL-1 that induce the secretion of metalloproteinases (has a role in remodeling cytokines & chemokines & extracellular remodeling enzymes.); which are known to cause joint destruction

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

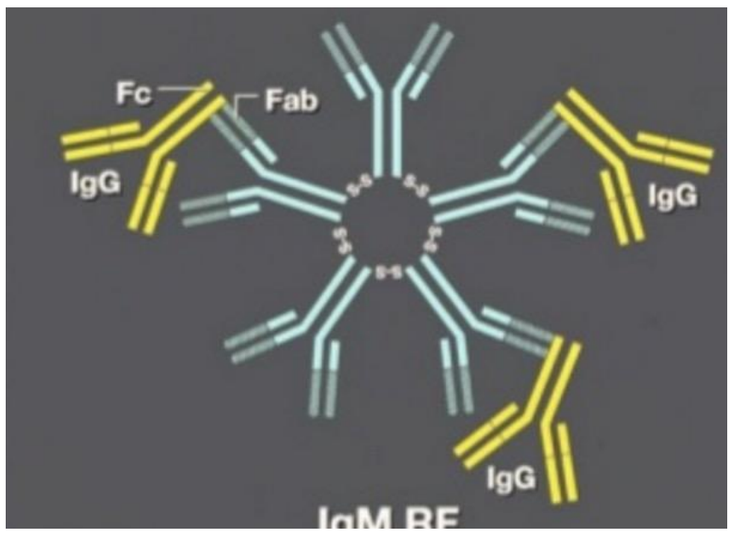
There is a lack of tolerance to citrullinated proteins and the appearance of autoantibodies directed against citrullinated proteins. (Anti-citrullinated protein antibodies (ACPAs) are autoantibodies to an individual's own proteins they are directed against peptides and proteins that are citrullinated. They are present in the majority of patients with rheumatoid arthritis.)

In rheumatoid arthritis, many individuals produce another group of autoantibodies known as **rheumatoid factor**

These antibodies react with determinants in the **Fc region of IgG**

Rheumatoid Factor:

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



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 (treatment):

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

So Rheumatoid Arthritis is an autoimmune disease initiated by an immune complex that induces an inflammatory response

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**

Useful videos

Graves Disease : https://www.youtube.com/watch?v=mad4hZqXJgE

SLE : https://www.youtube.com/watch?v=0junqD4BLH4

Rheumatoid Arthritis :

https://www.youtube.com/watch?v=nYjzl3Xc_0E

Myasthenia Gravis :

MCQs:

1-An autoimmune disease that affects the blood:

a) Pemphigus vulgaris b) Vitiligo

c) Multiple sclerosis d) Pernicious anemia

2- Graves' disease is:

a) An organ specific autoimmune disease and mediated by blocking autoantibodies.
b) A systemic autoimmune disease and mediated by blocking autoantibodies.
c) An organ specific autoimmune disease and mediated by stimulating autoantibodies.
d) A systemic autoimmune disease and mediated by stimulating autoantibodies.

3- In myasthenia gravis, which of the following is responsible for interacting with the postsynaptic AChR at the nicotinic neuromuscular junction (NMJ):

a) IgM b) IgG c) IgA D) IgD

4- In myasthenia gravis, the reduction in the number of functional AChR receptors by decreasing complement mediated degradation of receptors:

a) True b) False

5- The treatment\s for SLE:

a) NSAIDs b) Antimalarials (Hydroxychloroquine)

c) Immunosuppressive agents d) a & b & c

6-which of the following AG has a significance of autoantibodies in SLE by 70% and is associated with nephritis:

a) ds DNA b) Histones
c) Anti-neuronal d) Anti-ribosomal

7- Rheumatoid arthritis (RA) affects peripheral joints is characterized by:

a) Infection in the joint
b) Inflammation of the synovium

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

a) True
b) False

1-d
2-c
3-b
4-b
5-d
6-a
7-b
8-a

MEDICINE
KING SAUD UNIVERSITY

Contact us

Email: Immunology436@gmail.com

Twitter: Immunology436

IMMUNOLOGY
436's TEAMWORK

Team Leaders

Ghaida Alsaeed

Basel almeflh

Team members

Aroob Alhuthail

Ghada Alskait

Hanin Bashaikh

Rawan Alwadee