Musculoskeletal block

Autoimmune Diseases

Lecture 2

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Objectives:

I. **To know that the inflammatory processes in auto immune diseases are mediated by hypersensitivity reactions (type II, III and IV).**

II. **To know that autoimmune diseases can be either organ specific or may be generalized involving many organs or tissues.**

III. **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 (IgG antibodies to tissue antigens) Type III (IgG Immune complex) and Type IV (Delayed hypersensitivity) (Cell Mediated immunity) hypersensitivity reactions.

Autoimmune diseases are classified into:

1- Organ- specific autoimmune disease

2- Systemic autoimmune disease.

Note that in some cases the disease can be in gray zone where it affects both (systems and specific organs).

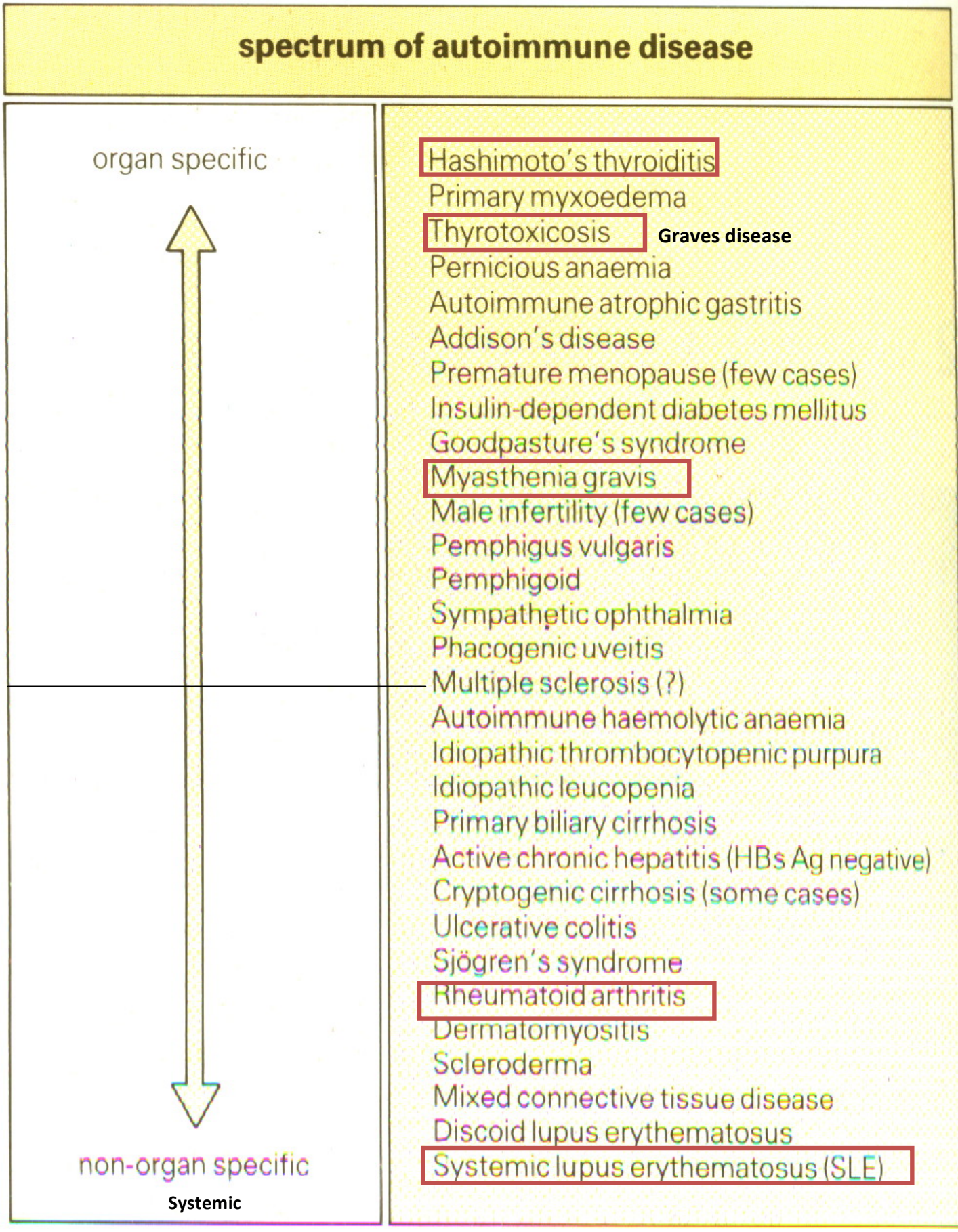
Down in boxes you will find the diseases the doctor focused on.

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

Delayed type hypersenstivity

Remember last lecture the doctor talked about our body response to self-antigens by either auto reactive B cells or in other words auto- antibodies and by auto reactive T cells. That does not mean that each disease noted in the table above has a specific response it depends according to the condition, also in some cases both auto reactive T-cells and B-cells overlap and work together.



At the top of the spectrum, the diseases are organ specific and at the bottom the diseases are systematic.
In the middle we have the gray zone where 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

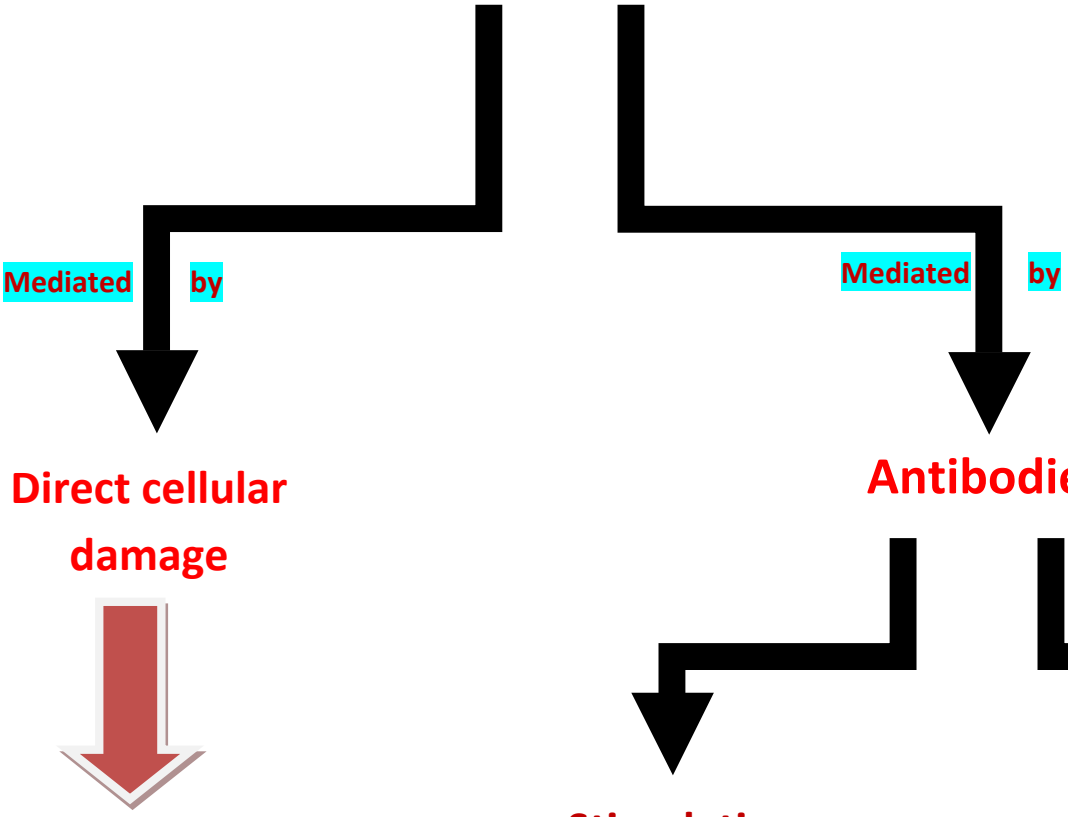
Multiple Organs, Musculoskeletal System

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

Based on what the doctor said in the lecture you only have to know the systems affected by autoimmune diseases

1- Organ specific

Autoimmune Disease



Example : Hashimoto's thyroiditis

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

Example : Graves' disease

Autoantibodies binding to the TSH receptors on thyroid cells

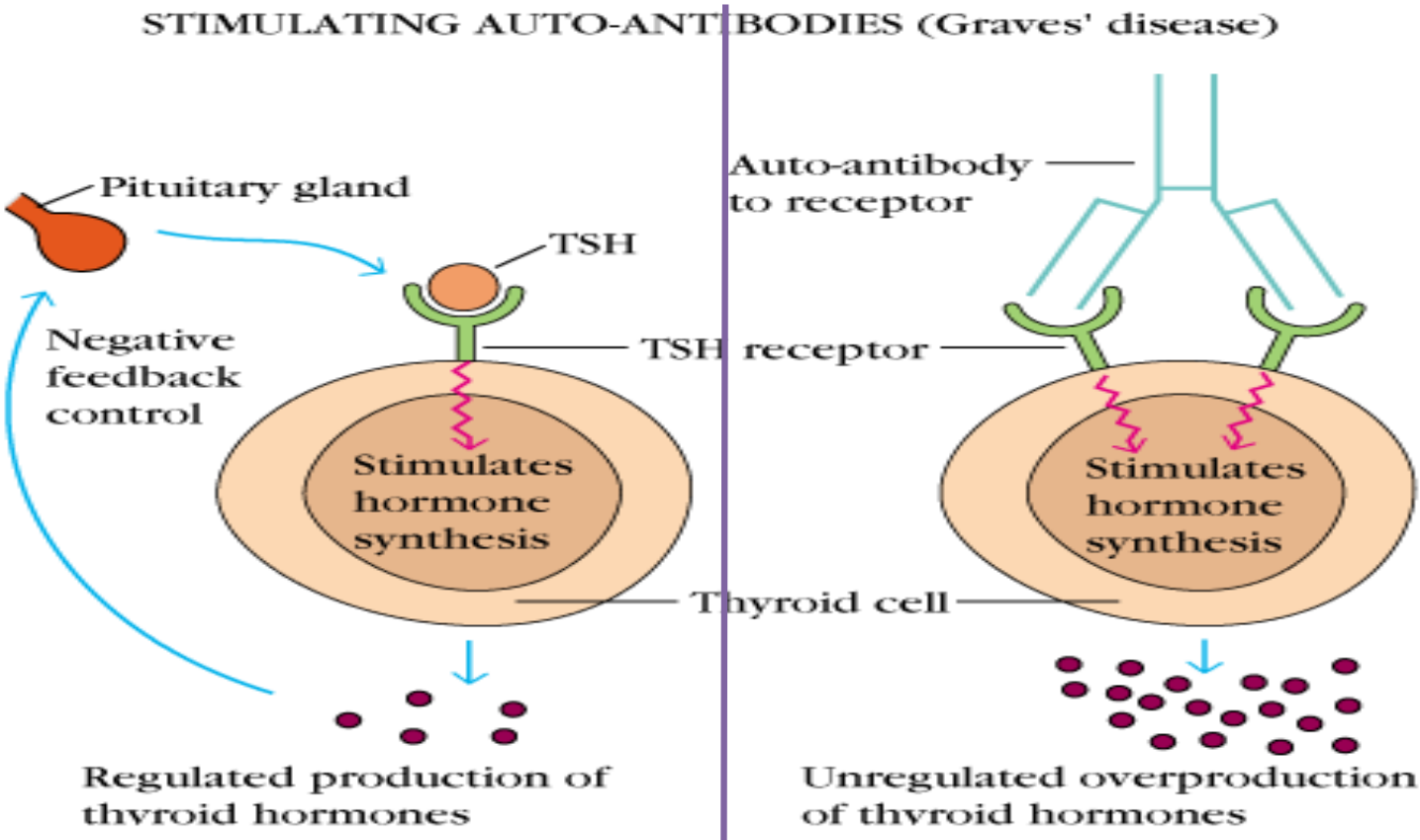
Blocking antibodies: Ab that blocks the receptors of the cell (inhibition) →preventing the agonist to do its work.

Example : Myasthenia Gravis

Autoantibodies blocking the acetylcholine receptors

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**



Pituitary gland secretes Thyroid Stimulating Hormone (TSH) when thyroid hormones are needed→TSH will bind to thyroid cells' receptors→stimulate the gland to secrete thyroid hormones.

When the body does not need thyroid hormones, pituitary gland will stop the secretion of TSH, which will end the stimulation of thyroid hormones and secretion stops.(normal)

In Graves disease: an auto antibody will mimic TSH and stimulate the thyroid gland. There is no termination (no negative feedback which is the primary reason for Graves' disease)→uncontrolled production of thyroid hormone, which will lead to over-stimulation of the thyroid gland.

*Example of molecule mimicry (2nd mechanism of proposed mechanisms) from last lecture.

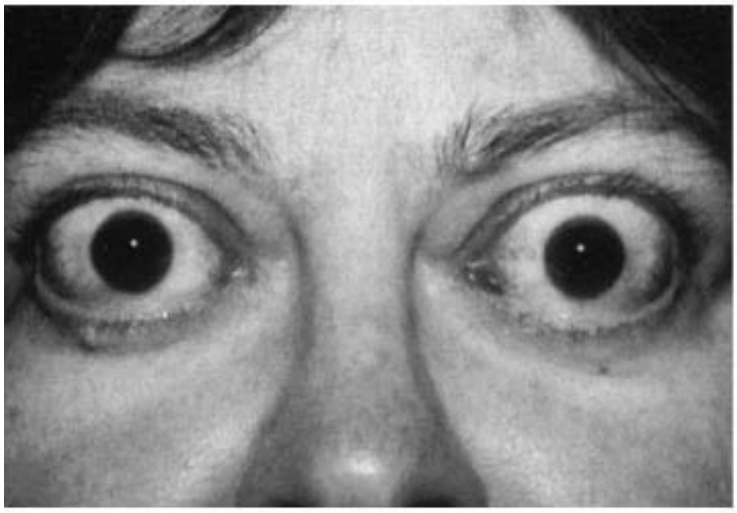


Fig. 1A

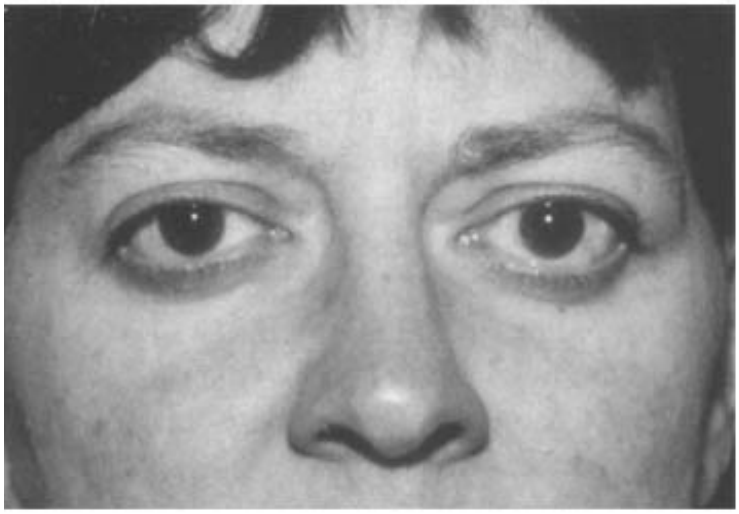


Fig. 1B

- **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**

Protrusion of the eye can happen in Graves' disease because of the proliferating tissue below the retina in the eye that causes the eye to look prominent, note that in Myasthenia gravis we have ptosis, which is different than protrusion of the eye in Graves' disease.

Graves' disease: symptoms associated with Graves' disease can be treated (not the auto immune disease (Graves' disease) itself) by antithyroid, radioactive iodine or surgery.

Myasthenia gravis

- **Clinically characterized by weakness and fatigability on sustained effort** جهد مستمر
- **Ab directed against acetylcholine receptor (AChR)**
- **IgG Antibodies 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.**

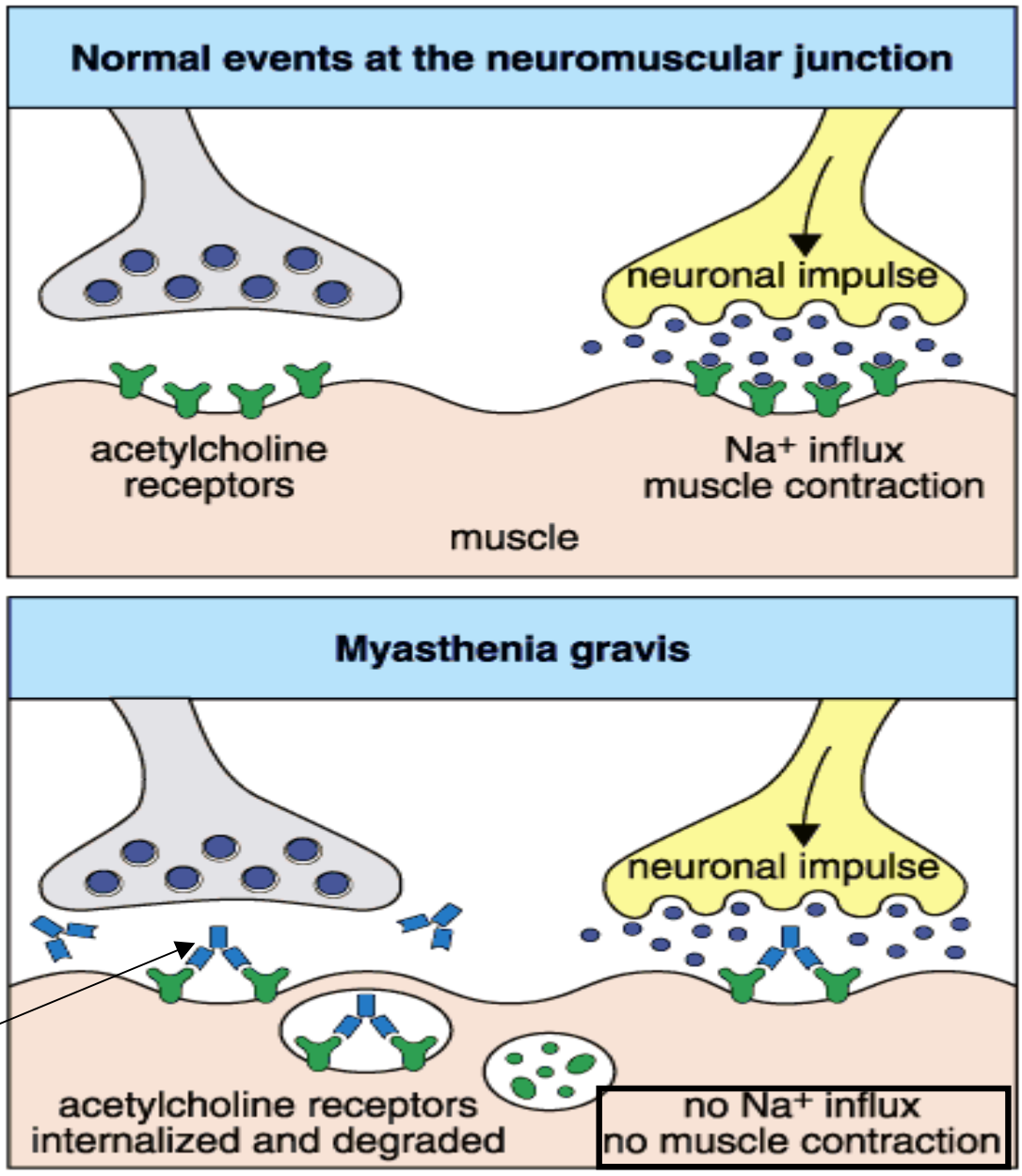


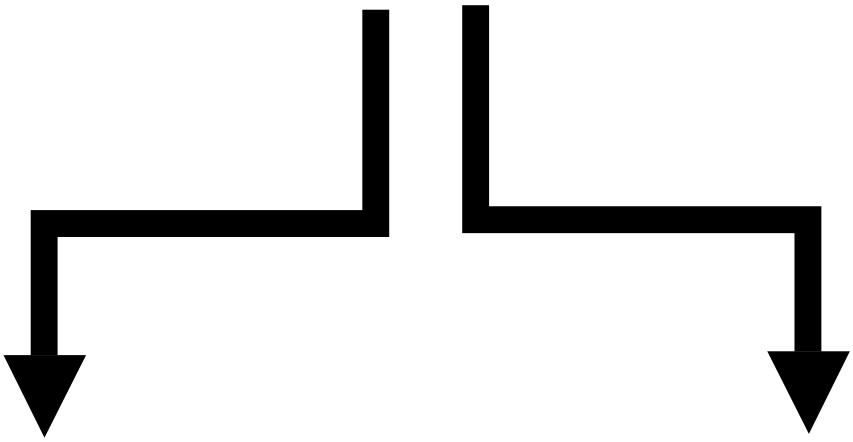
Fig 13.10 © 2001 Garland Science

In myasthenia gravis we have two scenarios depends on the severity of the disease:

1.AchR are totally degraded (Remember in foundation block when we talked about complement system activation. Here we have classical pathway that will occur when antigen binds to an antibody so the complement system will be activated).

2.AchR are totally occupied by autoantibodies.

2.Systemic autoimmune disease



Systemic lupus erythematosis (SLE)

Rheumatoid Arthritis

Systemic lupus erythematosis (SLE):

- Systemic lupus erythematosis is the most common autoimmune disorder

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

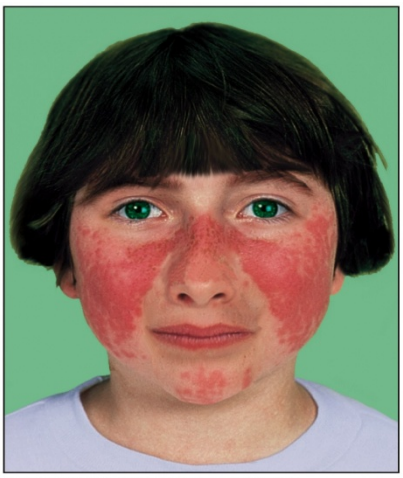
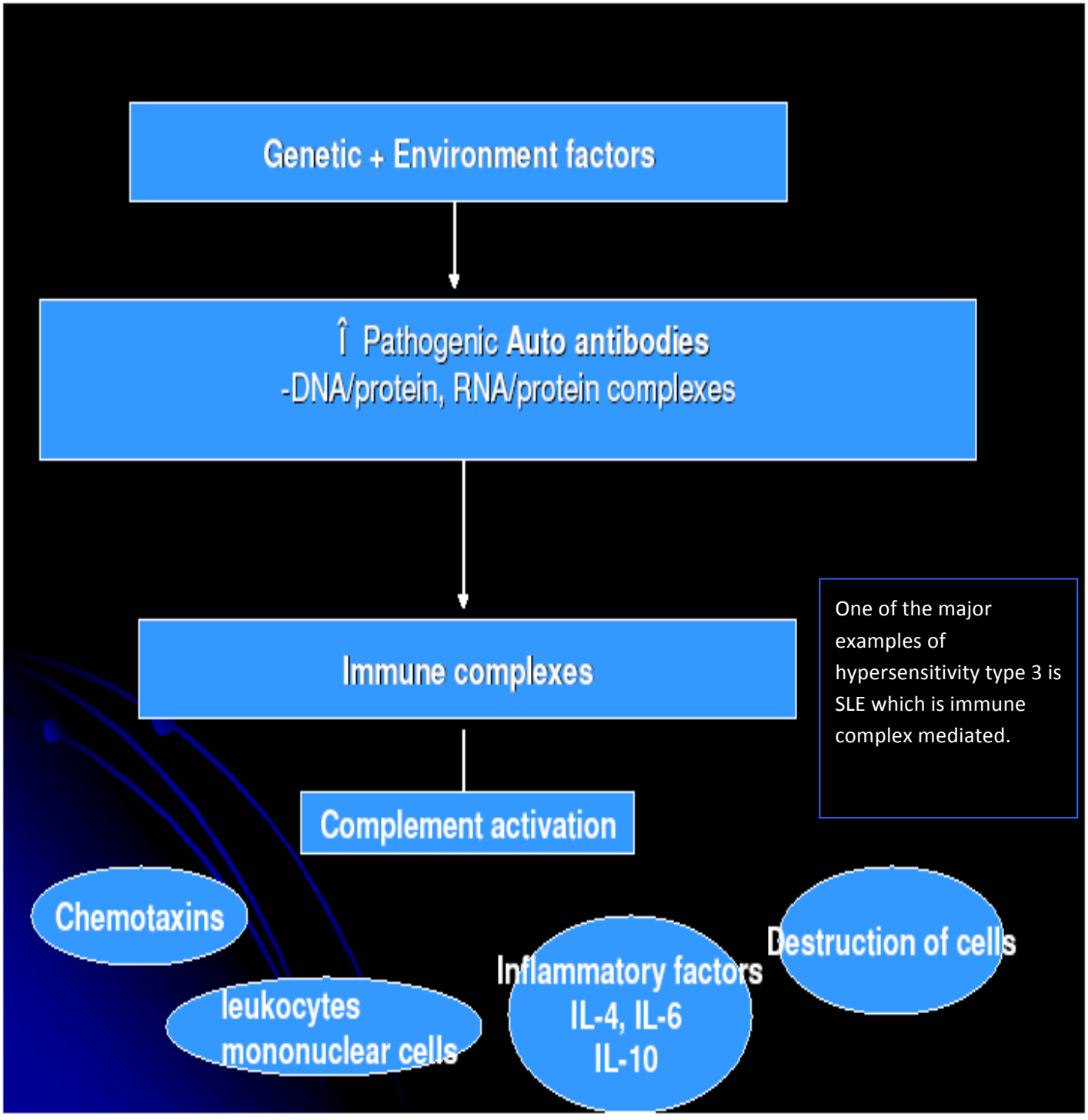


Figure 13.11 The Immune System, 3ed. (© Garland Science 2009)

- Lupus is a potentially fatal مميت autoimmune disease (One of the major things that happens as a side effect for SLE is renal toxicity which is fatal)

Systemic lupus erythematosis (SLE):



Systemic lupus erythmatosis (SLE)

Auto antibodies:

- **The anti-nuclear antibody (ANA) test is the best screening test for SLE (Screening test for all autoimmune disease not differential test for SLE only which basically measures the amount of ANA in the circulation) 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.**

In case of positive ANA test and the doctor suspected that the patient is affected by SLE he will most probably ask for Anti double stranded DNA titers test because as you can see it is the most self antigen associated 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 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 (complement hemolysis), C3, C4)**
- **ESR (Erythrocyte sedimentation rate)**
- **CRP (C-reactive protein) inflammatory marker**
- **Complement Split products**
- **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).**

Golden Role in treatment of autoimmune diseases that the disease itself can't be treated those are the drugs used to deal with the symptoms only. Why?? **Because as we said in the previous lecture autoimmune diseases have proposed mechanism) .**

Treatment

- **NSAIDs**
- **Antimalarials (Hydroxychloroquine)**
- **Immunosuppressive agent that will make the immune system weaker (compromised) as a side effect even in some cases it can lead to cancer cause many of the cancer patients have a very weak immune system.**

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**

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**

Rheumatoid Arthritis

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** (IgG here is the self-antigen)

The *classic*

rheumatoid factor is an

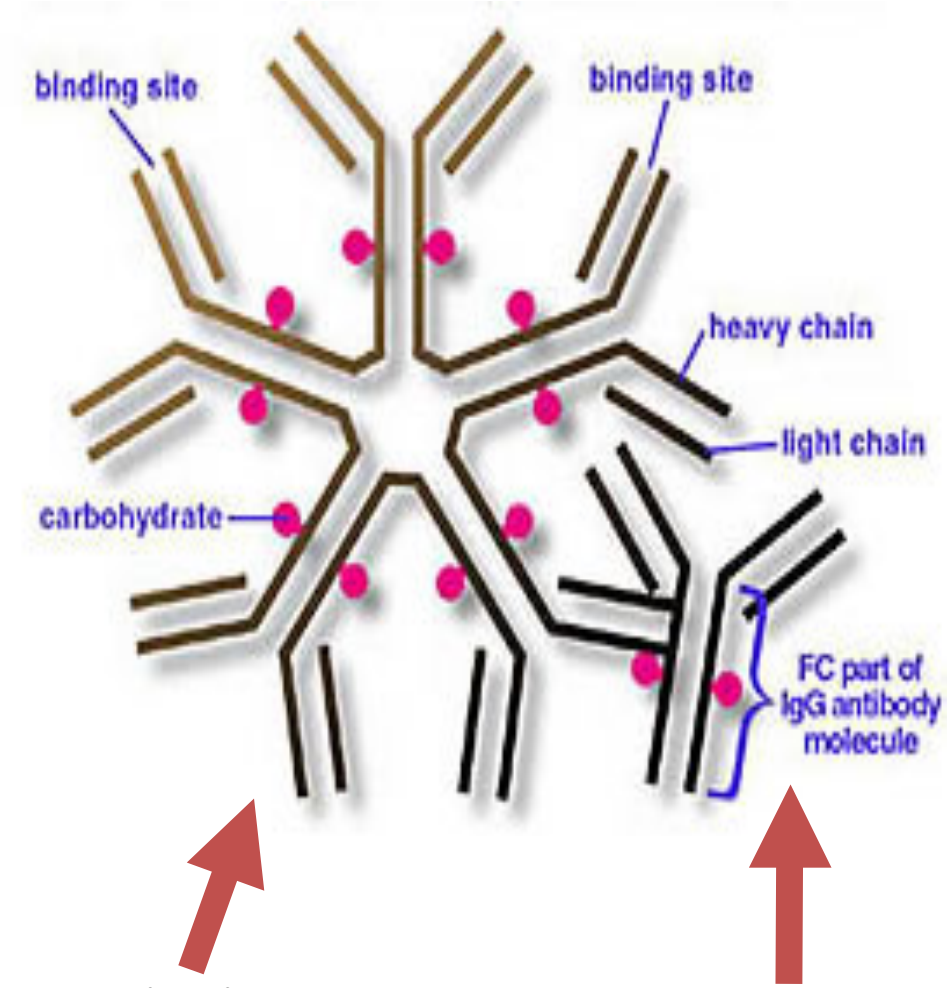
IgM antibody

with this kind

of reactivity.

In some cases we can have also IgA and IgG (not classical).

Remember: that type 3 hypersensitivity depends on IgG and in some cases IgM like this case.



IgM (penta)

Rheumatoid Arthritis

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

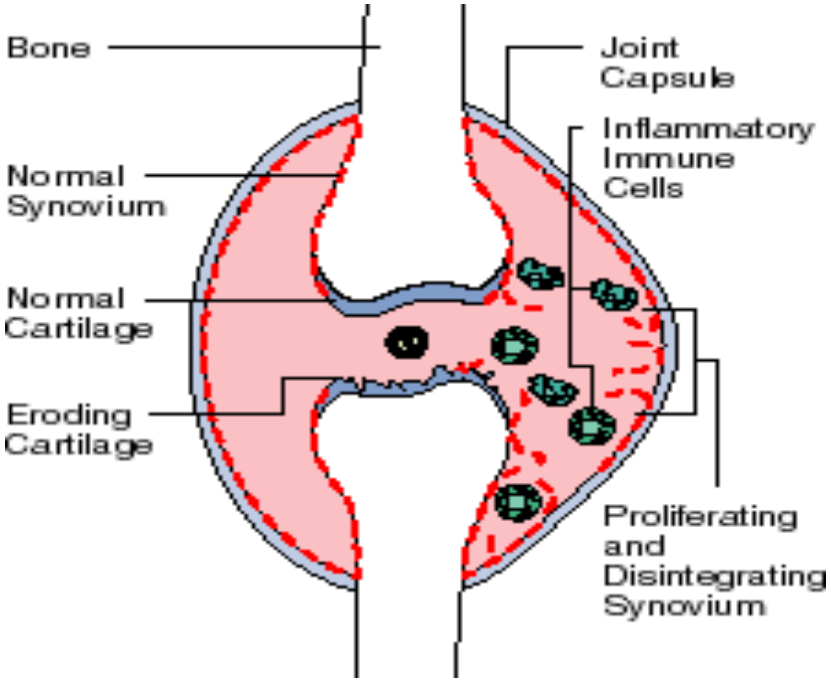
- The macrophages engulf the immune complexes and then release TNF and other pro-inflammatory cytokines e.g., IL-1

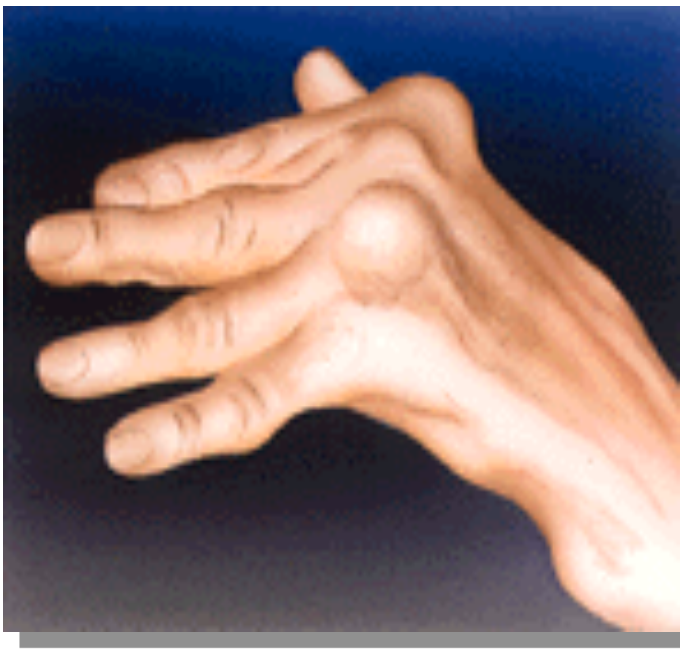
- TNF induces the secretion of metalloproteinases; which are known to cause joint destruction

- T cell activation due to unknown antigens also contributes to the inflammation in Rheumatoid arthritis.

Rheumatoid arthritis

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





Rheumatoid Arthritis

Treatment and Prognosis

Medications:

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

لا تنسونا من دعواتكم ..