Autoimmune Diseases

Immunology Unit
Department of Pathology
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Reference

Kuby Immunology 7th Edition 2013

Chapter 16 Pages 525-531

Objectives

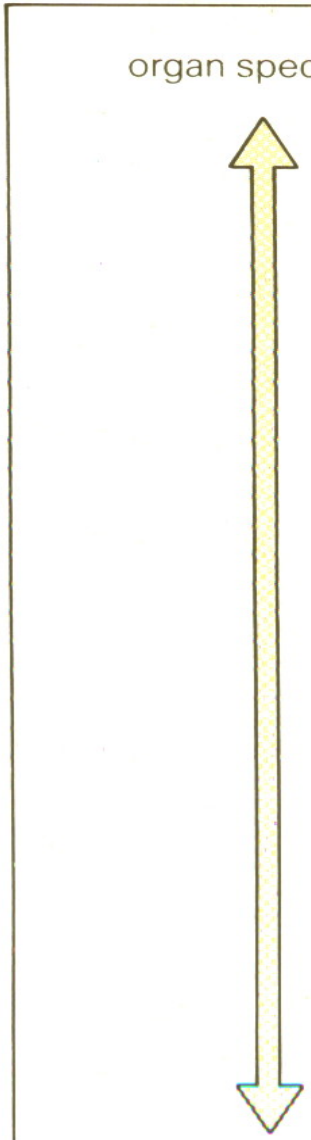
- To know that the inflammatory processes in auto immune diseases are mediated by hypersensitivity reactions (type II, III and IV)
- To know that autoimmune diseases can be either organ specific or may be generalized involving many organs or tissues
- To understand that the manifestations of autoimmune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

spectrum of autoimmune disease



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

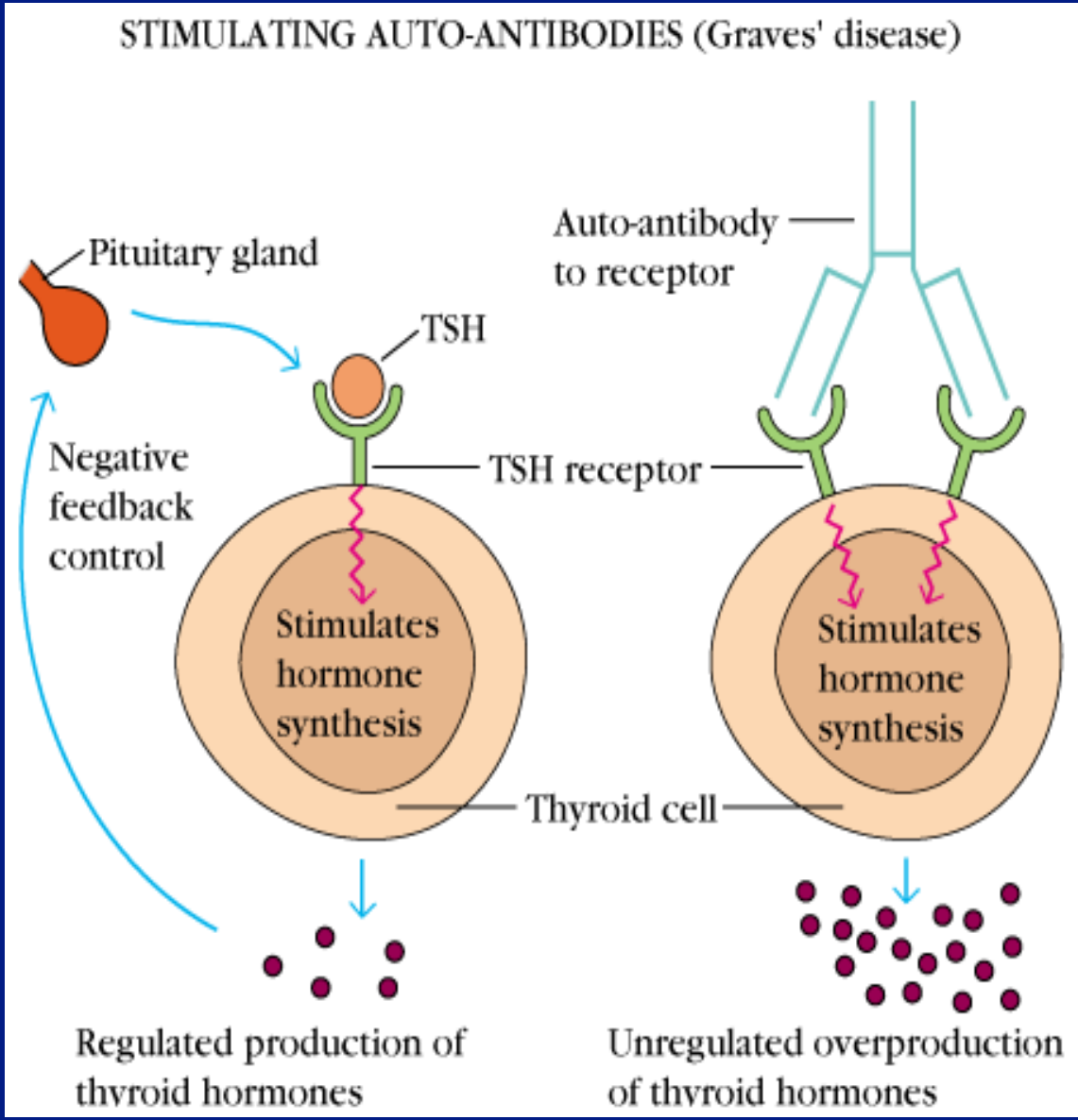
Organ Specific Autoimmune Diseases

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



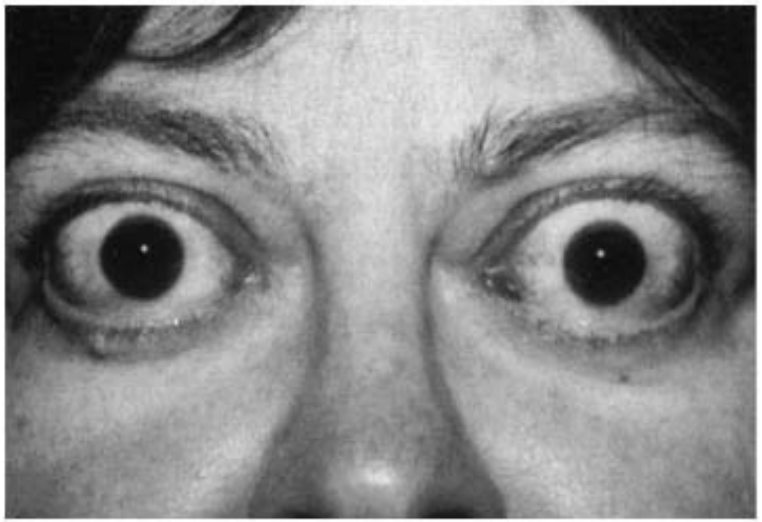


Fig. 1A

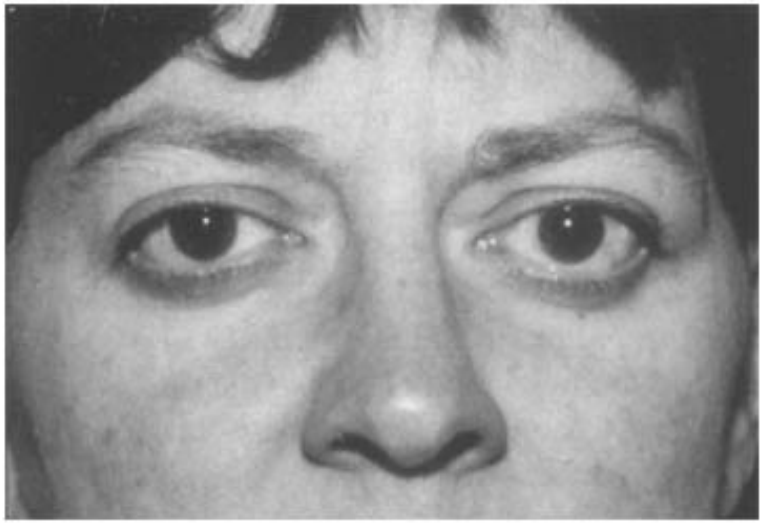


Fig. 1B

- 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

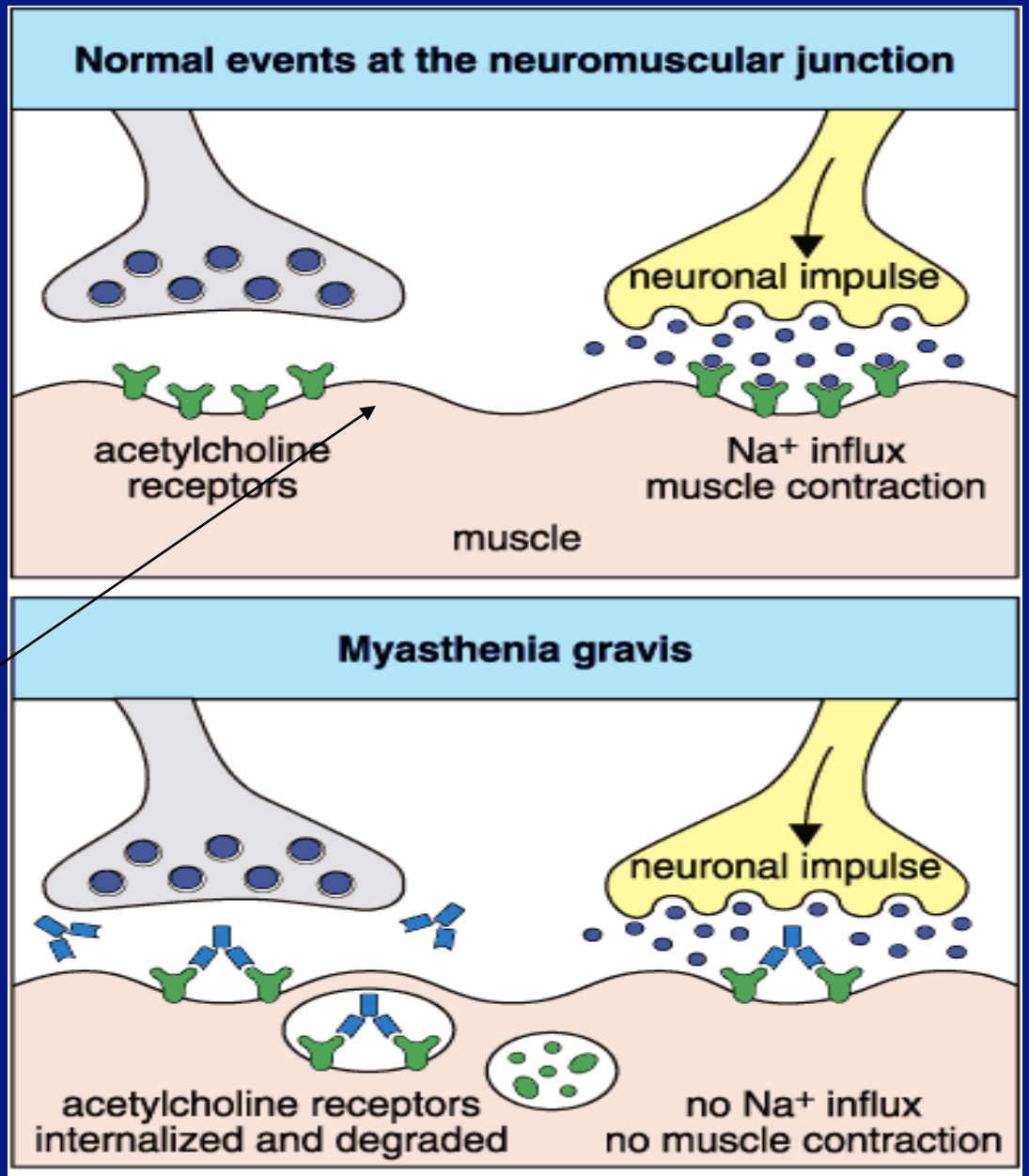


Fig 13.10 © 2001 Garland Science

Motor end-plates of muscles

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

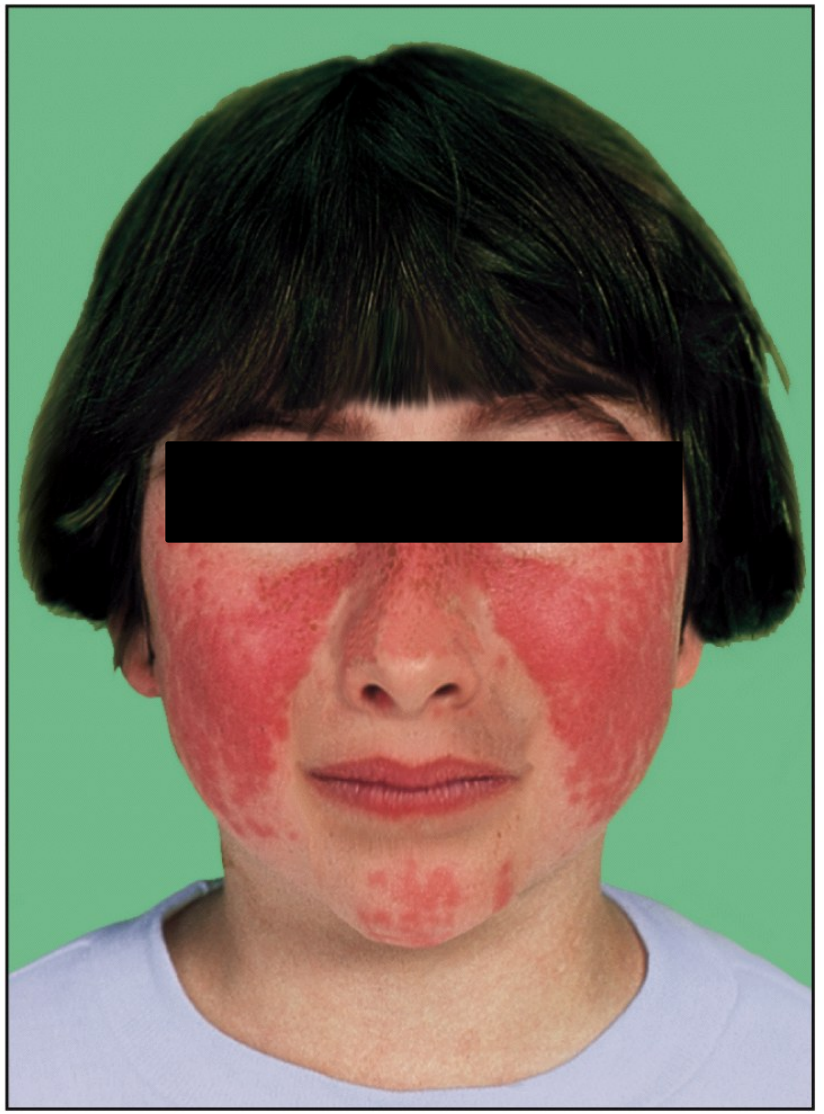
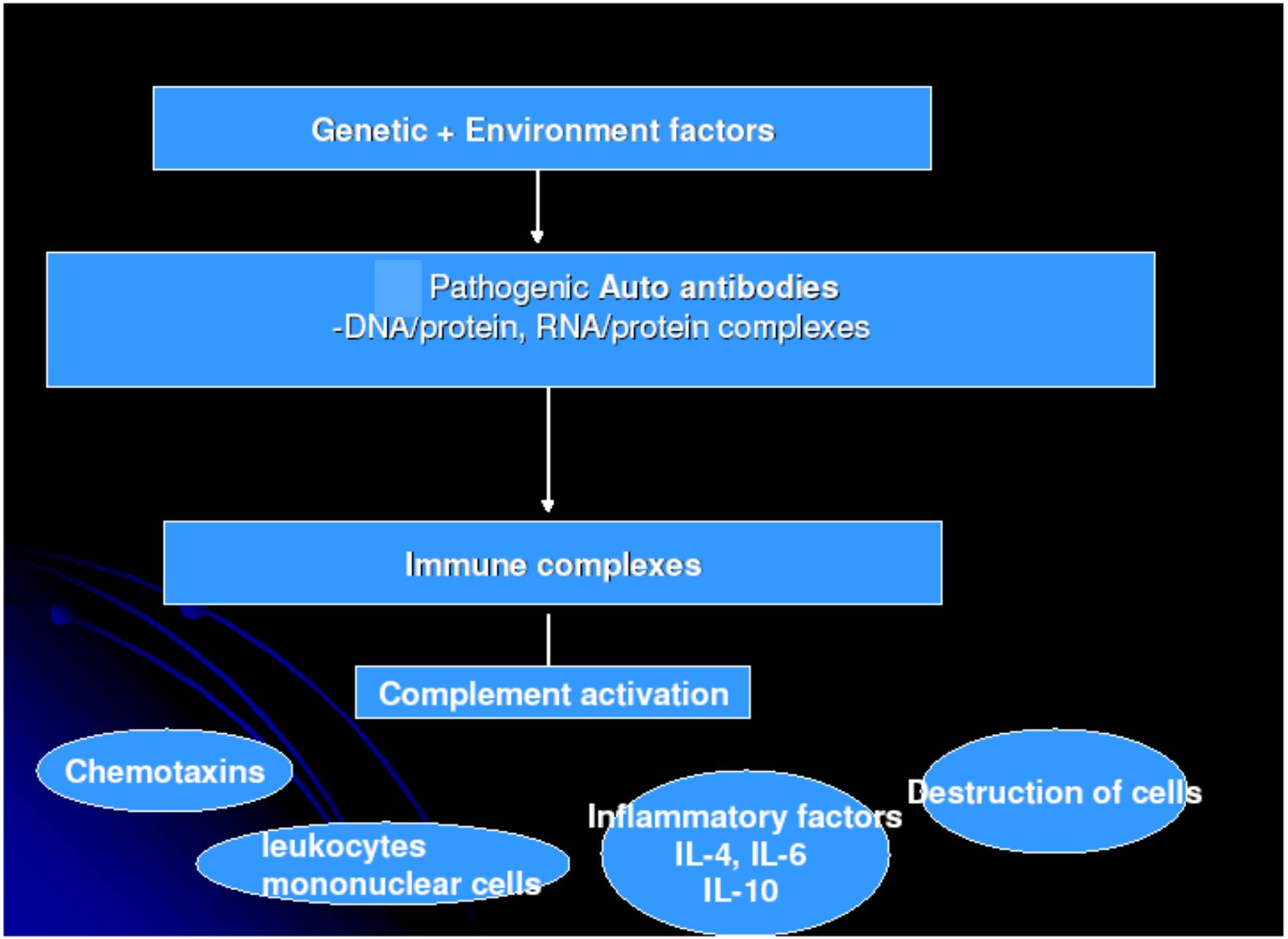


Figure 13.11 The Immune System, 3ed. (© Garland Science 2009)


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:

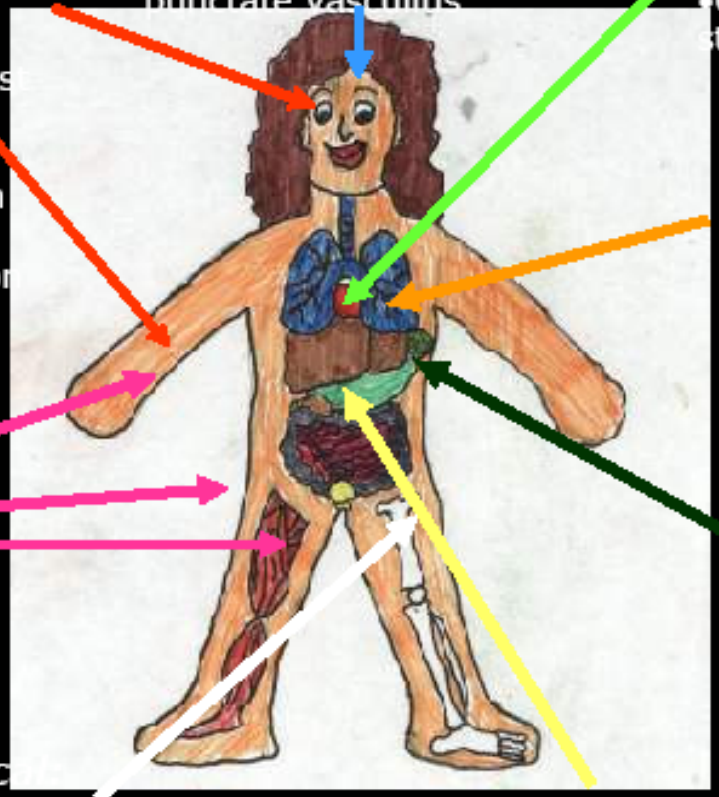
Weight change:

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 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:

•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

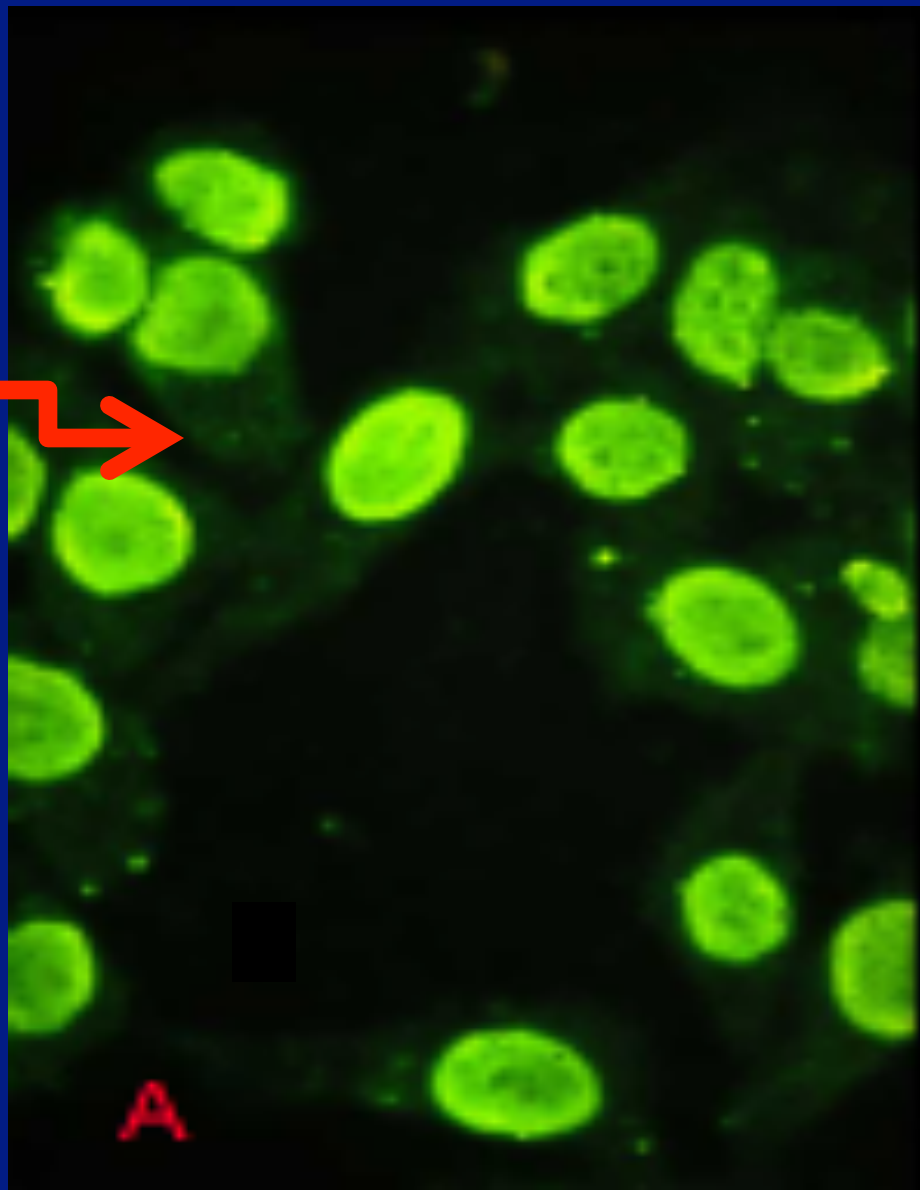
•Lupoid hepatitis

•hepatosplenomegaly

Auto antibodies

- The anti-nuclear antibody (ANA) test is the best screening test for SLE and is determined by **immunofluorescence**

- 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.

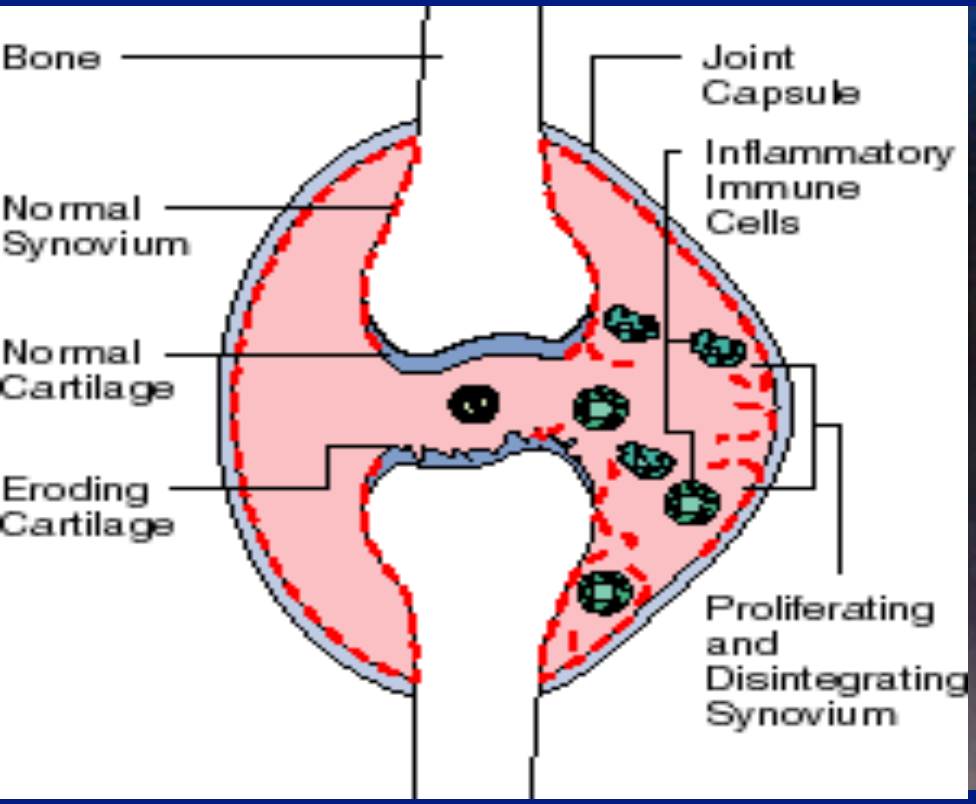
Rheumatoid Arthritis (*Contd.*)

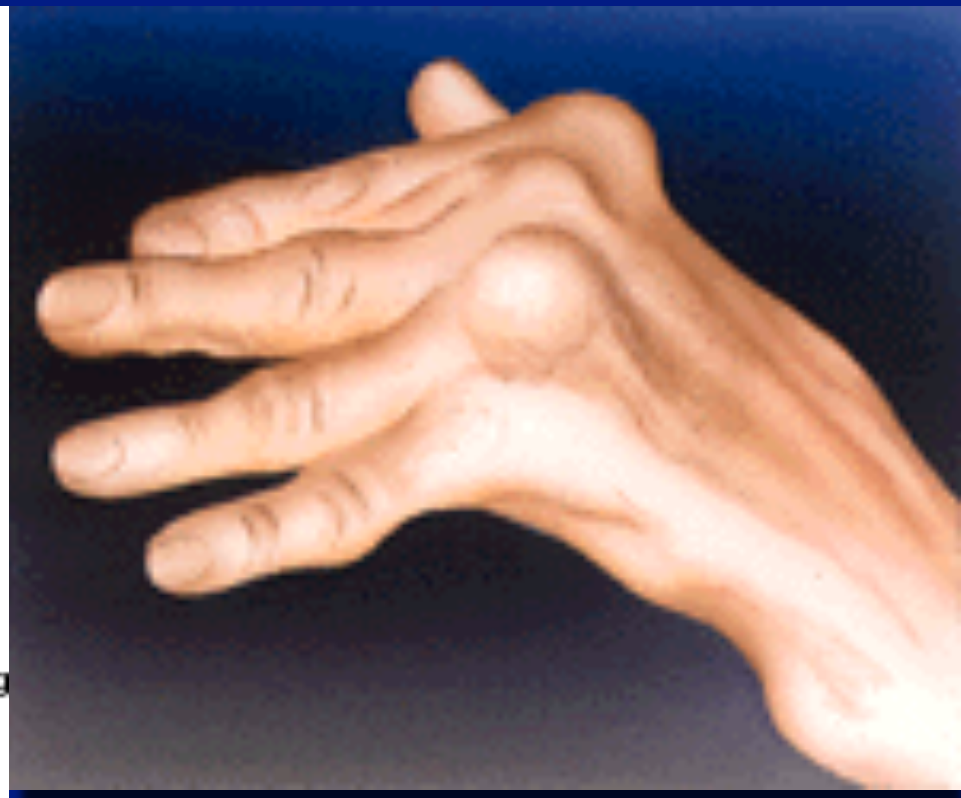
- **Both prevalence and incidence are 2-3 times greater in women than in men.**

- **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/ TNF-α, 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

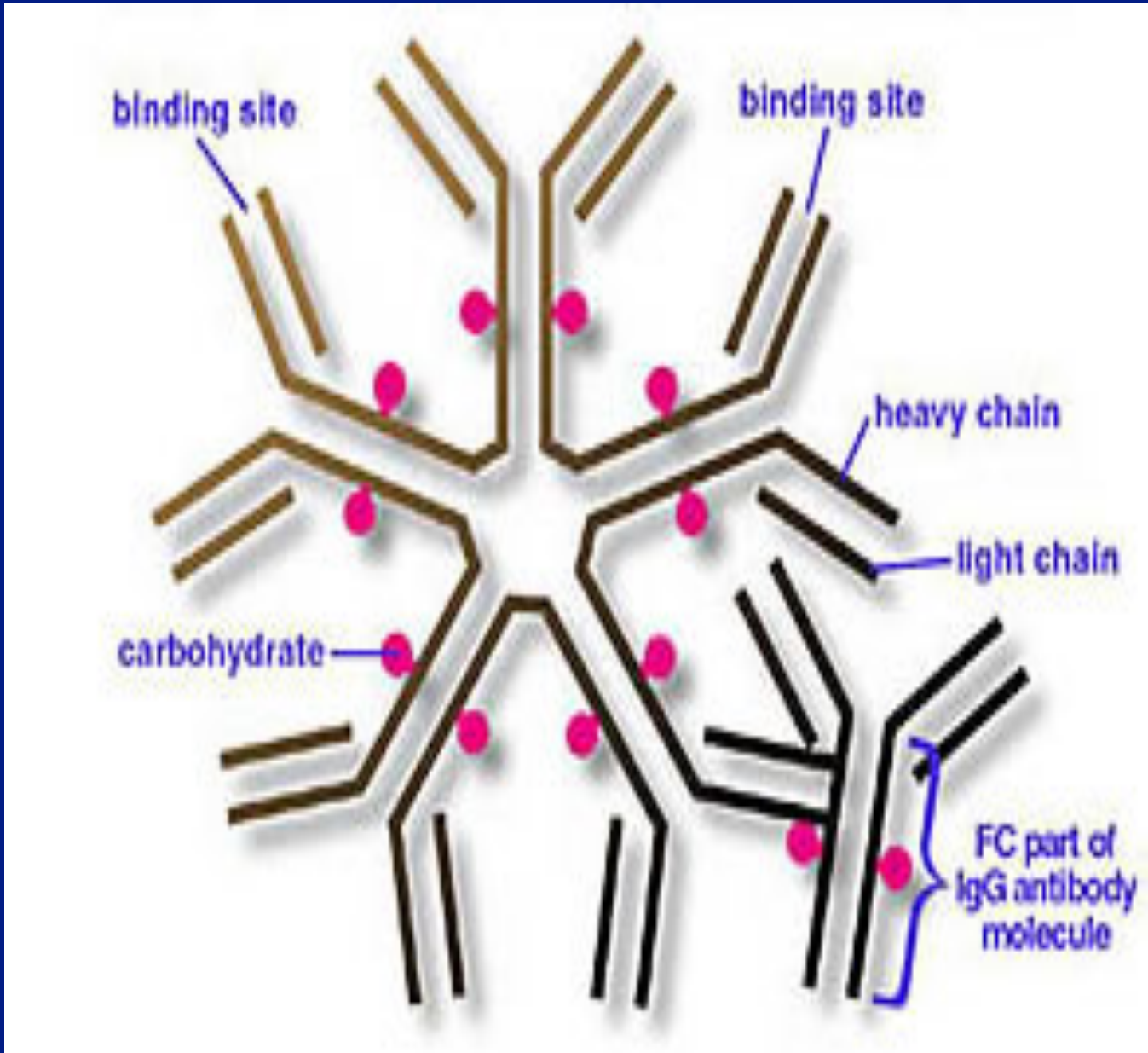
(Type III hypersensitivity reaction)

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

These antibodies react with determinants in the F_C 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