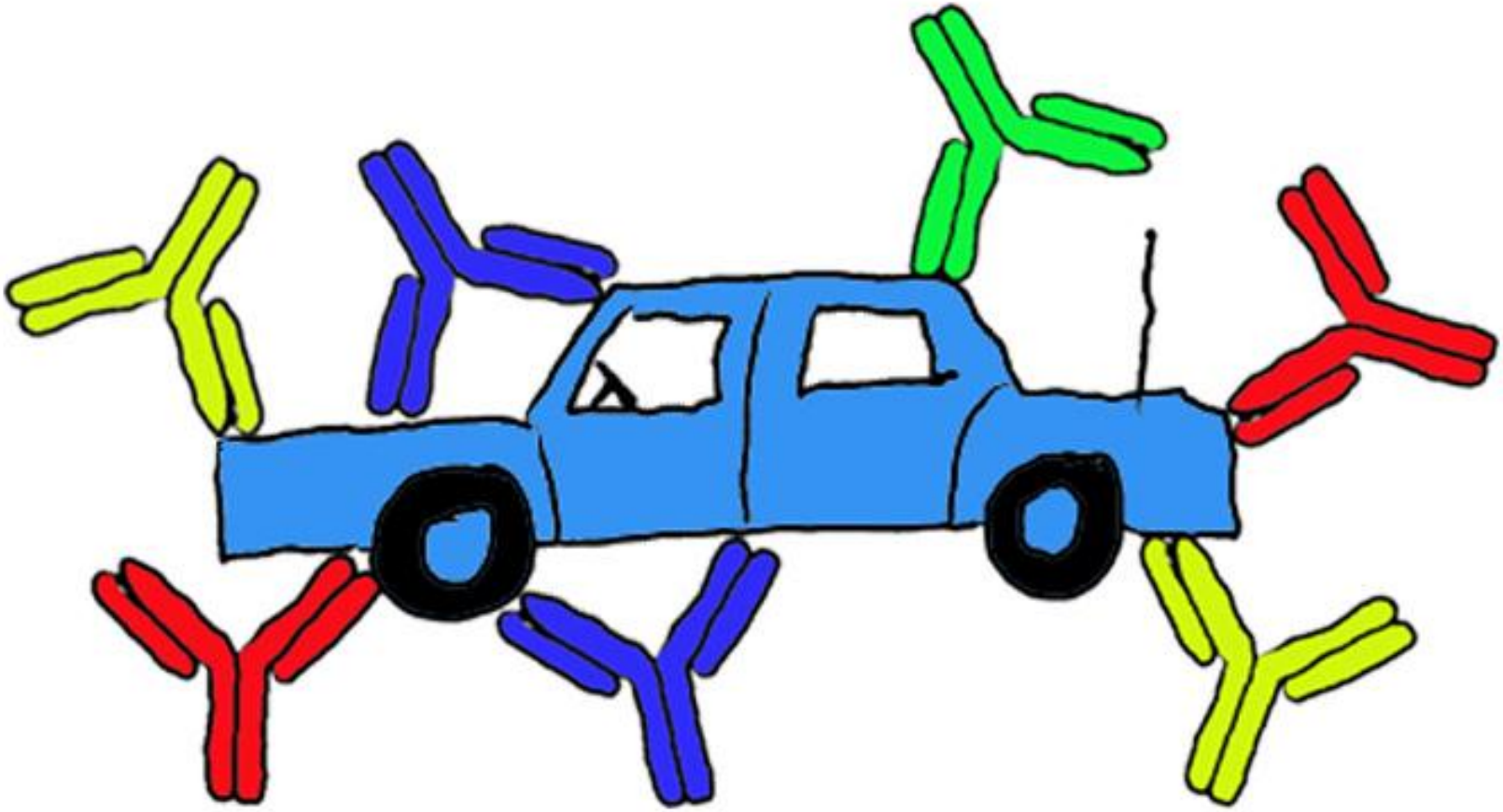
AUTOIMMUNITY AND AUTOIMMUNE DISEASES

DISORDERS OF THE IMMUNE SYSTEM

* Immunodeficiency
  - Too little
* Hypersensitivity
  - Too much
* Autoimmunity
  - Misdirected

AUTOIMMUNITY AND AUTOIMMUNE DISEASE

* Autoimmunity
  - Adaptive immune response specific for self-antigens (autoantigens)
  - Exists due to random generation of TCR and BCR
  - Represents failures of mechanisms that maintain self-tolerance in TCR and BCR
* Autoimmune disease
  - Disease in which the pathology is caused by immune responses to self antigens of normal cells and organs



Autoimmunity

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AUTOIMMUNITY

* Paul Ehrlich (1854 – 1915)
  * In 1906 predicted existence and coined term
* Referred to as
  * Horror autotoxicus
* Medical community
  * Autoimmunity was not possible

AUTOIMMUNE DISEASES

* A Group of 60 to 80 chronic inflammatory diseases with genetic predisposition and environmental modulation

* Prevalence of 5% to 8% in US

* Prevalence is greater for females than males
  - 75% of cases
  - 4th largest disease class in women

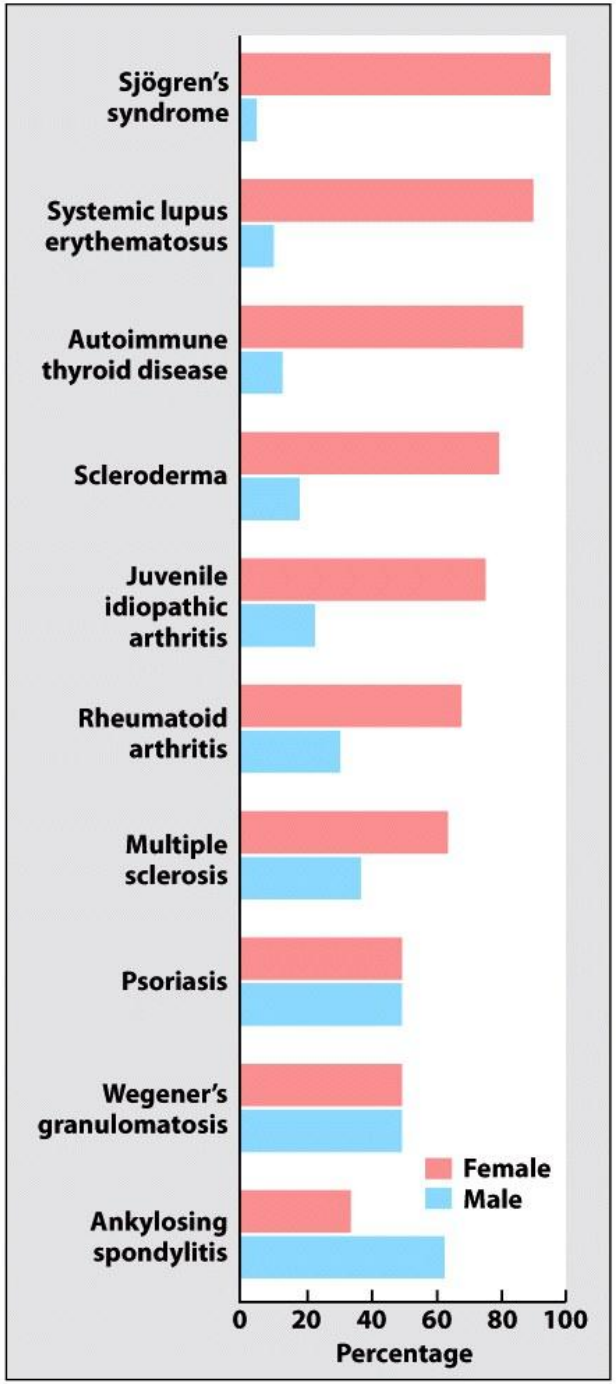


Figure 13.18 The Immune System, 3ed. (© Garland Science 2009)

RISK FACTORS FOR AUTOIMMUNE DISEASES

* Genetic (HLA type)
  * HLADR2 with SLE and MS
  * HLADR3 with Sjogren's syndrome, MG, SLE and DM-1
  * HLADR4 with RA and DM-1
* Female
  * X chromosome inactivation
* Environmental
  * Smoking with RA
* Drugs
  * Procainamide, minocycline, quinidine with DILE
* Infections

HLA TYPE AS RISK FACTOR FOR AUTOIMMUNE DISEASES

* Model 1
  - Certain HLA alleles are better at presenting pathogen peptides which resemble self peptides to T cells

* Model 2
  - Certain HLA alleles are less efficient at presenting self peptides to developing T cells
  - Results in failure of negative selection

CLASSIFICATION OF AUTOIMMUNE DISEASES

* Organ Specific
  - Insulin dependent diabetes mellitus (IDDM) - Type I
  - Graves' disease
  - Goodpasture's syndrome
  - Myasthenia gravis
  - Multiple sclerosis
* Systemic
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Sjogren's syndrome

CLASSIFICATION OF AUTOIMMUNE DISEASES BY EFFECTOR MECHANISMS

* Type II
  - Antibody against cell-surface or extracellular matrix antigens (Type II hypersensitivity)
* Type III
  - Formation and deposition of immune complexes (Type III hypersensitivity)
* Type IV
  - T cell mediated (Type IV hypersensitivity)

Autoimmune disease	Autoantigen	Consequence
Antibody against cell-surface or matrix antigens (type II)		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes anemia
Autoimmune thrombocytopenia purpura	Platelet integrin gpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Graves' disease	Thyroid-stimulating hormone receptor	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Progressive weakness
Insulin-resistant diabetes	Insulin receptor (antagonist)	Hyperglycemia, ketoacidosis
Hypoglycemia	Insulin receptor (agonist)	Hypoglycemia

Figure 11-1 part 1 of 3 The Immune System, 2/e (© Garland Science 2005)

Autoimmune disease	Autoantigen	Consequence
Immune-complex disease (type III)		
Subacute bacterial endocarditis	Bacterial antigen	Glomerulonephritis
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, arthritis

Autoimmune disease	Autoantigen	Consequence
T cell-mediated disease (type IV)		
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Multiple sclerosis	Myelin basic protein, proteolipid protein	Brain degeneration. Paralysis
Celiac disease	Gluten modified by tissue transglutaminase	Malabsorption of nutrients Atrophy of intestinal villi

Figure 11-1 part 3 of 3 The Immune System, 2/e (© Garland Science 2005)

TYPE II AUTOIMMUNE DISEASES

* IgG antibody is primary effector mechanism

* Attack more common
  - Cell surface antigens
    - Erythrocytes, neutrophils, platelets
  - Cell surface receptors
    - TSH, acetylcholine, insulin

* Attack less common
  - Extracellular matrix autoantigens

EFFECTOR MECHANISM OUTCOMES IN TYPE II AUTOIMMUNE DISEASE

* Cell surface antigen autoantibodies
  - Cell and tissue destruction

* Cell surface receptor autoantibodies
  - Agonistic
    - Stimulate receptor
  - Antagonistic
    - Inhibit receptor

Diseases mediated by antibodies against cell-surface receptors

Syndrome	Antigen	Antibody	Consequence
Graves' disease	Thyroid-stimulating hormone receptor	Agonist	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Antagonist	Progressive muscle weakness
Insulin-resistant diabetes	Insulin receptor	Antagonist	Hyperglycemia, ketoacidosis
Hypoglycemia	Insulin receptor	Agonist	Hypoglycemia

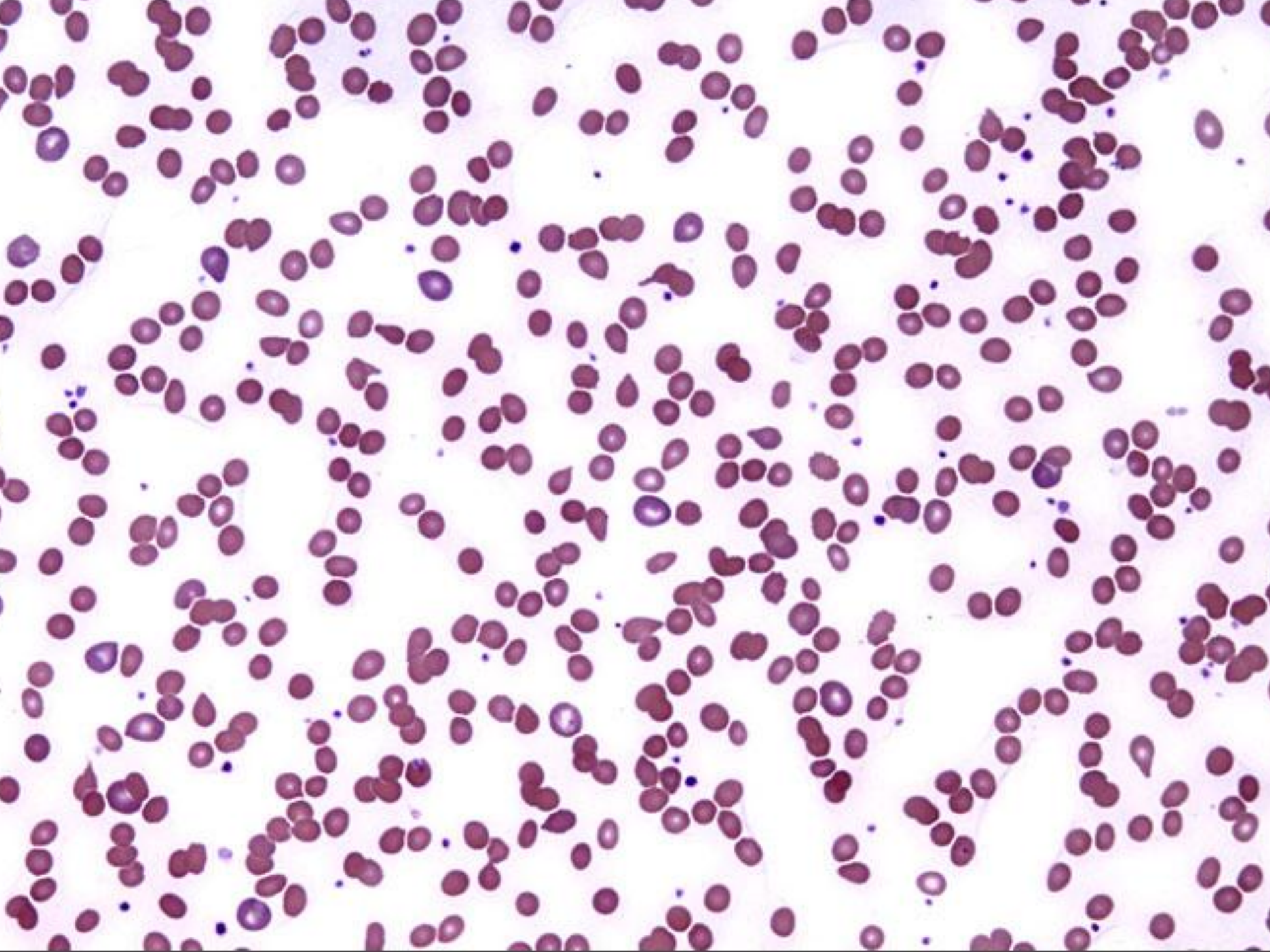
Figure 11-15 The Immune System, 2/e (© Garland Science 2005)

AUTOIMMUNE HEMOLYTIC ANEMIA

* Destruction of erythrocytes by autoantibodies

* Types
  - Warm (37 C) mediated by IgG
  - Cold (32 C) mediated by IgM

* Causes of Warm
  - Idiopathic in 50% of cases
  - Diseases
    - Chronic lymphocytic leukemia
    - Systemic lupus erythematosus
  - Drugs
    - Penicillin, methyldopa, quinidine



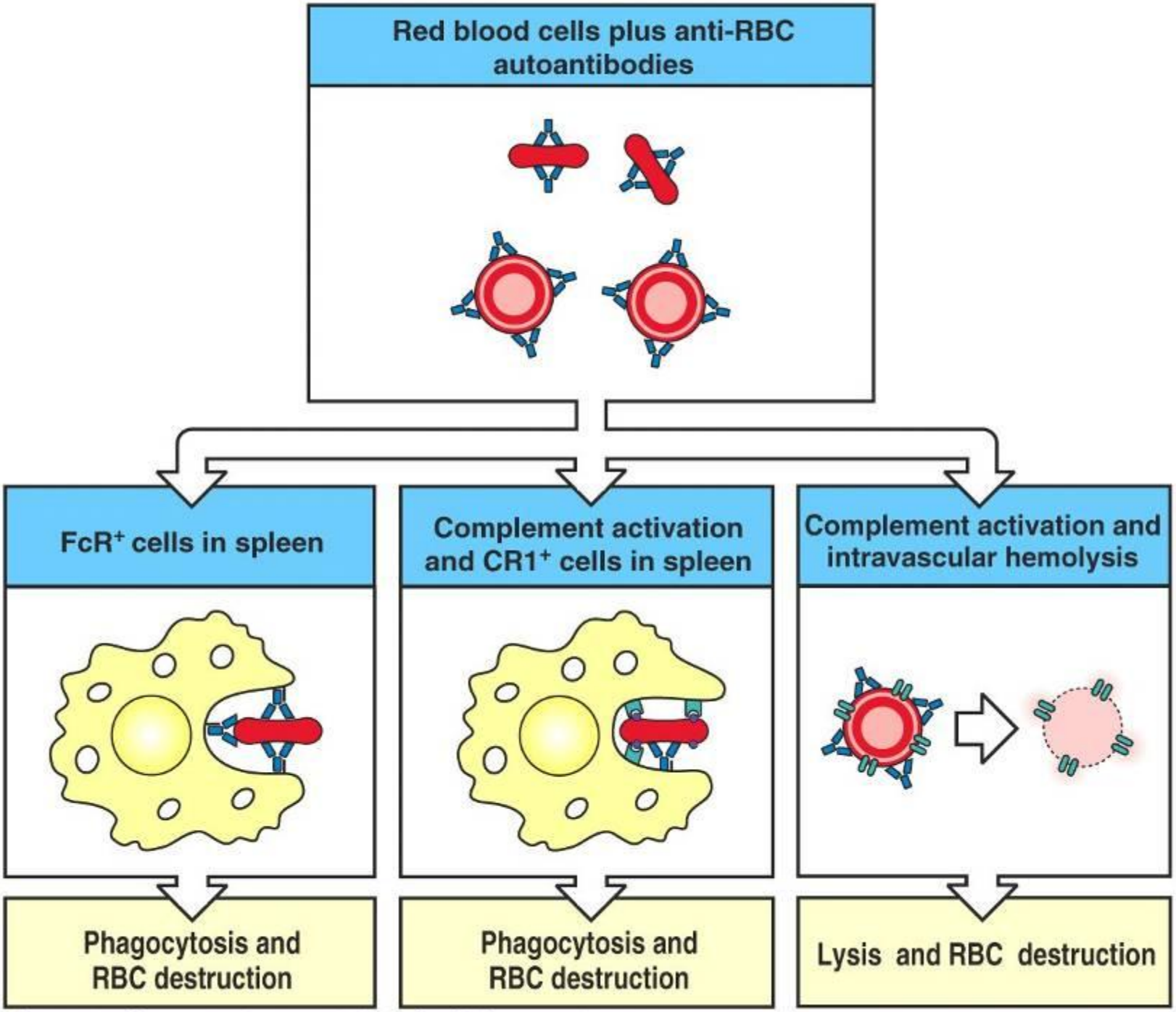
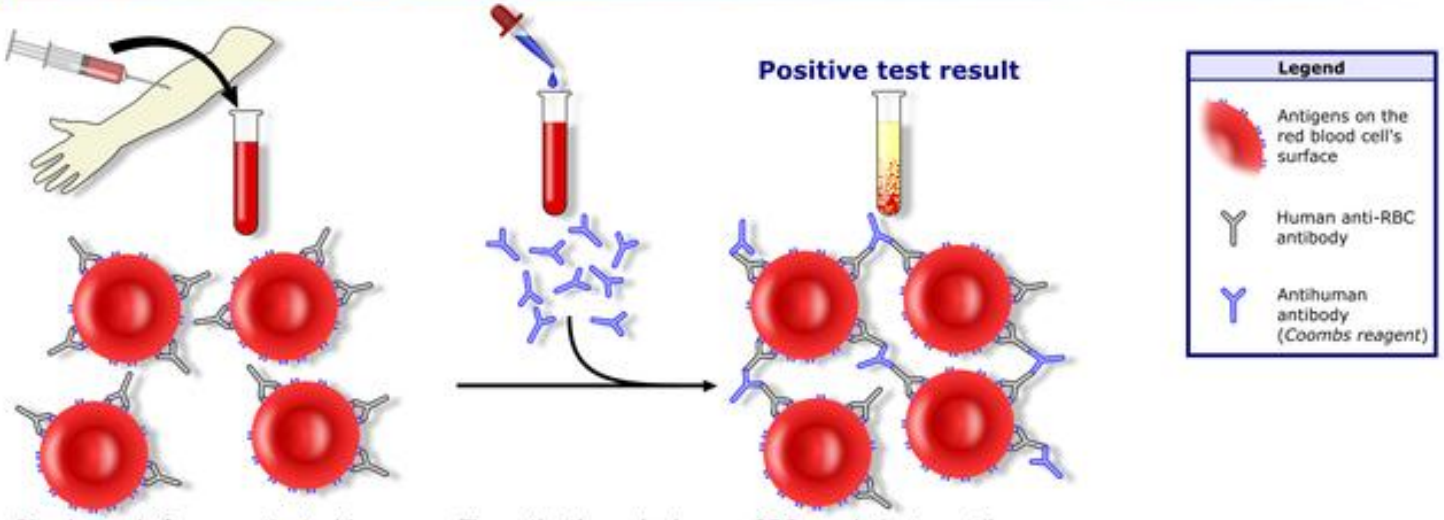


Figure 11-2 The Immune System, 2/e (© Garland Science 2005)

AUTOIMMUNE HEMOLYTIC ANEMIA

* Symptoms
  - Fatigue, pallor, SOB, tachycardia, jaundice, splenomegaly
* Laboratory diagnosis
  - Coombs' test
    - Direct (bound) and Indirect (free)
  - Elevated reticulocyte count
* Treatment
  - Prednisone
  - Splenectomy
  - Immunosuppressive agents

Direct Coombs test / Direct antiglobulin test

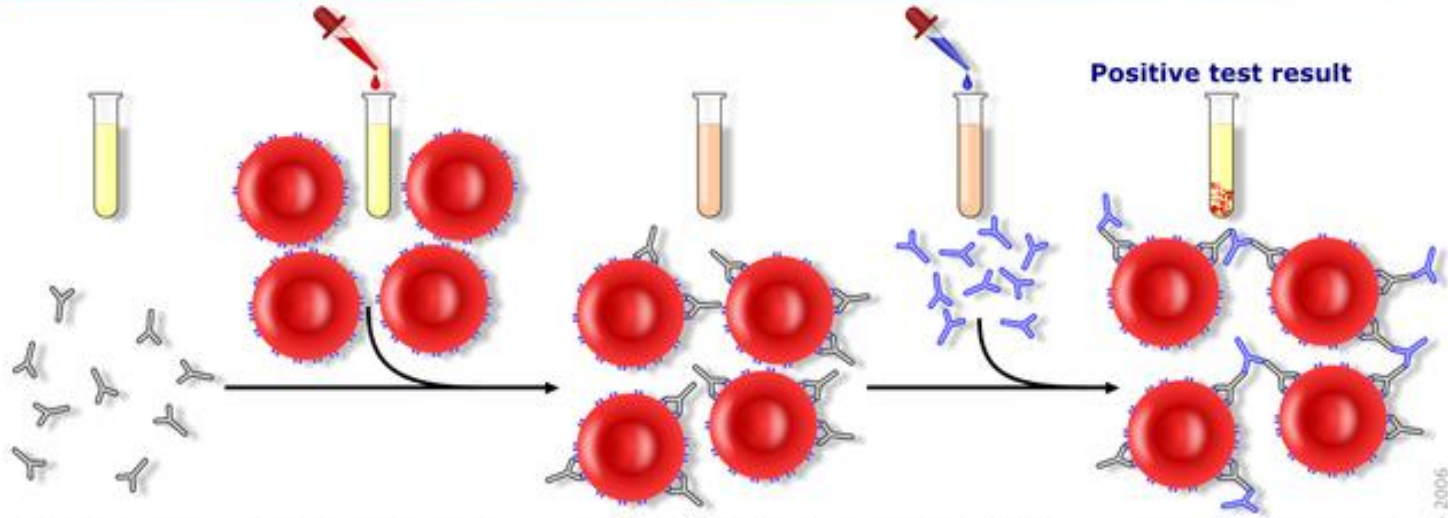


Blood sample from a patient with immune mediated haemolytic anaemia: antibodies are shown attached to antigens on the RBC surface.

The patient's washed RBCs are incubated with antihuman antibodies (*Coombs reagent*).

RBCs agglutinate: antihuman antibodies form links between RBCs by binding to the human antibodies on the RBCs.

Indirect Coombs test / Indirect antiglobulin test



Recipient's serum is obtained, containing antibodies (Ig's).

Donor's blood sample is added to the tube with serum.

Recipient's Ig's that target the donor's red blood cells form antibody-antigen complexes.

Anti-human Ig's (*Coombs antibodies*) are added to the solution.

Agglutination of red blood cells occurs, because human Ig's are attached to red blood cells.

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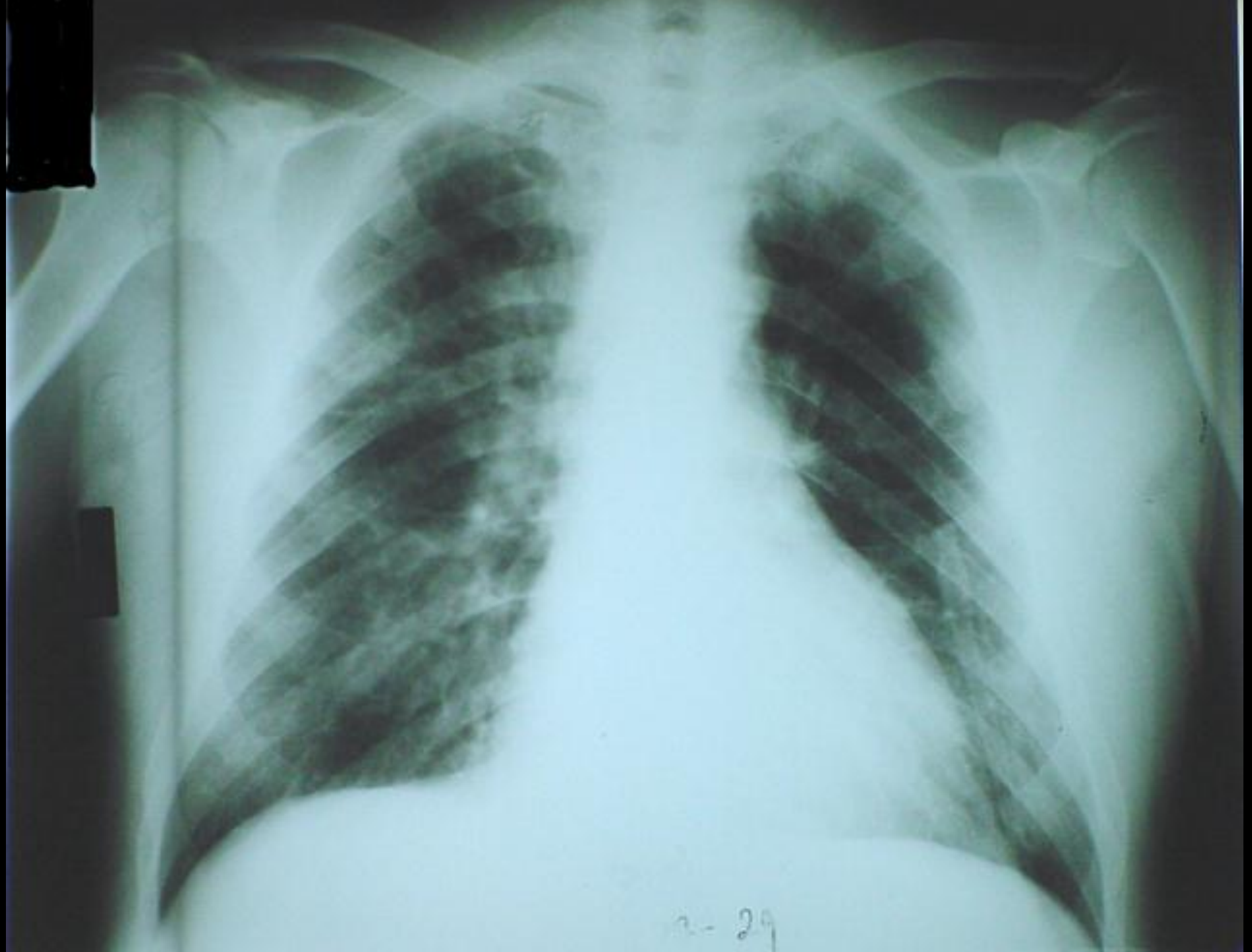
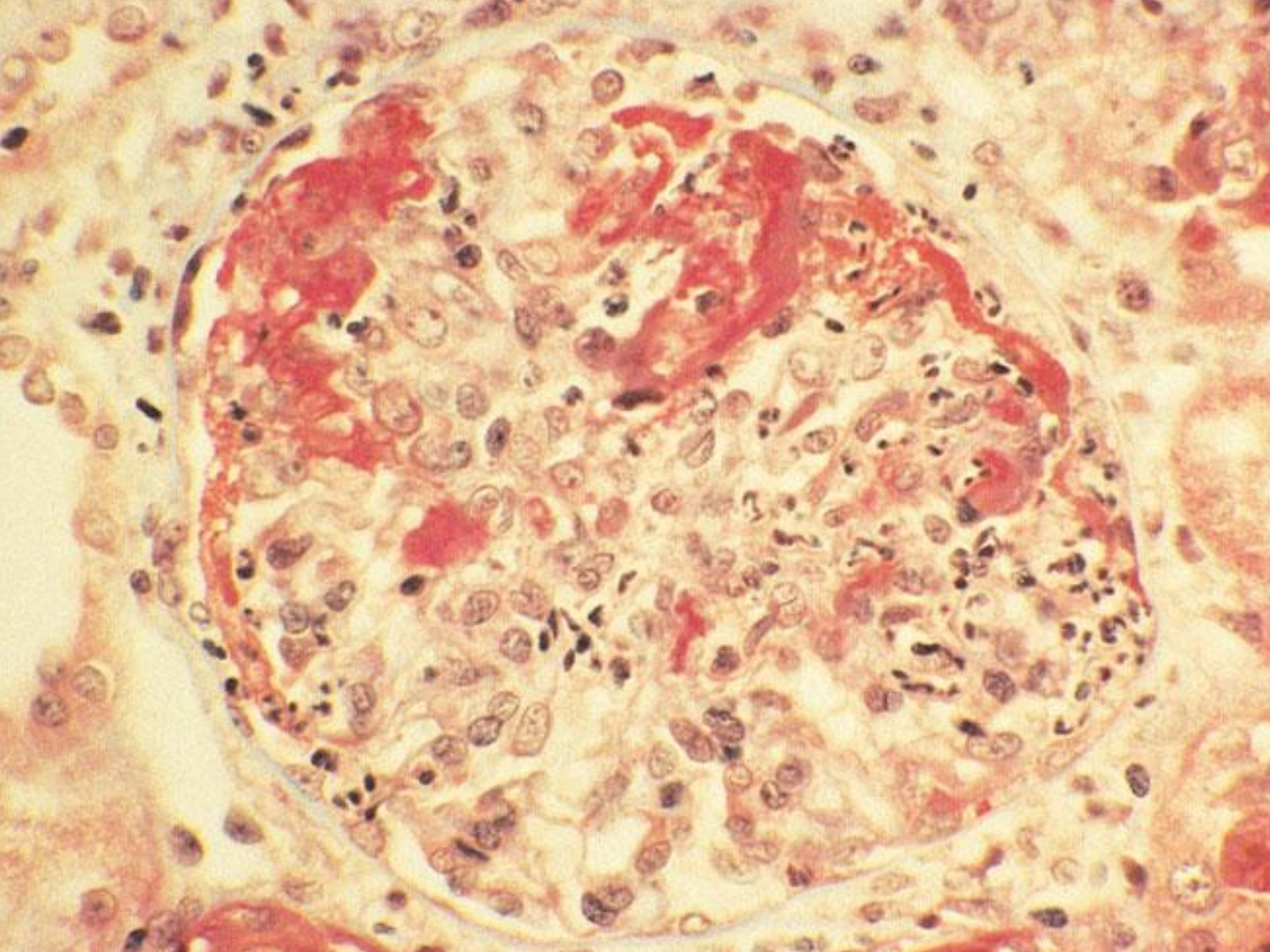
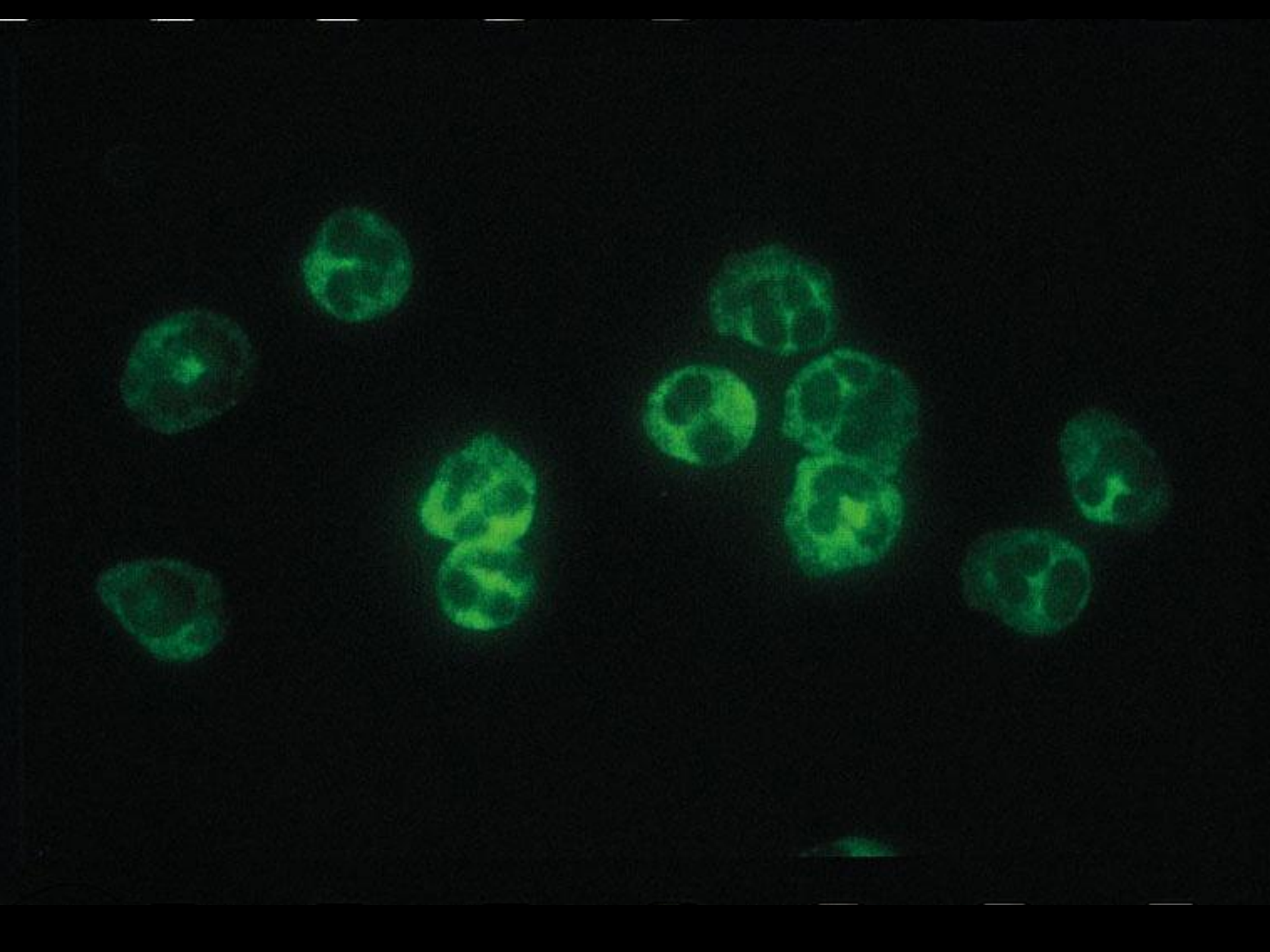
WEGENER'S GRANULOMATOSIS

* An uncommon pulmonary-renal disease
  * Characterized by granulomatous inflammation, necrosis and vasculitis primarily in URT, LRT and kidneys
* Pathophysiology
  - Autoantibodies to proteinase-3 in neutrophil granules
  - Proteinase-3 translocates to surface following activation of neutrophils
* Etiology is unknown and no genetic predispostion
* Laboratory diagnosis
  - Antineutrophil cytoplasmic autoantibodies (ANCA)
  - Biopsy of lung and kidney



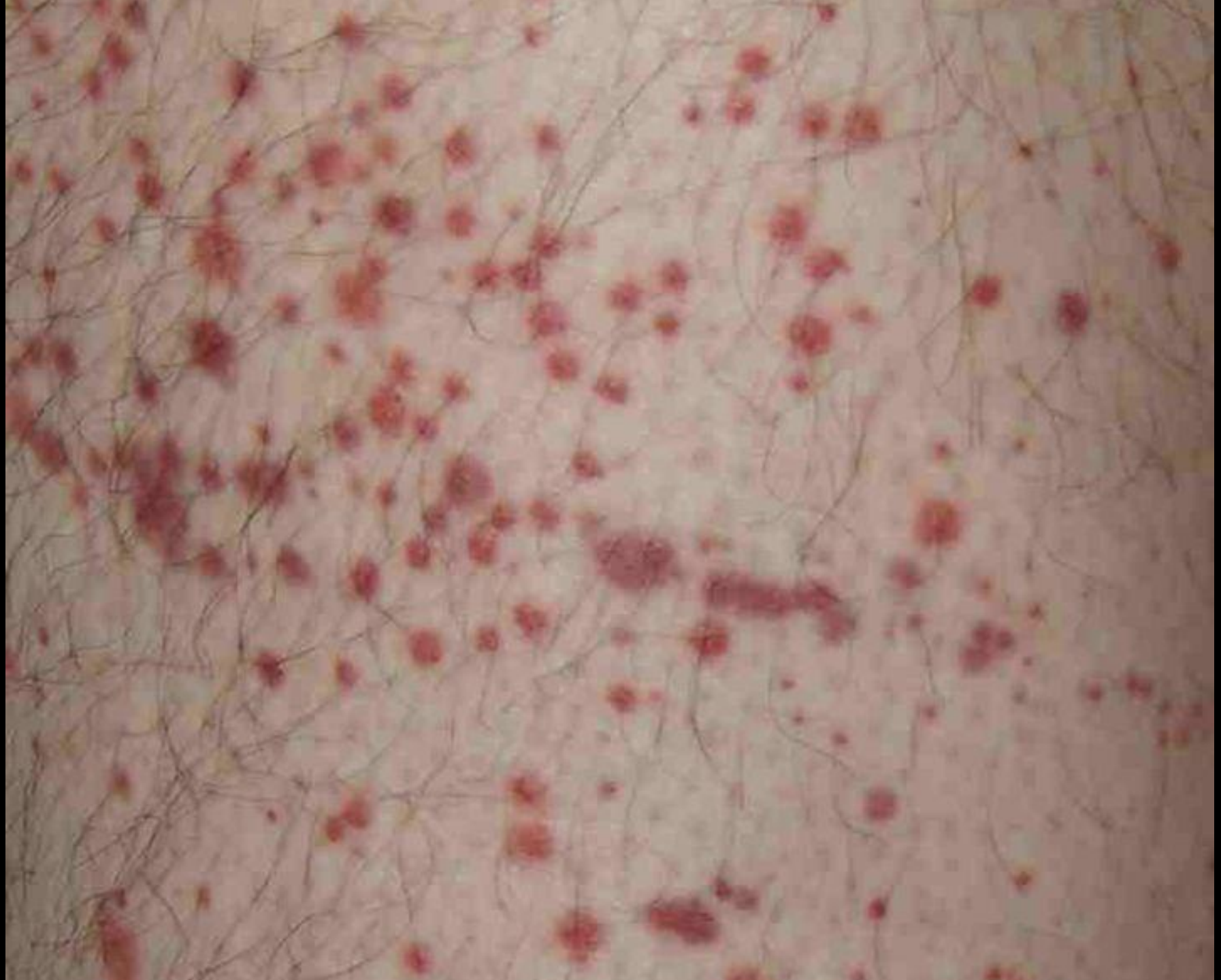


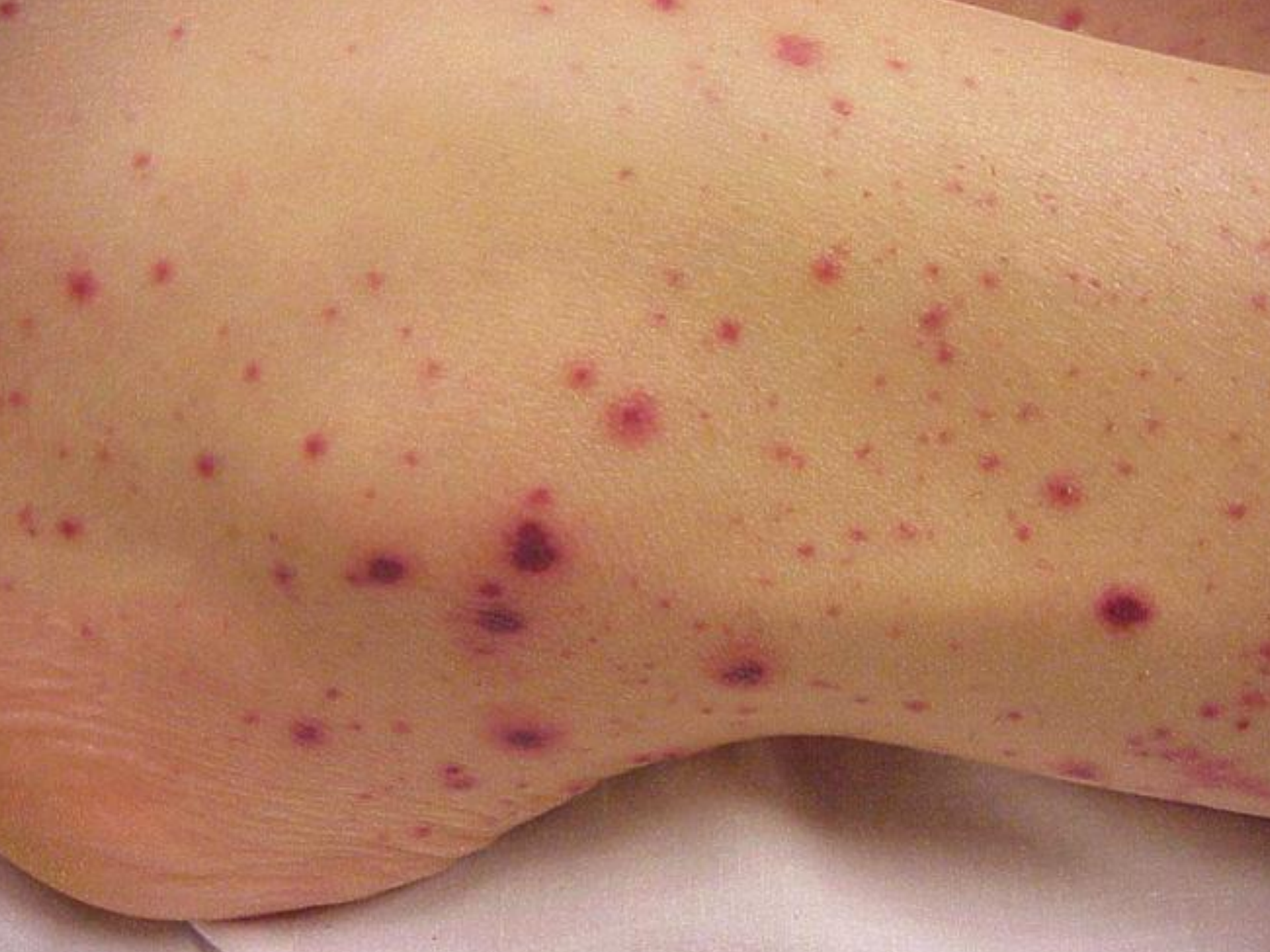


AUTOIMMUNE THROMBOCYTOPENIC PURPURA (ATP)

* Synonym
  * Idiopathic thrombocytopenic purpura (ITP)

* Pathophysiology
  - IgG autoantibodies against membrane glycoproteins on surface of thrombocytes (platelets)
    - Glycoprotein IIb/IIIa complex
  - Decrease in circulating thrombocytes (thrombocytopenia)
    - Reference range (150,000 to 450,000/uL)
    - Clinical significance (< 50,000/uL)
  - Results in hemorrhage



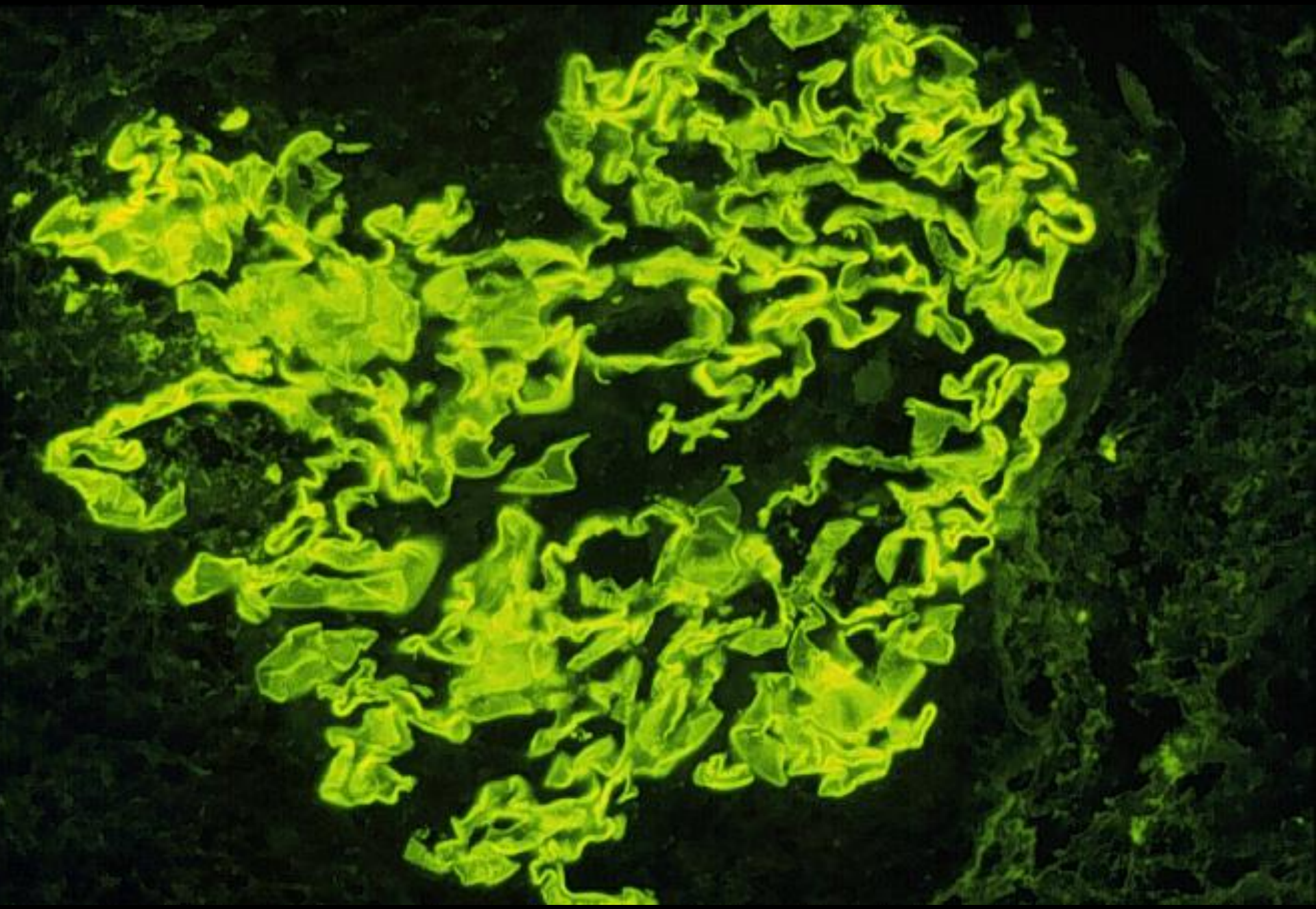


AUTOIMMUNE THROMBOCYTOPENIC PURPURA (ATP)

* Clinical forms
  - Acute in children (2 to 4 years)
    - Follows infection
  - Chronic in adults (20 to 50 years)
    - No specific cause
* Risk factors
  - Diseases
    - SLE, HIV / AIDS
  - Drugs
    - Sulfonamides, ibuprofen, ranitidine, phenytoin, tamoxifen
- Laboratory diagnosis
  - Complete blood count (CBC)

GOODPASTURE'S SYNDROME

* An uncommon pulmonary-renal syndrome
* Characterized by pulmonary hemorrhage and glomerulonephritis
* Pathophysiology
  - Antibodies to type IV collagen in alveolar and glomerular basement membranes
* Laboratory diagnosis
  - Anti-GBM (IgG to glomerular basement membrane)
  - Biopsy of lung and kidney



ACUTE RHEUMATIC FEVER (ARF)

* Non-suppurative sequelae to pharyngitis by Streptococcus pyogenes (Group A Streptococcus / GAS)
* 2 to 3 weeks following pharyngitis
* Characterized by
  - Painful polymigratory arthritis
  - Carditis
* Female to male ratio of 1:1
* Incidence of 0.5% to 3%

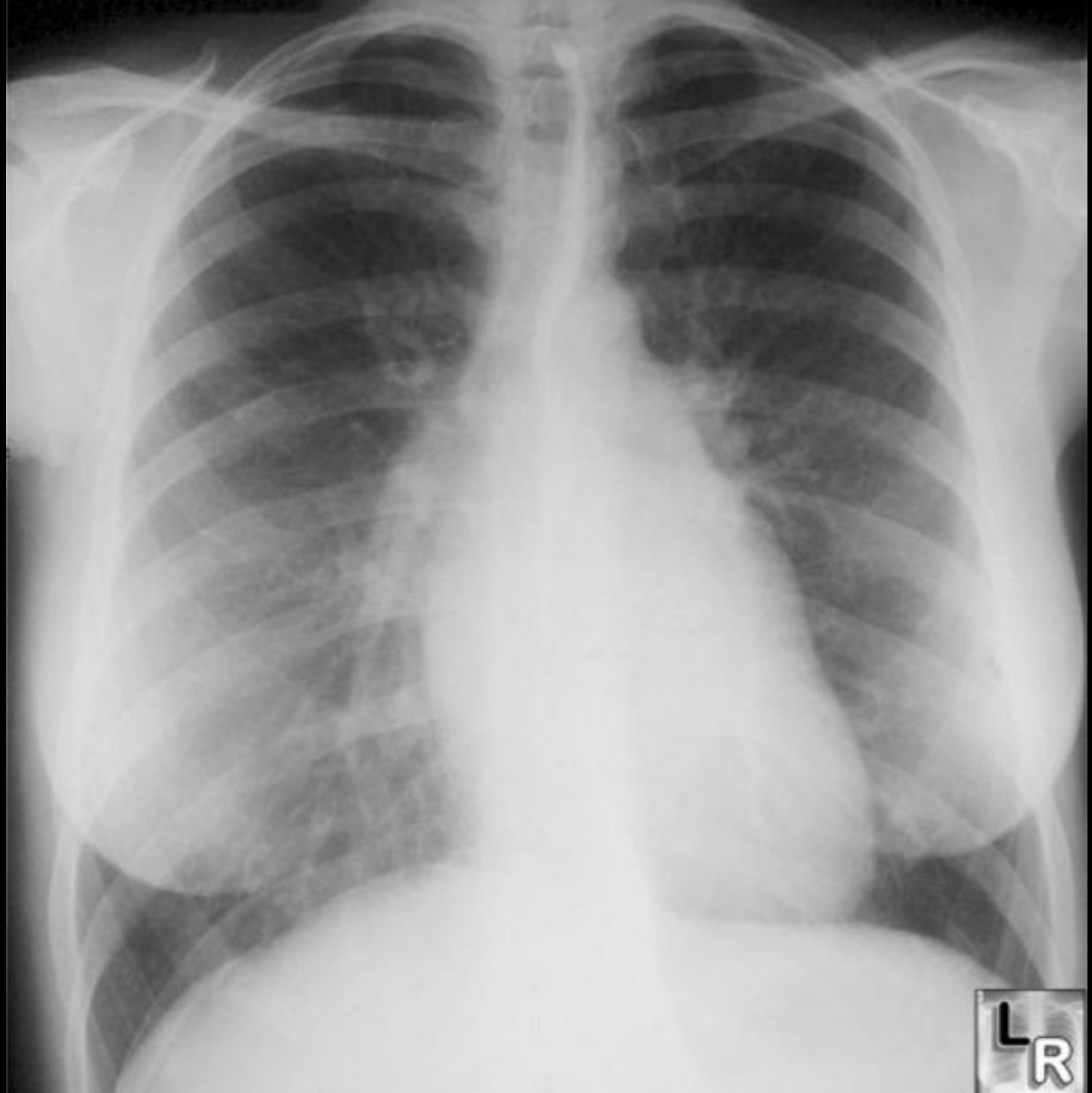
ACUTE RHEUMATIC FEVER (ARF)

* Highest incidence/prevalence between 6 and 20 years
  - Rare >30 years
* Effector mechanism
  - Antibodies to GAS “M” proteins cross reacting to antigens of heart and joints (molecular mimicry)
* Associated with rheumatogenic strains
  - M1, M3, M5, M6, M18

ACUTE RHEUMATIC FEVER (ARF)

* Radiographic diagnosis
  - CXR for cardiomegaly

* Laboratory diagnosis
  - Anti-streptolysin-O (ASO)
    - Reference ranges
      - 0 to 3 years ≤ 250 IL/mL
      - 4 to 17 years ≤400 IL/mL
  - Anti-DNaseB
  - CRP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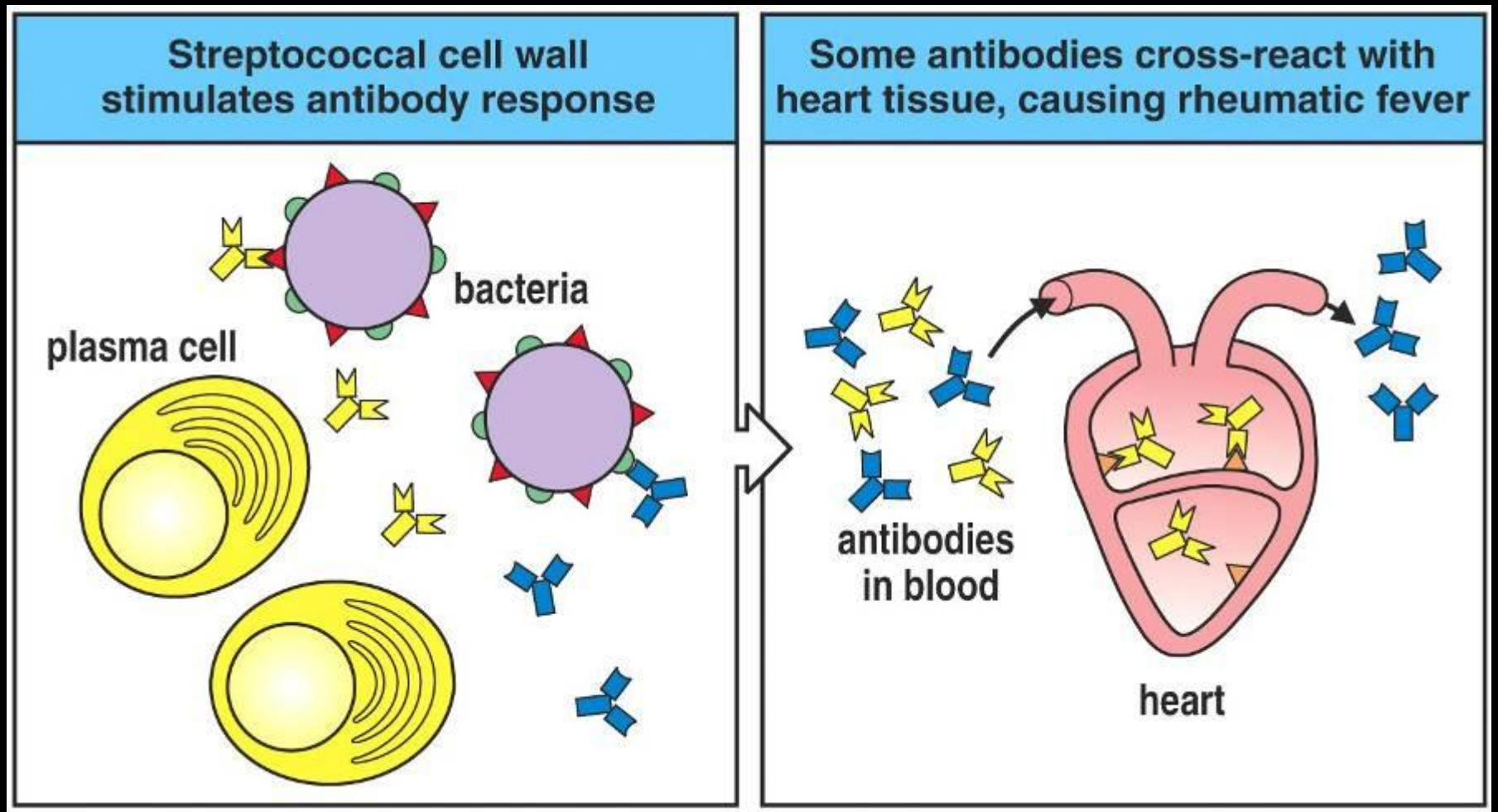


Figure 11-29 The Immune System, 2/e (© Garland Science 2005)

GRAVES' DISEASE

* Most common cause of hyperthyroidism (thyrotoxicosis)
  - Incidence of 50-80 cases / 100,000 population / year
  - Female to male ratio of 8:1

* Effector mechanisms involve auto-reactive antibodies
  - Thyroid stimulating hormone (TSH) receptor (Thyrotropin receptor)
  - Thyroid peroxidase / Thyroperoxidase (TPO)
  - Thyroglobulin
  - T3 and T4

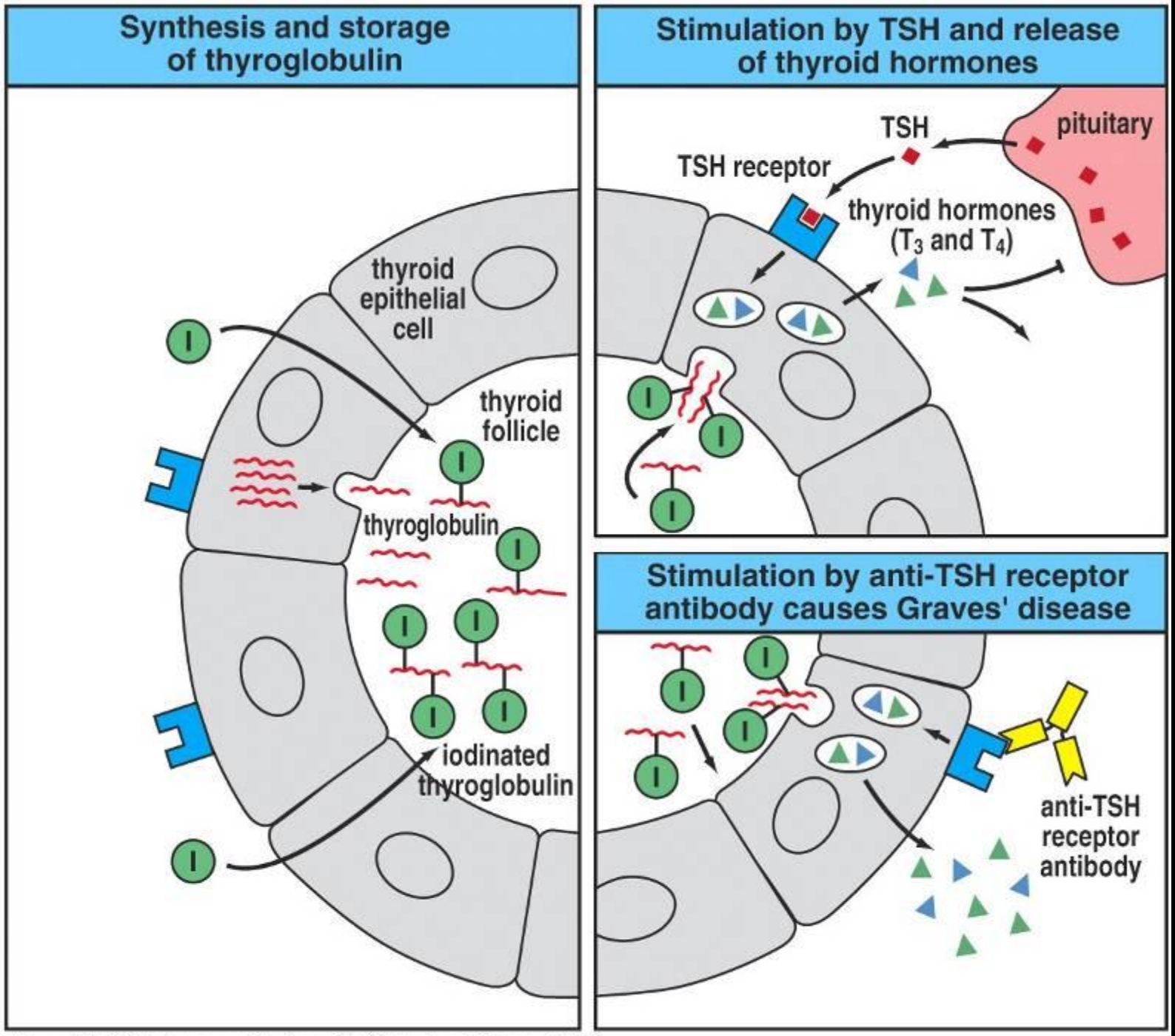


Figure 11-5 The Immune System, 2/e (© Garland Science 2005)

GRAVES' DISEASE

* Symptoms
  - Fatigue, heat intolerance, weight loss, anxiety, restlessness, insomnia, ophthalmopathy

* Laboratory diagnosis
  - Increase in free T3 (triiodothyronine) and T4 (thyroxine) serum levels
  - Decrease in thyroid stimulating hormone (TSH) serum level
  - Detection of thyroid stimulating hormone (TSH / Thyrotropin) receptor antibody in serum

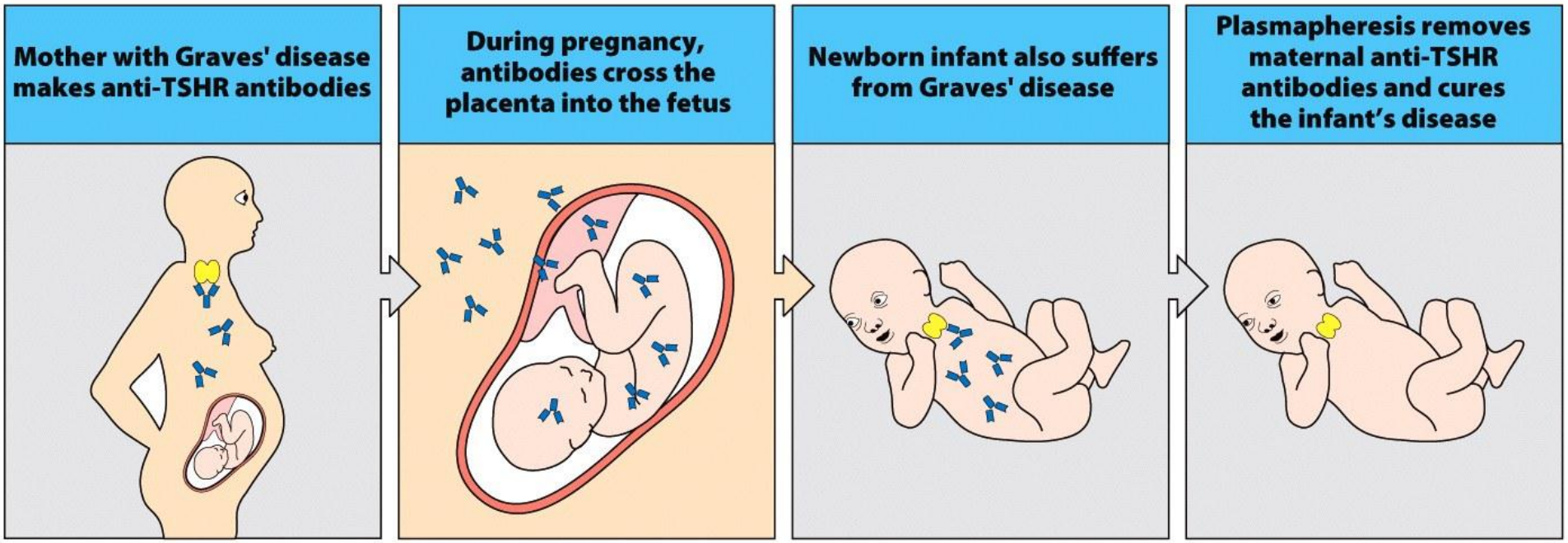
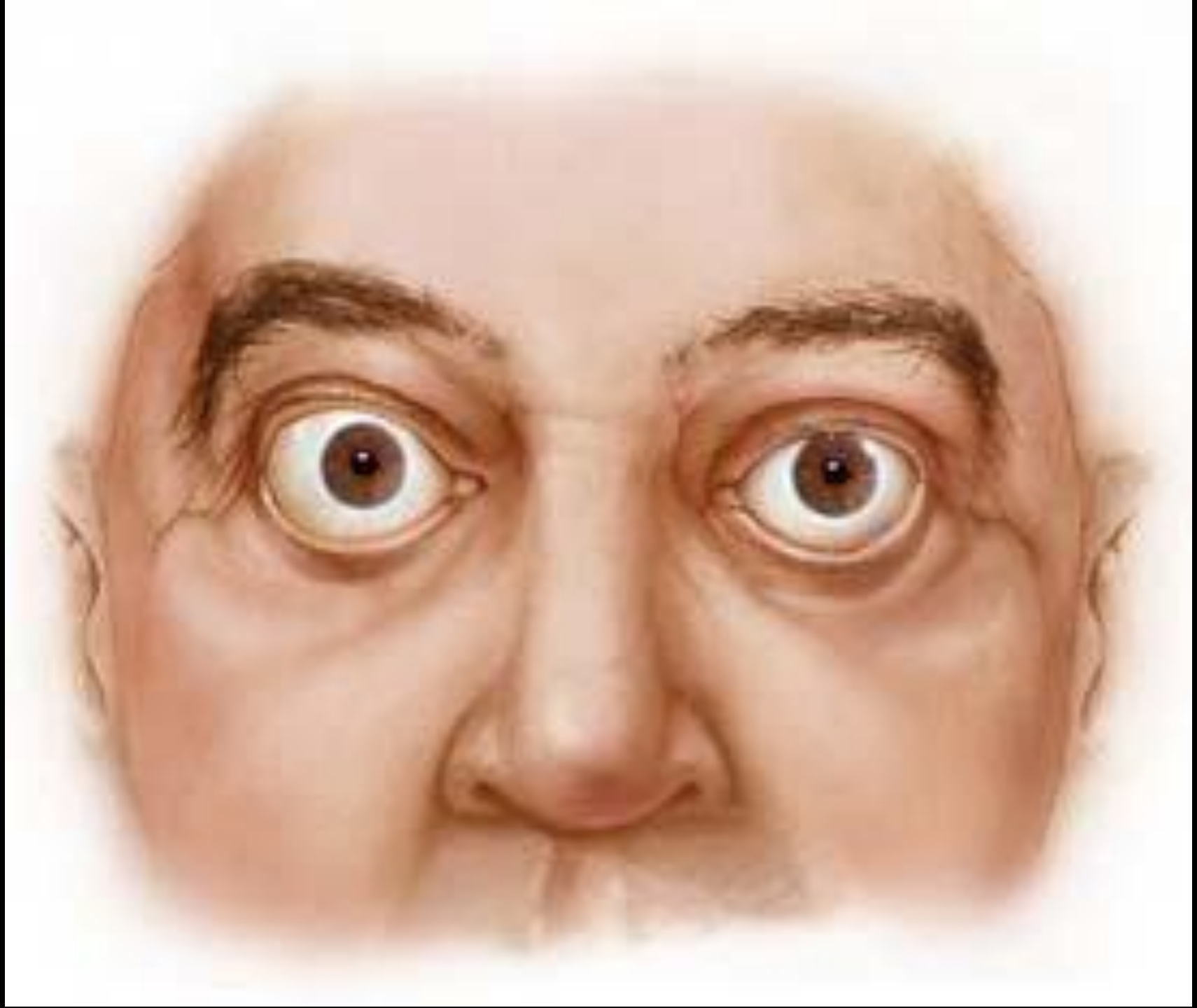


Figure 13.8 The Immune System, 3ed. (© Garland Science 2009)

GRAVES' DISEASE

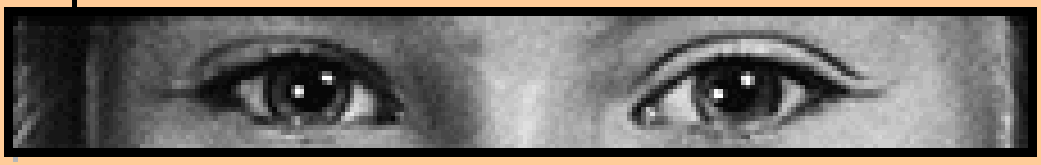
* Risk factors
  * HLADR3
  * Smoking for ophthalmopathy (5x)

* Treatment
  - Anti-thyroid drugs
    - Methimazole (Tapazole)
  - Radioactive iodine
    - I-131
  - Surgery
    - Thyroidectomy



Figures: Courtesy of David H. Wang, MD, MS

September 1990



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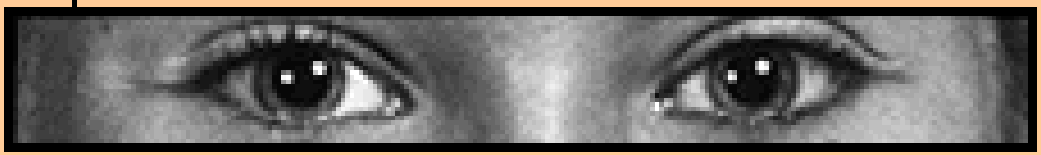

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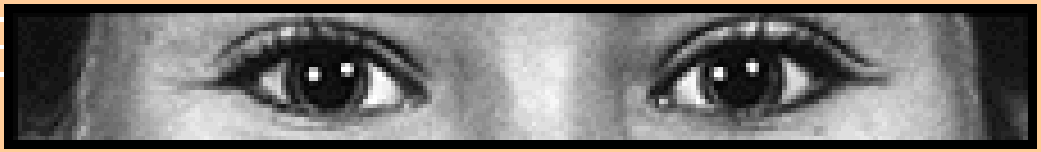

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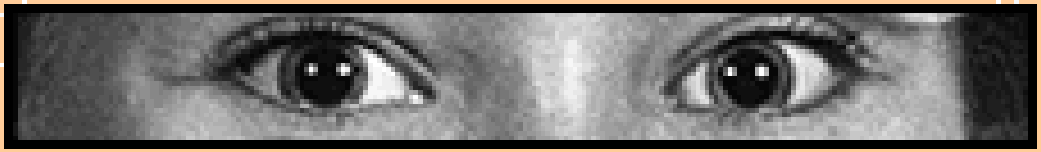

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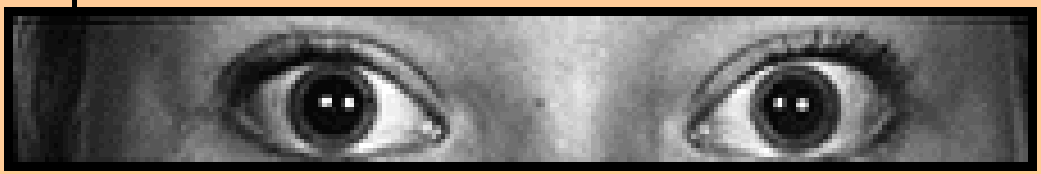


Figure 1. Five annual team photos of a college golfer demonstrate the gradual development of the characteristic ophthalmopathy of Graves' disease. At the time of diagnosis she had bilateral proptosis and eyelid retraction without lid lag.

HASHIMOTO'S DISEASE (THYROIDITIS)

* Alternative names
  - Chronic lymphocytic thyroiditis
  - Autoimmune thyroiditis
* Female to male ratio of 12:1
* Effector mechanisms
  - Autoantibodies specific for
    - Thyroglobulin
    - Thyroid peroxidase
  - CD8 T cells

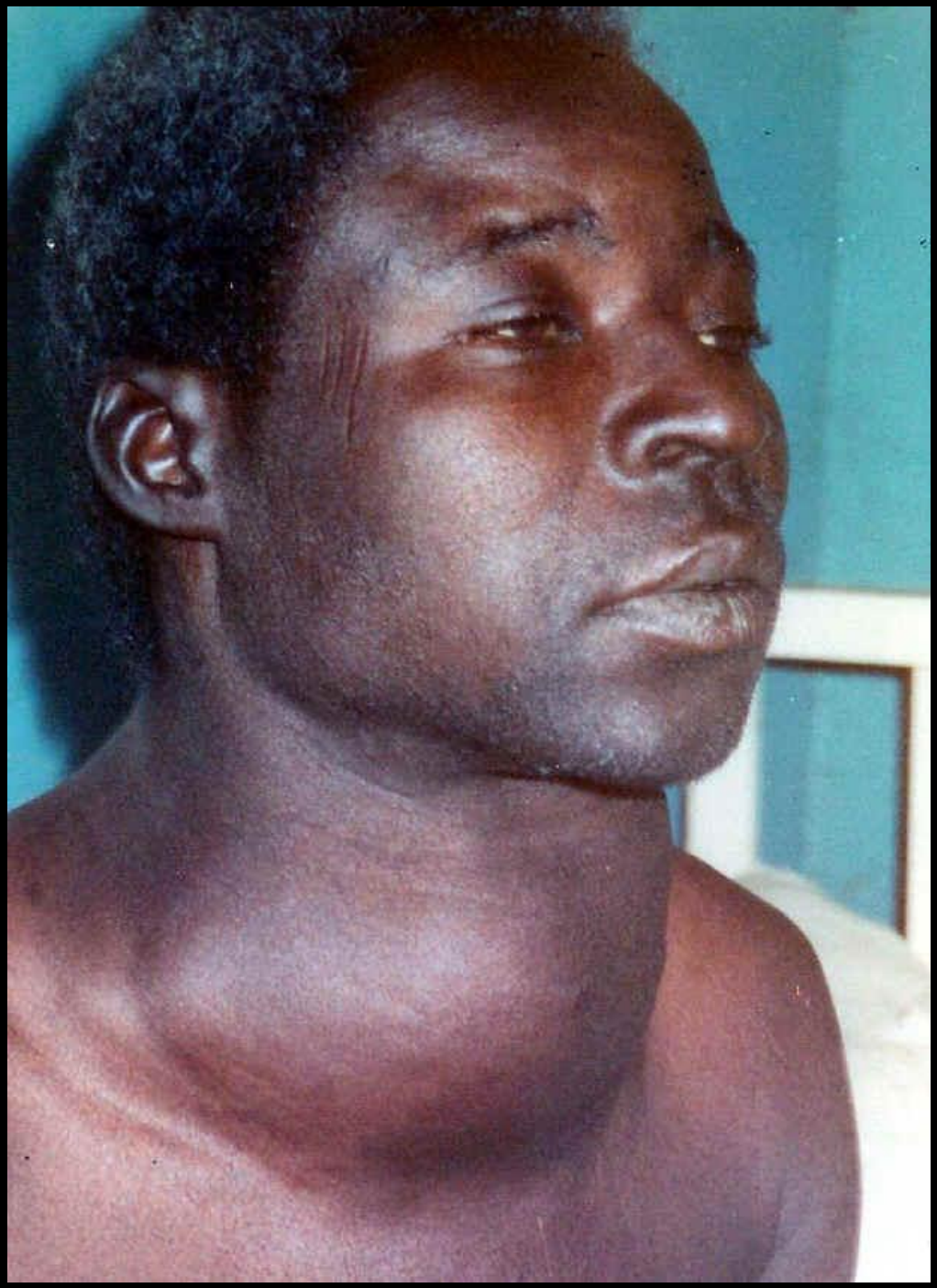
HASHIMOTO'S DISEASE (THYROIDITIS)

* Most common cause of hypothyroidism in US

* Symptoms
  - Fatigue, cold intolerance, weight gain, depression, enlarged gland

* Laboratory diagnosis
  - T3,T4 (decrease) and TSH (increase) serum levels
  - Autoantibodies to
    - Thyroid peroxidase (TPO)
    - Thyroglobulin

* Treatment
  - Replacement therapy (Levothyroxine)



INSULIN RESISTANCE (SYNDROME / DIABETES)

* Cells of body display impaired response to effects of insulin
* Obesity is most common cause
* Precedes Type 2 diabetes
* Etiology
  - Genetic
    - Mutational events
  - Acquired
    - Physical inactivity, medications, diet, aging process

ETIOLOGICAL CATEGORIES OF INSULIN RESISTANCE

* Pre-receptor
  - Abnormal insulin
  - Antibody to insulin
* Receptor
  - Decreased number of receptors
  - Mutated receptors
  - Autoantibody against receptors
    - Antagonistic
    - Agonistic
* Post-receptor
  - Defective signal transduction

AUTOIMMUNE INSULIN RECEPTOR DISEASE

* Results in either elevated or decreased levels of glucose in blood

* Mechanisms
  - Autoantibodies against insulin receptors on cells

* Autoantibodies
  - Antagonistic
    - Result in hyperglycemia
    - Insulin resistant diabetes
  - Agonistic
    - Results in hypoglycemia

TYPE III AUTOIMMUNE DISEASES

* Directed against autoantigens of many cells of body
  - Cell surfaces, cytoplasm and nucleus (nucleic acids and nucleoproteins)
  - Antibody binding initiates inflammatory reactions and soluble immune complexes

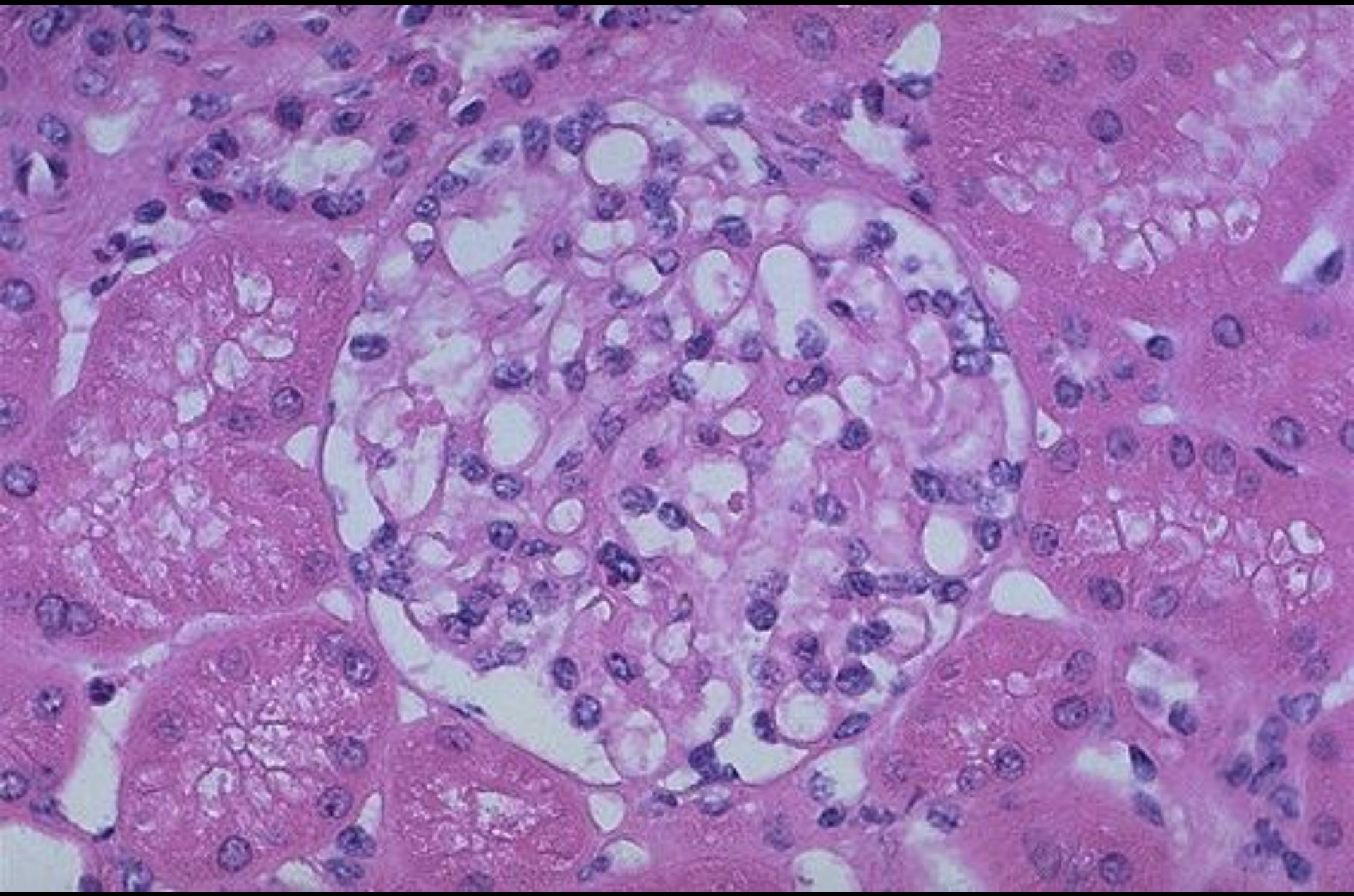
* Directed against one or two different tissue
  - Clinical manifestations are systemic

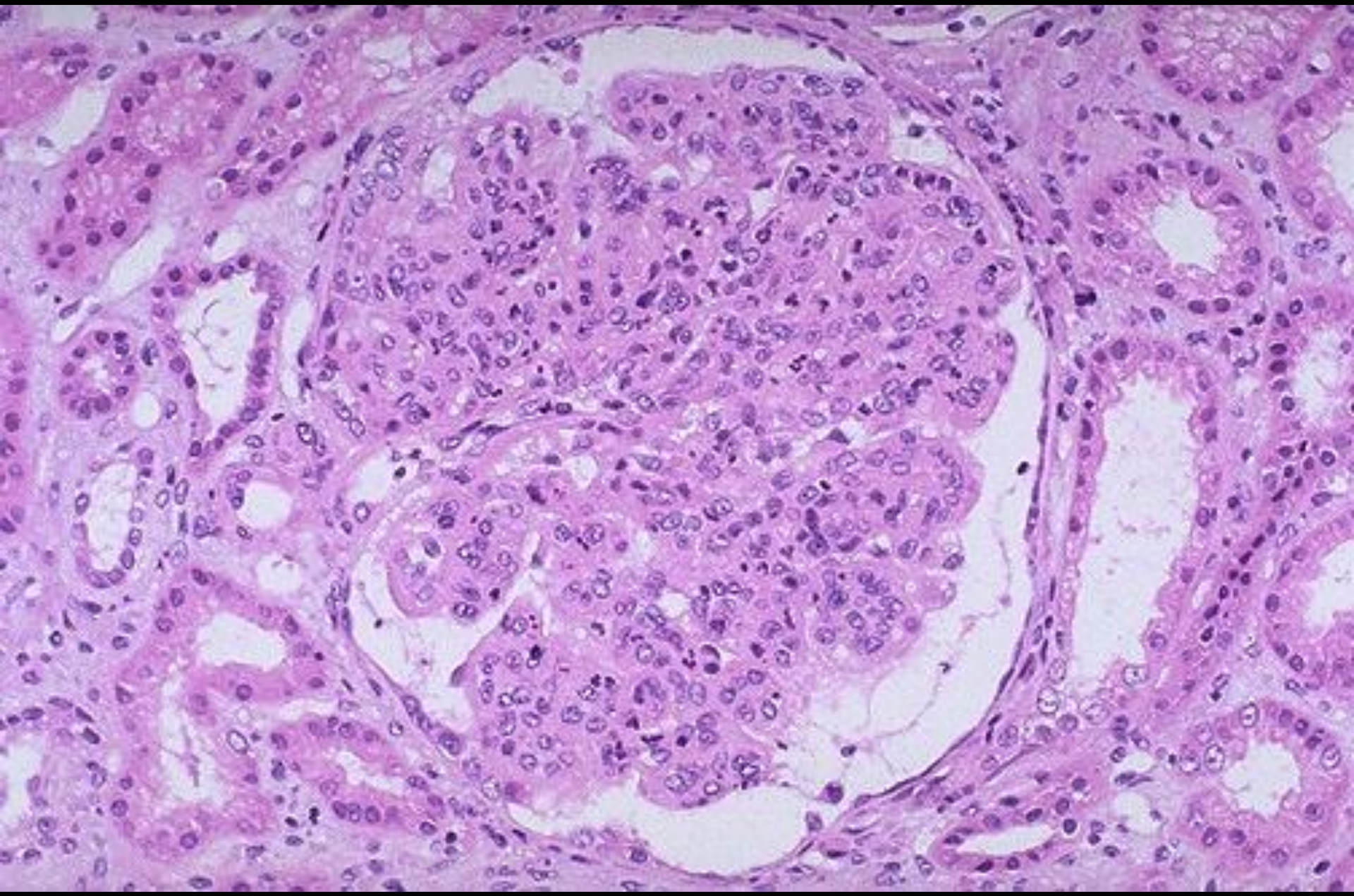
POST-STREPTOCOCCAL ACUTE GLOMERULONEPHRITIS (PSAGN)

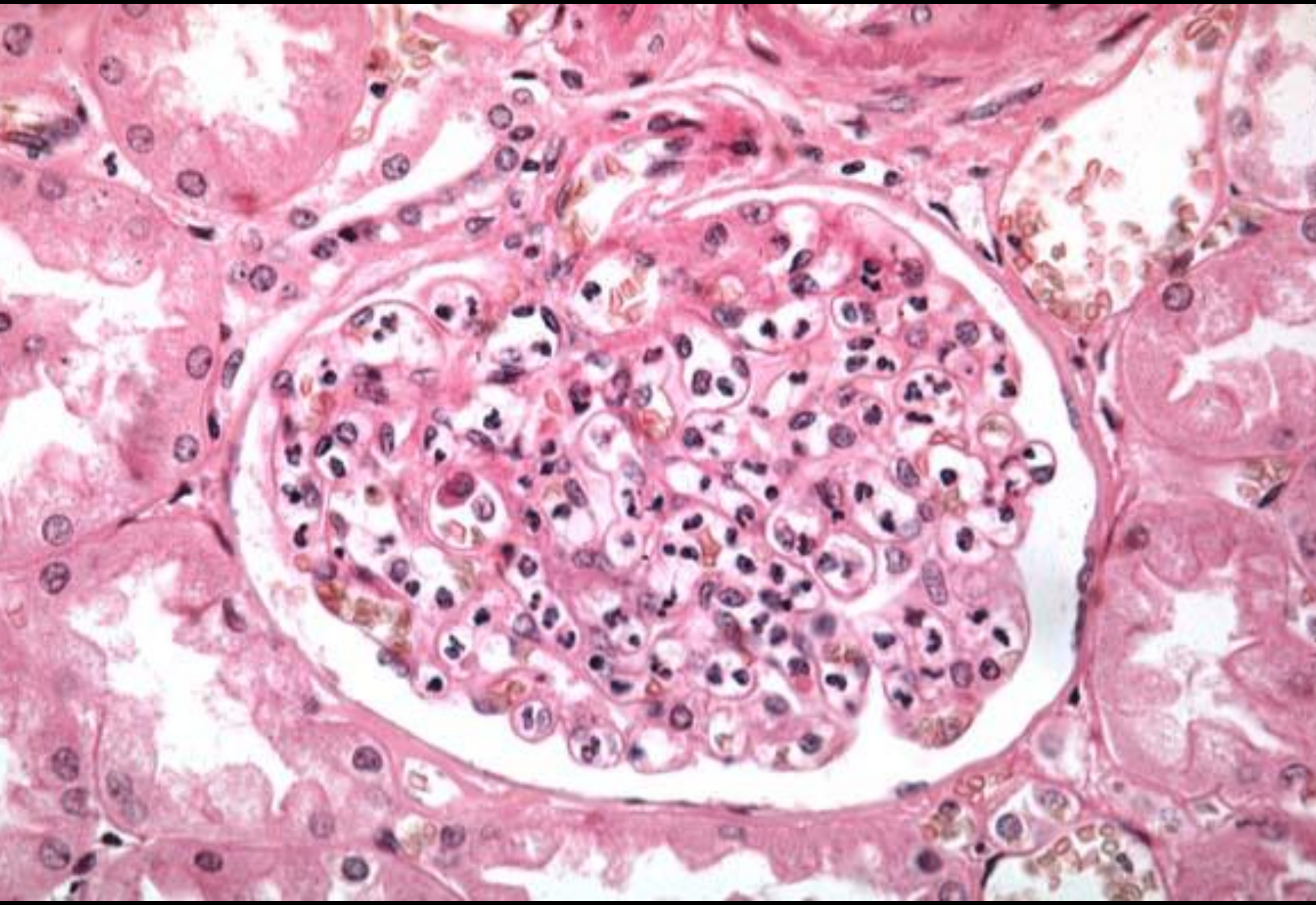
* Non-suppurative sequelae following pharyngitis and skin infections by Group A Streptococcus (GAS)
* 1 to 3 weeks following pharyngitis and skin infections
* Characterized by
  - Edema (peri-orbital)
  - Hematuria
  - Hypertension
* Male to female ratio of 2:1

POST-STREPTOCOCCAL ACUTE GLOMERULONEPHRITIS (PSAGN)

* Highest incidence/prevalence between 4 to 12 years
* Antigens from "Nephritogenic strains“
  * M2, M12, M49, M57, M59, M60
* Effector mechanism
  - Deposition of soluble immune complexes in glomeruli
* Laboratory diagnosis
  - Anti-streptolysin O (ASO) [skin infections show poor response]
  - Anti-DNaseB
  - C3







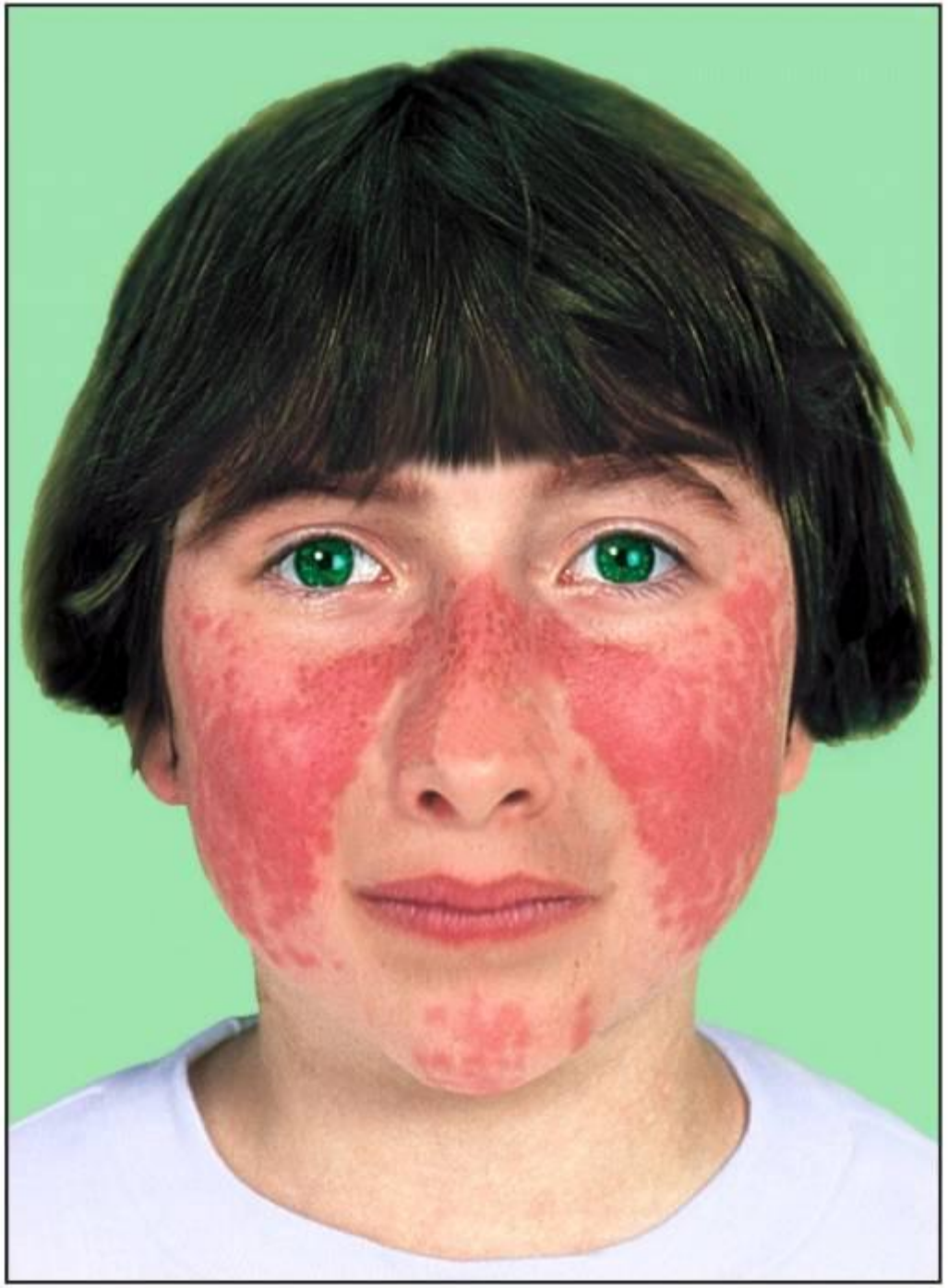
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

* Chronic, multi-system inflammatory disease with protean manifestations and remitting course

* Clinical manifestations
  * Musculoskeletal (joint and muscle pain)
  * Dermatological (malar rash)
  * Renal (glomerulonephritis)

* Female to male ratio of 9:1

* Etiology is unknown
  - Genetics, race, hormones, environment



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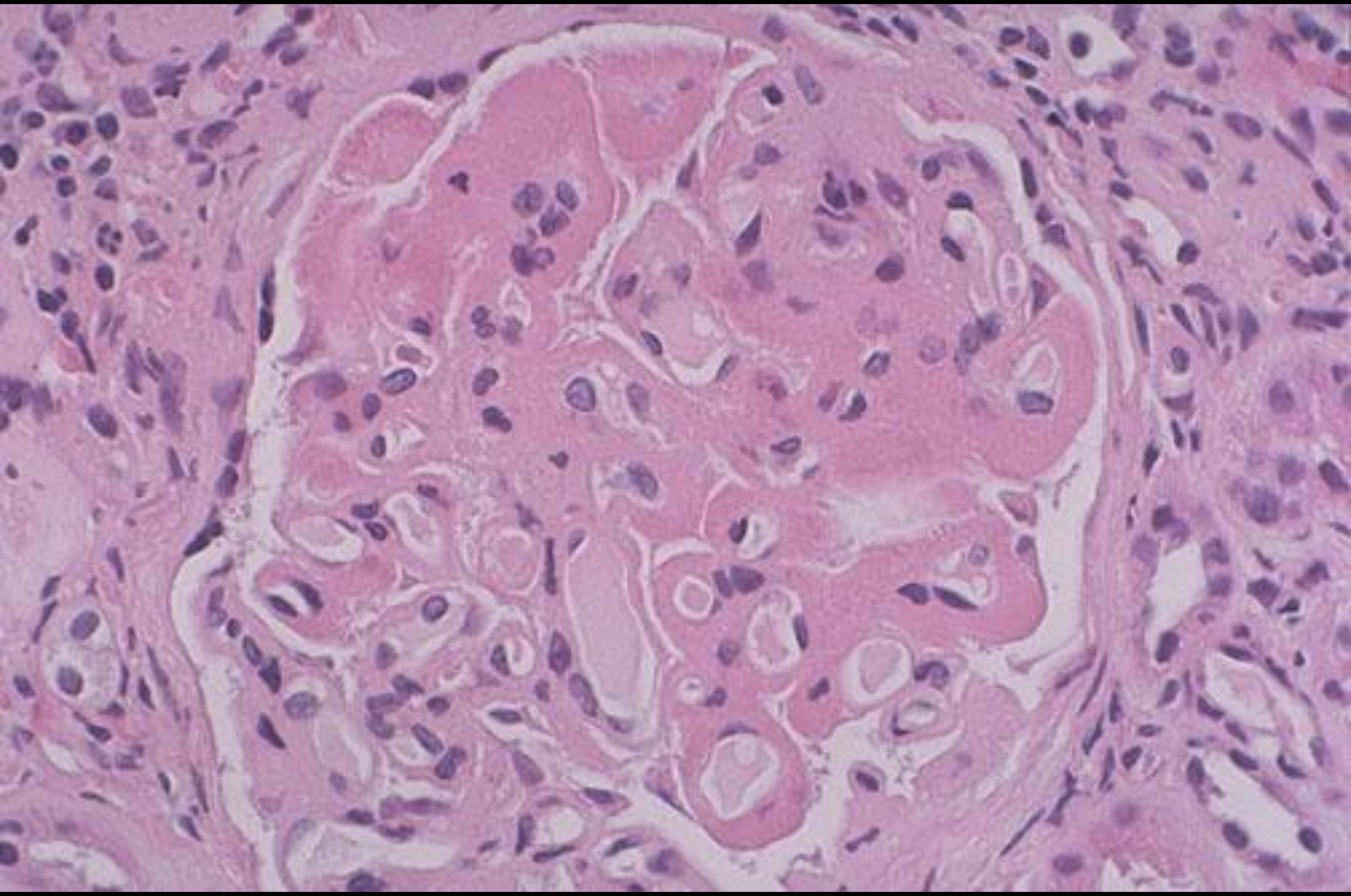
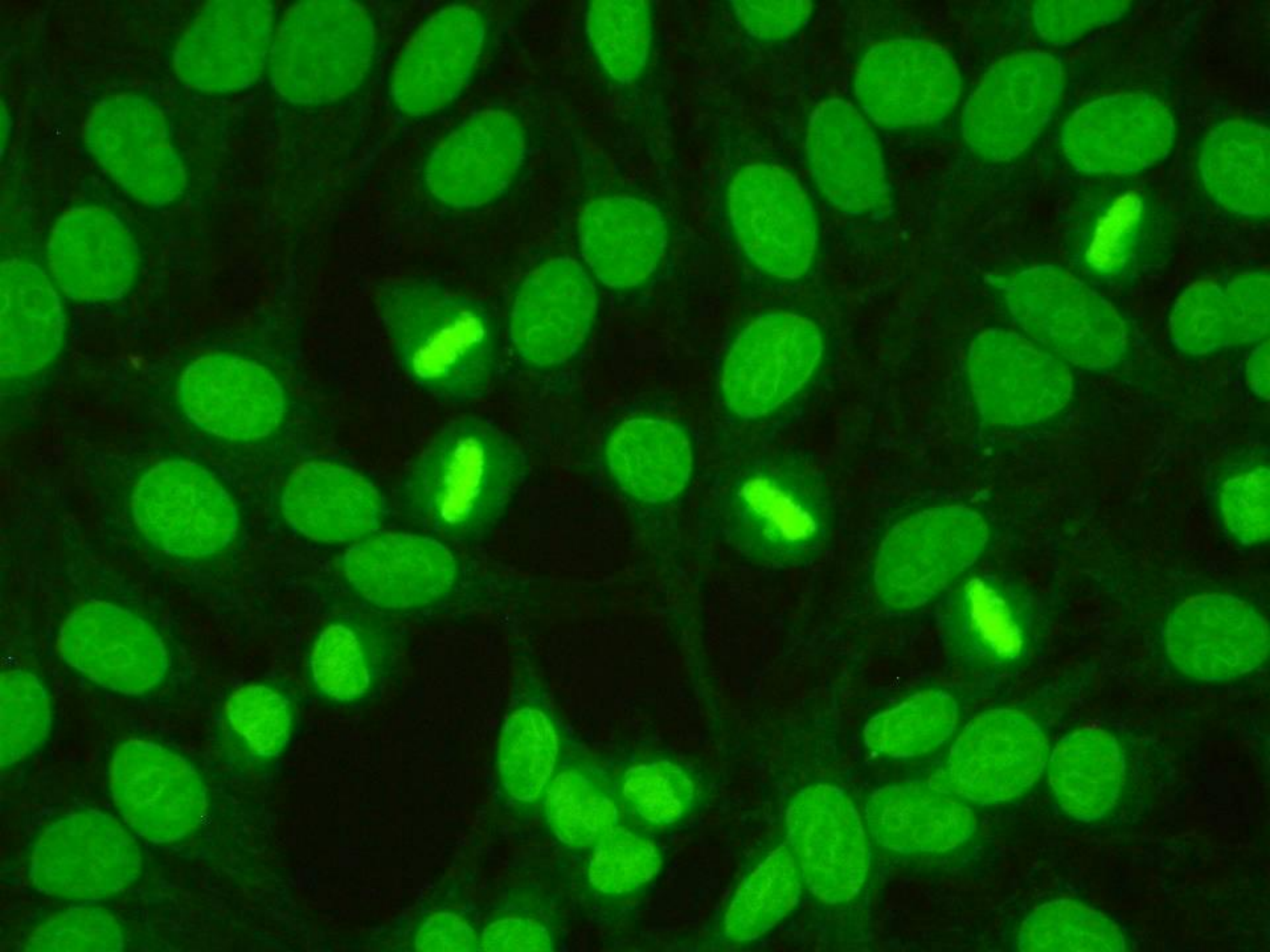
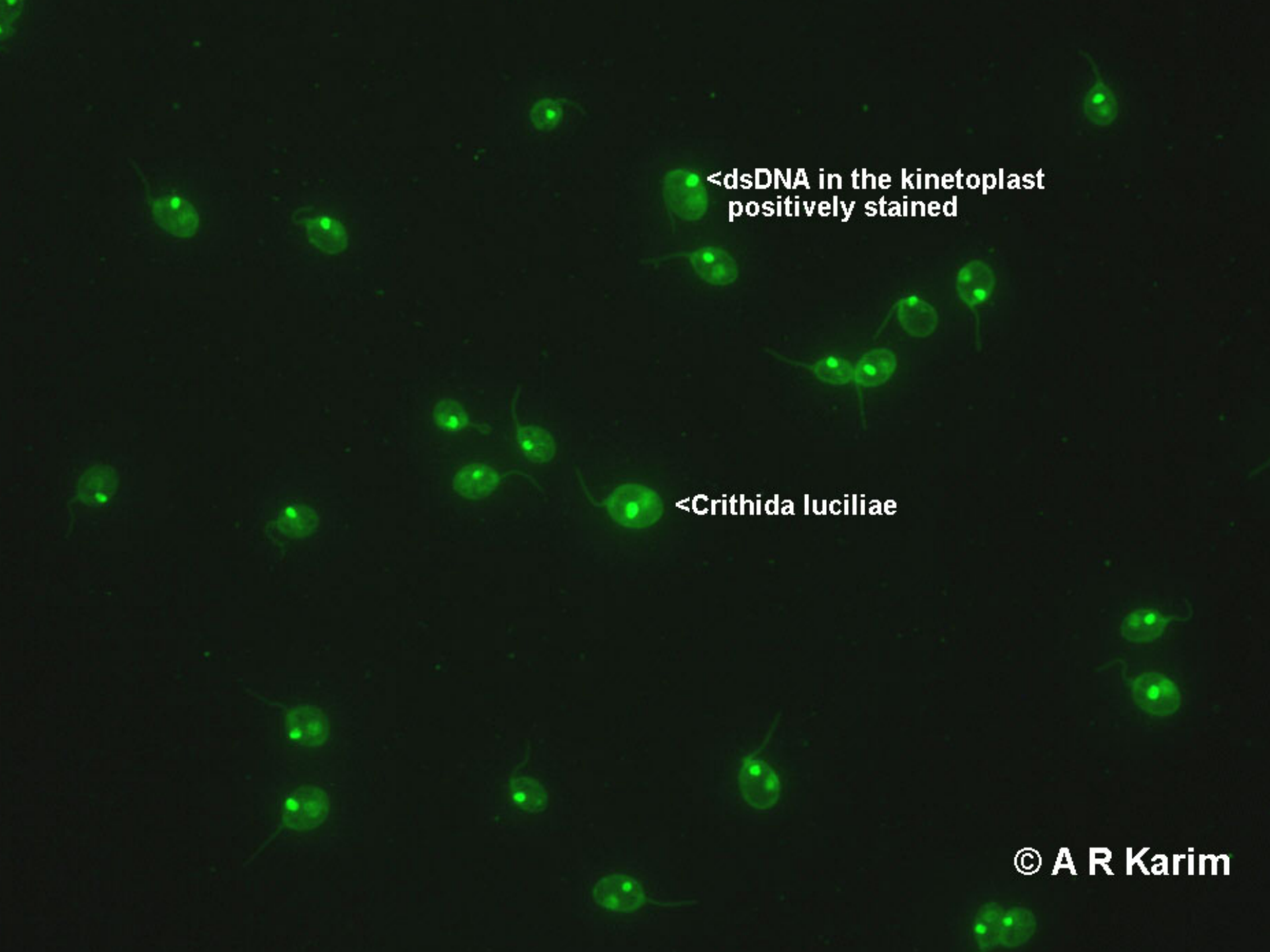


SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

* Effector mechanisms
  - Autoantibodies to many autoantigens
  - Most common autoantibody is to ds-DNA
  - Immune complex deposition on basement membranes with complement activation and inflammation

* Laboratory diagnosis
  - Anti-nuclear antibody (ANA)
    - IFA (indirect fluorescent antibody) assay using HEp-2 cells
    - Homogeneous pattern and titer $\geq$ 1:160
  - Anti ds-DNA
    - IFA assay using Crithidia lucilliae
  - C3 level




<dsDNA in the kinetoplast positively stained
<Crithida luciliae
© A R Karim

TYPE IV AUTOIMMUNE DISEASES

* Mediated by T cells
  - CD4 TH1
  - CD8

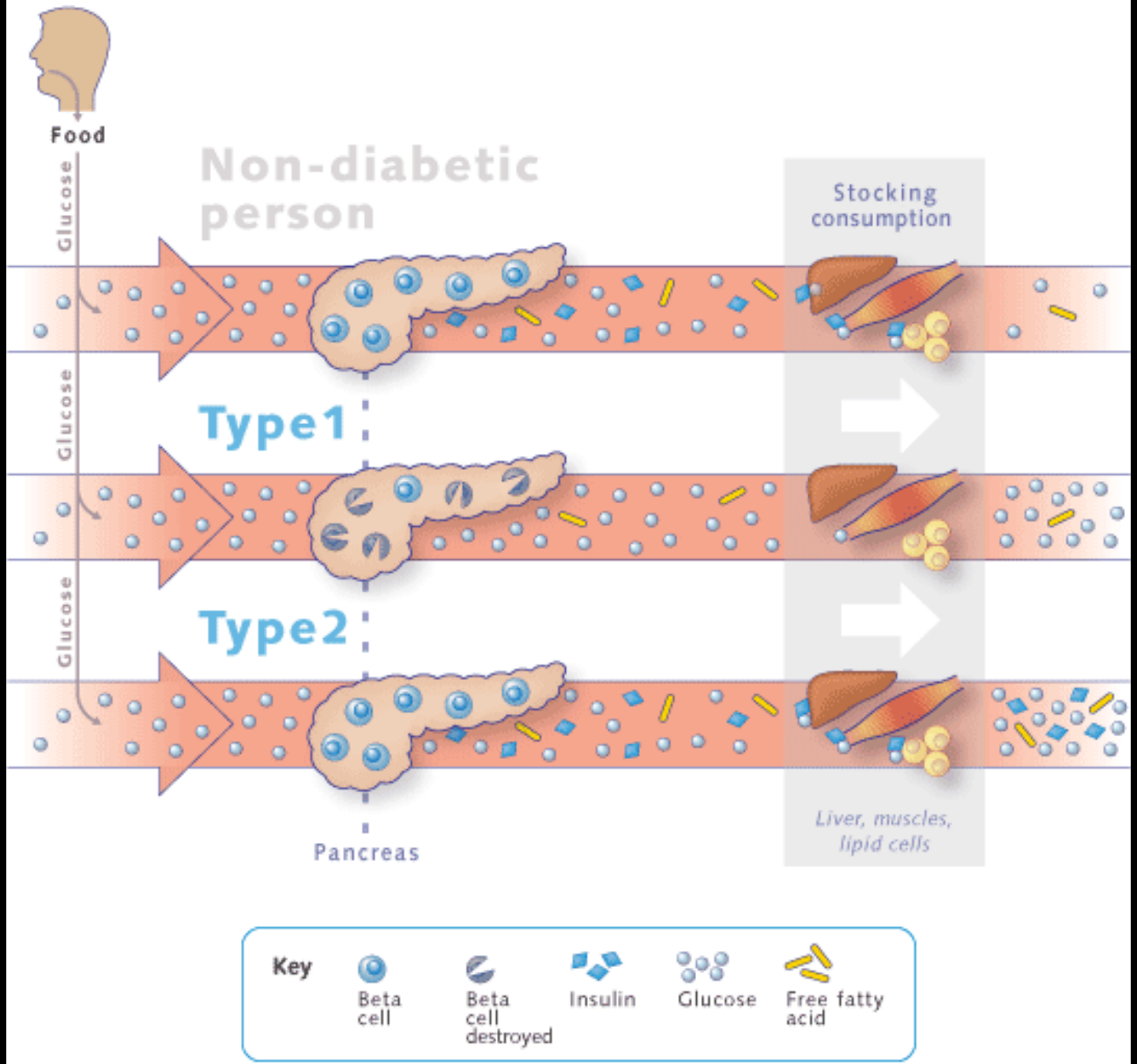
* Organ specific and systemic AD

* It is difficult to identify autoimmune T cells and the autoantigen

INSULIN-DEPENDENT DIABETES MELLITUS (IDDM)

* Synonym
  - Type I diabetes, DM-type I
* Accounts for 5% to 10% of diabetes in US
* Female to male ratio of 1:1
* Effector mechanisms
  - CD8 T cells and autoantibodies against beta cells
    - Glutamic acid decarboxylase (GAD)
    - Insulin

Two types of diabetes

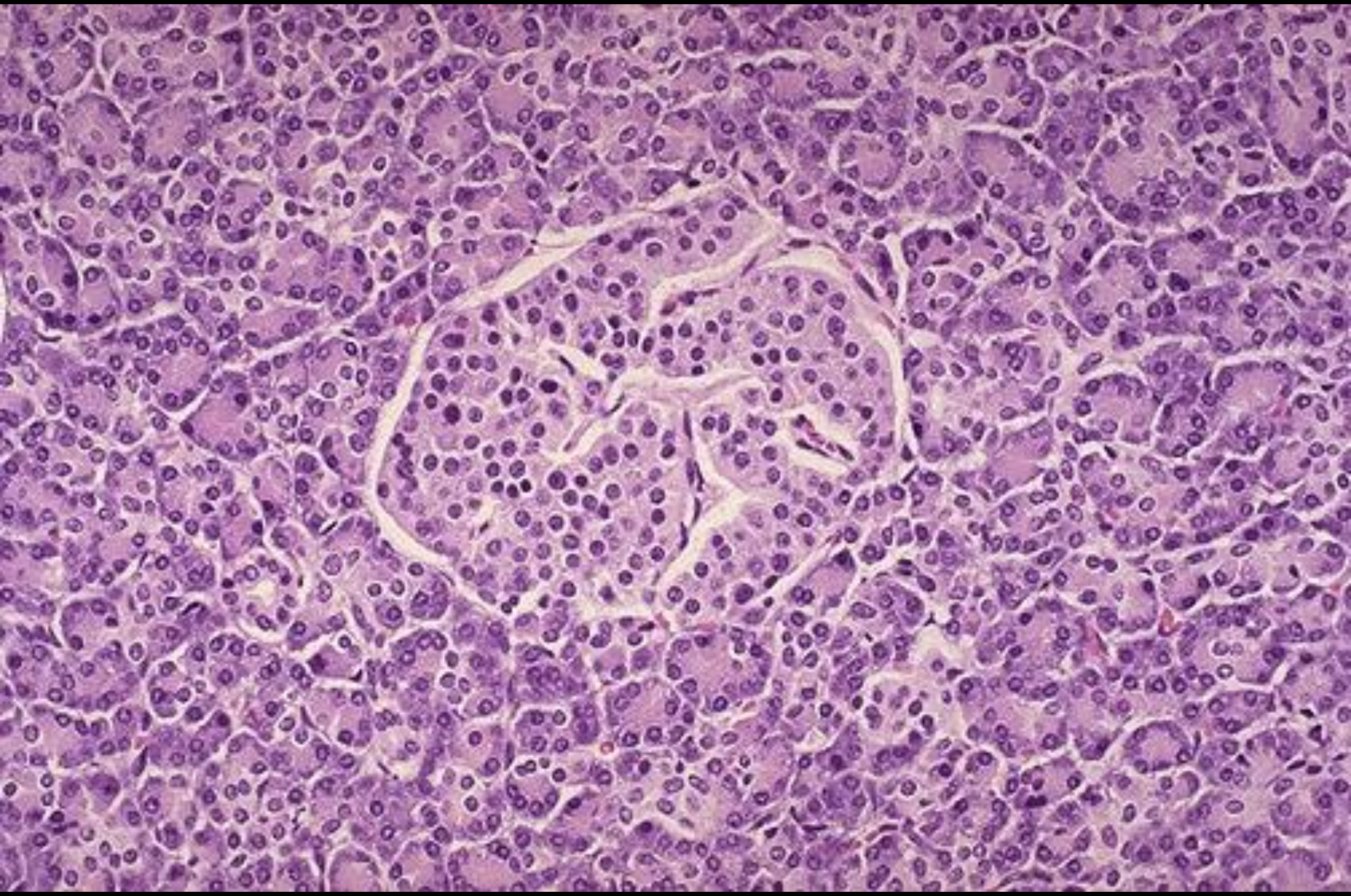


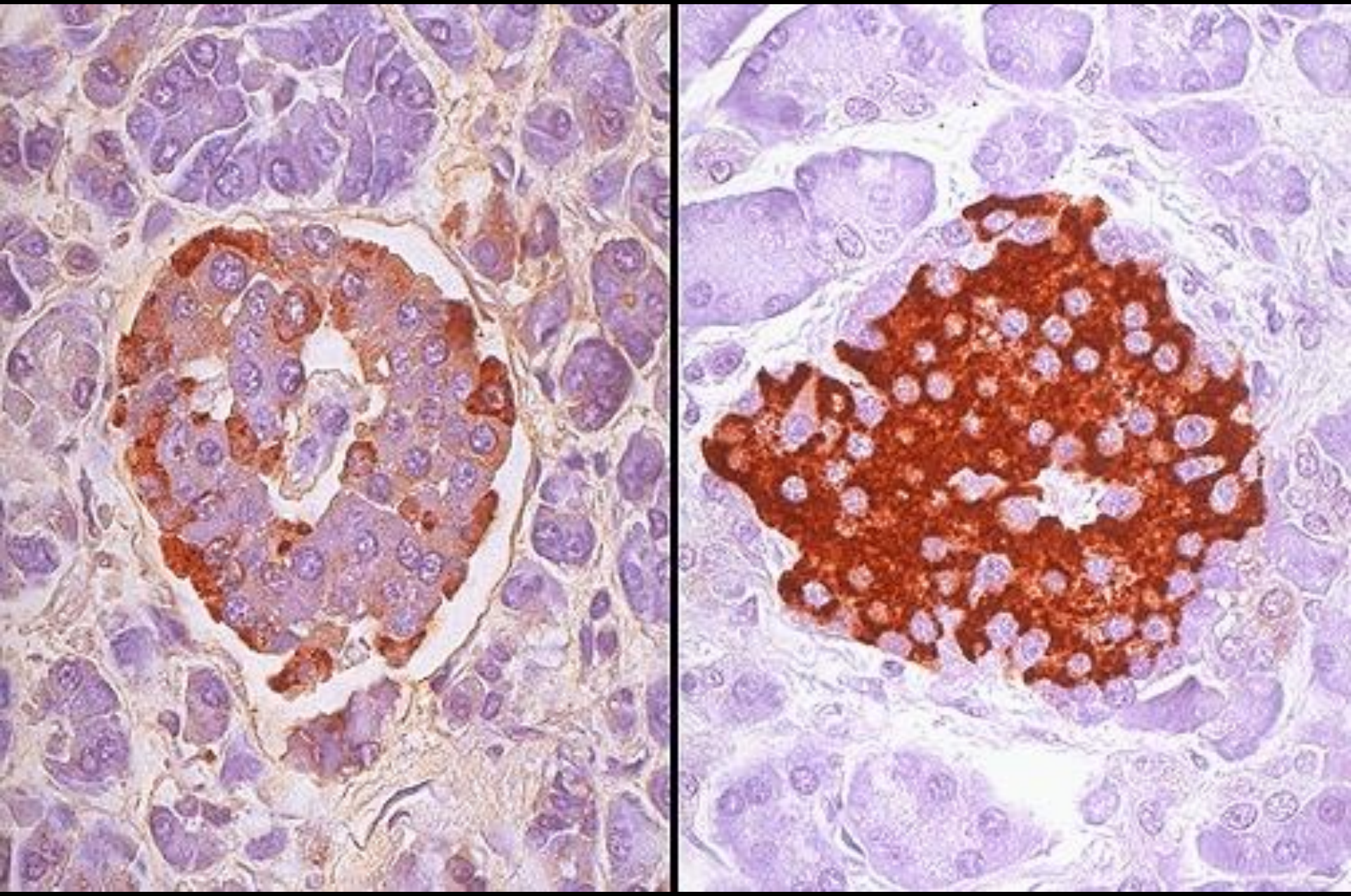
PATHOPHYSIOLOGY OF IDDM

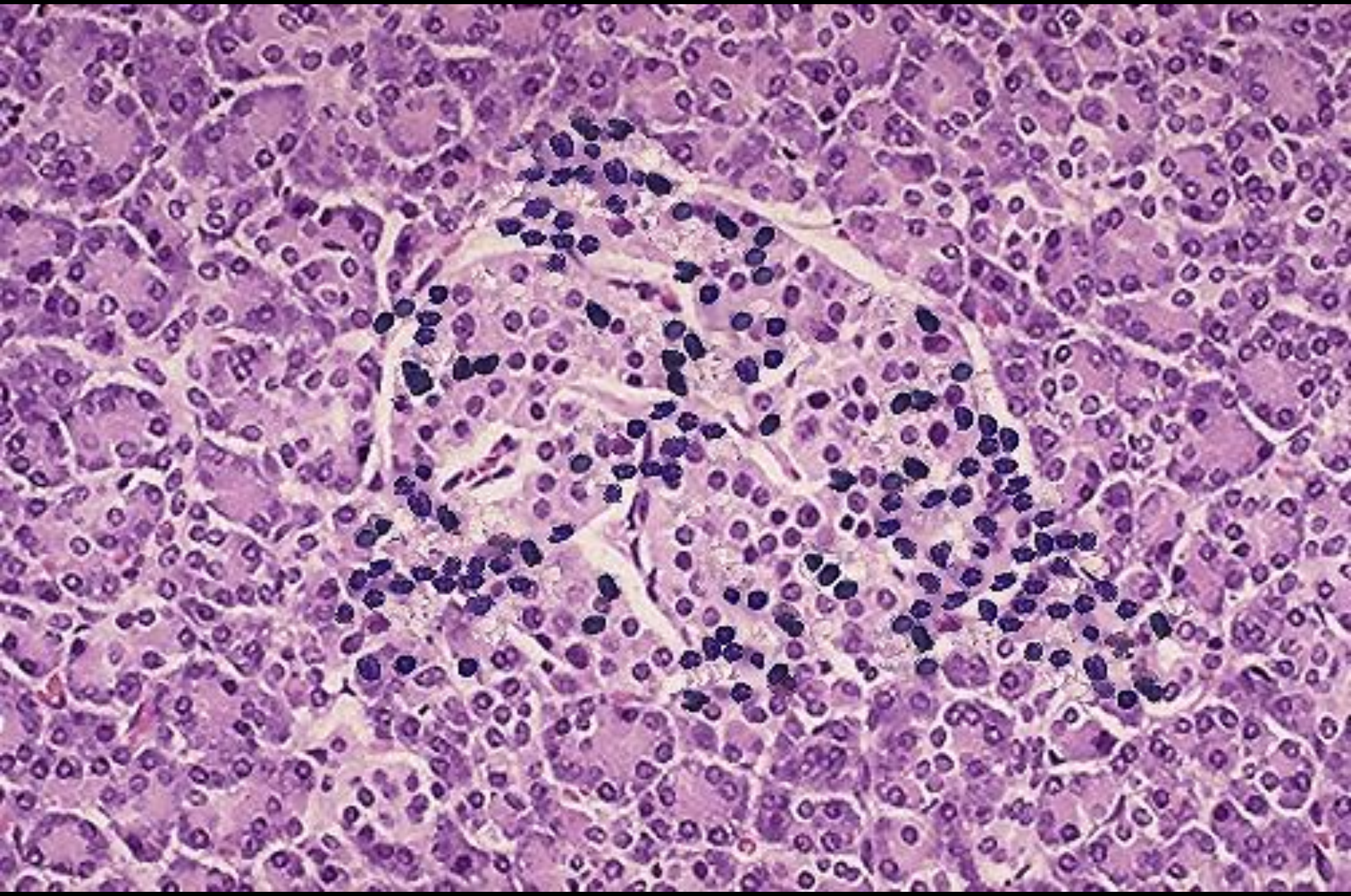
* Pancreatic beta cells are damaged by
  - Infectious agents
    - Mumps virus, rubella virus, coxsackie B virus
  - Toxic chemicals

* Damaged beta cells present antigens which trigger immune attack in genetically susceptible

* Genetic susceptibility
  - HLA-DQ
  - HLA-DR3
  - HLA-DR4







INSULIN-DEPENDENT DIABETES MELLITUS (IDDM)

* Symptoms
  - Increased thirst
  - Frequent urination
  - Increased hunger
  - Weight loss
  - Fatigue

* Laboratory diagnosis
  - Random blood glucose (>200 mg/dL)
  - Fasting blood glucose (≥126 mg/dL)

RHEUMATOID ARTHRITIS (RA)

* Characterized by inflammation of synovial membrane of joints and articular surfaces of cartilage and bone
* Vasculitis is a systemic complication
* Affects 3% to 5% of U.S. population
* Female to male ratio of 3:1
* HLA DR4 is genetic risk factor

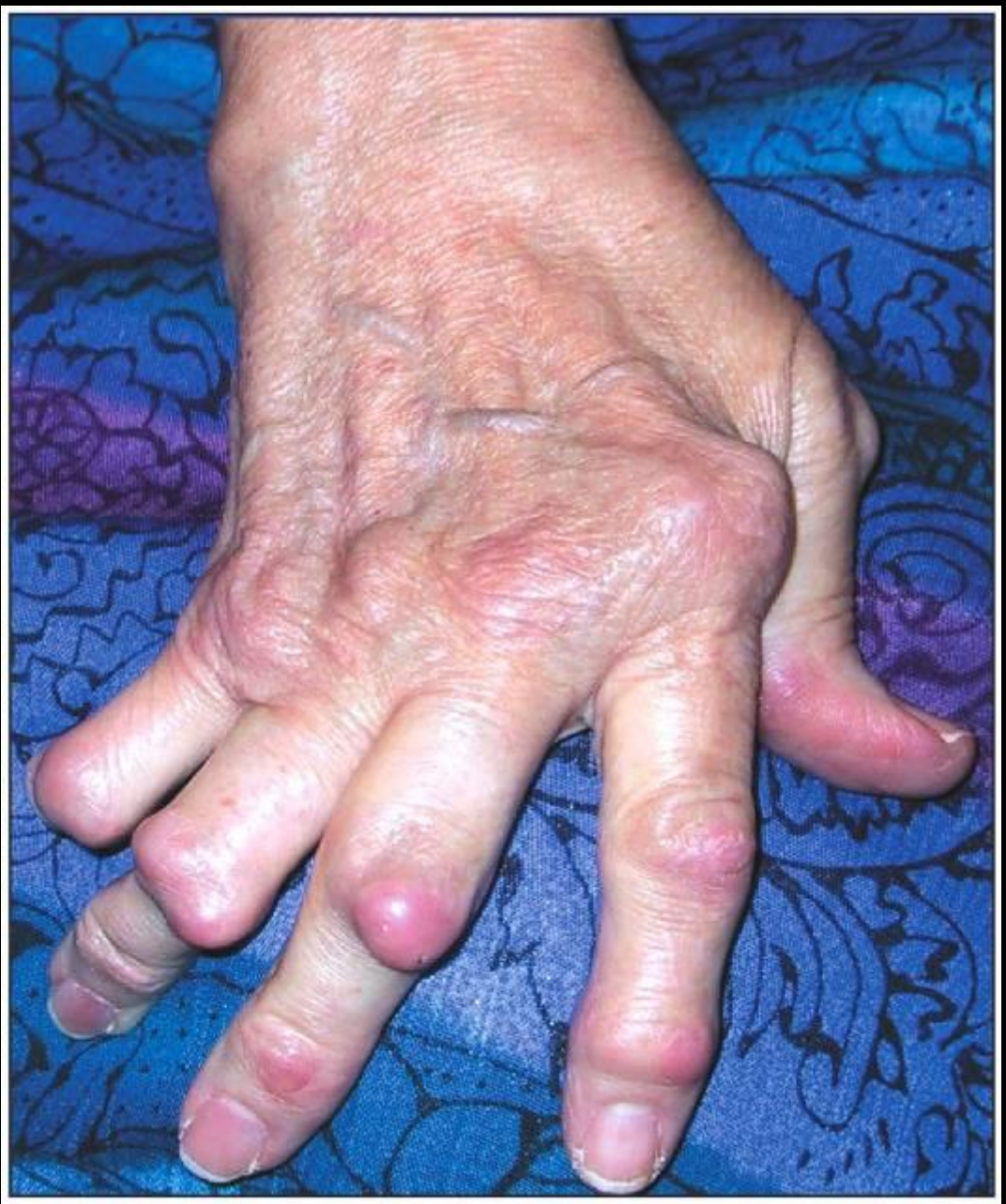


Figure 11-12 The Immune System, 2/e (© Garland Science 2005)

RHEUMATOID ARTHRITIS (RA)

* Effector mechanism
  - CD4 T cells, activated B cells, macrophages and plasma cells
  - 85% of patients have rheumatoid factor
* Rheumatoid factor
  - IgM, IgG and IgA specific for IgG
  - Immune complex formation exacerbates inflammation
* Laboratory diagnosis
  - Rheumatoid factor (RF)
  - Anti-cyclic citrullinated peptide (Anti-CCP)
  - C-reactive protein (CRP)

TREATMENT OF RHEUMATOID ARTHRITIS

* Fast-acting, first line drugs
  * Non-steroidal anti-inflammatory drugs (NSAIDs)
  * Corticosteroids
  * Analgesic drugs
* Slow-acting, second line drugs (Disease-Modifying Antirheumatic Drugs / DMARDs)
  * Hydroxychloroquine (Plaquenil)
  * Methotrexate (Rheumatrex)
  * Azathioprine (Imuran)
  * Human monoclonal antibody to TNF-alpha
    * Infliximab (Remicade)
    * Adalimumab (Humira)
    * Etanercept (Enbrel)

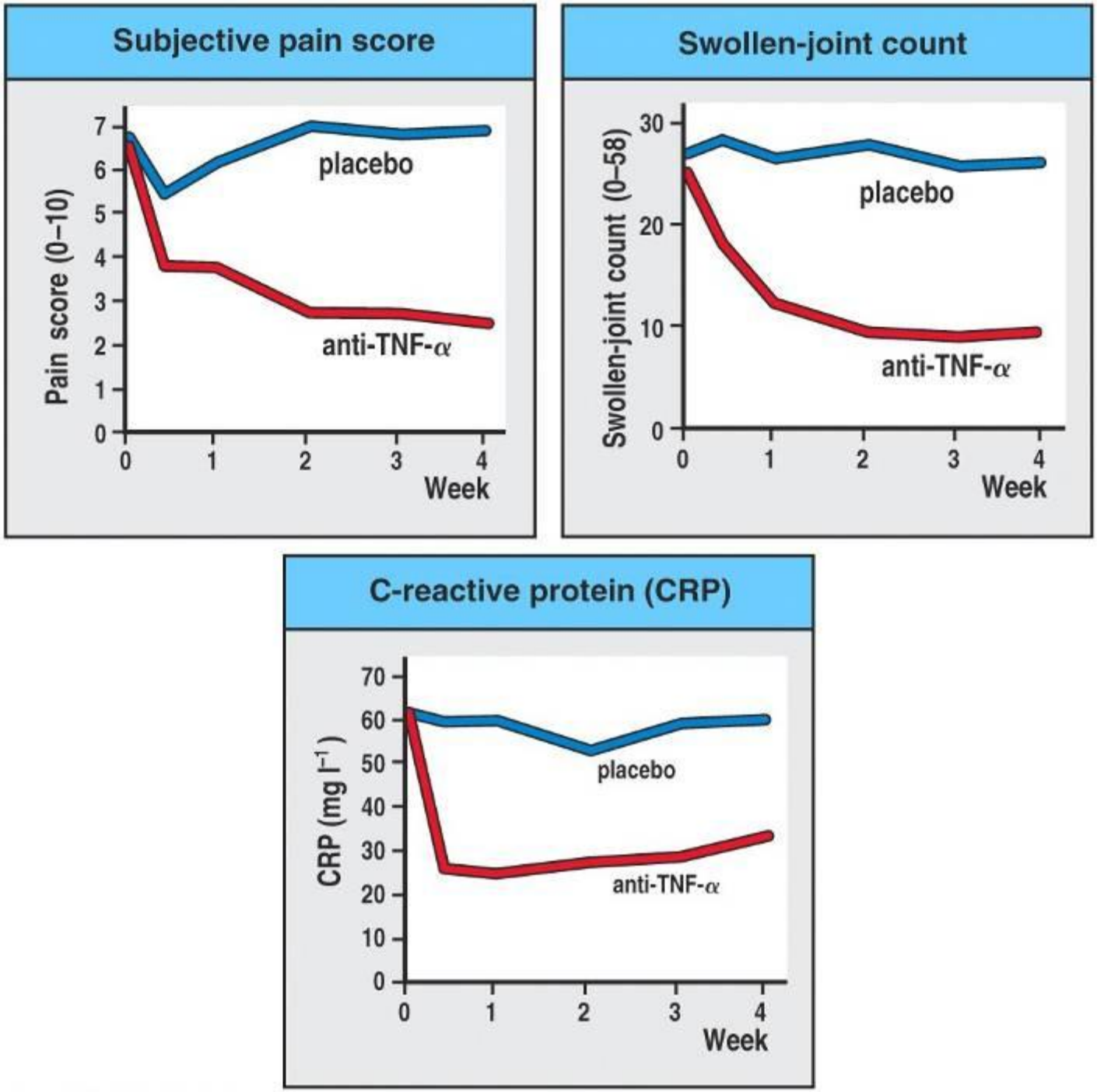


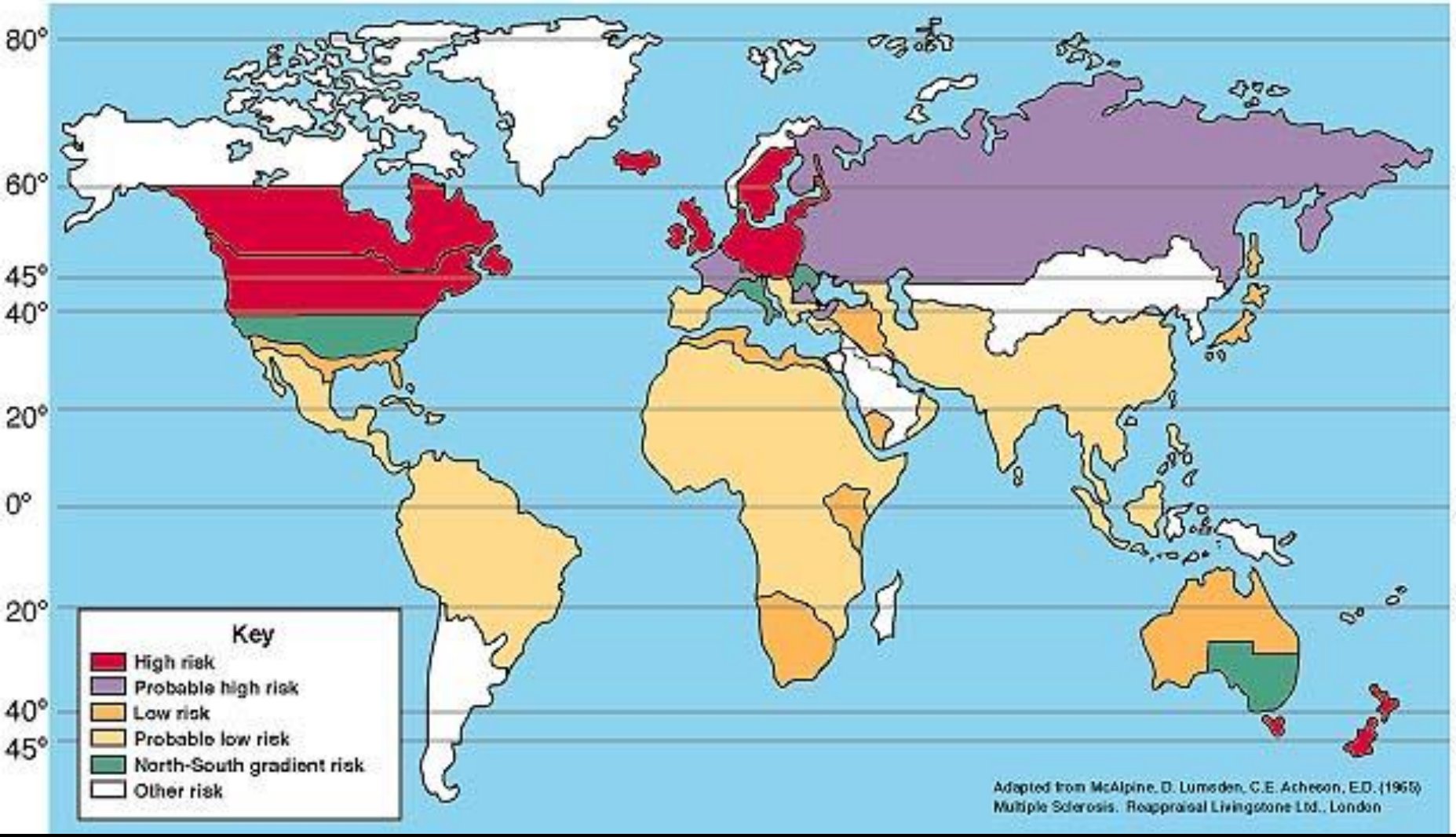
Figure 11-13 The Immune System, 2/e (© Garland Science 2005)

MULTIPLE SCLEROSIS (MS)

* Chronic unpredictable disease of CNS with four possible clinical courses
* Characterized by patches of demyelination and inflammation of myelin sheath
* Prevalence higher in Northern Hemisphere
  - North of 37th parallel (125 cases /100,000)
  - South of 37th parallel (70 cases /100,000)
* Female to male ratio of 2:1


Normal nerve cell
Nerve cell affected by MS
Brain
Spinal cord
Axon
Myelin
Nerve cell communication disrupted
Damage to myelin

World Distribution of Multiple Sclerosis

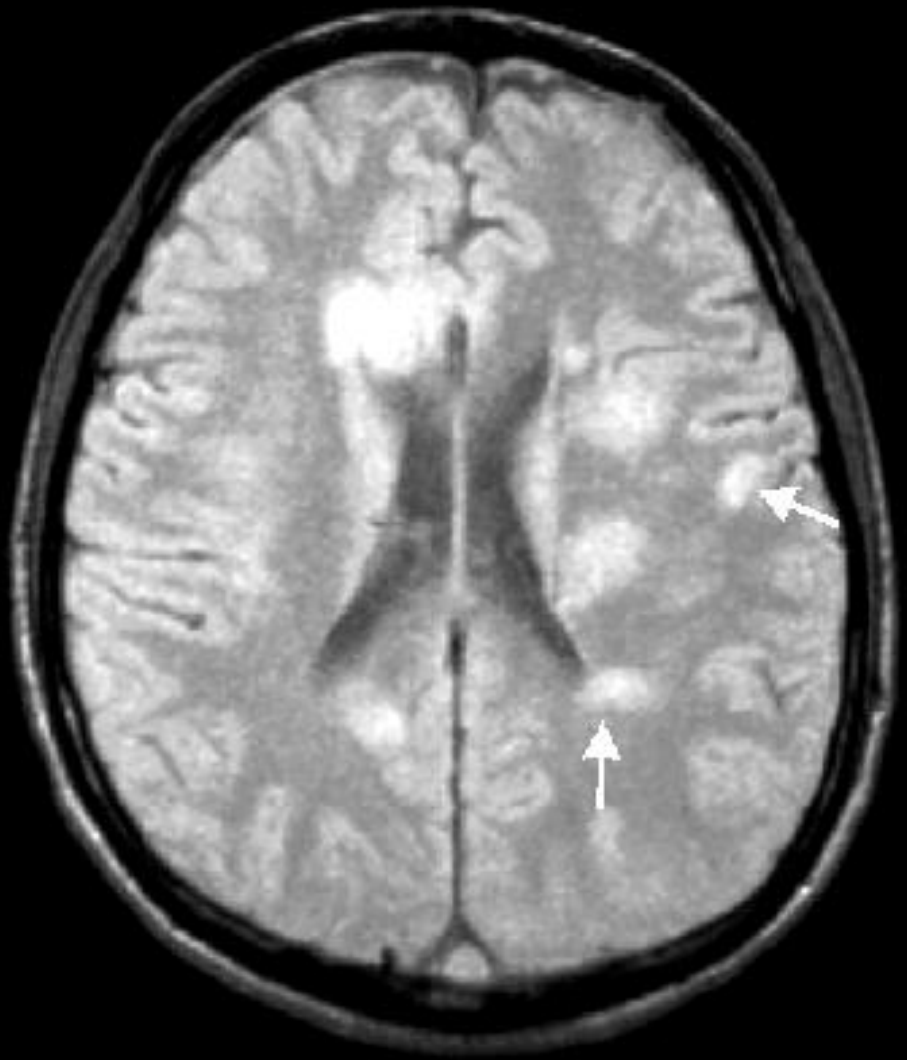


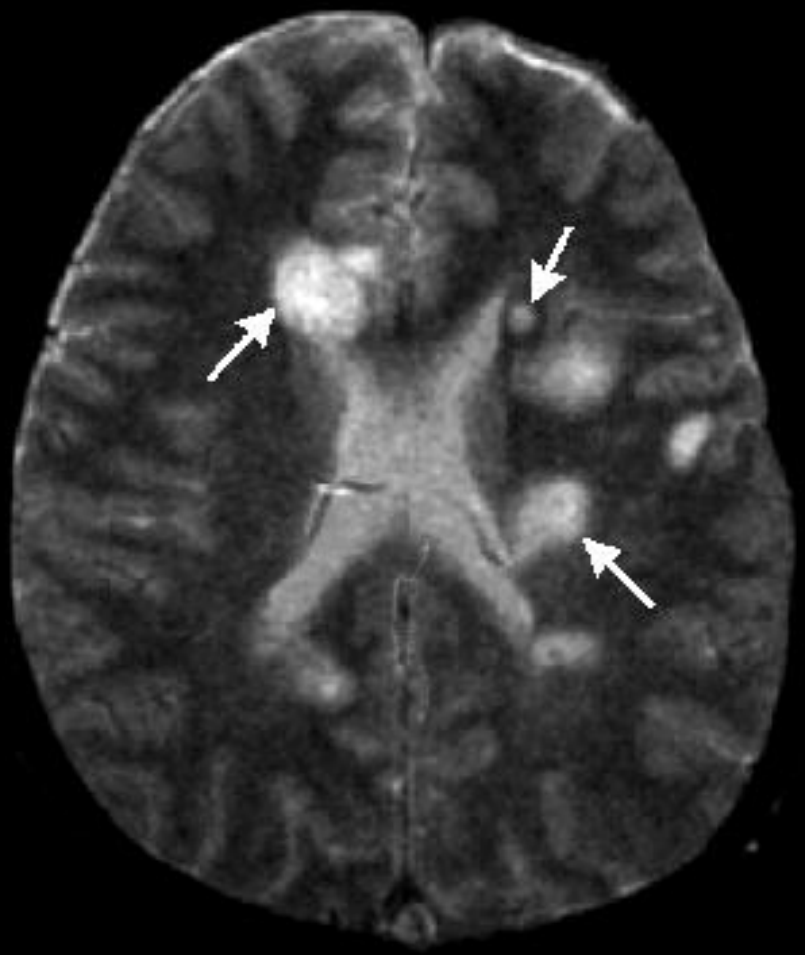
MULTIPLE SCLEROSIS (MS)

* Effector mechanisms
  - Myelin basic protein is primary autoantigen for CD4 TH1 cells

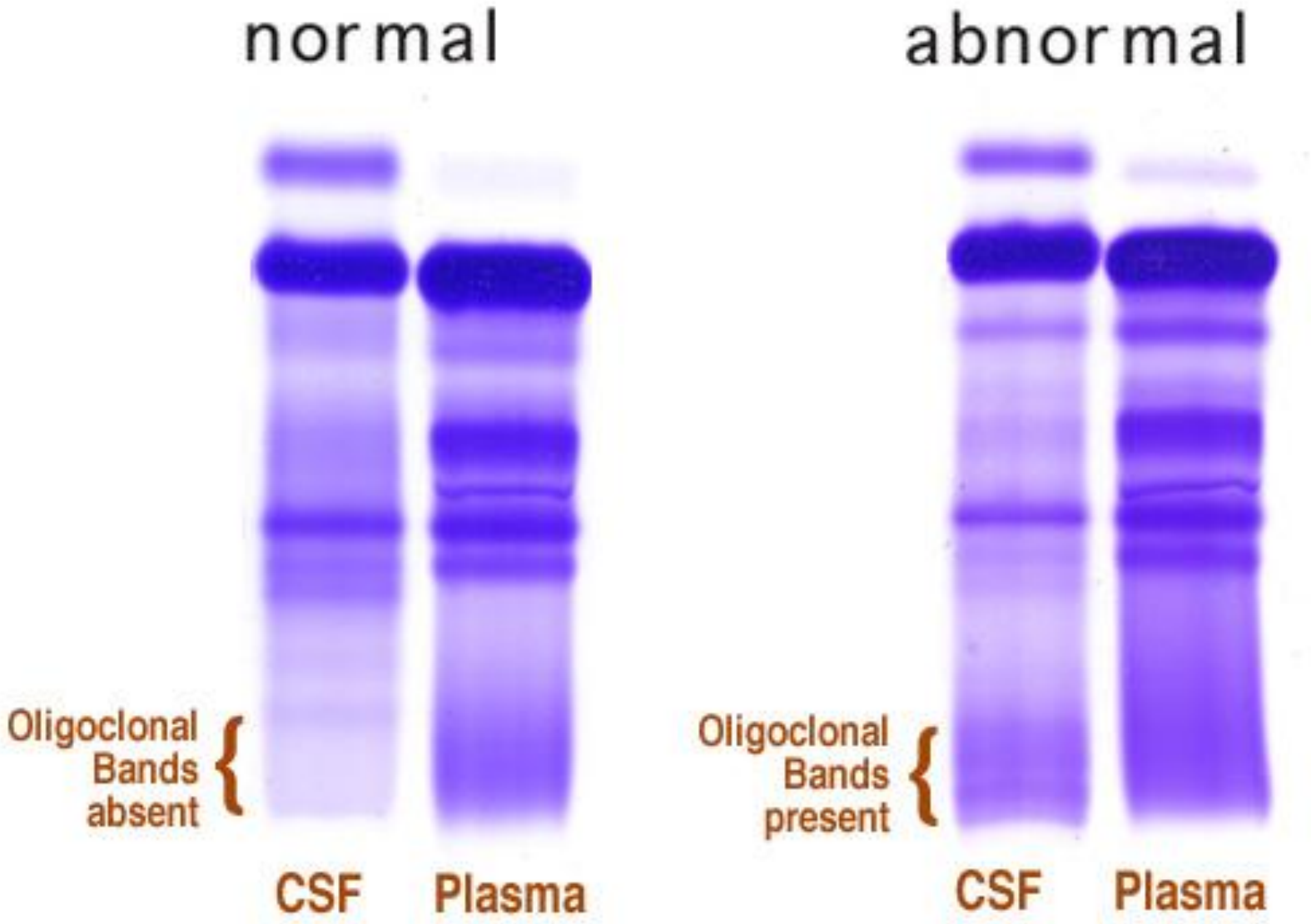
* Radiology diagnosis
  - MRI for detecting demyelinating lesions (plaques)

- Laboratory diagnosis
  - High resolution protein electrophoresis for
    - Oligoclonal bands in CSF





Oligoclonal Bands in CSF



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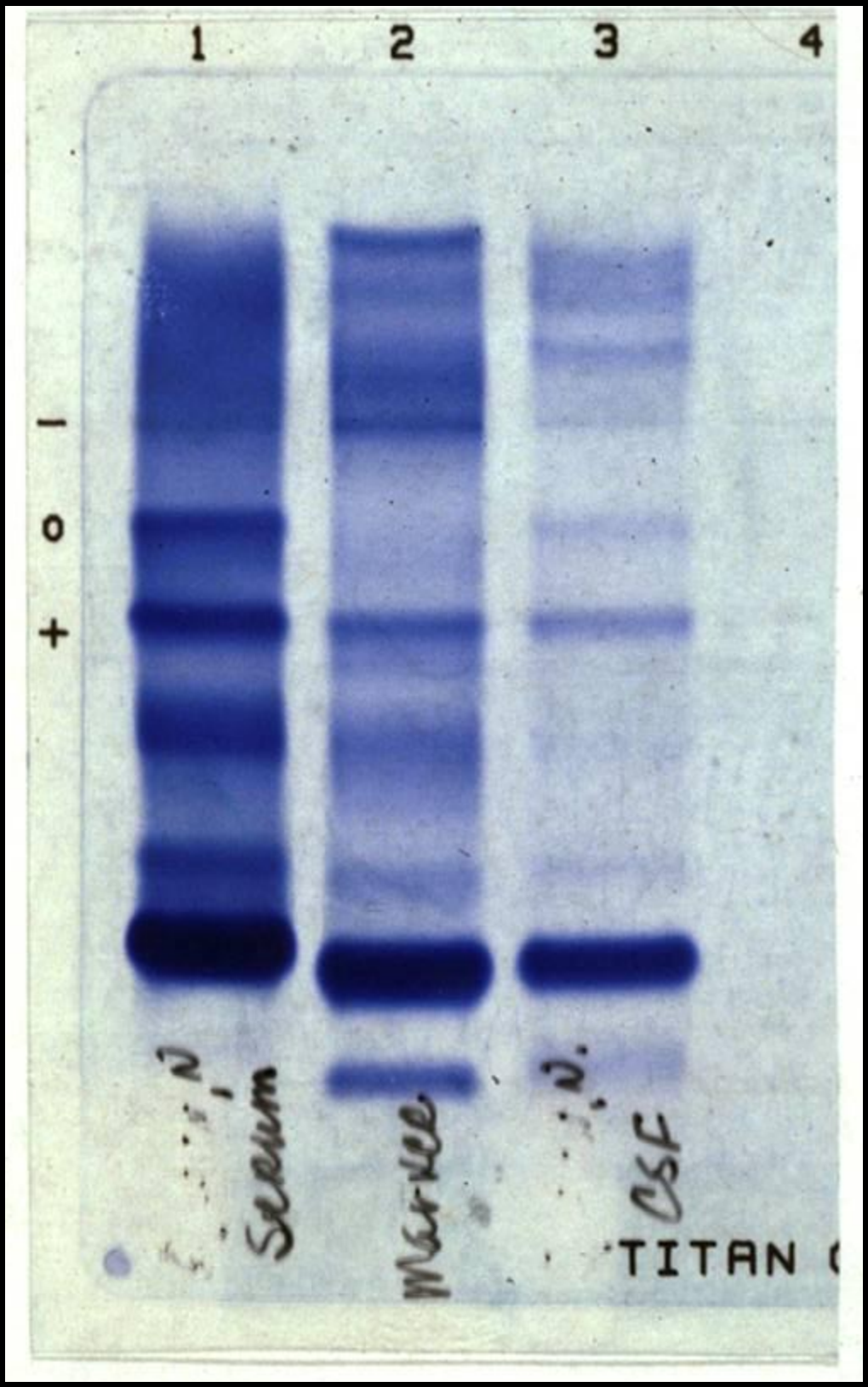
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