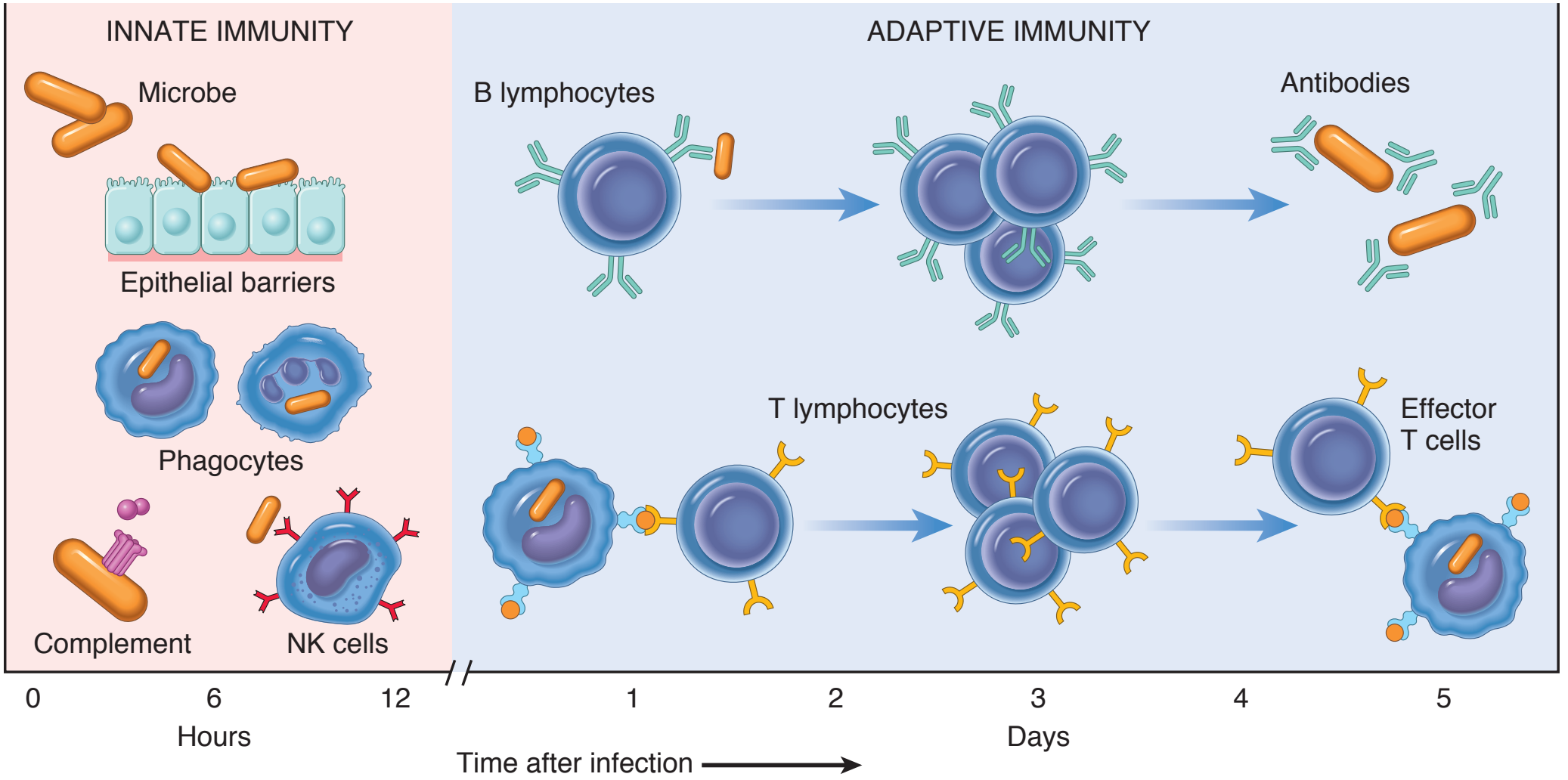
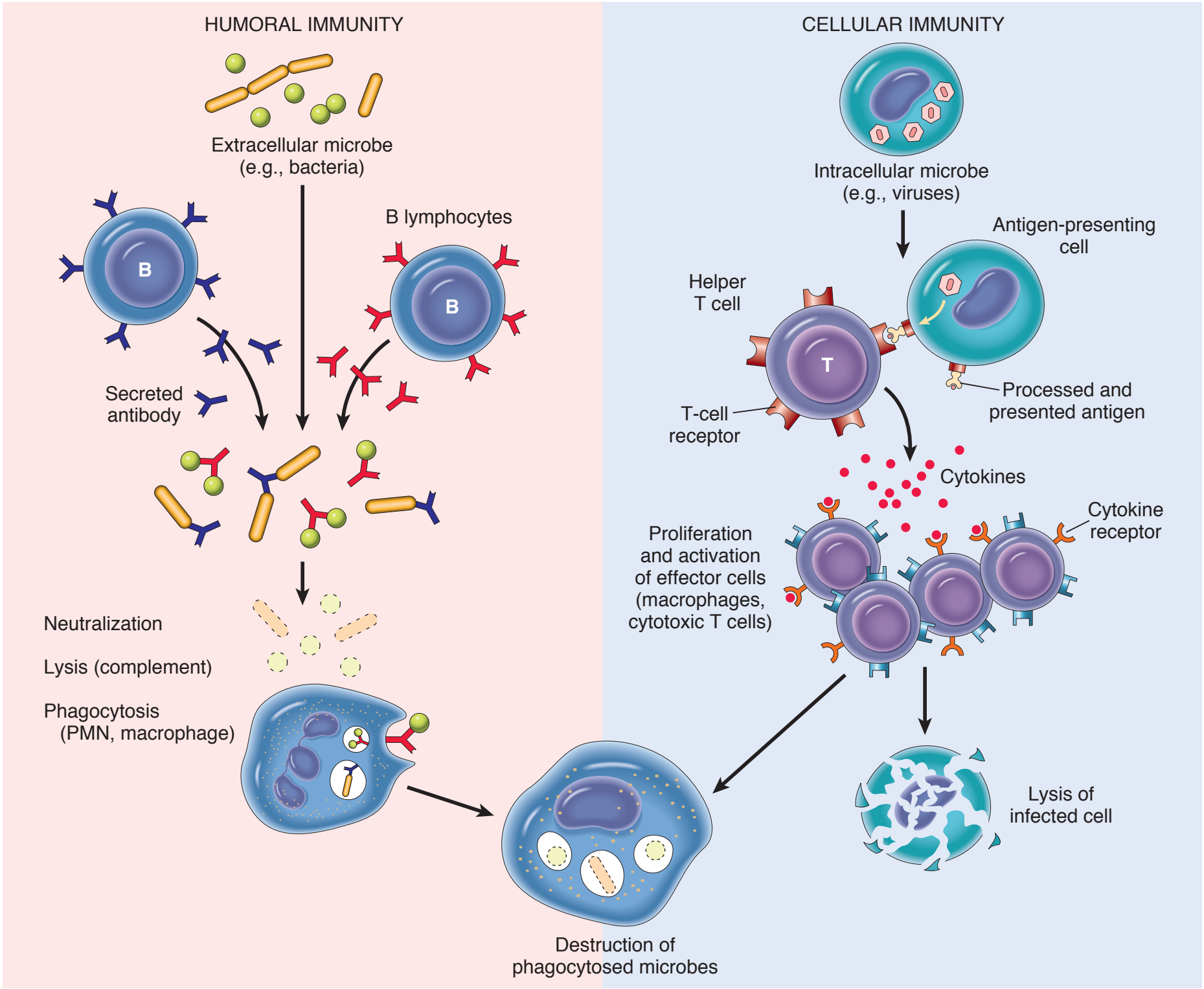
Immunopathology

Henry Sánchez, M.D.

Immune System




HUMORAL IMMUNITY
CELLULAR IMMUNITY
Extracellular microbe
(e.g., bacteria)
B lymphocytes
B
B
Secreted
antibody
Neutralization
Lysis (complement)
Phagocytosis
(PMN, macrophage)
Intracellular microbe
(e.g., viruses)
Antigen-presenting
cell
Helper
T cell
T
T-cell
receptor
Processed and
presented antigen
Cytokines
Cytokine
receptor
Proliferation
and activation
of effector cells
(macrophages,
cytotoxic T cells)
Lysis of
infected cell
Destruction of
phagocytosed microbes

Immunodeficiency Syndromes

- Primary immunodeficiencies
  - Primary B cell immunodeficiency diseases
  - Primary T cell immunodeficiency diseases
  - Primary B and T cell diseases
  - Disorders of complement system
  - Disorders of phagocytes

Severe Combined Immunodeficiency Disease

- Pathogenesis
  - Defects in lymphoid stem cells involving T cell and B cell precursors
- Two modes of transmission
  - Autosomal recessive (lack of adenosine deaminase - chromosome 20q)
  - X-linked (most common - mutation involving common gamma chain in IL receptors)

Severe Combined Immunodeficiency Disease

- Clinical features
  - Early onset of infection with virus, fungus, bacteria and protozoa
  - Failure to thrive
  - Chronic fungal infection
  - Adverse reactions to live virus immunization
  - Susceptible to *Pneumocystis carinii* infection

Severe Combined Immunodeficiency Disease

- Treatment
  - Histocompatible bone marrow transplant
  - Gene therapy
  - Intramuscular gamma globulin
  - Supportive therapy against infection

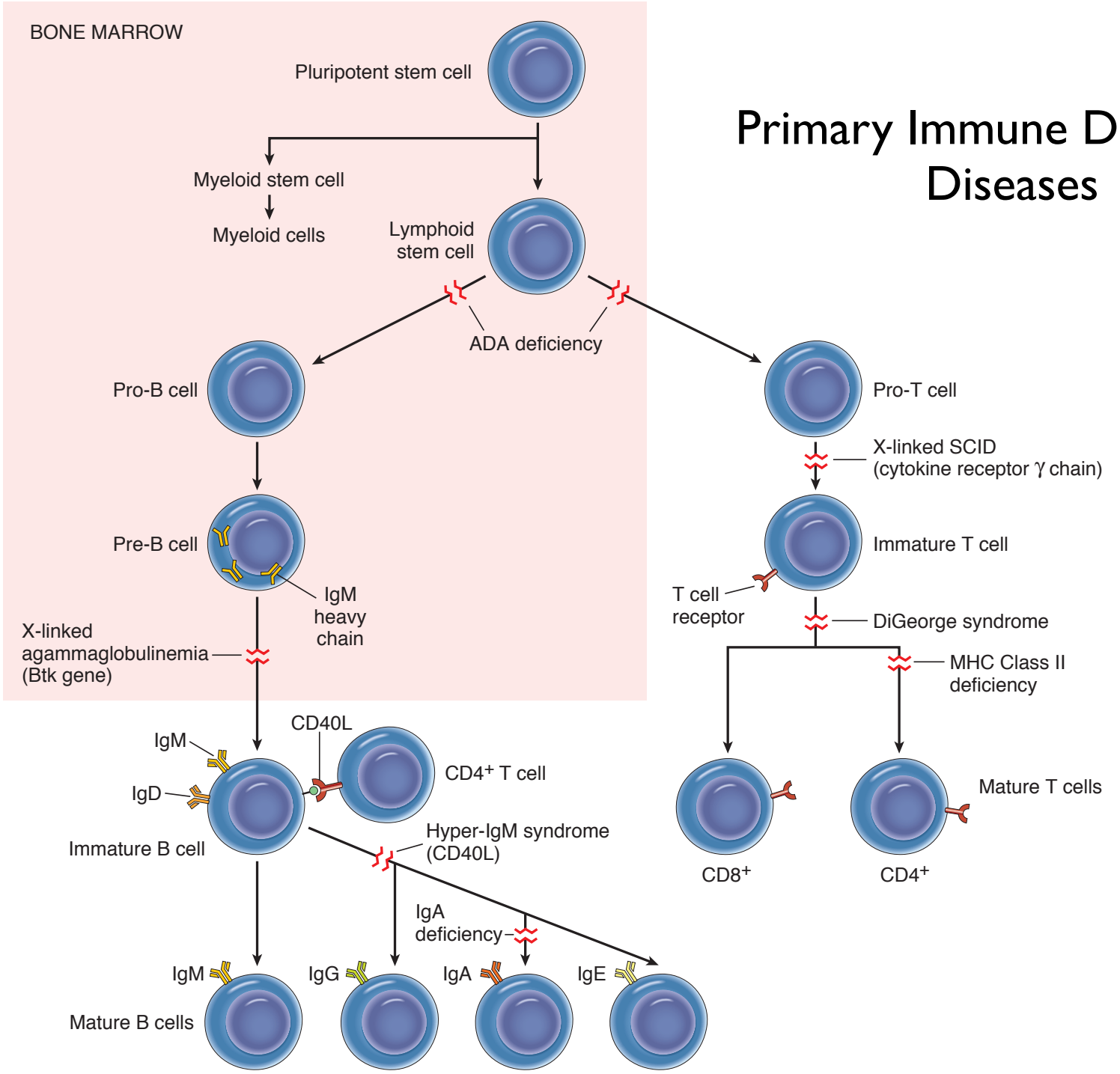
DiGeorge Syndrome

- Absence of thymus
- Decreased T-cells (blood, lymphoid tissue)
- Prone to fungal and viral infections
- Deficient, delayed type skin reactions
- Tetany in some cases (hypoparathyroidism)
- Early onset

X-linked Infantile Agammaglobulinemia

- B-cell deficiency (blood, lymphoid tissue)
- Immunoglobulins decreased
- Multiple bacterial infections
- Normal cellular immunity
- Family history (males)
- Early onset

Primary Immune Deficiency Diseases



Hypersensitivity Reactions

- Immediate (Type I) Hypersensitivity (anaphylactic type)
- Antibody-Mediated (Type II) Hypersensitivity
- Immune Complex-Mediated (Type III) Hypersensitivity
- Cell-Mediated (Type IV) Hypersensitivity

TABLE 6–2 Mechanisms of Immunologically Mediated Hypersensitivity Reactions

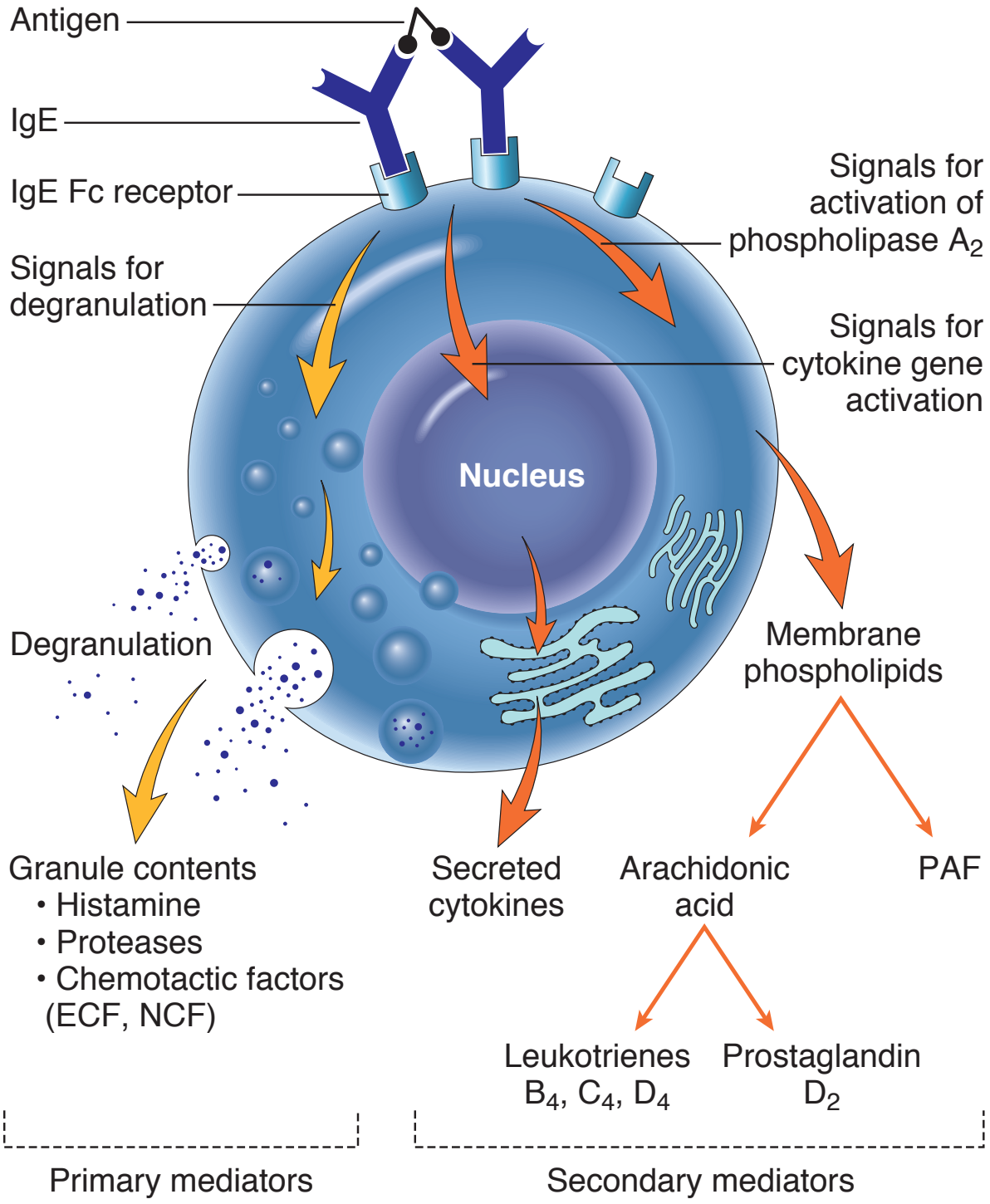
Type of Reaction	Prototypic Disorder	Immune Mechanisms	Pathologic Lesions
Immediate (type I) hypersensitivity	Anaphylaxis; allergies; bronchial asthma (atopic forms)	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; later recruitment of inflammatory cells	Vascular dilation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation
Antibody-mediated (type II) hypersensitivity	Autoimmune hemolytic anemia; Goodpasture syndrome	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Phagocytosis and lysis of cells; inflammation; in some diseases, functional derangements without cell or tissue injury
Immune complex–mediated (type III) hypersensitivity	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction	Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Inflammation, necrotizing vasculitis (fibrinoid necrosis)
Cell-mediated (type IV) hypersensitivity	Contact dermatitis; multiple sclerosis; type I diabetes; rheumatoid arthritis; inflammatory bowel disease; tuberculosis	Activated T lymphocytes → (i) release of cytokines → inflammation and macrophage activation; (ii) T cell–mediated cytotoxicity	Perivascular cellular infiltrates; edema; granuloma formation; cell destruction

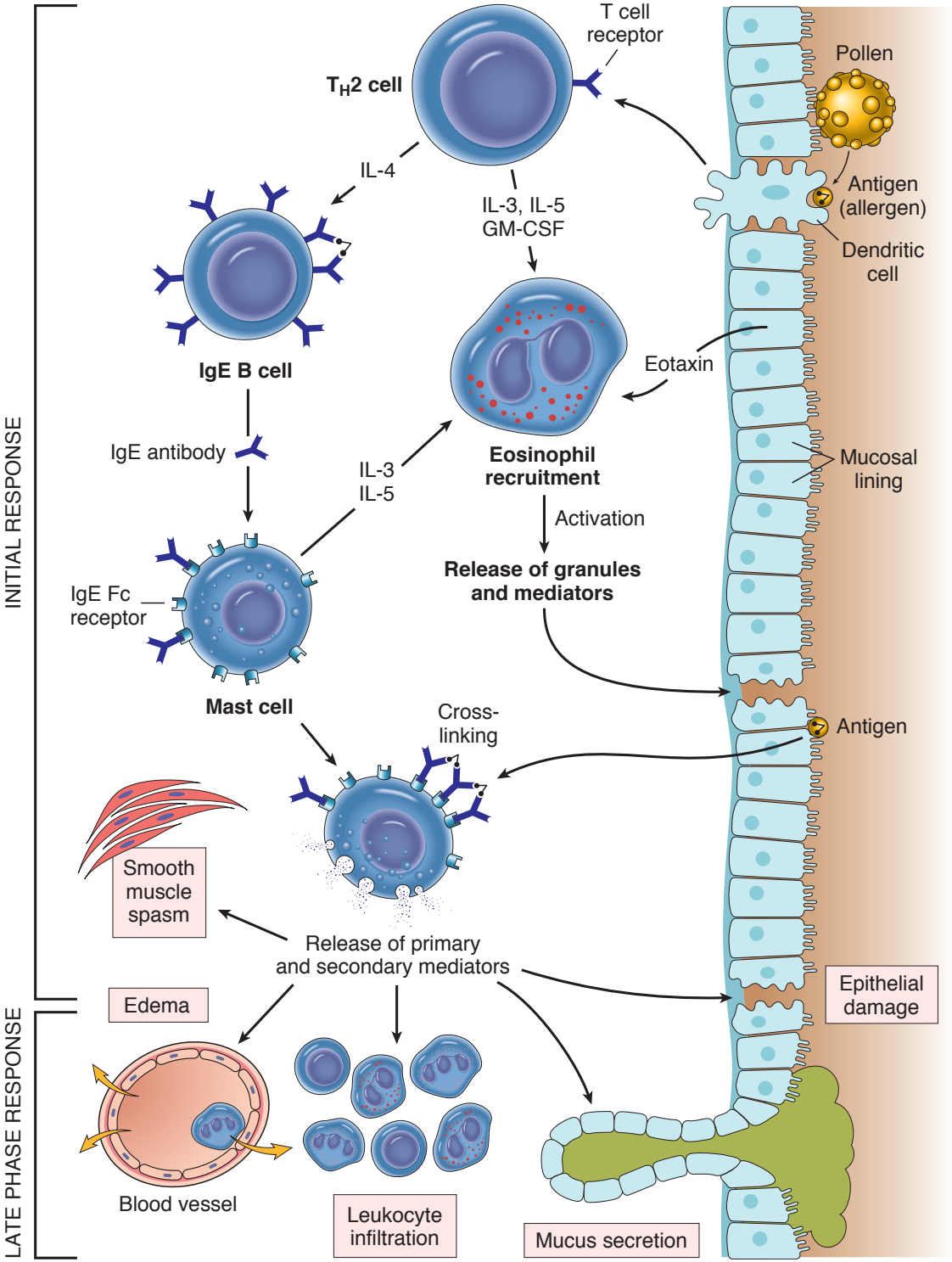
Immediate (Type I) Hypersensitivity: Anaphylactic Type

- IgE mediated release of chemical mediators of inflammation from mast cells and basophils including:
  - Histamine, heparin, enzymes (tryptase and beta-glucosaminidase)
  - ECF-A and NCF - chemotaxis of eosinophils and neutrophils
  - Synthesize SRS-A (LTC4+LTD4), prostaglandins, thromboxanes, PAF

Immediate (Type I) Hypersensitivity: Anaphylactic Type

- Examples:
  - Systemic anaphylaxis - protein (antisera) and drugs (e.g., penicillin)
  - Skin and food allergies - local reaction (atopy)


Antigen
IgE
IgE Fc receptor
Signals for degranulation
Signals for activation of phospholipase A_2
Signals for cytokine gene activation
Nucleus
Degranulation
Membrane phospholipids
Granule contents
• Histamine
• Proteases
• Chemotactic factors (ECF, NCF)
Secreted cytokines
Arachidonic acid
PAF
Leukotrienes B_4, C_4, D_4
Prostaglandin D_2
Primary mediators
Secondary mediators

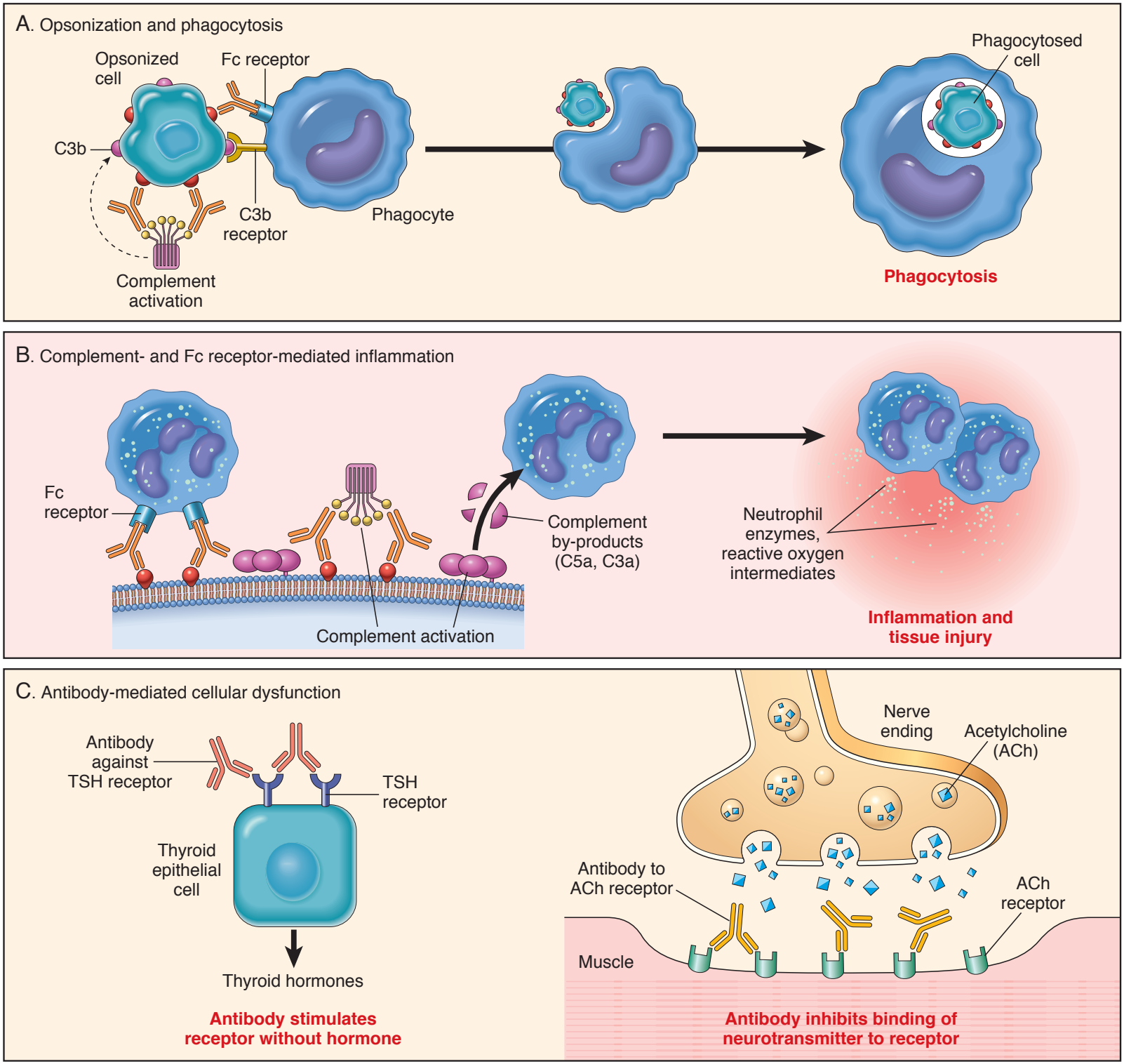

INITIAL RESPONSE
LATE PHASE RESPONSE
T cell receptor
T_H2 cell
Pollen
IL-4
IL-3, IL-5
GM-CSF
Antigen (allergen)
Dendritic cell
IgE B cell
Eotaxin
IgE antibody
IL-3
IL-5
Eosinophil recruitment
Mucosal lining
Activation
Release of granules and mediators
IgE Fc receptor
Mast cell
Cross-linking
Antigen
Smooth muscle spasm
Release of primary and secondary mediators
Epithelial damage
Edema
Blood vessel
Leukocyte infiltration
Mucus secretion

Antibody-Mediated (Type II) Hypersensitivity: Cytoxic

- Antibodies are formed (usually, IgM or IgG) that bind to antigen on target cell surface or tissue
- Types:
  - Complement dependent (e.g., autoimmune hemolytic anemias, erythroblastosis fetalis and Goodpasture syndrome)

Antibody-Mediated (Type II) Hypersensitivity: Cytoxic

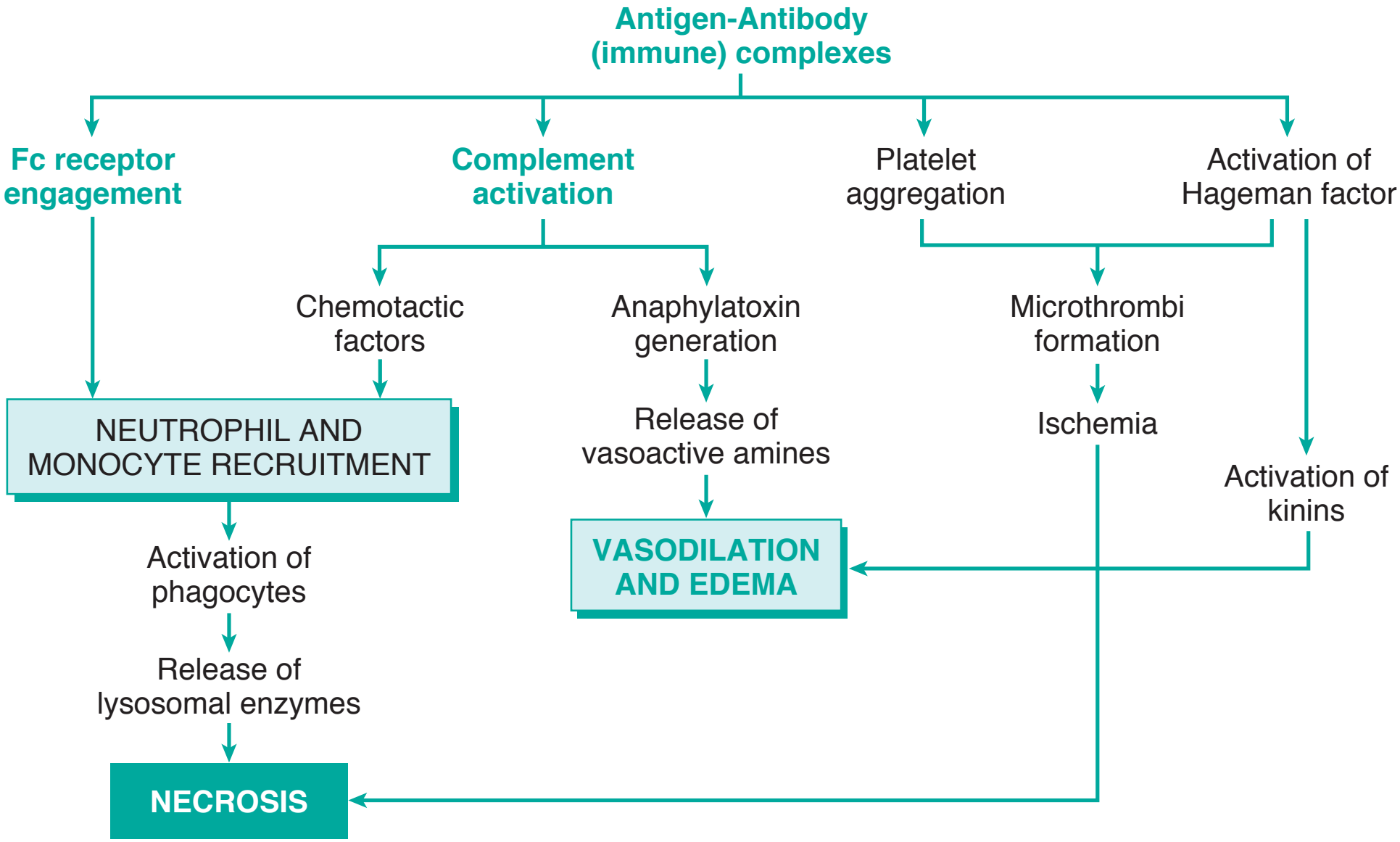
- Types:
  - Antibody-dependent cellular cytotoxicity (e.g., against parasites dependent upon IgE antibodies)
  - Antibody-mediated cellular dysfunction (e.g., myasthenia gravis, Graves disease)


A. Opsonization and phagocytosis
Opsonized cell
Fc receptor
C3b
C3b receptor
Phagocyte
Complement activation
Phagocytosed cell
Phagocytosis
B. Complement- and Fc receptor-mediated inflammation
Fc receptor
Complement by-products (C5a, C3a)
Complement activation
Neutrophil enzymes, reactive oxygen intermediates
Inflammation and tissue injury
C. Antibody-mediated cellular dysfunction
Antibody against TSH receptor
TSH receptor
Thyroid epithelial cell
Thyroid hormones
Antibody stimulates receptor without hormone
Nerve ending
Acetylcholine (ACh)
Antibody to ACh receptor
ACh receptor
Muscle
Antibody inhibits binding of neurotransmitter to receptor

Immune Complex-Mediated (Type III) Hypersensitivity: Immune Complex Disease

- Antigen-antibody complexes cause activation of complement initiating an acute inflammatory response leading to tissue injury

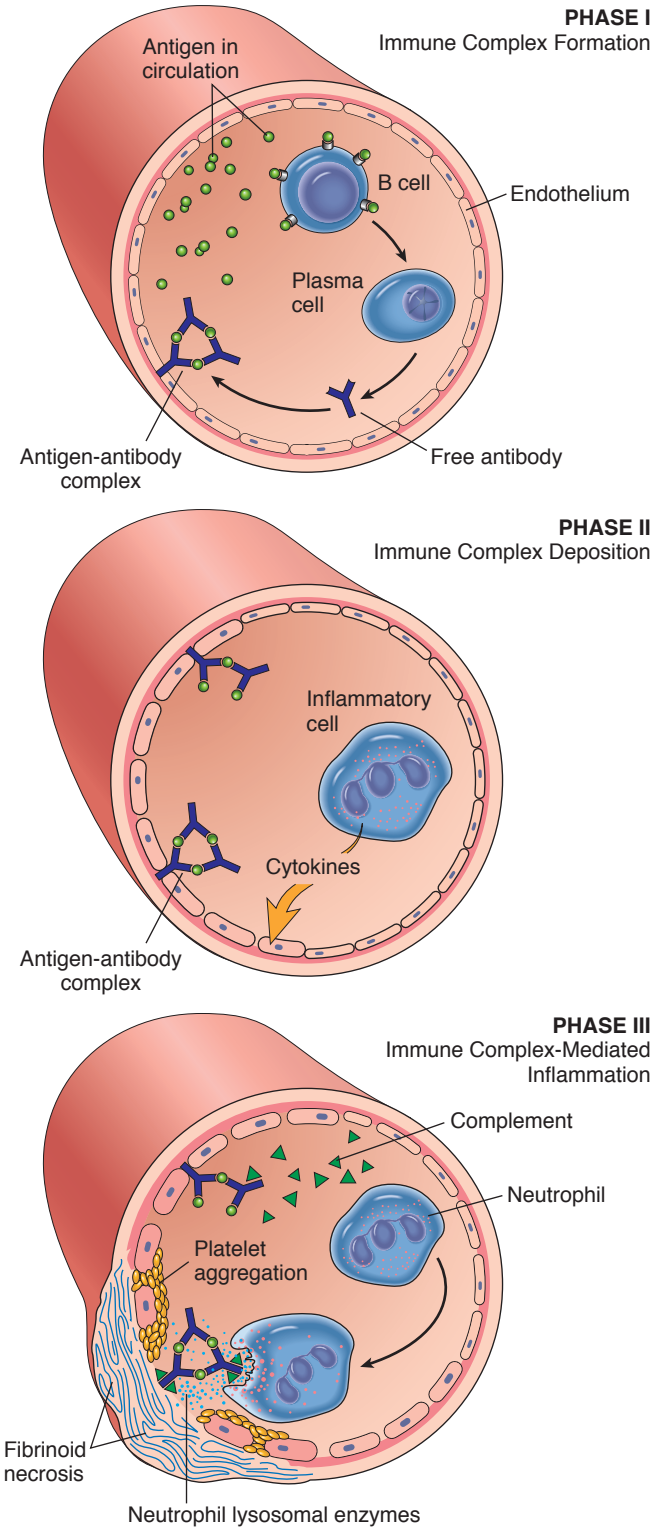
Pathogenesis of Immune Complexes



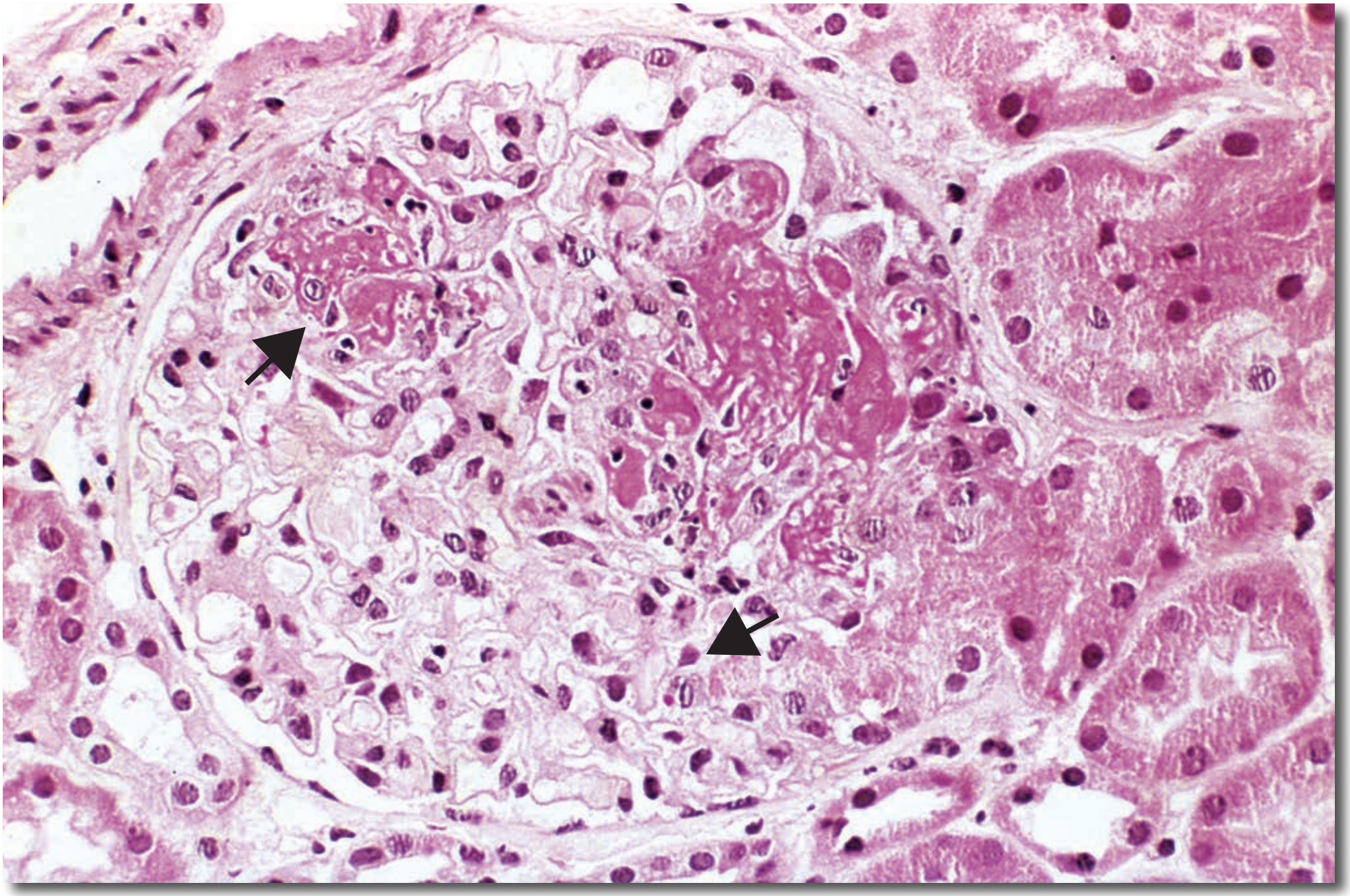
Immune Complex-Mediated(Type III) Hypersensitivity: Immune

- Examples:
  - Serum sickness (e.g., horse anti-tetanus serum)
  - System lupus erythematous (most visceral lesions)
  - Arthus reaction (localized area of tissue necrosis due to an acute immune complex vasculitis)
  - Certain forms of acute glomerulonephritis

Pathogenesis of Immune Complex Vasculitis



Acute Glomerulonephritis



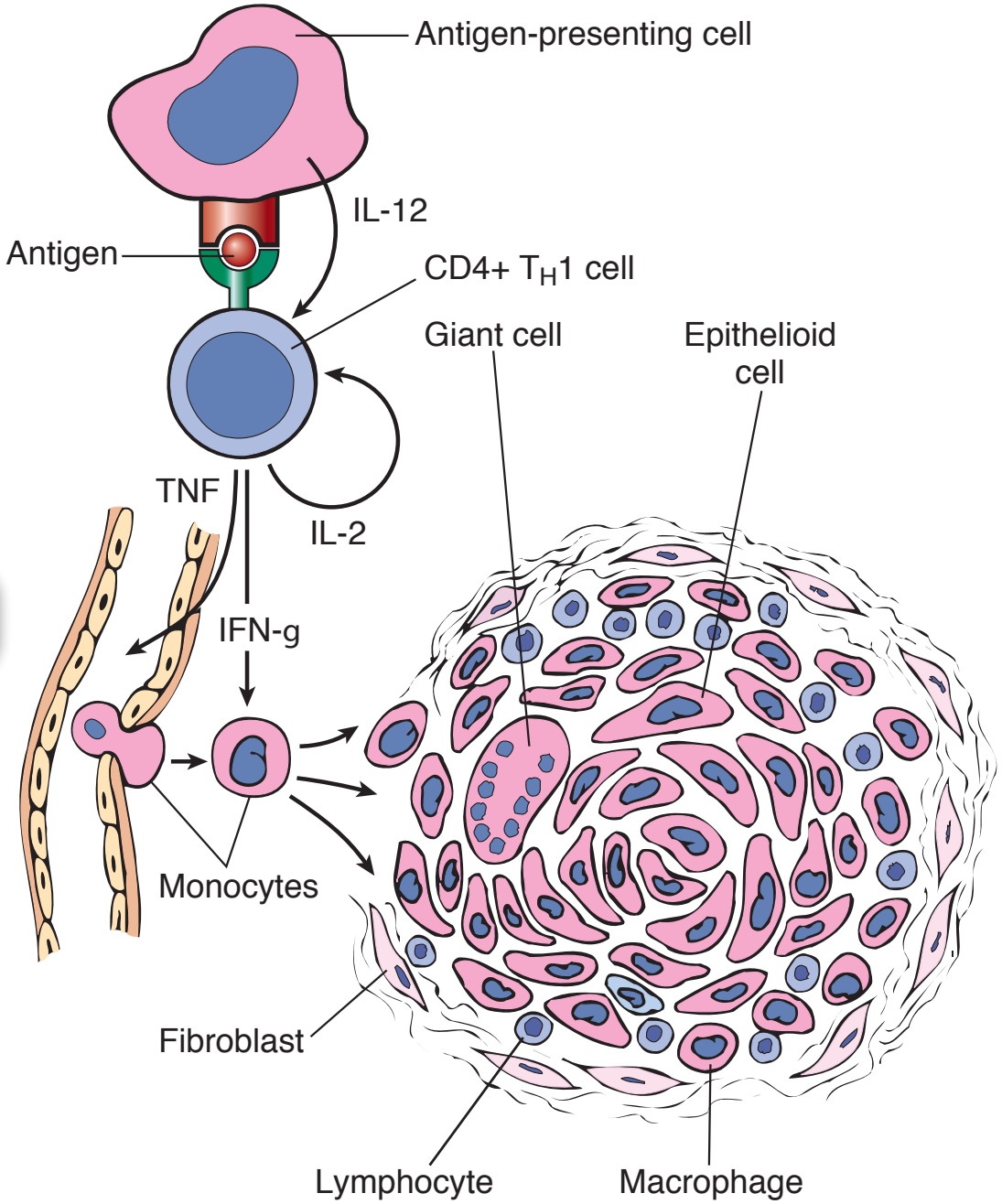
Cell-Mediated (Type IV) Hypersensitivity: Delayed, Cell-Mediated

- Sensitized T-cells exposed to specific antigens complexed to self MHC molecules
- Types:
  - Delayed type hypersensitivity (MHC II) - mediated by CD4+ T helper$_1$ cells that secrete cytokines leading to the recruitment of major effector cells (e.g., macrophages)
  - T cell-mediated cytotoxicity (MHC I) - mediated by CD8+ T cells that directly act as the effector cells

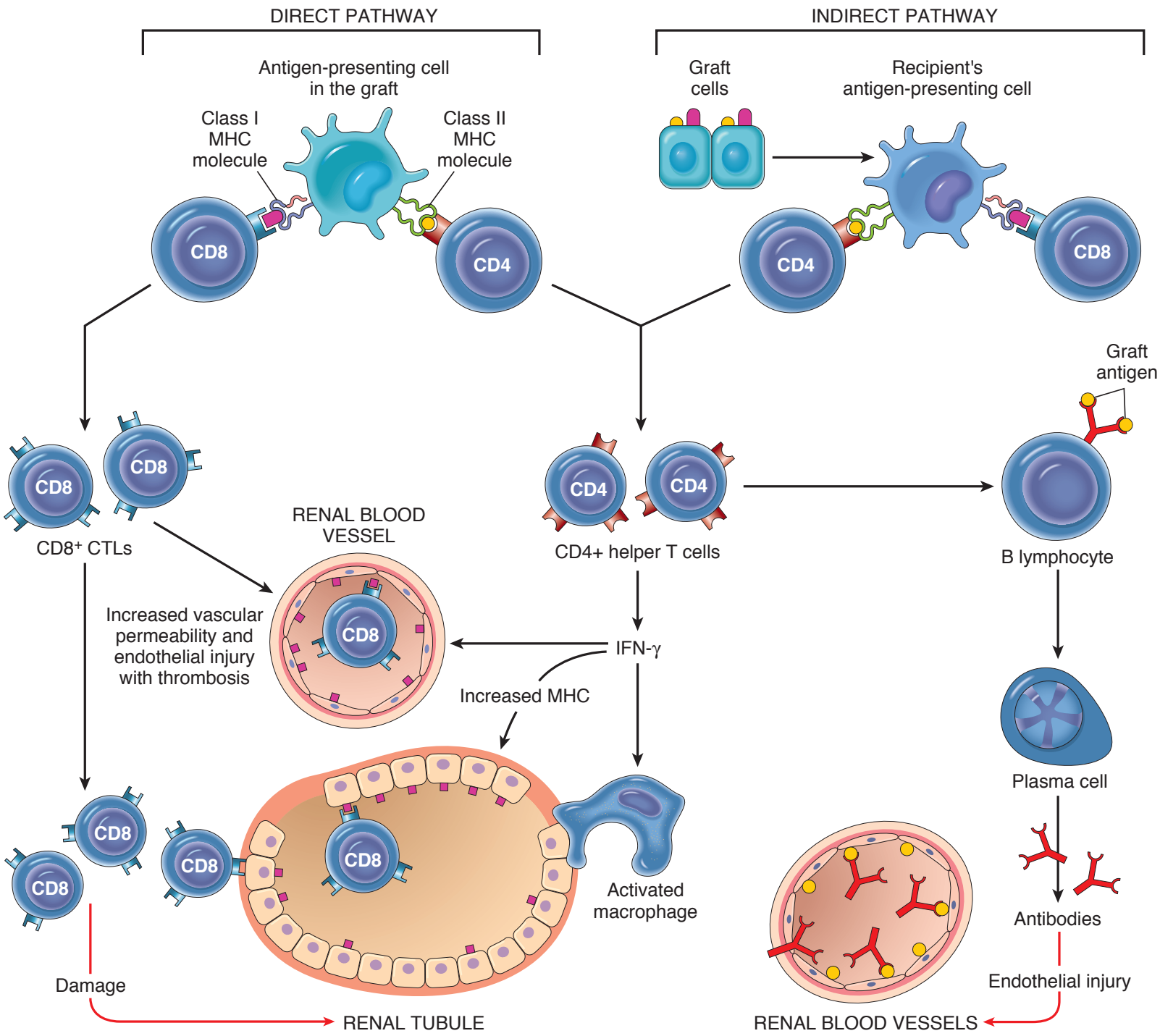
Cell-Mediated (Type IV) Hypersensitivity: Delayed, Cell-Mediated

- Examples:
  - CD4+ T-cells - tuberculin test, tuberculosis, etc.
  - CD8+ T-cells - viral infections, graft rejection, tumor-associated antigens, etc.

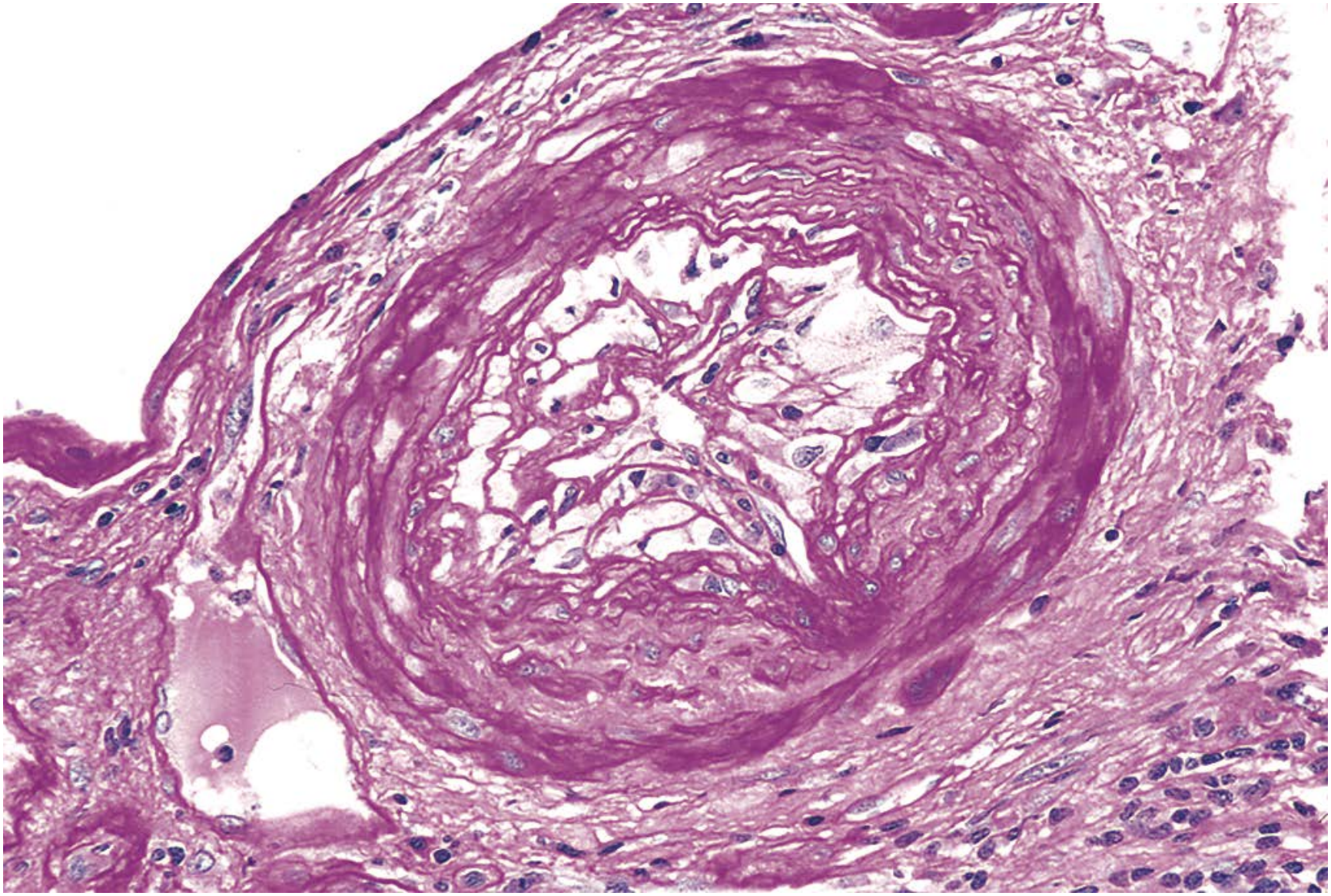
Granuloma Formation



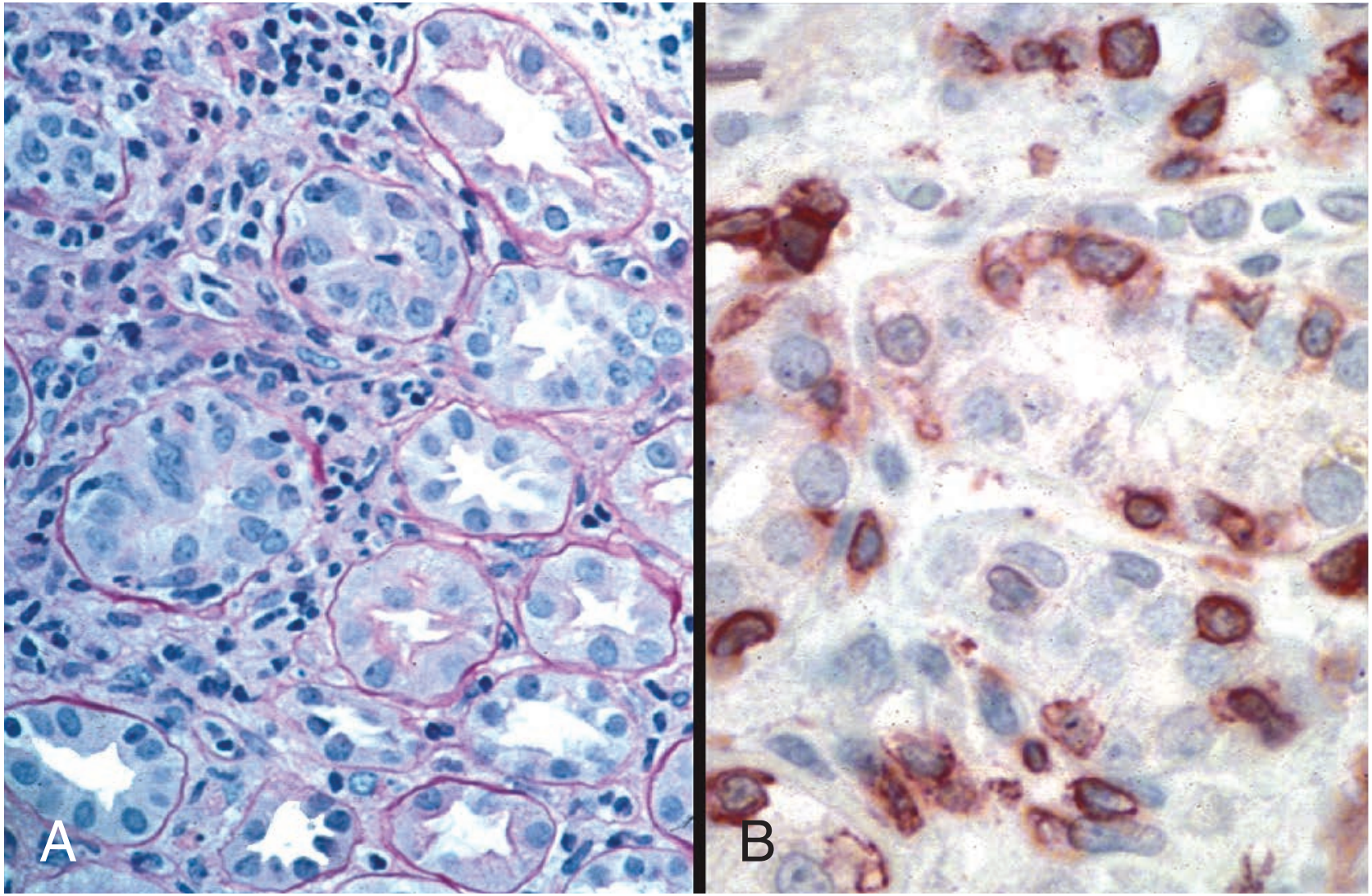
Renal Allograft Rejection



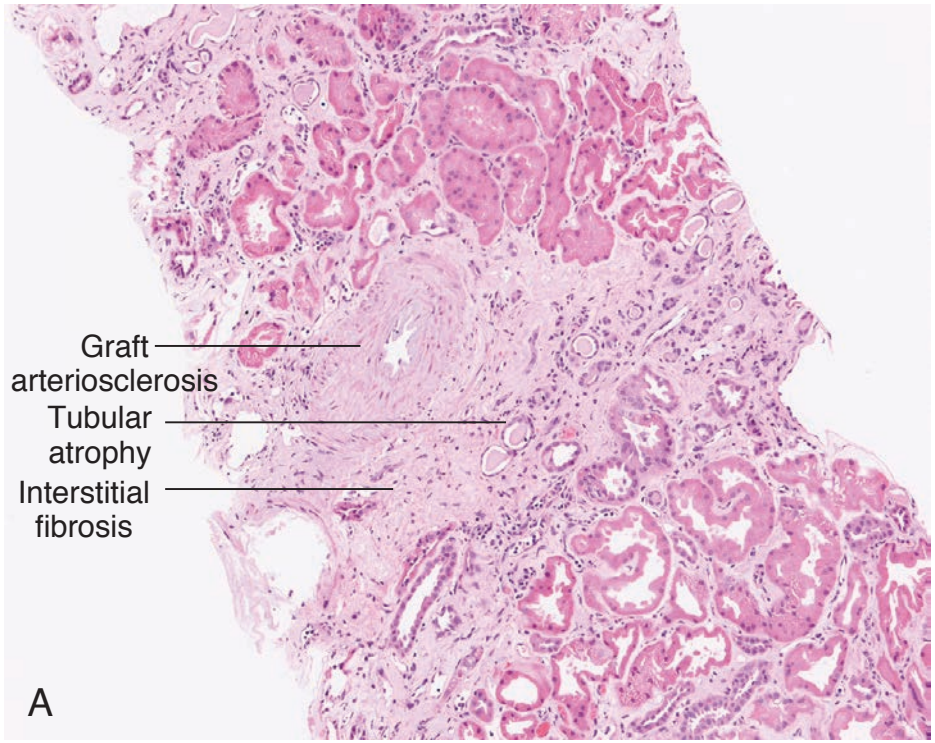
Acute Vascular Rejection

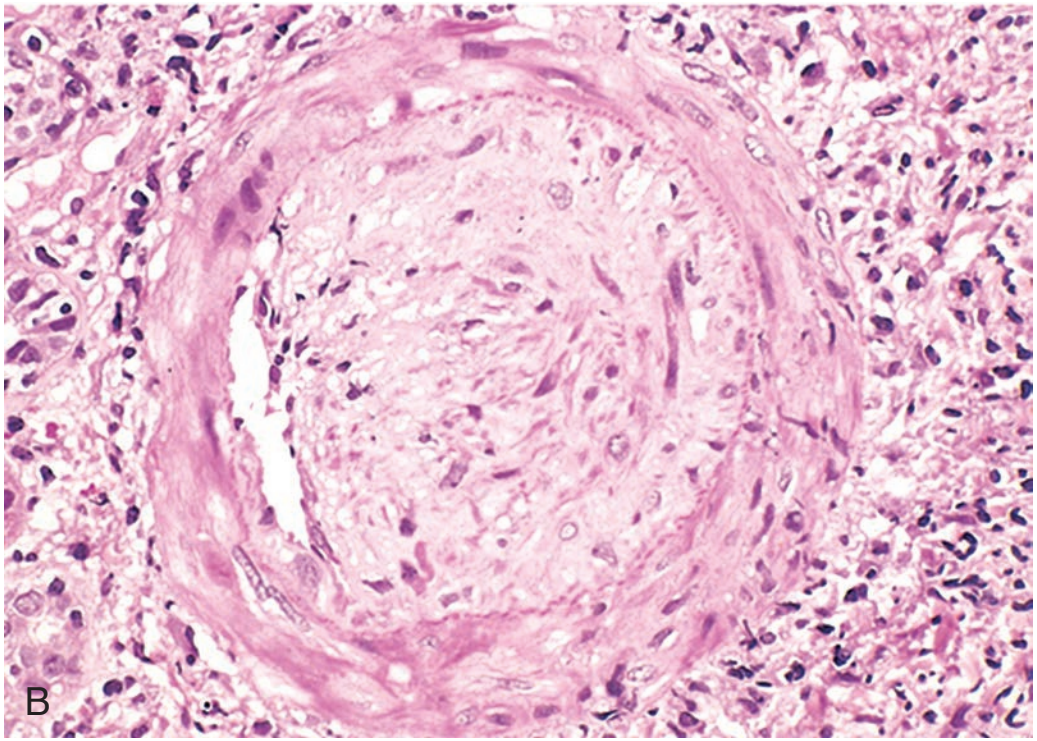


Acute Cellular Rejection



Chronic Rejection

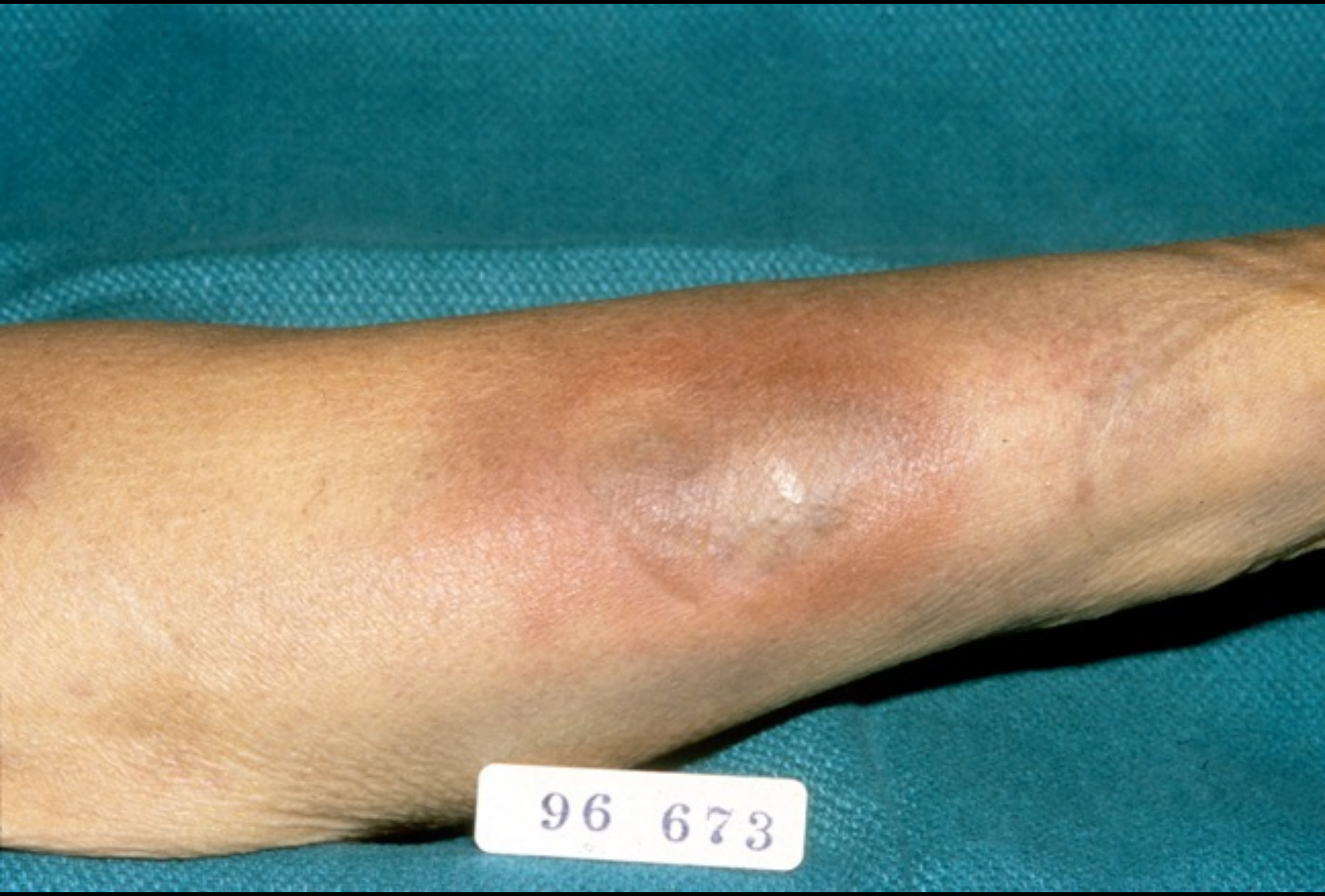


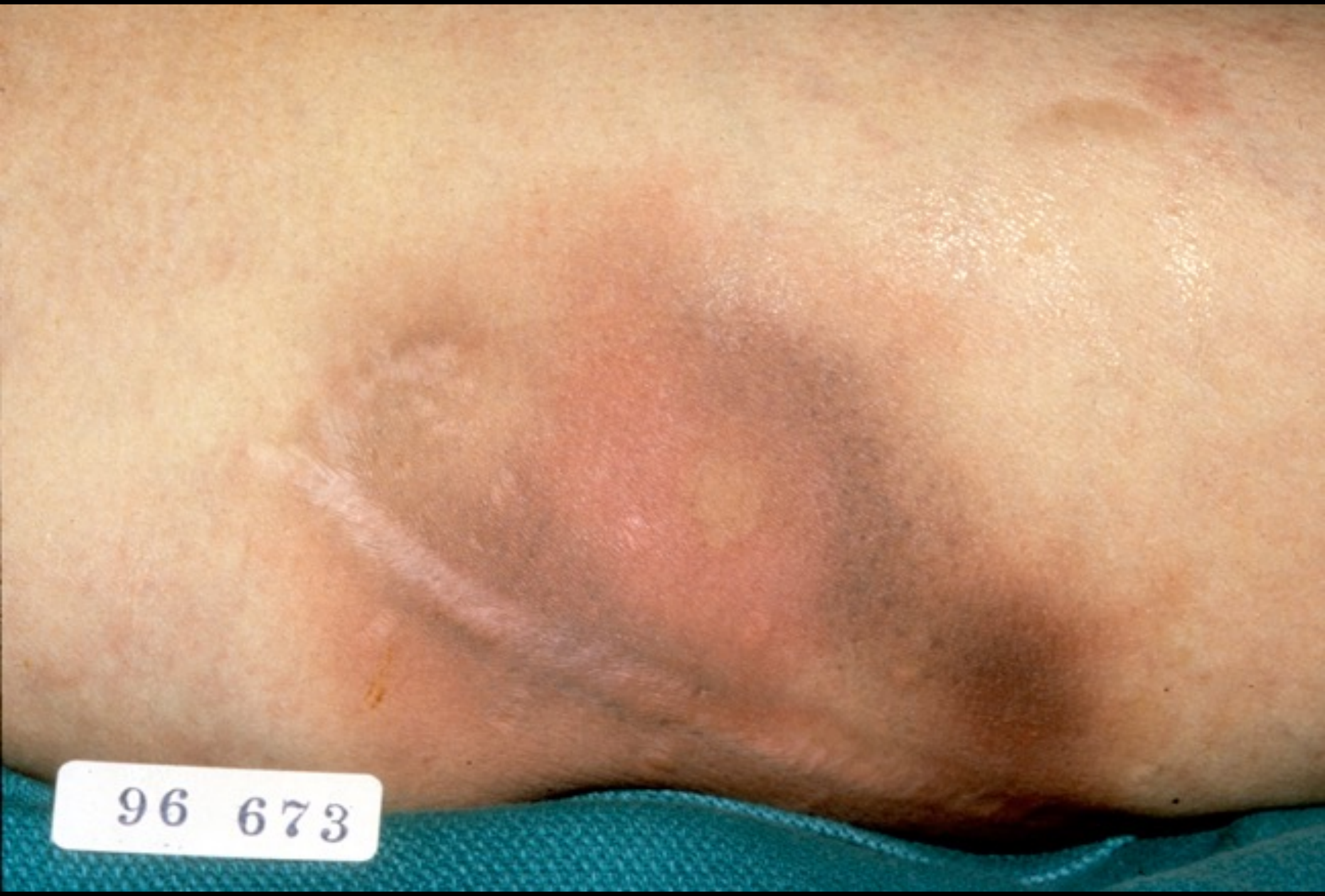


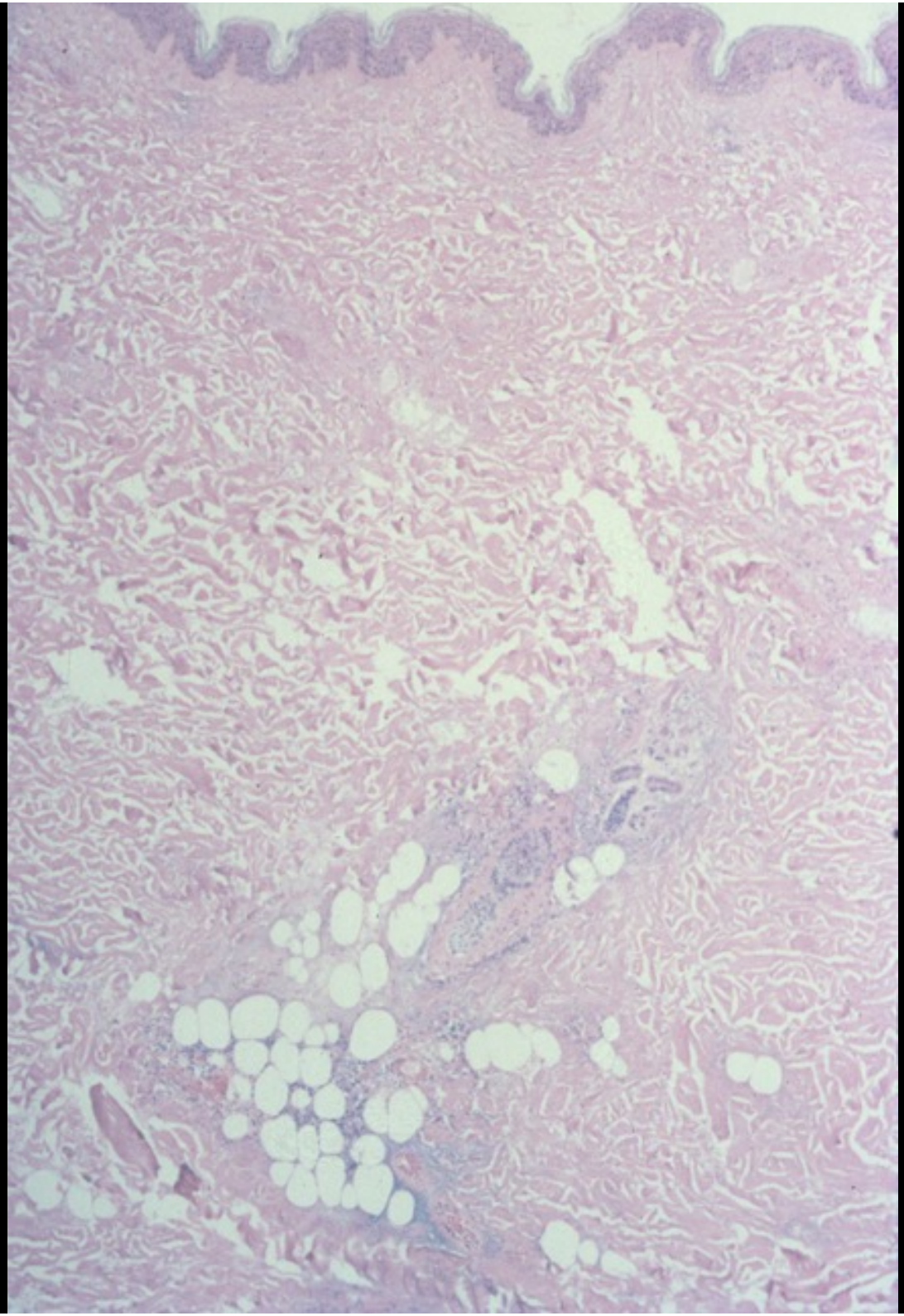
Acquired Immunodeficiences

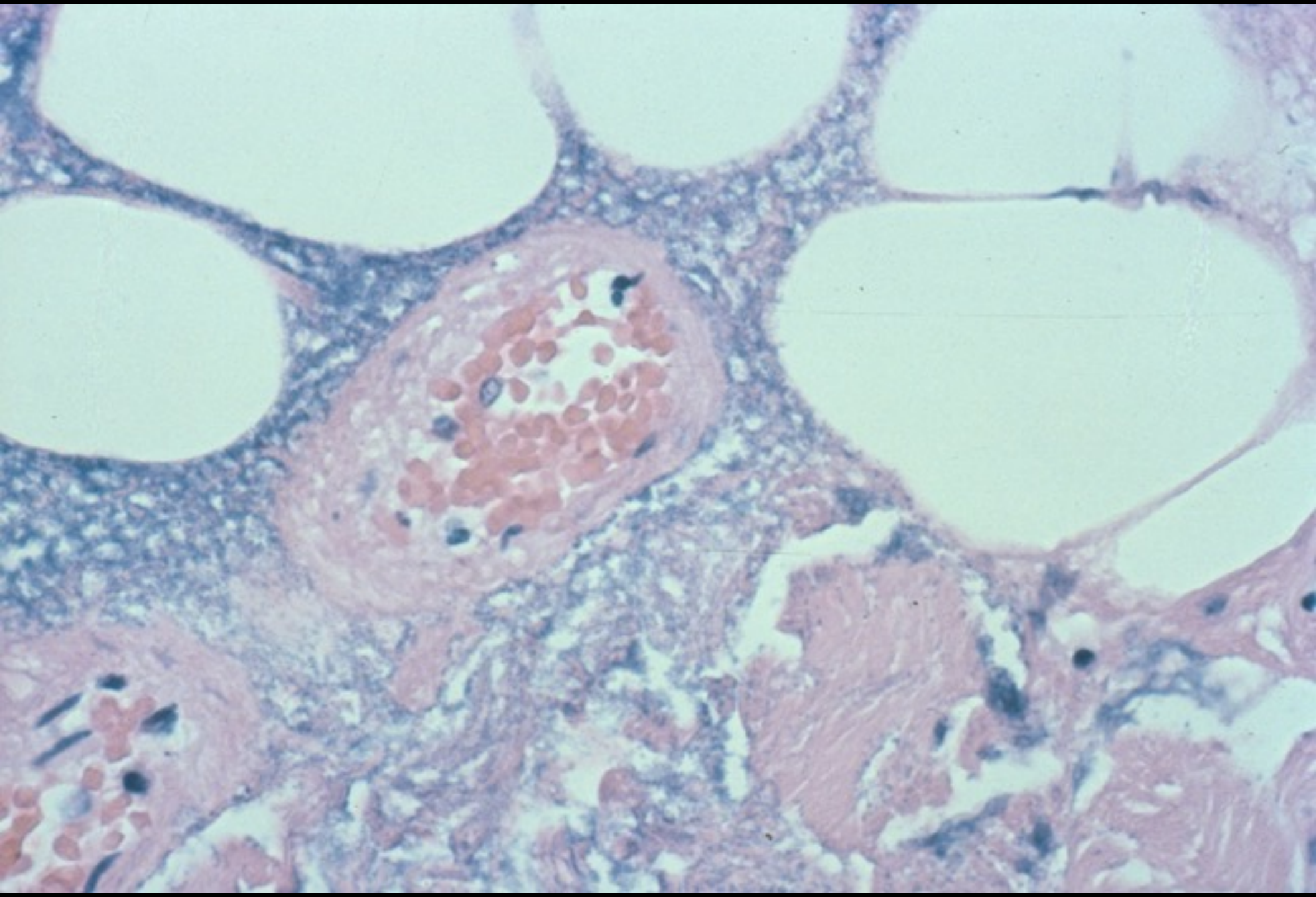
- HIV disease
- Iatrogenic
  - Irradiation
  - Immunosuppressive drugs
- Secondary to malignancy
- Systemic diseases
  - Autoimmune diseases (collagen vascular diseases)
  - Diabetes mellitus
  - Effects of alcohol

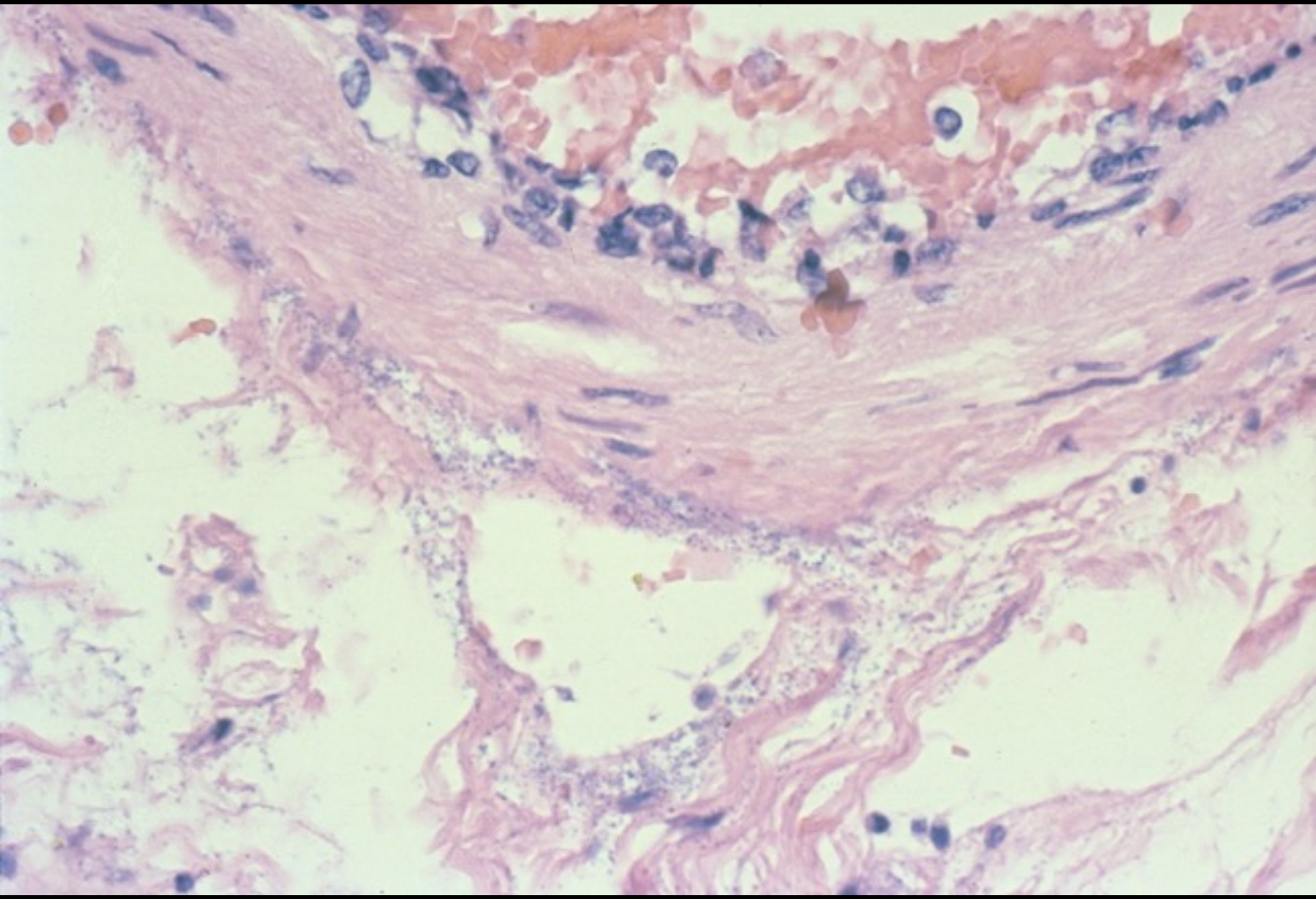

RAW
OYSTERS

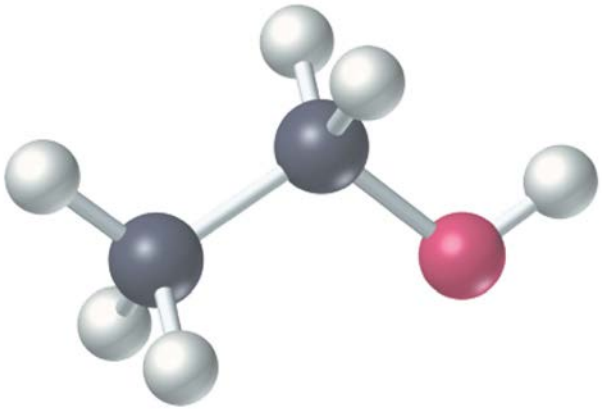

96 673


96 673



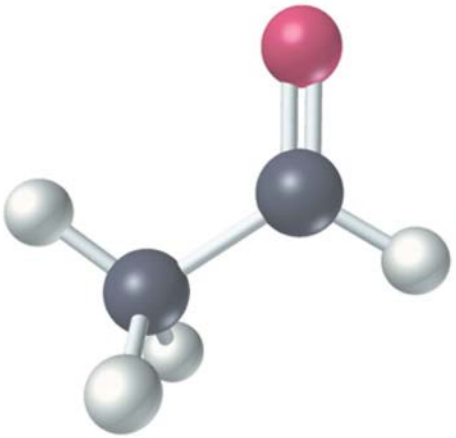






Ethyl alcohol
(CH_3CH_2OH, ethanol)

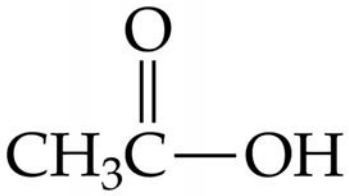
alcohol
dehydrogenase

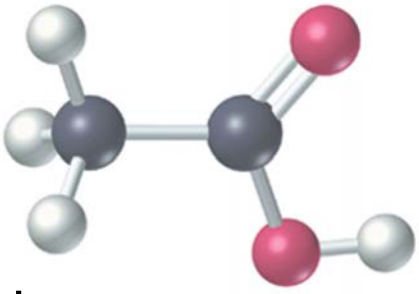


CH_3CHO

Acetaldehyde

acetaldehyde
dehydrogenase



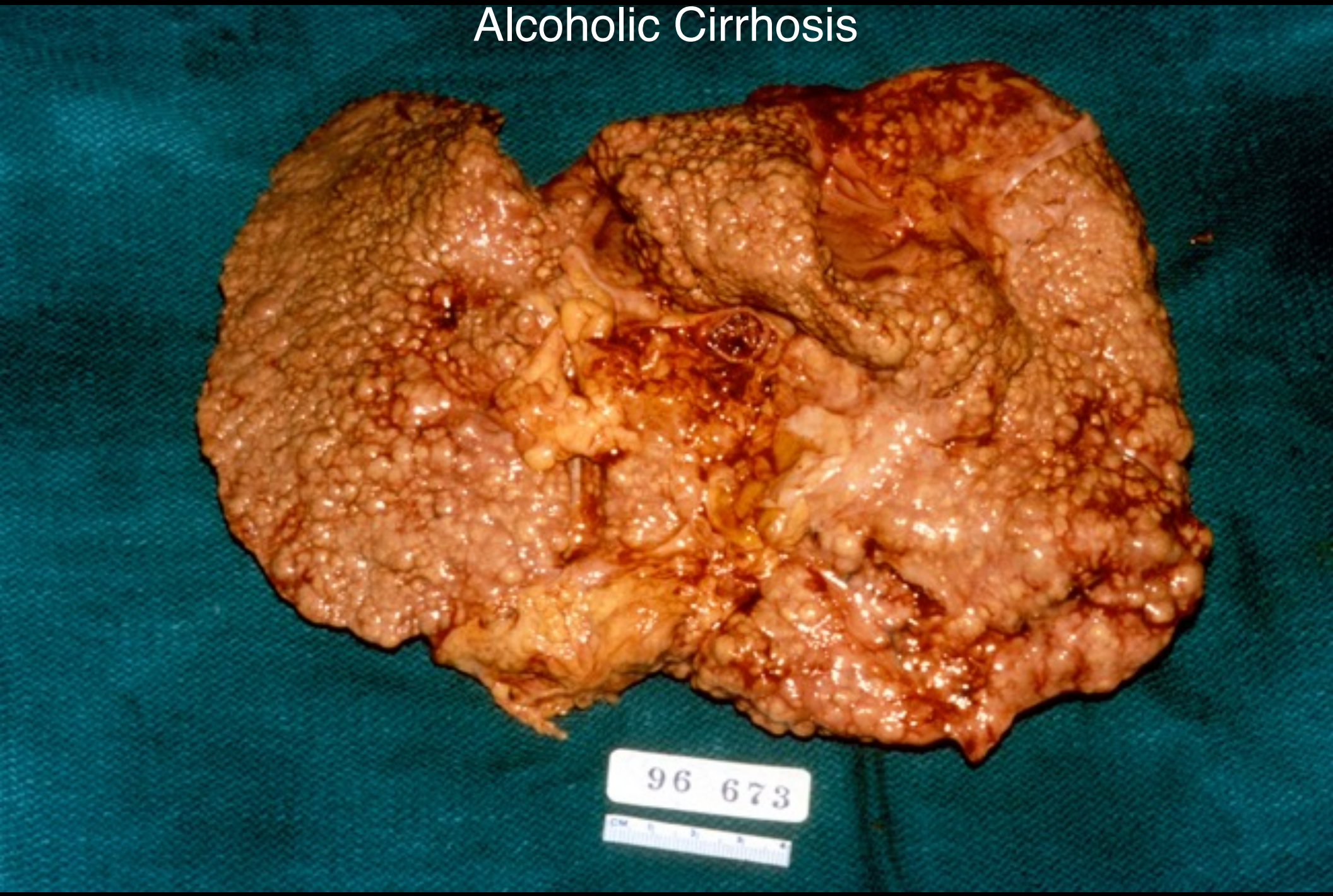


Acetate

Metabolic Consequences of Alcohol Metabolism

- Increase in NADH from alcohol metabolism leading to an inhibitory effect on all upstream metabolic processes that convert NAD+ to NADH
  - Kreb cycle
  - beta-oxidation
  - conversion of pyruvate to acetyl coA at the end of glycolysis
  - conversion of glycerol to DHAP in glycolysis
- Immunosuppressive effect on neutrophils

Alcoholic Cirrhosis



Autoimmune Diseases

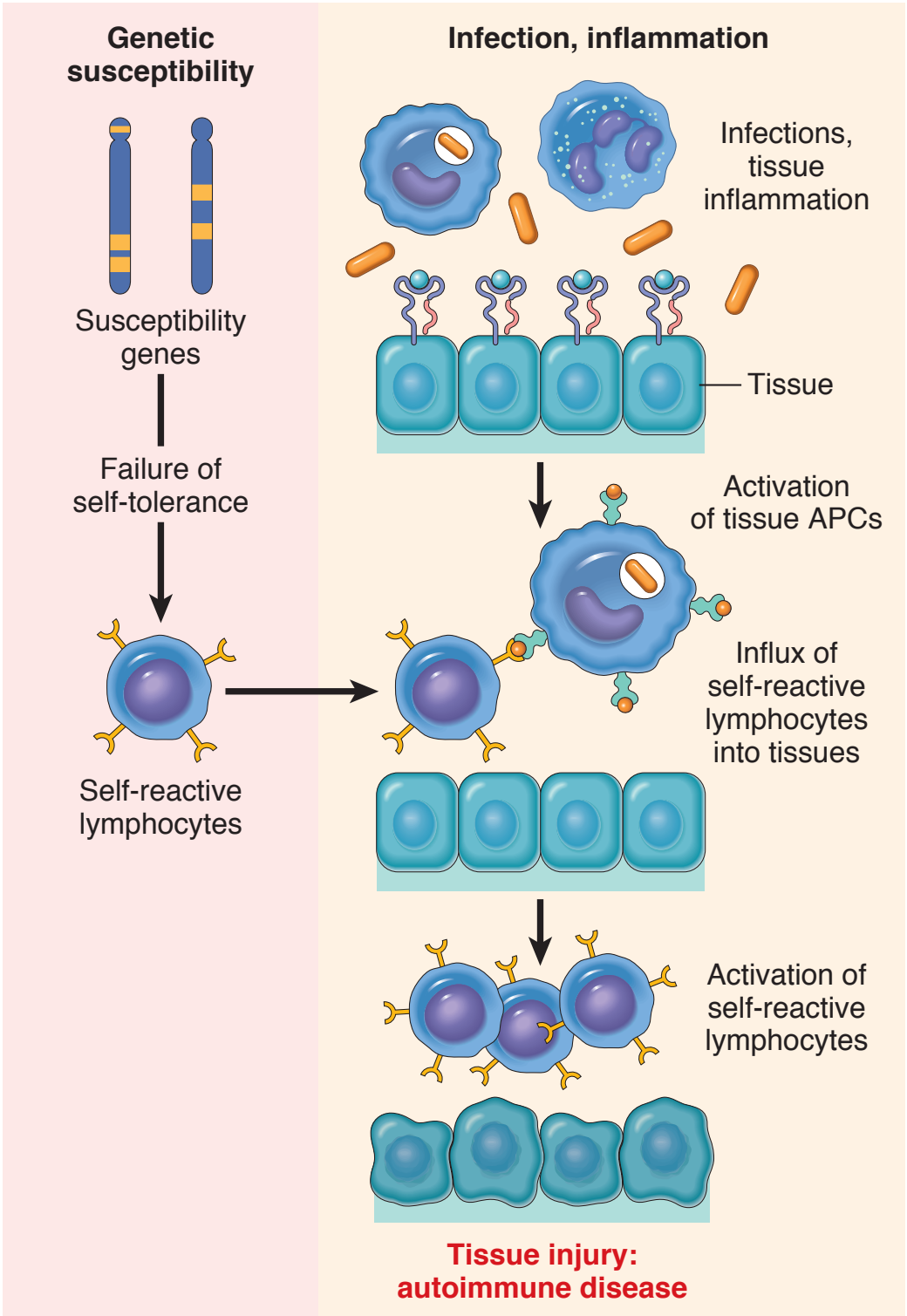

Genetic susceptibility
Susceptibility genes
Failure of self-tolerance
Self-reactive lymphocytes
Infection, inflammation
Infections, tissue inflammation
Tissue
Activation of tissue APCs
Influx of self-reactive lymphocytes into tissues
Activation of self-reactive lymphocytes
Tissue injury: autoimmune disease

TABLE 6–9 Antinuclear Antibodies in Various Autoimmune Diseases

Nature of Antigen	Antibody System	Disease, % Positive					
		SLE	Drug-Induced LE	Systemic Sclerosis—Diffuse	Limited Scleroderma—CREST	Sjögren Syndrome	Inflammatory Myopathies
Many nuclear antigens (DNA, RNA, proteins)	Generic ANA (indirect IF)	>95	>95	70–90	70–90	50–80	40–60
Native DNA	Anti–double-stranded DNA	40–60	<5	<5	<5	<5	<5
Histones	Antihistone	50–70	>95	<5	<5	<5	<5
Core proteins of small nuclear RNP particles (Smith antigen)	Anti-Sm	20–30	<5	<5	<5	<5	<5
RNP (U1RNP)	Nuclear RNP	30–40	<5	15	10	<5	<5
RNP	SS-A(Ro)	30–50	<5	<5	<5	70–95	10
RNP	SS-B(La)	10–15	<5	<5	<5	60–90	<5
DNA topoisomerase I	Scl-70	<5	<5	28–70	10–18	<5	<5
Centromeric proteins	Anticentromere	<5	<5	22–36	90	<5	<5
Histidyl-tRNA synthetase	Jo-1	<5	<5	<5	<5	<5	25

ANA, antinuclear antibodies; IF, immunofluorescence; LE, lupus erythematosus; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus.

Autoimmune Diseases

Example	Self-Antigen
Autoimmune hemolytic anemia	Red blood cells
Grave disease	TSH receptor
Goodpasture syndrome	Basement membrane (collagen type IV)
Hashimoto thyroiditis	Thyroglobulin
Immune adrenocortical insufficiency	Adrenal cortex
Immune thrombocytopenia purpura	Platelet
Myasthenia gravis	Acetylcholine receptor (motor endplates)
Primary biliary cirrhosis	Liver mitochondria
Rheumatoid arthritis	Immunoglobulin and joints
Scleroderma	DNA Topoisomerase I; Centromeric proteins
Sjögren syndrome	Nucleoproteins
Systemic lupus erythematosus (SLE)	DNA

Systemic Lupus Erythematosus (SLE)

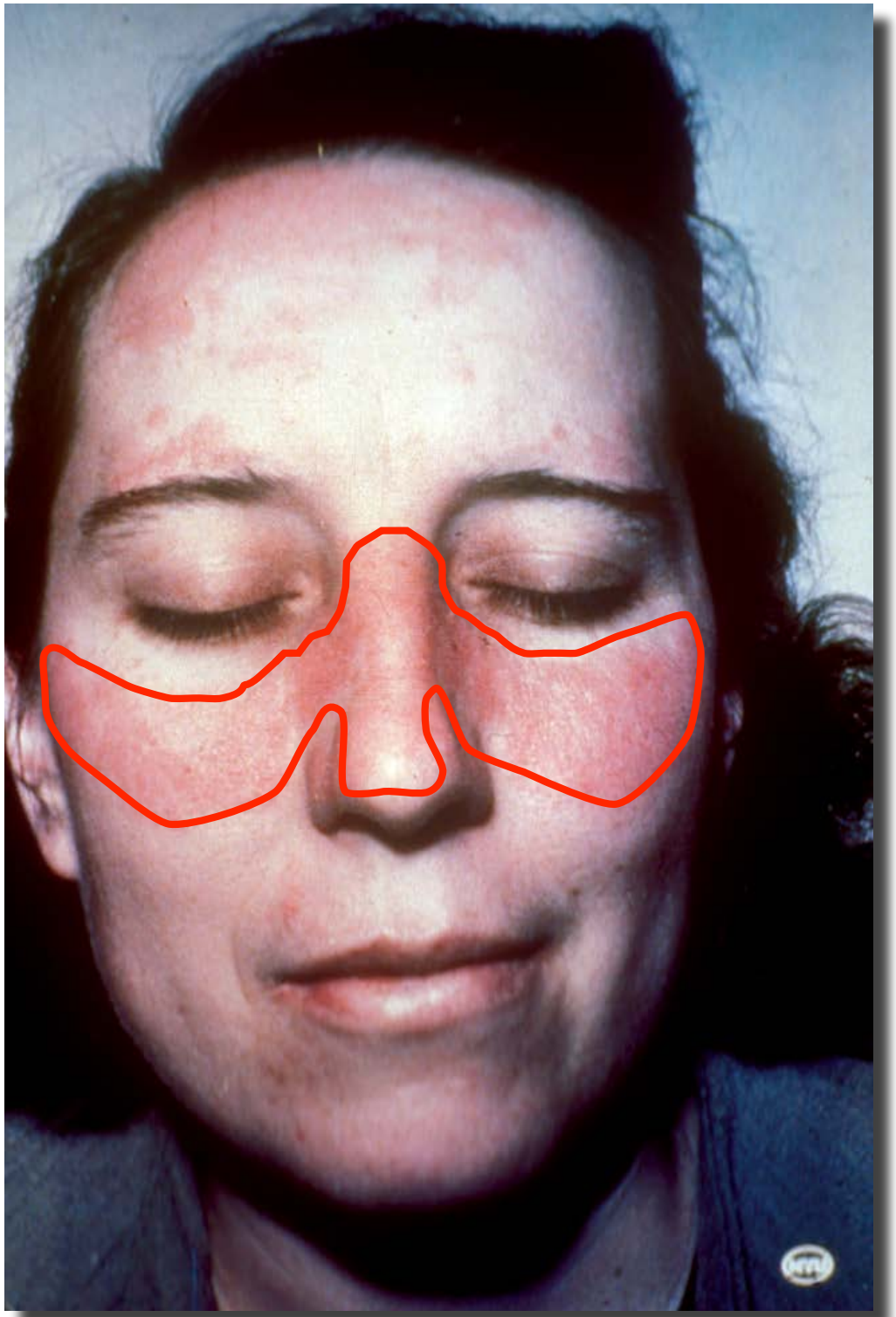
- Incidence of 1/2500
- Female to male ratio = 10:1
- Second or third decade of life
- Disease is more common and severe in black Americans

Systemic Lupus Erythematosus (SLE)

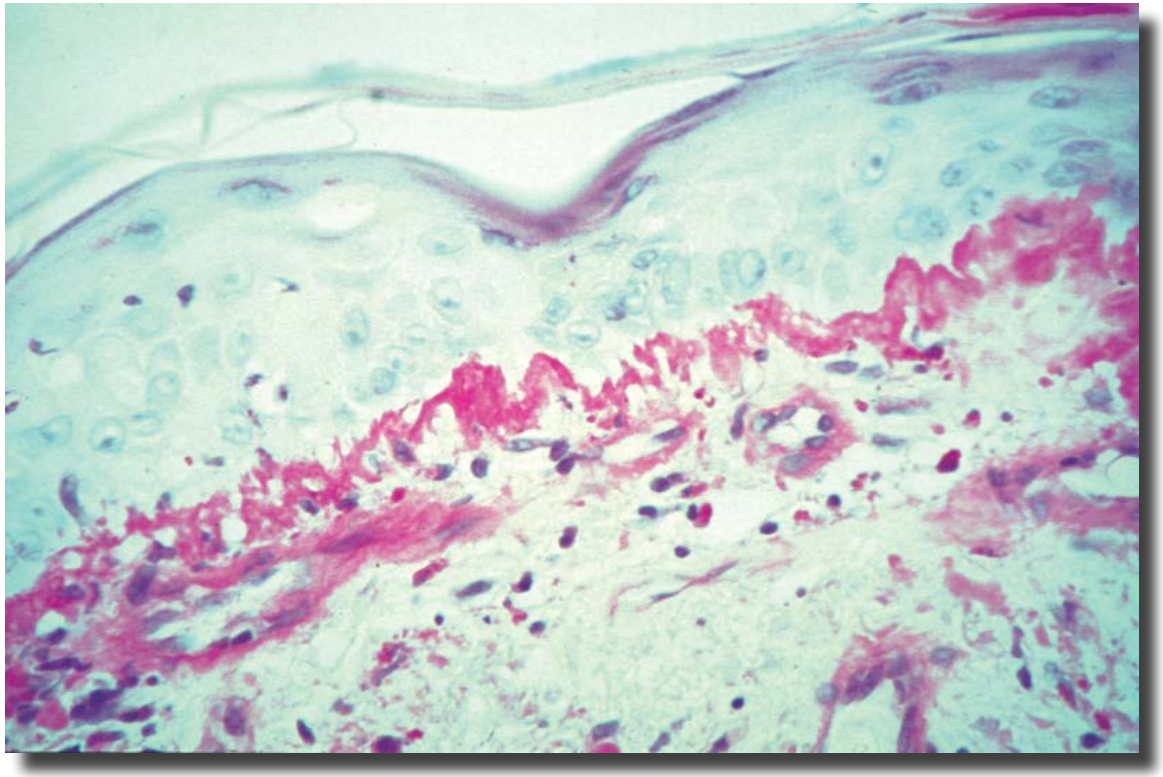
- Pathogenesis
- Failure of the regulatory mechanisms that sustain self-tolerance
- Antibodies are directed towards DNA, histones, non-histone proteins-RNA and nucleolar antigens (ANA [>95%], anti-dsDNA [40-60%] and anti-SM [20-30%], anti-phospholipid antibodies [40-50%]
- Clinical presentation
  - Skin, joints, kidneys, heart, serous membranes, etc.

SLE

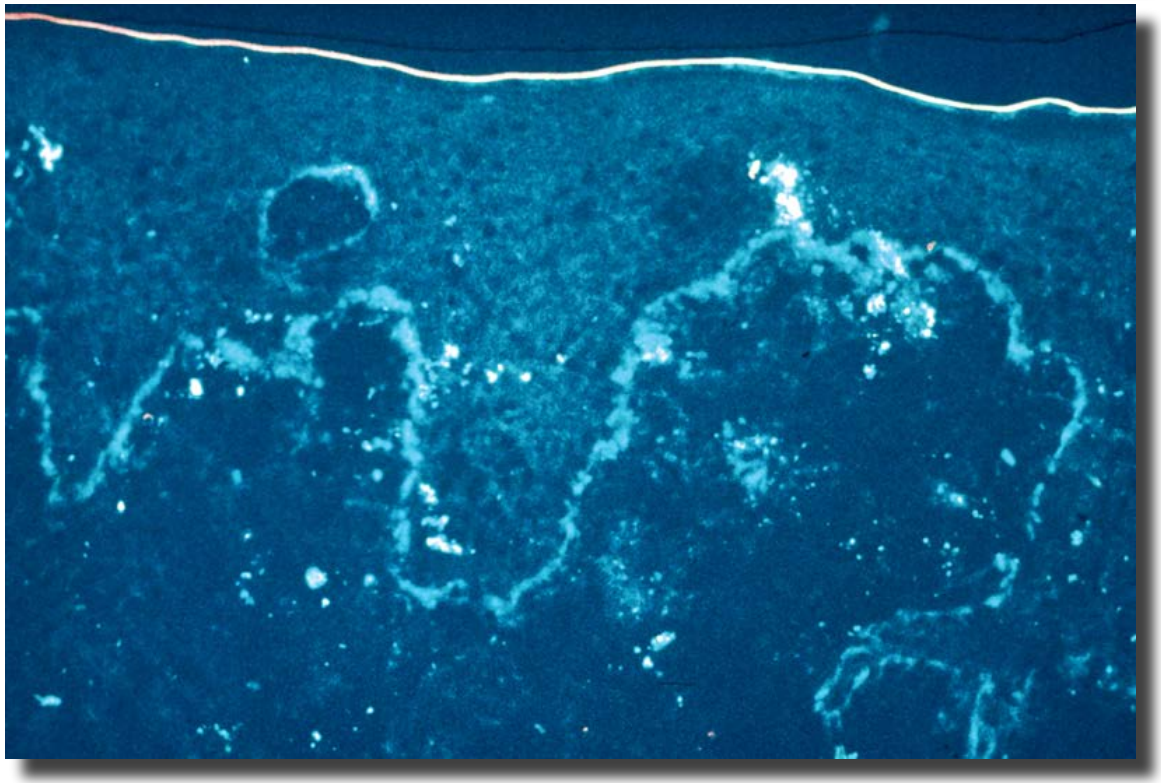
- Skin Pathology
  - Malar rash "butterfly pattern"
  - Maculopapular lesion - discoid lupus
  - Urticaria
  - Bullae
  - Ulcerations



PAS Stain



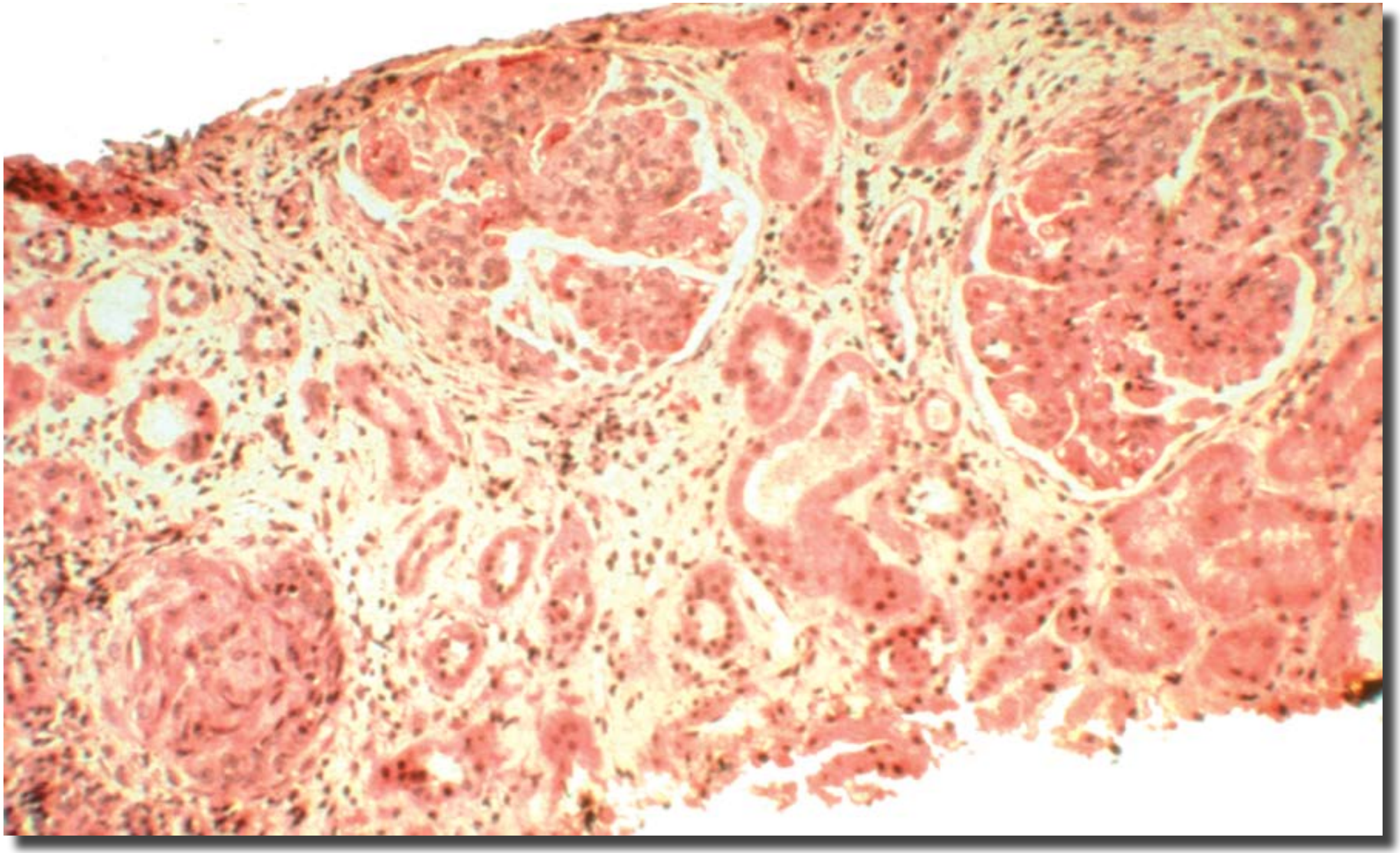
Immunofluorescence



SLE

- Renal Pathology
  - Class I - No morphologic changes on LM, IF, or EM
  - Class II - Mesangial lupus nephritis
  - Class III - Focal glomerulonephritis
  - Class IV - Diffuse proliferative glomerulonephritis
  - Class V - Membranous glomerulonephritis

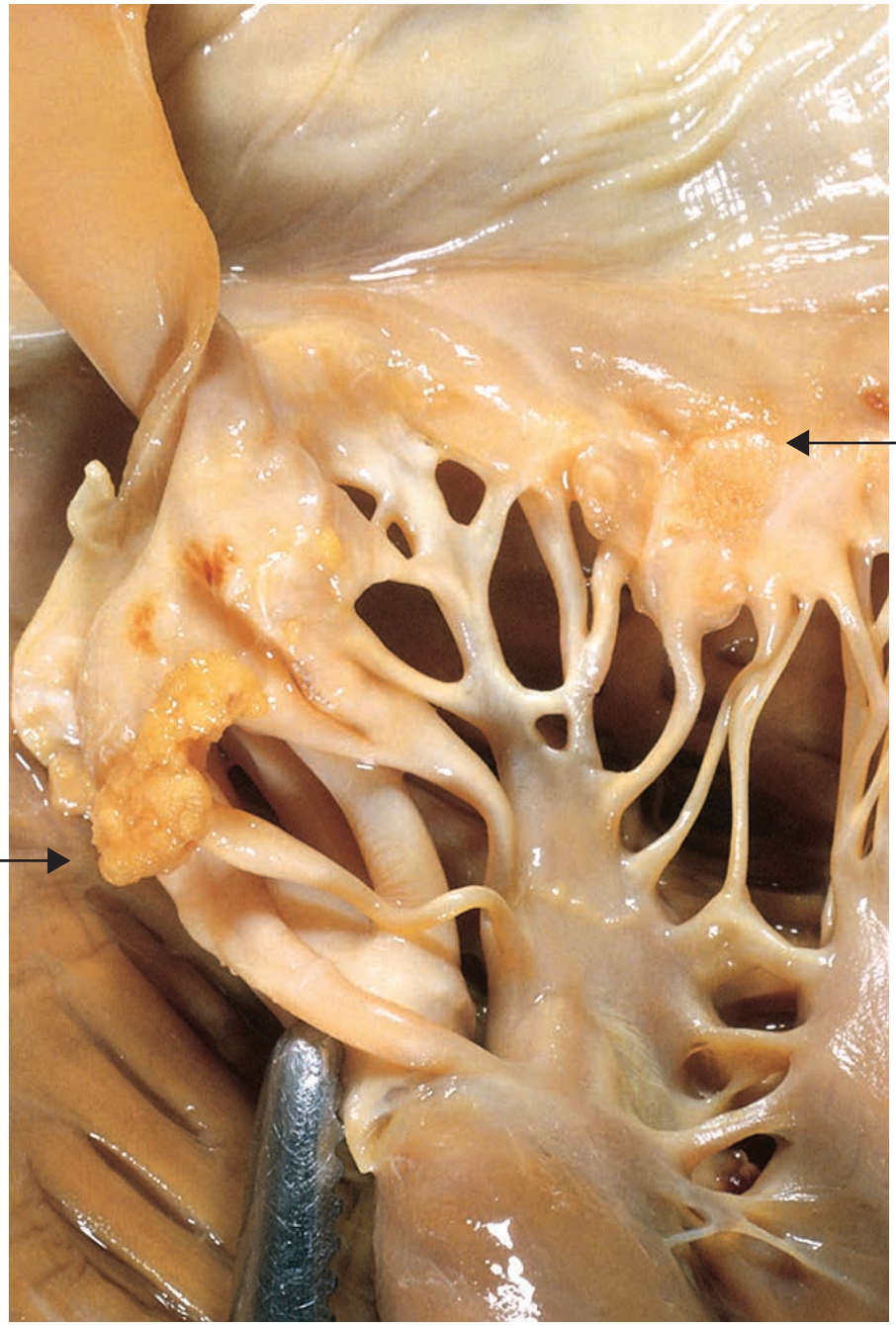
Diffuse Proliferative Glomerulonephritis



SLE

- Cardiac Pathology
  - Nonbacterial verrucous endocarditis (Libman-Sacks endocarditis)
  - Myocarditis
  - Pericarditis - acute, subacute, or chronic

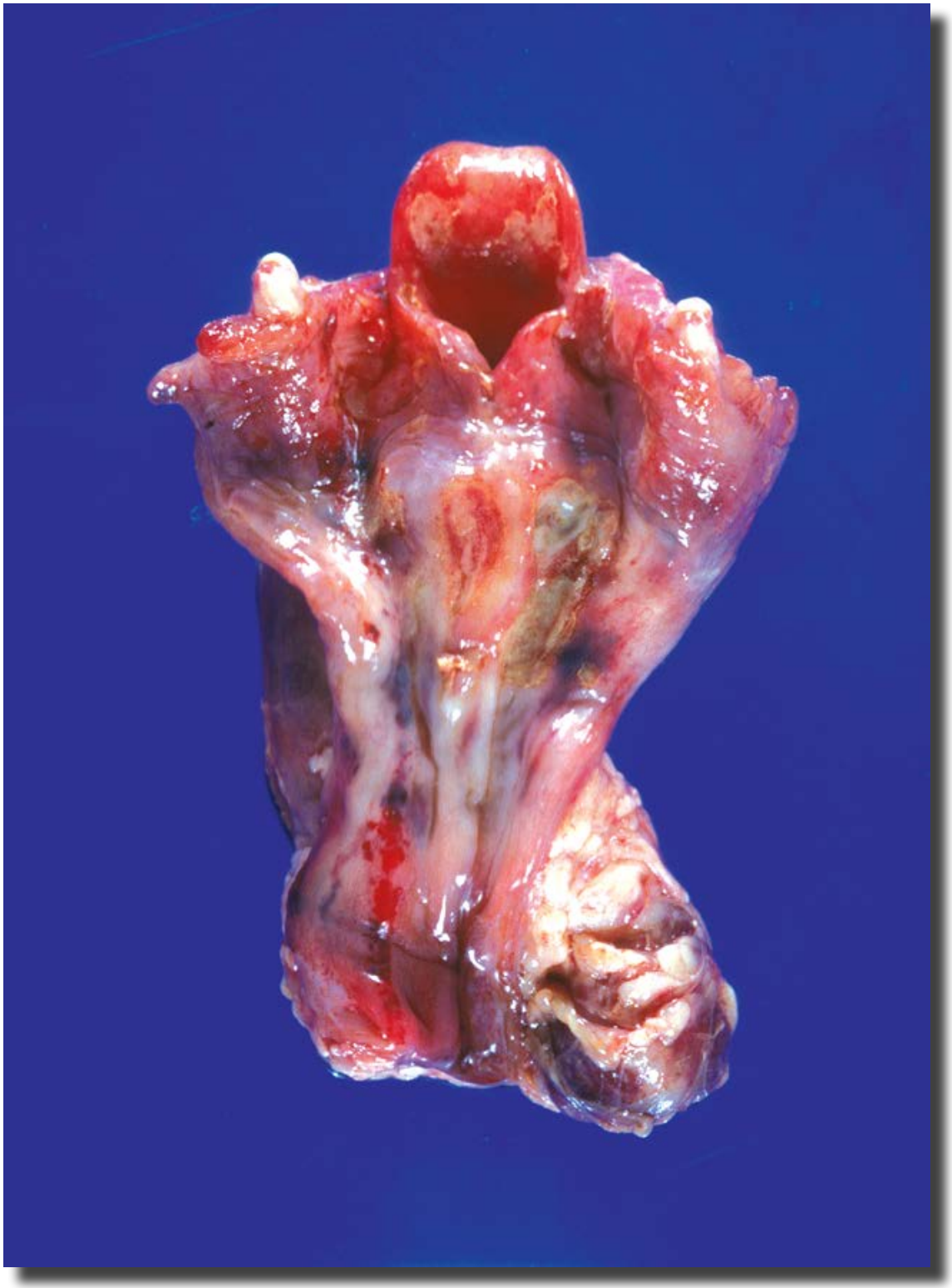
Nonbacterial Verrucous Endocarditis (Libman-Sacks Endocarditis)



SLE

- Clinical course
  - Variable and unpredictable
  - 86% survival at 5 years
  - Therapy - steroids and immunosuppressive drugs
  - Death from renal failure and opportunistic infections

Acute Invasive Candidiasis

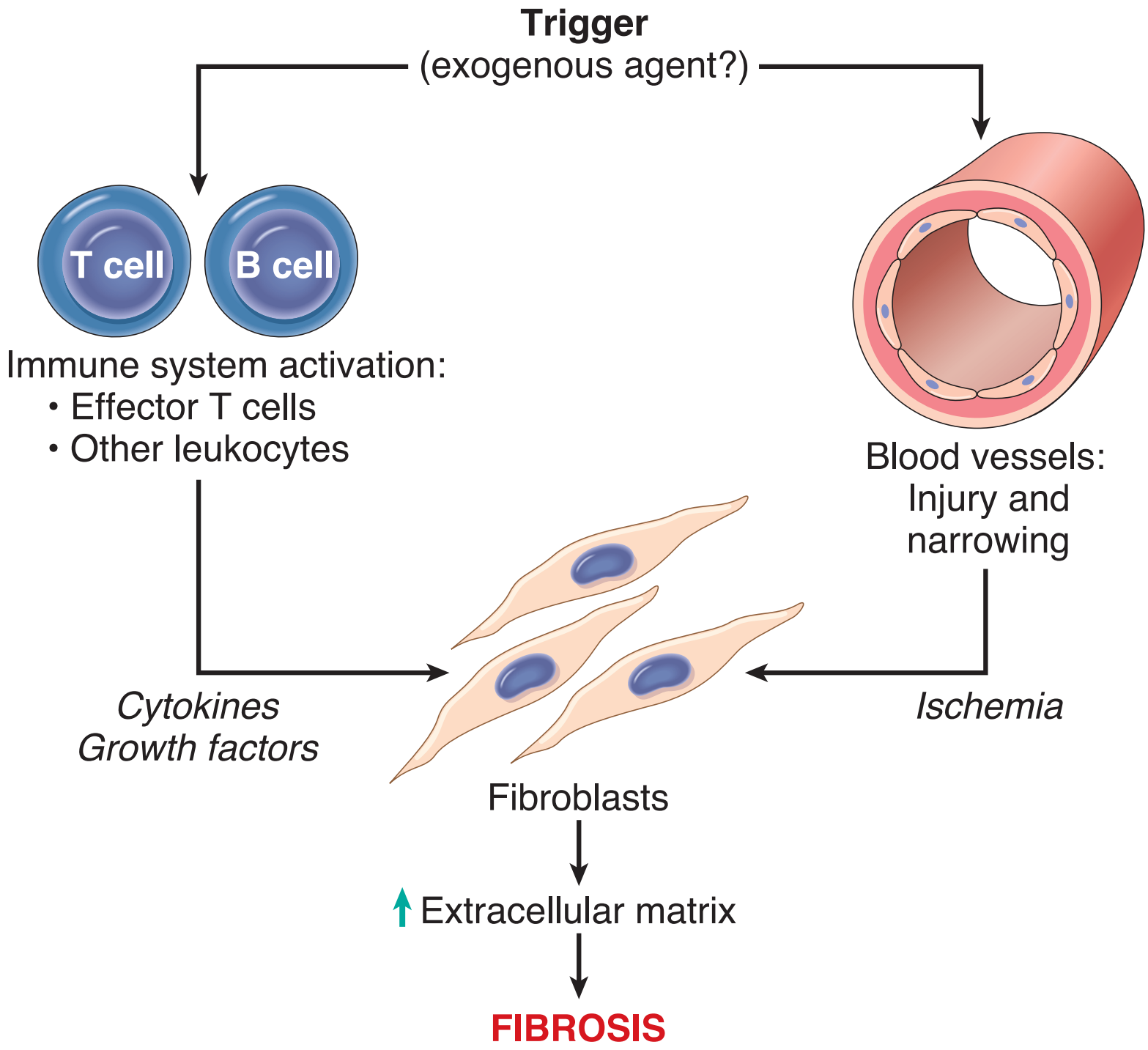


Scleroderma (Progressive Systemic Sclerosis)

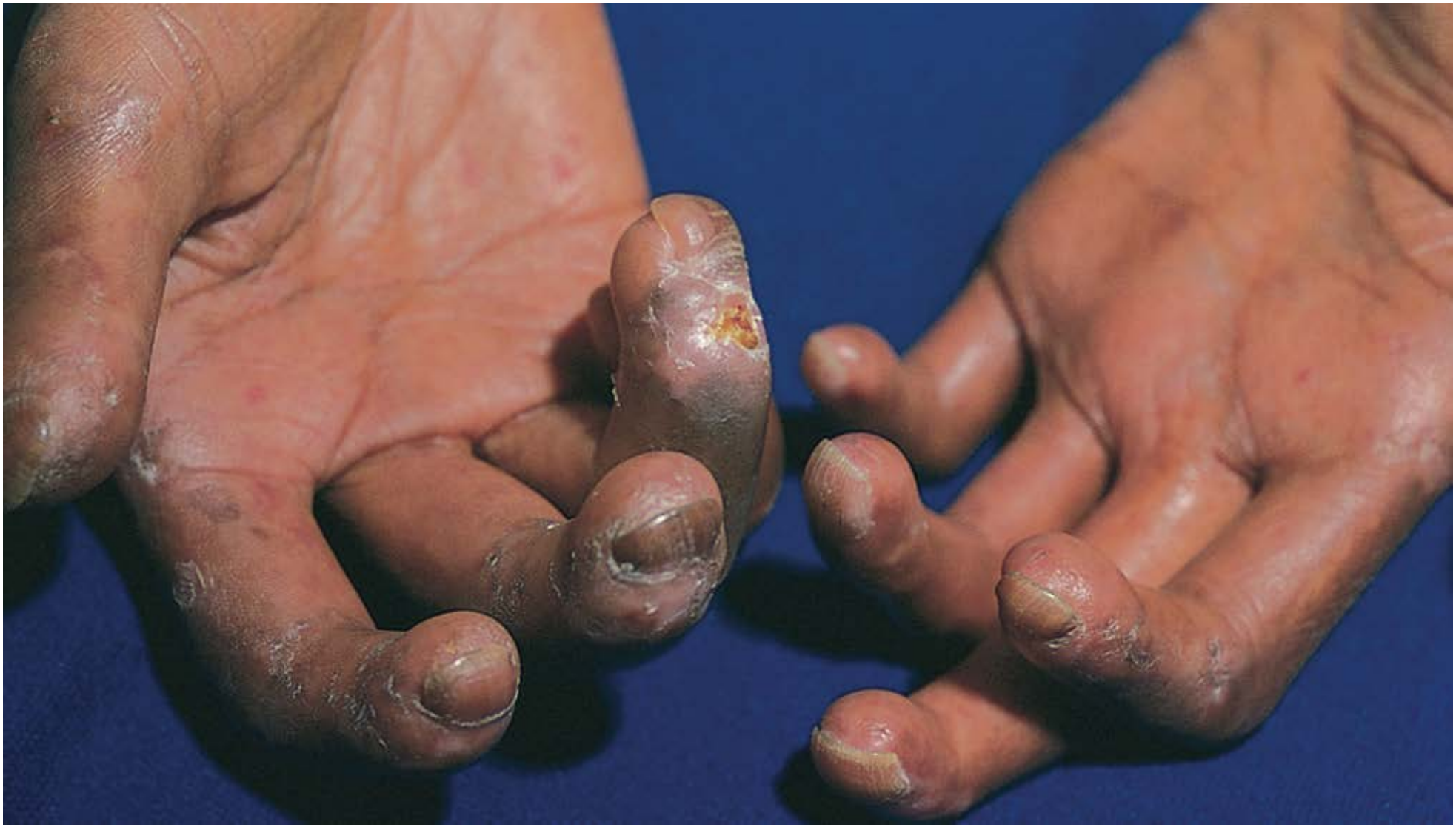
- Female to male ratio = 3:1
- Third and fifth decades of life

Scleroderma (Progressive Systemic Sclerosis)

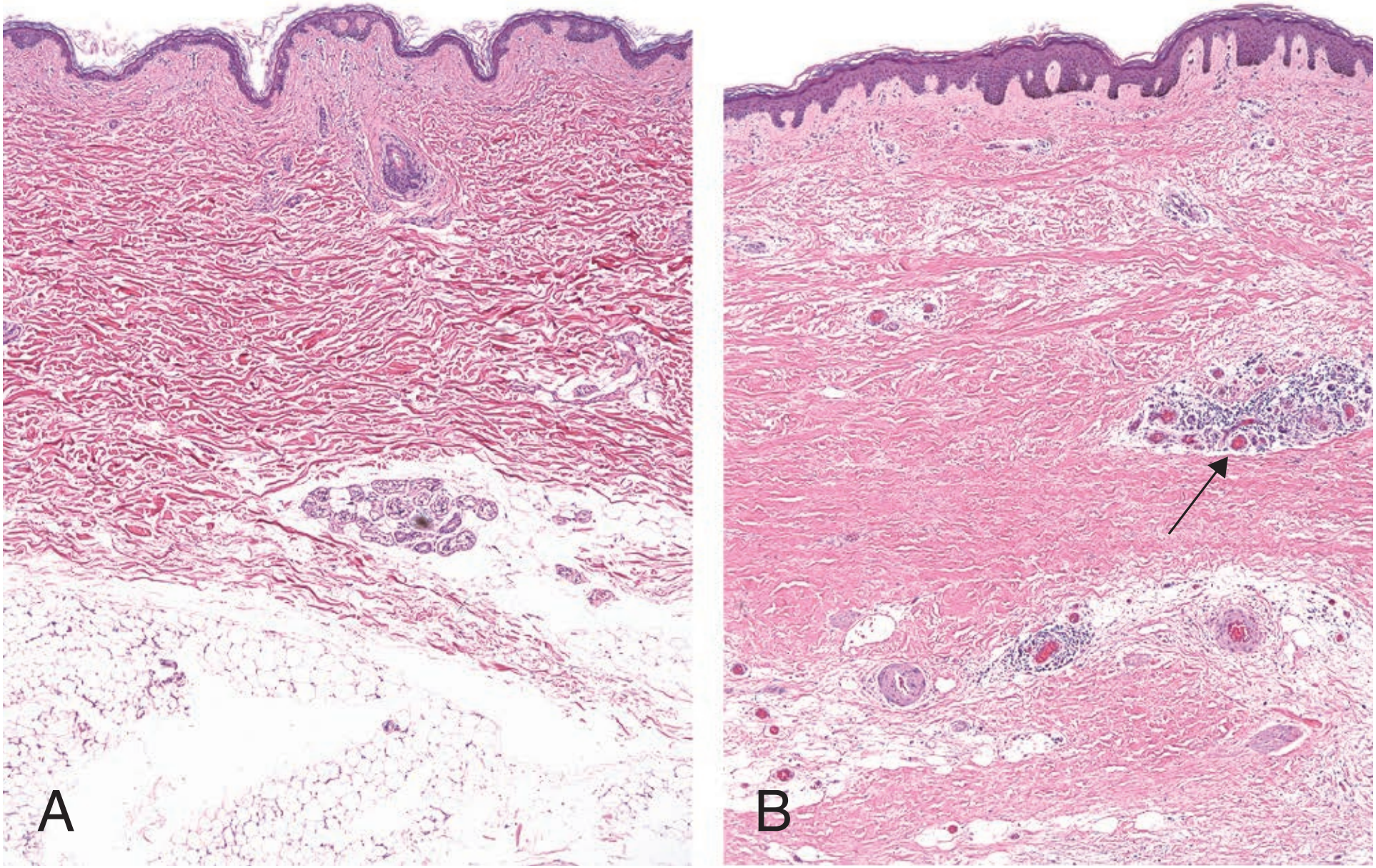
- Pathogenesis
  - Excessive fibrosis throughout the body via fibroblast activation (IL-1, TNF-alpha, TGF-beta, PDGF)
- Types
  - Diffuse scleroderma - Anti-DNA topoisomerase I antibody (Scl-70 [40-70%])
  - CREST syndrome - Anti-centromere antibody (90%)


Trigger
(exogenous agent?)
T cell
B cell
Immune system activation:
• Effector T cells
• Other leukocytes
Blood vessels:
Injury and
narrowing
Cytokines
Growth factors
Ischemia
Fibroblasts
Extracellular matrix
FIBROSIS

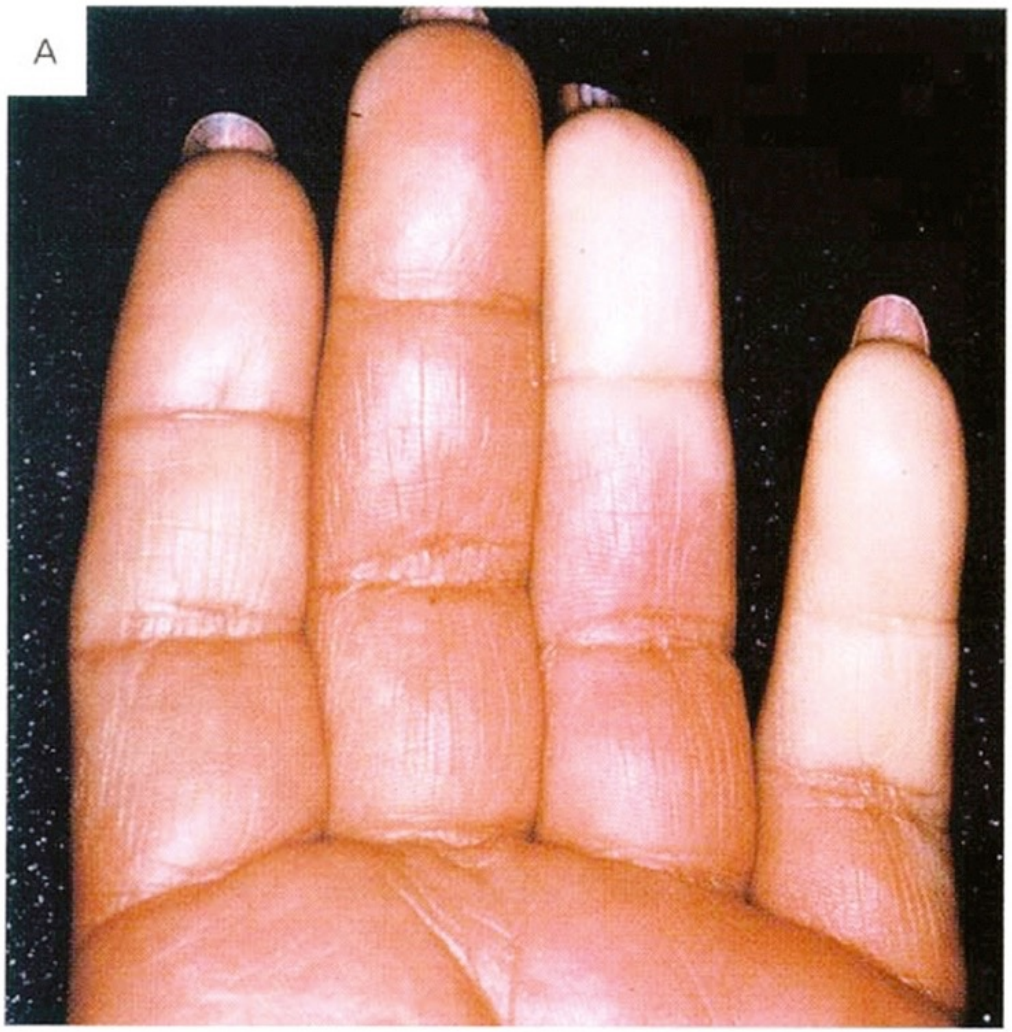
Sclerodactyly

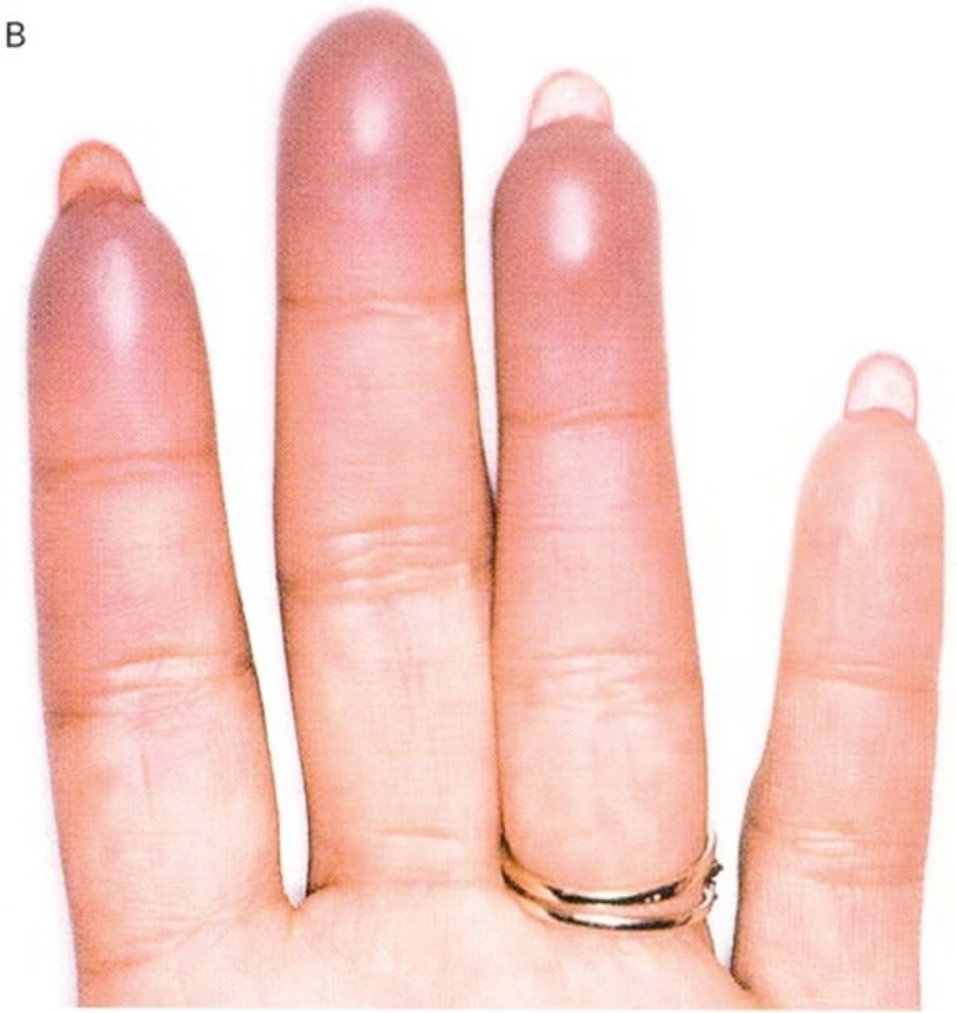


Systemic Sclerosis



Raynaud Phenomenon





Scleroderma (Progressive Systemic Sclerosis)

- Diffuse scleroderma
  - Widespread involvement of skin, rapid progression and early visceral involvement
- CREST syndrome
  - Calcinosis
  - Secondary Raynaud phenomenon
  - Esophageal motility
  - Sclerodactyly
  - Teleangiectasia