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Classification of Immune Mediated Tissue Injury:
Gell Coombs Classification

Mechanisms of Immune-Mediated Disorders

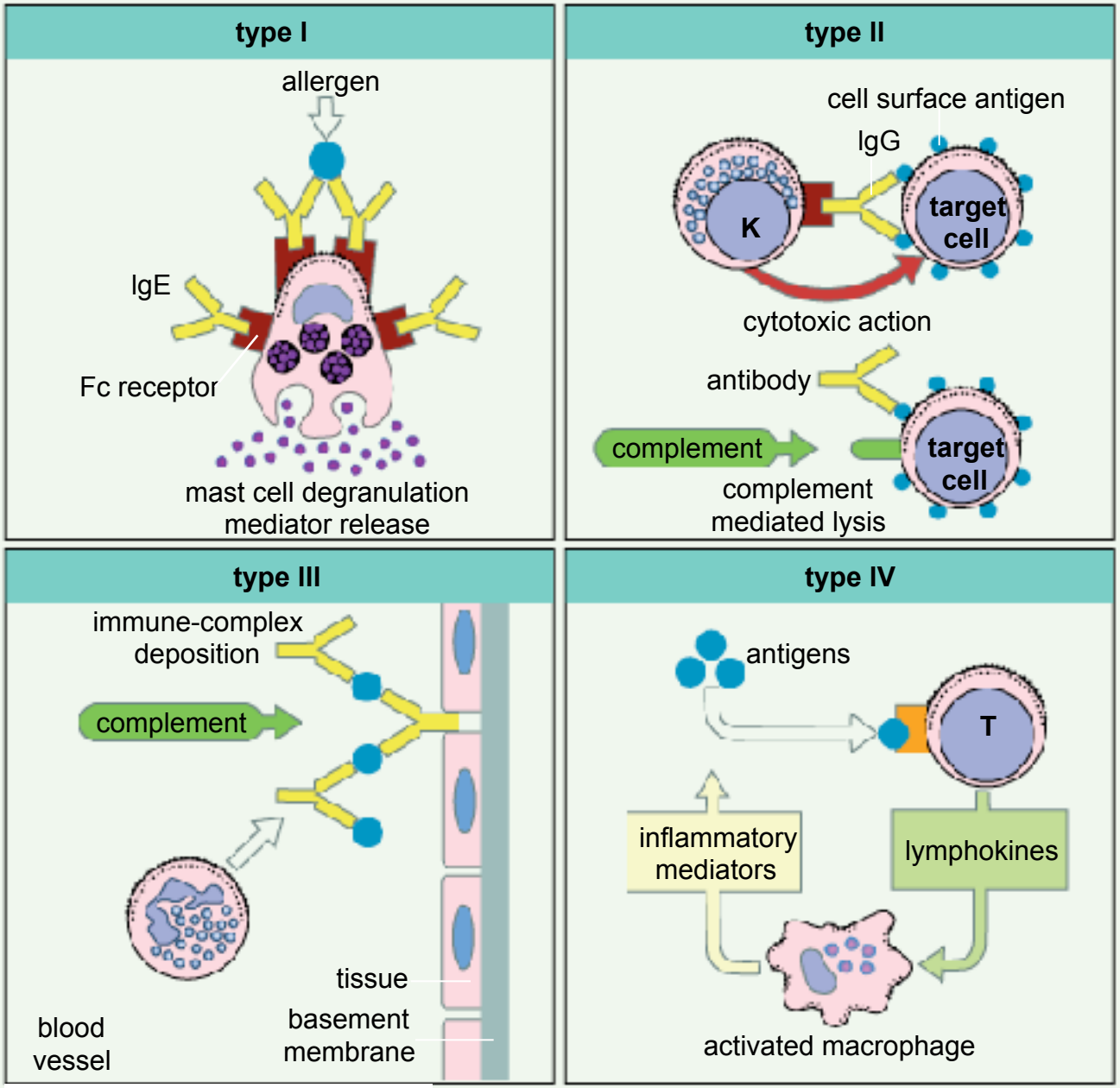
(4- types)

J. Fantone: Host Defense
2/17/09
10:00-12:00am

Winter 2009

University of Michigan
Medical School

The four types of hypersensitivity reaction



Type I Anaphylactic Type

- **Prototype Disorders**
  - Allergic rhinnitis
  - Allergic asthma
  - Anaphylaxis (insect venom)
- **Immune Mechanisms**
  - IgE-Mast cells
  - Vascular permeability
  - Eosinophils

Type II, Cytotoxic Type

- **Prototype Disorders**
  - Hemolytic reactions
  - Goodpastures Syndrome
  - Myasthenia Gravis
  - Grave's Disease (hyperthyroidism)
- **Immune Mechanisms**
  - IgG
  - Complement
  - Phagocytic cells
  - ADCC

Type III, Immune Complex Disease

- **Prototype Disorders**
  - Post-streptococcal glomerulonephritis
  - Vasculitis
    - Polyarteritis nodosa
- **Immune Mechanisms**
  - Ab-Ag reactions
  - Complement
  - Neutrophils
  - Fibrin, hemorrhage

Type IV, Cell-Mediated (Delayed) Hypersensitivity

- **Prototype Disorders**
  - Poison Ivy
  - Tuberculosis (granulomatous inflammation)
  - Cytotoxic T-cell
    - Dr. King's lectures
- **Immune Mechanisms**
  - T-lymphocytes
  - Monocyte/macro-phage

Antibody-Mediated Cell and Tissue Injury: IgE Mediated Hypersensitivity Reactions

Objectives:

To understand the pathophysiologic mechanisms associated with Type I anaphylactic hypersensitivity reactions

Objectives (cont.)

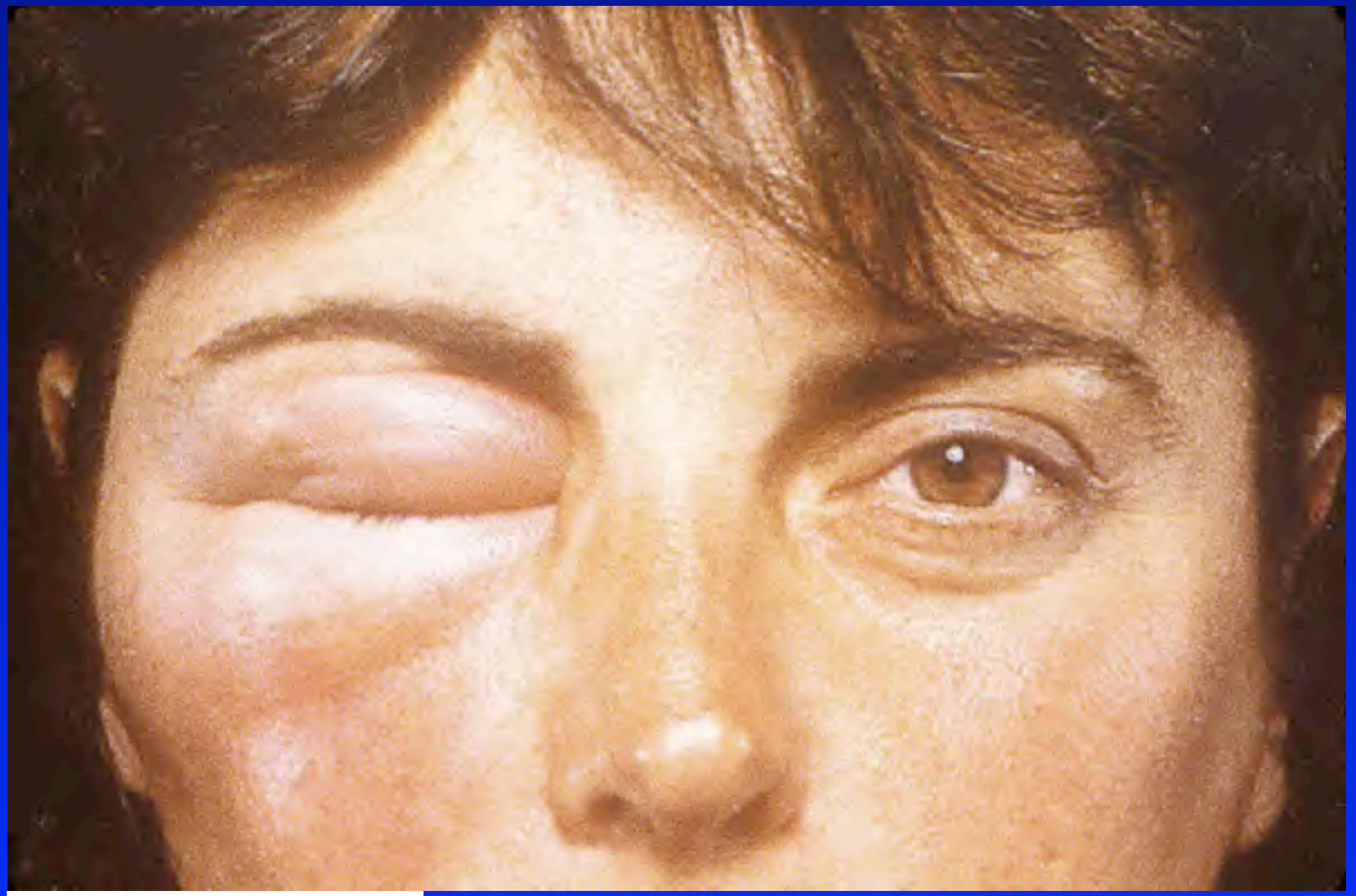
- The role of IgE-mediated Mast cell degranulation in Type I reactions
- The primary effector mediators released during Mast cell stimulation
- The pathologic changes observed in tissues associated with anaphylactic hypersensitivity reactions
- The modulatory role of eosinophils in these reactions
- To correlate the effect of mediators on target organs with the clinical expression of anaphylactic reactions

Clinical

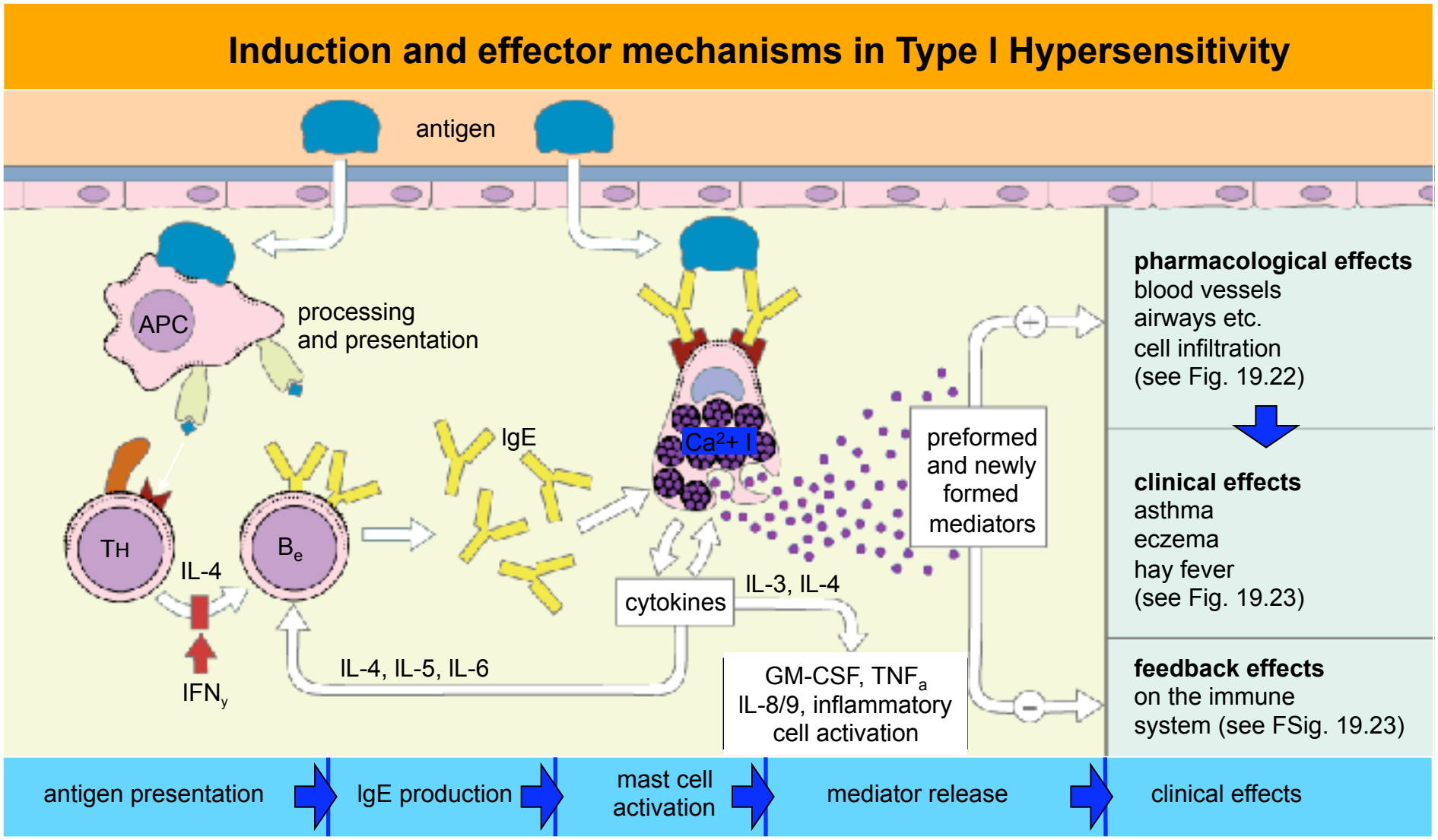
- Type I reactions are usually the result of exposure to environmental allergens in genetically susceptible individuals
- 1/10 persons in USA affected to varying degrees
- Genetics not clearly defined, although there is a familial association
- Atopy: a genetic predisposition for developing IgE responses to many antigens
- Local or systemic symptoms

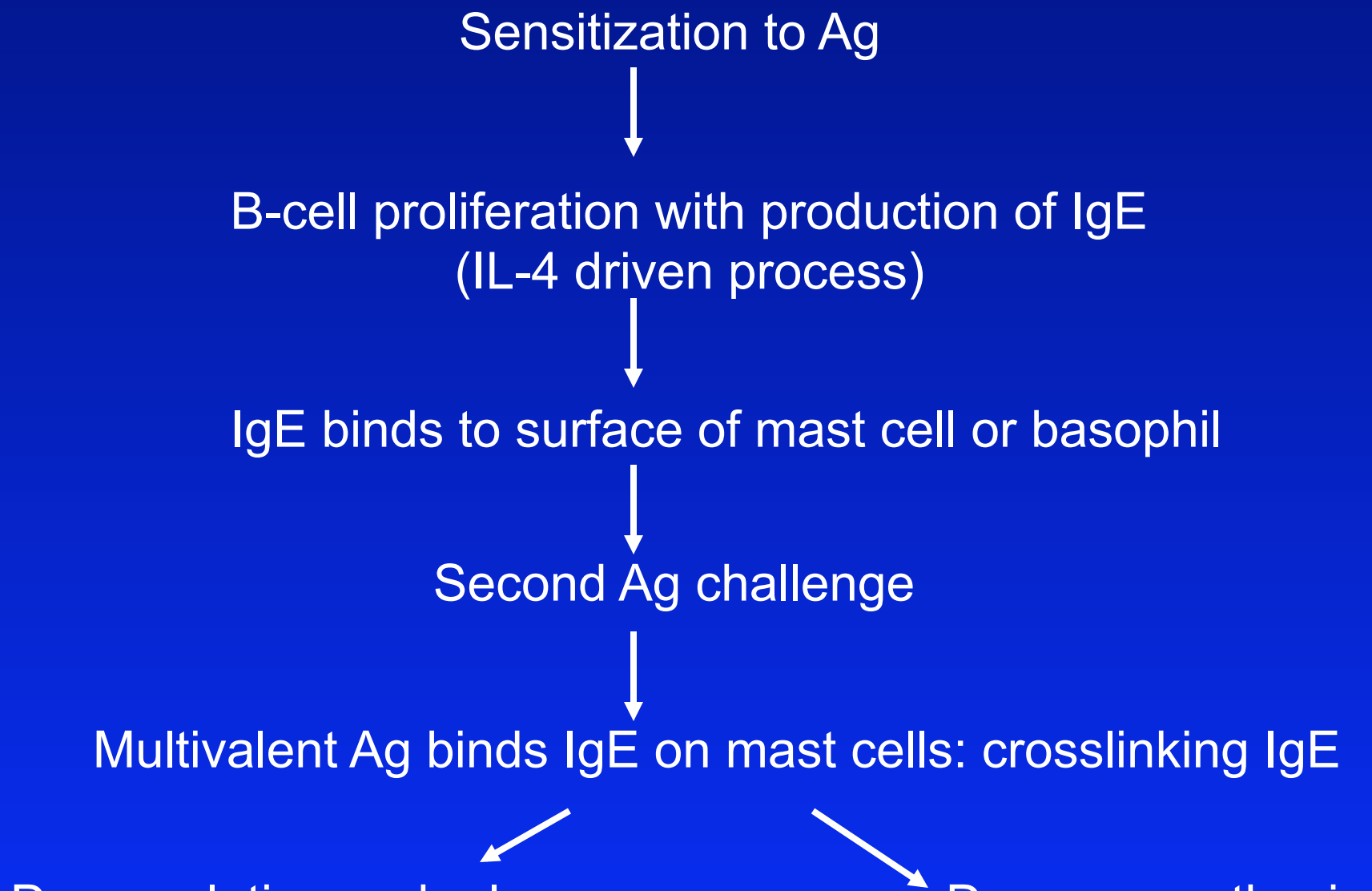
Clinical (cont.)

- Most common form - allergic rhinnitis
  - Also
    - Certain types of asthma
    - Atopic dermatitis (eczema)
    - Certain gastrointestinal food allergies
- Allergens
  - Pollens, molds, house dust mite, animal dander



Pathophysiology




Sensitization to Ag
B-cell proliferation with production of IgE
(IL-4 driven process)
IgE binds to surface of mast cell or basophil
Second Ag challenge
Multivalent Ag binds IgE on mast cells: crosslinking IgE
Degranulation and release
of preformed mediators
De novo synthesis
of mediators

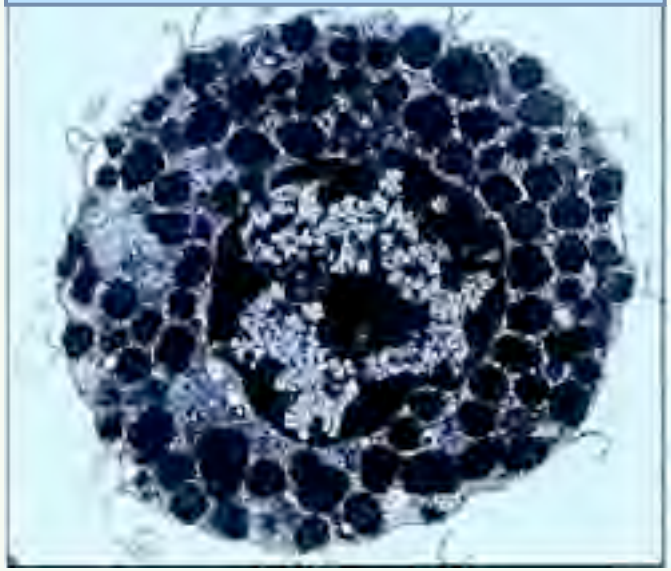
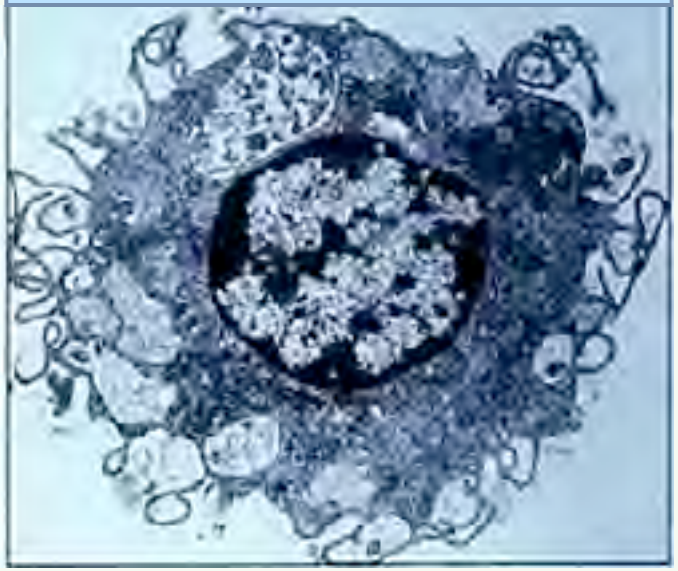
Degranulation and release of preformed mediators

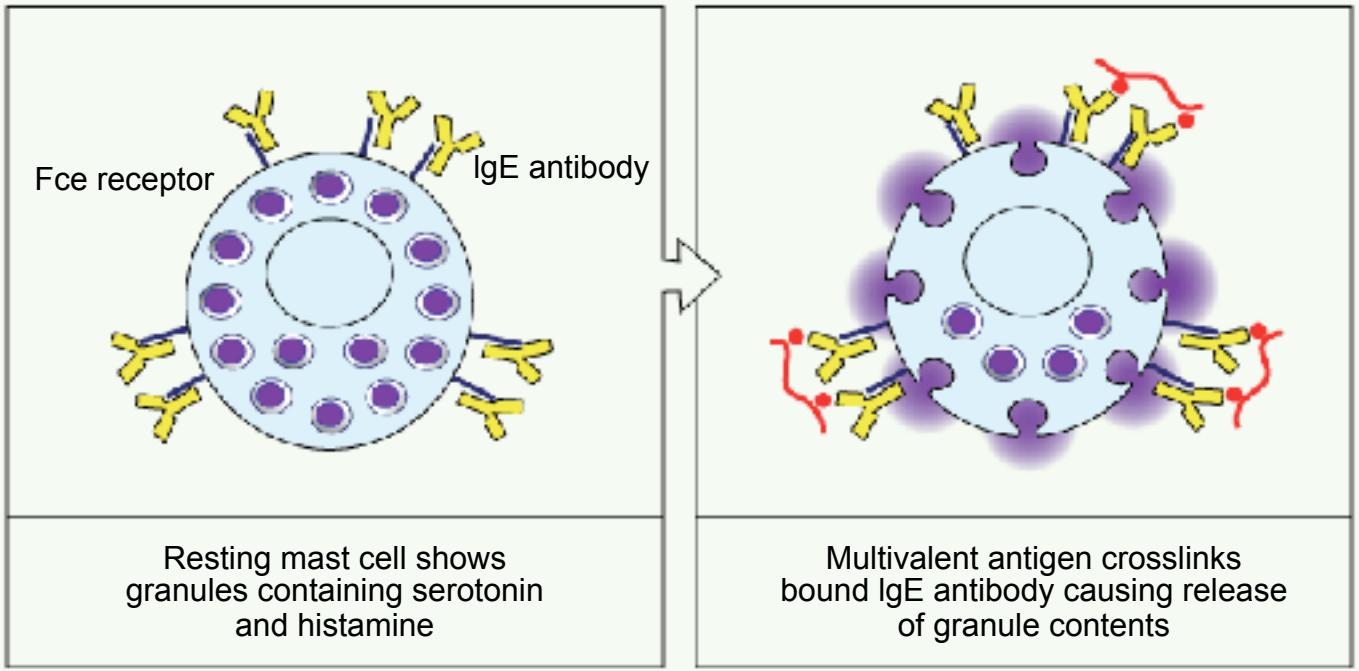
De novo synthesis of mediators

Histamine
Chemotactic factors
Proteases

Leukotrienes (C4, D4, E4)
Prostaglandins
Platelet activating factor
Cytokines

Smooth muscle: bronchial, GI,vascular
Vascular endothelium
Secretory glands (e.g. mucous)
Eosinophils

Resting mast cell	Activated mast cell
	



Resting mast cell shows granules containing serotonin and histamine

Multivalent antigen crosslinks bound IgE antibody causing release of granule contents

Effects of Mediators in Anaphylaxis: Reversible Response

- Histamine - vascular permeability, vasodilation (post-capillary venule), smooth muscle contraction
- Chemotactic Factors
- Cytokines
- Lipid mediators

Effects of Mediators in Anaphylaxis: Reversible Response (cont.)

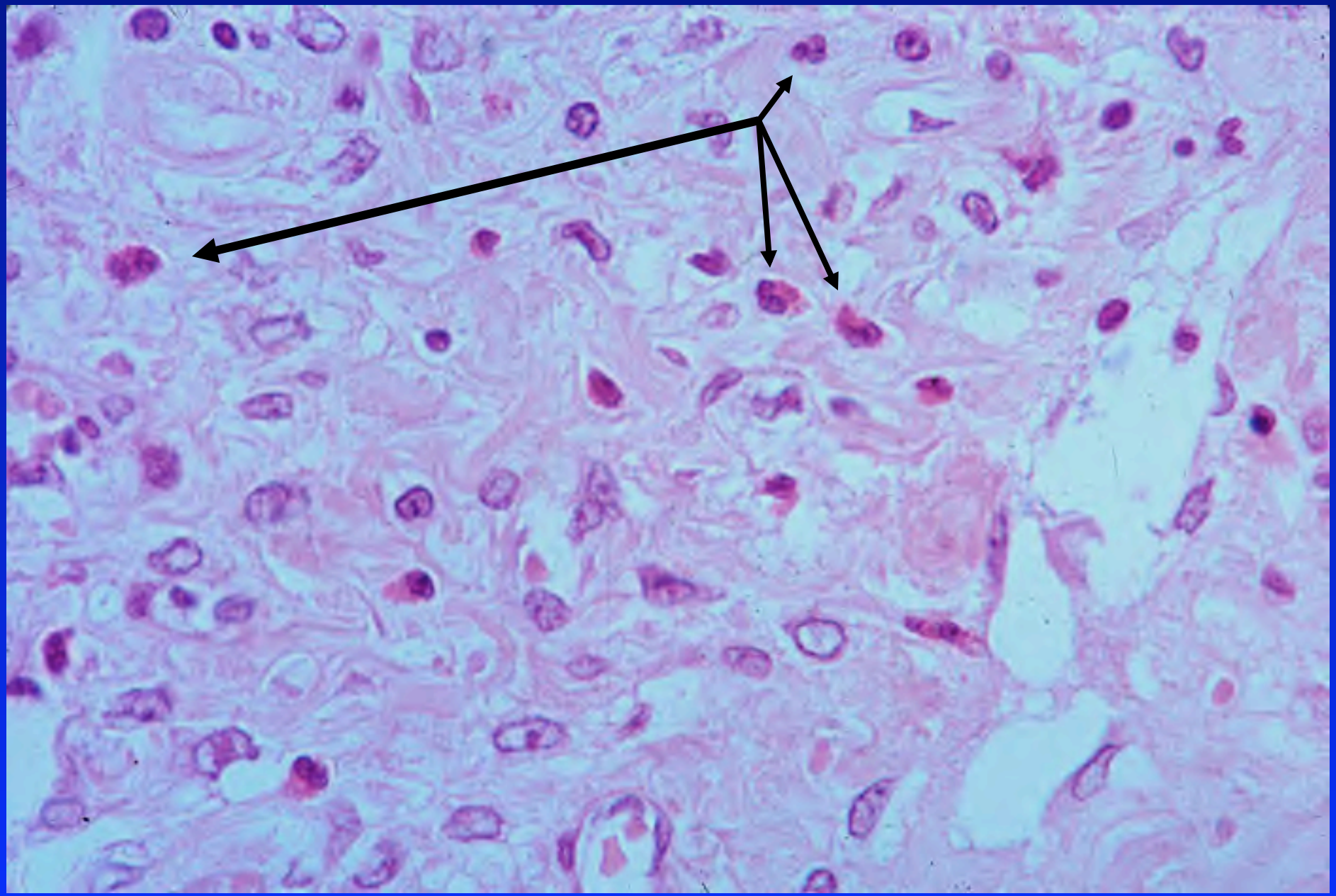
- Lipid Mediators: Arachidonic acid metabolites
  - Leukotriene C4, D4, E4 - smooth muscle contraction
  - Prostaglandins - vasodilation

Effects of Mediators in Anaphylaxis: Reversible Response (cont.)

- Lipid Mediators: PAF - platelet activating factor - low molecular weight lipid
  - Acetylated glycerol ether phosphocholine (AGEPC)
  - Activates phagocytic cells
  - Smooth muscle contraction

Role of Eosinophils in Anaphylaxis:

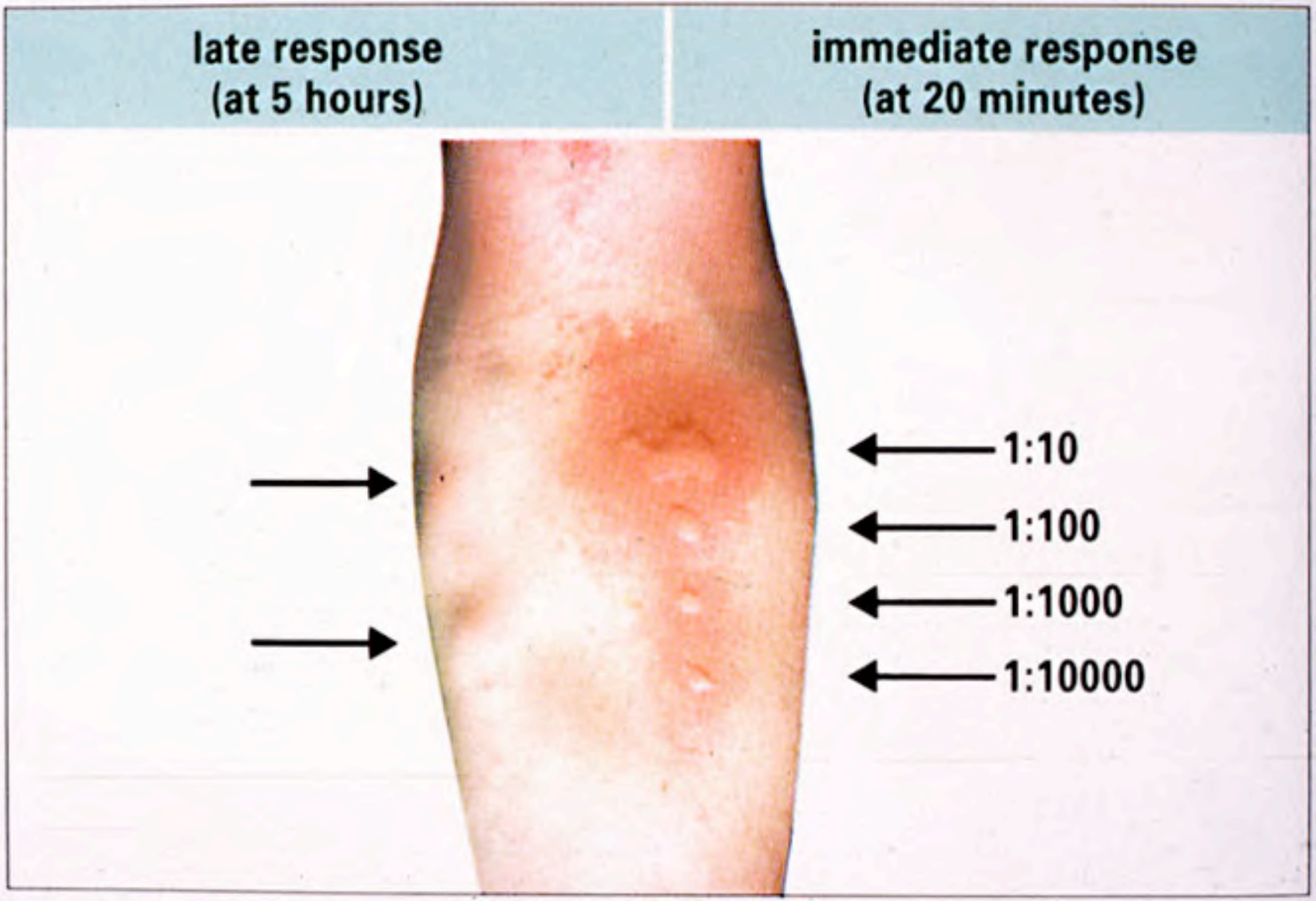
- Normal levels 2 to 3% circulating leukocytes
- Type 1 response: up to 10%+ circulating leukocytes
- Secretory products include:
  - NADPH oxidase-derived oxidants
  - Prostaglandins and Leukotrienes (LTC4)
  - Major basic protein (MBP): cytotoxic
  - Cytokines
  - others



Pathologic Changes Associated with Anaphylactic Reactions: Reversible

- Symptoms depend on target organ: skin
  - Gross: swelling, wheal and flare response
    - early response: preformed mediators
    - late response: synthesized mediators
  - Light microscopic: edema, eosinophils
  - Electron microscopic: edema, endothelial cell gaps

Immediate and late skin reactions



Pathologic Changes Associated with Anaphylactic Reactions: Reversible

- Mucous and serous glands
  - Increased secretion
- Bronchial and GI smooth muscle
  - Contraction

Therapeutic Approaches

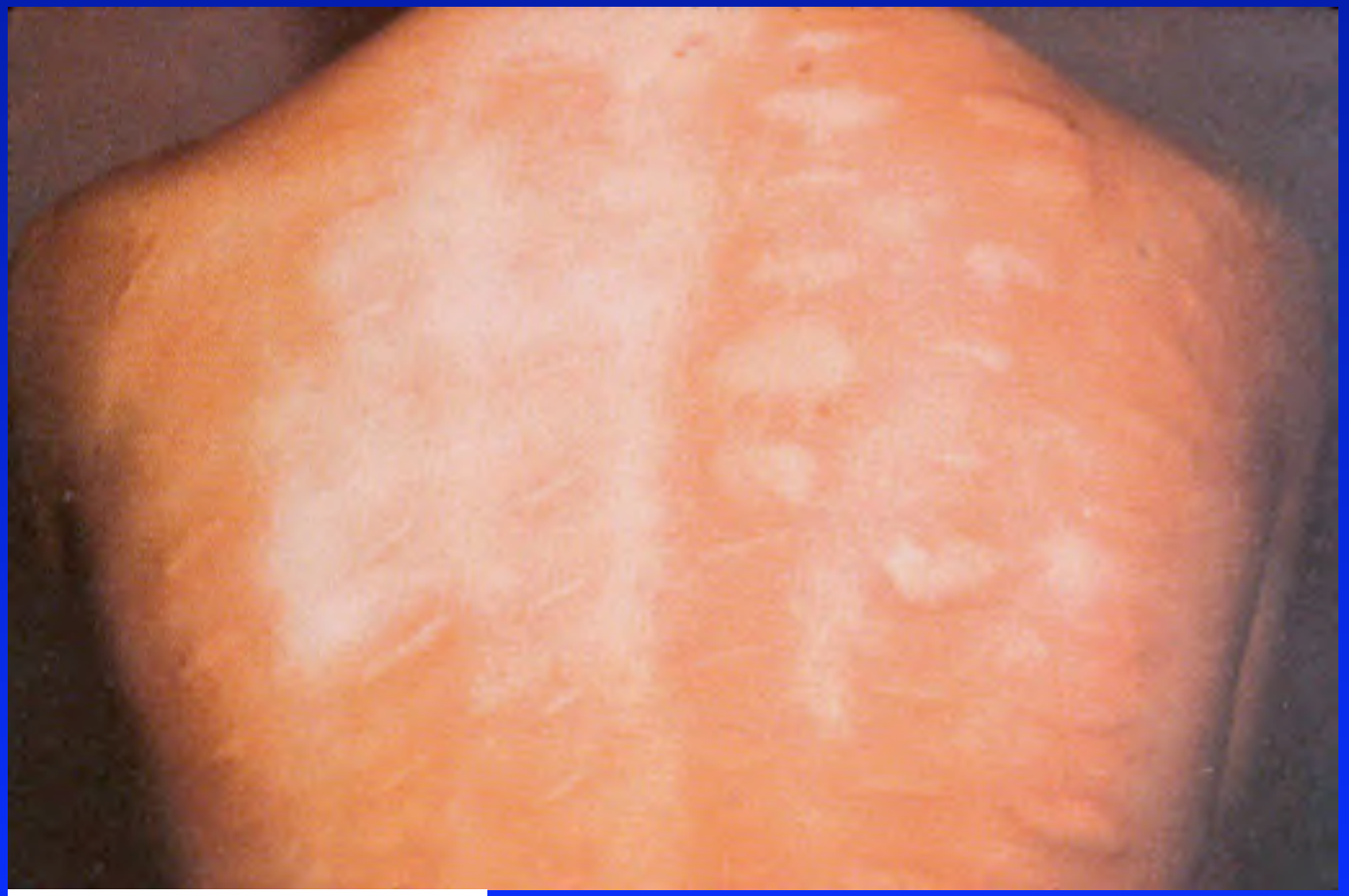
- Avoid antigen
- Mediator antagonists
  - anti-histamines: receptor antagonist
  - leukotriene inhibitors: lipase inhibitors, receptor antagonists
  - functional: sympathetic stimulants
- Inhibit mast cell degranulation
  - cromolyn
- Non-specific anti-inflammatory agents
  - corticosteroids
- Immunotherapy (“allergy shots”)

Comparison of Skin Tests

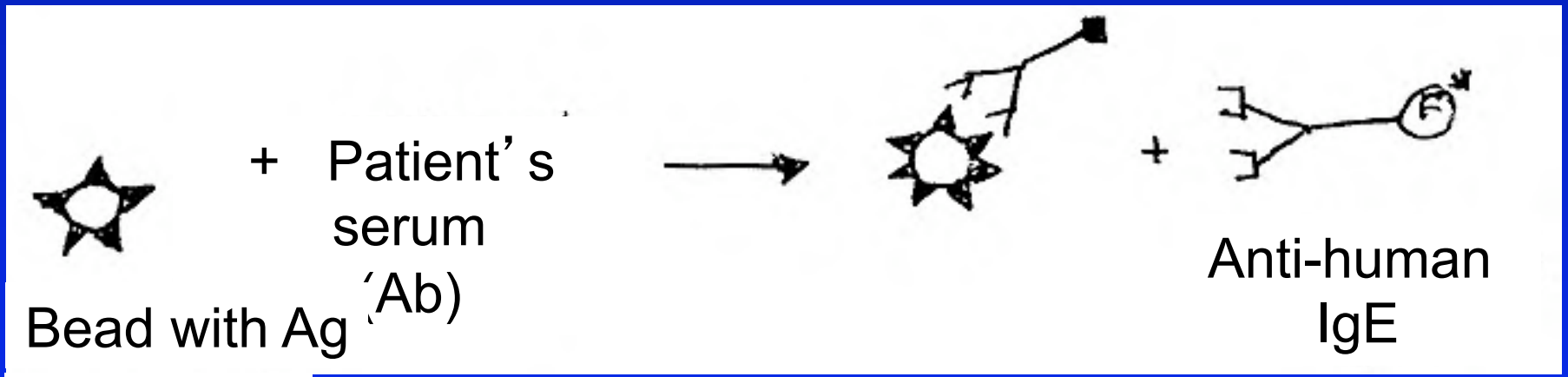
Hypersensitivity Type	Time	Features
Type 1	Minutes	Wheal: edema Flare: vasodilation Eosinophils

Diagnosis

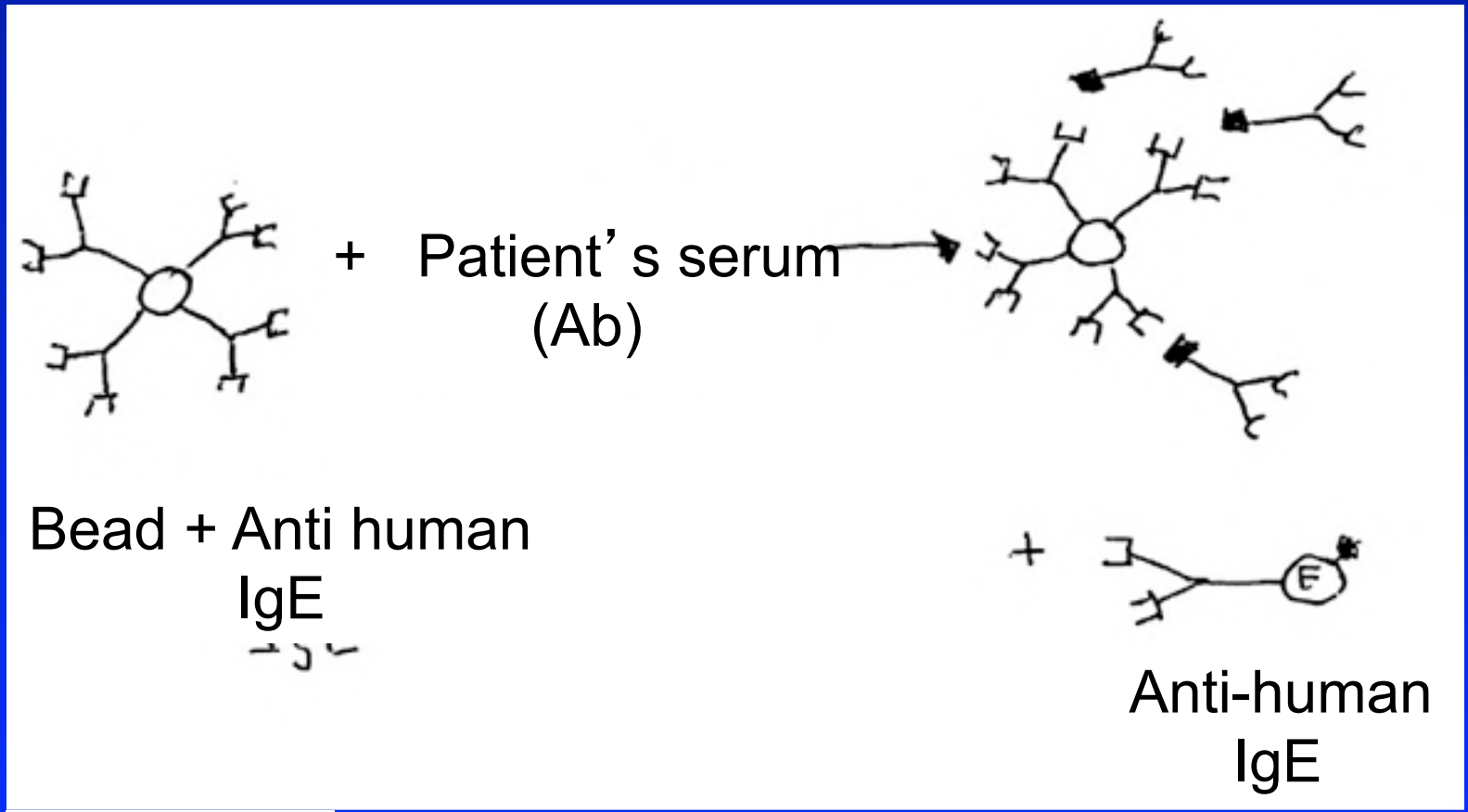
- Skin test - most frequently used



Serologic Tests: RAST - Radioallergosorbent Test - **Specific** IgE



RIST - Radioimmunosorbent **Test** - Total IgE



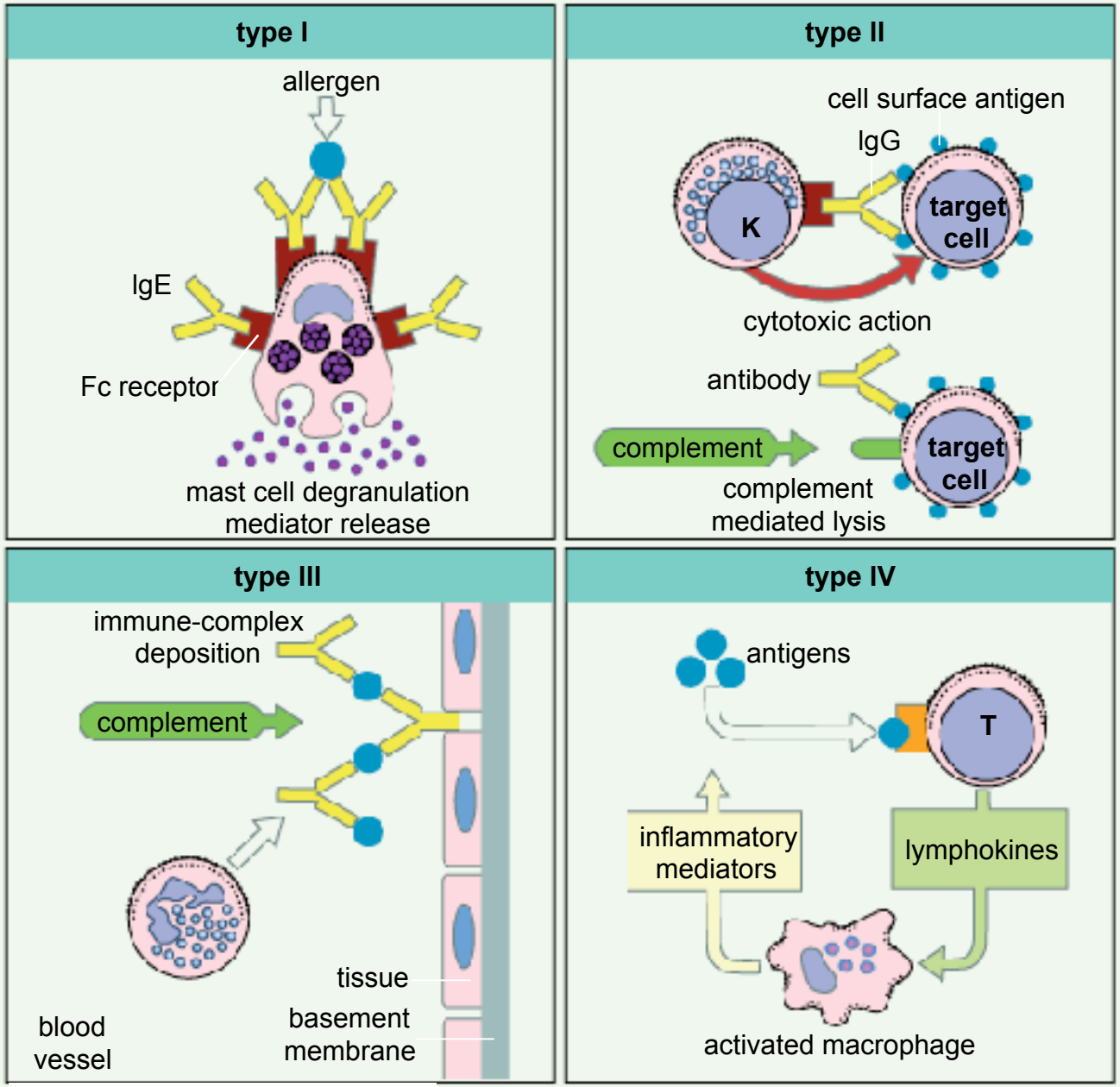
Summary: Type I Reaction

- Antibody: IgE
- Effector Cells: Mast Cell & Eosinophil
- Complement: No
- Reaction: Minutes

Antibody-Mediated Cell and Tissue Injury

(Type II and Type III Reactions)

The four types of hypersensitivity reaction

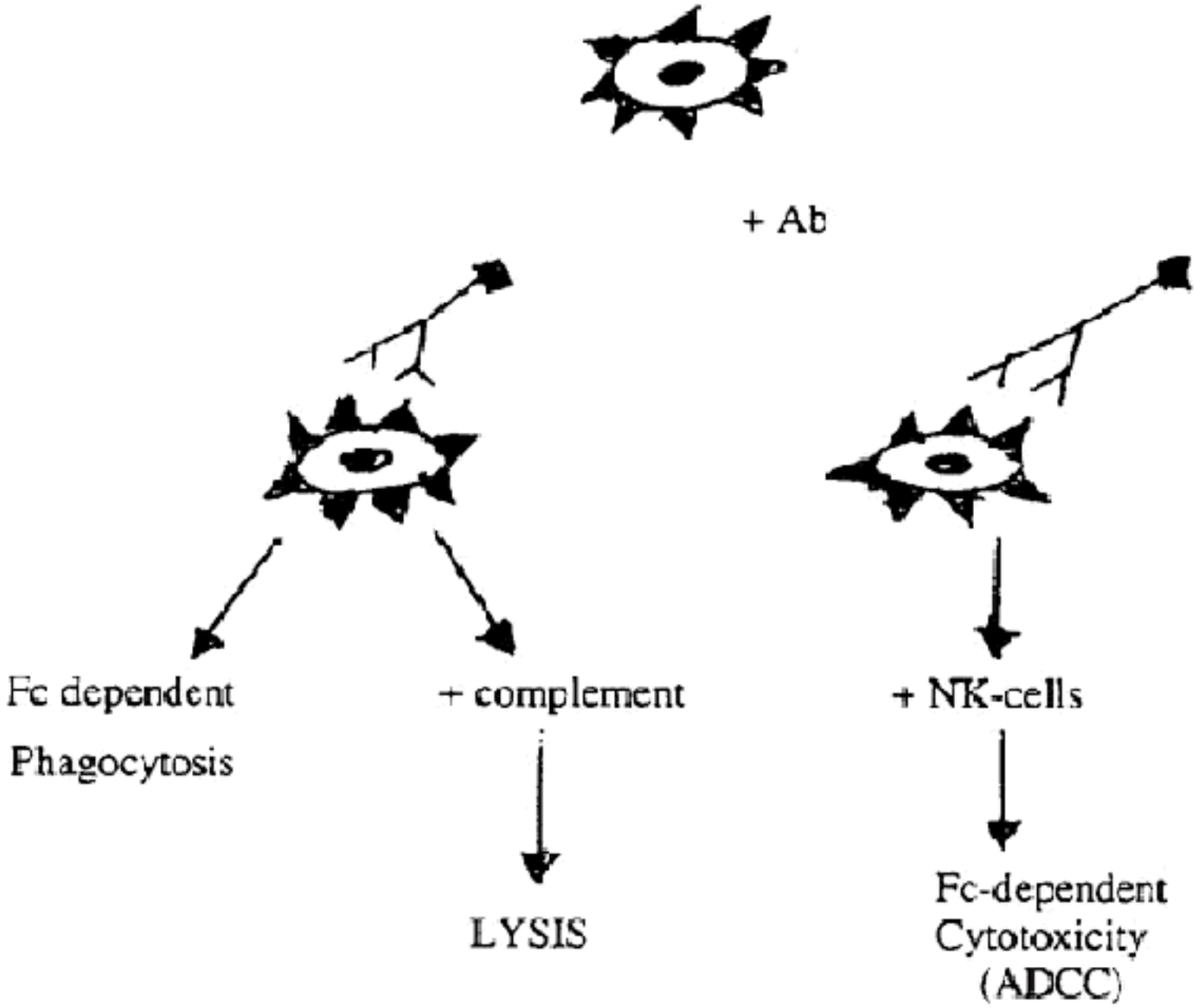


Pathophysiology

- Cytotoxic or Type II Reactions: Binding of Antibody (IgG or IgM) with cell membrane or tissue antigens
  - Red blood cell membrane antigens - hemolytic anemias
  - Platelet antigens - thrombocytopenia cell membrane - petechial hemorrhage
  - Basement Membrane - Goodpasture's syndrome
    - Kidney - proteinuria
    - Lung - hemorrhage

Mechanisms

- Opsonin dependent phagocytosis
- Complement-dependent Ab lysis
- Antibody-dependent cell cytotoxicity



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Rh Incompatibility in Newborn: Hemolytic Anemia

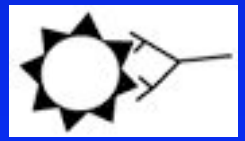
Pregnant woman
Rh-

Sensitized during birth of
Rh+ First child

forms circulating
IgG antibody (Anti-D)

2nd pregnancy
Rh+ child

IgG crosses placenta



hemolysis

Preventative Therapy: Block sensitization by giving mother anti-D (Rho) Immunoglobulin within 72 hours after first birth or abortion

Mechanisms (cont.)

- Antibody directed to tissue antigens: examples
  - Goodpasture's syndrome: antigen = basement membrane of kidney and lung
  - Dermatitis Herpetiformis: antigen = epidermis basement membrane reticulin
  - Bullous Pemphigoid: antigen = epidermis basement membrane
  - Pemphigus vulgaris: antigen = epidermis keratinocyte membranes

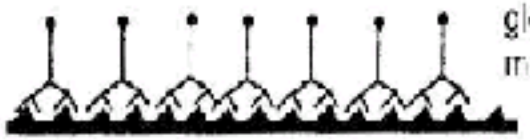
Goodpasture's Syndrome

- Hemoptysis
- Pulmonary infiltrates
- Renal failure
- Anemia

Pathology

- Circulating anit-GBM antibodies
- Lightmicroscopy: frequently neutrophils, hemorrhage
- Immunofluorescence: immunoglobulin and complement deposition; linear immunoflourescence
- Electron microsocpy: no electron dense deposits

Goodpastures Syndrome: Anti-GBM Disease



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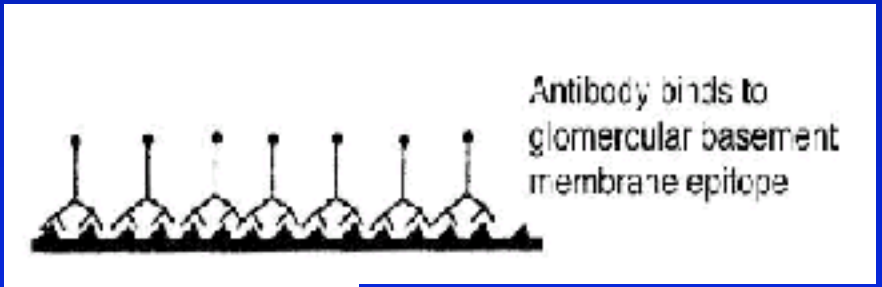
+ Complement → ↗C3b deposition
↘C3a + C5a
↓
← PMN recruitment

Proteases
+
reactive oxygen metabolites
↓
tissue injury

lung: hemorrhage, hemoptysis, alveolar infiltrates

kidney: proteinuria, hematuria, renal failure

Goodpastures Syndrome: Anti-GBM Disease



+ complement → C3a,C5a

↓

PMNs

↓

proteases
oxygen metabolites

↓

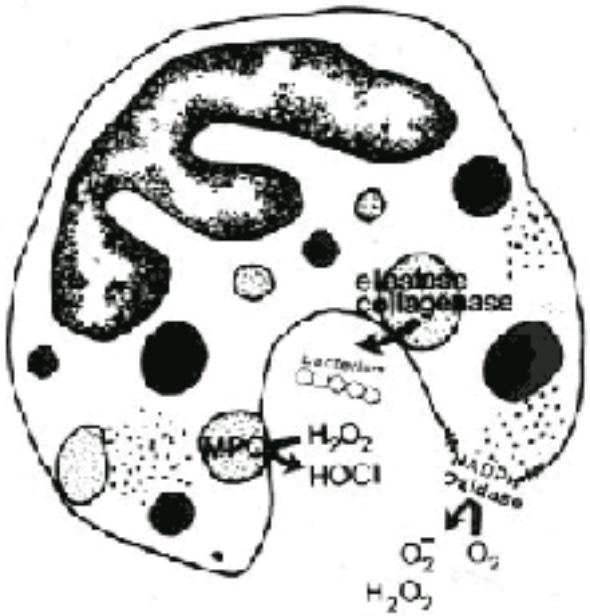
tissue injury

Lung: hemorrhage, hemoptysis, alveolar infiltrates

Kidney: proteinuria, hematuria, renal failure

cell phagocytosis → Oxygen radicals

cell phagocytosis → Elastase
Collagenase
Acid hydrolases



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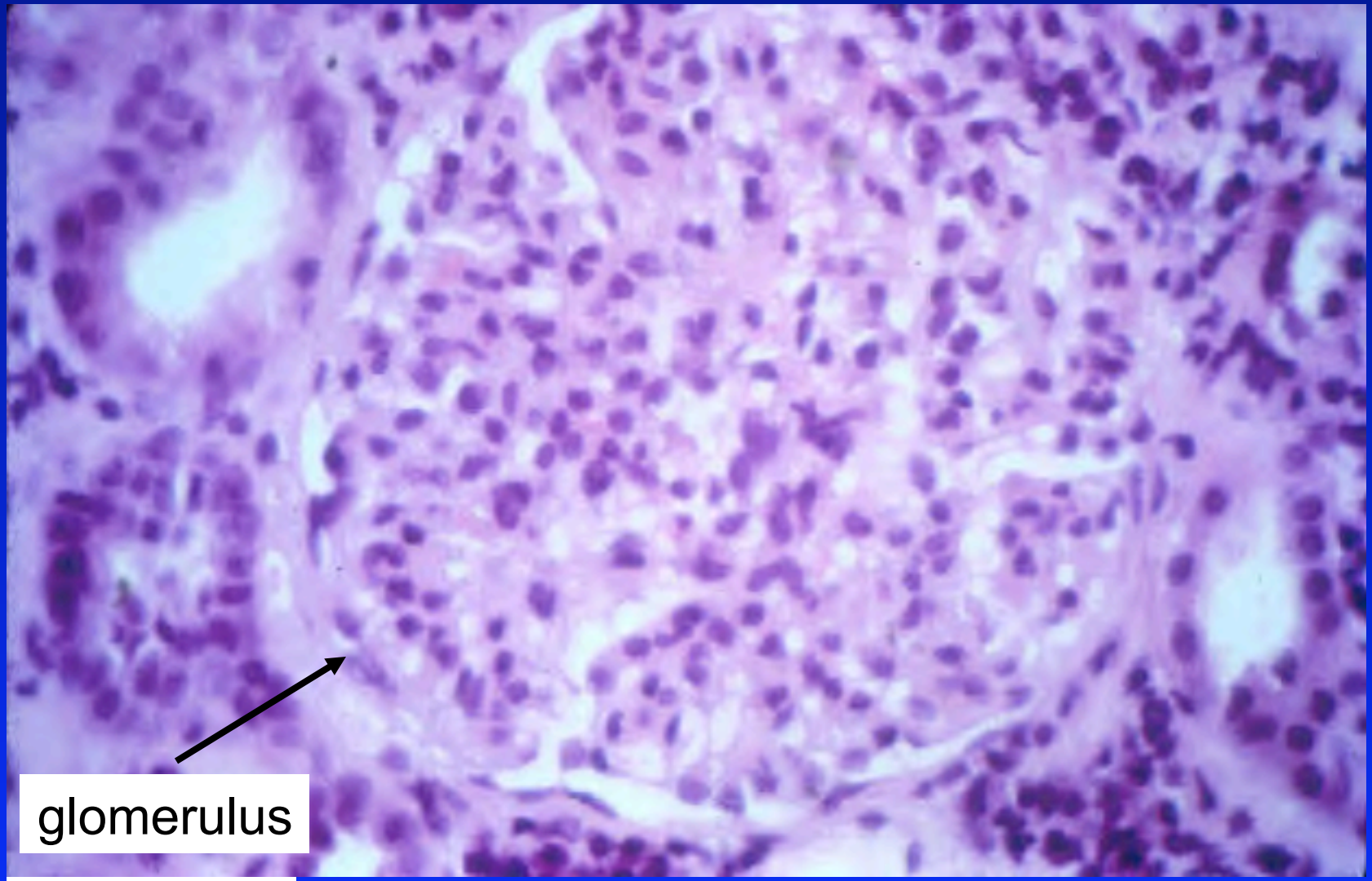

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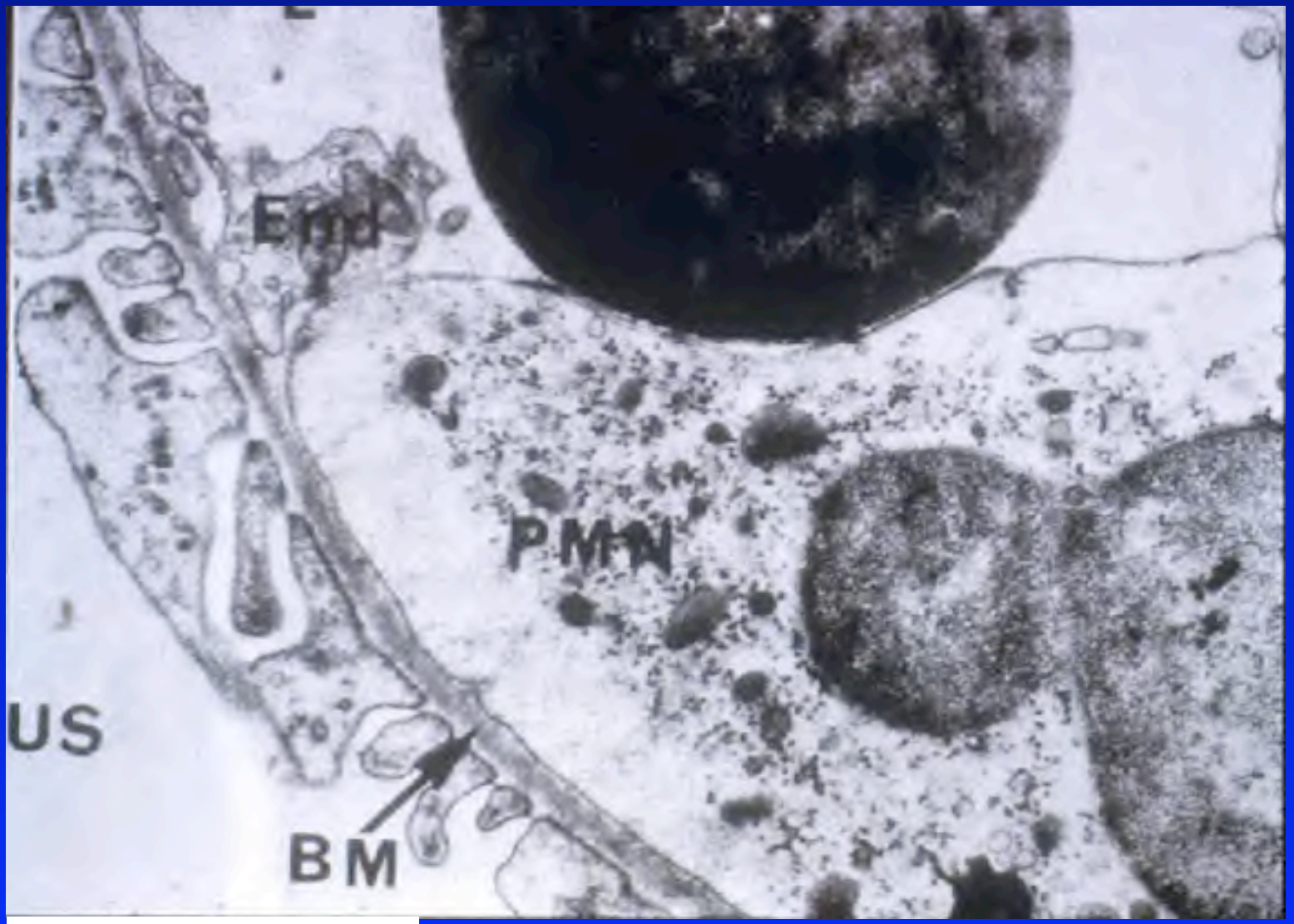
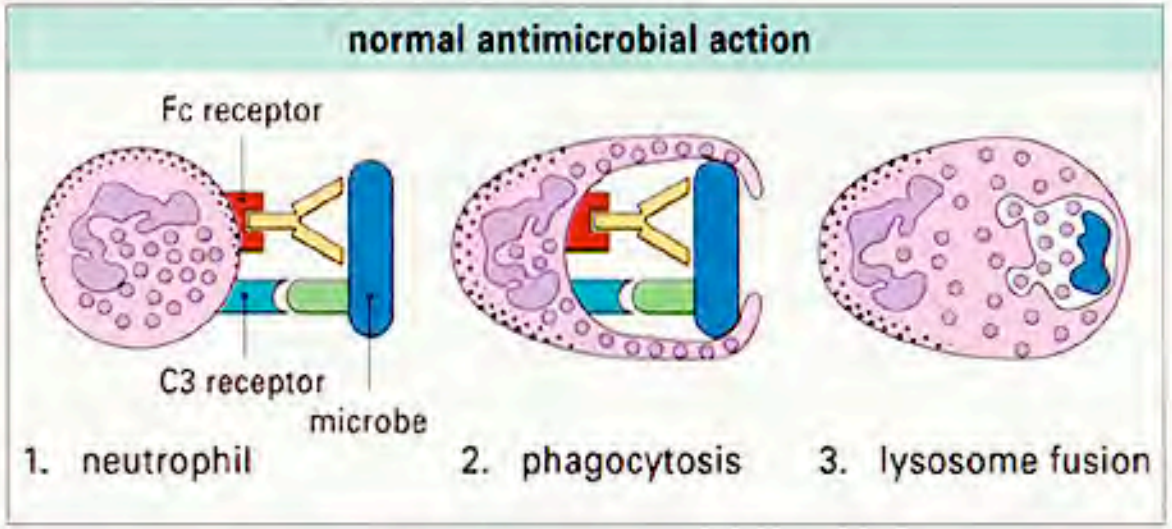
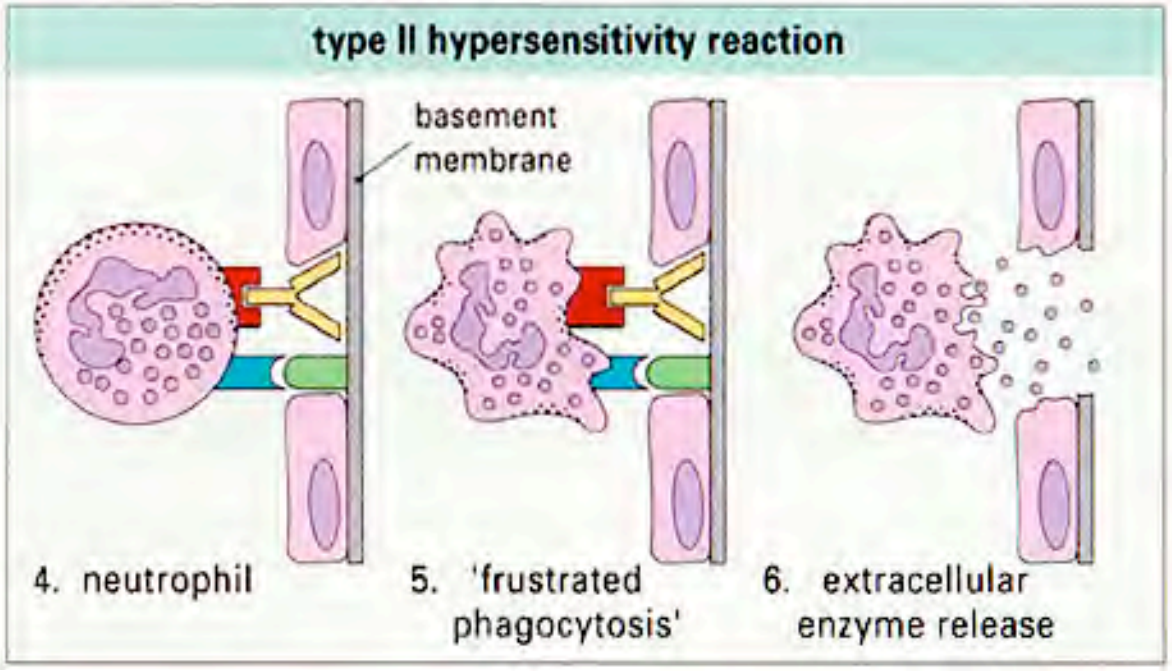
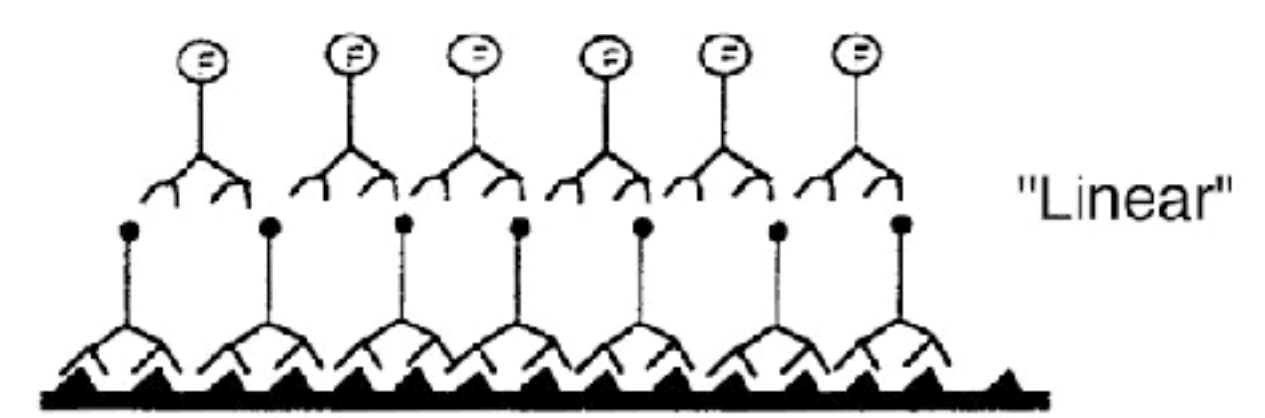


Damage mechanisms





Goodpastures Syndrome



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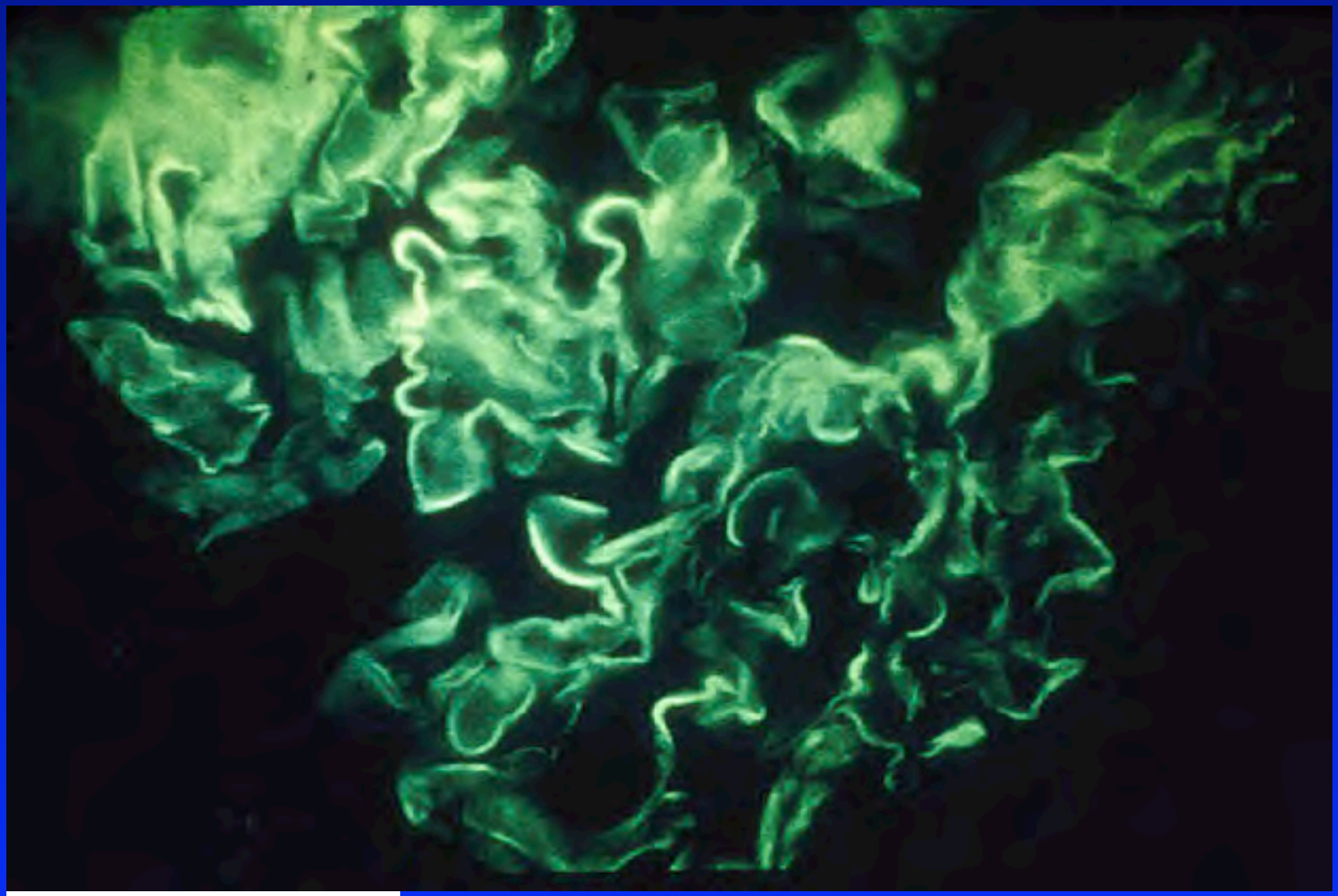
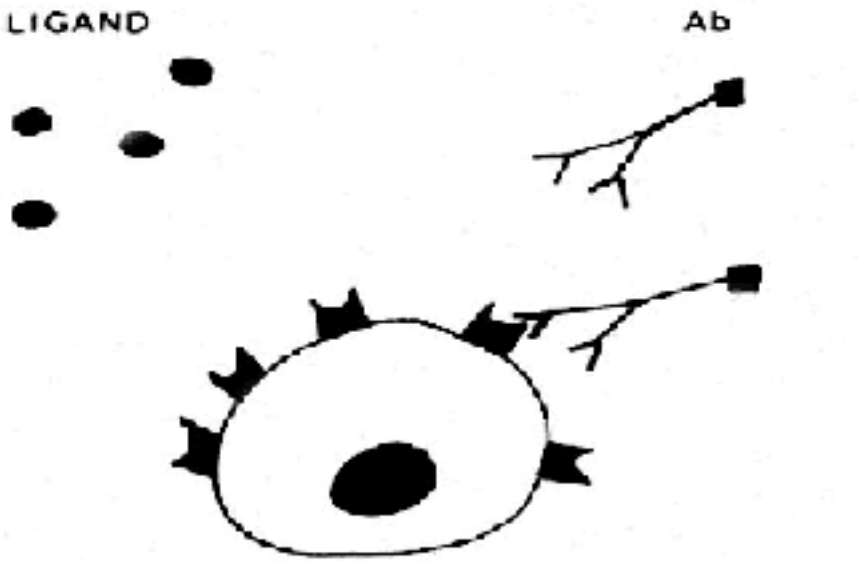
- Linear antigen distribution
- Linear antibody + complement distribution
- Linear secondary anti-human antibody to IgG or complement containing a fluorescent marker



Mechanisms (cont.)

- Antibody Binds to Cell Receptor (Type V Reactions)
  - Hyperthyroidism (Grave's Disease): Thyroid follicle cell - IgG antibody binds to thyroid stimulating hormone (TSH) receptor and **stimulates** cell
  - Myasthenia Gravis: antibody to acetylcholine receptor at neuromuscular synapse antibody blocks neuromuscular transmission (decreased receptors) causing muscle weakness

Antibody to Cell Receptors



A. STIMULATE CELL

B. BLOCK BINDING OF NATURAL LIGAND

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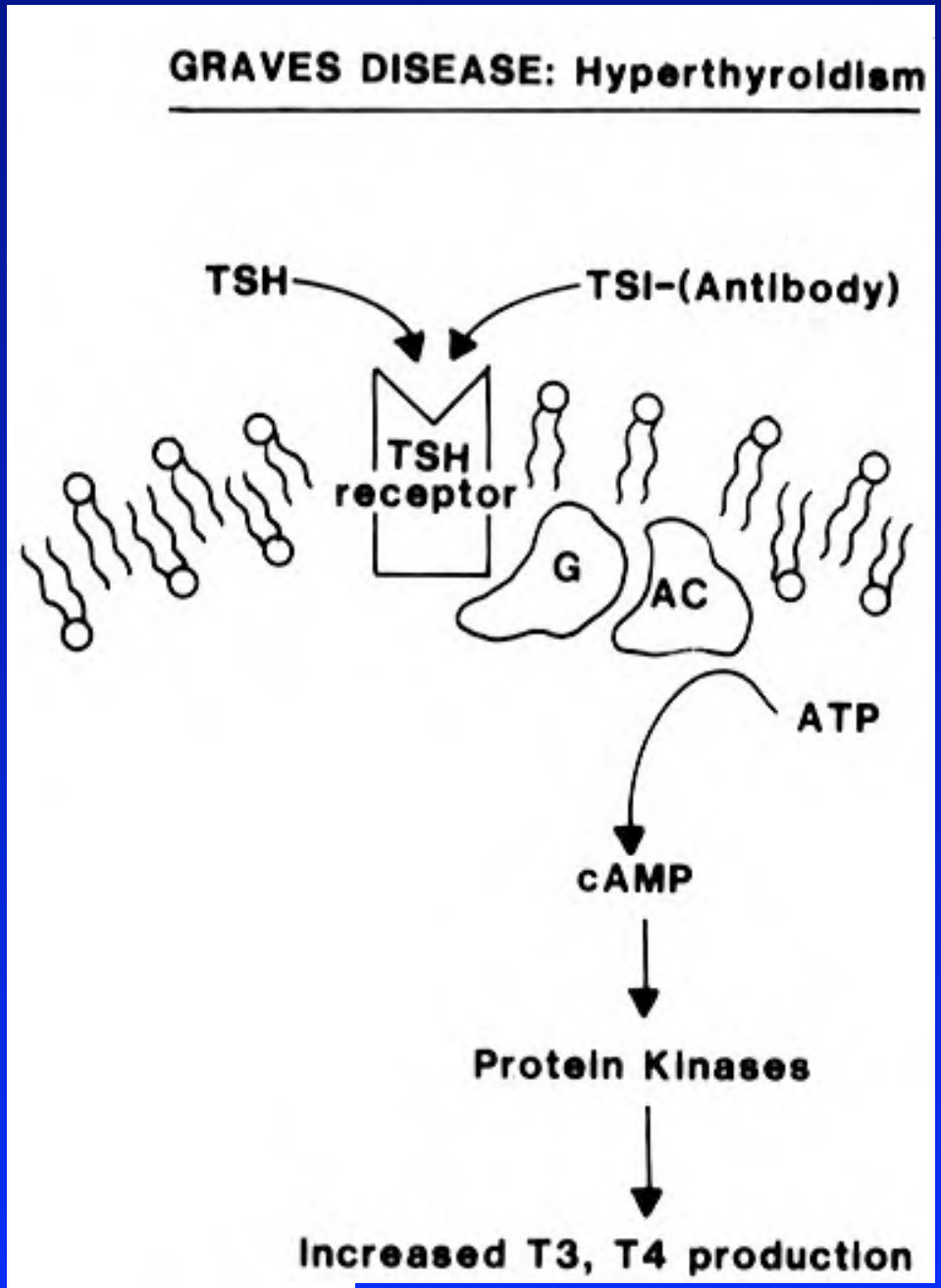

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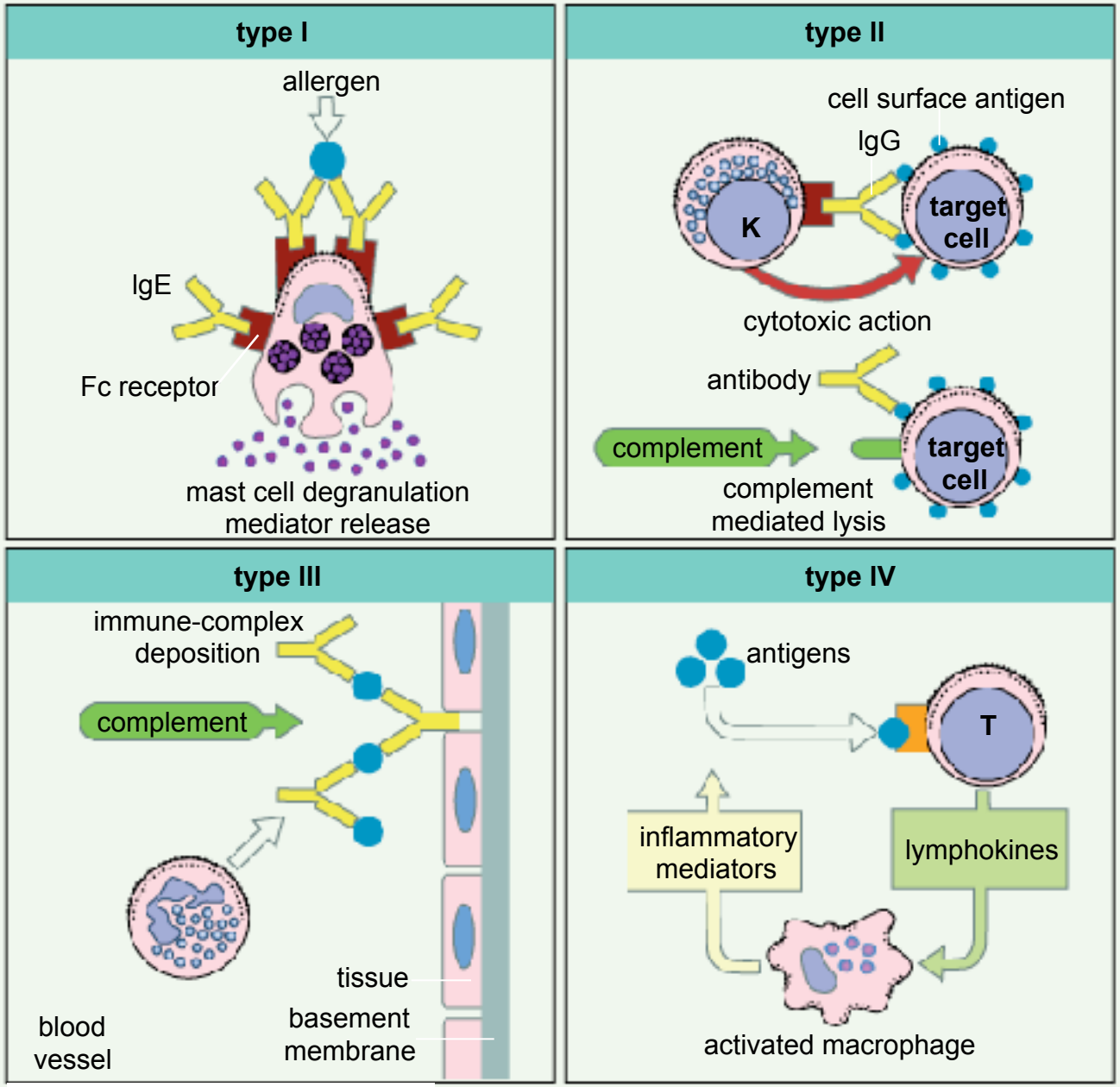
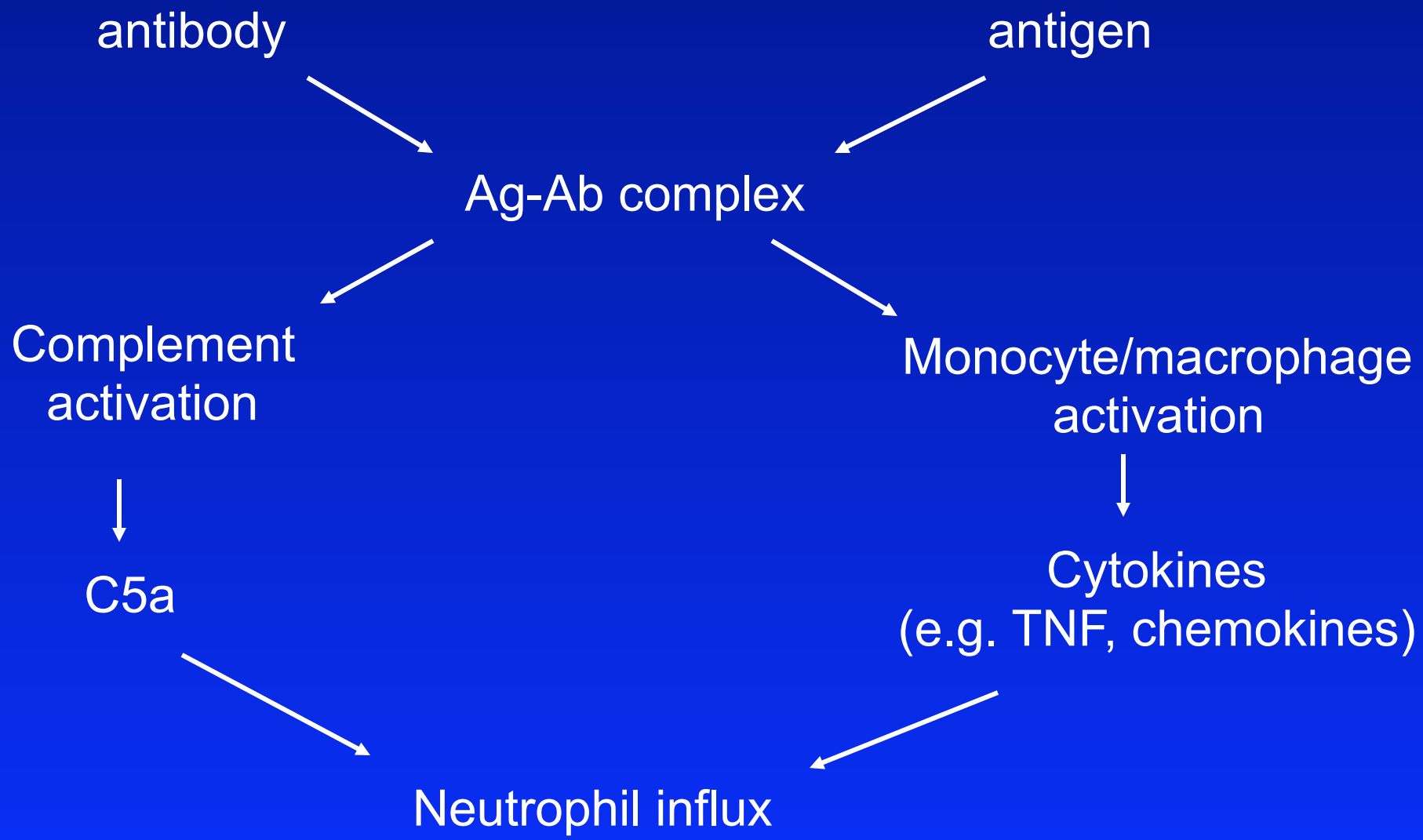
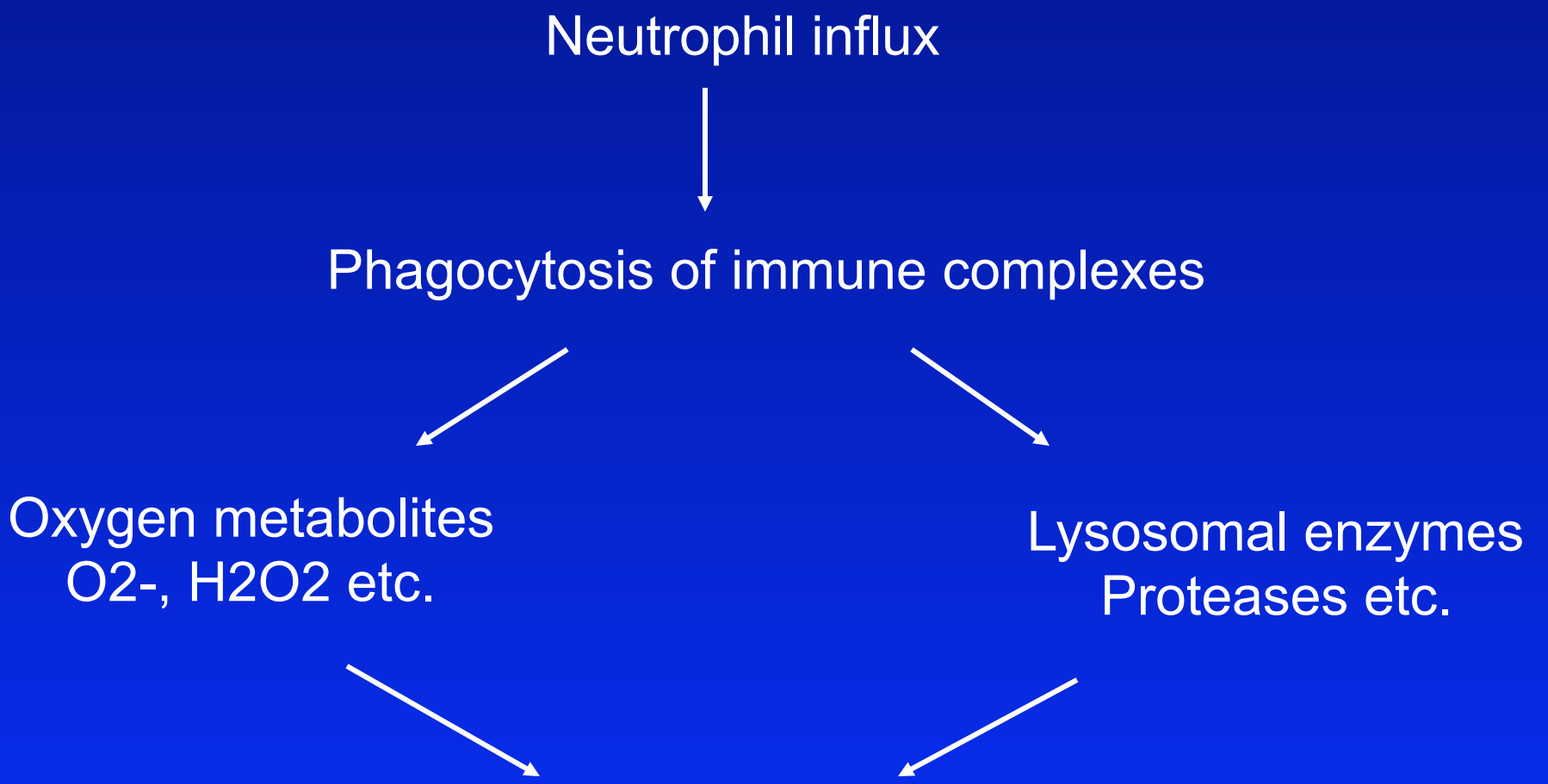
The four types of hypersensitivity reaction



Type III: Immune Complex Mediated Tissue Injury



Summary: Immune Complex Mediated Tissue Injury

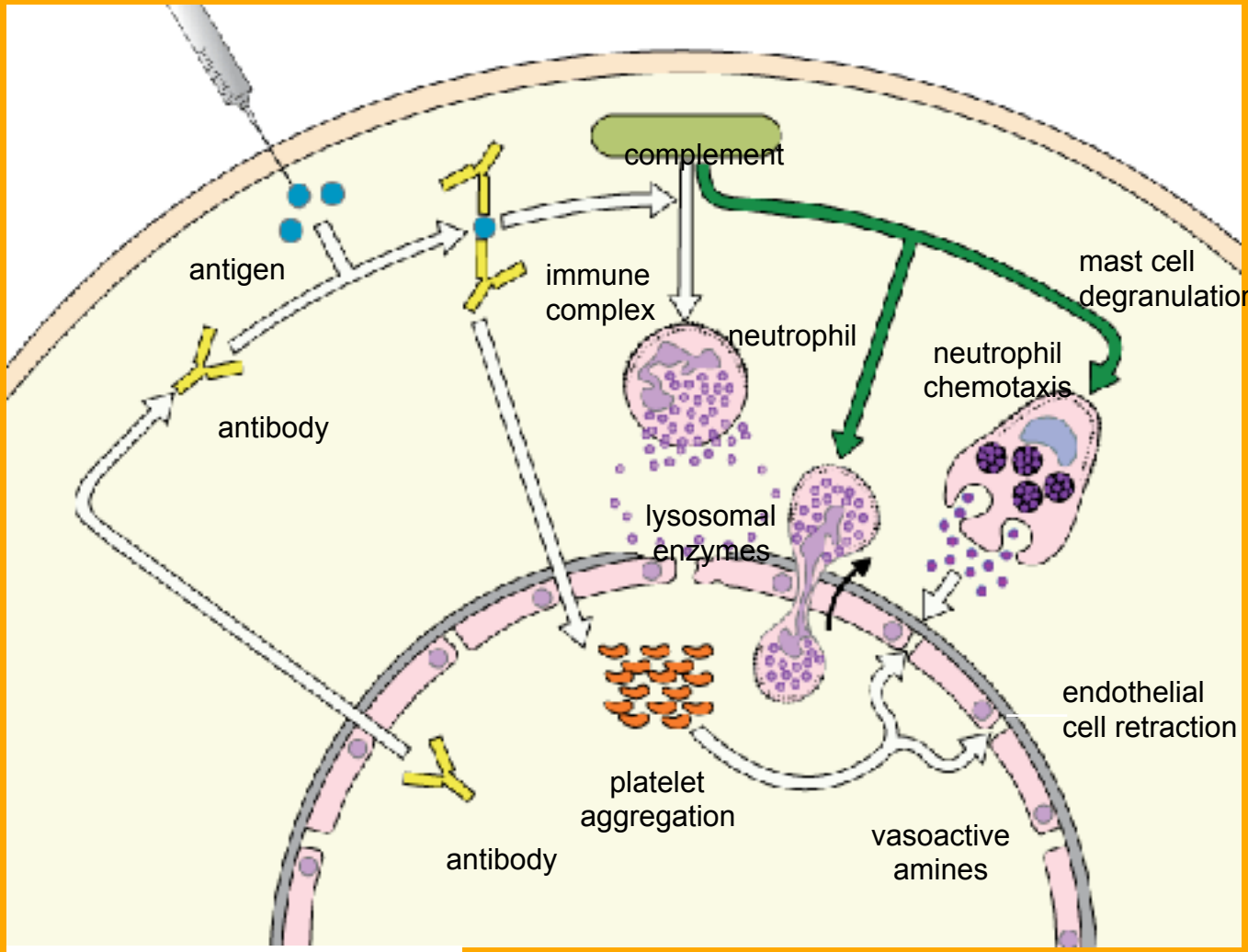


Pathology of Immune Complex Injury

- Fibrinoid necrosis
- Hemorrhage
- Neutrophils
- Antibody + Complement deposition
- EM: Electron dense depositis
- Granular immunofluorescence

Type III Hypersensitivity: Local I.C. Disease

The Arthus reaction



PD-INEL Source Undetermined

Immune Complex-Mediated Hypersensitivity (Type III) (cont.)

- Systemic immune complex disease

Foreign Ag injected I.V.

↓

Immune response w/Ab production (IgM, IgG)

↓

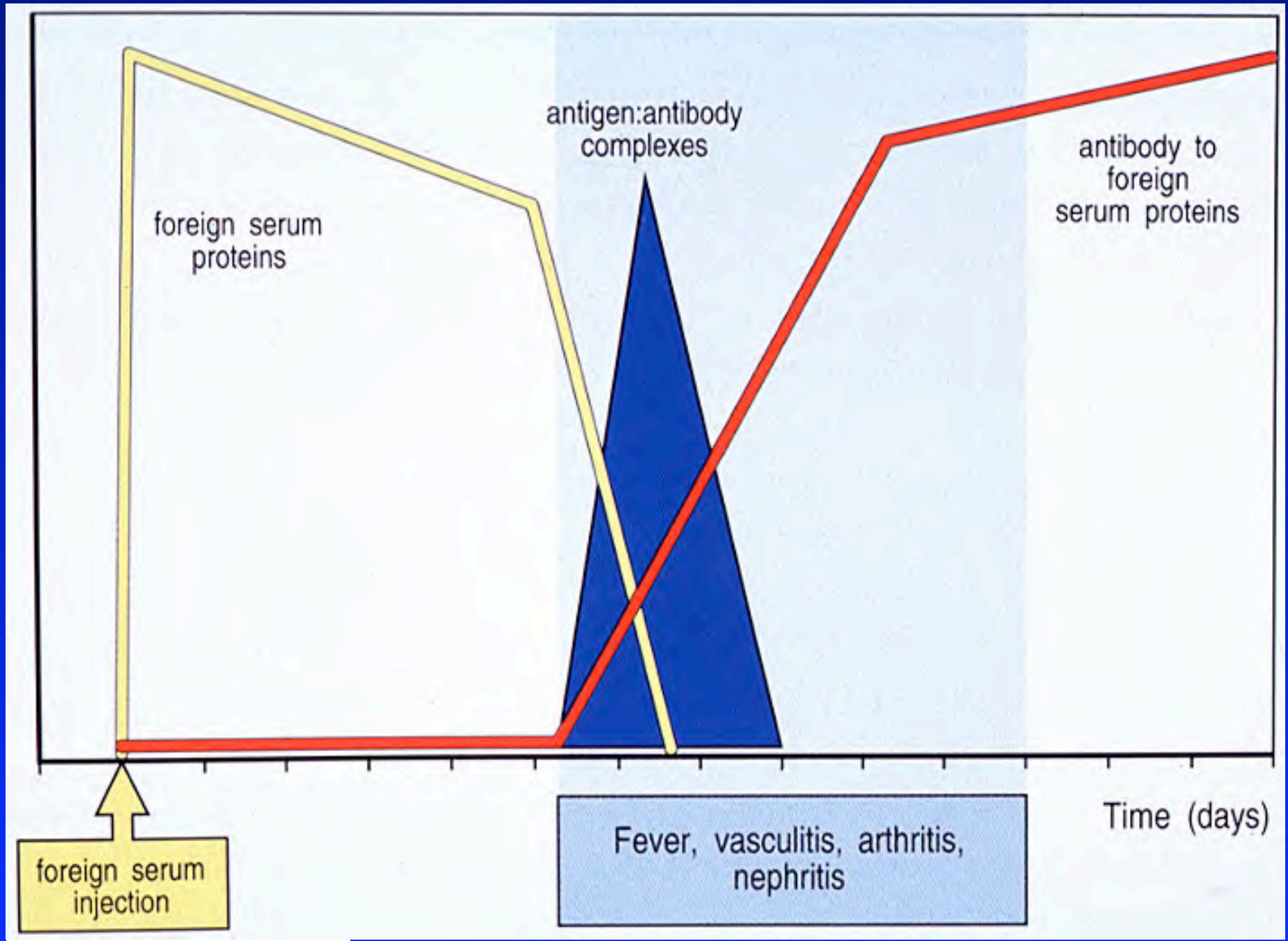
Circulating immune complexes formed

↓

Tissue deposition w/complement fixation

↓

Arteritis
Glomerulonephritis (w/proteinuria)

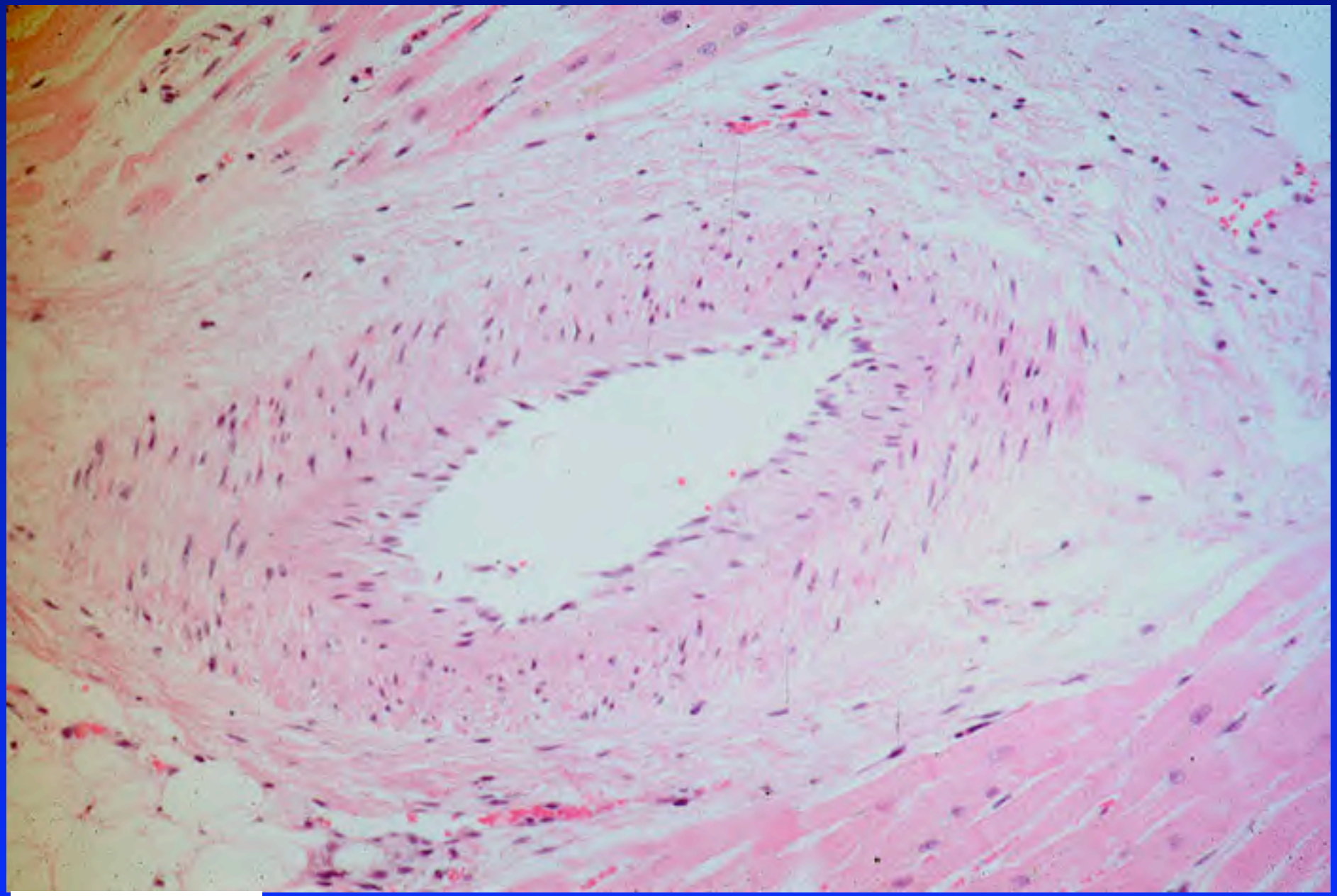


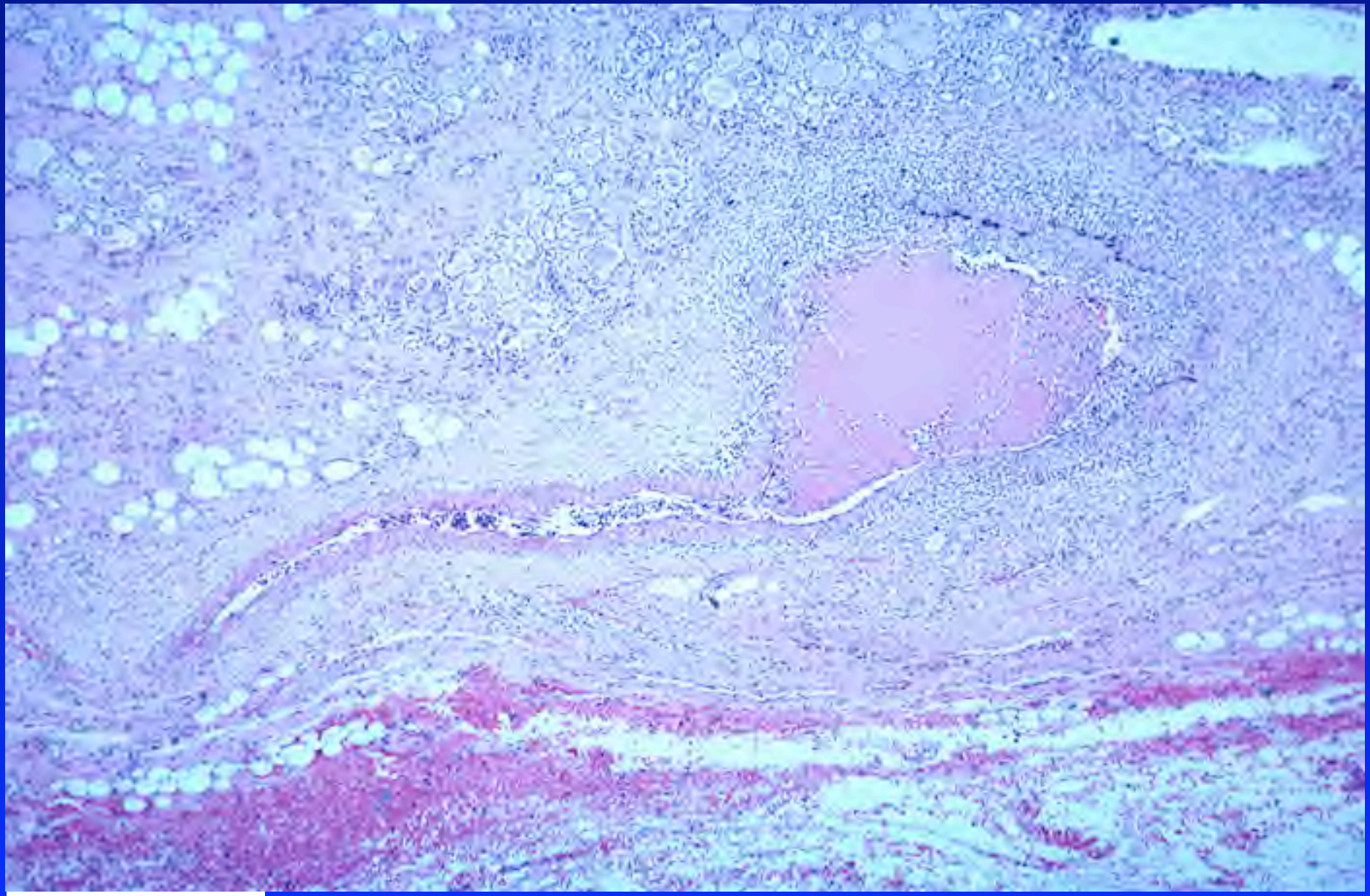
Immune Complex-Mediated Hypersensitivity (Type III) (cont.)

- Pathology
  - Light microscopy: neutrophils, hemorrhage, edema
  - Electron microscopy: electron dense deposits
  - Immunofluorescence: immunoglobulin and complement deposition, granular immunoflouresence pattern

Immune Complex-Mediated Hypersensitivity (Type III) (cont.)

- Clinical - depends on target organ and/or site of immune complex deposition
  - Synovium - rheumatoid arthritis
  - Kidney - glomerulus
    - Post-streptococcal glomerulonephritis
    - Systemic lupus erythematosus
  - Blood vessel walls - vasculitis
    - Polyarteritis nodosa
    - Early transplant rejection
  - Lung - hypersensitivity pneumonitis





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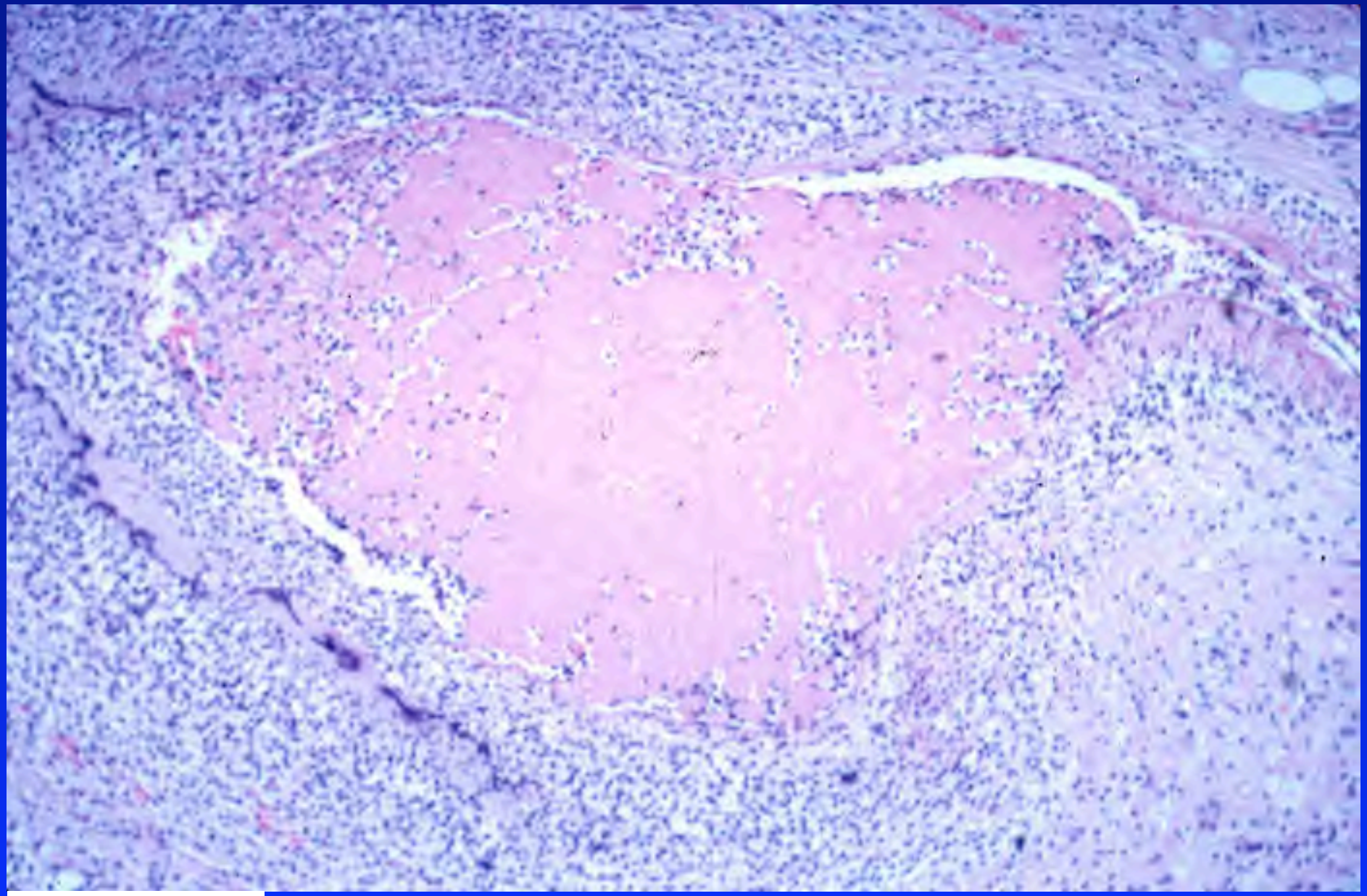

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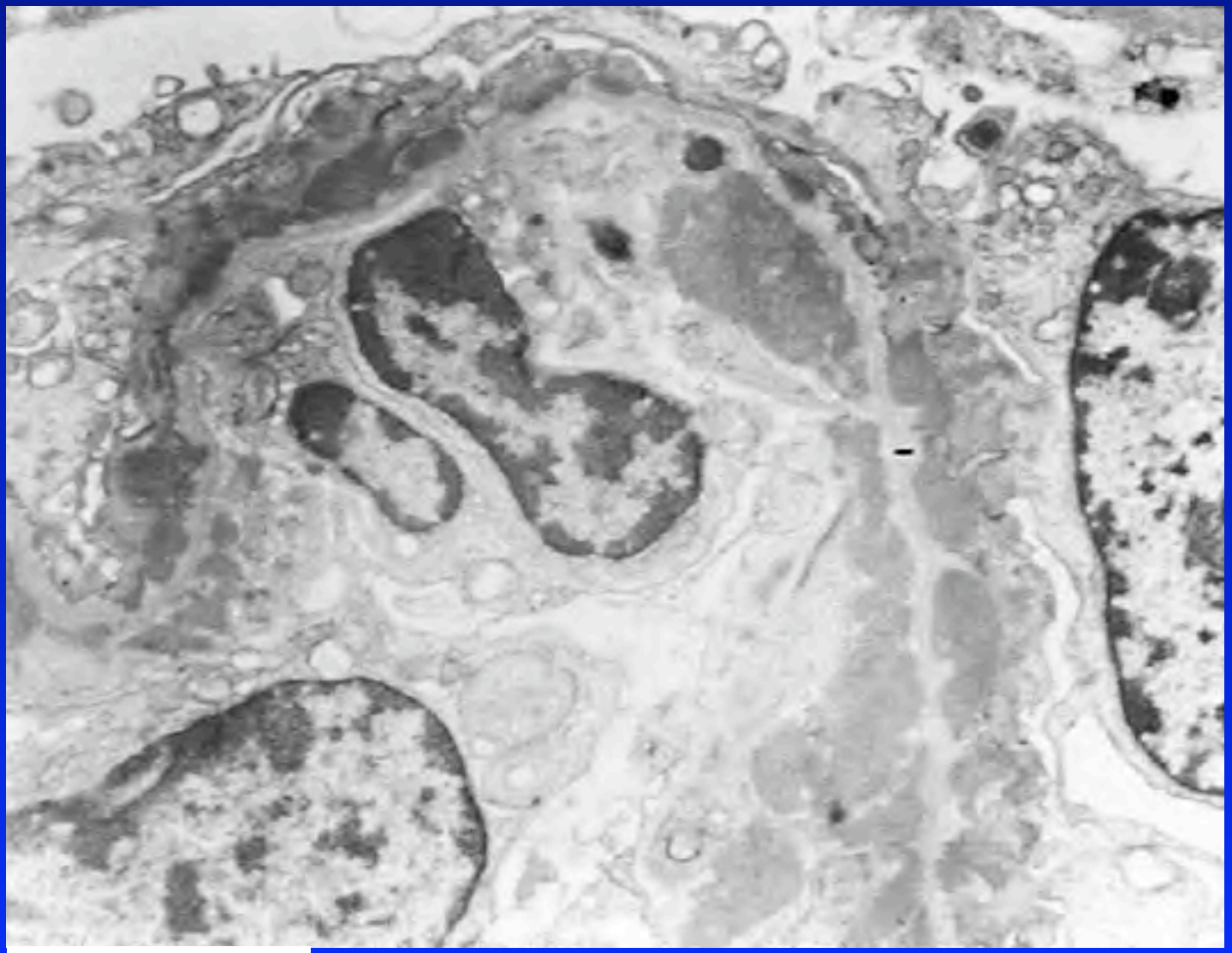

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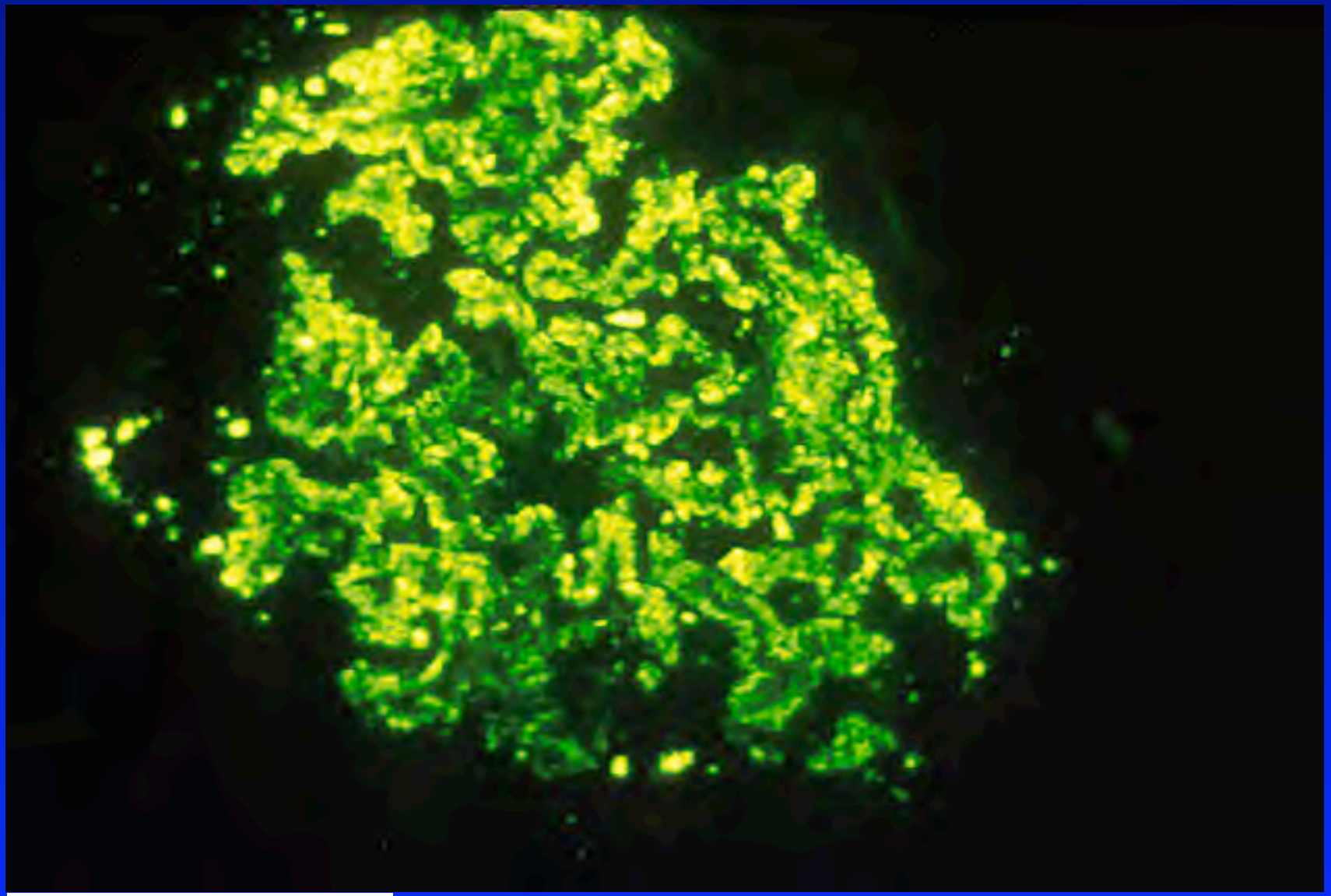
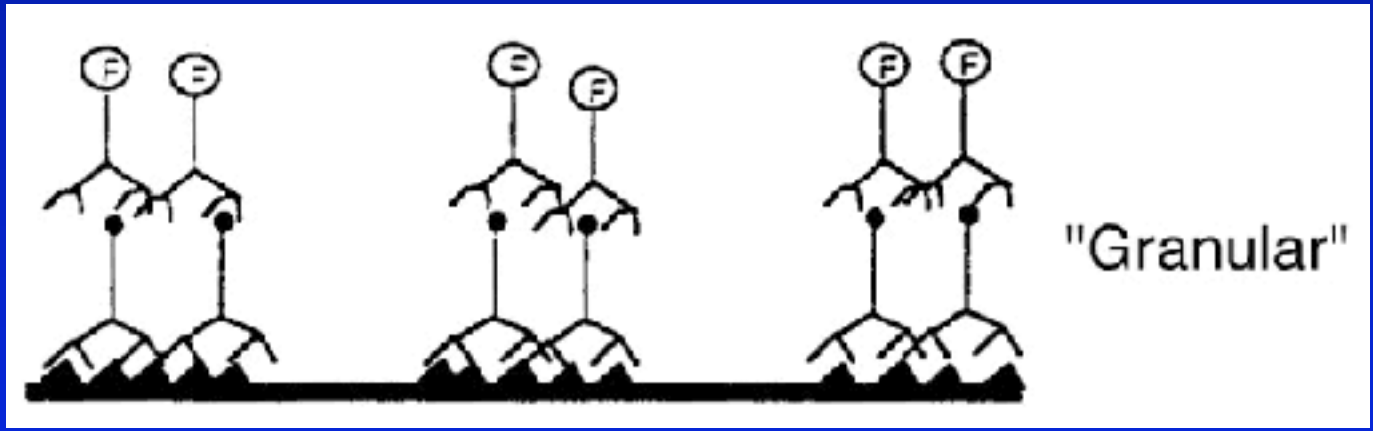


Immune Complex Disease (post-streptococcal glomerulonephritis)



- Irregular antigen distribution
- Irregular antibody + complement distribution
- Irregular secondary anti-human antibody to IgG or complement containing a fluorescent marker

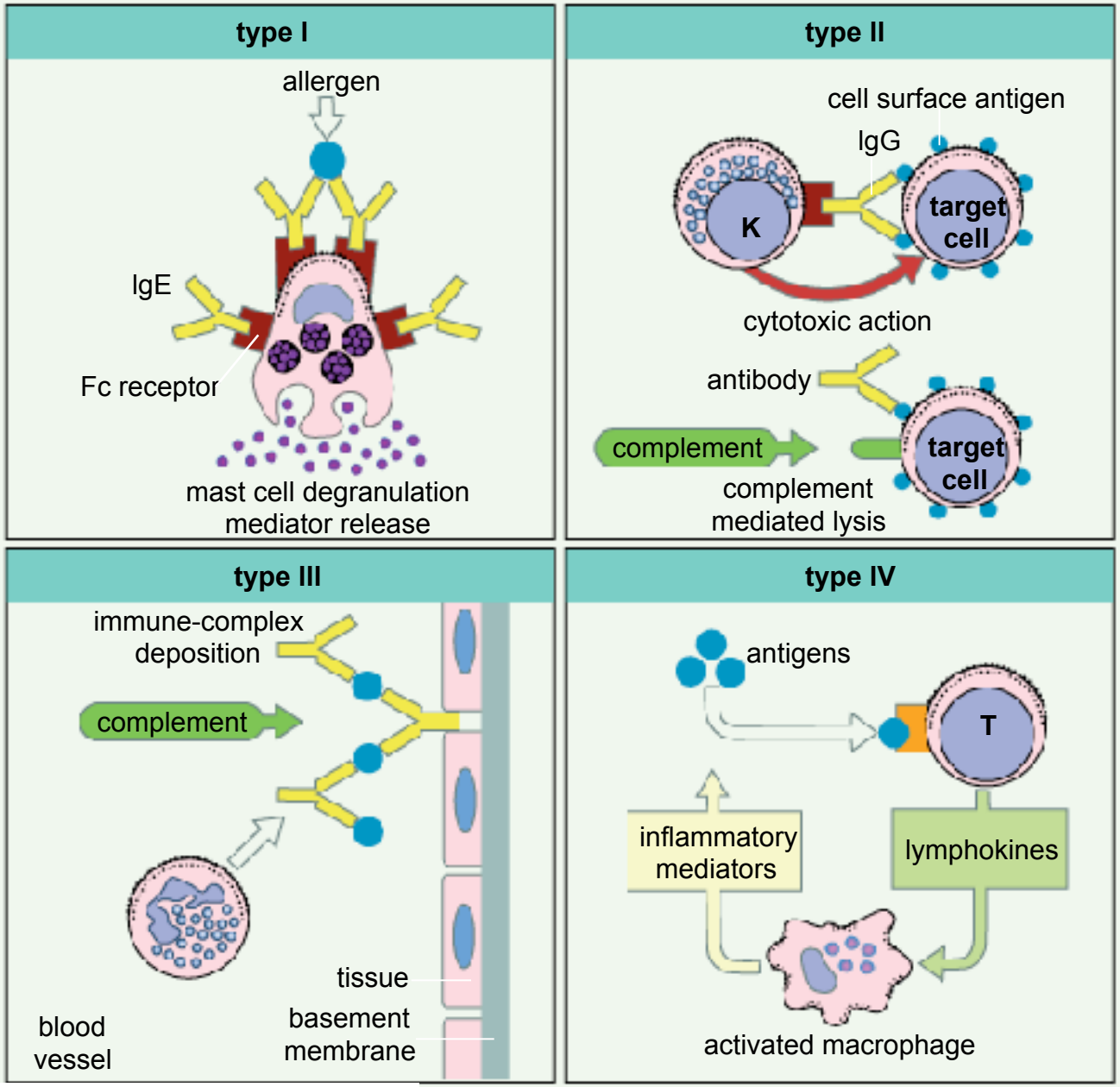
Immune Complex-Mediated Hypersensitivity (Type III) (cont.)

- Diagnosis
  - Skin tests for Type III reactions
- Therapy
  - Elimination of antigen - as in transfusion reactions, hypersensitivity lung reactions to foreign antigens, and certain drug reactions
  - Corticosteroid and immunosuppressive therapy (cytoxan, cylosporin)
  - Plasmapheresis

Summary: Type II/III Reaction

- Antibody: IgM & IgG
- Effector Cells: Phagocytic
- Complement: Yes
- Reaction: 6-24 hours

The four types of hypersensitivity reaction

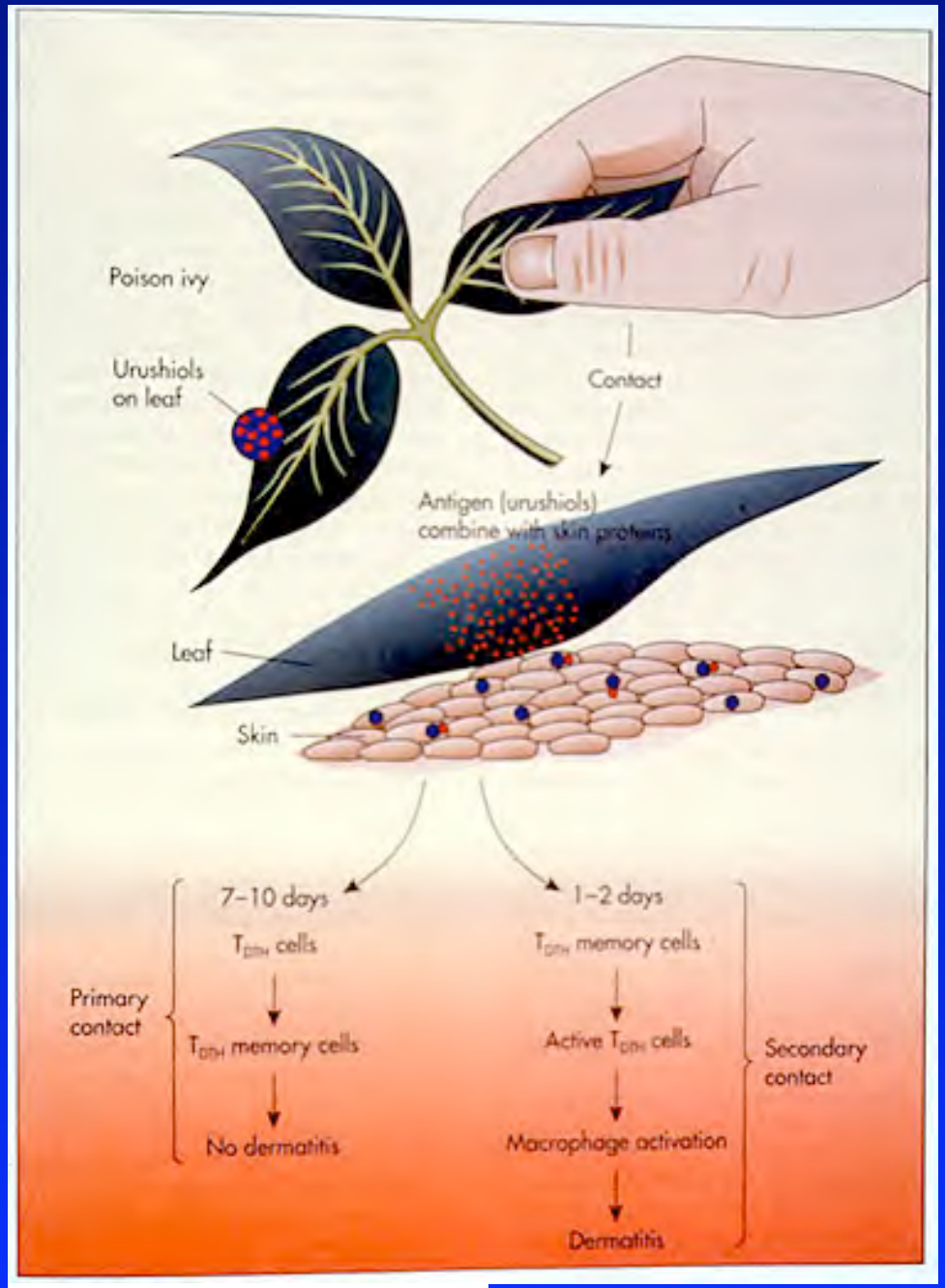


Type IV: Cell-Mediated Immune Reactions

- Objective
  - To define the primary mechanisms involved in contact hypersensitivity and delayed type hypersensitivity reactions
  - To review mechanisms of T-Cell mediated cytotoxicity (see Dr. King)
- Cell Components
  - Mononuclear inflammatory cells: lymphocytes, monocytes/macrophages and antigen presenting cells

Delayed hypersensitivity reactions

DTH type	characteristics			
	reaction time	clinical appearance	histological appearance	antigen
contact	48–72 hours	eczema	infiltration of lymphocytes and, later, macrophages, oedema of epidermis	epidermal: e.g. nickel, rubber, poison ivy usually a hapten
tuberculin	48–72 hours	local hardening and swelling ± fever	infiltration of lymphocytes, monocytes, and macrophages	intradermal injection used diagnostically: tuberculin, mycobacterial and leishmanial antigens
granulo-matous	4 weeks	hardening e.g. in skin or lung	granuloma containing epithelioid cells, giant cells, and macrophages; fibrosis ± necrosis	persistent Ag or Ag–Ab complexes in macrophages; or 'non-immunological', e.g talcum powder



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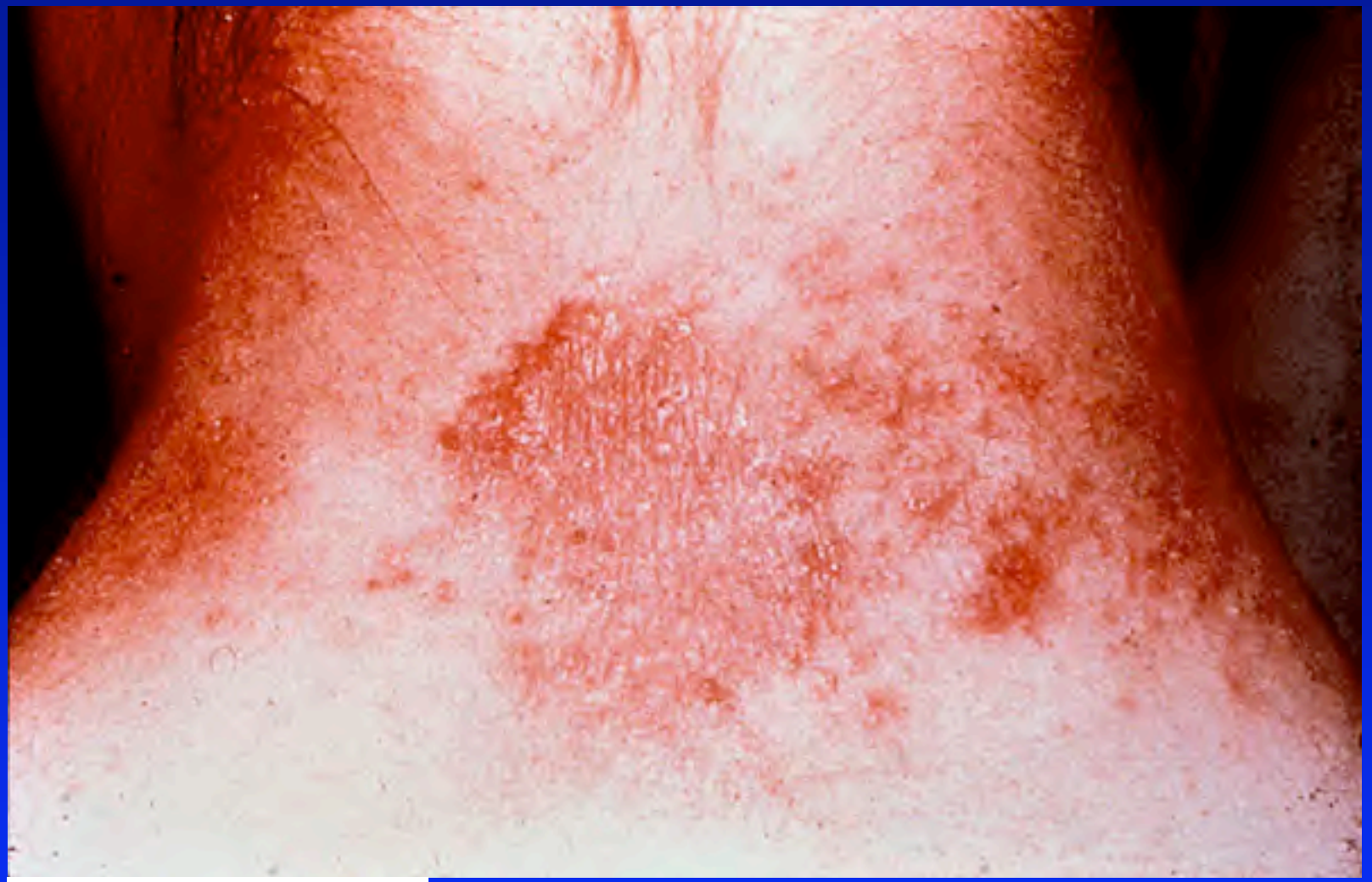
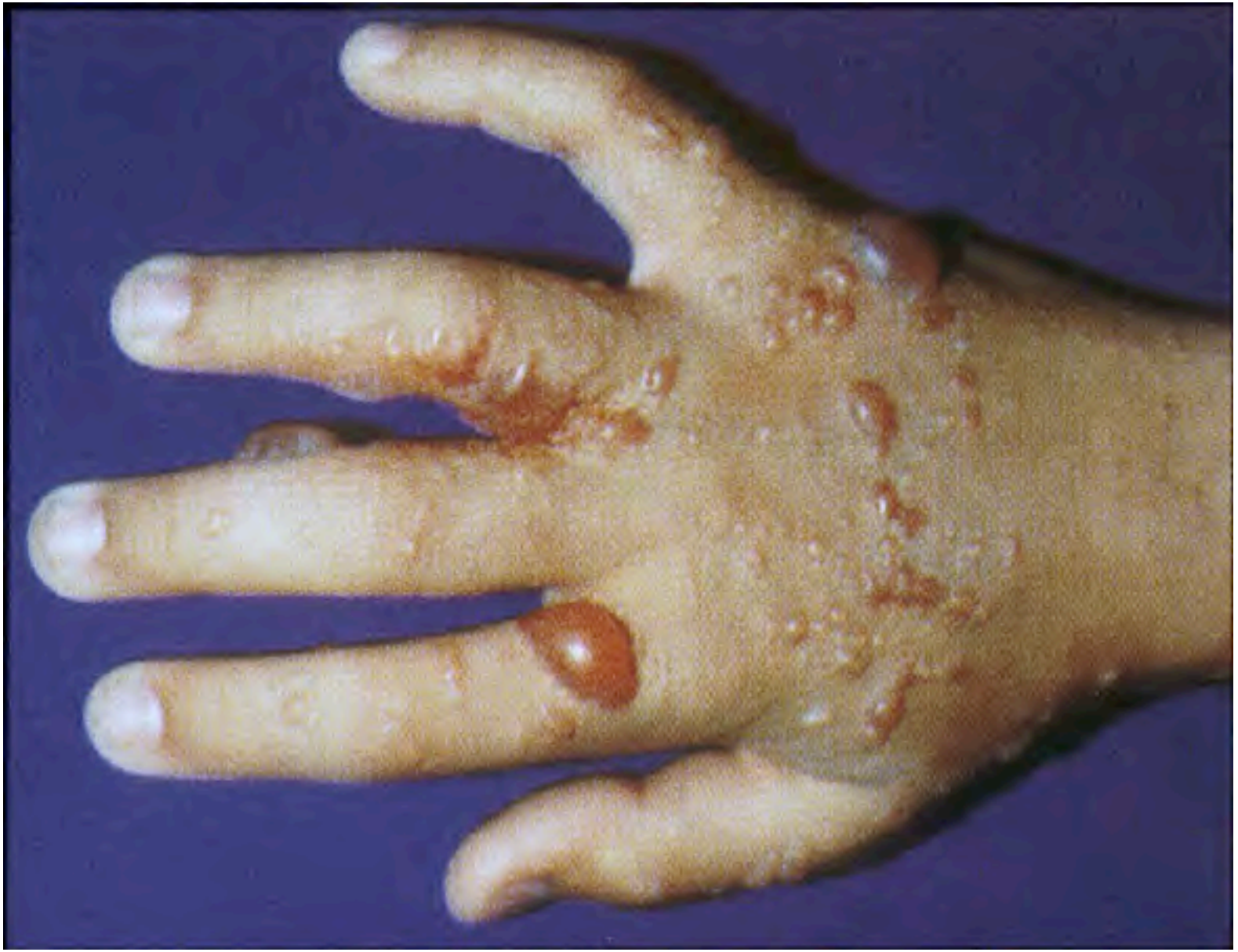
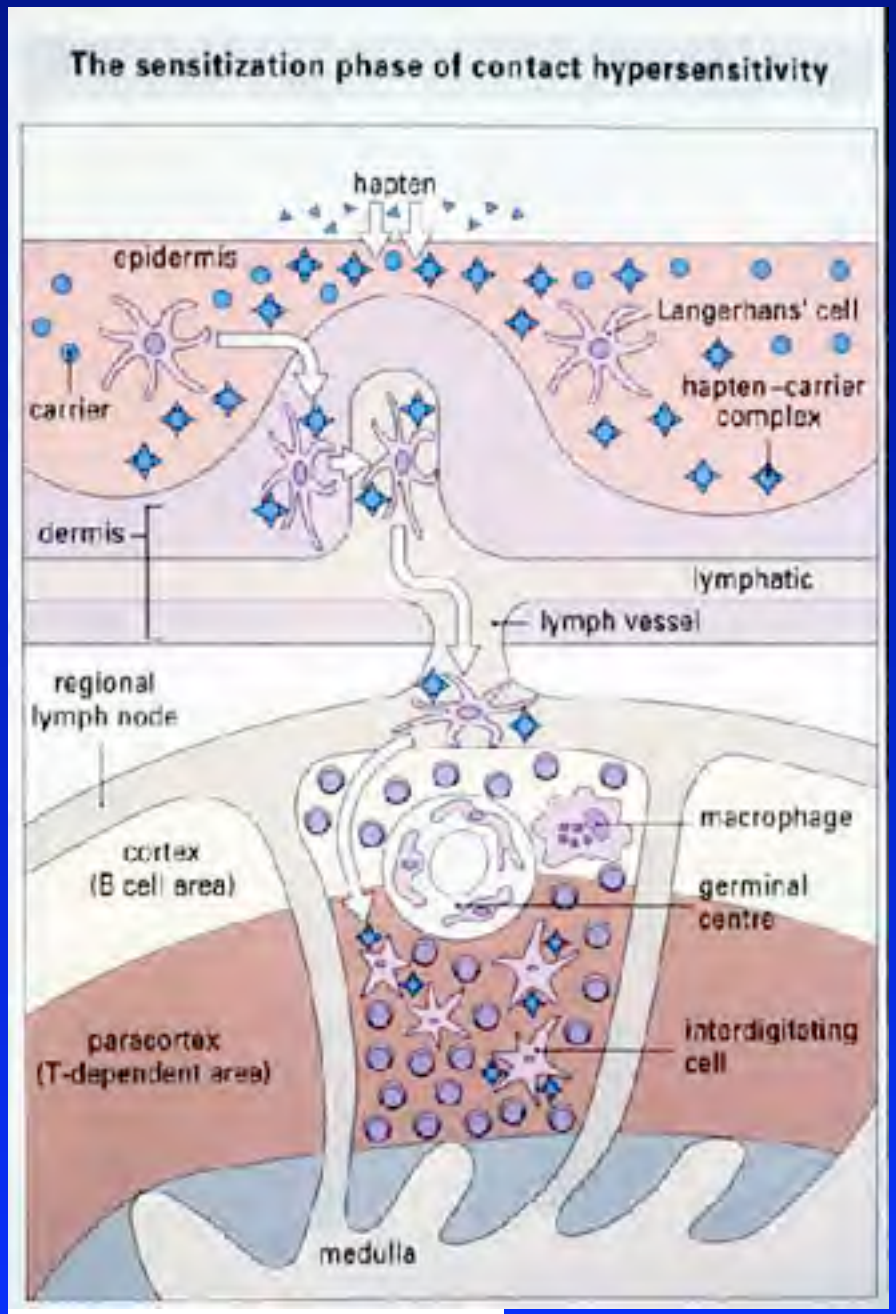
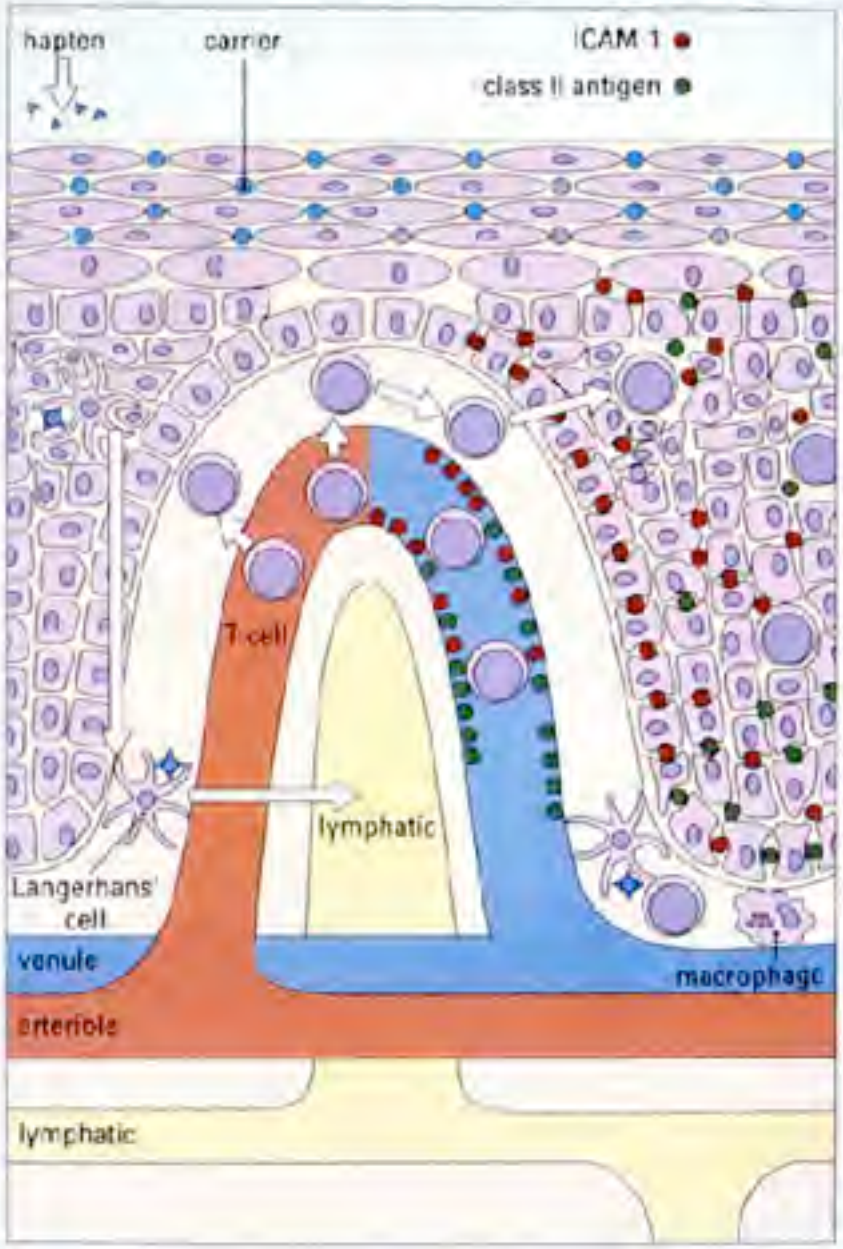
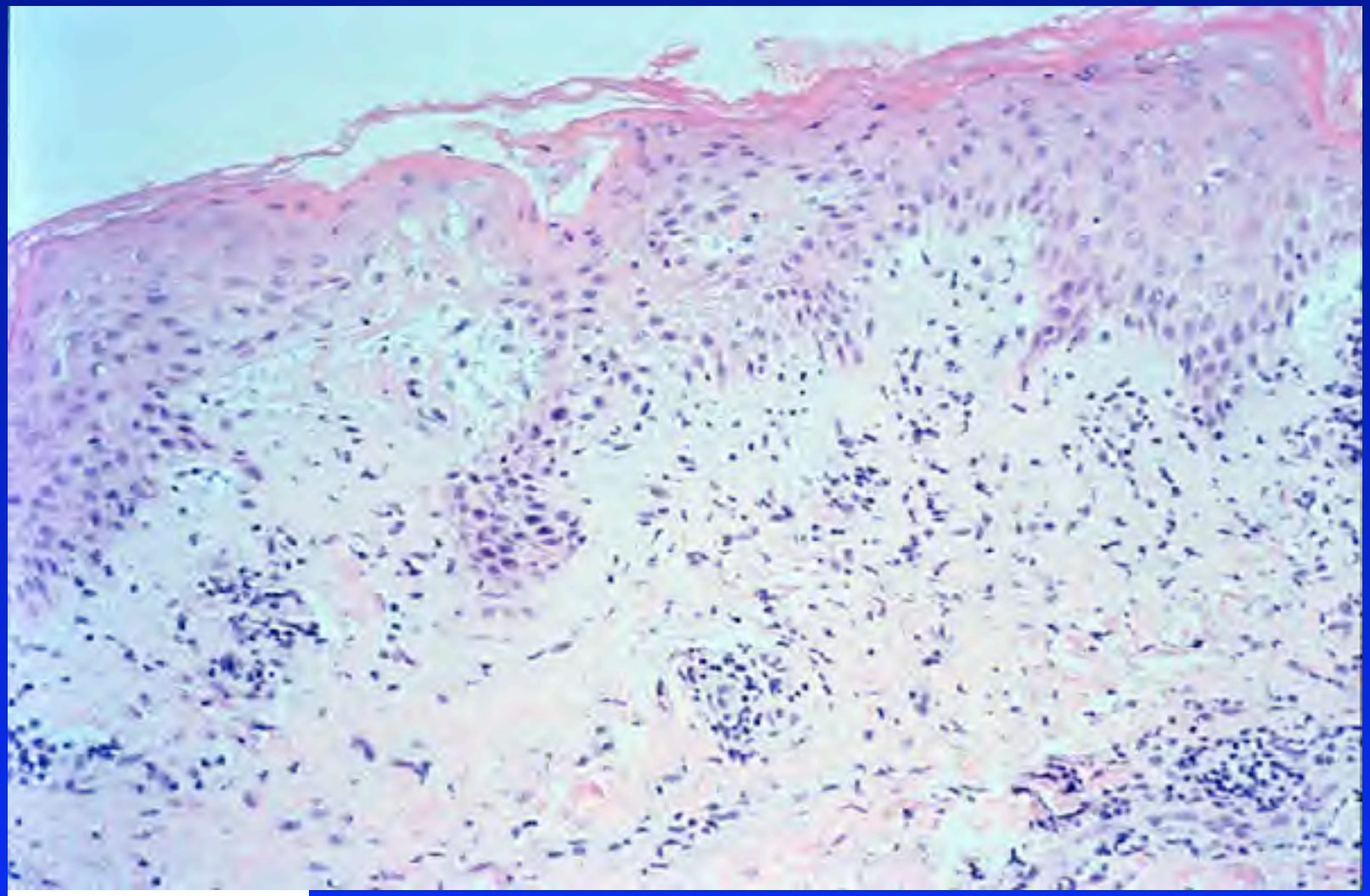






The elicitation phase of contact hypersensitivity





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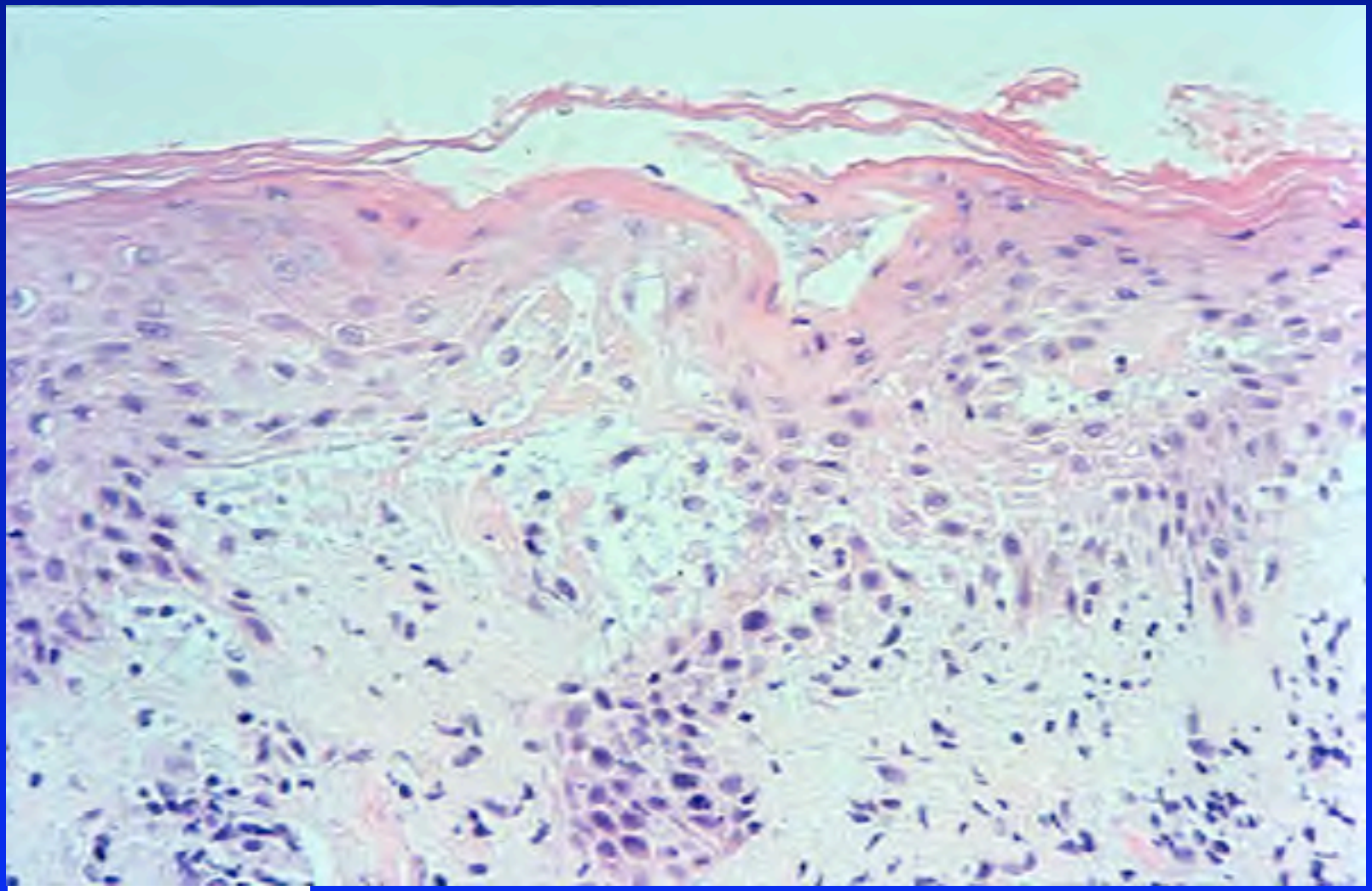

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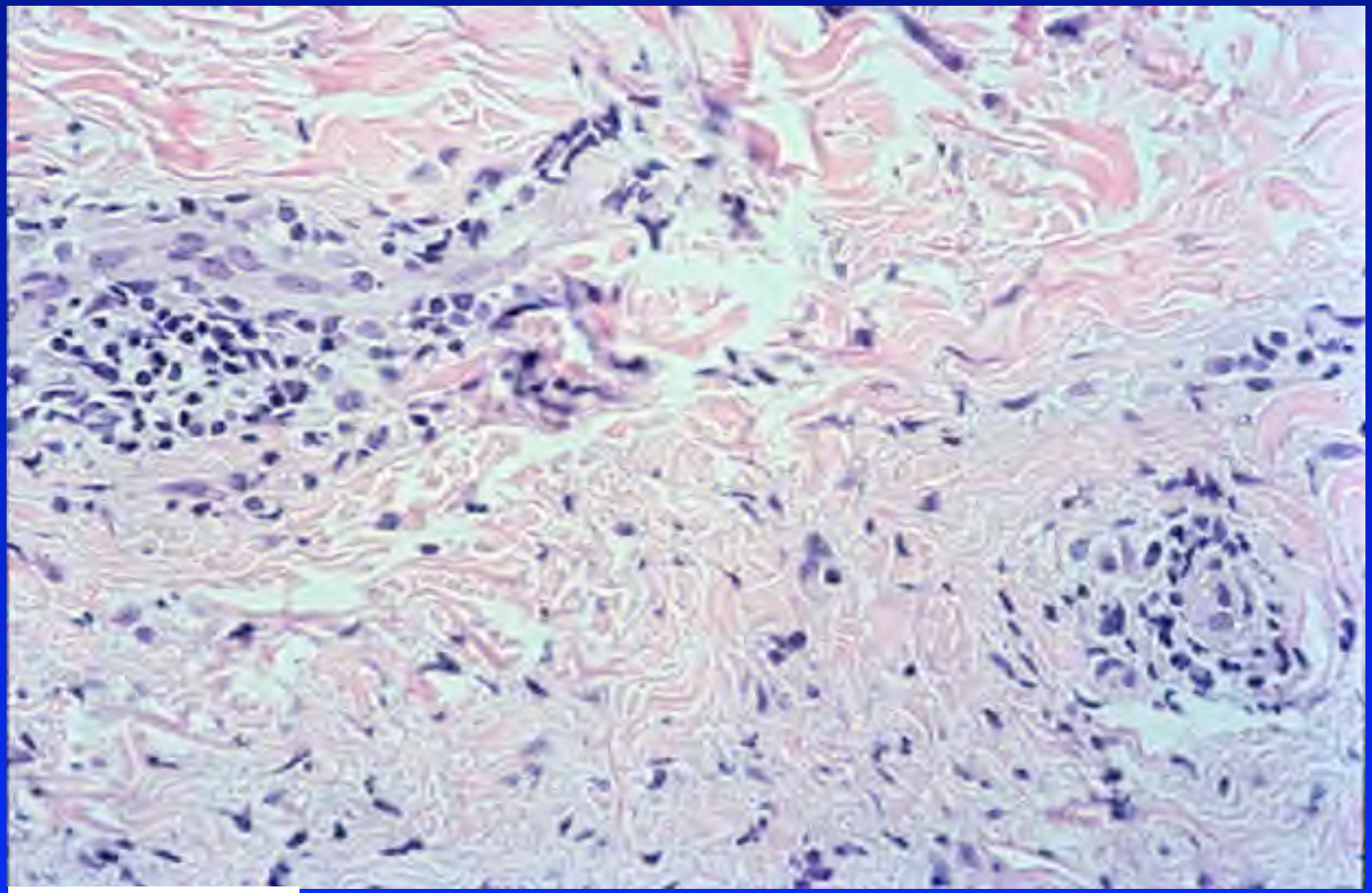
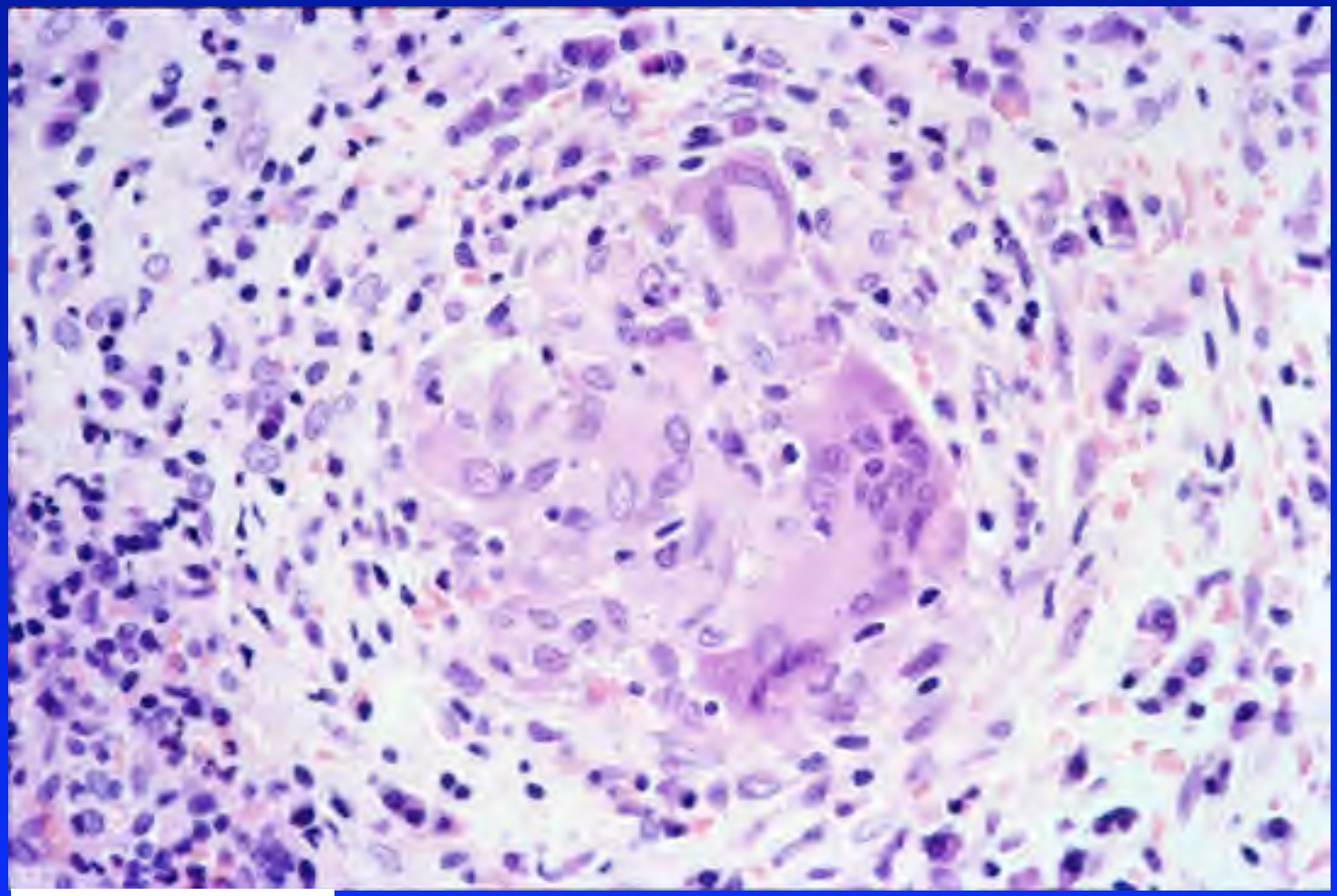


Granulomatous Inflammatory Reactions



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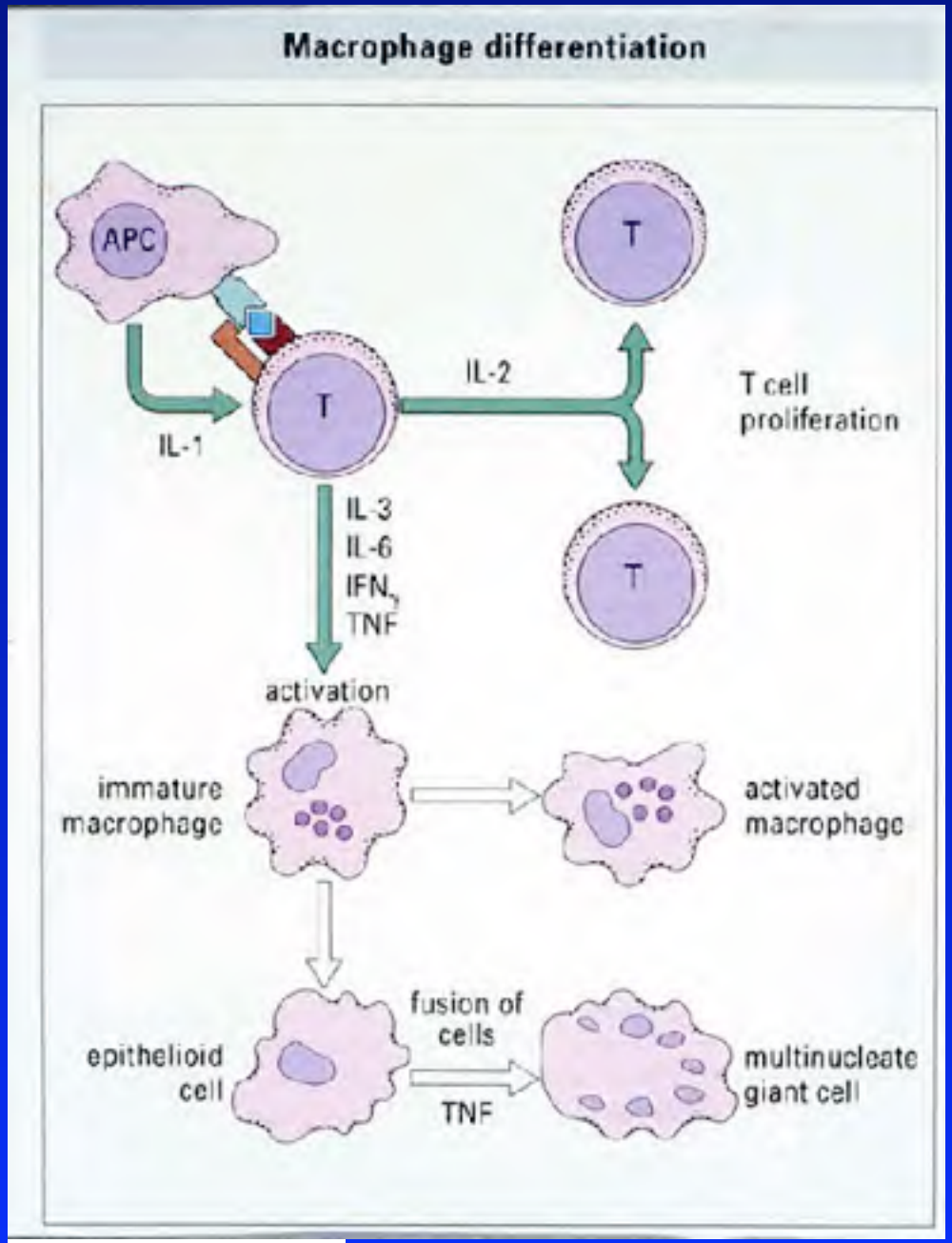

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Summary: Type IV Reaction

- Antibody: No
- Effector Cells: T-lymphocytes, Monocyte/Macrophage
- Complement: No
- Reaction: 48-72 hours (skin test)

Type IV: T-Cell Mediated Cytotoxicity

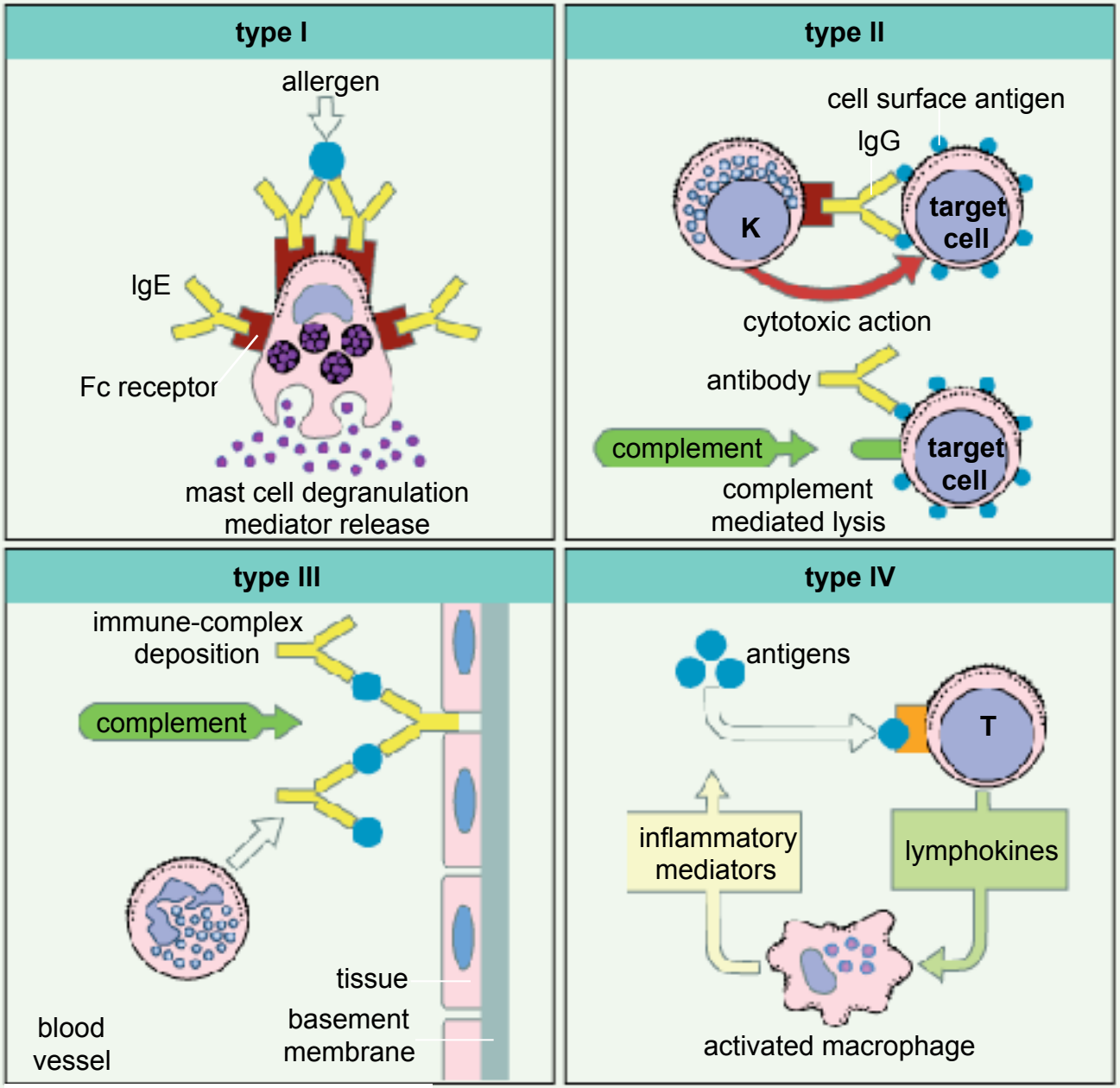
(see Dr. King's presentation)

- Mechanisms
  - CD8+ lymphocyte
  - Antigen expressed with Class I MHC
  - Interleukin-2 clonal expansion
  - Cytotoxic effector cell
    - Recognizes Ag+ class I MHC

T-Cell Mediated Cytotoxicity (cont.)

- Initiates programmed cell death (apoptosis)
  - Perforins/cytolysins
  - Proteolytic enzymes: granzymes
  - FAS-induced apoptosis: CD8+ T cell: FAS ligand target cell:FAS receptor
  - Cytokines
    - Interferon γ
    - Tumor Necrosis Factor α and β

The four types of hypersensitivity reaction



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