Hypersensitivity Reactions

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Hypersensitivity Reactions Outline

- Introduction

Introduction

- Normal immune reactions do their job without hurting the host.
- Sometimes, immune reactions can be excessive, resulting in disease.
- People who mount normal immune responses are sensitized to that antigen.
- People who have excessive responses are hypersensitive.

What antigens initiate these reactions?

- Bugs
- Environmental antigens
- Self antigens

What happens in these reactions?

- The immune response is triggered and maintained inappropriately.
- Hard to eliminate stimulus!
- Hard to stop response once it starts!
- …so hypersensitivity diseases are often chronic, debilitating, hard to treat.

Four types of hypersensitivity reactions

- Type I Hypersensitivity
- Type II Hypersensitivity
- Type III Hypersensitivity
- Type IV Hypersensitivity

Hypersensitivity Reactions Outline

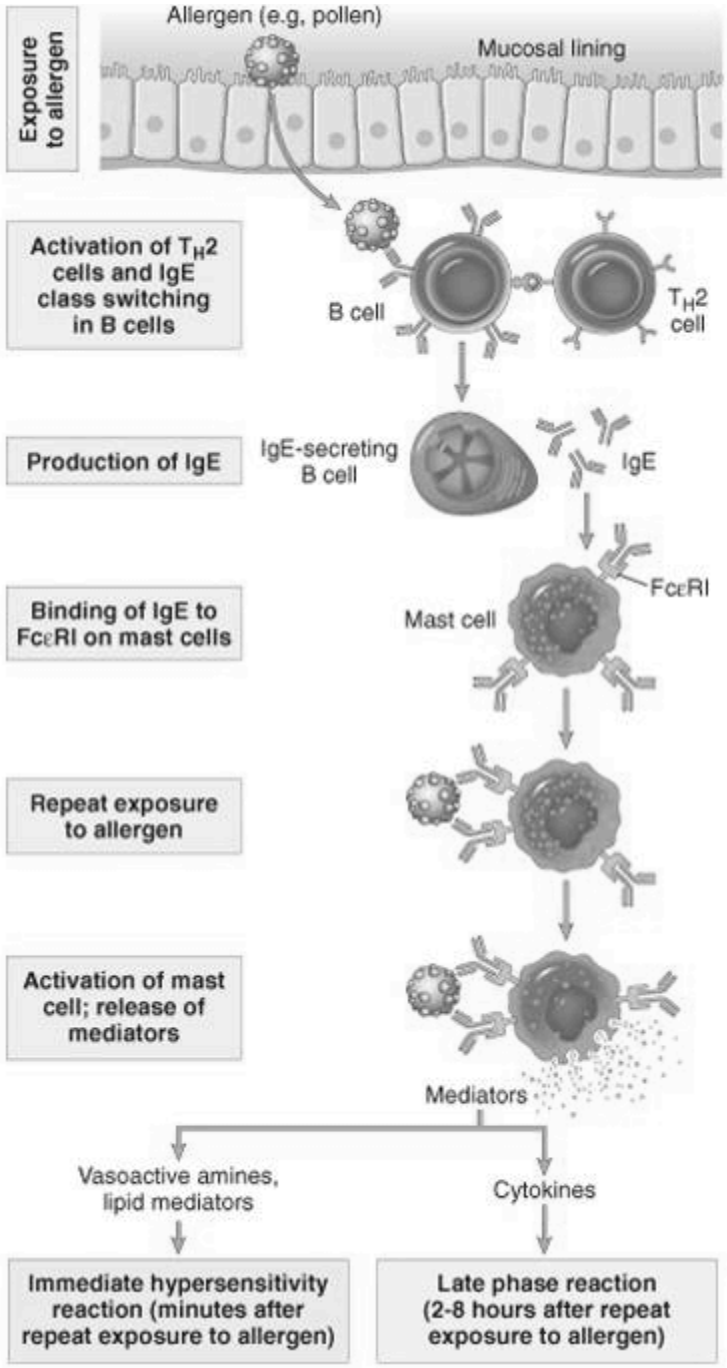
- Introduction
- Type I Hypersensitivity

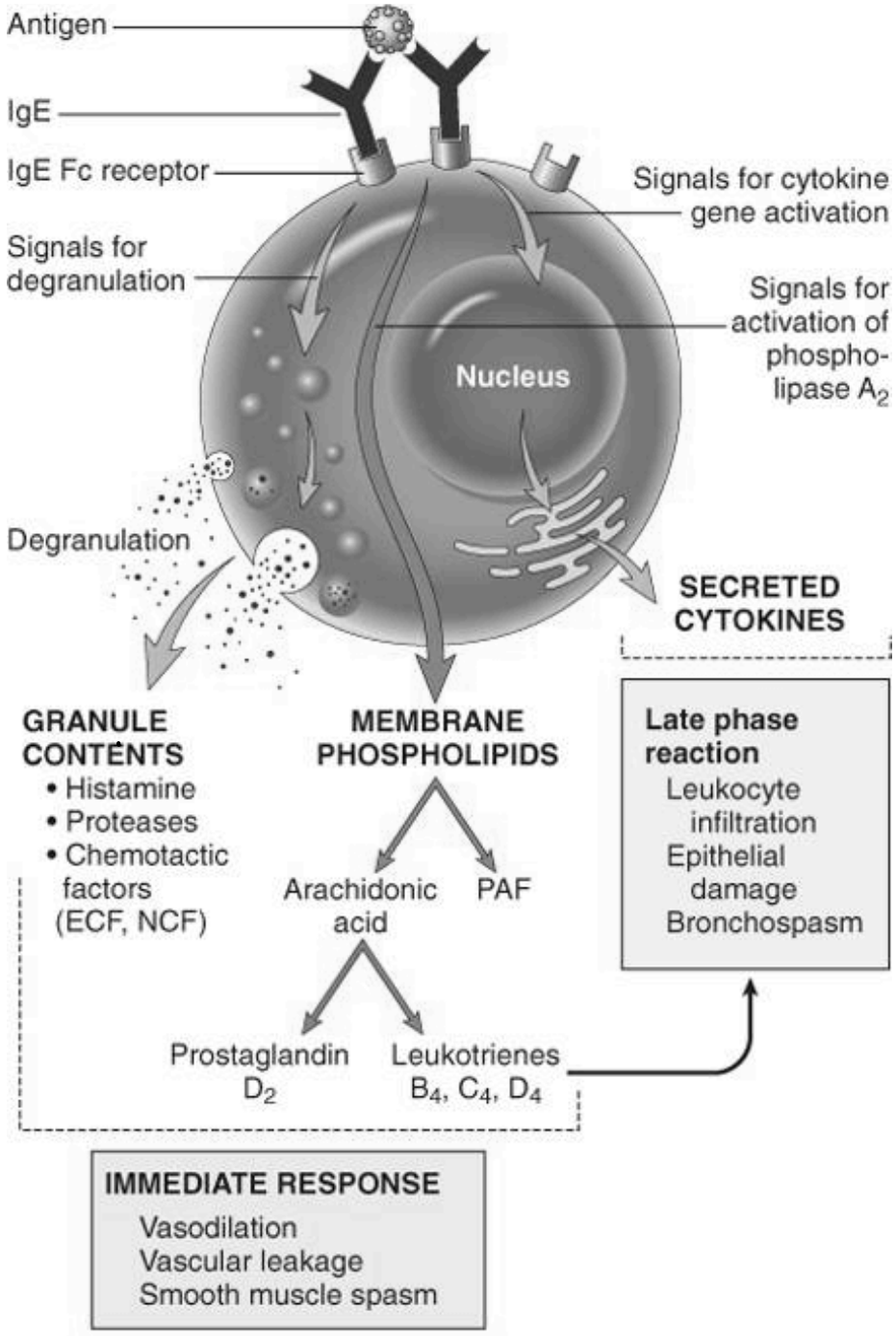
Type I Hypersensitivity

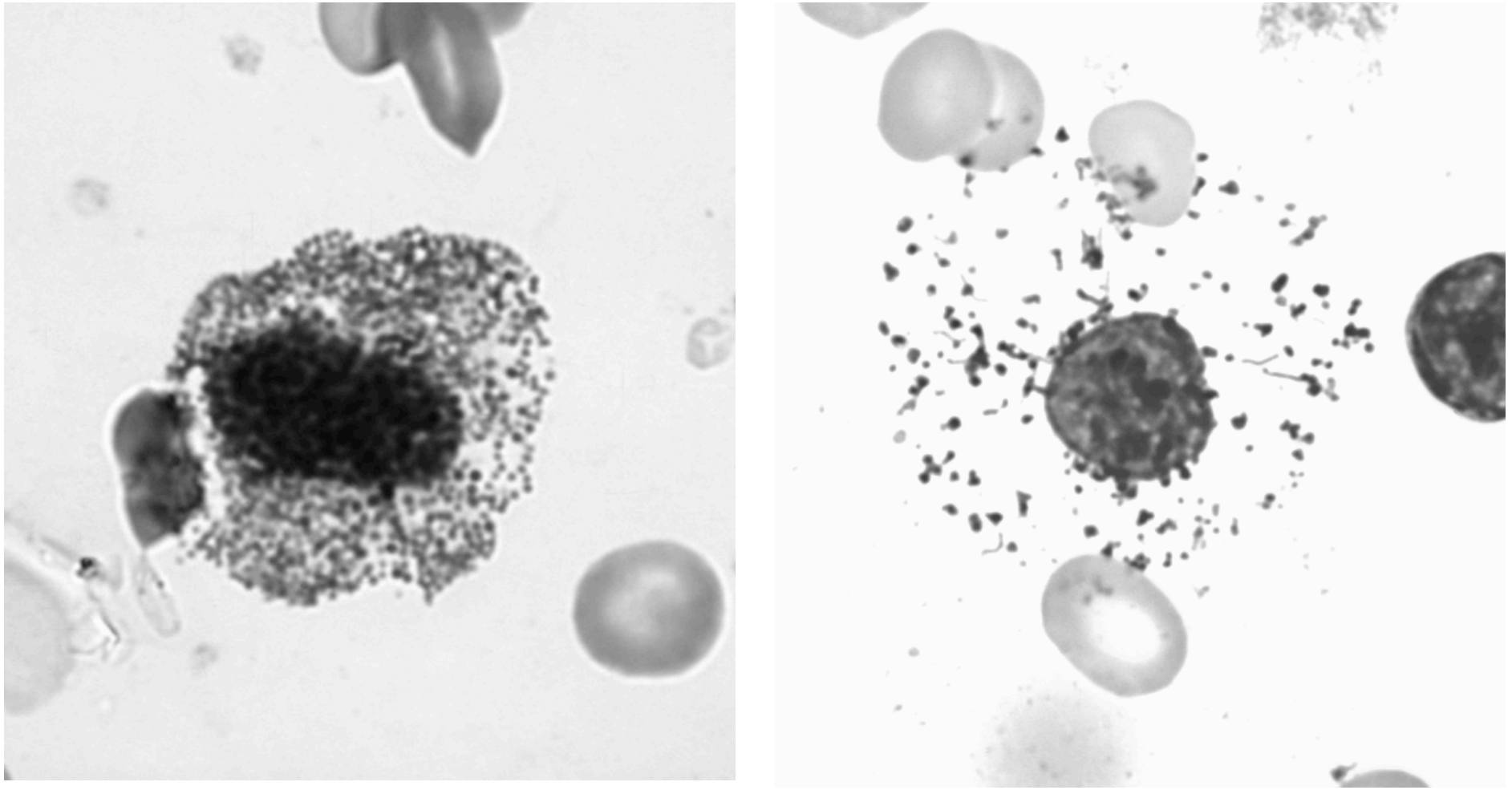
- ALLERGY
- "Immediate" hypersensitivity
- Antigen (allergen) binds to IgE antibodies on surface of mast cell
- Mast cell releases nasty mediators
- End result: vessels dilate, smooth muscle contracts, inflammation persists

Sequence of Events

- Allergen is inhaled/eaten/injected
- Allergen stimulates T_H2 production
- T_H2 cell secretes cytokines:
  - IL-4 stimulates B cells to make IgE
  - IL-5 recruits eosinophils
  - IL-13 stimulates mucous secretion
- Mast cell binds IgE
- Allergen bridges IgE on mast cell
- Mast cell degranulates


Exposure to allergen
Allergen (e.g, pollen)
Mucosal lining
Activation of T_H2 cells and IgE class switching in B cells
B cell
T_H2 cell
Production of IgE
IgE-secreting B cell
IgE
Binding of IgE to FcεRI on mast cells
FcεRI
Mast cell
Repeat exposure to allergen
Activation of mast cell; release of mediators
Mediators
Vasoactive amines, lipid mediators
Cytokines
Immediate hypersensitivity reaction (minutes after repeat exposure to allergen)
Late phase reaction (2-8 hours after repeat exposure to allergen)


Antigen
IgE
IgE Fc receptor
Signals for degranulation
Signals for cytokine gene activation
Signals for activation of phospho-lipase A_2
Nucleus
Degranulation
SECRETED CYTOKINES
GRANULE CONTENTS
• Histamine
• Proteases
• Chemotactic factors (ECF, NCF)
MEMBRANE PHOSPHOLIPIDS
Arachidonic acid
PAF
Prostaglandin D_2
Leukotrienes B_4, C_4, D_4
Late phase reaction
Leukocyte infiltration
Epithelial damage
Bronchospasm
IMMEDIATE RESPONSE
Vasodilation
Vascular leakage
Smooth muscle spasm



Mast cells: Normal (left) and degranulated (right)

What nasty stuff do mast cells release?

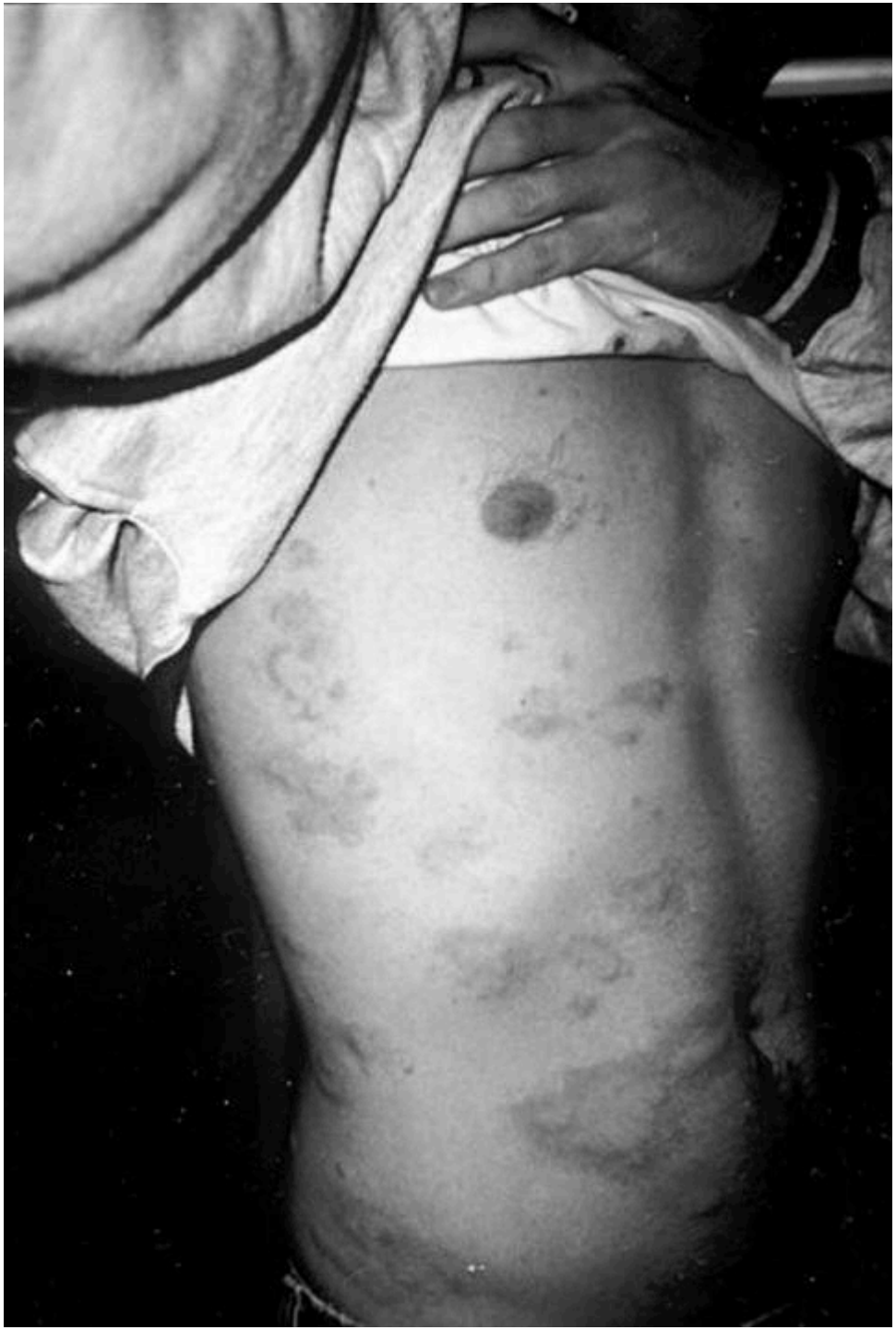
- Granule contents
  - histamine
  - some chemotactic factors
- Membrane phospholipid metabolites
  - prostaglandin D_2
  - leukotrienes
- Cytokines
  - TNF
  - interleukins
  - IL-13

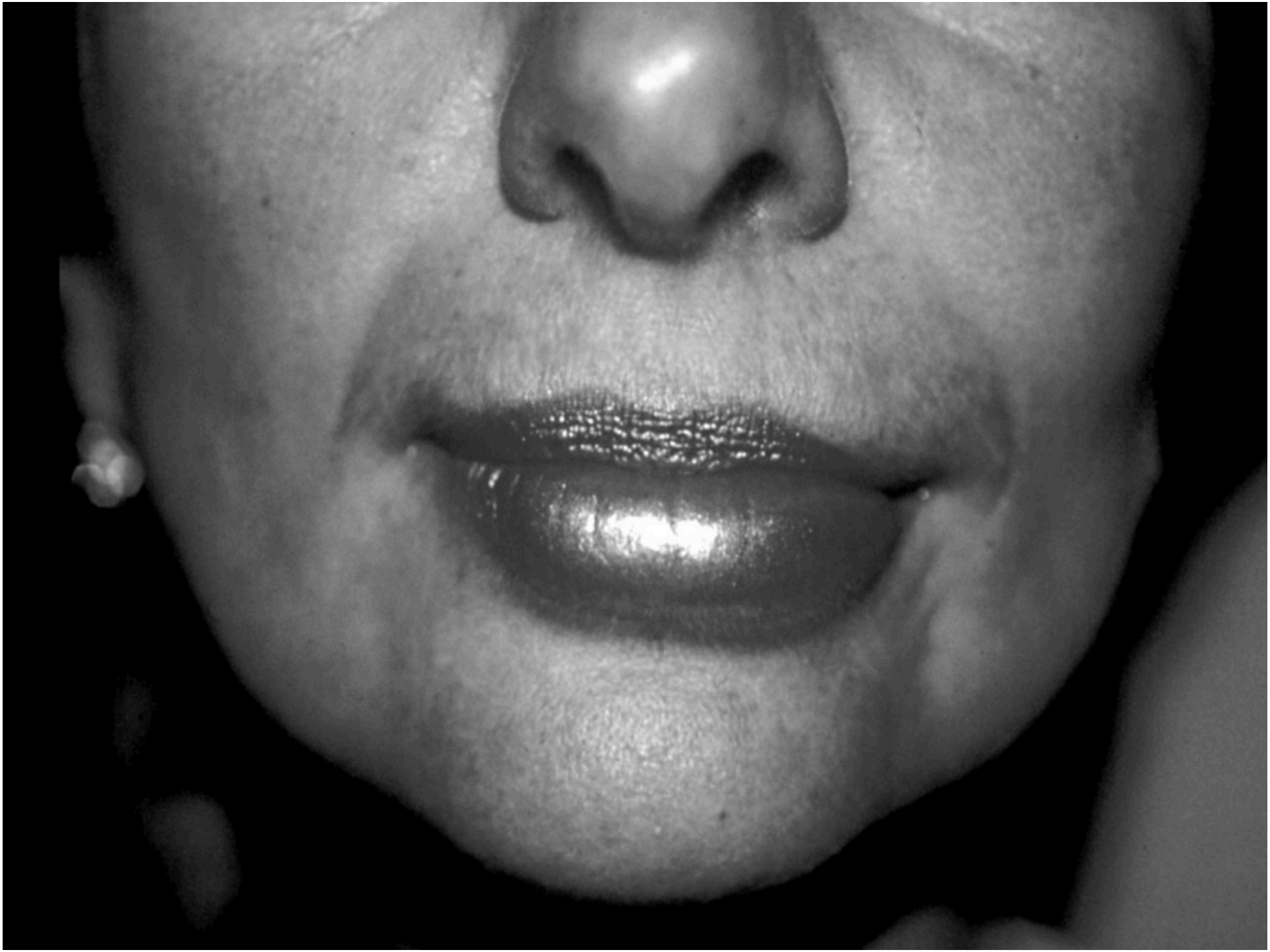
What do these nasty substances do?

- Act on blood vessels, smooth muscle, and WBCs.
- Immediate response (minutes)
  - vasodilation, vascular leakage, smooth muscle spasm
  - granule contents, prostaglandin, leukotrienes
- Late phase reaction (hours)
  - inflammation, tissue destruction
  - cytokines

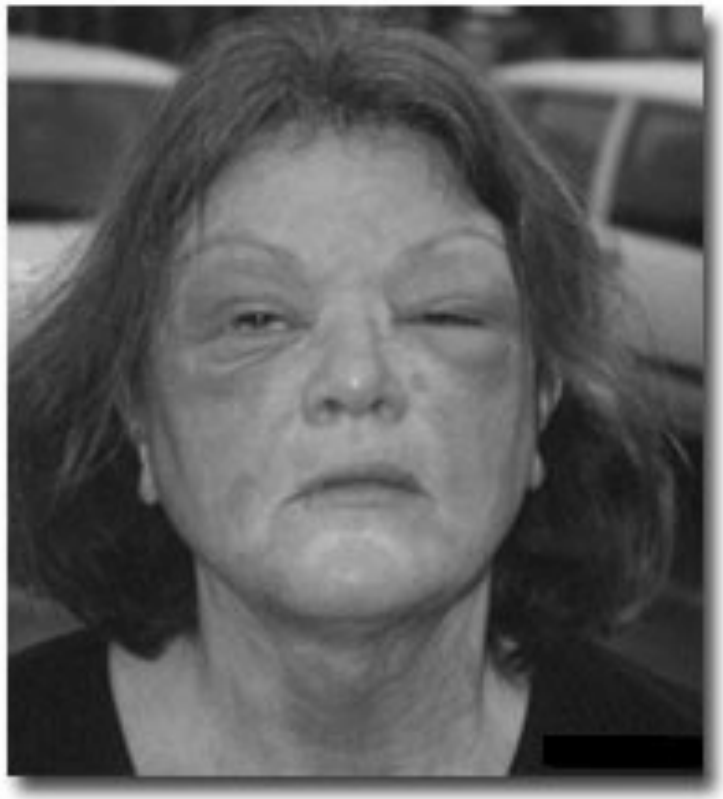
What happens to the patient?

- Local reactions
  - skin: itching, hives
  - GI: diarrhea
  - lung: bronchoconstriction
- Anaphylaxis
  - itching, hives, erythema
  - constriction of bronchioles, wheezing
  - laryngeal edema, hoarseness, obstruction
  - vomiting, cramps, diarrhea
  - shock
  - DEATH





Normal appearance



Severe allergic reaction
(anaphylaxis)

Hypersensitivity Reactions Outline

- Introduction
- Type I Hypersensitivity
- Type II Hypersensitivity

Type II Hypersensitivity

- ANTIBODIES
- "Antibody-mediated" hypersensitivity
- Antibodies bind to antigens on cell surface
- Macrophages eat up cells, complement gets activated, inflammation comes in
- End result: cells die, inflammation harms tissue

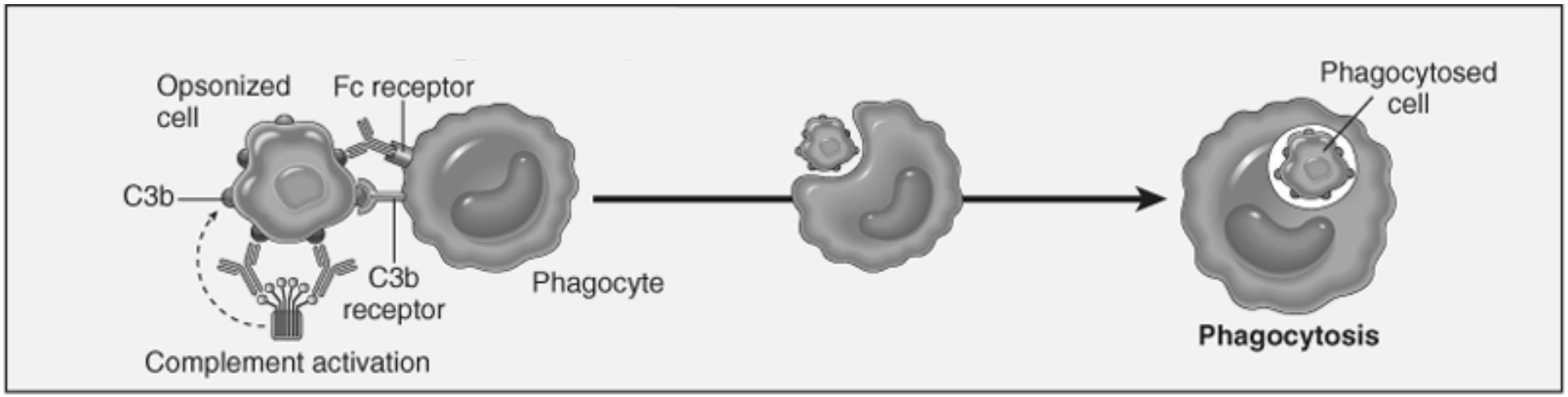
Which diseases involve type II hypersensitivity?

Disease	Antigen	Symptoms
Autoimmune hemolytic anemia	RBC antigens, drugs	Hemolysis
Pemphigus vulgaris	Proteins between epithelial cells	Bullae
Goodpasture syndrome	Proteins in glomeruli and alveoli	Nephritis, lung hemorrhage
Myasthenia gravis	Acetylcholine receptor	Muscle weakness
Graves disease	TSH receptor	Hyperthyroidism

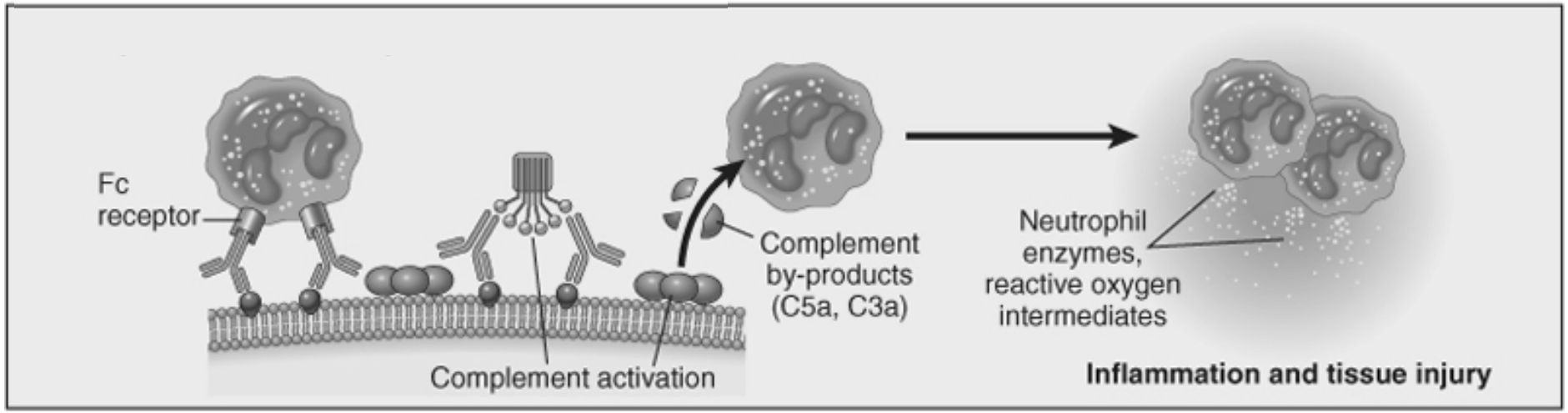
Sequence of Events

- Antibodies bind to cell-surface antigens
- One of three things happens:
  - Opsonization and phagocytosis
  - Inflammation
  - Cellular dysfunction

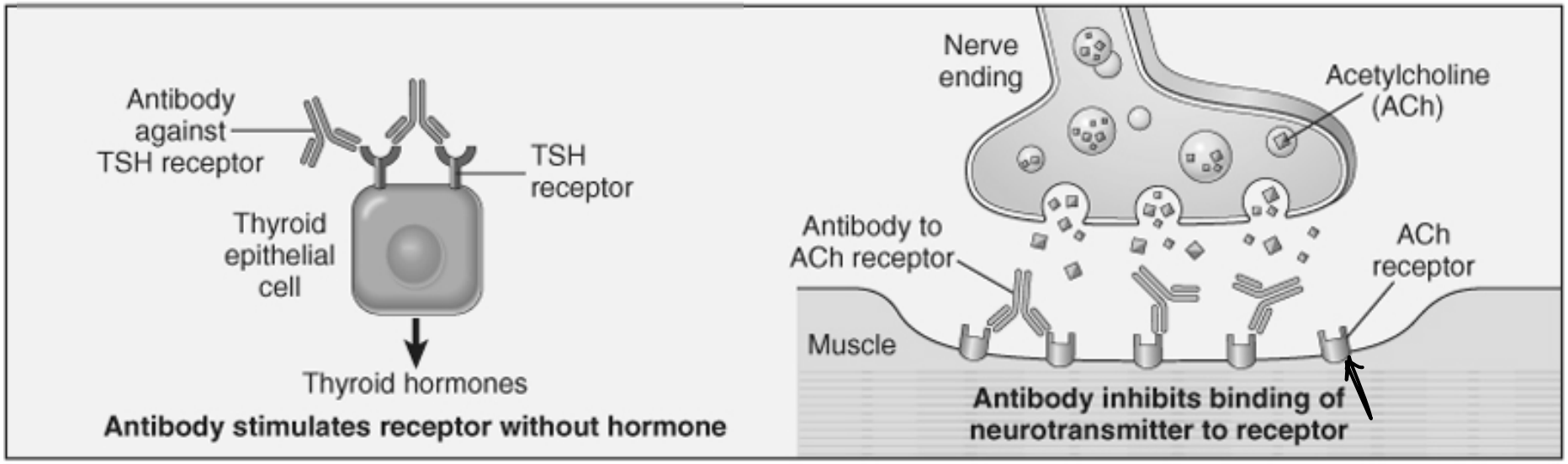
Opsonization and phagocytosis



Inflammation



Cellular dysfunction



Graves disease

Myasthenia gravis

Hypersensitivity Reactions Outline

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- Type III Hypersensitivity

Type III Hypersensitivity

- IMMUNE COMPLEXES
- "Immune complex-mediated" hypersensitivity
- Antibodies bind to antigens, forming complexes
- Complexes circulate, get stuck in vessels, stimulate inflammation
- End result: bad inflammation, necrotizing vasculitis

Which diseases involve type III hypersensitivity?

Disease	Antigen	Symptoms
Systemic lupus erythematosus	Nuclear antigens	Nephritis, skin lesions, arthritis…
Post-streptococcal glomerulonephritis	Streptococcal antigen	Nephritis
Polyarteritis nodosa	Hepatitis B antigen	Systemic vasculitis
Serum sickness	Foreign proteins	Arthritis, vasculitis, nephritis
Arthus reaction	Foreign proteins	Cutaneous vasculitis

Two Kinds of Type III Hypersensitivity Reactions

- Systemic immune complex disease
  - complexes formed in circulation
  - deposited in several organs
  - example: serum sickness
- Local immune complex disease
  - complexes formed at site of antigen injection
  - precipitated at injection site
  - example: Arthus reaction

Serum Sickness

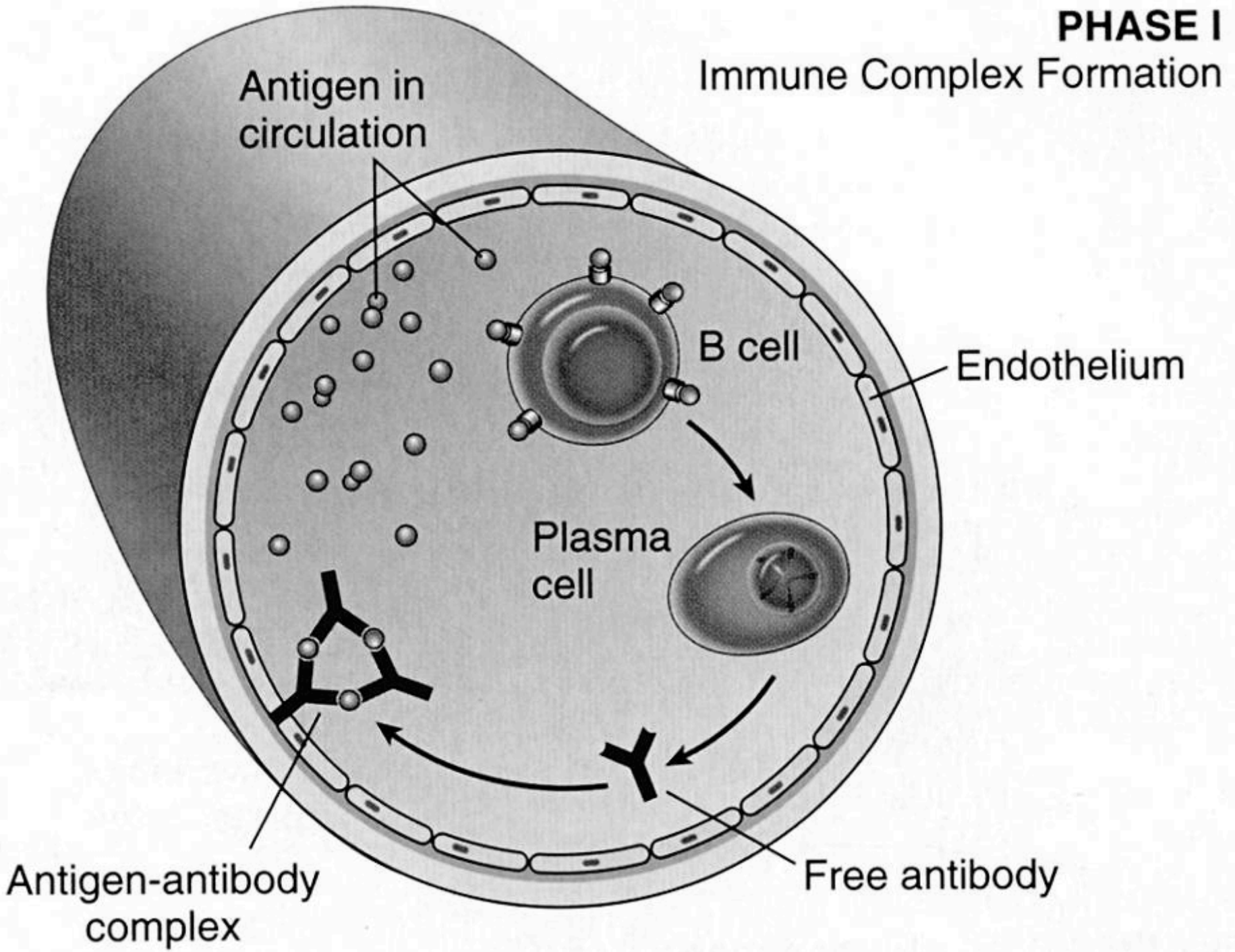
- In olden days: used horse serum for immunization
- Inject foreign protein (antigen)
- Antibodies are made; they form complexes with antigens
- Complexes lodge in kidney, joints, small vessels
- Inflammation causes fever, joint pain, proteinuria

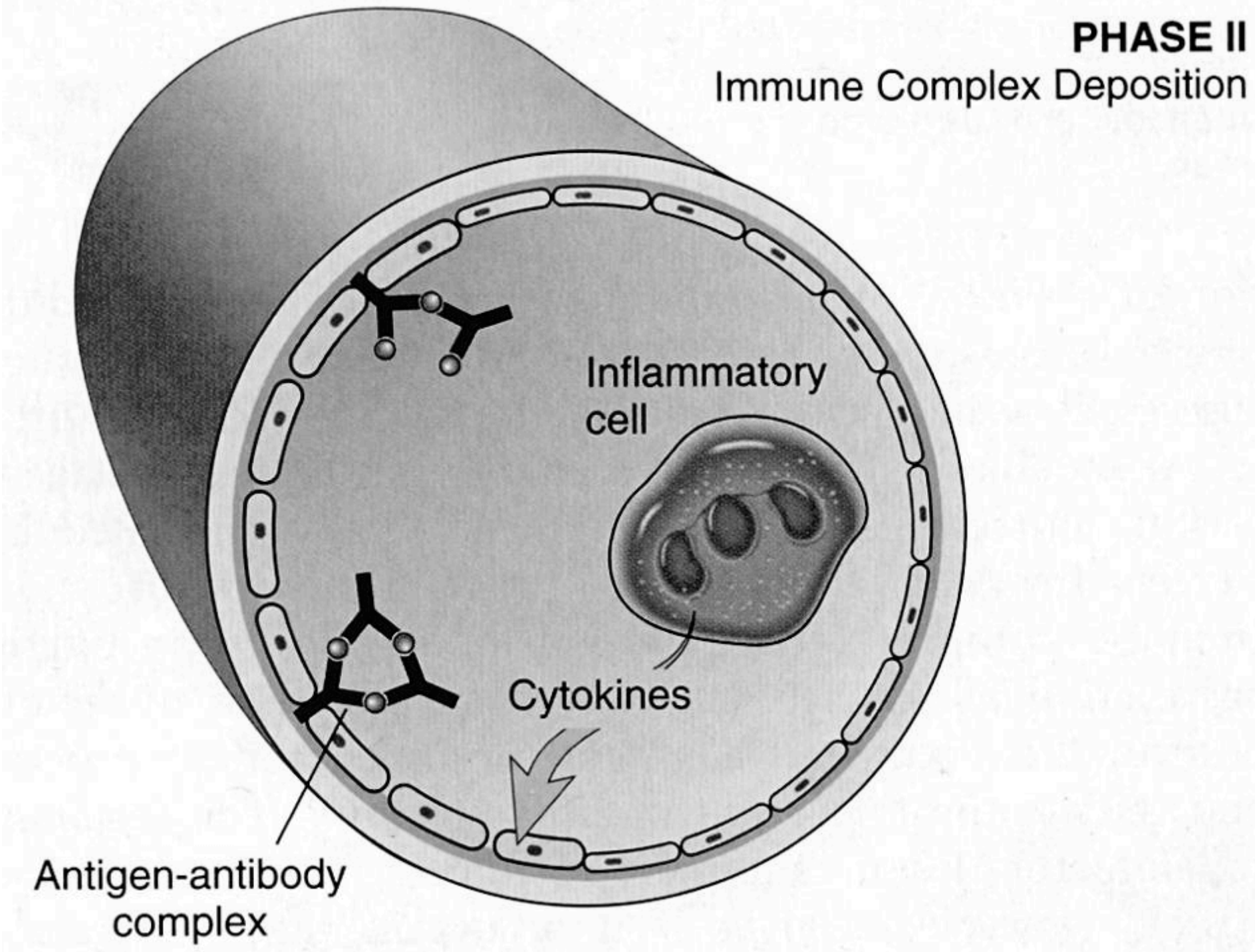
Arthus Reaction

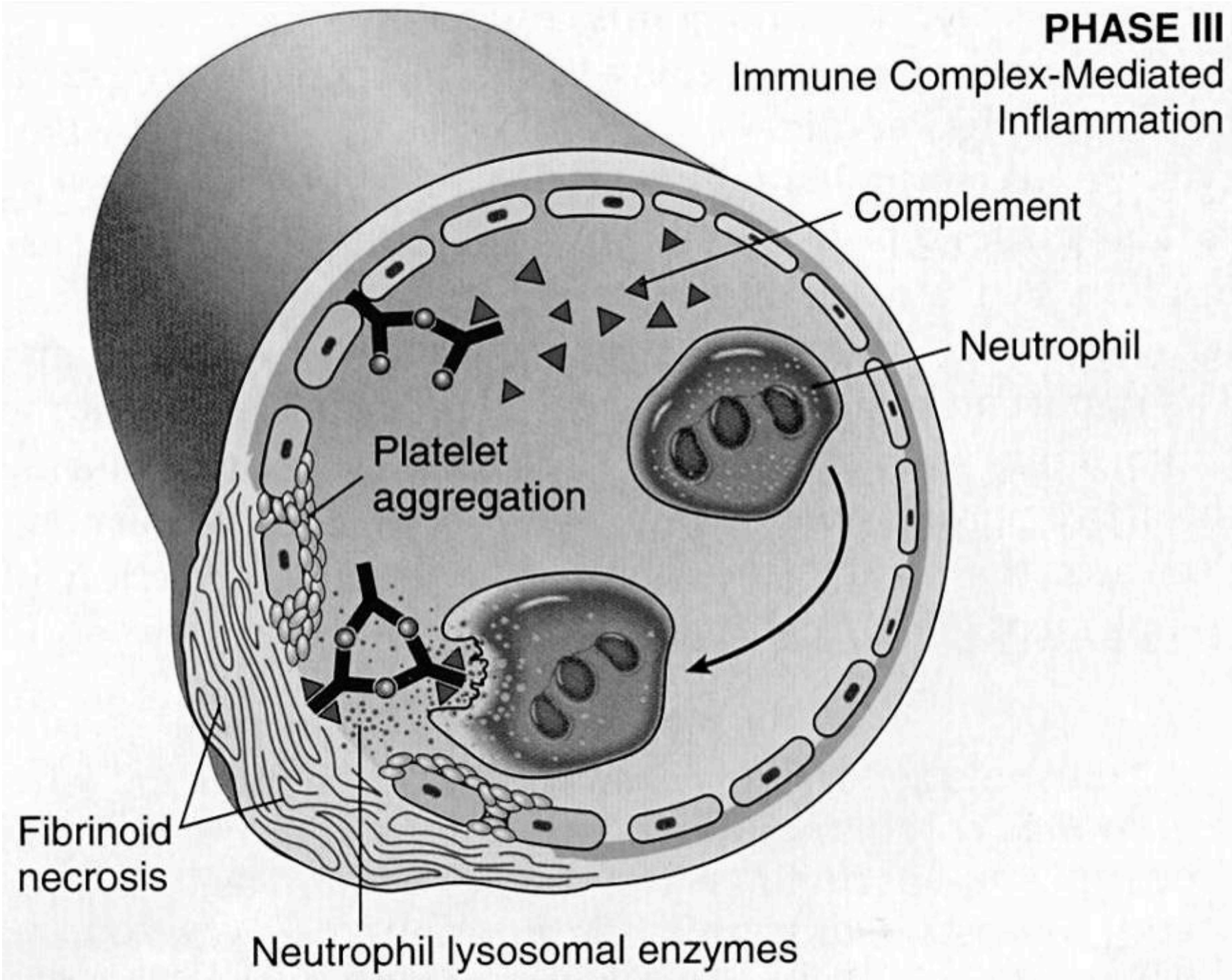
- "Arthus reaction" = localized area of skin necrosis resulting from immune complex vasculitis
- Inject antigen into skin of previously-immunized person
- Pre-existing antibodies form complexes with antigen
- Complexes precipitate at site of infection
- Inflammation causes edema, hemorrhage, ulceration

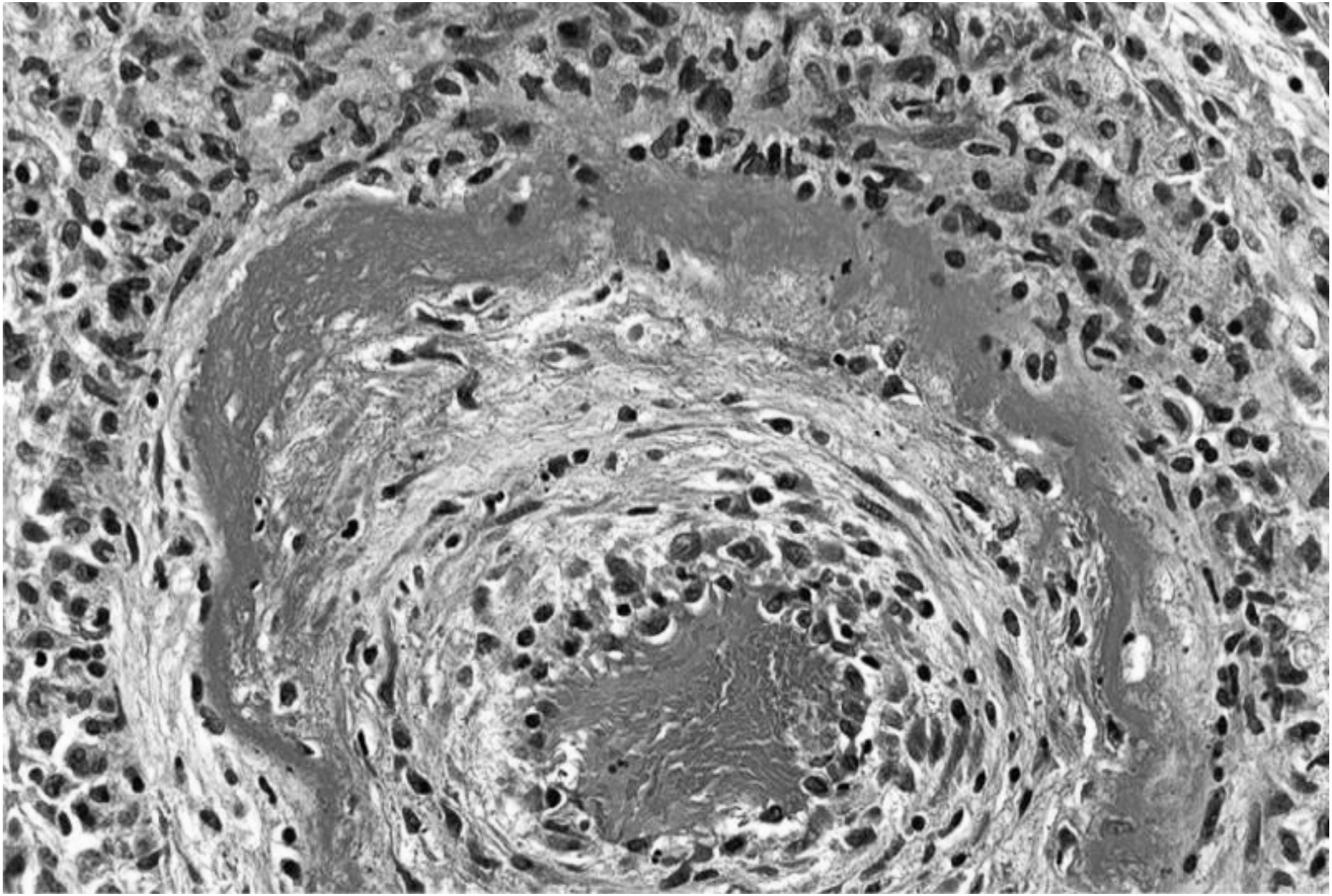
How do the complexes cause inflammation?

- Immune complexes activate complement, which:
  - attracts and activates neutrophils and monocytes
  - makes vessels leaky
- Neutrophils and monocytes release bad stuff (PG, tissue-dissolving enzymes, etc.)
- Immune complexes also activate clotting, causing microthrombi
- Outcomes: vasculitis, glomerulonephritis, arthritis, other -itises


PHASE I
Immune Complex Formation
Antigen in circulation
B cell
Endothelium
Plasma cell
Antigen-antibody complex
Free antibody


PHASE II
Immune Complex Deposition
Inflammatory cell
Cytokines
Antigen-antibody complex


PHASE III
Immune Complex-Mediated
Inflammation
Complement
Neutrophil
Platelet
aggregation
Fibrinoid
necrosis
Neutrophil lysosomal enzymes



Immune-complex-mediated vasculitis

What complement fractions are important to know?

- C3b: promotes phagocytosis of complexes (and bugs!)
- C3a, C5a (anaphylatoxins): increase permeability
- C5a: chemotactic for neutrophils, monocytes
- C5-9: membrane damage or cytolysis

C5a is chemotactic

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Type IV Hypersensitivity

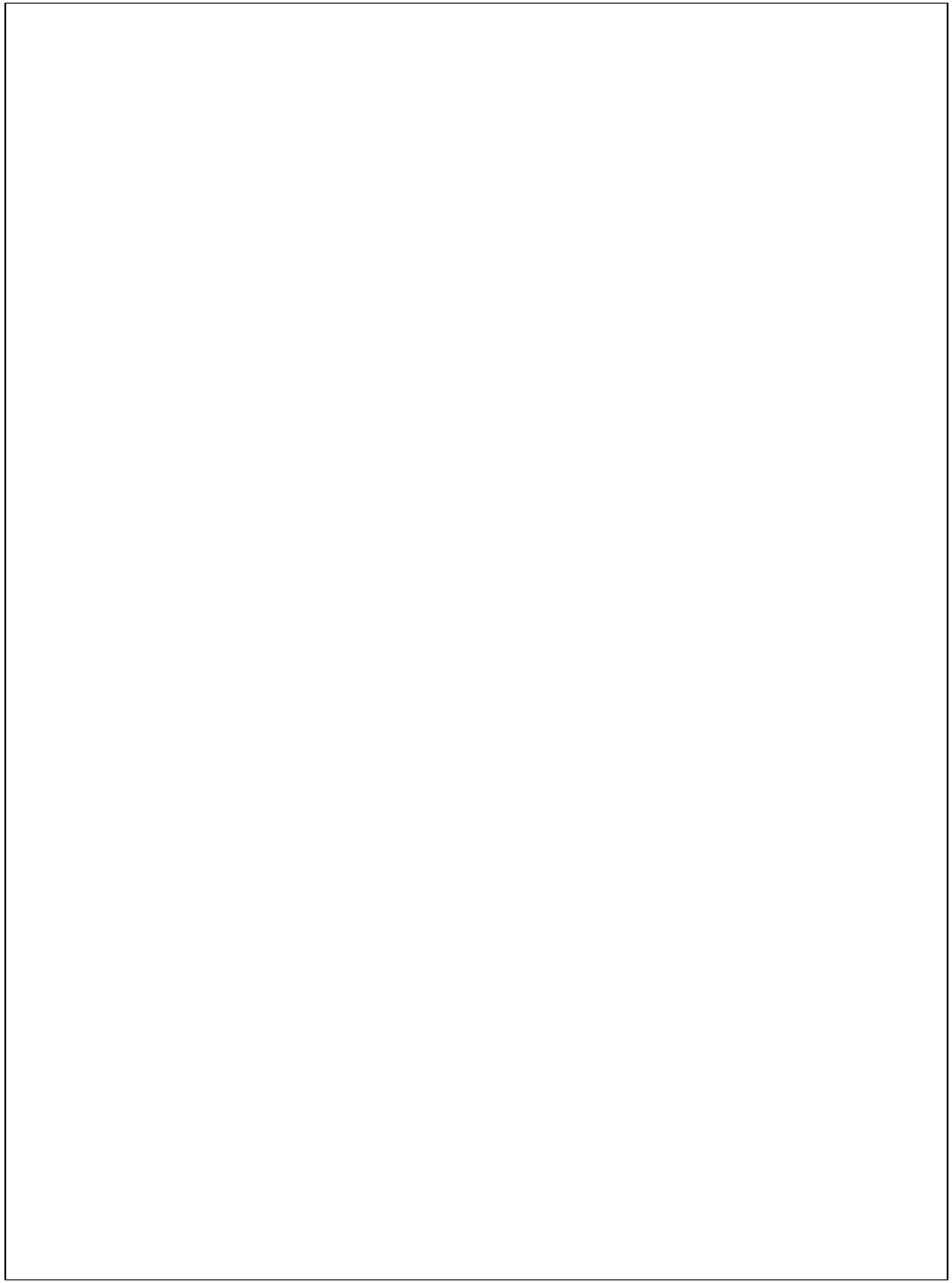
- T CELLS
- "T-cell-mediated" hypersensitivity
- Activated T cells do one of two things:
  - release cytokines that activate macrophages, or
  - kill cells directly
- This process is normally useful against intracellular organisms (viruses, fungi, parasites)
- Here, it causes bad stuff: inflammation, cell destruction, granuloma formation

Two Kinds of Type IV Hypersensitivity

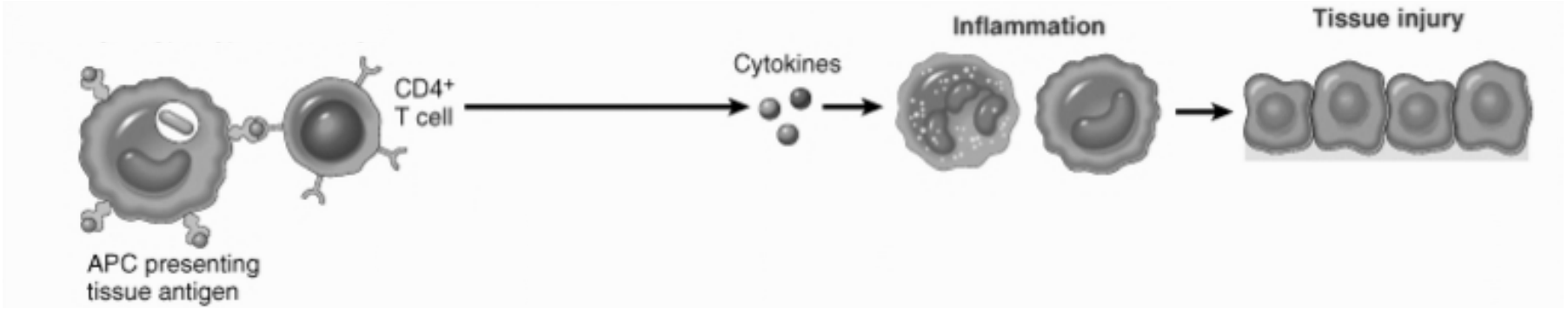
- Delayed-type hypersensitivity (DTH)
  - CD4+ T cells secrete cytokines
  - macrophages come and kill cells
- Direct cell cytotoxicity
  - CD8+ T cells kill targeted cells

Delayed-Type Hypersensitivity

- Patient exposed to antigen
  - APC presents antigen to CD4+ T cell
  - T cells differentiate into effector and memory T_H1 cells
- Patient exposed to antigen again
  - T_H1 cells come to site of antigen exposure
  - Release cytokines that activate macrophages, increase inflammation
- Results
  - Macrophages eat antigen (good)
  - Lots of inflammation and tissue damage (bad)



Delayed-Type Hypersensitivity (DTH)



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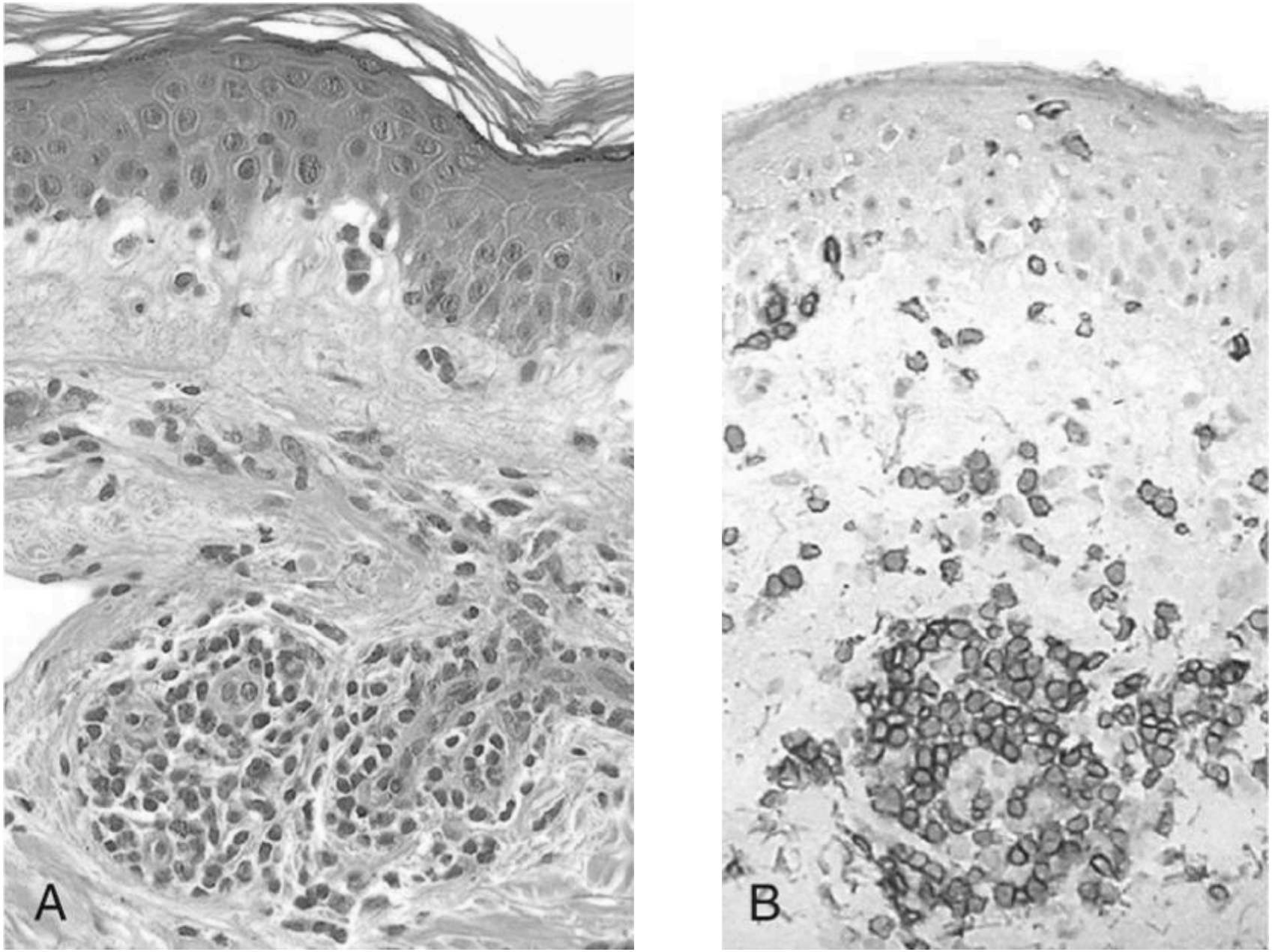


Perivascular cuffing by CD4+ cells

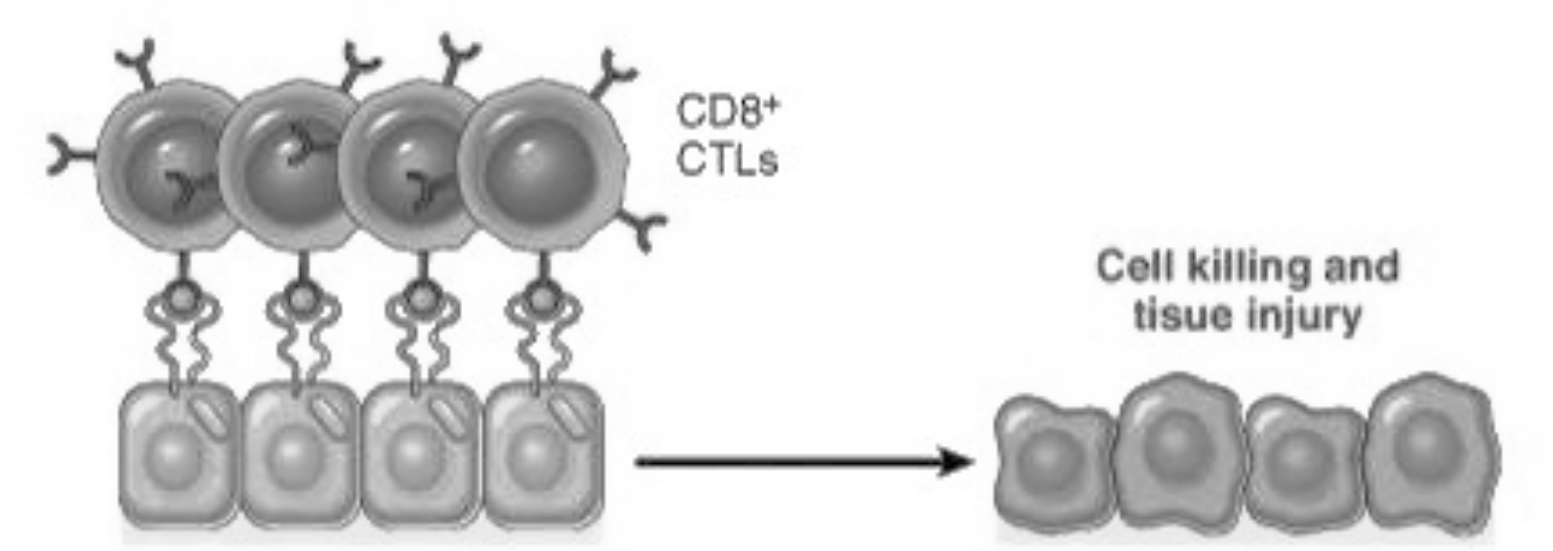
Delayed-Type Hypersensitivity

- Good example of DTH: positive Mantoux test
- Patient previously exposed to TB
- Inject (inactive) TB antigen into skin
- See reddening, induration. Peaks in 1-3 days

T-Cell Mediated Cytotoxicity

- CD8+ T cells recognize antigens on the surface of cells
- T cells differentiate into cytotoxic T lymphocytes (CTLs) which kill antigen-bearing cells
- CTLs normally kill viruses and tumor cells
- In T-cell mediated cytotoxicity, CTLs kill other things:
  - Transplanted organ cells
  - Pancreatic islet cells (Type I diabetes)

T-Cell-Mediated Cytotoxicity



Summary

Type I

- Allergy
- T_H2 cells, IgE on mast cells, nasty mediators

Type II

- Antibodies
- Opsonization, complement activation, or cell dysfunction

Type III

- Immune complexes
- Lodge, cause inflammation, tissue injury

Type IV

- CD4+ or CD8+ T cells
- DTH or T-cell-mediated cytotoxicity