Hypersensitivity Reactions

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Hypersensitivity Reactions Objectives

- Explain in general how hypersensitivity reactions are different than normal immune reactions.
- Explain how T_H2 cells, mast cells, IgE, and mediators (like histamine, prostaglandins, and cytokines) are involved in the mechanism of type I hypersensitivity reactions.
- Describe the local and systemic symptoms that can occur as a result of type I hypersensitivity reactions.
- Explain the three ways that antibodies mess things up in type II hypersensitivity reactions.

Hypersensitivity Reactions Objectives

- Describe how immune complexes lead to tissue damage in type III hypersensitivity reactions.
- Describe the mechanisms involved in both kinds of type IV hypersensitivity reactions.
- Know that type I hypersensitivity is the underlying mechanism for most allergies.

Hypersensitivity Reactions Outline

- Introduction and definitions
- Type I hypersensitivity
- Type II hypersensitivity
- Type III hypersensitivity
- Type IV hypersensitivity

What are hypersensitivity reactions?

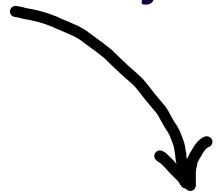
- Excessive, harmful immune reactions
- Elicited by environmental or endogenous antigens
- Often caused by a failure of normal regulatory mechanisms
- Often have a genetic basis (HLA or otherwise)
- Fall into four categories (type I, II, III, and IV hypersensitivity)

What happens in these reactions?

- The immune response is triggered and maintained inappropriately.
- Can be hard to eliminate triggers
- Can be hard to stop the response
- Diseases caused by hypersensitivity responses are often chronic, debilitating, and hard to treat.

The four types of hypersensitivity reactions

Might be a good idea to try to associate the types with a word or two, like this – just to make them easier to remember.



- Type I hypersensitivity (“allergy”)
- Type II hypersensitivity (“antibody”)
- Type III hypersensitivity (“immune complex”)
- Type IV hypersensitivity (“T-cell”)

Type I Hypersensitivity

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

Sequence of Events

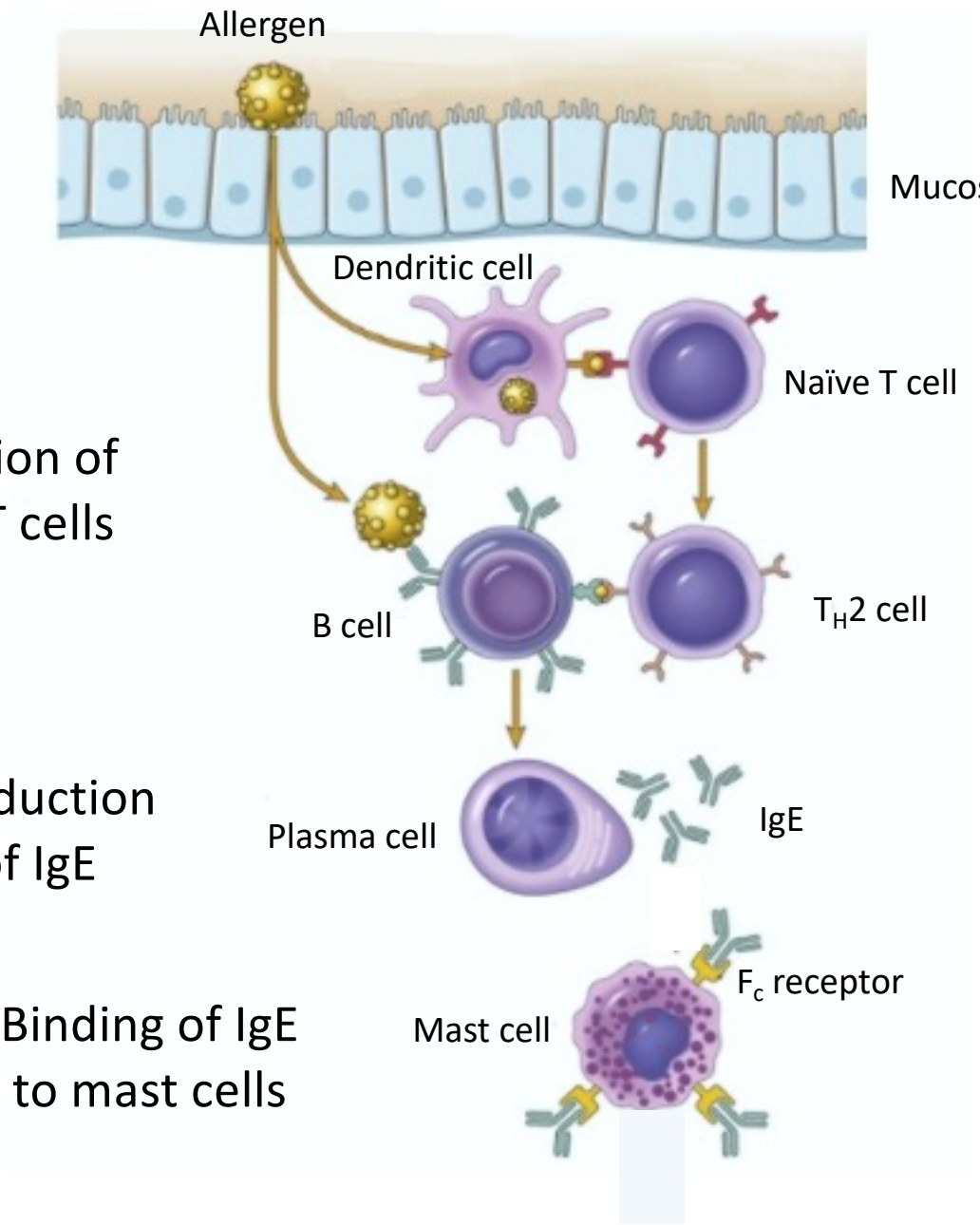
First exposure to allergen:

- Allergen is inhaled/eaten/injected
- Allergen stimulates T_H2 and IgE production
- IgE coats mast cells
- That's it – no symptoms occur!

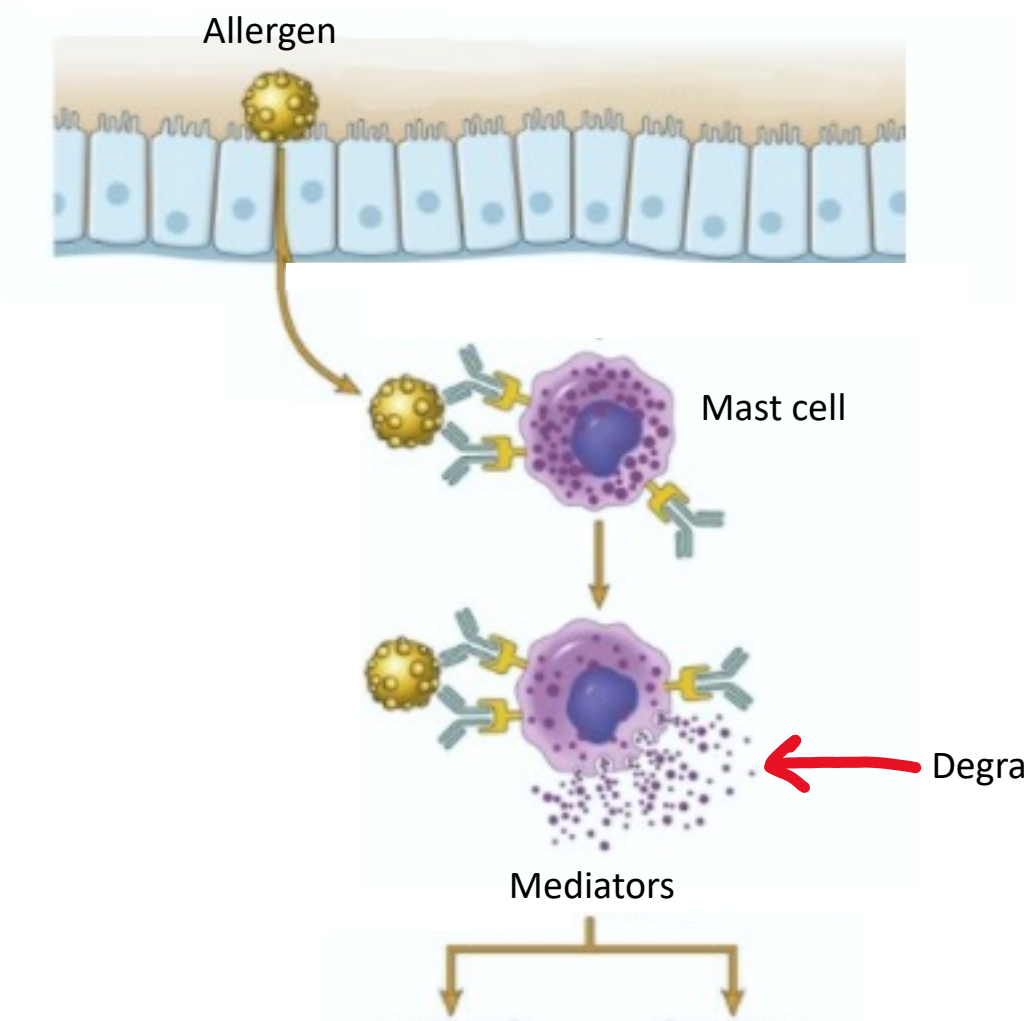
Subsequent exposures to allergen:

- Allergen bridges IgE on mast cell
- Mast cell degranulates
- SYMPTOMS!

First exposure to allergen



Repeat exposure to allergen

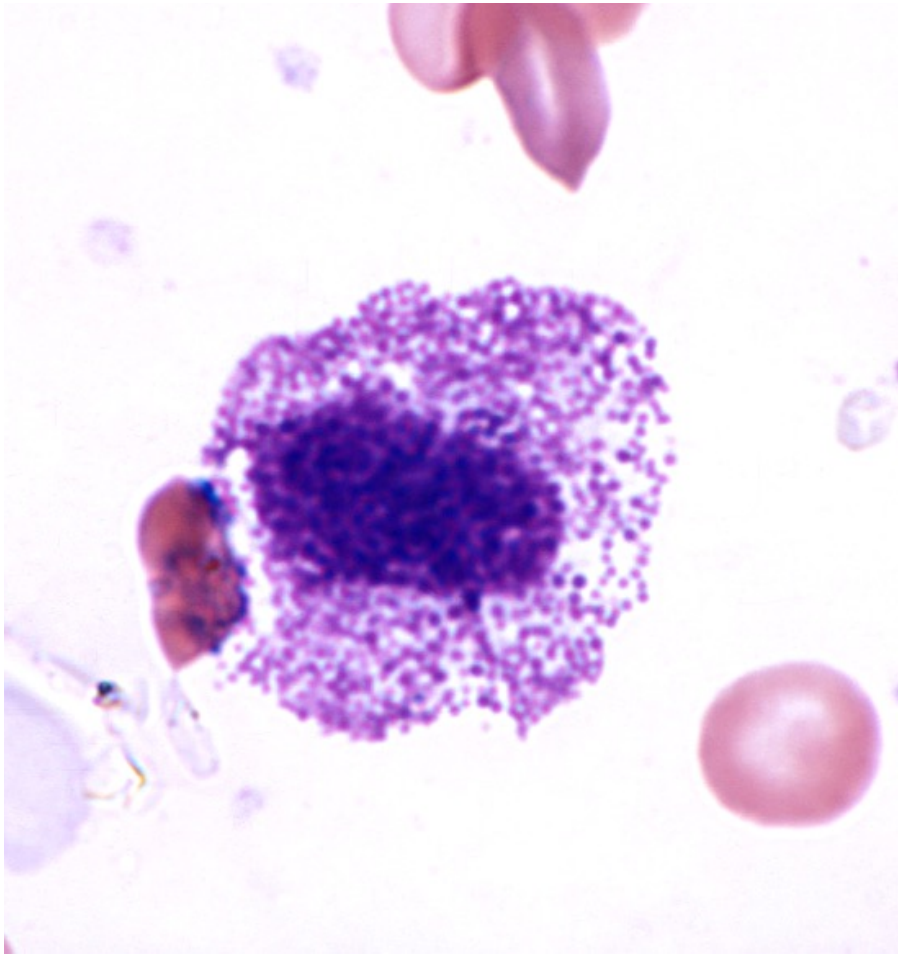


- vasodilation
- vascular leakage
- smooth muscle spasm

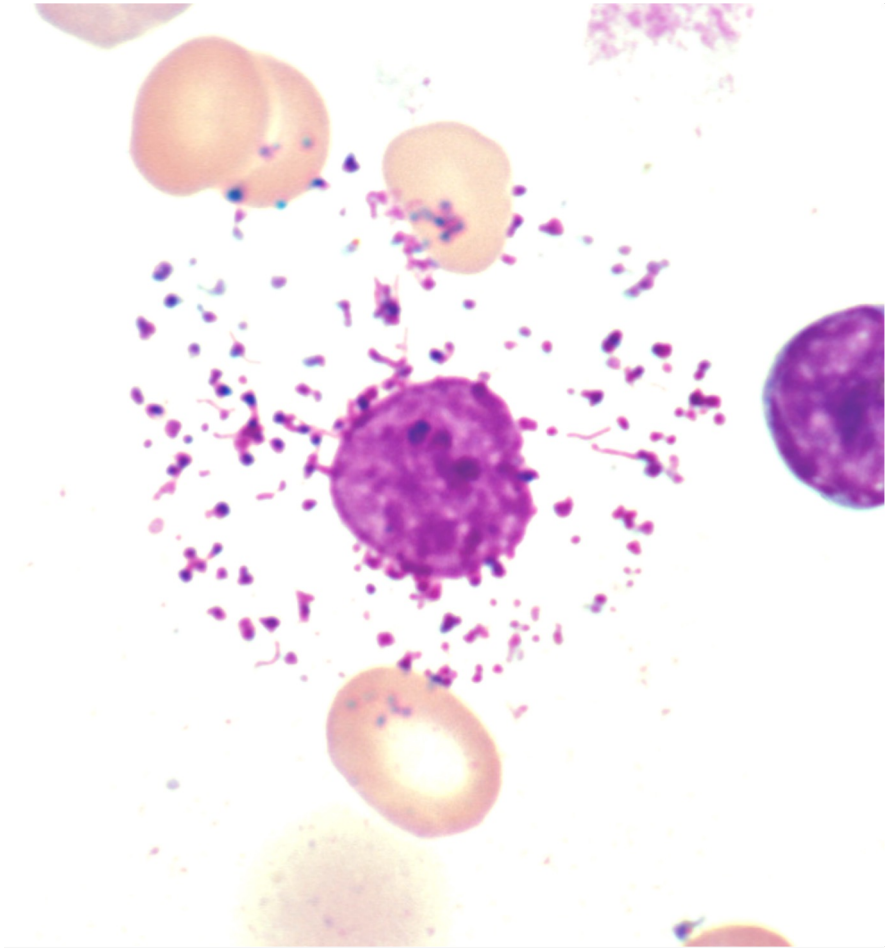
← Immediate reaction (minutes)

Late reaction (hours) →

- inflammation
- tissue destruction



Intact mast cell



Degranulated mast cell

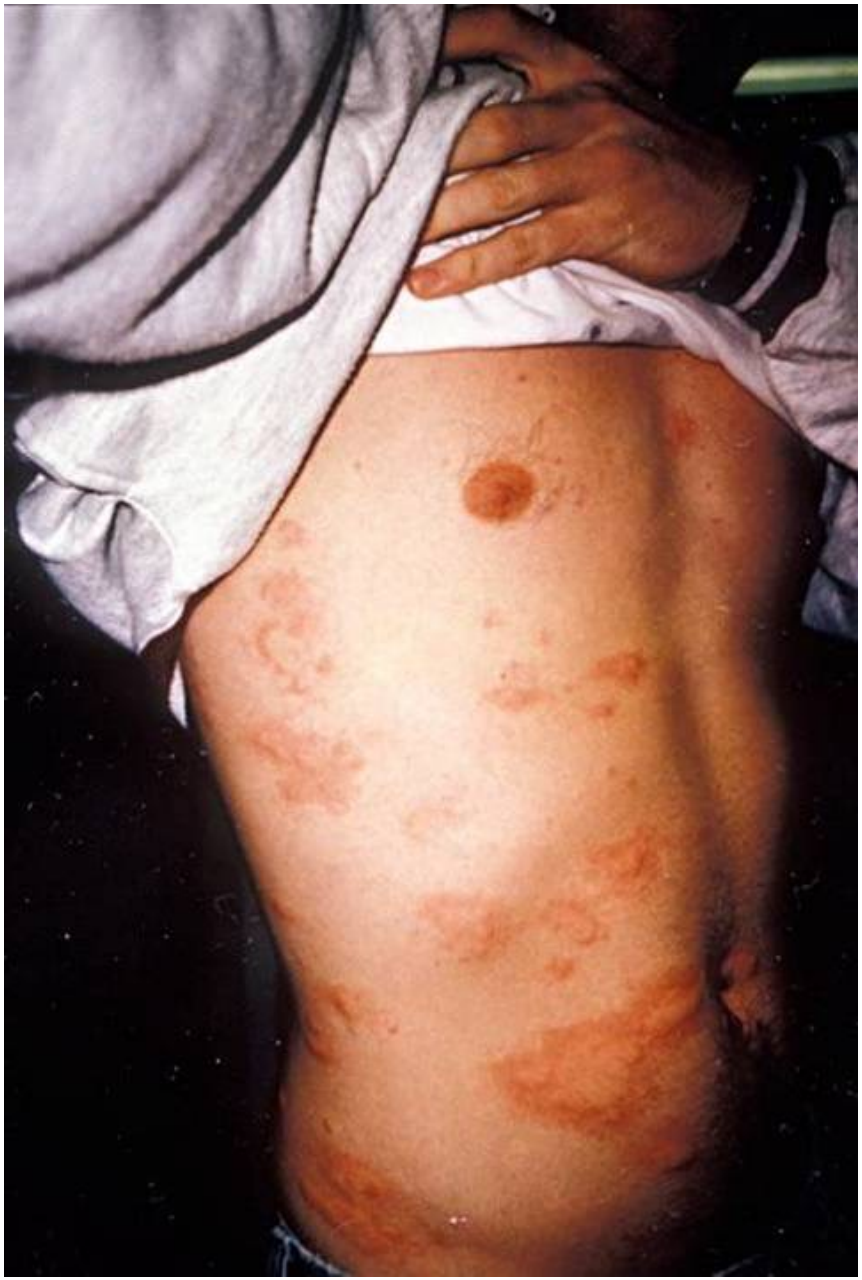
What happens to the patient?

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

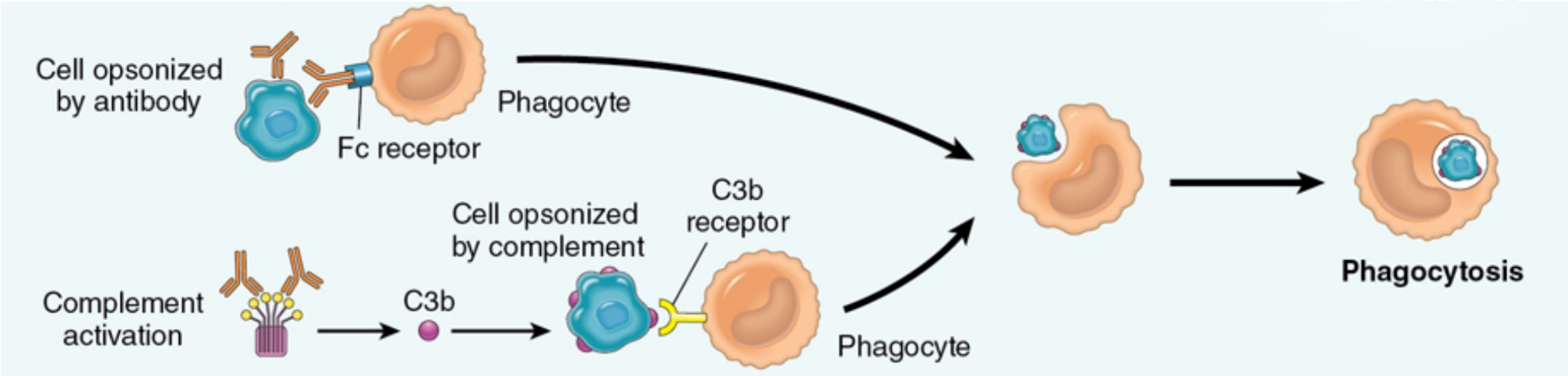


Hives

Type II Hypersensitivity

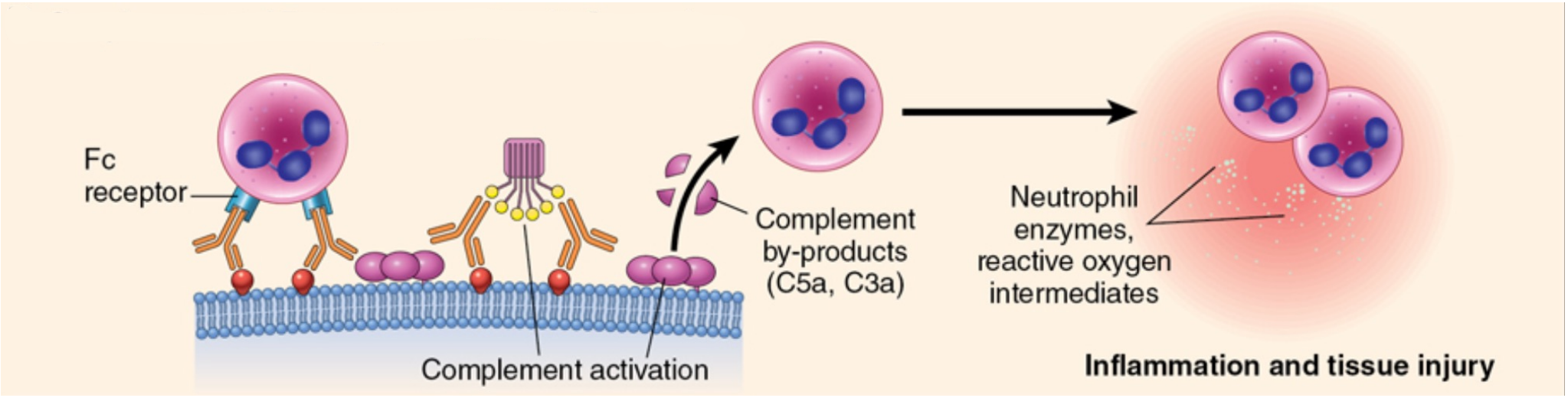
- ANTIBODIES
- “Antibody-mediated” hypersensitivity
- Antibodies bind to antigens on cell surfaces
- So what? What do these bound antibodies do that’s so bad? Three things can result:
  - Opsonization (and then phagocytosis)
  - Inflammation
  - Cellular dysfunction

Opsonization and phagocytosis

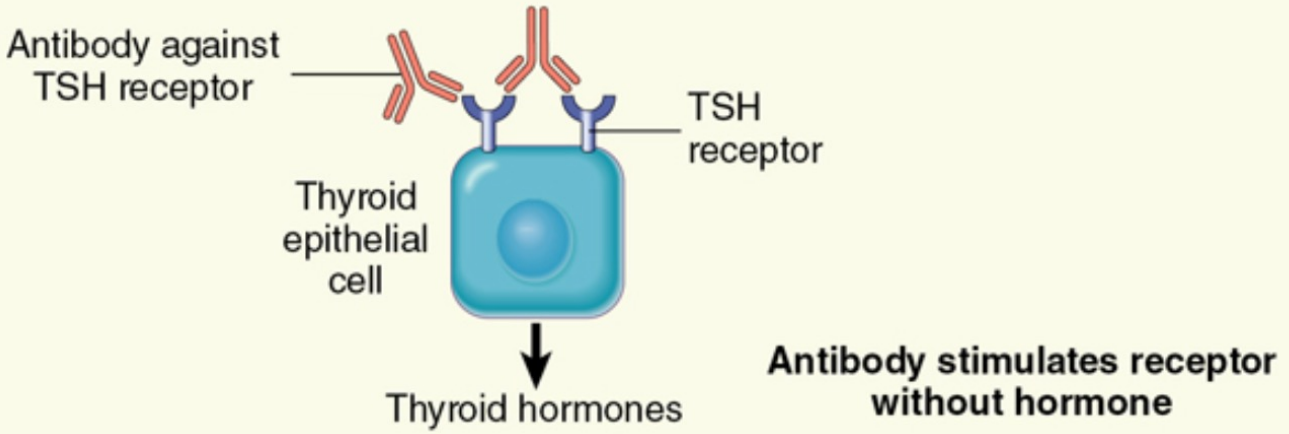


"opson" = Greek for "super yummy sauce"

Inflammation



Cellular Dysfunction



Diseases caused by type II hypersensitivity

Don’t memorize these now! We’ll talk about these diseases later.

Disease	Antigen	Symptoms
Autoimmune hemolytic anemia	RBC antigens	Hemolysis
Myasthenia gravis	Acetylcholine receptor	Muscle weakness
Graves disease	TSH receptor	Hyperthyroidism

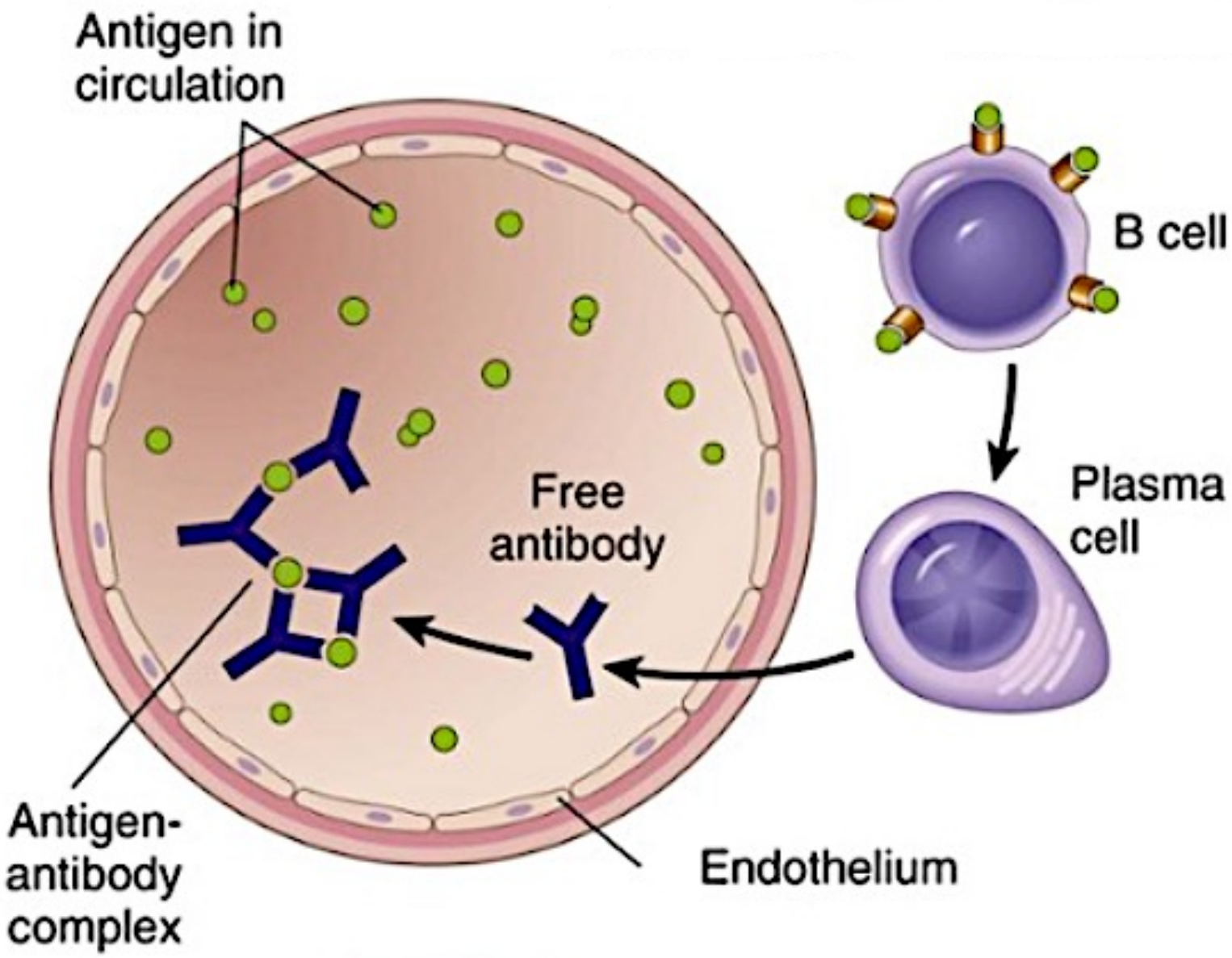
Type III Hypersensitivity

- IMMUNE COMPLEX
- “Immune complex-mediated” hypersensitivity
- Antibodies bind to antigens, forming complexes
- Complexes circulate, get stuck in vessel walls, stimulate inflammation
- Results: bad inflammation, necrotizing vasculitis

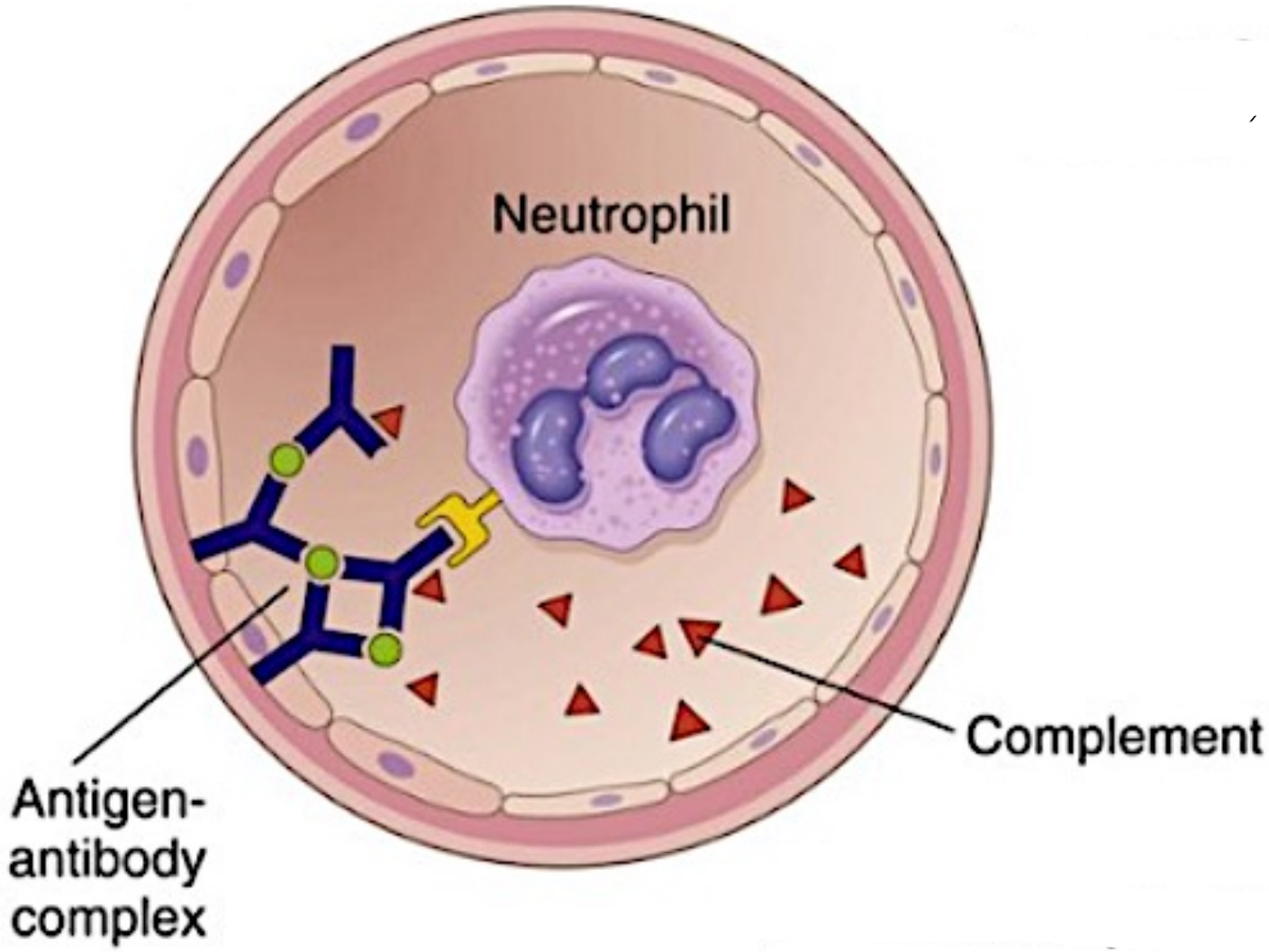
Why are immune complexes damaging?

- Immune complexes activate complement, which:
  - attracts and activates neutrophils
  - makes vessels leaky
- Neutrophils release tissue-dissolving enzymes
- Immune complexes also activate clotting, causing microthrombi
- Outcomes: vasculitis, glomerulonephritis, arthritis, other –itises
- Vessel walls can become so damaged that they undergo necrosis!

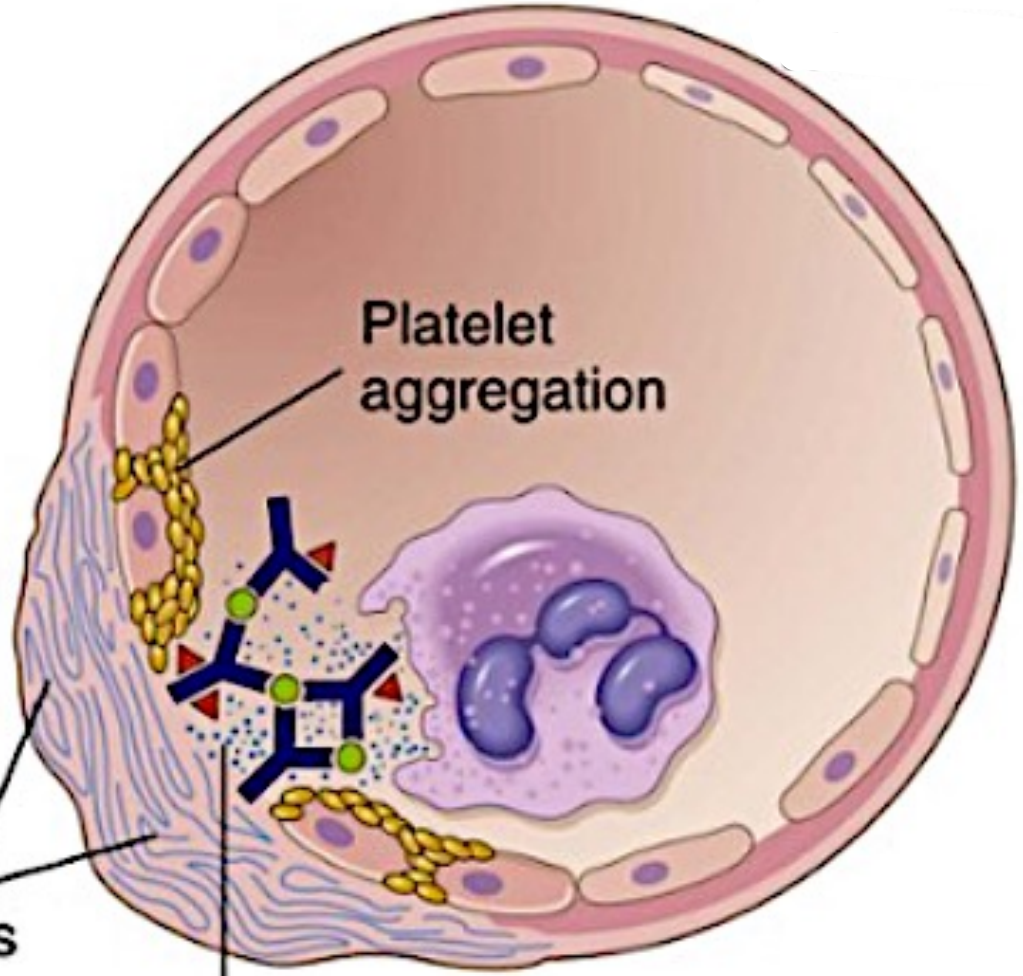
Immune complex formation

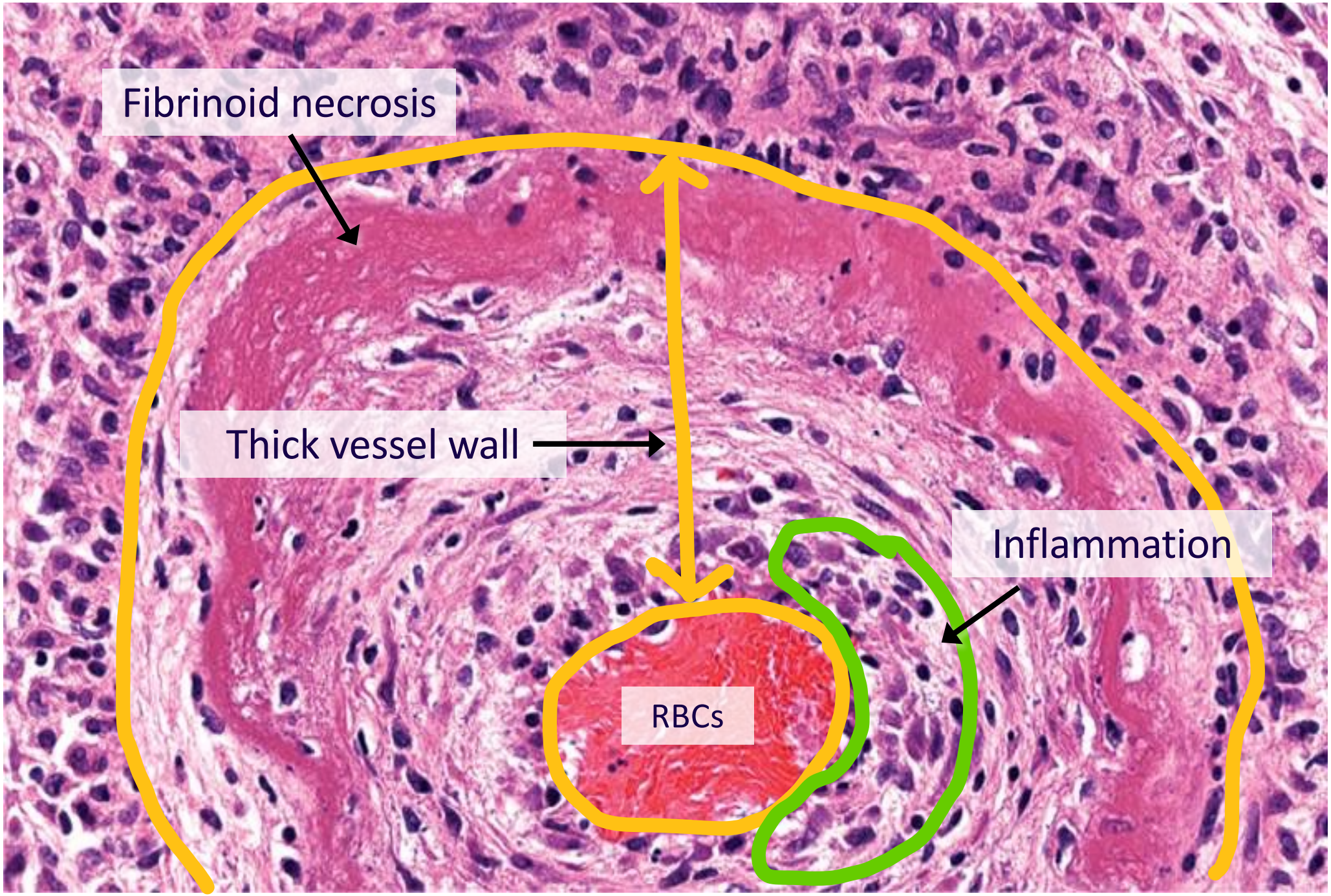


Immune complex deposition



Inflammation and tissue damage





Immune-complex-mediated vasculitis

Diseases caused by type III hypersensitivity

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Disease	Antigen	Symptoms
Systemic lupus erythematosus	Nuclear antigens	Nephritis, skin lesions, arthritis…
Polyarteritis nodosa	Hepatitis B antigen	Systemic vasculitis

Type IV Hypersensitivity

- T CELLS
- "T-cell-mediated" hypersensitivity
- Activated T cells do two different things:
  - release cytokines that activate macrophages, or
  - kill cells directly
- Results: inflammation, cell destruction

"delayed-type hypersensitivity"

"cell-mediated cytotoxicity"

Delayed-Type Hypersensitivity

First exposure to antigen:

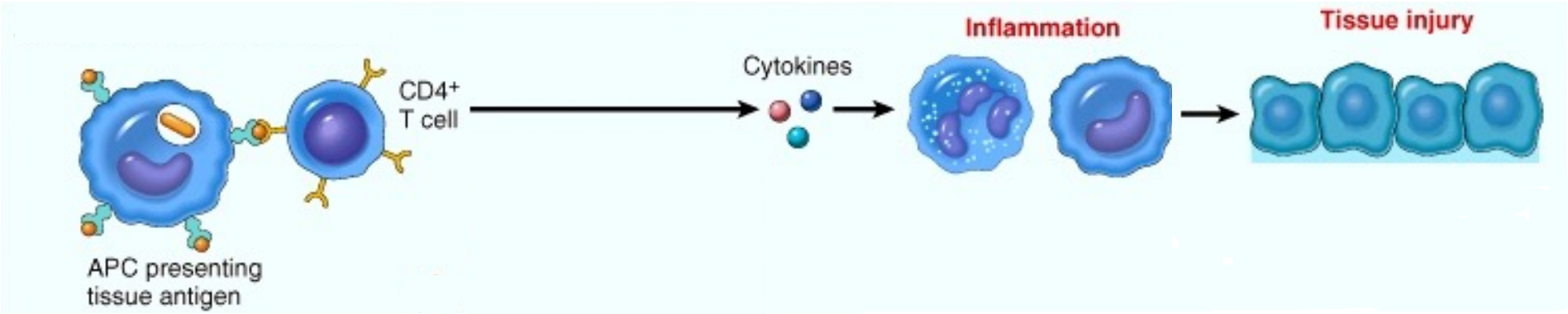
- APC presents antigen to CD4+ T cell
- CD4+ T cells differentiate into effector and memory T_H1 cells
- That's it! No symptoms occur.

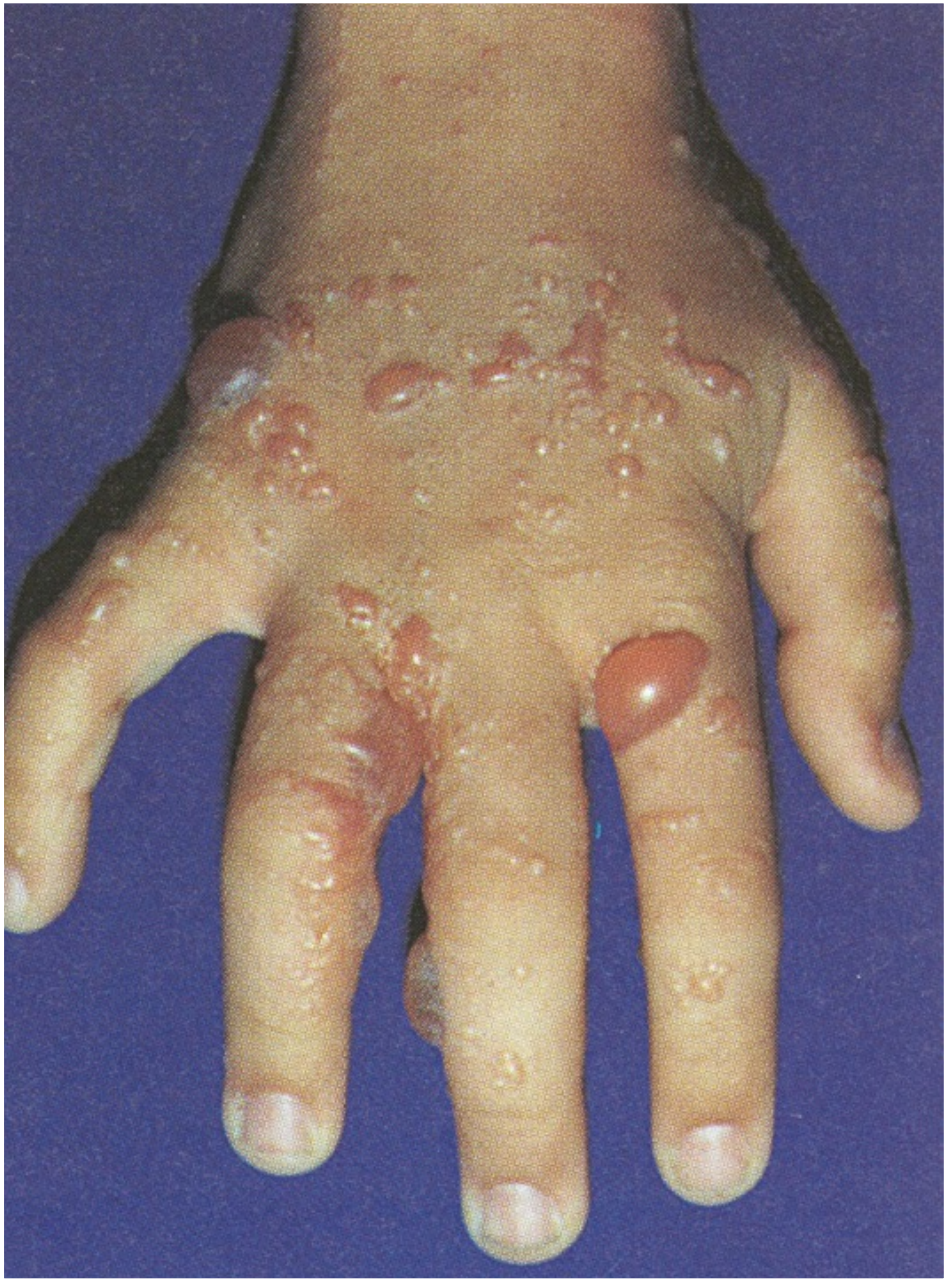
Subsequent exposures to antigen:

- T_H1 cells come to site of antigen exposure
- Release cytokines that activate macrophages, cause inflammation

Delayed-Type Hypersensitivity

Subsequent exposure to antigen:



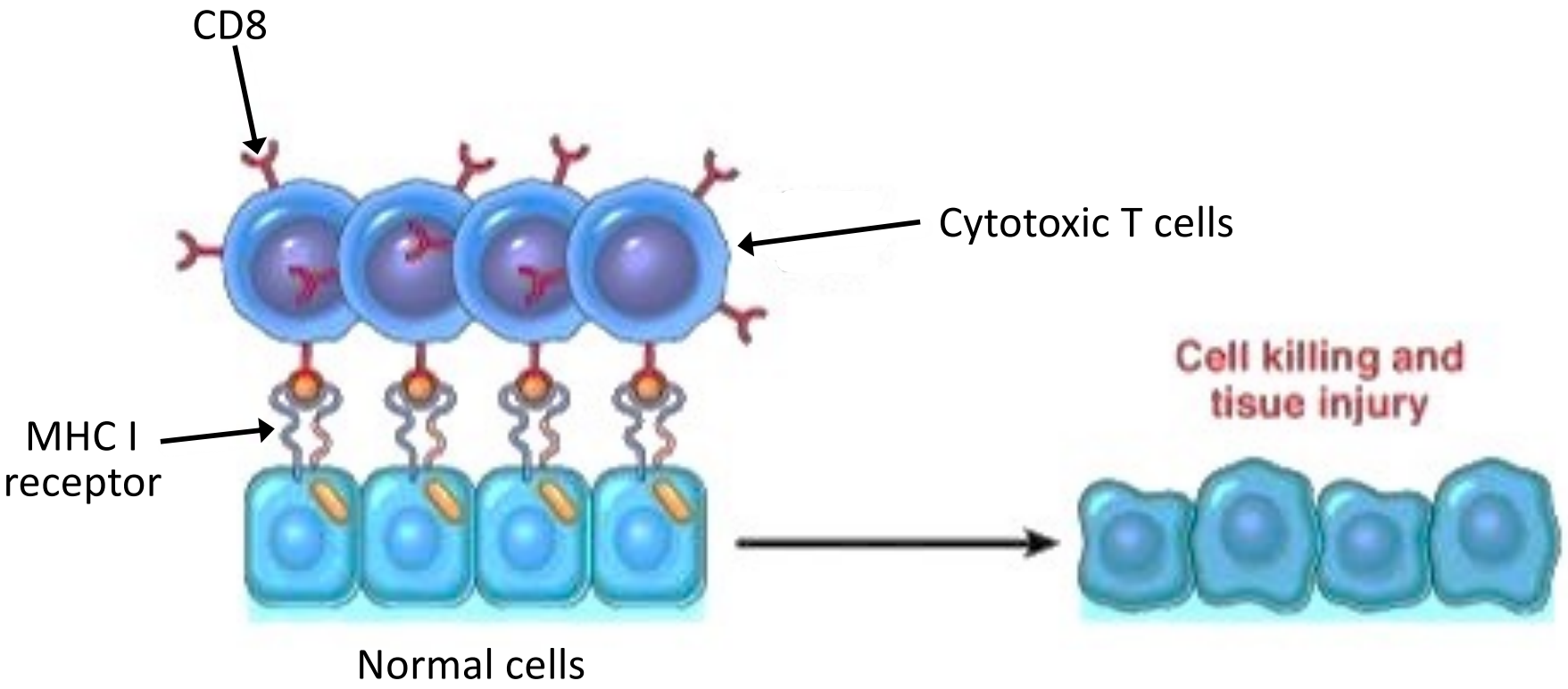


Poison ivy is caused by delayed-type hypersensitivity

Cell-Mediated Cytotoxicity

- CD8+ T cells differentiate into cytotoxic T lymphocytes (CTLs) which kill cells that have certain cell-surface antigens
- In normal immune reactions, CTLs kill infected cells
- In cell-mediated cytotoxicity, CTLs kill cells they shouldn't (e.g., pancreatic islet cells)

Cell-Mediated Cytotoxicity



Diseases caused by type IV hypersensitivity

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Disease	Mechanism	Symptoms
Multiple sclerosis	DTH against antigens in myelin	Neurologic symptoms such as paralysis
Type I diabetes	CTLs destroy insulin-producing islet cells	Hyperglycemia