

Classification of Hypersensitivity Reactions

Mechanism → tissue injury → clinical phenotype

Diseases of the immune system

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Learning objectives: Mechanism before memorization

- 1** Identify the immune effector that defines each hypersensitivity type.
- 2** Explain how each effector produces its characteristic tissue lesion.
- 3** Use clinical and morphologic evidence to classify representative diseases.
- 4** Recognize overlap and avoid treating classification as mutually exclusive.

Hypersensitivity is injurious immunity

An immune response becomes a cause of tissue injury

The same immune effectors that defend against pathogens can become excessive, inadequately regulated, or misdirected against harmless or self antigens.

Two broad sources of initiating antigen

Exogenous antigens

Environmental or microbial material: Pollen, foods, dust, drugs, microbial proteins and chemicals.

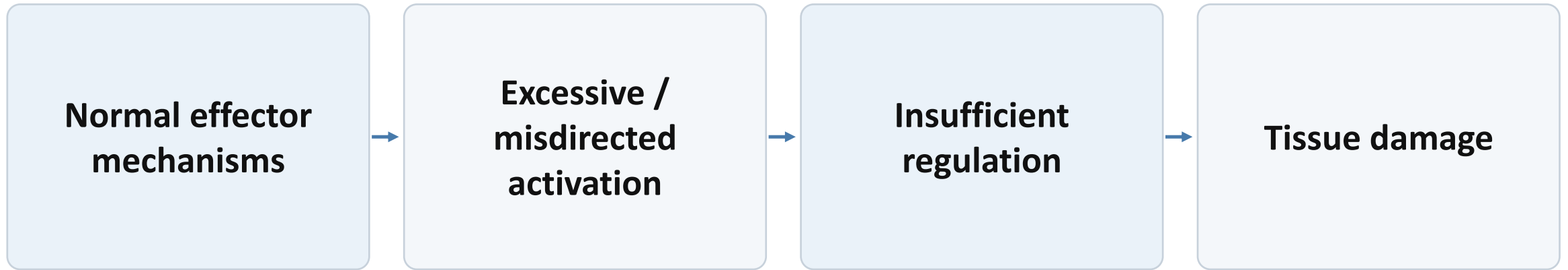
The initiating target may be otherwise harmless.

Endogenous self antigens

Autologous molecules targeted in autoimmune disease.

Recognition of self can provoke antibody-mediated or T-cell-mediated injury.

Why protective immunity becomes harmful



Pathogenicity depends on the target, magnitude, location and persistence of the response.

Sensitization changes subsequent responses

1

Initial antigen exposure may activate lymphocytes and generate specific effector or memory populations.

2

Repeat exposure can trigger a faster or stronger response in a sensitized individual.

3

The final manifestation depends on the effector pathway—not on the mere presence of prior exposure.

“Hypersensitivity” historically refers to acquired sensitivity after exposure.

Immune defense and immunopathology share effectors

Adaptive recognition

B-cell antibodies and antigen-specific T cells provide recognition and adaptive immune responses.

Innate tissue effectors

Mast cells, complement, phagocytes and inflammatory leukocytes amplify or execute tissue injury.

The classification is mechanistic—not merely temporal

Four major reaction types (I–IV)

Each category links an initiating immune mechanism with downstream effectors, histopathologic lesions and prototype clinical disorders.

The four mechanistic classes at a glance

TYPE I

IgE + mast cells

Immediate / allergic

TYPE II

IgG ($\pm$ IgM) at tissue target

Antibody-mediated

TYPE III

Antigen–antibody complexes

Immune complex–mediated

TYPE IV

CD4+ / CD8+ T lymphocytes

T-cell-mediated

Antibodies and T cells define different branches

Antibody-associated injury

Type I: IgE / mast cells.

Type II: Antibody directed at fixed cell or tissue antigens.

Type III: Deposited antigen–antibody complexes.

T-cell-associated injury

Type IV: Sensitized CD4+ or CD8+ T lymphocytes.

Cytokine-driven inflammation and/or direct cytotoxicity.

Location of the antigen clarifies the mechanism

Fixed target (Type II)

Cell surface receptor, blood-cell membrane or tissue basement membrane.

Antibody binds a pre-existing cellular / tissue location.

Deposited complexes (Type III)

Antigen and antibody form complexes in blood or locally; Deposits develop in tissues.

Complex-triggered inflammation is central.

Characteristic lesions are mechanistic fingerprints

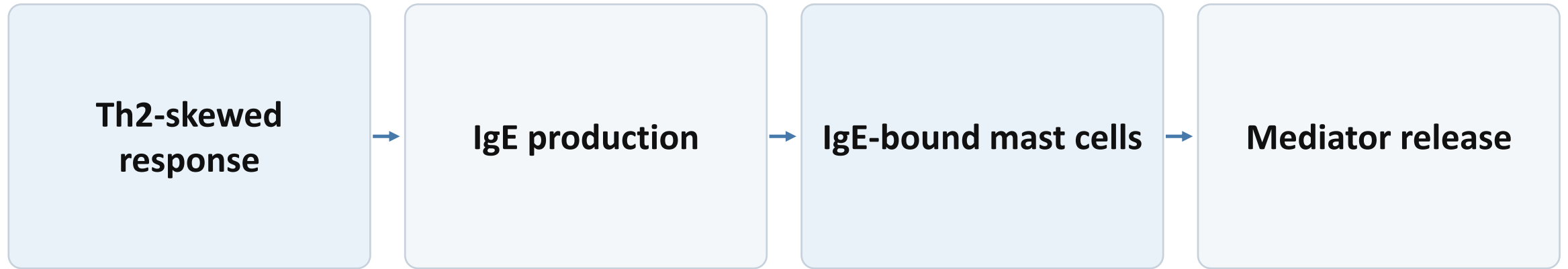
Type	Typical tissue response	Predominant mechanism
I	Edema, mucus, smooth muscle contraction	Mast-cell mediators; Often eosinophilic inflammation
II	Cell loss, inflammation or dysfunction	IgG / complement / Fc effector pathways
III	Inflammation, vasculitis and fibrinoid necrosis	Deposited immune complexes recruit leukocytes
IV	Mononuclear inflammation, granulomas or cell killing	Cytokine-driven and cytotoxic T-cell responses

Timing is a clue, not the definition

Classify by effector mechanism

“Immediate” is typical of sensitized IgE–mast-cell reactions and “delayed” is characteristic of some T-cell responses. Chronic diseases may combine multiple mechanisms.

Type I: IgE and mast cells initiate injury



The resulting vascular, smooth-muscle and inflammatory effects produce allergic disease.

Type I begins with immune sensitization

Allergen exposure



Th2 / Tfh help



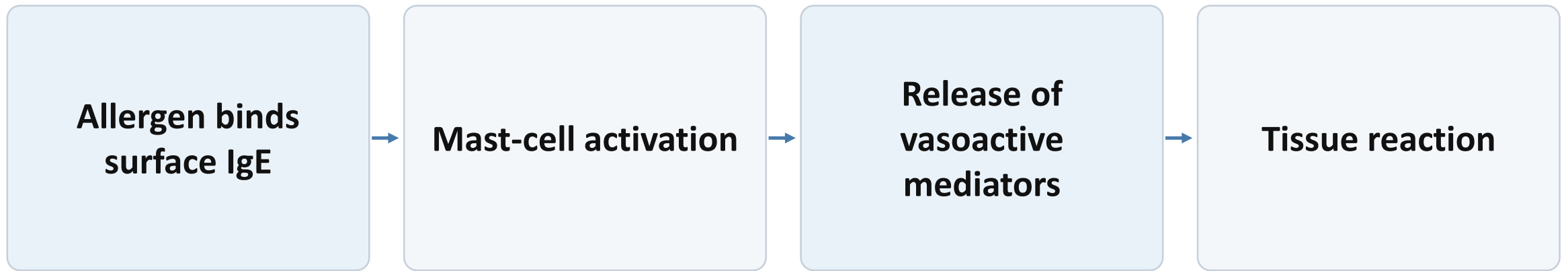
B-cell IgE production



IgE on mast cells

Subsequent allergen challenge activates surface-bound IgE–mast-cell systems.

Allergen challenge activates sensitized mast cells



The rapid reaction reflects pre-armed mast cells, not newly synthesized antibodies.

Type I has rapid and inflammatory components

Preformed / rapid mediators

Mast-cell products produce vasodilation, vascular leakage, smooth-muscle reactions and glandular secretion.

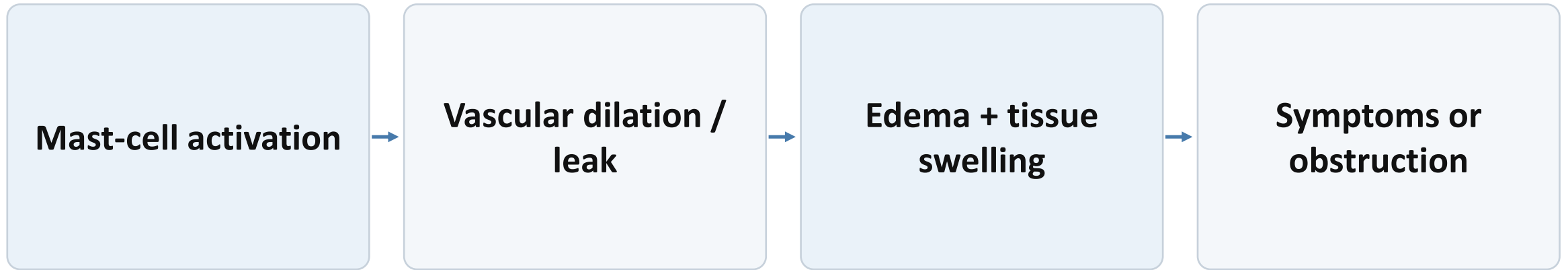
These appear within minutes.

Cytokine-mediated amplification

Mast cells and type 2 immune cells recruit eosinophils and additional leukocytes.

The late phase may persist for days.

IgE–mast-cell activation alters tissue function



Vascular changes account for wheals, mucosal swelling and portions of anaphylaxis.

Type I also acts on smooth muscle and glands

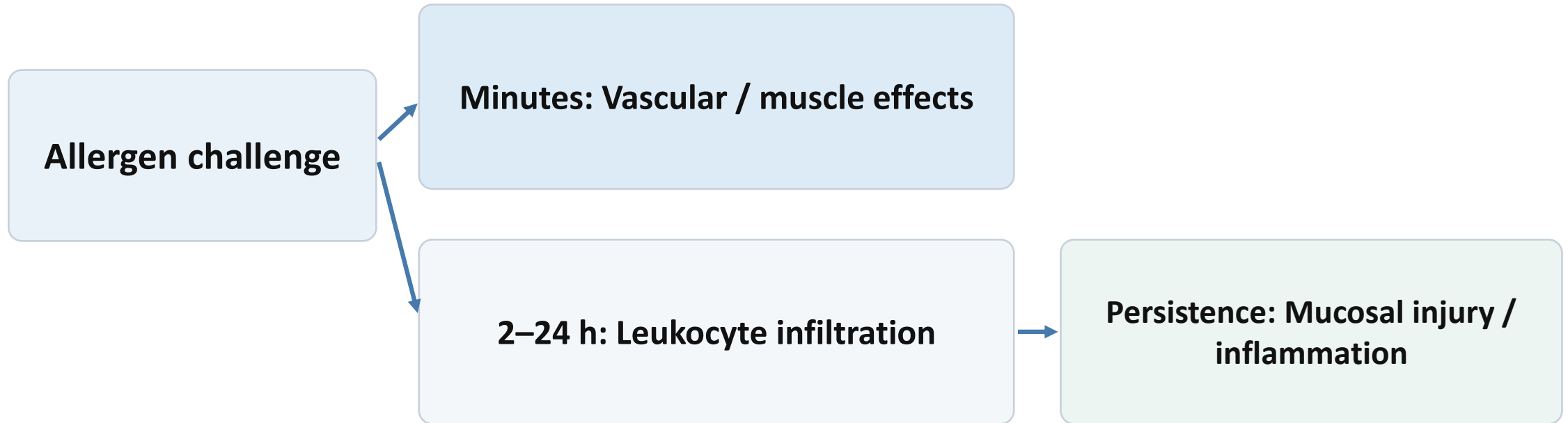
Smooth-muscle contraction

Airway smooth muscle contraction contributes to bronchospasm and airflow obstruction in allergic responses.

Glandular secretion

Increased secretions contribute to rhinorrhea and mucus-rich airway symptoms.

Early and late phases of Type I reactions



The late response can arise without a second antigen exposure.

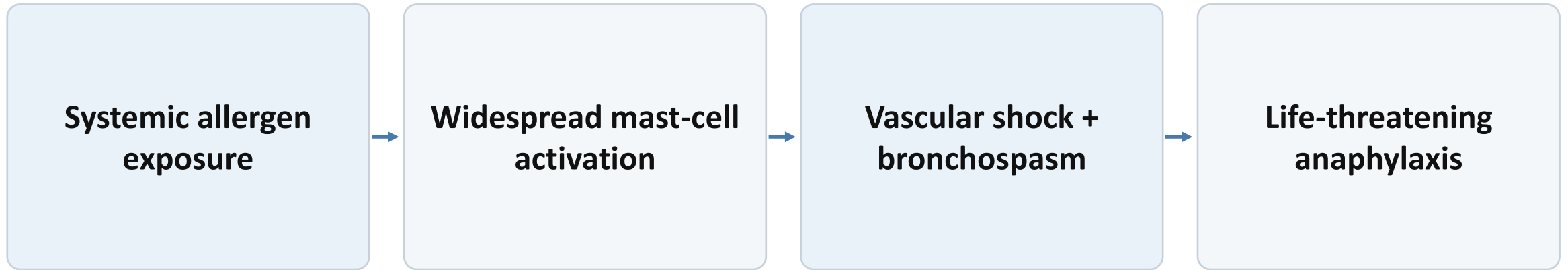
Inflammatory cells define the Type I late phase

- Eosinophils and other leukocytes enter the affected tissue.
- Neutrophils, basophils, monocytes and CD4+ T cells may also be present.
- Inflammatory infiltration can damage mucosal epithelial cells.
- Repeated episodes explain why many allergic disorders are chronic.

Type I phenotype follows the portal of exposure

Site	Key local response	Example presentation
Skin	Mast-cell mediator response	Urticaria, wheals or other cutaneous reactions
Nose / eye	Vascular leak and glandular secretion	Rhinitis and conjunctivitis
Airway	Bronchospasm, mucus and inflammation	Atopic bronchial asthma
Systemic	Widespread vascular and airway effects	Anaphylaxis

Systemic Type I hypersensitivity can be fatal



The same IgE–mast-cell pathway may produce localized allergy or systemic collapse.

Recognize Type I lesions at two time points

Immediate changes

Vasodilation, edema, glandular secretion and smooth-muscle spasm; Phenotype varies by organ.

Later tissue reaction

Eosinophils and additional recruited leukocytes;
Tissue inflammation and possible epithelial injury.

Type I classification depends on the pathway

IgE + mast cell + mediator injury

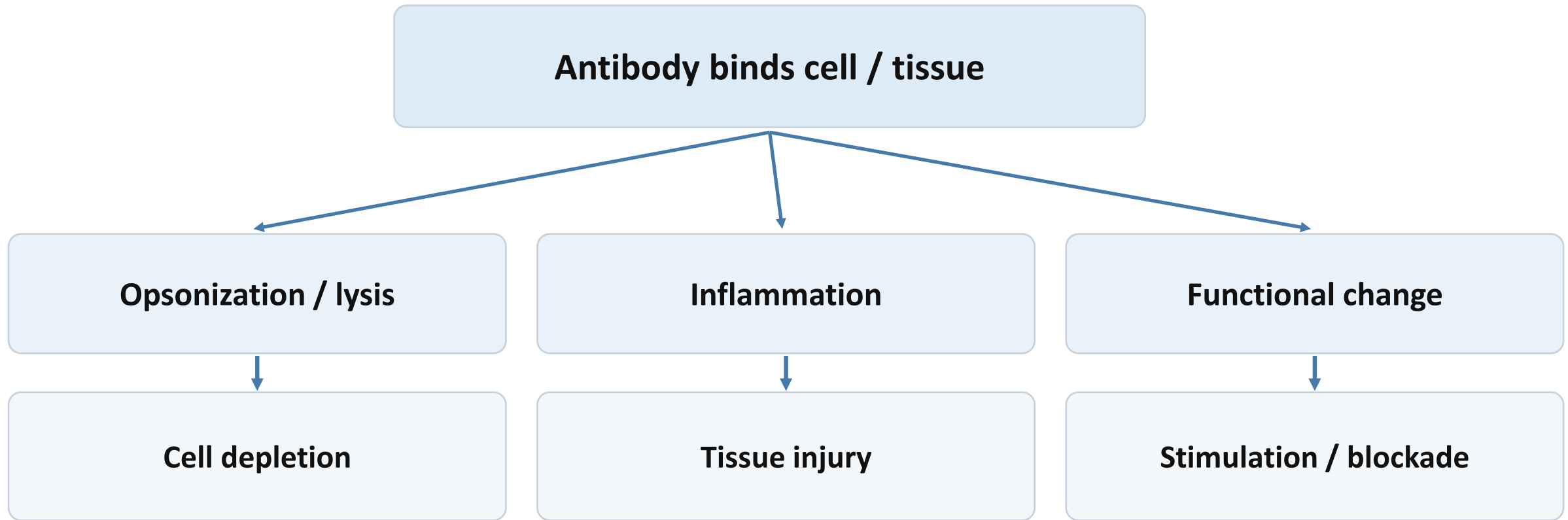
Anaphylaxis, allergic rhinitis and atopic asthma are prototypes; The presence of wheezing or edema alone is not enough to assign a hypersensitivity type.

Type II targets antigens at fixed sites

IgG (occasionally IgM) binds cell or tissue antigens

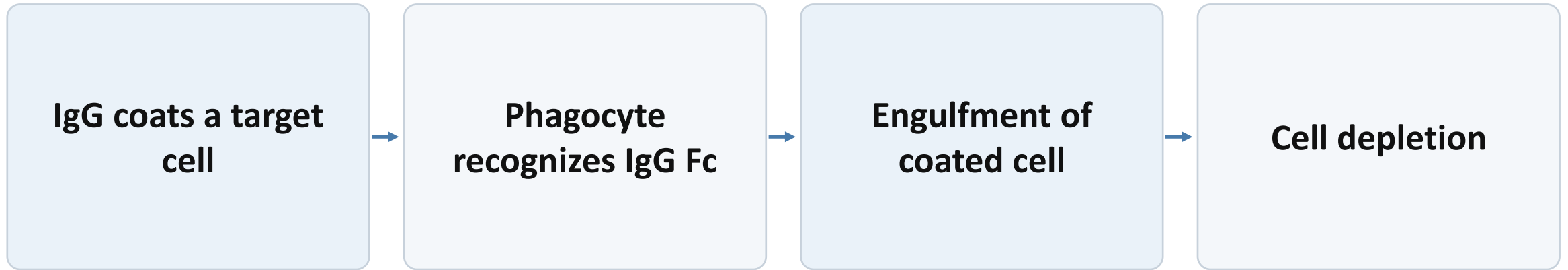
Cell destruction, complement/Fc receptor–mediated inflammation, or receptor dysfunction can follow direct antibody binding.

Type II has three major injury pathways



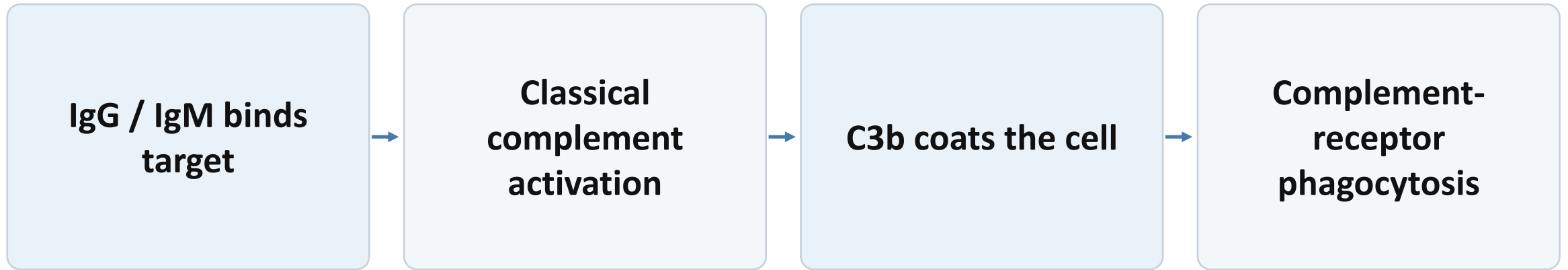
Different phenotypes; The common starting point is target-bound antibody.

Fc receptors enable Type II phagocytosis



Antibody-coated erythrocytes and platelets are particularly informative examples.

Complement amplifies Type II cell clearance



C3b is an opsonin: Complement activation need not always end in direct lysis.

Two antibody-associated ways to destroy cells

Phagocytosis

Fc- and C3b-receptor recognition promotes uptake and intraphagocytic destruction of coated cells.

Complement-mediated lysis

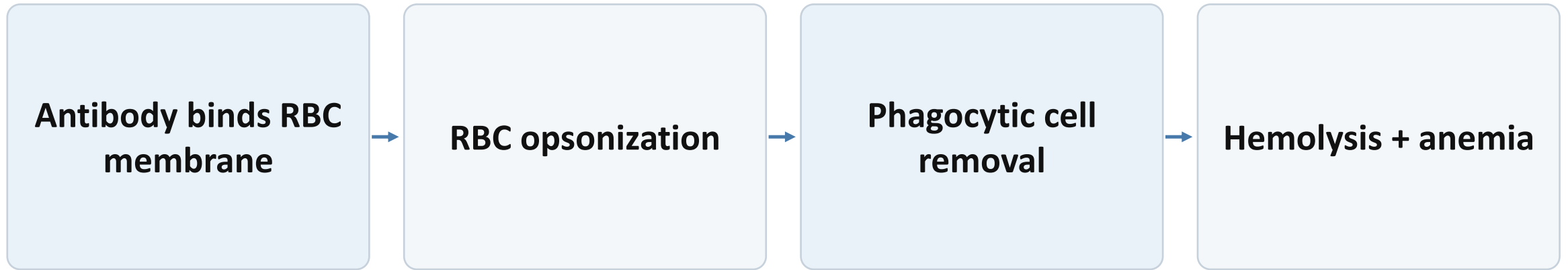
Terminal complement membrane attack complexes can disrupt target-cell membranes and cause osmotic lysis.

ADCC is a possible mechanism—not a universal explanation

Antibody-dependent cellular cytotoxicity

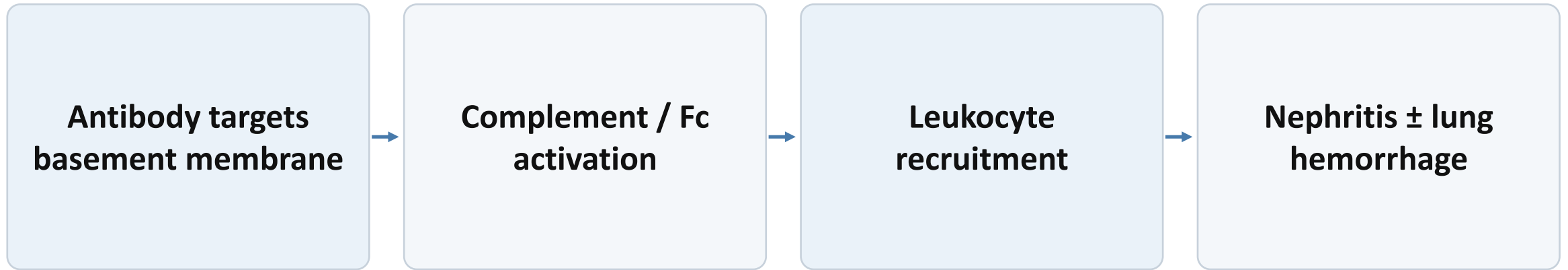
IgG-coated targets may be killed by Fc-receptor-bearing cells, including NK cells. Its contribution to common hypersensitivity diseases is uncertain.

Autoimmune hemolytic anemia exemplifies Type II cell loss



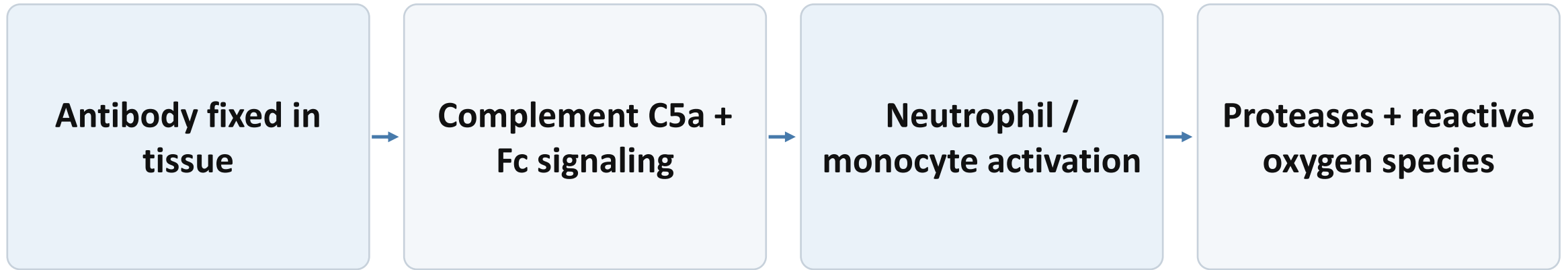
The primary injured target is the circulating erythrocyte itself.

Anti-basement-membrane disease exemplifies fixed-tissue injury



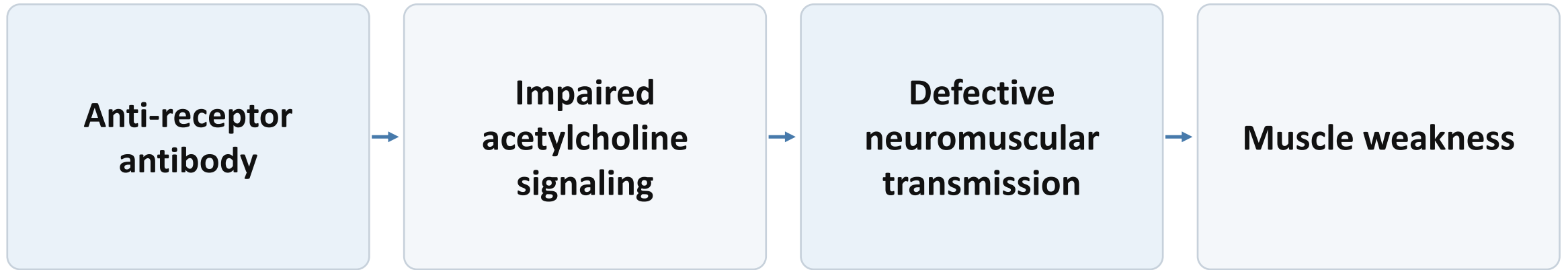
Goodpasture syndrome is the prototype listed Table 6.1.

Type II inflammation follows antibody deposition



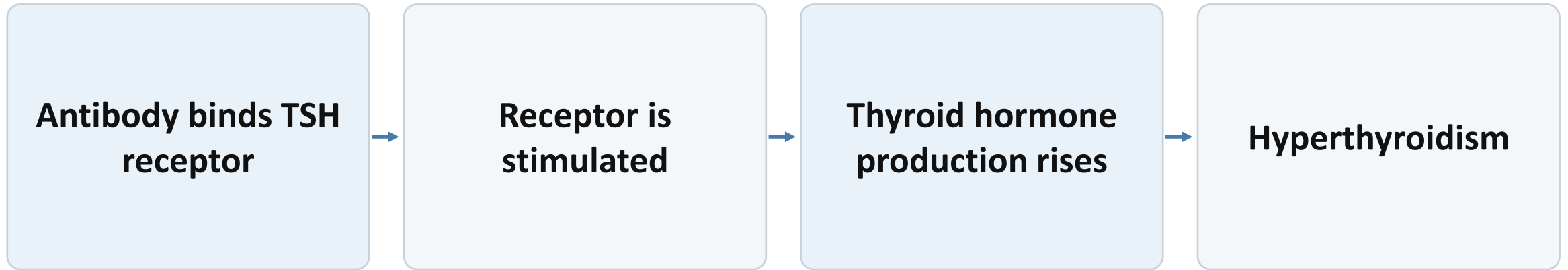
Inflammation damages extracellular matrix and nearby resident cells.

Receptor blockade: Myasthenia gravis



A functional antibody effect may predominate even without major visible tissue necrosis.

Receptor stimulation: Graves disease



Type II reactions can imitate a normal agonist rather than block receptor function.

Type II cellular loss differs from altered function

Destructive responses

Erythrocyte depletion, platelet loss or inflammation in fixed tissues can result from opsonization and complement/Fc effectors.

Non-destructive responses

Antibodies may block signaling (myasthenia gravis) or stimulate receptors (Graves disease).

Selected Type II prototypes distinguish submechanisms

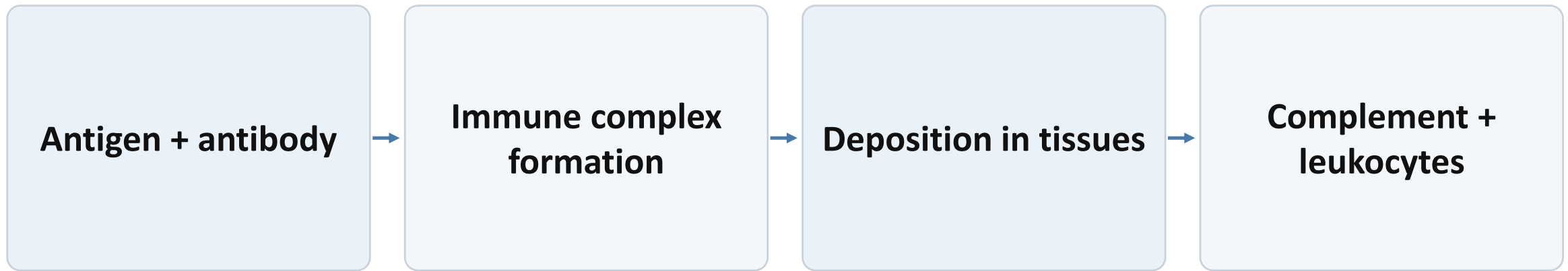
Disease	Fixed antigenic target	Dominant expression
Autoimmune hemolytic anemia	RBC membrane	Opsonization; Cell loss
Goodpasture syndrome	Glomerular / alveolar BM	Antibody-driven inflammation
Myasthenia gravis	Acetylcholine receptor	Transmission blockade $\pm$ complement injury
Graves disease	TSH receptor	Functional receptor stimulation

Type III injury requires pathogenic immune complexes

Antigen–IgG complexes deposit in tissues

Immune complexes formed in the circulation or locally recruit inflammatory effectors; The antigen need not be an intrinsic tissue structure.

Type III: Formation → deposition → inflammation



Release of injurious mediators causes vasculitis and other inflammatory lesions.

Type III complexes form in two settings

Circulating complexes

Antigen and antibody combine in the bloodstream, followed by tissue deposition—often in vessel walls.

In situ complexes

Antibody binds an antigen previously positioned (“planted”) in a tissue; Complexes form locally.

Complex deposition is conditional—not automatic

- Not all antigen–antibody complexes become pathogenic.
- Complex properties and local vascular conditions influence deposition.
- Medium-sized complexes may be especially pathogenic in the classic systemic model.
- Renal and synovial filtration conditions help explain target-organ patterns.

Type III frequently affects filtration interfaces

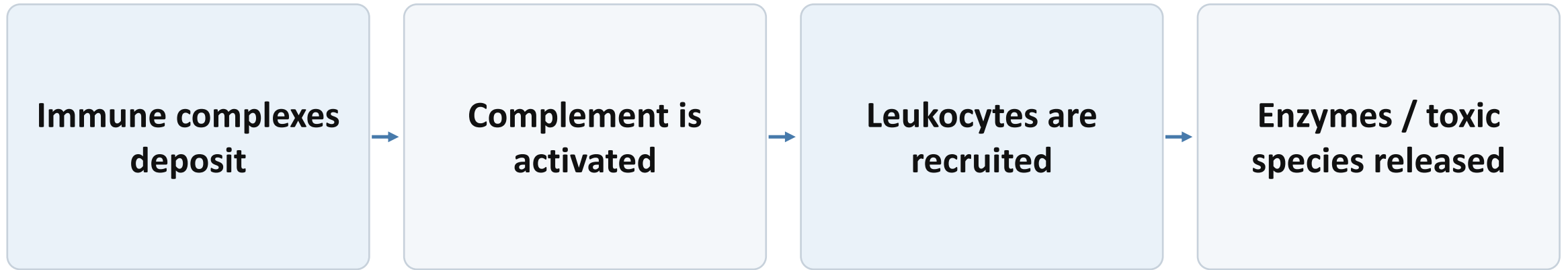
Glomeruli

Immune complexes may localize in renal filtering structures and provoke glomerulonephritis.

Synovium and small vessels

Deposition can produce arthritis and vasculitis; Distribution follows hemodynamic and tissue factors.

Complement recruits tissue-damaging leukocytes



The inflammatory response, rather than simple antibody binding, produces the characteristic lesion.

Necrotizing vasculitis is a Type III pattern

Inflammation with fibrinoid necrosis

Deposited immune complexes and activated inflammatory cells can cause vessel-wall damage; Fibrinoid necrosis is a characteristic morphologic consequence.

Serum sickness: The systemic prototype

1

Exposure to soluble foreign antigen elicits an antibody response.

2

Circulating antigen–antibody complexes form while antigen persists.

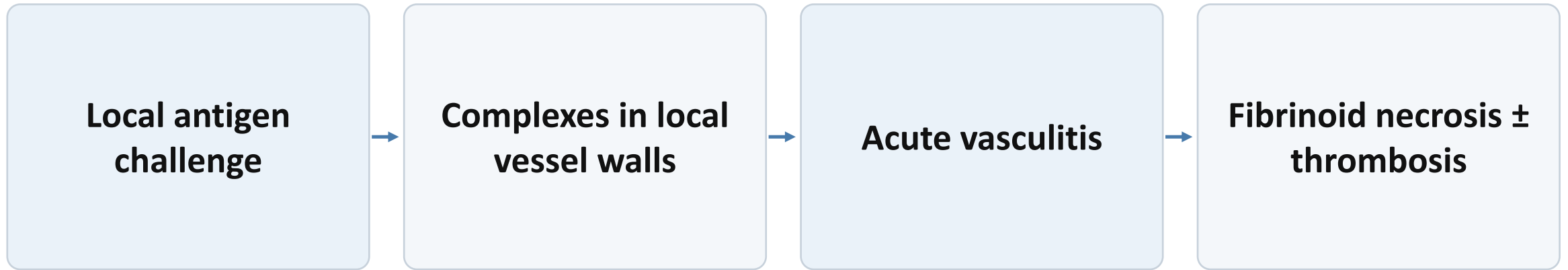
3

Complexes deposit in tissues, activating complement and leukocytes.

4

Fever, urticaria, arthralgia and proteinuria may accompany inflammation.

Arthus reaction: Localized immune complex injury



A Type III mechanism can be localized rather than systemic.

Immune complex disorders can be systemic or focal

Systemic pattern

SLE and serum sickness illustrate persistent or widespread immune complex responses affecting multiple organs.

Tissue-focused pattern

Some glomerulonephritis and Arthus reactions emphasize local sites of deposition and injury.

Type II versus Type III: Ask where antigen sits

Type II: Fixed target

Antibody binds an antigen intrinsic to or attached to a cell / tissue.

Loss, inflammation or functional disturbance follows.

Type III: Complex deposition

Soluble or locally formed antigen–antibody complexes deposit and recruit inflammation.

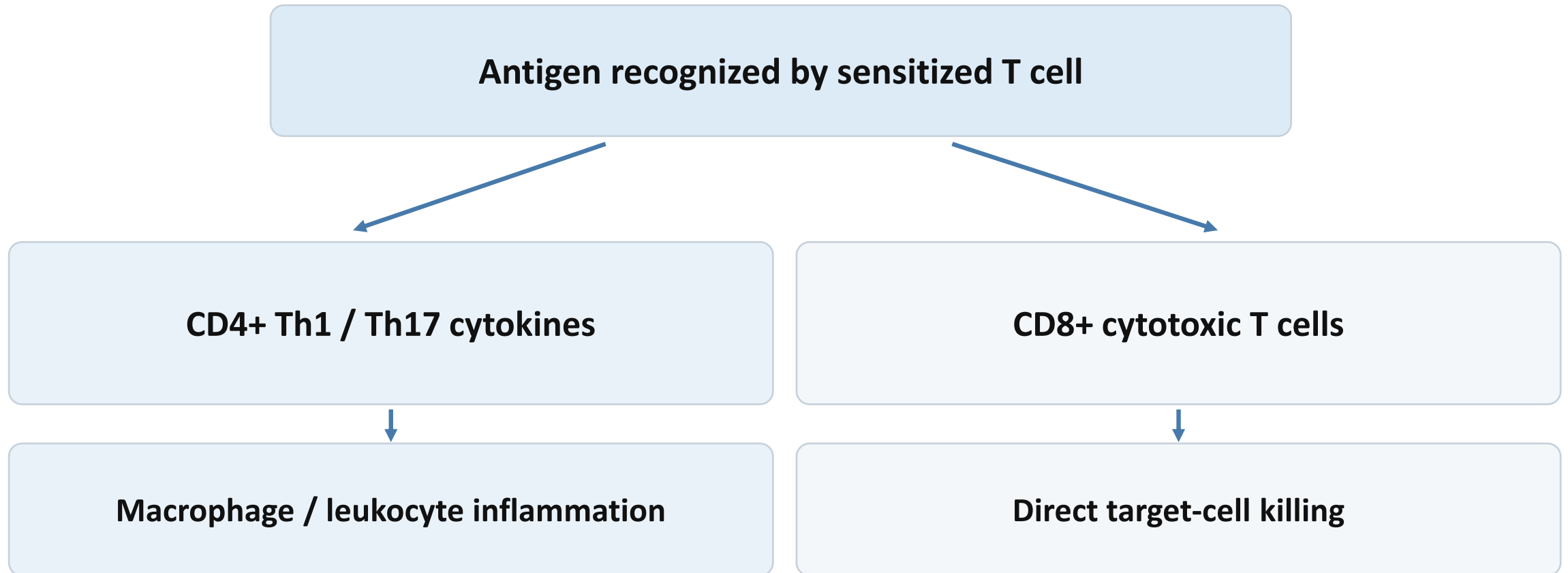
Distribution often involves vessels, glomeruli and joints.

Type IV hypersensitivity is T-cell mediated

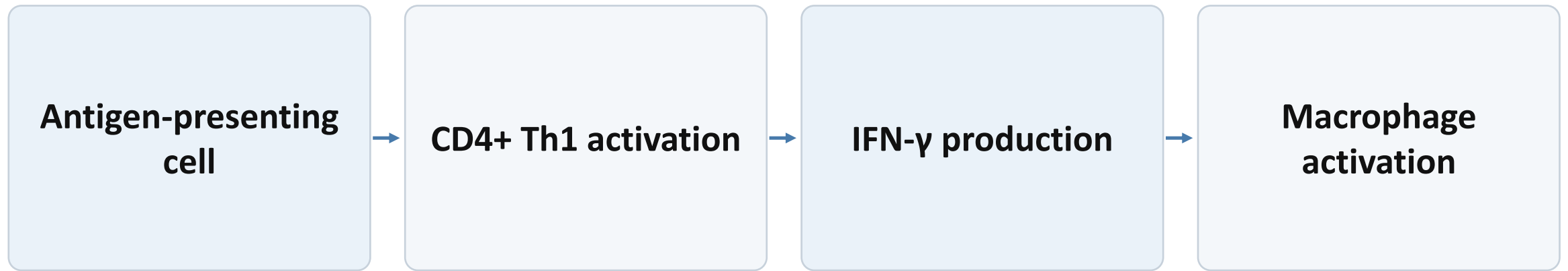
CD4+ inflammation or CD8+ target-cell killing

T lymphocytes—not deposited immune complexes or mast-cell IgE—are the defining pathogenic effectors.

Type IV branches into inflammation and cytotoxicity

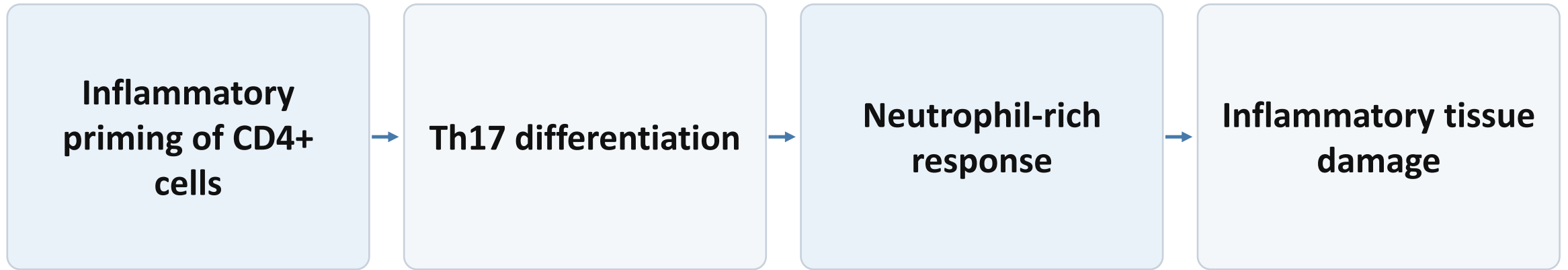


Th1 cells promote macrophage-dominated injury



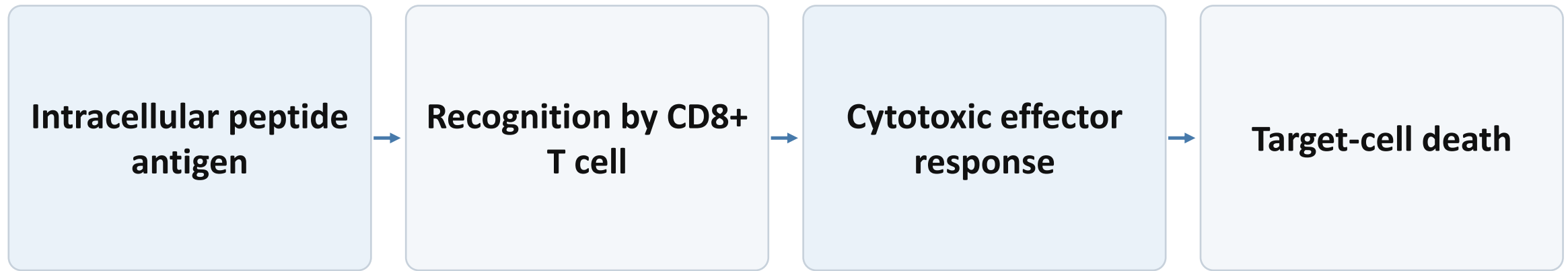
Persistent macrophage-rich inflammation can become tissue destructive.

Th17 responses preferentially recruit neutrophils



Type IV is not restricted to mononuclear infiltrates; Th17 responses add neutrophils.

CD8+ cytotoxic lymphocytes destroy target cells



This arm can dominate in selected autoimmune and virus-associated injury patterns.

Delayed-type hypersensitivity is a Type IV prototype

Clinical time course

A previously sensitized person develops a detectable skin response after antigen challenge, typically in 24–48 hours.

Mechanistic substrate

Antigen-specific T cells produce cytokines that recruit and activate inflammatory cells.

The “delay” reflects a cellular response.

Type IV generates different tissue patterns

Cytokine-mediated reaction

Perivascular infiltrates, tissue edema and chronic inflammatory injury; Macrophage activation may produce granulomas.

Cytotoxic reaction

Direct target-cell destruction by antigen-specific CD8+ T lymphocytes; Organ dysfunction follows cell loss.

Type IV prototypes represent different T-cell effects

Prototype	Primary tissue manifestation	Characteristic response
Contact dermatitis	Cutaneous cellular inflammation	Delayed T-cell skin reaction
Tuberculosis	Cell-mediated chronic inflammation	Granulomatous immune response
Type 1 diabetes	Islet-cell injury	T-cell-associated cell destruction
Multiple sclerosis	CNS inflammatory demyelination	T-cell-associated immune injury

Granulomas can result from persistent T-cell activation

Macrophage accumulation and organization

Some Type IV responses become granulomatous when cytokine-driven macrophage activation persists, as in tuberculosis. Granulomas are not obligatory in every Type IV disease.

Type IV differs from the antibody-associated classes

Primary effector

Antigen-specific CD4+ / CD8+ T lymphocytes and their cytokine or cytotoxic programs.

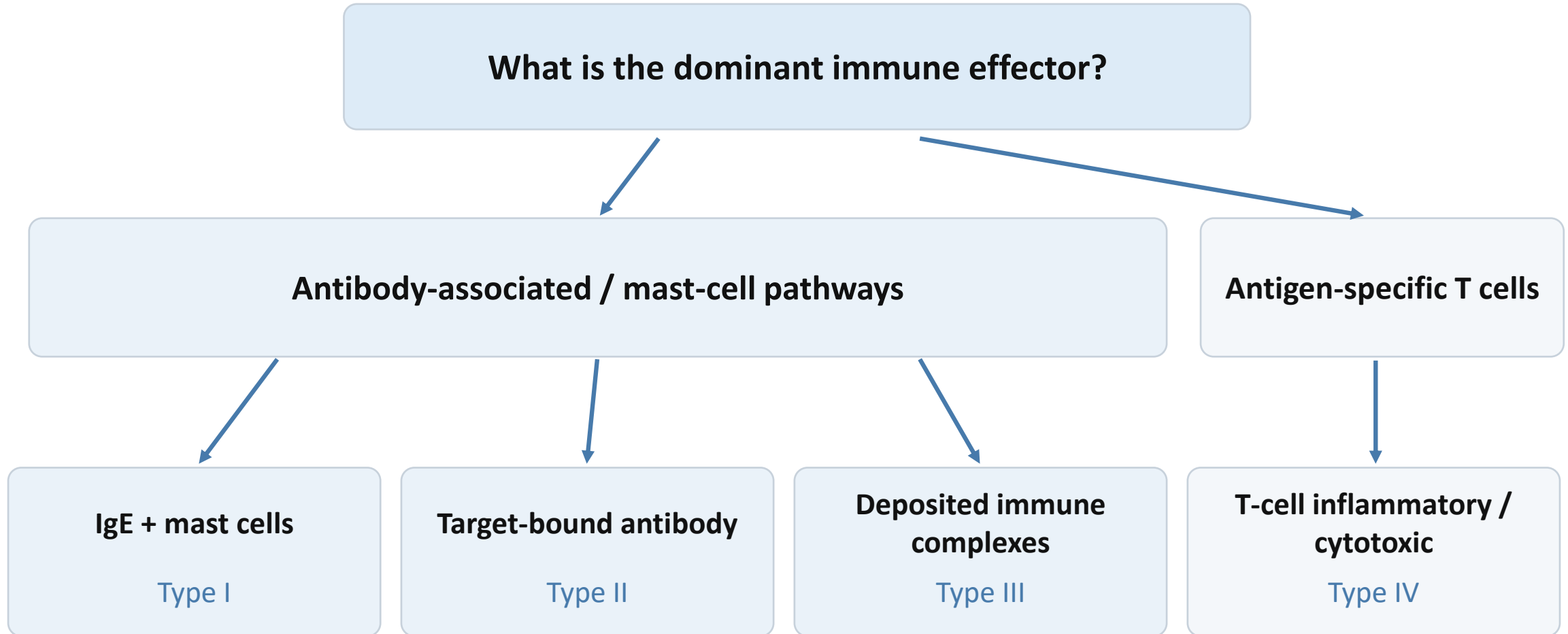
Typical pathology

Cellular inflammation, macrophage activation, granulomas or direct parenchymal cell destruction.

Diagnostic morphology: Compare the likely lesion

Type	Pathologic clue	How to interpret it
I	Edema, mucus, eosinophilic inflammation	Mediator-induced tissue reactions
II	Cell loss, tissue inflammation or normal morphology despite dysfunction	Direct target-specific antibody effects
III	Vascular inflammation, fibrinoid necrosis	Deposited complex-triggered inflammation
IV	Cellular infiltrates, granulomas, cell death	T-cell cytokines and cytotoxicity

Mechanistic classification: A practical reasoning tree



Dominant mechanism guides classification; Individual diseases may show overlap.

Applied case: Abrupt systemic allergic response

Clinical vignette

Minutes after a relevant exposure, a sensitized patient develops urticaria, bronchospasm and hypotension.

Decisive mechanistic clues

Rapid onset; Vascular leakage; Airway smooth-muscle contraction.

Classification and justification

Type I. IgE-bound mast cells release mediators that affect vessels and smooth muscle.

Applied case: Antibody-directed cell clearance

Clinical vignette

A patient develops hemolysis associated with antibodies recognizing erythrocyte surface antigens.

Decisive mechanistic clues

Target antigen resides on the red cell; Coated circulating cells are removed.

Classification and justification

Type II. IgG and/or complement opsonization promotes RBC destruction.

Applied case: Immune complex–associated nephritis

Clinical vignette

A patient with a compatible systemic immune response develops glomerular inflammation and immune complex deposition.

Decisive mechanistic clues

Antigen–antibody complexes localize in glomeruli and recruit inflammation.

Classification and justification

Type III. Deposited complexes activate complement and inflammatory leukocytes.

Applied case: Delayed contact reaction

Clinical vignette

A previously sensitized patient develops an inflamed skin lesion a day or two after renewed contact with an antigen.

Decisive mechanistic clues

Delayed cellular inflammatory reaction;
Antigen-specific T-cell effectors.

Classification and justification

Type IV. Sensitized T lymphocytes generate a delayed inflammatory response.

One disorder may recruit several hypersensitivity pathways

The four classes are explanatory models

That multiple immune mechanisms can operate in a single disease. Classification should identify the dominant demonstrated pathway rather than enforce artificial exclusivity.

Final synthesis: Effector, lesion and prototype

Class	Key effector	Signature lesion	Illustrative disorder
I	IgE / mast cells	Edema + smooth-muscle effects	Anaphylaxis / atopy
II	Target-specific IgG ($\pm$ IgM)	Cell loss / inflammation / dysfunction	Hemolytic anemia / Graves
III	Deposited IgG complexes	Complement-mediated inflammation	SLE / serum sickness
IV	CD4+ / CD8+ T cells	Cellular inflammation / cell killing	Contact dermatitis / TB

Four questions to test mechanistic understanding

- Is the initiating antibody IgE on mast cells—or does it bind a fixed cellular antigen?
- Are antigen–antibody complexes depositing in a tissue rather than binding a fixed target?
- Is tissue injury dominated by CD4+ inflammatory responses or CD8+ cytotoxic cells?
- Can more than one mechanism plausibly contribute to this disease phenotype?

Core reference and scope of this lecture

Robbins, Cotran & Kumar

Pathologic Basis of Disease · 11th edition (2026)

Chapter 6: Diseases of the Immune System

Classification and Table 6.1: pp. 181–182; mechanism discussion: pp. 182–190