

# Systemic Immune Complex Disease

Type III hypersensitivity • serum sickness • tissue injury

Pathogenesis, morphologic correlates and clinical interpretation

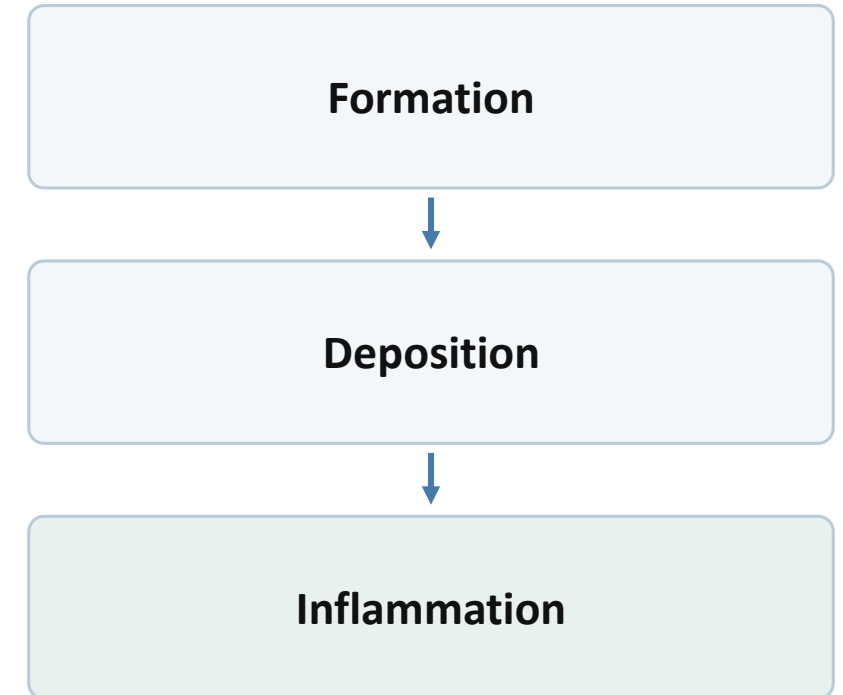
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# Learning objectives

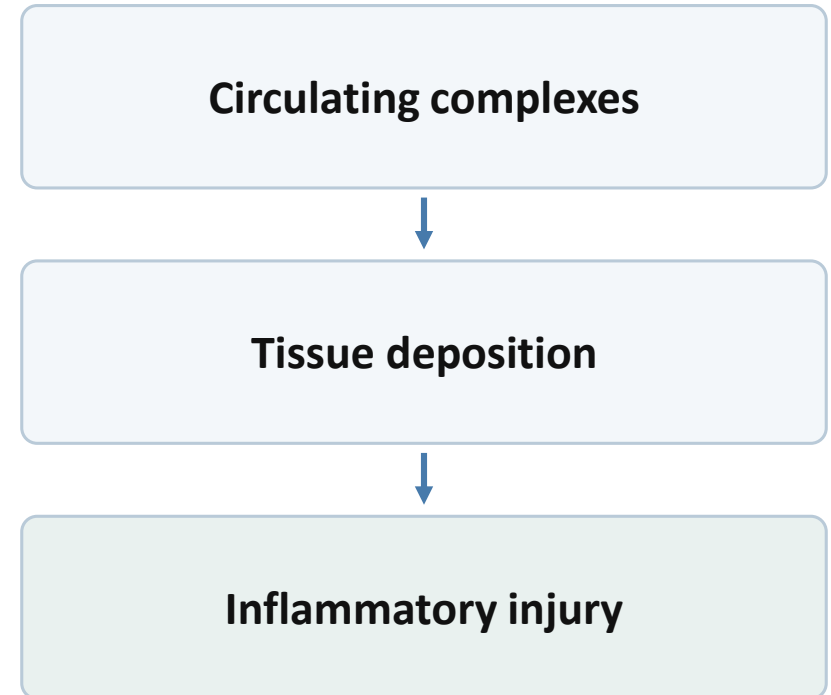
- Describe how circulating antigen–antibody complexes produce type III tissue injury.
- Explain the three phases of systemic immune complex disease and organ predilection.
- Relate complement consumption, vascular injury, and morphology to clinical findings.
- Distinguish self-limited serum sickness from persistent immune complex disorders.



*Organ injury and clinical manifestations*

## Type III hypersensitivity is a deposition-driven lesion

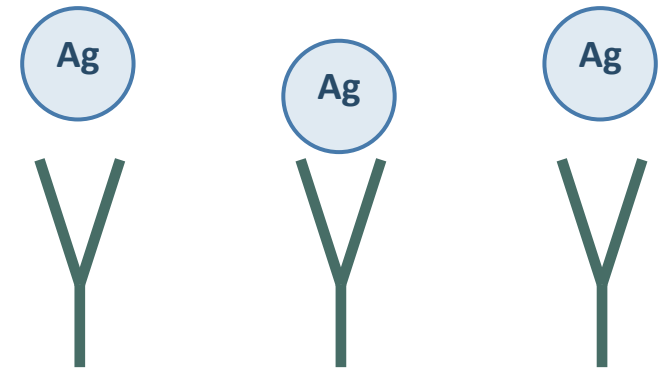
- Antigen–antibody complexes, usually containing IgG, initiate inflammation after depositing in tissue.
- Complexes most often form in blood and subsequently localize to vessel walls.
- The dominant injury is inflammatory—not simply the presence of antibody in plasma.



*Pathogenicity depends on location and host response*

# The immune complex has two essential components

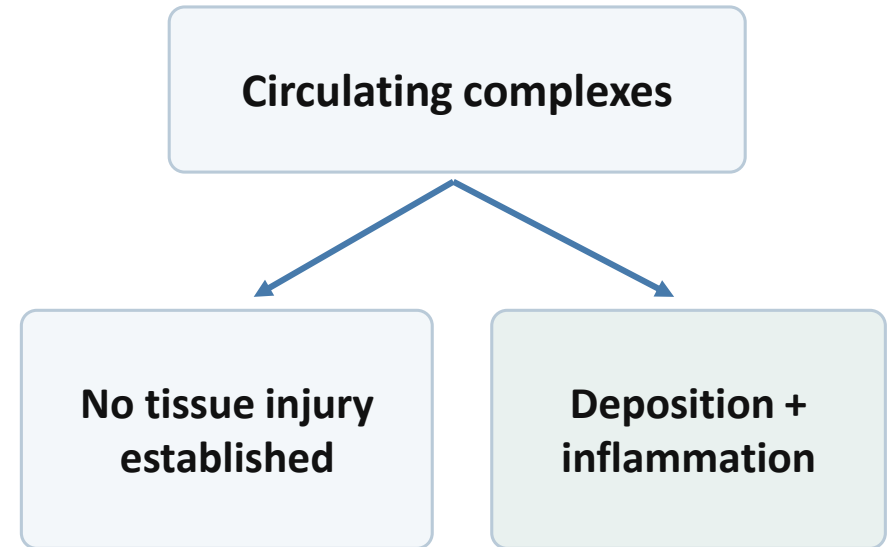
- Antigen provides the molecular target for antibody binding.
- Antibody binds antigen to create a multicomponent immune complex.
- The resulting complexes can circulate and, under certain conditions, deposit in tissues.



*Schematic antigen–IgG association (not to molecular scale)*

# Why immune complex formation is not always disease

- The relevant transition is from soluble complexes to tissue deposition with inflammation.
- Whether formed complexes deposit is influenced by complex properties and local vascular factors.
- These determinants are incompletely understood; Formation alone does not prove pathogenic injury.



*Not every circulating complex causes disease*

# Type III injury differs from direct antibody targeting

## Type II pattern

Antibody binds a fixed target

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Injury/dysfunction at the target

## Type III pattern

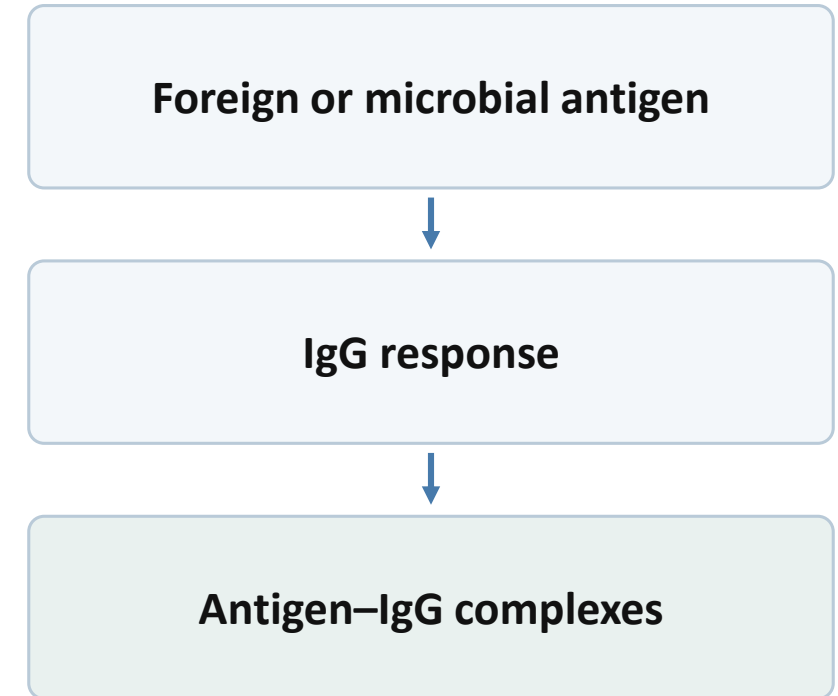
Complexes form with soluble antigen

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Deposits incite inflammation

# Exogenous antigens can trigger systemic disease

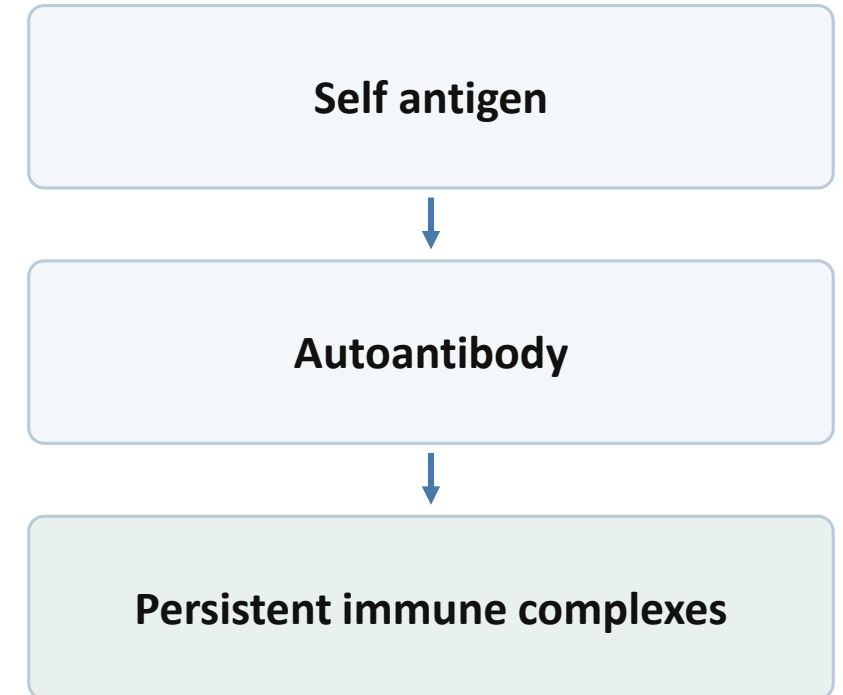
- Foreign proteins introduced into the body can provoke an antibody response.
- Microbial antigens also participate in selected immune complex disorders.
- An external antigen is pathogenic in this model when it persists and encounters specific antibody.



*Exogenous antigen source*

# Endogenous antigens can sustain complex formation

- Autoantigens become complex-forming targets when self-reactive antibodies are produced.
- Persistent autoantigen exposure supports continued formation of complexes.
- Systemic lupus erythematosus is a paradigmatic chronic autoimmune setting.



*Autoimmunity can maintain antigen–antibody exposure*

# Most complexes form in blood—not necessarily at the lesion

## Circulating formation

Antigen + IgG in bloodstream

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Complex later deposits in vessel/tissue

## In situ formation

Antigen localized in tissue first

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Antibody binds locally

# Systemic disease still has preferred target organs

- Small blood vessels are common deposition sites: Vasculitis.
- Glomeruli are vulnerable: Glomerulonephritis.
- Joint structures are vulnerable: Arthritis or arthralgia.

**Small vessels**

**Vasculitis**

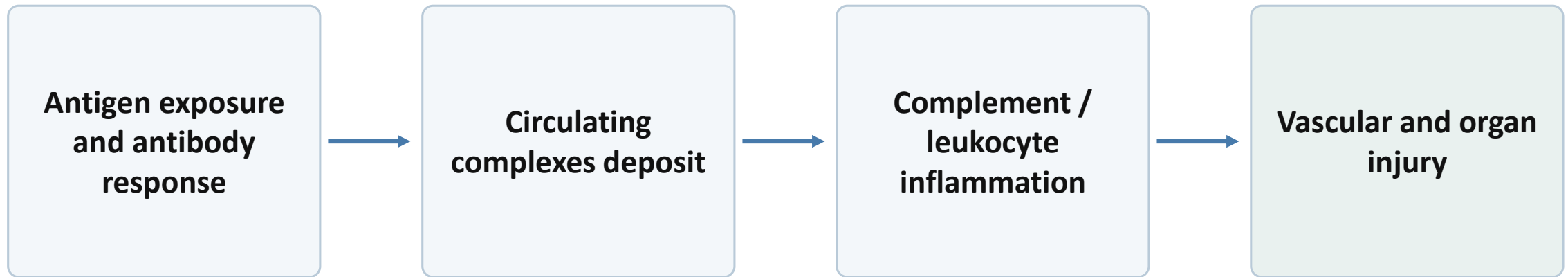
**Kidney**

**Glomerulonephritis**

**Joints**

**Arthritis / arthralgia**

## The three phases form one causal sequence

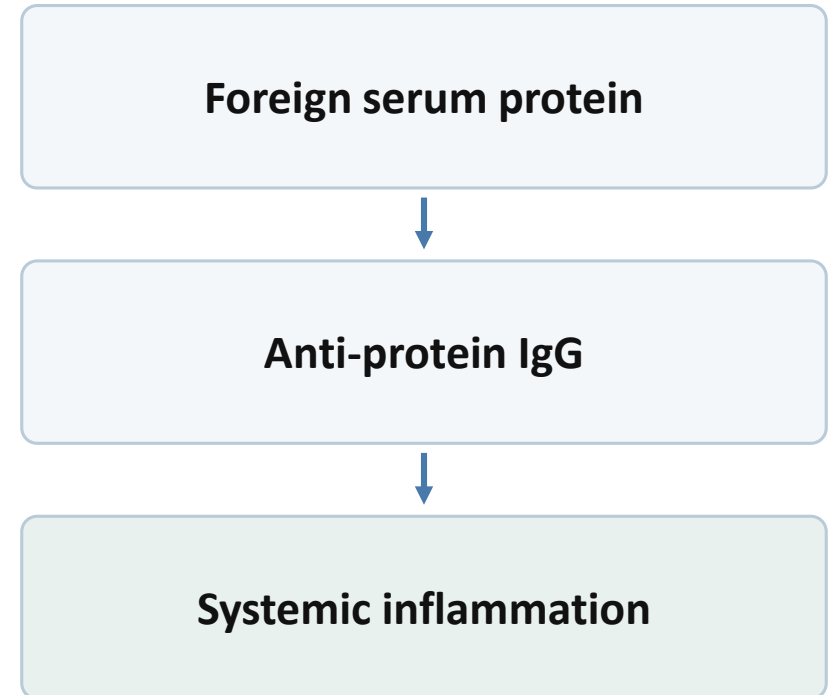


The same mechanism connects a delayed immune response to tissue-specific clinical findings.

*Schematic causal sequence*

# Serum sickness is the experimental and clinical prototype

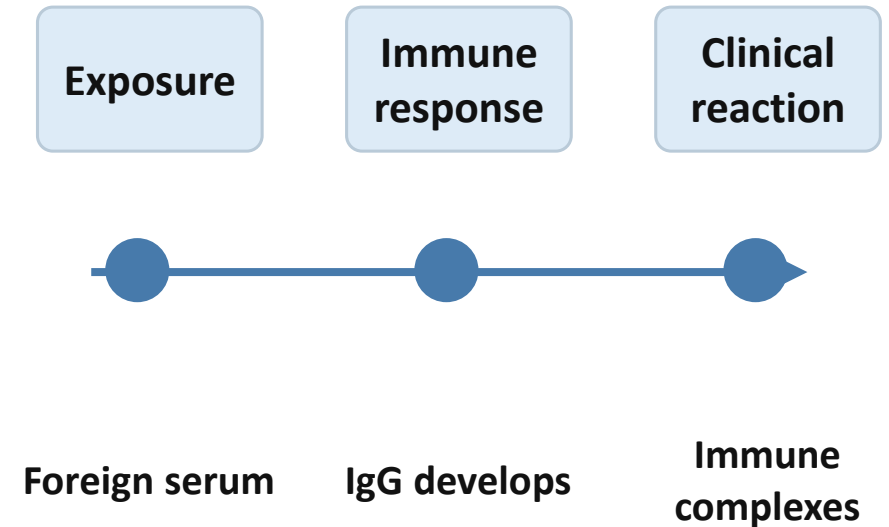
- Classic serum sickness followed exposure to large amounts of foreign serum proteins.
- The model is especially useful because the order of antigen exposure, antibody formation, and injury is clear.
- The model illustrates systemic type III hypersensitivity; It is not synonymous with every chronic immune complex disorder.



*Prototype: Serum sickness*

# Historical serum therapy revealed the syndrome

- Foreign serum from immunized horses was once used to prevent infections such as diphtheria.
- Recipients could subsequently develop serum sickness.
- The history establishes the antigenic trigger; It does not imply that the original infection caused the immune complexes.



# Modern serum sickness is relatively infrequent

- Modern serum sickness as uncommon.
- The discussion emphasizes exposures to antibodies obtained from other individuals or species.
- A history of relevant protein/antibody exposure provides etiologic context.

**Administered foreign protein**



**Host antibody response**

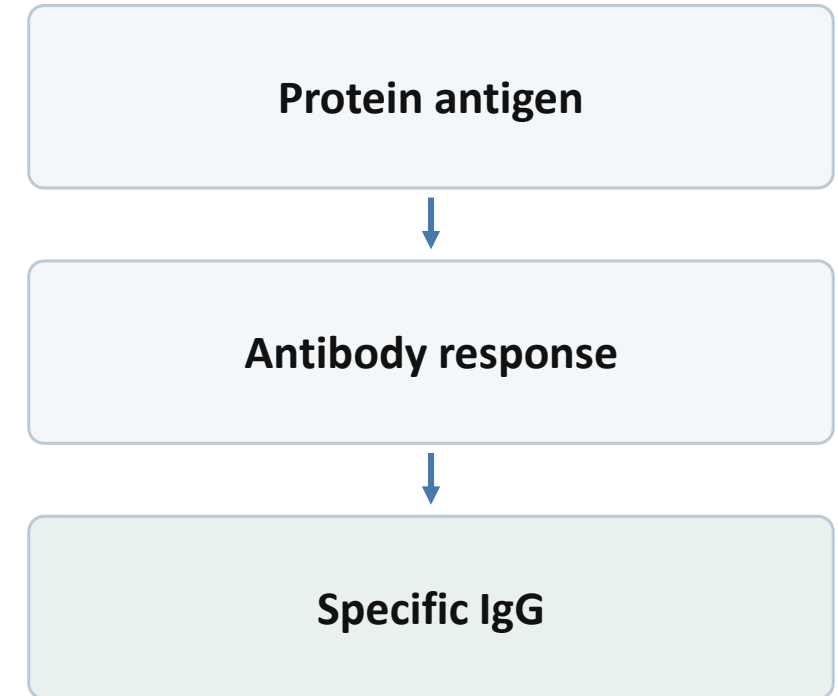


**Immune complexes**

*Source-derived clinical context; No frequency estimate inferred*

# Phase I: Antigen initiates a specific humoral response

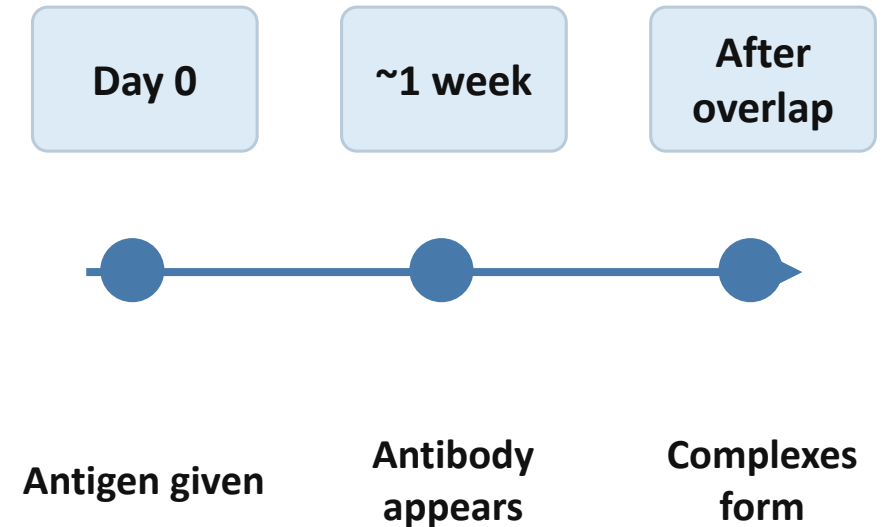
- The sequence begins when a protein antigen enters the host.
- Antigen exposure elicits production of antibodies directed against that protein.
- Complexes form only when sufficient antibody and persisting antigen overlap in time.



*Phase I — formation*

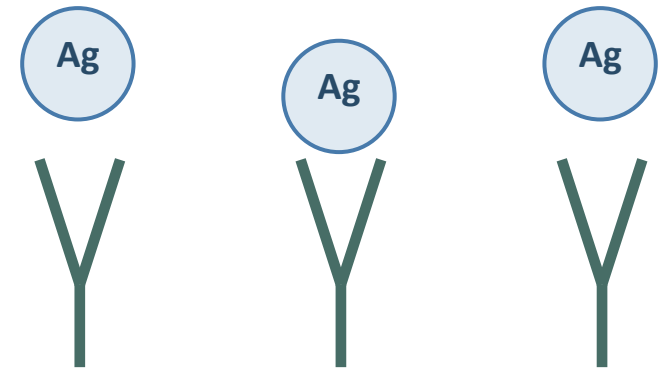
# The first antibody response requires an interval

- In the prototype, antibodies typically appear about one week after protein injection.
- This delay separates exposure from subsequent immune-complex formation.
- The timing describes the model, not an invariant latency for every patient or re-exposure.



# Persistent antigen permits antigen–antibody overlap

- Antigen may remain in circulation while the new antibody response develops.
- Newly secreted antibody then reacts with residual circulating antigen.
- The coexistence of antigen and antibody permits soluble complexes to assemble.

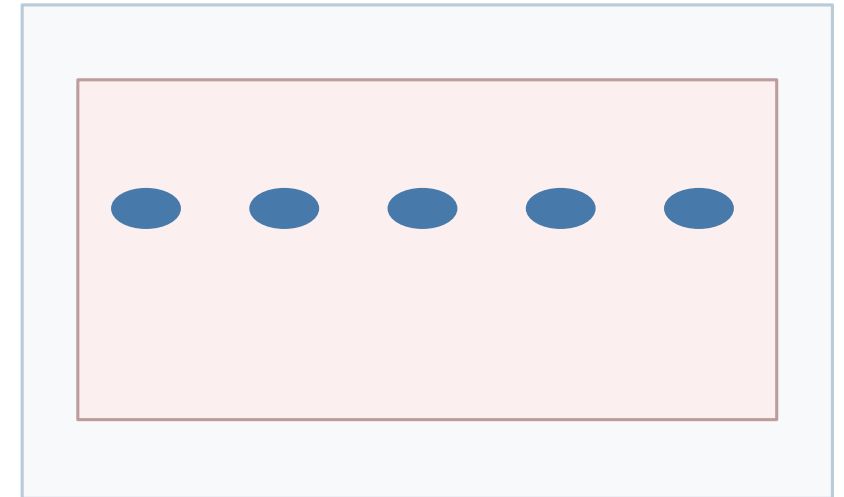


*Antigen persistence permits binding by newly produced IgG*

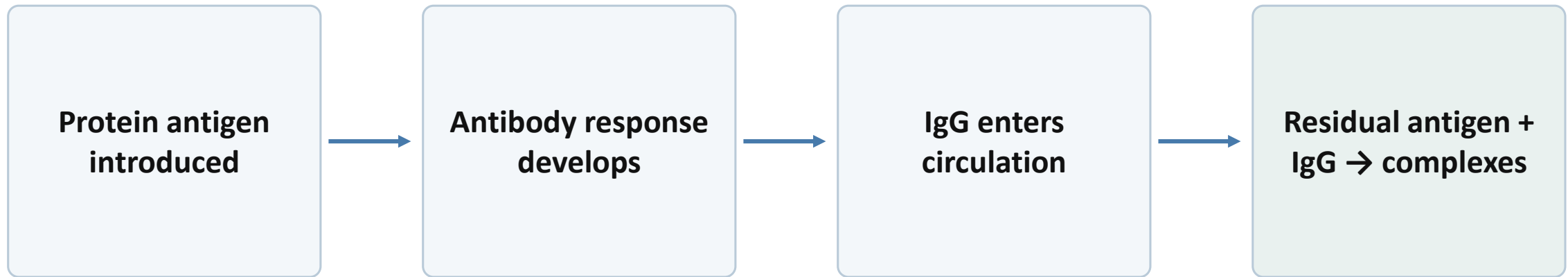
# Plasma antibodies encounter antigen in the circulation

- Antibodies are secreted into blood and bind their cognate circulating antigen.
- The resulting antigen–antibody complexes are not restricted to their site of entry.
- Circulatory distribution makes injury possible in more than one organ.

**Circulating antigen–antibody complexes**



## Phase I can be summarized as an exposure–response overlap



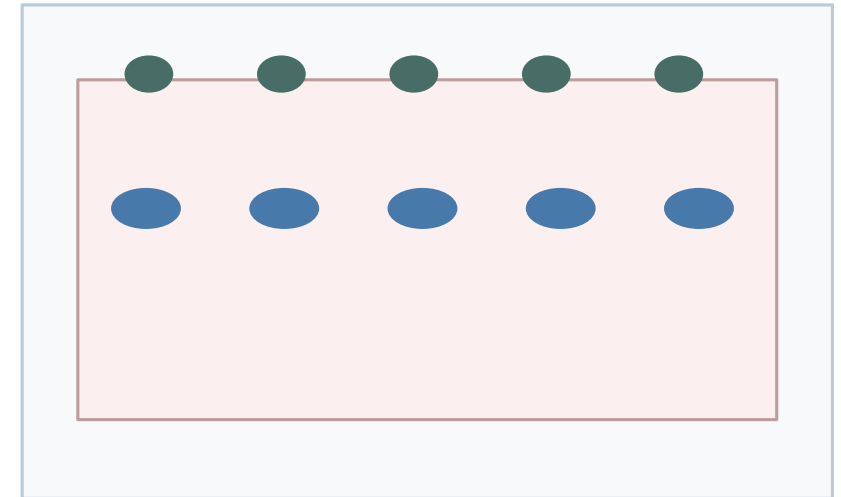
**A delayed antibody response explains why systemic signs follow, rather than coincide with, first antigen exposure.**

*Schematic causal sequence*

## Phase II: Deposits form from circulating complexes

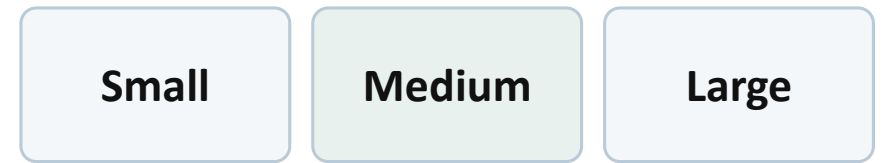
- Complexes formed in the blood may lodge in vessel walls.
- Deposition is a separate event from initial antigen–antibody binding.
- Tissue-specific localization helps explain the organ pattern of disease.

Immune complex deposition at vessel wall



# Medium-sized immune complexes are especially implicated

- Medium-sized complexes as relatively pathogenic.
- The relationship is a source-described tendency rather than a numerical size cutoff.
- Complex size contributes to deposition risk but does not independently predict disease.



Not singled out

Relatively  
pathogenic

Not singled out

*Qualitative pattern; No numerical size boundaries given*

## Slight antigen excess favors the pathogenic pattern

- Medium-sized complexes formed with slight antigen excess are described as especially pathogenic.
- The relative antigen–antibody balance influences complex characteristics.
- Do not substitute an arbitrary antigen:antibody ratio; None is specified in the source.

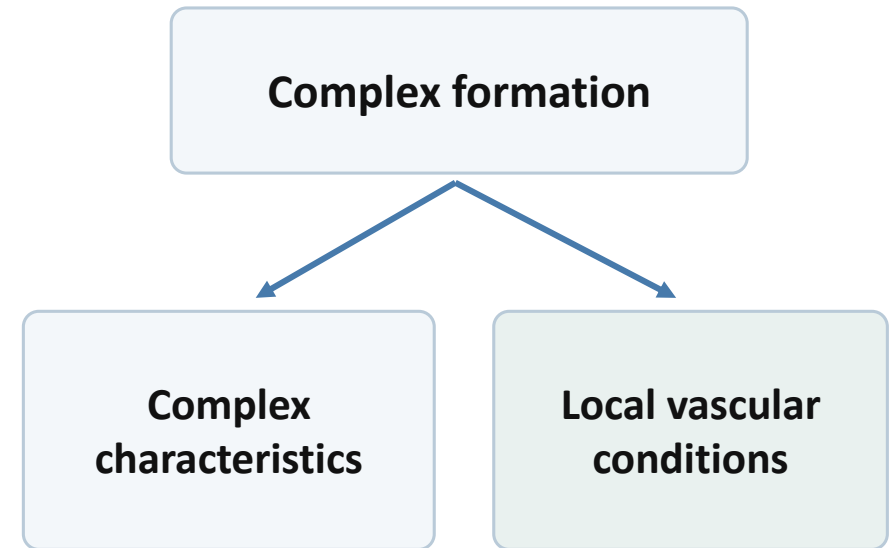


**Slight antigen excess**

*Context in which medium complexes are pathogenic*

# Depositional behavior is incompletely explained

- Why some immune complexes cause tissue disease is not fully understood.
- Complex characteristics and vascular alterations as major influences.
- Simple detection of immune complexes is therefore insufficient for an organ diagnosis.

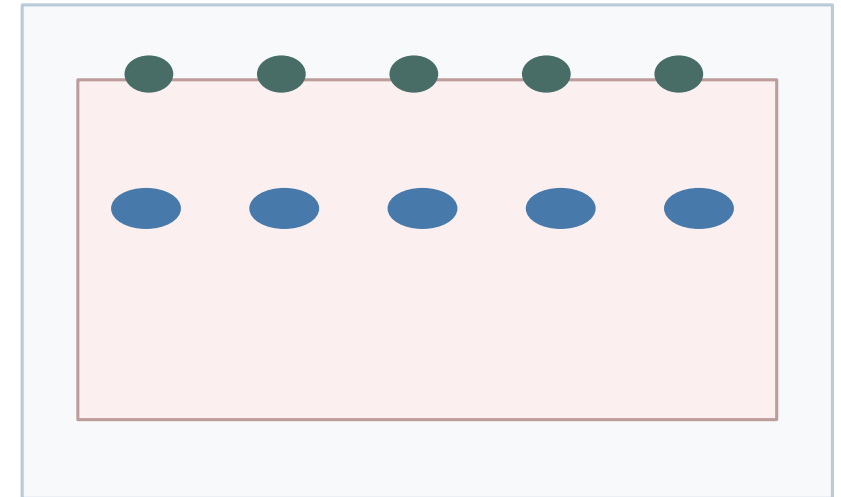


*Both influence likelihood and sites of deposition*

## Local vascular conditions modify where deposition occurs

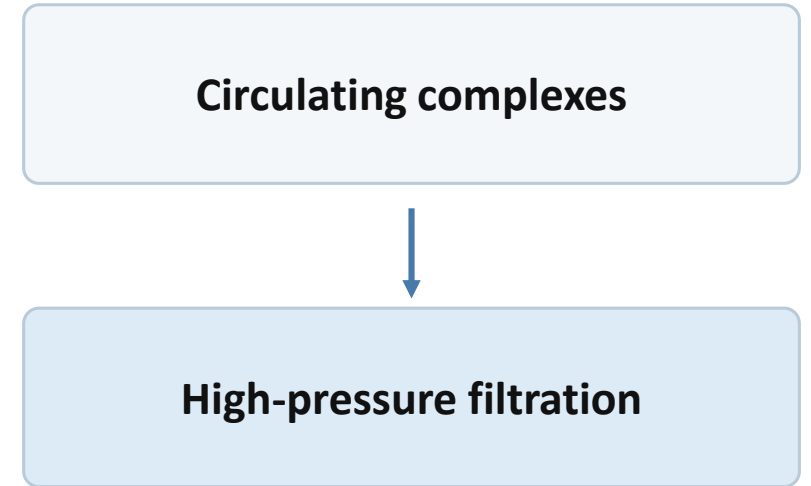
- The vessel environment contributes to trapping or retention of complexes.
- Vascular factors act alongside the properties of the complexes.
- This helps explain why the circulating trigger can yield focal or organ-predominant injury.

Immune complex deposition at vessel wall



# Filtration concentrates complexes at selected sites

- High-pressure filtration can concentrate circulating complexes locally.
- Kidney glomeruli filter blood to form urine.
- Joint environments associated with synovial fluid production are another common target.

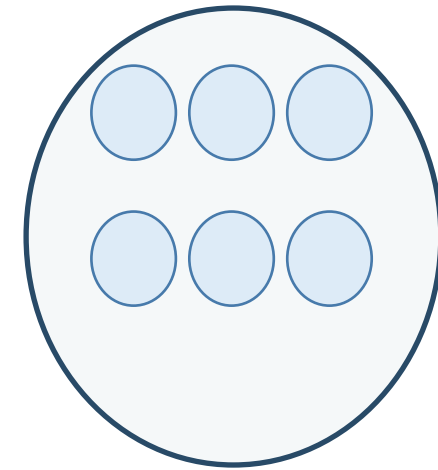


**Glomeruli • Joint environments**

# Glomerular involvement follows renal filtration

- Glomeruli are exposed to circulating complexes in a high-pressure filtering bed.
- Deposition can provoke inflammation within glomerular structures.
- The clinicopathologic result may be nephritis and abnormal protein leakage into urine.

**Glomerular capillary tuft**



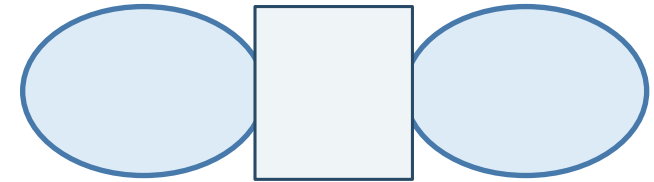
**Complex deposition → nephritis /  
proteinuria**

*Simplified conceptual schematic—not renal  
histology*

# Synovial involvement explains joint symptoms

- Complex deposition can occur at joints, another favored site.
- Local inflammation produces joint pain and can manifest as arthritis.
- Articular symptoms in systemic serum sickness belong to the same process as nephritis.

**Joint / synovial region**



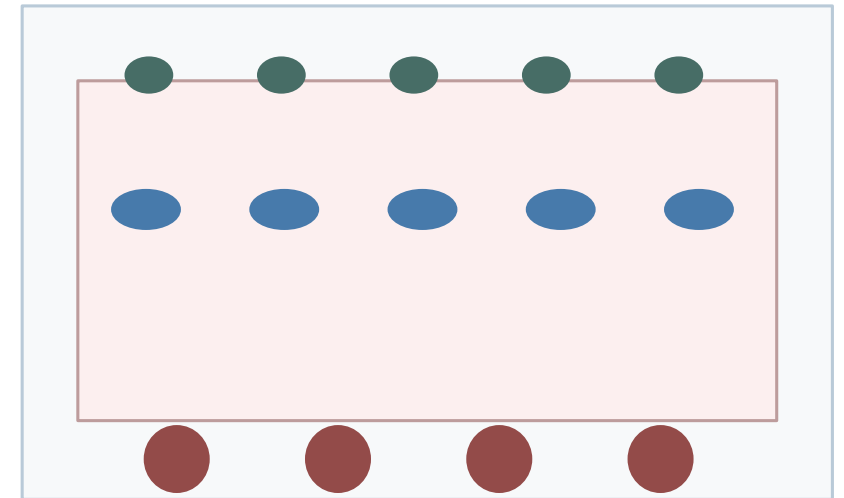
**Local complex-associated  
inflammation**

*Schematic only; Not anatomical scale*

# Small vessels express the vascular lesion

- Vessel walls commonly accumulate deposited complexes.
- Immune-complex inflammation can injure the wall, producing vasculitis.
- A vascular lesion provides a common mechanism linking several systemic manifestations.

**Vessel-wall inflammation**



*Schematic vessel section; Not histology*

# Organ predilection does not mean organ exclusivity

- Kidney, joints, and small blood vessels as common sites—not the only sites.
- The relative distribution of deposits determines the clinical pattern.
- The same antigenic trigger can therefore be associated with multiple affected tissues.

**Small vessels**

**Vasculitis**

**Kidney**

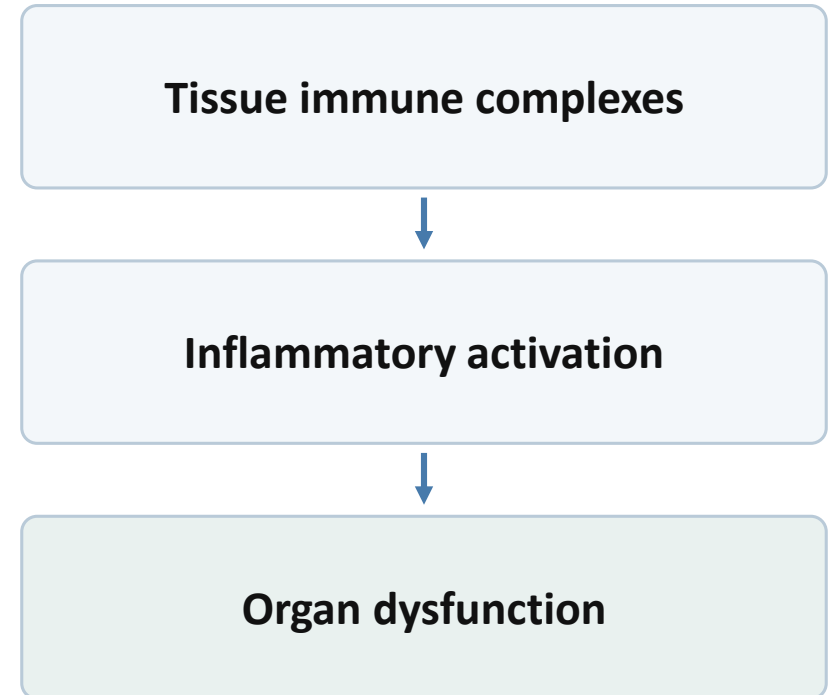
**Glomerulonephritis**

**Joints**

**Arthritis / arthralgia**

## Phase III begins after complexes deposit in tissues

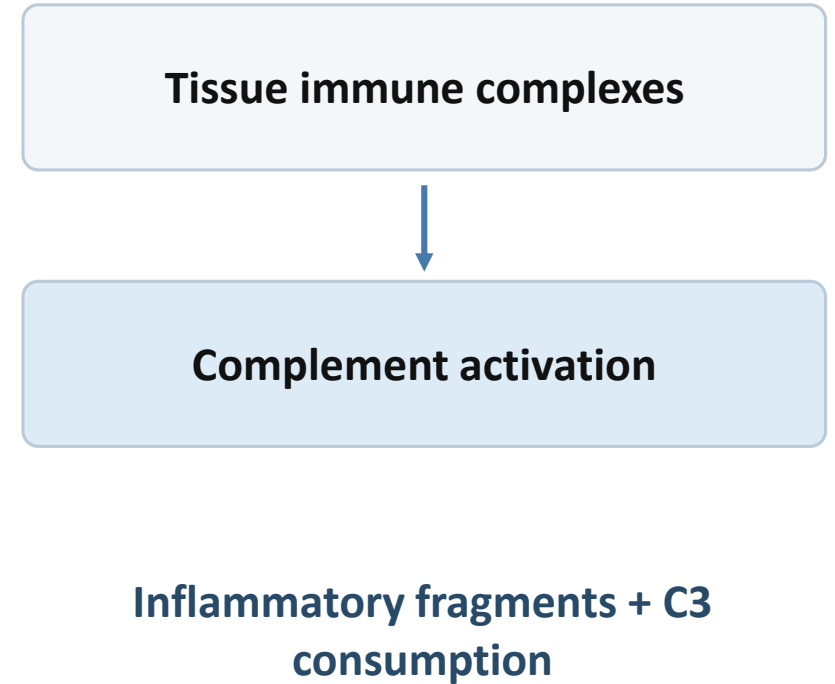
- Deposited antigen–antibody complexes initiate acute inflammation.
- Complement and leukocyte-mediated mechanisms turn deposits into damage.
- Clinical illness follows the local tissue reactions rather than simple antigen exposure.



*Phase III — inflammation and injury*

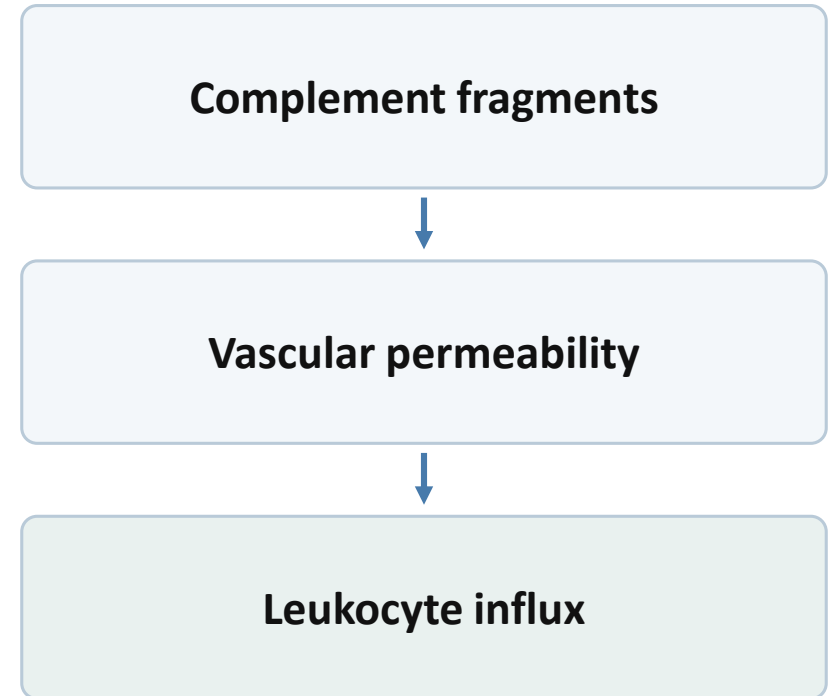
# Complement is a central inflammatory amplifier

- Complement components are detectable at sites of immune complex injury.
- Activation supplies mediators that promote inflammatory cell recruitment and vascular change.
- Consumption of complement during active disease helps explain reduced circulating C3.



## C3a and C5a contribute to vascular inflammation

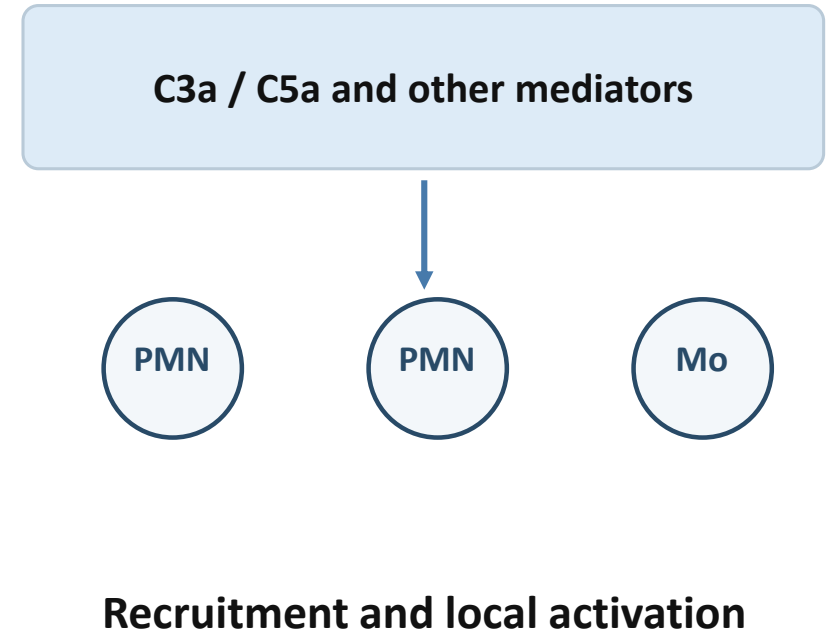
- The related antibody-mediated inflammation section identifies C3a and C5a as anaphylatoxins.
- These fragments increase vascular permeability; Complement products also recruit leukocytes.
- Greater permeability and cell influx intensify inflammation at injured vessels.



*Shared complement mechanism in antibody-mediated tissue injury*

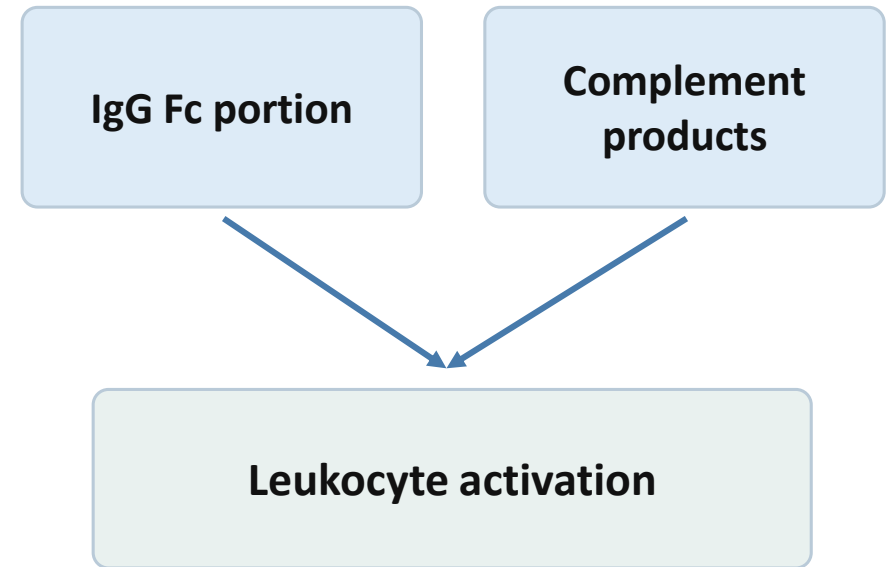
# Neutrophils and monocytes are effector cells

- Complement-derived mediators recruit granulocytes and monocytes.
- These cells accumulate near deposited immune complexes.
- Cellular activation transforms the site into an acute inflammatory focus.



# Fc and complement receptors activate recruited cells

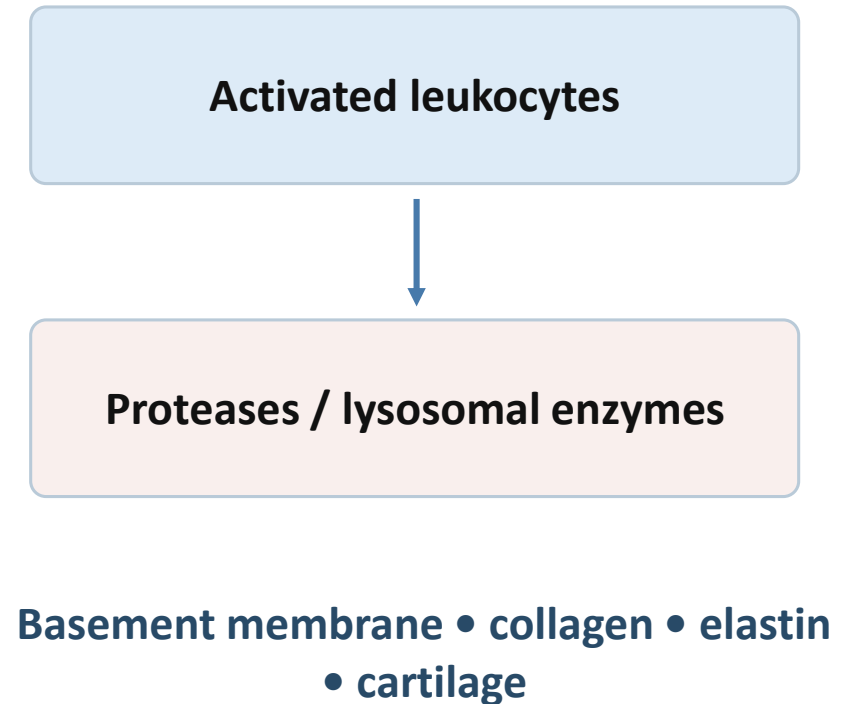
- Leukocytes respond to antibodies via Fc receptors.
- Complement receptor engagement supplies an additional activation route.
- Together these signals promote release of injurious inflammatory products.



*Both receptor routes can participate in injury*

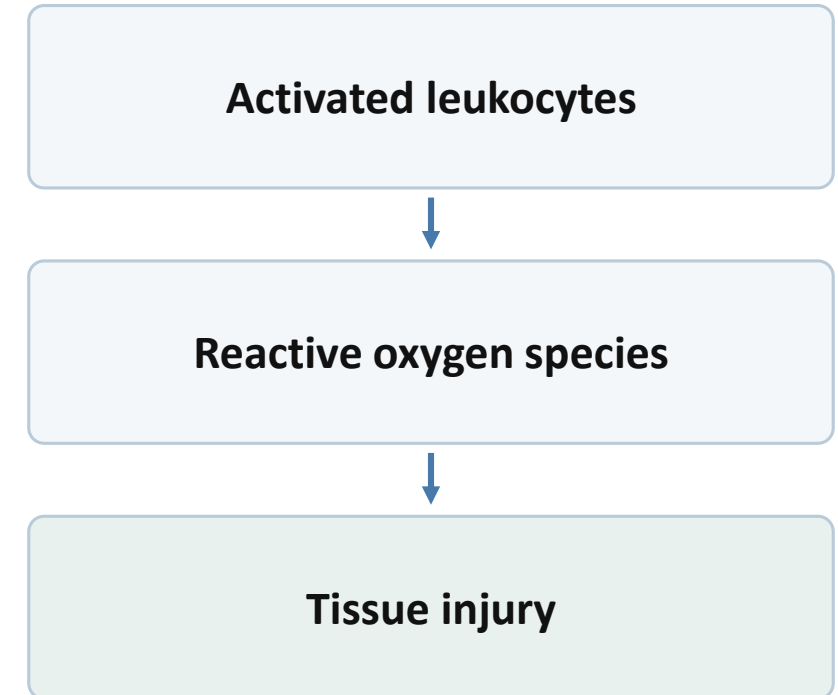
# Lysosomal enzymes directly damage tissue scaffolds

- Activated leukocytes release lysosomal enzymes and proteases.
- These enzymes can digest basement membrane, collagen, elastin, and cartilage.
- Destruction of extracellular structures explains structural tissue injury at inflamed sites.



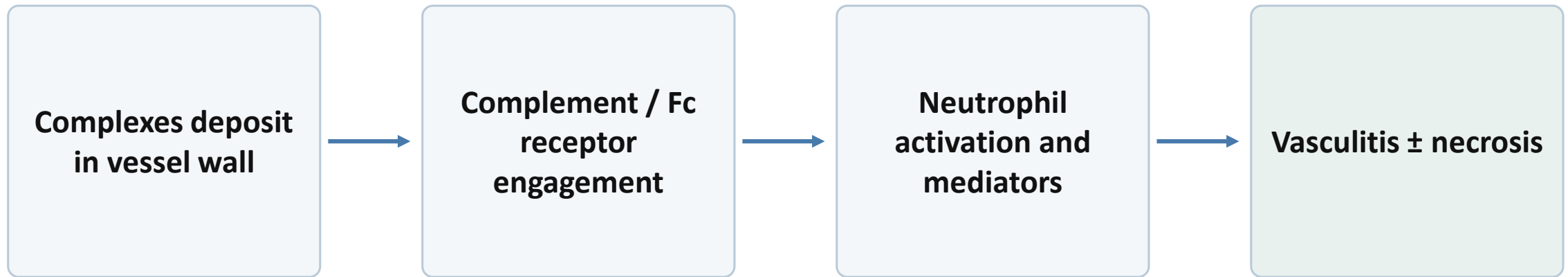
# Reactive oxygen species add tissue toxicity

- Activated inflammatory leukocytes generate reactive oxygen species.
- These mediators contribute to tissue injury after immune complex deposition.
- The injury is therefore mediated by host effectors rather than physical bulk of the deposits alone.



*A host-mediated effector mechanism*

# Deposits drive a vascular inflammatory sequence



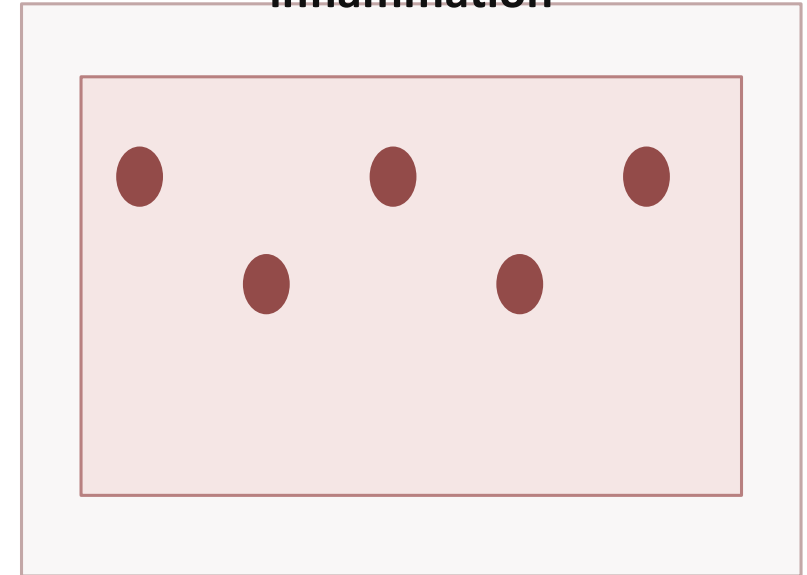
**The deposition site is the site at which inflammatory injury becomes anatomically manifest.**

*Schematic causal sequence*

# Acute vasculitis is the central tissue pattern

- The morphology section identifies acute vasculitis as the principal immune complex lesion.
- Vessel walls may show necrosis with intense neutrophilic inflammation.
- The histologic pattern should be linked to the site of antibody/complement deposition.

## Neutrophil-rich vascular inflammation

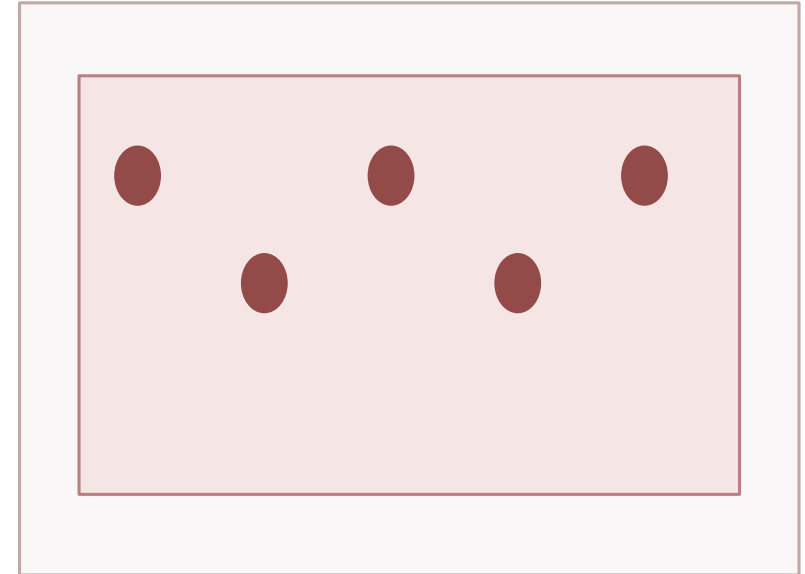


*Conceptual vessel-wall schematic—not H&E evidence*

# Fibrinoid necrosis reflects vessel-wall destruction

- Necrotic tissue is admixed with immune complexes, complement, and plasma proteins.
- The result is a smudgy eosinophilic appearance termed fibrinoid necrosis.
- This term describes an observed morphologic pattern, not a unique antigen.

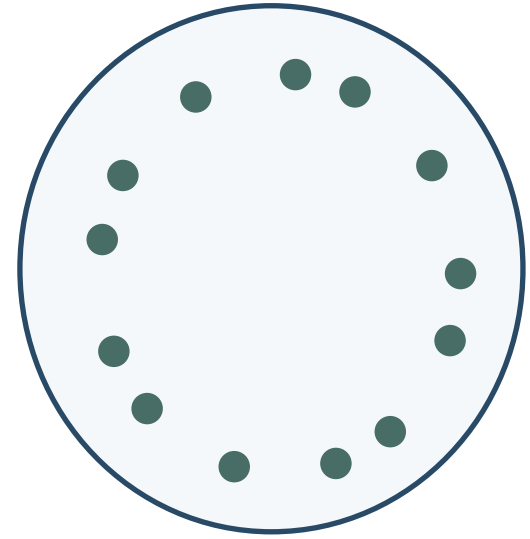
## Fibrinoid necrosis



*Conceptual vessel-wall schematic—not H&E evidence*

# Immunofluorescence demonstrates granular deposits

- In the kidney, immune complex deposits may appear as granular immunoglobulin and complement staining.
- The granular pattern supports a deposited-complex mechanism.
- A schematic cannot replace diagnostic immunofluorescence on an actual biopsy.



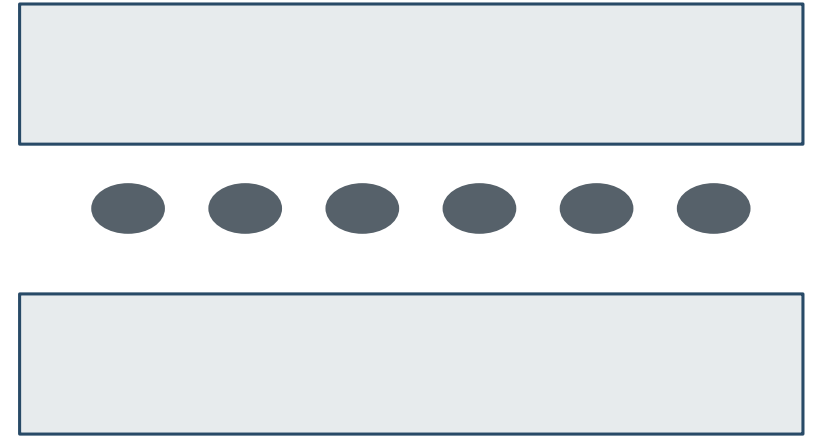
**Granular Ig / complement deposits**

*Schematic only—not an IF micrograph*

# Electron microscopy locates dense deposits

- Immune complexes may be visible as electron-dense deposits along the glomerular basement membrane.
- Ultrastructural demonstration provides anatomic evidence of deposited material.
- The source supplies no specific distribution subtype to infer for all systemic immune complex diseases.

**Glomerular basement membrane region**



**Electron-dense material**

*Conceptual depiction—not electron microscopy*

# Morphologic diagnosis integrates several observations

## Light microscopy

Vasculitis and wall necrosis

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Inflammatory tissue reaction

## IF / EM

Granular Ig + complement; Dense deposits

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Depositional evidence

# The clinical syndrome reflects multisite inflammation

- Systemic immune complex injury can cause fever, urticaria, joint pain, and lymph node enlargement.
- Proteinuria signals possible glomerular involvement.
- These manifestations arise during the inflammatory phase rather than as immediate direct toxicity of antigen.

**Small vessels**

**Vasculitis**

**Kidney**

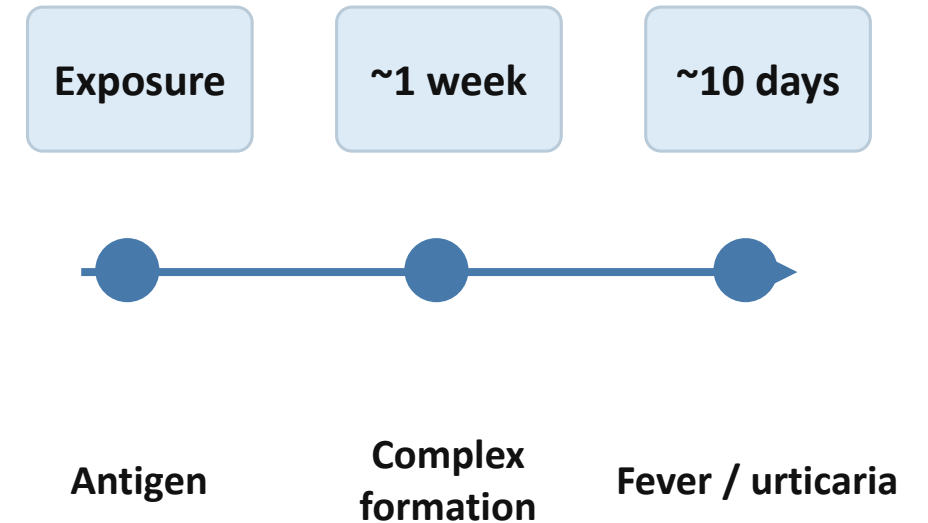
**Glomerulonephritis**

**Joints**

**Arthritis / arthralgia**

# Fever and urticaria are part of acute serum sickness

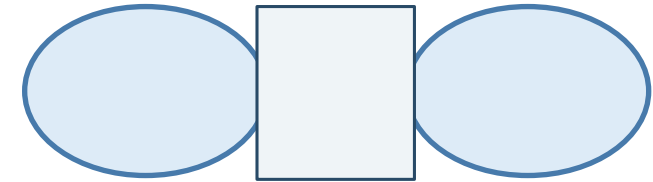
- Fever accompanies the systemic inflammatory phase.
- Urticaria is among the cutaneous manifestations.
- Their co-occurrence with joint or renal signs strengthens the multiorgan pattern.



# Joint pain reflects inflammatory localization

- Arthralgia occurs as immune complex-mediated inflammation affects joint tissues.
- Immune complex deposition provides a mechanistic link to the systemic syndrome.
- The prototype may involve joint pain together with vascular or glomerular abnormalities.

**Joint / synovial region**

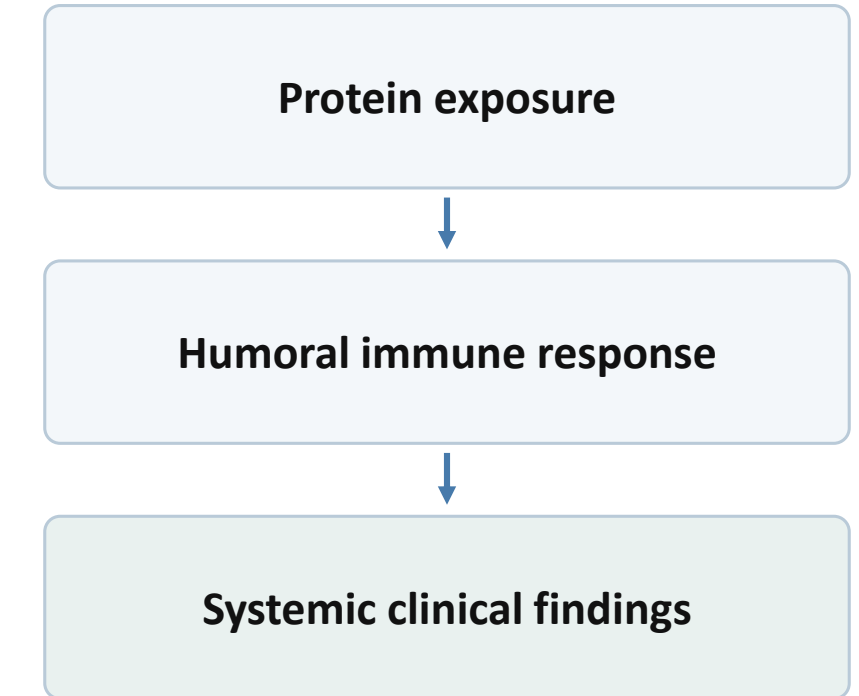


**Local complex-associated  
inflammation**

*Schematic only; Not anatomical scale*

# Lymph node enlargement occurs with the systemic response

- Lymphadenopathy is included among the acute inflammatory clinical features.
- It should be interpreted in conjunction with exposure timing and other manifestations.
- It is not a specific morphologic test for immune complex deposition.

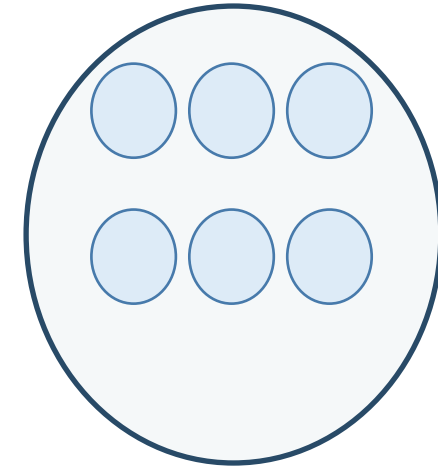


*Lymphadenopathy is a syndrome component, not proof alone*

# Proteinuria connects disease to glomerular injury

- Glomerular immune complex deposition can elicit nephritic inflammation.
- Proteinuria is specifically listed among clinical findings during the inflammatory phase.
- The source does not define a diagnostic urine protein threshold for the syndrome.

**Glomerular capillary tuft**

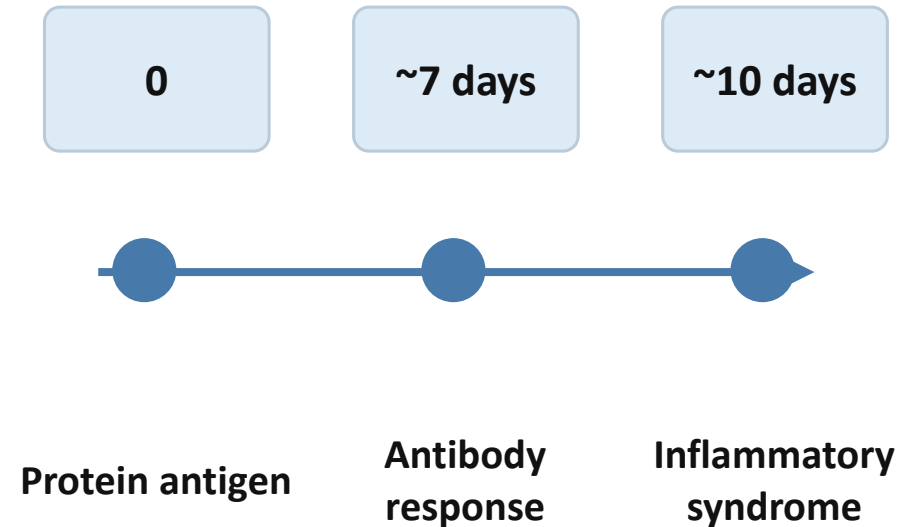


**Complex deposition → nephritis /  
proteinuria**

*Simplified conceptual schematic—not renal  
histology*

# The prototype reaction becomes apparent after a delay

- The inflammatory clinical phase at approximately ten days after antigen administration.
- The interval follows antibody generation at about one week.
- These are approximate observations from the prototype, not a rigid diagnostic clock.



# Serum C3 decreases when complement is consumed

- Complement is engaged at deposition sites during active disease.
- Active utilization can lower circulating serum C3.
- Local complement detection and systemic complement consumption provide mutually consistent evidence.

**Complement activation**

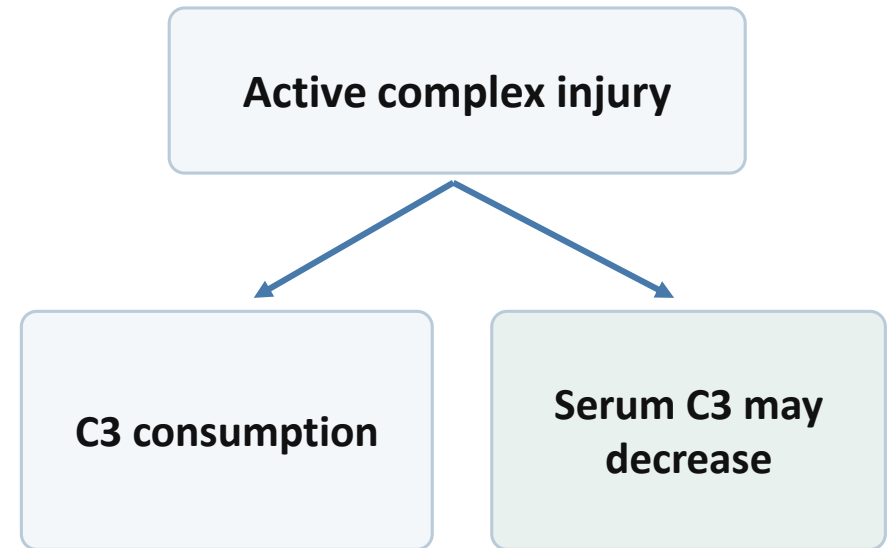


**Consumption of C3**

**Circulating C3 may fall**

# C3 may track activity in selected patients

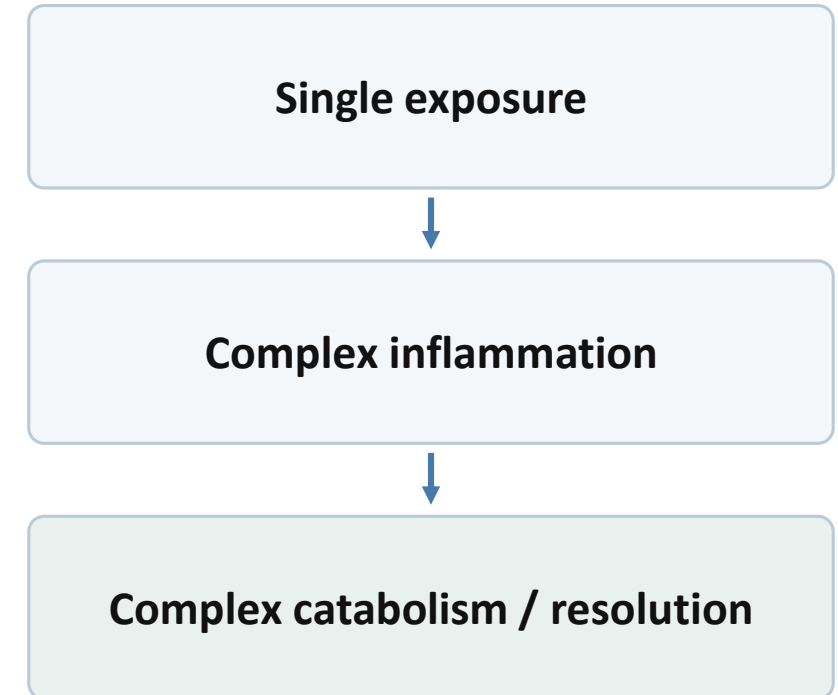
- Serum C3 can sometimes be used to monitor disease activity.
- A lower C3 is mechanistically interpretable as consumption during inflammation.
- The text does not establish universal sensitivity, specificity, or numerical cutoffs.



*Useful in some cases; Interpret with the clinical and tissue findings*

## Acute serum sickness may resolve after one exposure

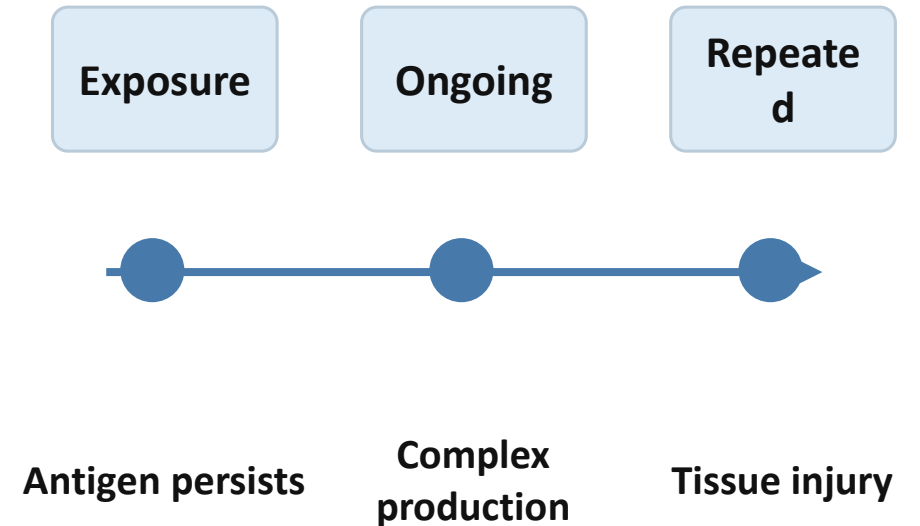
- A single large antigen exposure can produce an acute episode.
- Lesions tend to resolve as immune complexes are catabolized.
- The resolution model assumes that continued antigen exposure is absent.



*Acute, potentially self-limited course*

# Chronic immune complex disease requires persistence

- Repeated or prolonged antigen exposure can maintain circulating complexes.
- Continued antigen–antibody reactions can repeatedly drive deposition and injury.
- The chronic model differs fundamentally from clearance after a single exposure.



# Acute and chronic courses share the same mechanism

## Acute serum sickness

Single major antigen exposure

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Complexes are eventually catabolized

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Lesions tend to resolve

## Chronic complex disease

Repeated or sustained antigen

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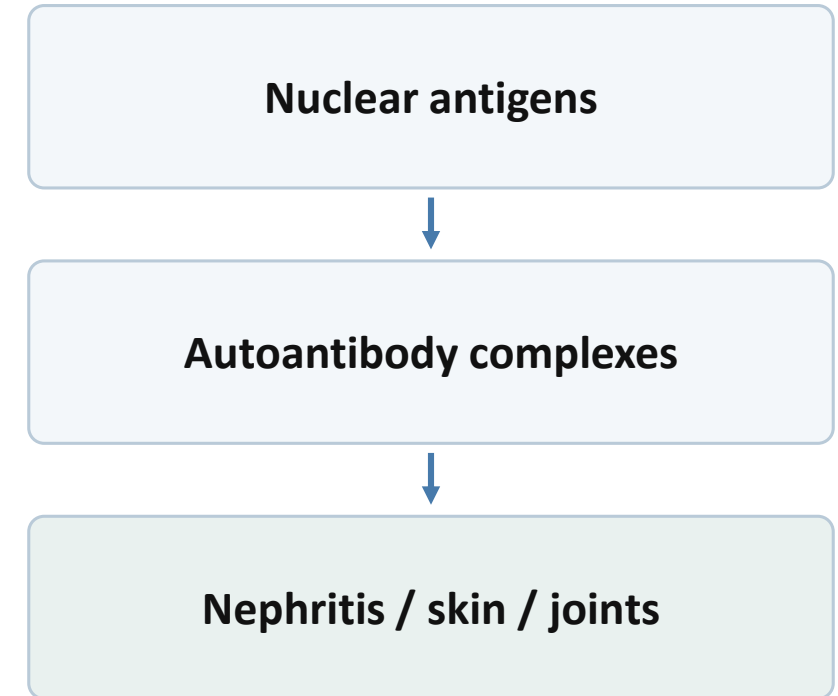
Continuing complexes and deposition

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Inflammation may persist

# Systemic lupus erythematosus sustains autoantigen exposure

- SLE features persistent antibody responses to self antigens.
- Nuclear antigens as immune complex targets.
- The resulting disease can affect kidneys, skin, joints, and other tissues.

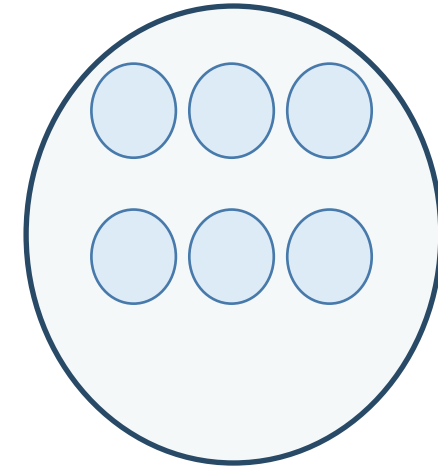


*Example of endogenous antigen–driven disease*

# Poststreptococcal nephritis illustrates microbial antigen

- Streptococcal cell-wall antigen(s) in poststreptococcal glomerulonephritis.
- Some antigen may be planted in the glomerular basement membrane.
- Its principal manifestation in the source table is nephritis.

**Glomerular capillary tuft**



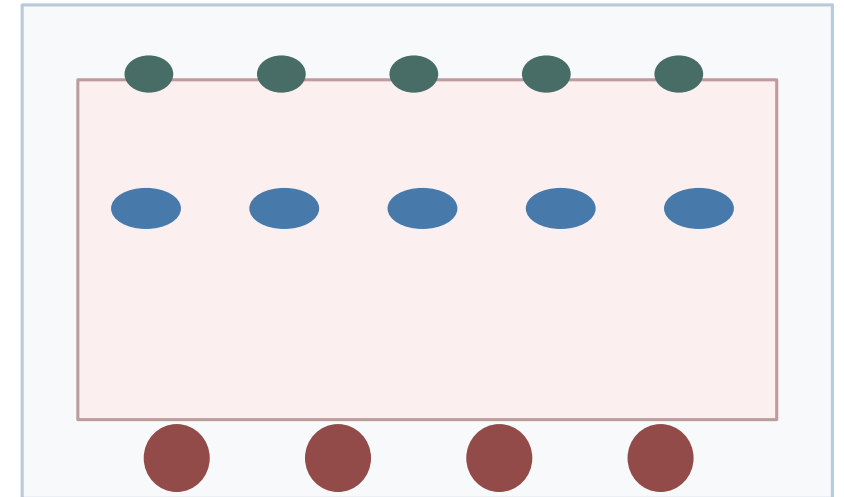
**Complex deposition → nephritis /  
proteinuria**

*Simplified conceptual schematic—not renal  
histology*

## Some polyarteritis nodosa has a viral antigen link

- Hepatitis B virus antigens are listed for a subset of polyarteritis nodosa cases.
- The clinical pathologic manifestation is systemic vasculitis.
- Do not generalize the HBV association to all polyarteritis nodosa.

**Vessel-wall inflammation**

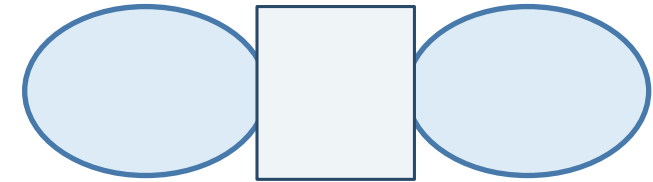


*Schematic vessel section; Not histology*

# Bacterial antigens appear in reactive arthritis

- Bacterial antigens, exemplified by Yersinia, among immune complex disease associations.
- The source table lists acute arthritis as the clinical manifestation.
- This is a mechanism example table, not a claim that every reactive arthritis case is proven immune complex-mediated.

**Joint / synovial region**



**Local complex-associated  
inflammation**

*Schematic only; Not anatomical scale*

## The disease examples share mechanism, not identical phenotype

| Example              | Antigen source         | Highlighted manifestation        |
|----------------------|------------------------|----------------------------------|
| Serum sickness       | Foreign proteins       | Arthritis, vasculitis, nephritis |
| SLE                  | Nuclear antigens       | Nephritis, skin, arthritis       |
| Poststreptococcal GN | Streptococcal antigens | Nephritis                        |
| Selected PAN         | HBV antigens           | Systemic vasculitis              |
| Reactive arthritis   | Bacterial antigens     | Acute arthritis                  |

## Systemic and local immune complex reactions differ by distribution

### Systemic serum sickness

Circulating antigen and antibody

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Deposits at multiple sites

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Systemic clinical syndrome

### Local Arthus reaction

Antigen introduced into sensitized site

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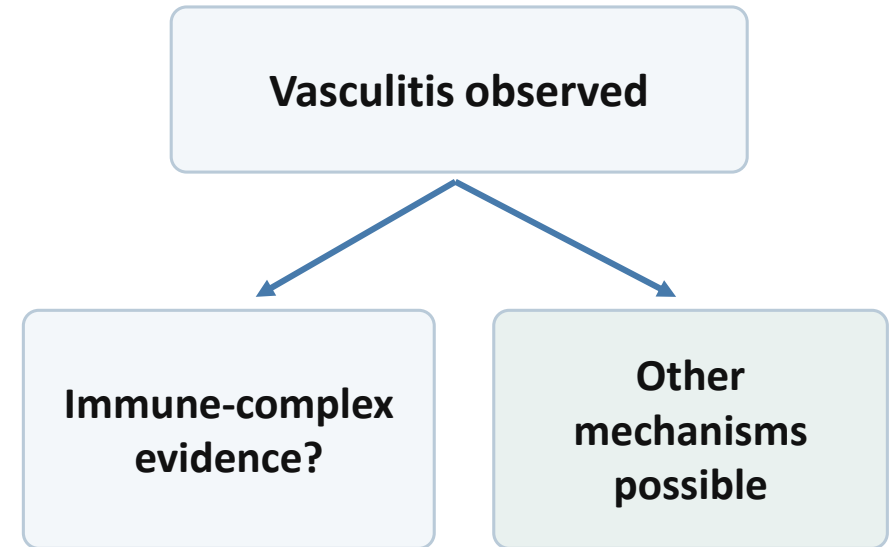
Complexes form in a local vessel wall

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Localized vasculitis / necrosis

# A vascular lesion alone does not establish Type III injury

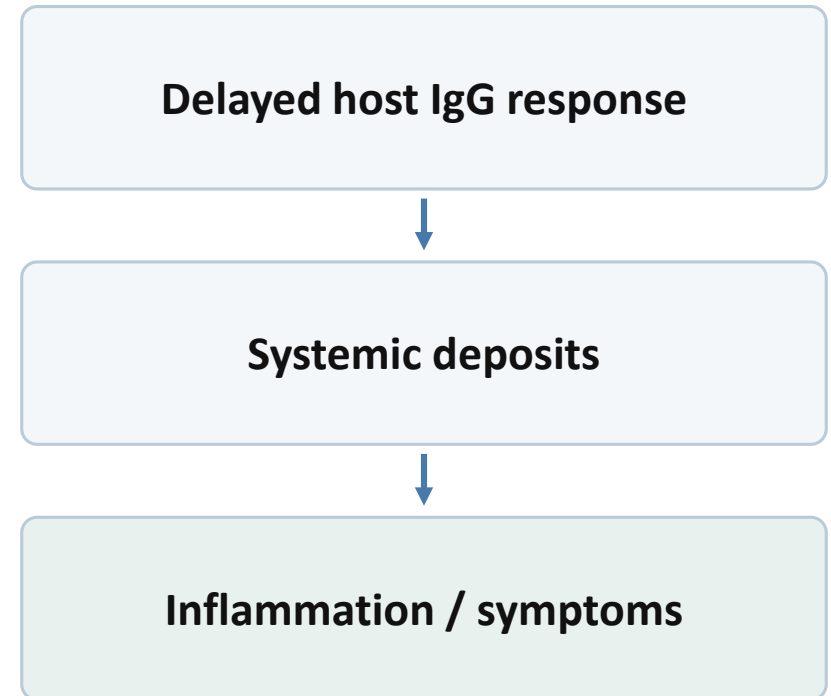
- Several antibody- and non-immune-complex mechanisms can inflame vessels.
- A deposited-complex mechanism requires evidence interpreted with the clinical setting.
- Look for antigenic context, complement findings, and relevant tissue deposition—not just vasculitis.



*Morphology and mechanism are distinct diagnostic questions*

## Clinical exercise: Delayed illness after a protein infusion

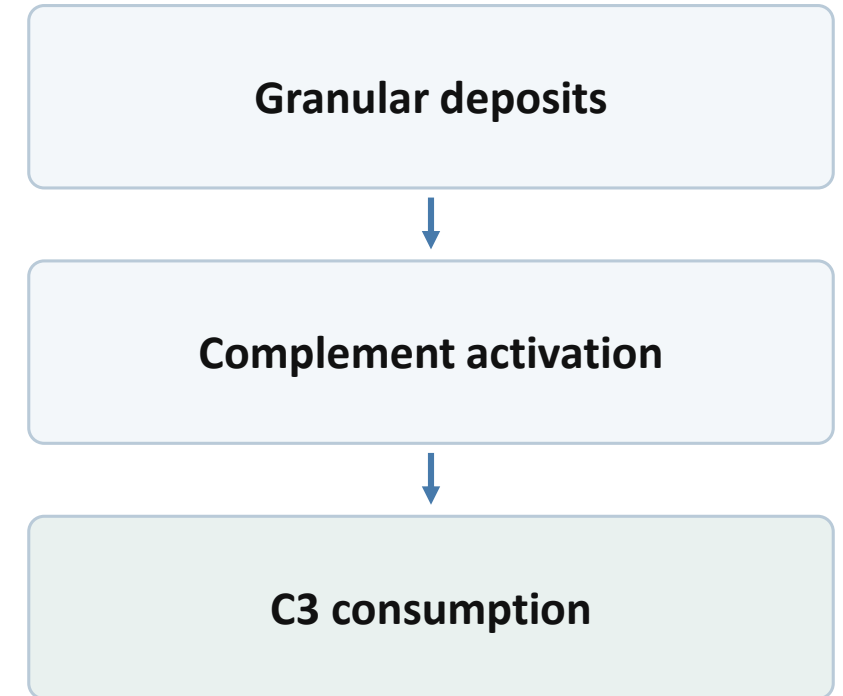
- A patient develops fever, urticaria, arthralgia and proteinuria several days after a foreign protein exposure.
- Question: Which sequence best links the exposure to these findings?
- Reasoned answer: Antibody formation → circulating complexes → deposition → complement/leukocyte injury.



*Hypothetical teaching case; No patient data*

## Clinical exercise: Low C3 with inflammatory nephritis

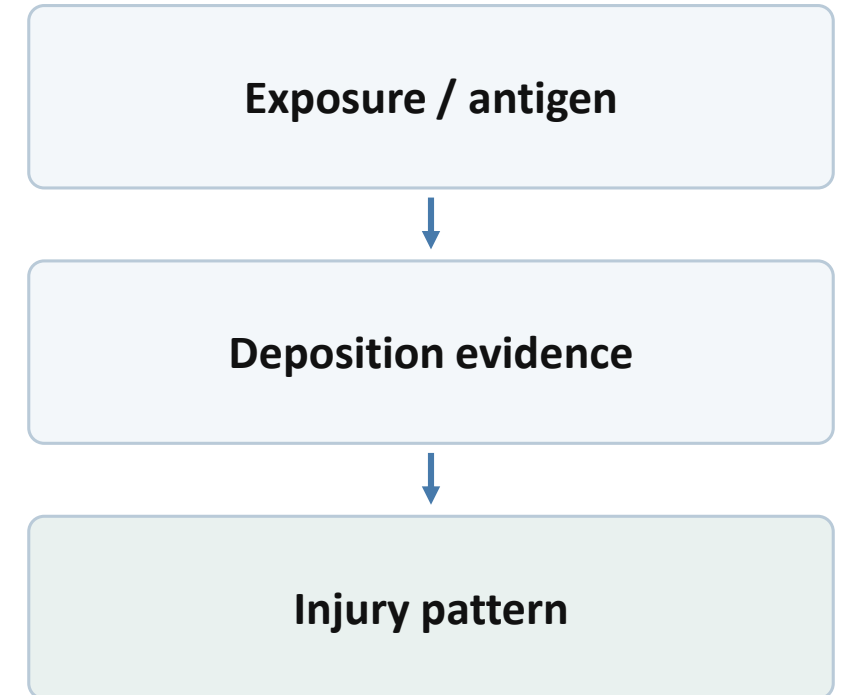
- A patient has nephritis with granular immune deposits and reduced circulating C3.
- Question: Which common mechanism connects these findings?
- Reasoned answer: Local immune complex deposition with complement activation and consumption.



*Hypothetical teaching case; No biopsy specimen depicted*

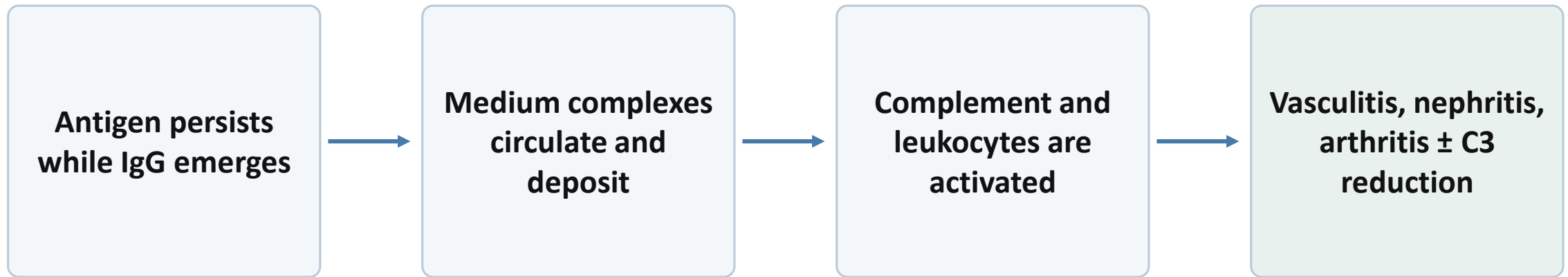
# Four reasoning pitfalls to avoid

- Antibody positivity does not, by itself, show tissue deposition.
- A low C3 may support activity in some cases; Robbins gives no universal cutoff.
- The prototype time intervals are approximate, not diagnostic criteria.
- Vasculitis or nephritis does not, alone, identify the responsible antigen.



*Require a coherent clinicopathologic mechanism*

## Integrated mechanism: From blood to injured organ



**A systemic trigger produces organ-predominant pathology through the distribution and inflammatory effects of deposits.**

*Schematic causal sequence*

# Primary reference and scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th edition (2026).
- Chapter 6: Immune complex–mediated (Type III) hypersensitivity; systemic immune complex disease, pp. 187–188.
- Adjacent source context: local immune complex disease, Table 6.4, Fig. 6.17, and morphology, pp. 188–189.
- Conceptual figures in this deck are original editable schematics; no textbook photomicrographs are reproduced.