

Development of Allergies

Genetic susceptibility • environment • type 2 immunity • clinical expression

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Learning objectives

- Define atopy and describe its characteristic clinical phenotypes.
- Interpret the genetic and environmental contributions to allergic susceptibility.
- Link type 2 immunity and IgE sensitization to clinical reactions.
- Distinguish IgE-dependent allergy from nonantigenic mast-cell activation.
- Critically interpret the hygiene hypothesis and early allergen exposure.

Why does an ordinary exposure provoke allergy?

Mechanistic question

- Common environmental substances are not inherently dangerous to most people.
- Atopic susceptibility favors an exaggerated type 2 response.
- Clinical manifestations require activation of tissue effector pathways.

Environmental encounter

Allergen reaches host surfaces



Susceptible immune response

Type 2 immunity and IgE production



Reexposure

Sensitized mast cells release mediators



Organ response

Airway, skin, gut or systemic manifestations

Atopy is a predisposition, not an acute reaction

Atopy

- Inherited propensity to develop allergic disease.
- May manifest through several clinical disorders.
- Associated with increased serum IgE and IL-4-producing Th2 cells.

Allergic episode

- An effector event following activation of relevant inflammatory pathways.
- In IgE-mediated allergy, reexposure cross-links mast-cell-bound IgE.
- Expression depends on involved tissue and released mediators.

Principal disorders within the atopic spectrum

Allergic rhinitis

Upper-airway mucus secretion and inflammation after allergen exposure.

Asthma

Bronchial smooth-muscle hyperreactivity; Late inflammatory injury can contribute.

Atopic dermatitis

An atopic inflammatory disorder of the skin.

Food allergy

A food-related allergic phenotype; Intestinal smooth-muscle effects may occur.

Atopy can affect more than one organ

Multiorgan phenotype

- Several atopic disorders often coexist in the same individual.
- Different involved organs may generate different symptoms.
- A single patient need not have every atopic condition.

Shared atopic susceptibility

Individual predisposition



Upper respiratory tract

Rhinitis



Lower respiratory tract

Asthma



Skin and gut

Dermatitis / food allergy

The atopic triad

Atopic dermatitis

Cutaneous atopic disease.

Allergic rhinitis

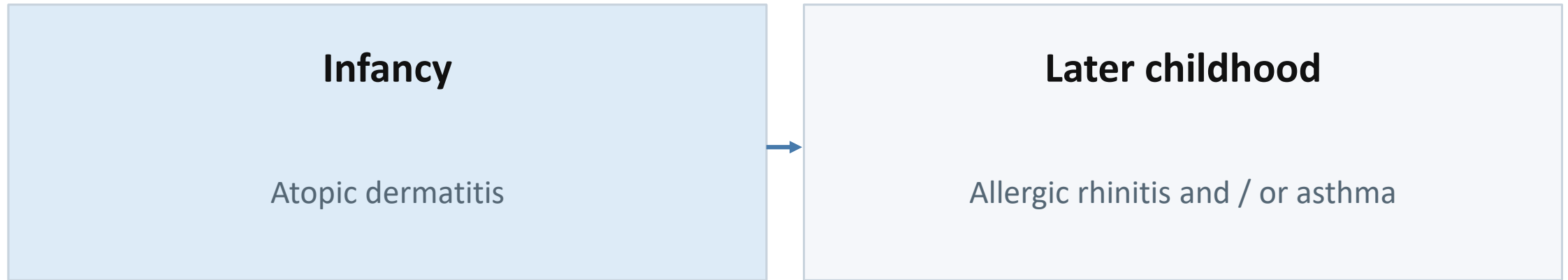
Nasal allergic inflammation.

Asthma

Allergic airway disorder.

Atopic march: The classical clinical pattern

Characteristic clinical sequence



- This is a descriptive sequence reported in some patients.
- The pattern does not establish that dermatitis necessarily causes later asthma.

What the atopic march does—and does not—mean

What it describes

- Atopic dermatitis in infancy followed by later respiratory atopy.
- A recognizable sequence of clinical phenotypes.
- Potentially more than one atopic disorder in the same individual.

What it does not establish

- An inevitable order in all atopic patients.
- A proven direct causal chain from one disorder to the next.
- A requirement for diagnosis of atopy.

Atopy is associated with a type 2 immune phenotype

Higher serum IgE
More IL-4–producing Th2 cells

- These observations characterize group-level tendencies in atopy.
- Neither observation alone establishes a clinical diagnosis of allergy.

IL-4 links type 2 immunity with IgE

Type 2 axis

- Atopic individuals tend to have more IL-4–producing Th2 cells.
- The parent mechanism shows type 2 immune help for IgE production.
- IgE subsequently sensitizes mast cells through high-affinity receptors.

Type 2 T-cell response

IL-4–associated activity



B-cell response

IgE class switching



Mast-cell binding

IgE attaches to FcεRI



Potential reactivity

Prepared for allergen reexposure

Familial susceptibility reflects inherited risk

Gene–environment framework

- Susceptibility to allergic disease has a genetic component.
- The mechanisms underlying familial predisposition remain incompletely understood.
- Genetic associations do not fully determine clinical phenotype.

Inherited variants

Host susceptibility



Immune-response tendency

Type 2 / allergen responsiveness



Environmental exposures

Encounter with relevant stimuli



Clinical expression

Possible atopic disease

Family history is common among atopic individuals

Almost 50%

- Almost half of atopic individuals have a positive family history of allergy.
- This describes the atopic group; It is not a risk estimate for a person with an affected relative.

How to interpret the family-history observation

Supported interpretation

- Affected relatives provide evidence of familial aggregation.
- The observation is compatible with inherited susceptibility.
- Family history is informative but not universal in atopy.

Unsupported inference

- “Half of all children with an affected parent become allergic.”
- “Family history is necessary for atopy.”
- “One gene explains all allergic disease.”

Cytokine-related loci linked to allergic phenotypes

IL-3 / IL-4

Reported linkage to polymorphisms in cytokine-related genes.

IL-5 / IL-9

Additional cytokine loci included in asthma association studies.

IL-13

A cytokine gene within the reported association set.

GM-CSF

GM-CSF is also listed among reported cytokine-related loci.

Genetic association is not mechanistic proof

The functional effects of the reported polymorphisms remain unclear.

- The role of these polymorphisms in allergy development is not yet established.
- Linkage identifies an association; It does not by itself reveal biological mechanism.

HLA variation may influence allergen reactivity

Proposed association

- HLA polymorphisms have also been linked to allergic susceptibility.
- The HLA region is on chromosome 6.
- The suggested implication is inherited responsiveness to particular allergens.

HLA polymorphism

Inherited genetic variation



Antigen recognition context

Possible differences in allergen responsiveness



Susceptible phenotype

Increased potential for allergic sensitization

Cytokine and HLA associations are distinct

Cytokine-linked loci

- Concern mediators that participate in allergic reactions.
- Include IL-3, IL-4, IL-5, IL-9, IL-13 and GM-CSF.
- Their contribution to the disease phenotype remains mechanistically uncertain.

HLA-linked loci

- Located in the chromosome 6 HLA region.
- Suggest variation in responsiveness to selected allergens.
- Are described as an association, not a deterministic genotype.

Inherited risk requires environmental context

Integrated model

- Genetic susceptibility influences which responses may arise.
- Environmental exposures contribute to the development of clinical disease.
- Observed allergy reflects both predisposition and effector activation.

Host factors

Atopic tendency / reported loci



Context

Environmental pollutants and other exposures



Immune events

IgE sensitization or nonimmune activation



Manifestation

Organ-specific allergic syndrome

Environment modifies allergy susceptibility

Allergic disease is not explained by genetic risk alone.

- Environmental pollutants are among the factors that predispose to allergy.
- It also identifies viral airway infections as triggers of asthma.

Pollutant exposure is a predisposing influence

Environmental susceptibility

- Environmental pollutants are particularly relevant in industrialized settings.
- Pollutant exposure is associated with predisposition to allergic disease.
- A predisposing association does not specify an individual risk magnitude.

Industrialized environment

Potential pollutant exposure



Predisposing influence

Greater allergic susceptibility



Possible clinical disease

Dependent on host and other exposures

Respiratory viruses can trigger asthma

Trigger vs predisposition

- Viral infections of the airways can trigger asthma.
- A triggering event is not the same as establishing inherited atopy.
- The detailed airway pathology belongs to the respiratory chapter.

At-risk airway

Asthma susceptibility



Viral airway infection

Environmental trigger



Clinical response

Asthma symptoms / exacerbation

Predisposition and trigger answer different questions

Predisposition

- Why a host is susceptible to allergic disease.
- Examples: Atopic genetic background and environmental influences.
- May exist before symptoms appear.

Trigger

- What precipitates a particular episode.
- Examples: Allergen reexposure or viral airway infection in asthma.
- Does not necessarily explain the underlying susceptibility.

Allergic disease frequency has increased with urbanization

A population trend does not identify a single cause.

- Many allergic diseases have become more frequent in developed countries.
- This observation helped motivate the hygiene hypothesis; Causation remains a separate question.

Different exposures can occupy different roles

Allergens

Environmental antigens that initiate type 2 immunity and IgE sensitization.

Pollutants

Environmental factors described as predisposing to allergic disease.

Airway viruses

Triggers of asthma rather than allergens in the usual IgE pathway.

Temperature / exercise

Nonantigenic stimuli that may evoke immediate hypersensitivity-like events.

Exposure alone does not define the mechanism

Antigen-dependent pathway

- An allergen evokes type 2 immunity and IgE production.
- The relevant tissue mast cells become sensitized.
- Repeated antigen exposure can trigger receptor cross-linking.

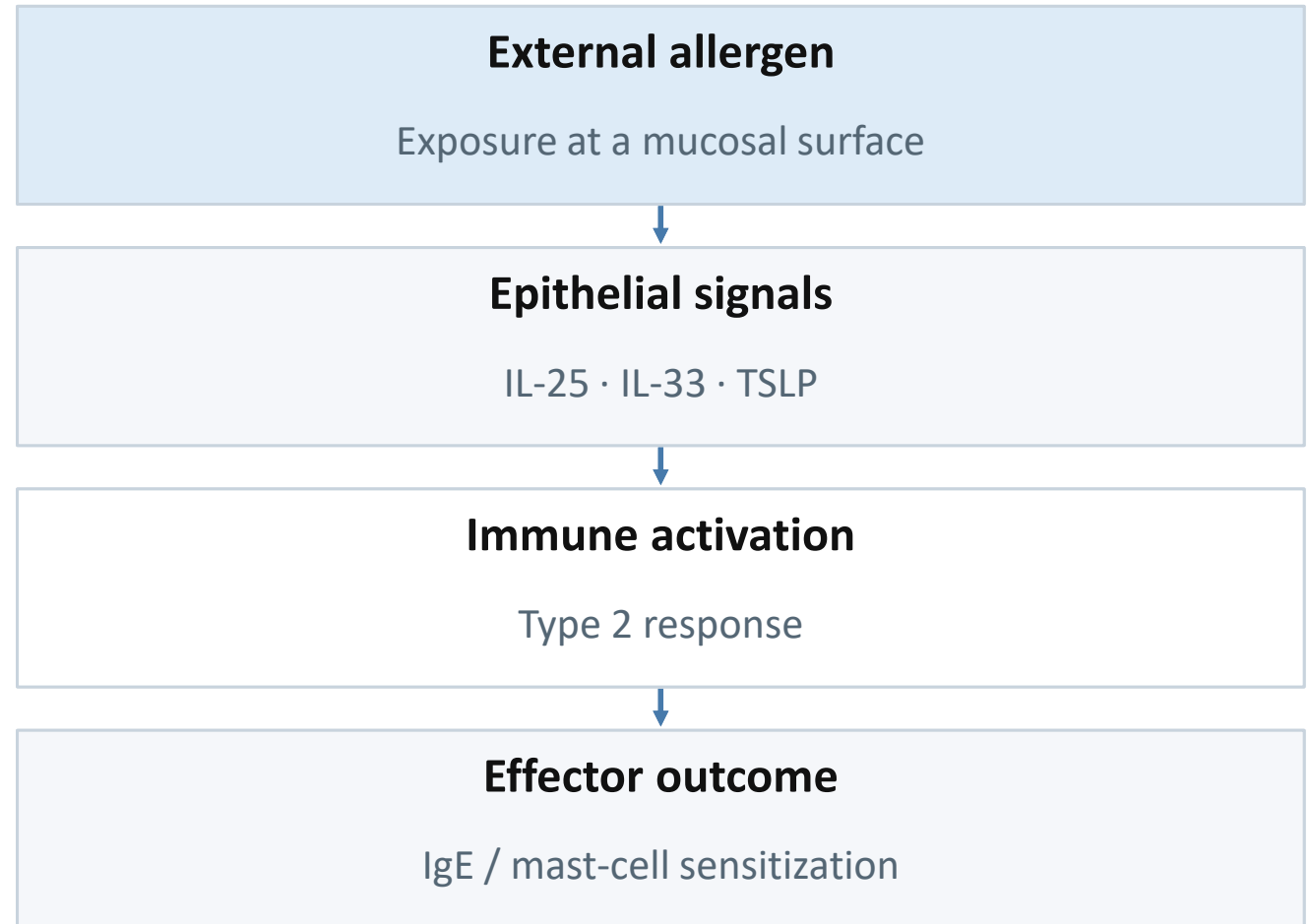
Antigen-independent pathway

- Some immediate reactions follow physical or other nonantigenic stimuli.
- This subset does not require Th2 cells or IgE.
- Mast-cell hypersensitivity to nonimmune stimuli is proposed.

Epithelial tissues participate in type 2 responses

Mucosal interface

- Mucosal tissues are an important interface for encountered allergens.
- Epithelial signals include IL-25, IL-33 and TSLP.
- These signals participate in the initiation of type 2 responses.



First exposure creates allergic sensitization

Sensitization sequence

- The parent section distinguishes first exposure from repeat encounter.
- Initial immune activation includes T-cell help and IgE class switching.
- IgE binds to high-affinity mast-cell FcεRI receptors.

First encounter

Allergen presented to immune system



Tfh and Th2 response

Support for IgE-producing B cells



IgE production

Plasma-cell output



Mast-cell sensitization

FcεRI occupancy

Tfh and Th2 cells have complementary roles

T follicular helper cells

- Provide B-cell help in lymphoid organs.
- IL-4– and IL-13–producing Tfh cells are part of the depicted pathway.
- Contribute to IgE class switching.

Th2 cells

- Contribute to type 2 cytokine responses in tissues.
- Atopic individuals tend to have more IL-4-producing Th2 cells.
- Help sustain eosinophilic inflammation.

IgE production makes allergen recognition actionable

IgE effector link

- Antigen-specific IgE is generated with appropriate T-cell help.
- IgE becomes attached to FcεRI on mast cells.
- Sensitized cells can respond rapidly during subsequent antigen exposure.

B-cell class switching

IgE-producing response



Circulating IgE

Specific binding to FcεRI



Resident mast cell

IgE is retained at tissue interface

Tissue mast cells are strategically located

Anatomical distribution

- Mast cells derive from bone marrow but reside widely in tissues.
- They are abundant near small vessels, nerves, and subepithelial sites.
- This distribution helps explain local vascular and mucosal reactions.

Subepithelial mast cell

Local effector cell



Nearby microvessels

Vascular leakage / edema



Nearby smooth muscle

Spasm / airflow effects

Repeat exposure cross-links mast-cell IgE

Activation sequence

- Multivalent antigen can bind adjacent cell-surface IgE molecules.
- FcεRI receptor clustering triggers intracellular activation.
- Preformed and newly synthesized mediators are then released.

Prior sensitization

IgE already bound to FcεRI



Repeat allergen

Cross-links neighboring IgE



Mast-cell activation

Degranulation and mediator synthesis

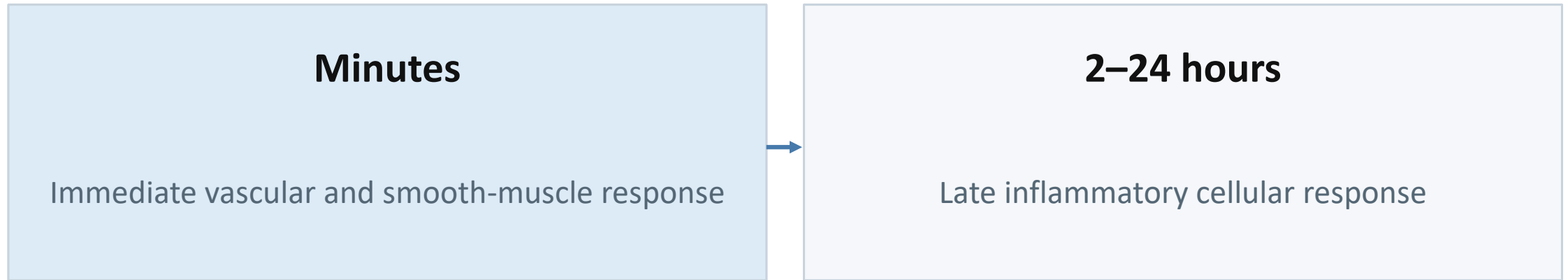


Clinical reaction

Immediate and subsequent late phase

The allergic effector response has two phases

Temporal organization of type I hypersensitivity



- Both phases can follow a single allergen encounter in a sensitized host.
- Late inflammation can persist without a second exposure to the antigen.

Preformed mast-cell mediators act rapidly

Histamine

Vascular permeability, smooth-muscle contraction, mucus secretion.

Neutral proteases

Tryptase and chymase participate in tissue effects.

Acid hydrolases

Included in granule contents and contribute to tissue injury.

Granule proteoglycans

Heparin and chondroitin sulfate store and package amines.

Newly synthesized lipid mediators extend the response

Leukotrienes C₄ / D₄

Strong vascular and bronchial smooth-muscle effects.

Leukotriene B₄

Chemotactic activity for leukocyte populations.

Prostaglandin D₂

Bronchospasm and increased mucus secretion.

Arachidonic-acid pathway

Substrate pathway giving rise to prostaglandins and leukotrienes.

Mast-cell cytokines recruit a late infiltrate

Late-phase cascade

- Mast cells produce TNF, IL-1 and chemokines.
- These promote recruitment of leukocytes into affected tissue.
- Inflammatory cells amplify mediator release and may injure epithelium.

Mast-cell activation

TNF · IL-1 · chemokines



Leukocyte recruitment

Inflammatory infiltrate



Further mediators

Amplified inflammatory activity



Tissue response

Epithelial damage / sustained symptoms

Eosinophils contribute to tissue injury

Eosinophil contribution

- IL-5 strongly activates eosinophils.
- Eosinophils release proteolytic proteins including major basic protein.
- These products contribute to epithelial damage in late reactions.

Th2-associated cytokines

IL-5



Activated eosinophil

Granule protein release



Epithelial injury

Sustained late-phase inflammation

Immediate and late tissue effects are different

Early phase

- Vasodilation, vascular leakage and edema.
- Contraction of smooth muscle.
- Mucus secretion.

Late phase

- Inflammatory infiltrate with eosinophils and other leukocytes.
- Additional mediator production.
- Epithelial damage and sustained inflammation.

Tissue effects translate into distinct symptoms

Nose / sinuses

Mucus secretion and upper-airway inflammation.

Bronchi

Airway narrowing from smooth-muscle effects and inflammation.

Gut

Altered peristalsis linked to intestinal muscle contraction.

Systemic vessels / larynx

Vasodilation and edema can produce shock or airway compromise.

In asthma, late inflammation may dominate symptoms

Mast-cell activation is only the beginning.

- Late-phase inflammation contributes substantially to some allergic asthma presentations.
- This explains why reducing inflammation can matter beyond blocking immediate histamine effects.

Why patients can present with different organ patterns

Shared upstream pathway

- Atopic susceptibility can support allergen-driven type 2 immunity.
- IgE sensitization and mast-cell mediator release are recurring mechanisms.
- Common underlying mechanism does not imply a single clinical presentation.

Different clinical expressions

- Nasal glands: Mucus and inflammation.
- Bronchial muscle: Airway narrowing.
- Skin and gut: Other atopic clinical phenotypes.

Not all immediate hypersensitivity-like reactions are IgE-mediated

The initiating stimulus may be nonantigenic.

- A subset of immediate reactions can be triggered by temperature extremes or exercise.
- These events are sometimes described as nonatopic allergy.

Estimated frequency of nonantigenic immediate reactions

20%–30% of immediate hypersensitivity reactions

- This estimate concerns immediate reactions induced by nonantigenic stimuli.
- It is not the population prevalence of allergic disease.

Atopic versus nonatopic immediate reactions

Atopic / classic type I

- Allergen-specific type 2 T-cell response.
- IgE class switching and FcεRI sensitization.
- Reexposure cross-links mast-cell-bound IgE.

Nonatopic / nonantigenic

- Trigger can be a temperature change or exercise.
- No Th2 or IgE requirement in the described subgroup.
- Abnormal mast-cell responsiveness is proposed.

Physical stimuli may activate mast cells

Heat

A potential direct physical trigger.

Cold

A physical stimulus that can activate mast cells.

Sunlight

Included among stimuli activating mast cells in parent section.

Exercise

Named as a nonantigenic trigger of immediate reactions.

Other mast-cell activation routes

Complement C3a / C5a

Anaphylatoxins can activate mast cells through their receptors.

Codeine / morphine

Drugs listed among possible mast-cell activators.

Adenosine / chemokines

Additional reported mast-cell activating stimuli.

Bee venom melittin

A non-IgE activating stimulus discussed in parent section.

Nonatopic reactions suggest altered effector sensitivity

Proposed mechanism

- Unusual mast-cell responsiveness to nonimmune stimuli is proposed.
- This is a hypothesis for the mechanism, not a complete causal explanation.
- The clinical endpoint can resemble IgE-dependent mediator effects.

Nonimmune stimulus

Physical or pharmacologic input



Mast-cell activation

Proposed increased sensitivity



Mediator effects

Edema / spasm / secretion

Similar symptoms need not imply the same pathogenesis

Shared effector result

- Mast-cell mediator release can cause vascular and smooth-muscle changes.
- A clinical pattern alone may not identify the initiating route.
- Anaphylaxis-like physiology is not itself proof of antigen-specific IgE.

Different initial route

- Classic type I: Allergen-specific IgE cross-linking.
- Nonantigenic: Mast-cell activation without Th2 / IgE in the described subset.
- Complement and selected drugs provide additional activation pathways.

The hygiene hypothesis arose from a population observation

More allergy in increasingly urbanized, developed settings

- The observation motivated a hypothesis about reduced early environmental or microbial exposure.
- The hypothesis is explanatory, not proof of a single causal pathway.

The proposed mechanism is early immune education

Hypothesis; Not proven sequence

- Early-life environmental, including microbial, antigen exposure may shape later responsiveness.
- The hypothesis includes prenatal and early-childhood windows.
- Its proposed effect is reduced later pathological responses to common allergens.

Prenatal / early childhood

Environmental antigen encounters



Immune education

Proposed developmental influence



Later allergen contact

Potentially less pathologic reaction

Separate observation, hypothesis and evidence

Observations

- Allergic diseases increased as developed societies urbanized.
- Atopic susceptibility also has genetic associations.
- An association does not uniquely identify the responsible exposure.

Explanatory interpretation

- Early microbial and environmental encounters may modulate immune development.
- Improved early hygiene might reduce protective exposures.
- This remains broader than a single experimentally proven mechanism.

Allergy susceptibility develops across life stages

Timing connects environmental hypotheses to clinical patterns



- The proposed early developmental influence does not imply fixed outcomes.
- Atopic march describes one observed clinical pattern, not a mandatory timetable.

Early peanut exposure is a specific protective example

Specific early-exposure example

- Small amounts of peanut-containing foods are given in infancy and early childhood in this example.
- Early exposure in the cited example reduces later peanut allergy incidence.
- This illustrates that some early exposures may be protective, not invariably sensitizing.

Early peanut-containing foods

Small amounts in early life



Developmental exposure

Context for immune response



Later outcome

Lower peanut allergy incidence in the cited example

What the peanut example does not establish

What the example supports

- Early peanut-containing food exposure can reduce later peanut allergy incidence.
- The example is consistent with developmental immune modulation.
- Exposure timing matters in the specific example.

What the example cannot establish

- Universal benefit of unrestricted allergen exposure.
- An unsupervised feeding recommendation for a particular infant.
- An identical protective effect for every allergen.

Allergic rhinitis: Local upper-airway expression

Clinicopathologic link

- Environmental allergen exposure can precipitate local immediate hypersensitivity.
- Histamine and other mediators drive mucus secretion.
- Upper-airway inflammation contributes to symptoms.

Airborne allergen

Upper-airway exposure



Sensitized mast cells

Rapid mediator release



Nasal response

Mucus secretion / inflammation

Asthma: Airway spasm plus inflammation

Clinicopathologic link

- Bronchial smooth-muscle hyperactivity contributes to airway obstruction.
- Late eosinophil-rich inflammation can cause injury and sustained symptoms.
- Viral airway infections are recognized triggers in susceptible patients.

Susceptible airway

Genetic / atopic context



Triggering event

Allergen or airway infection



Airway consequences

Smooth-muscle response + inflammation

Atopic dermatitis: Part of the atopic spectrum

Clinical pattern

- Atopic dermatitis is one of the most common clinical forms of atopy.
- It may be the first disorder in the described atopic march.
- Coexistence with later rhinitis or asthma is possible.

Atopic propensity

Shared underlying susceptibility



Skin phenotype

Atopic dermatitis



Potential later findings

Rhinitis and / or asthma

Food allergy: An atopic phenotype with gut effects

Clinicopathologic link

- Food allergy belongs to the spectrum of common atopic disorders.
- Intestinal muscle contraction can increase peristalsis during immediate reactions.
- Food allergens can also precipitate systemic reactions in sensitized hosts.

Food allergen

Exposure in sensitized host



Mediator effects

Intestinal smooth-muscle response



Clinical range

Local gut symptoms or systemic response

Local allergy and anaphylaxis differ in severity

Localized presentations

- Rhinitis, asthma, dermatitis, food-allergy phenotypes.
- Organ-related mucus, smooth-muscle and inflammatory effects.
- Can coexist within a single atopic individual.

Systemic anaphylaxis

- Potentially widespread vascular leakage and vasodilation.
- Edema, bronchospasm and hypotensive shock.
- Life-threatening even with very small triggering exposures.

Clinical reasoning: An evolving atopic phenotype

Clinical scenario

A child has atopic dermatitis in infancy, then develops allergic rhinitis and asthma during childhood.

Reason through the mechanism

- What clinical pattern does this illustrate?
- Does this history alone prove dermatitis caused asthma?
- What shared predisposition connects the disorders?

Clinical reasoning: An immediate nonantigenic trigger

Clinical scenario

An individual develops an immediate mast-cell–type reaction after a marked temperature change, without an identified allergen exposure.

Reason through the mechanism

- Which pathway is suggested by the trigger?
- Must allergen-specific IgE necessarily be involved?
- Which proposed effector abnormality is relevant?

Clinical reasoning: Early environmental exposure

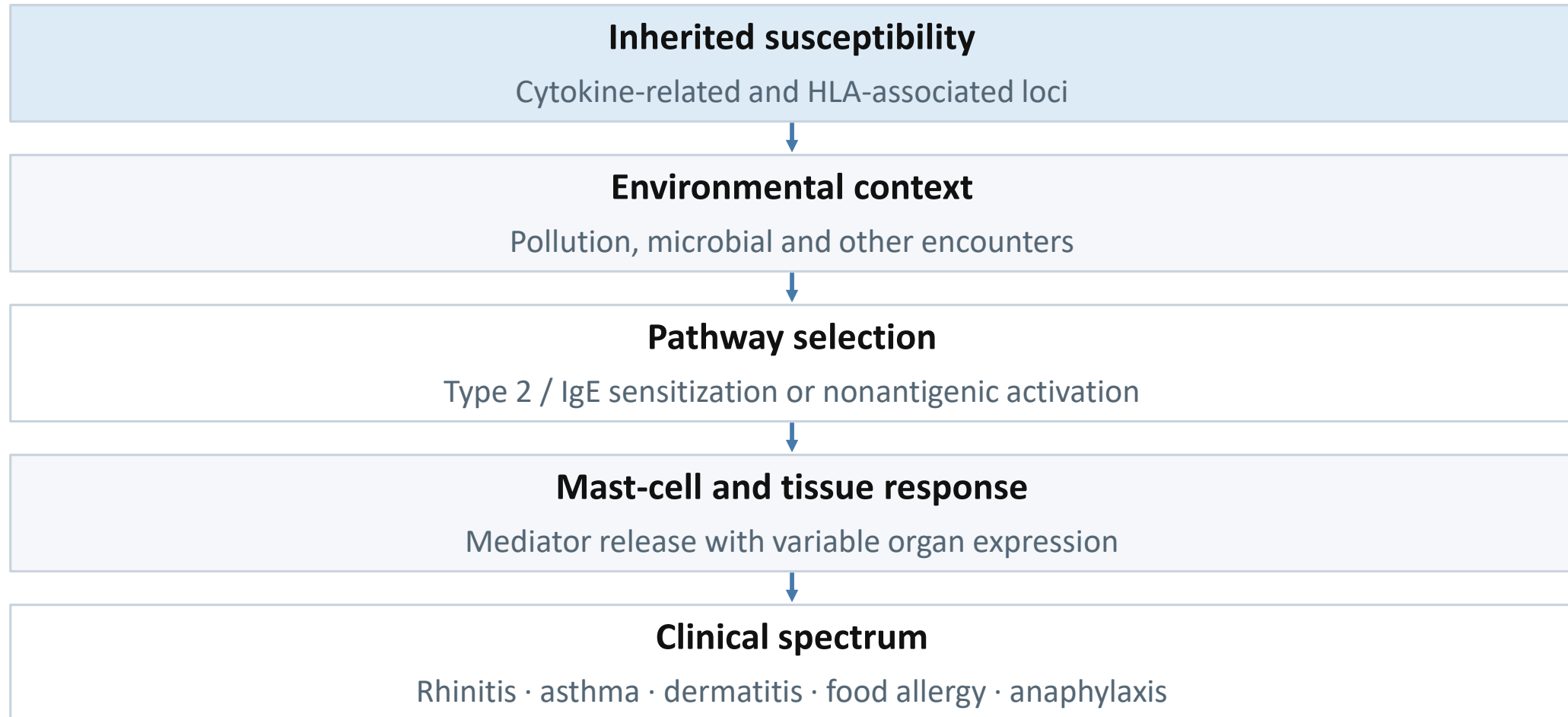
Clinical scenario

The frequency of allergy is reported to rise during urbanization, while early exposure to peanut-containing foods is associated with less subsequent peanut allergy.

Reason through the mechanism

- Which hypothesis addresses the population pattern?
- Which observation is specific to peanut allergy?
- Why should the two not be treated as identical evidence?

Integrated model: From predisposition to manifestations



Five durable conclusions

- Atopy denotes susceptibility; An allergic reaction is an event.
- Family and candidate-gene associations indicate risk but not deterministic causation.
- Environmental exposures may predispose, trigger, or modify immune development.
- IgE-mediated sensitization and nonantigenic mast-cell activation are mechanistically distinct.
- Organ phenotype and phase of inflammation determine the clinical presentation.

Primary reference and contextual sections

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026) — Diseases of the Immune System

Primary focus: Development of Allergies

Mechanistic context: sensitization and activation of mast cells; mediators and late-phase reactions.