

Chronic Nonspecific Lymphadenitis

Reactive patterns in lymph nodes and extranodal immune tissues

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Learning objectives

- Describe how chronic immune stimulation changes lymph-node architecture.
- Recognize three major reactive patterns and their dominant compartments.
- Identify morphologic features that favor reactive follicular hyperplasia.
- Link nodal morphology to clinical context and tertiary lymphoid structures.

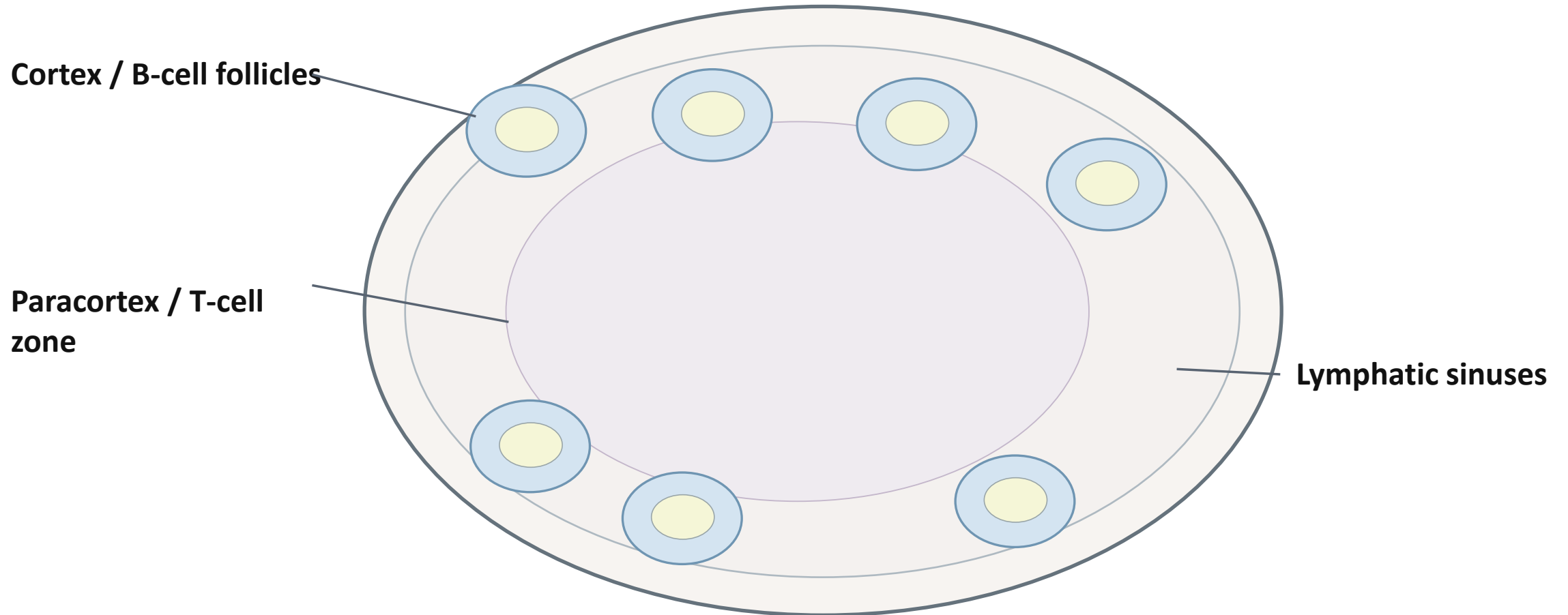
Chronic lymphadenitis is a pattern of immune reactivity

Multiple long-standing antigenic stimuli can produce nonspecific nodal enlargement.

- “Nonspecific” denotes stereotyped reactive changes rather than one unique etiology.
- Morphologic patterns may coexist within an individual lymph node.
- Interpret the pattern alongside the clinical distribution and history.

Secondary lymphoid tissue has distinct functional zones

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Compartments explain why stimuli produce different histologic patterns.

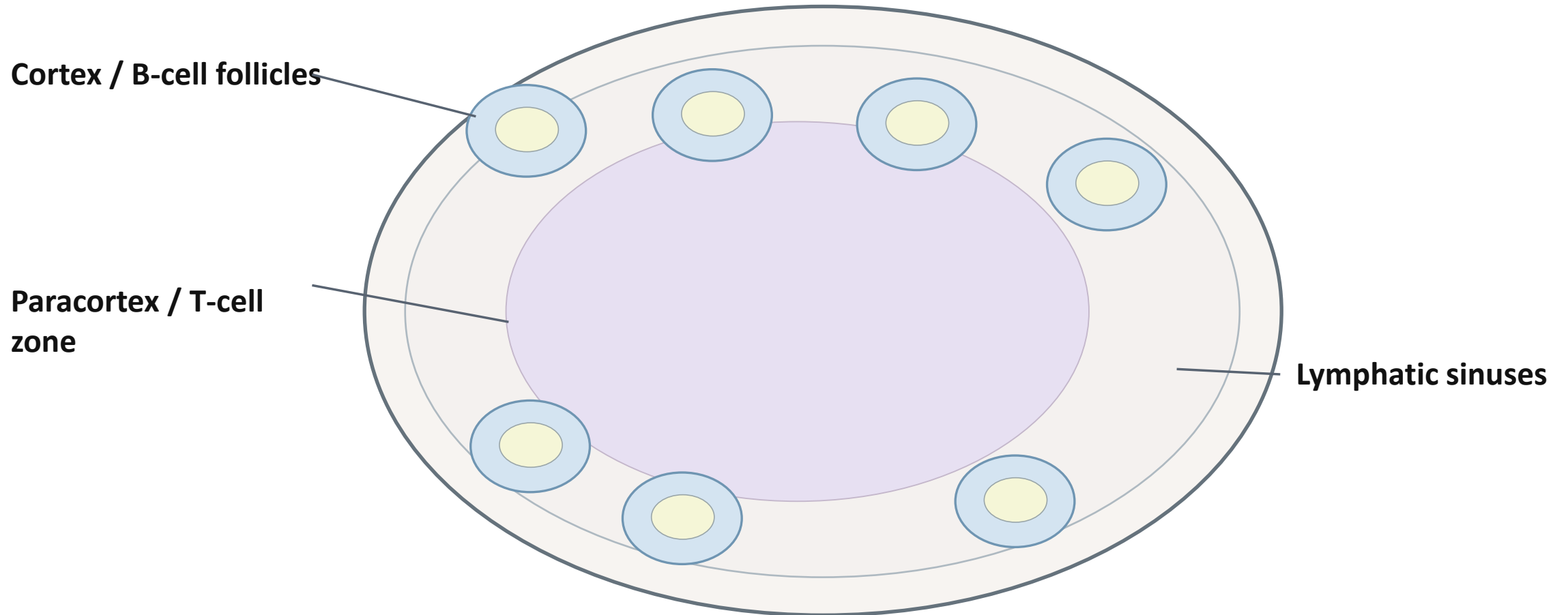
B-cell follicles are sites of humoral response

Resident B-cell follicles can develop reactive germinal centers after antigenic stimulation.

- Secondary follicles contain actively responding B cells.
- A peripheral mantle zone surrounds the germinal center.
- Follicular enlargement creates the follicular hyperplasia pattern.

The paracortex is the T-cell-rich compartment

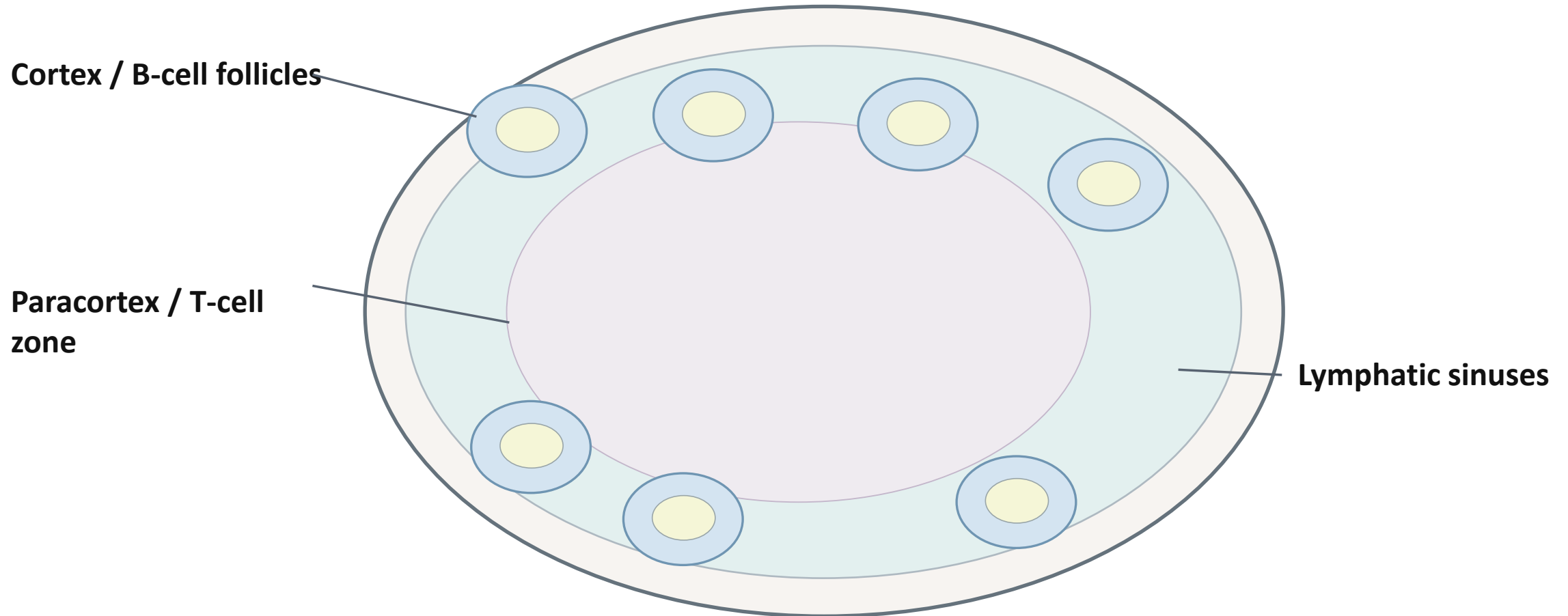
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Expansion of T-cell zones defines a different response pattern.

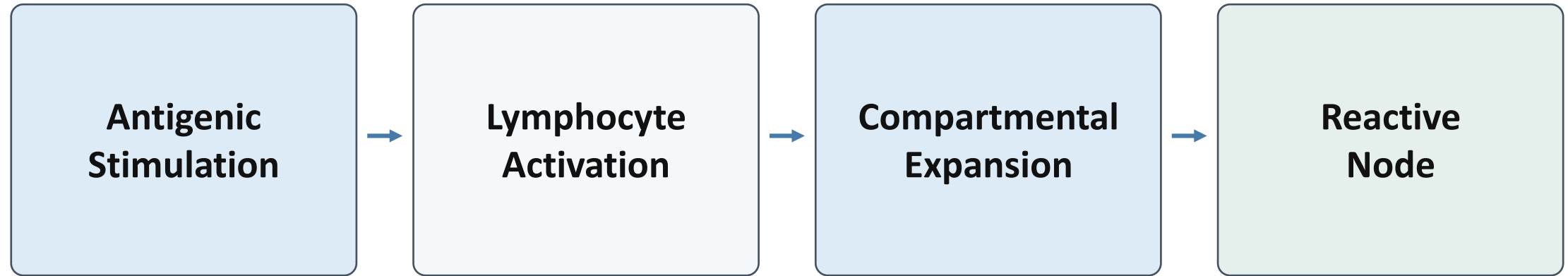
Lymphatic sinuses form another reactive compartment

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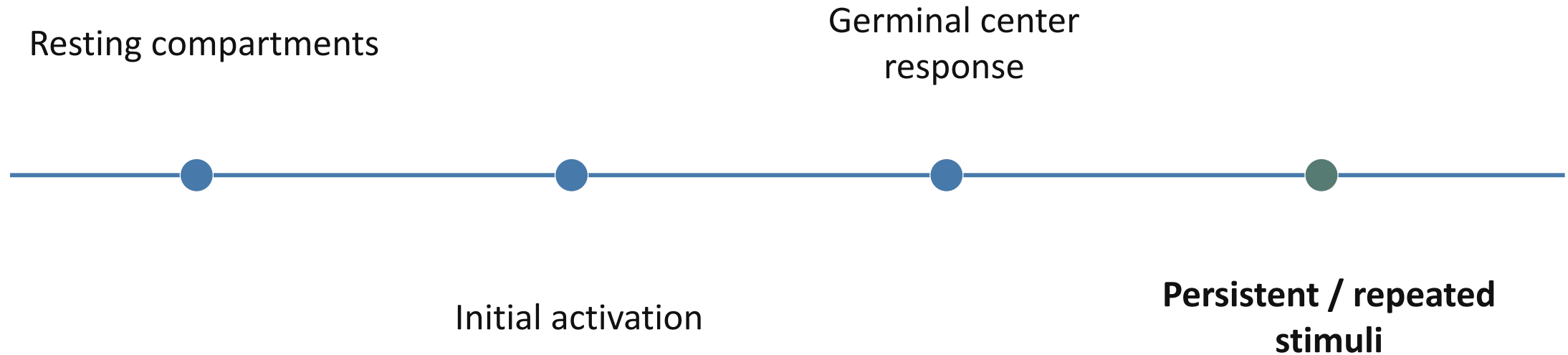
Sinuses contain lining cells and transit-associated phagocytes.

Antigenic exposure produces architectural change



The distribution of activated cells determines the dominant morphologic pattern.

Lymph nodes respond dynamically to repeated exposure



That adult lymph nodes frequently reflect prior immune exposures.

Acute and chronic nonspecific lymphadenitis

Acute reaction

- Often associated with microbial drainage or systemic infection
- Can show neutrophils and tissue damage
- May be painful or suppurative

Chronic reaction

- Many persistent immunologic triggers
- Follicular, paracortical and sinus patterns
- Typically slow enlargement and nontender nodes

Distinguish response pattern and tempo; The two are not mutually exclusive.

Three reproducible reactive morphologies

Follicular hyperplasia

Germinal-center / B-cell
compartment
predominates

Paracortical hyperplasia

T-cell zones expand with
activated immunoblasts

Sinus histiocytosis

Sinuses enlarge with lining
cells and macrophages

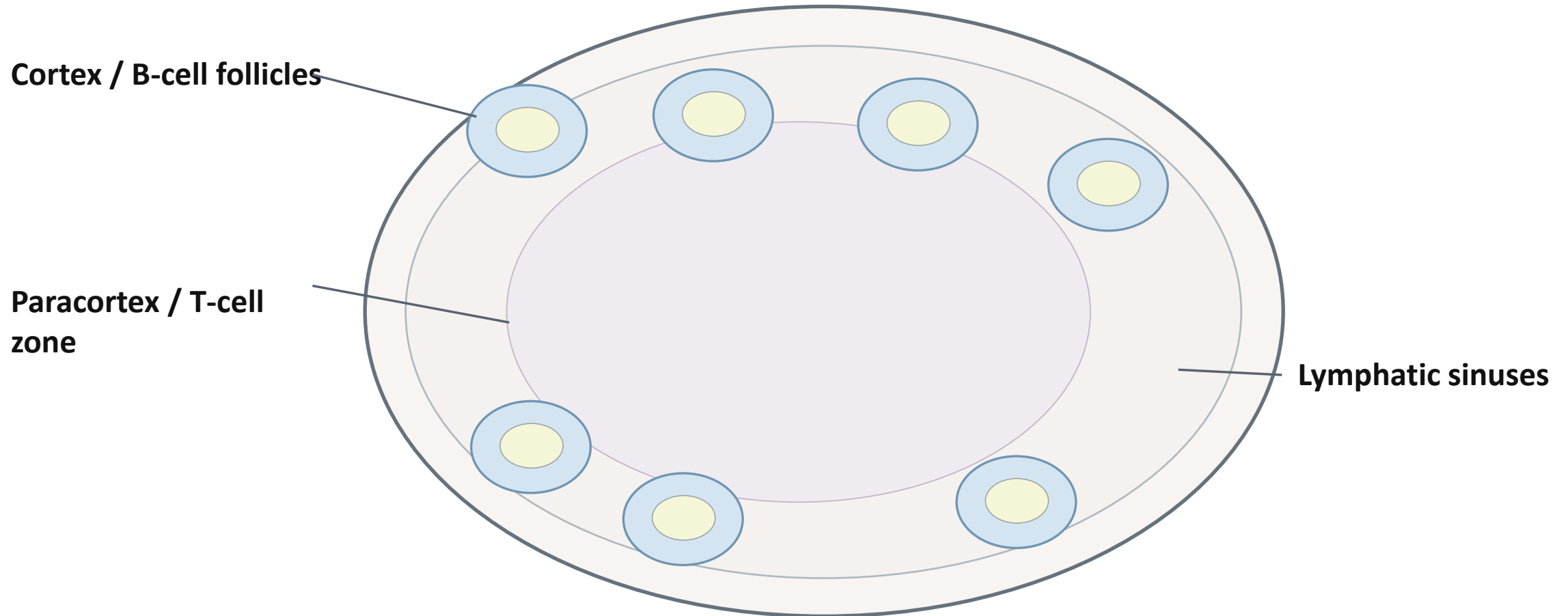
One node can show several reactive processes

A mixed pattern is expected, not a contradiction.

- Follicles, paracortex and sinuses respond to distinct immune inputs.
- Different compartments may expand simultaneously.
- Describe the dominant pattern without ignoring the others.

Assess the entire nodal architecture before naming a pattern

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Architecture is as important as the appearance of individual cells.

Patterns track the dominant immune compartment

Humoral reaction

- Secondary follicles enlarge
- Germinal-center polarity appears

T-cell reaction

- Paracortex expands
- Immunoblasts become conspicuous

Sinus response

- Sinuses dilate and distort
- Phagocytic macrophages accumulate

Interpret these as morphologic patterns, not etiologic diagnoses.

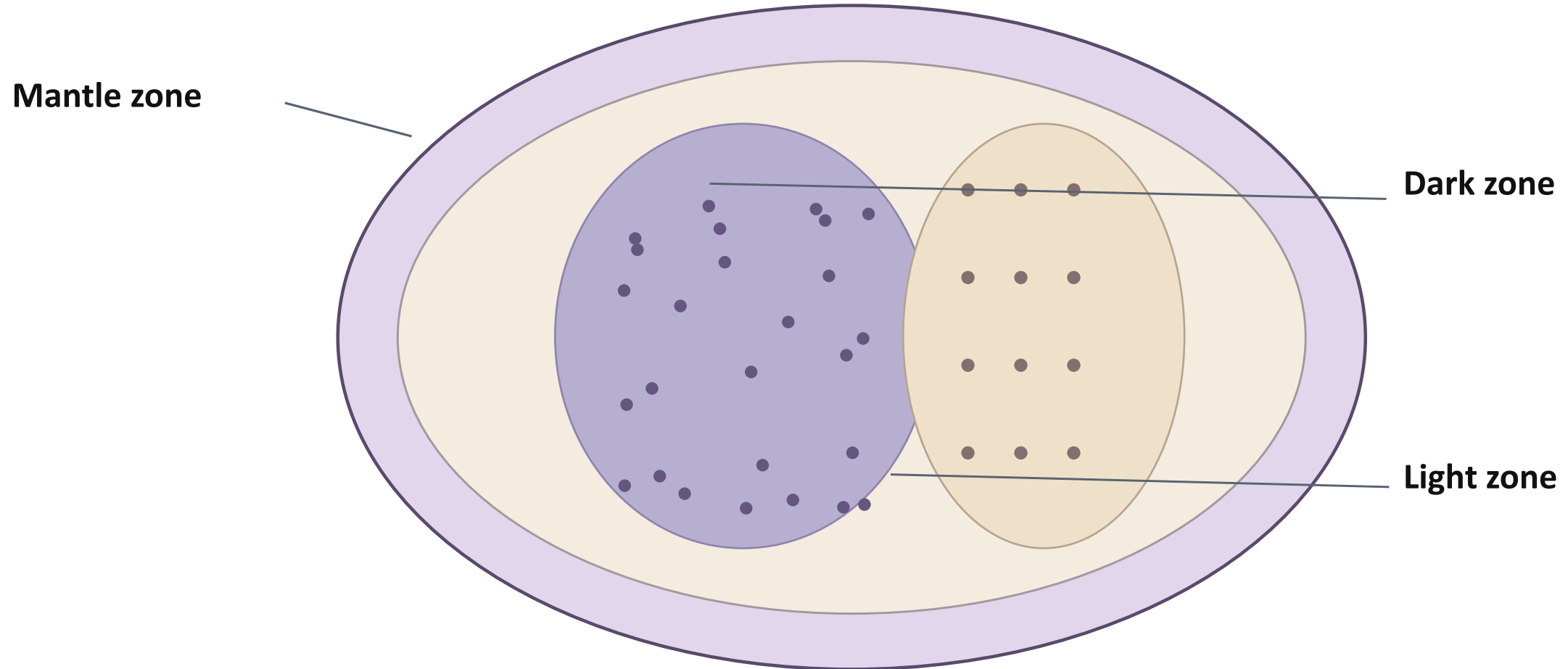
Follicular hyperplasia: The defining finding

Prominent large, oblong secondary follicles containing germinal centers.

- Each germinal center is surrounded by a mantle of small resting naive B cells.
- Germinal centers show distinct light and dark zones.
- The architecture outside the follicles remains important to interpretation.

The mantle zone surrounds the reactive germinal center

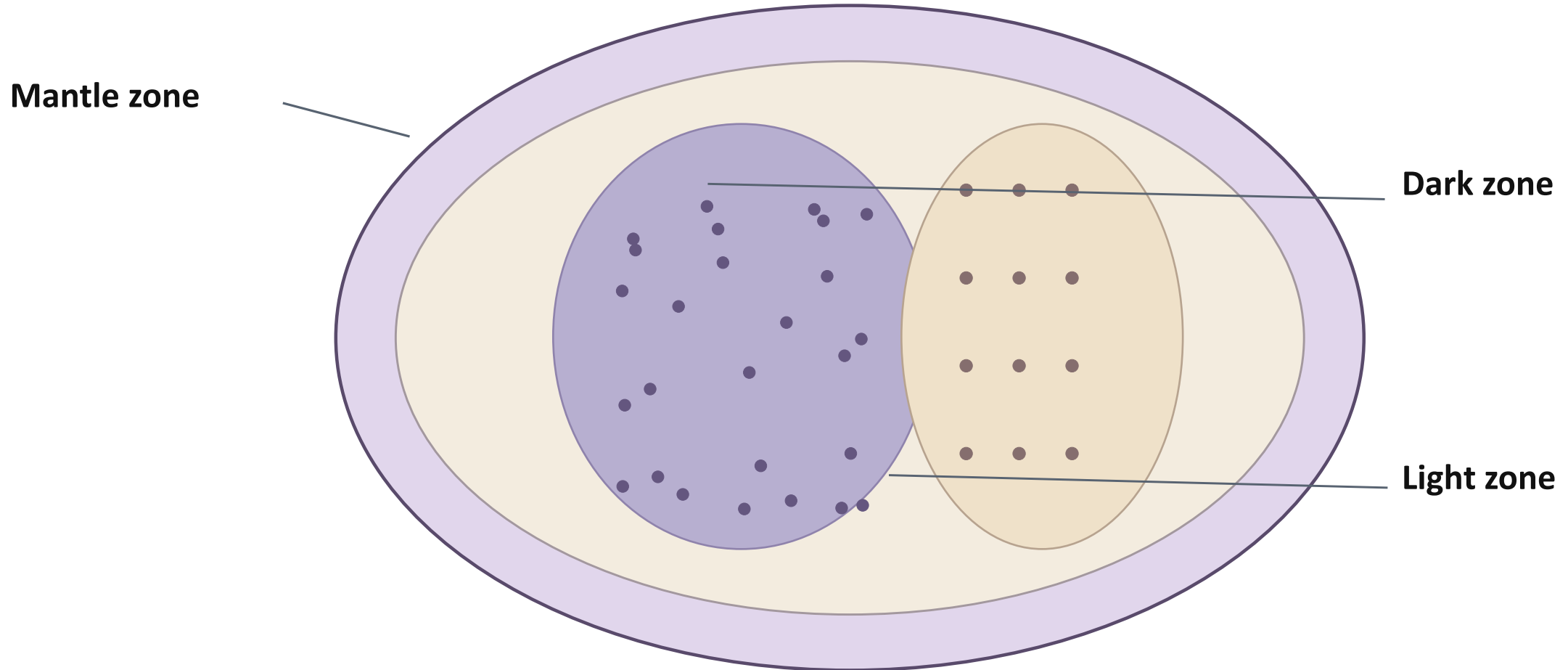
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The rim contains small resting naive B cells.

Dark and light zones reveal germinal-center polarity

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Polarity reflects different cellular populations and processes.

Dark zones contain proliferating centroblasts

The dark zone is enriched in blast-like dividing B cells.

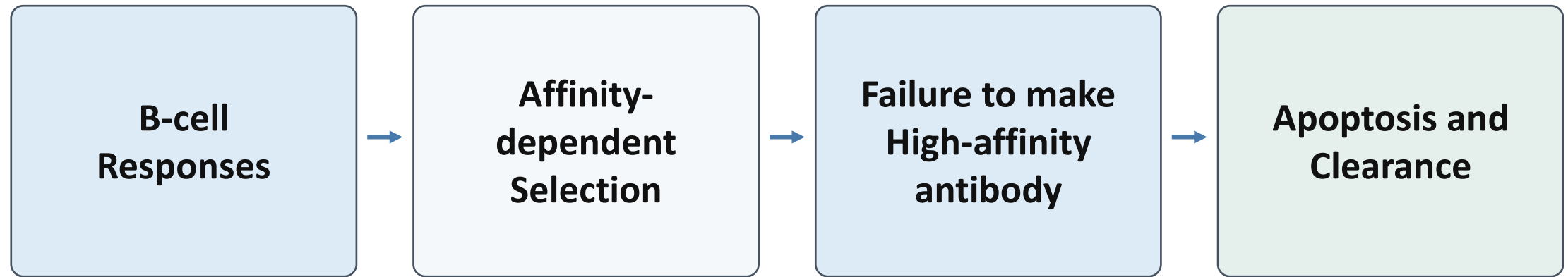
- Proliferation explains frequent mitotic figures.
- Prominent mitoses do not by themselves establish malignancy.
- Assess mitoses together with macrophages, polarity and architecture.

Light zones contain centrocytes

Centrocytes are B cells with irregular or cleaved nuclear contours.

- The light zone is morphologically distinct from the proliferative dark zone.
- Preserved light–dark zoning supports a reactive follicular process.
- The dark and light areas must be interpreted within an intact follicle.

Germinal-center B-cell selection and apoptosis



Failure pathway shown: Unsuccessful B cells undergo apoptosis and macrophage clearance.

Tingible-body macrophages reflect cellular turnover

Macrophages contain phagocytosed nuclear debris of apoptotic B cells.

- They are interspersed among responding germinal-center B cells.
- They provide a practical clue to reactive follicular activity.
- Interpret macrophages together with variable follicles and polarity.

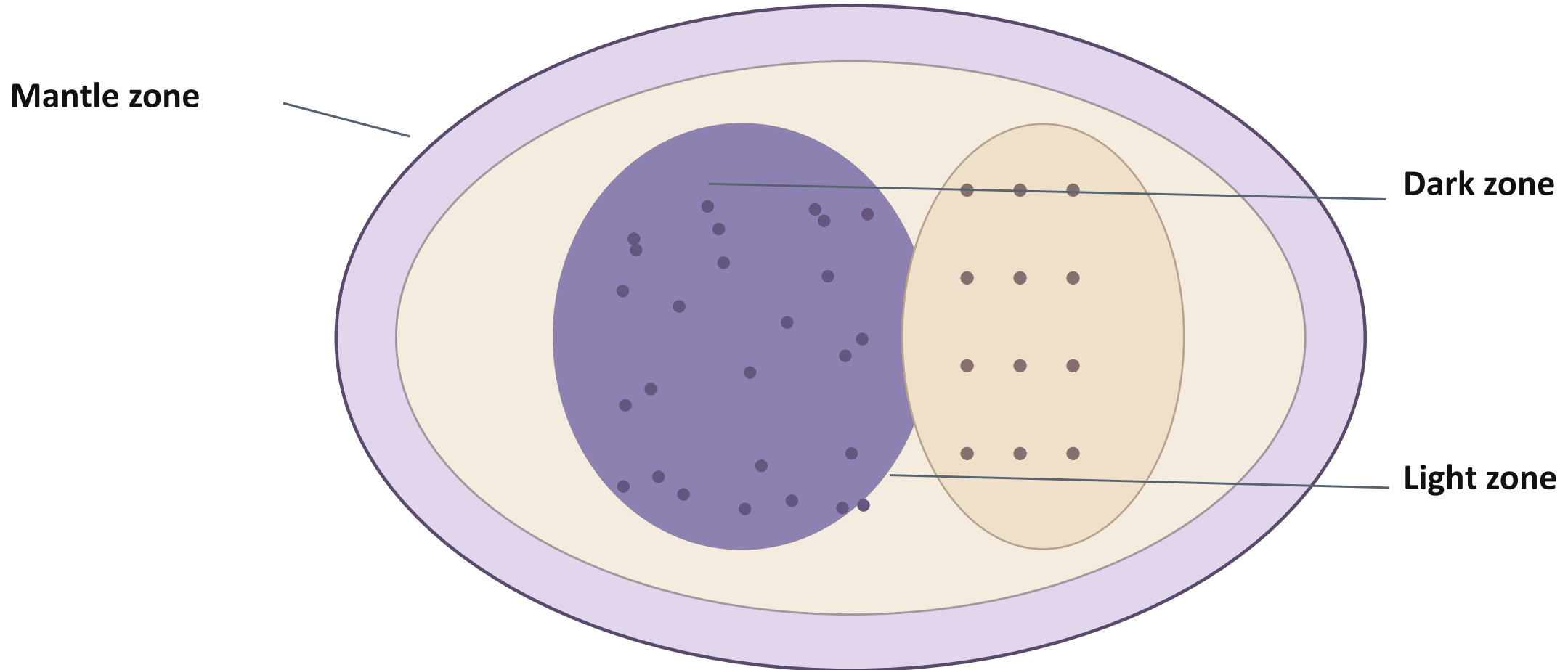
Follicular dendritic cells form a subtle supporting network

Antigen-presenting follicular dendritic cells reside within germinal centers.

- They support the microenvironment of the follicular immune response.
- This network is relatively inconspicuous by routine morphology.
- Their presence should not be confused with tingible-body macrophages.

Integrated morphology of a reactive secondary follicle

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Mantle, polarized germinal center, mitoses and macrophages are complementary clues.

Reactive follicle versus neoplastic follicle: Architecture

Reactive follicular hyperplasia

- Interfollicular T-cell zones remain
- Lymphatic sinusoids remain recognizable
- Follicles vary markedly in shape and size

Follicular lymphoma: Caution

- May resemble reactive follicles morphologically
- Loss of the typical reactive features raises concern
- Architecture alone is not an absolute diagnostic test

The source identifies reactive features favoring benignity; Ambiguous cases need additional studies.

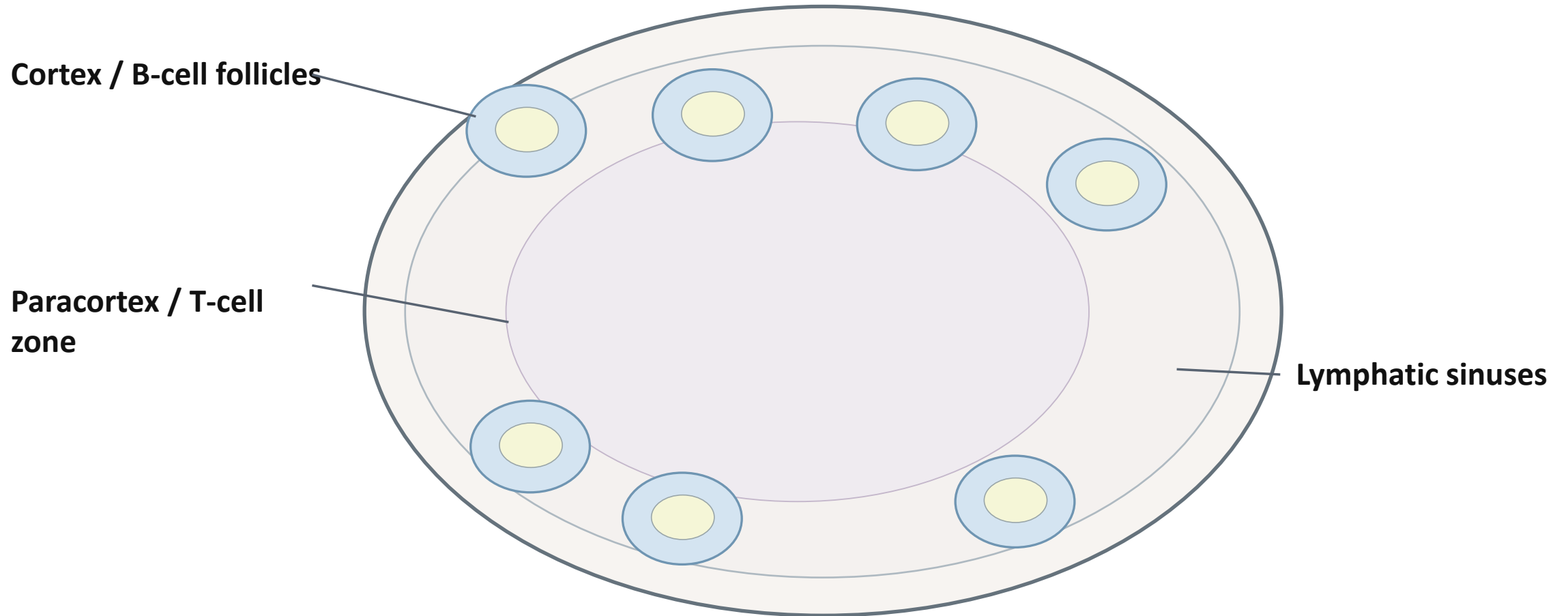
Variation among follicles supports a reactive process

Reactive follicles show substantial differences in both size and shape.

- A nonuniform population of follicles fits changing immune responses.
- Assess the follicle population at low magnification.
- Combine size variation with preservation of other nodal compartments.

Preserved interfollicular structures support reactivity

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Look for intact T-cell zones and sinuses between follicles.

Morphologic evidence for reactive follicular hyperplasia

Feature	Reactive interpretation	Why it matters
Variable follicle sizes	Heterogeneity across the node	Reactive follicles do not have to be uniform
Recognizable light / dark zones	Germinal-center polarity	Distinct functional compartments persist
Frequent mitoses	Active centroblast proliferation	High turnover can be physiologic
Tingible-body macrophages	Clearance of apoptotic cells	Supports active germinal-center selection
Preserved T zones / sinuses	Retained overall architecture	Argues against diffuse replacement

Contexts associated with follicular hyperplasia

Rheumatoid arthritis

A chronic inflammatory autoimmune stimulus

Toxoplasmosis

An infectious trigger of immune activation

Early HIV infection

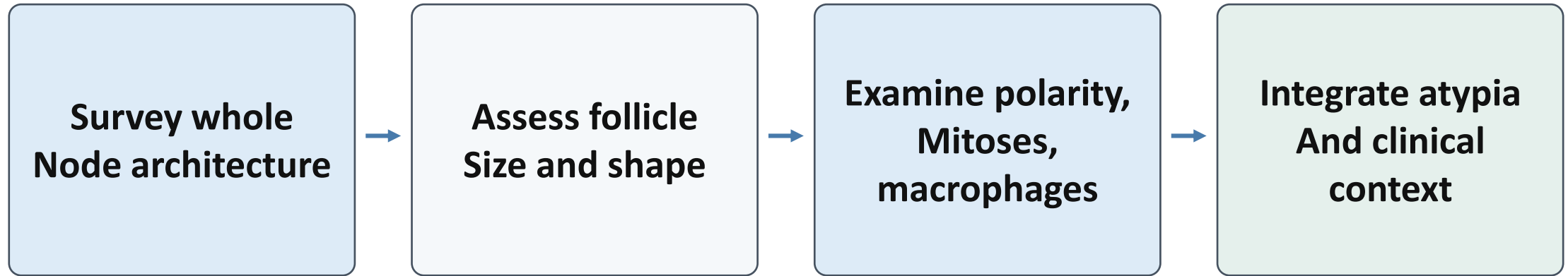
An early viral immune response

A reactive follicle can resemble follicular lymphoma

Histologic resemblance is the key diagnostic pitfall.

- Preserved compartments, follicle variability and germinal-center polarization favor reactivity.
- Reactive follicles typically show mitoses and tingible-body macrophages.
- If the pattern is ambiguous, morphology alone may not exclude neoplasia.

Practical review of follicle-rich lymph nodes



This is an educational morphology workflow, not a validated stand-alone diagnostic algorithm.

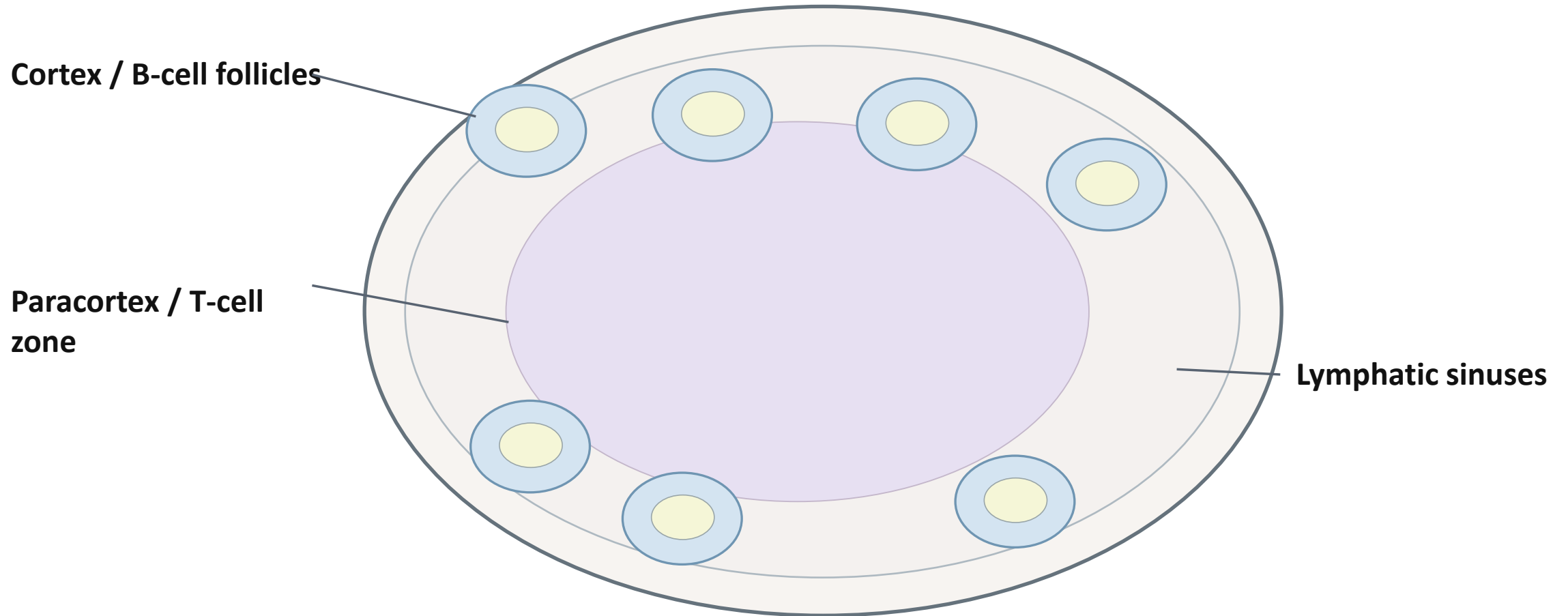
Paracortical hyperplasia reflects T-cell activation

Stimuli activating T-cell–mediated immunity expand the paracortex.

- Acute viral infections are a characteristic context.
- Infectious mononucleosis is a classic example.
- The expanded compartment lies between or around B-cell follicles.

Paracortical expansion changes the balance of compartments

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T-cell-rich tissue expands inward and toward follicles.

Immunoblasts are enlarged activated T cells

The paracortex can contain strikingly large reactive immunoblasts.

- Approximately three- to fourfold larger than resting lymphocytes.
- Round nuclei with open chromatin and prominent nucleoli.
- Moderate amounts of pale cytoplasm complete the described phenotype.

Resting lymphocytes versus reactive immunoblasts

Resting lymphocyte

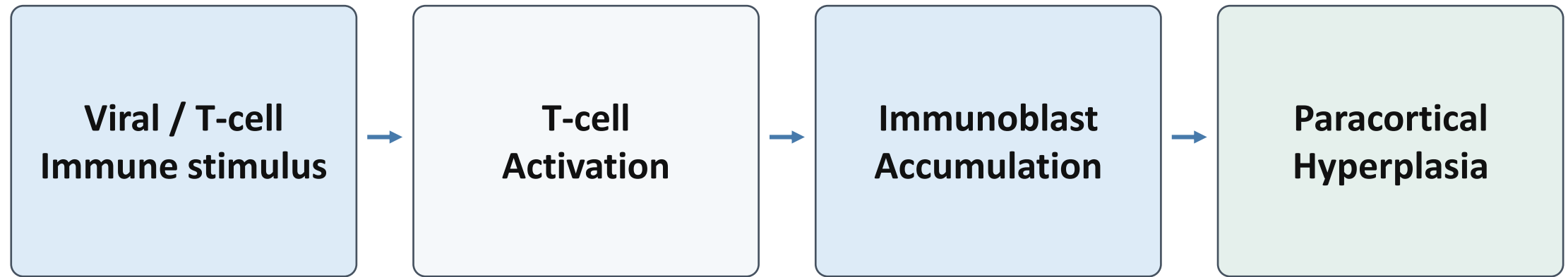
- Small cell size
- Condensed chromatin
- Inconspicuous nucleolus

Activated T-cell immunoblast

- Markedly larger size
- Open chromatin; Prominent nucleoli
- Moderate pale cytoplasm

Activated morphology can be alarming without implying a clonal tumor.

Why the paracortex becomes expanded



This schematic summarizes the source-described cellular pattern.

Exuberant paracortical reactions may obscure follicles

Expanded T-cell zones can encroach upon—and sometimes efface—B-cell follicles.

- Degree of expansion varies with the intensity of activation.
- Follicular effacement does not automatically imply malignancy.
- Evaluate the cytology and clinical stimulus as well as architecture.

Sinusoidal and vascular endothelium may hypertrophy

Paracortical reactions often include endothelial activation.

- Activated lining cells become more conspicuous.
- Changes may involve both sinuses and blood vessels.
- Interpret vascular change within the overall reactive process.

Reactive paracortices can contain accessory inflammatory cells

Macrophages and eosinophils may accompany T-cell zone expansion.

- They are secondary components rather than the defining population.
- The dominant pattern remains reactive T-cell activation.
- Cellular mixtures should be evaluated across the full node.

When immunoblasts mimic lymphoid neoplasia

Features supporting a reaction

- Recognizable infectious / immunologic context
- Mixture of activated and background immune cells
- Pattern centered in T-cell zones

Reason to investigate further

- Marked immunoblast-rich expansion
- Architectural effacement in exuberant cases
- Source notes special studies may be necessary

Avoid claiming that a large immunoblast is neoplastic solely because it is atypical.

Paracortical pattern: Three linked findings

Stimulus	Cell population	Architectural effect
T-cell–mediated activation, often viral	Immunoblast-rich expansion of T-cell zones	Follicles compressed or obscured in marked cases

Sinus histiocytosis is also called reticular hyperplasia

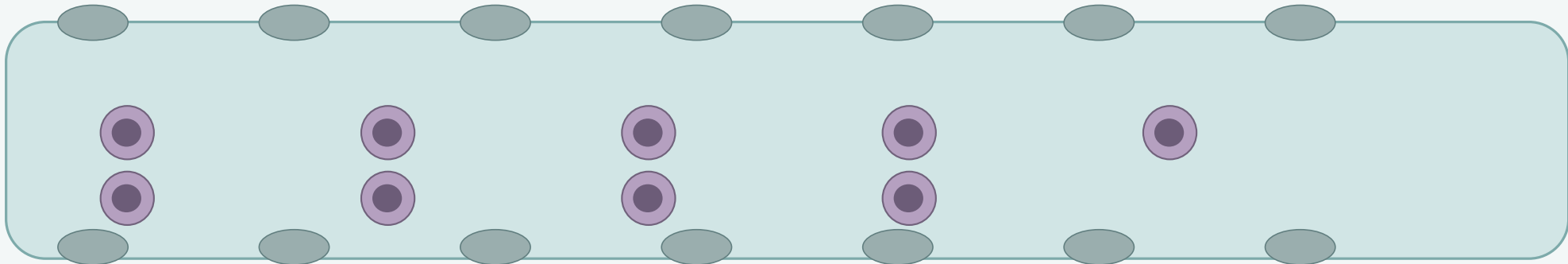
The characteristic change is expansion and distortion of lymphatic sinuses.

- Increased number and size of sinus-lining cells.
- Increased numbers of macrophages within sinuses.
- These changes can be substantial in nodes draining tumors.

Enlarged sinus-lining cells contribute to sinus expansion

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Enlarged sinus-lining cells



Intrasinusoidal macrophages

The lining-cell component accompanies macrophage accumulation.

Intrasinusoidal macrophages drive the histiocytic appearance

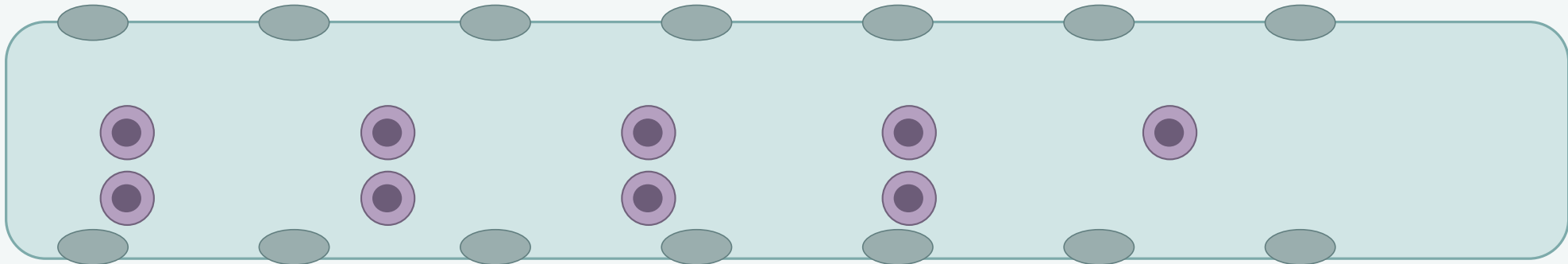
Accumulating macrophages enlarge the sinus compartments.

- They are found inside lymphatic sinuses.
- Together with enlarged lining cells, they distort sinus outlines.
- The word “histiocytosis” here denotes a reactive pattern.

Sinus histiocytosis preserves a recognizable sinus-based topology

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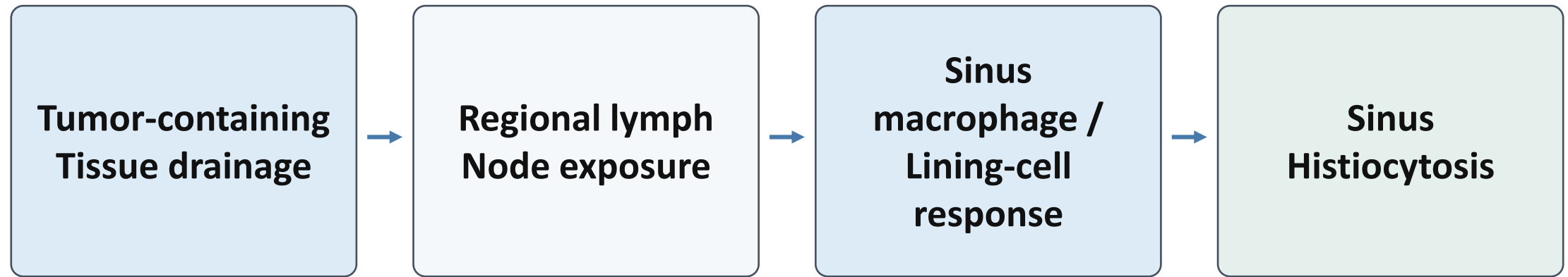
Enlarged sinus-lining cells



Intrasinusoidal macrophages

Identify the expanded sinus spaces rather than assuming a diffuse infiltrate.

Cancer-draining lymph nodes may show sinus histiocytosis



Breast carcinoma is Robbins' example of a setting with conspicuous sinus histiocytosis.

Sinus histiocytosis does not by itself mean metastasis

A reactive nodal pattern may accompany lymphatic drainage from a carcinoma.

- The described sinus change consists of macrophages and lining-cell enlargement.
- Presence of this pattern alone does not demonstrate tumor cells in a node.
- Tumor status requires assessment for actual neoplastic involvement.

Three-pattern diagnostic comparison

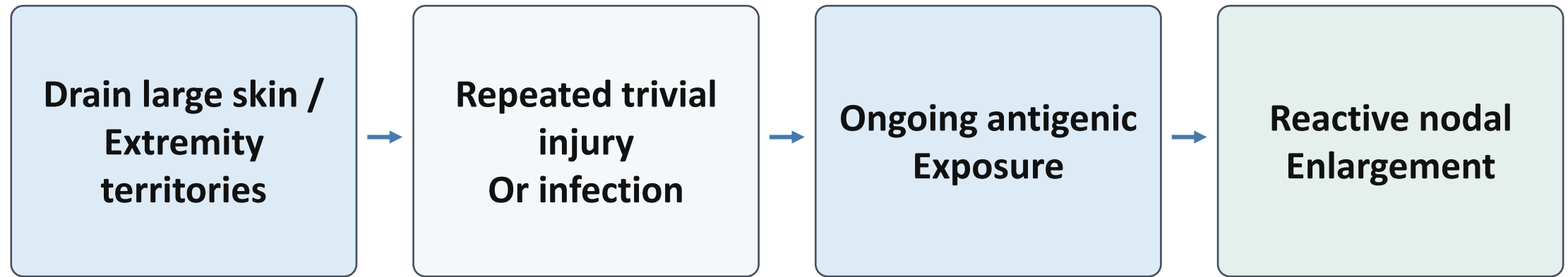
Pattern	Main compartment	Leading morphologic clues
Follicular hyperplasia	B-cell follicles	Oblong polarized germinal centers; Mantle; Tingible-body macrophages
Paracortical hyperplasia	T-cell paracortex	Immunoblast-rich expansion; Can obscure follicles
Sinus histiocytosis	Lymphatic sinuses	Enlarged lining cells and intrasinusoidal macrophages

Slow enlargement usually explains the absence of pain

Chronic lymphadenitis is characteristically nontender.

- Nodal growth usually occurs gradually.
- Acute tissue injury and associated inflammation are absent or limited.
- Tenderness is a clinical clue, not an absolute histologic classifier.

Why axillary and inguinal nodes often show chronic reactions



The source specifically emphasizes axillary and inguinal distributions.

Link a nodal site to its immune-drainage territory

Axillary / inguinal groups

- Large drainage territories
- Repeated low-grade peripheral immune challenges
- Common sites of chronic lymphadenitis

Other patterns of presentation

- Localized or generalized nodes require context
- Nodal distribution does not identify a single cause
- Morphology should be correlated with clinical findings

Compartment- and distribution-aware interpretation.

Case 1 · Persistent axillary lymphadenopathy

An axillary node enlarges slowly and is not tender. The region has experienced repeated minor skin injuries.

Interpret the tempo and likely nodal process.

The presentation is compatible with chronic reactive lymphadenitis; Histologic pattern still requires evaluation.

Case 2 · Immunoblast-rich node

Following an acute viral illness, a lymph node shows extensive expansion of its T-cell zones. Many large cells have open chromatin and prominent nucleoli.

What is the likely reactive pattern?

Paracortical hyperplasia. Numerous immunoblasts can necessitate further studies to exclude neoplasia.

Case 3 · Numerous enlarged germinal centers

A lymph node contains follicles of diverse sizes, identifiable mantle zones and polarized germinal centers. Many tingible-body macrophages are present.

Which process does this morphology favor?

Reactive follicular hyperplasia rather than a uniform neoplastic follicular proliferation.

Case 4 · A carcinoma-draining node

A lymph node draining a breast carcinoma has markedly expanded lymphatic sinuses, enlarged lining cells and abundant macrophages.

Name the reactive pattern; Does it prove nodal metastasis?

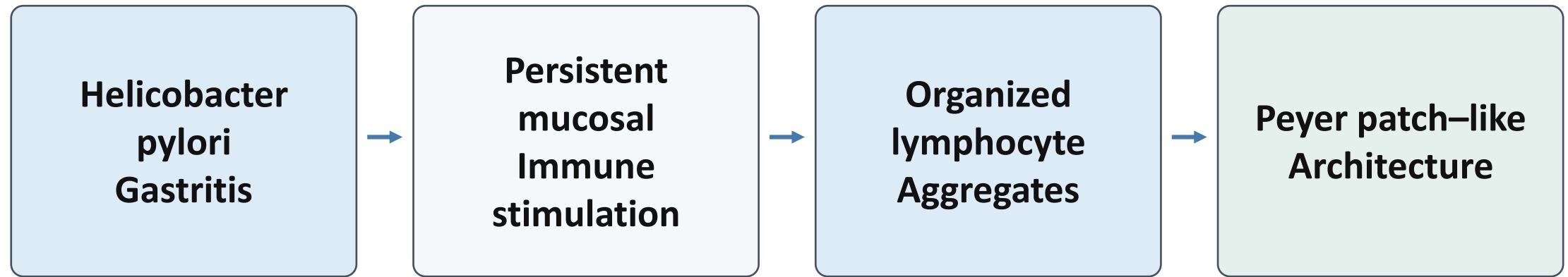
Sinus histiocytosis. No: Tumor cells must be demonstrated separately.

Tertiary lymphoid structures form outside normal lymphoid organs

Chronic immune reactions can organize lymphoid cell collections within nonlymphoid tissue.

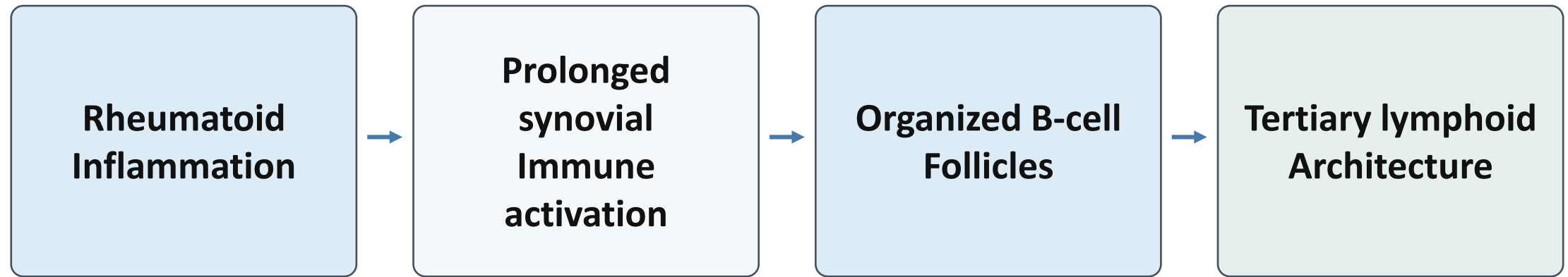
- These structures are sometimes called tertiary lymphoid structures.
- They resemble aspects of secondary lymphoid organization.
- They arise in the setting of chronic local inflammatory stimulation.

Chronic gastritis may create mucosal lymphoid aggregates



This is an extranodal example—not a lymph node.

Rheumatoid synovium may contain organized B-cell follicles



Anatomical location distinguishes these collections from nodal follicles.

Lymphotoxin is a proposed organizer of ectopic lymphoid tissue

Lymphotoxin as probably contributing to tertiary-structure formation.

- Lymphotoxin is required for normal secondary lymphoid-organ development.
- Its role in extranodal chronic inflammatory collections is presented as probable.
- Do not convert a proposed mechanism into an obligatory diagnostic criterion.

Secondary lymph nodes versus tertiary lymphoid structures

Lymph node

- Pre-existing, encapsulated secondary lymphoid organ
- Defined B-cell / T-cell compartments and sinuses
- Changes its morphology during immune responses

Tertiary lymphoid structure

- Immune collection developing in nonlymphoid tissue
- Appears with sustained local inflammation
- May organize follicle-like B-cell areas

Both illustrate structural organization of adaptive immune responses.

How to interpret a reactive lymph-node biopsy

Question	Observation to make	Inference supported
What expanded?	Follicles, paracortex or sinuses	Describe the dominant reaction
Is architecture preserved?	T-cell zones and sinuses between follicles	Helpful evidence for reactivity
What cells predominate?	Centroblasts, immunoblasts, macrophages	Links cytology to compartment
Is clinical context compatible?	Infection, autoimmunity, drainage territory	Refines interpretation—not proof of cause
Does a mimicker remain possible?	Extreme atypia or architectural disruption	Consider additional diagnostic investigation

Morphologic reactivity and malignancy are not simple opposites

Some reactive patterns resemble lymphoid neoplasia.

- Follicular hyperplasia may resemble follicular lymphoma.
- Immunoblast-rich paracortical reactions may suggest neoplasia.
- The source advises special studies in difficult paracortical reactions.

Integrated review · Mixed patterns in one node

A lymph node contains large reactive follicles, conspicuous paracortical immunoblasts, and dilated sinuses filled with macrophages.

Must one compartment exclude the others?

No. Chronic nonspecific lymphadenitis may show multiple reactive patterns in a single node.

Final synthesis: Interpret the compartment, not only cell size

B-cell follicle

Polarized germinal centers;
Tingible-body
macrophages

T-cell paracortex

Activated immunoblasts;
Expanding T-cell zones

Sinus compartment

Sinus-lining cells and
macrophages; Enlarged
sinuses

Reference and scope

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026). Reactive proliferations of white cells and lymph nodes;
chronic nonspecific lymphadenitis.

Morphologic drawings are original teaching schematics, not diagnostic photomicrographs.