

Metaplastic Lesions

Urinary bladder pathology

Reactive epithelial remodeling · Cancer precursors · Benign mimics

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Differentiate true metaplasia from metaplasia-like implantation.
- Recognize cystitis cystica, cystitis glandularis, and squamous replacement.
- Identify the patterns with carcinoma precursors.
- Explain why nephrogenic adenoma may mimic an invasive tumor.

Four patterns within one anatomic setting

Pattern	Core change	Diagnostic importance
Cystitis cystica	Cystic spaces in von Brunn nests	May coexist with glandularis
Cystitis glandularis	Cuboidal/columnar lining in nests	Intestinal metaplasia has a risk context
Squamous metaplasia	Squamous lining replaces urothelium	Keratinizing multifocal lesions are precursors
Nephrogenic adenoma	Renal-type cells grow at urothelial erosion	Can imitate neoplasia

True metaplasia versus a metaplasia-like lesion

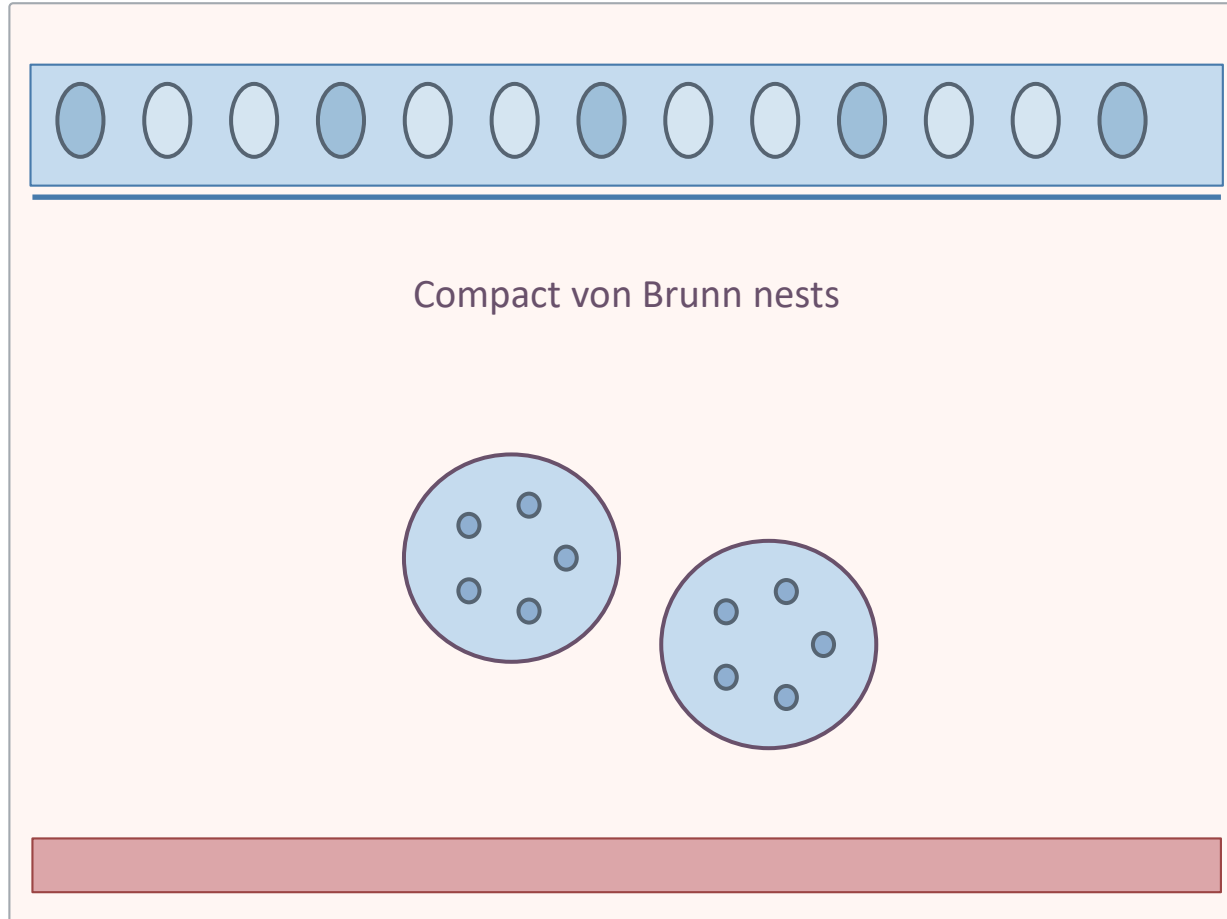
True metaplastic replacement

- Epithelial cells acquire a different mature phenotype.
- Examples: Glandular and squamous patterns.
- Often occurs with inflammation or chronic injury.

Implantation-based mimic

- Nephrogenic adenoma may have another cellular origin.
- Renal tubular cells can implant on injured urothelium.
- Its architecture can appear tumor-like.

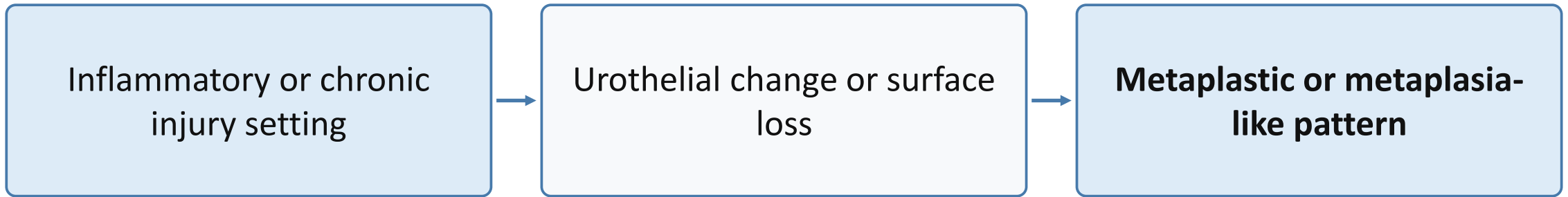
Bladder wall compartments organize interpretation



Schematic — not a histology image

- Urothelium lines the lumen.
- Lamina propria supports urothelial nests and glands.
- Detrusor is the bladder muscular wall.
- Anatomic location alone does not prove malignancy.

Chronic injury as a driver of remodeling



- Robbins explicitly links cystic/glandular lesions with inflammation.
- Squamous metaplasia is described as an adaptation to chronic injury.

Why bladder metaplasias matter clinically

Usually interpreted morphologically

- Recognition relies on architecture and epithelial phenotype.
- Several patterns may coexist at one site.
- Biopsy features must be interpreted in context.

Two distinct clinical concerns

- Some patterns precede defined malignancies.
- Other benign patterns can simulate bladder cancer.
- These concerns should not be conflated.

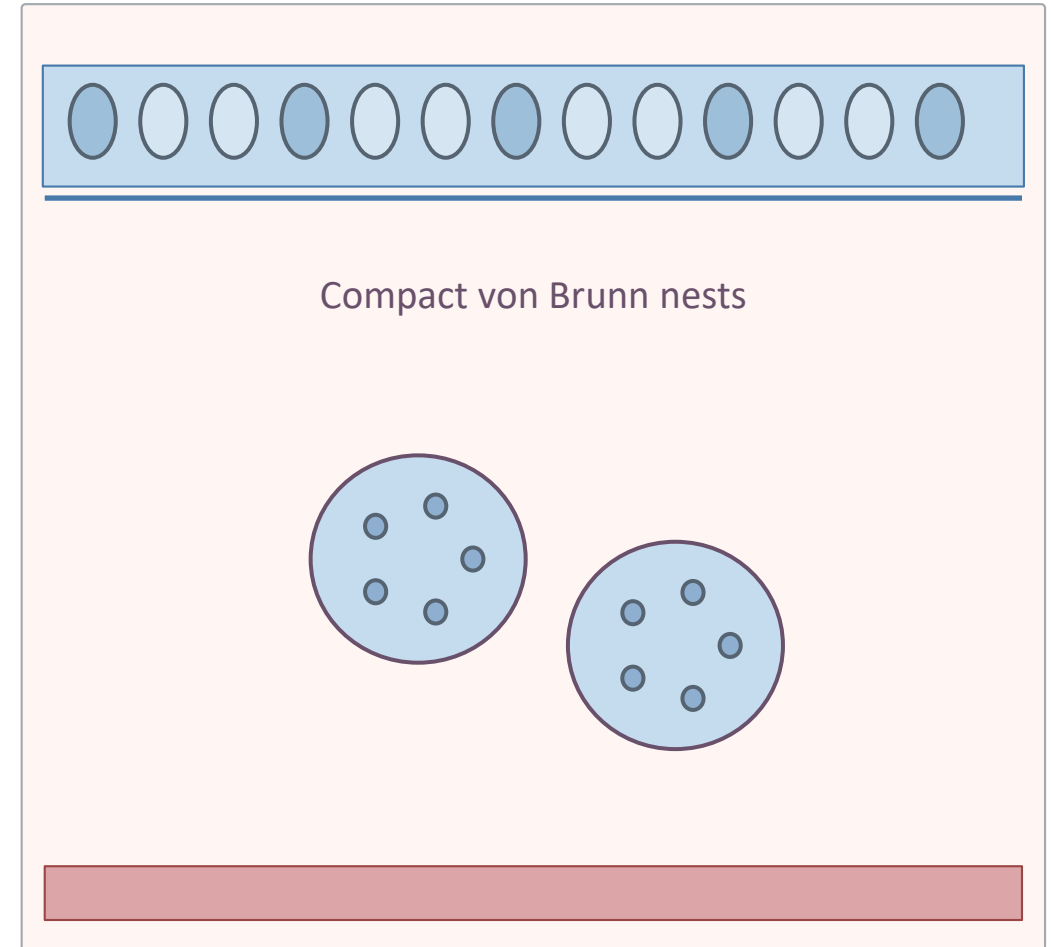
Cystitis cystica and glandularis: One family

A shared starting point: Downward growth of urothelial nests

- Von Brunn nests are epithelial structures in the lamina propria.
- Central cells may become glandular or form cyst-like spaces.
- Both changes commonly occur together.

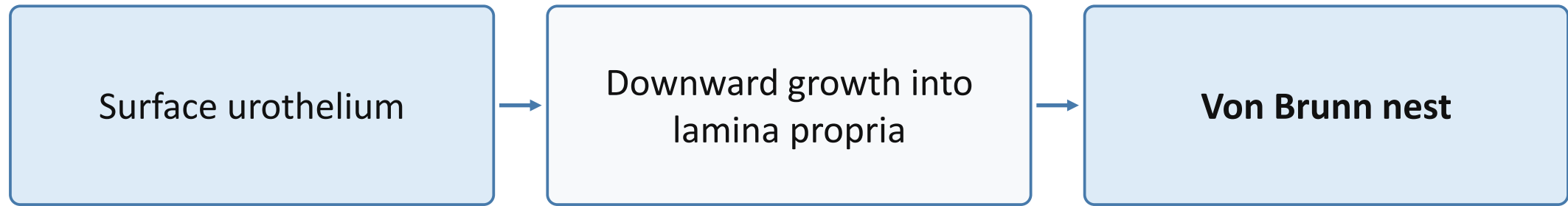
Von Brunn nests: Position is the first clue

- Nests extend from urothelium into the lamina propria.
- They form the architectural substrate for both variants.
- The nest center determines the pattern of change.



Schematic — not a histology image

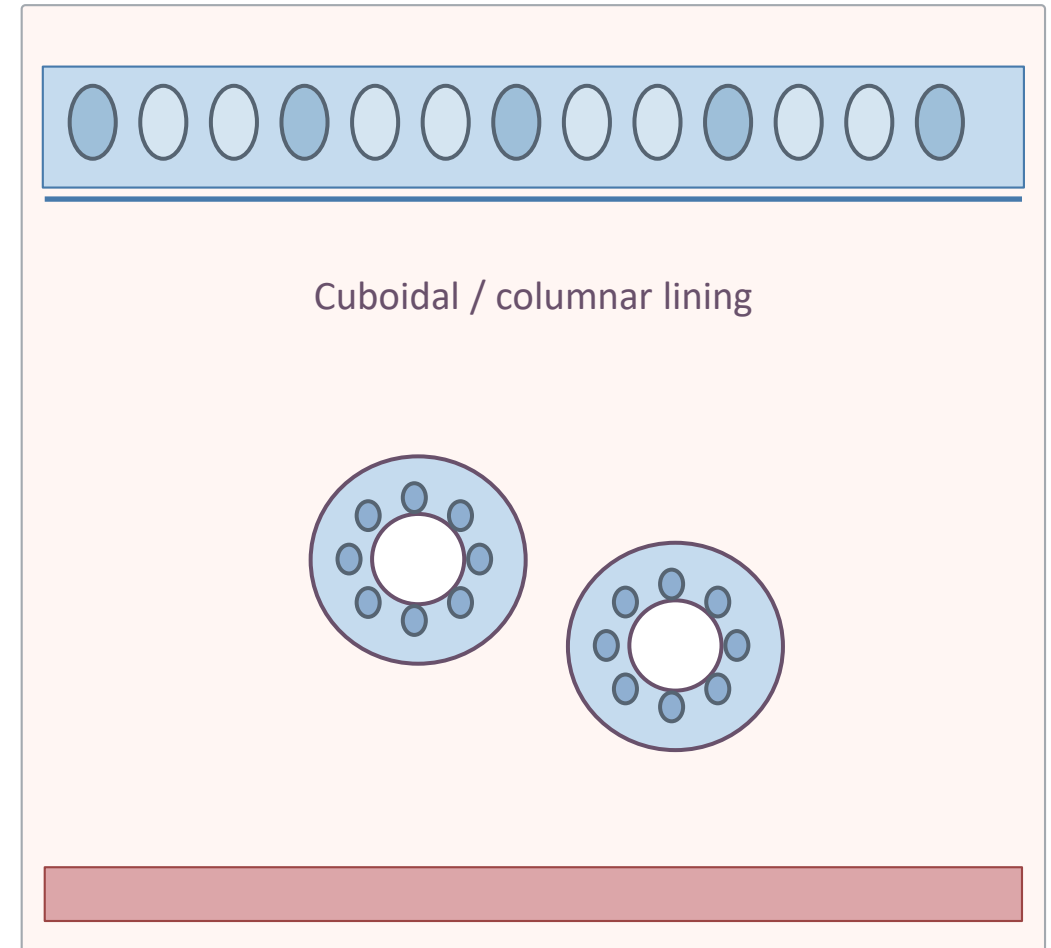
Formation of a subepithelial epithelial nest



- The term “nest” describes a compact urothelial aggregate.
- A subepithelial nest is not, by itself, proof of carcinoma.

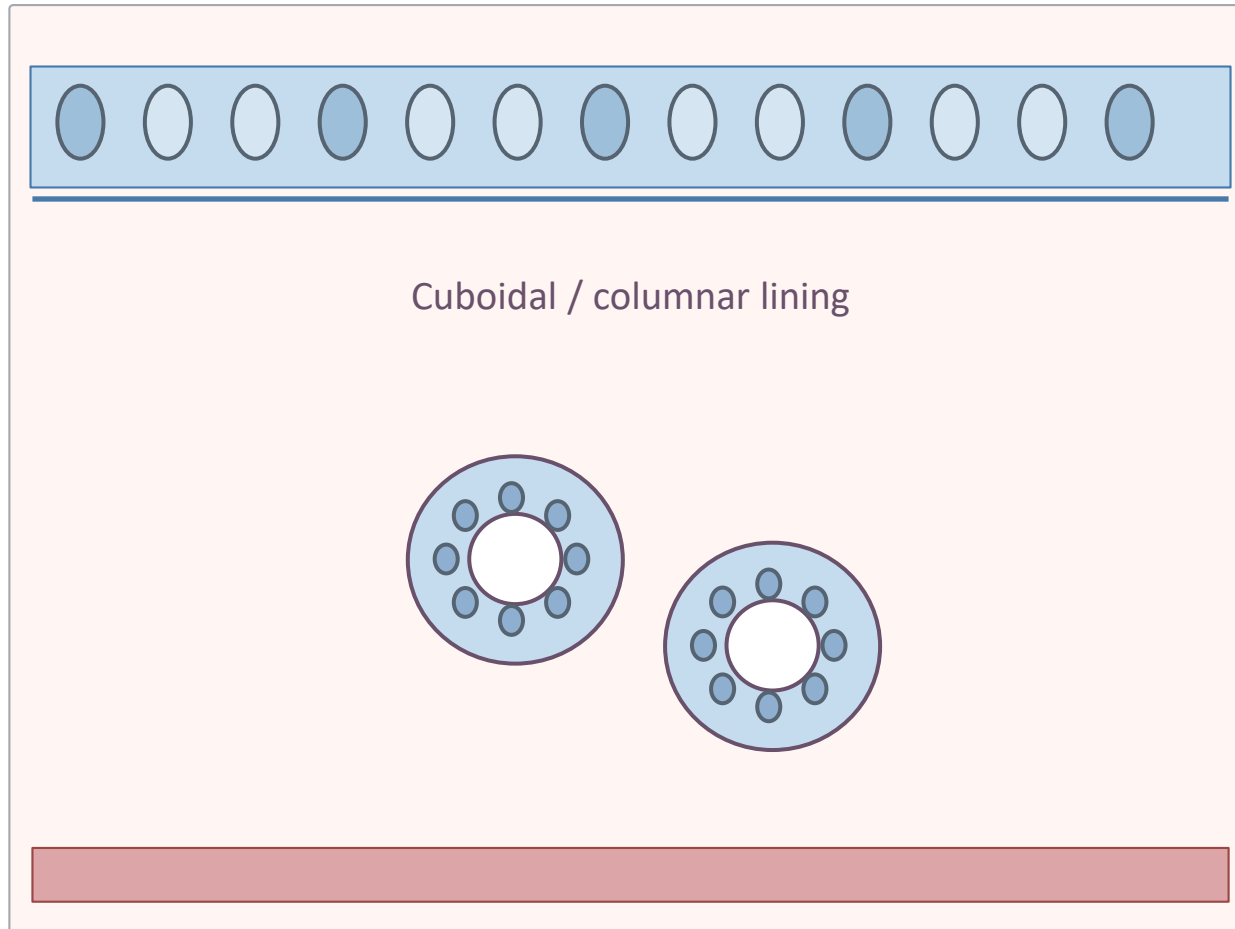
Cystitis glandularis: Epithelial phenotype changes

- Cells within nests adopt a cuboidal or columnar appearance.
- The new epithelial phenotype is the defining change.
- Recognize the altered lining in its urothelial-nest context.



Schematic — not a histology image

The columnar phenotype in cystitis glandularis



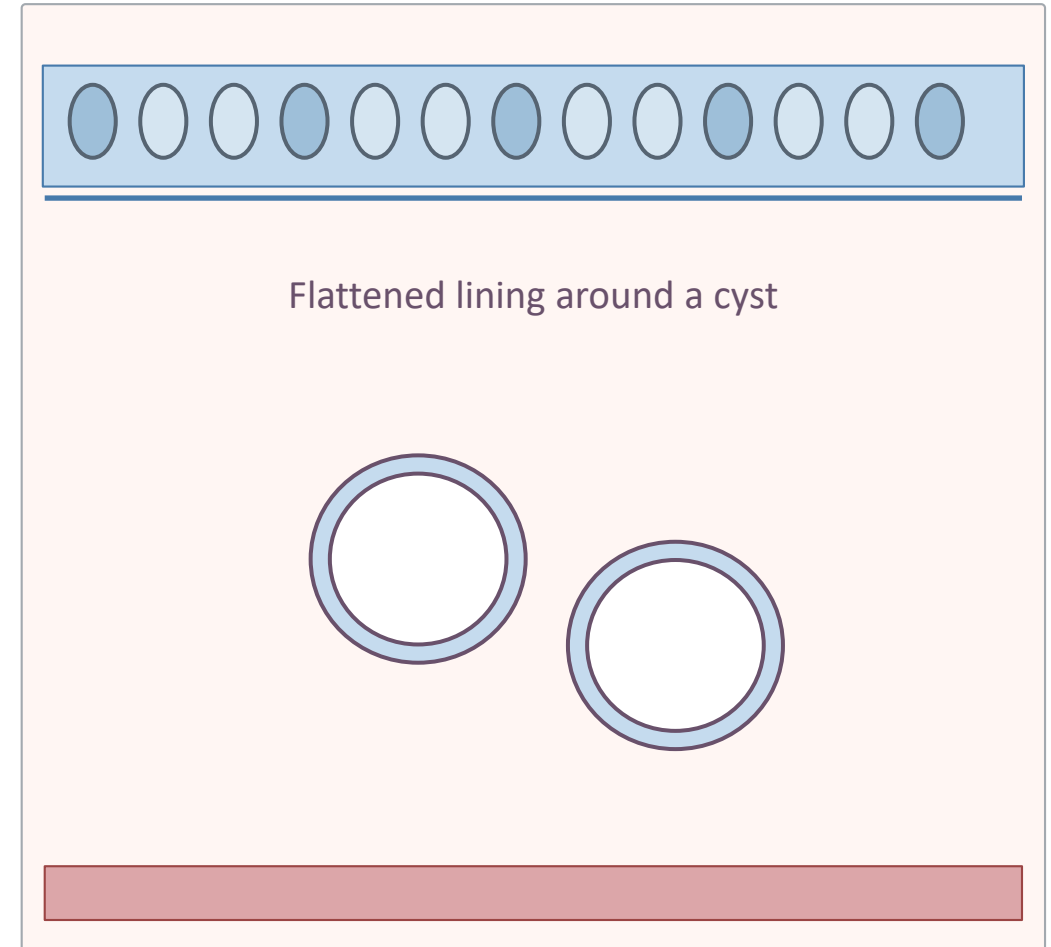
Cuboidal / columnar lining

- Central epithelial lining becomes taller and gland-like.
- Cystitis glandularis is not defined simply by a cavity.
- Identify the lining cells, not only the lumen.

Schematic — not a histology image

Cystitis cystica: Central retraction forms a lumen

- Central cells retract, creating cystic spaces.
- Flattened urothelium lines these spaces.
- The lining differs from cuboidal/columnar glandularis.



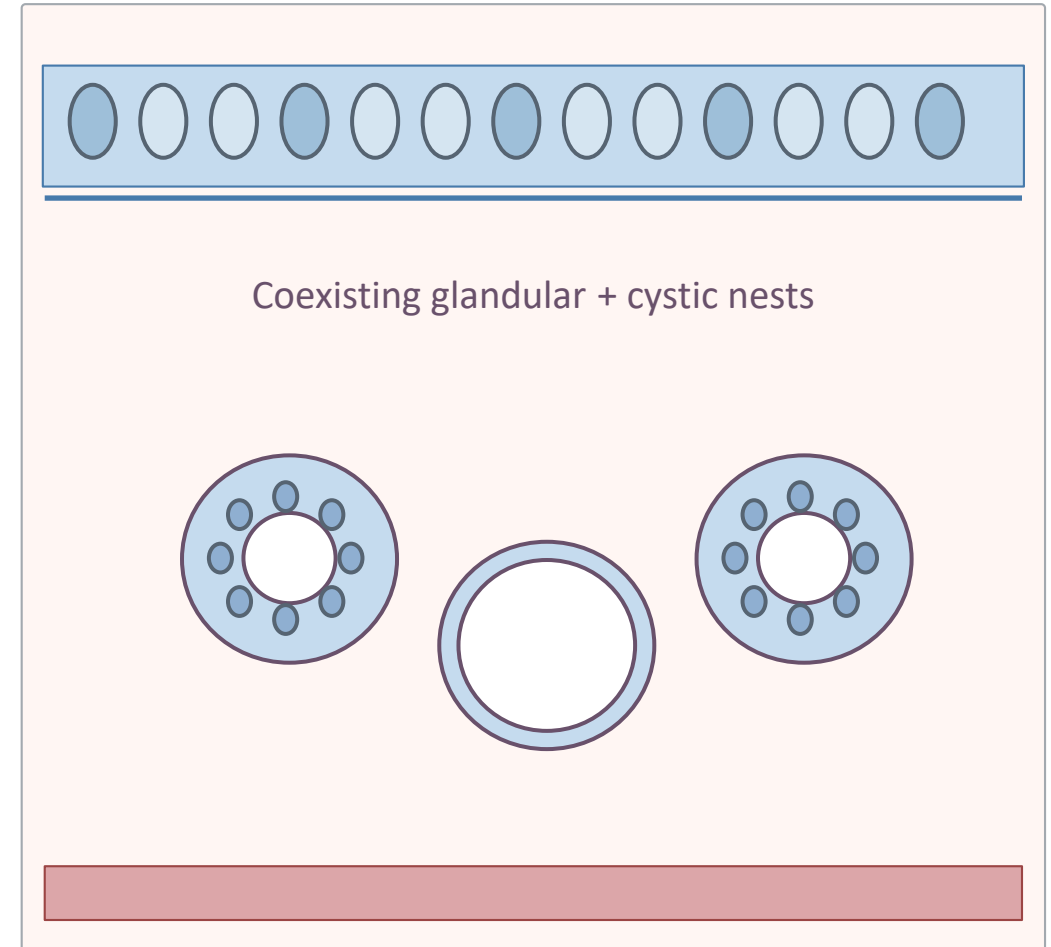
Schematic — not a histology image

Why “cystic” and “glandular” are not synonyms

Feature	Cystitis cystica	Cystitis glandularis
Underlying structure	Von Brunn nest	Von Brunn nest
Central phenomenon	Retraction → cystic space	Phenotypic change → glandular lining
Lining	Flattened urothelium	Cuboidal or columnar epithelium
Coexistence	Often present together	Often present together

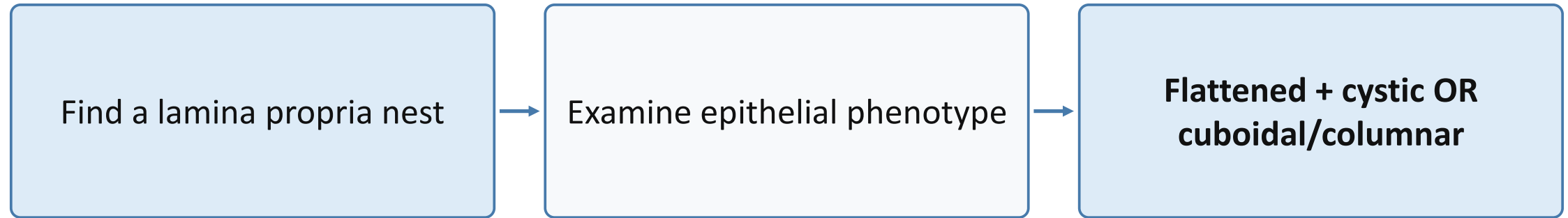
Cystitis cystica et glandularis: Coexistence

- Two microscopic patterns may arise in the same lesion.
- The combined term acknowledges this overlap.
- A specimen may contain both cystic and glandular areas.



Schematic — not a histology image

Examine the lining, then label the lesion



- This is a morphologic reasoning aid, not a complete diagnostic algorithm.
- Mixed patterns support the combined descriptive term.

Why subepithelial structures require context

Location beneath the urothelium is not equivalent to invasion

- Von Brunn nests grow downward into lamina propria.
- Nephrogenic adenoma may also extend to deeper layers.
- Interpret tissue architecture together with phenotype and clinical setting.

Inflammation and cystic/glandular change

Textbook association

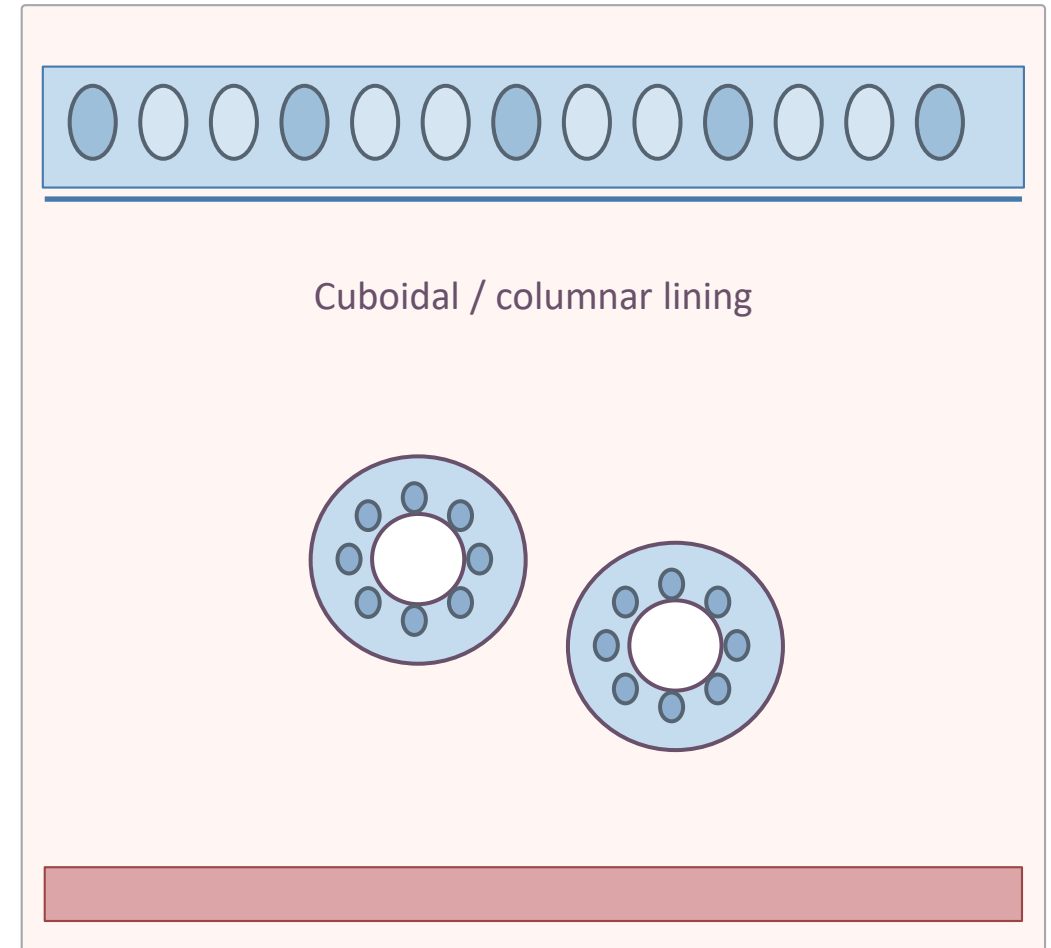
- Both variants may arise with inflammation.
- The histologic outcome can involve true metaplasia.
- The source does not define a mandatory cause for every case.

What to avoid assuming

- Not every nest must be malignant.
- Do not infer a specific infectious agent from morphology alone.
- Do not assign a cancer precursor label to every cystic nest.

Architectural reading: Glandular pattern

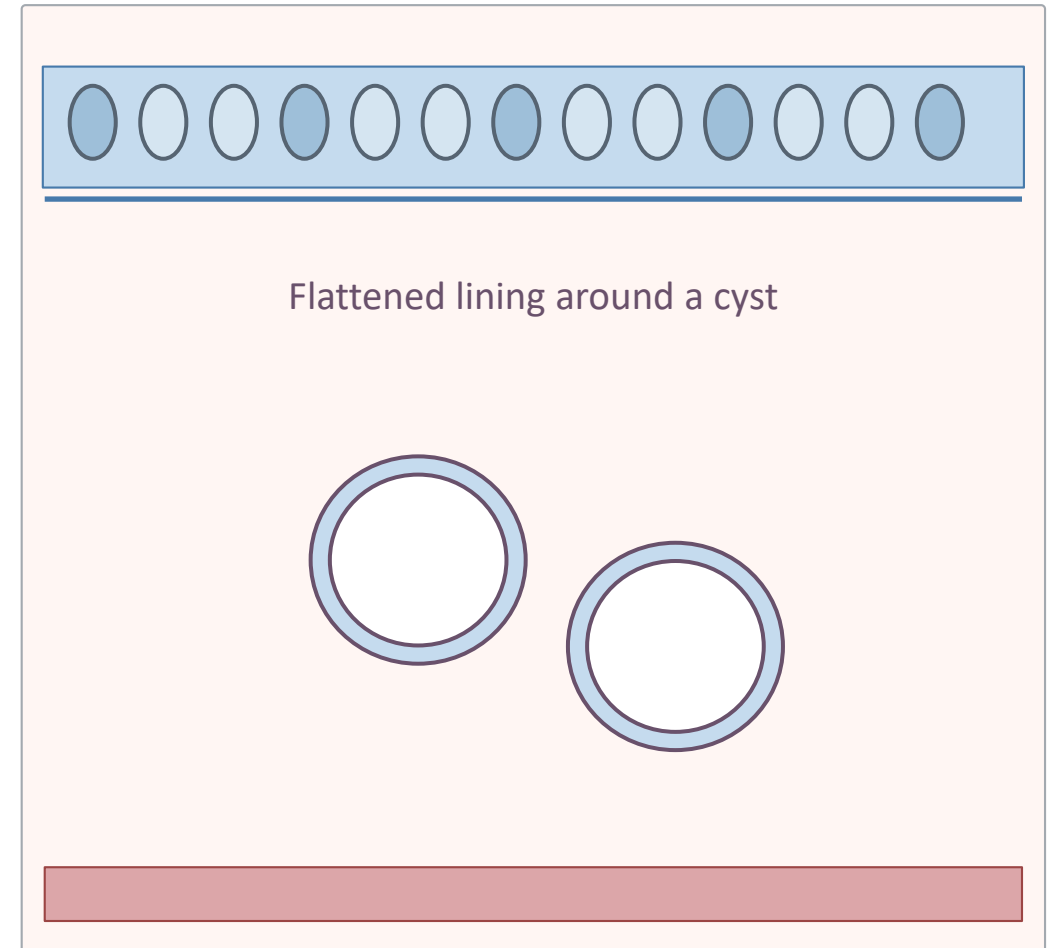
- Locate epithelial structures within lamina propria.
- Assess whether cells are cuboidal or columnar.
- Recognize the architecture as a metaplastic pattern.



Schematic — not a histology image

Architectural reading: Cystic pattern

- Identify dilated cyst-like spaces.
- Check whether the lining consists of flattened urothelium.
- Search for coexisting glandular areas.



Schematic — not a histology image

Intestinal metaplasia is a separate risk concept

Extensive, multifocal intestinal metaplasia as a precursor to adenocarcinoma

- This statement is not identical to saying all cystitis glandularis is premalignant.
- The distribution and intestinal phenotype are important qualifiers.
- Risk discussion must retain the words “extensive” and “multifocal.”

Extent and multifocality qualify the risk statement

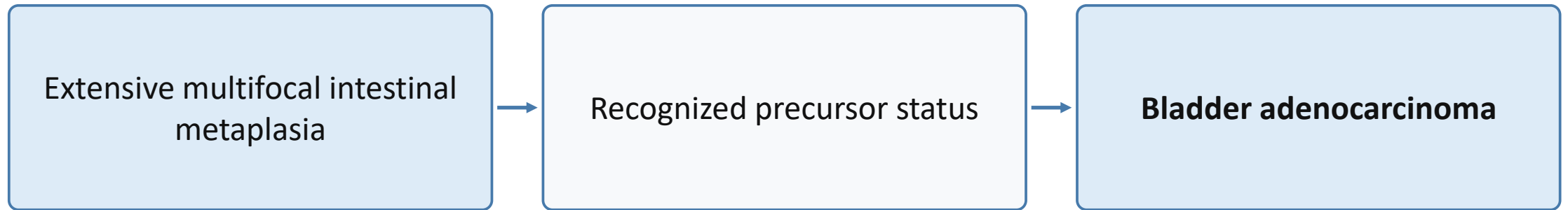
Intestinal phenotype

Extensive

Multifocal

- The specified precursor relationship concerns this combined context.
- A limited biopsy may not establish the full anatomic distribution.

Glandular precursor concept: Do not overgeneralize



A precursor relationship is not a claim that every lesion will progress.

Routine cystic/glandular change versus risk-associated intestinal metaplasia

Question	Common cystic/glandular change	Risk-associated pattern
Epithelium	Flattened or cuboidal/columnar	Intestinal metaplasia
Context	Often associated with inflammation	Extent and multifocality specified
Cancer implication	Not labeled uniformly precancerous	Adenocarcinoma precursor
Reporting principle	Describe actual pattern	Preserve qualifiers

Teaching case: Cystic and glandular structures

Illustrative teaching vignette

A bladder biopsy contains multiple lamina propria nests. Some have flattened linings around cystic lumina; Others contain cuboidal-to-columnar cells.

What combined descriptive diagnosis captures the findings?

Reasoning: Shared von Brunn–nest origin; Both cystic and glandular morphologies.

Case resolution: Two processes, one family

Cystitis cystica et glandularis

- Cystic spaces with flattened urothelial lining identify cystitis cystica.
- Cuboidal or columnar metaplasia identifies cystitis glandularis.
- The combination accounts for the coexisting features without implying carcinoma.

Squamous metaplasia: Epithelial substitution

- The urothelial lining is replaced by squamous epithelium.
- This is described as a response to chronic injury.
- The replacement is more durable in an injured environment.



Schematic — not a histology image

Two morphologic forms of squamous metaplasia

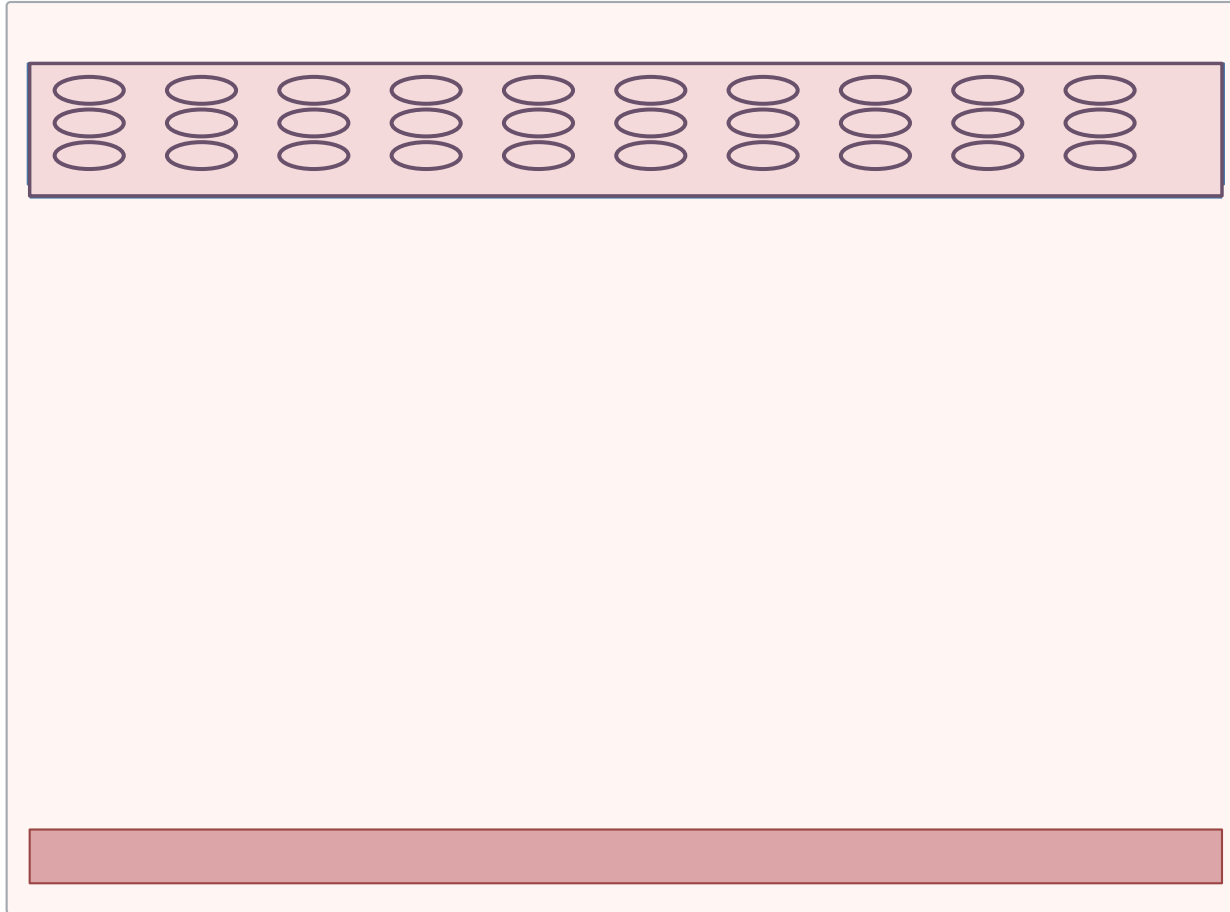
Nonkeratinizing

- Squamous epithelial replacement without surface keratinization.
- Distinguish from normal glycogenated trigonal epithelium.
- Interpret alongside location and history.

Keratinizing

- Squamous replacement with surface keratin formation.
- Extensive multifocal change is the specified precursor setting.
- Retain the extent qualifier when discussing cancer risk.

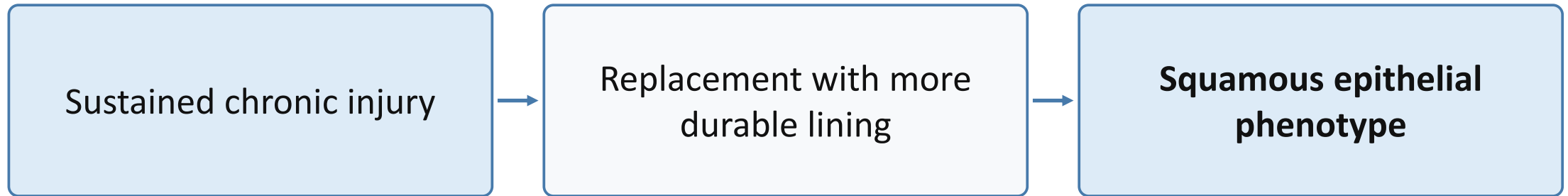
Squamous remodeling changes the surface phenotype



Schematic — not a histology image

- Transition from urothelial to squamous epithelial lining.
- The key observation is the epithelial type at the surface.
- Keratin status is assessed as a separate feature.

Why squamous metaplasia can be adaptive



- Adaptation does not mean that all squamous lesions are harmless.
- The keratinizing, extensive, multifocal subgroup has specific relevance.

The female bladder trigone is a crucial exception

- Glycogenated squamous epithelium can be present normally in the female trigone.
- It should not automatically be called injury-induced squamous metaplasia.
- Anatomic location is essential for interpretation.



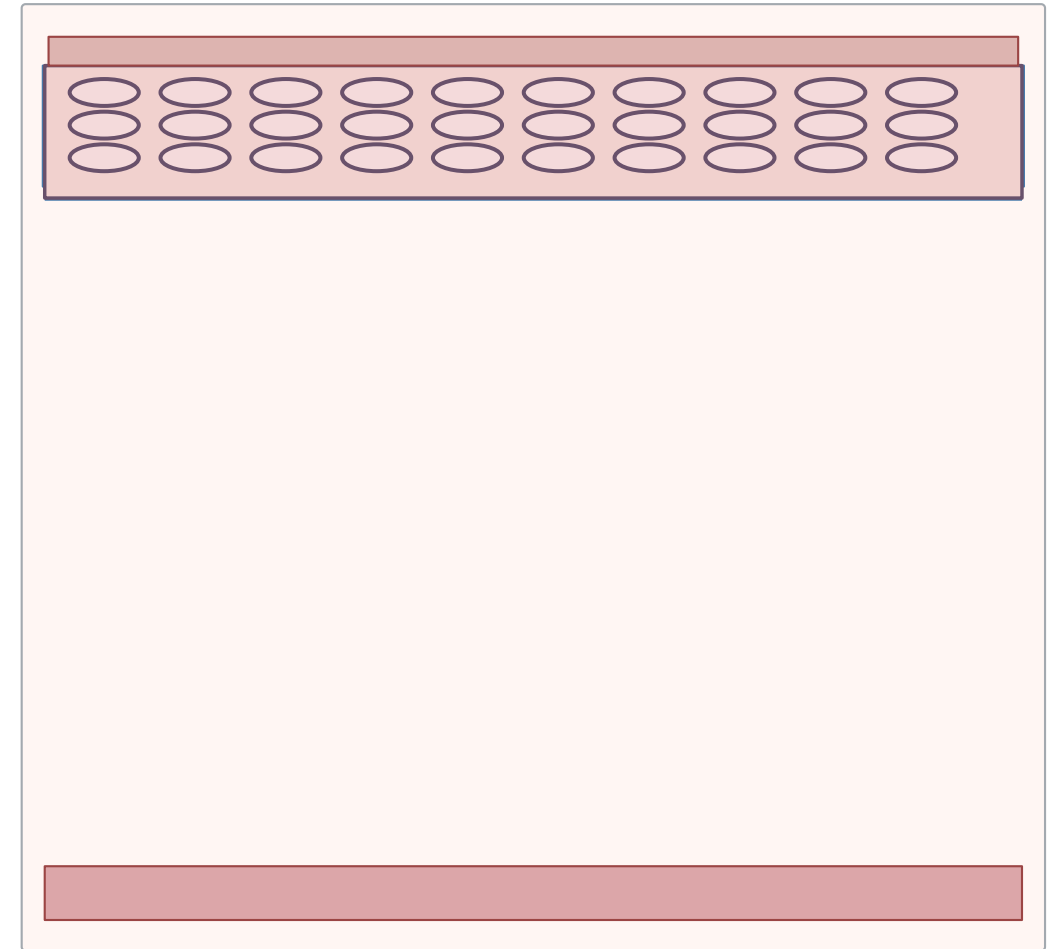
Schematic — not a histology image

Normal trigonal epithelium versus injury-associated change

Feature	Female trigonal glycogenated epithelium	Chronic-injury squamous metaplasia
Context	Physiologic at trigone	Response to chronic injury
Appearance	Squamous with glycogenation	Keratinizing or nonkeratinizing
Interpretation	Recognize a normal regional finding	Correlate with location and injury
Risk statement	Not described here as precursor	Specific risk in extensive multifocal keratinizing form

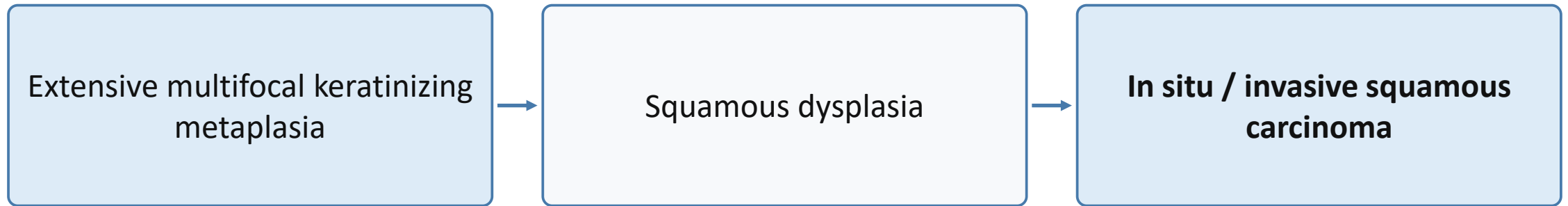
Keratinizing squamous metaplasia: Warning pattern

- Keratinization is distinct from nonkeratinizing squamous replacement.
- Robbins specifies extensive, multifocal keratinizing lesions as precursors.
- The precursor sequence includes dysplasia and squamous carcinoma.



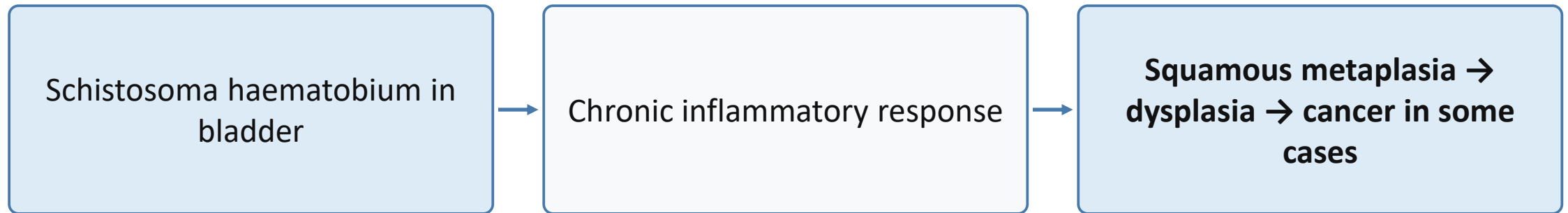
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Squamous progression: A defined morphologic sequence



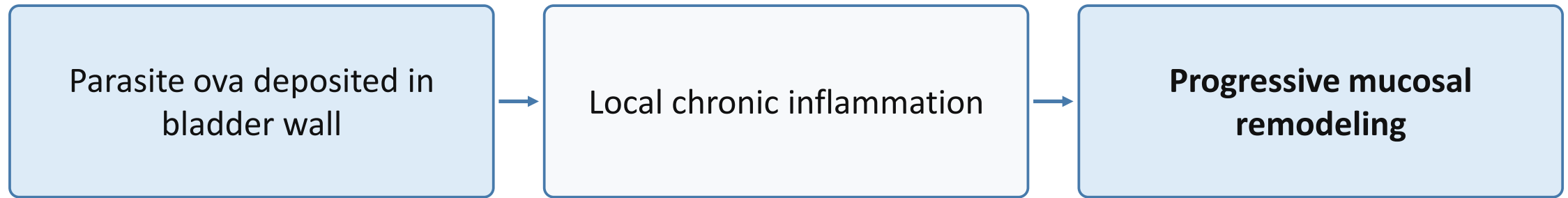
Conceptual risk sequence, not a quantified progression rate.

Schistosomiasis: A classic exposure-associated sequence



- Robbins gives schistosomiasis as the classic illustration.
- Infection-associated chronic mucosal injury links to squamous neoplasia.

Bladder wall eggs and persistent inflammation



Sequence follows the adjacent neoplasms discussion on schistosomiasis.

Association is not inevitability

A recognized precursor sequence is not a universal outcome

- Neoplasia develops in some instances of bladder schistosomiasis.
- Do not convert a qualitative association into an invented progression percentage.
- Risk communication must remain specific to the lesion pattern.

Three questions for squamous lesions

Where in the bladder?

Keratin present?

Focal or extensive/multifocal?

- Normal female trigonal glycogenation and chronic-injury change require distinction.
- The stated precursor association includes keratinization and distribution.

Teaching case: Metaplasia in a chronically injured bladder

Illustrative teaching vignette

A patient from a schistosomiasis-endemic setting has extensive, multifocal, keratinizing squamous replacement of the bladder mucosa.

Which precursor pathway is relevant?

Reasoning: Chronic schistosomal injury → keratinizing metaplasia → dysplasia → squamous carcinoma.

Case resolution: Retain the full risk qualifier

Extensive, multifocal keratinizing squamous metaplasia

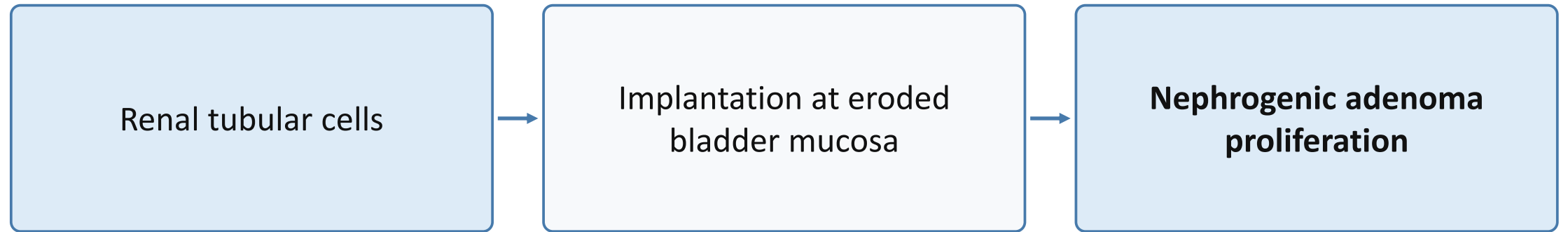
- It is the specifically named precursor context.
- The linked malignant endpoint is squamous cell carcinoma.
- Avoid equating this with glycogenated epithelium of the female trigone.

Nephrogenic adenoma: The metaplasia exception

An unusual lesion that may not represent true metaplasia

- It can involve replacement of urothelium by renal-type epithelium.
- Transplant observations support implanted renal tubular-cell origin in some lesions.
- Benign origin does not prevent a tumor-like microscopic appearance.

Origin hypothesis supported by transplantation evidence



- The observation is strongest in renal transplant recipients.
- At least some lesions follow this process.

Why implantation differs from transdifferentiation

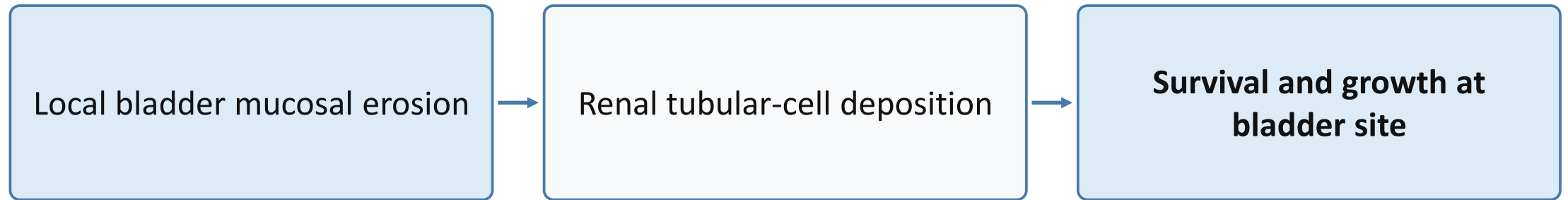
True metaplasia

- Resident epithelium changes phenotype.
- Squamous and glandular bladder patterns fit this framework.
- The epithelial lineage is remodeled in place.

Implantation mechanism

- Renal tubular cells are deposited in an injured site.
- These cells proliferate along bladder mucosa.
- At least some nephrogenic adenomas follow this process.

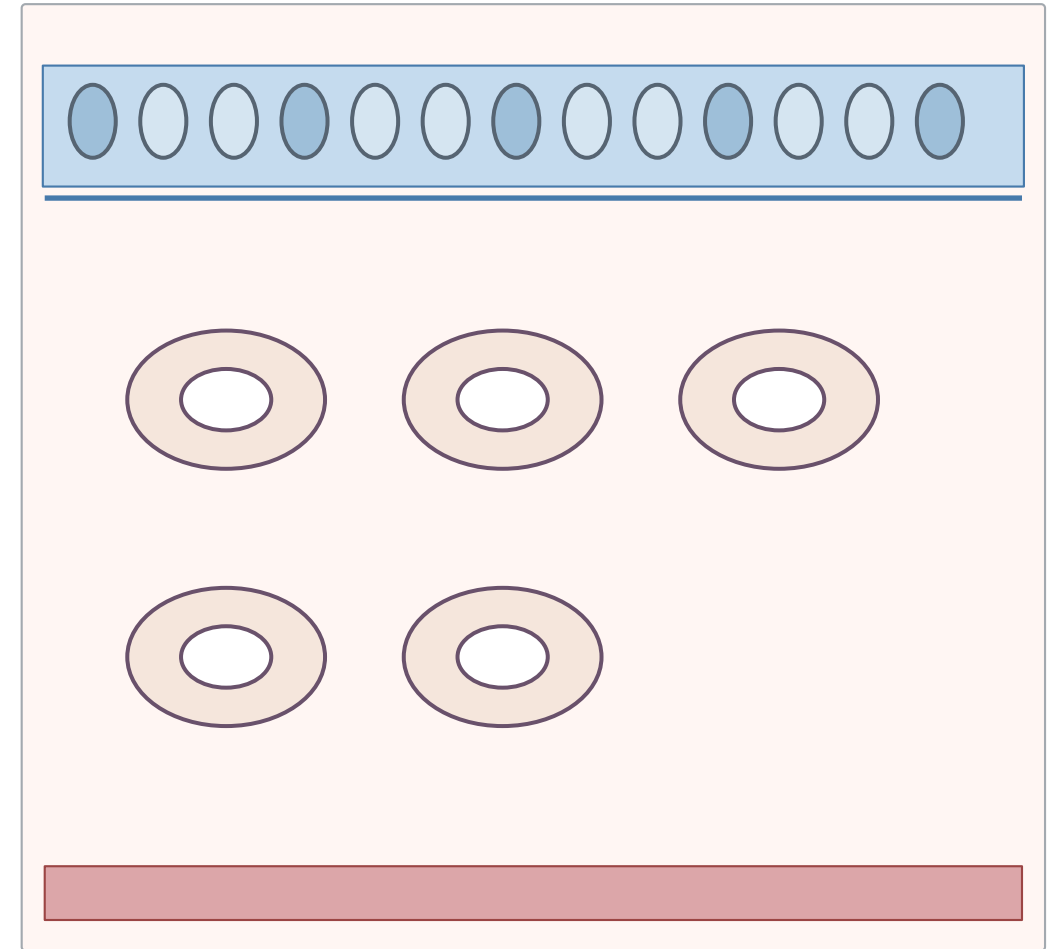
Mucosal erosion creates a permissive site



Conceptual interpretation of Robbins transplant-recipient evidence.

Renal-type cuboidal epithelium replaces urothelium

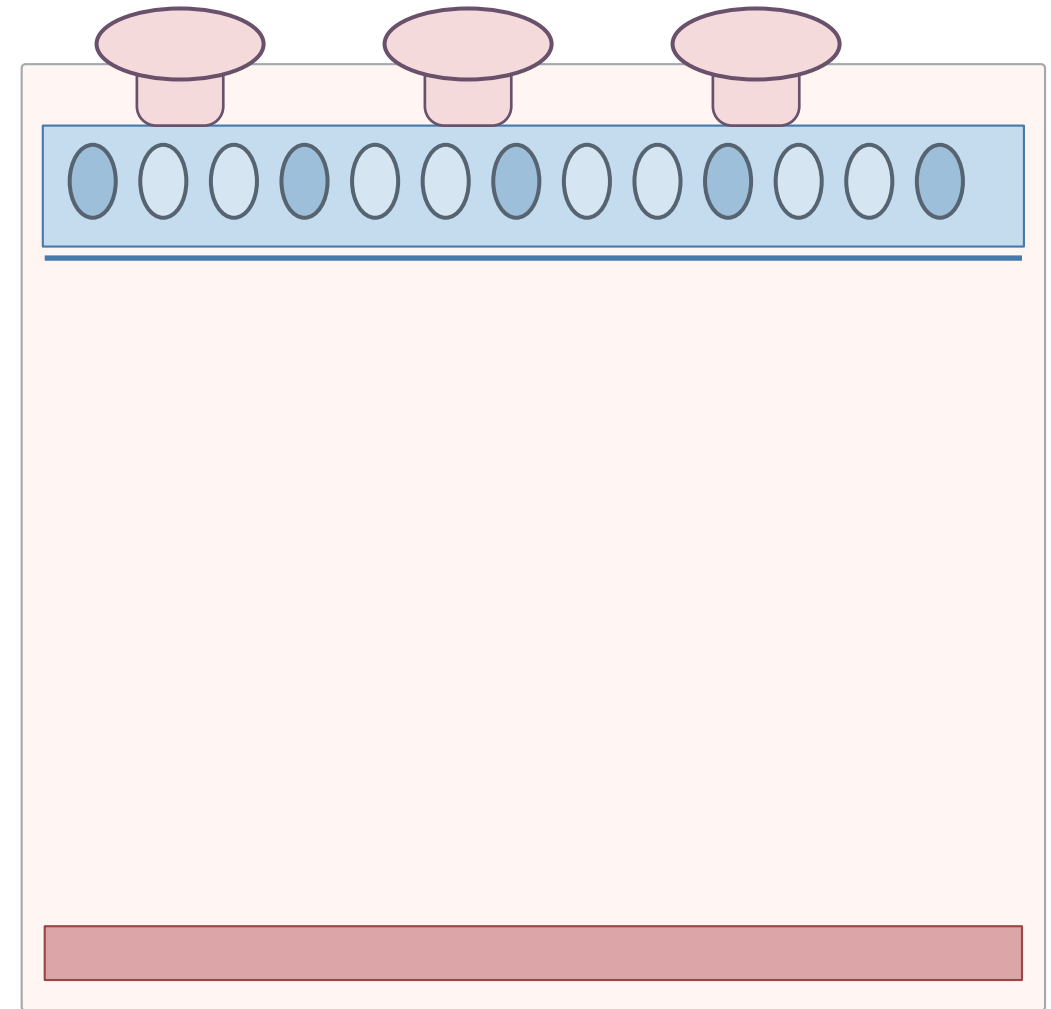
- Urothelium may be focally replaced by cuboidal epithelium.
- Architecture can include tubular arrangements.
- The epithelial type recalls renal tubular differentiation.



Schematic — not a histology image

Nephrogenic adenoma can grow in a papillary pattern

- A papillary growth pattern is.
- Papillary architecture is one reason for clinical concern.
- Do not conclude cancer from a papillary appearance alone.



Schematic — not a histology image

Typical lesion size and symptoms

Usually < 1 cm

Often asymptomatic

- Small nephrogenic adenomas are typically asymptomatic.
- Larger lesions can cause signs and symptoms that raise suspicion of cancer.

Larger nephrogenic adenomas may mimic bladder cancer

Why cancer is suspected

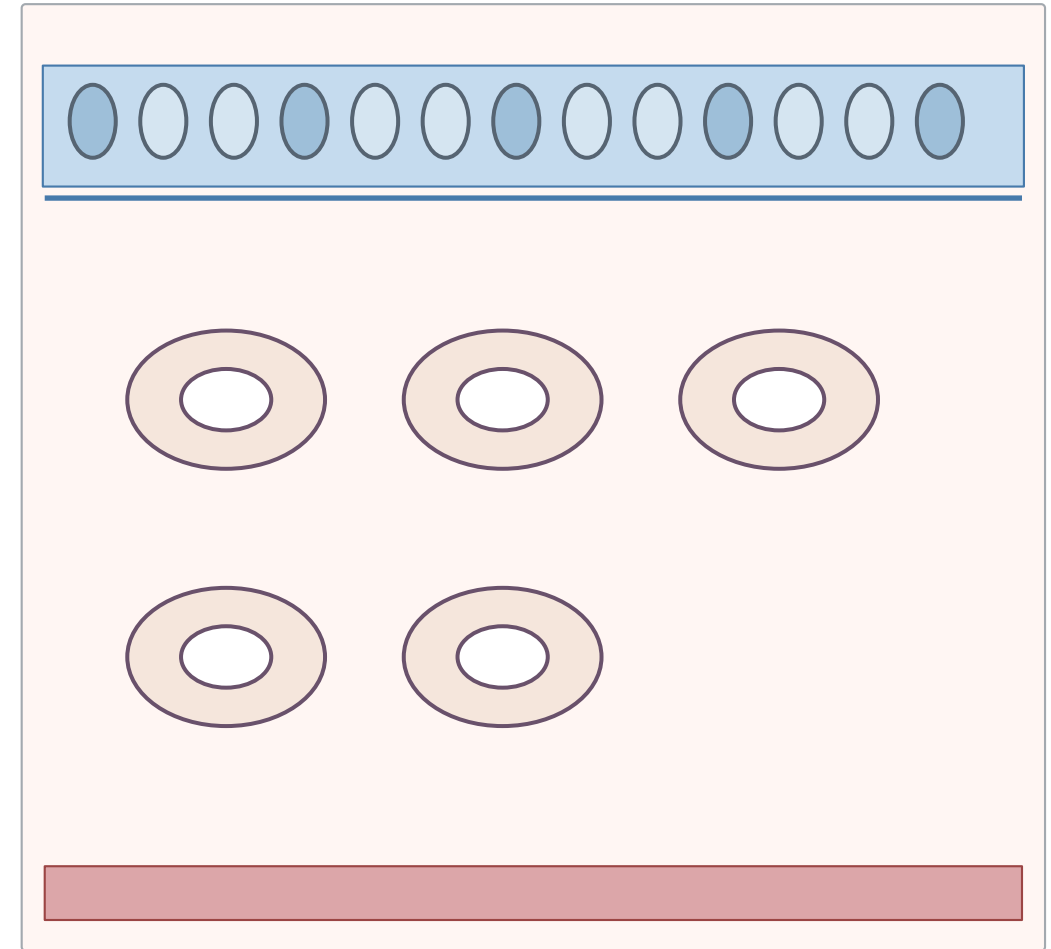
- The lesion may be unusually large.
- Patients can develop symptoms rather than incidental detection.
- Papillary/lesional appearance can trigger investigation.

Why histology is challenging

- Tubular proliferation may extend into lamina propria.
- It may also involve superficial detrusor muscle.
- Such placement can imitate invasive carcinoma.

Lamina propria extension can imitate invasion

- Tubular proliferation may occupy the lamina propria.
- “Below the surface” is not sufficient evidence for malignancy.
- Interpret tubules with the entity’s known benign mimicry.



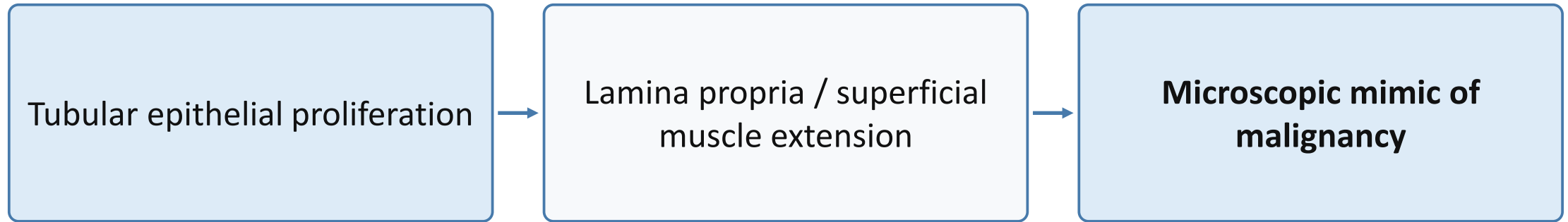
Schematic — not a histology image

Superficial detrusor involvement: An important pitfall

Nephrogenic adenoma may extend into superficial detrusor

- Muscle involvement often prompts concern for a malignant process.
- Robbins explicitly records superficial detrusor extension in nephrogenic adenoma.
- The architectural mimic requires careful clinicopathologic interpretation.

A benign proliferation can look infiltrative



This describes a pitfall, not proof that all muscle-involving tubular lesions are benign.

Nephrogenic adenoma: Benign context, alarming morphology

Feature	Usual description	Diagnostic implication
Nature	Unusual lesion; May not be true metaplasia	Do not infer origin from its name
Cell phenotype	Cuboidal replacement	Consider renal tubular-like cells
Growth	Papillary or tubular	May mimic neoplasm
Extent	Lamina propria / superficial muscle	Pseudo-invasive impression
Presentation	Usually small/asymptomatic	Larger lesions may prompt cancer suspicion

Teaching case: A deceptively deep lesion

Illustrative teaching vignette

A bladder specimen contains a cuboidal tubular proliferation extending into lamina propria and the superficial detrusor. The clinical lesion is small.

Which benign tumor-like entity merits consideration?

Reasoning: Nephrogenic adenoma can mimic malignancy even when tubules extend into superficial muscle.

Case resolution: Depth needs architectural context

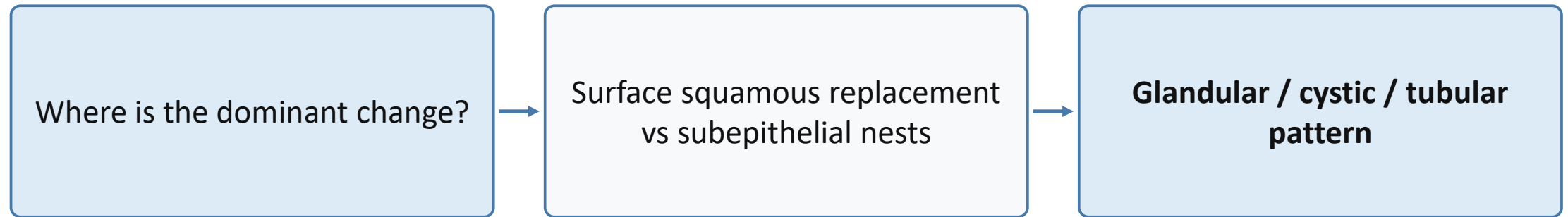
Consider nephrogenic adenoma as a cancer mimic

- Renal-type cuboidal epithelium and tubular growth are relevant.
- Proliferation can involve lamina propria and superficial detrusor.
- The supplied source does not provide a complete ancillary-test panel; Do not invent one.

Comparative matrix: The three lesion families

Attribute	Cystica / glandularis	Squamous metaplasia	Nephrogenic adenoma
Key morphology	Cysts or glandular lining in nests	Squamous urothelial replacement	Tubular / papillary cuboidal proliferation
Link to injury	Can accompany inflammation	Chronic injury response	Implantation at erosions in some
Source-defined risk	Extensive multifocal intestinal → adenocarcinoma	Extensive multifocal keratinizing → SCC	Can imitate carcinoma, not labeled as precursor
Core pitfall	Mistaking nests for invasive glands	Misreading normal female trigone	Mistaking deep benign tubules for invasion

Morphology-first classification pathway



- An initial architectural sorting step improves consistency.
- It is not a substitute for formal pathology diagnosis.

The anatomical location modifies interpretation

Location	Finding	Interpretive relevance
Female trigone	Glycogenated squamous epithelium	May be physiologic
Lamina propria	Von Brunn nests with central change	Cystica / glandularis possible
Lamina propria or superficial detrusor	Renal-type tubular proliferation	Nephrogenic adenoma may mimic invasion
Widespread bladder mucosa	Multifocal keratinizing squamous change	Specified precursor context

Boundary with the neighboring neoplasia topic

This topic primarily covers

- Common urothelial nest-related lesions.
- Injury-related squamous metaplasia.
- Nephrogenic adenoma as a benign mimic.

The next lecture covers

- Urothelial neoplasms and their precursor entities.
- Papillary tumors and flat urothelial carcinoma in situ.
- Invasive bladder tumors and cancer risk factors.

Biopsy interpretation: What the source supports

Separate three reporting questions

- What epithelial phenotype and architecture are present?
- Is the described pattern a recognized precursor, and under what qualifiers?
- Could a benign lesion explain a tumor-like or invasion-like appearance?

Integrated vignette: A bladder glandular lesion

Illustrative teaching vignette

A biopsy reveals cystic and columnar-lined urothelial nests. The available specimen does not establish extensive multifocal intestinal metaplasia.

What can be stated, and what cannot be inferred?

Supported: Cystitis cystica et glandularis. Not established: The specific extensive multifocal intestinal precursor context.

Integrated vignette: A papillary bladder lesion

Illustrative teaching vignette

A small bladder lesion shows cuboidal epithelium and papillary growth; Tubular elements are present in lamina propria.

What makes a benign mimic part of the differential?

Supported: Nephrogenic adenoma may be papillary and extend below urothelium; Confirm with complete workup.

High-yield synthesis: Lesion, morphology, significance

Lesion	Distinguishing change	Why it matters
Cystitis cystica	Cystic space lined by flattened urothelium	Common nest-based reactive pattern
Cystitis glandularis	Cuboidal / columnar lining	Intestinal extensive multifocal subset has cancer relevance
Squamous metaplasia	Squamous epithelial substitution	Extensive multifocal keratinizing subset is precursor
Nephrogenic adenoma	Tubules / papillae of cuboidal cells	Can simulate invasion

Final diagnostic principles

- Describe epithelial phenotype before assigning neoplastic significance.
- Retain exact qualifiers for intestinal and keratinizing precursor states.
- Distinguish the physiologic female trigonal epithelium.
- Remember nephrogenic adenoma when benign tubules look infiltrative.

References and image provenance

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. Chapter 21; urinary bladder, pp. 868–871.
- Primary topic: “Metaplastic Lesions,” p. 870; neighboring cystitis and neoplasia text used only for context.
- All tissue diagrams are original editable schematics; they are not micrographs.
- No photographic diagnostic specimens are reproduced in this deck.