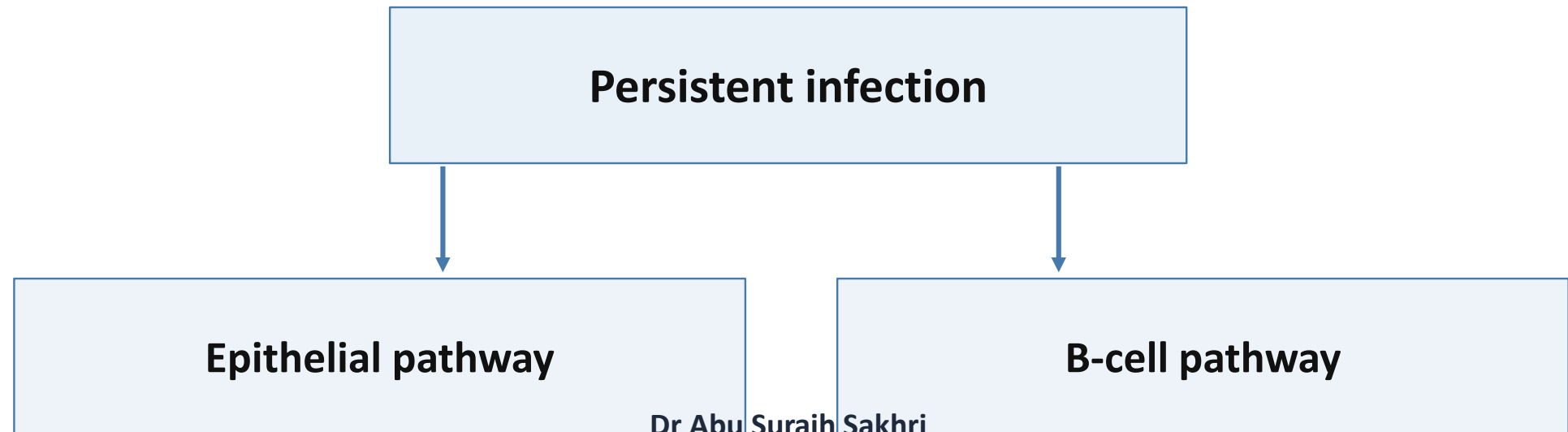


Helicobacter pylori

From persistent gastritis to gastric adenocarcinoma and MALT lymphoma



Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain how H. Pylori persists in gastric mucus and initiates chronic inflammation.
- Relate antral versus multifocal atrophic gastritis to divergent clinical outcomes.
- Trace the proposed sequence from chronic injury to gastric adenocarcinoma.
- Explain antigen-driven gastric MALT lymphoma and loss of dependence on infection.
- Interpret key histologic findings and diagnostic tests in clinical context.

One organism, two tumor lineages

Epithelial malignancy

- Chronic gastritis and injury of gastric epithelium
- Atrophy → intestinal metaplasia → dysplasia
- Gastric adenocarcinoma

Lymphoid malignancy

- Acquired mucosal lymphoid tissue
- Persistent antigen-specific T-cell help
- Extranodal marginal zone B-cell lymphoma (MALT lymphoma)

Why H. Pylori is a carcinogenic infection

- A bacterium can promote malignancy without invading the gastric epithelium.
- Persistent infection generates chronic inflammation, epithelial turnover, and immune stimulation.
- Bacterial virulence and host responses modify the carcinogenic trajectory.
- Only a minority of infected persons develop gastric malignancy.

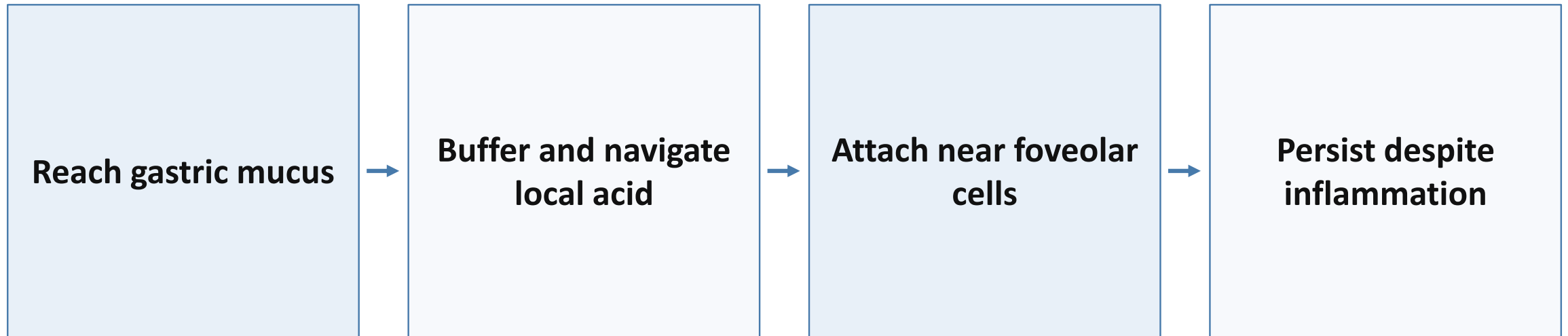
Morphology and microbial niche

- H. Pylori is a curved or spiral-shaped bacillus.
- The organisms live predominantly in gastric mucus near surface and neck epithelial cells.
- They adapt to strong luminal acidity by modifying and navigating their local microenvironment.
- Direct mucosal invasion is not required for oncogenic effects.

Colonization is commonly established in childhood

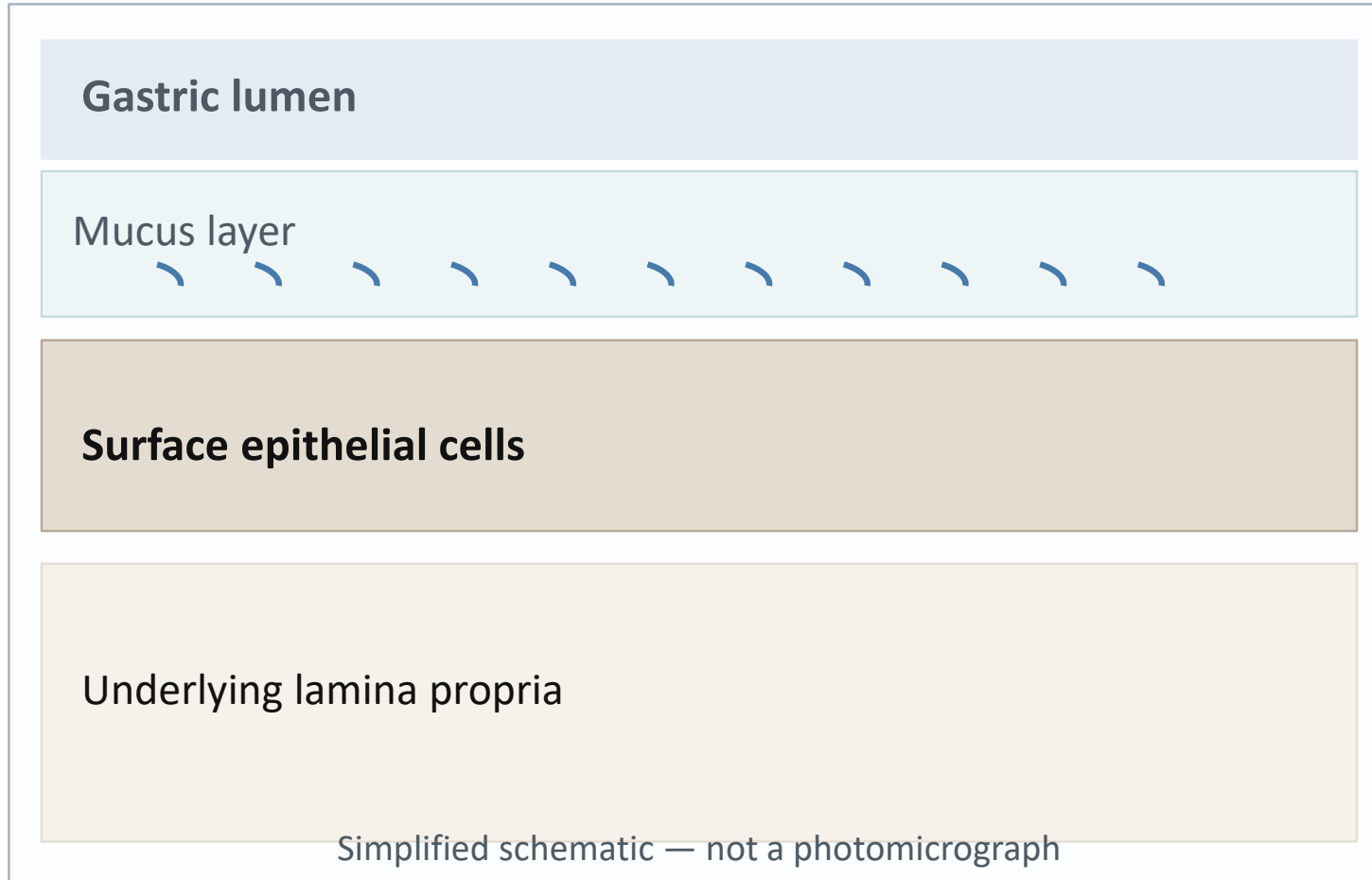
- Transmission is thought to be predominantly fecal–oral, with humans as the principal reservoir.
- Crowding and sanitation conditions during childhood influence acquisition.
- Untreated colonization may persist for decades or lifelong.
- Duration of chronic mucosal inflammation creates the setting for later complications.

Three stages of persistent colonization



Urease, flagella, and adhesins cooperate rather than act as isolated virulence factors.

Where the organism resides



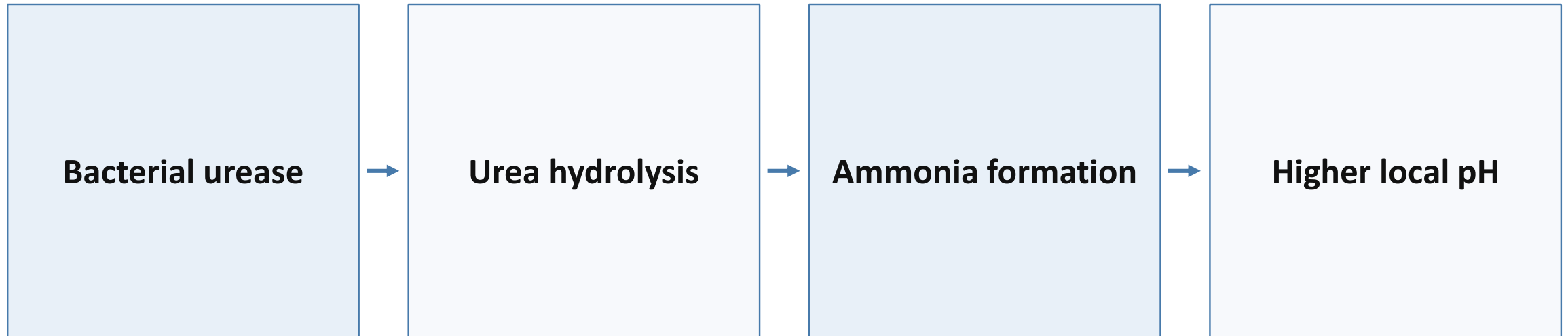
Tissue localization

- Bacteria concentrate within the superficial mucus.
- Organisms lie near surface and neck regions of gastric glands.
- Sampling may miss patchy colonization.

Flagella: Motility through viscous mucus

- Flagella permit movement through viscous gastric mucus.
- H. Pylori senses pH and avoids more acidic microenvironments.
- Motility helps the bacterium remain close to the epithelium.
- This spatial localization favors survival despite the acidic gastric lumen.

Urease creates a local acid buffer



Local neutralization facilitates survival; It does not abolish the stomach's overall acidity.

Adhesins stabilize mucosal colonization

- Adhesion proteins bind bacteria to gastric foveolar epithelial cells.
- Adherence anchors organisms at the epithelium–mucus interface.
- Urease and adhesins are highly conserved colonization determinants.
- Prolonged surface contact can sustain epithelial and immune activation.

Bacterial factors versus host response

Bacterial inputs

- Flagella and motility
- Urease-dependent acid buffering
- Adhesion to surface epithelial cells
- CagA and other virulence mediators

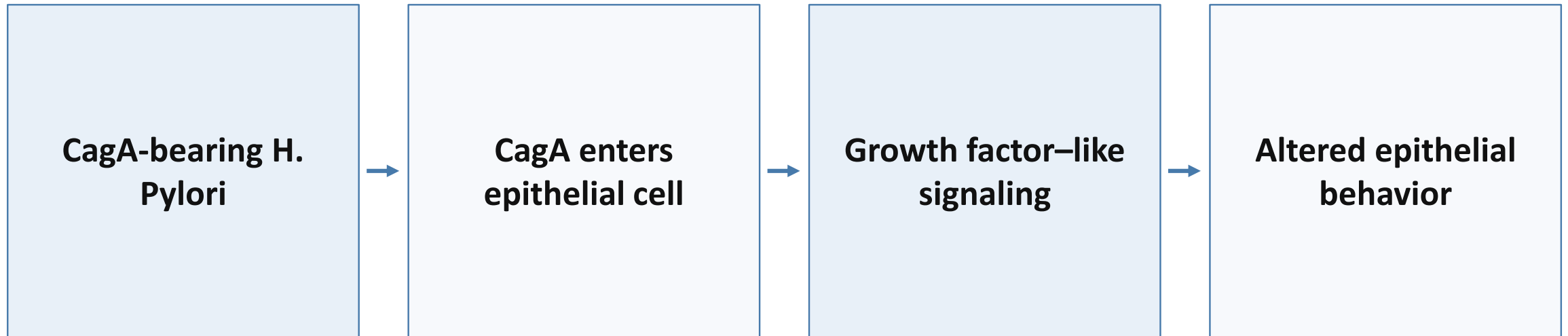
Host inputs

- Epithelial inflammatory responses
- TNF, IL-1, and other cytokines
- Immune-cell recruitment
- Host susceptibility polymorphisms

CagA defines a major virulence-associated pathway

- The CagA pathogenicity island is associated with strains linked to gastric adenocarcinoma.
- CagA is delivered into gastric epithelial-cell cytoplasm.
- Once intracellular, it influences cellular signaling and structural remodeling.
- Population associations do not prove that CagA alone determines individual cancer outcomes.

CagA: Proposed direct epithelial effects



The Chapter 7 account describes this as one component of multifactorial oncogenesis.

Direct bacterial effects are not the entire mechanism

Potential direct route

- CagA-associated signaling changes
- Cellular structural remodeling
- Altered epithelial proliferation

Inflammation-mediated route

- Persistent inflammatory infiltrates
- Reactive oxygen species and genotoxic stress
- Compensatory epithelial proliferation

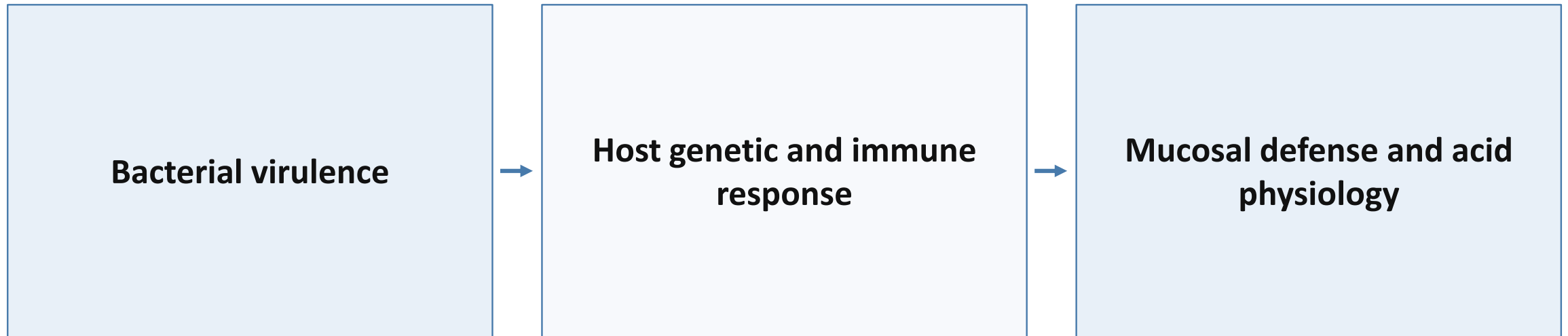
Interpreting virulence associations carefully

- CagA-associated strains are enriched in populations with higher gastric cancer prevalence.
- A pathogenicity factor is a risk modifier, not a deterministic cancer biomarker.
- The textbook explicitly characterizes some experimental virulence-factor contributions as correlative.
- The resulting phenotype depends on bacterial, mucosal, and host characteristics.

Host cytokine polymorphisms influence outcome

- Greater TNF or IL-1 expression may favor an exaggerated proinflammatory response.
- Reduced IL-10 expression may weaken anti-inflammatory restraint.
- Such inherited variants are associated with risk of pangastritis, atrophy, and metaplasia.
- Associations do not establish that a single polymorphism diagnoses future cancer.

Infection outcome emerges from three interacting systems

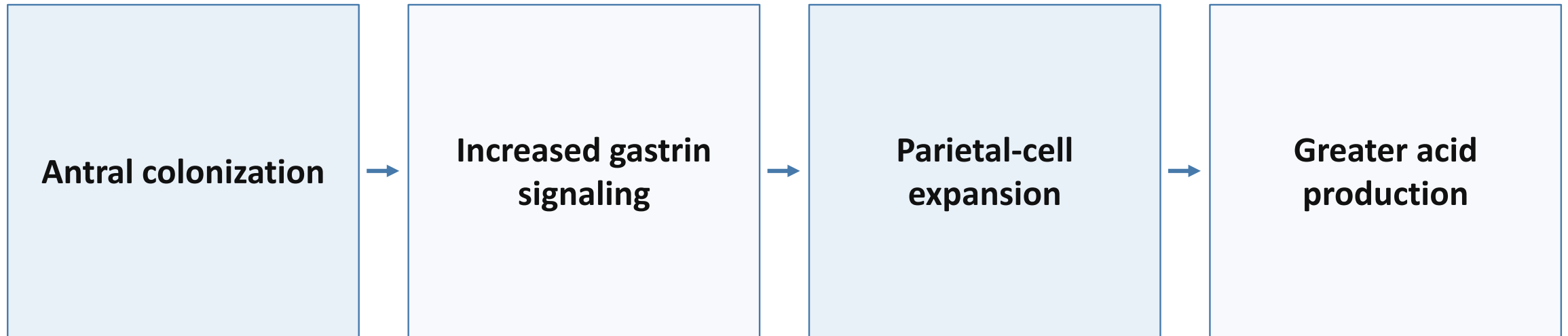


Their interplay, rather than organism presence alone, determines the observed pattern of gastritis.

Antrum-predominant gastritis is a common pattern

- Organisms are often most abundant in the antrum.
- Inflammation in this region enhances local gastrin production.
- Normal or increased acid secretion commonly persists.
- The clinical phenotype tends toward peptic-ulcer risk rather than atrophy-associated carcinogenesis.

Antral inflammation links infection to acid hypersecretion



In this phenotype, increased acid promotes gastric or duodenal peptic-ulcer disease.

Ulcer-prone and atrophy-prone phenotypes

Antrum-predominant

- Gastrin stimulation
- Normal/increased acid secretion
- Higher risk of duodenal peptic ulcer

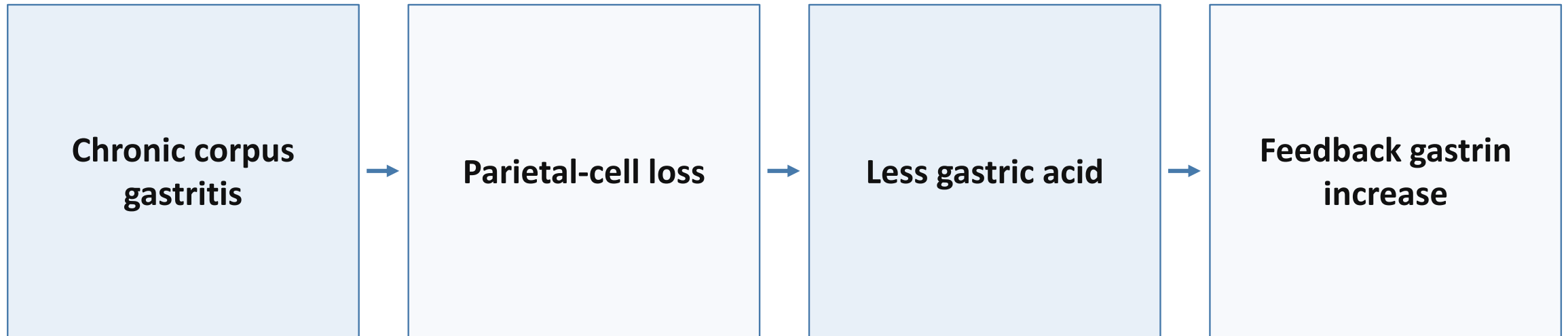
Corpus involvement / atrophy

- Loss of functional parietal-cell mass
- Decreased acid secretion
- Intestinal metaplasia and higher cancer risk

Progressive pangastritis changes the risk landscape

- Long-standing infection can extend from the antrum to body and fundus.
- Inflammatory injury may reduce oxyntic gland and parietal-cell mass.
- Patchy mucosal atrophy and intestinal metaplasia can develop.
- This atrophic phenotype is strongly linked to intestinal-type gastric carcinogenesis.

Oxyntic gland loss reduces acid production

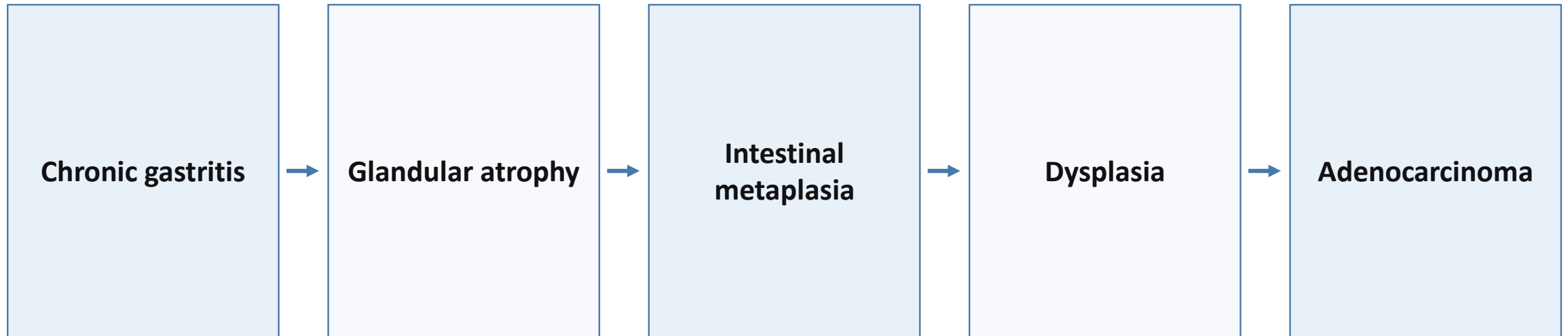


Some acid secretion can persist; Gastrin elevation is generally less extreme than in autoimmune gastritis.

Atrophy associated with H. Pylori is often patchy

- Oxyntic atrophy can be distributed irregularly.
- The pattern differs from the characteristic autoimmune oxyntic atrophy phenotype.
- H. Pylori–associated atrophy lacks the autoantibodies characteristic of autoimmune gastritis.
- Biopsy interpretation must account for anatomic site and sampling.

Proposed epithelial carcinogenesis sequence

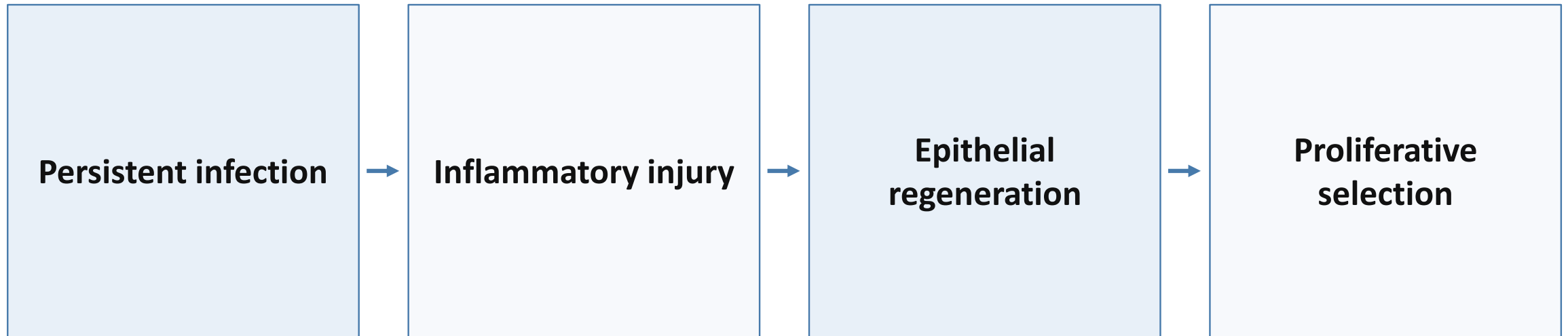


This is a conceptual progression, not an inevitable course for each infected person.

Why chronic inflammation promotes mutation accumulation

- Inflammatory cells release reactive oxygen species that may damage cellular DNA.
- Continued epithelial injury generates compensatory epithelial proliferation.
- Genotoxic stress during repeated cell division may favor selection of altered clones.
- Inflammation is therefore a carcinogenic microenvironment, not merely a secondary reaction.

Chronic injury connects inflammation with cell proliferation



Repeated turnover increases opportunities for acquired oncogenic alterations over time.

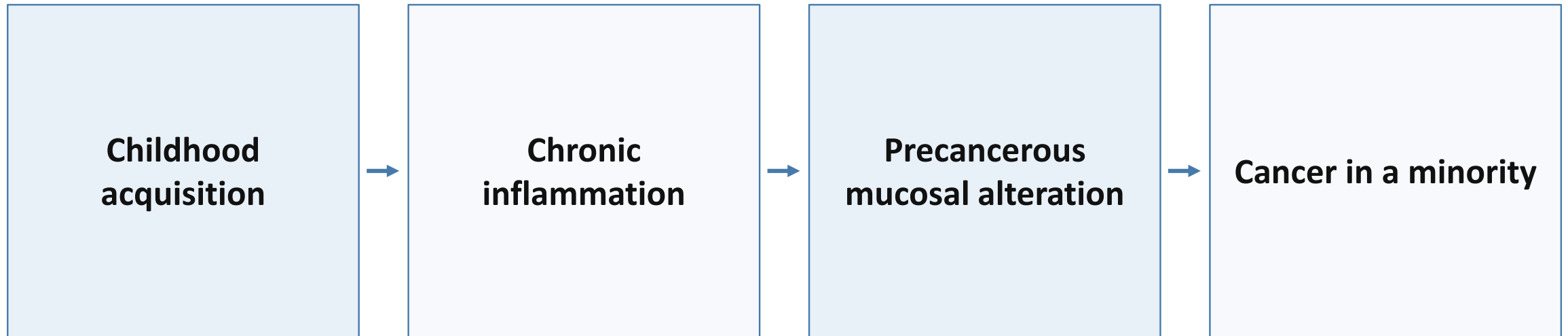
Intestinal metaplasia marks a changed epithelial program

- Gastric lining epithelial cells acquire intestinal-type differentiation.
- The change accompanies prolonged atrophic H. Pylori gastritis.
- It is a histologic marker within the proposed adenocarcinoma precursor sequence.
- Metaplasia is not synonymous with invasive malignancy.

Dysplasia is a neoplastic precursor, not invasive cancer

- Dysplastic gastric epithelium shows nuclear enlargement, elongation, hyperchromasia, and pseudostratification.
- Architectural complexity increases with higher-grade dysplasia.
- Cribriform glands and glandular budding may accompany high-grade lesions.
- Invasion distinguishes carcinoma from an intraepithelial dysplastic precursor.

The epithelial route is prolonged and selective



A decades-long sequence culminating in cancer in fewer than 5% of infected individuals.

Infection does not imply inevitable gastric cancer

- Progression to adenocarcinoma in fewer than 5% of infected people.
- The latency of progressive gastric carcinogenesis is often measured in decades.
- Host genetics, bacterial virulence, topographic inflammation, and other influences modify risk.
- Cancer risk cannot be assigned to an individual by infection status alone.

Inflammation-associated cancer versus alternative etiology

H. Pylori–associated pathway

- Chronic gastritis
- Atrophy and metaplastic change
- Predominantly implicated in intestinal-type pathway

Not all gastric cancers follow this route

- A subset of gastric cancers is associated with EBV.
- Diffuse cancers commonly involve cell-adhesion abnormalities.
- H. Pylori is not a sufficient explanation for every gastric cancer.

What distinguishes intestinal-type gastric adenocarcinoma?

- Neoplastic glands are formed by cohesive epithelial cells.
- Mass-forming or ulcerated infiltrative growth is typical.
- Cells may contain apical mucin; Gland lumina may contain mucin.
- Its association with chronic atrophy and metaplasia links morphology to the H. Pylori precursor pathway.

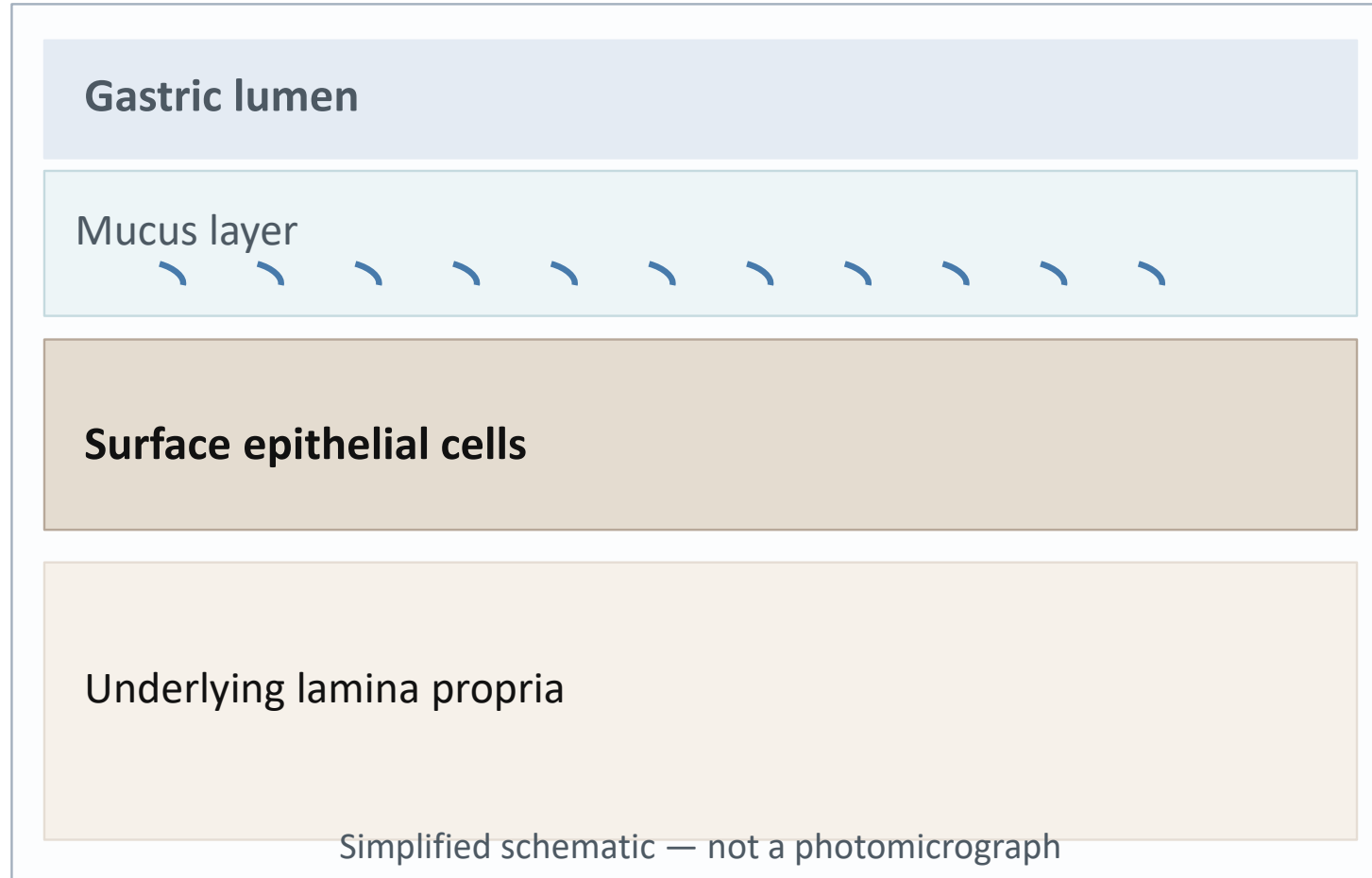
Intestinal-type and diffuse-type gastric carcinoma

Feature	Intestinal type	Diffuse type
Growth	Gland-forming; often bulky/ulcerated	Discohesive infiltration; wall thickening
Typical cytology	Columnar cells; mucin-containing glands	Signet-ring cells; absent glands
Precursor context	Chronic atrophy / intestinal metaplasia	No established morphologic precursor
Mechanistic theme	Inflammation-associated epithelial sequence	Adhesion defects, including E-cadherin loss

Endoscopic features may be subtle or misleading

- Infected antral mucosa can appear erythematous, coarse, or nodular.
- Severe inflammation can produce thickened rugal folds.
- Rugal thickening may mimic the endoscopic appearance of early gastric cancer.
- Endoscopic appearance alone cannot resolve inflammation from neoplasia.

Organisms cluster in surface mucus



Biopsy implications

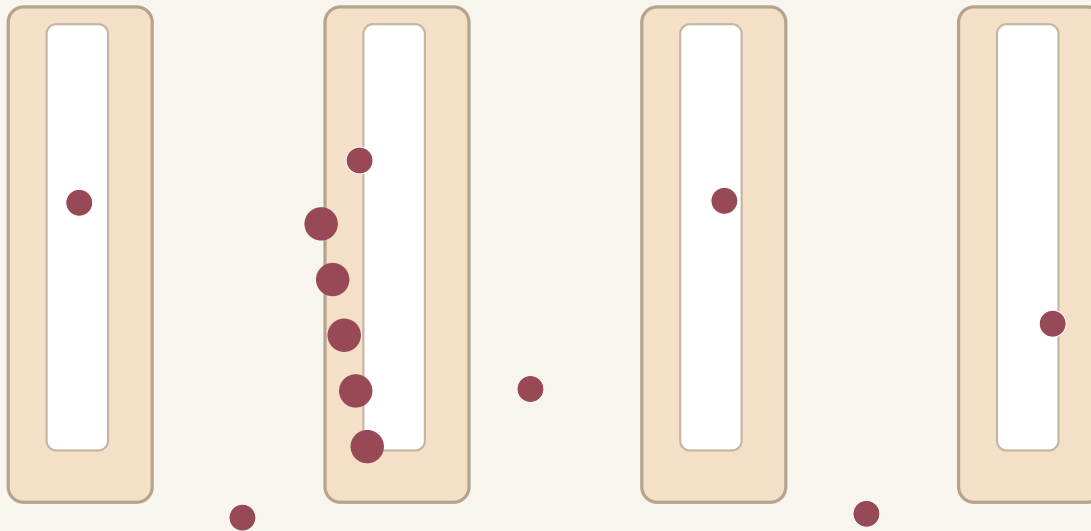
- Look near surface mucus and epithelial necks.
- Distribution can be irregular within a biopsy.
- Heavy and sparse foci may be adjacent.

Histologic detection of organisms

- Curved or spiral organisms can be identified in H&E-stained tissue.
- Histochemical methods such as Warthin–Starry silver stain may highlight organisms.
- Immunostaining often improves recognition, particularly in difficult samples.
- A negative limited biopsy must be interpreted with sampling and clinical context.

Active chronic gastritis involves several cell populations

Gastric surface epithelium



Simplified schematic — not a photomicrograph

Core tissue findings

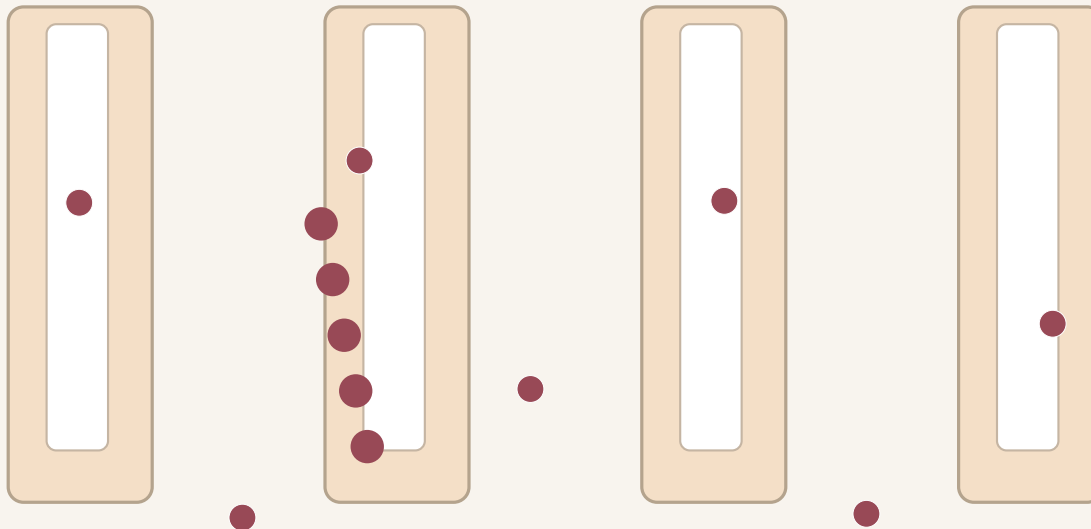
- Superficial plasma-cell-rich chronic infiltrate.
- Lymphocytes and macrophages in lamina propria.
- Neutrophils enter epithelium and gastric pits.

Plasma cells dominate the chronic component

- Plasma cells accumulate within superficial lamina propria.
- Clusters or sheets of plasma cells may be conspicuous.
- Lymphocytes and macrophages are also recruited.
- The pattern reflects sustained antigenic and inflammatory stimulation.

Neutrophils indicate active epithelial injury

Gastric surface epithelium

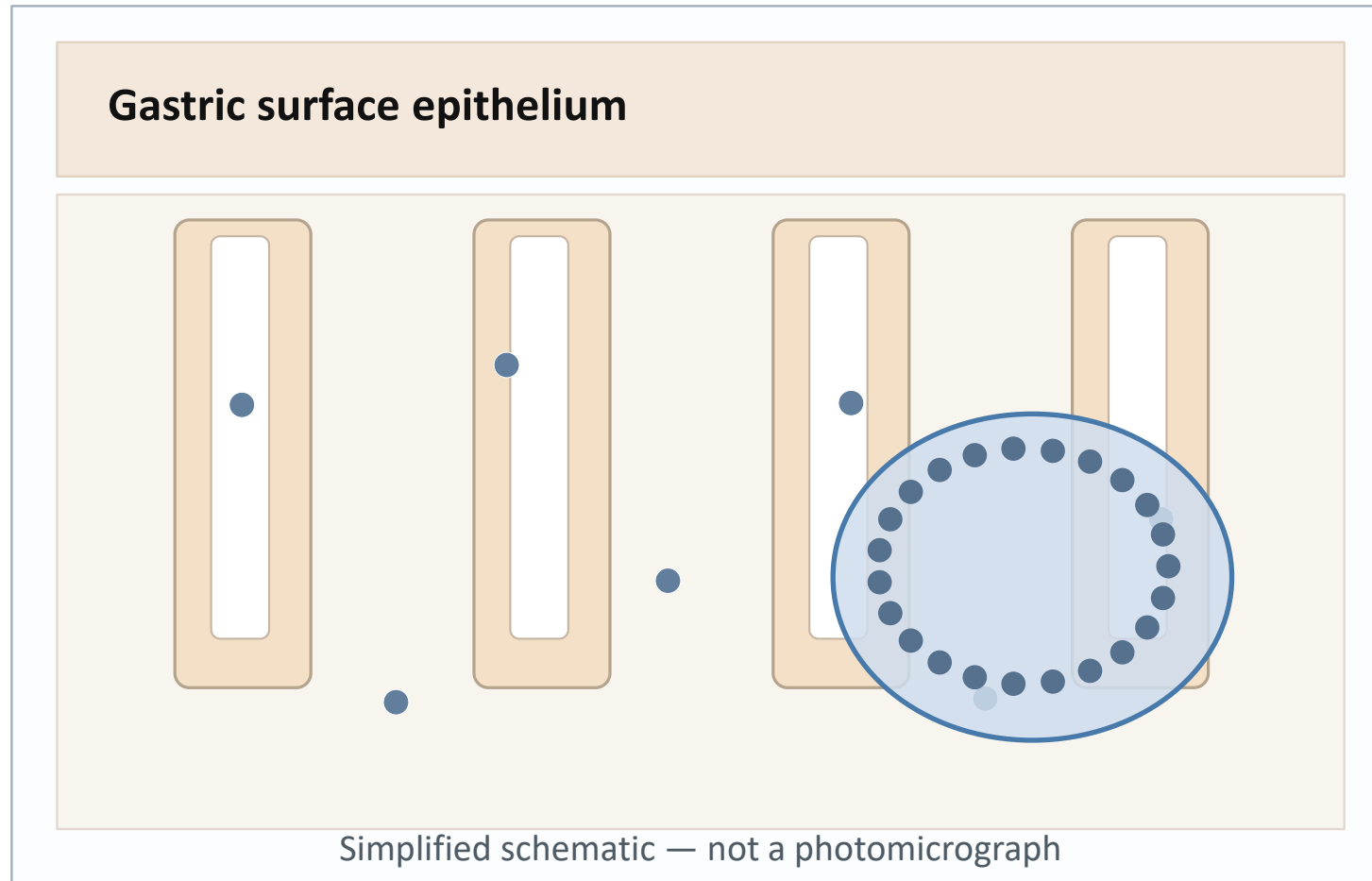


Simplified schematic — not a photomicrograph

Activity means neutrophils

- Neutrophils cross the epithelial basement membrane.
- They infiltrate surface or glandular epithelium.
- Accumulation in gastric pits produces pit abscesses.

Ectopic lymphoid follicles arise during infection



Acquired gastric MALT

- Lymphoid aggregates may form germinal centers.
- Normal stomach lacks organized mucosal lymphoid tissue.
- Chronic H. Pylori gastritis can induce organized mucosal lymphoid tissue.

Reactive follicles are not themselves lymphoma

Reactive immune response

- Aggregates and germinal centers
- Mixed inflammatory population
- Antigen-driven tissue organization

Features raising lymphoma concern

- Dense neoplastic B-cell infiltrates
- Invasion of glands: Lymphoepithelial lesions
- Clonal immunoglobulin gene or light-chain evidence

Atrophic H. Pylori and autoimmune gastritis

Feature	H. pylori–associated	Autoimmune
Distribution	Often patchy; can involve antrum + corpus	Predominantly oxyntic (body/fundus)
Causative association	Persistent bacterial infection	Autoimmune parietal-cell injury
Autoantibodies	Not a defining feature	Characteristic association
Gastrin response	Raised if acid reduced, often modest relative to autoimmune	Marked when acid loss is extensive

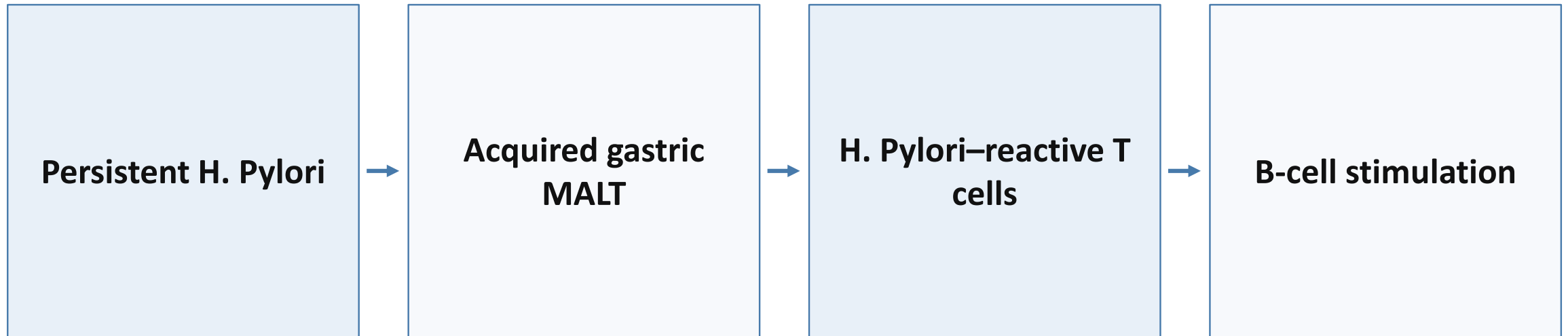
Diagnosis requires organism and pattern interpretation

- Identify H. Pylori with an appropriate validated tissue or noninvasive method.
- Describe distribution, inflammatory activity, atrophy, and metaplasia where sampled.
- Recognize that both neoplastic and reactive processes can coexist.
- Morphology and clinical findings jointly determine further assessment.

Available tests for H. Pylori infection

Approach	Examples	What the test contributes
Noninvasive	Urea breath test	Evidence of urease activity associated with infection
Noninvasive	Fecal bacterial detection	Evidence of infection without gastric biopsy
Noninvasive	Antibody serology	Exposure/immune response; not equivalent to ongoing infection
Biopsy-based	Histology; rapid urease; culture; PCR	Detection of bacteria, urease, or bacterial DNA

Gastric MALT lymphoma begins with a chronic immune stimulus

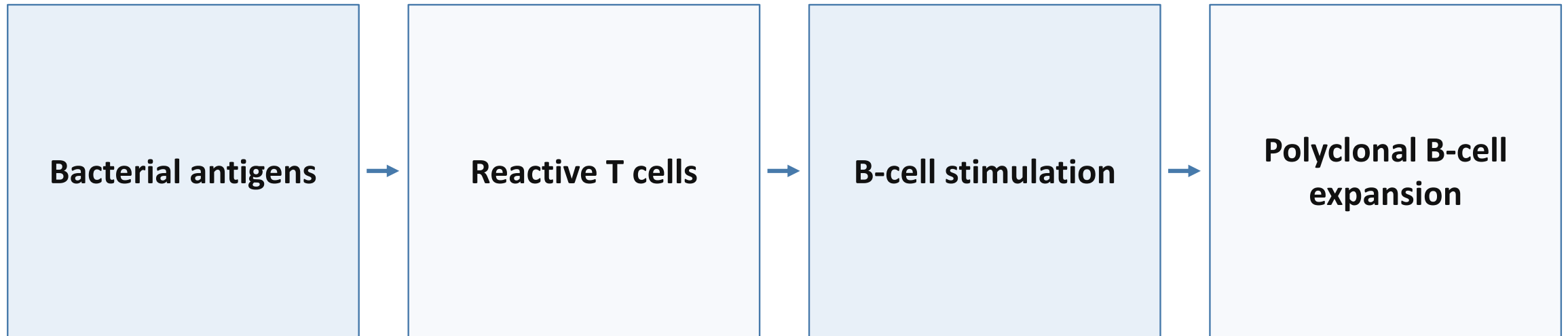


The earliest lymphoid expansion is antigen-dependent rather than autonomous cancer.

Why the normal stomach develops lymphoid tissue

- Organized mucosa-associated lymphoid tissue is not normally prominent in the stomach.
- Chronic antigenic stimulation can induce lymphoid aggregates and follicles.
- These provide an environment for T-cell–B-cell interactions.
- Only some persistent lymphoid expansions undergo neoplastic transformation.

T-cell help drives an initially polyclonal B-cell response

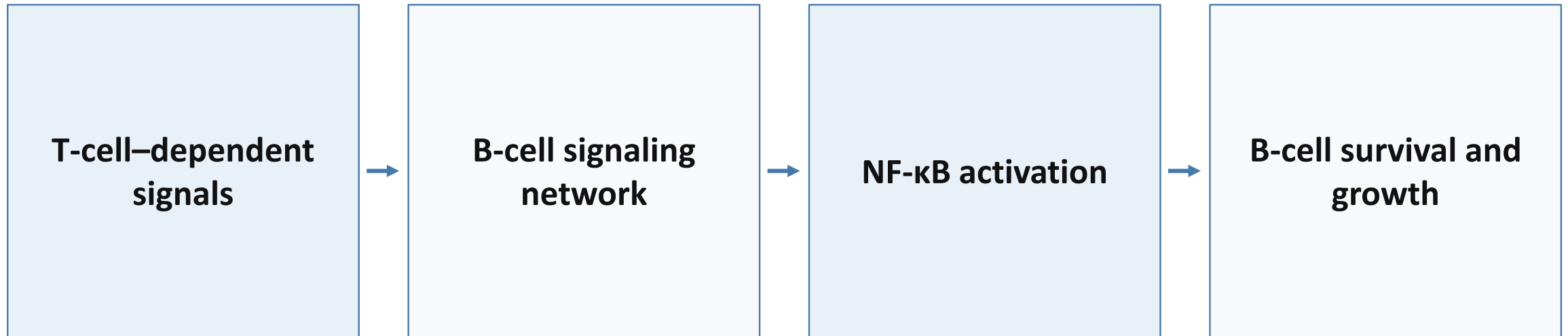


The bacterial signal acts indirectly through a reactive T-cell compartment.

Clonal selection converts reactive proliferation into lymphoma

- Persistent immune stimulation maintains opportunities for B-cell proliferation.
- Acquired mutations can confer a proliferative or survival advantage.
- A growth-advantaged B-cell clone may dominate, creating monoclonal lymphoma.
- Early lymphoma may still require antigen-dependent T-cell signaling.

NF- κ B links T-cell help to B-cell survival



In early gastric MALT lymphoma, pathway activation remains responsive to infection-dependent immune stimulation.

Early and late MALT lymphoma differ in dependence

Early / antigen-dependent

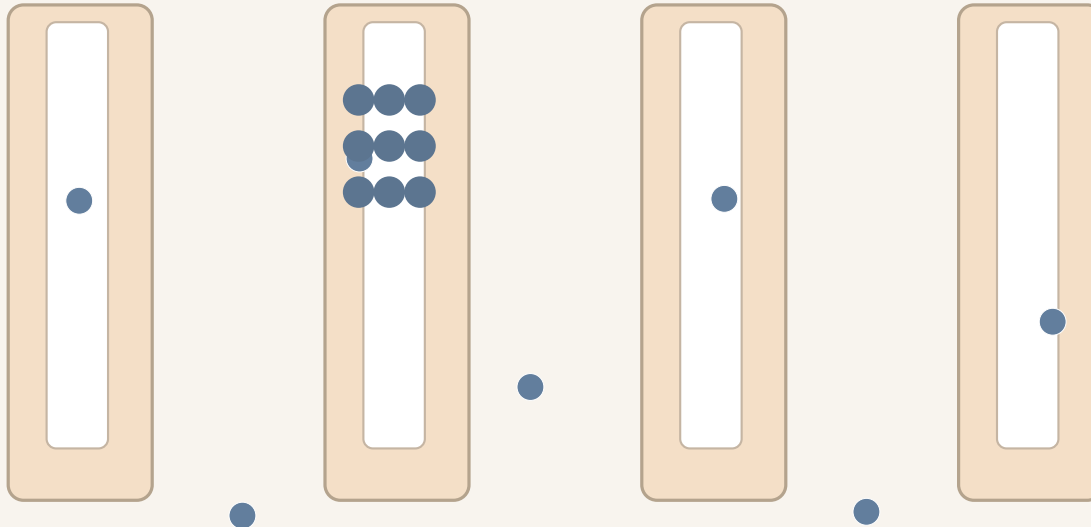
- Growth supported by H. Pylori–reactive T cells
- Localized gastric disease may respond to eradication
- NF- κ B activity depends on upstream immune signals

Later / more autonomous

- Acquired molecular alterations can activate NF- κ B constitutively
- Growth can persist without bacterial antigen
- Capacity for spread beyond stomach increases

Lymphoepithelial lesions are a key clue

Gastric surface epithelium



Simplified schematic — not a photomicrograph

Microscopic pattern

- Neoplastic small B cells permeate lamina propria.
- B cells infiltrate and disrupt gastric glands.
- Glandular infiltration creates lymphoepithelial lesions.

Gastric MALT lymphoma: Histologic architecture

- Lamina propria is expanded by a dense lymphocytic infiltrate.
- Lymphoepithelial lesions arise when lymphoma cells infiltrate gastric glands.
- Reactive-appearing B-cell follicles may coexist.
- Plasmacytic differentiation may also occur.

MALT lymphoma immunophenotype and clonality

Finding	Interpretation
CD19 and CD20 expression	Supports mature B-cell lineage
CD5 and CD10 negative	Characteristic immunophenotypic pattern described in Robbins
CD43 positive in some tumors	Potentially helpful adjunct, not a standalone criterion
Light-chain restriction or clonal IgH	Evidence supporting monoclonality when morphology is equivocal

Clonality must be interpreted in morphologic context

- Light-chain restriction can support a monoclonal B-cell process.
- Molecular detection of clonal IgH rearrangement may help selected cases.
- Immunophenotype alone does not substitute for tissue architecture.
- Small biopsies with overlapping reactive gastritis can present a diagnostic challenge.

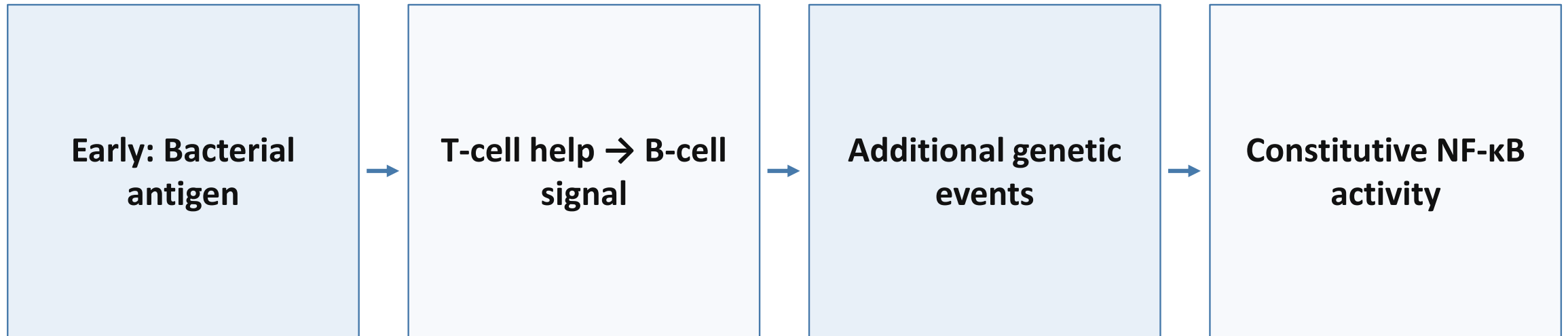
The API2::MALT1 fusion alters dependence on infection

- T(11;18)(q21;q21) creates an API2::MALT1 fusion.
- The fusion protein activates signaling that promotes B-cell growth and survival.
- Associated NF- κ B activity may become independent of the original antigenic stimulus.
- MALT lymphomas bearing this pathway alteration often resist H. Pylori eradication alone.

Selected molecular rearrangements in gastric MALT lymphoma

Rearrangement	Main target / effect
t(11;18)(q21;q21)	API2::MALT1 fusion
t(1;14)(p22;q32)	BCL10 expression increased
t(14;18)(q32;q21)	MALT1 expression increased
t(3;14)(p13;q32)	FOXP1::IGH; FOXP1 expression increased

The shift to autonomous NF- κ B signaling



This conceptual switch explains loss of dependence on H. Pylori–stimulated T cells.

Eradication therapy can remove the lymphoma stimulus

- Some localized gastric MALT lymphomas regress when H. Pylori is eradicated.
- Antibiotics remove the bacterial antigen driving reactive T-cell support.
- Therapeutic response depends on the molecular state of the lymphoma.
- Successful bacterial clearance does not guarantee regression of genetically autonomous lymphoma.

Why some gastric MALT lymphomas resist eradication

- MALT1/BCL10-related translocations may create constitutive survival signals.
- Invasion of muscularis propria and lymph node involvement correlate with resistance.
- Further evolution can permit spread beyond the gastric mucosa.
- Histologic follow-up must assess the tumor, not merely disappearance of H. Pylori.

MALT lymphoma and reactive gastritis can overlap

Shared findings

- Dyspepsia or epigastric pain
- Lymphoid aggregates in gastric biopsies
- Coincident H. Pylori gastritis
- Overlapping endoscopic appearance

Evidence favoring MALT lymphoma

- Dense monotonous or infiltrative B-cell population
- Lymphoepithelial lesions
- B-cell immunophenotype
- Light-chain restriction or clonal IgH when needed

Clinical correlation: Antral infection and ulcer phenotype

Clinical vignette

A patient has antral-predominant H. Pylori gastritis, raised gastrin activity, and preserved oxyntic mucosa.

Pathologic interpretation

An ulcer-prone physiology rather than the fully developed atrophic cancer precursor phenotype.

Mechanistic explanation

Antral inflammation can increase gastrin stimulation and acid secretion; The pathways diverge with corpus atrophy.

Clinical correlation: Multifocal atrophy and metaplasia

Clinical vignette

Gastric biopsies show chronic active gastritis, patchy gland loss, intestinal metaplasia, and H. Pylori.

Pathologic interpretation

A tissue background associated with the epithelial gastric carcinogenesis sequence.

Mechanistic explanation

Persistent injury plus epithelial turnover and inflammatory genotoxic mediators accompany atrophy and metaplasia.

Clinical correlation: Gastric lymphoid infiltrate

Clinical vignette

A biopsy shows a dense B-cell infiltrate and lymphoepithelial lesions in a stomach colonized by H. Pylori.

Pathologic interpretation

Consider extranodal marginal zone B-cell lymphoma of MALT type.

Mechanistic explanation

Chronic infection can induce acquired MALT;
Persistent B-cell stimulation and clonal selection
may produce lymphoma.

How the two neoplastic routes differ

Domain	Gastric adenocarcinoma	Gastric MALT lymphoma
Target cell	Gastric glandular epithelial cell	B lymphocyte in acquired MALT
Early drivers	Atrophy; metaplasia; inflammation-related genotoxicity	Persistent antigen-dependent T-cell help
Characteristic progression	Dysplasia → invasive carcinoma	Polyclonal → monoclonal B-cell expansion
Loss of stimulus	Precursor risk may persist after tissue alteration	Early tumors may regress with bacterial eradication

Four interpretive traps in H. Pylori neoplasia

- Not every H. Pylori–positive stomach develops a malignancy.
- A CagA-associated strain does not independently establish cancer.
- Reactive gastric lymphoid follicles are not equivalent to MALT lymphoma.
- Eradicating H. Pylori is not proof that an established lymphoma has regressed.

Integrating infection, topography, morphology, and clonality

- Document infection using appropriate testing and tissue sampling.
- Determine antral versus oxyntic involvement, activity, atrophy, and intestinal metaplasia.
- For epithelial atypia, separate metaplasia, dysplasia, and invasive carcinoma.
- For atypical lymphoid infiltrates, assess gland invasion, B-cell phenotype, and clonality where indicated.

Final synthesis: infection can create two oncogenic microenvironments

- Epithelial route: chronic inflammation → atrophy → metaplasia → dysplasia → carcinoma.
- Lymphoid route: induced MALT → antigen-dependent B-cell proliferation → clonality → possible NF- κ B autonomy.
- Both outcomes are modified by virulence, host genetics, duration, and additional acquired events.
- Pathologic interpretation requires both organism detection and the tissue response.