

Whipple disease

Infectious malabsorption with multivisceral pathology

Etiology • pathogenesis • morphology • clinicopathologic reasoning

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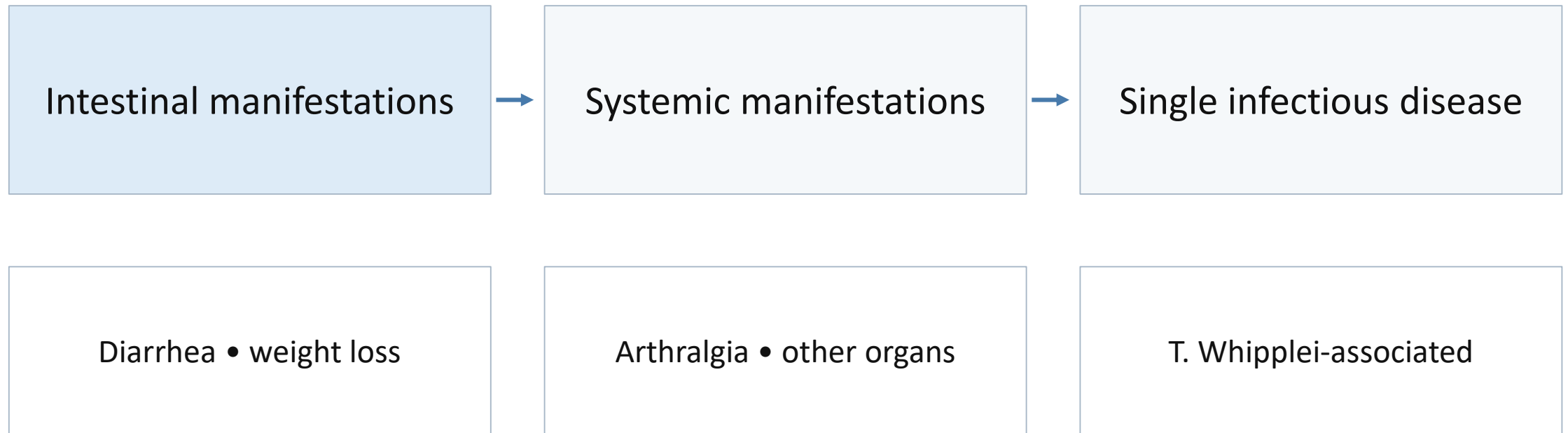
What this lecture will establish

- Explain why *Tropheryma whipplei* produces a chronic systemic syndrome.
- Trace foamy macrophage accumulation to intestinal lymphatic impairment.
- Recognize PAS-positive, diastase-resistant macrophages.
- Distinguish the tissue pattern from intestinal mycobacterial infection.

A rare disease with multiple organ targets

- Whipple disease is chronic and multisystemic rather than a purely local enteritis.
- Small-intestinal disease produces a malabsorptive diarrheal syndrome.
- Joint, neurologic, cardiac, lymphatic and pulmonary manifestations can complicate recognition.

Think beyond isolated intestinal symptoms



The causative organism

- The responsible bacterium is *Tropheryma whipplei*.
- It is an actinomycete.
- Its recognition transformed a morphologically distinctive syndrome into an etiologically defined infection.

Whipple's original description

1. Clinical syndrome
recognized

Malabsorption,
lymphadenopathy, arthritis

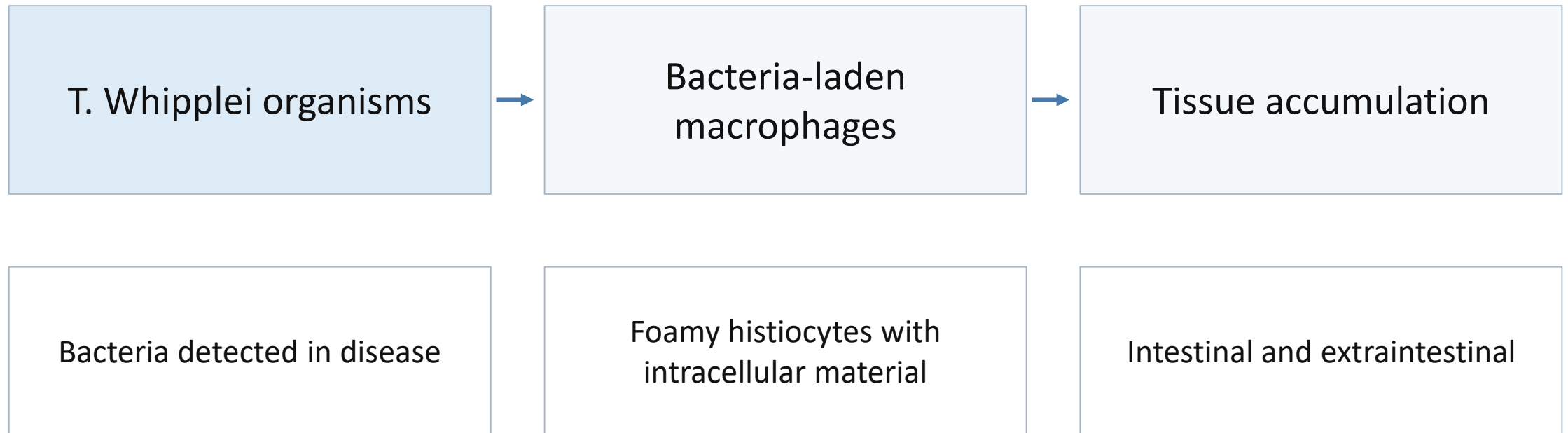
2. Macrophages containing
bacteria observed

Postmortem histologic findings

3. Organism identified as an
actinomycete in 1992

Tropheryma whipplei named

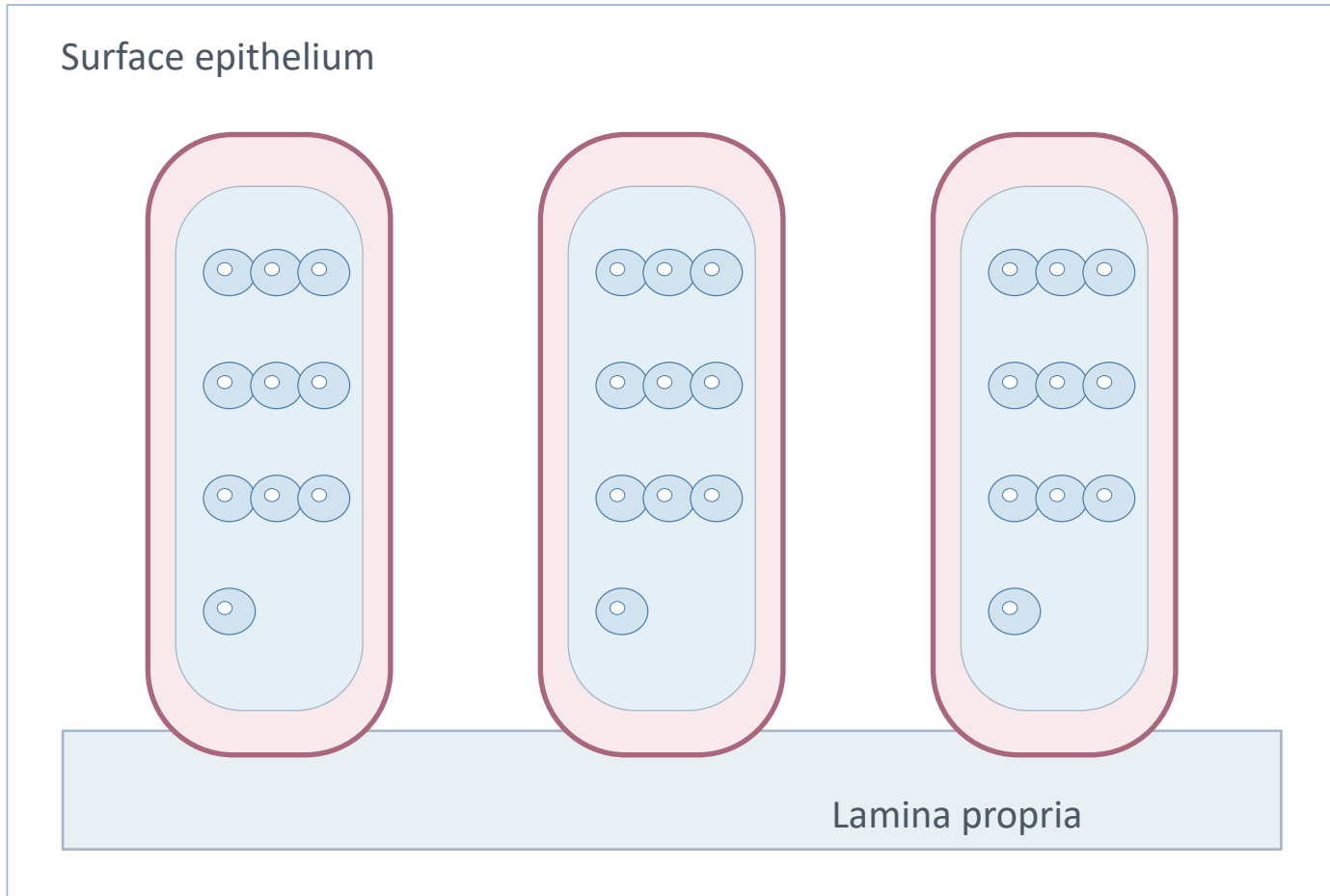
The first causal event is microbial persistence



Why the small intestine is central

- Macrophages collect densely in the small-intestinal lamina propria.
- Mesenteric lymph nodes are also involved.
- These sites link a systemic infection to impaired intestinal nutrient handling.

The lamina propria is the key compartment



Schematic — not a photomicrograph

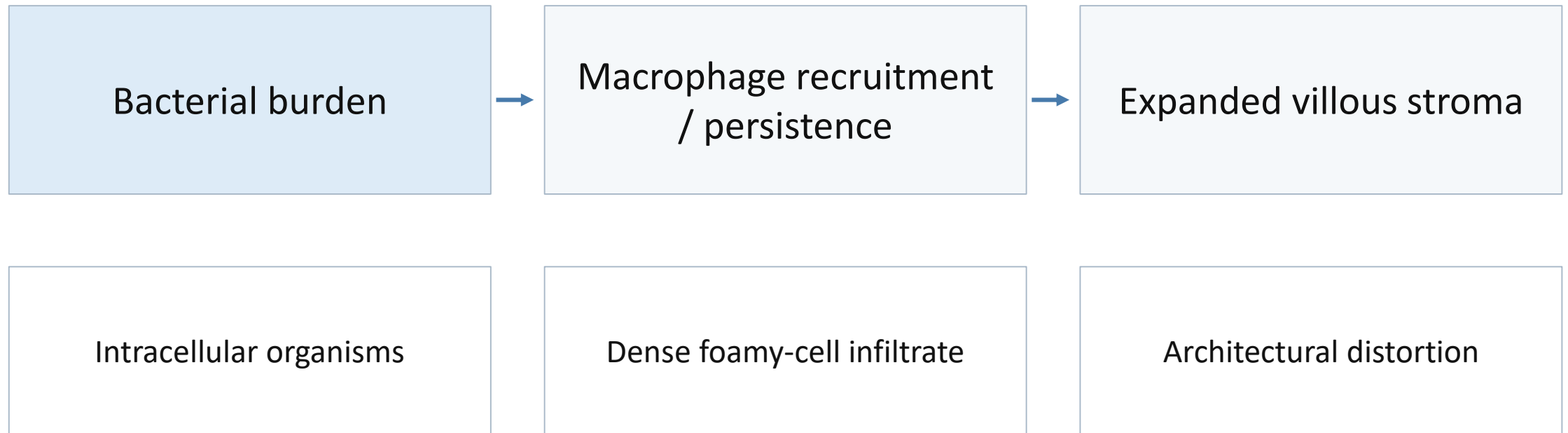
Interpretation

1. Surface epithelium
2. Lamina propria
3. Macrophage-rich expanded villus

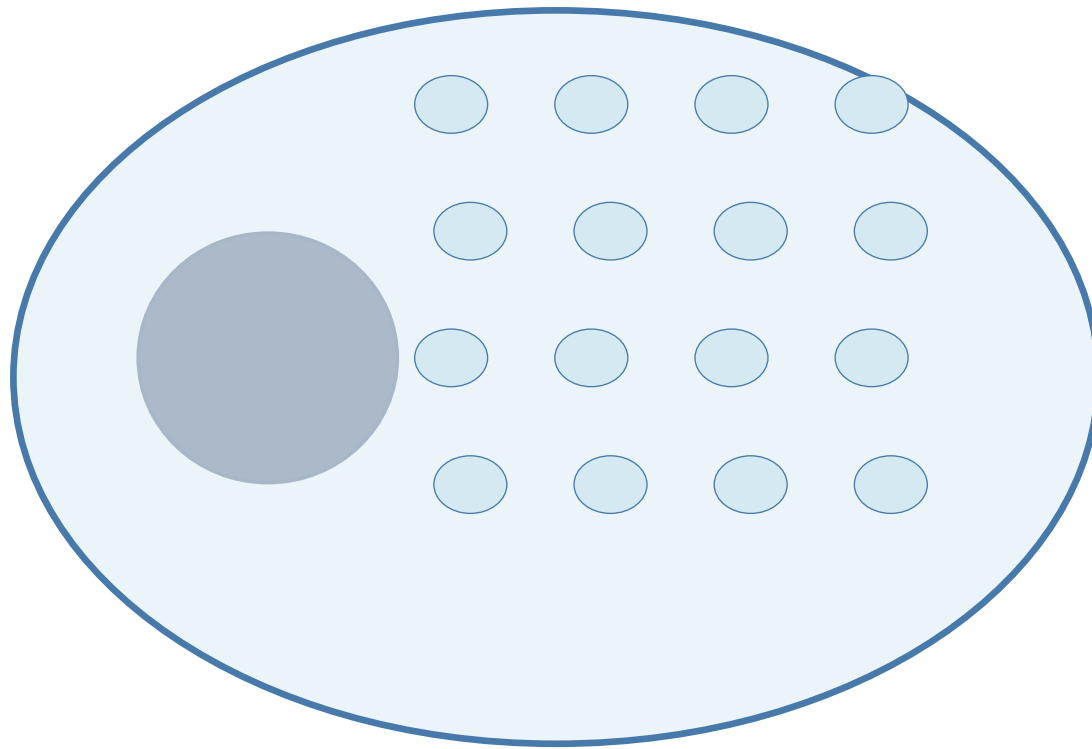
What foamy macrophages represent

- The intestinal lamina propria contains abundant enlarged macrophages.
- Their cytoplasm appears distended or foamy.
- Partially digested bacterial material inside macrophage lysosomes.

The dominant cellular response is accumulation



Bacteria occupy macrophage lysosomes

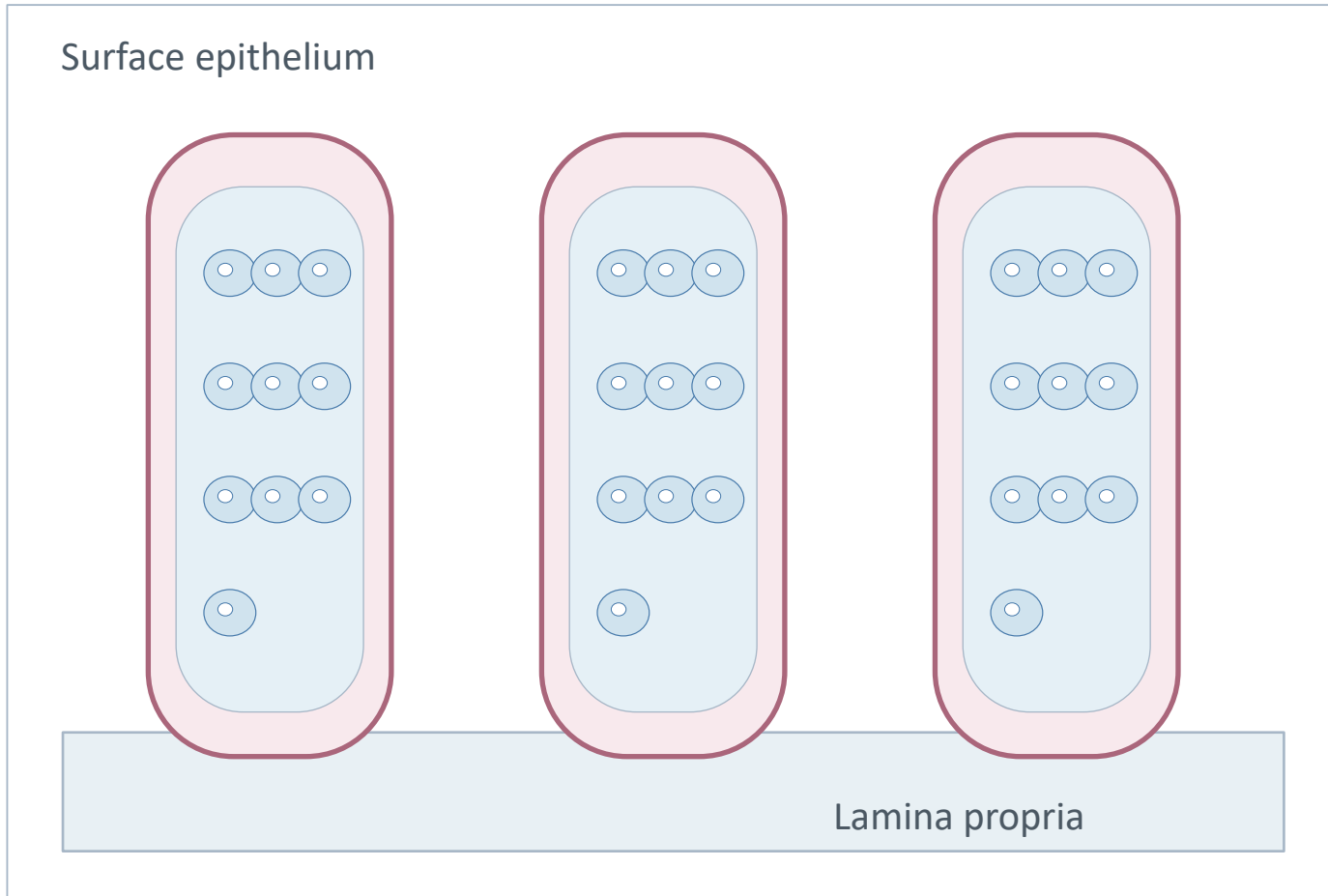


Schematic — not a photomicrograph

Cell-level interpretation

1. Macrophage
2. Lysosomal bacterial remnants
3. PAS-positive cytoplasmic granules

The intestinal wall becomes densely infiltrated



Interpretation

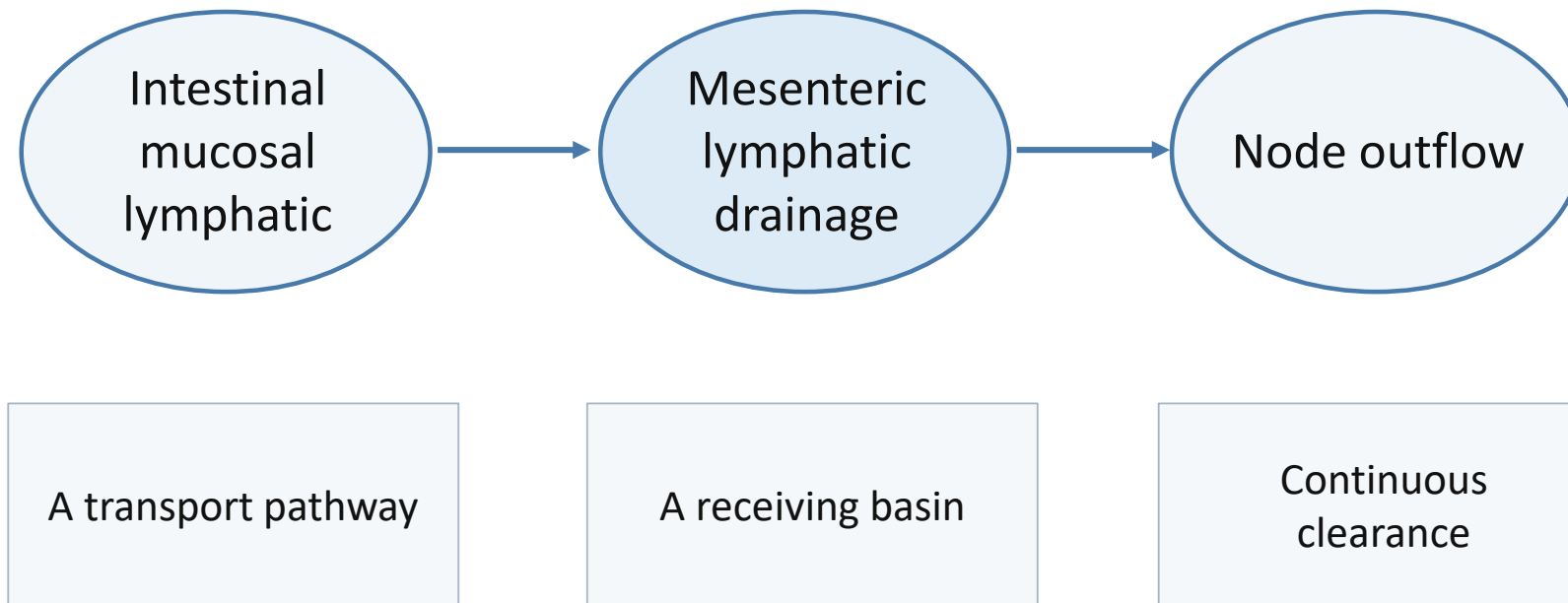
1. Macrophages crowd the lamina propria
2. Villus appears broadened
3. Normal stromal space is reduced

Schematic — not a photomicrograph

Mesenteric lymph nodes are an additional site

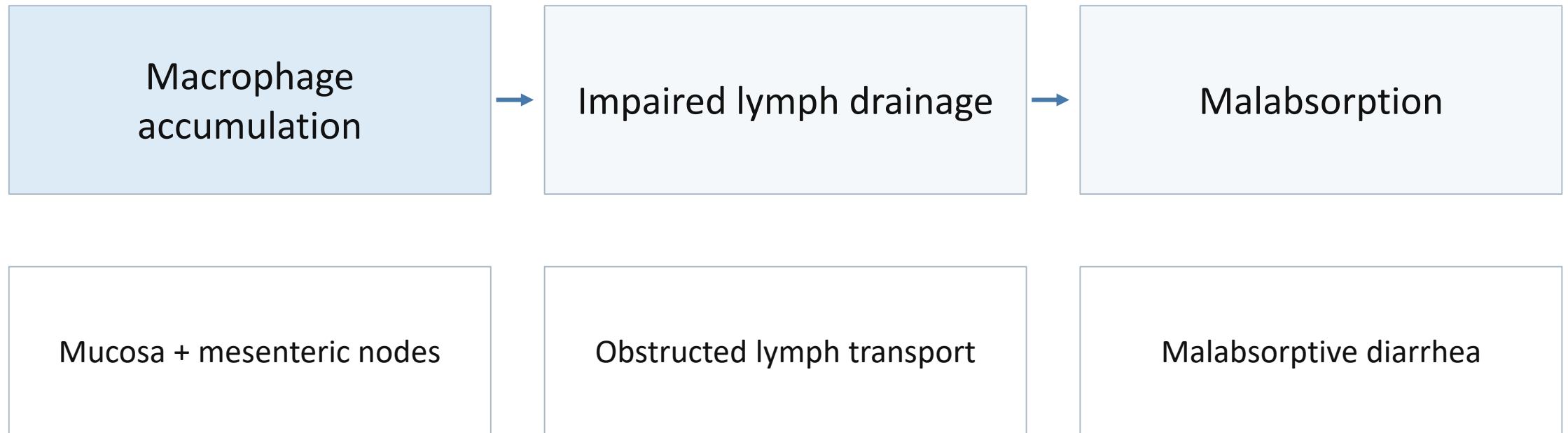
- Bacteria-laden macrophages accumulate in mesenteric lymph nodes.
- Together with intestinal infiltration, this can obstruct lymphatic pathways.
- Nodal disease helps explain the combination of malabsorption and lymphadenopathy.

Normal drainage provides the mechanistic context



Functional schematic

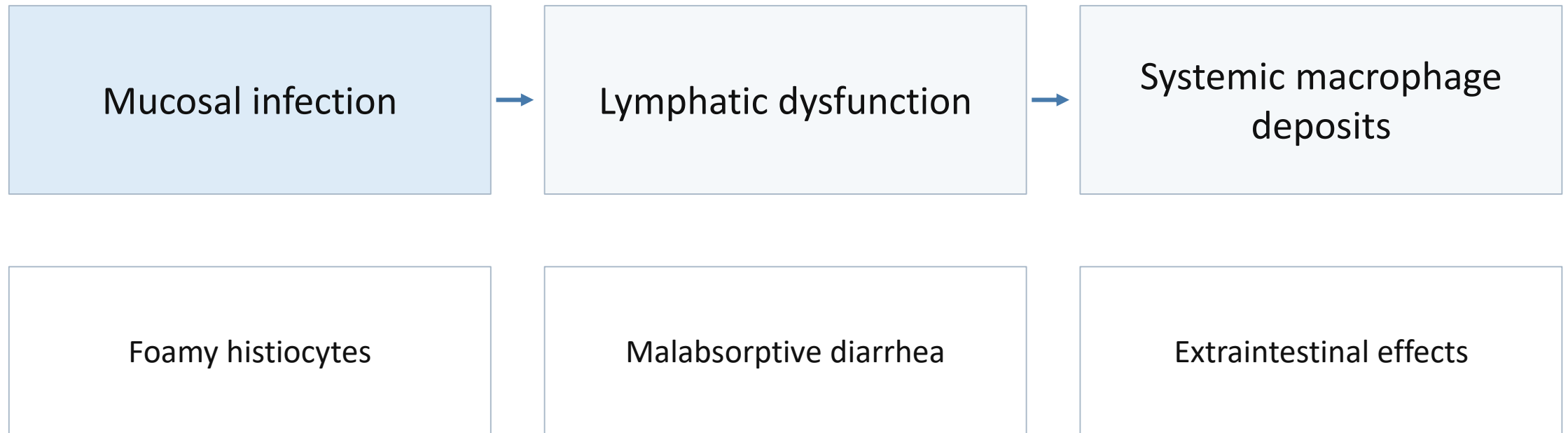
Lymphatic obstruction is the pivotal lesion



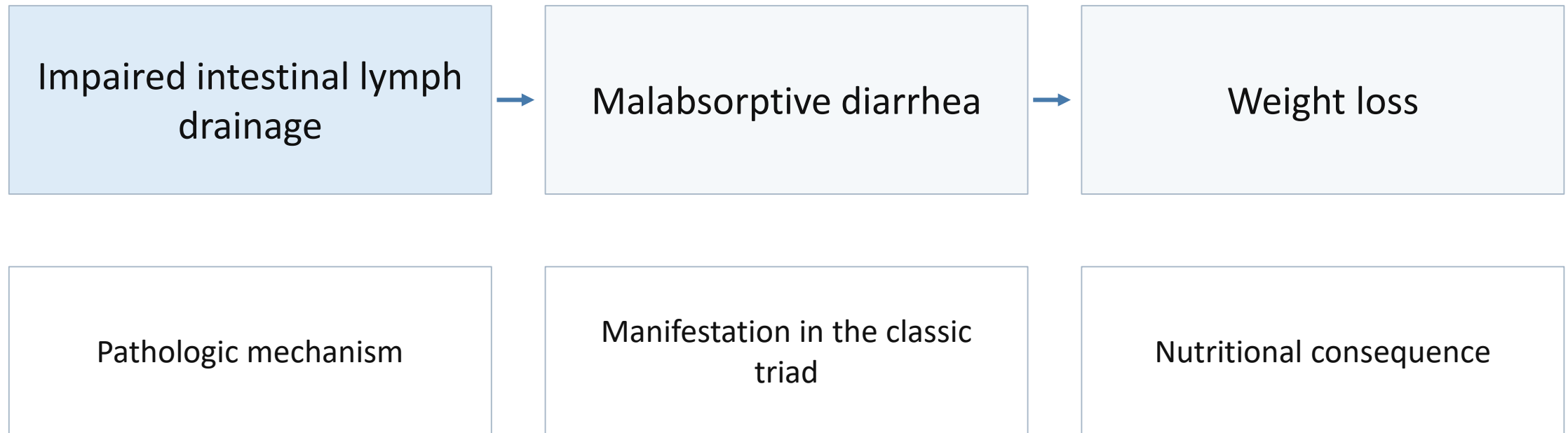
Whipple diarrhea is not simply acute enteritis

Whipple disease	Typical acute infectious gastroenteritis
Chronic multivisceral process	Often predominantly acute intestinal illness
Macrophage-rich tissue disease	Mechanisms vary by pathogen
Impaired lymph drainage is emphasized	No shared single mechanism

The mechanism linking gut and systemic disease



How malabsorption relates to weight loss



A conceptual map of affected tissue sites

Small intestine

Malabsorption

Mesenteric lymph nodes

Lymphadenopathy

Synovial membranes

Joint manifestations

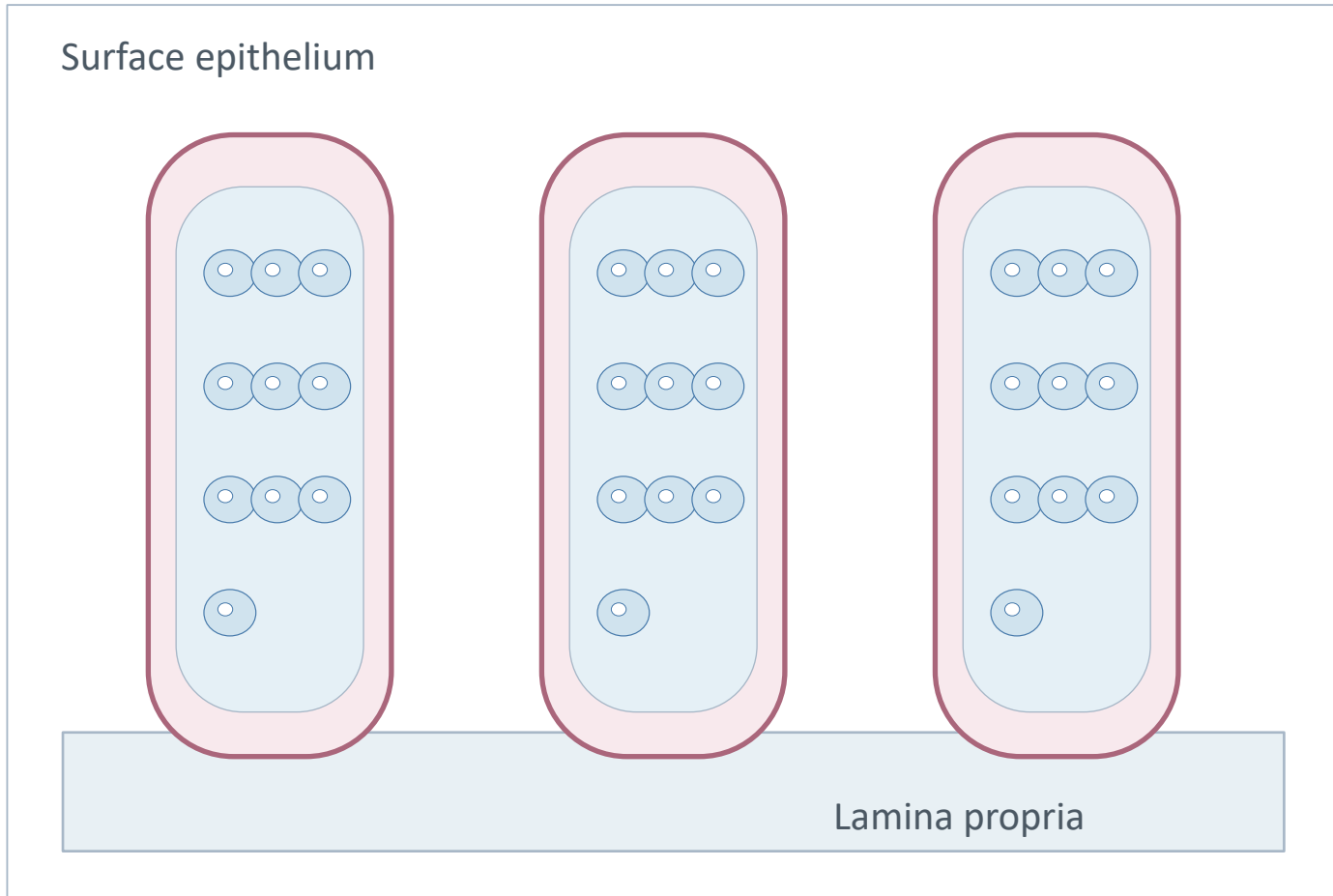
Cardiac valves

Cardiac disease

Brain

Neurologic disease

Low-power intestinal architecture



Interpretation

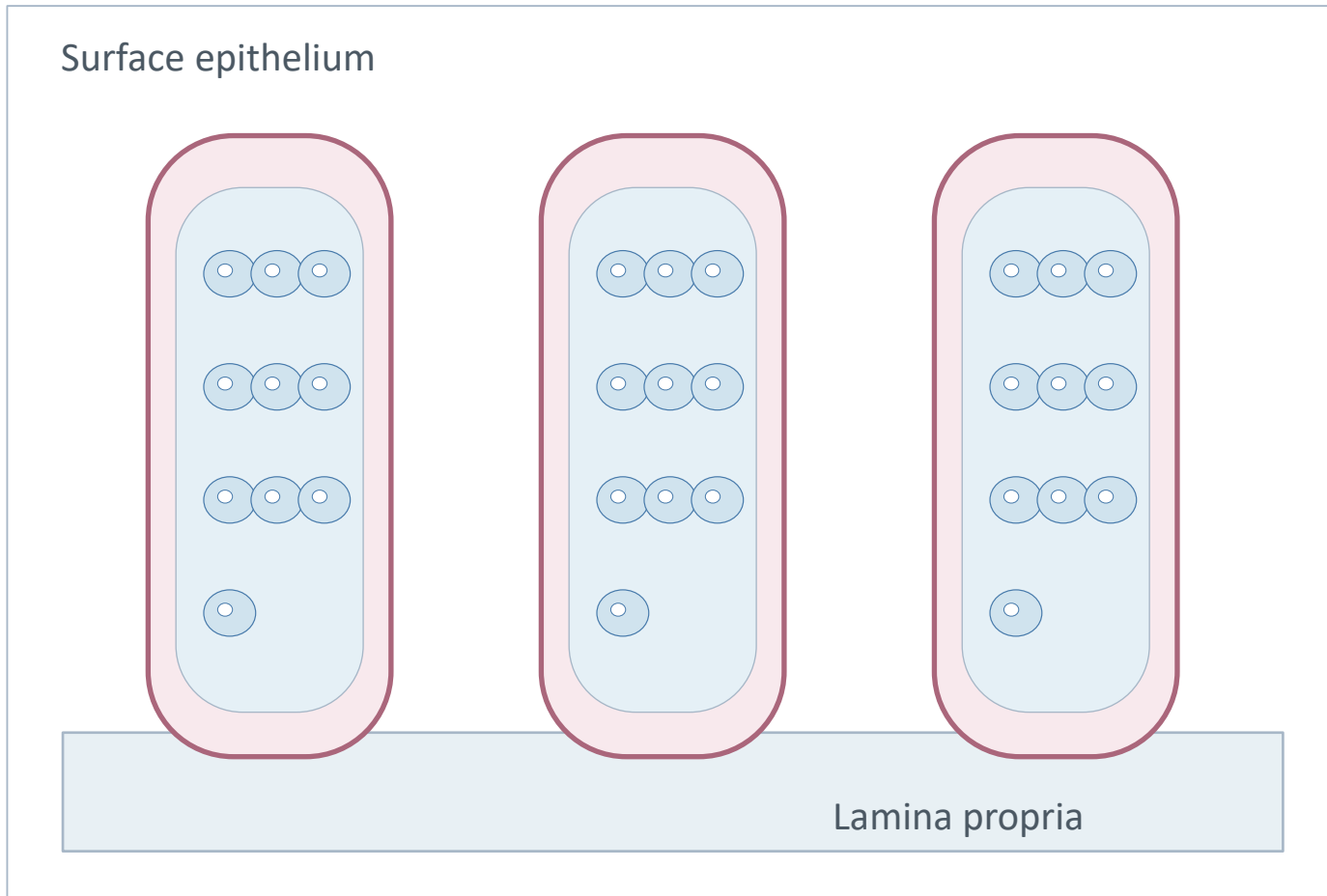
1. Widened mucosal villi
2. Foamy cells occupy the lamina propria
3. The mucosal outline becomes shaggy

Schematic — not a photomicrograph

What to recognize on an H&E section

- Look beneath the epithelium, inside the villous connective tissue.
- Dense sheets of distended pale macrophages replace normal-appearing lamina propria.
- This tissue distribution is more important than any isolated foamy cell.

Villous expansion produces a shaggy surface

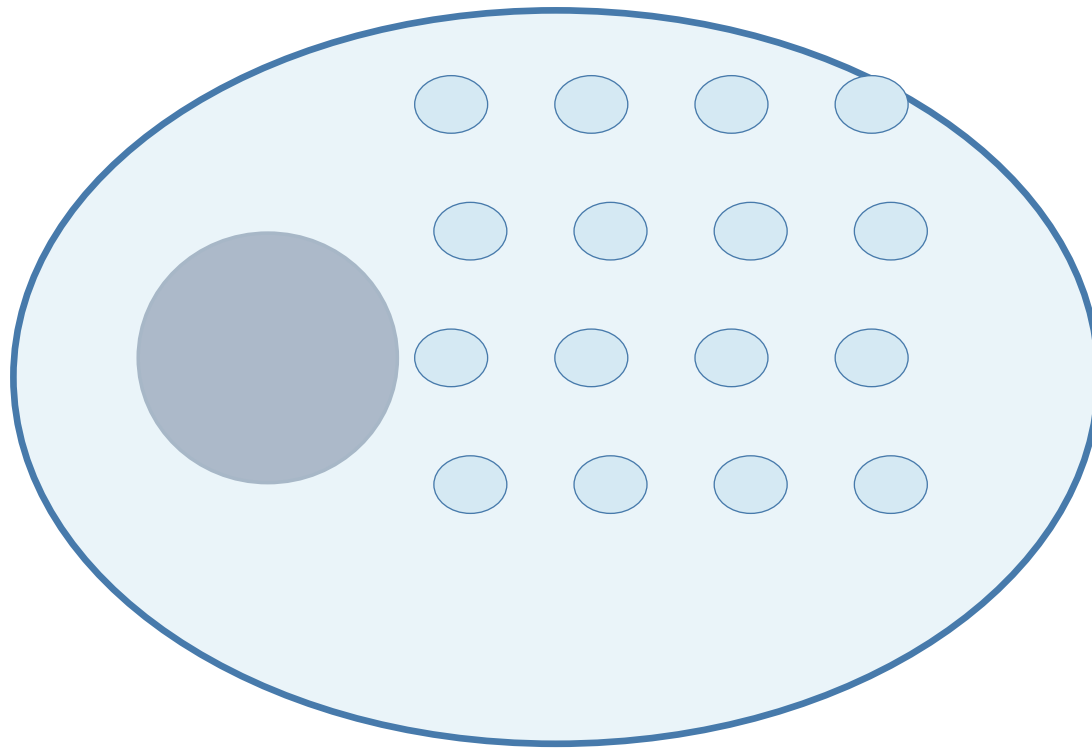


Interpretation

1. Macrophages expand the villous core
2. The mucosal surface looks irregular and shaggy
3. Architecture reflects the cellular infiltrate

Schematic — not a photomicrograph

Higher-power focus: The macrophage



Schematic — not a photomicrograph

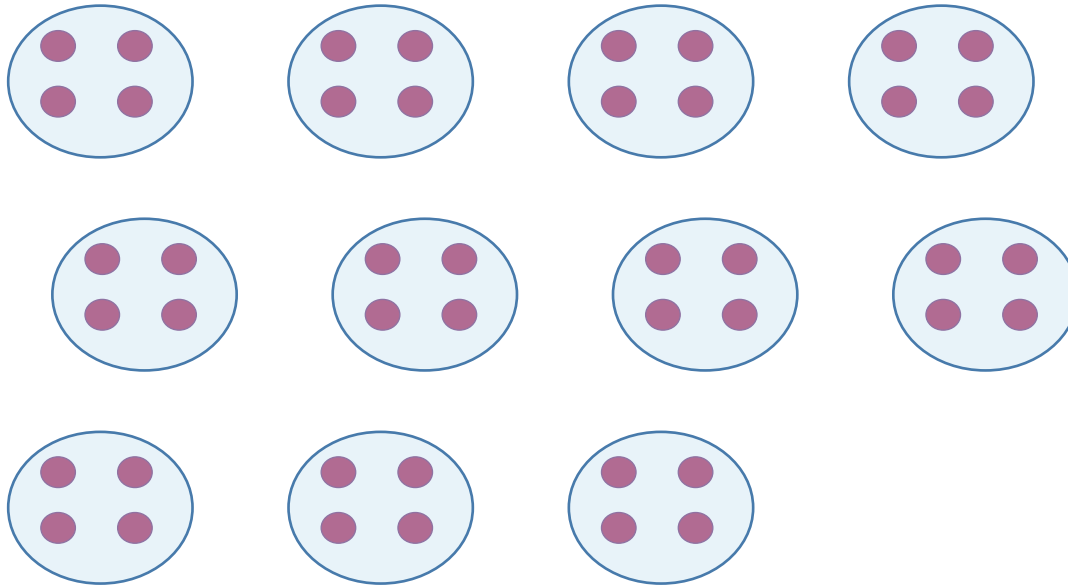
Cell-level interpretation

1. Enlarged foamy cytoplasm
2. Lysosomes containing bacterial material
3. Aggregated cells in villous stroma

Do not mistake a foam cell for a diagnosis

- Foamy macrophages are characteristic in the proper tissue pattern, not etiologically unique.
- Stain results and clinical distribution refine interpretation.
- Intestinal mycobacterial infection is the explicitly identified histologic mimic.

PAS highlights intracellular bacterial remnants



Schematic — stain reaction, not a tissue image

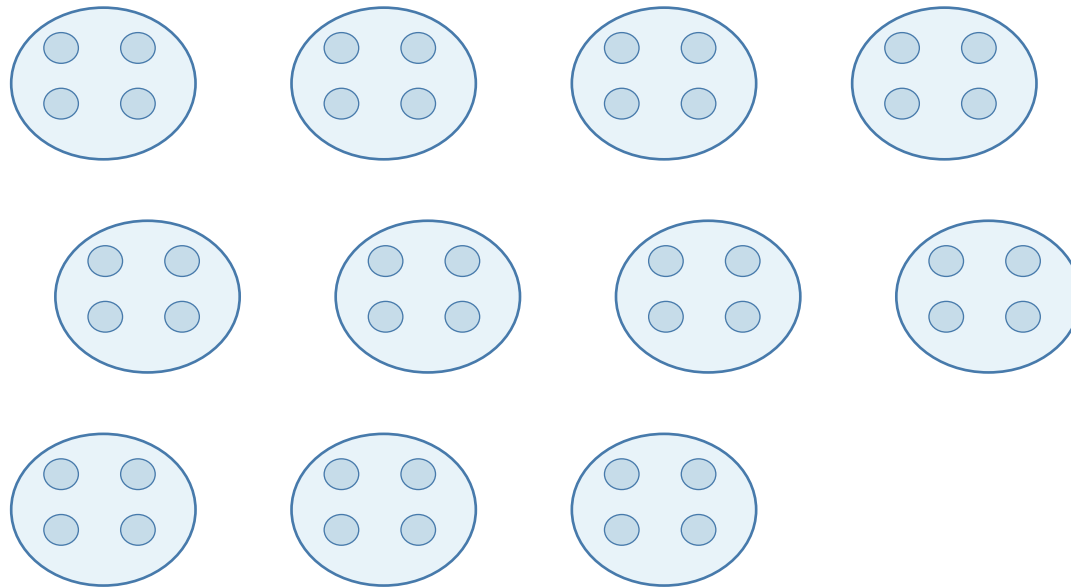
Stain principle

1. Foamy intestinal macrophage
2. PAS-positive cytoplasmic granules
3. Accumulated partially digested bacteria

PAS positivity is cytoplasmic and granular

- Periodic acid–Schiff staining highlights material within macrophage lysosomes.
- Positive granules reflect partially digested bacterial contents.
- Interpret their location in expanded lamina propria, not staining in isolation.

Diastase resistance strengthens the pattern



Schematic — stain reaction, not a tissue image

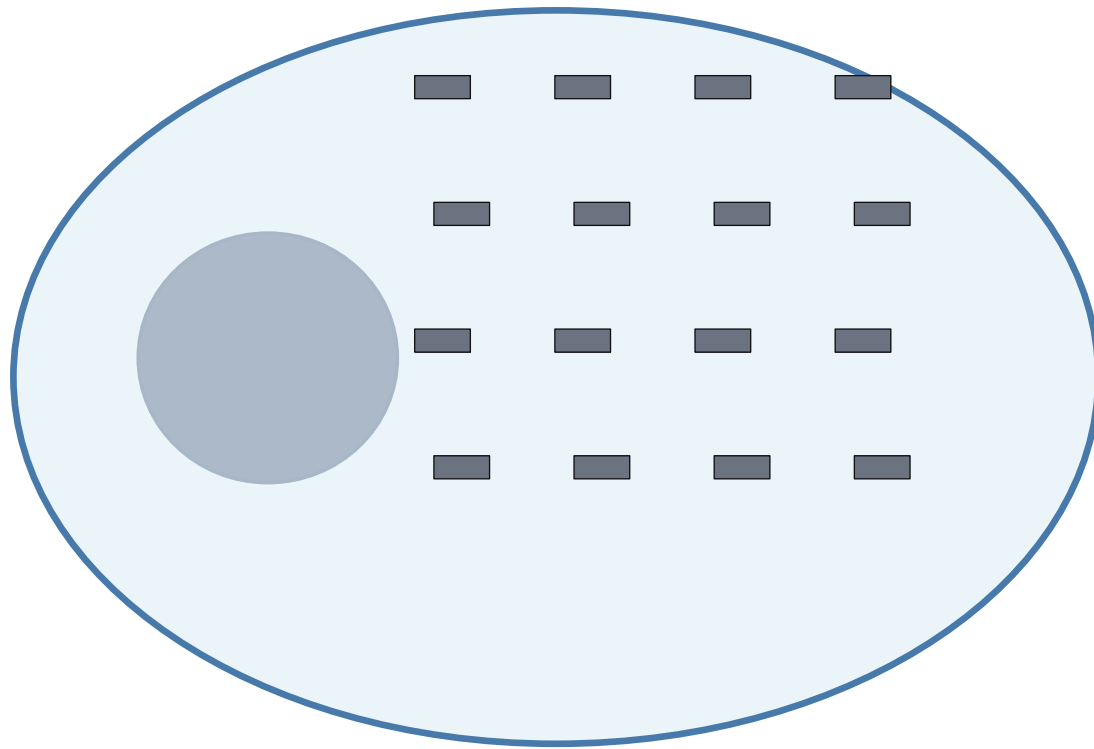
Stain principle

1. PAS reaction
2. Diastase predigestion
3. Positive macrophage granules persist

What “diastase-resistant” adds

- The source specifically describes macrophage granules as PAS-positive and diastase-resistant.
- This remains a staining phenotype rather than direct species identification.
- A compatible biopsy still requires differential diagnostic reasoning.

Electron microscopy can show intact rods



Schematic — not a photomicrograph

Cell-level interpretation

1. Distended macrophage
2. Intact rod-shaped bacilli
3. Ultrastructural demonstration

EM and PAS answer different questions

PAS / diastase-PAS	Electron microscopy
Highlights intralysosomal granular material	Can identify intact rod-shaped organisms
Routine light-microscopy tissue appearance	Ultrastructural morphology
Supports characteristic pattern	Supports organism-level morphology

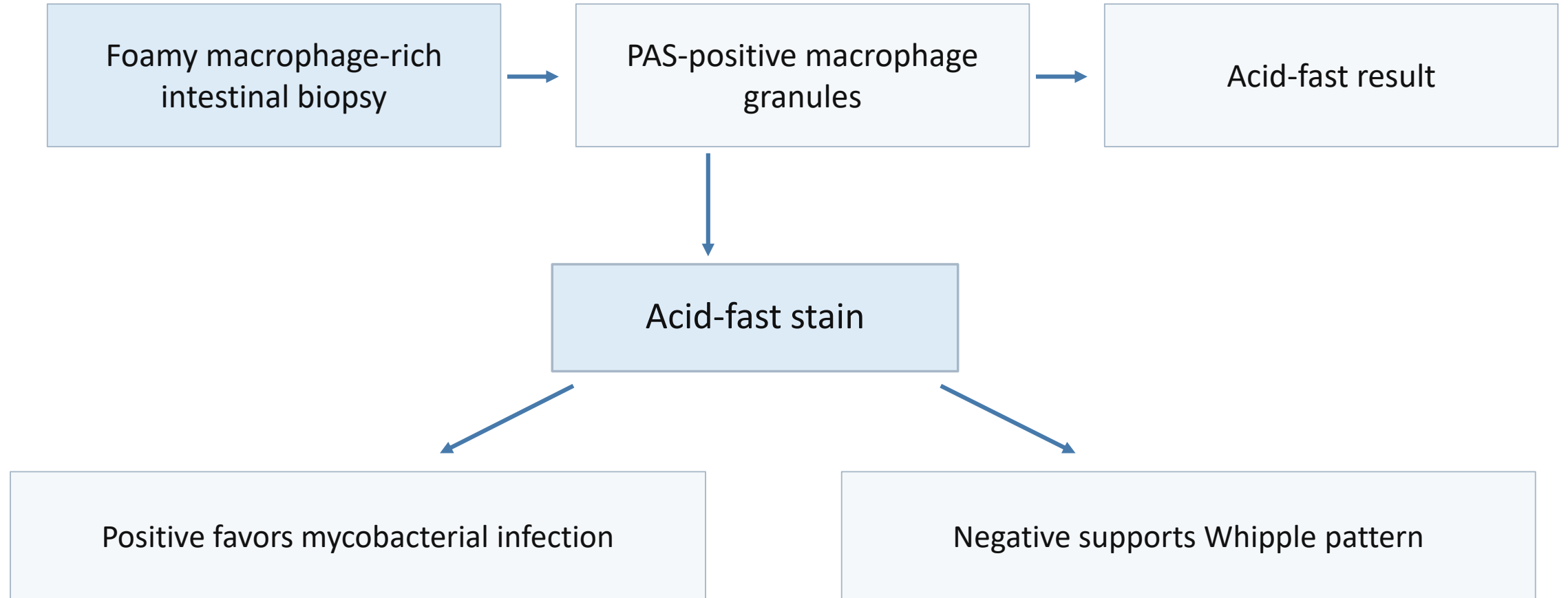
The most important infectious mimic

- Intestinal mycobacterial infection can produce a similar foamy macrophage infiltrate.
- Macrophages in both disorders may contain PAS-positive organisms.
- A second stain becomes discriminating.

Acid-fast staining separates the patterns

Whipple disease	Intestinal mycobacterial infection
PAS-positive intracellular material	PAS-positive intracellular material
T. Whipplei is acid-fast negative	Mycobacteria are acid-fast positive
Foamy lamina propria infiltrate	Foamy lamina propria infiltrate

A diagnostic stain sequence



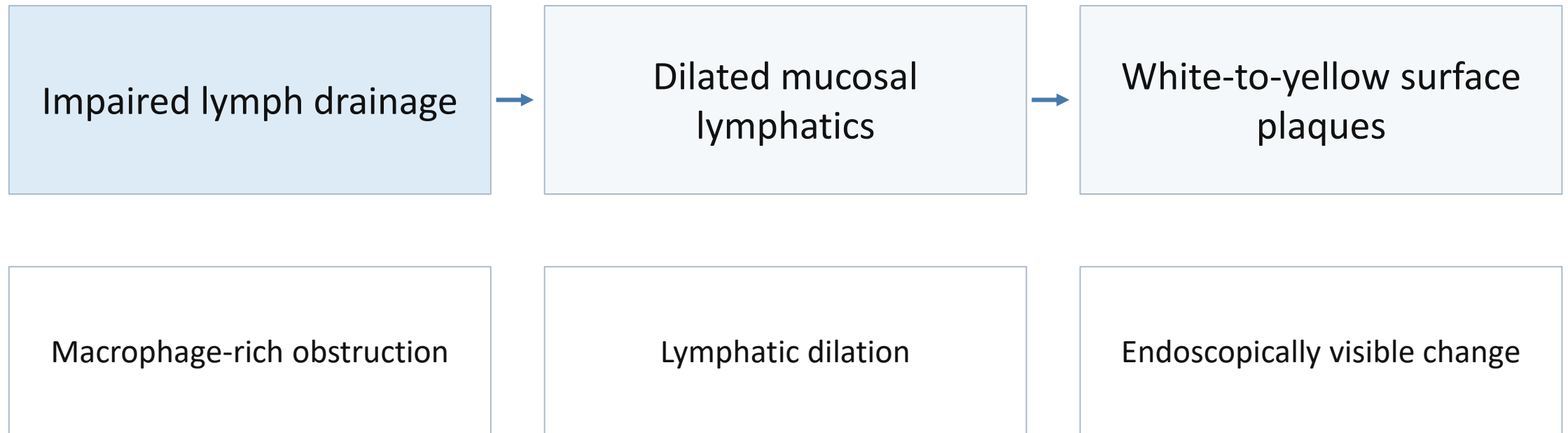
Why PAS alone cannot settle the differential

- The shared PAS reaction creates a morphologic trap.
- Acid-fast positivity points toward mycobacteria.
- Acid-fast negativity is consistent with *T. Whipplei* in an appropriate clinicopathologic setting.

The endoscopic surface may appear shaggy

- Dense villous macrophage infiltrates expand the mucosal architecture.
- The resulting mucosal surface may acquire a shaggy appearance.
- This gross finding expresses the underlying microscopic process.

Lymphatic dilation alters mucosal appearance



White–yellow plaques reflect tissue lipids

- White-to-yellow mucosal plaques to lymphatic dilation and mucosal lipid deposition.
- Plaques therefore illustrate disordered intestinal lymph transport.
- The appearance should be interpreted alongside the biopsy.

Correlating three levels of intestinal evidence

Endoscopy	H&E microscopy	PAS microscopy
Shaggy surface / pale plaques	Expanded villi with foamy macrophages	Diastase-resistant granules
Gross consequence	Cellular localization	Bacterial remnant signature

The classic clinical triad

Diarrhea

Weight loss

Arthralgia

Malabsorptive

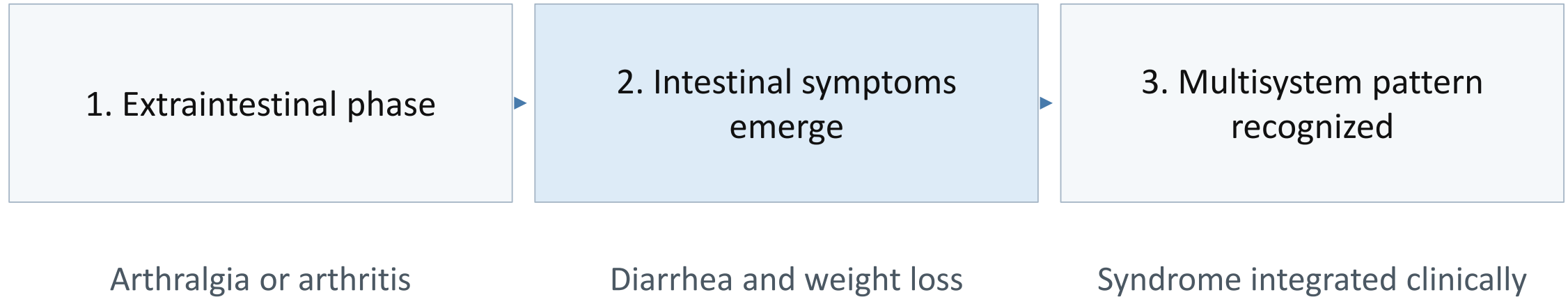
Chronic nutritional effect

Joint symptoms

Arthralgia is part of the core phenotype

- Joint pain belongs to the classic clinical triad.
- Extraintestinal manifestations may occur well before diarrhea becomes prominent.
- A prolonged rheumatologic history may obscure the unifying infectious cause.

Arthritis can precede intestinal disease



Mesenteric nodal disease and lymphadenopathy

- Macrophage accumulation is documented in mesenteric lymph nodes.
- Lymphadenopathy was part of the original clinical description.
- Nodal pathology has a mechanistic as well as clinical role in this disease.

Cardiac valve involvement

- Bacteria-laden macrophages may accumulate in cardiac valves.
- Cardiac disease is among the recognized extraintestinal manifestations.
- The systemic distribution warrants attention beyond a digestive-system label.

Neurologic manifestations indicate dissemination

- Macrophage deposits may be found in the brain.
- Neurologic disease is part of the described extraintestinal spectrum.
- Neurologic presentations can occur before overt malabsorptive symptoms.

Pulmonary disease also belongs to the spectrum

- Pulmonary disease among the possible extraintestinal presentations.
- Respiratory symptoms therefore do not exclude an intestinal-origin diagnostic pathway.
- No unique pulmonary histologic pattern is specified in the supplied section.

Systemic illness can include fever

- Fever is one of the extraintestinal clinical features described.
- It may coexist with arthralgia, lymphadenopathy and chronic intestinal symptoms.
- The constellation has greater diagnostic value than fever in isolation.

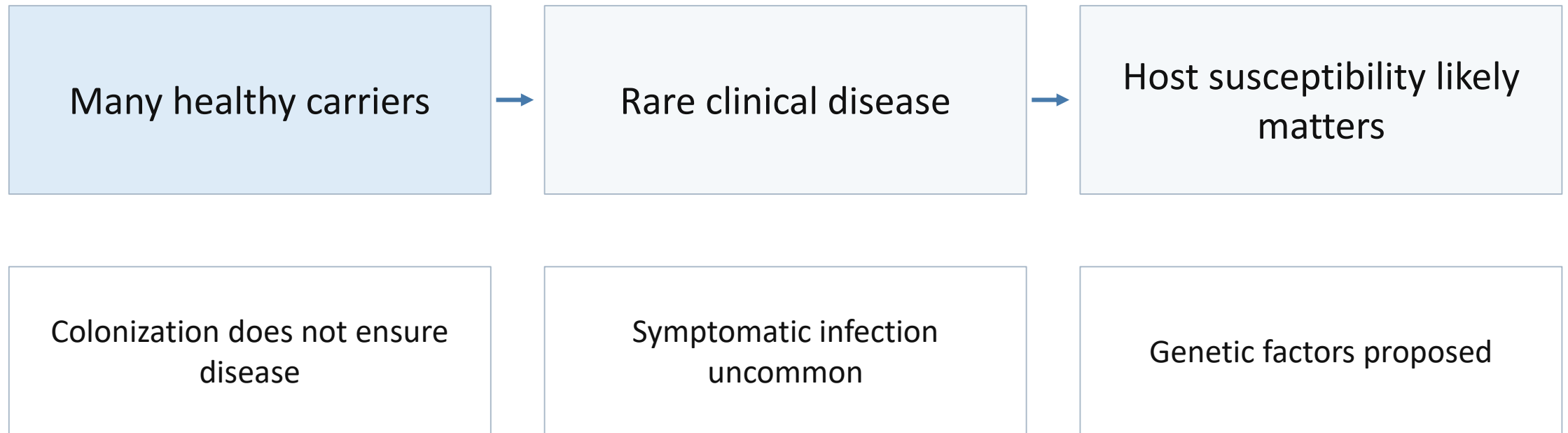
Reported demographic pattern

- Whipple disease is most common in males of Northern European descent.
- This association is epidemiologic and does not define an exclusive affected population.
- Pathology and clinical presentation remain central to recognition.

Occupational exposure is an association

- Farmers and others occupationally exposed to soil or animals.
- These are exposure associations rather than a proved individual transmission route.
- Exposure history may add context, but is not a tissue-based diagnostic criterion.

The carrier paradox



Why host genetic risk remains a hypothesis

- The source notes no consistent familial clustering.
- Disease is much rarer than healthy organism carriage.
- Genetic susceptibility is inferred, not assigned to a specific gene in this source.

Case: The early phase

Clinical observation

- A patient reports years of intermittent arthralgia and episodes of fever.
- A clear intestinal syndrome has not yet developed.

Reasoning task

Can this presentation be consistent with Whipple disease?

Teaching answer: Yes. Extraintestinal disease may precede malabsorption by months or years.

Case: The intestinal syndrome develops

Clinical observation

- The same patient develops persistent diarrhea and weight loss.
- Joint symptoms remain part of the history.

Reasoning task

What three symptoms now form the classic triad?

Teaching answer: Diarrhea, weight loss and arthralgia.

Case: The biopsy shows macrophage-rich villi

Clinical observation

- A small-intestinal biopsy shows a markedly expanded lamina propria.
- Numerous distended pale macrophages occupy the villous cores.

Reasoning task

What single histologic observation is most characteristic?

Teaching answer: Dense foamy macrophages in the small-intestinal lamina propria.

Case: Staining defines the differential

Clinical observation

- The macrophages have PAS-positive, diastase-resistant granules.
- An acid-fast stain is negative.

Reasoning task

Which infection is supported over the main mimic?

Teaching answer: Whipple disease is favored over intestinal mycobacterial infection.

Case: The heart and brain matter

Clinical observation

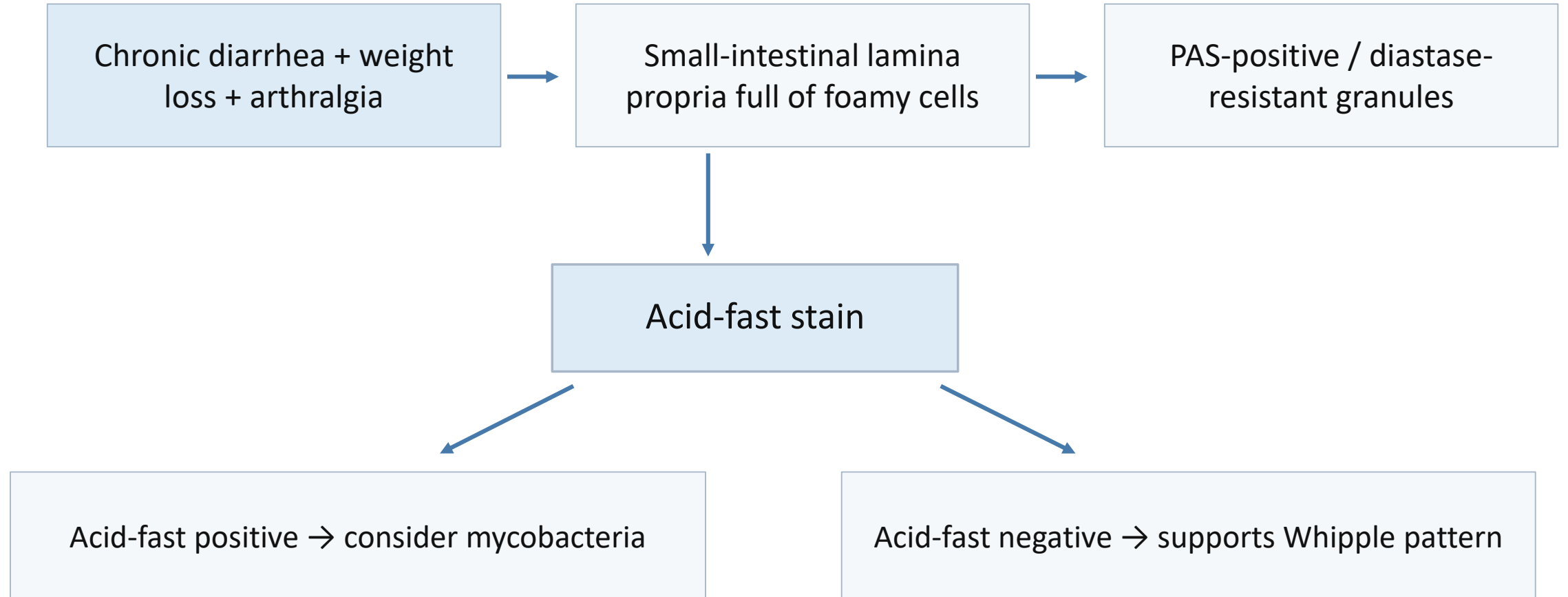
- A patient with compatible intestinal findings also has cardiac and neurologic symptoms.
- These findings are evaluated as potentially related rather than automatically unrelated.

Reasoning task

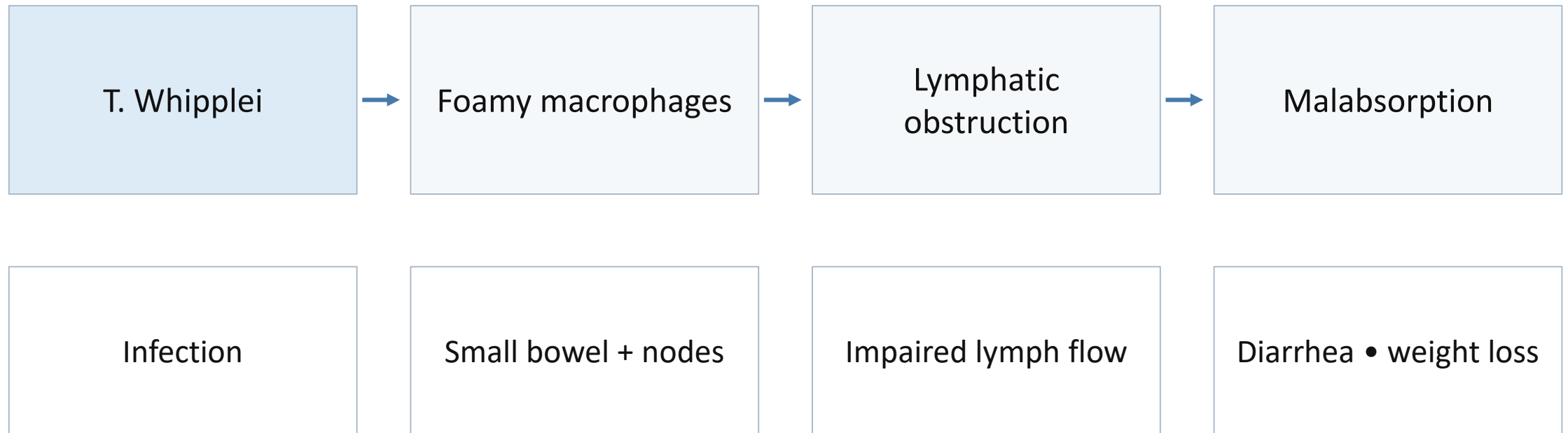
Which pathological feature makes this plausible?

Teaching answer: Bacteria-laden macrophages can accumulate at extraintestinal sites including cardiac valves and brain.

Pattern recognition: Clinic to slide



The complete pathogen-to-patient chain



Five discriminating facts to retain

- Organism: *Tropheryma whipplei*, an actinomycete.
- Tissue: Foamy macrophages in the small-intestinal lamina propria.
- Stain: PAS-positive, diastase-resistant intralysosomal granules.
- Mechanism: Impaired lymph drainage drives malabsorption.
- Key mimic: Intestinal mycobacteria are acid-fast positive.

Source and visual provenance

- Primary: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Chapter 17, Whipple Disease, pp. 722–723.
- Morphologic figure referenced in text: Fig. 17.33 (H&E, PAS, EM, mycobacterial comparison and acid-fast staining).
- All disease diagrams in this presentation are newly constructed native PowerPoint schematics; they are not photomicrographs.
- The supplied extracted text was used in preference to unverified outside diagnostic/treatment claims.