

Zollinger–Ellison syndrome

Gastrinoma, gastric hypersecretion, and peptic ulcer disease

Gastrin • Oxyntic hyperplasia • Peptic injury

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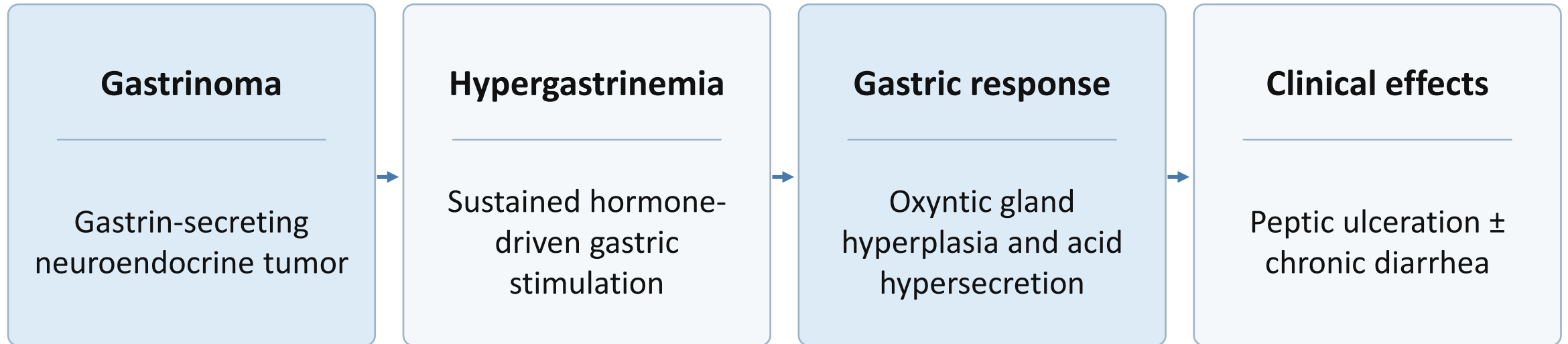
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Learning objectives

- Connect gastrinoma-derived gastrin to gastric epithelial growth and acid injury.
- Recognize the characteristic oxyntic mucosal response and ulcer distribution.
- Distinguish sporadic gastrinomas from MEN1-associated disease.
- Link gastric acid control, tumor localization, and neoplasm-directed management.

One endocrine lesion, two tissue-level consequences



Zollinger–Ellison syndrome is a functional neoplastic endocrine syndrome.

The syndrome is not a primary gastric neoplasm

Source lesion

Gastrinoma in small intestine, pancreas, or adjacent soft tissue.

Target organ

Oxyntic mucosa of the gastric body and fundus.

Clinical injury

Acid-related lesions in duodenum, stomach, or even jejunum.

Gastrinomas are neuroendocrine neoplasms

- The defining secretory product is gastrin.
- A functional tumor can cause major physiological disturbance without bulky local growth.
- An endocrine tumor and its downstream mucosal effects must be assessed separately.
- The gastric changes are a hormone-induced response, not a primary gastric gastrinoma.

Gastrinoma location: Bowel and pancreas

Duodenum / small bowel

An important primary site;
Particularly characteristic
in MEN1.

Pancreas

Typical location of many
solitary sporadic tumors.

Peripancreatic region

The endocrine chapter
includes soft tissues
around the pancreas
within the recognized
gastrinoma region.

The “gastrinoma triangle” is a clinical region

Small bowel

Duodenal primary gastrinoma.

Peripancreatic tissues

Extra-pancreatic sites in the regional soft tissues.

Pancreas

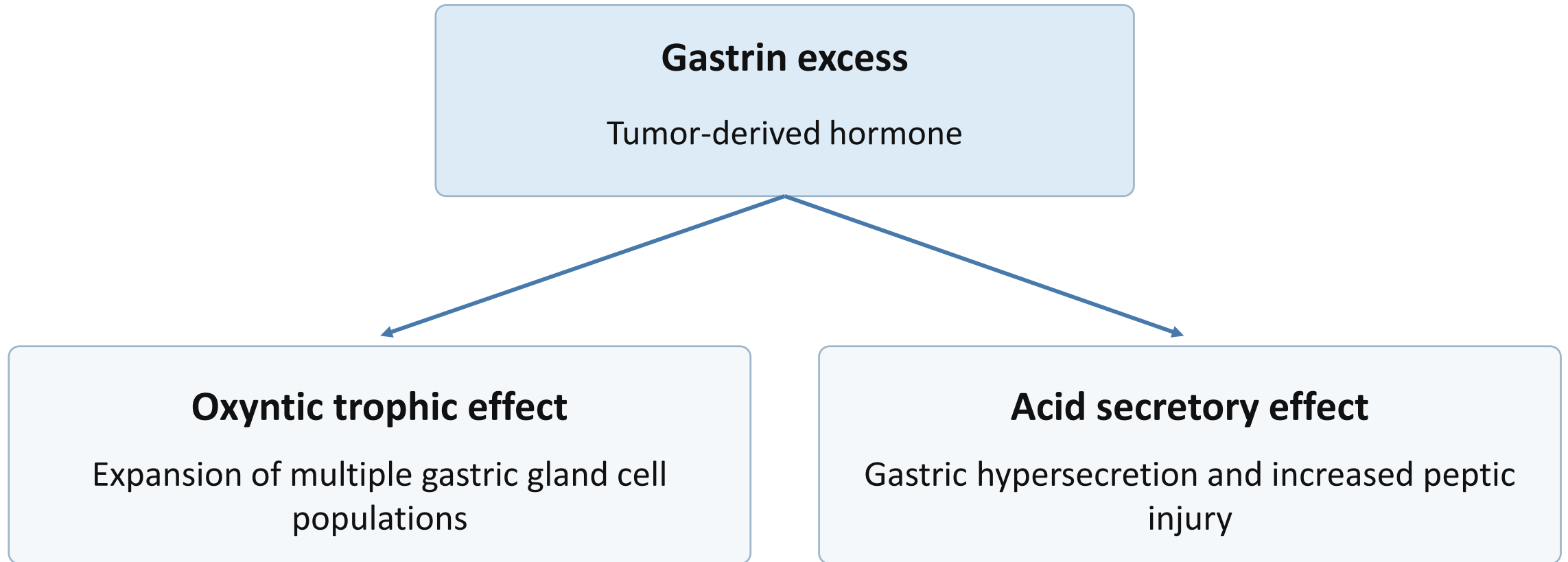
Pancreatic primary gastrinoma.

Site categories are schematic; No anatomic scale or spatial boundaries are implied.

Location and secretory phenotype answer different questions

Question	What it establishes	What it does not establish
Where is the lesion?	Anatomic origin and potential resectability	Whether acid hypersecretion is controlled
What does it secrete?	Gastrin-dependent syndrome	Tumor burden or metastatic extent
How has it spread?	Neoplastic dissemination	Degree of current gastric acid injury

Gastrin links endocrine and gastrointestinal pathology



Two parallel downstream effects of excess gastrin.

The oxyntic mucosa is the central target

Anatomic distribution

Predominantly gastric fundus and body.

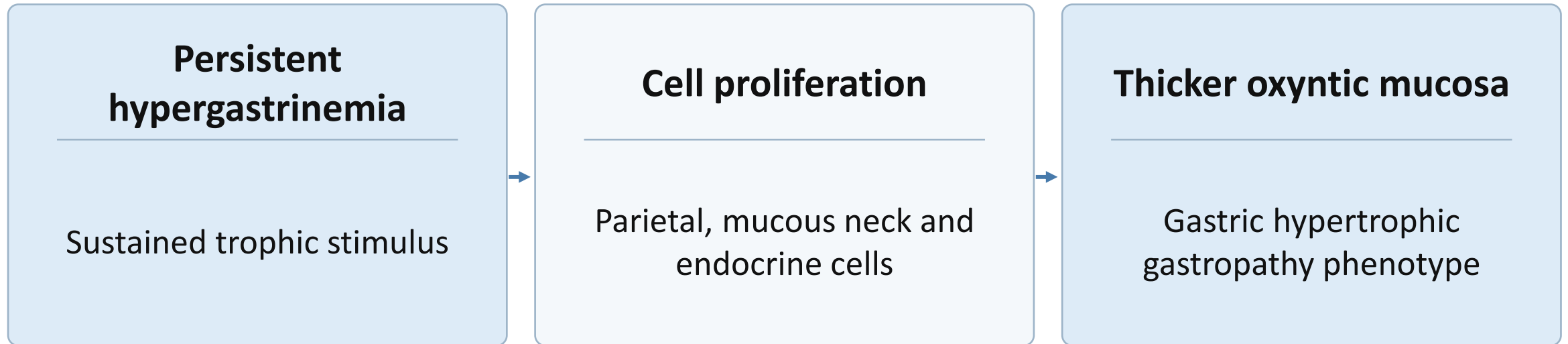
Baseline function

Acid-producing parietal-cell compartment.

ZES alteration

Markedly increased mucosal thickness and gland-cell populations.

Gastric thickening reflects gland-cell hyperplasia



“Hypertrophic” describes the macroscopic effect; The microscopic process is hyperplasia.

Parietal cell hyperplasia dominates the response

- Massive parietal-cell hyperplasia is the striking microscopic feature.
- Parietal cells populate the oxyntic mucosa of body and fundus.
- Increased secretory-cell mass accompanies acid hypersecretion.
- Thicker oxyntic mucosa provides a morphologic clue to a circulating stimulus.

Mucous neck cells also expand

- Gastrin promotes mucous neck cell hyperplasia.
- Expansion is part of a broader oxyntic gland response, not an isolated surface lesion.
- Cellular composition distinguishes Zollinger–Ellison syndrome from foveolar-predominant disorders.
- The phenotype is mixed glandular hyperplasia, despite parietal-cell predominance.

Endocrine cell hyperplasia accompanies the gland response

- Oxyntic endocrine cells also increase under the influence of gastrin.
- This component helps explain why multiple cell populations expand together.
- Gastric neuroendocrine cell hyperplasia may occur in several other settings.
- Context and acid physiology are necessary to interpret endocrine cell expansion.

Three cellular compartments respond to gastrin

Parietal cells

Massive hyperplasia: The defining tissue change.

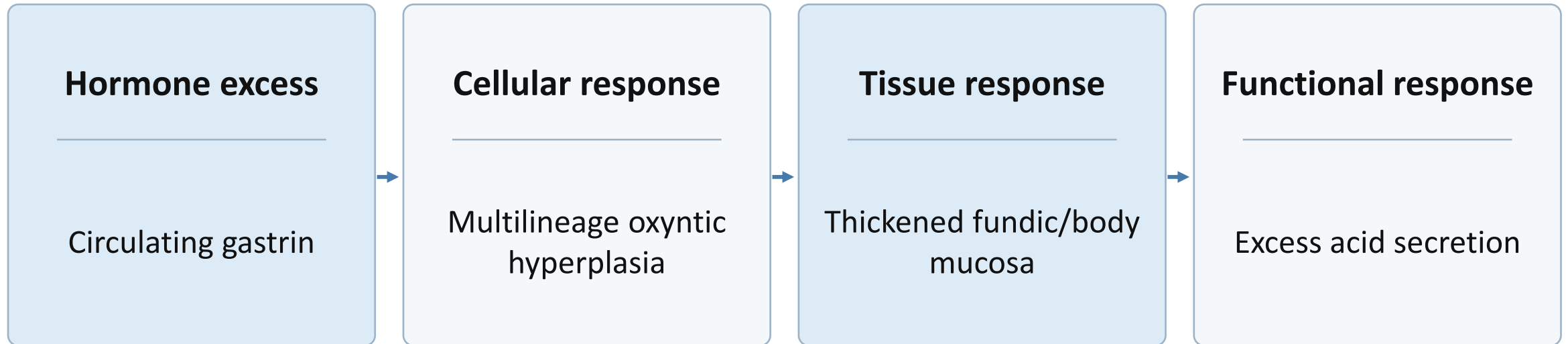
Mucous neck cells

Additional hyperplasia within gastric glands.

Endocrine cells

Associated oxyntic neuroendocrine hyperplasia.

The stomach displays a hormone-driven phenotype



Morphology and physiology should be interpreted together.

ZES belongs among hypertrophic gastropathies

- Hypertrophic gastropathies produce enlarged gastric rugal folds through epithelial hyperplasia.
- They can show a conspicuous, cerebriform macroscopic appearance.
- The key differential is the hyperplastic epithelial cell population.
- Ménétrier disease and Zollinger–Ellison syndrome exemplify distinct growth stimuli.

Enlarged folds are a pattern, not a diagnosis

Gross observation

Large gastric folds indicate expanded mucosal tissue.

Microscopic assignment

Identify parietal, mucous, and endocrine compartments.

Physiological interpretation

Ask whether acid is increased or reduced.

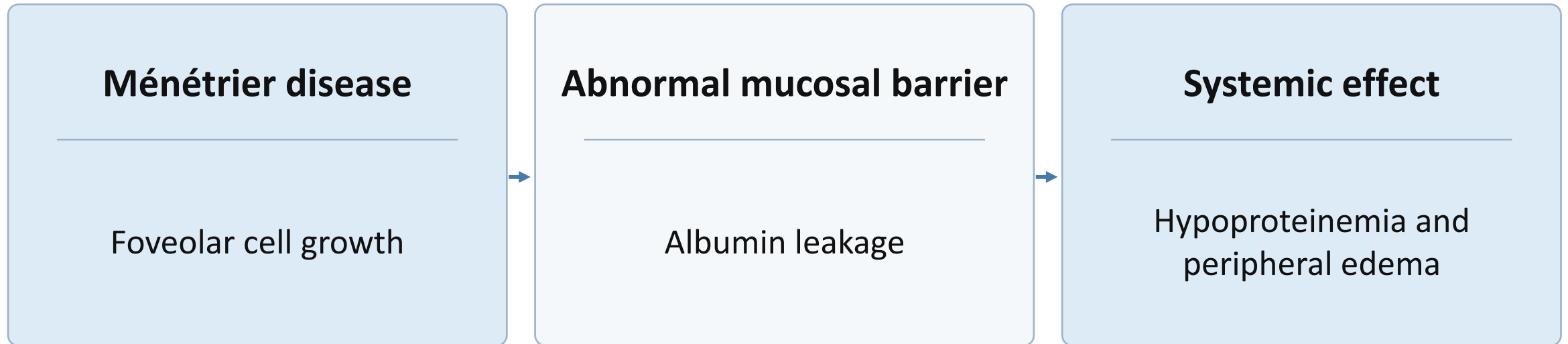
ZES versus Ménétrier disease: Cellular target

Feature	Zollinger–Ellison syndrome	Ménétrier disease
Primary stimulus	Gastrin excess	TGF- α $\rightarrow$ EGFR activation
Predominant mucosal response	Parietal cells; also neck and endocrine cells	Foveolar mucous-cell hyperplasia
Oxyntic cell status	Marked parietal hyperplasia	Parietal/chief cell hypoplasia may accompany foveolar growth

ZES versus Ménétrier disease: Clinical signature

Feature	Zollinger–Ellison syndrome	Ménétrier disease
Characteristic syndrome	Severe acid-related peptic injury	Protein-losing gastropathy
Prominent complications	Ulceration and possible perforation	Hypoproteinemia, edema and weight loss
Association in Robbins table	MEN1; no gastric dysplasia association noted	Increased gastric adenocarcinoma risk in adults

Why protein loss points away from classic ZES



A contrasting mechanism; It should not be substituted for gastrin-driven acid disease.

Oxyntic hyperplasia versus oxyntic atrophy

Feature	ZES	Autoimmune atrophic gastritis
Oxyntic mucosa	Thickened / hyperplastic	Atrophic / thinned
Parietal cells	Markedly increased	Depleted
Acid physiology	Hypersecretion	Decreased secretion
Elevated gastrin	Hormone produced by tumor	Compensatory response may occur with hypochlorhydria

High gastrin alone does not define one pathology

- In Zollinger–Ellison syndrome, gastrin originates from a gastrinoma.
- Autoimmune atrophic gastritis can show markedly increased gastrin despite reduced acid.
- The state of oxyntic glands discriminates these mechanisms.
- Interpret hormone measurements in their morphological and functional context.

Gastrinoma-associated ulcers versus common PUD

Feature	ZES-associated ulceration	Common peptic ulcer disease
Dominant driver	Gastrinoma-associated acid hypersecretion	Usually H. pylori, NSAIDs or smoking
Distribution	Stomach, duodenum; may include jejunum	Predominantly proximal duodenum or stomach
Multiplicity	May be multiple and persistent	More than 80% solitary in textbook PUD series
Diagnostic inference	Consider an endocrine source	Search for usual mucosal injurious factors

Peptic ulceration reflects defense–injury imbalance

Protective defenses

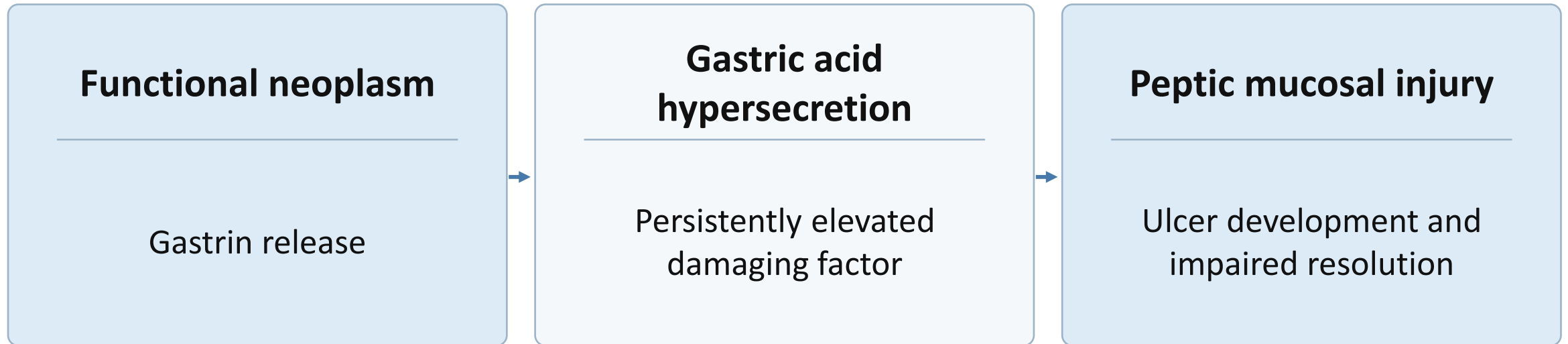
Mucus, epithelial repair and local mucosal blood flow counter acid injury.

Damaging factors

Gastric acid and peptic injury rise with gastrin-driven hypersecretion.

A relative excess of damaging activity favors chronic ulceration.

Why gastrinoma produces severe peptic injury



The neoplasm need not be gastric to injure the stomach or intestine.

Duodenal ulcers are a common presenting lesion

- Patients with Zollinger–Ellison syndrome often present with duodenal ulcers.
- The proximal duodenum is a frequent site of peptic injury generally.
- Ulcer identification is a manifestation of the syndrome, not a localization of gastrinoma.
- Multiple or treatment-resistant lesions strengthen suspicion of excess acid.

Jejunal ulcers are an unusually strong clue

Typical peptic disease

Duodenum and stomach are the predominant sites.

ZES-associated extension

Ulcers can appear at more distal sites, including jejunum.

Clinical inference

Intractable jejunal ulceration is emphasized as a reason to suspect ZES.

Multiplicity changes the interpretation of ulcer disease

- Usual peptic ulcer disease is solitary in more than four-fifths of patients.
- Gastrinoma-associated gastric and duodenal ulcers can be multiple.
- Morphology of any single ulcer may resemble ordinary peptic ulcer disease.
- Pattern and distribution carry additional diagnostic information.

Peptic ulcers have characteristic gross geometry

Surface defect

Round-to-oval, sharply punched-out mucosal lesion.

Edges

Often relatively level with adjacent mucosa; May overhang.

Important distinction

Heaped-up margins are more concerning for malignancy.

Histologic ulcer architecture is not ZES-specific

Luminal surface

Fibrinoid debris and neutrophils.

Reparative zone

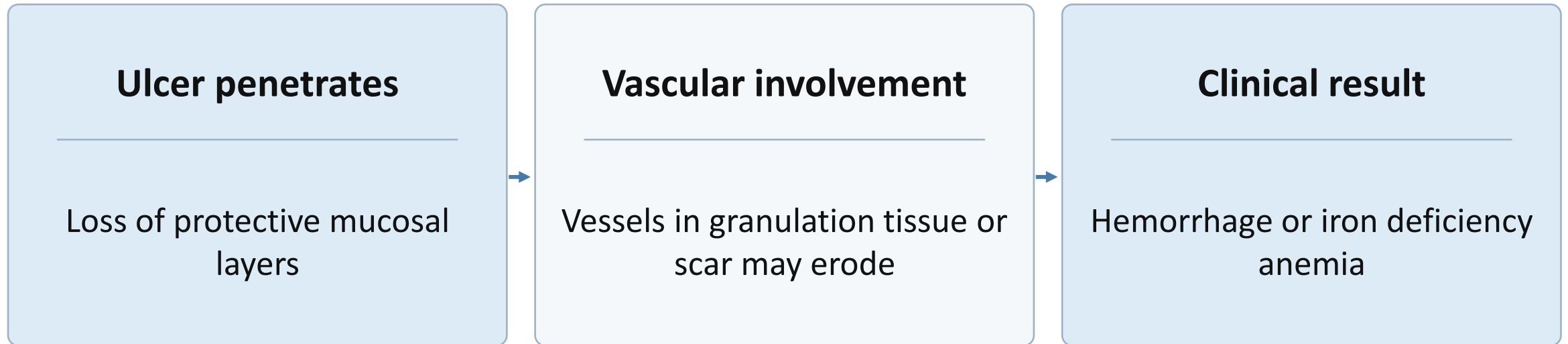
Granulation tissue and immature vessels.

Deep chronic zone

Fibrous scar and altered vessels.

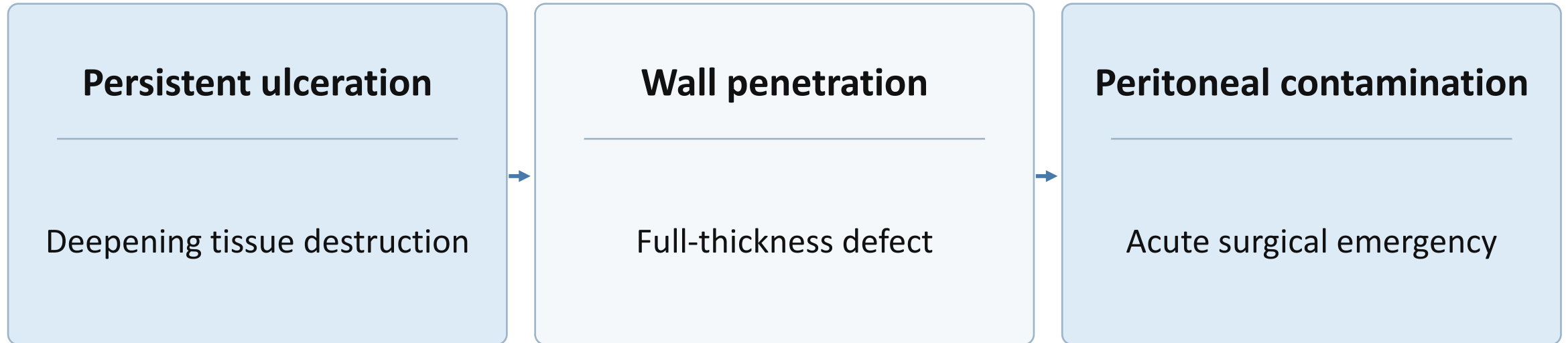
Layer descriptions are conceptual; Not an observed photomicrograph.

Ulcer bleeding arises from deep vessel injury



Major hemorrhage can be the first manifestation of peptic ulcer disease.

Perforation is an acid-injury emergency



Acid suppression as a means of preventing gastric perforation in ZES.

Chronic ulceration may produce obstruction

- Obstruction is a recognized complication of peptic ulcer disease.
- Edema and long-standing scar formation may narrow the outflow pathway.
- Pyloric channel ulcers are a typical setting; Duodenal ulcers may also obstruct.
- Crampy pain and intractable vomiting may indicate severe narrowing.

Ulcer complications can dominate clinical care

Complication	Structural lesion	Clinical consequence
Bleeding	Deep vascular erosion	Anemia or life-threatening hemorrhage
Perforation	Transmural ulcer defect	Peritonitis and emergency surgery
Obstruction	Edema or cicatricial narrowing	Persistent vomiting and impaired gastric emptying

Chronic diarrhea is part of the syndrome

- Chronic diarrhea is a common presenting feature of Zollinger–Ellison syndrome.
- Diarrhea may coexist with duodenal ulceration or predominate clinically.
- The combination of diarrhea and severe peptic disease should raise the diagnostic possibility.
- A diarrhea-only presentation should not be equated automatically with infectious enteritis.

Clinical suspicion comes from a pattern

Recurrent ulceration

Severe, multiple or otherwise difficult peptic ulcers.

Unusual distribution

Jejunal involvement beyond typical proximal sites.

Syndrome association

Chronic diarrhea or signs of another endocrine lesion.

Ulcers may look ordinary despite an unusual cause

- The endocrine chapter describes gastrinoma-associated ulcers as histologically identical to common peptic ulcers.
- What changes is the distribution, number, persistence and causal mechanism.
- Pathology should be integrated with clinical endoscopy and endocrine evaluation.
- Microscopy of an ulcer cannot, by itself, identify a gastrinoma.

Most gastrinomas are sporadic in the chapter 17 series

Sporadic disease

Approximately 75% of gastrinomas. Usually solitary.

MEN1-associated disease

Approximately 25%; Often younger patients with multiple lesions.

Textbook proportions; These are descriptive, not patient-level probabilities.

Sporadic gastrinomas often present as solitary lesions

- The chapter 17 description emphasizes a single tumor in sporadic disease.
- The pancreas is a characteristic site for sporadic lesions.
- Gastrin-secreting endocrine neoplasms can nonetheless be invasive or metastatic.
- An isolated lesion should not be assumed biologically benign from appearance alone.

MEN1-associated gastrinomas are often multiple

Typical patient context

Younger individual with hereditary endocrine neoplasia.

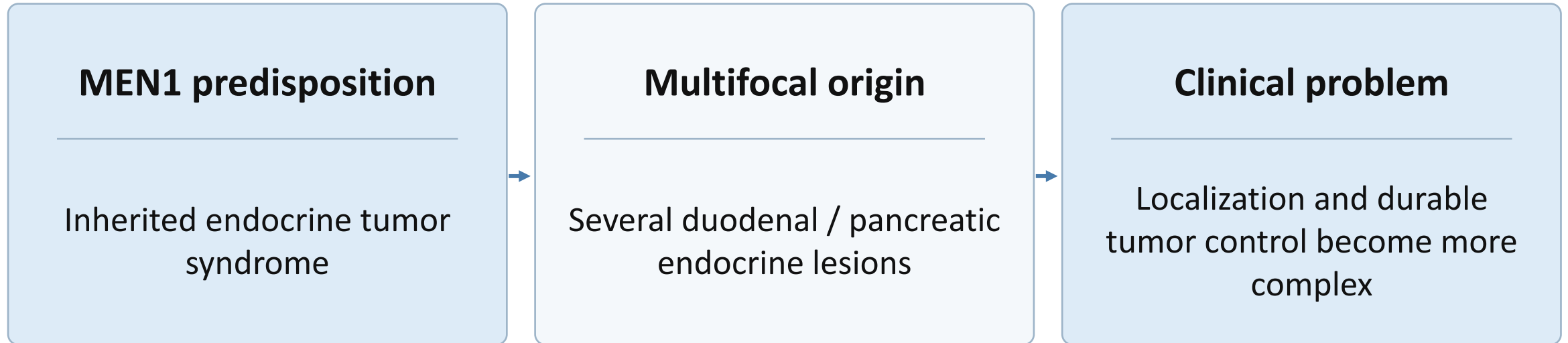
Anatomic pattern

Multiple small duodenal tumors are common.

Behavioral concern

Metastatic disease may occur even with small primary lesions.

MEN1 makes multiplicity a diagnostic clue



Do not assume a single dominant lesion accounts for all endocrine pathology.

MEN1 is caused by alterations of a tumor suppressor

- MEN1 syndrome results from germline pathogenic changes in the MEN1 tumor-suppressor gene.
- MEN1 encodes menin, a component of transcription-regulatory complexes.
- Its context-dependent partners can promote or restrict tumorigenesis.
- In sporadic gastrinomas, somatic MEN1 abnormalities also have biologic relevance.

MEN1: The three endocrine “P” organs

Parathyroid

Primary hyperparathyroidism;
Often the earliest manifestation.

Pancreas / enteropancreatic system

Functioning neuroendocrine tumors,
including gastrinomas and insulinomas.

Pituitary

Often prolactinoma; Other secretory tumors can occur.

Parathyroid clues can unmask MEN1

- Primary hyperparathyroidism is the most frequent MEN1 manifestation.
- Parathyroid lesions may be hyperplastic or adenomatous.
- PTH-associated hypercalcemia can manifest as nephrolithiasis.
- In a patient with ZES, a history of renal stones should prompt endocrine syndromic consideration.

Enteropancreatic MEN1 disease is often multifocal

- Tumors may arise simultaneously or at separate times.
- Numerous pancreatic microadenomas can coexist with dominant lesions.
- Duodenal gastrinomas are particularly important in MEN1.
- Functioning tumors cause distinct hormone-hypersecretion syndromes.

Pituitary disease extends the differential

- Prolactinomas are common pituitary lesions in MEN1.
- Somatotropin-producing tumors and acromegaly may occur.
- A multi-gland presentation points away from an isolated sporadic gastrinoma.
- The clinical history should identify both functioning and nonfunctioning endocrine tumors.

The endocrine syndrome can explain disparate symptoms

Gastrinoma

Intractable ulcers with or without diarrhea.

Parathyroid tumor

Hypercalcemia and nephrolithiasis.

Pituitary tumor

Clinical manifestations of prolactin excess.

Parallel manifestations of a common inherited predisposition; Not a causal sequence.

Gastrinoma cytology may look deceptively bland

- Gastrin-secreting tumors as often histologically bland.
- Gross or microscopic anaplasia need not be conspicuous.
- A bland endocrine tumor can be locally invasive or metastatic.
- Behavior cannot be inferred safely from atypia alone.

Neuroendocrine grade and stage are not synonyms

Attribute	Represents	Teaching caution
Differentiation / proliferation	Cellular phenotype and growth rate	Does not replace assessment of spread
Local invasion	Extension beyond site of origin	May occur in bland-appearing tumor
Metastasis	Documented neoplastic dissemination	A decisive adverse biologic feature

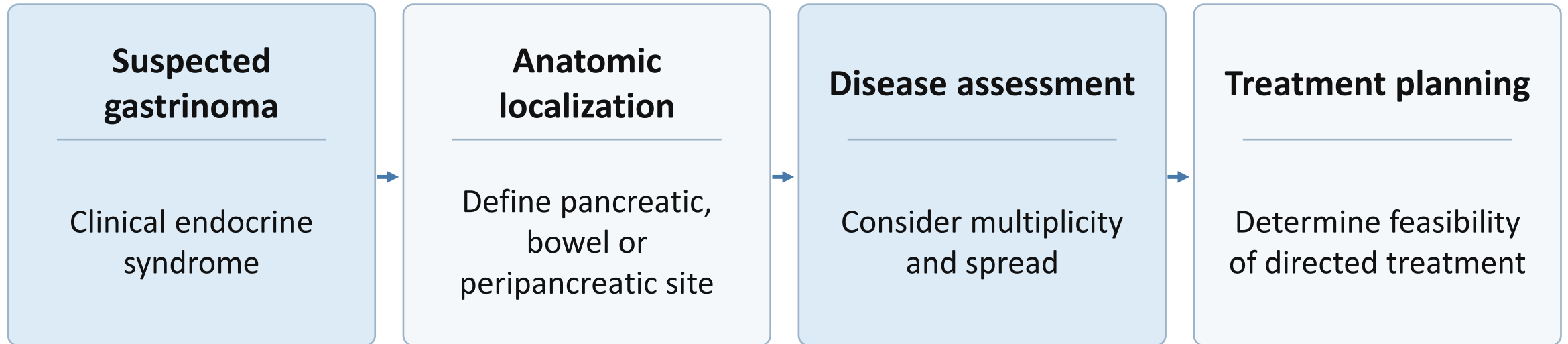
Metastatic disease shapes long-term prognosis

- The endocrine chapter describes more than half of gastrinomas as locally invasive or metastatic when diagnosed.
- The presence of hepatic metastases signals an adverse prognosis.
- Long-term outcome depends strongly on the underlying neoplasm, not simply ulcer control.
- Acid suppression treats the syndrome but does not itself remove metastatic tumor.

MEN1 mutations matter beyond inherited disease

- Somatic MEN1 mutations can be identified in some sporadic neuroendocrine tumors.
- MEN1-mutated sporadic gastrinomas with more frequent metastasis.
- This observation is about tumor biology, not a validated standalone individual prognostic threshold.
- Tumor genotyping and germline MEN1 syndrome should not be conflated.

Tumor localization is distinct from syndrome recognition



A positive ulcer finding does not reveal the tumor location.

Endoscopic ultrasonography can localize tumors

Modality

Endoscopic ultrasonography (EUS).

Clinical role

High-resolution assessment of suspected lesions near the gastrointestinal tract.

Interpretation limit

Localization imaging does not itself measure the physiological impact of gastrin.

Somatostatin receptor imaging exploits tumor biology

Modality

Somatostatin receptor scintigraphy, as.

Rationale

Tumor localization using neuroendocrine receptor expression.

Interpretation limit

Imaging complements rather than substitutes for endocrine and anatomic evaluation.

Tumor distribution changes localization strategy

Clinical setting	Expected tumor pattern	Implication
Sporadic gastrinoma	Often one pancreatic lesion	Search for a focal primary and spread
MEN1-associated ZES	Often multiple duodenal tumors	Evaluate multiplicity, not only the dominant mass
Disseminated disease	Metastatic deposits may occur	Stage burden in addition to identifying the origin

Management has two simultaneous targets

Physiological control

Suppress excessive gastric acid to heal ulcers and prevent injury.

Neoplasm-directed care

Treat or remove the underlying gastrinoma to address the source.

Parallel management objectives: Symptom control is not tumor eradication.

Proton pump inhibitors are first-line acid control

- Proton pump inhibitors suppress gastric acid hypersecretion in ZES.
- Effective acid suppression permits ulcer healing.
- Controlling acid injury reduces the danger of gastric perforation.
- Acid blockade stabilizes the patient while the gastrinoma is evaluated and treated.

Ulcer healing does not establish tumor cure

Measured outcome	Primarily reflects	Cannot establish alone
Pain/ulcer improvement	Successful acid suppression	Gastrinoma eradication
Endoscopic healing	Repair of gastric/duodenal injury	Absence of metastasis
Definitive tumor treatment	Neoplasm-directed management	Automatic reversal of every associated endocrine condition

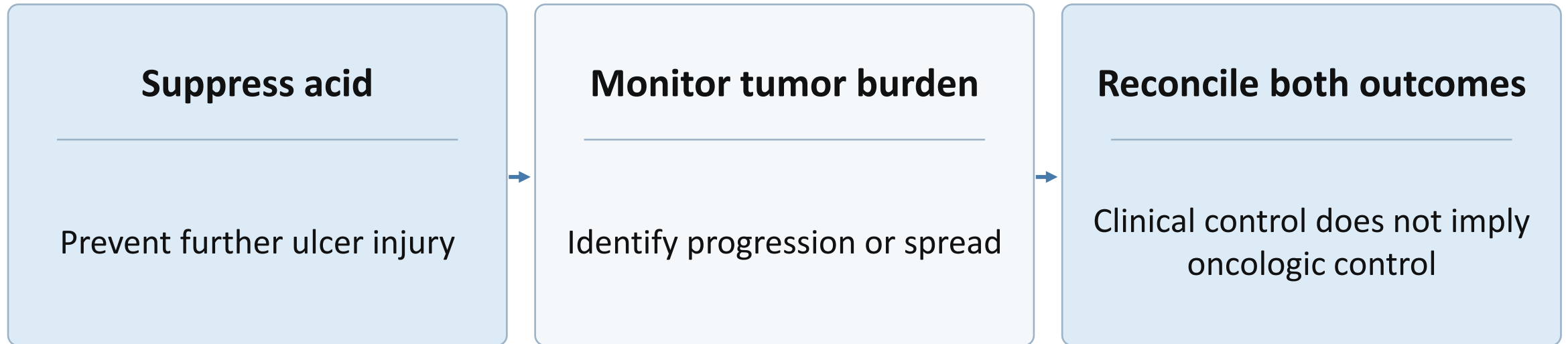
Resectability influences tumor-directed management

- When feasible, complete removal of the gastrinoma can eliminate the hormonal syndrome.
- Multifocal disease in MEN1 complicates complete tumor clearance.
- Extent and location of metastases influence long-term management.
- Acid suppression continues to address immediate peptic risk when tumor eradication is not possible.

Metastatic disease may benefit from somatostatin analogues

- Somatostatin analogues as potentially beneficial in metastatic gastrinoma.
- The neoplasm remains the central determinant of long-term survival.
- This treatment concept is distinct from proton pump inhibition of gastric acid.
- Specific contemporary drug regimens and response rates are not detailed in the supplied section.

Why both treatment goals must be reassessed



A patient can have healed ulcers and still harbor progressive neuroendocrine disease.

Case: Recurrent ulcers with diarrhea

Clinical scenario

An adult has repeated duodenal peptic ulcers despite treatment and also reports chronic diarrhea. No discrete gastric mass is identified.

Discussion prompts

- What syndrome unifies the presentation?
- Which organ contains the likely secretory source?
- Which gastric cell population would be increased?

Case analysis: Mechanism precedes location

Syndrome

Zollinger–Ellison syndrome should enter the differential.

Source

A gastrin-producing neuroendocrine lesion of bowel or pancreas.

Expected stomach

Marked parietal-cell hyperplasia with thicker oxyntic mucosa.

Case: Jejunal ulcer with renal stones

Clinical scenario

A younger patient has intractable jejunal ulceration and a history of recurrent nephrolithiasis.

Discussion prompts

- Which inherited endocrine syndrome should be considered?
- What other endocrine organs are commonly involved?
- Would multifocal or solitary gastrinoma be more characteristic?

Case analysis: Screen for an endocrine syndrome

Unifying predisposition

MEN1 is consistent with ZES plus potential parathyroid disease.

Further endocrine context

Parathyroid, enteropancreatic tissues and pituitary.

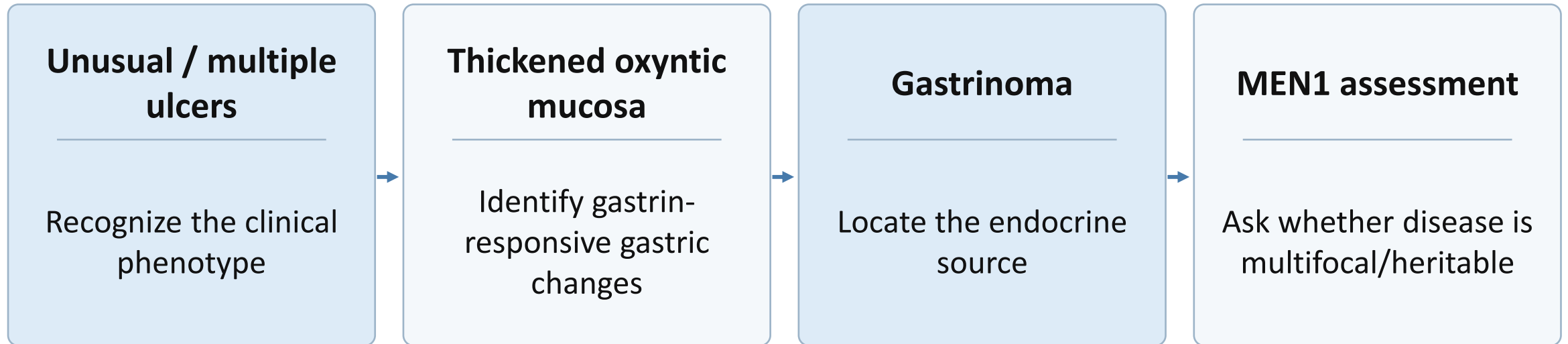
Gastrinoma pattern

Multiple small duodenal lesions are characteristic of MEN1.

Pattern recognition: Four different gastric settings

Setting	Dominant tissue process	Useful discriminant
Zollinger–Ellison	Parietal/neck/endocrine hyperplasia	Acid hypersecretion and unusual peptic ulcers
Ménétrier	Foveolar hyperplasia with oxyntic hypoplasia	Protein loss and edema
Autoimmune atrophic gastritis	Destruction of oxyntic glands	Low acid despite high gastrin
Common PUD	Ulceration without required global oxyntic hyperplasia	Usual H. pylori / NSAID / smoking context

From pathological observation to causal inference



The explanatory diagnosis connects three anatomic sites: Tumor, stomach and injured gut.

Core pathological synthesis

Causal lesion

Gastrin-secreting neuroendocrine tumor.

Signature morphology

Marked oxyntic parietal-cell hyperplasia, with neck/endocrine growth.

Clinical signature

Acid-related peptic ulceration, sometimes distal, plus chronic diarrhea.

Natural history

MEN1 status, multiplicity and metastasis modify prognosis.

Practical clinical synthesis

- Recognize the endocrine cause when ulcer distribution, multiplicity or course is atypical.
- Distinguish the source tumor from its hormone-driven gastric response.
- Use tumor localization and MEN1 context to frame disease extent.
- Suppress acid promptly, while continuing neoplasm-directed evaluation.

Source references

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 17: The Gastrointestinal Tract, pp. 699–704.

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 24: The Endocrine System, pp. 1011–1012 and 1025–1026.

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