

Zollinger–Ellison syndrome

Gastrinoma

Functional neuroendocrine neoplasm · Gastric pathology · MEN1

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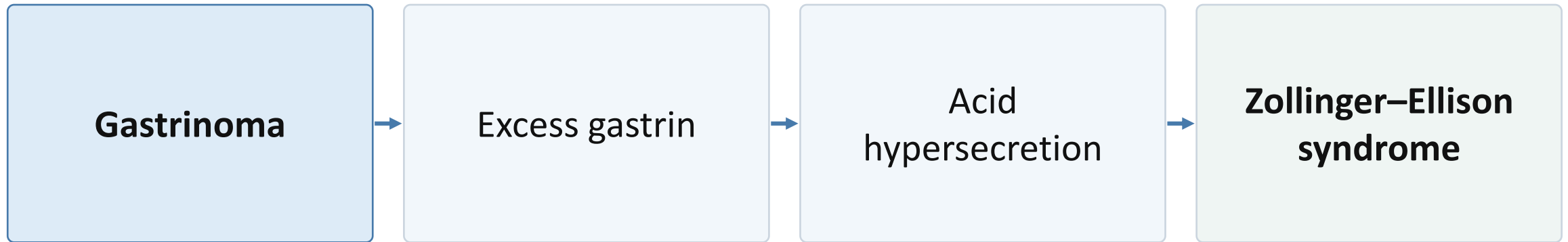
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Learning objectives

- Identify the hormone-producing lesion and its common locations.
- Explain how gastrin excess produces gastric changes and peptic ulceration.
- Distinguish sporadic gastrinoma from MEN1-associated disease.
- Relate morphology, localization and spread to clinical management.

The lesion and the syndrome are not synonymous



Functional tumor, distant target organ

- Gastrinoma: A gastrin-producing neuroendocrine neoplasm
- Stomach: Exaggerated secretory and trophic response
- Duodenum/jejunum: Acid-related mucosal injury

A secretory tumor can generate the dominant pathology outside its tissue of origin.

Original clinicopathologic association

**Endocrine tumor /
islet-cell lesion**

**Marked gastric acid
secretion**

**Severe peptic
ulceration**

Recognize all three components; The ulcer alone does not identify the tumor.

Typical clinical entry points

- Duodenal ulceration may be the presenting problem.
- Chronic diarrhea is another common presentation.
- Recurrent or unusually located ulceration strengthens suspicion.
- The primary tumor may remain clinically occult.

Anatomic origin is not confined to the pancreas

Recognized locations of a gastrin-producing neoplasm

Duodenum

**Peripancreatic soft
tissue**

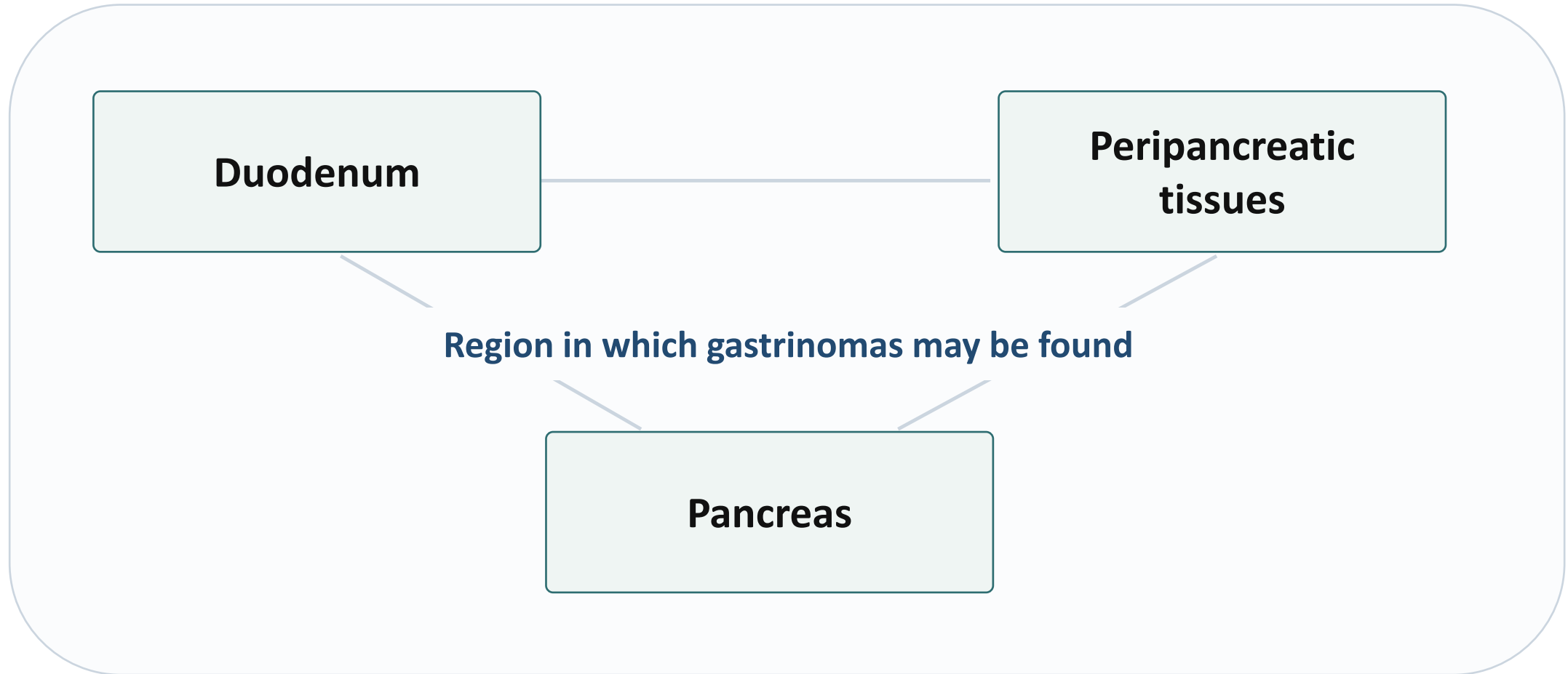
Pancreas



Red circles indicate possible tumor sites; Not a prevalence chart.

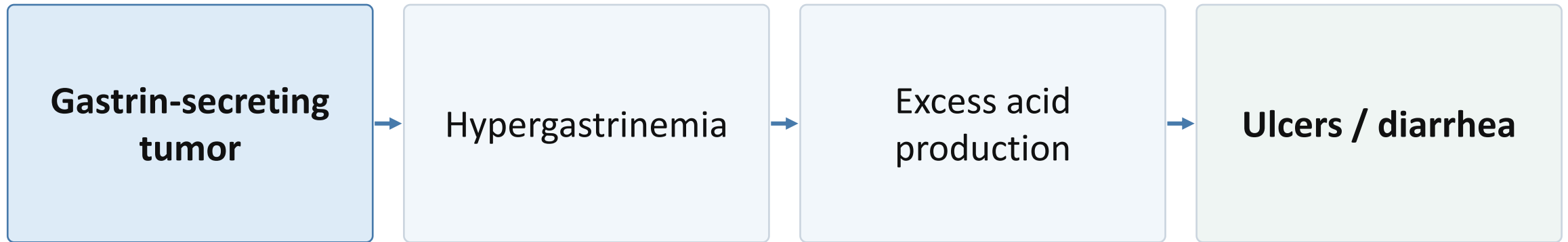
Frequent duodenal and peripancreatic locations as well as pancreatic tumors.

The “gastrinoma triangle” is a regional concept



Schematic localization concept — not an anatomical scale drawing or a definitive operative map.

Gastrin excess drives the clinicopathologic cascade

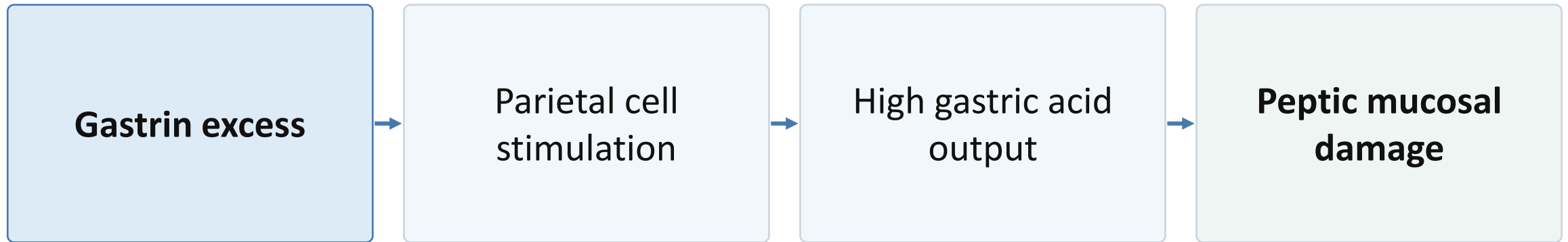


Hormonal hypersecretion is the initiating defect

- The neoplasm secretes excess gastrin.
- The syndrome is defined by systemic consequences of that excess.
- Small tumor burden does not necessarily mean mild hormone effects.

Tumor size and hormone-mediated severity are separate clinical dimensions.

Acid secretion is the major injurious effector



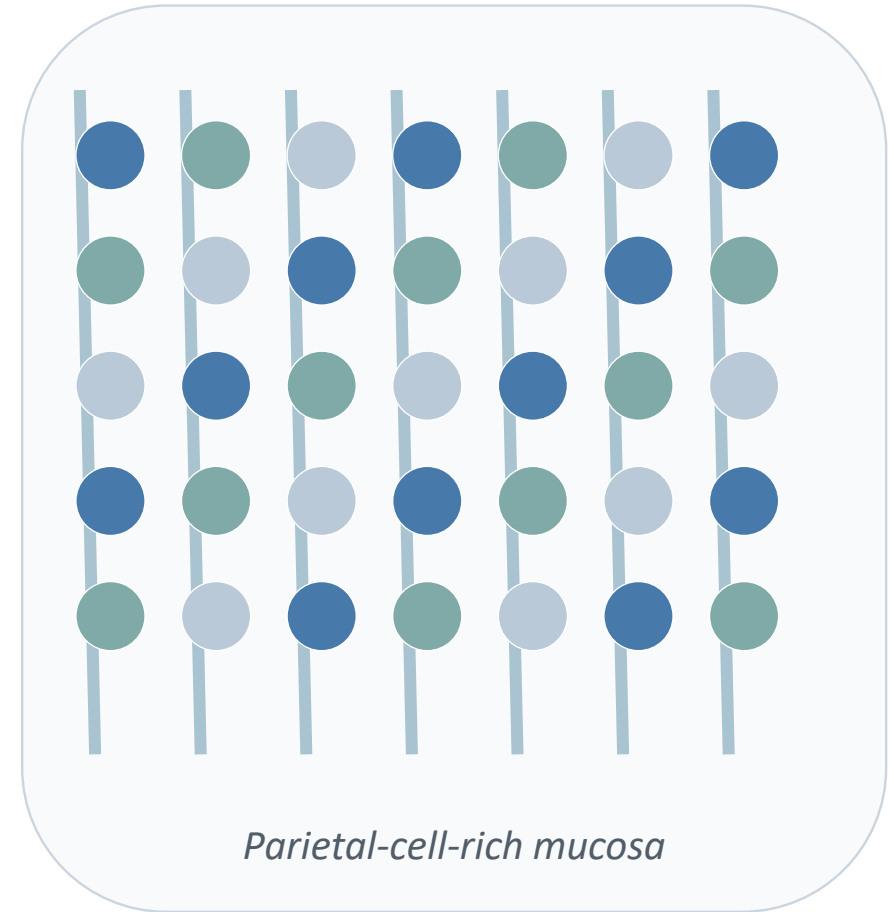
Gastrin also acts as a trophic signal

- Excess gastrin promotes mucosal cellular proliferation.
- The oxyntic mucosa becomes markedly thickened.
- Increased mucosal mass reinforces the acid-secretory phenotype.

The stomach changes are a hormone-driven response, not necessarily a gastric primary neoplasm.

Parietal cell hyperplasia explains acid output

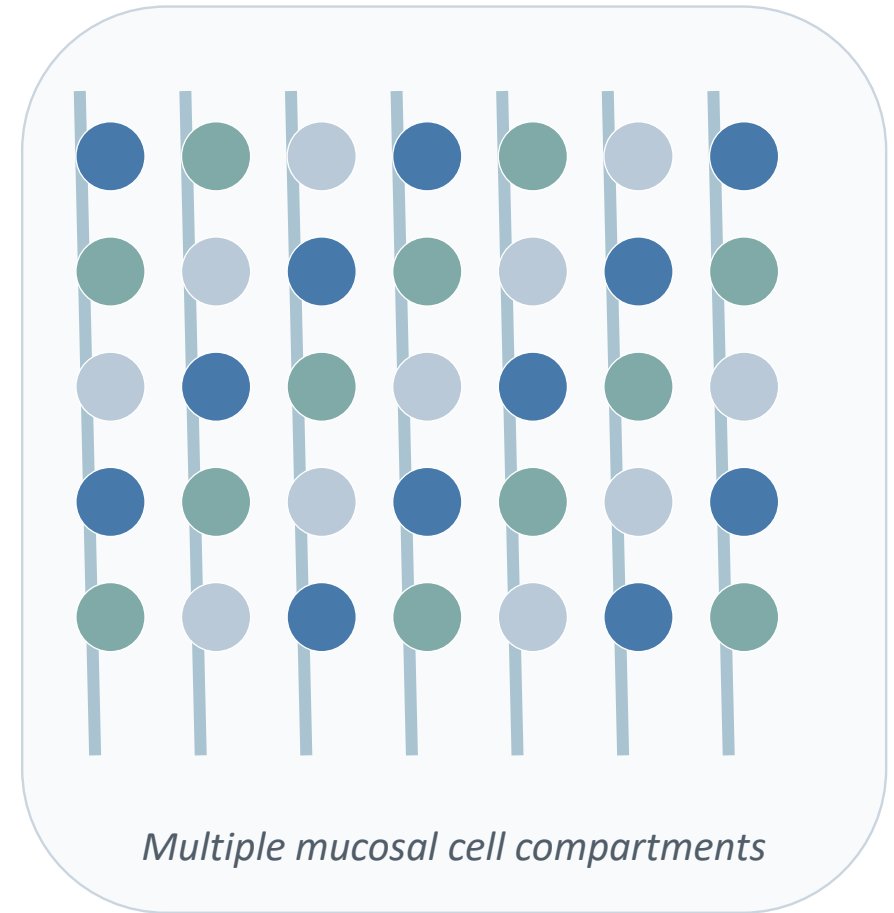
- Massive parietal cell hyperplasia
- Increased oxyntic mucosal thickness
- Heightened acid-secretory capacity



Schematic only; Not histologic evidence

Mucous neck and endocrine cells also proliferate

- Gastrin stimulates mucous neck cell hyperplasia.
- Endocrine-cell hyperplasia accompanies the oxyntic changes.
- Several cell populations contribute to mucosal thickening.

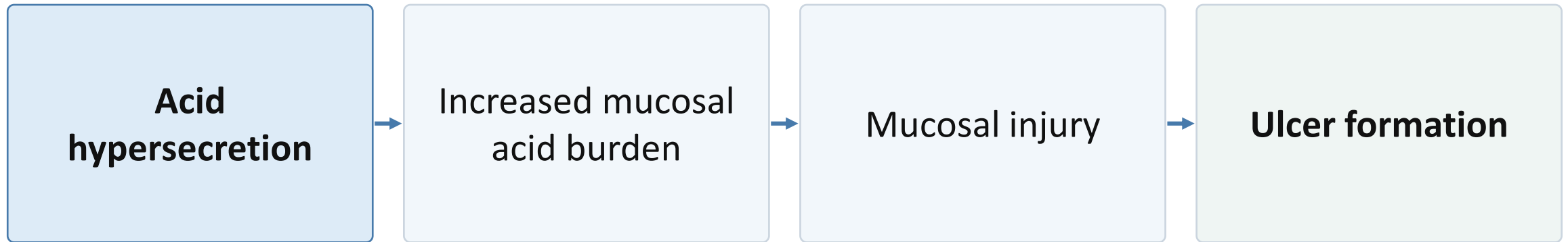


Schematic only; Not histologic evidence

Oxyntic mucosal thickening: An important clue

Finding	Interpretation
Thickened oxyntic mucosa	Hormone-mediated hyperplasia
Abundant parietal cells	Increased acid-producing compartment
Ulcerated duodenum	Downstream consequence of acid excess

Peptic ulceration follows excessive acid exposure



Duodenal ulcers are a common presentation

- Peptic ulcers in ZES may resemble ordinary peptic ulcers histologically.
- Disease can be severe despite no unique ulcer morphology.
- The clinical pattern and secretory context are critical.

Jejunal ulceration is a strong warning sign

- Ulcers can extend beyond usual duodenal sites.
- Intractable jejunal ulcers should prompt consideration of ZES.
- Location changes the diagnostic probability, not ulcer histology.

Multiplicity and treatment resistance matter

- Duodenal and gastric ulcers may be multiple.
- Ulcers may respond incompletely to conventional therapy.
- Persistent acid drive explains ongoing ulcer formation.
- Successful acid blockade permits ulcer healing.

Chronic diarrhea belongs to the syndrome

- Diarrhea may accompany or even dominate the presentation.
- It can coexist with recurrent peptic ulceration.
- In the Robbins account, both reflect a gastrin-producing tumor syndrome.

Do not require ulceration as the only presenting complaint.

Symptoms and morphology are connected

Source Source	Response Response	Manifestation Manifestation
Gastrinoma	Gastrin excess	Acid hypersecretion
Gastric oxyntic mucosa	Cell hyperplasia	Mucosal thickening
Duodenum / jejunum	Acid-mediated injury	Peptic ulcers

Gastrinoma belongs to the NEN family

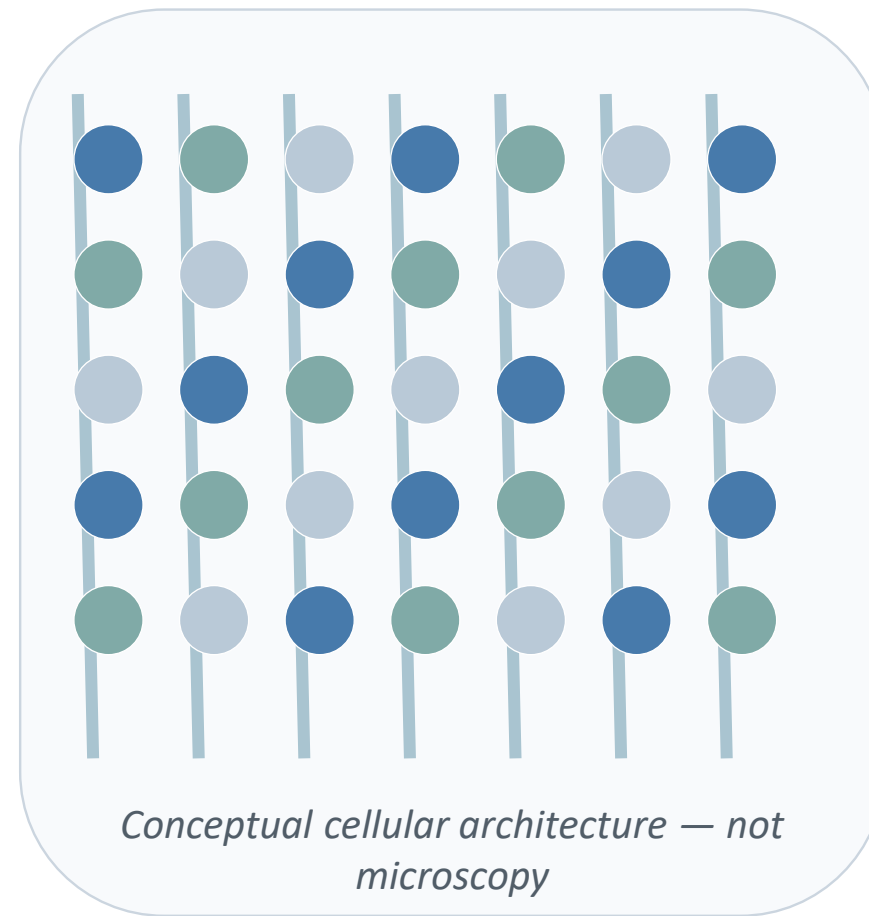
- Neuroendocrine neoplasms can be hormonally functional or nonfunctional.
- Pancreatic neuroendocrine neoplasms differ from exocrine pancreatic tumors.
- Gastrin production defines the functional identity of gastrinoma.

Well-differentiated NEN versus neuroendocrine carcinoma

Feature	Well-differentiated NEN	Neuroendocrine carcinoma
Morphology	Relatively organized; often bland	Poorly differentiated
Proliferation	Graded with mitoses and Ki-67	Typically highly proliferative
Interpretation	Do not infer benign behavior	Distinct aggressive category

Gastrinomas may look deceptively bland

- Tumor cells may be monotonous with little anaplasia.
- Bland nuclei cannot reliably exclude invasive behavior.
- Morphology requires correlation with tumor extent and metastasis.



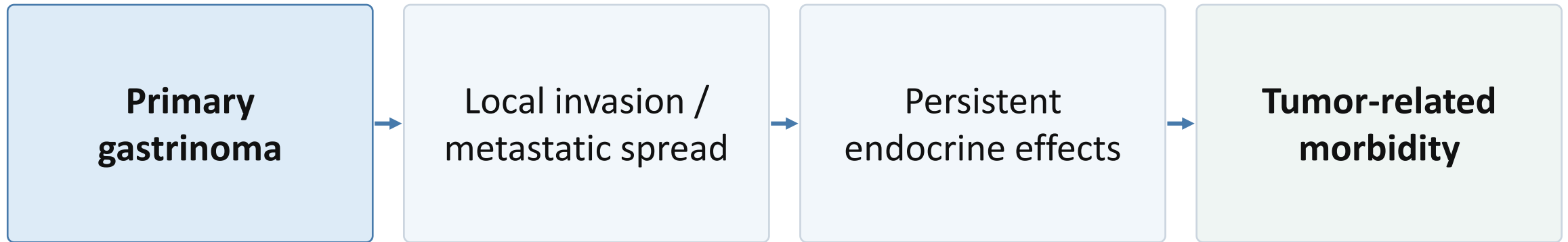
Schematic only; Not histologic evidence

Cytologic blandness does not imply benign biology

- More than half of gastrin-producing tumors are invasive or metastatic when diagnosed (Robbins).
- A neat, uniform microscopic appearance can coexist with aggressive disease.
- Document invasion and spread independently of bland cytology.

**A central pathology pitfall:
Morphology alone
underestimates biological
potential.**

Metastatic spread changes the clinical problem



Liver metastasis has major prognostic relevance

- Hepatic metastases are associated with shorter life expectancy.
- Progressive metastatic tumor burden may lead to liver failure.
- Long-term survival depends heavily on tumor behavior after acid control.

Approximately three-quarters are sporadic



75%

Sporadic

25%

MEN1-associated

Textbook proportions: Approximately 75% sporadic and 25% MEN1-associated.

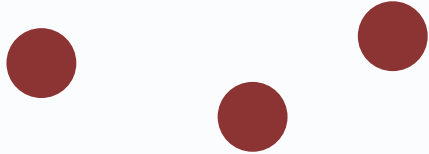
Sporadic lesions are generally solitary

- Most sporadic gastrinomas present as a single neoplasm.
- The pancreas is a recognized location in the sporadic group.
- Solitary does not mean nonmetastatic or low risk.

**Count and distribution assist
etiologic classification, not
grading.**

MEN1-associated lesions are often multifocal

Duodenum



Multiple possible duodenal primaries

Pancreas



A synchronous lesion can coexist

Each red circle represents a possible lesion, not a quantitative incidence estimate.

Duodenal primaries predominate in MEN1 and synchronous lesions can be present.

Sporadic and MEN1-associated gastrinoma differ

Feature	Sporadic	MEN1-associated
Approximate share	75%	25%
Multiplicity	Usually solitary	Often multifocal
Typical distribution	Pancreas or duodenum	Duodenum especially common
Broader disorder	Isolated NEN	Multigland tumor syndrome

The duodenum is central in MEN1

- Duodenal gastrinomas greatly exceed pancreatic gastrinomas in MEN1.
- Synchronous duodenal and pancreatic tumors can occur.
- Small or multifocal lesions challenge complete localization.

Look beyond the most conspicuous pancreatic lesion.

MEN1 involves the three classic endocrine sites

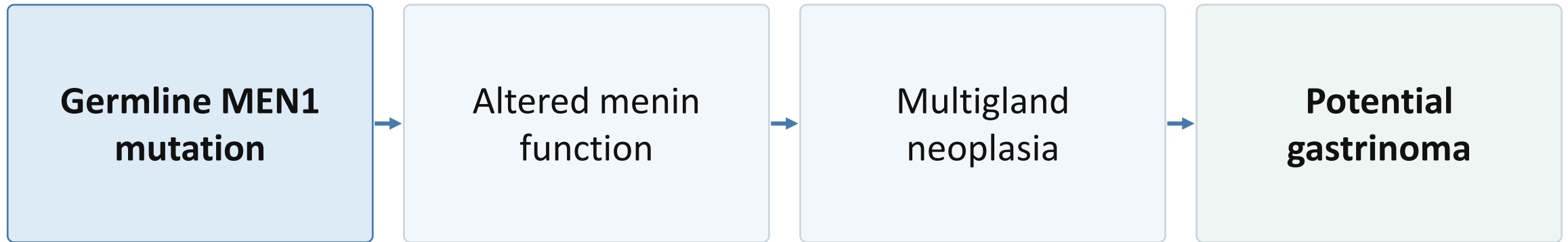
Parathyroids

**Pancreas /
duodenum**

Pituitary

The “three Ps” are a syndrome-level clue, not a description of a single multihormonal tumor.

MEN1 is a tumor-suppressor disorder



Menin is a regulator of transcriptional complexes

- The MEN1 gene encodes menin.
- Menin participates in transcription factor complexes.
- Its effects depend on binding partners and cellular context.

Avoid assigning a single universal downstream pathway to menin.

MEN1 causes more than gastrinoma

Organ	Common example	Clinical implication
Parathyroid	Hyperplasia / adenoma	PTH-mediated hypercalcemia
Pancreas / duodenum	Functioning NEN	ZES or hypoglycemia
Pituitary	Prolactinoma	Hormonal excess syndrome

Multihormonal tumor is not the same as MEN1

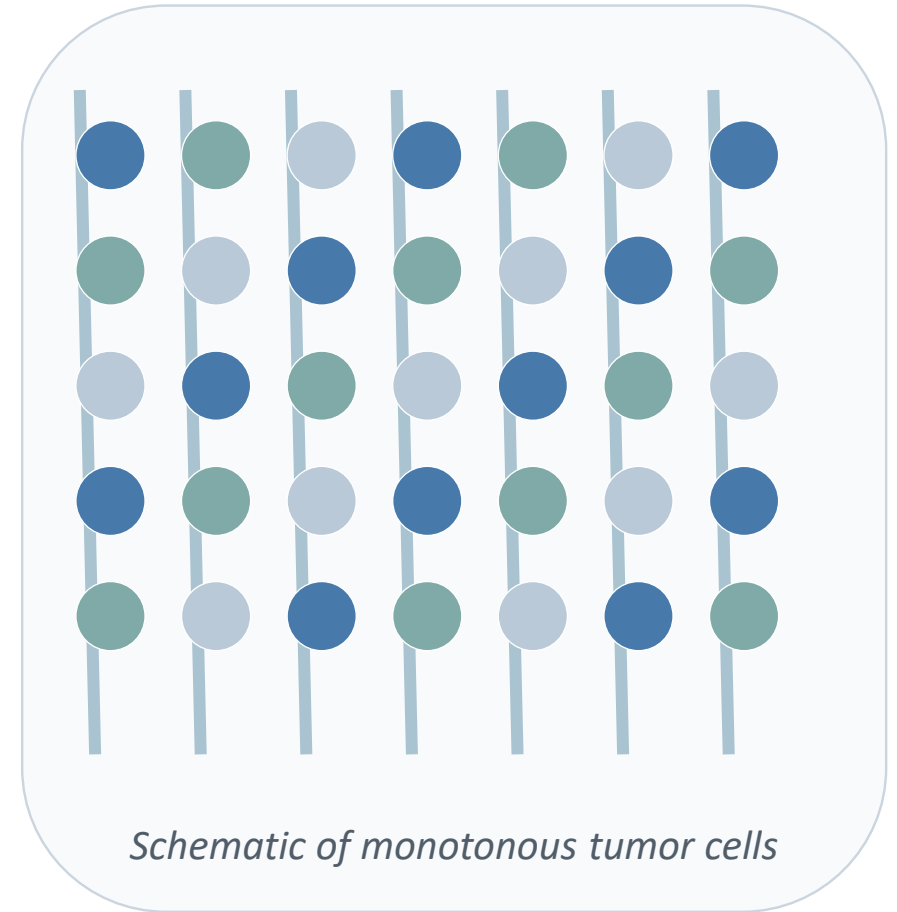
Multihormonal NEN	MEN1 syndrome
One tumor can secrete several hormone types	Separate neoplasms in multiple endocrine organs
Defined by hormone products of tumor	Defined by inherited multigland predisposition
May occur without inherited MEN1	Classically germline MEN1-related

PanNEN grading uses proliferation, not secretion

- Well-differentiated neuroendocrine neoplasms are evaluated with mitotic activity and Ki-67.
- Hormone production identifies a functional subtype.
- Grade and functional phenotype answer different pathology questions.

Cellular monotony must be interpreted cautiously

- The tumor may have uniform cells and limited pleomorphism.
- The gross and microscopic tumor extent still requires assessment.
- Invasion or metastases override reassuring cytologic blandness.



Schematic only; Not histologic evidence

Anatomic localization and tumor biology are separate

Question	Evidence needed
Where is it?	Regional localization studies
How widespread?	Extent and metastatic assessment
What does it secrete?	Clinical endocrine syndrome
How aggressive?	Differentiation, proliferation, invasion and spread

When should the clinician suspect ZES?

Recurrent / refractory ulceration



Unusual jejunal ulcer site



Chronic diarrhea with ulcer disease



Consider gastrinoma / ZES

Gastric biopsy and primary tumor biopsy answer different questions

Tissue examined	What it may show
Oxyntic gastric mucosa	Parietal, mucous neck and endocrine hyperplasia
Ulcer edge	Peptic injury (not specific to ZES)
Primary NEN	Tumor morphology and tumor classification

Endoscopic ultrasonography supports tumor localization

- Endoscopic ultrasonography is listed by Robbins among gastrinoma-localizing modalities.
- Localization is needed before decisions about definitive tumor treatment.
- Identification of one lesion may not exclude additional MEN1 lesions.

Localization is not a substitute for determining tumor extent.

Somatostatin receptor imaging is another modality

- Somatostatin receptor scintigraphy for gastrinoma localization.
- The method exploits neuroendocrine tumor biology.
- Imaging complements the clinicopathologic assessment.

This lecture reproduces the textbook modality without inserting unverified test-performance estimates.

MEN1 requires attention to multiplicity

Suspected MEN1-associated gastrinoma



Consider duodenal and pancreatic sites



Search for multifocal tumors



Integrate multigland context

Ordinary peptic ulcers can resemble ZES ulcers

Peptic ulcer disease	Zollinger–Ellison syndrome
May be clinically isolated	Caused by a gastrin-secreting tumor
Ulcers may share histologic appearance	Often multiple or difficult to treat
No endocrine tumor implied	Gastric oxyntic hyperplasia provides context

Contrast with Ménétrier disease

Feature	Ménétrier disease	Zollinger–Ellison syndrome
Predominant cells	Foveolar mucous cells	Parietal + mucous neck + endocrine cells
Gastric change	Enlarged rugae, gland alterations	Thickened oxyntic mucosa
Clinical clue	Protein loss / hypoproteinemia	Marked acid production / ulcers

Secretory diarrhea has other endocrine causes

Syndrome	Hormone / underlying lesion	Distinguishing context
ZES	Gastrin-producing NEN	Acid excess and peptic ulcers
VIPoma syndrome	Vasoactive intestinal peptide	Watery diarrhea, hypokalemia, achlorhydria

Clinical interpretation requires three compartments

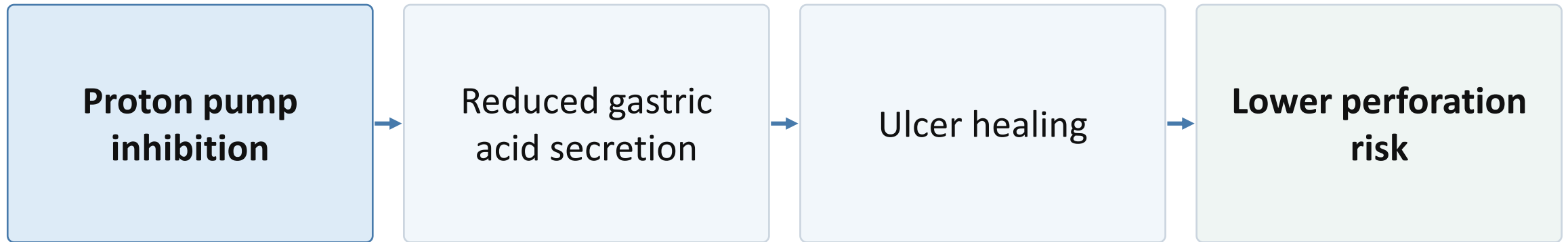
Hormone source

Gastric response

Intestinal injury

Diagnostic confidence improves when anatomic, physiologic and clinical evidence converge.

Proton pump inhibitors control the acid problem

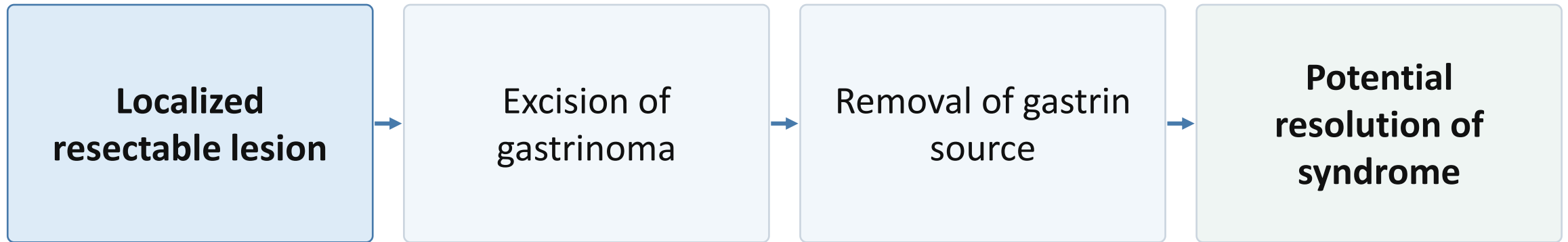


Acid blockade enables definitive tumor management

- Acid suppression treats the endocrine consequence.
- Effective blockade permits ulcer healing and lowers ulcer-related complications.
- Treatment can then concentrate on the causative gastrinoma.

**Control of acid is not
equivalent to eradication of
the tumor.**

Resection targets the hormone-producing lesion



Metastatic disease may need additional control

- Somatostatin analogues may benefit some patients with metastatic gastrinoma.
- Therapy must distinguish suppression of hormone-mediated effects from control of tumor progression.
- Tumor growth and liver involvement as key survival determinants.

No contemporary treatment algorithm or drug dosing is claimed here.

Treat the acid burden and the neoplasm

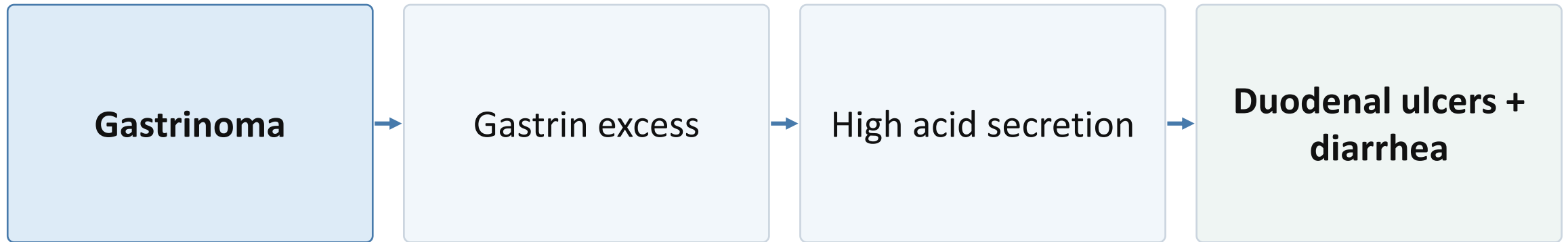
Aim	Primary concern	Robbins-described approach
Immediate control	Acid / ulcer complications	Proton pump inhibitors
Definitive treatment	Gastrinoma	Excision where possible
Metastatic context	Persistent or progressive NEN	Selected somatostatin analogues

Case 1: Recurrent severe ulcers

- An adult presents with recurrent duodenal ulcers and persistent diarrhea.
- Ulcers recur despite repeated symptomatic treatment.
- What unifying endocrine mechanism should be considered?

Identify the tumor–hormone–organ sequence.

Case 1: Clinicopathologic interpretation



Case 2: Multifocal endocrine disease

- A patient with parathyroid disease develops difficult-to-control peptic ulceration.
- Multiple small duodenal neuroendocrine lesions are identified.
- Which tumor predisposition syndrome is suggested?

Explain why multiplicity and the endocrine history matter.

Case 2: MEN1-associated gastrinoma

Parathyroid disease

**Duodenal
gastrinomas**

**Possible other
endocrine NENs**

MEN1 directs attention to multigland disease and multifocal, often duodenal tumors.

Case 3: Thickened gastric folds

- A gastric biopsy shows markedly increased oxyntic mucosal thickness.
- There is conspicuous parietal cell expansion and refractory peptic ulcer disease.
- Is the mucosal hyperplasia necessarily the primary tumor?

Separate gastric response from hormone-producing source.

Case 3: Gastric response versus primary lesion

Observed lesion	Meaning
Oxyntic parietal cell hyperplasia	Trophic response to high gastrin
Gastrinoma in duodenum/pancreas	Primary source of circulating gastrin
Duodenal / jejunal ulcer	End-organ acid-related injury

Clinicopathologic summary

Axis	Axis	Essential point	Essential point
Tumor		Gastrin-producing neuroendocrine neoplasm	
Function		Acid hypersecretion and oxyntic hyperplasia	
Clinical		Ulceration, diarrhea; jejunal ulcer is a red flag	
Etiology		Sporadic versus MEN1-associated	
Outcome		Tumor spread, especially liver involvement	

Primary references and visual provenance

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026.

Chapter 24: Endocrine Pancreas — pancreatic NENs and Zollinger–Ellison syndrome (pp. 1011–1012).

Chapter 17: The Gastrointestinal Tract — Zollinger–Ellison syndrome and hypertrophic gastropathies (pp. 702–703).

Chapter 24: MEN1 syndrome (pp. 1025–1026).

All diagrams: original editable PowerPoint teaching schematics; none represents a clinical specimen.