

PATHOLOGY OF THE STOMACH

- I. **DEVELOPMENTAL ANOMALIES:** Atresia, duplication, diverticula, cysts, and malposition are all very rare in the stomach, especially compared to other sites in the GI tract.

~~Congenital pyloric stenosis:~~ Main gastric developmental anomaly. Hypertrophied pyloric circular muscle, especially in males. Probably related to defect in myenteric plexus.

~~Therapy:~~ Muscle-splitting incisions.

- II. **PEPTIC ULCER DISEASE** Ulcer: A focal area of full thickness destruction of mucosa.

A. ~~Mucosal Erosion:~~ Partial focal loss of mucosa, i.e. less than full thickness. Can progress to ulcer or heal without scarring.

B. ~~Peptic Ulcer:~~ The focal destruction of mucous membrane and underlying tissues by gastric digestive juices; appears related to abnormalities in (1) the level of acid secretions, and (2) the protective cellular and mucous coating. It is one of the few examples of an autodigestive lesion. Others are chemical necrosis due to escape of pancreatic enzymes; e.g., fat necrosis in acute pancreatitis; abscess formation from escape of lysosomal enzymes from neutrophils.

Ulcers occur at a number of GI sites for a variety of reasons: infections, ischemia; but peptic ulcers occur only where gastric secretions have access.

C. ~~Mechanisms~~ for peptic ulceration:

1. Hyperacidity: controlled by gastrin, histamine, vagus, acetylcholine, etc.
2. Decreased mucosal protection: mucosal damage and decreased viscosity of mucus; vascular shunts; cell cohesion
Duodenal Ulcer: More related to hyperacidity and *H. pylori*
Gastric Ulcer: More related to mucosal weakness; NSAIDS
Mucin pH: upper GI=neutral; lower GI=acid
3. Motility: affects mixing of acid with neutralizing secretions in duodenum

D. ~~Treatment:~~ antacids - neutralize;
histamine-receptor antagonists and proton pump inhibitors-reduce acid secretion
Vagotomy - reduces acid secretion (old treatment)

Eradicate *H. pylori*

E. ~~Predisposing factors for peptic ulcer of stomach and duodenum~~

1. ***Helicobacter pylori*** - gastric infection strongly related to duodenal and gastric ulcers. Direct mucosal injury, increased acid secretion, and inflammatory reaction appear to play roles in ulcer production.
2. **Stress** - Typically associated with burns (Curling ulcer); following surgery, fractures, trauma
3. ~~Cerebral Lesions~~ - especially in hypothalamus. Vagus nerve controls secretion (vagotomy)

4. Tobacco Smoking
 5. Hormones - Increased adrenocortical steroids, gastrin, glucagon and parathyroid secretions
 6. Zollinger-Ellison syndrome - Severe peptic ulceration, often multiple, due to a gastrin producing tumor (gastrinoma) of the pancreas, stomach or intestine. Marked hyperacidity
 7. Genetic Factors
 8. **NSAIDS** - Nonsteroidal anti-inflammatory drugs are a major cause of erosions and ulcers in stomach and intestines.
- F. Frequency - Duodenal ulcer is more common than gastric in young adults. Gastric is more common in the elderly. Ulcers more common in males up to age 60, then approximate equality. Rare in children. Incidence of peptic ulcer decreasing over last 20 years. Chronic ulcers are usually single. Acute, especially stress ulcers, are more frequently multiple.
- G. Topography
1. Esophagus - Peptic ulcer in distal esophagus associated with hiatus hernia, exposure of mucosa to refluxed gastric juices.
 2. Stomach - Chronic ulcers typically found in pyloric type mucosa; lesser curvature or antrum; rarely in body mucosa (e.g. on greater curvature). Acute ulcers and erosions can occur in body mucosa as well as antral.
 3. Duodenum - First part, on anterior or posterior wall. In Zollinger-Ellison syndrome, ulcers in distal duodenum and even jejunum.
 4. Gastroenterostomy or gastric heterotopia (e.g. in Meckel diverticulum): ulcer in intestine just distal to gastric mucosa.
- H. Gross appearance - Peptic ulcers tend to have sharply defined clear-cut edges with abrupt drop into the crater; edges are not raised, rolled or heaped up (a feature of carcinoma); mucosa overhangs; most less than 2 cm.
- I. Acute vs Chronic Ulcer - Judged by scarring rather than by time; acute - no scar; often multiple; occurs anywhere: body and antrum
 chronic - muscle destroyed and replaced by scar; usually single
 submucosa thickened by scar; usually in antrum.
- J. Microscopic Appearance
- Chronic Peptic Ulcer: 4 layers
1. fibrinopurulent exudate on surface (also in acute ulcer)
 2. necrotic tissue; coagulative necrosis (also in acute ulcer)
 3. granulation tissue; capillaries, fibroblasts, chronic inflammation
 4. scar; often with lymphoid aggregates; muscle replaced by scar; muscularis propria and muscularis mucosae fuse at edges; vessels thrombosed often with endarteritis obliterans.
- K. Healing of Ulcers:
 Epithelium grows in from the sides, covers surface, grows down as tubules. Scars develop from granulation tissue.
 Repeated episodes occur.
- L. Complications of Peptic Ulcer
1. Perforation - More common for acute than chronic ulcer since scar resists perforation. Perforation anteriorly, where no neighboring structure can plug the gap, leads to severe peritonitis and profound shock. Penetration into pancreas.

2. Hemorrhage - Small amounts of hemorrhage accompany all ulcers due to erosion of capillaries. Massive hemorrhage follows erosion of large vessels; can lead to exsanguination. Thrombosis of vessels at base is protective.
3. Obstruction
Scarring can deform gastric outlet and cause obstruction.

The peptic ulcer is a good morphologic model for ulcers at all GI sites as well as other body sites.

III. GASTRITIS - Inflammation of the stomach typically of the mucosa. Clinically the term is used loosely to cover pain, heartburn, nausea and vomiting, i.e., dyspepsia.

- A. Acute Gastritis - Inflammation of gastric mucosa.
Infectious: bacterial: H. pylori; fungal: candida; viral: CMV
Chemical (gastropathy): alcohol, peptic, aspirin and other NSAIDS, bile

Morphologically: edema, hyperemia, increased mucus secretion, erosions and hemorrhage can occur.
Mucosal regeneration without scarring is usual.
- B. Chronic Gastritis - Chronic inflammation of gastric mucosa; associated with atrophy and intestinal metaplasia. Relation to acute gastritis is unclear. Low mortality, high morbidity.
Cause: Helicobacter pylori, autoimmune process.
- C. Histologic Patterns
 1. Chronic gastritis - Mucosa is infiltrated with chronic inflammatory cells; surface epithelium has reduced mucus; no loss of glands. H. pylori often found in surface mucus.
 2. Atrophic gastritis - Chief and parietal cells replaced by simple mucus-secreting cells; chronic inflammation; polypoid hyperplasia may occur.
 3. Intestinal metaplasia - Transformation of gastric glands to those resembling intestinal mucosa, namely acid mucin-containing goblet cells; Paneth cells; but no villus structures.
 4. Gastric atrophy - Extensive, not focal, thinning of mucosa with loss of acid and pepsin-secreting glands. Replaced by simple gastric mucus glands and intestinal metaplasia. The presence of acute inflammatory cells in all of the above denotes active destructive disease.

CHRONIC GASTRITIS

	<u>TYPE A</u>	<u>TYPE B</u>
Autoantibodies to parietal cells	+	-
Site	body	antrum
Mucosal atrophy	severe	less severe
Acid secretion	very low	slight decrease
Serum gastrin	high	low
Association with pernicious anemia	+	-

Incidence	low	more common
Etiology	?genetic	H. pylori

Type AB: no autoantibody; fundal and antral.

- D. ~~Gastropathy~~- mucosal damage with minimal inflammation; chemical agents, e.g. bile reflux, NSAIDS, alcohol.

IV. GASTRIC TUMORS

A. ~~Benign Epithelial Tumors: Adenomas~~

These present as ~~polyps~~ (localized mass which projects from wall into lumen); similar to colorectal polyps; unlike colon, gastric adenomas are uncommon and not the leading cause of carcinoma.

B. ~~Malignant Epithelial Tumors: Carcinoma~~

Interesting epidemiologically: incidence varies geographically and with socioeconomic levels; changes with migration; has dramatically fallen in certain countries; appears related to diet more than most other cancers; incidence shows relation to histologic types; highest incidence - Japan, Iceland, Finland, Chile; more frequent among poor than rich; Japanese migrants to Hawaii and California show a decreased gastric cancer incidence within one generation; gastric cancer incidence has fallen in North America over the past 50 years; smoked foods, salted foods, low fresh vegetable diet, and nitrosamines are associated with high gastric cancer rates.

C. ~~Precancerous Lesions and Conditions~~: increased risk of cancer

1. ~~Adenomas~~ - A precancerous lesion; adenomas not common in the stomach compared to colon; gastric carcinomas arise from "flat" mucosa more frequently than from adenoma - unlike the colon.
2. ~~Pernicious anemia~~ - A precancerous condition which may be mediated through increase in frequency of dysplasia in atrophic gastritis.
3. ~~Menetrier disease~~ - Giant rugal hypertrophy; greatly thickened gastric folds; increased mucous glands; adult males; proximal stomach; protein loss; anemia.
4. ~~Gastric peptic ulcer~~ - Not a high risk precancerous lesion. Confusion between an ulcerating cancer and a cancer arising in an ulcer. The latter must show the typical scars and muscle damage of a chronic ulcer with cancer arising at the edge, not in the base.
5. ~~Gastric stump~~ - Remnant after ulcer surgery may be site of carcinoma years later; may be related to bile reflux.
6. ~~H. pylori~~ - as a cause of chronic atrophic gastritis.

7. Atrophic Gastritis and Intestinal Metaplasia - Frequently associated with gastric carcinoma, adenoma and pernicious anemia; associations found on population level, patient level and topographically in stomach.
8. Epithelial Dysplasia - The most highly selective precancerous lesion through which most of the above go en route to carcinoma. Epithelium shows cytologic changes: enlarged hyperbasophilic, crowded, irregular nuclei and increased mitoses; histologic changes: irregularly arranged and misshapen glands; graded as mild, moderate and severe.

D. Carcinoma of the Stomach

1. Carcinoma in situ - Histologic features of carcinoma without evidence of invasion of the lamina propria. No metastatic potential. Difficult to exclude invasion.
2. Intramucosal Carcinoma - Cancer limited to the mucosa; low metastatic potential, about 5%.
3. Early Gastric Cancer - mucosa and submucosa involved.
4. Sites of Preference - Prepyloric region, antrum and on lesser curvature; where pyloric rather than body type mucosa prevails. Tumors do occur in all areas, however.
5. Signs - relate to ulceration, gastric bleeding, dyspepsia

E. Macroscopic Types

1. Nodular - Focal mural raised, but not very polypoid, mass; common.
2. Ulcerating - Large shallow bumpy crater with raised, irregularly thickened edges; usually distinct from peptic ulcer with its deeper, flask shape, clear-cut, sharp edge, overhanging mucosa, and normal adjacent mucosa; common. Nodular and ulcerating often mixed together.
3. Fungating - protuberant plant-like luminal mass; uncommon.
4. Linitis plastica - diffusely spreading tumor with extensive fibrosis which greatly thickens the gastric wall without showing a localized mass; relatively uncommon. Diagnostic problem: mucosa may be undermined; more scar than tumor; biopsy difficult to assess.
5. Superficial spreading - A tumor that grows widely in the mucosa and submucosa before invading deeper; rare.

F. Common Microscopic Types

1. Gland forming Adenocarcinoma: tubular and papillary patterns
Degree of differentiation, i.e., how closely tumor resembles non-neoplastic epithelium in gland formation and mucus production; well, moderately and poorly differentiated.

2. ~~Signet Ring Cell Carcinoma~~: individual cells with central mucous droplet and peripherally displaced nucleus; poorly differentiated.
3. ~~Mucinous Adenocarcinoma~~ - adenocarcinoma with much mucus, i.e. >50%.

G. Lauren and Ming Classifications of Gastric Carcinoma: -

1. ~~Intestinal type (Lauren) or Expanding Type (Ming)~~ - Forms glands and grows as a well demarcated mass. Predominant tumor in high incidence areas; males affected more than females; older age group; frequent association with intestinal metaplasia.
2. ~~Diffuse type or Infiltrative type~~ - Individual or small groups of poorly differentiated cells spread diffusely; uniformly distributed throughout the world; males and females equally affected; mean age under 50, not strongly associated with intestinal metaplasia.

H. Spread - Gastric carcinoma invades the wall and spreads to regional lymph nodes. Direct spread through the wall into neighboring organs is common as is spread on the peritoneal surfaces. Tumors at the cardia frequently go into the esophagus; spread into duodenum is less common. The liver is the most frequently affected distant site of metastasis.

I. Prognosis - related to depth of invasion and presence of lymph node and distant metastasis. It is poor because of relatively late diagnosis; may change with the increasing use of fiber-optic endoscopy, giving earlier diagnosis.

J. Stromal Tumors of the Stomach (and GI Tract)

Though uncommon compared to carcinomas, the GI tract is a not infrequent site of stromal (and to a lesser extent, smooth muscle) tumors, and of these the stomach is the most common site, (about 2% of gastric cancers). They arise within the wall and usually project into the lumen as a sessile polyp. Pressure on the mucosa causes atrophy, then ulceration and bleeding. It is frequently difficult to predict the behavior of these tumors, i.e. benign looking ones may metastasize. Mitotic rate and size are the best indicators of metastatic potential. In most cases, stromal tumors are less aggressive than are carcinomas. The above applies to the intestines as well.

The origin of the stromal tumors is unclear as they have features of a precursor of smooth muscle or neurogenic (Cajal-cell) elements. They have a specific immunohistochemical profile and may be sensitive to a specific molecular inhibitor even in cases with metastasis. Stromal tumors are commonly referred to as GISTs (Gastrointestinal stromal tumors).

K. Malignant Lymphomas of the GI Tract

The GI tract is the main extranodal site of primary malignant lymphomas, and of these the stomach is the main site. Most are B-cell lymphomas. Those that appear to arise from mucosa associated lymphoid tissue are referred to as MALT lymphomas. Much less common than carcinoma. They occur mainly in the body rather than antrum in contrast to carcinoma. More often multifocal than carcinoma. Histologically, may simulate carcinoma.

-Distinction from carcinoma important because of different therapeutic approaches and prognosis.

H. pylori implicated as a cause of gastric lymphoma due to development of gastric lymphoid hyperplasia. Treatment of the *H. pylori* infection can sometimes cure early, low grade MALT lymphomas.

Approximate distribution of GI lymphomas:

Stomach	55%
Small intestine	25%
Ileocecal	15%
Colorectal	5%

Prognosis of gastric lymphoma is better than carcinoma.

Prognosis of gastric lymphoma is better than intestinal lymphoma.

<u>Site of lymphoma</u>	<u>5_yr_survival</u>
	%
Stomach	44
Small intestine	23
Ileocecal	13
Colorectal	5

Spread beyond the original site to the lymph nodes or other organs, as with carcinoma, is the main determinant of prognosis.

Mediterranean lymphoma: A primary small intestinal malignant lymphoma associated with malnutrition and intestinal infections with two phases: a premalignant massive plasma cell infiltration of small bowel mucosa and a subsequent malignant lymphoma. Typically occurs in jejunum and frequently patients have an abnormal alpha chain paraprotein, alpha-chain disease. In contrast to Western type lymphomas, it affects younger patients, is preceded and accompanied by malabsorption and is more lethal.

L. Lymphoid Hyperplasia of the GI Tract

The GI tract mucosa is a major site of lymphoid tissue; this serves a protective function at the lumen-mucosa interface. Mucosa associated lymphoid tissue (MALT) is special lymphoid tissue (the main source of GI lymphomas) and is arranged as:

- 1 - diffusely in lamina propria in intestines, T-cells.
- 2 - solitary nodules at base of intestinal mucosa, B-cells.
- 3 - aggregate nodules: Peyer patches in small intestine, especially distal ileum; appendix; rectum, B-cells.

Reactive lymphoid hyperplasia occurs with many GI lesions, e.g. cancer, infection, ulcers. Lymphoid hyperplasia may in itself produce a mass and may simulate a malignant lymphoma. GI lymphoid hyperplasia usually fits into one of 4 groups:

1. Gastric lymphoid hyperplasia. Usually stimulated by H. pylori.
2. Focal lymphoid hyperplasia of small intestine. Typically affects terminal ileum (Peyer patches) of young people. May be large enough to cause intussusception. Adenovirus infection implicated in some cases.
3. Focal lymphoid hyperplasia of the rectum. Presents typically as a small rectal nodule (benign lymphoid polyp). Most regress.
4. Nodular lymphoid hyperplasia: numerous enlarged lymphoid nodules in a variable segment of intestine; not a solitary focal lesion as 1 to 3 above. Two forms:
 - a. With hypogammaglobulinemia: Probably a compensatory hyperplasia

to overcome a maturation defect in plasma cells (absent or decreased). Patients are adults with repeated respiratory infections and diarrhea. Giardia lamblia infestation of small intestine is frequent. Patients have increased risk of developing carcinoma or lymphoma.

- b. Without hypogammaglobulinemia: more frequent than "a"; asymptomatic; generally in children; plasma cells present; no giardia; a reactive response rather than a true lesion.

TNM classification of gastric carcinoma

T1	Lamina propria, submucosa
T2	Muscularis propria, subserosa
T3	Penetrates serosa
T4	Adjacent structures
N1	1 to 6 nodes
N2	7 to 15 nodes
N3	>15 nodes

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