# GASTRIC ULCERATION

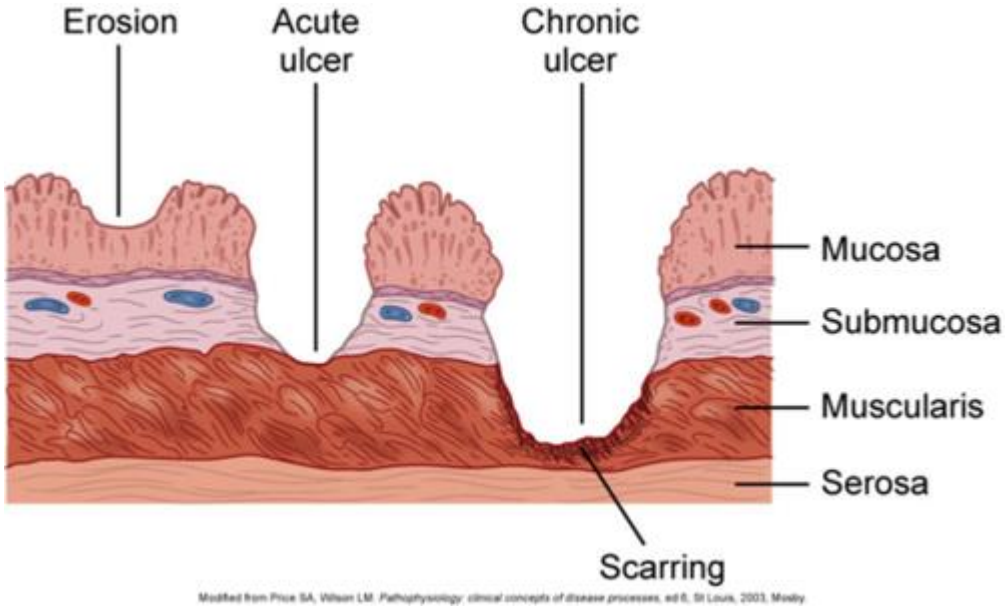
☼ **Histologically:**

►Erosions are breach in the mucosal epithelium only, which may heal within days, whereas healing of ulcers takes much longer time.

► Ulcers of the GIT are breach in the mucosa that extends through the muscularis mucosae into the submucosa or deeper.

- Although ulcers may occur anywhere in the GIT,

by far, the most common are the peptic ulcers (PU) that occur in the duodenum (Duodenal PU = DU) & stomach (gastric PU = GU).

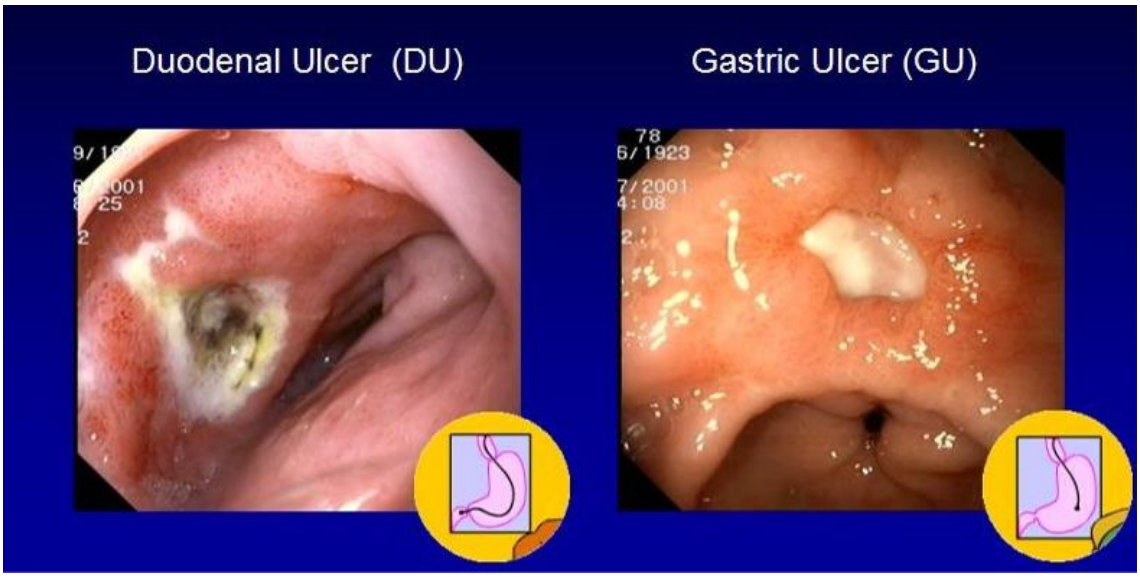


# Peptic Ulcers (PU)

- PU are lesions caused by acid peptic digestion of the wall in any portion of the GIT.

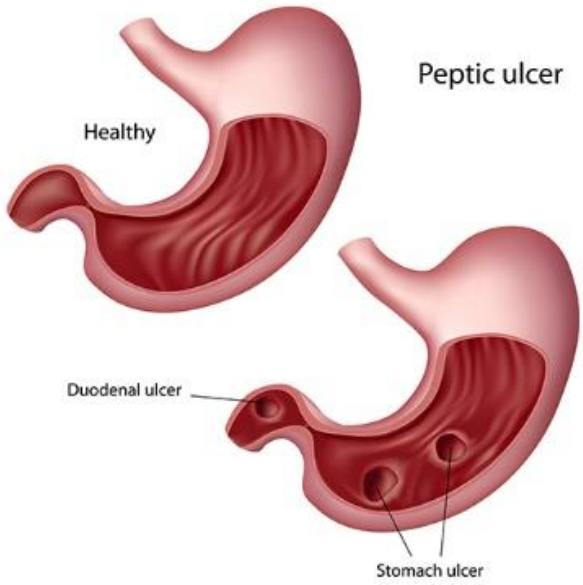
- They are chronic & mostly solitary.

- At least 98% of PU are either in the first portion of the duodenum or in the stomach,
  in a ratio of 4 DU: 1GU.



**Appearance: Gross**

- All PU, whether GU or DU, have identical appearance



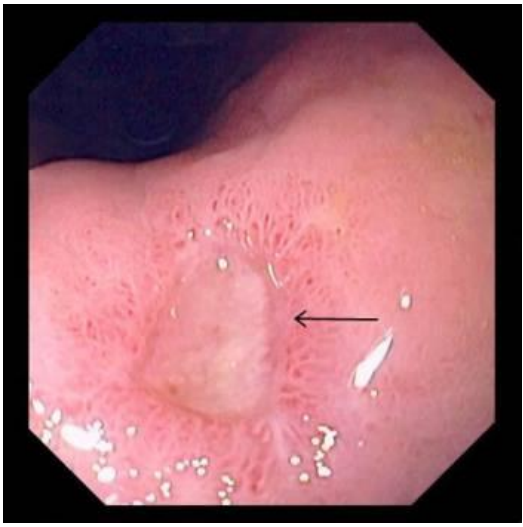

►PU are sharply punched-out craters (holes), 2-4 cm

►PU are round, usually single,

& favored sites are the anterior & posterior walls of the first portion of the duodenum & the lesser curvature of the stomach.

Occasional gastric PU occur on the greater curvature or anterior or posterior walls of the stomach, the very same locations of most ulcerative ca.

►PU are defects in the mucosa that penetrate at least into the submucosa, & often into the muscularis propria or deeper.



► PU crater margins are perpendicular & unlike ulcerated cancers there is no elevation or beading of the edges

►PU surrounding mucosal folds may radiate like wheel

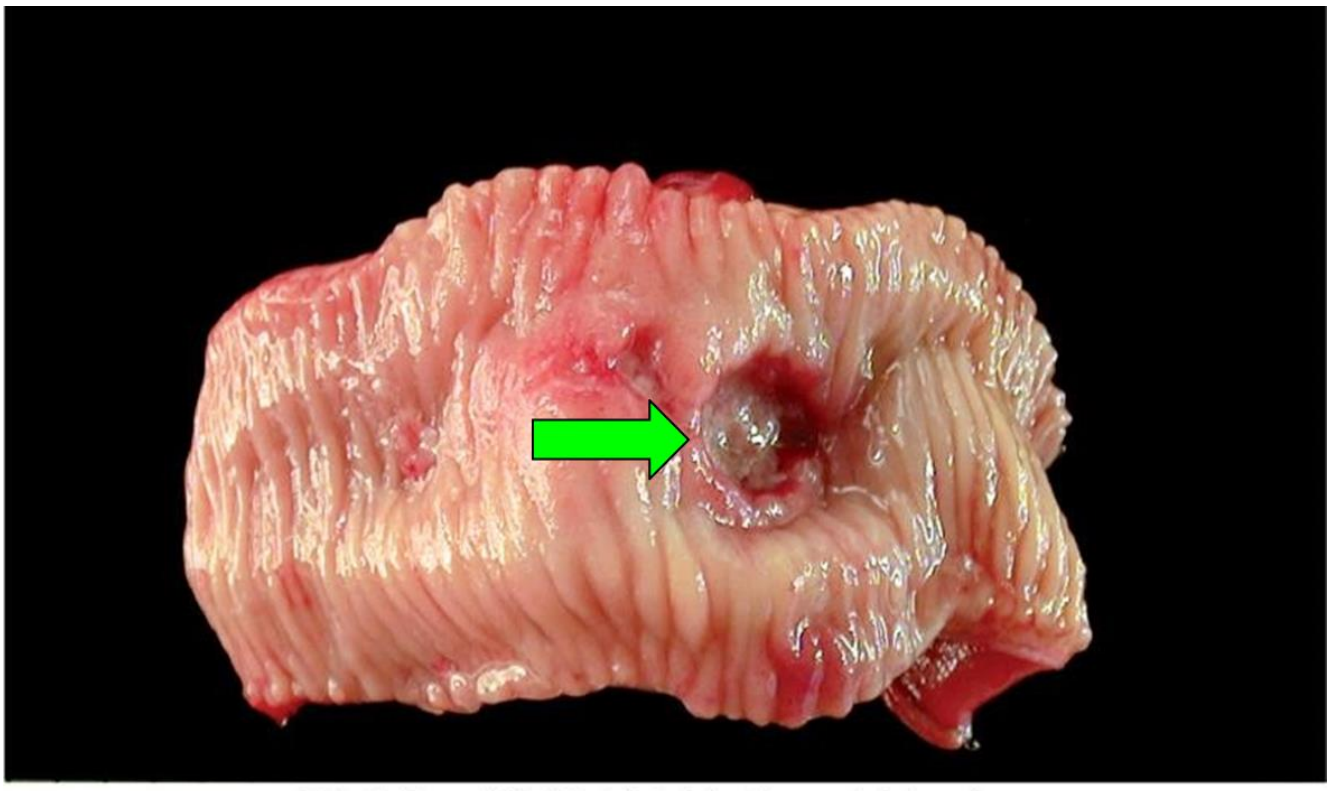
►PU crater base appears remarkably clean, as a result of peptic digestion of the exudate & necrotic tissue.

► Infrequently, an eroded artery is visible in the ulcer base.

►PU crater perforation through the duodenal or gastric wall (complicate 5% of PU) may leads to localized or generalized peritonitis.

Alternatively, the perforation is sealed by an adjacent structure like adherent omentum, pancreas or liver.

Peptic ulcer of the duodenum. Small ulcer (2cm in ?), with a sharply punched-out apperance. Unlike cancerous ulcers, the margins are not elevated. The ulcer base is clean
(compare with the ulcerated carcinoma in F5-19).



- In a chronic, open PU, four zones can be distinguished

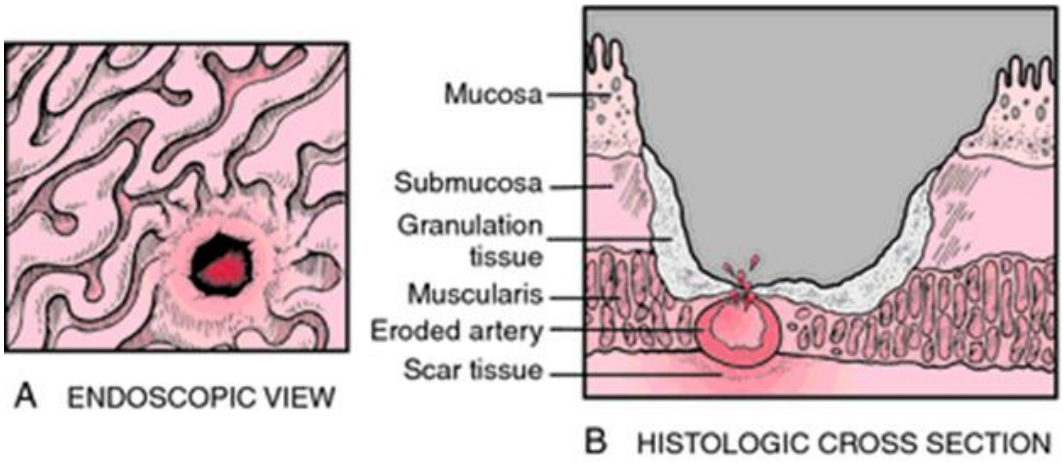
(1)PU base & margins have a thin layer of necrotic fibrinoid debris underlain by

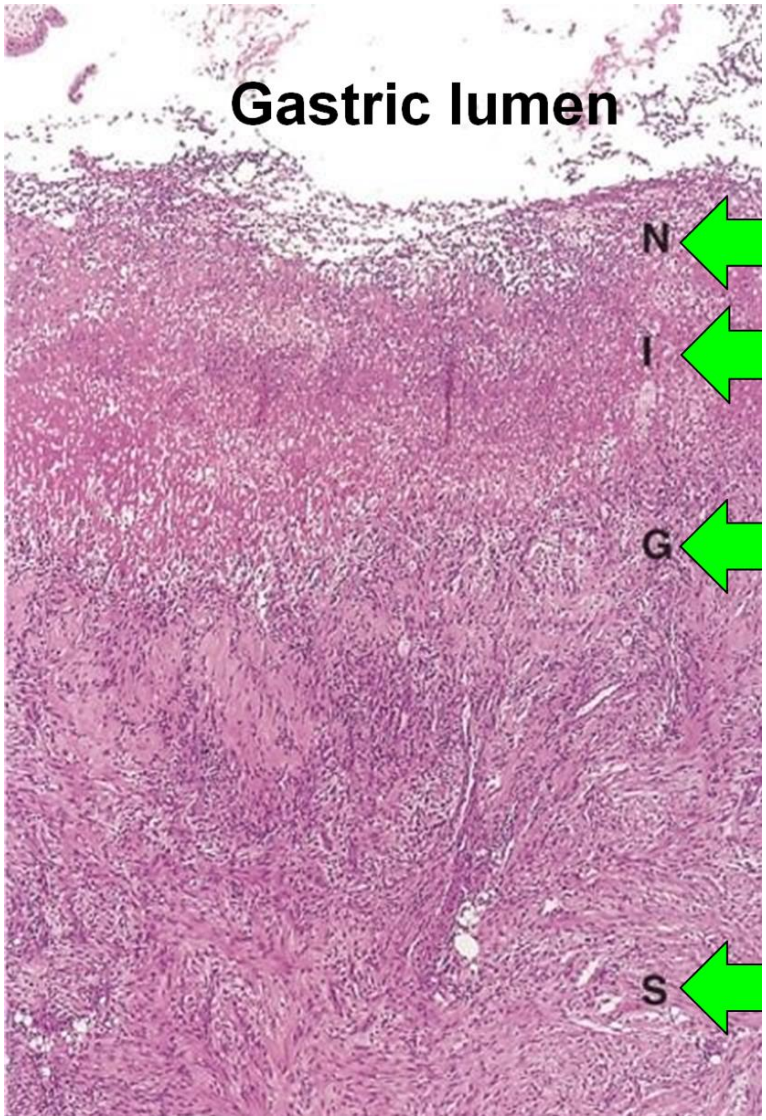
(2) A zone of active nonspecific inflammatory infiltration with neutrophils predominating, underlain by

(3) Granulation tissue, deep to which is

(4) Fibrous, collagenous scar that fans out widely from the margins of the ulcer.

Vessels trapped within the scarred ulcer base are characteristically thickened & obliterated, but sometimes they are widely patent (What is the effect on the patient?)






: Medium-power

detail of the base of a peptic ulcer, demonstrating the layers “moving from the luminal surface at the top down to the muscle wall at the bottom” of:

(N) Necrosis

(I) Acute Inflammation

(G) Granulation tissue

(S) Scar

: Chronic peptic ulcer: stomach.

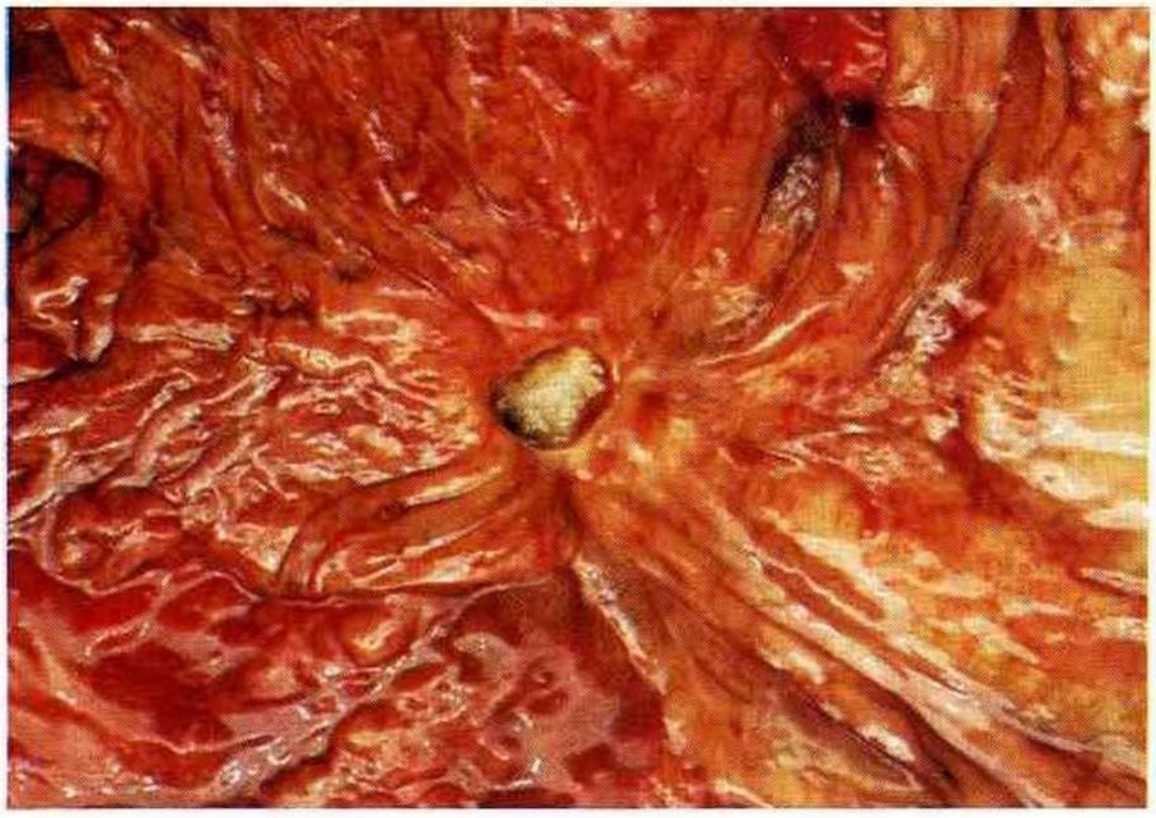
Single GU with :

(1) oval crater,

(2) base is covered with a greenish-yellow slough, consisting of necrotic granulation tissue,

(3) the ulcer is healing by fibrosis, as shown by the folds of mucosa radiating from the ulcer,

(4) punch-out edges, vertical or overhang to produce a flask-shaped apperance, but not raised or rolled .



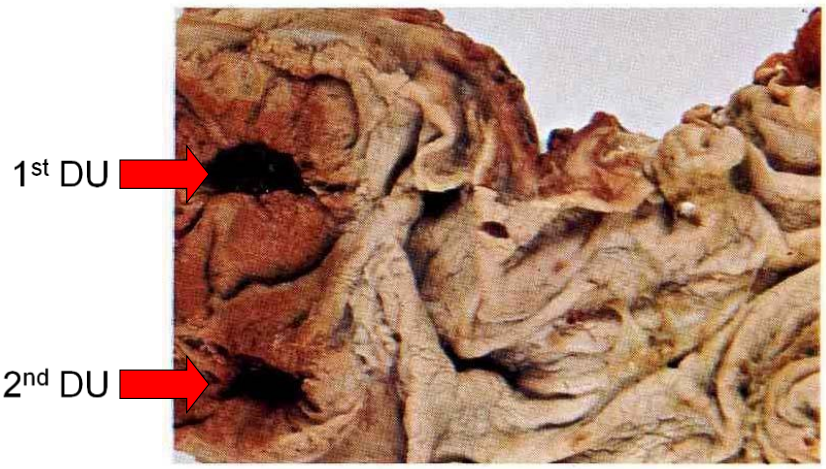
4.15 Chronic peptic ulcer: stomach

Chronic peptic ulcers: duodenum.

Immediately distal to the pylorus are two (Kissing) DU,

the base of one contains a recent blood clot,

{the patientdie from a massive hemorrhage due to penetration of the gastro-duodenal artery by the ulcer}.



4.16 Chronic peptic ulcers: duodenum

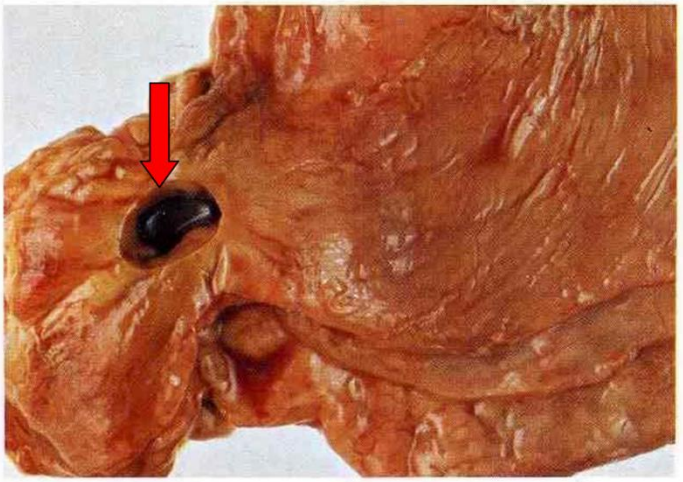
Q: what is the arterial vascular lesion which, if present, can prevent this serious or ? fatal complication?

Perforated chronic DU of the anterior duodenal wall.

The serosal aspect of the pyloric end of stomach & duodenum is shown,

with the large orifice of the perforated PU clearly visible.

The patient die from peritonitis


4.17 Perforated chronic peptic ulcer: duodenum

**Clinically**

- Most PU cause epigastric pain, (burning, or boring), tends to be worse at night

  & occurs usually 1 to 3 hours after meals during the day,

  & classically relieved by alkalis or food, but there are exceptions.

- Nausea, vomiting, bloating, belching, & significant weight loss are additional manifestations.
- A significant minority of patients present first with complications, including:

-Bleeding is the commonest complication, occurring in 1/3 of patients, & may be life-threatening.

- Perforation occurs in 5% of patients, accounts for 2/3 (most common cause of)

They are self-limited & usually resolve within few weeks, but they may recur in the same or a different location in the mouth.

**Pathogenesis of PU**

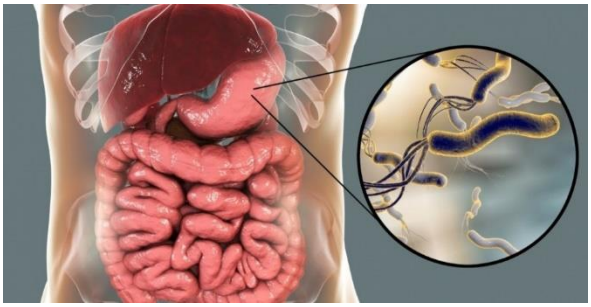
2 conditions are essential or key for the development of PU :

(1) H. pylori infection, which has a strong causal relationship with peptic ulcer development, &

(2) Mucosal exposure to gastric acid & pepsin.

- Nevertheless, many aspects of the pathogenesis of mucosal ulceration remain murky (dark or foggy).
  It is best perhaps to consider that PU are created by an imbalance between the gastroduodenal mucosal defenses & the damaging forces that overcome such defenses. Both sides of the imbalance are considered.

**H. Pylori**

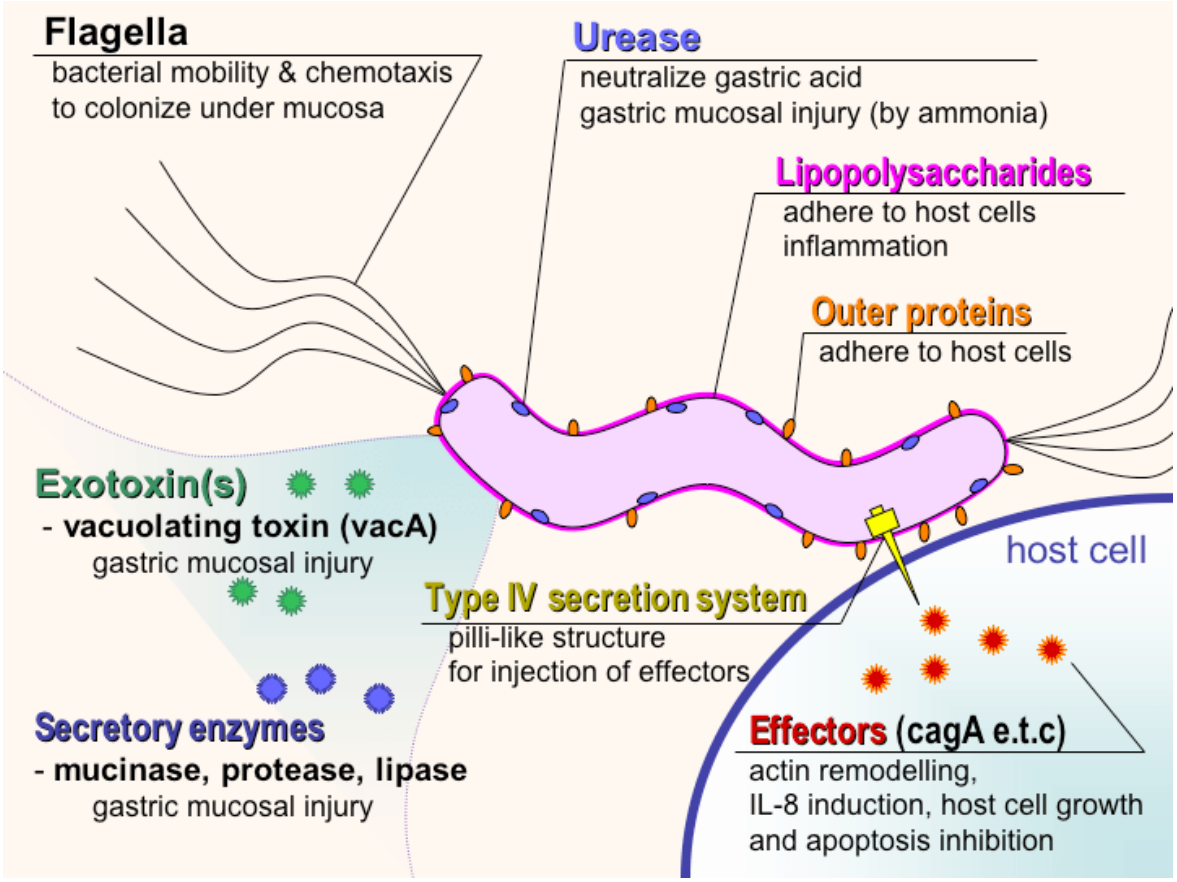


-H. pylori infection is the most important condition in the pathogenesis of PU.

-The infection is present in 70% to 90% of persons with DU & in about 70% of those with GU.

-Furthermore, antibiotic treatment of H. pylori infection promotes healing of ulcers & tends to prevent their recurrence.

►Pathogenesis:



►Pathogenesis:

The possible mechanisms by which the non- invasive H. pylori induces an intense inflammatory & immune response, tipping the balance of mucosal defenses are:

**(1)** There is production of *proinflammatory cytokines* such as :

TNF, IL-1, IL-6,, &, most notably, IL-8.

IL-8 is produced by the mucosal epithelial cells, & it recruits & activates neutrophils.

**(2)** Epithelial injury is mostly caused by a vacuolating toxin called *VacA,*

which is regulated by the cytotoxin-associated gene A (CagA) of the H. pylori .

**(3)** H. pylori secrete a *urease* that breaks down urea to form toxic ammonium chloride & monochloramine.

**(4)** H. pylori also elaborate *phospholipases* that damage surface epithelial cells. Bacterial phospholipases & proteases break down the glycoprotein-lipid complexes in the gastric mucus, thus weakening the first line of mucosal defense.

**(5)** H. pylori enhance gastric acid secretion & impair duodenal bicarbonate production, thus *reducing luminal pH* in the duodenum.

This altered milieu seems to favor gastric metaplasia (the presence of gastric epithelium in the first part of the duodenum).

Such metaplastic foci provide areas for H. pylori colonization.

**(6)** Several H. pylori proteins are *immunogenic* & they evoke a robust immune response in the mucosa.

**(6)** Several H. pylori proteins are immunogenic & they evoke a robust immune response in the mucosa.

Both activated T cells & B cells can be seen in H. pylori associated *chronic gastritis.*

The B lymphocytes aggregate to form follicles.

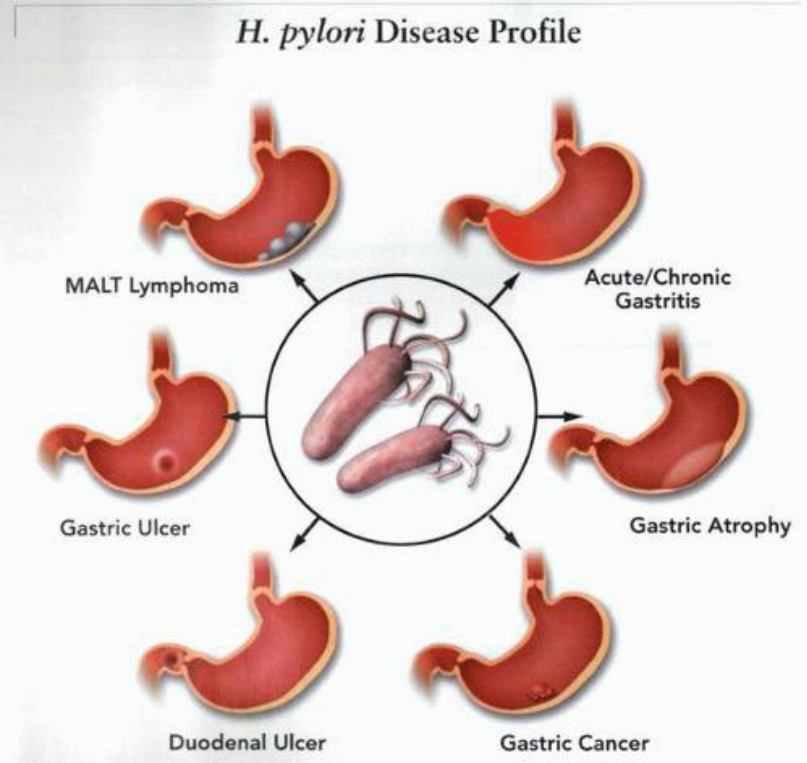
**-**The role of T & B cells in causing epithelial injury is not established,

but T-cell-driven activation of B cells may be involved in the pathogenesis of gastric lymphomas (MALT lymphomas, discussed later).

**-**Only 10% to 20% of individuals worldwide who are infected with H. pylori actually develop PU.

Hence, a key enigma is why most are spared & some are susceptible?

**(**Suffice it to say, that while the link between H. pylori infection & GU & DU is well established, variability in host-pathogen interactions leading to ulceration remains to be discovered!)



**NSAIDs**

- NSAIDS are the major cause of PU disease in persons who do not have H. pylori infection.
- The gastroduodenal effects of NSAIDs range from:
  superficial acute erosive gastritis & acute gastric ulceration
  To PU in 1% to 3% of users.

► Key to NSAID-induction of peptic ulceration is their suppression of mucosal prostaglandin synthesis,

resulting in:

-increased secretion of hydrochloric acid,

- decreased bicarbonate

- & decreased mucin production.

Loss of mucin degrades the mucosal barrier that normally prevents acid from reaching the epithelium.

- Synthesis of glutathione, a free-radical scavenger, is also reduced.

- Because NSAIDs are among the most commonly used medications, the magnitude of gastroduodenal toxicity caused by these agents is quite large.

- Risk factors for NSAID-induced gastroduodenal toxicity are

-increasing age,

- higher dose,

-& prolonged usage.

Thus, those who take these drugs for chronic RA are at particularly high risk.

- Other events may act alone or in concert with H. pylori & NSAIDs to promote peptic ulceration:

•Gastric hyperacidity may be strongly ulcerogenic.

• Excess production of gastric acid from a tumor in individuals with the Zollinger-Ellison syndrome causes multiple peptic ulcerations in the stomach, duodenum, & even the jejunum.

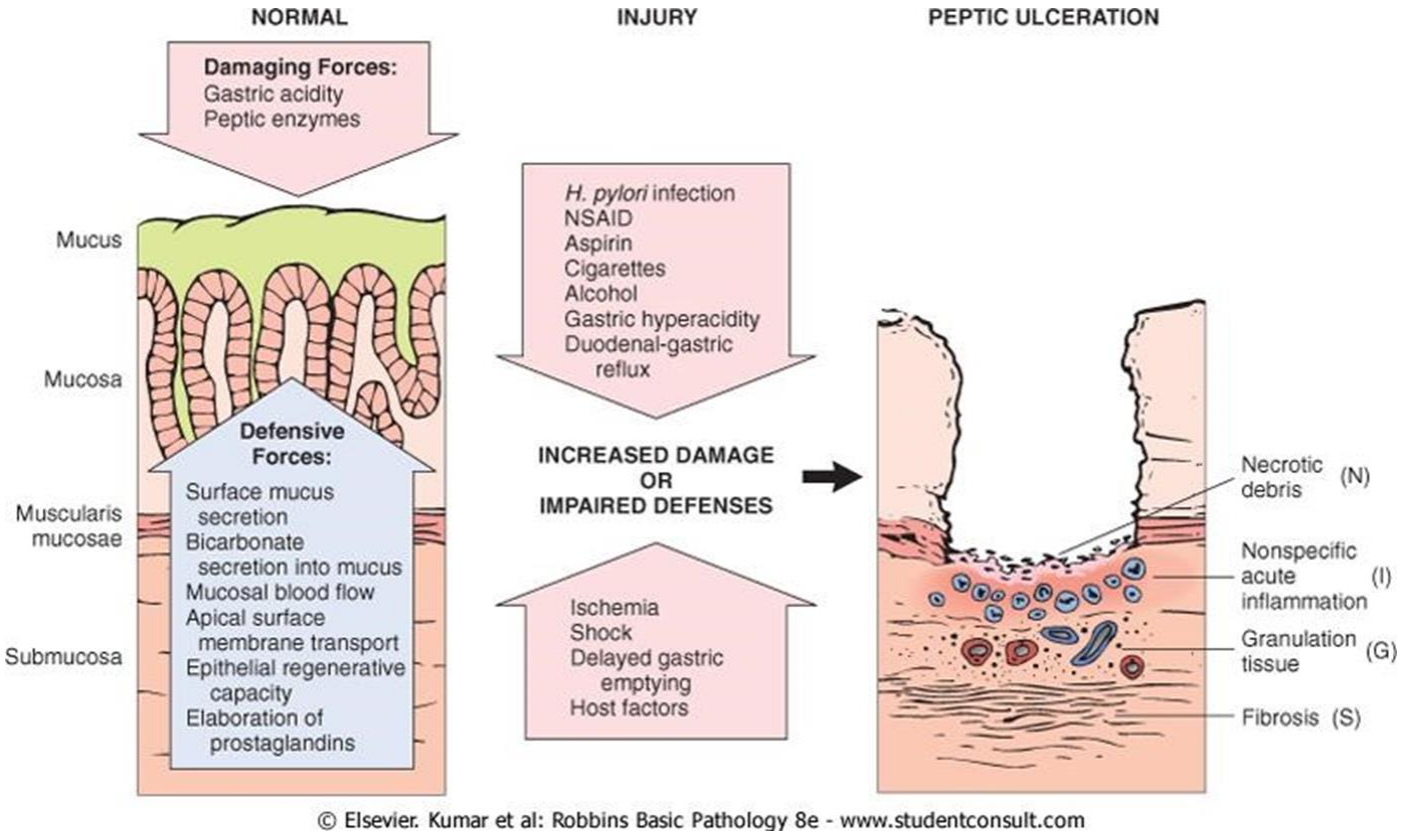
• Cigarette smoking impairs mucosal blood flow & healing.

•Alcohol has not been proved to directly cause peptic ulceration, but alcoholic cirrhosis is associated with an increased incidence of DU

•Corticosteroids in high dose & with repeated use promote ulcer formation.

•Personality & psychological stress are important contributing variables. Although this is now accepted as "common wisdom," actual data on cause & effect are lacking.

- With healing, the crater fills with granulation tissue from the bottom, followed by re-epithelialization from the margins & more or less restoration of the normal architecture, except for the permanent fibrous scarring of the lost muscularis properia (hence the prolonged healing times).





(Aggravating causes of & defense mechanisms against peptic ulceration. The right panel shows the basis of a peptic ulcer, demonstrating necrosis (N), inflammation (I), granulation tissue (G), & fibrosis.)

- Chronic gastritis is extremely common among persons with PU,
  & H. pylori infection is almost always demonstrable in those persons with gastritis.

  Similarly, individuals with NSAID-associated PU do not have gastritis unless there is coexistent H. pylori infection.

  This feature is helpful in distinguishing PU from acute gastric ulceration in which gastritis in adjacent mucosa is generally absent.

**Epidemiology**

- PU are remitting, relapsing lesions that are most often diagnosed in middle-aged to older adults,
  but they may first become evident in young adult life.

- PU often appear without obvious precipitating influences & may then heal after a period of weeks to months of active disease.
- Even with healing, however, the propensity to develop PU remains, in part because of recurrent infection with H. pylori.

- In US,

  about 10% of males

  & 4% of females have PU.

- The male/female ratio for DU is about 3:1.

- For both men & women in the US,
  the lifetime risk of developing PU is about 10% (i.e., 30 Million).

- DU are more frequent in persons with:

(1) chronic renal failure (CRF),

(2) hyperparathyroidism {in these conditions, hypercalcemia, whatever its cause, stimulates gastrin production & therefore acid secretion),

(3) alcoholic cirrhosis,

(4) chronic obstructive pulmonary disease (COPD)

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# Acute Gastric Ulceration (Stress ulcer)

Stress ulcers are focal, mostly multiple, acute mucosal defects that may appear after severe physiologic stress.

**►GROSSLY**

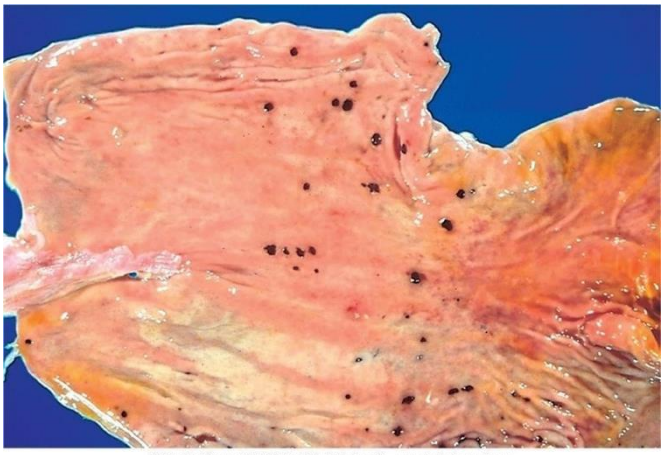
- acute stress ulcers are usually multiple, circular & small (<1 cm in□).
- The base is stained dark brown by the acid digestion of extruded blood.

- Unlike chronic PU, acute stress ulcers are:

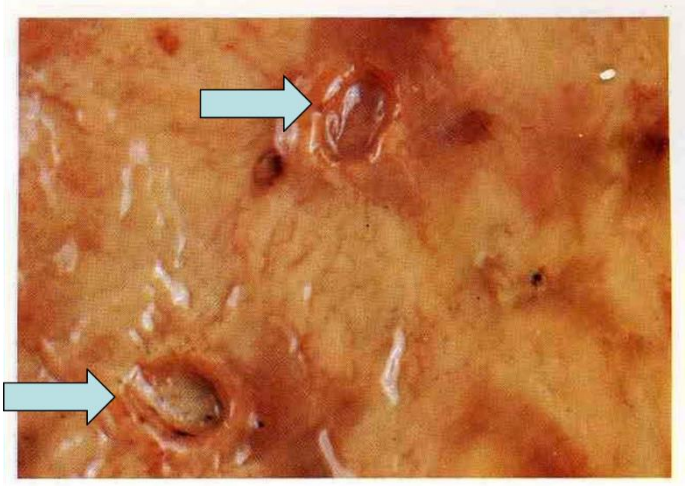
  (1) Although may occur singly, more often they are multiple &

  (2) Found anywhere in the stomach

  and located throughout the stomach & duodenum




Multiple (X28 stress ulcers) of the stomach, highlighted by the dark digested blood in their bases.



4.14 Acute 'stress' ulcers: stomach

Acute "stress" ulcers: stomach.

The patient sustained a severe head injury 10 days before his death.

On PM exam. 2 acute, so-called "Cushion" ulcers were situated in the fundus of the stomach are shown.

**Histology**

- acute stress ulcers are abrupt (sudden) lesions,
  with unremarkable normal adjacent mucosa, ranging in depth from:

  (A) Very superficial erosion, which are, in essence, an extension of acute erosive gastritis, to

  (B) Deeper ulcers involving the entire mucosal thickness (true ulceration) but do not penetrate the muscularis propria.

**Clinically**

►Stress ulcers are commonly seen in the following conditions:

(1) Severe trauma, including major surgical procedures, sepsis, shock, or grave illness of any type,

(2) Chronic exposure to gastric irritant drugs, particularly NSAIDs & corticosteroids,

(3) Extensive burns (Curling ulcers),

(4) Traumatic or surgical injury to the CNS or an intracerebral hemorrhage (Cushing ulcers; carry high risk of perforation).

A high percentage of persons admitted to hospital intensive care units with sepsis, severe burns, or trauma develop superficial gastric erosions or ulcers, which may be of limited clinical consequence or may be life-threatening.

- Acute stress ulcers can recover completely if the person does not die from the primary disease, & therefore,
  the single most important determinant of clinical outcome is the ability to correct the underlying condition.

Q: At the end of stress ulcer discussion, tabulate the differences between the acute stress ulcers & the PU.

[Etiology, Pathogenesis, Complications, Gross & □H features]

- Acute stress ulcers are not precursors of chronic PU.

**►Pathogenesis**

is uncertain & may vary with the setting.

- NSAID-induced ulcers are linked to decrease prostaglandin production.

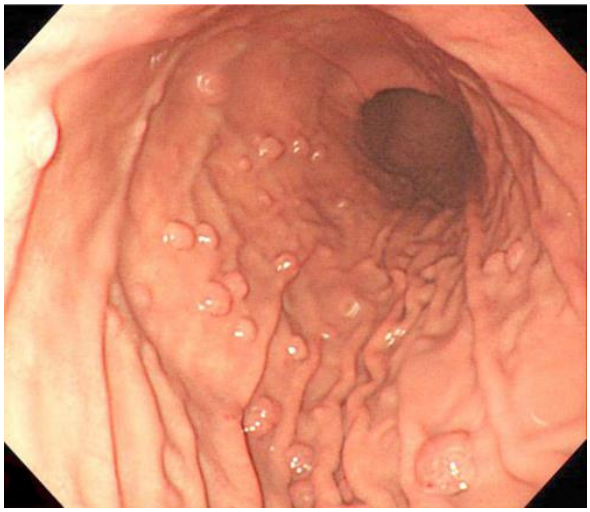
- The systemic acidosis that can accompany severe trauma & burns may contribute to mucosal injury presumably by lowering the intracellular pH of mucosal cells already rendered hypoxic by impaired mucosal blood flow.

- With cranial lesions, direct stimulation of vagal nuclei by intracranial pressure may cause gastric acid hypersecretion, which is common in these patients.

# GASTRIC TUMORS

## Gastric Polyps

- Generally, polyp is any nodule or mass that projects above the level of the surrounding mucosa.

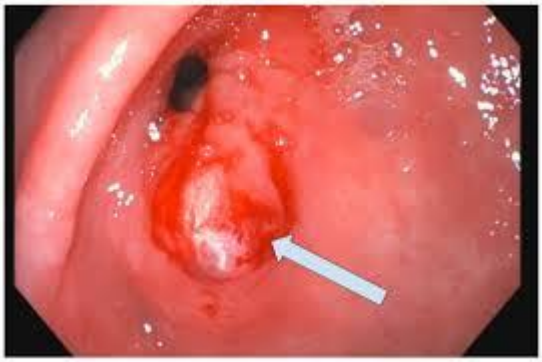


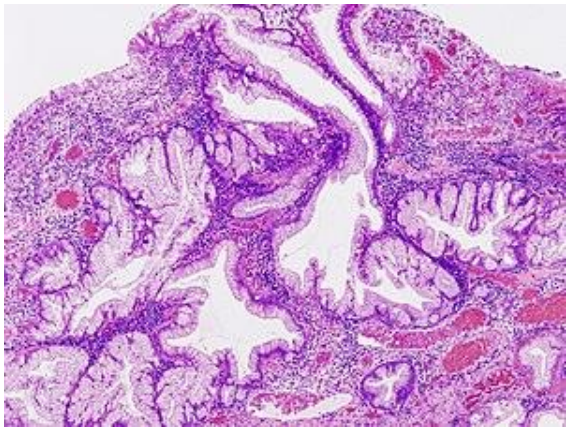
- BUT, because occasionally, a lipoma or leiomyoma arising in the wall of the stomach or intestine may protrude from under the mucosa to produce an apparent polypoid lesion,
  therefore, in the GIT polyp is restricted to → mass arising in the mucosa

- Gastric polyps are uncommon & found in 0.4% of adult autopsies, [compared with colonic polyps seen in 25% to 50% of older persons].

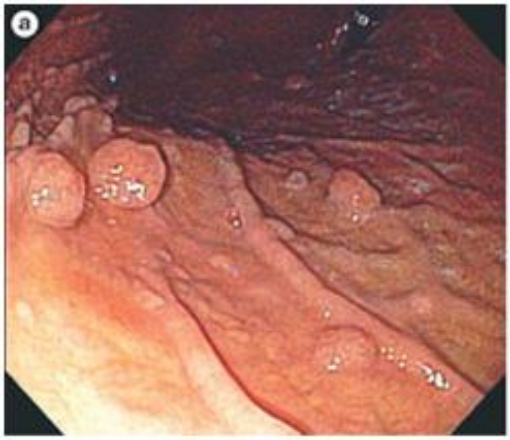
- In the stomach, three polyp types arise in the setting of chronic gastritis :

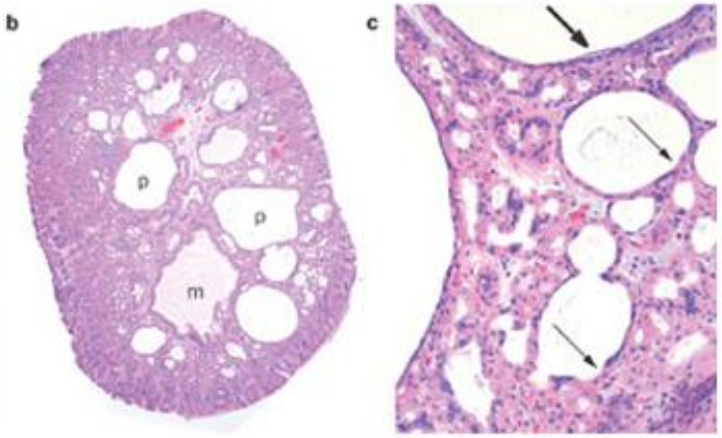
(1) Hyperplastic polyps (80% - 85%),
arise from an exuberant reparative response to chronic mucosal damage & hence are composed of a hyperplastic mucosal epithelium & an inflamed edematous stroma. They are not true tumors.





(2) Fundic gland polyps (10%),
are small collections of dilated corpus-type glands thought to be small hamartomas.

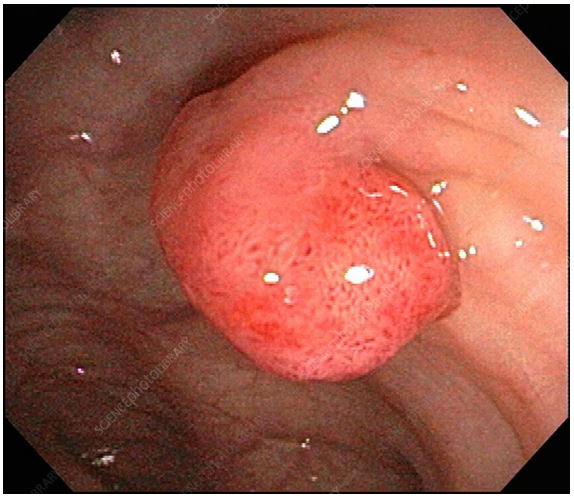


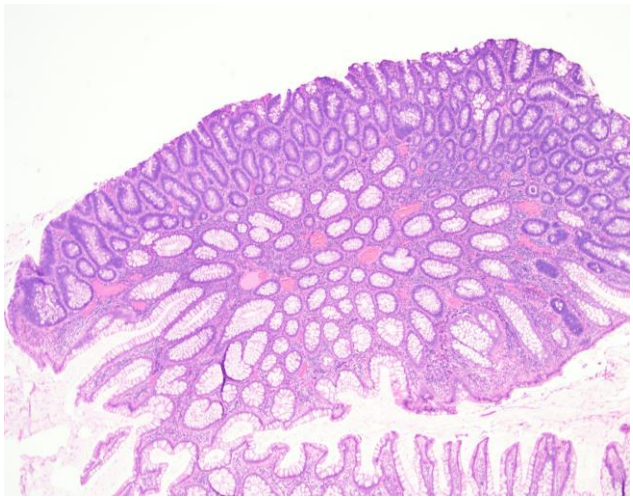




Both types 1 & 2 polyps are essentially innocuous,

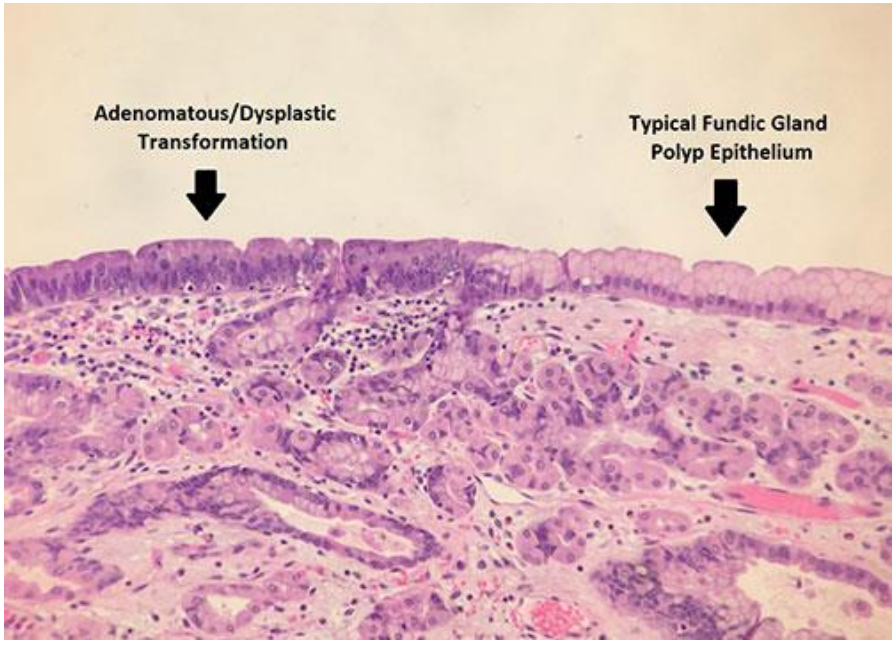
(3) Adenomatous polyps(5%)

are true tumors, contain dysplastic epithelium & in which, there is a definite risk of harboring adenocarcinoma, which increase with increased polyp size.





• **Histologic examination** is mandatory, because different types of gastric polyps cannot be distinguished by endoscopy,



**Gastric Tumors**

- The most common & most important malignant T of the stomachs is carcinoma (90%), (discussed below;)

- followed by: (which are discussed later )

  - lymphomas (4%),
  -carcinoids (3%),
  -& gastrointestinal stromal tumors {GISTs} (2%),

## Gastric Carcinoma (ca)

**Epidemiology:**

- Gastric ca is the 2nd leading cause of cancer-related deaths in the world (Lung is the first)

- Japan & South Korea have the highest incidence (X 8 to 9 times higher than in the US & Western Europe).

- Nevertheless, in most countries there has been a steady decline in the overall incidence & the mortality of gastric cancer (Why? refrigeration).

- The 5-year survival rate is less than 20%.

**►Classification:**

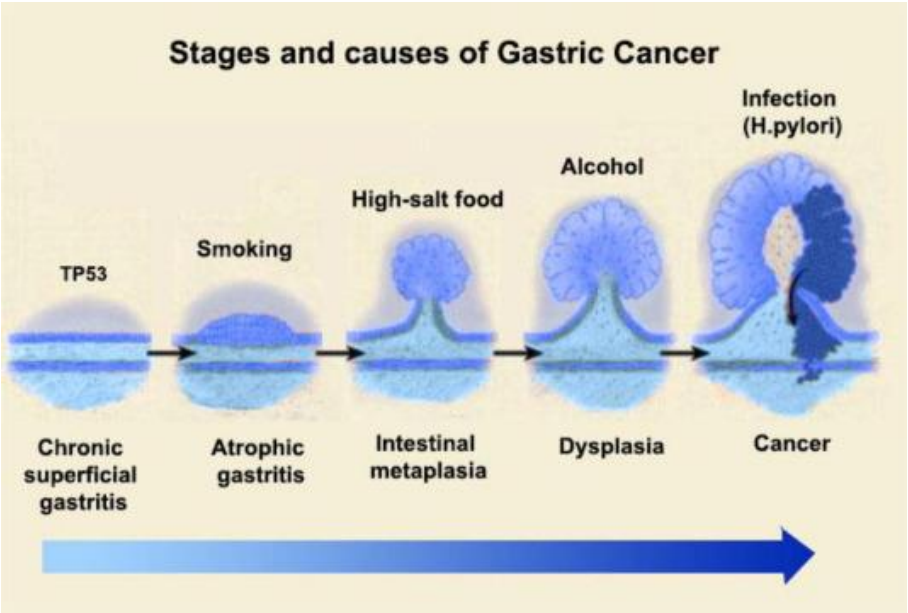
Gastric ca show 2 morphologic types: intestinal & diffuse types.

They can be considered as distinct entities, although their clinical outcome is similar.

**(I) Intestinal type:**

• initial chronic gastritis, accompanied by severe gastric atrophy & intestinal metaplasia, which are followed by dysplasia & intestinal type ca.

Initial chronic gastritis→ severe gastric atrophy→intestinal metaplasia→dysplasia→intestinal type ca




• it tends to be better differentiated

• is the more common type in high-risk populations.

• occur primarly after age 50 years

• 2:1 Male/Female ratio.

• Its incidence has progressively diminished in the US

**(II) Diffuse variant**:

• not associated with chronic gastritis, thought to arise de novo from native gastric mucous cells

• it tends to be poorly differentiated.

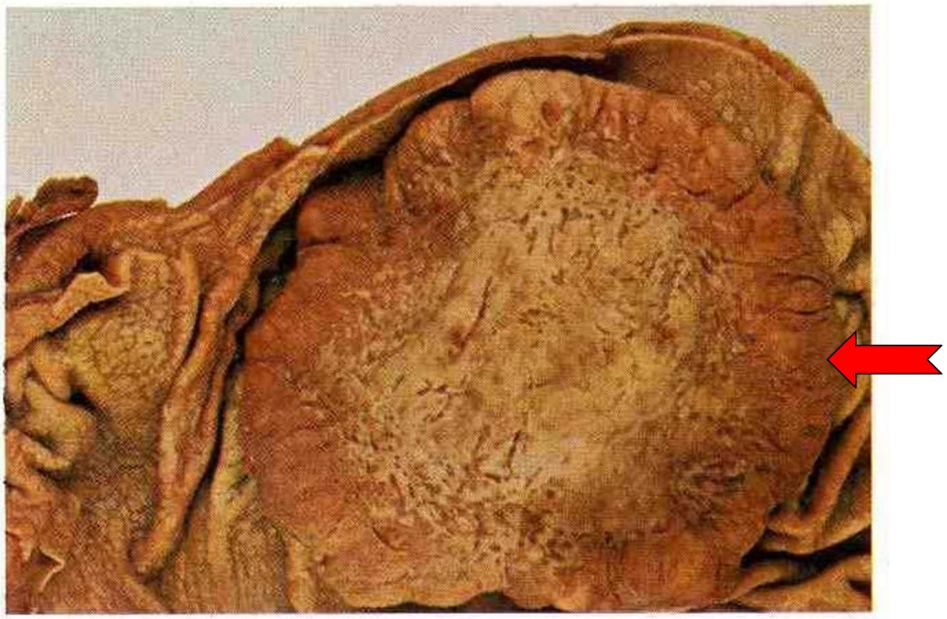
• occurs at an earlier age than the intestinal type

•with female predominance.

• The incidence of diffuse gastric ca has not significantly changed in US in the past 60 years & now constitutes approximately 50% of gastric ca in the US.

Carcinoma; stomach.

Very large, fungating, flat polypoidal tumor arising from the body of the stomach

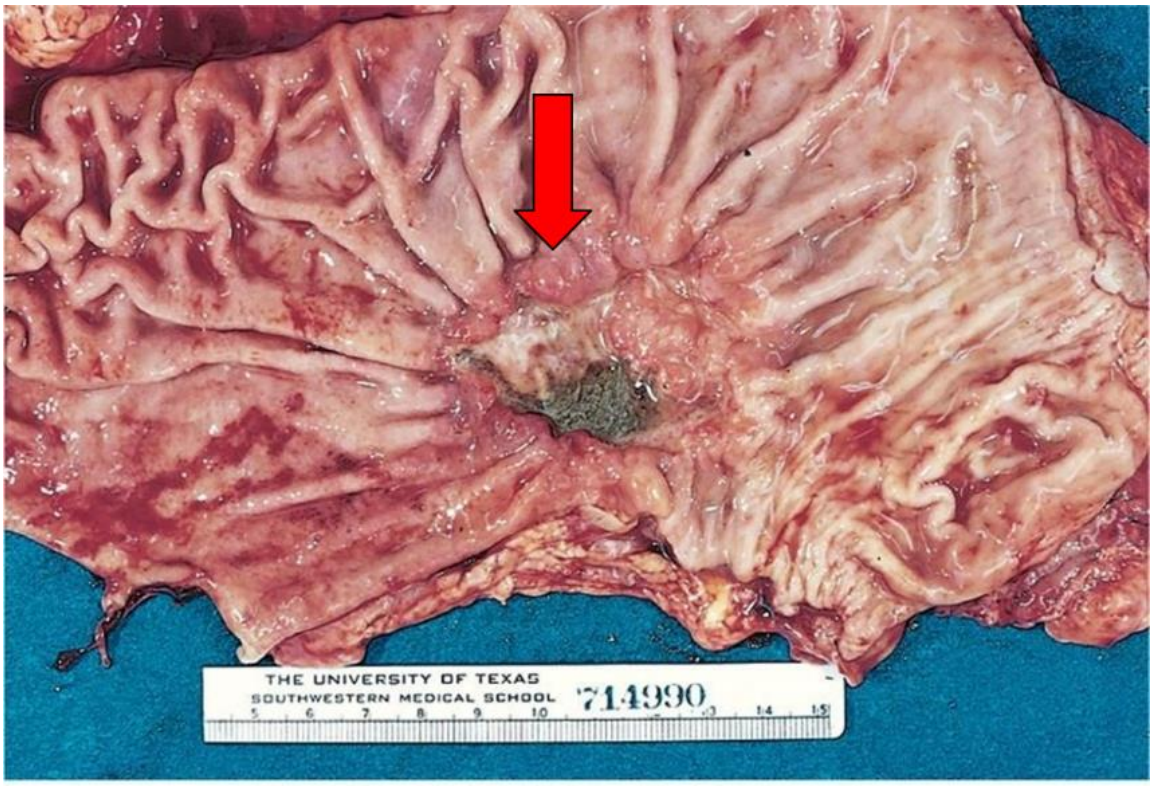


4.22 Carcinoma: stomach

: Ulcerating gastric carcinoma.

Large ulcer with irregular, heaped-up nodular margins

There is extensive excavation of the gastric mucosa with a necrotic gray area in the deepest portion. Compare with the PU in F15-16.



**Gastric ca is classified on the basis of**

(I) depth of invasion,

(II) gross growth pattern,

(III) histologic subtype.

**(I)** The morphologic feature having the greatest impact on clinical outcome is the depth of invasion.

-Early gastric ca is defined as a lesion confined to the mucosa & submucosa, regardless of the presence or absence of perigastric LN metastases.

-Gastric mucosal dysplasia is the presumed precursor lesion of early gastric cancer, which then in turn progresses to "advanced" lesions.

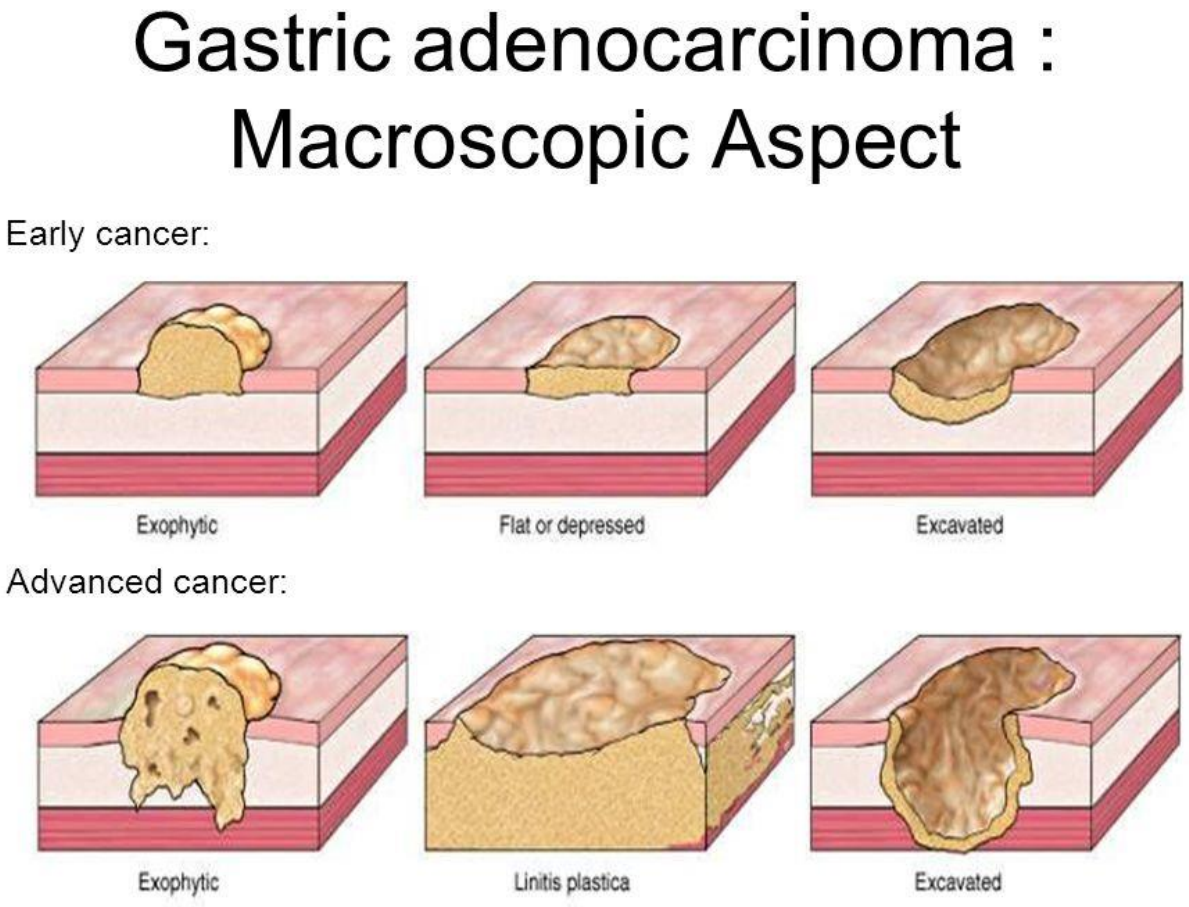
- Advanced gastric ca is a T that has extended below the submucosa into the muscular wall & has perhaps spread more widely.

**(II)** 3 gross growth patterns of gastric ca may be evident at both the early & advanced stages,

(1) Exophytic , with T mass protrusion into the lumen & the mass may contain portions of an adenoma,

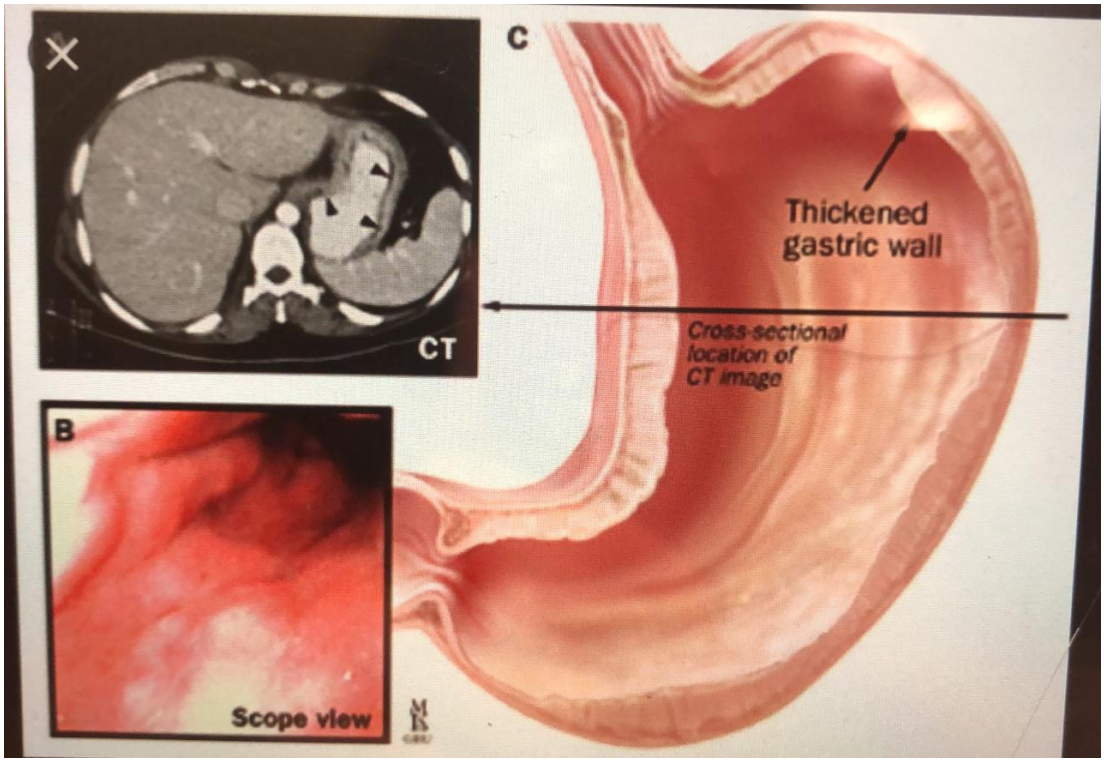
(2) Flat or depressed, which may presents only as regional effacement (flattening) of the normal surface mucosa & in which there is no obvious T mass within the mucosa; &

(3) Ulcerating T, whereby a shallow or deeply erosive ulcer crater is present in the wall of the stomach, which may mimic, in size & appearance chronic PU, although more advanced cases show heaped-up margins (F15-19).




The various morphologies of gastric adenocarcinoma

Uncommonly, a broad region of the gastric wall, or the entire stomach, is extensively infiltrated by ca, & the rigid & thickened stomach is called leather bottle stomach, or linitis plastica.



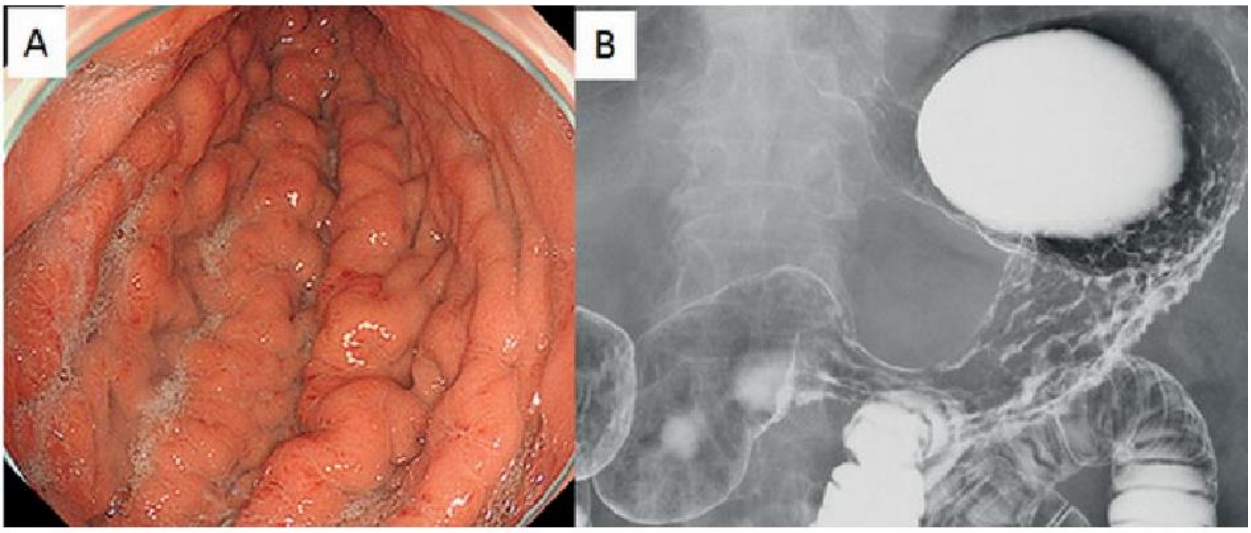




Fig. 1. A. Endoscopic findings showing circumferential thickening and rigidity of the gastric wall

**(III)** H, the intestinal-type variant is composed of malignant cells forming neoplastic intestinal glands resembling those of colonic, well or moderately-differentiated, adenocarcinoma.

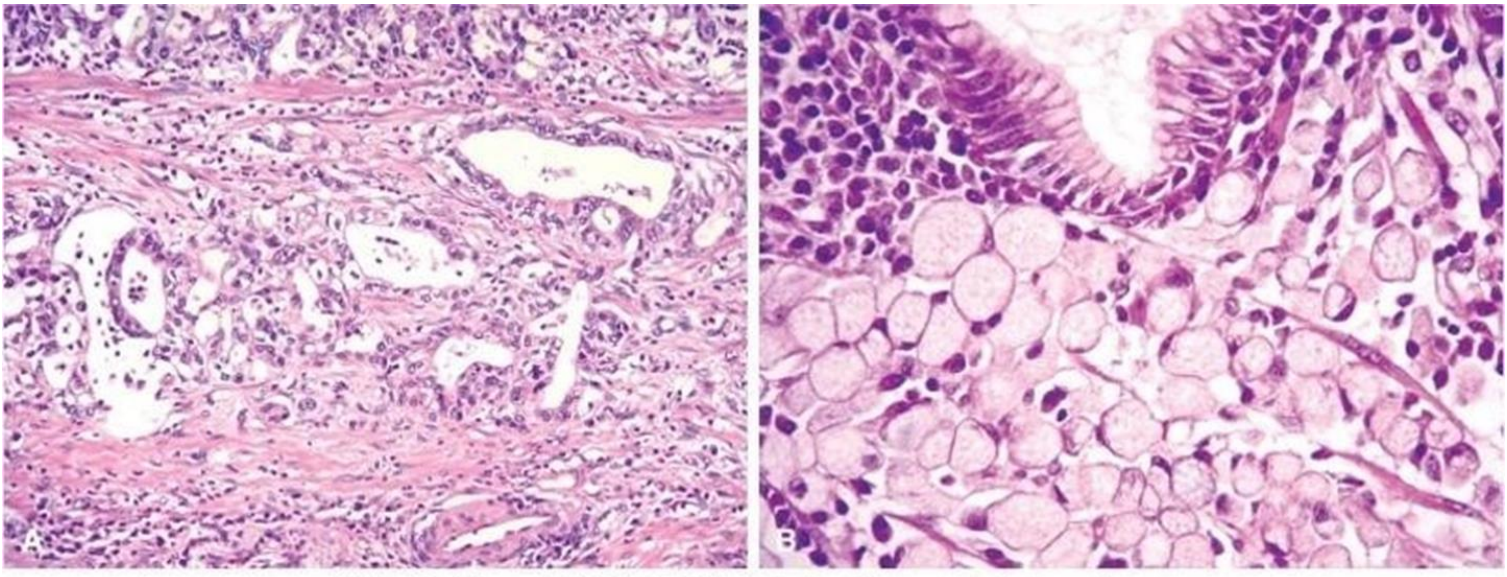
The diffuse type composed of gastric-type mucous cells that do not form glands (undifferentiated adenocarcinoma) but permeate the mucosa & wall as scattered individual "signet- ring" cells or small clusters in an" infiltrative" growth pattern.

Gastric cancer: H&E stain showing

A, intestinal type of gastric carcinoma, malignant cells forming glands that are invading the muscular

wall of the stomach.

B, Diffuse type of gastric carcinoma, with “signet ring” tumor cells; with no gland formation.



►All gastric ca eventually penetrate the wall to involve the serosa, spread to regional & distant LN, & metastasize widely.

- For unknown reasons, the earliest LN metastasis may involve a supraclavicular LN {Virchow node}.

- Intraperitoneal spread in females to both ovaries, gives rise to ovarian {Krukenberg tumor}.

► **Clinically,**

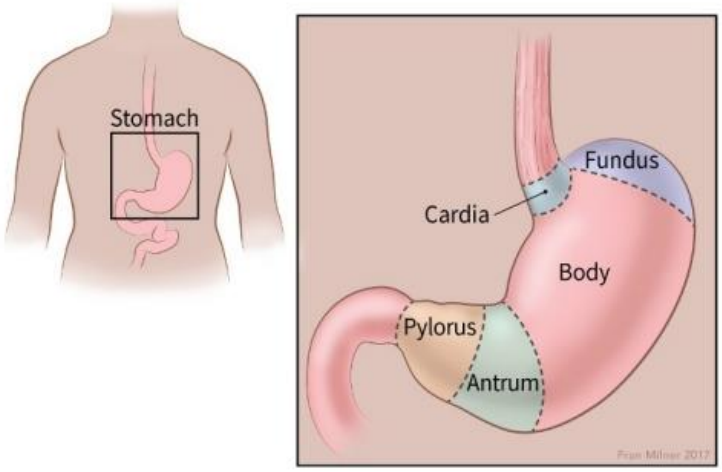
- all early gastric ca are asymptomatic & can be discovered only by repeated endoscopies of persons at high risk (as in Japan).

- Advanced ca may be asymptomatic, or it may present with abdominal discomfort, dysphagia (if ca affect the gastric cardia) or pyloric obstruction in case of pyloric canal ca, or weight loss.

- The only hope for cure is early detection & surgical removal, because the most important prognostic indicator is stage of the cancer at the time of resection (as in the colon ca).

►**GROSSLY,**

The location of gastric ca within the stomach is as follows:




-pylorus & antrum 60%;

-cardia, 25%;

-15% in the body & fundus.

-The lesser curvature is involved in about 40% & the greater curvature in 12%.

- Thus, a favored location is the lesser curvature of the antropyloric region.

- NB. An ulcerative lesion on the greater curvature is more likely to be malignant than benign.

## Etiology & Pathogenesis

## (I) Intestinal-Type Adenocarcinoma

The predisposing influences are many (see Table above), but their relative importance is changing.

- Dietary influences have drastically decrease in recent years with the use of refrigeration worldwide, which markedly decrease the need for food preservation by nitrates, smoking, & salt.

- While chronic gastritis associated with H. pylori infection constitutes a major risk factor for gastric ca, particularly high in individuals with chronic gastritis limited to the gastric pylorus & antrum.

- Chronic gastritis is generally accompanied by severe gastric atrophy & intestinal metaplasia, which are ultimately followed by dysplasia & intestinal type ca.

- The mechanisms of neoplastic transformation are not entirely clear.

- Chronic gastritis induced by H. pylori may release ROS, which eventually cause DNA damage, leading to an imbalance between cell proliferation & apoptosis, particularly in areas of tissue repair.

- Notably, individuals with H. pylori-associated DU (Not GU) are largely protected from developing gastric cancer!!!

## (II) Diffuse Adenocarcinoma

- The risk factors for this type of cancer remain undefined & precursor lesions have not been identified.
- Mutations in E-cadherin, which are not detectable in intestinal-type cancers, are present in 50% of diffuse cancers.
- A subset of patients may have a hereditary form of diffuse gastric ca. caused by germ-line mutation in E-cadherin.

- Amplification of HER-2/NEU & increased expression of β-catenin

- are present in 20% to 30% of intestinal-type adenoca cases

- are absent in diffuse- type ca.

- Mutations in FGFR2, & increased expression of metalloproteinases

- are present in about 1/3 of diffuse type cases,

- but are absent in intestinal type ca.

**Risk Factors for Gastric Carcinoma**

## (I) Intestinal-Type Adenocarcinoma

**1**-Chronic gastritis with intestinal metaplasia

**2**-Helicobacter pylori infection

**3**-Nitrites derived from nitrates may undergo nitrosation to form nitrosamines & nitrosamides.

(found in drinking water, food & used as preservatives in prepared meats)

Diets containing foods that may generate nitrites (smoked foods, pickled vegetables & excessive salt intake)

**4**-Decreased intake of fresh vegetables & fruits

(antioxidants present in these foods may inhibit nitrosation)

**5**-Partial gastrectomy

**6**-Pernicious anemia

## (II) Diffuse Carcinoma

-Undefined risk factors, except for a rare inherited mutation of E-cadherin

- Infection with H. pylori & chronic gastritis are often absent