

STOMACH

Chronic Gastritis

- The presence of chronic inflammatory changes in the mucosa leading eventually to mucosal atrophy and epithelial metaplasia.
- In the Western world the prevalence of chronic gastritis is higher than 50% in the later decades of life.

Pathogenesis

- The most important etiologic association is chronic infection by the bacillus *H. pylori*.
- This organism is a worldwide pathogen that has the highest infection rates in developing countries.
- Prevalence rates approaching 50% is seen in American adults older than age 50.
- In areas where the infection is endemic it is acquired in childhood and persists for decades.
- ***Most individuals with the infection also have the associated gastritis but are asymptomatic.***

- (Robin Warren, a pathologist, and Barry Marshall, a medical student at the time of the discovery, received the 2005 Nobel prize in Medicine for their identification in 1982 of *H. pylori*, originally called *Campylobacter*.)

Types of gastritis

- **(1) antral-type**
- **(2) pangastritis**
- **(3) autoimmune**

- *H. pylori* is a noninvasive, non-spore-forming, S-shaped gram-negative rod measuring approximately $3.5 \mu\text{m} \times 0.5 \mu\text{m}$.
- After initial exposure to *H. pylori*, gastritis may develop in two patterns:
- **(1) an antral-type** with high acid production and higher risk for the development of duodenal ulcer
- **(2) a pangastritis** with multifocal mucosal atrophy with low acid secretion and increased risk for adenocarcinoma.

- Chronic gastritis due to *H. pylori* usually improve symptomatically when treated with antibiotics and proton pump inhibitors.
- Improvement in the underlying chronic gastritis may take much longer.
- Relapses are associated with reappearance of this organism.

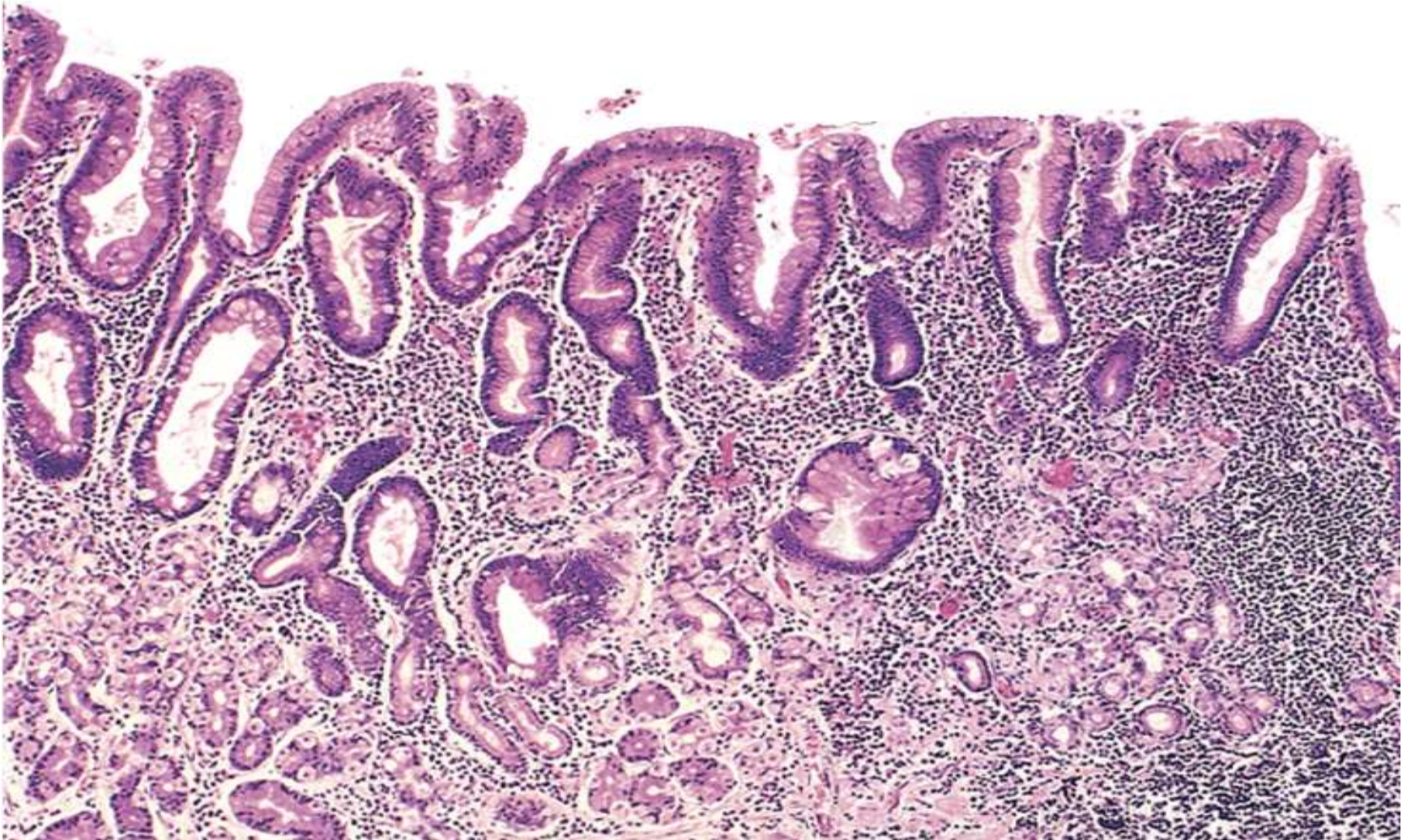
- **(3) Autoimmune gastritis**
- **10% of cases of chronic gastritis**
- **results from the production of autoAbs to the gastric gland parietal cells, in particular to the acid-producing enzyme H⁺,K⁺-ATPase.**
- **The autoimmune injury leads to gland destruction and mucosal atrophy with concomitant loss of acid and intrinsic factor production.**
- **The resultant deficiency of intrinsic factor leads to *pernicious anemia*.**
- **This form of gastritis is seen most often in Scandinavia in association with other autoimmune disorders such as Hashimoto thyroiditis and Addison disease.**

Morphology

- lymphocytic and plasma cell infiltrate in the lamina propria
- Occasionally neutrophilic inflammation of the neck region of the mucosal pits.
- The inflammation may be accompanied by variable gland loss and mucosal atrophy.
- *H. pylori* organisms are found nestled within the mucus layer overlying the superficial mucosal epithelium .
- In the autoimmune variant, loss of parietal cells is particularly prominent.

- **Intestinal metaplasia** refers to the replacement of gastric epithelium with columnar and goblet cells of intestinal variety.
- This is significant, because gastrointestinal-type carcinomas seem to arise from **dysplasia** of this metaplastic epithelium.
- *H. pylori*-induced proliferation of **lymphoid tissue** within the gastric mucosa has been implicated as a precursor of gastric lymphoma.

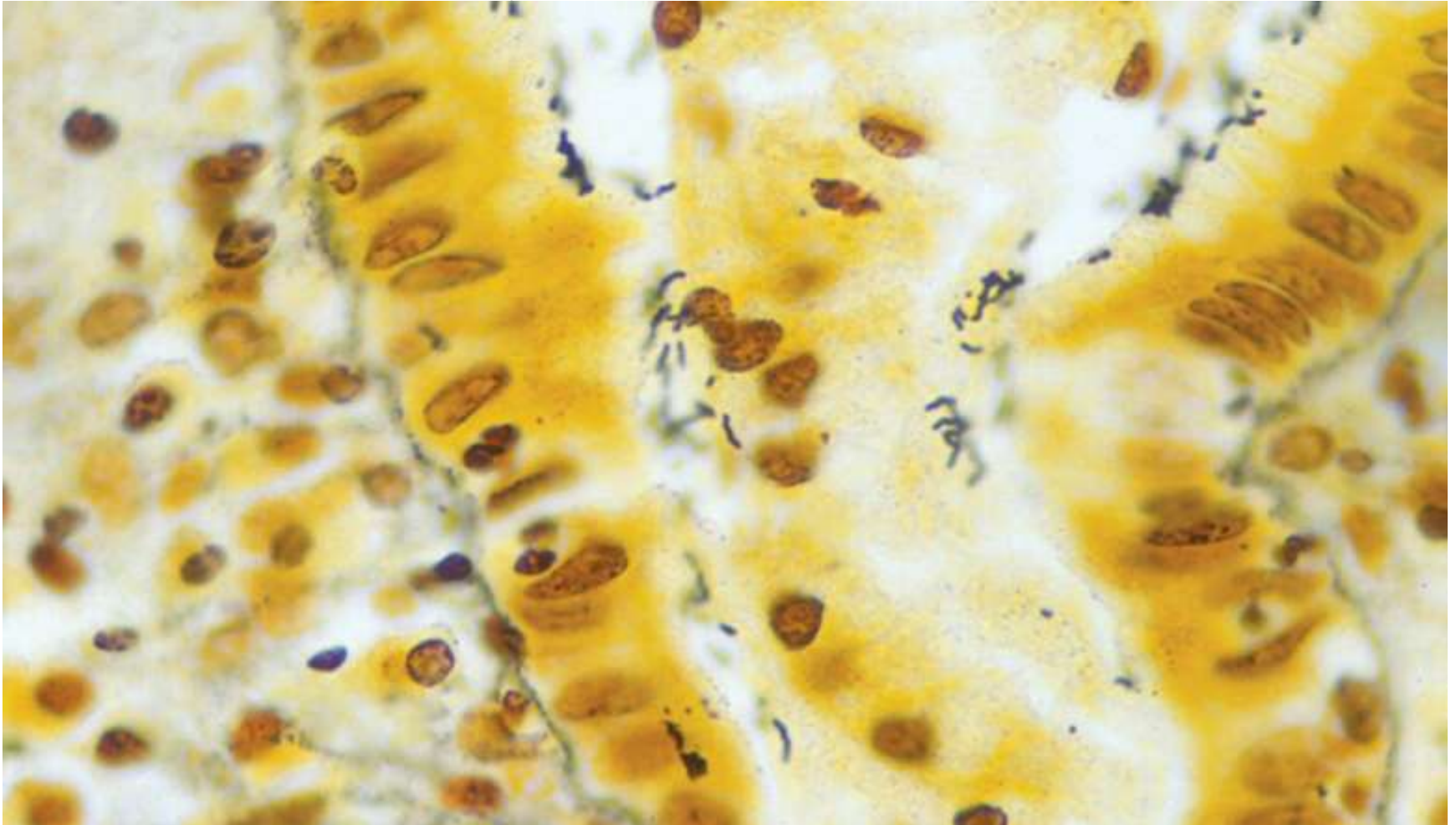
Chronic gastritis
intestinal metaplasia
inflammation of the lamina propria containing lymphocytes and plasma cells



***Helicobacter pylori* gastritis.**

numerous darkly stained *Helicobacter* organisms along the luminal surface of the gastric epithelial cells (silver stain)

There is no tissue invasion by bacteria



Clinical Features

- Asymptomatic
- upper abdominal discomfort and nausea and vomiting.
- hypochlorhydria or achlorhydria
- hypergastrinemia
- Individuals with chronic gastritis from other causes may be hypochlorhydric, but because parietal cells are never completely destroyed, these persons do not develop achlorhydria or pernicious anemia.
- Serum gastrin levels are either normal or only modestly elevated.

- Most important is the risk of the development of peptic ulcer and gastric carcinoma.
- The long-term risk of gastric carcinoma for persons with *H. pylori*-associated chronic gastritis is increased about 5X.
- For autoimmune gastritis, the risk for cancer is in the range of 2-4% of affected individuals.

Acute Gastritis

- *It is an acute mucosal inflammatory process, usually of a transient nature.*
- The inflammation may be accompanied by hemorrhage into the mucosa and in more severe circumstances by sloughing of the superficial mucosal epithelium (*erosion*).
- The severe erosive form of the disease is an important cause of acute gastrointestinal bleeding.

Pathogenesis

- **is frequently associated with:**
- **1-Heavy use of nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin**
- **2-Excessive alcohol consumption**
- **3-Heavy smoking**
- **4-Treatment with cancer chemotherapeutic drugs**
- **5-Uremia**
- **6-Systemic infections (e.g., salmonellosis)**
- **7-Severe stress (e.g., trauma, burns, surgery)**
- **8-Ischemia and shock**
- **9-Suicide attempts with acids and alkali**
- **10-Mechanical trauma (e.g., nasogastric intubation)**
- **11-Reflux of bilious material after distal gastrectomy**

Clinical Features

- **Asymptomatic**
- **Variable epigastric pain with nausea and vomiting**
- **Overt hematemesis, melena, and potentially fatal blood loss.**
- ***Hematemesis, particularly in alcoholics.***
- **25% of persons who take daily aspirin for rheumatoid arthritis develop acute gastritis at some time in their course, many with occult or overt bleeding.**
- **The risk of gastric bleeding from NSAID-induced gastritis is dose related.**

GASTRIC ULCERATION

- Ulcers of the alimentary tract are defined histologically as a breach in the mucosa that extends through the muscularis mucosae into the submucosa or deeper.
- Erosions is a breach in the epithelium of the mucosa only.
- Erosions may heal within days whereas healing of ulcers takes much longer.
- Ulcers may occur anywhere in the alimentary tract
- The most common sites of peptic ulcers are in the duodenum and stomach.

Peptic Ulcers

- chronic, most often solitary, lesions that occur in any portion of the gastrointestinal tract exposed to the aggressive action of acidic peptic juices.
- 98% of peptic ulcers are either in the first portion of the duodenum or in the stomach (ratio of about 4:1).

Epidemiology

- **In the American population 6-14% of males and 2- 6% of females have peptic ulcers.**
- **Middle-aged to older adults.**
- **They often appear without obvious precipitating influences and may then heal after a period of weeks to months of active disease.**
- ***Even with healing peptic ulcers can recur because of recurrent infection with H. pylori.***

- The M:F ratio for duodenal ulcers is about 3:1.
- For both men and women in the United States the lifetime risk of developing peptic ulcer disease is about 10%.

- Genetic or racial influences seem to have little or no role in the causation of peptic ulcers.
- Duodenal ulcers are more frequent in persons with:
 - 1- alcoholic cirrhosis
 - 2- chronic obstructive pulmonary disease
 - 3- chronic renal failure
 - 4- hyperparathyroidism
 - 5- hypercalcemia

Pathogenesis

- Two conditions are key for the development of peptic ulcers:
- (1) *H. pylori* infection which has a strong causal relationship with peptic ulcer development
- (2) mucosal exposure to gastric acid and pepsin

- It is best perhaps to consider that peptic ulcers are created by an imbalance between the gastroduodenal mucosal defenses and the damaging forces that overcome such defenses .

- **Causes of peptic ulceration:**
- **1-H.pylori infection**

- ***H. pylori* infection is the most important condition in the pathogenesis of peptic ulcer.**
- **The infection is present in 70-90% of persons with duodenal ulcers and in about 70% of those with gastric ulcers.**
- **Antibiotic treatment of *H. pylori* infection promotes healing of ulcers and tends to prevent their recurrence.**

- ***H. pylori* does not invade the tissues but it induces an intense inflammatory and immune response.**
- **There is increased production of proinflammatory cytokines such as interleukin (IL)-1, IL-6, TNF most notably, IL-8.**
- **IL-8 is produced by the mucosal epithelial cells, and it recruits and activates neutrophils.**
- **Several bacterial gene products are involved in causing epithelial cell injury and induction of inflammation.**

- **Epithelial injury is mostly caused by a vacuolating toxin called VacA, which is regulated by the cytotoxin-associated gene A (*CagA*).**
- **This gene is a component of the *Cag* pathogenicity island, a cluster of 29 genes, some of which encode pro-inflammatory proteins.**
- ***H. pylori* secretes a urease that breaks down urea to form toxic compounds such as ammonium chloride and monochloramine.**

- The organisms also elaborate **phospholipases** that damage surface epithelial cells .
- Bacterial proteases and phospholipases break down the glycoprotein-lipid complexes in the gastric mucus thus weakening the first line of mucosal defense.
- *H. pylori* **enhances gastric acid** secretion and impairs duodenal bicarbonate production thus reducing luminal pH in the duodenum.
- Gastric metaplasia in the first part of the duodenum.
- The metaplastic foci provide areas for *H. pylori* colonization.

- *H. pylori* proteins are immunogenic and they evoke a robust immune response in the mucosa.
- Both activated T cells and B cells can be seen in chronic gastritis caused by *H. pylori*.
- The B lymphocytes aggregate to form follicles.
- T-cell-driven activation of B cells may be involved in the pathogenesis of gastric lymphomas .

- Only 10-20% of individuals worldwide who are infected with *H. pylori* actually develop peptic ulcer.
- Perhaps there are interactions between *H. pylori* and the mucosa that occur only in some individuals.
- Strains producing VacA and CagA cause more intense tissue inflammation, more severe epithelial damage, and higher cytokine production.

- **2-NSAID**

- ***NSAIDs are the major cause of peptic ulcer disease in persons who do not have *H. pylori* infection.***
- **The gastroduodenal effects of NSAIDs range from acute erosive gastritis and acute gastric ulceration to peptic ulceration in 1-3% of users.**

- **Risk factors for NSAID-induced gastroduodenal toxicity are:**
- **1- increasing age**
- **2- higher dose**
- **3- prolonged usage.**

- Suppression of mucosal prostaglandin synthesis, which increases secretion of hydrochloric acid and reduces bicarbonate and mucin production.
- Loss of mucin degrades the mucosal barrier that normally prevents acid from reaching the epithelium.
- Synthesis of glutathione (free-radical scavenger) is reduced.

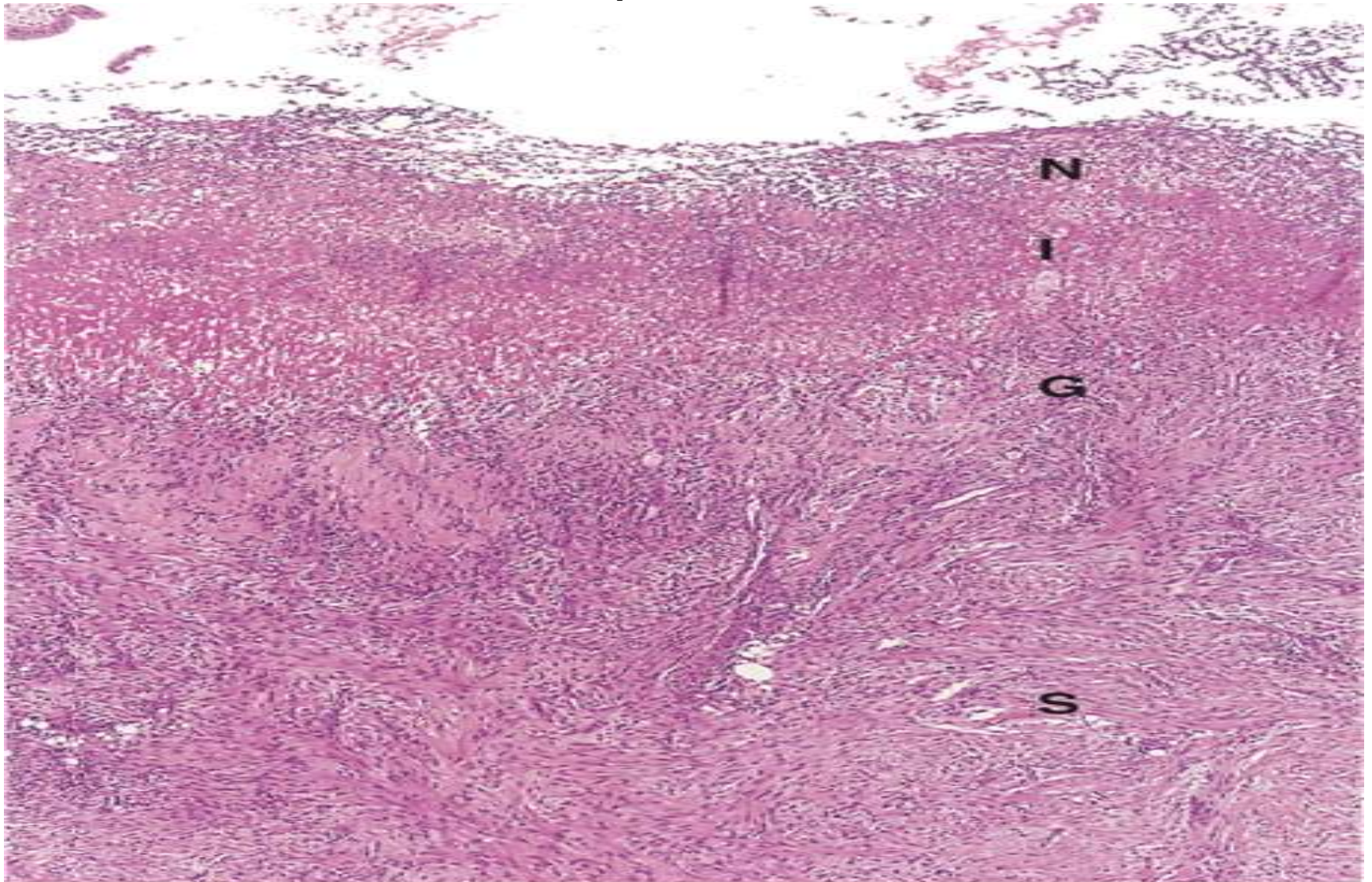
- **3-Gastric hyperacidity**
- Excess production of gastric acid from a tumor in individuals with the *Zollinger-Ellison syndrome* causes multiple peptic ulcerations in the stomach, duodenum, and even the jejunum.
- **4-Cigarette smoking** impairs mucosal blood flow and healing.
- Alcohol has not been proved to directly cause peptic ulceration, but alcoholic cirrhosis is associated with an increased incidence of peptic ulcers.
- **5-Corticosteroids in high dose** and with repeated use promote ulcer formation.
- **6-personality and psychological stress** are important contributing variables.

Peptic ulcer of the duodenum. Note that the ulcer is small with a sharply punched-out appearance. The margins are not elevated.

The ulcer base is clean



the base of a nonperforated peptic ulcer, demonstrating the layers of necrosis (N), inflammation (I), granulation tissue (G), scar (S) moving from the luminal surface at the top to the muscle wall at the bottom.



Clinical Features

- Epigastric pain.
- The pain tends to be worse at night.
- It occurs usually 1-3 hours after meals during the day.
- The pain is relieved by alkalis or food.
- Nausea, vomiting, bloating, belching
- significant weight loss

Complications

- 1-**Bleeding** is the chief complication, occurring in 33%.
- 2-**Perforation** occurs in about 5% of patients but accounts for two-thirds of deaths from this disease in the United States.
- 3-**Obstruction** of the pyloric channel is rare.
- 4-**Malignant transformation**
- occurs in about 2% of patients
- ulcers in the pyloric channel, and is very rare with gastric ulcers.

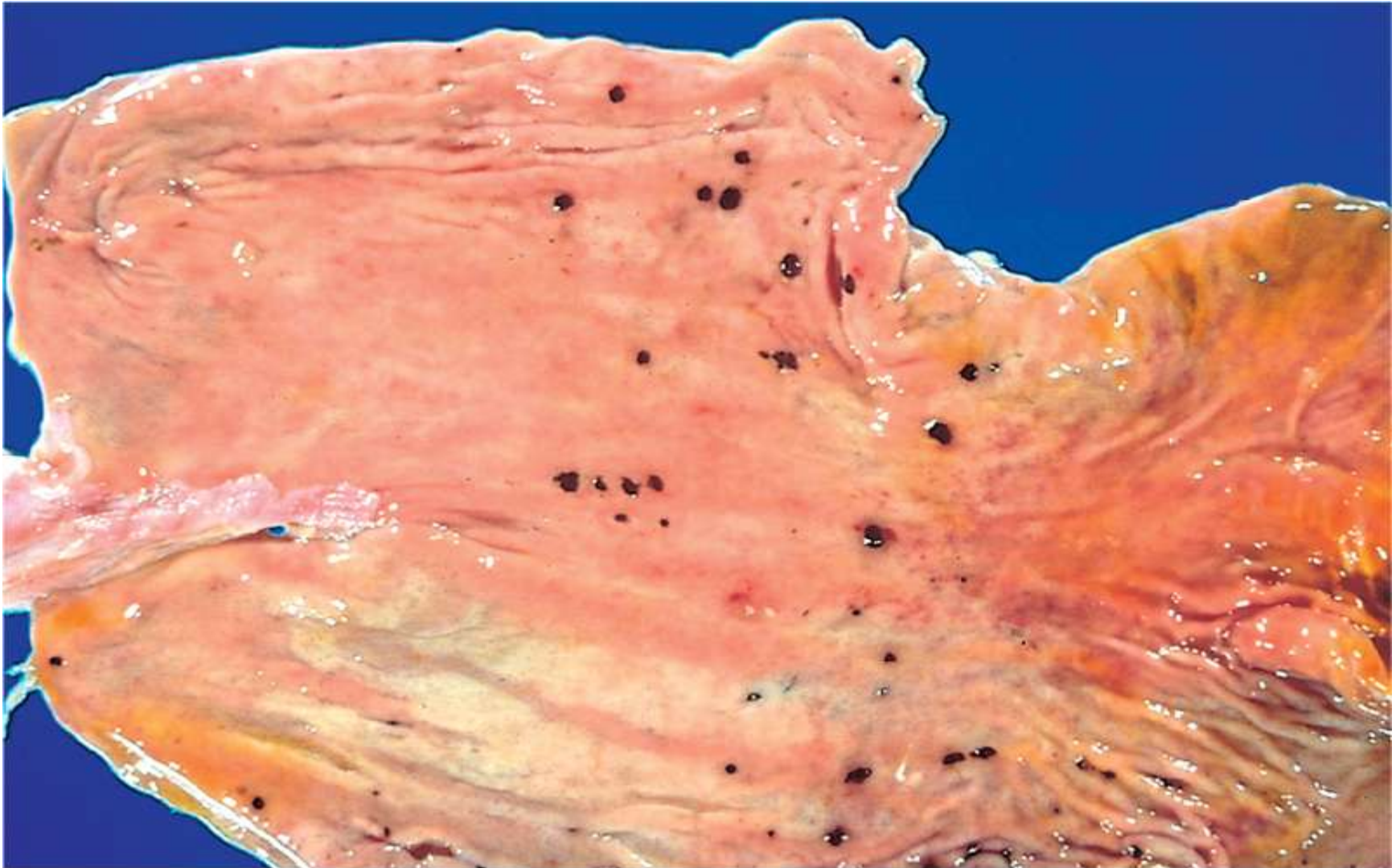
Acute Gastric Ulceration

- **Stress ulcers**
- Focal, acutely developing gastric mucosal defects that may appear after severe physiologic stress
- Multiple lesions located mainly in the stomach and occasionally in the duodenum.
- **Causes :**
- 1-Severe trauma, including major surgical procedures
- 2-sepsis
- 3-shock
- 4-grave illness of any type
- 5-chronic exposure to gastric irritant drugs, particularly NSAIDs and corticosteroids
- 6-extensive burns (Curling ulcers)
- 7-traumatic or surgical injury to the CNS or an intracerebral hemorrhage (Cushing ulcers).

Pathogenesis

- NSAID-induced ulcers are linked to decreased PG production.
- The systemic acidosis that can accompany severe trauma and 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 increased intracranial pressure may cause gastric acid hypersecretion which is common in these patients.

Multiple stress ulcers of the stomach showing dark digested blood in their bases



GASTRIC TUMORS

- Gastric Polyps

- *The term polyp is applied to any nodule or mass that projects above the level of the surrounding mucosa.*
- A lipoma or leiomyoma arising in the wall of the stomach may protrude from under the mucosa to produce an apparent polypoid lesion.
- *the term **polyp** in the gastrointestinal tract is generally restricted to mass lesions arising in the mucosa.*
- Gastric polyps are uncommon and are found in about 0.4% of adult autopsies

- **Types of gastric polyps:**
- (1) hyperplastic polyps (80% to 85%)
- (2) fundic gland polyps (~10%)
- (3) adenomatous polyps (~5%)

- All three types arise in the setting of chronic gastritis and so are seen in the same patient populations.
- Hyperplastic and fundic gland polyps are essentially innocuous.
- There is a definite risk of an adenomatous polyp harboring adenocarcinoma, which increases with polyp size.

Gastric Malignant tumors

- **1-Carcinoma (90% to 95%).**
- **2-lymphomas (4%)**
- **3-Carcinoids (3%)**
- **4-Stromal tumors (2%).**

Gastric Carcinoma

- **Gastric carcinoma is the 2nd leading cause of cancer-related deaths in the world**
- **Japan and South Korea have the highest incidence (8-9X higher than in the United States and Western Europe .**
- **The incidence in China and Chile and Costa Rica is also high.**
- **The 5-year survival rate is < 20%.**

- **Morphological types :**
- **1- *intestinal***
- **2- *diffuse.***

- ***The incidence of intestinal-type carcinoma has progressively diminished in the United States.***
- ***The incidence of diffuse gastric carcinoma has not significantly changed in the past 60 years and now constitutes approximately half of gastric carcinomas in the United States.***

Intestinal type gastric carcinoma

- **Arise from gastric mucous cells that have undergone intestinal metaplasia in the setting of chronic gastritis.**
- **This pattern of cancer tends to be better differentiated and is the more common type in high-risk populations.**
- **Occurs primarily after age 50 years**
- **M:F 2 : 1**

RISK FACTORS

- **1-Chronic gastritis with intestinal metaplasia.**
- **2-Infection with *Helicobacter pylori*.**
- **3-Nitrites derived from nitrates (found in food and drinking water and used as preservatives in prepared meats may undergo nitrosation to form nitrosamines and nitrosamides)**
- **4-Diets containing foods that may generate nitrites (smoked foods, pickled vegetables and excessive salt intake)**

- **5-Decreased intake of fresh vegetables and fruits (antioxidants present in these foods may inhibit nitrosation).**
- **6-Partial gastrectomy.**
- **7-Pernicious anemia.**
- **8-Amplification of *HER-2/NEU* and increased expression of β -catenin (in 20-30% of cases).**

Diffuse variant gastric carcinoma

- **Arise de novo from native gastric mucous cells.**
- **It is not associated with chronic gastritis and tends to be poorly differentiated.**
- **Occurs at an earlier age.**
- **F>M with female predominance.**

- Risk factors **undefined**, except for rare Inherited mutation of E-cadherin (50%).
- Infection with *H. pylori* and chronic gastritis often absent.
- Amplification of *HER-2/NEU* and increased expression of β -catenin are absent.
- Mutations in *FGFR2* and increased expression of metalloproteinases are present in ~1/3 of cases (absent in intestinal type) .

Clinical features

- Location :
- pylorus and antrum, 50- 60%.
- cardia, 25%.
- body and fundus 15 - 25 %
- Lesser curvature is involved in about 40%
- The greater curvature is involved in 12%.
- **The favored location is the lesser curvature of the antropyloric region.**
- An ulcerative lesion on the greater curvature is more likely to be malignant than benign.

- The morphologic feature having the greatest impact on clinical outcome is the **depth of invasion**.
- **Early gastric carcinoma** is defined as a lesion confined to the mucosa and submucosa regardless of the presence or absence of perigastric lymph node metastases.
- **Advanced gastric carcinoma** is a neoplasm that has extended below the submucosa into the muscular wall and has perhaps spread more widely.
- Gastric mucosal **dysplasia** is the presumed precursor lesion of early gastric cancer.

The macroscopic growth patterns

- Evident at both the early and advanced stages :
- (1) **exophytic**, with protrusion of a tumor mass into the lumen.
- (2) **flat or depressed**, in which there is no obvious tumor mass within the mucosa.
- (3) **excavated**, a shallow or deeply erosive crater is present in the wall of the stomach.

- (4) **linitis plastica** a broad region of the gastric wall, or the entire stomach, is extensively infiltrated by malignancy.
- The rigid and thickened stomach is termed a **leather bottle** stomach.

- Exophytic tumors may contain portions of an adenoma.
- Flat or depressed malignancy presents only as regional effacement of the normal surface mucosal pattern.
- Excavated cancers may mimic in size and appearance chronic peptic ulcers but may show heaped-up margins

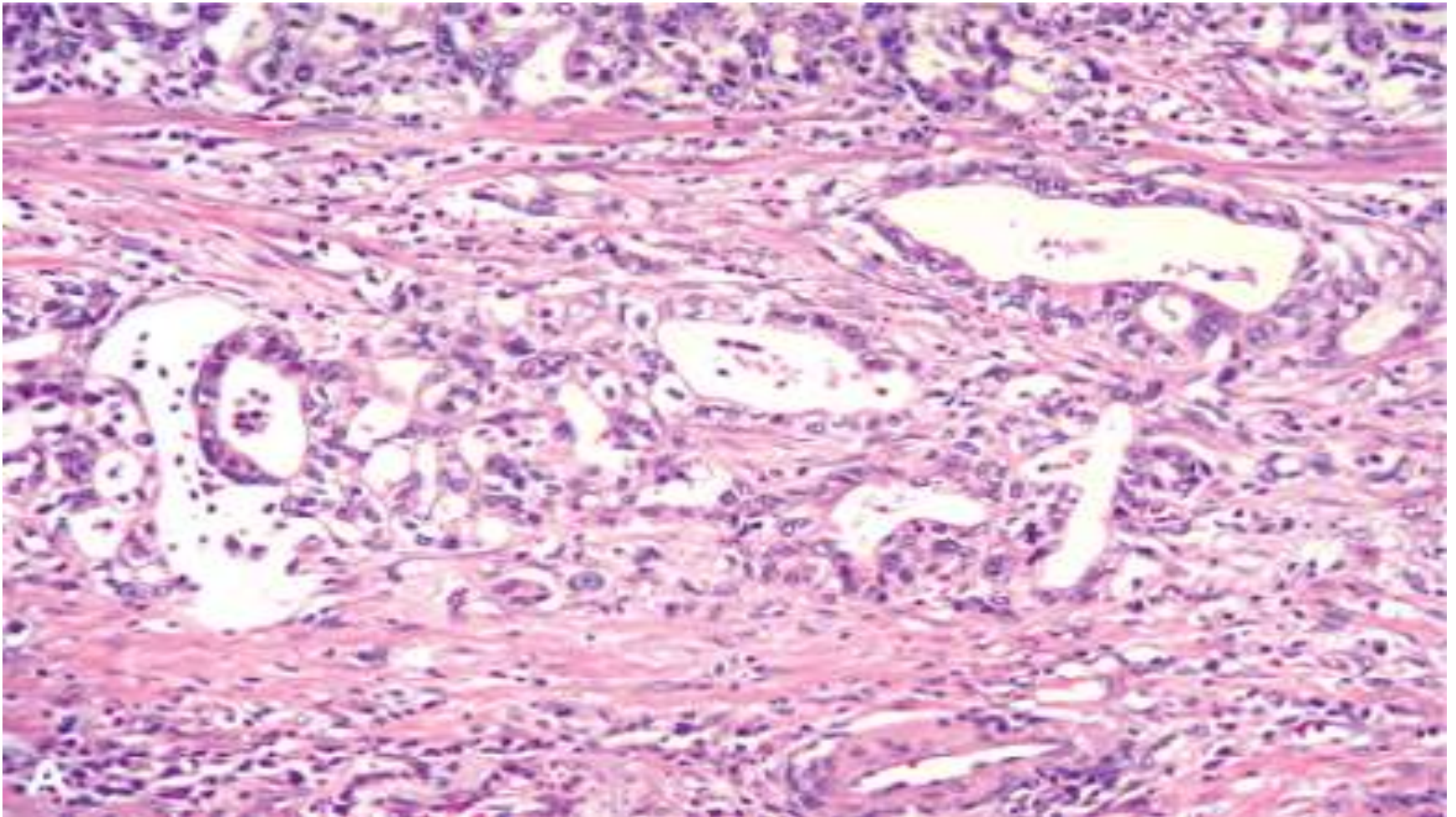
- Whatever the histologic variant, all gastric carcinomas eventually penetrate the wall to involve the serosa, spread to regional and more distant lymph nodes, and metastasize widely.
- The earliest lymph node metastasis may sometimes involve a supraclavicular lymph node (**Virchow node**).
- Intraperitoneal spread in females is to both the ovaries, giving rise to the so-called **Krukenberg tumor** .

Ulcerative gastric carcinoma.

The ulcer is large with irregular, heaped-up margins. There is extensive excavation of the gastric mucosa with a necrotic gray area in the deepest portion



intestinal type of gastric carcinoma with gland formation by malignant cells that are invading the muscular wall of the stomach



Diffuse type of gastric carcinoma with signet-ring tumor cells.

