CHAPTER FIVE
PATHOLOGY OF THE GIT

Objectives:
Upon successful completion of this lectures, students should be able to:

- Identify and describe the major disease processes including, inflammation, neoplasm and malabsorption conditions affecting different organs of GIT (oral cavity, esophagus, stomach, small and large intestine) in terms of, etiology pathogenesis, gross and microscopic changes, manifestations, and complications.
- Identify various bacterial, viral, fungal, and parasitic infections affecting GIT, and describe the principle manifestations, diagnosis, treatment, and prevention of each individual microorganism and parasitic agent affecting GIT.

THE ORAL CAVITY & OROPHARYNX
Many pathological processes can affect the constituents of the oral cavity. The more important and frequent conditions will covered in this lecture. Diseases involving the teeth and related structures will not be discussed.

PROLIFERATIVE LESIONS
The most common proliferative lesions of the oral cavity are
1. Irritation Fibroma and Ossifying fibroma
2. Ossifying fibroma
3. Pyogenic granuloma
4. Peripheral giant cell granuloma

**Irritation fibroma** is a nodular mass of fibrous tissue that occurs mainly in the buccal mucosa along the bite line & gingivo-dental margin. ([Fig. 5-2](#))

**Ossifying fibroma** is a common growth of the gingiva. Some may be due to maturation of a long-standing pyogenic granuloma.

**Pyogenic granuloma (granuloma pyogenicum)** is a highly vascular lesion that is usually seen in the gingiva of children, young adults, and pregnant women (*pregnancy tumor*). The lesion is typically ulcerated and bright red in color (due to rich vascularity) ([Fig. 5-3](#)). **Microscopically** there is vascular proliferation similar to that of granulation tissue. ([Fig. 5-3](#)) They lesion either regresses (particularly after pregnancy), or undergoes fibrous maturation and may develop into ossifying fibroma.

**Peripheral giant cell granuloma (giant cell epulis)** is a relatively common lesion that characteristically protrudes from the gingiva at sites of chronic inflammation. It is so named because microscopically there are aggregates of multinucleate giant cells separated by a fibro-vascular stroma. ([Fig. 5-4](#))

INFLAMMATORY CONDITIONS

**Inflammatory ulcerations**
The most common inflammatory ulcerations of the oral cavity are
1. Traumatic
2. Aphthous
3. Herpetic

**Traumatic ulcers**, usually the result of trauma (e.g. fist fighting) or licking a jagged tooth.

**Aphthous ulcers** are extremely common, single or multiple, painful, recurrent, superficial, ulcerations of the oral mucosa. The ulcer is covered by a thin yellow exudate and rimmed by a narrow zone of erythema. ([Fig. 5-5](#))

**Herpetic ulcers** (see under herpes simplex infection)

**Glossitis**
This is inflammation of the tongue, but sometimes it is also applied to the beefy-red tongue that occurs in certain deficiency states. The latter is the result of atrophy of the papillae and thinning of the mucosa, thus exposing the underlying vasculature. ([Fig. 5-6](#)) However, in some instances, the atrophy leads to inflammation (and even shallow ulcerations). Examples of such deficiency states that include
1. Vitamin B12 (pernicious anemia),
2. Riboflavin
3. Niacin
4. Pyridoxine
5. Iron-deficiency anemia

**Plummer-Vinson syndrome** is a combination of
1. Iron-deficiency anemia
2. Glossitis
3. Esophageal dysphagia (due to esophageal webs)

Glossitis (with ulcerations) may also be seen with
- Jagged carious teeth
- Ill-fitting dentures
- Exposure to hot fluids or corrosive chemicals
- Inhalation of burn fumes including excessive smoking
- Syphilis

**INFECTIONS**

1. **Herpes simplex infections**
   Most of these are caused by herpes simplex virus (HSV) type 1 & sometimes 2. Primary HSV infection typically occurs in children aged 2 to 4 years; is often asymptomatic, but sometime presents as acute herpetic gingivostomatitis, characterized by vesicles and ulcerations throughout the oral cavity. The great majority of affected adults harbor latent HSV-1 (the virus migrates along the regional nerves and eventually becomes dormant in the local ganglia e.g., the trigeminal). In some individuals, usually young adults, the virus becomes reactivated to produce the common but usually mild cold sore. (Fig. 5-7)

Factors activating the virus include
1. Trauma
2. Allergies
3. Exposure to ultraviolet light (sunlight)
4. Upper respiratory tract infections

The viral infection is associated with intracellular and intercellular edema, yielding clefts that may become transformed into vesicles. The vesicles range from a few millimeters to large ones that eventually rupture to yield extremely painful, red-rimmed, shallow ulcerations.

2. **Other Viral Infections**
   These include - Herpes zoster - EBV (infectious mononucleosis) - CMV - Enterovirus - Measles

3. **Oral Candidiasis (thrush)**
   This is the most common fungal infection of the oral cavity. The thrush is a grayish white, superficial, inflammatory pseudomembrane composed of the fungus enmeshed in a fibrino-suppurative exudates. (Fig. 5-8) This can be readily scraped off to reveal an underlying red inflammatory base. The fungus is a normal oral flora but causes troubles only
1. In the setting of immunosuppression (e.g. diabetes mellitus, organ or bone marrow transplant recipients, neutropenia, cancer chemotherapy, or AIDS) or
2. When broad-spectrum antibiotics are taken; these eliminate or alter the normal bacterial flora of the mouth.
3. In infants, where the condition is relatively common, presumably due to immaturity of the immune system in them.

4. **Deep Fungal Infections**
   Some fungal infections may extend deeply to involve the muscles & bones in relation to oral cavity. These include, among others, histoplasmosis, blastomycosis, and aspergillosis. The incidence of such infections has been increasing due to increasing number of patients with AIDS, therapies for cancer, & organ transplantation

5. **Diphtheria:** characterized grossly by dirty white, fibrino-suppurative, tough, inflammatory pseudomembrane over tonsils & posterior pharynx. (Fig. 5-9)
Many systemic diseases are associated with oral lesions & it is not uncommon for oral lesions to be the first manifestation of some underlying systemic condition.

1. Scarlet fever: strawberry tongue: white coated tongue with hyperemic papillae projecting (Fig. 5-10)
2. Measles: Koplik spots: small whitish ulcerations (spots) on a reddened base, about Stensen duct (Fig. 5-11)
3. Diphtheria: dirty white, fibrinosuppurative, tough pseudomembrane over the tonsils and retropharynx
4. AIDS
   a. opportunistic oral infections: herpesvirus, Candida, other fungi
   b. Kaposi sarcoma (Fig. 5-12)
   c. hairy leukoplakia
5. AML (especially monocytic leukemia): enlargement of the gingivae + periodontitis (Fig. 5-13)
6. Melanotic pigmentation (Fig. 5-14)
   a. Addison disease
   b. hemochromatosis
   c. fibrous dysplasia of bone
   d. Peutz-Jegher syndrome
7. Pregnancy: pyogenic granuloma ("pregnancy tumor")

Hairy Leukoplakia
Approximately 80% of patients with hairy leukoplakia have been infected with HIV; the remaining 20% are seen in association with other immunodeficiency states. The condition presents as a white fluffy ("hairy") patches that are situated on the lateral border of the tongue. (Fig. 5-15) EBV is now accepted as the cause of the condition. When hairy leukoplakia precedes HIV infection, manifestations of AIDS generally appear within 2 or 3 years.

TUMORS AND PRECANCEROUS LESIONS
Many of the oral cavity tumors (e.g., papillomas, hemangiomas, lymphomas) are not different from their homologous tumors elsewhere in the body. Here we will consider only oral squamous cell carcinoma and its associated precancerous lesions.

Leukoplakia and Erythroplakia are considered premalignant lesions of squamous cell carcinoma.

Leukoplakia (Fig. 5-16) is a white patch that cannot be scraped off and cannot be attributed clinically or microscopically to any other disease i.e. if a white lesion in the oral cavity can be given a specific diagnosis it is not a leukoplakia. As such, white patches caused by entities such as candidiasis are not leukoplakias. All leukoplakias must be considered precancerous (have the potential to progress to squamous cell carcinoma) until proved otherwise through histologic evaluation.

Erythroplakias (Fig. 5-17) are red velvety patches that are much less common, yet much more serious than leukoplakias. The incidence of dysplasia and thus the risk of complicating squamous cell carcinoma is much more frequent in erythroplakia compared to leukoplakias.
Both leukoplakia and erythroplakia are usually found between ages of 40 and 70 years, and are much more common in males than females. The use of tobacco (cigarettes, pipes, cigars, and chewing tobacco) is the most common incriminated factor.

Squamous cell carcinoma
The vast majority (95%) of cancers of the head and neck are squamous cell carcinomas; these arise most commonly in the oral cavity. The 5-year survival rate of early-stage oral cancer is approximately 80%, but this drops to about 20% for late-stage disease. These figures highlight the importance of early diagnosis & treatment, optimally of the precancerous lesions.
The pathogenesis of squamous cell carcinoma is multifactorial.
1. Chronic smoking and alcohol consumption
2. Oncogenic variants of human papilloma virus (HPV). It is now known that at least 50% of oropharyngeal cancers, particularly those of the tonsils and the base of tongue, harbor oncogenic variants of HPV.
3. Inheritance of genomic instability; a family history of head and neck cancer is a risk factor.
4. Exposure to actinic radiation (sunlight) & pipe smoking are known predisposing factors for cancer of the lower lip.

Gross features (Fig. 5-18 A)
Squamous cell carcinoma may arise anywhere in the oral cavity, but the favored locations are
1. The tongue 4. Soft palate
2. Floor of mouth 5. Gingiva
3. Lower lip
In the early stages, cancers of the oral cavity appear as roughened areas of the mucosa. As the lesion enlarges, it typically appears as either an ulcer or a protruding mass (fungating).

Microscopic features (Fig. 5-18 B)
- Early there is full-thickness dysplasia (carcinoma in situ) followed by invasion of the underlying connective tissue stroma.
- The grade varies from well-differentiated keratinizing to poorly differentiated.
As a group, these tumors tend to infiltrate and extend locally before they eventually metastasize to cervical lymph nodes and more remotely. The most common sites of distant metastasis are mediastinal lymph nodes, lung, liver and bones

SALIVARY GLANDS
There are three major salivary glands—parotid, submandibular, and sublingual. Additionally, there are numerous minor salivary glands distributed throughout the mucosa of the oral cavity.

Xerostomia refers to dry mouth due to a lack of salivary secretion; the causes include
1. Sjögren syndrome: an autoimmune disorder, that is usually also accompanied by involvement of the lacrimal glands that produces dry eyes (keratoconjunctivitis sicca).
2. Radiation therapy

Inflammation (Sialadenitis)
Sialadenitis refers to inflammation of a salivary gland; it may be
1. Traumatic
2. Infectious: viral, bacterial
3. Autoimmune
The most common form of viral sialadenitis is mumps, which usually affects the parotids. The pancreas and testes may also be involved.

Bacterial sialadenitis is seen as a complication of
1. Stones obstructing ducts of a major salivary gland (Sialolithiasis), particularly the submandibular. (Fig. 5-19)
2. Dehydration with decreased secretory function as is sometimes occurs in
   a. patients on long-term phenothiazines that suppress salivary secretion.
   b. elderly patients with a recent major thoracic or abdominal surgery. Unilateral involvement of a single gland is the rule and the inflammation may be suppurative. The inflammatory involvement causes painful enlargement and sometimes a purulent ductal discharge. Sjögren syndrome causes an immunolgically mediated sialadenitis i.e. inflammatory damage of the salivary tissues.

Mucocele
This is common salivary lesion results from interruption of salivary outflow due to blockage or rupture of a salivary gland duct. This leads to seepage of saliva into the surrounding tissues. The lower lip is the most common location due to exposure of this site to trauma (fist fighting, falling etc.). It presents as fluctuant swelling. Microscopically, there is accumulation of mucin with inflammatory cells. (Fig. 5-20)

Ranula is a mucocele of the sublingual gland; it may become extremely large.
NEOPLASMS OF SALIVARY GLANDS

Neoplasms of the salivary glands (benign and malignant) are generally uncommon, constituting less than 2% of human tumors. We will restrict our discussion on the more common examples.

The relative frequency distributions of these tumors in relation to various salivary glands are as follows:

<table>
<thead>
<tr>
<th>Salivary gland</th>
<th>Relative frequency of tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid gland</td>
<td>80%</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>10%</td>
</tr>
<tr>
<td>Minor salivary and sublingual glands</td>
<td>10%</td>
</tr>
</tbody>
</table>

The incidence of malignant tumors within the glands is, however, different from the above:

<table>
<thead>
<tr>
<th>Salivary gland affected</th>
<th>Relative frequency of malignant tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual tumors</td>
<td>80%</td>
</tr>
<tr>
<td>Minor salivary glands</td>
<td>50%</td>
</tr>
<tr>
<td>Submandibular glands</td>
<td>40%</td>
</tr>
<tr>
<td>Parotid glands</td>
<td>25%</td>
</tr>
</tbody>
</table>

These tumors usually occur in adults, with a slight female predominance. Excluded from this rule is Warthin tumor, which occurs much more frequently in males than in females. The benign tumors occur most often around the age of 50 to 60 years; the malignant ones tend to appear in older age groups. Neoplasms of the parotid produce distinctive swellings in front of, or below the ear. Clinically, there are no reliable criteria to differentiate benign from the malignant tumors; therefore, pathological evaluation is necessary. (Fig. 5-21)

Pleomorphic Adenomas (Mixed Salivary Gland Tumors)

These benign tumors commonly occur within the parotid gland (constitute 60% of all parotid tumors).

**Gross features (Fig. 5-22 A)**
- Most tumors are rounded, encapsulated masses.
- The cut surface is gray-white with myxoid and light blue translucent areas of chondroid.

**Microscopic features (Fig. 5-22 B)**
- The main constituents are a mixture of ductal epithelial and myoepithelial cells, and it is believed that all the other elements, including mesenchymal, are derived from the above cells (hence the name adenoma).
- The epithelial/myoepithelial components of the neoplasm are arranged as glands, strands, or sheets. These various epithelial/myoepithelial elements are dispersed within a background of loose myxoid tissue that may contain islands of cartilage-like islands and, rarely bone.
- Sometimes, squamous differentiation is present.
- In some instances, the tumor capsule is focally deficient allowing the tumor to extend as tongue-like protrusions into the surrounding normal tissue.

Enucleation of the tumor is, therefore, not advisable because residual foci (the protrusions) may be left behind and act as a potential source of multifocal recurrences. (Fig. 5-23) The incidence of malignant transformation increases with the duration of the tumor.

**Warthin Tumor** is the second most common salivary gland neoplasm. It is benign, arises usually in the parotid gland and occurs more commonly in males than in females. About 10% are multifocal and 10% bilateral. Smokers have a higher risk than nonsmokers for developing these tumors. **Grossly**, it is round to oval, encapsulated mass & on section display gray tissue with narrow cystic or cleft-like spaces filled with secretion. **Microscopically**, these spaces are lined by a double layer of neoplastic epithelial cells resting on a dense lymphoid stroma, sometimes with germinal centers. This lympho-epithelial lining frequently project into the spaces. The epithelial cells are oncocyes as evidenced by their eosinophilic granular cytoplasm (stuffed with mitochondria). (Fig. 5-24)

**Mucoepidermoid Carcinoma**

As the name indicates, these neoplasms are composed of variable mixtures of mucus-secreting cells (muco), and squamous cells (epidermoid). They are the most common form of primary malignant tumor of the salivary glands. They occur mainly in the parotids. Low-grade tumors may invade locally but do not metastasize. By contrast, high-grade neoplasms metastasize to distant sites in 30% of cases. **Grossly**, mucoepidermoid carcinomas are gray-white, infiltrative tumors that frequently show small, mucin-
containing cysts. *Microscopically*, there are cords, sheets, and cysts of squamous and mucous-secreting cells. (Fig. 5-25)

**Other Salivary Gland Tumors**
Two less common neoplasms worth brief description:

**Adenoid cystic carcinoma**: half of the cases are found in the minor salivary glands (in particular the palate). Although slow growing, they have a tendency to invade perineurial spaces and to recur. Eventually, 50% or more disseminate widely to distant sites such as bone, liver, and brain. *Microscopically*, they are composed of small cells having dark, compact nuclei and scant cytoplasm. These cells tend to be disposed in sieve-like (cribriform) patterns. The spaces between the tumor cells are often filled with a hyaline material thought to represent excess basement membrane. (Fig. 5-26)

**Acinic cell tumor** is composed of cells resembling the normal acinar cells (hence the name). Most arise in the parotids; the small remainder arises in the submandibular glands. On histologic examination, they reveal a variable architecture and cell morphology. Most characteristically, the cells have clear cytoplasm & are disposed in sheets, microcysts, glands, or papillae. About 10% to 15% of these neoplasms metastasize to lymph nodes. (Fig. 5-27)

**ESOPHAGUS**
The main functions of the esophagus are to 1. Conduct food and fluids from the pharynx to the stomach 2. Prevent reflux of gastric contents into the esophagus. These functions require motor activity coordinated with swallowing, i.e. wave of peristalsis, associated with relaxation of the LES in anticipation of the peristaltic wave. This is followed by closure of the LES after the swallowing reflex. Maintenance of sphincter tone (positive pressure relative to the rest of esophagus) is necessary to prevent reflux of gastric contents.

**CONGENITAL ANOMALIES**
Several congenital anomalies affect the esophagus including the presence of *ectopic* gastric mucosa & pancreatic tissues within the esophageal wall, *congenital cysts & congenital herniation* of the esophageal wall into the thorax. The latter is due to impaired formation of the diaphragm. *Atresia and fistulas* are uncommon but must be recognized & corrected early because they cause immediate regurgitation, suffocation & aspiration pneumonitis when feeding is attempted. In *atresia*, a segment of the esophagus is represented by only a noncanalized cord, with the upper pouch connected to the bronchus or the trachea and a lower pouch leading to the stomach. (Fig. 5-28)

**Webs, rings, and stenosis** (Fig. 5-29)

**Mucosal webs** are shelf-like, eccentric protrusions of the mucosa into the esophageal lumen. These are most common in the upper esophagus. The triad of upper esophageal web, iron-deficiency anemia, and glossitis is referred to as *Plummer-Vinson syndrome*. This condition is associated with an increased risk for postcricoid esophageal carcinoma.

**Esophageal rings** unlike webs are concentric plates of tissue protruding into the lumen of the distal esophagus. Esophageal webs and rings are encountered most frequently in women over age 40. Episodic dysphagia is the main symptom.

**Stenosis** consists of fibrous thickening of the esophageal wall. Although it may be congenital, it is more frequently the result of severe esophageal injury with inflammatory scarring, as from gastroesophageal reflux disease (GERD), radiation, scleroderma and caustic injury. Stenosis usually manifests as progressive dysphagia, at first to solid foods but eventually to fluids as well.

**LESIONS ASSOCIATED WITH MOTOR DYSFUNCTION** (Fig. 5-30)
Coordinated motor activity is important for proper function of the esophagus. The major entities that are caused by motor dysfunction of the esophagus are

1. **Achalasia**
2. **Hiatal hernia**
3. **Diverticula**
4. **Mallory-Weiss tear**
Achalasia

Achalasia means "failure to relax." It is characterized by three major abnormalities:
1. Aperistalsis (failure of peristalsis)
2. Increased resting tone of the LES
3. Icomplete relaxation of the LES in response to swallowing

In most instances, achalasia is an idiopathic disorder. In this condition there is progressive dilation of the esophagus above the persistently contracted LES. The wall of the esophagus may be of normal thickness, thicker than normal owing to hypertrophy of the muscular wall, or markedly thinned by dilation (when dilatation overruns hypertrophy). The mucosa just above the LES may show inflammation and ulceration. Young adults are usually affected and present with progressive dysphagia. (Fig. 5-31)

Complications of achalasia are
1. Aspiration pneumonitis of undigested food
2. Monilial esophagitis
3. Esophageal squamous cell carcinoma (about 5% of patients)
4. Lower esophageal diverticula

Lacerations (Mallory-Weiss Syndrome)

These refer to longitudinal tears at the GEJ or gastric cardia and are the consequence of severe retching or vomiting. They are encountered most commonly in alcoholics, since they are susceptible to episodes of excessive vomiting, but have been reported in persons with no history of vomiting or alcoholism. During episodes of prolonged vomiting, reflex relaxation of LES fails to occur. The refluxing gastric contents suddenly overcome the contracted musculature leading to forced, massive dilation of the lower esophagus with tearing of the stretched wall.

Pathological features
The linear irregular lacerations, which are usually found astride the GEJ or in the gastric cardia, are oriented along the axis of the esophageal lumen. The tears may involve only the mucosa or may penetrate deeply to perforate the wall. (Fig. 5-34) Infection of the mucosal defect may lead to inflammatory ulcer or to mediastinitis. Usually the bleeding is not profuse and stops without surgical intervention. Healing is the usual outcome. Rarely esophageal rupture occurs.

Esophageal Varices

Portal hypertension when sufficiently prolonged or severe induces the formation of collateral bypass veins wherever the portal and caval venous systems communicate. Esophageal varices refer to the prominent plexus of deep mucosal and submucosal venous collaterals of the lower esophagus subsequent to the diversion of portal blood through them through the coronary veins of the stomach. From the varices the blood is diverted into the azygos veins, and eventually into the systemic veins. Varices develop in 90% of cirrhotic patients. Worldwide, after alcoholic cirrhosis, hepatic schistosomiasis is the second most common cause of variceal bleeding.

Pathological features (Fig. 5-35)
The increased pressure in the esophageal plexus produces dilated tortuous vessels that are liable to rupture.
- Varices appear as tortuous dilated veins lying primarily within the submucosa of the distal esophagus and proximal stomach.
- The net effect is irregular protrusion of the overlying mucosa into the lumen. The mucosa is often eroded because of its exposed position.
- Variceal rupture produces massive hemorrhage into the lumen. In this instance, the overlying mucosa appears ulcerated and necrotic.

Rupture of esophageal varices usually produces massive hematemesis. Among patients with advanced liver cirrhosis, such a rupture is responsible for 50% of the deaths. Some patients die as a direct consequence of the hemorrhage (hypovolemic shock); others of hepatic coma triggered by the hemorrhage.
Esophagitis
This term refers to inflammation of the esophageal mucosa. It may be caused by a variety of physical, chemical, or biologic agents. **Reflux Esophagitis (Gastroesophageal Reflux Disease or GERD)** is the most important cause of esophagitis and signifies esophagitis associated with reflux of gastric contents into the lower esophagus. Many causative factors are involved, the most important is decreased efficacy of esophageal antireflux mechanisms, particularly LES tone. In most instances, no cause is identified. However, the following may be contributatory
   a. Central nervous system depressants including alcohol
   b. Smoking
   c. Pregnancy
   d. Nasogastric tube
   e. Sliding hiatal hernia
   f. hypothyroidism
   g. Systemic sclerosis
Any one of the above mechanism may be the primary cause in an individual case, but more than one is likely to be involved in most instances. The action of gastric juices is vital to the development of esophageal mucosal injury.

**Gross (endoscopic) features (Fig. 5-36 A)**
- These depend on the causative agent and on the duration and severity of the exposure.
- Mild esophagitis may appear grossly as simple hyperemia. In contrast, the mucosa in severe esophagitis shows confluent erosions or total ulceration into the submucosa.

**Microscopic features (Fig. 5-36 B)**
Three histologic features are characteristic:
1. Inflammatory cells including eosinophils within the squamous mucosa.
2. Basal cells hyperplasia
3. Extension of lamina propria papillae into the upper third of the mucosa.
The disease mostly affects those over the age of 40 years. The clinical manifestations consist of dysphagia, heartburn, regurgitation of a sour fluid into the mouth, hematemesis, or melena. Rarely, there are episodes of severe chest pain that may be mistaken for a "heart attack."

**The potential consequences of severe reflux esophagitis are**
1. Bleeding
2. Ulceration
3. Stricture formation
4. Tendency to develop Barrett esophagus

Barrett Esophagus (BE)
10% of patients with long-standing GERD develop this complication. BE is the single most important risk factor for esophageal adenocarcinoma. BE refers to columnar metaplasia of the distal squamous mucosa; this occurs in response to prolonged injury induced by refluxing gastric contents. Two criteria are required for the diagnosis of Barrett esophagus:
1. Endoscopic evidence of columnar lining above the GEJ
2. Histologic confirmation of the above in biopsy specimens.
The pathogenesis of Barrett esophagus appears to be due to a change in the differentiation program of stem cells of the esophageal mucosa. Since the most frequent metaplastic change is the presence of columnar cells admixed with goblet cells, the term "intestinal metaplasia" is used to describe the histological alteration.

**Gross features**
- Barrett esophagus is recognized as a red, velvety mucosa located between the smooth, pale pink esophageal squamous mucosa and the light brown gastric mucosa.
- It is displayed as tongues, patches or broad circumferential bands replacing the squamocolumnar junction several centimeters. **(Fig. 5-37 A)**
Microscopic features
• the esophageal squamous epithelium is replaced by metaplastic columnar epithelium, including interspersed goblet cells, & may show a villous pattern (as that of the small intestine hence the term intestinal metaplasia). (Fig. 5-37 B)
• Critical to the pathologic evaluation of patients with Barrett mucosa is the search for dysplasia within the metaplastic epithelium. This dysplastic change is the presumed precursor of malignancy (adenocarcinoma). Dysplasia is recognized by the presence of cytologic and architectural abnormalities in the columnar epithelium, consisting of enlarged, crowded, and stratified hyperchromatic nuclei with loss of intervening stroma between adjacent glandular structures. Depending on the severity of the changes, dysplasia is classified as low-grade or high-grade.
• Approximately 50% of patients with high-grade dysplasia may already have adjacent adenocarcinoma.

Other causes of esophagitis
In addition to GERD (which is, in fact, a chemical injury), esophageal inflammation may have many origins. Examples include ingestion of mucosal irritants (such as alcohol, corrosive acids or alkalis as in suicide attempts), cytotoxic anticancer therapy, bacteremia or viremia (in immunosuppressed patients), fungal infection (in debilitated or immunosuppressed patients or during broad-spectrum antimicrobial therapy; candidiasis by far the most common), and uremia.

TUMORS
Benign Tumors
Leiomyomas are the most common benign tumors of the esophagus. (Fig. 5-38)

Malignant Tumors
Carcinomas of the esophagus (5% of all cancers of the GIT) have, generally, a poor prognosis because they are often discovered too late. Worldwide, squamous cell carcinomas constitute 90% of esophageal cancers, followed by adenocarcinoma. Other tumors are rare.

Squamous Cell Carcinoma (SCC)
Most SCCs occur in adults over the age of 50. The disease is more common in males than females. The regions with high incidence include Iran & China. Blacks throughout the world are at higher risk than are whites.

Etiology and Pathogenesis
Factors Associated with the Development of Squamous Cell Carcinoma of the Esophagus are classified as

1. Dietary
   - Deficiency of vitamins (A, C, riboflavin, thiamine, and pyridoxine) & trace elements (zinc)
   - Fungal contamination of foodstuffs
   - High content of nitrates/nitrosamines
   - Betel chewing (betel: the leaf of a climbing evergreen shrub, of the pepper family, which is chewed in the East with a little lime.)

2. Lifestyle
   - Burning-hot food
   - Alcohol consumption
   - Tobacco abuse

3. Esophageal Disorders
   - Long-standing esophagitis
   - Achalasia
   - Plummer-Vinson syndrome
4. Genetic Predisposition
   - Long-standing celiac disease
   - Racial disposition

The marked geographical variations in the incidence of the disease strongly implicate dietary and environmental factors, with a contribution from genetic predisposition. The majority of cancers in Europe and the United States are attributable to alcohol and tobacco. Some alcoholic drinks contain significant amounts of such carcinogens as polycyclic hydrocarbons, nitrosamines, and other mutagenic compounds. Nutritional deficiencies associated with alcoholism may contribute to the process of carcinogenesis.

Human papillomavirus DNA is found frequently in esophageal squamous cell carcinomas from high-incidence regions.

Gross features (Fig. 5-39 A)
- Like squamous cell carcinomas arising in other locations, those of the esophagus begin as in situ lesions.
- When they become overt, about 20% of these tumors are located in the upper third, 50% in the middle third, and 30% in the lower third of the esophagus.
- Early lesions appear as small, gray-white, plaque-like thickenings of the mucosa but with progression, three gross patterns are encountered:
  1. Fungating (polypoid) (60%) that protrudes into the lumen
  2. Flat (diffuse infiltrative) (15%) that tends to spread within the wall of the esophagus, causing thickening, rigidity, and narrowing of the lumen
  3. Excavated (ulcerated) (25%) that digs deeply into surrounding structures and may erode into the respiratory tree (with resultant fistula and pneumonia) or aorta (with catastrophic bleeding) or may permeate the mediastinum and pericardium.
- Local extension into adjacent mediastinal structures occurs early, possibly due to the absence of serosa for most of the esophagus. Tumors located in the upper third of the esophagus also metastasize to cervical lymph nodes; those in the middle third to the mediastinal, paratracheal, and tracheobronchial lymph nodes; and those in the lower third most often spread to the gastric and celiac groups of nodes.

Microscopic features (Fig. 5-39 B)
- Most squamous cell carcinomas are moderately to well-differentiated,
- They are invasive tumors that have infiltrated through the wall or beyond.

The rich lymphatic network in the submucosa promotes extensive circumferential and longitudinal spread.

Esophageal carcinomas are usually quite large by the time of diagnosis, produces dysphagia and obstruction gradually. Cachexia is frequent. Hemorrhage and sepsis may accompany ulceration of the tumor.

The five-year survival rate in patients with superficial esophageal carcinoma is about 75%, compared to 25% in patients who undergo "curative" surgery for more advanced disease. Local recurrence and distant metastasis following surgery are common. The presence of lymph node metastases at the time of resection significantly reduces survival.

Adenocarcinoma
With increasing recognition of Barrett mucosa, most adenocarcinomas in the lower third of the esophagus arise from the Barrett mucosa.

Etiology and Pathogenesis
These focus on Barrett esophagus. The lifetime risk for cancer development from Barrett esophagus is approximately 10%. Tobacco exposure and obesity are risk factors. Helicobacter pylori infection may be a contributing factor.
Gross features: (Fig. 5-40 A)
- adenocarcinomas arising in the setting of Barrett esophagus are usually located in the distal esophagus and may invade the adjacent gastric cardia.
- As is the case with squamous cell carcinomas, adenocarcinomas initially appear as flat raised patches that may develop into large nodular fungating masses or may exhibit diffusely infiltrative or deeply ulcerative features.

Microscopic features (Fig. 5-40 B)
- Most tumors are mucin-producing glandular tumors exhibiting intestinal-type features.
- Multiple foci of dysplastic mucosa are frequently present adjacent to the tumor.

Adenocarcinomas arising in Barrett esophagus chiefly occur in patients over the age of 40 years and similar to Barrett esophagus, it is more common in men than in women, and in whites more than blacks (in contrast to squamous cell carcinomas). As in other forms of esophageal carcinoma, patients usually present because of difficulty swallowing, progressive weight loss, bleeding, and chest pain. The prognosis is as poor as that for other forms of esophageal cancer, with under 20% overall five-year survival. Identification and resection of early cancers with invasion limited to the mucosa or submucosa improves five-year survival to over 80%. Regression or surgical removal of Barrett esophagus has not yet been shown to eliminate the risk for adenocarcinoma.
STOMACH
In developed countries, peptic ulcers occur in up to 10% of the general population. Chronic infection of the gastric mucosa by the bacterium H. pylori is the most common infection worldwide. Gastric cancer is still a significant cause of death, despite its decreasing incidence.

CONGENITAL ANOMALIES
These include various heterotopias (normal tissues in abnormal locations), which are usually asymptomatic, e.g. pancreatic heterotopia. Congenital diaphragmatic hernia, which is due to defective closure of the diaphragm; this leads to herniation of abdominal contents into the thorax in utero. Congenital hypertrophic pyloric stenosis is encountered in male infants four times more often than females. Persistent, projectile vomiting usually appears in the second or third week of life. There is visible peristalsis and a firm, ovoid palpable mass in the region of the pylorus resulting from hypertrophy and hyperplasia of the muscularis propria of the pylorus. (Fig. 5-41)

Acquired pyloric stenosis in adults may complicate
1. Antral gastritis or peptic ulcers close to the pylorus.
2. Malignancy e.g. carcinomas of the pyloric region or adjacent panceas, or gastric lymphomas
3. Hypertrophic pyloric stenosis (rare) due to prolonged pyloric spasm

GASTRITIS this is by definition, "inflammation of the gastric mucosa". It is a microscopic diagnosis. The inflammation may be acute, with neutrophilic infiltration, or chronic, with lymphocytes and/or plasma cells.

Acute gastritis is usually transient in nature. The inflammation may be accompanied by hemorrhage into the mucosa (acute hemorrhagic gastritis) and, sometimes by sloughing (erosions) of the superficial mucosa (acute erosive gastritis). (Fig. 5-42) The latter is a severe form of the disease & an important cause of acute gastrointestinal bleeding. Although a large number of cases have no obvious cause (idiopathic), acute gastritis is frequently associated with
1. Heavy use of nonsteroidal anti-inflammatory drugs (NSAIDs) particularly aspirin, cancer chemotherapeutic drugs, or radiation
2. Excessive consumption of alcohol, heavy smoking, and ingestion of strong acids or alkali as in suicidal attempts
3. Uremia
4. Severe stress (e.g., trauma, burns, surgery)
5. Mechanical trauma (e.g., nasogastric intubation)
6. Distal gastrectomy (reflux of duodenal contents).

Chronic Gastritis is defined as "chronic inflammation of the gastric mucosa that eventuates in mucosal atrophy and intestinal metaplasia". The epithelial changes may progress to dysplasia, which constitute a soil for the development of carcinoma.

Pathogenesis
The major etiologic associations of chronic gastritis are:
1. Chronic infection by H. pylori
2. Autoimmune damage
3. Excessive alcohol consumption & heavy cigarette smoking
4. Post-antrectomy (due to reflux of bile-containing duodenal secretions)
5. Outlet obstruction, uremia, and other rare causes

Helicobacter pylori Infection and Chronic Gastritis
Infection by H. pylori is the most important etiologic cause of chronic gastritis. Effective treatment with antibiotics has revolutionized the management of chronic gastritis and peptic ulcer disease. Those with H. pylori-associated chronic gastritis are at increased risk for the development of
1. Peptic ulcer disease  2. Gastric carcinoma  3. Gastric lymphoma
H. pylori are curvilinear, gram-negative rods. They have adapted to survive within gastric mucus, which is lethal to most bacteria. The specialized features that allow these bacteria to flourish include:
1. Motility (via flagella), allowing them to swim through the viscous mucus
2. **Urease production**, which releases ammonia and CO$_2$ from endogenous urea, thereby buffering the harmful gastric acid in the immediate vicinity of the bacteria.

3. **Expression of adhesion molecules**, which enhances binding of the bacteria to adjacent foveolar cells. The bacteria appear to cause gastritis by stimulating production of *pro-inflammatory cytokines* as well as by directly damaging epithelial cells by the liberation of toxins & degrading enzymes e.g. vacuolating toxin (VacA), urease, proteases and phospholipases. After exposure to *H. pylori*, **gastritis occurs in two patterns:**

   1. **Antral-predominant gastritis** with high acid production and elevated risk for duodenal ulcer
   2. **Pan gastritis** with low acid secretion and higher risk for adenocarcinoma

**IL-1β** is a potent *pro-inflammatory cytokine* and a powerful gastric acid inhibitor. Patients who have higher IL-1β production in response to the infection tend to develop pangastritis, while patients who have lower IL-1β production exhibit antral-predominant gastritis.

**A number of diagnostic tests have been developed for the detection of *H. pylori***. (Fig. 5-43)

1. **Noninvasive tests including**
   a. Serologic test for antibodies
   b. Stool culture for bacterial detection
   c. Urea breath test: based on the generation of ammonia by bacterial urease.

2. **Invasive tests (through gastroscopy)**: detection of *H. pylori* in gastric biopsy tissue samples includin
   a. visualization of the bacteria in histologic sections with special stains (Fig.
   b. bacterial culture of the biopsy
   c. bacterial DNA detection by the polymerase chain reaction

**Autoimmune gastritis**

About 10% of chronic gastritis is autoimmune in nature. It results from the presence of autoantibodies to components of parietal cells, including the acid-producing enzyme H+/K+-ATPase, gastrin receptor, and intrinsic factor. Gland destruction and mucosal atrophy lead to loss of acid production (hypo- or achlorhydria). (Fig. 5-44) In the most severe cases, production of intrinsic factor is also impaired, leading to pernicious anemia. Affected patients have a significant risk for developing gastric carcinoma and endocrine tumors (carcinoid tumor).

**Pathological features of chronic gastritis**

- **Autoimmune gastritis** is characterized by diffuse mucosal damage of the body-fundic mucosa, with sparing of antral region (*Corpus-predominant gastritis*).
- **Environmental gastritis** i.e. due to environmental etiologies (including *H. pylori* infection) tends to affect antral mucosa (antral gastritis) or both antral and body-fundic mucosa (pangastritis).

**Gross (endoscopic) features**

- The mucosa of the affected regions is usually hyperemic and has coarser rugae than normal.
- With long-standing disease, the mucosa may become thinned and flattened because of atrophy.

**Microscopic features** (Fig. 5-45)

Irrespective of cause or location, the microscopic changes are similar:

- The mucosa is infiltrated by lymphocytes & plasma cells.
- Frequently the lymphocytes are disposed into aggregates i.e. follicles, some with germinal centers.
- Neutrophils may or may not be present.

**Several additional histologic features are characteristic; these include**

- **Intestinal metaplasia**: the mucosa may become partially replaced by metaplastic columnar cells and goblet cells of intestinal morphology; these may display flat or villous arrangement. If the columnar cells are absorptive (with ciliated border) the metaplasia is termed complete, otherwise it is incomplete.
- **Atrophy** as evidenced by marked loss of the mucosal glands. Parietal cells, in particular, may be absent in the autoimmune form.
- **Dysplasia**: with long-standing chronic gastritis, the epithelium develops dysplastic changes. Dysplastic alterations may become so severe as to constitute in situ carcinoma. *The development of dysplasia is*
thought to be a precursor lesion of gastric cancer. It occurs in both autoimmune and H. pylori- associated chronic gastritis.

- In those individuals infected by H. pylori, the organism lies in the superficial mucus layer on the surface and within the gastric pits. They do not invade the mucosa. These bacteria are most easily demonstrated with silver or Giemsa (special) stains.

**PEPTIC ULCER DISEASE**

An ulcer is defined as "a breach in the mucosa of the alimentary tract that extends into the submucosa or deeper." Although they may occur anywhere in the alimentary tract, they are most common in the duodenum and stomach. Ulcers have to be distinguished from erosions. The latter is limited to the mucosa and does not extend into the submucosa.

**Peptic Ulcers** are chronic, most often solitary lesions and usually small. They occur in any portion of the GIT exposed to the aggressive action of acid-peptic juices. They are located, in descending order of frequency in:

1. Duodenum (first portion)
2. Stomach, (usually antral, along the lesser curve)
3. Gastro-esophageal junction (complicating GERD or Barrett esophagus)
4. Margins of a gastro-jejunostomy
5. Multiple in the duodenum, stomach, and/or jejunum (in Zollinger-Ellison syndrome)
6. Within or adjacent to a Meckel diverticulum (containing ectopic gastric mucosa)

The male-to-female ratio for duodenal ulcers is 3:1, and for gastric ulcers 2:1. Women are most often affected at or after menopause.

**Pathogenesis of peptic ulcers**

- Peptic ulcers are produced by an imbalance between gastro-duodenal mucosal defenses and the damaging forces, particularly of gastric acid and pepsin.
- Hyperacidity is not necessary; only a minority of patients with duodenal ulcers has hyperacidity, and it is even less common in those with gastric ulcers.
- H. pylori infection is a major factor in the pathogenesis of peptic ulcer. It is present in virtually all patients with duodenal ulcers and in about 70% of those with gastric ulcers; that is why peptic ulcer disease is now considered infectious in nature. Antibiotic treatment of the infection promotes healing of ulcers and prevents their recurrence. The possible mechanisms by which this tiny organism impairs mucosal defenses include:
  1. H. pylori induce intense inflammatory and immune responses. As a result there is increased production of pro-inflammatory cytokines, most notably, IL-8, by the mucosal epithelial cells. This recruits and activates neutrophils with their damaging properties.
  2. Several bacterial products cause epithelial cell injury; this is mostly caused by a vacuolating toxin called VacA. H. pylori also secrete urease, proteases and phospholipases, which also cause direct epithelial damage.
  3. H. pylori enhance gastric acid secretion and impair duodenal bicarbonate production, thus reducing luminal pH in the duodenum with its damaging effects on the duodenal mucosa.
  4. Thrombotic occlusion of surface capillaries is provoked by a bacterial platelet-activating factor. Thus, an additional ischemic element may contribute to the mucosal damage. Most persons (80-90%) infected with H. pylori do not develop peptic ulcers. Perhaps there are unknown interactions between H. pylori and the mucosa that occur only in some individuals.
- Other factors may act alone or in concert with H. pylori to encourage peptic ulceration:
  1. Gastric hyperacidity: this when present, may be strongly ulcerogenic. The classic example is Zollinger-Ellison syndrome, in which there are multiple peptic ulcerations in the stomach, duodenum, and even jejunum. This is due to excess gastrin secretion by a gastrinoma and, hence, excess gastric acid production.
  2. Chronic use of NSAIDs: this suppresses mucosal prostaglandin synthesis; aspirin also is a direct irritant.
  3. Cigarette smoking: this impairs mucosal blood flow and healing of the ulcer.
  4. Corticosteroids: these in high doses and with repeated use encourage ulcer formation.
  5. Rapid gastric emptying: this is present in some patients with duodenal ulcers; this phenomenon exposes the duodenal mucosa to an excessive acid load & hence ulcerations.
6. Patients with the following diseases are more prone to develop duodenal ulcer exposes
   a. alcoholic cirrhosis
   b. chronic obstructive pulmonary disease
   c. chronic renal failure
   d. hyperparathyroidism.

   Chronic renal failure and hyperparathyroidism are associated with hypercalcemia. The latter stimulates gastrin production and therefore acid secretion.

7. Personality and psychological stress seems to be important contributing factors.

Gross features (Fig. 5-46)
- The vast majority of peptic ulcers are located in the first portion of the duodenum or in the stomach, in a ratio of about 4:1. Gastric and duodenal ulcers may coexist in up to 20% of the cases. Gastric ulcers are predominantly located along the lesser curvature.
- Although over 50% of peptic ulcers have a diameter less than 2 cm but about 10% are greater than 4 cm. Ulcerated carcinomas (which tend to be large) may be less than 4 cm in diameter and may be located anywhere in the stomach. Thus, size and location do not differentiate a benign from a malignant ulcer.
- The classic peptic ulcer is a round to oval with sharply demarcated crater. The margins are usually level with the surrounding mucosa or only slightly elevated. Heaping-up of these margins is rare in the benign ulcer but is characteristic of the malignant ones.
- Peptic ulcers penetrate the wall to a variable extent. When the entire wall is penetrated, the base of the ulcer may be formed by adherent pancreas, omental fat, or liver.
- The base of a peptic ulcer is smooth and clean, owing to peptic digestion of any exudate that may form. Sometimes, thrombosed or patent blood vessels (the source of life threatening hemorrhage) are evident at the base of the ulcer.
- Ulcer-related scarring may involve the entire thickness of the gastric wall; puckering of the surrounding mucosa creates mucosal folds that radiate from the crater in spoke-like fashion. This is different from malignant ulcers where there is flattening of the mucosal folds (because of malignant infiltration) in the immediately surrounding of the ulcerative.

Microscopic features (Fig. 5-46 B)
- In active ulcers four zones are recognized
  1. The base and walls have a superficial thin layer of necrotic fibrinoid necrosis.
  2. Beneath this layer is a zone of predominantly neutrophilic inflammatory infiltrate.
  3. Deeper still, there is granulation tissue infiltrated with inflammatory cells. This rests on
  4. Fibrous or collagenous scar.
- H. pylori-associated chronic gastritis is seen in up to 100% of patients with duodenal ulcers and in 70% with gastric ulcers. With present-day therapies aimed at inhibition of acid secretion (H2 receptor antagonists and parietal cell H+/K+-ATPase pump inhibitors), and eradication of H. pylori infection (with antibiotics), most ulcers heal within a few weeks.

The complications of peptic ulcer disease are
1. Bleeding is the most frequent complication (20%). It may be life-threatening; fatal in 25% of the affected patients. It may be the first warning of an ulcer.
2. Perforation is much less frequent (5% of patients) but much more serious being fatal in 60% of patients.
3. Obstruction (from edema or scarring) occurs in 2%, most often due to pyloric channel ulcers but may occur with duodenal ulcers. Total obstruction with intractable vomiting is rare.
4. Malignant transformation does not occur with duodenal ulcers and is extremely rare with gastric ulcers. When it occurs, it is always possible that a seemingly benign gastric ulcer was, from the outset an ulcerative gastric carcinoma.

Acute Gastric Ulceration
Focal, acutely developing gastric mucosal defects are a well-known complication of
1. Therapy with NSAIDs
2. Severe stress (stress ulcers) as in shock states, extensive burns & severe trauma; they usually occur in proximal duodenum (Curling ulcers)
3. Sepsis
4. Raised intracranial pressure or intracranial surgery; these are seen as gastric, duodenal, and esophageal ulcers & are designated as Cushing ulcers, which carry a high incidence of perforation.

Generally, acute ulcers are multiple lesions predominantly gastric but sometimes also duodenal. They range in depth from mere shedding of the superficial epithelium (erosions) to deeper lesions that involve the entire mucosal thickness and deeper (ulceration). *Acute ulcers are not precursors of chronic peptic ulcers.*

**Gross features (Fig. 5-47)**
- Acute ulcers are usually small (less than 1 cm) and circular.
- The ulcer base is frequently stained a dark brown by the acid digestion of blood.
- They differ from chronic peptic ulcers by the following
  1. They are found anywhere in the stomach, and are often multiple
  2. The margins and base of the ulcers are not indurated
  3. The related mucosal folds (rugae) are normal (cf. chronic peptic ulcer, which show convergence on the ulcer)

**Microscopically**
- There is focal loss of the mucosa & at least part of the submucosa
- Unlike chronic peptic ulcers, there is no chronic gastritis or scarring.
- Healing with complete re-epithelialization occurs after the causative factor is removed.

Bleeding from superficial gastric erosions or ulcers sufficient to require transfusion develops in up to 5% of these patients. If the underlying cause is corrected recovery is complete.

**TUMORS OF THE STOMACH**
These can be classified as benign and malignant lesions.

**BENIGN TUMORS**
**Gastric polyps**
In the alimentary tract, the term polyp is applied to any nodule or mass that projects above the level of the surrounding mucosa. They are uncommon and classified as non-neoplastic or neoplastic.

**Hyperplastic polyps** (the most frequent; 90%) are small, sessile and multiple in about 25% of cases. There is hyperplasia of the surface epithelium and cystically dilated glandular tissue. (Fig. 5-48)

**Adenomatous polyp (adenoma)** (10% of polypoid lesions) (Fig. 5-49): They contain proliferative dysplastic epithelium and hence have malignant potential. They are usually single, and may grow up to 4 cm in size before detection. Up to 40% of gastric adenomas contain a focus of carcinoma; there may also be an adjacent carcinoma that is why histologic examination of all gastric polyps is obligatory.

Other specific types of gastric polyps are relatively uncommon and include fundic gland polyps, hamartomatous Peutz-Jeghers polyps, juvenile polyps, and inflammatory fibroid polyp

**CANCERS OF THE STOMACH**
Carcinoma is the most important and the most common (90%) of malignant tumors of the stomach. Next in order of frequency are lymphomas (5%); the rest of the tumors are even rarer e.g. carcinoids, and gastrointestinal stromal tumors (GISTs), leiomyosarcoma, and schwannoma.

**Gastric Carcinoma** is a quite common tumor in the world. There are, however, marked geographical variations in its incidence; it is particularly high in countries such as Japan. It is more common in lower socioeconomic groups. There has been a steady decline in both the incidence and the mortality of gastric cancer. There are mainly two subtypes of carcinoma: intestinal and diffuse. These sub-types appear to have different pathogenetic mechanisms of evolution.
Pathogenesis
The major factors thought to affect the genesis of gastric cancer apply more to the intestinal type, as the risk factors for diffuse gastric cancer are not well defined.
1. Helicobacter pylori Infection: this generally increases the risk five-fold. The bacterial infection causes chronic gastritis, followed by atrophy, intestinal metaplasia, dysplasia, and carcinoma. Long-standing mucosal inflammation is associated with damage of epithelial cells, which leads to compensatory epithelial cell proliferation, and hence increased risk of genomic mutation. Since most individuals infected with H. pylori do not develop cancer, other factors must be involved in carcinogenesis.
2. Adenomatous polyps: 40% of adenomas harbor carcinomatous foci; also adjacent carcinoma is found in relation to adenomatous polyps in 30% of the cases.
3. Environmental factors: when families migrate from high-risk to low-risk areas (or the reverse), successive generations acquire the level of risk that prevails in the new environments. The diet is suspected to be a primary factor. Consumption of preserved and salted foods; water contamination with nitrates; and lack of fresh fruit and vegetables are common in high-risk areas. The intake of green, leafy vegetables and citrus fruits, which contain antioxidants such as vitamin C, vitamin E and beta-carotene, seems to play a protective role.
4. Autoimmune gastritis, like H. pylori infection, increases the risk of gastric cancer.

Gross features
• The most common location of gastric carcinomas is the pyloric antrum (50%). A favored location is the lesser curvature. Although less common, an ulcerative lesion on the greater curvature is more likely to be malignant.
• Depth of invasion is the most important determinant of prognosis. Early gastric carcinoma is defined as "a lesion confined to the mucosa and submucosa." Advanced gastric carcinoma is a neoplasm extending into the muscular wall.
• The three macroscopic growth patterns of gastric carcinoma, which may be evident at both the early and advanced stages, are: 1. Fungating (exophytic) 2. Flat or depressed 3. (Fig. 5-50) Ulcerative (excavated). Fungating tumors are readily identified by radiography and endoscopy in contrast to flat (depressed) malignancy. Ulcerative cancers may closely mimic chronic peptic ulcers. In advanced cases, there are heaped-up, beaded margins and necrotic bases. The neoplastic tissue extends into the surrounding mucosa and wall; this leads to flattening of the mucosa surrounding the ulcer. (Fig. 5-51)
• Uncommonly, a broad region of the gastric wall or the entire stomach is extensively infiltrated by malignancy, creating a rigid, thickened "leather bottle," termed linitis plastica. (Fig. 5-52)

Microscopic features
• There are two main microscopic type of gastric carcinoma; intestinal and diffuse.
• The intestinal variant is composed of neoplastic glands with mucin in their lumina. The diffuse variant is composed of mucus-containing cells, which do not form glands, but infiltrate the mucosa and wall as scattered individual and small clusters of cells. In this variant, mucin formation expands the malignant cells and pushes the nucleus to the periphery, creating "signet ring" morphology. (Fig. 5-53)
• Sometimes, there is excessive mucin production that generates large mucin lakes (mucinous carcinoma).
• Infiltrative tumors often evoke a strong desmoplastic reaction (fibrosis), in which the scattered cells are embedded; the fibrosis creates local rigidity of the wall.
• Whatever the microscopic type, all gastric carcinomas eventually penetrate the wall to involve the serosa and spread to regional and more distant lymph nodes.

For obscure reasons, gastric carcinomas frequently metastasize to the supraclavicular (Virchow) node as the first clinical manifestation of an occult neoplasm. (Fig. 5-54) The tumor can also metastasize to the periumbilical region to form a subcutaneous nodule. This nodule is called a Sister Mary Joseph nodule, after the nun who noted this lesion as a marker of metastatic carcinoma. (Fig. 5-55) Local extension of gastric carcinoma into the duodenum, pancreas, and retroperitoneum is also characteristic. At the time of death, widespread peritoneal seeding and metastases to the liver and lungs are common. A notable site of visceral metastasis is to one or both ovaries. Although uncommon, metastatic adenocarcinoma to the ovaries (from stomach, breast, pancreas, and even gallbladder) is distinctive & designated Krukenberg tumor. (Fig. 5-56)
Gastric carcinoma is an insidious disease that is generally asymptomatic until late in its course.
The symptoms include weight loss, abdominal pain, anorexia, vomiting, dysphagia, anemia, and hemorrhage. In Japan, where mass endoscopy screening programs are employed (because of the high incidence of the disease), early gastric cancer constitutes about one third of all newly diagnosed gastric cancers. In Europe and the United States, this figure is only 10% to 15%.

**Prognosis**
This depends primarily on
1. The depth of invasion and
2. The extent of nodal and distant metastasis
The histologic type (intestinal or diffuse) has minimal independent prognostic significance. The five-year survival rate of surgically treated early gastric cancer is 90%; this drops to below 15% for advanced gastric cancer.

**Gastric Lymphomas** represent 5% of all gastric malignancies. However, the stomach is the most common site for extra-nodal lymphoma (20%). Nearly all primary gastric lymphomas are B-cell type and of mucosa-associated lymphoid tissue (MALT lymphomas). The majority of gastric lymphomas (>80%) are associated with chronic gastritis and H. pylori infection. The role of H. pylori infection as an important etiologic factor for gastric lymphoma is supported by the elimination of about 50% of early gastric lymphomas with antibiotic treatment for H. pylori. Generally, the prognosis of gastric lymphoma is better than carcinoma.

**Gastrointestinal Stromal Tumors (GISTs)** these are thought to originate from the interstitial cells of Cajal (normally control gastrointestinal peristalsis). 95% of GISTs stain with antibodies against c-KIT (CD117). The tumor can protrude into the lumen or extrude on the serosal side of the gastric wall. Microscopically, the tumor can exhibit spindle cells, plump "epithelioid" cells, or a mixture of both. Most of the tumors are quite cellular but mitotic activity is variable.

**Gastric Neuroendocrine Cell (Carcinoid) Tumors**
Most gastric carcinoid tumors originate from the enterochromaffin-like cells (ECL) cells in the oxyntic mucosa. The tumor can arise in the setting of chronic atrophic gastritis. The underlying pathogenesis is probably related to the hypergastrinemia, resulting in ECL-cell hyperplasia, a presumed pre-neoplastic condition. Gastric carcinoid tumors exhibit similar histologic features to other carcinoid tumors. The clinical course is quite variable.

**SMALL & LARGE INTESTINE**
Several pathological conditions, such as infections, inflammatory diseases, motility disorders, and tumors, affect both the small and large intestines simultaneously. These two organs will therefore be considered together.

**CONGENITAL ANOMALIES**
Anomalies of the intestine are rarely encountered; these include duplication of the small intestine or colon; malrotation of the entire bowel; omphalocele (birth of an infant with herniation of abdominal contents into a ventral membranous sac related to umbilicus); heterotopia of pancreatic tissue or gastric mucosa; atresia and stenosis; imperforate anus (due to failure of the cloacal diaphragm to rupture).

**Meckel diverticulum** (Fig. 5-57) results from failure of involution of the vitelline duct, which embryologically connects the lumen of developing gut to the yolk sac. The small pouch lies on the antimesenteric side of the bowel, usually 30 cm proximal to the ileo-cecal valve. It consists of mucosa, submucosa, and muscularis propria. The mucosal lining may be that of normal small intestine, but heterotopic gastric mucosa or pancreatic tissue are frequently found. Meckel diverticula are present in 2% of the normal population, but most remain asymptomatic. When peptic ulceration occurs in the small intestinal mucosa adjacent to the heterotopic gastric mucosa, intestinal bleeding or symptoms simulating those of an acute appendicitis may result. Other complications include intussusception, incarceration, or perforation.
Congenital Aganglionic Megacolon (Hirschsprung Disease) (Fig. 5-58)
This congenital disorder is characterized by the absence of ganglia of the submucosal and myenteric neural plexuses, within a portion of the intestinal tract. The outcome is contraction and functional obstruction of the aganglionic segment with secondary proximal dilation. The rectum is always affected and most cases involve the rectum and sigmoid colon only (short-segment disease). In some cases longer segments, and rarely the entire colon may be aganglionic (long-segment disease). Proximal to the aganglionic segment, the ganglionic colon undergoes progressive dilation and hypertrophy, sometimes massively (megacolon). When distention overruns hypertrophy, the colonic wall becomes markedly thinned and may rupture. Diagnosis of Hirschsprung is made histologically by failure to detect ganglion cells in intestinal biopsy samples of the contracted (agnaglionic) segment. The disease usually manifests itself in the immediate neonatal period by failure to pass meconium, followed by obstructive constipation. Abdominal distention may secondarily develop. The major threats to life are superimposed enterocolitis with fluid and electrolyte disturbances and perforation with peritonitis.

ENTEROCOLITIS
These are divided into three etiological categories
I. Infectious (caused by microbiologic agents)
II. Malabsorption-associated
III. Idiopathic inflammatory bowel diseases

Diarrhea and Dysentery
Diarrhea is present when there is an increase in stool frequency, and/or stool fluidity. This consists of daily stool production in excess of 250 gm, containing 70% to 95% water. However, over 6 liters of fluid may be lost per day in severe cases of diarrhea (e.g. cholera); this is the equivalent of the circulating blood volume. Dysentery is characterized by low-volume, painful diarrhea with blood.

Malabsorption-associated diarrhea is the result of interference with absorption of nutrients, which produces bulky stools containing excess fat (steatorrhea).

INFECTION ENTEROCOLITIS
This is the cause of more than 12,000 deaths per day among children in developing countries, and constituting 50% of all deaths before the age of 5 years worldwide. Acute, self-limited infectious diarrhea is most frequently caused by enteric viruses (such as rotavirus and adenoviruses). Bacterial infections, such as that caused by enterotoxigenic Escherichia coli, are also common. In up to 50% of cases, the specific agent cannot be isolated.

Viral enterocolitis
The lesions caused by enteric viruses in the intestinal tract are similar. The small intestinal mucosa shows partial villous atrophy (shortening of the villi) with infiltration of the lamina propria by lymphocytes. However, in infants, rotavirus and adenoviruses can produce total villous atrophy (flat mucosa), thus resembling celiac disease (see later).

BACTERIAL ENTEROCOLITIS
Salmonellosis and Typhoid Fever
Salmonellae are gram-negative bacteria that cause either a self-limited food-borne and water-borne gastroenteritis (S. enteritidis, S. typhimurium, and others) or typhoid fever (S. typhi) a life-threatening systemic illness. In typhoid fever, Peyer patches in the terminal ileum become sharply prominent forming flat elevations. Shedding of the mucosa and the lymphoid tissue creates oval ulcers with their long axes parallel to that of the ileum. Microscopic examination reveals macrophages containing bacteria & red blood cells. Intermingled with the phagocytes are lymphocytes and plasma cells; the infiltrate is characteristically devoid of neutrophils.

Campylobacter Enterocolitis
This flagellated, comma-shaped bacterium may involve the entire intestine from the jejunum to the anus. The small intestine exhibits partial villous atrophy. In colonic infection, the colonic mucosa appears friable and superficially ulcerated. Microscopically, the formation of colonic crypt abscesses and mucosal ulceration may be confused with those of ulcerative colitis.

Cholera
**Vibrio cholerae** affect the proximal small intestine. The mucosa remains essentially intact as the bacteria never invade the epithelium but remain within the lumen and secrete an enterotoxin that stimulates excessive secretions from the enterocytes. The re-absorptive function of the colon is not affected but overwhelmed, thus liters of dilute "rice water" diarrhea containing flecks of mucus occurs. This causes dehydration and electrolyte disturbances. Because overall absorption in the gut remains intact, oral electrolytes-containing fluids can replace the massive sodium, chloride, bicarbonate, and fluid losses and reduce the mortality rate from 50% to less than 1%.

**Antibiotic-Associated Colitis (Pseudomembranous Colitis) (Fig. 5-59)**
This is an acute colitis characterized by formation of an adherent layer of pseudomembrane overlying sites of mucosal injury. It is caused by toxins of Clostridium difficile, which is a normal gut commensal. The disease mostly follows a course of broad-spectrum antibiotic therapy. Clostridium difficile flourish following alteration of the normal intestinal flora. Diagnosis is confirmed by the detection of the C. difficile cytotoxin in stool. Grossly, there are plaque-like adhesions of fibrinopurulent-necrotic debris and mucus to damaged colonic mucosa. Microscopically, the lesion is characteristic in that the superficially damaged crypts are distended by a mucopurulent exudate, which erupts out of the crypt to form a mushrooming cloud (akin to volcano eruption).

**Tuberculous enteritis**
Intestinal tuberculosis contracted by the drinking of contaminated milk was common as a primary focus of the disease. In developed countries today, intestinal tuberculosis is more often a complication of advanced pulmonary tuberculosis i.e. secondary to the swallowing of coughed-up infective sputum. Typically, the organisms are trapped in mucosal lymphoid aggregations of the small and large bowel, which then undergo inflammatory enlargement with ulceration of the overlying mucosa, particularly in the ileum (Fig. 5-60). Microscopy shows typical caseating granulomas that coalesce to form larger ones.

**General pathological features of bacterial enteric diseases**
- These are quite variable.
- Dramatic, even lethal, diarrhea may occur without a significant pathologic lesion, as in cholera.
- Characteristic histology may enable diagnosis with reasonable certainty, as with C. difficile-induced pseudomembranous colitis, and caseating granulomas of TB.

**PARASITIC ENTEROCOLITIS**
Parasitic diseases collectively affect over one-half of the world's population on a chronic or recurrent basis.

**The intestine** can harbor as many as 20 species of parasites, including roundworms Ascaris and Strongyloides, hookworms, pinworms, flatworms, tapeworms, flukes, and protozoa.

**Ascaris lumbricoides**
This is the most common nematode, infecting over a billion individuals worldwide. Adult worm masses can physically obstruct the intestine or the biliary tree. Diagnosis is usually made by detection of the eggs in the feces.

**Strongyloides**
The eggs of Strongyloides can hatch within the intestine and larvae can penetrate the mucosa, causing autoinfection. Hence, Strongyloides infection can persist in one individual for life. Immunosuppressed individuals can have overwhelming autoinfection. Strongyloides incites a strong tissue eosinophilic reaction associated with blood eosinophilia.

**Hookworm (Necator duodenale and Ancylostoma duodenale) infection**
This affects an estimated 1 billion people worldwide and causes significant morbidity. The worms attach to the mucosa of small intestine, suck blood, and reproduce. Long-term infection causes iron deficiency anemia. Diagnosis can be made by detection of the eggs in fecal smear.

**Enterobius vermicularis (pinworms)**
These do not invade host tissue and live their entire life within the intestinal lumen. Adult worms living in the intestine migrate to the anal orifice at night, where the female deposits eggs on the perirectal mucosa. As the eggs are quite irritating, rectal and perineal pruritus ensues. Diagnosis is easily made by applying cellophane tape to the perianal skin and examining the tape for eggs under the microscope.

**Amebiasis** is caused by the protozoan Entamoeba histolytica. The parasite infects approximately 500 million persons in developing countries resulting in approximately 40 million cases of dysentery and liver
abscesses. The presence in stool of trophozoites containing ingested red blood cells is diagnostic. The patient may present with abdominal pain & bloody diarrhea.

**Pathologic features (Fig. 5-61)**

- Amebiasis most frequently involves the cecum and ascending colon. In severe cases, however, the entire colon is involved (pancolitis).
- Amebae invade through the crypt epithelium and burrow into the mucosa and submucosa, eliciting a neutrophilic reaction.
- They are stopped by the muscularis propria thus forced to spread out laterally to create a flask-shaped ulcer with a narrow neck and broad base.
- The mucosa between ulcers is often normal.

**Giardiasis**

Giardia lamblia is the most common pathogenic parasitic infection in humans. Infection may cause acute or chronic diarrhea, steatorrhea, or constipation. Trophozoites multiply in the intestinal lumen. The flagellated trophozoite has two nuclei & resides in the duodenum, adhering to, but does not invade the intestinal epithelial cells. Tight contact between the parasite and the epithelial cell is made by a sucker-like disc. It also contains surface protein that resembles diarrhea-causing toxins secreted by certain snakes. The physical presence of rapidly proliferating trophozoites as well as their toxic proteins that damages the microvillus brush border are responsible for the associated malabsorption.

**Pathological features (Fig. 5-62)**

- In stool smears, G. lamblia trophozoites are pear shaped and binucleate.
- Duodenal biopsy specimens are often packed with sickle or pear-shaped trophozoites, which are tightly bound to the surface of the small intestinal villi.
- As Giardia does not invade the mucosa, small intestinal morphology is often normal.

**Diagnosis**

- This is readily made by
  1. Examination of stool for cysts & trophozoites
  2. Small intestinal biopsy or examination of a small intestinal aspirate that permit identification of the trophozoite

**COLLAGENOUS AND LYMPHOCYTIC COLITIS**

These distinctive disorders of the colon are characterized by chronic watery diarrhea (no blood). Collagenous colitis is characterized by band-like collagen deposits directly under the surface epithelium, whereas lymphocytic colitis is characterized by prominent intraepithelial infiltrate of lymphocytes. Collagenous colitis occurs primarily in middle-aged and older women; lymphocytic colitis affects males and females equally. Radiographic studies are unremarkable, and endoscopy characteristically reveals normal mucosa. The pathogenesis of these conditions remains unclear. While collagenous colitis and lymphocytic colitis are uncommon, they must be considered in every adult patient who presents with a noninflammatory, watery diarrhea.

**SOLITARY RECTAL ULCER SYNDROME**

This is an inflammatory condition of the rectum resulting from motor dysfunction of the anorectal musculature, in particular impaired relaxation of the anorectal sling. The latter may create sharp angulation of the anterior rectal wall. Abrasion of the overlying rectal mucosa creates an oval ulcer and surrounding mucosal inflammation. Associated partial prolapse of the rectal mucosa is common. Patients experience rectal bleeding & mucus discharge.
THE MALABSORPTION SYNDROMES

Malabsorption is characterized by defective absorption of fats, fat-soluble and other vitamins, proteins, carbohydrates, electrolytes and minerals, and water. The most common clinical presentation is chronic diarrhea, and the hallmark of malabsorption is steatorrhea (excessive fecal fat content). Although many causes of malabsorption can be established clinically, small intestinal mucosal biopsy may be required to satisfactorily identify or exclude celiac disease.

Major Malabsorption Syndromes

Clinically, the malabsorption syndromes resemble each other more than they differ. The consequences of malabsorption affect many organ systems. The passage of abnormally bulky, frothy, greasy, yellow, or gray stools (steatorrhea) is a prominent feature of malabsorption; this is accompanied by weight loss, abdominal distention, and muscle wasting.

The malabsorptive disorders most commonly encountered are

1. Celiac disease
2. Pancreatic insufficiency
3. Crohn disease

Pancreatic insufficiency

Primarily from chronic pancreatitis or cystic fibrosis, is a major cause of defective intraluminal digestion that leads to diarrhea and steatorrhea.

Celiac Disease

Celiac disease (gluten-sensitive enteropathy, GSE) is a chronic disease, in which there is a characteristic mucosal lesion of the small intestine and impaired nutrient absorption, which improves on withdrawal of wheat gluten from the diet.

Pathogenesis

- The fundamental disorder in celiac disease is sensitivity to gluten component called gliadin, which is a protein present in wheat and closely related grains (e.g. oat).
- There is a T-cell mediated chronic inflammatory reaction, which develops as a consequence of a loss of tolerance to gluten.
- Interplay between genetic predisposing factors, the host immune response, and environmental factors, is central to disease pathogenesis.
- The small intestinal mucosa, when exposed to gluten, accumulates intraepithelial CD8+ T cells and large numbers of lamina propria CD4+ T cells, which are sensitized to gliadin.
- Gliadin is deamidated by the enzyme transglutaminase; the resultant peptides are recognized by CD4+ T cells. This leads to secretion of interferon γ, which damages enterocytes.

Pathological features (5-63)

- By endoscopy, the duodenal mucosa appears flat (normally shows mucosal folds).
- Biopsies demonstrate enteritis with partial or total loss of villi (partial villous atrophy or completely flat mucosa respectively)
- The surface epithelium shows degeneration, loss of the microvillus brush border, and an increased number of intraepithelial lymphocytes.
- The crypts exhibit increased mitotic activity and are hyperplastic, so that, despite villous atrophy, the overall mucosal thickness remains the same.
- The lamina propria has an overall increase in plasma cells and lymphocytes.
- Although the above changes are characteristic of celiac disease, they can be mimicked by other diseases, most notably tropical sprue.
- Mucosal histology usually reverts to normal or near-normal following gluten exclusion from the diet.

Dermatitis herpetiformis (DH) is a characteristic itchy skin-blotching disease can occur in some patients with celiac disease.

Detection of serum anti-gliadin or "anti-endomysial" antibodies strongly favors the diagnosis of celiac disease.

Definitive diagnosis of celiac disease rests on

1. clinical documentation of malabsorption
2. demonstration of the intestinal lesions by small bowel biopsy and
3. Definite improvement in both symptoms and mucosal histology on gluten withdrawal from the diet.
4. If there is doubt about the diagnosis, gluten challenge (reintroduction of gluten to the diet) followed by rebiopsy has been advocated.
5. Serologic tests, mentioned above, are used for screening or treatment follow-up.

Most patients with celiac disease who adhere to a gluten-free diet remain well indefinitely and ultimately die of unrelated causes. However, there is a long-term risk of malignant disease, which includes small intestinal non-Hodgkin lymphoma (moderate risk), small intestinal adenocarcinoma, and esophageal squamous cell carcinoma (50- to 100-fold higher risk than the general population).

**Tropical Sprue (Postinfectious Sprue)**
This condition is a celiac-like disease that occurs almost exclusively in people living in or visiting the tropics. Malabsorption usually becomes apparent within days or a few weeks. The condition improves on treatment with broad-spectrum antibiotics. This supports an infectious etiology. Intestinal lymphoma does not appear to be associated with this disorder (cf. celiac disease).

**Whipple Disease**
Whipple disease is a rare systemic disease that principally affects the intestine, central nervous system, and joints. It is caused by the bacterium *Tropheryma whippellii*. The bacteria proliferate preferentially within macrophages. The hallmark of Whipple disease is a small-intestinal mucosa laden with distended macrophages (stuffed with the bacteria). Whipple disease is principally encountered in adults, with a strong male predominance. It usually presents as malabsorption with diarrhea and weight loss. Response to antibiotic therapy is usually rapid.

**Disaccharidase (Lactase) Deficiency**
The disaccharidases, of which the most important is lactase, are located in the apical cell membrane of the absorptive epithelial cells. Congenital lactase deficiency is a very rare condition, but acquired lactase deficiency is common. Incomplete breakdown of the disaccharide lactose into its monosaccharides glucose and galactose leads to osmotic diarrhea from the unabsorbed lactose. Bacterial fermentation of the unabsorbed sugars leads to increased hydrogen production, which is readily measured in exhaled air by gas chromatography. Malabsorption is quickly corrected when exposure to milk and milk products is terminated. In the adult, lactase insufficiency develops as an acquired disorder, sometimes in association with viral and bacterial enteric infections. Neither light nor electron microscopy has disclosed abnormalities of the mucosal cells of the bowel.

**Abetalipoproteinemia**
This condition is a rare autosomal recessive inborn error of metabolism and characterized by a defect in the synthesis and export of lipoproteins from intestinal mucosal cells. The failure to absorb certain essential fatty acids leads to lipid membrane defects, evident in the characteristic acanthocytic RBCs (burr cells) in blood films. The disease becomes manifest in infancy and is dominated by failure to thrive, diarrhea, and steatorrhea.
IDIOPATHIC INFLAMMATORY BOWEL DISEASE (IBD)
The two disorders known as inflammatory bowel disease (IBD) are Crohn's disease (CD) and ulcerative colitis (UC). These diseases have distinctly different clinical and pathological features. Both CD and UC are chronic, relapsing inflammatory disorders of obscure origin. CD is an autoimmune disease that may affect any portion of the gastrointestinal tract from mouth to anus, but most often involves the distal small intestine and colon. UC is a chronic inflammatory disease limited to the rectum and colon. Both exhibit extra-intestinal inflammatory manifestations.

Etiology and Pathogenesis
In the normal GIT, the mucosal immune system is always ready to respond against ingested pathogens but is unresponsive to normal intestinal microflora. In IBD, this state of homeostasis is disrupted, leading to two key pathogenic abnormalities
1. Strong immune responses against normal microflora
2. Defects in epithelial barrier that cause microflora to reach the lymphoid tissue of the intestine
The exact cause(s) leading to the above is still not established, hence the designation idiopathic. It is postulated that IBD result from exaggerated local immune responses to microflora in the gut, in genetically susceptible individuals.
Thus, the pathogenesis of IBD involves
1. Failure of immune regulation
2. Genetic susceptibility
3. Environmental triggers specifically microbial flora.
CD appears to be the result of a chronic delayed-type hypersensitivity reaction induced by IFN-γ-producing Th1 cells. This is supported by the presence of granulomas in this disease.
Experiments on animals suggest that UC is caused by excessive activation of Th2 cells.

Diagnosis of IBD
Since the exact etiology of IBD is not known, the diagnosis of IBD and the distinction between CD and UC depend on clinical history, radiographic examination, laboratory findings (serum ANCA is positive in 75% of UC Vs only 10% of CD.), and pathologic examination of tissues involved. Pathologic appearances, both macroscopic and microscopic, play a central role in establishing a definitive diagnosis.

CROHN DISEASE (CD)
This disease may involve any level of the alimentary tract. CD occurs at any age, but the peak age of incidence is between 10 and 30 years. Smoking has been found to be a strong risk factor.

Pathological features
When fully developed, Crohn disease is characterized pathologically by
1. Sharply segmental and typically transmural involvement of the bowel by an inflammatory process with mucosal damage
2. The presence of
   - Small noncaseating granulomas
   - Deep fissures that may eventuate in the formation of fistulae
In CD, there is involvement of the small intestine alone in about 40% of cases, of small intestine and colon in 30%, and of the colon alone in about 30%. Other portions of the GIT may also be uncommonly involved.

Gross features (Fig. 5-64 A)
- Segments of the small bowel involved by the disease show granular and dull gray serosa (normally transparent and glistening).
- Often the mesenteric fat wraps around the bowel (creeping fat)
- The involved bowel wall is thick and rubbery (because of edema, inflammation, and fibrosis). As a result, the lumen is narrowed.
- A classic feature of CD is the sharp demarcation of diseased bowel segments from adjacent uninvolved, essentially normal bowel (skip lesions).
• Early disease shows small mucosal ulcers that coalesce to form long, serpentine linear ulcers (i.e. long and twisted or sinuous).
• As the intervening mucosa (between the ulcers) tends to be accentuated by inflammation and edema, it acquires a cobblestone appearance. (Cobble-stone, is a rounded stone, esp. of the size used for paving).
• Narrow fissures develop between the mucosal folds, often penetrating deeply through the bowel wall. Further extension of these fissures leads to fistulae or sinus tracts formation, between the diseased intestinal segment and adherent structures (bowel loops, vagina, urinary bladder, skin of the abdomen) or the sinuses may end blindly within the abdominal cavity.
• Free perforation or localized abscesses may develop.

Microscopic features (Fig. 5-64 B)

The characteristic histologic features of CD are:

1. Acute mucosal inflammation: there is neutrophilic infiltration of the surface & crypt epithelium that eventually collects within the lumen of the crypts forming crypt abscesses.
2. Chronic mucosal damage: This is the hallmark of chronicity of CD (and UC). It manifests as architectural distortion (in the small intestine as villus blunting; in the colon, the crypts exhibit irregularity, and branching). Crypt destruction leads to progressive mucosal atrophy.
3. Ulcerations: are the usual outcome of severe active disease; these may be superficial, or may penetrate deeply (as fissures) into underlying tissue layers.
4. Transmural chronic inflammation affecting all layers: chronic inflammatory cells (lymphocytes and plasma cells) fill the affected mucosa and, to a lesser extent, all underlying intestinal layers. Lymphoid aggregates are usually scattered throughout the bowel wall.
5. Noncaseating granulomas: in about 50% of the cases, noncaseating small granulomas may be present in all tissue layers. Because they are not always present; the absence of granulomas does not rule out the diagnosis of CD.
6. Other mural changes: in diseased segments, the muscularis mucosae usually exhibits duplication & thickening. There is also fibrosis of the submucosa, muscularis propria, and serosa that eventually leads to stricture formation.
7. Dysplastic changes of the mucosal epithelial cells are particularly important in persons with long-standing chronic disease are. These may be focal or widespread, tend to increase with time, and are thought to be related to increased risk of carcinoma, particularly of the colon.

Clinical Features

The disease usually begins with intermittent attacks of diarrhea, fever, and abdominal pain, spaced by asymptomatic periods lasting for weeks to many months. In those with colonic involvement, occult or overt fecal blood loss may lead to anemia. During this lengthy, chronic disease, complications may arise from

1. Fibrosing strictures, particularly of the terminal ileum (intestinal obstruction)
2. Fistulas formed to other loops of bowel, urinary bladder, vagina, or perianal skin, or into a peritoneum. In the latter focal abscesses may occur.
3. Extensive involvement of the small bowel, including the terminal ileum, may cause
   a. marked loss of albumin (protein-losing enteropathy)
   b. generalized malabsorption
   c. specific malabsorption of vitamin B12 (pernicious anemia), or malabsorption of bile salts, leading to steatorrhea.

Extraintestinal manifestations of this disease include

1. Arthritis & finger clubbing
2. Red nodules of the skin (Erythema nodosum)
3. Primary sclerosing cholangitis, (but the association is not as strong as in UC).
4. Renal disorders secondary to trapping of the ureters in the inflammatory process sometimes develop and leading to hydronephrosis and pyelonephritis.
5. Systemic amyloidosis (rare late consequence).
6. An increased incidence of cancer of the GIT in patients with long-standing progressive CD; however, the risk of cancer in CD is considerably less than in patients with chronic UC.
ULCERATIVE COLITIS
In contradistinction to CD, ulcerative colitis is a chronic ulcero-inflammatory disease limited to the colon and affecting only the mucosa and submucosa; it extends in a continuous fashion proximally from the rectum. Well-formed granulomas are absent. However, like CD, UC is a systemic disorder associated in some patients with arthritis, uveitis, hepatic involvement (primary sclerosing cholangitis), and skin lesions. The onset of disease peaks between ages 20 and 25 years. Nonsmoking is associated with UC; ex-smokers are at higher risk for developing UC than never-smokers.

Pathological features
Ulcerative colitis involves the rectum and extends proximally in a retrograde fashion to involve the entire colon ("pancolitis") in the more severe cases. It is a disease of continuity, and "skip" lesions are not found (cf. CD).

Gross features (Fig. 5-65 A)
- A key feature of UC is that the mucosal damage is continuous from the rectum and extending proximally.
- The mucosa may exhibit reddening and granularity with easy bleeding.
- With fully developed severe, active inflammation, there may be extensive ulcerations of the mucosa.
- Isolated islands of regenerating mucosa bulge upward to create polypoid projections (pseudopolyps).
- With chronicity or healing of active disease, progressive mucosal atrophy occurs.
- Thickening of the bowel wall does not occur in UC; the serosal surface is usually completely normal (cf. CD).
- Only in the most severe cases of ulcerative disease (UC, CD, and other severe inflammatory diseases) does toxic damage to the muscularis propria and neural plexus lead to complete shutdown of neuromuscular function. In this instance the colon progressively swells and becomes gangrenous, a life-threatening condition called toxic megacolon.

Microscopic features (Fig. 5-65 B)
- The basic mucosal alterations in UC are similar to those of colonic CD, with inflammation, chronic mucosal damage, and ulceration.
- There is diffuse, predominantly chronic inflammatory infiltrate in the lamina propria.
- Neutrophilic infiltration of the epithelial layer may produce crypt abscesses. The latter are not specific for UC and may be observed in CD or any active inflammatory colitis.
- Unlike CD, there are no granulomas.
- Destruction of the mucosa leads to broad-based ulcerations that are superficial i.e. extending at most into the submucosa.
- Isolated islands of regenerating mucosa bulge upward to create pseudopolyps.
- Features of chronic but healed (inactive) disease include submucosal fibrosis; mucosal architectural distortion and atrophy.
- Particularly significant is the spectrum of epithelial dysplasias, which are divided into low-grade and high-grade depending on the severity. Invasive carcinoma is the ultimate lesion arising from dysplasia. To summarize UC differs pathologically from CD in the following
  a. Well-formed granulomas are absent.
  b. There are no skip lesions.
  c. The mucosal ulcers rarely extend below the submucosa, and
  d. There is surprisingly little fibrosis.
  e. Mural thickening does not occur, and the serosal surface is usually completely normal.
  f. There appears to be a higher risk of carcinoma development.

Course & prognosis
Ulcerative colitis typically presents as a recurrent attacks of bloody mucoid diarrhea that may persist for days, weeks, or months and then subside, only to recur after an asymptomatic interval of months to years. The outcome of UC depends on two factors:
1. The severity of active disease
2. The duration of the disease
The majority of the cases can be controlled medically; however, about 30% of patients require colectomy due to uncontrollable active disease. On rare occasion, the disease runs a fulminant course; unless medically or surgically controlled, this toxic form of the disease can lead to death soon after onset. The most serious long-term complication of UC is colonic carcinoma. There is a tendency for dysplasia to arise in multiple sites. The associated carcinomas are often infiltrative without obvious exophytic masses. Historically, the risk of cancer is highest in patients with pancolitis of 10 or more years’ duration. It is believed that with 10 years of disease limited to the left colon the risk is minimal, and at 20 years the risk is on the order of 2%. With pancolitis, the risk of carcinoma is 10% at 20 years and up to 25% by 30 years. Overall, the annual incidence of colon cancer in persons with ulcerative colitis of more than 10 years’ duration is 1%.

VASCULAR DISORDERS
Ischemic Bowel Disease
Ischemic lesions may be restricted to the small or large intestine, or may affect both, depending on the particular vessel(s) affected. Acute occlusion of one of the three major supply arteries of the intestines—celiac, superior mesenteric, and inferior mesenteric arteries—may lead to infarction of several meters of intestine. However, gradual occlusion of one vessel may be without effect, due to the rich anastomotic interconnections. Lesions within the end arteries, which penetrate the gut wall, produce small, focal ischemic lesions. Pathologically the outcome of ischemic injury is divided into
1. Transmural infarction, involving all layers (full thickness infarction)
2. Mural infarction involving the mucosa and submucosa.
3. Mucosal infarction extends no deeper than the muscularis mucosae.
   Almost always, transmural infarction is caused by occlusion of major mesenteric blood vessels, whereas mucosal or mural infarctions often result from hypoperfusion.
Mesenteric venous thrombosis is a less frequent cause of vascular insufficiency.
The predisposing conditions for ischemia are:
1. Arterial thrombosis complicating usually severe atherosclerosis.
2. Arterial embolism complicating cardiac vegetations and aortic atheroembolism.
3. Venous thrombosis complicating hypercoagulable states, oral contraceptives, intraperitoneal sepsis, etc.
4. Nonocclusive ischemia complicating cardiac failure, shock, dehydration, and vasoconstrictive drugs (e.g., digitalis, vasopressin, propranolol)
5. Miscellaneous such as radiation injury, volvulus, and internal or external herniae.
Pathological features (Fig. 5-66 A)
Transmural Infarction
• Small intestinal infarction may follow sudden and total occlusion of mesenteric arterial blood flow.
• It more often involves a considerable length of the bowel.
• The splenic flexure of the colon is also at greatest risk of ischemic injury because it is the watershed between the distribution of the superior and inferior mesenteric arteries. (Watershed area: a narrow zone between two areas that are supplied by two vessels).
• Mesenteric venous occlusion, with subsequent propagation of thrombus may lead to extensive infarction.
• The infarction appears hemorrhagic (dusky red) because of blood re-flow into the damaged area. The lumen of the affected segment commonly contains bloody mucus or frank blood.
• Within 1 to 4 days, intestinal bacteria produce gangrene and sometimes perforation of the bowel.
Microscopically, (Fig. 5-66 B)
• The picture is that of coagulative necrosis with inflammatory cell infiltration.
Chronic Ischemia: chronic vascular insufficiency, e.g. due to gradual atherosclerotic narrowing of the relevant vessel to a region of intestine, produces mucosal inflammation and ulceration. Submucosal chronic inflammation and fibrosis may also occur & lead to strictures.
Angiodysplasia: is characterized by tortuous dilations of submucosal and mucosal blood vessels are seen most often in the cecum or right colon, usually only after the age of 50 years. They are responsible for 20% of significant lower intestinal bleeding.
Hemorrhoids (Fig. 5-67) are essentially varices of the anal and perianal venous plexuses. They are extremely common affecting 5% of the general population. They develop secondary to persistently elevated venous pressure within the hemorrhoidal plexus. The most frequent predisposing influences are constipation
with straining at stool and the venous stasis of pregnancy. Except for pregnant women, they are rarely encountered in persons under the age of 30. Much more rarely, but much more importantly, hemorrhoids may reflect collateral anastomotic channels that develop because of portal hypertension (as in liver cirrhosis). The varicosities may develop in the inferior hemorrhoidal plexus and thus are located below the anorectal line (external hemorrhoids) or from dilation of the superior hemorrhoidal plexus (internal hemorrhoids). Commonly, both plexuses are affected (combined hemorrhoids). Microscopically these lesions consist of thin-walled, dilated, submucosal vessels. Superficial ulceration, fissure formation, and infarction of the hemorrhoids secondary to their strangulation may develop.

DIVERTICULAR DISEASE
A diverticulum is a blind pouch related to the alimentary tract. It is lined by mucosa that communicates with the lumen of the gut. Congenital diverticula is typified by Meckel diverticulum. Virtually all other diverticula are acquired and either lack or have an attenuated muscularis propria. The most common site of multiple diverticula is the left side of the colon, with the majority in the sigmoid colon; this is termed diverticular disease of the colon. It manifests mostly after the age of 30 years. They are much less frequent in underdeveloped tropical countries than in developed countries.

INTESTINAL OBSTRUCTION (Fig. 5-68)
The small intestine is most often involved due to its narrow lumen. Tumors and infarction, although the most serious, account for only up to 20% of small-bowel obstructions. The remaining 80% are due to
1. Hernias
2. Intestinal adhesions
3. Intussusception
4. Volvulus
The clinical manifestations include abdominal pain and distention, vomiting, constipation, and in complete obstruction failure to pass flatus.

Hernias (Fig. 5-69)
A weakness or defect in the wall of the peritoneal cavity may permit protrusion of a pouch-like sac of peritoneum called hernial sac. The usual sites of such weakness are at the
1. Inguinal canal
2. Femoral canal
3. Umbilicus
4. In surgical scars
Hernias are of concern chiefly because segments of viscera frequently protrude and become trapped in hernial sac. This is particularly true with inguinal hernias, since they tend to have narrow orifices and large sacs. The most frequent contents of a hernial sac are small-bowel loops, but portions of omentum or large bowel may also become trapped. Pressure at the neck of the pouch may impair venous drainage of the trapped bowel segment. The resultant stasis and edema increase the bulk of the herniated loop, leading to permanent trapping (incarceration). With time, interference with arterial supply and venous drainage (strangulation) leads to infarction of the trapped segment.

Adhesions (Fig. 5-70)
Surgical procedures, infection, and endometriosis often cause localized or more general peritonitis. As the peritonitis heals, adhesions may also develop between bowel segments and abdominal wall at the operative site. These fibrous bridges can create closed loops through which other viscera may slide and eventually become trapped (internal hernias). These internal hernias are liable for the same complications as external ones (obstruction and strangulation).

Intussusception (Fig. 5-71)
This occurs when one segment of the intestine, constricted by a wave of peristalsis, suddenly becomes telescoped into the immediately distal segment of bowel. Once trapped, the invaginated segment is propelled by peristalsis farther into the distal segment, pulling its mesentery along with it. When encountered in infants and children, there is usually no underlying anatomic lesion or defect in the bowel, but some cases of intussusception are associated with rotavirus infection, suggesting that localized intestinal inflammation may serve as a traction point for the intussusception. However, intussusception in adults signifies an intraluminal mass or tumor as the
point of traction. In both settings, intestinal obstruction ensues, and trapping of mesenteric vessels leads to infarction.

**Volvulus (Fig. 5-72)**

This signifies complete twisting of a loop of bowel about its mesenteric base of attachment. It produces intestinal obstruction and infarction. This lesion occurs most often in large redundant loops of sigmoid, followed in frequency by the cecum, and small intestine.

**TUMORS OF THE SMALL AND LARGE INTESTINE**

The large intestine is responsible for more primary neoplasms than any other organ in the body. The vast majority are adenocarcinomas. The small intestine, despite its great length (3/4 of the GIT), is an uncommon site for benign or malignant neoplasms.

**Tumors of the small intestine**

The most common benign tumors in the small intestine are *adenomas* (Fig. 5-73) and *mesenchymal tumors*. Of malignant tumors *adenocarcinomas* and *carcinoids* have roughly equal incidence, followed in order by lymphomas and sarcomas.

**Tumors of the Colon and Rectum**

*Non-neoplastic and benign neoplastic lesions of the colo-rectum are collectively known as polyps*, which are common in the older adult population. Epithelial polyps that arise as the result of proliferation and dysplasia are termed *adenomatous polyps* (adenomas). They are precursors of carcinoma.

**Non-Neoplastic Polyps include**

1. hyperplastic polyp
2. hamartomatous polyp
3. inflammatory polyp
4. lymphoid polyp

**Hyperplastic Polyps**

These are the most common polyps of the colon and rectum. They are small (usually <5 mm in diameter) and appear as smooth protrusions of the mucosa. They are often multiple and consists of well-formed glands and crypts lined by non-neoplastic epithelial cells.

**Hamartomatous Polyps**

1. **Juvenile polyps** (Fig. 5-74) are essentially hamartomatous proliferations, mainly of the lamina propria, enclosing widely spaced, dilated cystic glands. They occur most frequently in children younger than 5 years old but also are found in adults of any age; in the latter group they may be called *retention polyps*. The lesions are usually large in children (1-3 cm in diameter) but smaller in adults; they are rounded, smooth, or slightly lobulated and sometimes have a stalk as long as 2 cm. In general, they occur singly and in the rectum, and have no malignant potential. Juvenile polyps may be the source of rectal bleeding and in some cases become twisted on their stalks to undergo painful infarction.

2. **Peutz-Jeghers polyps** (Fig. 5-75) are also hamartomatous polyps that involve the mucosal epithelium, lamina propria, and muscularis mucosae. They may occur sporadically or in the setting *Peutz-Jeghers syndrome (PJS)*. *PJS* is a rare autosomal dominant syndrome characterized by
   a. multiple hamartomatous polyps scattered throughout the entire GIT
   b. melanotic mucosal and cutaneous pigmentation especially around the lips & in the oral mucosa.

   Patients with this syndrome are at risk for intussusception, which is a common cause of mortality. The polyps are present most frequently in the small intestine.
Adenomas (Adenomatous polyps)
Adenomas are intraepithelial neoplasms that range from small, often pedunculated lesions to large neoplasms that are usually sessile. The prevalence of colonic adenomas increases progressively with age. Males and females are affected equally. Adenomatous polyps are divided into three subtypes on the basis of the epithelial architecture (Fig. 5-76):

1. Tubular adenomas: compose of tubular glands
2. Villous adenomas: composed of villous projections
3. Tubulovillous adenoma: composed of a mixture of the above two.

All adenomas by definition arise as the result of dysplastic epithelial proliferation. The dysplasia ranges from low-grade to high-grade. There is strong evidence that adenomas are precursors for invasive colorectal adenocarcinomas. The risk of cancer is high (approaching 40%) in villous adenomas more than 4 cm in diameter. Adenomas may be single or multiple, may be asymptomatic, and many are discovered during evaluation of anemia (due to occult bleeding) through endoscopy. Villous adenomas are often are discovered because of overt rectal bleeding. The most distal villous adenomas may secrete sufficient amounts of mucoid material rich in protein and potassium to produce hypoproteinemia or hypokalemia. The only adequate treatment for adenomas is complete resection.

FAMILIAL POLYPOSIS SYNDROMES
These are uncommon autosomal dominant disorders. Their importance lies in their tendency for malignant transformation.

1. Peutz-Jeghers syndrome
2. Juvenile polyposis syndrome
3. Familial adenomatous polyposis (FAP)

Another hereditary condition in this context but is not associated with polyp formations is the hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome).

Familial Adenomatous Polyposis (FAP) Syndrome (Fig. 5-77)
This is caused by mutations of the adenomatous polyposis coli (APC) gene on chromosome 5. In the classic FAP syndrome, affected patients typically develop 500 to 2500 colonic adenomas that carpet the mucosal surface; the presence of a minimum of 100 polyps is necessary for a diagnosis. The lifetime risk of cancer development is 100%. Some patients already have cancer of the colon or rectum at the time of diagnosis. Cancer-prevention measures include early detection of the condition and prophylactic colectomy.

COLORECTAL CARCINOMA
A widely accepted proposal of carcinogenesis is the adenoma-carcinoma sequence (Fig. 5-78), i.e. most carcinomas arise from preexisting adenomas. This has been supported by the following observations:

1. Populations that have a high prevalence of adenomas have a high prevalence of colorectal cancer.
2. The distribution of adenomas parallel that of colorectal cancer.
3. The peak incidence of adenomas precedes that of carcinoma by some years.
4. When invasive carcinoma is identified at an early stage, a related adenoma is often present.
5. The risk of cancer is directly related to the number of adenomas, that is why carcinoma complicates all those with FAP syndrome.
6. Removal of all adenomas that are suspicious reduces significantly the incidence of cancerinoma. 98% of all cancers in the large intestine are adenocarcinomas. They usually arise in polyps and produce symptoms relatively early and at a stage generally curable by surgical resection. Yet, it is responsible for 10% of all cancer-related deaths. The peak incidence for colorectal carcinoma is between ages 60 and 79. When colorectal carcinoma is found in a young person, pre-existing ulcerative colitis or one of the polyposis syndromes must be suspected. Environmental factors, particularly dietary practices, are implicated in the striking geographic variations in incidence. Japanese families that have migrated from their low-risk areas to the United States (high-risk areas) have acquired, over the course of 20 years, the rate prevailing in the new environment; mainly because the immigrants adopted the common dietary practices of the U.S. population. The dietary factors receiving the most attention as predisposing to a higher incidence of cancer are

1. Excess dietary caloric intake relative to requirements
2. Low content of unabsorbable vegetable fibers & high content of refined carbohydrates
3. Intake of red meat
Several epidemiological studies suggest that the use of aspirin and other nonsteroidal anti-inflammatory drugs exerts a protective effect against colon cancer.

**Gross features (Fig. 5-79 A)**
- The rectosigmoid colon is the most frequent location (60%), followed by cecum/ascending colon (20%).
- Tumors in the proximal colon tend to grow as polypoid, exophytic masses; obstruction is uncommon. In the distal colon, they tend to be annular, encircling lesions that produce napkin-ring constrictions. The lumen is markedly narrowed leading to obstruction with secondary proximal distention.
- Both forms (polypoid and annular) directly penetrate the bowel wall over the course of time (probably years) and may appear as subserosal and serosal white, firm masses.

**Microscopic features (Fig. 5-79 B)**
- The features of right- and left-sided colonic adenocarcinomas are similar.
- Differentiation (grade) may range from well-differentiated tumors to undifferentiated, frankly anaplastic masses.
- Invasive tumor provokes a strong desmoplastic (fibrotic) stromal response (responsible for the characteristic firm, hard consistency of most carcinomas).
- Carcinomas arising in the anal canal are mostly of squamous cell type.

**Clinical features**
Colorectal cancers remain asymptomatic for years; symptoms develop insidiously and frequently have been present for months, sometimes years, before diagnosis. Patients with cecal and right colonic cancers are most often presented with iron-deficiency anemia (due to insidious blood loss). Left-sided lesions come to attention by producing occult bleeding, changes in bowel habit or intestinal obstruction. Iron-deficiency anemia in an older male means gastrointestinal cancer until proved otherwise. In females the situation is less clear, since menstrual losses, multiple pregnancies, or abnormal uterine bleeding may underlie such an anemia.

**Spread & metastasis**
All colorectal tumors spread by direct extension into adjacent structures and by metastasis through the lymphatics and blood vessels. The favored sites of metastatic spread are the regional lymph nodes, liver, lungs, and bones. In general, the disease has spread beyond the range of curative surgery in 25% of patients. The single most important prognostic factor of colorectal carcinoma is the extent of the tumor at the time of diagnosis (stage). Currently, the staging system most widely used is the tumor-nodes-metastasis (TNM). (Fig. 5-80) The principal aim is to discover these neoplasms when curative resection is possible. Indeed, each death from colonic cancer must be viewed as a preventable tragedy.

**CARCINOID TUMORS**
The term carcinoid means carcinoma-like lesion because it shows a much more indolent clinical course than genuine carcinoma. Carcinoid tumor is derived from resident endocrine cells, with the gastrointestinal tract and lung as the predominant sites of occurrence. They comprise less than 2% of colorectal malignancies but 50% of small intestinal malignant tumors. These tumors may be confined to the mucosa and submucosa or may be deeply invasive with metastatic spread to regional lymph nodes and the liver. Appendiceal and rectal carcinoids almost never metastasize.

**Gross features (Fig. 5-81)**
The appendix is the most common site of gut carcinoid tumors. In the appendix, they appear as rounded swellings of the tip. A characteristic feature is a solid, yellow-tan appearance on transection.

**Microscopic features**
The neoplastic cells may form islands, trabeculae, glands, or sheets. The tumor cells show very little if any variation in cell and nuclear size, having a scant, pink granular cytoplasm and a round to oval nucleus. Mitoses are infrequent or absent.

**Electron microscopy:** the cells contain dense-core secretory granules in the cytoplasm. Most carcinoids contain endocrine markers.
Gastrointestinal carcinoids only rarely produce local symptoms; many (especially rectal and appendiceal) are asymptomatic and are found incidentally. However, the secretory products of some carcinoids may produce a variety of syndromes such as Zollinger-Ellison syndrome (excess production of gastrin), Cushing syndrome (excess production of corticotrophin). Hyperinsulinism may also occur leading to hypoglycemia. Some neoplasms are associated with the distinctive carcinoid syndrome, which occurs especially with carcinoids associated with widespread metastases. Most manifestations are thought to arise from excess elaboration of serotonin (5-hydroxytryptamine, 5-HT). Elevated levels of 5-HT and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), are present in the blood and urine of most patients with the classic syndrome. The syndrome is characterized by

- Cyanosis of the face and anterior part of the chest
- Intermittent hypertension & palpitation
- Frequent watery stools

The tumor, sometimes, induces fibrosis of the right-sided cardiac valves that results in so-called carcinoid heart disease.

GASTROINTESTINAL LYMPHOMAS
Any segment of the gastrointestinal tract may be secondarily involved by systemic dissemination of nodal-based non-Hodgkin lymphomas. However, up to 40% of lymphomas arise in sites other than lymph nodes (extra-nodal lymphomas), and the gut is the most common location. Primary gastrointestinal lymphomas usually arise without an obvious predisposing factor but they also occur more frequently in certain patient groups

1. Chronic gastritis caused by H. pylori
2. Chronic celiac disease
3. Natives of the Mediterranean region (Mediterranean lymphoma)
4. Congenital immunodeficiency states, infection with HIV or following organ transplantation with immunosuppression

Most gut lymphomas are of B-cell type (over 95%) and are either low- or high-grade tumors. Early discovery is the key to survival. The depth of local invasion, size of tumor and its histologic grade as well as extension into adjacent viscera are important determinants of prognosis.

MESENCHYMAL TUMORS
Mesenchymal tumors may occur anywhere in the alimentary tract and include lipomas, leiomyosarcomas, gastrointestinal stromal tumors (GISTs) and Kaposi sarcomas.

TUMORS OF THE ANAL CANAL
Pure squamous cell carcinomas of the anal canal are closely associated with chronic HPV infection. The latter often causes precursor lesions such as condyloma acuminatum, squamous epithelium dysplasia, and carcinoma in situ. Pure adenocarcinoma of the anal canal is often the extension of rectal adenocarcinoma.

APPENDIX
ACUTE APPENDICITIS
Acute appendicitis is the most common acute abdominal surgical emergency. It is divided into

1. Acute appendicitis associated with obstruction (up to 80% of cases). The obstructing agent is usually a fecalith and, less commonly, a gallstone, tumor, or ball of worms (Entrobias vermicularis). Continued secretion of mucinous fluid in the obstructed portion leads to a progressive increase in intraluminal pressure that eventuates in compression and obstruction of the draining veins. The ischemic injury favors bacterial proliferation with additional inflammatory edema and exudation, which further interfere with the blood supply.
2. Acute appendicitis without obstruction, which is of unknown pathogenesis.

Gross features (Fig. 5-82 A)

- The transmural inflammatory reaction converts the normal glistening serosa into a dull, red membrane; this transformation signifies early acute appendicitis for the operating surgeon. Later the prominent neutrophilic exudate leads to fibrino-purulent reaction over the serosa.
- As the inflammatory process worsens, there is abscess formation within the wall, along with ulcerations and foci of suppurative necrosis in the mucosa. This constitutes acute suppurative appendicitis.
Further progression leads to large areas of hemorrhagic green ulceration of the mucosa and green-black gangrenous necrosis through the wall, extending to the serosa, creating acute gangrenous appendicitis, which is quickly followed by rupture and suppurative peritonitis.

**Microscopy (Fig. 5-82 B)**
- The microscopic criterion for the diagnosis of acute appendicitis is neutrophilic infiltration of the muscularis propria (transmural inflammation)
- Usually, neutrophils and ulcerations are also present within the mucosa.

**TUMORS OF THE APPENDIX**

**Carcinoid tumor (see above)**

**Conventional adenomas or adenocarcinomas** of the appendix
These are rare and pathologically identical to those of the large intestine and may cause a neoplastic enlargement of the appendix.

**MUCOCELE AND PSEUDOMYXOMA PERITONEI**

Mucocoele is the macroscopic description of a dilated appendix filled with mucin. The true pathologic nature of mucocoele runs the range from an innocuous obstructed appendix containing inspissated mucin, to a mucin-secreting adenoma (mucinous cystadenoma) and adenocarcinoma (mucinous cystadenocarcinoma). In the last instance, invasion through the appendiceal wall with intraperitoneal seeding and spread of tumor may occur, this may be associated with pseudomyxoma peritoneii. (Fig. 5-83) Mucocoeles are generally encountered as an incidental lesion. Mucinous cystadenomas and adenocarcinomas may present with pain, attributable to distention of the viscus. Laparotomy for presumed acute appendicitis is a typical diagnostic setting. For lesions confined to the resected specimen (appendix or more radical excision), the outlook is excellent. Pseudomyxoma peritoneii may be held in check for years by repeated debulking procedures but in most instances eventually runs its inexorable fatal course.