Lecture 1

ORAL CAVITY: ULCERATIVE & INFLAMMATORY LESIONS

Mechanical trauma & cancer can produce ulcerations in the oral cavity & must be considered in the differential diagnosis.

1. Aphthous Ulcers (Canker Sores)

- Extremely common ulcers
- Small (<5 mm in diameter)
- Painful, rounded, shallow ulcers
- Covered with a gray-white exudate & having an erythematous rim.
- Appear singly or in groups
- Occur: on the nonkeratinized oral mucosa, specially soft palate, buccolabial mucosa, mouth floor & tongue lateral borders.
- More common in the first 2 decades of life (but it can occur at any age)
- Often triggered by stress, fever, ingestion of certain foods, & activation of IBD (Inflammatory Bowl Disease).
- They are self-limited & usually resolve within few weeks, but they may recur in the same or a different location in the mouth.

2. Herpes Simplex Virus (HSV) Infection

- Herpetic stomatitis is an extremely common infection caused by HSV type1.

herpetic infection of the oral cavity معناها فتحة او فم فتأتي هنا بمعنى Stomo

- The virus is transmitted by kissing; by middle life over 3/4 of the population has been infected.
- In most adults the primary infection is asymptomatic, but the virus persists in a dormant state within ganglia about the mouth (e.g., trigeminal ganglia).
- With reactivation of the virus (which may be caused by fever, sun or cold exposure, RTI, or trauma), solitary or multiple small (<5 mm in diameter) vesicles containing clear fluid appear.
- They occur most often on the lips or about the nasal orifices & are well known as cold sores or fever blisters. (لطمة حمة)
- The vesicles soon rupture, leaving shallow, painful ulcers that heal within a few weeks, but recurrences are common.
- The vesicles begin as an intraepithelial focus of intercellular & intracellular edema.
- The infected cells become ballooned & develop intranuclear acidophilic viral inclusions.
- Sometimes adjacent cells fuse to form giant cells known as multinucleated polykaryons.
- Necrosis of the infected cells & the focal collections of edema fluid account for the intraepithelial vesicles detected clinically.
- Identification of the inclusion-bearing cells or polykaryons in smears of blister fluid constitutes the diagnostic Tzanck test for HSV infection.
- Antiviral agents may accelerate healing of the lesions.

- In 10% to 20% of those with Herpetic stomatitis, particularly in the immunocompromised, a more virulent disseminated eruption develops, producing multiple vesicles throughout the oral cavity, including the gingiva & pharynx (herpetic gingivostomatitis) & lymphadenopathy.

- In very severe cases, viremia may seed the brain (causing encephalitis) or disseminated visceral lesions.

- HSV type 1 may localize in many other sites, including the conjunctivae (keratoconjunctivitis) & the esophagus when a nasogastric tube is introduced through an infected oral cavity.

- As a result of changes in sexual practices, genital herpes produced by HSV type 2 (the agent of herpes genitalis) is increasingly seen in the oral cavity. The infection produces vesicles in the mouth, which have the same histologic characteristics as those that develop on the genital mucous membranes & external genitalia.

3. Oral Candidiasis

- Candida albicans is a normal inhabitant of the oral cavity found in 30% to 40% of the population; it causes disease only when there is impairment of the usual protective mechanisms.

- Thrush = moniliasis = pseudomembranous candidiasis is the most common fungal infection of the oral cavity.

- It is particularly common among persons rendered vulnerable by DM, AIDS, immunodeficiency, anemia, antibiotic or glucocorticoid therapy, or disseminated cancer.

- **GROSSLY**:
  typical oral candidiasis takes the form of an adherent, white plaque, curdlike, circumscribed anywhere within the oral cavity.
  The pseudomembrane can be scraped off to reveal an underlying granular erythematous inflammatory base.

- **H :**
  the pseudomembrane is composed of fungal organisms superficially attached to the underlying mucosa.
  In milder infections there is minimal ulceration, but in severe cases the entire mucosa may be denuded & lost.

- For unknown reasons, local vagina candidiasis may appear, not only in predisposed females, but also in apparently healthy young women, particularly during pregnancy, or in women who are using oral contraceptives or broad-spectrum antibiotics.

- **In the particularly vulnerable host, candidiasis may** :
  1. Spread into the esophagus, especially when a nasogastric tube has been introduced.
  2. it may produce wide-spread visceral lesions, when the fungus gains entry into the bloodstream.

- Disseminated candidiasis is a life-threatening infection that must be treated aggressively.

4. AIDS & Kaposi Sarcoma

- AIDS & less advanced forms of HIV infection, are often associated with lesions in the oral cavity which may take the form of candidiasis, herpetic vesicles, gingivitis, or glossitis.

- Hairy leukoplakia is an uncommon lesion seen virtually only in persons infected with HIV.

- Hairy leukoplakia : It consists of white confluent patches, anywhere on the oral mucosa, that have a "hairy" or corrugated surface resulting from marked epithelial thickening.
  *It is caused by Epstein-Barr virus (EBV) infection of epithelial cells. مهم

- More than 50% of individuals with Kaposi sarcoma develop intraoral purpuric discolorations or violaceous, raised, nodular masses; sometimes this involvement constitutes the presenting manifestation.

LEUKOPLAKIA & ERYTHROPLAKIA

- **Leukoplakia** : refers to a whitish, mucosal plaque caused by epidermal thickening (acanthosis + hyperkeratosis)مهمممم

- As defined by the WHO:
  leukoplakia is a white patch or plaque that cannot be scraped off & cannot be characterized as any other disease; (thus, this term is not applied to other white lesions, such as those caused by candidiasis or lichen planus).مهمم

- Leukoplakia plaques are more frequent among older men & are most often on the vermilion border of the lower lip, buccal mucosa, the hard & soft palates, & less frequently on the floor of the mouth & other intraoral sites.

- May appear as localized, diffuse, or multifocal smooth or roughened, leathery, white, discrete mucosal thickening.مهمم

- they vary, from simple hyperkeratosis without underlying epithelial dysplasia, to mild, up to severe dysplasia bordering on carcinoma in situ .

- Only histologic evaluation distinguishes these lesions from each other. مهم

- Leukoplakias are of unknown cause, except that there is a :
  a. Strong association
  with the use of tobacco, particularly pipe smoking & smokeless tobacco (pouches, snuff, chewing).
  b. Less strongly implicated factors are:
  1. chronic friction, as from ill-fitting dentures or jagged teeth
  2. alcohol abuse; & irritant foods.
  3. HPV antigen, more recently, has been identified in some tobacco-related lesions, raising the possibility that the virus & tobacco act in concert in the induction of Leukoplakia.

- Oral leukoplakia is an important, because 3% to 25% (depending somewhat on location) undergo malignant transformation to SCCa.

- The transformation rate is greatest with lip & tongue Leukoplakias & lowest with those on the floor of the mouth.

- **H** :
  the Leukoplakia that display significant dysplasia have greater probability of malignant transformation

  Remember: It is impossible to distinguish the innocent lesion from the ominous one on visual inspection.مهمممم

- **Three somewhat related lesions must be differentiated from the usual oral leukoplakia :**

1.Hairy leukoplakia	(see above) & seen virtually only in persons with AIDS, has a corrugated or "hairy" surface rather than the white, opaque thickening of oral leukoplakia & has not been related to the development of oral cancer.
2.Verrucous leukoplakia	shows a corrugated surface caused by excessive hyperkeratosis. This seemingly innocuous form of leukoplakia recurs & insidiously spreads over time, resulting in a diffuse warty-type of oral lesion that may yet harbor squamous cell carcinoma
3.Erythroplakia	refers to red, velvety, often granular, circumscribed areas that may or may not be elevated, having poorly defined, & irregular boundaries. **H** → erythroplakia almost invariably reveals marked epithelial dysplasia, & with malignant transformation rate of more than >50%, the recognition of this lesion becomes even more important than identification of oral leukoplakia!مهمم

CANCERS OF THE ORAL CAVITY AND TONGUE

- **Risk Factors for Oral Cancer :**

1.Leukoplakia, erythroplakia	Risk of transformation in leukoplakia 3% to 25%; More than 50% risk in erythroplakia
2.Tobacco use	Best-established influence, particularly pipe smoking & smokeless tobacco
3.Human papillomavirus (HPV) types 16 &18	Identified by molecular probes in 30% to 50% of oral cancers
4.Alcohol abuse	Weaker influence than tobacco use, but the two habits interact to greatly increase risk
5.Protracted irritation	Weakly associated

- The majority of oral cavity cancers are squamous cell (SCCa).
- Although they represent only 3% of all cancers in the US, they are important clinically
- All are readily accessible for early identification & biopsy
- BUT, unfortunately, 50% result in death within 5 years & indeed may have already metastasized by the time the primary lesion is discovered.

- Oral cancers occur in elderly & is rare before the age of 40y

- **Sites: the 3 predominant sites of origin of oral cavity cancer in order of frequency are the:**
  1. Vermilion border of the lateral margins of the lower lip
  2. Floor of the mouth
  3. Lateral borders of the tongue.

- **Grossly** :
  Early lesions appear as pearly white to gray, circumscribed thickenings of the mucosa, resembling leukoplakic patches.

  Later, they may grow in an exophytic, visible & palpable nodular mass & eventually fungating tumor, or they may assume an endophytic invasive pattern, with central necrosis to create malignant ulcer.

  SCCa are usually moderately to well-differentiated keratinizing tumors.

  Before the lesions become advanced it may be possible to identify epithelial atypia, dysplasia, or ca in situ in the margins, suggesting origin from leukoplakia or erythroplakia.

- Regional LN spread is present at the time of initial diagnosis: مهمم
  1. only rarely with lip cancer
  2. in 50% of cases of tongue cancer
  3. in > 60% of with cancer of the floor of the mouth.

- Distance metastases is less common than regional spread.

- **Clinically** :

1. many lesions are asymptomatic & therefore they are ignored by the patient
2. Some may cause local pain or difficulty in chewing.
3. When these cancers are discovered at an early stage, 5-year survival can exceed 90%. مهم
4. However, the overall 5-year survival rates (5ySR) after surgery & adjuvant radiation & chemotherapy are only 40% for ca of the base of the tongue, pharynx, & floor of the mouth without LN metastasis,
5. compared with less than 20% for those with LN metastasis.

SALIVARY GLAND DISEASES

1. Sialadenitis

- Mucocele, the most common lesion of the salivary glands results from blockage or rupture of a salivary gland duct, with consequent leakage of saliva into the surrounding tissues, most often found in the lower lip, as a consequence of trauma.
  *Sialadenitis is inflammation of the major salivary glands, may be of traumatic, viral, bacterial, or autoimmune origin.

- Mumps: is a common cause of sialadenitis.
  It is an infectious viral disease, caused by paramyxovirus, which may produce enlargement of all the major salivary glands, but predominantly the parotids.

- **H** :
  there is diffuse, interstitial inflammation marked by edema & a mononuclear cell infiltration & sometimes, by focal necrosis.

- Although childhood mumps is self-limiting disease, mumps in adults may be accompanied by orchitis (which, if bilateral, may causes permanent sterility), or pancreatitis.

- **Bacterial sialadenitis mostly occur secondary to**:

1. Ductal obstruction by stone (sialolithiasis)
2. Retrograde entry of oral cavity bacteria (most commonly Staphylococcus aureus & Streptococcus viridans), under conditions of severe systemic dehydration such as the postoperative state.

In addition, persons with chronic, debilitating medical conditions, or compromised immune function are at risk for acute bacterial sialadenitis.

The sialadenitis may be largely interstitial, may cause focal areas of suppurative necrosis, or even abscess formation.

- **Sjögren syndrome** :
  is a clinico-pathological entity, characterized by dry mouth (xerostomia) & dry eyes (keratoconjunctivitis sicca), resulting from immune-mediated destruction of all the major & minor salivary glands; as well as the lacrimal glands, and causes production of saliva & tears.

- The combination of salivary & lacrimal gland inflammatory enlargement, which is usually painless, xerostomia, whatever the cause, is sometimes referred to as **Mikulicz syndrome**.
  The causes include sarcoidosis, leukemia, lymphoma, & idiopathic lymphoepithelial hyperplasia.

Lecture 2

Salivary Gland Tumors (T)

- The salivary gland give rise to 30 types of tumors!
- About 80% of T occur within the parotid glands,10% in the submandibular, 10% in sublingual and minor salivary glands
- In the parotids, 70% of these T are benign,
- whereas 40% of submandibular glands & 50% of minor glands, & 80% of sublingual glands are cancerous.
- Thus, the likelihood that a salivary gland tumor is malignant is inversely proportional, roughly, to the size of the gland!
- M/F ratio is 1:1, & T usually occur in 6th or 7th decade.

- The most common malignant T of the salivary gland is mucoepidermoid carcinoma, 65% of which occurs in the parotids.
- When primary or recurrent benign T are present for many (10-20) years, malignant transformation may occur, referred to then as a malignant mixed salivary gland tumor.

Pleomorphic Adenoma (Mixed Tumor) of Salivary Glands

- accounts for more than 90% of BT of the salivary glands.
- a slowly-growing T, rarely exceeding 6 cm in diameter
- mostly arise in the superficial parotid, causing painless discrete mass & swelling at the angle of the jaw.

- Although the T is well-demarcated, & apparently encapsulated, histologic examination often reveals multiple sites where the T penetrates the capsule, therefore, adequate margins of resection are thus necessary to prevent recurrences.

- This may require sacrifice of the facial nerve, which pass through the parotid gland.
- 10% of T excisions are followed by recurrence.

- Characteristically, T is histologically heterogeneous with:

1. epithelial T cells forming ducts, acini, tubules, strands, or sheets. The cells are small, dark, & range from cuboidal to spindle forms, these epithelial cells are
2. These epithelial elements are intermingled with a loose, often myxoid connective tissue stroma sometimes containing islands of apparent cartilage or, rarely, bone

- Immunohistochemical evidence suggests that all of the diverse cell types in the T are of myoepithelial derivation.

Warthin Tumor (Papillary Cystadenoma Lymphomatosum)

- Infrequent BT, occurs only in the parotid gland.
- It is thought to arise from heterotopic salivary tissue trapped within a regional LN during embryogenesis.
- Usually, small, well-encapsulated, round mass, cut section (C/S) reveals mucin-containing cystic spaces within a soft gray background.
- H, it shows:
  1. a two-tiered epithelial layer lining the branching, cystic, or cleftlike spaces
  2. an immediately subjacent, well-developed lymphoid tissue + germinal centers.
- A recurrence rate of about 10% is attributed to incomplete excision, multicentricity, or a 2nd primary tumor.
- Malignant transformation is rare; about half of reported cases have had prior radiation exposure.

ESOPHAGUS

- Symptoms:
  All esophageal lesions produce Dysphagia (difficulty in swallowing), mostly due to narrowing or obstruction of lumen, or deranged esophageal motor function.

  Usually Heartburn (retrosternal burning pain) reflects regurgitation of gastric contents into the lower esophagus.

  Less commonly, Hematemesis (vomiting of fresh blood) & Melena (black, sticky & shiny stool due to the presence of altered blood) are evidence of severe inflammation, ulceration, or laceration of the esophageal mucosa. Massive hematemesis may be due to rupture of esophageal varices.

ANATOMIC & MOTOR DISORDERS

Infrequent Anatomic Disorders of the Esophagus:

Disorder	Clinical Presentation & Pathology
Stenosis	Adult with progressive dysphagia to solids & eventually, to all solid and liquid foods; usually due to lower esophageal narrowing resulting from chronic inflammatory disease, including gastroesophageal reflux
Atresia (absence of a lumen) & fistula	Newborn with aspiration, paroxysmal suffocation, pneumonia; esophageal atresia + tracheoesophageal fistula may occur together.
Webs, rings	Episodic dysphagia to solid foods; an acquired mucosal web or mucosal & submucosal concentric ring partially occluding the esophagus
Diverticula	An acquired outpouching of the esophageal wall resulting in episodic food regurgitation, especially nocturnal; sometimes pain is present

1. Achalasia

- Achalasia means "failure to relax", or incomplete relaxation of the lower esophageal sphincter (LES) due to :
  ↑ LES tone in response to swallowing, producing functional obstruction, with consequent dilation of the more proximal esophagus.
- **Achalasia characteristic triad are incomplete LES relaxation + ↑ LES tone + esophageal aperistalsis**

- **Achalasia occurs most commonly as**

(I) primary disorder	(II) Secondary achalasia
uncertain etiology, with loss of intrinsic inhibitory innervation of the LES, resulting in : 1. Progressive dilation of the esophagus, above the level of the LES. The wall of the esophagus may be of normal, thicker than normal {because of hypertrophy of the muscularis}, or markedly thinned by dilation. The myenteric ganglia are usually absent from the body of the esophagus (causes esophageal aperistalsis), but may/may not be reduced in number in the region of the lower esophageal sphincter. Inflammation in the location of the esophageal myenteric plexus is ® pathognomonic of the disease. 2. Food stasis produces secondary mucosal inflammation & ulceration proximal to the lower esophageal sphincter.	less common than the primary may arise from diverse pathologic processes that impair esophageal function, classic example is: • Chagas disease, caused by Trypanosoma cruzi, which causes destruction of the myenteric plexus of the esophagus, duodenum, colon, & ureter. • Disorders of the dorsal motor nuclei such as polio, & autonomic neuropathy in DM can cause secondary achalasia.

- **Clinically** : achalasia is characterized by
  1. progressive dysphagia.
  2. Nocturnal regurgitation
  3. Aspiration of undigested food may occur.

  Achalasia most serious complication is the hazard of developing esophageal SCCa reported to occur in about 5% of patients & typically at an earlier age than in those without it.

2. Hiatal Hernia (HH)

- Cause of HH is separation of the diaphragmatic crura & widening of the space between the muscular crura & the esophageal wall which permits a dilated segment of the stomach to protrude above the diaphragm.
- Two anatomic patterns of HH re recognized:

1. Sliding or axial HH
   constituting (95%) of cases; protrusion of the stomach above the diaphragm creates a bell-shaped dilation, bounded below by the diaphragmatic narrowing

2. Paraesophageal (rolling) or nonaxial HH
   (5%), in which a separate portion of the stomach (usually along the greater curvature), enters the thorax through the widened foramen.

- The cause of this deranged anatomy, whether congenital or acquired, is unknown!

- HH, on the basis of radiographic studies, are reported in 1% to 20% of adults, & ↑ in incidence with age,
  BUT only about 9% of these adults, suffer from heartburn or regurgitation of gastric juices into the mouth!

- Therefore, symptoms of HH are more likely result from :
  incompetence of the LES rather than from the HH per se & are accentuated by positions favoring reflux (bending forward, lying supine) & obesity.

- Although most individuals with sliding HH do not have reflux esophagitis, those with severe reflux esophagitis are likely to have a sliding HH.

- Other complications of both types of HH include:

1. mucosal peptic ulceration 2. bleeding 3. perforation.

- **Paraesophageal HH rarely induce reflux, but they can become strangulated or obstructed.**

3. Lacerations (Mallory-Weiss Syndrome)

- Mallory-Weiss tears are longitudinal tears in the lower esophagus, at the esophagogastric junction

- They may occur during severe vomiting for any reason, especially in chronic alcoholics after a bout (attack) of severe retching (the try for vomiting) or vomiting.

- **Cause**:
  inadequate relaxation of the musculature of the lower esophageal sphincter (LES) during vomiting, with stretching & tearing of the esophagogastric junction at the moment of expulsion of gastric contents.

- It account for 5% to 10% of upper GIT bleeding episodes.
  Mostly, the bleeding is not profuse & ceases without surgical intervention, But life-threatening hematemesis may occur.

VARICES

- When portal venous blood flow into the liver is impeded or obstracted (most common example is cirrhosis or fibrosis)
- The resultant portal hypertension induces the formation of collateral bypass channels wherever the portal & systemic systems communicate.
- Portal blood flow is thereby diverted through the stomach veins into the plexus of esophageal submucosal veins, thence into the azygos veins & the superior vena cava.
- The ↑ pressure in the esophageal plexus produces dilated tortuous vessels called varices.

- **Endoscopically** :

  when the varices are unruptured, they appear as tortuous dilated veins lying primarily within the submucosa of the distal esophagus & proximal stomach.
  The covering mucosa may be normal with irregular protrusion into the lumen, or eroded & inflamed because of its exposed position, resulting in further weakening of the tissue support of the dilated veins

- NB. {varices are collapsed in surgical or PM specimens}.
- Varices are asymptomatic until they rupture.
- Variceal rupture produces massive hemorrhage (H) into the lumen, & into the esophageal wall.
- Varices are present in 2/3 of all cirrhotic patients.
- In the US, esophageal varices are most often associated with alcoholic cirrhosis.

- 50% of deaths in cirrhotic patients result from rupture of a varix, either as a direct result of the H or from the hepatic coma triggered by the H

- However, even when varices are present, they account for less than 50% of all episodes of hematemesis, with bleeding from concomitant : gastritis, PU, or esophageal laceration accounts for the rest.

- Once begun, variceal H subsides spontaneously in 50% of cases.
- Treatment is by endoscopic injection of thrombotic agents (sclerotherapy) or balloon tamponade.
- When varices bleed, 20% to 30% of patients die during the 1st episode.
- Among survivors, rebleeding occurs in 70% within 1 year, with a similar rate of mortality for each episode.

ESOPHAGITIS

- Injury to the esophageal mucosa with subsequent inflammation (esophagitis) is a common condition worldwide.
- Esophagitis may be cause by
  1. ingestion of corrosive or irritant substances
  2. prolonged naso-gastric (NG) intubation
  3. uremia & radiation or chemotherapy, among other causes.

- Esophagitis prevalence in northern Iran is more than 80%; it is also extremely high in regions of China. The basis of this prevalence is unknown!
- The majority of cases in Western countries is attributable to reflux of gastric contents (reflux esophagitis, or gastroesophageal reflux GER disease).
- It affects about 0.5% of the US adult population (375Millons), (i.,e.,1 Million); & its dominant symptom is recurrent heartburn.

- ↓ Efficacy of esophageal antireflux mechanisms, CNS depressants, alcohol or tobacco exposure may be the contributing causes; But most often no obvious etiology is identifiable!
- **Grossly** :
  mild esophagitis may appear as simple hyperemia.
  In severe esophagitis, there may be confluent epithelial erosions or total ulceration into the submucosa.

- Three **histologic features** are characteristic of uncomplicated reflux esophagitis, although only one or two may be present:
  1. Intraepithelial eosinophils with/without neutrophils (Intraepithelial neutrophils are markers of severe injury);
  2. Basal zone hyperplasia
  3. Elongation of lamina propria papillae.

- **Clinically**:
  there is heartburn [the severity of which is not closely related to the presence & degree of anatomic esophagitis], sometimes accompanied by regurgitation of a sour brash.
  Complications of severe reflux esophagitis are: Bleeding, Ulceration, Stricture, & Barrett esophagus, with its predisposition to malignancy.

BARRETT ESOPHAGUS

- (D) Is replacement of the normal distal esophageal stratified squamous mucosa by metaplastic columnar epithelium containing goblet cells.

- Is a complication of long-standing gastroesophageal reflux, occurring in 5%-15% of persons with persistent symptomatic reflux disease.

- However has been detected in about the same proportions in asymptomatic populations!

- Affects males more than females (4:1) & is much more common in whites than in other races.

- **Pathogenesis** :
- prolonged & recurrent gastroesophageal
- Reflux produce inflammation & eventually
- Ulceration of the squamous epithelial lining.
- Healing occurs by ingrowth of progenitor cells & re-epithelialization. In the microenvironment of an abnormally acidic low pH in the distal esophagus caused by acid reflux, the cells differentiate into columnar epithelium.
- Metaplastic columnar epithelium is thought to be more resistant to injury from refluxing gastric contents

- **Complications** :
- Ulcer & stricture may develop, but the chief complication of Barrett e. is the risk of the development of adenocarcinoma.
- Barrett e. patients have a 30 to 100 fold greater risk of developing esophageal adenoca than do normal populations.
- The greatest risk being associated with high-grade dysplasia.
- Hence, periodic screening for high-grade dysplasia with esophageal biopsy is recommended for sufferers whom require therapeutic interventions.

- **GROSSLY** :
  Barrett e. appears as a salmon-pink, velvety mucosa between the smooth, pale-pink esophageal squamous mucosa & the lusher light brown gastric mucosa.

- It may exist as
  1. "tongues" extending up from the gastroesophageal junction
  2. an irregular circumferential band displacing the squamocolumnar junction cephalad (upwards)
  3. isolated patches (islands) in the distal esophagus.

ESOPHAGEAL CARCINOMA

- Worldwide, SCCa constitutes 90% of esophageal cancers,
- however, in US, there has been a very large ↑ (3 to 5 fold in the last 40 years) in the incidence of adenocarcinoma associated with Barrett esophagus, which has surpassed SCCa incidence in the US!

- Adenoca arising in Barrett e. is more common in whites than in blacks.
- By contrast, SCCa is more common in blacks worldwide.
- There are striking & puzzling differences in the geographic incidence of esophageal ca.

- In the US, there are 60 new cases/Million population/year, accounting for 1% to 2% of all cancer deaths; while
- In regions of Asia extending from the northern China to Iran, the prevalence is well over 1000 new cases/Million/year & 20% of cancer deaths are caused by esophageal ca, mainly SCCa!

- **Risk Factors for esophageal SCCa**

Esophageal Disorders	Long-standing esophagitis – Achalasia - Plummer-Vinson syndrome (esophageal webs, microcytic hypochromic anemia, atrophic glossitis)
Life-style	Alcohol consumption - Tobacco abuse
Dietary	Deficiency of vitamins (A, C, riboflavin, thiamine, pyridoxine) - Deficiency of trace metals (zinc, molybdenum) - Fungal contamination of foodstuffs - High content of nitrites/nitrosamines
Genetic Predisposition	Tylosis (hyperkeratosis of palms & soles)

1. Squamous Cell Carcinoma (SCCa)

- An important contributing variable is retarded passage of food through the esophagus, & prolonging mucosal exposure to potential carcinogens such as those contained in tobacco & alcohol
  These two agents are associated with the majority of SCCa in Europe & US.

- However, other influences, perhaps in the diet, must underlie the very high incidence of this cancer among the orthodox Moslems of Iran, whom neither drink nor smoke!

- The high levels of nitrosamines & fungi contained in some foods probably account for the very high incidence of this tumor in some regions of China. A strong association with Human Papilloma Virus (HPV) occurs only in high-incidence areas.

- Abnormalities affecting the p16/INK4 tumor suppressor gene & the EGFR are frequently present in SCCa of the esophagus.
- Mutations in p53 are detected in as many as 50% of these T & are generally correlate with the use of tobacco & alcohol. Unlike ca colon, mutations in the K-RAS & APC genes are uncommon.

- **Morphology** :
  SCCa are usually preceded by a long period of mucosal epithelial dysplasia, followed by ca in situ & finally, after invading the basement membrane, the emergence of invasive ca.

- **GROSSLY** :
  early lesions appear as small gray-white, plaque like thickenings or elevations of the mucosa.

  In months to years, these lesions enlarged, taking 1 of 3 forms:
  1. Polypoid exophytic masses, that protrude into the lumen
  2. Diffuse infiltrative T that cause thickening & rigidity of the wall & narrowing of the lumen.
  3. Ulcerating T that invade deeply & may erode the respiratory tree, aorta, or elsewhere

- Whichever the pattern of esophageal SCC; about 20% arise in upper 1/3 & the cervical esophagus, 50% in the middle 1/3, & 30% in the lower 1/3.

2. Adenocarcinoma (Adenoca)

- Barrett e. is the only recognized precursor of esophageal adenocarcinoma.
- The degree of dysplasia is the strongest predictor of the progression to cancer.
  Individuals with low-grade dysplasia have very low rates of progression to adenoca.

- But the progression to adenoca may be 10% or more per year in individuals with high-grade dysplasia.
- Overall, the risk for developing adenoca varies from 30 to more than 100-fold above normal.
- There are no specific markers that precisely identify the transition from high-grade dysplasia to cancer.

- **Grossly** :
  adenoca seem to arise from dysplastic mucosa in the setting of Barrett e.

  Unlike SCCa, they are usually in the distal one-third of the esophagus & may invade the subjacent gastric cardia.

  Initially appearing as flat or raised patches on intact mucosa, they may develop into large nodular masses or diffusely infiltrative, or show deeply ulceration.

- **H** :
  in keeping with the morphology of the preexisting metaplastic mucosa, the tumors are mucin-producing adenocarcinoma showing intestinal-type features.

- **Clinically** :
  all esophageal cancers, adenocarcinomas & SCCa are slow & insidious in onset, producing dysphagia with gradual & late obstruction, followed by anorexia, weight loss, fatigue, weakness & pain on swallowing.

- **Diagnosis** :
  is usually made by imaging, endoscopy & biopsy techniques.

- Surgical excision is rarely curative, because esophageal cancers extensively invade the rich lymphatic network & adjacent structures relatively early in their development, thus, much emphasis is placed on the surveillance procedures for individuals with persistent manifestations of chronic esophagitis or known Barrett e.

STOMACH

- Congenital Gastric Anomalies: Condition & Comment:

Pyloric stenosis	1 in 300-900 live births, M/Female ratio 3:1, = muscular hypertrophy of pyloric smooth muscle wall, persistent, nonbilious projectile vomiting in young infant
Diaphragmatic hernia – Rare	herniation of stomach & other abdominal contents into thorax through a diaphragmatic defect, Symptoms: acute respiratory distress in newborn
Gastric heterotopia	a nidus of gastric mucosa in the esophagus or small intestine ("ectopic rest") Uncommon asymptomatic, or an anomalous (atypical) PU in adult

- **Clinically** :
  gastric disorders give rise to symptoms similar to esophageal disorders:
  - primarily heartburn & vague epigastric pain.
  - With breach of the gastric mucosa & bleeding, either as a hematemesis or melena may ensue,
  - BUT unlike esophageal bleeding which is red & liquid, the blood quickly thrombose or solidify & turns brown in the acid environment of the stomach lumen; & therefore vomited blood has the appearance of coffee grounds, with black granules.

GASTRITIS

- Gastritis is simply defined as inflammation of the gastric mucosa.
  By far the majority of cases are chronic gastritis, but occasionally, distinct forms of acute gastritis are encountered.
- **Chronic Gastritis**
  (D) the presence of chronic inflammatory changes in the mucosa, leading eventually to mucosal atrophy & intestinal metaplasia.
- In the West, the prevalence of histologic changes of chronic gastritis is higher than 50% in the later decades of life.

- **Pathogenesis**

a. The important & the most common (90%) etiology for chronic gastritis is chronic infection {H. pylori associated chronic gastritis}.
   This organism is a worldwide pathogen, & American adults older than age 50 show prevalence rates approaching 50%.
   In endemically infected areas, the infection seems to be acquired in childhood & persists for decades, with most infected individuals having the associated gastritis, but are asymptomatic.

- (Robin Warren, a pathologist, & Barry Marshall, a medical student at the time of the discovery, received the 2005 Nobel prize in Medicine for their identification in 1982 of H. pylori, originally called Campylobacter, in 1875 !).

- H. pylori is a noninvasive, non-spore-forming, S-shaped gram-negative rod measuring 3.5 μm × 0.5 μm.
- The gastritis develops as a result of the combined influence of bacterial enzymes & toxins; & release of noxious chemicals by recruited neutrophils (see PU).

- H. pylori associated gastritis may develop in two patterns:
  1. Antral-type with high acid production & ↑ risk for the development of DU
  2. Pangastritis with multifocal mucosal atrophy, with low acid secretion & ↑ risk for gastric adenocarcinoma.

- **Most individuals with PU, whether DU or GU, have H. pylori infection.**

- Persons with H. pylori associated chronic gastritis usually improve symptomatically when treated with antibiotics & proton pump inhibitors.

Lecture 4

b. Autoimmune gastritis

is less common form of chronic gastritis (10% of cases) in the US, seen mostly in Scandinavia.

It results from the production of autoantibodies to the gastric gland parietal cells, specially to the acid-producing enzyme H+, K+ -ATPase, leading to mucosal atrophy & gland destruction with concomitant loss of :

1. intrinsic factor production leading to pernicious anemia
2. acid.

It may be seen in association with other autoimmune disorders e.g., Hashimoto thyroiditis & Addison disease.

- **H** :

in all (A & B) cases of chronic gastritis:

1. There is inflammatory lymphocytic & plasma cell infiltrate in the lamina propria, occasionally accompanied by neutrophilic inflammation of the neck region of the mucosal pits.

2. There is variable mucosal atrophy & gland loss.

3. When present, H. pylori are found nestled within the mucus layer overlying the superficial mucosal epithelium.

4. In the autoimmune type, loss of parietal cells is very prominent.

- **Two additional features are of note.**
  1. Intestinal metaplasia = replacement of gastric epithelium with columnar & goblet cells of intestinal variety.
     Dysplasia of this metaplastic epithelium predispose to intestinal-type carcinoma of the stomach.

  2. H. pylori-induced proliferation of lymphoid tissue within the gastric mucosa, a precursor of gastric lymphoma.

- **Clinically** : chronic gastritis is usually
  (a) asymptomatic; but
  (b) it may cause upper abdominal discomfort, nausea & vomiting.
  (c) In the setting of autoimmune gastritis, the severe parietal cell loss causes hypochlorhydria or achlorhydria with hypergastrinemia are characteristically present.

- The long-term risk of gastric carcinoma for persons with H. pylori-associated chronic gastritis is ↑ X 5 fold relative to the normal population.
- For autoimmune gastritis, the risk for ca is 2% to 4% of affected individuals, well above that of the normal population.

Acute Gastritis

- Is transient acute gastric mucosal inflammation, may be accompanied by hemorrhage into the mucosa &, in more severe cases, by sloughing of the superficial mucosal epithelium, i.e., erosive gastritis, which is an important cause of acute GIT bleeding.

- **Acute gastritis is frequently associated with:**
  1. NSAIDs heavy use, particularly aspirin,
  2. Alcohol excessive consumption,
  3. Smoking, heavy one
  4. Cancer chemotherapeutic drugs administration
  5. Uremia,
  6. Systemic infections (e.g., salmonellosis),
  7. Severe stress (e.g., trauma, burns, surgery),
  8. Ischemia & shock,
  9. Suicide attempts with acids & alkali,
  10. Mechanical trauma (e.g., nasogastric {NG} intubation),
  11. Reflux of bilious material after distal gastrectomy

- **pathogenesis** :
  is poorly understood, in part because normal mechanisms for gastric mucosal protection are not totally clear.

- One or more of the following influences are thought to be operative in the above settings:

1. Disruption of the adherent mucous layer
2. ↑ Stimulation of acid secretion with hydrogen ion back- diffusion into the superficial epithelium,
3. Decreased production of bicarbonate buffer by superficial epithelial cells
4. Reduced mucosal blood flow, & Direct damage to the epithelium.
5. Acute H. pylori infection induces acute gastritis.

- Not surprisingly, mucosal insults can act synergistically

- **Morphology** :
  On gastroscopic exam, acute gastritis ranges from extremely localized (as occurs in NSAID-induced injury) to diffuse, & from superficial inflammation to involvement of the entire mucosal thickness with hemorrhage & focal erosions.
  Concurrent erosion & hemorrhage is called acute erosive gastritis.

- **H** :
  All variants are marked by :
  mucosal edema + inflammatory infiltrate of neutrophils + monocytes + regenerative replication of epithelial cells in the gastric pits is usually prominent.

  Provided that the noxious event is short lived, acute gastritis may disappear within days with resolution & complete restitution of the normal mucosa.

- **Clinically** :
  depending on the severity, acute gastritis may be
  (a) entirely asymptomatic (b) may cause variable epigastric pain, nausea & vomiting,
  (c) may present as overt hematemesis, melena, & potentially fatal blood loss.

- Acute erosive gastritis is one of the major causes of hematemesis, particularly in alcoholics.

- 25% of persons who take daily aspirin for RA develop acute gastritis at some time in their course, many with occult or overt bleeding. The risk of gastric bleeding from NSAID- induced gastritis is dose related, thus ↑ the likelihood of this complication in persons requiring long-term use of such drugs.

GASTRIC ULCERATION

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

  Ulcers of the GIT are breach in the mucosa that extends through the muscularis mucosae into the submucosa or deeper.
  Although ulcers may occur anywhere in the GIT, by far, the most common are the peptic ulcers (PU) that occur in the duodenum (Duodenal PU = DU) & stomach (gastric PU = GU).

Peptic Ulcers (PU)

- are lesions caused by acid peptic digestion of the wall in any portion of the GIT. They are chronic & mostly solitary.
- At least 98% of PU are either in the first portion of the duodenum or in the stomach, in a ratio of 4 DU: 1GU.

- **Epidemiology :**
  PU are remitting, relapsing lesions that are most often diagnosed in middle-aged to older adults, but they may first become evident in young adult life.
  PU often appear without obvious precipitating influences & may then heal after a period of weeks to months of active disease
  Even with healing, however, the propensity to develop PU remains, in part because of recurrent infection with H. pylori.

  In US, about 10% of males & 4% of females have PU.
  The male/female ratio for DU is about 3:1.
  For both men & women in the US, the lifetime risk of developing PU is about 10% (i.e., 30 Million).

- **DU are more frequent in persons with**
  1. chronic renal failure (CRF),
  2. hyperparathyroidism {in these conditions, hypercalcemia, whatever its cause, stimulates gastrin production & therefore acid secretion)
  3. alcoholic cirrhosis
  4. chronic obstructive pulmonary disease (COPD)

- **Pathogenesis of PU** :
  2 conditions are essential or key for the development of PU :
  1. H. pylori infection, which has a strong causal relationship with peptic ulcer development
  2. Mucosal exposure to gastric acid & pepsin.

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

- H. pylori infection is the most important condition in the pathogenesis of PU.
  The infection is present in 70% to 90% of persons with DU & in about 70% of those with GU.
  Furthermore, antibiotic treatment of H. pylori infection promotes healing of ulcers & tends to prevent their recurrence.

- **Pathogenesis** :
  The possible mechanisms by which the non- invasive H. pylori induces an intense inflammatory & immune response, tipping the balance of mucosal defenses are:
  1. There is production of proinflammatory cytokines such as TNF, IL-1, IL-6,, &, most notably, IL-8. IL-8 is produced by the mucosal epithelial cells, & it recruits & activates neutrophils.

  2. Epithelial injury is mostly caused by a vacuolating toxin called VacA, which is regulated by the cytotoxin-associated gene A (CagA) of the H. pylori .

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

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

  5. H. pylori enhance gastric acid secretion & impair duodenal bicarbonate production, thus reducing luminal pH in the duodenum. This altered milieu seems to favor gastric metaplasia (the presence of gastric epithelium in the first part of the duodenum). Such metaplastic foci provide areas for H. pylori colonization

  6. Several H. pylori proteins are immunogenic & they evoke a robust immune response in the mucosa. Both activated T cells & B cells can be seen in H. pylori associated chronic gastritis. The B lymphocytes aggregate to form follicles.
     The role of T & B cells in causing epithelial injury is not established, but T-cell-driven activation of B cells may be involved in the pathogenesis of gastric lymphomas (MALT lymphomas, discussed later).

- Only 10% to 20% of individuals worldwide who are infected with H. pylori actually develop PU. Hence, a key enigma is why most are spared & some are susceptible?
  suffice it to say, that while the link between H. pylori infection & GU & DU is well established, variability in host-pathogen interactions leading to ulceration remains to be discovered!

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

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

  Risk factors for NSAID-induced gastroduodenal toxicity are increasing age, higher dose, & prolonged usage. Thus, those who take these drugs for chronic RA are at particularly high risk.

  Key to NSAID-induction of peptic ulceration is their suppression of mucosal prostaglandin synthesis, resulting in:
  1. ↕ secretion of hydrochloric acid
  2. ↓ bicarbonate & ↓ mucin production,
     Loss of mucin degrades the mucosal barrier that normally prevents acid from reaching the epithelium.
  3. Synthesis of glutathione, a free-radical scavenger, is also reduced.

- **Other events may act alone or in concert with H. pylori & NSAIDs to promote peptic ulceration:**
  1. Gastric hyperacidity may be strongly ulcerogenic.
  2. Excess production of gastric acid from a tumor in individuals with the Zollinger-Ellison syndrome causes multiple peptic ulcerations in the stomach, duodenum, & even the jejunum.
  3. Cigarette smoking impairs mucosal blood flow & healing.
  4. Alcohol has not been proved to directly cause peptic ulceration, but alcoholic cirrhosis is associated with an ↑ incidence of DU
  5. Corticosteroids in high dose & with repeated use promote ulcer formation.
  6. Personality & psychological stress are important contributing variables. Although this is now accepted as "common wisdom," actual data on cause & effect are lacking.

- **Grossly** : All PU, whether GU or DU, have identical appearance
  -PU are defects in the mucosa that penetrate at least into the submucosa, & often into the muscularis propria or deeper.

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

  -PU are round, usually single, & favored sites are the anterior & posterior walls of the first portion of the duodenum & the lesser curvature of the stomach. Occasional gastric PU occur on the greater curvature or anterior or posterior walls of the stomach, the very same locations of most ulcerative ca.

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

  -PU surrounding mucosal folds may radiate like wheel

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

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

  -PU crater perforation through the duodenal or gastric wall (complicate 5% of PU) may leads to localized or generalized peritonitis. Alternatively, the perforation is sealed by an adjacent structure like adherent omentum, pancreas or liver.

- **In a chronic, open PU, four zones can be distinguished :**
  1. PU base & margins have a thin layer of necrotic fibrinoid debris underlain by
  2. A zone of active nonspecific inflammatory infiltration with neutrophils predominating, underlain by
  3. Granulation tissue, deep to which is
  4. Fibrous, collagenous scar that fans out widely from the margins of the ulcer.
  Vessels trapped within the scarred ulcer base are characteristically thickened & obliterated, but sometimes they are widely patent

Lecture 5

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

- Chronic gastritis is extremely common among persons with PU, & H. pylori infection is almost always demonstrable in those persons with gastritis. Similarly, individuals with NSAID- associated PU do not have gastritis unless there is coexistent H.pylori infection. This feature is helpful in distinguishing PU from acute gastric ulceration in which gastritis in adjacent mucosa is generally absent.

- **Clinically** :
  Most PU cause epigastric pain, (burning, or boring), tends to be worse at night & occurs usually 1 to 3 hours after meals during the day,& classically relieved by alkalis or food, but there are exceptions. Nausea, vomiting, bloating, belching, & significant weight loss are additional manifestations.

  A significant minority of patients present first with complications, including:
  a. Bleeding → is the commonest complication, occurring in 1/3 of patients, & may be life-threatening.
  b. Perforation → occurs in 5% of patients, accounts for 2/3 (most common cause of) deaths from PU in US.
  c. Obstruction of the pyloric channel, is rare.
  d. Malignant transformation → occurs in about 2% of patients, generally from PU in the pyloric channel, BUT it is unknown in DU!

Acute Gastric Ulceration (Stress ulcer)

- Stress ulcers are focal, mostly multiple, acute mucosal defects that may appear after severe physiologic stress.
- **Clinically** :
  A high percentage of persons admitted to hospital intensive care units with sepsis, severe burns, or trauma develop superficial gastric erosions or ulcers, which may be of limited clinical consequence or may be life-threatening.

- **Stress ulcers are commonly seen in the following conditions:**
  (1) Severe trauma, including major surgical procedures, sepsis, shock, or grave illness of any type
  (2) Chronic exposure to gastric irritant drugs, particularly NSAIDs & corticosteroids
  (3) Extensive burns (Curling ulcers)
  (4) Traumatic or surgical injury to the CNS or an intracerebral hemorrhage (Cushing ulcers; carry high risk of perforation).

- **Pathogenesis** : is uncertain & may vary with the setting.
  NSAID-induced ulcers are linked to ↓ prostaglandin production.

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

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

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

  Unlike chronic PU, acute stress ulcers are:
  (1) Although may occur singly, more often they are multiple
  (2) Found anywhere in the stomach and located throughout the stomach & duodenum.

- **H** :
  acute stress ulcers are abrupt (sudden) lesions, with unremarkable normal adjacent mucosa, ranging in depth from:
  (A) Very superficial erosion, which are, in essence, an extension of acute erosive gastritis, to
  (B) Deeper ulcers involving the entire mucosal thickness (true ulceration) but do not penetrate the muscularis propria.

  Acute stress ulcers are not precursors of chronic PU.

  Acute stress ulcers can recover completely if the person does not die from the primary disease, & therefore,

  the single most important determinant of clinical outcome is the ability to correct the underlying condition.

GASTRIC TUMORS: Gastric Polyps

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

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

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

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

1.Hyperplastic polyps	80% -85%	arise from an exuberant reparative response to chronic mucosal damage & hence are composed of a hyperplastic mucosal epithelium & an inflamed edematous stroma. They are not true tumors
2.Fundic gland polyps	10%	are small collections of dilated corpus-type glands thought to be small hamartomas
3.Adenomatous polyps	5%	are true tumors, contain dysplastic epithelium & in which, there is a definite risk of harboring adenocarcinoma, which ↑ with ↑ polyp size

- Both types 1 & 2 polyps are essentially innocuous
- Histologic examination is mandatory, because different types of gastric polyps cannot be distinguished by endoscopy,

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- **Gastric Tumors**
  The most common & most important malignant T of the stomachs is carcinoma (90%), discuss below; [followed by lymphomas (4%), carcinoids (3%),& gastrointestinal stromal tumors {GISTs} (2%), which are discussed later].

1. Gastric Carcinoma (ca)

- Epidemiology: Gastric ca is the 2nd leading cause of cancer-related deaths in the world (Lung is the first)
  Japan & South Korea have the highest incidence (X 8 to 9 times higher than in the US & Western Europe).

- Nevertheless, in most countries there has been a steady decline in the overall incidence & the mortality of gastric cancer (Why? refrigeration).
  The 5-year survival rate is less than 20%.

- **Classification** :
  Gastric ca show 2 morphologic types : intestinal & diffuse types. They can be considered as distinct entities, although their clinical outcome is similar.

(I) Intestinal type	(II) Diffuse variant
initial chronic gastritis, accompanied by severe gastric atrophy & intestinal metaplasia, which are followed by dysplasia & intestinal type ca.	is not associated with chronic gastritis, thought to arise de novo from native gastric mucous cells
It tends to be better differentiated & is the more common type in high-risk populations.	tends to be poorly differentiated
It occurs primarily after age 50 years with a 2:1 Male/Female ratio	It occurs at an earlier age than the intestinal type with female predominance
Its incidence has progressively diminished in the US	The incidence of diffuse gastric ca has not significantly changed in US in the past 60 years & now constitutes approximately 50% of gastric ca in the US
Risk Factors : 1- Chronic gastritis with intestinal metaplasia 2- Helicobacter pylori infection 3- Nitrites derived from nitrates (found in drinking water, food & used as preservatives in prepared meats) may undergo nitrosation to form nitrosamines & nitrosamides. Diets containing foods that may generate nitrites (smoked foods, pickled vegetables & excessive salt intake) 4- Decreased intake of fresh vegetables & fruits (antioxidants present in these foods may inhibit nitrosation) 5- Partial gastrectomy 6- Pernicious anemia	Risk Factors : Undefined risk factors, except for a rare inherited mutation of E-cadherin Infection with H. pylori & chronic gastritis are often absent
Etiology & Pathogenesis *Dietary influences have drastically ↓in recent years with the use of refrigeration worldwide, which markedly ↓ the need for food preservation by nitrates, smoking, & salt. *While chronic gastritis associated with H. pylori infection constitutes a major risk factor for gastric ca, particularly high in individuals with chronic gastritis limited to the gastric pylorus & antrum. *The mechanisms of neoplastic transformation are not entirely clear. *Chronic gastritis induced by H. pylori may release ROS, which eventually cause DNA damage, leading to an imbalance between cell proliferation & apoptosis, particularly in areas of tissue repair. *Notably, individuals with H. pylori-associated DU (Not GU) are largely protected from developing gastric cancer! *Amplification of HER-2/NEU & ↑ expression of β catenin are present in 20% to 30% of intestinal-type adenoca cases & are absent in diffuse- type ca.	Etiology & Pathogenesis *precursor lesions have not been identified. *Mutations in E-cadherin, which are not detectable in intestinal-type cancers, are present in 50% of diffuse cancers. *A subset of patients may have a hereditary form of diffuse gastric ca. caused by germ-line mutation in E-cadherin. *Mutations in FGFR2, & ↑ expression of metalloproteinases are present in about 1/3 of cases, but are absent in intestinal- type ca.

- **GROSSLY** :
  The location of gastric ca within the stomach is as follows: pylorus & antrum 60%; cardia, 25%; &15% in the body & fundus. The lesser curvature is involved in about 40% & the greater curvature in 12%. Thus, a favored location is the lesser curvature of the antropyloric region.

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

- Gastric ca is classified on the basis of
  1. depth of invasion,
  2. gross growth pattern
  3. histologic subtype.

- **The morphologic feature** :
  having the greatest impact on clinical outcome is the depth of invasion.
  Early gastric ca is defined as a lesion confined to the mucosa & submucosa, regardless of the presence or absence of perigastric LN metastases.
  Gastric mucosal dysplasia is the presumed precursor lesion of early gastric cancer, which then in turn progresses to "advanced" lesions.

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

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

(1) Exophytic with T mass protrusion into the lumen & the mass may contain portions of an adenoma
(2) Flat or depressed, which may presents only as regional effacement (flattening) of the normal surface mucosa & in which there is no obvious T mass within the mucosa
(3) Ulcerating T, whereby a shallow or deeply erosive ulcer crater is present in the wall of the stomach, which may mimic, in size & appearance chronic PU, although more advanced cases show heaped-up margins.

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

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

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

- All gastric ca eventually penetrate the wall to involve the serosa, spread to regional & distant LN, & metastasize widely.
- For unknown reasons, the earliest LN metastasis may involve a supraclavicular LN {Virchow node}.
- Intraperitoneal spread in females to both ovaries, gives rise to ovarian {Krukenberg tumor}.

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

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

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