



PATHOLOGY



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Aphthous Ulcers (Canker Sores)



- *triggered by:*
stress, fever, ingestion of certain foods, & activation of IBD
 - *Description:*
 - Extremely common
 - small (<5 mm in \square), painful, rounded, shallow ulcers, covered with a gray-white exudate & having an erythematous rim.
 - Appear singly or in groups,
 - they may recur in the same or a different location in the mouth
 - *Appear on:*
the nonkeratinized oral mucosa, specially soft palate, buccolabial mucosa, mouth floor & tongue lateral borders.
 - *Appear when:*
the first 2 decades of life commonly
 - *Resolves:*
Its self-limited resolved within few weeks
-

Herpes Simplex Virus (HSV) Infection

Herpetic stomatitis is an extremely common infection

- caused by : HSV type 1 .
- 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 persist within dormant state in a ganglia of the mouth ,
trigeminal ganglia (the cell body)
- With reactivation of the virus (which may be caused by fever, sun or cold exposure, RTI, or trauma) 5 mm solitary or multiple small vesicles containing clear fluid appear

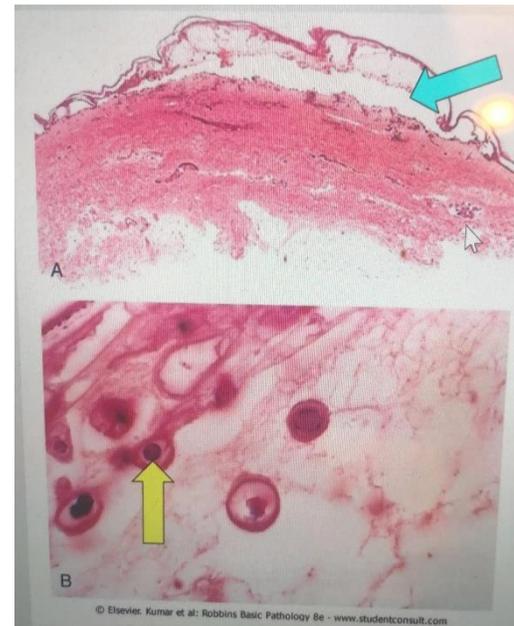
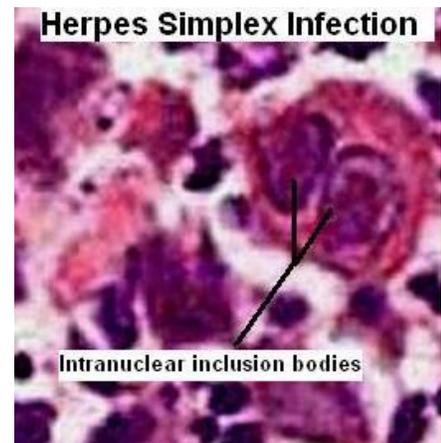
Appearance:

- >5 mm solitary or multiple small 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 .
- The vesicles soon rupture, leaving shallow, painful ulcers that heal within a few weeks, but recurrences are common.



Description:

- The vesicles begin as an intraepithelial focus of intracellular & intercellular 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.



healing:

- Antiviral agents may accelerate healing of the lesions.

Complications:

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

Spread:

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

Other:

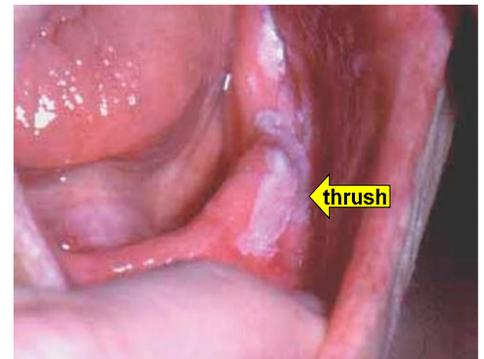
- As a result of changes in sexual practices, genital herpes produced by HSV type 2 (the agent of herpes genitalis) is increasingly seen in the oral cavity.
- The infection produces vesicles in the mouth, which have the same histologic characteristics as those that develop on the genital mucous membranes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

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.

(A white plaque, pseudo membrane like “composed of candidal pseudohyphae” coats the gingival mucosa of the left jaw)



- *Affects Who :*

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.



Histologically:

- 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

Spread:

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.

For unknown reasons, local vagina candidiasis may appear in:

- predisposed females

- apparently healthy young women particularly during pregnancy

- in women who are using oral contraceptives or broad-spectrum antibiotics

AIDS

AIDS & less advanced forms of HIV infection, are often associated with lesions in the oral cavity that may appear as:

- *candidiasis*
- *herpetic vesicles*
- *gingivitis, or glossitis*
- *Hairy leukoplakia*

- *Hairy leukoplakia is an uncommon lesion seen virtually only in persons infected with HIV.*
- *It consists of white confluent patches, anywhere on the oral mucosa, that have a "hairy" or corrugated surface resulting from marked epithelial thickening*
- *caused by Epstein Barr virus (EBV) infection of epithelial cells.*

Kaposi sarcoma

- ❖ *More than 50% of individuals with Kaposi sarcoma develop intraoral (purpuric discolorations or violaceous) nodular masses*



LEUKOPLAKIA

Description:

- whitish mucosal plaque caused by epidermal thickening (Hyperkeratosis and Acanthosis)

- white plaque or patch that cannot be scraped off & **cannot** be characterized as any other disease.

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



- they vary from simple hyperkeratosis without underlying epithelial dysplasia TO severe dysplasia bordering on carcinoma in situ

ONLY histologic evaluation distinguishes these lesions from each other

Appear on :

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.



❖ they are **more** frequent among older **men**

Causing factors:

Leukoplakias are of unknown cause, except that there is a

strong association with :

- the use of tobacco, particularly pipe smoking
- smokeless tobacco (pouches, snuff, chewing).

Less strongly implicated factors are:

- chronic friction, as from ill-fitting dentures or jagged teeth;
- alcohol abuse
- irritant foods.

- ❖ 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.

Malignancy:

- H, the Leukoplakia that display significant dysplasia have greater probability of malignant transformation
- 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.



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

Other lesions:

Three somewhat related lesions must be differentiated from the usual oral leukoplakia.

(1) Hairy leukoplakia,

- 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.
- caused by EBV



(2) Verrucous leukoplakia

- shows a corrugated surface caused by excessive hyperkeratosis.
- This innocuous form 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, almost invariably reveals marked epithelial dysplasia,
- & with malignant transformation rate of more than >50%,
- the recognition of this lesion is more important than identification of oral leukoplakia!



CANCERS OF THE ORAL CAVITY AND TONGUE

- Leukoplakia, erythroplakia:

Risk of transformation

in leukoplakia is 3% to 25%;

in erythroplakia is More than 50% risk

- Tobacco use:

Best-established influence, particularly pipe smoking & smokeless tobacco

- Human papillomavirus (HPV) types 16 & 18:

Identified by molecular probes in 30% to 50% of oral cancers.

- Alcohol abuse:

Weaker influence than tobacco use,

but the two habits interact to greatly increase risk.

- Protracted irritation:

Weakly associated

Oral cancers

Grossly, (SCC)

- 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.

occur in :

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.

The majority of oral cavity cancers are **squamous cell (SCCa)**.

- they represent only 3% of all cancers in the US,
- they are important clinically, as
 - 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.

- 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.

Invasive tumor islands show formation of keratin pearls



Metastases:

- Regional LN spread is present at the time of initial diagnosis
 - only rarely with lip cancer
 - in 50% of cases of tongue cancer, &
 - 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.

Recovery:

-When these cancers are discovered at an early stage, 5-year survival can exceed 90%.

-However, the overall 5-year survival rates (5ySR) after surgery & adjuvant radiation & chemotherapy are:

1) only 40% for ca of the base of the tongue, pharynx, & floor of the mouth without LN metastasis,

2) compared with less than 20% for those with LN metastasis

SALIVARY GLAND DISEASES

► Sialadenitis

- is inflammation of the major salivary glands,
- may be of traumatic, viral, bacterial, or autoimmune origin.

- Mumps: is a common cause of viral 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.



- childhood mumps is self-limiting disease,
- mumps in adults may be accompanied by orchitis (which, if bilateral, may cause 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.

- 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.

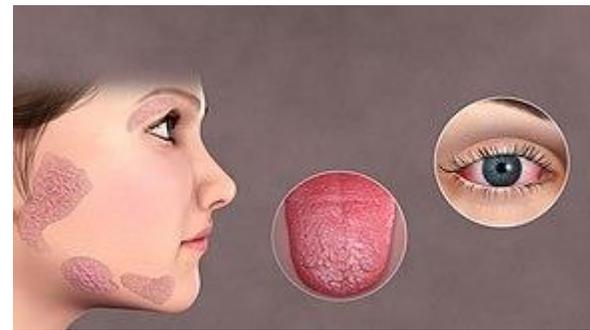
Mucocele,

- 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.



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 decreased production of saliva & tears.



Mikulicz syndrome.

Is The combination of salivary & lacrimal gland inflammatory enlargement, which is usually painless, & xerostomia,

The causes include

- sarcoidosis,
- leukemia,
- lymphoma,
- idiopathic lymphoepithelial hyperplasia.



Calculus:

The main duct of the Submandibular gland is obstructed by yellow stone (consist mainly of calcium carbonate),

causing :

(1) duct dilation

(2) atrophy of the normal gland parenchyma, {pinkish-white, due to replacement by fibrous tissue & fat}.

Recurrent attacks of acute bacterial sialadenitis may also complicate sialolithiasis.

Q: what is the typical complaint of patient with this lesion?



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
- Benign T include :
70% of the parotids
- Cancerous T include:
40% of submandibular glands &
50% of minor glands,
80% of sublingual glands

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
- mostly arise in the superficial parotid, causing painless discrete mass & swelling at the angle of the jaw.



Pleomorphic adenoma. Small, firm nodule located below the left ear in the parotid gland.

- 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.

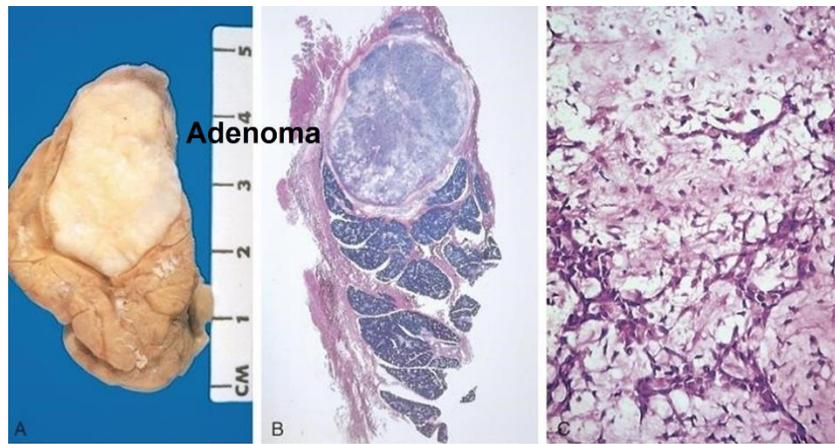


- 10% of T excisions are followed by recurrence.

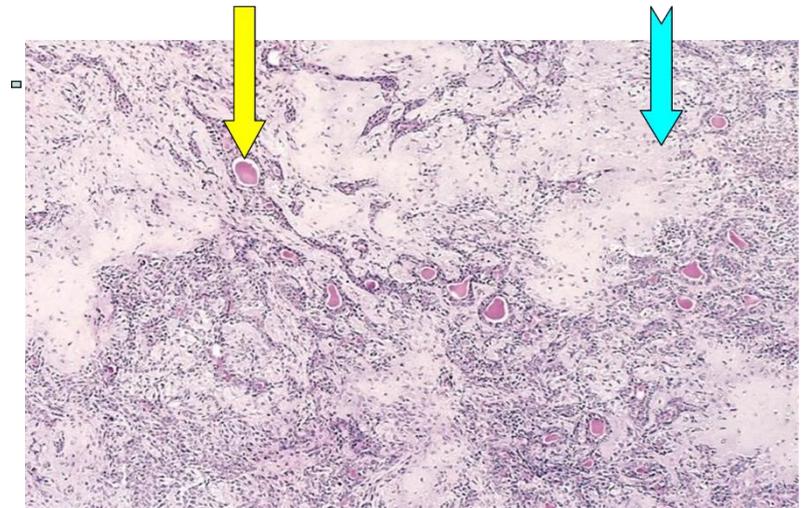
-Characteristically, T is histologically heterogeneous with:

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

High-power view showing amorphous myxoid stroma resembling cartilage, with interspersed islands & strands of myoepithelial cells.



Mixed tumor of the parotid gland contains epithelial cells forming ducts, & myxoid stroma that resembles cartilage

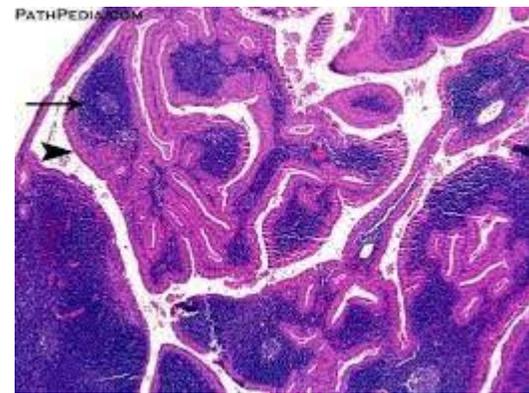
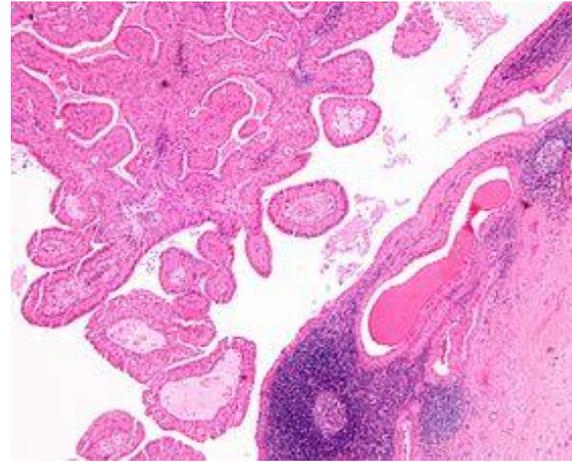


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-immunohistochemical evidence suggests that all of the diverse cell types in the T are of **myoepithelial derivation**.

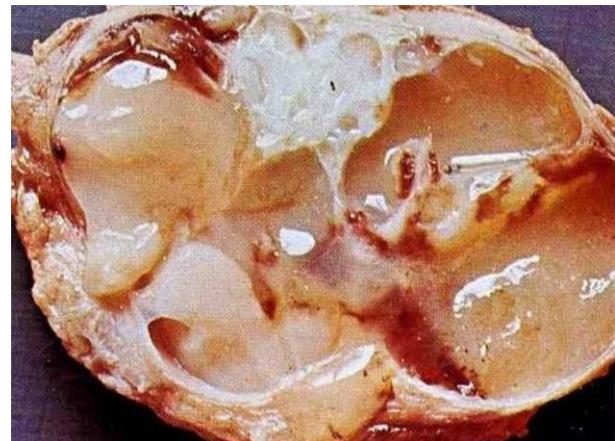
Warthin Tumor (Papillary Cystadenoma Lymphomatosum)

- 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 cleft like 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.

Adenolymphoma = Warthin Tumor = Papillary Cystadenoma Lymphomatosum, of parotid C/S shows well-encapsulated, ovoid tumor, revealing mucin-containing cystic spaces within a soft gray background.



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

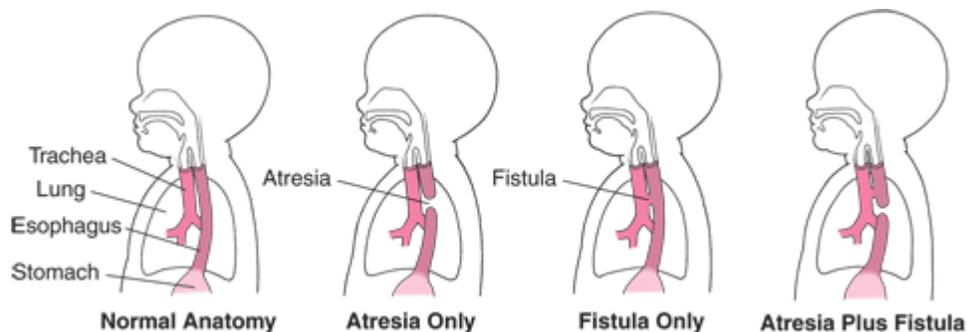
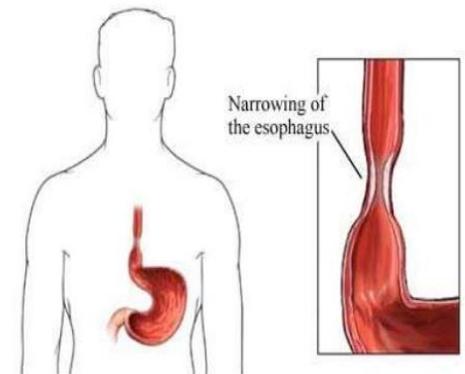
Infrequent Anatomic Disorders of the Esophagus:

(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.

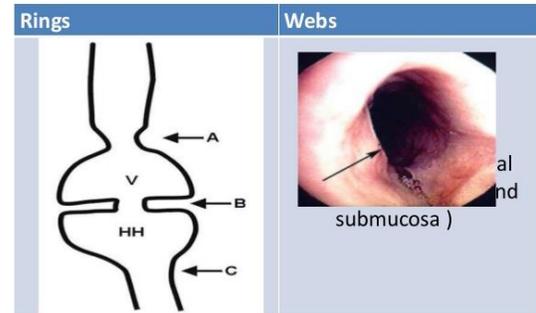


- Atresia (absence of a lumen) & fistula

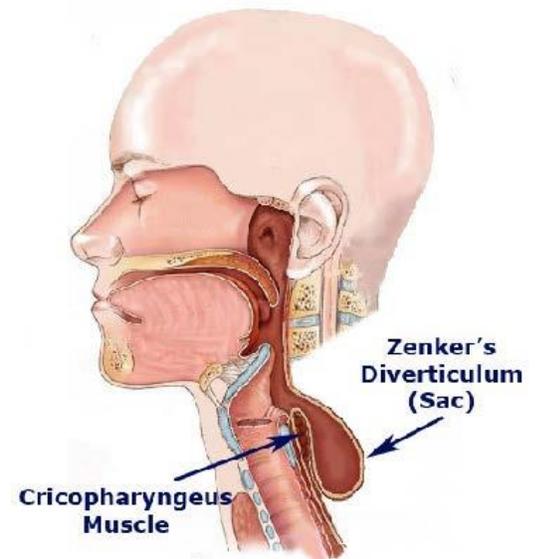
-Newborn with aspiration, paroxysmal suffocation, pneumonia

-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



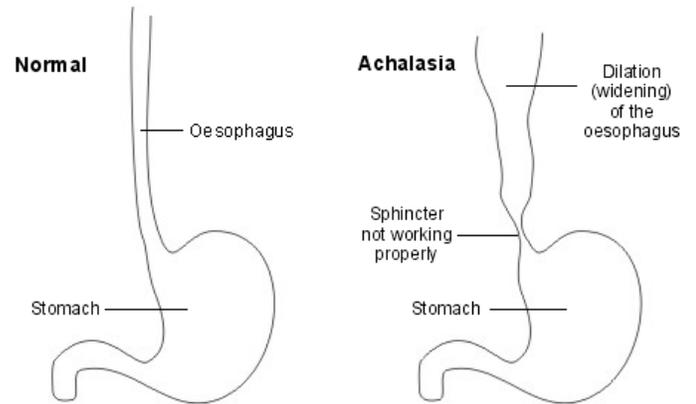
Achalasia

- *Achalasia means*

"failure to relax", or incomplete relaxation of the lower esophageal sphincter (LES)

due to increased LES tone in response to swallowing,

producing functional obstruction, with consequent dilation of the more proximal esophagus .

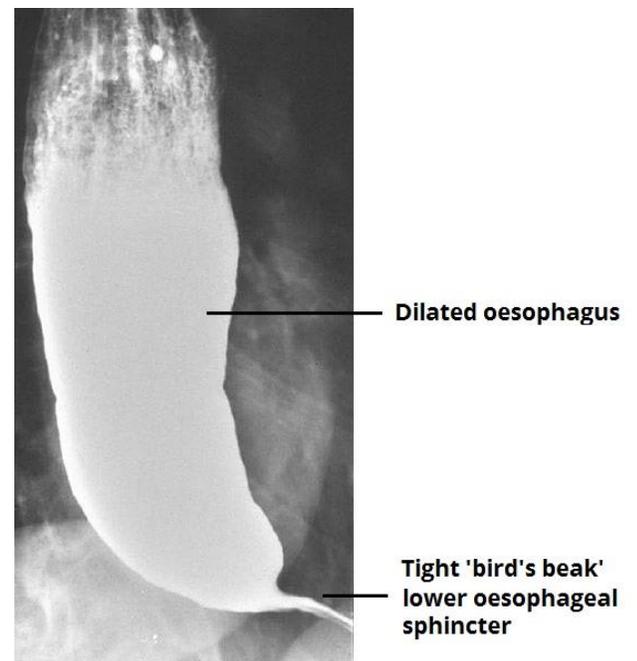


- *Achalasia characteristic (3) are:*

- incomplete LES relaxation
- increased LES tone
- esophageal aperistalsis

- *Clinically characteristic by:*

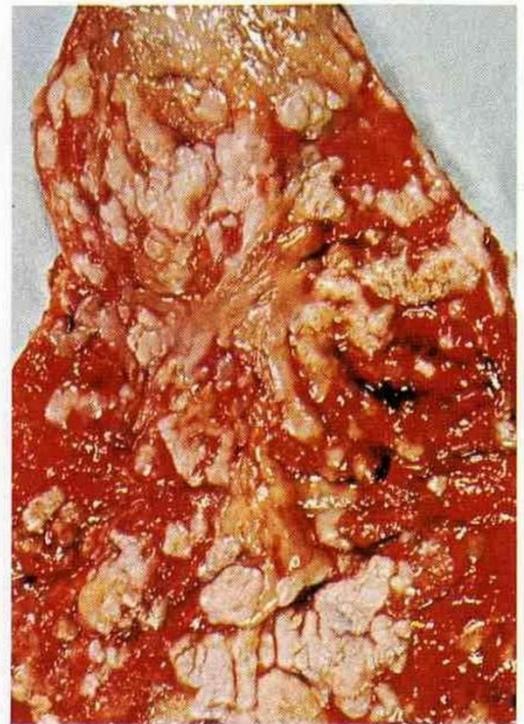
- progressive dysphagia.
- Nocturnal regurgitation
- & aspiration of undigested food may occur.



- *Achalasia Complications* :
 - 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.

(Stagnation of esophageal contents results in chronic mucosal inflammation & subsequent development of leukoplakia, a raised , irregular warty plaques.

Leukoplakia predisposes to the development of SCCa which was found in this specimen.



4.5 Achalasia, leukoplakia and squamous carcinoma: oesophagus

- Achalasia occurs as a primary and secondary ds :

- Primary Achalasia :
 - occurs most commonly
 - occur as primary disorder with an uncertain etiology,
 - with the 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.

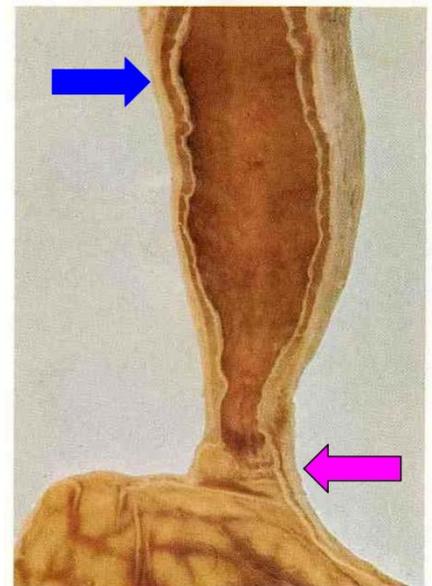
-The myenteric ganglia are usually absent from the body of the esophagus (causes esophageal aperistalsis),

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.

(There is marked dilatation & hypertrophy of the esophagus except for the lower esophageal sphincter in which the ganglion cells of the myenteric plexus are reduced or absent.

The result is functional obstruction, with consequent dilation of the more proximal esophagus.)



4.1 Achalasia of cardia (cardiospasm): oesophagus

(2) Food stasis produces secondary mucosal inflammation & ulceration proximal to the lower esophageal sphincter

- Secondary achalasia,
 - 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.

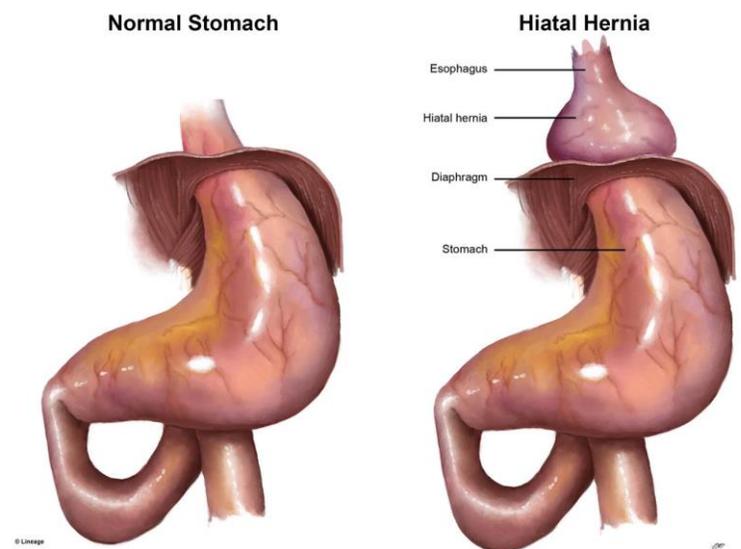
Hiatal Hernia (HH)

- *Cause of HH*

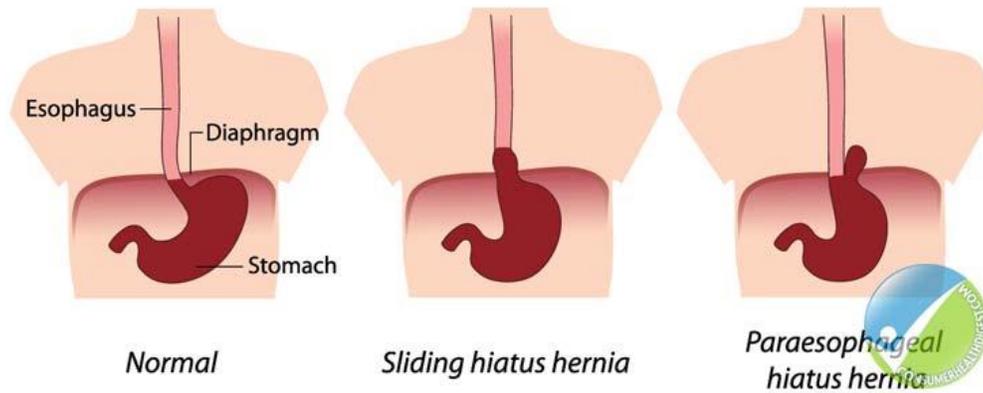
-is separation of the diaphragmatic crura

-& widening of the space between the muscular crura & the esophageal wall

-which permits a dilated segment of the stomach to protrude above the diaphragm.



Hiatus Hernia



- *Two anatomic patterns of HH :*

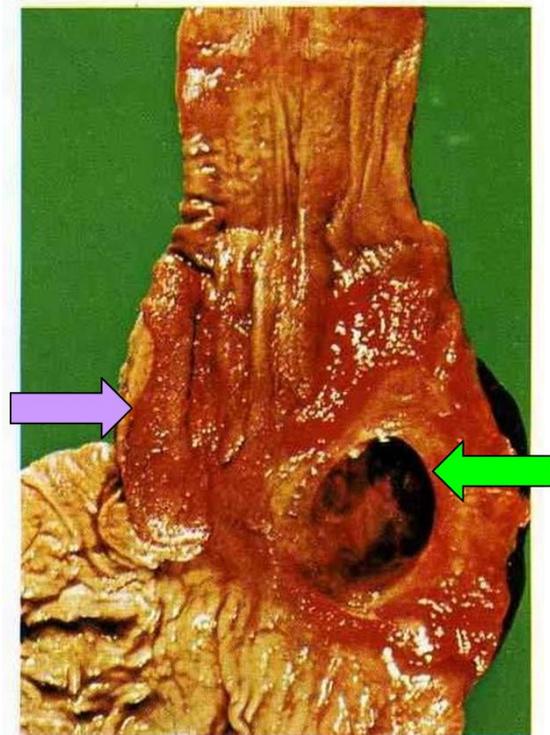
(1) Sliding or axial HH

- constituting (95%) of cases;
- protrusion of the stomach above the diaphragm creates a bell-shaped dilation,
- bounded below by the diaphragmatic narrowing,
- Although most individuals with sliding HH do not have reflux esophagitis, those with severe reflux esophagitis are likely to have a sliding HH.

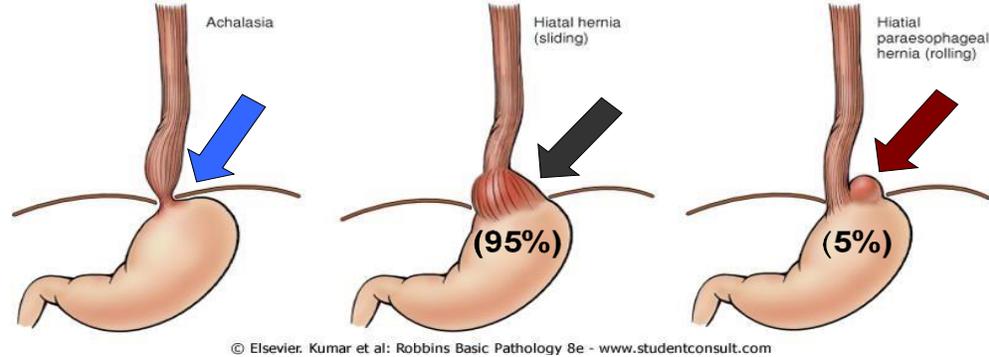
The distal esophagus & proximal part of stomach are visible, forming sliding hiatus hernia.

Reflux esophagitis cause mucosal congestion & peptic ulceration at the gastro-esophageal junction.

Q: what are the possible complications of this ulcer?



4.6 Hiatus hernia, oesophagitis and peptic ulcer: oesophagus



(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.

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

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

- complications of both types of HH include: mucosal peptic ulceration, bleeding, & perforation.

- *HH are reported in :*

- 1% to 20% of adults,

-increased in incidence with age,

-BUT only about 9% of these adults, suffer from heartburn or regurgitation of gastric juices into the mouth!

- *symptoms of HH are more likely result from:* incompetence of the LES rather than from the HH per se

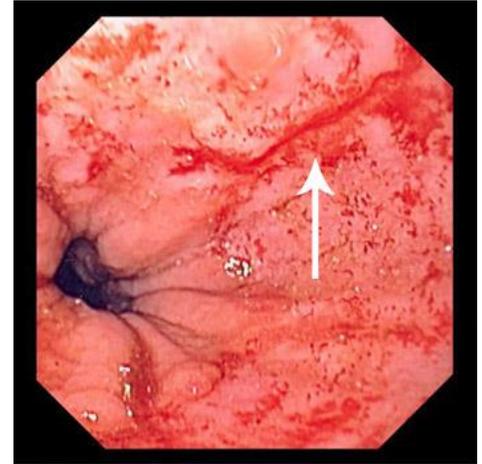
& are accentuated by :

-positions favoring reflux (bending forward, lying supine)

- obesity.

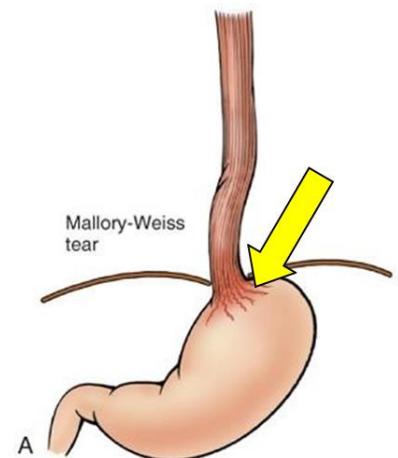
esophageal Lacerations (Mallory-Weiss Syndrome)

- *Mallory-Weiss tears are:*
longitudinal tears in the lower esophagus, at the esophagogastric junction
- *Occurrence:*
during severe vomiting for any reason, especially in chronic alcoholics after a bout (attack) of severe retching (the try for vomiting) or vomiting.

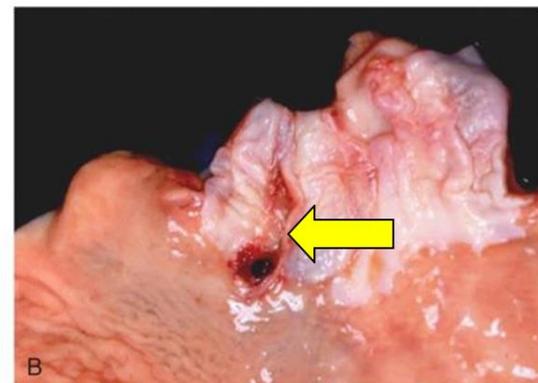


- *Cause:*
 - inadequate relaxation of the musculature of the lower esophageal sphincter (LES) during vomiting,
 - with stretching & tearing of the esophagogastric junction at the moment of expulsion of gastric contents.

- 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.



(Gross photograph demonstrating longitudinal laceration oriented in the long axis of the esophageal lumen (arrow), extending from the esophageal mucosa to the stomach mucosa)



VARICES

- *Varices happen when:*

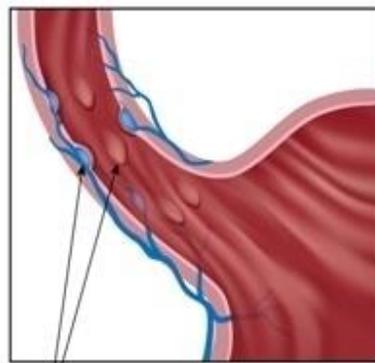
- When portal venous blood flow into the liver is impeded or obstructed (most common example is cirrhosis or fibrosis)...

-The resultant portal hypertension induces the formation of collateral bypass channels wherever the portal & systemic systems communicate.

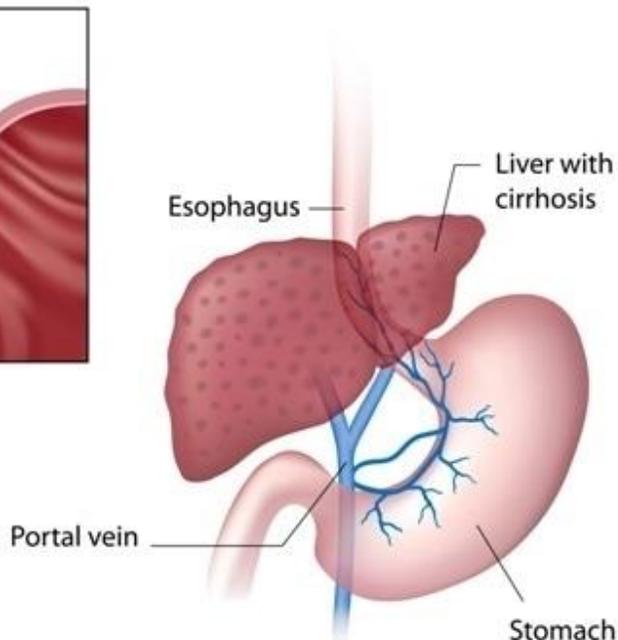
-Portal blood flow is thereby diverted through the stomach veins into the plexus of esophageal submucosal veins, thence into the azygos veins & the superior vena cava.

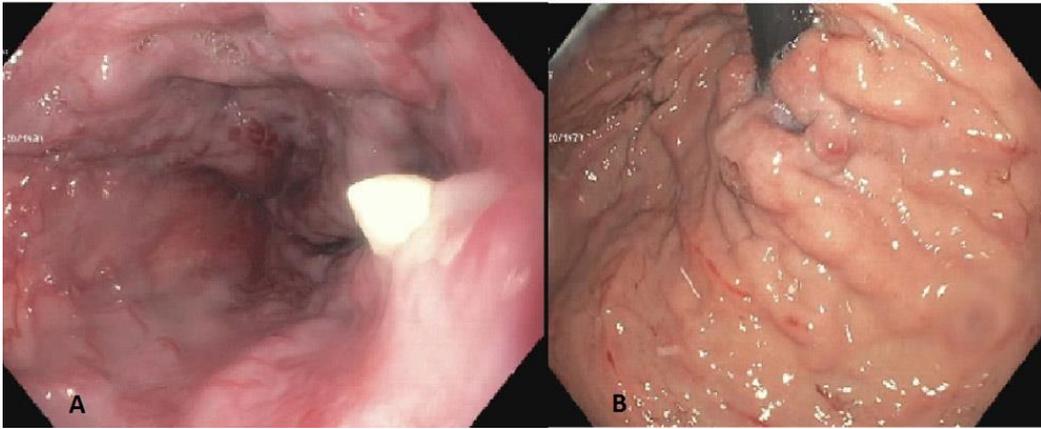
-The increased pressure in the esophageal plexus produces dilated tortuous vessels called varices.

Esophageal Varices



Esophageal varices





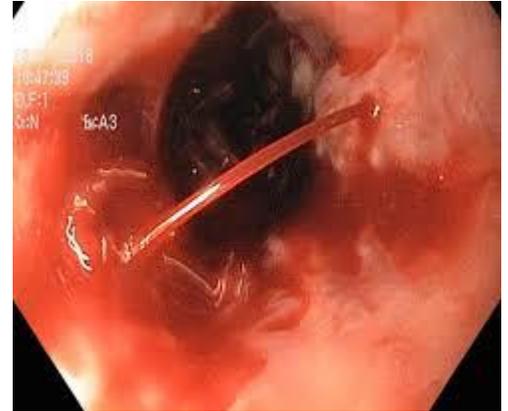
- Endoscopically, when the varices are unruptured, they appear as :
 - tortuous dilated veins lying primarily within the submucosa of the distal esophagus & proximal stomach.
 - The covering mucosa may be normal with irregular protrusion into the lumen, or eroded & inflamed because of its exposed position,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

A view of the everted esophagus & gastroesophageal junction, showing dilated submucosal veins (varices).

The blue-colored varices have collapsed in this post mortem (PM) specimen.



- Varices are asymptomatic until they rupture.
- Variceal rupture produces massive hemorrhage (H) into the lumen, & into the esophageal wall.



- 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.
- 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.

- *Treatment :*

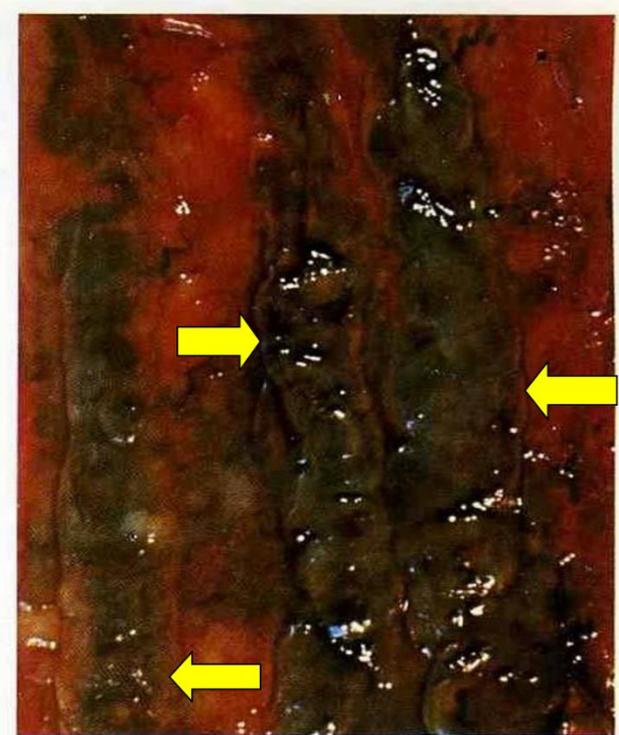
by endoscopic injection of thrombotic agents (sclerotherapy) or balloon tamponade

- 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 (How?)

Esophageal varices in portal hypertension (seen by esophagoscopy) .

Enormously-dilated, tortuous, bluish-black, longitudinally running submucosal venous channels,

prone to rupture, causing serious, & usually fatal GIT bleeding.



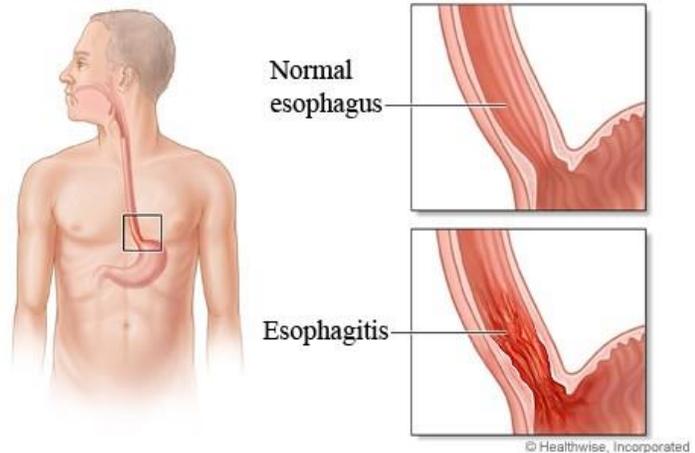
4.3 Varices: oesophagus

ESOPHAGITIS

- *esophagitis is :*

Injury to the esophageal mucosa with subsequent inflammation (esophagitis)

In which it's a common condition worldwide.

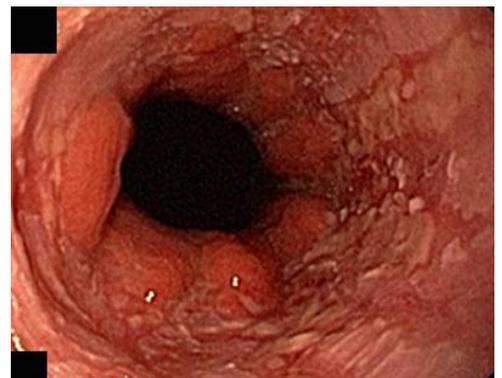


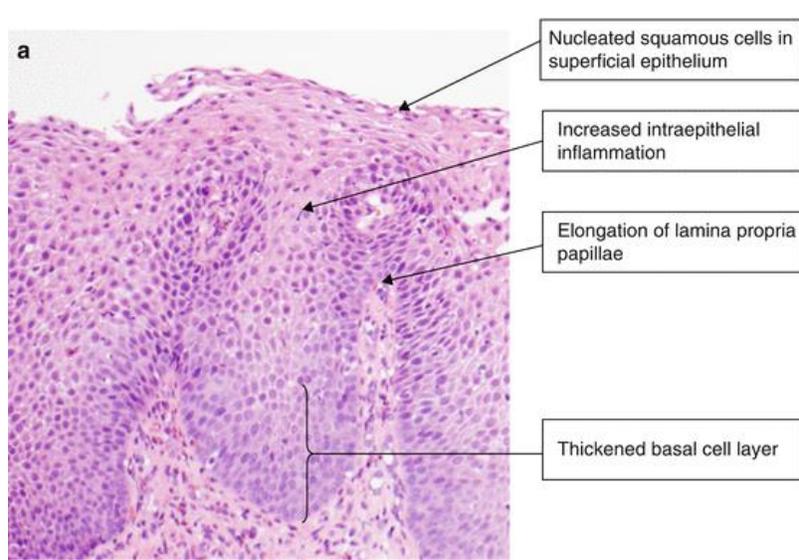
- Grossly,

- mild esophagitis may appear as simple hyperemia.



-In severe esophagitis, there may be:
confluent epithelial erosions or
total ulceration into the submucosa.





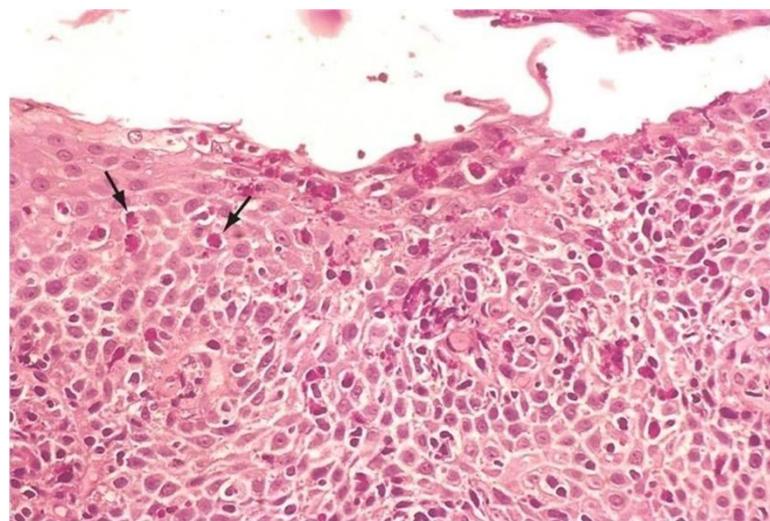
- histologic features (3):
are characteristic of uncomplicated reflux esophagitis,
although only one or two may be present:

- (1) Intraepithelial eosinophils with/without neutrophils
(Intraepithelial neutrophils are markers of severe injury);
- (2) Basal zone hyperplasia
- (3) Elongation of lamina propria papillae.

Reflux esophagitis showing the superficial portion of the mucosa .

Numerous eosinophils (arrows) are present within the mucosa,

& the stratified squamous epithelium has not undergone complete maturation because of ongoing inflammatory damage



- 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.

- *Causes:*

Esophagitis may be caused by :

- ingestion of corrosive or irritant substances,
- prolonged naso-gastric (NG) intubation,
- uremia,
- & radiation or chemotherapy, among other causes.

- Contributing causes :

Efficacy of :

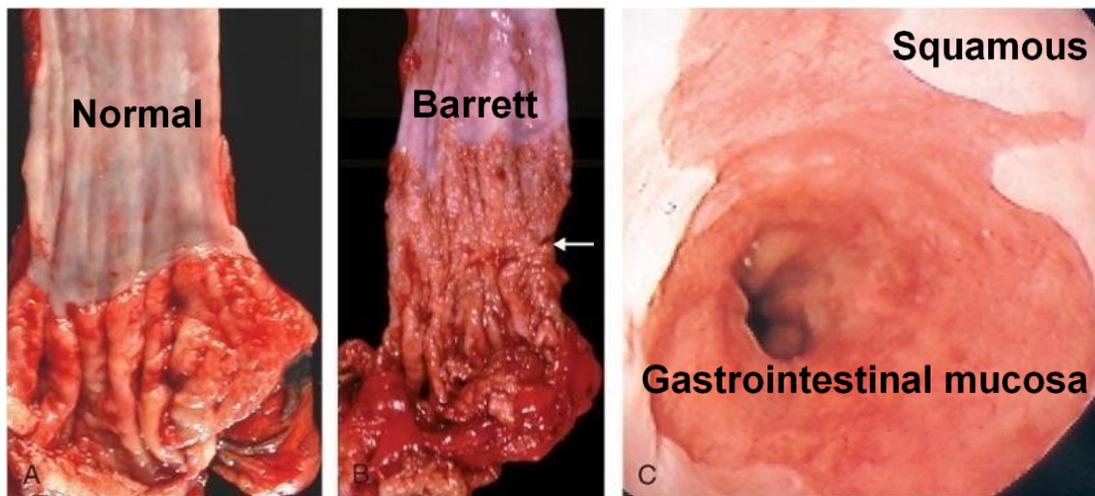
- esophageal antireflux mechanisms,
- CNS depressants,
- alcohol or tobacco exposure

But most often no obvious etiology is identifiable!

- *It Affects:*
 - It affects about 0.5% of the US adult population(375Millions), (i.,e.,1 Million);
- Prevalance of cases :
 - 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).
- *its dominant symptom:*
 - is recurrent heartburn.

BARRETT ESOPHAGUS

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



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Gross view of distal esophagus (top) & proximal stomach (bottom) showing (A) normal gastroesophageal junction & (B) the granular zone of Barrett esophagus (arrow). C, Endoscopic view showing red velvety gastrointestinal-type mucosa extending from the gastroesophageal orifice. Note paler squamous esophageal mucosa.

- *Pathogenesis:*

- prolonged & recurrent gastroesophageal Reflux produce inflammation & eventually Ulceration of the squamous epithelial lining.
- 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

- *Healing*

occurs by ingrowth of progenitor cells & re-epithelialization.

- *Complications of Barrett e.:*

- Ulcer & stricture may develop,
- but, the chief complication of Barrett e. is the risk of the development of adenocarcinoma.

- *Risks:*

- Barrett e. patients have a 30 to 100 fold greater risk of developing esophageal adenocarcinoma 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) as an irregular circumferential band displacing the squamocolumnar junction cephalad (upwards),
- (3) as an isolated patches (islands) in the distal esophagus.

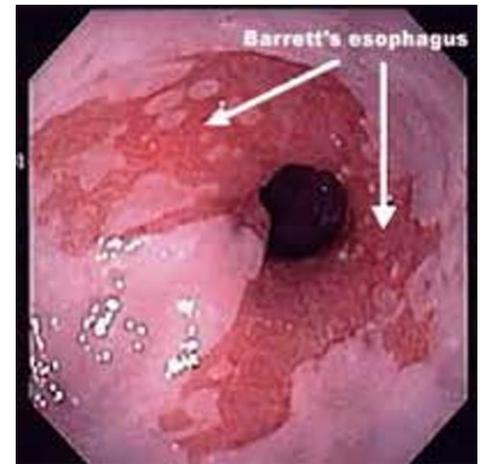
- Others:

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

▼ Barrett e. however has been detected in about the same proportions in asymptomatic populations!

▼ Barrett e. affects males more than females (4:1)

& is much more common in whites than in other races.



ESOPHAGEAL CARCINOMA

- Worldwide, SCCa constitutes 90% of esophageal cancers,
- however, in US, there has been a very large increase (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)

Squamous Cell Carcinoma (SCCa)

- *Morphology:*

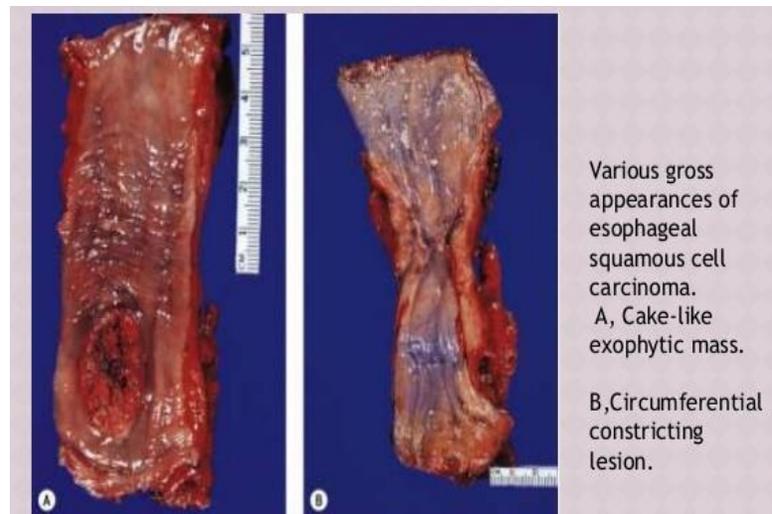
SCCa are usually preceded by :

- 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, plaquelike 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.

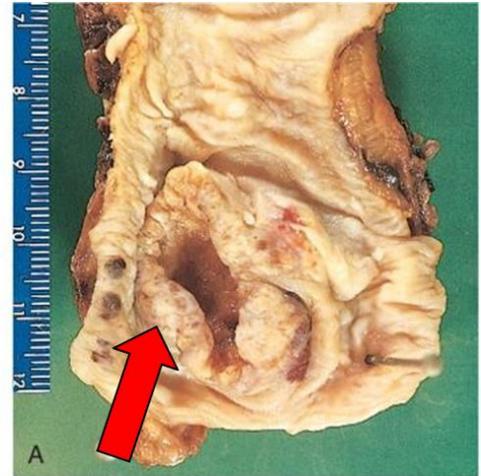
(3) Ulcerating T that invade deeply & may erode the respiratory tree, aorta, or elsewhere

- *Arise in :*

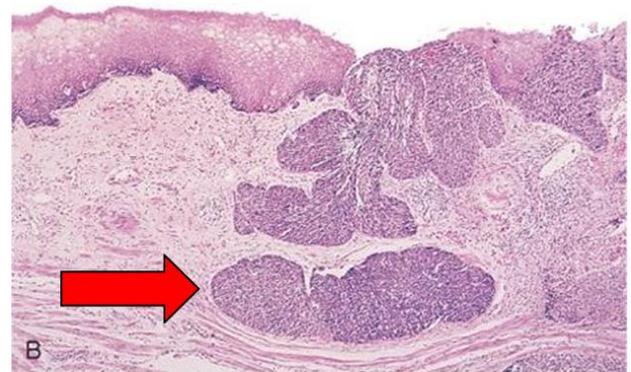
Whichever the pattern of esophageal SCC;

- 50% in the middle 1/3
- 30% in the lower 1/3.
- 20% arise in upper 1/3 & the cervical esophagus,

A, Large ulcerated squamous cell carcinoma of the esophagus.

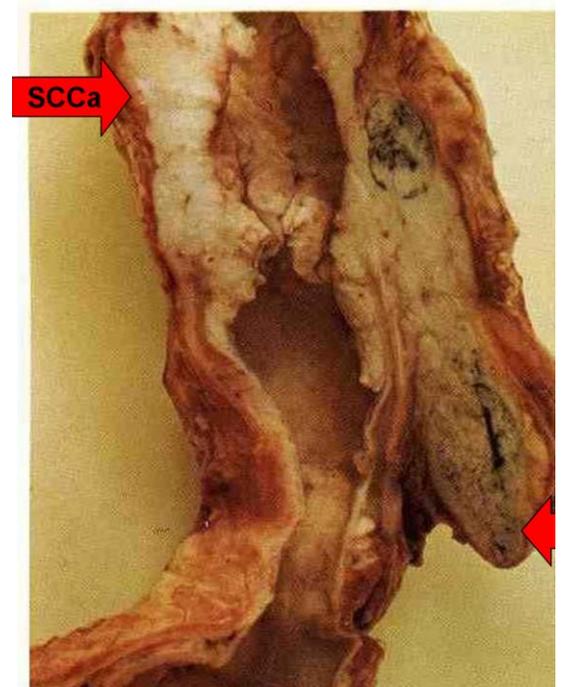


B, Low-power view of the squamous cell carcinoma invasion of the submucosa



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Squamous cell carcinoma: esophagus. Annular constricting whitish tumor invading the wall & infiltrate adjacent lymph nodes on the right.



Causes:

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

Adenocarcinoma (Adenoca)

- *Grossly:*

- 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.

- ❖ -Barrett e. is the only recognized precursor of esophageal adenocarcinoma

- 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.

- *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.

.

- *Risk of development :*

-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....

- individuals with high-grade dysplasia progress to adenoca may be 10% or more per year in.

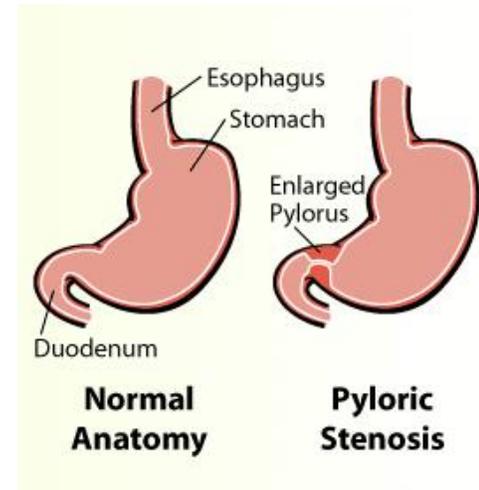
-Overall, the risk for developing adenoca varies from 30 to more than 100-fold above normal.

-There are no specific markers that precisely identify the transition from high-grade dysplasia to cancer.

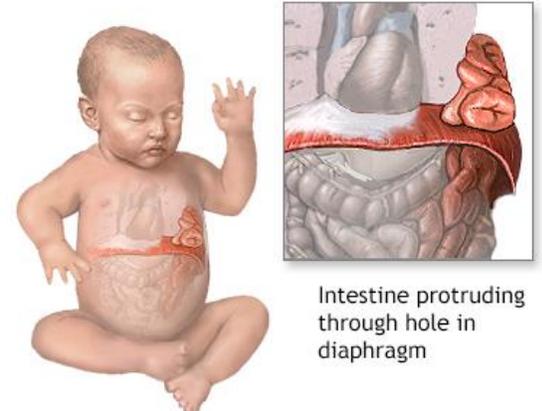
STOMACH

Congenital Gastric Anomalies:

- 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:

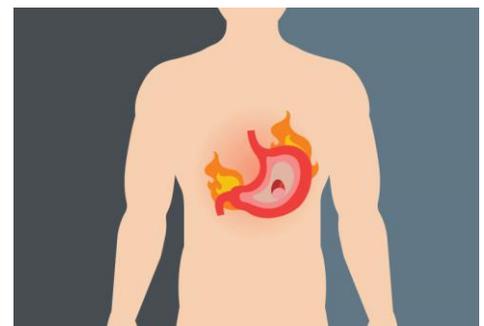
-primarily heartburn & vague epigastric pain.

-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.

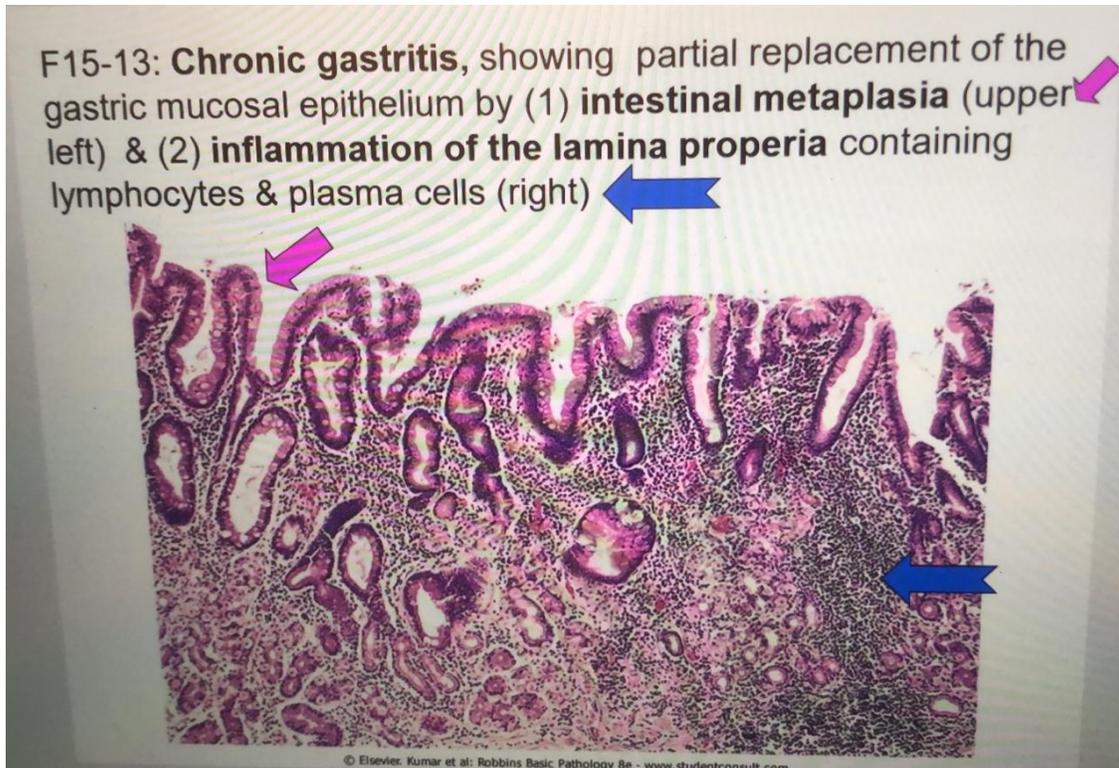
GASTRITIS

- 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+B)*

(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 !).

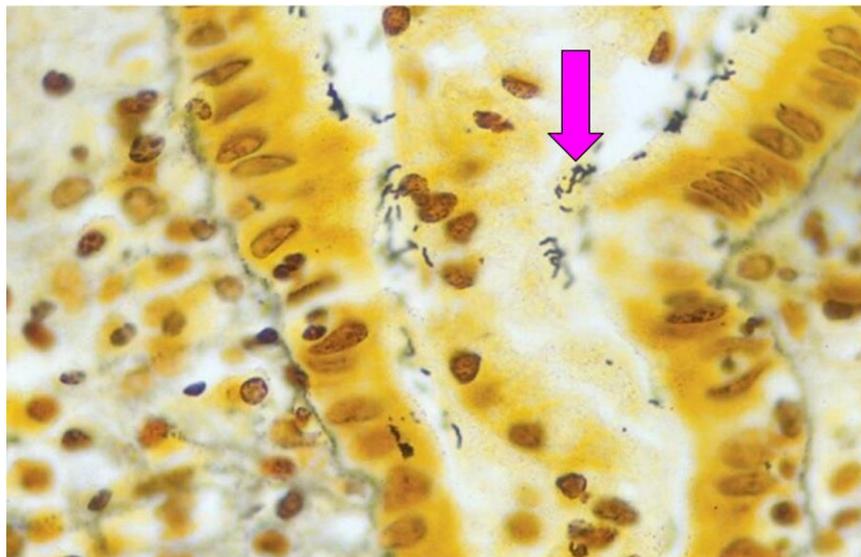
- H. pylori is a noninvasive, non-spore-forming, S-shaped gram-negative rod measuring $3.5 \mu\text{m} \times 0.5 \mu\text{m}$.

- 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 & increased risk for the development of DU,
 - (2) Pangastritis with multifocal mucosal atrophy, with low acid secretion & increased 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.

Helicobacter pylori gastritis.

-Silver stain demonstrate the numerous darkly stained Helicobacter organisms along the luminal surface of the gastric epithelial cells.

-There is no tissue invasion by the bacteria



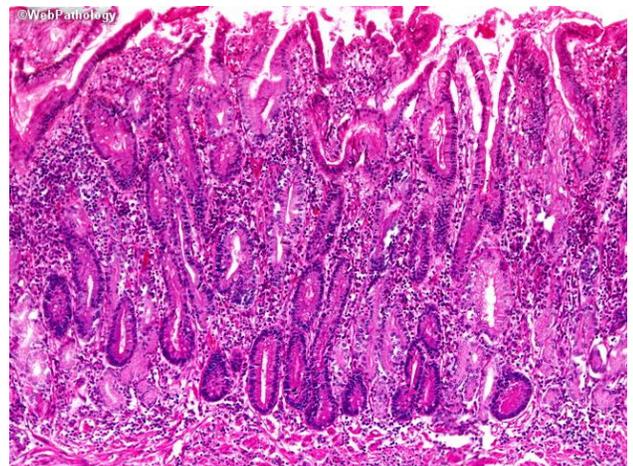
(B)

- 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 (A) intrinsic factor production leading to pernicious anemia & (B) of acid.
- It may be seen in association with other autoimmune disorders e.g., Hashimoto thyroiditis & Addison disease.

- *Histology*

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

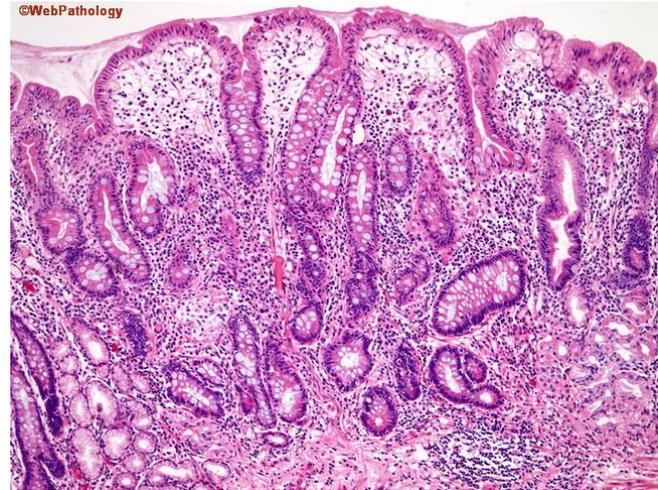
- (1) There is inflammatory lymphocytic & plasma cell infiltrate in the lamina propria, occasionally accompanied by neutrophilic inflammation of the neck region of the mucosal pits.
- (2) There is variable mucosal atrophy & gland loss.
- (3) When present , H. pylori are found nestled within the mucus 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.

- The long-term risk of gastric carcinoma for persons with *H. pylori*-associated chronic gastritis is increasingly 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.

► *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.

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

- ▶ The 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:

- Disruption of the adherent mucous layer,
- increased Stimulation of acid secretion with hydrogen ion back-diffusion into the superficial epithelium,
- Decreased production of bicarbonate buffer by superficial epithelial cells,
- Reduced mucosal blood flow,
- Direct damage to the epithelium.
- 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.

➤ *histology,*

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, or

(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 increasing the likelihood of this complication in persons requiring long-term use of such drugs