ORAL CAVITY: ULCERATIVE & INFLAMMATORY LESIONS

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

Aphthous Ulcers (Canker Sores)

★**Extremely common; small** (<5 mm in ∅), **painful, rounded, shallow ulcers**, covered with a gray-white exudate & having an erythematous rim. Appear **singly** or in groups, on the nonkeratinized oral mucosa, specially soft palate, buccolabial mucosa, mouth floor & tongue lateral borders.

★ More common in the first 2 decades of life & often **triggered** by stress, fever, ingestion of certain foods, & activation of IBD. They are **self-limited** & usually resolve within few weeks, but they may **recur** in the same or a different location in the mouth.

▷ but can occur at any age.

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 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 ∅) **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.** الخلايا المصابة بتتحد مع بعض.

Necrosis of the infected cells & the focal collections of edema fluid account for the **intraepithelial vesicles** detected clinically (F15-1). داخل الـ epidermis

▼Identification of the inclusion-bearing cells or polykaryons in smears of blister fluid constitutes the diagnostic ***Tzanck test*** **for HSV infection.** ~~لـ~~ جداً ما بنعمله نادر لأنه الـ clinical picture واضحة بتدلنا على هذا المرض

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.

التهاب اللثة والفم

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

infl. of the brain substance.

▼ 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.

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** (F15-2).

زي الجبنة

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.

تتعرّى وتختفي وتفقد

😐 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, or

(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.

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.** → التهاب اللسان.

☹ ***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** → متعرج **surface** resulting from marked epithelial thickening.
It is **caused by Epstein-Barr virus (EBV)** infection of epithelial cells. not HIV علما انه ممكن تكون موجودة في الـ AIDS.

☹ 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

لطخة بيضاء

► ***Leukoplakia refers to a white mucosal plaque*** معهم جدا "caused by epidermal thickening (**hyperkeratosis**)
hyperplasia of stratum spinosum.

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).
معهم جدا "
بعض ما بتعرف شو المرض

► ***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.
inner

☹ May appear as localized, diffuse, or multifocal smooth or roughened, leathery, white, discrete mucosal thickening.
معهم جدا "
■ they vary, from simple hyperkeratosis without underlying epithelial dysplasia, to mild, up to severe dysplasia bordering on carcinoma in situ (F15-3). 💣 **Only histologic evaluation distinguishes these lesions from each other.**
معهم جدا "
مهما كان شكله لازم ناخد خزعة ونفحصها

► 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: التدخين أو مثلاً مضغ التبغ أو الشم

☹ ***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.

☹ Oral leukoplakia is an important because 3% to 25% (depending somewhat on location) undergo malignant transformation to **SCCa (F15-3A)**.

☹ 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.

إذا شفت لطخة بيضاء مستحيل تعرف أنه شو نوعها الله يعين!!
هل هي حميدة أم سيئة.

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 **malig[illegible]formation rate of more than >50%, the** recogni[illegible]lesion becomes even more important than identification of oral leukoplakia!

CANCERS OF THE ORAL CAVITY AND TONGUE

Table 15-1 Risk Factors for Oral Cancer 🕷

Leukoplakia, erythroplakia: Risk of transformation in leukoplakia 3% to 25%; More than 50% risk in erythroplakia

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

★ ***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, 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.

★ **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, to the outside.
or they may assume an **endophytic invasive pattern, with central necrosis to create malignant ulcer.**

* كلمكان فيه surface الورم لما يظهر يا بكون exophytic ويعمل ورم كبير أو invasive ويعمل ulcer

◘ SCCa are usually moderately to well-differentiated keratinizing tumors (F15-4).

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.

carcinoma → with lymph. sarcoma → with blood.

☹ 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**.

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

لو اذا ماف LN involve. وكان بمكانه فقط هون منيح يكون

☹ 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,

بعيشوا لمدة 5years

▼compared with less than **20%** for those with LN **metastasis**.

لذلك الشغلة المهمة هو التشخيص المبكر.

SALIVARY GLAND DISEASES

Sialadenitis التهاب الغدد اللعابية

★ ***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**.

التهاب بالـ testis

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

(1) Ductal obstruction by stone (***sialolithiasis, F3.9***),

(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.

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 ∅.
★ 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: (I) **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…

(II) These epithelial elements are intermingled with a loose, often **myxoid connective tissue** stroma sometimes containing islands of apparent cartilage or, rarely, bone (F15-5 & 6-2).

★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 (F3-13) 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

Table 15-2: 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 ↑ LES tone in response to swallowing, producing **functional obstruction**, with consequent dilation of the more proximal esophagus (F15-6). Achalasia characteristic triad are incomplete LES relaxation + ↑LES tone + esophageal aperistalsis

★ ***Achalasia*** *occurs most commonly as* **(I)** *a* ***primary disorder*** *of uncertain etiology*, **with loss of intrinsic inhibitory innervation** of the LES, resulting in:

carcinoma: oesophagus

☹ (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.

*endoscopy is very imp. to investigate and Dx.

(II) 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.

► **Clinically,** achalasia is characterized by progressive **dysphagia**. **Nocturnal regurgitation & 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.

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 (F15-6):

(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: mucosal **peptic ulceration (F 4-6), bleeding, & perforation**. **Paraesophageal HH** rarely induce reflux, but they can become strangulated or obstructed.

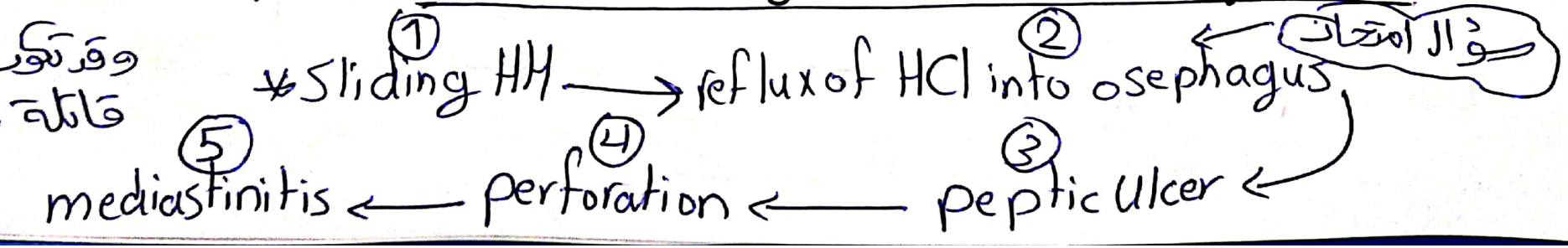
Lacerations (Mallory-Weiss Syndrome)

☹ ***Mallory-Weiss tears*** are **longitudinal tears** in the lower esophagus, at the esophagogastric junction (F15-7).

☹ 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:** is ➔ **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 elongation, dilatation, tortuous الدوالي.

► 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 (F15-8 & **F4.3**)

NB. {varices are **collapsed** in surgical or PM specimens}.

السلايد مهم جدا.

★ 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 (How?)**

☺ 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 ingestion of corrosive or irritant substances, prolonged naso-gastric (NG) intubation, 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!**

Scanned with CamScanner

☹ **Grossly,** mild esophagitis may appear as simple **hyperemia.** In severe esophagitis, there may be confluent epithelial **erosions** or **total ulceration into the submucosa.**

Very superficial injury to mucosa.

◘ 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 (F15-9); **&**

(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:** (oral cavity وصل للـ)

☹ **Complications** of severe reflux esophagitis are:

Bleeding, Ulceration, Stricture, & **Barrett esophagus**, with its predisposition to **malignancy.**

predisposing to Adenocarcinoma.

BARRETT ESOPHAGUS

▼ ***(D) Is replacement*** *of the normal distal esophageal stratified* ***squamous*** *mucosa by* ***metaplastic columnar*** *epithelium containing goblet cells.* (F15-11).

▼ ***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.

► **Pathogenesis**: ⇨ (1) prolonged & recurrent gastroesophageal
(2) ⇨ **Reflux** produce inflammation & eventually
(3) ⇨ **Ulceration** of the squamous epithelial lining.
(4) ⇨ **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.
(5) ⇨ **Metaplastic** columnar epithelium is thought to be more resistant to injury from refluxing gastric contents

☹ **Complications of *Barrett e.*: Ulcer & stricture may develop**, but, *the chief* **complication** *of Barrett e. is the* ***risk of the development of adenocarcinoma.*** most important one.

in lower part of esophagus mucin secreting lining mucosa

☹ **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**, (F15-10) **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, as (2) an **irregular circumferential band** displacing the squamocolumnar junction cephalad (upwards), or as **(3) isolated patches (islands)** in the distal esophagus.

Scanned with CamScanner

موضوع مهم جدا.

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!** تجاوز

😐 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.

cancer in osephagus.

😐 **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 100 **new cases/**Million/year & 20% of cancer deaths are caused by esophageal ca, mainly SCCa!

فرق هائل بين الـ US ← يعني 16 ضعف من الموجود في الـ US.

انتبه.

معلومة حفظ

Table 15-3 Risk Factors for esophageal SCCa

Esophageal Disorders - Long-standing *esophagitis* – *Achalasia* - *Plummer-Vinson syndrome* (esophageal webs, microcytic hypochromic anemia, atrophic glossitis) more in females.

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)

► 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** (Table 15-3). 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.

صار في أكثر من سبب بعض.

►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 *KRAS* & *APC* genes are uncommon.

rare in osephagus.

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:

تثخن لطحي. ينمو ويرتفع إلى التجويف.

(1) **Polypoid exophytic** masses, that protrude into the lumen
(2) **Diffuse infiltrative T** that cause thickening & rigidity of the wall & narrowing of the lumen. بضيق الlumen.
(3) **Ulcerating T** that invade deeply & may erode the respiratory tree, aorta, or elsewhere (F15-12 & 4.7) &

▼ 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.

most common site.

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

T15- 4 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.**

fresh → vomitting.
black → vomitting from stomach.

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.

(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.

★ إذا كنا عند autoimmune disease فقد يكون عنده مرض مناعي آخر.

■ H, in all (A & B) cases of chronic gastritis: (F15-13):

(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 (F15-14), ***H. pylori*** **are found *nestled*** within the mucus layer overlying the superficial mucosal epithelium.

يعشعش في mucus الي بغطي mucosa

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

. cancers الـ H.pylori ١٪ بسبب نوعين من ال

Two additional features are of note.

(1) **Intestinal metaplasia** = replacement of gastric epithelium with columnar & goblet cells of intestinal variety.

ليس لل تحول مفيد

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** (no acid) **with hypergastrinemia** are characteristically present. (decrease HCl)

increase in gastrin

☹ 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

سقوط

مهمة "جدا" عابرة وليست مزمنة

★ ***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.** → احرف ا

▶Acute gastritis is frequently associated with:

أهم وأكثر عامل.

(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

(bile) peptic ulcer. زمان كان لعلاج ال

►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:**

هي أول خط دفاع عن ال mucosa.

- **Disruption** of the adherent mucous layer,
- ⇧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.

H.pylori بتجوا من ال 5 complications أقل أسباب

😐 **Not surprisingly, mucosal insults can act synergistically**

1+1=5

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.**

without getting down into the submucosa.

◘H, All variants are marked by mucosal ① edema + ② inflammatory infiltrate of neutrophils + monocytes + ③ 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.

لو السبب كان قصير الأجل ال acute gastritis بتختفي (chronic مش زي ال

►***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.**

coffee ground ال fresh blood زي

☹ **Acute erosive gastritis** is one of the ***major causes*** **of *hematemesis***, *particularly in alcoholics* as it is irritant to the stomach.

☹ **25%** of persons who take **daily aspirin** for RA **develop** حفي. **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

معهم جدًا" الفرق بينهم

☼ Histologically: تقطع → acute بالعادة

▶ ***Erosions*** are **breach in the mucosal epithelium only,** which may heal within days, whereas healing of ulcers takes much longer time. → chronic بالعادة

▶ ***Ulcers*** of the GIT are **breach in the mucosa that extends through the muscularis mucosae into the submucosa or deeper.** بتفصل بين ال submucosa and mucosa

★ 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).

DU is more common than GU 4DU : 1GU

Peptic Ulcers (PU, Ω)

Ω 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

تروح وتيجي.

Ω 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. Ω 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 Ω PU remains, in part because of **recurrent infection** with H. pylori.*

لذلك لازم يتعمل بالعلاج ويعمل follow-up.

In US, about 10% of males & 4% of females have Ω PU. The male/female ratio for DU is about 3:1.

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

* قبل 40 أو 50 سنة

كل ٣٠ ذكر كان بصادف ٦ انثى هذا هيني زيادة عالية جدًا" عند الإناث

أثناء الحياة كلها

(سؤال امتحان) مهم جداً

★ **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).

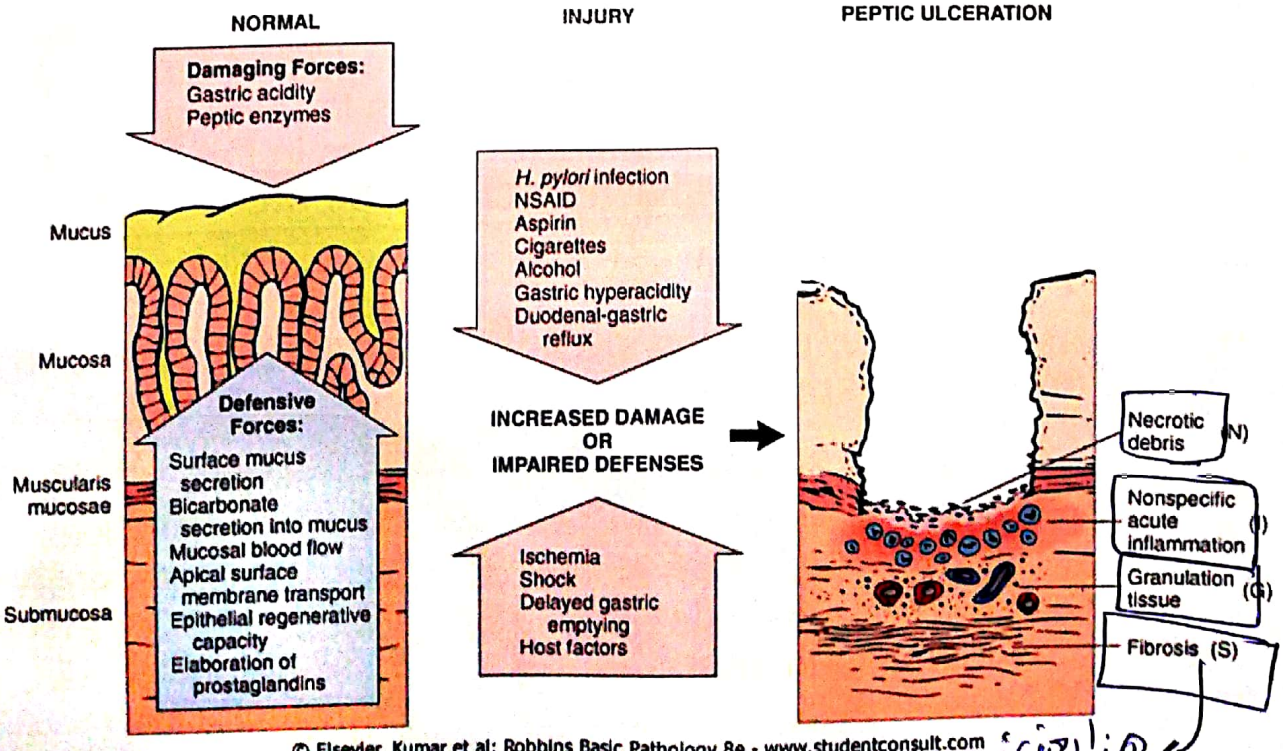
Pathogenesis of PU

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

*إذا في نقطة غير موجودة مابح يصير PU غير واضحة.

😐 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 (F15-15).

F15-15: **Aggravating causes of & defense mechanisms against peptic ulceration.** The right panel shows the basis of a peptic ulcer, demonstrating necrosis (N), inflammation (I), granulation tissue (G), & fibrosis.



هذا يعني أن القرحة هي مزمنة (chronic) وليس acute.

☹ *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: ⇧ secretion of hydrochloric acid, ⇩ bicarbonate & ⇩ mucin production,**. Loss of mucin degrades the mucosal barrier that normally prevents acid from reaching the epithelium. Synthesis of glutathione, a free-radical scavenger, is also reduced.

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

- Gastric ***hyperacidity*** may be strongly ulcerogenic.
- Excess production of gastric acid from a tumor in individuals with the ***Zollinger-Ellison syndrome*** causes **multiple peptic ulcerations** in the stomach, duodenum, & even the jejunum.
- ***Cigarette smoking*** impairs mucosal blood flow & healing.
- ***Alcohol*** has not been proved to directly cause peptic ulceration, but **alcoholic cirrhosis** is associated with an ⇧ incidence of DU

• ***Corticosteroids*** in high dose & with repeated use promote ulcer formation (type A individuals) معرضين للإصابة أكثر

• **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 ∅, معظم

► 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** (F15-16 & F 4.15).

لكن لازم ناخد biopsy حتى نتأكد histologically وندرس

4.15 Chronic peptic ulcer: stomach

▶ PU **surrounding mucosal folds** may radiate like wheel قاعدة الحفرة
▶ 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.
▷ most common cause of death from PU. بتخرج محتويات الـ stomach إلى الـ mediastinum.

◘ In a chronic, open PU, four zones can be distinguished
(1) PU base & margins have a thin layer of **necrotic** fibrinoid debris (F15-17) underlain by
(2) A zone of active **nonspecific inflammatory infiltration** with neutrophils predominating, underlain by
(3) **Granulation tissue**, deep to which is
(4) **Fibrous, collagenous scar** that fans out widely from the margins of the ulcer.

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

لما تستمر القرحة و لح يتحول الـ BV الموجودة في القاعدة لح تتـ ـكسر هذا الـ artery و هذا إنقاذ لحالة المريض من الـ hemorrhage

★ 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. مهم

* ال chronic gastritis ← دائماً تكون بال PU أما في حالة ال acute ulceration ماكو gastritis

▶***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:**

حافر — انتفاخ

Scanned with CamScanner

مهمة جداً جداً

☹ ***Bleeding*** (see F4.16) *is the* ***commonest complication***, occurring in **1/3** of patients, & may be life-threatening.
☹ **Perforation** (see F4.17) **occurs in 5%** of patients, accounts for **2/3** (most common cause of deaths from PU in US.) → مهمة
☹ **Obstruction** of the pyloric channel, is rare. → واذا كانت بالمعدة
☹ **Malignant transformation occurs in about 2% of patients**, generally from **PU in the pyloric channel, BUT it is unknown in DU!!!!!!** → النوع الأخير قد يكون سبب الـ Bleeding

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.**

acute gastric ulcerations الفرق بين الـ PU و الـ → بعد ما نخلص دراستها اعرف الفرق بين الـ

Q: At the end of stress ulcer discussion, tabulate the **differences** between the **acute** stress ulcers & the **PU**. [Etiology, Pathogenesis, Complications, Gross & ◘ H features]

* واذا كانت الـ ulcer في الـ duodenum → مستحيل تصير malignant لسبب غير معروف

► 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**, → acute ulceration following burns.

(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.

قهوة غامقة بسبب هضم الدم في المعدة.

▶ **GROSSLY,** acute stress ulcers are usually **multiple, circular & small (<1 cm in∅).** The **base** is stained dark brown by the acid digestion of extruded blood. Unlike chronic PU, acute stress ulcers are: **(1)** Although may occur singly, more often they are **multiple & (2)** Found **anywhere** in the stomach and located throughout the stomach & duodenum (F15-18 & 4.14).

معهم جدا"

(body of stomach)

◘ 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

هي ليست قرحة بل التهاب مع erosion

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

معهم.

☺ Acute stress ulcers are not precursors of chronic PU. will never change to chronic.

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

sepsis, burn, NSAID---

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

طالما عالجنا السبب المريض رح يرجع طبيعي والقرحة بسيطة كمان

معهم جدا"

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**

* pedinculated Liemyoma → from lipid -- وداخلة للتجويف

★ **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 :

زيادة في النمو.

(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**. مجرد فرط في النمو.

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

Both types 1 & 2 polyps are essentially **innocuous,** ← يعتقد انها زيادة في عدد الglands فقط.

النوع الخطير

you have to treat it.

(3) **Adenomatous polyps** (5%) are **true tumors**, contain dysplastic epithelium & in which, there is a definite risk of harboring **adenocarcinoma,** which ↑ with ↑ polyp **size**.

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

excision لذلك دائماً لازم نشيلها malignant or benign

Gastric Tumors

يعني مستحيل بالعين المجردة نعرف أنه الـ polyp هل هي

😐 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].

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).

Japan and south. عكس ذلك السرطان الذي أعلى بـ 8-9 أضعاف بـ US من

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

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

لأنه استغنينا عن تمليح الطعام أو تخميره أو دفنه

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

مهم جداً التمييز بينهم.

well differentiated.

(by H.pylori)

(I) ***Intestinal type:*** → • initial **chronic gastritis**, accompanied by severe **gastric atrophy** & → **intestinal metaplasia**, which are followed by → **dysplasia** & → ***intestinal type* ca.** It tends to be • **better differentiated** & is the • **more common type in high-risk populations.** It occurs primarily • after age 50 years with a • 2:1 Male/Female ratio.

☺ Its *incidence has progressively* ***diminished*** *in the US.*

سببها تريد الأكل وعدم استعمالها أي طريقة أخرى لحفظ الأكل.

(II) ***Diffuse variant:*** is • **not associated with chronic gastritis,** thought to arise **de novo** from native gastric mucous cells & tends to be • **poorly differentiated**. It occurs at an • **earlier age than the intestinal type** with • **female predominance**. • The *incidence of diffuse gastric ca has not significantly changed in US in the past 60 years* & now constitutes approximately **50%** of gastric ca in the US.

ما في الها سبب

قل بشما هذا اضل ثابت

عود الحالات ثابت

intestinal الـ

لذلك ما أهمية مبارت intestinal

مساوية لأهمية الـ

Table 15-5 Risk Factors for Gastric Carcinoma

(I) Intestinal-Type Adenocarcinoma

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.

اللحوم المعلبة

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

4-Decreased intake of fresh vegetables & fruits (antioxidants present in these foods may inhibit nitrosation)

5-Partial gastrectomy

6-Pernicious anemia

(II) Diffuse Carcinoma

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

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

Etiology & Pathogenesis

(I) Intestinal-Type Adenoca

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

☺ **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. → لو كان pangastritis بالعكس الخطر يقل.

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

★ The mechanisms of neoplastic transformation are not entirely clear. Chronic gastritis induced by *H. pylori* may release ROS, which eventually cause DNA damage, leading to an imbalance between cell proliferation & apoptosis, particularly in areas of tissue repair.

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

★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.

(II) Diffuse Adenocarcinoma

😐 The risk factors for this type of cancer **remain undefined** (Table 15-5), & **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** تقريباً بـ ٣ أضعاف

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

★ Gastric ca is classified on the basis of (I) **depth** of invasion, (II) gross growth **pattern**, & (III) **histologic** subtype.

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

😐 **Early gastric ca is defined as a lesion confined to the mucosa & submucosa**, regardless of the presence or absence of perigastric LN metastases. Gastric mucosal **dysplasia** is the presumed precursor lesion of early gastric cancer, which then in turn progresses to "advanced" lesions.

☹ **Advanced gastric ca** is a **T** that has extended below the submucosa **into the muscular wall** & has perhaps spread more widely. (invasion of the muscle)

surrounding tissue والـ serosa وحتى ممكن يعبر الـ

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

(1) **Exophytic** (F 4-22), with T mass protrusion into the lumen & the mass may contain portions of an adenoma,

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

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

على عكس الـ PU الـ margins بتكون مرتفعة وفيها عُقَد

★ 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**.

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

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

► 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)**. bilateral from gastric carcinoma.

► ***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).

SMALL & LARGE INTESTINES

Inflammatory diseases, & tumors, affect both small & large intestines, therefore, the two organs are considered together.

DEVELOPMENTAL ANOMALIES

★ ***Atresia*** = ***No lumen*** = complete failure of development of the intestinal lumen, e.g., ***imperforated anus***.

★ ***Stenosis***, is incomplete obstruction = narrowing of the intestinal lumen, may affect any segment of the small intestine, but **duodenal atresia** is the most common.

★ ***Duplication*** usually takes the form of well-formed saccular to tubular cystic structures, which may or may not communicate with the lumen of the small intestine

★ ***Omphalocele*** is a congenital defect of the periumbilical abdominal musculature that creates a membranous sac, into which the intestines herniate.

★ ***Gastroschisis*** is extrusion of the intestines caused by lack of formation of a portion of the abdominal wall.

بترتبط بين الـ umbilicus والـ intestine المفروض تتسكر لكن بتضل فاتحة.

★ *Meckel diverticulum*

- Is the most common congenital anomaly {2% of births}
- It results from failure of involution of the omphalomesenteric duct, leaving a persistent blind-ended tubular protrusion as long as 5 to 6 cm (=2 Inches, F15-21).
- The diameter is variable, sometimes approximating that of the small intestine itself. Located on the **antimesenteric** side of the small bowel, usually the ileum, about 2 feet proximal to the Ileocecal valve & are composed of all layers of the normal small intestine (i.e., ***Meckel is a* true** diverticulum).
- Generally are **asymptomatic**, except when they permit bacterial overgrowth that **depletes vitamin B12**, producing a syndrome similar to pernicious anemia.
- **Rarely**, **pancreatic rests** are found in it &
- In 50% of cases there are **heterotopic islands of functioning gastric mucosa**. **Peptic ulceration** in the adjacent intestinal mucosa sometimes is responsible for **mysterious** intestinal bleeding or symptoms resembling acute appendicitis. {☺ **Remember; in** 2% of births, 2 Inches in length, & 2 feet proximal to ilio-caecal valve}.

الغريب

★ ***Malrotation*** of the developing bowel can prevent the intestines from assuming their normal intra-abdominal positions, e.g., the **caecum** may be found anywhere in the abdomen, including the **left upper quadrant**, rather than in its normal position in the right lower quadrant. Confusion may arise when **appendicitis presents as left upper quadrant pain.** The large intestine is predisposed to **volvulus.** (بالقاعدة تبعتها بتحرك 360° حول نفسها وبتخنق نفسها.

★ **Hirschsprung Disease: Congenital Megacolon**

►Megacolon is distention of the colon to greater than 6 or 7 cm in ∅, it occurs either as a congenital or acquired disorder.

► Hirschsprung D (congenital megacolon) results when, during development, the migration of neural crest-derived cells along the GIT arrests at some point before reaching the anus.

الخلايا العصبية دائماً بتنمو مع ال GIT لكن إذا وقت رح تخلي جزء un-innervated

► Hence, an ***aganglionic*** **segment is formed that lacks both the Meissner submucosal & Auerbach myenteric plexuses**. This causes functional obstruction & progressive distention of the colon proximal to the affected segment. Ganglia are absent from the muscle wall & submucosa of the constricted segment but may be present in the dilated portion.

* يعني الي ما فيها innervation بتنكمش لكن الجزء القريب منها (innervated) بكون dilated.

- Hirschsprung D occurs 1 in 5000 to 8000 live births;
- It predominates in males, M/F is 4:1.
- It is much more frequent in those with other congenital anomalies like hydrocephalus, VSD, & Meckel diverticulum.

مهم ← ١١٩ ص — نفس مبدأ ال autoimmune disease بكونوا مع بعض.

■ H, the critical lesion in Hirschsprung disease is the **lack of ganglion cells, & of ganglia, in the submucosa & muscle wall of the affected collapsed segment** (aganglionic segment)

►**GROSSLY,** (1) It is the proximal, properly innervated, ganglionic segment that undergoes dilation. When only the distal colon is aganglionic, the proximal colon becomes **massively distended up to** a diameter of 15 to 20 cm. The dilated wall may be thinned by distention, or, is thickened by compensatory muscle hypertrophy.

* متابع، المنطقة ال constricted هي ال pathology.

(2) The mucosal lining of the distended portion may be intact or have shallow, so-called **stercoral ulcers** produced by impacted, inspissated feces.

← المادة الغائطية في القولون رح تسبب تقرحات.

► ***Clinically,*** in most cases a **delay** occurs in the initial passage of meconium, followed by vomiting in **48 to 72 hours**.

When a very short distal segment of the rectum alone is involved, the obstruction may not be complete & may not produce **manifestations until later in infancy**, in the form of alternating periods of obstruction & passage of diarrheal stools.

☹ The **principal threat to life is superimposed enterocolitis** with fluid & electrolyte disturbances. small and large intestine. الامعاء

◘ H, the **diagnosis** is established by **documenting** the absence of ganglion cells in the (*nondistended*) bowel segment. stenosed.

★ ***Acquired megacolon*** may result from (1) **Chagas disease**, in which the trypanosomes directly invade the bowel wall to destroy the plexuses; the other forms of megacolon are not associated with any deficiency of mural ganglia, including:

(2) **Organic obstruction** of the bowel by a tumor or inflammatory stricture, (acquired)

(3) **Toxic megacolon** complicating ulcerative colitis or Crohn disease, or (4) A **functional psychosomatic disorder.**

ganglia. ماني مشكلة بال

fecal material goes to the wall of intestine وبح تعمل مشاكل فتكون سبب

VASCULAR DISORDERS

Ischemic Bowel Disease

• Depending on the vessel or vessels involved, ischemic lesions may be restricted to the small or large intestine or, both.

• Acute occlusion of one of the **three major supply trunks of the intestines: ★celiac, ★superior & ★inferior mesenteric arteries-may lead to infarction of extensive segments of intestine.** → 4-5 meters in length (normal small intestine length).

• However, insidious loss of one vessel may be without effect, Thanks God for the rich vascular anastomoses.

• Lesions within the end-arteries that penetrate the gut wall produce small, focal ischemic lesions. ← arteries الـ .لصغيرة

As illustrated in F15-22, the severity ranges from:

(1) ***Transmural infarction*** involving all gut layers, ***always caused by acute occlusion of a major mesenteric artery***, to

(2) ***Mural infarction*** of the mucosa & submucosa, sparing the muscular wall, to

(3) ***Mucosal infarction***, if the lesion extends not deeper than the muscularis mucosae, → between mucosa and submucosa.

*Trans :- يعني كل الجدار مقلوب

- Both mural & mucosal infarctions are more often results from either physiologic hypoperfusion or more localized anatomic defects, & may be acute or chronic.
- Mesenteric venous thrombosis is a less frequent cause of vascular compromise. * أهم أنها تصيب الـ veins وليس الـ arteries هاي أهم سبب.

▲The **predisposing** conditions for all three infarctions are:

(1) ***Arterial thrombosis***: severe atherosclerosis (usually at the origin of the mesenteric vessel), systemic vasculitis, dissecting aneurysm, angiographic procedures, aortic reconstructive surgery, surgical accidents, hypercoagulable states, & oral contraceptives

(2) ***Arterial embolism***: cardiac vegetations (as with endocarditis), or MI with mural thrombosis, angiographic procedures, & aortic Atheroembolism.

(3) ***Venous thrombosis***: hypercoagulable states induced, for example, by **oral contraceptives** or antithrombin III deficiency, intraperitoneal **sepsis**, the postoperative state, **cancerous invasion of veins** (particularly hepatocellular ca), **cirrhosis**, & abdominal **trauma**

(4) *Nonocclusive ischemia:* cardiac failure, shock, dehydration, vasoconstrictive drugs (e.g., digitalis, vasopressin, propranolol),

(5) *Miscellaneous:* radiation injury, volvulus, stricture, & internal or external herniation

►**GROSSLY,**

(1) Transmural intestinal infarction may involve a short or long segment, depending on the ► particular vessel affected & the patency of the ►anastomotic supply.

★ Whether the occlusion is arterial or venous, **the infarction always has a dark red hemorrhagic** appearance because of reflow of blood into the damaged area (F15-23).

★ The ischemic injury usually **begins in the mucosa** & extends outward; within 18 to 24 hours there is a thin, fibrinous exudate over the serosa.

★ With **arterial** occlusion the **demarcation** from adjacent normal bowel is **fairly sharply** defined, but with venous occlusion the margins are less distinct.

■ H, the **Transmural infarction** changes are typical of ischemic coagulative necrosis with marked edema, interstitial hemorrhage, & sloughing of the mucosa. Within 24 hours intestinal bacteria produce gangrene & sometimes perforation of the bowel.

(2) Mural & (3) Mucosal infarctions are recognized by multi-focal lesions **interspersed** with spared areas. Their location depends in part on the extent of preexisting atherosclerotic narrowing of the arterial supply; lesions can be scattered over large regions of the small or large intestines. في حالة ال perforation

Affected foci may or may not **be visible** from the serosal surface, because **by definition** the ischemia does not affect the entire thickness of the bowel. مارح الاقيها

😐 When the bowel is opened, hemorrhagic edematous thickening of the mucosa, sometimes with superficial ulcerations, is seen. لما افتح البطن لأنه مش واصلة لبرا

complications of intestinal infarction

— infarction (1) → gangrene (2) → perforation (3) → death (5) ← generalized pertonitis (4)

بسيطة

■ H, in mural & mucosal infarction there is hemorrhage, edema, & outright necrosis of the affected tissue layers (F15-24). Inflammation develops at the margins of the lesions, & an inflammatory fibrin-containing exudate (**pseudomembrane**), usually secondary to bacterial superinfection, may coat the affected mucosa. كل الي حكيناه فوق هو acute.

★ Alternatively, **chronic vascular insufficiency** may produce a chronic inflammatory & ulcerative condition, mimicking IBD.

Clinical Features

- Ischemic bowel injury is most common seen in the **elderly**.
- With the **transmural lesions**, there is **sudden severe abdominal pain**, sometimes accompanied by bloody diarrhea.

☹ Because this condition **may progress to shock** & vascular collapse within hours, the diagnosis must be made promptly, & making it requires a **high index of suspicion** in the appropriate context (e.g., recent major abdominal surgery, atrial fibrillation, or vegetative endocarditis or recent MI).

مقياس عالي من الشك. يعني الشخص فقد دم كثير. thrombus يعني في من القلب وراح للintestine.

لا بهذه الحالة افتح وشوف حتى تنقذ حياة المريض.

Prognosis:

☠ **The mortality rate with transmural infarction of the bowel approaches 90%**, largely because of the short time between onset of symptoms & **perforation** caused by gangrene. generalized perotinitis ⇒ death of patient.

☺ **By contrast, mural & mucosal ischemia** may appear only as unexplained abdominal distention or GIT bleeding, sometimes accompanied by the gradual onset of abdominal pain or discomfort.

Suspicion is raised if the individual has experienced conditions that favor acute hypoperfusion of the bowel, i.e., episode of **cardiac failure** or **shock.**

☺ **Mucosal & mural infarctions** are **not** by themselves **fatal,** &, indeed, if the cause of hypoperfusion can be corrected, **the lesions may heal.** only ischemia to mucosa and/or submucosa

Angiodysplasia

☹ Tortuous dilations of mucosal & submucosal BV are seen most often in the cecum or right colon, usually only after the 6th decade of life. They are prone to **rupture & bleed into the lumen, *accounting for 20% of significant lower intestinal bleeding*.** The hemorrhage may be **chronic** & intermittent & only, causing severe anemia; but rarely is it acute & massive.

★Most often, these lesions are **isolated**, but sometimes they are **part** of a systemic disorder such as hereditary hemorrhagic telangiectasia **(Osler-Weber-Rendu syndrome)**.

Hemorrhoids → البواسير

☹ Hemorrhoids are **variceal dilations** of the anal & perianal submucosal venous plexuses. They are common after age 50 & develop in the setting of persistently elevated venous pressure within the hemorrhoidal plexus.

▲Common **predisposing conditions** are **straining** at stool in the setting of • **chronic constipation** & the venous stasis of • **pregnancy** in younger women.

• More rarely, hemorrhoids may reflect **portal hypertension**, usually resulting from liver cirrhosis. Hemorrhoids 2 types are

(1) Internal hemorrhoids are varicosities in the superior & middle hemorrhoidal veins, appearing above the anorectal line & are **covered by rectal mucosa**.

(2) External hemorrhoids are those that appear below the anorectal line, representing dilations of the inferior hemorrhoidal plexus & are **covered by anal mucosa**.

Both 1 & 2 are thin-walled, dilated vessels that **commonly**

▶ **Bleed,** {sometimes masking bleeding from far more serious ***malignant*** **proximal lesions**}. Sometimes they may become

▶ **Thrombosed**, particularly when subject to trauma from passage of stool.

▶ **Prolapse with strangulation** of the internal hemorrhoids may occur during straining at stool & then become trapped by the compressive anal sphincter, leading to **sudden, extremely painful,** edematous hemorrhagic enlargement.

* أي شخص كبير فوق الـ 60 بيجي عنده شكل hemorrhoid لازم نشك إنه قد تكون masking for cancer in the colon.

COLONIC DIVERTICULOSIS

Ω ***A diverticulum is a blind pouch that communicates with the lumen of the gut.*** Congenital {***Meckel***} ***diverticula*** have all three layers of the bowel wall (mucosa, submucosa, & muscularis propria) & are distinctly uncommon.

Ω Virtually all other diverticula are **acquired** & either without, or, having an attenuated muscularis propria.

Ω *Acquired diverticula may occur* ***anywhere*** *in the GIT, but by far, the most common location is the* ***colon,*** giving rise to *diverticular disease* of the colon (***diverticulosis***); **95% of which are in the sigmoid colon.**

▲The colon is unique in that the **outer longitudinal muscle coat** is not complete, but is gathered into three equidistant bands (the **taeniae coli**). Focal defects in the muscle wall are created where nerves & arterial vasa recta penetrate the inner circular muscle coat alongside the taeniae. The connective tissue sheaths accompanying these penetrating vessels provide potential sites for herniations.

٣ مناطق ضعيفة وإذا صار فيها ضغط رح تأدي إلى diverticulum.

Ω Colonic diverticulosis is relatively infrequent in native populations of non-Western countries. Although unusual in Western adults younger than 30 years of age, **in those older than the age of 60 the prevalence approaches 50%.**

١ من كل ٢ أغلبها asymptomatic

►This high prevalence is attributed to the consumption of a refined, low-fiber diet in Western societies, resulting in reduced stool bulk with increased difficulty in passage of intestinal contents. *Exaggerated spastic contractions* of the colon result in **segmentation** (isolate segments of the colon in which the intraluminal pressure becomes markedly elevated), with consequent herniation of the bowel wall through the anatomic points of weakness.

fecal material صعب تطلع لما يكون الـ diet فيها fibers

►Thus, *two* influences are important in the genesis of diverticular protrusions:

(1) ***Exaggerated peristaltic contractions*** with abnormal elevation of intraluminal pressure &

(2) ***Focal defects*** of the normal muscular colonic wall.

►**GROSSLY** • Most colonic diverticula are **small, Ω flasklike or spherical outpouchings, usually 0.5 to 1 cm in** Ø (F15-25A), located in the **sigmoid colon** in **95% of patients**.
• The exaggerated peristalsis often induces taenia coli & circular **muscular hypertrophy** in the affected segments. Diverticula frequently dissect into the appendices epiploicae & therefore may be inapparent on external inspection تغير للخارج من muscular wall.

😐 In the **uninflamed state** the walls are usually very thin, made up largely of mucosa & submucosa enclosed within fat or an intact peritoneal covering (F15-25B).

☹ **Inflammatory changes** may supervene to produce both diverticulitis & peridiverticulitis; perforation of which may lead to localized peritonitis or abscess formation. مع

😐 **When many closely adjacent diverticula become inflamed,** the bowel wall may be encased by fibrous tissue, with **narrowing** of the lumen, producing a remarkable **resemblance to a malignant stricture.**

Clinically, diverticular disease is mostly, **asymptomatic.** In 20% of patients there is intermittent cramping or discomfort.

Complications: superimposed (1) **diverticulitis** accentuates the symptoms & produces left lower quadrant tenderness & fever. Other **rare** complications include brisk (2) **hemorrhage**, (3) **perforation with pericolic abscess, or fistula formation.**

↑fibers → ↑bulky stool

Treatment is by a high-fiber diet, recommended on the theory that the increased stool bulk & ↓ the exaggerated peristalsis.

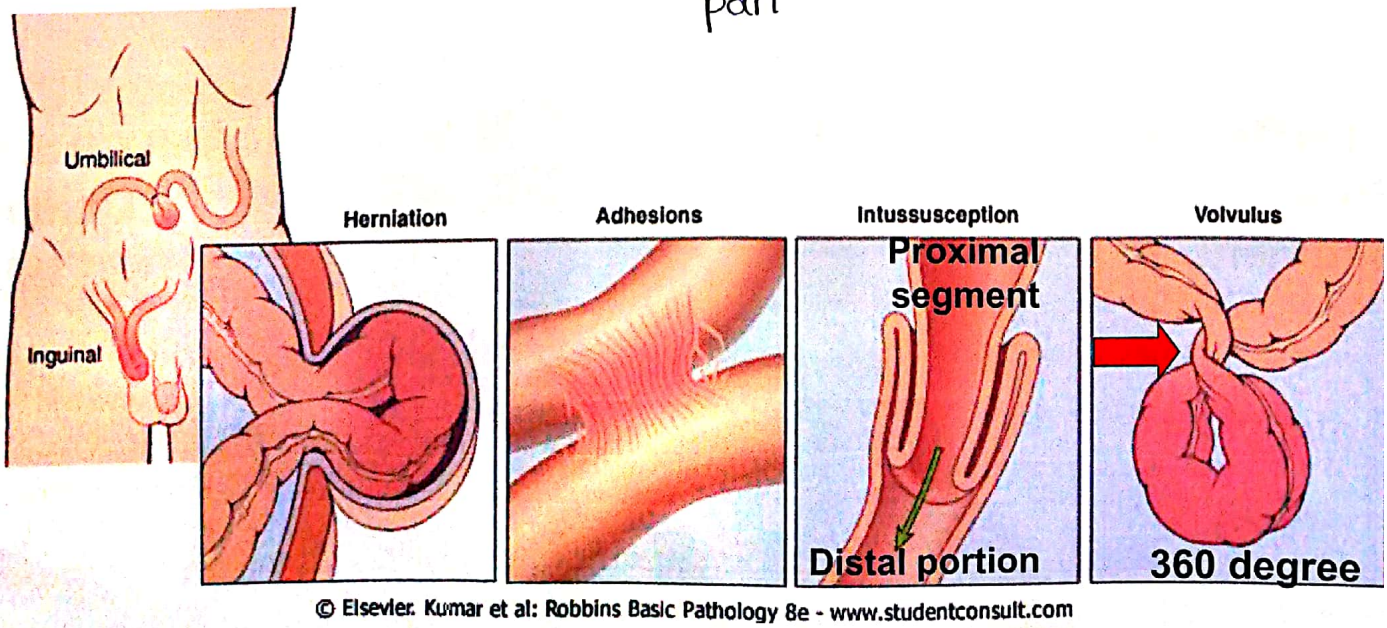
BOWEL OBSTRUCTION

Although any part of the gut may be involved, because of its narrow lumen, the **small bowel** is most commonly affected.

4 major Causes of Intestinal Obstruction are mechanical, {internal or external Hernias **+** Adhesions + Intussusception + Volvulus}, accounting for at least 80% of the cases (Table 15-6 & F15-26).

F15-26: **The four major causes of intestinal obstruction**:
(1) **Herniation** of a segment in the umbilical or inguinal regions,
(2) **Adhesions** between intestinal loops,
(3) **Intussusception,** → proximal portion يدخل على الـ lumen التالي
(4) **Volvulus**.

distal الـ part



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► **Less Frequent Causes:** Tumors, Inflammatory strictures, Obstructive gallstones (F 4.25), fecaliths, foreign bodies, Congenital stricture or bands, atresias, imperforate anus, Meconium in cystic fibrosis.

duodenal atresia

مادة غائطية متحجرة

Ω ***Hernias:*** when there is a weakness or defect in the wall of the peritoneal cavity, it may permit protrusion of a pouchlike, serosa-lined sac of peritoneum, which is called a ***hernial sac***.

®The usual sites of weakness are: anteriorly at the **inguinal & femoral canals +** at the **umbilicus +** in **surgical scars**.

☹ **S*egments of viscera,*** mostly **small bowel** loops (F4.29), or portions of omentum or large bowel, *frequently* ***intrude*** *&* *become trapped in hernias* ***(external herniation),*** particularly in the inguinal hernias, which have narrow orifices & large sacs.

→ **Pressure at the neck** of the ***hernial sac*** may
→ **Impair venous** drainage of the trapped viscus causes stasis & edema, ↑ the bulk of the herniated loop, leading to
→ ***incarceration***, **i.e.; permanent trapping** which further compromise its blood supply & drainage leading to
→ ***strangulation*** of the trapped segment, i.e.; **Infarction**

يزيد خطورته كل ما كانت الفتحة أصغر

leading gangrene → perforation

(1) Surgical procedures, infection, & even endometriosis often cause localized or general peritonitis. With healing…

(2) A*dhesions* may develop between the bowel segments or with the abdominal wall or the operative site. These fibrous bridges can create closed loops (rings) through which the intestines may slide & become trapped (***internal herniation***)

☹ The sequence of events is the same as with external hernias

تداخل الأمعاء.

(3) Intussusception (F4.27) **means telescoping of a proximal segment of the bowel into the immediately distal segment.**

In infants & children, intussusception sometimes occurs **without** apparent cause. بدون سبب

While in adults, such telescoping often points to an intraluminal mass (e.g., **tumor**) that becomes trapped by a peristaltic wave & pulls its point of attachment along with it, into the distal segment. Not only does **intestinal obstruction** ensue, but the vascular supply may be so compromised as to cause **infarction** of the trapped segment. **(Treatment ?)**

هنا يكون في الرسبا

(الأمعاء حتى تتخلص من الـ tumor بدها تدفعه هو والقاعدة تتبعه / إذا infarcted بتعمل resection / إذا الأمعاء عايشة بتعمل gentle movement / gangrene)

(4) ***Volvulus*** (see F4-28) refers to 360 degree **twisting of a loop of bowel** (or other structure e.g., ovarian cyst or tumor) **about its base of attachment, constricting the venous outflow & sometimes the arterial supply as well**. Volvulus affects the **small bowel** most often & rarely the **redundant sigmoid**. Intestinal obstruction & infarction may follow.

Malabsorption Syndrome

▶ Is **defective absorption** of fats, fat-soluble & other vitamins, proteins, carbohydrates, electrolytes & minerals, & water.

▶ The most common presentation is **chronic diarrhea**; the ® hallmark of malabsorption syndromes is **steatorrhea (excessive fat content of the feces).** high fats in stool.

▶ **Table 15-9 shows the Major Malabsorption Syndromes.**

▶ The most common malabsorptive disorders encountered in the US are ***pancreatic insufficiency, celiac disease, & Crohn disease.***

☺ **Basically**, *malabsorption is the **result** of disturbance of at least one of these normal digestive functions:*

(1) ***Intraluminal digestion***, in which carbohydrates, proteins, & fats are enzymatically broken down. The process begins in the mouth with **saliva**, receives a major boost from **gastric peptic** digestion, & continues in the small intestine, assisted by **pancreatic enzyme** secretion & the emulsive action of **bile**.

(2) ***Mucosal absorption*** in which water, electrolytes, & nutrients are absorbed & transported into the cell. **Absorbed** → **fatty acids** are converted to → **triglycerides** & are assembled with + **cholesterol & + apoprotein B** into **= chylomicrons.** Disturbances can be caused by (1) **primary mucosal cell abnormalities** or (2) **reduced** small intestinal surface area or (3) from mucosal **infections**.

(3) ***Nutrient delivery,*** involving the delivery of nutrients from the intestinal cells into the lymphatics. Disturbances may be caused by congenital defects, or be secondary to tuberculosis or retroperitoneal fibrosis.

Table 15-9 The Major Malabsorption Syndromes

Defective Intraluminal Digestion

- Digestion of fats & proteins:
  - → Pancreatic insufficiency, due to pancreatitis or cystic fibrosis
  - → Zollinger-Ellison syndrome, with inactivation of pancreatic enzymes by excess gastric acid secretion
- Solubilization of fat, due to defective bile secretion,
  - → hepatic dysfunction,
  - → Biliary obstruction, resulting in cessation of bile flow,
  - → Ileal dysfunction or resection, with ↓ bile salt uptake,
- Nutrient preabsorption or modification by bacterial overgrowth
- Distal ileal resection or bypass,
- Total or subtotal gastrectomy

Primary Mucosal Cell Abnormalities:

- Defective terminal digestion
  - → Disaccharidase deficiency (lactose intolerance)
  - → Bacterial overgrowth, with brush-border damage
- Defective transepithelial transport → Abetalipoproteinemia

Reduced Small Intestinal Surface Area

- Celiac disease • Crohn disease
- Short-gut syndrome, after surgical resections

Infections

- Acute infectious enteritis • Parasitic infestation
- Tropical sprue • Whipple disease

Lymphatic Obstruction

- Lymphoma • Tuberculosis & tuberculous lymphadenitis

▲ Here we give some examples of the most common malabsorption syndromes caused by defects in either intraluminal digestion or mucosal absorption. Crohn disease is discussed later.

Defects of Intraluminal Digestion

☹Typical features of defective intraluminal digestion are an ***osmotic diarrhea*** from undigested nutrients, & ***steatorrhea*** (excess output of undigested fat in the stool).

★The latter can arise either from inadequate action of pancreatic lipases or from inadequate solubilization of fat by hepatic bile secreted into the gut lumen.

The **most common causes** are ➔ ***pancreatic insufficiency associated with chronic alcoholism*** & ➔ **Crohn disease**. Other causes are➔ intestinal bacterial overgrowth, ➔ cholestatic liver disease, & surgical procedures such as ➔ extensive ileal resection & gastrojejunostomy.

Defects of Mucosal Absorption

☹***Lactose intolerance*** is caused by the deficiency of disaccharidase (*lactase*).

- The **inherited form is rare** but is of great consequence, because **in infants** it produces *milk intolerance*, leading to diarrhea, weight loss, & **failure to thrive**.
- The **acquired** deficiency is common among adults, particularly North American blacks. Aside from the need to avoid milk products, the disorder is of minimal consequence.
- The intestinal mucosa is morphologically **normal.**

▼ **Diagnosis** is made by **measurement of breath hydrogen level, which reflects bacterial overgrowth in the presence of excess intraluminal carbohydrate**.

☹ **Deficiency of apolipoprotein B**

➔**Apolipoprotein B** is the protein is required for the assembly of dietary lipids into chylomicrons, which are then secreted into intestinal lymphatics, In the case of @***betalipoproteinemia***, the mucosal epithelial cell is unable to export lipid.

• In this disease, mucosal absorptive cells contain vacuolated lipid inclusions, but the mucosa is otherwise normal. This deficiency causes diarrhea & steatorrhea in infancy & significant failure to thrive.

☹ ***Celiac disease (Gluten-sensitive enteropathy)***

Is a noninfectious cause of malabsorption resulting from a reduction in small intestinal absorptive surface area.

Celiac disease is believed to be **quite common**, affecting about **1 in 300 persons both in Europe & in the US (1 Million in US),** & many patients have subclinical disease.

☹ The **basic disorder** in celiac disease is **immunological sensitivity to gluten**, the component of wheat & related grains (oat, barley, & rye) that contains the water-insoluble protein **gliadin**. Gliadin peptides are efficiently presented by antigen-presenting cells in the lamina propria of the small intestine to CD4+ T cells, thereby driving an immune response to gluten. There is hence a strong genetic susceptibility, with **95%** of patients having an **HLA-DQ2 haplotype** & the remainder having HLA-DQ8.

☹ When the small intestinal mucosa exposed to gluten, it accumulates intraepithelial CD8+ T cells & large numbers of lamina propria CD4+ T cells sensitized to gliadin. The intestinal pathology may result from epithelial cell stress, perhaps induced by gliadin sensitivity, & **CD8+ T cell-mediated killing of these epithelial cells.**

★ The effect of the immune response is…

◘ **Total flattening of mucosal villi** (& hence loss of surface area), affecting the proximal more than the distal small intestine, with lymphocytic & plasma cell infiltration in the lamina propria.

► **Age** of presentation, with symptomatic diarrhea & malnutrition, varies from infancy to mid-adulthood;

☺ **Removal** of gluten from the diet is met with **dramatic improvement.**

☹ There is a low, long-term risk of **malignant disease**, with about a **twofold increase over the usual rate of Intestinal lymphomas** and other malignancies include **GI & breast carcinomas**.

★In some patients with celiac disease there is an associated skin disorder called **dermatitis herpetiformis.**

Tropical sprue

Resembles celiac disease in symptomatology, but occurs almost exclusively in persons living in or visiting the **tropics**: المناطق الاستوائية

😐 No specific causal agent has been clearly identified, **but** the **appearance of malabsorption** within days or few weeks of an acute diarrheal **enteric infection** strongly implicates an infectious process, as does the

☺ **Prompt response** to broad-spectrum antibiotic therapy!

☹ Small intestinal changes vary: from **near normal ➔to severe diffuse enteritis with villus flattening.**

In contrast to celiac disease, injury is seen at all levels of the small intestine, proximal and distal.

Whipple disease

Is a rare systemic infection that may involve any organ of the body but principally affects the intestine, CNS, & joints. The ® **hallmark** of Whipple disease is a small intestinal **mucosa laden with distended PAS-positive macrophages** in the lamina propria. The causal **organism** is a gram-positive & culture-resistant **actinomycete, *Tropheryma whippelii.***

★ Affecting principally males in the 4th to 5th decades of life, Whipple disease causes a malabsorptive syndrome.

★ **Response to antibiotic therapy is usually prompt, but relapses are common.**

► **CLINICALLY, All the malabsorption syndromes** resemble each other:

® **Steatorrhea**, the passage of abnormally bulky, frothy, greasy, yellow or gray stools is a prominent feature of malabsorption, accompanied by **weight loss**, anorexia, abdominal distention, borborygmi & flatus, & muscle wasting.

The consequences of malabsorption affect many organ systems:

- ***Hematopoietic system*: anemia** from iron, pyridoxine, folate, or vitamin B12 deficiency (vitamin B12 is normally absorbed in the ileum) & **bleeding** from vitamin K deficiency (a fat-soluble vitamin).
- ***Musculoskeletal system*: osteopenia** & **tetany** from defective calcium, magnesium, vitamin D, & protein absorption.
- ***Endocrine system*:** amenorrhea, impotence, & infertility from generalized **malnutrition**; & **hyperparathyroidism** from protracted calcium & vitamin D deficiency.
- ***Skin*: purpura & petechiae from vitamin K deficiency; edema** from protein deficiency; **dermatitis & hyperkeratosis from deficiencies of vitamin A** (fat soluble), zinc, essential fatty acids, & niacin; **mucositis** from vitamin deficiencies.
- ***Nervous system*: peripheral neuropathy** from vitamin A & B12 deficiencies

موضوع مهم

INFLAMMATORY BOWEL DISEASE (IBD)

- *Crohn's disease* (CD) & *Ulcerative colitis* (UC) are chronic relapsing inflammatory disorders of unknown (**idiopathic**) origin, collectively known as **idiopathic inflammatory bowel disease (IBD),** which share many common features.
- ***IBD result from an abnormal local immune response against the normal flora of the gut & probably against some self antigens in genetically susceptible individuals.***
- *CD may affect any portion of the GIT from esophagus to anus, but most often involves the **ileum (terminal ileitis)**; 50% of cases exhibit noncaseating **granulomatous** inflammation* ← اسمه الأول
- *UC is a **nongranulomatous** disease **limited to the colon.***
- *CD & UC* differ in many respects, including the disease natural history, pathological aspects, treatment & responses to treatment.
- Before considering these diseases separately, the **pathogenesis** of both CD & UC will be considered.

Etiology & Pathogenesis of both CD & UC

😐The normal intestine is in a steady state of "physiologic" inflammation, representing a dynamic balance between

(1) **Factors** that activate the host immune system, such as **luminal microbes, dietary antigens, & endogenous inflammatory stimuli**; &

(2) **Host defenses** that down-regulate inflammation & maintain the integrity of the mucosa.

😐 The search for the causes of loss of this balance in CD & UC has revealed many parallels, أسباب متعددة
😐 but the origins of *both diseases remain unexplained* (thus their designation as ***idiopathic***). ← سببها غير واضح

The **Genetic Predisposition, Immunologic Factors, & Microbial Factors** will be discuss.

Genetic Predisposition

▶There is little doubt that genetic factors are important in the occurrence of IBD. **First-degree relatives are 3 to 20 times more likely to develop the IBD, & 15% of persons with IBD have affected first-degree relatives.** In keeping with an underlying immunologic dysfunction, both CD & UC have been linked to specific major histocompatibility complex class II alleles. UC has been associated with *HLA-DRB1*, whereas *HLA-DR7* & *DQ4* alleles are associated with 30% of CD cases in North American white males.

Immunologic Factors

😐 It is **not known** whether the immune responses in IBD are **directed against self-antigens of the intestinal epithelium? or to bacterial antigens?**

➔ In both CD & UC, the primary damaging agents appear to be **CD4+ cells**. The inflammatory cytokine **TNF** may play an important pathogenic role in CD; this is suggested by the **effectiveness of treatment with TNF antagonists in CD.**

Microbial Factors

☹The sites affected by IBD-the distal ileum & the colon-are awash {covered by tides} in bacteria. While there is no evidence that these diseases are caused by microbes, it is quite likely that **microbes provide the antigenic trigger to a fundamentally dysregulated immune system.**

➔ This concept is *strengthened* by the observations that in **murine models**, IBD develops in the presence of normal gut flora but not in germ-free mice.

▼ **The Final Common Pathway for the Pathogenesis of IBD** is **Inflammation**, which is ultimately, the result of activation of inflammatory cells (neutrophils initially & mononuclear cells later) in the course, causing **mucosal destruction** & the **intermittent bloody diarrhea that is characteristic of IBD.**

☺ Most current therapeutic interventions act entirely or partly through nonspecific **down-regulation** of the immune system.

▼ **Among diagnostic tests**, the most useful is the detection of perinuclear antineutrophil cytoplasmic Abs, which are present in 75% of persons with UC & only 11% of individuals with CD.

Crohn's Disease (CD)

Epidemiology

- Worldwide in distribution, CD is much more prevalent in the US, GB, & Scandinavia than in Central Europe, & is rare in Asia & Africa.
- The **incidence & prevalence of CD** has been steadily **raising in the US & Western Europe**, with annual incidence in the US of **4 per 100,000** populations (12000 new cases/Year)
- It occurs at any age, from young childhood to advanced age, but **peak incidence** is between the **2nd & 3rd decades** of life. (10 - 30 yrs)
- Females are affected slightly more often than males.
- Whites appear to develop the disease 2 to 5 times more often than do nonwhites. In the US, CD occurs **3 to 5 times** more often among **Jews** than among non-Jews.

اليهود

► CD may affect any level of the GIT, **from mouth to anus**, but most commonly located at the **terminal ileum**. At first, the disease was thought to be limited to the ileum, & that is why it was referred to as **"terminal ileitis" or "regional enteritis"**.

إلتهاب بمنطقة معينة إلي هي الـ ileum.

▲ ***BUT, CD must be viewed as a systemic inflammatory disease with predominant GIT involvement***. Active cases of the disease are often accompanied by extra-intestinal complications of immune origin, such as uveitis, sacroiliitis, migratory polyarthritis, erythema nodosum, bile duct inflammatory disorders, & obstructive uropathy.

►**GROSSLY** • **Site**: In CD there is gross involvement of the **small intestine alone** in **30%** of cases, of **both** small intestine & colon in **40%**, & of the **colon alone in about 30%.**

- CD disease may involve the mouth, esophagus, stomach, & duodenum, but these sites are distinctly uncommon.

■ **Fully developed CD** characterized by:

→ **Classically, sharply limited, & demarcated** diseased bowel segments from adjacent uninvolved bowel.
→ **Transmural** inflammation involving all the bowel wall, with
→ **Mucosal damage** → **Fissuring** → **Fistula formation**
→ **Noncaseating granulomas in 50% of cases,**

• **The intestinal wall is rubbery & thick, the result of edema, inflammation, fibrosis, & hypertrophy of the muscularis propria.** As a result, the lumen is almost always **narrowed;** in the small intestine this is seen radiographically as → **("string sign,"** a thin stream of barium passing through the diseased segment (F4.37).

• In diseased segments, the serosa becomes granular & dull gray & often the mesenteric fat wraps around the bowel surface → **("creeping fat"** F15-30).

• When several bowel segments are involved, the intervening bowel is essentially normal **("skip" lesions).**

(مهم جداً سؤال ترتيب).

In the intestinal mucosa, early disease shows focal mucosal.....

zig-zag

★ **ulcers**, resembling aphthous ulcers, edema, & loss of the normal mucosal texture. Later, ulcers coalesce into long, serpentine **linear ulcers**, which tend to be oriented along the **axis of the bowel** (F15-30 & 4.39). Because the intervening mucosa tends to be relatively spared, it acquires a coarsely textured, ★**cobblestone appearance (F4.40).**

تجمع

قرح تؤدي إلى تشققات . ulceration ما صار فيها

★ **Fissures develop between the folds of the mucosa,** often penetrating deeply through the bowel wall all the way to the serosa. This may lead to…

★ **Adhesions** with adjacent loops of bowel. Further extension of fissures leads to…

★ **Fistula or sinus tract formation** to adherent **viscera**, to the outside **skin,** or into a blind cavity to form a localized **abscess.**

واحيانا لل urinary bladder. or vagina

{**Summary**: Cobblestone & Ulcers→ Fissures → Adhesions → Sinus → Fistula → Abscess}.

- H, mucosa show characteristic features (F15-31):

(1) **Inflammation,** with neutrophilic infiltration into the epithelial layer **(cryptitis)** & accumulation within crypts to form **crypt abscesses**;

(2) **Ulceration**, &

(3) **Chronic mucosal damage,** distortion & atrophy.

★ **Granulomas may be present any-where in the GIT,** even in individuals with CD limited to one bowel segment. However, the absence of granulomas does not exclude the diagnosis of CD. 50% → granulomatous

★ In diseased segments, the muscularis mucosae & muscularis propria are usually **markedly thickened, & fibrosis affects all bowel layers (Transmural inflammation)**.

★ Lymphoid aggregates scattered through the full intestinal wall & in the extramural fat are characteristic.

☹ Particularly important in persons with long-standing chronic CD are **dysplastic changes appearing in the mucosal epithelial cells**. These may be focal or widespread, tend to ↑ with time, & predispose to **a X 5-6 folds increased risk of carcinoma**, particularly of the colon.

►***Clinically,*** the presentation of CD disease is highly variable & unpredictable.

(1) The dominant manifestations are ***recurrent episodes of diarrhea & crampy abdominal pain.*** نتيجة obstruction

(2) In most patients, after an initial attack, the manifestations ***remit*** **either spontaneously or with therapy,** but characteristically they are followed by ***relapses***, & intervals between successive attacks grow shorter.

الفترات بين الـ relapsing بتصير أقصر

(3) Superimposed on this course are the potential development of **malabsorption & some of the extra-intestinal manifestations mentioned earlier.**

التأثيرات السلبية

☹ The debilitating consequences of CD include

(1) ***Fistula*** formation to other loops of bowel, urinary bladder, vagina, or perianal skin;

(2) ***Abdominal abscesses or peritonitis***; &

(3) ***Intestinal stricture or obstruction***.

Rare devastating events are (I) **massive intestinal bleeding**, (II) **toxic dilation** of the colon, or (III) **ca of the colon or small intestine.** Although the increased risk for ca is significant, it is substantially less than that associated with UC.

تأثيرات سلبية

مع جداً

Ulcerative Colitis (UC)

★ UC is an inflammatory-ulcerative disease affecting the colon only, which is limited to the mucosa & submucosa, except in the most severe cases. ما بيصير بالـ small intestine

★ Like CD, UC is a systemic disorder associated in some persons with migratory polyarthritis, sacroiliitis, ankylosing spondylitis, uveitis, erythema nodosum, & hepatic involvement (pericholangitis a & primary sclerosing cholangitis).

★ There are several **important differences between UC & CD** (F15-32 & Table 15-10): the most important are: • **In UC:**

- **Superficial colonic mucosal ulcers,** rarely extend below the submucosa & there is surprisingly little fibrosis; which means …
- **Serosal** surface is completely **normal.**
- **No Mural thickening;** there are
- **No granulomas,** &
- **No skip** lesions, there appears to be a
- **High risk of carcinoma** development in the colon.

Epidemiology

★ UC is slightly more common (Double) than CD in the US & Western countries, with an incidence of around 7 per 100,000 populations, but it is infrequent in Asia & Africa.

★ As with CD, the incidence of UC has risen in recent decades. In the US it is more common among whites than among nonwhites & exhibits no particular sex predilection.

★ UC may arise at any age, with a peak incidence between ages 20 & 25 years.

★ UC has a familial association; 20% of persons with the UC have affected relatives. Individuals with UC & ankylosing spondylitis have an increased frequency of the *HLA-B27* allele, but this association is related to the spondylitis & not to UC.

skip lesions بتتشر لحيث بتشمل المناطق الزعل كاملة بدون

►**GROSSLY,** ☹ **UC usually involves the rectum & sigmoid** & much less frequently involves the entire colon (F4-58).

☹ Colonic involvement is **continuous** from the distal colon, so that skip lesions are not encountered.

☹ **Active** UC denotes ongoing **inflammatory destruction of the mucosa,** with gross hyperemia, edema, granularity with friability & easy bleeding, &

☹ In severe UC there is extensive & **broad-based ulceration** of the mucosa in the distal, or the whole colon aligned along its long axis (F15-33). Isolated islands of regenerating mucosa bulge upward to create **pseudopolyps (F 4.59)**.

☹ In rare cases, the muscularis propria is so compromised as to permit **perforation & pericolonic abscess formation.**

gangrene may rupture, leading to perotinitis (fatal case)

☹ Exposure of the muscularis propria & neural plexus to fecal material also may lead to complete shutdown of neuromuscular function. When this occurs, the colon progressively swells & becomes gangrenous (**toxic megacolon**).

◘ The pathologic features of UC are those of mucosal inflammation, ulceration, & chronic mucosal damage (F15-34).

- **A diffuse, predominantly mononuclear inflammatory infiltrate in the lamina propria is almost universally present,**
- Neutrophilic infiltration of the epithelial layer may produce collections of neutrophils in crypt lumina (**crypt abscesses**), which are not specific for UC & may be observed in CD or any active inflammatory colitis.
- Unlike CD, there are **no granulomas**

relapse الراحة ما بعد ال
(attacks بين ال يوقف)

• **Further destruction** of the mucosa leads to outright **ulceration,** extending into the submucosa.

• With remission of active disease, **granulation tissue fills in the ulcer craters**, followed by regeneration of the mucosal epithelium. **Submucosal fibrosis & mucosal architectural disarray &** progressive mucosal **atrophy** leads to a flattened & attenuated mucosal surface, which **remain as residua of healed disease**

مهم جدا!!

☹ The **most serious complication of UC** is the development of **colon carcinoma.** Two factors govern the risk: duration of the disease & its anatomic extent.

★ It is believed that with 10 years of UC limited to the left colon the risk is minimal, & at 20 years the risk is on the order of 2%.

★ With **pancolitis,** the risk of carcinoma is **10% at 20 years & 15% to 25% by 30 years.**

Overall, the annual incidence of colon cancer in persons with UC of more than 10 years' duration is 1%.

Clinical Features of UC

• UC is a chronic relapsing disease marked by **attacks of bloody mucoid diarrhea that may persist for days, weeks, or months & then subside, only to recur later.**

• Presentation is usually insidious, with ***cramps***, ***tenesmus***, & **colicky lower abdominal pain that is relieved by defecation.**

• Grossly ***bloody stools*** **are more common** with UC than with CD, & the blood loss may be considerable.

• *Extra-intestinal manifestations, particularly* ***migratory polyarthritis****, are more common with UC than with CD.*

☹ Uncommon but *life-threatening complications* include • **severe diarrhea** & electrolyte derangements, • **massive hemorrhage**, • severe colonic dilation **(toxic megacolon**) with potential **rupture, perforation & peritonitis**.

▼ **Diagnosis** can usually be made by **endoscopic examination & biopsy.**

• Specific infectious causes must always be ruled out.

infectious بنعمل culture حتى نتأكد انه مش disease

TUMORS OF THE SMALL AND LARGE INTESTINES

🕷 **Colorectal cancer** is: the 1st commonest cancer in Jordanian males & the 2nd in females since 2004. In the US, it ranks 2nd to bronchogenic ca among the cancer killers; & about 🕷 **5% of Americans will develop colorectal cancer** & 40% of them will die from it & it represent 70% of all GIT malignancies.

Table 15-11 Tumors of the Small & Large Intestines

☺ **Non-neoplastic Polyps**

Hyperplastic + Hamartomatous {Juvenile} + Peutz-Jeghers + Inflammatory + & Lymphoid polyps.

Neoplastic Epithelial Lesions

Benign polyps: Adenomas

Malignant: Adenocarcinoma (98%) & SCC of the anus

Other Tumors

Gastrointestinal stromal tumors (GIST), Carcinoid tumor & Lymphoma.

☺ Several concepts pertaining to terminology must be emphasized (F15-35):

NB. Some polypoid lesions may be caused by submucosal or mural tumors. However, as with the stomach, the term polyp:

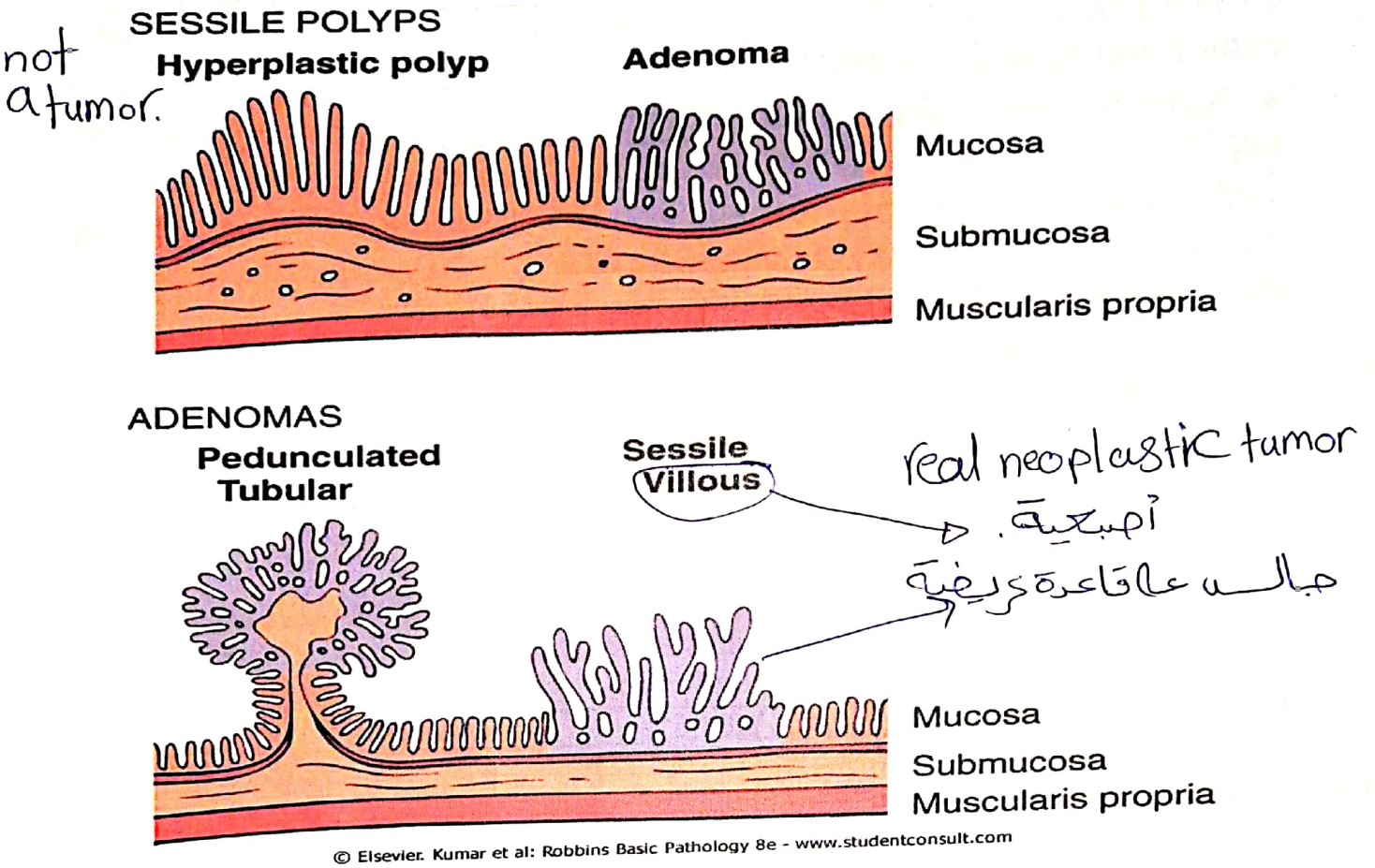
► ***In the GIT,* polyp (P) refers to protruding mass arising from the mucosal epithelium.** P may be ***sessile***, i.e., without a stalk, But traction on the mass may create a stalked, so it is ***pedunculated***.

☺ **P** may be formed as the result of abnormal mucosal inflammation, maturation, or architecture. These P are ***non-neoplastic*** & do not have malignant potential.

☹ **P** that arise as result of epithelial proliferation & dysplasia are termed ***adenomatous P* or *adenomas*** *and are ....* ***true neoplastic lesions & are precursors of carcinoma.***

☺ ***Hyperplastic P*** are the **most common polyps** of the colon & rectum. When single, they do not have malignant potential. However, ***sessile serrated adenoma lesion***, which has some similarities with hyperplastic **P**, may have malignant potential.

F15-35: Two forms of sessile polyp (hyperplastic & adenoma) & of two types of adenoma (pedunculated & sessile).



not a tumor.

real neoplastic tumor

Non-Neoplastic Polyps

Majority of intestinal P occurs sporadically, particularly in the colon, &↑ in frequency with age. Non-neoplastic P represent about **90%** of all epithelial P in the large **intestine** & are found in more than **50% of persons older than 60y.**

Hyperplastic polyps most important one.

✳ Are the **commonest** non-neoplastic P of the colon & rectum. Are small (<5 mm in∅), nipple-like, hemispherical, smooth protrusions of the mucosa, 50% found in the rectosigmoid area. May occur **singly**, but are **more often multiple**.

◘ H, they contain abundant crypts lined by well-differentiated goblet or absorptive epithelial cells, separated by a scant lamina propria. **Vast majority of hyperplastic polyps have *no malignant potential.***

BUT some, either solitary or multiple ("hyperplastic polyposis") so-called **sessile serrated adenomas**, which are located on the **right side of the colon**, may be precursors of colorectal ca.

☹ These P show microsatellite instability & can give rise to ca by the **mismatch** repair pathway.

Juvenile (Rectal) polyps

☺ Are essentially **hamartomatous** proliferations of the lamina propria, **enclosing widely spaced, dilated cystic glands.**

- Occur mostly in **children** younger than 5 years old, but also may be in found in adults of any age.
- Occur singly, in the rectum, 1-3 cm in ∅; rounded, smooth, or slightly lobulated & sometimes pedunculated.
- May cause **rectal bleeding** &
- May become **twisted** on their stalks (**torsion**) to undergo painful infarction.
- Because they are hamartomatous, they have **no** malignant potential.

Adenomas

- Adenomas are **neoplastic P** that range from small pedunculated to large sessile tumors.
- Prevalence of **colonic** adenomas is 20% -30% before age 40, rising to 50% after age 60. M/F ratio is 1:1
- ***All adenomatous*** *lesions arise as a result of epithelial* ***(proliferation & dysplasia)*** *which may range from mild to so severe as to represent transformation to carcinoma.*

▼There is a well-defined **familial predisposition to sporadic adenomas**, accounting for about a **X4 fold greater risk for adenomas** among first-degree relatives, & also a **X4** fold greater risk of colorectal ca in any person with adenomas.

☹ There is **strong evidence** that **most sporadic invasive colorectal adenocarcinomas arise in preexisting adenomatous lesions.**

➔The 4 subtypes of adenomatous P base on their epithelial architecture are:

►***Tubular adenomas,*** 90%; mostly small & pedunculated; showing tubular glands, recapitulating mucosal topology,

►***Villous adenomas,*** 1% - villous projections, tend to be **large & sessile**

►***Tubulovillous*** *adenomas,* 5% -10% - a mixture of the above,

►***Sessile serrated adenomas*** - serrated epithelium lining the crypts.

☹The malignant **risk** with an adenomatous P is correlated with 3 interdependent features - **polyp size, histologic architecture, &** severity of epithelial **dysplasia** - as follows:

😐 Cancer is rare in tubular adenomas smaller than 1 cm in ∅.

🕷 Cancer risk is high (approaching 40%) in sessile villous adenomas larger than 4 cm in∅.

🕷 Severe dysplasia, is often found in villous areas.

Among these variables, ***maximum diameter*** (F4-67) ***is the chief determinant of the risk*** *of an adenoma's harboring ca.*

↑diameter → ↑risk for malignant transformat

Tubular adenomas (F15-36A)

- May arise anywhere in the colon, however, **50%** are found in the rectosigmoid area.
- **50%** of tubular adenomas are single, in the other **50%**, two or more are present.
- **Small** tubular adenomas are **sessile,** while **Larger** ones are **pedunculated; having stalk &** with raspberry-like heads.

◘ **H,** the stalk of **tubular adenomas** is covered by normal colonic mucosa, but the head is composed of neoplastic epithelium, forming branching glands lined by hyperchromatic, tall cells, which may/may not show mucin secretion (F15-36B).

☺ In the clearly benign lesion, the branching glands are well separated by lamina propria, & the level of dysplasia or cytologic atypia is slight.

☹ However, **all degrees of dysplasia may be encountered**, ranging up to cancer confined to the mucosa (**intramucosal carcinoma**) or **invasive carcinoma** (F4-67) extending into the submucosa of the stalk.

A frequent finding in any adenoma is superficial ***erosion*** of the epithelium, the result of mechanical trauma.

► ***Clinically,*** the smaller adenomas are usually **asymptomatic**, until such time that **occult bleeding** (much more frequently from villous adenomas) leads to clinically significant ★ **anemia**

☹ **Villous adenomas** (1%) are larger, tend to occur in older persons, most **commonly in the rectum & rectosigmoid**, but they may be located elsewhere, are **sessile**, up to **10 cm** in ∅, **cauliflower-like masses** projecting above the surrounding mucosa (F4.66). رأس القرنبيط

◘ H, there is frond-like (finger-like) villiform projections of the mucosa covered by dysplastic, piled-up, columnar epithelium (F15-37). All degrees of dysplasia may be encountered, & invasive **carcinoma is found in as many as 40% of these lesions**, the frequency being correlated with the **size** of the P. هنا يخف نها خطيرة

★Villous adenomas may secrete sufficient amounts of mucoid material rich in protein & potassium to produce **hypoproteinemia or hypokalemia**.

(combination).

😐 **Tubulovillous adenomas** (5-10%) are composed of mix tubular & villous areas. They are **intermediate between** the tubular & the villous lesions in their frequency of, been pedunculated or sessile, their size, the degree of dysplasia, & the risk of harboring intramucosal or invasive carcinoma.

☹ **All** adenomas, are to be considered **potentially malignant**; therefore, ***prompt & adequate excision is mandated.*** واجبة

معظم

الحامل الأكبر بتحديد التحوّل هو الحجم. لذلك إذا حفتها دائماً لازم نشيلها.

Familial Polyposis Syndromes or FAP

★ The importance of this uncommon, autosomal dominant disorders, called familial polyposis syndromes, lies in the propensity (tendency) for malignant **transformation**.

▼ **Familial adenomatous polyposis (FAP)** individuals typically develop **500 to 2500** {a minimum of **100** is required for the diagnosis} **colonic adenomas that carpet the mucosal surface** (F15-38); Multiple adenomas may also be present elsewhere in the GIT, including almost a 100% lifetime incidence of **duodenal adenomas**. Most polyps are **tubular** adenomas; an occasional P have villous features. Polyps usually become **evident in adolescence or early adulthood**.

☹ The **risk of colonic cancer** is **virtually 100% by midlife**, (F4.64) unless a **prophylactic** colectomy is performed.

► The genetic defect underlying FAP has been localized to the **APC gene on chromosome 5q21.**

. APC بال

▼ ***Gardner syndrome*** & the much rarer ***Turcot syndrome*** share the **same genetic defect as FAP**. These syndromes differ from FAP with respect to the occurrence of extra-intestinal tumors in the latter two: osteomas, gliomas, & soft tissue tumors, to name a few.

in brain

. FAP زي ↑

▼ ***Peutz-Jeghers*** polyps are uncommon **hamartomatous** polyps that occur as part of the rare autosomal dominant Peutz-Jeghers syndrome, characterized in addition by **melanotic mucosal & cutaneous pigmentation**. (This syndrome is caused by germ-line mutations in the ***LKB1* gene**, which encodes a serine threonine kinase).

▼ ***Cowden syndrome*** is also characterized by hamartomatous polyps in the GIT & by an ⇧ risk of tumors of the thyroid, breast, uterus, & skin. This syndrome is caused by germ-line mutations in the ***PTEN*** (phosphatase & tensin homologue) tumor suppressor gene.

☹ **Peutz-Jeghers & Cowden syndromes, like the other familial polyposis syndromes, are associated with an ↑ risk of both intestinal & extraintestinal malignancies.**

very very important ← **Colorectal Carcinoma (Ca)**

🕷 Colorectal cancer is the 1st commonest cancer in Jordanian males & the 2nd in females since 2004. Adenocarcinomas comprise 98% of all colonic cancers (2% SCCa anal channal).

▼ It represent prime challenges to the medical profession, because they ***almost always arise in adenomatous polyps that are generally curable by resection*** .

Epidemiology

- Peak incidence for colorectal ca is **60 to 70 years of age**; fewer than 20% of cases occur before the age of 50 years.
- M/F ratio is 1.2:1.
- **Adenomas** are the **presumed precursor** lesion for most of the tumors; → اهو سبب. 0/89 of cases
- The frequency of colorectal cancer arises de novo from flat colonic mucosa remains undefined, but appears to be ***low.***

►Both genetic & environmental influences contribute to the development of colorectal ca.

(20-30-40)

► When colorectal cancer is found in a **young person,**
(1) preexisting **ulcerative colitis** or pancolitis
(2) one of the **polyposis syndromes** must be suspected.
(3) individuals with *hereditary nonpolyposis colorectal cancer syndrome* {**HNPCC,** also known as **Lynch syndrome,** also at risk of developing other tumors, such as cholangiocarcinomas}, caused by germ-line mutations of DNA mismatch repair genes, are at a high risk of developing colorectal cancers.

(in developed countries).

▲Colorectal ca has a worldwide distribution, with the **highest incidence** rates in the **US**, Canada, Australia, New Zealand, Denmark, Sweden, & other **developed** countries.

▼ Its incidence is substantially lower, up to 30-fold less, in India, Africa, & South America.

►Environmental influences, particularly dietary practices, are implicated in the striking geographic variation in incidence. The dietary factors receiving the most attention are a: