GI Pathology I- GI Tract

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OPTH 727

“Block 2”

- Next exam:
  - Multiple choice
  - Fill in the blank

- Topics
  - GI Pathology
  - CNS and Musculoskeletal Pathology
  - Dermatopathology
  - (Head and Neck – moved to OPTH 731)

Fill-in-the blank question format

- Clue
  - “Respiratory epithelium that has undergone metaplasia due to toxin exposure (e.g. from smoking) gives rise to this cancer.”

From respiratory pathology

- Your answer
  - “Squamous cell carcinoma of the lung”

GI Pathology

- GI tract
  - Oral cavity
    - Salivary glands
  - Esophagus
  - Stomach
  - Intestines
    - Appendix
- Other organs
  - Liver
  - Pancreas
  - Gall Bladder

You will take many, many courses on this- this lecture, we will touch on a few

Infectious diseases of GI system will mostly be covered in microbiology courses

Salivary gland diseases/pathology – disease entities that you should know

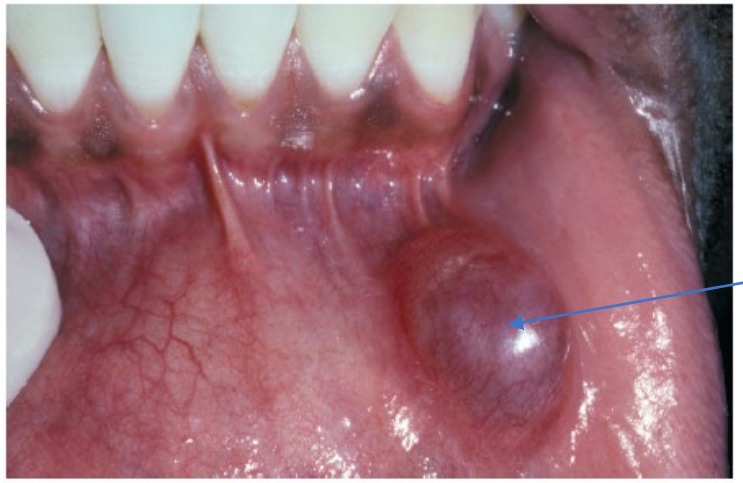
- Diseases and/or reactive conditions
  - **Sialolith**
  - **Mucocele**
  - **Salivary duct cyst**
  - **Sialadenitis**
  - **Xerostomia**
  - **Sjogren's disease**
- Tumors
  - Benign
    - **Pleomorphic adenoma**
    - **Warthin Tumor**
    - **Canalicular adenoma**
    - **Basal cell adenoma**
  - Malignant
    - **Mucoepidermoid carcinoma**
    - **Adenoid cystic carcinoma**
    - Numerous other **adenocarcinomas**

Salivary lesions

- **Sialolith** – calcified structures that develop within the salivary ductal system.
  - Calcification of debris found within duct
    - Debris includes mucin, bacteria, dead epithelial cells, etc.
  - Sialolith can affect major or minor glands
    - Submandibular gland most common (due to tortuous, upward path of Wharton duct)
  - Can appear as radio-opaque mass on radiograph
  - Often painful

Salivary lesions

- **Mucocele** – rupture of salivary duct that leads spillage of mucin into surrounding tissues
  - Due to trauma – i.e. biting lip
  - Mostly arise in minor salivary glands
    - Lower lip most commonly
    - Upper lip – almost never!
  - Mucocele in the floor of mouth is a **ranula** (arising from sublingual gland)
- **Salivary duct cyst** – epithelium lined cavity that arises from salivary tissue.
  - Presents as a swelling which looks similar to mucocele clinically



• **Fig. 11-2 Mucocele.** Blue-pigmented nodule on the lower lip.

This is a mucocele but many other salivary pathology may resemble these.

TABLE 11-1 Location of Mucoceles

Location	Number of Cases	Percentage of All Cases
Lower lip	1405	81.9
Floor of mouth	99	5.8
Ventral tongue	86	5.0
Buccal mucosa	82	4.8
Palate	23	1.3
Retromolar	9	0.5
Unknown	11	0.6
Upper lip	0	0.0
Total	**1715**	**100**

Data from Chi AC, Lambert PR 3rd, Richardson MS, et al. Oral mucoceles: a clinicopathologic review of 1,824 cases, including unusual variants, *J Oral Maxillofac Surg* 69:1086–1093, 2011.

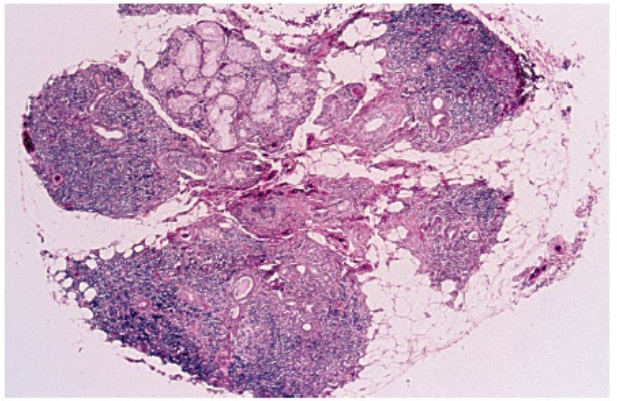
Salivary diseases/conditions

- **Sialadenitis** – inflammation of salivary glands
  - Can be of infectious or non-infectious causes
    - A common viral infection that causes sialadenitis (parotid) is mumps
  - May or may not lead to a visible/palpable swelling

- **Xerostomia** – the “feeling” of dry mouth, usually due to salivary gland hypofunction
  - Very common in elderly
    - Often is medication related
  - May lead to increased infections (decreased saliva produces decreased anti-microbial protection)
  - Can be caused by radiation therapy for Head and Neck cancers

Salivary diseases/conditions

- **Sjogren Syndrome**
  - Autoimmune disorder
    - Autoimmune attack against salivary and lacrimal glands
    - Leads to xerostomia (dry mouth) and xerophthalmia (dry eyes)
  - Histopathology: lymphocytes in salivary gland acini
  - Can be associated with other autoimmune diseases (Lupus, Rheumatoid Arthritis)

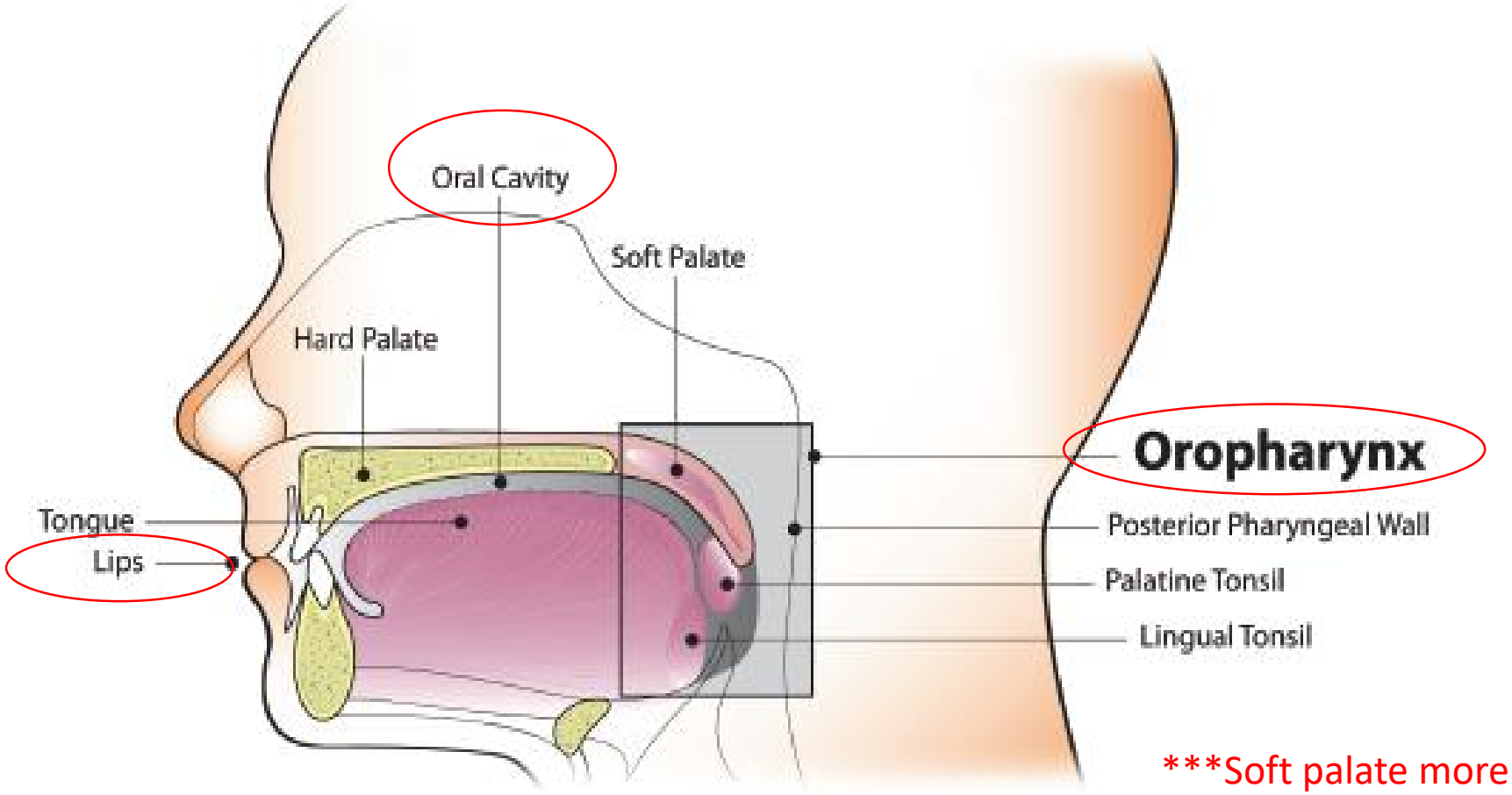


• **Fig. 11-27 Sjögren Syndrome.** Labial gland biopsy showing multiple lymphocytic foci.

Salivary Gland Tumors

- Benign
  - **Pleomorphic adenoma**-
    - MOST COMMON salivary tumor (BY FAR)
    - Nearly 50% of all salivary tumors
    - 80% of benign tumors
  - **Warthin Tumor** –
    - Parotid tumor, often bilateral.
  - Other benign tumors,
    - **Basal cell adenoma**
    - **Cannalicular adenoma**
    - Numerous others.
- Malignant
  - **Mucoepidermoid carcinoma**
    - Most common malignant salivary tumor overall
  - **Adenoid cystic carcinoma**
    - Most common malignant salivary tumor in submandibular gland.
  - Many others

Squamous cell carcinoma (SCC) of mouth. Three main types based on location and other factors.



<u>"Oral cavity" is:</u>
Mobile tongue
Buccal mucosa
Gingiva
Floor of mouth
Hard palate

<u>Oropharynx is:</u>
Base of tongue
Tonsils
Pharyngeal wall
***Soft palate

***Soft palate more recently designated as part of oropharynx

A very basic slide on oral squamous cell carcinoma

Squamous cell carcinoma (SCC) of mouth.

Location

- **SCC of lip** (vermillion)
  - Usually lower lip
- May behave like a skin cancer
  - Difficult to determine if cancer originated from “outside” the vermillion or “inside” the vermillion.

- **Oral cavity SCC**
- Location:
  - Ventrolateral tongue, floor of mouth are most common.
  - Gingiva and retromolar area also common.
  - Buccal mucosa is a common site in Asia (due to betel quid)

- **Oropharyngeal SCC**
- Location:
  - Tonsils are most common,
  - Base of tongue, pharyngeal wall, soft palate

  - Base of tongue cancer is difficult to detect visually
    - Even a large tumor not obvious.
    - Protruding tongue or displaced to one side

Squamous cell carcinoma (SCC) of mouth.

Risk Factors

- **SCC of lip** (vermillion)
  - UV exposure

- **Oral cavity SCC**
- Tobacco, Alcohol in USA
- In Asia: (Betel quid chewing)

- **Oropharyngeal SCC**
- HPV infection is common risk factor. (not all are HPV positive)
- HPV related SCC of oropharynx may have better prognosis – (all things being equal than non HPV)
- Tobacco/alcohol are risk factors also

Many cases occur in patients with no risk factors.

Diseases of esophagus, stomach, intestines, liver, gall bladder

- Who treats them?
- General practitioners
- Gastroenterologists
- GI surgeons
- General surgeons

- Infectious disease specialist

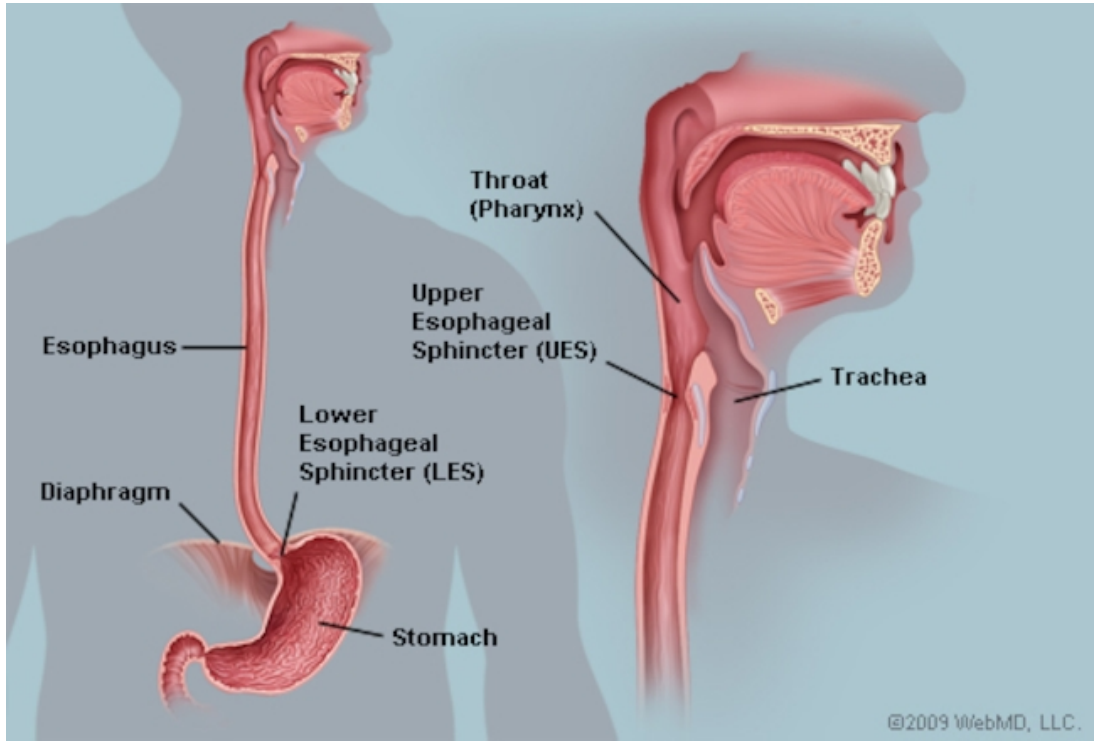
Diseases of esophagus, stomach, intestines

- Clinical exam:
  - Patient symptoms – heartburn, loss of appetite, diarrhea, constipation, flatulence, nausea
- Analysis of stool

- Endoscopy and endoscopic biopsy
  - Histopathological analysis
- Other imaging, CT, ultrasound, contrast agents.

Esophagus-

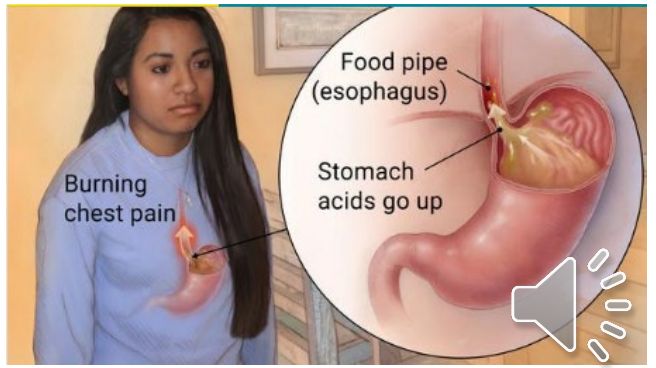
- **GERD**
  - Gastroesophageal reflux disease
- **Barrett's esophagus**
- Esophageal cancer (later in this lecture)
  - **Squamous cell carcinoma of esophagus**
  - **Adenocarcinoma of esophagus**
- **Hiatal hernia**



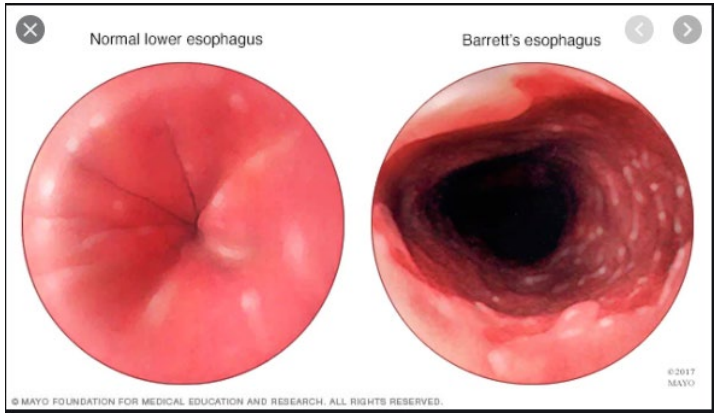
Esophagus - GERD

- **Acid reflux** or occurs when acid from the stomach regurgitates to the esophagus. This leads to a "burning sensation" in the chest
  - Note: Laryngopharyngeal reflux (LPR) is conceptually similar to GERD

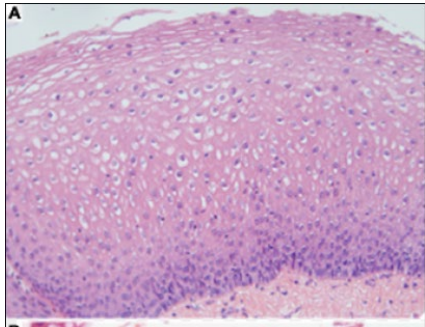
- **GERD** is a chronic disease where acid reflux happens frequently
  - Common condition
  - Pathogenesis: usually due to problems with lower esophageal sphincter (whose function is to prevent stomach acid from regurgitating to esophagus)
  - Management: through medications and diet
  - Risk factors: overweight, poor diet, pregnancy, **hiatal hernia,** many others
  - Complications:
    - Damage to lower esophagus
      - Damage to mucosa may lead to ulcers.
      - Damage may also leads to fibrosis and narrowing (**esophageal stricture**)
    - May also lead to **Barrett's esophagus**



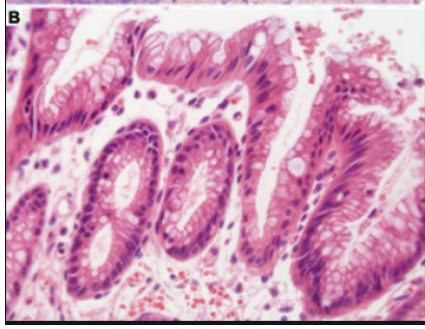
Esophagus – Barrett's esophagus



Normal esophagus stratified squamous epithelium



Barrett's esophagus Glandular epithelium (stomach)



- What is it?
  - A replacement of normal esophageal epithelium (stratified squamous epithelium) with glandular epithelium (similar to found in the stomach).
    - As you would expect, stomach epithelium is more resistant to damage from acid
    - This represents a type of metaplasia
  - Barrett's esophagus is a histological diagnosis

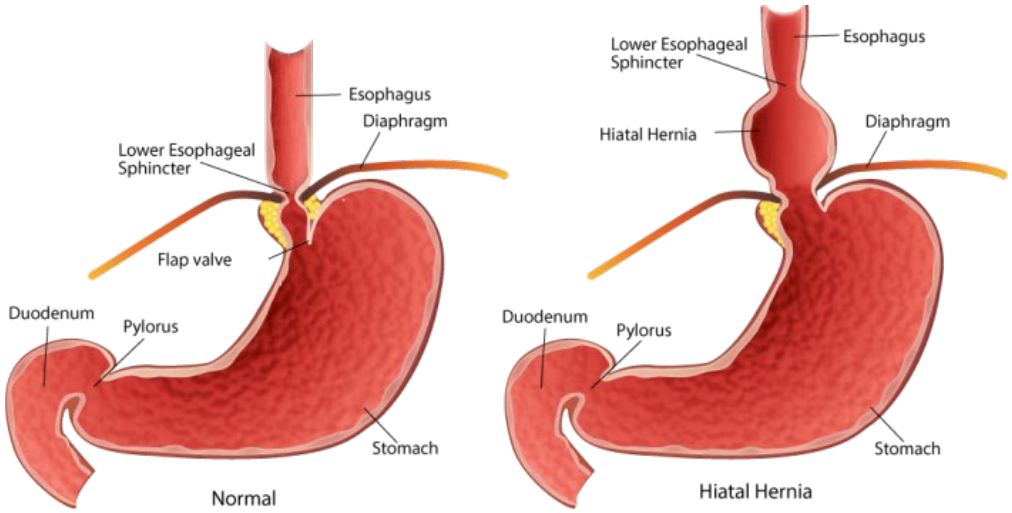
- Caused by chronic acid reflux (GERD)
  - Therefore as you would expect, it is more likely to occur in the lower esophagus
- May predispose to esophageal adenocarcinoma

Hiatal hernia

- A common condition where a part of the stomach moves through the diaphragm and into thoracic cavity.

- May be asymptomatic or may be a cause of GERD
  - Why? Tone to lower esophageal sphincter is provided by diaphragm. If LES is above diaphragm, then it is weaker, thus allowing stomach acid to move from stomach to esophagus.

- What causes a hiatial hernia?
  - Age related changes (less muscle tone)
  - Injury or surgery
  - Developmental – born with large hiatus
  - Intense pressure on surrounding muscles
    - Excessing coughing, vomiting, lifting heavy things, etc.



Stomach

- **Gastritis**
- **Peptic ulcers**
  - May occur in stomach, duodenum or esophagus
- **Adenocarcinoma of stomach (later in the lecture)**

Complications of bariatric surgery are becoming a larger problem as the procedure becomes more common

Gastritis – inflammation of gastric mucosa (stomach lining)-

- Acute gastritis-
  - Usually due to some traumatic event or ingestion of medication, heavy acute alcohol consumption.

The discomfort caused by gastritis (acute or chronic) is most often due to acid interacting with a compromised stomach lining

- Chronic gastritis- long term
  - More common than acute
  - Leads to mucosal atrophy
    - Predisposition to adenocarcinoma of stomach
  - Many causes (see next slide)
  - May lead to **peptic ulcers** and intestinal metaplasia
    - Intestinal metaplasia may eventually transform into cancers.
  - Produces many unpleasant symptoms, heartburn, indigestion, nausea, etc…

Causes of chronic gastritis

- Most common cause is H. pylori infection. *Helicobacter pylori.*
  - ~50% of world's population has H. pylori. Only small percentage develop chronic gastritis.
- Age
  - Stomach lining tends to thin with age
- Alcohol use:
  - Alcohol and irritate and erode your stomach lining
- Autoimmune chronic gastritis
  - Autoimmune attack on parietal cells – leads to pernicious anemia from vitamin B12 deficiency (which will be discussed later in the course).
    - Parietal cells secrete acid into stomach lumen and produce intrinsic factor
- "Reactive" gastritis
  - Sometimes unknown cause
  - Some cases due to NSAID administration

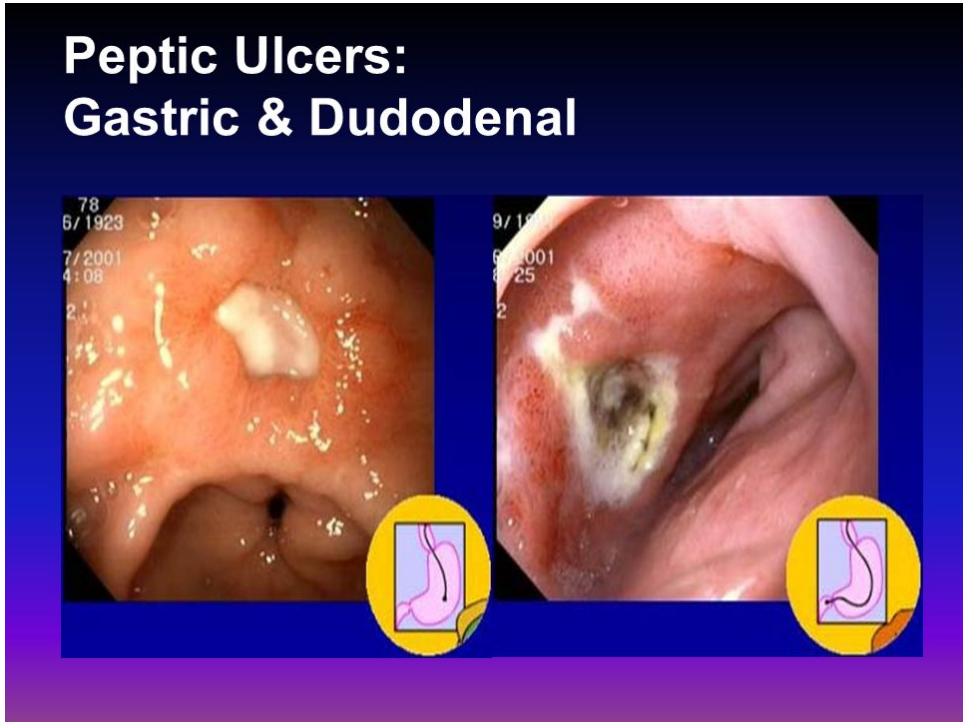
Peptic Ulcers

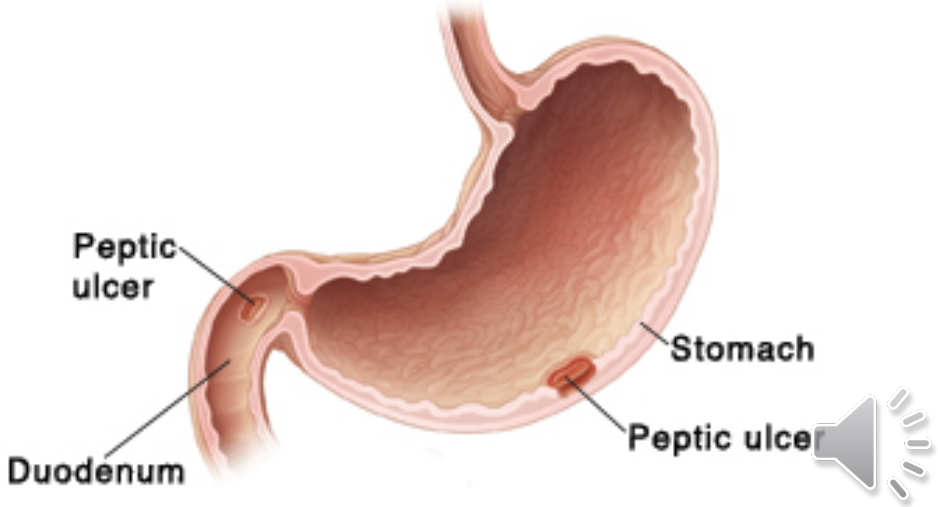
Q: What is an ulcer?

A: A breach of the continuity of skin, epithelium or mucous membrane, caused by inflamed or necrotic tissue **(you will learn plenty about oral ulcers!)**

Ulcers present throughout epithelial lined organs and <u>in general, ulcers are painful</u>!

Ulcers may short-lived or be ongoing.





Peptic ulcers

- Caused by damage to epithelium – by gastric secretions-- ACID
- Peptic ulcers may affect gastric, duodenal or esophageal lining
  - Esophageal ulcers produced by reflux (GERD)
  - Duodenal ulcers produced by hypersecretion of acid by the stomach
- Gastric ulcers produced by acid acting on compromised gastric epithelium
  - Areas of gastritis (inflamed epithelium) are highly susceptible to ulcer formation.
    - Therefore, h. pylori, NSAIDS play a role in ulcer formation… because they play a large role in chronic gastritis.
  - Other risk factors in addition to chronic gastritis include smoking, stress, bile reflux
- Areas of bariatric surgery (junction points) are highly susceptible to ulceration
- Some ulcers may bleed – this may be very dangerous

Small and large intestine pathology overview

- Infective disorders of the intestine are common (not covered in OPTH 727)
- Malabsorption syndromes
  - **Celiac disease**
- Chronic inflammatory bowel disease
  - **Crohn's disease**
  - **Ulcerative colitis**
- Neoplasia
  - Colon cancer is very common

Malabsorption syndromes

- There are 4 main elements to absorption of nutrients
  - Pancreas secretes digestive enzymes into the gut- necessary for breakdown of macromolecules
  - Liver secretes bile acids needed for solubilization and absorption of fat
  - Intestinal mucosa is specialized for absorption: mucosal folds and villi produce large surface area
  - Enzymes at intestinal brush border hydrolyze large molecules

Therefore, disruption to any of these processes may result in the inability to absorb nutrients. Diseases of pancreas or liver; status post surgery, parasites, inflammatory diseases, or structural changes to gut may produce malabsorption.

Celiac disease

*
- Caused by hypersensitivity to gluten (a protein in wheat flour)
- Disease can present at any age:
  - Infancy to adulthood
  - Celiac disease in infancy is an important cause of failure to thrive
    - Celiac disease believed to have genetic predisposition but is not a genetic disease
  - In adolescents and adults, celiac disease produces irritable bowel, fatigue, headaches, inability to concentrate
- Caused by an immune response to gluten
  - Immune mediated damage to intestinal villi (small intestine)
    - Leads to flattening of villi – (less absorption overall of nutrients)

*
- Diagnosis is based on:
  - Intestinal biopsy – examine the villous architecture, and the nature of inflammatory cells present around villi
  - Presence of anti-gluten antibodies in serum
- Definitive diagnosis of celiac disease versus non-celiac gluten sensitivity is difficult.
  - Diagnostic tests can be inconclusive
  - Is it necessary to distinguish the two entities if treatment for both conditions is the same?

Irritable bowel syndrome (IBS)

Note: IBS is often confused with IBD (inflammatory bowel disease)

- Common
- Symptoms: abdominal cramping, bloating, gas, diarrhea/constipation
- IBS is often a “disease of exclusion” – i.e. diagnosis rendered when more serious bowel diseases are ruled out, i.e. IBD, infections, cancer, etc.
  - When symptoms cannot be explained: i.e. no abnormalities in diagnostic procedures
- Stress often plays a role.
- Certain foods may trigger.

Inflammatory bowel disease

For exam, Please be able to compare and contrast the two diseases (see next slide)

- Refers to **Crohn's disease** and **Ulcerative colitis**
- Both are idiopathic (cause unknown)
- Both are caused by chronic inflammation of the GI tract. See specific locations on next slide.
- Both cause typical GI symptoms (abdominal pain, gas, indigestion, etc…)
- Both <u>may</u> produce <u>pyostomatitis vegetans</u> – yellow, pustular lesions in oral cavity. However, only Crohn's produces actual oral mucosal lesions (see next slide)

Pyostomatitis vegetans

Comparison of Crohn's vs Ulcerative Colitis (UC)

Feature	Crohn's disease	Ulcerative colitis
Involvement	Entire GI tract	Colon/rectum
Inflammation	Transmural	Mucosal
Disease pattern	Skip lesions	Continuous
Mucosal appearances	Cobblestone	Pseudopolyps
Strictures	Common due to scarring	Rare
Fissures	Common	None
Mucosal ulceration	Deep, fissured	Mucosal only
Granulomas	Yes	No
Bowel wall	Thickened wall Narrow lumen	Thin wall Dilated lumen
Serosal appearances	Creeping fat	Normal
Adhesions	Multiple due to fissuring inflammation and repeated surgery	None
MHC Class II	HLA-DR1/DQw5	HLA-DR2
Cancer risk	Raised	High

Very important… Crohn's disease may produce lesions throughout the GI tract (from lips to anus). In contrast, UC involves only the large bowel and rectum. Note: A patient with Crohn's disease may only present with bowel inflammation. Other factors will distinguish between UC vs. Crohn's…. As you can see from the chart, many differences

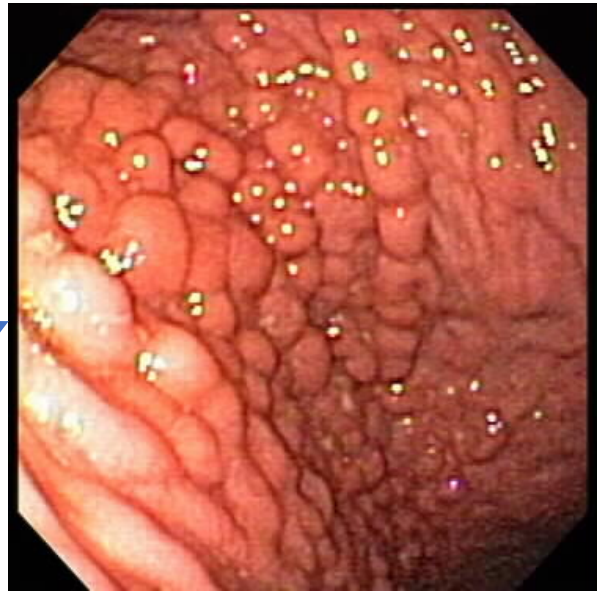
Cobblestoning and fissuring of oral mucosa in Crohn's… UC produces more "polypoid lesions".

Crohn's disease produces granulomatous inflammation (granulomas). UC does not. (do you remember what is granulomatous inflammation? Do you remember which other diseases produce granulomatous inflammation? Common board questions…

Polyps and polypoid lesions often lead to GI cancers. Therefore, as you might expect, UC leads to higher risk of cancer.

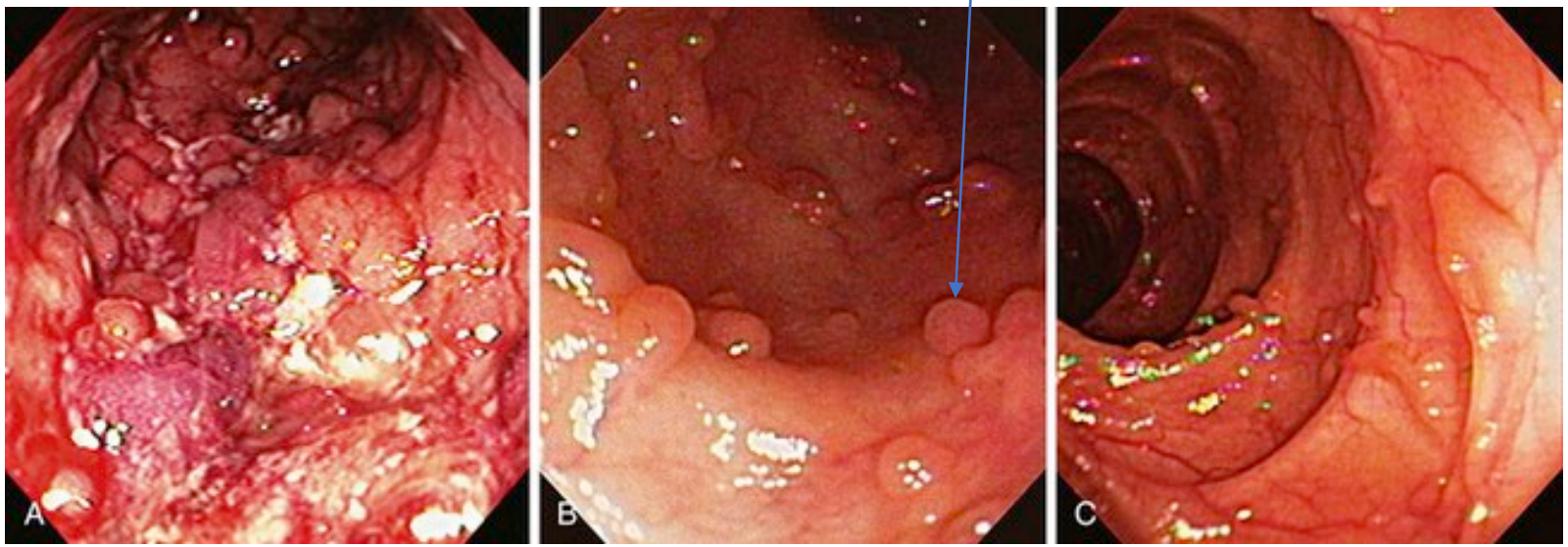
Crohn’s disease

Cobblestoning and fissuring of oral mucosa in Crohn’s… similar lesions may be seen in other parts of the GI tract.



Ulcerative colitis

Lesions may be more “polypoid”



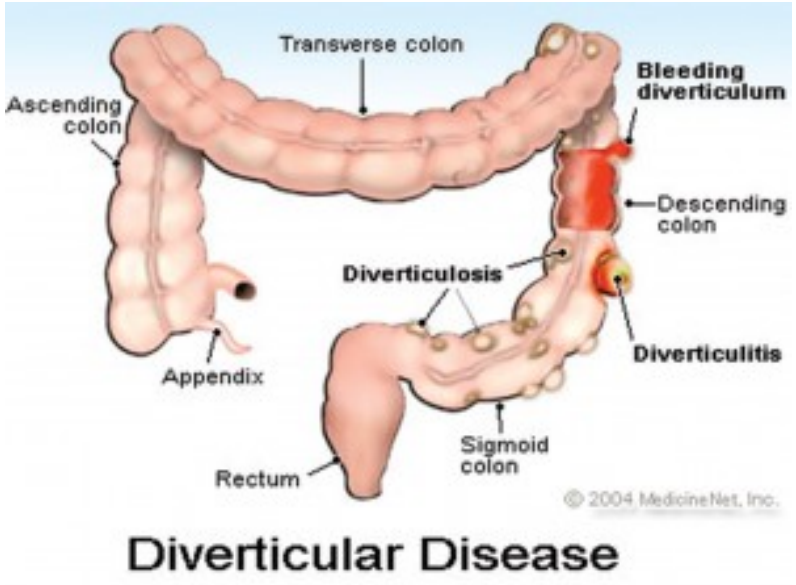
Ulcerative colitis produces a wide range of changes

Other intestinal malformations

- **Diverticulum**
  - "An outpouching of a hollow structure in the body"
    - Can be in many different organs, but usually the large bowel.
  - A diverticulum is usually asymptomatic, however, they can get infected and/or inflamed and produce "**diverticulitis**"

- **Diverticulosis**
  - Common condition in older people
  - Numerous diverticula present in gut

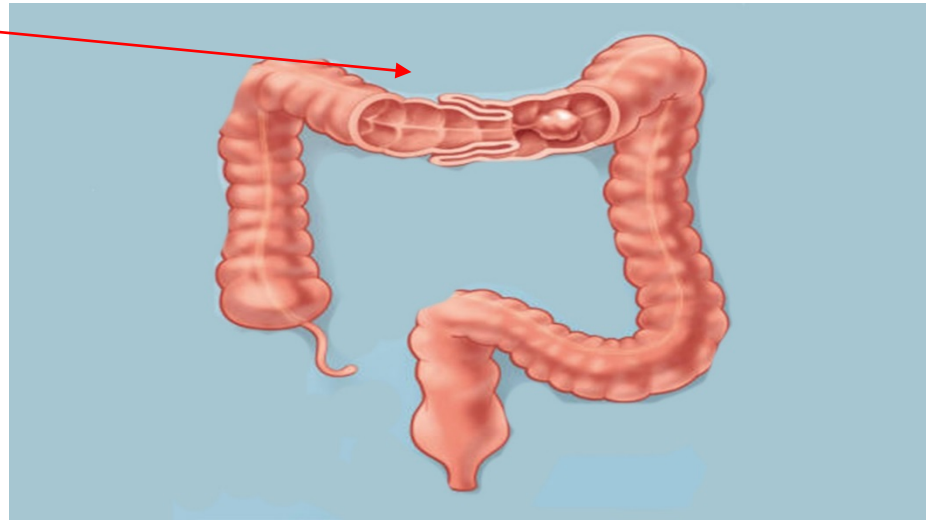
- **Diverticulitis**- inflamed diverticula
  - Produces GI symptoms, abdominal pain, nausea, change in bowel habits, etc.
  - May rupture and produce hemorrhage or **peritonitis**
  - Diagnosis confirmed on CT scan

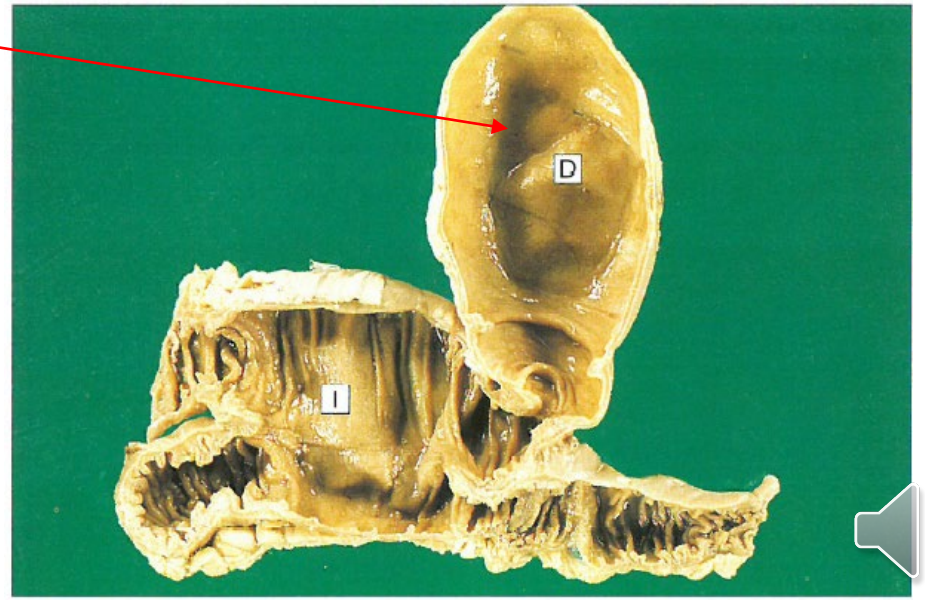


Diverticular Disease

Other intestinal malformations/diseases (developmental)

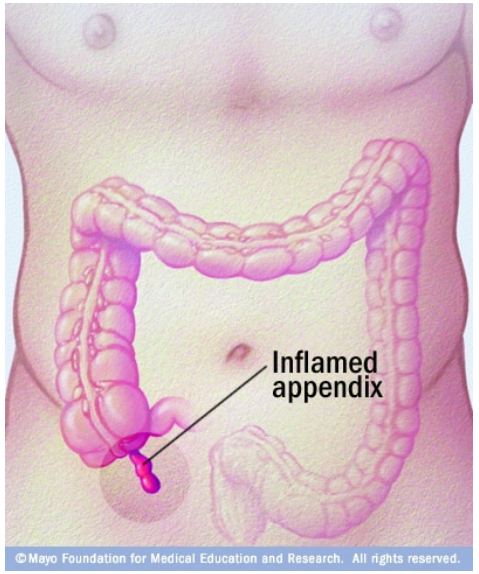
- **Intussusception**
  - Part of intestine “telescoping” on itself
  - Causes intestinal blockage and cuts off of blood supply (thereby may produce ischemia/tissue death/necrosis)
  - Seen in young children
- **Meckel’s diverticulum**
  - Congenital abnormality
  - Large diverticulum, usually in small intestine
- **Hirschsprung disease**
  - Failure of the normal motility of the bowel due to absence of the myenteric plexus (myenteric plexus provides nerve supply to muscular layer of the gut)





Appendix

- **Acute appendicitis**
  - Seen mostly in adolescents/young adults
    - 2nd and 3rd decade
  - Very painful, mid-right abdomen
  - Often due to blockage of appendix (i.e. fecolith – calcified feces)
    - Subsequent infection
  - Complications: appendix may burst and produce **peritonitis**
  - Treatment: surgery (appendectomy) and antibiotics

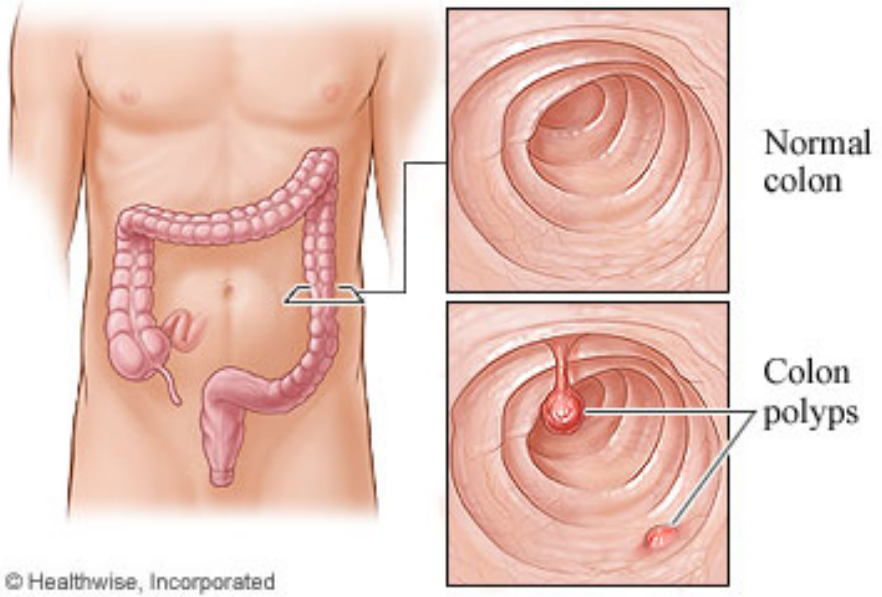


Peritonitis

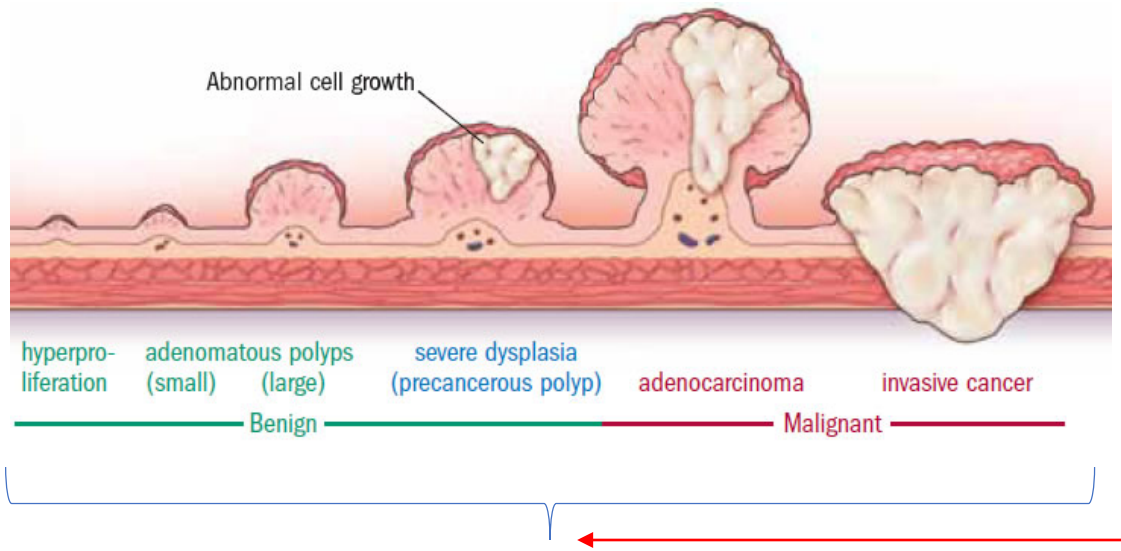
- Inflammation of the peritoneum (peritoneum is the membranous sac covering your abdominal organs)
- **Peritonitis** is often due to infection (but not always)
- Often due complications of advanced GI diseases- anything that compromises the gut structure
  - For example, peptic ulcers, appendicitis, diverticulitis, inflammatory bowel diseases, pancreatitis, and many other GI diseases
  - Remember… numerous infectious organisms in gut – if these spill out, they can infect surrounding tissue.
- Peritonitis may be life threatening. Antibiotics and invasive procedures (drainage) are often required.
  - Accumulation of excess fluid in the peritoneum are called **ascites**

GI Polyps (mostly found in **large bowel**, but can appear throughout the gut)

- What is a polyp?
  - An abnormal growth of tissue projecting from a mucous membrane INTO the lumen
  - Polyps are found throughout the body
    - Nasopharynx, larynx, uterus and GI
- GI Polyps (especially **colorectal polyps**) are common
  - Most polyps cause no problems
  - However, polyps may be precancerous
    - Obviously not all polyps are precancerous
    - Colorectal cancer is the 4th most common cancer (non-skin related) in the USA
  - Evaluation and identification of colonic polyps is a large part of GI medical practice
    - Colonoscopy recommended every 5 years after the age of 50. (and perhaps more often depending on findings).

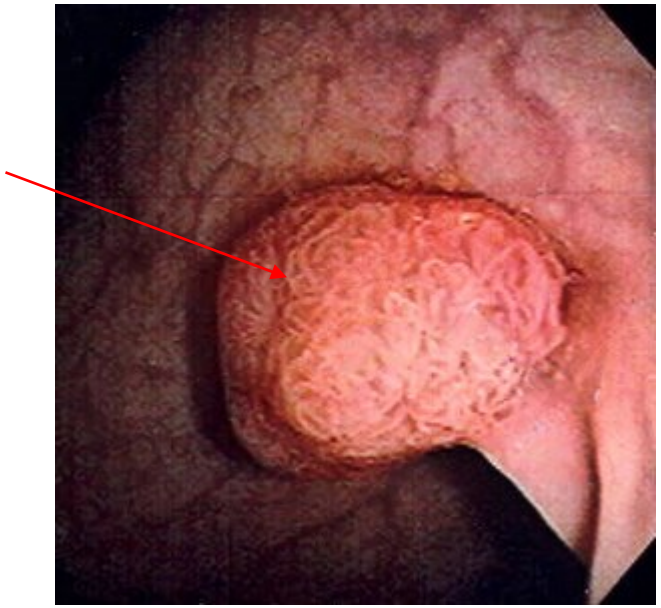


GI Polyps may lead to cancer (adenocarcinoma)



Large polyp visualized on colonoscopy…

polyp gets excised during the colonoscopy procedure…



The excised polyp gets examined histologically to look for cellular changes that indicate malignant or premalignant (dysplasia) transformation

Colorectal vs other GI Cancers – a few facts

- Colorectal cancer is **by far** the most common GI cancer
  - Number of colorectal cancers is greater than all other GI cancers combined (not counting oral cancers)
  - # colon cancer cases is greater than the number of cancers of esophagus + stomach + small intestine + liver + gall bladder + pancreas
- Interestingly, 5-year survival rates for colorectal cancer (~60%) is far higher than other GI cancers (typically 30% and below)
  - Why might this be?
- Pancreatic cancer has lowest 5-year survival rate (< 10%).
- Overwhelmingly, GI cancers are found in adults > 40

Colorectal cancer - Numerous predisposing factors- which may change regimen for colon cancer screening, e.g. colonoscopy more often…

- Ethnicity?
  - African Americans, Ashkenazi Jewish
- Family history
  - Has a close relative had colon cancer?
- Diet?
- ** Prior history of polyps?
  - Size of polyps?
  - Number of polyps?
  - Histological grading of polyps
- ** Inflammatory bowel disease - especially **Ulcerative colitis** (remember… lesions can be polypoid)
- ** Genetic diseases (see next slide)

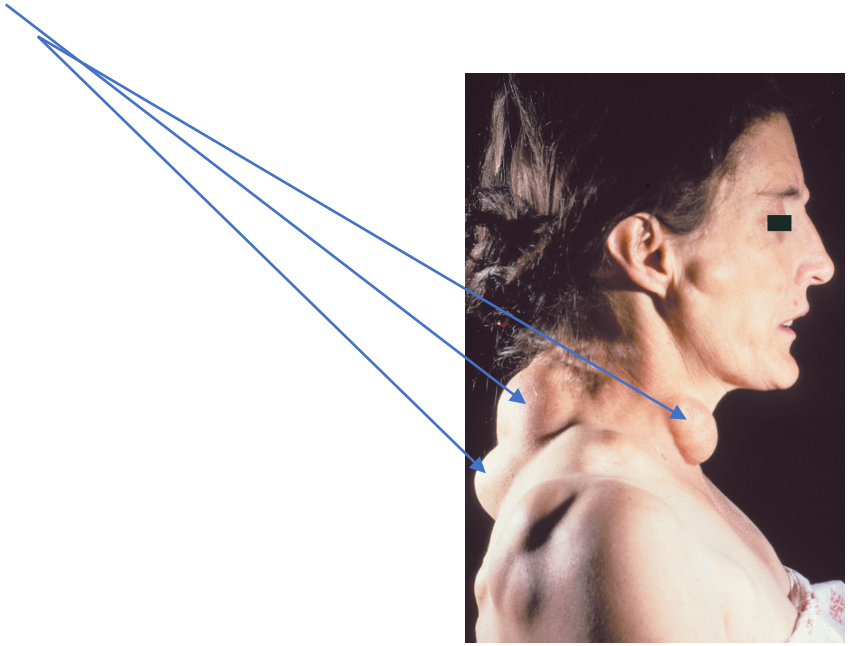
Genetic diseases related to colorectal cancer.

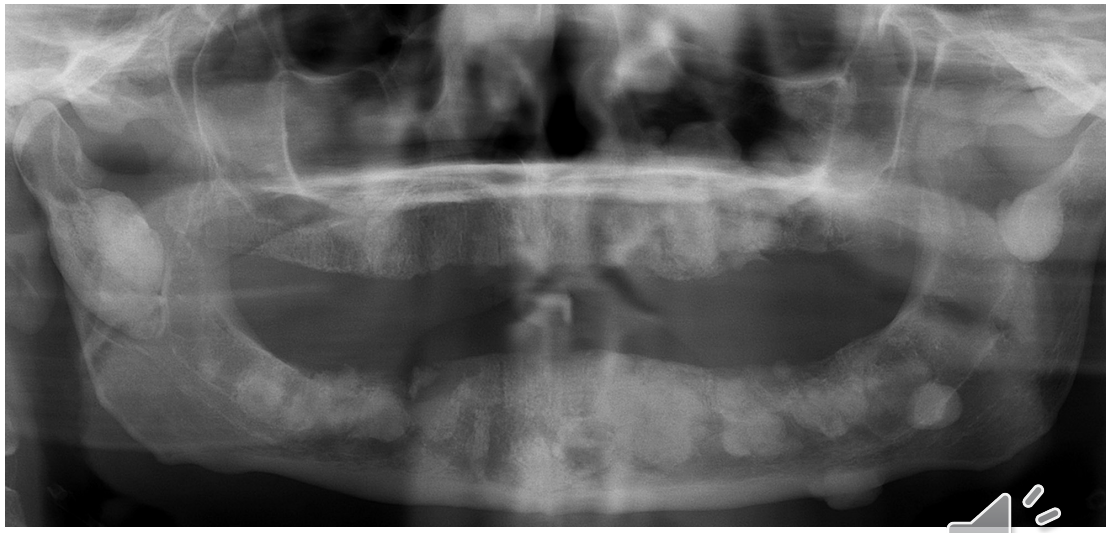
- **Familial Adenomatous Polyposis** (**FAP**)
  - Caused by mutations in the APC gene
  - FAP is a rare genetic disease leads to large numbers of colorectal polyps
  - Polyps begin to form in childhood
    - By age 30, hundreds of polyps may be present
    - **Nearly 100% chance that adenocarcinoma of the colon will develop**
  - One variant of FAP is **Gardner Syndrome** (see next slide)
- **Hereditary non-polyposis colorectal cancer** (**Lynch Syndrome**)
  - A genetic disease that leads to greatly increased incidence of numerous cancers (ovary, endometrium, stomach, colon).
  - ~50-80% will develop adenocarcinoma of colon at some point in their life
  - Mutations in MLH and MSH genes (do not need to know these)

Note: most cases of colorectal cancer NOT related to these genetic diseases

Gardner Syndrome

- Mutation in APC gene (like FAP)
  - **Gardner syndrome** is considered a variant of FAP
- Disease involves all aspects of FAP (polyposis and inevitable colorectal cancer)… <u>PLUS</u>
- Multiple osteomas (bone growths) esp in head and neck area
- Multiple epidermoid cysts





Multiple osteomas

Other GI cancers

- Esophagus
  - **Squamous cell carcinoma**
    - Alcohol and smoking are risk factors
    - Middle to lower esophagus
  - **Adenocarcinoma**
    - Barrett's esophagus is a risk factor
      - Lower esophagus
- Stomach
  - **Adenocarcinoma**
    - Intestinal metaplasia is a risk factor
      - Note: intestinal metaplasia is a result of chronic gastritis
  - **MALT lymphoma** (see below)
- Small intestine – cancers developing in small bowel are very rare.

- **MALT lymphoma** – a lymphoma (malignancy arising from lymphocytes) that arises from the lymphoid tissue found in the gut. Stomach is most common location.