



Gastrointestinal Pathology II.

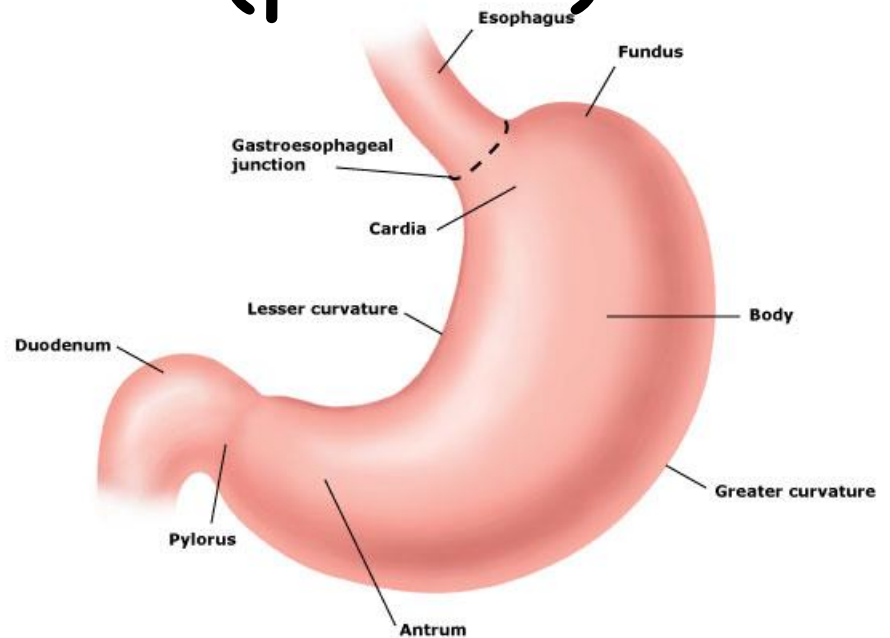
Stomach (part 2), Small bowel Appendix

Lilla Madaras MD PhD

*250 years of EXCELLENCE
in medical education,
research & innovation
and healthcare*

17th February 2020

STOMACH (part2)

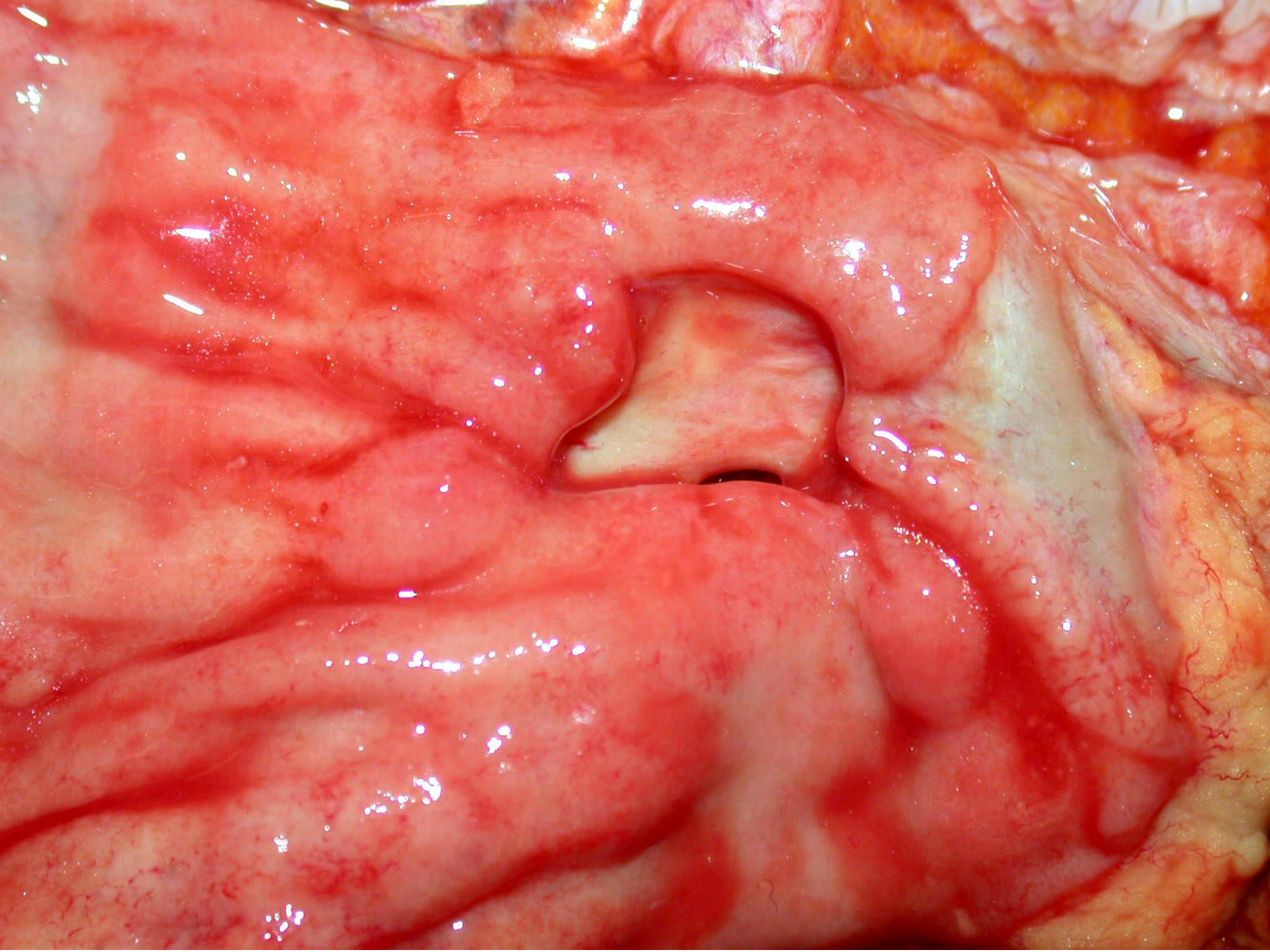


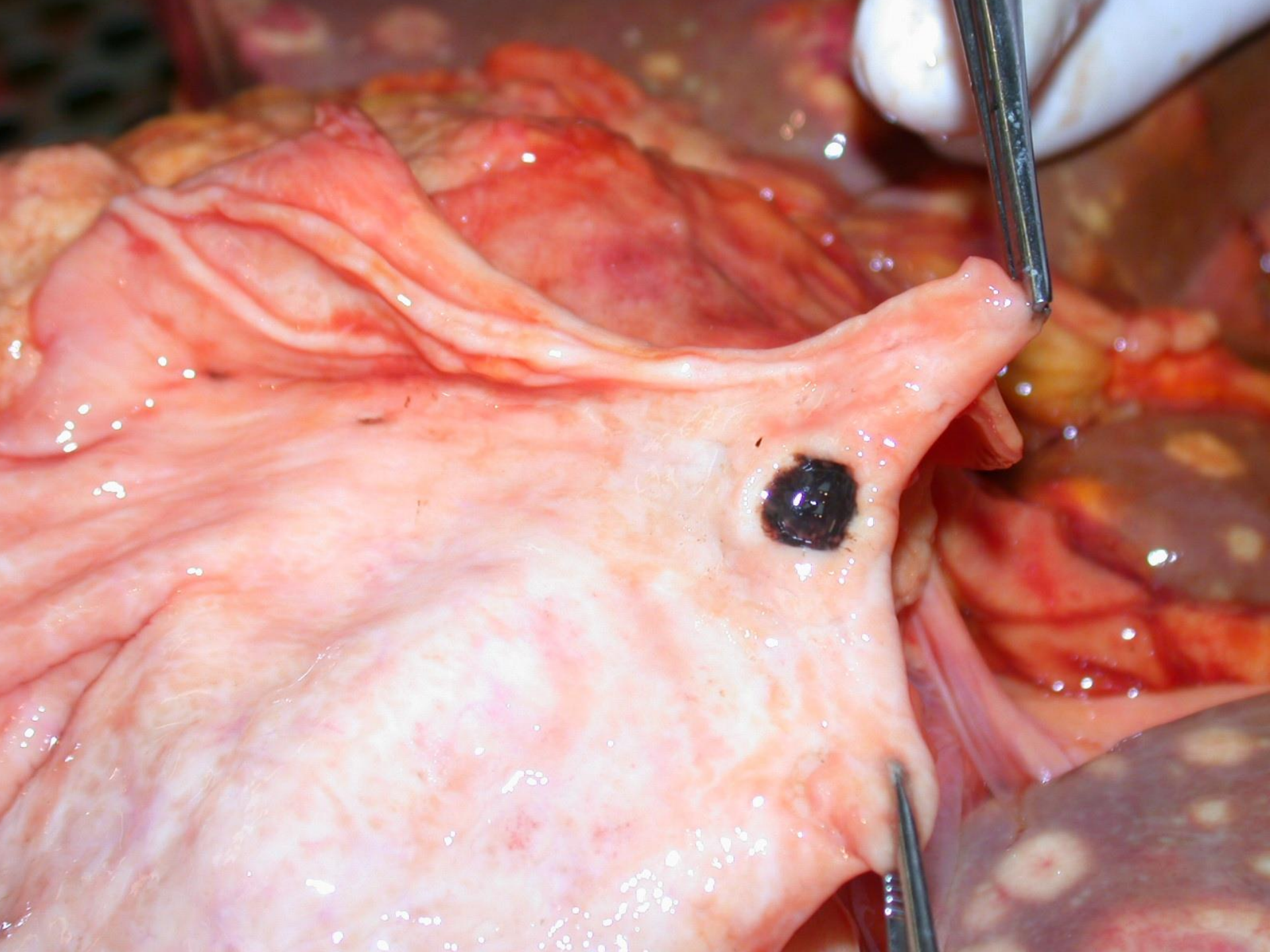
3. Peptic Ulcer Disease

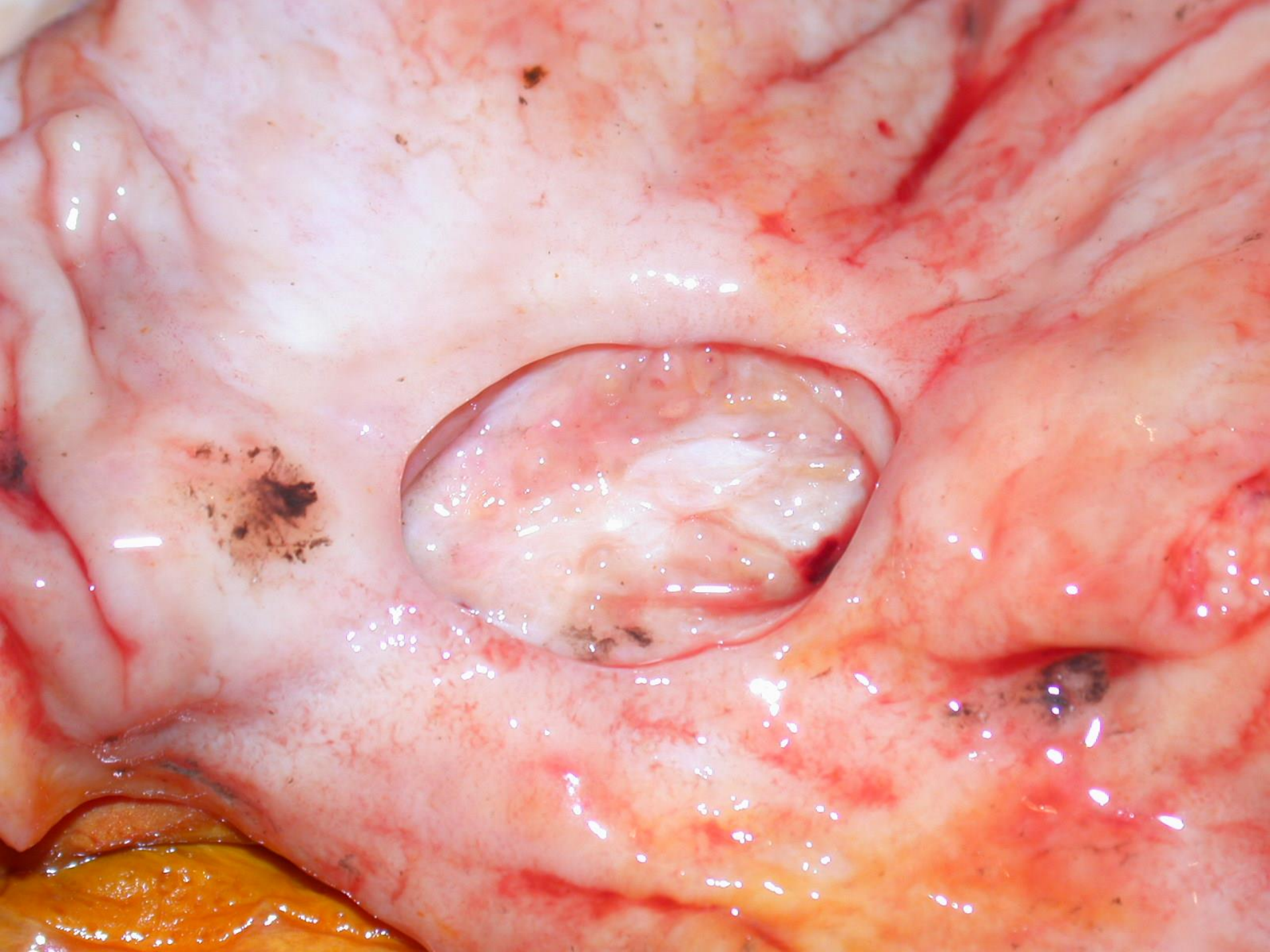
- **Ulcer**- mucosal defect deeper than the muscularis mucosae (\leftrightarrow erosion)
- Location:
 - duodenum (98%)
 - antrum (lesser curvature)
 - gastroesophageal junction (GERD, Barrett)
 - in Meckel diverticulum (gastric heterotopia)
- male predominance
- due to an imbalance between mucosal defense and damaging injury
- *H.pylori* associated most commonly

Ulcer- macroscopy

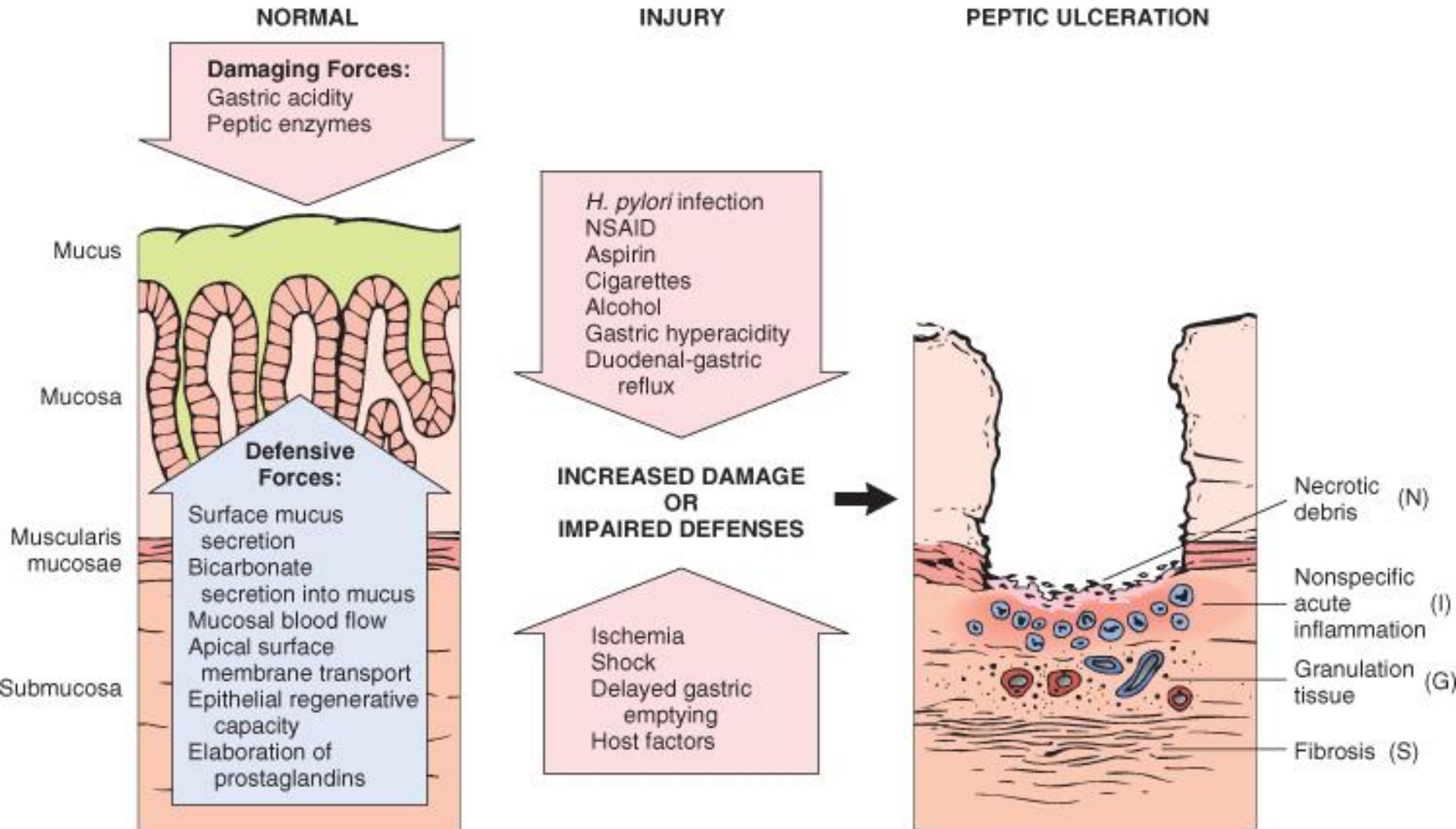
- punched-out defect
- margins level with the surrounding mucosa
- (heaped up margins- sign of malignancy)
- penetration (to the pancreas, liver, omentum)
- perforation (to the abdominal cavity)
- thrombosed blood vessel (may be seen) at the base







PEPTIC ULCER DISEASE

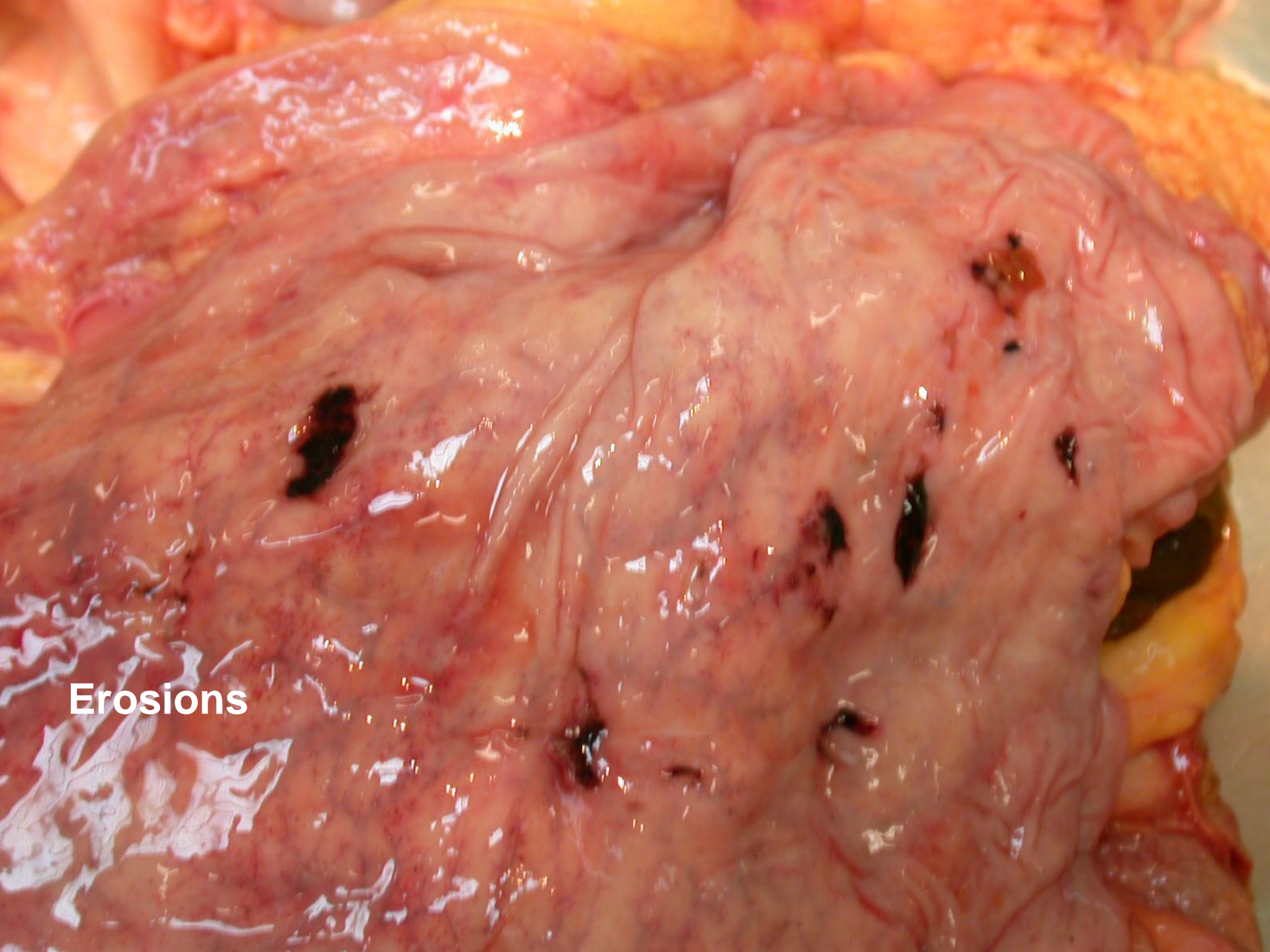


Ulcer- symptoms

- epigastric pain, nausea, vomiting
- iron-deficiency anemia
- gastrointestinal bleeding (hematemesis, melena)
- if perforation - signs of muscular defense, shock, peritonitis
- if penetration - may mimic AMI

Acute gastric ulceration

- **Stress erosions and ulcers-** in shock, with burns, sepsis, trauma, surgery, intracranial injury
 - **CURLING** ulcers- with burns or trauma
 - **CUSHING** ulcers- with intracranial injury



Erosions

(4. Miscellaneous Conditions)

- Gastric dilation
- Gastric rupture
- Phytobezoars
- Trichobezoars
- Hypertrophic gastropathy
 - Ménétrier disease
 - Hypertrophic- hypersecretory gastropathy
 - Zollinger- Ellison syndrome

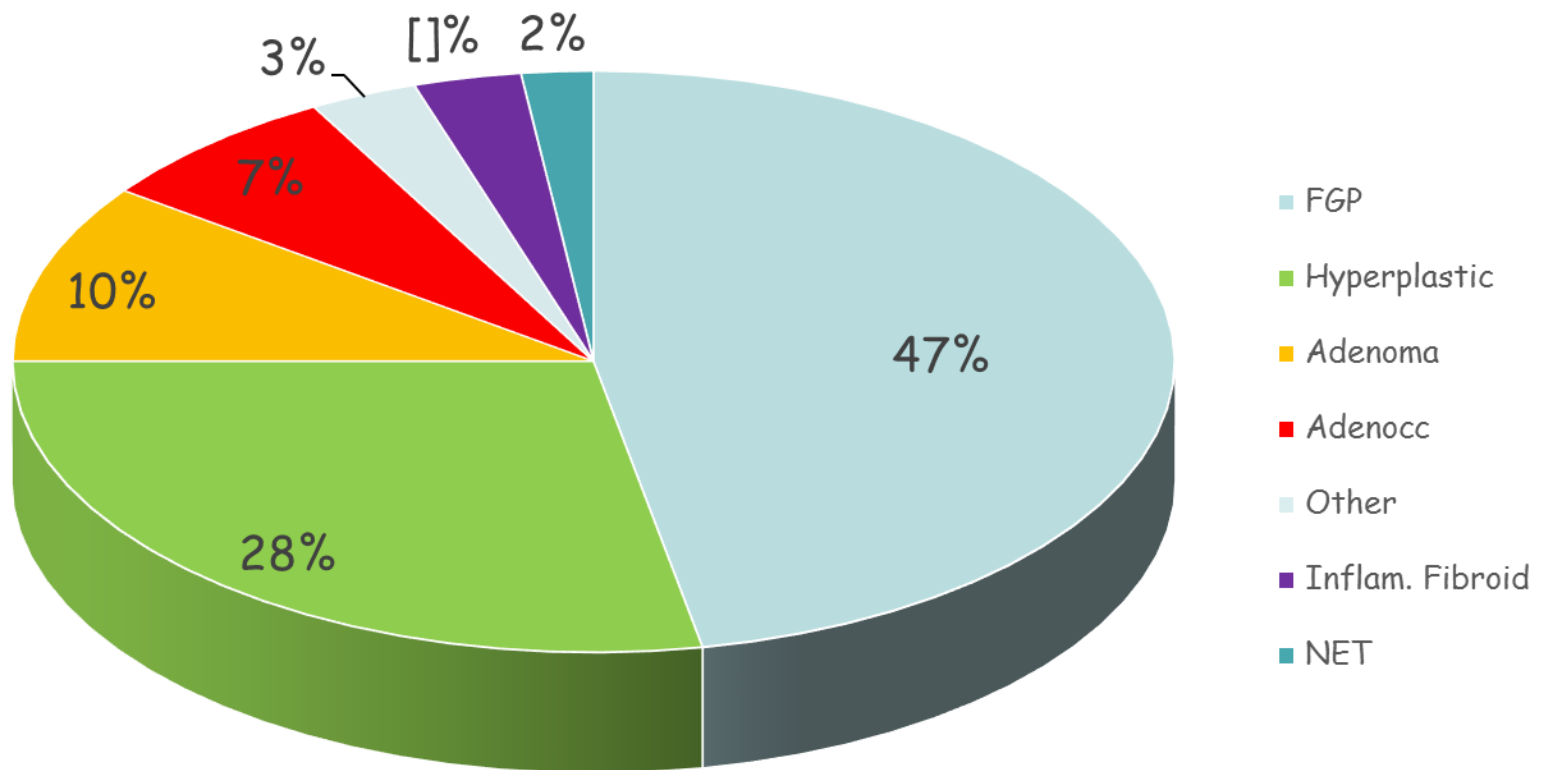


trichobezoar

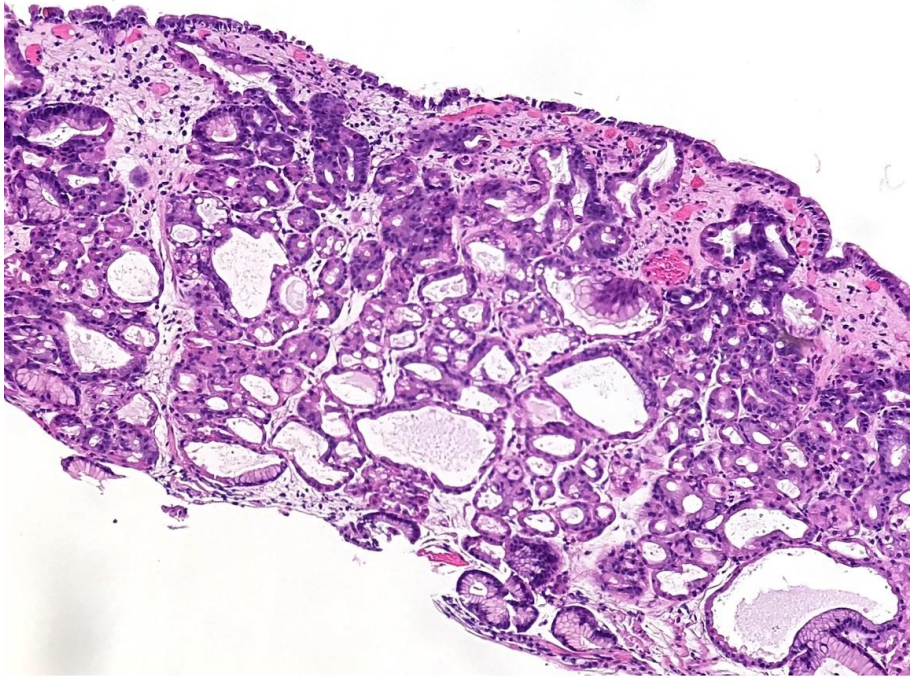
5. Gastric polyps and Neoplasms

- Polyps
- Malignant tumors
 - Gastric adenocarcinoma
 - Gastric lymphoma
 - Metastatic tumors
- Gastrointestinal Stromal Tumor (GIST)
- Gastric Neuroendocrine Tumor

Gastric polyps



Fundic gland polyp



- APC/ β -catenin signaling pathway alterations in sporadic and FAP associated FGP
- Sporadic FGP due to PPI
- The most common polyp in the stomach

Adenomas

- present as polyps
- 10% of polyps- neoplastic polyps- adenomas
- 50-60y old male patients
- FAP
- Almost always on the background of atrophy and intestinal metaplasia
- MA: usually solitary, less than 2 cm, within the antrum
- MI: dysplasia by definition

Gastric cancer (adenocarcinoma)

- the most common malignancy in the stomach (95%)
- High incidence in **Japan**, Chile, China, Portugal, Russia

Gastric cancer- Etiology

- H.pylori infection (in intestinal type gastric cc)
- Diet (nitrites from water, smoked and salted foods, chili pepper, lack of fresh fruit and vegetables)
- Low socioeconomic status
- Smoking
- Chronic gastritis with intestinal mtpl
- partial gastrectomy
- adenomas
- Genetic factors (Lynch sy, familial history of gastric cancer, Familial gastric carcinoma syndrome (CDH1 mutation)

Gastric cancer- location

- Antrum and pylorus- 50-60%
- Cardia-25%
- Body- 15-25%
- more commonly on the lesser curvature

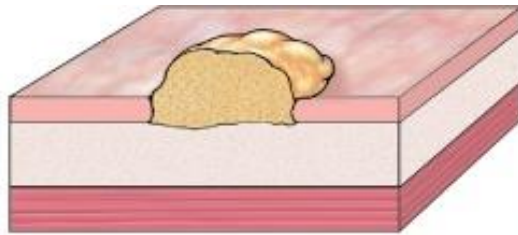
Classification I.

1. On the depth of invasion

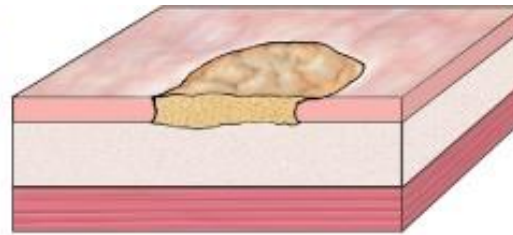
1. In situ carcinoma
2. Early gastric cancer- confined to the mucosa and submucosa with or without lymph node metastasis
3. Advanced gastric cancer- invasion within the muscularis propria and beyond

2. On macroscopic growth pattern

Classification II.



A. Exophytic

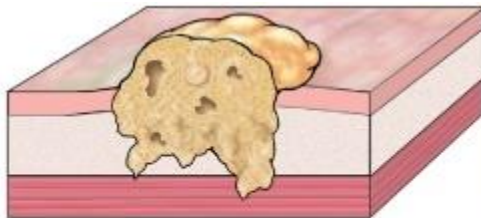


Flat or depressed

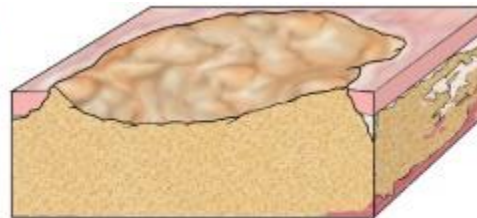
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Excavated



B. Exophytic



Linitis plastica

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Excavated

Classification III.

3. On histological subtypes WHO classification

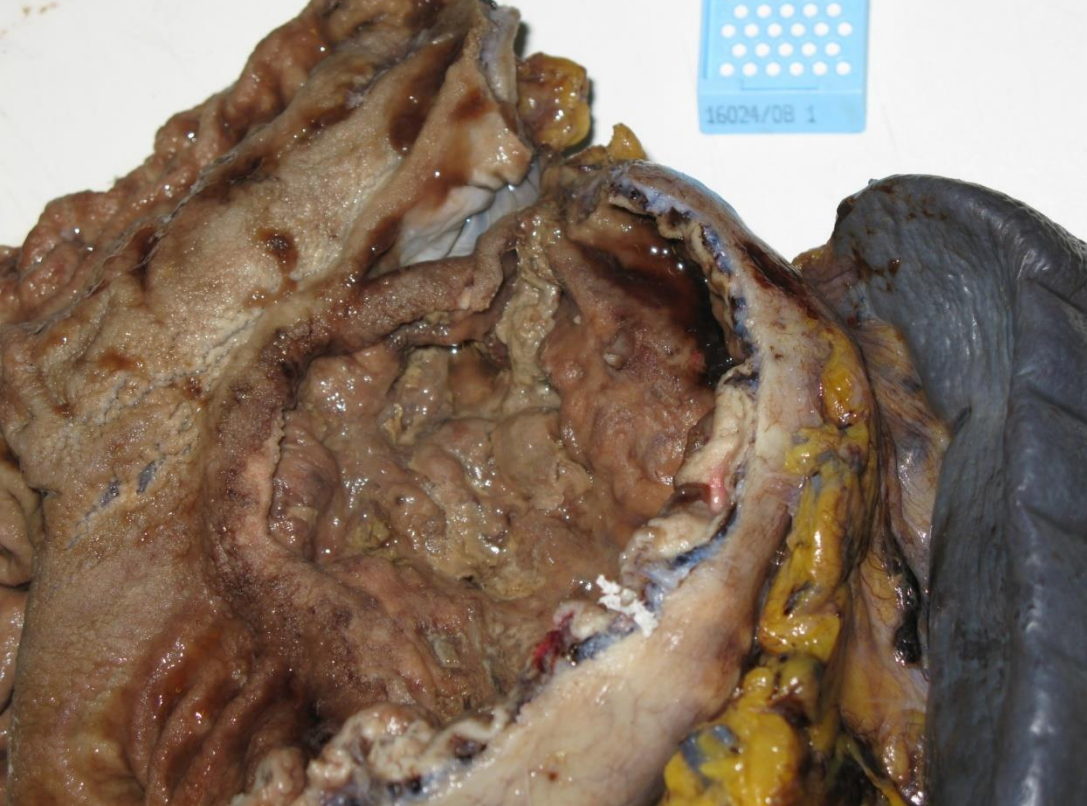
Laurén classification:

intestinal type

diffuse type

Spread

1. Local spread to surrounding structures (duodenum, pancreas, retroperitoneum, peritoneum)
2. Regional lymph nodes
3. Liver, lung
4. Peculiar sites:
 1. Virchow's node- left supraclavicular lymph node
 2. Sister Mary Joseph nodule- periumbilical
 3. Krukenberg tumor- bilateral ovarian metastases



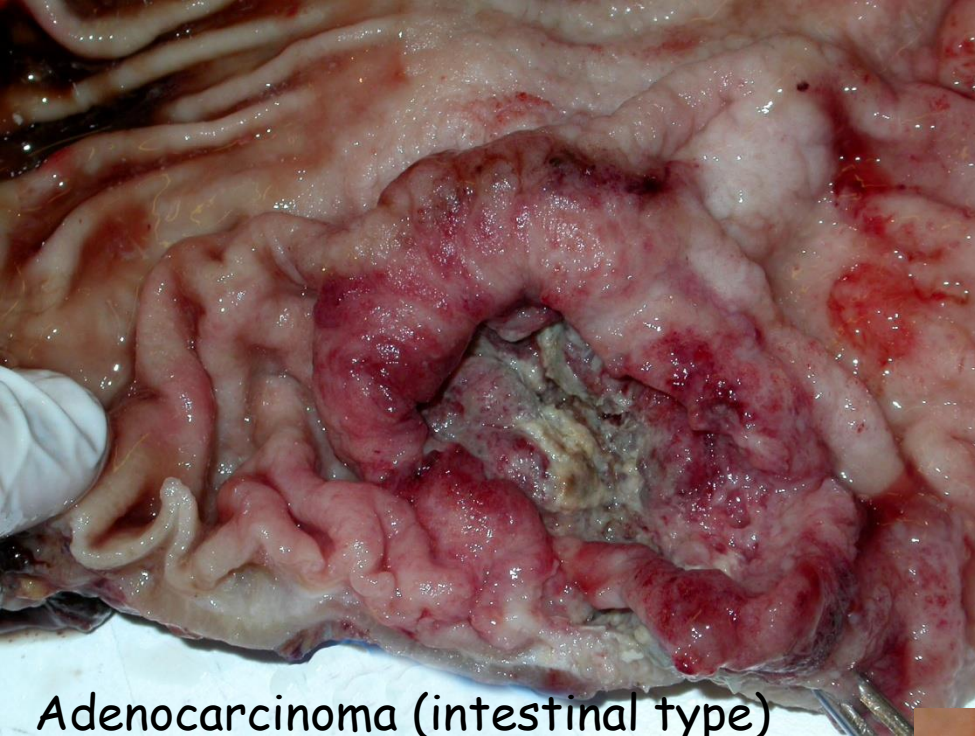
Sister Mary Joseph nodule

Penetration to the spleen



Symptoms

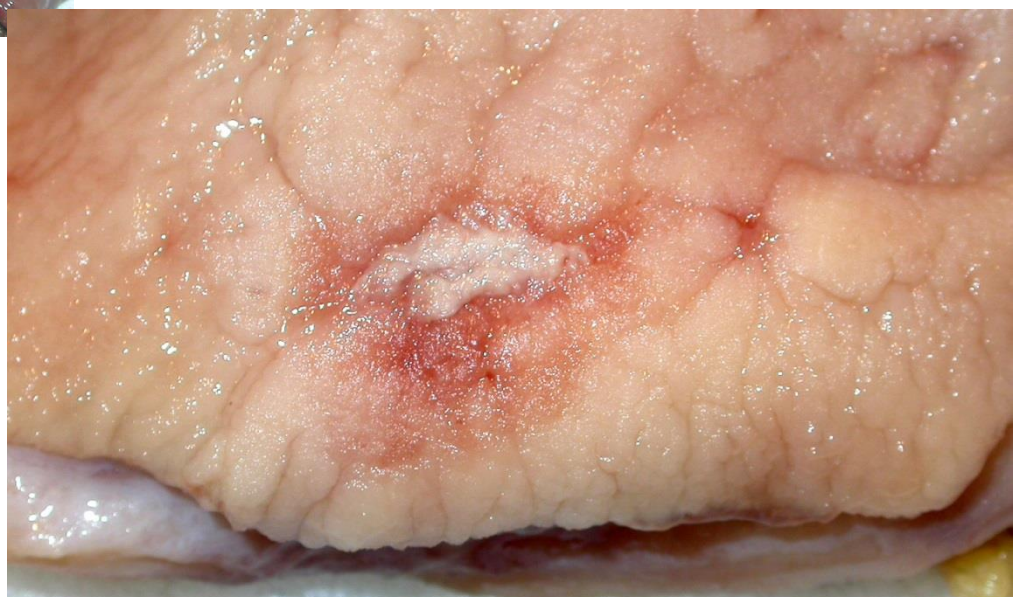
- generally asymptomatic until late
- pain, weight loss, vomiting, nausea, anemia, bleeding



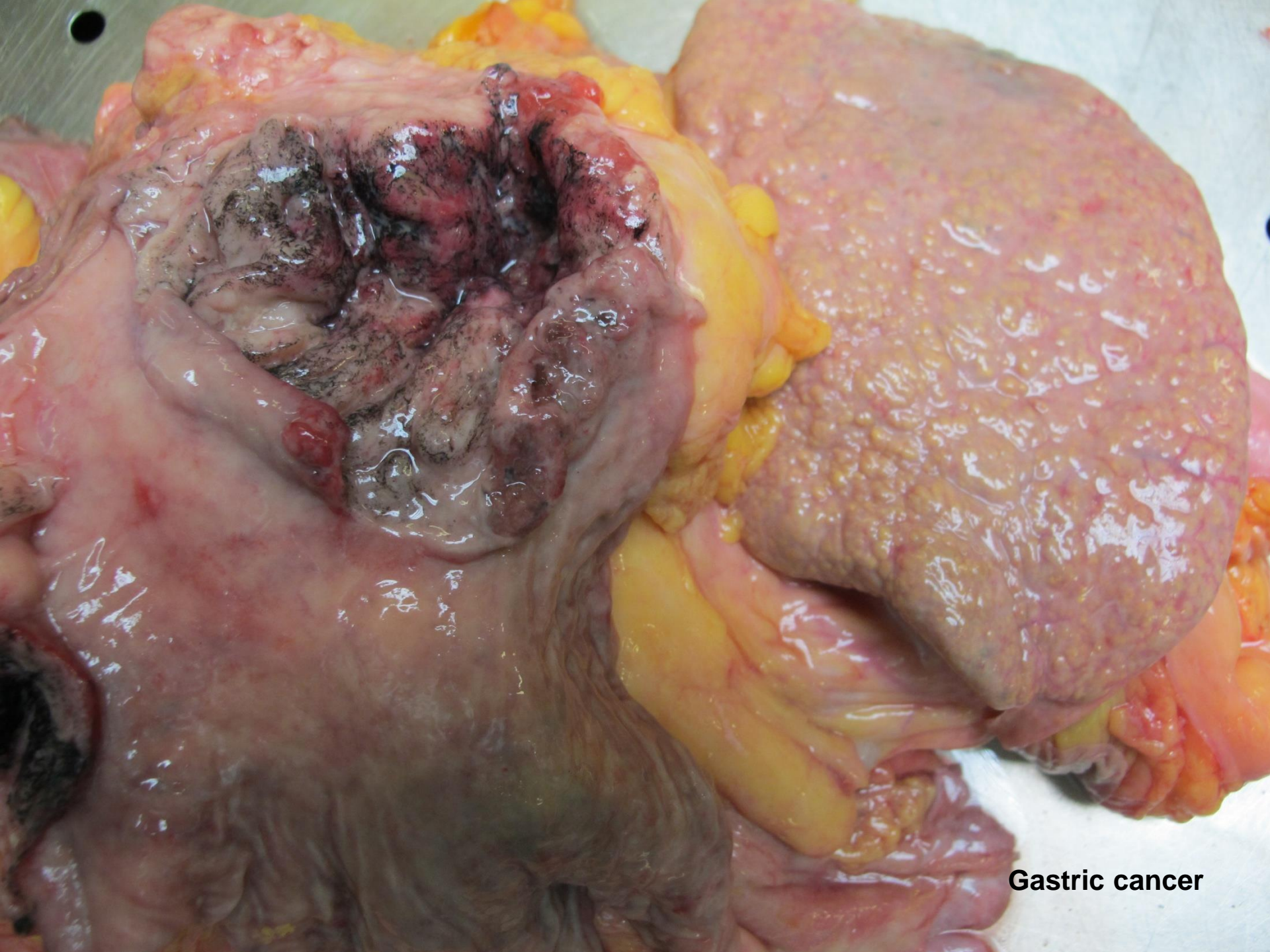
Adenocarcinoma (intestinal type)



Shigillocellular cc-diffuse type



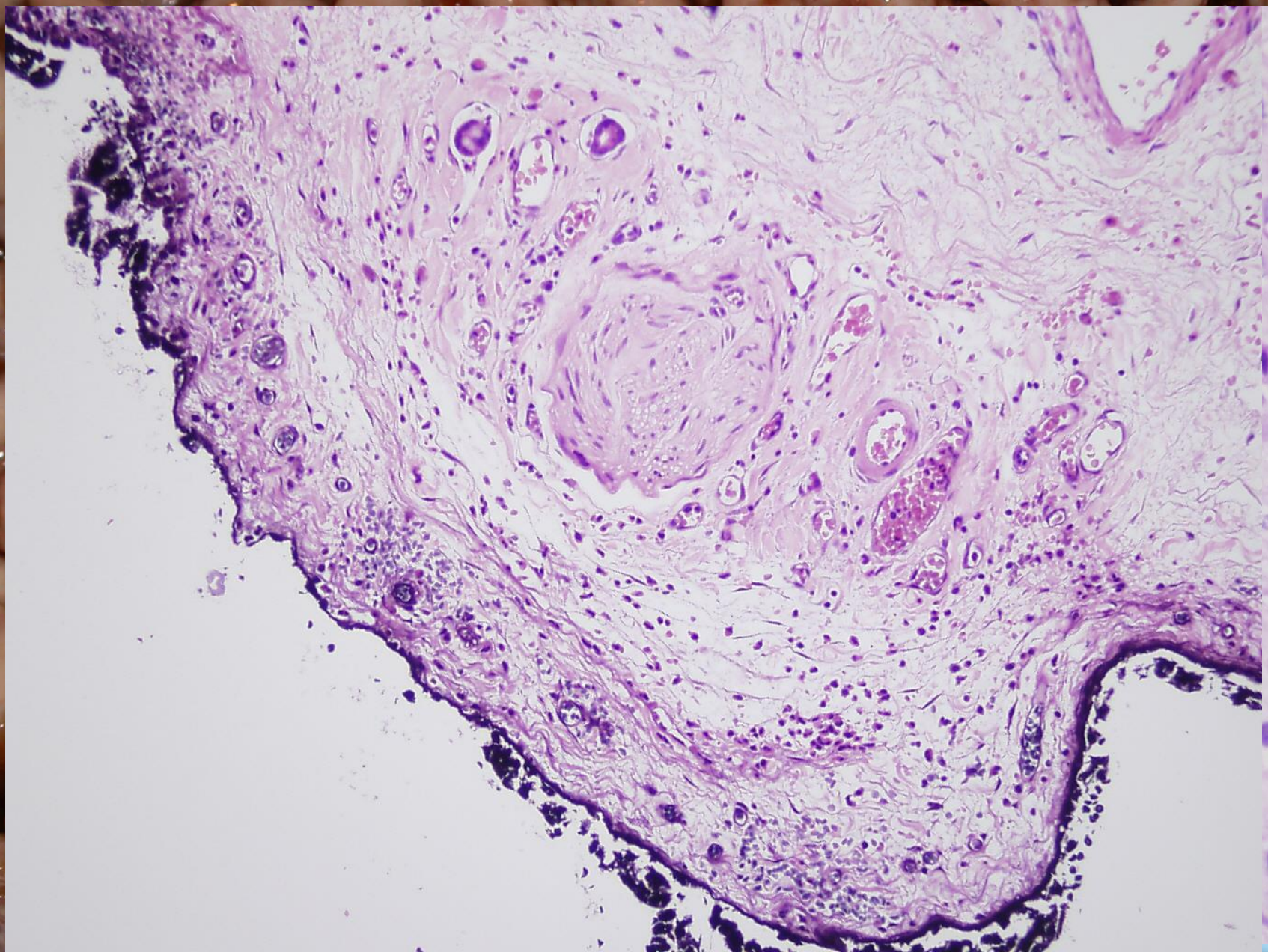
Shigillocellular carcinoma-diffuse type
(Signet ring cell cc)



Gastric cancer

Case 1

- 34 y old male patient



Case 2

- 12y old girl



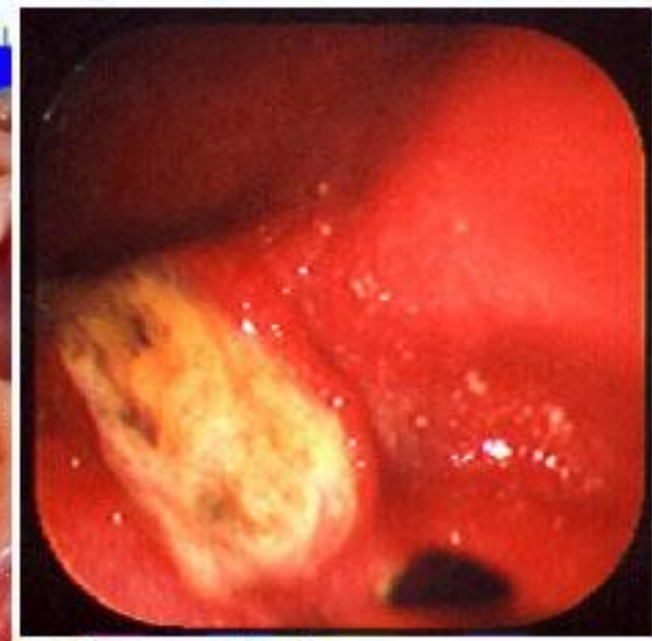
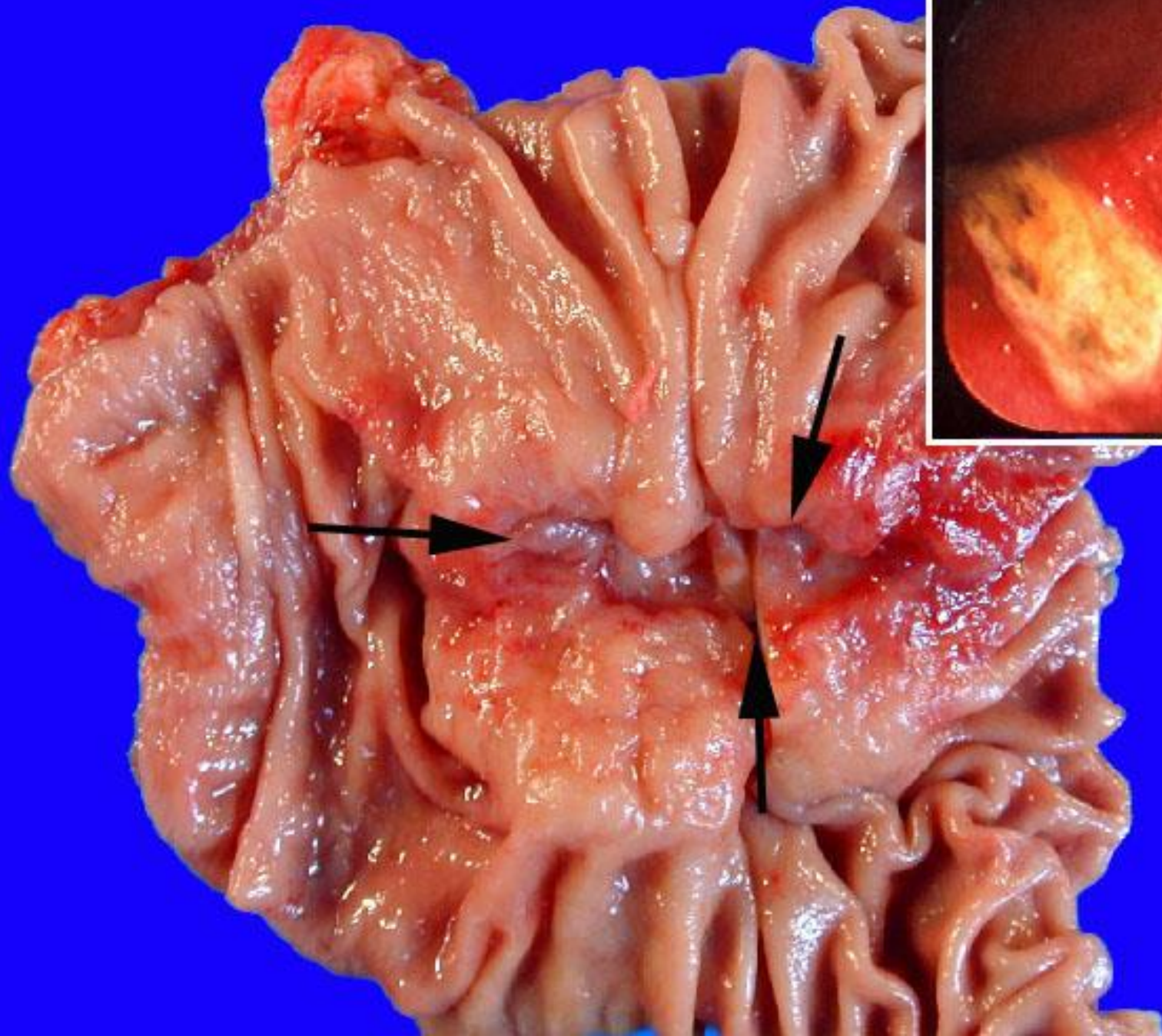
12 y old girl

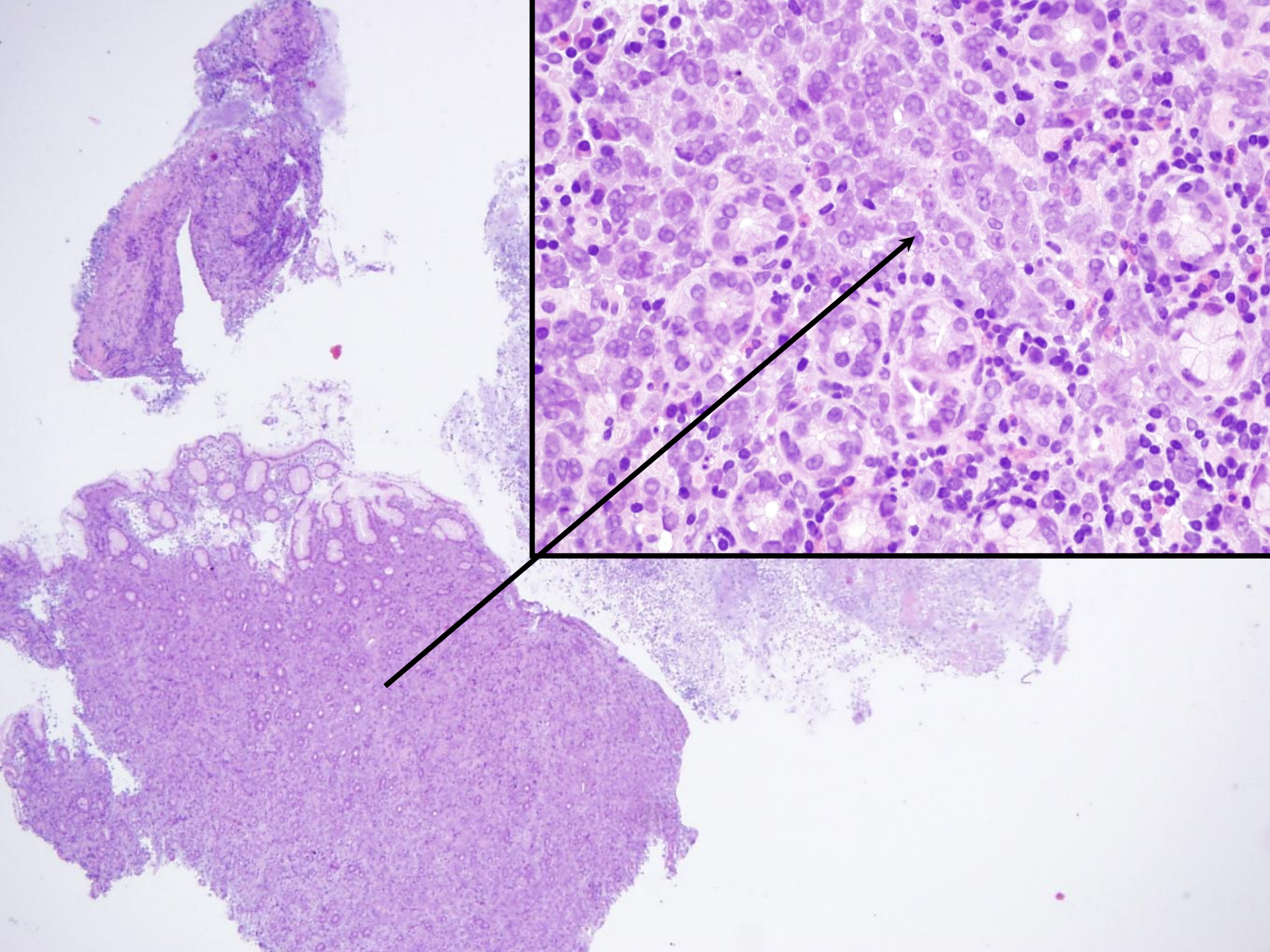
This histological slide shows a tissue section from a 12-year-old girl, stained with Periodic acid–Schiff (PAS). The image displays a dense population of cells with prominent magenta-colored glycogen deposits within their cytoplasm. The nuclei are stained blue with hematoxylin. The overall appearance is characteristic of a glycogen-rich tissue, such as the liver or spleen, in a pediatric patient.

PAS

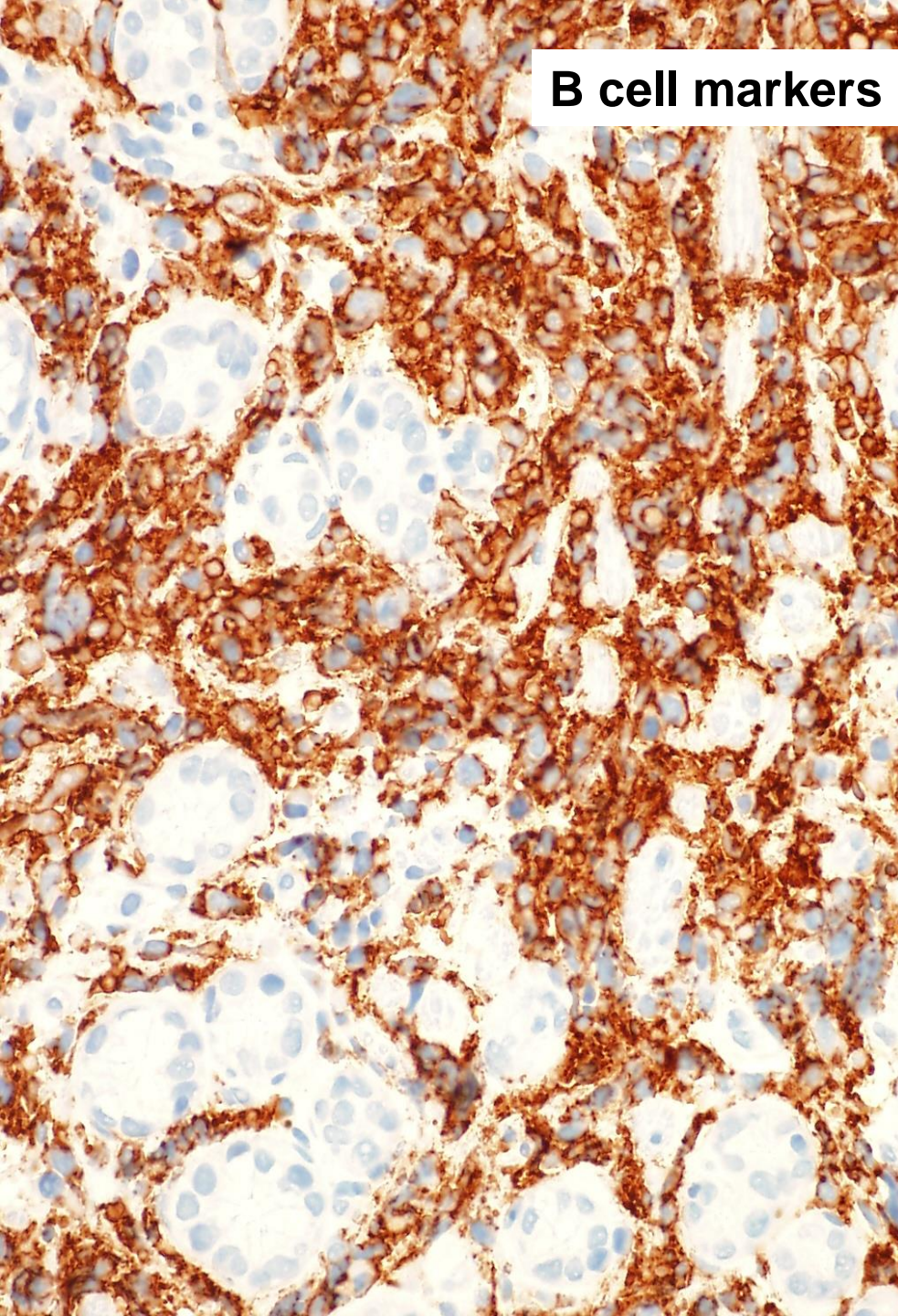
Gastric Lymphoma

- Stomach is the most common site of extra-nodal lymphomas
- 5% of gastric malignancies
- MALT lymphoma- B cell type
- 80% associated with *H. pylori*

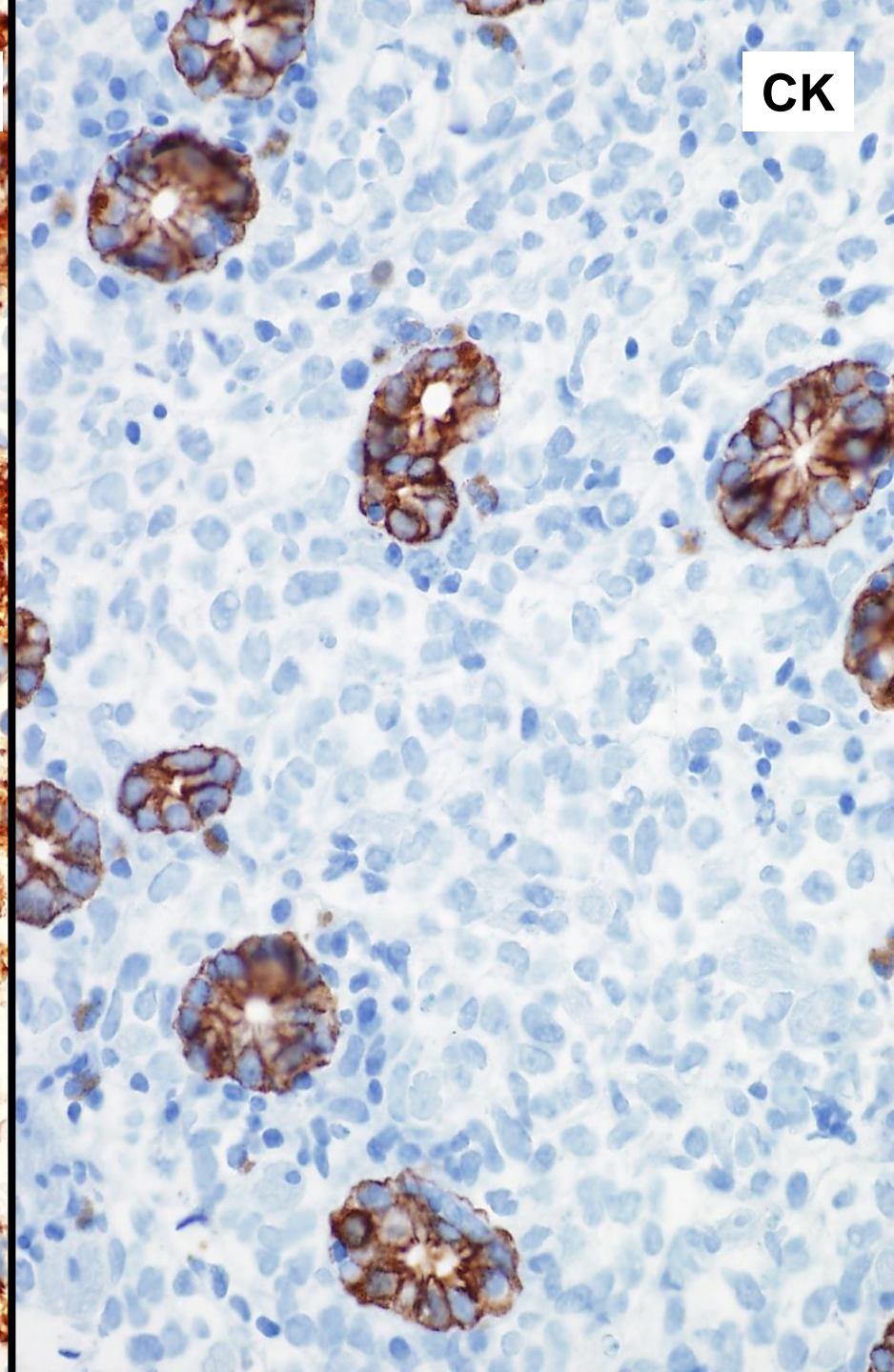




B cell markers



CK



Metastatic cancer

- Breast cc
- Lung cc
- Malignant melanoma

Mesenchymal tumors

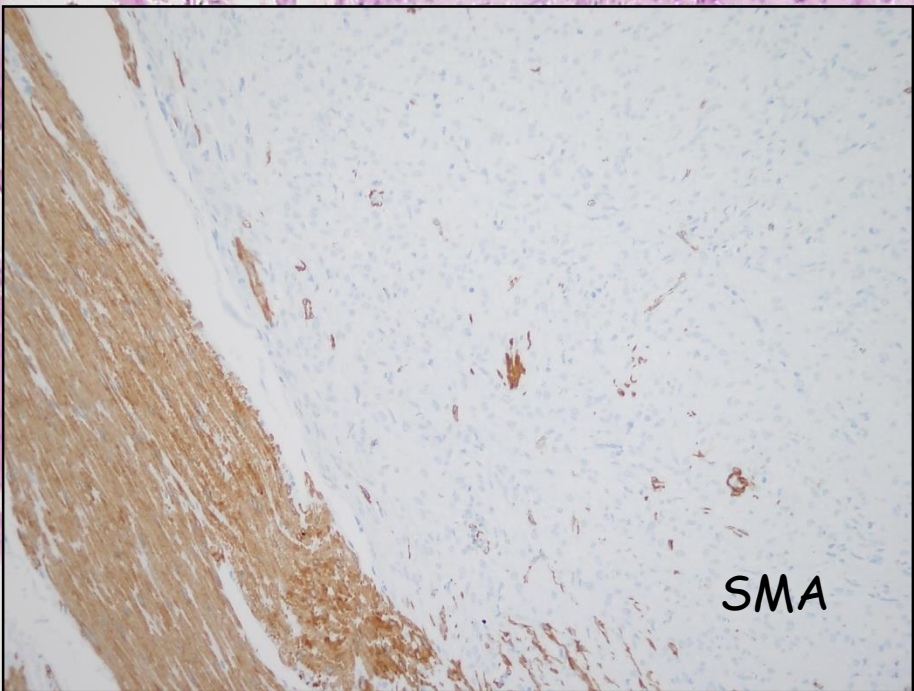
- Leiomyoma, leiomyosarcoma, schwannoma etc.
- GIST- the most common mesenchymal tumor of the GI
- >50% of GISTs within stomach

Gastrointestinal Stromal Tumor (GIST)

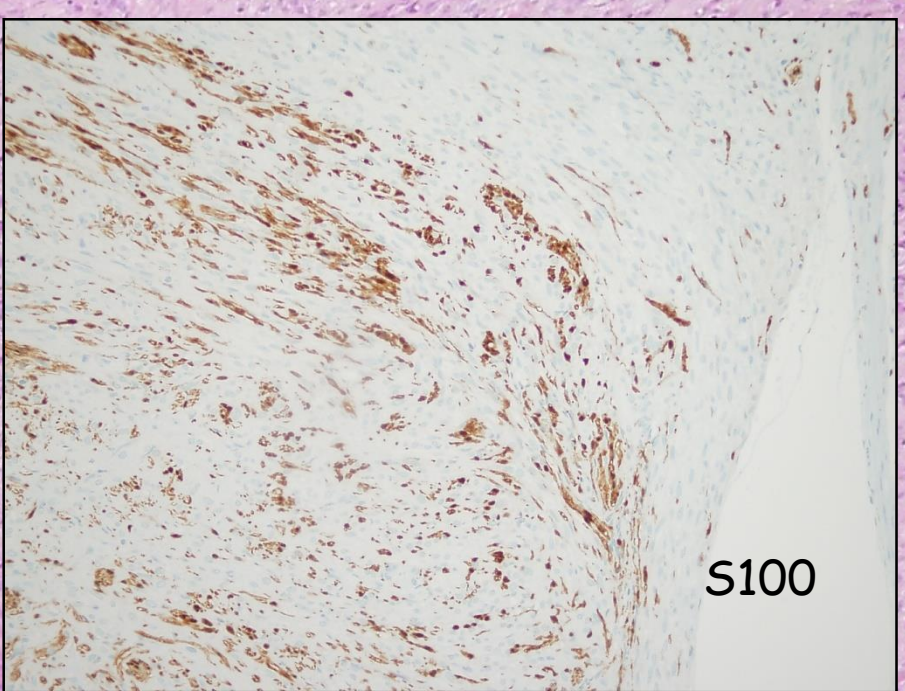
- Typically in male patients around 60 y
- originates from the „pacemaker cells“ the interstitial cells of CAJAL
- the majority express c-kit(CD117), Dog1 and CD34
- different immunophenotypes
 - smooth muscle
 - neurogenic
 - both
 - none
- spindle cells or epithelioid cells

Gastrointestinal Stromal Tumor (GIST)

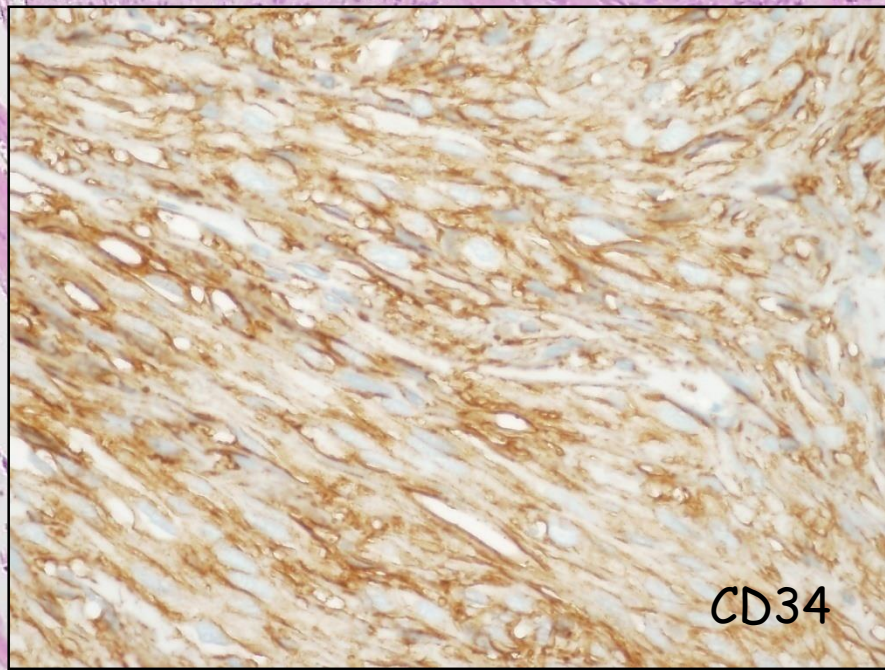
- Biological behaviour depends on size, mitotic index
- 80% have c-KIT mutation
- 8% of tumors with normal c-kit have PDGFRA mutation
- Both c-KIT and PDGFRA receptor tyrosine-kinases produce intracellular signals and activate the RAS and PI3K/AKT pathways
- uncontrolled proliferation, apoptosis inhibition
- drug: imatinib-Glivec® (tyrosin kinase inhibitor used in CML also)



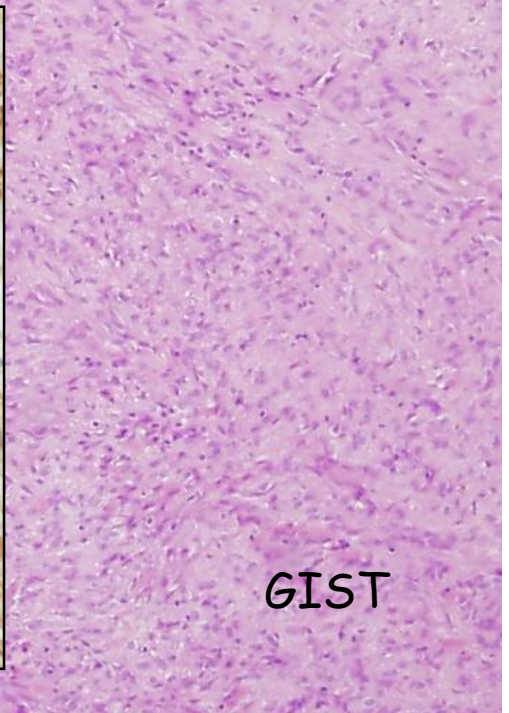
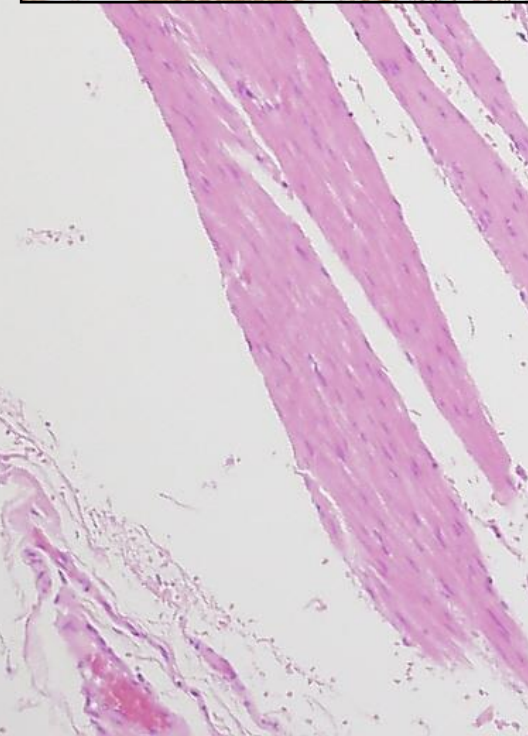
SMA



S100



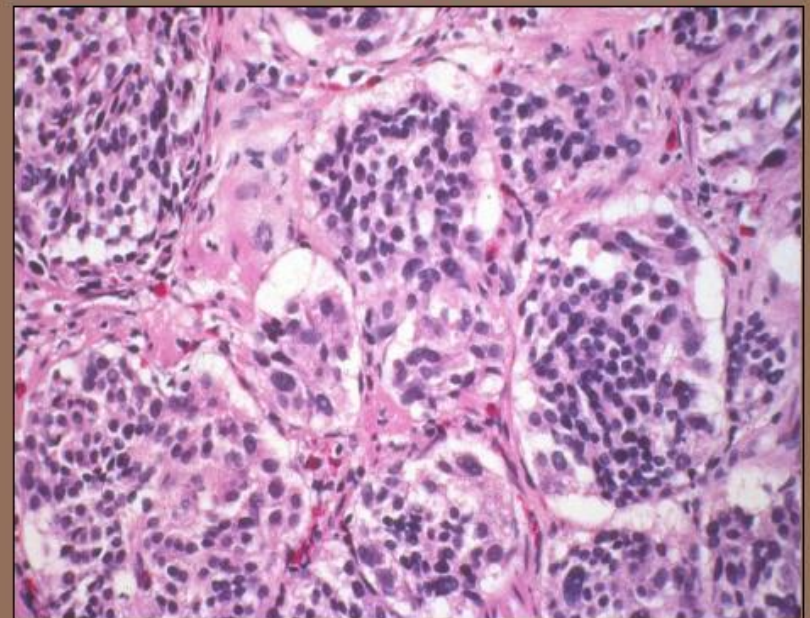
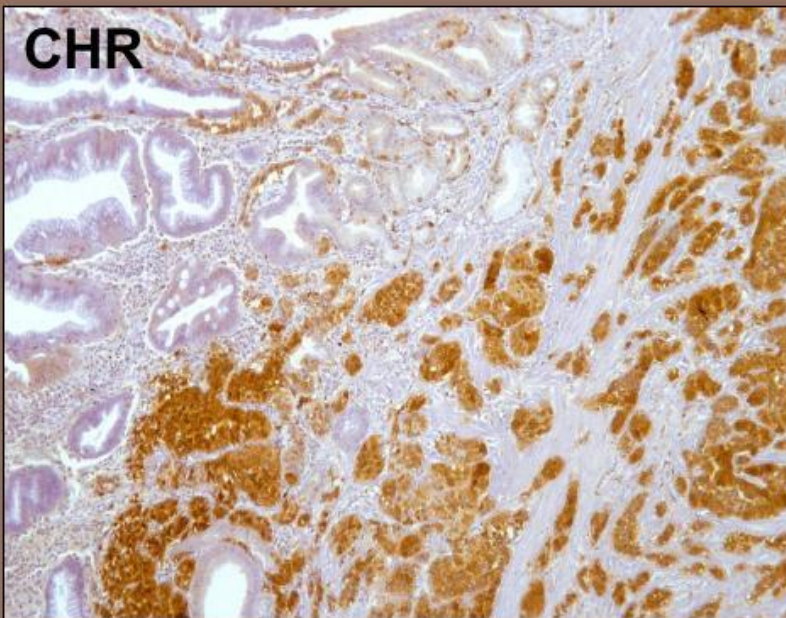
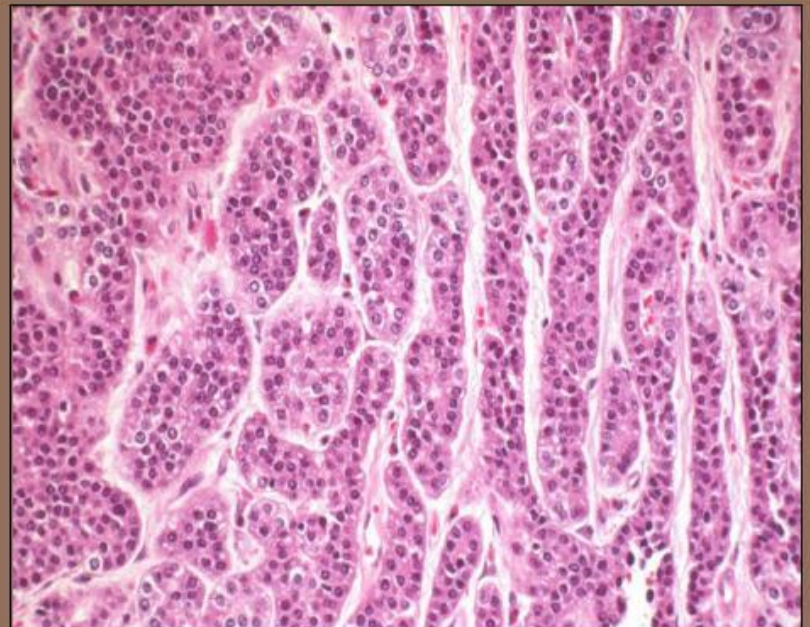
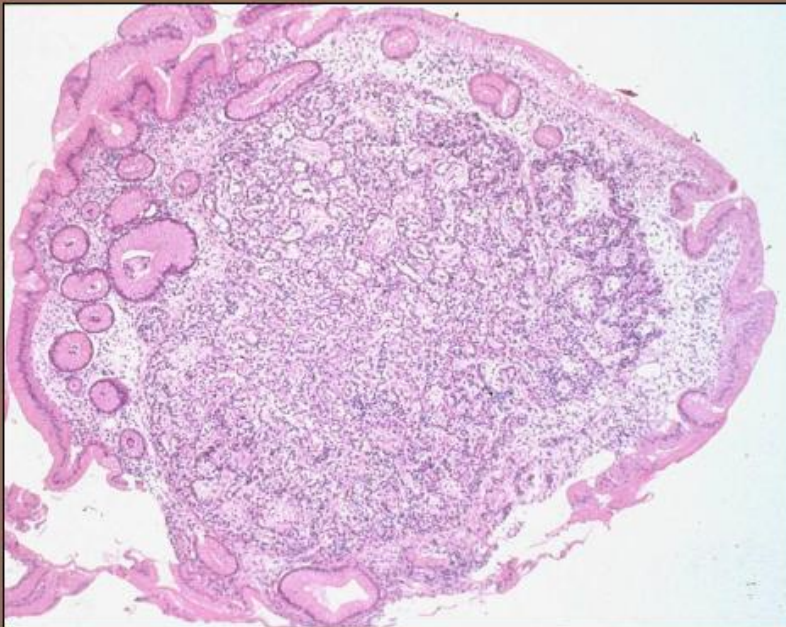
CD34

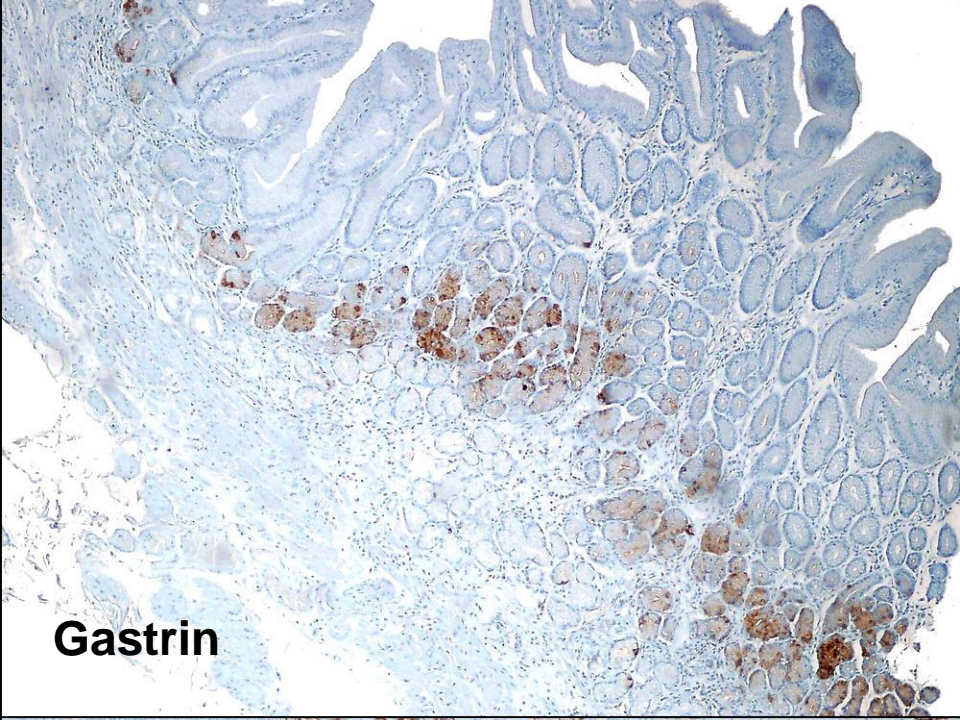
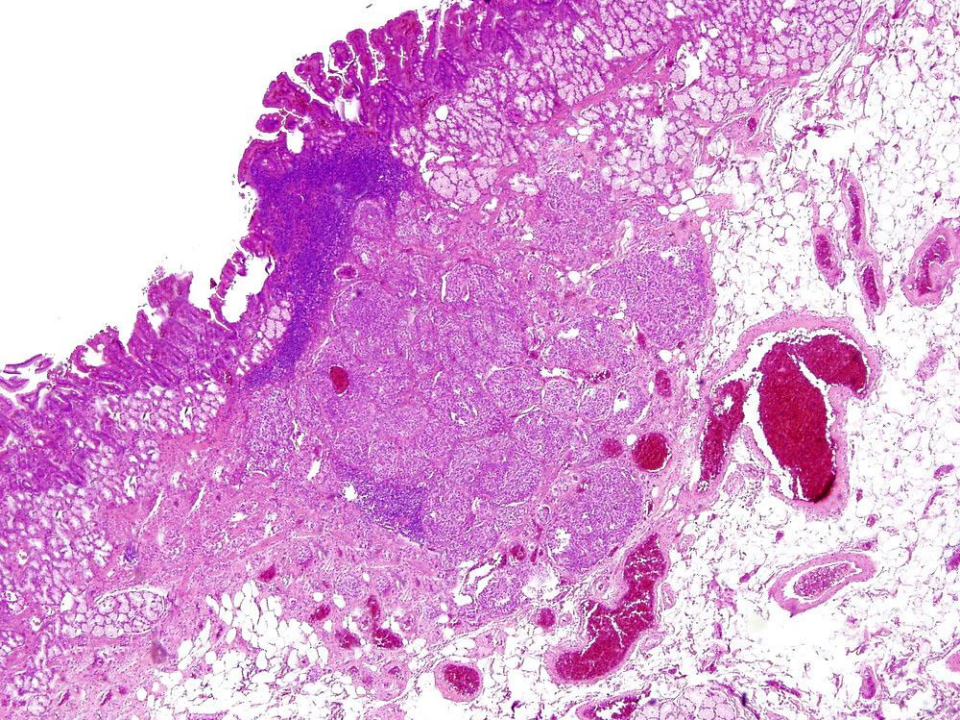


GIST

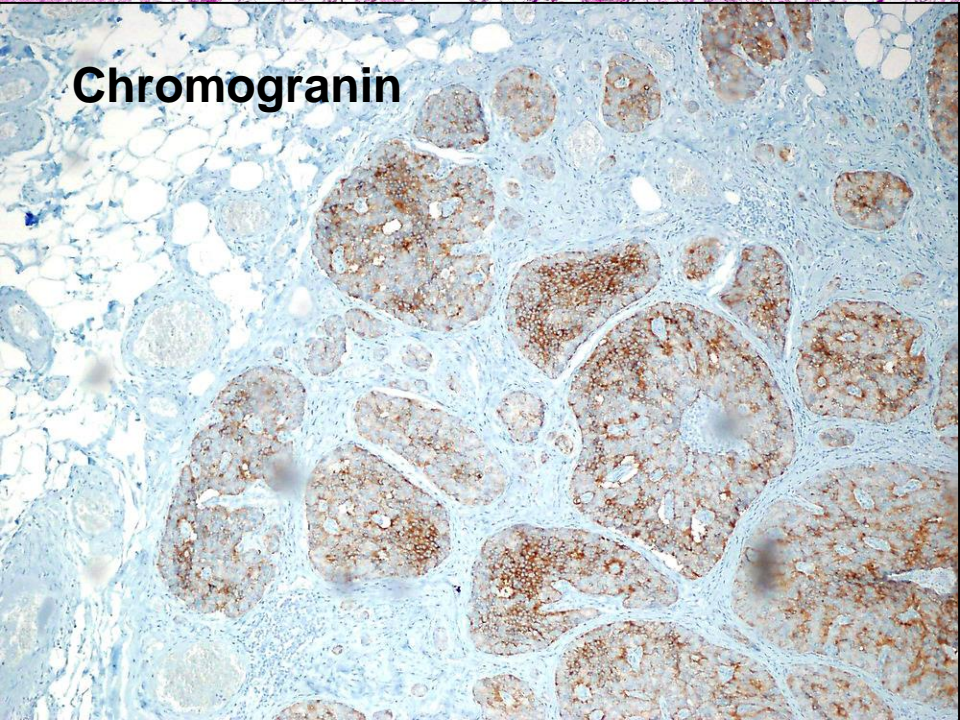
Gastric Neuroendocrine Tumor

- from ECL cells
- MEN 1
- Zollinger-Ellison syndrome
- Malignant potential
- Grade based on mitotic activity ($\geq 2-20/10\text{HPF}$)
- TNM
- WHO 2010

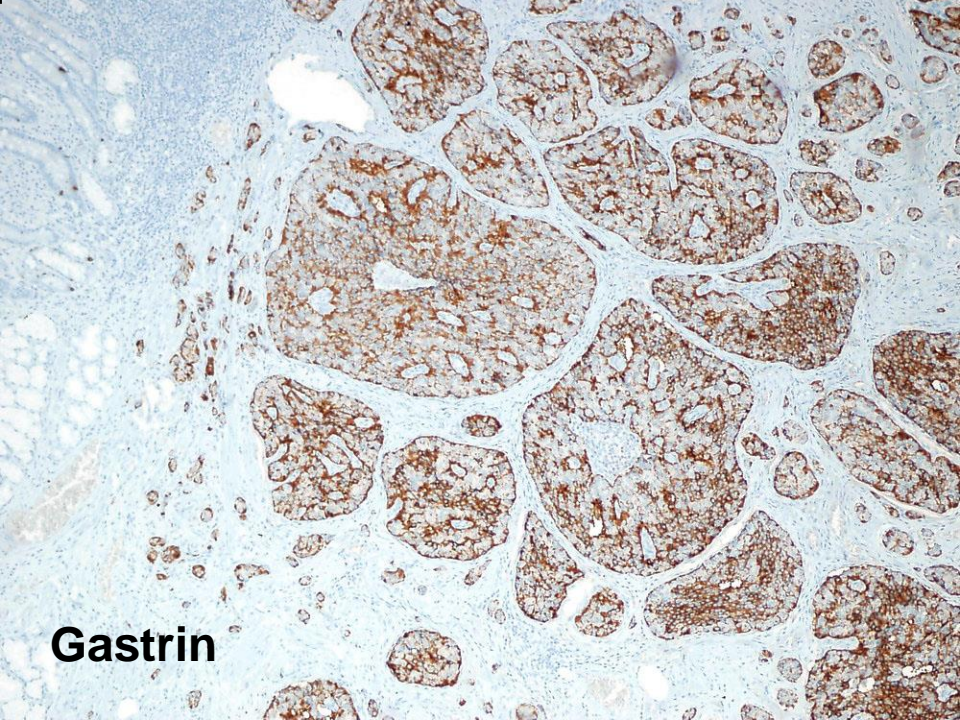




Gastrin



Chromogranin



Gastrin

Small bowel

Anatomy

- length approx. 6 m
- duodenum, jejunum, ileum
- villi, crypts (4:1)
- absorptive cells (with microvilli), goblet cells, endocrine cells, Paneth cells
- Mucosa associated lymphoid tissue (MALT)



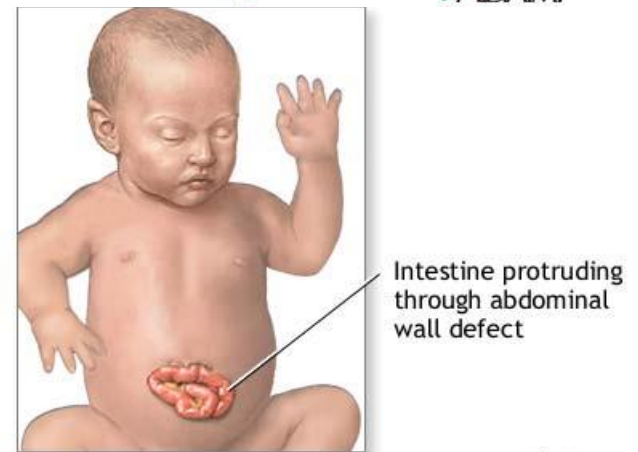
Small intestinal disorders

1. Congenital anomalies
2. Inflammatory conditions
3. Malabsorption syndromes
4. Vascular disorders
5. Intestinal obstruction
6. Polyps and Neoplasms

1. Congenital anomalies

Congenital anomalies I.

- **Heterotopia**- gastric, pancreatic
- Duplication - cysts
- Malrotation
- **Omphalocele**- no abdominal musculature, herniation of abdominal structures into a membranous sac
- **Gastroschisis**- extrusion of the intestines due to incomplete „closure“ of the abdominal wall



Congenital anomalies II.

- **Atresia, stenosis** - duodenal mostly (in jejunum, ileum- may occur)
- **Meckel diverticulum** - within 85 cm from IC valve on the antimesenteric side
 - true diverticulum
 - due to involution failure of the vitelline (omphalomesenteric) duct
 - gastric or pancreatic heterotopia common
 - intussusception, perforation
 - The rule of 2s



2. Inflammatory conditions

Inflammatory conditions

- Infectious Enterocolitis
- Others
- Inflammatory bowel disease affecting the small bowel (Crohn disease, Ulcerative colitis)

Enterocolitis symptoms

- **Diarrhea:** increase in stool mass and frequency, decrease in consistency
 - Secretory diarrhea
 - Osmotic diarrhea
 - Exudative diseases
 - Malabsorption
 - Deranged motility
- **Dysentery:** low volume, painful, bloody diarrhea

Infectious enterocolitis

- Viruses

- **Rotavirus**

- Children 6-24mo old
 - **The most common cause of diarrhea (and diarrheal mortality) in children**
 - Destroys enterocytes → immature secretory cells in surface epithelium → excessive secretion of water and electrolytes → secretory (and osmotic) diarrhea
 - Person-to-person, food and water- ways of transmission
 - incubation- 2days
 - Vomiting, watery diarrhea

- **Calicivirus**

- Sapporo-like (rare) and Norovirus (previously Norwalk-like)
 - Schools, hospitals, nursing homes, cruise ships
 - Person-to-person, food and water- ways of transmission
 - incubation- 1-2days
 - **Half of all gastroenteritis outbreaks ww**

Infectious enterocolitis

- **Viruses**

- **Adenovirus**

- Moderate gastroenteritis of children <2years (2nd most common after rotavirus)
 - Incubation 1 week
 - Person-to-person
 - Atrophy of villi and hppl of crypts

- **Astrovirus**

- Anorexia, fever, headache
 - Incubation 1-2 days
 - Person-to-person, food and water- ways of transmission

Major Causes of Bacterial Enterocolitis

Organism	Pathogenic Mechanism	Source	Clinical Features
<i>Escherichia coli</i>			Traveler's diarrhea, including:
• ETEC	Cholera-like toxin, no invasion	Food, water	Watery diarrhea
• EHEC	Shiga-like toxin, no invasion	Undercooked beef products	Hemorrhagic colitis, hemolytic-uremic syndrome
• EPEC	Attachment, enterocyte effacement, no invasion	Weaning foods, water	Watery diarrhea, infants and toddlers
• EIEC	Invasion, local spread	Cheese, water, person-to-person	Fever, pain, diarrhea, dysentery
<i>Salmonella</i>	Invasion, translocation, lymphoid inflammation, dissemination	Milk, beef, eggs, poultry	Fever, pain, diarrhea or dysentery, bacteremia, extraintestinal infection, common source outbreaks
<i>Shigella</i>	Invasion, local spread	Person-to-person, low-inoculum	Fever, pain, diarrhea, dysentery, epidemic spread
<i>Campylobacter</i>	Toxins, invasion	Milk, poultry, animal contact	Fever, pain, diarrhea, dysentery, food sources, animal reservoirs
<i>Yersinia enterocolitica</i>	Invasion, translocation, lymphoid inflammation, dissemination	Milk, pork	Fever, pain, diarrhea, mesenteric adenitis, extraintestinal infection, food sources
<i>Vibrio cholerae</i> , other <i>Vibrios</i>	Enterotoxin, no invasion	Water, shellfish, person-to-person spread	Watery diarrhea, cholera, pandemic spread
<i>Clostridium difficile</i>	Cytotoxin, local invasion	Nosocomial environmental spread	Fever, pain, bloody diarrhea, following antibiotic use, nosocomial acquisition
<i>Clostridium perfringens</i>	Enterotoxin, no invasion	Meat, poultry, fish	Watery diarrhea, food sources, "pigbel"
<i>Mycobacterium tuberculosis</i>	Invasion, mural inflammatory foci with necrosis and scarring	Contaminated milk, swallowing of coughed-up organisms	Chronic abdominal pain; complications of malabsorption, stricture, perforation, fistulae, hemorrhage

Infectious enterocolitis

- Parasitic
 - *Ascaris lumbricoides*
 - *Strongyloides*
 - *Enterobius vermicularis*
- Protozoa
 - *Giardia lamblia* (*Giardiasis*)

Others

- AIDS-related
- GVHD
- Radiation enterocolitis
- Drug-induced injury

Idiopathic Inflammatory Bowel Disease affecting the small bowel

- Crohn disease
- Ulcerative colitis (backwash ileitis)

3. Malabsorption

Malabsorption

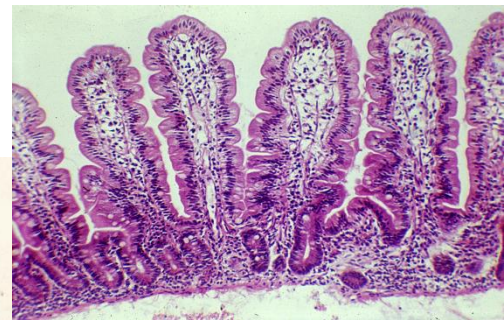
- Inadequate absorption of fat, vitamins, carbohydrates, proteins, minerals and water
- Chronic diarrhea with **steatorrhea**
- Consequences: abdominal pain, weight loss, anemia, bleeding, petechiae, purpura, edema, peripheral neuropathy, amenorrhea, infertility, hyperparathyreoidism, osteopenia, tetany etc.
- The most common causes: **celiac disease**, **pancreatic insufficiency** and **Crohn disease**

Celiac disease (celiac sprue, gluten-sensitive enteropathy)

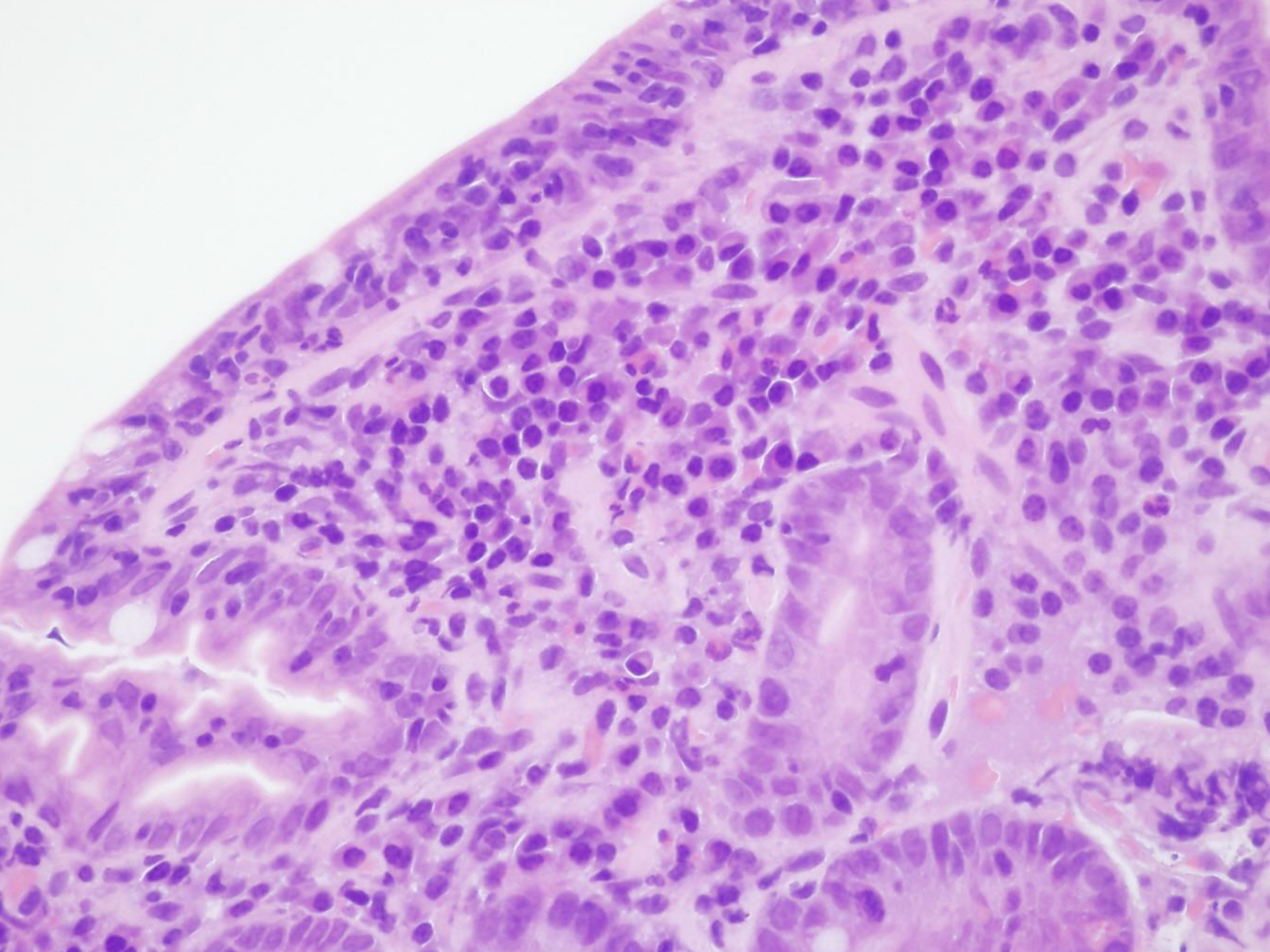
- gluten (gliadin) sensitivity (in wheat, rye, barley and oat)
- autoimmune, T-cell mediated, familial
- children and adults (silent or latent)
- proximal small bowel more seriously involved
- SY: weight loss, fatigue, bloating, diarrhea, dermatitis herpetiformis
- increased risk of small intestinal adenocarcinoma, non-Hodgkin lymphoma

Celiac disease (celiac sprue, gluten-sensitive enteropathy)

- Endoscopy: flat small bowel mucosa
- MI: atrophy or total loss of villi
 - pseudostratification of surface epithelium
 - lymphocytes (T) within surface epithelium ↑
 - ↑ mitotic activity in elongated crypts
 - ly, plasma cells, eo, macrophages in the lamina propria
 - Marsh grading
- Dg: detection of circulating anti-gliadin or anti-endomysial antibodies or antibodies against tissue transaminase
 - duodenal biopsy→gluten-free diet→rebiopsy







Tropical sprue (Postinfectious sprue)

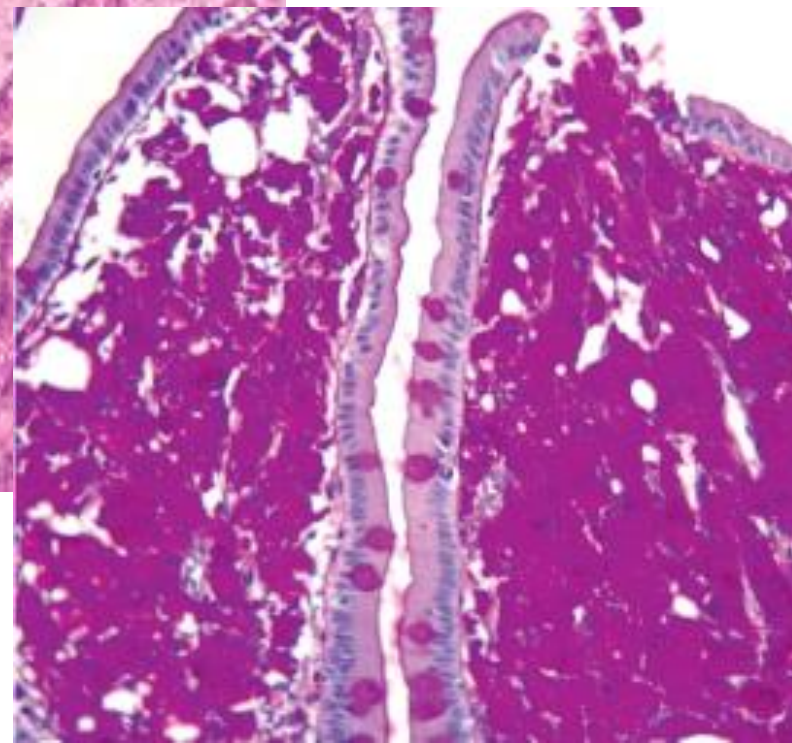
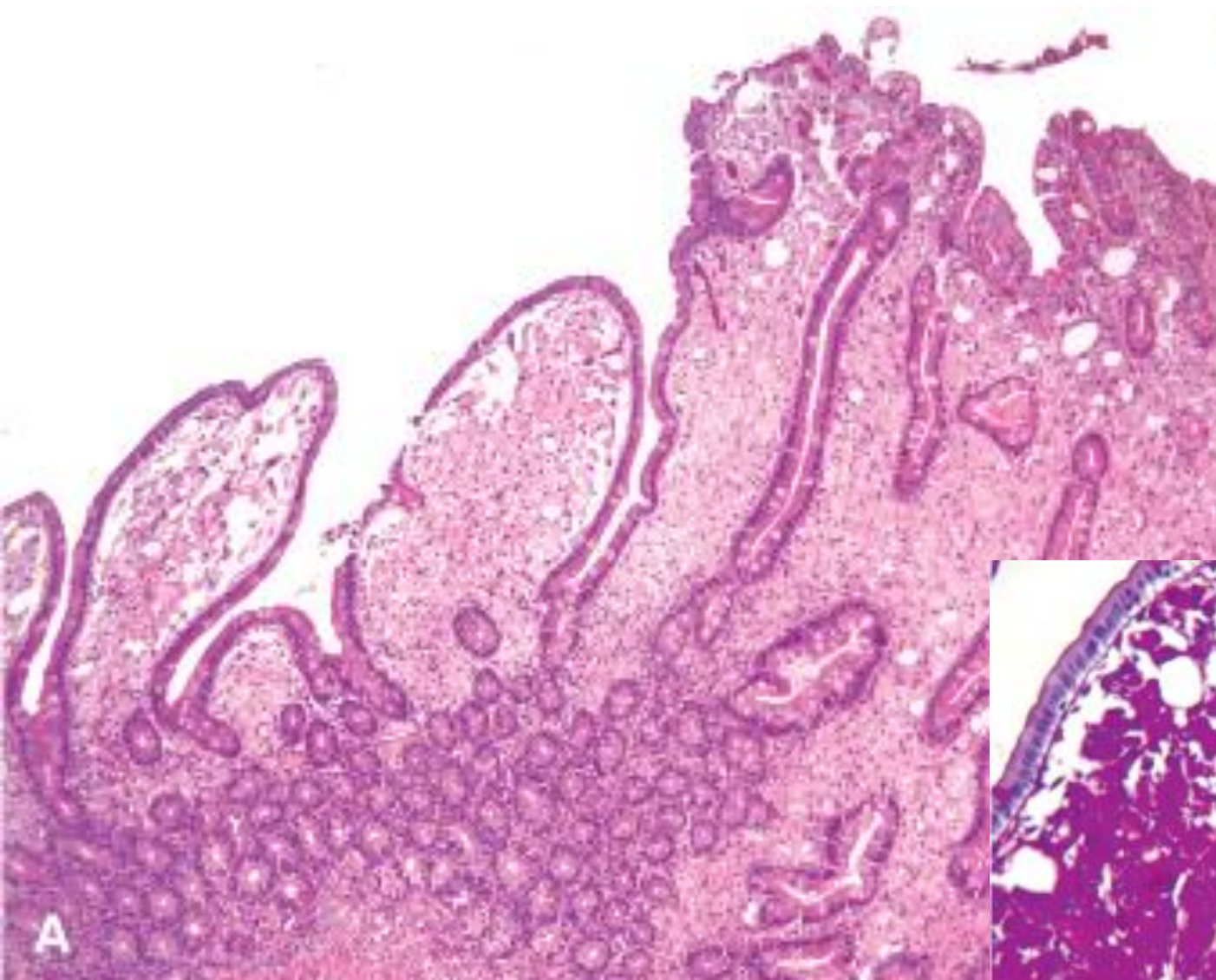
- in persons living in or visiting the tropics
- no specific agent associated
- bacterial overgrowth by enterotoxin producing bacteria may have a role
- near normal to severe enteritis at **all levels** of the small bowel
- megaloblastic change in epithelial cells due to B12 and folate deficiency

Whipple disease

- *Tropheryma whippelii* (Gram+ actinomycete proliferating within macrophages)
- intestine, CNS, joints, lymph nodes
- intestinal lipodystrophy- 1907 by George Whipple
- SY: weight loss, diarrhea, arthropathy, psychiatric disorders, lymphadenopathy, cardiac anomalies

Whipple disease

- MA: thickened intestinal wall, shaggy mucosa
- MI: Villi filled with macrophages containing bacteria (PAS+), no inflammation
- mesenteric lymph nodes involved, lymphatics dilated, same macrophages within joints' synovial membrane, brain and cardiac valves
- Dg: based on biopsy
- Therapy: AB



Whipple disease

Other malabsorption syndromes

- Lactase deficiency
 - children: inherited
 - adults: acquired
- Abetalipoproteinemia
 - AR disorder
 - apolipoprotein B is missing → no chylomicrons, LDL or VLDL) → lipid membrane defects

4. Vascular disorders

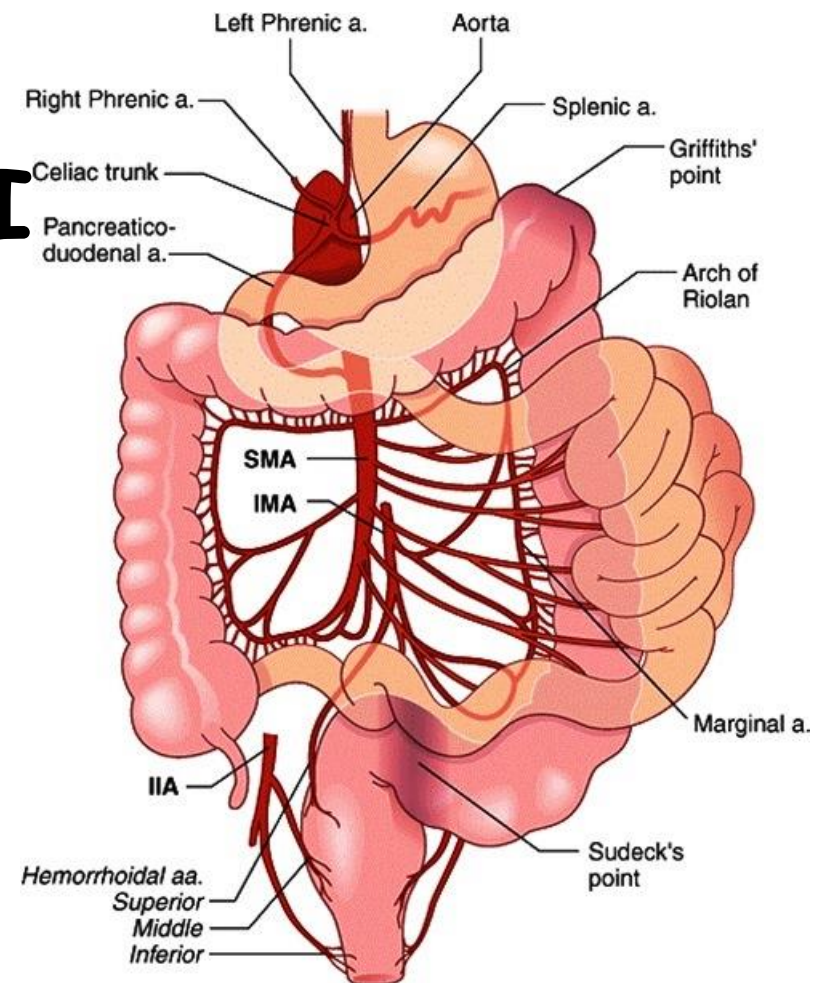
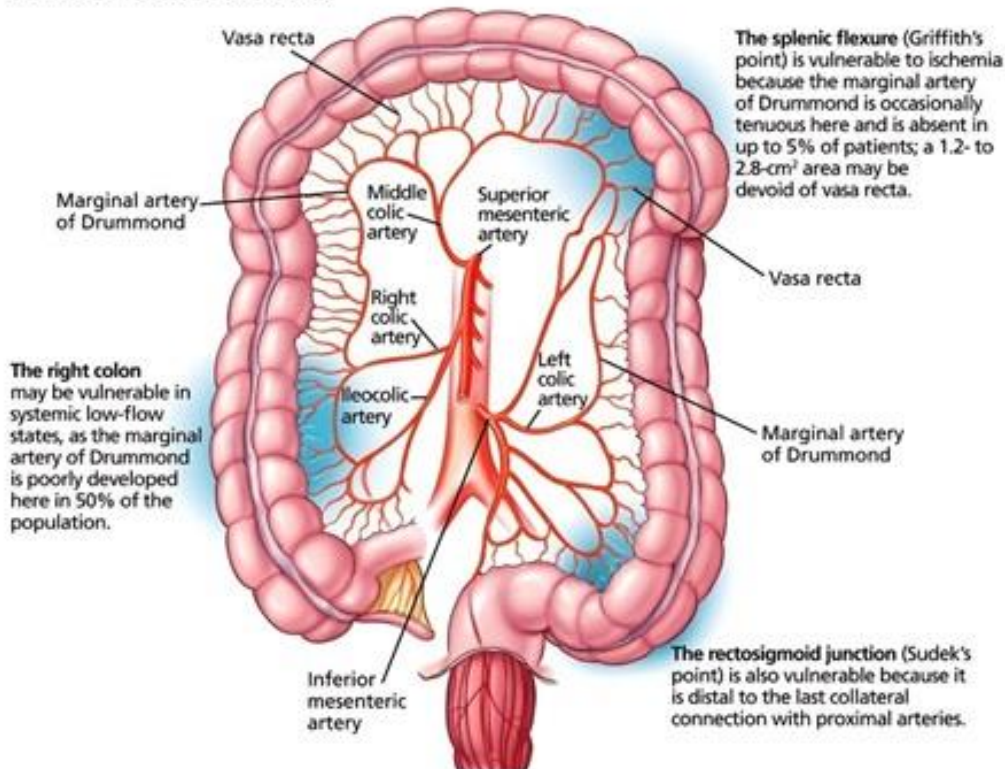
Vascular disorders

- Ischemic bowel disease
- Angiodysplasia

Blood supply to the GI

Why some areas of the colon are prone to ischemia

The colon is protected from ischemia by a collateral blood supply via the marginal artery of Drummond, a system of arcades connecting the major arteries. The anatomy is highly variable, however, and certain areas are more vulnerable in some people.



http://www.medicinemcq.com/index.php/journals/sub_de tails/91/33/INTESTINAL-ISCHEMIA

Ischemic bowel disease

- small or large bowel or both
- acute obstruction of celiac, superior or inferior mesenteric artery → **infarction**
 - Transmural
 - Mural
 - Mucosalresult of hypoperfusion
- Mesenteric venous thrombosis (due to hypercoagulability, sepsis, hepatocellular cc, cirrhosis etc)- less frequent cause of infarction
- initial hypoxic injury followed by reperfusion injury
- SY: pain, défense musculaire, vomiting, bloody diarrhea
- Complications: peritonitis, ileus, shock, 50-75% death rate



Angiodysplasia

- Malformed vessels (tortuous, ectatic veins, venules and capillaries) in mucosa and submucosa
- Right colon mainly (cecum)
- >60 y
- It is rare but 20% of lower intestinal bleeding is due to ~

5. Intestinal obstruction

Intestinal obstruction

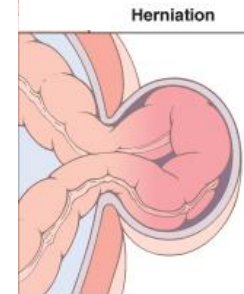
- mostly within the small intestine

- Mechanical obstruction:

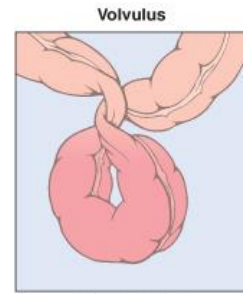
- Adhesions
- Hernias
- Volvulus
- Intussusception
- Tumors
- Strictures
- gallstones, foreign bodies
- meconium in mucoviscidosis



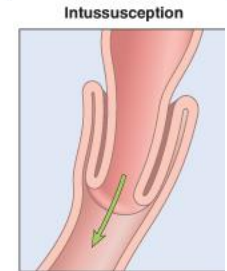
Adhesions



Herniation



Volvulus

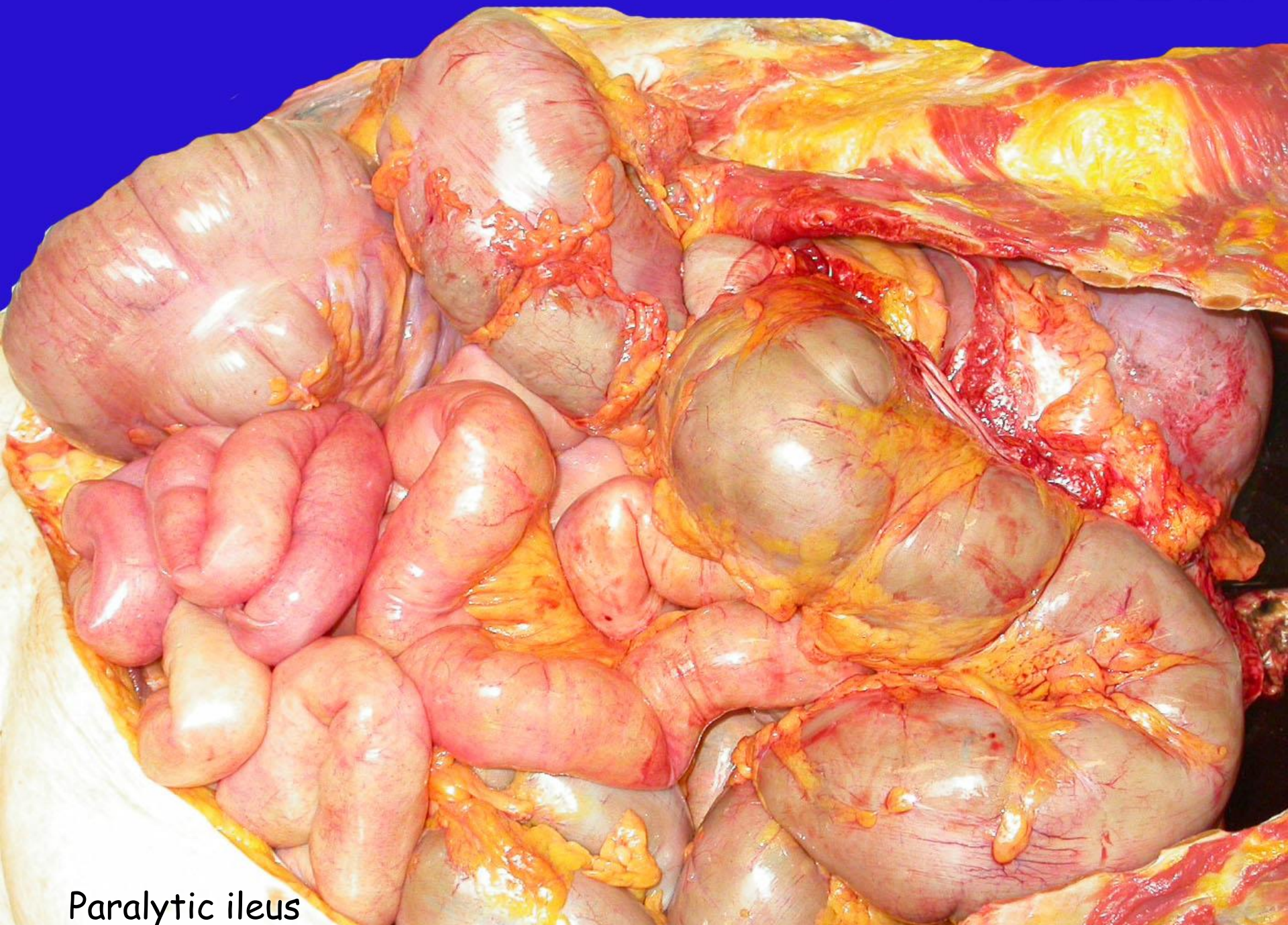


Intussusception

80 % of obstructions

- Pseudo-obstruction

- Paralytic ileus
- infarction
- myopathies, neuropathies (eg. Hirschprung disease, Chagas disease)



Paralytic ileus

6. Polyps and Neoplasms

Polyps and Neoplasms

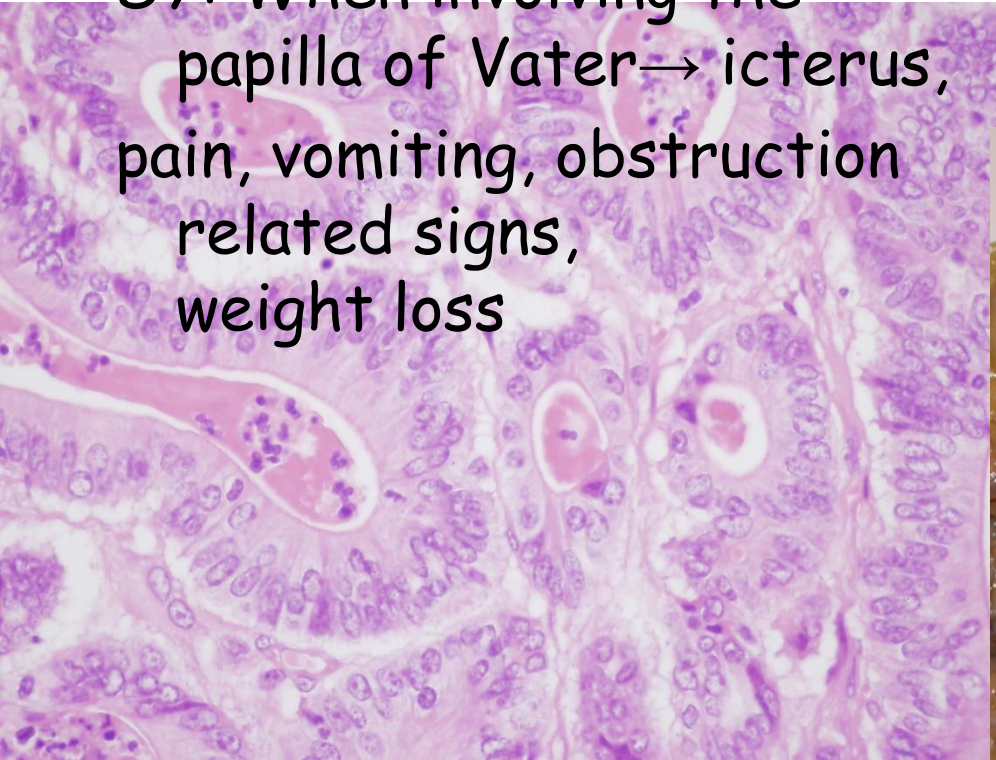
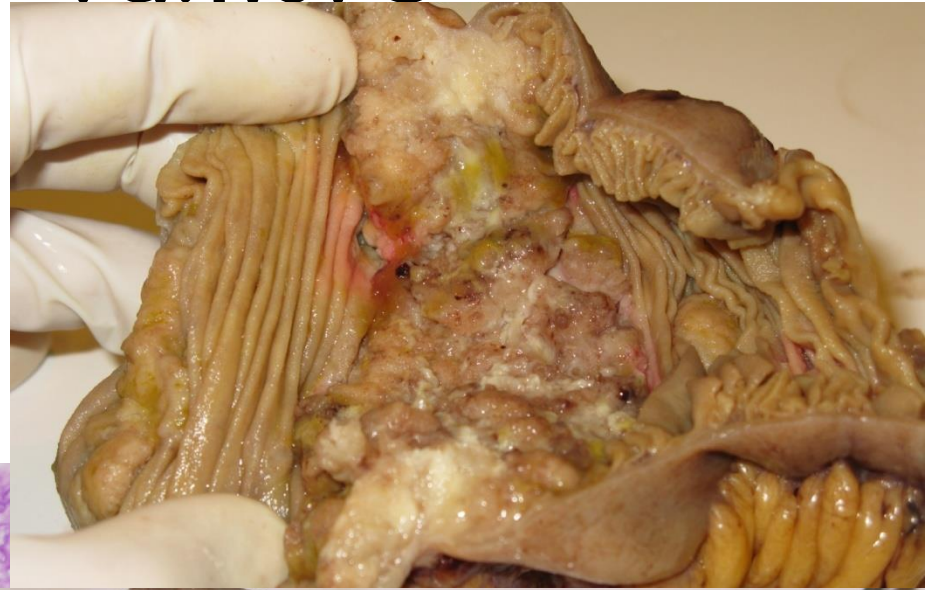
- 3-6 % of all GI tumors arising in the small bowel
- **Non-neoplastic and neoplastic polyps**
(see large bowel)
- **Adenocarcinoma**
- **Neuroendocrine tumor (carcinoid tumor)**
- Mesenchymal tumors: **GIST**, lipoma, neuroma, angioma etc.- (see stomach)
- Lymphomas (see stomach)
- Metastases

Malignant tumors

- **Adenocarcinoma**

If within small bowel,
majority in the **duodenum**

SY: When involving the
papilla of Vater → icterus,
pain, vomiting, obstruction
related signs,
weight loss



Neuroendocrine

Tumor/Neuroendocrine Carcinoma

(formerly known as Carcinoid tumor)

- From diffuse components of the endocrine system
- >40% within the small bowel (respiratory tract 2nd most common site)
- WHO 2010
 - NET: G1-2
 - NEC: G3
 - Grade depends on mitotic activity: $>2-20/10$ HPF: G1-3
 - TNM staging always- since these are tumors with a malignant potential

Neuroendocrine Tumor/Neuroendocrine Carcinoma

(formerly known as Carcinoid tumor)

- 6th decade
- SY: related with **obstruction** and eventual **hormone** production (Zollinger-Ellison sy, etc.)
- Prognosis depends on location
- Appendiceal and rectal carcinoids: metastases infrequent
- Malignant tumors: deeply invasive, large size, mainly in stomach, ileum, proximal colon

Location of NET and prognosis

- **Foregut NET**

- Esophagus, stomach, duodenum
- Stomach: maybe atrophic gastritis related (better prognosis than without predisposing factors)
- Rarely metastasize

- **Midgut NET**

- Jejunum, ileum
- Multiple
- Aggressive, poor outcome

- **Hindgut NET**

- Appendix, colon, rectum
- Incidental
- Proximal colon: may be large and metastasize
- Rectum: hormone production but metastasis is rare

Features of GI NET

Feature	Esophagus	Stomach	Proximal Duodenum	Jejunum and Ileum	Appendix	Colorectum
Fraction of GI NETs	<1%	<10%	<10%	>40%	<25%	>25%
Mean patient age (yr)	Rare	55	50	65	All ages	60
Location	Distal	Body and fundus	Proximal third, peri-ampullary	Throughout	Tip	Rectum > cecum
Size	Limited data	1–2 cm, multiple; >2 cm, solitary	0.5–2 cm	<3.5 cm	0.2–1 cm	>5 cm (cecum); <1 cm (rectum)
Secretory product(s)	Limited data	Histamine, somatostatin, serotonin	Gastrin, somatostatin, cholecystokinin	Serotonin, substance P, polypeptide YY	Serotonin, polypeptide YY	Serotonin, polypeptide YY
Symptoms	Dysphagia, weight loss, reflux	Gastritis, ulcer, incidental	Peptic ulcer, biliary obstruction, abdominal pain	Asymptomatic, obstruction, metastatic disease	Asymptomatic, incidental	Abdominal pain, weight loss, incidental
Behavior	Limited data	Variable	Variable	Aggressive	Benign	Variable

Carcinoid syndrome

- Affects <10% of patients with NET/NEC
- Serotonin production
- Vasomotor disturbances (flushing, cyanosis)
- Intestinal hypermotility (diarrhea, vomiting)
- Bronchoconstriction (cough, wheezing)
- Systemic fibrosis (cardiac: pulmonary and tricuspid valve thickening, right ventricular fibrosis, retroperitoneal and pelvic fibrosis)
- In patients with metastatic disease

Neuroendocrine tumor (Carcinoid)

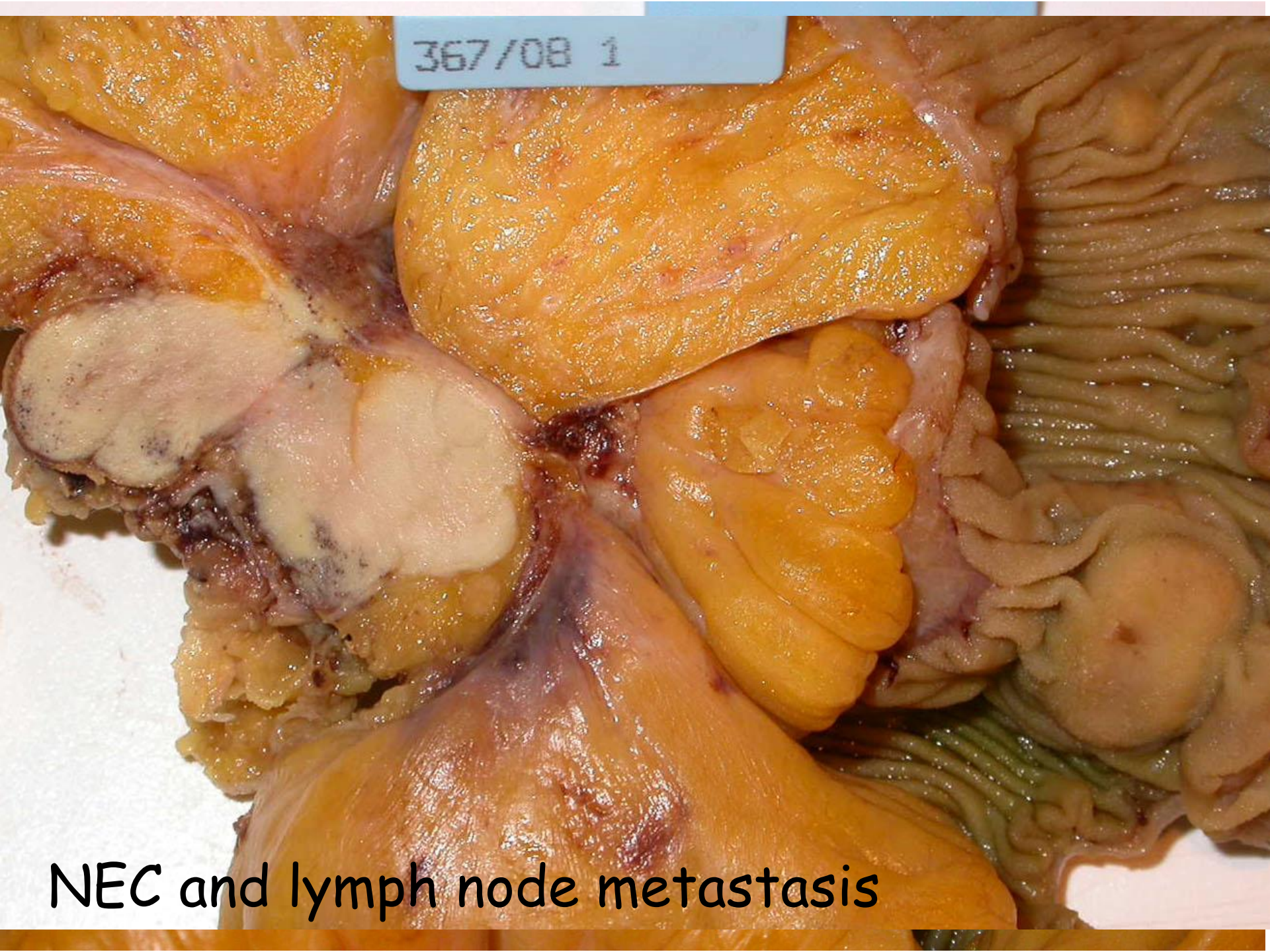
- MA: yellow tan solid tumor
- MI: islands of monomorphic cells, vesicular nuclei with „salt and pepper“ chromatin pattern

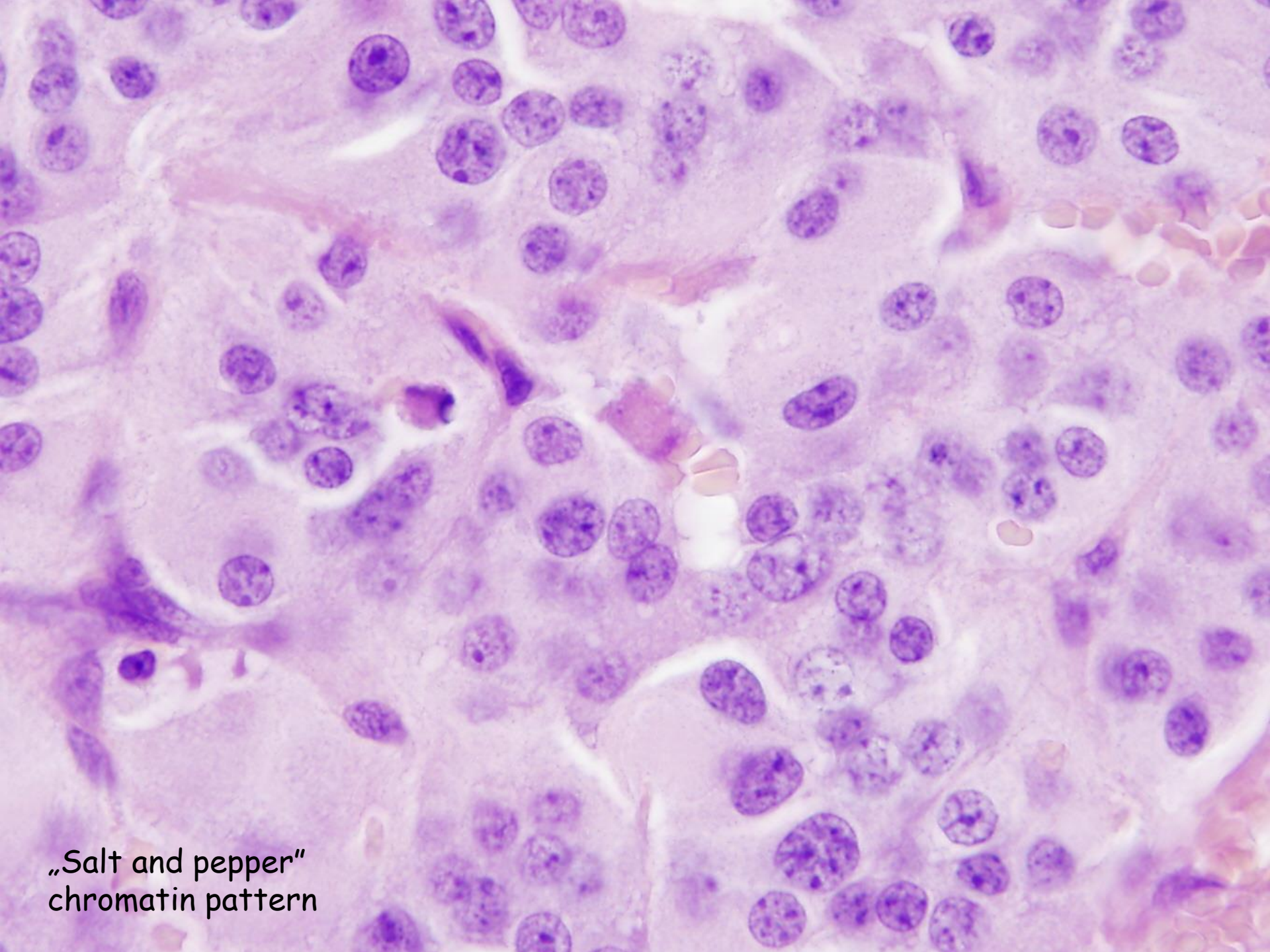


NET

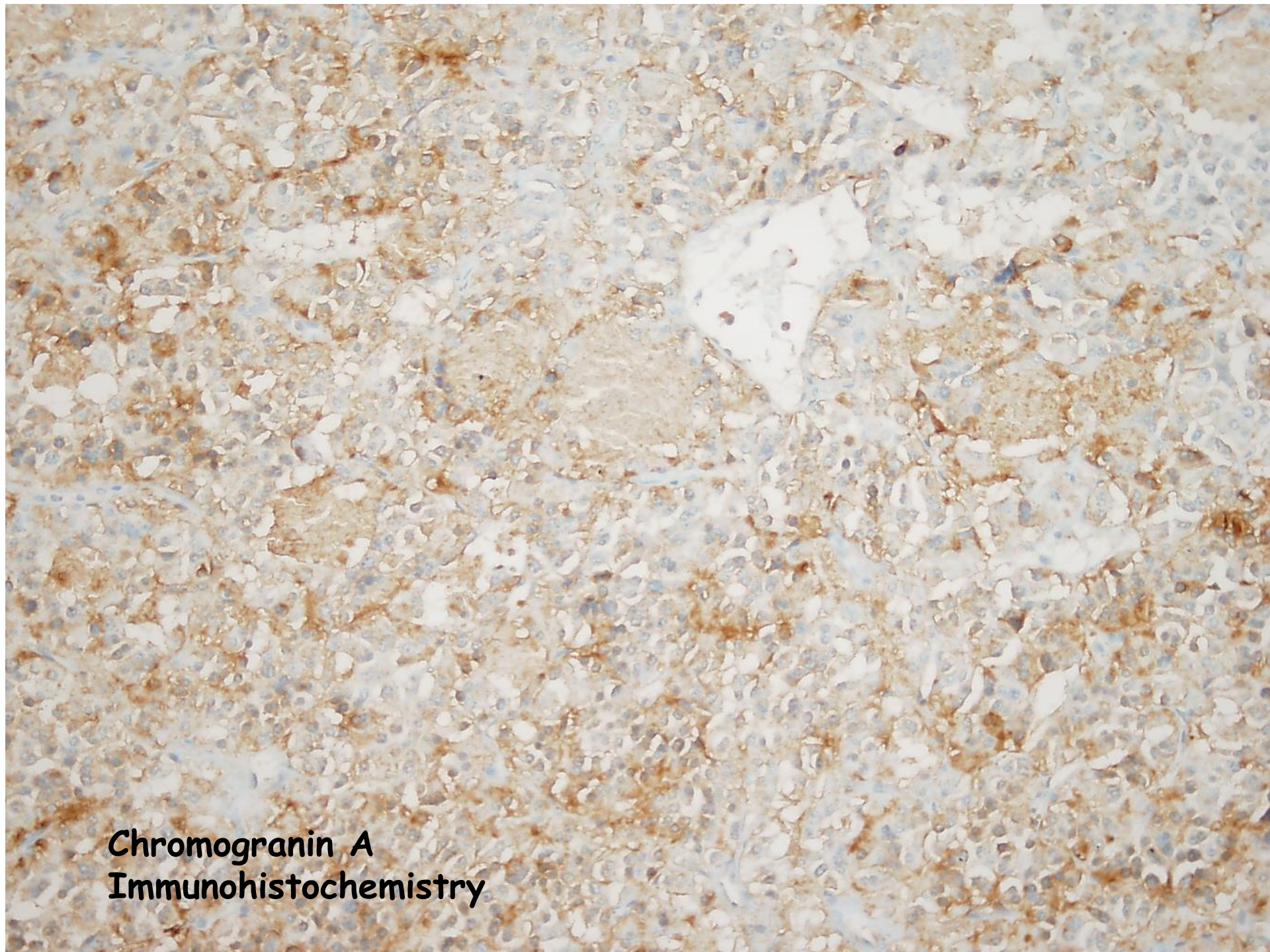
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NEC and lymph node metastasis





„Salt and pepper“
chromatin pattern



Chromogranin A
Immunohistochemistry

Gastrointestinal Stromal Tumor (GIST)

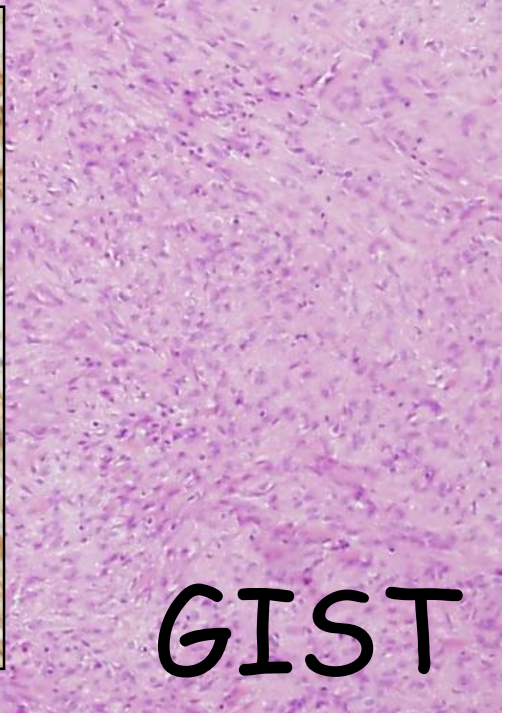
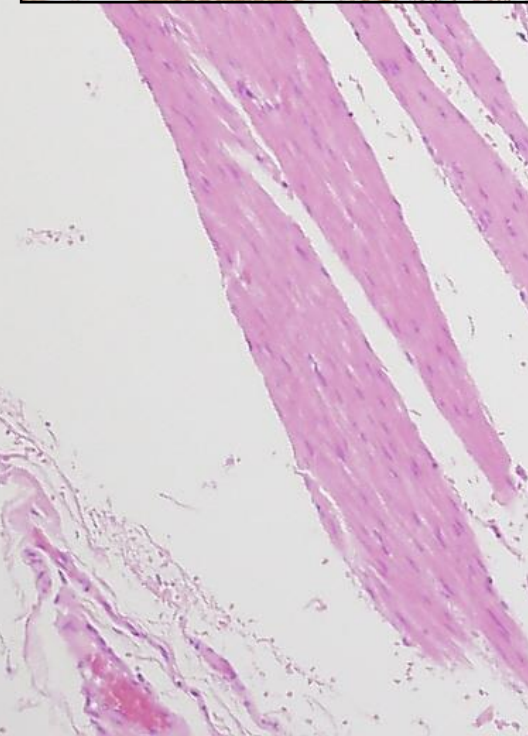
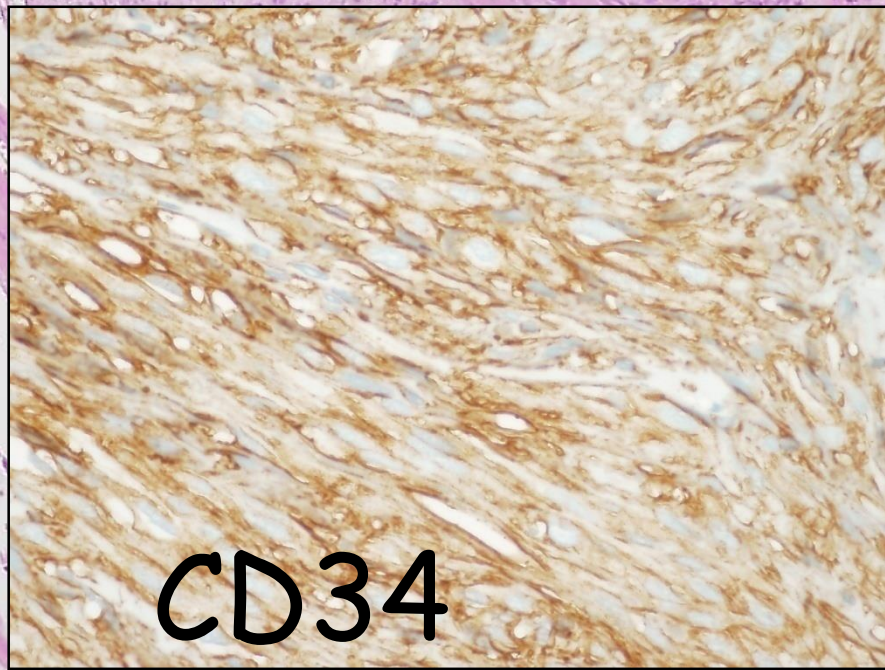
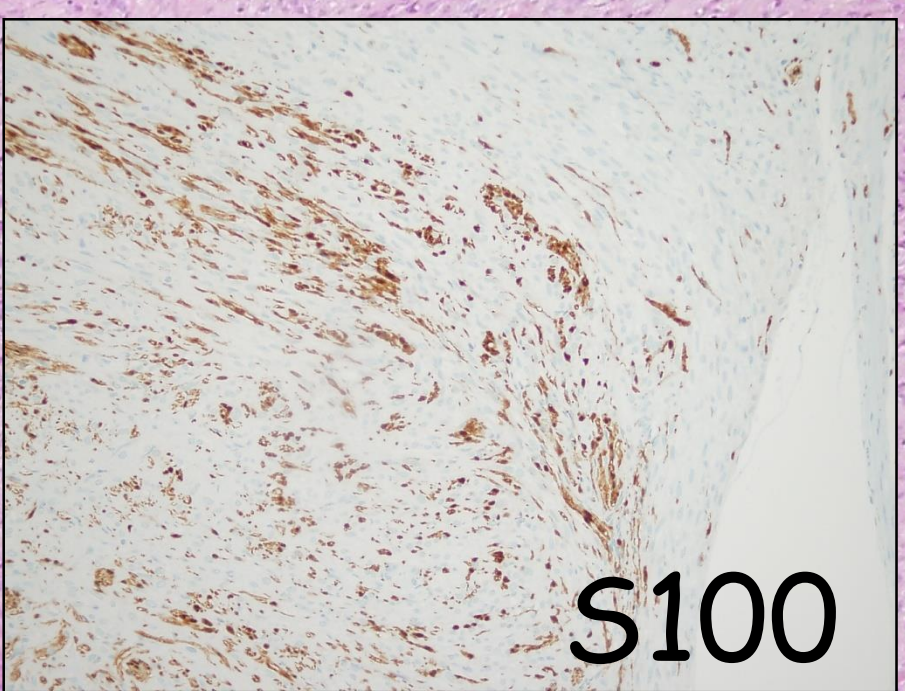
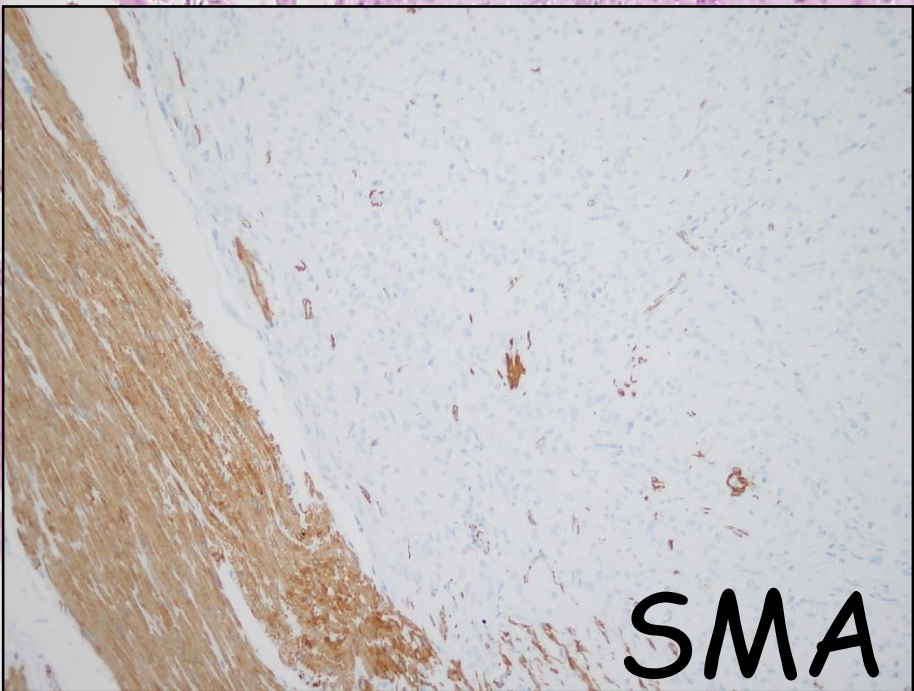
- Typically in male patients around 60 y
- originates from the „pacemaker cells“ the interstitial cells of CAJAL
- the majority express c-kit(CD117) and CD34
- different immunophenotypes
 - smooth muscle
 - neurogenic
 - both
 - none
- spindle cells or epithelioid cells

Gastrointestinal Stromal Tumor (GIST)

- Biological behaviour depends on size, mitotic index, location
- **Gastric GIST less aggressive than those within the small bowel**
- 80% have c-kit mutation
- 8% of tumors with normal c-kit have PDGFRA mutation
- both lead to continuous activation of the tyrosin-kinase signaling pathway (uncontrolled proliferation, apoptosis inhibition)
- drug: imatinib-Glivec® (tyrosin-kinase inhibitor also used in CML)



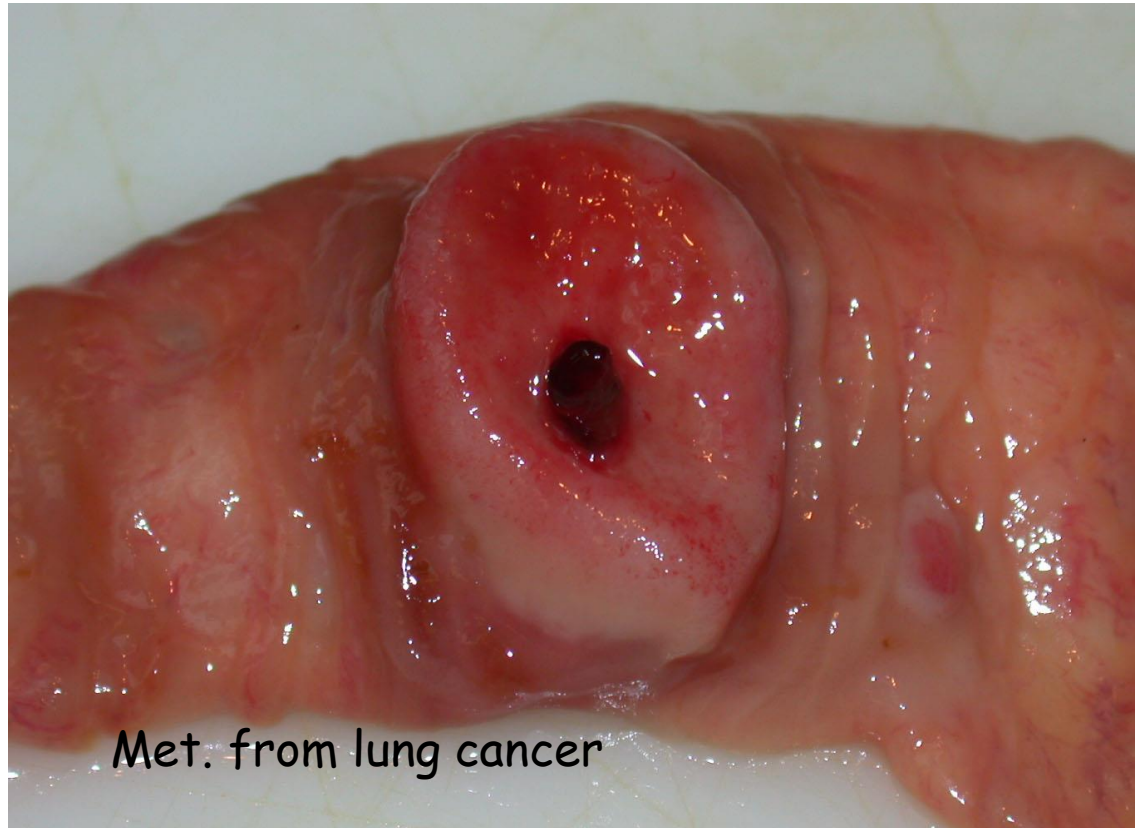
GIST-small bowel



GIST

Metastases

- Lung
- Breast
- Melanoma malignum



Met. from lung cancer

APPENDIX

Anatomy

- Residuum of cecum
- 6 cm
- Mucosa, submucosa, muscularis propria, serosa

Acute appendicitis

- Early acute appendicitis
- Acute suppurative appendicitis
- Acute gangrenous appendicitis-perforation→peritonitis
- SY: pain (Mc Burney, Lantz p.), vomiting, fever, leukocytosis
- MA: serosal surface dull (fibrino-purulent exudate)
- MI: neutrophils within the wall (muscularis propria!)

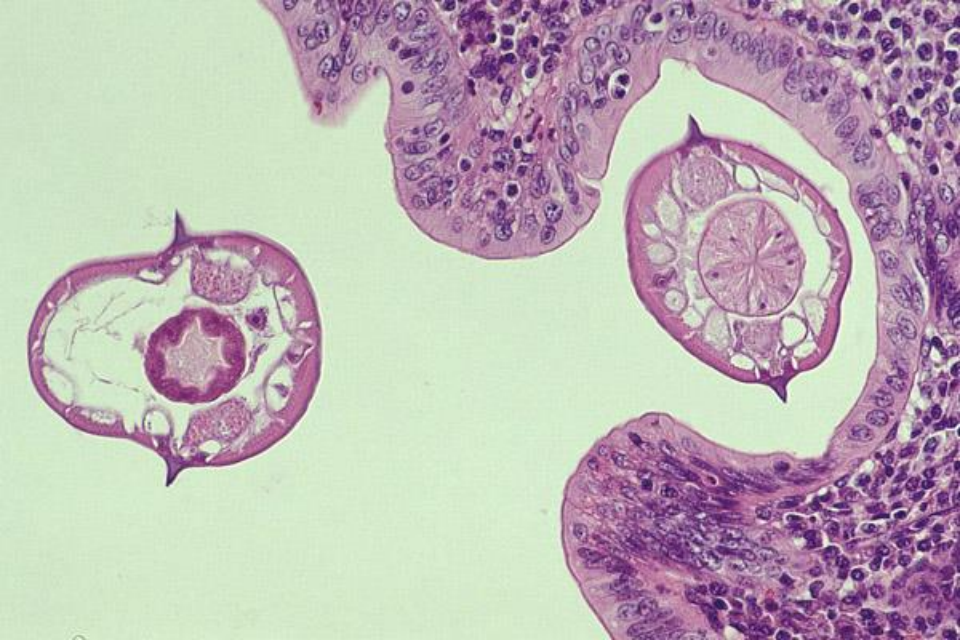
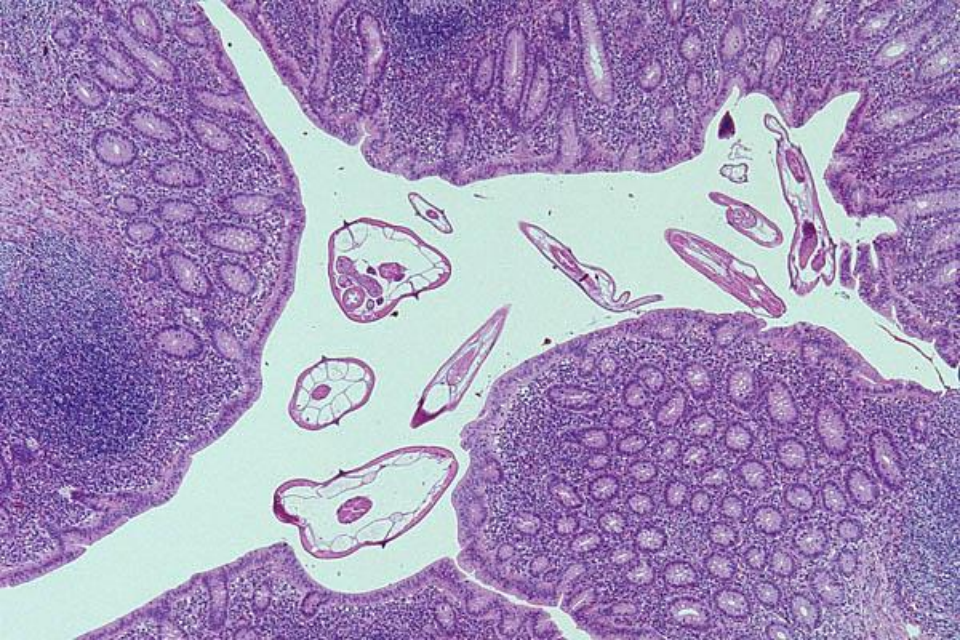


A high-magnification histological image of a tissue section stained with hematoxylin and eosin (H&E). The image displays a dense, diffuse infiltrate of inflammatory cells, primarily neutrophils, within the lamina propria. The cells are characterized by their purple nuclei and are scattered throughout the pink-stained connective tissue. The overall appearance is consistent with acute inflammation, such as that seen in acute appendicitis.

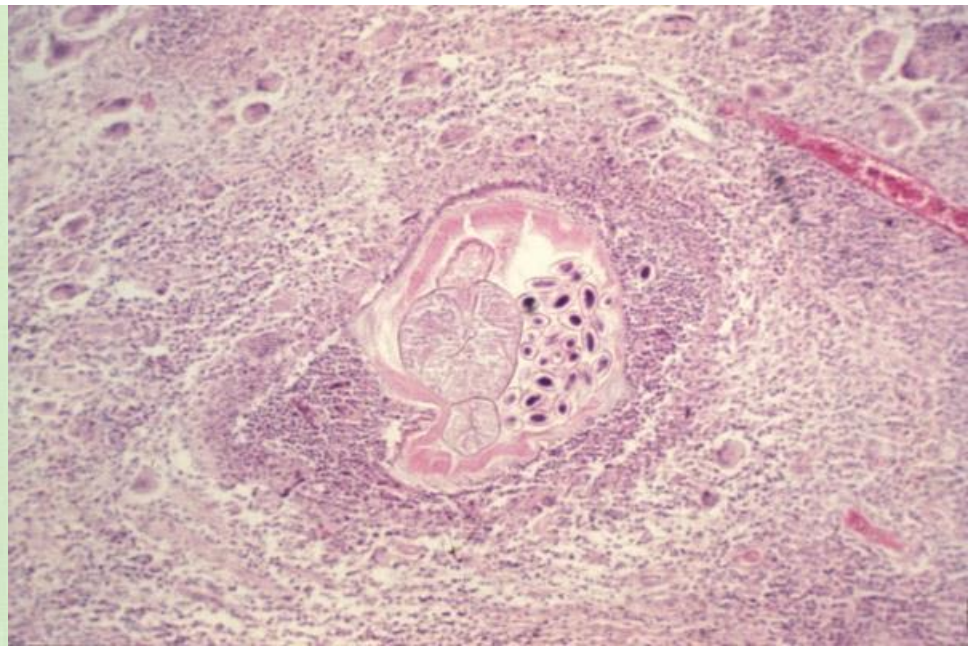
Acute appendicitis

A histological slide stained with hematoxylin and eosin (H&E) showing a cross-section of an appendix. The tissue is heavily infiltrated with inflammatory cells, particularly neutrophils, which are visible as small, dark purple nuclei. There is significant edema and hemorrhage throughout the tissue, with areas of necrosis and gangrene evident. The overall appearance is one of severe inflammation and tissue damage.

Acute gangrenous appendicitis



Enterobius vermicularis



Polyps and Neoplasms

- Neuroendocrine tumor (formerly carcinoid)- the most common tumor
- Non-neoplastic and neoplastic polyps
- Adenocarcinoma
- Mucinous cystadenoma
- Mucinous cystadenocarcinoma
- Mesenchymal tumors

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Neuroendocrine tumor

Mucocele

- Clinical term
- Mucinous cystadenoma, LAMN
- Dilation of appendix by mucus
- Result of obstruction
- Incidental- surgery for supposed appendicitis
- Rupture may occur



Mucocele